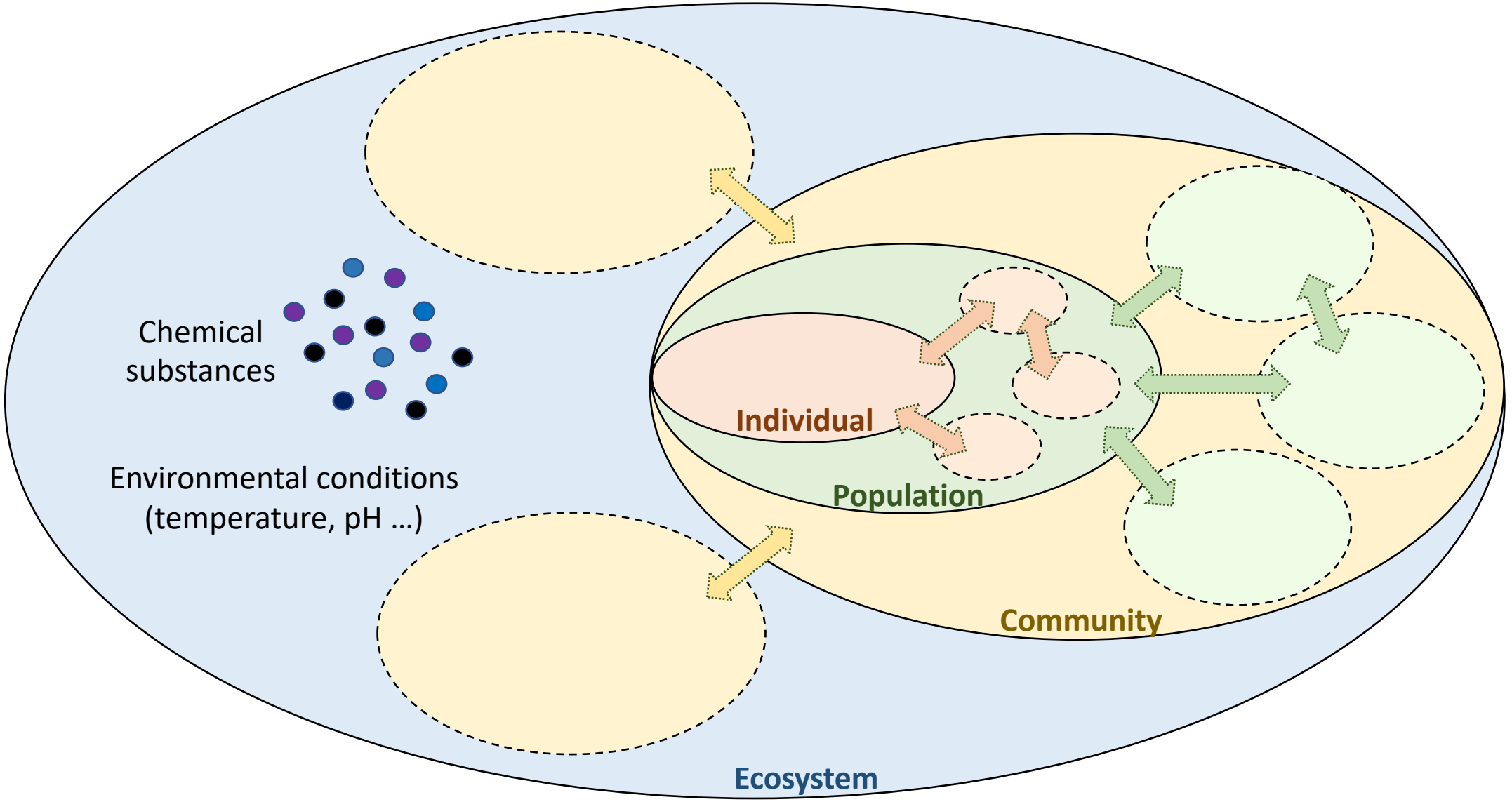
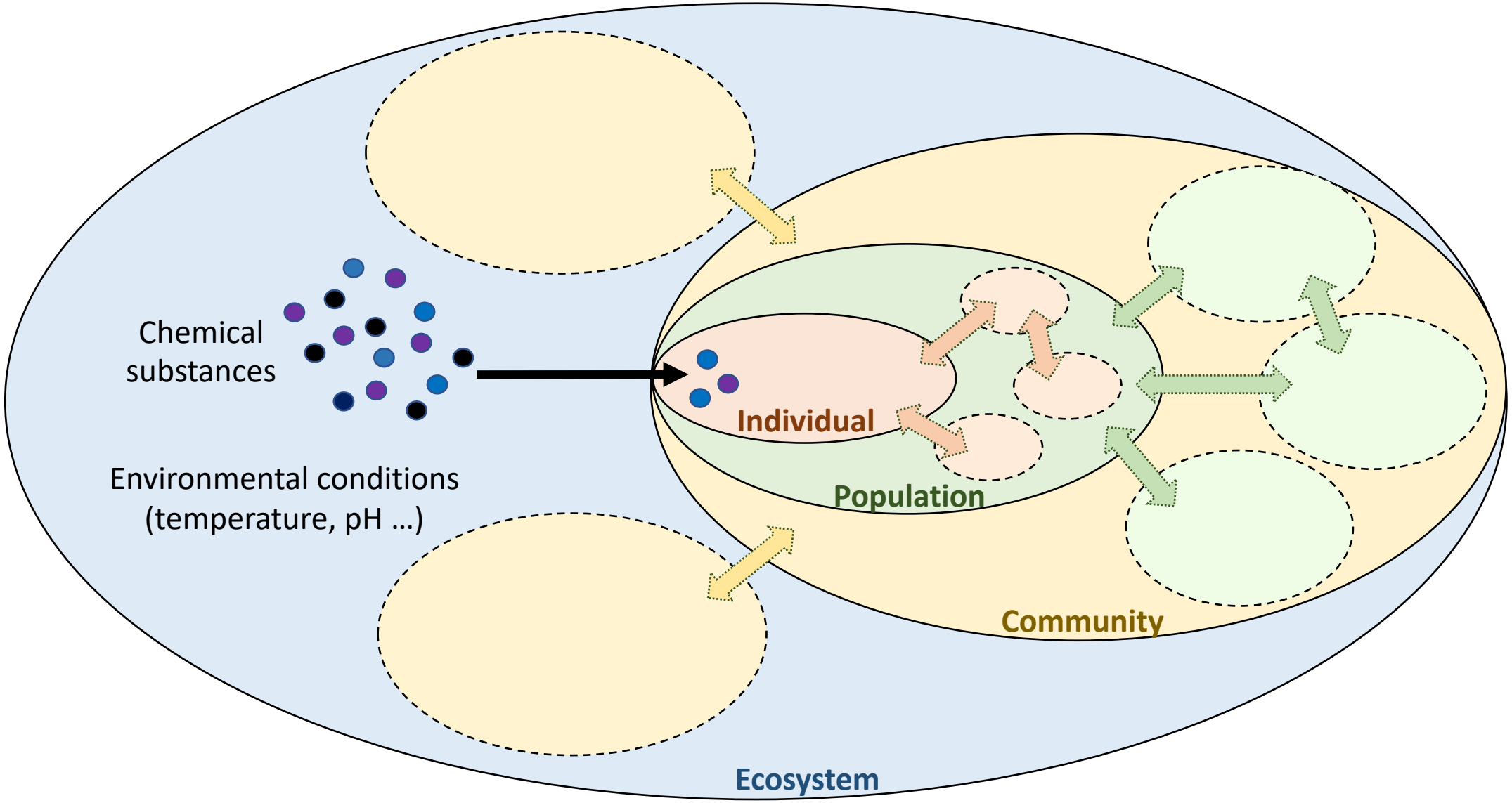
Toxico-Kinetic (TK) modelling

Christelle Lopes
christelle.lopes@univ-lyon1.fr

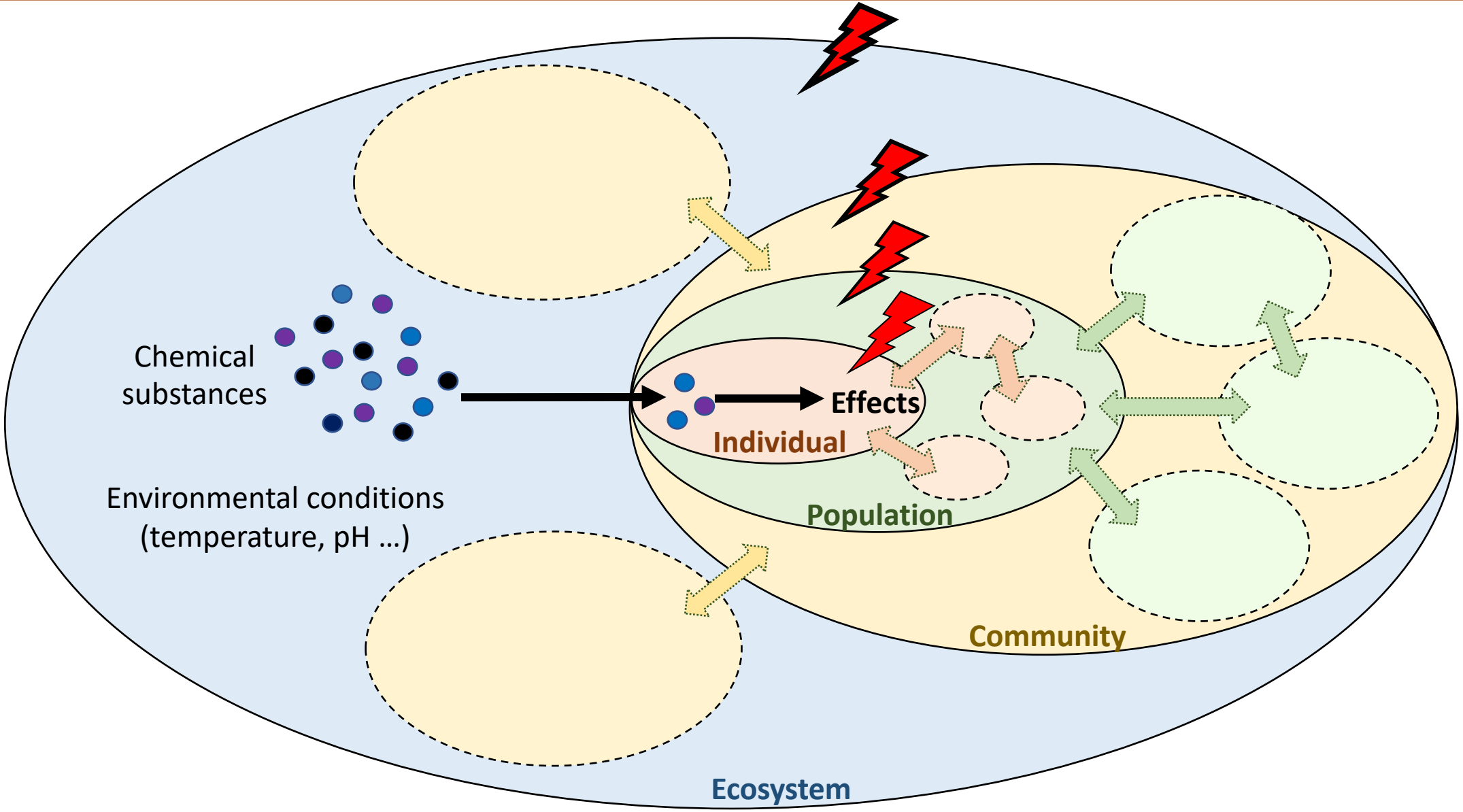
Aquatic ecosystems, made of several communities



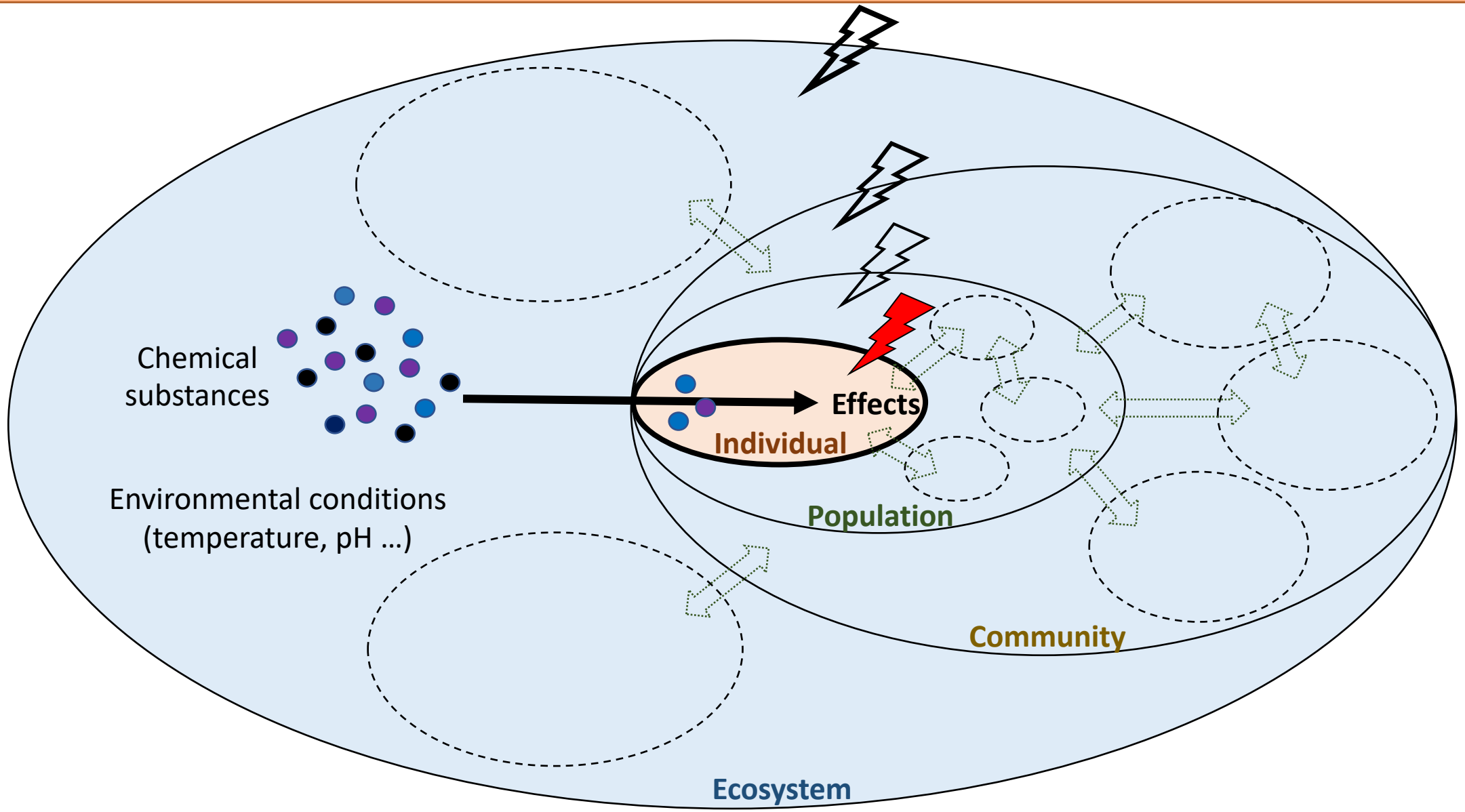
Communities are exposed to chemicals via individuals



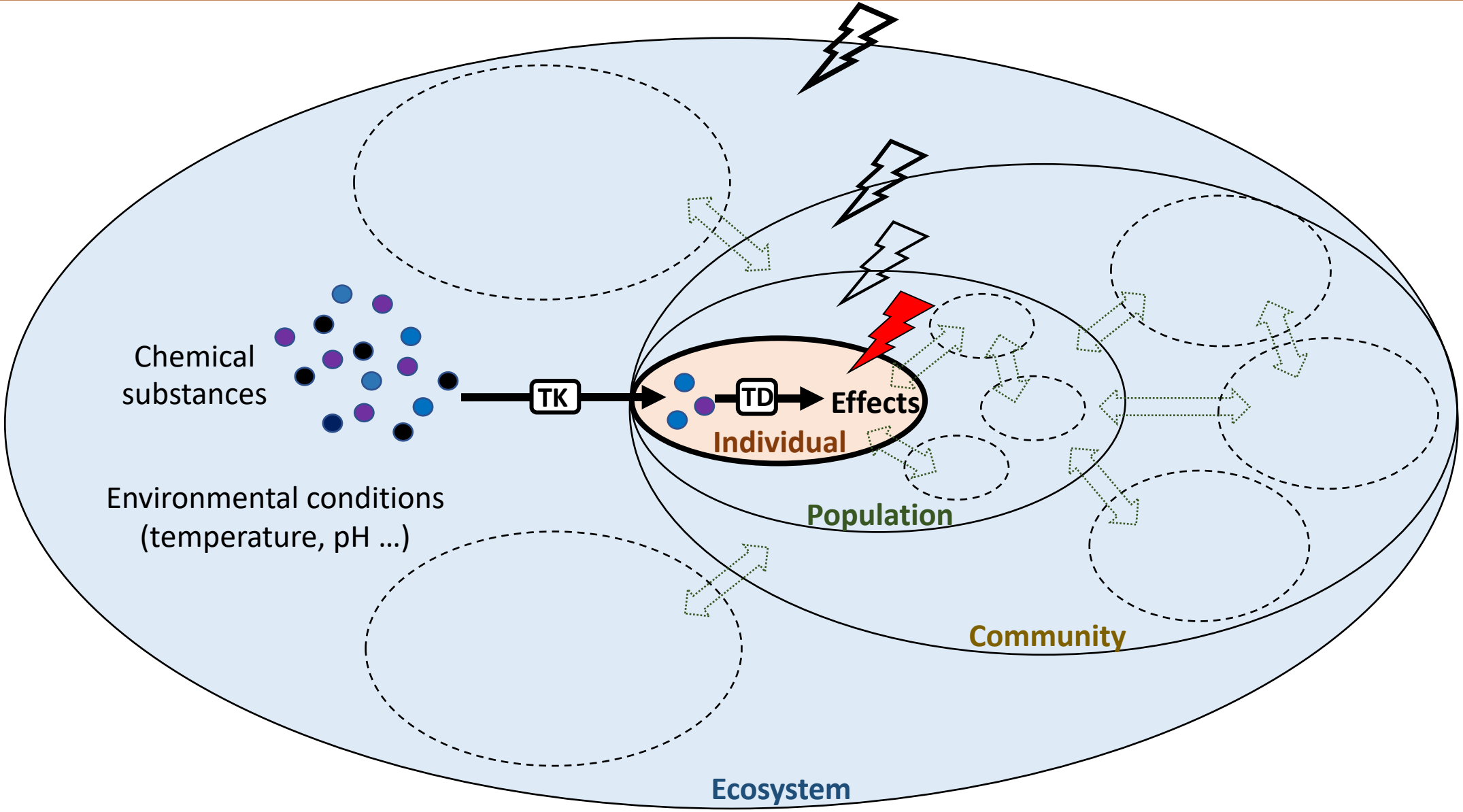
Evaluation of chemical effects at different biological levels



Central role of the individual level : estimation de LC/ECx



Central role of the individual level : modèles TKTD



Importance of TK in environmental risk assessment (ERA)

1. Characterize chemical state of aquatic ecosystem (European WFD)
2. Make the link between exposure concentration and individual effects
3. Understand and describe bioaccumulation processes

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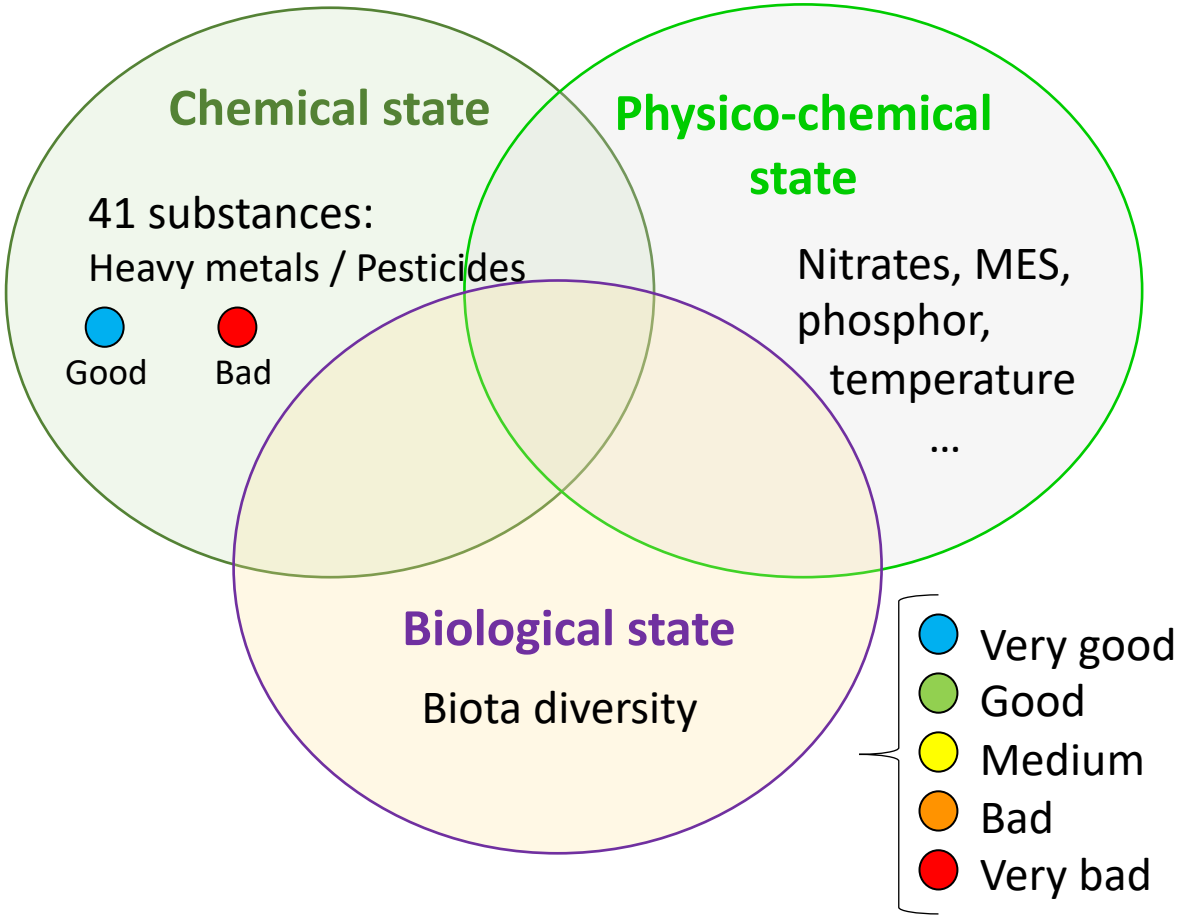

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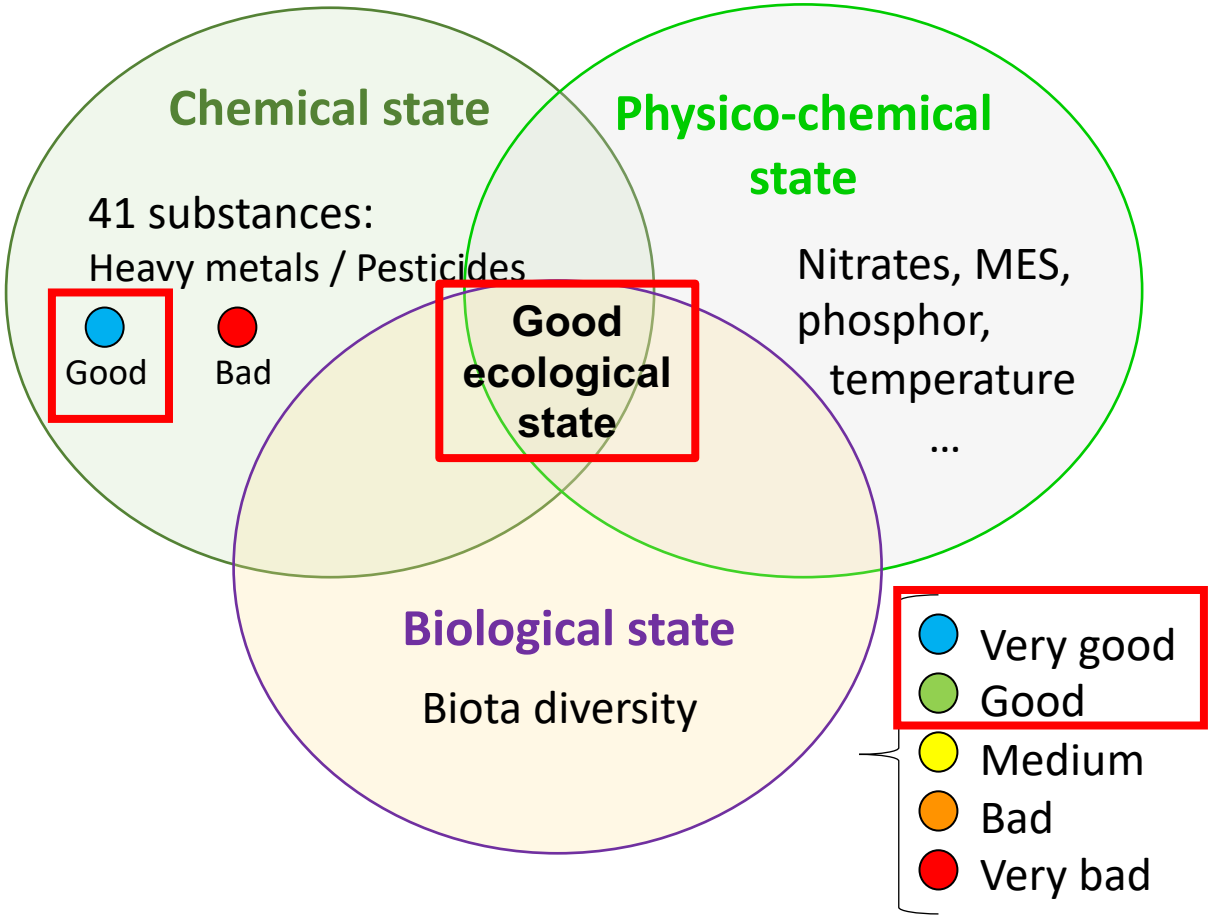

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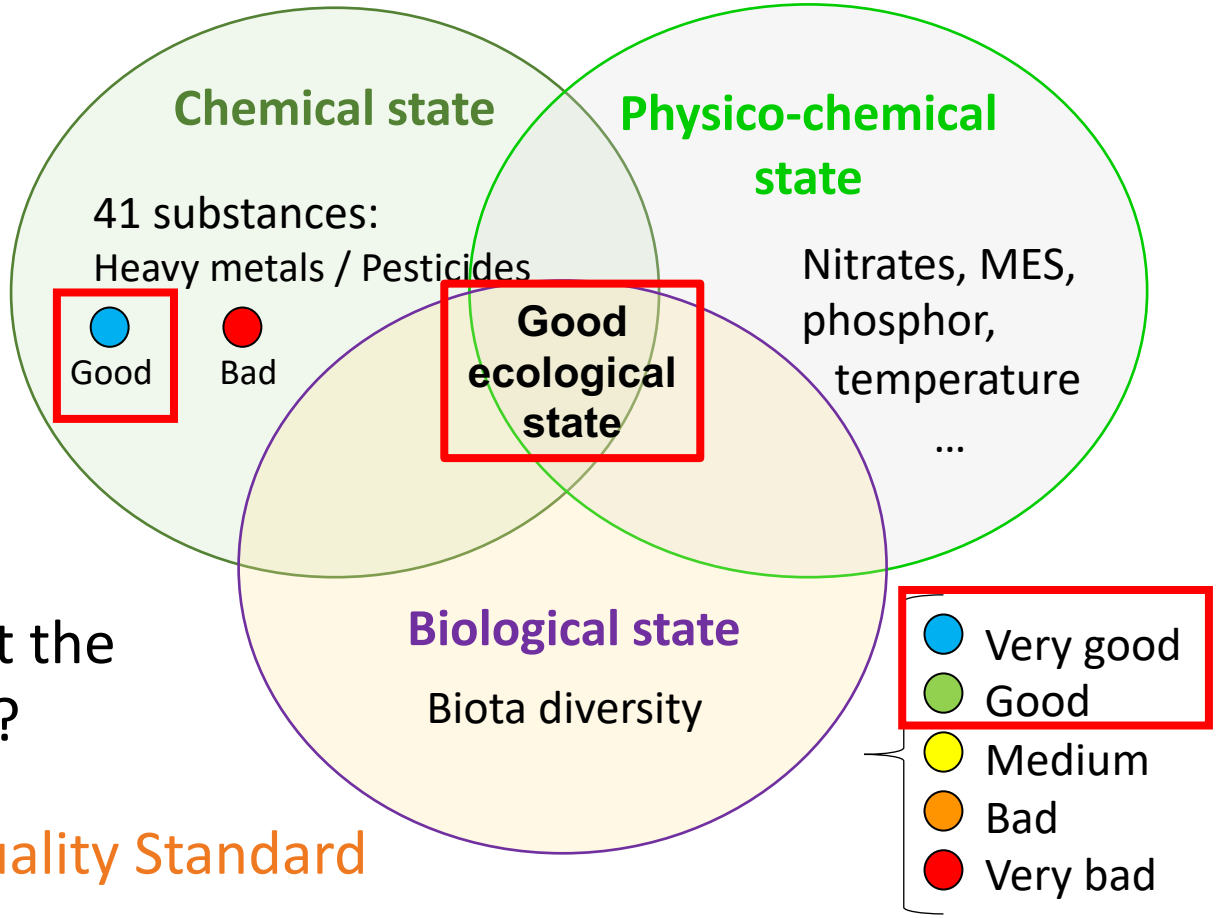

How to determine that the chemical state is good?

Environmental Quality Standard

Environmental Quality Standard (EQS)

« *Concentration of a pollutant or group of pollutants which must not be exceeded, in order to protect human and environmental health* »

- EQS for water
- EQS for sediment
- EQS for biota

↪ Derived from extrapolation of effects, not from bioaccumulation capacity of the chemicals within the body of organisms

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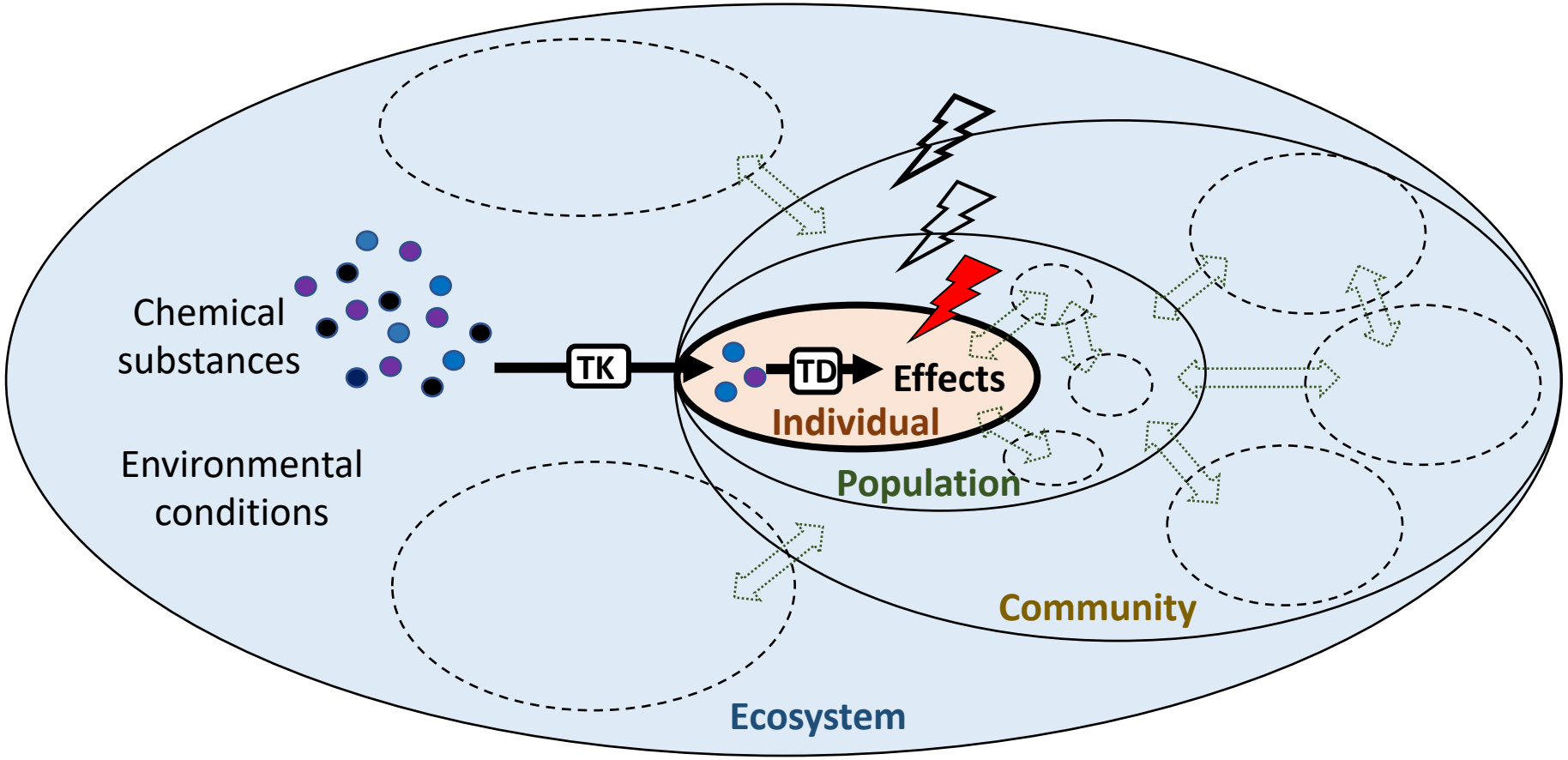
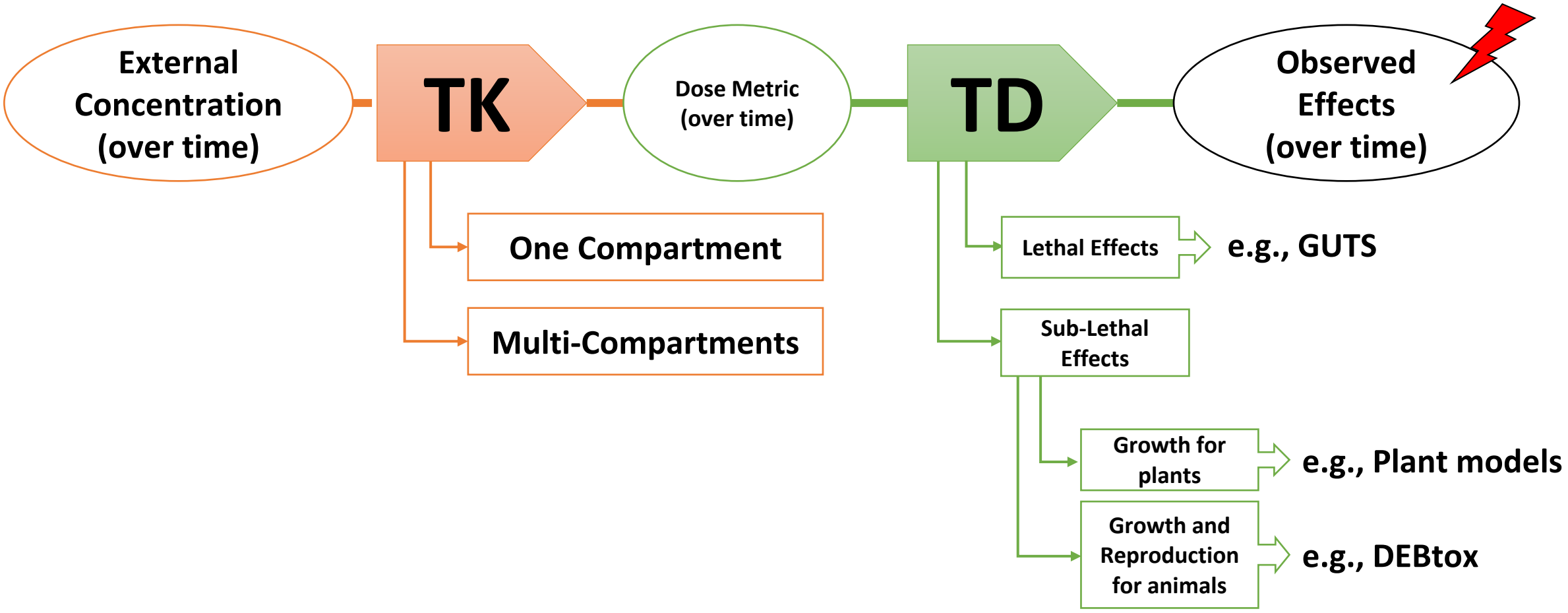


Toxico-Kinetic and Toxico-Dynamic framework

- Translate (time-varying) external concentrations to time patterns of effects.

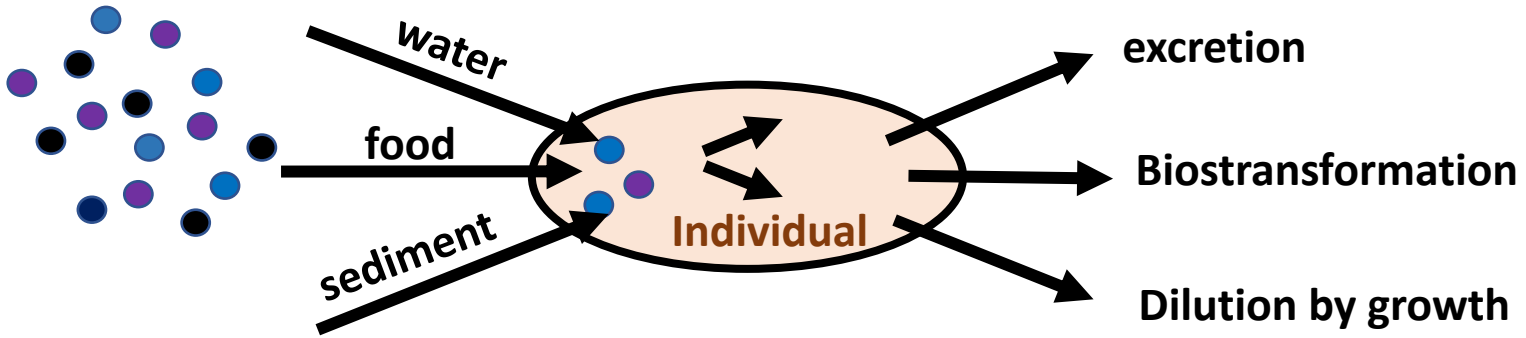


Importance of TK in environmental risk assessment (ERA)

1. Characterize chemical state of aquatic ecosystem (European WFD)

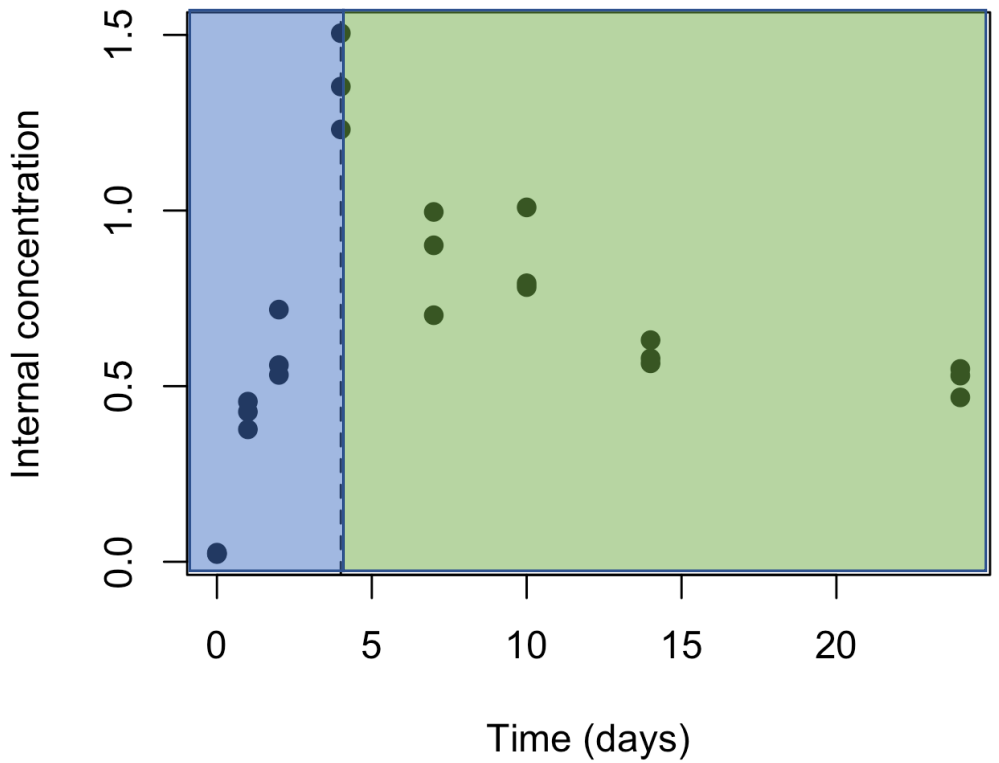
2. Make the link between exposure concentration and individual effects

3. Understand and describe bioaccumulation processes
   → ADME = Absorption, Distribution, Metabolism, Excretion



TK data

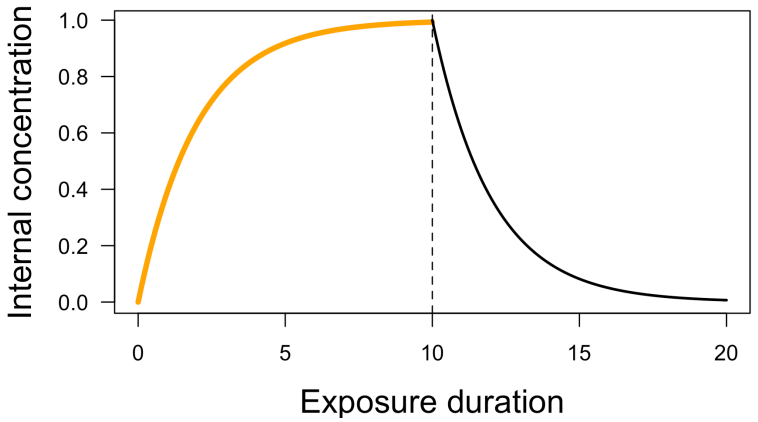
- **TK data**: accumulation and depuration phases
  - **Accumulation phase**: individuals exposed at a given (*constant*) concentration (all ADME processes may occur) during a pre-defined time
  - **Depuration phase**: individuals in clean medium (*without toxicant*) (only depuration processes occur)



TK data and TK models

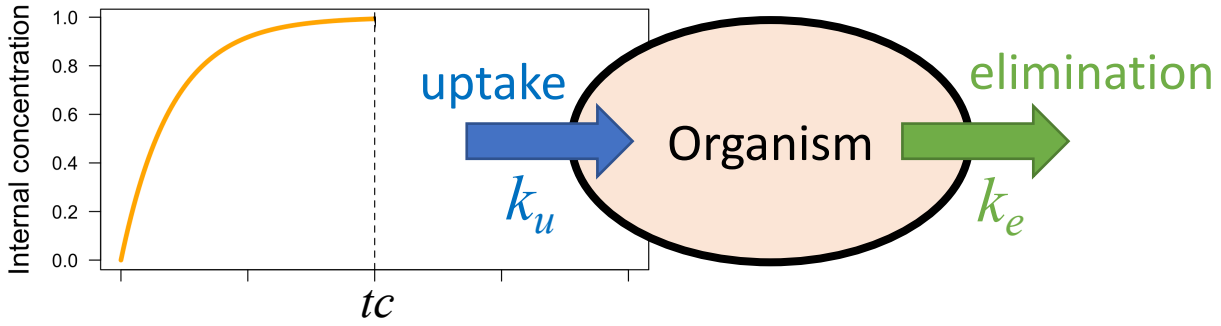
- TK data: accumulation and depuration phases
  - Accumulation phase: individuals exposed at a given (constant) concentration (all ADME processes occur) during a defined time
  - Depuration phase: individuals in clean medium (without toxicant) (only elimination processes occur)

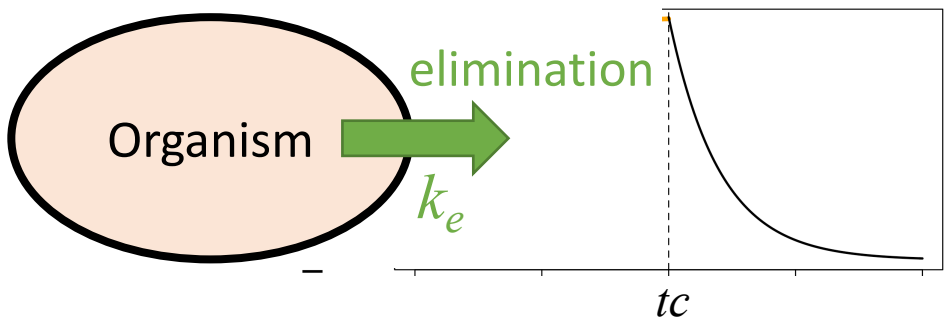
- **TK models**: compartment models; the chemical is assumed to be evenly distributed within the compartment(s).
  - One-compartment models
  - Multi-compartments models



One-compartment models: Theory

Very simplistic and general one-compartment model





- The organism is reduced to a single well-mixed compartment
- There is one single homogeneous **internal** concentration: $C_i(t)$
- The uptake flux is proportional to the external concentration: $k_u \; C_w(t)$
- The elimination flux is proportional to the internal concentration: $k_e \; C_i(t)$

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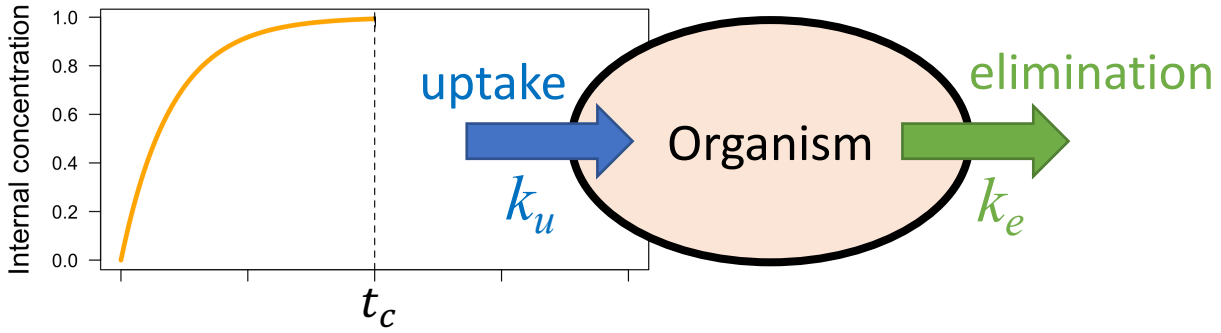

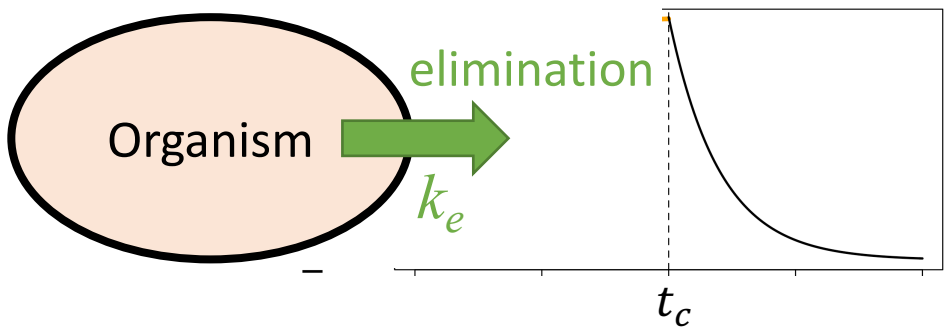

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$$\begin{cases} \dfrac{dC_i(t)}{dt} = k_u \times C_w(t) - k_e \times C_i(t) & \text{if } 0 \le t \le t_c \\ \dfrac{dC_i(t)}{dt} = -k_e \times C_i(t) & \text{if } t > t_c \end{cases}$$

t_c : duration of the accumulation phase

Very simplistic and general one-compartment model

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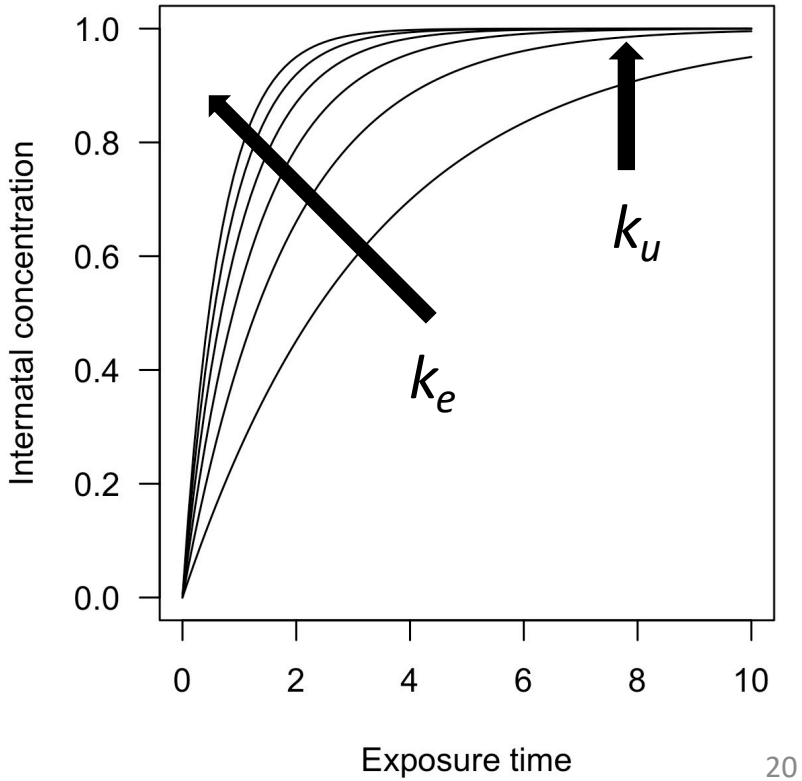
- k_e [time]$^{-1}$ influences the shape of the curve, and the time to reach *x* % of the steady-state
- k_u [time]$^{-1}$ influences the height of the curve, that is the level of the steady-state



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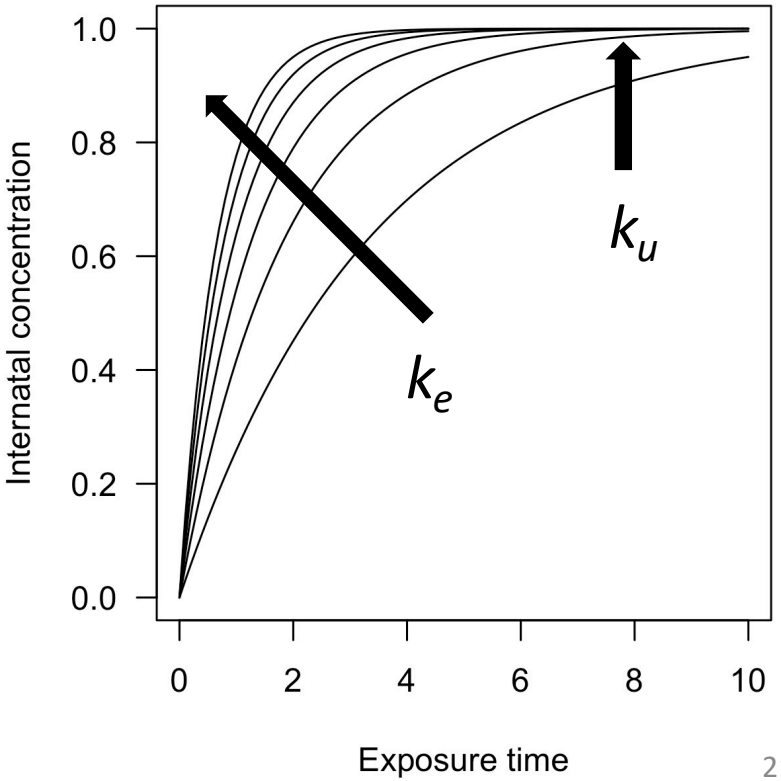

- If the steady state is rapidly achieved, the chemical effects will appear soon after the exposure to the chemical starts.
- If the accumulation process is slow, the chemical effects will only appear after a more prolonged exposure.

Very simplistic and general one-compartment model

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- Analytical solution if C_w is **constant** over time

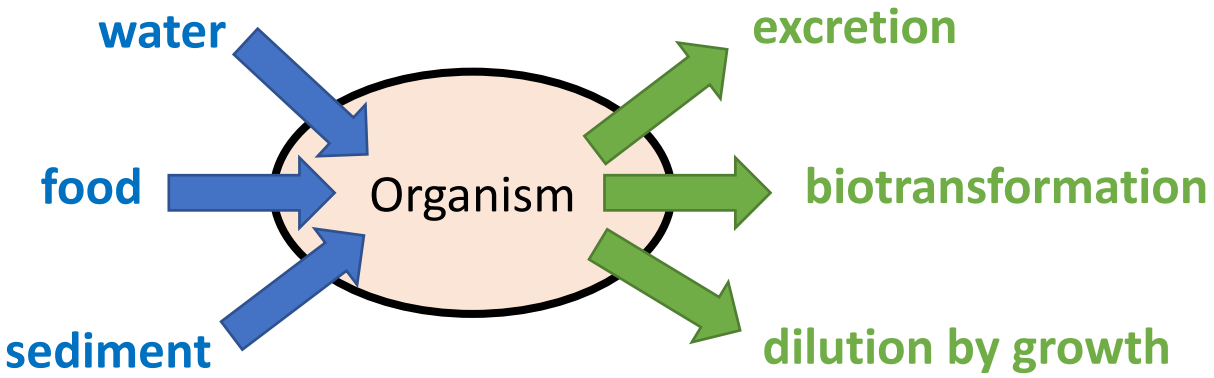
$$\begin{cases} C_i(t) = \frac{k_u \times C_w}{k_e} + \left(C_0 - \frac{k_u \times C_w}{k_e}\right) \times e^{-k_e \times t} & \text{if } 0 \le t \le t_c \\ C_i(t) = \frac{k_u \times C_w}{k_e} \times e^{-k_e \times (t - t_c)} + \left(C_0 - \frac{k_u \times C_w}{k_e}\right) \times e^{-k_e \times t} & \text{if } t > t_c \end{cases}$$

Ratier et al., 2019

Charles et al., 2021

More complex one-compartment models

- Several uptake routes and eliminations processes



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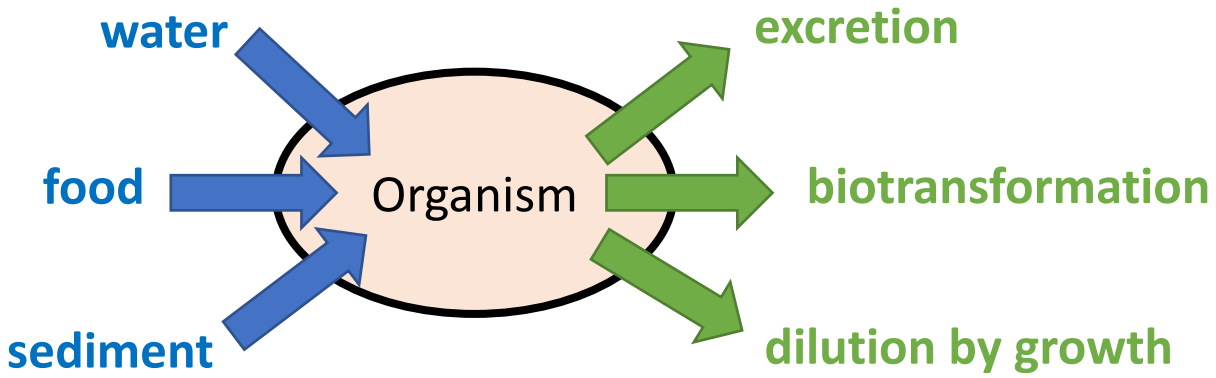

$$\begin{cases} \dfrac{dC_i(t)}{dt} = \sum_{u=1}^{n} k_u \times C_u(t) - \sum_{j=1}^{m} k_j \times C_i(t) & \text{if } 0 \le t \le tc \\ \dfrac{dC_i(t)}{dt} = -\sum_{j=1}^{m} k_j \times C_i(t) & \text{if } t > tc \end{cases}$$

n uptake routes (k_u)
- k_w : water
- k_s : sediment
- k_l : leaves
- ...

m elimination processes (k_j)
- k_e : excretion
- k_g : growth
- k_m : biotransformation
- ...

Ratier et al. 2019.

More complex one-compartment models

- Choice according to experimental data

Constant exposure by **water** and **sediment**

Excretion and **Growth**

C_i: internal concentration

L: growth variable

$$\begin{cases} \dfrac{dC_i(t)}{dt} = (k_w \times C_w) + (\boldsymbol{k_s} \times \boldsymbol{C_s}) - (k_e + k_g) \times C_i(t) \\ \dfrac{dL(t)}{dt} = k_g \times (L_\infty - L(t)) \end{cases}$$

More complex one-compartment models

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Constant exposure by **water**
Excretion and **biotransformation**
(1 metabolite)

C_p: internal parent concentration
C_m: internal metabolite concentration

$$\begin{cases} \dfrac{dC_p(t)}{dt} = k_w \times C_w - (k_{e,p} + \boldsymbol{k_m}) \times C_p(t) \\ \dfrac{dC_m(t)}{dt} = \boldsymbol{k_m} \times C_p(t) - k_{e,m} \times C_m(t) \end{cases}$$

Derivation of Bioaccumulation metrics

- To evaluate the bioaccumulation potential of chemical substances
- Three metrics according to the source of exposure
  - BCF: Bio-Concentration Factor (exposure via water)
  - BSAF: Biota-Sediment Accumulation Factor (exposure via sediment)
  - BMF: Bio-Magnification Factor (exposure via food)

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- For each metric, two types of calculation according to the “shape” of the data during the accumulation phase
  - If the internal concentration reaches a plateau at the end of the accumulation phase

    => Steady-state bioaccumulation metric
  - If not

    => Kinetic bioaccumulation metric

Derivation of Bioaccumulation metrics

	Steady-state bioaccumulation metric	Kinetic bioaccumulation metric
➢ BCF	$BCF_{ss} = \frac{C_i(t_c)}{C_w}$	$BCF_k = \frac{k_w}{\sum_{j=1}^{m} k_j}$

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Fit one-compartment models: practice

Stochastic part of a model

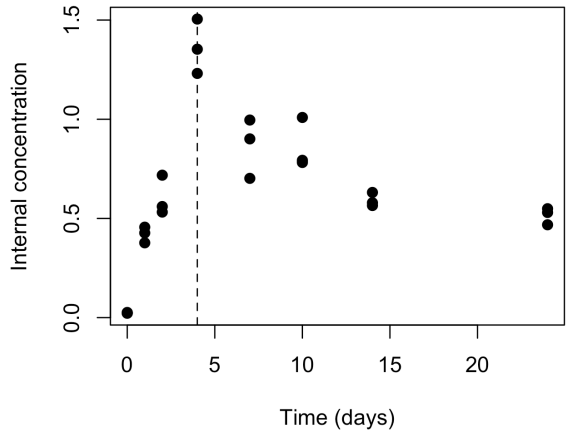
- All models are composed of a deterministic part and a stochastic part
- Deterministic part describes the mean tendency as deduced from the data, while the stochastic part describes the variability around this mean tendency
- Here internal concentration = quantitative continuous data => Gaussian stochastic part

$$C_{obs}(t) \sim \mathcal{N}(C_i(t), \sigma)$$

Bayesian Inference

➢ Fit of the model on accumulation and depuration data simultaneously

Experimental data



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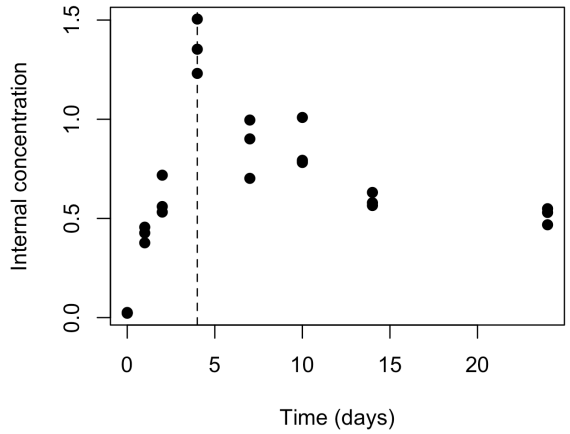

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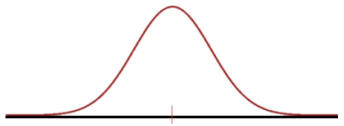
+ **Information *a priori***



Prior distribution on model parameters

Bayesian Inference

➢ Fit of the model on accumulation and depuration data simultaneously

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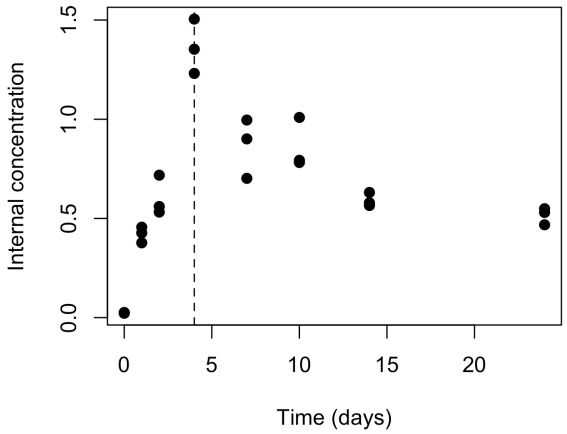
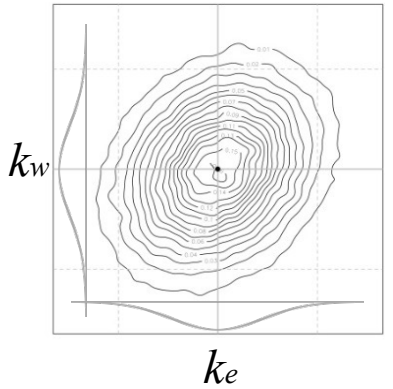


Joint posterior distribution
- Correlation
- Marginal distributions
- Median and 95% CI



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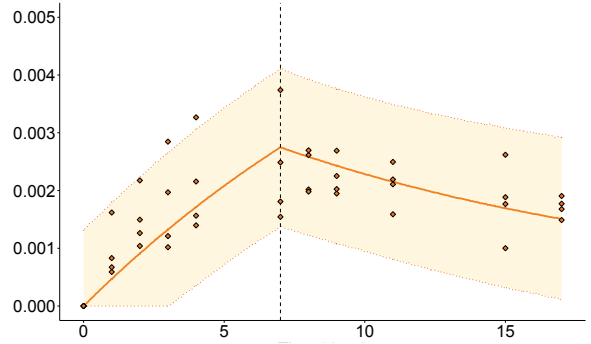
Bayesian Inference

JAGS-4.2.0

'*rjags*' package

Predictions



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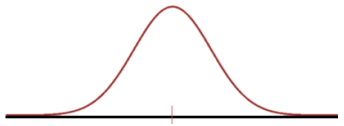


Prior distribution on model parameters

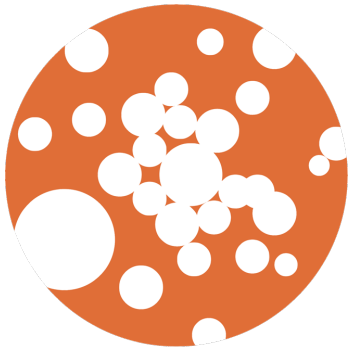
Other goodness-of-fit criteria

MOSAIC$_{bioacc}$

- All-in-one web platform to fit one-compartment models to uptake and elimination experimental data

- All implemented models may combine
  4 exposure routes (water, sediment, food, pore water)
  3 elimination processes (excretion, dilution by growth and biotransformation for phase I metabolites)

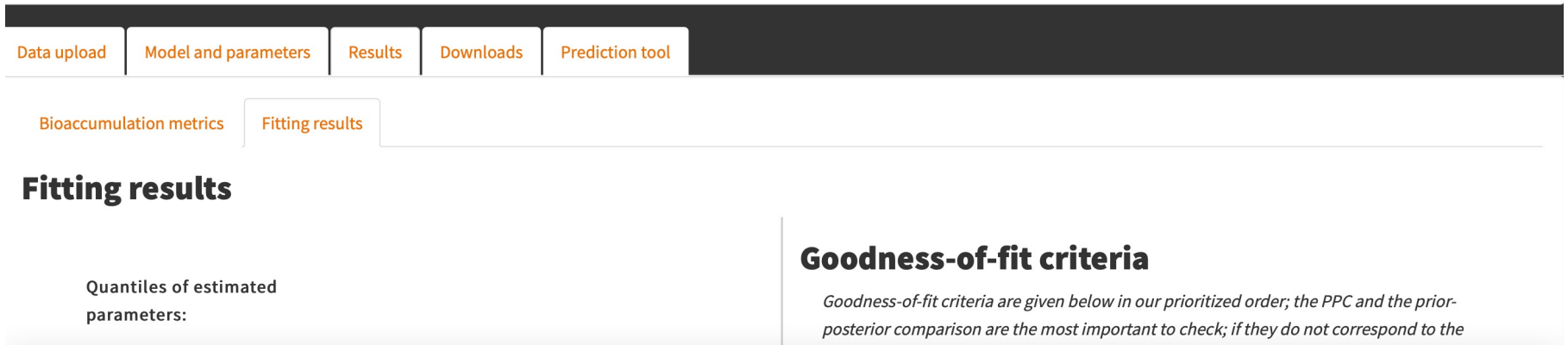
- Automatic fit of the one-compartment model corresponding to the input experimental data



bioacc

MOSAIC$_{bioacc}$

http://lbbe-shiny.univ-lyon1.fr/mosaic-bioacc/



$MOSAIC_{bioacc}$: output

- Bioaccumulation metrics
- Parameters estimates: median and bounds of the 95% CI (quantiles of marginal posterior distributions)
- Fit of the median prediction with its uncertainty band superimposed to observed data
- Goodness-of-fit criteria

Goodness-of-fit criteria

- PPC
- Prior / posterior distributions
- Correlation between parameters
- Convergence criteria (Gelman and Rubin)
- WAIC
- MCMC traces

Package `rbioacc`

https://CRAN.R-project.org/package=rbioacc

rbioacc: Inference and Prediction of ToxicoKinetic (TK) Models

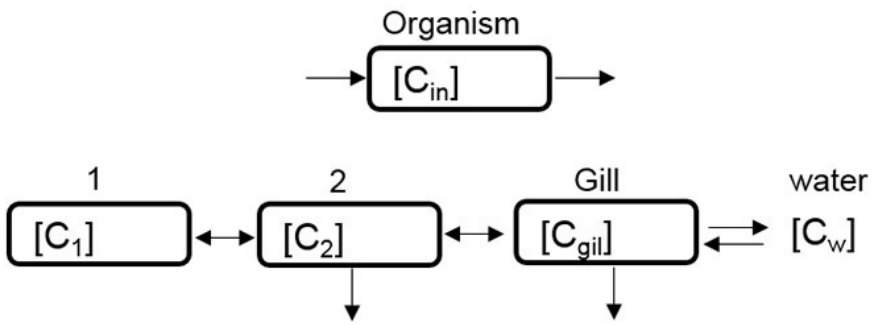
The MOSAICbioacc application is a turnkey package providing bioaccumulation factors (BCF/BMF/BSAF) from a toxicokinetic (TK) model fitted to accumulation-depuration data. It is designed to fulfil the requirements of regulators when examining applications for market authorization of active substances. See Ratier et al. (2021) <doi:10.1101/2021.09.08.459421 CRAN >.

Version:	1.1-0
Depends:	R (≥ 3.5.0)
Imports:	ggplot2, methods, Rcpp, rstan (≥ 2.18.1), rstantools (≥ 2.1.1), ggmcmc, GGally, loo, stringr, stats, zoo
LinkingTo:	BH (≥ 1.66.0), Rcpp, RcppEigen (≥ 0.3.3.3.0), RcppParallel (≥ 5.0.1), rstan (≥ 2.18.1), StanHeaders (≥ 2.18.0)
Suggests:	knitr, rmarkdown, testthat
Published:	2022-01-12
Author:	Virgile Baudrot [aut], Sandrine Charles [aut], Ophélia Gestin [ctb], Mélina Kaag [aut], Christelle Lopes [ctb], Gauthier Multari [ctb], Alain Pavé [ctb], Aude Ratier [aut], Aurélie Siberchicot [aut, cre]
Maintainer:	Aurélie Siberchicot <aurelie.siberchicot at univ-lyon1.fr>
BugReports:	https://github.com/aursiber/rbioacc/issues
License:	MIT + file LICENSE
URL:	https://github.com/aursiber/rbioacc

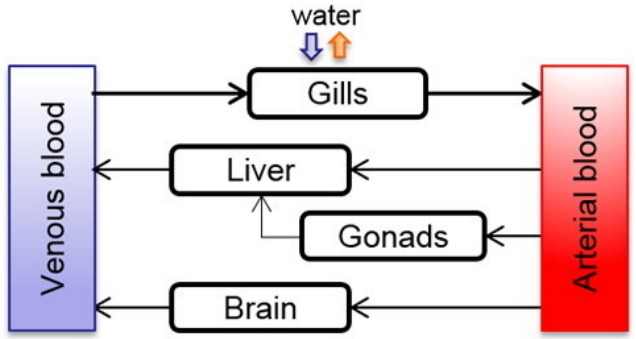
Multi-compartment models: Theory

Multi-compartment models

- The organism is divided into different compartments
- There is one single homogeneous internal concentration for each compartment: $C_x(t)$
- The compartments are linked to each others and with the environment

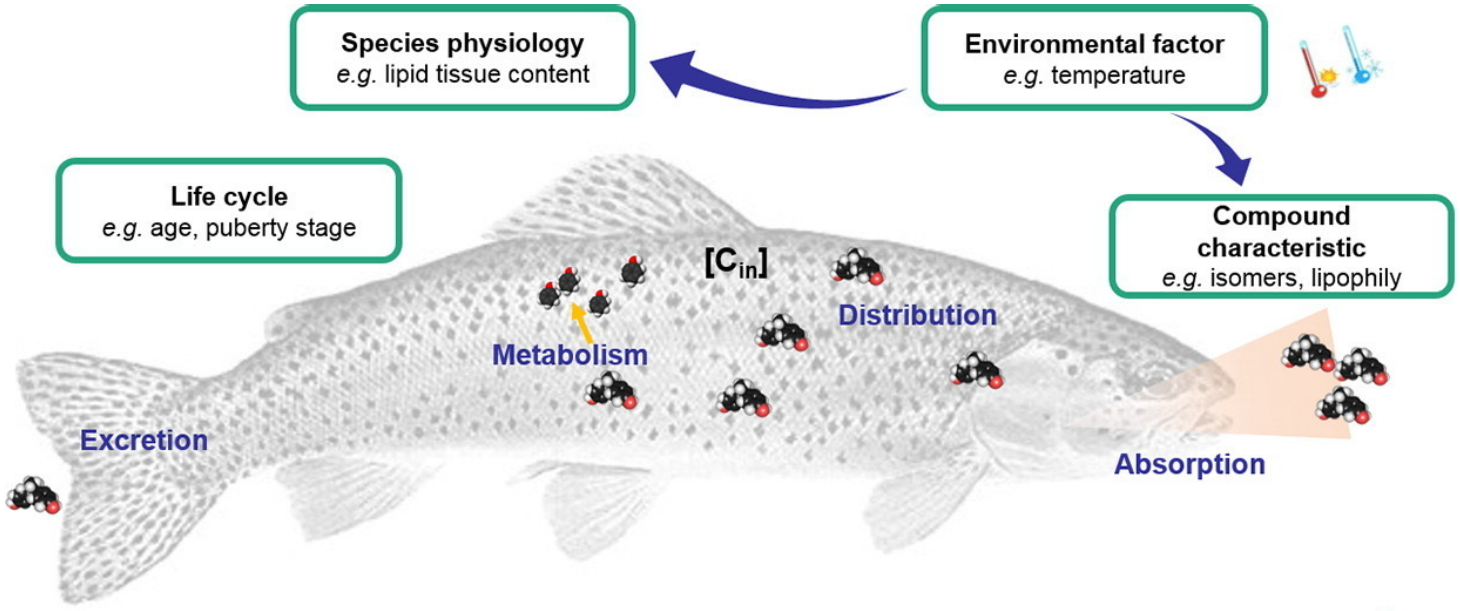


Compartmental models



Mechanistic models

Multi-compartment models



Generally restricted to large-bodied organisms (e.g., fish or mammals)

Grech A, Brochot C, Dorne J-L, Quignot N, Bois FY, Beaudouin R. 2016. Toxicokineticmodels and related tools in environmental risk assessment of chemicals. *Sci. Total Environ*.

Specific to the studied species