PET kinetic course

Basic Mathematics

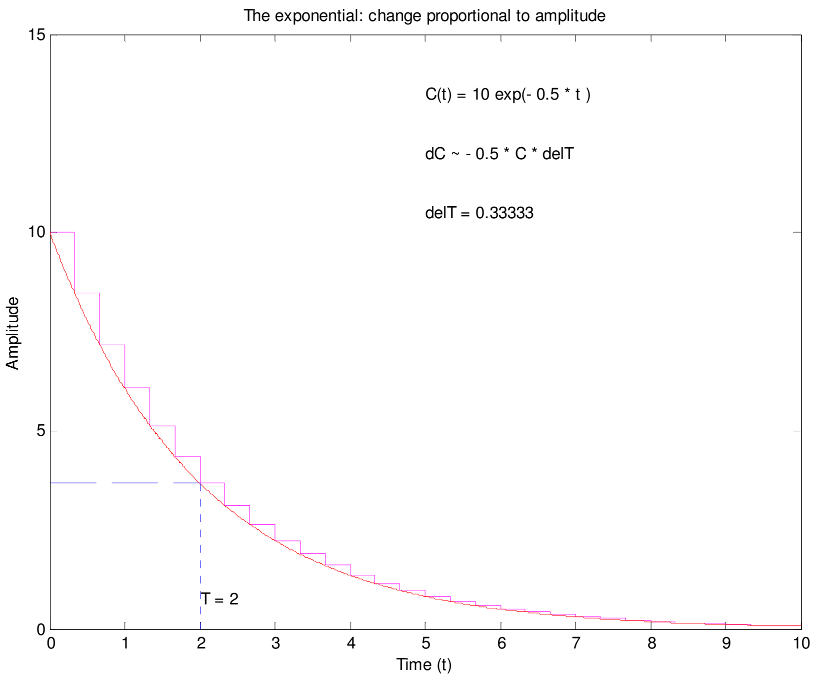
- **Exponential function**
- **Differential equation**
- **Integral**
- **Convolution**
- **Fitted parameters**
- **Definitions and abbreviations**

Exponential function

Definition:

The exponential function is normally written as: $N(t) = K\exp(at)$

- t – time
- a – exponential constant



Differentiation: $$\frac{\partial N(t)}{\partial t} = Ka \bullet \exp(at)$$

other rules: $$t = \frac{\ln(N(t)/K)}{a}$$

Half-time:

In many cases we want to find the rateconstant *a*. This can be done e.g. by identifying the half-time and using the equations as:

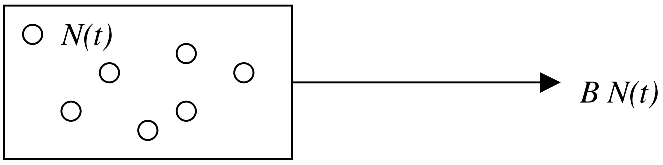
$$1/2 \bullet K = K\exp(at_{1/2)})$$
$$\Updownarrow$$
$$\ln(1/2) = at_{1/2}$$
$$\Updownarrow$$
$$a = \frac{\ln(1/2)}{t_{1/2}} \approx \frac{-0.6931}{t_{1/2}}$$

Differential equation

Definition:

The simplest differential equation has the form:

$$\frac{\partial N(t)}{\partial t} = BN(t)$$

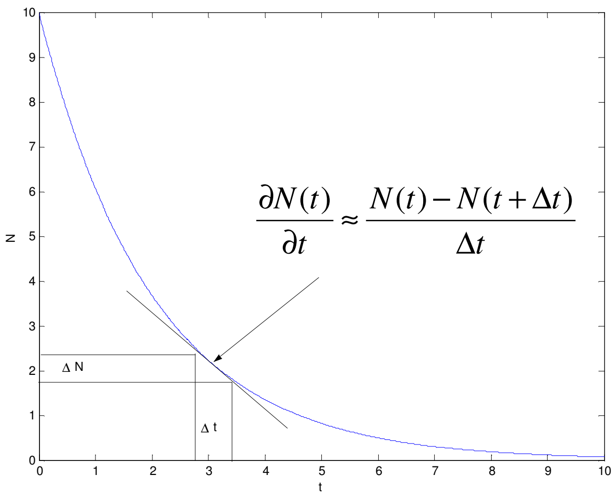


By solving the equation be can find out how the system *N(t)* behaves. We guess that the exponential equation is a solution and therefor fill in the equations from the previous page as:

$$Ka\exp(at) = BK\exp(at)$$
$$\Updownarrow$$
$$B = a$$

From this we can see that *B=a* the exponential equation defined at the previous page is a solution.

- $\frac{\partial N(t)}{\partial t}$ - Term "differential" references to the small difference in time (dt) assumed



Integral (area under the curve)

We have a function *f(t)*. We then define the integral function of *f(t)* to be *F(t)*. *F(t)* fulfills the following:

$$\frac{\partial F(t)}{\partial t} = f(t)$$

Further, we can write the integral of the function *f(t)* as:

$$\int_{t=t_0}^{t_1} f(t)\partial t = F(t_1) - F(t_0)$$

this is called the **area under the curve** as will be seen in the example

As an example we can look at the exponential function again. For this function we have:

$$f(t) = K\exp(at)$$
$$F(t) = K/a\exp(at)$$

We can show that this is true by differentiating *F(t)*:

$$\frac{\partial F(t)}{\partial t} = \frac{\partial (K/a\exp(at))}{\partial t} = K/a\frac{\partial \exp(at)}{\partial t} = K/a \bullet a\exp(at) = K\exp(at) = f(t)$$

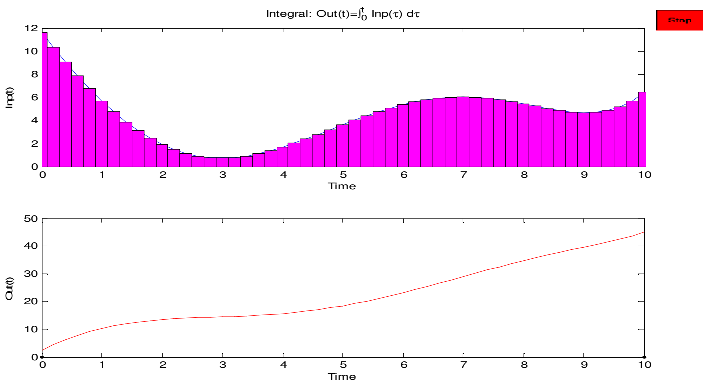
For the exponential function we can then compute the area *A* under the curve as:

$$A = \int_{t=t_0}^{t_1} f(t)\partial t = F(t_1) - F(t_0) = K/a\left[\exp(at_1) - \exp(at_0)\right]$$

Using the discrete approximation we can see why it is called area under the curve as this can be written as:

$$A = \sum_{t=t_0}^{t_1} f(t)\Delta t$$

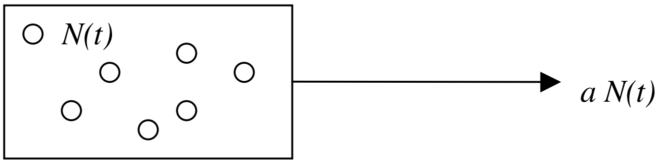
This is also called numerical integration and it can be used as an approximation for all function, also the functions where you don't know *f(t)* and therefor need to use an approximation, as can be seen in this example (upper curve – *f(t)*, lower curve – *F(t)*):



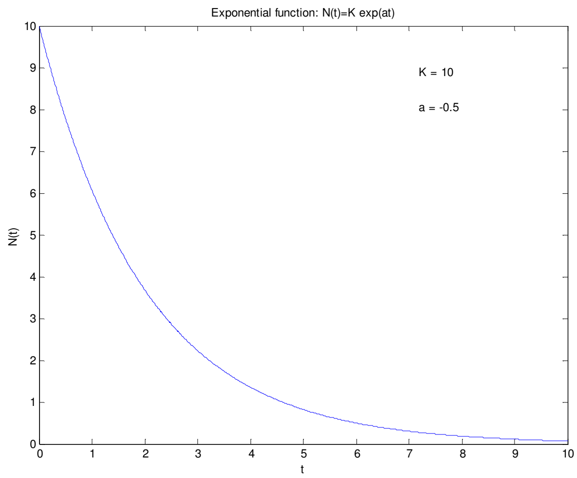
Convolution

Convolution we will go through using a simple example. This of course could also take more complicated forms which could be found in mathematics books.

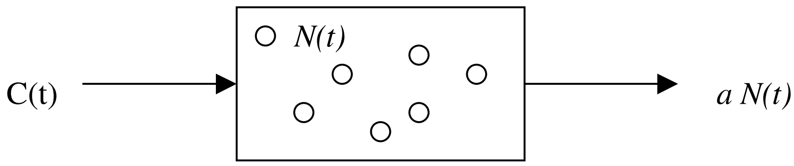
We take the example from previous pages with a system like:



where we saw the solution could be written as $N(t) = K\exp(at)$. From this it is seen that $K = N(0)$. The solution for ($K = 10$, $a = -0.5$) looks like:



A more realistic system for our purpose is a system with an inflow *C(t)* and an outflow *aN(t)* as:

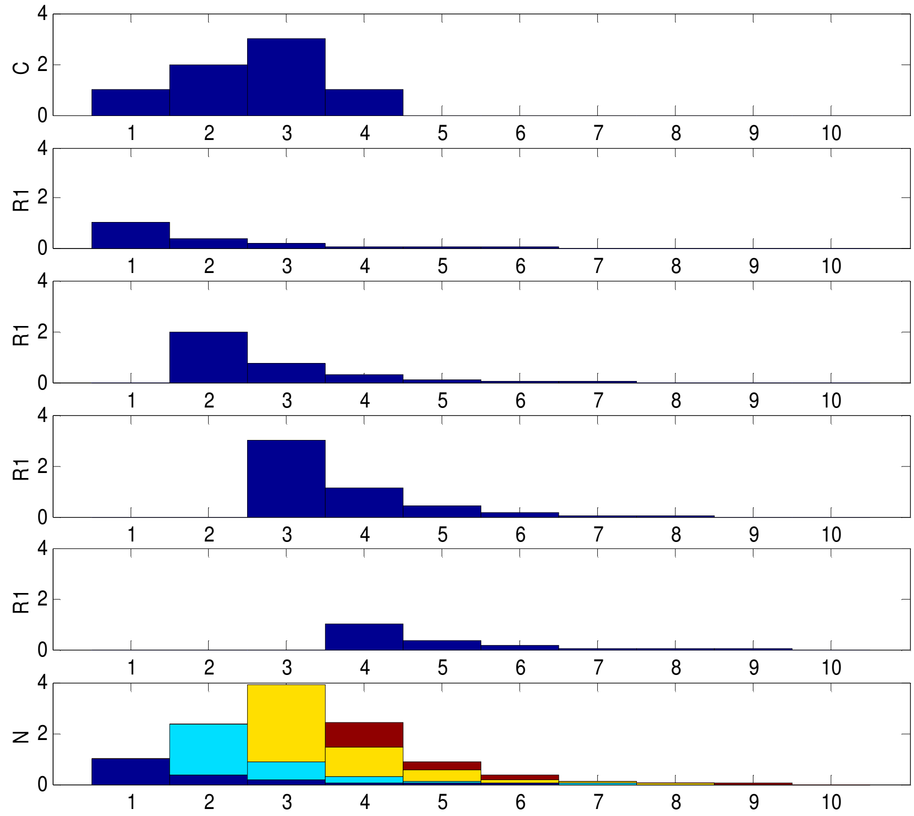


The only change from the previous example is that we have a flow into the system *C(t)*. The rest of the system is then behaving as before. We therefor have the following differential equation describing the system:

$$\frac{\partial N(t)}{\partial t} = aN(t) + C(t)$$

The solution to this differential equation is dependent of the form of the inflow *C(t)*.

To get an understanding of how this system behaves, we are discretizing the example. For each time step t=0, 1, 2, 3, 4 we have a flow into the system which could be found as $C(t)\Delta T$ (ΔT is the length of each time step). This means that for each discrete time *t* this amount is equal to *N(t)*. The flow out of the system is described by the differential equation with the exponential function as the solution, therefor we could simulate the system as sketched in this figure:



The upper curve is the discrete input function *C(t)*. The next four curves show the system response (a discrete exponential function, exp(-0.5t)) to the inflow in each time interval t=0, 1, 2, … $N(t) = C(t)\Delta T$. The lower curve shows the outflow from the system. This kind of calculation is called a **convolution** of the input signal (upper curve) and the response function (the following four curves).

As indicated in the plot the discrete convolution for this simple example can be written as:

$$N(t) = \sum_{\tau=0}^{t} (I(\tau)\Delta T) K \exp(a(t-\tau)) = \sum_{\tau=0}^{t} I(\tau) K \exp(a(t-\tau))\Delta T$$

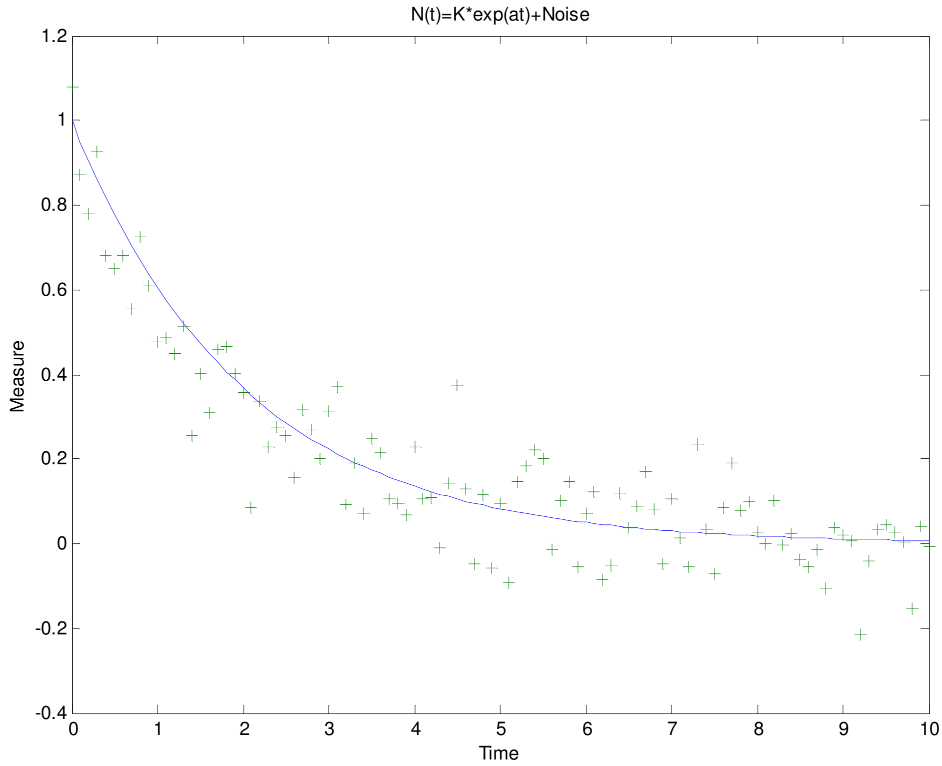
In the continuos case this can rewritten as:

$$N(t) = \int_{\tau=0}^{t} I(\tau) K \exp(a(t-\tau)) \partial\tau$$

The *I(t)* is the in most cases the unknown input function (it can be measured, but not described exactly by an equation). Therefor it is for most cases impossible to find the exact solution for this differential equation and instead numerical integration could be used for identifying the area under the curve.

Fitting parameters to an equation

In this case we have a set of measurements that we want to describe by an equation e.g. a exponential function. We have a set of measurements like shown by the "+"s:



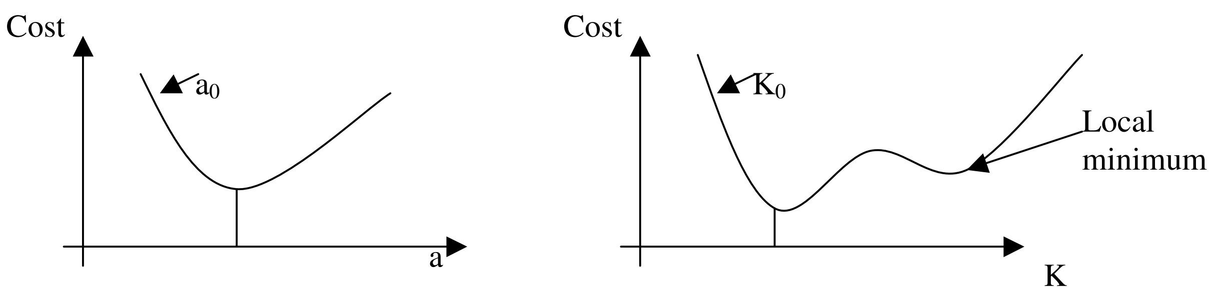
A good guess will be that the data follows a single exponential function. like:

$$\hat{N}(t) = \hat{K}\exp(\hat{a}t)$$

The unknown parameters *K* and *a* that should be estimated from the data. We then have to define a cost-function that tells how well the function described by the parameters, fits to the measured data *N(t).* A often used cost-function is the squared error between measurement and model output, described by the following equation:

$$Cost = \frac{1}{T}\sum_{t=0}^{T}(\hat{N}(t) - N(t))^2 = \frac{1}{T}\sum_{t=0}^{T}(\hat{K}\exp(\hat{a}t) - N(t))^2$$

The cost-function has a dependency of both parameters *K* and *a*. We don't know how the cost-function dependency of the parameters looks like, but it could be like:



What we are searching for is the minimum for the cost-function, where the model output follows the measurements best. As the graphs indicate a way to approach that will be to take a step in the opposite direction of the gradient of the cost-function. There is though a chance that the parameters will be caught in a local minimum as indicated in the right graph. First, we have to calculate the 1st order derivative of the cost-function with regard to the two parameters. These can be calculated as (using the rule of partial differentiation):

$$\frac{\partial Cost}{\partial \hat{a}} = \frac{1}{T}\sum_{t=0}^{T} 2(\hat{K}\exp(\hat{a}t) - N(t))\hat{K}\exp(\hat{a}t)t$$

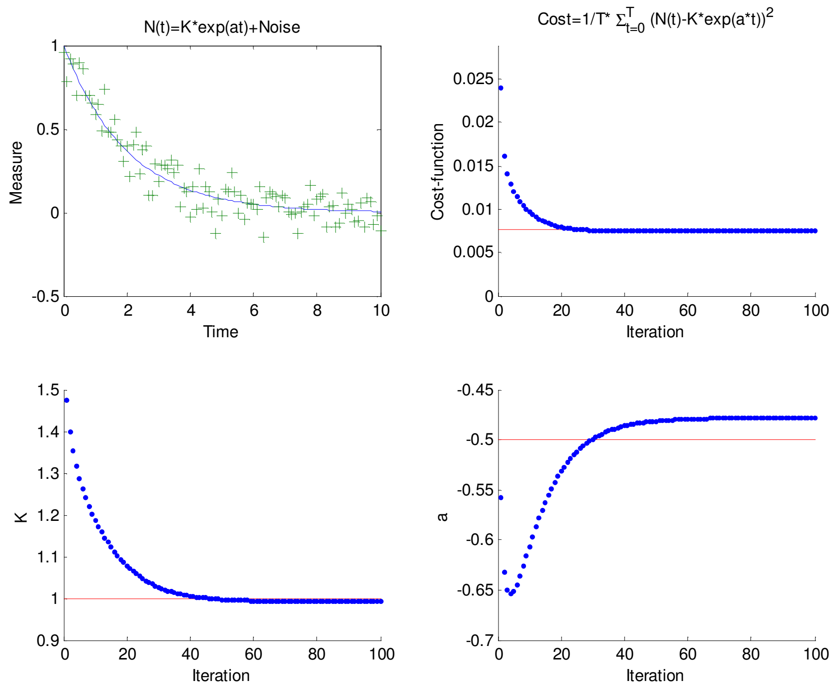
$$\frac{\partial Cost}{\partial \hat{K}} = \frac{1}{T}\sum_{t=0}^{T} 2(\hat{K}\exp(\hat{a}t) - N(t))\exp(\hat{a}t)$$

Using these two equations for calculating the gradient, we then are able to take a small step in the opposite direction for each parameter. This can be done iteratively so we calculate the gradients, take a small step, calculate the gradient, take a small step, and so on. until the cost-function doesn't decrease anymore. By using this approach the parameters can then iteratively be estimated:

$$K_{n+1} = \lambda\frac{\partial Cost}{\partial K_n} + K_n$$

$$a_{n+1} = \lambda\frac{\partial Cost}{\partial a_n} + a_n$$

For the simple example an iteratively learning scheme for the parameters *K* and *a* could look like:



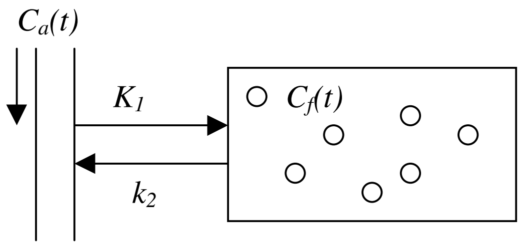
From the curves (upper right) it is seen that the cost-function is minimized iteratively. The lower two curves shows that the parameters is approached (the continuos lines) but there is an offset error. This is due to the measurement noise.

Definitions and Abbreviations

One tissue compartmental model (sometimes called two compartment model)

Definition:

In a one tissue compartment model there is one compartment with free ligand like sketched here:



Where $C_a(t)$ is the concentration of tracer in blood , $C_f(t)$ is the concentration of free (unbound) tracer in brain tissue, and K_1 and k_2 are the two rateconstants for the system. The differential equation for this system could be written as:

$$\frac{\partial C_f(t)}{\partial t} = K_1 C_a(t) - k_2 C_f(t)$$

and the simple solution for this is:

$$C_f(t) = K_1 \exp(-k_2 t) \otimes C_a(t)$$

In a scanner what is measured is $C_i(t)$ a combination of $C_f(t)$ and $C_a(t)$. This is normally written as:

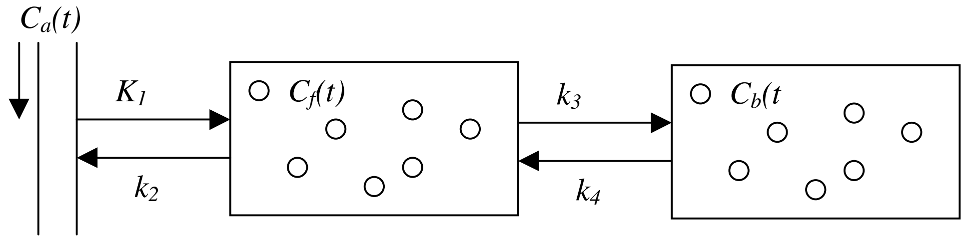
$$C_i(t) = V_b C_a(t) + (1 - V_b) C_f(t)$$

where V_b is the blood volume part of each brain measurement.

Two tissue compartmental model (sometimes called three compartment model)

Definition:

This is the extension to the one tissue compartment model with an extra bound tissue compartment. This can be sketched as:



where $C_a(t)$, $C_f(t)$, K_1 and k_2 are defined as before. $C_b(t)$ is then the concentration of the bound tracer in brain tissue, and k_3 and k_4 are the two rateconstants for the binding system. The differential equation for this system could be written as:

$$\frac{\partial C_f(t)}{\partial t} = K_1 C_a(t) - k_2 C_f(t) - k_3 C_f(t) + k_4 C_b(t)$$
$$\frac{\partial C_b(t)}{\partial t} = k_3 C_f(t) - k_4 C_b(t)$$

A general solution for these equations is not simple to find. If we could simplify the equations a bit by assuming that k_4 is zero, as is the case for e.g. the tracer FDG we can find a simple solution:

$$C_f(t) = K_1 \exp(-(k_2 + k_3)t) \otimes C_a(t)$$
$$C_b(t) = \frac{K_1 k_3}{(k_2 + k_3)} \left[1 - \exp(-(k_2 + k_3)t) \otimes C_a(t)\right]$$

In a scanner what is measured is $C_i(t)$ a combination of $C_f(t)$, $C_b(t)$, and $C_a t)$. This is normally written as:

$$C_i(t) = V_b C_a(t) + (1 - V_b)(C_f(t) + Cb(t))$$

where V_b is the blood volume part.

Abbreviations

Extraction: $E = \frac{C_a(t) - C_v(t)}{C_a(t)}$**,** where $C_a(t)$ is concentration in incoming substance and $C_v(t)$ is concentration in outgoing substance.