Constraints on Metabolic Network Analysis in Bacterial Physiology

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Table of contents

Introduction

Overview

PRX Life PRX Life 3, 022001 Published 1 April 2025 [9].

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Main ideas of this paper are:

- Characterize emergent properties of biological interactions in bacterial cells.
- These constraints are equivalent to Kirchhoff's laws and Ohm's law.
- Bacterial growth physiology can be analyzed quantitatively as electrical circuits ⇒ coarse-graining. [1]

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Laws of Bacterial Physiology

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"Life is required to make more life."

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Many emergent behaviors can be described by simple phenomenological laws:

(i) Rate at which environmental materials are assimilated is balanced according to composition

(ii) Rates are constrained by the autocatalytic nature of life

Exponential Growth

- When environmental nutrient is unlimited, population increases like

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- Balanced growth characterizes exponential phase: In order for cells to accumulate exponentially, generating processes must happen at balanced rates.

Metabolic Networks Are Complicated

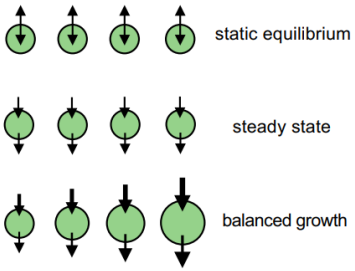

Figure 1: Comparison of equilibrium, steady state, and balanced growth [6].

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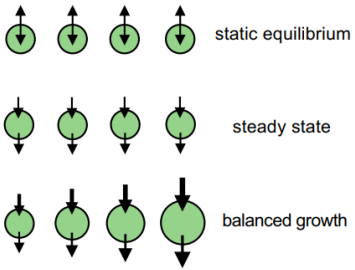

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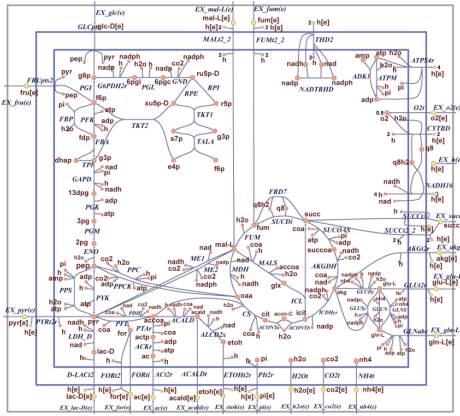

Figure 2: Core metabolic network of E. coli [7].

Flux Balance Analysis

- Stoichiometric matrix $S \in M_{m \times n}(R)$, biomass vector $X \in \mathbb{R}^n$:

$$\frac{dX}{dt} \equiv J = SX \tag{2}$$

S is *underspecified* (metabolism is an open system) and *sparse*.

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- Evolution selects cells that grow fast: $Z \propto \lambda$
- Metabolic reaction rates must be balanced during steady-state [2] growth: $J = 0$.

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Flux Balance is a Linear Programming Problem

Constrained Optimization

Maximize the objective function $Z = c \cdot x$
subject to

$$J = Sx = 0 \quad \text{(balanced growth)}, \qquad (3)$$

and

$$\text{lb}_i \leq x_i \leq \text{ub}_i \quad \text{(bounded rates)}. \qquad (4)$$

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Proteome Partition of E. coli

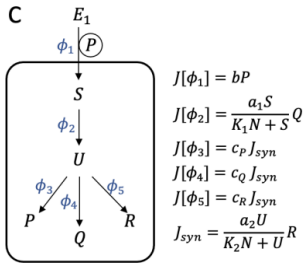

Figure 3: Three-sector proteome partition model (Lin, Wei-Hsiang, 2025) [9, 5]

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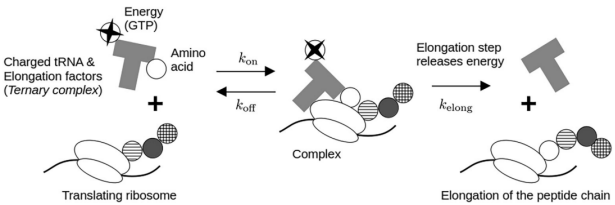

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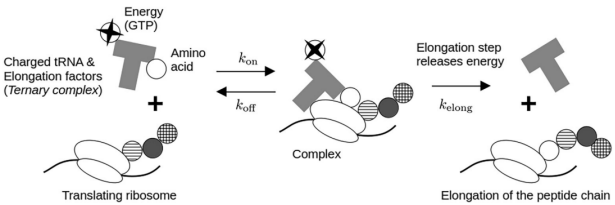

Figure 4: Ribosomes follow similar kinetics to those of enzymes: they turn charged tRNA into uncharged tRNA.

(Haldane) Abundance of the substrate far exceeds the abundance of the enzyme.

$$\text{rate} \propto [\text{Rb}] \times \frac{[\text{tRNA}]}{K_M + [\text{tRNA}]}. \quad (5)$$

Global Constraints

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Ohm's law: $\Delta V = I/G$.

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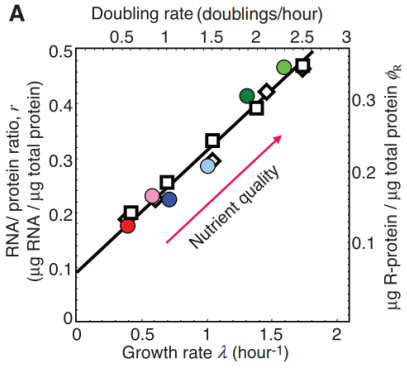

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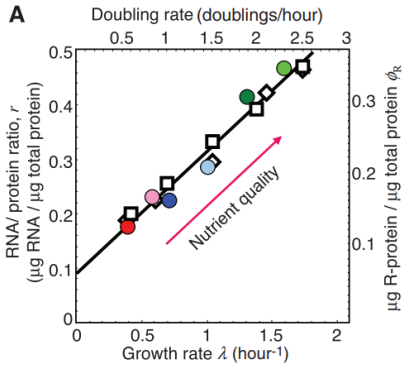

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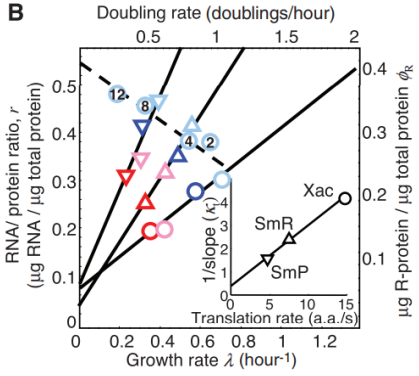

Figure 6: Growth rate is modulated by translational inhibition [8].

Proteomic Coarse-Graining and Electric Circuit

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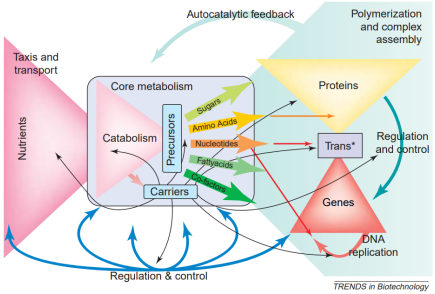

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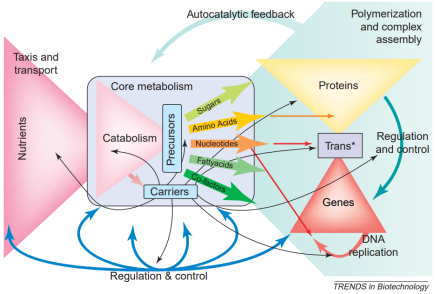

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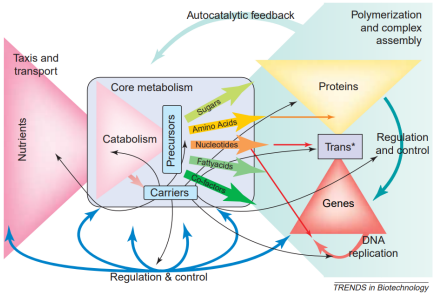

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- Bacterial metabolism and transcriptional machinery exhibits bow tie architecture
- Proteins can be partitioned into only few classes

Equivalent Circuits and Kirchhoff's Laws

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Kirchhoff's Laws

Governing laws for DC circuits

$$\sum_{\text{node } m} j_n = 0 \text{ (current law)}, \tag{7}$$

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j_n is proportional to λ.

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Thevenin's Law

A network of voltage sources and resistors can be replaced by an equivalent circuit with one voltage source and one resistor.

Anti-Correlation Among Proteome Sectors

- Proteome partition: coarse-graining proteins into sectors that behave similarly under specific probes, e.g. functionality

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- Proteome partition: coarse-graining proteins into sectors that behave similarly under specific probes, e.g. functionality
- Two sectors: $\phi_M^0 + \phi_R^0 = 1$
- Antibiotic decreases λ without affecting ϕ_M^0: modulates κ_R alone.
- Nutrient quality modulates κ_M.

Ohmics

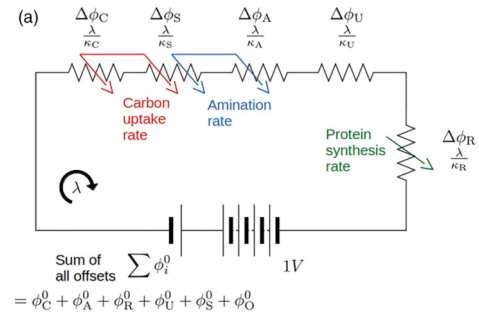

Figure 8: Six-sectors: ribosomes (R), carbon uptake (C), a.a. biosynthesis (A), carbon uptake + a.a. biosynthesis (S), **λ**-dependent but not inhibited (U), not **λ**-dependent [4].

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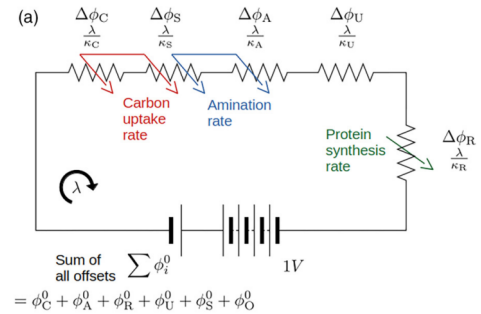

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Coarse-grain according to proteins' response to probes.

$$\lambda = \frac{1 - \phi_C^0 - \phi_A^0 - \phi_R^0 - \phi_U^0 - \phi_S^0 - \phi_O^0}{1/\kappa_C + 1/\kappa_A + 1/\kappa_R + 1/\kappa_U + 1/\kappa_S} \quad (9)$$

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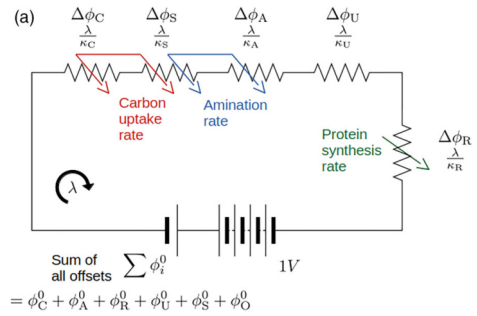

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Growth on ***N*** carbon sources:

$$\frac{1}{\kappa_C} \longrightarrow \frac{1}{\kappa_{C_1} + \kappa_{C_2} + \cdots + \kappa_{C_N}} \quad (10)$$

Applications

Antibiotic Transport and Binding

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- Qualitatively different behavior based on binding affinity.

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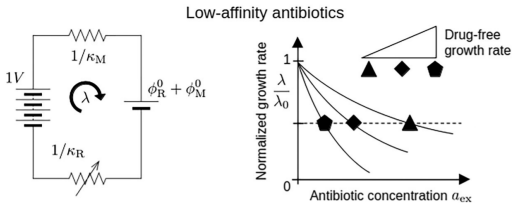

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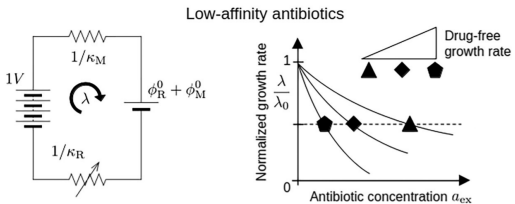

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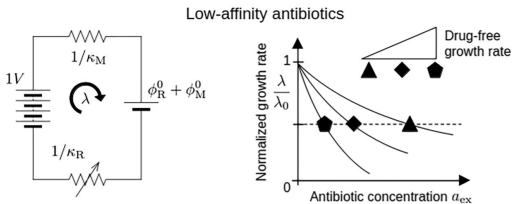

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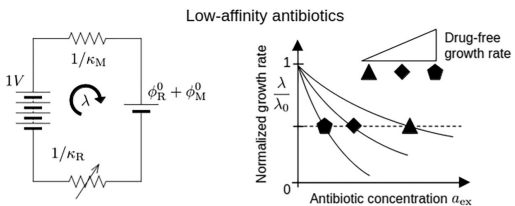

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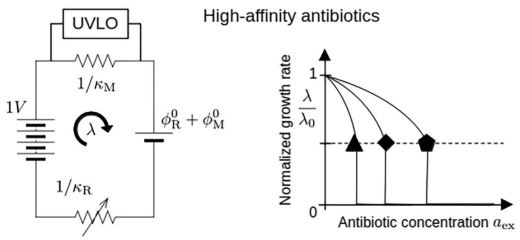

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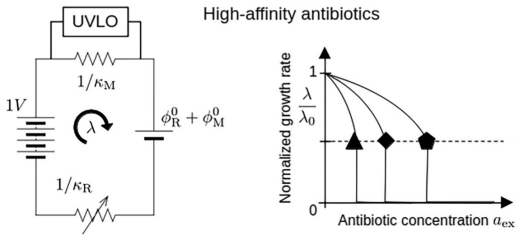

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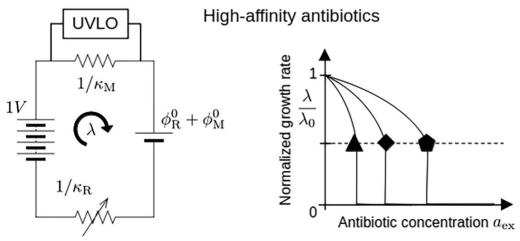

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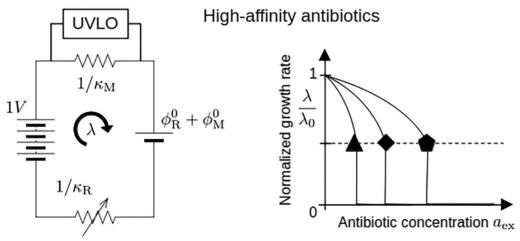

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- Mechanistic explanation:
  - $\boldsymbol{\phi}_{\mathrm{O}}^{0}$:decrease in porin *OmpF*
  - $\boldsymbol{\phi}_{\mathrm{A}}^{0}, \boldsymbol{\phi}_{\mathrm{S}}^{0}$: enzymes associates with pyruvate kinase *PykF*.

Concluding Remarks

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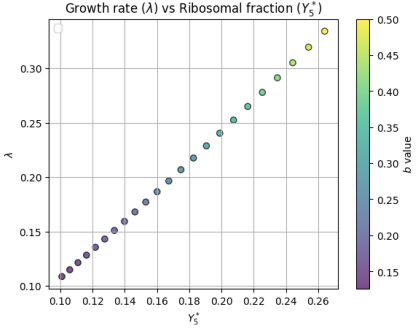

Figure 11: Three-sector partition (low nutrient).

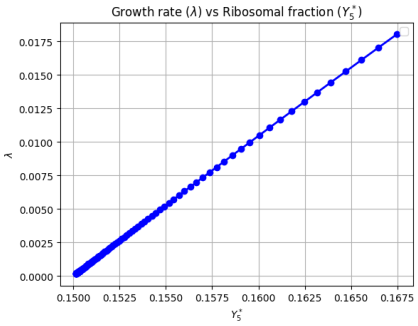

Figure 12: Six-sector partition (low nutrient).

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- Mechanistic justification for coarse-graining complex biochemical networks with circuits.
- Wealth of large-Ohmics data $\longrightarrow$ opportunity for synthetic biology.

Thank You

Q & A

References

References i

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