COMPARTMENTAL MODELING: TIME-ACTIVITY CURVE SIMULATION AND ESTIMATION OF RAT PULMONARY REDOX REACTIONS

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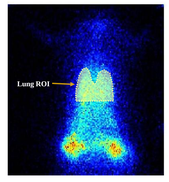
INTRODUCTION

In the lung, redox reactions occur in blood and lung tissue. The relative concentration of oxidants vs. anti-oxidants has been shown to play an important role in lung diseases, including carcinoma, asthma, acute respiratory distress syndrome, and neonatal respiratory distress syndrome. Thus, investigation and understanding of the role of oxidizing and reducing agents in the lung is important for the assessment and subsequent treatment of such diseases.

[^{99m}Tc]-Hexamethyl-Propylene Amine Oxime (HMPAO) is a clinically-used agent that is radiolabeled and thus can be detected using single photon emission computed tomography (SPECT). HMPAO exists in both an oxidized and reduced form.

Process:

- Inject HMPAO into blood stream
- Travels into pulmonary circulation and taken up by the lung tissue (endothelial cells)
- Image the lung during passage of HMPAO
- Determine curves that represent the activity as a function of time in the lung ROI
- Use curves to determine kinetic parameters descriptive of the redox status of the lung
- Long-term goal is to determine changes in these parameters using HMPAO with different lung injuries or diseases



OBJECTIVE

Develop a mathematical model of the pulmonary uptake of HMPAO.

Forward simulate curves representative of those measured in real experiments.

Estimate “unknown” kinetic parameters from simulated curves.

COMPARTMENTAL MODEL

HMPAO Biochemistry

Both HMPAO forms exist in the blood and lung tissue.

Oxidized form:

- lost electrons
- diffusible: can diffuse into, and back out of, endothelial cells which line the walls of the blood vessels
  $C_{BD}(t)$ = concentration of diffusible in blood
  $C_{LD}(t)$ = concentration of diffusible in lung tissue

Reduced form:

- gained electrons
- nondiffusible: cannot diffuse into, or out of, endothelial cells
  $C_{BND}(t)$ = concentration of nondiffusible in blood
  $C_{LND}(t)$ = concentration of nondiffusible in lung tissue

Compartmental Interactions

HMPAO injection: $C_{inj}(t)$

Blood: diffusible ↔ nondiffusible (k_5, k_6)

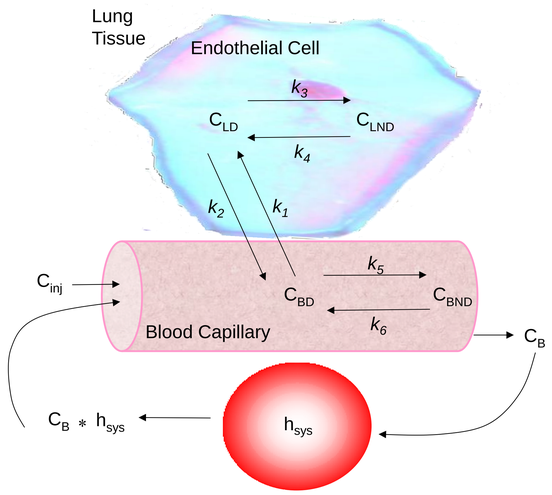
Lung: diffusible ↔ nondiffusible (k_3, k_4)

Diffusion: blood ↔ lung (k_1, k_2)

Recirculation: time-delay (μ) and dispersion (σ)

METHODS

Kinetic model of pulmonary distribution of HMPAO



Mass-balance equations

$$\frac{dC_{BD}}{dt} = -k_1 C_{BD} + \frac{V_L}{V_B} k_2 C_{LD} - k_5 C_{BD} + k_6 C_{BND} + \frac{F}{V_B}\left(\alpha C_{inj} - C_{BD} + C_{BD} * h_{sys}\right)$$

$$\frac{dC_{LD}}{dt} = \frac{V_B}{V_L} k_1 C_{BD} - k_2 C_{LD} - k_3 C_{LD} + k_4 C_{LND}$$

$$\frac{dC_{BND}}{dt} = k_5 C_{BD} - k_6 C_{BND} + \frac{F}{V_B}\left((1-\alpha) C_{inj} - C_{BND} + C_{BND} * h_{sys}\right)$$

$$\frac{dC_{LND}}{dt} = k_3 C_{LD} - k_4 C_{LND} \ ,$$

V_L and V_B : endothelial cell and blood capillary volumes, respectively,

F : blood capillary flow rate constant,

α : ratio of injected diffusible to nondiffusible HMPAO,

$*$: convolution of blood concentrations and h_{sys} modeling systemic recirculation,

h_{sys} : systemic circulation blood distribution function

$$h_{sys}(t) = \frac{1}{\sigma\sqrt{2\pi}} e^{\left(\frac{-(t-\mu)^2}{2\sigma^2}\right)}$$

where μ is the mean recirculation time and σ is the standard deviation.

Furthermore,

$$C_{BD}(t) * h_{sys}(t) = \int_0^t C_{BD}(\tau) h_{sys}(t-\tau) d\tau$$

$$C_{BND}(t) * h_{sys}(t) = \int_0^t C_{BND}(\tau) h_{sys}(t-\tau) d\tau$$

$$C_{inj}(t) = \alpha C_{inj}(t) + (1-\alpha) C_{inj}(t)$$

$$C_{in}(t) = C_{inj}(t) + \left(C_{BD}(t) + C_{BND}(t)\right) * h_{sys}(t)$$

= total HMPAO input concentration at time t.

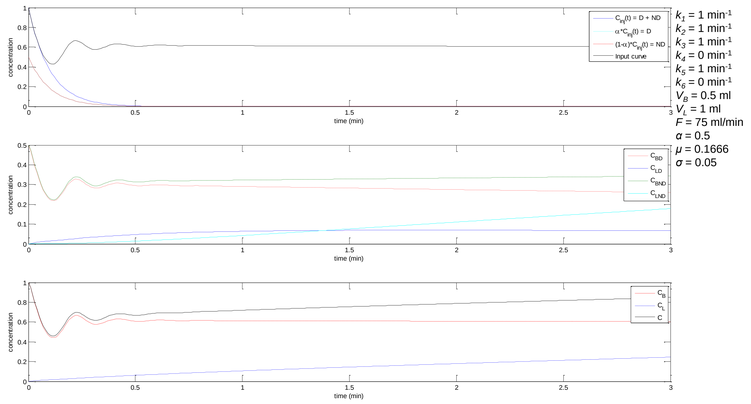
MATLAB (ode45) was used to solve this system of differential equations to determine the unknown concentration curves: C_{BD}, C_{LD}, C_{BND}, C_{LND}.

RESULTS

Forward simulation

Model was used to simulate concentration curves resembling those obtained from experiments.

Example: Assume nondiffusible form is trapped (irreversible reaction) ⇔ $k_4 = k_6 = 0$ and other parameters set at physiologically relevant values.

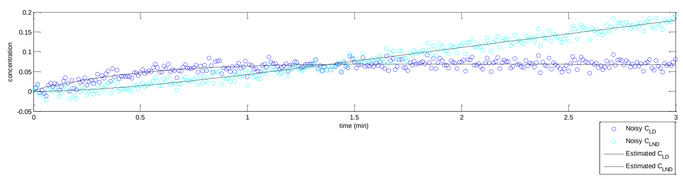


k_1 = 1 min^{-1}
k_2 = 1 min^{-1}
k_3 = 1 min^{-1}
k_4 = 0 min^{-1}
k_5 = 1 min^{-1}
k_6 = 0 min^{-1}
V_B = 0.5 ml
V_L = 1 ml
F = 75 ml/min
α = 0.5
μ = 0.1666
σ = 0.05

Parameter estimation

Normally distributed random noise (mean = 0, SD = 0.01) was added to simulated lung concentration curves shown above.

Nonlinear least squares (lsqnonlin) was used to estimate rate constants k_1 through k_6.



Process was repeated 5 times to obtain mean estimates:

	k_1	k_2	k_3	k_4	k_5	k_6
mean	1.010	1.011	1.004	0.002	1.237	3.966e-008
SD	0.040	0.093	0.016	0.003	0.333	8.867e-008
TRUE	1	1	1	0	1	0

SUMMARY

A mathematical model of the pulmonary uptake of a SPECT agent (HMPAO) was constructed. This result is a compartmental model consisting of a system of 4 differential equations.

The model included conversion between diffusible and nondiffusible forms, diffusion, and recirculation.

The model was used to forward simulate time-activity or concentration curves using known parameter values obtained from previous experiments. The resulting diffusible and nondiffusible concentration curves for both the blood and the lung tissue regions resembled those obtained in real experiments.

Conversely, the inverse method assumed the concentration curves were known (i.e. obtained in experiments) and implemented a nonlinear least squares algorithm to estimate the “best” k values.

The shapes of the C_{LD} and C_{LND} concentration curves depend heavily on α, ratio of diffusible to nondiffusible HMPAO in the original injection. These curves tend to increase to a plateau quicker when the diffusible form constitutes a larger fraction, (i.e. if all nondiffusible, no accumulation in the endothelial cells.)

Duration of IV injection and/or subsequent, intermittent injections causes significant change in the input curve and resulting blood and lung concentration curves. Oscillations due to recirculation are observable in input C_{in} provided duration of injection exceeds μ.

CONCLUSIONS

Compartmental model is able to produce concentration curves resembling those measured in real experiments.

Model can be used to estimate kinetic parameters of the distribution and uptake of HMPAO in the blood and the lung tissue.

FUTURE

Use model to estimate kinetic parameters from real experimental data.

Model will be used to determine changes in kinetic parameters in different animal models of lung disease.

REFERENCES

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