**Table 1.** Comparison of methods for transcription data integration

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Name** | **Year** | **Returns a context -specific model** | **Thresholding** | **Gene mapping** | **Data Requirements** | **Is maintained nowadays** | **Availability in third party software** |
| Akesson | 2003 | No | Yes,  one user-specified threshold | Not found | A genome-scale metabolic network reconstruction. | No | Not found |
| Gene Inactivity Moderated by Metabolism  and Expression (GIMME) | 2008 | Yes | Yes,  one user-specified threshold | Expression data has to be mapped to reactions before calling the algorithm, can be done using Cobra Toolbox pre-processing functions | 1. A genome-scale metabolic network reconstruction, 2. specified objective function, 3. one threshold, 4. one gene expression data set, 5. calculated reaction expression levels (gene mapping) | Yes | MATLAB,  Cobra Toolbox |
| Integrative metabolic analysis  tool (iMAT) | 2008 | Yes | Yes,  two user-specified thresholds (lower threshold and upper threshold) | Expression data has to be mapped to reactions before calling the algorithm, can be done using Cobra Toolbox pre-processing functions | 1. A genome-scale metabolic network reconstruction, 2. two specified thresholds, 3. one expression data set, 4. calculated reaction expression levels (gene mapping) | Yes | MATLAB,  Cobra Toolbox |
| E-Flux | 2009 | Flux distribution only | Yes,  one user-specified threshold | Not found | 1. A genome-scale metabolic network reconstruction, 2. a function to convert expression levels into an upper bound on fluxes, 3. gene expression data, 4. threshold | Not found | Not found |
| Probabilistic regulation of metabolism  (PROM) | 2010 | Flux distribution only | Yes,  one predefined low threshold (default: 33rd percentile) | Not found | 1. A genome-scale metabolic network reconstruction, 2. a range of expression data from various environmental and genetic perturbations, 3. transcriptional regulatory network | Not found | Not found |
| Toolbox for Integrating Genome-scale Metabolism, Expression, and Regulation (TIGER) | 2011 | Yes | Facilitated GIMME, iMAT and MADE methods | Yes,  converting GPR associations into mixed integer linear program (MILP) | 1. A genome-scale metabolic network reconstruction, 2. gene expression data, 3. transcriptional regulatory network | Not found | Not found |
| Metabolic Adjustment by Differential Expression (MADE) | 2011 | Flux distribution only | No | Not found | 1. A genome-scale metabolic network reconstruction, 2. two or more gene expression data sets 3. a mixed-integer linear program solver | No | Linux / Windows/ MacOsX  MATLAB (requires a mixed-integer linear program solver)  (The most recent version of MADE, along with other tools for integrating expression data, is available as part of the TIGER software package.) |
| Integrative Network Inference for Tissues  algorithm (INIT) | 2012 | Yes | Yes,  optional minimum flux threshold for expressed reactions (default 1e-8) and positive or negative weights for each reaction | Expression data has to be mapped to reactions before calling the algorithm, can be done using Cobra Toolbox pre-processing functions | 1. A genome-scale metabolic network reconstruction, 2. gene expression data | Yes | MATLAB,  Cobra Toolbox |
| Lee–12 | 2012 | Flux distribution only | Not found | Not found | 1. A genome-scale metabolic network reconstruction, 2. gene expression data | Not found | Cobra Toolbox (MATLAB) |
| Fang–12 | 2012 | Flux distribution only | Not found | Not found | Not found | Not found | Not found |
| RELATive CHange (RELATCH) | 2012 | Flux distribution only | Not found | Not found | 1. Gene expression data, 2. fluxomic data from a reference state | Not found | Not found |
| Temporal Expression-based Analysis of Metabolism (TEAM) | 2012 | Flux distribution only | Yes,  threshold determination using background M3D data set | Not found | 1. Initial media composition data, 2. temporal gene expression data 3. temporal biomass data | Accessible but only for microarray experiments | Not found |
| Gene-expression FBA (GX–FBA) | 2012 | Flux distribution only | Not found | Not found | 1. Not found | Not found | Not found |
| metabolic Context-specificity Assessed by Deterministic Reaction Evaluation (mCADRE) | 2012 | Yes | Yes,  uses a core set of reactions that should be active based on gene expression evidence and a sensitivity parameter: ratio cutoff | Mapped protein staining data to reactions according to gene-reaction associations and set a reaction score | 1. A genome-scale metabolic network reconstruction, 2. gene expression data | Yes,  code is open source | MATLAB,  Cobra Toolbox |
| Transcriptional regulated flux balance analysis (TRFBA) | 2016 | Limits upper bounds of reactions and predicts growth rate | No | Yes | 1. A genome-scale metabolic network reconstruction, 2. set of expression data for various perturbations, 3. transcriptional regulatory network | Yes,  code is open source | MATLAB,  Cobra Toolbox |
| ΔFBA (deltaFBA) | 2021 | Yes | Yes,  one global threshold | Using AND/OR = MIN/MAX GPR rule | 1. A genome-scale metabolic network reconstruction, 2. gene expression data from two different conditions, 3. threshold | Yes | MATLAB,  Cobra Toolbox |
| IgemRNA | 2021 | Yes | Yes,  possible thresholds:   1. Global T1 (GT1), 2. Local T1 (LT1), 3. Local T2 (LT2) | Included, possible options:   1. Only irreversible reactions, 2. All reactions, 3. Growth not affecting gene deletion only, 4. Meet minimum growth requirements, 5. AND/OR = MIN/MAX, 6. AND/OR = MIN/SUM, 7. AND/OR = GM/MAX, 8. AND/OR = GM/SUM | 1. A genome-scale metabolic network reconstruction, 2. gene expression data, 3. external metabolite uptake data (optional), 4. threshold/-s | Yes | MATLAB,  Cobra Toolbox |