

Saemix: Open Source R package for mixed effects modeling

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Welcome to mixed effects modeling in R

The `saemix` project is an R package available in CRAN that implements the Stochastic Approximation of the EM (SAEM) algorithm introduced in ([Kuhn and Lavielle, 2004](#)). This algorithm is state-of-the-art method for fitting, possibly non linear, models in agronomy, animal breeding or Pharmacokinetics-Pharmacodynamics (PKPD) analysis.

The main area using the package thus far is Pharmacology, especially to understand how drugs, under development, behave in the body or how the body reacts to a drug during clinical trials.

`saemix` is licensed under [GPL-2](#) | [GPL-3](#) [expanded from: GPL (≥ 2)].



Chapter 1

Introduction

The **saemix** package for R provides maximum likelihood estimates of parameters in nonlinear mixed effect models (NLMEM), using a modern and efficient estimation algorithm, the Stochastic Approximation of the Expectation-Maximisation (SAEM).

Longitudinal data arise in many fields, such as agronomy, spatial analysis, imagery, clinical trials, and have been particularly prominent in the field of pharmacokinetics (PK) and pharmacodynamics (PD), where increasingly complex models involving mechanistic and empirical processes have been developed to describe the time course of and responses to drugs. Nonlinear models pose unique challenges in terms of estimation methods, and have driven the research to provide better estimation of parameters as well as the associated uncertainty, diagnostics of model misspecification and more informative designs. The SAEM algorithm, based on two highly cited publications by one of our project members Marc Lavielle, see (Delyon et al., 1999) and (Kuhn and Lavielle, 2004), was implemented in R in 2011 in the **saemix** R package~(Comets et al., 2017). Several applications of SAEM in agronomy, animal breeding and PKPD analysis have been published using **saemix**.

PK/PD analyses are now a fundamental element of the registration file submitted to health authority for the approval of new drugs, but NLMEM are also increasingly applied to other areas. In clinical trials, they complement the point analyses by offering a unique understanding of the evolution of disease or treatment action. In cohort studies, they allow to model trajectories such as growth or cognitive decline. Joint models are now routinely used to link the evolution of markers with the occurrence of an event. Making use of S4 classes and methods to provide user-friendly interaction, **saemix** provides a new estimation tool with a powerful exact algorithm to the R community. The **saemix** package for R provides maximum likelihood estimates of parameters in nonlinear mixed effect (NLME) models, using a modern and efficient estimation algorithm, the Stochas-

tic Approximation of the Expectation-Maximisation (SAEM) algorithm based on two highly cited publication by one of our project member Marc Lavielle, see ([Delyon et al., 1999](#)) and ([Kuhn and Lavielle, 2004](#)). Making use of S4 classes and methods to provide user-friendly interaction, this package provides a new estimation tool to the R community.

Chapter 2

Installation

`saemix` can be installed and used on several platforms. Installation can range from easy to challenging, depending on the platform. We are in the process of streamlining this process, and any help or suggestions are greatly appreciated!

2.1 `saemix`

Information on how to install ‘saemix’ and its dependencies on different platforms can be found on the [saemix pkgdown site](#). Separate information can be found on [RxODE pkgdown site](#).

2.1.1 Installation via GitHub

To Complete

2.2 `shinyMixR`: project management tool

A user-friendly tool was developed for `saemix` based on [Shiny](#)

Chapter 3

Materials

3.1 User's Guide

- Saemix User's Guide: PDF

3.2 Posters and Presentations

- PAGE 2011, Athens, Greece: PosterPAGE

Various other publications can be found [here](#).

Chapter 4

Case Studies

Some basic Case Studies are demonstrated in this chapter; the vignettes will be discussing the application in more depth.

4.1 saemix

```
library(saemix)
?saemix
```

4.1.1 Rationale

saemix estimation routines have their own way of specifying models.

Initial Values

saemix models are contained in a R function with two blocks:

Some R Code

4.1.2 Some examples

4.1.2.1 A two-compartment PK model

The model:

```
theomodel <- function() {
  ini({
    tka <- log(1.14)
```

```

tcl <- log(0.0190)
tv2 <- log(2.12)
tv3 <- log(20.4)
tq <- log(0.383)
wteff <- 0.35
sexeff <- -0.2
eta.ka ~ 1
eta.cl ~ 1
eta.v2 ~ 1
eta.v3 ~ 1
eta.q ~ 1
prop.err <- 0.075
})
model({
  ka <- exp(tka + eta.ka)
  cl <- exp(tcl + wteff*LWT + eta.cl)
  v2 <- exp(tv2 + sexeff*SEX + eta.v2)
  v3 <- exp(tv3 + eta.v3)
  q <- exp(tq + eta.q)
  d/dt(depot) = -ka * depot
  d/dt(center) = ka * depot - cl / v2 * center + q/v3 * periph - q/v2 * center
  d/dt(periph) = q/v2 * center - q/v3 * periph
  cp = center / v2
  cp ~ prop(prop.err)
})
}

fit <- saemix()

```

Contacts

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Please address any questions, bug notice or suggestions.

Bibliography

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