

# Quorum sensing and quorum quenching in the phycosphere of phytoplankton: a case of chemical interactions in ecology

Jean-Luc Rolland, Didier Stien, Sophie Sanchez-Ferandin, Raphaël Lami

► **To cite this version:**

Jean-Luc Rolland, Didier Stien, Sophie Sanchez-Ferandin, Raphaël Lami. Quorum sensing and quorum quenching in the phycosphere of phytoplankton: a case of chemical interactions in ecology. *Journal of Chemical Ecology*, Springer Verlag, 2016, 42 (12), pp.1201-1211. 10.1007/s10886-016-0791-y . hal-01472696

**HAL Id: hal-01472696**

**<https://hal-sde.archives-ouvertes.fr/hal-01472696>**

Submitted on 27 Aug 2020

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

5 JEAN LUC ROLLAND<sup>1</sup>, DIDIER STIEN<sup>2,3</sup>,  
6 SOPHIE SANCHEZ FERANDIN<sup>4,5</sup>, RAPHAËL LAMI<sup>2,3,\*</sup>  
7

8 <sup>1</sup>*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 <sup>2</sup>*UPMC University Paris 06, USR3579, LBBM, Observatoire Océanologique,*  
13 *66650 BANYULS SUR MER, France*

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

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

18 <sup>5</sup>*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

22 Review, revision of MS (JOCE-D-16-00049) submitted to *Journal of Chemical Ecology*

23 The authors declare no conflict of interest  
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 2µm, around algae varying in between 2 and 200µm  
57 (Sieburth et al. 1978). The phycosphere supports bacteria in higher concentrations than  
58 in the water column. For example, the concentration of  $8.2 \times 10^8$  to  $2.6 \times 10^{11}$  bacteria ml<sup>-1</sup>  
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<sup>-1</sup> 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 (C<sub>4</sub> to C<sub>18</sub>) 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  $\gamma$ -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 *Gloeothecae* 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- $\gamma$ -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

#### 457 **ACKNOWLEDGMENTS**

458 We thank the CNRS for funding this research (grant EC2CO-ROSEOCOM) and Sheree Yau  
459 for her help in English grammar and spelling.

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

#### 468 **BIBLIOGRAPHY**

469 Acar M, Mettetal JT, van Oudenaarden A (2008) Stochastic switching as a survival  
470 strategy in fluctuating environments. *Nat Genet* 40(4):471-475

471 Alavi M, Miller T, Erlandson K, Schneider R, Belas R (2001) Bacterial community  
472 associated with *Pfiesteria*-like dinoflagellate cultures. *Environ Microbiol*  
473 3(6):380-396

474 Amin SA, Parker MS, Armbrust EV (2012) Interactions between diatoms and bacteria.  
475 *Microbiol Mol Biol Rev* 76(3):667-684

476 Andersen JB, Heydorn A, Hentzer M, Eberl L, Geisenberger O, Christensen BB, Molin S,  
477 Givskov M (2001) gfp-based N-acyl homoserine-lactone sensor systems for  
478 detection of bacterial communication. *Appl Environ Microbiol* 67(2):575-585

479 Bachofen R, Schenk A (1998) Quorum sensing autoinducers: do they play a role in  
480 natural microbial habitats? *Microbiol Res* 153(1):61-63

481 Bainton NJ, Stead P, Chhabra SR, Bycroft BW, Salmond GP, Stewart GS, Williams P (1992)  
482 N-(3-oxohexanoyl)-L-homoserine lactone regulates carbapenem antibiotic  
483 production in *Erwinia carotovora*. *Biochem J* 288(3):997-1004

484 Bell W, Mitchell R (1972) Chemotactic and growth responses of marine bacteria to algal  
485 extracellular pre-activated products. *Biol Bull* 143(2):265-277

486 Berger M, Neumann A, Schulz S, Simon M, Brinkhoff T (2011) Tropodithietic acid  
487 production in *Phaeobacter gallaeciensis* is regulated by N-acyl homoserine  
488 lactone-mediated quorum sensing. *J Bacteriol* 193(23):6576-6585

489 Biebl H, Allgaier M, Tindall BJ, Koblizek M, Lunsdorf H, Pukall R, Wagner-Dobler I (2005)  
490 *Dinoroseobacter shibae* gen. nov., sp. nov., a new aerobic phototrophic bacterium  
491 isolated from dinoflagellates. *Int J Syst Evol Microbiol* 55(3):1089-1096

492 Borchardt SA, Allain EJ, Michels JJ, Stearns GW, Kelly RF, McCoy WF (2001) Reaction of  
493 acylated homoserine lactone bacterial signaling molecules with oxidized halogen  
494 antimicrobials. *Appl Environ Microbiol* 67(7):3174-3179

495 Brinkhoff T, Bach G, Heidorn T, Liang L, Schlingloff A, Simon M (2004) Antibiotic  
496 production by a *Roseobacter* clade-affiliated species from the German Wadden  
497 Sea and its antagonistic effects on indigenous isolates. *Appl Environ Microbiol*  
498 70(4):2560-2565

499 Bruhn JB, Nielsen KF, Hjelm M, Hansen M, Bresciani J, Schulz S, Gram L (2005) Ecology,  
500 inhibitory activity, and morphogenesis of a marine antagonistic bacterium  
501 belonging to the *Roseobacter* clade. *Appl Environ Microbiol* 71(11):7263-7270

502 Buchan A, LeCleir GR, Gulvik CA, Gonzalez JM (2014) Master recyclers: features and  
503 functions of bacteria associated with phytoplankton blooms. *Nat Rev Microbiol*  
504 12(10):686-698

505 Chen X, Schauder S, Potier N, Van Dorsselaer A, Pelczer I, Bassler BL, Hughson FM  
506 (2002) Structural identification of a bacterial quorum-sensing signal containing  
507 boron. *Nature* 415(6871):545-549

508 Choi H, Mascuch SJ, Villa FA, Byrum T, Teasdale ME, Smith JE, Preskitt LB, Rowley DC,  
509 Gerwick L, Gerwick WH (2012) Honaucins A-C, potent inhibitors of inflammation  
510 and bacterial quorum sensing: synthetic derivatives and structure-activity  
511 relationships. *Chem Biol* 19(5):589-598

512 Christie PJ, Atmakuri K, Krishnamoorthy V, Jakubowski S, Cascales E (2005) Biogenesis,  
513 architecture, and function of bacterial type IV secretion systems. *Annu Rev*  
514 *Microbiol* 59:451-485

515 Cornforth DM, Popat R, McNally L, Gurney J, Scott-Phillips TC, Ivens A, Diggle SP, Brown  
516 SP (2014) Combinatorial quorum sensing allows bacteria to resolve their social  
517 and physical environment. *Proc Natl Acad Sci U S A* 111(11):4280-4284

518 Darch SE, West SA, Winzer K, Diggle SP (2012) Density-dependent fitness benefits in  
519 quorum-sensing bacterial populations. *Proc Natl Acad Sci U S A* 109(21):8259-  
520 8263

521 Davies DG, Parsek MR, Pearson JP, Iglewski BH, Costerton JW, Greenberg EP (1998) The  
522 involvement of cell-to-cell signals in the development of a bacterial biofilm.  
523 *Science* 280(5361):295-298

524 Decho AW, Visscher PT, Ferry J, Kawaguchi T, He L, Przekop KM, Norman RS, Reid RP  
525 (2009) Autoinducers extracted from microbial mats reveal a surprising diversity  
526 of N - acylhomoserine lactones (AHLs) and abundance changes that may relate to  
527 diel pH. *Environ Microbiol* 11(2):409-420

528 Defoirdt T, Sorgeloos P, Bossier P (2011) Alternatives to antibiotics for the control of  
529 bacterial disease in aquaculture. *Curr Opin Microbiol* 14(3):251-258

530 Delong EF, Franks DG, Alldredge AL (1993) Phylogenetic diversity of aggregate-attached  
531 vs free-living marine bacterial assemblages. *Limnol Oceanogr* 38(5):924-934

532 Dicke M, Sabelis MW (1988) Infochemical terminology: based on cost-benefit analysis  
533 rather than origin of compounds? *Funct Ecol*:131-139

534 Diggle SP, Crusz SA, Cámara M (2007) Quorum sensing. *Curr Biol* 17(21):R907-R910

535 Doberva M, Sanchez-Ferandin S, Toulza E, Lebaron P, Lami R (2015) Diversity of  
536 quorum sensing autoinducer synthases in the Global Ocean Sampling  
537 metagenomic database. *Aquat Microb Ecol* 74(2):107-119

538 Dobretsov S, Abed RMM, Al Maskari SMS, Al Sabahi JN, Victor R (2010) Cyanobacterial  
539 mats from hot springs produce antimicrobial compounds and quorum-sensing  
540 inhibitors under natural conditions. *J Appl Phycol* 23(6):983-993

541 Dobretsov S, Teplitski M, Bayer M, Gunasekera S, Proksch P, Paul VJ (2011) Inhibition of  
542 marine biofouling by bacterial quorum sensing inhibitors. *Biofouling* 27(8):893-  
543 905

544 Dong YH, Wang LH, Xu JL, Zhang HB, Zhang XF, Zhang LH (2001) Quenching quorum-  
545 sensing-dependent bacterial infection by an N-acyl homoserine lactonase. *Nature*  
546 411(6839):813-817

547 Dong YH, Wang LY, Zhang LH (2007) Quorum-quenching microbial infections:  
548 mechanisms and implications. *Philos Trans R Soc Lond B Biol Sci*  
549 362(1483):1201-1211

550 Doucette GJ (1995) Interactions between bacteria and harmful algae: a review. *Nat*  
551 *Toxins* 3(2):65-74

552 Eberhard A, Burlingame AL, Eberhard C, Kenyon GL, Nealson KH, Oppenheimer NJ  
553 (1981) Structural identification of autoinducer of *Photobacterium fischeri*  
554 luciferase. *Biochemistry* 20(9):2444-2449

555 Fandino LB, Riemann L, Steward GF, Long RA, Azam F (2001) Variations in bacterial  
556 community structure during a dinoflagellate bloom analyzed by DGGE and 16S  
557 rDNA sequencing. *Aquat Microb Ecol* 23(2):119-130

558 Fuqua WC, Winans SC, Greenberg EP (1994) Quorum sensing in bacteria: the LuxR-LuxI  
559 family of cell density-responsive transcriptional regulators. *J Bacteriol*  
560 176(2):269-275

561 Gao MS, Teplitski M, Robinson JB, Bauer WD (2003) Production of substances by  
562 *Medicago truncatula* that affect bacterial quorum sensing. *Mol Plant Microbe*  
563 *Interact* 16(9):827-834



564 Geng H, Bruhn JB, Nielsen KF, Gram L, Belas R (2008) Genetic dissection of tropodithietic  
565 acid biosynthesis by marine roseobacters. *Appl Environ Microbiol* 74(5):1535-  
566 1545

567 Geng HF, Belas R (2010) Expression of tropodithietic acid biosynthesis is controlled by a  
568 novel autoinducer. *J Bacteriol* 192(17):4377-4387

569 Givskov M, de Nys R, Manefield M, Gram L, Maximilien R, Eberl L, Molin S, Steinberg PD,  
570 Kjelleberg S (1996) Eukaryotic interference with homoserine lactone-mediated  
571 prokaryotic signalling. *J Bacteriol* 178(22):6618-6622

572 González JM, Kiene RP, Moran MA (1999) Transformation of sulfur compounds by an  
573 abundant lineage of marine bacteria in the  $\alpha$ -subclass of the class proteobacteria.  
574 *Appl Environ Microbiol* 65(9):3810-3819

575 Gram L, Grossart HP, Schlingloff A, Kiorboe T (2002) Possible quorum sensing in marine  
576 snow bacteria: production of acylated homoserine lactones by *Roseobacter*  
577 strains isolated from marine snow. *Appl Environ Microbiol* 68(8):4111-4116

578 Greer EM, Aebischer D, Greer A, Bentley R (2008) Computational studies of the tropone  
579 natural products, thiotropocin, tropodithietic acid, and troposulfenin.  
580 Significance of thiocarbonyl-enol tautomerism. *J Org Chem* 73(1):280-283

581 Harvey EL, Deering RW, Rowley DC, El Gamal A, Schorn M, Moore BS, Johnson MD,  
582 Mincer TJ, Whalen KE (2016) A Bacterial quorum-sensing precursor induces  
583 mortality in the marine Coccolithophore, *Emiliania huxleyi*. *Front Microbiol* 7:59

584 Hasegawa Y, Martin JL, Giewat MW, Rooney-Varga JN (2007) Microbial community  
585 diversity in the phycosphere of natural populations of the toxic alga, *Alexandrium*  
586 *fundyense*. *Environ Microbiol* 9(12):3108-3121

587 Henke JM, Bassler BL (2004) Three parallel quorum-sensing systems regulate gene  
588 expression in *Vibrio harveyi*. *J Bacteriol* 186(20):6902-6914

589 Hense BA, Kuttler C, Müller J, Rothballer M, Hartmann A, Kreft J-U (2007) Does efficiency  
590 sensing unify diffusion and quorum sensing? *Nat Rev Microbiol* 5(3):230-239

591 Hmelo L, Van Mooy BAS (2009) Kinetic constraints on acylated homoserine lactone-  
592 based quorum sensing in marine environments. *Aquat Microb Ecol* 54(2):127-  
593 133

594 Hmelo LR, Mincer TJ, Van Mooy BA (2011) Possible influence of bacterial quorum  
595 sensing on the hydrolysis of sinking particulate organic carbon in marine  
596 environments. *Environ Microbiol Rep* 3(6):682-688

597 Holden MT, Ram Chhabra S, de Nys R, Stead P, Bainton NJ, Hill PJ, Manefield M, Kumar N,  
598 Labatte M, England D and others (1999) Quorum-sensing cross talk: isolation and  
599 chemical characterization of cyclic dipeptides from *Pseudomonas aeruginosa* and  
600 other gram-negative bacteria. *Mol Microbiol* 33(6):1254-1266

601 Jatt AN, Tang K, Liu J, Zhang Z, Zhang XH (2015) Quorum sensing in marine snow and its  
602 possible influence on production of extracellular hydrolytic enzymes in marine  
603 snow bacterium *Pantoea ananatis* B9. *FEMS Microbiol Ecol* 91(2):1-13

604 Johnson WM, Kido Soule MC, Kujawinski EB (2016) Evidence for quorum sensing and  
605 differential metabolite production by a marine bacterium in response to DMSP.  
606 *ISME J* doi 1751-7362/16

607 Kaufmann GF, Sartorio R, Lee SH, Rogers CJ, Meijler MM, Moss JA, Clapham B, Brogan AP,  
608 Dickerson TJ, Janda KD (2005) Revisiting quorum sensing: Discovery of  
609 additional chemical and biological functions for 3-oxo-N-acylhomoserine  
610 lactones. *Proc Natl Acad Sci U S A* 102(2):309-314

611 Keller L, Surette MG (2006) Communication in bacteria: an ecological and evolutionary  
612 perspective. *Nat Rev Microbiol* 4(4):249-258

613 Kim JS, Kim YH, Seo YW, Park S (2007) Quorum sensing inhibitors from the red alga,  
614 *Ahnfeltiopsis flabelliformis*. Biotechnol. Bioprocess 12(3):308-311

615 Kuo J-C, Chang Y-H, Chen T-Y, Chen Y-M (2014) Elucidation of anti-*Vibrio* factors  
616 associated with green alga *Picochlorum* sp. strain S1b. J Appl Phycol 27(1):257-  
617 265

618 Kwan JC, Meickle T, Ladwa D, Teplitski M, Paul V, Luesch H (2011) Lyngbyoic acid, a  
619 "tagged" fatty acid from a marine cyanobacterium, disrupts quorum sensing in  
620 *Pseudomonas aeruginosa*. Mol Biosyst 7(4):1205-1216

621 Labbate M, Zhu H, Thung L, Bandara R, Larsen MR, Willcox MDP, Givskov M, Rice SA,  
622 Kjelleberg S (2007) Quorum-sensing regulation of adhesion in *Serratia*  
623 *marcescens* MG1 is surface dependent. J Bacteriol 189(7):2702-2711

624 Lazdunski AM, Ventre I, Sturgis JN (2004) Regulatory circuits and communication in  
625 Gram-negative bacteria. Nat Rev Microbiol 2(7):581-592

626 McLean RJ, Whiteley M, Stickler DJ, Fuqua WC (1997) Evidence of autoinducer activity in  
627 naturally occurring biofilms. FEMS Microbiol Lett 154(2):259-263

628 Meyer JL, Gunasekera SP, Scott RM, Paul VJ, Teplitski M (2016) Microbiome shifts and  
629 the inhibition of quorum sensing by Black Band Disease cyanobacteria. ISME J  
630 10(5):1204-1216

631 Miller TR, Belas R (2006) Motility is involved in *Silicibacter* sp TM1040 interaction with  
632 dinoflagellates. Environ Microbiol 8(9):1648-1659

633 Moran MA, Kujawinski EB, Stubbins A, Fatland R, Aluwihare LI, Buchan A, Crump BC,  
634 Dorrestein PC, Dyhrman ST, Hess NJ and others (2016) Deciphering ocean carbon  
635 in a changing world. Proc Natl Acad Sci U S A 113(12):3143-3151

636 Nadell CD, Xavier JB, Levin SA, Foster KR (2008) The evolution of quorum sensing in  
637 bacterial biofilms. PLoS Biol 6(1):e14

638 Nakashima T, Miyazaki Y, Matsuyama Y, Muraoka W, Yamaguchi K, Oda T (2006)  
639 Producing mechanism of an algicidal compound against red tide phytoplankton  
640 in a marine bacterium gamma-proteobacterium. Appl Microbiol Biotechnol  
641 73(3):684-690

642 Natrah F, Kenmegne MM, Wiyoto W, Sorgeloos P, Bossier P, Defoirdt T (2011) Effects of  
643 micro-algae commonly used in aquaculture on acyl-homoserine lactone quorum  
644 sensing. Aquaculture 317(1):53-57

645 Nealson KH (1977) Autoinduction of bacterial luciferase. Occurrence, mechanism and  
646 significance. Arch Microbiol 112(1):73-79

647 Neumann A, Patzelt D, Wagner - Döbler I, Schulz S (2013) Identification of new N -  
648 acylhomoserine lactone signalling compounds of *Dinoroseobacter shibae* DFL -  
649 12T by overexpression of luxI genes. ChemBioChem 14(17):2355-2361

650 Newton RJ, Griffin LE, Bowles KM, Meile C, Gifford S, Givens CE, Howard EC, King E,  
651 Oakley CA, Reisch CR and others (2010) Genome characteristics of a generalist  
652 marine bacterial lineage. ISME J 4(6):784-798

653 Onaka H, Ando N, Nihira T, Yamada Y, Beppu T, Horinouchi S (1995) Cloning and  
654 characterization of the A-factor receptor gene from *Streptomyces griseus*. J  
655 Bacteriol 177(21):6083-6092

656 Paerl HW. 1982. Interactions with bacteria. In: Press UoC, editor. The biology of  
657 cyanobacteria. p 441-461.

658 Parsek MR, Greenberg EP (2005) Sociomicrobiology: the connections between quorum  
659 sensing and biofilms. Trends Microbiol 13(1):27-33

660 Patzelt D, Wang H, Buchholz I, Rohde M, Grobe L, Pradella S, Neumann A, Schulz S,  
661 Heyber S, Munch K and others (2013) You are what you talk: quorum sensing

662 induces individual morphologies and cell division modes in *Dinoroseobacter*  
663 *shibae*. ISME J 7(12):2274-2286

664 Paul C, Pohnert G (2011) Interactions of the algicidal bacterium *Kordia algicida* with  
665 diatoms: regulated protease excretion for specific algal lysis. PLoS One  
666 6(6):e21032

667 Pesci EC, Milbank JB, Pearson JP, McKnight S, Kende AS, Greenberg EP, Iglewski BH  
668 (1999) Quinolone signaling in the cell-to-cell communication system of  
669 *Pseudomonas aeruginosa*. Proc Natl Acad Sci U S A 96(20):11229-11234

670 Platt TG, Fuqua C (2010) What's in a name? The semantics of quorum sensing. Trends  
671 Microbiol 18(9):383-387

672 Popat R, Cornforth DM, McNally L, Brown SP (2015) Collective sensing and collective  
673 responses in quorum-sensing bacteria. J R Soc Interface 12:20140882

674 Porsby CH, Nielsen KF, Gram L (2008) *Phaeobacter* and *Ruegeria* species of the  
675 *Roseobacter* clade colonize separate niches in a Danish Turbot (*Scophthalmus*  
676 *maximus*)-rearing farm and antagonize *Vibrio anguillarum* under different  
677 growth conditions. Appl Environ Microbiol 74(23):7356-7364

678 Prol Garcia M, D'Alvise P, Rygaard A, Gram L (2014) Biofilm formation is not a  
679 prerequisite for production of the antibacterial compound tropodithietic acid in  
680 *Phaeobacter inhibens* DSM17395. Journal of applied microbiology 117(6):1592-  
681 1600

682 Rajamani S, Bauer WD, Robinson JB, Farrow JM, 3rd, Pesci EC, Teplitski M, Gao M, Sayre  
683 RT, Phillips DA (2008) The vitamin riboflavin and its derivative lumichrome  
684 activate the LasR bacterial quorum-sensing receptor. Mol Plant Microbe Interact  
685 21(9):1184-1192

686 Rao D, Webb JS, Holmström C, Case R, Low A, Steinberg P, Kjelleberg S (2007) Low  
687 densities of epiphytic bacteria from the marine alga *Ulva australis* inhibit  
688 settlement of fouling organisms. *Applied and environmental microbiology*  
689 73(24):7844-7852

690 Rao D, Webb JS, Kjelleberg S (2006) Microbial colonization and competition on the  
691 marine alga *Ulva australis*. *Appl Environ Microbiol* 72(8):5547-5555

692 Rasmussen TB, Manefield M, Andersen JB, Eberl L, Anthoni U, Christophersen C,  
693 Steinberg P, Kjelleberg S, Givskov M (2000) How *Delisea pulchra* furanones affect  
694 quorum sensing and swarming motility in *Serratia liquefaciens* MG1.  
695 *Microbiology* 146(12):3237-3244

696 Redfield RJ (2002) Is quorum sensing a side effect of diffusion sensing? *Trends Microbiol*  
697 10(8):365-370

698 Rivas MO, Vargas P, Riquelme CE (2010) Interactions of *Botryococcus braunii* cultures  
699 with bacterial biofilms. *Microb Ecol* 60(3):628-635

700 Romero M, Diggle SP, Heeb S, Camara M, Otero A (2008) Quorum quenching activity in  
701 *Anabaena* sp. PCC 7120: identification of AiiC, a novel AHL-acylase. *FEMS*  
702 *Microbiol Lett* 280(1):73-80

703 Romero M, Martin-Cuadrado AB, Roca-Rivada A, Cabello AM, Otero A (2011) Quorum  
704 quenching in cultivable bacteria from dense marine coastal microbial  
705 communities. *FEMS Microbiol Ecol* 75(2):205-217

706 Rooney-Varga JN, Giewat MW, Savin MC, Sood S, LeGresley M, Martin JL (2005) Links  
707 between phytoplankton and bacterial community dynamics in a coastal marine  
708 environment. *Microbial Ecology* 49(1):163-175

709 Rosenberg E, Keller KH, Dworkin M (1977) Cell density-dependent growth of  
710 *Myxococcus xanthus* on casein. *J Bacteriol* 129(2):770-777

711 Sapp M, Schwaderer AS, Wiltshire KH, Hoppe HG, Gerdts G, Wichels A (2007) Species-  
712 specific bacterial communities in the phycosphere of microalgae? *Microb Ecol*  
713 53(4):683-699

714 Schaefer AL, Greenberg EP, Oliver CM, Oda Y, Huang JJ, Bittan-Banin G, Peres CM,  
715 Schmidt S, Juhaszova K, Sufrin JR and others (2008) A new class of homoserine  
716 lactone quorum-sensing signals. *Nature* 454(7204):595-599

717 Schertzer JW, Boulette ML, Whiteley M (2009) More than a signal: non-signaling  
718 properties of quorum sensing molecules. *Trends Microbiol* 17(5):189-195

719 Schulz S (2014) A New Bacterial Chemical Signal: Mapping the Chemical Space Used for  
720 Communication. *ChemBioChem* 15(4):498-500

721 Seyedsayamdost MR, Carr G, Kolter R, Clardy J (2011a) Roseobacticides: small molecule  
722 modulators of an algal-bacterial symbiosis. *J Am Chem Soc* 133(45):18343-18349

723 Seyedsayamdost MR, Case RJ, Kolter R, Clardy J (2011b) The Jekyll-and-Hyde chemistry  
724 of *Phaeobacter gallaeciensis*. *Nat Chem* 3(4):331-335

725 Sharif DI, Gallon J, Smith CJ, Dudley E (2008) Quorum sensing in Cyanobacteria: N-  
726 octanoyl-homoserine lactone release and response, by the epilithic colonial  
727 cyanobacterium *Gloeotheca* PCC6909. *ISME J* 2(12):1171-1182

728 Sheridan CC, Steinberg DK, Kling GW (2002) The microbial and metazoan community  
729 associated with colonies of *Trichodesmium* spp : a quantitative survey. *J Plankton*  
730 *Res* 24(9):913-922

731 Sieburth JM, Smetacek V, Lenz J (1978) Pelagic ecosystem structure: heterotrophic  
732 compartments of the plankton and their relationship to plankton size fractions.  
733 *Limnol Oceanogr* 23(6):1256-1263

734 Singh RP (2015) Attenuation of quorum sensing-mediated virulence in Gram-negative  
735 pathogenic bacteria: implications for the post-antibiotic era. *MedChemComm*  
736 6(2):259-272

737 Skerratt JH, Bowman JP, Hallegraef G, James S, Nichols PD (2002) Algicidal bacteria  
738 associated with blooms of a toxic dinoflagellate in a temperate Australian  
739 estuary. *Mar Ecol Prog Ser* 244:1-15

740 Slightom RN, Buchan A (2009) Surface colonization by marine roseobacters: integrating  
741 genotype and phenotype. *Appl Environ Microbiol* 75(19):6027-6037

742 Smith RS, Iglewski BH (2003) *P. aeruginosa* quorum-sensing systems and virulence. *Curr*  
743 *Opin Microbiol* 6(1):56-60

744 Sohn JH, Lee JH, Yi H, Chun J, Bae KS, Ahn TY, Kim SJ (2004) *Kordia algicida* gen. nov., sp.  
745 nov., an algicidal bacterium isolated from red tide. *Int J Syst Evol Microbiol*  
746 54(3):675-680

747 Teplitski M, Chen H, Rajamani S, Gao M, Merighi M, Sayre RT, Robinson JB, Rolfe BG,  
748 Bauer WD (2004) *Chlamydomonas reinhardtii* secretes compounds that mimic  
749 bacterial signals and interfere with quorum sensing regulation in bacteria. *Plant*  
750 *Physiol* 134(1):137-146

751 Thiel V, Brinkhoff T, Dickschat JS, Wickel S, Grunenberg J, Wagner-Dobler I, Simon M,  
752 Schulz S (2010) Identification and biosynthesis of tropone derivatives and sulfur  
753 volatiles produced by bacteria of the marine Roseobacter clade. *Org Biomol Chem*  
754 8(1):234-246

755 Thole S, Kalhoefer D, Voget S, Berger M, Engelhardt T, Liesegang H, Wollherr A,  
756 Kjelleberg S, Daniel R, Simon M and others (2012) *Phaeobacter gallaeciensis*  
757 genomes from globally opposite locations reveal high similarity of adaptation to  
758 surface life. *ISME J* 6(12):2229-2244



759 Tuomainen J, Hietanen S, Kuparinen J, Martikainen PJ, Servomaa K (2006) Community  
760 structure of the bacteria associated with *Nodularia* sp. (Cyanobacteria)  
761 aggregates in the Baltic Sea. *Microb Ecol* 52(3):513-522

762 Van Mooy BA, Hmelo LR, Sofen LE, Campagna SR, May AL, Dyhrman ST, Heithoff A, Webb  
763 EA, Momper L, Mincer TJ (2012) Quorum sensing control of phosphorus  
764 acquisition in *Trichodesmium consortia*. *ISME J* 6(2):422-429

765 Wagner-Dobler I, Thiel V, Eberl L, Allgaier M, Bodor A, Meyer S, Ebner S, Hennig A, Pukall  
766 R, Schulz S (2005) Discovery of complex mixtures of novel long-chain quorum  
767 sensing signals in free-living and host-associated marine alphaproteobacteria.  
768 *ChemBioChem* 6(12):2195-206

769 Waters CM, Bassler BL (2005) Quorum sensing: cell-to-cell communication in bacteria.  
770 *Annu Rev Cell Dev Biol* 21:319-346

771 West SA, Winzer K, Gardner A, Diggle SP (2012) Quorum sensing and the confusion  
772 about diffusion. *Trends Microbiol* 20(12):586-594

773 Wood DW, Pierson LS (1996) The *phzI* gene of *Pseudomonas aureofaciens* 30-84 is  
774 responsible for the production of a diffusible signal required for phenazine  
775 antibiotic production. *Gene* 168(1):49-53

776 Yates EA, Philipp B, Buckley C, Atkinson S, Chhabra SR, Sockett RE, Goldner M, Dessaux  
777 Y, Camara M, Smith H and others (2002) N-acylhomoserine lactones undergo  
778 lactonolysis in a pH-, temperature-, and acyl chain length-dependent manner  
779 during growth of *Yersinia pseudotuberculosis* and *Pseudomonas aeruginosa*. *Infect*  
780 *Immun* 70(10):5635-5646

781 Zhai C, Zhang P, Shen F, Zhou C, Liu C (2012) Does *Microcystis aeruginosa* have quorum  
782 sensing? *FEMS Microbiol Lett* 336(1):38-44

783 Zhang HB, Wang LH, Zhang LH (2002) Genetic control of quorum-sensing signal  
784 turnover in *Agrobacterium tumefaciens*. Proc Natl Acad Sci U S A 99(7):4638-  
785 4643  
786