Notes for Adding Hypoxia Stress to DEBkiss Model

General concepts

* Need to add data for the four different oxygen levels: 8, 4, 3, and 2.5 mg l-1.
  + Use the actual oxygen means not the target levels.
  + The response variables are length, egg buffer, and survival over time.
* Need to add stress function to change the parameter(s) of interest for different oxygen levels.
  + Start with ones from Jager book and then change if want different shape.
  + Threshold comes from Pcrit? That doesn’t make sense because the Pcrit I measured is ~2 mg/L and the treatments at which we observed effects were all greater than that. I guess the exact threshold doesn’t matter because we have four discrete levels, so just use a threshold between the one at which effects started.
    - The length, hatch time, and survival were all effects of chronic exposure.
    - The Pcrit (RMR) is an effect of acute exposure.
    - These could have different pMoA. Maybe we can have one parameter affected at a higher threshold and one at a lower? But we don’t exactly have data for the acute threshold.
* Ideally the output would include predicted response variable levels for the existing x-values for which we have data, in addition to the AIC and NLL.

Is it added exactly the same as a toxicant?

* Jager’s BYOM manual shows how to add data for different levels of a toxicant or treatment, and how to set the initial values for those levels or a level for which you don’t have data (simulation).
* In Desforges et al (2017) they describe how a stress factor is used to affect the parameters.
  + Physiological modes of action (pMoA) – effect of toxicant on different DEB parameters. This helps us understand the metabolic process affected by the toxicant.
  + Replace a parameter with its associated stressed version.
* Toxicant Effects in DEBkiss book by Jager (section 5.2)
  + “When the damage level exceeds a threshold, the value of one or more of the primary parameters changes proportional to the amount by which damage exceeds the threshold. For survival, the affected parameter is the hazard rate, and survival will have its own threshold and proportionality (the effects strength).”
  + Hazard rate for survival effects:
    - So you multiply the effects strength (b) by the amount by which scaled damage (D) is over the threshold (z). The *i* means it can either be mass or volume specific. Units of concentration-1 time-1.
    - Can be linked to survival probability:
  + Sub-lethal effects, use linear relationship with threshold for stress level (s) with similar implementation:
    - Generally the threshold is lower than the mortality threshold.
    - Units of concentration-1.
  + The use of ‘scaled damage’ instead of ‘scaled internal concentration’ makes this a good approach for hypoxia, because there isn’t a toxicant to have a concentration of, but the more general damage approach gets around this.
  + Stress increases or decreases parameter (p) with p(1+s) or p\*max(0,1-s).
  + “For the growth process, we use the yield *yVA* as a primary parameter, which is the grammes of structure produced from 1 gramme of assimilates. Thus, a linear effect on growth costs should be implemented as *yVA*(1-s) (which is equivalent to a linear *increase* in the overheads of the growth process). We could, however, also rewrite our model to work with the growth costs: the grammes of assimilates needed to produce 1 gramme of structure, and thus with a parameter whose value is 1/*yVA*. An increase in growth costs due to stress should then be implemented as *yVA*/(1+s).”
    - In the latter way, the larger s is, the smaller yVA gets, and the larger the parameter gets (more assimilates required to produce each gram of structure). Assuming assimilation flux stays constant this should have the same effect as implementing it the first way. But if feeding can change too then this implementation could go hand in hand with increased feeding (and therefore assimilation) under hypoxia, for hatched fish only.
    - Aside from the implications for the model, the physiological mechanisms may also be an important consideration in choosing how to do this. If we think hypoxia is causing increased use of anaerobic respiration, then the overhead costs of growth could increase and thus reduce yVA directly (but this could also apply to the second approach).
  + Physiological mode of action (pMoA) a.k.a. DEB mode of action in this context.
* BYOM Walkthrough
  + State variables are external and internal concentration of toxicant, with four scenarios, and the parameters control the change in both of those – including how external concentration affects internal concentration.
  + It seems like I need to add oxygen as a state variable and keep it constant.
    - Do I need to put oxygen levels for every time point used in the other data?

There seem to be three components to attend to:

1. Adding the data for different DO levels.
   1. This involves entering the data for different scenario numbers, including weights and initial values (X0mat). For missing data use NaN.
2. Adding the stress function to alter a parameter at different DO levels.
   1. This will include telling it what the DO levels are for each scenario.
3. Getting the model to estimate parameters for all scenarios at once.
   1. Need AIC, predicted and observed data
      1. AIC wouldn’t be comparable between different DO levels because of the different data and missing data at low DO levels.
   2. Would there be different parameters for each DO level? I think we want to keep all fixed except the ones that are changed with the stress function.
   3. Alternatively, maybe I would paste in the data for each treatment separately and run the model, but only if there isn’t a way to do it all at once.

Progress so far in editing the code:

* Added data for two different oxygen levels and successfully plotted both datasets with different colors and corresponding legend labels.
* Added DO as a state variable with oxygen constant with two data points at beginning and end of time period, and added a derivative dDO=0 to keep it constant (not really sure if this is even necessary actually, but maybe it is necessary to have a continuous DO dataset for the full time period if we later need to use the DO at any given time point to control the parameter value as the other predicted data are calculated).
* Still need to:
  + Check measured mean DO levels
  + Check the sample sizes (weights) of the data types for different DO levels.
  + Add the third and fourth DO levels and the other types of data.

Check out these references from the DEBkiss book:

Physiological modes of action:

2. O. Alda Álvarez, T. Jager, E. Marco Redondo, and J. E. Kammenga. Physiological modes of action of toxic chemicals in the nematode *Acrobeloides nanus*. *Environmental Toxicology and Chemistry*, 25:3230-3237, 2006.

4. R. Ashauer and T. Jager. Physiological modes of action across species and toxicants: the key to predictive ecotoxicology. *Environmental Science-Processes & Impacts*, 20(1):48-57, 2018.

Applying stress functions:

64. T. Jager, T. Vandenbrouck, J. Baas, W. M. De Coen, and S. A. L. M. Kooijman. A biology-based approach for mixture toxicity of multiple endpoints over the life cycle. *Ecotoxicology*, 19:351-361, 2010.

65. T. Jager and E. I. Zimmer. Simplified Dynamic Energy Budget model for analysing ecotoxicity data. *Ecological Modelling*, 225:74-81, 2012.

75. S. A. L. M. Kooijman and J. J. M. Bedaux. Analysis of toxicity tests on *Daphnia* survival and reproduction. *Water Research*, 30(7):1711-1723, 1996.