

**Supplemental Table S2: Predicted hypoxia-induced changes in biomass composition of wild type *Mycobacterium tuberculosis* H37Rv and the  $\Delta dosR$  deletion mutant.**

Normoxic coefficients were set to be the same as the original coefficients of the corresponding metabolites in the biomass function of the *iNJ661m* metabolic network [42]. The hypoxic coefficients were predicted by integrating the metabolic network with gene expression data for the wild type strain (or the  $\Delta dosR$  deletion mutant strain) of *Mycobacterium tuberculosis* H37Rv under hypoxia [25]. Changes in the coefficients indicated an altered biomass composition of *M. tuberculosis* H37Rv upon exposure to hypoxia. “Increase” (or “Decrease”) indicated that a predicted hypoxic coefficient was greater (or smaller) than the corresponding normoxic coefficient.

| Index | Metabolite name                                   | Normoxic coefficient in biomass | Wild type                      |                           | $\Delta dosR$                  |                           | Note                                                       |
|-------|---------------------------------------------------|---------------------------------|--------------------------------|---------------------------|--------------------------------|---------------------------|------------------------------------------------------------|
|       |                                                   |                                 | Hypoxic coefficient in biomass | Change in the coefficient | Hypoxic coefficient in biomass | Change in the coefficient |                                                            |
| 1     | Acyl phosphatidylinositol mannoside               | $1.7 \times 10^{-3}$            | $5.4 \times 10^{-3}$           | Increase                  | $6.6 \times 10^{-3}$           | Increase                  | Phosphatidylinositol mannosides, cell-wall components [57] |
| 2     | Acyl phosphatidylinositol mannoside di-mannose    | $1.5 \times 10^{-3}$            | $4.7 \times 10^{-3}$           | Increase                  | $5.8 \times 10^{-3}$           | Increase                  |                                                            |
| 3     | Acyl phosphatidylinositol mannoside tri-mannose   | $1.3 \times 10^{-3}$            | $4.3 \times 10^{-3}$           | Increase                  | $5.2 \times 10^{-3}$           | Increase                  |                                                            |
| 4     | Acyl phosphatidylinositol mannoside tetra-mannose | $1.2 \times 10^{-3}$            | $3.9 \times 10^{-3}$           | Increase                  | $4.7 \times 10^{-3}$           | Increase                  |                                                            |
| 5     | Di-acyl phosphatidylinositol mannoside di-mannose | $1.3 \times 10^{-3}$            | $4.1 \times 10^{-3}$           | Increase                  | $5.0 \times 10^{-3}$           | Increase                  |                                                            |
| 6     | Phosphatidylinositol mannoside                    | $2.1 \times 10^{-3}$            | $6.6 \times 10^{-3}$           | Increase                  | $8.1 \times 10^{-3}$           | Increase                  |                                                            |
| 7     | Phosphatidylinositol mannoside di-mannose         | $1.8 \times 10^{-3}$            | $5.7 \times 10^{-3}$           | Increase                  | $7.0 \times 10^{-3}$           | Increase                  |                                                            |
| 8     | Phosphatidylinositol mannoside tri-mannose        | $1.6 \times 10^{-3}$            | $5.0 \times 10^{-3}$           | Increase                  | $6.1 \times 10^{-3}$           | Increase                  |                                                            |
| 9     | Phosphatidylinositol mannoside tetra-mannose      | $1.4 \times 10^{-3}$            | $4.5 \times 10^{-3}$           | Increase                  | $5.5 \times 10^{-3}$           | Increase                  |                                                            |
| 10    | Phosphatidylinositol mannoside penta-mannose      | $1.3 \times 10^{-3}$            | $4.1 \times 10^{-3}$           | Increase                  | $4.9 \times 10^{-3}$           | Increase                  |                                                            |
| 11    | Phosphatidylinositol mannoside hexa-mannose       | $1.2 \times 10^{-3}$            | $3.7 \times 10^{-3}$           | Increase                  | $4.5 \times 10^{-3}$           | Increase                  |                                                            |

|    |                                                                                                                  |                      |                      |          |                      |          |                                                              |
|----|------------------------------------------------------------------------------------------------------------------|----------------------|----------------------|----------|----------------------|----------|--------------------------------------------------------------|
| 12 | Undecaprenyl-diphospho-N-acetylmuramoyl-N-acetylglucosamine-L-alanyl-D-glutamyl-L-lysyl-D-alanyl-D-alanine       | $1.0 \times 10^{-3}$ | $2.1 \times 10^{-3}$ | Increase | $2.4 \times 10^{-3}$ | Increase | Precursors of peptidoglycan, a cell-wall component [56]      |
| 13 | Undecaprenyl-diphospho-N-acetylmuramoyl-N-acetylglucosamine-L-alanyl-gamma-D-glutamyl-L-lysyl-D-alanyl-D-alanine | $1.0 \times 10^{-3}$ | $2.1 \times 10^{-3}$ | Increase | $2.4 \times 10^{-3}$ | Increase |                                                              |
| 14 | Undecaprenyl-diphospho-N-acetylmuramoyl-N-acetylglucosamine-L-ala-D-glu-meso-2-6-diaminopimeloyl-D-ala-D-ala     | $9.9 \times 10^{-4}$ | $2.1 \times 10^{-3}$ | Increase | $2.4 \times 10^{-3}$ | Increase |                                                              |
| 15 | Undecaprenyl-diphospho-N-glycolylmuramoyl-N-acetylglucosamine-L-ala-D-glu-meso-2-6-diaminopimeloyl-D-ala-D-ala   | $9.8 \times 10^{-4}$ | $2.1 \times 10^{-3}$ | Increase | $2.3 \times 10^{-3}$ | Increase |                                                              |
| 16 | Peptidoglycan subunit1                                                                                           | $1.9 \times 10^{-2}$ | $4.0 \times 10^{-2}$ | Increase | $4.5 \times 10^{-2}$ | Increase |                                                              |
| 17 | Peptidoglycan subunit2                                                                                           | $1.9 \times 10^{-2}$ | $4.0 \times 10^{-2}$ | Increase | $4.5 \times 10^{-2}$ | Increase |                                                              |
| 18 | Keto mycolate (2 cyclopropanated rings)                                                                          | $3.3 \times 10^{-3}$ | $8.2 \times 10^{-3}$ | Increase | $1.1 \times 10^{-2}$ | Increase | Mycolates and related derivatives, cell-wall components [56] |
| 19 | Keto mycolate (1 cyclopropanated ring)                                                                           | $3.3 \times 10^{-3}$ | $8.1 \times 10^{-3}$ | Increase | $5.0 \times 10^{-7}$ | Decrease |                                                              |
| 20 | Methoxy mycolate (1 cyclopropanated ring)                                                                        | $3.4 \times 10^{-3}$ | $8.3 \times 10^{-3}$ | Increase | $5.0 \times 10^{-7}$ | Decrease |                                                              |
| 21 | Mycolate (2 cyclopropanated rings)                                                                               | $1.1 \times 10^{-2}$ | $2.7 \times 10^{-2}$ | Increase | $3.7 \times 10^{-2}$ | Increase |                                                              |
| 22 | Tetramycolyl hexaarabinoside 1                                                                                   | $1.1 \times 10^{-3}$ | $2.7 \times 10^{-3}$ | Increase | $3.7 \times 10^{-3}$ | Increase |                                                              |
| 23 | Tetramycolyl hexaarabinoside 2                                                                                   | $1.1 \times 10^{-3}$ | $2.7 \times 10^{-3}$ | Increase | $3.7 \times 10^{-3}$ | Increase |                                                              |
| 24 | Tetramycolyl hexaarabinoside 3                                                                                   | $1.1 \times 10^{-3}$ | $2.7 \times 10^{-3}$ | Increase | $3.7 \times 10^{-3}$ | Increase |                                                              |
| 25 | Tetramycolyl hexaarabinoside 4                                                                                   | $1.1 \times 10^{-3}$ | $2.7 \times 10^{-3}$ | Increase | $1.3 \times 10^{-3}$ | Increase |                                                              |

|    |                                                    |                      |                      |          |                      |           |             |
|----|----------------------------------------------------|----------------------|----------------------|----------|----------------------|-----------|-------------|
| 26 | Adenosine monophosphate (AMP)                      | $1.4 \times 10^{-1}$ | $1.8 \times 10^{-1}$ | Increase | $1.4 \times 10^{-1}$ | No change | Nucleotides |
| 27 | Guanosine monophosphate (GMP)                      | $2.4 \times 10^{-1}$ | $3.1 \times 10^{-1}$ | Increase | $3.2 \times 10^{-1}$ | Increase  |             |
| 28 | Deoxyadenosine monophosphate (dAMP)                | $3.5 \times 10^{-3}$ | $6.1 \times 10^{-3}$ | Increase | $3.5 \times 10^{-3}$ | No change |             |
| 29 | Deoxyguanosine monophosphate (dGMP)                | $6.7 \times 10^{-3}$ | $8.5 \times 10^{-3}$ | Increase | $8.8 \times 10^{-3}$ | Increase  |             |
| 30 | Deoxythymidine monophosphate (dTMP)                | $3.7 \times 10^{-3}$ | $6.4 \times 10^{-3}$ | Increase | $3.7 \times 10^{-3}$ | No change |             |
| 31 | L-Cysteine                                         | $2.2 \times 10^{-2}$ | $1.6 \times 10^{-2}$ | Decrease | $2.2 \times 10^{-2}$ | No change | Amino acids |
| 32 | Glycine                                            | $3.4 \times 10^{-1}$ | $5.0 \times 10^{-7}$ | Decrease | $5.0 \times 10^{-7}$ | Decrease  |             |
| 33 | L-Methionine                                       | $3.5 \times 10^{-2}$ | $2.5 \times 10^{-2}$ | Decrease | $3.5 \times 10^{-2}$ | No change |             |
| 34 | L-Phenylalanine                                    | $4.8 \times 10^{-2}$ | $2.2 \times 10^{-2}$ | Decrease | $2.0 \times 10^{-2}$ | Decrease  |             |
| 35 | L-Serine                                           | $1.4 \times 10^{-1}$ | $1.0 \times 10^{-1}$ | Decrease | $1.4 \times 10^{-1}$ | No change |             |
| 36 | L-Tryptophan                                       | $2.0 \times 10^{-2}$ | $1.5 \times 10^{-2}$ | Decrease | $2.0 \times 10^{-2}$ | No change |             |
| 37 | L-Tyrosine                                         | $3.2 \times 10^{-2}$ | $1.4 \times 10^{-2}$ | Decrease | $1.3 \times 10^{-2}$ | Decrease  | Cofactors   |
| 38 | 5-6-7-8-Tetrahydrofolate                           | $1.0 \times 10^{-6}$ | $1.8 \times 10^{-6}$ | Increase | $2.3 \times 10^{-6}$ | Increase  |             |
| 39 | 7-8-Dihydrofolate                                  | $1.0 \times 10^{-6}$ | $1.8 \times 10^{-6}$ | Increase | $2.3 \times 10^{-6}$ | Increase  |             |
| 40 | Menaquinol-8                                       | $1.0 \times 10^{-6}$ | $1.9 \times 10^{-6}$ | Increase | $1.0 \times 10^{-6}$ | No change |             |
| 41 | Nicotinamide adenine dinucleotide (NAD)            | $1.0 \times 10^{-6}$ | $2.8 \times 10^{-6}$ | Increase | $3.1 \times 10^{-6}$ | Increase  |             |
| 42 | Nicotinamide adenine dinucleotide phosphate (NADP) | $1.0 \times 10^{-6}$ | $2.8 \times 10^{-6}$ | Increase | $3.1 \times 10^{-6}$ | Increase  |             |
| 43 | Quinolate                                          | $1.0 \times 10^{-6}$ | $2.8 \times 10^{-6}$ | Increase | $3.1 \times 10^{-6}$ | Increase  |             |
| 44 | Protoheme                                          | $1.0 \times 10^{-6}$ | $2.5 \times 10^{-6}$ | Increase | $3.2 \times 10^{-6}$ | Increase  |             |
| 45 | Thiamin                                            | $1.0 \times 10^{-6}$ | $1.9 \times 10^{-6}$ | Increase | $2.3 \times 10^{-6}$ | Increase  |             |
| 46 | Hydroxymethylbilane                                | $1.0 \times 10^{-6}$ | $1.9 \times 10^{-6}$ | Increase | $2.6 \times 10^{-6}$ | Increase  |             |
| 47 | Flavin mononucleotide                              | $1.0 \times 10^{-6}$ | $1.3 \times 10^{-6}$ | Increase | $1.3 \times 10^{-6}$ | Increase  |             |
| 48 | Riboflavin                                         | $1.0 \times 10^{-6}$ | $1.3 \times 10^{-6}$ | Increase | $1.3 \times 10^{-6}$ | Increase  |             |
| 49 | Pantetheine 4'-phosphate                           | $1.0 \times 10^{-6}$ | $7.2 \times 10^{-7}$ | Decrease | $1.0 \times 10^{-6}$ | No change |             |

|    |                                                    |                      |                      |           |                      |           |       |
|----|----------------------------------------------------|----------------------|----------------------|-----------|----------------------|-----------|-------|
| 50 | Iron-III-chelated carboxymycobactin-T              | $1.5 \times 10^{-3}$ | $1.0 \times 10^{-3}$ | Decrease  | $1.5 \times 10^{-3}$ | No change | Other |
| 51 | Phenolic glycolipid                                | $1.2 \times 10^{-3}$ | $1.2 \times 10^{-3}$ | No change | $6.6 \times 10^{-4}$ | Decrease  |       |
| 52 | Phosphatidylethanolamine (dihexadecanoyl, n-C16:0) | $4.1 \times 10^{-3}$ | $2.9 \times 10^{-3}$ | Decrease  | $4.1 \times 10^{-3}$ | No change |       |
| 53 | Phenol phthiocerol dimycocerosate                  | $2.6 \times 10^{-4}$ | $2.6 \times 10^{-4}$ | No change | $1.5 \times 10^{-4}$ | Decrease  |       |