

CHRR: Coordinate hit-and-run with rounding for uniform sampling of metabolic networks

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Project Goals: Development of a framework for mass conserved elementary kinetic modelling of metabolic networks [1, 2, 3, 4, 5]. This collaborative project was motivated by a need for data to constrain and validate metabolic models. Sampling algorithms have demonstrated applications in measurement and estimation of kinetic parameters, steady state fluxes and metabolite concentrations for biochemical systems [6, 7, 8].

In constraint-based modelling, physicochemical and biochemical constraints define a set of feasible states of a biochemical network. Steady state mass conservation and limits on substrate uptake constraints are specified by a set of linear equalities and inequalities that define a polyhedral convex set of feasible flux vectors. Uniform sampling of this set provides an unbiased characterisation of the metabolic capabilities of a biochemical network [9]. However, reliable uniform sampling of genome-scale biochemical networks is challenging due to their high dimensionality and inherent anisotropy. Here, we apply a new sampling algorithm, coordinate hit-and-run with rounding (CHRR) [?], to metabolic networks of increasing dimensionality. This algorithm is based upon the provably efficient hit-and-run random walk [10] and crucially, it uses a preprocessing step to round the anisotropic flux set. CHRR provably converges to a uniform stationary sampling distribution and does so several times faster than a popular artificial centering hit-and-run (ACHR) algorithm [11]. We demonstrate the effects of improved convergence rate on predictions of the metabolic capabilities of *Bacillus Subtilis* [12].

References

- [1] Sun Y, Fleming RM, Thiele I, Saunders MA (2013) Robust flux balance analysis of multiscale biochemical reaction networks. *BMC Bioinformatics* 14: 240.
- [2] Noor E, Haraldsdóttir HS, Milo R, Fleming RMT (2013) Consistent Estimation of Gibbs Energy Using Component Contributions. *PLoS Comput Biol* 9: e1003098.
- [3] Artacho FJA, Fleming RMT (2014) Globally convergent algorithms for finding zeros of duplomonotone mappings. *Optimization Letters* : 1–16.
- [4] Artacho FJA, Fleming RMT, Vuong PT (2015) Accelerating the DC algorithm for smooth functions. arXiv:150707375 [math, q-bio] .
- [5] Haraldsdóttir HS, Fleming RMT (2016) Identification of Conserved Moieties in Metabolic Networks by Graph Theoretical Analysis of Atom Transition Networks. *PLOS Computational Biology* 12: e1004999.
- [6] Yang L, Mahadevan R, Cluett W (2010) Designing experiments from noisy metabolomics data to refine constraint-based models. In: *American Control Conference (ACC)*, 2010. pp. 5143–5148. doi:10.1109/ACC.2010.5530678.
- [7] Schellenberger J, Zielinski DC, Choi W, Madireddi S, Portnoy V, et al. (2012) Predicting outcomes of steady-state ¹³C isotope tracing experiments using Monte Carlo sampling. *BMC systems biology* 6: 9.
- [8] Khodayari A, Zomorodi AR, Liao JC, Maranas CD (2014) A kinetic model of *Escherichia coli* core metabolism satisfying multiple sets of mutant flux data. *Metabolic Engineering* 25: 50–62.
- [9] Lewis NE, Nagarajan H, Palsson BO (2012) Constraining the metabolic genotype–phenotype relationship using a phylogeny of in silico methods. *Nature Reviews Microbiology* .
- [10] Lovasz L, Vempala S (2006) Hit-and-run from a corner. In: *SIAM journal on computing*. Society for Industrial and Applied Mathematics, volume 35, pp. 985–1005.
- [11] Schellenberger J, Que R, Fleming RMT, Thiele I, Orth JD, et al. (2011) Quantitative prediction of cellular metabolism with constraint-based models: the COBRA Toolbox v2.0. *Nature Protocols* 6: 1290–1307.
- [12] Oh YK, Palsson BO, Park SM, Schilling CH, Mahadevan R (2007) Genome-scale reconstruction of metabolic network in *Bacillus subtilis* based on high-throughput phenotyping and gene essentiality data. *The Journal of Biological Chemistry* 282: 28791–28799.

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