

# Physiological Modelling of Dynamic Oxygen-Enhanced MRI in the Lung: Model Fitting and Parameter Interpretation

C. J. ROSE<sup>1,2</sup>, P. L. HUBBARD<sup>1,2</sup>, C. ROBERTS<sup>1,2</sup>, S. S. YOUNG<sup>3</sup>, J. H. NAISH<sup>1,2</sup>, AND G. J. PARKER<sup>1,2</sup>

<sup>1</sup>THE UNIVERSITY OF MANCHESTER BIOMEDICAL IMAGING INSTITUTE, THE UNIVERSITY OF MANCHESTER, MANCHESTER, GREATER MANCHESTER, UNITED KINGDOM,

<sup>2</sup>MANCHESTER ACADEMIC HEALTH SCIENCE CENTRE, THE UNIVERSITY OF MANCHESTER, MANCHESTER, GREATER MANCHESTER, UNITED KINGDOM, <sup>3</sup>ASTRAZENECA R&D CHARNWOOD, LOUGHBOROUGH, LEICESTERSHIRE, UNITED KINGDOM

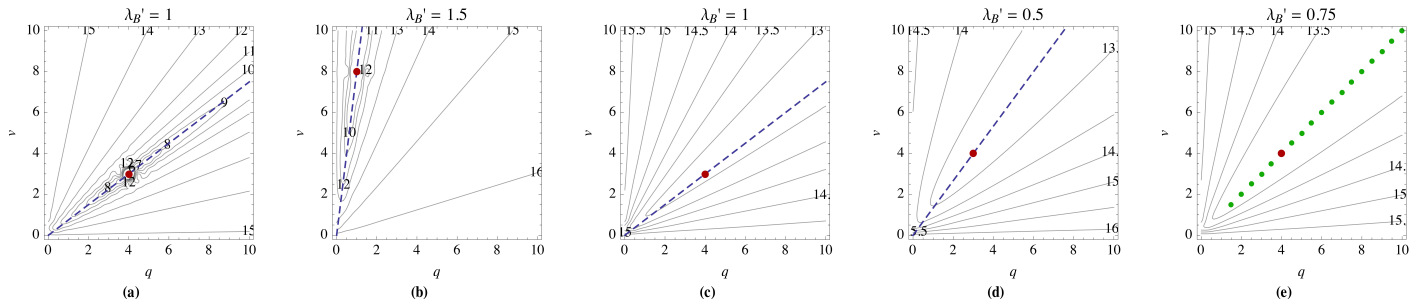
**INTRODUCTION** Oxygen-enhanced magnetic resonance imaging (OE-MRI) of the lung employs hyperoxia to induce signal change in the parenchyma to facilitate lung function assessment via the paramagnetic effect of dissolved oxygen<sup>1</sup>. It has recently been shown that by modelling gas exchange processes in the lung throughout dynamic OE-MRI time series, it is possible to measure the ventilation-to-perfusion ratio ( $V/Q$ ) at individual voxels<sup>2</sup>. Using simulations, this work considers the problem of fitting the model to observed data and studies the topology of the sum of squared differences (SSD) loss function. Our results reveal an interesting property of the SSD loss function for this model, with important implications both for fitting the model to observed data and for interpreting fitted model parameters.

**MODELLING VENTILATION & PERFUSION** The model described in Ref. 2 assumes that each lung voxel has two compartments. The first models the space within alveoli, where  $O_2$  exists in the gaseous state. The second models the parenchymal water found in tissue and blood within alveolar capillaries, where  $O_2$  is dissolved in tissue water and blood plasma, and is also bound to haemoglobin. The net transfer of  $O_2$  into the alveolar compartment (via the airway), across alveolar membranes, and through the parenchymal compartment is modelled in terms of alveolar ventilation and parenchymal perfusion, with alveolar membrane diffusion assumed to be rapid. We consider experiments in which the lungs are imaged dynamically while the subject switches from breathing medical air to an elevated concentration of  $O_2$ . The resulting model is:

$$\frac{\Delta P_{wO_2}(t)}{P_{B-H_2O}} = \frac{v}{q \lambda_B} \Delta F_{IO_2} (1 - e^{-t(q \lambda_B + v)}) + q \int_0^t \Delta C_{VO_2}(t') e^{(t'-t)(q \lambda_B + v)} dt' \quad (1)$$

where  $t$  is time (min);  $\Delta P_{wO_2}(t)$  is the change in partial pressure of  $O_2$  in the parenchymal space at time  $t$  (mm Hg);  $P_{B-H_2O}$  is the barometric pressure minus the saturated vapour pressure of water at body temperature (mm Hg);  $\Delta F_{IO_2}$  models the switch between medical air and  $O_2$  in terms of fractional inspired oxygen concentration (no units);  $\Delta C_{VO_2}$  is the change in venous  $O_2$  concentration over time (an input function to be measured or assumed; ml  $O_2$ /ml blood);  $\lambda_B$  is the product of  $P_{B-H_2O}$  and the solubility of oxygen in blood (ml  $O_2$ /ml water) (where solubility has units ml/ml/mmHg; cf the Bunsen solubility); and  $v = V/(1-v_w+v_w\lambda^*)$  &  $q = Q/(1-v_w+v_w\lambda^*)$ , where  $V$  &  $Q$  are ventilation & perfusion (ml  $O_2$  or blood/ml lung/min),  $v_w$  is the relative volume of the parenchymal (water) space (no units), and  $\lambda^*$  is the product of the solubility of oxygen in the parenchymal space and  $P_{B-H_2O}$  (ml  $O_2$ /ml water). A key concept to understand is that, while we are ultimately interested in ventilation and perfusion ( $V$  &  $Q$ ), Eqn. 1 does not parameterise them; however, by taking the ratio  $v/q$ , we can obtain the ratio  $V/Q$ —a quantity that has historically provided useful information on lung function, but has not previously been modelled using proton MRI. At each voxel, a time series of  $R_1$  ( $=1/T_1$ ) is obtained and converted to changes in partial pressure<sup>3</sup>, to yield  $\Delta P_{wO_2}(t)$ . Eqn. 1 is fitted to estimate  $v$ ,  $q$  &  $\lambda_B$ .

**METHOD** Nonlinear regression is often posed as an optimisation problem in which model parameters are varied to minimise the SSD between the prediction corresponding to those parameter values and observed data. Simulations were performed to better understand the nature of this optimisation problem as it applies to Eqn. 1. **Experiment 1** used the SSD loss function to compare a vector of noise-free  $\Delta P_{wO_2}(t)$  time series values corresponding to known parameter values ( $v'$ ,  $\lambda_B'$ ,  $q'$ ) to vectors of  $\Delta P_{wO_2}(t)$  values corresponding to other positions in the parameter space. The topology of the SSD loss function can be visualised using plots showing contours of equal SSD (using a logarithmic scale for display purposes). Contour plots were constructed for multiple known parameter values to determine how topology varies as a function of known parameter values. **Experiment 2** repeated the first, except a realistic amount of noise,  $\sim N(\mu=0, \sigma=100)$ , was added to the  $\Delta P_{wO_2}(t)$  time series calculated for the known parameter values. Experiment 2 will reveal the topology corresponding to observed data with *particular* random noise, but does not show the *expected* (average) topology for given known parameters and noise level. In **Experiment 3**, Monte Carlo simulations (1000 runs) were performed to produce plots showing contours of equal mean SSD (again, on a logarithmic scale). Simulations were performed using Mathematica v7 (Wolfram Research Inc, Champaign, IL).



**Fig. 1** Plots of the sum of squared differences (SSD) between model instances for known parameter values ( $v'$ ,  $\lambda_B'$ ,  $q'$ ) (red dots) and instances corresponding to other locations in the parameter space (contours of equal SSD are shown on a logarithmic scale). The correct ventilation-to-perfusion ratio,  $V/Q$ , is equal to the  $v'/q'$  value corresponding to a red dot; dashed blue lines also have gradient  $V/Q=v'/q'$ . Examples are shown for: noise-free instances (a) & (b); a known model instance with noise (c); and a Monte Carlo simulation showing the expected topology for a particular  $V/Q$  value (d). Subfigure (e)—constructed using a single noisy instance—shows that multiple equally-good model fits may be found (green dots): while the  $V/Q$  values corresponding to these fits will be equal, interpreting fitted values of  $v$  and  $q$  independently may result in poor scan-rescan repeatability.

**RESULTS** Fig. 1 shows example results for each experiment. In each plot, the known values  $v'$  and  $q'$  are indicated by a red dot and the known value  $\lambda_B'$  is specified above the plot. Results for **Experiment 1** (the noise-free case) are shown in subfigures (a) and (b): the minimum of the SSD loss function lies in a tight fissure oriented along a line with gradient equal to  $V/Q=v'/q'$ . Results for **Experiment 2** (where noise was introduced) are shown in subfigure (c): the topology of the loss function is flatter and there is an elongated valley, oriented with approximate gradient  $V/Q$ , in which equally-good model fits can be found. In the presence of noise, the valley and the  $V/Q=v'/q'$  line are not quite collinear. Results for **Experiment 3** (the Monte Carlo simulation) are shown in subfigure (d), suggesting that on average, the valley floor and the  $V/Q=v'/q'$  line are collinear. Subfigure (e) shows that multiple equally good fits—to within a particular tolerance, related to the noise—can be found along the valley floor, and consequently particular values of fitted  $v$  and  $q$  may vary considerably; however, the ratio  $v/q=V/Q$  is stable along the valley floor.

**CONCLUSIONS** Our study of the topology of the SSD loss function revealed a tight fissure of gradient  $V/Q=v'/q'$ . When  $\Delta P_{wO_2}(t)$  is subject to realistic levels of noise, the fissure becomes an elongated and flat valley floor with expected gradient  $V/Q=v'/q'$ . In the presence of noise, multiple equally good fits can be found along the valley floor: therefore  $v$  and  $q$  should not be interpreted independently, but in ratio as a measurement of  $V/Q$ .

**REFERENCES** 1 Edelman RR et al., Nat Med 1996, 2:1236. 2 Naish JH & Parker GJ, Proc ISMRM 2010, #2516. 3 Zaharchuk G et al., Acad Radiol 2006, 13:1016.