Interpretation of Real-Time Breath Data Through a Model

Using the three compartment model for isoprene observations

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Abstract

Real time measurements of breath data are a convenient and save method to observe a proband. But only in the most trivial cases they can be interpreted directly. We demonstrate the feasibility of applying a model to interpret the observations through the parameter of such a model.

Introduction

It is known that at begin of an exercise phase there is a pronounced peak of isoprene that quickly diminishes. This can not be explained using the Farhi equation [1] (which would predict a momentary decrease in isoprene as it gets diluted in greater volume).

King et al.[2] suggest this is result of a compartment storing isoprene that is washed out during exercise and demonstrated that a fit which agrees to the observation data can be constructed. The interpretation of this model is in contrast to the predominant hypothesis the isoprene might be a byproduct of cholesterol synthesis (which would take place in the liver which is richly perfused).

Experimental Methods

We set up an ergometer experiment as described in [2].

A proband was asked to lie on a lying ergometer and rest for approximately $20'$, afterwards was asked to pedal at low resistance for $20'$ and finally rest again for $20'$.

A *Task Force Monitor* device was used to record metabolic data. Breath data was collected using a heated transfer line directly injected in a *PTR-MS-TOF 8000* device.

For this experiment three volunteers were recruited who performed the experiment on three separate sessions.

Data Analysis

Modelling

Modelling is often likened to curve fitting. Although there are fundamental differences. For one the algorithm is limited to a small number of feasible functions. On the other hand the parameter in the model have physical meaning and can so be compared.

The experiment was modelled as three compartment model. The relations are shown in figure 1. The interesting part of the model is not only the cardiac output and breath rate vary but also the partition of blood stream flowing into the periphery compartment is changing.

A few facts are already known about this model:

- the parameter are theoretically identifiable
- it does not oscillate
- at long times a steady state is reached

Data Preparation

As the PTR-MS-TOF was recording during the preparation of the volunteer it was necessary to identify the section where actual breath was recorded. The ion of isoprene was used for this task.

The input data consisting of cardiac output and breath flow has a very noisy structure. Great care must be taken to chose a smoother that will preserve the switching points, especially nasty is when smoothers introduce non causal behaviour (e.g. blood flows increasing before exercise). To simplify the input it was considered a two state case and fitted via *kmeans*. A typical profile is shown in figure 2. This also leads to an easy to interpret behaviour of the partition function between the compartment which then also becomes a simple switch between two states.

Observed concentration data was not smoothed in any way to preserve the exact shape of the peak.

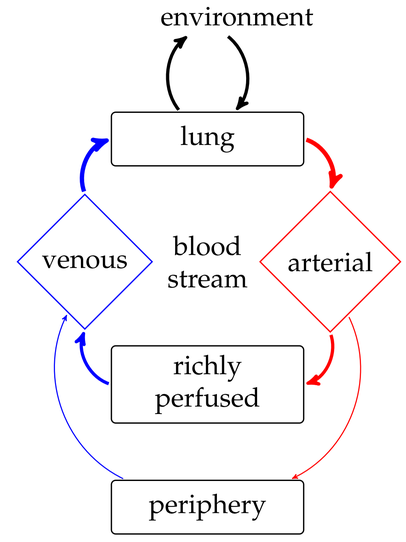

Figure 1: Model of three compartment model. The compartments are interconnected by blood stream, and to the environment via breathing.

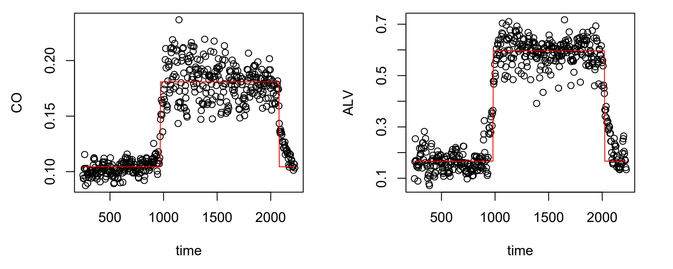

Figure 2: Typical observations of observed cardiac output and breath flow in $[l/s]$. The standard deviation of cardiac output is of similar magnitude as the difference to the rest state. An efficient method of smoothing is required.

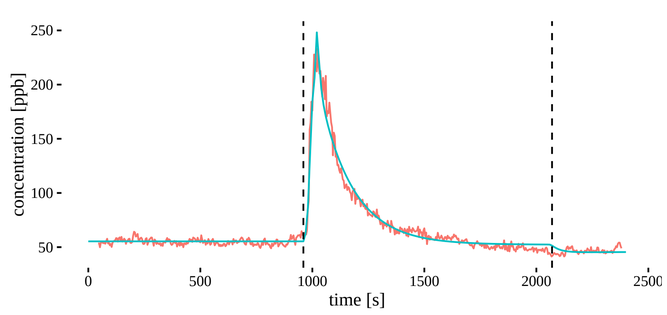

Figure 3: A good agreement of the fit (blue) to observed data (red) can be seen despite seriously simplifying the input signal. Sensitivity analysis shows that the regions or highest information are the $30\,s$ around the state switches (dashed lines).

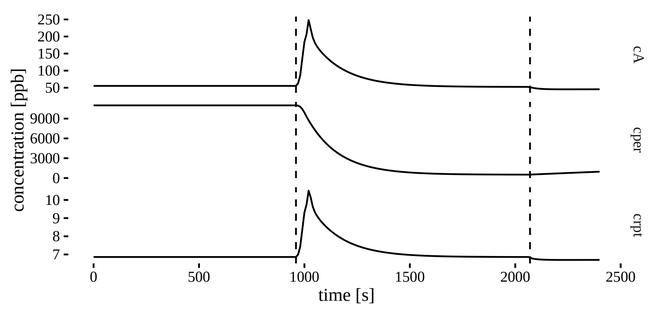

Figure 4: The behaviour in the hidden compartments shows how the periphery compartment is washed out causing increase of concentration in the alveolar as well as periphery compartment. Also the buildup again happens rather slowly.

Simulation

The model is written as differential equation.

$$\partial_t \vec{c} = \mathbf{A}\vec{c} + \mathbf{B}$$

This can be solved using a regular ODE solver. The main issue is that the matrices $\mathbf{A}$ and $\mathbf{B}$ depend on the observed breath and cardiac output at each time point. The deviation from observed data points is calculated and used to calculate the likelihood of this set of parameters.

The global maximum likelihood sometimes due to physical constraints may not be physically feasible.

The famous quote *"With four parameters I can fit an elephant, and with five I can make him wiggle his trunk."* attributed to John von Neumann comes to mind when interpreting the results. This may be problematic in a model of this complexity. The model has 14 parameter making it challenging to attribute each parameter directly to observation.

Results

Fit

As expected it is possible to fit this model to the observed concentration profile.

Although it is important to note that gradient based algorithms quickly get stuck at the nearest local maxima and will not converge to a global one, this is especially troubling as the results will then depend on the initial guesses. In this study we found simulated annealing to be effective under such circumstances.

Although strictly speaking each parameter of the model is identifiable it is required to show that these are also *practically identifiable*. Analysis around the global optimum show that collinearity is sufficiently low - although around the initial starting estimates collinearity allowed for just 4 independent parameter.

Estimated Values

parameter	value	IQR	unit
$k_{p,per}$	9.50	[5 - 9.7]	mol/l/s
$k_{m,per}$	0.01	[0.0013 - 0.011]	1/s
$k_{p,rpt}$	0.10	[0.095 - 0.1]	mol/l/s
$k_{m,rpt}$	0.08	[0.044 - 0.23]	1/s
V_{alv}	4.90	[4.1 - 5.8]	l
V_{per}	9.40	[4.6 - 9.7]	l
V_{rpt}	6.10	[6 - 6.3]	l

Table 1: Estimation results of physiological parameter over volunteer group.

It is interesting that production in the periphery compartment is much higher (order 100 times) than in the richly perfused. Metabolization in the richly perfused is about 8 times higher than in periphery. It is reassuring that compartment volumina are in realistic range and the periphery compartment volume shows great individual variance.

Forthcoming Research

The simulation shows good agreement between the model and real live behaviour. To better interpret the data a series of experiments was made which in addition deuterated isoprene was inhaled. This additional trace will describe the same model but without any endogenous production. In this case it will be possible to further clarify observed parameter.

References

[1] L. E. Farhi. Elimination of inert gas by the lung. *Respir Physiol*, 3(1):1–11, 1967.

[2] J. King, A. Kupferthaler, K. Unterkofler, H. Koc, S. Teschl, G. Teschl, W. Miekisch, J. Schubert, H. Hinterhuber, and Anton Amann. Isoprene and acetone concentration profiles during exercise on an ergometer. *Journal of Breath Research*, 3(2):027006, 2009.