Non-steady State Optimization Algorithms

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- **Dynamic Flux Balance Analysis (dFBA) <-Still assume the steady state, use LP to search the optimum in the solution space**

  - dFBA extends the traditional Flux Balance Analysis (FBA) by incorporating time-dependent changes in metabolic fluxes. It involves integrating ordinary differential equations (ODEs) to model metabolite concentrations and applying FBA at each time step to optimize the cellular objective.
  - Advantages: Captures dynamic behavior and time-dependent changes in metabolic fluxes, making it suitable for simulating non-steady states.
  - References: Mahadevan R, Schilling CH. The effects of alternate optimal solutions in constraint-based genome-scale metabolic models. Metabolic engineering. 2003 Sep 1;5(4):264-76.

- **Kinetic Modeling**

  - Kinetic models use rate equations to describe the dynamics of metabolic reactions based on enzyme kinetics. This involves a detailed mechanistic representation of biochemical reactions and enzyme properties.
  - Advantages: Provides a mechanistic understanding of enzyme kinetics and reaction dynamics, enabling accurate simulation of transient metabolic states.
  - References: Teixeira AP, Rêgo AT, Pereira H, et al. ReconNET: automated reconstruction, topology modeling, and simulation of metabolic networks. Bioinformatics. 2009 Oct 15;25(20):2707-9.

- **Hybrid Approaches (Constraint-Based + Kinetic Modeling):**

  - Combines the advantages of constraint-based and kinetic models. Constraint-based models provide a framework for steady-state behavior, and kinetic models capture transient dynamics.
  - Advantages: Allows for accurate representation of both steady-state and dynamic behaviors, important for simulating non-steady states.
  - References: Chubukov V, Gerosa L, Kochanowski K, Sauer U. Coordination of microbial metabolism. Nature Reviews Microbiology. 2014 Oct;12(5):327-40.

- **Evolutionary Algorithms (e.g., Genetic Algorithms):**

  - Use evolutionary algorithms, such as Genetic Algorithms (GAs), to optimize the metabolic pathway for specific objectives like maximizing substrate production. GAs iteratively evolve a population of solutions to find the optimal or near-optimal solution.
  - Advantages: Enable global optimization and exploration of a large solution space, suitable for finding optimal flux distributions for substrate maximization.
  - References: Selvarasu S, Karimi IA, Ghim GH, Lee DY. Genome-scale modeling and in silico analysis of mouse cell metabolic network. Molecular BioSystems. 2012 Mar 1;8(3):640-53.