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Infobiotics

A systems analysis of the AHL Quorum Sensing system in *Pseudomonas aeruginosa*

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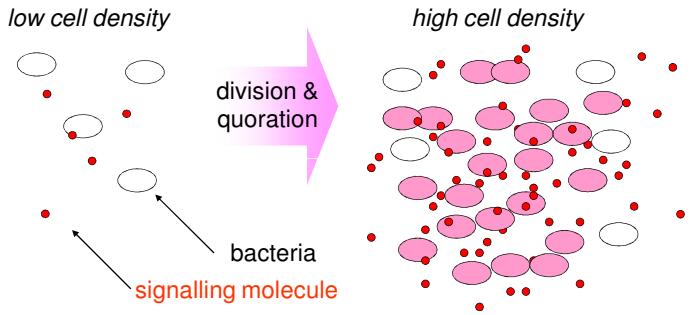
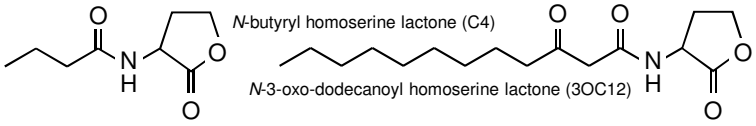
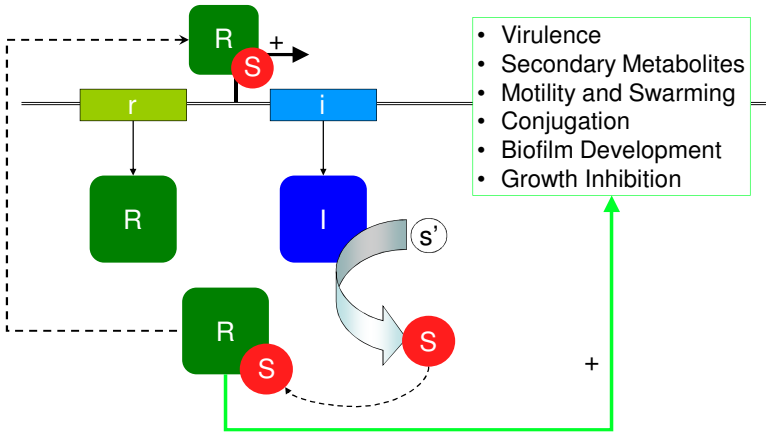
Quorum sensing is a *cell density* dependent gene regulation system whereby populations of bacteria communicate through small diffusible signalling molecules in order to coordinate the expression of specific genes such as virulence factors depending on the their numbers, exhibiting population-level behaviour.[1]



Quorum sensing relies on the synthesis, accumulation and subsequent sensing of these signals, particularly *N*-acylhomoserine lactones (AHLs) in *P. aeruginosa:*



In most QS systems the signals, S, are synthesised by an I enzyme encoded by a geneI. A receptor protein R encoded by a geneR interacts with S to form an active transcription factor R·S which binds to geneI amplifying the production of I protein and therefore synthesis of S. This transcription factor also regulates many other genes.



Modelling quorum sensing therefore requires a colony-level view with many individual copies of the same quorum sensing gene network in different states. Ordinary differential equations are problematic for modelling gene networks, as low numbers of molecules decrease the signal to noise ratio due to the finite number effect ($\eta \sim 1/\sqrt{N}$).

P systems represent a novel *discrete*, *stochastic* and *mesoscopic* framework for modelling cellular systems[2] that facilitates the assembly of transcriptional *modules*, mass duplication of cells and realistic kinetics using the well-studied Gillespie algorithm, for the observation of emergent behaviours through simulation.

A P system consists of a nested membrane structure (colonies, cells or intracellular compartments), containing multisets of objects (genes, complexes, metabolites) which are rewritten by rules (reactions).

Biological entity	P system specification
Population of molecules	Multisets of objects a^2b^3c
Compartments	Membranes $[\ ]_{label}$
Molecular interactions	Rewriting rules on objects $a \xrightarrow{c} b$ a is transformed into b with rate c
Modules	Sets of rules with input vectors $Name(\{molecules,...\}\{constants,...\}\{labels\})$

Composing a quorum sensing module

In our methodology a *module* is a set of rules that define a integrated biological function, such as unregulated gene expression consisting of production and degradation of the *LasR* protein from gene *lasR*:

$$UnReg(\{lasR, LasR\},\{c_1,c_2\},\{b\}) = \begin{cases} [\ lasR\ ]_b \xrightarrow{c_1} [\ lasR + LasR\ ]_b, \\ [\ LasR\ ]_b \xrightarrow{c_2} [\ ]_b \end{cases}$$

Modules can be assembled into larger modules. Here a *LasI UnReg* module, *enz*ymatic *3OC12* synthesis and *diff*usion, *com*plexation and *pos*itive gene regulation modules are composed into the quorum sensing module $QS(\{LasR,...,RsaL{\cdot}lasI\},\{c_1,...,c_{24}\},\{b\})$ =

$$UnReg(\{lasI, LasI\},\{c_3,c_4\},\{b\}) = \begin{cases} [\ lasI\ ]_b \xrightarrow{c_3} [\ lasI + LasI\ ]_b, \\ [\ LasI\ ]_b \xrightarrow{c_4} [\ ]_b \end{cases}$$

$$Enz(\{LasI, 3OC12\},\{c_5\},\{b\}) = \{[\ LasI\ ]_b \xrightarrow{c_5} [\ LasI + 3OC12\ ]_b$$

$$Diff(\{3OC12\},\{c_6\},\{b\}) = \{[\ 3OC12\ ]_b \xrightarrow{c_6} [\ ]_b\ 3OC12$$

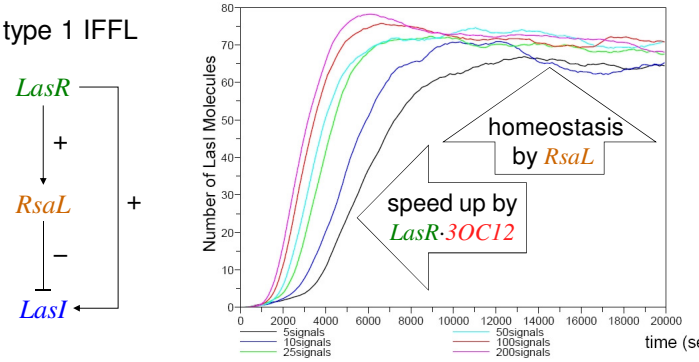
$$Com(\{LasR, 3OC12, LasR.3OC12\},\{c_8,c_9\},\{l\}) = \begin{cases} [\ LasR + 3OC12\ ]_b \xrightarrow{c_8} [\ LasR.3OC12\ ]_b \\ [\ LasR.3OC12\ ]_b \xrightarrow{c_9} [\ LasR + 3OC12\ ]_b \end{cases}$$

$$Pos(\{LasR.3OC12, lasI, LasR.3OC12.lasI, LasI\}, LasR.3OC12.lasI, LasI\},\{c_{11},c_{12},c_{13},c_{14}\},\{b\}) = \begin{cases} [\ LasR.3OC12 + lasI\ ]_b \xrightarrow{c_{11}} [\ LasR.3OC12.lasI\ ]_b \\ [\ LasR.3OC12.lasI\ ]_b \xrightarrow{c_{12}} [\ LasR.3OC12 + lasI\ ]_b \\ [\ LasR.3OC12.lasI\ ]_b \xrightarrow{c_{13}} [\ LasR.3OC12.lasI + LasI\ ]_b, \\ [\ LasI\ ]_b \xrightarrow{c_{14}} [\ ]_b \end{cases}$$

When coupled to a negative gene regulation module through *lasI*

$$Neg(\{RsaL, lasI, RsaL.lasI\},\{c_{23},c_{24}\},\{b\}) = \begin{cases} [\ RsaL + lasI\ ]_b \xrightarrow{c_{23}} [\ RsaL.lasI\ ]_b \\ [\ RsaL.lasI\ ]_b \xrightarrow{c_{24}} [\ RsaL + lasI\ ]_b \end{cases}$$

a *3OC12* controlled type 1 incoherent feed-forward loop[3] emerges.



In *P. aeruginosa* *LasR* stimulates *LasI*, and *RsaL* which supresses *LasI*. This ensures the rapid but controlled production of AHL-synthesis required to coordinate a population phenotype.

References

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