Constructing a Dynamical Model of Nutrient-Dependent Growth

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1 Theoretical Underpinnings

1.1 Translation-Limited Growth

We begin by considering balanced exponential growth on a single carbon source. For the time being, we will consider a growth regime where translation is limiting and we will assume that nutrients are in abundance. In this phase of growth, we can consider the formation of protein mass as the most resource-intensive process and can relate the total protein mass of the cell M to the characteristic growth rate λ via

$$\frac{dM}{dt} = \lambda M. \tag{1}$$

This protein mass M is the product of the pool of ribosomes which catalyze the formation of peptide bonds via translation. Equation (1) can be cast in terms of the total number of actively translating ribosomes $N_R^{(act.)}$ as

$$\frac{dM}{dt} = N_R^{(act.)} k_R, \tag{2}$$

where k_R represents the average translation rate per active ribosome with dimensions of $[MT^{-1}]$. It's important to note that here we are considering only the *actively* translating ribosomes. Whether through active regulation (such as through ppGpp) or ribosomes waiting to bind an mRNA or awaiting the arrival of a charged tRNA, there is always some pool of ribosomes that are *inactive*, $N_R^{(inact)}$. Given knowledge of the total number of ribosomes $N_R = N_R^{(act.)} + N_R^{(inact.)}$, we can state

$$\frac{dM}{dt} = \left[N_R - N_R^{(inact.)}\right] k_R. \tag{3}$$

Equating this with Equation (1) yields an expression for the growth rate λ,

$$\lambda = \frac{\left[N_R - N_R^{(inact.)}\right] k_R}{M}. \tag{4}$$

Rather than keeping track of the number of ribosomes, we can refer to the total ribosomal mass M_R and $M_R^{(inact.)}$ given knowledge of the unit mass of one ribosome m_R,

$$M_R = m_R N_R. \tag{5}$$

Doing so allows us to cast Equation (4) in terms of the *ribosomal mass fraction* ϕ_R and $\phi_R^{(inact.)}$,

$$\lambda = \frac{\left[M_R - M_R^{(inact.)}\right] k_R}{M m_R} = \gamma \left[\phi_R - \phi_R^{(inact.)}\right] \tag{6}$$

where we've introduced $\gamma = \frac{k_R}{m_R}$, a term commonly referred to as the *translational capacity*. This term γ has dimensions of $[T^{-1}]$ and can be thought of as effective translation rate. The inverse of this term has dimensions of $[T]$ and defines the amount of time it takes for the synthesis of one ribosomes' worth of protein mass. Equation (**??**) can be rearranged to describe the mass fraction ϕ_R as a function of the growth rate,

$$\phi_R = \phi_R^{(inact.)} + \frac{\lambda}{\gamma}. \tag{7}$$

In the limit where the cell is not growing (i.e. $\lambda \to 0$), we find that $\phi_R = \phi_R^{(inact.)}$, illustrating that $\phi_R^{(inactt.)}$ is the *minimal* fraction of the protein mass that is occupied by ribosomes. Therefore, we will make the definition of

$$\phi_R^{(inact.)} \equiv \phi_R^{(min)} \tag{8}$$

for notational clarity.

1.2 Nutrient-Limited Growth

We now turn our attention to the fact that, in order for ribosomes to form peptide bonds, nutrients must be metabolized to produce tRNAs charged with amino acids. Thus, the nutritional extent of the growth medium will dependent on how the cell maximizes the flux from raw nutrients to amino acids.

Let's consider some amino acid a whose total mass in the cell is M_a. In balanced exponential growth, this mass M_a is defined by the flux of of a into the cell (via a combination of transport of nutrients and metabolism to form a) and the rate at which they are consumed via translation. Mathematically, this can be stated as

$$\frac{dM_a}{dt} = J_a - \beta \frac{dM}{dt}, \tag{9}$$

where J_a is the flux of a into the cell and β is the frequency with which it is integrated into the proteome. For example, if we are considering a single species of amino acid and we make the approximation that amino acids are used with equal frequencies, $\beta = \frac{1}{20}$.

In reality, there is always some non-zero concentration of free amino acids that the cell must maintain. We can consider the relative masses of the standing pool of amino acids and the mass of the total proteome as a measure of concentration,

$$\theta_a \equiv \frac{M_a}{M}. \tag{10}$$

Given this formulation, Equation (9) can be amended to include maintenance of the free amino acid concentration as

$$\frac{dM_a}{dt} = J_a - (\beta + \theta_a) \frac{dM}{dt}. \tag{11}$$

Dividing both sides of Equation 11 by the total proteome mass M reparameterizes the entire dynamics in

terms of the nutrient mass fraction θ_a, yielding

$$\frac{1}{M}\frac{dM_a}{dt} = \frac{d\theta_a}{dt} = \frac{J_a}{M} - \lambda(\beta + \theta_a). \tag{12}$$

In steady-state growth, the fluxes are balanced, allowing us to enumerate an expression for the growth rate λ as

$$\lambda = \frac{J_a}{M\left(\beta + \theta_a\right)}. \tag{13}$$

The inward flux of nutrients to produce charged tRNAs J_a represents the concerted action of a battery of metabolic enzymes, including transporters and potentially entire metabolic pathways. We can coarse-grain this entire process by considering the total protein mass of all of the metabolic proteins involved in processing a given nutrient as M_P. Together, these proteins produce amino acids at some effective rate k_P such that

$$J_a = k_P M_P, \tag{14}$$

where k_P has dimensions of $[T^{-1}]$. It is important to note that this is not exactly an enzymatic rate, however, but represents the total mass of nutrient that can be transported/synthesized per unit mass of metabolic protein per unit time. Plugging Equation (14) into Equation (**??**) yields a complete expression for the growth rate

$$\lambda = \frac{k_P}{\beta + \theta_a}\frac{M_P}{M} = \frac{k_P}{\beta + \theta_a}\phi_P, \tag{15}$$

where we have introduced the notation ϕ_P to denote the mass fraction of the proteome occupied by metabolic proteins.

In Section 1.1, we used similar notation to denote the mass fraction of the proteome which is occupied by ribosome ϕ_R. As ϕ_P and ϕ_R are both bounded by the total mass of the proteome, they must by definition compete for resources. If we consider these two categories are the only classes of proteins making up the proteome, there exists the constraint that

$$\phi_P + \phi_R = 1. \tag{16}$$

However, neither ϕ_P nor ϕ_R can ever be equal to 1. Rather, we can state that there exists a maximum fraction of the proteome that can be occupied by either class of proteins. For consistency with Section 1.1, we can cast this constraint in terms of the maximal ribosomal mass fraction $\phi_R^{(max)}$ as

$$\phi_P + \phi_R = \phi_R^{(max)}, \tag{17}$$

which captures the fact that any increase in ϕ_P must come at the expense of ϕ_R.

Using this constraint, Equation (15) can be defined in terms of the ribosomal mass fraction as

$$\lambda = \frac{k_P}{\beta + \theta_a}\left[\phi_R^{(max)} - \phi_R\right]. \tag{18}$$

In typical physiological conditions, the standing pool of amino acids is small when compared to its incorporation in the the proteome, permitting the approximation that $\beta + \theta_a \approx \beta$. Making this approximation

allows us simplify Equation 18 to yield

$$\lambda = \frac{k_P}{\beta}\left[\phi_R^{(max)} - \phi_R\right] = \nu\left[\phi_R^{(max)} - \phi_R\right]. \tag{19}$$

The parameter ν is often referred to as the *nutritional capacity*. This parameter relates the rate at which nutrient mass (per unit mass of metabolic protein) is produced to its corresponding frequency of usage. This result is classically rewritten to express the ribosomal mass fraction ϕ_R as a function of growth rate,

$$\phi_R = \phi_R^{(max)} - \frac{\lambda}{\nu}. \tag{20}$$

1.3 Condition-Dependent Regulation of γ and ν

Thus far, we have presented γ and ν as constants. For a given growth condition (such as a single growth medium) this is approximately true. However, both of these parameters are the target of regulation given the availability of precursors or charged tRNAs. There are many ways we can consider how these parameters are tuned as a function of the environment.

For now, we can make the reasonable assumption that the translational capacity γ follows a simple Michaelis-Menten dependence on the standing pool of the amino acid concentration θ_a,

$$\gamma(\theta_a) = \frac{\gamma^{(max)}}{1 + \frac{\theta_0}{\theta_a}}, \tag{21}$$

where θ_a^* is the Michaelis-Menten constant and represents the concentration of amino acids at which the translational capacity is half maximal. In this formulation, the translational capacity will be maximized when the standing pool of the amino acids is large such that $\theta_a >> \theta_0$. As the nutrient conditions dwindle, however, γ will asymptotically approach 0 as $\theta_a << \theta_0$.

In a similar fashion, we can make the assumption that the nutritional capacity of a given growth condition will be dependent on the concentration of the nutrients. In the condition when nutrients are plentiful, the yield of amino acids per unit mass of metabolic protein should be maximal. This should be true of ν *for a given nutrient source*, assuming that nutrient's concentration is the tunable parameter. Thus, the standing amino acid pool θ_a is less important in setting the value of ν than is the concentration of the actual nutrient, which we will denote hereafter as c. For a given concentration, we can define the nutritional capacity as having the form of a Monod expression,

$$\nu(c) = \frac{\nu^{(max)}}{1 + \frac{K_M}{c}}, \tag{22}$$

where K_M is the Monod constant for growth on the specific nutrient source.

As ν depends on the composition of the *medium* (rather than the intercellular composition), we must now describe how the nutrient composition c changes as the biomass of the culture increases. In virtually all realistic situations, the nutrients in the growth medium need to pass through a complex metabolic pathway to be "converted" into amino acids that are charged to tRNAs. Thus, to keep track of the nutrient concentration, we have to specify a yield parameter Ω that describes the mass of amino acids produced

per unit mass of nutrient. The dynamics of the growth medium is then described by

$$\frac{dc}{dt} = -\frac{\nu(c)\left(\phi_R^{(max)} - \phi_R\right)}{\Omega}. \tag{23}$$

2 A Dynamical Model for Diauxic Growth

2.1 Growth on a Single Carbon Source

With the preceding sections, we now have a complete dynamical description for growth on a single nutrient source. To summarize, the system of equations is governed by the accumulation of biomass via

$$\frac{dM}{dt} = \gamma(\theta)\phi_R M. \tag{24}$$

The dynamics of the pool of amino acids θ_a is defined by the action of the metabolic sector of the proteome ϕ_P as

$$\frac{d\theta_a}{dt} = \nu(c)\phi_P M - \frac{dM}{dt} = \nu(c)\left[\phi_R^{(max)} - \phi_R\right] M - \frac{dM}{dt}. \tag{25}$$

These amino acids, as described in the last section, ultimately come from the nutrients of the medium, which are at some concentration c. The dynamics of this component is governed by

$$\frac{dc}{dt} = -\frac{\nu(c)\phi_P M}{\Omega} = -\frac{\nu(c)\left[\phi_R^{(max)} - \phi_R\right] M}{\Omega}. \tag{26}$$

Finally, the translational and nutritional capacities of the system are governed by the size of the amino acid pool and the nutrient concentration of the growth medium, respectively. These dependencies are codified mathematically as

$$\gamma(\theta) = \gamma^{(max)}\left(1 + \frac{\theta_0}{\theta_a}\right)^{-1} \; ; \; \nu(c) = \nu^{(max)}\left(1 + \frac{K_m}{c}\right)^{-1}. \tag{27}$$

This set of equations [Equation (24) – (27)] completely describe growth on a single nutrient source. Figure 1 shows how the biomass, nutrient concentration, and amino acid pool size changes as a function of time using parameters that are characteristic of *E. coli* growing on glucose. It is important to note that, for the parameters considered here, there exists an "optimal" ribosomal mass fraction ϕ_R where the rate of biomass growth is maximized. This can be clearly seen in Figure 1(A) as the darkest and lightest color show slower growth of biomass compared the the light blue or teal curves which are between the two extremes.

2.2 Growth on Two Carbon Sources

Given a dynamical model of growth on a single nutrient source, it becomes relatively simple to include the presence of a second nutrient source whose metabolism is not preferred.

Let us consider two nutrient sources x and y. Nutrient x is the "preferred" nutrient, meaning that its metabolism is prioritized over y. The As x and y are different substrates, they require different sets

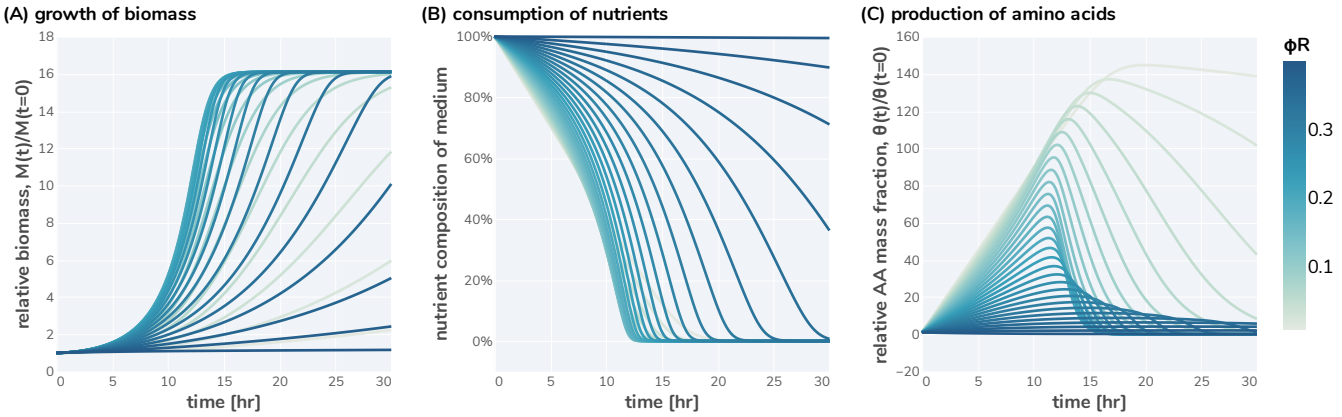

Figure 1: **Dynamics of growth on a single nutrient source.** (A) Biomass of the system relative to the initial condition $M(t=0)$. (B) The fractional concentration of the nutrients in the growth medium relative to that of $c(t=0)$. (C) The relative mass fraction of amino acids θ_a relative to $\theta_a(t=0)$. For all plots, parameters were chosen to be approximately similar to growth of *E. coli* on a glucose-based medium. Explicitly, the model parameters used here are $\phi_R^{(max)} = 0.4$, $\gamma^{(max)} = 8.25\,\mathrm{hr}^{-1}$, $\nu^{(max)} = 2.5\,\mathrm{hr}^{-1}$, $\theta_0 = 0.002$, $c = 50\,\mathrm{mM}$, $\Omega = 0.3$, and $K_M = 5\,\mu\mathrm{M}$. The initial conditions were arbitrarily set to be $M_0 = 0.001$ and $\theta_a = \frac{M_0}{10}$.

of metabolic proteins M_x and M_y and corresponding proteome mass fractions ϕ_x and ϕ_y. Additionally, as the nutrients are different, so too are the nutritional capacities ν_x and ν_y which are determined given the concentrations c_x and c_y and Monod constants $K_{M,x}$ and $K_{M,y}$, respectively. The translational capacity, however, is shared between the two nutrient sources as it is dependent only on the amino acid pool θ_a resulting from the metabolism of x or y.

How do we define a "preferred" substrate? In order to regulate what is metabolized, we must think of how the expression of the metabolic proteins are regulated. We will begin by considering that the expression of the metabolic proteins responsible for consuming each the preferential nutrient x will be proportional to its concentration c_x. Mathematically, we can model the mass fraction ϕ_x to have Monod-like dependence on the concentration c_x, yielding

$$\phi_x(c_x) = \frac{\phi_x^{(max)}}{1 + \frac{K_{M,x}}{c_x}}. \tag{28}$$