

## Model Equations

$$\begin{aligned} \frac{d[cp]}{dt} &= \frac{vmax1 [bc][glu][atp]}{\left(1 + \frac{[utp]}{K_{utp}}\right) (K_{atp} + [atp])(K_{bc} + [bc])(K_q + [glu])} - \frac{vmax2 [cp][asp]}{\left(1 + \frac{[utp]}{K_{utp}}\right) (K_{m2} + [cp])(K_{asp} + [asp])} - d[cp] \\ \frac{d[ca]}{dt} &= \frac{vmax2 [cp][asp]}{\left(1 + \frac{[utp]}{K_{utp}}\right) (K_{m2} + [cp])(K_{asp} + [asp])} - \frac{vmax3 [ca]}{K_{m3} + [ca]} - d[ca] \\ \frac{d[dho]}{dt} &= \frac{vmax3 [ca]}{K_{m3} + [ca]} - \frac{vmax4 [dho]}{K_{m4} + [dho]} - d[dho] \\ \frac{d[oro]}{dt} &= \frac{vmax4 [dho]}{K_{m4} + [dho]} - \frac{vmax5 [oro][prpp]}{K_{m5} + [oro][prpp]} - d[oro] \\ \frac{d[omp]}{dt} &= \frac{vmax5 [oro][prpp]}{K_{m5} + [oro][prpp]} - \frac{vmax6 [omp]}{K_{m6} + [omp]} - d[omp] \\ \frac{d[ump]}{dt} &= \frac{vmax6 [omp]}{K_{m6} + [omp]} - \frac{vmax10 [ump]}{K_{m10} + [ump]} - d[ump] \\ \frac{d[udp]}{dt} &= \frac{vmax10 [ump]}{K_{m10} + [ump]} - \frac{vmax7 [udp]}{K_{m7} + [udp]} - d[udp] \\ \frac{d[utp]}{dt} &= \frac{vmax7 [udp]}{K_{m7} + [udp]} - \frac{vmax8 [utp]}{K_{m8} + [utp]} - \frac{g_{pyr} [utp]}{K_{Mp} + [utp]} - d[utp] \\ \frac{d[ctp]}{dt} &= \frac{vmax8 [utp]}{K_{m8} + [utp]} - \frac{g_{pyr} [ctp]}{K_{Mp} + [ctp]} - d[ctp] \end{aligned}$$

**Supplemental Figure 1.** Lineage-specific dN/dS estimates for the local URA1 tree around *Saccharomyces cerevisiae*. Numbers in bold are the dN/dS values for the given branch.

**Supplemental Figure 2** Lineage-specific dN/dS estimates for the local URA2 tree around *Saccharomyces cerevisiae*. Numbers in bold are the dN/dS values for the given branch.

**Supplemental Figure 3.** Lineage-specific dN/dS estimates for the local URA3 tree around *Saccharomyces cerevisiae*. Numbers in bold are the dN/dS values for the given branch.

**Supplemental Figure 4.** Lineage-specific dN/dS estimates for the local URA4 tree around *Saccharomyces cerevisiae*. Numbers in bold are the dN/dS values for the given branch.

**Supplemental Figure 5.** Lineage-specific dN/dS estimates for the local URA5 tree around *Saccharomyces cerevisiae*. Numbers in bold are the dN/dS values for the given branch.

**Supplemental Figure 6.** Lineage-specific dN/dS estimates for the local URA10 tree around *Saccharomyces cerevisiae*. Numbers in bold are the dN/dS values for the given branch.

**Supplemental Figure 7.** Lineage-specific dN/dS estimates for the local URA6 tree around *Saccharomyces cerevisiae*. Numbers in bold are the dN/dS values for the given branch.

**Supplemental Figure 8.** Lineage-specific dN/dS estimates for the local URA7 tree around *Saccharomyces cerevisiae*. Numbers in bold are the dN/dS values for the given branch.

**Supplemental Figure 9.** Lineage-specific dN/dS estimates for the local YNK1 tree around *Saccharomyces cerevisiae*. Numbers in bold are the dN/dS values for the given branch.

**Supplemental Figure 10.** Lineage-specific dN/dS estimates for the local ATCase tree around *Saccharomyces cerevisiae*. Numbers in bold are the dN/dS values for the given branch.

**Supplemental Figure 11.** Lineage-specific dN/dS estimates for the local CPSase tree around *Saccharomyces cerevisiae*. Numbers in bold are the dN/dS values for the given branch.

**Supplemental Figure 12.** Phylogeny of the URA1 gene family. **A.** Complete phylogeny of URA1 gene family. Taxa used in dN/dS analysis are colored in dark gray. **B.** Collapsed version of the URA1 gene family. Subtree used in the dN/dS analysis is marked in gray.

**Supplemental Figure 13.** Phylogeny of the URA2 gene family. **A.** Complete phylogeny of URA2 gene family. Taxa used in dN/dS analysis are colored in dark gray. **B.** Collapsed version of the URA2 gene family. Subtree used in the dN/dS analysis is marked in gray.

**Supplemental Figure 14.** Phylogeny of the URA3 gene family. **A.** Complete phylogeny of URA3 gene family. Taxa used in dN/dS analysis are colored in dark gray. **B.** Collapsed version of the URA3 gene family. Subtree used in the dN/dS analysis is marked in gray.

**Supplemental Figure 15.** Phylogeny of the URA4 gene family. **A.** Complete phylogeny of URA4 gene family. Taxa used in dN/dS analysis are colored in dark gray. **B.** Collapsed version of the URA4 gene family. Subtree used in the dN/dS analysis is marked in gray.

**Supplemental Figure 16.** Phylogeny of the URA5 gene family. **A.** Complete phylogeny of URA5 gene family. Taxa used in dN/dS analysis are colored in dark gray. **B.** Collapsed version of the URA5 gene family. Subtree used in the dN/dS analysis is marked in gray.

**Supplemental Figure 17.** Phylogeny of the URA10 gene family. **A.** Complete phylogeny of URA10 gene family. Taxa used in dN/dS analysis are colored in dark gray. **B.** Collapsed version of the URA10 gene family. Subtree used in the dN/dS analysis is marked in gray.

**Supplemental Figure 18.** Phylogeny of the URA6 gene family. **A.** Complete phylogeny of the URA6 gene family. Taxa used in dN/dS analysis are colored in dark gray. **B.** Collapsed version of the URA6 gene family. Subtree used in the dN/dS analysis is marked in gray.

**Supplemental Figure 19.** Phylogeny of the URA7 gene family. **A.** Complete phylogeny of the URA7 gene family. Taxa used in dN/dS analysis are colored in dark gray. **B.** Collapsed version of the URA7 gene family. Subtree used in the dN/dS analysis is marked in gray.

**Supplemental Figure 20.** Phylogeny of the YNK1 gene family. **A.** Complete phylogeny of the YNK1 gene family. Taxa used in dN/dS analysis are colored in dark gray. **B.** Collapsed version of the YNK1 gene family. Subtree used in the dN/dS analysis is marked in gray.

**Supplemental Figure 21.** Phylogeny of the ATCase domain of the URA2 gene family . **A.** Complete phylogeny of the ATCase domain family. Taxa used in dN/dS analysis are colored in dark gray. **B.** Collapsed version of the ATCase domain family. Subtree used in the dN/dS analysis is marked in gray.

**Supplemental Figure 22.** Phylogeny of the CPSase domain of the URA2 gene family . **A.** Complete phylogeny of the CPSase domain family. Taxa used in dN/dS analysis are colored in dark gray. **B.** Collapsed version of the CPSase domain family. Subtree used in the dN/dS analysis is marked in gray.