

MODELLING HOST-PATHOGEN INTERACTIONS

Taylor Dunn

Andrew Rutenberg

January 16, 2015

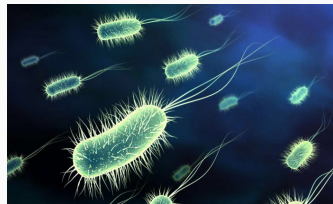


How do pathogenic bacteria invade and replicate within the host cytosol?

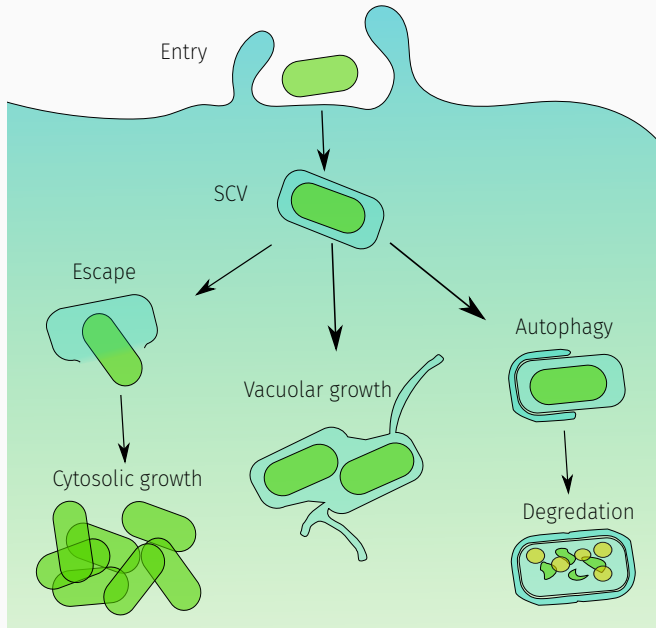
- a rich multiscale problem with significant stochasticity.
- quantitative modelling provides insight.

Salmonella enterica

- Gram-negative enteric bacterium.
- Serovar Typhimurium (**S. Typhimurium**) is a leading cause of human gastroenteritis.
- Two type III secretion systems (**TTSS-1** and **TTSS-2**).
- Bimodal lifestyle:
 - within the **SCV**: *Salmonella*-containing vacuole.
 - in the host cytosol.

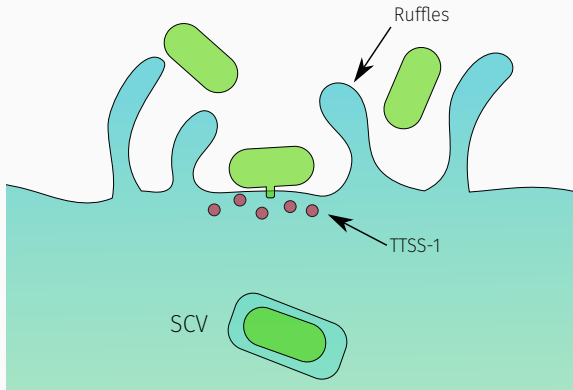


INFECTION MODEL



CAPTURE AND ENTRY


- Nearby *Salmonella* land on cell surface and attach.
- Type III secretion system 1 (TTSS-1): inject effectors into host cytosol.
- Effectors manipulate host cell into forming membrane **ruffles**.
- Ruffles facilitate landing of additional bacteria – **cooperative**.



Near Surface Swimming of *Salmonella* Typhimurium Explains Target-Site Selection and Cooperative Invasion

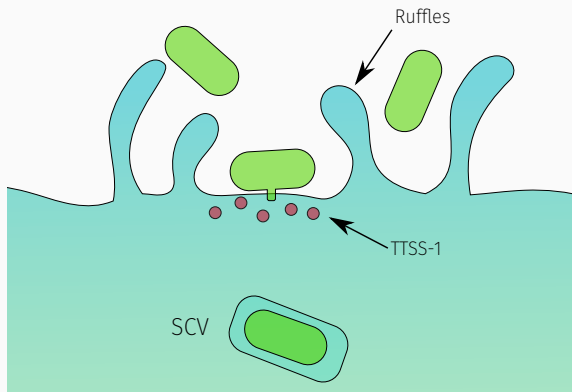
Benjamin Misselwitz^{1,3}, Naomi Barrett^{1,3}, Saskia Kreibich¹, Pascale Vonaesch¹, Daniel Andrichke¹, Samuel Rout¹, Kerstin Weidner¹, Milos Sormaz², Pascal Songhet¹, Peter Horvath³, Mamta Chabria⁴, Viola Vogel⁴, Doris M. Spori², Patrick Jenny⁵, Wolf-Dietrich Hardt^{1*}

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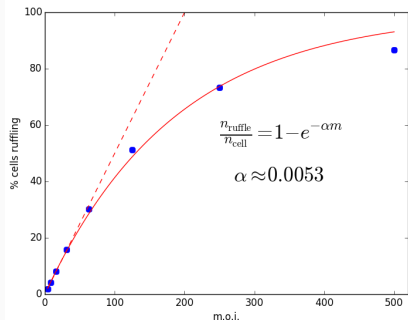
Near Surface Swimming of *Salmonella* Typhimurium Explains Target-Site Selection and Cooperative Invasion

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- Shows fraction of cells with ruffles.
- Roughly linear at low m.o.i.
- Parameter α is approximately the chance of bacteria landing and causing a ruffle.
- $\alpha m \approx$ number of ruffles per cell.

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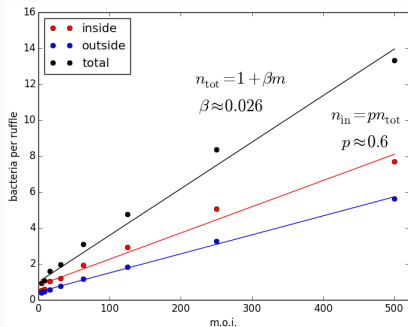
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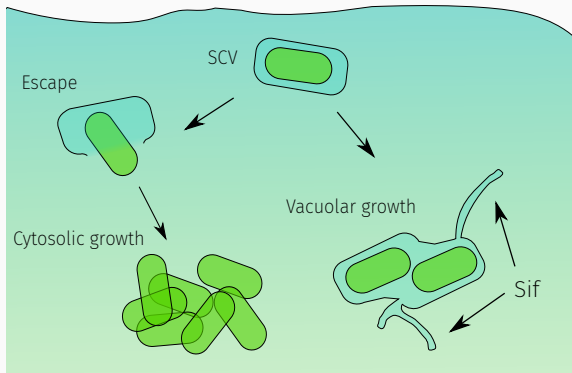
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- Total bacteria per ruffle n_{tot} is number of extracellular bacteria n_{out} plus number of intracellular bacteria n_{in} .
- Linear in m.o.i.
- Parameter β is the chance of bacteria capture.
- For all bacteria captured, p is the fraction that enter the cell.

VACUOLAR ESCAPE

- The TTSS-1 contributes to lysis of the **SCV** (*Salmonella*-containing vacuole).
- These bacteria **hyper-replicate** (≥ 100 bacteria/cell).
- Vacuolar *Salmonella* replication is slower and coincides with the appearance of **Sifs** (*Salmonella*-induced filaments).



Quantitative Assessment of Cytosolic *Salmonella* in Epithelial Cells

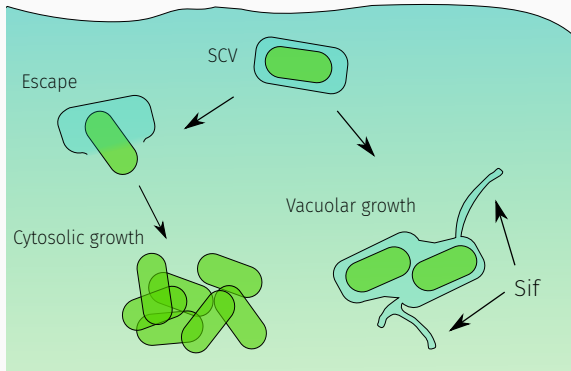
Leigh A. Knodler^{1,2*}, Vinod Nair³, Olivia Steele-Mortimer²

1 Paul G. Allen School for Global Animal Health, College of Veterinary Medicine, Washington State University, Pullman, Washington, United States of America, **2** Laboratory of Intracellular Parasites, Rocky Mountain Laboratories, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Hamilton, Montana, United States of America, **3** Research Technologies Branch, Rocky Mountain Laboratories, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Hamilton, Montana, United States of America

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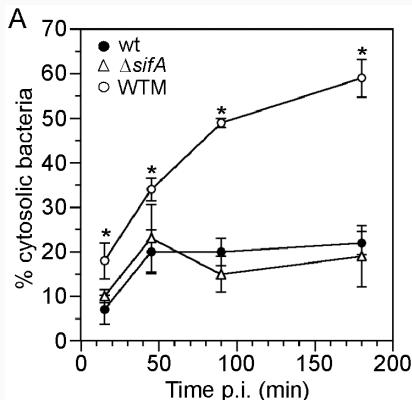
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- Fixed fraction of cytosolic wild type (wt) *Salmonella*.
- Let $q \approx 0.2$ be probability of vacuolar escape.

QUANTITATIVE MODEL

Parameter	Definition	Value	Source
α	Ruffle rate	0.0053	Misselwitz et al. (2012)
β	Capture rate	0.028	Misselwitz et al. (2012)
p	$P(\text{enter})$	0.6	Misselwitz et al. (2012)
q	$P(\text{escape})$	0.2	Knodler et al. (2014)

- Ruffles per cell:

$$n_{\text{ruffle}} = \alpha m$$

- Bacteria entering by ruffles:

$$n_{\text{in}} = n_{\text{ruffle}} n_{\text{tot}} p = \alpha m (1 + \beta m) p$$

- Bacteria per ruffle:

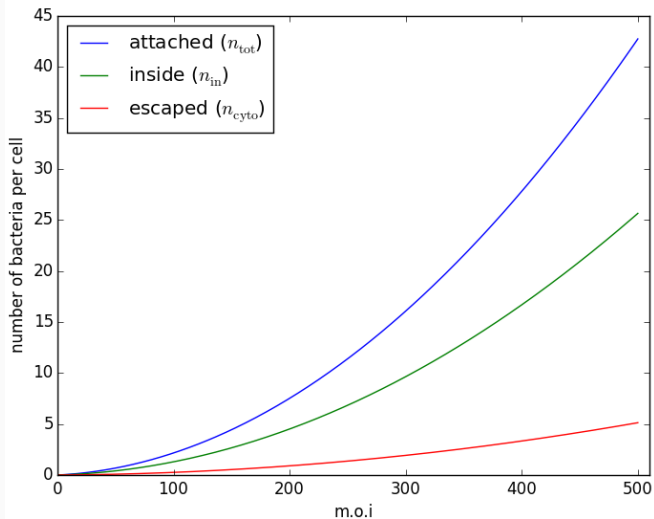
$$n_{\text{tot}} = 1 + \beta m$$

- Bacteria escaping vacuole:

$$n_{\text{cyto}} = q n_{\text{in}} = \alpha m (1 + \beta m) p q$$

QUANTITATIVE MODEL

$$\langle n_{\text{cyto}} \rangle = \alpha m(1 + \beta m)pq$$



Additions:

- Other entry mechanisms ("zipper", Mijouin et al. 2012):

$$n_{\text{in}} = n_{\text{trigger}} + n_{\text{zipper}}$$

- Autophagy (vacuolar and cytosolic):

$$n_{\text{free}} = \epsilon n_{\text{cyto}}$$

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- Growth:

$$n_{\text{free}}(t) = \sigma(t)n_{\text{free}}(0)$$

- Cooperativity in escape: $q(m)$
- Population context: cell density, size, state,... (Snijder et al. 2009)
- Immune response:
 - Bystander effect (Ablasser et al. 2013)
 - Anti-superinfection (Jorgensen et al. 2011)

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CELLPROFILER

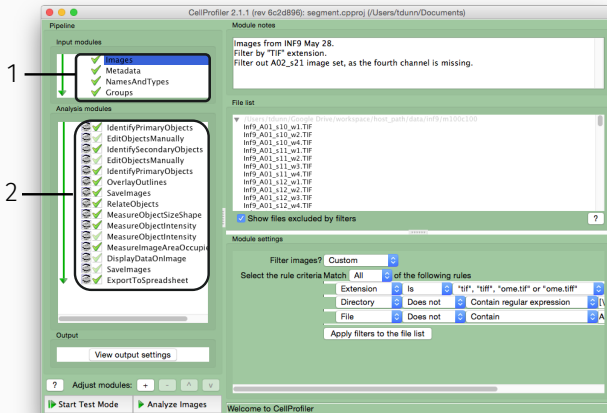


1. Input modules:

- Choose images, extract metadata, assign names and groups.

2. Pipeline:

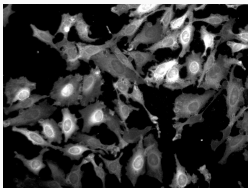
- A set of sequential image analysis modules.



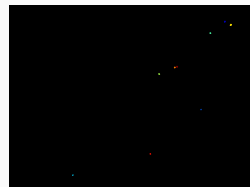
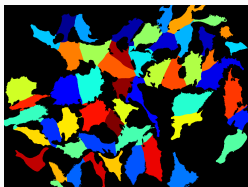
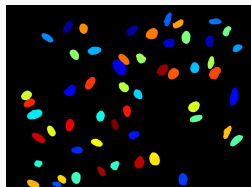
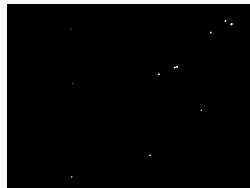
nuclei

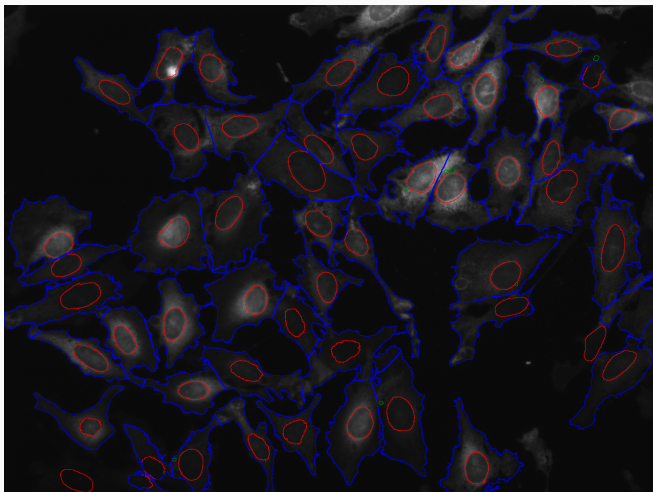


cells

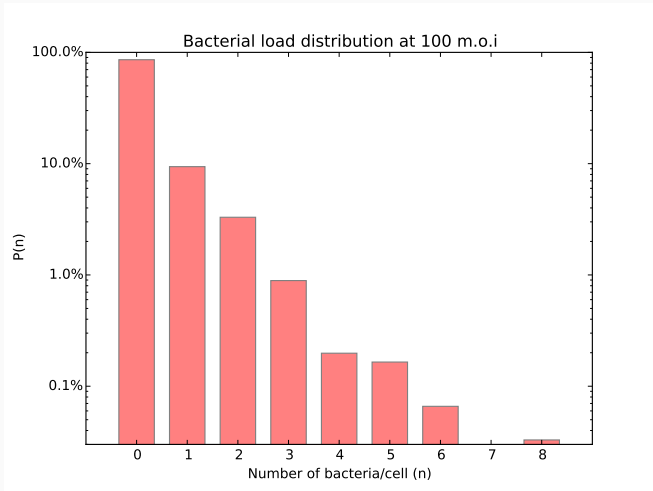


bacteria





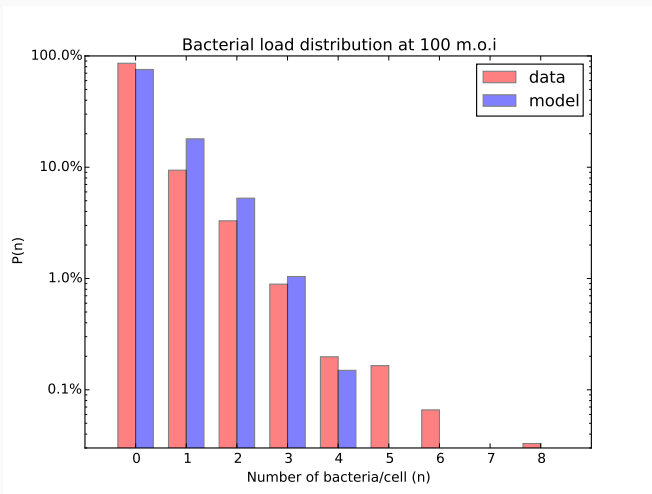
From many images, get bacterial counts $P(n)$...



DATA AND MODEL

$$\langle n \rangle = \alpha m(1 + \beta m)pq$$

- Computationally sample to get theoretical distribution $P(n)$.



New images from Pasteur soon:

- Multiple m.o.i.: 25, 50, 100.
 - Investigate cooperativity.
- Multiple time points post infection: 30min, 1h, 2h, 4h, 6h.
 - Investigate growth.