Event Timing in Single Cells: Application to Phage Lysis

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Measuring lysis time at single-cell level

Lysogen

Thermal Induction

Lysis

42°C

37°C

Arkin et al, Genetics, 1998;
St-Pierre and Endy, PNAS, 2008;
Zeng et al, Cell, 2010;
Data reveals precision in lysis timing

Mean = 65 mins
Standard deviation = 3.5 mins
Holins: Lysis time keepers

Holin expression and accumulation

Hole formation

Cell before lysis

Hole formation

Lysed cell (~5s after hole formation)

White et al., PNAS, 2010; Dennehy and Wang, BMC Microbiology., 2011
Event timing as a first-passage time problem

Event threshold

Event timing histogram

Protein level/cell

Time

\[ FPT = \inf(t \geq 0 : x(t) \geq X) \]
- $k_m$: Transcription rate
- $b$: Mean protein burst size
- $X$: FPT threshold

\[ FPT = \inf(t \geq 0 : x(t) \geq X) \]

\[ \langle FPT \rangle \approx \frac{X}{bk_m} \]

\[ CV_{FPT}^2 \approx \frac{1 + 2b}{X} \]

$\ b = \frac{k_p}{\gamma m}$
Testable model predictions

\[
\langle FPT \rangle \approx \frac{X}{bk_m} \quad CV_{FPT}^2 \approx \frac{1 + 2b}{X} \quad b = \frac{k_p}{\gamma m}
\]
Lower mean lysis times associated with higher cell-to-cell variability

Changes in lysis threshold

Model prediction
Experimental data

Coefficient of variation squared

Mean first-passage time (minutes)
\[
\langle FPT \rangle = \frac{1}{k_m} + \frac{1}{b} \sum_{i=1}^{X} \frac{1}{k_m + (i-1)\gamma_p} \left[ 1 + \sum_{j=i+1}^{X} \prod_{l=i}^{j-1} \frac{lb\gamma_p}{(k_m + l\gamma_p)(1+b)} \right]
\]

\[
\langle FPT^2 \rangle = \frac{2}{b^2} \sum_{i=1}^{X} \frac{1}{k_m + (i-1)\gamma_p} \left[ \xi_i + \sum_{r=i+1}^{X} \prod_{l=i}^{r-1} \frac{lb\gamma_p}{(k_m + l\gamma_p)(1+b)} \right]
\]

\[
\eta_i = \frac{b}{k_m} \delta_{i-1} + \frac{1}{k_m + (i-1)\gamma_p} \left[ 1 + \sum_{j=i+1}^{X} \prod_{l=i}^{j-1} \frac{lb\gamma_p}{(k_m + l\gamma_p)(1+b)} \right] \xi_i = (b + 1)\eta_i + \sum_{j=1}^{i-1} \eta_j
\]
Noise in FPT with Holin decay

FPT threshold

Transcription rate

Mean protein burst size

FPT $\gamma = 0 \text{ min}^{-1}$

FPT $\gamma = 0.05 \text{ min}^{-1}$

FPT $\gamma = 0.1 \text{ min}^{-1}$
An incoherent feedforward circuit in the lytic pathway

- Removing anti-holin increases lysis time CV by two-fold
- Anti-holin minimizes lysis time CV by reducing holin translation burst size?
Can feedback minimize variability in first-passage time?

For a fixed $X$ and mean $FPT$, what functions $k_m(x)$ will minimize noise in $FPT$?

$$FPT = \inf(t \geq 0 : x(t) \geq X)$$
Can feedback minimize variability in first-passage time?

Optimal function minimizing variability in $FPT$

$$k_m = \frac{X}{b\langle FPT \rangle}$$
Factors controlling cell-to-cell lysis time differences?

Stochastic holin expression

How is precision in lysis times achieved?

Low translational burst size; Feedforward; No feedback

Why is precision needed?

Optimal lysis time
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