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# 1 **Microbial small-talk: Does quorum sensing play a** 2 **role in beer fermentation?**

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30 **Keywords**

31 quorum sensing; cell-to-cell signaling; sociomicrobiology; fermentation; yeast; 2-phenylethanol; tryptophol;  
32 tyrosol

## 33 **ABSTRACT**

34 Inter- and intraspecies communication between microorganisms is recognized to play an influential role  
35 across many relevant applications, such as bioethanol production, food preservation, bioremediation, wastewater  
36 treatment, and in the clinical environment. At high population densities, the accumulation of small hormone-like  
37 molecules in the extracellular environment has been demonstrated to play a role in transcriptional regulation of  
38 both prokaryotic and eukaryotic microorganisms. This mechanism enables independent cells, known as the  
39 quorum, to trigger coordinated, community-wide gene expression, increasing their prospect of survival in crowded  
40 and ever-changing conditions. This density-dependent phenomenon has been shown to influence community-wide  
41 behavioral factors, such as biofilm formation, virulence factor secretion, social motility, cellular adhesion,  
42 autolysis, secondary metabolite production, and nutrient uptake across a range of organisms. In *Saccharomyces*  
43 *cerevisiae*, aromatic alcohols 2-phenylethanol, tryptophol, and tyrosol have already been demonstrated to act as  
44 quorum sensing molecules under certain environmental conditions, such as low-nitrogen availability. This review  
45 discusses the underlying mechanisms of quorum sensing, with an emphasis on brewer's yeast, while offering  
46 insights into how cell density-dependent signaling could influence the commercial brewing industry.

## 47 **INTRODUCTION**

48 Microorganisms do not live a cloistered, solitary self-reliant existence. Instead, these microscopic  
49 lifeforms cohabitate, establish complex communities, and regularly interact with each other across many different  
50 environments (Allen et al., 2019; Butler & O'Dwyer, 2018; Florenza, Tamminen, & Bertilsson, 2019; Fröls, 2013;  
51 Kent & Triplett, 2002; Laureys, Britton, & De Clippeleer, 2020; Little, Robinson, Peterson, Raffa, & Handelsman,  
52 2008; Montgomery, Charlesworth, LeBard, Visscher, & Burns, 2013; Mosel, Dumitru, Hornby, Atkin, &  
53 Nickerson, 2005; Niemann et al., 2006; Pereira, Cabezas, Etchebehere, Chernicharo, & de Araújo, 2017; Rankin,  
54 Gibson, Franzmann, & Burton, 1996; Shade, McManus, & Handelsman, 2013; Shank, 2018; Wood, 2019;  
55 Zengler & Zaramela, 2018). As a means of survival, many microorganisms have evolved the capacity to  
56 communicate via the exchange, and detection of molecular cues referred to as autoinducers (AI) or quorum sensing  
57 molecules (QSM) (Fuqua et al., 1994). Although diversity exists between the quorum sensing mechanisms  
58 discovered in archaea, bacteria, and fungi, particularly the chemical identity of the signaling molecule and the  
59 behavior regulated, every quorum-sensing system (QSS) requires the molecular machinery to synthesize, sense,  
60 and react to secreted communication molecules (Albuquerque & Casadevall, 2012; Atkinson & Williams, 2009;  
61 Avbelj, Zupan, Kranjc, & Raspor, 2015; Bassler, 2002; March & Bentley, 2004; Montgomery et al., 2013; Padder,  
62 Prasad, & Shah, 2018; Pour, 2018; Sifri, 2008; Waters & Bassler, 2005). As a population of "quorum competent"  
63 microorganisms arises, a proportional increase in these intercellular signaling molecules (ISMs) occurs, and once  
64 the "quorate" threshold is achieved, this results in the quorum-associated transcriptional control of specific target  
65 genes (Albuquerque & Casadevall, 2012; Avbelj et al., 2015; De Sordi & Mühlischlegel, 2009; Hense & Schuster,  
66 2015; Hogan, 2006a, 2006b; Padder et al., 2018; Schuster, Lostroh, Ogi, & Greenberg, 2003; Sifri, 2008; Verbeke  
67 et al., 2017). At the transcriptome level, the coordinated response to a quorum-sensing signal can be substantial,  
68 for instance in the bacterium *Pseudomonas aeruginosa* hundreds of genes, representing more than 5% of the entire  
69 genome, were identified as either quorum-induced or quorum-repressed (Schuster et al., 2003; Schuster, Sexton,  
70 & Hense, 2017; Wagner, Bushnell, Passador, Brooks, & Iglewski, 2014). Although, there is evidence of signal-  
71 blind organisms synthesizing, but that are incapable of responding to, QSMs in order to manipulate the behavior  
72 of neighboring cells, and examples of signal eavesdropping, where nearby cells will detect, and respond to, QSMs

73 not produced by their own genotype (Katzianer, Wang, Carey, & Zhu, 2015; Miller & Bassler, 2001; Özkaya,  
74 Xavier, Dionisio, & Balbontín, 2017; Wellington & Greenberg, 2019).

75 It is now widely accepted that quorum-sensing (QS) mechanisms promote population density-dependent  
76 advantages that result from a synchronized cooperative behavioral response, these include biofilm regulation;  
77 bioluminescence; sporulation; competence; fruiting body development; social motility; cellular adhesion;  
78 population density control; virulence; exopolysaccharide and antibiotic production; secondary metabolite  
79 production; stress adaptation mechanisms; cell morphology and dimorphism; spatially heterogeneous behavior,  
80 and modifications to nutrient uptake amongst others, which enable them to benefit from collective cooperative  
81 behaviors, often these can be in the form of secreted products, such as exopolysaccharide or extracellular enzymes,  
82 occasionally referred to as "public goods" (Albuquerque & Casadevall, 2012; An et al., 2014; Darch et al., 2012;  
83 Diggle, Crusz, et al., 2007; Diggle, Gardner, et al., 2007; Gómez-Gil et al., 2019; Hense et al., 2012; Hornby et  
84 al., 2001; Labbate et al., 2007; Miller & Bassler, 2001; Mosel et al., 2005; Nealson & Hastings, 2006; Nickerson  
85 et al., 2006; Padder et al., 2018; Pai et al., 2012; Pena et al., 2019; Ramage et al., 2002; Schuster et al., 2017;  
86 Waters & Bassler, 2005; Westwater et al., 2005; Williams et al., 2007; Wongsuk et al., 2016). These diffusible  
87 extracellular products provide an advantage to cells co-existing at higher cell density, but little advantage those in  
88 less dense populations. However, recent studies have demonstrated several non-diffusible cell-bound products,  
89 referred to as "private goods" , such as cytosolic- or surface-bound proteins and metabolites, to also be under QS  
90 control, where the beneficial advantage may be associated with "private goods" is either directly or indirectly  
91 involved in the cooperative behavior (Schuster et al., 2017). Furthermore, it is not yet apparent why cellularly-  
92 bound products are subject to QS regulation, as it was previously assumed, due to their intracellular or membrane-  
93 bound nature, that the benefits associated with "private goods" were limited to the individual cell.

94 Although defined as a density-dependent behavior, it should not be generally assumed that the biological  
95 functions of QSMs are exclusively restricted to provoking synchronized behavioral adaptation; conversely, some  
96 researchers have proposed a less socially motivated explanation, primarily that AI may be used by cells as a means  
97 to assess diffusion efficacy within the local environment (Redfield, 2002; West, Winzer, Gardner, & Diggle, 2012).  
98 Presumably, diminished diffusion rates, as assessed by increasing AI concentrations, may be advantageous for the  
99 transcriptional expression or repression of particular gene products. Although some experimental evidence  
100 supports this hypothesis, the recognition of diffusion sensing as the generalized model for small molecule-based  
101 signaling remains to be widely accepted.

102 Regardless, whether present in nature or a synthetic environment, microorganisms are in constant  
103 interaction with themselves (autoinduction) and each other. In principle, commercially fermented products, like  
104 beer, are defined by the metabolic activity of a dense population that is likely influenced by the chemical 'small-  
105 talk' occurring between these organisms. However, while the metabolic activity related to beer fermentations have  
106 been exhaustively investigated for more than two centuries (Barnett, 1998), the impact of density-dependent  
107 signaling within the commercial brewing ecosystem remains to be explored. As it is highly plausible that these  
108 underlying social mechanisms influence the brewing fermentation and resultant product; this review presents the  
109 current understanding of quorum sensing, particularly in the brewer's yeast *Saccharomyces cerevisiae*, while also  
110 offering insights on how density-dependent signaling could unknowingly impact the commercial brewing process.

## 111 **DEFINING QUORUM SENSING MOLECULES**

112 A fundamental problem when studying quorum sensing is the lack of consensus on what defines a QSM  
113 explicitly. As a wide-range of microbial metabolites can be found within commercial fermentations, at least in  
114 principle, each of these metabolites could potentially act as a QSM. Previously, a few groups have proposed  
115 minimum criteria to designate a specific chemical compound as a QSM. These minimal criteria were recently  
116 summarized by (Winters, Arneborg, Appels, & Howell, 2019); however, they also offered a more restrictive  
117 definition, which proposes that QSM, as a sub-set of ISM, must additionally meet the essential criteria for  
118 classification as an ISM. As proposed by Winters and colleagues (2019) and summarized in Table 1, their criteria  
119 would require that: **I)** the compound be known, secreted, and accumulate in the external environment in a manner  
120 where it is accessible to other cells (Albuquerque & Casadevall, 2012; Monds & O’Toole, 2014), **II)** specific  
121 receptors and signaling cascade mechanisms that detect and respond to the compound should be present and  
122 identified (Monds & O’Toole, 2014; Winzer, Hardie, & Williams, 2002), **III)** the purified compound reproduces  
123 the biological response at concentrations found in the experimental conditions (Monds & O’Toole, 2014), **IV)** the  
124 biological response to the compound maximizes the fitness of the community involved in signaling (March &  
125 Bentley, 2004; Monds & O’Toole, 2014), **V)** the compound must be synthesized in a concentration proportional  
126 to cell density in a diffusion-limited environment, and **VI)** a concerted biological response, other than  
127 detoxification or metabolism of the compound itself, is induced once quorate threshold is reached..

128 Nevertheless, debate still exists on specific criteria needed to classify QSM, mainly whether a compound  
129 must be created exclusively for intercellular signaling (IS), or if a compound may also serve a coexisting metabolic  
130 function (Monds & O’Toole, 2014). Monds & O’Toole (2014) advocated that metabolites are well-suited to be  
131 ISMs, and consequently, QSMs difunctionality is energetically favorable for the organism. Although this has been  
132 less thoroughly investigated in fungal systems, as far as the authors are aware, several studies support the  
133 suggestion that metabolites, such as antibiotics, serve as QSMs in bacteria without violating the VI criterion  
134 (Davies, Spiegelman, & Yim, 2006; Morcia et al., 2017; Struss, Pasini, Flomenhoft, Shashidhar, & Daunert, 2012;  
135 Yim, Wang, & Davies, 2007). Certain antibiotics, like erythromycin and rifampin, were shown to even activate  
136 transcription at sub-MIC concentrations, despite being well-recognized inhibitors of translation and transcription,  
137 respectively (Goh et al., 2002). The divergent effect of antibiotics (hormesis), presenting both a stimulatory and  
138 inhibitory effects on transcription, at low and high doses, respectively has been demonstrated in numerous studies  
139 (Andersson & Hughes, 2014; Davies et al., 2006; Hoffman et al., 2005; Laureti, Matic, & Gutierrez, 2013; Patel  
140 et al., 2006; Rachid, Ohlsen, Witte, Hacker, & Ziebuhr, 2000; Yim et al., 2007).

141 Therefore, the authors concur with the restrictive definition and criteria established proposed by Winters  
142 and colleagues (2019) for QSMs, and do not support the addition of criteria that would restrict the definition to  
143 compounds used exclusively for IS, as substantial evidence exists for a difunctional role of QSMs as metabolites  
144 in bacteria.

## 145 **QUORUM SENSING MECHANISMS**

146 Quorum sensing, as a term, was initially introduced by Fuqua et al., (1994), and can be best described as  
147 a subset of IS chemical cues that facilitate cell-density dependant gene expression after a critical concentration of  
148 the signaling compound has been achieved in the external environment (Begley et al., 2008; Miller & Bassler,  
149 2001; Winzer et al., 2002). Every quorum sensing system can be separated into four distinct phases: **I)** synthesis  
150 of autoinducer QS molecules by the cell; **II)** release of the QS molecules, either actively or passively, into the

151 extracellular environment; **III**) recognition of the QS molecules by a cognate receptor-regulator, and **(IV)** initiating  
152 changes in gene regulation, either induction or repression, in receiver cells once the threshold concentration is  
153 exceeded (Engebrecht et al., 1983; Sifri, 2008). Consequently, QS provides a significant evolutionary advantage  
154 by allowing microbial populations to adapt to swift environmental changes. Miller and Bassler (2001) proposed  
155 that QS could be a neo-Darwinian mechanism of evolution that contributed to the emergence of multicellular  
156 organisms roughly 600 million years ago.

157 The diversity of QSMs within microorganisms are wide-ranging in terms of chemical structure and  
158 function. Presently, four primary classes of QSMs are widely recognized; these include lactones, alcohols,  
159 sesquiterpenes, and peptides (Barriuso, Hogan, Keshavarz, & Martínez, 2018; Winters et al., 2019). However, the  
160 recent discovery of QS mechanisms in yeast and dimorphic fungi, employing amino acid-derived aromatic  
161 alcohols, have been proposed as an entirely new class of QSMs (Winters et al., 2019).

## 162 **QUORUM SENSING MECHANISMS IN BACTERIA**

163 In bacteria, quorum-sensing systems can be divided into four primary classes based on autoinducer type  
164 and the associated cellular detection machinery; **I**) LuxI/R-type, **II**) autoinducer oligopeptide (AIP) transcription  
165 factor binding, **III**) Gram-positive two-component and **IV**) Gram-negative two-component circuits (Miller &  
166 Bassler, 2001; Rutherford & Bassler, 2012). Most quorum sensing gene regulatory systems existing in Gram-  
167 negative bacteria are regulated via the binding of acylated homoserine lactone molecules (AHL), a LuxI-type  
168 synthase that catalyzes a reaction between S-adenosylmethionine (SAM) and an acyl carrier protein (ACP), or an  
169 alternate molecule similarly dependant on SAM, to a cognate cytosolic LuxR-type transcription factor that binds  
170 DNA and regulates differential gene expression (Ball et al., 2017; Miller & Bassler, 2001; Rutherford & Bassler,  
171 2012; Yong & Zhong, 2012). It is noteworthy to mention that AHLs are not exclusively manufactured by LuxI-  
172 type proteins and that AHLs of dissimilar bacteria possess side chains of varying lengths, from C4 – C18, and may  
173 include side-chain decorations like carbonyl and hydroxy moieties (Fuqua et al., 2001; Ng & Bassler, 2009).  
174 Structural diversity among AHLs may aid in intraspecies-specific communication via interaction with high-  
175 specificity cognate LuxR proteins, which are only stabilized to fold, bind DNA, and modulate transcription once  
176 bound to QSMs (Engebrecht et al., 1983; Engebrecht & Silverman, 1984; Stevens et al., 1995; Zhu & Winans,  
177 1999, 2001). However, when not bound to QSMs, LuxR-type proteins are undergo swift degradation, likely to  
178 inhibit bacteria from side-stepping their own innate QS systems (Rutherford & Bassler, 2012).

179 Autoinducer oligopeptides (AIPs), or quorum sensing peptides (QSPs), are the signaling molecules, often  
180 post-translational modified, used by Gram-positive bacteria for cell-to-cell communication (Ansaldi, Marolt,  
181 Stebe, Mandic-Mulec, & Dubnau, 2002; Otto, Süßmuth, Jung, & Götz, 1998; Rajput, Gupta, & Kumar, 2015). In  
182 these QS systems, precursor AIPs (pro-AIPs) are secreted, processed by extracellular proteases, and afterwards  
183 imported into the cell where their direct binding to a DNA response regulator alters the transcriptional regulation  
184 of associated quorum-sensing genes (Slamti & Lereclus, 2002).

185 Alternatively, Gram-positive bacteria may also rely on two-component QS circuits, where oligopeptide  
186 AIPs, or other molecules, are instead are detected by membrane-bound signal transduction systems  
187 (Esmailshirazifard, De Vizio, Moschos, & Keshavarz, 2017; Håvarstein, Coomaraswamy, & Morrison, 1995; Ji,  
188 Beavis, & Novick, 1995; Kleerebezem, Quadri, Kuipers, & De Vos, 1997; Monnet, Juillard, & Gardan, 2016).  
189 Within this third class of QS circuits, AIPs are encoded as precursors (pro-AIPs), processed and transported to the  
190 external milieu via specialized transporters to yield AIPs, typically 5 to 17 amino acids in length, which afterwards

191 are detected by membrane-bound two-component histidine kinase receptors (Esmailshirazifard et al., 2017;  
192 Monnet et al., 2016; Rutherford & Bassler, 2012). After binding of the AIP to the two-component kinases,  
193 autophosphorylation of conserved histidines occurs, where afterwards the phosphoryl group is transferred from  
194 histidine to a conserved aspartate residue on a cognate cytoplasmic response-regulator (Rutherford & Bassler,  
195 2012). Lastly, Gram-negative bacteria, in certain instances, have also demonstrated the capability to detect AIs via  
196 two-component histidine kinase receptors that function analogously to those described in Gram-positive  
197 bacteria. As LuxI/LuxR, autoinducer oligopeptide (AIP) transcription factor binding, and two-compartment  
198 sensing systems in bacteria have already been extensively reviewed; the authors recommend reviewing the  
199 publications by Abisado, Benomar, Klaus, Dandekar, & Chandler, (2018); Pappenfort & Bassler, (2016); and  
200 Rutherford and Bassler (2012) for further information.

## 201 **QUORUM SENSING MECHANISMS IN FUNGI**

202 In fungi, it has for a long-time been widely accepted that QS is responsible for the regulation of a wide  
203 range of critical biological processes controlled by chemical messengers, such as alcohols, small peptides, lipids,  
204 small molecules, and volatile compounds (Cottier & Mühlischlegel, 2012; Jones & Bennett, 2011; Palkova et al.,  
205 1997; Richard, Bakker, & Teusink, 1996). However, unlike bacteria, the existence of QS in eukaryotic organisms  
206 was unknown until farnesol was demonstrated to be a QSM in *Candida albicans*, a well-described human  
207 pathogen, less than two decades ago (Hornby et al., 2001). Since then, aromatic alcohols like tyrosol (Chen, Fujita,  
208 Feng, Clardy, & Fink, 2004; Gori, Knudsen, Nielsen, Arneborg, & Jespersen, 2011; Rossignol et al., 2007), 2-  
209 phenylethanol (Chen & Fink, 2006; Gori et al., 2011; Huang et al., 2020), and tryptophol (Chen & Fink, 2006;  
210 Gori et al., 2011; Verbrugghe, Adriaensen, Martel, Vanhaecke, & Pasmans, 2019) have been shown to act as QSM  
211 in across many different fungal species. However, the role of farnesol and tyrosol in the regulation of yeast-to-  
212 hyphal transition, within the model organism *Candida albicans*, remains the most exhaustively investigated  
213 eukaryotic QSS (Chen et al., 2004; Hornby et al., 2001; Lindsay, Deveau, Piispanen, & Hogan, 2012; Polke et al.,  
214 2017).

215 Tyrosol, tryptophol, and 2-phenylethanol are created from the transamination, decarboxylation, and  
216 reduction of the amino acids tyrosine, tryptophan, and phenylalanine, respectively via the Ehrlich pathway  
217 (Ehrlich, 1907; Hazelwood, Daran, Van Maris, Pronk, & Dickinson, 2008; SentheShanuganathan, 1960). Tyrosol  
218 is generated via the transamination of tyrosine into the  $\alpha$ -keto acid p-hydroxy 3-phenylpyruvate, which is then  
219 decarboxylated to the higher aldehyde p-hydroxy 3-phenylacetaldehyde and then subsequently reduced by alcohol  
220 dehydrogenase to the higher alcohol tyrosol (Mas et al., 2014; SentheShanuganathan, 1960). In a comparable  
221 mechanism, tryptophol is synthesized by the transamination of tryptophan to indol-3-pyruvate, decarboxylated to  
222 indole-3-aldehyde, and reduced to the higher alcohol tryptophol (Iraqi, Vissers, Cartiaux, & Urrestarazu, 1998;  
223 Mas et al., 2014), while phenylalanine is transaminated to phenylpyruvate, decarboxylated to 2-  
224 phenylacetaldehyde, and then reduced to 2-phenylethanol (Etschmann, Bluemke, Sell, & Schrader, 2002;  
225 Etschmann & Schrader, 2006; Mas et al., 2014). As it relates to these aromatic alcohols, transamination is catalyzed  
226 by aromatic aminotransferases I and II encoded by *ARO8* and *ARO9*, respectively; decarboxylated by aromatic  
227 decarboxylase encoded by *ARO10* and pyruvate decarboxylases (*PDC6*, *PDC5*, and *PDC1*); and reduced by  
228 alcohol dehydrogenases (*SF1*, *ADH4*, and *ADH5*) (Iraqi et al., 1998; Mas et al., 2014).

229 Aromatic alcohols in yeast were already shown to influence the differential expression of hundreds of  
230 genes (Chen & Fink, 2006; Wuster & Babu, 2009). An investigation by Wuster & Babu (2009) revealed 2-

231 phenylethanol has the highest impact with the differential expression of 412 genes in *Saccharomyces cerevisiae*,  
232 while tryptophol and tyrosol led to the differential expression of 264 and 251 genes, respectively. Similarly,  
233 investigations conducted by Jin et al. (2018) demonstrated 580 differentially expressed genes when exposed to 2-  
234 phenylethanol. Previously, Chen & Fink (2006) demonstrated that transcription factors Flo8p and Aro80p were  
235 regulated in the presence of the aromatic alcohols phenylethanol and tryptophol. Subsequent investigations by  
236 Wuster & Babu (2009) suggest that other transcription factors, like Msn2p, Mig1p, Rgm1p, Sip4p, and Cat8p,  
237 differentially regulate specific genes in the presence of 2-phenylethanol; similarly, Cat8p and Mig1p were also  
238 shown to be involved in differential transcription in the presence of tryptophol and tyrosol, which implies these  
239 genes are essential for aromatic alcohol QS in *Saccharomyces cerevisiae*. *Cat8p* has mostly been shown to be an  
240 activator of gluconeogenic genes, while *Mig1p* is involved in the regulation of enzymes that participate in response  
241 to glucose repression by influencing activators of respiration (Frolova, Johnston, & Majors, 1999; Haurie et al.,  
242 2001; Rahner, Hiesinger, & Schüller, 1999). Further transcriptional analysis, also revealed the transcription factor  
243 Pdr1p, which regulates the expression of the pleiotropic drug-resistant (PDR) transporters and amino acid  
244 metabolic genes, was shown to be regulated by tryptophol and tyrosol (Hlaváček, Kučerová, Harant, Palková, &  
245 Váchová, 2009; Nawrocki, Fey, Roepstorff, & Larsen, 2001; Wuster & Babu, 2009).

246 Aromatic alcohols as potential QSMs of *S. cerevisiae* will be further discussed, as **I**) aromatic alcohols  
247 are the only molecules meeting the criteria for QSMs in fungi, **II**) QS in yeasts beyond *S. cerevisiae* were already  
248 reviewed by (Albuquerque & Casadevall, 2012; Barriuso et al., 2018; Nickerson et al., 2006), and most importantly  
249 **III**) *S. cerevisiae* serves as a model research organism and is regularly used by brewers for the production of top-  
250 fermented beers.

## 251 **QUORUM SENSING IN *S. CEREVISIAE***

252 QS community-level behavior in *S. cerevisiae* has predominantly been associated with primary  
253 flocculation (Chen & Fink, 2006; Smukalla et al., 2009) and filamentation (Avbelj et al., 2015; Chen & Fink, 2006;  
254 González et al., 2018; Lenhart, Meeks, & Murphy, 2019; Lorenz, Cutler, & Heitman, 2000). However, as indicated  
255 recently by Winters and coworkers (2019), it is difficult to assess whether these shifts in morphology meet the  
256 criteria for a QS system. This hurdle represents a challenge as **I**) the exact point of differential gene expression has  
257 not been thoroughly examined in *S. cerevisiae* and **II**) populations undergoing morphological switches, such as  
258 filamentation, will inevitably contain both morphologies.

259 Previous studies conducted by Smukalla and associates (2018) investigated the physiological effect of the  
260 aromatic alcohols 2-phenylethanol, tryptophol, and tyrosol on the flocculence behavior in the diploid strain EM93  
261 that typically does not exhibit flocculent behavior in nutrient-rich medium. The results of this investigation  
262 demonstrated that tryptophol induced a significant difference in flocculation behavior at concentrations of 100  $\mu$ M  
263 and 1000  $\mu$ M, compared to the control (Smukalla et al., 2008). These authors suggested that mutual adhesion,  
264 leading to the formation of flocs, substantially impairs diffusion, therefore, providing the innermost cells physical  
265 protection from harmful compounds in the exterior environment. As flocculence requires a sizeable microbial  
266 population, and Flo adhesins expression is only functional at higher population densities, it stands to reason that  
267 this particular adaptive trait, flocculation behavior in *S. cerevisiae*, would be expressed when exposed to the QSM  
268 tryptophol.

269 Initial investigations by Chen and Fink (2006) have served as the foundational evidence for a QS  
270 mechanism in *S. cerevisiae* by demonstrating that the fungal QSMs 2-phenylethanol and tryptophol stimulated



271 pseudohyphal growth under nitrogen-limited conditions. Broadly, this investigation demonstrated the  
272 aforementioned aromatic alcohols were proportionally produced according to cell density, and that the secretion  
273 of these compounds was subject to positive feedback regulation in nitrogen-limited conditions starvation (Chen &  
274 Fink, 2006).

275 Avbelj and colleagues (2015) investigated the kinetics of 2-phenylethanol, tyrosol, and tryptophol in *S.*  
276 *cerevisiae* and confirmed some of the foundational work conducted by Chen and Fink (2006), by demonstrating  
277 the concentration of 2-phenylethanol, tyrosol and tryptophol were cell-density and growth-phase-dependent. In  
278 this investigation, aromatic alcohols 2-phenylethanol, tyrosol, and tryptophol were shown correlate well with the  
279 expression of *ARO8*, *ARO9*, and *ARO10* (Avbelj et al., 2015), encoding for aromatic aminotransferases I and II  
280 and an aromatic decarboxylase, respectively (Iraqi, Vissers, André, & Urrestarazu, 1999; Iraqi et al., 1998).  
281 Moreover, it was revealed that *S. cerevisiae* begins with the release of 2-phenylethanol in exponential phase, with  
282 peak synthesis occurring in the declining growth phase, followed later by tyrosol production, while the peak  
283 production of tryptophol corresponds with the stationary phase of cell growth (Avbelj et al., 2015).

284 However, more recent investigations conducted by Lenhart and associates (2019) revealed significant  
285 phenotypic variation among environmental isolates of *S. cerevisiae* collected from fermentations, clinical patients,  
286 soil, plant, and insects upon exposure to the 2-phenolethanol and tryptophol, suggesting the filamentous  
287 phenotypic response may be a strain-specific effect. Broadly, the results indicated that exogenous exposure to 2-  
288 phenolethanol and tryptophol exhibited a minimal effect on pseudohyphae formation, while in reality, a few strains  
289 even significantly decreased pseudohyphae formation in response aromatic alcohol exposure (Lenhart et al.,  
290 2019). Moreover, the conclusion of Lenhart and colleagues is to question whether the model laboratory strains of  
291 *S. cerevisiae* are representative of the broader population of *Saccharomyces spp.* used in the commercial production  
292 of beer.

## 293 **ELEMENTS INFLUENCING QUORUM SENSING MOLECULE SYNTHESIS**

294 The synthesis of the aromatic alcohols in *S. cerevisiae* are regulated by local cellular density; therefore,  
295 when cells achieve quorum, the transcription of *ARO9* and *ARO10* genes is up-regulated rousing the production  
296 of aromatic alcohols (Avbelj et al., 2015; Chen & Fink, 2006). Moreover, aromatic alcohol production can likewise  
297 be autostimulated via the transcription factor Aro80p by tryptophol, which activates ARO9 and ARO10  
298 transaminase and decarboxylase expression yielding a positive feedback loop (Iraqi et al., 1999, 1998).  
299 Consequently, *S. cerevisiae* within higher population density environments generates more 2-phenylethanol and  
300 tryptophol than cells at lower population densities (Avbelj et al., 2015; Avbelj, Zupan, & Raspor, 2016; Chen &  
301 Fink, 2006). Avbelj et al. (2015) expanded upon the initial research by Chen & Fink to further demonstrate that  
302 the production of 2-phenylethanol, tryptophol, and tyrosol in *S. cerevisiae* were all cell density dependant by  
303 comparing fermentations with low and high initial cell concentrations.

304 Aromatic alcohol production by *S. cerevisiae* was previously demonstrated to also be influenced by  
305 nitrogen availability in the local environment. Chen & Fink, (2006) reported that aromatic alcohols, like 2-  
306 phenylethanol, tyrosol, and tryptophol, were found in conditions with high concentrations of ammonium, as this  
307 represses the expression of transaminases, decarboxylases, and dehydrogenases that are required for the synthesis  
308 of aromatic alcohols (Avbelj et al., 2016). Previously, it was also demonstrated by Chen & Fink, (2006) that  
309 aromatic alcohol production occurs at their highest levels when the ammonium concentrations were less than or  
310 equal to 50  $\mu$ M, and were significantly reduced at concentrations greater than 500  $\mu$ M.

311 Furthermore, ethanol was also demonstrated to negatively influence the overall rate and commencement  
312 of 2-phenylethanol, tryptophol, and tyrosol synthesis (Avbelj et al., 2015). However, it remains unclear whether  
313 the reduction is linked to the suppression of aromatic alcohol synthesis or whether a quorate population was never  
314 achieved due to ethanolic inhibition. On the contrary, Avbelj and colleagues assert that *S. cerevisiae* produces  
315 higher concentrations of 2-phenylethanol, tryptophol, and tyrosol when grown in anaerobic conditions than  
316 aerobic conditions, however, the authors were unable to locate any literature to support this claim despite the  
317 phenomenon having been demonstrated in other fungal species, like *Candida albicans* (Avbelj et al., 2016; Ghosh,  
318 Kebaara, Atkin, & Nickerson, 2008). As ethanol and anaerobic conditions are environmental conditions frequently  
319 observed by brewer's yeast in a commercial brewing, it is probable that these two factors could have a significant  
320 impact on existing QS-induced behavior in brewer's yeast during fermentation.

321 Beyond external factors, previous studies have shown that phenotypic variation among natural isolates  
322 exposed to aromatic alcohols indicate that QS-phenotypes, at least filamentation, may be strain specific and  
323 strongly influenced by allelic variation (Lenhart et al., 2019). However, it is currently unknown to the authors  
324 whether any further investigations have been conducted to assess the impact of naturally occurring allelic variants  
325 on the QS-induced filamentous behavior in *S. cerevisiae*. As some isolates from the investigation by Lenhart (2019)  
326 were sources from industrial fermentations, this begs the questions whether commercial brewing strains are  
327 differently influenced by QS compounds than research-derived strains, such as  $\Sigma 1278b$ .

## 328 **FUTURE CONSIDERATIONS**

329 QS molecules have already been demonstrated to be synthesized and secreted by a comprehensive  
330 collection of food-associated microbiota, including *S. cerevisiae*; however, limited knowledge exists on how QS  
331 may influence the brewing process and the quality and consistency of the finished product. Nevertheless, recent  
332 achievements over the past decade associated with the manipulation of microbial behavior through the use of  
333 QSMs or quorum quenching (QQ) (Grandclément, Tannières, Moréra, Dessaux, & Faure, 2015), has renewed  
334 interest regarding the impact of density-dependent communication on fermented food and beverages, including  
335 beer.

336 In brewing, further investigations into QS could reveal the genes associated with QS circuits in  
337 *S. cerevisiae* which could have a sizeable impact on; the rate of fermentation, efficiency of ethanol production, the  
338 formation of ester/higher alcohols, biomass generation in propagation, yeast physiology and vitality, and  
339 flocculation to only mention a select few. It is feasible that even the solution for significant industry concerns,  
340 such as premature yeast flocculation (PYF) in commercial fermentations, a phenomenon recognised by brewing  
341 scientists but where the mechanisms are still poorly understood. In PYF, yeast will sediment from fermenting wort  
342 earlier or more heavily before reaching full attenuation, resulting in higher residual extract, reduced alcohol and  
343 CO<sub>2</sub> production, and increased flavor anomalies which could be attributed to cell-to-cell interactions resulting from  
344 quorum sensing.

345 At the time of publication, the authors are unaware of any current or prior investigations specifically  
346 aimed at investigating the impact and application of quorum sensing on commercial brewing operations. However,  
347 considering the potential significance of quorum sensing to the brewing industry, future investigations could  
348 consider **I**) diving deeper into the effect of different QS associated gene knockouts (e.g. *ARO9*, *ARO10*) on brewing  
349 fermentations rate and yeast propagation compared to wild-type strains, **II**) examining the QS variation in  
350 behavioral response that may exist between commercially relevant brewing strains, **III**) determining the role of

351 QS in mixed cultured fermentation and its impact on increasing the consistency of sour beers, or **IV**) unraveling  
352 the role of QS in the biofilm formation of brewery spoilage organisms and how QQ could be employed as an  
353 alternative strategy to prevent the establishment of these detrimental microbial consortiums.

354 Therefore, even though research over the past decade has demonstrated the importance and impact of QS  
355 systems on a wide variety of fermented foods and beverages, little investigations thus far have been done on  
356 whether, and to what extent, QS influences commercial brewing and the quality of the finished product. Certainly,  
357 the further investigation into the QSS of *S.cerevisae* and its applications towards commercial brewing is clearly  
358 warranted.

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- 360 Abisado, R. G., Benomar, S., Klaus, J. R., Dandekar, A. A., & Chandler, J. R. (2018). Bacterial quorum sensing  
361 and microbial community interactions. *MBio*, *9*(3), 1–14. <https://doi.org/10.1128/mBio.02331-17>
- 362 Albuquerque, P., & Casadevall, A. (2012). Quorum sensing in fungi a review. *Medical Mycology*, *50*(4), 337–345.  
363 <https://doi.org/10.3109/13693786.2011.652201>
- 364 Allen, M. E., Piefer, A. J., Cole, S. N., Werner, J. J., Benziger, P. T., Grieneisen, L., & Britton, S. J. (2019).  
365 Characterization of Microbial Communities Populating the Inflorescences of *Humulus lupulus* L. *Journal of*  
366 *the American Society of Brewing Chemists*, 1–8. <https://doi.org/10.1080/03610470.2019.1667739>
- 367 An, J. H., Goo, E., Kim, H., Seo, Y. S., & Hwang, I. (2014). Bacterial quorum sensing and metabolic slowing in  
368 a cooperative population. *Proceedings of the National Academy of Sciences of the United States of America*,  
369 *111*(41), 14912–14917. <https://doi.org/10.1073/pnas.1412431111>
- 370 Andersson, D. I., & Hughes, D. (2014). Microbiological effects of sublethal levels of antibiotics. *Nature Reviews*  
371 *Microbiology*, *12*(7), 465–478. <https://doi.org/10.1038/nrmicro3270>
- 372 Ansaldi, M., Marolt, D., Stebe, T., Mandic-Mulec, I., & Dubnau, D. (2002). Specific activation of the *Bacillus*  
373 quorum-sensing systems by isoprenylated pheromone variants. *Molecular Microbiology*, *44*(6), 1561–1573.  
374 <https://doi.org/10.1046/j.1365-2958.2002.02977.x>
- 375 Atkinson, S., & Williams, P. (2009). Quorum sensing and social networking in the microbial world. *Journal of the*  
376 *Royal Society Interface*, *6*(40), 959–978. <https://doi.org/10.1098/rsif.2009.0203>
- 377 Avbelj, M., Zupan, J., Kranjc, L., & Raspor, P. (2015). Quorum-Sensing Kinetics in *Saccharomyces cerevisiae*: A  
378 Symphony of ARO Genes and Aromatic Alcohols. *Journal of Agricultural and Food Chemistry*, *63*(38),  
379 8544–8550. <https://doi.org/10.1021/acs.jafc.5b03400>
- 380 Avbelj, M., Zupan, J., & Raspor, P. (2016). Quorum-sensing in yeast and its potential in wine making. *Applied*  
381 *Microbiology and Biotechnology*, *100*(18), 7841–7852. <https://doi.org/10.1007/s00253-016-7758-3>
- 382 Ball, A. S., Chaparian, R. R., & Kessel, J. C. Van. (2017). *Quorum Sensing Gene Regulation by LuxR/HapR Master*  
383 *Regulators in Vibrios*. *199*(19), 1–13.
- 384 Barnett, J. A. (1998). A history of research on yeasts 1: Work by chemists and biologists 1789-1850. *Yeast*, *14*(16),  
385 1439–1451. [https://doi.org/10.1002/\(SICI\)1097-0061\(199812\)14:16<1439::AID-YEA339>3.0.CO;2-Z](https://doi.org/10.1002/(SICI)1097-0061(199812)14:16<1439::AID-YEA339>3.0.CO;2-Z)
- 386 Barriuso, J., Hogan, D. A., Keshavarz, T., & Martínez, M. J. (2018). Role of quorum sensing and chemical  
387 communication in fungal biotechnology and pathogenesis. *FEMS Microbiology Reviews*, *42*(5), 627–638.  
388 <https://doi.org/10.1093/femsre/fuy022>
- 389 Bassler, B. L. (2002). Small talk: Cell-to-cell communication in bacteria. *Cell*, *109*(4), 421–424.  
390 [https://doi.org/10.1016/S0092-8674\(02\)00749-3](https://doi.org/10.1016/S0092-8674(02)00749-3)
- 391 Begley, T. P., Wuster, A., & Babu, M. M. (2008). Chemical Molecules that Regulate Transcription and Facilitate  
392 Cell-to-Cell Communication. *Wiley Encyclopedia of Chemical Biology*.  
393 <https://doi.org/10.1002/9780470048672.webc501>
- 394 Butler, S., & O'Dwyer, J. P. (2018). Stability criteria for complex microbial communities. *Nature*  
395 *Communications*, *9*(1). <https://doi.org/10.1038/s41467-018-05308-z>
- 396 Chen, H., & Fink, G. R. (2006). Feedback control of morphogenesis in fungi by aromatic alcohols. *Genes and*  
397 *Development*, *20*(9), 1150–1161. <https://doi.org/10.1101/gad.1411806>
- 398 Chen, H., Fujita, M., Feng, Q., Clardy, J., & Fink, G. (2004). Farnesol as a quorum-sensing molecule in *Candida*  
399 *albicans*. *PNAS*, *101*(14), 5048–5052. <https://doi.org/10.3314/jjmm.49.281>
- 400 Cottier, F., & Mühlshlegel, F. A. (2012). Communication in fungi. *International Journal of Microbiology*, *2012*.  
401 <https://doi.org/10.1155/2012/351832>
- 402 Darch, S. E., West, S. A., Winzer, K., & Diggle, S. P. (2012). Density-dependent fitness benefits in quorum-  
403 sensing bacterial populations. *Proceedings of the National Academy of Sciences of the United States of*  
404 *America*, *109*(21), 8259–8263. <https://doi.org/10.1073/pnas.1118131109>
- 405 Davies, J., Spiegelman, G. B., & Yim, G. (2006). The world of subinhibitory antibiotic concentrations. *Current*  
406 *Opinion in Microbiology*, *9*(5), 445–453. <https://doi.org/10.1016/j.mib.2006.08.006>

- 407 De Sordi, L., & Mühlischlegel, F. A. (2009). Quorum sensing and fungal-bacterial interactions in *Candida albicans*:  
408 A communicative network regulating microbial coexistence and virulence. *FEMS Yeast Research*, *9*(7),  
409 990–999. <https://doi.org/10.1111/j.1567-1364.2009.00573.x>
- 410 Diggle, S. P., Cruz, S. A., & Cámara, M. (2007). Quorum sensing. *Current Biology*, *17*(21), 907–910.  
411 <https://doi.org/10.1016/j.cub.2007.08.045>
- 412 Diggle, S. P., Gardner, A., West, S. A., & Griffin, A. S. (2007). Evolutionary theory of bacterial quorum sensing:  
413 When is a signal not a signal? *Philosophical Transactions of the Royal Society B: Biological Sciences*,  
414 *362*(1483), 1241–1249. <https://doi.org/10.1098/rstb.2007.2049>
- 415 Ehrlich, F. (1907). Über die Bedingungen der Fuselölbildung. *Berichte Der Deutschen Chemischen Gesellschaft*,  
416 *40*(1), 1027–1047. <https://doi.org/10.1002/cber.190704001156>
- 417 Engebrecht, J. A., & Silverman, M. (1984). Identification of genes and gene products necessary for bacterial  
418 bioluminescence. *Proceedings of the National Academy of Sciences of the United States of America*, *81*(13  
419 I), 4154–4158. <https://doi.org/10.1073/pnas.81.13.4154>
- 420 Engebrecht, J., Nealson, K. H., & Silverman, M. (1983). Bacterial bioluminescence: Isolation and genetic analysis  
421 of functions from *Vibrio fischeri*. *Cell*, *32*(3), 773–781. [https://doi.org/10.1016/0092-8674\(83\)90063-6](https://doi.org/10.1016/0092-8674(83)90063-6)
- 422 Esmaeilshirazifard, E., De Vizio, D., Moschos, S. A., & Keshavarz, T. (2017). Genomic and molecular  
423 characterization of a novel quorum sensing molecule in *Bacillus licheniformis*. *AMB Express*, *7*(1).  
424 <https://doi.org/10.1186/s13568-017-0381-6>
- 425 Etschmann, M., Bluemke, W., Sell, D., & Schrader, J. (2002). Biotechnological production of 2-phenylethanol.  
426 *Applied Microbiology and Biotechnology*, *59*(1), 1–8. <https://doi.org/10.1007/s00253-002-0992-x>
- 427 Etschmann, M., & Schrader, J. (2006). An aqueous-organic two-phase bioprocess for efficient production of the  
428 natural aroma chemicals 2-phenylethanol and 2-phenylethylacetate with yeast. *Applied Microbiology and  
429 Biotechnology*, *71*(4), 440–443. <https://doi.org/10.1007/s00253-005-0281-6>
- 430 Florenza, J., Tamminen, M., & Bertilsson, S. (2019). Uncovering microbial inter-domain interactions in complex  
431 communities. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *374*(1786).  
432 <https://doi.org/10.1098/rstb.2019.0087>
- 433 Frolova, E., Johnston, M., & Majors, J. (1999). Binding of the glucose-dependent Mig1p repressor to the GAL1  
434 and GAL4 promoters in vivo: Regulation by glucose and chromatin structure. *Nucleic Acids Research*, *27*(5),  
435 1350–1358. <https://doi.org/10.1093/nar/27.5.1350>
- 436 Fröls, S. (2013). Archaeal biofilms: Widespread and complex. *Biochemical Society Transactions*, *41*(1), 393–398.  
437 <https://doi.org/10.1042/BST20120304>
- 438 Fuqua, C., Parsek, M. R., & Greenberg, E. P. (2001). Regulation of gene expression by cell-to-cell communication:  
439 Acyl-homoserine lactone quorum sensing. *Annual Review of Genetics*, *35*, 439–468.  
440 <https://doi.org/10.1146/annurev.genet.35.102401.090913>
- 441 Fuqua, W. C., Winans, S. C., & Greenberg, E. P. (1994). Quorum sensing in bacteria: The LuxR-LuxI family of  
442 cell density- responsive transcriptional regulators. *Journal of Bacteriology*, *176*(2), 269–275.  
443 <https://doi.org/10.1128/jb.176.2.269-275.1994>
- 444 Ghosh, S., Kebaara, B. W., Atkin, A. L., & Nickerson, K. W. (2008). Regulation of aromatic alcohol production  
445 in *Candida albicans*. *Applied and Environmental Microbiology*, *74*(23), 7211–7218.  
446 <https://doi.org/10.1128/AEM.01614-08>
- 447 Goh, E. B., Yim, G., Tsui, W., McClure, J. A., Surette, M. G., & Davies, J. (2002). Transcriptional modulation of  
448 bacterial gene expression by subinhibitory concentrations of antibiotics. *Proceedings of the National  
449 Academy of Sciences of the United States of America*, *99*(26), 17025–17030.  
450 <https://doi.org/10.1073/pnas.252607699>
- 451 Gómez-Gil, E., Franco, A., Madrid, M., Vázquez-Marín, B., Gacto, M., Fernández-Breis, J., ... Cansado, J. (2019).  
452 Quorum sensing and stress-activated MAPK signaling repress yeast to hypha transition in the fission yeast  
453 *Schizosaccharomyces japonicus*. *PLoS Genetics*, *15*(5), 1–26. <https://doi.org/10.1371/journal.pgen.1008192>
- 454 González, B., Vázquez, J., Morecillo-Parra, M. Á., Mas, A., Torija, M. J., & Beltran, G. (2018). The production of  
455 aromatic alcohols in non-*Saccharomyces* wine yeast is modulated by nutrient availability. *Food*

- 456 *Microbiology*, 74, 64–74. <https://doi.org/10.1016/j.fm.2018.03.003>
- 457 Gori, K., Knudsen, P. B., Nielsen, K. F., Arneborg, N., & Jespersen, L. (2011). Alcohol-based quorum sensing  
458 plays a role in adhesion and sliding motility of the yeast *Debaryomyces hansenii*. *FEMS Yeast Research*,  
459 11(8), 643–652. <https://doi.org/10.1111/j.1567-1364.2011.00755.x>
- 460 Grandclément, C., Tannières, M., Moréra, S., Dessaux, Y., & Faure, D. (2015). Quorum quenching: Role in nature  
461 and applied developments. *FEMS Microbiology Reviews*, 40(1), 86–116.  
462 <https://doi.org/10.1093/femsre/fuv038>
- 463 Haurie, V., Perrot, M., Mini, T., Jenö, P., Saggiocco, F., & Boucherie, H. (2001). *The Transcriptional Activator*  
464 *Cat8p Provides a Major Contribution to the Reprogramming of Carbon Metabolism during the Diauxic Shift*  
465 *in Saccharomyces cerevisiae* \*. 276(1), 76–85. <https://doi.org/10.1074/jbc.M008752200>
- 466 Håvarstein, L. S., Coomaraswamy, G., & Morrison, D. A. (1995). An unmodified heptadecapeptide pheromone  
467 induces competence for genetic transformation in *Streptococcus pneumoniae*. *Proceedings of the National*  
468 *Academy of Sciences of the United States of America*, 92(24), 11140–11144.  
469 <https://doi.org/10.1073/pnas.92.24.11140>
- 470 Hazelwood, L. A., Daran, J. M., Van Maris, A. J. A., Pronk, J. T., & Dickinson, J. R. (2008). The Ehrlich pathway  
471 for fusel alcohol production: A century of research on *Saccharomyces cerevisiae* metabolism. *Applied and*  
472 *Environmental Microbiology*, 74(8), 2259–2266. <https://doi.org/10.1128/AEM.02625-07>
- 473 Hense, B. A., Müller, J., Kuttler, C., & Hartmann, A. (2012). Spatial heterogeneity of autoinducer regulation  
474 systems. *Sensors*, 12(4), 4156–4171. <https://doi.org/10.3390/s120404156>
- 475 Hense, B. A., & Schuster, M. (2015). Core Principles of Bacterial Autoinducer Systems. *Microbiology and*  
476 *Molecular Biology Reviews*, 79(1), 153–169. <https://doi.org/10.1128/mmbr.00024-14>
- 477 Hlaváček, O., Kučerová, H., Harant, K., Palková, Z., & Váchová, L. (2009). Putative role for ABC multidrug  
478 exporters in yeast quorum sensing. *FEBS Letters*, 583(7), 1107–1113.  
479 <https://doi.org/10.1016/j.febslet.2009.02.030>
- 480 Hoffman, L. R., D'Argenio, D. A., MacCoss, M. J., Zhang, Z., Jones, R. A., & Miller, S. I. (2005). Aminoglycoside  
481 antibiotics induce bacterial biofilm formation. *Nature*, 436(7054), 1171–1175.  
482 <https://doi.org/10.1038/nature03912>
- 483 Hogan, D. A. (2006a). Quorum Sensing: Alcohols in a Social Situation. *Current Biology*, 16(12), 457–458.  
484 <https://doi.org/10.1016/j.cub.2006.05.035>
- 485 Hogan, D. A. (2006b). Talking to themselves: Autoregulation and quorum sensing in fungi. *Eukaryotic Cell*, 5(4),  
486 613–619. <https://doi.org/10.1128/EC.5.4.613-619.2006>
- 487 Hornby, J. M., Jensen, E. C., Lisec, A. D., Tasto, J. J., Shoemaker, R., Dussault, P., & Nickerson, K. W. (2001).  
488 Quorum Sensing in the Dimorphic Fungus. *Applied and Environmental Microbiology*, 67(7), 2982–2992.  
489 <https://doi.org/10.1128/AEM.67.7.2982>
- 490 Huang, C., Qian, Y., Viana, T., Siegumfeldt, H., Arneborg, N., Larsen, N., & Jespersen, L. (2020). The quorum-  
491 sensing molecule 2-phenylethanol impaired conidial germination, hyphal membrane integrity and growth of  
492 *Penicillium expansum* and *Penicillium nordicum*. *Journal of Applied Microbiology*, 0–2.  
493 <https://doi.org/10.1111/jam.14621>
- 494 Iraqui, I., Vissers, S., André, B., & Urrestarazu, A. (1999). Transcriptional Induction by Aromatic Amino Acids  
495 in *Saccharomyces cerevisiae*. *Molecular and Cellular Biology*, 19(5), 3360–3371.  
496 <https://doi.org/10.1128/mcb.19.5.3360>
- 497 Iraqui, I., Vissers, S., Cartiaux, M., & Urrestarazu, A. (1998). Characterisation of *Saccharomyces cerevisiae* ARO8  
498 and ARO9 genes encoding aromatic aminotransferases I and II reveals a new aminotransferase subfamily.  
499 *Molecular and General Genetics*, 257(2), 238–248. <https://doi.org/10.1007/s004380050644>
- 500 Ji, G., Beavis, R. C., & Novick, R. P. (1995). Cell density control of staphylococcal virulence mediated by an  
501 octapeptide pheromone. *Proceedings of the National Academy of Sciences of the United States of America*,  
502 92(26), 12055–12059. <https://doi.org/10.1073/pnas.92.26.12055>
- 503 Jin, D., Gu, B., Xiong, D., Huang, G., Huang, X., Liu, L., & Xiao, J. (2018). A Transcriptomic Analysis of  
504 *Saccharomyces cerevisiae* Under the Stress of 2-Phenylethanol. *Current Microbiology*, 75(8), 1068–1076.

- 505 <https://doi.org/10.1007/s00284-018-1488-y>
- 506 Jones, S. K., & Bennett, R. J. (2011). Fungal mating pheromones: Choreographing the dating game. *Fungal*  
507 *Genetics and Biology*, 48(7), 668–676. <https://doi.org/10.1016/j.fgb.2011.04.001>
- 508 Katzianer, D. S., Wang, H., Carey, R. M., & Zhu, J. (2015). “Quorum non-sensing”: Social cheating and deception  
509 in *Vibrio cholerae*. *Applied and Environmental Microbiology*, 81(11), 3856–3862.  
510 <https://doi.org/10.1128/AEM.00586-15>
- 511 Kent, A. D., & Triplett, E. W. (2002). Microbial Communities and Their Interactions in Soil and Rhizosphere  
512 Ecosystems. *Annual Review of Microbiology*, 56(1), 211–236.  
513 <https://doi.org/10.1146/annurev.micro.56.012302.161120>
- 514 Kleerebezem, M., Quadri, L. E. N., Kuipers, O. P., & De Vos, W. M. (1997). Quorum sensing by peptide  
515 pheromones and two-component signal- transduction systems in Gram-positive bacteria. *Molecular*  
516 *Microbiology*, 24(5), 895–904. <https://doi.org/10.1046/j.1365-2958.1997.4251782.x>
- 517 Labbate, M., Zhu, H., Thung, L., Bandara, R., Larsen, M. R., Willcox, M. D. P., ... Kjelleberg, S. (2007). Quorum-  
518 sensing regulation of adhesion in *Serratia marcescens* MG1 is surface dependent. *Journal of Bacteriology*,  
519 189(7), 2702–2711. <https://doi.org/10.1128/JB.01582-06>
- 520 Laureti, L., Matic, I., & Gutierrez, A. (2013). Bacterial responses and genome instability induced by subinhibitory  
521 concentrations of antibiotics. *Antibiotics*, 2(1), 100–114. <https://doi.org/10.3390/antibiotics2010100>
- 522 Laureys, D., Britton, S. J., & De Clippeleer, J. (2020). Kombucha Tea Fermentation: A Review. *Journal of the*  
523 *American Society of Brewing Chemists*, 0(0), 1–10. <https://doi.org/10.1080/03610470.2020.1734150>
- 524 Lenhart, B. A., Meeks, B., & Murphy, H. A. (2019). Variation in filamentous growth and response to quorum-  
525 sensing compounds in environmental isolates of *Saccharomyces cerevisiae*. *G3: Genes, Genomes, Genetics*,  
526 9(5), 1533–1544. <https://doi.org/10.1534/g3.119.400080>
- 527 Lindsay, A. K., Deveau, A., Piispanen, A. E., & Hogan, D. A. (2012). Farnesol and cyclic AMP signaling effects  
528 on the hypha-to-yeast transition in *Candida albicans*. *Eukaryotic Cell*, 11(10), 1219–1225.  
529 <https://doi.org/10.1128/EC.00144-12>
- 530 Little, A. E. F., Robinson, C. J., Peterson, S. B., Raffa, K. F., & Handelsman, J. (2008). Rules of Engagement:  
531 Interspecies Interactions that Regulate Microbial Communities. *Annual Review of Microbiology*, 62(1), 375–  
532 401. <https://doi.org/10.1146/annurev.micro.030608.101423>
- 533 Lorenz, M. C., Cutler, N. S., & Heitman, J. (2000). Characterization of Alcohol-induced Filamentous Growth in.  
534 *Molecular Biology of the Cell*, 11(January), 183–199.
- 535 March, J. C., & Bentley, W. E. (2004). Quorum sensing and bacterial cross-talk in biotechnology. *Current Opinion*  
536 *in Biotechnology*, 101(14), 5048–5022. <https://doi.org/10.1016/j.copbio.2004.08.013>
- 537 Mas, A., Guillamon, J. M., Torija, M. J., Beltran, G., Cerezo, A. B., Troncoso, A. M., & Garcia-Parrilla, M. C.  
538 (2014). Bioactive compounds derived from the yeast metabolism of aromatic amino acids during alcoholic  
539 fermentation. *BioMed Research International*, 2014. <https://doi.org/10.1155/2014/898045>
- 540 Miller, E. L., Kjos, M., Abrudan, M. I., Roberts, I. S., Veening, J. W., & Rozen, D. E. (2018). Eavesdropping and  
541 crosstalk between secreted quorum sensing peptide signals that regulate bacteriocin production in  
542 *Streptococcus pneumoniae*. *ISME Journal*, 12(10), 2363–2375. <https://doi.org/10.1038/s41396-018-0178-x>
- 543 Miller, M. B., & Bassler, B. L. (2001). Quorum Sensing in Bacteria. *Annual Review of Microbiology*, 55(1), 165–  
544 199. <https://doi.org/10.1146/annurev.micro.55.1.165>
- 545 Monds, R., & O’Toole, G. (2014). Metabolites as Intercellular Signals for Regulation of Community-Level Traits.  
546 In S. Winans & M. Basslet (Eds.), *Chemical Communication among Bacteria* (pp. 105–129).  
547 <https://doi.org/10.1128/9781555815578.ch8>
- 548 Monnet, V., Juillard, V., & Gardan, R. (2016). Peptide conversations in Gram-positive bacteria. *Critical Reviews*  
549 *in Microbiology*, 42(3), 339–351. <https://doi.org/10.3109/1040841X.2014.948804>
- 550 Montgomery, K., Charlesworth, J. C., LeBard, R., Visscher, P. T., & Burns, B. P. (2013). Quorum sensing in  
551 extreme environments. *Life*, 3(1), 131–148. <https://doi.org/10.3390/life3010131>

- 552 Morcia, C., Tumino, G., Ghizzoni, R., Bara, A., Salhi, N., & Terzi, V. (2017). In vitro evaluation of sub-lethal  
553 concentrations of plant-derived antifungal compounds on FUSARIA growth and mycotoxin production.  
554 *Molecules*, 22(8). <https://doi.org/10.3390/molecules22081271>
- 555 Mosel, D. D., Dumitru, R., Hornby, J. M., Atkin, A. L., & Nickerson, K. W. (2005). Farnesol concentrations  
556 required to block germ tube formation in *Candida albicans* in the presence and absence of serum. *Applied*  
557 *and Environmental Microbiology*, 71(8), 4938–4940. <https://doi.org/10.1128/AEM.71.8.4938-4940.2005>
- 558 Nawrocki, A., Fey, S. J., Roepstorff, P., & Larsen, P. M. (2001). The effects of transcription regulating genes.  
559 *Proteomics*, 1, 1022–1032.
- 560 Nealon, K. H., & Hastings, J. W. (2006). Quorum sensing on a global scale: Massive numbers of bioluminescent  
561 bacteria make milky seas. *Applied and Environmental Microbiology*, 72(4), 2295–2297.  
562 <https://doi.org/10.1128/AEM.72.4.2295-2297.2006>
- 563 Ng, W.-L., & Bassler, B. L. (2009). 基因的改变 NIH Public Access. *Annu Rev Genet*, 43, 197–222.
- 564 Nickerson, K. W., Atkin, A. L., & Hornby, J. M. (2006). Quorum sensing in dimorphic fungi: Farnesol and beyond.  
565 *Applied and Environmental Microbiology*, 72(6), 3805–3813. <https://doi.org/10.1128/AEM.02765-05>
- 566 Niemann, H., Lösekann, T., De Beer, D., Elvert, M., Nadalig, T., Knittel, K., ... Boetius, A. (2006). Novel  
567 microbial communities of the Haakon Mosby mud volcano and their role as a methane sink. *Nature*,  
568 443(7113), 854–858. <https://doi.org/10.1038/nature05227>
- 569 Otto, M., Süßmuth, R., Jung, G., & Götz, F. (1998). Structure of the pheromone peptide of the *Staphylococcus*  
570 *epidermis* agr system. *FEBS Letters*, 424(1–2), 89–94. [https://doi.org/10.1016/S0014-5793\(98\)00145-8](https://doi.org/10.1016/S0014-5793(98)00145-8)
- 571 Özkaya, Ö., Xavier, K. B., Dionisio, F., & Balbontín, R. (2017). Maintenance of microbial cooperation mediated  
572 by public goods in single- and multiple-trait scenarios. *Journal of Bacteriology*, 199(22), 1–14.  
573 <https://doi.org/10.1128/JB.00297-17>
- 574 Padder, S. A., Prasad, R., & Shah, A. H. (2018). Quorum sensing : A less known mode of communication among  
575 fungi. *Microbiological Research*, 210(February), 51–58. <https://doi.org/10.1016/j.micres.2018.03.007>
- 576 Pai, A., Tanouchi, Y., & You, L. (2012). Optimality and robustness in quorum sensing (QS)-mediated regulation  
577 of a costly public good enzyme. *Proceedings of the National Academy of Sciences of the United States of*  
578 *America*, 109(48), 19810–19815. <https://doi.org/10.1073/pnas.1211072109>
- 579 Palkova, Z., Janderova, B., Gabriel, J., Zikanova, B., Pospisek, M., & Forstova, J. (1997). Ammonia mediates  
580 communication between yeast colonies. *Nature*, 390(6659), 532–536. <https://doi.org/10.1038/37398>
- 581 Papenfort, K., & Bassler, B. L. (2016). Quorum sensing signal-response systems in Gram-negative bacteria. *Nature*  
582 *Reviews Microbiology*, 14(9), 576–588. <https://doi.org/10.1038/nrmicro.2016.89>
- 583 Patel, C. N., Wortham, B. W., Lines, J. L., Fetherston, J. D., Perry, R. D., & Oliveira, M. A. (2006). Polyamines  
584 are essential for the formation of plague biofilm. *Journal of Bacteriology*, 188(7), 2355–2363.  
585 <https://doi.org/10.1128/JB.188.7.2355-2363.2006>
- 586 Pena, R. T., Blasco, L., Ambroa, A., González-Pedrajo, B., Fernández-García, L., López, M., ... Tomás, M. (2019).  
587 Relationship between quorum sensing and secretion systems. *Frontiers in Microbiology*, 10(JUN).  
588 <https://doi.org/10.3389/fmicb.2019.01100>
- 589 Pereira, A. D., Cabezas, A., Etchebehere, C., Chernicharo, C. A. de L., & de Araújo, J. C. (2017). Microbial  
590 communities in anammox reactors: a review. *Environmental Technology Reviews*, 6(1), 74–93.  
591 <https://doi.org/10.1080/21622515.2017.1304457>
- 592 Polke, M., Sprenger, M., Scherlach, K., Martin, R., Hertweck, C., Hube, B., & Jacobsen, I. D. (2017). *A functional*  
593 *link between hyphal maintenance and quorum sensing in Candida albicans*. 103(October 2016), 595–617.  
594 <https://doi.org/10.1111/mmi.13526>
- 595 Pour, A. K. (2018). Communication for a Collective Response to Environmental Stress. *Microbial Sensing in*  
596 *Fermentation*, 169–199. <https://doi.org/10.1002/9781119248002.ch8>
- 597 Rachid, S., Ohlsen, K., Witte, W., Hacker, J., & Ziebuhr, W. (2000). Effect of subinhibitory antibiotic  
598 concentrations on polysaccharide intercellular adhesin expression in biofilm-forming *Staphylococcus*



- 599 epidermidis. *Antimicrobial Agents and Chemotherapy*, 44(12), 3357–3363.  
600 <https://doi.org/10.1128/AAC.44.12.3357-3363.2000>
- 601 Rahner, A., Hiesinger, M., & Schüller, H. J. (1999). Deregulation of gluconeogenic structural genes by variants of  
602 the transcriptional activator Cat8p of the yeast *Saccharomyces cerevisiae*. *Molecular Microbiology*, 34(1),  
603 146–156. <https://doi.org/10.1046/j.1365-2958.1999.01588.x>
- 604 Rajput, A., Gupta, A. K., & Kumar, M. (2015). Prediction and analysis of quorum sensing peptides based on  
605 sequence features. *PLoS ONE*, 10(3), 1–16. <https://doi.org/10.1371/journal.pone.0120066>
- 606 Ramage, G., Saville, S. P., Wickes, B. L., López-ribot, J. L., & Lo, L. (2002). Inhibition of *Candida albicans*  
607 Biofilm Formation by Farnesol , a Quorum-Sensing Molecule Inhibition of *Candida albicans* Biofilm  
608 Formation by Farnesol , a Quorum-Sensing Molecule Downloaded from <http://aem.asm.org/> on September  
609 16 , 2013 by Danish Veterina. *Applied and Environmental Microbiology*, 68(11), 5459–5463.  
610 <https://doi.org/10.1128/AEM.68.11.5459>
- 611 Rankin, L. M., Gibson, J. A. E., Franzmann, P. D., & Burton, H. R. (1996). The Chemical Stratification and  
612 Microbial Communities of Ace Lake, Antarctica: A Review of the Characteristics of a Marine-Derived  
613 Meromictic Lake. *Polarforschung*, 66(1--2), 33–52.
- 614 Redfield, R. J. (2002). Is quorum sensing a side effect of diffusion sensing? *Trends in Microbiology*, 10(8), 365–  
615 370. [https://doi.org/10.1016/S0966-842X\(02\)02400-9](https://doi.org/10.1016/S0966-842X(02)02400-9)
- 616 Richard, P., Bakker, B. M., & Teusink, B. (1996). Acetaldehyde Mediates the Synchronization of Sustained  
617 Glycolytic Oscillations in Populations of Yeast Cells - Richard - 2004 - European Journal of Biochemistry -  
618 Wiley Online Library. *European Journal of ...*, 241, 238–241. Retrieved from  
619 [http://onlinelibrary.wiley.com/doi/10.1111/j.1432-  
620 1033.1996.00238.x/abstract%5Cnpapers2://publication/uuid/316F651A-61B2-41B6-8485-  
621 DE9CE8D62123](http://onlinelibrary.wiley.com/doi/10.1111/j.1432-1033.1996.00238.x/abstract%5Cnpapers2://publication/uuid/316F651A-61B2-41B6-8485-DE9CE8D62123)
- 622 Rossignol, T., Logue, M. E., Reynolds, K., Grenon, M., Lowndes, N. F., & Butler, G. (2007). Transcriptional  
623 response of *Candida parapsilosis* following exposure to farnesol. *Antimicrobial Agents and Chemotherapy*,  
624 51(7), 2304–2312. <https://doi.org/10.1128/AAC.01438-06>
- 625 Rutherford, S. T., & Bassler, B. L. (2012). Bacterial quorum sensing: Its role in virulence and possibilities for its  
626 control. *Cold Spring Harbor Perspectives in Medicine*, 2(11), 1–25.  
627 <https://doi.org/10.1101/cshperspect.a012427>
- 628 Schuster, M., Lostroh, C. P., Ogi, T., & Greenberg, E. P. (2003). Identification, Timing, and Signal Specificity of  
629 *Society*, 185(7), 2066–2079. <https://doi.org/10.1128/JB.185.7.2066>
- 630 Schuster, M., Sexton, D. J., & Hense, B. A. (2017). Why quorum sensing controls private goods. *Frontiers in*  
631 *Microbiology*, 8(MAY), 1–16. <https://doi.org/10.3389/fmicb.2017.00885>
- 632 SentheShanuganathan, S. (1960). The mechanism of the formation of higher alcohols from amino acids by  
633 *Saccharomyces cerevisiae*. *The Biochemical Journal*, 74, 568–576. <https://doi.org/10.1042/bj0740568>
- 634 Shade, A., McManus, P. S., & Handelsman, J. (2013). Unexpected Diversity during Community Succession in  
635 the Apple Flower Microbiome. *MBio*, 4(2), 1–12. <https://doi.org/10.1128/mBio.00602-12.Editor>
- 636 Shank, E. A. (2018). Considering the Lives of Microbes in Microbial Communities. *MSystems*, 3(2), 3–6.  
637 <https://doi.org/10.1128/msystems.00155-17>
- 638 Sifri, C. D. (2008). Healthcare Epidemiology: Quorum Sensing: Bacteria Talk Sense. *Clinical Infectious Diseases*,  
639 47(8), 1070–1076. <https://doi.org/10.1086/592072>
- 640 Slamti, L., & Lereclus, D. (2002). A cell-cell signaling peptide activates the PlcR virulence regulon in bacteria of  
641 the *Bacillus cereus* group. *EMBO Journal*, 21(17), 4550–4559. <https://doi.org/10.1093/emboj/cdf450>
- 642 Smukalla, S., Caldara, M., Pochet, N., Beauvais, A., Guadagnini, S., Yan, C., ... Verstrepen, K. J. (2008). FLO1  
643 Is a Variable Green Beard Gene that Drives Biofilm-like Cooperation in Budding Yeast. *Cell*, 135(4), 726–  
644 737. <https://doi.org/10.1016/j.cell.2008.09.037>
- 645 Smukalla, S., Caldara, M., Pochet, N., Beauvais, A., Yan, C., Vincens, M. D., ... Verstrepen, K. J. (2009).  
646 Cooperation in Budding Yeast. *Cell*, 135(4), 726–737. <https://doi.org/10.1016/j.cell.2008.09.037.FLO1>

- 647 Stevens, A. M., Dolan, K. M., & Greenberg, E. P. (1995). Synergistic binding of the *Vibrio fischeri* LuxR  
648 transcriptional activator domain and RNA polymerase to the lux promoter region. *Proceedings of the*  
649 *National Academy of Sciences*, 92(8), 3631–3631. <https://doi.org/10.1073/pnas.92.8.3631-a>
- 650 Struss, A. K., Pasini, P., Flomenhoft, D., Shashidhar, H., & Daunert, S. (2012). Investigating the effect of  
651 antibiotics on quorum sensing with whole-cell biosensing systems. *Analytical and Bioanalytical Chemistry*,  
652 402(10), 3227–3236. <https://doi.org/10.1007/s00216-012-5710-7>
- 653 Verbeke, F., De Craemer, S., Debunne, N., Janssens, Y., Wynendaele, E., Van de Wiele, C., & De Spiegeleer, B.  
654 (2017). Peptides as quorum sensing molecules: Measurement techniques and obtained levels in vitro and in  
655 vivo. *Frontiers in Neuroscience*, 11(APR), 1–18. <https://doi.org/10.3389/fnins.2017.00183>
- 656 Verbrugghe, E., Adriaensen, C., Martel, A., Vanhaecke, L., & Pasmans, F. (2019). Growth regulation in amphibian  
657 pathogenic chytrid fungi by the quorum sensing metabolite tryptophol. *Frontiers in Microbiology*, 10(JAN),  
658 1–12. <https://doi.org/10.3389/fmicb.2018.03277>
- 659 Wagner, V. E., Bushnell, D., Passador, L., Brooks, A. I., & Iglewski, B. H. (2014). *Microarray Analysis of*  
660 *Pseudomonas aeruginosa Quorum-Sensing Regulons: Effects of Growth Phase and Environment*  
661 *Microarray Analysis of Pseudomonas aeruginosa Quorum-Sensing Regulons: Effects of Growth Phase and*  
662 *Environment* †. 185(7), 2080–2095. <https://doi.org/10.1128/JB.185.7.2080>
- 663 Waters, C. M., & Bassler, B. L. (2005). QUORUM SENSING: Cell-to-Cell Communication in Bacteria. *Annual*  
664 *Review of Cell and Developmental Biology*, 21(1), 319–346.  
665 <https://doi.org/10.1146/annurev.cellbio.21.012704.131001>
- 666 Wellington, S., & Greenberg, P. E. (2019). Quorum Sensing Signal Selectivity and the Potential for Interspecies  
667 Cross Talk. *MBio*, 10(2), 1–14.
- 668 West, S. A., Winzer, K., Gardner, A., & Diggle, S. P. (2012). Quorum sensing and the confusion about diffusion.  
669 *Trends in Microbiology*, 20(12), 586–594. <https://doi.org/10.1016/j.tim.2012.09.004>
- 670 Westwater, C., Westwater, C., Balish, E., Balish, E., Scho, D. a., & Scho, D. a. (2005). *Candida albicans*-*Candida*  
671 *albicans*-Conditioned Medium Protects Yeast Cells from Oxidative Stress: a Possible Link between Quorum  
672 Sensing and Oxidative Stress Resistance Caroline. *Microbiology*, 4(10), 1654–1661.  
673 <https://doi.org/10.1128/EC.4.10.1654>
- 674 Williams, P., Winzer, K., Chan, W. C., & Cámara, M. (2007). Look who's talking: Communication and quorum  
675 sensing in the bacterial world. *Philosophical Transactions of the Royal Society B: Biological Sciences*,  
676 362(1483), 1119–1134. <https://doi.org/10.1098/rstb.2007.2039>
- 677 Winters, M., Arneborg, N., Appels, R., & Howell, K. (2019). Can community-based signalling behaviour in  
678 *Saccharomyces cerevisiae* be called quorum sensing? A critical review of the literature. *FEMS Yeast*  
679 *Research*, 19(5), 1–11. <https://doi.org/10.1093/femsyr/foz046>
- 680 Winzer, K., Hardie, K. R., & Williams, P. (2002). Bacterial cell-to-cell communication: sorry, can't talk now —  
681 gone to lunch! *Current Opinion in Microbiology*, 216–222. Retrieved from  
682 <papers3://publication/uuid/CD387931-31DE-461F-822B-7508C3E25950>
- 683 Wongsuk, T., Pumeesat, P., & Luplertlop, N. (2016). Fungal quorum sensing molecules: Role in fungal  
684 morphogenesis and pathogenicity. *Journal of Basic Microbiology*, Vol. 56, pp. 440–447.  
685 <https://doi.org/10.1002/jobm.201500759>
- 686 Wood, K. (2019). Microbial Ecology: Complex Bacterial Communities Reduce Selection for Antibiotic  
687 Resistance. *Current Biology*, 29(21), R1143–R1145. <https://doi.org/10.1016/j.cub.2019.09.017>
- 688 Wuster, A., & Babu, M. M. (2009). Transcriptional control of the quorum sensing response in yeast. *Molecular*  
689 *BioSystems*, 6(1), 134–141. <https://doi.org/10.1039/b913579k>
- 690 Yim, G., Wang, H. H., & Davies, J. (2007). Antibiotics as signalling molecules. *Philosophical Transactions of the*  
691 *Royal Society B: Biological Sciences*, 362(1483), 1195–1200. <https://doi.org/10.1098/rstb.2007.2044>
- 692 Yong, Y.-C., & Zhong, J.-J. (2012). Impacts of Quorum Sensing on Microbial Metabolism and Human Health.  
693 *Advances in Biochemical Engineering/Biotechnology*, 131(July 2015), 25–61.  
694 [https://doi.org/10.1007/10\\_2012\\_138](https://doi.org/10.1007/10_2012_138)
- 695 Zengler, K., & Zaramela, L. S. (2018). The social network of microorganisms — how auxotrophies shape complex

696 communities. *Nature Reviews Microbiology*, 16(6), 383–390. <https://doi.org/10.1038/s41579-018-0004-5>

697 Zhu, J., & Winans, S. C. (1999). Autoinducer binding by the quorum-sensing regulator TraR increases affinity for  
698 target promoters in vitro and decreases TraR turnover rates in whole cells. *Proceedings of the National*  
699 *Academy of Sciences of the United States of America*, 96(9), 4832–4837.  
700 <https://doi.org/10.1073/pnas.96.9.4832>

701 Zhu, J., & Winans, S. C. (2001). The quorum-sensing transcriptional regulator TraR requires its cognate signaling  
702 ligand for protein folding, protease resistance, and dimerization. *Proceedings of the National Academy of*  
703 *Sciences of the United States of America*, 98(4), 1507–1512. <https://doi.org/10.1073/pnas.98.4.1507>

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<b>TABLE 1.</b>		
<b>Attribute</b>	<b>Description</b>	<b>Citation</b>
<b>Proportional to Cell-Density:</b>	QSMs are created throughout the growth phase of the organism in a concentration proportional to cell density when cultured in a diffusion-restricted environment	(Albuquerque & Casadevall, 2012; Monds & O'Toole, 2014; Winzer et al., 2002)
<b>Triggered Response:</b>	The biological response, beyond the detoxification or metabolism of the QSM, is stimulated once a critical threshold concentration, the quorum, in the extracellular environment is reached	(Albuquerque & Casadevall, 2012; Monds & O'Toole, 2014; Winzer et al., 2002)
<b>Extracellular &amp; Identifiable:</b>	QSMs are secreted and accumulate within the surrounding extracellular environment so that the cues are readily available to neighboring cells, and should be a recognized compound.	(Albuquerque & Casadevall, 2012; Monds & O'Toole, 2014; Winzer et al., 2002)
<b>Defined Signaling Mechanisms:</b>	Specific receptors and cascade mechanisms exist to respond specifically to a QSM, and be identified. However, Monds and O'Tool (2008) deemed these criteria too restrictive, as some cells internalize QSMs and sense it at an intercellular concentration.	(Monds & O'Toole, 2014; Winzer et al., 2002)
<b>Reproducible Physiological Response:</b>	Application of a purified QSM reproduces the biological observable response at concentrations that are physiologically relevant	(Monds & O'Toole, 2014)
<b>Community Adaptive:</b>	The resultant biological response maximizes the fitness of the community involved in the signaling. Consideration of the evolutionary constraints implicit in ascribing biological function to the QSM required	(March & Bentley, 2004; Monds & O'Toole, 2014)
<b>Catabolism Byproduct:</b>	QSMs are not exclusively a chemical product derived from metabolic catabolism. Monds & O'Toole argue that metabolites are excellent candidates for cell-to-cell signaling, as these molecules are would play a dual-role and consequently be more time and energy-efficient, however in order to claim functionality as a QSM, these moleculares must elicit a community response dissimilar to its metabolic purpose.	(Monds & O'Toole, 2014)