Simple 3-state Partitioned Survival model in R

The DARTH workgroup

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- Jalal H, Pechlivanoglou P, Krijkamp E, Alarid-Escudero F, Enns E, Hunink MG. An Overview of R in Health Decision Sciences. Med Decis Making. 2017; 37(3): 735-746. https://journals.sagepub.com/doi/abs/10.1177/0272989X16686559
- Krijkamp EM, Alarid-Escudero F, Enns EA, Jalal HJ, Hunink MGM, Pechlivanoglou P. Microsimulation modeling for health decision sciences using R: A tutorial. Med Decis Making. 2018;38(3):400–22. https://journals.sagepub.com/doi/abs/10.1177/0272989X18754513
- Krijkamp EM, Alarid-Escudero F, Enns E, Pechlivanoglou P, Hunink MM, Jalal H. A Multidimensional Array Representation of State-Transition Model Dynamics. BioRxiv 670612 2019.https://www.biorxiv.org/content/10.1101/670612v1

```r
rm(list = ls())      # clear memory (removes all the variables from the workspace)
```

01 Load packages

```r
if (!require('pacman')) install.packages('pacman'); library(pacman) # use this package to conveniently
# load (install if required) packages from CRAN
p_load("here", "dplyr", "devtools", "gems", "flexsurv", "survminer", "survHE", "ggplot2", "msm", "igrapl
```

02 Load functions

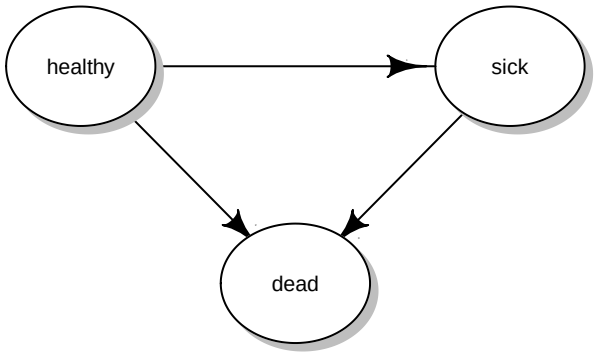
```r
source("survival_functions.R")
```

03 Input model parameters

```r
v_n       <- c("healthy", "sick", "dead")  # state names
n_s       <- length(v_n)                   # No of states
n_i       <- 5000                          # number of simulations
c_l       <- 1 / 12                        # cycle length (a month)
n_t       <- 30                            # number of years (20 years)
times     <- seq(0, n_t, c_l)              # the cycles in years
set.seed(2020)                             # set the seed
```

Create a transition probability matrix with all transitions indicated and numbered.

```r
tmat <- matrix(NA, n_s, n_s, dimnames = list(v_n,v_n))
tmat["healthy", "sick"]  <- 1
tmat["healthy", "dead"]  <- 2
tmat["sick"   , "dead"]  <- 3

layout.fig <- c(2,1)
plotmat(t(tmat), t(layout.fig), self.cex = 0.5, curve = 0, arr.pos = 0.76,
        latex = T, arr.type = "curved", relsize = 0.85, box.prop=0.8,
        cex = 0.1, box.cex = 0.7, lwd = 1)
```



Generate data.

```
source("data.R")
```

```
## Simulating patient:1
## Simulating patient:100
## Simulating patient:200
## Simulating patient:300
## Simulating patient:400
## Simulating patient:500
```

```
head(true_data)
```

```
##           healthy     sick      dead
## Patient 1       0 1.448160 10.650946
## Patient 2       0 2.082438  2.539559
## Patient 3       0 2.332880  3.304383
## Patient 4       0 7.613460  7.856301
## Patient 5       0 5.521759 60.000000
## Patient 6       0 4.836634 34.077378
```

```
head(sim_data)
```

```
##           healthy      sick      dead
## Patient 1       0 1.4481602 4.6703210
## Patient 2       0 0.2330877 0.2330877
```

```
## Patient 3       0 2.3328803 3.3043830
## Patient 4       0 5.0000000 5.0000000
## Patient 5       0 1.1391762 1.1391762
## Patient 6       0 4.8366340 5.0000000
```

```
head(status)
```

```
##   healthy sick dead
## 1       1    1    0
## 2       1    0    0
## 3       1    1    1
## 4       1    0    0
## 5       1    0    0
## 6       1    1    0
```

```
head(OS_PFS_data)
```

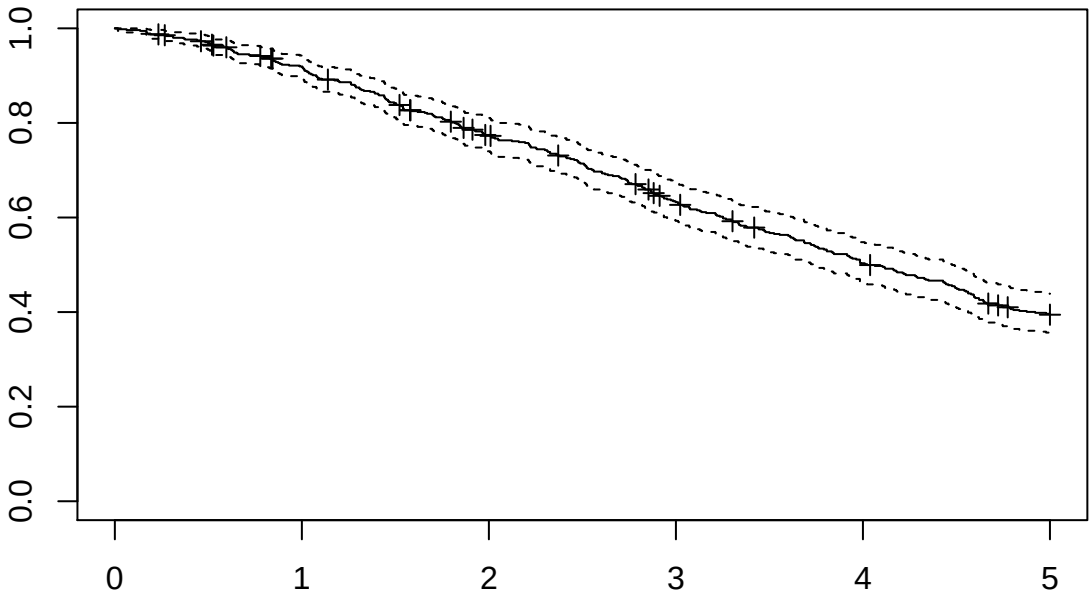
```
##    PFS_time PFS_status   OS_time OS_status
## 1 1.4481602          1 4.6703210         0
## 2 0.2330877          0 0.2330877         0
## 3 2.3328803          1 3.3043830         1
## 4 5.0000000          0 5.0000000         0
## 5 1.1391762          0 1.1391762         0
## 6 4.8366340          1 5.0000000         0
```

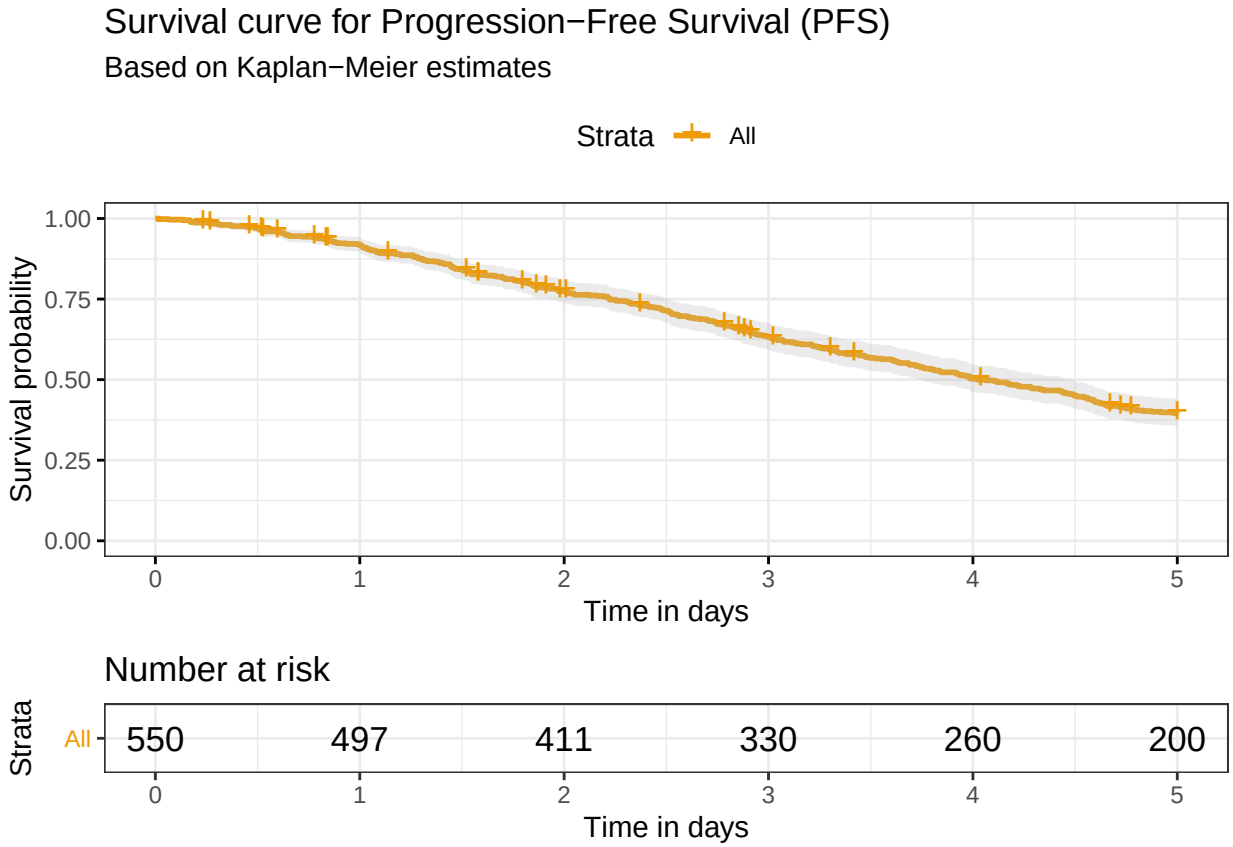
04 Analysis

Showcasing the use of packages `survival`, `flexsurv`.

```
fit_KM   <- survfit(Surv(time = OS_time, event = OS_status) ~ 1, data = OS_PFS_data,
                        type ="fleming-harrington")
plot(fit_KM, mark.time = T)


# a prettier way of plotting!!

ggsurvplot(
  fit_KM,
  data = OS_PFS_data,
  size = 1,                 # change line size
  palette = c("orange2"),    # custom color palettes
  conf.int = TRUE,          # Add confidence interval
  pval = TRUE,              # Add p-value
  risk.table = TRUE,        # Add risk table
  risk.table.height = 0.25,  # Useful to change when you have multiple groups
  ggtheme = theme_bw(),      # Change ggplot2 theme
  xlab = 'Time in days',     # Change X-axis label
  title    = "Survival curve for Progression-Free Survival (PFS)",
  subtitle = "Based on Kaplan-Meier estimates"
)
```

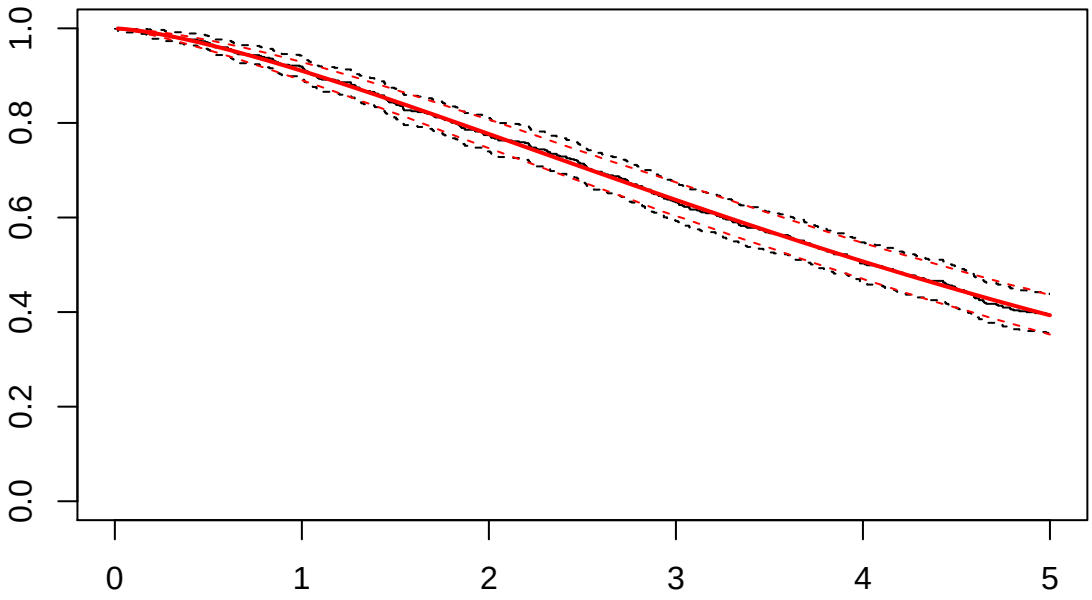
```
## Warning in .pvalue(fit, data = data, method = method, pval = pval, pval.coord = pval.coord, : There a
##  This is a null model.
```


0.0
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
5

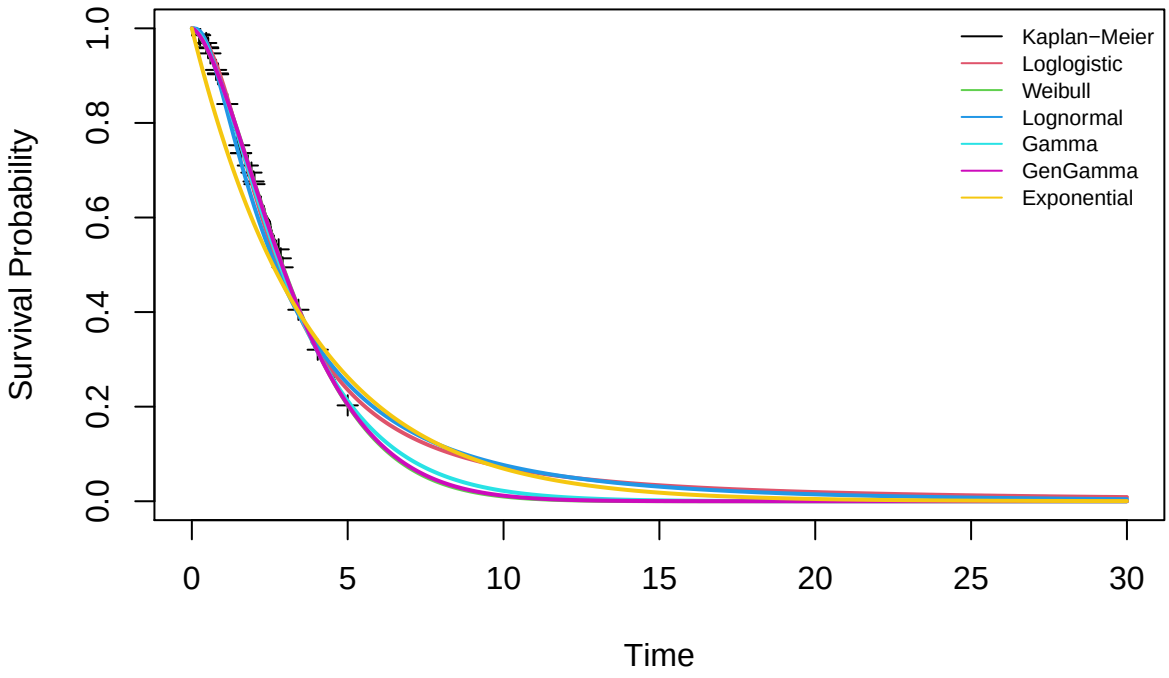


04.1 Partitioned Survival model

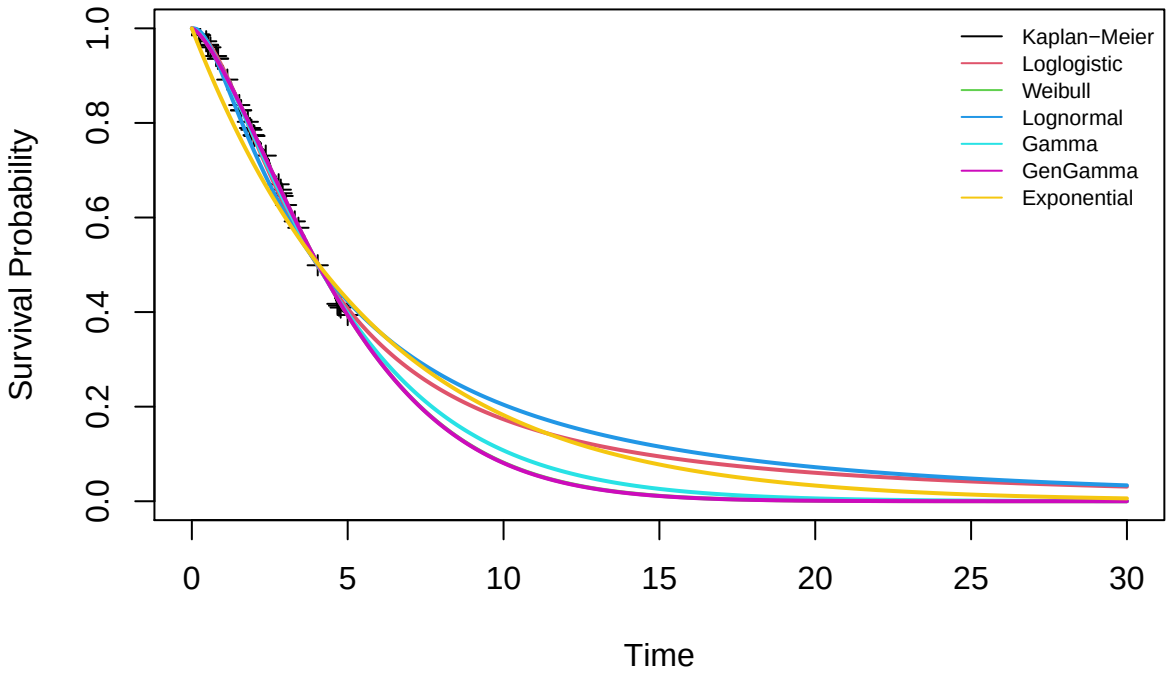
```
# Flexsurv allows parametric fitting of curves
fit_weib <- flexsurvreg(Surv(time = OS_time, event = OS_status) ~ 1, data = OS_PFS_data,  dist = "weibul
plot(fit_weib)
```




```
# fit all parametric models to the data and extract the AIC/BIC.
# Select the one with the most appropriate fit
# Repeat for PFS and OS



fit_PFS  <- fit.fun(time  = "PFS_time", status = "PFS_status", data = OS_PFS_data,
                    times = times, extrapolate = T)
```




```
fit_OS   <- fit.fun(time  = "OS_time", status  = "OS_status" , data = OS_PFS_data,
                    times = times, extrapolate = T)
```



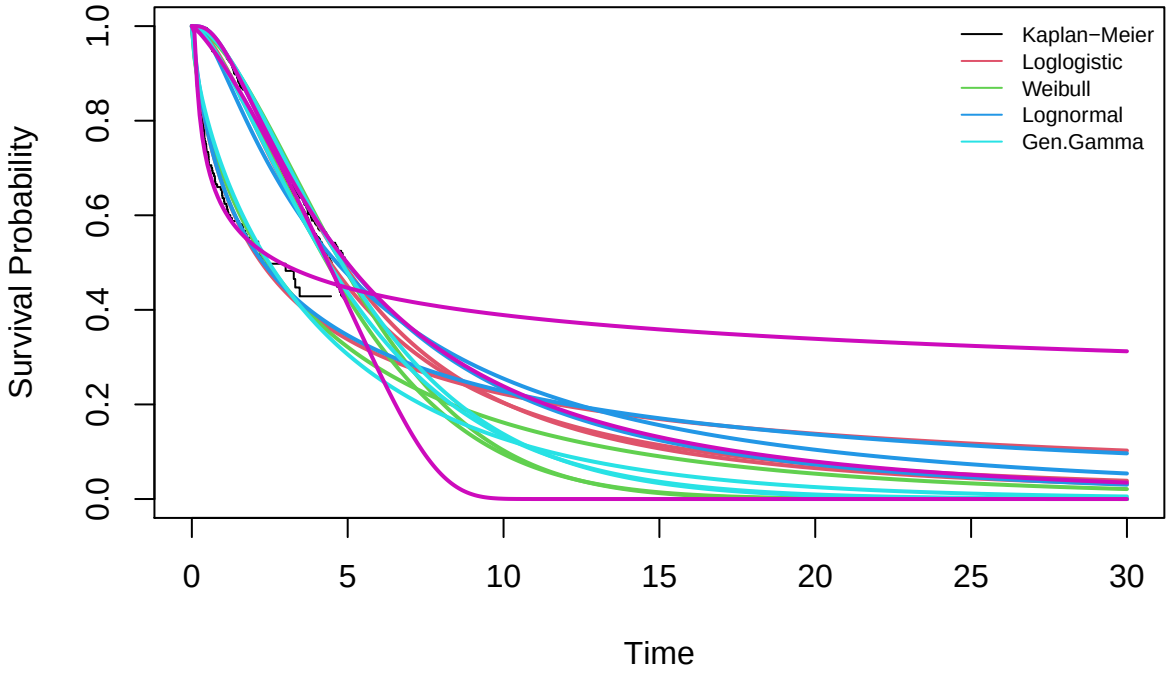

```
best_PFS <- fit_PFS[["Weibull"]]
best_OS  <- fit_OS [["Weibull"]]

# construct a partitioned survival model out of the fitted models
m_M_PSM <- partsurv(best_PFS, best_OS, time = times)$trace
```

04.2 MultiState modeling method 1

- Fit all parametric multistate models simultaneously.

```
# The existing functions in R require the data in a long rather than a wide format
# convert the data in a way that flexsurv understands using the mstate package
data_long       <- msprep(time = sim_data, status = status, trans = tmat )
data_long$trans <- as.factor(data_long$trans) # convert trans to a factor

data_long$from  <- case_when(data_long$from == 1 ~ "healthy",
                             data_long$from == 2 ~ "sick",
                             data_long$from == 3 ~ "dead")

data_long$to    <- case_when(data_long$to == 1 ~ "healthy",
                             data_long$to == 2 ~ "sick",
                             data_long$to == 3 ~ "dead")

# fit all parametric multistate models simultaneously to the data and extract the AIC/BIC
# Select the one with the lowest AIC
fits <- fit.mstate(time ="time", status = "status", trans, data = data_long,
                   times = times, extrapolate = T )
```

```
## Warning in (function (q, shape, rate = 1, scale = 1/rate, lower.tail = TRUE, :
## NaNs produced
```




```
best.fit <- fits[["Loglogistic"]]
```

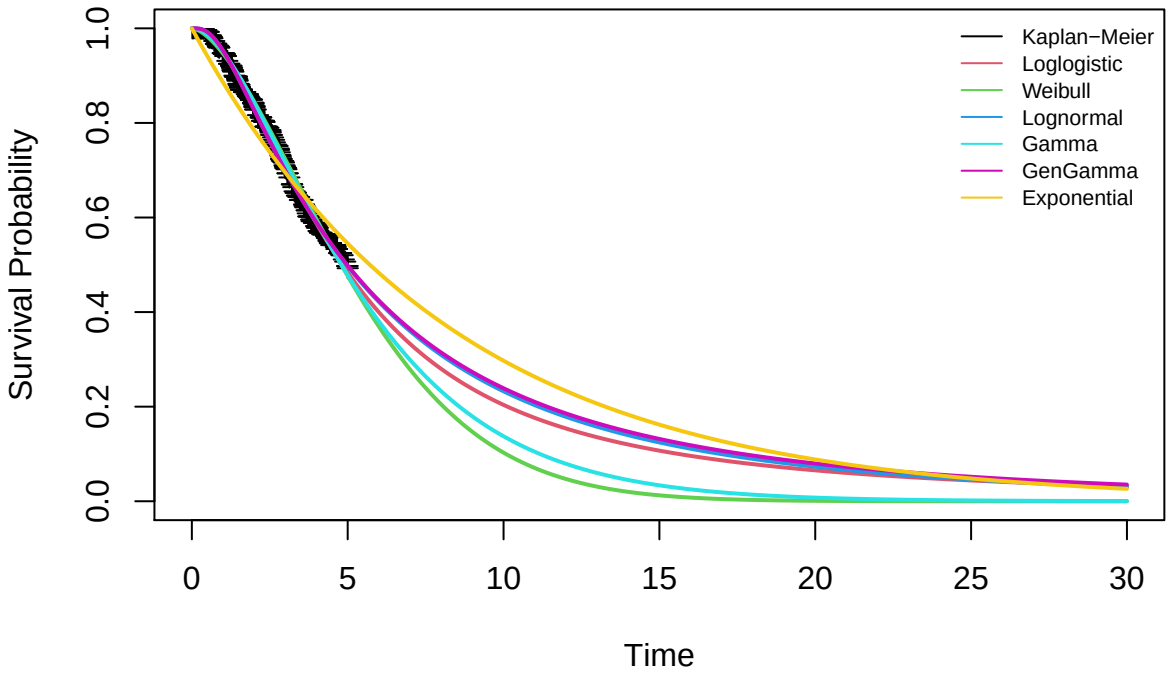
- Construct a DES model out of the simultaneously fitted multistate model.

```
# Construct a DES model out of the simultaneously fitted multistate model
DES_data <- sim.fmsm(best.fit, start = 1, t = n_years, trans = tmat, M = n_i)
m_M_DES  <- trace.DES(DES_data, n_i  = n_i , times = times, tmat = tmat)
```

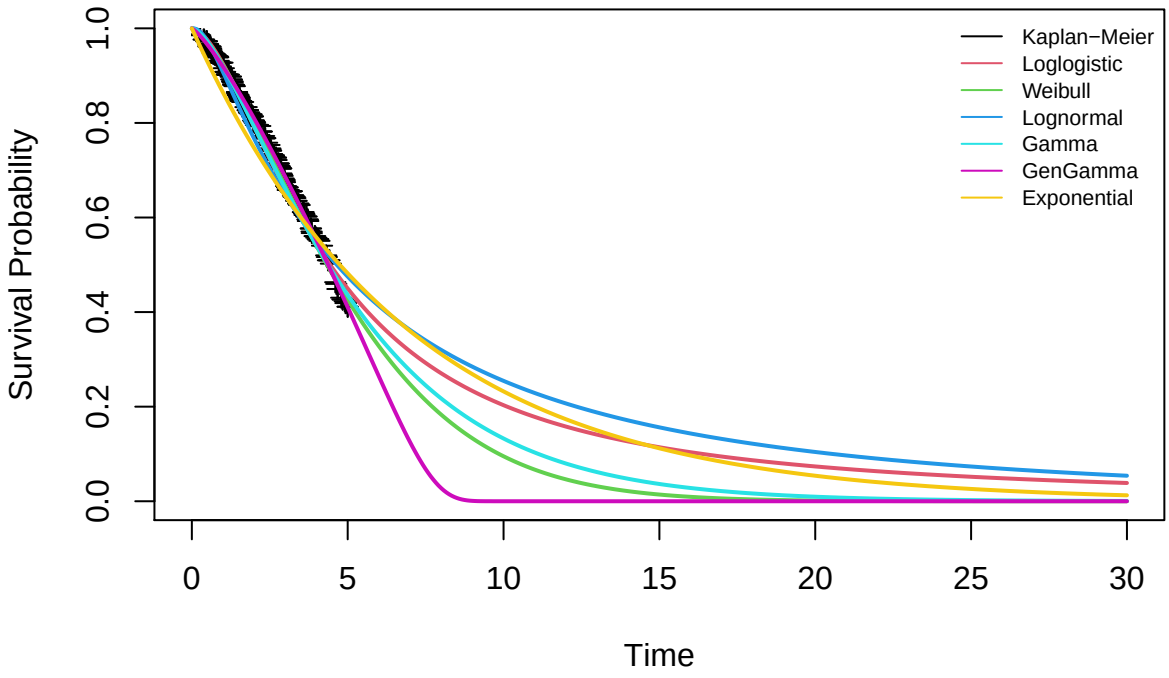
04.3 MultiState modeling method 2

- Multistate models can be fitted independently for each transition.

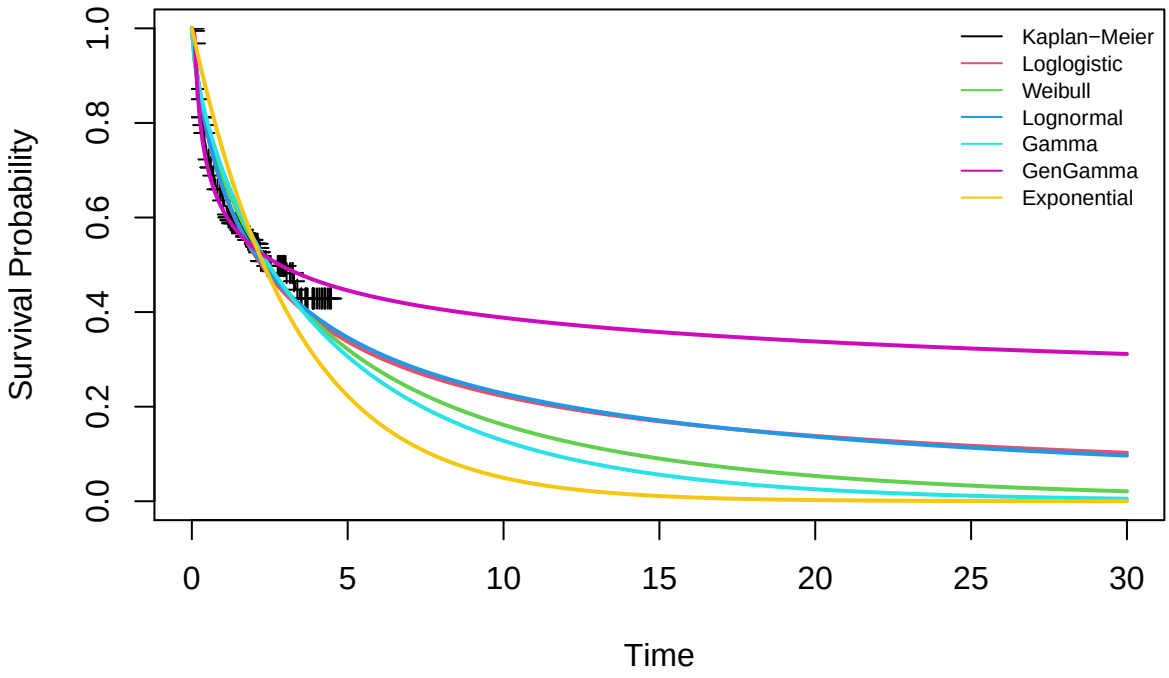
```
# Multistate models can be fitted independently for each transition.This is more flexible!
# Create subsets for each transition
data_HS <- subset(data_long, trans == 1)
data_HD <- subset(data_long, trans == 2)
data_SD <- subset(data_long, trans == 3)


# fit independent models for each transition and pick the one with the lowest AIC
fit_HS <- fit.fun(time = "time", status = "status", data = data_HS, times = times,
                  extrapolate = T)
```




```
fit_HD <- fit.fun(time = "time", status = "status", data = data_HD, times = times,
                  extrapolate = T)
```




```
fit_SD <- fit.fun(time = "time", status = "status", data = data_SD, times = times,
                  extrapolate = T)
```




```
best.fit_HS <- fit_HS[["Gamma"]]
best.fit_HD <- fit_HD[["Weibull"]]
best.fit_SD <- fit_SD[["Lognormal"]]
```

- A microsimulation can be fitted instead of a DES.
- more computationally expensive but it provides more freedom to the modeller.
- For the Microsimulation to be run, we need transition probabilities per unit of time.

```
# Extract transition probabilities from the best fitting models
p_HS <- flexsurvreg_prob(object = best.fit_HS, times = times)
p_HD <- flexsurvreg_prob(object = best.fit_HD, times = times)
p_SD <- flexsurvreg_prob(object = best.fit_SD, times = times)

# everyone starts in the "healthy" state and therefore has not spent time in "sick"
v_M_init  <- rep("healthy", times = n_i)
v_Ts_init <- rep(0, n_i)  # a vector with the time of being sick at the start of the model

# function that generates the transition probabilities per cycle
Probs <- function(M_t, v_Ts, t) {
  # Arguments:
    # M_t: health state occupied by at cycle t (character variable)
    # v_Ts: vector with the duration of being sick
    # t:     current cycle
  # Returns:
    # transition probabilities for that cycle

  # create matrix of state transition probabilities
```

```
  m_p_t           <- matrix(0, nrow = n_s, ncol = n_i)
  # give the state names to the rows
  rownames(m_p_t) <-  v_n

  # update m_p_t with the appropriate probabilities
  # transition probabilities when healthy
  m_p_t[, M_t == "healthy"] <- rbind(1 - p_HD[t] - p_HS[t], p_HS[t], p_HD[t])
  # transition probabilities when sick
  m_p_t[, M_t == "sick"]    <- rbind(0, 1 - p_SD[v_Ts], p_SD[v_Ts])
  # transition probabilities when dead
  m_p_t[, M_t == "dead"]    <- rbind(0, 0, 1)
  return(t(m_p_t))
}
```

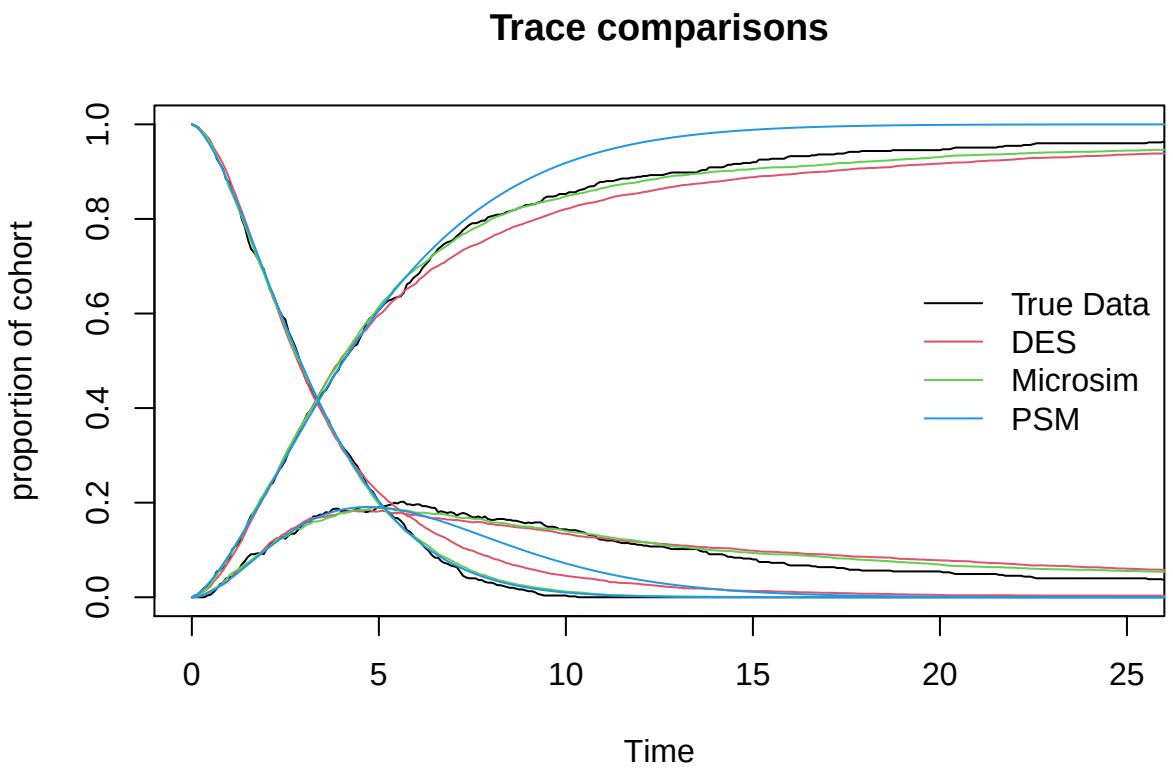
04.3.1 Run Microsimulation

```
MicroSim <- function(n_i,  seed = 1) {
  # Arguments:
  # n_i:     number of individuals
  # seed:    default is 1

  set.seed(seed) # set the seed

  # m_M is used to store the health state information over time for every individual
  times     <- seq(0, n_t, c_l)  # the cycles in years

  m_M  <-  matrix(nrow = n_i, ncol = length(times) ,
                  dimnames = list(paste("ind" , 1:n_i, sep = " "),
                                  paste("year", times, sep = " ")))

  m_M[, 1] <- v_M_init           # initial health state for individual i
  v_Ts     <- v_Ts_init          # initialize time since illness onset for individual i

  # open a loop for time running cycles 1 to n_t
  for (t in 1:(length(times)-1)) {
    # calculate the transition probabilities for the cycle based on health state t
    m_p <- Probs(m_M[, t], v_Ts, t)
    # sample the current health state and store that state in matrix m_M
    m_M[, t + 1]  <- samplev(m_p, 1)

    # update time since illness onset for t + 1
    v_Ts <- ifelse(m_M[, t + 1] == "sick", v_Ts + 1, 0)

    # Display simulation progress
    if(t %in% seq(1,(length(times)),10)) { # display progress every 10%
      cat('\r', paste(round(t/length(times)*100,0), "% done", sep = " "))
    } else if (t == (length(times)-1)) {cat('\r', paste("100% done"))}

  } # close the loop for the time points

  # store the results from the simulation in a list
  results <- list(m_M = m_M)
```

```
  return(results)  # return the results

} # end of the MicroSim function

# Run the simulation model
Micro_data <- MicroSim(n_i, seed = 1)

# create the microsimulation trace
m_M_Micro <- t(apply(Micro_data$m_M, 2, function(x) table(factor(x, levels = v_n,
                                                                 ordered = TRUE))))
m_M_Micro <- m_M_Micro / n_i    # calculate the proportion of individuals
colnames(m_M_Micro) <- v_n
rownames(m_M_Micro) <- paste("Cycle", times, sep = " ")
```

05 Compare all methods

```
# Calculate trace for the real data
m_M_data <- transitionProbabilities(generate$cohort, times = times)@probabilities

# visually compare all methods
matplot(times,m_M_data, type='l', lty = 1, col = 1, ylab= "proportion of cohort", xlab = "Time",
        main = "Trace comparisons",xlim=c(0,25))
matlines(times, m_M_DES,   col = 2, lty = 1)
matlines(times, m_M_Micro, col = 3, lty = 1)
matlines(times, m_M_PSM,   col = 4, lty = 1)
legend("right", c("True Data", "DES","Microsim",  "PSM"),
        col = 1:4, lty = rep(1,4), bty= "n")
```


Trace comparisons
proportion of cohort
0.0
0.2
0.4
0.6
0.8
1.0
0
5
10
15
20
25
Time
True Data
DES
Microsim
PSM