In Vivo Imaging of Hypoxia: Hemodynamic Model of Tumor Oxygenation

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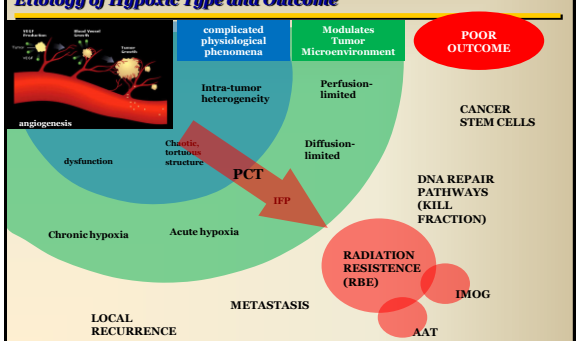
Outline

- Etiology of Hypoxia
- Biophysical Model
- Photoacoustic Computed Tomography (PCT)
  - Spectroscopy, Hemoglobin Status
  - Dynamic contrast-enhanced (DCE) Imaging, physiology
- Radiation Therapy
  - PCT *'plus'* IMOG

Introduction
Etiology of Hypoxic Type and Outcome



Biophysical Model

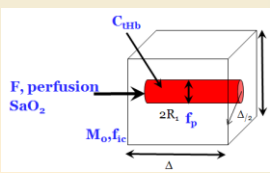
The objective is to develop and validate a multivariate *in vivo* hemodynamic model of tissue oxygenation ($MiHMO_2$) based on 3D photoacoustic Imaging.

Hemoglobin Status
SaO_2 and C_{tHb}

Physiological State
Perfusion (F), f_p, PS, f_{ic}

Hypoxia
pO_2, HF

Biophysical Model
Krogh Cylindrical Model



Under steady-state conditions (e.g., scan time), the tumor oxygen concentration at the cancer cells is the defined by the difference in the rate of the oxygen delivered (source) and consumed (sink). The source is a function of the hemoglobin concentration, C_{tHb}, multiplied by the bound oxygen, SaO_2, as well as the perfusion and vascular volume; the sink term depends on oxygen diffusion rate and length, as well as metabolic or respiration rate of the cancer cells. From this brief description, the oxygen concentration within the cancer cells depend a multivariate combination of factors including hemoglobin concentration, oxygen saturation, blood perfusion, blood volume, hemotacrit, glucose metabolisms, pH, etc. Fusion of the tumor hemodynamic and microenvironmental parameters as prescribed by a mathematical model provides a measure of tissue oxygen concentration, pO_2. This technique is dubbed the Multivariate *in vivo* Hemodyamic Model of tumor Oxygen concentration, or $MiHMO_2$.

Biophysical Model
MiHMO2, *Multivariate in vivo Hemodynamic Model of Oxygen Concentration*

Oxygen Concentration

$$C_T(r,z) \equiv \left(C_p\right)^4 - PD(r,z) \quad (1)$$

Perfusion and Diffusion of Oxygen

$$PD(r,z) = M_0 \left(\frac{1}{F \cdot (1+m)} \cdot G_1(R_t,\Delta) \cdot z + \frac{1}{D} \cdot G_2(R_t,\Delta;r) \right) \quad (2)$$

where $m = \frac{n \cdot C_{tHb}}{4 \cdot \alpha P_{50}}$

Geometric Form-Factors

$$G_1(R_t,\Delta) = \left(\sqrt{2 \cdot \left(\frac{\Delta}{R_t}\right)^2} \right) - 1, \quad (3)$$

$$G_2(R_t,\Delta;r) = \frac{\Delta^2}{8} \ln \frac{r}{R_t} + \frac{R_t^2}{4} \left(1 - \left(\frac{r}{R_t}\right)^2 \right) \quad (4)$$

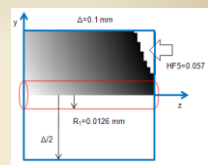


Figure 3. A Krogh cylinder (red) is used to model the oxygen concentration within a voxel of tissue given the following hemodynamic measurements: PCT-S, SaO_2=0.91 and C_{tHb}=5g/dL; DCE-CT, F=0.15mL/min/g, f_p=0.0275mL/g, and f_{ic}=0.5. Numerical solution to equation (1) is used to extract the pO_2 (mmHg) distribution in the voxel, which is represented by the 2D grey scale image.

Hemodynamic Parameters: Perfusion (F), SaO_2, C_{tHb}, f_p, f_{ic}

Photoacoustic Imaging
Experimental Protocol

MCF-7

MCF-7^{VEGF}

PCT-S
Hemoglobin Status

Small Animal PCT Scanner (OptoSonics, Inc.)

128 transducer array
2.5 MHz Center Frequency
690-940 nm NIR Spectral Range
2-5 min Acquisition Time

DCE-CT
Physiological State

Brilliance Clinical CT Scanner (Phillips, Inc.)

OxyLite
Oxygen Partial Pressure, pO_2

Oxford-Optronix OxyLite utilizes a minimally invasive fiber optic probe (250-300mm) to measure the lifetime of fluorescence which is inversely proportional to the concentration of dissolved oxygen (quenching),and is interpreted to provide an absolute value for pO_2 in mmHg

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Photoacoustic Imaging
Experimental Protocol

MCF-7

MCF-7^{VEGF}

PCT-S
Hemoglobin Status

Nexus 128 PCT Scanner (Endra, Inc.)

128 transducer array
5.0 MHz Center Frequency
690-940 nm NIR Spectral Range
3-6 sec Aequisition Time

DCE-PCT
Physiological State

OxyLite
Oxygen Partial Pressure, pO_2

Oxford-Optronix OxyLite utilizes a minimally invasive fiber optic probe (250-300mm) to measure the lifetime of fluorescence which is inversely proportional to the concentration of dissolved oxygen (quenching),and is interpreted to provide an absolute value for pO_2 in mmHg

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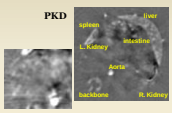
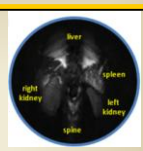
Photoacoustic Computed Tomography
Morphology

PKD

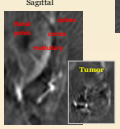


Kidney Hemoglobin Content is low and heterogeneous



Whole body image of mouse (courtesy of Dr.Robert Kruger, OptoSonics, Inc.)

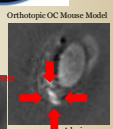
Sagittal



CROP IMAGES

Normal Mouse

Orthotopic OC Mouse Model



A lesion appears near the spine and contra lateral to the spleen

Timothy G Morgan[1], Robert A Kruger[2], Paul A Picot[1], Bo Liu[1], Keith M Stantz[1,4] **In Vivo Molecular Imaging Applications of Volume** ... **by for Small Animals** . *World Molecular Imaging Congress*, Nice, France, 2009

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Photoacoustic Computed Tomography Spectroscopy (PCT-S)

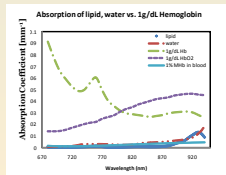
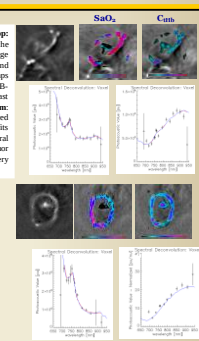


Fig 3. (B) Top: Displayed are the cropped intensity image (left), C_{tHb} (center) and oxygen saturation maps (*right*) for a MDA-MB-231 xenograft breast tumor. **Bottom:** Example near infrared spectral plots and fits for a voxel in the central region of the tumor (SaO_2=0) and periphery (SaO_2 =1.0).



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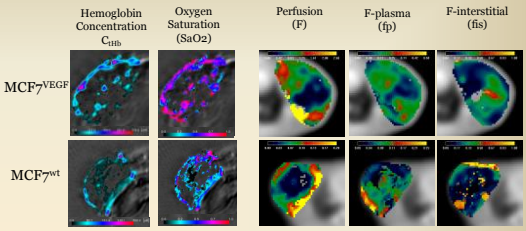
Parametric Images
MCF7^{wt} and MCF7^{VEGF} Breast Tumors



MCF7^{VEGF} (top) and MCF7^{wt} (bottom) breast tumors were imaged using both PCT and CT scanners. Spectroscopic analysis of photoacoustic images were used to obtain the hemoglobin concentration (C_{tHb}) and oxygen saturation levels (SaO_2) within the tumor; and compartmental models were used to estimate tumor perfusion, fractional plasma and interstitial volumes within the based on voxel-wise contrast-enhanced dynamics of a radio-opaque contrast agent (Isovue^{TM}).

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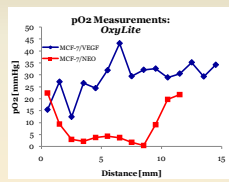
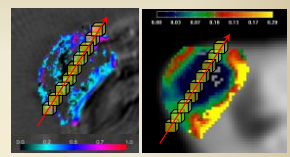
Methodology

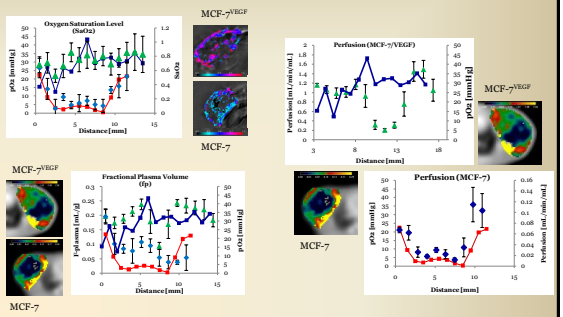


Subcutaneous xenograft MCF7^{wt} and MCF7^{VEGF} breast tumors were growth to a diameter of 10-15 mm. PCT-S and DCE-CT scans of each tumor was performed, and immediately after scanner, an OxyLite^{TM} fiber-optic sensing probe was used to obtain oxygen partial pressure measurements (pO_2). OxyLite measurements were compared to parametric images by placing a 1.0 mm^3 ROI along a long through the center of the tumor, the approximate path of the oxygen probe. A visual depiction is shown for the SaO_2 (PCT-S) and perfusion images (DCE-CT) of the MCF7^{wt} breast tumor.

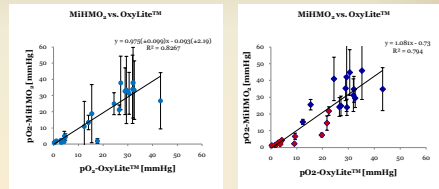


A 1.0 mm^3 ROI was placed at position along a straight line through the center of the tumor, which approximates the actual position of the OxyLite probe (red).

Comparison Between OxyLite™ Probe and Tumor Hemodynamics



Comparison Between OxyLite™ Probe and MiHMO$_2$



Using equation (1), the value for the oxygen partial pressure (pO_2) was calculated based on the hemodynamic parameters measured using PCT-S and DCE-CT. These values were compared to values measured using the OxyLite™ probe.

Perfusion and fractional plasma volume measurements

DYNAMIC CONTRAST-ENHANCED PCT (DCE-PCT)

Dynamic Contrast-Enhanced Imaging

Measurements of Vascular Physiology

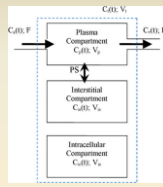


Fig. 1: Schematic diagram of a two-compartmental model (2CM) describing the infusion of contrast medium into plasma compartment (V_p) as represented by the vascular perfusion (F) and bidirectional diffusion between plasma (V_p) and interstitial compartment (V_i) as represented by the bi-directional trans-luminal permeability-surface area product (PS). $C_a(t)$ is the concentration of contrast in the feeding artery and $C_v(t)$ is contrast concentration in the vein which can be approximated by contrast concentration in plasma compartment $C_p(t)$.

Table 1: Physiological Symbols, Definitions and Units

Symbol	Definition	Unit
C_a	arterial input function	mg-I/mL
C_p	contrast concentration in plasma volume	mg-I/mL
C_m	contrast concentration in interstitial volume	mg-I/mL
C_t	measured tissue contrast concentration	mg-I/mL
f_c	fractional intravascular volume	mL/mL
f_i	fractional interstitial volume	mL/mL
f_p	fractional plasma volume	mL/mL
Hct	Hematocrit in major vessels	
Hct$_t$	Hematocrit in local tissue	
F	Blood Perfusion	mL/min/mL
PS	Permeability surface area product	mL/min/mL

$$\frac{dC_p(t)}{dt} = \frac{F}{f_p}\left(\frac{C_a(t)}{1-Hct} - C_p(t)\right) - \frac{PS}{f_p}\left[C_p(t) - C_m(t)\right]$$

$$\frac{dC_m(t)}{dt} = \frac{PS}{f_m}\left[C_p(t) - C_m(t)\right]$$

$$C_t(t) = f_p \cdot C_p(t) + f_m \cdot C_m(t)$$

Fig. 3: a Parametric map of fp for a slice through a representative MCF7/VEGF breast tumor. b Plots of the DCE curves for four individual voxels (A–D) within this same tumor and the arterial input function obtained from the left ventricle of the mouse. c These DCE curves (A–D of Fig. 3a) are fit to a two compartmental model to obtain their physiological parameters F, fp, PS, and fis (see text). Displayed are the fitted curves (solid line).

DCE-PCT

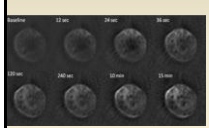


Figure 2: Contrast-enhanced PCT images prior to and after an i.v. injection of ICG.

Displayed are the contrast-enhanced PCT images (baseline subtracted) of a representative slice through the central portion of an MDA-MD-231 xenograft breast tumor at different times post-injection. For this tumor, the plasma flow begins at the upper right portion of the tumor, then across the tumor from left to right and towards the center of the tumor, where it times collects in the upper left region of the tumor. These images clearly demonstrate a long-term uptake of ICG, which suggests regions of hyperpermeability.

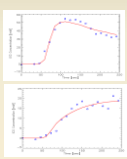


Figure II.2: (*top*) PCT image of a slice within an MDA-MB-231 tumor which displays the position of three voxels for further analysis. (*second from top*) The dynamic contrast-enhanced PCT curves for three representative voxels. (*bottom plots*) Displayed are the one compartmental fits of voxels 2 and 6.

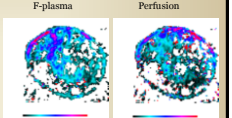
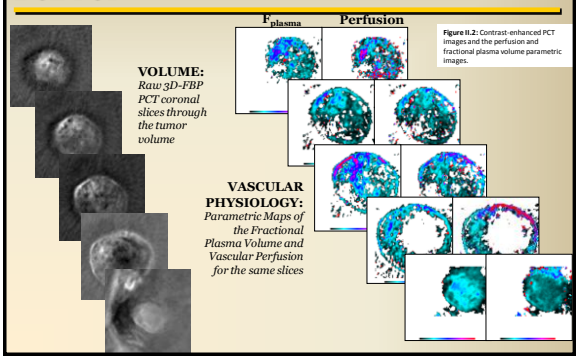


Figure 3: Physiological maps as determined by compartmental fits of contrast-enhanced ICG dynamics. **F-plasma ranges from 0 to 0.3 mL/g; Perfusion ranges from 0 to 0.8 mL/min/g.**

Displayed are fractional plasma volume, perfusion, and delay (in arrival) times for the MDA-MD-231 xenograft breast tumor displayed in figure 2. Given that ICG binds to albumin in the blood plasma, this contrast agent was modeled as a blood pool agent. Therefore, the DCE-PCT curves were fit to a 1 compartmental model over the first 4 minutes.

DCE-PCT



VOLUME: *Raw 3D-FBP PCT coronal slices through the tumor volume*

VASCULAR PHYSIOLOGY: *Parametric Maps of the Fractional Plasma Volume and Vascular Perfusion for the same slices*

Figure II.2: Contrast-enhanced PCT images and the perfusion and fractional plasma volume parametric images.

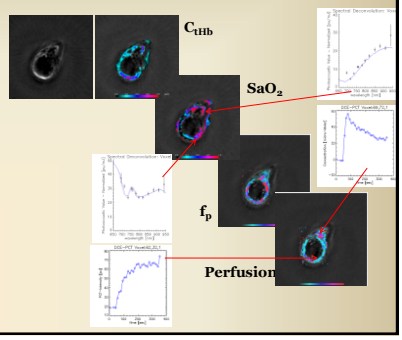
Dynamic Contrast-Enhanced PCT

Using PCT to Measure Vascular Physiology

PCT-S
12 wavelengths 700-930nm
60 angles/acquisition
Acquisition time: 2 min

DCE-PCT
i.v.; 250mM in 0.2mL of DMSO; at a rate of 0.5 mL/min)
scanprior to and every 1-second for up to 4-minutes and at 15-minutes post-injection

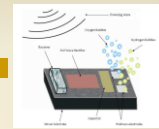
DCE-CT
i.v.; 300 mg/L in 0.2mL of PBS; at a rate of 0.5 mL/min)
Scan prior to and every 1-second for up to 2-minutes and 2-second sfor next 2 minutes, and20-seconds up to 6-minutes post-injection



PCT *'plus'* Implantable Micro Oxygen Generator (IMOG)

Metastatic Lesions

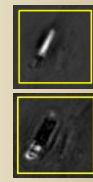
IMOG



- Anti-angiogenic therapy, radio-sensitize/chemo-sensitize tumors
- Image Tumor Hypoxic Response to AAT
- Mitigate tumor progression

- Device inserted into tumor via biopsy needle, which can be guided by US or PCT
- Wireless ultrasonic powering excites the receiver, which can be induced by PCT transducer array (or potentially the resulting ultrasound)
- Receiver coverts wireless power and generate DC voltage
- Voltage electrolyzes water in tumor to generate oxygen and hydrogen, which can be detected by elevated SaO2 levels as measured by PCT-S
- Oxygen will increase radiotherapy efficacy

PCT Images of IMOG



Yellow box is 12.5 x 12.5 mm² in size

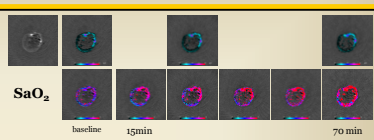
http://www.mayoclinic.org/images/distal-pancreatectomy-enlg.jpg

Oxygen Production

as Measured by PCT-S

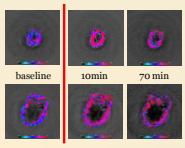
Subcutaneous BxPC-3 Xenograft Tumors

SaO_2



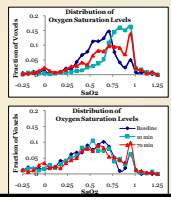
baseline 15min 70 min

IMOG

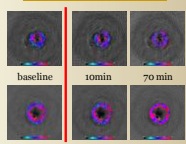


baseline 10min 70 min

Laser (10min)



Inactivated IMOG

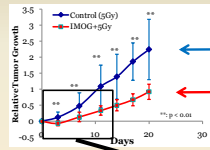


baseline 10min 70 min

Laser (10min)

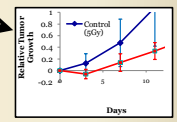
IMOG 'plus' Radiation Therapy

Tumor Growth Curves



Control (5Gy) (n = 5): tumor implanted with inactivated IMOG and received 5 Gy x-ray

IMOG+5Gy (n = 11): tumor implanted with functional IMOG and received 5 Gy x-ray immediately after IMOG stimulation



Statistics:
- $p < 0.01$ between *control (5Gy)* and *IMOG+5Gy* groups at all time points;
- $p < 0.05$ between *5 Gy* and *IMOG+5Gy* groups for over 2 weeks;
- No statistical differences between *control (5Gy)* and *control* groups;

Summary

- **The is the first set of experiments comparing intra-tumor measurements of SaO2 and C_{tHb} using PCT-S to pO2 values.**
- **Developed and tested a biophysical model to determine local pO2 measurements and parameters contributing to hypoxia.**
- **Demonstrated a new medical device that can modulate the tumor oxygen microenvironment to improve RT**

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