JAGIELLONIAN UNIVERSITY
IN KRAKOW

R for pharmacokineticists – simulation of steady-state concentrations of amiodarone in heart compartmental model as an example

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1. PK Model

State variables: D, Cc, Ht, PF

Model equations:

$$Abs = k_a \times D \times F$$

$$\frac{dCc}{dt} = Abs + k_{ht\_out} \times Ht - k_e \times Cc - k_{ht_{in}} \times Ht$$

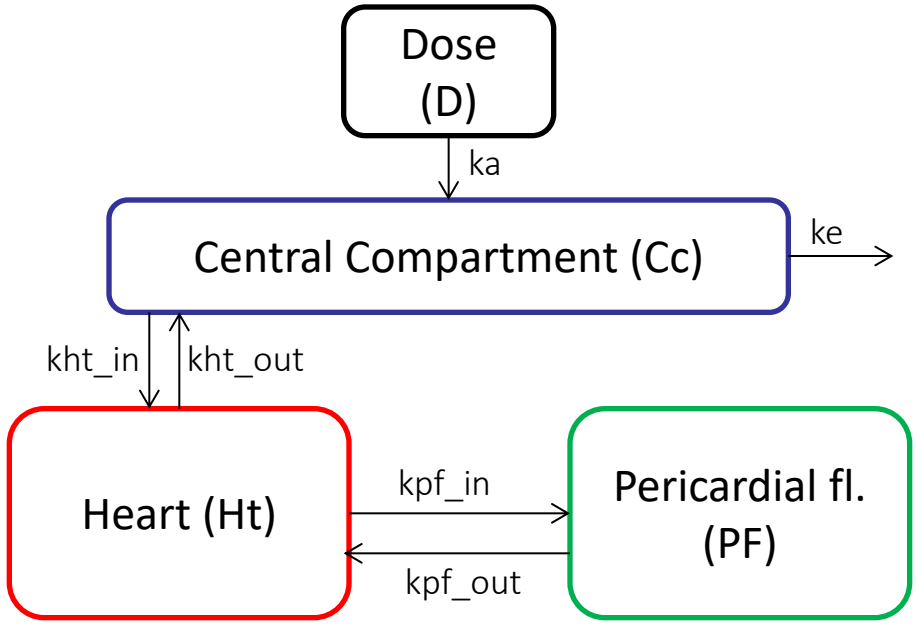
$$\frac{dHt}{dt} = k_{ht\_in} \times Cc + k_{pf\_out} \times PF - k_{ht_{out}} \times Ht - k_{pf_{in}} \times Ht$$

$$\frac{dPF}{dt} = k_{pf\_in} \times Ht - k_{pf\_out} \times PF$$

$$\frac{dD}{dt} = -Abs$$

Initial conditions:

Cc(0)=Ht(0)=PF(0)=0, D(0)=PODOSE=1500



Used packages:

deSolve (Solvers for Initial Value Problems of Differential Eq.)

FME (A Flexible Modelling Environment…)

2. library(deSolve)

Model specification:

```
>parameters <- c(ka = 0.323,
+                ke = 20,
+                kht_in = 0.13,
+                kht_out = 0.85,
+                kpf_in = 0.12,
+                kpf_out = 4.55 )
```

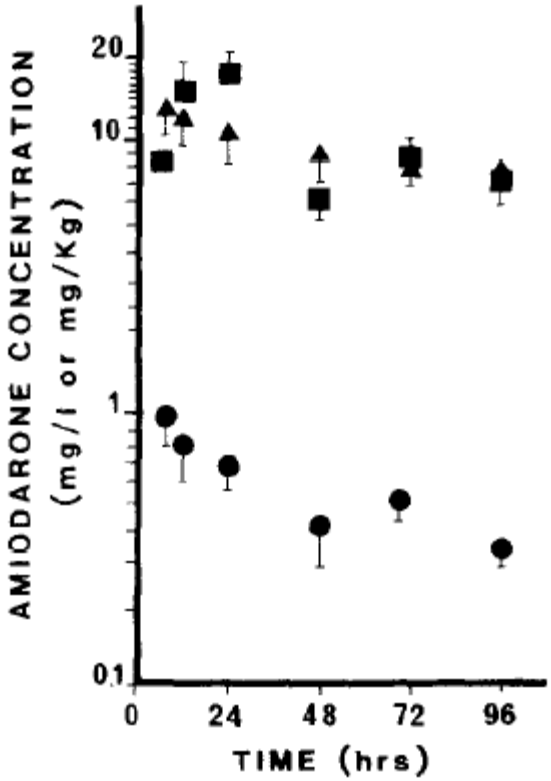
```
state <- c(D = PODOSE,
+          Cc = 0,
+          Ht = 0,
+          PF = 0,
+          F = 0)
```

```
Model<-function(t, state, parameters) {
+ with(as.list(c(state, parameters)), {
+ Absorption <- ka*D*Fab
+ dD <- -Absorption
+ dCc <- Absorption + kht_out*Ht - ke*Cc - kht_in*Ht
+ dHt <- kht_in*Cc + kpf_out*PF - kht_out*Ht - kpf_in*Ht
+ dPF <- kpf_in*Ht - kpf_out*PF + dF <- ke*Cc
+ list(c(dD, dCc, dHt, dPF, dF))
+ })
```

Model application :

```
>times <- seq(0, 150, by = 0.1)
> out <- ode(y = state, times = times, func = Model,
+ parms = parameters)
```

3. library(FME) #A Flexible Modelling Environment for Inverse Modelling, Sensitivity, Identifiability and Monte Carlo Analysis



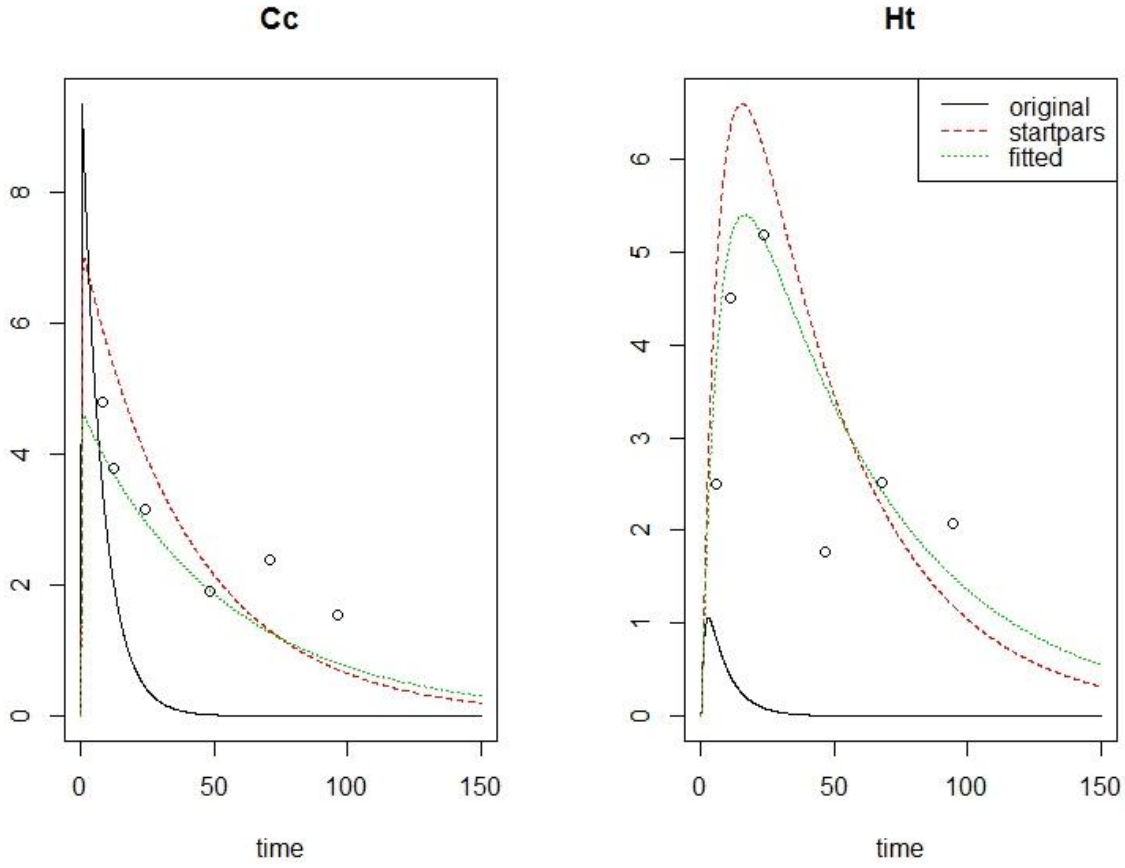

```
modelCost <- function(p) {
+ out <- ode(y = state, func = Model, parms = p,
+ times = yobs$time)
+ return(modCost(out, yobs))  }

> startpars <- c(ka=0.038, kht_in = 0.2, kht_out = 0.15,
kpf_in = 0.68, kpf_out = 9.7, ke = 5)

> fit <- modFit (f = modelCost, p =startpars, upper =pupper,
+ lower = plower, control = list(nprint = 1))
```

Escoubet et al., “Am. J. Cardiol.” 1985, 55 (6), 696–702.

```
>out2 <- ode(y = state, parms = startpars, times = times, func = Model)
>out3 <- ode(y = state, parms = fit$par, times = times, func = Model)
>plot(out, out2, out3, obs = yobs)
>legend("topright", legend=c("original", "startpars", "fitted"),  col = 1:3, lty = 1:3)
```



4. Events (deSolve package)

two-months standard dosage schedule of amiodarone (200 mg t.i.d. as a priming dose, and 100 mg q.d. as a sustaining dose)

```
>eventdat <- data.frame(var=rep("D", times=74),
+ time = c(seq(1,168, by=8), seq(192,1440, by=24)),
+ value = c(rep(200, times=21), rep(100, times=53)),
+ method = rep("add", times=74))
```

	var	time	value	method
1	D	1	200	add
2	D	9	200	add
3	D	17	200	add
4	D	25	200	add
5	D	33	200	add
6	D	41	200	add
7	D	49	200	add
8	D	57	200	add
9	D	65	200	add
10	D	73	200	add
11	D	81	200	add
12	D	89	200	add
13	D	97	200	add
14	D	105	200	add
15	D	113	200	add
16	D	121	200	add
17	D	129	200	add
18	D	137	200	add
19	D	145	200	add
20	D	153	200	add
21	D	161	200	add
22	D	192	100	add
23	D	216	100	add
24	D	240	100	add

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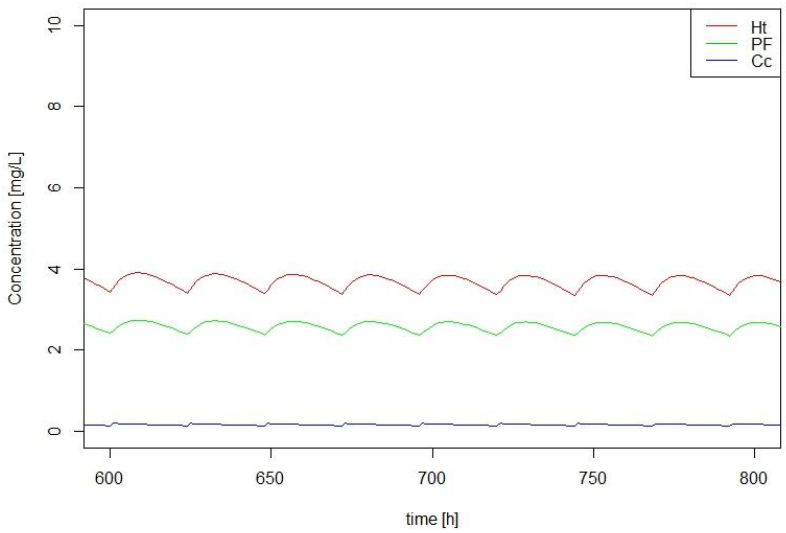
two-months standard dosage schedule of amiodarone (200 mg t.i.d. as a priming dose, and 100 mg q.d. as a sustaining dose)

```
>eventdat <- data.frame(var=rep("D", times=74),
+ time = c(seq(1,168, by=8), seq(192,1440, by=24)),
+ value = c(rep(600, times=21), rep(100, times=53)),
+ method = rep("add", times=74))
```

```
>out_events <- ode(y = state, times = times,
func = Model, parms = parameters,  events =
list(data=eventdat))
```



Thank you for your attention.