Model and analysis of cell population density estimation via Quorum Sensing

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Molecular bio-nano communication networks

- Advances in bio-nano technology and biology
  - bio-inspired nano-devices, biological nanosensors, prosthetic devices
- Biomedical, industrial, environmental applications
- Comm. networks & protocols at nanometer length scales
  - Actuation, coordination, chemotaxis, etc.

Source: http://www.ece.gatech.edu/research/labs/bwn/monaco/
Molecular bio-nano communication networks

- Electromagnetic comm. unfeasible
- Communication via molecular diffusion
- Most recent literature: [Nakano & al.’13], [Akyildiz & al.’08], [Mian & Rose, ’11], [Eckford, ’07], [Einolghozati & al.’13], [Kadloor & al.’12], [Arjmandi & al.’13]...
- Capacity achieving schemes?
  - Any simpler scheme?

Source: http://www.ece.gatech.edu/research/labs/bwn/monaco/
What is Quorum Sensing?

- Quorum sensing in bacteria:
  - Gene expression = \( f(\text{cell density}) \)
  - How does it work?
    1. AutoInducers (AI) produced
    2. AI concentration = \( f(\text{cell density}) \)
    3. AI reception activates gene expression
  - Regulates biofilm formation, virulence, diseases, antibiotic resistance, etc.
What is Quorum Sensing?

- Light emission *very demanding*, should be done only when population size is large enough
- Symbiotic relationship
  - The squid provides nutrients to *V. Fischeri* to grow
  - *V. Fischeri* provides light to hide from predators
  - Every morning, the squid gets rid of 95% of bacteria, & the process repeats

*Hawaiian bobtail squid*
Motivation

- Quorum Sensing enables coordination among large populations of cells
- Coordinate mechanism in future nanonetworks
- **Goals:**
  - Develop a model of Quorum Sensing
  - Necessary conditions for QS to function
  - Analysis of QS dynamics & cell population density estimation
Towards a model of QS

- “Ingredients” of QS
  1. Microbial community (e.g., Vibrio Fischeri)
Towards a model of QS

“Ingredients” of QS

1. Microbial community (e.g., Vibrio Fischeri)
2. *Autoinducers (AI)*
   - Produced by each cell and released in the extracellular environment

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Reception

Actuation
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Towards a model of QS

“Ingredients” of QS

1. Microbial community (e.g., Vibrio Fischeri)
2. Autoinducers (AI)
   - Produced by each cell and released in the extracellular environment
3. Receptors (R)
   - They bind to AIs within each cell to form complexes
4. Complexes (C)
   - 1 AI bound to 1 R

Actuation
Towards a model of QS

“Ingredients” of QS

1. Microbial community (*e.g.*, *Vibrio Fischeri*)
2. Autoinducers (AI)
   - Produced by each cell and released in the extracellular environment
3. Receptors (R)
   - They bind to AIs within each cell to form *complexes*
4. Complexes (C)
   - 1 AI bound to 1 R
5. Synthases (S)
   - “machines” that produce AIs
6. DNA binding sites
   - C activates DNA transcription (produce more S,R)
   - *Costly* gene expression
Model of each cell

- Synthases & Receptors produced at low basal rate
Model of each cell

- Synthases produce AIs inside cell
Transmission: AI diffusion across cell membrane (in/out)
**Model of each cell**

- $A_{\text{ext}}(t)$: AIs (outside)
- $A_i(t)$: AIs (inside)
- $R_i(t)$: receptors
- $S_i(t)$: synthases
- $\gamma$:
- $\beta$:
- $C_i(t)$: complexes
- Sites 1, 2, 3

**Reception:** Complex formation
Model of each cell

- **Actuation**: DNA binding → gene expression
Each cell modeled by queues

Cell population $N(t)$
- Increases with cell growth

Huge complexity!

Cells coupled via AI queue

AI leakage
Simulation tools based on queuing model

[Michelusi & al. 2015]

**OPEN SYSTEM:** cells grow in open space & closely packed (no boundaries → leakage of AI)

**CLOSED SYSTEM:** cells grow in finite box & sparse (boundaries → no leakage)
Simulations

- Higher density in open system
  - > Al concentration
  - Faster activation time

**OPEN SYSTEM**: cells grow in open space & closely packed (no boundaries → leakage of Al)

**CLOSED SYSTEM**: cells grow in finite box & sparse (boundaries → no leakage)
Simplified model

More comprehensive model

AIs generate more AIs

Simplified model

DNA
Internal Al s for each cell (local state) & external Al s

- $A_i(t)$: local Al
- Al diffusion in-out proportional to Al concentration, $\lambda \alpha$

Local: $\alpha_i(t) = \frac{A_i(t)}{V_c}$

Ext: $\alpha_{ext}(t) = \frac{A_{ext}(t)}{V - NV_c}$

- Al synthesis proportional to local Al availability $\rho_S, 0 + \rho_S A_i(t)$
Simplified model

- **Local AI** $A_i(t)$:
  - **Diffusion out-in**: *Augments* w.r. $\lambda \alpha_{ext}(t)$
  - **Diffusion in-out**: *Diminishes* w.r. $\lambda \alpha_i(t)$
  - **Synthesis**: *Augments* w.r. $\rho_{S,0} + \rho_S A_i(t)$
  - **AI & complex deg.**: *Diminishes* w.r. $\mu_D A_i(t)$

- **External AI** $A_{ext}(t)$:
  - **Diffusion out-in**: *Diminishes* w.r. $N \lambda \alpha_{ext}(t)$
  - **Diffusion in-out**: *Augments* w.r. $\lambda \sum_{i=1}^{N} \alpha_i(t)$
  - **AI degradation**: *Diminishes* w.r. $\mu_{D,ext} A_{ext}(t)$

- **Cells coupled through external AI**

- **Local AI captures local state and cell fluctuations**
Analysis of expected AI evolution

- State is $(\alpha_{ext}(t), \alpha_1(t), \alpha_2(t), \ldots, \alpha_N(t))$
- We want to compute $\bar{\alpha}_{ext}(t) = \mathbb{E}[\alpha_{ext}(t)] \& \bar{\alpha}_{cell}(t) = \mathbb{E}[\alpha_i(t)]$
  (note: $\bar{\alpha}_{cell}(t)$ is the same for all cells)
- $\bar{\alpha}_{cell}(t)$ characterizes cell sensitivity to population density
- Asymptotic analysis $V \to \infty$ with $\beta = \frac{N}{V}$ fixed

$$\frac{d}{dt} \begin{bmatrix} \bar{\alpha}_{ext}(t) \\ \bar{\alpha}_i(t) \end{bmatrix} = \mathbf{W} \begin{bmatrix} \bar{\alpha}_{ext}(t) \\ \bar{\alpha}_i(t) \end{bmatrix} + \begin{bmatrix} 0 \\ \frac{\rho_{s,0}}{V_c} \end{bmatrix}$$

- Study eigenvalues of $\mathbf{W}$: 0s of $\det(\mathbf{W} - s\mathbf{I}) = 0$, $s^{(+)}$, $s^{(-)}$
Analysis of expected AI evolution

- **Average response:**

\[
\begin{align*}
\bar{\alpha}_{ext}(t) & \approx X_{ext}^{(+) \ s(t)} + C_{ext} \\
\bar{\alpha}_{cell}(t) & \approx X_{cell}^{(+) \ s(t)} + C_{cell}
\end{align*}
\]

- **Response driven by largest eigenvalue, \( s^{(+)}(\rho) \)**
  - \( s^{(+)}(\rho) > 0 \): **exponential increase**, positive feedback loop
  - \( s^{(+)}(\rho) = 0 \): **linear** increase, positive feedback loop
  - \( s^{(+)}(\rho) < 0 \): **exponential decay**, steady state regime
Desirable properties of QS

- In the limit $\beta \to 0$, response should decay, $s^{(+)}(0) < 0$

$$\rho_S < \frac{\lambda}{V_c} + \mu_D$$

- Why? Positive feedback loop only for $\beta \geq \beta_{th}$
- Intuition: if synthesis > diffusion + degradation, local AI grows unbounded, not informative!
Desirable properties of QS

- Response should be stronger for larger $\beta$, $\frac{ds^{(+)}(\beta)}{d\beta} > 0$

$$\mu_D - \mu_{D,ext} < \rho_S < \frac{\lambda}{V_c} + \mu_D$$

- **Why?** QS activity should increase for larger population size
- **Intuition:** if internal degradation too intense, diffusion to the external environment is negligible
Convergence speed is driven by largest eigenvalue $s^{(+)}$.

Steady-state concentration difference between in & out:
- net flow from inside cells to external environment
- Difference due to external degradation

\[
\begin{align*}
\lambda &= 1 \\
\mu_{D,ext} &= 1 \\
\rho_{S,0} &= 1 \\
\rho_S &= 1 \\
\mu_D &= 1 \\
Vc &= 1 \\
\beta &= 0.5
\end{align*}
\]
Asymptotic analysis

- External signal is deterministic!
- Internal signal exhibits fluctuations over time and across cells

![Graph showing exponential growth]

Population concentration $\beta$ vs. Al concentration
Asymptotic analysis

- Fluctuations in local AI concentration $\rightarrow$ noisy cell concentration estimate
- Different cells have different estimates
- However, external signal is deterministic!
Cell concentration estimation

- Error can be reduced by filtering local Al concentration sequence

\[
\hat{\alpha}_{k+1,i} = (1 - \gamma \Delta) \hat{\alpha}_{k,i} + \gamma \Delta \alpha_{k+1,i}
\]

\[
\text{var}(\hat{\alpha}) = \frac{\gamma}{\gamma + \text{const}} \text{var}(\alpha)
\]

- Conv. time \(\propto \frac{1}{|s^{(+)}/\gamma|} + \frac{1}{\gamma}\)
Conclusions

- Quorum Sensing has evolved over millions of years as a coordination mechanism among large populations of cells.
- It can serve to coordinate nanonetworks as well.
- We have
  - Developed a model of Quorum Sensing
  - Found necessary conditions for QS to function
  - Analysis of QS dynamics & cell population density estimation