Chapter 9

Universal features of autocatalytic systems

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Chapter overview

- A stoichiometric theory of autocatalysis is outlined, which is based on the notion of productivity (either economical or chemical). The framework is applied to the von Neumann universal constructor model as an example. New methods of identification of autocatalytic subnetworks in complex chemical networks follow from this approach.
- The expanding economic model of von Neumann model is a linear model of a circular and productive economy also based on stoichiometric considerations. As shown in [1], a notion of growth factor introduced in this model has valuable applications for the characterization of autocatalytic chemical reaction networks.
- A special case of the von Neumann model is the Leontief model, from which the Leontief production function can be derived. This approach is useful to model certain features of cell metabolism, such as cell growth laws and the inhibition of bacterial growth by various types antibiotics.

9.1 Stoichiometric versus dynamical autocatalysis

9.1.1 Stoichiometric autocatalysis

According to IUPAC, "an autocatalytic reaction is a chemical reaction in which a product (or a reaction intermediate) also functions as a catalyst. In such a reaction, the observed rate of reaction is often found to increase with time from its initial value". While this definition provides a sound kinetic characterization of autocatalysis, it is not easy to use it to identify autocatalysis in situations in which kinetics is poorly known. Such situations arise frequently when trying to analyze complex chemical mixtures, such as astrophysical samples analyzed by researchers studying the origin of life research, or man-made prebiotic systems such as complex interacting RNA networks, in which most of the species and reactions are unknown.

On the theory side, the concept of autocatalytic sets was introduced by S. Kauffman in 1971, and played an important role in his early investigations of the Origin of order in living systems. In 2004, W. Hordijk and M. Steel expanded this original work by introducing the concept of reflexively autocatalytic food-generated networks (RAFs), namely self-sustaining networks that collectively catalyze all their reactions using only compounds from the food sets [2]. This formalism is based on the assumption that any compound (or

a fraction of them) involved in randomly picked reactions has a certain probability to be catalytic [3]. Although very nice results follow from that assumption, such as the existence of a phase transition controlled by the connectivity of the network, this assumption is a bit problematic, because a given species can act as a catalyst or not depending on the presence of other molecules and depending on the reactions it is part of. In other words, the probability for a reaction to be catalytic is context dependent and strongly constrained by the topology of the network itself. To address both issues, namely the lack of available data on the kinetics and the shortcomings of the RAF formalism, a better starting point is to define autocatalysis from stoichiometry rather than from kinetics. While alternate definitions of autocatalysis are possible [4], we now detail the definition of [5], which encompasses autocatalytic sets and RAFs as particular cases.

Given a complete chemical network, autocatalysis is defined at the level of a subnetwork of stoichiometric matrix **N**, i.e. for a subset of species and reactions of the full network. Species which are not part of the autocatalytic subnetwork can still play an important role, as for instance food species or building blocks. The autocatalysis of this subnetwork requires two essential properties: *autonomy* (i) and *productivity* (ii). The *autonomy* condition is there to exclude direct injection or loss of species from the environment within the set of autocatalysts. More precisely, this condition requires that each species is produced by at least one reaction (each row of the stoichiometric matrix has at least one positive entry) and each reaction must at least consume one species (each column has at least one negative entry). This notion of autonomy is a close analog of the notion of circular economy in the economical context, provided species are replaced by goods, and reactions are replaced by industry sectors of an economy. *Productivity* (ii) means the absence of mass-like conservation laws and is related to the notion of a productive economy. More precisely, this condition requires the existence of a non-zero reaction vector **v**, such that

$$\Delta \mathbf{n} = \mathbf{N} \cdot \mathbf{v} > 0, \tag{9.1}$$

element-wise. The existence of the flux vector \mathbf{v} guarantees that there is a set of species and reactions such that all species of the set are produced by the autocatalytic subnetwork. The proof that this property is equivalent to the absence of mass-like conservation law is the content of Gordan's theorem of linear algebra, which is explained in the box 9.A.

A third more technical condition introduced in Ref. [5] is that N should be *non-ambiguous* (iii) which means that a species can not be both a reactant and a product of the same reaction. This condition (iii) is less essential but is convenient as it ensures that catalytic steps can be distinguished at the level of stoichiometric matrix. Indeed, otherwise the stoichiometric matrix would be ambiguous in the sense that it would not be possible to separate the contribution of the consumption of reactants from the production of products. In practice it is always possible to transform an ambiguous reaction into a non-ambiguous one provided

🖄 Math box 9.A Gordan's theorem

Gordan's theorem is the following result of linear algebra which takes the form of an alternative:

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$$\exists \mathbf{v} \quad \text{s.t.} \quad \mathbf{N} \cdot \mathbf{v} > 0, \tag{9.2}$$

or

$$|\boldsymbol{\rho} > 0 \quad \text{s.t.} \quad \mathbf{N}^{\top} \cdot \boldsymbol{\rho} = 0.$$
 (9.3)

The first side of the alternative in 9.2 corresponds to the stoichiometric definition of autocatalysis, the second side of the alternative in 9.3 corresponds to the existence of a so called mass-like mass conservation law, i.e. a conservation law with only strictly positive entries, in which case no autocatalysis is present. Note that when autocatalysis is present, only mass-like conservation are forbidden but not general conservation laws in which the entries of ρ are positive and negative. An example of an autocatalytic network with non-mass like conservation law is given in [6], which also provides a nice geometric interpretation of conservation laws as manifolds. Note also that a stronger condition for autocatalysis is the absence of any conservation law, which mathematically means ker $\mathbf{N}^{\top} = 0$.

Stoichiometric versus dynamical autocatalysis



Figure 9.1: Five minimal autocatalytic motifs (figure taken from [5]). Yellow circles represent species, black lines connecting them represent reactions and the orange squares indicate the locations where further reactions could be added while preserving the motif type.

intermediates in the reaction are added. Another way to get around the issue of ambiguity without having to transform the network, is to define the chemical network from the start by two stoichiometric matrices instead of one as we will do in section 9.2.

Remarkably, this mathematical definition is enough to guarantee the existence of a small number of minimal autocatalytic motifs called autocatalytic cores. The minimality of these cores means that they cannot contain smaller cores in them. In [5], it was found that with the above assumptions, only five minimal motifs could exist, which are represented in Fig. 9.1. It also follows from that construction that an orientation of the reactions in a core must exist such that v has only non-negative components [7].

As a simple illustration of this framework, let us consider the universal constructor which von Neumann introduced in 1940 [8]. This is an idealized machine U, that would be able to construct any object including itself when given some set of instructions I. von Neumann identified a potential recursion issue related to the self-replication of the machine together with its instructions and he also understood that for such a machine to evolve without compromising its replication, an additional player in addition to U and I was needed. This additional player would be a universal copy machine X that would copy the instructions without translating them [9]. With this remarkable insight, von Neumann foresaw the essential mechanism of the DNA based translation-transcription machinery that we know today. We can summarize the reactions in which the universal constructor U, the universal copy machine X and the instructions I are involved by the following simple chemical network :

$$X + I \longrightarrow 2I + X,$$

$$U + I \longrightarrow 2U + I,$$

$$U + I \longrightarrow U + I + X.$$
(9.4)

When written in this way, the sub-network of these three reactions with the set $\{U, I, X\}$ contains several catalytic steps, so that neither conditions (i) nor (iii) are satisfied. To solve the issue, let us introduce food species F_1 , F_2 and F_3 , intermediate species XIF_1 , UIF_2 and UIF_3 and their corresponding reactions so that the network is no longer explicitly catalytic :

$$\begin{array}{ll} F_1 + X + I \longrightarrow XIF_1, & XIF_1 \longrightarrow 2I + X, \\ F_2 + U + I \longrightarrow UIF_2, & UIF_2 \longrightarrow 2U + I, \\ F_3 + U + I \longrightarrow UIF_3, & UIF_3 \longrightarrow U + I + X. \end{array}$$

$$\begin{array}{ll} \textbf{(9.5)} \end{array}$$

Now the subnetwork of species $\{U, I, X\}$ satisfies the conditions (i) (*autonomy*) and (iii) (*non-ambiguity*), and also condition (ii) (*productivity*) because the reaction vector that corresponds to summing all the reactions produces all the species of the set, according to the overall reaction $X + 2U + 3I \longrightarrow 2X + 3U + 4I$. Therefore this network is autocatalytic from the point of view of stoichiometry. Note also that all reactions have been assumed to be irreversible here, which is allowed within the framework of [5], since thermodynamic compatibility is not considered.

A significant benefit of the stoichiometric definition of autocatalysis outlined above is that linear program-

ming algorithms, which are a classic tool of analysis of optimization problems, can be used to search effectively for autocatalytic subnetworks within large chemical networks [10, 1, 7]. In carrying out this program, the authors of [1] found that the number of autocatalytic subnetworks typically grow exponentially with system size. In practice, a much smaller number of subnetworks is expected to be relevant dynamically in large networks, an issue which we address now.

9.1.2 Dynamical autocatalysis

Historically, autocatalysis as studied in classic chemistry has been related to a certain type of kinetic pattern. To distinguish this classic definition from the previous based on stoichiometry, we will call this form of autocatalysis, dynamical autocatalysis. In this view, dynamical autocatalysis is defined as a chemical process in which one of the products catalyzes its own formation according to

$$\frac{\mathrm{d}x_i}{\mathrm{d}t} = k(\mathbf{X}) \cdot x_i^n + f(\mathbf{X}), \text{ for } \mathbf{k} > 0, \mathbf{n} > 0, |\mathbf{k}| \gg |\mathbf{f}|,$$
(9.6)

where **X** is the vector of all the concentrations x_i , the term $k(\mathbf{X}) \cdot x_i^n$ describes the contribution from autocatalysis while the function f describes the contribution coming from the rest of the chemical system [11]. It follows from this definition that diverse forms of autocatalysis are possible depending on $k(\mathbf{X})$ and n, and that these forms could remain concealed if $f(\mathbf{X})$ is too large. It also follows from this definition that when $k(\mathbf{X})$ is constant, autocatalysis can generate exponential growth for n = 1, but also over-exponential n > 1 or sub-exponential n < 1 evolution. In practice, the exponential growth regime is anyway limited to an intermediate time window either because the reaction eventually runs out of substrates (at long times) or due to product inhibition, which can trigger sub-exponential behavior. Further, k and n are not independent factors since they arise from shared physical factors (availability and diffusion of ligands, size and flexibility of the molecules...) resulting in a trade-off between these two parameters that is relevant for designing catalysts or autocatalysts from bottom up [12].

From the definition in Eq. 9.6, it follows that dynamical autocatalysis has the potential to destabilize a dynamical state, which would otherwise have remained stable. Recently, the connection between the topology of the autocatalytic reaction network and its dynamical stability has been explored in two separate works that address different sides of that issue. In the first one, it was proven that for fully connected dilute systems with no degradation, the stoichiometric definition of autocatalysis leads to dynamical autocatalysis, characterized by a strictly positive Lyapunov exponent [13]. In the second one, for a certain class of parameter-rich kinetics, it was shown that the stoichiometric definition of autocatalysis implies a choice of reaction rates for which an unstable fixed point necessarily exists [14]. In a nutshell, the first work provides explicit results regarding the relation between stoichiometric and dynamical aspects of autocatalysis but the results are limited to the diluted regime, while the second work does not have this limitation, but is only a proof of existence: it does not provide an explicit method to obtain the reaction rate stated in the result.

Several recent studies have explored growing systems from the point of view of non-equilibrium thermodynamics [15]. In particular, in [6], Kamimura et al. have built a comprehensive chemical thermodynamic theory of open systems which are also self-replicating. This approach clarifies the thermodynamic conditions under which growth is possible in a system in which the volume is also growing [6]. To include this change of volume, these researchers developed an extension of traditional chemical thermodynamics theory. The growth of the volume is an important feature of autocatalysis, which manifests itself in certain experiments such as that of [16]. In this work, small-molecule autocatalytic reactions occur in compartments made of water in oil droplets. Small molecules, which act as fuel in these reactions, can diffuse between compartments while the large molecules which are produced inside the compartments cannot diffuse across compartments. This work provides a stunning demonstration that autocatalysis can drive compartment growth, competition and reproduction.

The question of how to connect stoichiometric, kinetic and thermodynamic features of autocatalysis is an ongoing active area of research which is pursued by several groups theoretically [7, 17, 6, 18]. For

instance, in [17], a framework has been proposed to derive structural and thermodynamic bounds for autocatalytic chemical networks assuming mass-action law kinetics. The term structural means that these bounds depend on the topology of the network but not on the value of the rate constants. Another important structural property of biochemical networks is for instance robust perfect adaptation (RPA). This property means that there exist some subnetworks, with specific topological features, whose parameters are irrelevant to the steady-state properties of the rest of the network [19].

In [7], the authors proved there always exists a well-defined CRN corresponding to an autocatalytic core, where by well-defined, we mean that there exists a list of chemical species with finite concentrations and a list of reversible chemical reactions obeying mass action law kinetics that realize this network dynamically. Within these assumptions, they also showed that thermodynamic constraints prevent certain associations of autocatalytic cores, which suggests that only a restricted number of cores is relevant for the dynamics of a given autocatalytic network.

9.2 von Neumann's model of an expanding economy

Besides his theory of the universal constructor mentioned above, J. von Neumann made another essential contribution to our topic by proposing in 1945 a model for an expanding economy. The model assumes the economy to be circular, which means that products (or goods) are produced from other goods and from building blocks using a number of processes with a certain intensity v_j [20]. There are n goods and m processes with n < m, which are characterized by constant ratios of inputs to outputs. The model is formulated in terms of an output matrix B and an input matrix A. Since the total amount of good produced must match the internal and external demand, described by the positive vector \mathbf{d} , we have the equation

$$\mathbf{B} \cdot \mathbf{v} = \mathbf{A} \cdot \mathbf{v} + \mathbf{d}. \tag{9.7}$$

This economic model can be directly mapped onto a chemical reaction network, if goods are interpreted as chemical species, the vector \mathbf{v} represent chemical fluxes [21] and d could represent a dilution or degradation. To formalize this analogy, it is convenient to split the stoichiometric matrix \mathbf{N} into the part that concerns the production of products denoted \mathbf{N}^+ and the part that concerns the consumption of goods or species \mathbf{N}^- , so that we can use $\mathbf{B} = \mathbf{N}^+$, $\mathbf{A} = \mathbf{N}^-$ and $\mathbf{N} = \mathbf{N}^+ - \mathbf{N}^-$. We say that an economy is productive when there exists a non-negative vector \mathbf{v} such that $\mathbf{B} \cdot \mathbf{v} > \mathbf{A} \cdot \mathbf{v}$. This condition maps exactly to the notion of productivity introduced in Eq. 9.1 for stoichiometric autocatalysis, while the condition of circular economy maps to the notion of autonomy introduced at the same time.

Obviously, we must require the positivity of the vectors \mathbf{v} and the condition $\sum_i v_i > 0$. Another condition is that the economic system is irreducible, which means that it cannot be decomposed into isolated independent sub-parts (a sub-part being here a subset of goods which does not require goods from outside the subset to produce all the goods of the subset). To show the existence and unicity of the dynamic equilibrium for such economies, J. von Neumann introduced the function

$$\alpha(\mathbf{v}) = \min_{i} \frac{\sum_{j} N_{ij}^{+} v_{j}}{\sum_{j} N_{ij}^{-} v_{j}},\tag{9.8}$$

where the minimum is taken over all goods *i*, and he proved that the function α is uniquely defined from the vector **v**, which is itself part of the solution. The quantity

$$\alpha = \max \alpha(\mathbf{v}),\tag{9.9}$$

represent a growth factor of the economic system and the value of the vector \mathbf{v} at the maximum describes the set of goods that defines a dynamic economic equilibrium.

In [21], Blanco et al. applied this framework to the study of autocatalytic reaction networks. They underlined the importance of α for chemical reaction networks, which they call the maximum growth factor



Figure 9.2: Autonomous subnetworks with highest value of MGF are shown for the formose network (A) and for the *E. coli* metabolism (B). The intensity of fluxes in each subnetwork is shown with the color scale. The figure is reproduced from [1] with permission from the authors.

(MGF). Note that this maximum growth factor is different from the dynamical growth rate of species within the network. The MGF does not have dimensions of a growth rate, instead it is a dimensionless factor, which can be evaluated based only stoichiometry. Blanco et al. proved that this MGF is strictly larger than one, if the network is autocatalytic [21]. Conversely, if an autonomous network (where autonomy is now defined at the level of N^- and N^+) has an MGF strictly larger than one, then it is autocatalytic. As an illustration, the autocatalytic nature of the network of Eq. 9.1.1 can be assessed without the need of introducing intermediates, because one can show that its MGF is strictly larger than one and that it is autonomous.

Blanco et al. also developed efficient algorithms to identify the strongest, maximal and minimal autocatalytic subnetworks, and used them to study the formose and E. coli reaction networks. The formose network is an important prebiotic network, which is known to be autocatalytic. Their results are markedly different for the two networks as shown in Fig. 9.2. From an analysis of MGF of subnetworks, they found that in the formose network, a single subnetwork dominates all the others but is fragile with respect to perturbations. In contrast, the *E. coli* network is built from interlinked cores, which together forms a robust structure.

9.2.1 Leontief's production function

Wassily W. Leontief won the Nobel prize in economics for his work on input-output relations in economic systems, which he started in 1936 [25]. He later developed this mathematical tool to study the American economy, and in particular the interdependency between industries.

The Leontief model is the special case of the von Neumann model, in which each productive activity has a single output (no joint products) whereas there may be many activities producing the same output and each good is produced by at least one industry. As in the von Neumann model, it is also assumed in the Leontief model that goods are produced with fixed ratios of production factors. This assumption leads to the Leontief production function discussed in the box 9.B.

We can think of this production function as the outcome of a supply chain where production factors have to be assembled in fixed proportions in order to form a product. For instance, in order to build one bike,

Economics analogy 9.B Production functions

In economics, production functions relate the quantities of outputs to that of inputs in a system. There are various production functions commonly used in economics, one of the most well-known is the Cobb-Douglas production function [22, 23], which can be written in a general way:

$$y = c \prod_{i} x_i^{\alpha_i}, \tag{9.10}$$

where x_i are production factors (which could be labor, capital or other factors), y is an amount of product and c, α_i are positive coefficients. Mathematically, this law bears similarities with the mass action law in chemistry, where the rate of production of a species is related to the product of the concentrations of the reactants to the power of their associated stoichiometric coefficient. A more general production function is the constant elasticity of substitution (CES) production function [24]. This function accounts for the fact that one product may be substituted with another one and can be written in the form:

$$y = c \left(\sum_{i} \alpha_{i} x_{i}^{\rho}\right)^{\frac{1}{\rho}}.$$
(9.11)

Here, ρ is the coefficient of substitution and α_i is the weight of the production factor *i* in the total production $(\sum_i \alpha_i = 1)$. Instead of ρ , one often uses the elasticity of substitution σ which is such that $\rho = \frac{\sigma - 1}{\sigma}$. Here it is assumed that the elasticity of substitution is the same for all pairs of production factors. Note that

 σ could also be defined as an elasticity coefficient that compares the change in the ratio of inputs to changes in the ratio of marginal products. Indeed, the marginal product with respect to factor j is $y_j = \partial y/\partial x_j = c\rho\alpha_j x_j^{\rho-1} \left(\sum_i \alpha_i x_i^{\rho}\right)^{\frac{1-\rho}{\rho}}$ and represents the sensitivity of the product to the amount of production factor j. Therefore, $y_j/y_k = \alpha_j x_j^{\rho-1}/\alpha_k x_k^{\rho-1}$, and we recover that :

$$\sigma = \frac{\partial \ln(x_j/x_k)}{\partial \ln(y_k/y_j)}.$$
(9.12)

Therefore, σ measures precisely how the ratio of two production factors is modified when the ratio of two corresponding marginal products is modified. Now, three famous cases can be considered [24]:

- $\sigma \to \infty$: In this case, any modification in the ratio of marginal products would require an infinite modification in the ratio of production factors. This means that the ratio of marginal products remains constant whatever the modification in the ratio of production factor. This is the so called *perfect factor substitution* limit. Indeed, the CES production function becomes linear ($\rho = 1$), $y = c \sum_i \alpha_i x_i$, and any production factor can be substituted by another (even if $\exists i, x_i = 0$, it can be replaced by any other x_j).
- O $\sigma = 1$: In this case, a modification in the ratio of marginal products translates to the same modification in the ratio of production factors. If we want the dependency of the production in production factor j, we need to double the amount of production factor j. This limit corresponds to $\rho \to 0$, in which case we recover the *Cobb-Douglas* production function $y = c \prod_i x_i^{\alpha_i}$. This means that the level of substitution of a any production factor is null (if one of the $x_i = 0$, then y = 0). Interestingly, for all values of $\sigma \in [0, 1]$, there is no possible substitution between production factors.
- O $\sigma = 0$: This case is particularly interesting, it means that the ratios of the production factors x_j/x_k are fixed whatever the ratios y_j/y_k . In this limit we recover the so called *Leontief function with fixed factor proportions*. There is still no substitution between the products (if one $x_i = 0$, then y = 0), but this also means that forming one unit of product always requires the production factors in the same proportions. This corresponds to $\rho \rightarrow -\infty$, which gives $y = c \min(x_i)$. Interestingly, this is a way to get rid of the coefficients α_i which represent the share of each production factor in the total production. This boils down to saying that production is limited by the scarcest resource.

you need two wheels, one saddle, two pedals, etc. Those ratios are fixed, or equivalently the elasticity of substitution is $\sigma = 0$ as discussed in the box 9.B. If you want to form a product P, for which you need to assemble n_1 units of R_1 , n_2 units of R_2 , ... up to n_N units of R_N , the production rate will be limited by the smaller value of R_j/n_j , that is the number of sets of resource j required to produce P. If the minimum time to produce one unit of P is τ_P , and the minimum time to use resource R_j in order to produce one P

is τ_i , we can write

$$\frac{\mathrm{d}P}{\mathrm{d}t} = \frac{1}{\tau_P} \min\left(\frac{\tau_P}{\tau_1} \frac{R_1}{n_1}, \frac{\tau_P}{\tau_2} \frac{R_2}{n_2}, ..., \frac{\tau_P}{\tau_N} \frac{R_N}{n_N}\right).$$
(9.13)

Indeed, $\tau_P/\tau_j n_j$ is the number of products which can be simultaneously produced from one resource j. This result holds true if resources are fully allocated to the production of P, but if several products P_i need to be produced in parallel, one resource may be used by different production chains simultaneously, meaning that a fraction $\alpha_{i,j}$ of total available resources R_j must be used for the specific product P_i , so that :

$$\frac{\mathrm{d}P_i}{\mathrm{d}t} = \frac{1}{\tau_P} \min\left(\alpha_{i,1} \frac{\tau_P}{\tau_1} \frac{R_1}{n_1}, \alpha_{i,2} \frac{\tau_P}{\tau_2} \frac{R_2}{n_2}, ..., \alpha_{i,N} \frac{\tau_P}{\tau_N} \frac{R_N}{n_N}\right).$$
(9.14)

Then the prefactor before R_i represents the maximal number of copies of the product that you can produce simultaneously from one unit of resource *i*. The fact that resources may not be substituted with other resources has important consequences for cell metabolism [26].

In the problem 9.1, we study a single resource - single product industry or workstation and we show that a Leontief production function emerges from mass-action law kinetics when a certain time scale separation holds. This example is important because it illustrates that the Leontief production function not only involves fluxes associated to reactions or industries but can typically also include stocks associated to goods or metabolites, which are only available in finite amounts.

Further applications of this formalism to describe for instance the ability of a metabolic network to switch from one behavior to another one (as in the crabtree or Warburg effects in biology and in the Giffen behavior in economics) is studied in [27] and in a coming chapter to be written.

9.2.2 Liebig's law

Interestingly, the idea that the production rate could be limited by the scarcest resource is present in the field of agronomy under the name of *Liebig's law of minimum* [28, 29, 30, 31]. It was initially used to describe plant growth, which requires various resources, and where it is observed that varying the amount of fully available resources did not modify the final production. This suggests that only scarce resources will limit production and translates to the principle that when a population is growing using various resources, the scarcest will set the growth rate, and the others will be consumed accordingly. This law can be used to model the growth of an organism in an environment where resources are constrained. The link between mass action laws and Liebig's law of minimum has been studied [30]. The interest of this method is to obtain equations that are easier to solve on domains where one resource is scarcest. One main difference between the Leontief production function and Liebig's law of the minimum is that for the latter, the minimum is not necessary taken between the numbers of each production factor, but between the yields of those production factors (which can be non-linear functions) [32]. In particular, this means that the rate of production is set by the minimum of the yields of each production factor :

$$\frac{\mathrm{d}Y}{\mathrm{d}t} = \frac{1}{\tau} \min\left(\{f_i(x_i)\}\right),\tag{9.15}$$

where f_i are functions of the production factors x_i . To model the requirements of plants in nutrients, yields given by Michaelis-Menten kinetics can be used [30]. Instead of directly comparing the numbers of each production factors, it consists in comparing the yields. However, the idea that one resource will be limiting remains the same.

9.2.3 Application to metabolism

The law of minimum was used to build simplified models of metabolism as an ensemble of coupled autocatalytic cycles [26]. Metabolism is seen as a supply chain, where production factors must first be produced and then assembled in fixed proportions to form a product. We call P the number of proteins of one type, produced by translating mRNA (of number m) with ribosomes (of number R) and substrates (of number S). Using the Leontief production function, we can write (following the method of [26]) :

$$\frac{\mathrm{d}P}{\mathrm{d}t}\Big|_{\mathsf{prod}} = \frac{1}{\tau_P} \min\left(\alpha_P R, \ \alpha_P S, \ \frac{\tau_P}{\tau_e s_R} m, \ \ldots\right)$$
(9.16)

Ribosomes and substrates have to be used simultaneously to produce different types of proteins, α_P is the fraction of the total population of ribosomes (and substrates) used to produce the particular protein P. The minimum time to produce one P is τ_P , the minimum time to elongate the polymer by one amino acid is τ_e , and s_R is the size of the domain on the mRNA that has to be dedicated to the production of one polymer P at a given time. As explained in [26], $\tau_P/\tau_e s_R$ is then the maximum number of ribosomes that can translate simultaneously one mRNA, and thus the maximum number of copies of P you can produce simultaneously from one unit of mRNA. This is indeed what was predicted from Leontief's model for inputoutput systems: the prefactor before every amount of resources is the maximum number of copies of the protein you can produce simultaneously from this specific resource. This term is that of production of the protein, now the protein could be consumed to form a product, or degraded.

To use ribosomes, you first need to form ribosomes by assembling proteins and ribosomal RNA. Similarly, to use mRNA you must first polymerize RNA. This suggests that a minimal autocatalytic network that begins to capture the structure of the transcription-translation machinery is made of two coupled autocatalytic cycles associated respectively to RNA and ribosomes. These two cycles will then be described by coupled equations with production terms described by Leontief's production function [26].

From such an framework [26], one can derive the various growth laws that characterize the cell metabolism, which have been discussed in detail in various chapters of this book. Let us mention briefly two recent works that follow this line of research : In the first one carried out in [33], the authors noticed that RNA polymerase, and mRNA levels correlate in experiments with growth rates in contrast to the belief that ribosomes should be the sole drivers of the growth rate. To explain these observations, the authors developed a theoretical framework building on [26], which account for the joint role of all these factors in the observed growth rate.

Another recent application of the above framework concerns a model for the inhibition of bacterial growth by antibiotics [34]. In that work, the cell metabolism is modeled as two coupled autocatalytic cycles, in which one cycle describes the production of ribosomes, while the other describes RNA-polymerase production as shown in Fig. 9.3. It is assumed that the antibiotic inhibits one of these two essential autocatalytic cycles by targeting some essential metabolites in them. Growth laws can be recovered from the model as shown in Fig. 9.3B. A first law describes the increase of ribosome fraction as a function of growth rate when nutrient quality is increased (solid magenta curve) while a second growth law describes the upregulation of ribosomes as a result of the inhibition of translation by ribosome inhibitors (colored solid lines). In addition, the model successfully describes the experimental dependence of the growth rate on various types of antibiotics and confirms the existence of growth bistability, namely a regime in which two possible values of the growth rates are possible in the same range of physical parameters.

9.3 Concluding remarks

In this chapter, we have established a connection between the universal constructor model and the expanding economic model, which were both introduced by von Neumann. Interestingly, von Neumann himself did not discuss the relation between these two works, which we make in this chapter. This expanding economic model of von Neumann (1945) and the input-output model of Leontief (1936, 1941)



Figure 9.3: (A) Scheme of coupled autocatalytic networks interacting with a toxic agent. The orange box linking two arrows represents the Leontief production function. B_1 represents active ribosomes; C_1 active RNA polymerases; similarly $B_2, ..., B_{N-1}$ and $C_2, ..., C_{K-1}$ are intermediates, R_N, R_K are building blocks. We suppose that "toxic" inhibiting agents in numbers A can bind to one of the autocatalysts (chosen here to be B_1 for simplicity). (B) Illustration of the growth laws when varying either the amount of antibiotics or the nutrient quality linked to pre-exposure growth rate λ_0 displayed on the right scale. This figure is reproduced from [34] with permission.

laid the foundation of a modern framework for economic analysis. Their framework turned out to be essential to quantify the relative interdependency of various parts of an economy and the nature and the structure of economic equilibria. Remarkably, these tools continue to inspire developments in other fields as recent studies of autocatalytic chemical networks show. Thanks to linear programming methods, we are now able to identify autocatalytic subnetworks efficiently and characterize them using notions such as the maximum growth factor or using thermodynamic bounds. More work is needed to understand the interactions between autocatalytic networks, and their role in the emergence of chemical complexity linked to pre-Darwinian evolution.

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Recommended readings

This book chapter is mainly based on these two recent articles: "A unifying autocatalytic network-based framework for bacterial growth laws" by Roy et al. [26], and "Universal motifs and the diversity of autocatalytic systems" by Blokhuis et al. [5].

Problems

Problem 9.1 Production function of a workstation with a single resource and single product

We model a workstation with a single resource and a single product [32]. Let x be the amount of available resource or stock, r the supply rate of this stock, q the specific rate with which the stock is being lost or degraded. Further, let u (resp. v) be the number of idle (resp. busy) machines which can process the stock. The processing time is $1/\beta$, b is the number of output products per machine, a is rate of capture of stock by machines, α is how many machines get involved per unit resource/stock.

1. Assuming mass action law for the processing of the stock, show that the equations of the problem

are

$$\dot{x} = r - aux - qx,$$

$$\dot{u} = \beta v - \alpha ux,$$

$$\dot{v} = -\beta v + \alpha ux,$$

$$\dot{y} = bv.$$

- 2. Show that the total number of machines is a constant denoted u_0 . Derive the steady state number of busy machines \bar{v} in terms of the steady state amount of stock \bar{x} . Comment on the form of the output production that you find.
- 3. Introduce the variables $\gamma = q/(au_0)$ and $\rho = \alpha r/(a\beta u_0)$. Derive the expression of \bar{v} in the limit $\gamma \ll 1$ and $\gamma \ll |\rho 1|$ and show that it has a Leontief form. Interpret this form in terms of how the stock is handled in the regime $\rho < 1$ and $\rho > 1$.
- 4. Show that for small but non-zero γ , the input-output function falls below the line boundary defined by the Leontief function.

Problem 9.2 UPF model

The UPF model is a toy model of metabolism made of two coupled autocatalytic cycles [26]. In the model, a fraction α of machines of type U catalyze themselves. The remaining machines synthetize another type of machines P. The P machines convert an external substrate f to an internal substrate F, which is used by U to make more copies of itself and new Ps. To simplify, we assume that to make one more unit of U by the first reaction, one unit of F is needed, and one unit to make one unit of P by the second reaction.

The model is defined by the following set of equations

$$\begin{split} \mathbf{U} + \mathbf{F} & \xrightarrow{\alpha} 2 \, \mathbf{U}, \\ \mathbf{F} + \mathbf{U} & \xrightarrow{1-\alpha} \mathbf{P} + \mathbf{U}, \\ \mathbf{f} + \mathbf{P} & \longrightarrow \mathbf{F} + \mathbf{P}, \\ \mathbf{U} & \longrightarrow \emptyset. \end{split}$$

1. Let n_i be the number of molecules of type i, where $i \in \{U, P, F, f\}$. The life type of a machine of type U is τ_L , the incorporation time of f into F is τ_F and the incorporation time of one unit F is τ_a . Show that within the framework of Leontief production functions, the equations of the model are

$$\frac{\mathrm{d}n_U}{\mathrm{d}t} = \frac{\alpha \min(n_U, n_F)}{\tau_a} - \frac{n_U}{\tau_L}$$

$$\frac{\mathrm{d}n_F}{\mathrm{d}t} = \frac{(1-\alpha)\min(n_U, n_F)}{\tau_a}$$

$$\frac{\mathrm{d}n_F}{\mathrm{d}t} = \frac{\min(n_F, n_f)}{\tau_F} - \frac{\min(n_U, n_F)}{\tau_a}.$$
(9.17)

- 2. Discuss the four limiting regimes of the model: (i) $n_F \gg n_U$ and $n_f \gg n_P$, (ii) $n_F \gg n_U$ and $n_f \ll n_P$, (iii) $n_F \ll n_U$ and $n_f \gg n_P$ and (iv) $n_F \ll n_U$ and $n_f \ll n_P$. Simplify the equations for each regime by introducing a common growth rate μ .
- 3. Summarize your results by deriving the growth laws of the various regimes in a single plot representing α vs. μ .

Problem 9.3 MGF of two simple networks

1. Calculate the MGF introduced in Eq. 9.9 for the following two simple networks :

$$A \longrightarrow B$$

$$B \longrightarrow 2 A.$$
(9.18)

and

$$\begin{array}{l} 2 \operatorname{A} \longrightarrow \operatorname{B} \\ \operatorname{B} \longrightarrow \operatorname{A} . \end{array} \tag{9.19}$$

2. Comment on the values obtained in the previous question.

Solutions to problems

Problem 1.1 : Production function of a workstation with a single resource and single product

Question 1 The equations follow directly from the definitions of the variables and an assumption similar to mass-action law kinetics.

Question 2 Since the total number of machines (busy machines and idling machines) is constant, we have

$$u + v = u_0.$$
 (9.20)

It follows from this that the steady state solution ($\dot{x} = \dot{v} = 0$) of the dynamical equations takes the form

$$a\frac{\beta\bar{v}}{\alpha} + q\bar{x} = r, \tag{9.21}$$

$$\alpha \bar{x}(u_0 - \bar{v}) = \beta \bar{v}, \tag{9.22}$$

which leads to

$$\bar{v} = \frac{\alpha u_0 \bar{x}}{\beta + \alpha \bar{x}}.$$
(9.23)

Therefore, the output rate dy/dt which equals $b\bar{v}$ saturates as a function of the amount of stock x. This saturation due to an excess of stock is similar to the one present in Michaelis-Menten enzyme kinetics.

Question 3 One finds from the previous questions that \bar{v} satisfies a second order equation which can be written in the form

$$\frac{\bar{v}}{u_0} = \frac{\rho + 1 + \gamma}{2} \pm \frac{1}{2}\sqrt{(\rho + 1 + \gamma)^2 - 4\rho}.$$
(9.24)

As a result, to lowest order in $\gamma \ll 1$,

$$\frac{\bar{v}}{u_0} = \min(1,\rho). \tag{9.25}$$

Thus, the output approaches the Leontief production function in the limit $\gamma \rightarrow 0$. This function describes two separate regimes: when $\rho < 1$, only a fraction of machines ρ are busy which limits the production. Instead when $\rho > 1$, all machines are busy, and the production is limited by the total number of machines u_0 . Thus, the Leontief function can describe limitations due to fluxes (term due to ρ) but also due to the amount of stocks (term due to u_0).

Problem 1.2 : UPF model

Question 1 The equations follow directly from the definitions of the variables and from the use of Leontief production function.

Question 2 In Regime I where $n_F \gg n_U$ and $n_f \gg n_P$, the equations simplify to :

$$\frac{\mathrm{d}n_U}{\mathrm{d}t} = \frac{\alpha n_U}{\tau_a} - \frac{n_U}{\tau_L}$$

$$\frac{\mathrm{d}n_P}{\mathrm{d}t} = \frac{(1-\alpha)n_U}{\tau_a}$$

$$\frac{\mathrm{d}n_F}{\mathrm{d}t} = \frac{n_P}{\tau_F} - \frac{n_U}{\tau_a}.$$
(9.26)

Therefore, the growth rate μ at which all species grow exponentially is $\mu = \alpha/\tau_a - 1/\tau_L$. Note that α is an increasing function of μ .

Similarly, in regime II where $n_F \ll n_U$ and $n_f \gg n_P$, and the growth rate satisfies the second order equation

$$\mu^{2} + \frac{\mu}{\tau_{a}} - \frac{1 - \alpha}{\tau_{a}\tau_{F}} = 0,$$
(9.27)

so that

$$\mu = \frac{1}{2\tau_a} \left(2\sqrt{1 + \frac{4(1-\alpha)\tau_a}{\tau_F}} - 1 \right),$$
(9.28)

thus now, α is a decreasing function of μ .

In regime III, where $n_F \gg n_U$ and $n_f \ll n_P$, the growth rate is the same as in regime I and in regime IV, where $n_F \ll n_U$ and $n_f \ll n_P$, and the growth rate is the same as in regime II.

As a result, the plot of μ versus α contains a linear part and part of a parabola, and one can put the four regimes in a single table in which the columns are $n_f \ll n_P$ and $n_f \gg n_P$, while the rows are U starved or U non starved, as done in A. Roy et al., PNAS (2020).

Problem 1.3: MGF for two simple networks

Question 1 Let $\mathbf{v} = (v_1, v_2)^T$ be the flux vector. After splitting the stoichiometric matrix into \mathbf{N}^+ and \mathbf{N}^- , we find for the first network:

$$\alpha(\mathbf{v}) = \min(\frac{2v_2}{v_1}, \frac{v_1}{v_2}).$$
(9.29)

Thus, either $\alpha(\mathbf{v}) = 2v_2/v_1$ if $2v_2/v_1 \leq v_1/v_2$, then $v_2/v_1 \leq 1/\sqrt{2}$ and $\alpha(\mathbf{v}) \leq \sqrt{2}$, or $\alpha(\mathbf{v}) = v_1/v_2$ if $2v_2/v_1 \geq v_1/v_2$, then $v_1/v_2 < 1/\sqrt{2}$ and $\alpha(\mathbf{v}) \leq 1/\sqrt{2}$. Thus in the end, $\alpha = \max_{\mathbf{v}} \alpha(\mathbf{v}) = \sqrt{2}$.

The second network follows a similar calculation which leads to $\alpha = 1/\sqrt{2}$. For the first network, there is autocatalytic growth because $\alpha > 1$, while in the second network, there is degrowth (or shrinking) because $\alpha < 1$.

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