“DEBtox”, a brief history and extension to mixtures and plants

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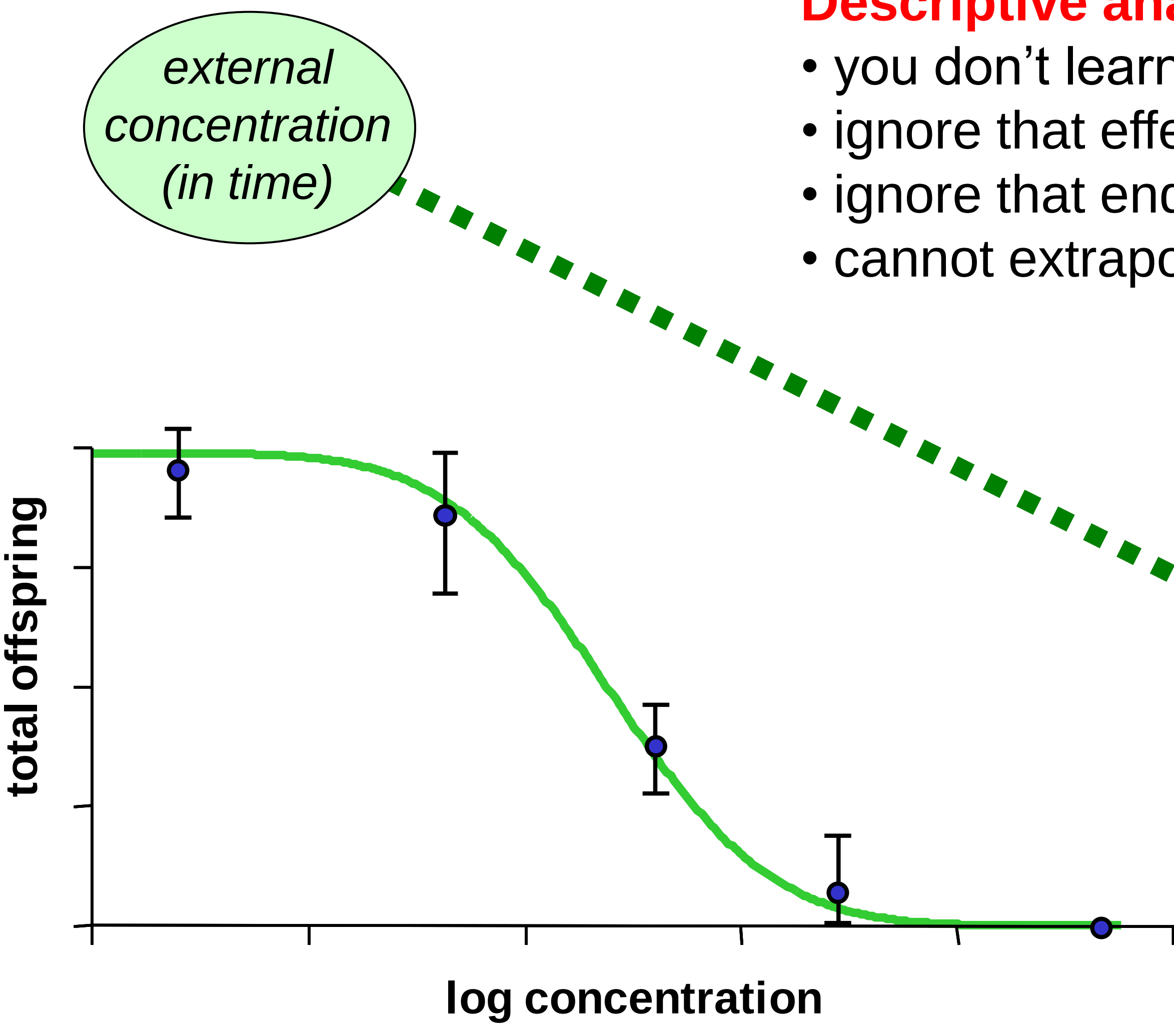
Contents

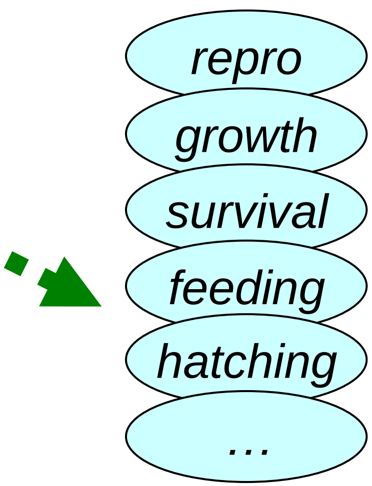
- Brief history of toxicants in DEB
  - the “DEBtox” family tree
- Case study with toxicants in DEB3
  - nonylphenol in *Capitella teleta*
- How to extend DEBtox to mixtures
  - overview of progress made in NoMiracle framework
- How to extend DEBtox to plants
  - what makes plants different from animals?

Background

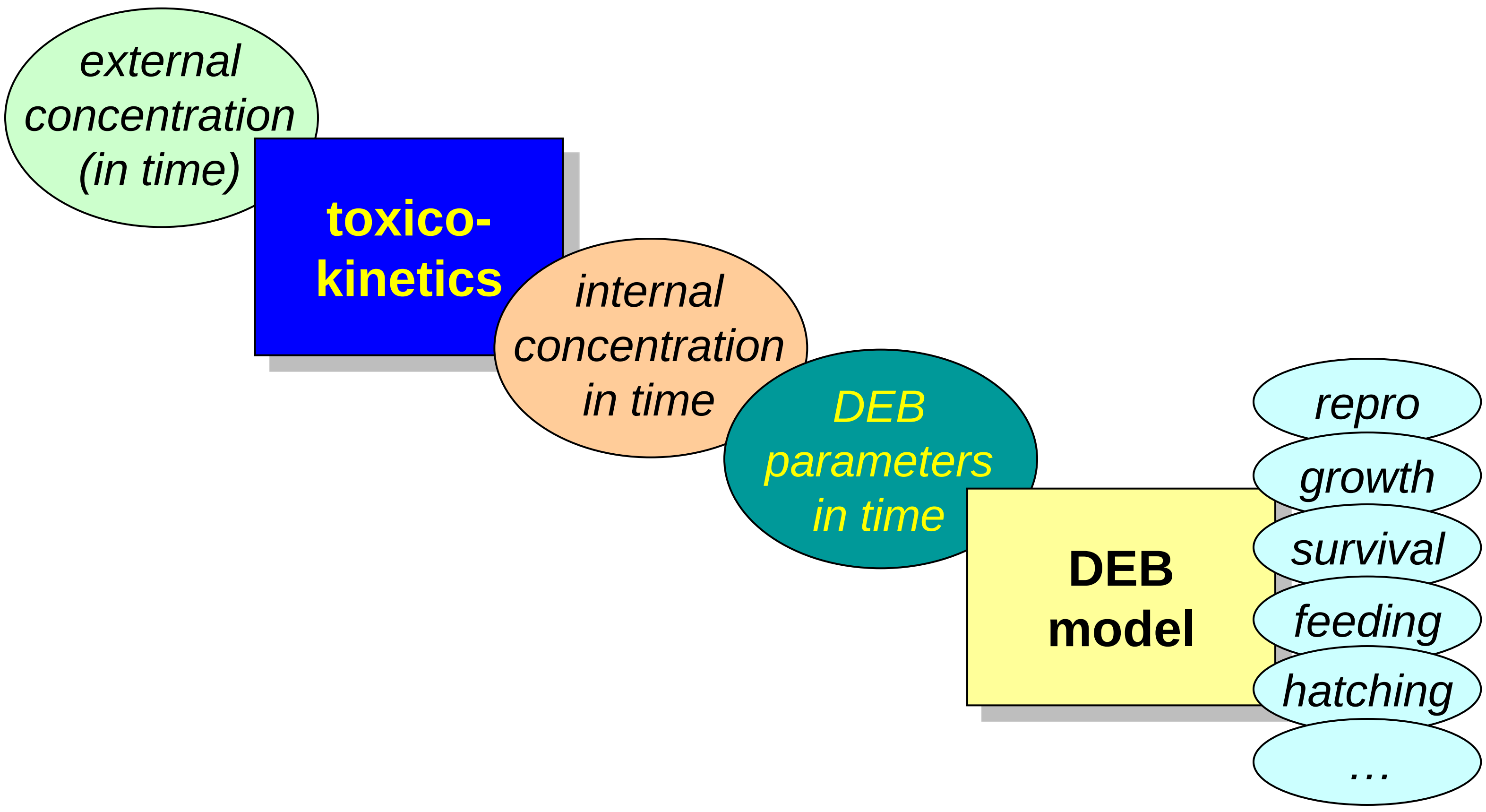


Descriptive analysis

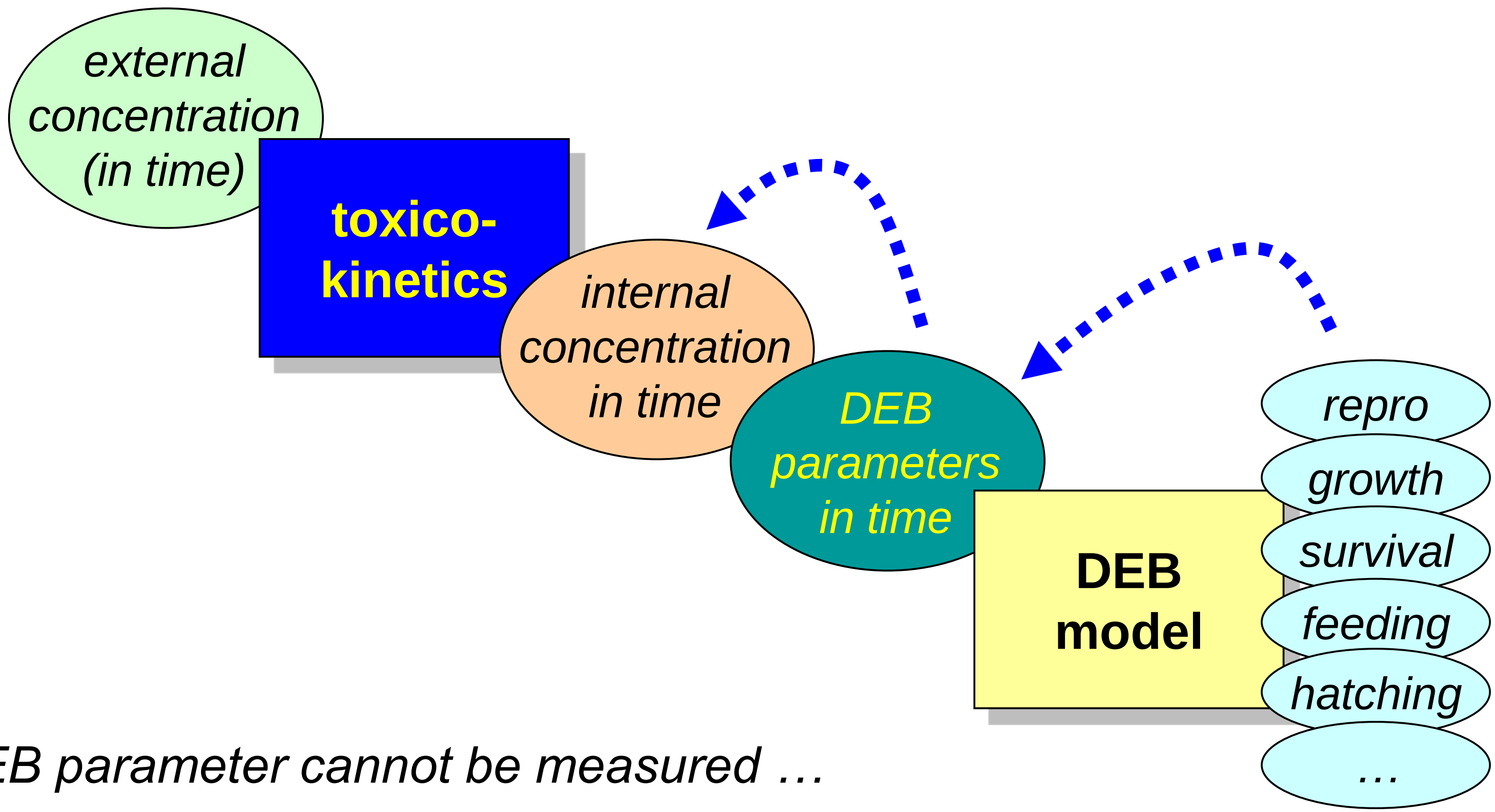
- you don't learn anything,
- ignore that effects change in time
- ignore that endpoints are linked
- cannot extrapolate to other situations



The DEBtox concept



The DEBtox concept

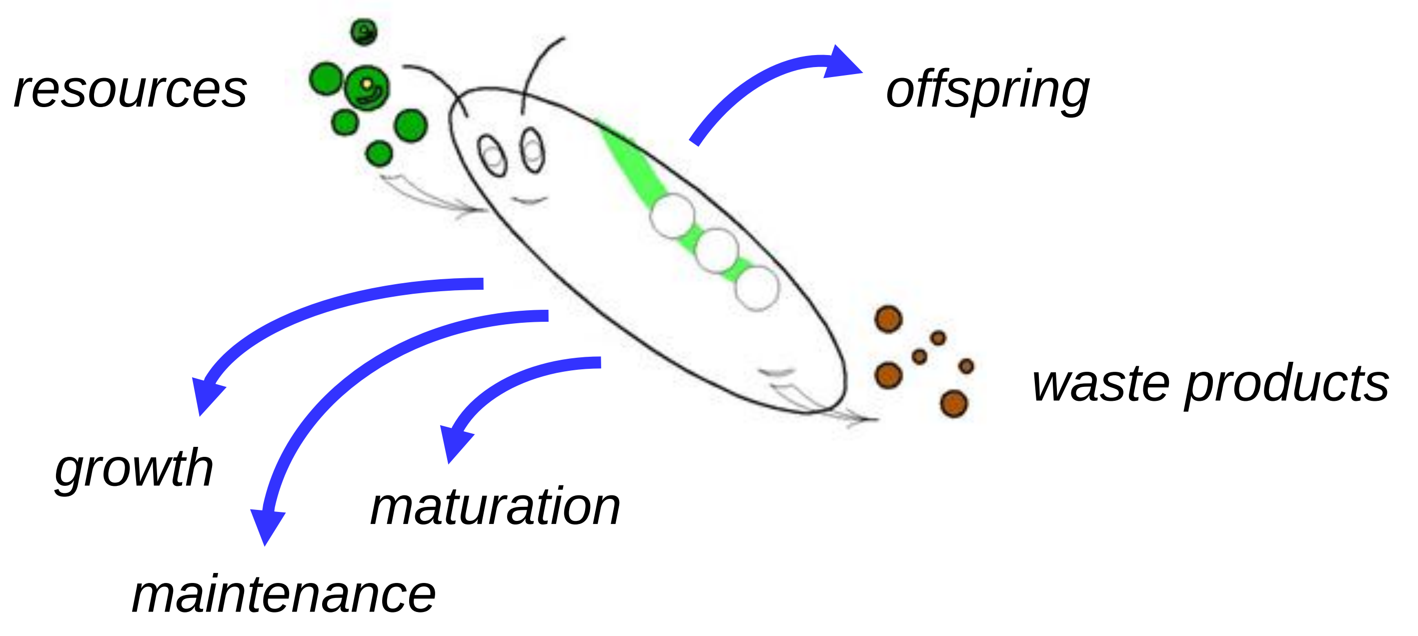


DEB parameter cannot be measured …

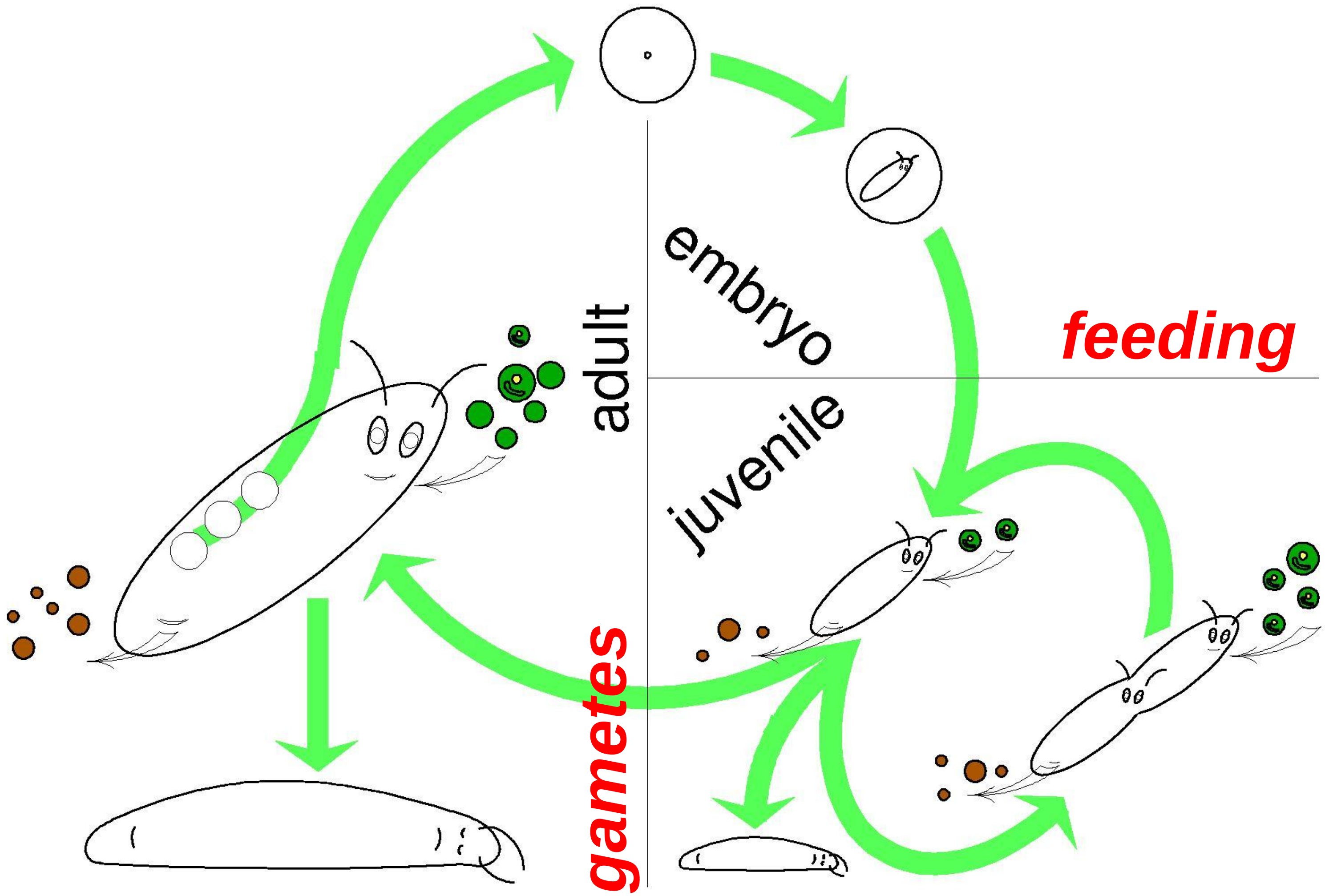
Internal concentration are often not measured …

DEB theory

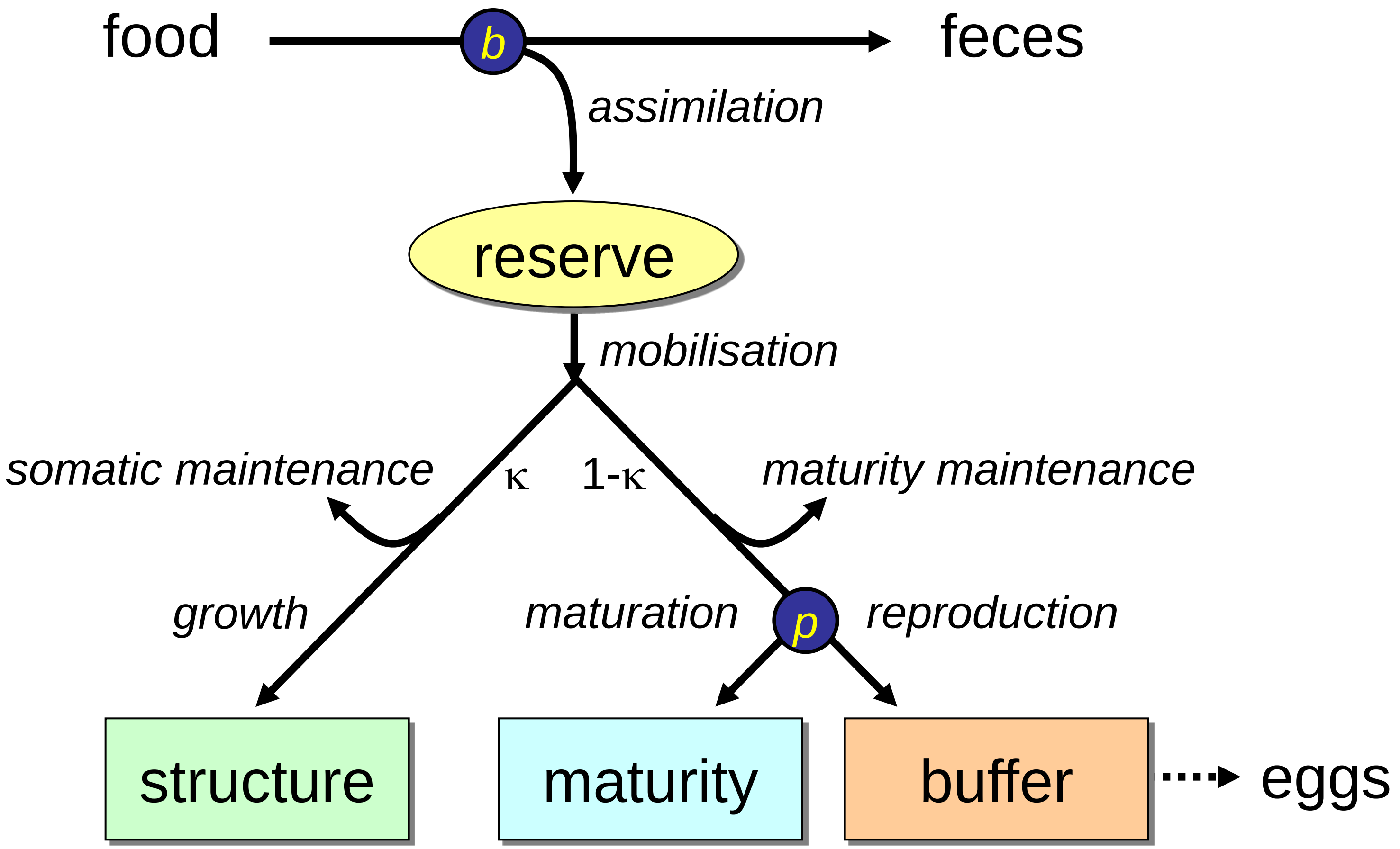
- Organisms obey mass and energy conservation
  - find the simplest set of rules ...
  - over the entire life cycle ...
  - for *all* organisms (related species follow related rules)
  - most appropriate DEB *model* depends on species and question



Generalised life cycle



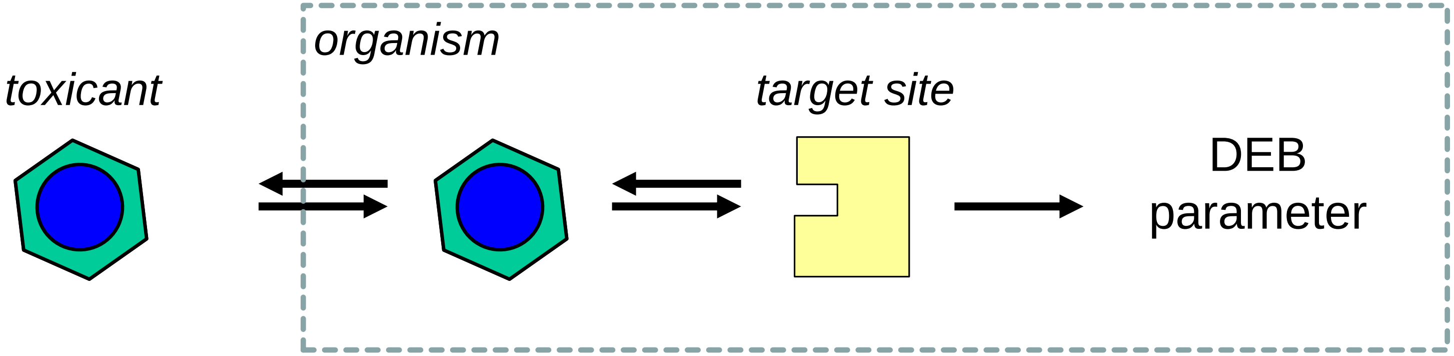
Standard DEB model for animal



Targets link to DEB parameters

Assumption

– toxicant affects target site linked to one (or more) DEB parameter(s)

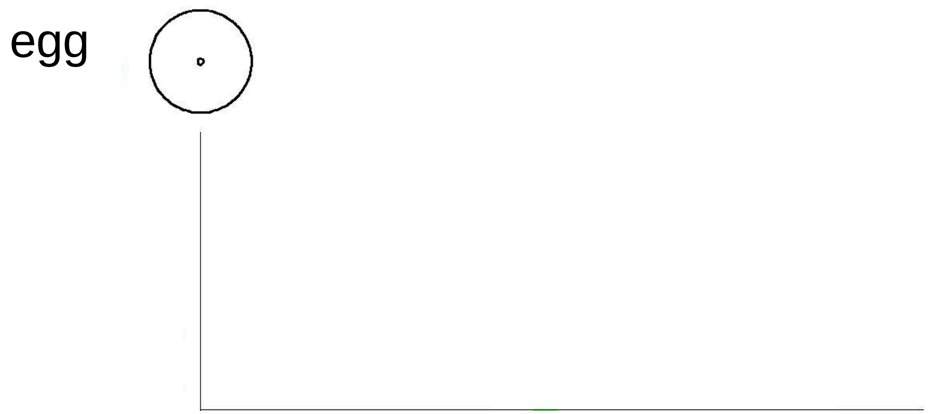


Assumptions

– there is a threshold for effects (the NEC)

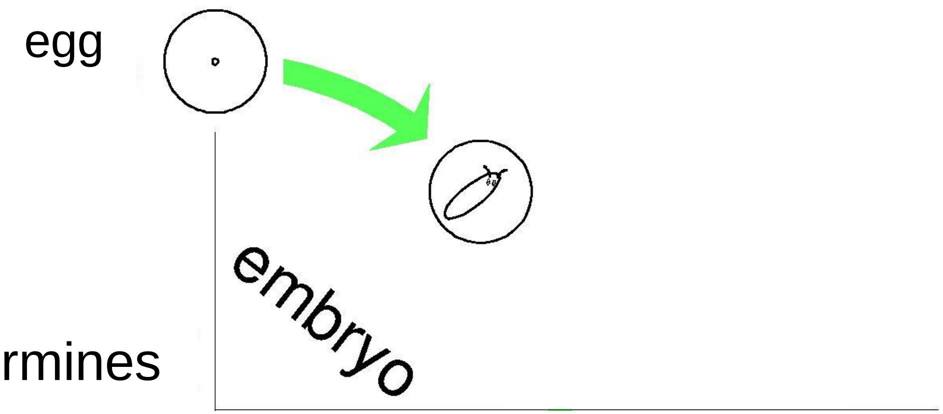
– above the NEC, parameter changes linearly with internal concentration ...

A brief history of 'DEBtox'



Corresponds with origin of DEB in 1979

A brief history of 'DEBtox'

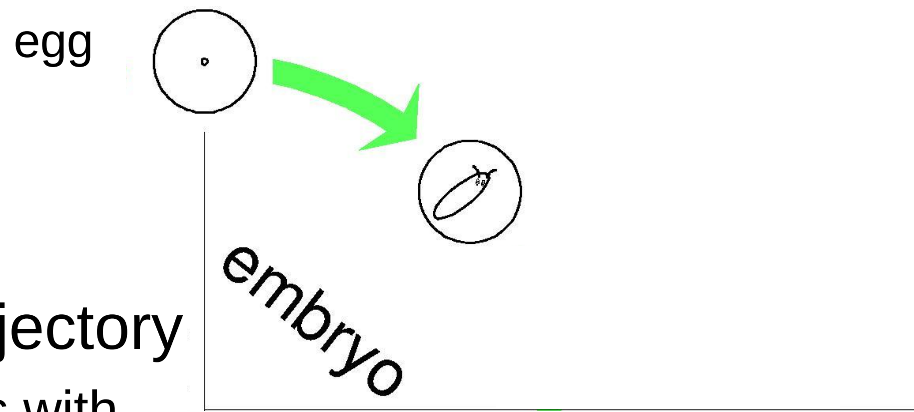


The 80's …

- Kooijman (1981)
  - toxicokinetics determines survival pattern

- Kooijman & Metz (1984)
  - toxicants affect energy budgets and thereby population response

A brief history of 'DEBtox'



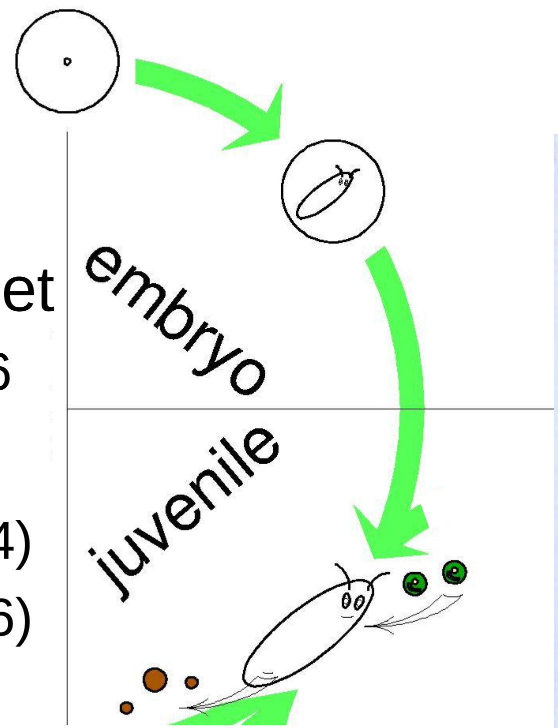
The early 90's …

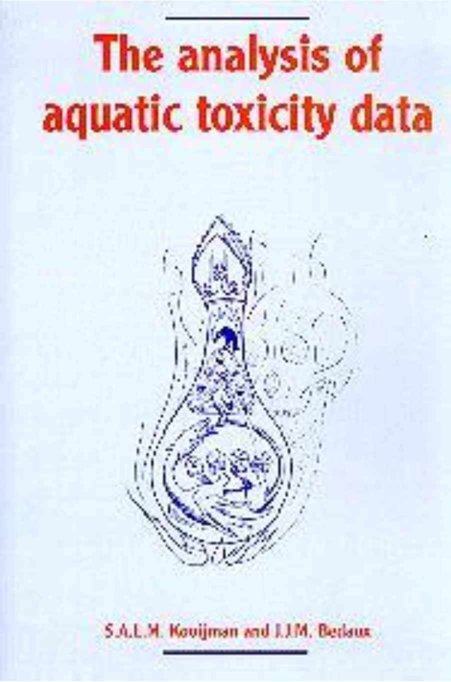
- Parallel to OECD trajectory
  - review test guidelines with respect to statistical analysis

A brief history of 'DEBtox'

Birth in 1996 …

- Windows software/booklet
  - Kooijman & Bedaux, 1996
- Series of papers
  - Bedaux & Kooijman (1994)
  - Kooijman & Bedaux (1996)
  - Kooijman *et al* (1996)

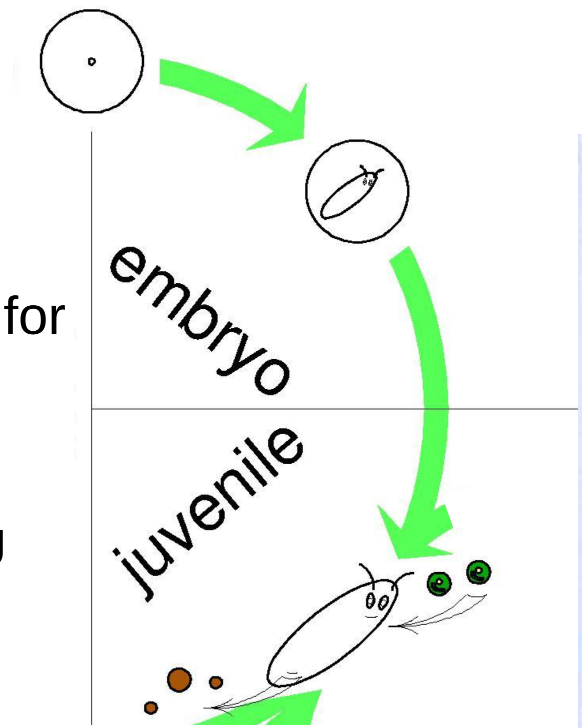


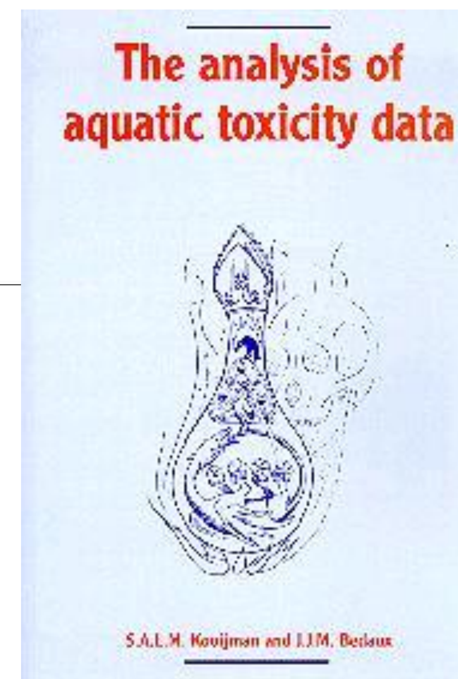


A brief history of 'DEBtox'

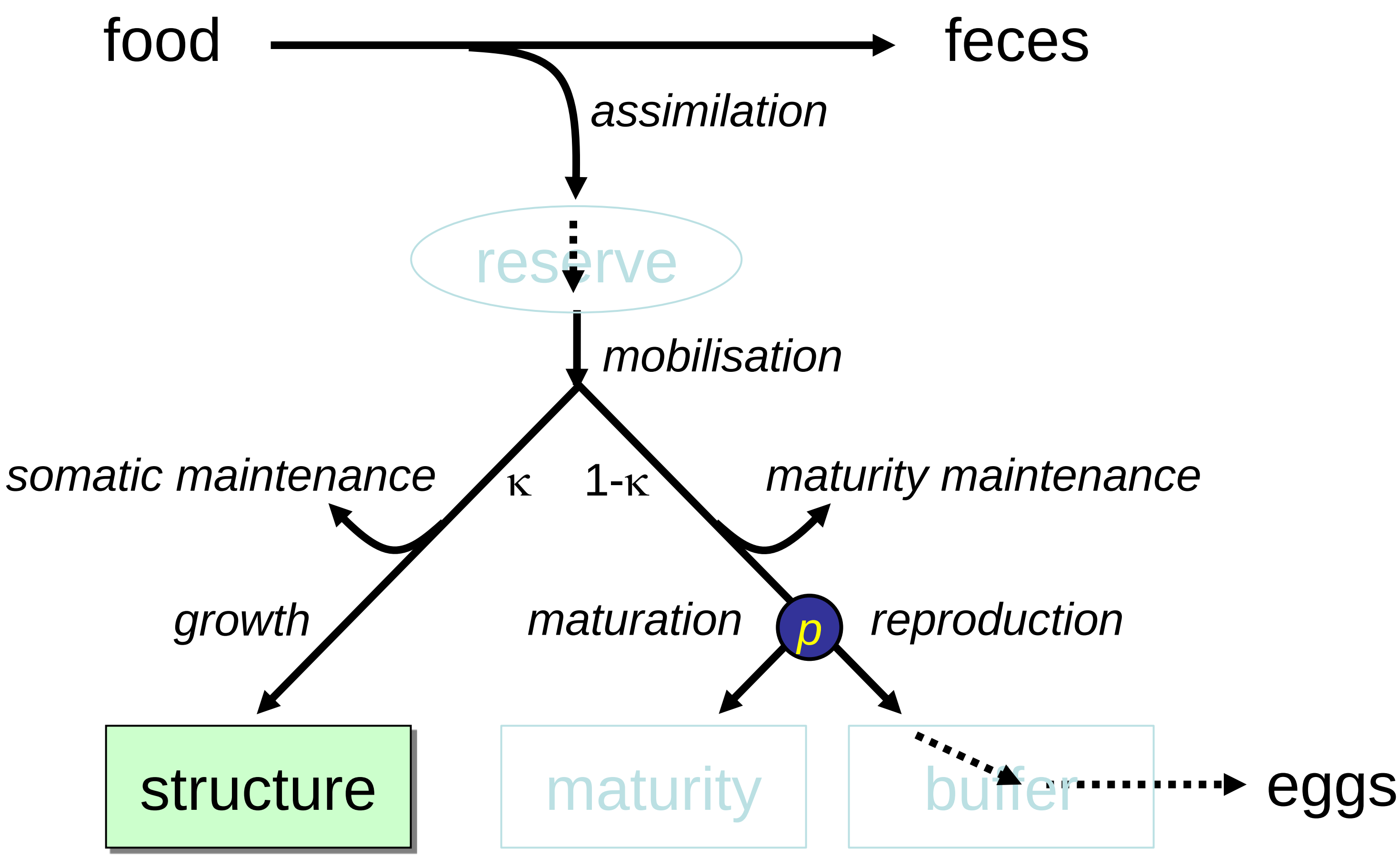
And 10 years later …

- ISO/OECD (2006)
  - DEBtox next to methods for NOEC and EC50
- ECB workshop (2007)
  - presenting DEBtox to EU regulators





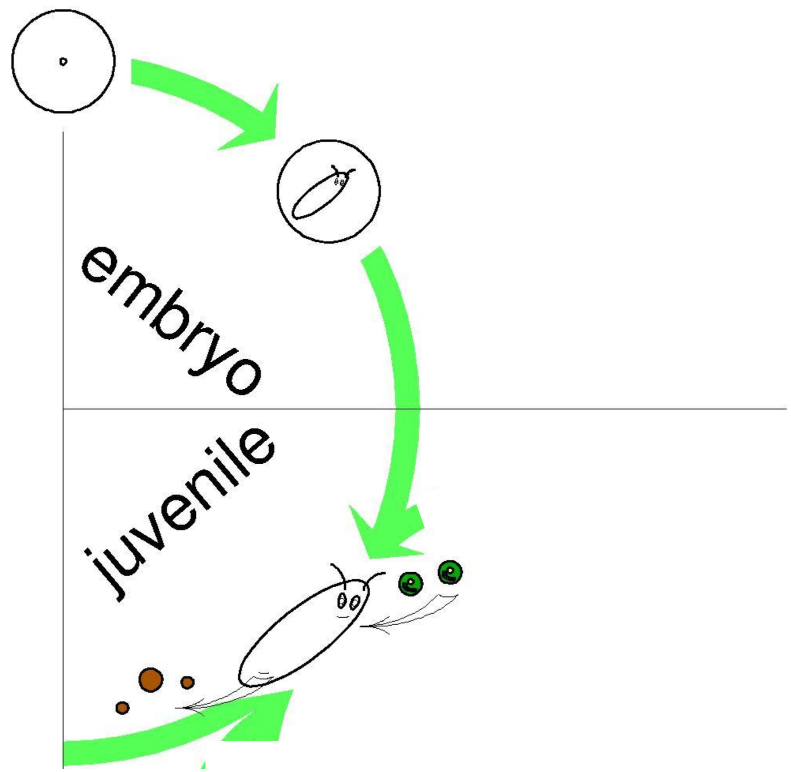
Simplified DEB animal



A brief history of 'DEBtox'

The 2000's …

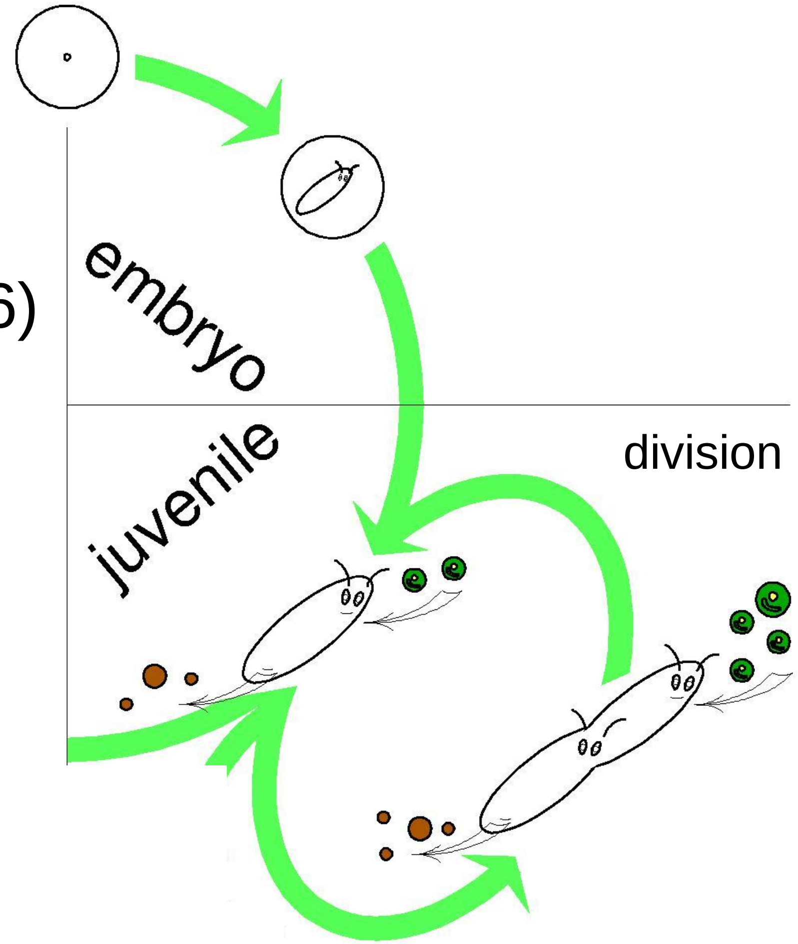
- Péry *et al* (2002, 2003)
  - modifications for midges
- Ducrot *et al* (2004, 2007)
  - midges and snails
- Lopes *et al* (2005)
  - link to matrix models
- Billoir *et al* (2007, 2008)
  - Bayes, new derivation
- Muller *et al* (2010)
  - alternative formulation



A brief history of 'DEBtox'

In our group …

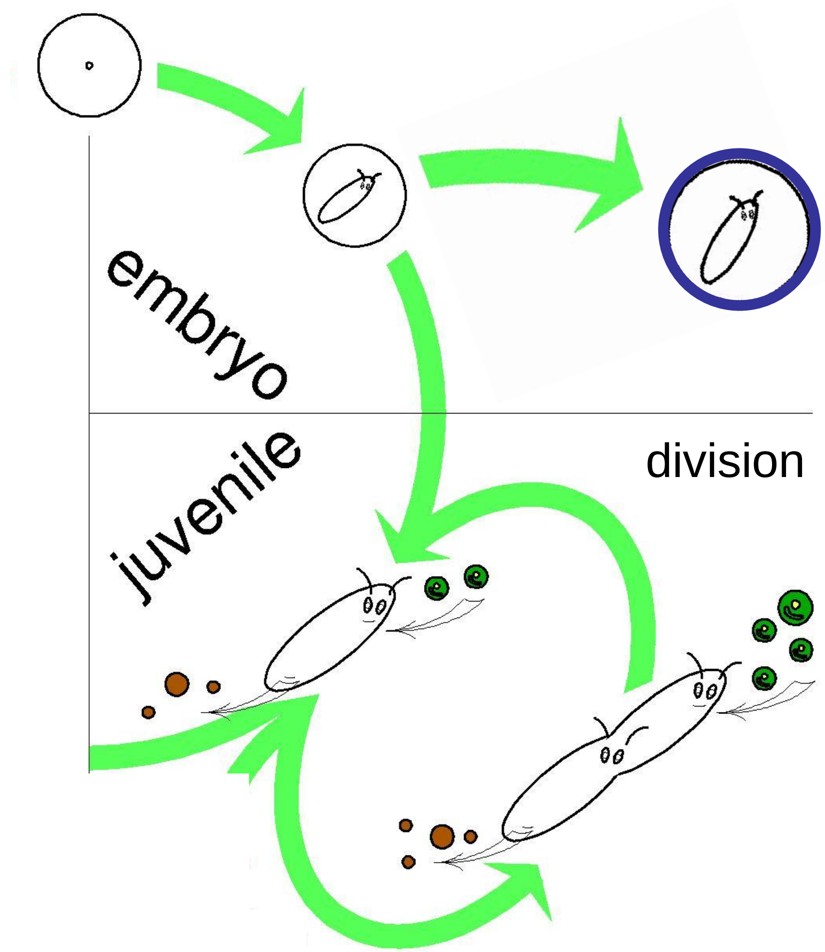
- Jager *et al* (2004), Alda Álvarez *et al* (2005, 2006)
  - multiple endpoints and ageing
  - population (Euler-Lotka)
- Baas *et al* (2007, 2009)
  - mixtures: lethal effects



A brief history of 'DEBtox'

Embryo division …

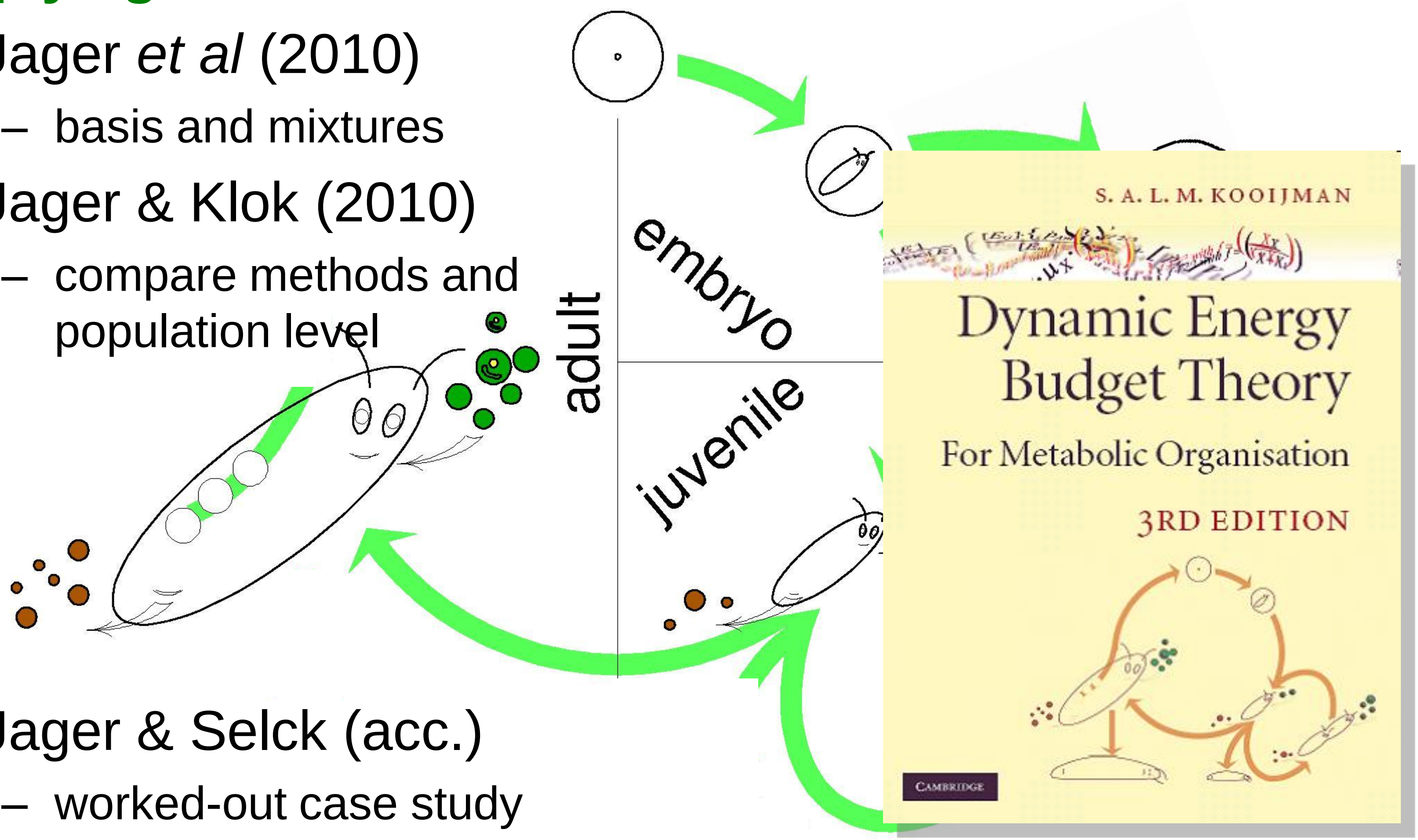
- Klok & De Roos (1996), Klok *et al* (1997, 2007)
  - earthworm matrix model, Bayesian approach



A brief history of 'DEBtox'

Applying 'DEB3' …

- Jager *et al* (2010)
  - basis and mixtures
- Jager & Klok (2010)
  - compare methods and population level
- Jager & Selck (acc.)
  - worked-out case study

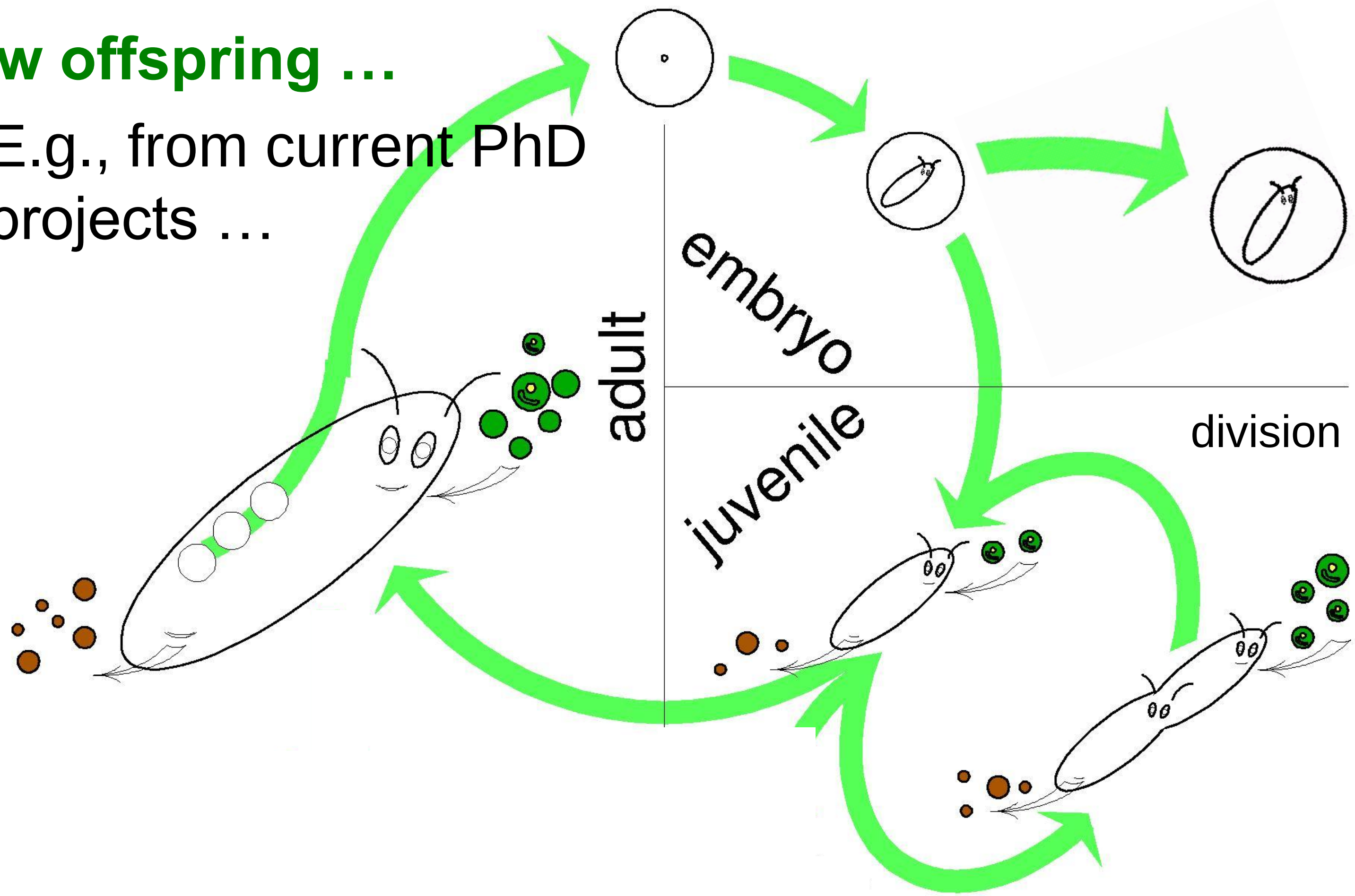


Kooijman (2010)

A brief history of 'DEBtox'

New offspring …

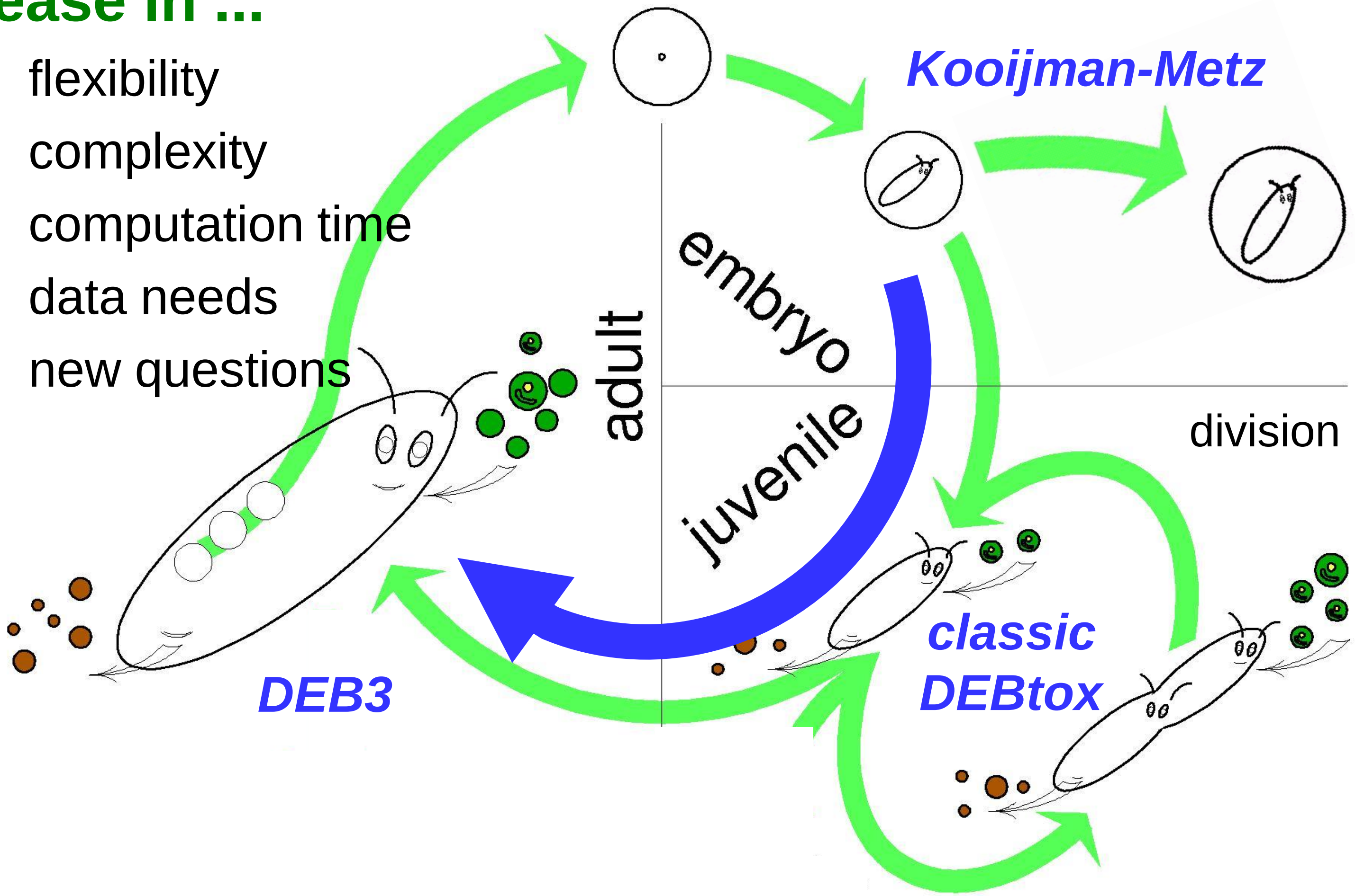
- E.g., from current PhD projects …



A brief history of 'DEBtox'

Increase in ...

- flexibility
- complexity
- computation time
- data needs
- new questions



A “DEB3” DEBtox case study

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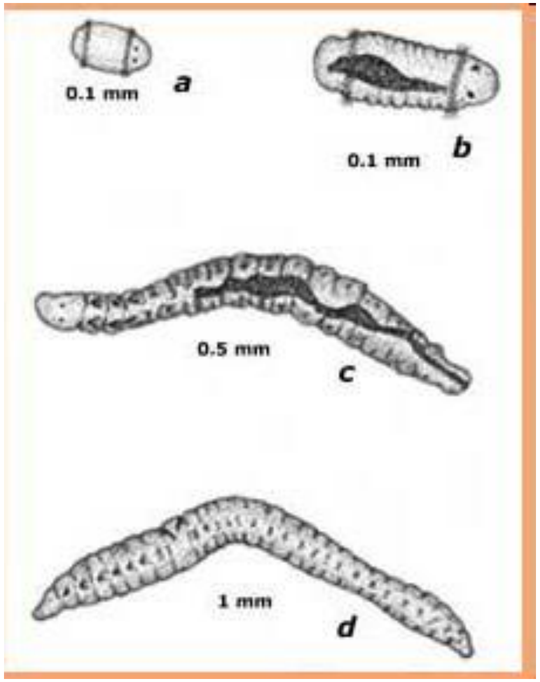
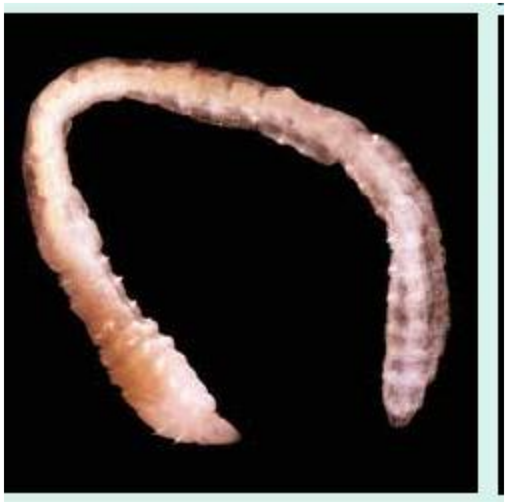
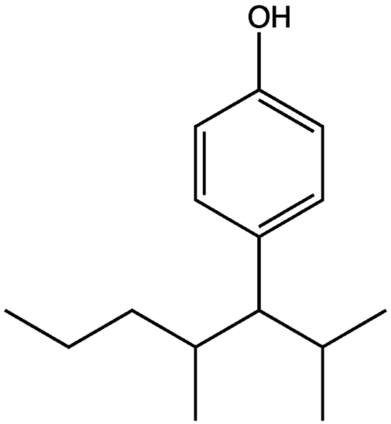
Toxicant case study

- Marine polychaete *Capitella* (Hansen *et al*, 1999)
  - exposed to nonylphenol in sediment
  - body volume and egg production followed
  - no effect on mortality observed



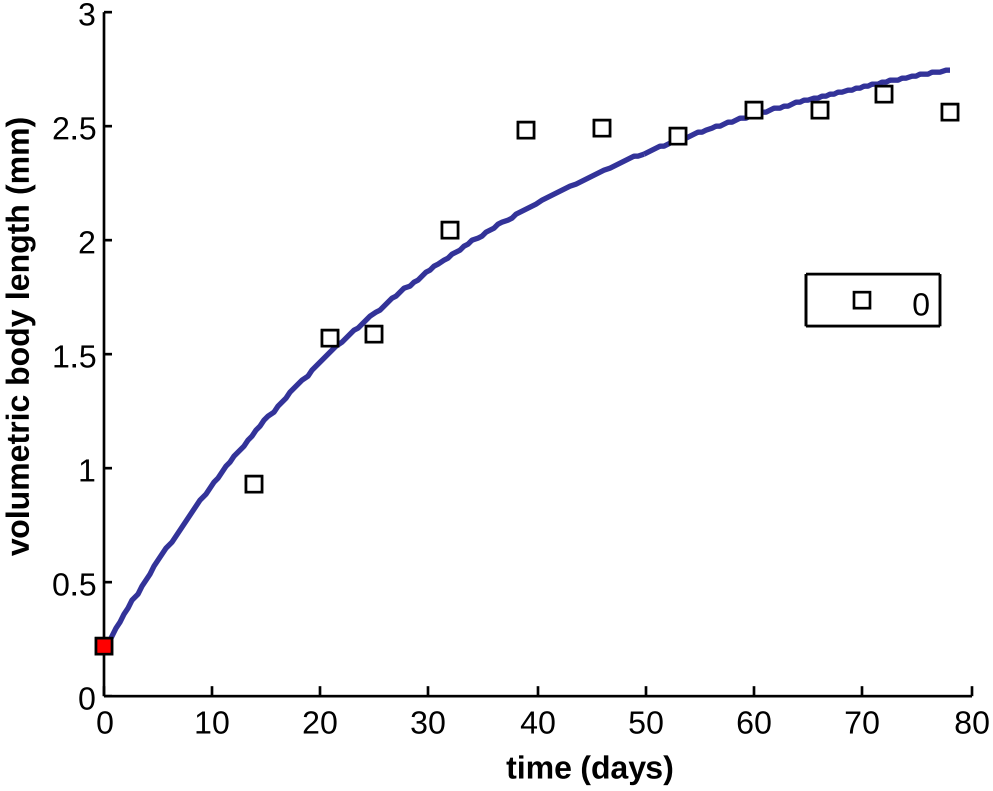




Jager and Selck (acc. J. Sea Res.)

Control growth

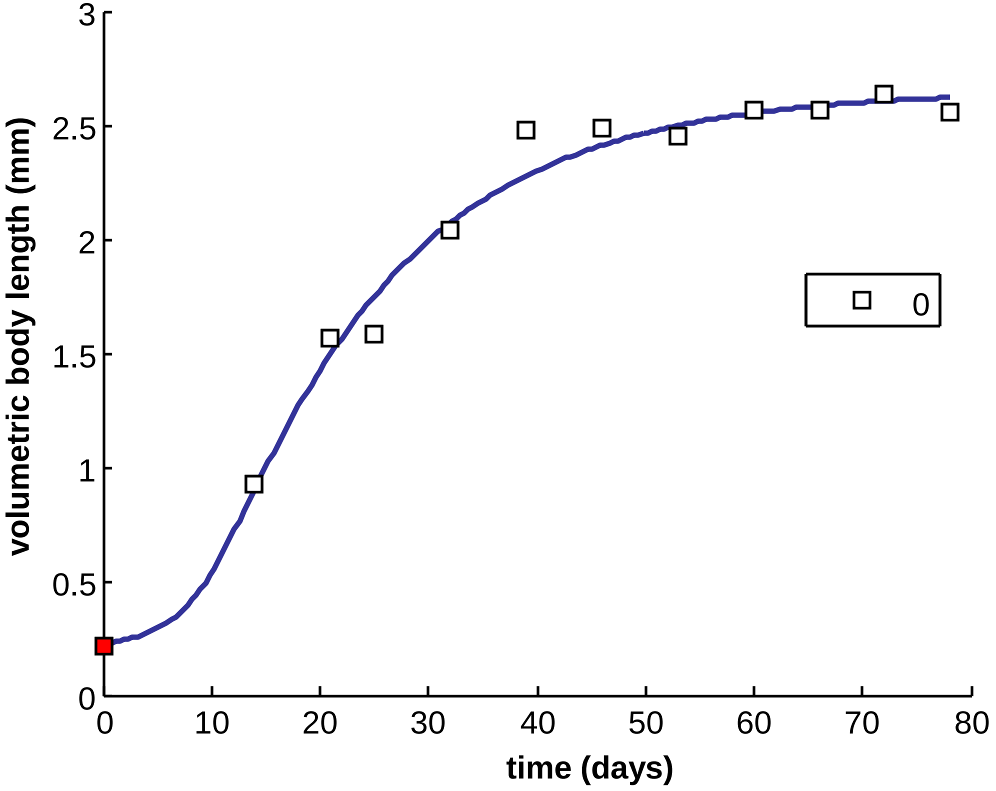
- Volumetric body length in control
  - here, assume no contribution reserve to volume …



Control growth

Assumption

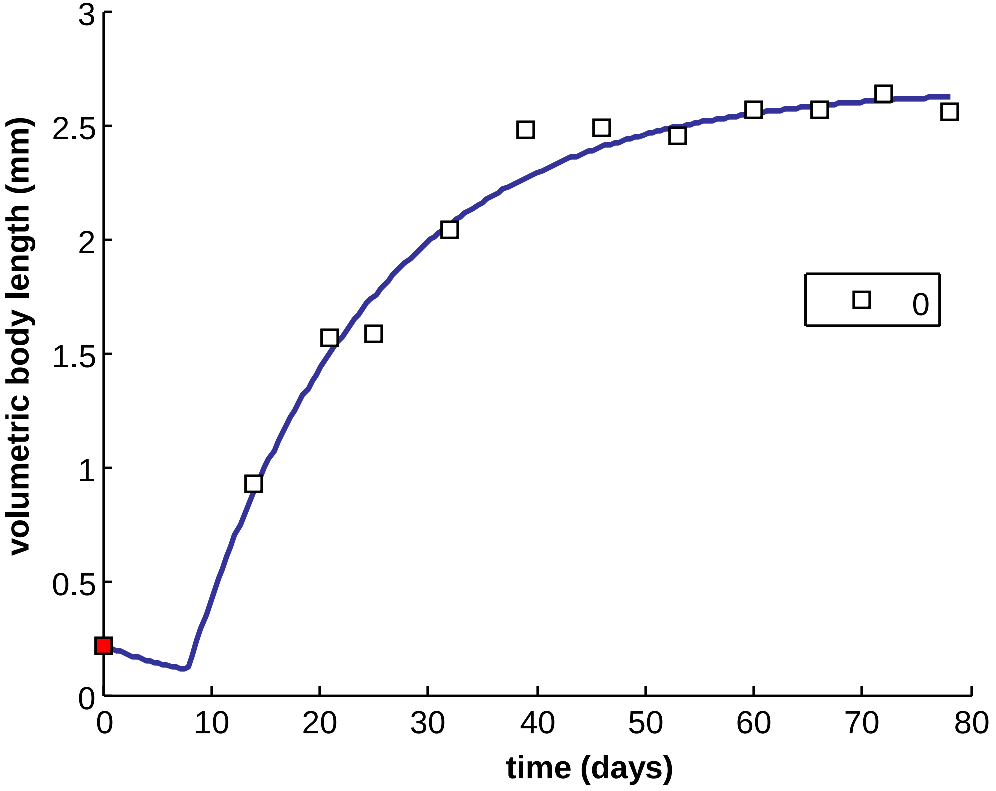
– effective food density depends on body size



Control growth

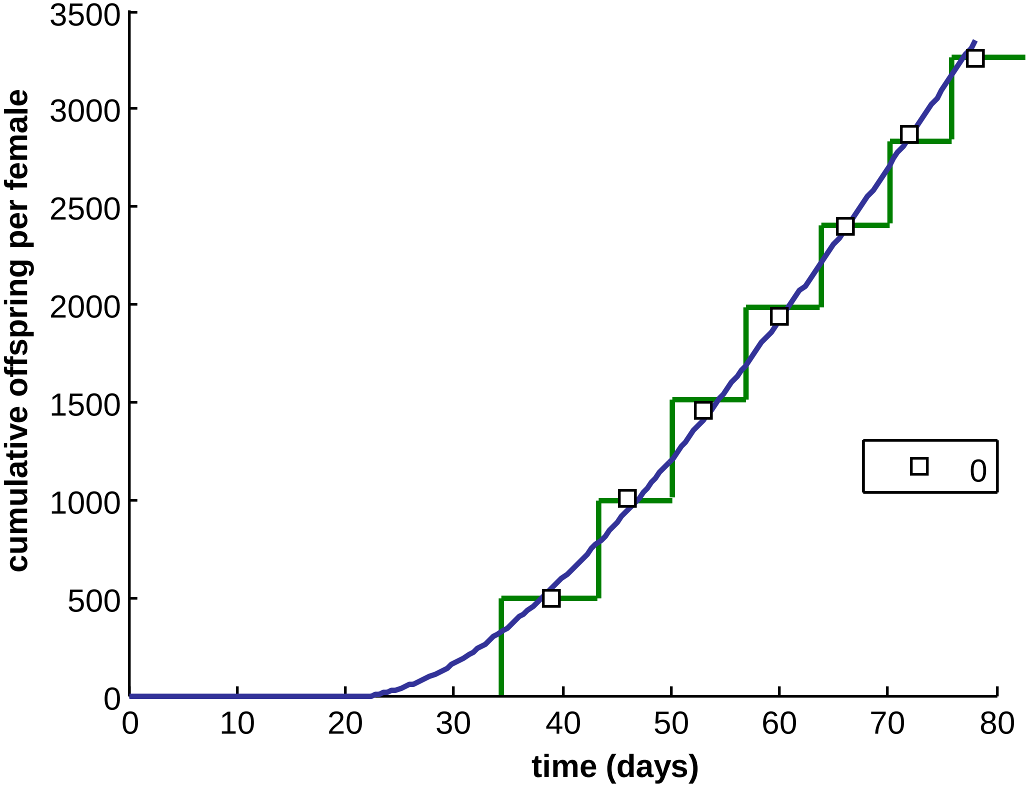
Assumption

– initial starvation (swimming and metamorphosis)



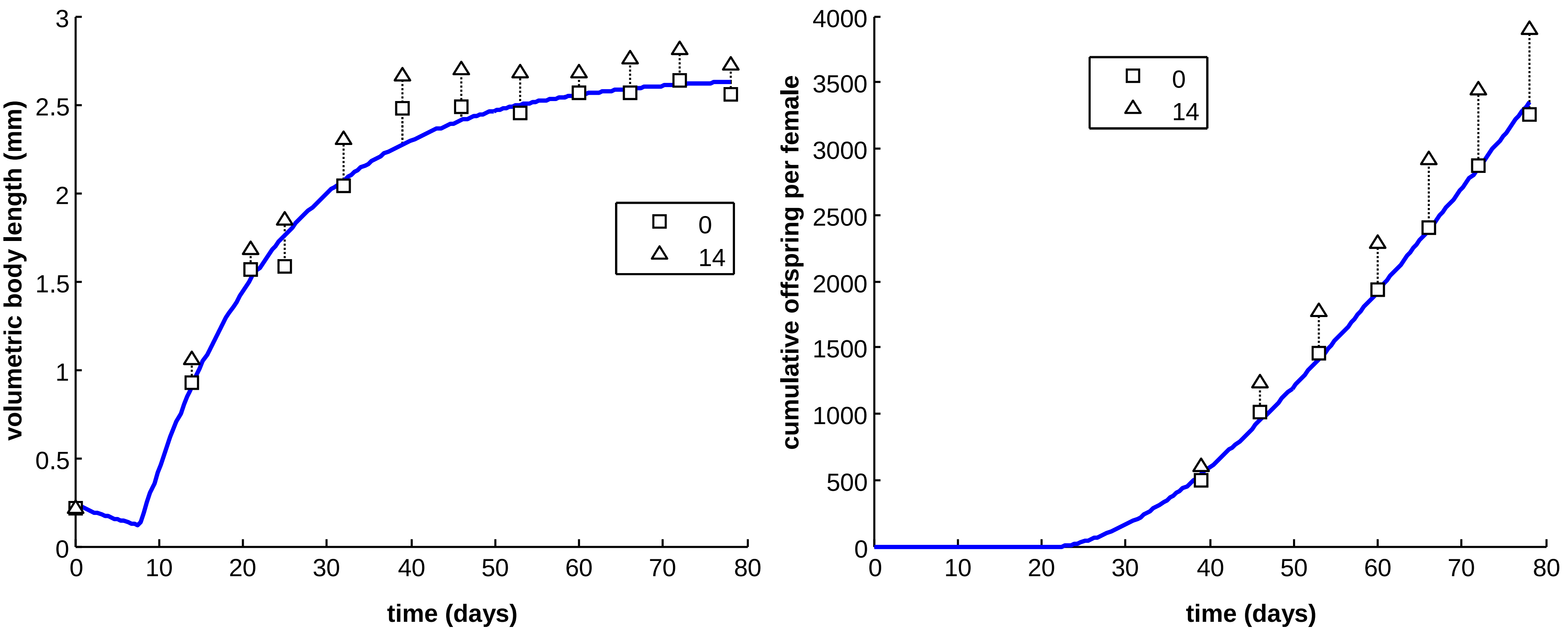
Control reproduction

- Compare to *mean* reproduction rate DEB
  - ignore reproduction buffer …



NP effects

- Compare the control to the first dose

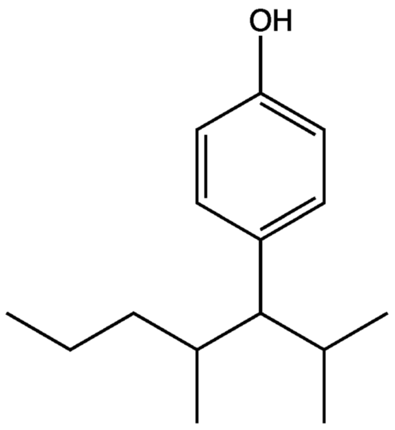


“Hormesis”

- Requires a mechanistic explanation …
  - conservation of mass and energy must hold!

Potential assumptions

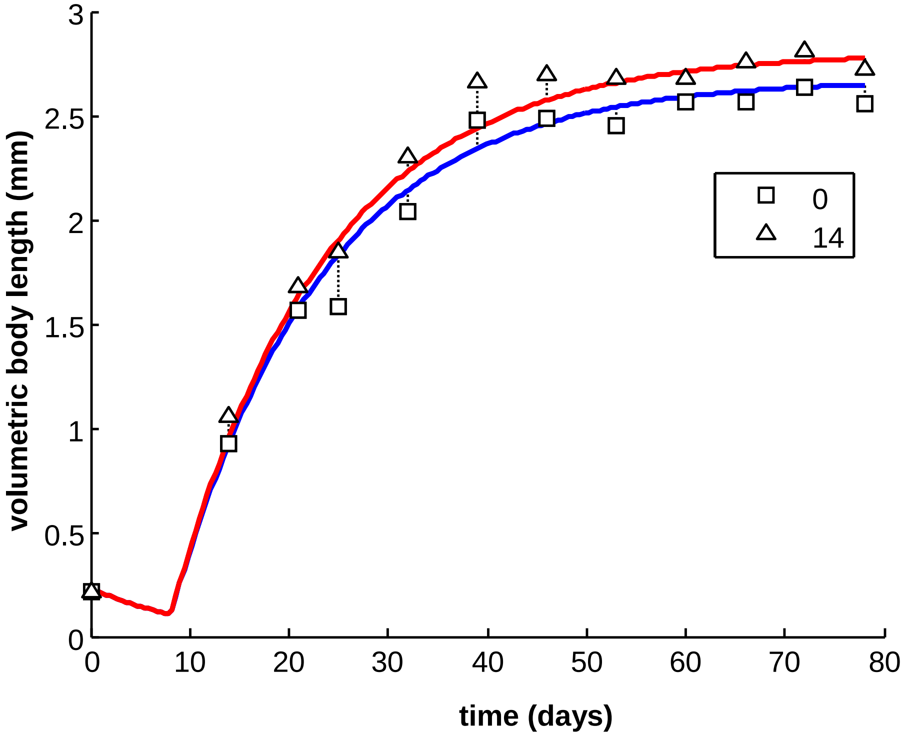
- NP is a micro-nutrient
- decreased investment elsewhere (e.g., immune system)
- NP relieves a secondary stress (e.g., parasites or fungi)
- NP increases the food availability/quality

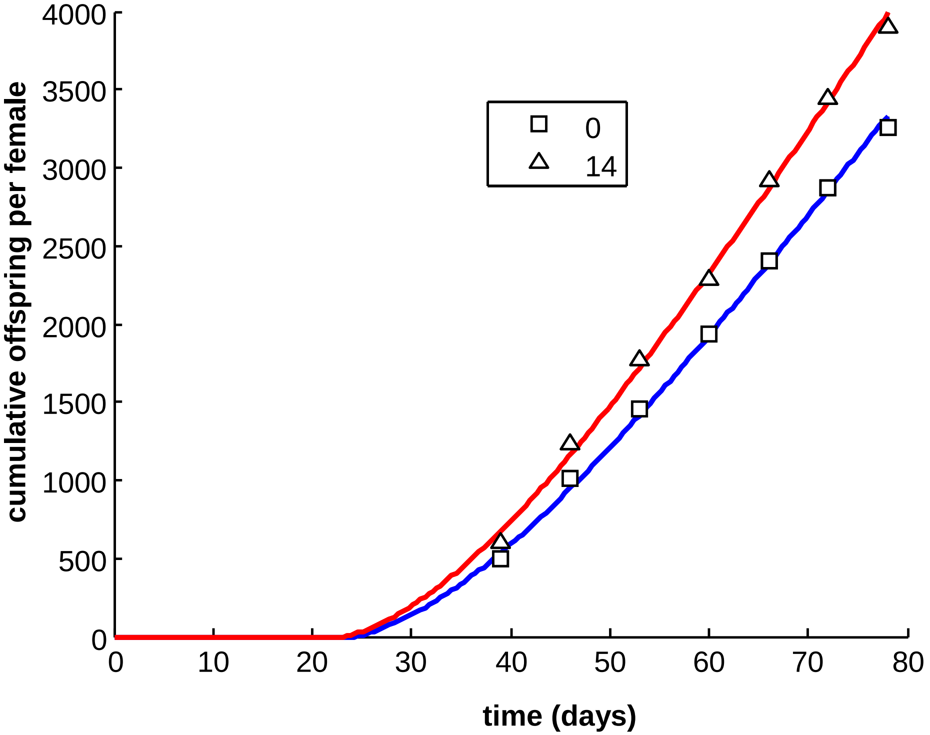


NP effects

Assumption

– NP increases food density/quality

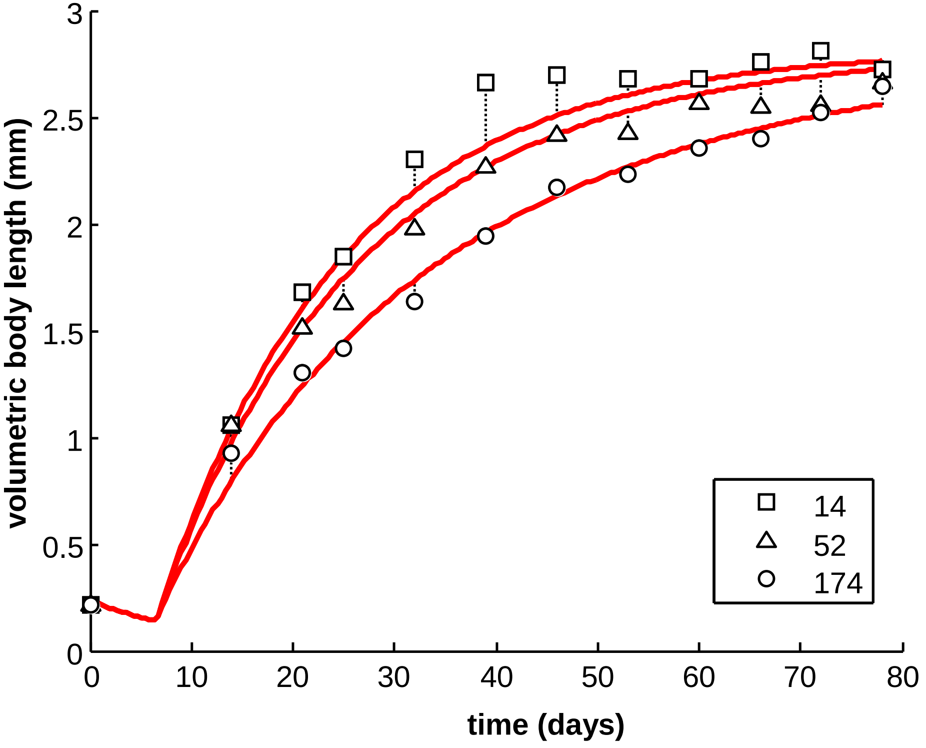




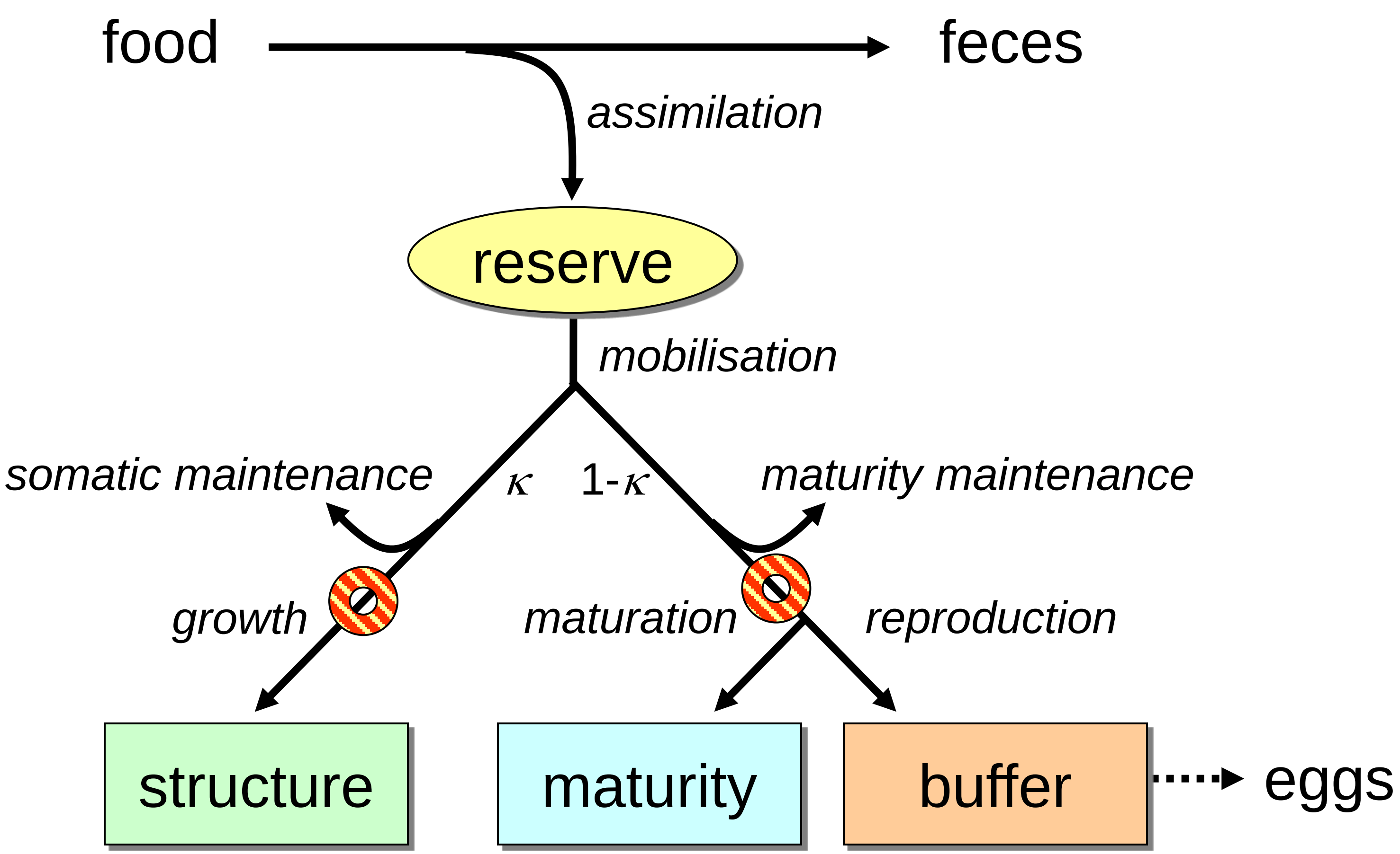
NP effects

Assumption

– NP affects costs for making structure
– somatic = maturity maintenance coefficient



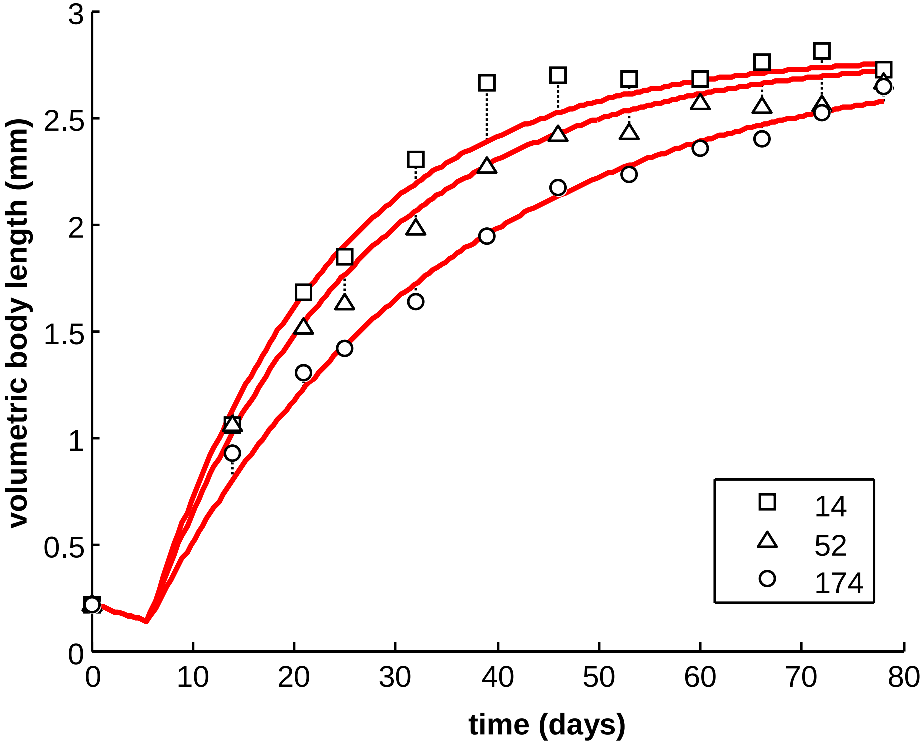
Standard DEB animal

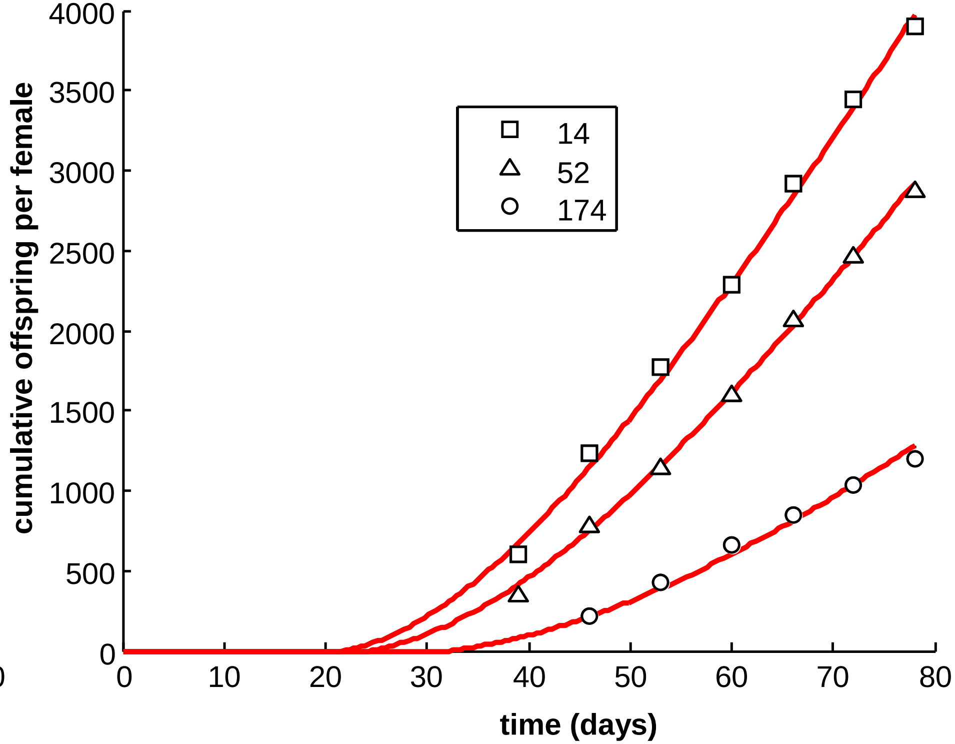


NP effects

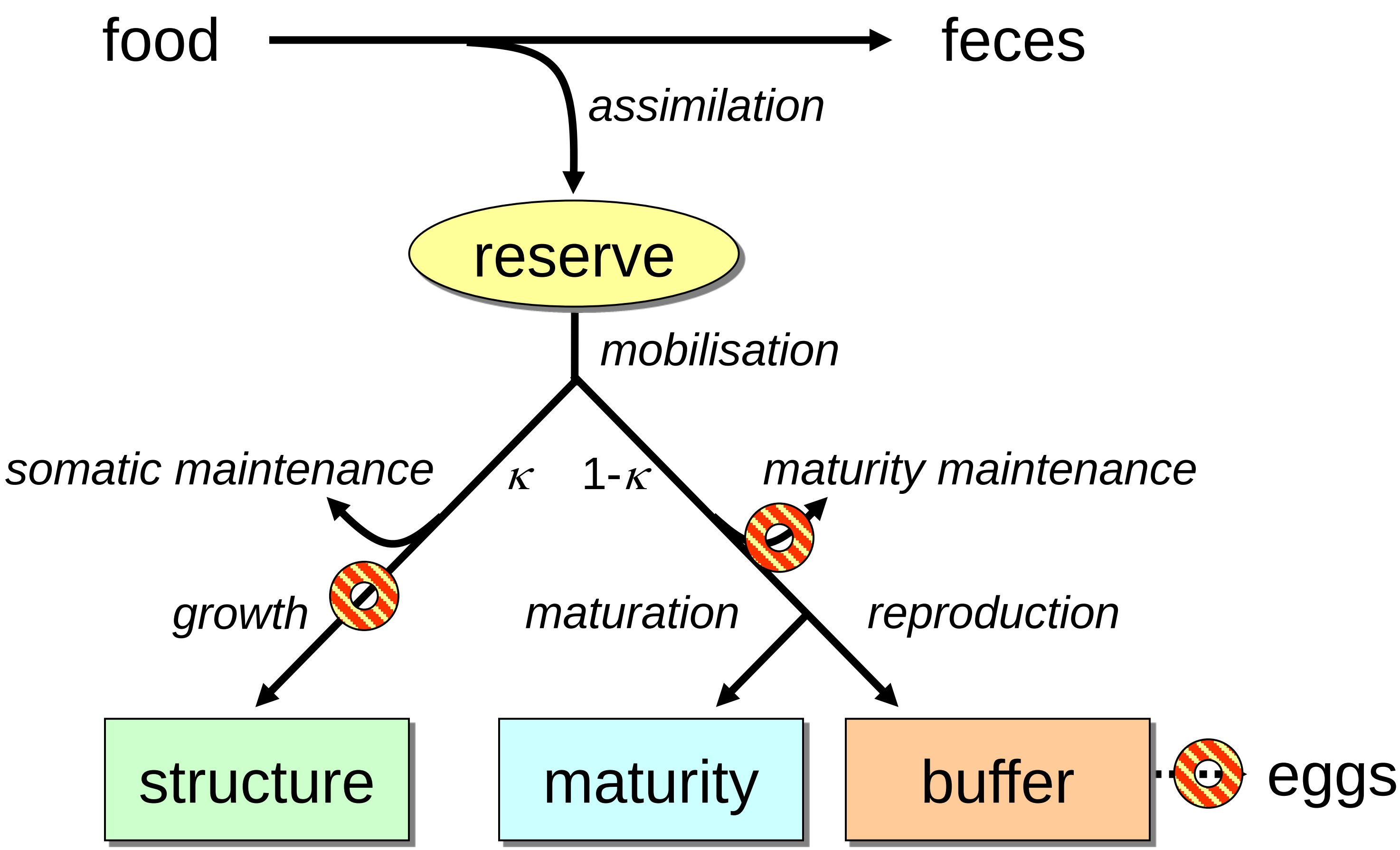
Assumption

– NP *also* affects costs for maturation and reproduction

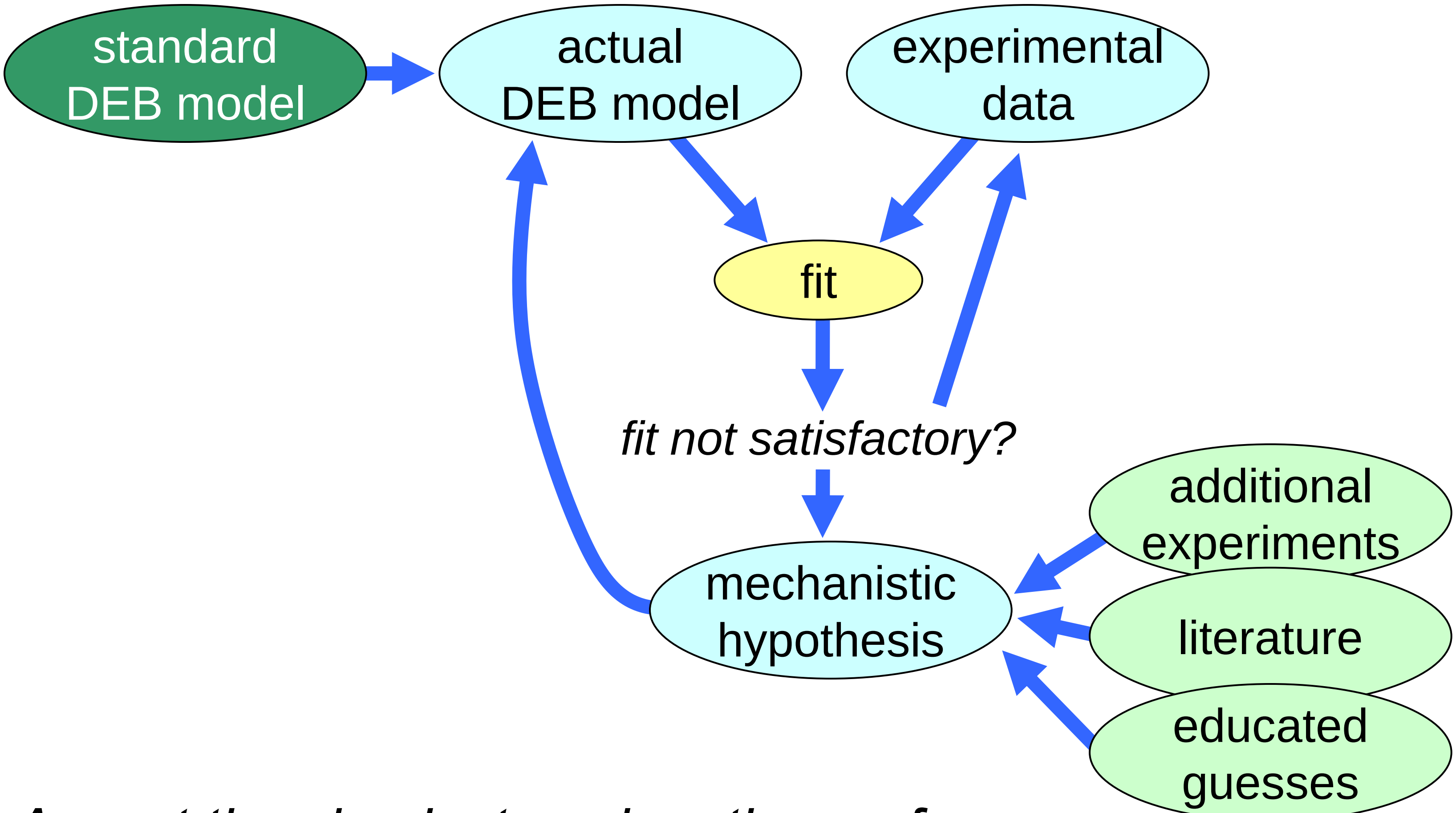




Standard DEB animal



Strategy for data analysis



Accept the simplest explanation … for now

DEBtox extensions: mixtures of toxicants

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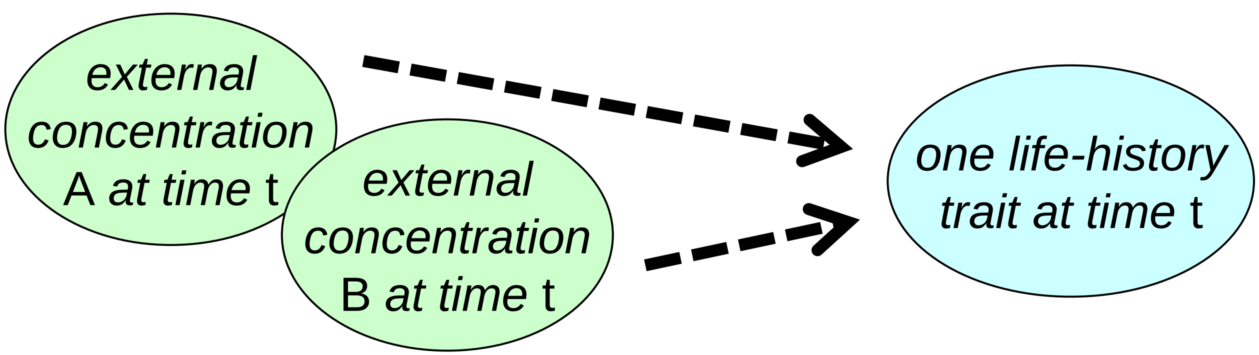
The challenge ….

- some 100,000 man-made chemicals …
- large range of natural toxicants and other stressors …
- for animals alone, >1 million species described …
- complex exposure situations …
- effects depend on exposure time, endpoint, …

The challenge ….

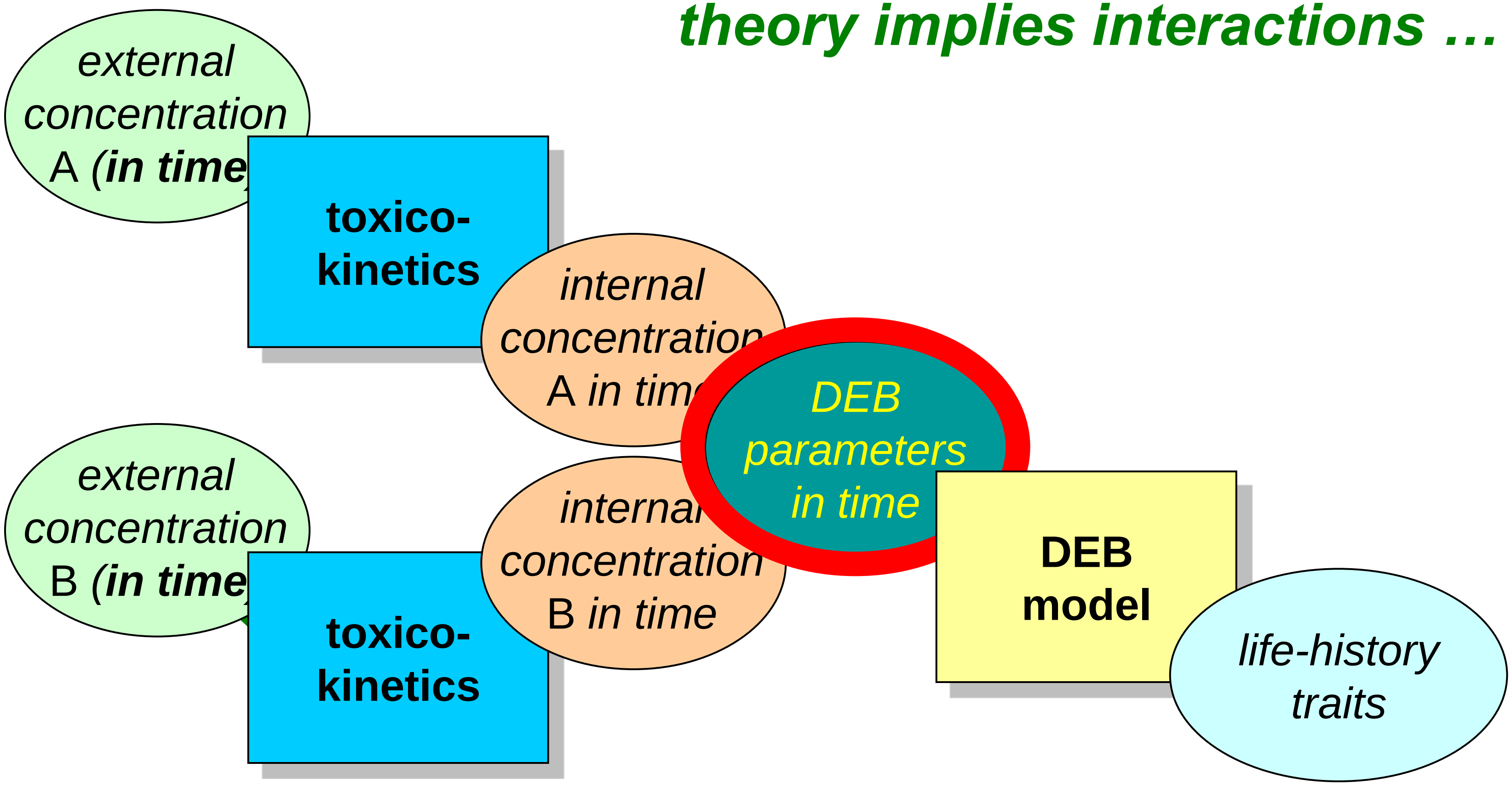
- some 100,000 man-made chemicals …
- large range of natural toxicants and other stressors …
- for animals alone, >1 million species described …
- complex exposure situations …
- effects depend on exposure time, endpoint, …

Descriptive approaches like CA and IA are of little use!

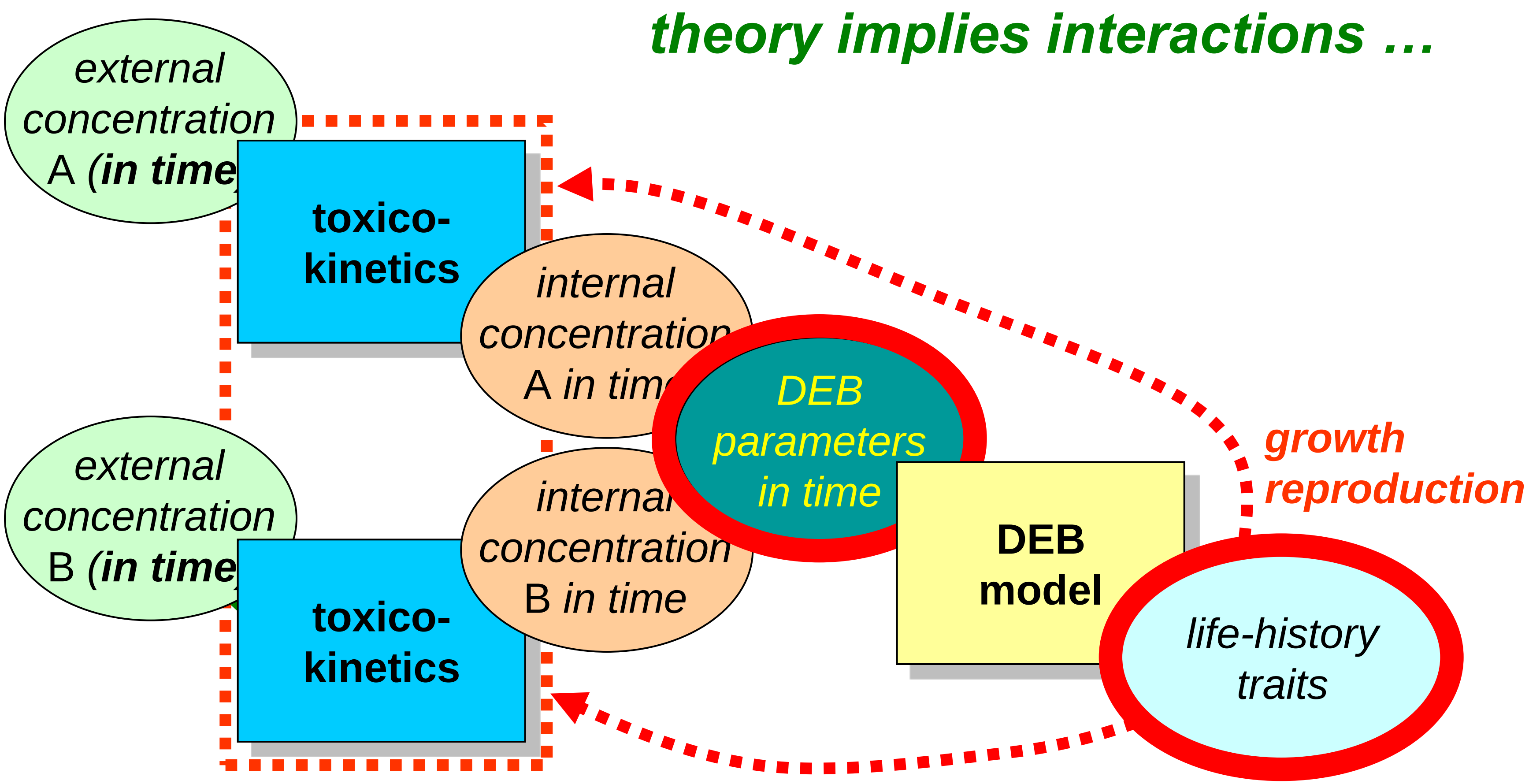


Mixtures in DEB

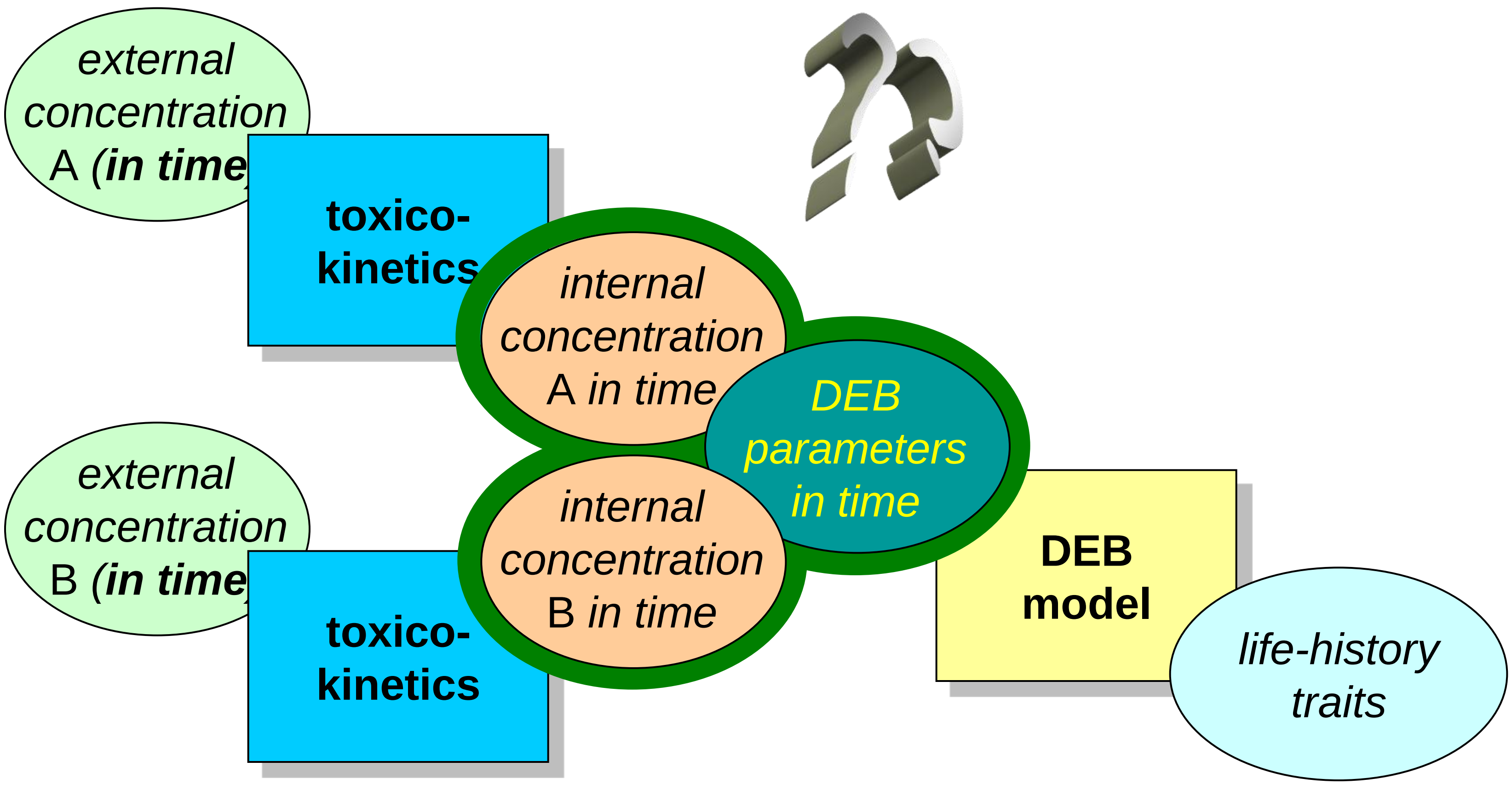
theory implies interactions …



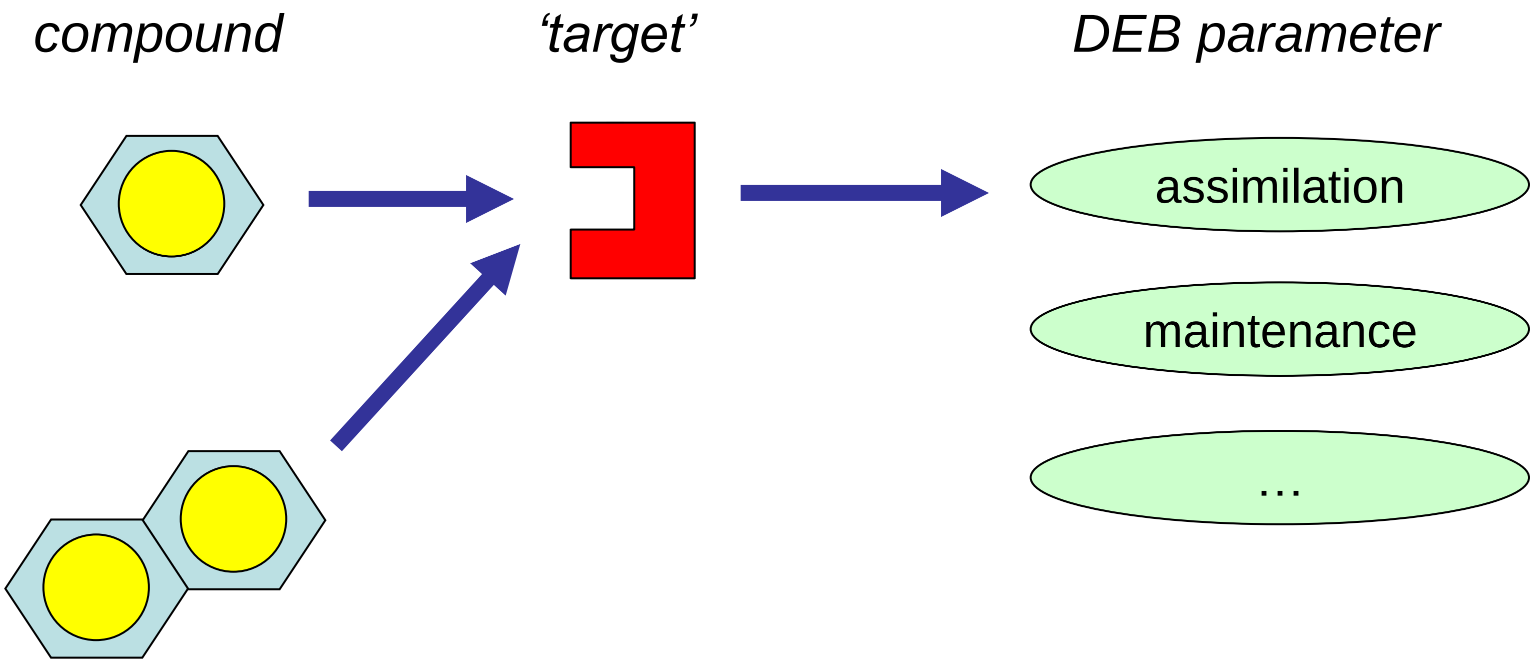
Mixtures in DEB



Mixtures in DEB

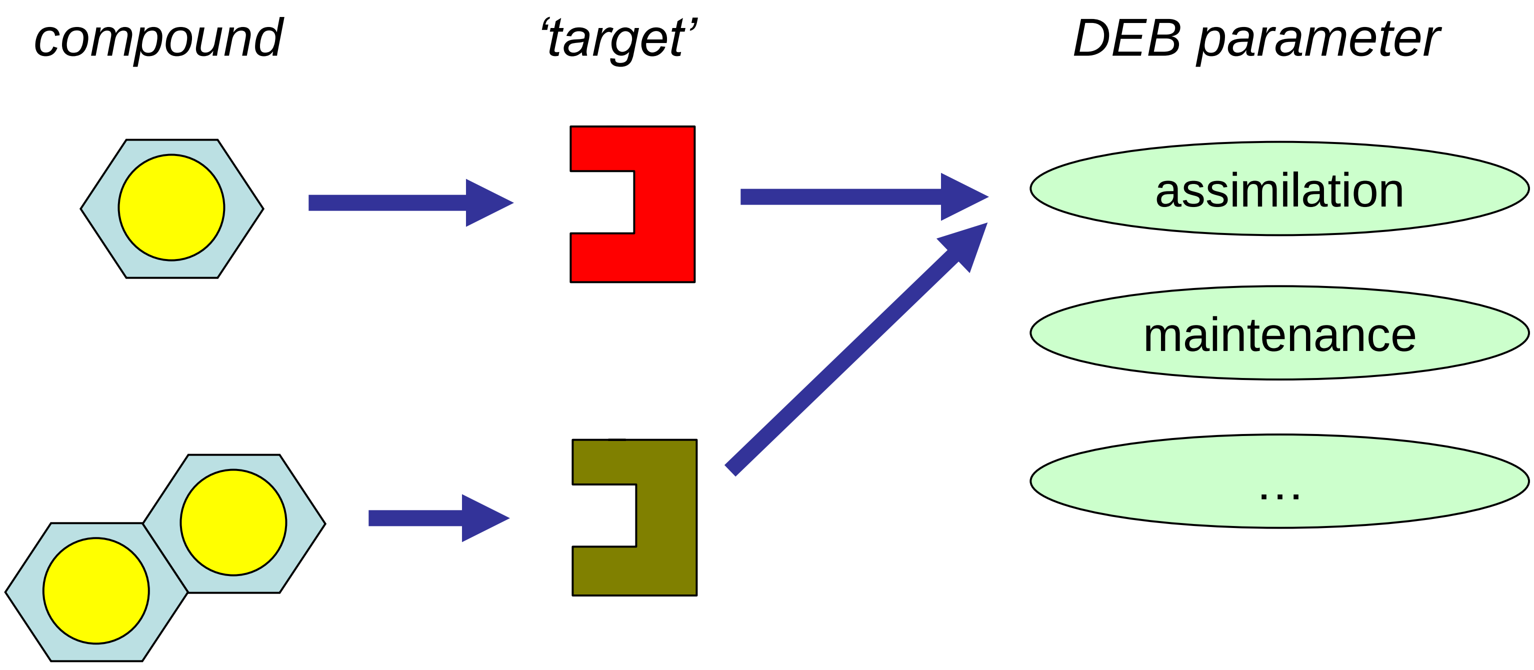


Simple mixture rules

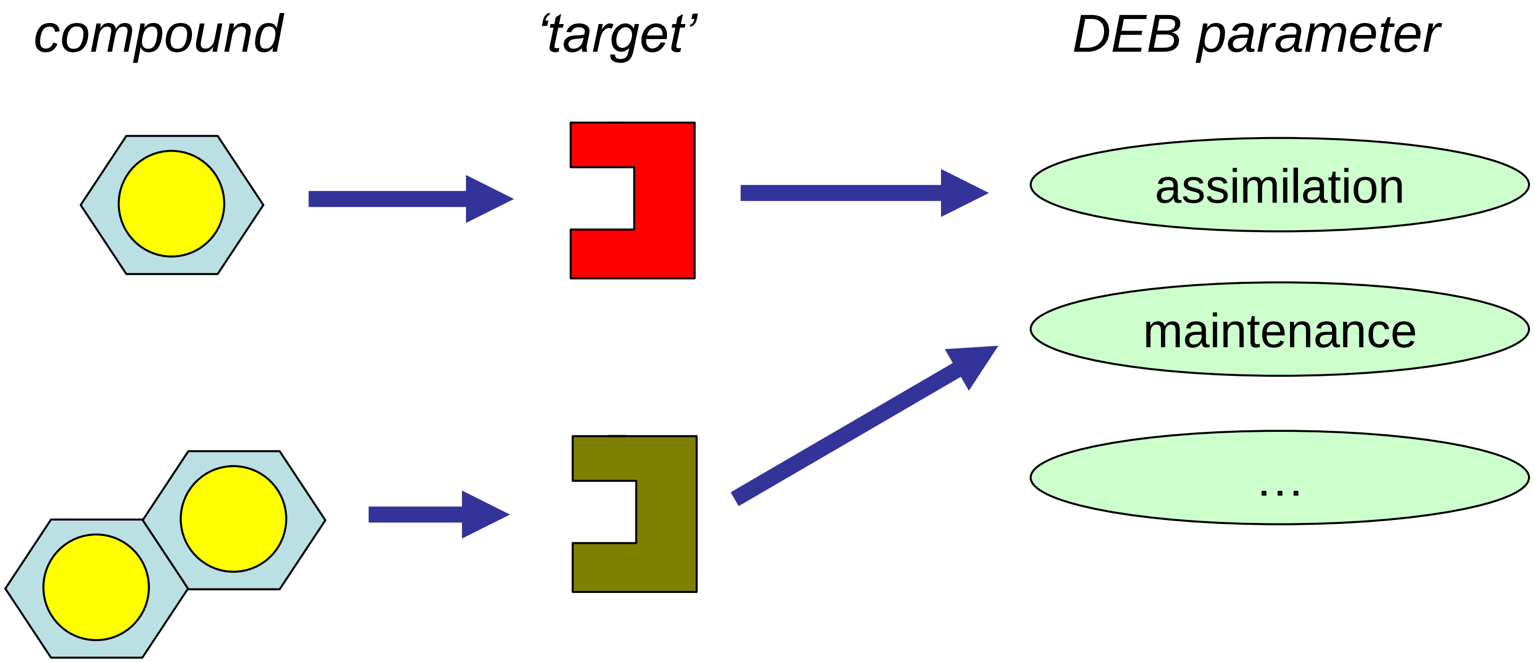


toxicity parameters linked (compare CA)

Simple mixture rules



Simple mixture rules

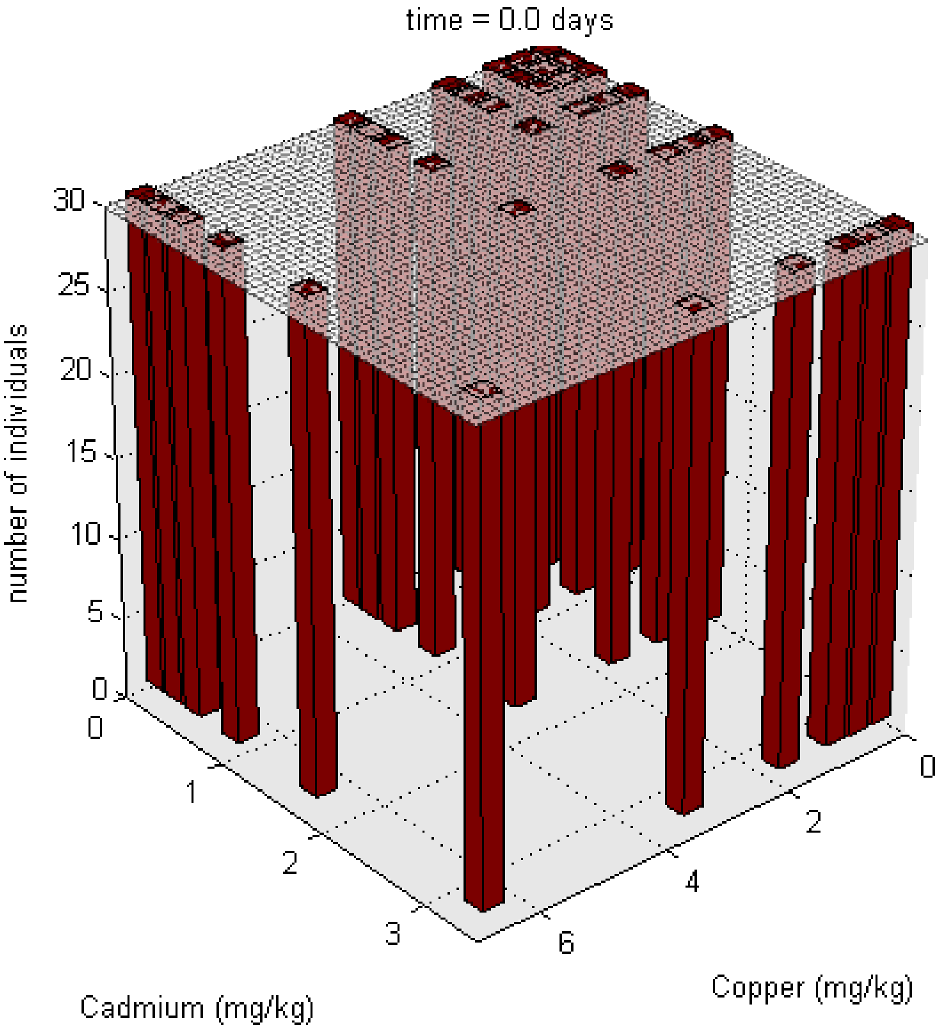


toxicity parameters independent (compare IA)

Visual representation

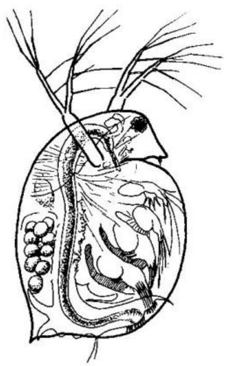
- For binary mixture, model represents surface over time …
  - example Cu and Cd in *Folsomia candida*

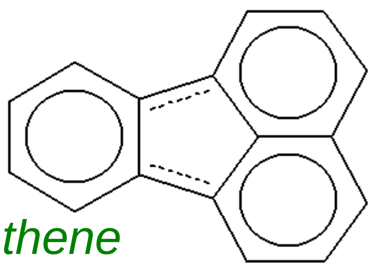
Baas *et al* (2007)



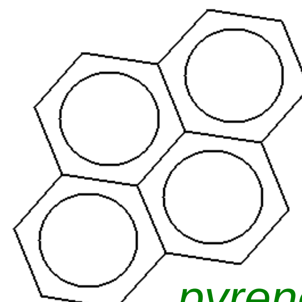
PAHs in Daphnia

- Based on standard 21-day OECD test
  - 10 animals per treatment
  - length, reproduction and survival every 2 days
  - no body residues (TK inferred from effects)





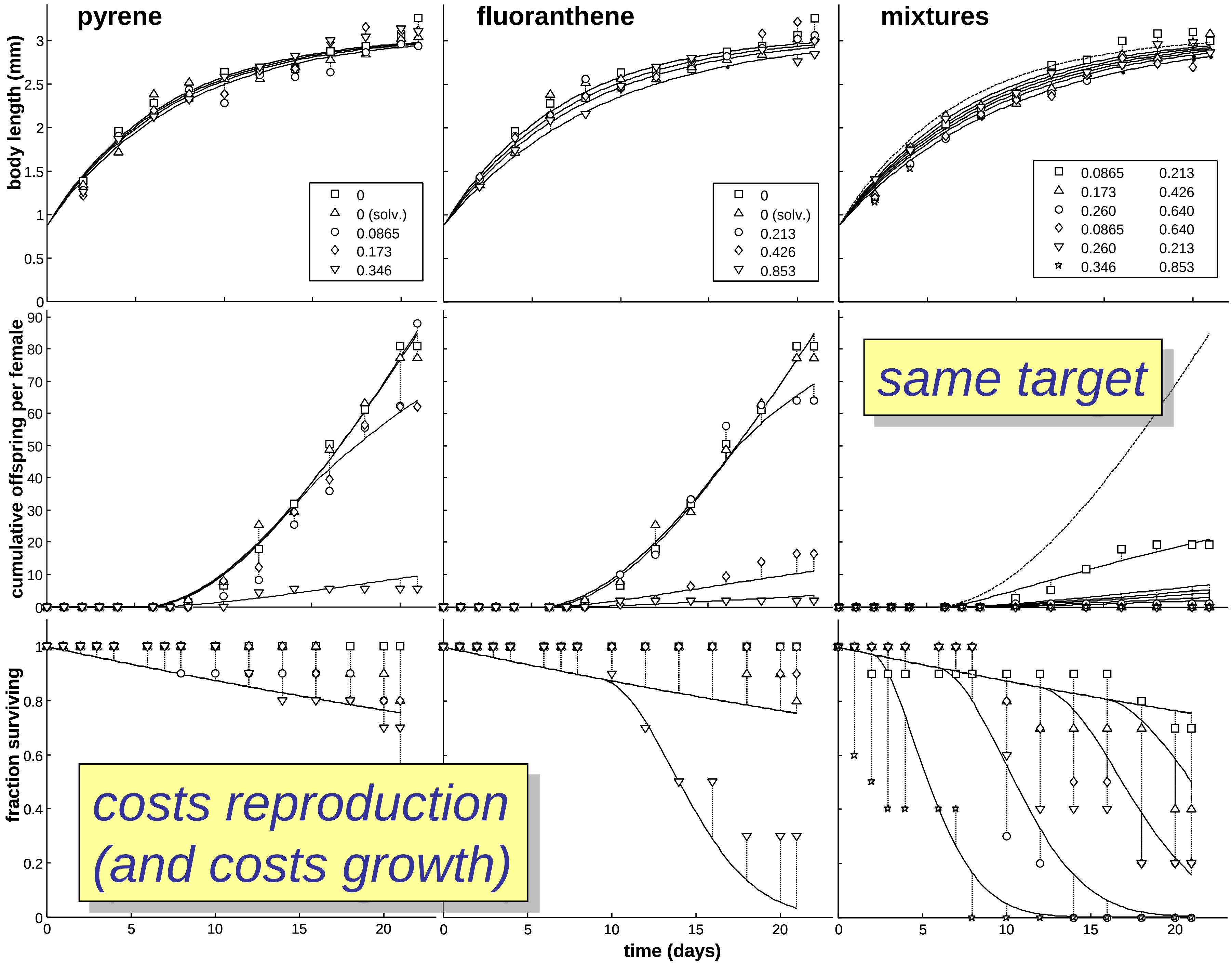
fluoranthene



pyrene

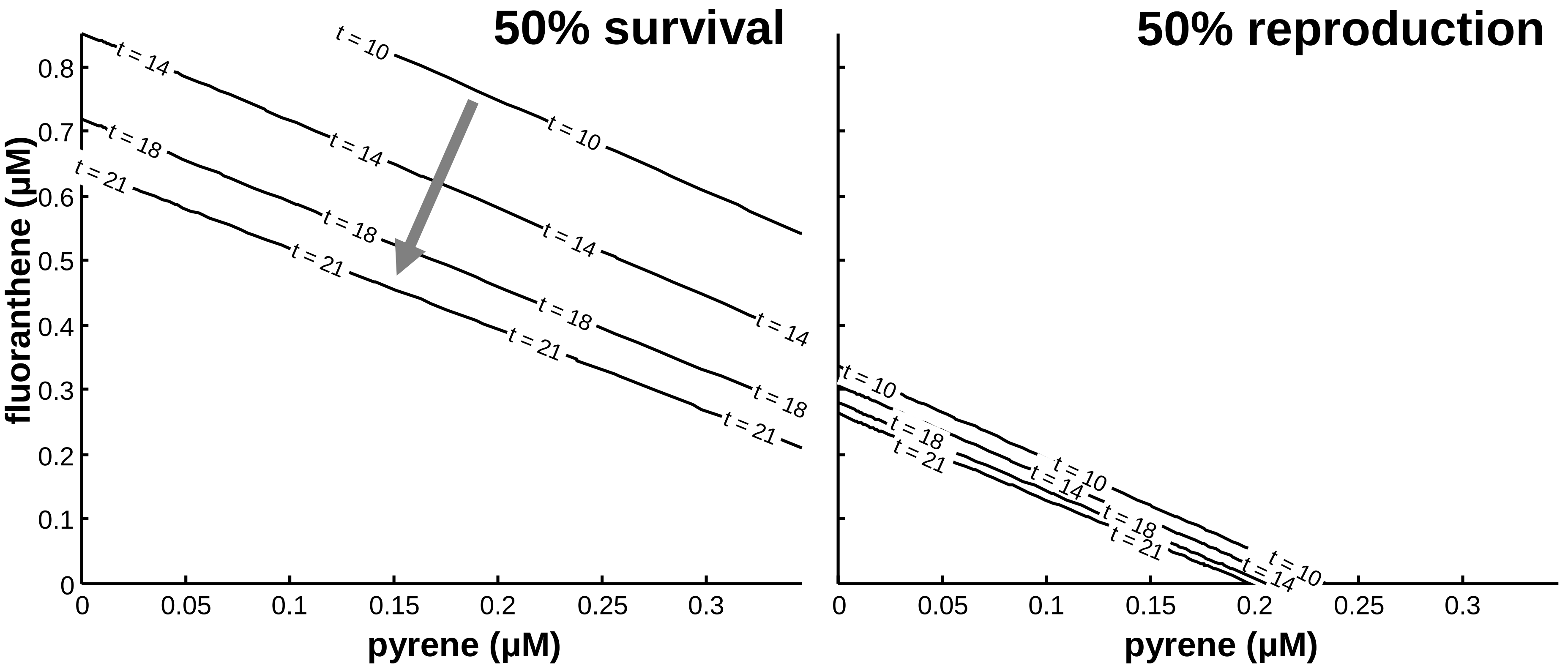
Jager *et al* (2010)

Universiteit Antwerpen



pyrene
fluoranthene
mixtures
body length (mm)
cumulative offspring per female
fraction surviving
time (days)
0
0 (solv.)
0.0865
0.173
0.346
0
0 (solv.)
0.213
0.426
0.853
0.0865 0.213
0.173 0.426
0.260 0.640
0.0865 0.640
0.260 0.213
0.346 0.853
same target
costs reproduction
(and costs growth)

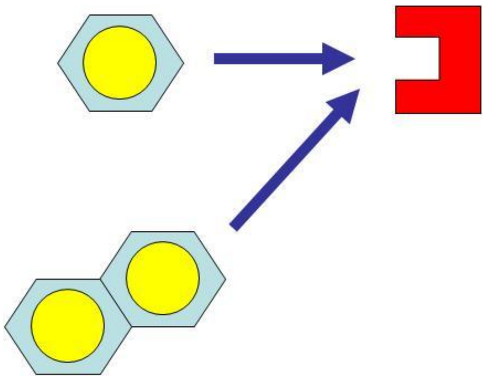
Iso-effect lines



for body length <50% effect

Mixture conclusions

- Multiple TK modules link to *one* DEB model
  - either through the same or different target
- We have ‘proof of concept’
  - but lack of suitable data …
  - more data need to be analysed
- For more complex mixtures, other interactions are inevitable
  - which require mechanistic assumptions



DEBtox extensions: what makes plants different?

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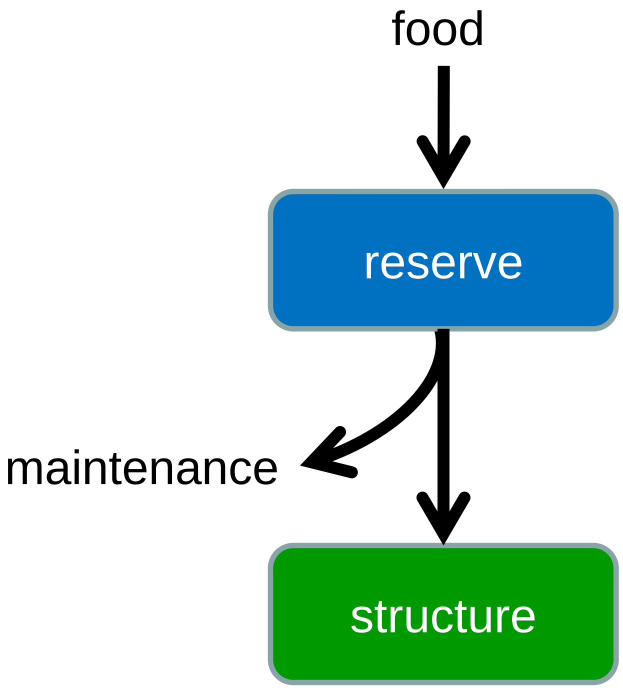
About reserve and structure

- Abstractions, in DEB theory:
  - reserves buffer metabolism from environment
  - structure and reserve have *constant* composition
  - composition *can* be different between both
  - their can be multiple reserves and structures ...

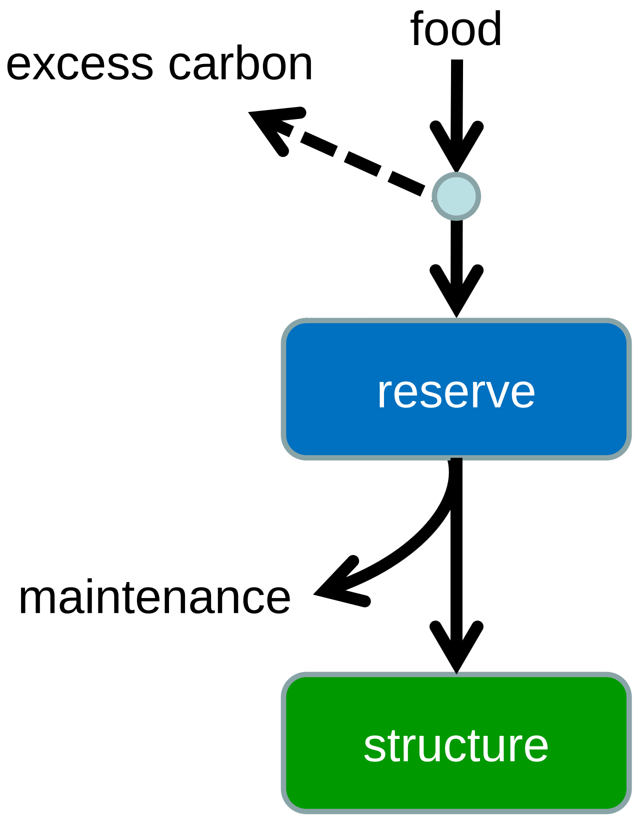
Animals that feed on animals

- food has similar composition as body



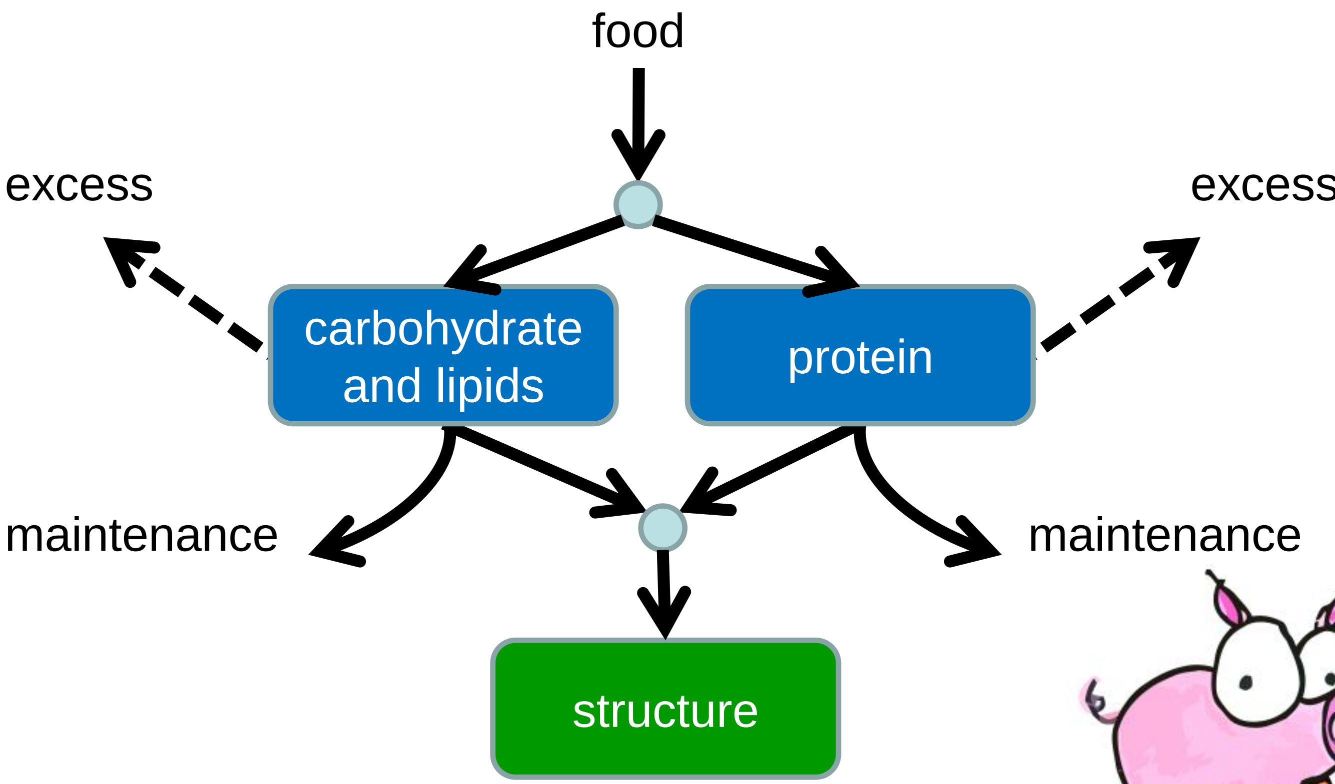
Animals that feed on plants

- food has different (but constant) composition as body



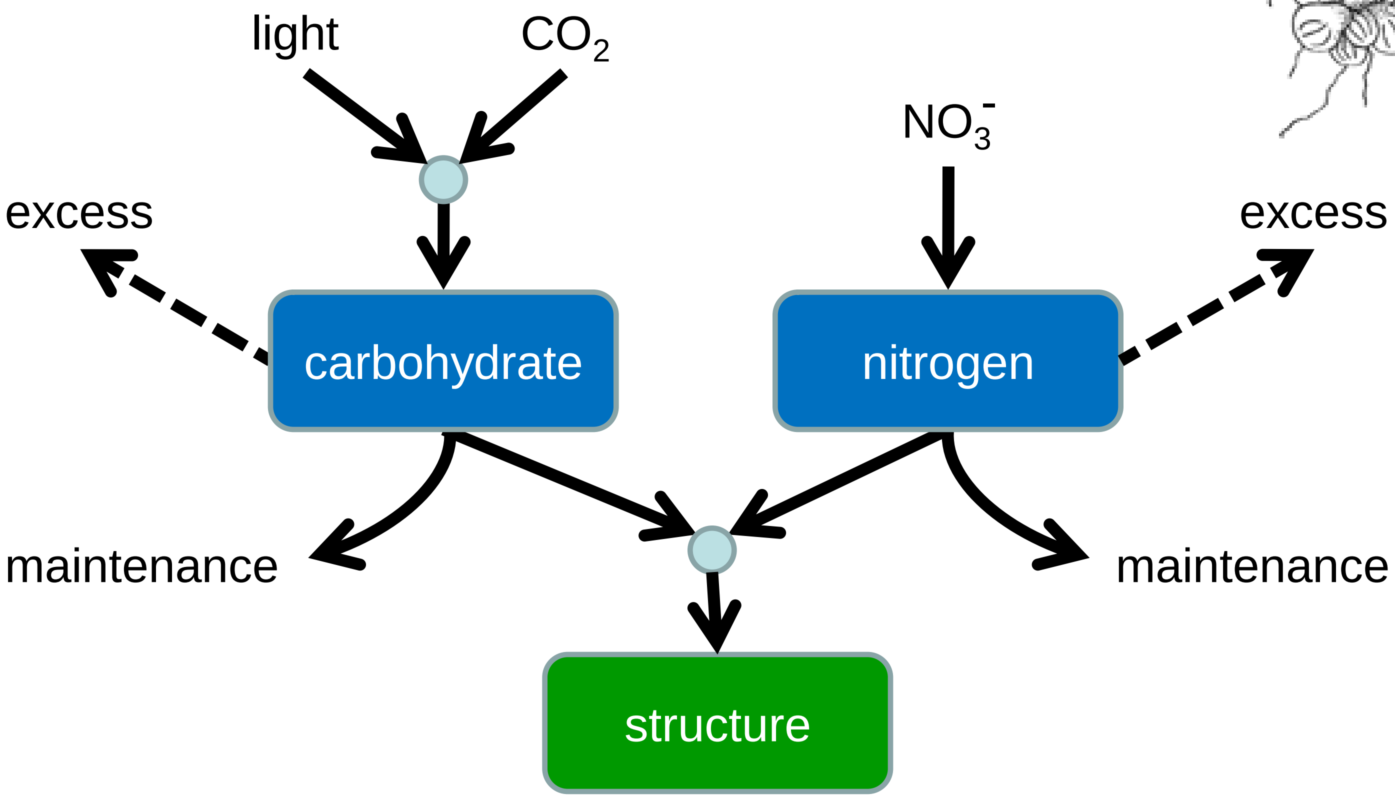
Animals that feed on anything

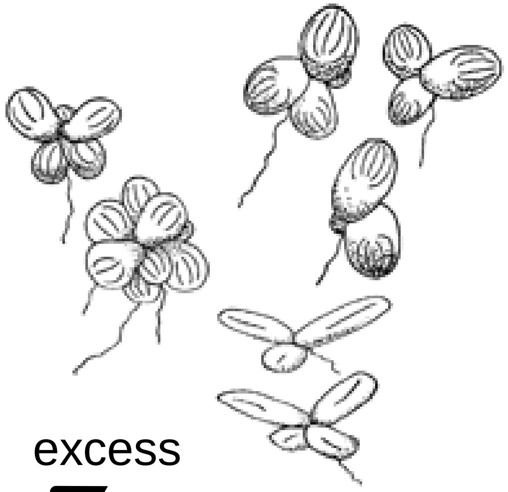
- food has different (varying) composition as body



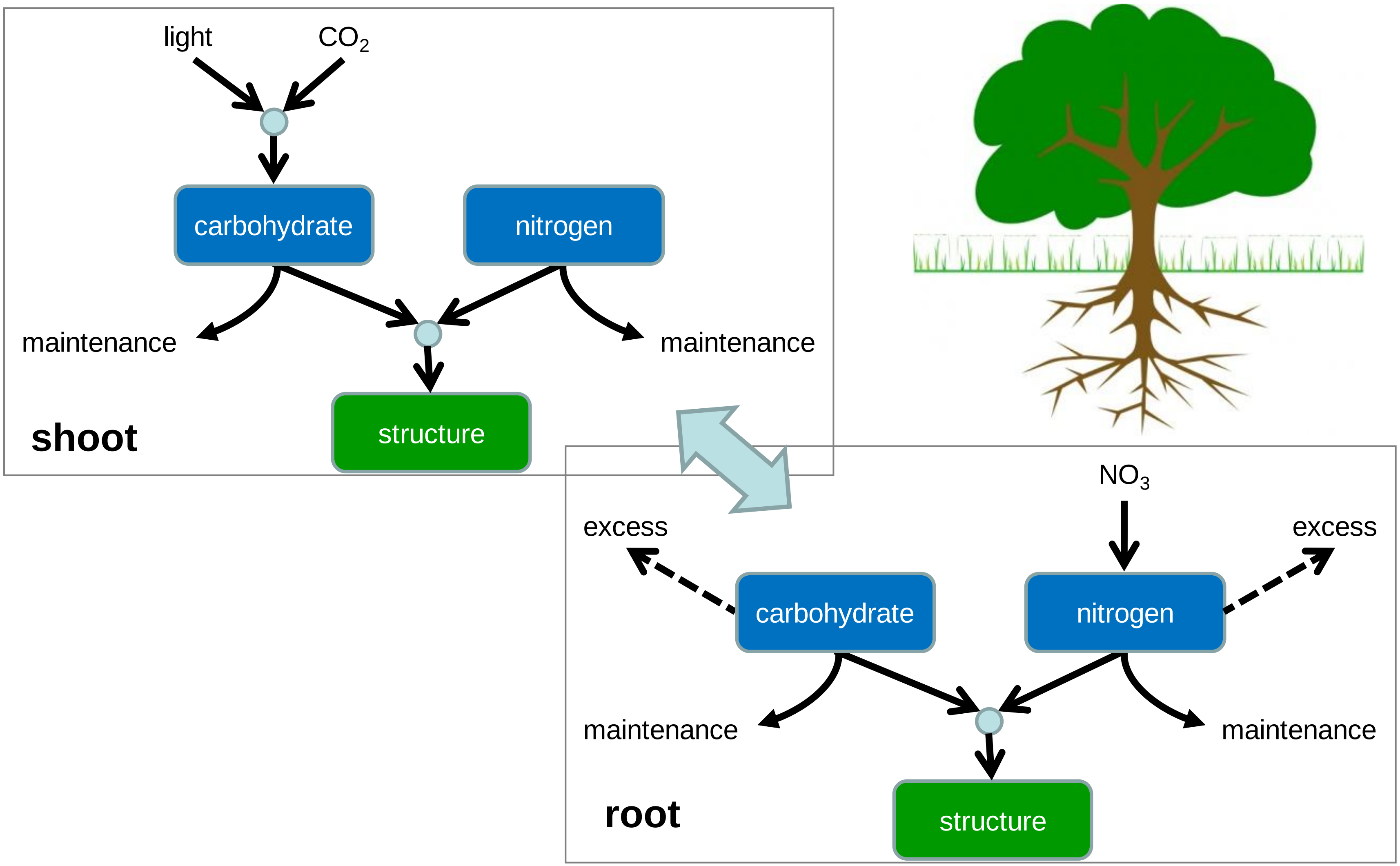
Plants that use light

- energy and building blocks *separately*





Roots and shoots ...

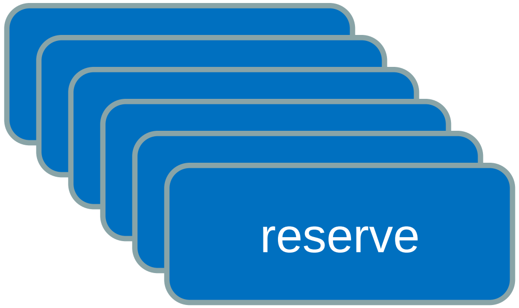


How many reserves?

Depends on organism *and* on question

- Nutrients may need a reserve compartment
  - if they are (can be) limiting
  - if they vary in time

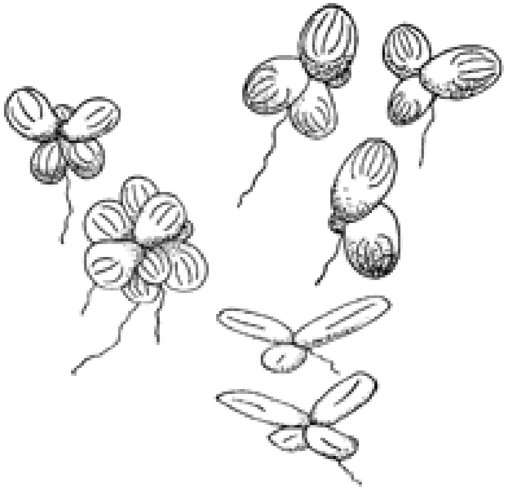
- DEBtox for algal growth in standard test ...
  - constant light, excess nutrients
  - thus: *no* reserves needed
  - (Kooijman *et al*, 1996)



Looking for simplicity

For things like algae and *Lemna* ...

- Maturation and reproduction may be ignored
  - not so clear how these concepts work in plants
- No large distinction between individual and population
  - population can be modelled as one individual
  - with surface area proportional to volume



Wrapping up

What is DEBtox?

- a specific piece of software (not available anymore)
- principle: toxicants affect parameters of *any* DEB-based model

Analysis of mixtures

- follows naturally from the DEB perspective
- more work needed to see how far this idea can get us

Extension to plants

- differ from animals; resources not from one flux
- DEB theory includes plants, so DEBtox approaches can be developed

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