Queues & Bacteria: 

a Tale of Modeling and Experiment

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Bacteria and RF analogies?

*for their discoveries concerning genetic control of enzyme and virus synthesis*

François Jacob

Genetics of the bacterial cell

*Nobel Lecture, December 11, 1965*

If I find myself here today, sharing with André Lwoff and Jacques Monod this very great honor which is being bestowed upon us, it is undoubtedly because, when I entered research in 1950, I was fortunate enough to arrive at the right place at the right time. At the right place, because there, in the attics of the Pasteur Institute, a new discipline was emerging in an atmosphere of enthusiasm, lucid criticism, nonconformism, and friendship. At the right time, because then biology was bubbling with activity, changing its ways of thinking, discovering in microorganisms a new and simple material, and drawing closer to physics and chemistry. A rare moment, in which ignorance could become a virtue.
Bacterial Communities

- Analyze electron transport in bacterial cables
- Develop models for quorum sensing
Why bacteria?

- Unicellular organisms
- One of the earliest forms of life (3-4 billion years ago)
- Aggregate biomass larger than all other plants/animals combined
- Relevant for bioremediation, plant growth, human and animal digestion, global elemental cycles including the carbon-cycle, and water treatment
Not as simple as they seem..
What is communication?

The fundamental problem of communication is that of reproducing at one point either exactly or approximately a message selected at another point.

Claude Shannon, A Mathematical Theory of Communication, 1948

TX  RX
Bacteria as “devices” that sense the environment, estimate, react

Idea: tools from information theory and communications to model & predict bacterial networks:
- Interactions, dynamics, formation
- Do bacteria realize optimal control strategies?
- E.g.: optimize MFC growth

What is capacity for bacteria?
How to achieve the sweet spot?

- Microbes on a 2D electrode
- Population grows as a function of time
- What happens at 15h?
- How are bacteria interacting?
- What is electron transport?

From Ken Nealson group, USC, Earth Sciences
Fundamental (and well known) process in cellular respiration

- $e^-$ flow creates proton gradient to pump synthesis of Adenosine triphosphate (ATP, cell’s energy currency)
- Cells need a constant electron flow to produce energy (ATP)
e⁻ transport

- e⁻ transport over cm-lengths
  - bacterial nanowires, biofilms, bacterial cables

multi-hop communication "network" from e⁻ donor (ED) to e⁻ acceptor (EA)

Bacterial cable (1D), Source: [Reguera, Nature’12]
- $e^-$ transport over cm-lengths
  - bacterial nanowires, biofilms, bacterial cables

- **Use communication strategies to optimize $e^-$ transfer**

- **Capacity as proxy for maximal $e^-$ transfer**

- New dimension (& new models)
  - *information-energy coupling*
    - Capacity $\neq$ bottleneck, vs wireless communications
    - Instead, local interactions & energy coupling, cells may die

![Bacterial cable (1D), Source: [Reguera, Nature’12]](image)
Stochastic queuing model

- **BEFORE**: modeling via deterministic ODE/PDE
  - E.g., [Klapper&Dockery,’10], [Picioreanua et al.,’07], [Marcus et al.,’07]
  - Detailed master equations & chemical reactions → huge complexity

- **NOW**: abstraction → stochastic queuing model inspired by W-COM
  - Chemical/electron concentrations → queues
  - Small-scale, local interactions as nuisances → stochastic model
  - *Still high complexity, but tools for complexity reduction from W-COM can be exploited*
Stochastic queuing model

- External high energy membrane: $e^-$ from previous cell
- $e^-$ participate in electron transport chain to produce ATP

$e^-$ from previous cell
Internal $e^-$ carrier pool: $e^-$ from external ED

$e^-$ participate in electron transport chain to produce ATP

Nicotinamide adenine dinucleotide (NADH)
Stochastic queuing model

- ATP pool: ATP molecules produced via $e^-$ transport
- ATP consumed to sustain cell

ATP molecules generated via ET
External low energy membrane carries $e^-$ after ETC. 2 paths:
- Reduction to EA
- $e^-$ transfer to next cell or electrode
Stochastic queuing model

- Molecular diffusion & $e^-$ transfer coexist
- ATP level = energetic state of the cell
  - *Energy dimension*: ATP low $\rightarrow$ cell may die
  - *Information dimension*: ATP level too high $\rightarrow$ clogging
Isolated cell: experimental validation

- Setup [Ozalp & al., Journal of Biological Chemistry, ’10]
  - Suspension of yeast *Saccharomyces cerevisiae* (isolated cells)
  - ED added abruptly to starved cells
  - NADH (electron-carrier pool) and ATP levels measured

- Use experimental data to fit parameters

\[
(\hat{x}, \hat{\pi}_0) = \arg \min_{x \geq 0, \pi_0 \in \mathcal{P}} \frac{1}{2} \sum_{k=0}^{N} \left\| y_k - \pi_0^T \prod_{j=1}^{k} P_\Delta(x, s_{E,j-1})^{n_j-n_{j-1}} Z \right\|^2_F
\]

- Measured ATP/NADH (average over population)
- State distribution
- Fixed matrix: State indicator
Isolated cell: experimental validation

- Good fitting of experimental curve and model
- Stochastic queuing model simpler than detailed “physical” models, but captures salient features

30mM GLUCOSE ADDED

MODEL

EXPERIMENTAL DATA
[Ozalp et al.,’10]
Information theoretic aspects
Multihop Capacity

- Cascade of links
  - Persistently studied

- Via cut-set bounds can show that capacity is that of worst-case link
  \[ C = \min_j C_j \]
  - Achieved by decode-and-forward

- What happens in biological systems?
  - Communication over channels with state!
  - There is coupling between the links
Bacterial cable as communication system

- **Challenge**: signal is coupled with energetic state of cells (channel state)
- ATP level = energetic state of the cell
  - **Energy dimension**: ATP low $\rightarrow$ cell may die
  - **Information dimension**: ATP high $\rightarrow$ clogging, $e^-$ transfer stopped
Simplified cable model

- $S(t) =$ Interconnection of all cells’ states

- **Simplified model:** $S(t) =$ # $e^-$ in the cable
  - *Local* interactions averaged out over spatial dimension
  - *Global* effects captured by clogging state $A(s)$
    - $S(t)$ small $\rightarrow$ cells “starved”
    - $S(t)$ large $\rightarrow$ ATP saturation, clogging
    - $A(s) =$ ratio of $e^-$ accepted
Communication over Poisson channels with states

\[ X(t) \sim \mathcal{P}(A(S(t))\lambda(t)) \]

\[ Y(t) \sim \mathcal{P}(\mu(S(t))) \]
Prior Work

- **Uncontrolled case, no CSI:** [Goldsmith&Varaiya’96] iid coding
- **Uncontrolled case, partial CSIT, CSIR:** [Yuksel&Tatikonda’07]
- **I.i.d. state controlled by actions, CSIT:** [Weissman’10], [Choudhuri&Mitra,’12]
- **Controlled case, no CSI:** [Pfister et al.’01] i.i.d. coding; **with FB:** [Tatikonda&Mitter] POMDP
- **Controlled case, full CSI & FB:** [Chen&Berger’05] optimality of Markov coding, optimization via DP
- **In our case, Markov state controlled by signal, full CSI case**
- **Finite-state continuous-time Markov Poisson channel**
  - **Static** Poisson channels [Wyner’88]
  - **We extend to finite-state Markov channels (dynamic)**
  - Discrete-time: upper & lower bounds [Lapidoth&Moser’09]
**Assumption:** “small” slot duration $\Delta$ [Wyner’88]

\[
1 - A(s)\overline{\lambda}(s)\Delta - \mu(s)\Delta
\]

- **Other events:** probability $o(\Delta^2) \rightarrow$ neglected
- **Only consider adjacent states**
Discrete time model: approximation

Assumption: “small” slot duration \[Wyner’88\]

Channel with state (ENC controls intensity only)

State “controlled” by input process; state-dependent output
  - Finite-state Markov \[Chen&Berger’05\]
Stationary Markov coding optimal \[Chen&Berger’05\]

Capacity as dynamic program

- Action/control: rate selection
- Reward: \(I_f^{(\Delta)}(s)\) mutual information conditioned on past state, control function

**THEOREM**: capacity achieved by feedback independent inputs

- \[Chen&Berger’05\] assumes feedback
Asymptotic capacity of Poisson Markov channels

- **Information-Energy coupling:**
  - **Energy dimension:**
    - Determined by $\bar{\lambda}(s)$
  - **Information dimension:**
    - **PROP:** Stationary distribution $\pi_f(S)$ depends only on $\bar{\lambda}(s) = \mathbb{E}[\lambda | s]$
    - **Impact:** Optimize over ENC functions $f$ with same $\bar{\lambda}(s)$

- **THEOREM:** Binary signal optimal $\lambda_k \in \{\lambda_{\text{min}}, \lambda_{\text{max}}\}$
  - **Impact:** easier to operate with a binary signal

$$C^* = \max_{\lambda} \max_{f \in \mathcal{F}(\lambda)} \sum_{s=0}^{S_{\text{max}}} \pi_{\bar{\lambda}}(s) I_f(s)$$

$$I_f(s) = \mathbb{E}[f(\lambda)]$$

$$\lambda_{\text{min}} \quad \bar{\lambda}(s) \quad \lambda_{\text{max}}$$
Myopic scheme

- Myopic scheme: maximizes $I_f(s)$ in each slot
  - Can compute average rate in closed form
  - Independent of state $s$, no CSIT required (however, CSIR still required)

- **THEOREM:** $\bar{\lambda}^*(s) \leq \bar{\lambda}_{MP}$ (otherwise, fast recharges & low rate)
  - **Proof:** properties of $n$-step value function
MP & OPT

- Myopic scheme: greedy one step

- OPT 10% better than MP
  - MP: Greedy information transfer maximization achieves poor performance

- Information transfer maximization vs “wellness” maximization
Q: Can we apply these queueing theoretic approaches to OTHER bacterial networks?

A: YES!

- Quorum sensing...
Queuing models for Quorum Sensing
• Gene expression regulation in response to fluctuations in cell-population density
• Bacteria produce autoinducers that increase in concentration as a function of cell density
• regulates many diseases
Cellular Control of the Synthesis and Activity of the Bacterial Luminescent System

KENNETH H. NEALSON, TERRY PLATT, AND J. WOODLAND HASTINGS

Biological Laboratories, Harvard University, Cambridge, Massachusetts, 02138 and
Marine Biological Laboratory, Woods Hole, Massachusetts 02534

Received for publication 30 April 1970

Luminescent bacteria growing in shake flasks, the enzyme luciferase has proven to be synthesized in a relatively short burst during the period of exponential growth. The luciferase gene appears to be completely inactive in a freshly inoculated culture; the pulse of preferential luciferase synthesis which occurs later is sequence of its activation at the level of deoxyribonucleic acid transcription attributed to an effect of a “conditioning” of the medium by the growing of although cells grown in a minimal medium also exhibit a similar burst of synthesis, the amount of synthesis is quantitatively less, relative to cell mass. Under such conditions, added arginine results in a striking stimulation of bioluminescence. This is attributed to a stimulation of existing patterns of synthesis and not to induction or derepression per se.
Towards a model of QS

“Ingredients” of QS

1. Microbial community (e.g., *Pseudomonas Aeruginosa*)
2. ♦ Autoinducers $A(t)$ only global parameter, others by cell, i
   - Emitted by each cell in the environment
3. ⊘ Receptors $R_i(t)$
   - They bind to autoinducers within each cell to form *complexes*
4. ⊙ Complexes $C_i(t)$
   - 1 autoinducer bound to 1 receptor
5. □ Synthases $S_i(t)$
   - “machines” that produce autoinducers
6. DNA binding sites
   - Complexes bind to them to produce *synthases, receptors & virulence factors*
Gene Expression

- The promoter region between genes determines which proteins to make

- Decision of whether or not to transcribe a gene depends on binding to operators and the promoter

From James Boedicker, USC
Autoinducers bind to receptors to create complexes

- Number of autoinducers/receptors decrease by 1

Complexes can bind to one of three sites to create
- Synthases (create autoinducers)
- Receptors
- Virulence factors (BAD) cause disease, don’t affect QS
- Each have unique binding rates

Complexes, synthases, receptors can degrade

Cells do not die, but can duplicate
Abstraction of QS

A(t) autoinducers

\( S_i(t) \) synthases

\( \gamma \)

\( R_i(t) \) receptors

\( C_i(t) \) complexes

\( \epsilon_{C,1} \), \( \epsilon_{C,2} \), \( \epsilon_{C,3} \)

Sites 1, 2, 3

Virulence factors

CELL
Queuing model of QS
Compact state space representation

- **THEOREM:**
  \[
  (N(t), C_{TOT}(t), R_{TOT}(t), S_{TOT}(t))
  \]
  is a sufficient statistic for QS activation

- Don’t need to track \((C_i(t), R_i(t), S_i(t))\) for each cell,
  track \((C_{TOT}(t), R_{TOT}(t), S_{TOT}(t))\) at the population level
  - Lower complexity!
Simulations

- Simulation tools based on queuing model
  - Cell density is higher in open system
    - Larger concentration of autoinducers
    - Faster activation time

OPEN SYSTEM: cells grow in open space (no boundaries → leakage of autoinducers)
CLOSED SYSTEM: cells grow in finite box (boundaries → no leakage)
Simulations

- Simulation tools based on queuing model
  - Model allows realistic performance evaluation in short time
  - Use of complexity reduction tools from wireless comm

**OPEN SYSTEM**: cells grow in open space (no boundaries → leakage of autoinducers)

**CLOSED SYSTEM**: cells grow in finite box (boundaries → no leakage)
Experimental results

- Closed system
- *Escherichia coli* cells grown in LB media at 37°C
- Green Fluorescence protein (GFP) monitored (~ gene expression activity)
Experimental results

- Closed system
- *Escherichia coli* cells grown in LB media at 37°C
- Green Fluorescence protein (GFP) monitored (~gene expression activity)
- Model & experiments:
  - Similar qualitatively
  - But GFP=0 before QS activation (low basal expression rate) → further investigation needed
It is much more complicated...

- The hierarchy quorum sensing network in Pseudomonas aeruginosa, Lee & Zhang, Protein&Cell 2015, 6(1):26–41
- Both stimulatory and suppressive interactions

Schematic representation of the four QS signaling networks in *P. aeruginosa* and their respective regulons
Bacterial Models
Large Scale Networks

- Can use CS on graphs
- Can learn cost functions (e.g. throughput, SINR, BER, etc.)
- Can learn with two orders magnitude fewer samples
Use your favorite CS method

- Using Least Squares Residual
  Compressed sensing handles
  instability
  - Vaswani, IEEE Trans on SP
    8/2010

Diffusion Wavelet based CS learning

Levorato, M & Goldsmith, EURASIP Wireless Comm & Net, 8/12
Summary

- Stochastic queuing theoretic model
  - Captures salient features, amenable to complexity reduction using W-COM tools (vs detailed physical models)
- IT aspects, coupling between
  - *Coupling between wellness & information transfer*
  - *Impact*: state estimation to adapt signal and optimize this trade-off
- Quorum sensing modeling
  - Need to consider multiple signaling mechanisms
  - Experimental data analysis
  - Optimization to mitigate virulence factors
Thanks to...

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