Kinetics of the Tracer in PET

Davide Poggiali

November 8, 2013

Calendar of seminars

Sept. 19 **Physical Basis of Magnetic Resonance Imaging** ☑

spin under a magnetic field, RF pulses, Bloch equations

Sept.27 **Sequences and Reconstruction in MRI** ☑

K-space, aliasing, sequences

Oct. 18 **Positron Emission Tomography: an introduction** ☑

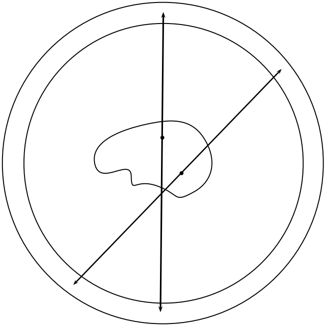
general introduction, attenuation correction, level set methods

Nov. 8 **Kinetics of the Tracer in PET** ☐

compartment model for ^{18}FdG

Nov. 22 **Dual-Modality Imaging** ☐

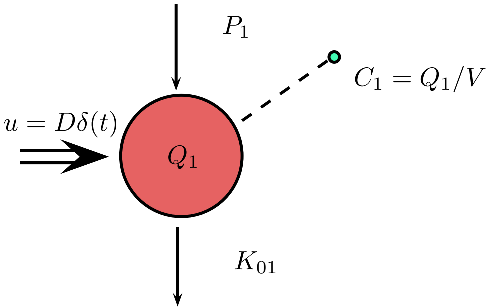
Positron emission tomography (PET) is a nuclear medical imaging technique that produces an image of functional processes in the body. The PET machine detects pairs of gamma rays, or positrons emitted by the annihilation of a tracer (as the ^{18}FdG), introduced into the body.



The particularity of PET stands in the possibility of recover a sequence of images as a time series. This allows the researchers to study the evolution of the tracer kinetics, which will be treated in the next seminar.
Since the positrons are emitted two by two, before considering a couple of data as the product of the same annihilation process, the machine filters only the pairs of positrons incoming in the same (small) temporal window $\triangle t$. This allows to reduce the effect of scattering, so the data collected after this filtering is quiet reliable.

A (multi-)compartment model is a type of mathematical model used for describing how materials or energies are transmitted among the compartments of a system. Each compartment is assumed to be a homogeneous entity. Hence a compartment represents, in medical application, a group of organs exchanging material at the same speed one with another.
The kinetics of the material is described by an ordinary differential equations system with as unknown functions the concentration of the considered material in each compartment.

A simple example:



$$\begin{cases} \dot{Q}_1 = P_1 - K_{01} Q_1 + D\delta(t) \quad , \quad Q_1(0) = Q_{10} \\ C_1 = \frac{Q_1(t)}{V} \end{cases}$$

The general model for compartment model is the following:

General model

$$\begin{cases} \dot{Q}_i = \sum_{j \neq i} F_{ij}(Q) - \sum_{j \neq i} F_{ji}(Q) + P_i + u_i(t) \quad , \quad Q_i(0) = Q_{i0} \\ C_i = \frac{Q_i(t)}{V_i} \quad \text{or} \quad C_i = 0 \end{cases}$$

A tracer is a small quantity of substance used for tracking purposes.
The tracer:

1. can be measured independently from the traced
2. follows the dynamics of the traced and do not perturb the state of the system (small quantity)
3. is kinetically indistinguishable from the traced

From the third assumption we can get the following principle:

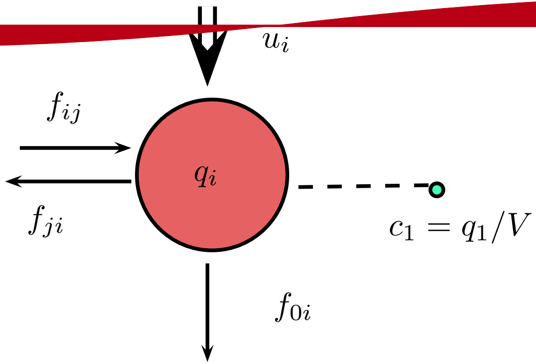
$$P(\text{a particle leaving } j \text{ is tracer}) = P(\text{a particle in } j \text{ is tracer})$$

this means that

$$\frac{f_{ij}}{F_{ij} + f_{ij}} = \frac{q_j}{Q_j + q_j}$$

equivalently

$$\frac{F_{ij}}{Q_j} = \frac{f_{ij}}{q_j} = k_{ij}(Q)$$



$$\begin{cases} \dot{q}_i = \sum_{j\neq i} f_{ij}(Q,q) - \sum_{j\neq i} f_{ji}(Q,q) + u_i(t) \quad , \quad q_i(0) = q_{i0} \\ c_i = \dfrac{q_i(t)}{V_i} \quad \text{or} \quad c_i = 0 \end{cases}$$

If we suppose that all the functions $k_{ij}(Q) = k_{ij}$ are constant then $f_{ij}(Q) = k_{ij} q_j$ and the model becomes

Tracer model

$$\begin{cases} \dot{q}_i &= \displaystyle\sum_{j \neq i} k_{ij} q_j - \sum_{j \neq i} k_{ji} q_i + u_i(t) \quad , \quad q_i(0) = q_{i0} \\ c_i &= \dfrac{q_i(t)}{V_i} \qquad \text{or} \qquad c_i = 0 \end{cases}$$

Under this hypothesis the model goes under the category of Linear Time-Invariant model in state-space form

LTI state-space

$$\begin{cases} \dot{x} &= Ax + Bu \quad , \quad x(0) = x_0 \\ y &= Cx \end{cases}$$

Where u is the input, y the output and the system is determined by (A, B, C).

The system (A, B, C) is equivalent to the direct input-output relation

$$y(y) = Cx(t) = (C\ \exp(tA)\ B) * u(t)$$

so we define the impulse response function

$$\phi(t) = C\ \exp(tA)\ B$$

and its Laplace transform, the transfer function

$$\hat{\phi}(s) = C\ (sI - A)^{-1}\ B$$

so that $y = \phi * u$ and $\hat{y} = \hat{\phi}\hat{u}$.

Moreover under the hypothesis the the input is a bolo

$$u(t) = D\delta(t)$$

we get that

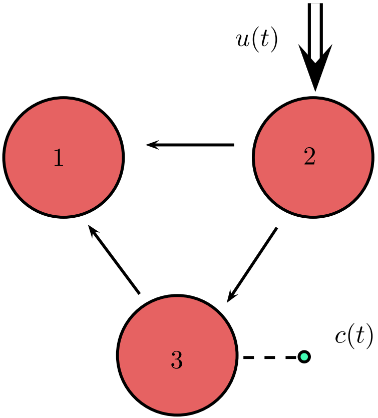
$$y(t) = \phi(t) * u(t) = \phi(t) * D\delta(t) = D\phi(t).$$

Definition

The model (A, B, C)

$$\begin{cases} \dot{x} & = & Ax + Bu \quad , \quad x(0) = x_0 \\ y & = & Cx \end{cases}$$

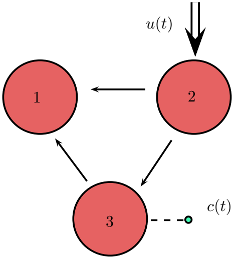
is (uniquely) identifiable if it is possible to determine (uniquely) the nonnegative entries of A, given B, C, and the exact data x_0, y, u.



Is this model identifiable?

Definition

1. A Compartment k is in/out-put reachable if $\exists$ a path from an in-out-put compartment to k.
2. A system (A, B, C) is in/out-put reachable if every compartment is in/out-put reachable.

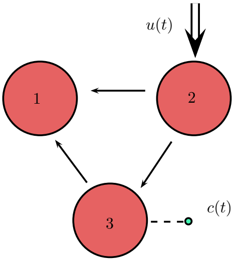


Example: this system is input reachable but not output reachable.

Theorem (necessary conditions)

Let (A, B, C) be an identifiable system, then:

1. The system is input reachable
2. every compartment with an outgoing path is output reachable



Example: this system could be reachable.

Observation

The transfer function $\hat{\phi}(s)$ is a rational function of the form

$$\hat{\phi}(s) = \frac{N(s)}{D(s)} \quad \text{with} \quad N \in \mathcal{P}^{n-1}, D \in \mathcal{P}^{n}$$

where $n = dim(A)$.

In fact

$$\hat{\phi}(s) = C\,(sI - A)^{-1}\,B = C\frac{adj(sI - A)}{det(sI - A)}B$$

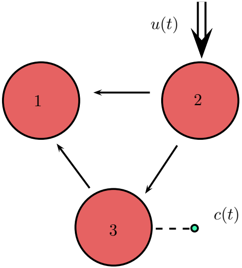
and $adj(A) = \sum_{k=0}^{n-1} R_k s^k$

Theorem (sufficient conditions 1)

If the equation of the numerator and denominator have a (unique) solution, then the system (A, B, C) is (uniquely) identifiable.

Theorem (sufficient conditions 2)

If the equations $\phi^{(k)}(0) = CA^k B, \;$ for $k = 0, \ldots, n-1$ have a (unique) solution and the denominator is never null, then the system (A, B, C) is (uniquely) identifiable.



Example: the system

$$A = \begin{pmatrix} 0 & k_1 & k_3 \\ 0 & -(k_1 + k_2) & 0 \\ 0 & k_2 & 0 \end{pmatrix},$$

$$B = (0, 1, 0), C = (0, 0, 1/V_3)$$

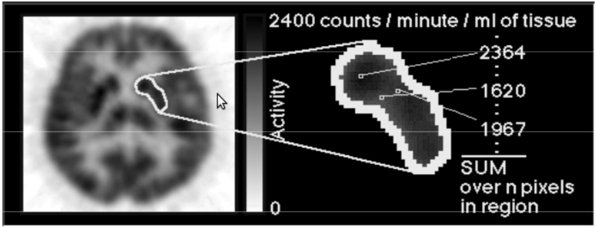
is identifiable, not uniquely.

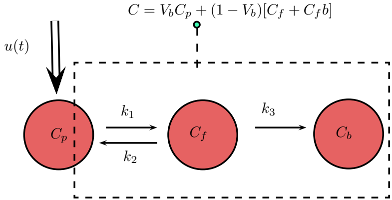
Identification can be made using the results of the two sufficient conditions, but such techniques has revealed to be numerically inaccurate. So the calculation of the parameters is given by a (weighted) nonlinear least squares method.

$$A = \arg\min ||y - y_A||^2 = ||y - \phi_A * u||^2 =$$

$$= ||y - (C \, \exp(tA) \, B) * u||^2$$

The Sokoloff model (1970s) is the main model studying the kinetics of the tracer ^{18}FdG in the brain. It uses a sequence of PET reconstructed images as input.





The model is the following

$$A = \begin{pmatrix} -k_1 & k_2 & 0 \\ k_1 & -(k_2 + k_3) & 0 \\ 0 & k_3 & 0 \end{pmatrix},$$

$$B = (1, 0, 0),$$

$$C = (V_b, 1 - V_b, 1 - V_b).$$

Is this model identifiable?

$$det(sI - A) = s^3 + (k_1 + k_2 + k_3)s^2 - k_1 k_2$$

$$C\ adj(sI - A)\ B = V_b s^2 + (V_b k_1 + k_2)s.$$

Is this model identifiable?

$$det(sI - A) = s^3 + (k_1 + k_2 + k_3)s^2 - k_1 k_2$$
$$C\ adj(sI - A)\ B = V_b s^2 + (V_b k_1 + k_2)s.$$

Answer: yes it is.

From the values k_1, k_2, k_3 we can compute the value of the local glucose metabolism

$$MR = K\frac{\hat{C}_p}{LP}$$

where with this model $K = \frac{k_1 k_3}{k_2+k_3}$, $\hat{C}_p$ is concentration of glucose in the plasma (in stationary state) and LP is the lumped constant.

Essential bibliography

- Anderson D.H, *Compartmental Modeling and Tracer Kinetics*, Springer Berlin Heidelberg, 1983.
- Carson R. E. , Herscovitch P., Daube-Witherspoon M. E. *Quantitative Functional Brain Imaging with Positron Emission Tomography*, Academic Press, 1998
- Cobelli C., Carson E., *Introduction to modeling in physiology and medicine*, AP, 2008
- Cobelli C., Foster D., Toffolo G. *Tracer kinetics in biomedical research*, Springer, 2001.
- Juweid M. E., Hoekstra O. S., *Positron Emission Tomography*, Humana Press, 2011.