A library of parent – metabolite models for the MonolixSuite

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MODULAR PARENT – METABOLITE (PM) LIBRARY

Global					Parent		Metabolite	
Administration	First Pass Effect	Delay	Absorption	Transformation	Distribution	Elimination	Distribution	Elimination
Bolus	No first pass effect	No delay	Zero order	Uni-directional	1 compartment	Linear	1 compartment	Linear
Infusion	With dose apportionment	Lag time	First order	Bi-directional	2 compartments	Michaelis-Menten	2 compartments	Michaelis-Menten
Oral	Without dose apportionment	Transit compartments			3 compartments		3 compartments	
Oral + Bolus								

Accessible

Ready to use large combination of models integrated in MonolixSuite 2021 with modular filters - a simple workflow to help you test many different hypothesis.

Flexible

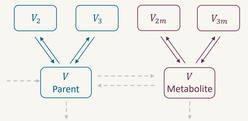
Editable models written with the Mlxtran macros and compatible with joint and intermediate approach - adapt the modeling process to your needs with minimal effort.

Efficient

Faster calculations thanks to the analytical solutions - boost your analysis and productivity.

DISTRIBUTION & ELIMINATION & TRANSFORMATION

Parent		Metabolite	
Distribution	Elimination	Distribution	Elimination
1 compartment	Linear	1 compartment	Linear
2 compartments	Michaelis-Menten	2 compartments	Michaelis-Menten
3 compartments		3 compartments	



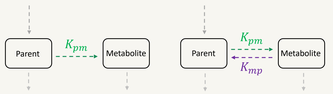
- The same volume of the central compartment for parent and metabolite (identifiability issue when only parent drug is administered)
- Independent number of compartments and elimination process
- Linear and non-linear (Michaelis – Menten) elimination

PARAMETRIZATION

With exchange rates:
- k12, k21 (k13, k31) for parent and k12m, k21m (k13m, k31m) for metabolite for the second (third) compartment
- Volume of central compartment is V
- Elimination: k, km (linear) ; Vm, Km for parent and Vmm, Kmm for metabolite (non-linear)

With inter – compartment clearance:
- Q2, V2 (Q3, V3) for parent and Q2m, V2m (Q3m, V3m) for metabolite for the second (third) compartment
- volume of central compartments is V1 to be compatible with the PK models in case of sequential or intermediate model development
- Elimination: Cl, Clm (linear) ; Vm, Km for parent and Vmm, Kmm for metabolite (non-linear)

PARENT – METABOLITE TRANSFORMATION



Uni-directional

Bi-directional

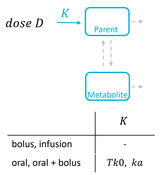
- Kpm – transformation rate from parent to metabolite
- Kmp – transformation rate from metabolite to parent

ADMINISTRATION & ABSORPTION

Intravenous (bolus, infusion):
- No First Pass Effect (administration only to the central compartment)
- time delay (Tlag)

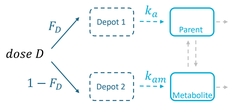
Oral:
- With or without the First Pass Effect
- Zero (Tk0, Tk0m) or First order absorption (ka, kam)
- Time delay (Tlag) or transit compartments (Mtt, Ktr)
- Oral + bolus: bioavailability F

Without First Pass effect



First Pass Effect

With Dose Apportionment

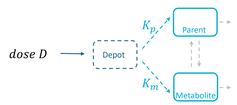


$$\begin{cases} \frac{dA_{d1}}{dt} = -k_a \cdot A_{d1} + \cdots, & A_{d1}(0) = D \cdot F_D \\ \frac{dA_P}{dt} = k_a \cdot A_{d1}, + \cdots, & A_P(0) = 0 \\ \frac{dA_{d2}}{dt} = -k_{am} \cdot A_{d2} + \cdots, & A_{d2}(0) = D \cdot (1 - F_D) \\ \frac{dA_M}{dt} = k_{am} \cdot A_{d2}, + \cdots, & A_M(0) = 0 \end{cases}$$

$$A_P(t) = D \cdot F_D \cdot \left(1 - e^{-k_a \cdot t}\right) \ldots$$

$$A_M(t) = D \cdot (1 - F_D) \cdot \left(1 - e^{-k_{am} \cdot t}\right) \ldots$$

Without Dose Apportionment



$$\begin{cases} \frac{dA_d}{dt} = -(k_a + k_{am}) \cdot A_d + \cdots, & A_d(0) = D \\ \frac{dA_P}{dt} = k_a \cdot A_d + \cdots, & A_P(0) = 0 \\ \frac{dA_M}{dt} = k_{am} \cdot A_d + \cdots, & A_M(0) = 0 \end{cases}$$

$$A_P(t) = D \cdot \frac{k_a}{k_a + k_{am}} \cdot \left(1 - e^{-(k_a + k_{am}) \cdot t}\right) \ldots$$

$$A_M(t) = D \cdot \frac{k_{am}}{k_a + k_{am}} \cdot \left(1 - e^{-(k_a + k_{am}) \cdot t}\right) \ldots$$

The above formulas assume the first order absorption process. In case of zero order absorption, the absorption rates k_a, k_{am} are replaced with absorption times T_{k0}, T_{k0m}.

FIRST PASS EFFECT

- Occurs when a drug undergoes a biotransformation – for example transformation of parent to metabolite before reaching its site of action or the systemic circulation.
- Can be clinically relevant when the metabolized fraction is high or when it varies significantly from individual to individual or within the same individual over time → variable or erratic absorption.

ANALYTICAL SOLUTIONS

Parent – metabolite models in the Monolix library are implemented with Mlxtran macros.
For example: a model with oral absorption (rate ka) of a dose D, one compartment for parent (cmt = 1) and metabolite (cmt = 2), linear elimination (rates k, km) and unidirectional transfer (rate Kpm) is given by the following set of macros:

$$\begin{cases} \frac{dC_p}{dt} = \frac{k_a \cdot D}{V} \cdot e^{-k_a t} - k \cdot C_p - K_{pm} \cdot C_p \\ \frac{dC_m}{dt} = K_{pm} \cdot C_p - k_m \cdot C_m \\ C_p(0) = 0, \; C_m(0) = 0 \end{cases}$$

Implementation with Mlxtran macros

```
; PK model definition for Parent
compartment(cmt = 1, volume = V, concentration = Cp)
oral(cmt = 1, ka)
elimination(cmt = 1, k)

; PK model definition for Metabolite
compartment(cmt = 2, volume = V, concentration = Cm)
elimination(cmt = 2, k = km)
transfer(from = 1, to = 2, kt = Kpm)
```

Implementation with Mlxtran macros allows to use analytical solutions, which

are more accurate than approximate numerical solutions

are faster than ODE solvers

Analytical solutions are available if:
- Drug is administrated to the central parent compartment only,
- Parameters are not time dependent
- Elimination is linear and only from the central compartments,
- there are no transit compartments (linear models),
- transfer between parent and metabolite is only between their central compartments,
- there are maximally two peripheral compartments for parent or for metabolite.

Comparison of the computational time (in seconds) of the parameter estimation (SAEM) using analytical solutions (AS) and numerical solutions (ODE) for models with different number of compartments:
Dataset: 100 individuals, single or multidose, 20 measurements for each observation
SAEM settings: 500 iterations for the exploratory phase, 200 for the smoothing phase

Number of cmt: Parent + metabolite	Single dose			Multidose		
	AS	ODE		AS	ODE	
1 + 1 (2dim)	27	100	**3.7**	27	130	**4.8**
2 + 1 (3dim)	48	150	**3.1**	44	180	**4**
2 + 2 (4dim)	71	210	**3.0**	66	230	**3.5**
3 + 2 (5dim)	96	260	**2.7**	91	290	**3.2**
3 + 3 (6dim)	140	310	**2.2**	130	340	**2.6**