Supplementary Material (11 pages) for "Low-Order Mechanistic Models for Capnography" by Murray, You, et al.

Partial pressure, Section I

The ideal gas law states that at absolute temperature T the pressure P exerted by n moles of an ideal gas confined to a volume V (hence at molar concentration $c = n/V$) is given by $P = RTc$, where R is the universal gas constant (Boltzmann's constant times Avogadro's number). If this gas comprises multiple non-interacting species, where there are n_i moles of species i (with corresponding molar concentration $c_i = n_i/V$), then the total pressure P is the sum of the partial pressures $P_i = RTc_i$ (this is Dalton's law). Thus, at a fixed T, the partial pressure of a component of a gaseous mixture is proportional to its molar concentration in the mixture. Throughout the paper, we quote the partial pressure of CO_2 in units of mmHg (multiplying by 0.133 gives the partial pressure in kilopascals or kPa).

The partial pressure of a gaseous species dissolved in a liquid (such as CO_2 dissolved in blood plasma) is defined via the partial pressure of the species in a gas mixture contacting the liquid, with the gas and liquid concentrations in steady equilibrium. The concentration of the species in the liquid is the product of this partial pressure and the solubility of the species in the liquid.

Diffusive "blurring" of the interface between alveolar gas and inhaled air at commencement of exhalation, Section II.A

We can get an approximate sense of how — near the start of exhalation — diffusion might "blur" whatever boundary may exist between CO_2-rich alveolar gas and the previously inhaled atmospheric air (which is essentially CO_2-free).

Consider the one-dimensional case of a cylinder containing alveolar gas with CO_2 at concentration $\overline{p}_A$ on one side of a planar separator, and atmospheric air with CO_2 concentration 0 on the other. When the separating boundary is removed at time $t = 0$, and in the absence of any convective airflow, the CO_2 will diffuse into the atmospheric air on the other side of the boundary. (There is clearly convective flow during exhalation, but we ignore it to simplify the calculation here, essentially considering the viewpoint of a frame traveling with the boundary.)

At time t and a distance x into the side containing atmospheric air, the CO_2 concentration is given by

$$\frac{\overline{p}_A}{2}\left(1 - \operatorname{erf}\frac{x}{2\sqrt{Dt}}\right) ,$$

where D is the diffusion coefficient for CO_2 in atmospheric air (see for example Eq. 2.13 in *Random Walks in Biology* by H.C. Berg, Princeton University Press, 1983). At body temperature, $D \approx 0.2\,\mathrm{cm}^2/\mathrm{s}$, see for example *CRC Handbook of Chemistry and Physics Online* (section on "Diffusion of Gases").

From tabulated values of the erf function, we see that when

$$\frac{x}{2\sqrt{Dt}} = 1.6$$

the expression for the concentration becomes $0.012\,\overline{p}_A$. Solving the preceding equation for x when $t = 0.2\,\mathrm{s}$ — which Fig. 1 suggests is roughly the time needed for the interface to reach V_M and the CO_2 concentration in V_M to start rising — we find $x = 0.64\,\mathrm{cm}$. Thus, at this distance from the original boundary, and assuming no convective flow, the concentration has risen from 0 to only 1.2% of $\overline{p}_A$.

For comparison, from Table 3 of [22] (which was the reference for the volumes V_M and V_L quoted in Fig. 2), we see that the nominal aggregate length of the laminar-flow region (generations 6–16) is around 4.8 cm. This suggests that the interface between alveolar gas and atmospheric air remains reasonably well defined during its transit through the laminar-flow region V_L at the start of exhalation.

Solution of (1) with input (3)

For a step-plus-exponential $p_A(V)$ that starts at $p_M(V_L)$, i.e.,

$$p_A(V) = p_M(V_L) + K_1 + K_2 \left(1 - e^{-\frac{V-V_L}{\nu}}\right) ,$$

the analytical solution of (1) works out to be

$$p_M(V) = p_M(V_L) + (K_1 + K_2) - \left(K_1 + K_2 \frac{V_M}{V_M - \nu}\right) e^{-\frac{V-V_L}{V_M}} + K_2 \frac{\nu}{V_M - \nu} e^{-\frac{V-V_L}{\nu}} .$$

The slope of this at $V = V_L$ is K_1/V_M.

The case considered in the paper is $K_1 = 0$ and $K_2 = K$. Having a positive K_1 allows a positive initial slope, which would be desirable since the slope of Vcap at our $p(V_L)$ is indeed positive. However, the introduction of a further parameter into the model could make the estimation less robust. We leave exploration of this to future work.

Solution of (6)

First-order linear time-*variant* state-space models have an explicit analytical solution, though this is not generally the case for higher-order versions (see Chapter 9 of *Linear Systems*, T. Kailath, Prentice-Hall 1980). It can be directly verified that

$$p_M(t) = e^{-w(t)} \left(e^{w(0)} p_M(0) + \int_0^t e^{w(\sigma)} \dot{w}(\sigma) p_A(\sigma)\, d\sigma \right)$$

satisfies (6) and evaluates to $p_M(0)$ at $t = 0$, as required.

Solution of (9)

The solution of (9) is

$$w(t) = c_1 e^{\frac{-\tau+\sqrt{\tau^2-4\delta\tau}}{2\delta\tau}t} + c_2 e^{\frac{-\tau-\sqrt{\tau^2-4\delta\tau}}{2\delta\tau}t} + \alpha \; .$$

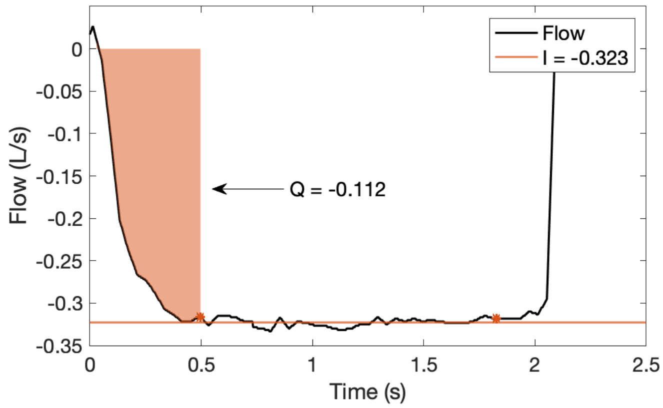
The constants c_1 and c_2 are chosen such that this solution matches the given initial conditions.

If we assume zero initial conditions, i.e., $w(0) = 0$ and $\dot{w}(0) = 0$, and if $\delta \ll \tau$, the analytical solution for normalized volume $w(t)$ and airflow $\dot{w}(t)$ can be approximated as

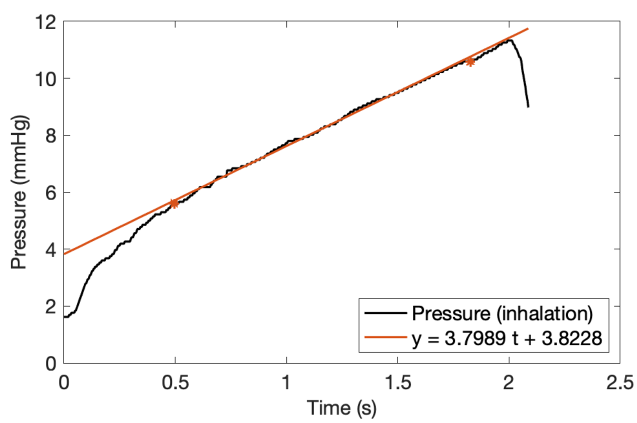
$$\begin{aligned} w(t) &\approx \frac{\delta\alpha}{\tau-\delta} e^{-\frac{t}{\delta}} - \frac{\tau\alpha}{\tau-\delta} e^{-\frac{t}{\tau}} + \alpha \; , \\ \dot{w}(t) &\approx -\frac{\alpha}{\tau-\delta} e^{-\frac{t}{\delta}} + \frac{\alpha}{\tau-\delta} e^{-\frac{t}{\tau}} \; . \end{aligned}$$

Thus the fast transient is essentially governed by time-constant δ, and the slow transient by time-constant τ.

Fitting forced inhalations; estimating R and C, Section III.E

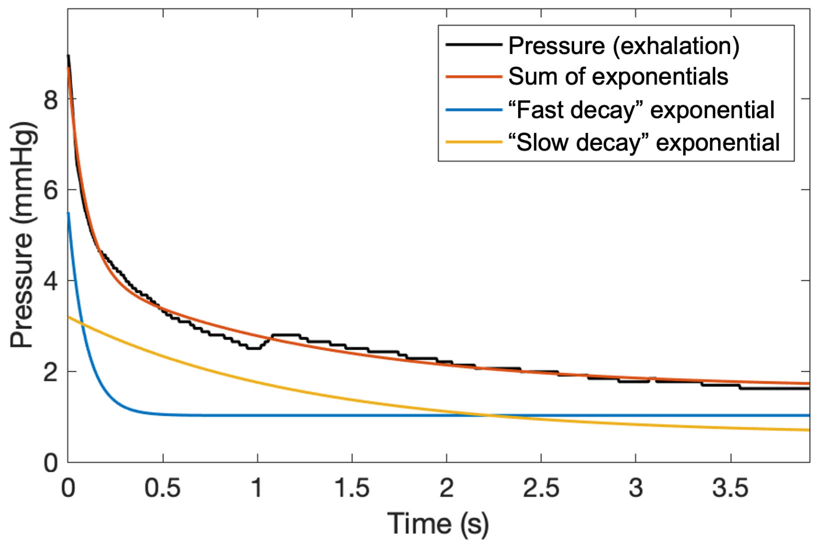


SM Fig. 1: Total insufflated volume V_{ins}, i.e., integral of airflow, during the transient before constant airflow $-F$ sets in, for the same example as in Fig. 1.



SM Fig. 2: Airway pressure ramping up with slope F/C when airflow is constant at $-F$, allowing determination of C — for the example in Fig. 1.

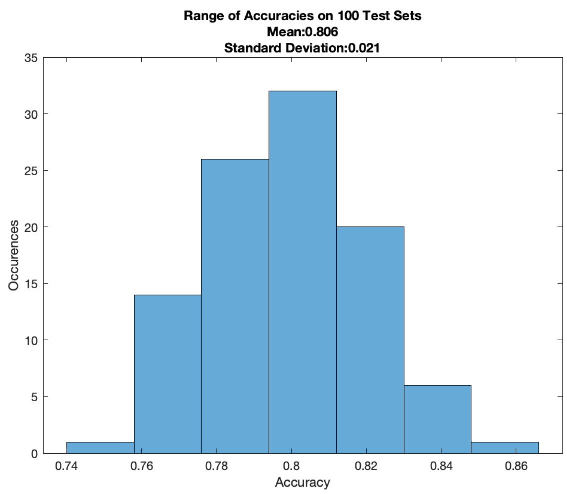
Least-mean-square-error fit of sum of two exponentials to airway pressure during exhalation, Section IV.B



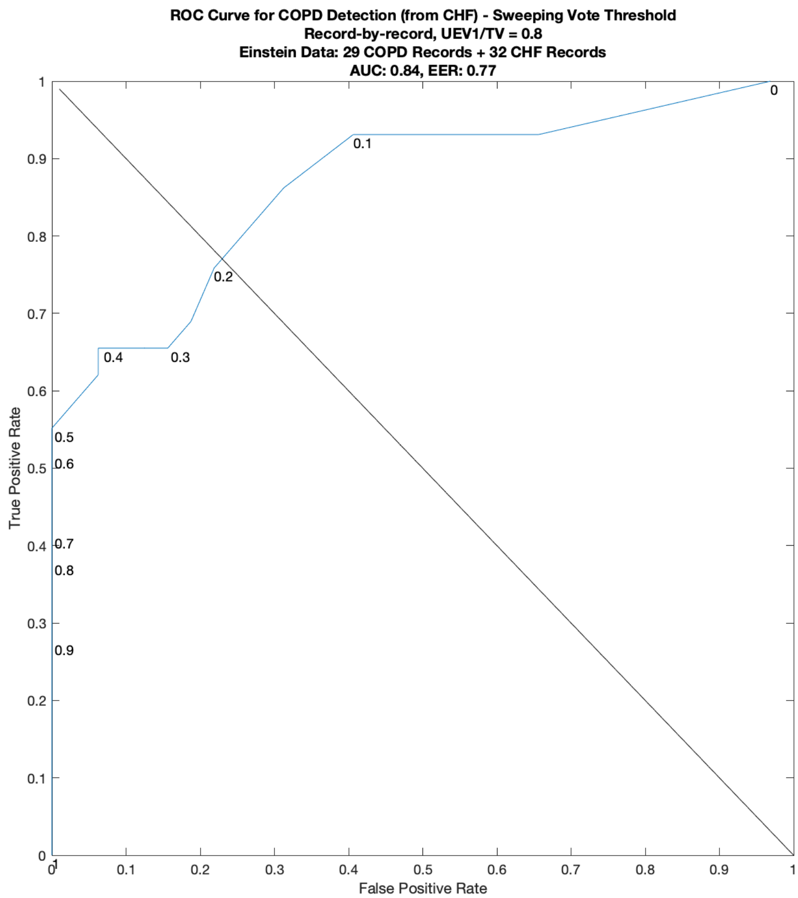
SM Fig. 3: Least-mean-square-error fit of sum of two exponentials to airway pressure during exhalation, for the example used in Fig. 1. The time constant of the fast exponential is $\delta'(\approx \delta)$, and that of the slow exponential is $\tau'(\approx \tau)$.

Performance of new Tcap-based test for COPD–CHF discrimination, Section IV.C

The figures below relate to the experiments described in Section IV.C (see captions for details).

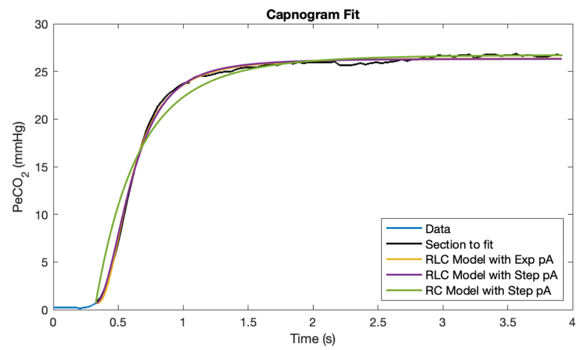


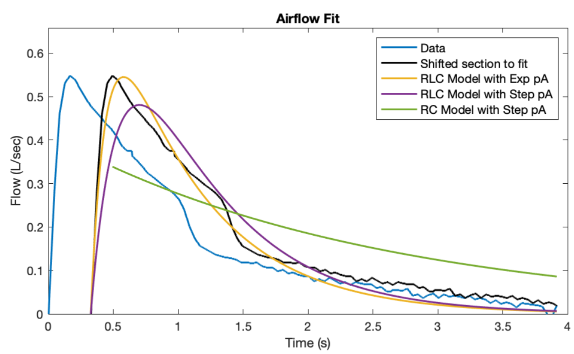
SM Fig. 4: Accuracy distribution over 100 experiments with COPD–CHF classification using our new Tcap-based test. In each experiment, we randomly select 15 exhalations from each record in the trimmed test set, Section III.A(2), and classify the record as COPD if $u < 0.8$ on at least 8 exhalations, where u is the UEV1/TV ratio that we are using for classification. Accuracies range from 74.1% to 86.2% (mean 80.6%, stdev 2.1%).



SM Fig. 5: ROC curve for our new Tcap-based test acting on each record in the full test set, Section III.A.(2). A record is classified as COPD if $u < 0.8$ on at least a fraction f of the exhalations, where u is the UEV1/TV ratio that we are using for classification. The ROC curve is obtained by sweeping f from 0 to 1. The area under the ROC curve (AUROC) is 0.84, and the equal-error-rate is 77%, obtained for $f = 0.2$.

Comparison of fits to Tcap and exhaled airflow using different models, Section V





SM Fig. 6: Model fits to Tcap and exhaled airflow

We compare the fits to Tcap and to exhaled airflow (after shifting and scaling), as in Fig. 5, for three models. The figure here shows these fits for the example in Fig. 1. We quote below the rmse values averaged over all available 310 exhalations:

Model 1: RLC with exponential $\overline{p}_A(t)$, Tcap rmse 0.57 mmHg (stdev 0.25 mmHg), flow rmse 42 mL/s (stdev 13 mL/s).

Model 2: RLC with step $\overline{p}_A(t)$, Tcap rmse 0.61 mmHg, flow rmse 42 mL/s.

Model 3: RC with step $\overline{p}_A(t)$, Tcap rmse 1.13 mmHg, flow rmse 79 mL/s.

It is evident that the *RLC* Model 1, with the extra parameter ϵ governing the exponential alveolar discharge in (7), provides a somewhat better Tcap fit on average than the *RLC* Model 2, which has a step alveolar discharge, while not adding much to the flow fit on average (though in the example of SM Fig. 6 above, Model 1 does visibly better). On the other hand, the *RC* Model 3 does substantially worse.