Current and future applications of sampling algorithms in modelling biochemical networks

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Sampling Algorithms and Geometries on Probability Distributions
Simons Insitute for the Theory of Computing
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Outline

- Constraint-based modelling of biochemical networks

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Notation

- Unless specified otherwise, all variables are real valued.
- Householder notation:
  - A, matrix; b, column vector; b_i is the i^{th} entry in a column vector
  - Ω, set; ω, scalar.
  - $\phi(x)$ is a scalar valued function of a vector variable
  - $f(x)$ is a vector valued function of a vector variable
- I is an identity matrix
- $\mathbf{1}$ is a vector of ones
- $[A, B]$ horizontal concatenation of two matrices
- $\log(x)$ is the component-wise logarithm of each element

Generic versus mechanistic modelling

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  - Mathematical modelling approaches that do not satisfy any mechanistic principles
    - e.g. network inference with no limitation on the class of network topology being inferred

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- **Mechanistic modelling**
  - Mathematical model that satisfy certain mechanistic principles
    - e.g. network inference where the inferred biochemical network topology must satisfy mass conservation

Main mechanistic modelling approaches

- **Differential equation based modelling**
  - input: biochemical network topology, uniquely specified initial conditions and parameters
  - output: unique temporal trajectory

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- **Differential equation based modelling**
  - input: biochemical network topology, uniquely specified initial conditions and parameters
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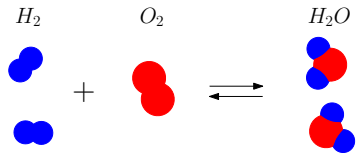
- **Constraint-based modelling**
  - input: biochemical network topology, non-unique initial conditions and parameters
  - output: non-unique set of temporal trajectories

A reversible elementary reaction



- An example elementary reaction
  - c_1 c_2 and c_3 denote the concentration of molecular species H_2, O_2 and H_2O respectively
- **Chemically** all reactions are reversible in principal, but in practice only one direction may be **biochemically** feasible.

Dynamics under elementary rection kinetics

$$2\underbrace{H_2}_{c_1} + \underbrace{O_2}_{c_2} \rightleftharpoons 2\underbrace{H_2O}_{c_3}$$

- Assuming elementary kinetics, the forward and reverse elementary rate functions are $v_f(c) := k_f c_1^2 c_2$ and $v_r(c) := k_r c_3^2$, where k_f,k_r are (elementary) kinetic parameters.
- The dynamical equations are

$$\begin{aligned}
\frac{dc_1}{dt} &= -2k_f c_1^2 c_2 + 2k_r c_3^2 \\
\frac{dc_2}{dt} &= -k_f c_1^2 c_2 + k_r c_3^2 \\
\frac{dc_3}{dt} &= -2k_r c_3^2 + 2k_f c_1^2 c_2
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- Let $N := \begin{bmatrix} -2 \\ -1 \\ 2 \end{bmatrix} \in \mathbb{Z}^{m \times n}$ denote a **stoichiometric matrix**, then given k_f,k_r we have

$$\frac{dc}{dt} = N(v_f(c) - v_r(c))$$

- One approach is to define $v(c) := v_f(c) - v_r(c)$ as some composite of many elementary reactions.

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- Correct representation of known chemical rate laws
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- Currently computationally intractable at genome-scale (high dimensional systems)

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  - Physicochemical constraints, e.g., mass conservation
  - Biochemical constraints, e.g., vitamin C is essential for human but not murine metabolism
- Underdetermined systems of equations –> Non-unique predictions

Mass conservation and steady-state

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- Instead, we assume that the set of feasible steady states is defined implicitly by

$$Nv = 0$$

where $v \in \mathbb{R}^n$ is a variable vector of net reaction rates (*fluxes*) and $N \in \mathbb{Z}^{m \times n}$ is a given stoichiometric matrix, typically $m < n < \operatorname{rank}(N)$.

Flux balance analysis

- A prototypical constraint-based modelling approach (Orth, J.et. al. (2010) Nat Biotech 28, 245–248)

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- Hypothesise a particular linear objective coefficient vector $d \in \mathbb{R}^n$, then obtain bounds on net reaction rates $l, u \in \mathbb{R}^n$ from, e.g., thermochemical data, then

$$\begin{aligned} \underset{v \in \mathbb{R}^n}{\text{minimise}} \quad & d^T v \\ \text{s.t.} \quad & Nv = 0 \\ & l \leq v \leq u \end{aligned} \tag{FBA}$$

where $N \in \mathbb{Z}^{m \times n}$ is a stoichiometric matrix, typically $m < n < \text{rank}(N)$.

Advantages of flux balance analysis

- Given a linear objective coefficient vector $c \in \mathbb{R}^n$, a stoichiometric matrix $N \in \mathbb{Z}^{m \times n}$ and bounds on net reaction rates $l, u \in \mathbb{R}^n$

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- Convex (linear) optimisation problem
  - efficient optimisation software
- Applicable to genome-scale models (high dimensional)
- Methodology is accessible to a broad user base
  - wide variety of variations and applications

A disadvantage of flux balance analysis

- We must first hypothesise a particular biochemical objective, i.e., $d \in \mathbb{R}^n$ in

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- It is unknown what the biochemical objective function is for many systems

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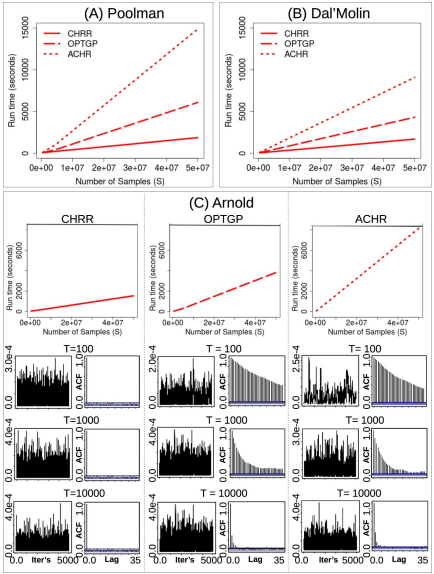

- Herrmann, H.A., et al. Flux sampling is a powerful tool to study metabolism under changing environmental conditions. npj Syst Biol Appl 5, 32 (2019).
- **CHRR**: coordinate hit-and-run with rounding (MATLAB, Haraldsdottir, H. S., et al. Bioinformatics 33, 1741–1743 (2017))
- **OPTGP**: optimized general parallel sampler (Python; Megchelenbrink, W., et al. PLoS ONE 9, e86587 (2014).)
- **ACHR**: artificially centered hit-and-run (MATLAB, Python, Kaufman, D. E. et al. Oper. Res. 46, 1 (1998).)

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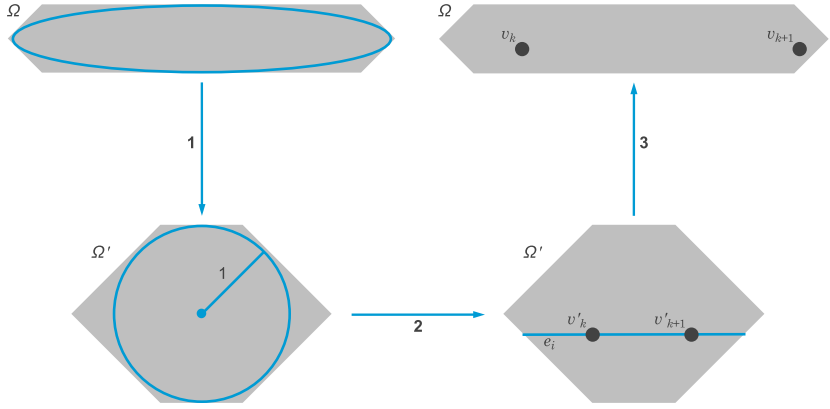
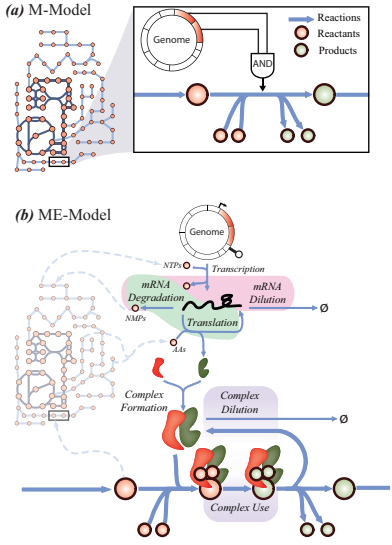


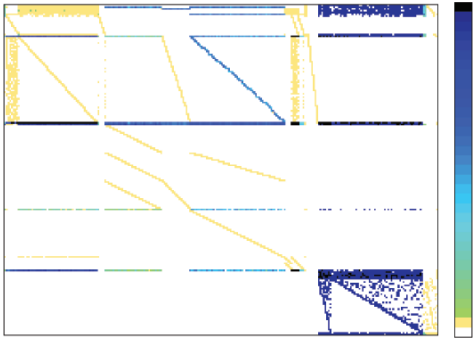
- Haraldsdóttir, H. S., Cousins, B., Thiele, I., Fleming, R. M. T. & Vempala, S. Bioinformatics 33, 1741–1743 (2017).
- Laddha, A. & Vempala, S. S. Convergence of Gibbs Sampling: Coordinate Hit-And-Run Mixes Fast. 12 (2021).
- Aditi Laddha, Algorithms for Sampling Convex Bodies, Simons Institute Workshop on Sampling Algorithms and Geometries on Probability Distributions, 2021

Sampling challenge 1: anisotropy



- Multiscale constraint-based models
- Examples
  - **M**etabolism ± integration with Macromolecular **E**xpression
  - Macro & micronutrients
  - Organ & cellular scales

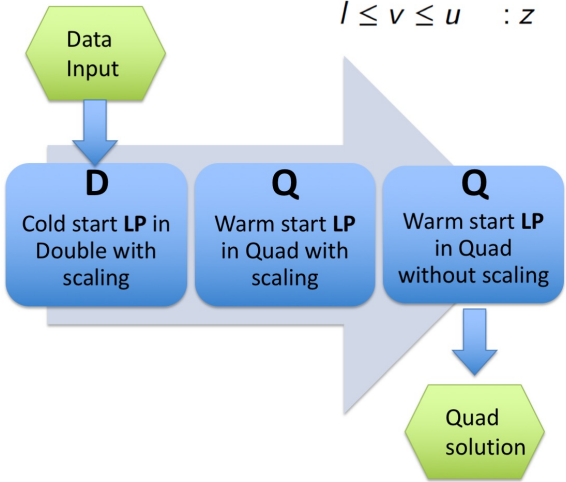
A multiscale stoichiometric matrix



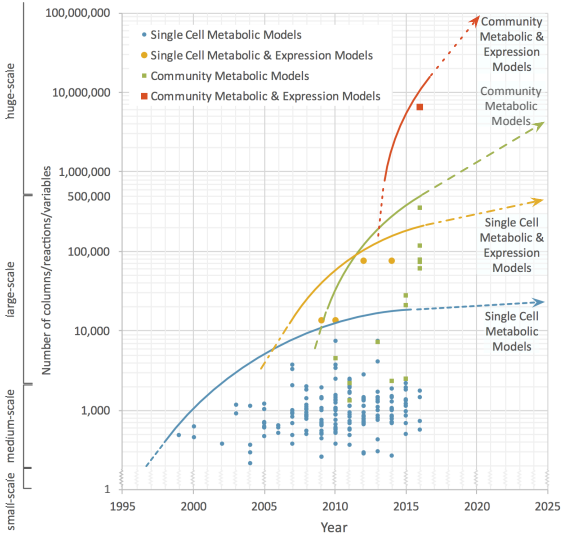
- **Stoichiometric matrix**, $\dim(N) = 60{,}000 \times 80{,}000$, of an integrated metabolic and macromolecular expression model in E. coli (Thiele et. al. 2012).
- **Coefficients** are sparse, but spread over 5 orders of magnitude.
- **Colorbar**: tiny absolute values are light orange, large magnitudes are black. In the midrange, the median of log10 of the nonzero values, 1 one standard deviation, range from light green to deep blue.
- Flux bounds are also spread over multiple orders of magnitude (not shown)

Adapting to anisotropy with novel linear optimisation methods

$$\underset{v \in \mathbb{R}^n}{\text{minimise}} \quad d^T v$$
$$\text{s.t.} \quad Nv = b \quad : y$$
$$l \leq v \leq u \quad : z$$

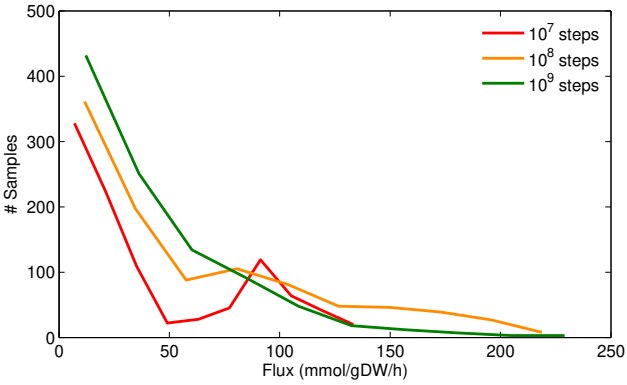


Sampling challenge 2: dimensionality



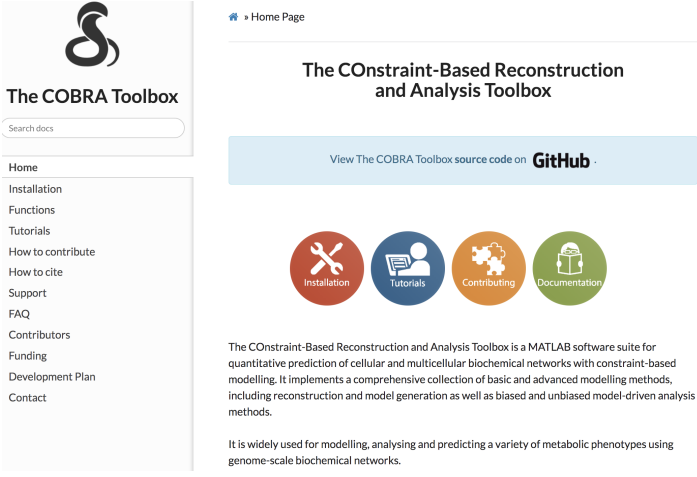
- Models will continue to grow in size

Sampling challenge 3: convergence criteria



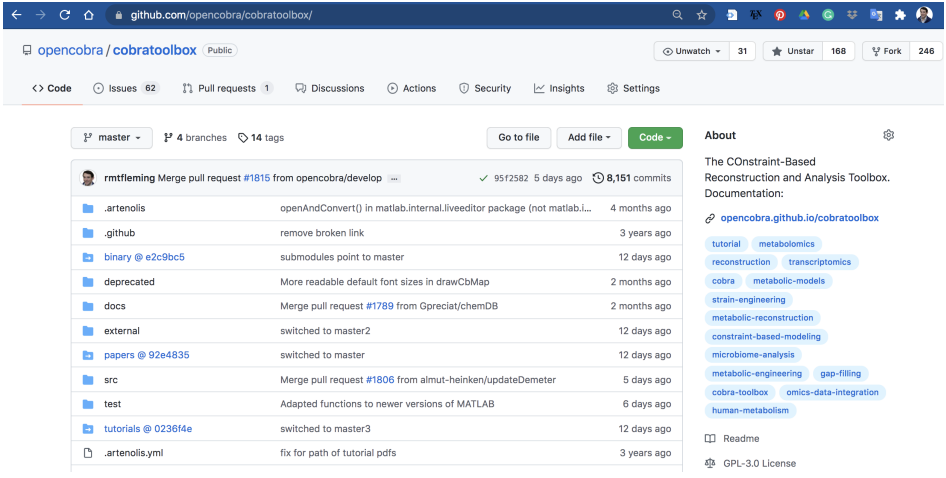
- **Convergence to a stationary sampling distribution, but when is it uniform?**
- Pre- (red and orange) and post- (green) convergence margninal sampling distributions of thioredoxin reductace flux samples obtained with CHRR in a constraint-based model of human metabolism (Recon 2, $\dim(\Omega) = 2{,}430$).

COBRA Toolbox



The **COBRA Toolbox** is a MATLAB software suite for quantitative prediction of cellular and multicellular biochemical networks with constraint-based modelling.

COBRA Toolbox



- Heirendt, L. et al. Creation and analysis of biochemical constraint-based models using the COBRA Toolbox v.3.0. Nature Protocols 14, 639 (2019).
- 421 citations (Google scholar, 28/9/21), ~1000 website visits/month, ~120 git clones/month.

Log-concave sampling of polyhedral convex constraint-based models

- Uniform sampling of a polyhedral convex set

$$\Omega := \{Sv = 0,\ l \leq v \leq u\}.$$

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- Sampling of certain log-concave functions over a polyhedral convex set

$$\begin{aligned} \mathcal{K} \quad := \quad & \{Sv = 0, \\ & l \leq v \leq u, \\ & v_j \propto \exp(-\sum f_j(v_i))\}, \end{aligned}$$

where $f_i(v_i)$ is a convex function.

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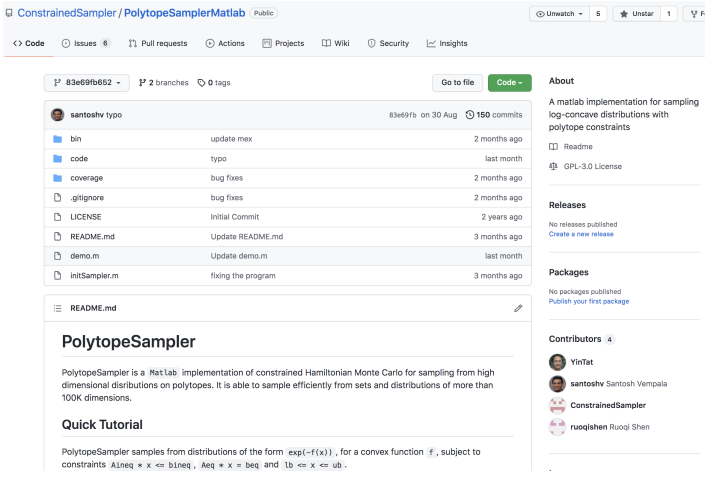
  where $f_i(v_i)$ is a convex function.
- Think of a log-concave function as roughtly equivalent to a unimodal function, e.g., propability density of a normal distribution

Log-concave sampling of polyhedral convex constraint-based models

- Example: Biochemical reaction flux constraints from experimental data: mean $\bar{v} \in \mathbb{R}^n$ $\pm$ covariance matrix $\Sigma \in \mathbb{R}^{n \times n}$

$$\begin{aligned} \mathcal{K} \quad := \quad & \{Sv = 0, \\ & l \leq v \leq u, \\ & v \propto \frac{1}{\sqrt{(2\pi)^n \det(\Sigma)}} \exp(-\frac{1}{2}(v - \bar{v})\Sigma^{-1}(v - \bar{v}))\}, \end{aligned}$$

Riemannian Hamiltonian Monte Carlo sampling



- Implementation: Ruoqi Shen, Yin Tat Lee, Santosh Vempala
- Lee, Y. T. & Vempala, S. S. Convergence Rate of Riemannian Hamiltonian Monte Carlo and Faster Polytope Volume Computation. arXiv:1710.06261 (2017).
- Santosh Vempala Sampling Convex Bodies: A Status Report, Simons Institute Workshop on Sampling Algorithms and Geometries on Probability Distributions, 2021

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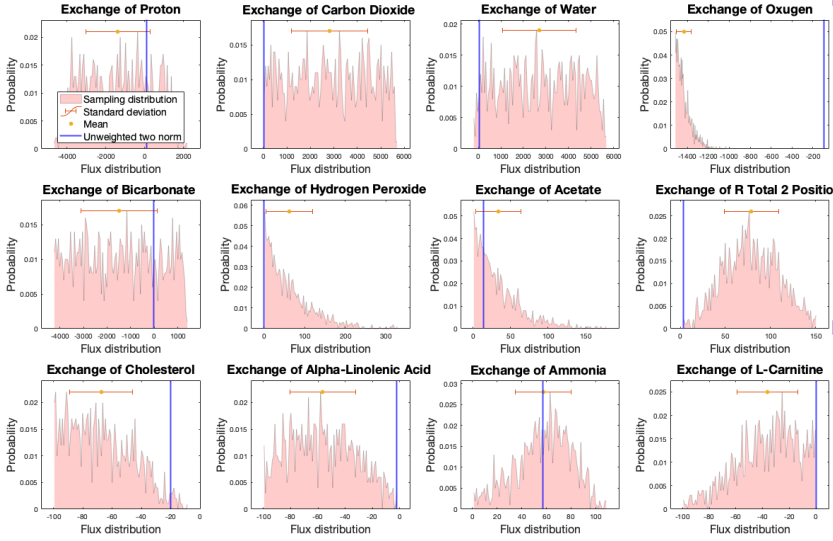
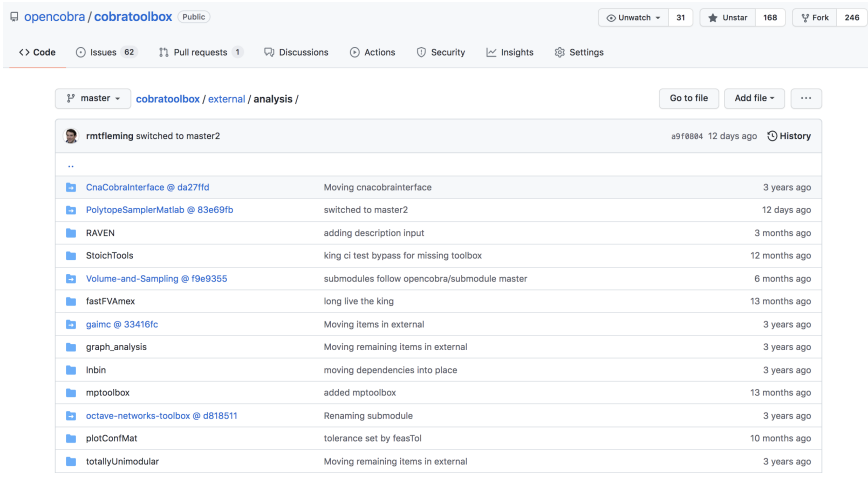


- Riemannian Hamiltonian Monte Carlo sample predictions compared with experimentally measured metabolite uptake and secretion.
- 1000 samples from ~900 dimensional model

Riemannian Hamiltonian Monte Carlo sampling in COBRA Toolbox



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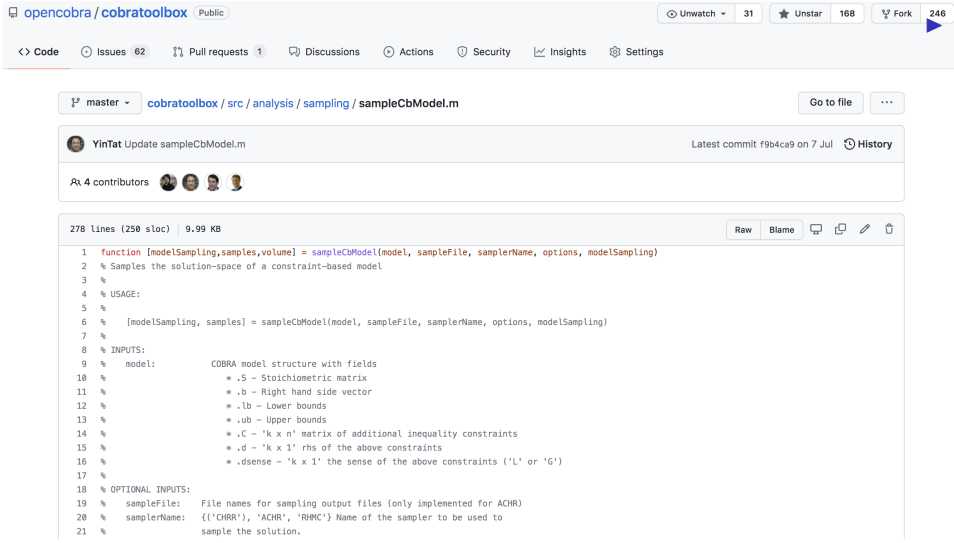
COBRA Toolbox: shared interface to multiple sampling algorithms



Implementation: Ben Cousins, Hulda Haraldsdottir, Ruoqi Shen, Yin Tat Lee, Santosh Vempala, German Preciat, Ronan Fleming & others.

Sampling challenge 4: FAIR software

- Findability, Accessibility, Interoperability, and Reuse (FAIR) of sampling software is essential to increase the impact of theoretical and computational sampling research. https://www.go-fair.org/fair-principles/

Sampling challenge 4: FAIR software

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- Increasing the impact of theoretical and computational sampling research will facilitate greater investment in fundamental and applied research in this area.

A disadvantage of flux balance analysis

- Even if we know the biochemical objective, i.e., $d \in \mathbb{R}^n$ in

$$\begin{aligned} \underset{v \in \mathbb{R}^n}{\text{minimise}} \quad & d^T v \\ \text{s.t.} \quad & Nv = b \\ & l \leq v \leq u \end{aligned} \tag{FBA}$$

- Important constraints are missing, e.g., energy conservation, the second law of thermodynamics, etc.

Biochemistry as a linear resistive network

- Assume that we are given a vector of resistances $r \in \mathbb{R}^n_{++}$ and that Maxwell's minimum heat theorem is the variational principle underlying this network, that is

$$\begin{array}{lll} \underset{v}{\text{minimise}} & \frac{1}{2} v^T \operatorname{diag}(r) v & \\ \text{s.t.} & Nv = b & : y \end{array}$$

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- Kirchhoff's current & voltage laws. Ohm's law: current linearly proportional to change in electrical potential.
- However, r is unknown, motivating efforts to sample the non-convex set of optimal solutions to QP.

Sampling challenge 5: Interdisciplinary communication

- Several papers have been published in the biochemical literature that report algorithms and software for sampling non-convex feasible sets that are **broadly** of the form

$$\mathcal{J} \coloneqq \{r \in \mathbb{R}^n_{++}, y \in \mathbb{R}^m \mid N\mathrm{diag}(1/r)N^T y = b\}.$$

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- What is the relationship between these algorithms in the computational biology literature and the theoretical and computational results of the mathematics and computer science community?
- For example, the following papers:
  - Gollub, M.G., Kaltenbach H.M., Stelling, J. Probabilistic thermodynamic analysis of metabolic networks, Bioinformatics, 2021, btab194.
  - Saldida, J. et al. Unbiased metabolic flux inference through combined thermodynamic and 13C flux analysis bioRxiv 2020.06.29.177063.
  - Pedro A. Saa, Lars K. Nielsen, ll-ACHRB: a scalable algorithm for sampling the feasible solution space of metabolic networks, Bioinformatics, Volume 32, Issue 15, 1 August 2016, Pages 2330–2337.

Sampling challenge 6: relationship to optimial solution sets?

- Every constraint-based modelling problem may be formulated as an optimisation problem
- Development of constraint-based modelling requires consideration of more general optimisation problems, e.g.,

$$\begin{array}{ll} \underset{z \in \mathbb{R}^m}{\text{minimise}} & \phi(z) \\ \text{s.t.} & f(z) = 0 \\ & g(z) \leq 0 \end{array} \tag{1}$$

  where ϕ is a scalar valued continuous and convex function, and where f and g are vector valued functions.
- How do the established sampling algorithms map onto the sets of solutions to different classes of optimisation problems?

Nonlinear resistive network

- Introduce unidirectional fluxes $v_f, v_r \in \mathbb{R}^n_{\geq 0}$ such that $v_f - v_r =: v$
- Maximise weighted linear sum of forward and reverse flux $c^T(v_f + v_r)$
- Maximise entropy of unidirectional fluxes (Fleming, et. al. J. Theor. Biol. 292, 71–77 (2011)).

$$\begin{aligned} \underset{v_f, v_r > 0}{\text{minimise}} \quad & v_f^T \log(v_f) + v_r^T \log(v_r) + c^T(v_f + v_r) \\ \text{s.t.} \quad & N v_f - N v_r = b \\ & l \leq v_f - v_r \leq u \end{aligned}$$

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- Energy conservation, 2nd law of thermodynamics hold at optimal solution.
- Information theory interpretation as the least biased prediction, given the data.
- However, again, $c \in \mathbb{R}^n$ is a vector of free parameters. How to sample the set of optimal solutions?

Sampling and entropy optimisation

Entropy maximisation

$$\begin{aligned} \underset{x>0}{\text{minimise}} \quad & c^T x + x^T \log(x) \\ \text{s.t.} \quad & Ax = b \end{aligned}$$

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where $\mathcal{K}_{exp}$ denotes a set of n exponential cones. For $p, q, r \in \mathbb{R}$,$\mathcal{K}_{exp} := \{p, q, r \mid p \geq q \exp\left(\frac{r}{q}\right), q > 0\}$. Can the set of solutions to this optimisation problem, as a function of a convex and compact set of parameters c, be sampled?

Summary

- Constraint-based modelling of biochemical networks provides a strong demand for sampling algorithms and a host of challenges
  1. Intrinsic anisotropy
  2. High dimensionality
  3. Convergence criteria
  4. FAIR software
  5. Interdisciplinary communication
  6. Feasible sampling problems and parametric solution sets of optimisation problems

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