PhD Thesis title: 'ENHANCED DYNAMIC ELECTRON PARAMAGNETIC RESONANCE IMAGING OF IN VIVO PHYSIOLOGY'

Author: Gage Redler
Email: Gage@uchicago.edu
Institution: University of Chicago
Supervisors: Dr. Howard J. Halpern
Graduation Date: 6/14/2014
Available on line: n/a

ABSTRACT:

It is well established that low oxygen concentration (hypoxia) in tumors strongly affects their malignant state and resistance to therapy. The importance of tumor oxygenation status has led to increased interest in the development of robust oxygen imaging modalities. One such method is electron paramagnetic resonance imaging (EPRI). EPRI has provided a non-invasive, quantitative imaging modality with sensitivity deep in tissues, capable of investigating static oxygen concentration (pO_2) in vivo and has helped to corroborate the correlation between chronic states of hypoxia and tumor malignancy. However, when studying the complicated physiology of a living animal, the situation tends to be inherently dynamic. It has been found that in certain tumor regions there may exist steady states of hypoxia, or chronic hypoxia, whereas in other regions there may exist transient states of hypoxia, or acute hypoxia. It has been postulated that the negative prognostic implications associated with hypoxic tumors may be amplified for acutely hypoxic tumors. However, controversial data and a current lack in methods with the capability to noninvasively image tumor pO_2 in vivo with sufficient spatial, temporal, and pO_2 resolution preclude definitive conclusions on the relationships between the different forms of hypoxia and the differences in their clinical implications. A particularly promising oxygen imaging modality that can help to study both chronic and acute hypoxia and elucidate important physiological and clinical differences is rapid Dynamic EPRI. The focus of this work is the development of methods enabling Dynamic EPRI of *in vivo* physiology as well as its potential applications.

This work describes methods which enhance various aspects of EPRI in order to establish a more robust Dynamic EPRI capable of noninvasively studying and quantifying acute hypoxia in vivo. These enhancements are achieved through improvements that span from methods for the acquisition of individual projections to techniques for the reconstruction of complete 3D images of pO_2. A hybrid T_1/T_2 imaging methodology is developed for acquiring individual projections using a specific series of pulse sequences, which enhances the accuracy of measured spin probe concentration and pO_2. A maximally spaced projection sequencing algorithm is devised for more optimized acquisition of a full set of projections. Principal component analysis filtration is applied for post processing of acquired projection data in order to enhance signal to noise ratio (SNR) and isolate temporal features in Dynamic EPRI data. Image reconstruction techniques are improved by accelerating 3D image reconstruction using a GPU implementation as well as a rapid lookup table fitting method for determination of the spectral dimension and generation of pO_2 images. Additionally, novel nitroxide EPRI imaging agents are presented which can

differentially target the intracellular tumor environment and thus potentially provide higher SNR tumor imaging.

Dynamic EPRI, as enabled using the above methods, is shown to provide a methodology with great potential for furthering our understanding of acute hypoxia and its role in the progression of cancer to a malignant state as well as how it affects therapeutic efficacy. Dynamic EPRI will help to disentangle the relationship between chronic and acute hypoxia in tumors and will aid in the determination of how to integrate tumor oxygenation status into clinical practice and the treatment of cancer.

References to author publications that relate specifically to the dissertation:

1. **G. Redler**, B. Epel, and H. J. Halpern, "Principal component analysis enhances SNR for dynamic electron paramagnetic resonance oxygen imaging of cycling hypoxia in vivo," *Magn. Reson. Med.* **71(1)**, 440–450 (2014).

2. **G. Redler**, E. D. Barth, K. S. Bauer, J. P. Y. Kao, G. M. Rosen, and H. J. Halpern, " In vivo electron paramagnetic resonance imaging of differential tumor targeting using cis-3, 4-di (acetoxymethoxycarbonyl)-2, 2, 5, 5-tetramethyl-1-pyrrolidinyloxyl," *Magn. Reson. Med.* **71(4)**, 1650–1656 (2014).

3. **G. Redler**, B. Epel, and H. J. Halpern, "EPR Image Based Oxygen Movies for Transient Hypoxia," *Adv. Exp. Med. Biol.* **812**, 127–133 (2014).

4. B. Epel, **G. Redler**, and H. J. Halpern, "How In Vivo EPR Measures and Images Oxygen," *Adv. Exp. Med. Biol.* **812**, 113–119 (2014).