Supporting Information for

Fast and accurate multi-scale reduced-order model for prediction of multi-breath washout curves of human respiratory system

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Derivation of the inert gas dynamic equation

Each respiratory airway is considered as a straight duct with a diameter of d and a cross-sectional area of A surrounded by a sleeve of alveoli. The effective diameter of respiratory airway is denoted by d_{eff} which is the diameter of a duct with the same length and volume of respiratory airway. The total surface area of each airway is denoted by S_t. The mean concentration along the airways satisfies the one-dimensional equation for a gas [1] as given in Eq. (S1) where J_R is radial flux of inert gas through the respiratory membrane. Since no reaction occurs in the tissue, the amount of inert gas transported into the blood is also equal to J_R. Therefore, the dynamic of inert gas concentration in surrounding blood can be obtained by Eq. (S2) [1].

$$A_{eff}\frac{\partial C}{\partial t} + uA\frac{\partial C}{\partial z} = DA\frac{\partial^2 C}{\partial z^2} - S_t J_R \qquad \text{(S1)}$$

$$V_b\frac{dC_b}{dt} = S_t J_R \qquad \text{(S2)}$$

The above equation can be written in terms of partial pressure as follows in which S_{td} is the ratio of total surface area to cross-sectional area. It should be noted that $P_i = C_i RT$ in gas phase while $C_{i,b} = \sigma P_{i,b}$ in the blood[1] where σ is the solubility of inert gas in the blood.

$$d_{eff}^2\frac{\partial P_i}{\partial t} + ud^2\frac{\partial P_i}{\partial z} = Dd^2\frac{\partial^2 P_i}{\partial z^2} - 4dS_{td}RTJ_R \qquad \text{(S3)}$$

$$V_b\sigma\frac{dP_{i,b}}{dt} = S_t J_R \qquad \text{(S4)}$$

The driving force for the transport of inert gas into the blood is $(P_i - P_{i,b})$. Therefore J_R can be written as $k.(P_i - P_{i,b})$. Weibel et.al [2] showed that the material properties of tissue, surface lining, and plasma layer are similar respect to diffusion. Therefore, the tissue and plasma layer can be considered as a single coherent barrier. Since the species transports through the barrier only by diffusion, J_R can be written as fallows:

$$J_R = D_M \frac{(C_{ta} - C_{i,b})}{\delta} = \frac{D_M \sigma}{\delta}(P_i - P_{i,b}) = k(P_i - P_{i,b}) \qquad \text{(S5)}$$

Where C_{ta} represents the concentration in the interface of barrier and airway in the tissue side. D_M and δ are the diffusion coefficient through the barrier and thickness of the barrier, respectively. Since the properties of tissue and plasma layer for the diffusion are similar, assuming equilibrium at the interface gives $C_{ta} = \sigma P_i$.

Finally, Eqs. (S3) and (S4) can be written as follows.

$$d_{eff}^2 \frac{\partial P_i}{\partial t} + ud^2 \frac{\partial P_i}{\partial z} = Dd^2 \frac{\partial^2 P_i}{\partial z^2} - 4d.S_{td}.K(P_i - P_{i.b});\ K = kRT \qquad \text{(S6)}$$

$$\frac{\partial P_{i,b}}{\partial t} = \frac{kS_{tb}}{\sigma}(P_i - P_{i,b}) \qquad \text{(S7)}$$

References

1. Swan, A. J.; Tawhai, M. H., Evidence for minimal oxygen heterogeneity in the healthy human pulmonary acinus. *Journal of applied physiology* **2010,** 110, (2), 528-537.
2. Weibel, E. R.; Federspiel, W. J.; Fryder-Doffey, F.; Hsia, C. C.; König, M.; Stalder-Navarro, V.; Vock, R., Morphometric model for pulmonary diffusing capacity I. Membrane diffusing capacity. *Respiration physiology* **1993,** 93, (2), 125-149.