Background: Genome-scale models of metabolism and macromolecular expression (ME) significantly expand the scope and predictive capabilities of constraint-based modeling. ME models present considerable computational challenges: they are much (>30 times) larger than corresponding metabolic reconstructions (M models), are multiscale, and growth maximization is a nonlinear programming (NLP) problem, mainly due to macromolecule dilution constraints. Results: Here, we address these computational challenges. We develop a fast and numerically reliable solution method for growth maximization in ME models using a quad-precision NLP solver (Quad MINOS). Our method was up to 45% faster than binary search for six significant digits in growth rate. We also develop a fast, quad-precision flux variability analysis that is accelerated (up to 60× speedup) via solver warm-starts. Finally, we employ the tools developed to investigate growth-coupled succinate overproduction, accounting for proteome constraints. Conclusions: Just as genome-scale metabolic reconstructions have become an invaluable tool for computational and systems biologists, we anticipate that these fast and numerically reliable ME solution methods will accelerate the wide-spread adoption of ME models for researchers in these fields. Electronic supplementary material The online version of this article (doi:10.1186/s12859-016-1240-1) contains supplementary material, which is available to authorized users.

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