

Biological Stoichiometry: The Elements at the Heart of Biological Interactions

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1. Introduction

All organisms in their complexities of shapes, structures and functions use the same building blocks, elements, assembled and cemented together by energy. But only a subset of the elements available on Earth is used by the organisms in their biomass (Figure 1). Furthermore, the elements most commonly used by living beings (e.g., H, C, N, O, P, S, Na, K, Ca, Fe) are essential components of all organisms biomass. This reveals on one hand the common origin of all species and on the other hand the very specific requirements of the various life processes, to which only a subset of the elements are adapted (see Fraústo da Silva & Williams 2001 for a thorough discussion of the adequacy of elements to their biological functions).

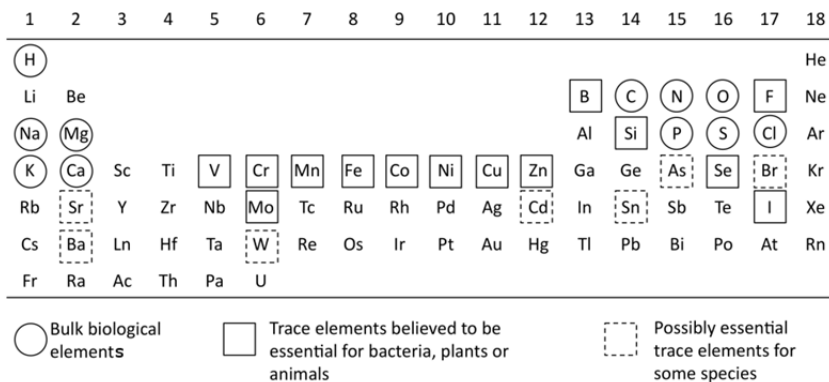


Fig. 1. The distribution of elements essential for life in the periodic table (from Fraústo da Silva & Williams 2001).

Organisms need to get their elements from the environment. To do so, they engage in a variety of interactions with their physical environment and with the other species surrounding them. This fundamental need for elements and energy is thus the fulcrum of many ecological interactions. Furthermore, the sum of all element and energy consumption

rates in an ecosystem represents a major driver of the biogeochemical cycles of elements. On geological timescales, organism-driven cycling of elements has effected great changes at a biosphere level, which fed back on life itself (Lovelock & Margulis 1974; Mcelroy 1983).

One would thus expect that the elemental nutrition of organisms would have been an early concern of ecologists and biogeochemists. Oddly enough, this was not the case, despite the fact that, very early on, Alfred James Lotka, a founding figure of ecology, called the attention of ecologists towards the crucial role of elements in shaping what he called the “drama of life”, i.e., the sum of all ecological interactions (Lotka 1925). His call has been mostly ignored during the following six decades. Instead, ecologists focused almost exclusively on energy fluxes between organisms. Apart from some specialized fields of ecology, and until recently, most ecological approaches ignored the potential role of elements in shaping ecological interactions, emphasizing instead the importance of energy acquisition. The reasons are many, some conceptual, others practical. Energy in ecosystems is generally fixed from light in newly-formed organic matter by photosynthetic plants (hence the term primary producers used to describe photosynthetic organisms). It is then transmitted to those organisms that consume plant production, herbivores and decomposers. Energy then moves up the food web, thanks to predators eating other consumers. Once organic matter is consumed, the energy is either used for growth, excreted in molecules that cannot be used by plants, or dissipated as heat. Hence, there is no recycling of energy back to plants. The fate of all energy entering ecosystems through plants is either to be rapidly degraded into heat or buried into organic matter recalcitrant to decomposition. Energy flow within ecosystems is thus relatively simple. Consequently, its study led to straightforward, successful theories and concepts, such as Eltonian pyramids (Elton 1927), ecological efficiencies and food webs (Lindeman 1942).

On the other hand, the nutrients flow in ecosystems is a cycle. For a given element, autotrophic organisms are those that incorporate in their biomass the element in its mineral form from the environment. Generally, they are also primary producers, but many heterotrophic microorganisms show this ability, too. Mineral elements in ecosystems come partly from external outputs, but the bulk comes from the decomposition of carcasses and wastes from the organisms themselves. On very long timescales, because the Earth is virtually a closed system, most available elements should cycle at least once through living organisms, short of those spurted from the depths of the planet by volcanoes. This cycling adds a level of complexity that can hardly translate into simple, general laws, as is the case for energy (Loreau 2010). Faced with this complexity, few theoreticians attempted to look for generalities about the flows of matter in food webs and ecosystems, despite Lotka’s (1925) longstanding call (DeAngelis 1992).

Admittedly, there have been some fields in which approaches based on elemental composition were applied. Moreover, there have been some sporadic attempts at taking into account the repercussions of the organisms elemental composition on their interactions or on the availability of nutrients in ecosystems. The next section is dedicated to a presentation of these fields that considered the role of elements in biology, but did not serve in their time as stepping stones towards a comprehensive theory of the role of elements in biological interactions. The field of ecology had to wait until the early nineties for such a theory, called “Ecological Stoichiometry”, to emerge. It is a recent, exciting theory, presented in the third section, which tackles the role of elements in ecological interactions with a novel and

promising approach. It views organisms as a single molecule, made of a combination of the various essential elements (C, N, P, Fe...). Accordingly, it treats ecological interactions as chemical reactions, during which elements are exchanged between a consumer, its resource and the environment. It generally assumes that the organisms stoichiometry is constant, i.e., that their elemental composition is homeostatic. But this assumption is not essential to the theory. More essential is the mass conservation principle, which constrains the ecologists to track the fate of all the important elements exchanged in an ecological interaction.

This theory has led to major advances in our understanding of ecological interactions across biological scales. Among them, there are: the realization that the growth of higher, complex organisms can be limited by the availability of one specific element in their food (Urabe & Watanabe 1992); the uncovering of indirect effects from plants on their supply of mineral nutrients through herbivores, because of mismatches between their elemental compositions (Sternner 1990); the exposure of a causal relationship between the elemental compositions of organisms and their growth rates (Elser *et al.* 2003a). Surprising insights from the theory also extend to other fields of biology, such as reproductive biology (Bertram *et al.* 2006), human cancer (Elser *et al.* 2007), evolution (Souza *et al.* 2008) and genomics (Acquisti *et al.* 2009). The earliest contributions of ecological stoichiometry to biology are covered in the 4th section. The latest contributions are covered in the 5th section. These advances led to the coinage of a new term, "Biological Stoichiometry". This term is meant to emphasize the potential of the theory to link processes across all the scales of biology, from molecules to the biosphere. The last section of this chapter will briefly evaluate how far the theory has gone in this unifying endeavour and what are the challenges ahead of biological stoichiometry, before it can claim to realistically portray some of the important interrelations between molecular and ecosystemic processes.

2. The long road to ecological stoichiometry

Justus von Liebig was probably the first influential scientist to apply chemistry to study plant and animal physiologies in a systematic way. It is probably his vision, that there was no distinction between chemical reactions within and outside organisms, that led him to investigate the elemental compositions of organisms and the effects of this composition on biotic processes such as plant growth and decomposition (Playfair & Liebig 1843).

He came to realize that plant nutrition could be entirely satisfied by inorganic compounds, as long as they contained all the elements that made up plant biomass. Liebig's law of the minimum (Figure 2) emerged from this work and has become a central law of ecology. This law was the first example of an application of the principle of conservation of matter to the biological realm, albeit restricted to plants. For society at large, Liebig's work led to the invention and large-scale application of inorganic fertilizers, in other words, what was later known as the "Green Revolution".

Liebig's work on plant mineral nutrition started a long tradition of research on plant growth limitation by elements. It also oriented researchers towards the pursuit of the original source of mineral nutrients in soils. Quickly, it was understood that microbes (bacteria and fungi) were the main providers of mineral nutrients to plants through their decomposition of organic matter in soils. This organic matter itself originates from dead parts of plants (shed leaves, fallen twigs and trunks, dead roots...) or from animal waste.

To a lesser degree, Liebig's work also attracted attention to the role of animals as resuppliers of elements to plants. Overall, it helped entrench a prevalent view of ecosystems where plants are at the centre, bringing inorganic nutrients into the world of organic matter, and consumers are dissipators of energy and resuppliers of inorganic nutrients to plants, with decomposers taking the largest stack. The abiotic components of ecosystems considered are mainly those that affect mineral uptake by plants and the decomposition of organic matter into minerals (e.g., atmospheric deposition of minerals, leaching, temperature, light conditions...). This model came to reinforce the energy-based food chain model formalized by Lindeman (1942). The effect of elements on the growth and reproduction of animals and microbes was seldom considered, although Liebig himself invoked the possibility that the availability of elements in an animal's diet could limit its growth (Playfair & Liebig 1843). Elements were not yet seen as a factor able to affect the food webs structure and dynamics.

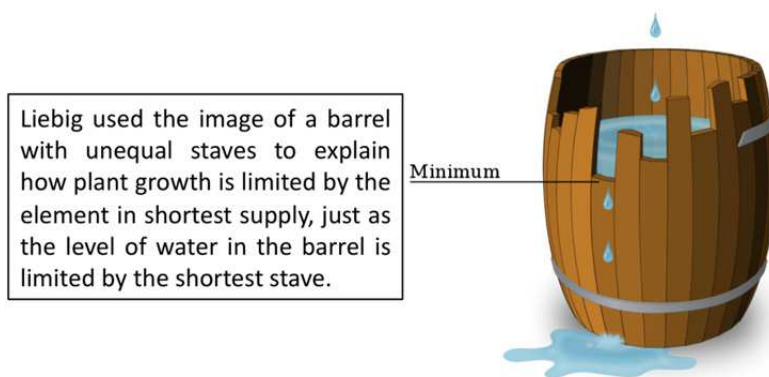


Fig. 2. Liebig's Law of the Minimum and the barrel analogy.

Later developments, however, made it harder to ignore the importance of the elemental needs of some consumers, both for their growth and for their recycling of nutrients. For example, it was known since a long time that microbial decomposers could, in some circumstances, take up inorganic elements instead of mineralize them (Waksman 1917). This uptake of mineral nutrients by heterotrophic microbes was called immobilization. It was quickly understood that the main controlling factor for microbial decomposition or immobilization of nutrients was the mineral content of the microbial biomass in relation to the content of organic matter (Figure 3).

The ecological consequences of the microbial decomposers making up shortages of essential elements in their resource by tapping into the stocks of inorganic nutrients were worked out later on (Bratbak & Thingstad 1985; Harte & Kinzig 1993; Daufresne & Loreau 2001a; Cherif & Loreau 2007). Nutrient-limited primary producers tend to generate carbon-rich organic matter, promoting microbial immobilization. This leads to a paradox, with nutrient-limited plants driving themselves towards stronger nutrient limitation by promoting immobilization. How, then, do limiting nutrients cycle back to plants and support continuous primary productivity if they are locked into the biomass of microbial decomposers? The solution to this paradox was found when food web studies in both

aquatic and terrestrial ecosystems established that most bacterial production is generally consumed by heterotrophic predators also called microbivores (mainly protists, such as amoebae, ciliates and flagellates and, in soils, nematodes). The elements locked in the biomass of the ingested microbial decomposers are then mineralized as catabolic by-products, or because microbivores themselves fall prey to other predators higher up the food web, closing what was called the “microbial loop” (Caron 1994; Clarholm 1994; figure 4).

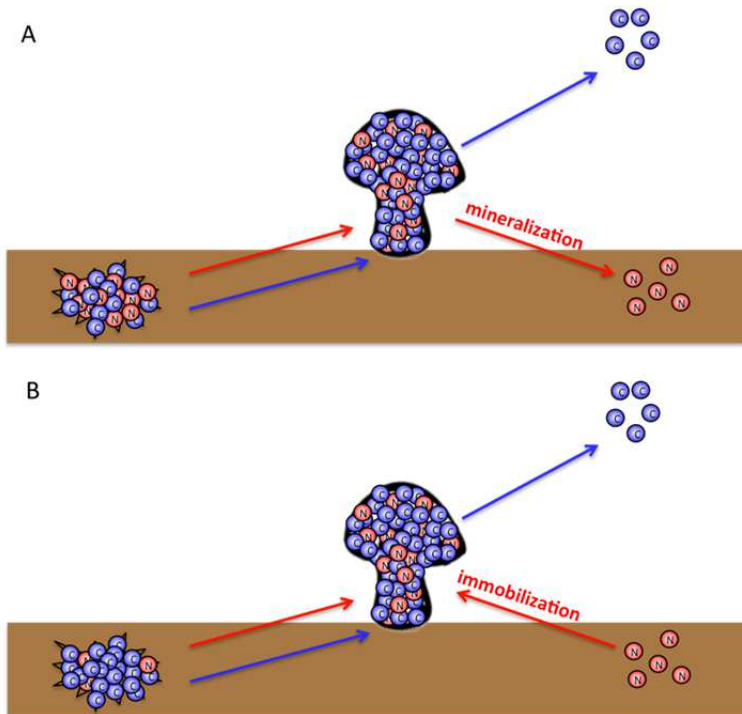


Fig. 3. Mineralization (A) and immobilization (B) of mineral nitrogen by a microbial decomposer, depending on whether organic matter is too rich or too poor in nitrogen, respectively, in comparison to the decomposer nitrogen requirement.

Following the breakthrough of the microbial loop concept, a change in the paradigm of decomposition occurred. Now, the whole detrital food web, not only microbial decomposers, was seen as contributing to the mineralization of the elements essential to plant growth. In this new model, the elemental composition of microbial decomposers plays a central role. On one hand, it determines the extent of immobilization occurring. On the other hand, it also affects the excretion of elements by microbivores, since elements in excess of microbivores needs are excreted (Nakano 1994). Unfortunately, this increasing awareness of the roles of the elemental compositions of microbes, organic matter and microbivores within the communities of researchers interested in soils, did not spread to other fields of ecology, at least until the emergence of the ecological stoichiometry theory.

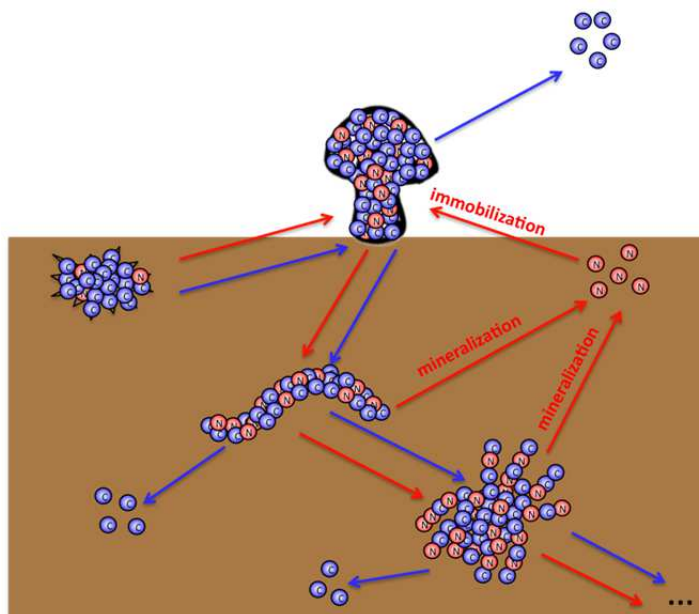


Fig. 4. The microbial loop in soils. Microbial decomposers (fungi and bacteria) immobilize the inorganic elements (here N). They are consumed by microbivores (here nematodes) who release the immobilized N as a by-product of catabolism and are consumed by other consumers (here mites).

The closest to an early stoichiometric thinking, anterior to the ecological stoichiometry theory, appeared in oceanography, a discipline interested into patterns at a larger spatial scale than most other disciplines, but which turned its attention towards the phytoplankton, among the smallest organisms on the planet. Biomass elemental composition was part of oceanographic thinking since at least the 40s, thanks to the work of Alfred Clarence Redfield (1934). Redfield compared the contents of carbon, nitrogen and phosphorus in the phytoplankton of open ocean areas to dissolved nutrient concentrations in surface water and regenerated in the deep ocean (Table 1). The similarity between these ratios led him to state that the plankton chemical composition determined, on geological time, the chemical composition of the ocean (Redfield 1958).

	P	N	C
Analyses of plankton	1	16	106
Changes in sea water	1	15	105
Available in sea water	1	15	1000

Table 1. Atomic ratios of elements in components of the oceanic biochemical cycle (Adapted from Redfield 1958)

Furthermore, Redfield proposed that the phytoplankton balanced its consumption of nitrogen relative to phosphorus by fixing the atmospheric nitrogen when P was in excess, so that their ratio became equal to that of their chemical composition (the now famous N:P Redfield ratio equal to 16). This is equivalent to assuming that it was the phosphorus that, on geological timescales, limited the growth of phytoplankton, while nitrogen was simply adjusted by the biological activity of the nitrogen-fixing phytoplankton (Redfield 1958).

This stoichiometric model of the oceanic biogeochemical cycle has prompted work on the elemental stoichiometry of recycling in oceans (e.g., Berner). Moreover, it encouraged much speculation on the genesis and maintenance of the ocean and the atmosphere chemical properties (Walker 1974; Griffith *et al.* 1977; Lovelock & Watson 1982). Curiously, this did not lead to any serious attempt to generalize these results to other ecosystems, other elements beyond nitrogen, phosphorus and carbon, or the roles of other trophic levels beyond the phytoplankton.

On the other hand, the assertion that phosphorus should be the element limiting the growth of phytoplankton contradicted accumulated empirical evidence showing that the oceanic phytoplankton was primarily limited by nitrogen (Smith 1984). This contradiction spurred several decades of studies on the growth and chemical composition of phytoplankton grown in the presence of several potentially limiting factors, especially nitrogen and phosphorus (Droop 1974; Rhee 1978; Goldman *et al.* 1979; Tett *et al.* 1985). These experiments showed that both the chemical composition and type of growth-limiting element vary among phytoplankton species. Although constant at the scale of ocean basins, the Redfield ratio is thus probably the result of several processes rather than a fixed property of the phytoplankton (Falkowski 2000; Geider & La Roche 2002; Klausmeier *et al.* 2004).

The accumulation of knowledge on the diversity of elemental requirements, limitations and chemical compositions among phytoplankton species led to believe that it was possible to explain the "paradox of the plankton" proposed by George Evelyn Hutchinson (1961). Hutchinson wondered how the phytoplankton could harbour so many species (in the order of several tens) in the relatively homogeneous environment of surface waters, despite the low number of resources shared by these species. This seemed to contradict the principle of competitive exclusion, which predicts that there cannot be more species than limiting resources at equilibrium (Hardin 1960).

Based on earlier work (MacArthur & Levins 1964; Rapport 1971; Leon & Tumpson 1975), David Tilman developed a theory that could predict the outcome of resource competition between several species of phytoplankton according to their elemental requirements, their chemical compositions and external supplies of elements in the ecosystem (Tilman 1980). Later, expanding his theory to integrate spatiotemporal fluctuations in external supplies, he demonstrated that these variations allowed the coexistence of more species than resources (Tilman *et al.* 1982). He thus provided what he considered as a definitive response to Hutchinson's "paradox of the plankton". Furthermore, seeking to explain possible sources of variation in the supplies of elements, he advanced the hypothesis that "If some nutrients (e.g., phosphorus) are regenerated more rapidly than others, zooplankton may significantly affect phytoplankton community structure by changing nutrient supply rates and ratios" (Tilman *et al.* 1982). Only a few steps remained until the ecological stoichiometry theory.

3. Ecological stoichiometry: An attempt at a systematic approach

In 1988, Elser and colleagues observed a correlation between the type of element limiting the growth of the phytoplankton and the species composition of the zooplankton community of experimental lakes in Michigan (Elser *et al.* 1988). When the zooplankton community was dominated by copepods, the phytoplankton was limited by nitrogen, whereas it was limited by phosphorus when dominated by cladocerans such as *Daphnia*. They already knew that the zooplankton recycled nitrogen and phosphorus with different efficiencies (Lehman 1984). They could not explain, though, the different effects of copepods and cladocerans, especially since many differences between the two types of zooplankton could intervene: copepods are mainly small and select the species they consume, while cladocerans are generally larger (up to several millimetres) and consume very effectively all the species captured in their filters. An explanation was soon offered by R. W. Sterner (1990) when he showed theoretically that zooplankton species with different chemical compositions should recycle elements with different efficiencies, provided that their chemical composition is kept constant over time. Andersen and Hessen (1991) then found that copepods and cladocerans were widely dissimilar in their chemical composition; copepods are rich in nitrogen while *Daphnia* are richer in phosphorus. Moreover, they found little variation in their compositions over time, despite variations in the composition of their resources.

All these related observations and hypotheses merged together to give the first fully-stoichiometric description of a trophic interaction: "Herbivore species with a high ratio of N:P in their tissues should resupply nutrients at a relatively low N:P ratio compared to herbivore species with low body N:P" (Sterner *et al.* 1992). The increased availability of the element in excess of the herbivores needs should drive the phytoplankton to a limitation by the same factor that limits the growth of herbivores (N for herbivores with a high ratio of N:P and P for those with a low N:P) (Figure 5).

Surprisingly, the main criticisms of this hypothesis concerned a point that is not essential to the mechanism that underlies it, but derives from subsequent works (Hessen 1992; Urabe & Watanabe 1992). The possibility of a direct limitation of the growth of the zooplankton by mineral elements, either N or P, raised many objections from researchers thinking that resource limitation of growth was possible only by biochemical substances such as amino acids or fatty acids (Brett 1993, Müller-Navarra 1995). Links between growth rate and diet elemental content were seen as simple correlations. Much research was then devoted to prove or disprove the negative effects of nitrogen and phosphorus-deficient phytoplankton on the growth of the zooplankton (Sterner *et al.* 1993; Anderson & Hessen 1995; Urabe *et al.* 1997; Urabe & Sterner 2001).

Regeneration of nitrogen and phosphorus by the zooplankton with a ratio reflecting the difference between its chemical composition and that of its resources is a part of the hypothesis that was largely confirmed afterwards (Sterner & Smith 1993; Urabe 1993; Balseiro *et al.* 1997; Elser & Urabe 1999). On the other hand, the alteration of phytoplankton limitation that is supposed to result from this differential recycling of elements by zooplankton was, if not less studied, rarely highlighted. Some studies showed indeed a strong effect of herbivore chemical composition and recycling on the phytoplankton growth limitation (Carpenter *et al.* 1993; Rothhaupt 1997; MacKay & Elser 1998). Other results did not concur with the predictions from the stoichiometric hypothesis (Moegenburg & Vanni

1991; Urabe 1993). Daufresne and Loreau (2001b) provided an elegant explanation of these discrepancies by showing theoretically that the effect of herbivores on the plants limitation depends not only on their chemical composition, but also on the physiological response of plants to herbivory. Indeed, the decrease in plant biomass caused by herbivory results in increased elemental requirements of plants to compensate for the loss. These additional requirements can vary between elements and between phytoplankton species. The nature of the limiting element promoted by herbivores is determined by the result of these physiological adjustments and the differential recycling of elements by herbivores.

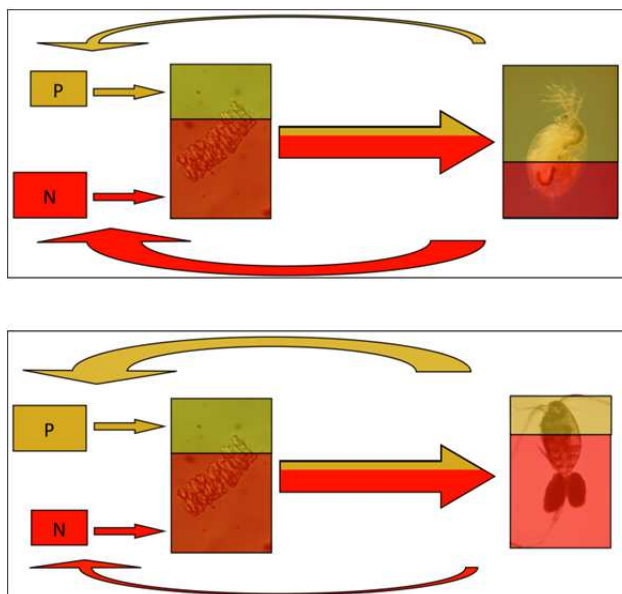


Fig. 5. The stoichiometric hypothesis of consumer-driven elemental limitation of phytoplankton. P-rich *Daphnia* (upper panel) ingest N in excess from the phytoplankton. Getting rid of this excess, they enrich the environment in N and thus drive the phytoplankton towards P limitation. N-rich copepods (lower panel) drive the phytoplankton towards N limitation by a similar mechanism.

Efforts were also undertaken to broaden the stoichiometric approach beyond the sphere of pelagic freshwater organisms and towards other ecosystems. Several studies have therefore turned to other habitats: marine (Elser & Hassett 1994), arctic (Dobberfuhl & Elser 2000), terrestrial (Elser *et al.* 2000), benthic (Frost *et al.* 2002), arid (Schade *et al.* 2003) and even fossil ecosystems (Elser *et al.* 2006). Other organisms and trophic levels were also investigated: bacteria (Chrzanowski & Kyle 1996; Makino *et al.* 2003), protists (Grover & Chrzanowski 2006), vertebrates (Vanni *et al.* 2002), and insects (Woods *et al.* 2002; Markow *et al.* 2006).

Most of the advances in ecological stoichiometry, from its birth to the early years of this century are well summarized in the book "Ecological stoichiometry: The biology of elements from molecules to the biosphere" published in 2002 by Sterner and Elser. It is worth noting though, that no comprehensive review of the topic has appeared since then.

4. Understanding stoichiometry: The biological bases of the economy of elements in organisms

Different organisms vary widely in their elemental composition. This variation is what makes the study of stoichiometry relevant for developing a better understanding of ecological interactions. On a different level, these elemental differences also lead to questions about the underlying biological causes for these differences. Sterner and Elser's synthetic book (2002) represents the first attempt at an in-depth investigation of the origins of the differences among the elemental stoichiometries of organisms.

A first obvious source of stoichiometric diversity is the various extents to which organisms invest in structural materials that often present distinct stoichiometric signatures. Well-known examples are the investment of molluscs in calcium carbonate shells, which should increase their calcium content, the hydroxyapatite-based bones of vertebrates, the siliceous frustules of diatoms and the carbon-rich, nitrogen-poor woody stems of many terrestrial plants. A precursor to the ecological stoichiometry theory, William A. Reiners (1986) assumed a fixed composition for the protoplasm of all organisms (the cellular components, without any structural material) and assigned all variations in elemental composition to variations in the proportions of different structural material. Since then, it became obvious that protoplasm can differ in their elemental compositions, such that even relatively taxonomically close species can show different stoichiometries (Andersen & Hessen 1991). The basic building blocks of organic matter (amino-acids, lipids, carbohydrates, nucleotides...) and the polymers assembled from them (proteins, nucleotides...) show obvious stoichiometric differences (Figure 6).

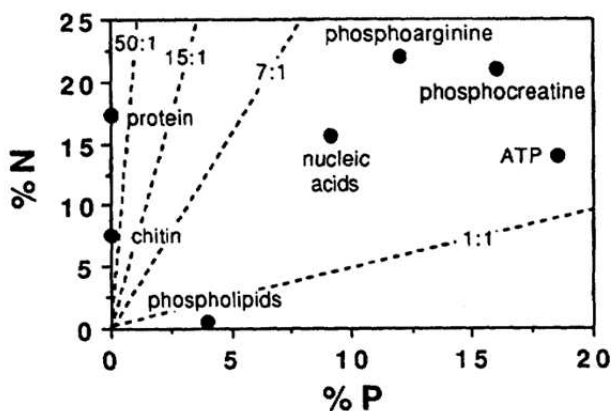


Fig. 6. Nitrogen and phosphorus composition of important biomolecules. Percentage nitrogen and percentage phosphorus are given in terms of weight. Dotted lines depict standard values of atomic (molar) N:P ratios, the most commonly used units reported in ecological stoichiometry studies (reproduced from Elser *et al.* 1996)

Among these biomolecules, proteins and nucleic acids stand out, being very abundant and having contrasting elemental compositions. Proteins are rich in N and nucleic acids are rich in P. It was postulated and then shown that otherwise close organisms that differ in their

proportions of proteins and nucleic acids also differ in their N:P ratios (Sterner & Elser 2002). The next step was to look at the distribution of these molecules within cell components and organelles. Through cell fractionation techniques and calculations, it quickly became clear that ribosomal RNA (rRNA) generally represent the major stock of nucleic acids and P within cells (Elser *et al.* 1996). Proteins and associated N atoms are more evenly distributed within cells, although mitochondria emerge as a particularly N-rich organelles (Sterner & Elser 2002). These observations led to one of the first and major unexpected predictions to stem from the ecological stoichiometry theory, namely the “growth rate hypothesis”. This hypothesis is simply a causal link made between the observation that rRNA generally represent the major stock of P in cells and organisms on one side, and the observation that the need for ribosomes increases with growth rate on the other side (Elser *et al.* 1996). From there came the hypothesis that there should be a direct relation between the growth rate of organisms and their P content. Since proteins and nucleic acids have similar N contents, replacing one with another should not alter the N content. So, there should be also a direct relation between growth rate and the N:P ratio. The hypothesis was put to test, using data collections and experiments. Many studies showed results that are congruent with the growth rate hypothesis in various taxa (Elser *et al.* 2003a; Karpinets *et al.* 2006). However, it was found to be of limited validity across other taxa, because of species-specific differences in the percentage of P linked to RNA (Matzek & Vitousek 2009). Moreover, maintenance costs for high P levels in biomass can also impair the relation between P content and growth rate (Urabe & Shimizu 2008). Finally, P content was often decoupled from growth rate when organisms were grown under a limiting factor other than P, probably because they can store P that is in excess of their needs (Elser *et al.* 2003a; Matzek & Vitousek 2009).

Curiously, although there is a strong association between mitochondria and cell N content, there was no hypothesis set forth to predict potential relations between cell N content and physiological correlates of mitochondrial cellular density. More generally, the role of N content has been understudied in biological stoichiometry, probably reflecting the fact that: i) N content is less variable than P content ii) P-rich *Daphnia* are model organisms in many fields of ecology and genetics and iii) P is thought to be the predominant limiting factor in freshwater ecosystems and the main agent of anthropogenic eutrophication.

In summary, there are three main factors that determine the elemental composition of organisms: i) the relative amounts of important biomolecules in cells, such as proteins and RNA; ii) the type and amount of structural material in the organism; and iii) the reserves of elements that are supplied in excess of the organismal requirement. Each of these three factors is related to ecologically relevant life history traits, thus building a bridge between the stoichiometry and the ecology of organisms. For example, P content in P limited organisms, is related to RNA content which itself is a function of growth rate (the Growth Rate Hypothesis). Organisms with more structural material, tending to be larger than related species with fewer structures, show lower specific metabolic rates (Brown *et al.* 2004). Species storing non-limiting resources fare better than similar organisms without storage when the resource becomes limiting, but at the expenses of a higher maximum growth rate (Sommer 1985). Hence, progress in understanding the underlying biological determinants of the organisms stoichiometry is relevant, not only because it advances our knowledge of the physiology of organisms, but also because it sheds light on the ecology of organisms as

affected by their stoichiometry. The previous section described how Ecological Stoichiometry opened up the way to link the organisms stoichiometry to the biogeochemical cycles within ecosystems. This section shows how Biological Stoichiometry represents a link from molecules to the ecology of organisms. Since Biological Stoichiometry encompasses Ecological Stoichiometry, then it is a theory that has the potential to link molecules to ecosystems, as claimed by its main proponents in their reference work (Sterner & Elser 2002). Nevertheless, the theory just set the tools (the elemental composition regulation in organisms) and the method (balancing the multi-elemental exchanges between organisms) to reach such integration across the levels of biology, without offering a-priori predictions about how processes at different biological levels articulate. These predictions need to be worked out by mixing stoichiometric reasoning with observations. Such was the case for the Growth Rate Hypothesis, which stemmed from the observations that a majority of P in cells is associated with rRNA, itself associated with growth rate, and concluded that fast-growing organisms should be P-rich and thus more sensitive to P deficiencies in their food. The next section is meant to present some of the most recent advances towards this integrative goal.

5. Recent advances in biological stoichiometry

Following Sterner and Elser's 2002 book, researchers in the field of biological stoichiometry pursued two main directions. On one hand, there was an urge to have a more accurate knowledge of the mechanisms by which organisms regulate their elemental composition, in order to more realistically link their stoichiometric properties to their impacts on the cycles of elements. On the other hand, other researchers carried on with the process of extending the use of the stoichiometric approach to other fields in biology, always with the objective of integrating seemingly separate fields.

Consumers that strive to keep their elemental composition constant, in the face of stoichiometrically imbalanced resources, need to alter their gross growth efficiencies for elements in a controlled way (Figure 7). These gross growth efficiencies, in turn, determine the differential recycling of elements by consumers (Sterner 1990).

How consumers regulate their gross growth efficiencies was, and still is, largely unknown. In the absence of empirical data, in early stoichiometric models, the gross growth efficiency of the element limiting the consumer growth was set to a maximum value, ensuring maximal growth, while the gross growth efficiencies of the other elements were adjusted to yield a constant stoichiometry for the consumer (Figure 7). But theoretically, there is an infinite number of possible alternative strategies (Andersen 1997). Recent experiments also show that net assimilation of the limiting element is not necessarily at its maximal efficiency (DeMott *et al.* 1998) and that non-limiting elements too have impacts on growth (Boersma & Elser 2006; Zehnder & Hunter 2009). Moreover, it was shown that the quantity of resources, besides their stoichiometric compositions, affects the gross growth efficiencies of elements (Anderson & Hessen 2005). Furthermore, models that included a description of the distribution of elements among the various biomolecules in cells have shown that it is not even always possible to set one element as the growth-limiting factor (Anderson *et al.* 2004). It thus became clear that more physiologically grounded models of the use of elements by organisms were needed. Anderson *et al.*'s now classical model (2005) strikes a good balance between physiological realism and simplicity, including processes such as biomass

turnover, assimilation costs, maintenance costs, and respiration. These endeavours to understand the regulation of organismal stoichiometry by including the metabolism of biomolecules lead to connections between biological stoichiometry and nutritional sciences (Raubenheimer *et al.* 2009).

<p>A</p> $G_X = I_X - F_X - R_X$ $G_Y = I_Y - F_Y - R_Y$	<p>C</p> $\theta_{XY} = G_X / G_Y$ $= (GGE_X \times I_X) / (GGE_Y \times I_Y)$ $= (GGE_X / GGE_Y) \times (I_X / I_Y)$ $= (GGE_X / GGE_Y) \times \Phi_{XY}$
<p>B</p> $GGE_X = G_X / I_X$ $GGE_Y = G_Y / I_Y$	<p>D</p> <p>X is limiting:</p> $GGE_X = GGE_{Xmax}$ $GGE_Y = GGE_X \times (\Phi_{XY} / \theta_{XY})$ $= GGE_{Xmax} \times (\Phi_{XY} / \theta_{XY})$

G_X : X newly accumulated in biomass	GGE_X : gross growth efficiency for X
I_X : X ingested from resource	θ_{XY} : consumer's X:Y ratio
F_X : X egested with fecal matter	Φ_{XY} : resource X:Y ratio
R_X : X excreted due to catabolism	

Fig. 7. Relation between the gross growth efficiencies of two unspecified elements (X and Y) as imposed by the constraint of a homeostatic regulation of the stoichiometry of a consumer. A) Mass balance equations for consumption. B) Definition of the gross growth efficiency. C) Stoichiometric constraint imposed on the GGEs for X and Y, as a consequence of the constancy of the X:Y ratio of consumers. D) A simple model that assumes a maximal GGE for the limiting element leads to the GGE of the non-limiting element to be a function of the maximal GGE, and the X:Y ratios of the consumer and its resource (adapted from Sterner 1990).

Physiological adaptation is the short-term response of consumers to imbalanced resources. Analyses at the levels of genomes and transcriptomes, showed that transcriptional changes are among the mechanisms used by consumers to achieve stoichiometric homeostasis. For example, transcriptional changes in the expression of phosphate transporters, activation of alternative metabolic pathways, changes in allocations to roots (for plants), are triggered under P deficiency (Jeyasingh & Weider 2007). Recent studies uncovered long-term evolutionary responses to element deprivations: N-deprived organisms react by substituting N-rich amino-acids by amino-acids with N-poor residues in their expressed proteins or by expressing shorter mRNAs (Grzymiski & Dussaq 2011). They also show RNAs with more N-poor nucleotides (Elser *et al.* 2011). As for DNA, since GC and AT pairs have almost the same N content, N limitation seems to have less effect. These advances on the links between elemental limitation and cell polymer composition lead to the coining of a new term: "stoichiogenomics" (Elser *et al.* 2011).

Away from these ventures into the heart of the cellular machinery, other researchers looked for new insights from applying stoichiometric approaches to yet untouched fields. For example, models and experiments had shown that primary producers with a very low nutrient content could drive grazers to extinction and prevent their invasion of a habitat where they are absent (Andersen *et al.* 2004). This barrier to herbivore establishment led to speculations that the lack of grazers before the early Cambrian explosion and their “sudden” appearance afterwards could be linked to a change in the P supply at the scale of the globe (Elser *et al.* 2006). The same authors tested the hypothesis using modern stromatolites, which are very similar to the fossilized Cambrian stromatolites.

Another unexpected fallout from the application of the stoichiometric approach is the uncovering of stoichiometry-related effects on the relation between sexes and on the process of sexual selection. Sexes often differ in their investment in sex-related characters and organs. This difference is likely to be reflected in their elemental needs and use of their resources (Morehouse *et al.* 2010). A well-studied example is the positive correlation found between the phosphorus body content in male crickets and their song performance. Another area in which the stoichiometric approach proved fruitful hits closer to our everyday concerns: our health. An ingenious application of the growth rate hypothesis to cancer, gave rise to the hypothesis that fast-growing cancerous tumours should be richer in P. Thus, they should enter into competition with their neighbouring healthy cells for P and possibly see their growth be P-limited (Elser *et al.* 2007). This hypothesis brought forth by ecologists, that sees tumours as an ecosystem in itself, attracted favourable attention from the medical world (Baudouin-Cornu 2008; Pienta *et al.* 2008) and has potential medical applications ((Elser *et al.* 2003b). Because pathogens share the same requirements for elements as their hosts, they too can be affected by shortages in some key elements, such as iron (Smith 2007). Competition between host cells and pathogens for elements as well as external supplies of elements become an important parameter of the outcome of infections (Hall *et al.* 2009). Hence, the stoichiometry of diseases opens the door for more rational medical treatments through nutrition (Cotter *et al.* 2011).

6. Future needs and challenges ahead

Biological stoichiometry proved to be astonishingly successful in bringing new insights in seemingly disconnected fields of biology, such as molecular evolution, palaeontology and parasitology. But these advances have not yet allowed us to draw a complete picture of the elements role in structuring biological entities from molecules to ecosystems. Huge gaps remain between levels: for example, the stoichiometric theory currently attributes a unique elemental composition to all individuals within one population. But it is known that stoichiometry varies with ontogeny (E.g., Main *et al.* 1997). Hence, the stoichiometry of a population probably differs from the stoichiometry of its individual components and might vary through time, a fact rarely considered (Nakazawa 2011).

Life is complex: different organisms might show different strategies to regulate their elemental composition (Mitra & Flynn 2005, 2007); food webs are diverse, both horizontally (i.e., within the same trophic level) and vertically (i.e., across trophic levels). Predictions that apply to one trophic level may prove erroneous if they neglect other species from the same (Danger *et al.* 2008) or from different trophic levels (Cherif & Loreau 2009). These additional

complexities need to be fully incorporated into the theory of Biological Stoichiometry before it really can link molecules to ecosystems. This is obviously a long journey but the road is already drawn on the map!

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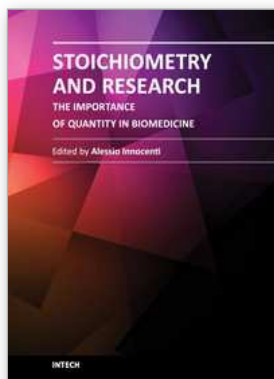
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The aim of this book is to provide an overview of the importance of stoichiometry in the biomedical field. It proposes a collection of selected research articles and reviews which provide up-to-date information related to stoichiometry at various levels. The first section deals with host-guest chemistry, focusing on selected calixarenes, cyclodextrins and crown ethers derivatives. In the second and third sections the book presents some issues concerning stoichiometry of metal complexes and lipids and polymers architecture. The fourth section aims to clarify the role of stoichiometry in the determination of protein interactions, while in the fifth section some selected experimental techniques applied to specific systems are introduced. The last section of the book is an attempt at showing some interesting connections between biomedicine and the environment, introducing the concept of biological stoichiometry. On this basis, the present volume would definitely be an ideal source of scientific information to researchers and scientists involved in biomedicine, biochemistry and other areas involving stoichiometry evaluation.

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