Modelling Host-Pathogen Dynamics

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Bioblast
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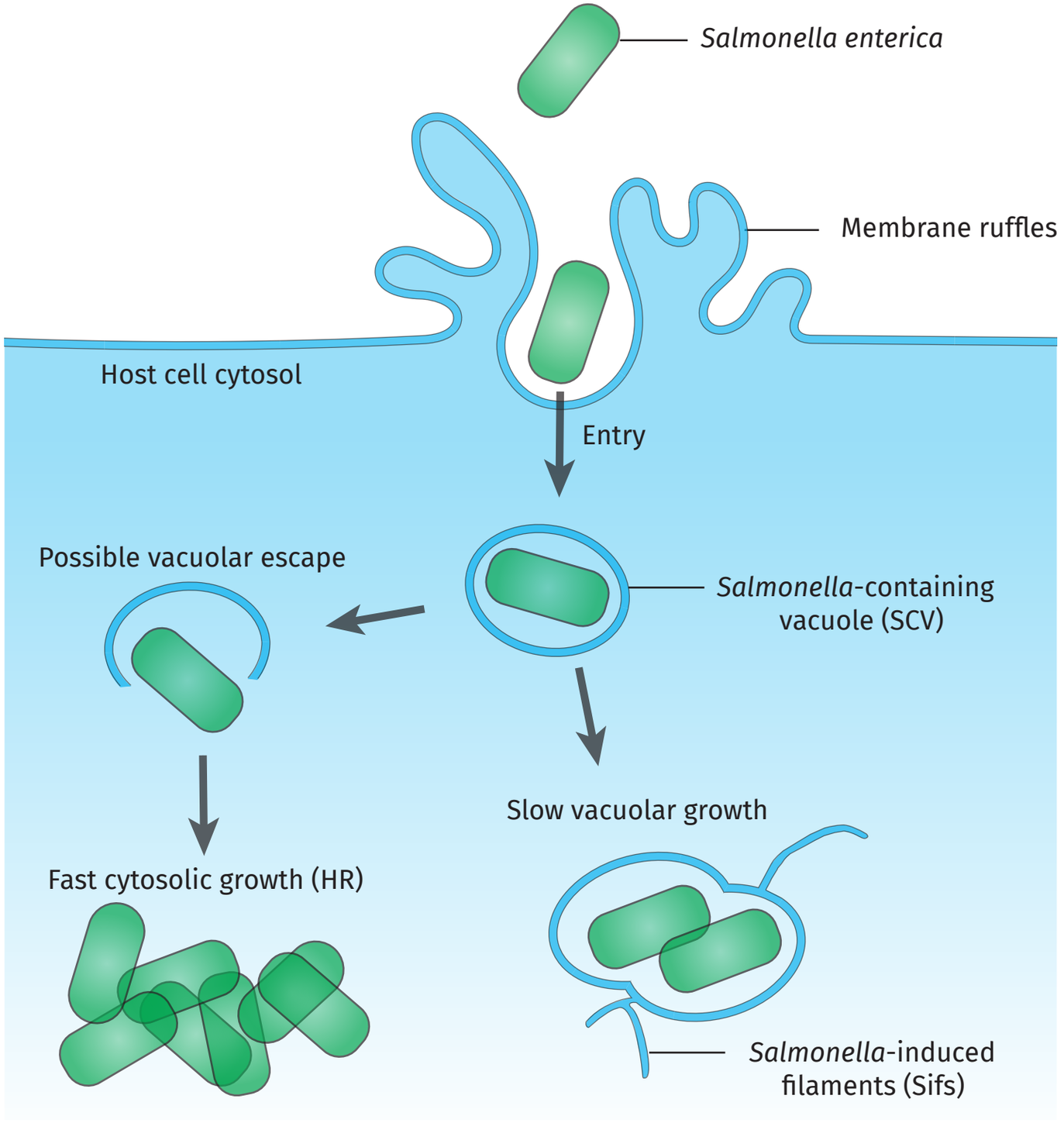
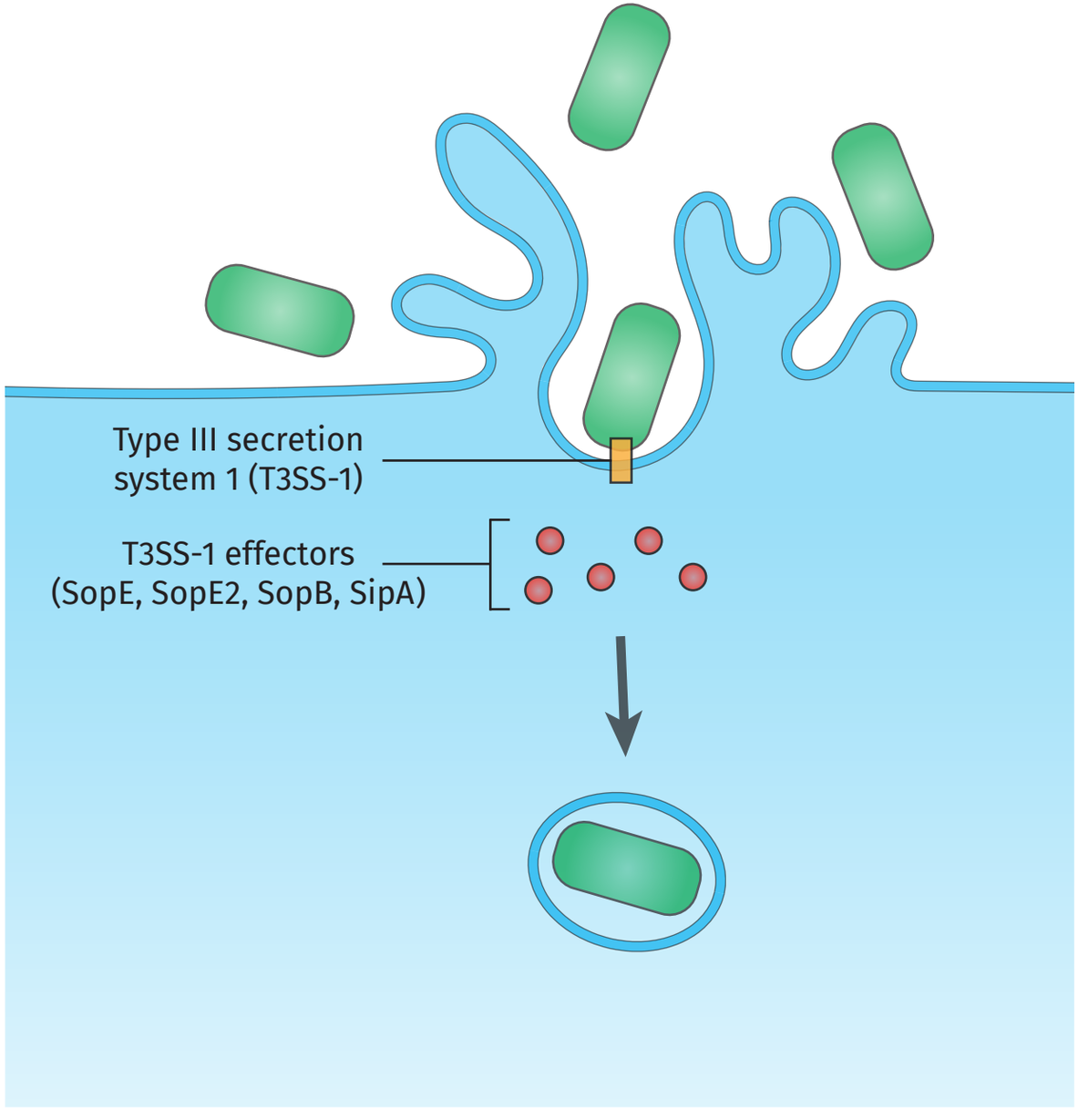
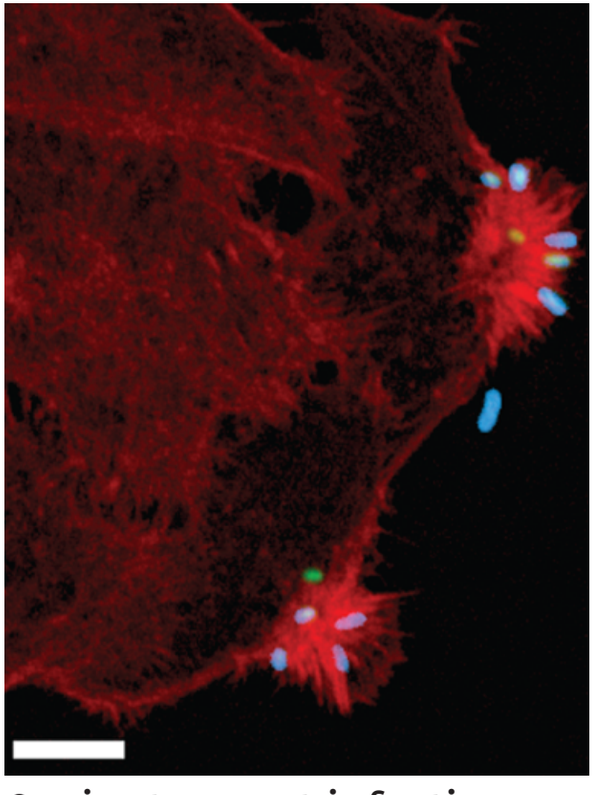
A simple invasion model



Cooperative invasion via ruffles



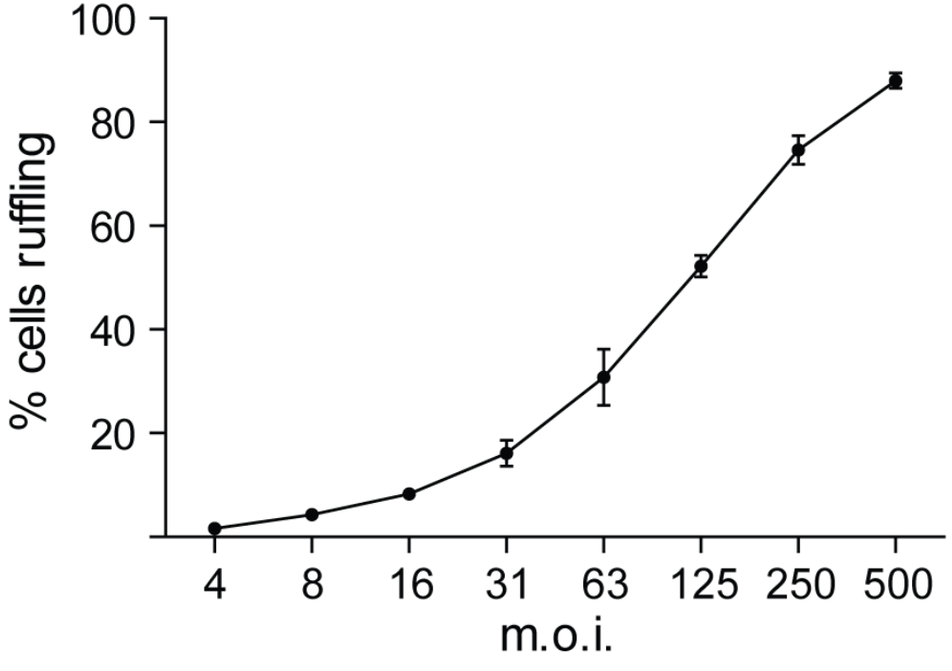
Misselwitz et al. (2012)

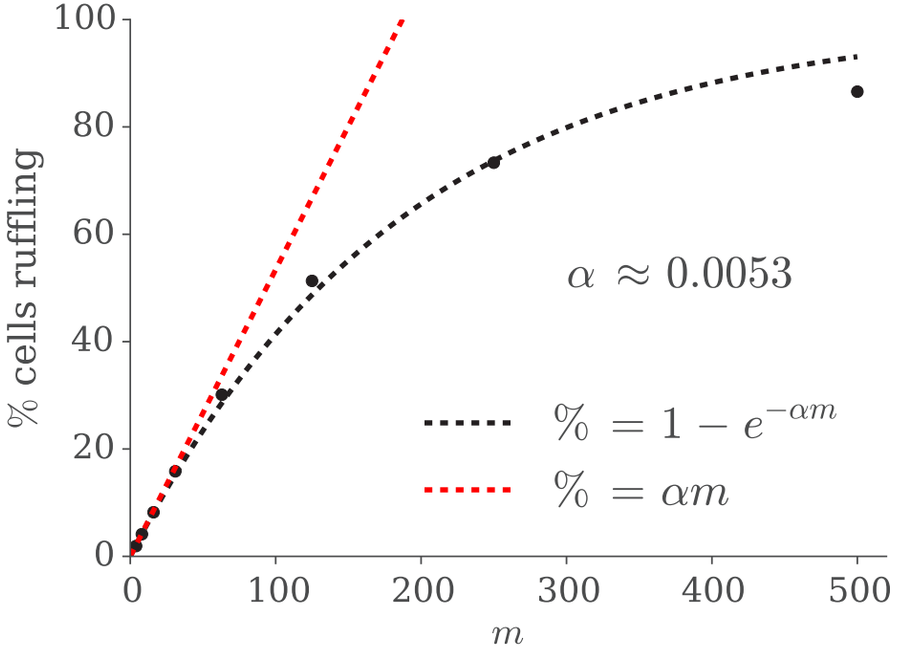


6 minutes post infection
***Salmonella* inside**
***Salmonella* outside**
HeLa cell actin
Scale bar: 10 µm

Cooperative invasion via ruffles

Misselwitz et al. (2012)



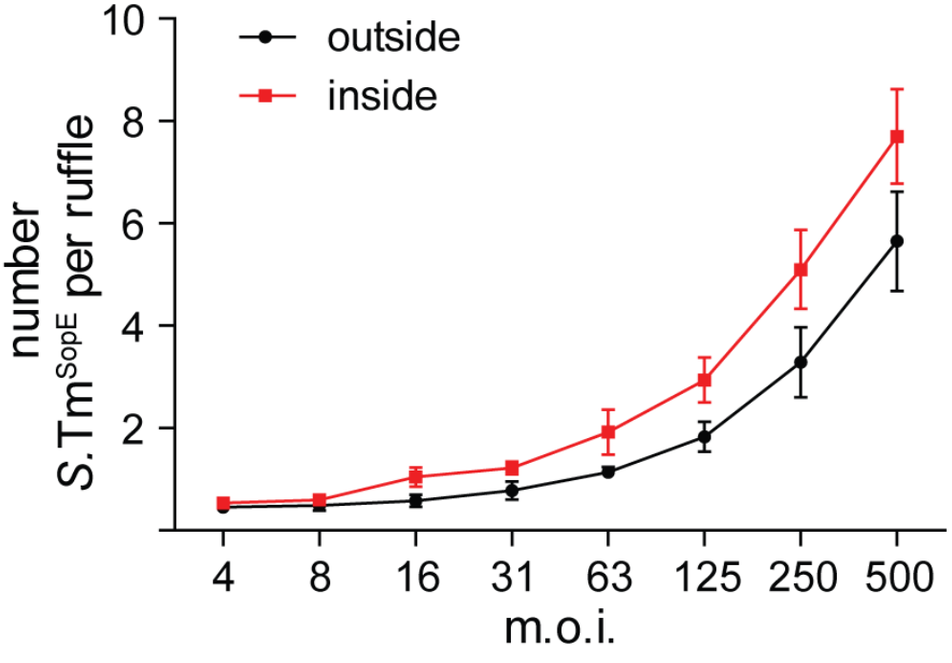


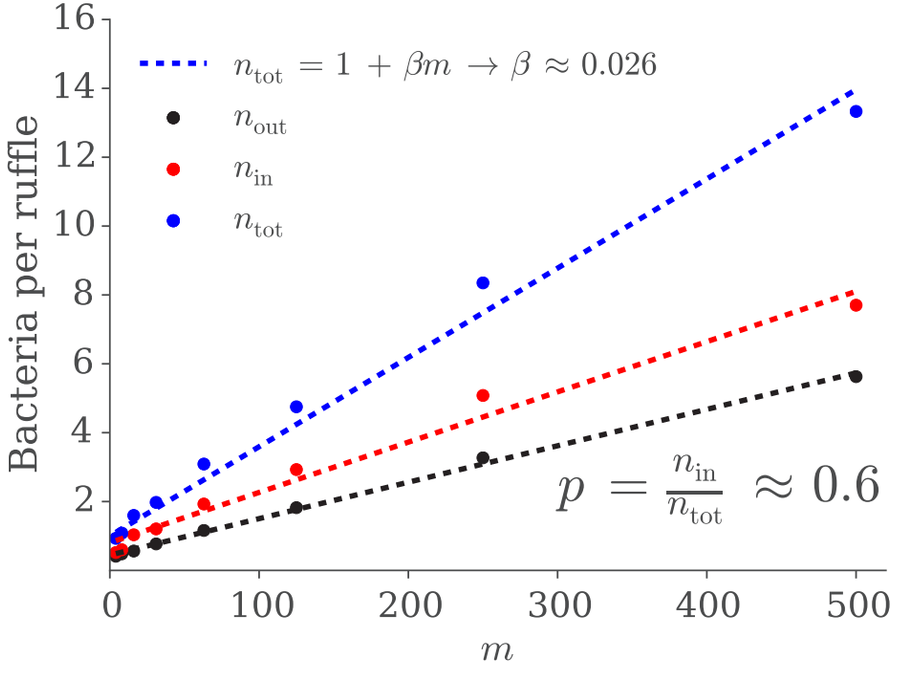
Removing log-scale reveals linear scaling at low multiplicities of infection (**MOI**).

α = probability of a bacterium landing and causing a ruffle to form.

Cooperative invasion via ruffles

Misselwitz et al. (2012)



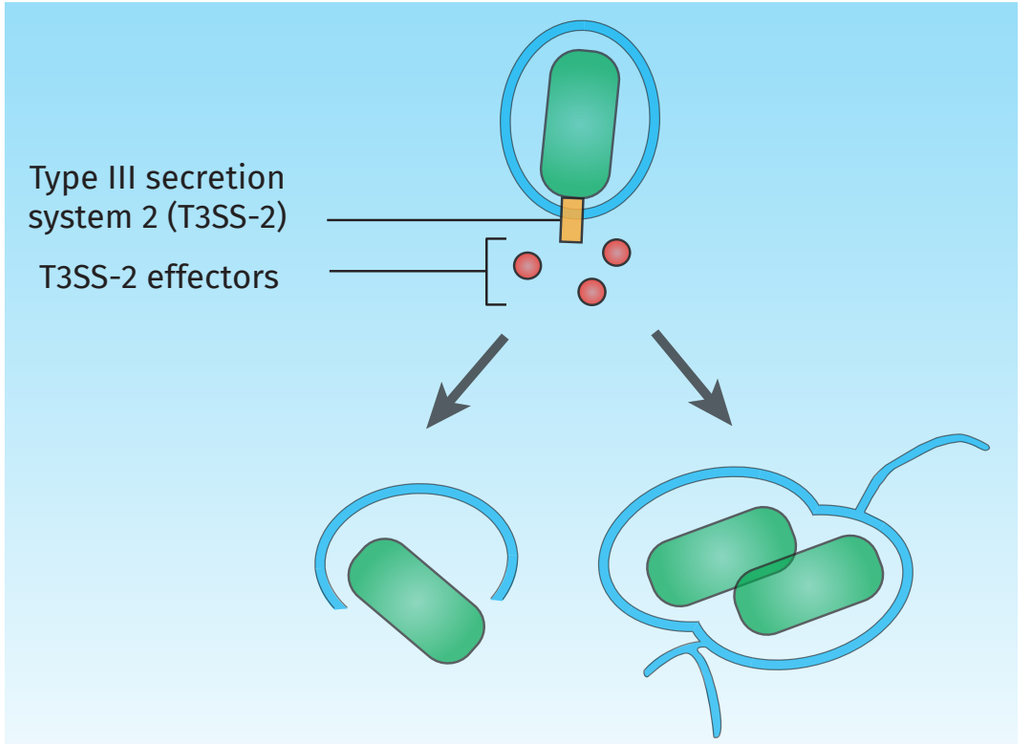


Removing log-scale reveals linear relationship between MOI and bacteria capture.

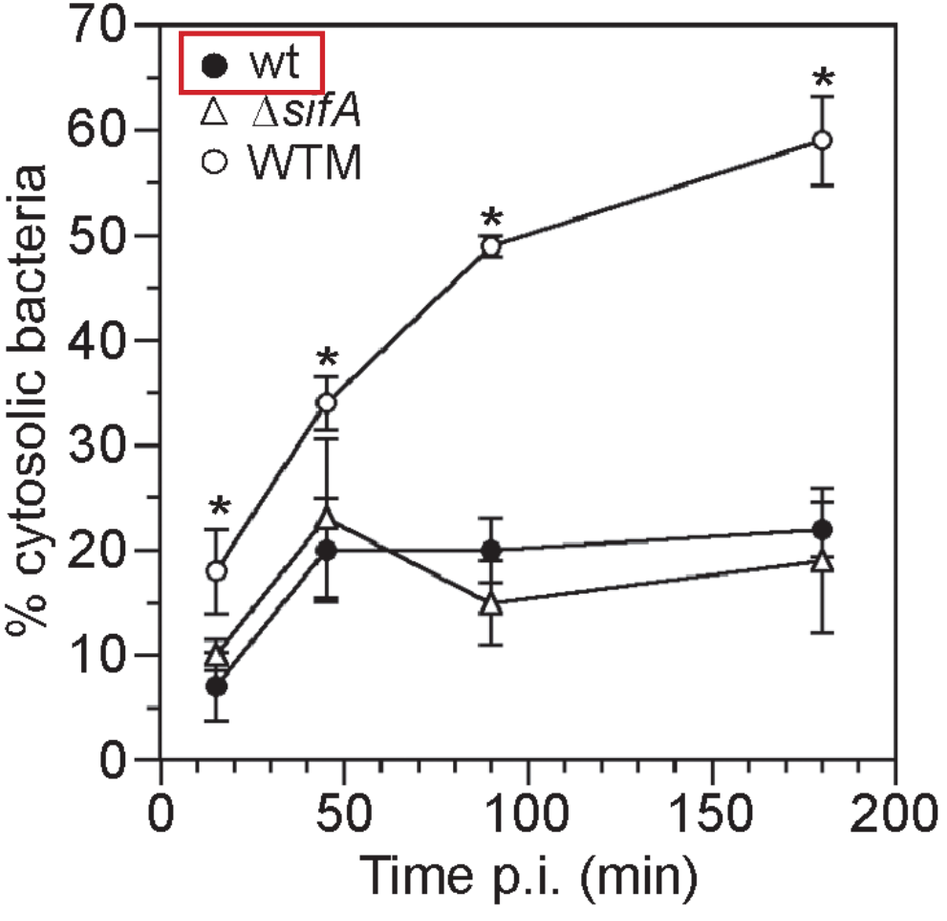
β = probability of bacteria capture onto ruffle.

p = probability of captured bacteria entering the cell.

Vacuolar escape

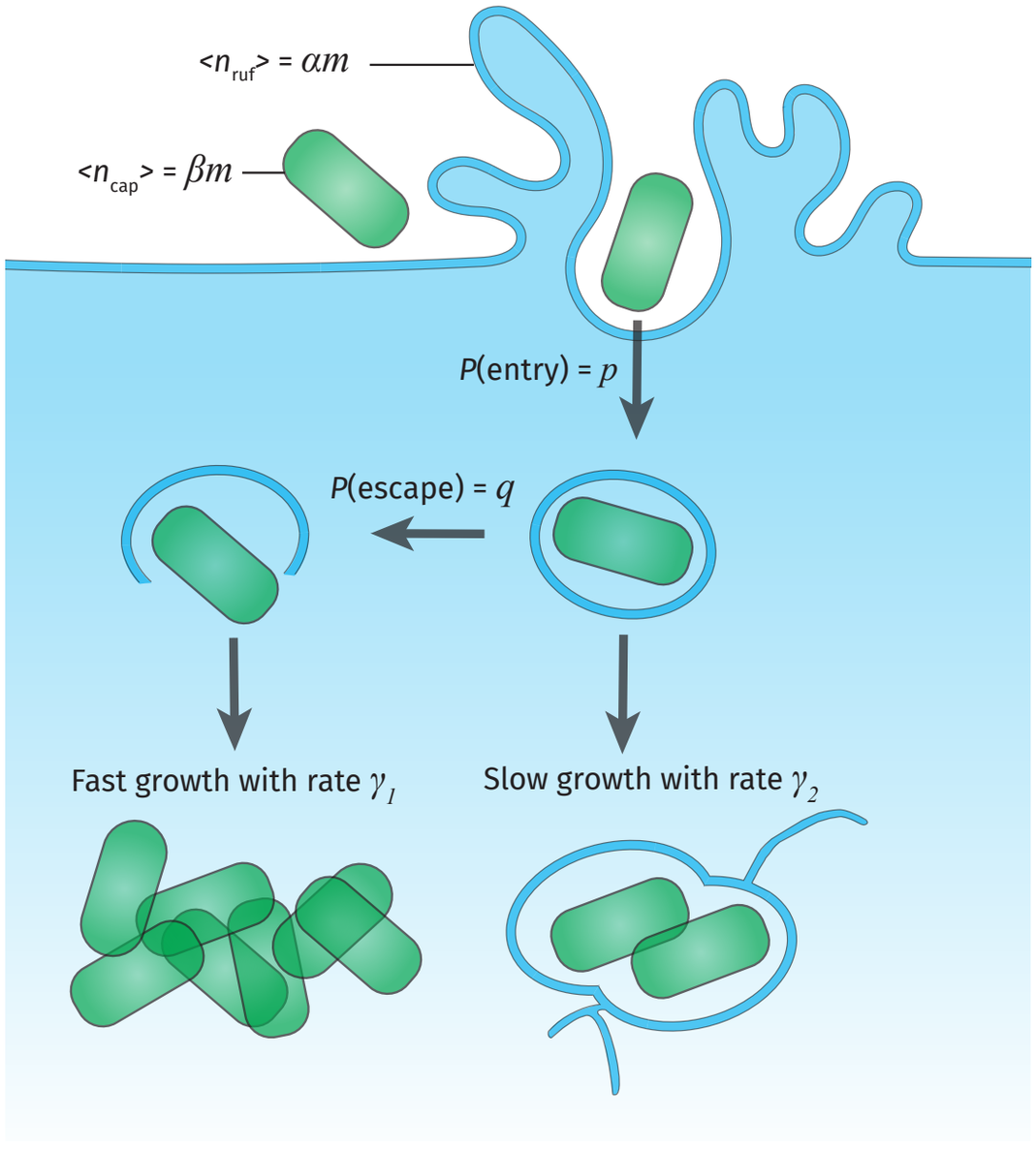


Knodler et al. (2014)



$q \approx 0.2$ = probability of vacuolar escape (fixed fraction).

Quantitative model of invasion



Ruffles per cell:

$$n_{\text{ruf}} \sim \text{Poisson}(\alpha m)$$

Bacteria captured per ruffle:

$$n_{\text{cap}} \sim 1 + \text{Poisson}(\beta m)$$

Bacteria entering the cell:

$$n_{\text{in}} \sim \text{Binomial}(n_{\text{cap}}, p)$$

Bacteria escaping the vacuole:

$$\begin{aligned} n_{\text{cyt}} &\sim \text{Binomial}(n_{\text{in}}, q) \\ n_{\text{vac}} &= n_{\text{in}} - n_{\text{cyt}} \end{aligned}$$

Bimodal growth:

$$\begin{aligned} n_{\text{cyt}}(t) &= n_{\text{cyt}}(0)\ \mathrm{e}^{\gamma_1 t} \\ n_{\text{vac}}(t) &= n_{\text{vac}}(0)\ \mathrm{e}^{\gamma_2 t} \end{aligned}$$

Stochastic simulations

10,000 cells at 25, 50 and 100 MOI with parameters from the literature (α, β, p, q) and average growth rates γ_1 = 0.7 h^{-1} (cytosolic HR) and γ_2 = 0.1 h^{-1} (vacuolar).

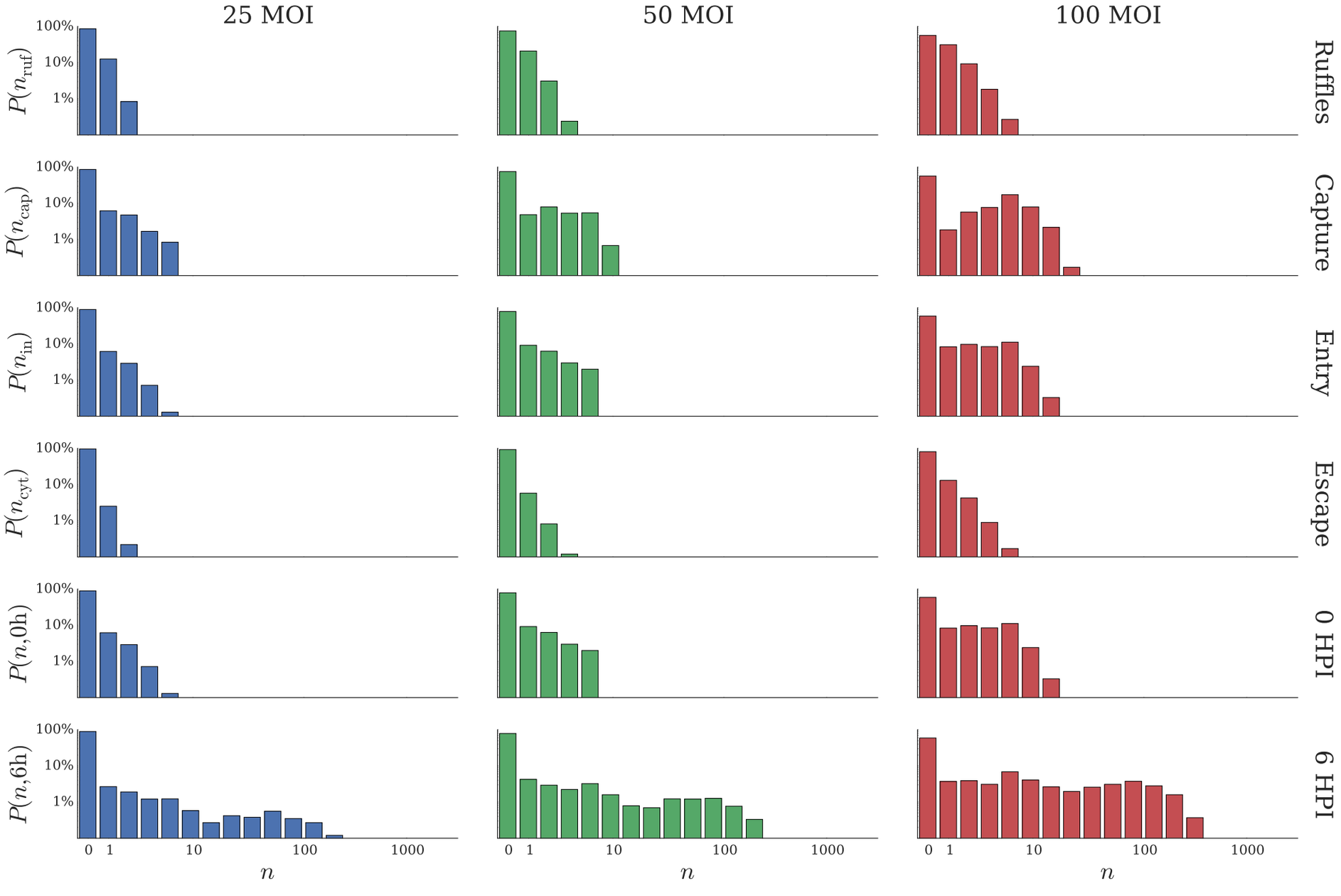


Image analysis software

CellProfiler™
cell image analysis software

1. Input modules:
   choose images, extract metadata, assign names and groups.

2. Pipeline:
   a set of sequential analysis modules to segment images, take measurements and output data

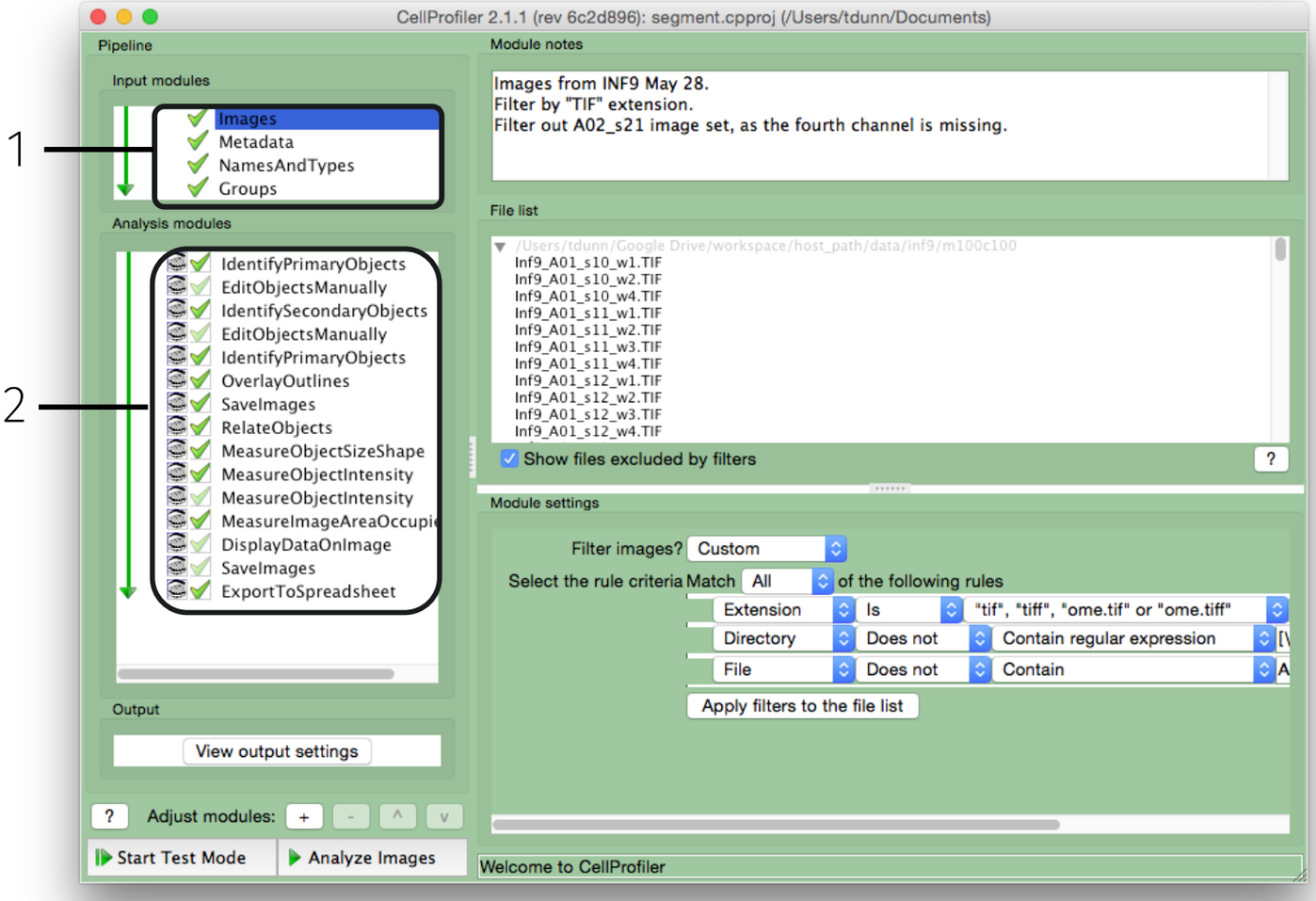


Image segmentation

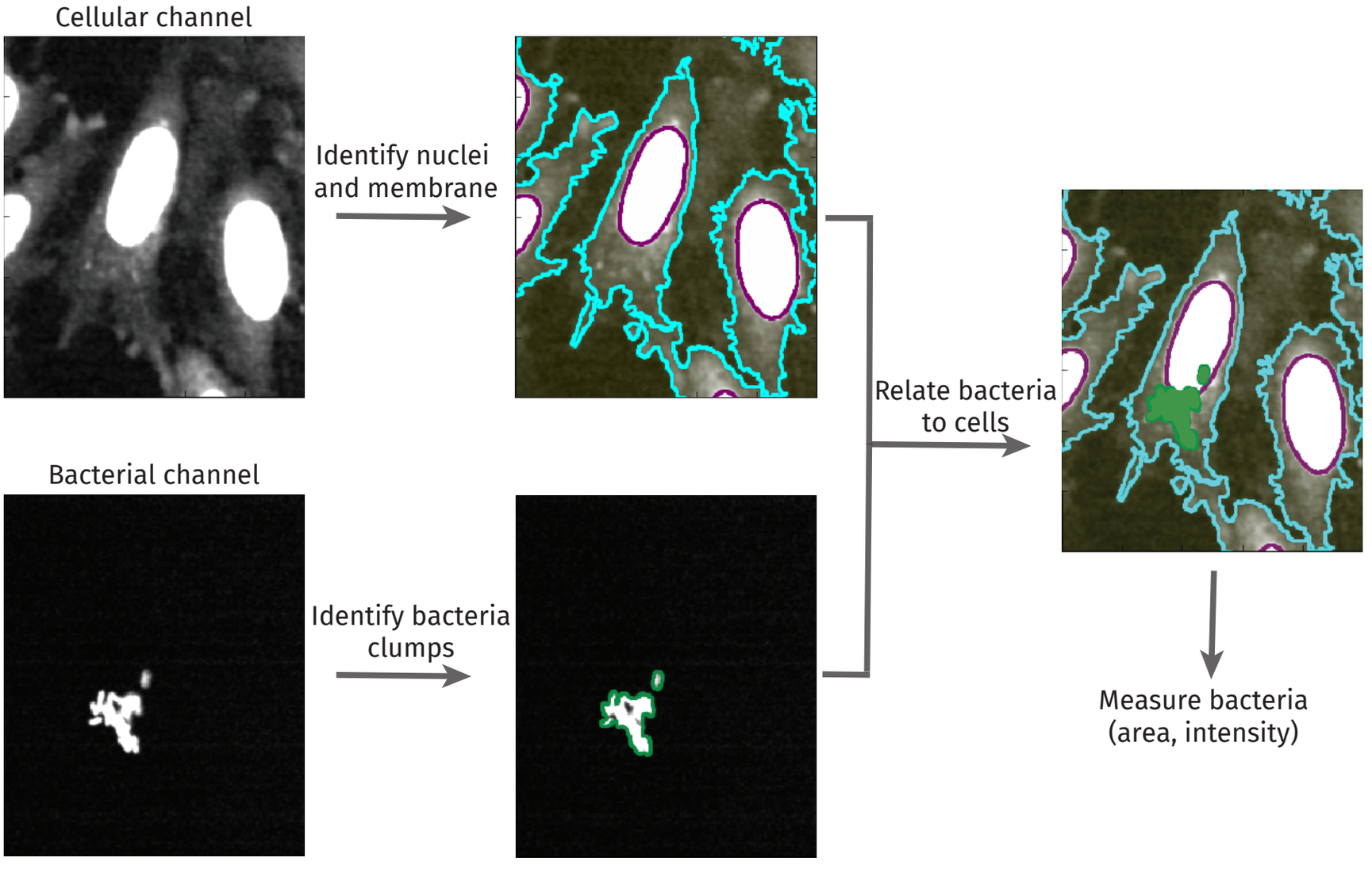
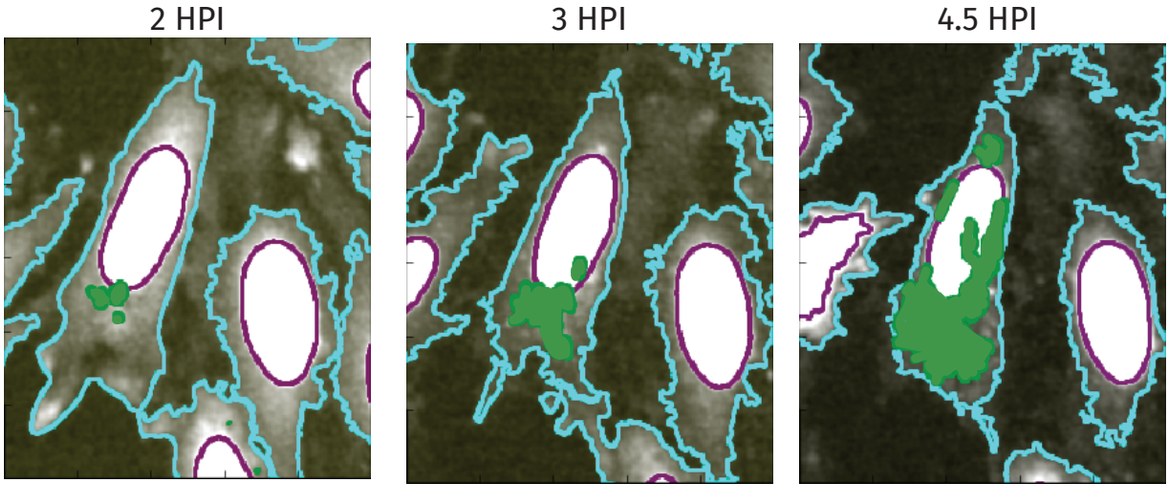
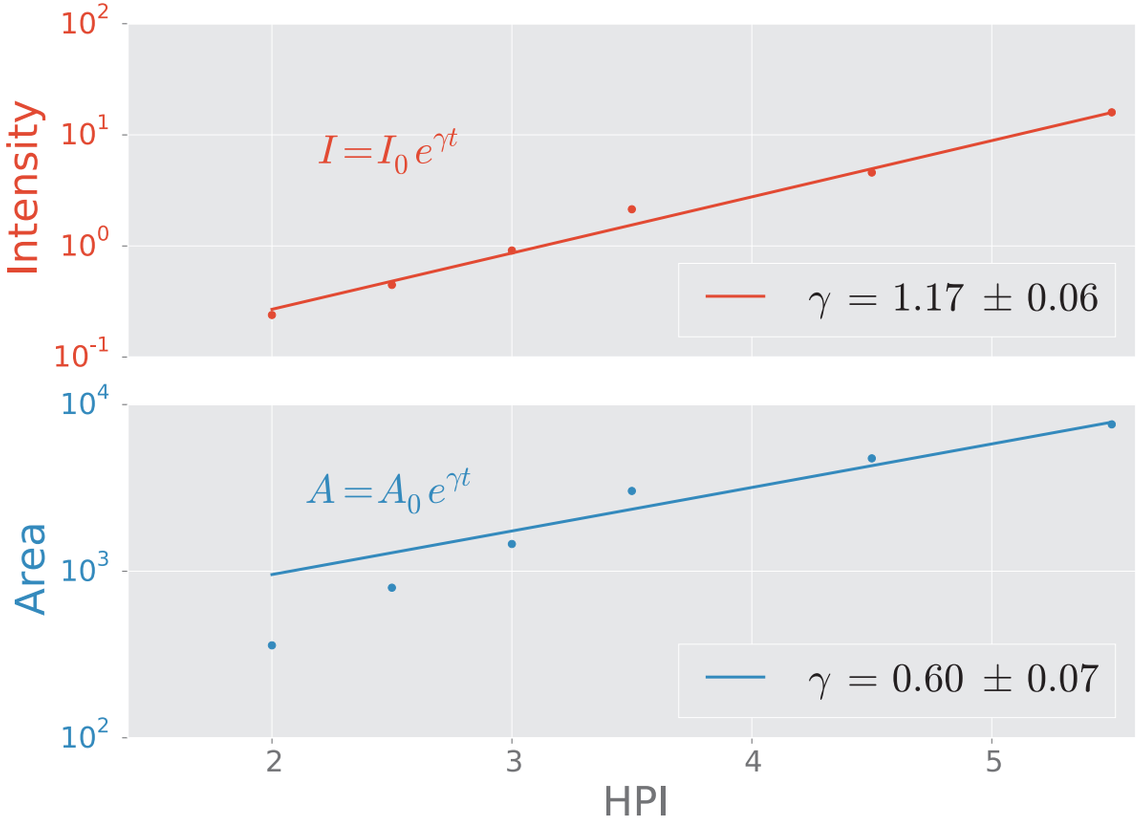
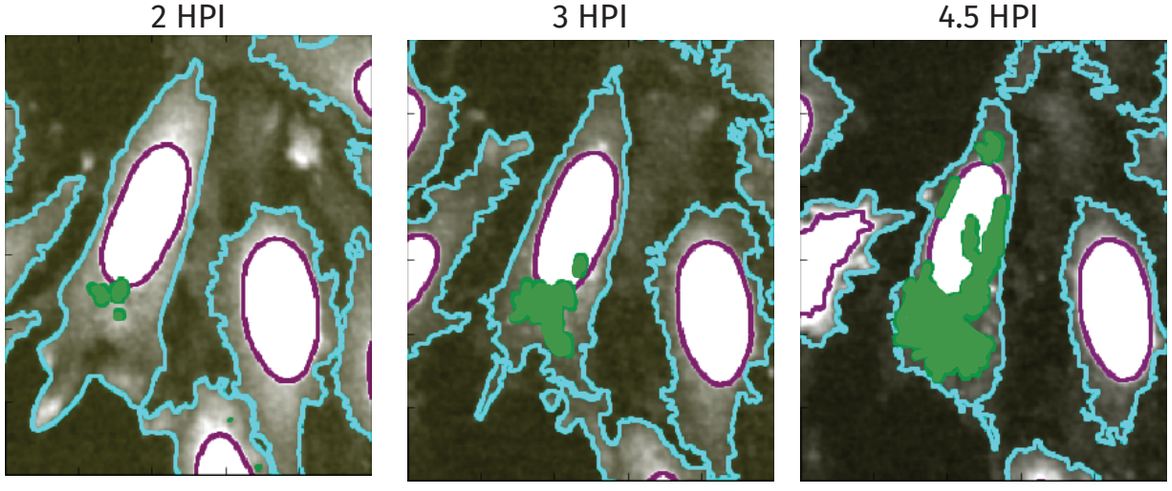


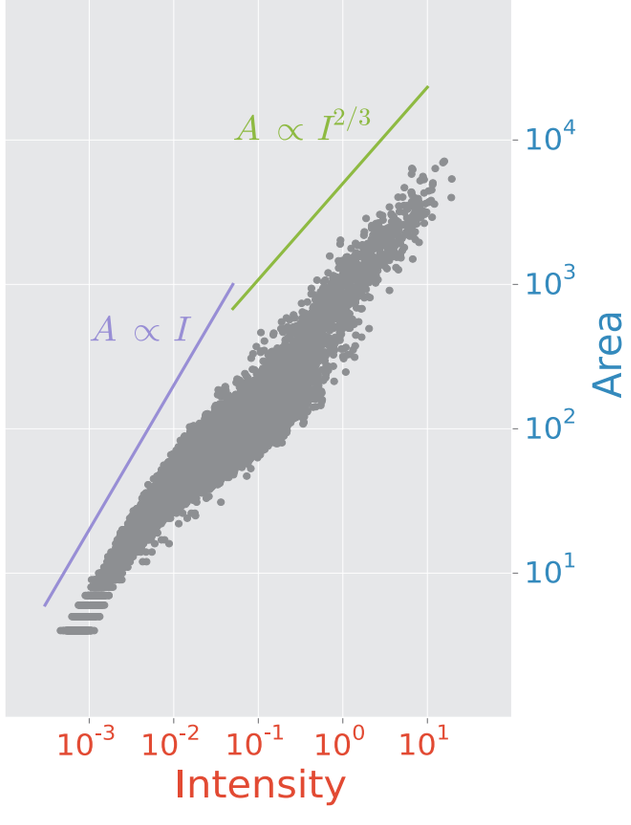
Image segmentation





Area vs intensity of bacteria





Intensity $I(t)$ the superior proxy for number of bacteria $n(t)$ because it captures the height of large bacterial clumps

From analyzing intensity growth in ~50 HR cells at MOI 10, 25 and 50:

$$\gamma_1 \approx 0.78 \pm 0.15$$

Slow vacuolar growth was too slow to get an accurate over the time period of 5.5 hours:

$$\gamma_2 << \gamma_1$$

Bacterial load distribution *P(n, t)*

How to estimate HR fraction (fraction of infected cells that contain hyper-replicating *Salmonella*)?

<u>Simulation parameters</u>

10,000 cells

$m = 50$

$\alpha = 0.0053$

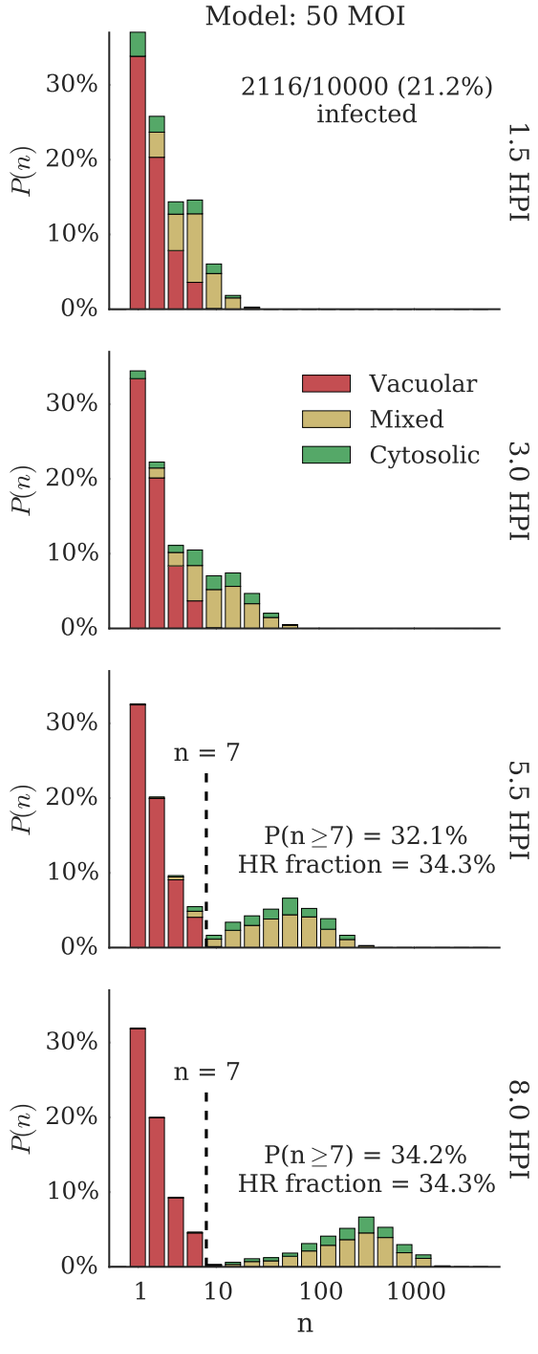
$\beta = 0.026$

$p = 0.6$

$q = 0.2$

$\gamma_1 = 0.78$

$\gamma_2 = 0.01$



Bacterial load distribution *P(I, t)*

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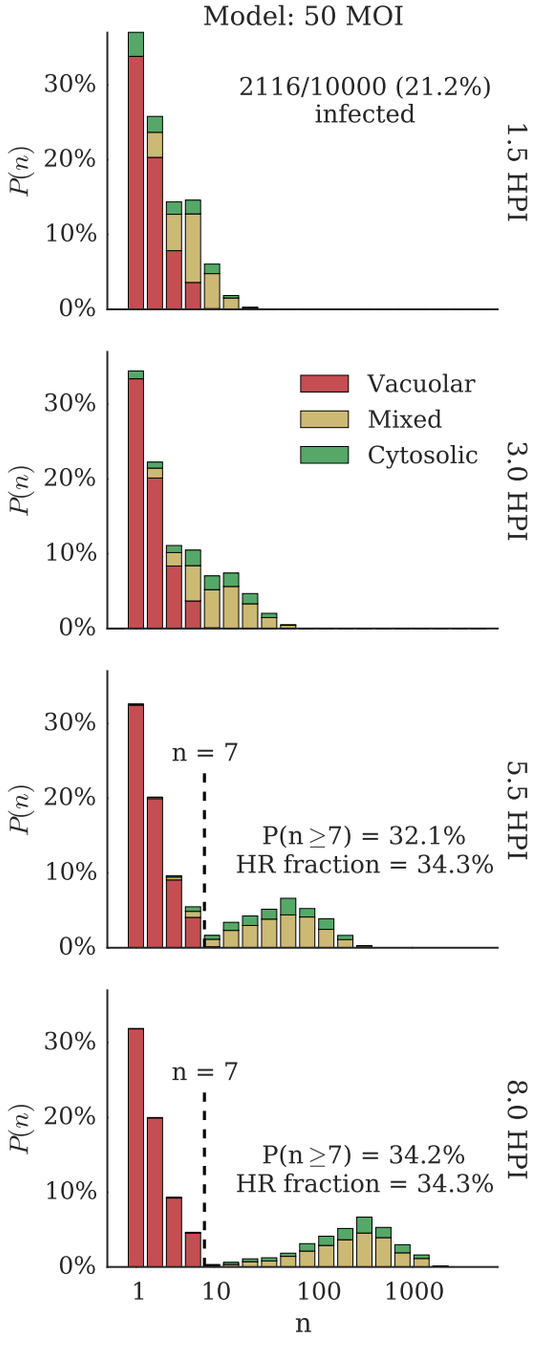
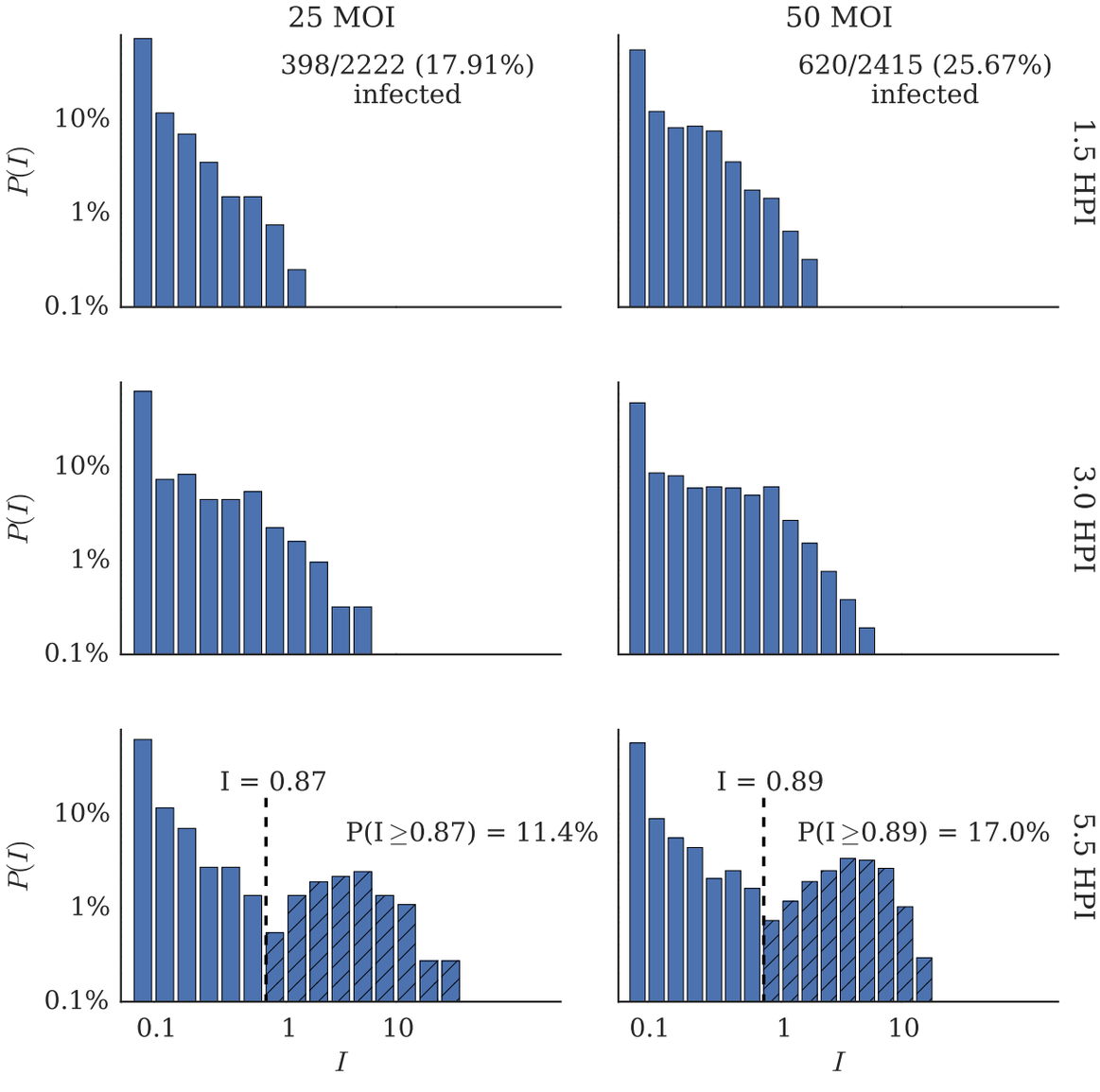
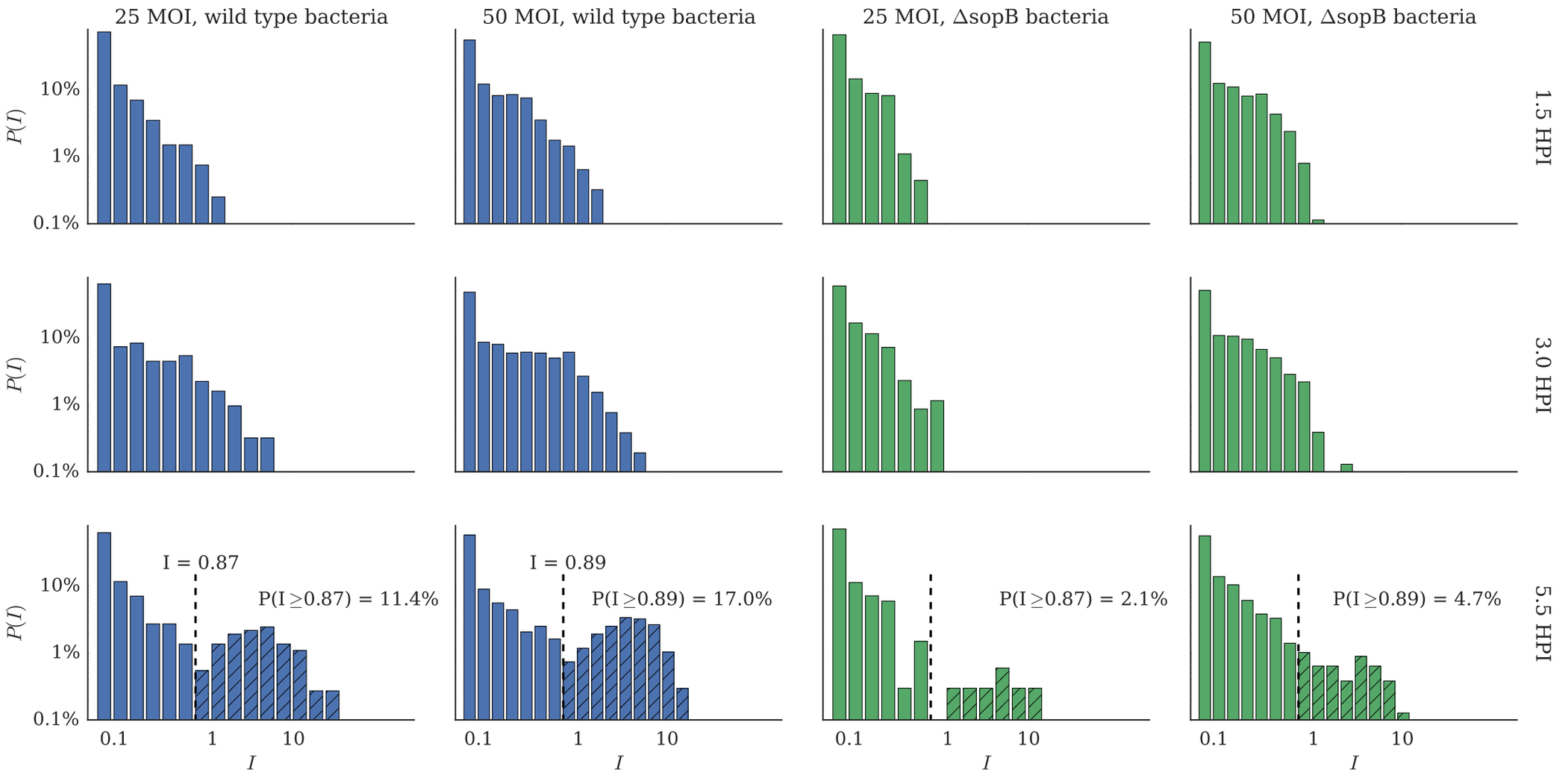




This intensity cutoff method likely gives a good estimate of the HR fraction, but a later timepoint (e.g. 8 HPI) would be better.

Bacterial load distribution *P(I, t)*

Using the cutoff method and wild type bacteria as a control, we can estimate HR fraction for different genetic conditions.



In absence of the SopB effector protein, *Salmonella* HR fraction decreaes from 11.4% to 2.1%, and 17.0% to 4.7% for MOI 25 and 50, respectively.

Future work

New images from Pasteur soon:
- Higher resolution (20X → 40X magnification).
- Z-stack images (multiple planes).
- Earlier and later (6.5 HPI) times points.

Current data:
- Fit $P(I,t)$ distributions to extract model parameters.
- Improve single-cell tracking to get distributions of growth parameters $P(\gamma_1)$ and $P(\gamma_2)$.
- Incorporate autophagy into model.

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- 13-14: Bacterial load distribution *P(I, t)*