Photoacoustics 10 (2018) 54–64

Contents lists available at ScienceDirect

Photoacoustics

journal homepage: www.elsevier.com/locate/pacs

Research article

# A light-fluence-independent method for the quantitative analysis of dynamic contrast-enhanced multispectral optoacoustic tomography (DCE MSOT)

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ARTICLE INFO

*Article history:*
Received 5 January 2018
Received in revised form 24 April 2018
Accepted 26 April 2018
Available online 3 May 2018

*Keywords:*
Dynamic contrast enhanced imaging
Multispectral optoacoustic tomography
Pharmacokinetics models
Linear models
Permeability

ABSTRACT

MultiSpectral Optoacoustic Tomography (MSOT) is an emerging imaging technology that allows for data acquisition at high spatial and temporal resolution. These imaging characteristics are advantageous for Dynamic Contrast Enhanced (DCE) imaging that can assess the combination of vascular flow and permeability. However, the quantitative analysis of DCE MSOT data has not been possible due to complications caused by wavelength-dependent light attenuation and variability in light fluence at different anatomical locations. In this work we present a new method for the quantitative analysis of DCE MSOT data that is not biased by light fluence. We have named this method the two-compartment linear standard model (2C-LSM) for DCE MSOT.


## 1. Introduction

A variety of biomedical imaging modalities, including magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET), have been used to measure the Dynamic Contrast Enhancement (DCE) after intravenous injection of a non-specific contrast agent [1–3]. These DCE imaging methods can be utilized to evaluate vascular characteristics in patients with cancer and in mouse tumor models [4]. These vascular characteristics can be used to assess tumor angiogenesis and changes in tumor vasculature caused by anti-angiogenic and anti-vascular therapies [5]. DCE imaging methods can also gauge the vascular patency of some tumors to predict potential for intravenous drug delivery to the tumor. Therefore, DCE imaging methods have substantial value for pre-clinical and clinical diagnoses [6,7].

DCE imaging results can be analyzed with moderate-to-advanced pharmacokinetics models to quantitatively estimate $K^{trans}$, the transport rate of a contrast agent from plasma to the extracellular extravascular space within a tumor [8]. These analysis methods can also quantitatively estimate $k_{ep}$, the rate of transport of an agent from extracellular space to the plasma. However, accurate estimates of $K^{trans}$ and $k_{ep}$ require rapid image acquisitions to provide fast temporal resolution of the DCE results [9]. Unfortunately, routine MRI, CT, or PET protocols often have low temporal resolution, or sacrifice spatial resolution to gain temporal resolution [10]. Advanced MRI or CT protocols that can obtain fast temporal resolution while retaining fine spatial resolution often require expensive instrumentation and substantial expertise. For these reasons, DCE imaging methods have typically only been used for qualitative assessments of tumors rather than providing quantitative measurements of vascular characteristics.

In this work, we sought to introduce a new model for quantitative DCE MultiSpectral Optoacoustic Tomography (MSOT) that can provide DCE imaging with high temporal resolution and spatial resolution. This relatively new imaging technique directs pulses of light into tissue, which are absorbed by chromophores in the tissue. The absorption of light leads to transient heating and subsequent thermoelastic expansion, giving rise to ultrasound waves that can be detected by an ultrasound transducer [11]. The signal creation is rapid, allowing for DCE MSOT studies at high temporal resolution. Due to the detection of relatively low-scattered ultrasound waves, MSOT provides multi-spectral optical contrast at ~2-3 cm depth and high spatial resolution, overcoming

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https://doi.org/10.1016/j.pacs.2018.04.003

the traditional optical imaging limitation of reduced resolution *in vivo* [12,13]. Although MSOT has a lower depth of view relative to MRI and CT, the ~2-3 cm depth of view is still sufficient for imaging the whole mouse torso and for imaging solid tumors in some patients who have cancer.

Although qualitative and semi-quantitative DCE MSOT studies have shown utility for specific applications [14,15], the development of a quantitative DCE MSOT analysis method has not yet been demonstrated. So far, the quantitative analysis of optoacoustic images has been aimed at correcting for optical light fluence, and calculating the absolute concentration of the contrast agent from the acoustic pressure maps formed by a reconstruction algorithm [16]. Furthermore, a true assessment of response to therapy with DCE MSOT requires a quantitative representation of the observed kinetics [17].

In this report, inspired by methods used in quantitative DCE PET and DCE MRI [18–20], we deviate from the current paradigm and present a new model for the quantitative analysis of DCE MSOT that does not require the estimation of the absolute concentration of a contrast agent in a certain pixel as an input, and can overcome the problem of light fluence [21]. We have called this model the two-compartment linear standard model (2C-LSM) for DCE MSOT.

## 2. Theory

### 2.1. Derivation of the two-compartment model for DCE MSOT

In this work we have adapted the notation and symbolic conventions previously described for DCE MRI and DCE PET studies assuming a two-compartment model (Fig. 1A) [22,23]. A differential equation describes the temporal evolution of a single contrast agent in a tissue of interest (*TOI*),

$$\frac{dC_{TOI}(t)}{dt} = K^{trans}C_P(t) - k_{ep}C_{TOI}(t) \tag{1}$$

where $C_{TOI}(t)$ is the concentration (nM) of the contrast agent in the *TOI* at time *t*, $C_P(t)$ is the concentration of the contrast agent in plasma at time *t*, $K^{trans}$ is the rate ($min^{-1}$) at which the contrast agent leaves the plasma and enters the extravascular extracellular space of the *TOI*, and $k_{ep}$ is the rate ($min^{-1}$) at which the agent returns from the extravascular extracellular space to the plasma [22]. Eq. (1) assumes that the concentration of the contrast agent is known. However, the optoacoustic signal $S(\lambda,r,\mu)$ does not directly represent the concentration of the contrast agent, and it is instead a linear combination of the product of light fluence and absorption scaled by the Grüneisen parameter [24],

$$S(\lambda,r) = \Gamma\Phi(\lambda,r)\mu(\lambda,r) = \Gamma\Phi(\lambda,r)\sum_{j=1}^{N}\varepsilon_j(\lambda)C_j. \tag{2}$$

A more rigorous version of Eq. (2) could be presented but all additional terms would eventually be canceled during our derivation [11]. In Eq. (2), $\Gamma$ is the Grüneisen parameter, $\Phi(r,\lambda)$ is the light fluence ($J/cm^2$), $\mu(\lambda,r)$ is the absorption coefficient ($cm^{-1}$), while $\varepsilon j(\lambda)$ and $Cj$ are the molar extinction coefficient ($L\,mol^{-1}cm^{-1}$) and concentration ($mol\,L^{-1}$) respectively for each absorber j for a set of N total absorbers. The relative position and wavelength are given by $r$ and $\lambda$ repectively. Eq. (2) can be rewritten as Eq. (3) where the optoacoustic signal has been separated into its background and contrast agent components, assuming that pharmacokinetics studies with MSOT are acquired over several minutes at a fixed excitation wavelength and using a single contrast agent:

$$S(\lambda,r,t) = S(\lambda,r,t)^{CA} + S(\lambda,r,t)^{Background} \tag{3a}$$

$$S(\lambda,r,t) = \Gamma\Phi(\lambda,r)\varepsilon^{CA}(\lambda)C^{CA}(t) + \Gamma\Phi(\lambda,r)\varepsilon^{Background}(\lambda)C^{Background}(t). \tag{3b}$$

Assuming that the background optoacoustic signal and fluence remain constant over time in a given pixel for the duration of the experiment, Eq. (3) can be rearranged to obtain Eq. (4), which relates the change in optoacoustic signal as a function of time to the concentration of the contrast agent:

$$S(\lambda,r,t) - S(\lambda,r,t=0)^{Background} = \Delta S(\lambda,r,t) = \Gamma\Phi(\lambda,r)\varepsilon^{CA}(\lambda)C^{CA}(t) \tag{4a}$$

$$\frac{\Delta S(\lambda,r,t)}{\Gamma\Phi(\lambda,r)\varepsilon^{CA}(\lambda)} = C^{CA}(t) \tag{4b}$$

The approach described above can be used for $C_{TOI}$ or $C_P$. Thus, replacing $C_{TOI}(t)$ and $C_P(t)$ in Eq. (1) by their corresponding equations derived from Eqs. (4b) yields (5), the two compartment model for MSOT:

$$\frac{1}{\Gamma\Phi(\lambda,r_{TOI})\varepsilon^{CA}(\lambda)}\frac{d\Delta S^{TOI}(\lambda,r_{TOI},t)}{dt} = \frac{K^{trans}}{\Gamma\Phi(\lambda,r_P)\varepsilon^{CA}(\lambda)}\Delta S^{P}(\lambda,r_P,t) - \frac{k_{ep}}{\Gamma\Phi(\lambda,r_{TOI})\varepsilon^{CA}(\lambda)}\Delta S^{TOI}(\lambda,r_{TOI},t) \tag{5}$$

This equation can be simplified further by multiplying both sides by $\Gamma\Phi(\lambda,r_{TOI})\varepsilon^{CA}(\lambda)$ and removing the explicit dependency on $\lambda$, $r$, and $t$,

$$\frac{d\Delta S^{TOI}}{dt} = K^{trans}\frac{\Phi(r_{TOI})}{\Phi(r_P)}\Delta S^{P} - k_{ep}\Delta S^{TOI} \tag{6a}$$

$$\frac{d\Delta S^{TOI}}{dt} = K^{trans*}\Delta S^{P} - k_{ep}\Delta S^{TOI} \tag{6b}$$

where $r_{TOI}$ and $r_P$ indicate the location of the *TOI* and plasma, respectively. This simplification is possible because $\Gamma$ remains

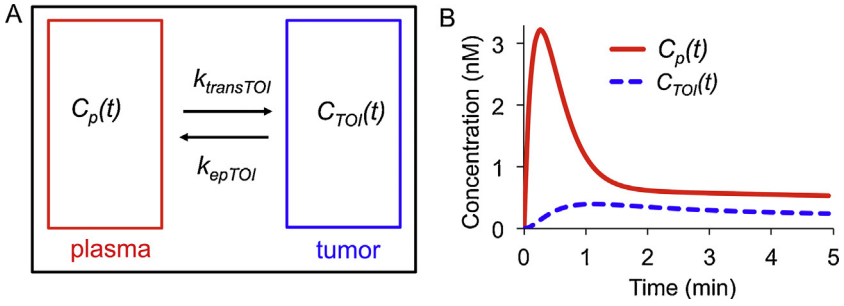


**Fig. 1.** The two-compartment linear standard model (2C-LSM).
A. The model depicts a tissue of interest (tumor, $C_{TOI}(t)$) and the arterial input function (plasma, $C_P(t)$). B. Curves for $C_{TOI}(t)$ and $C_P(t)$ were simulated with an injection speed of 10 s, $K^{trans} = 0.25\ s^{-1}$ and $k_{ep} = 0.64\ s^{-1}$. The concentration is not directly detected by MSOT, but the optoacoustic signal is proportional to concentration.