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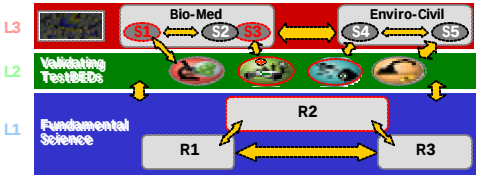
Overview of the Strategic Research Plan



Compartmental Modeling of ICG Pharmacokinetics for Breast Tumors

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Abstract

This paper investigates the pharmacokinetics of the optical contrast agent indocyanine green (ICG) as a malignancy indicator for breast cancer. Several authors have conducted optical measurements using Indocyanine green (ICG) in animal models (Colacino, Cuccia, Gurfinkel) and human patients (Colacino, Edwards, Ntziachristos, Intes, Nioka, and others). These results suggest clinical utility of ICG as a kinetic agent. Here, we present data collected with near infrared optical devices as part of a continuing study on breast cancer patients. Additionally, we have histopathological data on lesions clinically proven to be suspicious and information from several other diagnostic modalities.

We investigate four, three and two-compartment models for ICG kinetics in animal and breast tumors. Our results from Fischer rat data analysis indicate that two-compartment model is sufficient and that ICG pharmacokinetics can distinguish between different tumor types.

State of the Art

Gurfinkel[3] presented a two-compartment model for ICG kinetics for an animal subject and estimated model parameters.

Cuccia[4] presented a study of the dynamics of ICG in an adenocarcinoma rat tumor model. A two-compartmental model describing the ICG dynamics is used to quantify kinetic rates related to capillary permeability.

Intes[5] presented the uptake of ICG by breast tumors using a continuous wave diffuse optical tomography apparatus. A two-compartment model is used to analyze the pharmacokinetics of ICG.

Challenges and Significance

Due to highly non-linear nature of the pharmacokinetic parameter estimation, variation in parameter values from one subject to another, and sparse data available in clinical and laboratory settings a *systematic and robust* approach is needed to model, estimate and analyze ICG pharmacokinetics.

Such an approach must include: *i*) a method for compartmental model order selection, *ii*) a robust method of estimating ICG pharmacokinetic parameters, and ICG concentration in different compartments, and *iii*) a method of validating the selected model and the estimation results.

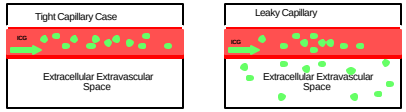
Technical Approach

In normal tissue:

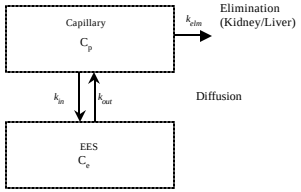
Blood flow indicator in tight capillaries of normal vessel.

In tumor :

May act as a diffusible extravascular flow in leaky capillary of cancer vessels.



The region around the tumor is assumed to be composed of two compartments:



C_p and C_e : Plasma and EES ICG concentrations

k_{in} and k_{out} : The leakage into and the drainage out of the EES.

k_{elm} : The ICG elimination from the body is through kidneys and the liver.

The leakage and the drainage out of the EES is given by:

$$\frac{dC_e(t)}{dt} = k_{in}C_p(t) - k_{out}C_e(t)$$

The leakage and the drainage out of the plasma is given by:

$$\frac{dC_p(t)}{dt} = -(k_{in} + k_{elm})C_p(t) + k_{out}C_e(t)$$

Actual bulk ICG concentration:

$$m(t) = v_p C_p(t) + v_e C_e(t)$$

v_e and v_p are the plasma and the EES volume fractions

Extended Kalman Filtering (EKF) for the estimation of ICG concentrations and pharmacokinetic constants:

Provides:

- Recursive estimation of time-varying pharmacokinetic model parameters
- Statistical validation of estimated concentrations and error bounds on the pharmacokinetic parameter estimates
- Potential real-time monitoring of ICG pharmacokinetic parameters and ICG concentrations

Fisher Rat Data Analysis

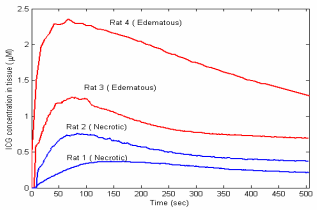
Data acquired from four Fischer rats adenocarcinoma tumor cells with two different tumor stages.

Rats 1, 2: Necrotic

- Low tissue oxy-hemoglobin
- Low total Hb
- Low Gd-DTPA enhancement levels

Rats 3, 4: Edematous

- High water content

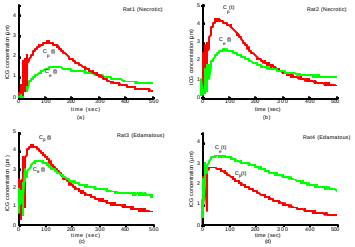


ICG concentrations measured by NIR

Fisher Rat Data Results

	$k_{in}^{(1)}$ $(sec^{-1}10^{-2})$	$k_{out}^{(1)}$ $(sec^{-1}10^{-2})$	$k_{out}^{(2)}$ $(sec^{-1}10^{-2})$	$v_e^{(1)}$ (10^{-2})	$v_p^{(1)}$ (10^{-2})
Rat 1 (Necrotic)	2.47±0.043	1.06±0.052	4.61±0.073	21.8±1.92	1.41±0.053
Rat 2 (Necrotic)	3.54±0.082	2.98±0.086	4.83±0.092	25.4±3.49	2.42±0.088
Rat 3 (Edematous)	6.90±0.101	4.93±0.072	5.95±0.048	30.4±2.81	4.84±0.120
Rat 4 (Edematous)	8.40±0.114	7.77±0.091	4.02±0.068	53.0±4.73	7.03±0.321

Permeability rates and volume fractions are higher for edematous cases.

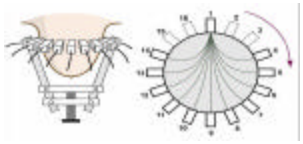


ICG concentrations in plasma and EES

Breast Data Analysis

Apparatus

- 16 light sources located on a circular holder at an equal distance from each other with 22.5 degree apart.
- 16 detectors are situated in the same plane and tuned to 805 nm, the absorption peak of ICG.
- The breast is arranged in a pendular geometry with the source-detector probes gently touching its surface.
- A set of data for one source is collected every 500 ms.
- The total time for a whole scan of the breast is 8.8 seconds.



Schematic of apparatus used to collect data for DOT reconstruction of ICG

Tumor information

Three different patients with different tumor types are included in this study.

Case 1: Fibroadenoma

Tumor : 1-2 cm in diameter, located around 6-7 o'clock, breast size 9 cm diameter.

Case 2: Adenocarcinoma

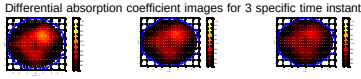
Tumor : 2-3 cm in diameter, located around 4-5 o'clock, breast size 7.7 cm diameter.

Case 3 : Invasive ductal carcinoma,

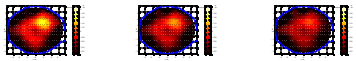
Tumor : 3-4 cm in diameter and located around 6 o'clock.

Breast Data Results

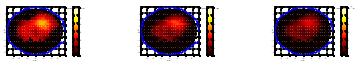
Differential absorption coefficient images for 3 specific time instants



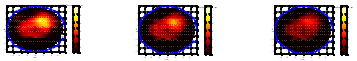
Bulk ICG concentration images for 3 specific time instants



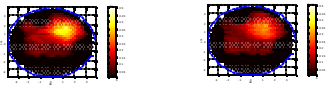
Estimated ICG concentration images in EES for 3 specific time instants



Estimated ICG concentration images in plasma for 3 specific time instants



Estimated pharmacokinetic rate images for k_{in} and k_{out} for 3 specific time instants



The k_{in} and k_{out} values from inside and outside the tumor region are statistically different with a p-value of 0.0001.

Accomplishments and Plans

- Develop compartmentalized pharmacokinetic modeling of ICG for Fischer rats carrying tumors.
- Estimate pharmacokinetic rates and concentrations in different compartments, simultaneously.
- Obtain 2D maps of pharmacokinetic constants describing transition rates between different comportments for breast cancer tumors.
- Use these parameters to characterize tumor metabolism and angiogenesis.
- Investigate kinetics of different contrast agents.
- Direct reconstruction of pharmacokinetic rate images using NIR source/detector measurements.

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