Model Equations

$$\frac{d[cp]}{dt} = \frac{\text{vmax1 }[bc][glu][atp]}{\left(1+\frac{[utp]}{Kutp}\right)\left(K_{atp}+[atp]\right)\left(K_{bc}+[bc]\right)\left(K_q+[glu]\right)} - \frac{\text{vmax2 }[cp][asp]}{\left(1+\frac{[utp]}{Kutp}\right)\left(K_{m2}+[cp]\right)\left(K_{asp}+[asp]\right)} - d[cp]$$

$$\frac{d[ca]}{dt} = \frac{\text{vmax2 }[cp][asp]}{\left(1+\frac{[utp]}{Kutp}\right)\left(K_{m2}+[cp]\right)\left(K_{asp}+[asp]\right)} - \frac{\text{vmax3 }[ca]}{K_{m3}+[ca]} - d[ca]$$

$$\frac{d[dho]}{dt} = \frac{\text{vmax3 }[ca]}{K_{m3}+[ca]} - \frac{\text{vmax4 }[dho]}{K_{m4}+[dho]} - d[dho]$$

$$\frac{d[oro]}{dt} = \frac{\text{vmax4 }[dho]}{K_{m4}+[dho]} - \frac{\text{vmax5 }[oro][prpp]}{K_{m5}+[oro][prpp]} - d[oro]$$

$$\frac{d[omp]}{dt} = \frac{\text{vmax5 }[oro][prpp]}{K_{m5}+[oro][prpp]} - \frac{\text{vmax6 }[omp]}{K_{m6}+[omp]} - d[omp]$$

$$\frac{d[ump]}{dt} = \frac{\text{vmax6 }[omp]}{K_{m6}+[omp]} - \frac{\text{vmax10 }[ump]}{K_{m10}+[ump]} - d[ump]$$

$$\frac{d[udp]}{dt} = \frac{\text{vmax10 }[ump]}{K_{m10}+[ump]} - \frac{\text{vmax7 }[udp]}{K_{m7}+[udp]} - d[udp]$$

$$\frac{d[utp]}{dt} = \frac{\text{vmax7 }[udp]}{K_{m7}+[udp]} - \frac{\text{vmax8 }[utp]}{K_{m8}+[utp]} - \frac{g_{pyr}\,[utp]}{K_{Mp}+[utp]} - d[utp]$$

$$\frac{d[ctp]}{dt} = \frac{\text{vmax8 }[utp]}{K_{m8}+[utp]} - \frac{g_{pyr}\,[ctp]}{K_{Mp}+[ctp]} - d[ctp]$$

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.