Results

# Model V2 changes

Major systems were analyzed, and compared to the published *C. elegans* iCEL1273 network.

Brugia model is using half of the TCA (still no glucose). Some flux goes from oaa to akg through the cycle (producing 1 NADH), but more goes directly from oaa to akg through R00355 (producing no energy, but consuming a glutamate). All of the akg is being converted to glutamate (consuming an NADPH) through R00248.

Neither model is using glucose.

* Because C00031 is being imported, and is generic glucose. The glucose used in metabolism is either a-D-glucose or b-D-glucose. There is no conversion between them.
  + Added those conversions as ARTIFICIAL\_1 and ARTIFICIAL\_2.
* The a-D-glu-6-P is coming from a-D-glu-1-P, which is coming from starch (369), and producing amylose. INFINITE cycle here, as R02110 converts amylose back into starch for free.
  + Blocked R02110 to kill the cycle. Glycogen can still be utilized, but isn’t infinite.
* iCEL1273 has R01602, converting a-D-glu <=> b-D-glu. Probably not necessary.
* I think glucose is being used to produce pyruvate (22) and GTP (44) from phosphoenol-pyruvate (74) and GDP (35) by R00430. Then R00330 converts GTP + ADP to produce ATP and recycle GDP. It’s doing that instead of feeding into the TCA. **Why?**

**At 100 glucose**, ov is sometimes using low TCA, bm never uses the front half. At 200 glucose, ov front TCA goes down a bit, and bm now always uses front TCA.

The models were using generic cofactors. C15602/15603, C00028/30 are 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. Used the reactions in iCEL1273 as a guide.

* 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.
* R01025: replaced 28/30 with 16/1352.
* R02661, R03172: replaced 28/30 with 4253/4570.
* R03814, R03814\_1, R07063, R07933: replaced 30/28 with 999/996 (and modified coefs).
* R06519: replaced 30/28 with 5+80/6

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 cycle.

* 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.
* Additional changes:
  + R00431 was reversible in iCEL1273. Irreversible in KEGG, and produces CO2 so I set to irreversible. R00726 uses ITP instead of GTP, also set irreversible.
  + R00316 + R00236 = R00235; including ID of gene. 316 & 236 were removed.

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.
  + Reactions 575, 1397, and 1993 (all carried out by *pyr-1*) are Wolbachia-specific.
* 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 real 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.
* Ov sometimes imports, sometimes exports ethanol. Removed import.

# 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.