TO LYSE OR NOT TO LYSE: TRANSIENT-MEDIATED STOCHASTIC FATE DETERMINATION IN CELLS INFECTED BY BACTERIOPHAGES

w/Richard Joh (GA Tech, left), Yuriy Mileyko (GA Tech/Duke, right) & others

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Wanna go lyse some cells?

About time you asked.

...) hey, what about me?

Yeah, let's go!
Central Questions in Today’s Talk

1) Does co-infection alter cell fate, and if so, in what way?
   
   *Yes, lysis and lysogeny depend on co-infection*

2) How can viral genomes interact intracellularly to collectively determine cell fate?
   
   *Coupling of transcription with viral protein pool*

3) How can a simple model of fate determination be reconciled with observed single-cell level data?
   
   *Stochastic dynamics & a gene dosage compensation mechanism provide an alternative explanation for cell fate determination in co-infected hosts*

**Experimental work:** Kourilsky (Mol Ge. Genet, 1973), Kobiler et al. (PNAS, 2005), St. Pierre and Endy (PNAS, 2008), Zeng et al. (Cell 2010)

**Theoretical work:** Weitz et al. (Biophys J., 2008), Mileyko et al. (PNAS 2008), Joh & Weitz (PLoS Comp Biol, in press)
From intracellular mechanisms to traits

Ecological Model

\[ \frac{dV}{dt} = \beta \phi N V - m V \]

Trait space

\{ ..., \beta_1, \beta_2, \beta_3, ... \}

Evolutionary model

Phage trait, e.g. burst size

Time

Biophysics & Gene regulation
Outline

- Determination of alternative cell fates
- Quantitative model of lysis-lysogeny decisions
- Heterogeneity of decisions: gene dosage effect on lysis-lysogeny
Stochastic cell fates in unicellular organisms

- Eukaryotes
  - *S. cerevisiae* mating

- Bacteria
  - Bacterial persistence to antibiotics
  - Competence: *Bacillus subtilis*

- Viruses?
Viruses also drive alternative cell fates: lysis or lysogeny.
Strategies and the Cellular Multiplicity of Infection

Which of these is what phages really do?
Chance of lysogeny critically depends on cellular multiplicity of infection (MOI)

- API = # phage / # host

- Lysogeny is more likely when a host cell is multiply infected

Kourilsky (1973)
Intuition from Classic Gene Dosage Expectation: Expression is Linearly Related to Viral Copy Number

“In general, the amount of transcript produced by a gene is directly proportional to the number of copies of that gene in a cell.”

Griffiths et al., Intro. to Genetic Analysis
A “Simple” Decision Switch: In Reality, a Coupled Set of Regulatory Networks

Communal gene products form the basis for “viral communication”
SO, Gene Expression May be Nonlinearly Related to Gene Copy Number:
Cell volume is another critical parameter.

- **Lysis-lysogeny is stochastic**
- **Cell fate determination depends on concentration of viral genome**

St. Pierre and Endy (2008) PNAS
Viral concentration is key to lysis-lysogeny switch

- Explicit consideration of viral genome concentration
- Based on asymptotic behaviors of gene regulation
- Small change in viral copy number can shift between lysis and lysogeny

Weitz, Mileyko, Joh and Voit (2008) Biophys J
Experiments confirmed concentration dependence

A stochastic model of phage lambda is necessary

Outline

- Determination of alternative cell fates
- Quantitative model of lysis-lysogeny decisions
- Heterogeneity of decisions: gene dosage effect on lysis-lysogeny
Core GRN for lysis-lysogeny

- CI (repressor): lead to and maintain lysogeny
- CRO: control repressor
- CII: transcription activator
- Q: activate late lytic genes

Cumulative work of many (Ptashne, Kobiler, Oppenheim, and many more).
Quantitative model of lysis-lysogeny

\[
\frac{dm_y}{dt} = \frac{M}{V} \alpha_y f_R - \gamma_m m_y
\]

Transcription

Degradation

\[
\frac{dY}{dt} = \sigma m_y - \gamma_y Y
\]

Translation

Degradation
Full model of lysis-lysogeny

# of coinfecting phages

\[
\begin{align*}
\frac{dx}{dt} &= \sigma m_x - \gamma_x X , \\
\frac{dy}{dt} &= \sigma m_y - \gamma_y Y , \\
\frac{dz}{dt} &= \sigma m_z - \gamma_z Z , \\
\frac{dQ}{dt} &= \sigma m_Q - \gamma_Q Q ,
\end{align*}
\]

\[
\begin{align*}
\frac{d[cl\ mRNA]}{dt} &= \frac{M}{V} \alpha_x f_{RM}^{basal} + \frac{M}{V} \beta_x f_{RM}^{act} + \frac{M}{V} \delta_x f_{RE} - \gamma_m m_x , \\
\frac{d[crO\ mRNA]}{dt} &= \frac{M}{V} \alpha_y f_R - \gamma_m m_y , \\
\frac{d[cII\ mRNA]}{dt} &= \frac{M}{V} \alpha_z f_R - \gamma_m m_z , \\
\frac{d[Q\ mRNA]}{dt} &= \frac{M}{V} \alpha_Q f_R - \gamma_m m_Q - \zeta m_Q m_{aQ} , \\
\frac{d[aQ\ mRNA]}{dt} &= \frac{M}{V} \delta_{aQ} f_{aQ} - \gamma_m m_{aQ} - \zeta m_Q m_{aQ} ,
\end{align*}
\]

Host cell volume
Parameters for lysis-lysogeny

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reference value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\gamma_x$</td>
<td>0.01 (min$^{-1}$)</td>
<td>$\approx 0$ [62], 0.042 [25]</td>
</tr>
<tr>
<td>$\gamma_y$</td>
<td>0.06 (min$^{-1}$)</td>
<td>0.016 [63]</td>
</tr>
<tr>
<td>$\gamma_z$</td>
<td>0.10 (min$^{-1}$)</td>
<td>0.16 w/o CIII [64]</td>
</tr>
<tr>
<td>$\gamma_q$</td>
<td>0.01 (min$^{-1}$)</td>
<td></td>
</tr>
<tr>
<td>$\gamma_m$</td>
<td>0.1 (min$^{-1}$)</td>
<td>0.12 [65]</td>
</tr>
<tr>
<td>$\alpha_x$</td>
<td>0.06 (min$^{-1}$)</td>
<td>0.06 [36]</td>
</tr>
<tr>
<td>$\alpha_y$</td>
<td>0.84 (min$^{-1}$)</td>
<td>0.84 [36], 3 [62]</td>
</tr>
<tr>
<td>$\alpha_z$</td>
<td>0.8 (min$^{-1}$)</td>
<td>$&lt; \alpha_y$</td>
</tr>
<tr>
<td>$\alpha_q$</td>
<td>0.75 (min$^{-1}$)</td>
<td>$&lt; \alpha_z$</td>
</tr>
<tr>
<td>$\beta_x$</td>
<td>0.66 (min$^{-1}$)</td>
<td>0.66 [36], 3.42 [66]</td>
</tr>
<tr>
<td>$\delta_x$</td>
<td>0.9 (min$^{-1}$)</td>
<td>0.9 [25]</td>
</tr>
<tr>
<td>$\delta_{aq}$</td>
<td>2 (min$^{-1}$)</td>
<td></td>
</tr>
<tr>
<td>$c_{x}^d$</td>
<td>0.05 (nM$^{-1}$)</td>
<td>0.05 [67], 0.18 [68]</td>
</tr>
<tr>
<td>$c_{y}^d$</td>
<td>5.8 (nM$^{-1}$)</td>
<td>5.8 [69], 307 [70]</td>
</tr>
<tr>
<td>$c_{d}^2$</td>
<td>0.05 (nM$^{-1}$)</td>
<td></td>
</tr>
<tr>
<td>$c_{i}^a$</td>
<td>0.05 (nM$^{-1}$)</td>
<td></td>
</tr>
<tr>
<td>$c_{p}^aQ$</td>
<td>0.2 (nM$^{-1}$)</td>
<td></td>
</tr>
<tr>
<td>$\sigma$</td>
<td>0.5 (min$^{-1}$)</td>
<td></td>
</tr>
<tr>
<td>$\zeta$</td>
<td>0.1 (nM$^{-1}$min$^{-1}$)</td>
<td>0.02 [71]</td>
</tr>
<tr>
<td>$V$</td>
<td>1 ($\mu$m$^3$)</td>
<td>0.5~2.0</td>
</tr>
</tbody>
</table>
Stochastic simulations by Gillespie algorithm

- Stochastic simulation: time evolution trajectory using Gillespie algorithm

Threshold concentrations for decisions
- Reaching CI threshold: lysogeny
- Reaching Q threshold: lysis
First passage: lysis
First passage: lysogeny

Lysogeny
Fraction of lysogeny determined by multiple stochastic simulations

\[ M = 1 \]

Lysis 90%

Lysogeny 10%
Thresholds as evolvable traits

Fraction of Lysogeny when $M=1$

Lysogeny is favored

Lysis is favored
Average decision time can also be tuned by thresholds.

Average decision time when $M = 1$

- Slower decision
- Faster decision
What are essential features of alternative decisions?

- Is bistability necessary for alternative decisions?

- Can two systems behave the same way due to similarity of transient dynamics?
Asymptotically divergent GRN

- $M = 1$: Q expression level stays high.
- $M > 1$: $Q \rightarrow 0$. 
Transientsly divergent GRN

- At all $M$, $Q \rightarrow 0$.
- Maximum transient levels of $Q$ are different.
Similarity of transient dynamics leads to same response

- Responses can be very similar even if steady-state behaviors are qualitatively distinct
Experiments show much more heterogeneity than simulations


How can we explain this discrepancy?
Outline

- Determination of alternative cell fates
- Quantitative model of lysis-lysogeny decisions
- Heterogeneity of decisions: gene dosage effect on lysis-lysogeny
What can explain the variance of lysogeny?

At same $\mathcal{M}/V$, a singly infected cell has much higher probability of lysogeny than a doubly infected cell.

Quasi-independent decision proposed by Zeng et al (2010)

Phages are independent

Phages know the presence of other phages

\[ P_{lysg} = (P_{1\text{phage}})^M \]
When phages are totally independent

- Assume phages have no way of detecting other phages within a host

$$f\left(\frac{\mathcal{M}}{V}\right) \rightarrow f\left(\frac{1}{V}\right)$$
Gene dosage compensation

- Gene expressions is not always proportional to copy number

\[ \text{Tot transcription} = M^\lambda \, \text{transcription/copy} \]

Data can also be collapsed by partial dosage compensation

- Effective copy number is smaller than actual copy number

Data supports $\lambda = 0.5$
Comparison of different rescaling schemes

- Quasi-independent decisions:
  - Decision for each phage is independent
  - However, the decision rule for each phage depends on the concentration of all phages

- Gene dosage compensation
  - Mechanism by which resource limitation impacts viral gene production
  - Effective number of viral genomes is predicted to be less than the actual number
Stochastic simulations support effect of dosage compensation

Replace $\mathcal{M}$ with $\mathcal{M}^\lambda$ in our simulation

Data

Simulation, unscaled

Simulation, rescaled

Stochastic simulations supports partial gene dosage compensation
Conclusions

- Feedback and transient dynamics of gene regulation are sufficient for lysis and lysogeny.

- Systems with qualitatively distinct steady state behaviors might lead to similar decisions if their transient dynamics are similar.

- Gene dosage compensation can explain observed variation of MOI dependence.

- Future work involves predicting cell fate based on partial information of gene regulatory state.
Other Things We Do

Eco-evolutionary dynamics of phages and their hosts

Dangerous nutrients: top-down vs. bottom up forces impact evolution of resource uptake
Menge & Weitz (2009) JTB 257: 104

Host-state impacts phage effectiveness and subsequent host-phage dynamics

Quantifying enzymatic lysis

Cell fate determination by viruses
Joh & Weitz (in press) PLoS Comp Biol

Systems biology and biophysics of phage traits

CRISPR-induced co-evolutionary dynamics
Weitz & collaborators (in prep)

A - UNDIRECTED MUTATION OF VIRUSES
Mutation of a protospacer becomes novel allele on viral genome
Pre-immune response

B - DIRECTED MUTATIONS OF HOSTS
Blow-up of host CRISPR locus
Pre-immune response
Post-immune response

Novel spacer acquired from viral protospacer
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References
Joh and Weitz (in press) To lyse or not to lyse: transient-mediated stochastic fate determination in cells infected by bacteriophages. PLoS Computational Biology

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Questions?

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