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PUBLICATION
X. Chen et al., "Structural identification of a bacterial quorum-sensing signal containing boron," *Nature*, **415**, 545 (2002).

FUNDING
National Institutes of Health
National Science Foundation
Office of Naval Research
Deutsche Akademischer Austauschdienst (Germany)

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Structural Identification of a Bacterial Quorum Sensing Signal Containing Boron

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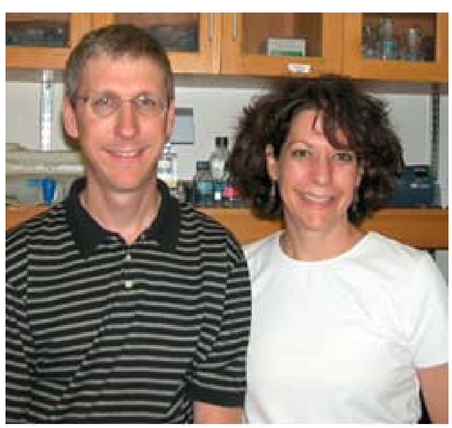
In a process known as quorum sensing, bacteria communicate with one another using chemical signalling molecules called autoinducers. This cell-cell communication allows a population of bacteria to coordinate the gene expression, and therefore the behavior, of the group. Recent work by researchers from Princeton University and the School of Chemistry, Polymers and Materials in Strasbourg, France, has led to the identification of a novel autoinducer, AI-2, that may serve as a 'universal' signal for communication between different bacterial species. AI-2 unexpectedly contains boron, an element that, while ubiquitous in the biosphere, has seldom been observed to play a role in biological processes.

Quorum sensing allows a population of bacteria to coordinate their gene expression, and therefore their collective behavior. Usually, quorum sensing controls processes that are effective when a large number of bacteria act together. Some bacteria, for example, produce visible light in response to autoinducers that accumulate in dense cultures. Pathogenic bacteria can use quorum sensing to evade the immune system, express toxic virulence factors, or coordinate the formation of antibiotic-resistant biofilms.

Recently, we identified a novel autoinducer, AI-2, that has the potential to mediate communication among different bacterial species. The presence of AI-2 can be detected by adding it to a specially engineered strain of the bioluminescent marine bacterium *V. harveyi,* which emits light in the presence of AI-2. Using this assay, it was possible to show that a large number of bacterial species produce AI-2. These and other findings suggest that communication via AI-2 could be a common mechanism that bacteria employ for inter-species interaction in natural environments.

The chemical identity of AI-2 was ascertained in a somewhat unusual way using x-ray crystallography. AI-2 was crystallized in a complex with its *V. harveyi* receptor protein, LuxP. Crystals formed by the LuxP-AI-2 complex diffracted beyond 1.5 Å resolution at NSLS Beamline X-12C. Because of the high quality of the resulting electron density maps, it was straightforward to construct an atomic model for AI-2 (Figure 1).

Earlier work had suggested that AI-2 is derived from the precursor 4,5-dihydroxy-2,3-pentanedione. The cyclic form of this precursor is a plausible substrate for the addition of borate. We were nonetheless surprised to find that the AI-2 electron density appears to match this borate addition product. Confirmatory evidence, including ^{11}B-NMR spectra and the ability of boric acid to stimulate bioluminescence in *V. harveyi* supported the conclusion that AI-2 is a novel furanosyl borate diester. Thus, interspecies quorum sensing represents one of the first biochemically defined roles for boron in biology.



Members of the Princeton University team: Team leader Fred Hughson (left) and collaborator Bonnie Bassler.

Many questions remain. For example, it is not yet clear how, or whether, the use of boron enhances signal transmission or signal specificity. Also, we do not yet know whether the use of boron in cell-cell signaling is confined to bacteria that live in marine environments or is more widespread. Nonetheless, biotechnological research is focused on the development of molecules that are structurally related to AI-2. Such molecules may be useful as anti-microbial drugs aimed at bacteria that control virulence through AI-2 quorum sensing. Since many bacteria produce AI-2, drugs that target AI-2 quorum sensing could be broadly used in the future.

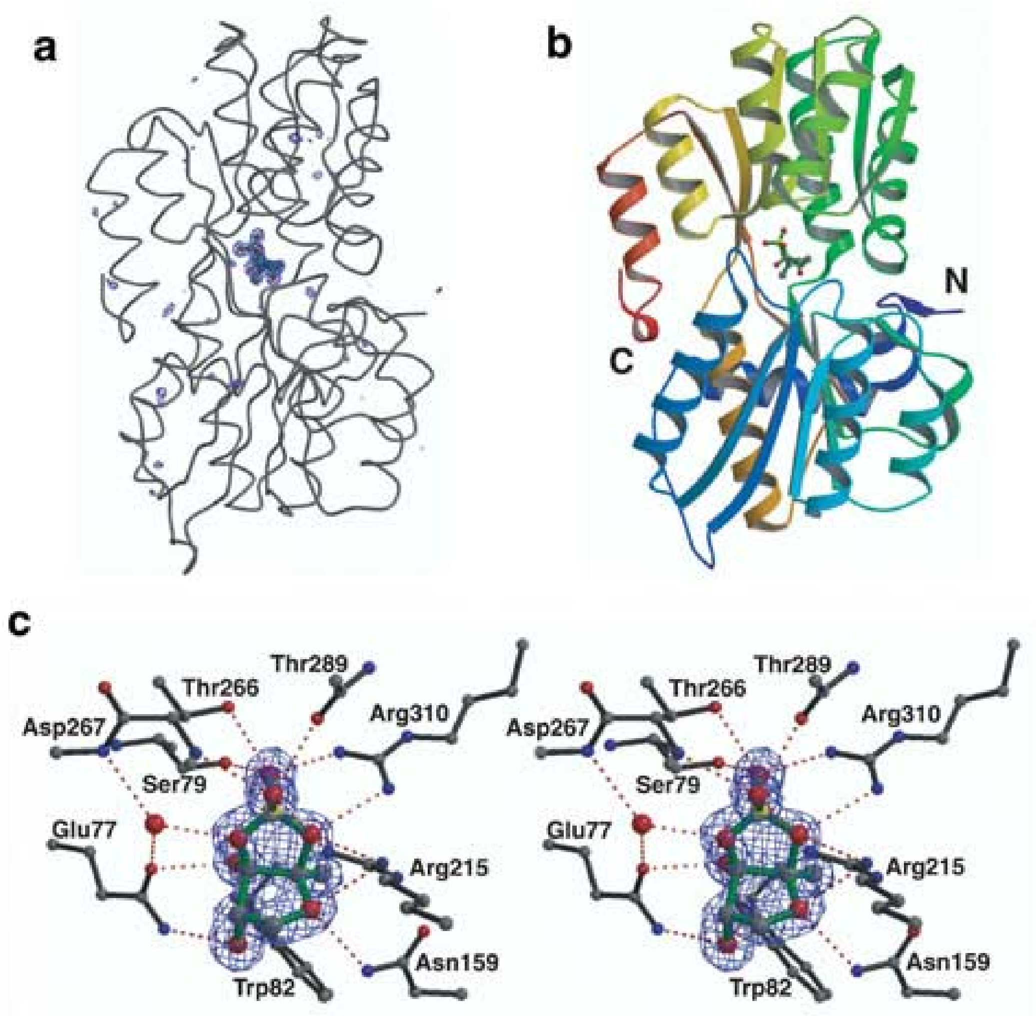


Figure 1. *Structure of the LuxP-AI-2 complex.* ***a.*** *Electron density from which the LuxP contribution has been subtracted to highlight the electron density for AI-2 in the center.* ***b.*** *Overview showing AI-2 (stick figure) bound to LuxP (ribbon). The Lux P protein backbone is shown in rainbow colors from its N- to its C-terminus.* ***c.*** *Stereoview close-up of AI-2 bound to LuxP, in the form of an electron density map (prior to AI-2 addition to the model). Boron, oxygen, nitrogen, and carbon are colored yellow, red, blue, and gray, respectively.*