Balancing growth and division in fluctuating environments

KC Huang
Stanford University
Cell size scales with growth rate

(Schaechter J Gen Microbiol 1958)
Bacterial cells achieve size homeostasis as “adders”

Outline

• Tuning of cell size and fitness
• Can we quantitatively predict how cells change shape as the environment changes?
• How do cells balance surface area and volume synthesis?
• How general are morphological responses across species?
Linear scaling of fitness with cell width

Monds et al. Cell Reports 2014
Mutants show differential lag-phase advantages

Cell shape can “easily” be tuned, and directly impacts physiology

Monds et al *Cell Reports* 2014
Can we predict cell size in a dynamic environment?
Bacterial culture in lab face stresses
Bacterial populations constantly face stresses
Bacterial populations constantly face stresses
Bacterial populations constantly face stresses.
Cell size changes with growth phases

Stationary phase

Exponential phase
How do cells coordinate cell shape, growth, and division across growth phases?
Cells actively change shape during growth

Shi et al., in preparation
Similar dynamics in time-lapse
Surface area to volume ratio (SA/V) linked to cell shape

$SA_0, V_0$
Surface area to volume ratio (SA/V)
linked to cell shape

\[ 1.47SA_0, 2V_0 \]

\[ 0.74 \frac{SA_0}{V_0} \]
Surface area to volume ratio (SA/V) linked to cell shape
SA/V varies in bulk culture

Shi et al., in preparation
Similar dynamics across species

- *Vibrio cholerae*
- *Caulobacter crescentus*
- *Bacillus subtilis*
… even eukaryotic microbes

Schizosaccharomyces pombe

SA/N (μm⁻¹)

0 100 200 300 400 500 600 700

Time (min)
Is cell division explicitly coupled to elongation dynamics?
Cephalexin alters cell morphology via division inhibition

\[ \text{cell} + \text{cephalexin} \Rightarrow \]
Cephalexin alters cell morphology via division inhibition
Blocking cell division affects both length and width + cephalexin ⇒
SA/V is maintained under cephalaxin treatment
In minimal medium, SA/V is (almost) maintained.
Can we quantitatively predict SA/V dynamics?
Model for SA and V growth for pseudo-steady state

\[ \frac{dV}{dt} = \alpha V(t) \]
\[ \frac{dA}{dt} = \beta V(t) \]

Harris et al., Cell 2016

<table>
<thead>
<tr>
<th>V</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Surface area</td>
</tr>
<tr>
<td>(\alpha)</td>
<td>Volume growth rate</td>
</tr>
<tr>
<td>(\beta)</td>
<td>Scaling factor linking volume to instantaneous surface growth rate</td>
</tr>
</tbody>
</table>
Model for $A$ and $V$ growth for pseudo-steady state

\[ \frac{dV}{dt} = \alpha V(t) \quad \frac{dA}{dt} = \beta V(t) \]

$\alpha$: volume growth rate
$\beta$: surface growth rate

\[ \left( \frac{A}{V} \right)_{ss} = \frac{\beta}{\alpha} \]

Harris et al., Cell 2016
Steady state SA/V is growth dependent

Harris and Theriot, *Cell* (2016)

\[ \frac{\beta}{\alpha} \quad \beta = f(\alpha) \]

S et al., *BioRxiv* (2016)
Model for SA and V growth for pseudo-steady state

\[
\frac{dV}{dt} = \alpha V(t) \quad \frac{dA}{dt} = \beta V(t)
\]

\[\alpha: \text{volume growth rate} \quad \beta: \text{surface growth rate}\]

\[
\frac{d}{dt} \left( \frac{A}{V} \right) = \beta - \alpha \frac{A}{V}
\]

\[
\beta = f(\alpha)
\]

Harris et al., Cell 2016
Steady-state model does not fit experimental data

Shi et al., in preparation
Changes of $\beta$ and $\alpha$ may be desynchronized

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Shi et al., in preparation
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Shi et al., in preparation
Changes of $\beta$ and $\alpha$ may be desynchronized

\[
\frac{dV}{dt} = \alpha V(t) \quad \frac{dA}{dt} = \beta V(t)
\]

Modification for fast-changing conditions:

\[
\beta(t) = f(\alpha(t - \Delta t))
\]

Shi et al., in preparation
Time-delay model predicts SA/V dynamics

Shi et al., in preparation
Quantifying protein expression levels

A comprehensive library of fluorescent transcriptional reporters for Escherichia coli

Alon Zaslaver, Anat Bren, Michal Ronen, Shalev Itzkovitz, Ilya Kikoin, Seagull Shavit, Wolfram Liebermeister, Michael G Surette & Uri Alon


pmrcB-gfp
pmurA-gfp
cytoplasmic
prplL-gfp
surface
prpsU-gfp
Delay in surface-protein expression supports time-delay model

Dots: time point with 10% increase within the whole dynamic range
Can we test the time-delay model?
Model prediction 1: SA/V drops with inhibition of $\beta$

Shi et al., in preparation
A22 alters cell morphology via surface growth inhibition
Model prediction 1: SA/V drops with inhibition of $\beta$

$\text{Shi et al., in preparation}$
Model prediction II: $\Delta t$ alters SA/V dynamics

$\Delta t = 25$ min
$\Delta t = 20$ min
$\Delta t = 15$ min
$\Delta t = 11$ min

Shi et al., in preparation
Model prediction II: $\Delta t$ alters SA/V dynamics

Shi et al., in preparation
Model prediction III: cells increase width upon growth resumption

\[
\frac{dV}{dt} = \alpha V(t) \quad \frac{dA}{dt} = \beta V(t)
\]
Model prediction III: cells increase width upon growth resumption

\[ \frac{dV}{dt} = \alpha V(t) \quad \frac{dA}{dt} = \beta V(t) \]

Upon growth resumption, $\alpha$ increases while $\beta$ remains close to zero, causing SA/V to decrease.
Model prediction III: cells increase width upon growth resumption

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Upon growth resumption, \( \alpha \) increases while \( \beta \) remains close to zero, causing \( SA/V \) to decrease.
Model prediction III: cells increase width upon growth resumption

\[
\frac{dV}{dt} = \alpha V(t) \quad \frac{dA}{dt} = \beta V(t)
\]

Upon growth resumption, $\alpha$ increases while $\beta$ remains close to zero, causing $SA/V$ to decrease.
Conclusions

• Bacterial cells actively tune their morphologies to adapt to environmental fluctuations
• Surface synthesis adjusts to changes slower than volume synthesis, in nutrient dependent manner
• Cells have remarkable ability to change shape when nutrients change
• Simple model with time delay due to proteome reallocation predicts that cells actively adjust dimensions to optimize SA/V
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