Results

# Model V2 changes

Major systems were analyzed, and compared to the published *C. elegans* network.

**Neither model** is using glucose right now. Probably why the TCA is messed up. Used the directionality from the iCEL1273 elegans model, modifying 58 reactions to be reversible, and 31 to be irreversible. Doing this reduced the maximum flux, but made the model use the TCA.

* Some exceptions:
  + R02164 is irr in elegans. Ascaris has an enzyme (R01867) that runs this in reverse during metabolism in the microaerobic environment of the gut; was also set as irreversible. Before this, the model was running both reactions backwards to generate UQH2.
  + R04737/4738, 4739/4740, 4741/4170, and 4743/4744 are reversible and part of the fatty acid elongation pathways in mitochondria. In peroxisomes they should be irreversible, as part of the peroxisomal fatty acid beta oxidation. If I add this compartment, implement this.
* C15602 is quinone, a generic redox cofactor. Should be replaced by C00016, which is FAD, or NAD or NADP or ubiquinone, which are the specific ones used by eukaryotes. I think this is part of why glucose isn’t being used.
  + R01253 was set to 0. It is Wolbachia only, and will be reinstated after compartimentalization. The brugia version is R01248.
  + R01868 was modified to replace 15602/15603 with 399/390.
  + R02164 was modified to replace 15602/15603 with 399/390.

The ATP synthase (R00086) reaction was constrained in the wrong direction (it used ATP only, couldn’t produce any).

* This caused the ATP to come from GTP, UTP, ITP, acetyl adenylate, and some from succoa->succ.
* UQH2 was being produced by Complex I and R01868 (337->QH2). This comes from aspartate and the conversion of glutamine to glutamate.
* Have to compartmentalize, and be sure protons are accounted for.

Reactions I blocked:

* 1324, as it is equivalent to 1325/1900.
* 1899 & 268, as they are equivalent to 267 (irreversible, so no rael cycles), and they are not present in the elegans model.
* 281, as it is a generic version of ETC complex I.

Major import/exports:

* Water diffusion is always maxed; when unconstrained added 9/20 to flux, FVA bounds between -1300 and -3100. For now, set lower bound to -3000.
* O2 import usually maxed, but not always.
* CO2 export always maxed.
* Diphosphate import always -620.
* Phosphate export always maxed.
* Ov sometimes imports, sometimes exports ethanol. Removed import.

TCA cycle.

* Made 351, 267, 268, 709 irreversible. 643/591
* Citrate synthase (R00351) is annotated as backwards compared to biology, so L/U bounds were set to -1000/0.
  + Ov and Bm FVA went from 750/1k & 576/576 to 0.
* R00709/R00267 should be irreversible, set to 0/1000.
* After these changes, Ov & Bm flux went from 724 & 665 to 643 & 591.
  + No flux from 2-oxoglutamate to succinate, and again from fumarate to citrate.
  + No flux through 351, 621/3316/2570 (2-oxoglutarate to succinyl-coa), 405, 1082, 342.
    - There is flux through 7618, looks like through leucine degredation.
  + 26 is being produced, but then shunted somewhere else. Why? Some gets converted to 91 by R08549 (=R01197), but not much.

# Model comparison Ov vs Bm

The Bm objective function had no coefficients and produced 32 flux compared to 724 from Ov. After copying the Ov coefficients, Bm produced 665 flux.

TCA cycle has major differences.

* R00267 and R00709 both convert isocitrate into 2-oxoglutarate + CO2 + H+. The former also converts NADP+ into NADPH, while the latter converts NAD+ into NADH.
  + Ov has 1000 flux through R00267, Bm has -341. Ov has 0 flux through R00709, Bm has 1000.
  + So in this part of the cycle, Ov is producing NADPH (standard), while Bm is producing NADH and NADP+ (probably wrong).
* Bm has no flux around the TCA cycle.
  + R00342,
* Ov doesn’t seem to be using TCA properly.
  + 17 flux of fumarate (C00122) is converted to malate (C00149), but 983 is converted to succinate (C00042); 1000 succinate is converted back to fumarate. It seems like it’s using this cycle to convert hydroquinone and orotate into quinone (C15602) and S-dihydroorotate (C00337). These products are then converted back into hydroquinone and orotate. It’s a futile cycle.
  + FVA shows citrate (C00158) and oxaloacetate (C00036) are used in a max flux cycle to convert ADP & P into ATP and water. This is one of the main sources of ATP production, but the reactions involved are going the wrong way as biology.

The pentose phosphate pathway has some differences too.

* Ov has -340 through R02739, while Bm has -68. So Ov is converting more b-D-glucose-6-P to a-D-glucose-6-P. Most of the a- is produced by R00959 in both species, and both convert it to b-D-fructose-6-P, but Ov produces more overall; this excess is used to generate ATP and a-D-glucose.
  + Most of the b-D-fructose-6-P is converted to b-D-fructose-1-6-P2 (which goes into glycolysis), but some is converted into b-D-glucose-6-P (less in Bm).
* Ov has 158 through R01049, while Bm has -676; Ov produces 5-P-a-D-ribose-1-diP (AKA PRPP) + AMP, while Bm produces D-ribose-5-P + ATP.
  + PRPP feeds into purine, pyrimidine, and histidine metabolism.
  + Ov seems to use PRPP to consume adenine and guanine (minor) to produce AMP/GMP.
  + Bm seems to use PRPP to produce ATP and D-ribose-5-P.

# C. elegans model

iCEL1273 was downloaded on Feb 21 2017 from <http://wormflux.umassmed.edu/>.

# Modeling Brugia life stages

The microfilariae appears to be covered in N-acetyl-D-glucosamine (Kaushal, Simpson, Hussain, & Ottesen, 1984).

* The infective larvae and adults lacked evidence of these lectins.