



# Modeling survival under time variable chemical exposure

## Bayesian implementation with R & JAGS

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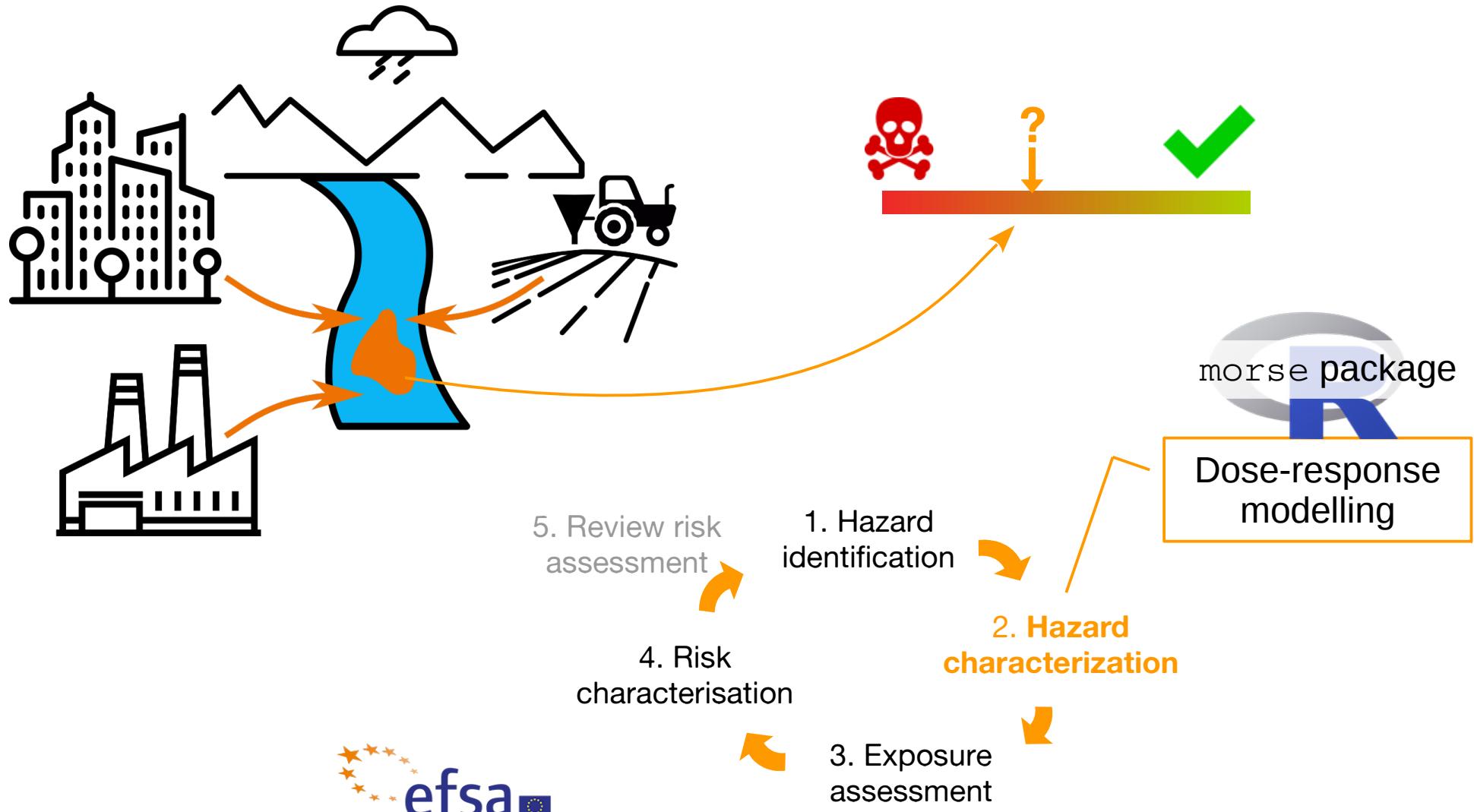
Virgile Baudrot, Philippe Veber & Sandrine Charles



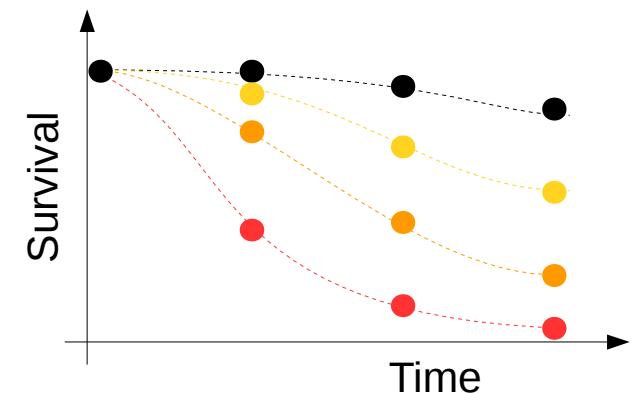
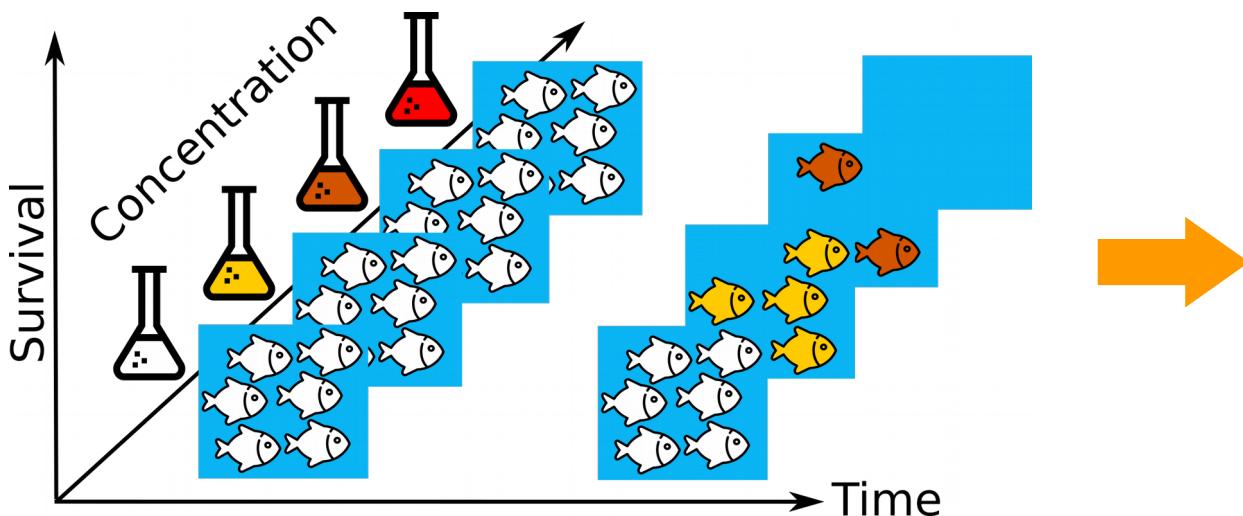
# Environmental Risk Assessment



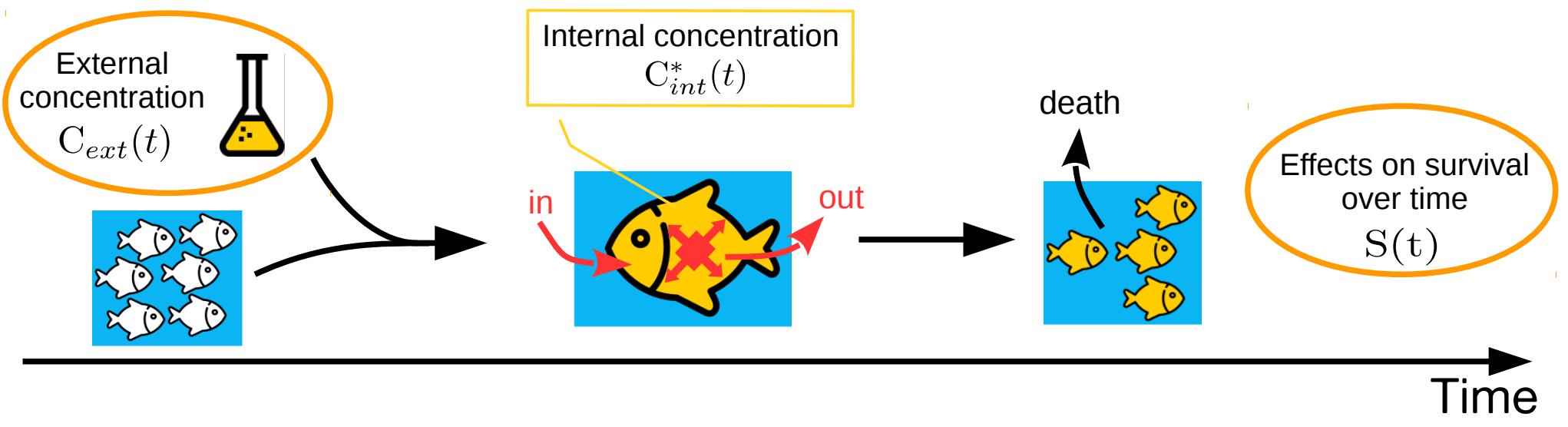
# Environmental Risk Assessment



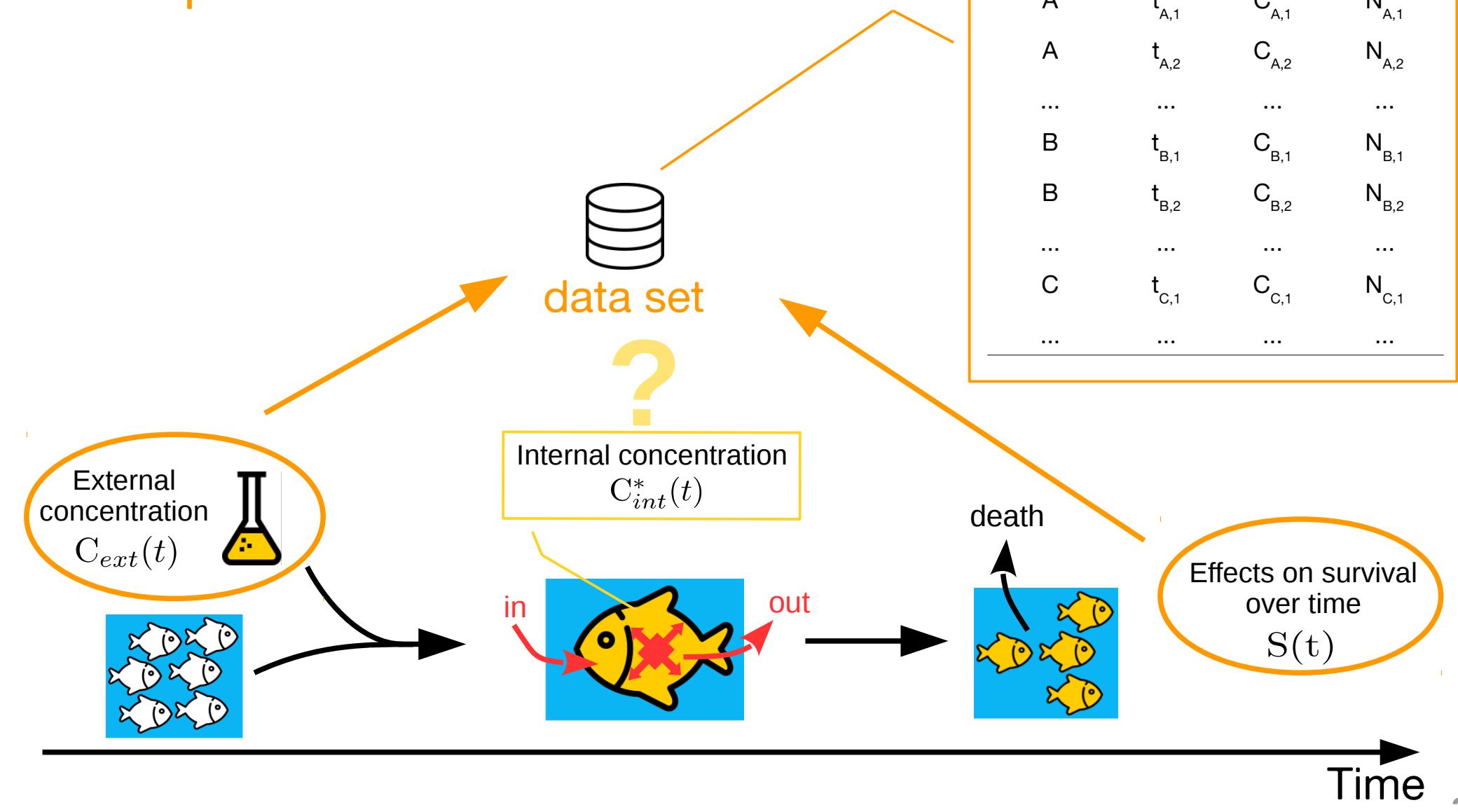
# Experiment



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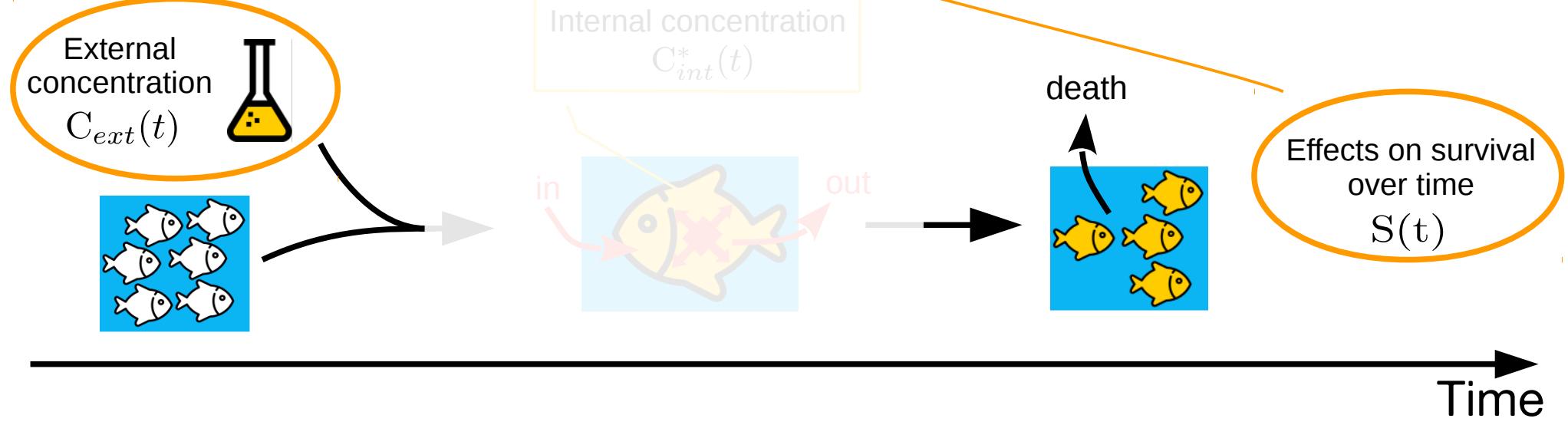


# Experiment



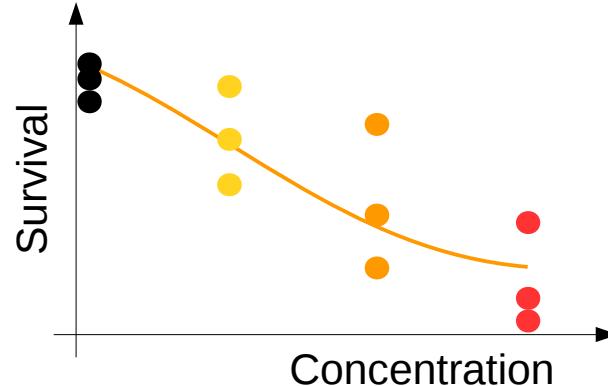
# Modelling : Target Time (TT)

$$S = \frac{d}{1 + (C_{ext}/LC_{50})^b}$$



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Least-squares estimates



function `drcm` from `drc` package (Ritz et al., 2015)

Bayesian inference



+ **JAGS**  
Just Another Gibbs Sampler



function `survFitTT` from `morse` package  
(Delignette-Muller et al., 2016)



web interface

<http://pbil.univ-lyon1.fr/software/mosaic/>



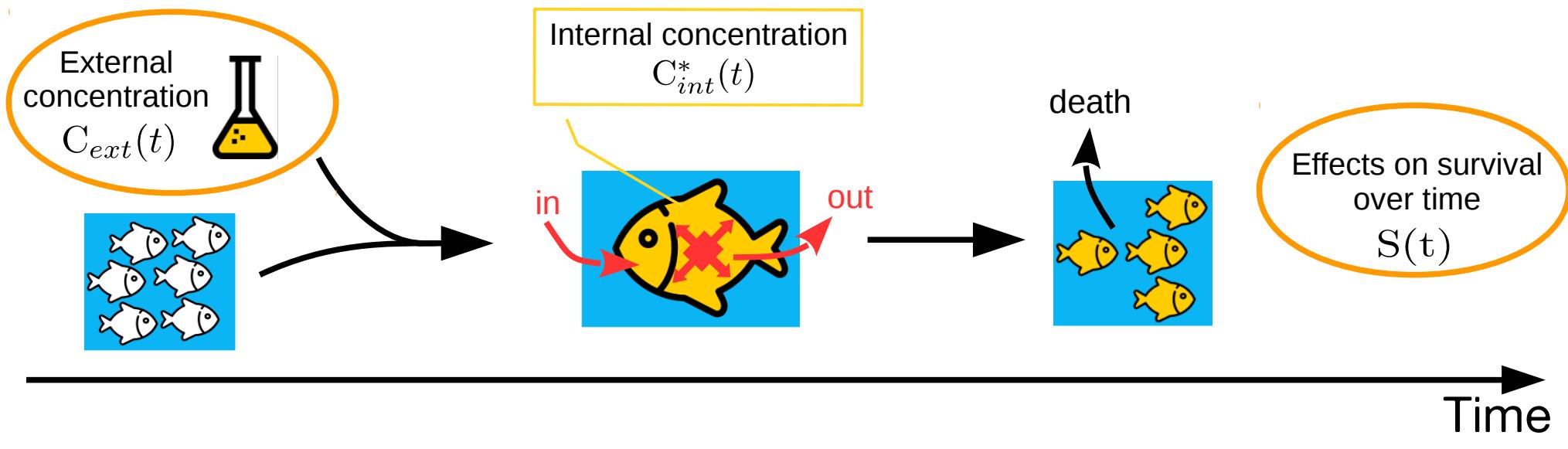
# Modelling: TKTD

- Bioaccumulation
- Distribution
- Biotransformation
- Elimination

- Toxic mechanism
- Biochemical effects
- Physiological effects
- Mortal., Repro., Behav.

Toxicokinetics (TK)

Toxicodynamics (TD)



# TKTD advantages

- Bioaccumulation
- Distribution
- Biotransformation
- Elimination

- Toxic mechanism
- Biochemical effects
- Physiological effects
- Mortal., Repro., Behav.



## Science

- **mechanism** rather than describe effects (e.g., Grimm et al., 2009 ; Forbes et al., 2009)
- **temporal aspects of exposure & toxicity** (non -constant profiles) (e.g., Ashauer et al., 2007)
- derive time-independent **toxicity parameters** (e.g., Jager et al., 2011)
- make **predictions** for untested situations (e.g., Ashauer et al., 2007)
- effects of **mixture** over-time (Jager et al., 2010)

## Policies

- TKTD model are **promoted by OECD** (series on testing and assessment N°54, 2006)
- part of **ERA of PPPs** (Plant Protection Products)
- can be used for **REACH dossier**



# Modelling: TKTD



$$\left\{ \begin{array}{l} \frac{dC_{int}^*(t)}{dt} = k_d(C_{ext}(t) - C_{int}^*(t)) \\ C_{int}^*(t = 0) = 0 \end{array} \right.$$

$$\Rightarrow C_{int}^*(t) = k_d e^{-k_d t} \int_0^t e^{k_d \tau} C_{ext}(\tau) d\tau$$



# Modelling: TKTD



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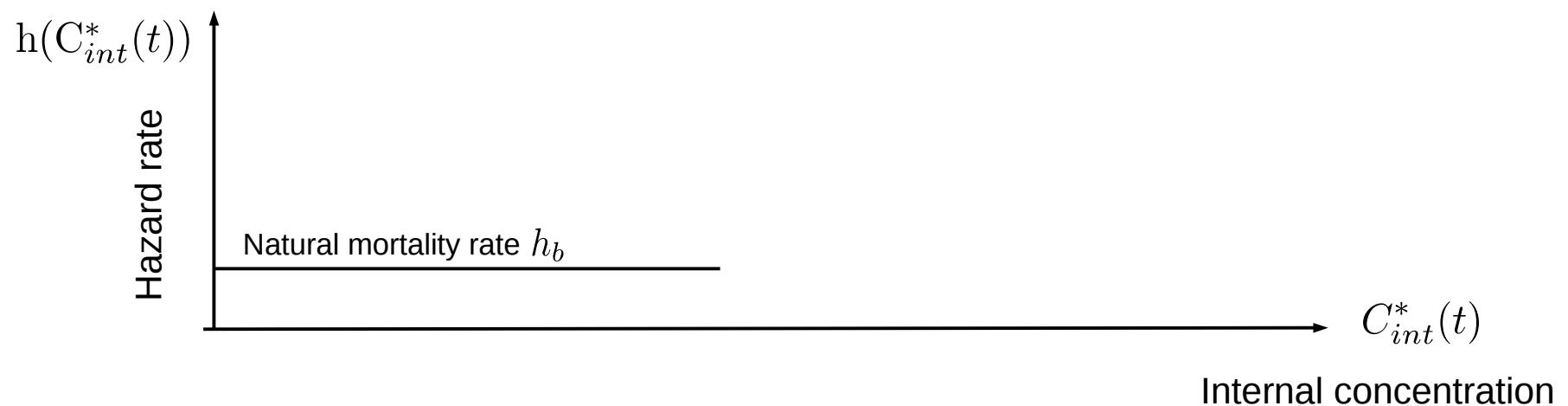
General Unified Threshold model of Survival (GUTS)  
(Jager et al., 2011 ; Ashauer et al., 2013)

Two complementary death mechanisms:

- 1. Stochastic Death (SD)**
- 2. Individual Tolerance (IT)**

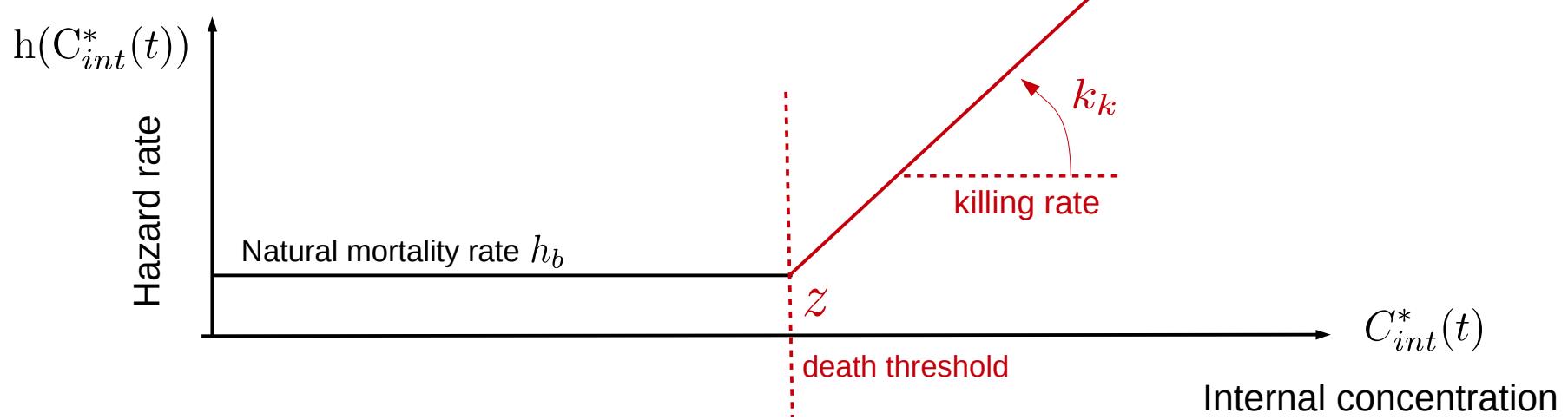


# Modelling: TKTD



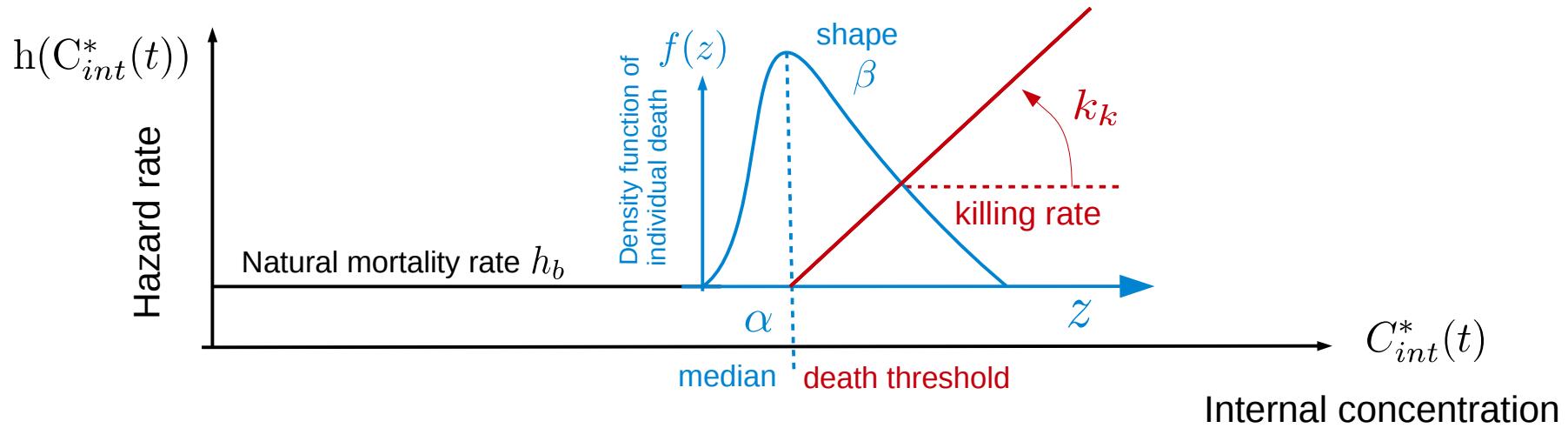
(Jager *et al.*, 2011)

# Modelling: TKTD



(Jager *et al.*, 2011)

# Modelling: TKTD

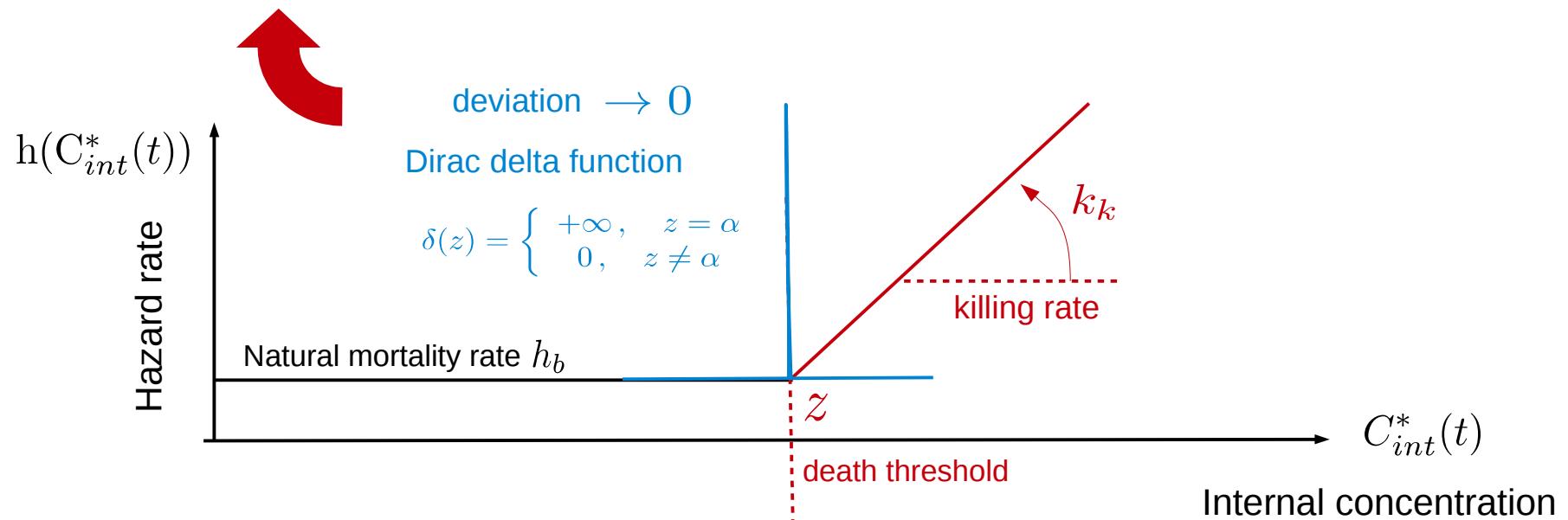


(Jager et al., 2011)

# Modelling: TKTD

## Stochastic Death (SD)

$$S_{SD}(t) = \exp \left( - \int_0^t k_k \max(C_{int}^*(\tau) - z, 0) + h_b d\tau \right)$$



(Jager et al., 2011)

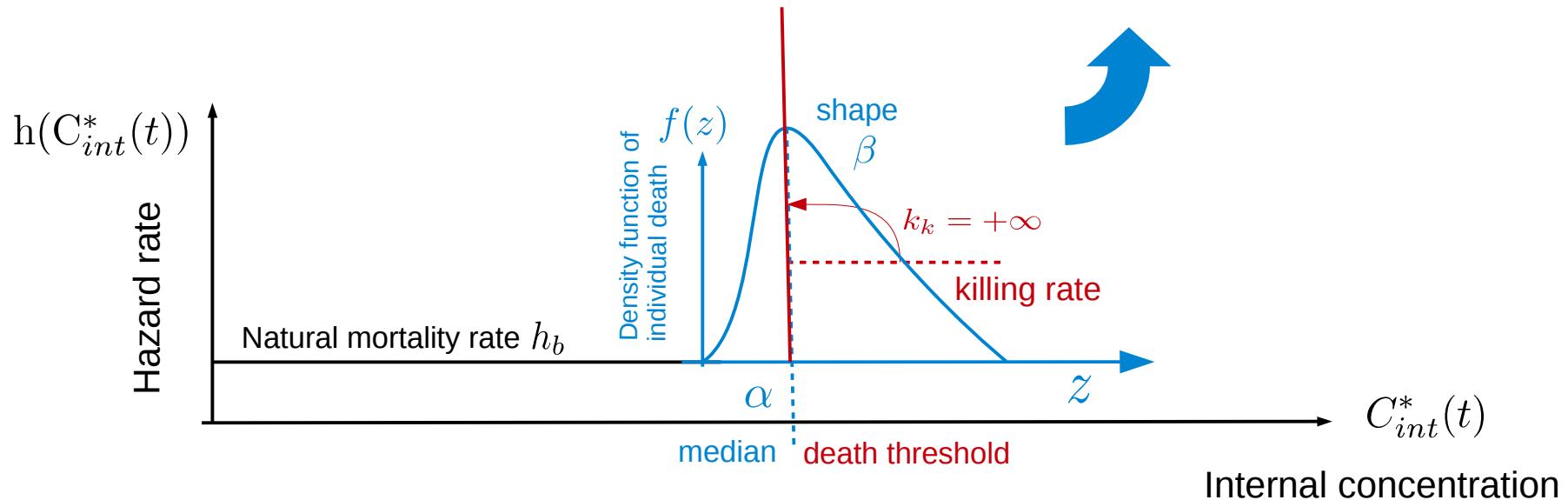
# Modelling: TKTD

- Death is immediate if  $C_{int}^* > z$
- Individuals differ in  $z$

## Individual Tolerance (IT)

$$S_{IT}(t) = e^{-h_b t} \int_{\max_{0 \leq \tau \leq t} C_{int}^*(\tau)}^{+\infty} f(z) dz$$

$$= e^{-h_b t} \left( 1 - F \left( \max_{0 < \tau < t} C_{int}^*(\tau) \right) \right)$$



(Jager et al., 2011)

# Modelling: TKTD

Toxicokinetics  
(TK)



$$\begin{cases} \frac{dC_{int}^*(t)}{dt} = k_d(C_{ext}(t) - C_{int}^*(t)) \\ C_{int}^*(t = 0) = 0 \end{cases}$$



Stochastic Death (SD)

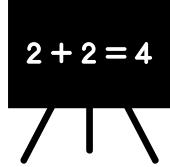
Individual Tolerance (IT)

Toxicodynamics  
(TD) - GUTS

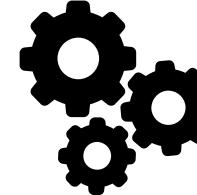
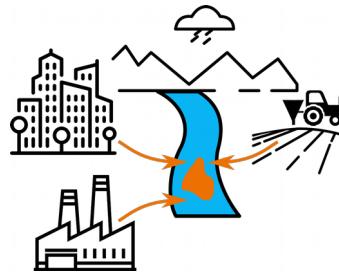
$$S_{SD}(t) = \exp \left( - \overbrace{\int_0^t k_k \max(C_{int}^*(\tau) - z, 0) + h_b d\tau}^{h(C_{int}^*(\tau))} \right)$$

$$\begin{aligned} S_{IT}(t) &= e^{-h_b t} \int_{\max_{0 \leq \tau \leq t} C_{int}^*(\tau)}^{+\infty} f(z) dz \\ &= e^{-h_b t} \left( 1 - F \left( \max_{0 < \tau < t} C_{int}^*(\tau) \right) \right) \end{aligned}$$

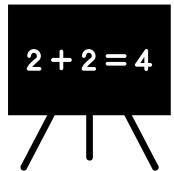




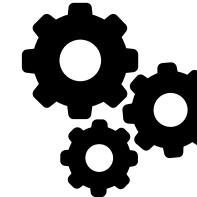
to be applied



1. Easy to use
2. Minimize user influence on calibration of parameters



to be applied



## 1. Easy to use

## 2. Minimize user influence on calibration of parameters



morse (  , JAGS )  
Just Another Gibbs Sampler



web interface

<http://pbil.univ-lyon1.fr/software/mosaic/>

MOSAIC   SSD   Reproduction   Survival   Courses   Contact

### MOSAIC<sub>surv</sub>

Information: MOSAIC<sub>surv</sub> is currently under development, but its main features are already available. Suggestions and comments are very welcomed, please drop us an [email](#).

The tool MOSAIC<sub>surv</sub> provides a complete analysis of bioassay survival data, including descriptive summaries of the data and an estimation of LC<sub>x</sub> values (x% Lethal Concentration). MOSAIC<sub>surv</sub> does not expect any input besides the survival dataset: the service will select the most appropriate model and optimize its parameters automatically.

All calculations are based on a companion R package named MORSE, and more details about the underlying modeling can be found in the corresponding [vignette](#).

You can upload a tabular file containing your own survival data under plain text (see the [format specification](#)). Time must be expressed in day units.

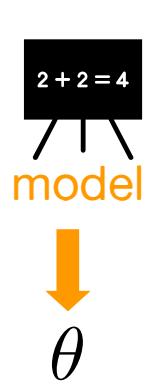
Aucun fichier sélectionné.

Concentration unit:

y-label:  per individual-day

# Bayesian workflow

replicate	time	conc	survival
A	$t_{A,1}$	$C_{A,1}$	$N_{A,1}$
...	...	...	...
B	$t_{B,1}$	$C_{B,1}$	$N_{B,1}$
...	...	...	...
C	$t_{C,1}$	$C_{C,1}$	$N_{C,1}$
...	...	...	...



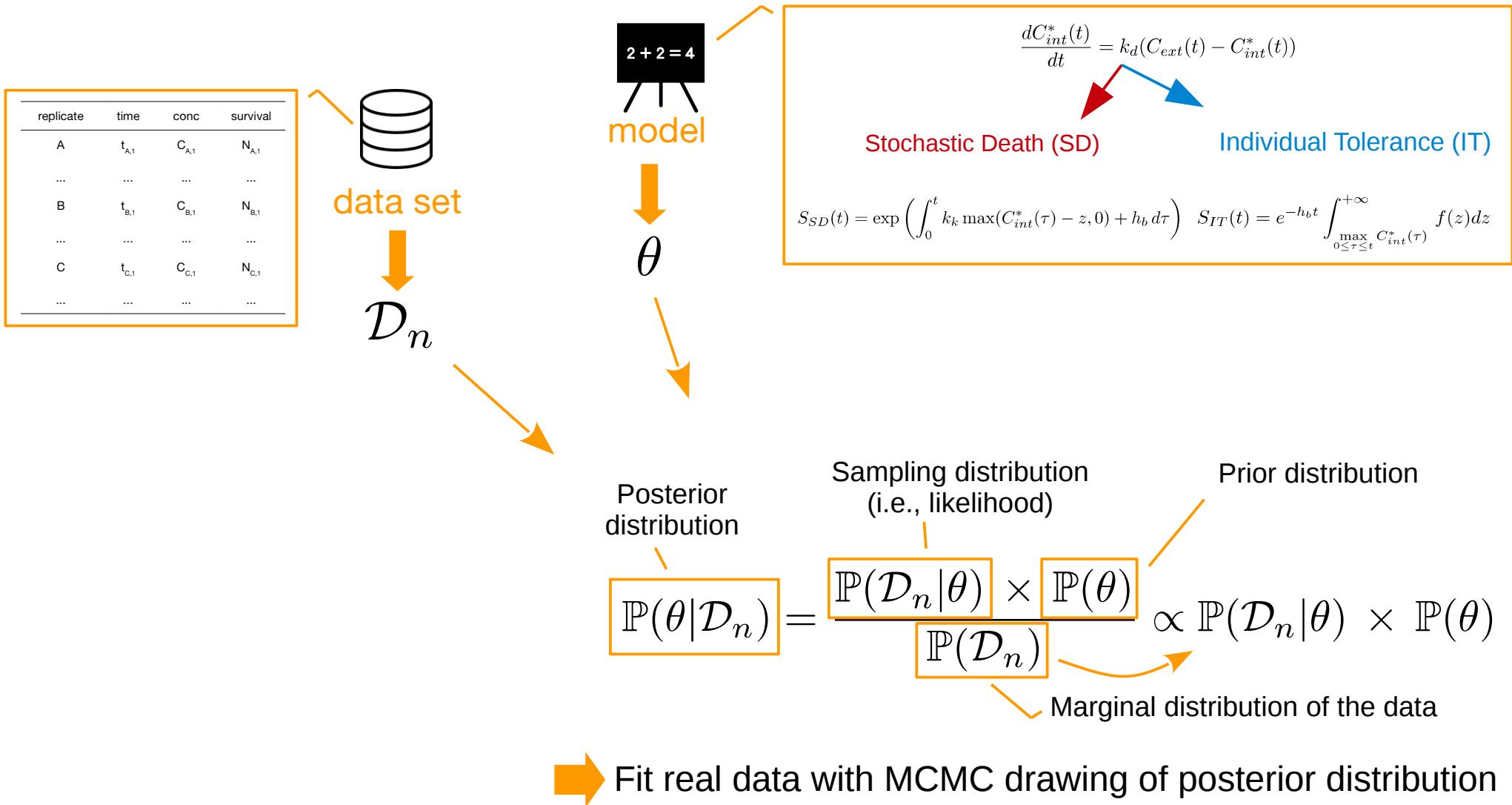
Stochastic Death (SD)

$$S_{SD}(t) = \exp \left( \int_0^t k_k \max(C_{int}^*(\tau) - z, 0) + h_b d\tau \right)$$

Individual Tolerance (IT)

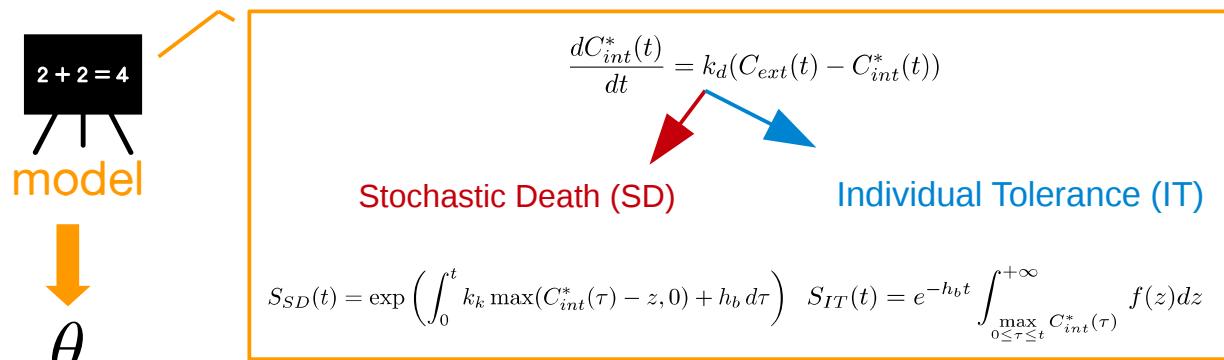
$$\frac{dC_{int}^*(t)}{dt} = k_d(C_{ext}(t) - C_{int}^*(t))$$
$$S_{IT}(t) = e^{-h_b t} \int_{\max_{0 \leq \tau \leq t} C_{int}^*(\tau)}^{+\infty} f(z) dz$$

# Bayesian workflow



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...	...	...	...
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...	...	...	...
C	$t_{C,1}$	$C_{C,1}$	$N_{C,1}$
...	...	...	...



Automatically determined based on the experimental design

$$\mathbb{P}(\theta|\mathcal{D}_n) = \frac{\mathbb{P}(\mathcal{D}_n|\theta) \times \mathbb{P}(\theta)}{\mathbb{P}(\mathcal{D}_n)} \propto \mathbb{P}(\mathcal{D}_n|\theta) \times \mathbb{P}(\theta)$$

Posterior distribution

Sampling distribution (i.e., likelihood)

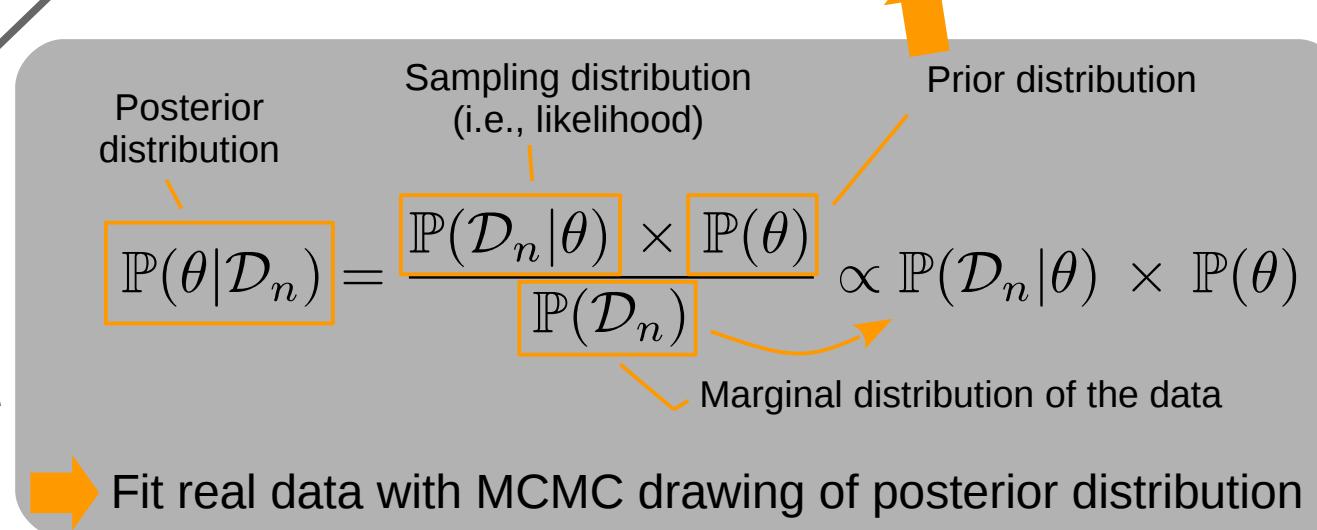
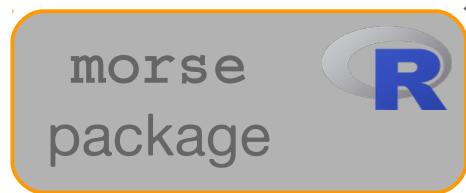
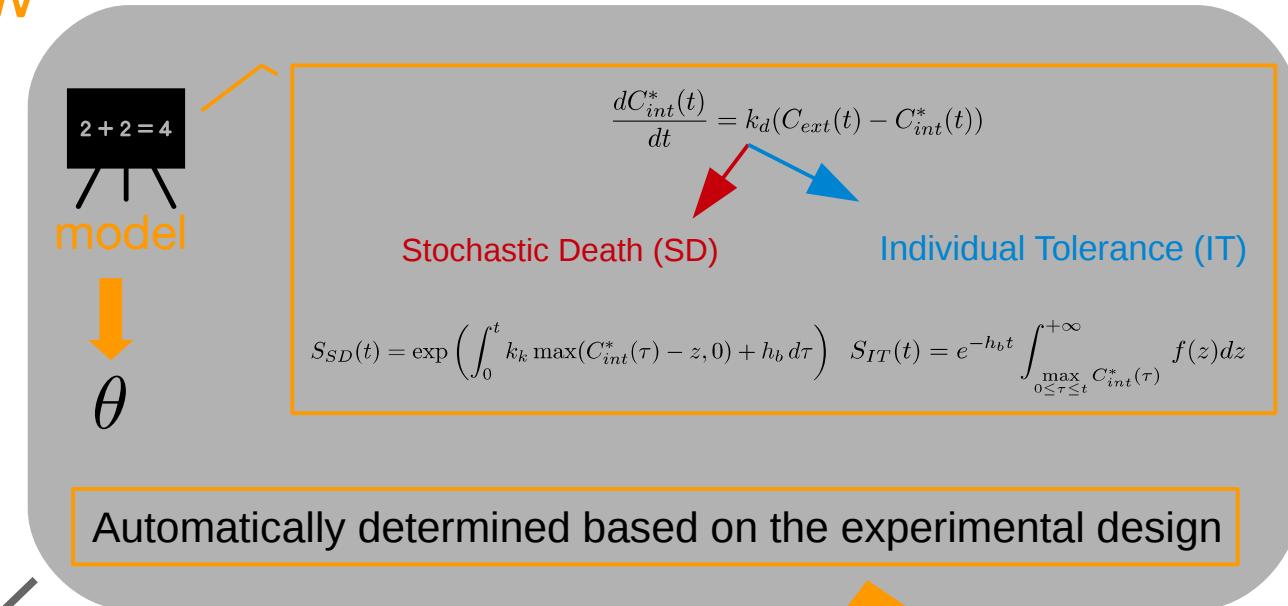
Prior distribution

Marginal distribution of the data

Fit real data with MCMC drawing of posterior distribution

# Bayesian workflow

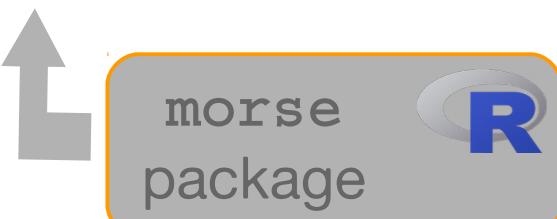
replicate	time	conc	survival
A	$t_{A,1}$	$C_{A,1}$	$N_{A,1}$
...	...	...	...
B	$t_{B,1}$	$C_{B,1}$	$N_{B,1}$
...	...	...	...
C	$t_{C,1}$	$C_{C,1}$	$N_{C,1}$
...	...	...	...



# Bayesian workflow

## User work

replicate	time	conc	survival
A	$t_{A,1}$	$C_{A,1}$	$N_{A,1}$
...	...	...	...
B	$t_{B,1}$	$C_{B,1}$	$N_{B,1}$
...	...	...	...
C	$t_{C,1}$	$C_{C,1}$	$N_{C,1}$
...	...	...	...



$2 + 2 = 4$   
model  
 $\theta$

$$\frac{dC_{int}^*(t)}{dt} = k_d(C_{ext}(t) - C_{int}^*(t))$$

Stochastic Death (SD)

$$S_{SD}(t) = \exp \left( \int_0^t k_k \max(C_{int}^*(\tau) - z, 0) + h_b d\tau \right) \quad S_{IT}(t) = e^{-h_b t} \int_{\max_{0 \leq \tau \leq t} C_{int}^*(\tau)}^{+\infty} f(z) dz$$

Individual Tolerance (IT)

Automatically determined based on the experimental design

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Marginal distribution of the data

Fit real data with MCMC drawing of posterior distribution

# MORSE: MOdelling tools for Reproduction and Survival data in Ecotoxicology



CRAN

Version : 2.2.0

(Delignette-Muller *et al.*, 2016 and 2017)

```
install.packages ("morse")
```

In development, Github  
Version : 3.0.0



```
library("devtools")  
install_github(repo = "pveber/morse")
```



# Example – constant exposure concentration

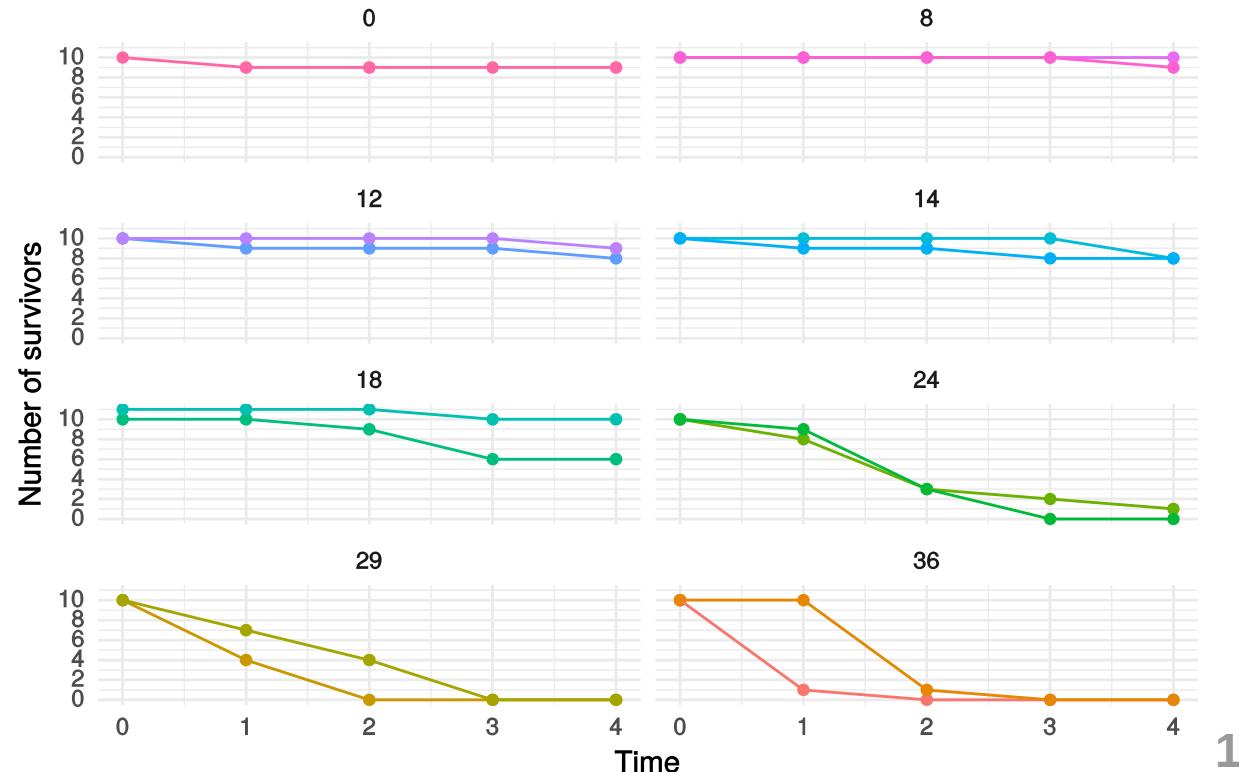
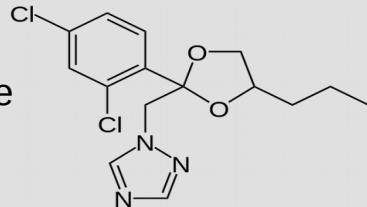
```
# (1) load dataset  
data(propiconazole)  
# (2) create a `survData` object  
propic_cst <- survData(propiconazole)  
# (3) represent the number of survivor as a function time  
plot(propic_cst)
```



*Gammarus pulex*

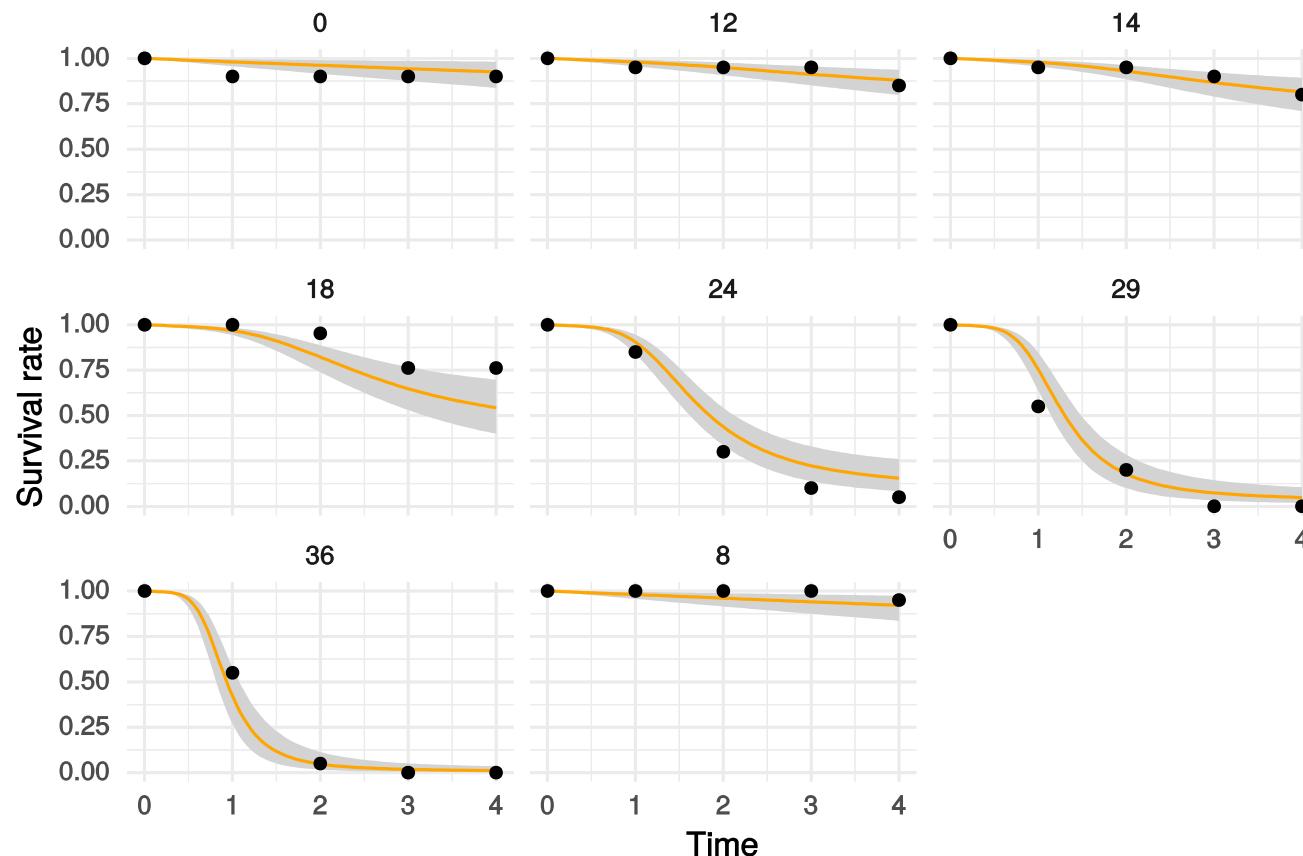
Propiconazole  
(fungicide)

(Nyman et al., 2012)



# Example – constant exposure concentration

```
# (4) fit a TKTD model, SD  
fit_cstSD <- survFit(propic_cst, model_type = "IT")  
# (5) plot a `survFit` object : survival rate  
plot(fit_cstSD)
```



# Example – constant exposure concentration

```
# (6) summary of the object 'fit_cstSD'  
summary(fit_cstSD)
```

```
Summary:  
Priors on parameters (quantiles):  
      50%    2.5%   97.5%  
kd    4.157e-02 2.771e-04 6.236e+00  
hb    1.317e-02 2.708e-04 6.403e-01  
alpha 1.697e+01 8.121e+00 3.546e+01  
beta  1.000e+00 1.259e-02 7.943e+01
```

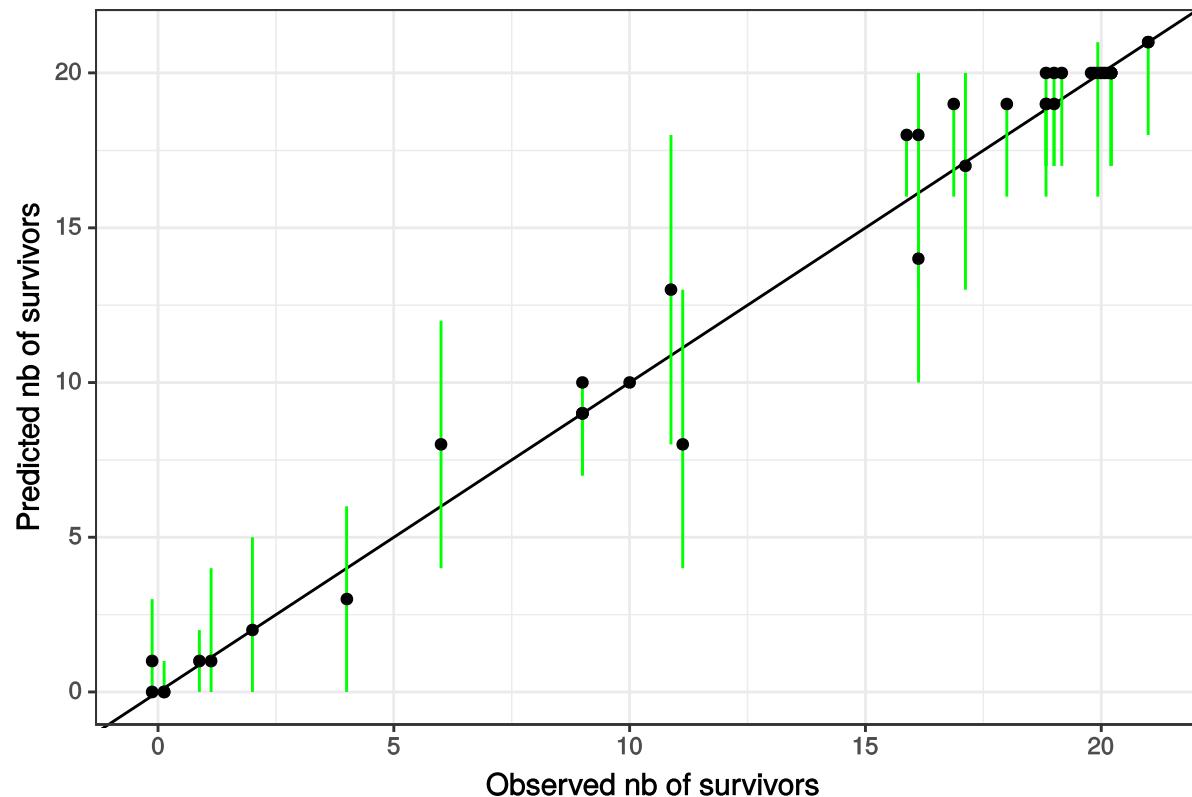
```
Posterior of the parameters (quantiles):  
  parameters   median     Q2.5     Q97.5  
1          kd  0.73355870  0.542755327  0.9536752  
2          hb  0.01947378  0.004633722  0.0442195  
3          alpha 17.96646351 15.379791021 20.4561464  
4          beta  6.83101158  4.991422714  9.2080804
```

```
alpha <- 10^do.call("rbind", fit_cstIT$mcmc) [, "alpha_log10"]  
qplot(alpha, geom = "density", # [...]
```



# Example – constant exposure concentration

```
# (6) summary of the object 'fit_cstSD'  
summary(fit_cstSD)  
# (7) plot Posterior Predictive Check  
ppc(fit_cstSD)
```



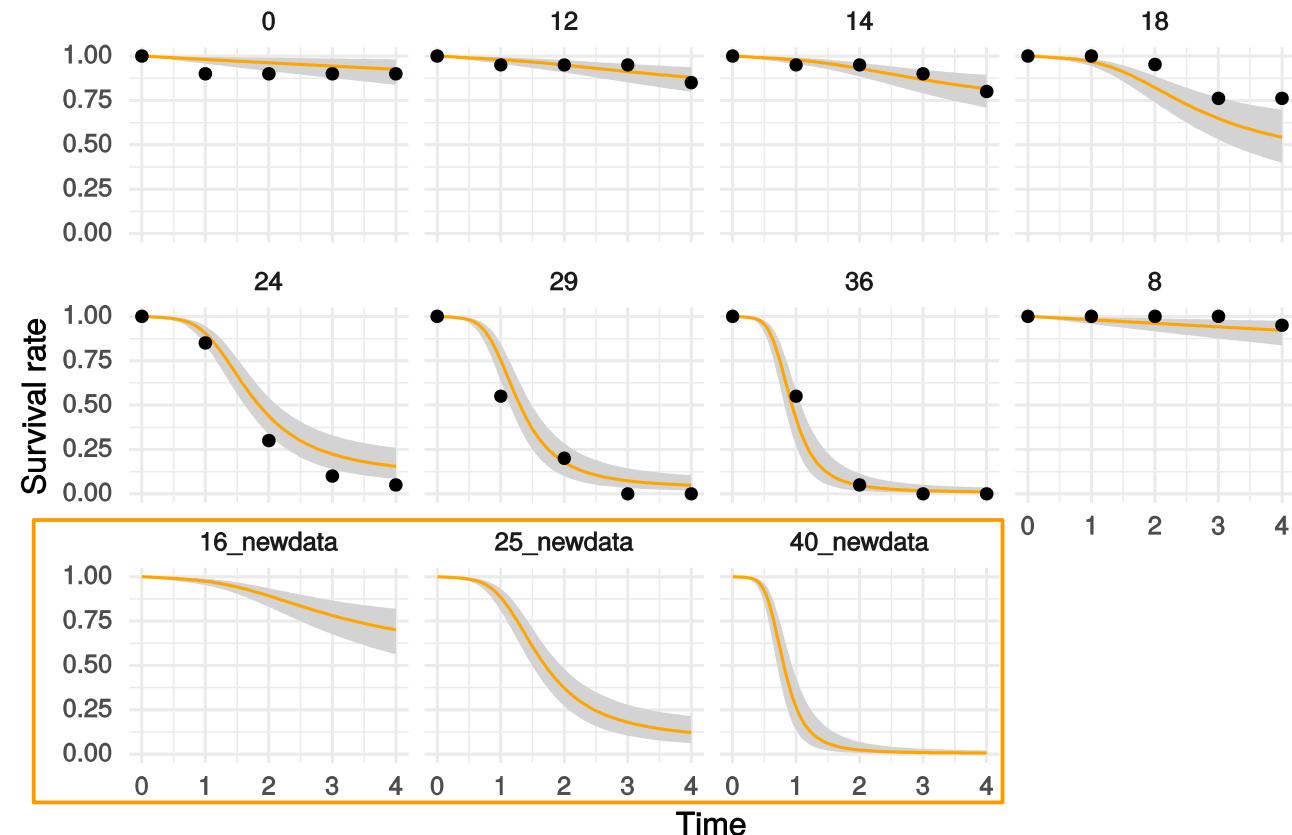
# Example – constant exposure concentration

```
# (8) Prediction  
predict_fit_cstSD <- predict(object = fit_cstSD, newdata = data_4casting)  
# (9) plot the prediction  
plot(predict_fit_cstSD, adddata = TRUE)
```

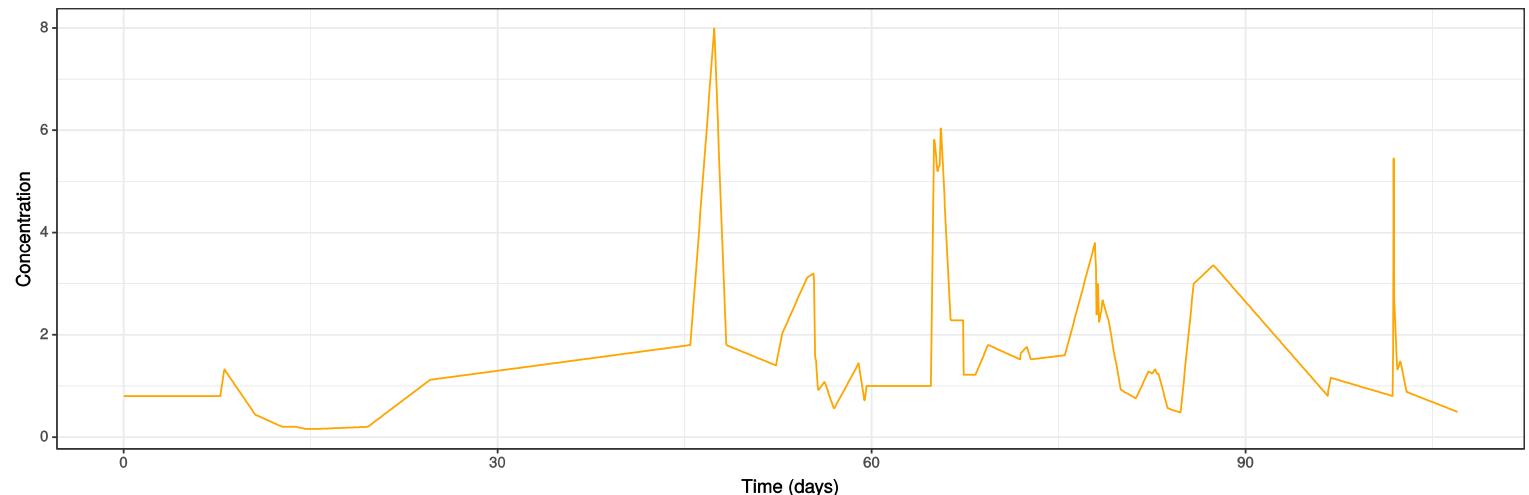
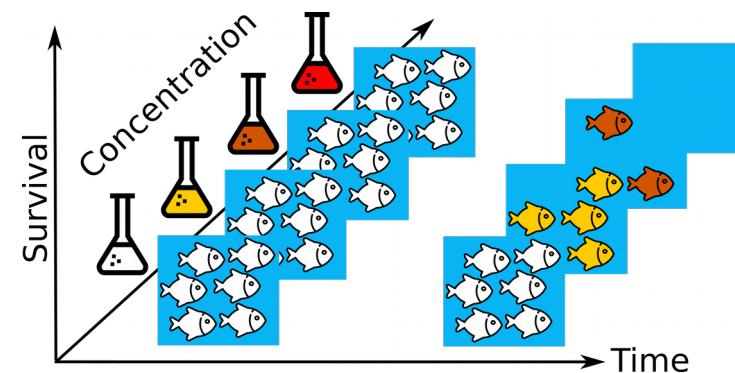
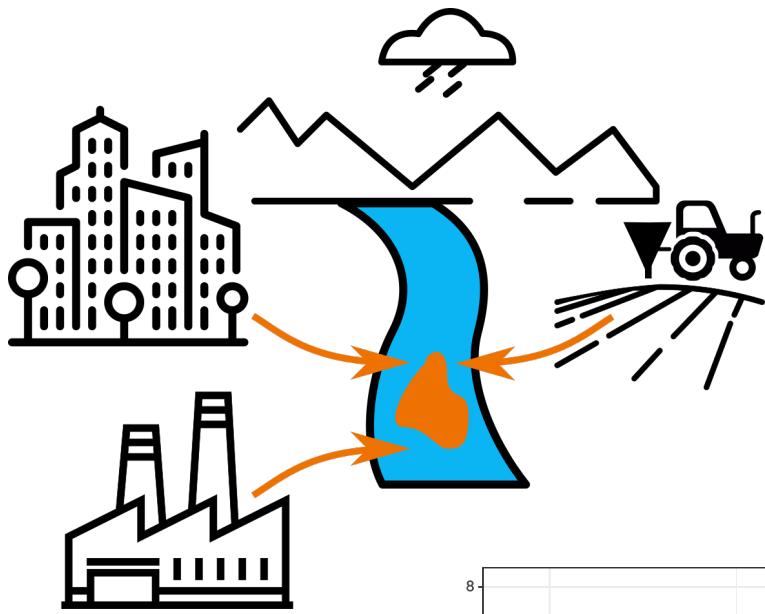
```
data_4casting <- data.frame(time =  
rep(0:4,3), conc = rep(c(16,25,40),  
rep(5,3)), replicate =  
c( rep("16_newdata",5),  
rep("25_newdata",5),rep("40_newdata",5)))
```



New datasets

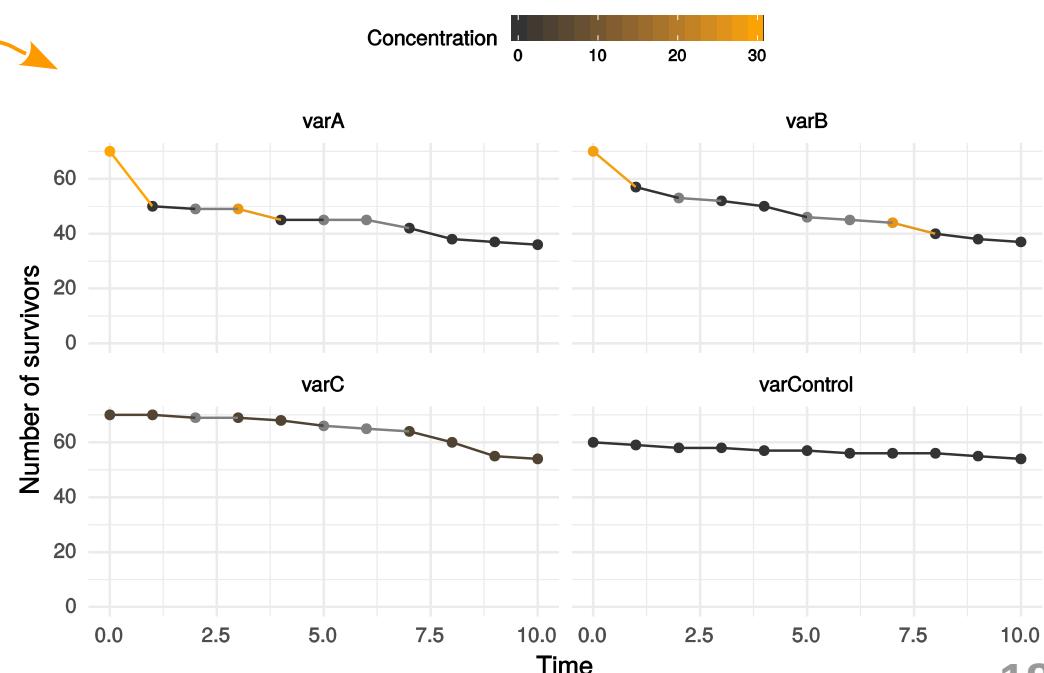
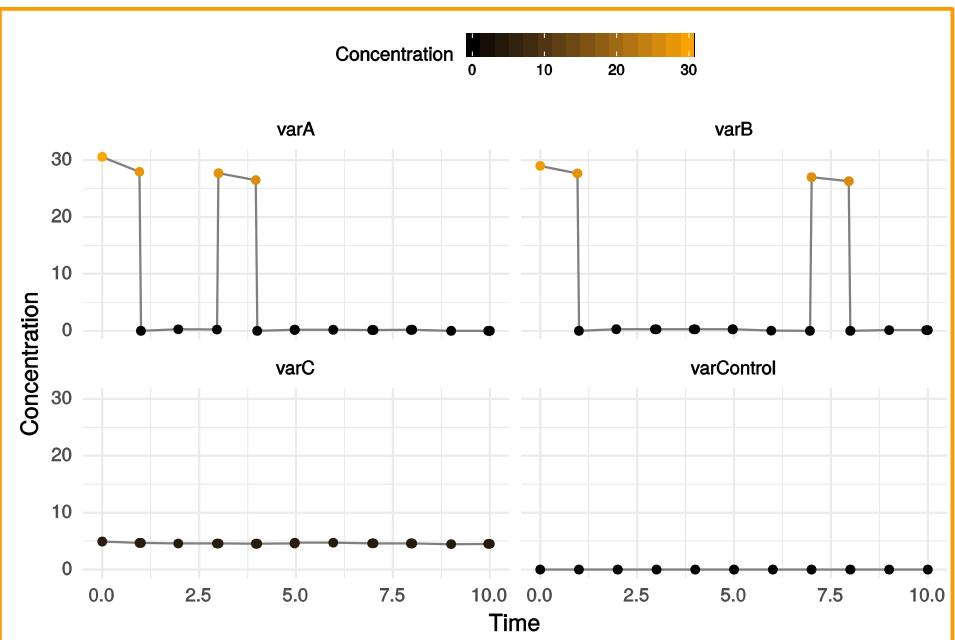


## Example – variable exposure concentration



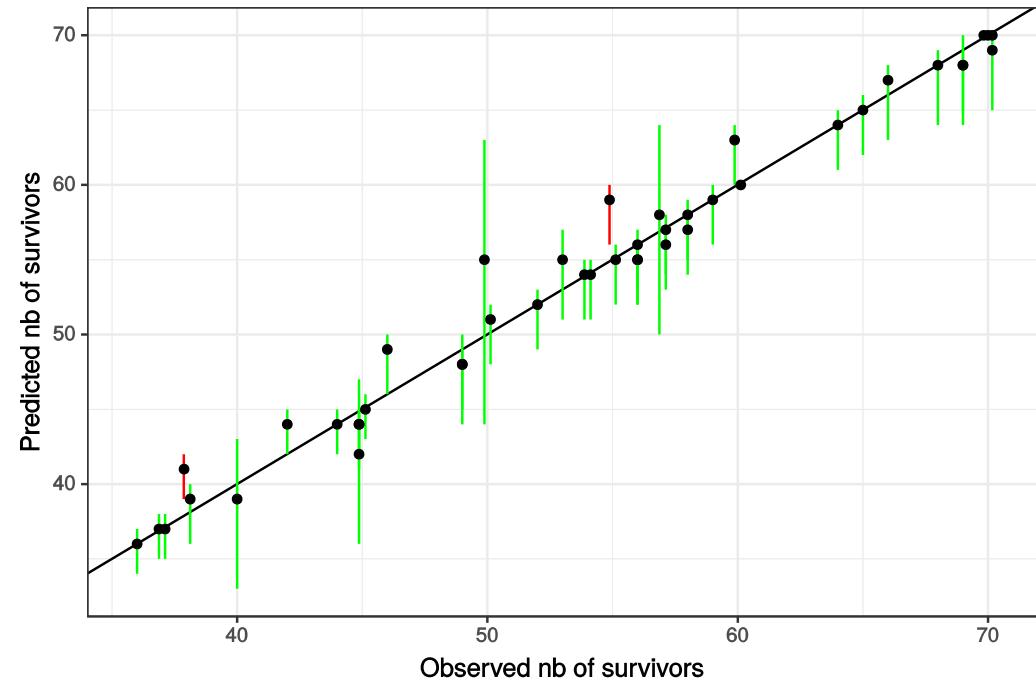
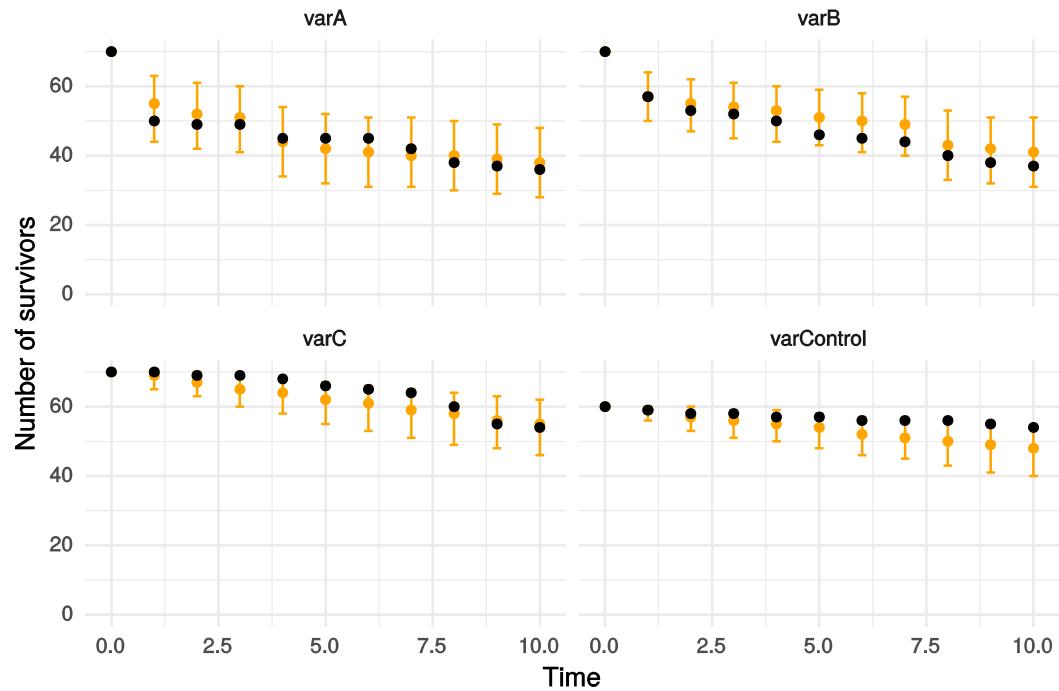
# Example – variable exposure concentration

```
# (1) load data 'propiconazole_pulse_exposure'  
data("propiconazole_pulse_exposure")  
# (2) create a `survData` object  
dat_var <- survData(propiconazole_pulse_exposure)  
# (3) represent the number of survivor as a function time  
plot(dat_var)
```



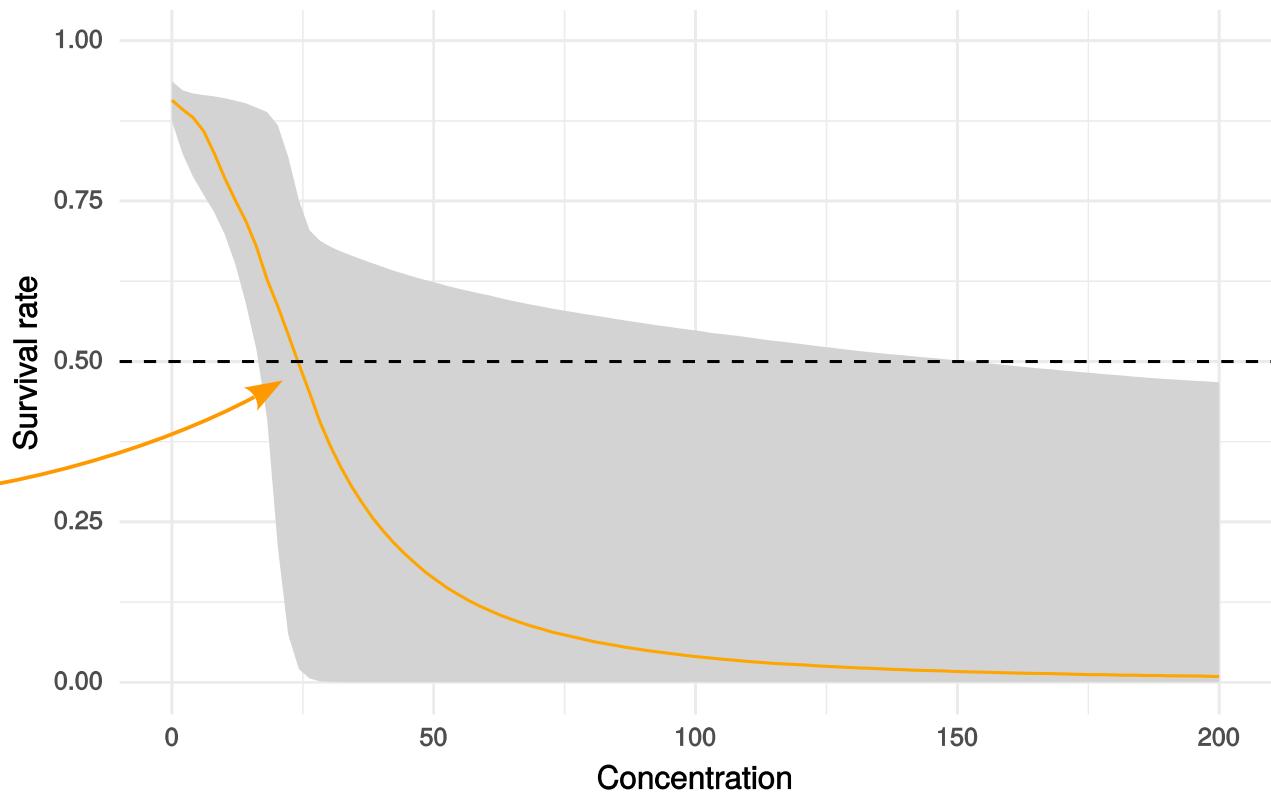
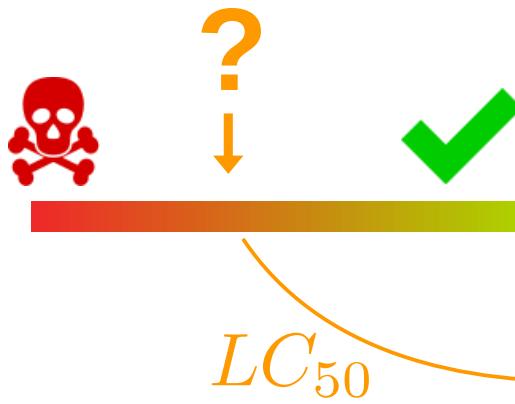
# Example – variable exposure concentration

```
# (4) fit and plot TKTD model  
fit_varSD <- survFit(dat_var, model_type = "SD")  
# (5) plot fit object  
plot(fit_varSD, data_type = "number")  
# (6) check validity with PPC  
ppc(fit_varSD)
```



# Example – variable exposure concentration

```
# (5) create the object LCx  
LC50_VarSD <- LCx(fit.varSD, time.LCx = 4, x.LCx = 50, conc.min = 0, conc.max = 100)  
# (6) plot a LCx object  
plot(LC50_VarSD)
```

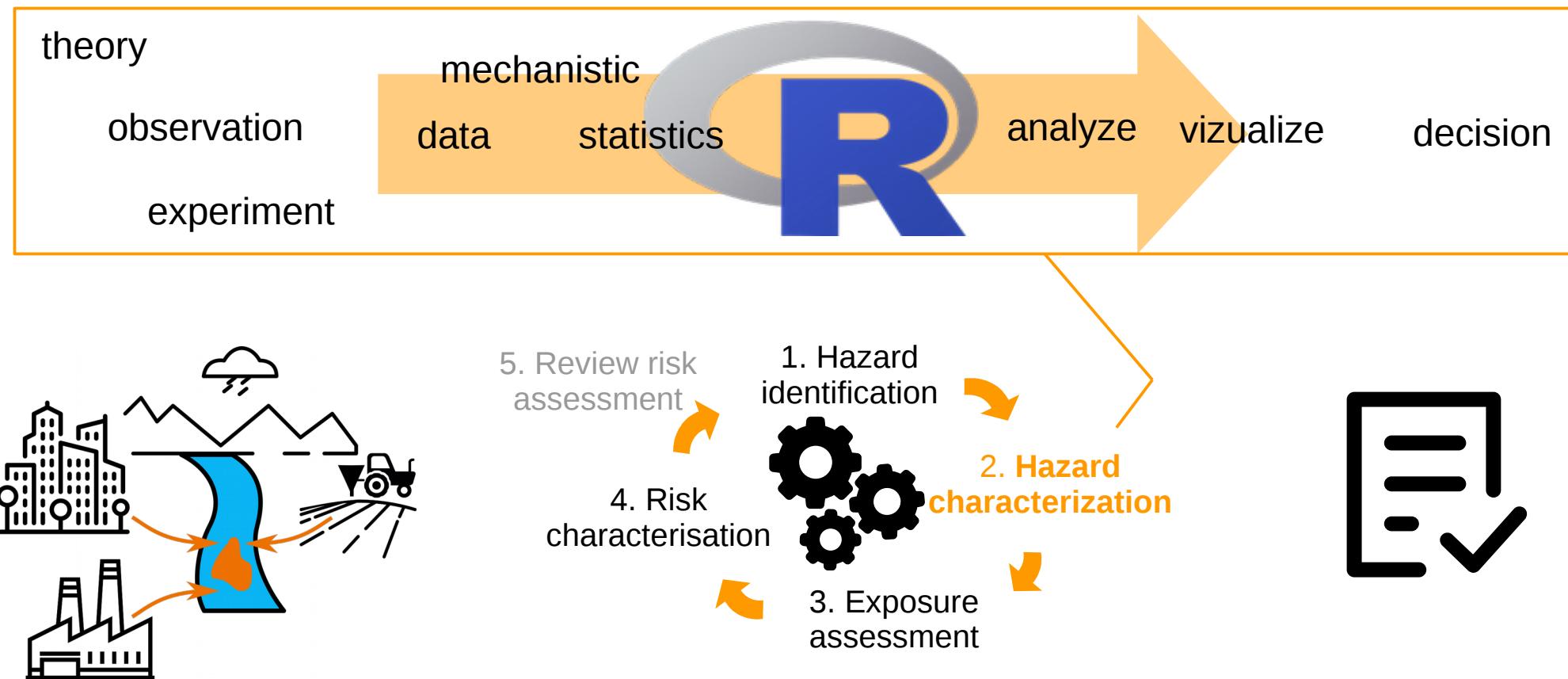


# Transdisciplinarity

- **Easy to apply complex model** : load data → analyze (select ‘SD’ or ‘IT’) → vizualize
- Next step: **Integration of ‘morse 3.0.0’ R package** in the **MOSAIC web-platform**

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- Next step: Integration of 'morse 3.0.0' R package in the MOSAIC web-platform





# Thank you for your attention

---

$$\mathbb{P}(\text{Thanks}|\text{Attention}) = \frac{\mathbb{P}(\text{Attention}|\text{Thanks}) \times \mathbb{P}(\text{Thanks})}{\mathbb{P}(\text{Attention})}$$

↖ ↗

Law(interesting)

