A mesoscopic model underlying DEB

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1. Introduction

Dynamic Energy Budget (DEB) theory is an approach to model mass and energy flows of (biological) individuals. It is a general starting point since all forms of life we know are almost by definition shaped by the mass and energy flows that flow through them. Although in principle these flows can take on different forms, the key to life lies in the chemical energy that allows an organism to grow and maintain its existence.
In principle DEB works the same for all organisms in spite of very big differences in the precise structure of the underlying chemical reaction networks, and for this reason we might expect that there is somehow a general scheme which applies to how these chemical reaction networks are build up on the one hand, and on the other hand that somehow a general principle may work as to how chemical networks either manifest their behavioral patterns on a macroscopic scale.
We hope that by investigating what microscopic principles may lie behind DEB that we gain insight into this world, thereby reaching towards scientists who try to do just that by reconstructing microscopic reaction networks from microscopic observations. Perhaps we may even find some cases where slight modifications/additions to DEB theory could be relevant. Taking this biological world as a study object can be very rewarding also from a physics point of view we believe, since through its study we may learn how far from equilibrium systems behave and are well described. As a starting point we here look into a imaginary world that should lie somewhere in between the macroscopic world of DEB and the microscopic world of highly complex chemical reaction networks.

1.1. Core DEB theory.

In this work we will try to find a mesoscopic description that coincides with what we will call *core DEB* theory. It is the simplest description possible of an isomorphic ectothermic organism within DEB theory and describes the dynamics of one Reserve E and one Structure V with the following two differential equations

$$\frac{d\mathrm{E}}{dt} = \dot{p}_A - \dot{p}_C \tag{1}$$

$$\frac{d\mathrm{V}}{dt} = \dot{p}_C - [\dot{p}_M]\mathrm{V} \tag{2}$$

where $\dot{p}_A = \{\dot{p}_{Am}\}\frac{X}{X_K+X}\mathrm{V}^{2/3}$ is the assimilation rate and $\dot{p}_C = \frac{[\mathrm{E}]}{[\mathrm{E}]+K}K(\dot{v}\mathrm{V}^{2/3}+\dot{k}_M\mathrm{V})$ the catabolic rate, and $[\dot{p}_M]$ the volume specific maintenance cost

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(a constant)[2]. Conform the notation in the DEB book we use $[\mathrm{E}] = \mathrm{E}/\mathrm{V}$, and have defined $K = [\mathrm{E}_G]/\kappa$. We have so far and shall continue to stick to the notation used in the DEB book as much as possible. Let it be clear that the above serves in no way as an explanation for DEB theory for that we refer to the book [1].

2. Model I

For starters we try to stay as close as possible to the statespace of the most simple DEB model where there is only structure V and reserve E: $\Omega = (\mathrm{E}, \mathrm{V}) = \mathbb{R}^{+\,2}$. The reality that we imagine behind this statespace is that structure is in fact a reaction complex that can reconstruct itself by consuming a fixed quantity of reserve which is a set of smaller high-energetic molecules, the nutrients. By assuming homeostasis of the chemical composition of structure we avoid the complication of changing dynamics, also the volume of the cell is now proportional to the amount of structure V.

2.1. **Assimilation.**

Only the smaller molecules get transported over a cell membrane and therefore only reserve may be assimilated directly from the environment. The rate at which this assimilation takes place $\dot{p}_A$ depends on the amount of receptors in the membrane and of course the availability of nutrients X in the environment. The amount of receptors in the membrane is the size of the membrane A times the density of receptors in the membrane ρ_a =constant. At least some of the fraction of this transport is active and therefore a small amount of reserve is needed to assimilate one amount of reserve, this decreases the efficiency η of the assimilation. The fact that the receptors have a limited capacity (it takes some finite amount of time to deal with a molecule) causes a Michaelis-Menten type behavior[3] in terms of the concentration of nutrients outside the cell X, with an associated M-M concentration X_K and maximal throughput rate v_m.

$$\dot{p}_A = \eta \rho_a A \frac{X}{X + X_K} v_m \tag{3}$$

with $f \equiv \frac{X}{X+X_K}$, $A = c\mathrm{V}^{2/3}$ for isomorphs and $\eta \rho_a c v_m = \{\dot{p}_{Am}\}$ this is (not surprisingly) equivalent with the result found in DEB.

$$\dot{p}_A = \{\dot{p}_{Am}\} f \mathrm{V}^{2/3} \tag{4}$$

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[2] Other constants are the "surface-area specific maximum assimilation rate" $\{\dot{p}_{Am}\}$, the "saturation coefficient of food" X_K, the "energy conductance" $\dot{v}$, the "maintenance rate coefficient" $\dot{k}_M$ and the "fraction of catabolic power spent on maintenance plus growth" κ.

[3] in principle this is valid only for a system in steady-state very far from equilibrium but here we make the quasi steady state assumption QSSA, see for instance [2].

2.2. **Reactions.** We imagine two relevant processes: creation of structure from reserve and spontaneous decay of structure. In order to create structure, free reserve E_F needs to bind to unoccupied or free structure V_F which then becomes bound in a structure/reserve complex V·E.

$$\mathrm{E}_F/[\mathrm{E}_G] + \mathrm{V}_F \rightleftarrows \mathrm{V{\cdot}E} \rightarrow 2\mathrm{V}_F \tag{5}$$

with $[\mathrm{E}_G]$ the volume specific costs for growth, we however may rescale E so that $[\mathrm{E}_G] = 1$, without loss of generality. The *total* reserve is the sum of free and bound reserve $\mathrm{E} = \mathrm{E}_F + \mathrm{V{\cdot}E}$; analogously for structure $\mathrm{V} = \mathrm{V}_F + \mathrm{V{\cdot}E}$.

Even though it seems we couldn't be farther away from reality [3], we assume that the contents of the cell are well mixed. In practice this means that all correlations and therefore organization in time-space is disregarded, but this should hardly affect the mean characteristics of the reactions. One unit of reserve then binds at a rate proportional to the density of free structure with r_B the proportionality constant, so the total binding rate for reserve becomes $\mathrm{E}_F \frac{\mathrm{V}_F}{V} r_B$. Unbinding of the structure/reserve complex into free structure and reserve goes at a rate $\mathrm{V{\cdot}E}\, r_U$. Lastly (free) structure is created at a rate $2\mathrm{V{\cdot}E}\, r_R$ thereby consuming structure/reserve complex at a rate $\mathrm{V{\cdot}E}\, r_R$.

The "spontaneous"[4] decay of structure is assumed to be independent of the state it is in so

$$\mathrm{V}_F \rightarrow \emptyset \tag{6}$$

$$\mathrm{V{\cdot}E} \rightarrow \mathrm{E}_F \tag{7}$$

with rates $\mathrm{V}_F r_D$ and $\mathrm{V{\cdot}E}\, r_D$ respectively.

The differential equations that follow for reserve and structure are

$$\tfrac{d\mathrm{E}_F}{dt} = \dot{p}_A - \mathrm{E}_F \frac{\mathrm{V}_F}{\mathrm{V}} r_B + \mathrm{V{\cdot}E}(r_U + r_D) \tag{8}$$

$$\tfrac{d\mathrm{V{\cdot}E}}{dt} = \mathrm{V}_F \frac{\mathrm{E}_F}{\mathrm{V}} r_B - \mathrm{V{\cdot}E}(r_U + r_R + r_D) \tag{9}$$

$$\tfrac{d\mathrm{V}_F}{dt} = \mathrm{V{\cdot}E}(r_U + 2r_R) - \mathrm{V}_F(\frac{\mathrm{E}}{\mathrm{V}} r_B + r_D) \tag{10}$$

2.3. **Analysis model I.** The central question we seek to answer in this subsection is: to what extent do the differential equations of core DEB (1)-(2) coincide with the differential equations (8)-(10) of model I?

In order for the reserve dynamics of model I to coincide with DEB theory, the catabolic rate (what is consumed of reserve) has to display Michaelis-Menten behavior in terms of the reserve concentration (compare to (3.44) on page 111 in [1]). Moreover the maintenance should be proportional to structure. Here we show how to see that this is at least approximately the case for model I.

Reasoning qualitatively towards our goal we notice two main points.

1.) The system closely resembles a normal enzymatic reaction system with two notable differences: The substrate concentration is subject to

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[4] The *denaturation* of most proteins is in fact regulated by the cell, but this should not influence the rates of decay in its dependency on V[4].

change and the product is structure itself creating an additional flow. Both influences will be investigated in the course of this text.
2.)Structure deteriorates with a rate proportional to the amount of structure, so of total growth a fraction proportional to the amount of structure is needed to compensate for this effect. We interpret that fraction as the maintenance that needs to be done on the structure and it should be closely related to what is called maintenance in DEB.

To allow a better interpretation we rewrite the above set of differential equations in terms of reserve $\mathrm{E} = \mathrm{E}_F + \mathrm{V{\cdot}E}$, total structure $\mathrm{V} = \mathrm{V}_F + \mathrm{V{\cdot}E}$ and fraction of bound structure $\rho_B = \mathrm{V{\cdot}E}/V = [\mathrm{V{\cdot}E}]$

$$\tfrac{d\mathrm{E}}{dt} = \dot{p}_A - \dot{p}_C^I \tag{11}$$

$$\tfrac{d\mathrm{V}}{dt} = \dot{p}_C^I - \mathrm{V} r_D \tag{12}$$

$$\tfrac{d\rho_B}{dt} = [\mathrm{E}_F](1-\rho_B) r_B - \rho_B r_U - \rho_B(1+\rho_B) r_R \tag{13}$$

where $\dot{p}_C^I = \mathrm{V}\rho_B r_R$.

2.4. **Quasi steady state assumption.** The only thing needed to let (11)-(13) coincide with core DEB is to assume a quasi steady state (QSSA) for (13). Here we can validate the QSSA in the limit of fast binding and unbinding and in the limit of a high free reserve to bound reserve ratio.
To see this, take $r_B \to \infty$ while $r_U/r_B = K'$. In that case the density of bound structure will always go immediately to its quasi-stationary value given some reserve density. This is clear from the above set of differential equations because the first two equations do not depend on r_U or r_B. If we would additionally have $[\mathrm{E}_F] \to [\mathrm{E}]/\alpha$ the Michaelis-Menten form would follow. We see then that the third differential equation above would have the following limit

$$\lim_{[\mathrm{E}_F]\to[\mathrm{E}]/\alpha} \lim_{r_B\to\infty} \frac{d\rho_B}{dt} = 0 \Rightarrow \lim_{[\mathrm{E}_F]\to[\mathrm{E}]/\alpha} \lim_{r_B\to\infty} \rho_B^* = \frac{[\mathrm{E}]}{[\mathrm{E}] + \alpha K'} \tag{14}$$

The catabolic rate is then also according to the DEB model, except for the fact that cell surface effects have not been taken into account and that therefore the term proportional to surface area in the catabolic rate of the core DEB model is not represented.

$$\lim_{[\mathrm{E}_F]\to[\mathrm{E}]/\alpha} \lim_{r_B\to\infty} \dot{p}_C^I = \frac{[\mathrm{E}]}{[\mathrm{E}] + \alpha K'} r_R \mathrm{V} \tag{15}$$

Since it is inconsistent to take $[\mathrm{E}_F] \to [\mathrm{E}]/\alpha$ generally, it seems only reasonable to check the quasi stationary solution of (13) more generally. We then find with $[E_F] = [E] - \rho_B$

$$\lim_{r_B\to\infty} \frac{d\rho_B}{dt} = 0 \Rightarrow \lim_{r_B\to\infty} \rho_B^* = Z([E]) - \sqrt{Z([E])^2 - [E]} \tag{16}$$

where $Z([E]) = ([E] + 1 + K')/2$. This is clearly not M-M behavior, it is however a close approximation as can be seen from the accompanying Figure 1.

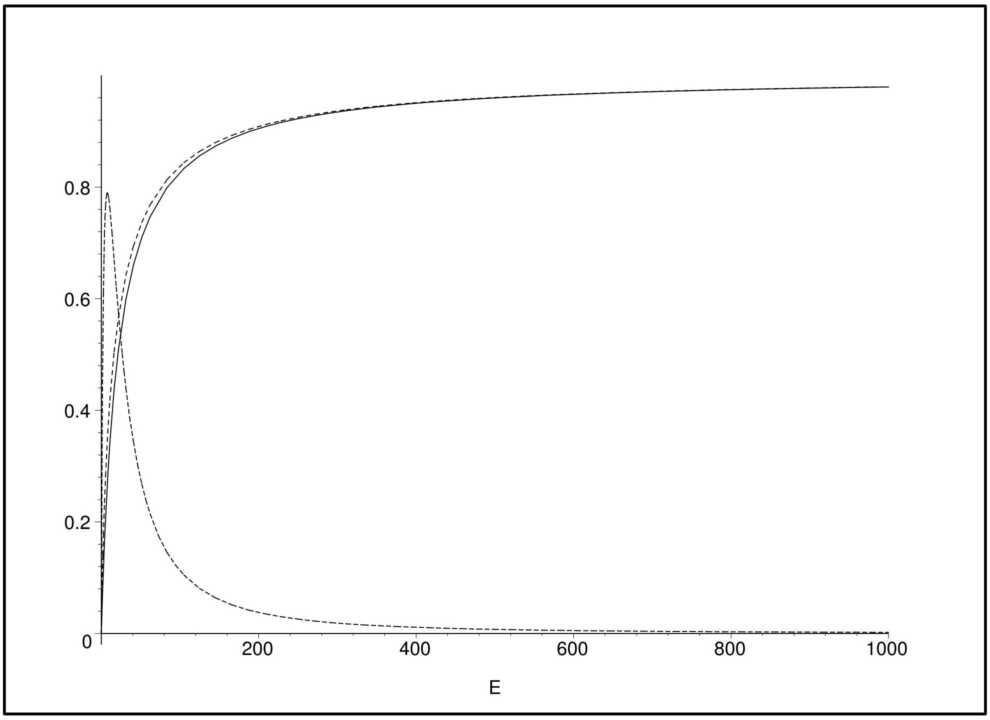

Figure 1. The solid line (——) is a normalized Michaelis-Menten function (14), the dashed line (- - - -) is the function from (16), the dashed dotted line (-.-.-.-) is 10x the difference between these plots.

We have shown that by model I we can represent core DEB theory almost completely given some approximations. It will be interesting to see however to what extent the coincidence will hold if the assumptions are relieved.

3. Model II

In this section we define a model that takes surface effect of the growth of a cell into account. In this way we make the link with DEB theory complete.

3.1. **Geometrical considerations.** In reality the structure of a cell consists of two main parts that behave differently as the cell grows: a volume part and a surface part here for convenience referred to as *interior (structure)* I and *membrane* M respectively that together make up *structure* V. The membrane of a cell is not necessarily the only thing that contributes to membrane, other structures in the cell may also grow as a surface, this should however not interfere with the current considerations. The dynamics for structure of model I will be taken as a reference for the dynamics of the plasm. For isomorphs the characteristic length L will change as $M^{1/2}$ and as $I^{1/3}$.

$$\frac{dL}{dt} \propto \frac{dM^{1/2}}{dt} \propto \frac{dI^{1/3}}{dt} \tag{17}$$

so then we derive, using the dynamics of model I for the interior

$$\frac{dM}{dt} = \frac{2}{3}\frac{M}{I}\frac{dI}{dt} = \frac{2}{3}M(\rho_B r_R - r_D) \tag{18}$$

where now $\rho_B = I_B/I$.
Thus inversely it follows that –however the membrane growth is regulated by the cell (and it certainly is)– if we assume exactly the same dynamics for the growth of the membrane as for the growth of the interior, the organism will grow isomorphically without any further regulation. On the other hand we also notice that it seems that what is called maintenance in DEB theory is missing a term accounting for maintenance of the membrane.

3.2. **The model.** A naive mesoscopic model that reproduces core DEB theory approximately would then be

$$\begin{aligned} \tfrac{d\mathrm{E}_F}{dt} = \{\dot{p}_{Am}\}f(X)M - [\mathrm{E}_F](I_F r_{BI} + M_F r_{BM}) \\ + I_B(r_{UI} + r_{DI}) + M_B(r_{UM} + r_{DM}) \quad (19) \\ \tfrac{d\mathrm{E}_B}{dt} = [\mathrm{E}_F](I_F r_{BI} + M_F r_{BM}) - I_B(r_{UI} + r_{RI} + r_{DI}) \\ - M_B(r_{UM} + r_{RM} + r_{DM}) \quad (20) \end{aligned}$$

$$\tfrac{dI_F}{dt} = I_B(r_{UI} + 2r_{RI}) - I_F([\mathrm{E}_F]r_{BI} + r_{DI}) \tag{21}$$

$$\tfrac{dI_B}{dt} = [\mathrm{E}_F]I_F r_{BI} - I_B(r_{UI} + r_{RI} + r_{DI}) \tag{22}$$

$$\tfrac{dM_F}{dt} = M_B(r_{UM} + 2r_{RM}) - M_F([\mathrm{E}_F]r_{BM} + r_{DM}) \tag{23}$$

$$\tfrac{dM_B}{dt} = [\mathrm{E}_F]M_F r_{BM} - M_B(r_{UM} + r_{RM} + r_{DM}) \tag{24}$$

where $[\mathrm{E}_F] = \mathrm{E}_F/I$.

3.3. **Reduction of the model.** Combining equations (18) and (23)+(24) we find the following restriction

$$(\rho_{BM} r_{RM} - r_{DM}) = \frac{2}{3}(\rho_{BI} r_{RI} - r_{DI}) \tag{25}$$

Since in terms of "particles" we have $\mathrm{V} = I + M$ and since we would like to have conservation of particles in terms of reserve transformed we find by adding (21)-(24) and then applying (25)

$$\frac{d\mathrm{V}}{dt} = \frac{dI}{dt} + \frac{dM}{dt} = \rho_{BI} r_{RI}(I + \frac{2}{3}M) - (I + \frac{2}{3}M)r_{DI} \tag{26}$$

For the reserve we find

$$\frac{d\mathrm{E}}{dt} = \frac{d\mathrm{E}_F}{dt} + \frac{d\mathrm{E}_B}{dt} = \dot{p}_A - r_{RI}(\rho_{BI} I + \frac{2}{3}\rho_{BM} M) \tag{27}$$

We have used here that $r_{RM} = \frac{2}{3} r_{RI}$ which follows from particle conservation.
The equations for the density of bound interior and membrane are

$$\frac{d\rho_{B\cdot}}{dt} = [\mathrm{E}_F](1 - \rho_{B\cdot})r_{B\cdot} - \rho_{B\cdot} r_{U\cdot} - \rho_{B\cdot}(1 + \rho_{B\cdot})r_{R\cdot} \tag{28}$$

3.4. **QSSA for model II.** Further simplification towards core DEB is possible under some assumptions and limits. If we –as we did for model I– take the limit of $r_{B\cdot} \to \infty$ while $r_{UI}/r_{BI} = r_{UM}/r_{BM} = K'$, thus again qualifying for the QSSA with respect to the density of bound membrane or interior, and we take again $[E_F] \to [E]/\alpha$, then the quasi stationary solution is

$$\lim_{[\mathrm{E}]\to[\mathrm{E}]/\alpha} \lim_{r_{B\cdot}\to\infty} \tfrac{1}{r_{B\cdot}} \tfrac{d\rho_{B\cdot}}{dt} = [\mathrm{E}]/\alpha(1-\rho_{B\cdot}) - K'\rho_{B\cdot} \Rightarrow \tag{29}$$

$$\rho^*_{B\cdot} = \frac{[E]}{[E]+\alpha K'} \tag{30}$$

so that $\rho^*_{BI} = \rho^*_{BM} = \rho^*_B$
We may now use that $I \to V$ and $M \to kV^{2/3}$ in the limit of $M/I \to 0$. Using this and the above limits we summarize

$$\tfrac{d\mathrm{E}}{dt} = \dot{p}_A - \dot{p}_C^{II*} \tag{31}$$

$$\tfrac{d\mathrm{V}}{dt} = \dot{p}_C^{II*} - (\mathrm{V} - \tfrac{2}{3}k\mathrm{V}^{2/3})r_D \tag{32}$$

where $\dot{p}_C^{II} = \rho^*_B r_R(\mathrm{V} + \tfrac{2}{3}k\mathrm{V}^{2/3})$.
Under the QSSA the catabolic rate of model II coincides with the catabolic rate in core DEB theory if the constants are chosen in the following way:

$$\begin{aligned} K'\alpha &= K \\ r_R &= [E_G]k_M/\kappa \quad \Rightarrow \quad \dot{p}_C^{II*} = \dot{p}_C \\ k &= \frac{3}{2}[E_G]\dot{v}/r_R\kappa \end{aligned} \tag{33}$$

The only notable difference between model II and core DEB is a surface dependent maintenance or decay rate, but if we choose $r_D = [\dot{p}_M]$ we end up with a mesoscopic model that is reasonably close to core DEB. Note that the ratio between the surface and volume dependence of the catabolic rate is the same as for the decay rate, this is a direct consequence of the fact that the organism is isomorphic (both growing and shrinking) and that only decay of particles contribute to maintenance. It would be interesting to see whether or not model II would make a good or even better fit than core DEB when confronted directly with data, and thus whether or not we should consider a slightly more elaborate model.

4. FUTURE WORK

We have constructed a simple and naive yet effective mesoscopic description that coincides at least by approximation with core DEB theory. We now have a starting point to consider more specific questions like how exactly are the assumptions made here related to the assumptions made in DEB theory. How could these assumptions be lessened, or replaced by introducing regulatory mechanisms that explain rather than assume why there is homeostasis and why the membrane grows in the right pace with the interior. Is it straightforward to model mesoscopically other parts of DEB theory, like for instance ageing. Also would it be interesting to see to what extent the ideas applied in "A Markov Model for Kinesin"

[5] can be applied to derive characteristic free energy differences of various parts of an organism. But firstly it should be checked that the above made considerations apply to multicellular organisms and non-isomorphs as well.

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