Addition File for “Modular co-evolution of metabolic networks”

1. Reference organisms

Table A1  List of the 115 reference organisms applied in the computation of phylogenic profiles of enzymes in the *H. sapiens* metabolic network

| Category | Taxonomy | Organism                  |
|----------|----------|---------------------------|
| Eukaryotes | 1 | 1 | hsa | Homo sapiens (human) |
|          | 2 | 2 | ptr | Pan troglodytes (chimpanzee) |
|          | 3 | 3 | mmu | Mus musculus (mouse) |
|          | 4 | 4 | rno | Rattus norvegicus (rat) |
|          | 5 | 5 | cfa | Canis familiaris (dog) |
|          | 6 | 6 | xla | Xenopus laevis (African clawed frog) |
|          | 7 | 7 | xtr | Xenopus tropicalis (western clawed frog) |
|          | 8 | 8 | dre | Danio rerio (zebrafish) |
|          | 9 | 9 | dme | Drosophila melanogaster (fruit fly) |
|          | 10 | 10 | cel | Caenorhabditis elegans (nematode) |
|          | 11 | 11 | ath | Arabidopsis thaliana (thale cress) |
|          | 12 | 12 | sce | Saccharomyces cerevisiae |
|          | 13 | 13 | spo | Schizosaccharomyces pombe |
|          | 14 | 14 | pfa | Plasmodium falciparum |
|          | 15 | 15 | tbr | Trypanosoma brucei |
|          | 16 | 16 | ehi | Entamoeba histolytica |
| Bacteria | 15 | 17 | eco | Escherichia coli K-12 MG1655 |
|          | 18 | 18 | ecj | Escherichia coli K-12 W3110 |
|          | 19 | 19 | ece | Escherichia coli O157 EDL933 |
|          | 20 | 20 | ecs | Escherichia coli O157 Sakai |
|          | 21 | 21 | ecc | Escherichia coli CFT073 |
|          | 22 | 22 | sty | Salmonella typhi |
|          | 23 | 23 | stm | Salmonella typhimurium |
|          | 24 | 24 | ype | Yersinia pestis CO92 |
|          | 25 | 25 | ypk | Yersinia pestis KIM |
|          | 26 | 26 | sfl | Shigella flexneri |
|          | 27 | 27 | buc | Buchnera sp. APS |
|          | 28 | 28 | bas | Buchnera aphidicola Sg |
|          | 16 | 29 | hin | Haemophilus influenzae |
|          | 30 | 30 | pmu | Pasteurella multocida |
|          | 31 | 31 | xfa | Xylella fastidiosa |
|          | 32 | 32 | xcc | Xanthomonas campestris |
|          | 33 | 33 | xac | Xanthomonas axonopodis |
|          | 17 | 34 | vch | Vibrio cholerae |
|          | 18 | 35 | pae | Pseudomonas aeruginosa |
| 19 | 36 | son | Shewanella oneidensis |
| 20 | 37 | nme | Neisseria meningitidis MC58 (serogroup B) |
| 21 | 39 | rso | Ralstonia solanacearum |
| 22 | 40 | hpy | Helicobacter pylori 26695 |
| 23 | 42 | cje | Campylobacter jejuni |
| 24 | 43 | rpr | Rickettsia prowazekii |
| 25 | 45 | mlo | Mesorhizobium loti |
| 26 | 47 | atu | Agrobacterium tumefaciens C58 (UWash/Dupont) |
| 27 | 53 | bsu | Bacillus subtilis |
| 28 | 61 | lla | Lactococcus lactis |
| 29 | 70 | cac | Clostridium acetobutylicum |
| 30 | 72 | tte | Thermoanaerobacter tengcongensis |
| 31 | 73 | mge | Mycoplasma genitalium |
| 32 | 74 | mpn | Mycoplasma pneumoniae |

| 19 | 36 | nma | Neisseria meningitidis Z2491 (serogroup A) |
| 20 | 37 | nme | Neisseria meningitidis MC58 (serogroup B) |
| 21 | 39 | rso | Ralstonia solanacearum |
| 22 | 40 | hpy | Helicobacter pylori 26695 |
| 23 | 42 | cje | Campylobacter jejuni |
| 24 | 43 | rpr | Rickettsia prowazekii |
| 25 | 45 | mlo | Mesorhizobium loti |
| 26 | 47 | atu | Agrobacterium tumefaciens C58 (Cereon) |
| 27 | 53 | bsu | Bacillus subtilis |
| 28 | 61 | lla | Lactococcus lactis |
| 29 | 70 | cac | Clostridium acetobutylicum |
| 30 | 72 | tte | Thermoanaerobacter tengcongensis |
| 31 | 73 | mge | Mycoplasma genitalium |
| 32 | 74 | mpn | Mycoplasma pneumoniae |
| No. | Reference | Organism |
|-----|------------|----------|
| 75  | mpu        | Mycoplasma pulmonis |
| 76  | uur        | Ureaplasma urealyticum |
| 77  | mtu        | Mycobacterium tuberculosis H37Rv (lab strain) |
| 78  | mtc        | Mycobacterium tuberculosis CDC1551 |
| 79  | mle        | Mycobacterium leprae |
| 80  | egl        | Corynebacterium glutamicum |
| 81  | cef        | Corynebacterium efficiens |
| 82  | sco        | Streptomyces coelicolor |
| 83  | blo        | Bifidobacterium longum |
| 84  | fmu        | Fusobacterium nucleatum |
| 85  | ctr        | Chlamydia trachomatis |
| 86  | cmu        | Chlamydia muridarum |
| 87  | cpn        | Chlamydia pneumoniae CWL029 |
| 88  | cpa        | Chlamydia pneumoniae AR39 |
| 89  | cpj        | Chlamydia pneumoniae J138 |
| 90  | bbu        | Borrelia burgdorferi |
| 91  | tpa        | Treponema pallidum |
| 92  | lil        | Leptospira interrogans |
| 93  | syn        | Synechocystis sp. PCC6803 |
| 94  | tel        | Thermosynechococcus elongatus Anabaena sp. PCC7120 (Nostoc sp. PCC7120) |
| 95  | ana        | Thermotoga maritima |
| 96  | cte        | Chlorobium tepidum |
| 97  | dra        | Deinococcus radiodurans |
| 98  | aae        | Aquifex aeolicus |
| 99  | tma        | Thermotoga maritima |

Archaea

| 43  | mja        | Methanococcus jannaschii |
| 44  | mac        | Methanosarcina acetivorans |
| 45  | mth        | Methanobacterium thermoautotrophicum |
| 46  | mka        | Methanopyrus kandleri |
| 47  | afu        | Archaeoglobus fulgidus |
| 48  | hal        | Halobacterium sp. NRC-1 |
| 49  | tac        | Thermoplasma acidophilum |
| 50  | pho        | Pyrococcus horikoshii |
| 51  | ape        | Aeropyrum pernix |
| 52  | sso        | Sulfolobus solfataricus |
| 53  | sto        | Sulfolobus tokodaii |
2. Comparison the *H. sapiens* metabolic network with its random counterparts

2.1 topological null model

| Module | Inter-module degree | number of nodes |
|--------|---------------------|-----------------|
| 14     | 3                   | 27              |
| 25     | 3                   | 16              |
| 7      | 4                   | 45              |
| 13     | 7                   | 33              |
| 22     | 8                   | 35              |
| 16     | 11                  | 32              |
| 20     | 11                  | 33              |
| 19     | 14                  | 28              |
| 9      | 18                  | 39              |
| 15     | 20                  | 29              |
| 5      | 21                  | 36              |
| 23     | 22                  | 20              |
| 8      | 25                  | 34              |
| 4      | 26                  | 40              |
| 10     | 27                  | 46              |
| 1      | 28                  | 44              |
| 21     | 29                  | 36              |
| 2      | 30                  | 37              |
| 11     | 32                  | 39              |
| 17     | 33                  | 43              |
| 18     | 34                  | 37              |
| 12     | 39                  | 44              |
| 24     | 41                  | 51              |
| 6      | 52                  | 60              |
| 3      | 56                  | 64              |
2.2 biological null model

Figure A1 - Cartographic representation of the metabolic network for *H. sapiens*, in which enzymes were randomly shuffled. The topology of the network is unchanged compared with the *Homo sapiens* network, but the reactions are coupled with different enzymes.
Figure A2 Comparison of the similar extent of phylogenetic profiles for enzymes pairs within each module with that within the global random network.

(A) Average Jaccard coefficient (JC) of enzyme pairs within modules. The red column represents the global network. The modules are ordered according to their average JC in a decreasing way.

(B) Percentage of enzyme pairs within modules with JC\geq0.66 (threshold definition). The red column represents the global network. The modules are drawn in the same order as in (A).