PK/PD equations for OpenMalaria

(written by Ian Hastings)

This is the one-compartment model with drug conversion taken from the following paper:

Kay, K. and I. M. Hastings (2013). "Improving pharmacokinetic-pharmacodynamic modeling to investigate anti-infective chemotherapy with application to the current generation of antimalarial drugs." PLoS Comput Biol **9**(7): e1003151.

The construction is as follows:

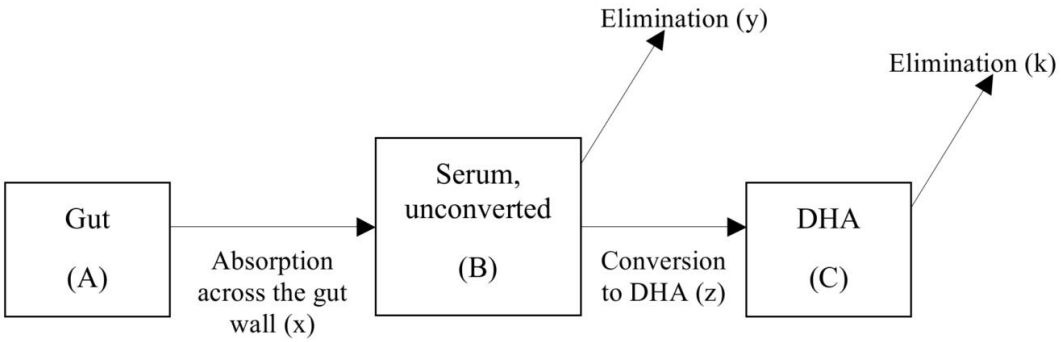

Figure 1. The standard one-compartment pharmacokinetic model. A standard PK one-compartment model allowing for absorption of a drug from the gut (component A) at rate x, into the unconverted form in the serum (component B) where it is eliminated at a rate y and converted into an active form (DHA in this example; component C) at rate z. DHA is then eliminated at rate k.
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So that setting z=0 allows us to simulate a drug that is not converted. The way in which the converted and unconverted drugs combine to kill parasites is discussed more fully in the Kay and Hastings paper. At the moment OM returns a value based on the highest kill rate of the parent and metabolites (it assumes it is an artesunate/DHA choice); just to confuse matters it returns the lowest survival fraction (rather than the highest kill rate).

Implementation in OM.

This was initially done by Diggory Hardy and herein I attmpt to re-derive and document his method as implemented in OM.

First note that the "A,B,C" nomenclature in Figure 1 has been (sensibly) replaced by Diggory as "G,P,M" as indicating gut, parent drug, metabolite.

It is likely that the same equation will be called repeatedly for the same patient so that values of x,z,y etc will remain the same and only t (i.e. time) and drug amounts at the start of the time period (e.g. p.qtyG) will vary. Diggory therefore did all the sums involving x,y,z etc once at the beginning to avoid repeatedly doing the same calculation every time that equation is invoked for the same patient. This seems eminently sensible. I have tried to document the equivalent terms on Table 1. My one concern is that we usually deals with negatives of x,y,z so we'll have to be extremely careful with addition/subtraction when re-deriving Kay and Hastings Equations 5 and 6.

(1) Calculation of gut drug concentrations over time in OpenMalaria.

There is no killing by drug of malaria parishes while in gut but we have to keep track of the amount of drug in the gut each time step as it contribute to parental drug concertation in the central compartment in the next time step. Integrating Equation 2 of Kay and Hasting is

$$A(t) = (D + A') * \exp(-t * x)$$

Noting the OM nomenclature that (Table 1)

compartment 'A' has become 'G' for gut

p.qtyG= (D+A') the quantity in the gut at time t=0

expAbsorb=exp(-xt)

then

$$G(t) = p.qtyG * \exp Absorb$$

[Equation 1]

(2) Calculation of parental drug concentrations over time in OpenMalaria.

So first try and re-derive Equation 5 from Kay and Hastings i.e.

$$B(t) = \frac{x(D + A`)}{(x - (y + z))}\left(e^{-(y+z)t} - e^{-xt}\right) + B`e^{-(y+z)t}$$ [Equation 2]

noting that:

compartment B has become compartment P

p.qtyG= (D+A') the quantity in the gut at time t=0

p.qtyP= (B') the quantity of the parent form at time t=0

-p.f=x/(x-y-z); see Table 1

So

$$P(t) = -p.f * p.qtyG(\exp Ploss - \exp Absorb) + p.qtyP * \exp Ploss$$

[Equation 3]

Get rid of the brackets…

$$P(t) = -p.f * p.qtyG * \exp Ploss - (-p.f) * p.qtyG * \exp Absorb + p.qtyP * \exp Ploss$$

[Equation 4]

Collect terms in the exponentials

$$P(t) = p.f * p.qtyG * \exp Absorb + (p.qtyP - p.f * p.qtyG) * \exp Ploss$$

[Equation 5**]**

As in the OM code.

(2) Calculation of drug metabolite concentrations over time in OpenMalaria.

Now for equation 6 of Kay and Hastings…… i.e.

$$C(t) = \left(\begin{array}{l} zx(D + A`)\left[ \frac{e^{-kt}}{(y+z-k)(x-k)} + \frac{e^{-qt}}{(k-(y+z))(x-(y+z))} + \frac{e^{-xt}}{(k-x)(y+z-x)} \right] \\ + \frac{zB`}{(y+z-k)}\left(e^{-kt} - e^{-(y+z)t}\right) \\ + C`e^{-kt} \end{array} \right) \frac{M_C}{M_B}$$

[Equation 6**]**

Where q=y+z (Equation 1.7 of SI). Diggory has used the same tactic as above i.e. collect constants into single terms and then distribute them across each of the three exponential terms. So re-write the equation noting that C(t) now become M(t) and substituting q=(y+z) and

p.qtyG= (D+A') the quantity in the gut at time t=0

p.qtyP= (B') the quantity of the parent form at time t=0

p.qtyM= (C') the quantity of the metabolite form at time t=0

First expand the terms

(there is a lot of cut-and-pasting going on so need to re-check)

$$M(t)=\left(\begin{array}{l}\left[\dfrac{z*x*p.qtyG}{(y+z-k)(x-k)}e^{-kt}+\dfrac{z*x*p.qtyG}{(k-(y+z))(x-(y+z))}e^{-(y+z)t}+\dfrac{z*x*p.qtyG}{(k-x)(y+z-x)}e^{-xt}\right] \\ +\dfrac{z*p.qtyP}{(y+z-k)}e^{-kt}-\dfrac{z*p.qtyP}{(y+z-k)}e^{-(y+z)t} \\ +p.qtyM*e^{-kt}\end{array}\right)\frac{M_C}{M_B}$$

[Equation 7]

And collecting terms in the exponentials

$$M(t)=\left(\begin{array}{l}\dfrac{z*x*p.qtyG}{(k-x)(y+z-x)}e^{-xt} \\ +(\dfrac{z*x*p.qtyG}{(k-(y+z))(x-(y+z))}-\dfrac{z*p.qtyP}{(y+z-k)})e^{-(y+z)t} \\ +(\dfrac{z*x*p.qtyG}{(y+z-k)(x-k)}+\dfrac{z*p.qtyP}{(y+z-k)}+p.qtyM)e^{-kt}\end{array}\right)\frac{M_C}{M_B}$$

[Equation 8]

And substituting the OM code names/function for the exponentials

$$M(t)=\left(\begin{array}{l}[\dfrac{z*x}{(k-x)(y+z-x)}]p.qtyG*\exp Absorb \\ +[\dfrac{z*x}{(k-y-z)(x-y-z)}p.qtyG-\dfrac{z}{(y+z-k)}*p.qtyP]\exp Ploss \\ +[\dfrac{z*x}{(y+z-k)(x-k)}*p.qtyG+\dfrac{z}{(y+z-k)}*p.qtyP+p.qtyM]\exp(p.nkM*t)\end{array}\right)\frac{M_C}{M_B}$$

[Equation 9]

So this is exactly the same structure as the OM code where p.g, p.h and p.i are substituted for the calculations in k,x,y,z. So using the symbols in Table 1, I can re-write this equation as

$$M(t) = \begin{pmatrix} p.g * p.qtyG * \exp Absorb \\ +[-p.h * p.qtyG - p.i * p.qtyP] \exp Ploss \\ \\ +[p.j * p.qtyG + p.i * p.qtyP + p.qtyM] \exp(p.nkM * t) \end{pmatrix}$$

[Equation 10]

or

$$M(t) = \begin{pmatrix} p.g * p.qtyG * \exp Absorb \\ -[p.h * p.qtyG + p.i * p.qtyP] \exp Ploss \\ \\ +[p.j * p.qtyG + p.i * p.qtyP + p.qtyM] \exp(p.nkM * t) \end{pmatrix}$$

[Equation 11]

Note that p.qtM is not scaled by mol. wt. ratio in the last term of eqn 1. I think this makes sense in the OM context. In Kay and Hasting the converted weight/concentrations were never stored so it made sense to re-weight the metabolite each calculation. In OM the quantity of metabolite is stored the previous time-step. Assuming it is stored after re-weighing for change in mol. mass then it should not be re-weighted again (IH to (i) check the preceding makes sense (ii) if so, check the OM code and confirm that it is done).

Table 1. The equivalence between Diggory's names and the nomenclature used in Kay and Hastings. Taken from Diggory's comments in his code.

Diggory's variable name	Equivalent in Kay and Hastings
nkP	-y
nconv	-z
p.nka=nka	-x
p.nkM	-k
p.n1	-(y+z)
Rz=MWR*nconv	-(MWR*z)
Leading to some new variables……	
expAbsorb=exp(p.nka*t)	e^{-xt}
expPloss=exp(p.nl*t)	$e^{-(y+z)t}$
p.f=nka/(p.n1-nka)	See below
p.g=MWR*nconv*nka/((nka-pnl)*(nka-p.nkm)))	See below
p.h=p.g*(nka-p.nkM)/(p.nkm-p.nl) =MWR*nconc*nka/[(nka-pn1)*(p.nkm-pn1)]	See below
p.i=MWR*nconv/(p.nl-p.nkM)	See below
p.j=MWR*nconv*nka/[(p.nkM-p.n1)(p.nkM-nka)]	See below

MWR=molecular weight ratio M_C/M_B which I assume is returned by the function molecular_weight_ratio

$$p.f = nka/(p.n1 - nka)$$

$$\frac{-x}{-(y+z)--x} = \frac{-x}{x-y-z}$$ [Equation 12]

or

$$-p.f = \frac{x}{x-y-z}$$

the latter by multiplying both sides by -1.

$$p.g = \frac{rz * nka}{(nka - n1) * (nka - nkM)}$$

$$= MWR\frac{-z*(-x)}{(-x-(-(y+z))*(-x-(-k))}$$ [Equation 13]

$$= MWR\frac{zx}{(-x+y+z)*(-x+k)}$$

$$= MWR\frac{zx}{(y+z-x)*(k-x)}$$

$$p.h =$$

$$MWR\frac{zx}{(y+z-x)*(k-x)}*\frac{[-x-(-k)]}{-(y+z)-(-k)}$$

$$= MWR\frac{zx}{(y+z-x)*(k-x)}*\frac{k-x}{k-y-z}$$

$$= MWR\frac{zx}{(y+z-x)*(k-y-z)}$$ [Equation 14]

$$= MWR\frac{-zx}{(x-y-z)*(k-y-z)}$$

or

$$-p.h = MWR\frac{zx}{(x-y-z)*(k-y-z)}$$

The penultimate form of p.h was by multiplying numerator and denominator by -1 and using -1 to multiply the first term of the denominator.

$$p.i = \frac{rz}{(n1 - nkM)}$$

$$MWR\frac{-z}{-(y+z)-(-k)} \quad \text{[Equation 15]}$$

$$= MWR\frac{-z}{k-(y+z)}$$

$$= MWR\frac{z}{(y+z)-k}$$

(the two alternative forms of p.i are obtained by multiplying denominator and numerator by -1)

$$p.j = \frac{rz * nka}{(nkM - n1) * (nkM - nka)}$$

$$MWR\frac{-z * -x}{[-k-(-(y+z))] * [-k-(-x)]} \quad \text{[Equation 16]}$$

$$= MWR\frac{z * x}{[-k+(y+z)](-k+x)}$$

$$= MWR\frac{zx}{(y+z-k)(x-k)}$$

Appendix 1. Katherine's Equations in R (sent by KK to IH on 8/5/15). They work so can be used to check for typos in the equation presented in Kay and Hastings and in the C++ code

```
# parent drug

startGutAmount = doseAmount[dd] * Wt # this should be a mg dose - assuming the dose is given in mg/kg, multiply by the weight to get the mg dose
startUnconvertedAmount       = 0

#parent drug amount
drugAmount = (( x*startGutAmount / (x-y-z) * (exp(-(y+z)*t )-exp(-x*t))) + (startUnconvertedAmount * exp((-(y+z)* t))))

# parent drug conc
drugConc = drugAmount / (Wt * Vd)                    # assuming Vd is in L/kg - note the denominator is equivalent to dividing by Vd (L)
```

metabolite drug

startGutAmount = doseAmount[dd] * Wt # this should be a mg dose - assuming the dose is given in mg/kg, multiply by the weight to get the mg dose

startUnconvertedAmount = 0

startDHAamount = 0

metabolite drug amount

drugAmount = (((z * x * startGutAmount)*(((exp((-k)* t))/((y+z-k)*(x-k)))+((exp(-(y+z)* t))/((k-y-z)*(x-y-z)))+ ((exp(-x* t))/((k-x)* (y+z-x))))) + (((z*startUnconvertedAmount)/(y+z-k)) * ((exp((-k)* t))-exp(-(y+z)* t))) + (startDHAamount * exp((-k)* t))) * (DHA_molecularWeight/UC_molecularWeight)

metabolite drug conc

drugConc = drugAmount / (Wt * Vd)