DEB 2025

Dynamic Energy Budget models in Ecotoxicology

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deb2025.sciencesconf.org

DEB 2025

Ecotox Lecture 1: “Dynamic Energy Budget theory in ecotoxicology”

- What is ecotoxicology?
- Why develop general theory?
- Toxicokinetics (TK) and toxicodynamics (TD)
- Modeling triad: DEB/TK/TD
- A new DEB state variable – “damage”
- Case study on oxidative stress with damage variable

References:

- Chapter 6 of DEB3 [*Core ideas*]
- Jager T. (2019 or later updates). *Making Sense of Chemical Stress. Application of Dynamic Energy Budget Theory in Ecotoxicology and Stress Ecology*. Leanpub: https://leanpub.com/debtox_book. [*Key recommended reading*]
- Klanjscek, T. et al (2016) J. *Theor. Biol*. 404, 361–374; also Stevenson et al. (2023) Env.Tox. & Chem 422040–2053. [*Case studies on the damage variable*]

Ecological Risk Assessment

DEB 2025

Ecotoxicology: effects of toxic substances on living organisms at multiple levels of ecological organization*.

ERA**: *the process for evaluating how likely it is that the environment may be impacted as a result of exposure to one or more environmental stressors.*

ERA addresses societally determined questions. Different approaches may be required when focused on decisions on reguation of new chemicals versus legacy contaminants.

*ERA involves predicting effects of exposure on populations, communities and ecosystems** – including "ecosystem production functions" such as nutrient cycling and "ecosystem services".*

* http://www.epa.gov/risk_assessment/ecological-risk.htm

** Rohr, Salice, Nisbet: *Critical Reviews in Ecotoxicology* (2016) DOI: 10.1080/10408444.2016.1190685.

Why predictive ecotoxicology is hard

Need general theory:

- Too many chemicals, organisms, environments

Feedbacks

- *Physiology*: e.g. regulatory processes within and among cells and organs
- *Physico-chemical environment*: e.g. excretion products may impact toxicity
- *Ecological interactions:* e.g. resource limitation, mutualism
- *Plasticity, acclimation and adaptation:* e.g. epigenetics/gene expession

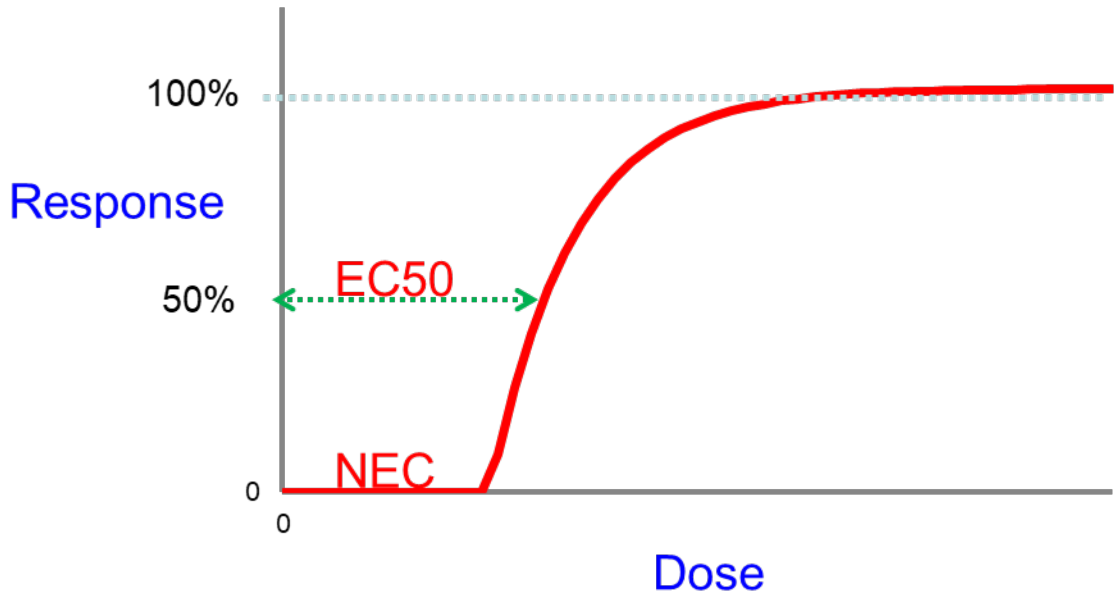
Emergent properties

- Found at every link between levels of organization, e.g. tipping points

Rohr, Salice, Nisbet, *Critical Reviews in Toxicology,* 2016.

Standardized toxicity tests

- Primary aim is to guide regulation of chemicals by identifying “safe” levels in the environment
- Tests for both acute (lethal) and chronic (non-lethal) toxicity
- Use strictly specified protocols on small number of focal organisms (e.g. Daphnia, algae, fish for freshwater)



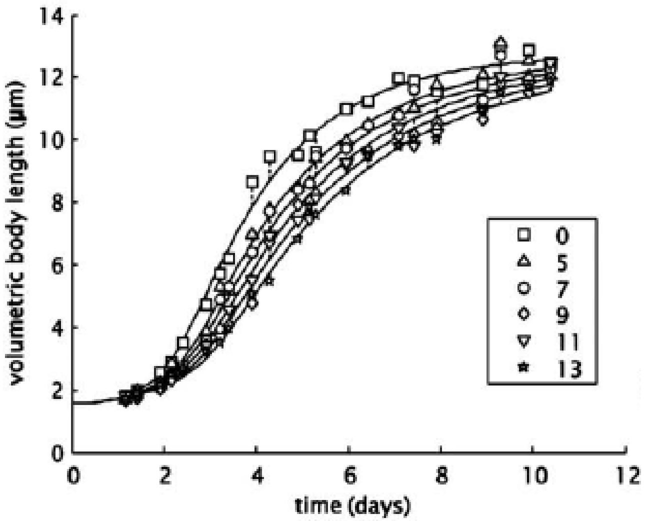
- EC50 (LC50) = dose at which response (mortality) is 50% of maximum
- NEC = dose below which there is no “harm” to organism
- Permitted level some fraction of NEC or EC50

Problem with standardized tests

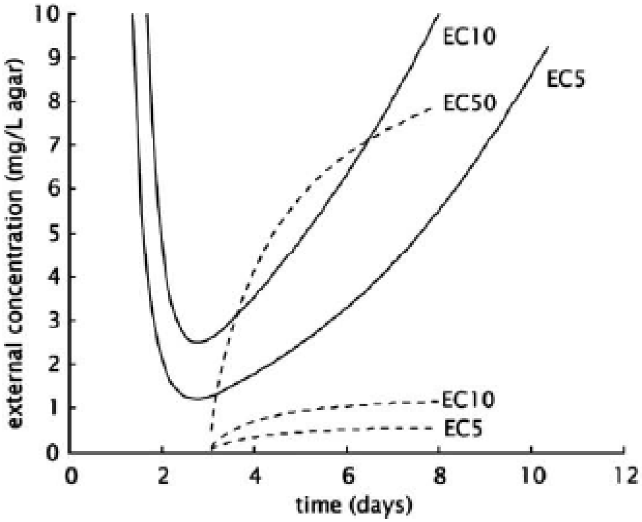
Definition: EC_x is concentration of a compound where x% of its maximal effect is observed.

Problem: value depends on duration of study

Example: *C. elegans* growth exposed to pentachlorobenzene



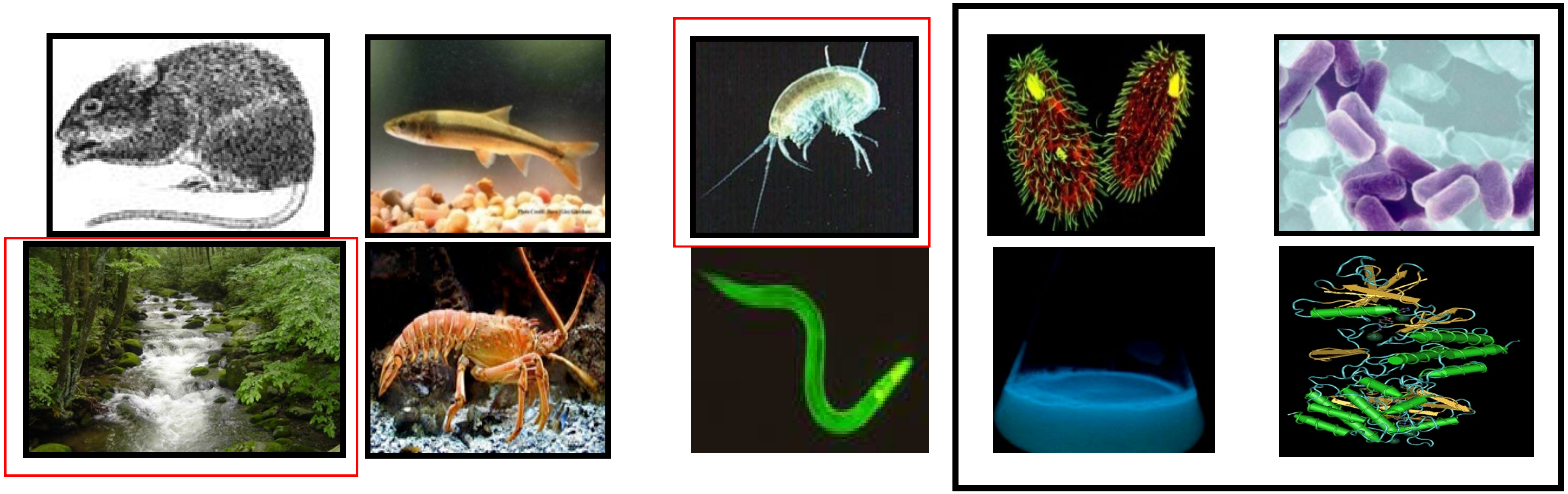
Length versus time for different toxicant levels



EC_x related to duration of exposure (cont. lines – length; broken lines – reproduction)

* J. Baas et al. *Science of the Total Environment*, doi:10.1016/j.scitotenv.2009.10.066

Other sources of data



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

Routes to general theory

Option I: follow the chemical

- Absorbed by organism
- Distributed within organism
- Chemically transformed
- Excreted

TOXICOKINETICS (TK)

- Interacts with tissue
- “Damages” tissue
- Impacts survival(hazard)
- Impacts growth, reproduction, ………….

TOXICODYNAMICS (TD)

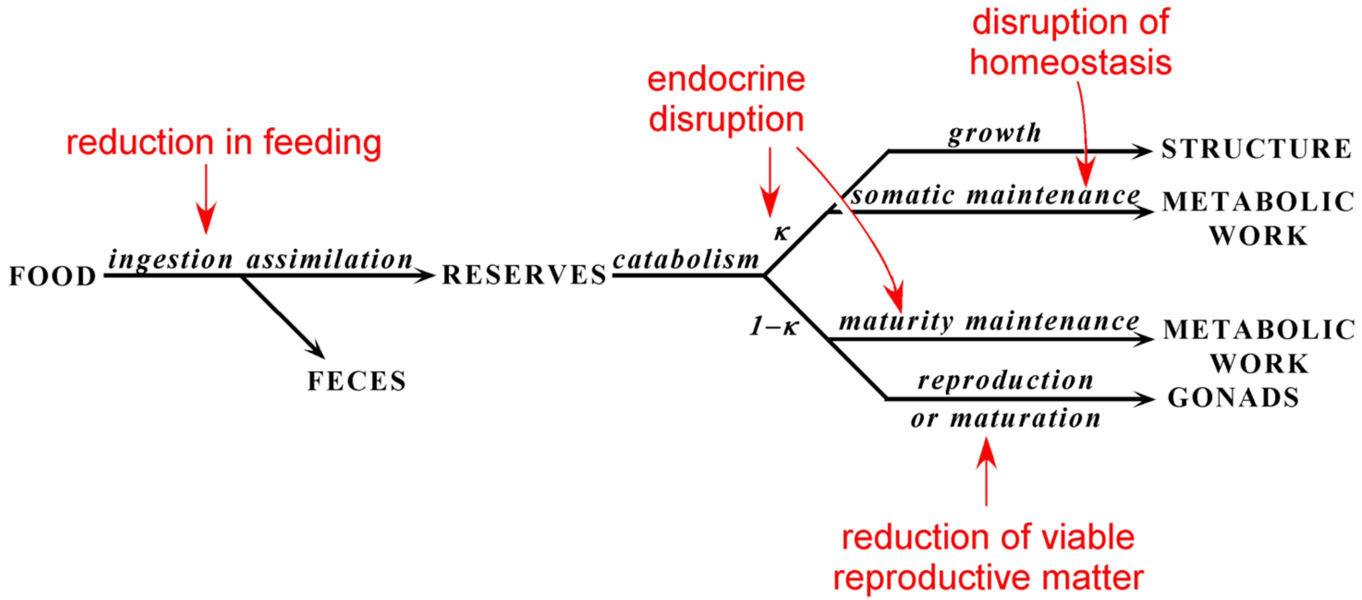
- Identify “Molecular Initiating Event” (MIE)
- Identify “Pathways” linking MIE to apical endpoints (reproduction and survival)
- Identify “Key Events” on pathway

ADVERSE OUTCOME PATHWAY (AOP)

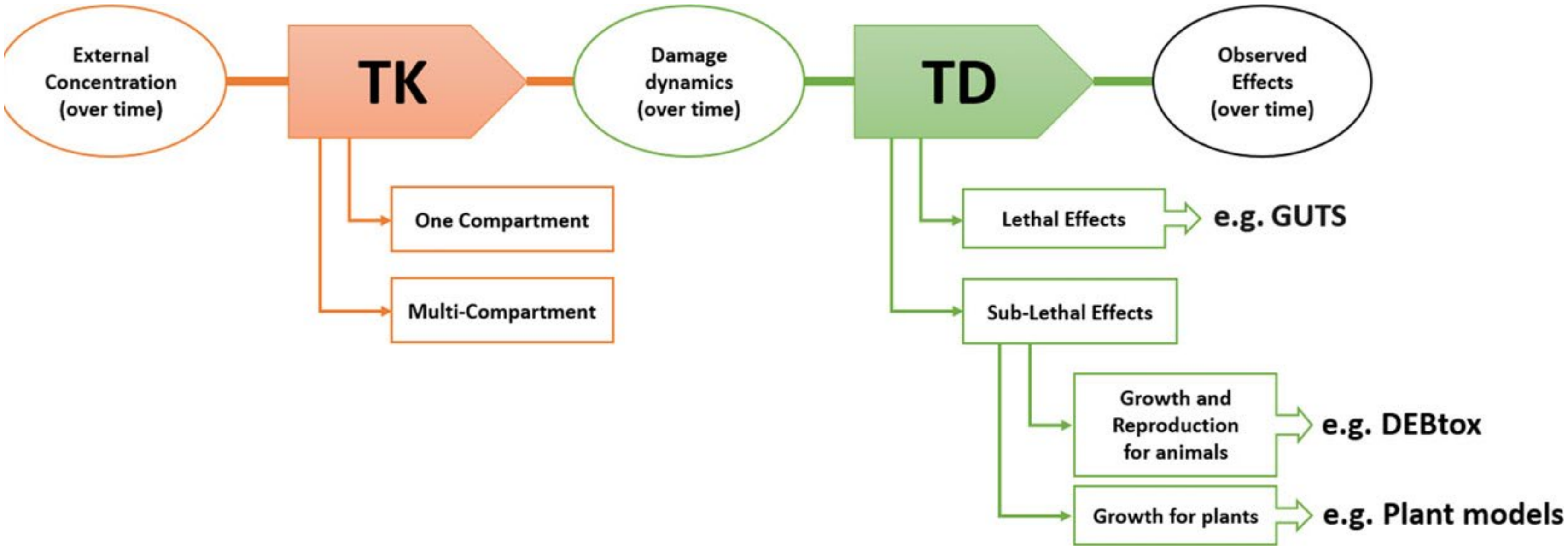
Routes to general theory

Option II: follow the complete organism

- ***Use DEB!!***
- Each chemical transformation could in principle be affected by chemical stress – different Physiological Models of Action (pMoA)
- Identify some measure of stress and assume that different DEB (primary) parameters are functions of stress
- Fit data on growth, reproduction, or mortality assuming different pMoA(s).
- Identify “winner” statistically (e.g. likelihood ratios or AIC)

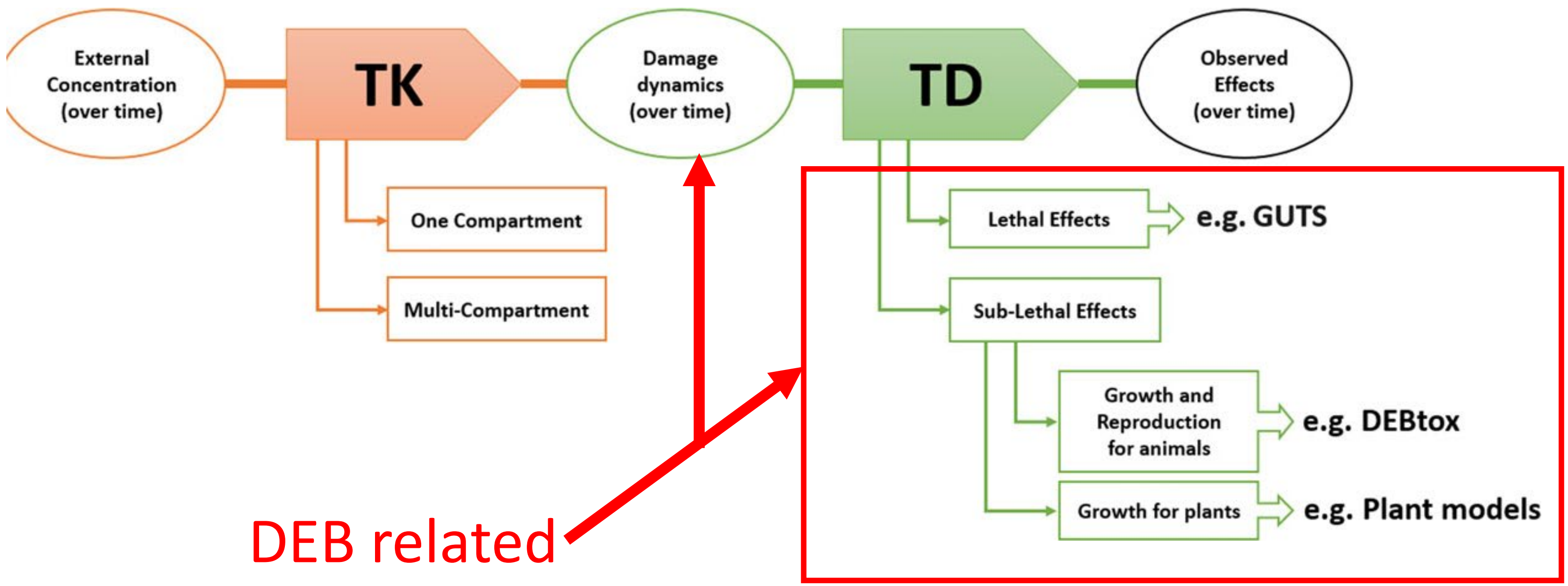


Synthesis



Ockleford et al (2008): doi: 10.2903/j.efsa.2018.5377 *EFSA Scientific Opinion on the state of the art of Toxicokinetic/ Toxicodynamic (TKTD) effect models for regulatory risk assessment of pesticides for aquatic organisms* doi: 10.2903/j.efsa.2018.5377

SYNTHESIS: The TK-TD-DEB triad



Ockleford et al (2018): doi: 10.2903/j.efsa.2018.5377 *EFSA Scientific Opinion on the state of the art of Toxicokinetic/ Toxicodynamic (TKTD) effect models for regulatory risk assessment of pesticides for aquatic organisms* doi: 10.2903/j.efsa.2018.5377

The TK-TD-DEB triad

- Dynamic energy budget (DEB) model describes the assimilation and utilization of energy and elemental matter by living organisms
- Toxicants may enter organism directly from environment or via food – represented by toxicokinetic (TK) model.
- Toxicants impact one or more energy and material flows (“mode-of-action”-MoA) – represented by toxicodynamic (TD) model

MISSSING LINK: DEB TO TOXICODYNAMICS

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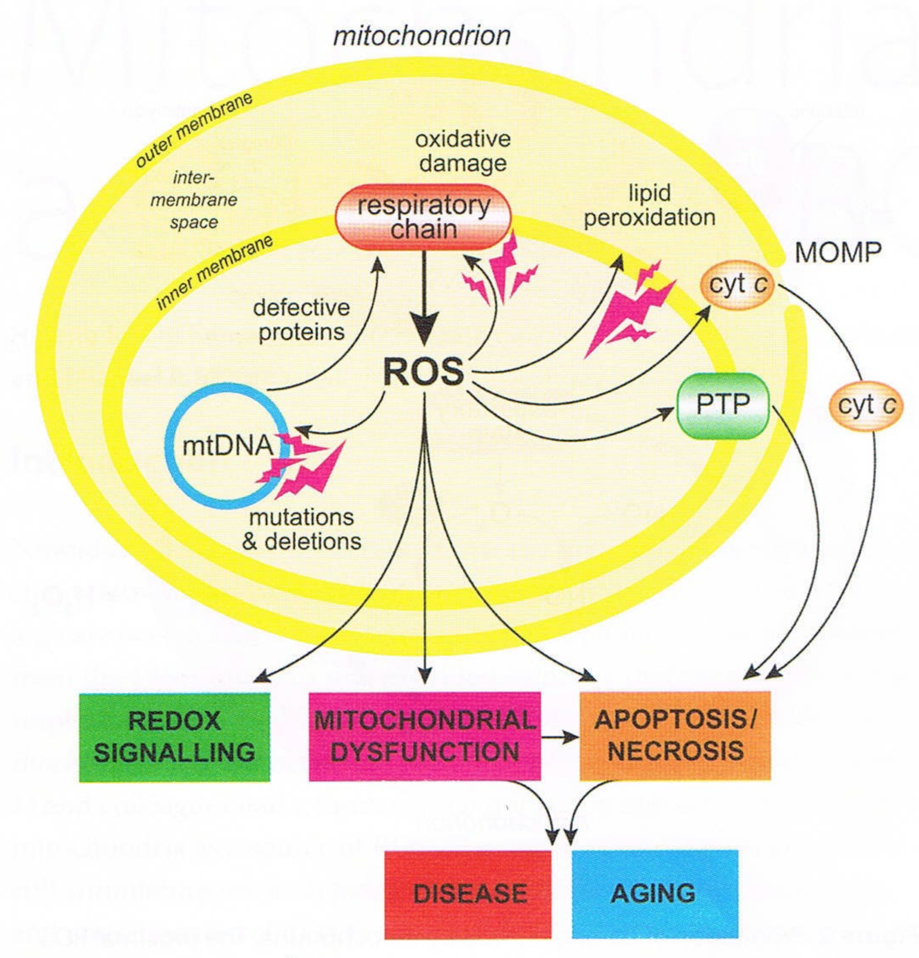
MISSSING LINK: DEB TO TOXICODYNAMICS

USE NEW DEB VARIABLE REPRESENTING “DAMAGE”*

* Chapter 6 of DEB3

Example: oxidative stress



Reactive oxygen species (ROS) and immediate products

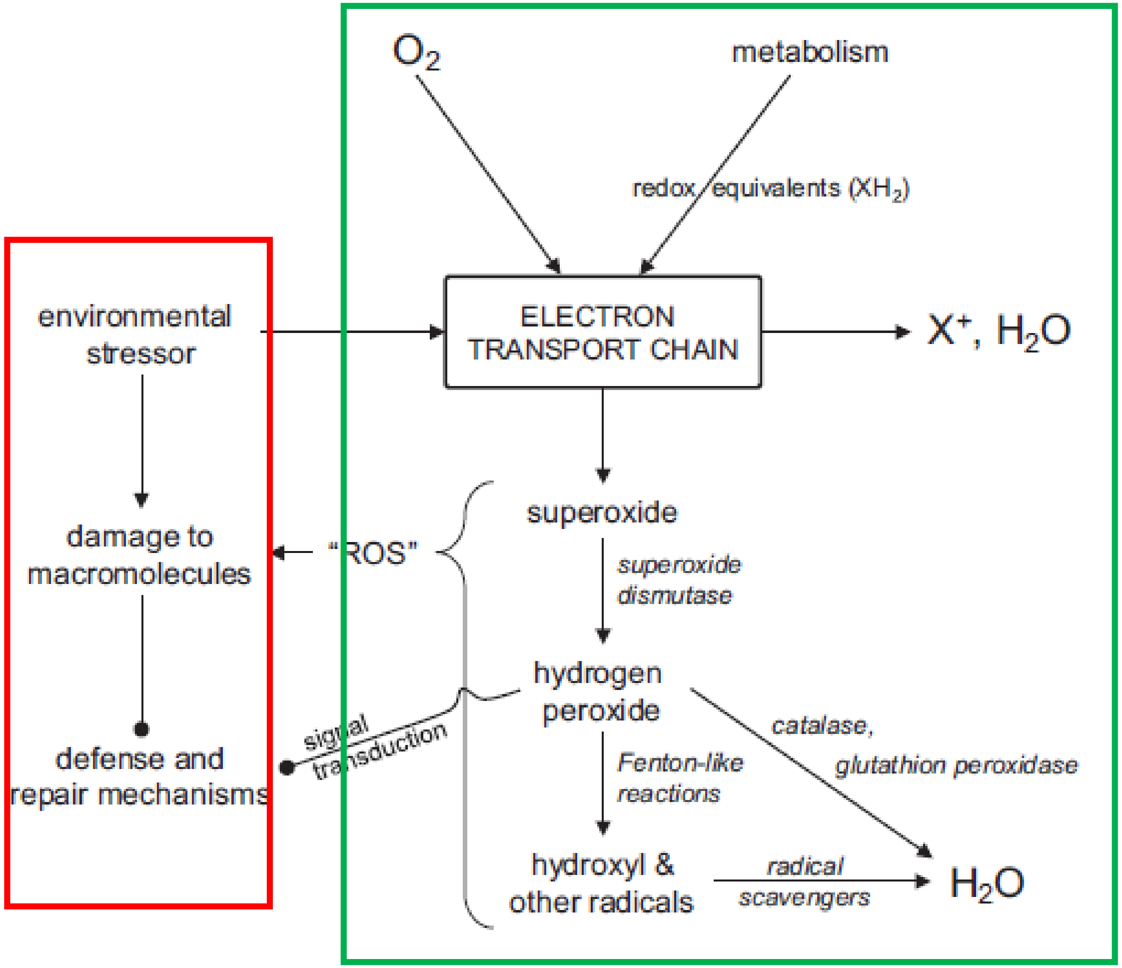
↓

Damaged proteins, membranes, DNA

* Figure from Bas Kooijman's "Comments" at http://www.bio.vu.nl/thb/deb/

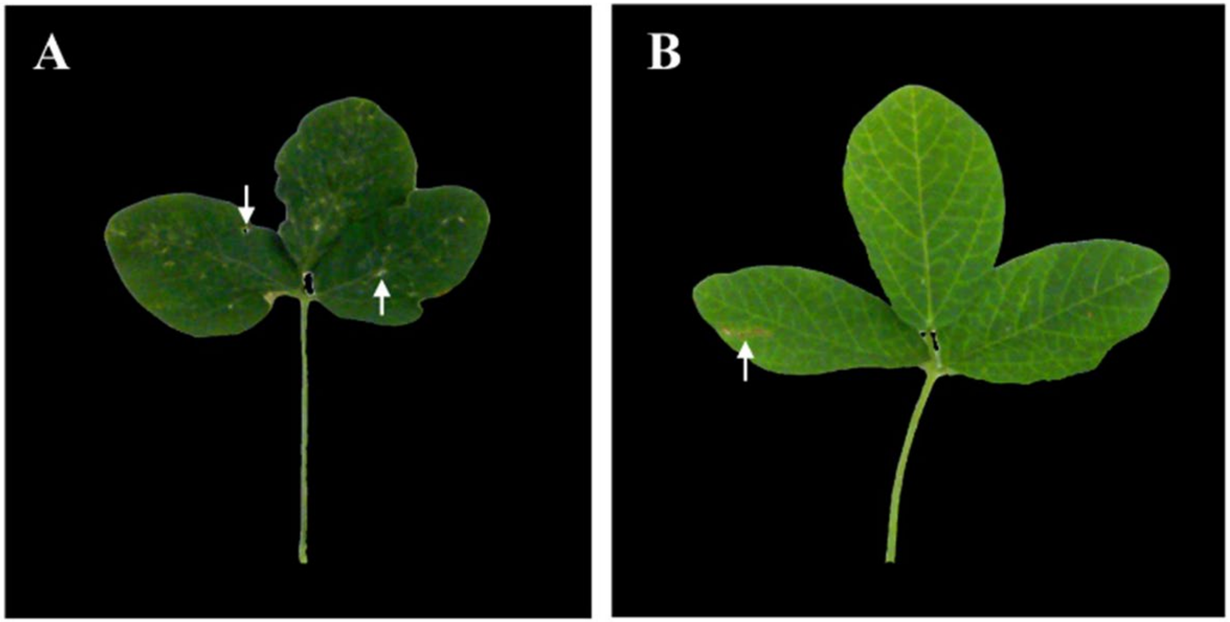
Linking abstract quantities to observables

ABSTRACT



OBSERVABLE

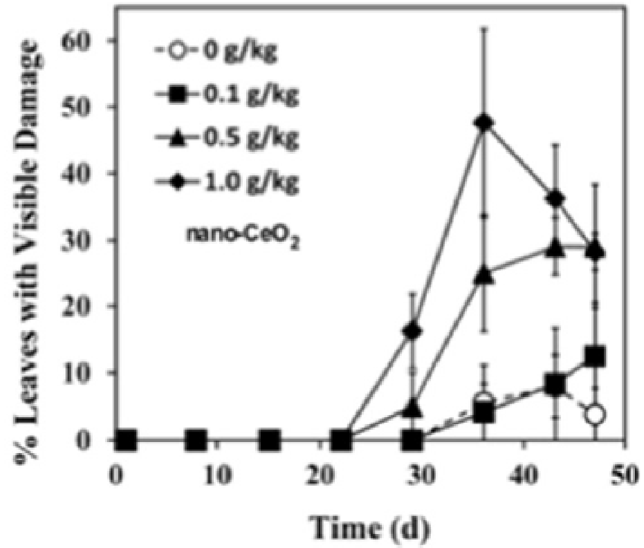
Observable can really mean observable



Soybean leaves grown in soils augmented with CeO_2 (left) or ZnO (right) nanoparticles (J.H. Priester et al. Since of the total environment (2017). Dark spots are "damage". a

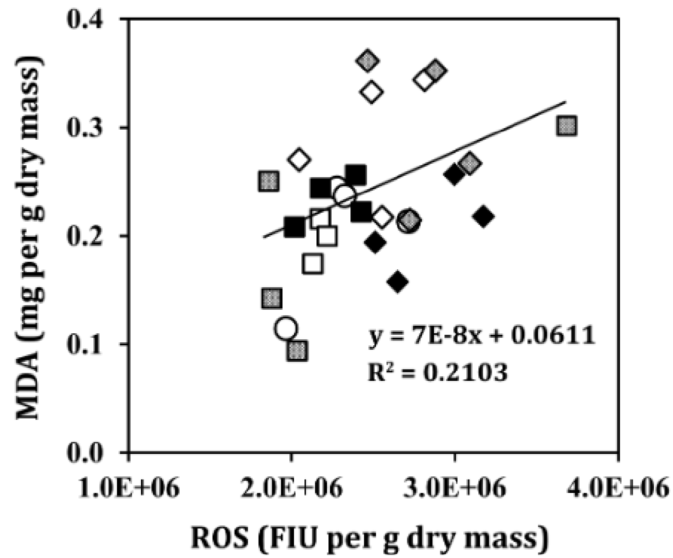
Quantifying damage for DEB

Count damaged leaves
(unhelpful for DEB)

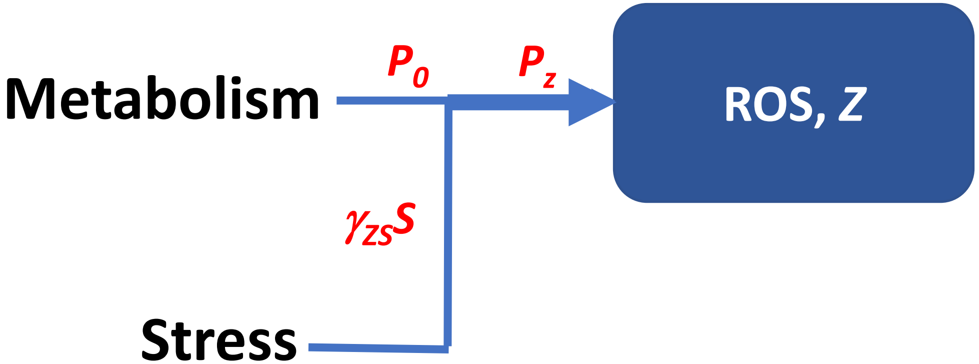


Link to chemistry

- ROS = damage inducing compound
- Damage = MDA (Measure of lipid peroxidation)

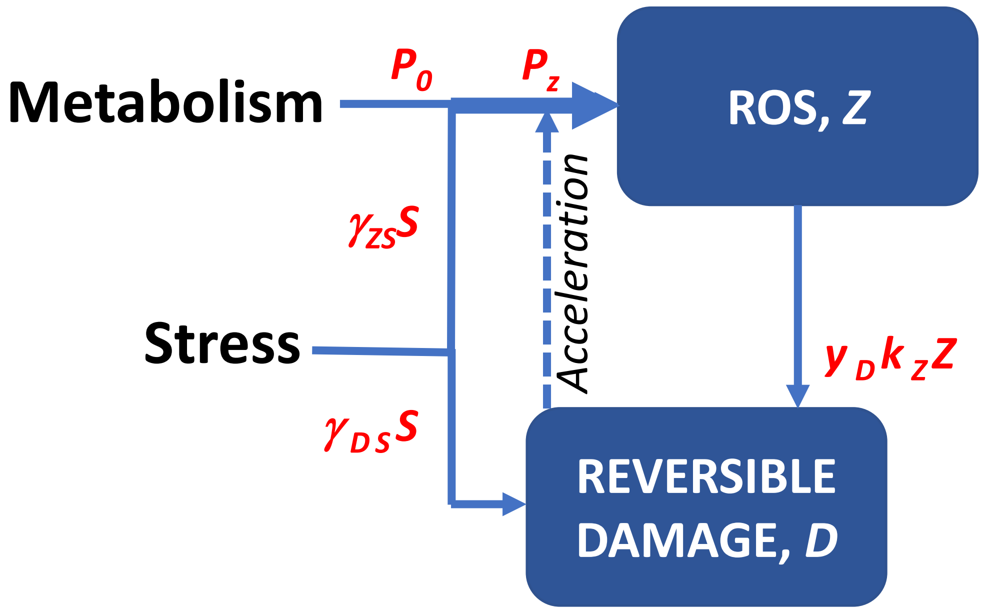


Modeling Oxidative Stress*



*T. Klanjscek, E.B. Muller and R.M. Nisbet. J. Theor. Biol. (2016)

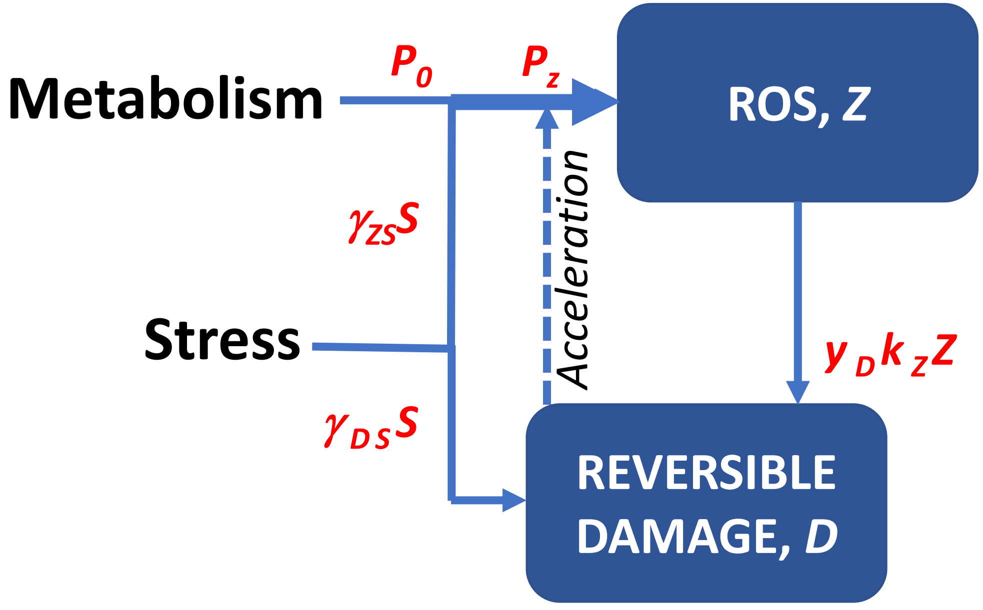
Modeling Oxidative Stress



Modeling Oxidative Stress

ROS production rate, P_Z, with acceleration being

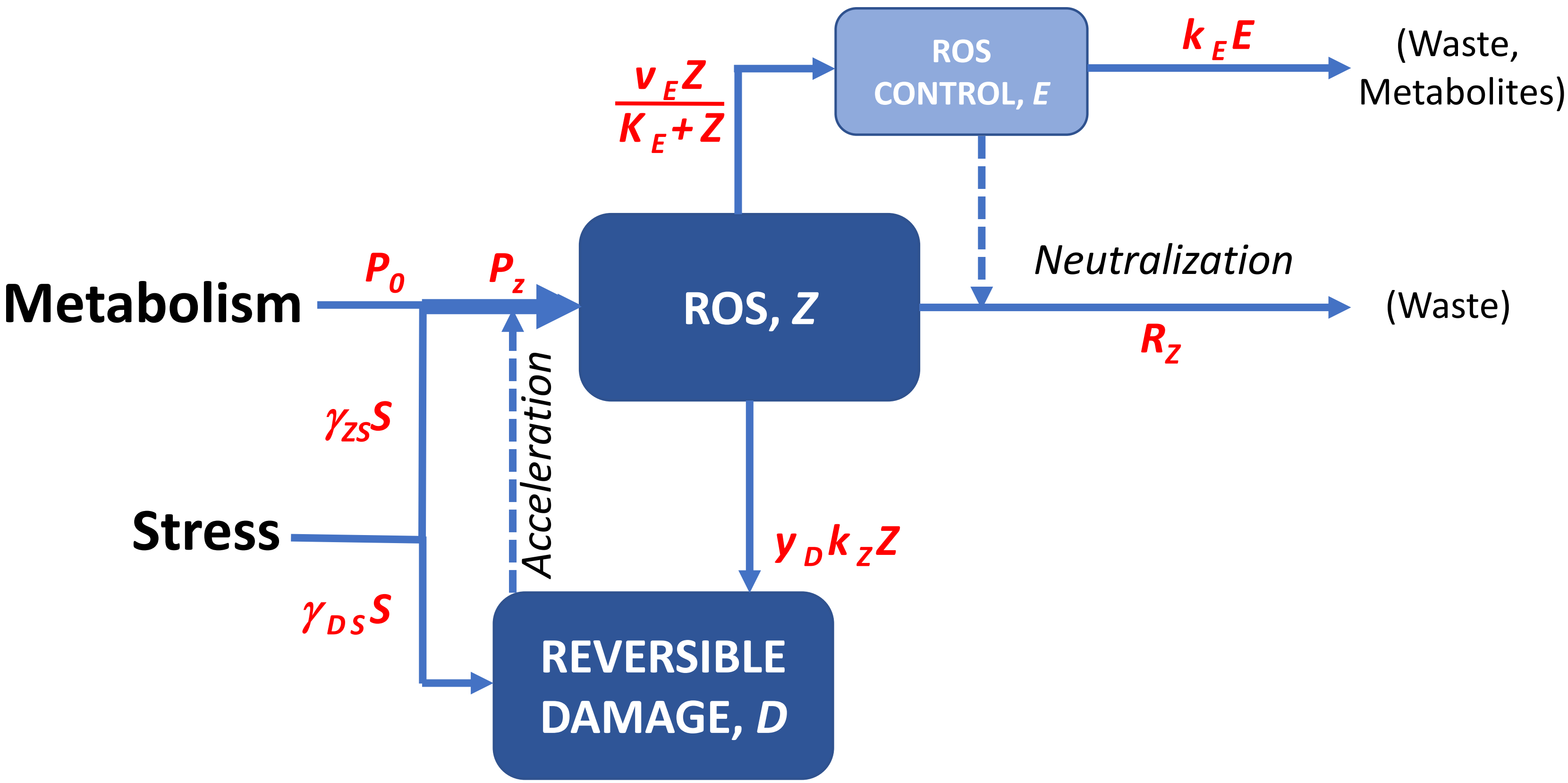
- additive feedback of damage: $P_Z = P_0 + \gamma_{ZS}S + \gamma_{ZD}D$
- multiplicative feedback of damage: $P_Z = (P_0 + \gamma_{ZS}S)(1 + \gamma_{ZD}D)$



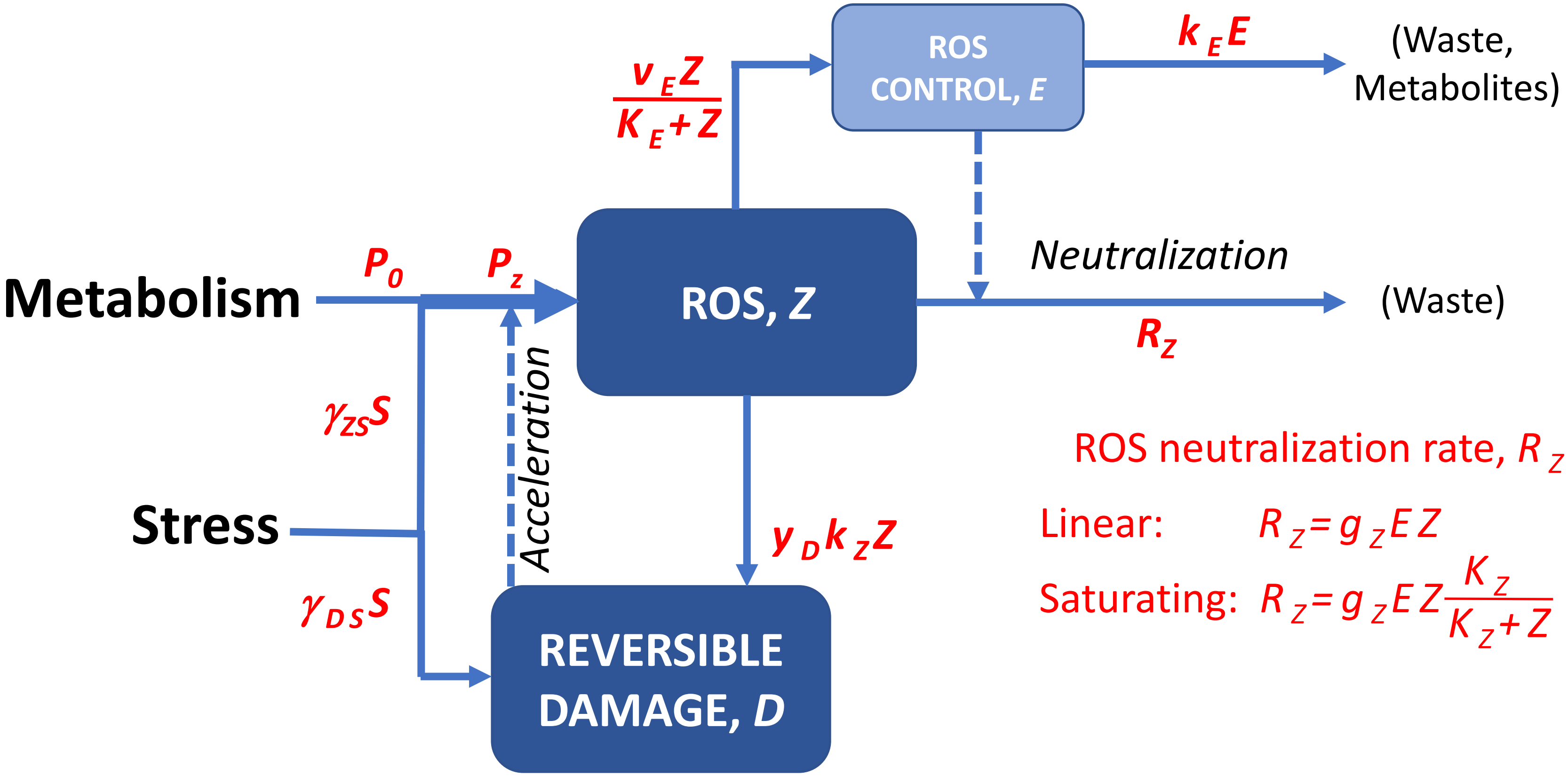
Damage production rate, P_D:

$$P_D = \gamma_{DS}S + y_D k_Z Z$$

Modeling Oxidative Stress



Modeling Oxidative Stress

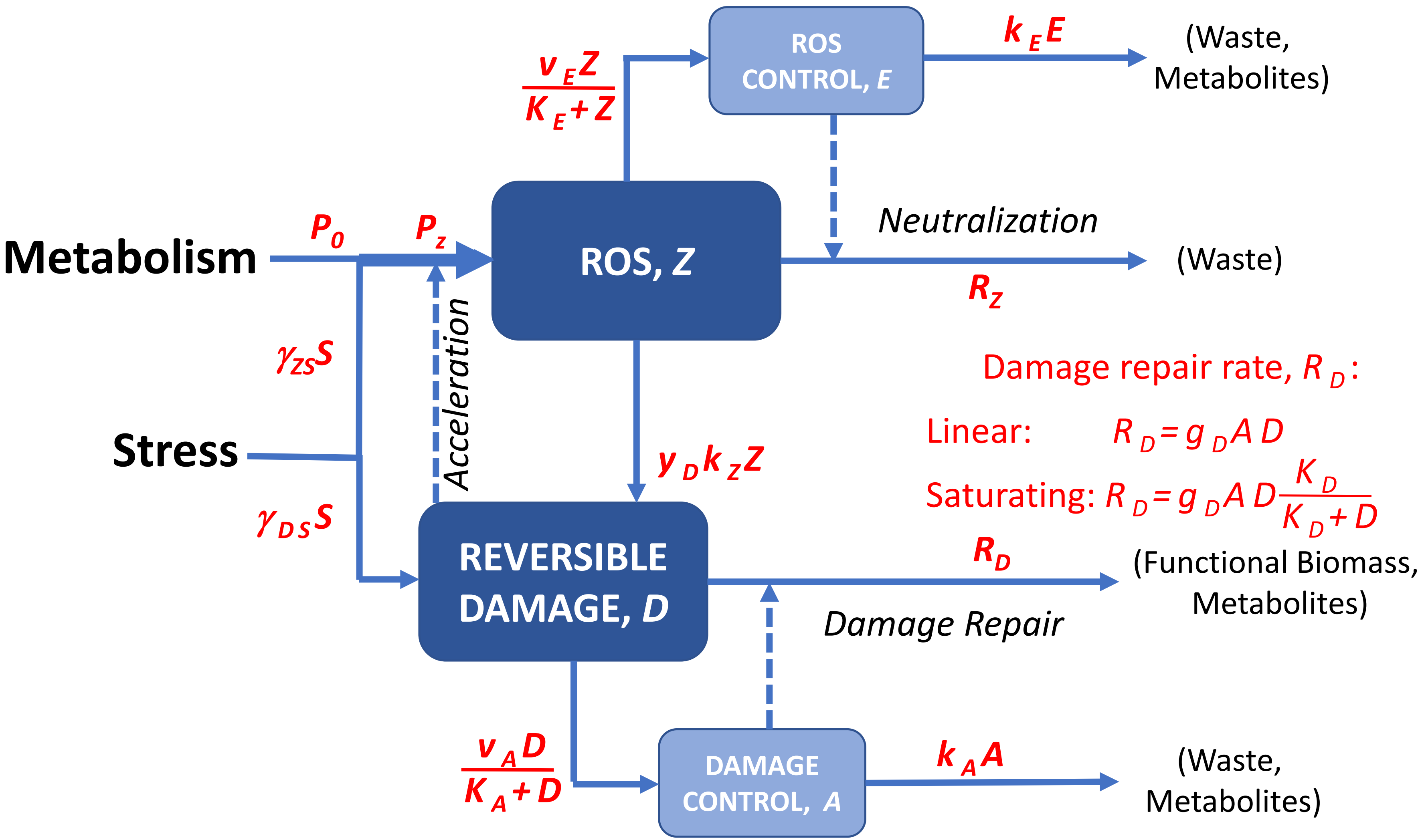


ROS neutralization rate, R_Z:

Linear: $R_Z = g_Z E Z$

Saturating: $R_Z = g_Z E Z \frac{K_Z}{K_Z + Z}$

Modeling Oxidative Stress

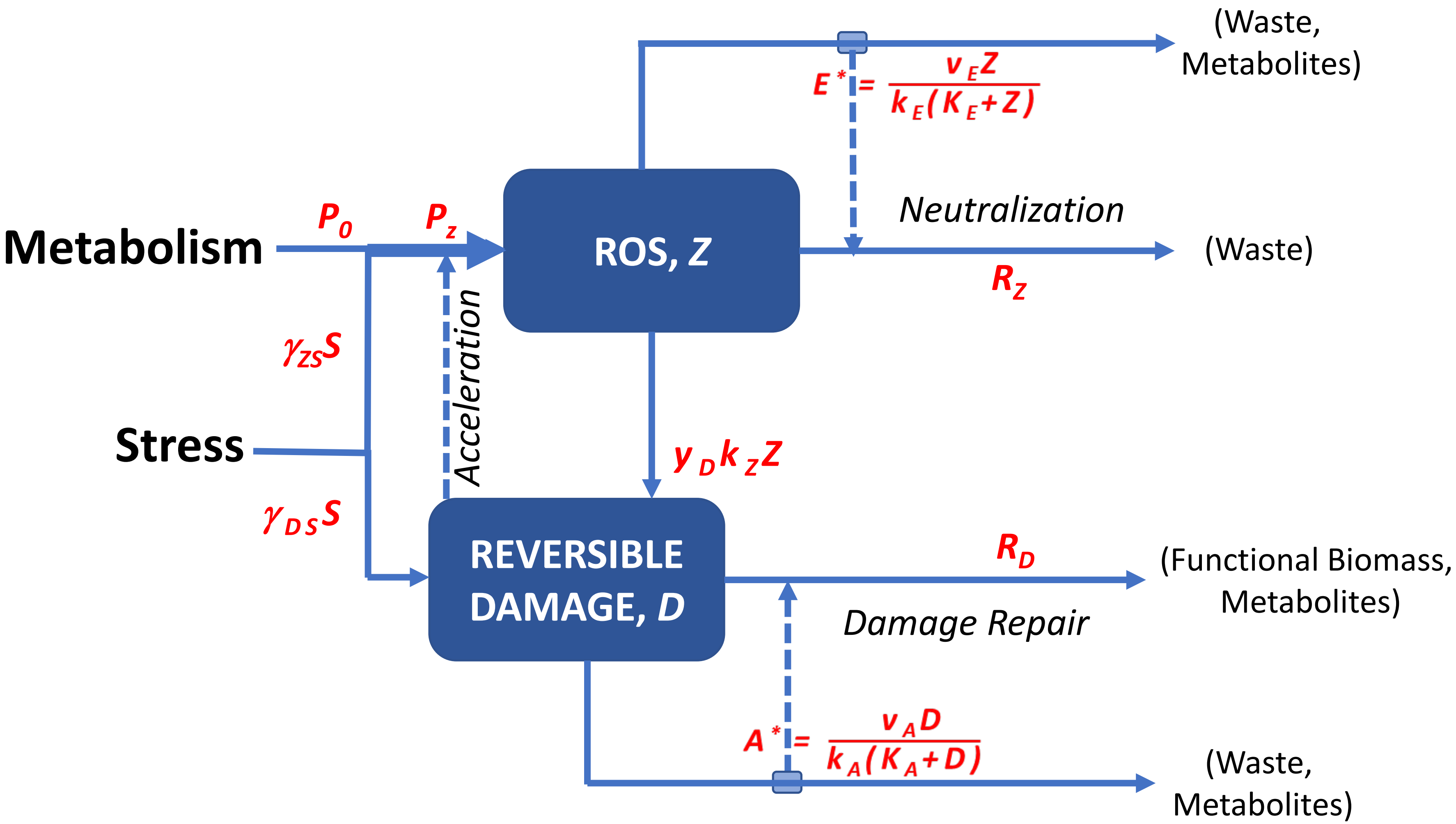


Damage repair rate, R_D:

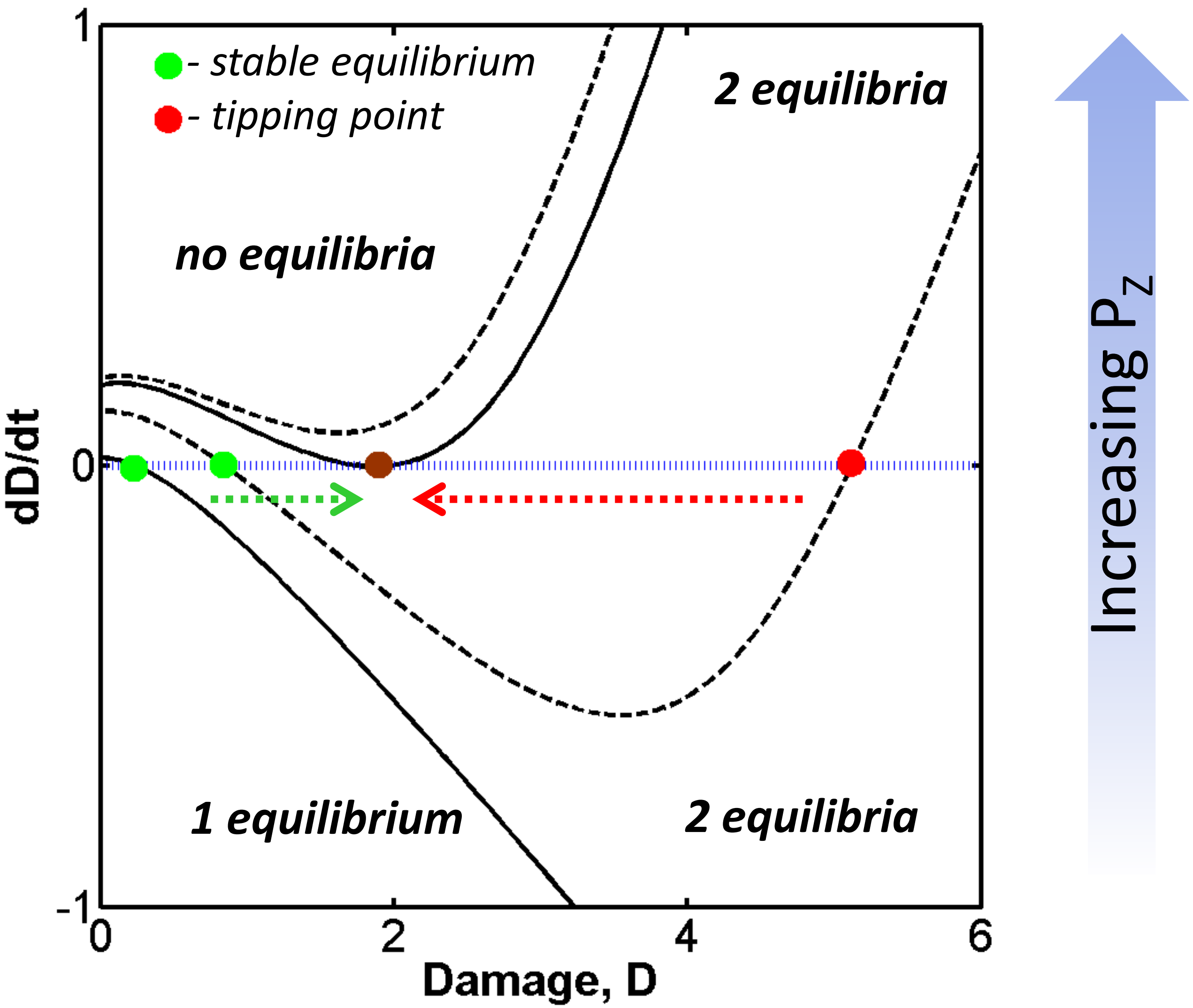
Linear: $R_D = g_D A D$

Saturating: $R_D = g_D A D \frac{K_D}{K_D + D}$

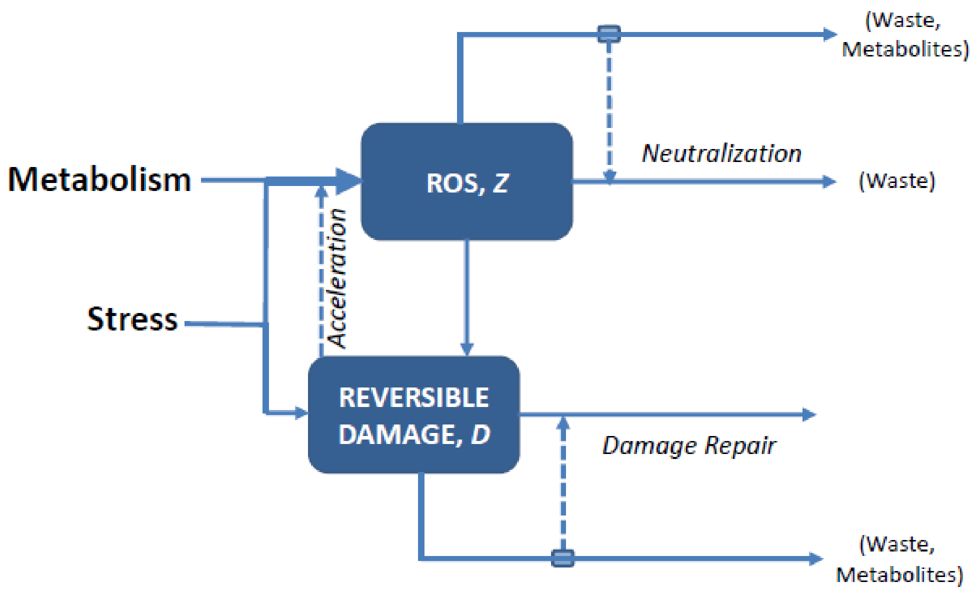
Relatively Fast Dynamics of Controllers
for Steady State Approximation



Damage Equilibria with Increasing ROS production, P_Z



Oxidative stress model properties



- Predicts co-variation of ROS and damage in response to NP exposure <u>– often related to available data</u>
- Takes account of exposure history
- Predicts "<u>tipping points</u>" caused by break-down of regulation (previous slide)
- Provides <u>mechanistic basis for no-effect concentrations</u>
- **Testing requires time-series data**

Added value to data by using DEB models?

DEB offers potential biology-based generality:

- **Species of organism** → DEB has recipe for interspecies comparisons
- **Exposure mode** → DEB allows natural coupling to TK and TD models
- **Duration** → DEB model is dynamic, so output is time-dependent
- **Environmental conditions** → DEB can handle multiple environmental stressors

BUT:

- DEB processes are **abstract**. Interpretable connection to measured and **measurable data** essential.
- Ecotox question are societally determined so appropriate **level of generality can be problem specific**