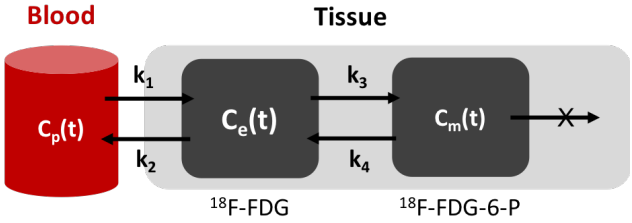
Biomedical Imaging

Exercise NUC #2 – Quantitative PET Data Analysis

The purpose of the exercise is to implement and study kinetic modeling and data fitting for quantitative PET data analysis of ^{18}F-FDG tracer experiments.

Task 2.1

Upon injection, ^{18}F-FDG is taken up by tissue via glucose transporters and converted to ^{18}F-FDG-6-phosphate (^{18}F-FDG-6-P) as shown schematically in the figure below. For the analysis of rate constants (k_2, k_3, k_4) we consider the two tissue compartments (c_e, c_m) and treat the blood/plasma compartment (c_p) separately, i.e. we solve the equations for an ideal delta input function (impulse response) and convolve the results with the actual input signals.



- Derive and write down the differential equations for the concentrations of extracellular ($c_e(t)$) and metabolized ^{18}F-FDG ($c_m(t)$) ; assume that the input from the blood plasma is a delta function, i.e. $c_e(0) = k_1$ and $c_m(0) = 0$, also assume k_4=0.

$$\frac{dc_e(t)}{dt} = -k_2 c_e(t) - k_3 c_e(t)$$

$$\frac{dc_m(t)}{dt} = +k_3 c_e(t)$$

$$c_e(t=0) = k_1, c_m(t=0) = 0$$

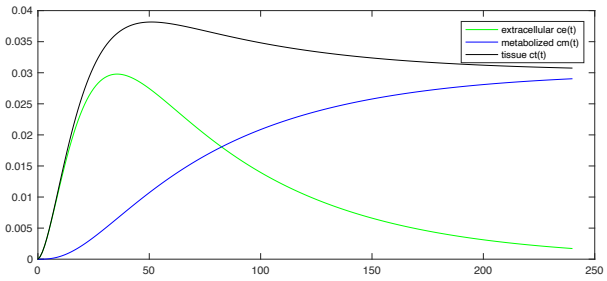
- Learn about solving differential equations in Matlab using dsolve (type help dsolve on Matlab prompt) and implement the differential equations derived above to obtain the impulse response functions of the extracellular compartment $c_e(t)$ and the metabolized compartment $c_m(t)$.

```
syms k1 k2 k3 ce(t) cm(t)

h = dsolve(diff(ce) == -k2*ce-k3*ce, ...
           diff(cm) == +k3*ce, ...
              ce(0) == k1, ...
              cm(0) == 0 );
```

- Now implement convolution of the impulse response functions with the blood plasma input curve $c_p(t)$.

```
ce = filter(cp,1,h_ce(k1,k2,k3,t));          % conc-time curve of ce
cm = filter(cp,1,h_cm(k1,k2,k3,t));          % conc-time curve of cm
ct = ce+cm;                                  % conc-time curve of tissue comp ct
```

- Inspect the tissue concentration-time curves for $c_e(t)$ and $c_m(t)$ using the following values: k_1=0.1 min^{-1}, k_2=0.3 min^{-1}, k_3=0.6 min^{-1}.



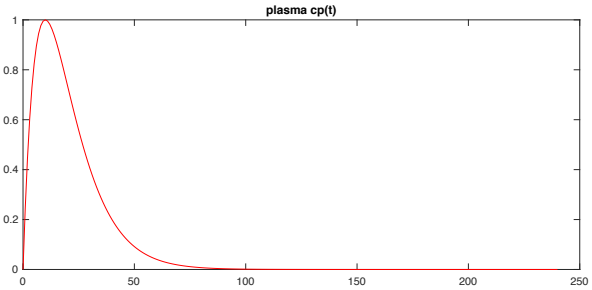
- Rate constant k_4 was assumed to be zero – justify why such an assumption is valid by considering the process of ^{18}F-FDG tracer uptake and metabolization in tumors.

  In most tumor cells, the activity of the enzyme that catalyzes the dephosphorylation of 18F-FDG-6-P (glucose-6-phosphatase) is low. Thus, k_4 can be assumed to be negligible.

Task 2.2

In a real-word experiment, blood plasma concentration $c_p(t)$ is measured in a blood vessel near the tissue of interest $\left(c_e(t) + c_m(t)\right)$ and both measurements are input to a fitting procedure to obtain the kinetic rate constants (k_1, k_2, k_3).

- Inspect the blood plasma concentration-time curve $c_p(t)$ as available in the code.



- Add Poisson noise to $c_p(t)$ and $c_t(t)$ by converting concentrations into photon counts such as to obtain a peak SNR of 100 of the blood plasma signal; inspect the resulting concentration-time curves.

```
% ------------------------------------------------------------------
% Task 2.2. Convert concentrations into counts N by assuming
% a peak SNR of blood plasma activity of 100
% ------------------------------------------------------------------
N0      = SNR^2;                                % SNR = sqrt(N)
Ncp     = N0*cp;
Nct     = N0*ct;

% ------------------------------------------------------------------
% Task 2.2. Add noise to cp(t) and ct(t) = ce(t) + cm(t)
% ------------------------------------------------------------------
Ncp_noise = poissrnd(Ncp);
Nct_noise = poissrnd(Nct);

% ------------------------------------------------------------------
% Task 2.2.Convert from counts N back to concentrations
% ------------------------------------------------------------------
cp_noise  = Ncp_noise/N0;
ct_noise  = Nct_noise/N0;
```

- Implement the fit function to determine the rate constants (k_1, k_2, k_3) from noisy $c_p(t)$ and $c_t(t)$ input.

  Type in h_ce and h_cm on Matlab prompt to display the impulse response functions of the extracellular and metabolizing compartments; the convolution $c_p(t)$ and the sum of the two need to be implemented as fit function as follows:

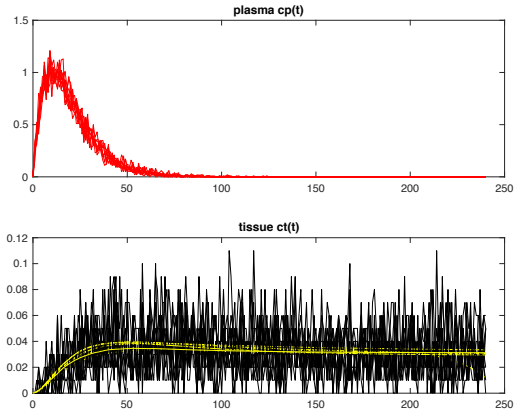
```
% ------------------------------------------------------------------
% Task 2.2 Define fit function using
% ct_noise(t) = int(ct_plasma(tau)*(h_t(t-tau))dtau
% ------------------------------------------------------------------
fun = @(k,t)filter(cp_noise,1,k(1).*exp(-t.*(k(2)+k(3))) + ...
        (k(1).*k(3))./(k(2)+k(3))-(k(1).*k(3).*exp(-t.*(k(2)+k(3)))./(k(2)+k(3)));

k0 = [0.01 0.01 0.01]                       % Starting values for fit

k_fit  = nlinfit(t,ct_noise,fun,k0);
```

- Determine mean and standard deviation of the fitted rate constants (k_1, k_2, k_3) for multiple repetitions of adding noise and fitting the noisy data.

```
% ------------------------------------------------------------------
% Task 2.2. Display mean +/- standard deviation of k1, k2, k3
% ------------------------------------------------------------------
fprintf('Mean  [k1 k2 k3]: %f %f %f\n',mean(k_result,2));
fprintf('StDev [k1 k2 k3]: %f %f %f\n',std(k_result,1,2));
```

- Reduce the SNR by a factor 10 and repeat the experiments above; how do mean and standard deviation of fitted rate constants change? Which conclusion do you draw in terms of required signal-to-noise ratio of the input PET data?

  In general, one can compute the coefficient of variation (CoV) i.e. standard deviation over the mean of repeat experiments. At an SNR of 100, the CoV of k_1, k_2, k_3 is below 10% which is acceptable for diagnostics. At an SNR of 10, however, the CoV of k_1, k_2, k_3 is well above 10%, even peaking to 500%, which means no reliable information on k_1, k_2, k_3 can be extracted from a single measurement. In consequence, the experiments would need to be repeated many times to obtain precise estimates, which limits the use of the method for in-vivo applications.



Questions?

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