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1 QUORUM SENSING AND QUORUM QUENCHING
2 IN THE PHYCOSPHERE OF PHYTOPLANKTON:
3 A CASE OF CHEMICAL INTERACTIONS IN ECOLOGY
4

5 JEAN LUC ROLLAND¹, DIDIER STIEN^{2,3},
6 SOPHIE SANCHEZ FERANDIN^{4,5}, RAPHAËL LAMI^{2,3,*}
7

8 ¹*Institut Français de Recherche pour l'Exploitation de la Mer (IFREMER), Interactions-*
9 *Hôtes-Pathogènes-Environnements (IHPE UMR 5244), University of Perpignan Via*
10 *Domitia, Centre National de la Recherche Scientifique (CNRS), University of Montpellier,*
11 *Montpellier F-34095.*

12 ²*UPMC University Paris 06, USR3579, LBBM, Observatoire Océanologique,*
13 *66650 BANYULS SUR MER, France*

14 ³*Centre National de la Recherche Scientifique, USR 3579, LBBM,*
15 *Observatoire Océanologique, 66650 Banyuls-sur-Mer, France*

16 ⁴*UPMC University Paris 06, UMR7232, BIOM, Observatoire Océanologique,*
17 *66650 BANYULS SUR MER, France*

18 ⁵*Centre National de la Recherche Scientifique, UMR7232, LBBM,*
19 *Observatoire Océanologique, 66650 Banyuls-sur-Mer, France*
20

21 *Corresponding author: raphael.lami@obs-banyuls.fr

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24

25 **Key words** - quorum sensing, quorum quenching, phytoplankton, phycosphere

26 **ABSTRACT**

27 The interactions between bacteria and phytoplankton regulate many important
28 biogeochemical reactions in the marine environment, including those in the global
29 carbon, nitrogen and sulfur cycles. At the microscopic level, it is now well established
30 that important consortia of bacteria colonize the phycosphere, the immediate
31 environment of phytoplankton cells. In this microscale environment, abundant bacterial
32 cells are organized in a structured biofilm and exchange information through the
33 diffusion of small molecules called semiochemicals. Among these processes, quorum
34 sensing plays a particular role as, when a sufficient abundance of cells is reached, it
35 allows bacteria to coordinate their gene expression and physiology at the population
36 level. By contrast, quorum quenching mechanisms are employed by many different
37 types of microorganisms to limit the coordination of antagonistic bacteria. This review
38 synthesizes quorum sensing and quorum quenching mechanisms evidenced to date in
39 the phycosphere of phytoplankton, emphasizing the implications that these signaling
40 systems have for the regulation of bacterial communities and their activities. The
41 diversity of chemical compounds involved in these processes is examined. We further
42 review the bacterial functions regulated in the phycosphere by quorum sensing, which
43 includes biofilm formation, nutrient acquisition and emission of algaecides. Quorum
44 quenching compounds, their function in the phycosphere and their potential
45 biotechnological applications are also discussed. Overall, the current state of the art
46 demonstrates quorum sensing and quorum quenching regulate a balance between a
47 symbiotic and a parasitic way of life between bacteria and their phytoplankton host.

48

49

50

51 REVIEW

52 1. Definition of phycosphere of phytoplankton

53 The term “phycosphere”, was first used in the 70’s (Bell and Mitchell 1972) to describe
54 the immediate region surrounding an algal cell, chain or colony. It describes a microbial
55 habitat deeply shaped by the alga. This microenvironment is composed of bacteria
56 measuring between 0.2 and 2 μ m, around algae varying in between 2 and 200 μ m
57 (Sieburth et al. 1978). The phycosphere supports bacteria in higher concentrations than
58 in the water column. For example, the concentration of 8.2×10^8 to 2.6×10^{11} bacteria ml⁻¹
59 reported to surround the alga *Trichodesmium* (Paerl 1982; Sheridan et al. 2002) is much
60 higher than the average concentration of $5\text{--}6 \times 10^5$ cells ml⁻¹ found in the seawater.
61 Similarly, $10^7\text{--}10^8$ culturable bacterial cells have been reported per gram of
62 *Botryococcus braunii*, a green microalga (Rivas et al. 2010). Several studies have
63 revealed that the phycosphere bacterial communities from different phytoplankton cells
64 are complex and taxonomically diverse (Delong et al. 1993; Fandino et al. 2001;
65 Hasegawa et al. 2007; Rooney-Varga et al. 2005; Sapp et al. 2007; Tuomainen et al.
66 2006). In addition, this microscale environment is regulated by the release of
67 extracellular products by the algae, feeding a large consortium of inhabiting bacteria
68 (Bell and Mitchell 1972).

69

70 2. Quorum sensing in the phycosphere of phytoplankton

71 2.1 Definition of quorum sensing

72 Quorum sensing is a term describing a cell-to-cell bacterial communication system,
73 allowing bacteria to adapt their physiological response to the ambient bacterial density
74 (Fuqua et al. 1994; Nealson 1977). Bacteria engaged in quorum sensing emit small
75 semiochemicals named autoinducers (Schulz 2014) and simultaneously detect their

76 concentration. At low bacterial concentrations, few autoinducers are present in the
77 nearby environment and cells display individual phenotypes and behaviors. When the
78 concentration of autoinducers reaches a certain threshold, reflecting an increase in local
79 cell density, bacteria switch their genetic and physiological program and display
80 collective phenotypes and compartments (Fuqua et al. 1994). These communication
81 mechanisms induce numerous transduction cascades and regulate the expression of
82 many genes (Bassler 1999). They are known to influence bacterial metabolism and
83 phenotypes, including the establishment of biofilms (Parsek and Greenberg 2005),
84 bioluminescence (Nealson 1977; Waters and Bassler 2005) and virulence (Smith and
85 Iglewski 2003) among other functions (Diggle et al. 2007).

86

87 **2.2 Experimental approaches used to characterize quorum sensing in the** 88 **phycosphere**

89 Most of the studies reported in this review are based on a similar workflow. First,
90 bacterial strains are isolated from natural seawater sampled during a phytoplankton
91 bloom (Bachofen and Schenk 1998) or are isolated from algae cultures (Geng and Belas
92 2010; Gram et al. 2002; Schaefer et al. 2008; Wagner-Dobler et al. 2005). The capacity of
93 the isolated strains to communicate using quorum sensing is then tested using bacterial
94 whole cell sensing-systems (biosensors) (Patzelt et al. 2013; Rivas et al. 2010; Wagner-
95 Dobler et al. 2005), such as *Escherichia Coli* JB523 (Andersen et al. 2001), *Chromatium*
96 *violaceum* CV026 (McLean et al. 1997) and *Vibrio harveyi* JMH612 (Henke and Bassler
97 2004) to name several examples among many others. These genetically modified
98 organisms encode the purple pigment violacein (**1**) or the Green Fluorescent Protein
99 (GFP) or and luminesce in the presence of exogenous acylhomoserine lactones (AHLs),
100 the most studied semiochemical. Such approach using genetically modified organisms to

101 detect AHLs expression is required, as these compounds are present in low
102 concentrations in water and technically very difficult to be directly quantified *in situ* in
103 bulk seawater (Hmelo and Van Mooy 2009). A few report mention the possibility to
104 detect AHLs directly in seawater particles (Hmelo et al. 2011), which can also avoid
105 potential false positive results acquired when using biosensors (Holden et al. 1999).

106 In a further step, AHLs can be characterized. In general, bacterial supernatants
107 containing AHLs are extracted, usually with ethyl acetate. Preliminary studies relied on
108 Thin Layer Liquid Chromatography (TLC) (Gram et al. 2002; Rivas et al. 2010). More
109 recent studies are frequently based on Liquid Chromatography and Mass Spectrometry
110 (LC-MS) (Schaefer et al. 2008), Gas Chromatography Mass Spectrometry (GC-MS)
111 (Wagner-Dobler et al. 2005) and MS/MS approaches (Van Mooy et al. 2012), sometimes
112 preceded by microfractionation, which allows greater separation and concentration of
113 the extracted metabolites. In some cases, double bond location has been determined by
114 derivatization with dimethyl disulfide (Neumann et al. 2013), and irrevocable
115 characterization can be achieved by 1D and 2D Nuclear Magnetic Resonance (NMR)
116 analyses.

117 The experimental approaches to evaluate the functional roles of quorum sensing
118 are more diverse. Most of studies have based their work on model strains where key
119 genes involved in autoinducer biosynthesis pathways are mutated, in particular in *lux*-
120 like genes. Characterization of the growth and phenotypes of mutant strains elucidates
121 the potential physiological functions regulated by quorum sensing (Patzelt et al. 2013).

122

123 **2.3 Occurrence in the phycosphere**

124 There is strong evidence that quorum sensing occurs in microbial communities
125 inhabiting the phycosphere of phytoplankton cells. A pioneering study published in

126 1998 revealed the presence of AHLs in cyanobacterial blooms (Bachofen and Schenk
127 1998), which is not surprising since the high bacterial densities required for quorum
128 sensing occur in the phycosphere. Since then, many reports have directly detected the
129 existence of quorum sensing in various phycosphere samples. These very diverse
130 bacteria were isolated from equally diverse phytoplankton, indicating that quorum
131 sensing is not restricted to a particular type of bacteria–algae interaction. This wide
132 diversity of phytoplankton includes dinoflagellates (isolated bacteria: *Dinoroseobacter*
133 *shibae*, *Hoeflea phototrophica*, *Roseovarius mucosus*), and other picoplankton cultures
134 (isolated bacteria: *Sulfitobacter sp.*, *Thalassospira lucentensis*) (Wagner-Dobler et al.
135 2005). Similarly, another study revealed two bacterial strains (*Pseudomonas* and
136 *Rhizobium*) able to communicate by quorum sensing in a *Botryococcus braunii*
137 associated biofilm (Rivas et al. 2010). These results are in line with observations of
138 quorum sensing in bacterial communities attached to sinking particulate organic matter
139 (Gram et al. 2002; Hmelo et al. 2011), in the 0.8 – 3 µm fraction from filtered seawater
140 (Doberva et al. 2015) and in microbial mats, which include layers of cyanobacteria or
141 eukaryotic algae (Decho et al. 2009; McLean et al. 1997). Interestingly, a few reports also
142 noticed the capacity of certain bacterial phytoplankton (cyanobacteria) to produce AHLs
143 in their phycosphere (Sharif et al. 2008; Zhai et al. 2012).

144

145 **2.4 Nature of molecules involved in these chemical interactions**

146 Diverse secondary metabolites have been identified as quorum sensing mediators
147 (Keller and Surette 2006). Among them, AHLs (or autoinducer type 1, AI-1), constitute a
148 widespread class of quorum sensing molecules (Eberhard et al. 1981; Lazdunski et al.
149 2004). These semiochemicals are made of a lactonized homoserine ligated through an
150 amide bond to a fatty acyl chain, which is of variable length (C₄ to C₁₈) and oxidation

151 state and gives the signal its specificity. However, many other types of metabolites have
152 been identified that are involved in quorum sensing, including the *p*-coumaroyl
153 homoserine lactones (Schaefer et al. 2008), Furanosyl Diester Borate (FDB, autoinducer
154 type 2, AI-2) (Chen et al. 2002), quinolones (Pesci et al. 1999), peptides (Onaka et al.
155 1995) and γ -butyrolactones (Onaka et al. 1995).

156 Many different types of AHLs have been identified from bacteria isolated from the
157 phycosphere. Rivas et al. (2010) identified short chain AHLs (C4-AHL (2) and C8-AHL
158 (3)) in *Pseudomonas* sp. and *Rhizobium* sp. associated with the microalga *Botryococcus*
159 *braunii*. However, it appears that long-chain AHLs (more than 8 carbons in the acyl side
160 chain) tend to dominate in these cultures. This trend is sometimes interpreted as an
161 adaptation to increase the stability of these molecules in aquatic environments (Hmelo
162 and Van Mooy 2009; Yates et al. 2002). LC-MS analysis revealed that *Dinoroseobacter*
163 *shibae*, isolated from the surface of the dinoflagellate *Prorocentrum lima* (Biebl et al.
164 2005), produces C18:1-AHL (or C18-en HSL) (4) and C18:2-AHL (or C18-dien HSL) (5),
165 including one to two unsaturated bonds in the acyl side chain. In addition, the strain DFL
166 18 is reported to produce a C8-AHL (3) (Neumann et al. 2013; Wagner-Dobler et al.
167 2005). *Roseovarius mucosus* strains, also isolated from dinoflagellate cultures, produce
168 C18:1 (4) and C14:1 (6) AHLs (Wagner-Dobler et al. 2005). *Vibrio* strains isolated from
169 *Trichodesmium* colonies produce 3-oxo-C8-AHL (7), while the *Erythrobacter* strains
170 obtained over the same experiment produce C14-HSL (Van Mooy et al. 2012). The AHLs
171 produced by a few cyanobacterial strains have also been characterized. *Microcystis*
172 *aeruginosa* is probably able to produce AHLs (Zhai et al. 2012) (8), while the
173 cyanobacterium *Gloeothoece* PCC6909 produces a C8-AHL (3) (Sharif et al. 2008). The
174 AHLs are still the main quorum sensing molecules characterized in the bacteria isolated
175 from the phycosphere, probably because not many studies have focused on other

176 compounds. Two exceptions are the report of AI-2 (9) producing *Vibrios* in the epibiont
177 populations of *Trichodesmium* (Van Mooy et al. 2012) and the report of a potential role
178 for AI-2 in the control of the algaecide activity against the dinoflagellate *Gymnodinium*
179 *catenatum* (Skerratt et al. 2002).

180 Some recent publications also highlighted the role of tropodithietic acid (TDA)
181 (10) as an autoinducer in many *Rhodobacterales* species (Geng and Belas 2010). This
182 molecule is produced by different bacterial strains, including the genus *Phaeobacter*,
183 *Silicibacter* and *Ruegeria*, known to be frequently associated to unicellular algae
184 (Brinkhoff et al. 2004; Bruhn et al. 2005; Geng et al. 2008; Porsby et al. 2008). A series of
185 genetic-based experiments demonstrated that TDA acts as an autoinducer in *Silicibacter*
186 sp. TM1040 (Berger et al. 2011; Geng and Belas 2010), an isolate from the phycosphere
187 of the dinoflagellate, *Pfiesteria piscicida* (Alavi et al. 2001; Miller and Belas 2006). These
188 approaches demonstrated that TDA induces the transcription of *tda* genes, and that the
189 production of TDA is density dependent (Geng and Belas 2010), two key conditions in
190 recognizing TDA as a quorum sensing mediator. Interestingly, TDA production has been
191 shown to be 3.7 to 17.4 times greater in standing compared to shaking cultures,
192 suggesting that it plays an important role in bacterial biofilm function within the
193 phytoplankton phycosphere (Geng and Belas 2010).

194

195 **2.5 Roles of quorum sensing in the phycosphere**

196 **2.5.1 Formation of biofilms**

197 Quorum sensing is commonly hypothesized to play a role in niche colonization, in
198 particular because quorum sensing is known to be involved in biofilm formation and
199 surface attachment (Davies et al. 1998; Labbate et al. 2007; Nadell et al. 2008). Some
200 studies support the idea that quorum sensing may help bacteria to colonize particles of

201 organic matter or the phytoplankton phycosphere in the marine environment (Gram et
202 al. 2002; Hmelo et al. 2011). The capacity of *Roseobacter* to attach to surfaces has been
203 linked with an ability to communicate by quorum sensing (Rao et al. 2006). Similarly,
204 the emission of AHLs by the cyanobacterium *Microcystis* correlates with the switch to a
205 biofilm lifestyle (Zhai et al. 2012). The same hypothesis has been proposed to interpret
206 the capacity of *Phaeobacter* (isolated from a dinoflagellate culture) to produce TDA as an
207 autoinducer, as the expression of *tda* genes coincided with biofilm-formation (Geng and
208 Belas 2010). However, the relationship between biofilm formation and emission of
209 quorum sensing compounds is more complex. For example, *Silicibacter lacuscaerulensis*
210 and *Silicibacter pomeroyi* both harbor quorum sensing systems, but do not present the
211 same traits for surface colonization (Slightom and Buchan 2009). Other authors
212 demonstrated that biofilm formation is not necessary for TDA production in
213 *Phaeobacter inhibens* (Prol Garcia et al. 2014). Also, to our knowledge, no study has
214 demonstrated that quorum sensing facilitates biofilm formation within the phycosphere.

215

216 **2.5.2 Acquisition of nutrients**

217 The hypothesis that quorum sensing may favor nutrient acquisition in bacteria has been
218 well supported from experiments on model strains in niches other than the
219 phycosphere (Popat et al. 2015; Rosenberg et al. 1977). For example, it has been shown
220 in *Pseudomonas aeruginosa* that the secretion of proteases confers a greater benefit to
221 the whole population (Darch et al. 2012).

222 The phycosphere, as initially described, is a source of algal nutrients available to
223 bacteria in its immediate environment (Bell and Mitchell 1972). Thus, it is not surprising
224 that one of the hypothesized functions of quorum sensing in the phycosphere is that cell
225 coordination favors nutrient acquisition. A recent article clearly showed that epibionts

226 of *Trichodesmium* use quorum sensing to up-regulate phosphate acquisition by alkaline
227 phosphatases. AHLs were involved in this process, while AI-2 (**9**) lead to a decrease of
228 phosphate uptake (Van Mooy et al. 2012). Similarly, it has been shown that *Ruegeria*
229 *pomeroyi* overproduces N-(3-oxotetradecanoyl)-L-homoserine lactone (**11**) when
230 grown with dimethylsulfoniopropionate (DMSP) as an energy source, which is
231 metabolized into dimethyl sulfide (DMS) (Johnson et al. 2016). This AHL production is
232 also consistent with important modifications in the cell metabolome, suggesting that in
233 the presence of algal DMSP, *Roseobacter* switches to a cooperative lifestyle (Johnson et
234 al. 2016) . Interestingly, it has been shown that *p*-coumaric acid (**12**), a product of algal
235 lignin degradation released by decaying phytoplankton cells, is also the precursor of the
236 *p*-coumaroylhomoserine lactone (**13**) involved in *Rhodopseudomonas palustris* quorum
237 sensing (Schaefer et al. 2008). Thus, the emission of semiochemicals linked with the
238 release of phytoplanktonic molecules may also convey information about environmental
239 conditions in the phycosphere, such as the availability of exogenously supplied
240 substrates (Buchan et al. 2014; Schaefer et al. 2008). In a similar vein, it has been shown
241 in the algae symbiont, *Dinoroseobacter shibae*, that quorum sensing controls flagellar
242 biosynthesis (Patzelt et al. 2013), potentially enabling chemotaxis to microalgae and
243 thus favoring nutrient acquisition.

244 The large-scale biogeochemical consequences of bacterial coordination for
245 nutrient acquisition within the phycosphere remain poorly explored. A few articles
246 explored this question by focusing on particulate organic carbon and marine snow-
247 associated communities, which may provide some pieces for a relevant conceptual
248 framework. For example, some AHLs were detected in organic particles collected near
249 Vancouver Island (Hmelo et al. 2011). They also reported an enhancement of hydrolytic
250 enzyme activities in microcosms when adding synthetic AHLs to particulate organic

251 carbon collected in seawater (Hmelo et al. 2011). Similarly, alkaline phosphatase activity
252 is enhanced by C10-AHL (**14**) in a *Pantoea ananatis* isolated on marine snow (Jatt et al.
253 2015). Such results reveal that quorum sensing in particle-attached bacteria may drive
254 oceanic mineralization kinetics. However, more research is needed to better
255 characterize biogeochemical implications of quorum sensing expression (and more
256 generally the importance of cell-cell interactions) in such microenvironments, including
257 in the phycosphere (Moran et al. 2016).

258

259 **2.5.3 Regulation of microbial population dynamics**

260 It is well established that quorum sensing is involved in antimicrobial compound
261 synthesis (Bainton et al. 1992; Wood and Pierson 1996), and this activity has been
262 documented in strains directly isolated from the phycosphere or known to be able to
263 colonize such microenvironments (Bruhn et al. 2005; Gram et al. 2002; Wagner-Dobler
264 et al. 2005). It has also been reported that quorum sensing regulates the production of
265 different algaecides compounds.

266 TDA (**10**), reported above as an autoinducer (Berger et al. 2011; Geng and Belas
267 2010) inducing its own synthesis, acts as an antimicrobial molecule (Berger et al. 2011;
268 Bruhn et al. 2005; Geng et al. 2008; Porsby et al. 2008). Its synthesis is also controlled by
269 quorum sensing AHLs in many *Roseobacter* (Berger et al. 2011; Rao et al. 2007; Thole et
270 al. 2012). The production of TDA by *Silicibacter* may protect dinoflagellates from
271 pathogen attack (Bruhn et al. 2005; Geng et al. 2008).

272 Similarly, *Phaeobacter gallaeciensis* BS107, associated with *Emiliana huxleyi* ,
273 provides the alga with growth inducers like auxins during bloom conditions and
274 produces antibiotics like TDA, which fight algal pathogens (Geng et al. 2008; Greer et al.
275 2008; Thiel et al. 2010). In return, *Phaeobacter gallaeciensis* beneficiates of the DMSP

276 produced by the algae as a sulfur source (González et al. 1999; Newton et al. 2010).
277 Thus, it at first engages in a symbiotic relationship with *Emiliana huxleyi*. By contrast, at
278 the end of the phytoplankton bloom, *Phaeobacter gallaeciensis* liberates diverse
279 roseobacticides (troponoids) that act as algaecides. These metabolites are emitted in
280 response to *p*-coumaric acid (**12**), sinapic acid, ferulic acid and cinnamic acid (all lignin
281 precursors) released by decaying *Emiliana huxleyi* cells (Seyedsayamdost et al. 2011a;
282 Seyedsayamdost et al. 2011b). At this stage, *Phaeobacter gallaeciensis* switches to
283 becoming a parasite of its host algae (Seyedsayamdost et al. 2011a; Seyedsayamdost et
284 al. 2011b).

285 Various algaecides have been identified from bacteria inhabiting the
286 phycosphere, and sometimes a regulation of their emission by quorum sensing has been
287 either demonstrated or is highly likely (Nakashima et al. 2006; Paul and Pohnert 2011;
288 Skerratt et al. 2002). For example, the strain *Kordia algicida*, although isolated from a
289 red tide composed of the diatom *Skeletonema costatum* (Sohn et al. 2004), demonstrated
290 an algicidal activity against the diatoms *Skeletonema costatum*, *Thalassiosira weissflogii*,
291 *Phaeodactylum tricornutum*, but not against *Chaetoceros didymus*. This algaecide activity
292 is mediated by the excretion of proteases, which experimental data suggest is regulated
293 by quorum sensing based on AHLs (Paul and Pohnert 2011). In a similar vein, a potential
294 AI-2 based regulation of bacterial algaecide activity against the dinoflagellate
295 *Gymnodinium catenatum* has also been suggested (Skerratt et al. 2002).

296 In a similar way, the recently isolated 2-heptyl-4-quinolone (**15**) emitted by
297 *Pseudolateromonas piscicida* induces mortality of the marine coccolithophore *Emiliana*
298 *huxleyi* (Harvey et al. 2016). The 2-heptyl-4-quinolone is also reported as an antibiotic
299 and as a precursor of the quorum sensing mediator 2-heptyl-3-hydroxy-4-quinolone and
300 designated the « *Pseudomonas* quinolone signal » (PQS). However, interestingly, this

301 quorum sensing compound is not produced by *Pseudoalteromonas piscicida* (Harvey et
302 al. 2016).

303

304 **2.5.4 Induction of phenotypic heterogeneity**

305 Another potential function of quorum sensing in the phycosphere is the preservation of
306 population heterogeneity which is thought to be a survival strategy in fluctuating and
307 unpredictable environment. It has been recently highlighted in *Dinoroseobacter shibae*
308 (Patzelt et al. 2013), a strain isolated from a dinoflagellate culture (Biebl et al. 2005) that
309 the combination of genetic and transcriptomic analysis revealed that the lack of AHL
310 production deeply affects cell physiology, with 344 genes differentially transcribed. This
311 research reveals that quorum sensing is implied in many physiological activities,
312 including cell division, flagellar biosynthesis, sigma factor synthesis, as well as T4SS
313 production, a protein implied in both DNA and protein secretion systems (Christie et al.
314 2005). Also, the authors demonstrated the implication of quorum sensing in the
315 induction of individual morphological heterogeneity within a single population of
316 *Dinoroseobacter*. The *luxI* mutant led to single ovoid morphology of *Dinoroseobacter*
317 cells, while the wild-type phenotype, restored with C18-AHL, included ovoid, rod-
318 shaped and very elongated cells. The maintenance of such heterogeneity in a population
319 may convey ecological advantages at the population level, for example during
320 phytoplankton blooms where cell shape dependent processes such as grazing may be
321 more intense (Patzelt et al. 2013). A population might enhance its fitness by allowing
322 individual cells to stochastically transition among multiple phenotypes, thus ensuring
323 that some cells are always prepared for an unforeseen environmental fluctuation (Acar
324 et al. 2008). The authors in 2013 suggest that quorum sensing induced heterogeneity

325 ensures at least a subpopulation of cells maintains a high fitness under constantly
326 changing environment such as seasonal planktons bloom.

327

328 **2.6 Microalgal stimulation of quorum sensing**

329 Enhancements of quorum sensing activities have been observed, in particular in the
330 freshwater alga *Chlamydomonas reinhardtii*. This alga synthesizes a dozen chemical
331 compounds that mimics AHL activity, and so is able to readily stimulate various types of
332 quorum sensing receptors (Teplitski et al. 2004). Also, colonies of both *Chlamydomonas*
333 *reinhardtii* and *Chlorella* sp. were able to enhance the quorum sensing dependent
334 luminescence of *Vibrio harveyi* (Teplitski et al. 2004). Some of these compounds emitted
335 by *Chlamydomonas* have been identified: the vitamin riboflavin (**16**) and its derivative
336 lumichrome (**17**) are able to stimulate Las R receptors in *Pseudomonas aeruginosa* and
337 thus are the first eukaryotic quorum sensing agonists (Rajamani et al. 2008). The
338 ecological function of these metabolites remains to be investigated. Collectively, these
339 data reveal that microalgae chemically influence bacterial quorum sensing in the
340 phycosphere.

341

342 **3. Quorum quenching in the phycosphere**

343 **3.1 Definition of quorum quenching**

344 By contrast to quorum sensing, quorum quenching describes the mechanisms which
345 inactivate quorum sensing (Dong et al. 2001; Givskov et al. 1996). A few potential
346 functions of quorum quenching have been characterized so far, including the
347 inactivation of pathogens, virulence or competitors by the bacteria producing these
348 quorum quenching molecules, or self modulation of quorum sensing signals (Romero et
349 al. 2008; Zhang et al. 2002). However, many functional effects of quorum quenching

350 remain unknown. Quorum quenching based mechanisms are highly diverse and include,
351 for example, AHLs degradation by oxidization (Borchardt et al. 2001) and enzymatic
352 hydrolysis of AHLs lactones by either lactonases or acylases (Dong et al. 2007; Romero
353 et al. 2008). The synthesis of inhibitors or analogs of quorum sensing signals by algae,
354 invertebrates, plants and bacteria have also been described as quorum quenching
355 mechanisms (Gao et al. 2003; Givskov et al. 1996; Kim et al. 2007).

356

357 **3.2 Occurrence in the phycosphere of microalgae**

358 Quorum quenching activities have been previously detected in marine bacteria (Hmelo
359 and Van Mooy 2009; Hmelo et al. 2011; Romero et al. 2011; Van Mooy et al. 2012) and in
360 macroalgae (Rasmussen et al. 2000). The presence of quorum quenching molecules in
361 the phytoplankton phycosphere has also been verified. *Chlorella saccharophila*, *Chlorella*
362 *vulgaris*, *Nannochloropsis* sp., *Isochrysis* sp., *Tetraselmis suecica* and *Tetraselmis striata*
363 were identified as a quorum quenching compounds producers, inhibiting color and
364 fluorescence produced by the AHL-based reporting strains *Chromatium violaceum* and
365 *Escherichia coli* JB523 (Natrah et al. 2011). Interestingly, it has also been shown that
366 *Chlorella saccharophila*, *Nannochloris atomus* and *Nannochloropsis oculata* inhibit the
367 AHL based quorum sensing reporter strain *Vibrio harveyi* JMH612, revealing that
368 biosensors detect different types of algae quorum quenching activities. However, the
369 molecules responsible of the observed quorum quenching effect are still unknown.
370 Similarly, a novel acylase has been identified in *Anabaena* sp. PCC7120 and homologous
371 sequences of this enzyme were also detected in the filamentous cyanobacteria, *Nostoc*
372 *punctiforme*, *Gloeobacter violaceus* and *Synechocystis* sp. (Romero et al. 2008).
373 Halogenation of the acyl chains in AHLs can also inhibit quorum sensing mechanisms.

374 Interestingly, sequences encoding potential halogenases were found in public databases
375 containing the genome of the diatom *Fragilariopsis cylindrus* (Amin et al. 2012).

376

377 **3.3 Control of pathogenic bacteria virulence**

378 Quorum sensing controls many genes involved in virulence. Thus, inhibiting quorum
379 sensing can help to limit bacterial induced diseases. In light of the increasing concern
380 over widespread antibiotic resistance, an understanding of other strategies to limit
381 bacterial growth and virulence is invaluable. From this point of view, quorum quenching
382 molecules appear very promising for biotechnological purposes (Singh 2015), in
383 particular to fight bacterial diseases in aquaculture (Defoirdt et al. 2011). For example,
384 microalgae producing quorum quenching metabolites have the potential in aquaculture
385 to protect against aquatic pathogens (Natrah et al. 2011). A few studies have shown that
386 marine cyanobacteria have quorum quenching activity against *Vibrio* spp., one of the
387 most important pathogens in aquaculture, but also against other pathogens including
388 *Pseudomonas aeruginosa* (Dobretsov et al. 2010; Kwan et al. 2011). Cyanobacteria of the
389 genus *Lyngbya* appear to be particularly active emitters of quorum quenching
390 compounds that include amides, peptides and lipids (Dobretsov et al. 2011; Meyer et al.
391 2016). Similarly, *Leptolyngbya crossbyana* produces (S)-3-hydroxy- γ -butyrolactones
392 (Honaucines (**18,19,20**)), which inhibits quorum sensing-dependent bioluminescence of
393 *Vibrio harveyi* BB120. Similar quorum quenching activity by the microalga *Picochlorum*
394 sp. S1b against *Vibrio* is also suspected (Kuo et al. 2014), and the cyanobacterium
395 *Blennothrix cantharidosmum* produces tumonoic acids which moderately inhibits
396 bioluminescence of a wild strain of *Vibrio harveyi* without affecting growth. Along these
397 biotests, tumonoic acid F (**21**) appears to be the most active (Choi et al. 2012).

398

399 **4. Controversies**

400 The role of quorum sensing in microbiomes remains controversial (Cornforth et al.
401 2014; Platt and Fuqua 2010; West et al. 2012), and its function in the phycosphere is still
402 a large and open field of investigation (Bachofen and Schenk 1998; Decho et al. 2009;
403 Hmelo et al. 2011). Clearly, AHLs carry information and act as semiochemicals (Dicke
404 and Sabelis 1988). However, additional functions of these compounds have also been
405 described, including antimicrobial activity and iron chelation (Kaufmann et al. 2005;
406 Schertzer et al. 2009). This is also the case for TDA, which was first known in
407 *Rhodobacterales* as an antibacterial agent (Brinkhoff et al. 2004) before being described
408 as a quorum sensing autoinducer (Geng and Belas 2010). Clearly, quorum sensing
409 molecules display versatility and play different roles, depending on both the emitting
410 and targeted cells..

411 Another source of controversy is whether sensing autoinducer concentrations
412 actually functions to detect the rate mass transfer in the environment (“diffusion-
413 sensing”) rather than the local density of other bacteria (“pure” quorum sensing)
414 (Redfield 2002). The concept of “efficiency-sensing” unifies diffusion-sensing and
415 quorum sensing as specific cases within a more general framework whereby
416 autoinducer sensing allows bacteria to infer, in combination, mass transfer, cell density
417 and spatial distribution of other cells (Hense et al. 2007). This concept of efficiency-
418 sensing could aid in the interpretation of signaling events observed in the complexity of
419 the phycosphere where the environment is structured on a microscale by physical
420 barriers (cells are embedded in a complex matrix of polymers), subject to fluid motions
421 (Amin et al. 2012) and variable spatial clustering of bacteria and cell abundance
422 (Doucette 1995). By contrast, the “pure” quorum sensing framework arose from well-
423 controlled laboratory studies on clonal populations (Hense et al. 2007).

424

425 **Conclusions and perspectives**

426 The objective of this review was to shed light on quorum sensing communication in the
427 phycosphere of microalgae. Many reports have revealed the presence of this
428 communication system in bacteria isolated from phytoplankton blooms or associated
429 with microalgae cultures. It appears from the literature that quorum sensing is a
430 common type of bacterial communication in the phycosphere. It is performed by diverse
431 bacteria within the phycosphere of a large diversity of microalgae. The metabolites
432 involved seem dominated by long-chain AHLs, however some reports mention the
433 potential importance of AI-2. The emerging picture greatly needs further research to
434 evaluate the extent of bacterial and chemical diversity involved in quorum sensing
435 processes within the phycosphere. Little is known about the potential involvement of
436 diverse types of AHLs and other quorum sensing molecules, including gamma-
437 butyrolactones, quinolones, and others.

438 Already, very diverse functions have been identified in the phycosphere involving
439 quorum sensing. These functions include biofilm formation and nutrient acquisition, as
440 well as the regulation of algacide production, antibiotic synthesis and cell shape.
441 Probably, this list remains far from the real extent of biological functions governed by
442 quorum sensing within the phycosphere. Recent advances coupling genomics with
443 metabolomics approaches will give interesting new insights in this field of research. A
444 promising experimental approach to answer these questions is simultaneous tracking of
445 transcriptomic and metabolomic variations within model organisms grown in co-
446 culture. This method enables the characterization of metabolic pathways affected by
447 quorum sensing expression in both algae and bacteria. Furthermore, the large scale

448 impacts of quorum sensing in the phycosphere remain very poorly characterized,
449 particularly in terms of biogeochemistry and evolution.

450 This review also described the importance that quorum quenching has in the
451 phycosphere of microalgae. Many studies revealed the emission of quorum quenching
452 molecules either by algae or diverse bacteria in the phycosphere. These molecules have
453 important biotechnological potential, as they are able to control growth and virulence of
454 microorganisms. Again, more research is needed to characterize new molecules with
455 such activities, and to better characterize their mechanism of action.

456

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460

461 **FIGURE LEGENDS**

462 Figure 1 to 7: Major compounds cited in the text

463 Figure 8: Synthetic view of quorum sensing processes in the phycosphere of
464 phytoplankton

465 Figure 9: Synthetic view of quorum quenching processes in the phycosphere of
466 phytoplankton

467

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