Physics of metabolic organization

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Introduction / Motivation

Timeline of major milestones:

2008 First encounter with DEB

Early 2009 First attempts to make a DEB model

Late 2009 **Depression**

Early 2010 Visited Bas at VU

Mid 2010 Parameters estimated

2011 **First DEB paper published**

Introduction / Motivation

“DEB is an extremely simple theory for describing extremely complex phenomena.”

Bas Kooijman

Introduction / Motivation

“REALLY!?!?”

Marko Jusup

Introduction / Motivation

Several years later...

“Aaah! Now I get it.”

Introduction / Motivation

Limiting the amount of information. Out of approximately 90 naturally occurring elements, only 11 are ubiquitous in living organisms. Out of these 11 elements, the main four (C, H, O, and N) comprise about 99% of living biomass. A modeler, therefore, hardly needs to keep track of a large number of mass balances to capture the effects of many important metabolic processes.

Introduction / Motivation

Focusing on aggregate (macrochemical) effects. In metabolic networks (i.e., graph-theoretical representations of metabolism), nodes corresponding to metabolites have an approximately scale-free degree distribution. Exceptionally high-degree nodes (hub metabolites) do exist and their presence is essential to the proper functioning of metabolic networks.

Introduction / Motivation

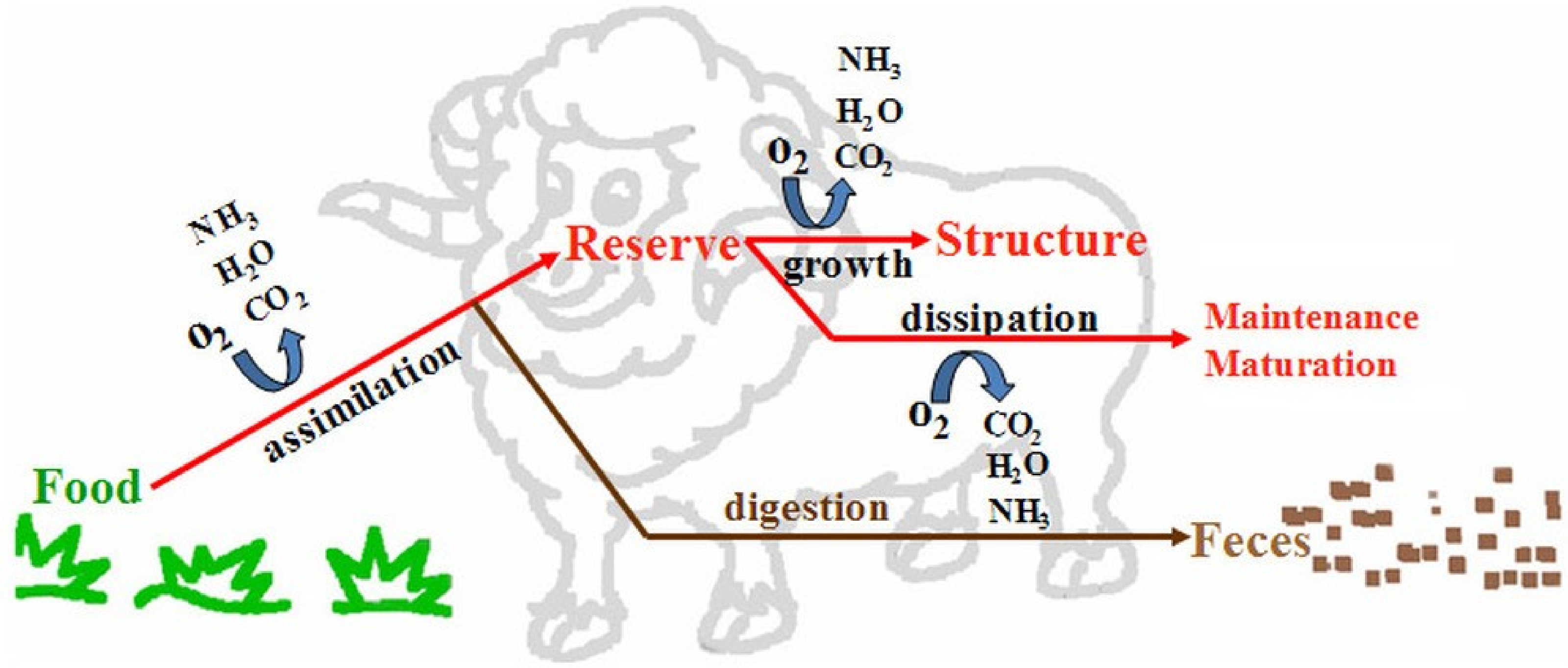
Cell similarity. The metabolic similarity of cells is mostly independent of organism size. Once a successful metabolic pathway evolves, it can be preserved by evolution to serve very similar functions in various organs or even the same function in different species. A famous example is the cyclic AMP pathway used in cell communication by all animals investigated, including bacteria and other unicelluar organisms.

Today's aims

(1) Revisit some of the fundamentals of DEB theory

(2) Discuss the potential future directions for development

DEB theory: intuition



Schematic representation of the basic metabolic processes in DEB organisms (heterotrophic aerobes). Typically, food is assimilated into reserve in the presence of oxygen during which carbon dioxide, water, and nitrogenous waste are excreted into the environment. Reserve is used to power (i) growth, and (ii) various dissipative metabolic processes, where the latter keep the organism alive and allow it to mature. The egestion of feces occurs in parallel with assimilation due to the inefficiencies of digestive tracts.

DEB theory: intuition

Why two compartments?

(1) There is a “buffer” between the changing environment and the relatively constant “internals”. Organisms can survive starvation.

(2) Even if **compartments have constant chemistry***, the organism's overall chemistry can change by changing the relative state of these compartments.

***Strong homeostasis arises as a natural assumption.**

DEB theory: formalism

Table 1: The three types of macrochemical reactions for a heterotrophic aerobe.

Assimilation	$y_{XE}CH_{n_{HX}}O_{n_{OX}}N_{n_{NX}} + c_{11}O_2 \rightarrow CH_{n_{HE}}O_{n_{OE}}N_{n_{NE}} + c_{12}CO_2 + c_{13}H_2O + c_{14}NH_3 + y_{PE}CH_{n_{HP}}O_{n_{OP}}N_{n_{NP}}$
Growth	$CH_{n_{HE}}O_{n_{OE}}N_{n_{NE}} + c_{21}O_2 \rightarrow y_{VE}CH_{n_{HV}}O_{n_{OV}}N_{n_{NV}} + c_{22}CO_2 + c_{23}H_2O + c_{24}NH_3$
Dissipation	$CH_{n_{HE}}O_{n_{OE}}N_{n_{NE}} + c_{31}O_2 \rightarrow c_{32}CO_2 + c_{33}H_2O + c_{34}NH_3$
Symbols	$n_{*X}, n_{*V}, n_{*E}, n_{*P}$: chemical indices for food, structure, reserve, and feces y_{XE}, y_{PE}, y_{VE}: yields (food on reserve, feces on reserve, structure on reserve) c_{ij}, $i \in \{1, 2, 3\}$, $j \in \{1, 2, 3, 4\}$: stoichiometric coefficients

What is the interpretation of the macrochemical reactions in Table 1? Taking assimilation as an example, we see that food gets transformed into reserve in the presence of oxygen, whereby building 1 C-mol of reserve requires ingesting y_{XE} C-moles of food and breathing in c_{11} moles of oxygen. In addition, y_{PE} C-moles of feces are produced because food cannot be processed fully in the digestive system. If we assume that reserve is assimilated at a rate $\dot{J}_{EA}$, these simple considerations imply a food ingestion rate of $\dot{J}_X = y_{XE}\dot{J}_{EA}$, and a feces egestion rate of $\dot{J}_P = y_{PE}\dot{J}_{EA}$. In addition, food assimilation accounts for a (variable) fraction of the organism's oxygen consumption by contributing amount $c_{11}\dot{J}_{EA}$ to the respiration rate ($\dot{J}_O$).

DEB theory: formalism

Table 2: Flows of organic and inorganic compounds.

Flow of substance	Description
$\dot{J}_X = y_{XE}\dot{J}_{EA}$	Ingestion
$\dot{J}_V = y_{VE}\dot{J}_{EG}$	Growth
$\dot{J}_E = \dot{J}_{EA} - \dot{J}_{EG} - \dot{J}_{ED}$	Net reserve assimilation
$\dot{J}_P = y_{PE}\dot{J}_{EA}$	Egestion
$\dot{J}_O = c_{11}\dot{J}_{EA} + c_{21}\dot{J}_{EG} + c_{31}\dot{J}_{ED}$	Oxygen
$\dot{J}_C = c_{12}\dot{J}_{EA} + c_{22}\dot{J}_{EG} + c_{32}\dot{J}_{ED}$	Carbon dioxide
$\dot{J}_H = c_{13}\dot{J}_{EA} + c_{23}\dot{J}_{EG} + c_{33}\dot{J}_{ED}$	Water
$\dot{J}_N = c_{14}\dot{J}_{EA} + c_{24}\dot{J}_{EG} + c_{34}\dot{J}_{ED}$	Ammonia

Metabolism is surprisingly constrained: **there are only three degrees of freedom**.
Making the strong homeostasis assumption, **energy representation naturally emerges**.

DEB theory: formalism

define assimilation, growth, and dissipation energy flows by $\dot{p}_i \equiv \bar{\mu}_E \dot{J}_{Ei}$, $i \in \{A, G, D\}$

Table 3: Dynamic equations in units of energy.

Equation	Description
$\frac{dE_X}{dt} = \kappa_A \dot{p}_A$	Ingestion
$\frac{dE}{dt} = \dot{p}_A - \dot{p}_G - \dot{p}_D$	Reserve dynamics
$\frac{dE_V}{dt} = \kappa_G \dot{p}_G$	Growth
$\frac{dE_P}{dt} = \kappa_P \dot{p}_A$	Egestion
$\kappa_A \equiv y_{XE} \frac{\bar{\mu}_X}{\bar{\mu}_E}$	Assimilation ratio[a]
$\kappa_G \equiv y_{VE} \frac{\bar{\mu}_V}{\bar{\mu}_E}$	Growth efficiency
$\kappa_P \equiv y_{PE} \frac{\bar{\mu}_P}{\bar{\mu}_E}$	Egestion efficiency

[a]In DEB-based literature (e.g., [7, 60]), it is customary to define the assimilation efficiency as $\kappa_X \equiv 1/\kappa_A$. For all efficiencies, it holds $0 < \kappa_* < 1$, whereas $\kappa_A > 1$.

DEB theory: formalism

To go from theory to applications, it is necessary to express energy flows in terms of state variables.

Jusup et al., Phys Life Rev 20: 1-39 (2017)

Standard DEB model

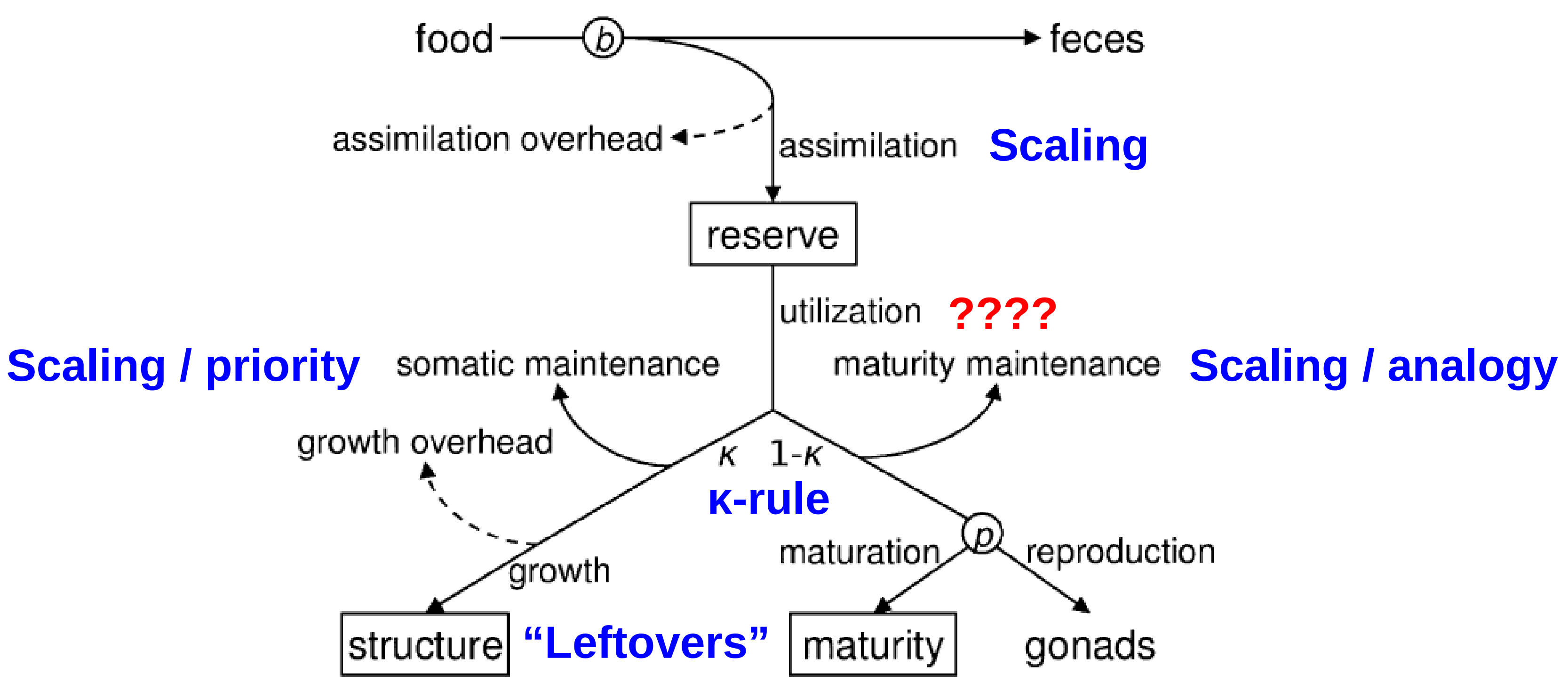


Fig. 2. **Schematic representation of energy flows in the standard DEB model.** Commonly tracked state variables are denoted by rectangles. Nodes b and p indicate metabolic switches at birth (onset of feeding) and puberty (onset of reproduction). The utilization flow is split in accordance with the kappa rule. Overheads, quantitatively represented by assimilation and growth efficiencies, result from the chemical transformations of food into reserve and reserve into structure, respectively.

Utilization / mobilization flow

Reserve density dynamics is the key

$$\frac{d[E]}{dt} = \frac{\dot{p}_A - \dot{p}_C}{L^3} - 3\frac{[E]}{L}\frac{dL}{dt}$$

Three approaches:

(1) Educational / practical (Jaap van der Meer): reserve density follows a first order dynamics

(2) Standard (Bas Kooijman): weak homeostasis

(3) Middle: contrast energy inputs and outputs

$$\frac{d}{dt}(E + E_V) = \dot{p}_A - \dot{p}_D - (1-\kappa_G)\dot{p}_G =$$

$$\dot{p}_A - \dot{p}_S - (1-\kappa)\dot{p}_C - (1-\kappa_G)\dot{p}_G$$

Standard DEB model

$$\frac{dE}{dt} = \dot{p}_A - \dot{p}_C, \qquad \text{Reserve dynamics}$$

$$\frac{dL}{dt} = \frac{\dot{p}_G}{3L^2\,[E_G]}, \quad \text{and} \qquad \text{Growth}$$

$$\frac{dE_H}{dt} = \begin{cases} \dot{p}_R, & \text{if } E_H < E_H^p \\ 0, & \text{if } E_H = E_H^p \end{cases}. \qquad \text{Maturation}$$

$$\dot{p}_A = \begin{cases} 0, & \text{if } E_H < E_H^b \\ \{\dot{p}_{Am}\}\,fL^2, & \text{otherwise} \end{cases} \qquad \text{Assimilation}$$

$$\dot{p}_C = [E]\,\frac{\dot{v}\,[E_G]\,L^2 + [\dot{p}_M]\,L^3 + \{\dot{p}_T\}\,L^2}{[E_G] + \kappa\,[E]}, \qquad \text{Utilization}$$

$$\dot{p}_G = [E_G]\,\frac{\kappa\dot{v}\,[E]\,L^2 - [\dot{p}_M]\,L^3 - \{\dot{p}_T\}L^2}{[E_G] + \kappa\,[E]}, \quad \text{and} \qquad \text{Growth}$$

$$\dot{p}_R = (1-\kappa)\,\dot{p}_C - \dot{k}_J E_H. \qquad \text{Maturation}$$

DEB theory: applications

State of affairs:

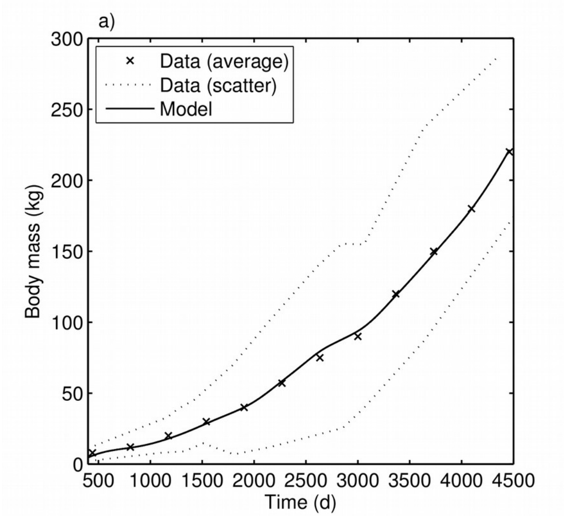
Consistent and applicable theory.

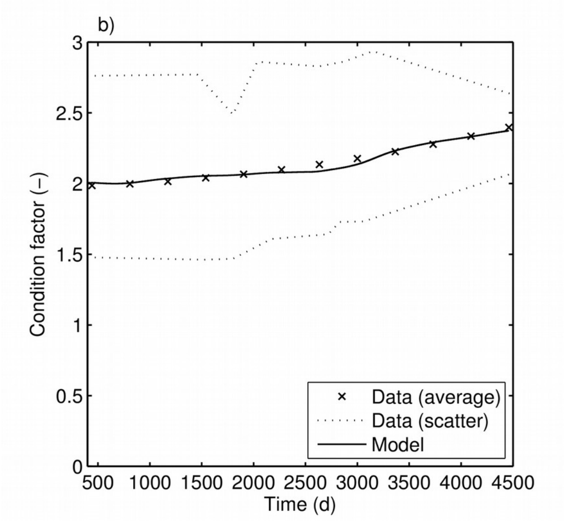
Best ever! It's fantastic! Everybody agrees.

But does it work?

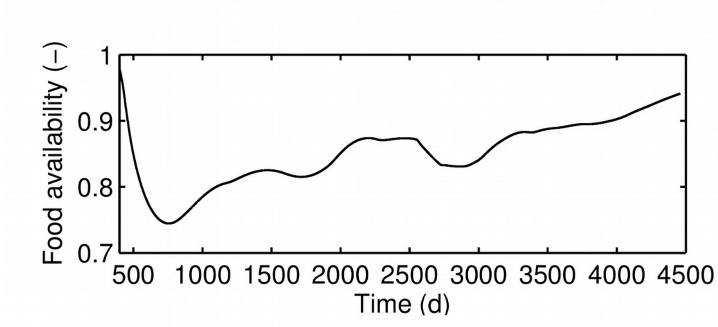
DEB theory: applications

Fit model to data

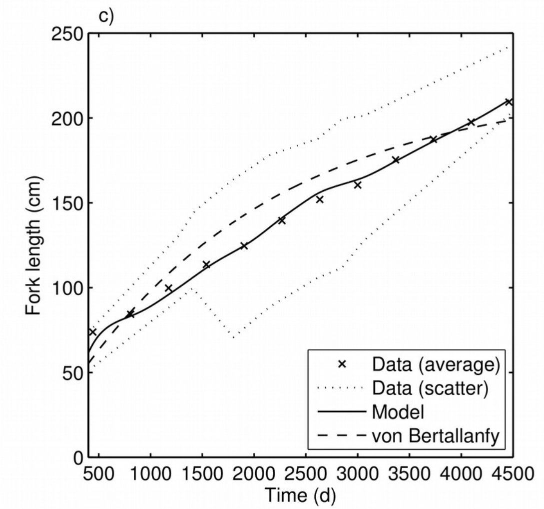


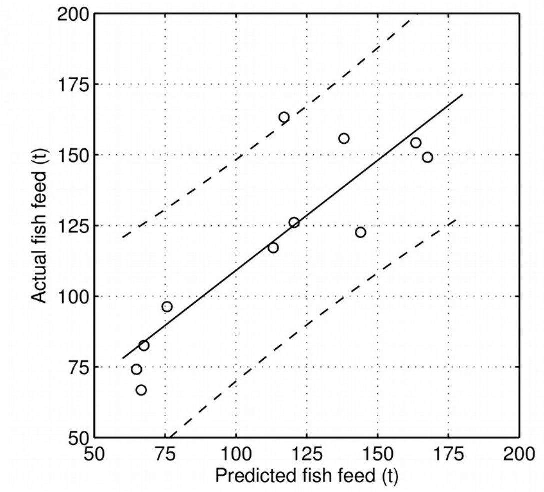


Estimate feeding history



Simulate growth again



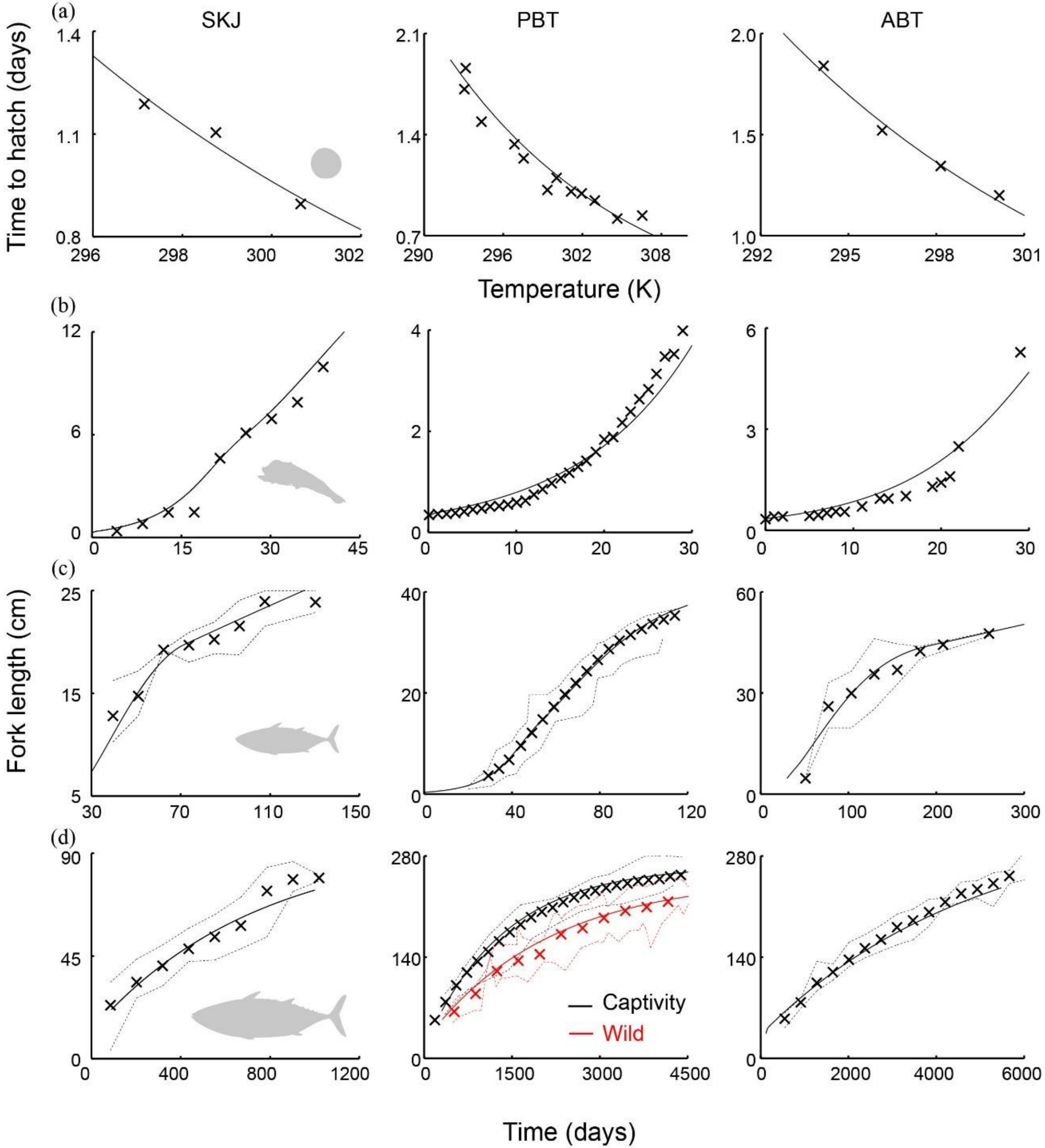


Compare predictions & measurements

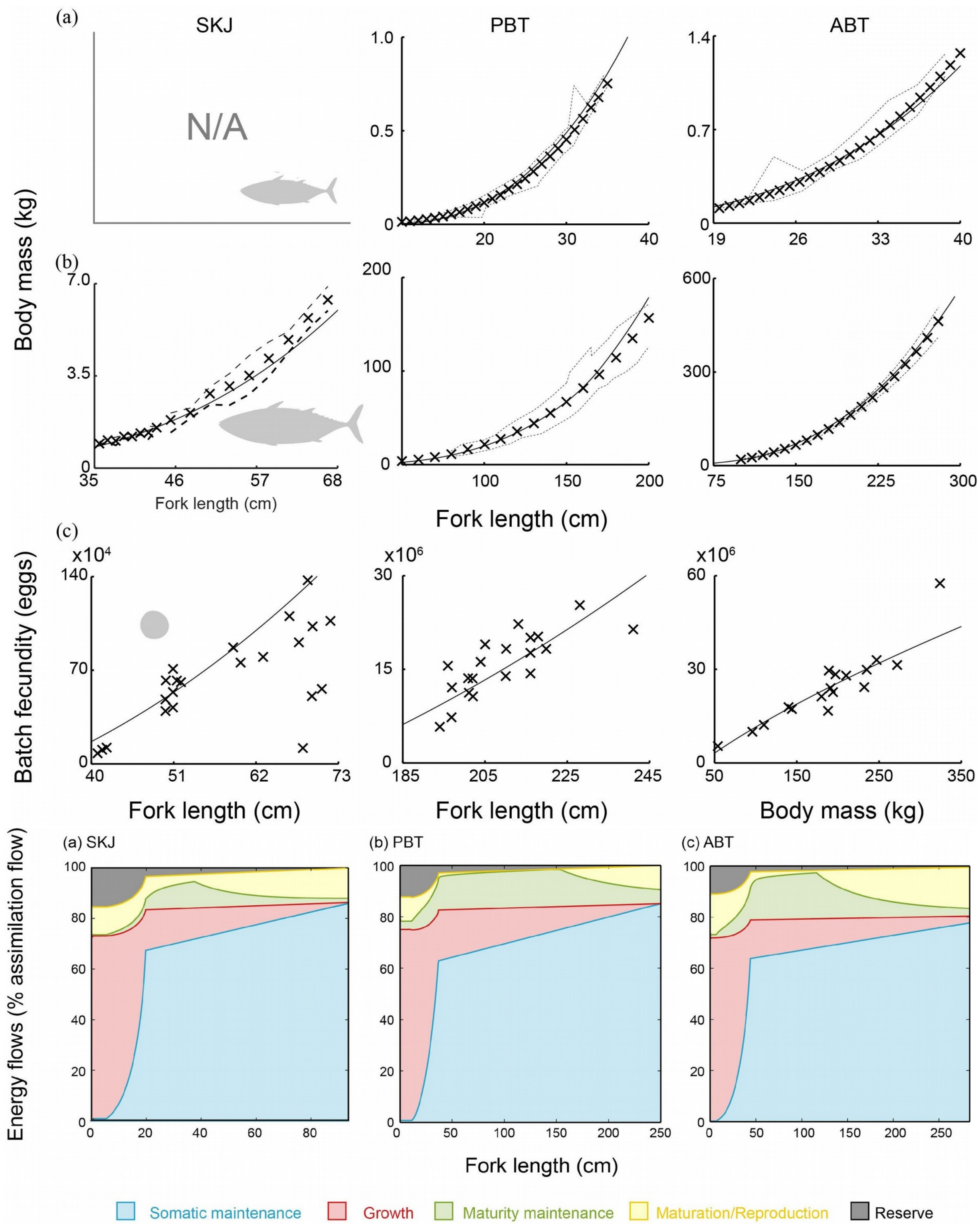
DEB theory: applications

- Wild Pacific bluefin tuna reproduce at age 5 or 6
- In captivity, reproduction is possible even at age 3
- However, in the studied case it took 7 years
- P**redicted onset of reproduction after 2555 days**

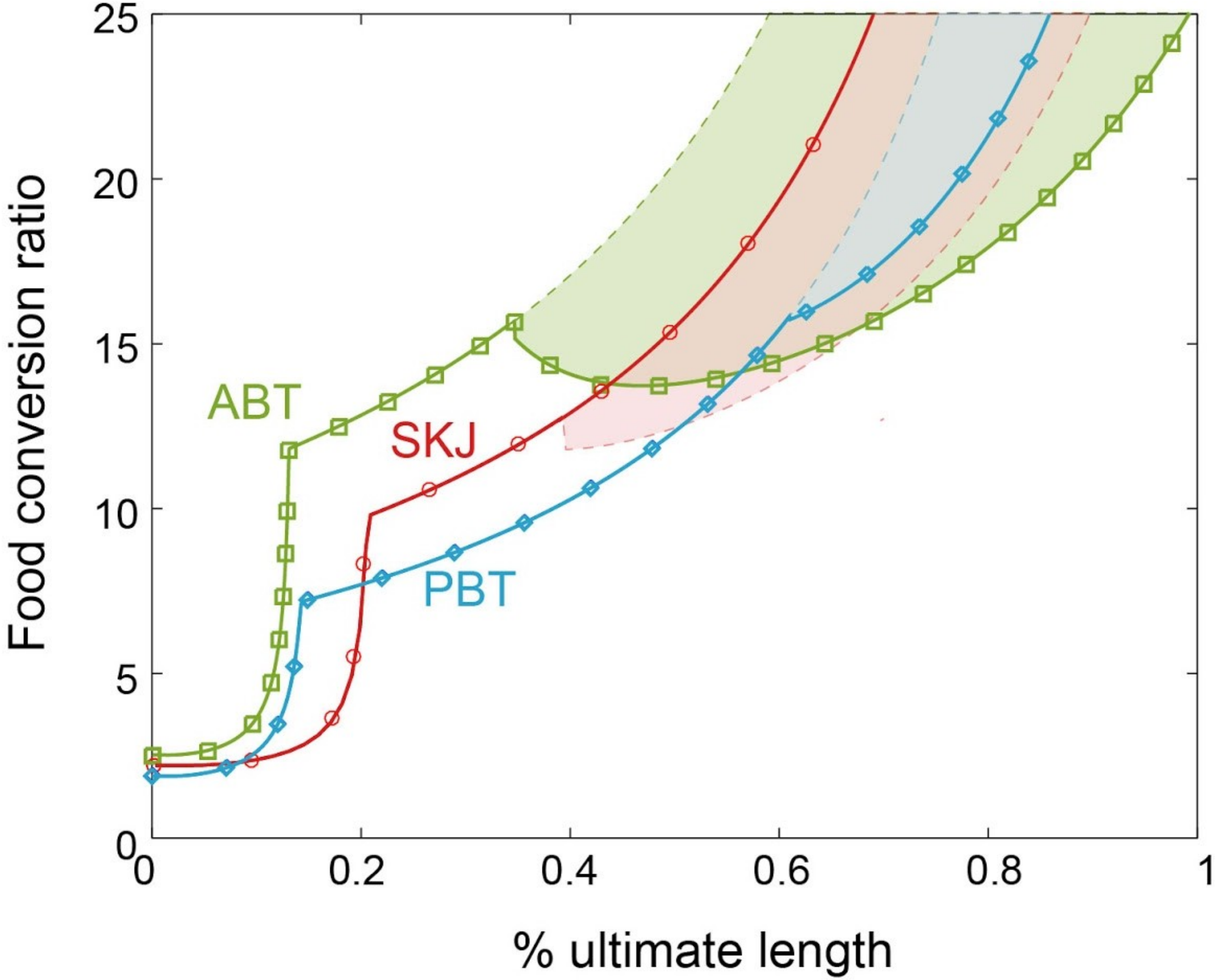
Applications



Applications



DEB theory: applications



DEB theory: applications

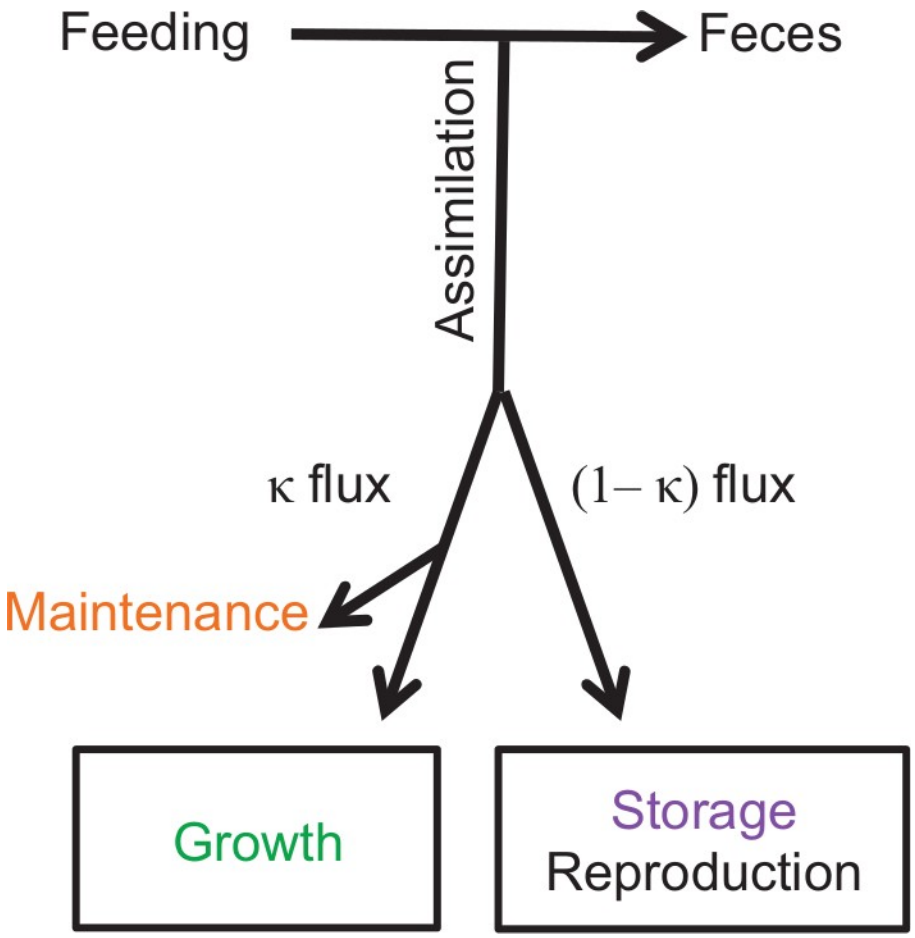
Where tuna DEB model struggles:

- FCR in juveniles and adults seems to be similar
- Spawning moderately changes condition of adults
- Juveniles can considerably change lipid content

DEB theory: future

What if?

Martin et al.,
J Anim Ecol (2017)



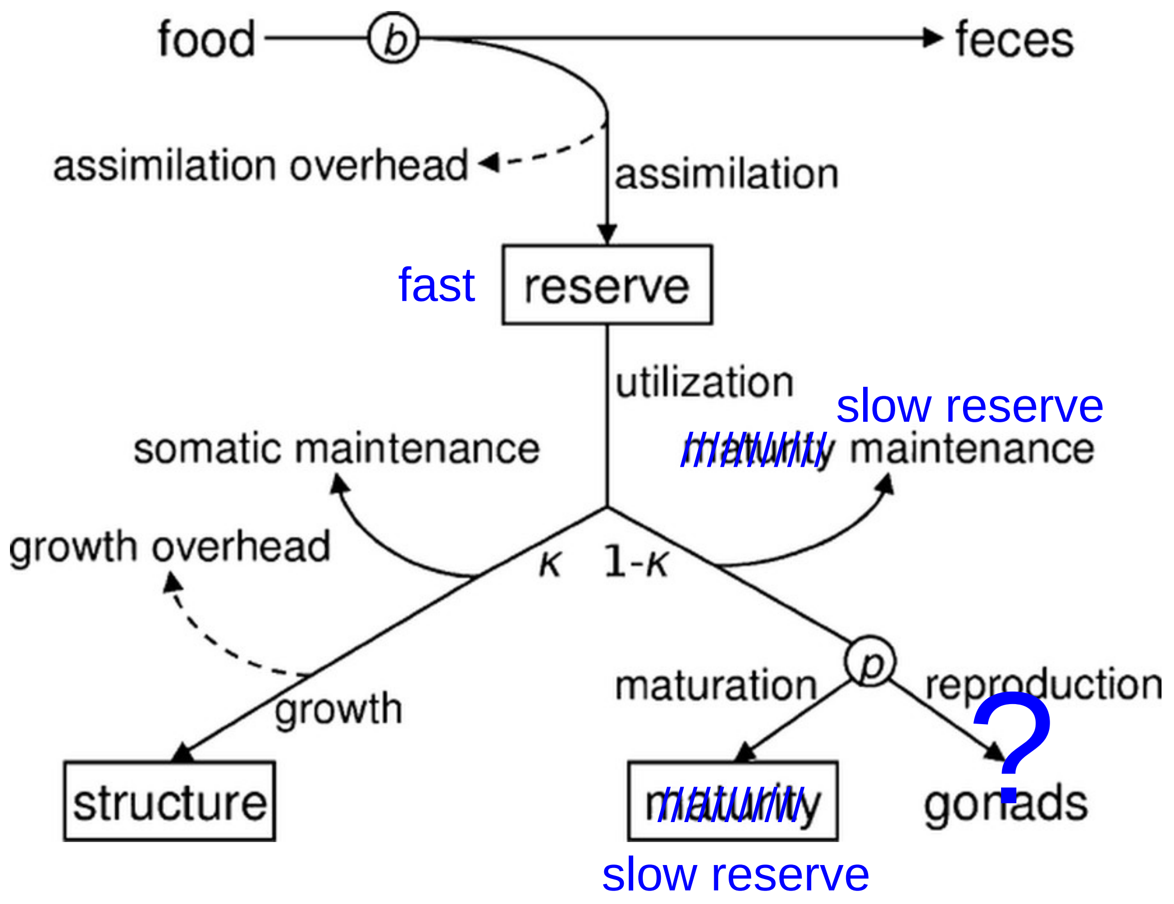
DEB theory: future

Model by Martin et al. discards:

- Reserve
- Maturity

Perhaps a bit too much.

DEB theory: future



Thank you for your attention!

ご清聴ありがとうございました。