New open source R libraries for simulation & visualization: PKPDsim and vpc

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PKPDsim

The PKPDsim R library offers functionality for model simulation and exploration, similar to Berkeley Madonna but within the R environment so that the user can take advantage of R's powerful statistics and visualization tools. The library facilitates simulation of dosing regimens for PKPD mixed-effects models, leveraging the fast Boost C++ library (or optionally using R::deSolve) for numerical integration. The PKPDsim library generates ggplot-ready data and can be used from the R command line but can also dynamically generate Shiny frontends to allow interactive use for model exploration and teaching purposes.

Example 1. Simulate using PK model from builtin library:

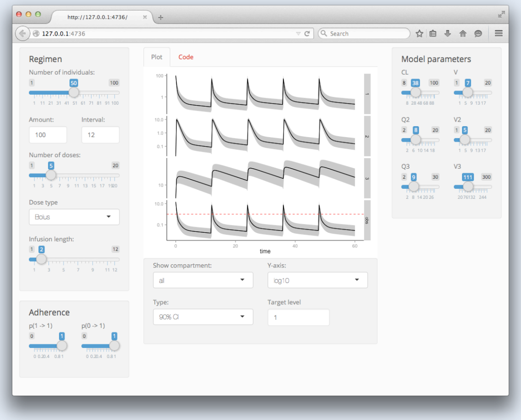
```
P   <- list(CL = 1, V  = 10, KA = 0.5)
pk1 <- new_ode_model("pk_1cmt_oral")
r1  <- new_regimen(
  amt = 100, times = c(0, 12, 24, 36))
dat <- sim_ode (
  ode = "pk1", par = p, n_ind = 40,
  omega = c(0.1,
              0.05, 0.1),
  regimen = r1))
```

Example 2. Define custom model (PKPD):

```
pkpd_model <- new_ode_model(
  code =  "
    dAdt[1] = -(CL/V) * A[1] + rate
    conc = A[1]/V
    dAdt[2] = KIN * 1/(1+EFF*conc) - KOUT*A[2]
  ",
  state_init = "A[2] = KIN/KOUT"
)
```

Example 3. Generate Shiny app ‘on-the-fly’

```
sim_ode_shiny(ode = "pkpd", par = p,
              regimen = r1, omega = omega)
```



http://127.0.0.1:4736/

127.0.0.1:4736

Regimen

Number of individuals: 50

Amount: 100

Interval: 12

Number of doses: 5

Dose type: Bolus

Infusion length: 2

Adherence

p(1 -> 1): 1

p(0 -> 1): 1

Show compartment: all

Y-axis: log10

Type: 90% CI

Target level: 1

Model parameters

CL: 38

V: 7

Q2: 8

V2: 5

Q3: 9

V3: 111

vpc

Visual Predictive Checks are an essential part of pharmacometric workflows. Most modelers will be familiar with the functionality offered by e.g. PsN[4]/ Xpose[5] or Monolix[6]. These tools are somewhat inflexible, however, as they are limited to one specific simulation software and produce plots that are not easily tweakable and/or extensible. This new R library **vpc** includes:

- plots for continuous (`vpc`), categorical (`vpc_cat`), censored continuous (`vpc_cens`), and survival data (`vpc_tte`)
- prediction-correction (*pred_corr=TRUE* argument)
- Kaplan-Meier Mean Covariate plots[7] (*kmmc* argument to `vpc_tte`)
- npde plots with prediction intervals[8] (*npde=TRUE* argument)

Example 1. Default vpc, using R data.frames or PsN folder as source data

```
vpc(sim = sim, obs = obs)

vpc(psn_folder = ‘vpc-dir1’)
```

Example 2. vpc with more extensive optional arguments

```
vpc(sim = sim, obs = obs,
    obs_cols = list(dv = "dv”, idv = "time"),
    sim_cols = list(dv = "sdv", idv = "time"),
    bins = “kmeans”,
    show = list(obs_dv = TRUE, pi_ci = TRUE)
    stratify = c("sex"),
    pi = c(0.05, 0.95),
    ci = c(0.05, 0.95),
    pred_corr = FALSE)
```

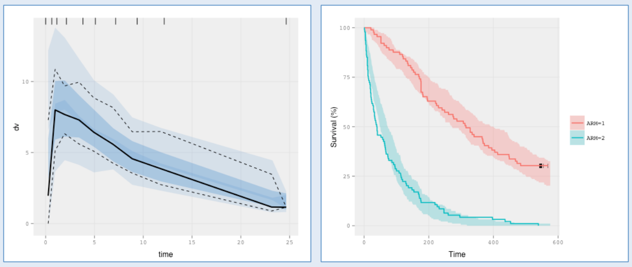
Example 3. vpc for survival-type data, with explicit bin method selection

```
vpc_tte(sim = rtte_sim_nm, obs = rtte_obs_nm,
    stratify = c("sex","drug"),
    rtte = FALSE, bins = "kmeans",
    n_bins = 20, smooth = TRUE)
```

Example 4. vpc for categorical data, with explicit column selection

```
vpc_cat (sim = sim_cat, obs = obs_cat,
    obs_cols = list(dv = "SMXH"),
    sim_cols = list(dv = "SMXH"))
```

Example 5. VPCs for continuous and survival data with default layout



Installation: The PKPDsim and vpc libraries are currently only available from GitHub, but will be released to CRAN as soon as possible. For more information about their installation and usage please see http://ronkeizer.github.io/PKPDsim and http://ronkeizer.github.io/vpc.

References: [1] Chotsiri et al. WCoP 2012 Korea. PM6-2 [http://www.go-wcop.org/data/WCoP_ProgramAbstract.pdf] [2] http://simulx.webpopix.org/ [3] http://shiny.rstudio.com [4] http://psn.sf.net [5] http://xpose.sf.net [6] http://www.lixoft.eu [7] Hooker et al., PAGE 21 (2012) Abstr 2564 [www.page-meeting.org/?abstract=2564] [8] Comets et al. PAGE 22 (2013) Abstr 2775 [www.page-meeting.org/?abstract=2775]