Dynamic Networks of Microbial Biofilms

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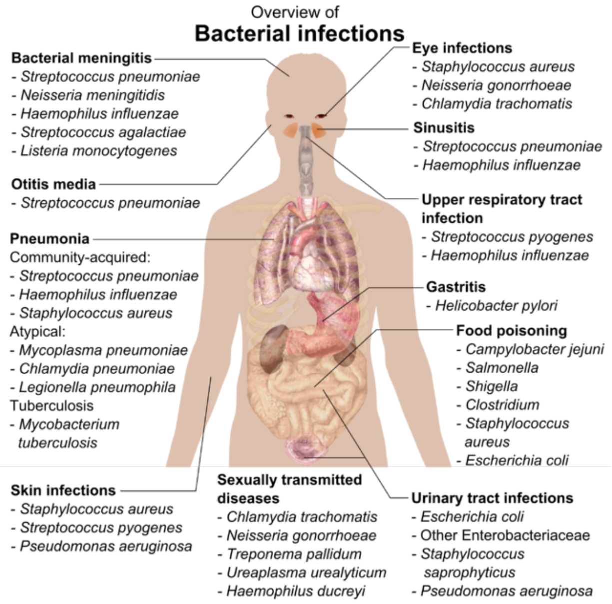
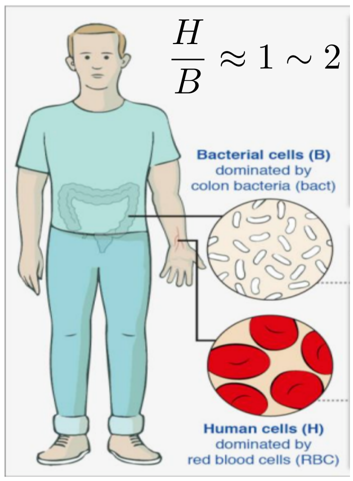
Big problem: Antibiotic resistance

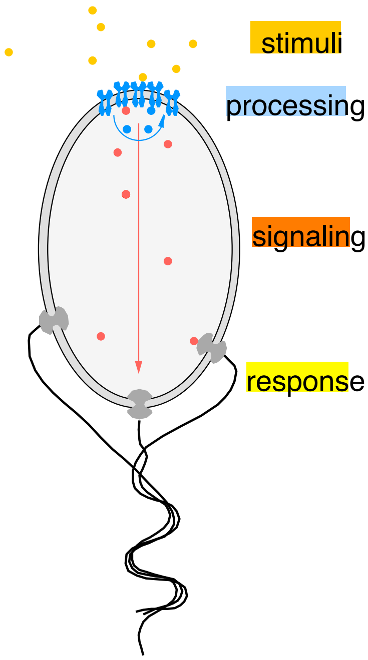




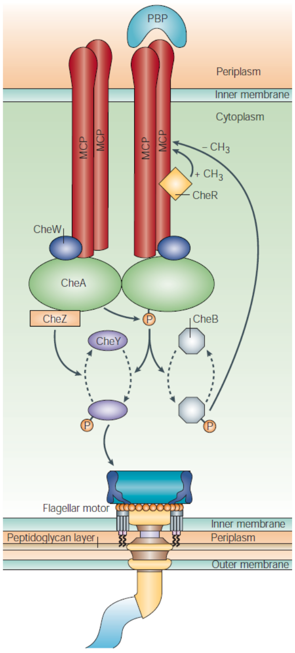
23,000 deaths annually
2,000,000 sickened
USA more than $35 billion/yr

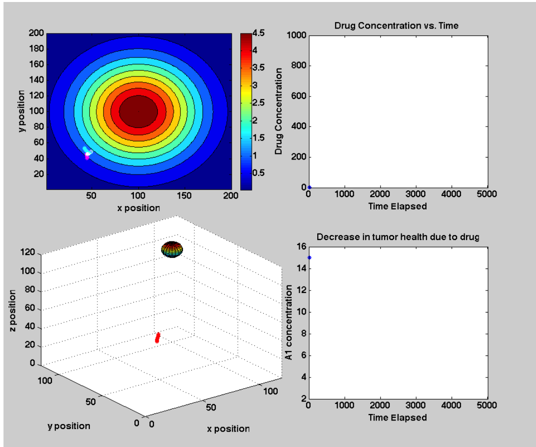
WHO 2014 report reveals that antibiotic resistance is no longer a prediction for the future; it is happening right now

Bacteria bring together computation, communication, and control



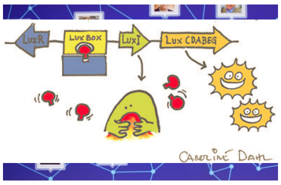
E. coli chemosensory system





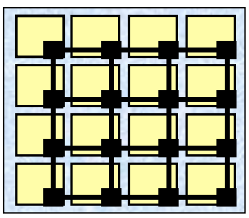
[Wadhams&Armitage, Nature, Dec 2004]

This presentation puts the "network" at very center of this socio-microbiological perspective on pathogens



Intra-cellular networks
Quorum sensing modeling

Inter-cellular networks
Biofilm dynamics

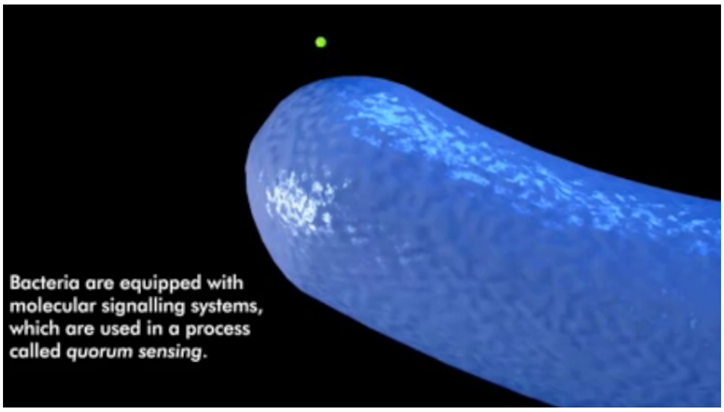


Applications
Network control

Understanding and engineering "Molecular Tweeting" could hold the key to busting superbugs

What is quorum sensing (QS)?

- Bacteria use quorum sensing (QS) to monitor the environment and regulate their collective behaviors
  - Biofilm formation
  - Virulence expression



https://www.youtube.com/watch?v=be-mjOGiquk

[B. L. Bassler and R. Losick. Bacterially speaking. Cell, 125(2):237–46, Apr. 2006.]

How to model QS?

LuxR-AI dynamics

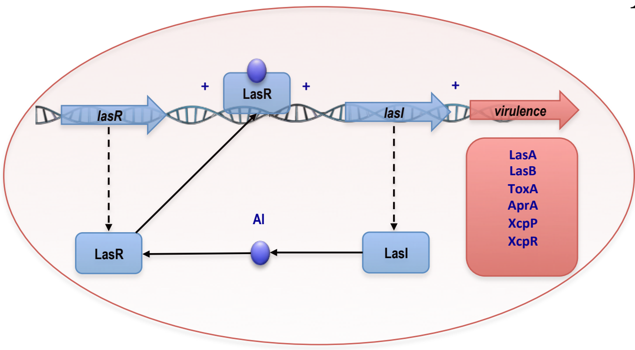
$$\frac{[C]}{dt} = \alpha[R][A] - \delta[C]$$

R : LasR

A : AI

A_E : Extracellular AI

C : LasR-AI



QS upregulates multiple virulence genes

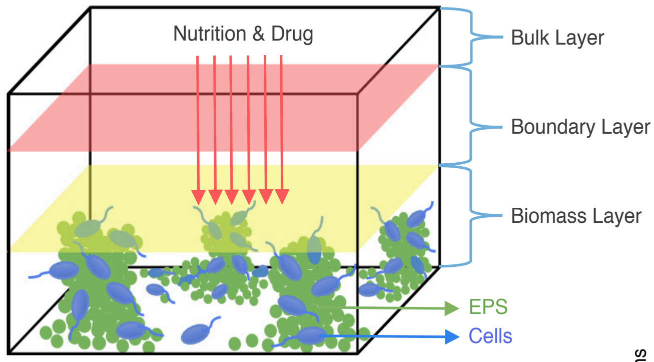
AI dynamics

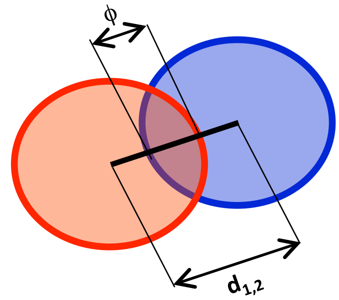
$$\frac{[A]}{dt} = -\alpha[R][A] + \delta[C] - b[R] + \frac{V[C]}{K + [C]} + r + \frac{d}{\rho}([A_E] - [A])$$

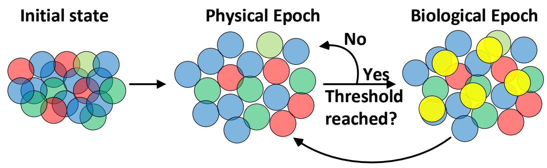
$$\frac{[A_E]}{dt} = -d([A_E] - [A]) - b[A_E]$$

Gram-negative bacteria use largely homologous QS networks, where the AIs are detected and regulated via genetic circuits

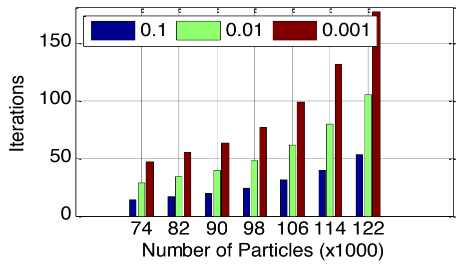
Bacterial population dynamics is a complex problem. Direct wet-lab experimentation is costly and often impractical





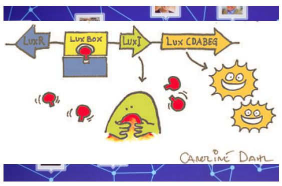


High-Accuracy = More iterations



Experimenting with efficient GPU kernels using NVIDIA Thrust allows to achieve 100x acceleration with GTX980 GPUs

This presentation puts the "network" at very center of this socio-microbiological perspective on pathogens



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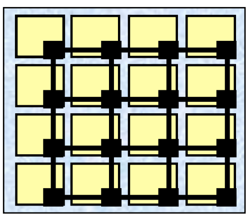

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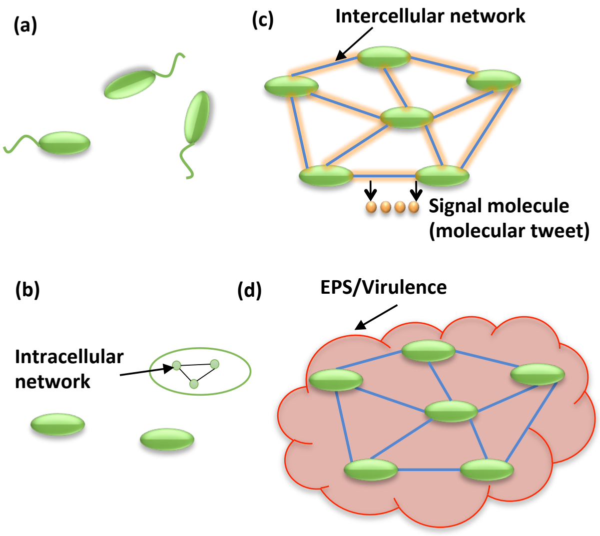
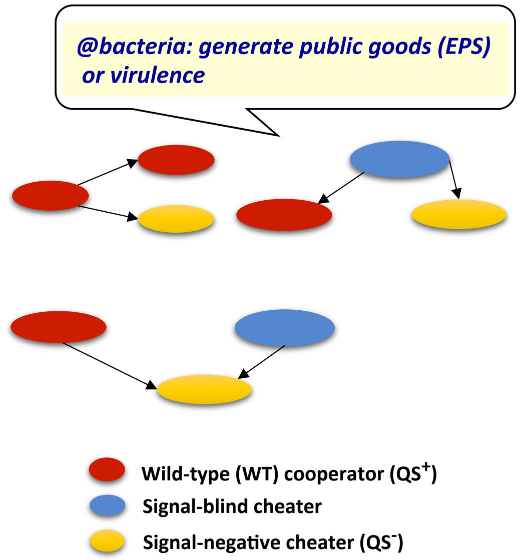
Bacterial biofilm: Use Twitter-like metaphor to explain participants and network formation



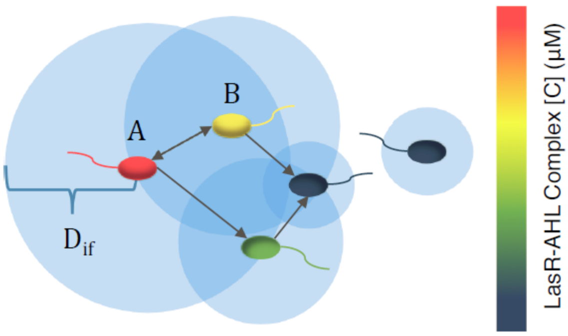
$$\frac{d[EPS]}{dt} = K_{eps}\frac{[C]}{[C]+K_R}$$



[G. Wei et al., ACM BCB, 2015]

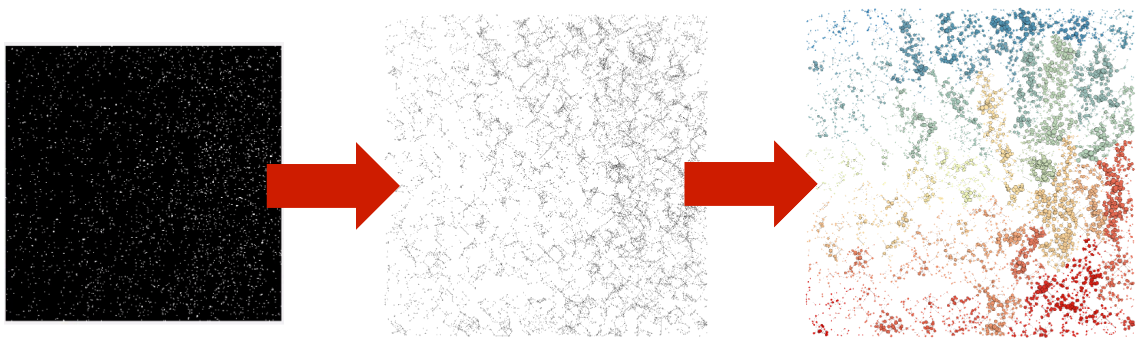
The structure and dynamics of the inter-cellular communication network is heavily influenced by its environment

Network formulation is based on the QS activity



$$S_{ij} = Q\frac{I_{ij}}{max(I)}$$

$$R_{ij} = \frac{\log(S_{ij})}{D}$$

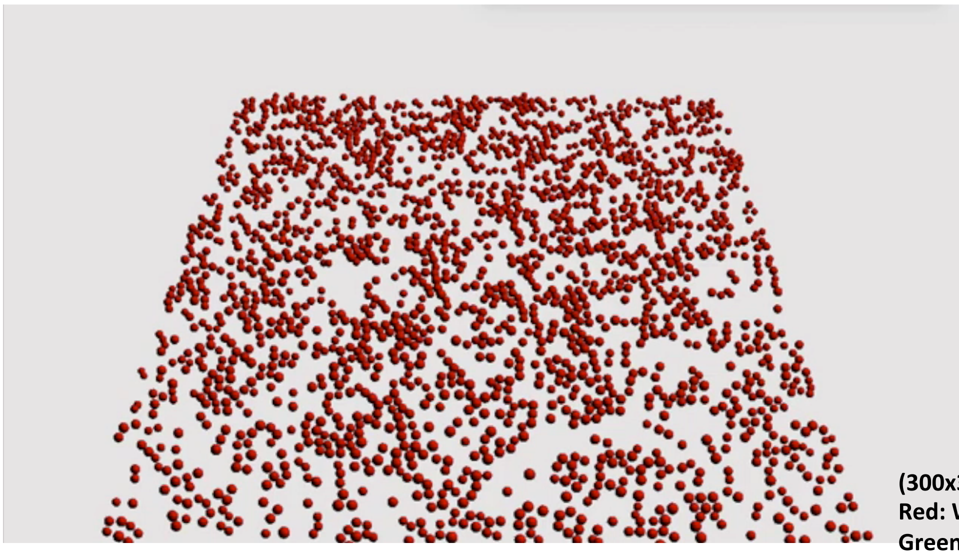


Network metrics

- **Clustering coefficient:** Measures the degree to which network nodes are clustered together. A high clustering coefficient means that the network nodes are not only highly active but also in close proximity to one another.

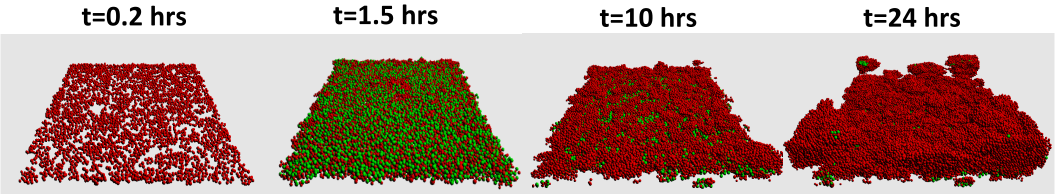
- **Communities:** Groups of nodes with high clustering coefficient. If the two cell groups have a large impact on one another (e.g., gene expression synchronization), then they are considered to belong to the same community.

Pure wild type (WT): All bacteria tweet and retweet the message of producing EPS

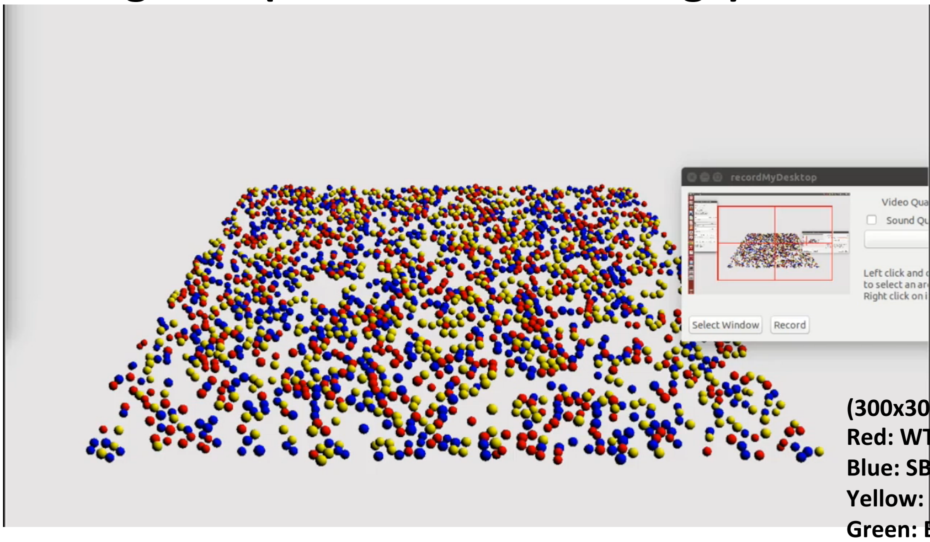


($300 x 300 x 500 \mu m^3$)
Red: WT
Green: EPS

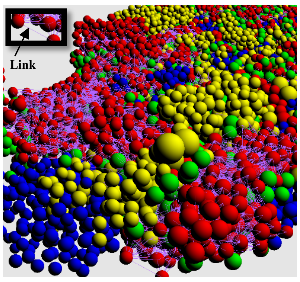
t=0.2 hrs | t=1.5 hrs | t=10 hrs | t=24 hrs

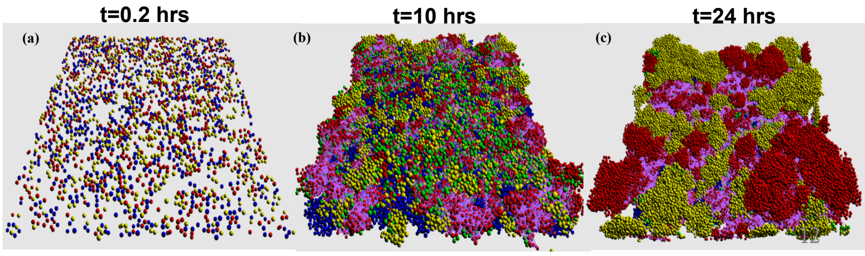


1/3WT, 1/3SB, 1/3SN: Bacteria communication enables social intelligence ("molecular tweeting")

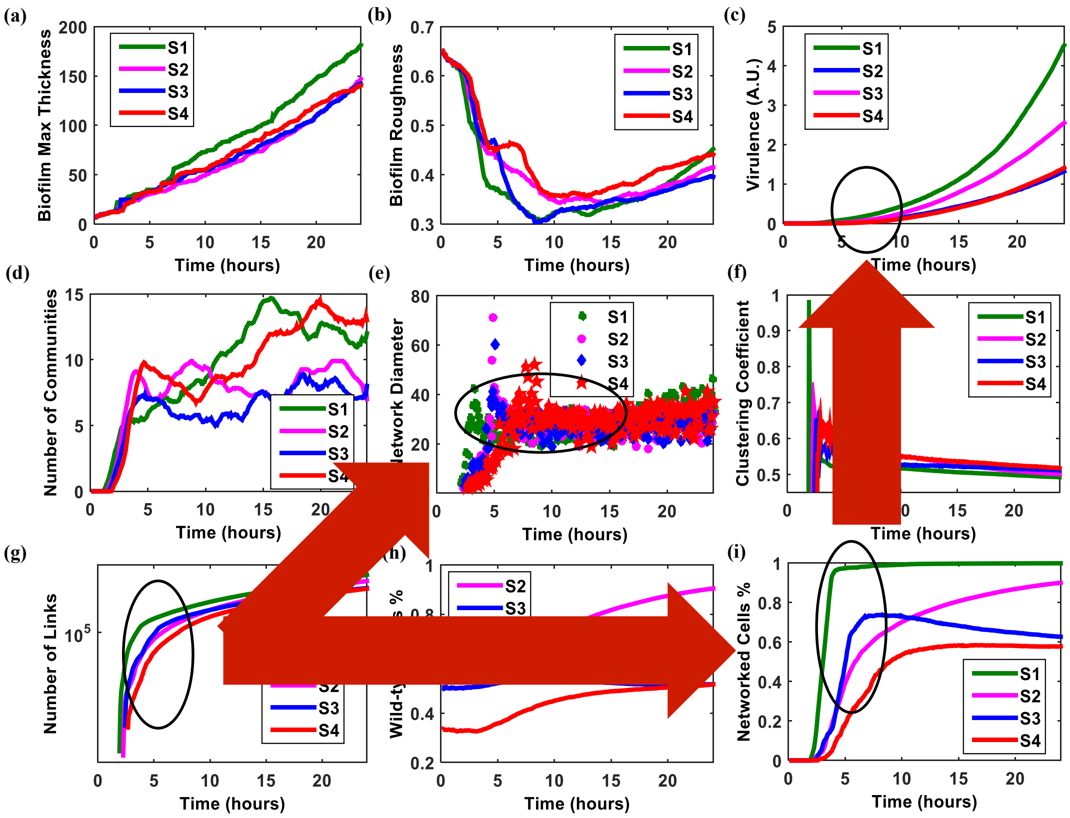


($300x300x500\mu m^3$)
Red: WT
Blue: SB
Yellow: SN
Green: EPS



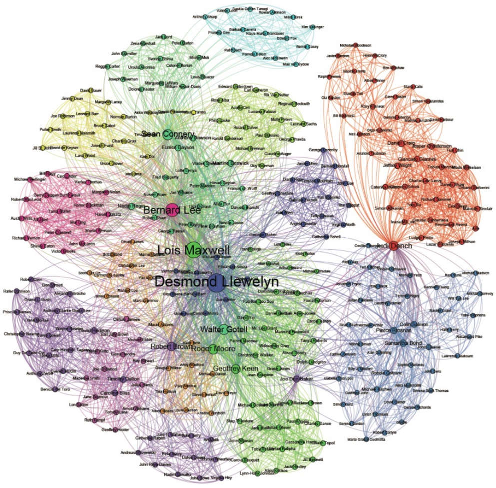


Dynamics of network evolution

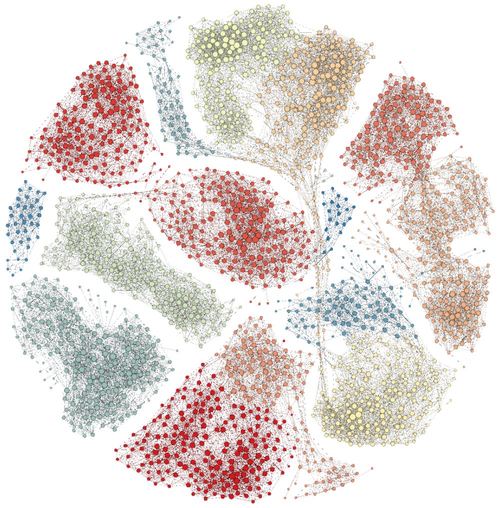


Do bacteria have a social life?

James Bond Movie Actor Network



Bacteria network



Category	Network	Type	*Nodes*	*Links*	$Degree_{avg}$	$PathLength_{avg}$	*Clustering*
Social	Film actors	Undirected	449,913	25,516,482	113.43	3.48	0.20
	Math coauthorship	Undirected	253,339	496,489	3.92	7.57	0.15
Biological	Protein interactions	Undirected	2,115	2,240	2.12	6.80	0.07
	Neural network	Directed	307	2,359	7.68	3.97	0.18
Technological	Internet	Undirected	10,697	31,992	5.98	3.31	0.04
	Power grid	Undirected	4,941	6,594	2.67	18.99	0.10
Social Biology	Bacteria society (S1)	Directed	24,244	880,225	36.31	12.54	0.52
	Bacteria society (S2)	Directed	16,254	496,511	30.55	8.56	0.55
	Bacteria society (S3)	Directed	16,906	494,971	29.28	9.84	0.53
	Bacteria society (S4)	Directed	12,226	307,469	25.15	6.74	0.53

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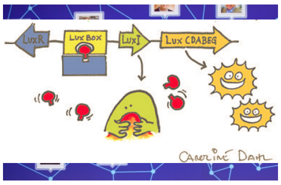

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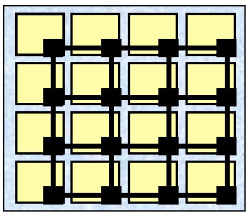

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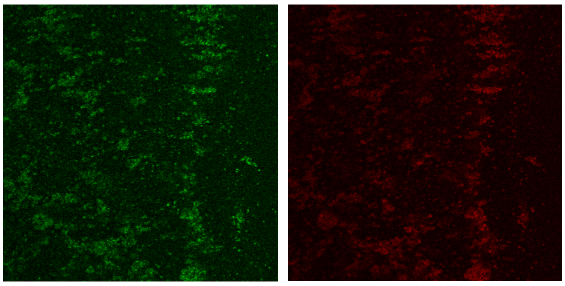
Effect of QSIs



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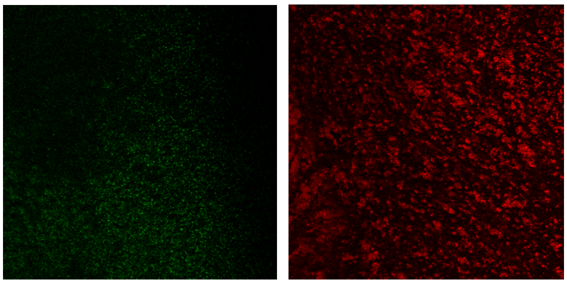

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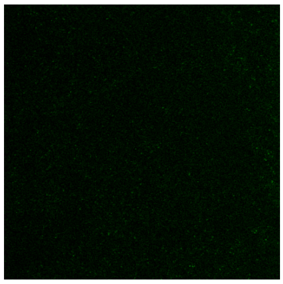
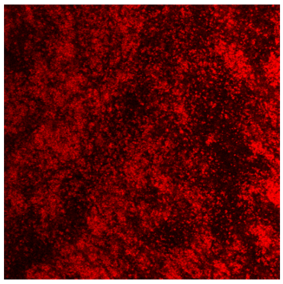
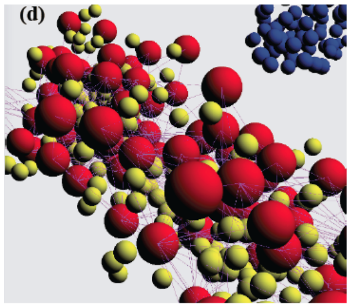


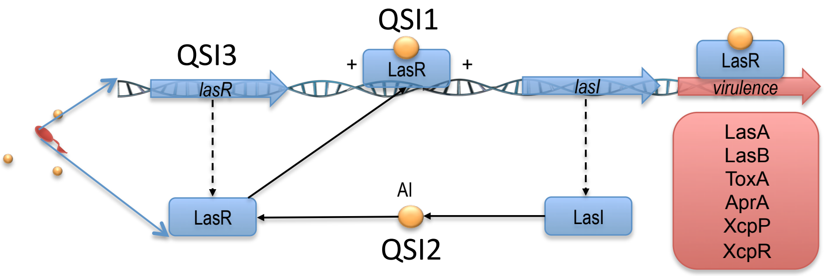
14:00



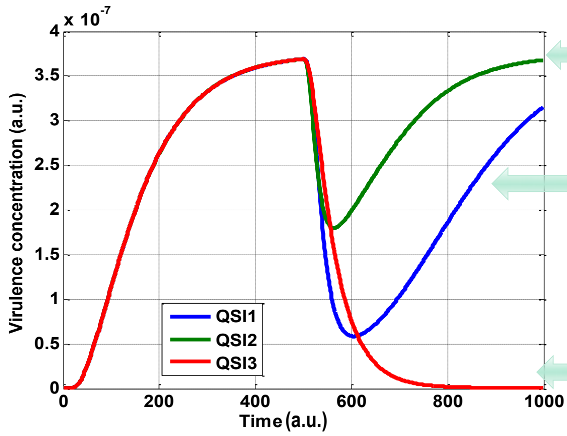


QSI1: targeting **LasR receptor**
C-30 furanone (AI analog)

QSIs can effectively reduce the virulence



Consider **only** wild type cells

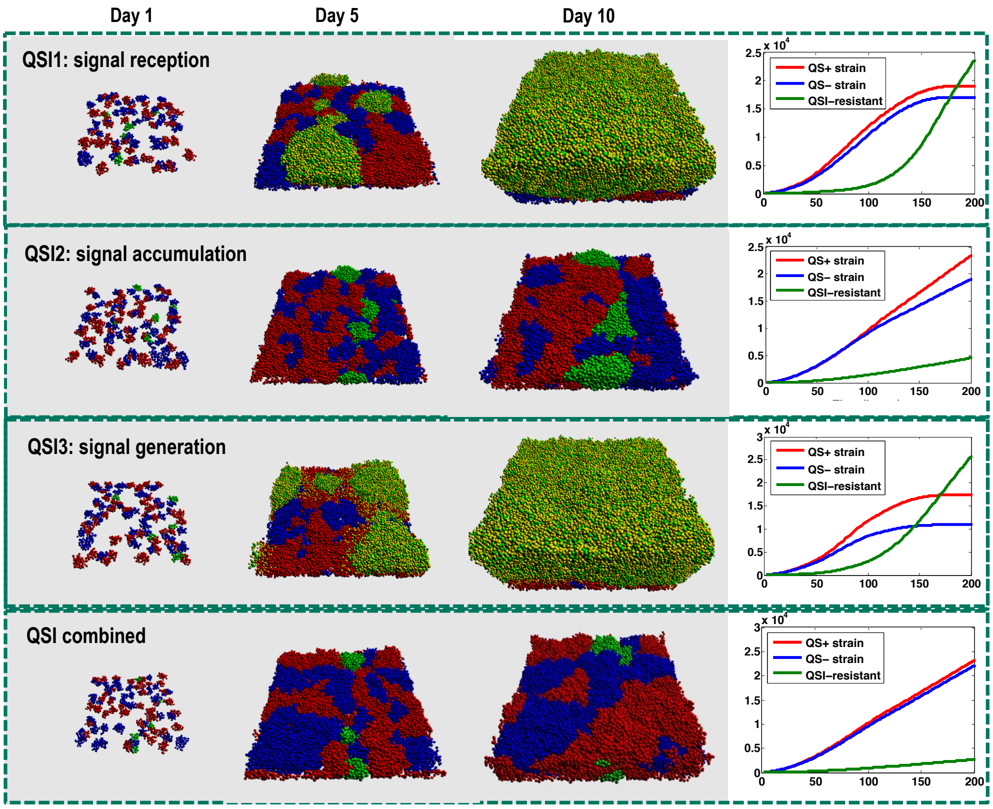


QSI2 targets AI

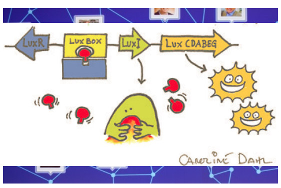
QSI1 targets LasR

QSI3 targets the gene which produces LasR

QSI strategies



Summary



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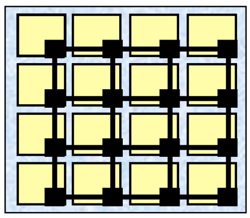

Applications
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Contributors (in no particular order…)

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