



Marine sponge aquaculture towards drug development: An ongoing history of technical, ecological, chemical considerations and challenges

Mathilde Maslin^a, Nabila Gaertner-Mazouni^a, Cécile Debitus^b, Nicole Joy^{c,d}, Raimana Ho^{a,*}

^a Univ. Polynesie Francaise, Ifremer, ILM, IRD, EIO UMR 241, Tahiti, French Polynesia

^b IRD, Univ Brest, CNRS, Ifremer, LEMAR, 29280, Plouzané, France

^c Marine Biodiversity, Naturalis Biodiversity Center, PO Box 9517, 2300 RA, Leiden, the Netherlands

^d Institute of Environmental Sciences (CML), Leiden University, PO Box 9518, 2300 RA, Leiden, the Netherlands

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ABSTRACT

Marine sponges have a long history of farming, starting with bath sponges over 5000 years ago in the Mediterranean. Many species have since been found appropriate for distinct types of commercial assessment. Drug development relies on the isolation of sponge-derived secondary metabolites as natural compounds having a wide range of ecological functions, from deterring predation to preventing microbial infection/proliferation on the sponge body. For human society, they feature a broad array of pharmacological properties with some applications still being discovered. Their limited supply has however been faced as a major obstacle to the conduct of clinical trials. Marine aquaculture has to prove more integrated and sustainable to remain an interesting way to ensure sufficient amounts of biological substances for the early processing and production of drugs. This review presents sponge farming methods that were tested, the undergoing challenges they faced and the interest they raised on environmental and metabolic factors to explain contrasting spatiotemporal performances. Through global experiments, sometimes involving other marine organisms, technicity of sponge aquaculture has long been evolving to ensure efficient and cost-effective strategies. Further ways to make sponge farming more attractive and diversify its commercial applications are investigated, such as recent studies in collagen or chitin production for bone tissue engineering or bioremediation as an alternative to existing wastewater management. Overall, marine sponges exhibit astonishing intra and interspecific variation, which is why they should be considered with respect to the purpose of their economic valuation, their environmental context and all the symbiotic interactions they rely on.

1. Introduction

Marine sponges (phylum Porifera) represent an important part of the benthic biomass and diversity in many areas and provide several important ecosystem functions such as shelter, food or regulating substrate settlement (Ayling, 1981; Costello and Myers, 1987; Dayton et al., 1974; de Goeij et al., 2013; Maldonado et al., 2012, 2015; Pawlik and McMurray, 2019). Like many other sessile invertebrates, they have developed an efficient chemical system based on the production of bioactive secondary metabolites for defense and communication purposes (Becerro et al., 2003; Green, 1977; Hay, 1996; Helber et al., 2018; Hogg et al., 2010; Jones et al., 2005; Kovalchuk et al., 2019; Mehub et al., 2016; Muzychka et al., 2021; Sim and Bakus, 1986). The

synthesized molecules generated by these macrofilter feeders and their associated microsymbionts are particularly useful to fight diseases and to repel their surface colonization by harmful biofouling (Aguila-Ramírez et al., 2014; Fang et al., 2017; Thompson et al., 1985). Such chemical defenses avoid the detrimental repercussions that colonizing organisms may generate on sponge metabolism, like obstruction of the excurrent openings called “oscula” (Fig. 1) or degradation of the superficial regions referred to as “ectosome” (Borges and Simoes, 2019; Britstein et al., 2018; Corra and Sanchez, 1996; Kelly et al., 2003; Littler and Littler, 1995). These facts explain for instance that healthy wild sponges are indeed rarely covered by epiphytic fauna or flora (Abarzua and Jakubowski, 1995).

Since Greek antiquity, marine sponges have always had a wide range

* Corresponding author at: B.P.6570, c/o Université de la Polynésie française, 98702, Faa'a, Tahiti, French Polynesia.

E-mail addresses: mathilde.maslin@doctorant.upf.pf (M. Maslin), nabila.gaertner-mazouni@upf.pf (N. Gaertner-Mazouni), cecile.debitus@ird.fr (C. Debitus), nicole.devoogd@naturalis.nl (N. Joy), raimana.ho@upf.pf (R. Ho).

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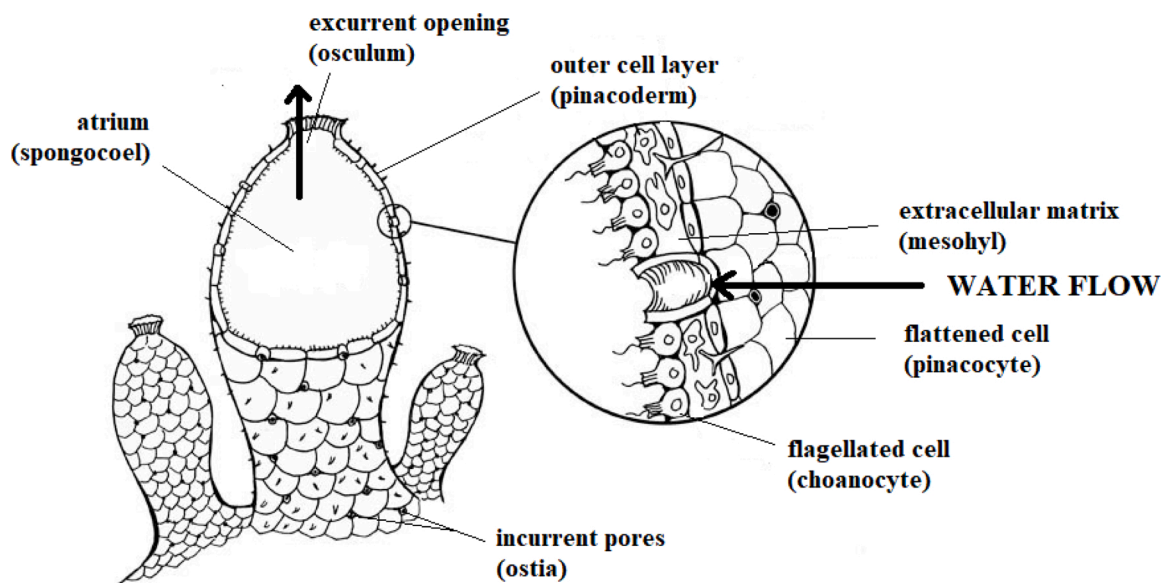
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of uses, ranging from hygienic and artistic tools to their medical employment against infections or inflammations (Starkey et al., 2008; Voultziadou, 2007). The harvesting and preparation of some sponge species being used as “bath sponges” for the absorptive properties of their fibrous skeleton dates back to the Roman Empire in some Mediterranean countries such as Egypt, Greece and Phoenicia (Ehrlich et al., 2018; Jesionowski et al., 2018; Pronzato and Manconi, 2008). First literary data can be found in the 13th edition of *Systema Naturae*, written by Linné in 1789. In Florida, Moore produced an early report in 1910 to inform about the existence of natural sponge beds and describe the methodology and prospects of sponge aquaculture starting from eggs or cuttings. Bath sponges then gradually began to be farmed on a small scale in the Mediterranean, on the off-coast of Florida and in several regions of the Pacific (Cahn, 1948; Croft, 1989; Handley et al., 2003; Storr, 1957, 1964). As demand grew, so did imports and domestic productions worldwide. Yet, episodic disease outbreaks such as in the Mediterranean and the “blight” infection in Florida also combined with the overfishing of bath sponges in the late 1980s gradually contributed to threatening wild populations and depleted entire sponge habitats (Bertolino et al., 2017; Croft, 1990; Pronzato, 2003). Local and international directories are now protecting several species of Mediterranean sponges, which show a high level of endemism compared to Pacific taxa, with different levels of regulation depending on their potential use as commercial products or by-products (Dailianis et al., 2011). Bath sponge production, either raw or processed, has progressively entered the international trade over the past two decades and is currently well-established in some countries as mainly dedicated to the local tourism industry (Fourt et al., 2018; Hawes et al., 2010). Still, despite many research efforts worldwide, no industry specifically targeting sponge or sponge symbionts towards metabolites production has already reached the market scale (Belarbi et al., 2003a; de Voogd, 2007a; Page et al., 2005; Osinga et al., 2010).

Investigations on population dynamics of Porifera have progressively been undertaken and widespread since their beginning in the early 1970s (Hartman and Reiswig, 1973; Stone, 1970). New roles and potentials of these organisms, along with their associated symbionts, were revealed such as their ability to act as bioremediators (Gökçalp et al., 2020; Milanese et al., 2003; Stabili et al., 2006) capturing heavy metals (Berthet et al., 2005; Cebrian et al., 2007; Patel et al., 1985) or reducing

pathogenic bacterial densities and organic particles excess from the environment (Alexander et al., 2014; Ledda et al., 2014; Reiswig, 1971; Yahel et al., 2003). Most metabolic mechanisms of sponges and sponge microbiome still remain unaddressed, yet their reported importance in nutrient cycling is making some of the existing food web models incomplete when they do not consider such taxa as essential drivers and modulators of marine consumer resources (de Goeij et al., 2017; Engelberts et al., 2020). A lack of accomplishment still clearly exists in this regard. Last but not least, the most diverse class of sponges called Demospongiae accounts with species with a fibrous skeleton made of spongin, a collagen-derived protein which has extreme properties in terms of thermic and mechanical resistance (Petrenko et al., 2019; Szatkowski et al., 2017). This biopolymer, along with many other that can be found incorporated into sponge skeletons (i.e. collagen chitin, silica), is thus under recent considerations towards bioengineering and extreme biomimetics applications (Khrunyk et al., 2020; Szatkowski et al., 2018).

Fortunately, sponge ability to colonize adjacent similar biotopes in optimal specific conditions can be presumed (Padiglia et al., 2018). Their elevated dispersion rate, exceptional abundance in benthic communities and impact on the cycling rates of nutritive compounds, while ensuring natural stocks preservation and expenditure, are making them highly favorable for aquaculture process. Farming sponges for chemical extraction is a consideration that experienced great advances in the last century (Duckworth, 2001). For some sponge-related compounds, aquaculture was even reckoned as the only viable medium-term option to start pre-clinical tests towards drug development (Koopmans et al., 2009). Many metabolites have already been described in the literature; indeed, marine sponges and sponge microbiome are considered as the most prolific oceanic source of new bioactive substances (Blunt et al., 2004; Laport et al., 2009; Carroll et al., 2019; Pawlik and McMurray, 2019; Zhang et al., 2005). In the past 50 years, more than 9700 novel molecules were discovered and isolated from sponge extracts, including their associated microbial communities, which nearly represents 30 % of all marine molecules discovered to date (Database: MarinLit 2020). Recent large-scale biological screening experiments have highlighted the potential of bioactive metabolites present in such extracts for applications in biotechnologies and the pharmaceutical industry (Kumar and Pal, 2016; Lowe et al., 2016; Pomponi, 2001). Antifouling,



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Fig. 1. Simplified morphological organization of a marine sponge. The surrounding water enters the spongocoel through small openings called ostia, is waved by monoflagellated choanocytes within the atrium and is finally ejected through large oscula.

anti-inflammatory, antibiotic, antioxidant, antitumor and antiviral properties were progressively revealed (Abarzua and Jakubowski, 1995; Bechmann et al., 2018; Drechsel et al., 2020; Duckworth, 2001; Ruiz et al., 2013).

Bergmann and Feeney (1951) were the first scientists to characterize two bioactive natural products, the nucleosides spongothymidine and spongosine, from the Caribbean marine sponge *Tectitethya crypta* (as *Tethya crypta*). Since, some sponge-derived compounds now synthesized *in vitro* such as Cytarabine (trademarks: Cytosar-U®; Depocyt®), Vidarabine (trademark : Vira-A®) and Eribulin mesylate (trademark : Halaven®) are available in the pharmacological market after being approved as drugs by the Food and Drug Administration or the European Medicines Agency (Martins et al., 2014; Dyshlovoy and Honecker, 2020). Therapeutic effects of cytarabine encompass the treatment of myeloid and meningeal leukaemia and lymphoma, while vidarabine is prescribed against various herpes and RNA tumour viruses (Lichtman, 2013; Shen et al., 2009). They both have been in the lead of antiviral and anticancer therapy for many years (Lloyd-Evans, 2005). Eribulin mesylate has shown high potential in the cure of metastatic breast cancer (Hirata and Uemura, 1986; Towle et al., 2001). Speaking of costs, 50 mg of Vira-A® as an adenosine analog can be purchased for 100–145 \$ US (Abcam Inc 2015) while 1 mg of Halaven® is generally ordered for more than 1000 \$ US (Eisai Inc 2020). Not unexpectedly, many individual compounds still not approved as drugs are yet available to purchase and their prices reveal a very strong potential with significant economic benefits for the culture of sponges towards pharmaceutical exploitation (Binnewerg et al., 2020).

Due to their many commercial and technological applications, the exploitation of marine sponges must be rational in order to protect wild stocks from an excessive harvesting pressure. To ensure sustainable production and successful operations, it is essential to collect information on the biological needs of the selected taxa, as well as their population dynamics (Gifford et al., 2006). Nevertheless, despite their importance in all aquatic ecosystems in terms of abundance and diversity, spatial and temporal trends for the understanding of marine sponge assemblages and bioactivity are still poorly studied in many regions (Gökalp et al., 2020c; Pawlik and McMurray, 2019; Sacristán-Soriano et al., 2012). Global scientific effort on those organisms for the development of new physiochemical perspectives now encompass the Mediterranean Sea, the Caribbean Sea and the Great Barrier Reef as hotspots of Porifera diversity (Bell et al., 2015; Gerovasileiou and Voultsiadou, 2012; Longo et al., 2018; Padiglia et al., 2018). Such geographical areas where sponge species producing metabolites, already either commercialized or still subject to approval, can be encountered are indeed firstly concerned when developing a perennial production system due to the proximity and conceivable direct availability of raw material (Dyshlovoy and Honecker, 2020).

This statement is particularly true for the Pacific region, where the pharmaceutical industry, along with live seafood markets, clearly represents the best opportunity for aquaculture development (Adams et al., 2001; Pedrosa et al., 2020). Experiments began with the Micronesian wool sponge *Coscinoderma matthewsi* in the early 1940s in Japan. The Japanese started sponge mariculture using vertical lines through with sponges hanged in the water column, either directly from the main line or using a loop, with bottles as floats (Croft, 1990; Kelly et al., 2004). It eventually became an important commercial activity in the Federated States of Micronesia, where the sponges were coming from (Adams et al., 1995). Requiring rather low capital and labor investment, the business generated great interest among local populations who had found an additional and a rapid source of income (Croft, 1990; MacMillan, 1996). They had to stop with the outbreak of the Second World War and the consequent lack of technical support from participating companies (Lee and Aways, 2003). The activity experienced a resurgence in the 1980s and from there sponge farming was increasingly seen as an opportunity to attract new rural businesses to the Pacific region, where sponge species suitable for aquaculture are widespread and most of the time

abundant such as the reported demosponges *Crambe crambe*, *Pseudosuberites andrewsi*, *Rhopaloeides odorabile*, *Coscinoderma* sp. and *Neopetrosia* sp. (Duckworth, 2009; Louden et al., 2007; Osinga et al., 1999a; Schiefenhövel and Kunzmann, 2012). For instance, in Fiji, small-scale sponge aquaculture is currently mainly dedicated to the tourism industry through the trade of dried bath sponges offered as souvenirs to visitors (Hawes et al., 2010). From a conservation perspective, marine sponges from the Western Pacific are not considered endangered although there may be local threats such as overexploitation, microbial infections, introduction of non-native species (e.g. the epilithic green seaweed *Caulerpa scalpelliformis*) and habitat fragmentation (Bell et al., 2015).

The invention of the synthetic sponge, much cheaper than natural bath sponges, and the increasing development of reliable synthesis of bioactive metabolites have led to a decrease of sponge farming activities (Butler, 2008; Hogg et al., 2010). Considerable efforts have been put on developing alternative production methods than *in situ* exploitation such as *in vitro* cell culture by fermentation process (Mendola, 2003; Carballo et al., 2009). Still, this technique has not been very successful so far, as nutritional requirements and culture media for establishing continuous primmorph cell lines and clones are still poorly understood (Custodio et al., 1998; Schippers et al., 2011; Yang et al., 2018). Specific gene clusters isolation of marine sponge microbiomes is another strategy for driving the production of bioactive compounds, as some genes of the microbial metagenome can be cloned and later artificially expressed (Brinkmann et al., 2017; Carballo et al., 2009; Piel et al., 2004; Rutledge and Challis, 2015; Sipkema et al., 2005b). Efforts were also made toward promoting reproduction of sponges, aiming at producing larvae that could be grown in tanks (de Caralt et al., 2007). The method led to high growth and survival rates, yet it requires essential knowledge of the factors promoting settlement, survival and development of sponge juveniles and thus still require more investigation (de Caralt et al., 2010). Indeed, those considerations are highly species-dependent, especially regarding nutritional needs and cannot be generalized for protocol optimization towards metabolites production at the market scale. That is why aquaculture trials, promoting the growth of the organism in its natural or artificially replicated habitat, have been and still are extensively tested until chemistry issues can be overcome (Gomes et al., 2016; Martins et al., 2014).

Sponges are known as huge reservoirs of bacterial chemosymbionts, the majority of which actually being the ultimate source of marine bioactive metabolites (Faulkner et al., 1993; Indraningrat et al., 2016; Mori et al., 2018; Pawlik and McMurray, 2019; Piel, 2004). Some sponges coat themselves with a specific mucus into which selective bacteria can broadly spread (Jackson and Buss, 1975; Müller et al., 2013; Simpson, 1984; Thompson et al., 1985). Marine chemical symbiosis is driving many ecological processes such as structuring populations, establishing defense, escape and competitive strategies or defining suitable habitats and feeding solutions (Alves et al., 2018; Hay, 2009). Chemotaxis has therefore been facing troubles in assigning compounds either to the sponge itself or to its microbiome, mostly due to metabolites resemblance with bacterial chemicals architecture (Erpenbeck and van Soest, 2007; Mori et al., 2018). However, some experiments done on bacteria isolated from marine sponge revealed a proven microbial origin of compounds (Piel et al., 2004; Schirmer et al., 2005). Research efforts are thoroughly made towards finding interactions with bacterial abundance and activity on sponges and biological or environmental factors, including sponges being exploited through aquaculture.

In this review, the literature was searched to debate the farming methods that were first developed at an early stage for bath sponges trade and later marine natural products exploitation. Environmental and physiological studies that are still showing today major effects on sponge culturing performances (i.e. growth, survival, metabolites production) are explored. We discuss as well the key roles of sponge endosymbionts in ecological processes and bioactive compounds production. Finally,

we deal with the new perspectives recently brought in addition to the aquaculture of marine sponges towards drug development which call for their many other ecological functions and roles.

2. The continuous evolution of marine aquaculture techniques and structures

Sponge aquaculture requires simple techniques, minor specialized equipment and little investment in community infrastructure (Duckworth, 2009). From relatively dense and heavy organisms, it generates a product that is both light in weight and soft, making transportation, processing and storage requirements less worrisome (Duckworth, 2001; Hawes et al., 2010; MacMillan, 1996). Those facts justified the increased in efforts over time to multiply the designs and tests in every oceanic region of the world, using many different sponge species.

2.1. Reasoning aquaculture set-up

At first, sponges were considered difficult animals to study due to a lack of *in vitro* maintenance and *in situ* monitoring methods. Also, marine sponges were thought to be extremely difficult to cultivate, unlike freshwater sponges (Fell, 1967; Kinne, 1977) and it was only in 1983 that Langenbruch found the production of sponges in land-based tanks for biological studies to be successful with the breadcrumb demosponge *Halichondria panicea*, most probably due to a demonstrated strong ability in adapting its filtration rates and oscula dynamics towards changing flow and feeding conditions (Kealy et al., 2019; Kumala et al., 2017; Langenbruch, 1983). Sponge samples transferred to semi-enclosed aquariums with monitored conditions (temperature, salinity and feeding period) were used to assess growth and survival parameters and compared them to natural populations (Barthel, 1986). Those two measures were and are still today major requirements to assess the effectiveness of the farming devices, either in land or sea-based systems, as species requirements may vary depending on where they occur in the wild (Duckworth, 2009; Mohite et al., 2020; Ou et al., 2020; Santiago et al., 2019). Growth assessments can be performed through the measurement of volumetric gain using graded cylinder, the acquisition of biomass metrics (wet, freeze-dried or ash-free dried weights) or even by taking scaled pictures underwater at regular time intervals during the experiment (Barthel, 1986; de Voogd, 2007a; van Treeck et al., 2003; Ledda et al., 2014).

Land-based aquaculture allows controlled conditions in terms of temperature, salinity and nutrient inputs, although the optimal values of those parameters can be subject to large variations between species (Duckworth, 2001; Osinga et al., 1999b). The cultivation of marine species on land indeed facilitates observation, sampling and harvesting (Bergman et al., 2011). Moreover, it is easier to test the influence of a single parameter while limiting the variability of the others, as in Duckworth et al. (1997) where only the impact of temperature was tested on sponge healing. However, the use of such a system implies a continuous monitoring of the water flow and aeration, as well as an adequate sponge density that must be reasoned according to spatial restrictions (Gunda and Janapala, 2009). Indeed, the risk of bacterial infections increases if the number of organisms exceeds a maximum, especially since diseases and parasitic infestations can spread rapidly (Bergman et al., 2011). As probably species-dependent, this value can for instance be adjusted by testing different concentrations of sponges within tanks and assessing microbial loads. New farmed individuals, referred to as “explants”, of Indo-Pacific species *Neopetrosia* sp. and *Stylissa massa* growing in tanks showed lower rates in terms of survival, growth and attachment than the ones developing *in situ* (Schiefenhövel and Kunzmann, 2012). Similarly, in the Mexican Pacific Ocean, the growth of *Mycale cecilia* during *in situ* mariculture trials of 60 days was three times higher than in closed systems (Carballo et al., 2009). Ensuring sufficient food supply and a suitable aeration of tanks, through frequent seawater change providing both new particles loads and

oxygen, is a major barrier towards the success of land-based cultivation (Schippers et al., 2012). Costs for food supply and good water quality when regular seawater refill is difficult can be really high, to the point that land-based aquaculture of some species having higher feeding requirements are not considered economically viable because of being too costly (Duckworth, 2009; Duckworth and Pomponi, 2005; Mendola, 2003; Osinga et al., 1999b).

Sea-based farming structures rely on existing and unlimited water resources. The open space available reduces the risk of eutrophication and local depletions. Production costs including farm set-up are not exceeding few thousand dollars especially for locally managed, small-scale aquaculture activities (Adams et al., 1995; MacMillan, 1996). This scheme is therefore cheaper than land-based systems, sometimes significantly enough for the costs to be halved (Sipkema et al., 2005b). The hazards of rough weather losses and heavy predation (e.g. herbivory fishes, nudibranchs and sea turtles) must be kept to a minimum through good infrastructure designs (i.e. correct attachment of the explants) and suitable management techniques such as reasoning sponge density and ensuring a mortality vigilance (Duckworth, 2009; Page et al., 2011; Smith, 1941).

2.2. Sponge sampling techniques

Sampling is based on taking a fragment from a parental sponge to obtain an independent, self-growing organism. Indeed, sponges are known since the early 20th century for their ability to regenerate after damage and face mutilation (de Laubenfels, 1949; Galtsoff, 1925; Huxley, 1921). They can reproduce sexually, being mostly hermaphrodites, but may also spread by releasing propagules or through fragmentation, leading to resistant “gemmules”, when some of their parts are removed by strong currents (Leong and Pawlik, 2010; Pawlik, 2011). Once allowed to settle nearby on the seabed, those fragments can create new explants. All an explant needs to naturally regenerate and form a complete sponge is a proper cutting technique and time (Balakrishnan, 2017; Nickel and Brümmer, 2003; Pozzolini et al., 2019; Sánchez, 1984). Sectioning clean pieces of healthy-looking sponges collected throughout the year remains the easiest, most economical and fastest way to proceed while minimizing harvesting and environmental impact (Duckworth, 2001). Thanks to a high-performance metabolic pathway identified for many species, such as in oxygen transfer and healing rates (i.e. through elevated telomerase activity), the same explant can be harvested many times to obtain several generations from a single individual (Belarbi et al., 2003a; Duckworth, 2001; Loudon et al., 2007; Osinga et al., 1999b). The number of farmed sponges required is therefore decreasing over time and so are the costs and potential harvesting impacts on natural populations (Duckworth, 2009).

To improve culture protocols and approaches such as proper sampling procedure, factors regulating sponge survival have been identified. Among them, ensuring that the knife used to excise the sponge is always sharp is crucial, so that a dull blade does not lead the diver to press the animal to cut it (Oronti et al., 2012). A minimal damage is expected during both harvest and transport. Squeezing the organism for instance could lead to its death or the dysfunction of its metabolic activities, especially for species known as highly vulnerable to mutilation due to their specific growth form or internal structuration such as the basket-shaped *Geodia* sp. or the vase-shaped *Mycale laxissima* (Freese, 2001; Oakland, 2013; Reiswig, 1973). Leaving healthy pinacoderm parts intact with pre-existing oscula during the explant harvesting stage can be important, as a correlation was found between the presence of intact pinacoderm showing remaining oscula and a better tolerance to oxidative stress for the demosponge *Haliclona pigmentifera* (Gunda and Janapala, 2009; Kelly-Borges, 1994, 1995; Mergner, 1964). The development of new oscula recreating a complete functional surface and an actively pumping system lasts between a few days to several months, depending on the species (Osinga et al., 2010). During this time, oxygen and nutrient supplies are hampered by surface layers regeneration

(Hoffmann et al., 2005). That is mainly why the excised sponge must remain permanently immersed in oxygenated seawater during transportation, in order to avoid the inexorable anoxia that occurs barely a few moments after removing the organism from the water. Survival can be greatly influenced by the shape of the fragments or the proportion of sponge body size to the extent of the wounded parts of the pinacoderm (Duckworth et al., 1997). It is now commonly accepted that a minimum volume of about one-third of the sponge should be left behind for the animal to survive and grow back (Duckworth and Wolff, 2007).

Despite taking all precautions during sponge sampling, damaged sponges take a long time to recover and, in some part of the world, they have undergone local extinctions (Gaino and Pronzato, 1989; Rizzello et al., 1997). Indeed, the regeneration process requires significant increase in energy supply for excised individuals (Barthel and Theede, 1986). If recovery takes too long, mesohyl suspended cells abandon the sponge matrix and leave the skeleton exposed (Duckworth et al., 1997). The evaluation of surface development or subsurface cellular reorganization of the sponge pinacoderm once it has been damaged is possible using a scanning electron microscope or light and transmission microscopy (Witte et al., 1994). Even though damaging and potentially stressing the sponge in the process, such techniques only require very small amounts of biological material (i.e. less than 2 mm³) and inform about ultrastructural rearrangements for both sponge cells and associated bacteria (de Caralt et al., 2003). Indeed, it is important to ensure that the process of internal healing, through the consolidation of collagen, occurs quickly. Both collagen content and growth were reduced when transplanting the sponge *Chondrosia reniformis* (Cebrian et al., 2007). Yet collagen yield appeared to be influenced by depth and could be optimized for this same species through genotype and environmental investigations (Gökalp et al., 2020a). For the tropical sponges *Rhopaloeides odorabile* and *Coscinoderma* sp., the restoration of sponge collagen production starts within only 24 h after either damage or cut

(Louden et al., 2007). We can suggest from these results that collagen production is playing a role in pinacoderm restructuring and biomass gain once the sponge has been under stress. Several sponge species may also rely on the incorporation of foreign elements into their layers or on the development of specific melanin cells (Bergquist et al., 1980). Monitoring these metabolic operations could help diagnose the progress of explants healing and their overall health once the cut has been made.

2.3. Contrasting effects of aquaculture designs

Because sponges are known to constantly adapt their morphology to the space allocated to them while growing, sponge aquaculture can hardly be based on the visual recognition of individuals as progenitors for future generations (Barthel, 1986). Nevertheless, interesting prospects of culturing species with pharmaceutical potential is that, unlike bath sponges that must reach high quality standards, no specific aspect of the sponge body is required for them to be commercialized. Sponge species with a great diversity of shapes are promising candidates for successful marine aquaculture towards chemical valorization (Fig. 2). Given those facts, a wide range of cultivation methods that we aim to discuss here can be applied to satisfy industrial demand and secure production over time (Duckworth et al., 1997; Duckworth and Wolff, 2007).

Vertical and horizontal lines where the sponge hangs in the water column using ropes or fishing nets are two suspension structures that have been extensively tested (Barthel, 1986; Croft, 1990; de Voogd, 2007a; Handley et al., 2003; Kelly-Borges, 1995; Schiefenhövel and Kunzmann, 2012). Both systems were experimented for the aquaculture of the common bath sponge, the Mediterranean *Spongia officinalis* (Corriero et al., 2004). No differences were found in terms of efficiency (i.e. through the average weight and volume of the explants over time) between the two cultivation designs. Lines are usually threaded through

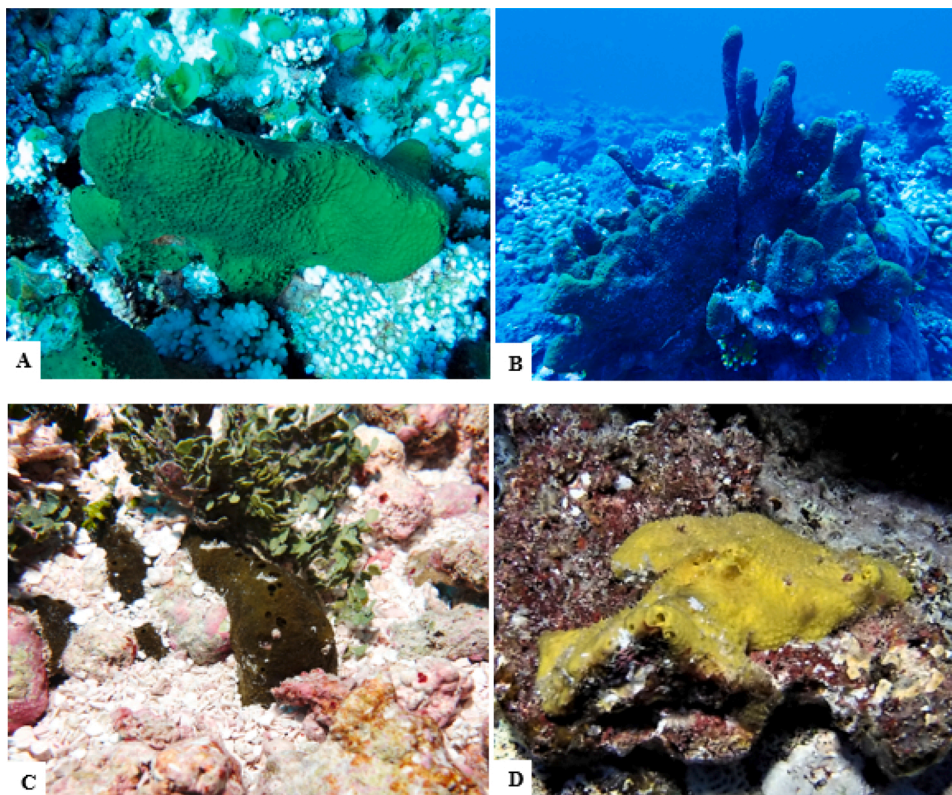


Fig. 2. The sponge *Dactylospongia metachromia* (de Laubenfels, 1954). Whether if growing exposed on the coral reef (A, B) or hidden inside crevices (C, D) in the South Pacific region, this marine sponge presents an incredible diversity of shapes and appearances.

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sponge explants either straight by hand if the material is soft enough or using a needle and loop, such as the “hanging rope” method described by Croft (1990) and Ellis et al. (2008) in Micronesia. Due to the lack of a natural substrate as support, explants are mainly growing round-shaped and without many irregularities of the pinacoderm such as in wild populations (Corriero et al., 2004). Sponges grown with this type of construction are directly exposed to the environment. However, lines should be placed deeper than the wave breaking area to avoid injuries caused by severe water movement.

Suspended structures featuring lines sometimes consist of cages (Barthel, 1986) or frames (Pronzato et al., 1999) where explants are attached to vertical or horizontal grids. They can be either fixed by stakes directly anchored in the substrate or simply held at a certain depth using dead weights and floats to ensure good buoyancy (Duckworth et al., 1997; Hadas et al., 2005; Thomassen and Riisgård, 1995). Horizontal lines and frames ensure a certain morphological homogeneity of the explants besides being highly adaptable and cost-effective (Fig. 3).

Mesh bags, between which explants are sandwiched, have also been gradually deployed as a less-damaging alternative to the threading of sponges (Duckworth and Battershill, 2003a; Kelly et al., 2004). Bags are suspended above the sea bottom by subsurface buoys and explants can even sometimes be grouped into the same nets called “lanterns” (Duckworth et al., 1997; Ruiz et al., 2013). Those systems are anchored to the sea bottom by a benthic rope (Duckworth and Battershill, 2003b; Duckworth and Wolff, 2007) or buckets filled with cement into which vertical poles are placed (Ruiz et al., 2013). Threaded lines and mesh panels were tested and compared for the bath sponge *Coscinoderma* sp. aquaculture, with better results for mesh treatments (Duckworth and Wolff, 2007). Nevertheless, both studies faced serious problems of biofouling on the lanterns, in addition to the fact that constructs were cumbersome and difficult to handle. Experimental conclusions stated that this design was finally rather unsuitable for commercial farming. Actually, the major disadvantage of this system is that explants are not

directly exposed to the seawater column, but hindered by the mesh strands. Limiting the volume available for filtration thus sponge food accessibility, it also increases growing competition with unwanted fouling life forms (Duckworth and Wolff, 2007). After more than a year of testing the lantern method in New Zealand, the average volume of explants was either only slightly larger or even smaller than at the beginning of the experiment for most stations (Kelly et al., 2004). The anchoring system was inadequate, resulting in the loss of structures under storm surge conditions. High levels of biofouling and mesh entanglement when marking the explants were deplored. Similarly, in the Caribbean region of Colombia, high survival rate was reached but overall biomass growth was only quite moderated (Ruiz et al., 2013). The hanging mesh bags method is not repeatedly suitable to reach admissible aquaculture performance.

Threaded lines seem in many cases the best compromise between easy installation and satisfactory performance (Schiefenhövel and Kunzmann, 2012). Used in Micronesia for *Coscinoderma mathewsi*, in New Zealand for *Spongia (Heterofibria) manipulatus* and in the Mediterranean for *Spongia (Spongia) agaricina*, it was indeed proved quite successful in distinct geographical locations with high survival and good adherence of sponges to the ropes (Croft, 1990; Handley et al., 2003; Kelly-Borges, 1995; Verdenal and Vacelet, 1990). Yet, exceptions may occur as mortality during aquaculture trials on the pink sponge *Dysidea avara* in the Mediterranean was the highest for explants hanged on horizontal ropes, while survival into cages offered more promising results (de Caralt et al., 2010). In the same study, authors found growth was also very low for ropes in the first six months, but a rapid increase of growth rates occurred after the tenth month until reaching similar results than cages method.

Therefore, we cannot firmly conclude on the better efficiency of this particular method, as it obviously depends of the species and location. Still, lines system remains the most commonly used technique, having proven its worth on many occasions.

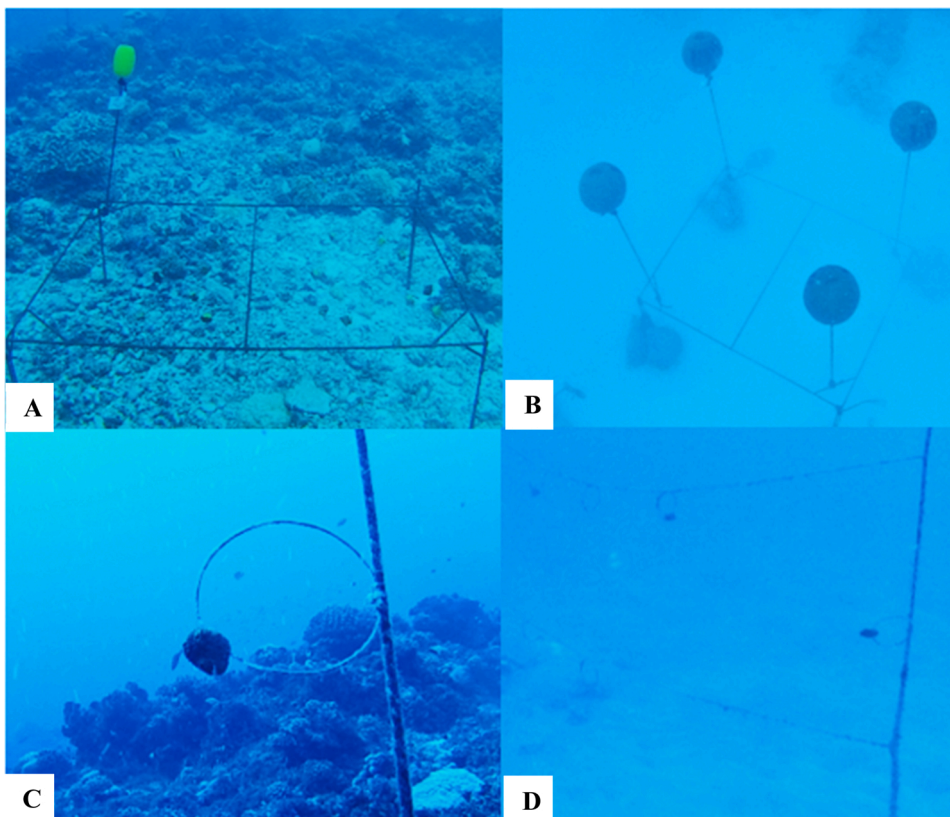


Fig. 3. Different aquaculture designs built according to the environmental context. (A) Horizontal culture frame anchored in a barrier reef, (B) Horizontal culture frame maintained by buoys in a lagoon area, (C) Vertical polypropylene ropes with nylon buckles anchored in a barrier reef, (D) Vertical polypropylene ropes with nylon buckles weighted with concrete blocks in a lagoon area. ©Mathilde MASLIN (UPF, UMR 241 - EIO).

2.4. Material performances on growth and survival

The continuous optimization of methods has always aimed to increase production yields while reducing harvesting effort (MacMillan, 1996). The materials that make up the structures are mainly selected for their strong resistance to unstable environmental conditions, their affordability and the ease with which they can be handled and transported. Thread lines that were firstly used were raffia or vegetable ropes (Hawes et al., 2010). Still, natural fiber ropes did not seem suitable for farming activities because they degrade quickly in seawater through rotting and disintegration (Duckworth and Battershill, 2003a). Modern components have then gradually replaced the first materials, showing better performances such as nylon (Barthel, 1986), polyvinyl alcohol (PVA) with its bristly composition that promotes explants fastening and survival (Duckworth and Battershill, 2003a), polypropylene or High-Density Poly Ethylene (HDPE) rot-proof fishing ropes (de Voogd, 2007a; Loudon et al., 2007), Poly Vinyl Chloride (PVC) pipes or sheets (Hadas et al., 2005) and galvanized iron or polyethylene cable frames (Bergman et al., 2011; Verdenal and Vacelet, 1990). A new construction called “Shish Kebab Method” for the aquaculture of *D. avara*, aimed at rapidly promoting sponge growth and reducing both costs and labor (Osinga et al., 2010). PVC pins carrying *D. avara* explants and framed between parallel-pounded drilled steel bars surpassed the results obtained with nylon lines as enhancing growth, achieving 100 % survival after 4 months of culture and coming with a rapid and effective recovery of the explants. Yet, construction did not last more than a year and explants eventually detached from the frames that were found disrupted by the authors and lying on the seabed at the end. Low-carbon steel has indeed high flexibility and bending capacity that reduces construction time of the structures and better resists to dynamic loading. However, it is not resistant to seawater corrosion and outdoor exposure conditions such as galvanized iron (Safiuddin, 2005; Thangavel et al., 1995). HDPE is far less affected by saline environments, but is also very expensive. Nylon nets or yarns are economical, lightweight and fairly resistant to seawater; they offered significantly higher growth performances compared to PVC nets for the cultivation of the magnificent fire sponge *Negombata magnifica* in the Red Sea (Hadas et al., 2005). Nylon twines also performed well for the mariculture trials of the grass sponge *Spongia tubulifera* and the hardhead sponge *Spongia pertusa* in the Bahamas as well as for the encrusting *Raspailia agminata* in New Zealand (Duckworth et al., 1997; Oronti et al., 2012).

in vitro survival rate has long seemed to be higher when the sponge pieces are suspended and can hang freely from their support in the water column (Barthel and Theede, 1986). Nylon threads led to more satisfactory results than when tying the explants to glass slides, another technique rarely employed but which was proved successful in some cases (Osinga et al., 1999a; Xue et al., 2009). Nevertheless, the use of nylon yarn thicker than 0.5 mm might damage sponge pinacoderm without repair for some species, leading to their impending death (MacMillan, 1996). On the contrary, a rope too thin can easily disintegrate in seawater, which may distort the results obtained for explants mortality. If choosing mesh bags, the choice of net should likewise be well considered as different and complementary criteria can directly influence the survival of sponge explants, such as the thickness of the strands and the mesh size (Duckworth and Battershill, 2003a). Yet, rather than the material itself, sponge survival could mainly depend on the species, the culture method chosen for farming trials and the total duration of the experiment, with highest mortality rates expected within the days following the excision of parental sponges (Loudon et al., 2007).

2.5. Making choices to face unsolved issues

An adequately structured sponge farming system must ensure the sustainable production of individuals for commercial success. However, there is no miracle material and choices must be balanced in the light of

the species studied and the technical or economic constraints that arise. Mariculture was considered in the past decades as the unique sustainable, well-understood and relatively cheap method to produce sponges for bioactive compounds having pharmaceutical applications (Belarbi et al., 2003b; Duckworth, 2009; Gomes et al., 2016; Koopmans et al., 2009; Murray et al., 2013; Pronzato and Manconi, 2008; Schippers et al., 2012). For the next chapter of this review, we will only consider infrastructures that have been tested in the marine environment for *in situ* mariculture.

The technique of hanging sponge to ropes has many advantages. Attaching sponges to any type of surface needs more time than simply inserting a yarn through pinacoderm, if loose enough, not to mention that it is sometimes more stressful for the animal (Barthel and Theede, 1986). Given the very encouraging results obtained with nylon yarn, in addition to its low cost and reusability, it has gradually been adopted as a key material in aquaculture constructions (de Caralt et al., 2010; Handley et al., 2003; Pérez-López et al., 2017; Sankar et al., 2016). Factors strengthening the effectiveness of the methods using lines were thus deeper investigated and the principles that follow were proved valid regardless of the mariculture design.

Ropes placed perpendicularly to the water flow should maximize its effect while attracting fewer fouling organisms (McDonald et al., 2003; Ruiz et al., 2013). Size of the explants during the initial cutting is another consideration that does seem to have an effect on aquaculture performances. Smaller explants exhibited lower growth rates than larger ones in sheltered locations from the Caribbean (Moore, 1990) and Indonesia (de Voogd, 2007b). This observation could be explained by a different ratio between damaged surface and body volume, being smaller for the largest explants which reduces stress, facilitates feeding along with promoting waste expulsion and inhalation/exhalation processes. Similarly, in New Zealand, the smallest explants experienced higher death rates and biomass loss due to a weaker ability to redirect energy into regeneration (Duckworth et al., 1997). In the same country, initial explant size did influence growth, but the effect differed depending on the location with clearly opposite trends (Kelly et al., 2004). In Australia, different survival and growth rates were registered according to the explants size at the end of a 6-months experiment using threaded lines, with larger explants (>300 cm³) better tolerating the cultivation process than the smaller ones (± 40 cm³) (Duckworth and Wolff, 2007).

Explants of *S. officinalis* featured higher growth rates when they attached completely to their fastening rope compared to unsteady ones (Verdenal and Vacelet, 1990). Releases of explants forming large holes and becoming very poorly attached (Fig. 4) have later been reported against threaded lines (Duckworth and Wolff, 2007; Osinga et al., 2010). The chemical nature of the farming supports, especially those directly in contact with the explants, should be investigated according to the species, as it could explain the adhesion or rejection of the material by the sponge (Duckworth and Battershill, 2003a).

Lastly, installations shall be kept clean and regularly removed from biological infestation. Fouling had no influence on the growth rate of *N. magnifica* explants that were suspended horizontally on cleansed nylon yarns, yet it had a significant negative impact on the development of explants in soiled net structures (Hadas et al., 2005). On a continuous basis, biofouling can be a serious problem in aquaculture systems because it increases weight and drag, reduces buoyancy of the installations and hampers seawater exchanges (Fitridge et al., 2012).

3. The environment as a major factor driving aquaculture efficiency and sponge ecophysiology

In situ growth rates can reach very high thresholds, such as 960 % within 6 months in New Zealand for *Latrunculia brevis* (Duckworth, 2001). In the same country, *Mycale hentscheli* presented an impressive annual growth of 3365 ± 812 % (Page et al., 2005). In the Eastern Mediterranean, a yearly increase of 1100 % was estimated for the pink

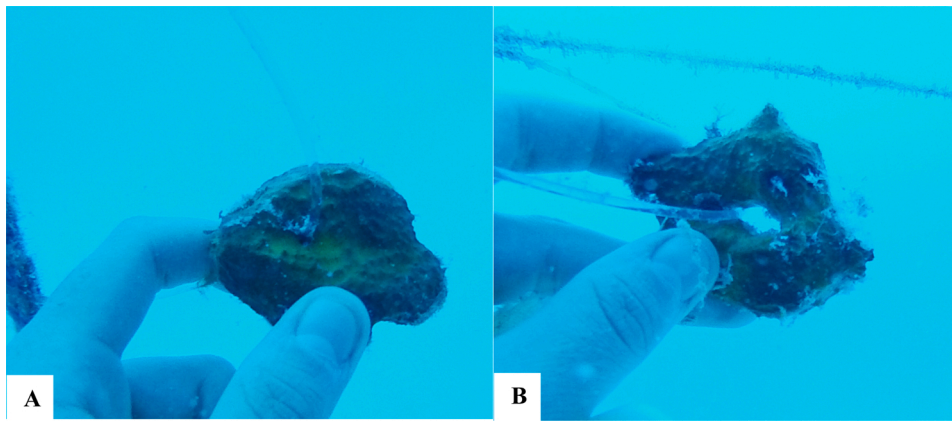


Fig. 4. Examples of different success in the attachment of sponge explants to their fastening nylon rope. (A) The explant has completely merged with its support, (B) The explant grew forming a huge hole where the yarn is passed through.
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Dysidea avara (Osinga et al., 2010). Still, some results obtained for the same species are quite contrasted. Hence the importance of continuously monitoring environmental parameters (e.g. light intensity, water turbidity, current strength, temperature) applicable in the concerned regions that can be intrinsically linked to each other. As an example, exposure to seasonal ambient current is affecting respectively the planktonic concentration of the seawater column and the supply of this primary food source for the farmed sponges (Duckworth, 2001; Duckworth et al., 2004). Optimal conditions regarding these parameters, i.e. those that promote sponge growth, explants survival and the production of bioactive compounds, have been explored and will be discussed in this chapter (de Caralt et al., 2010; Duckworth et al., 1997; Duckworth, 2009; Hadas et al., 2005).

3.1. Environmental considerations for growth and survival optimization

Among localities, sponge growth and food accumulation in the environment are not following a linear relationship. Sponges are indeed sensitive to the concentration of suspended particles which, if too high, decreases their filtration rate, i.e. the volume of water expelled by the osculum per time unit (Osinga et al., 2001). Tipping points for effective sponge pumping regarding particle density are driven by abiotic factors such as depth and turbidity. Suspension of large particles is indeed favored in shallow environments, where a correlation was found between depth and oscula diameter for *Chondrosia reniformis* (Gökalp et al., 2020a). Sponges of deeper water zones featured smaller oscula but in greater numbers than those from subsurface habitats, making the last ones more efficient regarding specific pumping rates. Nevertheless, depth did not impact the metabolism, pumping capacity and growth rate of *C. reniformis*. To a lesser extent, turbidity can also affect sponge pumping rates in a negative way and filtering activity can even cease when inorganic or organic loads are high enough to obstruct the outflow and make the sponge suffocate (Gökalp et al., 2020b; Reiswig, 1971).

Sponge respiration is a process that involves a cutaneous transfer of oxygen through the skeleton. There is clear linearity between respiration rates and growth for *Halichondria panacea* (Thomassen and Riisgård, 1995) or wet weight for the Red Sea sponge *Negombata magnifica* (Hadas et al., 2008). Sponges do not compensate well the long-lasting decrease in partial oxygen pressure, especially when exposed to high suspended particles rates (Barthel and Theede, 1986; Kutti et al., 2015). Dissolved oxygen (DO) concentration in seawater thus seems an important survival parameter that could significantly affect sponge metabolism and energetics.

Light can be responsible of affecting the microbial communities associated with the sponge, especially through photosynthesis activity, and consequently the host metabolism (Wilkinson and Vacelet, 1979).

Yet, sponge cells can also directly be impacted through their inner polar compounds composition such as glucose content (de Rosa et al., 2001). Light intensity instead of temperature prevented the growth of *D. avara* in shallow water, as the species rather develops in deep locations or hide into caves when occurring close to the surface (Osinga et al., 2010). Light stimuli and current conditions appear to control demosponge larval settlement or post-colonization survival. Shallow-water sponge larvae display a preferential photonegative behavior to colonize dark crevices where they would face fewer predators and substrate competitors (Maldonado and Young, 1996). The negative effect of elevated UV radiation on sponge growth and survival rates, with exposition ranging from darkness to full sunlight, was early evidenced for Hawaiian specimens by Jokiel (1980) with mass mortality experienced within two days of exposure. Symptoms described by the author were broad, such as discoloration and necrosis or pinacoderm loss for the encrusting *Mycale cecilia* and the branching *Zygomycala parishi*, yet the cryptic *Chondrosia chucalla* appeared to withstood light conditions even when maximized. Similarly, Mediterranean species reacted very differently depending on their preference in natural conditions, such as a fourfold increase in growth and uniform coloration for *Verongia aerophoba* after 47 weeks of light exposure whereas *Petrosia ficiformis* specimens appeared healthier and cleaner (i.e. without sediment or filamentous covers) under opaque shields (Wilkinson and Vacelet, 1979). In New Zealand, higher survival rates were reached for *Psammocinia hawere* and *Raspailia agminata* in sheltered area compared to more exposed locations (Duckworth et al., 1997). Variation in water movement intensity between both environmental configurations could also explain this trend. In unsuitable areas with low current activity and murky waters, explants covered with sediment would most probably be unable to efficiently perform their filtering activity, thus affecting their overall growth which result hindered (Kelly et al., 2004). Yet, subtle effects of sedimentation and predation could attenuate potential detrimental UV impact on sponges, even in deep environments (Jokiel, 1980).

Combining sponge mariculture with other kind of farmed organisms can also have an impact on growth rates depending of the interaction (i.e. commensalism, competition) that they develop (de Voogd, 2007a). Indeed, a good influence of cultured mussels vicinity on growth rate of *M. hentscheli* was demonstrated when the mollusks were placed adjacent to the sponge farming system (Page et al., 2011). Sponges might benefit from the elevated nutrient release linked to the high density of macrofilters and biofoulers in a reduced area. However, biotic interaction must be cautiously favored as biofouling pressure can have a significant impact on sponge death. In fact, sessile marine animals are the most threatened by pro- or eukaryotic colonization and research on sponges has been investigating the antifouling properties of certain associated bacteria (Bovio et al., 2019; Müller et al., 2013). Placing mesh

panels at greater depths could reduce the proliferation of macroalgae or ascidians, thus reducing the frequency of monitoring and cleaning tasks (Duckworth and Wolff, 2007). In the Solomon Islands, epiphyte growth was reduced when the structures were placed near the reef slope at about 20 m deep compared to 10 m and above (Hawes et al., 2010). Evidences thus exist that biofouling is not only due to the type of designs but can also be heterogeneous depending on the environmental conditions.

3.2. Energetics budget

Sponges exhibit an impressive retention rate of small particles (<0.5 µm in size), reflecting the high performance of their filtration system and post-capture selection of preys (Beate and Hentschel, 2017; McMurray et al., 2016; Yahel et al., 2006, 2007). They can adapt their clearance rate of suspended picoplanktonic cells according to the particles size and concentration as well as seasonal factors (Gökalp et al., 2020a; Maldonado et al., 2010; Ramoino et al., 2011). Distinct energetics investments are thus required for sponge feeding activity, depending on the kind of available food uptakes. Assimilation of dissolved organic matter (DOM) by *Halisarca caerulea* was processed within 1 h, meanwhile particulate organic matter (POM) and glucose required much more time in order to preserve the energy invested in nutrition to ensure other metabolic functions (de Goeij et al., 2008). Sponge-associated bacteria are also actively involved in DOM consumption, therefore reducing the energy investment of their host regarding this purpose (Ribes et al., 1999; Yahel et al., 2003).

Oxygen consumption is evaluated according to the respiratory rate of aerobic organisms and believed to having a crucial role in total energy expenditure dedicated to metabolic activities, i.e. digestion or growth (Barthel and Theede, 1986; Hadas et al., 2008; Hoffmann et al., 2008; Kutti et al., 2015). Cultured sponges were found to perform respiration activity at higher rates than other macrobenthos organisms sharing the same living areas (Dries, 1975; Hadas et al., 2008). Oxygen depletion by sponges increases together with the temperature, but may vary depending of the metabolic activity of the species, its morphological integrity (i.e. presence of damages or biofoulers), lifetime and size (Morganti et al., 2019; Pfannkuchen et al., 2009; Pile et al., 1997). *Haliclona pigmentifera* specimens which pinacoderm was damaged or infested by foreign biomaterial died within two days when facing anoxia (<0.3 ppm DO) and exhibited very low survival rates under hypoxic conditions (1.5–2 ppm DO) in culture flasks (Gunda and Janapala, 2009). Interestingly enough, intact sponges of the same study demonstrated the highest *in vitro* survival and adhesion to substrate under hypoxic conditions, rates being 8-fold superior than for normoxic (>4 ppm DO) settings.

The intrinsic morphology of the species also plays a role in its energetic budget dedicated to biomass gain. Dense sponges with compact spongin networks grow slower than species lacking a collagen skeleton (Kelly et al., 2004). Siliceous and calcareous sponges indeed invest less energy and resources into the spongin skeleton production, allowing higher growth rates (Duckworth and Wolff, 2007). Morphological differences are also believed to be related to the microbial abundance hold by a sponge. Sponges are indeed frequently classified into two distinct groups, being either high or low microbial abundance (HMA and LMA sponges, respectively) (Gloeckner et al., 2014; Kamke et al., 2010). HMA species usually feature a denser mesohyl and exhibit lower filtration activity (i.e. 50–90 % reduced pumping rates) than LMA sponges (Weisz et al., 2008). Differences in the aquiferous system composition are actually suggesting an evolutionary divergence between both groups, partly related to their respective symbionts. Recorded oscular outflows for video analysis revealed a positive yet site-dependent correlation between pumping rate velocity and osculum diameter (Gökalp et al., 2020b). Featuring larger oscula might help the sponge towards low food availability, but the energy required to generate a strong exhalant current matching the higher internal pressure is much greater. Hypothesis

towards the origin of sponge ability to adjust the width of the outflow system (e.g. phenotypic or genotypic adaptation) were raised and should be deeper examined. The aquiferous structure of sponges, through their oscula morphology, seems anyway to be adjustable when needed, confirming sponge metabolism as highly adaptable and commercially exploitable.

3.3. Seasonality in growth and survival rates

Seasonal variation in growth and survival have indeed been evidenced in some populations, with very different trends depending on the locations (Duckworth et al., 1997; Koopmans and Wijffels, 2008; Storr, 1964; Turon et al., 1998). Temperature was early cited as one of the factors limiting sponge biomass gain, showing ranges beyond which individuals fail to develop even if they managed to fix the structure and survive (Barthel and Theede, 1986). In temperate areas, sponge growth is generally higher at the beginning of summer with a corresponding peak in estimated energy demand (Handley et al., 2003; Kelly et al., 2004; Page et al., 2005). In tropical Australia, growth rate of *Coscino-derma* sp. was highest with increasing water temperature for cultivated explants at the end of winter (Duckworth and Wolff, 2007). This trend could be supported by the resumption of primary production and nutrient release in the euphotic zone during warmest months (Barthel, 1986; Morganti et al., 2019; van Treeck et al., 2003). Tropical changes of food abundance are poorly known and their effect on marine sponge growth, although being extensively studied, still needs deeper investigation (Duckworth, 2009; Pawlik et al., 2018; Wooster et al., 2019).

Depth impact throughout the year was proved highly contrasting in sponge farming studies. No influence of depth on growth was observed for the demosponges *M. hentscheli* in New Zealand (Page et al., 2011) or *C. reniformis* in the Eastern Mediterranean (Gökalp et al., 2020a). Depth neither affected biomass decrease, weight loss, size reduction and body aspect modification (i.e. from compact to stringy) of the breadcrumb sponge *H. panicea* in the Baltic Sea (Barthel, 1988). Yet, sponges placed in shallow water during the winter season in the Mediterranean Sea and Gulf of Mexico experienced a reduction in volume (Storr, 1964; Verdenal and Vacelet, 1990). In temperate waters of New Zealand and Florida, growth rates of sponges varied between depth and season as driving changes in water flow (Butler et al., 1995; Duckworth and Battershill, 2003; Duckworth et al., 2004). We infer from those results that rather investigating depth alone, it should actually be considered in association with the year period, as combined effect can prevail regarding abiotic parameters. Depth and light are for instance tightly connected and together can negatively affect phototrophic bacterial (including cyanobacteria) communities among sponge symbionts, which in turn may impact the host metabolism to an extend level (Wilkinson and Evans, 1989).

Like growth, survival might easily be driven by seasonal context such as water temperature cycles and food availability as well as bio-interactions between sponges and other life forms (Ayling, 1981, 1983; Verdenal and Vacelet, 1990). In temperate regions, such as New Zealand, survival appears to be lower in summer (from February to April) due to high water temperatures related to greater stress for sponges during transfer process (Duckworth et al., 2004). Cooler temperatures were also found to enhance survival by reducing respiration rates and stress during transportation as well as promoting pinacoderm healing while reducing microbial growth both *in vitro* and *in situ* (Butler et al., 1995; Duckworth et al., 1997, 2004; Hummel et al., 1988). Duckworth et al. (1997) monitored pinacoderm healing for temperate sponges under two different temperature conditions, respectively low (14 °C) and high (19 °C). Results in survival rates were similar to those obtained *in situ*, with better healing of cut sides occurring in cold conditions while less mortality was recorded during winter (August), independently from depth. However, in a tropical context such as Australia and despite temperature changes, no effect of seasonality on survival rates was observed (Duckworth and Wolff, 2007).

Periodic trends in survival could be positively related to the degree to which sponges are invested in reproduction (Duckworth and Battershill, 2003b; Verdenal and Vacelet, 1990). First of all, some sponges are reproducing all year around, while recruitment of new individuals for other species is highly seasonal (Duckworth and Battershill, 2001). In New Zealand, only some individuals from the local populations of sponges were active in reproduction at any given time (Ayling, 1981). Reproduction of the bath sponge *Spongia officinalis* was found higher in winter in the Mediterranean as explants shelter more larvae inside their mesohyl during this period (Corriero et al., 2004). In West Mediterranean, spring rains might reduce salinity enough to compromise the survival of farmed sponge (Ledda et al., 2014). However, in the Baltic Sea, changes in salinity had no influence on reproductive rate (Witte et al., 1994). Secondly, the reproduction investment of sponges coming from tropical ecosystems is probably more impacted under changing environmental conditions (i.e. temperature, salinity, redox potential) than for species coming from marine habitats of regular seasonal variation such as temperate, subpolar and polar oceans (Duckworth et al., 2003). Finally, biotic interactions like predation can affect reproduction and might definitely have a significant influence on survival. As an example, the short breeding period of *H. panicea* in the temperate Atlantic region was linked with a corresponding increase in abundance of a sponge predator, the nudibranch *Lamellodoris muricata* (Barthel, 1986, 1988).

Seasons thus appear as major drivers of culture performances to a broad extent of parameter likely to change during throughout the year. However, some sponge species do not show any significant annual pattern for either growth or survival, sometimes even for both (Ayling, 1983; Costa et al., 2015; Hoppe, 1988). The numerous contradictory results, depending of the organisms that were studied, highlight the existence of inter and intraspecific variation according to the environmental context (Duckworth et al., 1997; Ferretti et al., 2009; Morganti et al., 2019; Padiglia et al., 2018). Volumetric expansion and viability are highly variable between explants coming from the same individual and different hypothesis were raised to explain such trends like chemically undefended parts of the skeleton or distinct rates in cell reaggregation (Lavrov et al., 2020; Loudon et al., 2007; Pawlik et al., 1995). In a particular ecosystem, it is therefore imperative to be able to distinguish taxa and individuals that will acclimatize well from those that will not resist cultivation process. Even though this work appears difficult and risky, initiatives concerning the monitoring of parental sponges must be further developed in order to judge their performances and to select the most satisfactory.

3.4. Towards the selection of best sponge donors in a given area

Brood stock selection appeared to be an essential option since field experiments have revealed considerable variations between the annual growths of explants coming from different donors (Hawes et al., 2010; Kelly-Borges, 1995; Stevely et al., 1978; Verdenal and Vacelet, 1990). After 2 years of harvesting, it is possible to identify fast-growing individuals in the sponge population and to keep them as brood stock for the next generations (Duckworth, 2009; MacMillan, 1996). They usually consist of wild sponges growing near the farm to minimize transport time and effort (Ellis et al., 2008).

To optimize the aquaculture performance of the explants once they are cut, factors which could have a direct effect on growth or survival were sought through the rise of selective breeding. Initial size of the sponge donor does not seem to influence neither the survival nor the growth rates of its explants (Duckworth and Battershill, 2001). On the contrary, the abundance of choanocytes constitutes an important parameter regarding filtration efficiency between brood stock sponges. These monoflagellated cells contribute to the active pumping and filtering of seawater through the animal (Maldonado et al., 2010; Ramoino et al., 2011). Their number can greatly vary between two individuals coming from the same population (Duckworth, 2009).

Volumetric growth of the explants could also be concomitant with the organic content of the sponge, i.e. protein, lipid and carbohydrates concentrations, such as for the species *Haliclona cinerea* and *Halichondria panicea* from the Baltic Sea or *Negombata magnifica* from the Red Sea (Barthel, 1986; Elvin, 1979; Hadas et al., 2005). Finally, studies have revealed that explants growth can directly depends on the skeletal structure of the parental sponge (de Voogd, 2007b; Page et al., 2005). If featuring dense and compact spongin fibers network, such as for sponges belonging to the Thorectidae family (Fig. 5), explants would better bear the threading process contrarily to siliceous encrusting individuals with softer bodies (Duckworth et al., 1997; Duckworth and Battershill, 2003b; van Treeck et al., 2003).

It was observed that growth does not systematically start where the cutting was performed on the explant, leading to raising evidences of variability depending on the initial donor shape (e.g. branch-forming or compact). Shape and skeletal characteristics of sponges indeed seem to have an impact on their post-injury recovery process, such as evidenced by Loudon et al. (2007) with the two demosponges *Rhopaloeides odorabile* and *Coscinoderma* sp. coming from the same Spongiidae family yet featuring distinct morphological traits. As an example, encrusting siliceous sponges respond better to environmental damage than fibrous and massive ones (Ayling, 1983). Some parts of the sponge skeleton could perform better than others. Indeed, it was sometimes noticed that sponge growth only occurs in the tips of branches and the attachment point to substrate or shows correlation with water movement exposure (Bell and Barnes, 2000; Kaandorp and de Kluijver, 1992). On the contrary, the expansion of other species can be unpredictable and very irregular (de Voogd, 2007a; Diaz et al., 2019; Hope, 1988).

Overall, given the contrasting and unpredictable results obtained regarding the influence of key environmental factors on different sponge species culturing, no measure should systematically be excluded from experiments based on previous outcomes. Favorable conditions such as adequate water movement, correct illumination and non-detrimental temperature ranges can even differ on small geographical scales (Duckworth et al., 1997). Along with the environment, it is clear that a regular monitoring of sponge physiological traits and metabolism is essential to assess the effectiveness of the devices over time. Besides the control of the explants, surrounding populations are studied to assess the differences in their performance as brood stock, answering important biological and ecological questions. Still, for sponges dedicated to drug development, the purpose of launching an aquaculture system remains the production of secondary metabolites in sufficient amounts for the activity to be viable. That is why, for those species, chemical properties are very important to understand both from sponges and from their associated organisms such as symbiotic bacteria. In the last part of this review, we will consider the sponges directed towards chemical valorization and the essential parameters likely to change their production and concentration of bioactive compounds.

4. Considerations regarding sponge or sponge-derived chemical bioproducts exploitation

4.1. Sponge metabolites in the marine natural products industry

It is acknowledged that sponges, along with their microbial communities, have the highest bioactivity spectrum from all marine invertebrates (Rangel and Falkenberg, 2015). Marine sponges and sponge-associated microorganisms enzymes that can generate multiple compounds due their metabolic plasticity and ability to synthesize many synthase enzymes (Caroll et al., 2019; Debbab et al., 2010; Yong et al., 2008). Secondary metabolites are indeed sometimes present in astonishing diversity and quantities (Ogunola and Onada, 2016; Sim and Bakus, 1986). Regardless of their proper origin, such substances are useful as protection against diseases or infections (Indraningrat et al., 2016; Sipkema et al., 2005a), biofouling (Proksch, 1994) predation (Bakus and Green, 1974; Becerro et al., 1997; Pawlik et al., 1995;

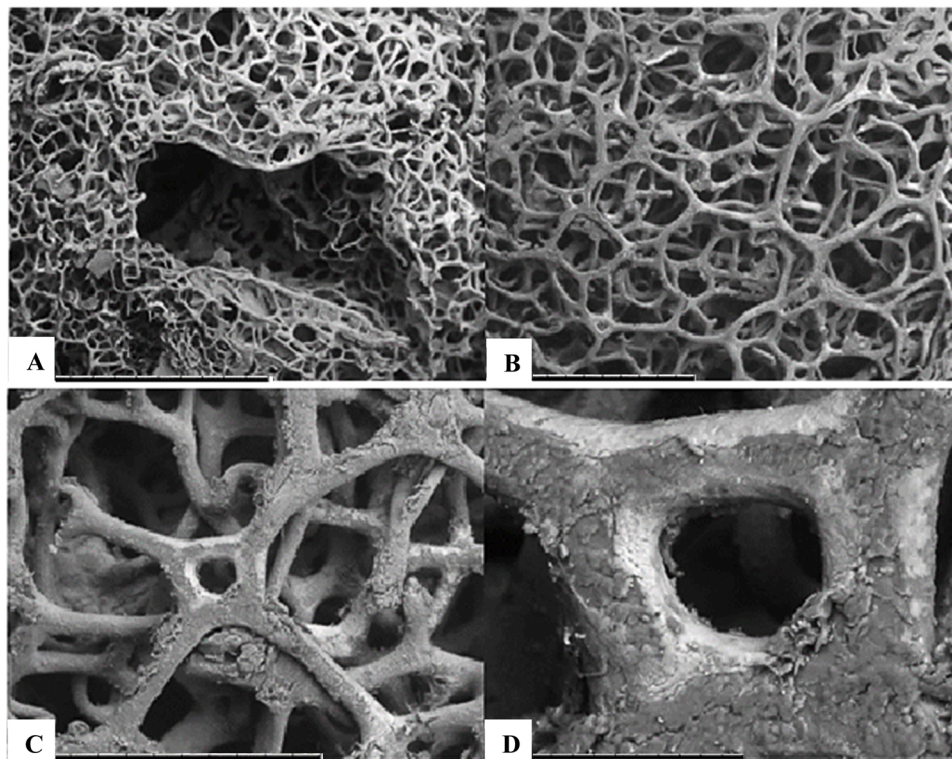


Fig. 5. Details of spongin fibers from a tropical demosponge species. Pictures were taken under scanning electron microscope. Scale bars: (A) 2 mm, (B) 1 mm, (C) 500 μm , (D) 100 μm .
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Thomas et al., 2010) or towards competition for an increase of the living space available (de Voogd et al., 2003; Pawlik et al., 2007; Suchanek et al., 1983).

Genes sequencing following DNA/RNA extractions of sponge or bacterial isolates provide information on potential analogous species with similar bioactivity patterns in a common geographical area (Wilson et al., 2014). Phylogenetic analyses of gene fragments, such as conducted with *Ancorina alata*, *Polymastia* sp. and *Diacarnus erythraenus*, provided insights to microbial activity revealing sponge-specific lineages and evidenced possible vertical transmission of bacterial communities, as many were also present in the sponge larvae (Bergman et al., 2011). Glycogen, lipid and protein contents can also be good indicators of both metabolic activity and symbiotic characterization. The lipid composition of sponge yolk may either favor or restraint larval survival, settlement and development, as well as the subsequent expression of metabolites against sympatric predators as it was early evidenced for *Mycale laxissima* (Lindquist and Hay, 1996). In Antarctica, *Mycale acerata* lipid-enriched yolk provided a clear energetic adaptation of the sponge larvae towards low food availability compared to a species of the same genus coming from the Caribbean, *Mycale laevis*, whose yolk lipid content was only 30 % (Riesgo Gil et al., 2015). Some proteins were found potentially involved into the membrane crossing of biological substances, including metabolites of interest with pharmacological properties such as aerophobin-2 binding proteins found in cell membranes of the Mediterranean sponge *Aplysina aerophoba* (Proksch et al., 2010). Similar components can also induce the expression of key genes mediating the appropriate colonization of the sponge pinacoderm by bacterial communities (Pita et al., 2013). As many microorganisms were proved actively involved in metabolites production, proper genetic grounds can ensure correct biosynthesis of natural compounds.

Generally, secondary metabolites are directly searched within the sponge or sponge-associated organic extracts (Hertiani et al., 2010; Höller et al., 2000; Unson et al., 1994; Yong et al., 2008). For sponges dedicated to drug development, bioactivity tests are numerous. As an

example, a possible test for anti-cancer applications is to assess the concentration of metabolites required to reduce the growth of mouse tumour cell lines by 50 % compared to control (Duckworth and Battershill, 2001; Frank et al., 2019; Pettit et al., 1994; Zhang et al., 2017). In addition, antimicrobial activity of the compounds can be tested against marine benthic bacteria, including pathogenic strains for humans or aquaculture organisms (Liu et al., 2017; Mohan et al., 2016; Wright et al., 1987).

Still, when considering chemical exploitation, many constraints are faced. The time required to obtain sufficient biomass to perform meaningful extraction processes and clinical trials can take decades, requiring numerous expensive steps (Carballo et al., 2009). As an example, antitumoral halichondrin B that can be isolated from the New Zealand sponge *Lissodendoryx* sp. requires more than 100 steps towards its complete synthesis and, being optimistic, 7000 tons of the sponge would be required to treat only a quarter of diagnosed melanoma patients in the world while barely few hundreds of tons are known to exist in nature (Sipkema et al., 2005b). Same authors calculated that 75 tons of the Mediterranean *Dysidea avara* would be needed on a yearly basis to cure 10 % of psoriasis patients in Europe and North America only, through the 20-steps synthesis of avarol. Delivery issues can arise, such as if the sponge has to be exported frozen. Ensuring the cold chain continuity between remote locations remains a major challenge. Lyophilization can be a solution for transportability needs, but might also be expensive and damaging to the molecules. Bioreactors can be employed as *in vivo* culture systems and successful operations were already reported with *Pseudosuberites andrewsi* (Osinga et al., 2003). Nevertheless, authors warned about the need of a continuous monitoring of ambient food concentrations, as filtration activity of sponges was found enhanced when placed into the system. Because pharmaceutical companies require continuous significant quantities, the need to maintain a regular production of natural compounds throughout the year made scientists wonder about the factors that can balance the sponge production of metabolites *in situ*.

4.2. Culturing parameters, ecophysiological factors and seasonality driving bioactive compounds concentration

Production of various metabolites is known to increase compared to wild populations when sponges are enduring mariculture operations (Duckworth, 2001; Duckworth and Battershill, 2003a; Hadas et al., 2005; Osinga et al., 2010). Indeed, the use of artificial material and initial damages probably generate a defensive response of the organism towards chemical aggression, sometimes including higher rates of metabolites synthesis.

In the study of Ruiz et al. (2013), the hanging mesh bags method had a positive influence on the concentration of bioactive metabolite discodermolide from *Discodermia dissoluta* explants, which increased of about one-third during the 6-month experiment. Yet, compared to donor sponges with initially high concentrations, farmed explants exhibited lower yields of discodermolide. Differences may be due to the aquaculture treatment. The demosponge *Dysidea avara* was farmed for 10 months using the horizontal ropes method, which was found to enhance the bioactivity of the explants compared to cages or attachment to artificial substrates placed at a similar depth of 8 m (de Caralt et al., 2010). Yet, no effect of farming structures on the bioactivity of the explants was found for *Latrunculia wellingtonensis* and *Polymastia crocea* (Duckworth and Battershill, 2003b). Both mesh arrays and hanging ropes seemed suitable methods and choices should therefore be made regarding the nature of the sponge itself (i.e. composition of the skeleton). Similarly, the culturing depth did not limit the bioactivity of *Mycale hentscheli* explants for the production of peloruside A (Page et al., 2011).

Bioactivity can also be affected by sponge size, although literature remains very scarce regarding this matter. Explants taken from the red encrusting sponge *Crambe crambe* exhibited more biologically active profile in the case of medium-sized parental individuals (Becerro et al., 1995). Actually, sponges of dimensions <1000 mm² or >10,000 mm² reached notably lower toxicity rates although no qualitative differences were assessed in terms of compounds structure. A given explanation is that smallest specimens might invest more energy into growth than defense purposes and biggest ones should promote reproduction activity over metabolites production (Uriz et al., 1995). More studies shall indeed be needed to strengthen this interesting pattern. Yet, one must ensure to establish limited explants volumes so as to allow various replicates from the same donor sponge without being lethal, especially if the adult form of the species do not reach large dimensions or the sponge is considered endangered.

Bioactivity of farmed explants was found species-dependent, being sometimes similar over time (Duckworth, 2001). Yet, seasonal and temporal variations in biochemical composition of marine sponges have long been demonstrated (Barthel, 1986; Elvin, 1976; Storr, 1976; Thompson et al., 1985). In temperate regions, concentrations of metabolites are mostly lower in winter and they increase in late spring/early summer (Ivanisevic et al., 2011; Sacristán-Soriano et al., 2012). A peak, which period varies depending of the species concerned, is usually reached as temperature increases (Sacristán-Soriano et al., 2012). This is in agreement with Elvin (1979) who validated the relation between the biochemical composition of the purple encrusting sponge *Haliclona permollis* and its reproductive cycle. In tropical regions, highest concentrations were recorded during spring for *Latrunculia* sp. (Duckworth and Battershill, 2001) and *M. hentscheli* (Page et al., 2005, 2011) but toxicity was enhanced in summer for *Haliclona* sp. (Abdo et al., 2007).

Yet, results of metabolites concentration vary considerably from one species to another (Turon et al., 2009). If seasonal bioactivity patterns to prevent biofouling or predation have been identified for some sponges, biosynthesis of compounds in others showed no variation due to environmental conditions (Duckworth and Battershill, 2001; Duckworth et al., 2004). Those results have led to a recent interest in the study of “sponge chemotypes” to find the more suitable donors and select them towards the optimization of natural product yields (Page et al., 2011).

4.3. The role of marine sponge symbionts in metabolites production

Sponges are known as great reservoirs of marine microbes of up to 63 different phyla, undoubtedly allowing their exceptional diversity worldwide (Moitinho-Silva et al., 2017; Thomas et al., 2016; Webster et al., 2010). Most abundant groups that can be found include Proteobacteria, Actinobacteria and Cyanobacteria, the latter being perhaps one of the oldest forms of microbial interactions with multicellular animals (Beate and Hentschel, 2017; Webster and Thomas, 2016). Research aimed at studying the microbiome of marine sponges from very different distribution areas is increasing to assess its role on growth and survival parameters. Examples of universal sponge microbiota studies are numerous, such as for the Indo-Pacific *Dactylospongia metachromia*, the Great Barrier Reef *Rhopaloides odorabile*, the Mediterranean *Aplysina aerophoba*, the breadcrumb sponge *Halichondria panicea* from the North Sea and the tubular dome sponge *Theonella swinhoei* from Israel in the Red Sea (Hentschel et al., 2001; In-Hye and Jin-Sook, 2013; Mori et al., 2018; Webster and Hill, 2001; Wichels et al., 2006).

Symbionts are acquired through horizontal and vertical transmissions within the sponge body (Tout et al., 2017). They mostly live either closed to the choanocyte chambers located inside the sponge mesohyl or directly beneath the pinacoderm, where they can perform their phototrophic activity as being exposed to the sunlight (Webster and Thomas, 2016). Sponge symbionts are believed to feed on discarded cells and other elements coming from the mesohyl of their host (Slaby et al., 2017). In exchange, they might play a key role in pinacoderm cleaning and healing as well as ensuring global health functions (Liu et al., 2017). Seemingly defenseless sponges that are lacking protective crystalline spikes or “spicules” mostly rely on the symbiotic interactions they develop with their specific microbiome for chemical protection, as the bioactive metabolites it releases often show antibacterial activities against marine or even human pathogens (Bewley and Faulkner, 1998; Faulkner et al., 1993; Piel, 2004; Proksch, 1994). This way, they could limit the formation of harmful biofilms through the activation of bacterial chemoreceptors (Amsler and Iken, 2001; Kelly et al., 2003). Some of the bioactive compounds generated by cyanobacterial symbionts can account for over an impressive 10 % of the sponge dry weight (Schorn et al., 2019).

Interestingly enough, studies have highlighted that some marine natural products of chemical interest found in sponges have outstanding analogies to those produced by their symbiotic microorganisms, indicating metabolic synergy between the organisms (Fan et al., 2012; Liu et al., 2012; Piel et al., 2004; Proksch et al., 2002; Thiel and Imhoff, 2003; Reiter et al., 2020). Investigations aimed at assessing whether the microbiome itself is partly responsible for maintaining the symbiosis process revealed an effective role of symbionts towards the sponge-microbial chemotaxis (Tout et al., 2017). Some of the bioactive natural compounds found in marine sponges are actually imported into or synthesized by their endosymbiotic communities and have a wide range of applications like anticancer or antibiotic activities (Agarwal et al., 2017; Hentschel et al., 2012; Indraningrat et al., 2016; Thomas et al., 2010; Webster and Thomas, 2016). Hundreds of bioactive metabolites have been isolated so far from sponge-associated marine fungi or bacteria (Blunt et al., 2018; Frank et al., 2019). Those discoveries are of great importance when considering pharmaceutical valorization or reasoning sponge aquaculture. Indeed, given the recent advances of microbiological biosynthesis and efforts deployed to overcome difficulties in culturing some symbionts (Erpenbeck and van Soest, 2007; Karthik and Li, 2019; Schorn et al., 2019), we accredit that isolating and producing marine bacteria should be preferred when possible as a long-term solution over trials to obtain sponge material from the sea.

Great challenges are facing the attribution of marine natural products in a symbiotic interaction to a particular organism, as the origin of a same compound can be of multiple sources (Mori et al., 2018). The great variability of natural compounds production among sponges is making their biochemical activity difficult to study because stability is often

required for the chemotaxonomy to be accurate (Cárdenas, 2016). Multiple factors can be apprehended as potential causes of contrasted bioactivity patterns among sponges, including the possible shifting of symbionts between hosts that was cited as “sponge-sponge contamination” (Erpenbeck and van Soest, 2007). Biotic or abiotic signals can either initiate or stop the production of natural compounds for defensive purposes. The abundance and diversity of microsymbionts are also either favoring or lessening the output of metabolites precursors. Several sponge species rather depend on one symbiont in particular for biochemical defense than a whole community of bacterial strains (Schorn et al., 2019). Indeed, symbiont richness and activity are highly heterogeneous depending on the sponge species and its environment (Kamke et al., 2010). Moreover, it can be related to existing farming activities. During some sponge farming trials, bacterial populations varied significantly between aquaculture and wild specimens. Microbial diversity of the loggerhead sponge *Ircinia strobilina* and the vase sponge *Mycale laxissima* increased when individuals were moved into cultivation process (Mohamed et al., 2008a, 2008b). The need to look for possible functional redundancy and equivalence among sponge-associated microorganisms was early suggested and, as it was evidenced for the intertidal *Hymeniacidon heliophila*, appears of major importance today to apprehend sponge holobiome vulnerability and resilience towards changing environmental conditions (Fan et al., 2013; Weigel and Erwin, 2017; Webster and Thomas, 2016).

5. Conclusions and recommendations

5.1. Technicity and performance

To meet commercial production requirements, farming systems must therefore be inexpensive, easy to install and maintain within a minimum surface area to reduce the risk of instability and biofouling. Because mesh grids did not meet these later requirements, they were gradually abandoned in favor of nylon ropes simply threaded through explants (de Voogd, 2007b; Duckworth, 2001). Regular net changes, delicate scrubbing of harmful biofilms on sponges or structures, the moderate use of non-toxic surface coatings and an increase in the accessibility of farming facilities to herbivorous organisms could help reduce the spread of biofouling among cultured stocks (Fitridge et al., 2012). There is also the absolute need of permanently maintaining sponges underwater during each farming operation. Sponges need well-aerated marine habitats without frequent oxygen depletion leading to hypoxic conditions they do not always recover from (Barthel and Theede, 1986; Chu et al., 2018). This fact justifies the design of suspended ropes or loops, where the explants are directly exposed to the perpendicular water flow.

Even if authors sometimes concur on better technical performances, results of the literature are highly dependent on species and geographical context. Studies rightly emphasize that different species require different aquaculture design to maximize growth and survival rates (de Voogd, 2007b; Osinga et al., 2010). Responses to a particular treatment also differ according to the region along with the species diversity it hosts. Intra and interannual variations in marine sponge diversity can be highly contrasting depending on the studied area, with local events of massive mortality reported (Bell and Smith, 2004; Carballo et al., 2009; Cebrian et al., 2011; Ereskovsky et al., 2019). Threatened and endangered species should therefore be avoided, or considered very sparingly and treated carefully to ensure that their population density is not overused later, as possibility of extinction shall never be completely withdrawn (Müller, 1998). Those facts emphasize the need to monitor trends in wild populations, especially those with strong aquaculture potential, in relation to their environmental context.

Growth rates should increase over time, survival should be high and associated with a stable bacterial community, and metabolites production should be constant during the farming process (Bergman et al., 2011). Final survival rate shall exceed 90 % and the size of farmed sponges must at least double each year to guarantee commercial success

(Duckworth and Wolff, 2007). However, no general rule can be applied for all cultivable species, as growth is not linear but generally subject to wide variations over time (Verdenal and Vacelet, 1990). The differences in individual growth rates might be partially explained by the fact that some sponges may invest more energy in reproduction than in biomass expansion (Duckworth and Battershill, 2001).

It is our belief that commercial sponge farming must be carried out in compliance with essential points. The optimal model of sponge rearing is always context-specific, including both the design of mariculture and the selection of breeding individuals. Therefore, it requires specific investigation and research programs, established in a preliminarily manner to ensure a minimum of negative influence on the local economy and ecology.

The aquaculture industry shall contribute to the economic development and social well-being of the local people. Ongoing dialogue with local populations is essential to establish and must be conducted carefully to ensure sustainability. Economic return has to be sufficient for the harvesting and farming to be viable over time (Hawes et al., 2010). In addition, all legislative perspectives should be taken into account including access, ownership, operating rights and safety issues. Finally, the activity must be environmentally sustainable, balancing economic and social gains against environmental costs within an explicit regulatory framework. Environmental impacts on targeted and adjacent habitats should be addressed. An effective management includes monitoring ambient parameters and maintaining the performance of technical facilities.

5.2. Environmental and physiological investigation

General observations of environmental parameters could be useful in predicting zootechnical trends (Turon et al., 1996). Salinity, temperature, oxygen and water exchange (sometimes referred as habitat “openness”) are among the essential parameters to evaluate in order to estimate the probability of sponge species growth and survival (Ledda et al., 2014; Longo et al., 2016; Osinga et al., 1999b). Their continuous monitoring, such as through the use of wireless sensor networks or remotely operated vehicles equipped with modules linked to an online monitoring program, is thus helpful when selecting a species for farming in a particular environment (Simbeye et al., 2014; Parra et al., 2018). Furthermore, they have an impact on sponge microbiota, which are actively involved in both the production/release of metabolites and the general health of sponges (Borchert et al., 2016; Erwin et al., 2012; Pita et al., 2018; Unson et al., 1994; Webster et al., 2008).

For site selection towards farming trials, other criteria shall be assessed such as light exposure, weather conditions and seabed substrate. In contrasting biotopes, sponges are facing different challenges towards acclimation (e.g. reduced light intensity, sedimentation rate, sanding cover proportion). Rather than depth, which effect was proven highly circumstantial, the stability of surrounding environmental factors seems essential for sponge distribution and species richness (Hawes et al., 2010; Longo et al., 2016; Padiglia et al., 2018). The environmental context is undoubtedly responsible for the partition and discontinuities in Porifera community composition, depending on the species metabolic requirements (e.g. photophilous taxa that grow better when exposed to strong light) and ability to disperse once settled. Sponge energetics dedicated to metabolism is highly context-dependent and, although directly affecting vital requirements, difficult to estimate with accuracy (Duckworth et al., 2003; Gatti et al., 2002). In the context of highly variable interspecific responses of sponges to a broad spectrum of environmental factors, our belief is that starting an aquaculture design close or directly within the habitat of natural sponge populations should be prioritized whenever possible.

Sponge feeding requirements such as food types and concentrations are subject to a major research effort aimed at understanding their role in growth (Osinga et al., 1999). The concentration of chlorophyll-a was selected as a good indicator of food accessibility, attributed to

phytoplankton on which many marine sponges feed (Duckworth and Pomponi, 2005; Ribes et al., 1999). Bacteria and microalgae represent another important food source for those organisms (Barthel and Theede, 1986; de Caralt et al., 2003; Lesser, 2006; Osinga et al., 2001) but so are particulate and dissolved organic matter to a lesser extent (de Goeij et al., 2008; Ramoimo et al., 2011). Sponge ability to retain DOM, also known as “sponge loop” in the food chain, modulates nutrient fluxes and emphasizes the importance of sponges in benthic-pelagic coupling (de Goeij et al., 2017; Maldonado et al., 2012). Sponges have access to these microparticles by the prevalent ocean currents, which actively contribute to the availability of the planktonic food otherwise remaining away from the pinacoderm (Leichter and Witman, 1997; Palumbi, 1984). Accessibility of seawater column components, their size and digestibility are key limiting factors regarding sponge feeding activity (Ledda et al., 2014; Maldonado et al., 2010; Yahel et al., 2006). We assume those are important parameters to assess prior to large-scale aquaculture launching. Radiometric measurements or bio-optical imagery, through the acquisition of reflectance spectra from satellites or multi spectral imagers, have already given very promising results in the monitoring of phytoplanktonic biomass applied to suspension feeders farming, including when facing turbid waters (Gernez et al., 2017; Soriano-González et al., 2019).

5.3. Metabolites production

Artificial synthesis of metabolites or related analogues can be a secure source of natural compounds supply, independently from natural and geopolitical hazards. Still, synthetic chemistry comes with elevated costs and long proceedings, thus securing a strong potential for natural substances in the pharmacological market. *in situ* metabolites production yet comes with prior performances that need to be satisfy regarding consecutive aquaculture exploitation. Sponges must feature high growth and survival rates in order to be commercially exploitable for marine natural products industry (Duckworth et al., 1997). Then, concentration of targeted compounds within the explants shall be either stable or increasing through the aquaculture process for the valorization of natural populations. To perform efficient chemistry lab work in establishing the origin of the compounds or investigating their applications, the presence of secondary metabolites in sponge extracts must be ensured in the largest possible quantity. Hence the importance of an adequate brood stock selection, with donors featuring both fast growth and high production rates for the secondary metabolites of interest. Continuous monitoring of sponge biochemical activity should thus be recommended when trying to understand the changes in metabolites production of the explants throughout the year and between different habitats. It can also help to observe whether if the initial location of the explant on the donor has an influence on the subsequent concentration of natural compounds or not. Nevertheless, in some cases a viable prospect of sponges for drug development is probably only achievable if the expected quantities of chemicals are small enough to be reachable (de Voogd, 2007a).

Growth and sponge chemotype are two intraspecific parameters that were proved highly variable (Becerro et al., 1995; Page et al., 2011). This variability among individuals is believed to be mostly due to inherent metabolism (i.e. energetic reserves), choanocyte chambers number and organization within the sponge body as well as external variables from the surrounding environment (Becerro et al., 1995; de Voogd, 2007a; Verdenal and Vacelet, 1990). Farmed explants and wild organisms can differ in bioactivity due to individual responses to damage and defense strategies (Duckworth, 2001). Variations in food abundance that might be occurring throughout the year with more or less perceivable patterns also play a role in sponge natural products biosynthesis (Duckworth et al., 2003). Not to be forgotten, the design of the installations itself can influence the release of chemical substances by the organism. The fact that some farmed species have revealed a higher synthesis of biologically active metabolites than uncut ones is very encouraging for the future development of sponge mariculture

towards drug development (Duckworth and Battershill, 2003a).

5.4. Microbial associations

Relationships between sponges and the symbionts they host are driven by numerous factors, including biometric (i.e. microbiome density and composition) and environmental considerations (Ramsey et al., 2011). Most of the sponge endosymbionts are either generalists or specialists showing amensal and/or commensal interactions, compared to a lower proportion of opportunists (Thomas et al., 2016). Yet, although microbial associations within sponges exist worldwide, the biomolecular processes driving those interactions remain insufficiently identified (Bart et al., 2020; Bewley and Faulkner, 1998; Lurgi et al., 2019; Taylor et al., 2007). Genes involved in microbial defense against free alien DNA or sponge matrix colonization and utilization were found highly abundant in many endosymbiotic genomes (Slaby et al., 2017). Deeper investigation into both microbial community and sponge amplicon sequencing are required to improve our understanding of the inter-specific interactions and genomic considerations leading to metabolites biosynthesis (Webster and Thomas, 2016).

Today, genomic tools such as PCR combined with metabolomics are allowing deeper research in finding the biosynthetic abilities of these microbes (Harvey et al., 2015; Wilson et al., 2014). Techniques like bacterial co-cultivation, NMR spectroscopy, microbiome sequencing and cell sorting allow to express silent genetic assemblages and sometimes to discriminate natural bioactive compounds to either the sponge itself or its numerous symbionts (Agarwal et al., 2017; Brakhage and Schroeckh, 2011; Crawford and Clardy, 2011). Still, assessing the real origin of the metabolites isolated from sponge extracts remains challenging as the chemical range of products they harbor is extremely broad while the amounts produced are often scarce (Mori et al., 2018; Reiter et al., 2020; Schorn et al., 2019). Complex and analogous genes are indeed hard to identify without doubts. Moreover, symbionts are difficult to remove safely from the sponge without deteriorating it, making the hypothesis of obligate symbiosis interactions largely acknowledged nowadays. Regarding endosymbionts cultivation, some of them were actually found difficult to growth *in vitro*, suggesting that they can be incapable of living outside their sponge host (Hinde et al., 1994; Webster and Thomas, 2016). For the past decade, extensive research has been done to overcome cultivation issues of bacteria isolated from sponges, such as testing different growth conditions (i.e. temperature, light and oxygen gradients for storage and incubation) and oligotrophic media sometimes supplied with antibiotics for many species such as *Haliclona* (Gellius) sp., *Aplysina aerophoba*, *Corticium candelabrum* and *Petrosia ficiformis* (Gutleben et al., 2020; Sipkema et al., 2011; Versluis et al., 2017). Still, today entire Phyla are exclusively constituted by uncultivated bacteria (Reiter et al., 2020). In fact, the sponge matrix remains a unique, highly specific environment that is problematic to recreate without imperfections and uncertainty regarding the future synthesis of metabolites by isolated symbionts (Unson et al., 1994). Finally, genes that are not implicated in metabolic pathways such as those dedicated to growth or cell specialization might not be expressed under artificial conditions (Hertweck, 2009).

5.5. Other prospects of sponge mariculture valorization

Aquaculture of sponges is currently still a great opportunity to provide sustainable sources of marine organisms and secondary metabolites until structure elucidation has been completed (Martins et al., 2014; Page et al., 2011). Yet, the trace amounts of natural compounds present in sponge extracts as well as the ecological and economic constraints that were addressed for the most part in this study are making natural drugs development highly challenging. Current leads still need to be encouraged and supported by the establishment of more sustainable and efficient supply methods (de Voogd, 2007a). Species featuring high yields of the needed compounds are to be prioritized into research

investigation and selection as they do not need to be massively collected to fulfill biomass requirements (Binnewerg et al., 2020). A realistic bioeconomical study of active molecules production based on the sponge model retained should systematically be addressed for each compound in compliance, if available, with its current market price. Also, various prospects to enhance the attraction for sponge mariculture towards drug development shall be more investigated in the future, as it is facing major concurrency with *in vitro* alternative techniques.

Different aspects of sponge valorization through *in situ* farming activities are being raised, such as collagen or chitin production, nutrient cycling and nutrient loading reduction in polluted areas compared to pristine sites (Binnewerg et al., 2020; Fassini et al., 2020; Ledda et al., 2014). Firstly, as the many contributions of organic collagen to human society were assessed (Silva et al., 2014), it would be of interest to explore more deeply the link between sponge mariculture process (i.e. installations design and experiment time) and the synthesis of these ubiquitously abundant proteins. As for chitinous scaffolds, they also have an extremely wide range of applications such as biocompatible cellular matrices for tissue engineering and regenerative medicine, adsorbents to intercept pollutants or suitable framework for metal deposition (Binnewerg et al., 2020; Khrunyk et al., 2020; Klinger et al., 2019; Petrenko et al., 2017; Tsurkan et al., 2020; Wysokowski et al., 2015). Multiple chitin representatives from those sponges often come with specific compounds, named bromotyrosines, which are recognized bioactive metabolites and antibacterial agents with cytotoxic properties (Drechsel et al., 2020; Kovalchuk et al., 2019; Kunze et al., 2013; Muzychka et al., 2021). Last but not least, spongin scaffolds were recently found useful in extreme biomimetics when creating 3D composites that proved thermally stable and are preserving the structural features of natural biopolymers (Petrenko et al., 2019; Szatkowski et al., 2017; Tsurkan et al., 2020).

In addition, exploiting the renewal of nutrients fluxes by sponge is believed to be a suitable strategy, especially in reef habitats where sponges covering areas in the exposed or cryptic surfaces can be broad (de Goeij et al., 2008). Moreover, sponge renowned filtering capacity and ability to adjust it depending on specific metabolic requirements is of major interest regarding the decay of microparticles loads from polluted waters (Gökalp et al., 2020c; Stabili et al., 2006). Sponge bioremediation was tested close to contaminated sources and proved effective, as growth rates were enhanced compared to pristine sites (Gökalp et al., 2020a; Osinga et al., 2010). Sponges are indeed counting among the most efficient marine macrofilter feeders, being able to accumulate and chemically transform many substances including organic particles from wastewater (Gifford et al., 2006; Ledda et al., 2014; Pawlik and McMurray, 2019). As sponges select their food through complex and multifactorial processes, insurance of sponge feeding on the targeted microbes must be firstly established to avoid unwanted proliferation of opportunistic pathogens (Gökalp et al., 2020c; Maldonado et al., 2010). Focusing on sponge inherent skeletal frameworks might provide a promising new lead, as some sponge-derived chitin scaffolds have already shown absorbing properties against heavy metals such as uranium (Khrunyk et al., 2020; Schleuter et al., 2013). Exploiting sponges as bioremediators through mariculture systems thus appears as a great way to mitigate urban or agricultural pollution and should be discussed when reasoning the development of aquaculture infrastructures. Efforts still need to be addressed to apprehend sponge removal efficiency towards more contextual microorganisms, such as specific marine pathogens including those which develop as a result of locally intensive aquaculture.

Lastly, integrated aquaculture should also be seen as a way to obtain sponge-associated natural products while avoiding common monoculture outbreaks (i.e. diseases or pest infestation) and reasoned adequately for the sponges to benefit from the co-culture releases (Milanese et al., 2003; Page et al., 2011). Because sponges modify their diet according to the food types available, they can well compete with marine metazoans and especially other filter-feeding invertebrates for

food accessibility (Perea-Blázquez et al., 2013; Ribes et al., 1999; Thomassen and Riisgård, 1995). This singular capacity can favor the farming process of marine sponge species in combination with other aquaculture productions, depending on the local availability of the food source.

CRedit authorship contribution statement

Mathilde Maslin: Writing - Original draft, Writing - Review & Editing, Visualization. **Nabila Gaertner-Mazouni, Cécile Debitus:** Writing - Original draft, Project administration, Funding acquisition. **Nicole De Voogd, Raimana Ho:** Writing - Original draft, Supervision.

Data Availability Statement

Data sharing not applicable
No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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