Automated Kinetic Modeling of Perfusion and Metabolism Based on Dynamic Hyperpolarized ^{13}C Data With Open-Source SIVIC Software

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Target Audience: This work is targeted at researchers interested in application of hyperpolarized (HP) ^{13}C imaging and modeling of metabolism kinetics and perfusion of hyperpolarized tracers.

Purpose: Magnetic resonance spectroscopy (MRS) of HP substrates is a powerful tool for investigating tissue metabolism and kinetics *in vivo*[1]. In particular, HP [1-^{13}C] pyruvate is extremely valuable for the study of cancer because the conversion of pyruvate into lactate catalyzed via the lactate dehydrogenase (LDH) enzyme is highly elevated in tumor cells[2]. Real-time exchange of HP [1-^{13}C] pyruvate to HP [1-^{13}C] lactate has shown great potential for the early diagnosis of tumor formation, response to therapy, and progression in preclinical models of cancer[1]. Following these promising preclinical studies, a pioneering first-in-man clinical trial using HP [1-^{13}C] pyruvate in prostate cancer patients was successfully completed[3]. Here we present a free, open-source implementation of kinetic and perfusion models for processing dynamic HP MRS data.

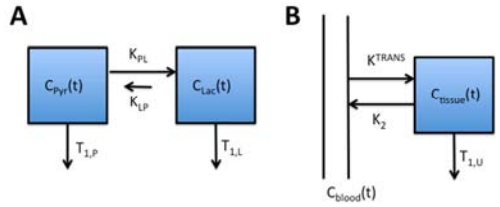

Figure 1. (a) Two-site exchange and **(b)** Perfusion kinetic models for hyperpolarized Carbon-13 MR used in algorithm.

Considerable attention has been dedicated to investigating the dynamics of real-time exchange of hyperpolarized signals to understand the underlining pathophysiology[4-8]. Derivation of reaction rate kinetics from a HP substrate often requires complex, multi-compartmental models to describe dynamic data. The results are prone to misinterpretation and are model-dependent. Moreover, as the technology moves into the clinic, there is a need for standardization, simplification of complicated workflows, and delivery of data to PACS. The present open-source package processes and quantifies dynamic HP spectroscopic data in a two-step scheme. First each metabolite is quantified at each time point to produce time series of maps. These dynamic images represent the time variation of the HP signals that are then processed to produce multiple parameters to fully describe the pathophysiology including quantification of dynamics, perfusion, and reaction rate kinetics. The resulting model parameters (Figure 2) are represented as 3D maps which can be exported as standard DICOM images.

Implementation: The two-site exchange model (Figure 1a) and a single-tissue (Figure 1b) compartment model were implemented in C++ in the open-source SIVIC package[9,10]. The models were tested for accuracy and sensitivity to noise in matlab. The source code, as well as a command-line tool (svk_mrs_kinetics) and GUI (sivic) application are freely available for download. The SIVIC package reads several vendors' MRS data formats and can also read, visualize and fit dynamic metabolite maps encoded as DICOM MR Image Storage SOP instances. The SIVIC C++ class (svkMRSKinetics) can easily be extended to support other kinetic models.

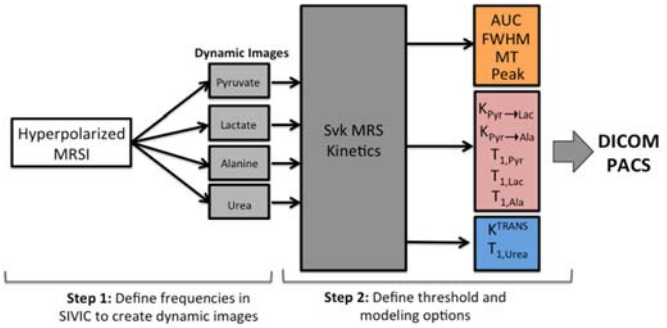

Figure 2. Simple two step method, which processes dynamic MR spectroscopic imaging to multiple parameters to fully describe the pathophysiology including quantification of dynamics (orange), perfusion and blood flow (blue), and kinetics (red). These can displayed with anatomical images with ease using SIVIC, an open source software package.

Discussion: Within a single step, dynamic volumetric images are masked to total carbon (tCar) signal-to-noise (SNR) above an input threshold. Then, the algorithm creates volumetric maps quantifying the dynamics, which includes the maximum signal (Peak), area under the curve (AUC), Full width half max (FWHM), and Mean Time (MT) for each metabolite, which provides information on uptake, perfusion, retention, and vascularization[7]. It then produces maps of the metabolic kinetics (Figure 3a) which includes the rate of conversion of pyruvate-to-lactate ($K_{Pyr->Lac}$), but can be extended to include pyruvate-to-alanine conversion ($K_{Pyr->Ala}$) or lactate-to-pyruvate conversion ($K_{Lac>Pyr}$) as well as maps of the longitudinal relaxation of pyruvate ($T_{1,Pyr}$), lactate ($T_{1,Lac}$), alanine ($T_{1,Ala}$), and urea ($T_{1,Urea}$). Finally, with a reference voxel and HP perfusion agent such as ^{13}C-Urea[8], perfusion maps (Figure 3b) can be produced including the transport rate constant from plasma to tissue (K^{TRANS}) but can be extended to include the rate constant between extracellular extravascular space (K_2).

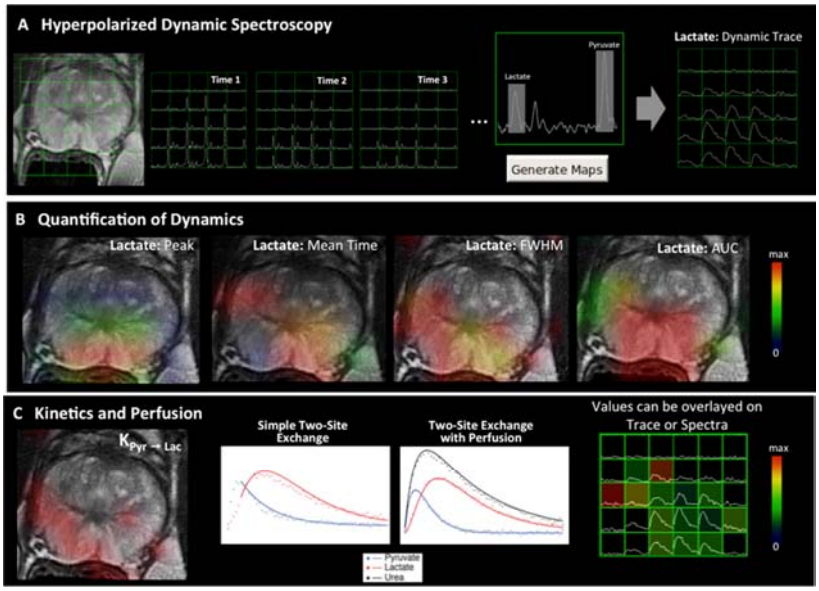

Figure 3. Output from processing of dynamic MR spectroscopic imaging from Phase I clinical trial. **(a)** MRSI data is converted to dynamic metabolic images. Then **(b)** maps of parameters describing the dynamics are produced and **(c)** maps of metabolic and perfusion kinetic parameters are produced all within a single step.

References: [1] Kurhanewicz, et al. *Neoplasia.* 2011; 13(2): 81-97. [2] Warburg. On the origin of cancer cells. *Science* 1956. 24;123(3191):309-14 [3] Nelson et al. *Science Translational Med* 2013; 5(198):198ra108 [4] Zierhut et al. *J Magn Reson.* 2010; 202(1): 85-92. [5] Harris et. *Proc Natl Acad Sci* 2009;106(43):18131-6 [6] Leon-Swisher et al. *Magn Reson Med*, 2013; epub ahead of print. [7] Larson et al. *Magn Reson Med,* 2010;63(3):582-91 [8] Von Morze et al. *Magn Reson Imaging.* 2012;30(3):305-11. [9] Crane et al. *Int J of Biomed Imaging*, 2013; 2013: 169526. [10] **http://sourceforge.net/apps/trac/sivic/**

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