AZRsim Documentation

AstraZeneca

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User Guide

The user guide documents the functionality for the AZRsim R package which can be used to simulate ordinary differential equations in C and NONMEM.

In order to simulate the model in the AZRsim package we have to,

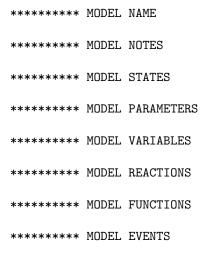
- 1. Create an appropriate text file representation of the model.
- 2. Compile the model with the create_model() function.
- 3. Simulate the compiled model with the simulate() function.

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Chapter 1

Model Specification

In order to simulate the time varying variables of a system of ordinary differential equations you need to provide a specific representation of your mathematical model in a text file (a file with extension .txt). Every text file representation of a model must contain the following blocks presented exactly as defined below. Notice that each block name is preceded with ten *s. It is possible to comment out a line of code using %.



The remainder of this section deals with what each block is used for.

1.1 Model Name and Model Notes

Model Name and Model Notes are descriptive blocks that allow the user to specify a model name and any notes about the model. The name of the model will be presented when an azrmod object is printed to the console.

Below are the model name and model notes blocks for the simple harmonic oscillator example in the \mathbf{AZRsim} package ($\mathtt{sho.txt}$).

```
****** MODEL NAME
Harmonic Oscillator

****** MODEL NOTES
```

Harmonic Oscillator ODE example.

Here is what the associated azrmod object looks like after calling create_model on the text file.

```
sho <- create_model(system.file("examples/sho.txt", package="AZRsim"))
sho</pre>
```

AZRmodel

Name: Harmonic Oscillator

NumberStates:2NumberParameters:1NumberVariables:0NumberReactions:0NumberFunctions:0

1.2 Model States

The Model States block is where the user describes the system of differential equations followed by the initial conditions for each variable. The left hand side of each differential equation must be declared as d/dt(x) where x is a variable name chosen by the user.

The initial conditions must be defined, and they must be defined after the system of differential equations is defined. If variable x in the preceding paragraph had an initial condition value of 3 then we can declare x(0) = 3 after defining the system of differential equations.

1.3 Model Parameters

The Model Parameters block is where the user defines the values of the parameters in the system of differential equations defined in Model States.

1.4 Model Variables

The Model Variables block provides a way to reparametrize parts of the model. Variables for intermediate calculations should be defined under Model Variables.

```
******* MODEL STATES

d/dt(A) = -R
d/dt(B) = R
A(O) = 1
B(O) = 0

******** MODEL PARAMETERS
k1 = 0.5

******* MODEL VARIABLES
R = k1*A
```

1.5 Model Reactions

The Model Reactions block provides a way to reparametrize parts of the model. Reaction rates should be defined under Model Reactions.

```
******* MODEL STATES

d/dt(A) = -R
d/dt(B) = R
A(O) = 1
B(O) = 0

******** MODEL PARAMETERS
k1 = 0.5

******* MODEL REACTIONS
R = k1*A
```

1.6 Model Functions

The Model Functions block can be used to define reoccuring calculations.

1.7 Model Events

The Model Events block can be used to define discrete state events.

There are essentially two parts to defining a discrete event in the model:

- 1. When does the event take place?
- 2. What is the event?

Below is an example of a event block.

```
****** MODEL EVENTS

event1 = eq(time, 1), y, y+40

event2 = eq(time, 2), y, y+40
```

The term eq(time, 1) pertains to (1). This says that the event occurs when the time step is strictly equal to 1. The term y, y+40 pertains to (2). This is the event that is to take place. In this case the event involves variable y and we want to add 40 units of the drug this variable, y+40. (Note that events cannot take place at time 0.) In summary, the above block defines adding 40 to the value of y at time steps 1 and 2.

We can issue multiple events. The event defined below specifies resetting the value of x to 1 and y to 0 when x is equal to 0.1.

```
****** MODEL EVENTS

event = eq(x, 0.1), x, 1, y, 0
```

Below is a summary of the options that can be used to declare when an event takes place.

• eq(a, 0) implies variable a is strictly equal to 0.

- lq(a, 0) implies variable a is less than or equal to 0.
- gq(a, 0) implies variable a is greater than or equal to 0.
- 1t(a, 0) implies variable a is strictly less than 0.
- $\mathsf{gt(a, 0)}$ implies variable a is strictly greater than 0.

Chapter 2

Modeling Functions

This section specifies the user-facing functions required to simulate the system of ordinary differential equations.

2.1 create_model

The create_model function is used to create the C code based on the text file representation of the model. This function returns and object of class azrmod. Once you create a model you can print a summary of the model in R. Below is an example of printing the simple harmonic oscillator, which is part of the AZRsim package.

```
sho <- create_model(system.file("examples/sho.txt", package="AZRsim"))
sho
AZRmodel
=======</pre>
```

Name: Harmonic Oscillator

Number States:2Number Parameters:1Number Variables:0Number Reactions:0Number Functions:0

In this model, the system of differential equations involves two states $(y_1 \text{ and } y_2)$ and one parameter (θ) .

2.2 simulate

Once you have created an azrmod object with create_model you can use the simulate generic to simulate the state variables over a specified number of time steps. Note that the simulate function requires an object of class azrmod, and will return an object of class azrsim and data.frame.

In the simple harmonic oscillator example above we have two states, so calling simulate(sho, seq(1, 100, by=0.1)) will provide a simulation of these two states over the time sequence 1 to 100 at 0.1 intervals.

2.3 plot

The plot generic can be called on an azrsim object and, by default, will construct a lattice plot of the first 9 parameters over time.

2.4 shiny_plot

The shiny_plot function must be called on an azsim object and will launch a shiny app that will allow the user to interactively include/exclude any state variable estimated.

Chapter 3

Examples

- 3.1 Michaelis-Menten
- 3.2 Two Compartment Model