Dynamic Energy Budget models in Ecotoxicology II: linking levels of biological organization

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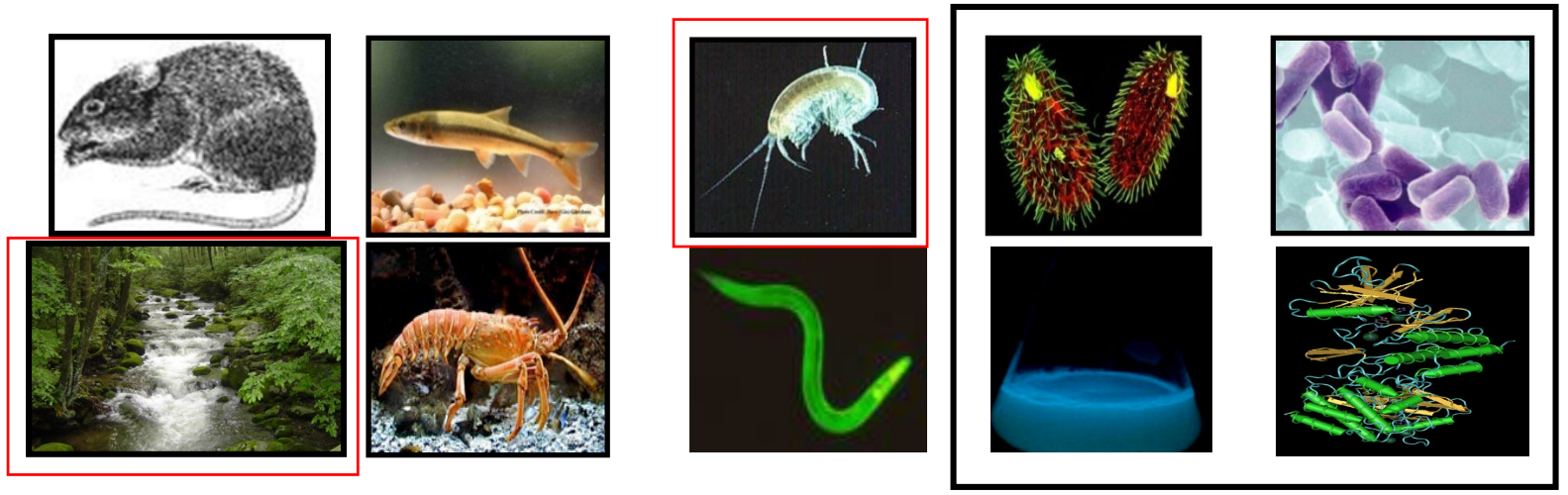
Special thanks to **Ben Martin**, **Tin Klanjscek**, **Erik Muller**, **Louise Stevenson** and all members of NIMBioS working group “Molecules to individuals”

Data sources



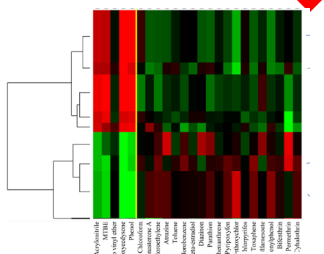
few/year | 100's/year | 1000's/year | 10,000's/day | 100,000's/day

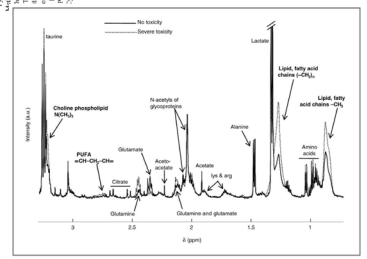
High Throughput Bacterial, Cellular, Yeast, Embryo or Molecular Screening

Expensive *in vivo* testing and ecological experiments

Challenge for theorists: to use information from organismal and suborganismal studies to prioritize, guide design, and interpret ecological studies and inform ERA, i.e. progress towards predictive ERA

Biological organization





What we measure

Molecules

Cells

Organs

Individuals

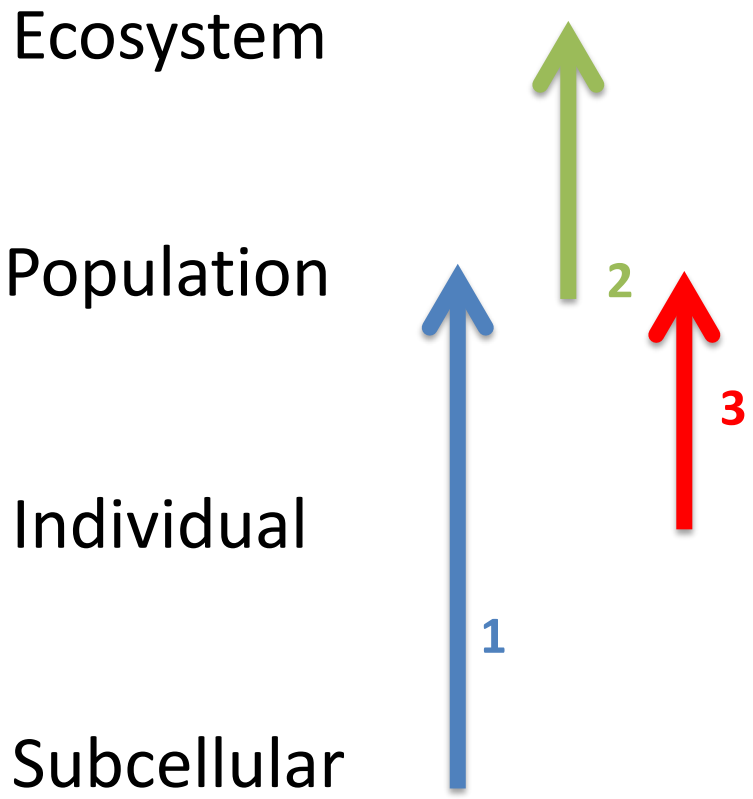
Populations

Communities + Ecosystems

What we care about

DEB-based predictions across levels of organization

Three tales of success, failure, and ambiguity using microcosms



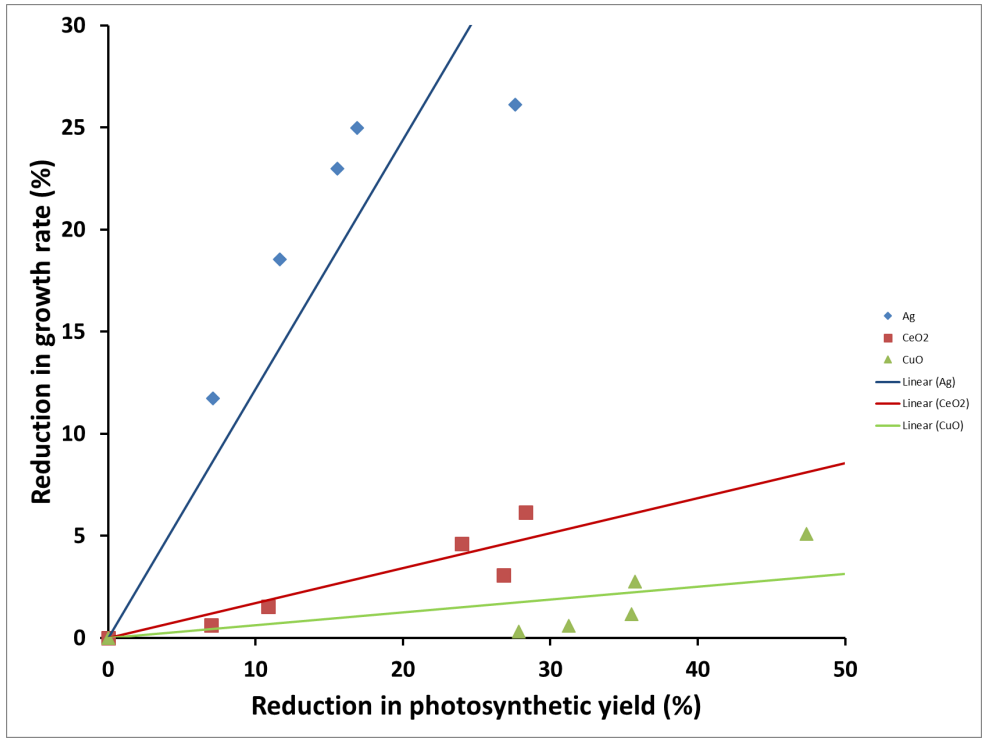
1 – Phytoplankton and nanoparticles

2 – Phytoplankton and nanoparticless

3 – *Daphnia* + herbicide

SUBORGANISMAL → POPULATION

Hypothesis: population response to nanoparticle exposure can be predicted from rapid high content measurements



DEB model

$$\frac{dX}{dt} = rX \quad \text{with } r = \frac{k_E - gk_m}{1+g}$$

Parameter proportional to photosynthetic efficiency

R.J. Miller, E.B Muller et al 2017

SUBORGANISMAL → POPULATION

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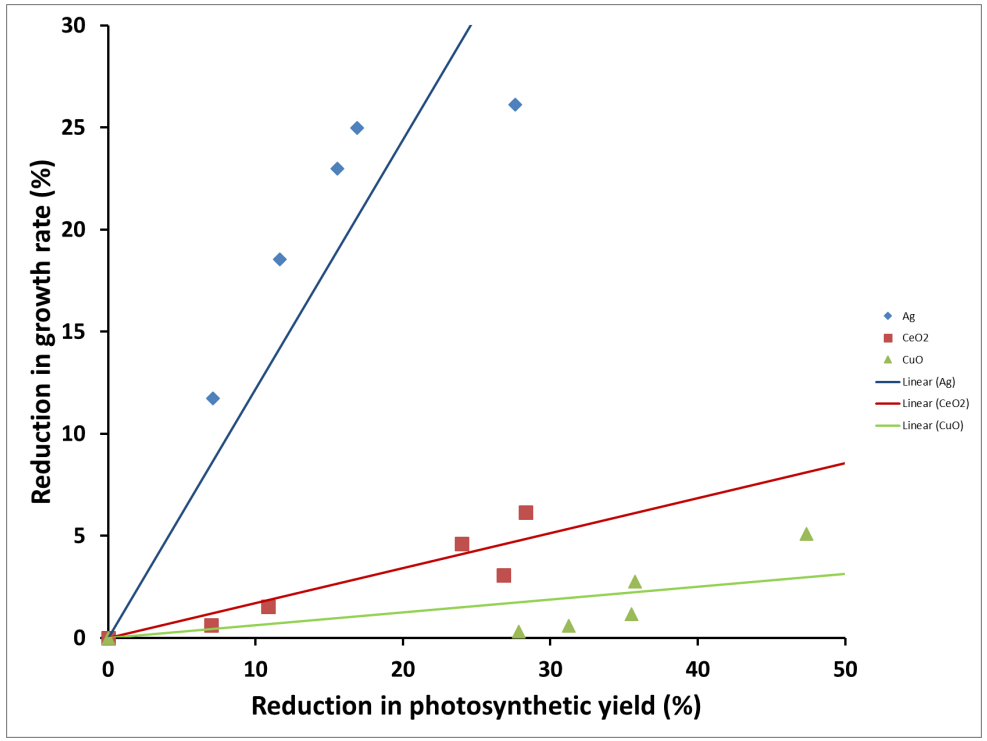


DEB model

$$\frac{dX}{dt} = rX \quad \text{with } r = \frac{k_E - gk_m}{1+g}$$

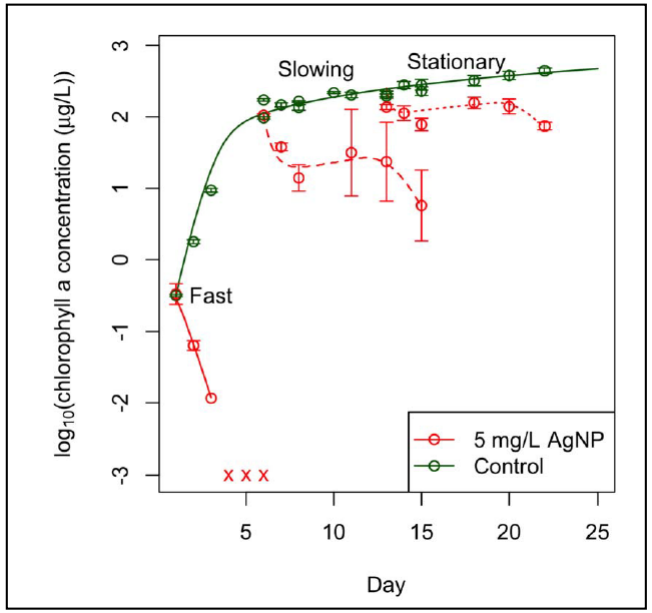
Parameter proportional to photosynthetic efficiency

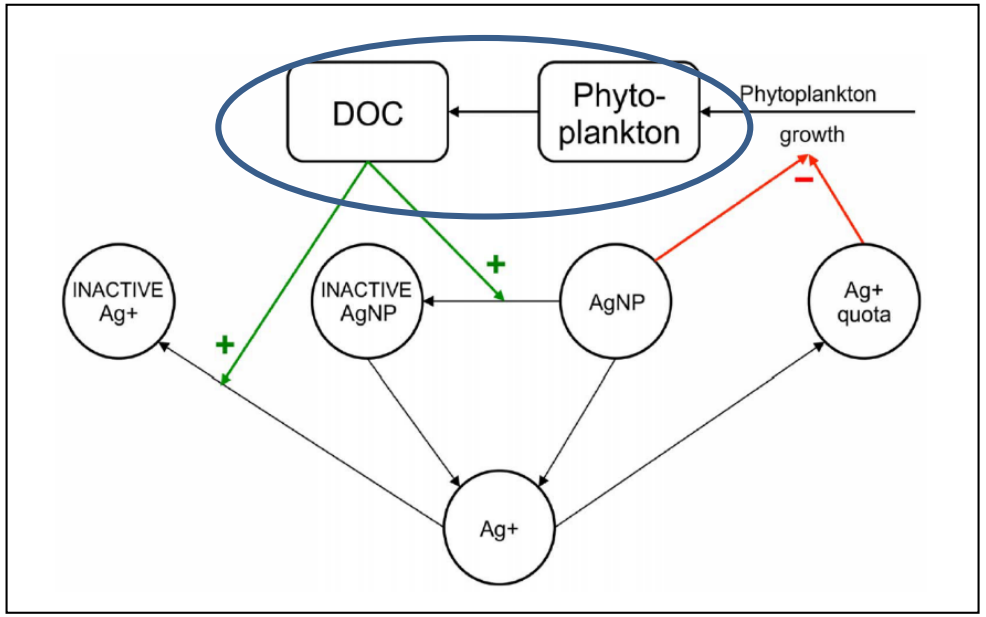
BUT

Other metrics from high content screening were uncorrelated with population growth rate

R.J. Miller, E.B Muller et al 2017

Batch cultures of microalgae exposed to silver nanoparticles*





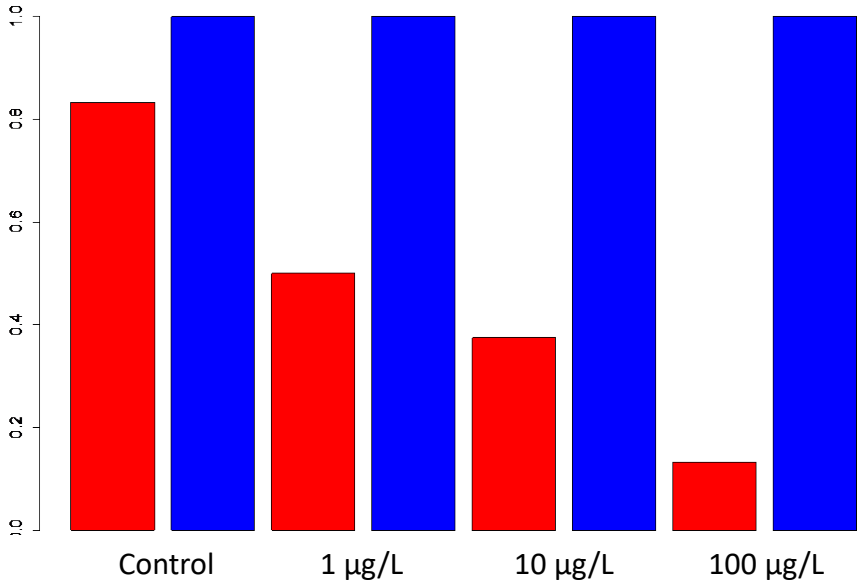
- **Silver NPs were added to batch cultures of *Chlamydomonas reinhardtii*** after 1, 6 and 13 days
- Environment (not cells) changed between treatments
- dynamic model included: algal growth, nanoparticle dissolution, bioaccumulation , **DOC production**, **DOC-mediated inactivation of nanoparticles and of ionic silver**.

Stevenson et al. 2013

Environmental Question

Can algal-produced organic material protect other aquatic species?

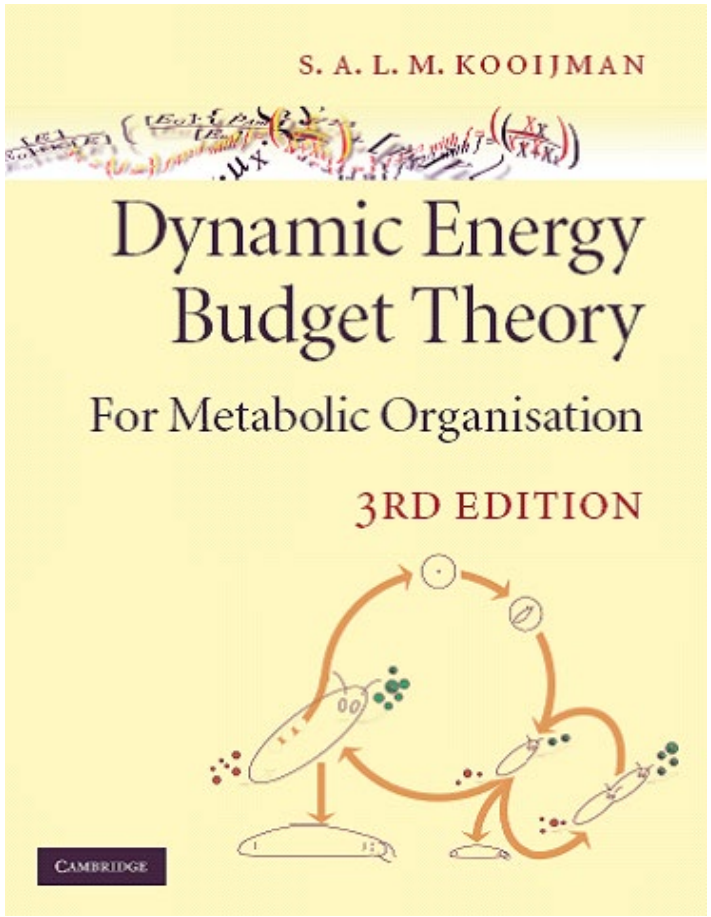
Daphnia 48-hr survival when exposed to silver nanoparticles

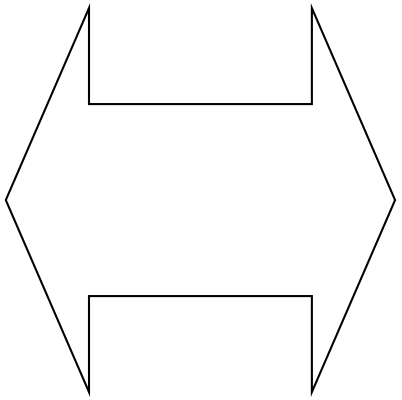


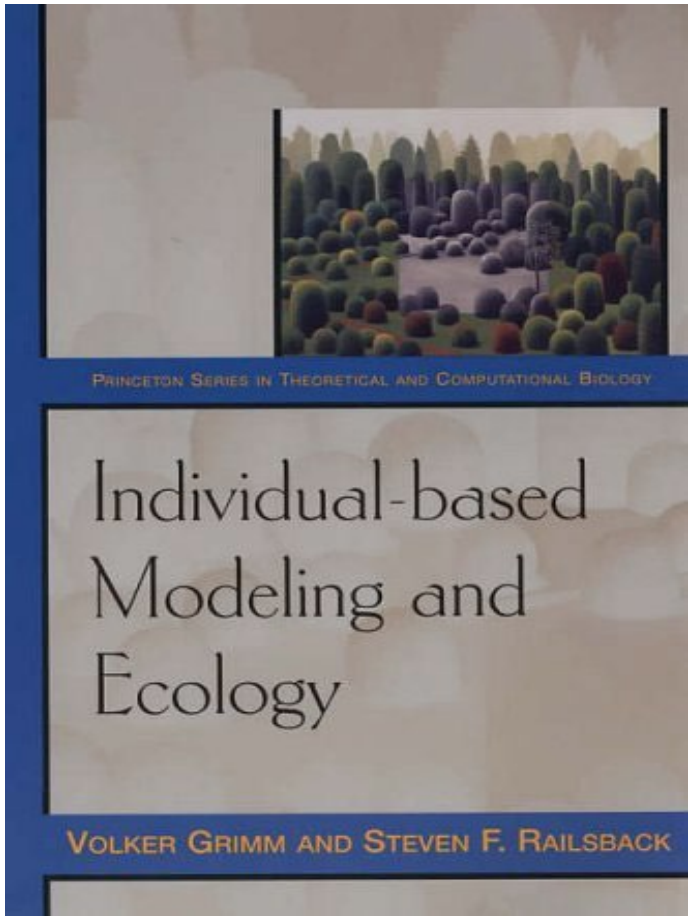
Red = standard medium;
Blue = standard medium with added organic material from algal cultures

INDIVIDUAL → POPULATION

DEB-IBM

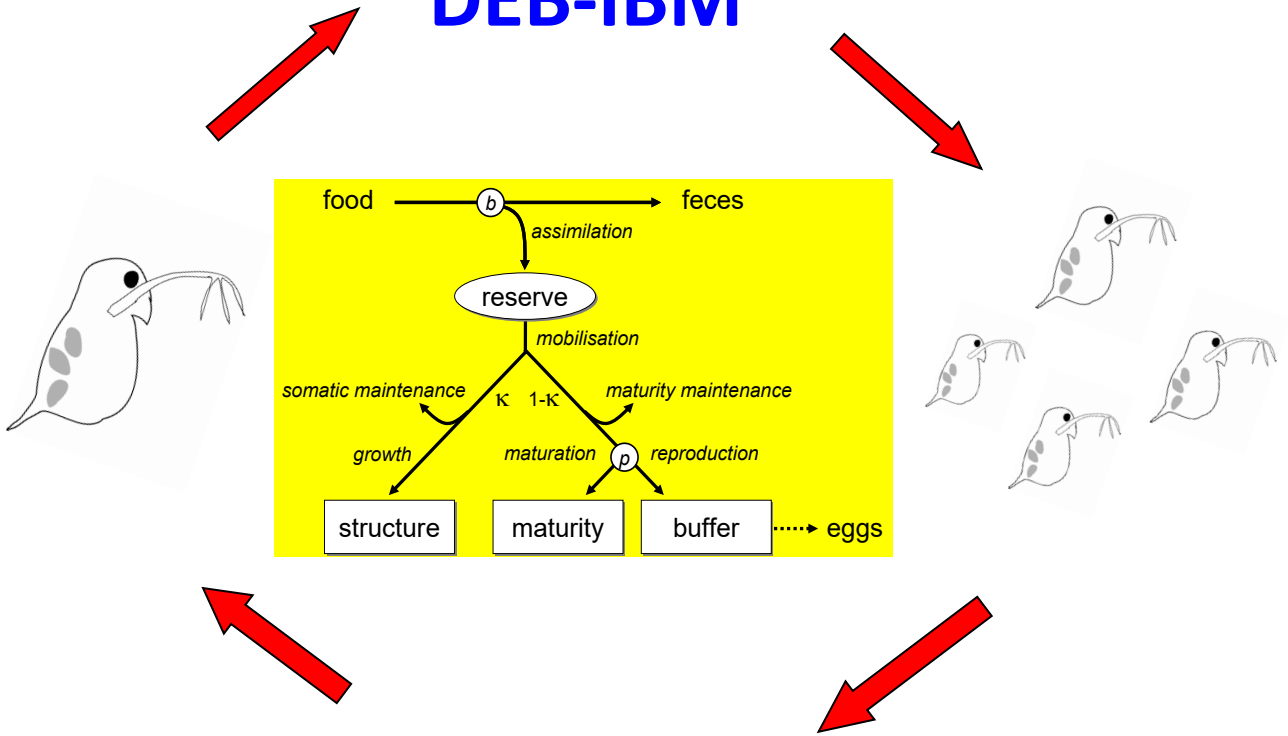






INDIVIDUAL → POPULATION

DEB-IBM



- Implemented in *Netlogo* (Free)
- Computes population dynamics in simple environments with minimal programming
- User manual with examples

* B.T. Martin, E.I. Zimmer, V.Grimm and T. Jager (2012). *Methods in Ecology and Evolution* 3: 445-449

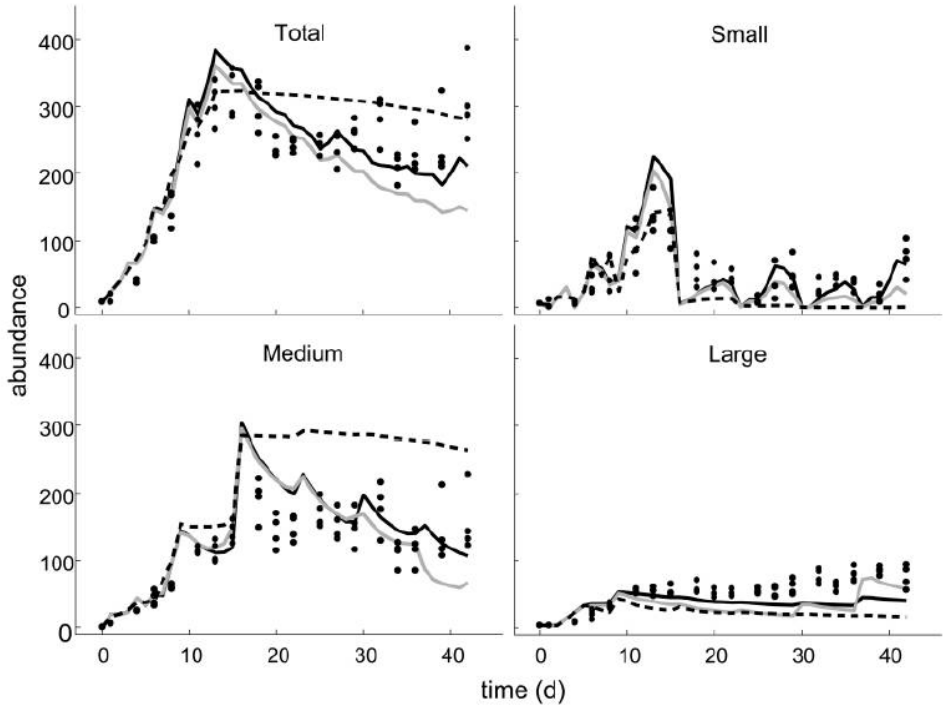
INDIVIDUAL → POPULATION

Hypothesized explanation: Omission of enhanced mortality due to low food availability

Model modification: Add extra juvenile mortality term (and parameter) – no change in other parameters

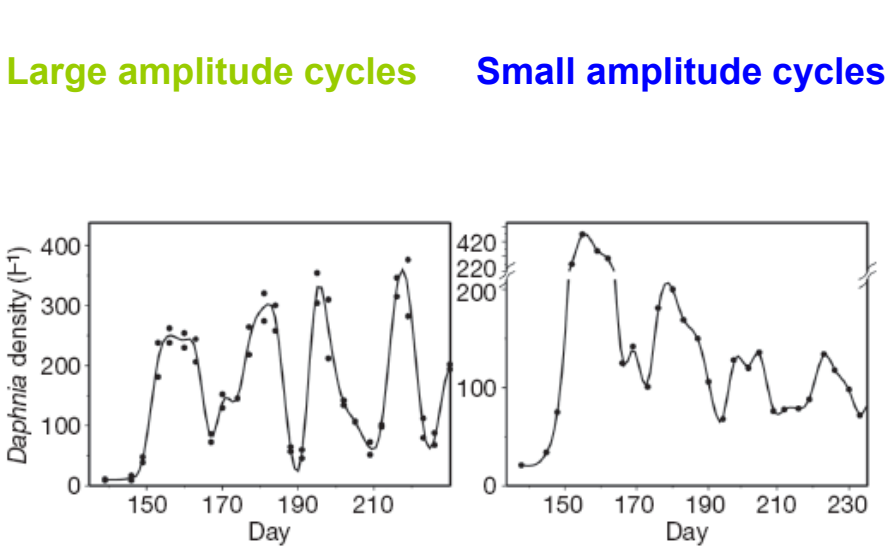
Test: Fit new parameter from one food level – test on others

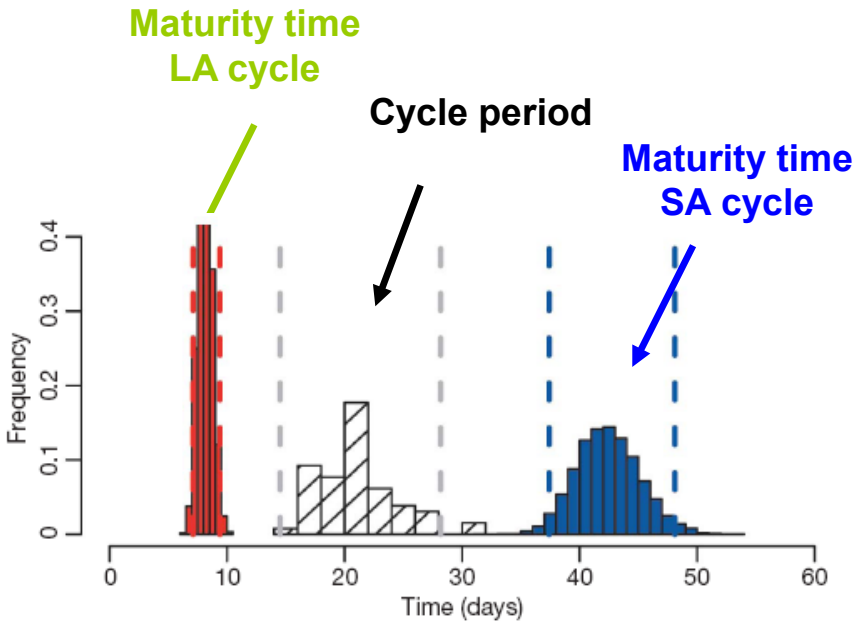
Prediction:



INDIVIDUAL → POPULATION

Independent validation: Daphnia populations in large lab systems with dynamic food *

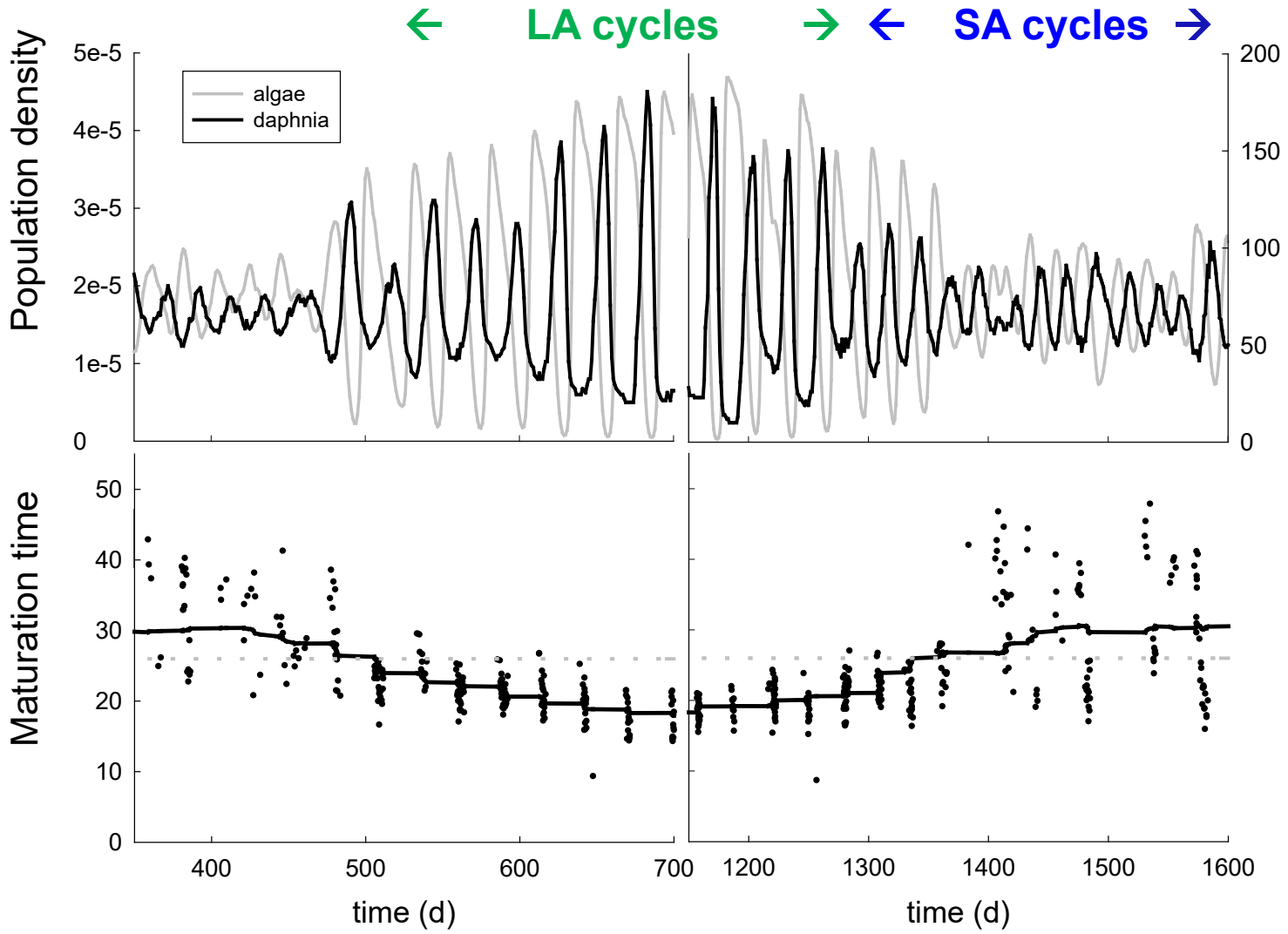




* McCauley, E., Nelson, W.A. and Nisbet, R.M. 2008. Small amplitude prey-predator cycles emerge from stage structured interactions in *Daphnia*-algal systems. *Nature*, **455**: 1240-1243.

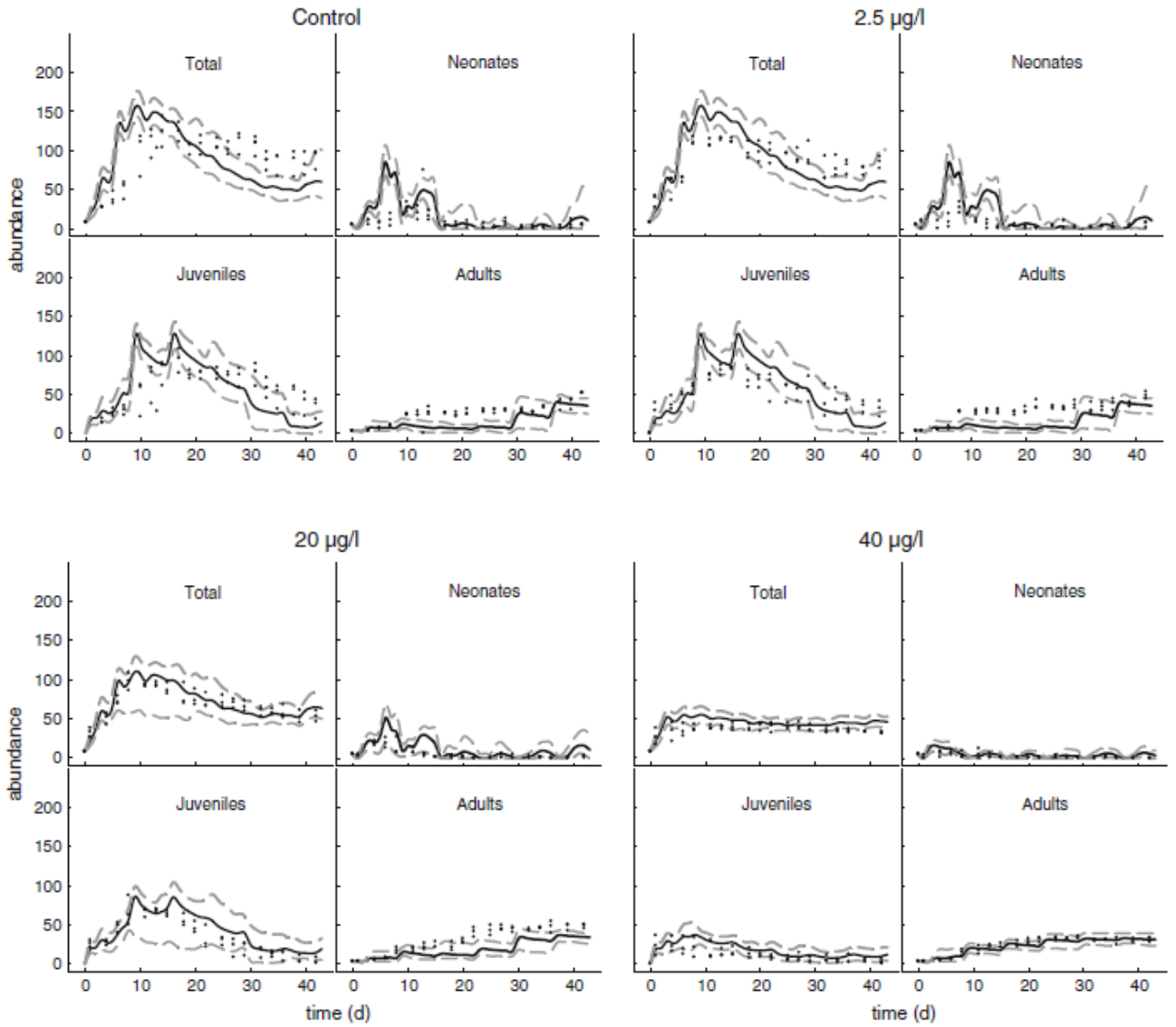
INDIVIDUAL → POPULATION

DEB-IBM dynamics



INDIVIDUAL → POPULATION

Predicted effect of herbicide on Daphnia populations



SO WHAT HAVE WE LEARNED?

- Suborganismal metrics may, but may not, be predictive of oganismal response to stressors

- Ecological feedbacks matter
  - via abiotic environment
  - via resources

IMPLICATIONS?

- Suborganismal metrics may, but may not, be predictive of oganismal response to stressors

  Relate to **Adverse Outcome Pathway (AOP)** models

- Feedbacks and interactions at higher levels matter

  Relate to exisiting ecological (population, community, ecosystem) models

IMPLICATIONS?

- Suborganismal metrics may, but may not, be predictive of oganismal response to stressors

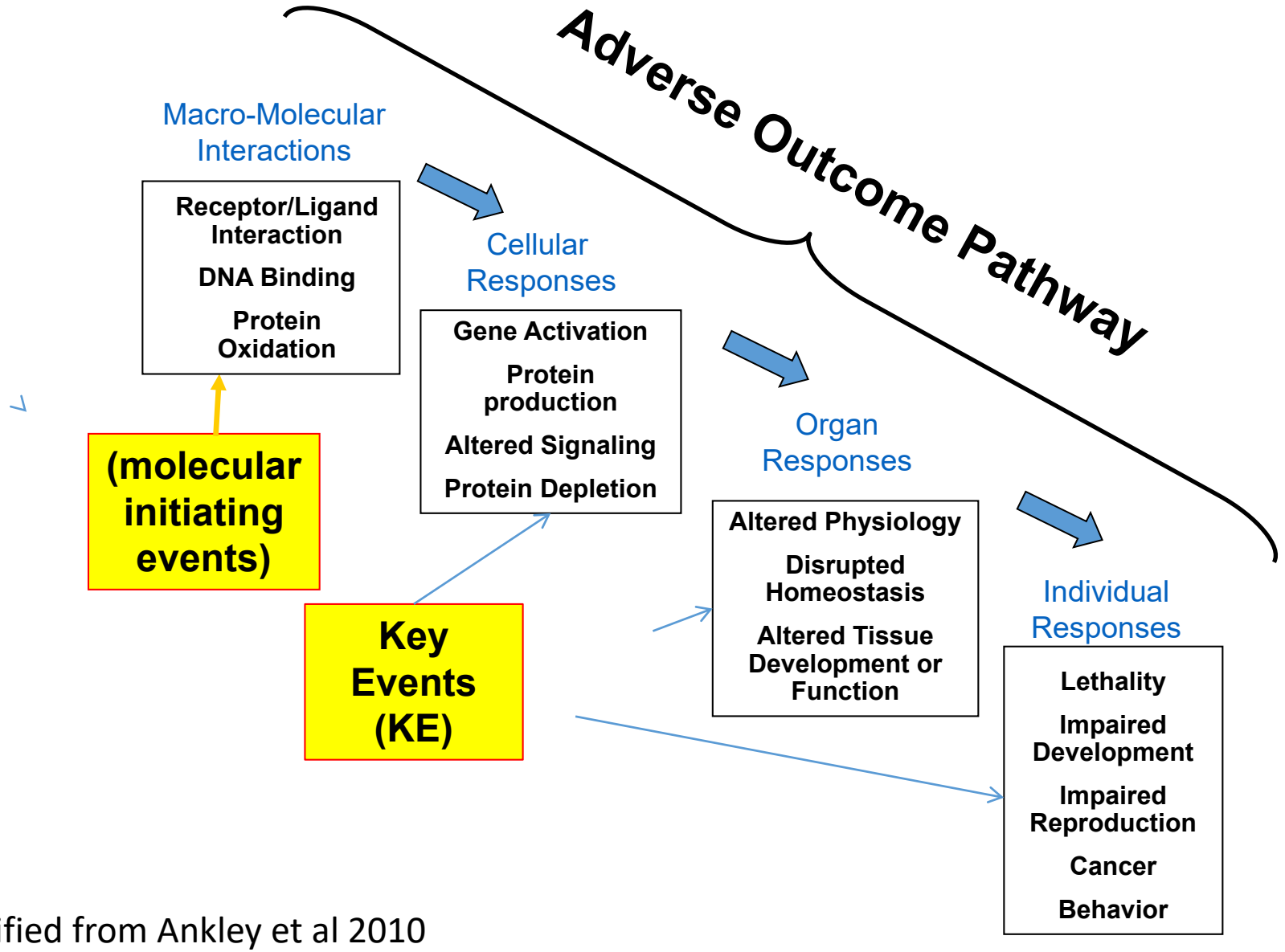
  Relate to **Adverse Outcome Pathway (AOP)** models

- Feedbacks matter

  Relate to ecological (population, community?, ecosystem models

AVOID REDISCOVERING THE WHEEL

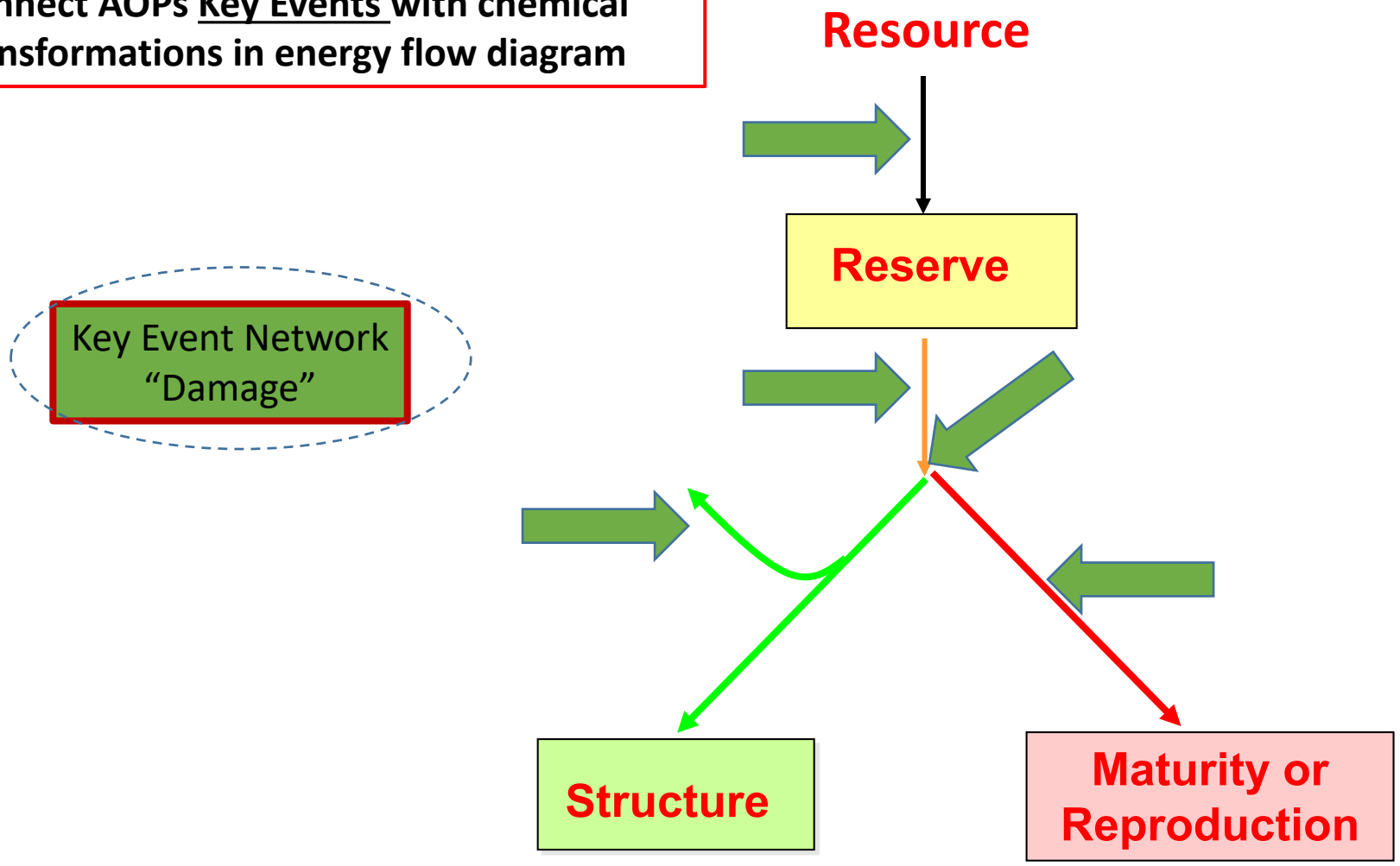
WHAT ARE AOPs?



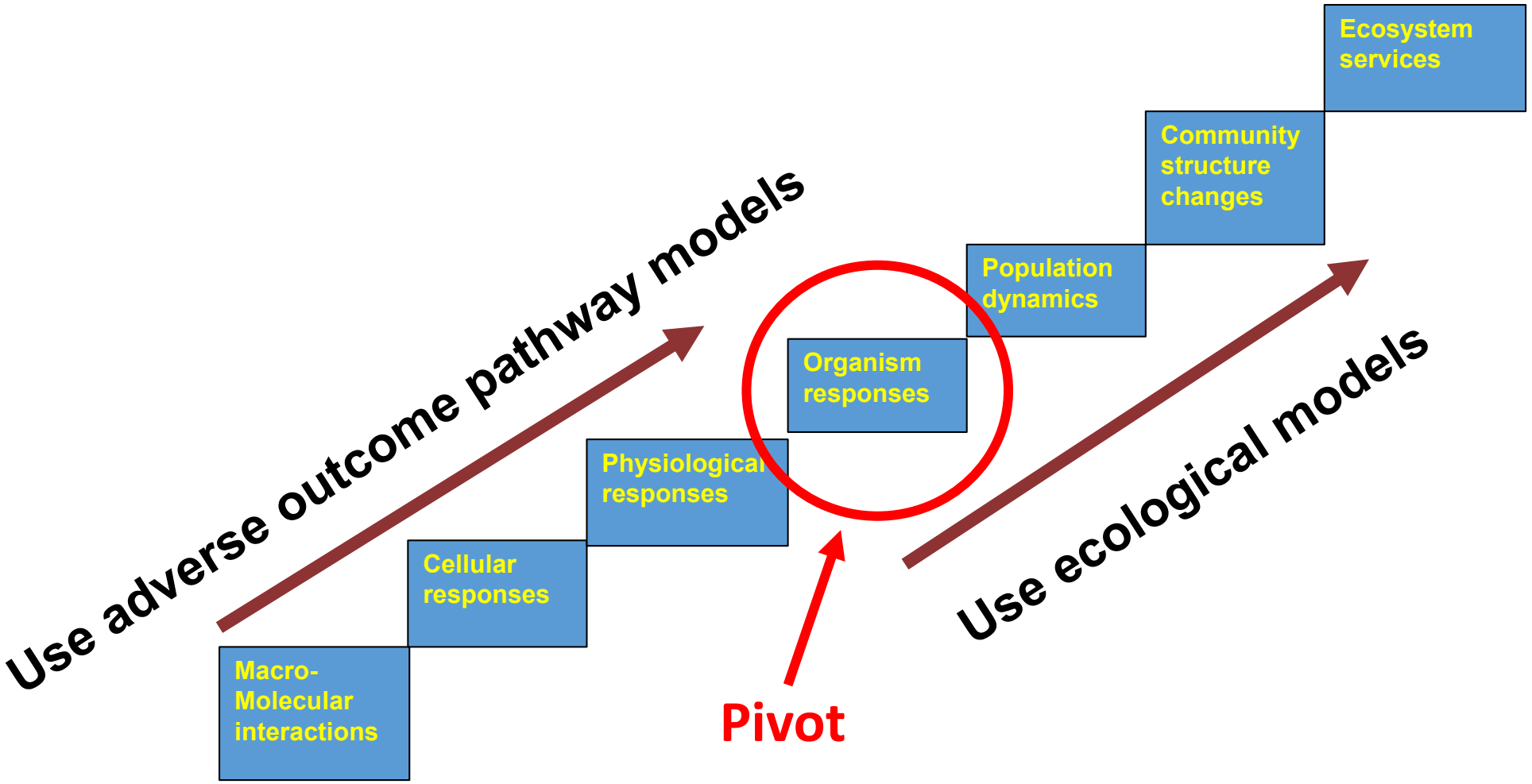
Modified from Ankley et al 2010

Approach to linking AOP and DEB models?

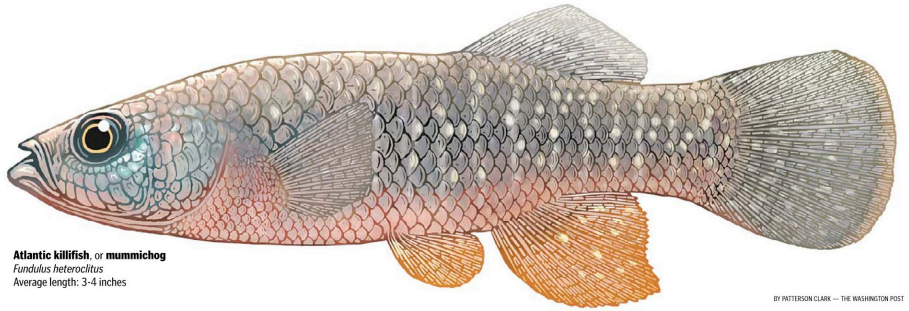
Connect AOPs Key Events with chemical transformations in energy flow diagram



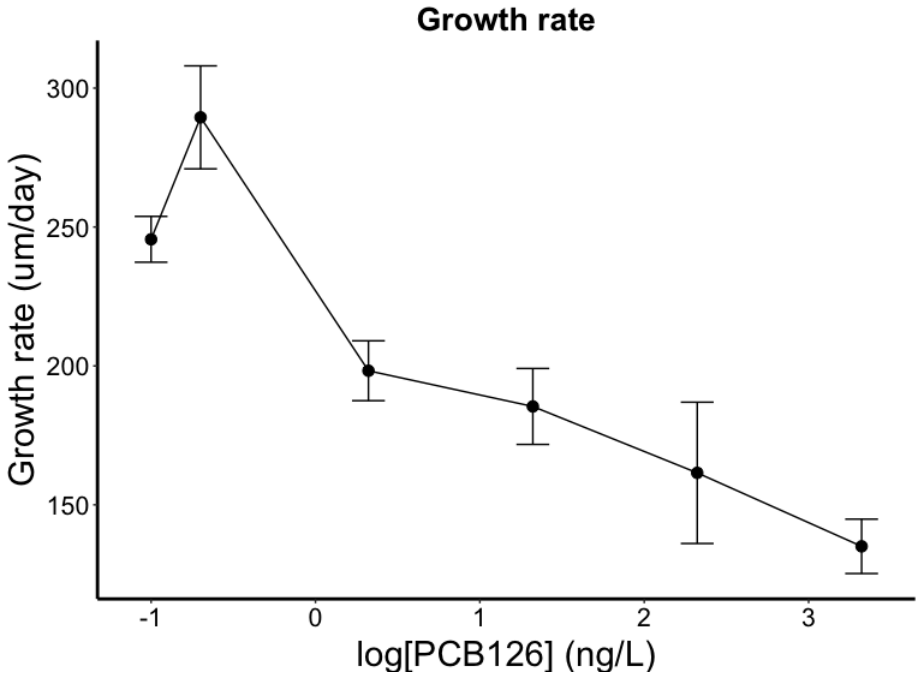
DEB models as “pivot point” linking suborganismal to ecological processes?



Case Study: *Fundulus* and dioxin-like chemicals (DLCs)



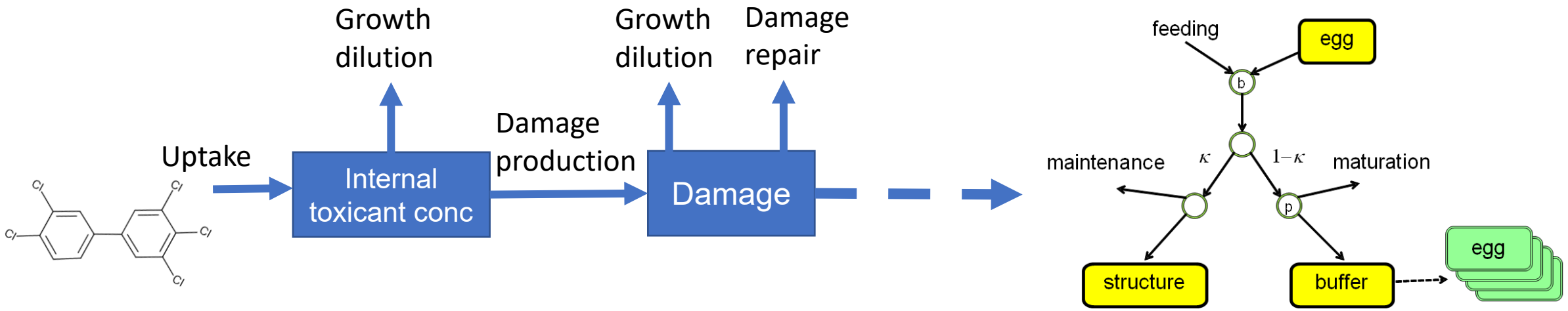
- *Fundulus heteroclitus*
- Established AOP for DLC – AHR pathway activation
  - Precise mode of action unknown
- DLCs in *Fundulus*
  - Embryo-larval exposures result in **lethality at ng/L concentrations**
  - AHR binding evident (CYP1A -> EROD) at **sublethal concentrations**
  - **Sublethal effect on larval growth** for embryos surviving exposures (unpublished data)



Stevenson, Clark, Muller, Nacci, Whitehead, Nisbet (In press) *Environmental Toxicology and Chemistry*

Connect molecular responses to DEB via "damage"

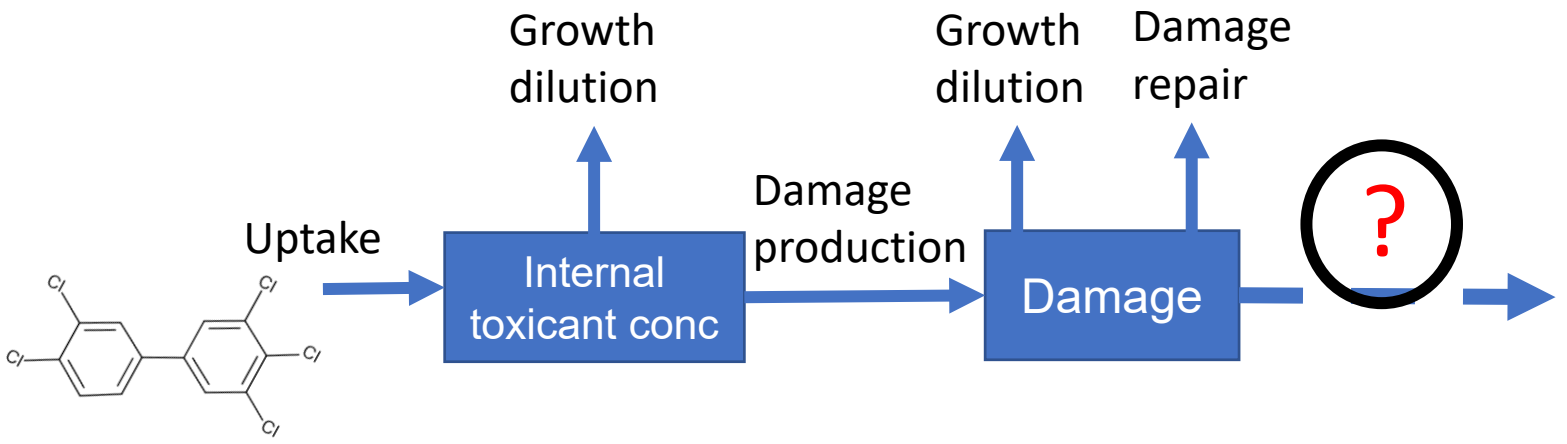
- Mechanistic theoretical framework consisting of 3 connected models:
  1. **Toxicokinetic** model of PCBs in embryonic exposures
  2. **Damage** accumulation and regulation model of sublethal effects on growth and mortality as a tipping point when damage breaks regulation
  3. **Bioenergetic** model of embryonic hatching and larval growth (DEBkiss[1])

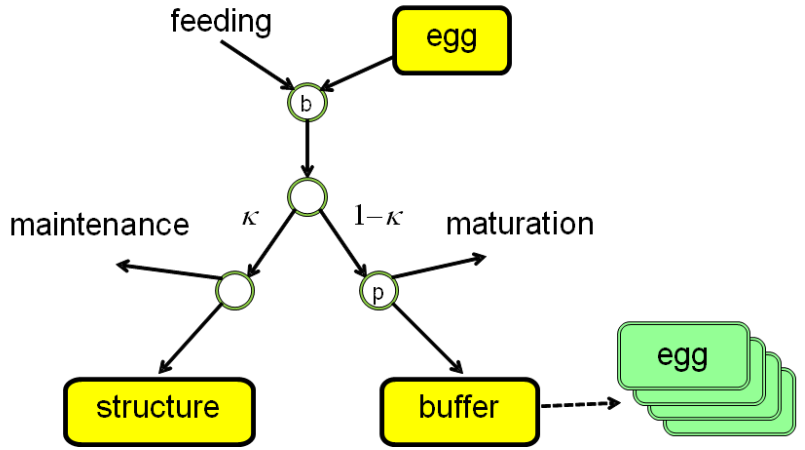


[1]Jager et al. 2013, figure from http://www.debtox.info/about_debkiss.html

Connect molecular responses to DEB via "damage"

How to link "damage" to bioenergetic process (DEB)?

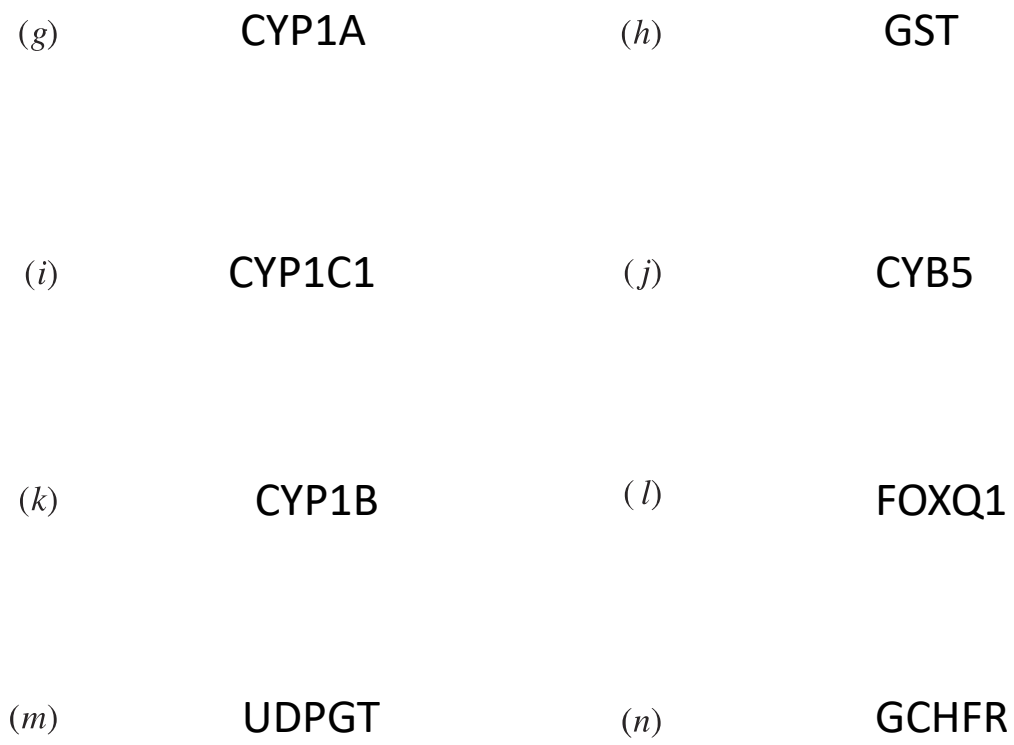




Transcriptomic response to sublethal DLC exposure

- Killifish exposed to PCB-126
  - Sensitive and resistant at effects matched doses

→ How to summarize extensive transcriptomic information to connect to bioenergetic model?



Whitehead et al. Proc. R. Soc. B (2012) 279, 427–433

Transcriptomic response to sublethal DLC exposure

- Killifish exposed to PCB-126

→ How to summarize extensive transcriptomic information to connect to bioenergetic model?

- **D**atabase for **A**nnotation, **V**isualization and **I**ntegrated **D**iscovery (**DAVID**)
  - Enrichment analysis
  - Functional annotation clustering tool
- Hundreds of significantly differentially expressed genes compressed to a handful of significantly enriched clusters

Huang et al. 2008 *Nature protocols* 4:1.

(g) CYP1A (h) GST

(i) CYP1C1 (j) CYB5

(k) CYP1B (l) FOXQ1

(m) UDPGT (n) GCHFR

Transcriptomic response to sublethal DLC exposure

- Clusters common among concentrations:

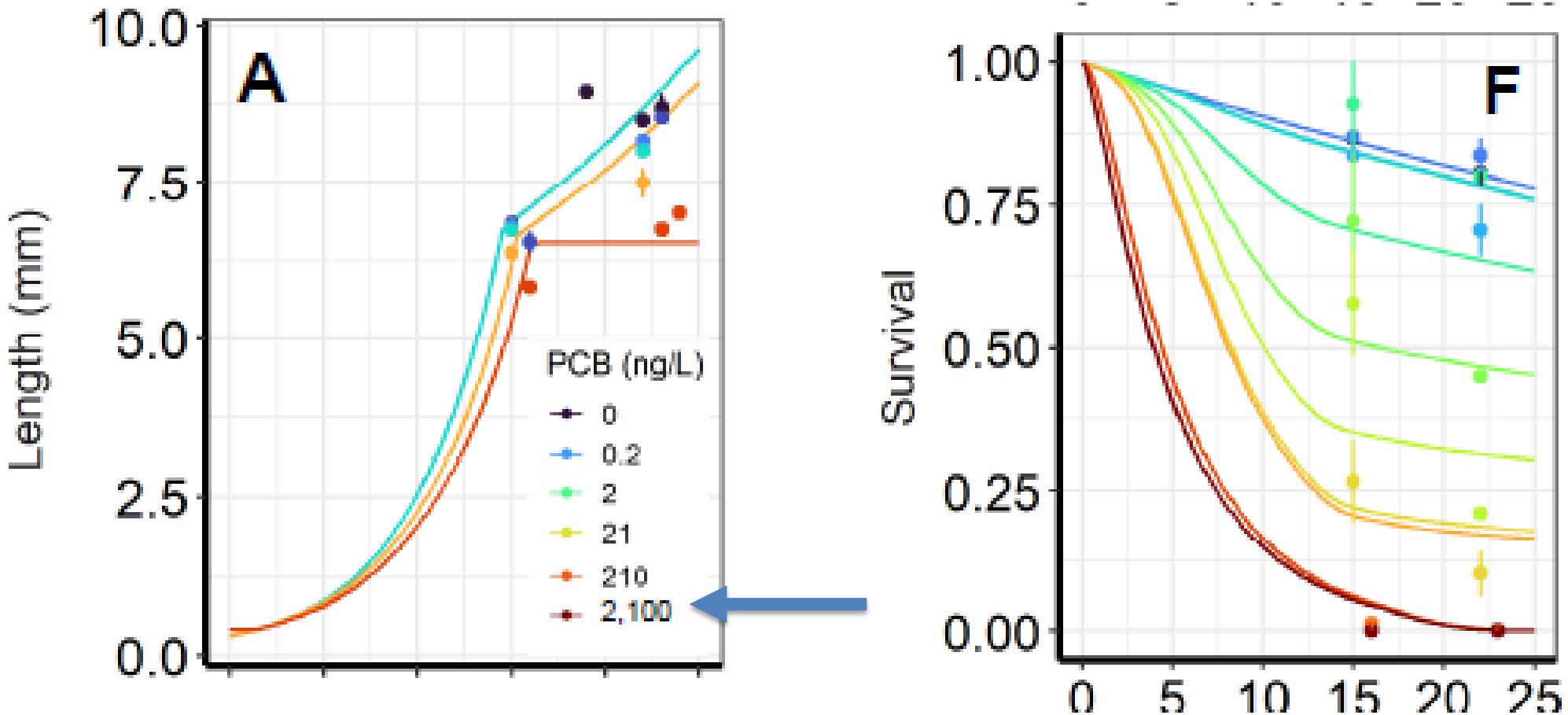
  - Up regulated
    - Oxidoreductase (stress response)
    - Signaling (neurotransmission, muscle contraction, proper heart function)
    - Cytochrome P450
    - Xenobiotic metabolism
  - Down regulated
    - Muscles (muscle proteins, tropomyosin, and actin filaments), specifically muscle contraction
    - Glycolysis

<u>OVERALL:</u>

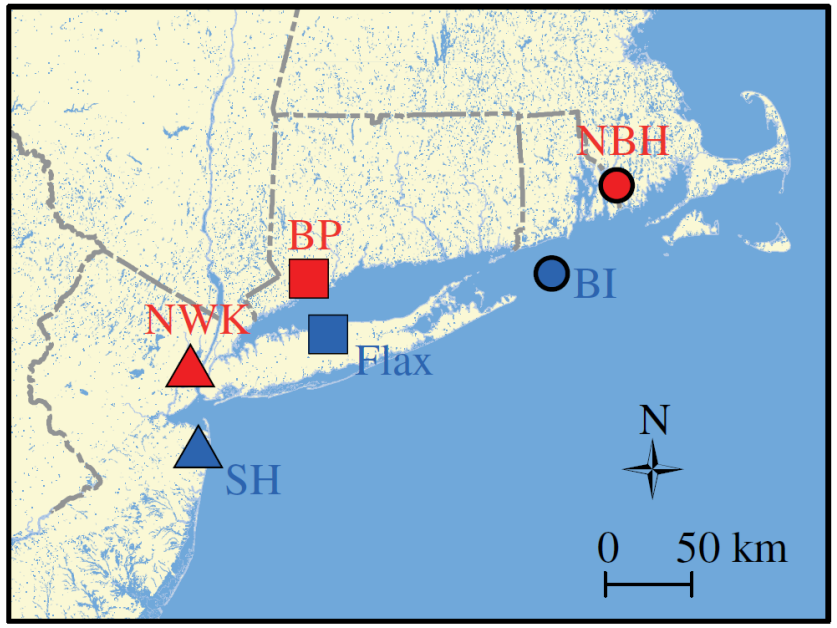
- Increase in detoxification response
- Signs of AhR pathway activation (e.g. CYPs)
- Cardiac impairment (PCBs teratogenic by messing with heart development

→ Hypothesis: **maintenance costs increasing with DLC exposure**

Model Fits – sensitive fish



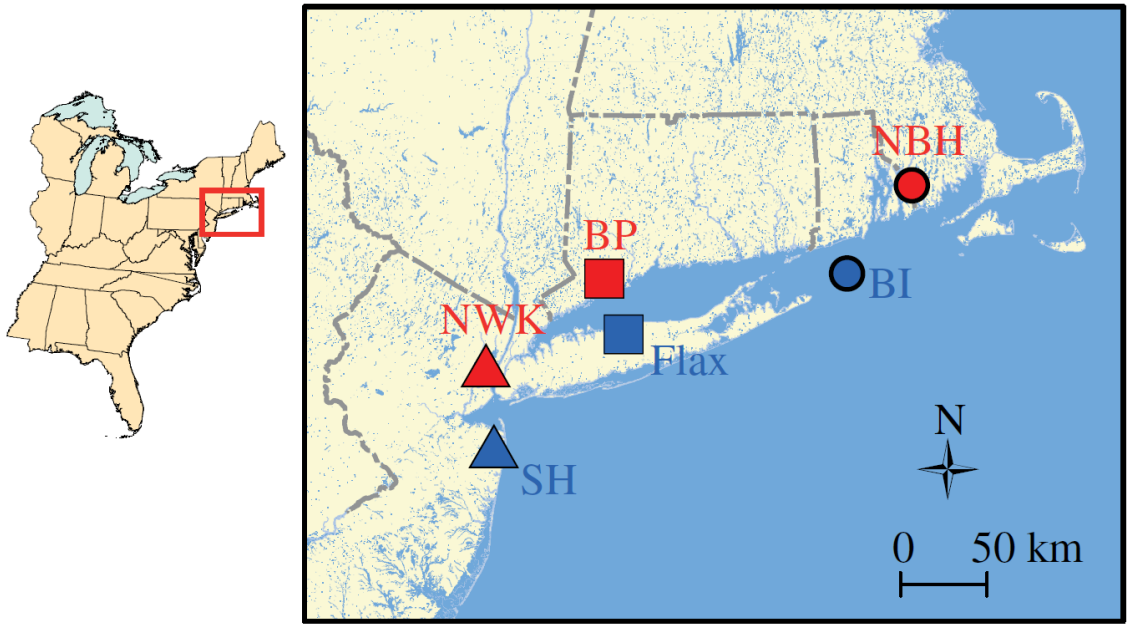
“Postdiction”/model verification of resistant populations

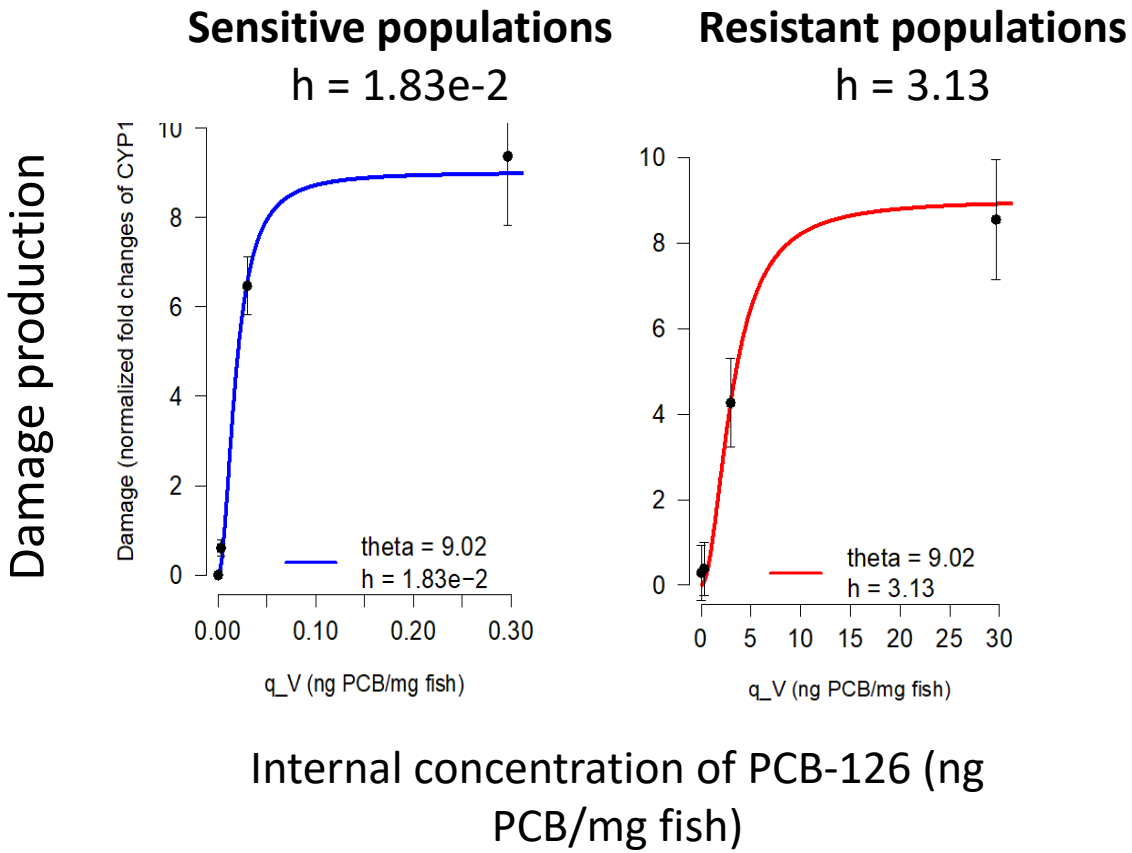


- Matched sensitive (blue) and tolerant (red) populations of *Fundulus heteroclitus*
- Model fit to sensitive fish, can it predict impact of DLCs on resistant fish?

Whitehead et al. Proc. R. Soc. B (2012) 279, 427–433

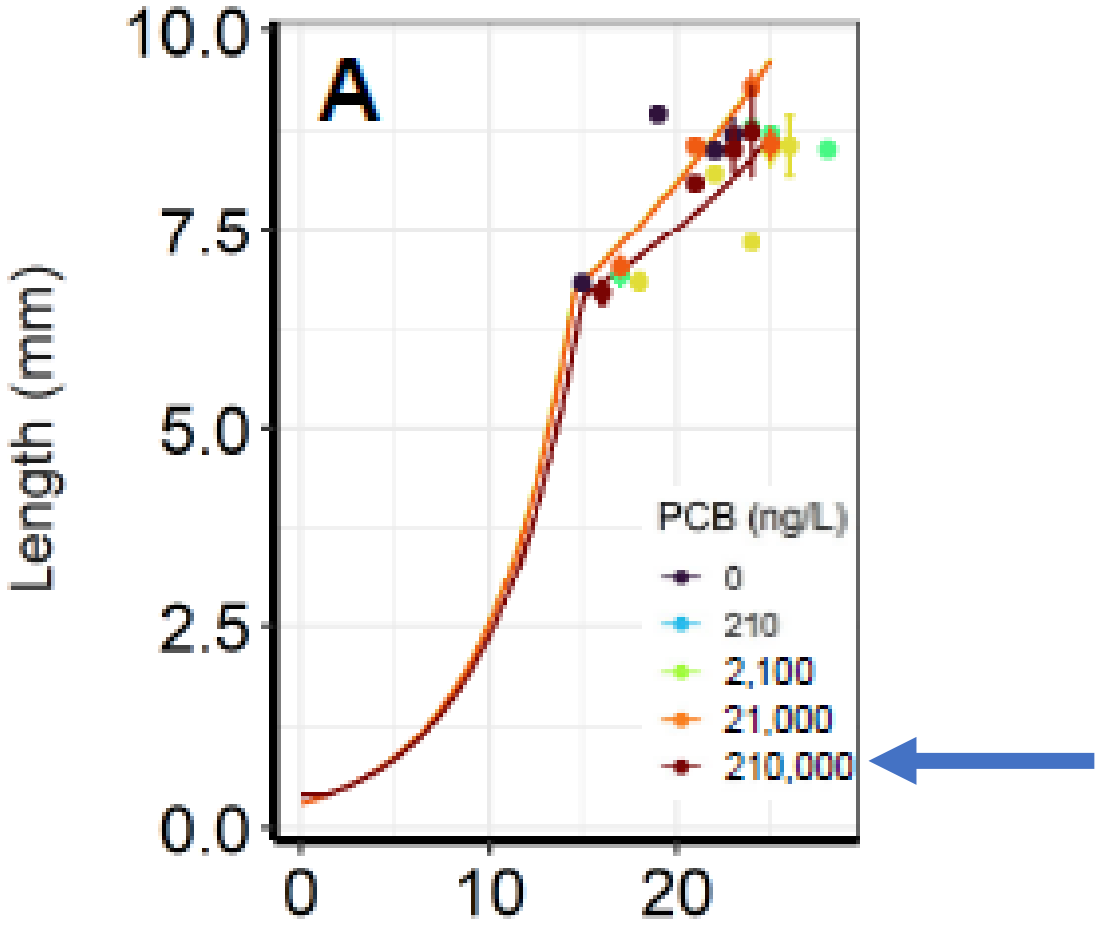
“Postdiction”/model verification of resistant populations

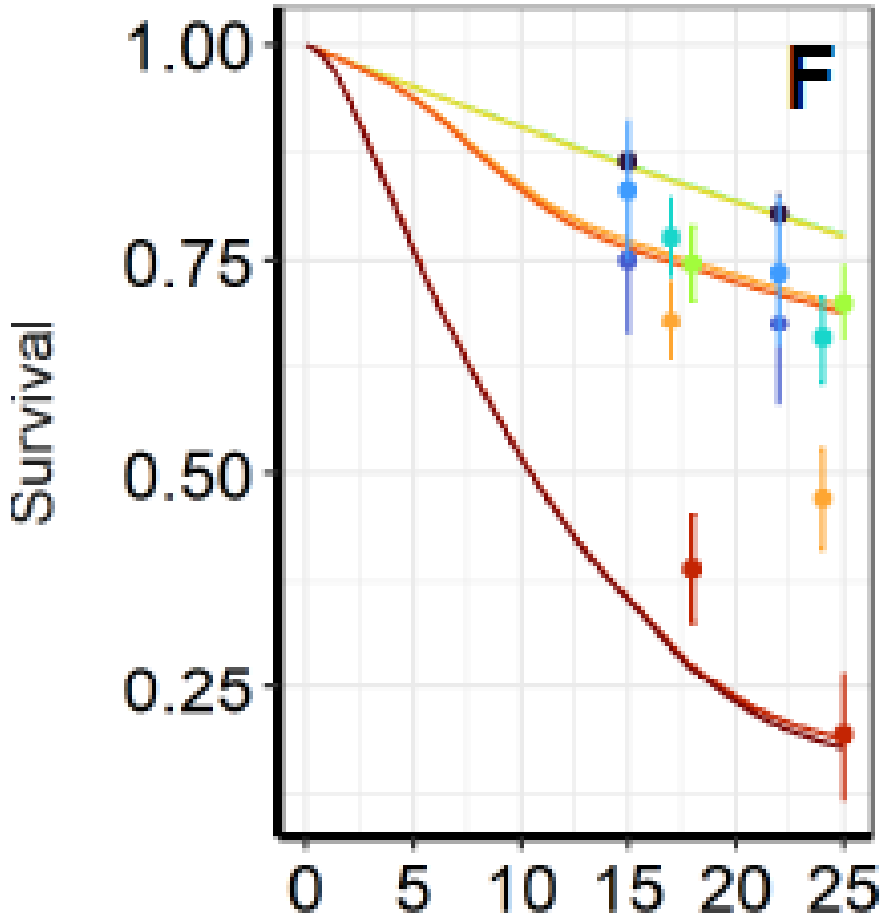




Changed **one parameter** between sensitive and tolerant populations (*h* describing damage production) → how well does model “postdict” resistant data?

Model Fits – tolerant fish (after two parameter changes)





Take home messages from killifish study

- Transcriptomic data gives clues to connection between damage and bioenergetic process
- Model can “postdict” lethal impacts on other populations
- Generalizable damage model predicts lethal tipping point in concentration
- Model framework potentially generalizable to multiple case studies

Take home messages from ecotox lectures

- Data increasingly from low levels of organization
- Feedbacks matter
- Damage variable is a powerful abstraction