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Models of growing cells

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Abstract

In this chapter, we discuss the principles underpinning models of microbial growth, articulating the foundational assumptions that govern these systems. These premises serve as tools to unravel a sequence of progressively intricate examples, each with a unique layer of complexity that challenges and expands our understanding of microbial metabolic systems. Notably, the solutions derived from these models succeed in reproducing the core growth laws characteristic of microbial proliferation. The chapter also contemplates fundamental concepts in modeling, specifically, granularity and the determination of model assumptions. We aim to empower students with a robust theoretical framework and practical skill set for exploring microbial growth dynamics, fostering their ability to formulate, evaluate, and refine their own models.

Keywords: Model granularity, Modeling assumptions, Growth laws, Growth constraints, Flux balance, Proteome allocation

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Chapter highlights

- A comprehensive description of fundamental growth laws in microbial growth, elucidating the core principles that govern biological growth patterns.
- A detailed exploration of the contrasts between coarse-grained and fine-grained modeling is presented, offering insights into the varying levels of detail that each approach encompasses.
- A thorough breakdown of the key assumptions in the modeling of metabolic systems is provided, underlining the foundational premises that are crucial for accurately representing these complex systems.
- The process of deriving fundamental growth laws by modeling key assumptions is meticulously demonstrated, enabling a clear understanding of how theoretical constructs translate into biological realities.

8.1. Introduction

A key feature of living systems is that they are able to grow and reproduce. The reproductive success in a given environment defines the fitness of a living system. The study of the growth of bacteria and other microorganisms is crucial for better understanding their capacity to cause diseases in humans or for better exploiting their use in biotechnological or environmental processes. Beyond their interest for a variety of applications, bacteria and other microorganisms have shown themselves ideal model systems for investigating fundamental questions on the relation between growth, fitness and characteristics of the environment.

One of the first to systematically and quantitatively study the growth of bacterial cultures was Jacques Monod in the 1940s. He performed so-called diauxic growth experiments, in which bacteria were cultured in a medium containing two different limiting carbon sources. He showed that the bacteria first deplete one carbon source before starting to assimilate the second carbon source. The order in which the primary and secondary carbon source were consumed was determined by the growth rate they support: the preferred carbon source allows the culture to grow at a higher rate. Further work on the molecular basis of diauxic growth led to the discovery that cells inhibit the expression and activity of functions for the use of secondary carbon sources when a preferred carbon source is present, a global regulatory mechanism known as carbon catabolite repression [1, 2].

Monod characterized bacterial growth by means of batch culture experiments in a well-defined growth medium allowing bacteria to reach a state of balanced growth, where the accumulation of biomass can be described by a single constant, the exponential growth rate. Together with the chemostat, a device allowing continuous culture of microorganisms at a predefined growth rate [3], these methods have become standard in microbial physiology. They notably underlie the discovery of a number of so-called growth laws, relating the growth rate to a variety of properties of the physiology of growing bacteria. The growth laws are conserved across different organisms and a broad range of experimental conditions. Here, we list three well-known growth laws [4, 5]:

1. **Dependency of the growth rate on nutrient availability** [6]: In his characterization of bacterial growth, Monod discovered the first growth law. He observed that the growth rate of bacteria depends upon the nutrient concentration in the medium in a hyperbolic fashion .
2. **Correlation between growth rate and nutrient uptake rate** [7]: In continuous cultures, the growth rate was shown to vary linearly with the nutrient uptake rate . The slope of this linear relation is called the biomass yield and the offset the 'maintenance energy', as it is assumed to be derived from the energy spent on processes required to maintain the basic processes of the cell, in the absence of growth [8].
3. **Correlation between growth rate and cellular composition** [9, 10]: In 1959, Schaechter, Maaløe and Kjeldgaard showed that RNA, DNA and the number of nuclei in *Salmonella typhimurium* linearly correlate with the growth rate. Later, it was further shown that other physiological parameters, such as the mass fraction of ribosomes in growing populations, also linearly correlate with the growth rate [10] . Initially, it was believed that the correlation between ribosomal mass fraction and growth was strictly positive, however, Scott et al. [11] showed that when growth is inhibited through translation-inhibiting drugs, growth rate and ribosomal mass fraction exhibit a negative

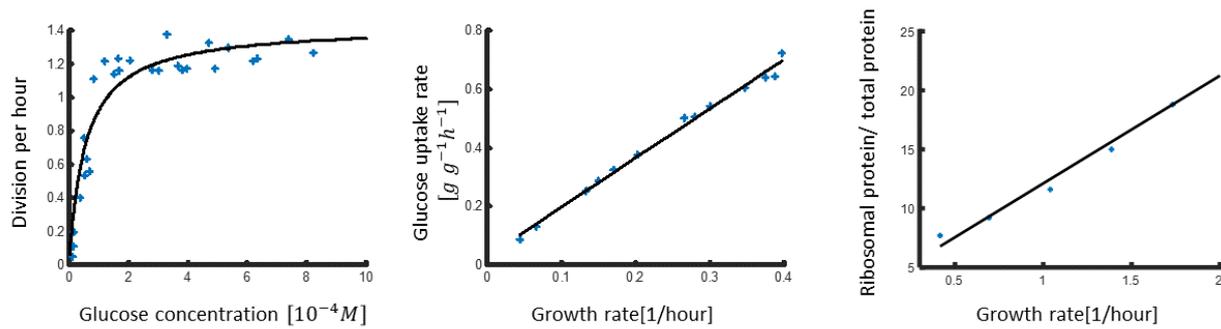


Figure 8.1: Growth laws of bacterial growth. A. Monod growth law: growth rate dependency on nutrient availability [Data from [6]]. B. Correlation between growth rate and nutrient uptake rate [Data from [12]]. C. Correlation between growth rate and cellular composition [Data from [10]]

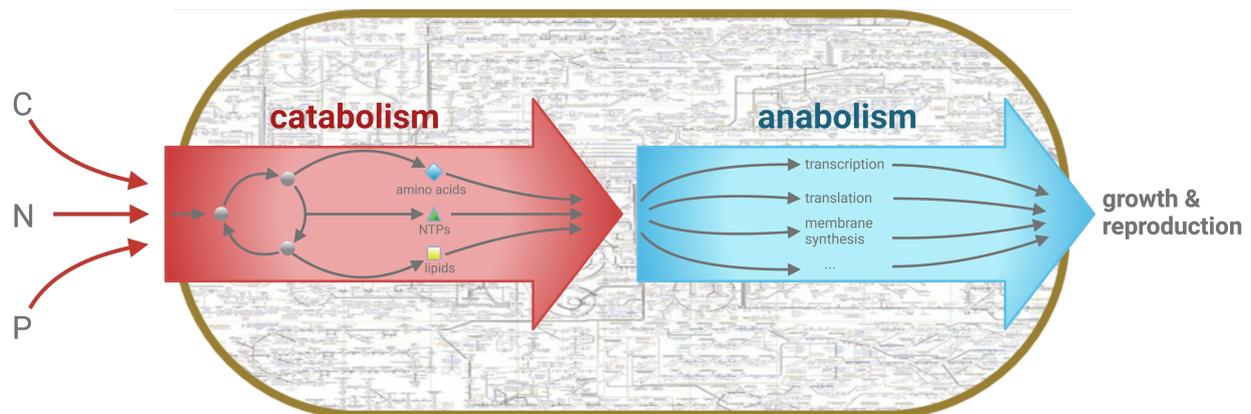


Figure 8.2: Coarse grained modelling of cellular growth. Compared to genome-scale FBA and whole-cell models, coarse grained models zoom out of the molecular detail and focus on key processes.

(near-)linear relation.

The conserved nature of the growth laws has led scientists to ask whether there are fundamental principles governing bacterial growth. To answer this question, different types of mathematical models have been developed. One approach aims at integrating all known molecular constituents of the cell and the reactions involving these constituents into a big model, an *in-silico* copy, or 'digital twin', of the cell. Such models, known as fine-grained models, can be useful to predict emergent phenotypes, but they are difficult to construct and maintain, and their complexity makes it hard to grasp certain principles that underpin growth. In this chapter, we will focus on coarse-grained models of bacterial growth. Rather than assembling individual reactions in a bottom-up manner, these models are based on the top-down definition of a limited number of basic cellular functions or processes involved in growth, described by appropriate macro-reactions. Coarse-grained models are smaller and therefore easier to construct and analyze. The lack of molecular detail can make their predictions less accurate, but their simplicity allows a focus on how basic cellular functions and their interactions shape bacterial growth. How much detail is included in a model depends on the specific scientific question asked, and similarly, models may vary in their underlying assumptions. Oftentimes, assumptions are based on biochemical principles governing intracellular reactions, on physical limitations faced by cells, on optimality principles, or on a combination of these.

In this chapter, we show how to understand and, ultimately, how to develop coarse-grained models of cellular growth. We present a number of coarse-grained models with increasing levels of granularity. The models have been chosen to also represent a variety of commonly used assumptions, for example, based on growth rate maximization or on phenomenological or mechanistic constraints. Despite these differences, however, models we discuss generally recover

the basic growth laws, and we show how the latter can be derived from solving two of the simplest coarse-grained models. The goals of this chapter are:

1. To enable the reader to understand and analyze any model of microbial growth from the literature.
2. To enable the reader to develop their own coarse-grained model of a metabolic system that is directed at their specific scientific question.
3. To provide the reader with a new perspective on modeling of complex systems and specifically the biological cell.

8.2. Fundamental modeling assumptions of microbial growth

The models of microbial growth we consider here are based on fundamental assumptions that follow from biochemical and biophysical constraints. In this section, we discuss and mathematically define assumptions that are found, explicitly or implicitly, in most coarse-grained models of microbial growth. The assumptions are formulated in an abstract manner to hold for any self-replicating biological system, irrespective of the specifics of the underlying molecular mechanisms. In the next section, we use these assumptions to construct increasingly complex models of microbial growth and show how the latter can be used to derive the experimentally observed growth laws presented in the introduction of this chapter.

The growth of microorganisms consists of the uptake of nutrients from the environment and the conversion of these nutrients into new microbial cells through a number of coupled metabolic processes. This description brings out the self-replicating or autocatalytic nature of microbial growth: cells transform nutrients from the environment into new cells. In what follows, we consider growth on the population level, that is, an increase in the total amount of cells or, equivalently in many situations, an increase of the biomass of the population. This leads to the well-known model of microbial growth, where the change in biomass over time is proportional to the amount of biomass (λ):

$$\frac{dB}{dt} = \lambda B, \quad (8.1)$$

where t [h] denotes time, B in gram dry weight [gDW] the biomass and λ [1/h] the population growth rate.

If the growth rate is constant, the solution to Eq. (8.1) describes exponential growth of the biomass:

$$B = B_0 e^{\lambda t}, \quad (8.2)$$

where B_0 [gDW] is the initial biomass at $t = 0$.

The growth rate is a key parameter that is often used as a proxy for the fitness of microorganisms. It is dependent on the metabolic processes, that is, how a cell utilizes the nutrients to synthesize new biomass (self-replication). The simplest description of metabolism is that it takes up a nutrient, breaks it down into metabolites (catabolism), and then utilizes these metabolites to produce new biomass (anabolism). Catabolic and anabolic processes comprise a variety of biochemical reactions that are carried out by different sets of proteins and enzymes. The reaction rates of these processes are limited biochemically and biophysically. We formulate these limitations as modeling assumptions and define them as mathematical constraints, four of which we briefly review below.

8.2.1. Conservation of mass and quasi-steady-state assumption

Dry biomass is often a more readily measurable quantity than cell volume. The latter relates absolute abundances of cell components to their intracellular concentrations. Yet, because bacterial cells have been observed to maintain approximately constant cell density across various growth conditions [13, 14] (though transient exceptions have been observed at the single-cell level [15]), biomass can be regarded a proxy for volume and is therefore assumed to be proportional to cell volume in many growth models. All models considered in this chapter are based on the assumption of constant cell density and approximate the concentration x of a cellular component x (we use normal font for cell components and italic font for their concentrations) by its absolute abundance divided by the cell mass.

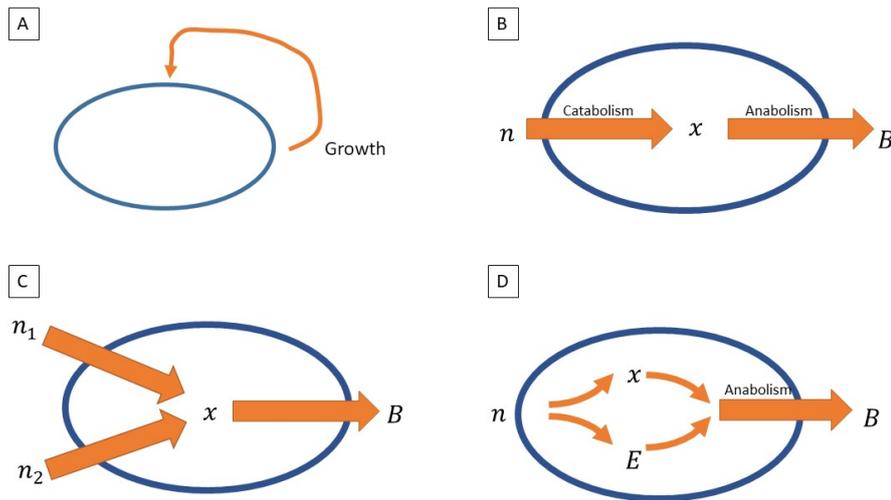


Figure 8.3: Coarse grained models of metabolic systems with increasing complexity. A. A self replicating system. B. The simplest description of a metabolic system: coupled catabolic and anabolic reactions. C. A metabolic system that can catabolize two different nutrient sources. D. A catabolic system requiring two substrates to grow: x and E .

According to the law of mass conservation, the change of mass is equal to the inflow minus the outflow of mass. As a consequence, the change in concentration of a cell component, for example a metabolite pool, is determined by the sum of the rates of the reactions consuming and producing this cell component. The mass balance for any cell component x is given by the following equation:

$$\frac{dx}{dt} = \sum_y r_{y \rightarrow x} - \sum_k r_{x \rightarrow k}, \quad (8.3)$$

where $r_{y \rightarrow x}$ denotes the rate of the reaction converting cell component y into cell component x (production of x), and $r_{x \rightarrow k}$ the rate of the reaction converting cell component x into cell component k (consumption of x). Typically, cell component concentrations have units mg/gDW or mmol/gDW , so that rates of metabolic reactions are expressed in units $\text{mg}/(\text{gDW h})$ or $\text{mmol}/(\text{gDW h})$.

In the simple system of B, there are two reactions: one converting the nutrient source n into metabolite x and one utilizing the metabolite for the synthesis of biomass. According to (8.3), the flux balance of metabolite pool x is given by $dx/dt = r_{n \rightarrow x} - r_{x \rightarrow B}$.

A key assumption is that intracellular concentrations are in quasi-steady state. This means that cell component pools remain constant:

$$\frac{dx}{dt} = 0, \text{ for all cell components } x. \quad (8.4)$$

The quasi-steady-state assumption simplifies the mathematical analysis of the system significantly and holds for balanced growth of the microbial population. In this chapter, we focus mostly on situations in which the quasi-steady-state assumption applies, but also give an example of a model with metabolic dynamics. In metabolic modeling, the rates of reactions at steady state are called fluxes, denoted by the symbol J . With the quasi-steady-state assumption, Eq. (8.3) becomes

$$\sum_y J_{y \rightarrow x} = \sum_k J_{x \rightarrow k} \quad (8.5)$$

that is, for every cell component, the sum of production fluxes equals the sum of consumption fluxes. In the example system, we have $J_{n \rightarrow x} = J_{x \rightarrow B}$.

8.2.2. Proteome allocation assumption

The biochemical reactions breaking down nutrients into intracellular metabolites, and the reactions utilizing these metabolites for the synthesis of new biomass, do not occur spontaneously. The reactions are catalyzed mostly by proteins complexes, in particular metabolic enzymes and ribosomes. In coarse-grained models, well-defined sets of biochemical reactions are grouped together into macro-reactions. The cell components that are necessary to catalyze the individual steps of a macro-reaction are grouped together into a corresponding so-called proteome sector. A proteome sector includes mostly proteins that catalyze metabolic reactions but also ribosomes catalyzing the reaction of protein biosynthesis. Proteins constitute most of the biomass of the cell [16]. As a first approximation, therefore, the sum of the proteome sectors equals the total biomass of the growing population measured in units of g :

$$\sum_{r \in \{x \rightarrow y\}} P_r = B, \quad (8.6)$$

where $P_{x \rightarrow y}$ is the proteome sector catalyzing the macro-reaction that transforms cell component x into cell component y . The proteome sectors as defined above are extensive quantities, summed over the entire growing population, like the total biomass B . For the models, we are rather interested in intensive quantities, the amount of a proteome sector relative to the total amount of biomass (protein), corresponding to protein concentrations or protein fractions. Dividing the left-hand and right-hand sides of Eq. (8.6) by B , we thus obtain:

$$\sum_{r \in \{x \rightarrow y\}} p_r = 1 \quad (8.7)$$

where $p_{x \rightarrow y}$ is the fraction of the proteome converting x into y , defined by $p_{x \rightarrow y} = P_{x \rightarrow y}/B$. Proteome fractions are dimensionless and sum to one.

In the simple example of , we distinguish two macro-reactions: a catabolic reaction and an anabolic reaction (biomass synthesis). We therefore define two proteome sectors, corresponding to enzymes and ribosomes, respectively, with fractions $p_{n \rightarrow x}$ and $p_{x \rightarrow B}$, respectively. In later examples in the chapter, the catabolic and anabolic processes are further broken down into smaller macro-reactions and so are the proteome sectors.

8.2.3. Mathematical description of reaction fluxes

The rate at which a reaction is converting one cell component, e.g., a metabolite, into another is determined by the proteome fraction, the concentrations of the substrates of the reaction and possible regulation by other cell components in the system. While mass-action kinetics provide a principled framework to develop rate equations for biochemical reactions, in practice, various approximations based on mechanistic assumptions are often used to obtain simplified equations [17]. Below are a few examples of rate laws defining the fluxes in coarse-grained models:

1. *Excess substrate and no allosteric interactions.* The simplest relation of the flux to the relevant proteome sector is linear, such that

$$J_{x \rightarrow y} = p_{x \rightarrow y} \beta_{x \rightarrow y}, \quad (8.8)$$

where $\beta_{x \rightarrow y}$ is a parameter describing the efficiency of proteome sector $p_{x \rightarrow y}$ in generating a flux from x to y . This expression assumes substrate x is in excess and disregards any regulation of the flux by allosteric interactions of the enzymes and other cell components.

2. *Limited substrate and allosteric interactions.* A more complex relation is obtained when the substrate is in excess and allosteric interactions involving a cell component n play a role in the modulation of the flux. The expression of the flux is multiplied by two regulatory functions $f(x)$ and $g(n)$ describing the modulation of the flux by the

substrate and the allosteric cell component, respectively:

$$J_{x \rightarrow y} = p_{x \rightarrow y} \beta_{x \rightarrow y} f(x) g(n). \quad (8.9)$$

It is important to note that both $f(x)$ and $g(n)$ return values between 0 and 1, and that the flux remains linear in the proteome fraction. Typically, a Michaelis-Menten relation is taken for the effect of the concentration of substrate x on the flux, such that $f(x) = x/(k_{x \rightarrow y} + x)$. When the concentration x is in excess, such that $x \gg k_{x \rightarrow y}$, the function $f(x)$ becomes approximately 1. Other types of regulatory functions can be used depending on the macroreactions concerned and the growth conditions.

8.2.4. Volume and surface area assumptions

The intracellular volume as well as the surface area of the cell are limited. Obviously, the total volume occupied by the components of the cell, in particular proteins, cannot be larger than the cell volume. As such, the total volume of the cell is larger than the sum of the volume of the proteome sectors that are functioning inside the cell plus some constant volume taken up by other cell components such as DNA. This gives the following constraint:

$$\text{Cell volume} \geq \sum_{r \in \{x \rightarrow y\}} p_r v_r + v_0 \quad (8.10)$$

where $v_{x \rightarrow y}$ is the volume of proteome sector $p_{x \rightarrow y}$ and v_0 is some constant volume filled by other cell components. Similarly, the total surface occupied by proteins and lipids making up the cell membrane has to equal the surface area of the cell. This constraint gives:

$$\text{Cell surface area} \geq \sum_{r \in \{x \rightarrow y\}} p_r s_r + l_0 \quad (8.11)$$

where $s_{x \rightarrow y}$ is the surface area of proteome sector $p_{x \rightarrow y}$ and l_0 is the surface area of the lipids in the cell membrane.

8.3. Derivation of growth laws from basic modeling assumptions

In the following section, we will build upon the fundamental assumptions discussed earlier to construct models of microbial metabolism with increasing complexity. We will introduce additional assumptions as necessary to solve each model, and use them to derive one of the growth laws presented in the introduction of this chapter that have been experimentally observed in microorganisms.

Example 1 - Basic metabolic system with saturating substrate concentrations In this example, we will use the basic metabolic model to derive the relationship between the concentration of ribosomes and the growth rate in microorganisms. The most basic metabolic model involves the uptake of a single nutrient from the environment, the catabolism of that nutrient into a metabolite x , and the use of this metabolite in anabolic processes to synthesize biomass. This model consists of two reactions and two proteome sectors. According to the proteome allocation constraint, the sum of the proteome sectors must sum to one (according to Eq. (8.7)):

$$p_{n \rightarrow x} + p_{x \rightarrow B} = 1. \quad (8.12)$$

For simplicity, we assume that the rate of each reaction is proportional to the allocation of the proteome to that reaction (according to Eq. (8.8)), so that:

$$J_{n \rightarrow x} = p_{n \rightarrow x} \beta_{n \rightarrow x}; \quad J_{x \rightarrow B} = p_{x \rightarrow B} \beta_{x \rightarrow B}. \quad (8.13)$$

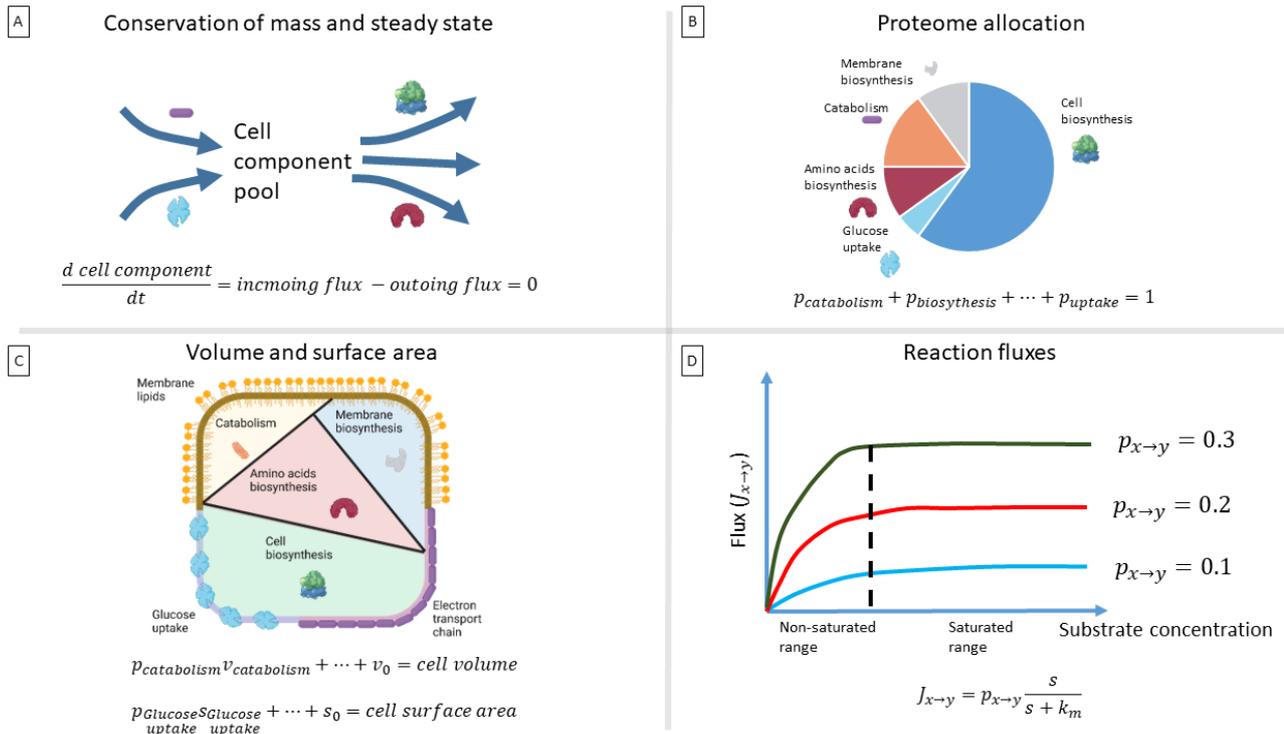


Figure 8.4: Fundamental assumptions in the modeling of microbial growth. A. Conservation of mass and steady-state assumption: The change in concentration of a cell component is equal to the incoming flux minus the outgoing flux. At steady state, the concentration of the cell component is constant. B. Proteome allocation assumption: the proteome is divided into different proteome sectors. The number of proteome sectors in a model depends on the model granularity. The sum of all the proteome sectors always equals 1. C. Volume and surface area assumption: The volume of the cell is limited and is filled with intracellular cell components such as proteins. The sum of the volumes of the intracellular cell components is equal to the cell volume. Similarly, the surface area of the cell is limited and contains membrane cell components such as lipids. The sum of the surface areas of membrane cell components is equal to the cell surface area. D. Example of flux assumption according to Michaelis-Menten kinetics: the reaction $x \rightarrow y$ is carried out by proteome sector $p_{x \rightarrow y}$. The maximal rate is reached for saturating substrate concentrations and is determined by the size of the proteome sector.

The mass conservation constraint, with the assumption of a steady state for metabolite x , gives (according to Eq. (8.5)):

$$J_{n \rightarrow x} = J_{x \rightarrow B}. \quad (8.14)$$

Finally, due to conservation of mass, the biomass synthesis flux equals the growth rate:

$$\lambda = J_{x \rightarrow B}. \quad (8.15)$$

Solving equations (8.12)-(8.15) gives a prediction for the growth rate:

$$\lambda = \frac{\beta_{x \rightarrow B} \beta_{n \rightarrow x}}{\beta_{x \rightarrow B} + \beta_{n \rightarrow x}}. \quad (8.16)$$

Solution (8.15) for the growth rate is based solely on *mechanistic assumption* - that is, assumptions that are based on the mechanistic properties of the biochemical reactions in the cell. In this case, that is that the fluxes are linear to the relevant proteome sector. Because we have taken a steady state approximation and the rates of the two reactions must be equal, the growth rate is determined by the relative values of the catalytic constants.

Using this model, we can now derive the relationship between the concentration of ribosomes and the growth rate.

Combining Eq. ((8.12)) and ((8.14)) gives:

$$\lambda = p_{x \rightarrow B} \beta_{x \rightarrow B} \quad (8.17)$$

This shows that the the growth rate is linearly proportional to the anabolic sector. Given that the anabolic sector is composed mostly of ribosomes, this fits well with the experimentally observed linear relationship between the concentration of ribosomes and the growth rate, which was first described by Schaechter *et al.*[9] and later confirmed by Bremer *et al.*[10]. It is important to notice that this relation is due to the assumption that the biomass synthesis flux is linear in the ribosomal proteome sector.

In summary, we have derived the linear relationship between the concentration of ribosomes and the growth rate using only basic assumptions about the properties of the biochemical reactions in the cell and the conservation of mass. This relationship is one of the experimentally observed growth laws in microbial systems.

Example 2 - Growth on two nutrient sources In this example, we consider a metabolic system that grows on two different nutrient sources, n_1 and n_2 . We use the fundamental assumptions outlined in Section 1.2 and an additional assumption of growth-rate maximization to demonstrate how cells may exhibit catabolite repression - a phenomenon in which cells utilize only one nutrient even when multiple nutrients are available in the environment [2].

The metabolic system in this example catabolizes both nutrient sources to the same metabolite x , but at different efficiencies. The anabolic reaction is the same as in Example 1. There are now three proteome sectors in this model: two for catabolism of the nutrients and one for anabolism. Thus, according to the proteome allocation constraint (Eq. 8.7), we have:

$$p_{n_1 \rightarrow x} + p_{n_2 \rightarrow x} + p_{x \rightarrow B} = 1. \quad (8.18)$$

As before, we assume a linear correlation between reaction rates and proteome sector fractions (according to Eq. (8.8)). The different efficiencies of the catabolic sectors is represented as $\beta_{n_2} > \beta_{n_1}$. Applying the mass conservation assumption for metabolite x , combined with the steady state assumption, gives

$$J_{n_1 \rightarrow x} + J_{n_2 \rightarrow x} = J_{x \rightarrow B}. \quad (8.19)$$

The growth rate is again equal to biomass synthesis flux, as in Example 1:

$$\lambda = J_{x \rightarrow B} \quad (8.20)$$

Given that there are more variables than constraints in this example, solving eqs reveals that there is no unique solution for the growth rate, but rather a solution space with one free variable $p_{n_1 \rightarrow x}$:

$$\lambda = \frac{\beta_{x \rightarrow B} \beta_{n_2 \rightarrow x}}{\beta_{x \rightarrow B} + \beta_{n_2 \rightarrow x}} + p_{n_1 \rightarrow x} \left(\frac{\beta_{n_1 \rightarrow x} - \beta_{n_2 \rightarrow x}}{\beta_{x \rightarrow B} + \beta_{n_2 \rightarrow x}} \right) \beta_{x \rightarrow B} \quad (8.21)$$

The solution shows that the metabolic system has a decision to make regarding how much of the proteome to invest in sector $p_{n_1 \rightarrow x}$. To solve this system, we introduce an additional assumption of *growth rate optimization* – that is, to maximize its fitness, the metabolic system maximizes the growth rate in a given condition. In this example, to maximize the growth rate, the cell uses only the more efficient catabolic system, setting $p_{n_1 \rightarrow x} = 0$ and the solution for the growth rate is as in example 1. The model predicts that the cells will only utilize the nutrient source with the higher efficiency, even if both nutrient sources are available in the environment. This solution fits the catabolite repression experimental result presented in the introduction in which in which the metabolic system represses the use of a less efficient nutrient source in favor of a more efficient one.

Problems

Problem 8.1 A system is composed of a set of 2 linear reactions: nutrient \rightarrow metabolite $x_1 \rightarrow$ metabolite $x_2 \rightarrow$ biomass. Using the same approximations as in example 1, solve for the growth rate. What would be the solution for a system composed of N reactions? Show that the least efficient reaction determines the growth rate.

Problem 8.2 Solve Example 2 when the nutrients are not available in excess. Use Michaelis-Menten relations for the catabolic reactions. At what point does the metabolic system switch to use the other nutrient source?

Problem 8.3 A simple model with allosteric regulation of catabolic reaction: A metabolic system is growing in an environment with one nutrient available. The system regulates its catabolic reaction according to the concentration of metabolite x . What is the growth rate as function of catabolic sector proteome size? What is the catabolic sector proteome size that maximizes the growth rate? (

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