原 著

Indocyanine Green Dye Transport in a Living Tissue

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インドシアニンググリーンの生体組織内伝搬

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Abstract

Monte Carlo simulation method and diffusion approximation method are proposed to examine the time decay constants of indocyanine green, the so called plasma disappearance rate from the liver. The decay constants were estimated using an optically homogeneous turbid slab as a tissue model. Simulation results showed the diffusion approximation to be more stable than the Monte Carlo simulation. The calculated decay constants in a turbid media based on the diffusion approximation produced lower numbers compared to the constants in a clear media. This result fitted well with the reported clinical data.

Key words : Liver function test, ICG test, Monte Carlo method, Diffusion approximation

要 旨

インドシアニンググリーンの血漿消失率測定につき、モンテカルロ法と光子拡散理論による近似解法を用いて評価した。消失率の評価は光学的に均一に混濁な組織モデルに対して実施した。シミュレーション結果により、本モデルに対しては、拡散近似による方法がモンテカルロ法より安定であった。拡散近似により求めた混濁組織モデルでの血漿消失率は、混濁度を考慮しない場合に比して低い値を示した。本結果は、よく臨床結果を反映していると考えられた。

キーワード : 肝機能検査, ICG検査, モンテカルロ法, 拡散近似

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Introduction

Indocyanine green (ICG)¹⁾ is a tri-carbo-cyanine dye that has been used for measuring cardiac output and hepatic function in humans for 30 years. Particularly in Japan, it has been widely used as a sensitive tracer in hepatic dye clearance tests²⁾. In 1969 a standardized method using ICG was adopted by the Japanese Society of Gastroenterology³⁾. However, several blood samplings are required to determine the plasma disappearance rate (k) of ICG by using a spectrophotometer. Recently, an ICG test without blood sampling, the finger piece method using an optical sensor was developed^{4, 5)}. Briefly, the finger piece method was carried out as follows; an optical sensor consisting of two LEDs and a photodiode is fixed to the tip of the finger. Calibration is conducted by raising and lowering the arm to compensate the changing of the blood volume at the measuring site, then ICG is administered intravenously and the optical sensor measures the optical transmittance through the finger to calculate k . The calculation to determine k is based on the transmittance, though tissues such as the finger tip should be considered as highly scattering media.

In such a light-tissue interaction, it is necessary to model light transport in biological tissues, which are turbid media. Among the available models are Monte Carlo simulations⁶⁻¹²⁾, diffusion theories¹³⁻¹⁹⁾, and finite difference methods²⁰⁾. As a mathematical model to treat turbid tissues, Monte Carlo simulations of photon propagation offer a flexible yet rigorous approach toward photon transport^{21, 22)}. But, it takes a long time to get the result using Monte Carlo simulation. On the other hand, diffusion approximation

has a possibility to give an adequate solution for the same problem in a short time. Therefore, in this paper, the both methods are applied the light propagation in a slab model. The simulation results are compared with in vivo result to examine the usefulness of the simulation.

Materials and methods

Materials

A tissue such as the fingertip is first considered as optically homogeneous. Incident light comes in from the upper layer of the tissue model and a detector detects transmitted light from the bottom layer of the tissue model. Optical properties for tissue and blood at the wavelength with the maximum ICG absorption, 805nm, are taken from published data²³⁾. ICG optical properties at various concentrations in a 0.5%-albumin solution are measured at 805nm using a spectrophotometer.

Methods

Monte Carlo simulation

The Monte Carlo method is a means to estimate the exact solution to light distributions. This is done by tracing a large set of possible paths of photons through objects. The Monte Carlo program is written for turbid media such as tissues to compute the light distributions according to tissue geometry and optical properties, including refractive index (n), absorption coefficient (μ_a), scattering coefficient (μ_s), and anisotropy factor (g). The delta-scattering technique is used for photon tracing to greatly simplify the algorithm by allowing a photon packet to be traced without worrying about the interfaces between tissues. This technique can

be used only for refractive-index-matched tissues, although it allows the ambient clear media (e. g., air) and the tissue to have mismatched refractive indices. The tissue system is assumed to have multiple tissue types with matched refractive indices. The interaction coefficient of the i th tissue type, defined as the sum of μ_s and μ_a , is denoted by, $\mu_i = \mu_s + \mu_a$.

The techniques is briefly summarized as follows.

Step 1 : Define the largest interaction coefficient μ_m , $\mu_m \geq \mu_i$, for all i tissues.

Step 2 : Select a distance R ,

$$R = -\ln(\xi) / \mu_m, \quad (1)$$

where ξ is uniformly distributed random number between 0 and 1 ($0 < \xi < 1$). Then, determine the tentative next collision site r_j , by :

$$r_j = r_{j-1} + Ru_{j-1}, \quad (2)$$

where r_{j-1} is the current site and u_{j-1} is the direction of the flight.

Step 3 : Select among possible propagation outcomes :

- a. With a probability of $\mu(r_j) / \mu_m$, accept this point as a real interaction site ($r_j = r_j$) ;
- b. Otherwise, do not accept r_j as a real interaction site but select a new path starting from r_j with the unchanged direction μ^{j-1} (i. e., set $r_{j-1} = r_j$, and return to Step 2).

An imaginary interaction event that changes neither the weight nor the direction of the photon is introduced to understand the validity of this algorithm. this definition

implies that such imaginary interactions are not physically observable, i. e., they can be introduced with any interaction coefficient at any point. Now if the majorant interaction coefficient (μ_m) is a sum of the real (μ_{re}) and imaginary (μ_{im}) interaction coefficients, then in the procedure outlined above, a fraction of the interactions,

$$1 - \frac{\mu_{re}}{\mu_m} = \frac{\mu_{im}}{\mu_m} \quad (3)$$

are imaginary interactions. On the average, for every μ_m total interactions, there will be μ_{re} interactions accepted as real interactions. The mean free path for the majorant interactions in the delta-scattering method is $1 / \mu_m$ and the mean free path for the real interactions in the direct method is $1 / \mu_{re}$. Therefore, the photon will move to the correct interaction site using the delta-scattering technique as it would using the direct method, i. e.,

$$\mu_m (1 / \mu_m) = \mu_{re} (1 / \mu_{re}) \quad (4)$$

where the left-hand side is the average distance traveled by the photon packet with μ_m total steps or with μ_{re} real interactions in the delta-scattering method and the right-hand side is the average distance traveled with μ_{re} real interactions in the direct method. During the tracing of each weighted photon, the light absorption, reflectance, or transmittance are correspondingly scored in to different arrays according to the spatial and temporal positions of the photon. Multiple photons are traced to achieve an acceptable statistical variation.

Diffusion theory

When using photon diffusion theory the optical properties needed are the absorption coefficient (μ_a) and reduced scattering coe-

fficient ($\mu_s' = (1-g)\mu_s$). Two related coefficients are the transport interaction coefficient (μ_t') and the effective attenuation coefficient (μ_{eff}), which are respectively expressed by the following relationship :

$$\mu_t' = \mu_a + \mu_s' \quad (5)$$

and

$$\mu_{eff} = \sqrt{3\mu_a\mu_t'} \quad (6)$$

The inverse of the transport interaction coefficient is defined as one transport mean path ($mfp' = 1/\mu_t'$).

Diffusion theories for semi-infinite tissues have been presented elsewhere¹⁹⁾. Here, diffusion theory is extended for tissue slabs such as the fingertip. An infinitely narrow laser beam (pencil beam) is incident upon a tissue slab whose optical properties are refractive index n , μ_a , μ_s' , and thickness d . The pencil beam is approximated by an isotropic point source that is 1 mfp' below the tissue surface. A cylindrical coordinate system is set up, where the z axis originated on the top tissue surface and points downward perpendicularly to the tissue surface. The steady state diffusion equation for a homogeneous medium is :

$$S - \mu_a = -D \Delta^2 \phi(z, r, z_s) \quad (7)$$

In this cylindrical coordinate system, where z and r are the cylindrical coordinates of the observation point, the fluence caused by an isotropic point source at a depth $z=z_s$ in an otherwise infinite medium has been analytically solved. The fluence rate from a point source S is :

$$\phi(z, r, z_s) = \frac{1}{4\pi D} \frac{\exp(-\mu_{eff}\rho)}{\rho} \quad (8)$$

and is the distance between the observation point and the source, i. e.,

$$\rho = \sqrt{(z-z_s)^2 + r^2} \quad (9)$$

and D is the diffusion constant in cm,

$$D = \frac{1}{3\mu_t'} \quad (10)$$

Since we are interested in the local diffuse transmittance, J in photons per unit area, at the exit of the model slab, on the bottom tissue surface, the contribution of this isotropic point source is :

$$J(z=1, r, z_s) = D \left. \frac{\partial \phi}{\partial z} \right|_{z=1} = \frac{(1-z_s)(1+\rho)\exp(-\mu_{eff}\rho)}{4\pi\rho^3} \quad (11)$$

To compute the fluence caused by an isotropic point source in a tissue slab based on Eq. 8 we need to convert the slab into an infinite medium by satisfying the boundary condition with an array of image sources. Since the fluence on the two real boundaries is not zero, two extrapolated virtual boundaries where the fluence is approximately zero are used. The two virtual boundaries are the distance Zb away from the tissue surfaces, where Zb is

$$Zb = 2AD, \quad (12)$$

where A a function of the internal reflection r_i . When the boundary has matched refractive indices, $A = 1$; otherwise, A can be estimated :

$$A = \frac{1+r_i}{1-r_i} \quad (13)$$

where

$$r_i = -1.440n_{rel}^2 + 0.710n_{rel} - 1 + 0.668 + 0.0636n_{rel} \quad (14)$$

Figure 1 Distribution of the image source for a tissue slab. The original isotropic point source is $z=1$ mfp' below the tissue surface.

Figure 2 ICG concentration versus absorption coefficient in a clear media in albumin solution at 805 nm wavelength.

and where n_{rel} is the relative refractive index of the tissue. Figure 1 shows the positions of the original isotropic point source and its image sources about the two virtual boundaries. Each mirroring changes the sign of the point source.

The z coordinate of i th positive or negative image source is

$$Z_i(\pm) = -Z_b + i(d + 2Z_b) + (z_o + Z_b). \quad (15)$$

Once these image sources are used, the boundary condition is approximately satisfied, and hence the true boundaries can be removed. The problem is converted into an array of isotropic sources of both signs in an infinite medium. A linear combination of Eq. (8) for different source positions will, therefore, yield the fluence of the isotropic point source positions will, therefore, yield the fluence of the isotropic point source in the original tissue slab, and a linear combination of Eq. (11) for different source positions will yield the local diffuse transmittance.

Results

ICG optical property using a spectro-photometer

Figure 2 shows the ICG concentration in a 0.5% -albumin solution versus its absorption coefficient, μ_{ai} [$1/\text{cm}$], at 805 nm using a spectrophotometer. Albumin solution is used as a clear media. As shown, the linear relationship can be found between the ICG concentration and μ_{ai} . From the equation fitted, μ_{ai} in [cm^{-1}] is

$$\mu_{ai} = 2.58C_{ig} \quad (16)$$

where C_{ig} is the ICG concentration in the 0.5% albumin solution. Since the low concentration albumin solution can be considered as non scattering, spectrophotometric analysis is only affected by absorption.

Simulation results of the Monte Carlo method and diffusion approximation.

First, a typical set of tissue optical properties, relative refractive index between air and tissue $n_{rel} = 1.37$, $g = 0.95$, $\mu_t = 0.478 + \mu_{ai}$ cm^{-1} , $\mu_s = 545.2 \text{ cm}^{-1}$ and $\mu_s' = 27.3 \text{ cm}^{-1}$ is assigned.

Figure 3 Diffuse transmittance of a pencil beam incident upon a tissue slab are computed with the diffusion theory and compared with the Monte Carlo simulation. The slab thickness is 1 cm, and the optical properties of the tissue are refractive index $n_{refl}=1.37$, $\mu_{abs}=0.478\text{cm}^{-1}$, and $\mu_s'=27.3\text{cm}^{-1}$.

Figure 4 Diffuse transmittance with various background absorptions and scattering.

igned to the model. Second, the background absorption or scattering are varied to estimate their effect to the decay constant. In **Fig. 3**, the local diffuse transmittance for a range of ICG absorption coefficients is computed using the diffusion theory the Monte Carlo method, in which the Monte Carlo simulation uses enough photons for the resul-

ts to be considered accurate. For the local diffuse transmittance, the diffusion theory seems to be accurate, but the Monte Carlo simulation result is too noisy to permit a definitive conclusions because of statistical errors at low ICG concentration. The other disadvantage of the Monte Carlo method is the length of time that programs have to run to give accurate estimates.

Following the law of large numbers, average values are estimated without bias, but the standard deviation of the estimated average values only decreases as $1/\sqrt{N}$, where N is the number of photons generated. In this case the 1,000,000 photons used required a calculation time of 24 hours by Sun workstation.

Therefore, the diffusion approximation can give an analytically appropriate result to examine the dependence of scattering in this model with a simple geometry such as a slab model.

Figure 4 shows the local diffuse transmittance, T , of a tissue model with ICG having different background absorption coefficient. According to these simulation results, when the tissue has high absorption such as $1.2\text{ [cm}^{-1}\text{]}$ or more, the relationship between the ICG absorption coefficient determined by the concentration and the local diffuse transmittance is a pure exponential, but a tissue with low background $0.8\text{ [cm}^{-1}\text{]}$ is not a pure exponential.

A transmittance measurement was made using a photodetector, yielding $-\ln(T)/d$ is equal to μ_{app} which can be called an apparent absorption coefficient. **Figure 5** shows the relationship between calculated μ_{app} by the diffusion approximation and ICG absorption coefficient. This also implies

Figure 5 Relationship between calculated μ_a (app) by diffusion approximation versus ICG absorption coefficient for various background absorption and scattering.

Figure 6 Typical ICG clearance curves estimated using k values determined by (a) the diffusion theory, and (b) a spectrophotometer.

the non-linearity between ICG concentration and measured values of $-\ln(T)/d$, because of the scattering and background effect. Estimation of the decay constant of ICG using the diffusion approximation Using the above simulation results based on diffusion theory, the decay constant, the so-called plasma disappearance rate, k in min^{-1} , is examined for various conditions. The k is defined as

Figure 7 Relationship between kt and kc with various background absorption (μ_b) and scattering (μ_s') coefficient. Clinical data are shown as in vivo.

$$C_{ig} = C_0 \exp(-k t) \quad (17)$$

where C_0 in mg/dl is initial ICG concentration, and t in minutes is time after ICG was injected intravenously. Usually, C_{ig} is measured as ICG concentration in blood plasma using spectrophotometer.

The plasma samples including ICG are treated as non-scattering media. Therefore, there is a linear relationship between μ_{ai} and C_{ig} described above. In a turbid media such as biological tissues, however, there is no linear relationship between $\mu_{a(app)}$ and C_{ig} determined by the absorption coefficient of ICG, μ_{ai} . Figure 6 shows typical ICG clearance curves estimated using k values determined by a spectrophotometer and the diffusion theory. It is clear that the curves in a clear media are different from the curves measured by the diffuse transmittance through the model proposed. This implies calculated k in a clear media, kc , is different from k in a turbid media, kt .

Expanding these results, Fig. 7 shows the relationship between kc and kt . The linear

regression equation between k_c and k_t is calculated as $k_t = 0.816k_c$ for clinical in vivo data on humans. Therefore, the diffusion approximation also gives a well fitted results compared to the clinical data.

Discussion

The ICG test is one of the most sensitive way to diagnose liver diseases such as liver cirrhosis. In order to measure the decay constant of a dye concentration such as ICG directly from a measuring site in vivo, the finger piece method gives a non-invasive way of diagnosis. There was a high correlation between the results of blood sampling method using spectrophotometer and the finger piece method and this results were considered the finger piece method as a useful method clinically. Knowing optical properties, however, such as the absorption and scattering coefficient is important to determine the decay constants because the scattering and background absorption produced lower numbers for decay constants. The diffusion approximation explained the difference of two parameters, k_t in a turbid media and k_c in a clear media. Combining much clinical data may give the consequence of the difference between k_t and k_c values practically, but theoretical analyses are powerful ways to analyze the scattering and background effect. In general, this simulation gives the aspect of interaction between light and turbid media such as biological tissues.

Conclusion

An optical tissue model for ICG test is proposed to simulate the light propagation in the finger tip using the Monte Carlo method and diffusion theory. The diffuse trans-

mittance based on the diffusion theory gave more stable results than that based on the Monte Carlo simulation for this model. The simulation results show that scattering and background absorption produce smaller values of the decay constants than the values measured using a spectrophotometer. Clinical data fit well to the simulation result.

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