How Bacteria Form Micro-Colonies: A Network Formation Game Model

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How did I fell in love with bacteria?
Micro-colonies of bacteria
Motivation:
Biofilms – protect bacteria against anti-microbials
Methods to understand and influence the evolution of bacterial micro-colonies are needed to treat and prevent biofilm-related diseases

Goal:
Construct a first network formation model for bacterial micro-colonies formation and evolution
Quantify how well model fits/predicts experimental data
Understand how to influence bacterial self-organization

Why model bacterial self-organization?
Bacterial micro-colonies

Antibiotic tolerance develops very early in the formation of a biofilm

Why?

Past studies have attributed this to bacteria producing and sharing resources

- Bacteria move along a surface, produce resources (e.g., polysaccharides) which spread in space
- Resources produced give a benefit to all bacteria which can get access to them
Bacterial micro-colonies as networks

• If two bacteria remain close => they formed a “link”
• Why do bacteria “link”?  
  – Bacterium obtains a benefit whenever it links to another bacterium, because it exploits part of the resources produced but not used by it  
  – Links in the form of inter-cellular adhesins (polysaccharides)
• “Bacteria form networks”
Dynamic Network Formation Game

Micro-colony formation - as a dynamic game

• In each time slot:
  1) Bacteria *meet* (preferential attachment process)
     - *decide* whether to *form a new link*
     - a link is formed *bilaterally*
  2) Bacteria *decide* whether to *maintain their existing links*
     - a link is maintained *bilaterally* (i.e., broken *unilaterally*)

Not all bacteria “act” in all time slots
Network model

Discrete-time model

- **Link**: if two bacteria $i$ and $j$ are close
  - links are formed and broken over time
  A link in time slot $n$ is denoted by $g_{ij}^{(n)} = 1$

- **Connected bacteria** $i \leftrightarrow j$: if there exist links from $i$ to $j$

- **Network**: the set of links $\mathcal{G}^{(n)} \triangleq \{(i, j) : g_{ij}^{(n)} = 1\}$

- **Distance** $d_{ij}^{(n)}$: smallest number of links between $i$ and $j$

- **Meeting process** – driven by a *signaling mechanism* that attracts bacteria towards areas rich of resources
  - Preferential attachment
Micro-colonies: a network definition

- **Stable link**: if it will be maintained “forever”, regardless of the randomness in the system
- **Micro-colony \( \mathcal{M} \)**: a component of *stable* links
Model: A starting point

Model does not consider

- the mobility and motility models of bacteria (which depend on the particular strain of bacteria)
- the geometric properties of the surface and the positions of bacteria
- etc.
Two types of bacteria:

- **high type** bacteria ($t_i = H$) *increase* their resource production rate when linked to others
- **low type** bacteria ($t_i = L$) have *constant* resource production rate regardless of their links

$K(L), K(H)$ – total number of Low/High Bacteria

Model: Utility

\[
u_i(t, G^{(n)}) = \sum_{j \leftrightarrow i} \delta^{d_{ij} - 1} f(t_j) - c(t_i)
\]

- \(f(H), f(L)\): benefit obtained from a direct link with High/Low type bacteria, \(f(H) > f(L)\)
- \(\delta \in (0, 1)\) spread factor – spread of resources; fit to the properties of specific polysaccharides
- \(c(H), c(L)\): cost high and low type bacteria pay to be linked, \(c(H) > c(L) = 0\)

Bacteria are *self-interested* and *myopic “agents”*
Higher benefits when linking to a bacterium that is already connected to many bacteria -> *increasing returns to link formation*

Desirable and efficient for bacteria to be part of large-size components

-> agrees with the experimental observation that biofilm exhibits enhanced antibiotic tolerance
Decisions are based on information about resources/types

Two scenarios

1st case
Bacteria have a long time to sample the environment and integrate inputs
- This corresponds to \textit{slow motility} compared to gene expression and protein synthesis response time
or environmental conditions are \textit{slowly varying} in time

\textbf{Complete information}: a bacterium knows the \textit{utility} it will receive by forming a link
\rightarrow \textit{links} are \textit{formed and maintained strategically}
Decisions are based on information about resources/types

2nd case
Bacteria move quickly relative to their response times or environmental conditions vary significantly in time

**Incomplete information:** a bacterium does not know the utility it will receive by forming a link

→ links are *always formed (opportunistic!)* but are *maintained strategically*
• Is there a minimum size a micro-colony of L-type bacteria must have before an H-type bacteria joins? YES!

• (necessary size): Let $\mathcal{M}$ be a micro-colony. If $|\mathcal{M}| < N_{th,1}$ then $\mathcal{M}$ does not contain H-type bacteria.
Analysis: Complete information

• **Convergence to a stable network:** $G^{(n)}$ converges with probability 1 to a stable network if and only if either

1) $f(H) \geq c(H)$ , or

2) $(1 + \delta)f(L) \geq c(H)$ and $K(L) \geq 2$ , or

3) $K(H) = 0$.

$G^{(n)}$ does not converge to a stable network with probability 1 if and only if

$$f(H) < c(H) \& K(H) > 0 \& K(L) < N_{th,1} - 1$$
L-type bacteria play a fundamental role in the initial phase of the micro-colony formation process.
Analysis: Complete information

Robustness of micro-colonies

We can characterize the conditions under which a stable network *remains* stable if some links are broken:
- Conditions on the system parameters
- Conditions on the number of broken links
Analysis: Incomplete information

- **Necessary size**: Let $\mathcal{M}$ be a micro-colony. If $f(H) < c(H)$ and $|\mathcal{M}| < N_{th,3} = \frac{c(H)}{f(H)} + 1$ then $\mathcal{M}$ does not contain bacteria of high type.

- **Sufficient size**: If $f(L) < c(H)$ and $\delta > \frac{c(H) - f(L)}{c(H)}$, there exists $N_{th,4}(f(L), c(H), \delta)$, increasing in $c(H)$ and decreasing in $f(L)$ and $\delta$, such that all the components $\mathcal{C}$ with size $|\mathcal{C}| \geq N_{th,4}(f(L), c(H), \delta) + 1$ are micro-colonies.
• Convergence to a stable network: if $\ell_{min} = 1$ as in the complete information case.

If $\ell_{min} \geq 2$, the $G^{(n)}$ converges with probability 1 to a stable network if $K(H) \geq N_{th,4} - 2$ and $K \geq N_{th,4}$; whereas $G^{(n)}$ does not converge to a stable network with probability 1 if $f(H) < c(H), K < N_{th,3}$ and $K(H) > 0$. 

Analysis: Incomplete information
Complete vs. Incomplete Information

1. Under incomplete information it is possible to form *smaller-sized* micro-colonies containing H-type bacteria than in the complete information.

2. If bacteria *cannot break links immediately* after a link is formed (“inertia”), then under incomplete information bacteria can form large size components before they have the possibility to break their links → this can spur the formation of micro-colonies.

3. Other findings....
Comparison between experimental data and results predicted by our model

Bacteria type: Pseudomonas aeruginosa strain
Incomplete information setting
Conclusions

Just the beginning....

• We propose a parametrizable, dynamic network model for bacteria self-organization into micro-colonies

• We characterize the properties of networks emerging in equilibrium and provide insights on how the network dynamically evolves

Final goal: understanding bacterial self-organization into micro-colonies to develop therapeutic strategies that influence on-the-fly the evolution of the network

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