

Generic solution of TK models

One-compartment TK model with accumulation, depuration and biotransformation

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Introduction

In this document, we consider a very generic one-compartment model with several exposure sources (e.g., by water, sediment and/or food), several elimination processes (e.g., direct elimination, dilution by growth and/or biotransformation) and several metabolites of the parent chemical compound.

In theory, the exposure concentration may be variable over time, but in this case, there is no analytical solution of the TK model; only a numerical solution can be calculated with an appropriate algorithm. This document then assumes a constant exposure concentration for all exposure sources and provides the corresponding exact solution of the one-compartment TK model.

Symbols

Symbol	Meaning
I	total number of exposure sources
J	total number of elimination processes
L	total number of metabolites
i	index of exposure sources, $i = 1 \dots I$
j	index of elimination processes, $j = 1 \dots J$
ℓ	index of metabolites, $\ell = 1 \dots L$
t	time (expressed in time units)
c_i	exposure concentration of route i (in $\mu g.mL^{-1}$)
$C_p(t)$	internal concentration of the parent compound at time t (in $\mu g.g^{-1}$)
$C_{m_\ell}(t)$	internal concentration of metabolite ℓ at time t (in $\mu g.g^{-1}$)
k_{u_i}	uptake rate of exposure source i (expressed per time units)
k_{e_j}	elimination rates of elimination process j (expressed per time units)
k_{e_ℓ}	elimination rates of metabolite ℓ (expressed per time units)
k_{m_ℓ}	metabolization rate of metabolite ℓ (expressed per time units)
t_c	duration of the accumulation phase

General notations

Letter	Meaning (when possible)
$U = \sum_{i=1}^I k_{u_i} c_i$	sum of all uptake terms
$E = \sum_{j=1}^J k_{e_j}$	sum of all elimination terms for the parent compound
$M = \sum_{\ell=1}^L k_{m_\ell}$	sum of all elimination terms for metabolite ℓ

Intermediate notations

Letter	Meaning (when possible)
$R = \frac{U}{E+M}$	
$D_\ell = k_{e_\ell} - (E + M) \quad \forall \ell = 1 \dots L$	
$Q = C_0 - R(1 - e^{(E+M)t_c})$	

Accumulation phase ($0 \leq t \leq t_c$)

System of ordinary differential equations

For the accumulation phase, the system of ordinary differential equations (ODE) can be written in two generic accumulation equations (AE) as follows:

$$\begin{cases} \frac{dC_p(t)}{dt} = U - (E + M)C_p(t) & (AE_1) \\ \frac{dC_{m_\ell}(t)}{dt} = k_{m_\ell}C_p(t) - k_{e_\ell}C_{m_\ell}(t) \quad \forall \ell = 1 \dots M & (AE_2) \end{cases}$$

Solution for the parent compound (eq. AE_1)

Equation (AE_1) is a linear first ODE with constant coefficient and a second member admitting $C_{part}(t) = \frac{U}{E+M} = R$ as a particular solution.

The solution of (AE_1) without the second member writes:

$$C_p(t) = Ke^{-(E+M)t} \text{ with } K \in \mathbb{R}^+$$

leading to the following general solution for equation (AE_1):

$$C_p(t) = Ke^{-(E+M)t} + R \text{ with } K \in \mathbb{R}^+$$

From the initial condition $C(t=0) = C_0$ ($C_0 \geq 0$), we finally get the expression of the internal concentration of the parent compound for the accumulation phase:

$$C_p(t) = (C_0 - R)e^{-(E+M)t} + R \quad (AS_1)$$

Solution for metabolite ℓ (eq. AE_2)

Equation (AE_2) is also a linear first ODE with constant coefficients and a second member.

The solution of (AE_2) without the second member writes:

$$C_{m_\ell}(t) = Ke^{-k_{e_\ell}t} \text{ with } K \in \mathbb{R}^+$$

The method known as variation of constants consists of writing the general solution of (AE_2) as:

$$C_{m_\ell}(t) = K(t)e^{-k_{e_\ell}t}$$

and to find function $K(t)$, by deriving and re-injecting the result into (AE_2) . The derivative writes:

$$\frac{dC_{m_\ell}(t)}{dt} = \frac{dK(t)}{dt} e^{-k_{e_\ell} t} - K(t) k_{e_\ell} e^{-k_{e_\ell} t}$$

The re-injection into (AE_2) leads to:

$$\frac{dK(t)}{dt} = k_{m_\ell} ((C_0 - R)e^{D_\ell t} + R e^{k_{e_\ell} t})$$

which integrates into:

$$K(t) = k_{m_\ell} \left(\frac{C_0 - R}{D_\ell} e^{D_\ell t} + \frac{R}{k_{e_\ell}} e^{k_{e_\ell} t} \right) + C \text{ with } C \in \mathbb{R}$$

The general solution of (AE_2) finally writes as follows:

$$C_{m_\ell}(t) = k_{m_\ell} \left(\frac{C_0 - R}{D_\ell} e^{-(E+M)t} + \frac{R}{k_{e_\ell}} \right) + C e^{-k_{e_\ell} t} \text{ with } C \in \mathbb{R}$$

From the initial condition $C_{m_\ell}(t=0) = 0$, we finally get the expression of the internal concentration of metabolite ℓ for the accumulation phase:

$$C_{m_\ell}(t) = k_{m_\ell} \left(\frac{C_0 - R}{D_\ell} \left(e^{-(E+M)t} - e^{-k_{e_\ell} t} \right) + \frac{R}{k_{e_\ell}} \left(1 - e^{-k_{e_\ell} t} \right) \right) \quad (AS_2)$$

Depuration phase ($t > t_c$)

System of ordinary differential equations

For the depuration phase, the system of ODE can be written in two generic depuration equations (DE) as follows:

$$\begin{cases} \frac{dC_p(t)}{dt} = -(E+M)C_p(t) & (DE_1) \\ \frac{dC_{m_\ell}(t)}{dt} = k_{m_\ell} C_p(t) - k_{e_\ell} C_{m_\ell}(t) \quad \forall \ell = 1 \dots M & (DE_2) \end{cases}$$

Solution for the parent compound (eq. DE_1)

Equation (DE_1) has a general solution of the following form:

$$C_p(t) = K e^{-(E+M)t}$$

For the depuration phase and the parent compound, the initial condition comes the calculation of the internal parent compound concentration at the end of the accumulation (*i.e.*, $t = t_c$) from solution (AS_1) , that is:

$$C_p(t_c) = (C_0 - R) e^{-(E+M)t_c} + R$$

From the general solution of (DE_1) , we get $C_p(t_c) = K e^{-(E+M)t_c}$ leading to:

$$K = C_0 - R + R e^{(E+M)t_c}$$

Then, the final expression of the internal concentration of the parent compound for the depuration phase writes:

$$C_p(t) = \left(C_0 - R \left(1 - e^{(E+M)t_c} \right) \right) e^{-(E+M)t} \quad (DS_1)$$

Solution for metabolite ℓ (eq. DE_2)

Temporarily, solution (DS_1) above can be written as $C_p(t) = Qe^{-(E+M)t}$ with constant Q defined at the beginning of the document.

Equation (DE_2) is a linear ODE of first order with constant coefficients and a second member.

The solution of the equation without the second member writes:

$$C_{m_\ell}(t) = Ke^{-k_{e_\ell}t}$$

As earlier, we use the variation of constants method by writing the general solution of (DE_2) as $C_{m_\ell}(t) = K(t)e^{-k_{e_\ell}t}$ and searching for function $K(t)$.

The derivative of $C_{m_\ell}(t)$ is $\frac{dK(t)}{dt}e^{-k_{e_\ell}t} - k_{e_\ell}K(t)e^{-k_{e_\ell}t}$.

The re-injection of this derivative into (DE_2) leads to:

$$\frac{dK(t)}{dt} = k_{m_\ell}Qe^{D_\ell t}$$

which integrates into:

$$K(t) = k_{m_\ell} \frac{Q}{D_\ell} e^{D_\ell t} + C \text{ with } C \in \mathbb{R}$$

finally leading to the general solution of (DE_2):

$$C_{m_\ell}(t) = k_{m_\ell} \frac{Q}{D_\ell} e^{-(E+M)t} + Ce^{-k_{e_\ell}t}$$

Constant C is determined with the initial condition, i.e., the internal concentration of metabolite ℓ at $t = t_c$ both at the end of the accumulation phase and at the beginning of the depuration phase.

From the previous equation, we get $C_{m_\ell}(t_c) = k_{m_\ell} \frac{Q}{D_\ell} e^{-(E+M)t_c} + Ce^{-k_{e_\ell}t_c}$.

From solution (AS_2), we get $C_{m_\ell}(t_c) = k_{m_\ell} \left(\frac{C_0 - R}{D_\ell} (e^{-(E+M)t_c} - e^{-k_{e_\ell}t_c}) + \frac{R}{k_{e_\ell}} (1 - e^{-k_{e_\ell}t_c}) \right)$.

We finally get the following expression for constant C :

$$C = k_{m_\ell} \left(\frac{R}{k_{e_\ell}} (e^{k_{e_\ell}t_c} - 1) - \frac{C_0 - R}{D_\ell} - \frac{R}{D_\ell} e^{k_{e_\ell}t_c} \right)$$

Replacing constant C gives the final expression of the internal concentration of metabolite ℓ for the depuration phase:

$$C_{m_\ell}(t) = k_{m_\ell} \left(\frac{Q}{D_\ell} e^{-(E+M)t} + \frac{R}{k_{e_\ell}} (e^{-k_{e_\ell}(t-t_c)} - e^{-k_{e_\ell}t}) - \frac{C_0 - R}{D_\ell} e^{-k_{e_\ell}t} - \frac{R}{D_\ell} e^{-k_{e_\ell}(t-t_c)} \right)$$

Replacing constant Q by its own expression gives:

$$C_{m_\ell}(t) = k_{m_\ell} \left(\frac{C_0 - R}{D_\ell} (e^{-(E+M)t} - e^{-k_{e_\ell}t}) + \frac{R}{k_{e_\ell}} (e^{-k_{e_\ell}(t-t_c)} - e^{-k_{e_\ell}t}) + \frac{R}{D_\ell} (e^{-(E+M)(t-t_c)} - e^{-k_{e_\ell}(t-t_c)}) \right) \quad (DS_2)$$

Final set of solutions for both phases

Reminding the following intermediate notations $R = \frac{U}{E+M}$ and $D_\ell = k_{e_\ell} - (E + M)$ we can obtain the final set of solutions for both phases:

- Internal concentration of the parent compound for the accumulation phase:

$$C_p(t) = \left(C_0 - \frac{U}{E+M} \right) e^{-(E+M)t} + \frac{U}{E+M} \quad (AS_1) \quad \forall 0 \leq t \leq t_c$$

- Internal concentration of metabolite ℓ for the accumulation phase:

$$C_{m_\ell}(t) = \frac{k_{m_\ell}}{k_{e_\ell}} \frac{U}{E+M} (1 - e^{-k_{e_\ell}t}) + \frac{k_{m_\ell}}{k_{e_\ell} - (E+M)} \left(C_0 - \frac{U}{E+M} \right) (e^{-(E+M)t} - e^{-k_{e_\ell}t}) \quad (AS_2)$$

- Internal concentration of the parent compound for the deuration phase writes:

$$C_p(t) = \left(C_0 - \frac{U}{E+M} (1 - e^{-(E+M)t_c}) \right) e^{-(E+M)t} \quad (DS_1) \quad \forall t > t_c$$

- Internal concentration of metabolite ℓ for the deuration phase:

$$\begin{aligned} C_{m_\ell}(t) &= \frac{k_{m_\ell}}{k_{e_\ell} - (E+M)} \left(C_0 - \frac{U}{E+M} \right) (e^{-(E+M)t} - e^{-k_{e_\ell}t}) \\ &+ \frac{k_{m_\ell}}{k_{e_\ell}} \frac{U}{E+M} (e^{-k_{e_\ell}(t-t_c)} - e^{-k_{e_\ell}t}) \\ &+ \frac{k_{m_\ell}}{k_{e_\ell} - (E+M)} \frac{U}{E+M} (e^{-(E+M)(t-t_c)} - e^{-k_{e_\ell}(t-t_c)}) \end{aligned} \quad (DS_2) \quad \forall t > t_c$$

In the end, we could replace constants U , E and M by $U = \sum_{i=1}^I k_{u_i} c_i$, $E = \sum_{j=1}^J k_{e_j}$ and $M = \sum_{\ell=1}^L k_{m_\ell}$, respectively, in order to write the very final set of solutions with all the parameters to estimate from observed data using an inference process.