An introduction to stochastic and probabilistic P systems

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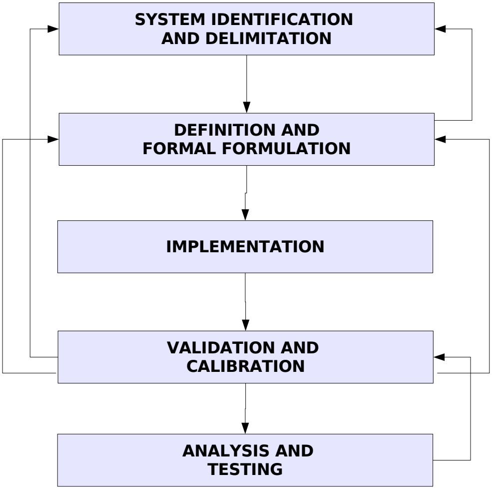
Models:

- Scientists regularly use abstractions of the reality.
- Abstractions of the real-world onto a mathematical domain.
- They highlight some key features while ignoring others that are assumed to be irrelevant.
- They should be seen as statements of *our* current knowledge of the phenomenon under research.

Properties:

- Relevance.
- Understandability.
- Extensibility.
- Computability and Mathematical tractability.

The modelling process



Modelling based on Membrane Computing

Modelling cell systems:

- The non deterministic and maximally parallel approach produces two inaccuracies:
  - Reactions do not occur at a correct rate.
  - All time steps are equal and do not represent the time evolution of the real cell system.

These two problems are interdependent and must be addressed when devising a relevant modelling framework for cell systems as it has been done in other computational approaches.

Multienvironment P systems: Syntax

Multienvironment P system of degree (q, m, n) taking T time units: $(G, \Gamma, \Sigma, T, \mathcal{R}_E, \mu, \mathcal{R}, \Pi_1, \ldots, \Pi_n)$ where:

- $G = (V, S)$ is a directed graph. Let $V = \{e_1, \ldots, e_m\}$ whose elements are called environments;
- Γ is the working alphabet and $\Sigma \subsetneq \Gamma$ is an alphabet (objects in the environments);
- T is a natural number that represents the simulation time of the system;
- $\mathcal{R}_E$ is a finite set of communication rules between environments of the following forms

$$(x)_{e_j} \xrightarrow{p_r} (y_1)_{e_{j_1}} \cdots (y_h)_{e_{j_h}} \quad \text{and} \quad (\Pi_k)_{e_j} \xrightarrow{p_{r'}} (\Pi_k)_{e_{j'}}$$

  where $p_r, p_{r'}$ are computable functions whose domain is $\{1, \ldots, T\}$.
- μ is a rooted tree with q nodes, called membranes, injectively labelled by elements of $\{1, \ldots, q\} \times \{0, +, -\}$. The root of the tree is labelled by 1 and the initial charge is 0.
- $\mathcal{R}$ is a finite set of rules of the type $u[v]_i^{\alpha} \xrightarrow{f_r} u'[v']_i^{\alpha'}$ such that:
  - f_r is a computable function whose domain is $\{1, \ldots, T\}$.
- $\Pi_k = (\Gamma, \mu, \mathcal{M}_{1,k}, \ldots, \mathcal{M}_{q,k}, \mathcal{R})$ is a P system of degree q. All of them have the same working alphabet, the same membrane structure and the same set of rules.

Multienvironment P systems: Semantics (I)

Initially:

- The multiset of objects associated with any environment is empty.
- The electrical charges of all membranes are neutral.

Applicability of:

- A rule of the type: $(x)_{e_j} \xrightarrow{p_r} (y_1)_{e_{j_1}} \cdots (y_h)_{e_{j_h}}$
- A rule of the type: $(\Pi_k)_{e_j} \xrightarrow{p_{r'}} (\Pi_k)_{e_{j'}}$
- A rule of the type: $u[v]_i^{\alpha} \xrightarrow{f_r} u'[v']_i^{\alpha'}$

At any instant, the value of the computable functions represent the affinity of applicable rule to be applied.

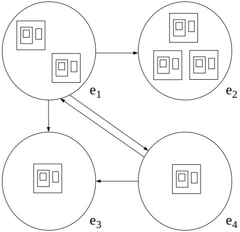
Multienvironment P systems: Semantics (II)

- Instantaneous description (configuration)
- A transition step.
- A computation of the system.

Multicompartmental P systems: Syntax

Multienvironment P systems of degree (q, m, n) taking T time units such that:

- The computable functions associated with the rules within each environment are the *propensities*, computed from the stochastic constants.
- Initially, P systems will be distributed randomly over the different environments.

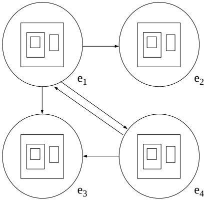


- Rules of the type $(x)_{e_j} \xrightarrow{p_r} (y_1)_{e_{j_1}} \cdots (y_h)_{e_{j_h}}$ verify $h = 1$.

Population Dynamics P systems: Syntax

Multienvironment P systems of degree (q, m, m) taking T time units such that:

- Initially, each environment e_j contains exactly a P system (denoted by Π_j).



- Computable functions p_r have a range contained in $[0,1]$, and:
  - For each $e_j \in V$, $x \in \Sigma$, the sum of functions associated with rules of the type $(x)_{e_j} \xrightarrow{p_r} (y_1)_{e_{j_1}} \cdots (y_h)_{e_{j_h}}$ is the constant function equal to 1.
  - If a rule is of the type $(x)_{e_j} \xrightarrow{p_r} (y_1)_{e_{j_1}} \cdots (y_h)_{e_{j_h}}$, then there is not a rule from $\mathcal{R}$ whose left-hand side is $u[v]_1^{\alpha}$, with $x \in u$.
- Functions $p_{r'}$ associated with rules of the type $\mathcal{R}_E$ $(\Pi_k)_{e_j} \xrightarrow{p_{r'}} (\Pi_k)_{e_{j'}}$ are constant and equal to 0.
- For each $r \in \mathcal{R}$ of Π_j, function f_r depends on (e_j) (we will denote $f_{r,j}$), and its range is contained in $[0,1]$. Besides, for each $u, v \in M_f(\Gamma)$, $1 \le i \le q$ and $\alpha, \alpha' \in \{0,+,-\}$, the sum of functions $f_{r,j}$ with $r \equiv u[v]_i^{\alpha} \rightarrow u'[v']_i^{\alpha'}$, is the constant function equal to 1.

Semantics

Multicompartmental P systems:

- The semantics of a multicompartmental P system can be simulated by the *multicompartmental Gillespie's algorithm*.

Population Dynamics P systems:

- The semantics of a Population Dynamics P system can be simulated by the *DCBA algorithm*.

Multicompartmental P systems: A case study

Quorum sensing in Vibrio fischeri

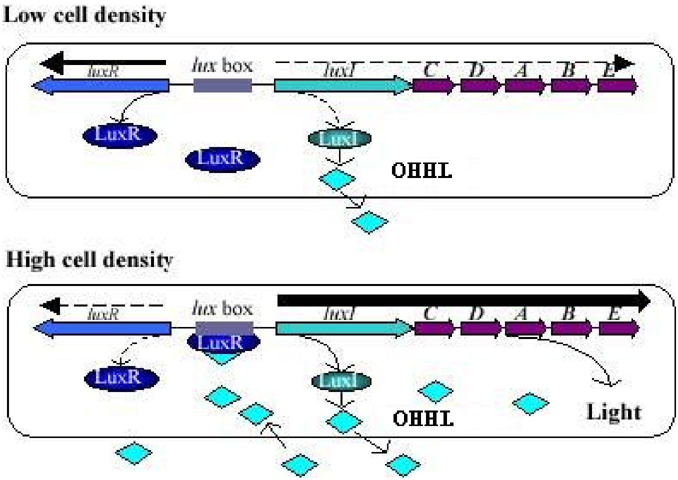
- Bacteria are generally considered to be independent unicellular organisms.
- *Vibrio fischeri* exhibit coordinated behaviour which allows an entire population of bacteria to regulate the expression of certain or specific genes in a coordinated way depending on the size of the population.
- This cell density dependent gene regulation system is referred to as *quorum sensing*.

Quorum sensing in Vibrio fischeri (II)

- Vibrio fischeri exists naturally either in a free-living planktonic state or as a symbiont of certain luminescent squid.
- The bacteria colonise specialised light organs in the squid.
- The source of the luminescence is the bacteria themselves.
- Luminescence in the squid is involved in the attraction of prey, camouflage and communication between different individuals.

Quorum sensing in Vibrio fischeri (III)

Molecular mechanisms (K.H. Nealson y J.W. Hasting, 1979; K.L Visic et al., 2000):



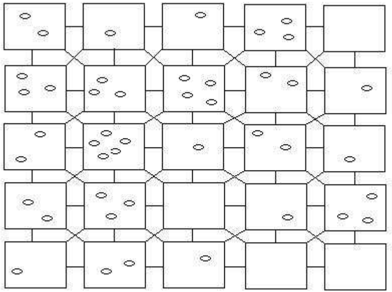
Modelling Quorum Sensing System in Vibrio fischeri (I)

We will study the behaviour of a population of N bacteria placed inside a multicompartmental P system of degree $(25, 1, N)$. [1].

$$\mathbf{ME} = (G, \Gamma, \Sigma, T, \mathcal{R}_E, \mu, \mathcal{R}, \Pi_1, \ldots, \Pi_N)$$

where:

- $G = (V = \{e_1, \ldots, e_{25}\}, S)$ is the following directed graph.



[1] F.J. Romero, M.J. Pérez-Jiménez. A model of the Quorum Sensing System in Vibrio Fischeri using P systems. *Artificial Life*, **14**, 1 (2008), 95–109.

Modelling Quorum Sensing System in Vibrio fischeri (II)

- $\Gamma = \{\text{LuxR}, \text{LuxR.OHHL}, \text{LuxBox}, \text{LuxR.OHHL.LuxBox}, \text{OHHL}\}$.
- $\Sigma = \{\text{OHHL}\}$.
- $T \geq 1$.
- Rules from $\mathcal{R}_E$.

$$r_1 : (\ \text{OHHL}\ )_{e_i} \xrightarrow{c_1} (\ \ )_{e_i}$$
$$r_2 : (\ \text{OHHL}\ )_{e_i} \xrightarrow{c_2} (\ \text{OHHL}\ )_{e_j}$$
$$r_3 : (\ [\ ]_b\ )_{e_i} \xrightarrow{c_3} (\ [\ ]_b\ )_{e_j}$$

- $\mu = [\ ]_b$.

Modelling Quorum Sensing System in Vibrio fischeri (III)

- Rules from $\mathcal{R}$:

$$
\begin{array}{rl}
r_4 : & OHHL\ [\ ]_b \xrightarrow{c_4} [\ OHHL\ ]_b \\
r_5 : & [\ LuxBox\ ]_b \xrightarrow{c_5} [\ LuxBox + OHHL\ ]_b \\
r_6 : & [\ LuxBox\ ]_b \xrightarrow{c_6} [\ LuxBox + LuxR\ ]_b \\
r_7 : & [\ LuxR + OHHL\ ]_b \xrightarrow{c_7} [\ LuxR.OHHL\ ]_b \\
r_8 : & [\ LuxR.OHHL\ ]_b \xrightarrow{c_8} [\ LuxR + OHHL\ ]_b \\
r_9 : & [\ LuxR.OHHL + LuxBox\ ]_b \xrightarrow{c_9} [\ LuxR.OHHL.LuxBox\ ]_b \\
r_{10} : & [\ LuxR.OHHL.LuxBox\ ]_b \xrightarrow{c_{10}} [\ LuxR.OHHL + LuxBox\ ]_b \\
r_{11} : & [\ LuxR.OHHL.LuxBox\ ]_b \xrightarrow{c_{11}} [\ LuxR.OHHL.LuxBox + OHHL\ ]_b \\
r_{12} : & [\ LuxR.OHHL.LuxBox\ ]_b \xrightarrow{c_{12}} [\ LuxR.OHHL.LuxBox + LuxR\ ]_b \\
r_{13} : & [\ OHHL\ ]_b \xrightarrow{c_{13}} OHHL\ [\ ]_b \\
r_{14} : & [\ OHHL\ ]_b \xrightarrow{c_{14}} [\ ]_b \\
r_{15} : & [\ LuxR\ ]_b \xrightarrow{c_{15}} [\ ]_b \\
r_{16} : & [\ LuxR.OHHL\ ]_b \xrightarrow{c_{16}} [\ ]_b
\end{array}
$$

Modelling Quorum Sensing System in Vibrio fischeri (IV)

- $\Pi_k = (\Sigma, L, \mu, M_1, \mathcal{R})$, $1 \leq k \leq N$, where:
  - $\Sigma = \{\text{OHHL}\}$.
  - $L = \{b\}$.
  - $\mu = [\ ]_b$.
  - $M_1 = \{LuxBox\}$.

Stochastic Constants associated with the rules:

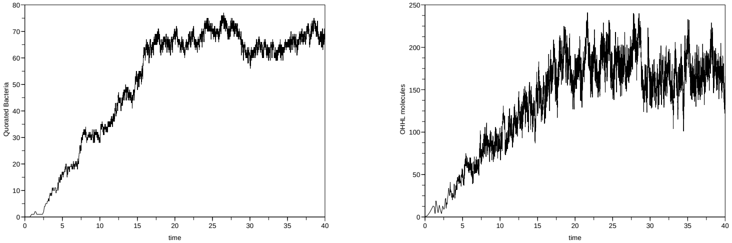
$c_1 = 5, c_2 = 8, c_3 = 2, c_4 = 1, c_5 = 2, c_6 = 2, c_7 = 9, c_8 = 1,$
$c_9 = 10, c_{10} = 2, c_{11} = 250, c_{12} = 200, c_{13} = 50, c_{14} = 30, c_{15} = 20, c_{16} = 20.$

Results and Discussions

- The model has been represented in SBML (Systems Biology Markup Language).
- The SBML code was generated using CellDesigner.
- The semantics has been captured by the multicompartmental Gillespie's algorithm.
- We have run our simulations using a program written in C with input file the SBML file specifying our model.
- The emergent behaviour of the system has been studied for three populations of different size to examine how bacteria can sense the number of bacteria (*quorum*).

A population of 100 bacteria

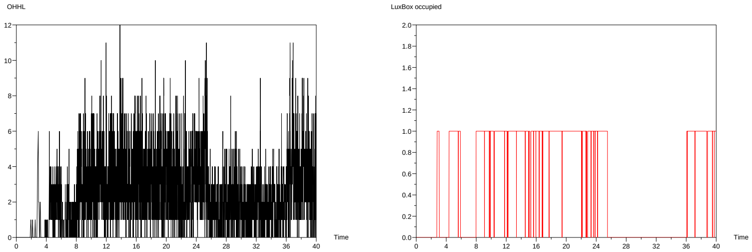
Evolution over time of the number of quorated bacteria [2] and the number of signals (OHHL) in the environment.



Number of quorated bacteria (left) and signals in the environment (right)

[2] We will say that a bacterium is quorated if the LuxBox in this bacterium is occupied by the complex producing the transcription of the enzymes involved in the production of light.

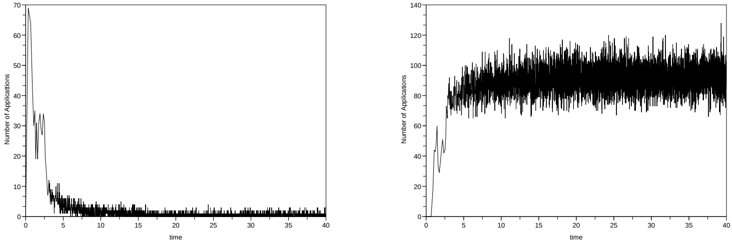
In our approach the behaviour of each individual in the population can be tracked.



Number of signals and occupation of the LuxBox in a bacterium

A population of 300 bacteria

We can also study how rules are applied across the evolution of the system.

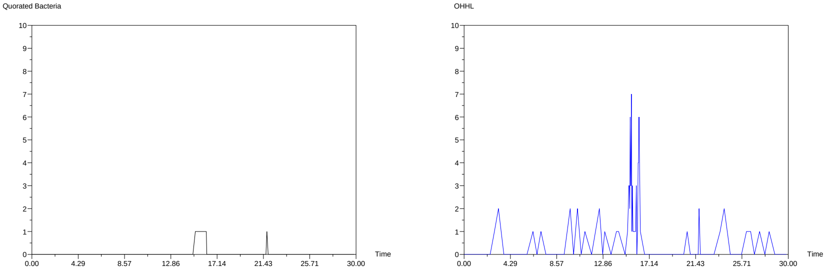


Number of applications of rules r_5 and r_{11} in a population of 300 bacteria

r_5 : $[\ \text{LuxBox}\ ]_b \xrightarrow{c_1} [\ \text{LuxBox} + \text{OHHL}\ ]_b$

r_{11} : $[\ \text{LuxR.OHHL.LuxBox}\ ]_b \xrightarrow{c_7} [\ \text{LuxR.OHHL.LuxBox} + \text{OHHL}\ ]_b$

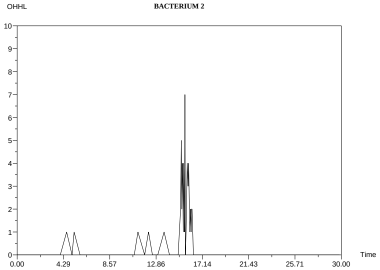
A population of 10 bacteria



Quorated bacteria and signals in the environment in a population of 10 bacteria.

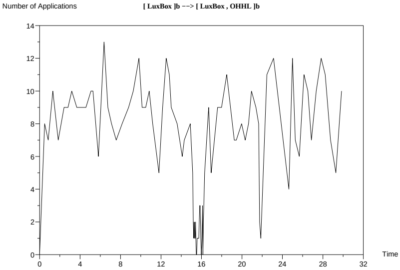
In this case no recruitment process takes place and the signal does not accumulate in the environment.
Only one of the bacteria guessed wrong the size of the population and got upregulated.

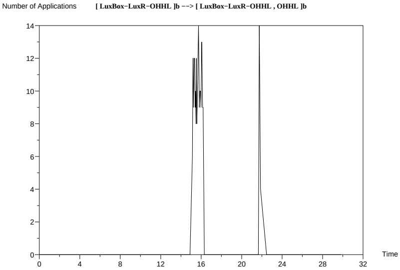
Next figure depicts the behaviour of the bacterium that got quorated.



Behaviour of a bacterium in a population of 10 bacteria.

Finally, we observe that for only 10 bacteria the system remains in a downregulated state.





Number of applications of rules r_5 and r_{11} in a populaton of 10 bacteria.

Conclusions

- A model of the quorum sensing system in Vibrio fischeri within the framework of multicompartmental P systems.
- Our approach takes into account the discrete nature of the components of the system, the level of noise and the role played by membranes.
- We have been able to study the emergent behaviour of different populations of bacteria in an heterogeneous environment.
- The results of our model show that
  - On the one hand bacteria remain dark at low cell densities.
  - On the other hand in big size populations bacteria are able to sense the number of individuals and the population starts to emit light in a coordinated way.
- These results agree well with in vitro observations.

THANK YOU!