Microbial Intelligence

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The Motivation

- Microorganisms play an important role in everything from human health to biogeochemical cycles
- To put it simply, microbes run the world
- They usually occur in complex communities
- The community interaction is so important for the microbes that it has been found that most microbes can't be grown independently in the lab

What is intelligence?

- Is it IQ? Is it the presence of a brain?
- Are micro-organisms intelligent?
- Acquiring information, storage, processing, use of information, perception, learning, memory, and decision-making
- Parallels exist not only at the heuristic level of functional analogues, but also at the level of molecular mechanisms
- From complex adaptive behavior shown by single cells to the cooperative behavior in populations of like or unlike cells

The idea

- The various levels of control in a microbial cell can be broadly separated into two layers
    - Regulatory layer: A network of proteins and RNA that regulate the genes
    - Metabolic layer: A complex network of interconversion of metabolites
- A new modeling framework
    - A neural network as the regulatory layer utilizing reinforcement learning as a proxy for learning through adaptation to the environment
    - A constraint-based linear programming model as the metabolic layer

Questions to address

1. Would this framework help us model the adaptation of a single bacterial cell to dynamic changes in its environment?
2. Would a community of these microbes modeled using this framework learn to exhibit the same properties as natural microbial communities?
3. Would the underlying structure and weight distribution of the neural network give us any insight into the structure of the regulatory network inside a cell?

The Model

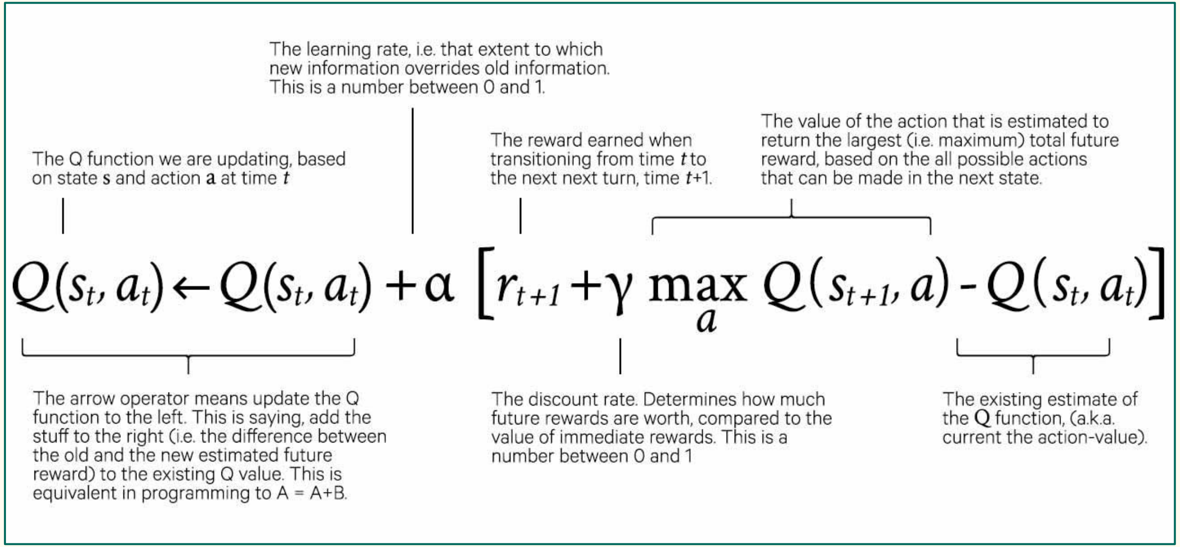
Modeling Framework

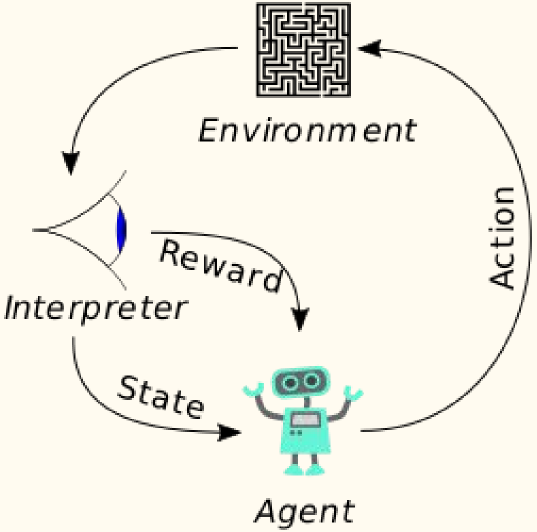
Components

1. Reinforcement Learning
2. Linear Optimization

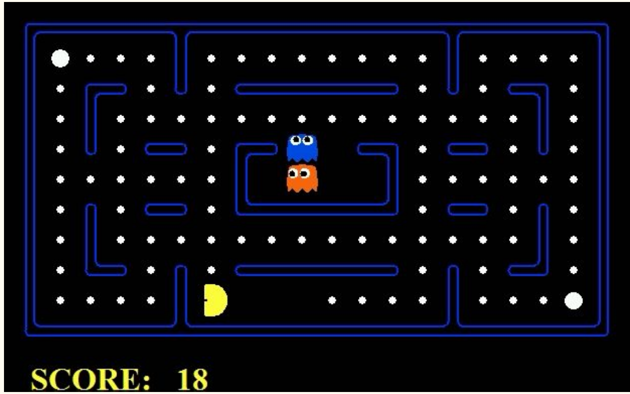
Reinforcement Learning

- How does an agent undertake actions in an environment so as to maximize cumulative reward?
- Exploration vs. Exploitation





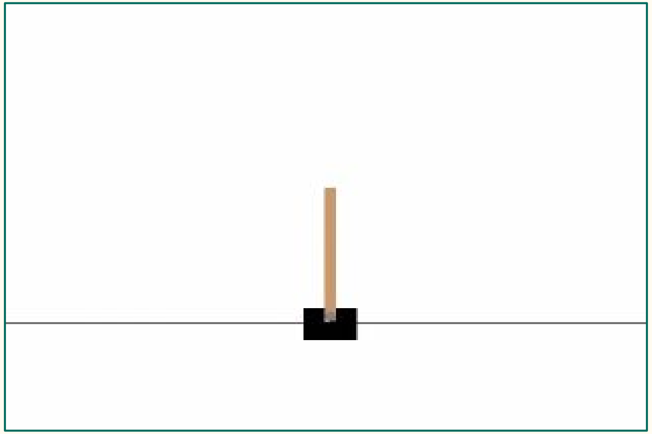
https://www.datahubbs.com/reinforcement-learning/



http://www.cs.princeton.edu/~andyz/pacmanRL

Reinforcement Learning - Tools

- RL algorithms
  - Deep Q Learning (DQN) [1], [2]
  - Double DQN [3]
  - Deep Deterministic Policy Gradient (DDPG) [4]
  - Continuous DQN (CDQN or NAF) [6]
  - Cross-Entropy Method (CEM) [7], [8]
  - Dueling network DQN (Dueling DQN) [9]
  - Deep SARSA [10]
- ML frameworks
  - Keras
  - Pytorch
- Model testing framework
  - OpenAI gym

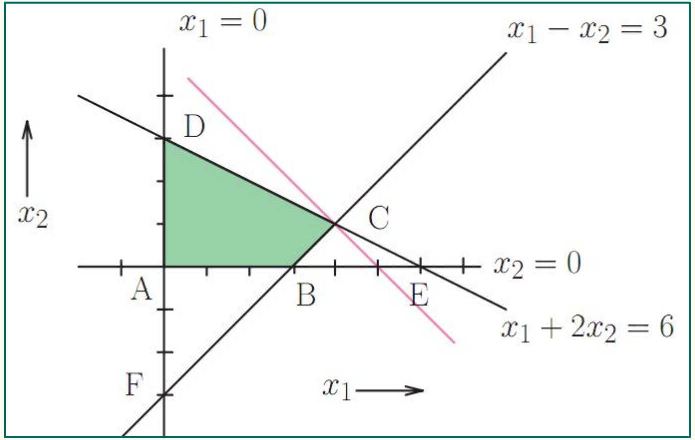


Linear Optimization

- Technique for the optimization of a linear objective function, subject to linear equality and linear inequality constraints

$$\text{Maximize} \quad P = p_1x_1 + p_2x_2 + \cdots + p_kx_k$$

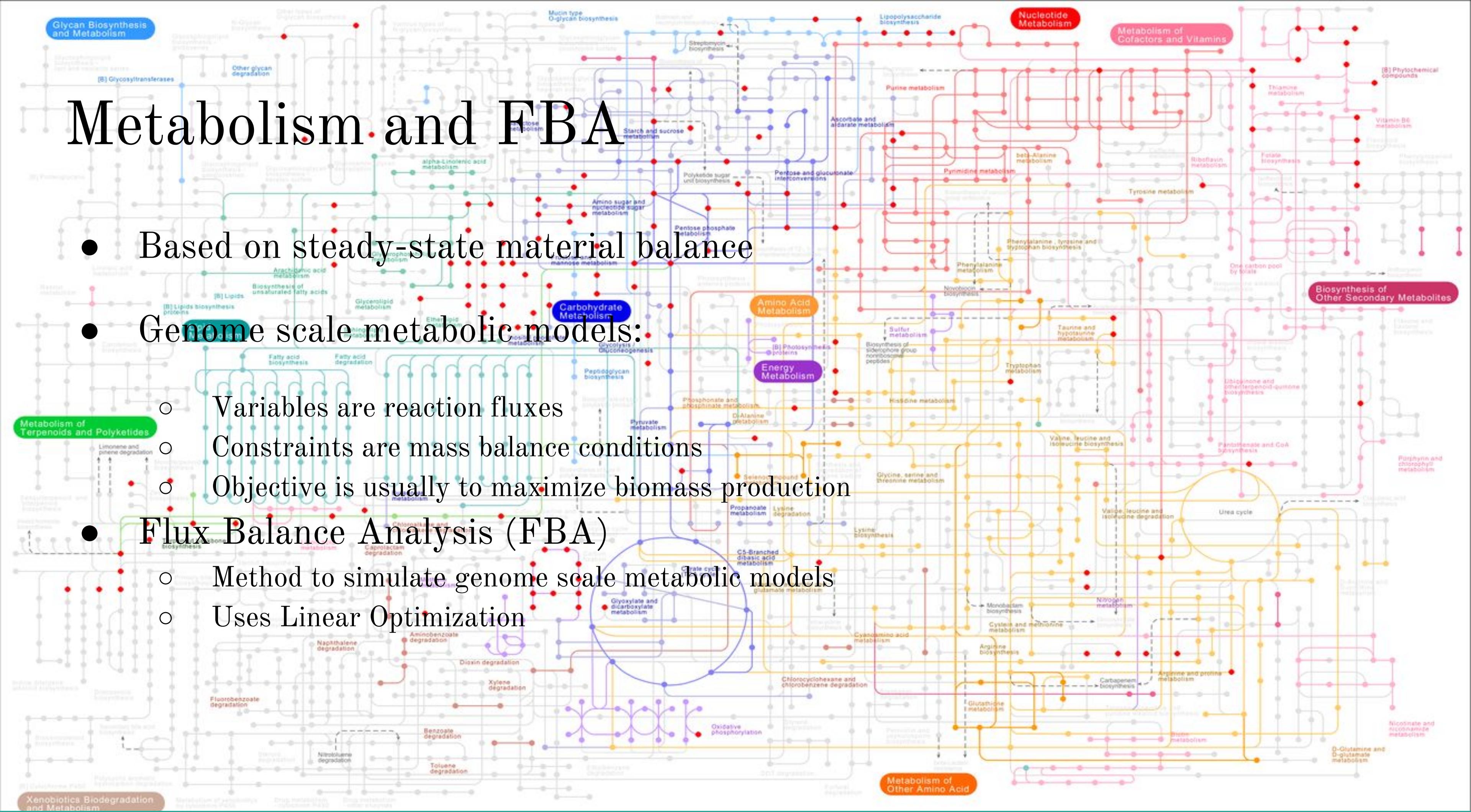
$$\begin{aligned}
\text{Subject to:} \quad & a_{11}x_1 + a_{12}x_2 + \cdots + a_{1k}x_k \le q_1 \\
& a_{21}x_1 + a_{22}x_2 + \cdots + a_{2k}x_k \le q_2 \\
& \vdots \\
& a_{n1}x_1 + a_{n2}x_2 + \cdots + a_{nk}x_k \le q_n \\
& x_1,\ x_2, \cdots x_k \ge 0
\end{aligned}$$



http://www.statslab.cam.ac.uk/~rrw1/opt/

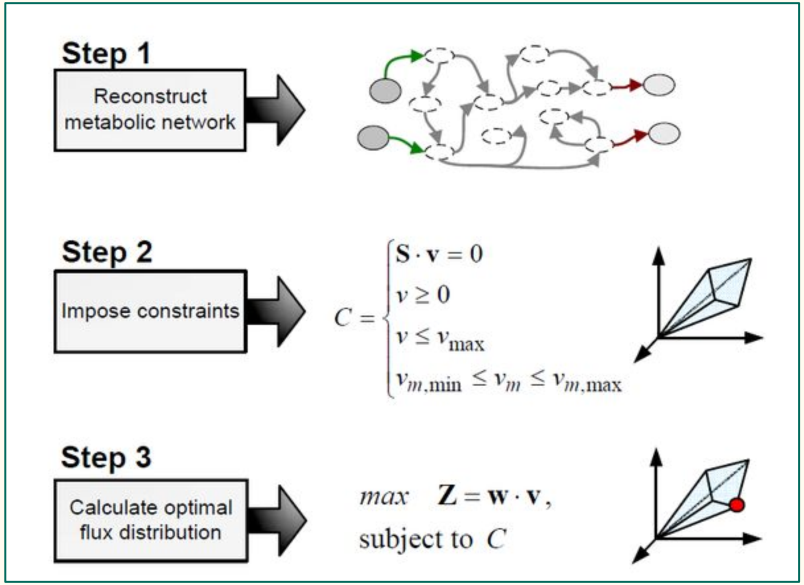
Metabolism and FBA

- Based on steady-state material balance
- Genome scale metabolic models:
  - Variables are reaction fluxes
  - Constraints are mass balance conditions
  - Objective is usually to maximize biomass production
- Flux Balance Analysis (FBA)
  - Method to simulate genome scale metabolic models
  - Uses Linear Optimization



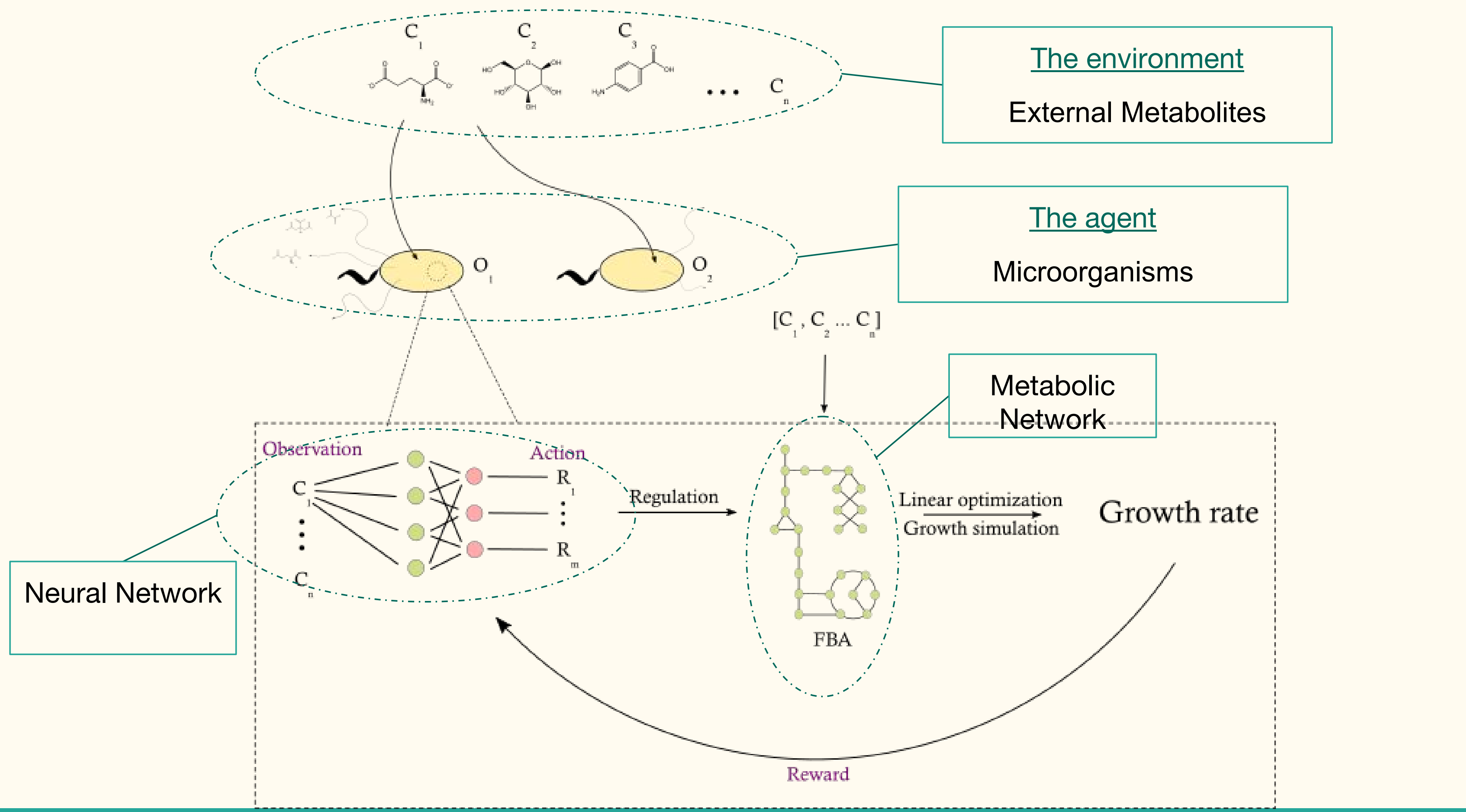
Linear Optimization - Tools

- Algorithms
  - Flux Balance Analysis (FBA)
- FBA frameworks
  - Cobrapy
- Optimization frameworks
  - CPLEX
  - Gurobi



http://2014.igem.org/Team:Valencia_UPV/Collaboration

The Big Picture



The environment
External Metabolites
C1
C2
C3
Cn
The agent
Microorganisms
O1
O2
[C1, C2 ... Cn]
Metabolic Network
Observation
Action
C1
Cn
R1
Rm
Regulation
FBA
Linear optimization
Growth simulation
Growth rate
Neural Network
Reward

Inputs

- Concentrations of metabolites at each step
- A vector of contiguous values with size equal to the number of possible metabolites that can exist in the environment

Outputs

- The result of the FBA algorithm
    - Growth rate (biomass production rate)
- This value is the reward
- The agent performs actions in order to maximize this reward

Recap

A new modeling framework that utilizes a neural network as the regulatory layer and reinforcement learning as a proxy for learning through adaptation to the environment

This layer controls the usual constraint based metabolic network model

The framework might help us understand the adaptation of microorganisms to dynamic environments

Thank you

https://github.com/dileep-kishore/microbial-ai