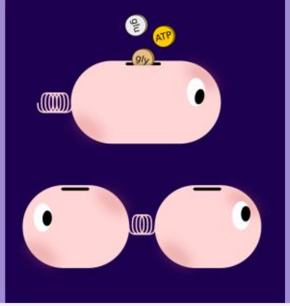
Economic Principles in Cell Biology

Paris, July 10-14, 2023



Return on investment (ROI) in microbial metabolism and interactions

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Main topics to be covered

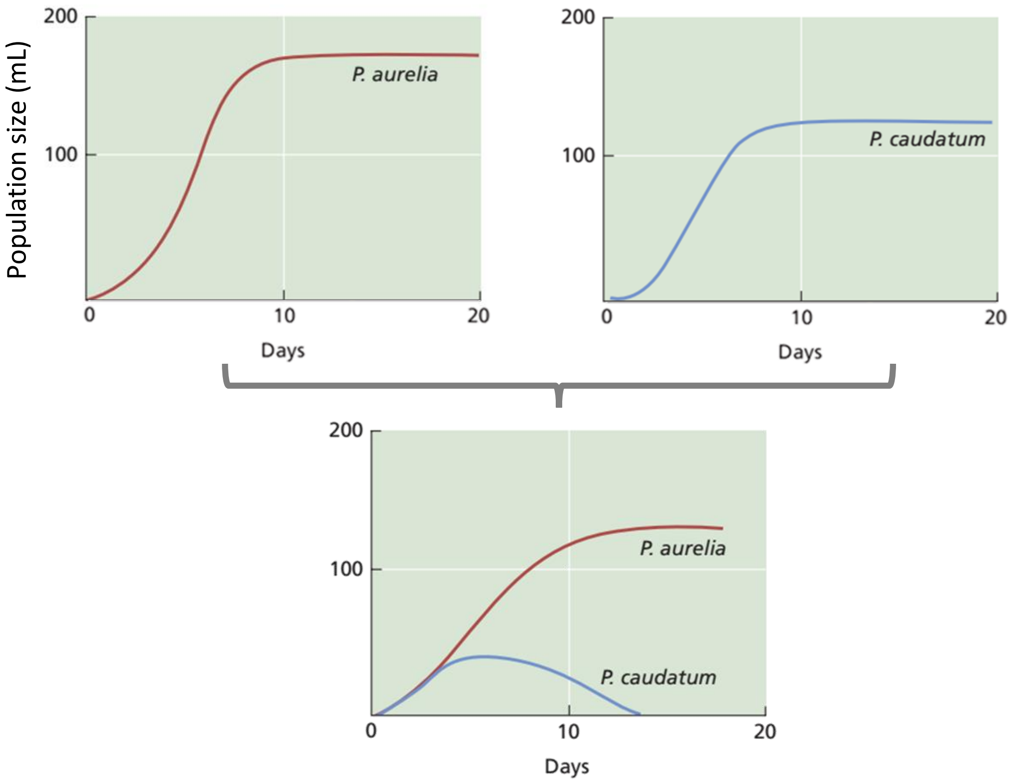
- Survival strategies of microorganisms
  - Innovation in metabolism
  - Building partnerships
- Return-on-investment (ROI) in metabolism
- Cybernetic modeling
  - Basic concept
  - How does the cybernetic approach incorporate ROI into modeling?
  - Modeling examples

Main topics to be covered (cont'd)

- Modeling of microbial interactions
  - Major issues
  - How does the cybernetic modeling enable predicting microorganisms' social behaviors from individualistic perspectives?
  - Modeling examples
- Concluding remarks

Competition drives microorganisms to evolve towards increasing their survival chance

- Microorganisms in natural environments face a constant battle for resources
- Competitive exclusion principle: a cornerstone of community ecology
- Microorganisms have evolved to develop survival strategies into multiple directions
  - Innovation in metabolism
  - Building partnerships

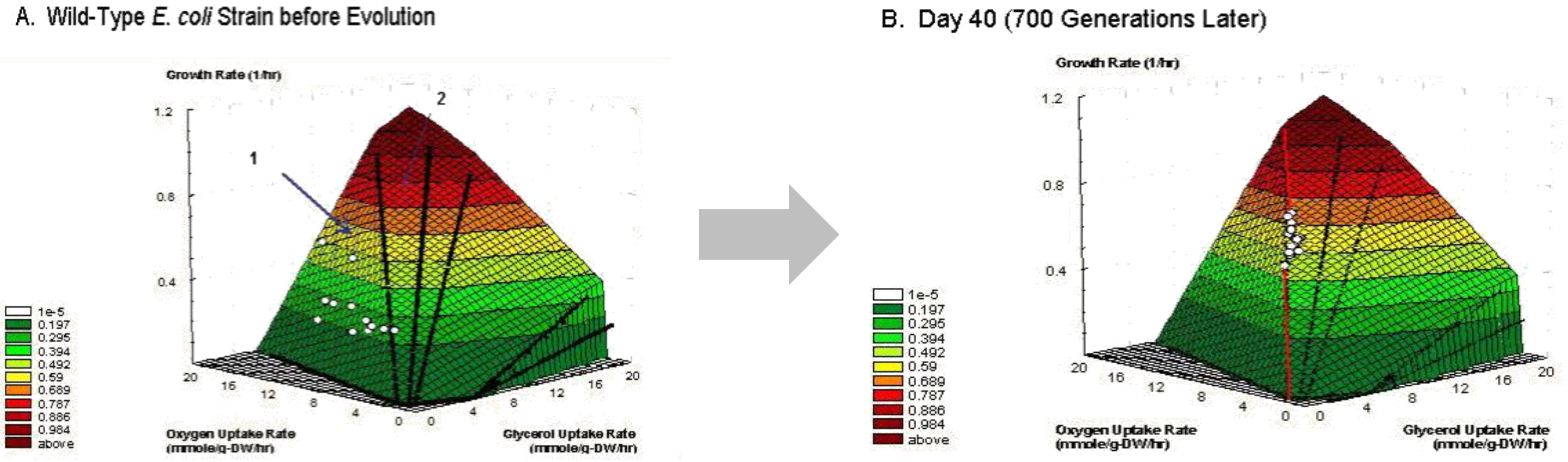


Gause experiment (1934)

(Images taken from Mittelbach and McGill, Community Ecology, 2nd Ed., 2019)

Innovation in metabolism: optimal growth

Evolution of *E. coli* towards optimal growth predicted by flux balance analysis

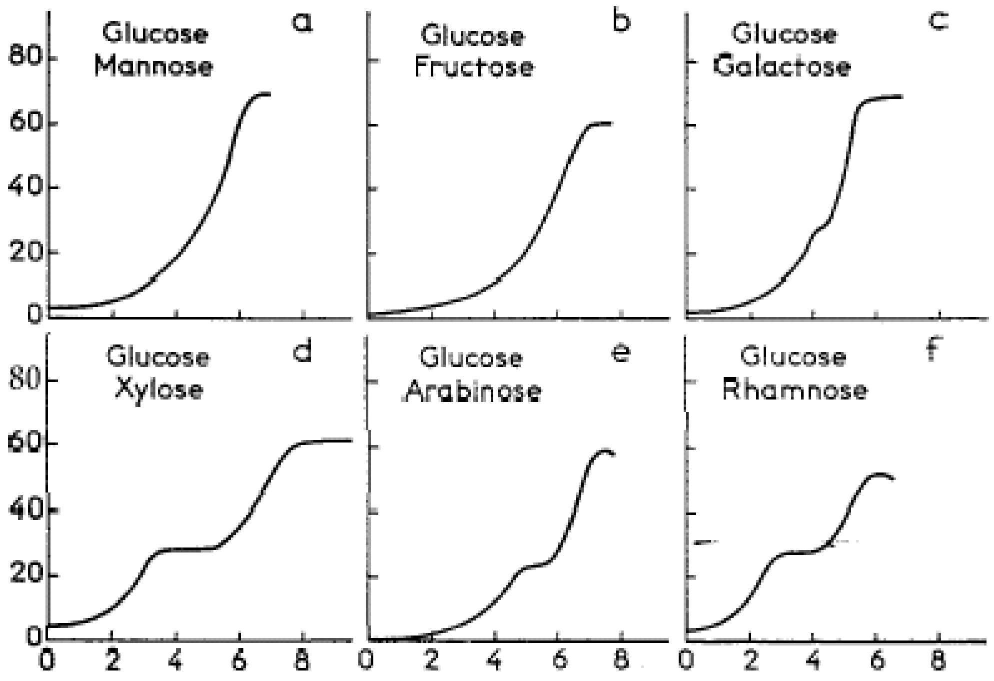


Ibarra et al. (Nature, 2002)

https://www.nsf.gov/od/lpa/news/02/pr0292.htm

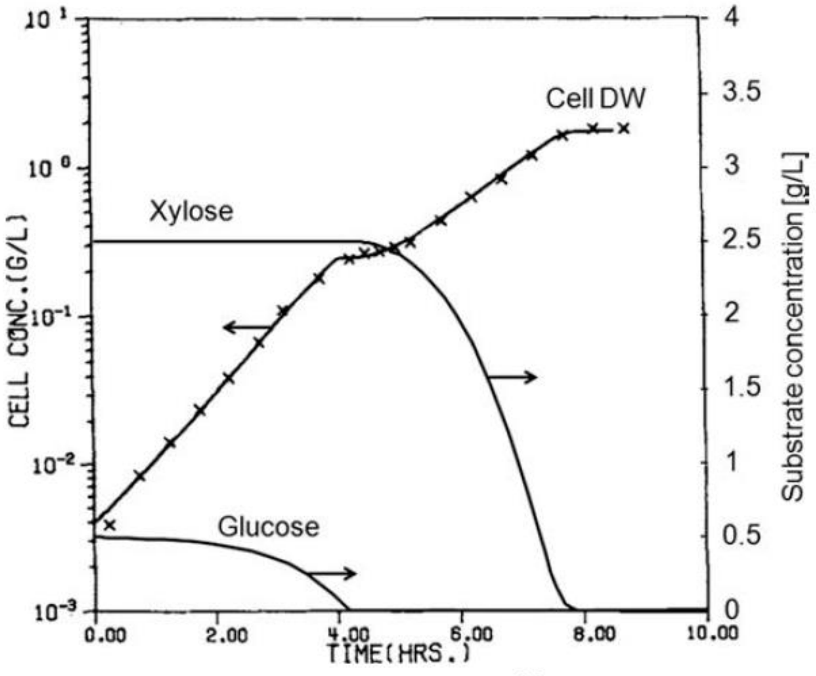
Innovation in metabolism: optimal metabolic switching

Growth of *E. coli* on different carbohydrate pairs
(Monod's experiments in 1940s)



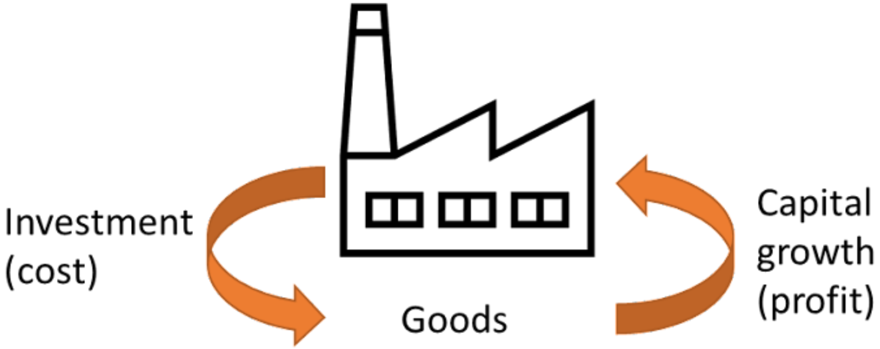
http://science.sciencemag.org/content/154/3748/475

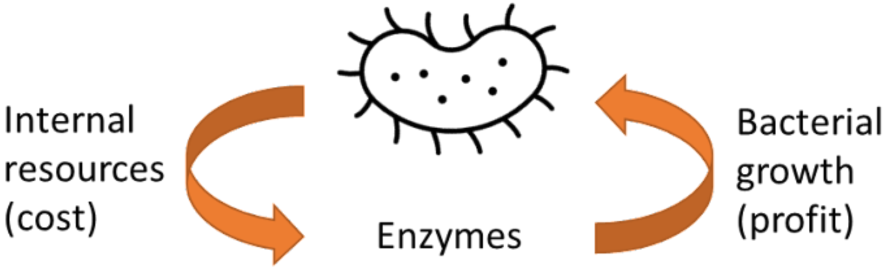
Diauxic growth of *K. oxytoca* on glucose and xylose
predicted by cybernetic modeling



Kompala et al. (Biotech Bioeng, 1986)

Return-on-investment (ROI) is an important concept to understand optimal microbial growth





$$ROI = \frac{Net\ Profit}{Cos\ of\ Investment}$$

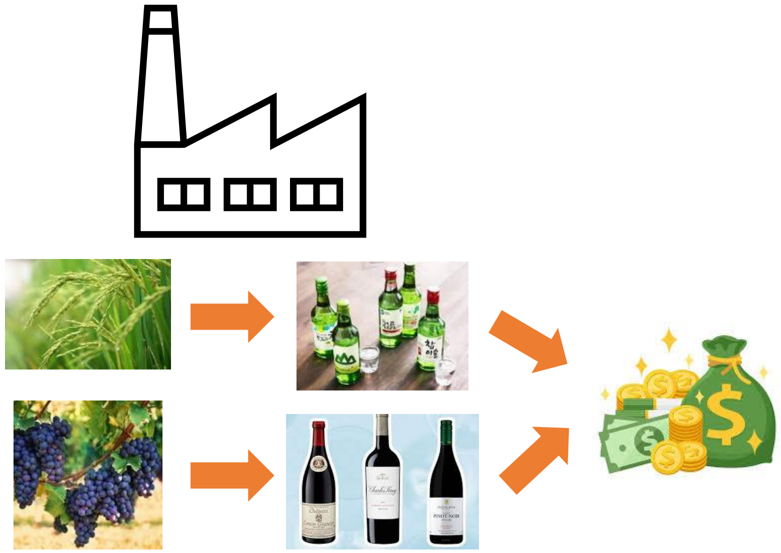
$$mROI = \frac{Net\ Growth}{Cost\ for\ Enzyme\ Production}$$

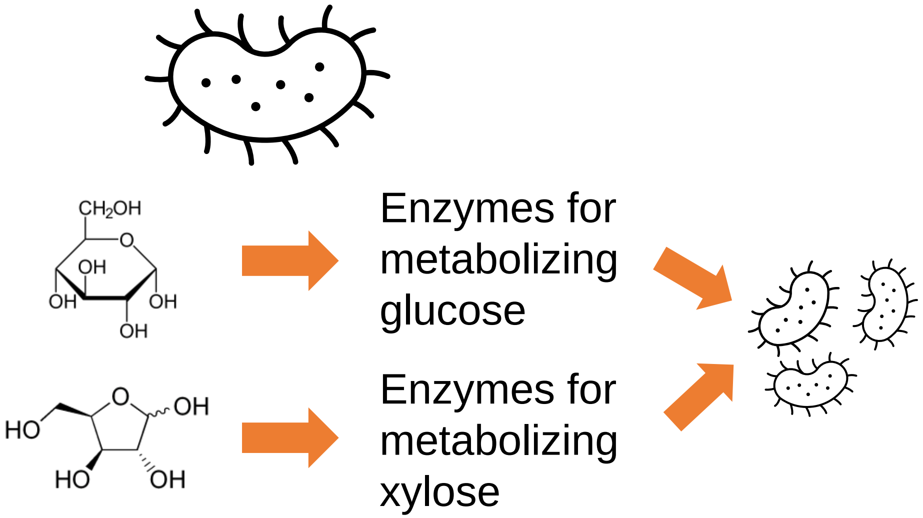
$$ROI = \frac{Gain\ from\ Investment\ - Cost}{Cost}$$

$$mROI = \frac{\Delta Growth - Cost}{Cost}$$

(mROI = Metabolic ROI)

Return-on-investment (ROI) can also explain optimal metabolic switching



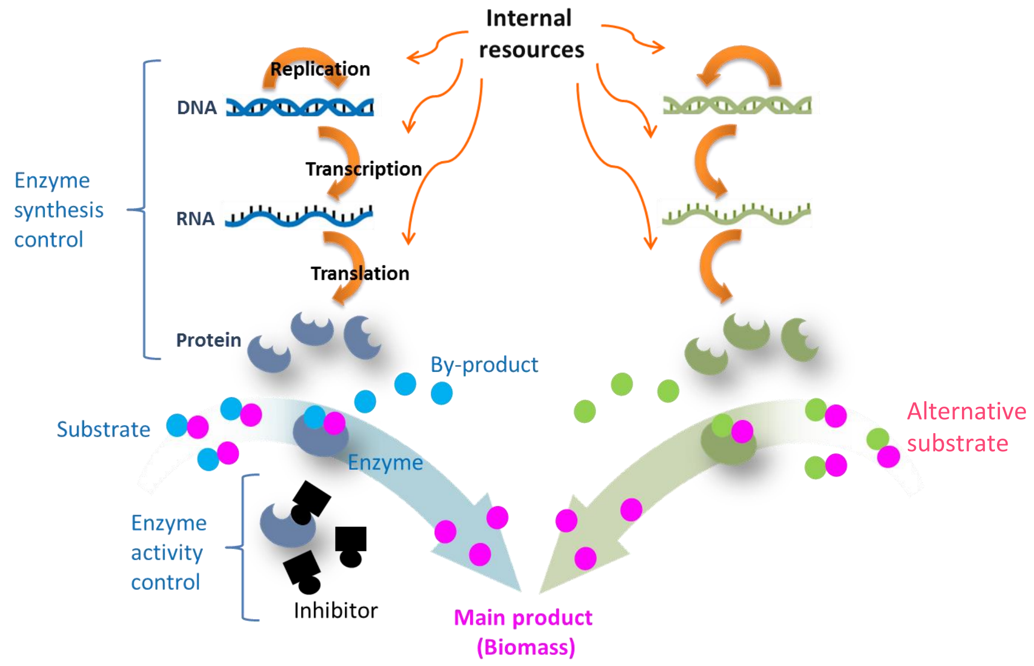


- Cannot simultaneously process both rice and grapes for production of Soju and wine due to limited budget/facilities
- The raw material that leads to higher ROI may be preferred

- Cannot synthesize enzymes to consume both glucose and xylose due to limited internal resources
- The substrate that leads to higher growth (ROI) may be preferred

‘Return’ and ‘cost of investment’ in metabolism

Ribosomes, RNA polymerases, ATP, etc.

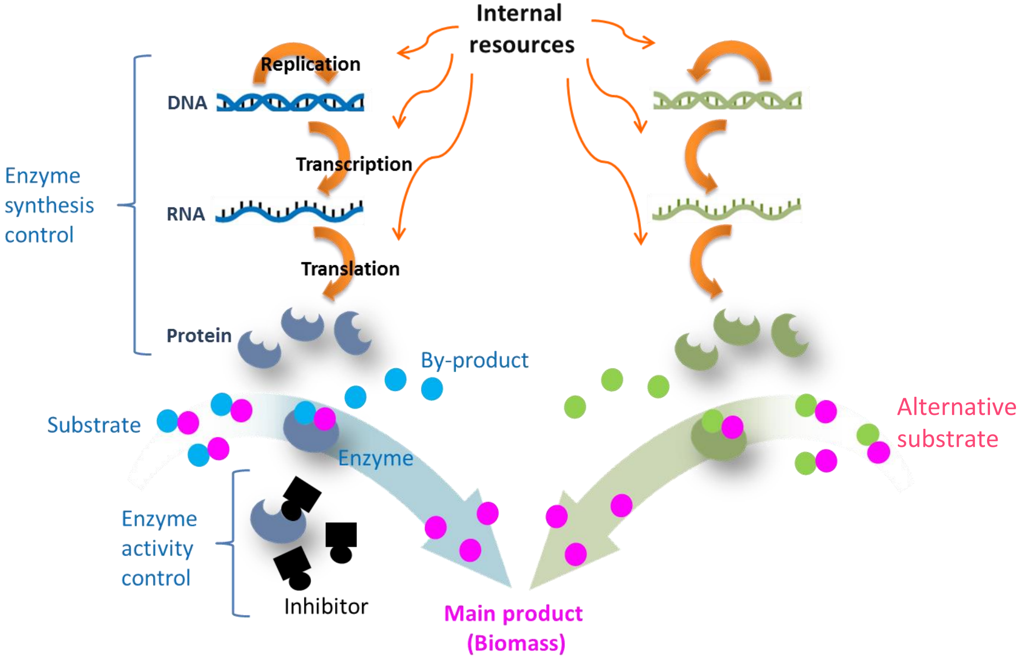


$$mROI = \frac{Gain\ from\ Investment\ - Cost}{Cost}$$

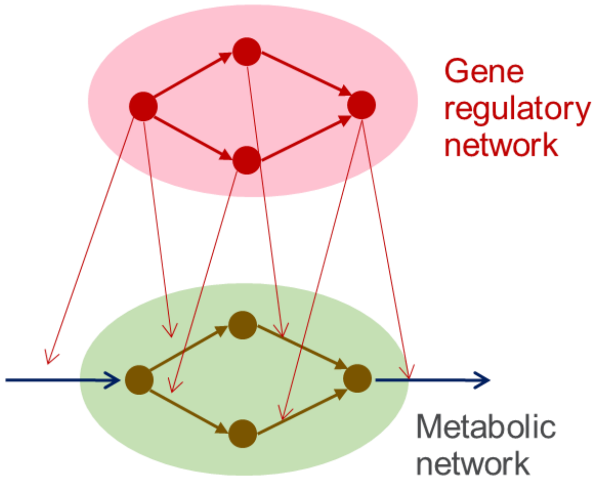
- Net profit or return
  - Cellular growth rate (commonly used)
  - Maintenance (ATP production)
  - Substrate uptake rate
  - Others
- Cost of investment or resources
  - Material and bioenergetic costs required for producing the defined net profit
  - Internal resources: ribosomes, RNA polymerases, ATP, etc.

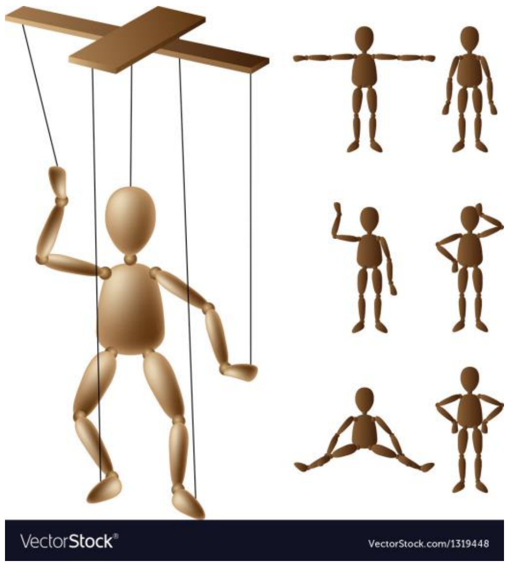
Regulation of metabolism through optimal allocation of resources is key for maximizing ROI

Ribosomes, RNA polymerases, ATP, etc.

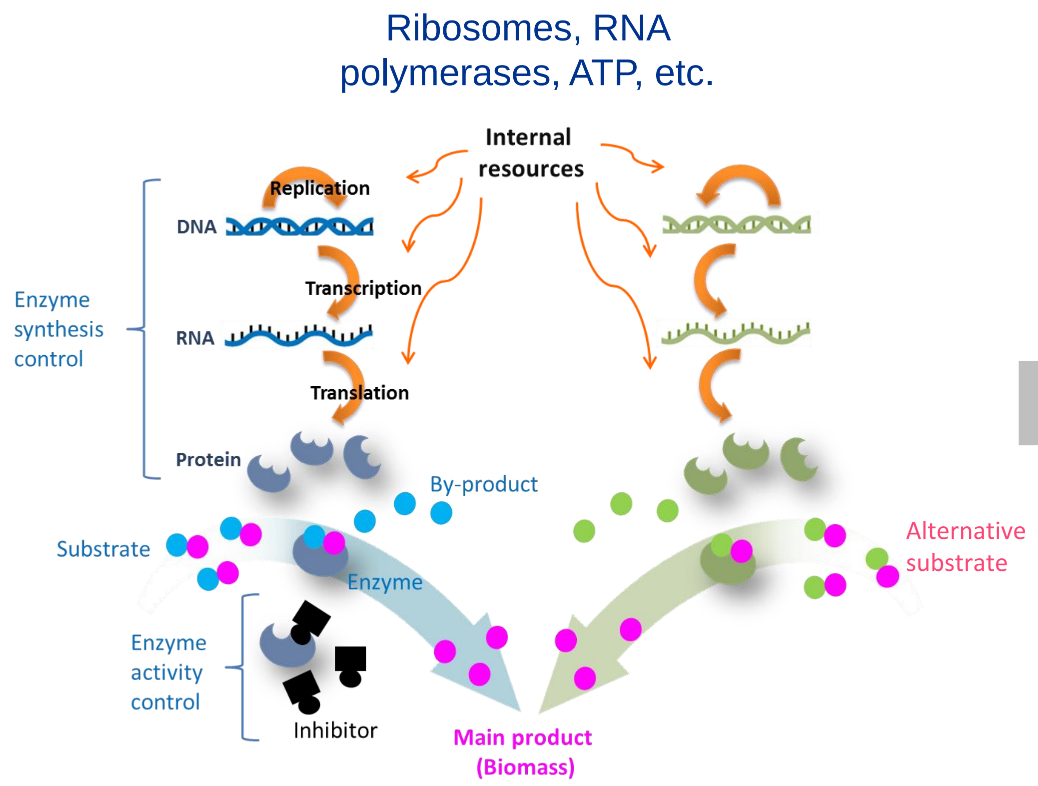


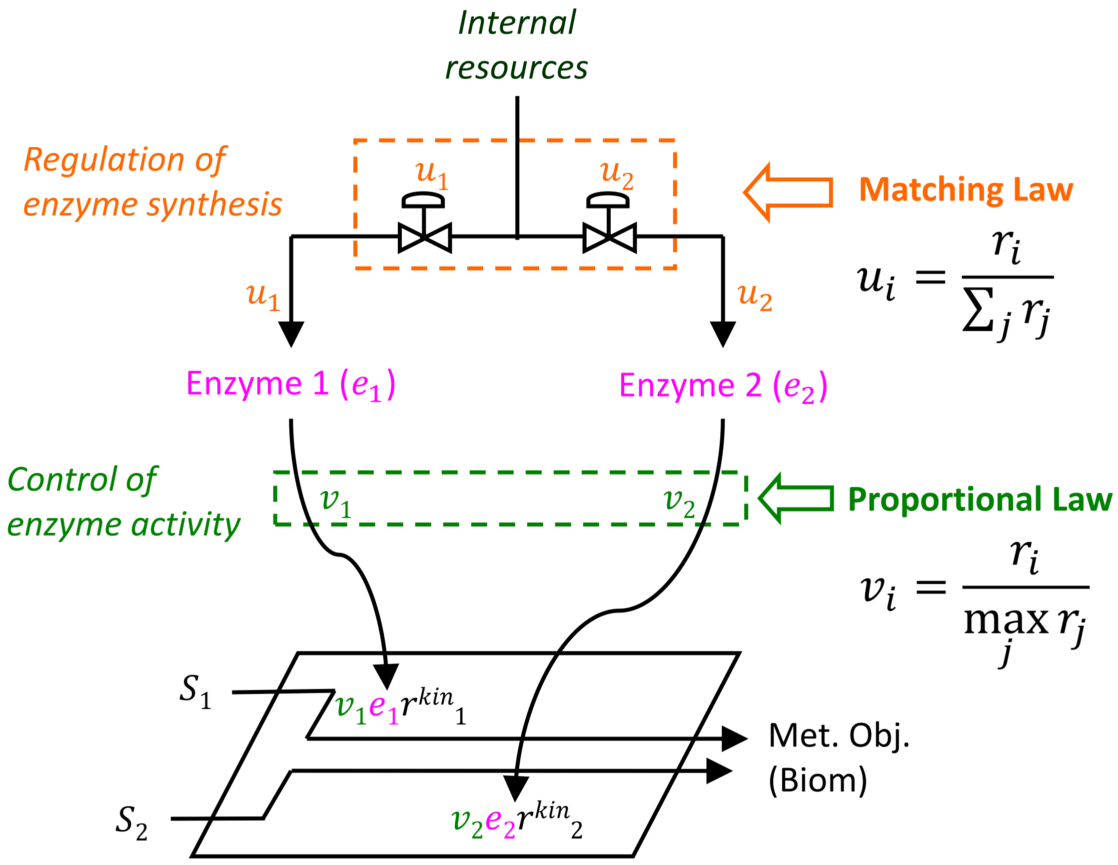
Gene regulatory circuit: control tower





Accounting for ROI and optimal resource allocation in cybernetic modeling

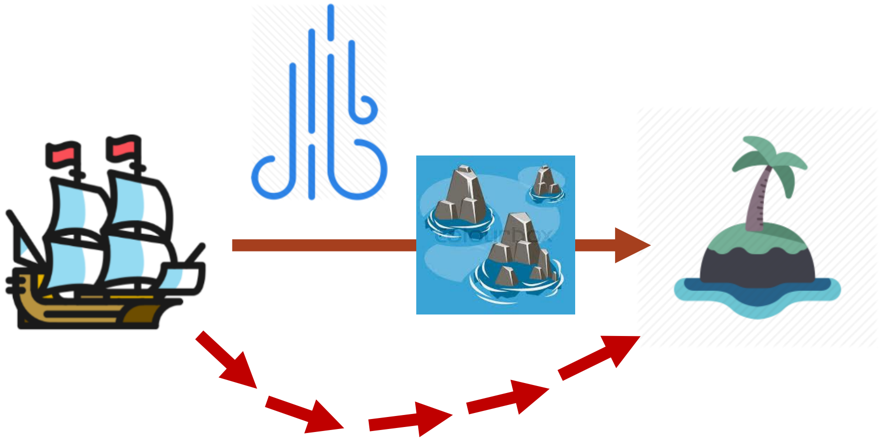




- Mechanistic details of regulation are replaced with the direct description on enzyme synthesis and activity control

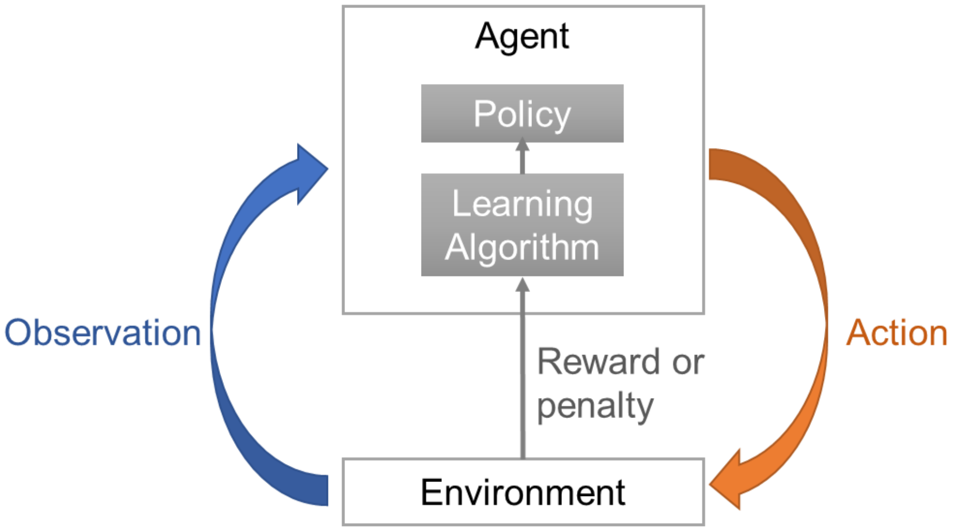
The cybernetic approach views microbes as AI systems that optimally regulate metabolic actions towards maximizing ROI

- “Cybernetics” comes from a Greek word meaning “the art of steering”
- Cybernetics sets a goal and takes action to achieve that goal
- The cybernetic model solves an optimal control problem to simulate cellular behavior

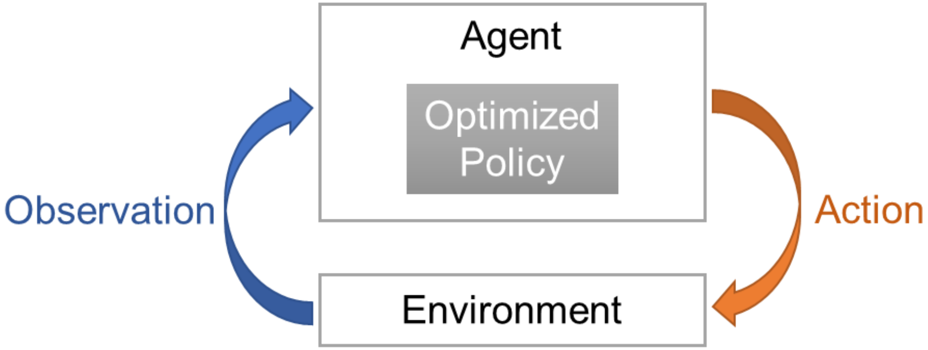


The cybernetic approach views microbes as AI systems that optimally regulate metabolic actions towards maximizing ROI

Reinforcement learning



Cybernetic modeling



- Both cybernetic modeling and reinforcement learning implement intelligence through dynamic feedback loops
- Reinforcement learning evaluates the outcomes of taken actions as rewards or penalties to update the policy to get the most reward over time
- Cybernetic modeling performs optimal control based on the already optimized policy

In cybernetic modeling, resources are optimally allocated such that metabolic ROI is maximized

Derivation of cybernetic control laws by solving a linear quadratic regulator problem

$$\max J\left(= \underbrace{\mathbf{q}^T \boldsymbol{\Delta}\mathbf{y}(t+\Delta t)}_{=\ \Delta\text{Growth}} - \underbrace{\frac{\sigma}{2}\int_t^{t+\Delta t} \mathbf{u}^T \mathbf{u}\, d\tau}_{=\ \text{Cost for enzyme production}} \right)$$

$$= \frac{\mathbf{q}^T \boldsymbol{\Delta}\mathbf{y}(t+\Delta t) - \frac{\sigma}{2}\int_t^{t+\Delta t} \mathbf{u}^T \mathbf{u}\, d\tau}{\sum_i u_i} = mROI$$

$\sum_i u_i$ =1

The total amount of resources (100%) to be allocated

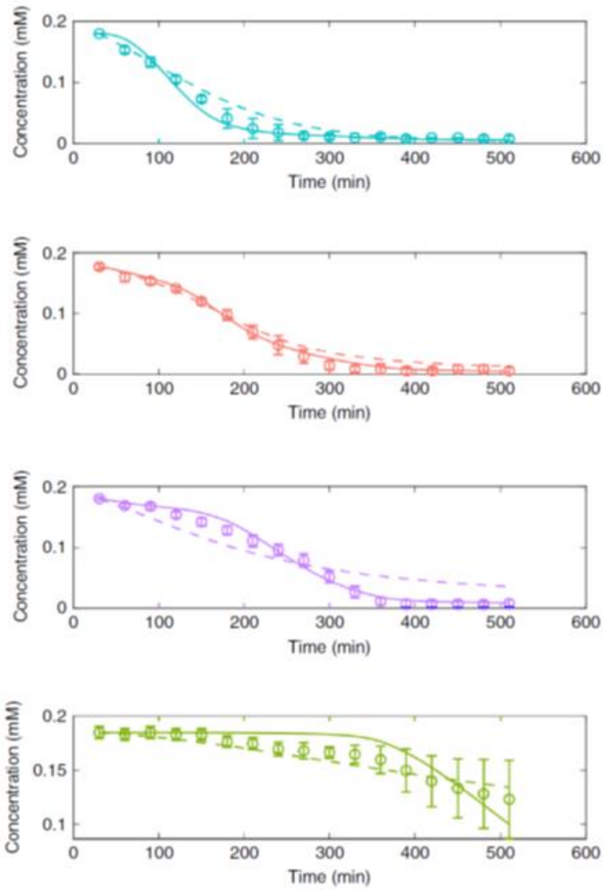
Generalized form of cybernetic control laws

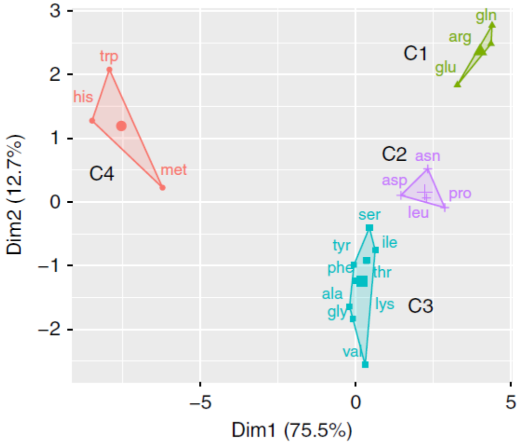
$$\mathbf{u}(t) = \frac{1}{\sigma}\mathbf{B}^T \mathbf{e}^{\mathbf{A}^T \Delta t}\mathbf{q}$$

$\Delta t = 0$

$$u_i = \frac{r_i}{\sum_j r_j}$$

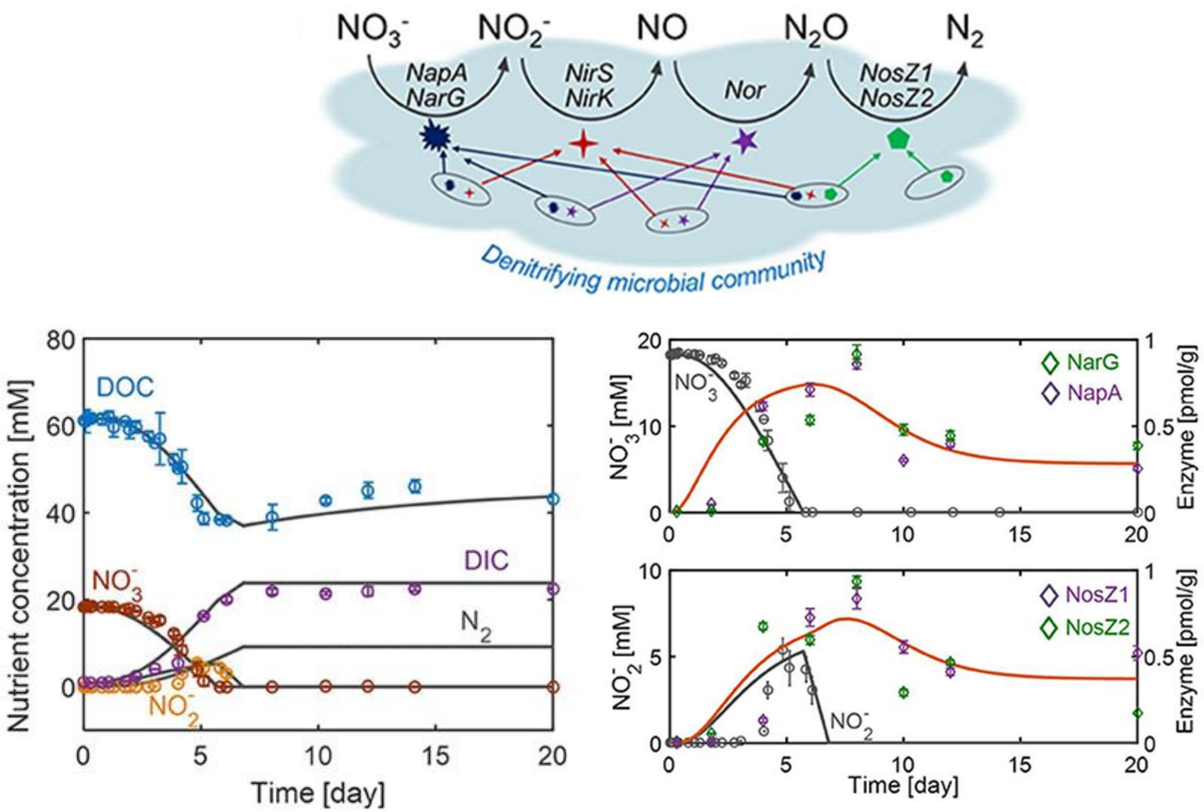
Simulation of microbial growth on alternative carbon sources and electron acceptors





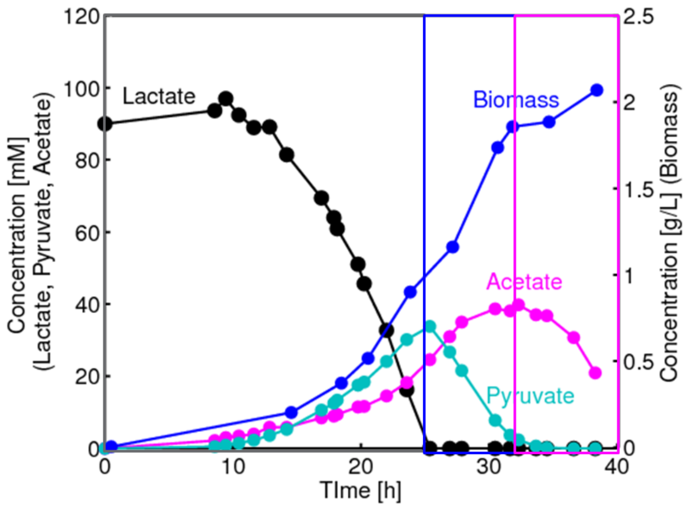
Cybernetic model
Kinetic model

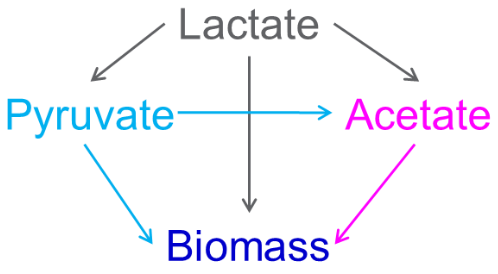
Perrin et al. (Nat Comm, 2020)

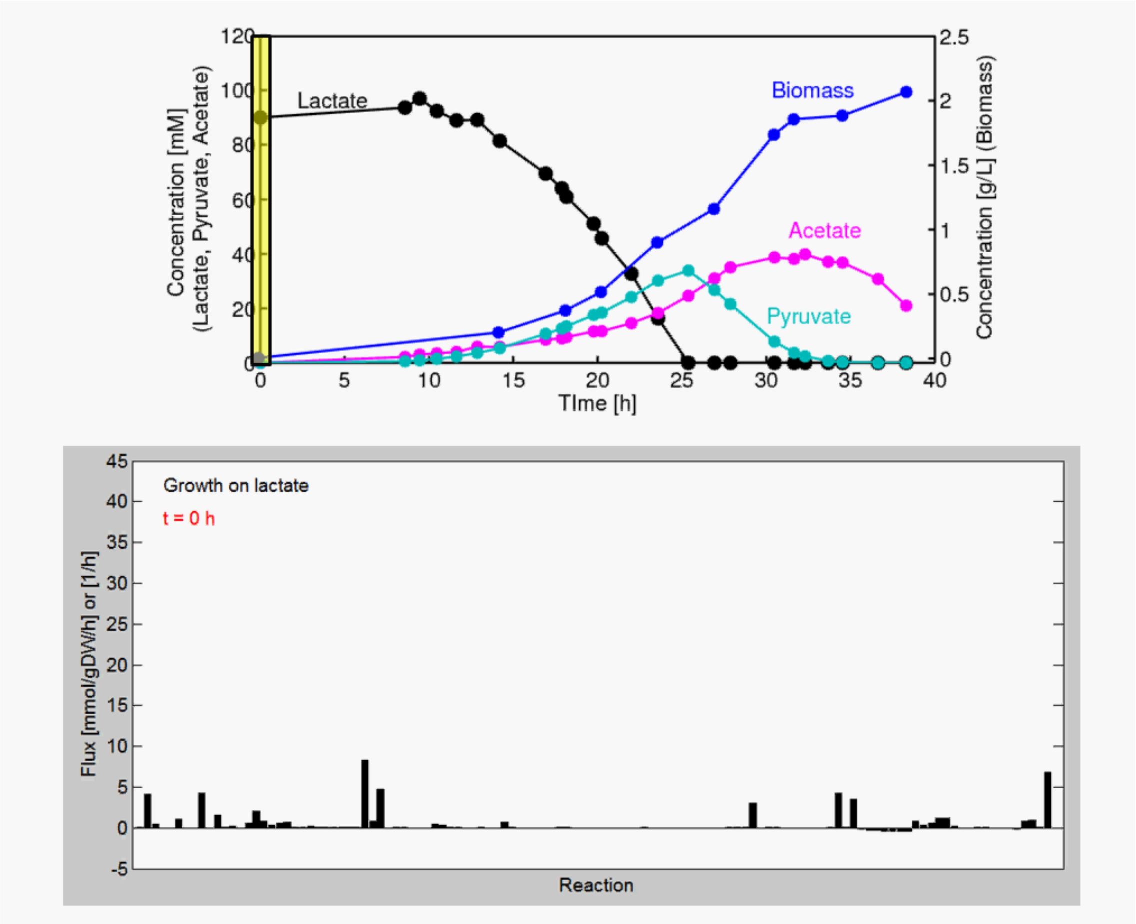


Song et al. (Front Microbiol, 2017)

Simulation of dynamic metabolic switching in *Shewanella oneidensis* MR-1



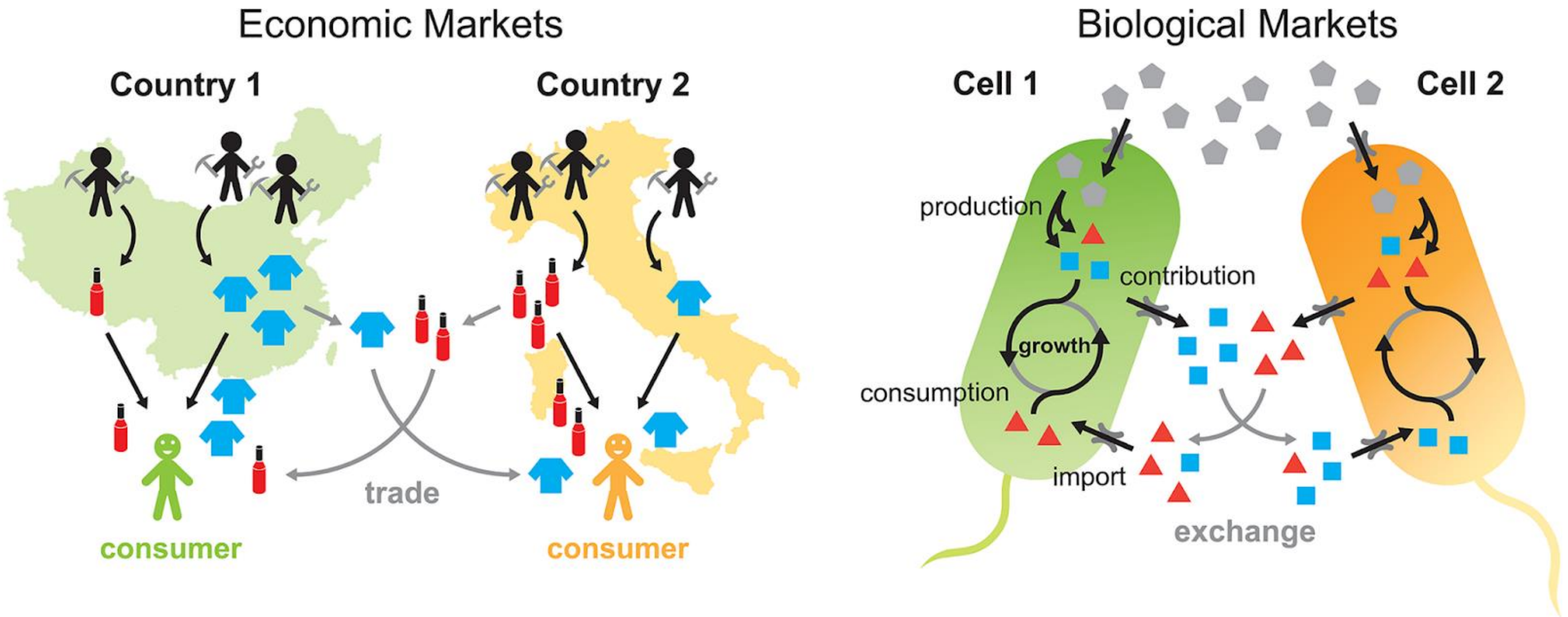




Song et al. (Metab Eng, 2013)

Economics in microbial interactions

- Innovation in metabolism: maximization of **direct** ROI
- Building partnerships: maximization of **indirect** ROI



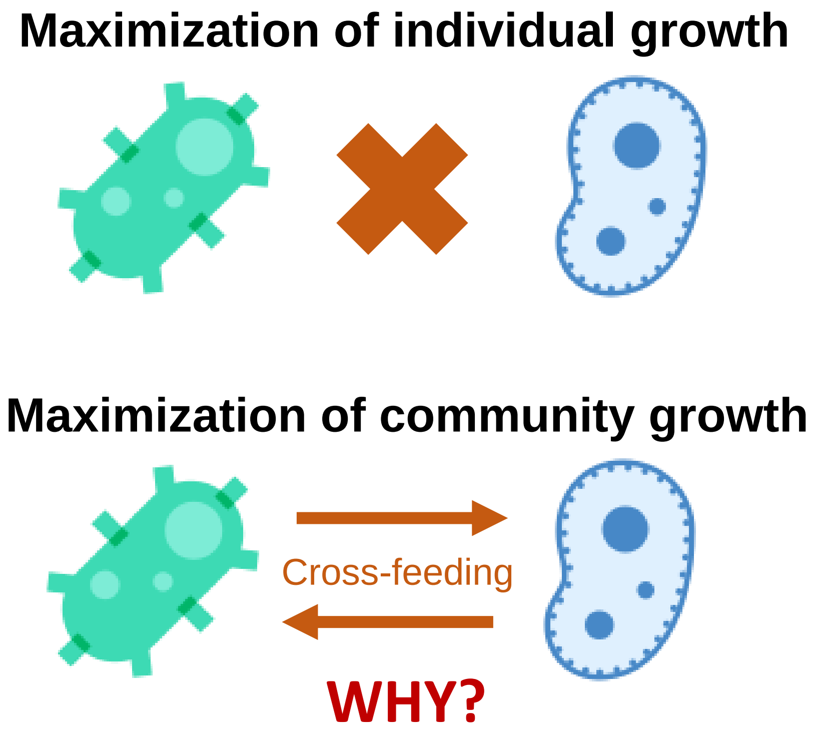
Tasoff et al. (PLOS ONE, 2015)

https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0132907

Two major issues in modeling interspecies interactions in microbial communities

Issue #1: What would be a relevant choice of metabolic objective to maximize?
Individual vs. community growth

- Maximization of the growth of individual species fails to predict interspecies social behaviors of microorganisms such as division of labor or cross-feeding.
- The use of maximization of the total (or community) growth is criticized by ecologists favoring individualistic perspectives of microbial communities – it is difficult to justify cell's altruism.

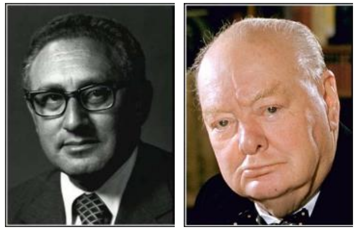


Two major issues in modeling interspecies interactions in microbial communities (cont'd)

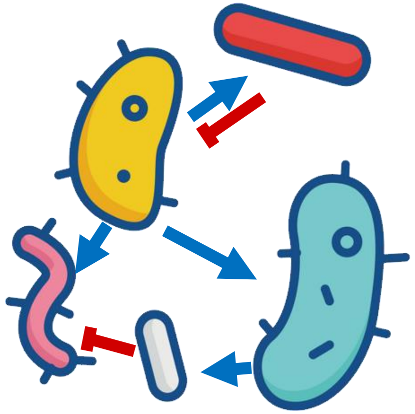
Issue #2: How to predict context dependency in microbial interactions?

- Context dependency: the strength and/or the sign of the interaction changes as biotic and abiotic contexts change (Chamberlain et al., 2014)
- Microbial interactions are a function of multiple factors, including:
  - Community membership
  - Environment
  - Host
  - History
  - Life stage

We have no lasting friends, no lasting enemies, only lasting interests.



So do microbes!



Cybernetic modeling resolves these issues by using generalized cybernetic control laws

- Choice of metabolic objective to maximize
- Context dependency in microbial interactions

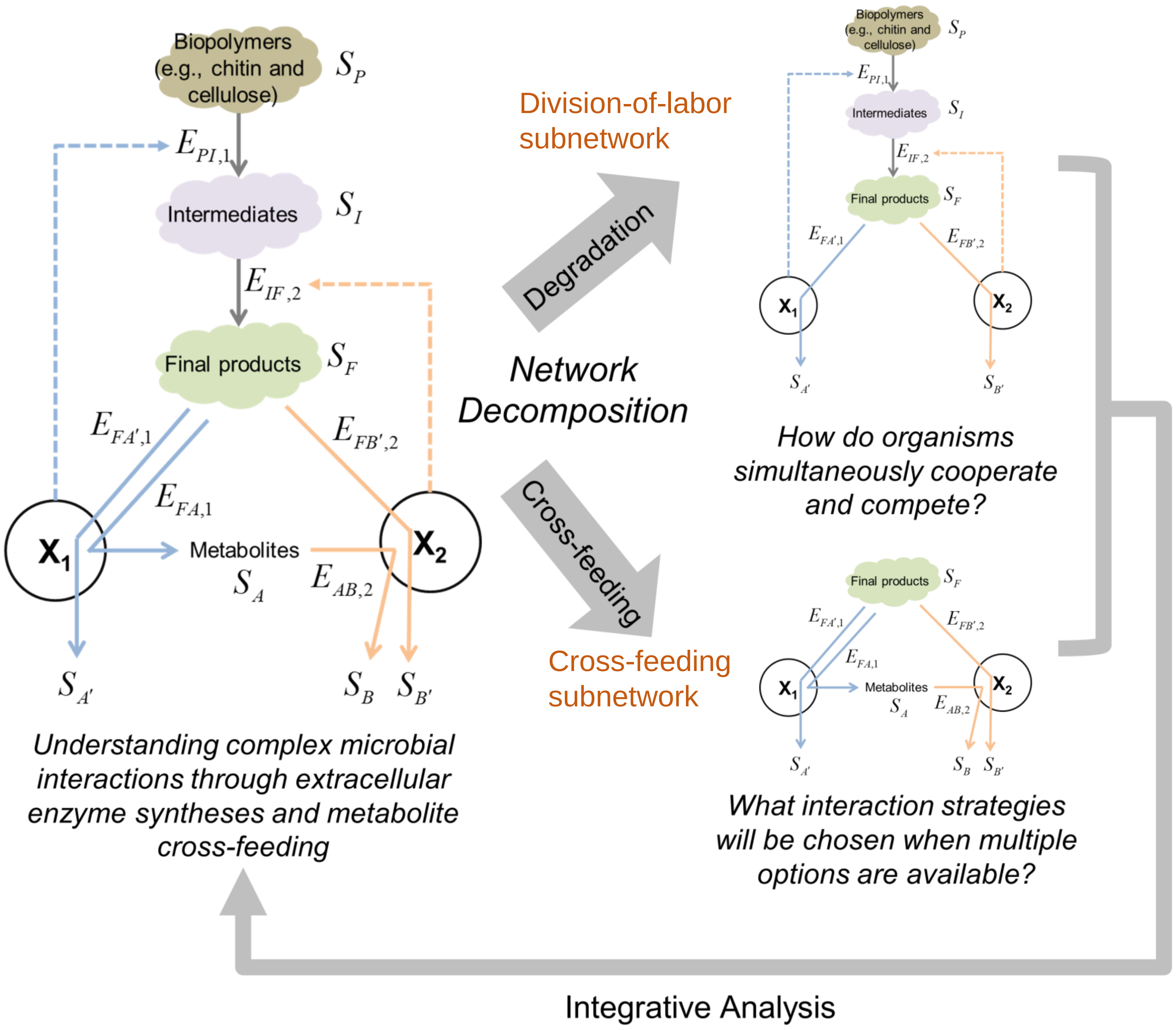
Maximizing **individual ROI** ***over a finite time horizon***

$$\mathbf{u}(t) = \frac{1}{\sigma}\mathbf{B}^T \mathbf{e}^{\mathbf{A}^T \Delta t}\mathbf{q}$$

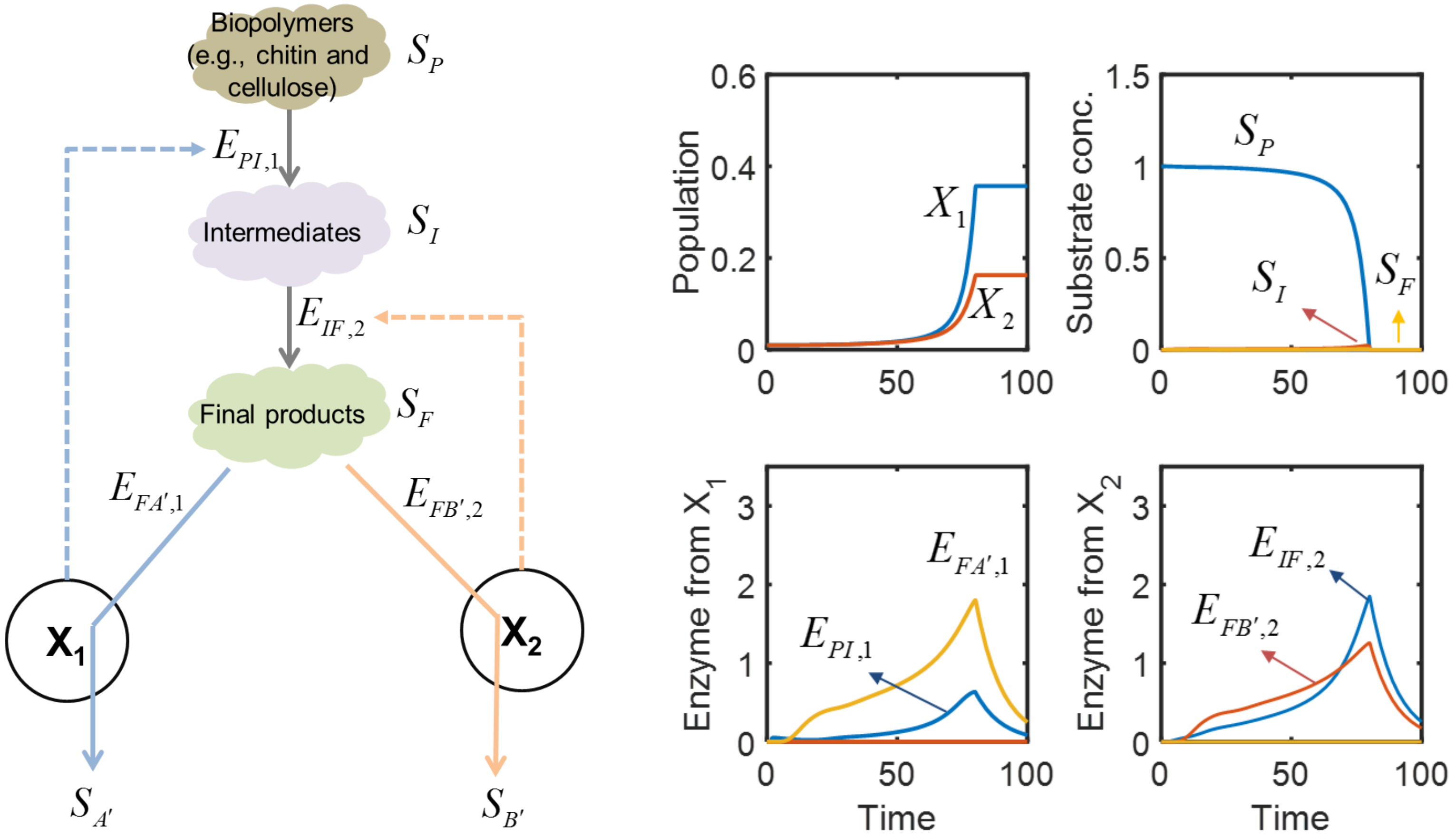
The resulting community model enables predicting:

- Social behaviors of microorganisms such as division of labor and cross-feeding
- Context-dependent changes in interactions

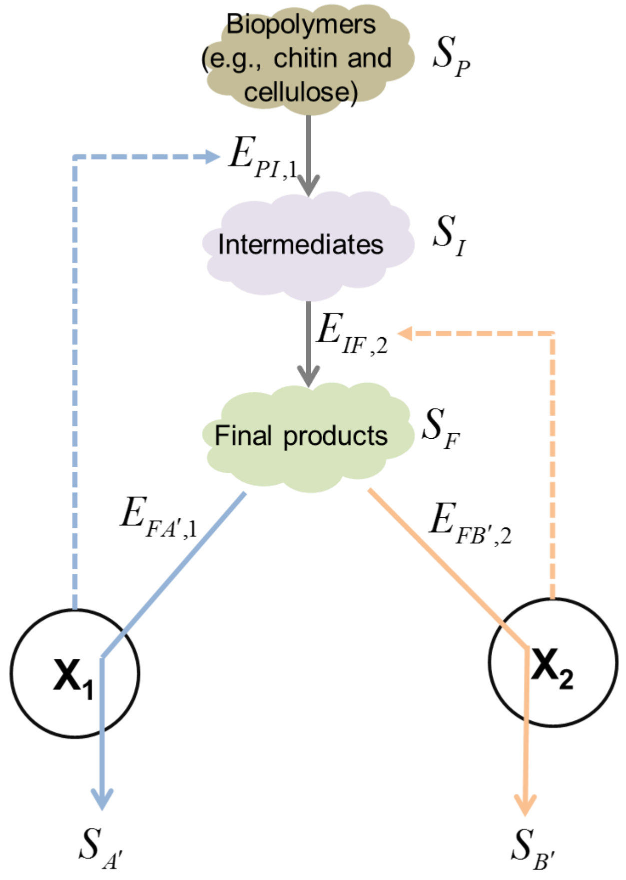
Complex interactions in biopolymer degradation networks

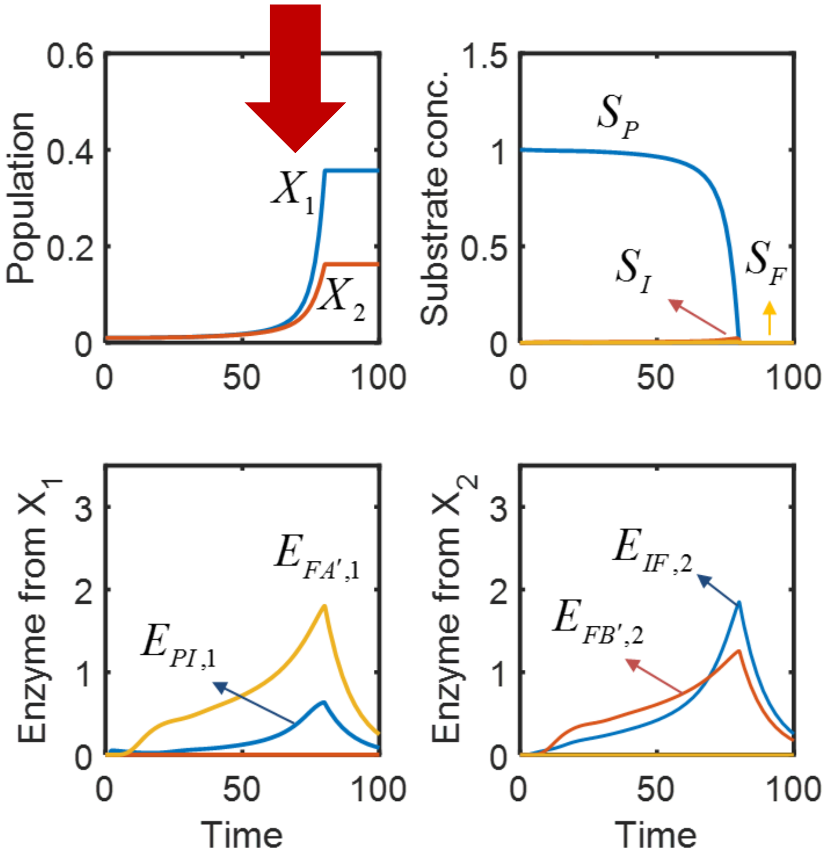


Microbial interactions in the division-of-labor (DoL) subnetwork



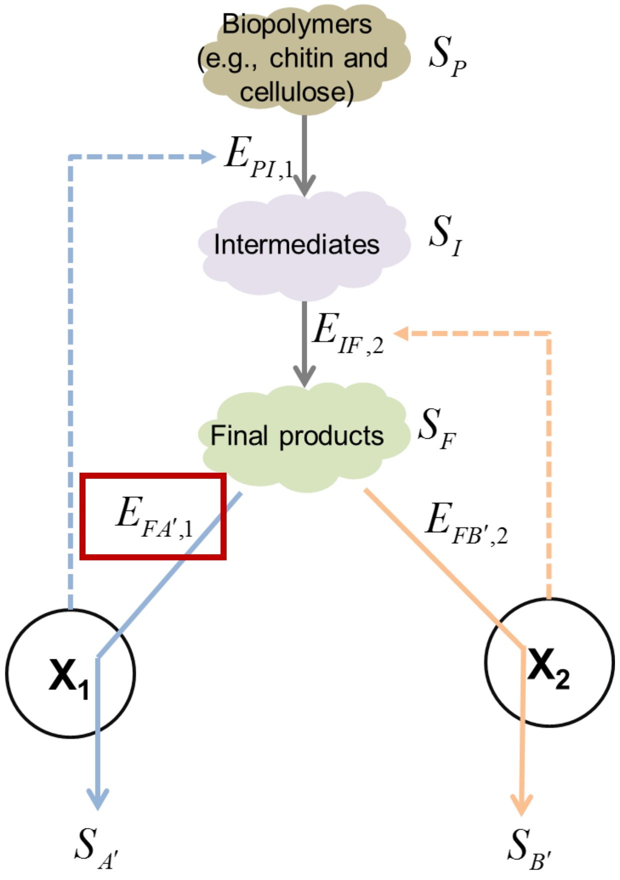
Microbial interactions in the DoL subnetwork

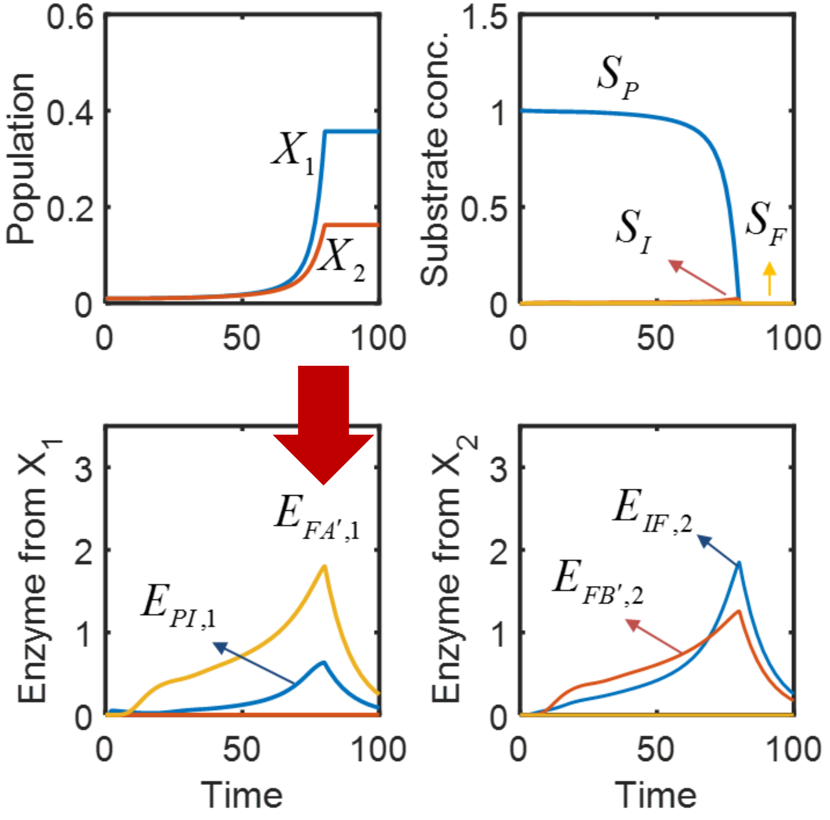




- The primary degrader (X_1) wins the competition

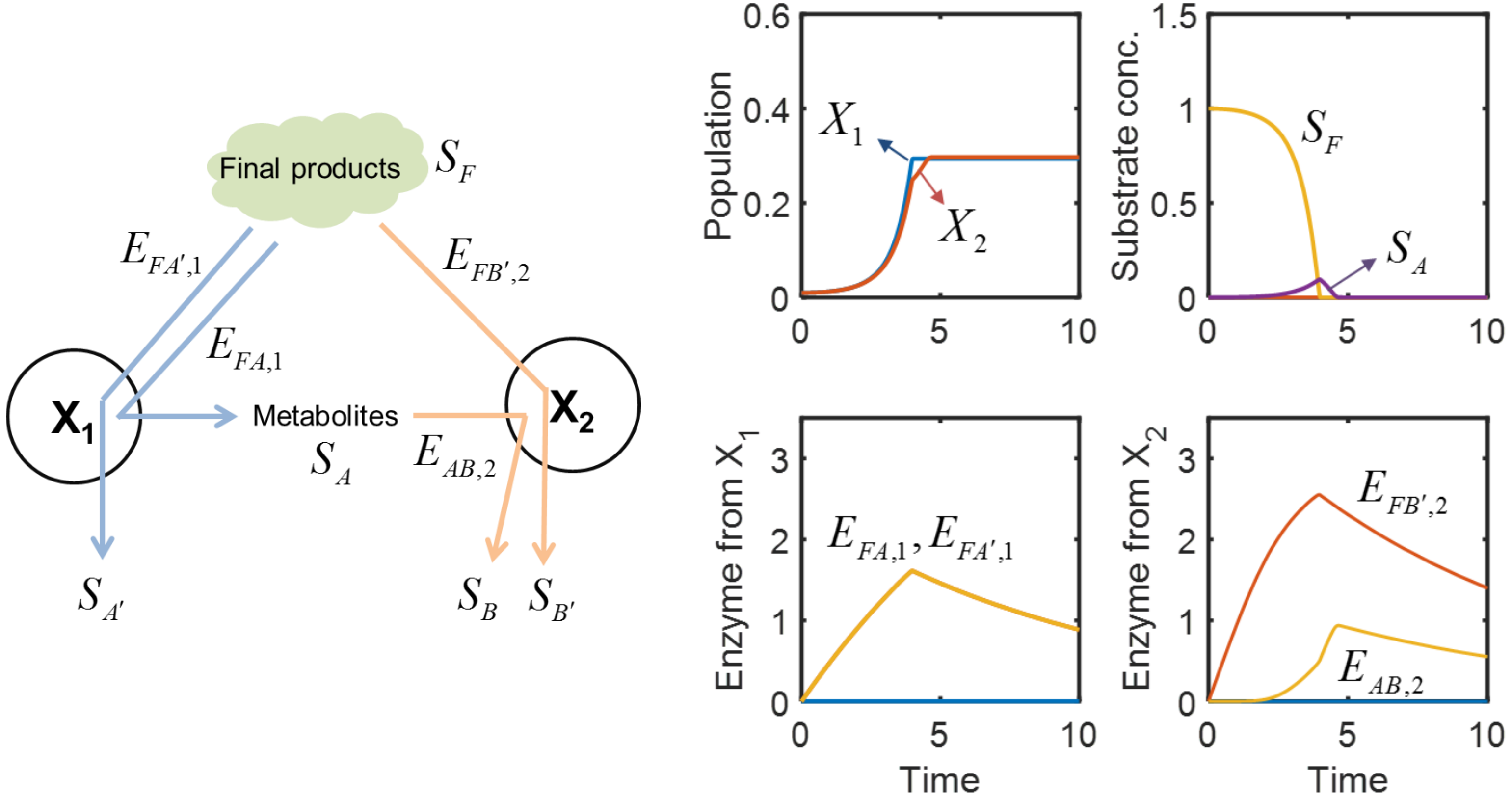
Microbial interactions in the DoL subnetwork



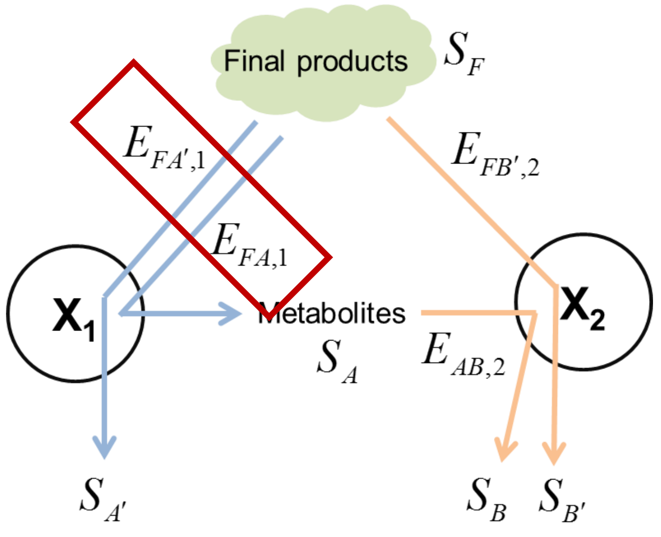


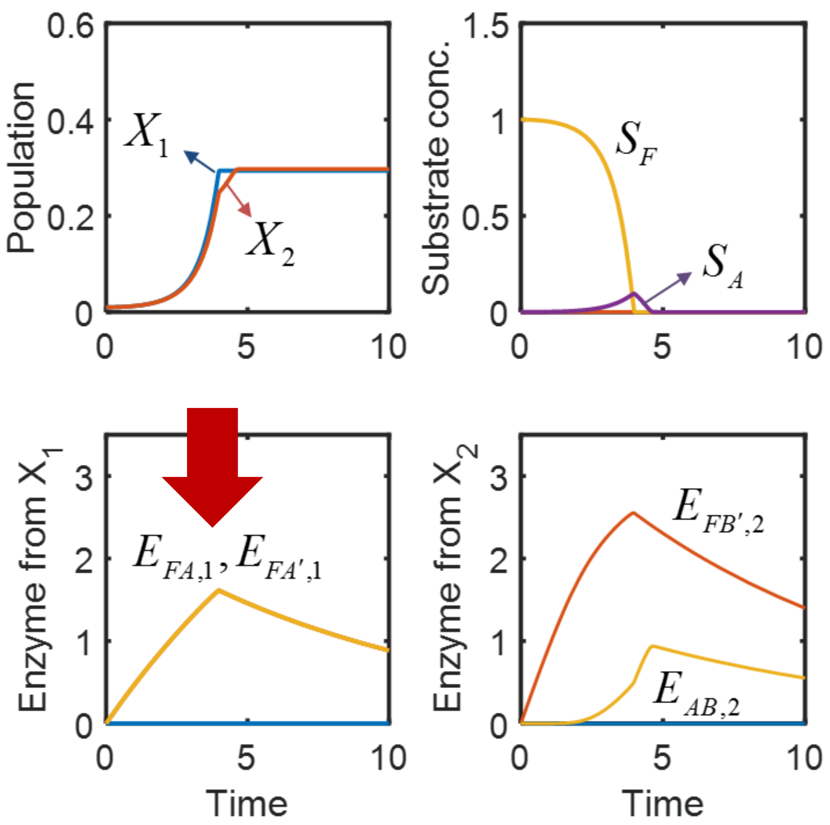
- The primary degrader (X_1) wins the competition
- X_1 proactively prepares for the consumption of hydrolysis products

Microbial interactions in the cross-feeding (CF) subnetwork



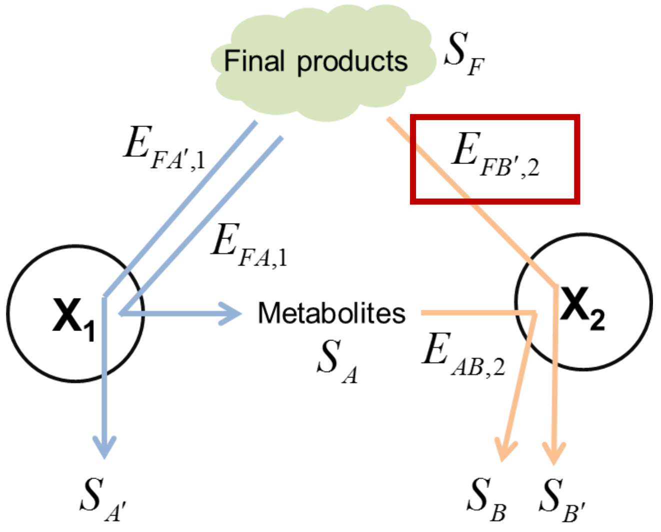
Microbial interactions in the CF subnetwork

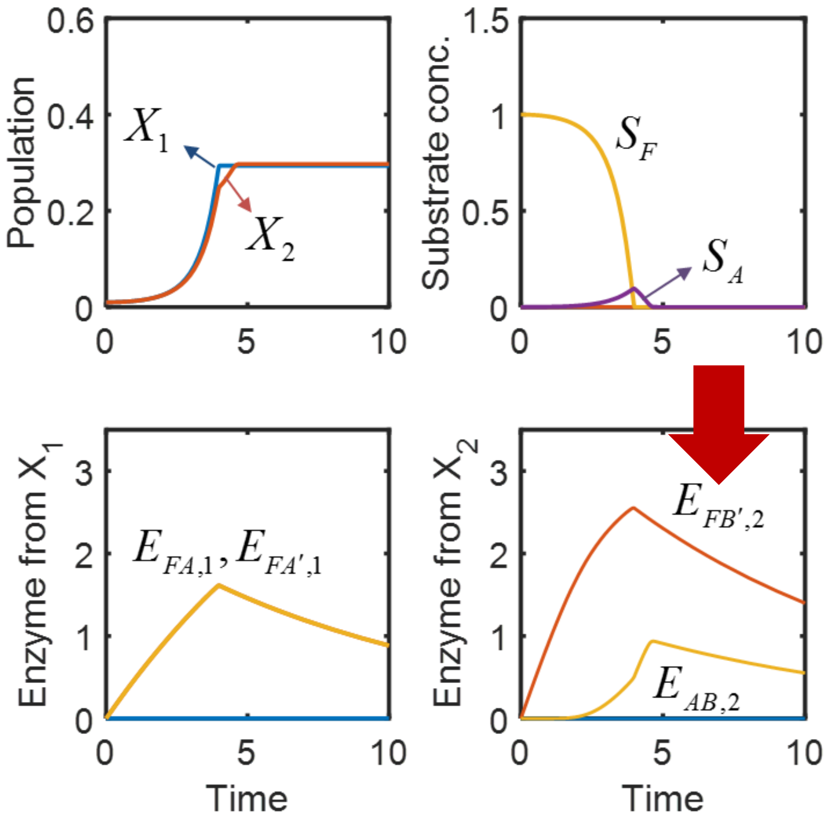




- X_1 constantly synthesizes equal amount of the two enzymes

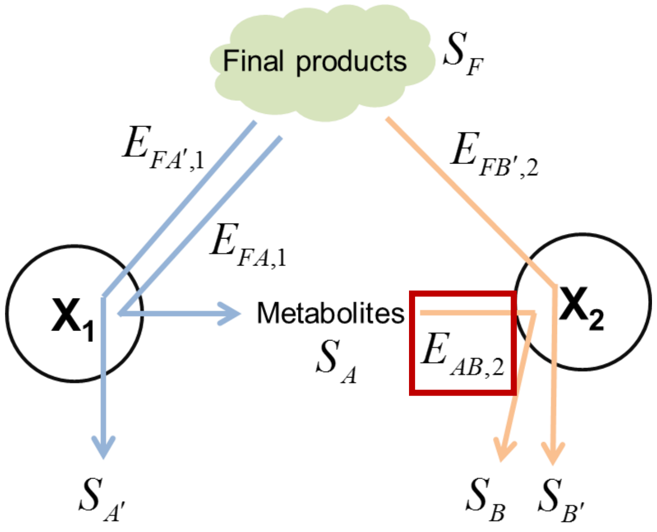
Microbial interactions in the CF subnetwork

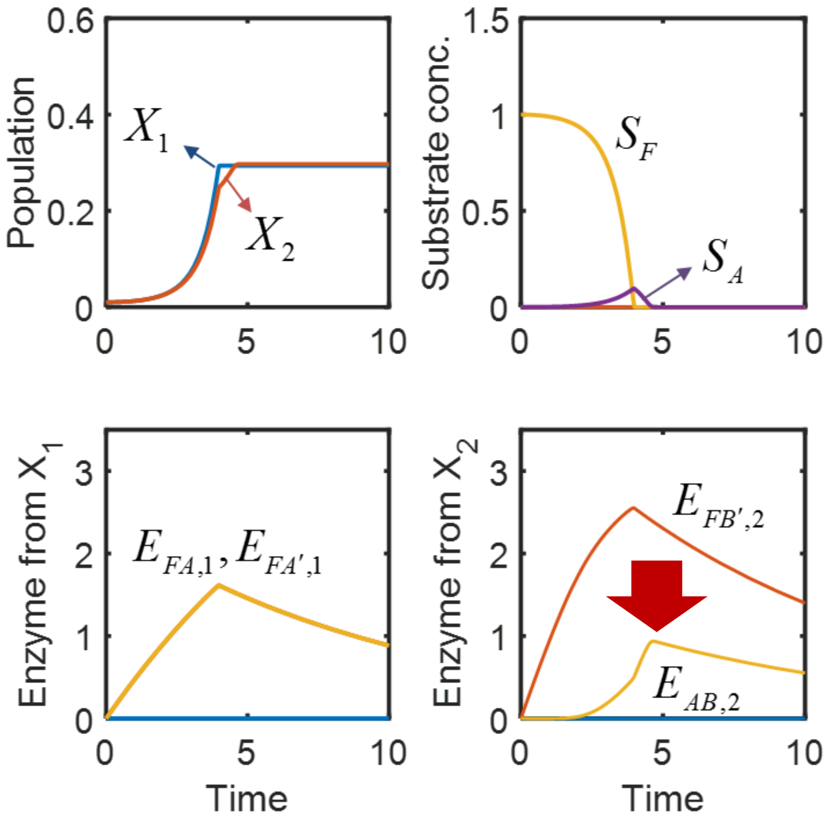




- X_1 constantly synthesizes equal amount of the two enzymes
- Initially, X_2 chooses to compete with X_1 for the hydrolysis product (S_F)

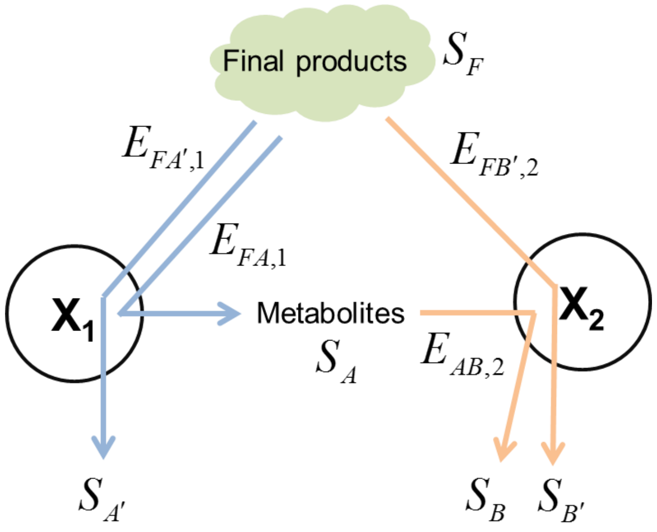
Microbial interactions in the CF subnetwork

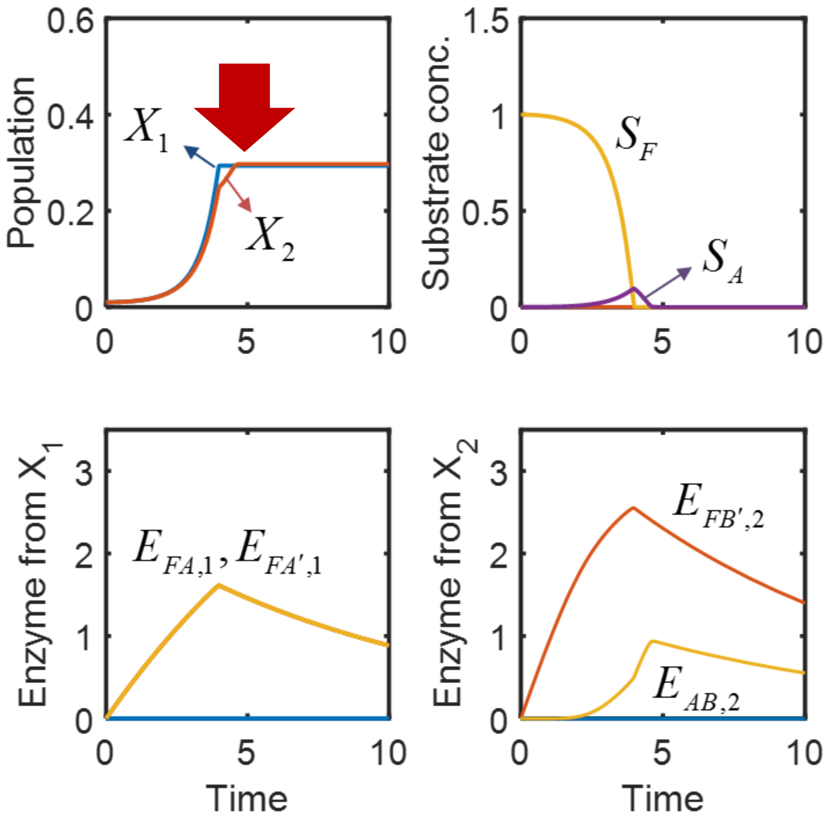




- X_1 constantly synthesizes equal amount of the two enzymes
- Initially, X_2 chooses to compete with X_1 for the hydrolysis product (S_F)
- As S_F becomes less available, X_2 avoids competition by taking S_A

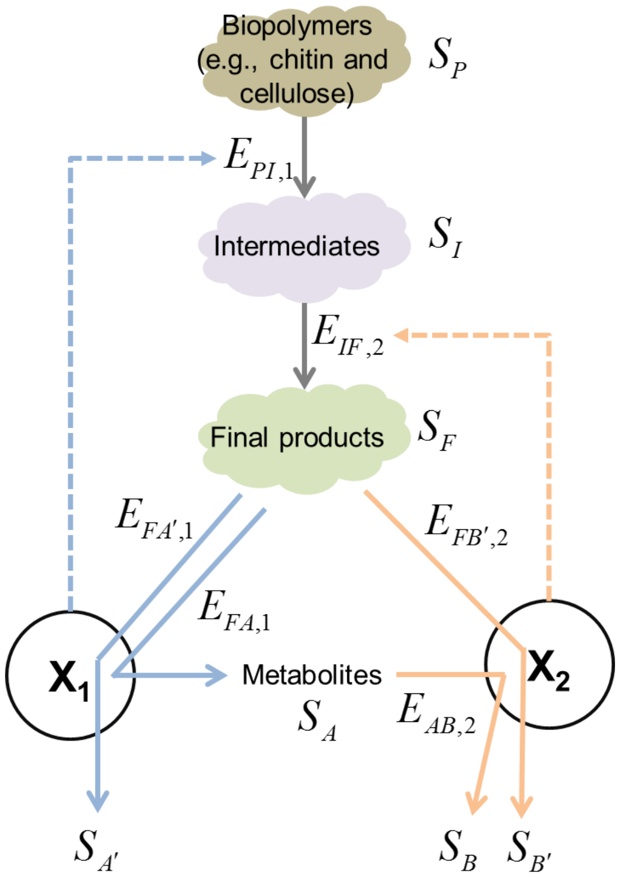
Microbial interactions in the CF subnetwork

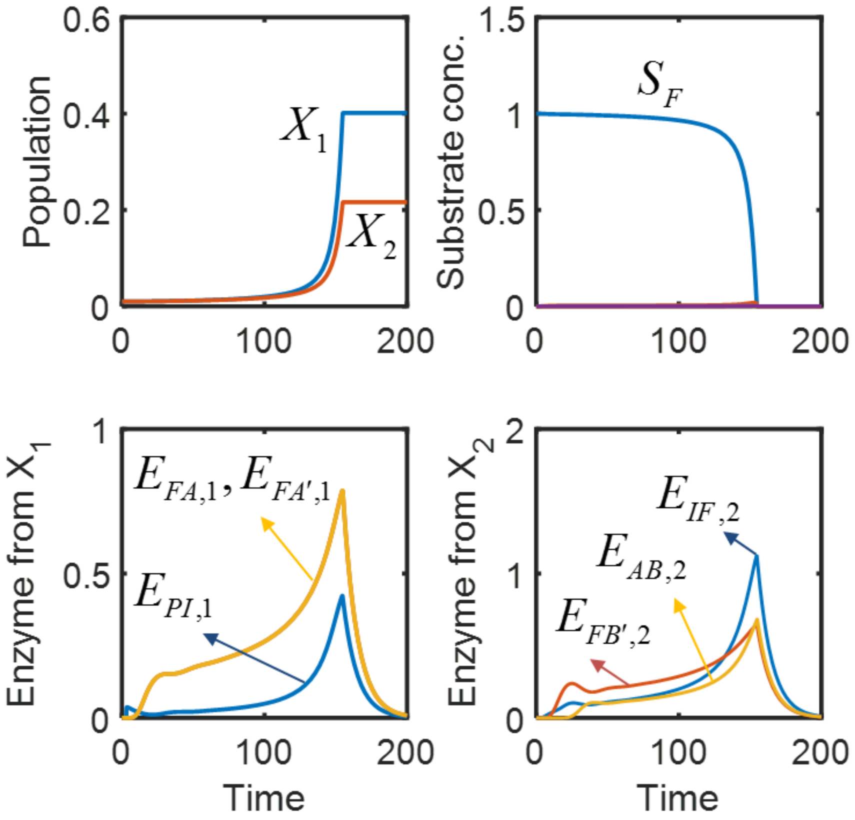




- X_1 constantly synthesizes equal amount of the two enzymes
- Initially, X_2 chooses to compete with X_1 for the hydrolysis product (S_F)
- As S_F becomes less available, X_2 avoids competition by taking S_A
- X_2 temporarily grows less during this transition, but catches up later

Microbial interactions in the combined network





- It shows striking similarities with the results from the DoL subnetwork
- Biopolymer degradation process governs the overall community dynamics!
- Prolonged timescales are only the difference

Concluding remarks

- Survival strategies of microorganisms
  - Innovation in metabolism
    - Optimal growth
    - Optimal switching
  - Building partnerships
- All survival strategies addressed above are well explained by economic behaviors of microorganisms maximizing return-on-investment (ROI)
- Cybernetic modeling uniquely accounts for metabolic ROI and optimal resource allocation to predict complex microbial dynamics
  - Prokaryotic cells
  - Eukaryotic cells
- Cybernetic modeling enables predicting microorganisms' social behaviors such as division of labor or cross-feeding from individualistic perspectives

Key references

Doraiswami Ramkrishna, the Harry Creighton Peffer Distinguished Professor of Chemical Engineering

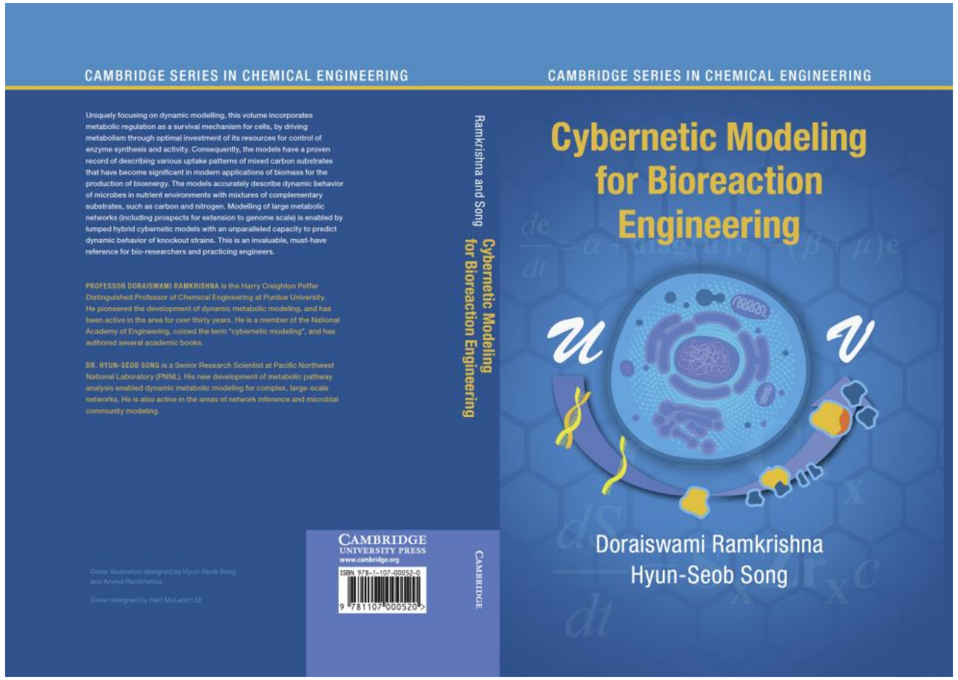
JOURNAL REVIEW

Dynamic Models of Metabolism: Review of the Cybernetic Approach

Doraiswami Ramkrishna and Hyun-Seob Song
School of Chemical Engineering, Purdue University, West Lafayette, IN 47907

DOI 10.1002/aic.13734
Published online February 2, 2012 in Wiley Online Library (wileyonlinelibrary.com).

The cybernetic approach to metabolic modeling tracing its progress from its early beginnings to its current state with regard to its relationship to other modeling approaches, applications to bioprocess modeling, metabolic engineering, and future prospects are described. The framework is shown to handle large metabolic networks in making dynamic predictions from limited data with looming prospects of extending to genome scale networks. © 2012 American Institute of Chemical Engineers *AIChE J*, 58: 986–997, 2012



Cambridge University Press (2018)