A Quantitative Comparison of Strategies for Growth Rate Maximization in Steady State Growth

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The Self Replicator Model

We begin by presenting a complete derivation of the self-replicator model of bacterial growth. We follow a similar approach taken by others [1, 2, 3] but without reliance on empirical measurements of ribosome content as function of growth rate as a motivating force. Rather, we consider the fundamental processes of bacterial growth as is cartooned in Figure 1, formulating intuitive, quantitative expressions which capture the dynamics of nutrient consumption to form charged-tRNAs and their subsequent consumption to form new proteins.

Protein Translation

We consider a growth regime in which the synthesis of new protein mass M is the most resource intensive task of a growing cell. This synthesis results from the concerted action of a pool of ribosomes N_R, each of with forming new protein mass at a rate k_R such that

$$\frac{dM}{dt} = k_R N_R. \tag{1}$$

Rather than explicitly considering the total number of ribosomes in the system, we can relate this to the the total ribosomal mass M_R noting that a single ribosome as a proteinaceous mass m_R, yielding

$$\frac{dM}{dt} = \frac{k_R M_R}{m_R} = \gamma M_R. \tag{2}$$

Here, we have introduced the parameter $\gamma = \frac{k_R}{m_R}$, commonly referred to in the literature as the *translational capacity*[1]. This parameter, with dimensions of inverse time, represents the fraction of a ribosome's protein mass that can be synthesized per unit time. The inverse of this parameter corresponds to the amount of time it takes to synthesize the protein components of a single ribosome, which for *E. coli* is approximately 7 minutes [4].

The individual units of protein mass are amino acids, which are supplied to the elongating ribosome as a charged tRNA molecule. When these are in abundance, the enzymatic process of forming a new peptide bond becomes the rate limiting step, yielding a maximal translational capacity γ_{max}. However, when charged-tRNA is limiting, the recruitment of charged tRNA to the elongating ribosome can become the dominant time scale, reducing the translational capacity from its maximal value. These time scales can be related mathematically as

$$\frac{1}{\gamma} = \frac{1}{\gamma_{max}} + \frac{1}{k_{on} c_{AA}} \tag{3}$$

where c_{AA} denotes the concentration of the charged tRNAs present in the cell and k_{on} is the effective on rate of the charged tRNA to the A-site of the ribosome. Equation 3 can be rearranged to the form of a Michaelis-Menten relation with the effective dissociation constant $K_D = \frac{\gamma_{max}}{k_{on}}$,

$$\gamma(c_{AA}) = \gamma_{max} \frac{c_{AA}}{c_{AA} + K_D}. \tag{4}$$

While we have presented the charged tRNAs as a concentration, it will prove helpful for us to think of it rather as the relative abundance of the total charged tRNA mass m_{AA} to the total biomass M, $c_{AA} = \frac{m_{AA}}{M}$. The mass fraction and true concentration are related to one another via an empirical constant and can be easily interconverted, as has been demonstrated previously [3, 2].

Production of charged-tRNAs

In typical laboratory conditions (and in the data we explore later in this work), the amino acids attached to the tRNAs must be synthesized *de novo* from minimal nutrient sources such as simple sugars and inorganic salts. Thus, for a given combination of nutrients, the dynamics of the charged-tRNA concentration c_{AA} can be written as competition of production and consumption processes,

$$\frac{dc_{AA}}{dt} = J_{AA} - \frac{1}{M}\frac{dM}{dt}(1 + c_{AA}). \tag{5}$$

Here, we denote the production flux of charged-tRNAs from nutrients in units of concentration as J_{AA}. The consumption of the charged-tRNAs occurs directly from the direct incorporation of the charged-tRNAs in the growing biomass as well as by dilution.

The formation of these amino acids is the result of the combined action of a battery of metabolic proteins which have a total mass M_P. This pool of metabolic proteins includes elements such as transporters and enzymes directly

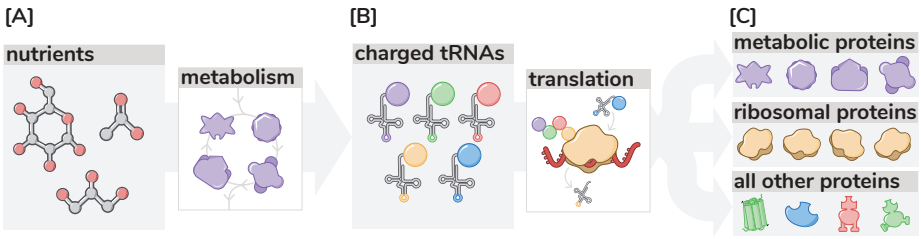

Figure 1: The flow of mass from nutrients to proteins. The self replicator model describes [A] the consumption of environmental nutrients via the cellular metabolic machinery to [B] produce charged-tRNAs. The subsequent pool of charged-tRNAs are consumed primarily through the process of protein translation via ribosomes to yield [C] new protein biomass partitioned in to metabolic, ribosomal, and "other" sectors.

involved in the metabolism of the nutrient as well as all of the accessory proteins which facilitate the flux of material through the pathway. While this represents a large number of biochemical reactions, we can generalize that the synthesis of amino acids from this collection of proteins proceeds at an effective rate ν, yielding an expression for the charged-tRNA influx J_{AA} of

$$J_{AA} = \nu \frac{M_P}{M}. \tag{6}$$

The effective rate ν is typically referred to as the *nutritional capacity* and is unique to a particular environmental condition. It represents the mass of charged-tRNA that can be produced per mass of metabolic protein per unit time. For conditions with "high quality" nutrients, such as glucose as the sole carbon source, the nutrient capacity is large. Poor quality nutrients, such as acetate supplemented growth, have a correspondingly smaller value for the nutritional capacity.

The nutritional capacity ν is dependent on the concentration of the nutrients in the environment, c_N. When nutrients are plentiful, their conversion to charged-tRNAs via the metabolic pathways operates at a maximal level ν_{max}. However, as the concentration dwindles, so too does the nutritional capacity. Using similar logic to our treatment of the charged-tRNA concentration dependence of the translational capacity, the nutritional capacity can also be written in the form of a Michaelis-Menten relation,

$$\nu(c_N) = \nu_{max} \frac{c_N}{c_N + K_M}, \tag{7}$$

where we have introduced the parameter K_M to represent the Monod constant for growth on a given nutrient. As there are myriad steps involved in the conversion of a single nutrient to a charged-tRNA, we find it more appropriate to consider the Monod constant instead of an effective dissociation constant.

Consumption of nutrients

By conservation of mass, the the accumulation of biomass necessitates a decrease in the nutrient concentration c_N. The corresponding dynamics are negatively proportional to the the production of charged-tRNAs via metabolism J_{AA} scaled by a prefactor

$$\frac{dc_N}{dt} = -\frac{\nu M_P}{\Omega}. \tag{8}$$

The parameter Ω, termed the yield coefficient, represents the efficiency by which a given concentration of nutrient is converted to concentration of charged-tRNA. A yield coefficient of $\Omega = 1$ implies that for each mass of nutrient consumed, an equivalent mass of charged-tRNA is produced. However yield coefficients are rarely so high and are typically < 1, even for preferential nutrient sources such as glucose in *E. coli*.

Allocation of resources

The production of charged-tRNAs from raw nutrients and their incorporation into new protein biomass, as detailed in Equations 2 - 8 depend on masses of metabolic M_P and ribosomal M_R proteins, respectively. While we have defined how the total biomass M evolves in time, we have not defined how the resources are partitioned into the growing pools of M_P and M_R.

We note that, while we consider only M_P and M_R as being directly involved in the dynamics of biomass production, there are many other proteins M_O that are also translated. Considering this accounts for all protein production, we can parameterize the masses of each protein class as

$$\phi_R = \frac{M_R}{M} \; ; \; \phi_P = \frac{M_P}{M} \; ; \; \phi_O = \frac{M_O}{M} \tag{9}$$

under the constraint

$$\phi_R + \phi_P + \phi_O = 1. \tag{10}$$

Assuming that the corresponding partitioning of mass between these fractions is constant in time for growth on a given nutrient, we can state the mass dynamics of each class of proteins as

$$\frac{dM_R}{dt} = \phi_R \frac{dM}{dt} \; ; \; \frac{dM_P}{dt} = \phi_P \frac{dM}{dt}, \tag{11}$$

which now provides the final piece in our derivation of the self replicator model.

Assembling the model

Equations 2 – 11 provide a complete description of the flow of mass from nutrients to proteins as depicted in Figure 1. In Figure 2 [A], we present all of these equations together with the major parameters defined as appropriate. With these equations in hand, we can explore the dynamics they encode by numerically integrating them over a range of physiologically meaningful values, such as those defined in Figure 2[B].

Figure 2[C] shows the result of this integration over a range of values for the maximal nutritional capacity ν_{max}. While the allocation parameters ϕ_R and ϕ_P are held constant, varying ν_{max} is comparable to tuning the quality of the growth medium, defining different effective rates at which the nutrients are converted into charged-tRNAs.

It is immediately apparent in Figure 2 [C] that there is a precisely linear region (on a semi-logarithmic scale) of biomass production, indicating exponential growth of biomass. During this phase of growth, as shown in Figure 2 [D], the intracellular abundance of charged-tRNAs (c_{AA}) reaches a plateau at the steady-state concentration. The magnitude of this concentration is dependent on the he nutritional capacity ν_{max} with larger capacities corresponding to larger steady-state charged-tRNA concentrations. While a steady-state concentration of charged-tRNA is reached during this phase of growth, the nutrient concentration continues to steadily decrease until it rapidly approaches zero.

As the nutrients become limiting, The exponential phase of growth concludes and the biomass approaches a saturating bound (plateau in Figure 2[C]). This point corresponds to a rapid plummet in the intracellular concentration of charged-tRNAs to a new steady state value of 0, indicating that the nutrients of the growth medium have been exhausted and new biomass can no longer be produced.

Steady State Growth

References

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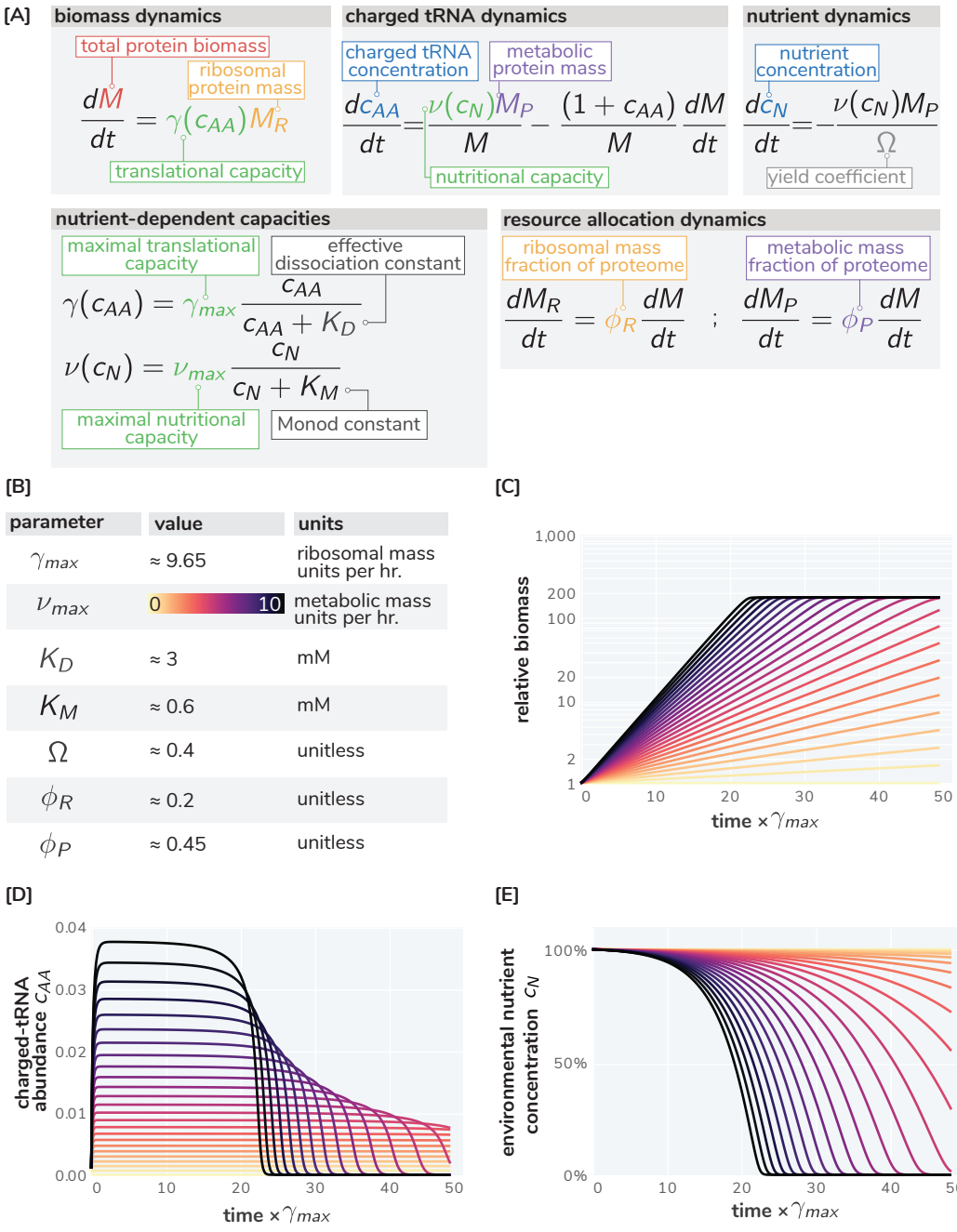

Figure 2: The equations of the self-replicator model and their dynamic behavior [A] The differential equations defining the self-replicator model with key parameters identified and defined. [B] Physiologically meaningful ranges of the parameters given literature values of *E. coli* growth physiology [GC: note, inlcude BNIDs and add referenences where appropriate]. The dynamics of [C] the total biomass, [D] the concentration of charged-tRNAs c_{AA}, and [E] the dynamics of the nutrients in the environment are shown for a range of values for the nutritional capacity ν_{max}.