Breath Research from Dornbirn 2004 to Rostock 2024

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Seminar lecture on Jochen's retirement, Rostock, February 29, 2024

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Overview

History

2001 Start of my first project with A. Amann in the life sciences (algorithms for the detection of ventricular fibrillation).

2004 Local Chair Organizer of the conference: Breath Gas Analysis for Medical Diagnostics, Vorarlberg University of Applied Sciences, Dornbirn, September 23 to 26, 2004, https://itp.tugraz.at/~karl/BreathConferenceDornbirn2004.pdf.

2006-2009 BAMOD: Breath-gas analysis for molecular-oriented detection of minimal diseases (with Rostock), https://cordis.europa.eu/project/id/19031, 3 articles, e.g., [2].

2010 King et al., Physiological modeling of isoprene dynamics in exhaled breath [3].

2011 King et al., A mathematical model for breath gas analysis of volatile organic compounds with special emphasis on acetone [4].

2015 Unterkofler et al., Modeling-based determination of physiological parameters of systemic VOCs by breath gas analysis: a pilot study [6].

2016 -2020 IMPACT: Ion-Molecule Processes for Analytical Chemistry Technologies (with Rostock) https://cordis.europa.eu/project/id/674911.

2017 First International Conference on Soft Chemical Ionisation Mass Spectrometry and Applications to Trace Gas Analysis https://itp.tugraz.at/~karl/CSCIMS_abstracts.pdf.

2018 Ager et al., Modeling-based determination of physiological parameters of systemic VOCs by breath gas analysis, part 2 [7].

2023 Mochalski et al., A review on isoprene in human breath. https://iopscience.iop.org/article/10.1088/1752-7163/acc964

Dornbirn 2004

Figure: Front row: Patrik Španěl, second row: Anil Modak, third row: Terence Risby, Wolfram Miekisch, Jochen Schubert, and Marieann Högman, last row: Susanne Teschl, K.U.

Dornbirn 2004

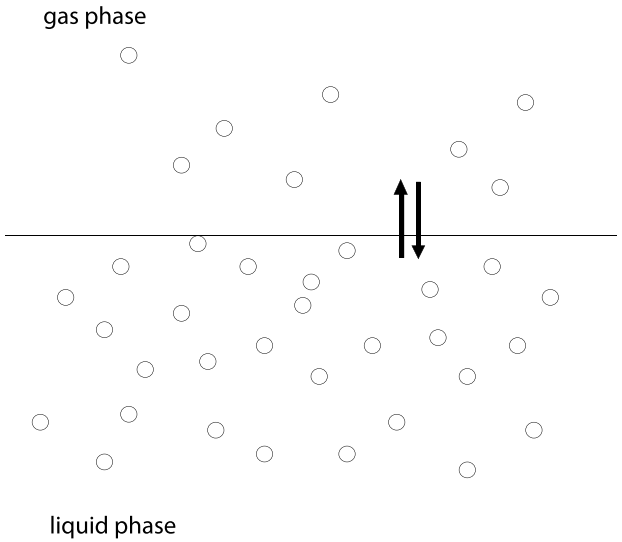
Figure: Jochen at the Rolls-Royce Museum Dornbirn

Figure: Jochen at the CSCIMS (IMPACT) conference, Dornbirn 2017

Henry's law

states that the amount of dissolved gas in a liquid is proportional to its partial pressure above the liquid, when in a state of equilibrium. Using the ideal gas law we get the dimensionless form (no equilibrium means no correlation with blood and no reproducible breath concentration data, C... concentration, a ... arterial, A ... alveolar)

$$\lambda_{l:g} := \frac{C_l}{C_g}, \qquad \text{e.g.,} \quad C_\mathrm{a} = \lambda_{\mathrm{b:air}}\, C_\mathrm{A} \tag{1}$$



Mass balance $m = V_A C_A$: single compartment

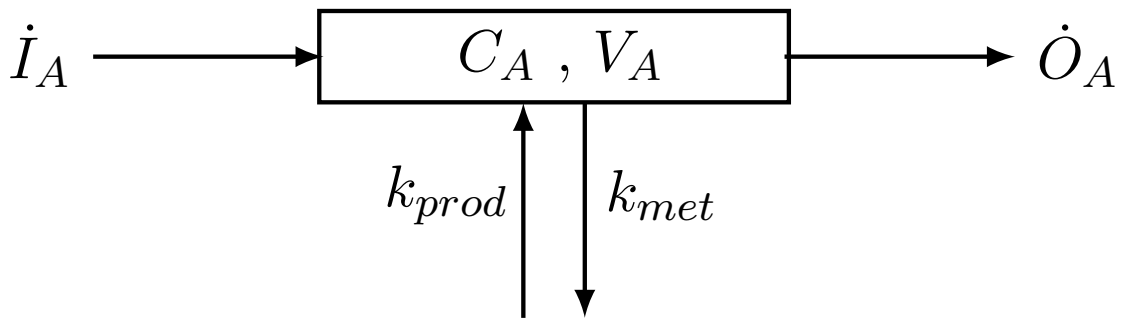


Figure: A single compartment A (functional unit) with input rate $\dot{I}_A$, output rate $\dot{O}_A$, *linear* metabolic rate k_{met}, and production rate k_{prod}. C_A denotes the concentration and V_A the constant volume.

$$\frac{\mathrm{d}\left(V_A C_A\right)}{\mathrm{d}t} = V_A \frac{\mathrm{d}C_A}{\mathrm{d}t} = \dot{I}_A - \dot{O}_A + k_{\mathrm{prod}} - k_{\mathrm{met}} C_A. \qquad (2)$$

Example: Farhi equation

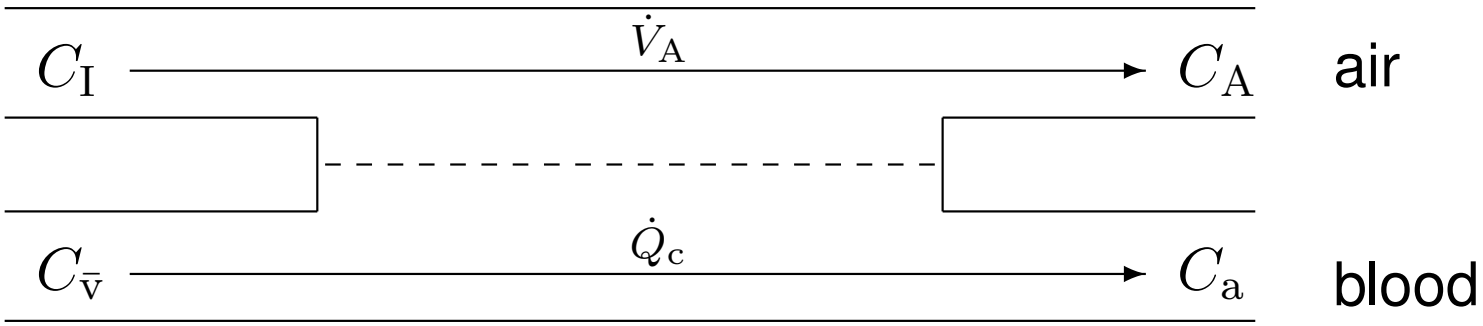


Figure: Diagram of gas exchange in an average alveolus symbolized by a dashed line.

This leads to the following mass balance equation for the lung

$$\underbrace{V_{\mathrm{A}} \frac{dC_{\mathrm{A}}}{dt}}_{\text{concentration change in lung}} = \underbrace{\dot{V}_{\mathrm{A}}(C_{\mathrm{I}} - C_{\mathrm{A}})}_{\text{clearance by breath}} + \underbrace{\dot{Q}_{\mathrm{c}}(C_{\bar{\mathrm{v}}} - C_{\mathrm{a}})}_{\text{contribution by blood}} . \qquad (3)$$

A steady state is reached, when $\frac{dC_{\mathrm{A}}(t)}{dt} = 0$ and $\dot{V}_{\mathrm{A}}(t), \dot{Q}_{\mathrm{c}}(t)$ are constant.
We assume that $C_{\mathrm{I}}(t) = 0$ and an equilibrium according to Henry's law $C_{\mathrm{a}} = \lambda_{\mathrm{b:air}} C_{\mathrm{A}}$ is also reached

$$V_{\mathrm{A}} \underbrace{\frac{dC_{\mathrm{A}}}{dt}}_{\text{change is zero}} = \dot{V}_{\mathrm{A}}(\underbrace{C_{\mathrm{I}}}_{=0} - C_{\mathrm{A}}) + \dot{Q}_{\mathrm{c}}(C_{\bar{\mathrm{v}}} - \underbrace{C_{\mathrm{a}}}_{=\lambda_{\mathrm{b:air}} C_{\mathrm{A}}}), \tag{4}$$

then the differential equation (4) reduces to

$$0 = -\dot{V}_{\mathrm{A}} C_{\mathrm{A}} + \dot{Q}_{\mathrm{c}}(C_{\bar{\mathrm{v}}} - \lambda_{\mathrm{b:air}} C_{\mathrm{A}}). \tag{5}$$

Farhi equation continued

Solving this equation yields Farhi's equation (1967) [1]

$$C_{\mathrm{A}} = \frac{C_{\bar{\mathrm{v}}}}{\lambda_{\mathrm{b:air}} + \frac{\dot{V}_{\mathrm{A}}}{\dot{Q}_{\mathrm{c}}}}. \tag{6}$$

This equation yields the alveolar concentration for all VOCs, but only for low water soluble VOCs ($\lambda_{\mathrm{b:air}} < 10$) we have

$$C_{\mathrm{A}} = C_{\mathrm{end-tidal}} \tag{7}$$

Example 1: Consequences of the Farhi equation demonstrated

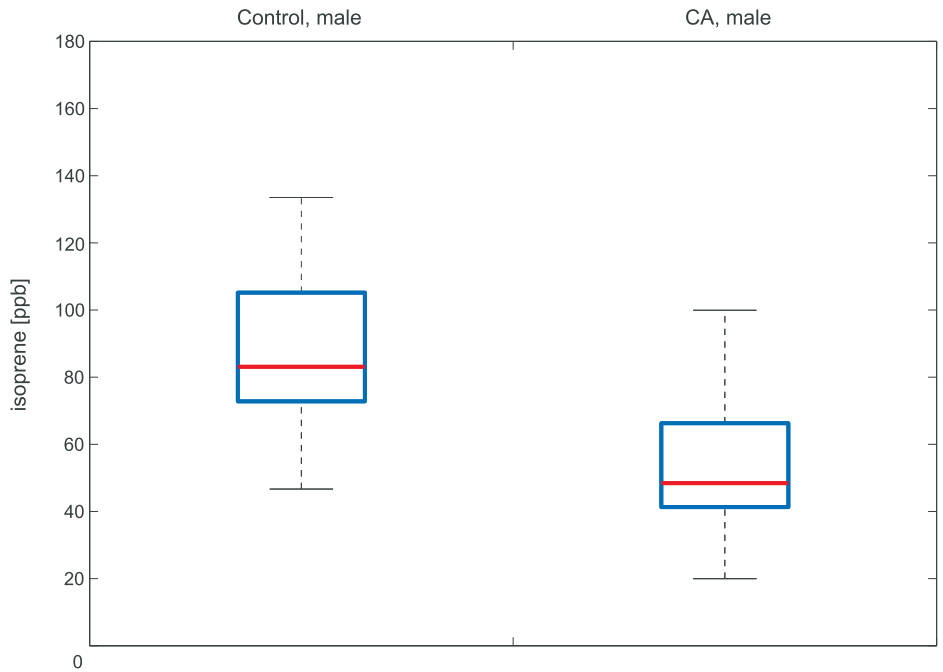


Figure: Example isoprene: consider the two boxplots associated with healthy test subjects and lung cancer patients.

Example 1: Consequences of the Farhi equation demonstrated

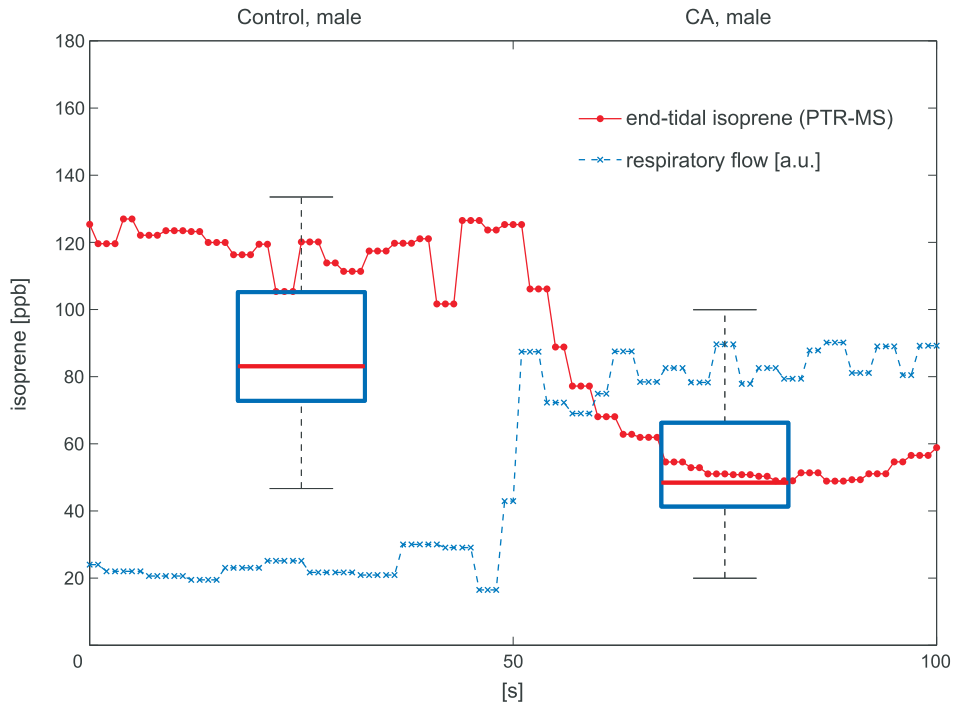


Figure: Overlay depicting the variability of end-tidal isoprene concentrations during hyperventilation of one single volunteer

Example 2: inhaling deuterated isoprene [6]

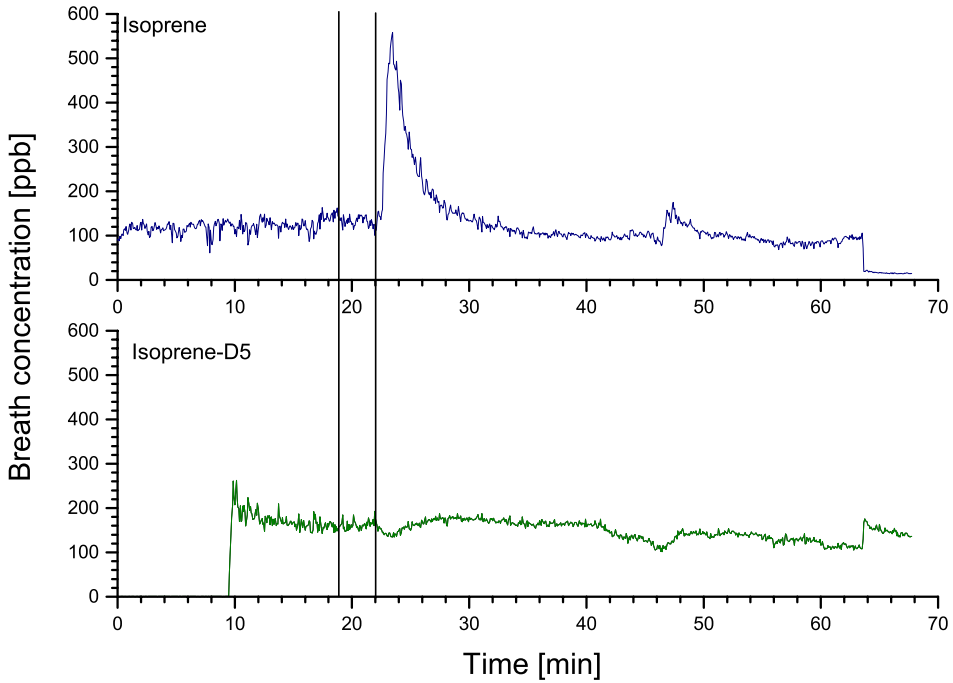


Figure: Typical isoprene and inhaled isoprene-D5 breath concentration profile when exercising with 75 Watts, [6].

Interpretation of concentration profiles in example 2:

An experiment that confirmed the prediction of the model [3] that isoprene is produced in muscle tissue was one undertaken on an exercise bicycle for which a low concentration of d5-isoprene was introduced into the laboratory air [6].

At the onset of exercise, unlabeled endogenous isoprene (blue line) shows a peak as it is well known. This peak results from the increase in fractional blood flow through the muscles which increases the mixed venous isoprene concentration. Due to the production of isoprene in the muscle tissue, the muscle compartment has a very high concentration.
As one can deduce from the figure, deuterated d5-isoprene, which has a blood:air partition coefficient of about 1, enters the arterial blood stream quickly and it takes only about one minute until it reappears in breath. Thus, an equilibrium is rapidly established between the d5-isoprene room air concentrations and the volunteer's blood concentrations.
Given that d5-isoprene is not produced in the body, its concentration in breath is zero at the beginning of the experiment. However, after inhalation and equilibration, in every compartment of the body, the venous d5-isoprene concentration is uniformly distributed and hence any change of the fractional blood flows cannot change the mixed venous concentration. At the onset of exercise, the ventilation-perfusion ratio goes up and the d5-isoprene in exhaled breath declines in accordance with the Farhi equation, because the venous blood still has an unaltered isoprene level for about two minutes (see minute 22 to 24 in Figure). However, due to the increased inhalation of d5-isoprene from the room air, the mixed venous blood gains a higher concentration level too, and the exhaled concentration of d5-isoprene reaches its former level (see minute 24 to 40). This decline of d5-isoprene also excludes that the peak of endogenous breath isoprene at the start of exercise is due to a storage effect or due to a delayed rise of cardiac output compared to alveolar ventilation. Thus, d5-isoprene does not exhibit a peak at start of exercise but behaves according to the Farhi equation and this is exactly what one would expect from the model in [3].

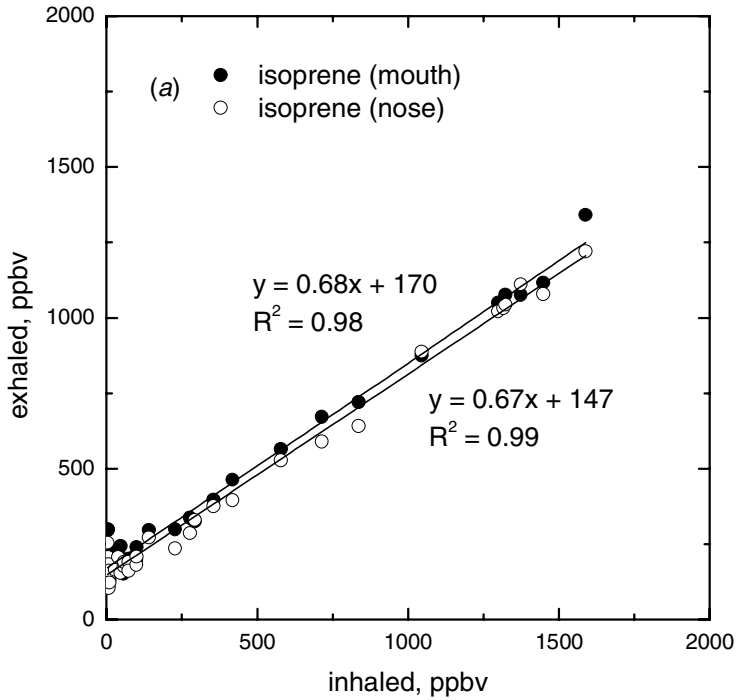
Remark: To improve the data quality of collected breath samples we suggest to use for VOCs with $\lambda_{\mathrm{b:air}} < 5$ instead of C_{A} the value

$$C_{\mathrm{A}} \left(\lambda_{\mathrm{b:air}} + \frac{\dot{V}}{\dot{Q}} \right) \tag{8}$$

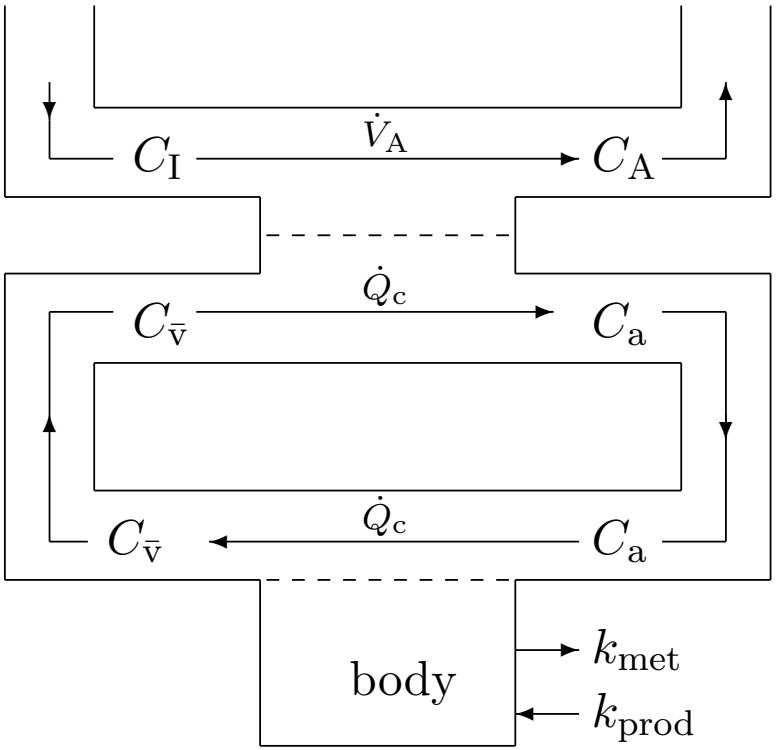
for normalization.

Inhaling VOCs

In 2013 Spanel et al. [5] measured a linear relation between inhaled (short time) and exhaled concentrations for seven VOCs at trace levels, e.g., isoprene



Case $\lambda_{\mathrm{b:air}} < 10$: Extend Farhi equation by adding a body compartment



lung compartment

blood:gas barrier

body compartment

Two compartments:

(i) lung compartment

$$V_{\mathrm{A}} \frac{dC_{\mathrm{A}}}{dt} = \dot{V}_{\mathrm{A}}(C_{\mathrm{I}} - C_{\mathrm{A}}) + \dot{Q}_{\mathrm{c}}(C_{\bar{\mathrm{v}}} - C_{\mathrm{a}}), \tag{9}$$

(ii) body compartment

$$\tilde{V}_B \frac{dC_B}{dt} = \dot{Q}_{\mathrm{c}}(C_{\mathrm{a}} - C_{\bar{\mathrm{v}}}) - \lambda_{b:B} k_{met} C_B + k_{prod}. \tag{10}$$

When in a steady state (i.e., $\frac{dC_{\mathrm{A}}}{dt} = 0$, $\frac{dC_B}{dt} = 0, \dot{V}_{\mathrm{A}}, \dot{Q}_{\mathrm{c}}$ constant) we use Equations (9), (10), and Henry's law $C_{\bar{v}} = \lambda_{b:B}\, C_B$ to get

Unterkofler's Theorem 1 (2015 [6]):
Assume $\lambda_{\mathrm{b:air}} < 10$ and a linear metabolism. Then the steady state end-tidal concentration C_{A} depends linearly on the inhaled concentration[1]:

$$C_{\mathrm{A}}(C_{\mathrm{I}}) = C_{\mathrm{A}}(0) + a\, C_{\mathrm{I}}, \tag{11}$$

$$\text{with slope } a = \frac{1}{1+\frac{\lambda_{\mathrm{b:air}}}{\frac{\dot{V}_{\mathrm{A}}}{\dot{Q}_{\mathrm{c}}}+\frac{\dot{V}_{\mathrm{A}}}{k_{\mathrm{met}}}}} \text{ and } C_A(0) = \frac{\frac{k_{\mathrm{prod}}}{k_{\mathrm{met}}}}{\frac{\dot{V}_{\mathrm{A}}}{\dot{Q}_{\mathrm{c}}}+\frac{\dot{V}_{\mathrm{A}}}{k_{\mathrm{met}}}+\lambda_{\mathrm{b:air}}}. \tag{12}$$

Consequence: to obtain the concentration when the inhaled concentration is zero $C_{\mathrm{A}}(0)$, we must not subtract C_{I}, but we must subtract $a\, C_{\mathrm{I}}$!
$(1-a)\, C_{\mathrm{I}}$ of the inhaled concentration is eliminated by the body.

[1] Mathematically exact: is an "affine function" $y = ax + b$.

Case $\lambda_{\mathrm{b:air}} > 10$: we need to consider the bronchial blood flow since for highly water soluble VOCs ($\lambda_{\mathrm{b:air}} > 10$) we have

$$C_{\mathrm{bro}} = C_{\mathrm{end-tidal}} \neq C_{\mathrm{A}}$$

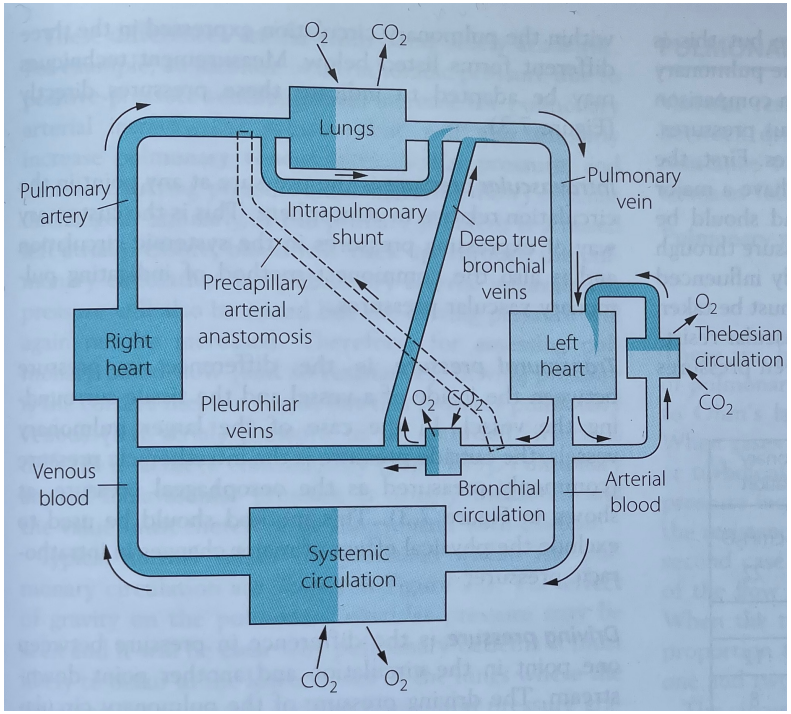


Figure: Bronchial circulation from Nunn's Applied Physiology

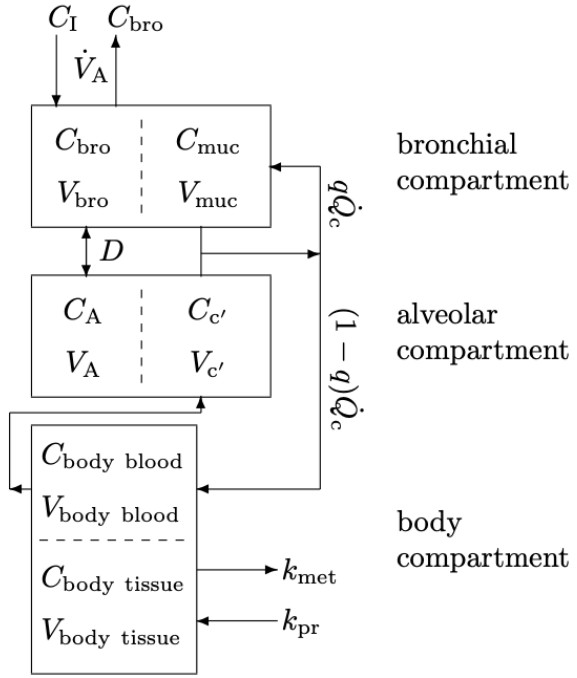


Figure: $\lambda_{\mathrm{b:air}} > 10$: we need at least three distinct functional units: bronchial/mucosal compartment (gas exchange), alveolar/end-capillary compartment (gas exchange) and one body compartment (metabolism and production). The conductance parameter D [L/t] quantifies an effective diffusion barrier between the bronchial and the alveolar tract. Though q is very small, $q = 0.01$ the effective volume is large when $\lambda_{\mathrm{b:air}}$ is large.

Unterkofler's Theorem 2 (2018 [7]):
Assume $\lambda_{\mathrm{b:air}} > 10$, a linear metabolism and a steady state has been reached. Then the end-tidal concentration $C_{\mathrm{bro}}(0)$ depends "linearly" on the inhaled concentration:

$$C_{\mathrm{bro}}(C_{\mathrm{I}}) = C_{\mathrm{bro}}(0) + a\, C_{\mathrm{I}}$$

with slope

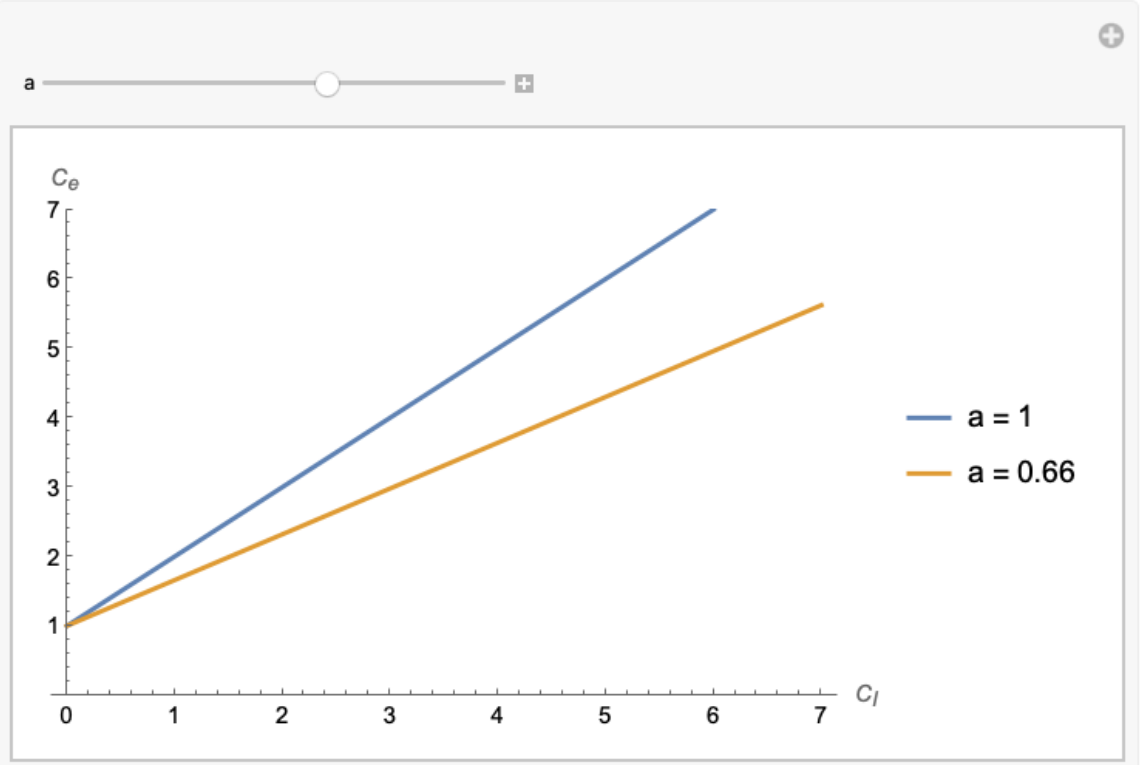
$$a = \frac{1 + D\left(\frac{1+(1-q)\frac{\dot{Q}_{\mathrm{c}}}{k_{\mathrm{met}}}}{(1-q)\lambda_{\mathrm{b:air}}\dot{Q}_{\mathrm{c}}(1+(1-q)q\frac{\dot{Q}_{\mathrm{c}}}{k_{\mathrm{met}}})}\right)}{1 + \frac{\lambda_{\mathrm{m:air}}}{\lambda_{\mathrm{m:b}}}\frac{\dot{Q}_{\mathrm{c}}}{\dot{V}_{\mathrm{A}}}\frac{q(1-q)}{1+q(1-q)\frac{\dot{Q}_{\mathrm{c}}}{k_{\mathrm{met}}}} + D\left(\frac{1+(1-q)\frac{\dot{Q}_{\mathrm{c}}}{k_{\mathrm{met}}}+(1-q)^2\lambda_{\mathrm{b:air}}\frac{\dot{Q}_{\mathrm{c}}}{\dot{V}_{\mathrm{A}}}+q(1-q)\frac{\lambda_{\mathrm{m:air}}}{\lambda_{\mathrm{m:b}}}\frac{\dot{Q}_{\mathrm{c}}}{\dot{V}_{\mathrm{A}}}}{(1-q)\lambda_{\mathrm{b:air}}\dot{Q}_{\mathrm{c}}(1+(1-q)q\frac{\dot{Q}_{\mathrm{c}}}{k_{\mathrm{met}}})}\right)} \tag{13}$$

More details can be found in [7]. For large $\lambda_{\mathrm{b:air}}$, e.g. acetone $\lambda_{\mathrm{b:air}} = 340$ we can take $D \approx 0$ and get (remark: however, hyperventilation will increase D)

$$a = \frac{1}{1 + \frac{\lambda_{\mathrm{m:air}}}{\lambda_{\mathrm{m:b}}}\frac{\dot{Q}_{\mathrm{c}}}{\dot{V}_{\mathrm{A}}}\frac{q(1-q)}{1+q(1-q)\frac{\dot{Q}_{\mathrm{c}}}{k_{\mathrm{met}}}}}$$

Summary: influence of short-term inhaled VOCs

When $k_{\text{met}} = 0$ then $a = 1$, when $k_{\text{met}} > 0$ then $a < 1$. Here $C_e(0) = 1$.



C_e denotes end-tidal (either C_{A} or C_{bro}), $C_{room} = C_{\text{I}}$

My suggestions for the scientific breath research community:

Determine the slope a for all VOCs of interest.

Measure back ground concentrations and correct for back ground concentrations by subtracting $a\,C_{\mathrm{I}}$.

Measure cardiac output $\dot{Q}_{\mathrm{c}}$ and alveolar ventilation $\dot{V}_{\mathrm{A}}$ and correct concentrations for VOCs with $\lambda_{\mathrm{b:air}} < 10$ using the Farhi equation $C_{\bar{\mathrm{v}}} = C_{\mathrm{A}}\left(\lambda_{\mathrm{b:air}} + \frac{\dot{V}}{\dot{Q}}\right)$.

Measure all other parameters (e.g., body mass, height, etc.) that could influence VOC concentrations.


L. E. Farhi,
Elimination of inert gas by the lung, Respiration physiology **3** (1967), no. 1, 1–11.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A mathematical model for breath gas analysis of volatile organic compounds with special emphasis on acetone, J. Math. Biol. **63** (2011), 959–999.


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A quantitative study of the influence of inhaled compounds on their concentrations in exhaled breath. *J. Breath Res.*, **7**)2013) 017106.


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Modeling-based determination of physiological parameters of systemic VOCs by breath gas analysis: a pilot study. *J. Breath Res.*, **9** (2015) 036002.


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Modeling-based determination of physiological parameters of systemic VOCs by breath gas analysis, part 2. *J. Breath Res.*, **12** (2018) 036011,.


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