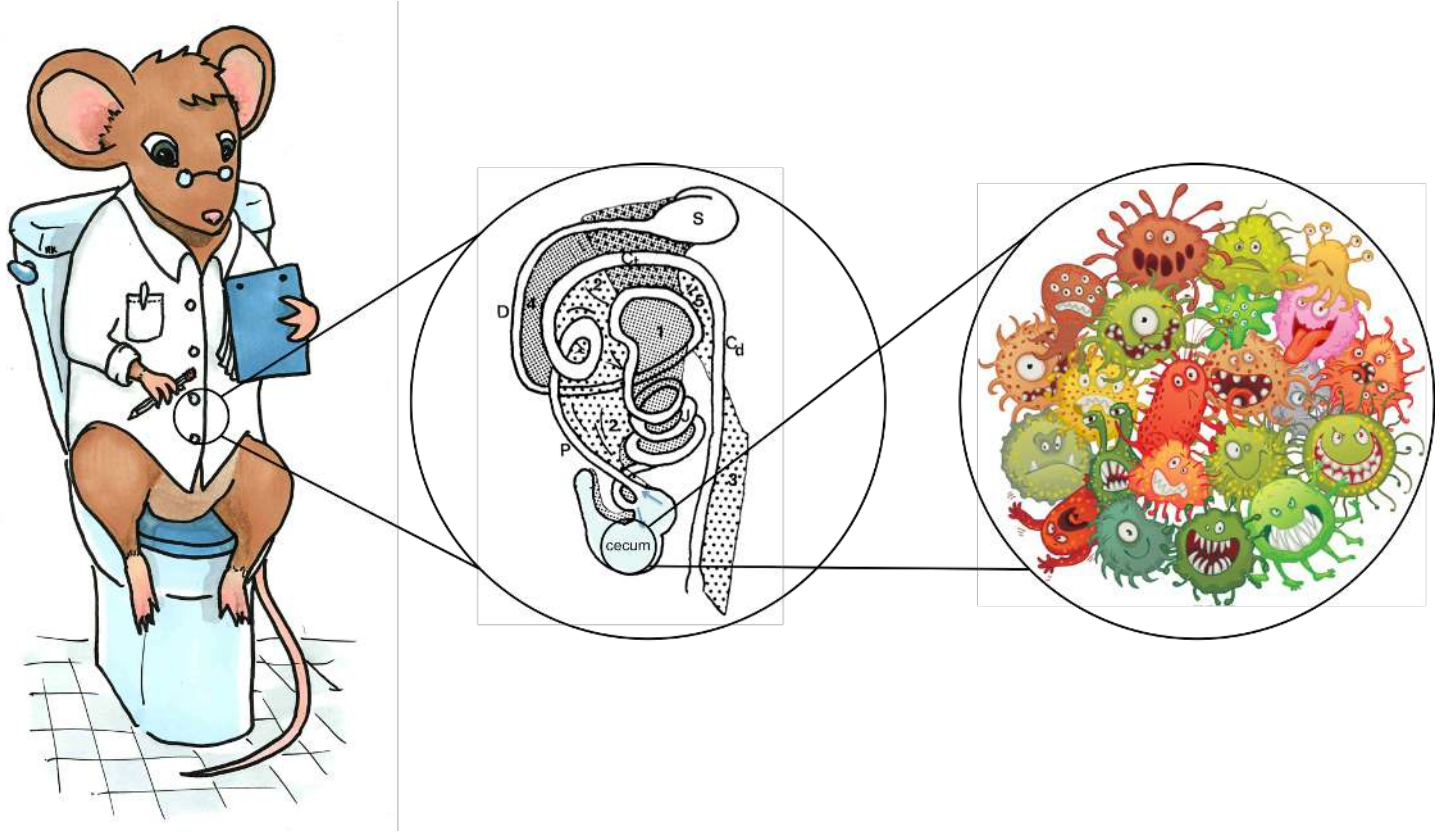
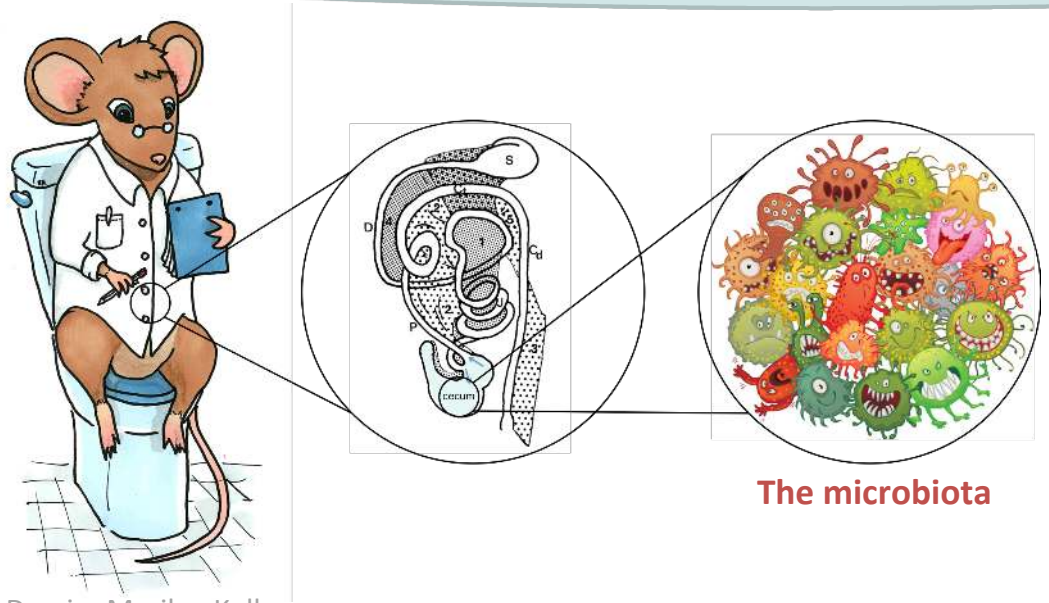
Modeling the physical mechanisms underlying immune system/bacteria interaction in the gut



Florence Bansept

Laboratoire Jean Perrin, Sorbonne Université - CNRS (Paris, France)

How to regulate gut microbiota?



Dessin: Marilyn Keller

The microbiota

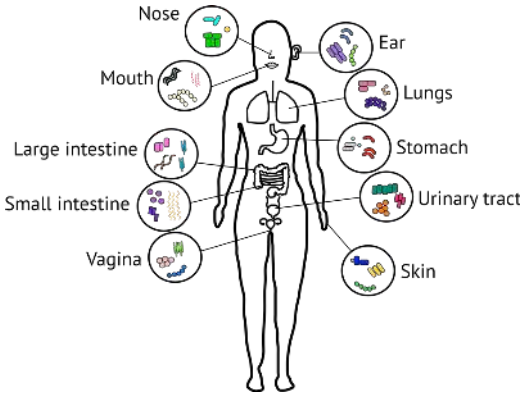
Did you know?

- There are at least as many bacteria as human cells in a human body ($\approx 10^{13}$)

Inside the organism: any bacteria is an enemy

VS

In the gut (= topologically outside): bacteria are important



- **How does the immune system distinguish “bad” bacteria from the “good” ones?**

Vaccination-triggered IgA production

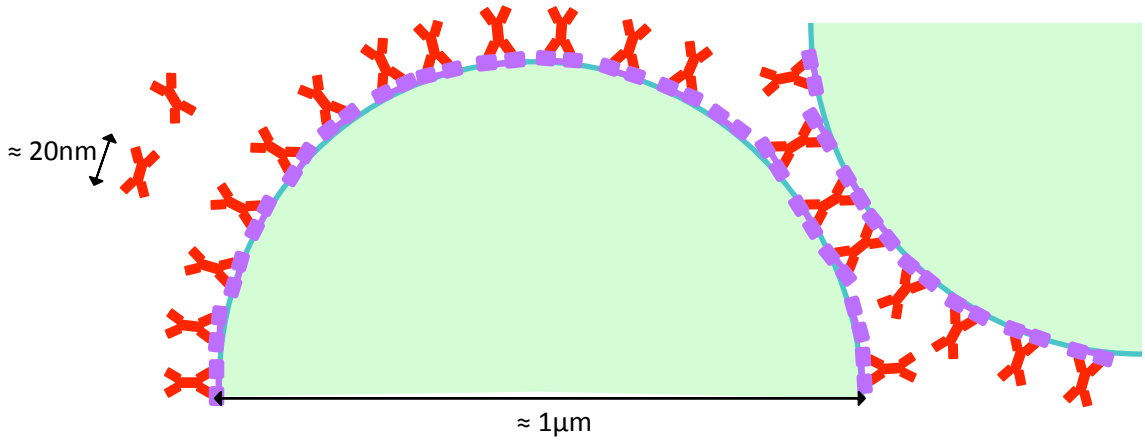
Collaboration with Emma Slack's group (ETH Zürich)

- Vaccination

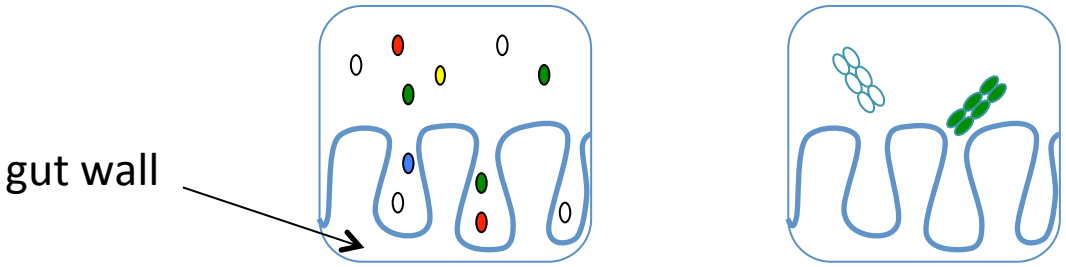
↓

high secretion of IgA (antibody)

- IgA do not kill bacteria
- But can agglutinate bacteria together

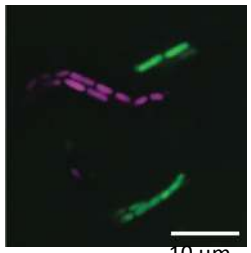


- Bacteria in clusters cannot invade the organism:



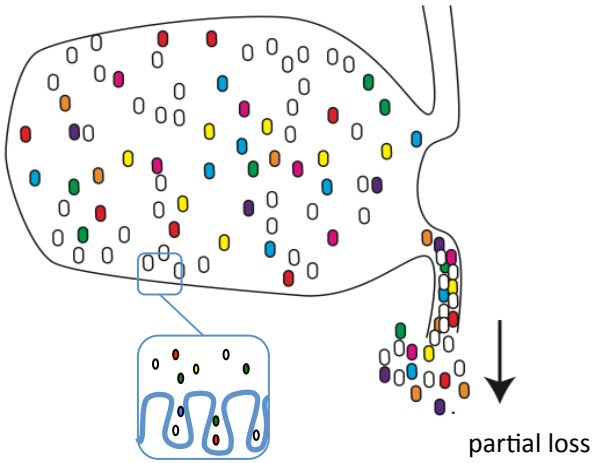
Classical idea: agglutination happens when bacteria meet randomly
BUT : not realistic at the typical concentrations

How is the mouse truly protected?

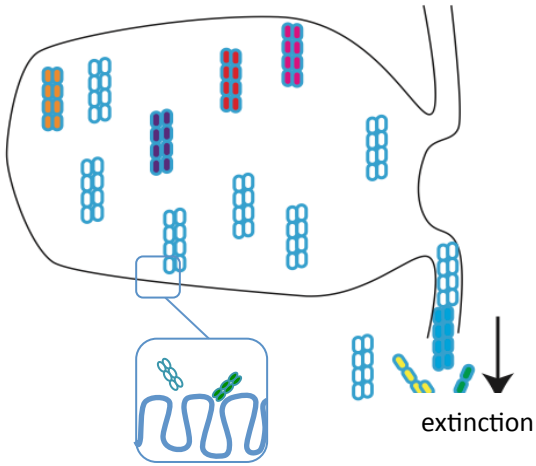


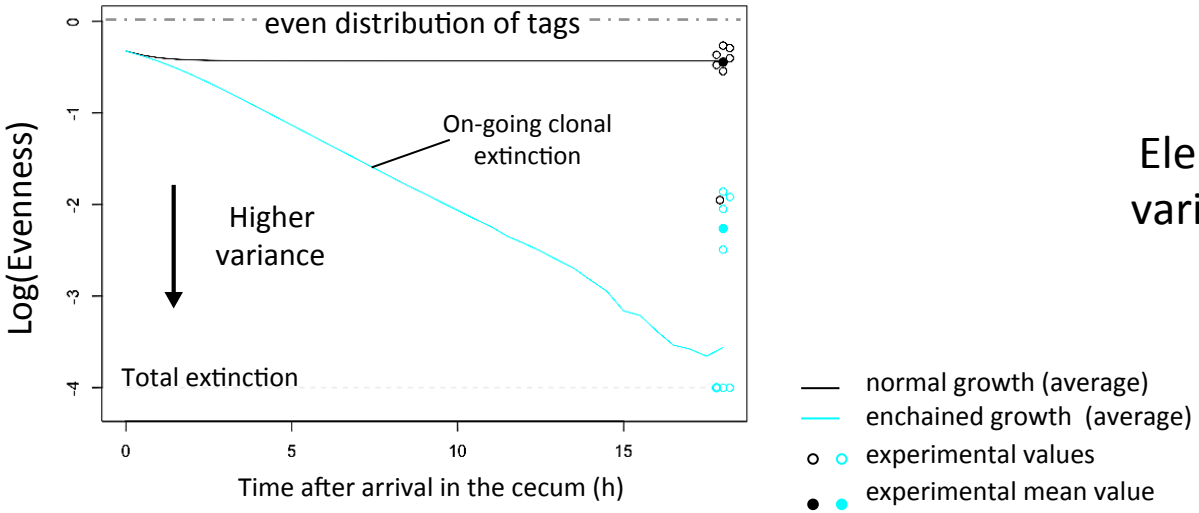
What actually happens : ***enchained growth***

normal growth



IgA-driven enchained growth





Element of proof: higher variability in genetic tags distribution

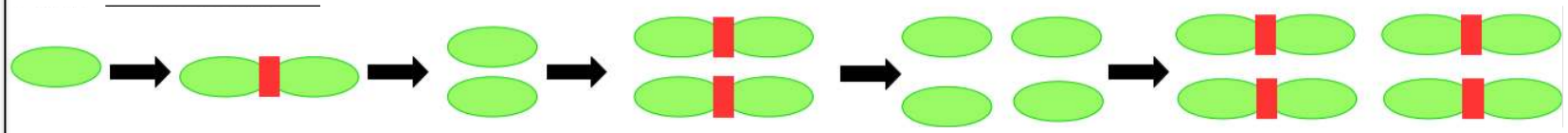
K. Moor et al., *Nature, 2017*

Clusters may break.

How does clusters fragmentation interplays with bacterial growth?

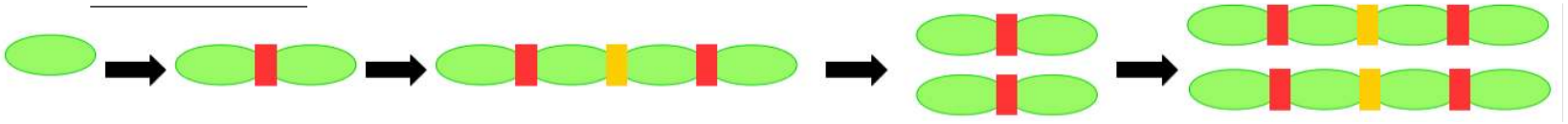
Simplified model: division at τ_{div}, adhesion breaks at τ_{break}

$\tau_{div} > \tau_{break}$



- Either free bacteria or 2-bacteria clusters

$\tau_{div} < \tau_{break}$



- Larger and larger clusters, no free bacteria

- Only fast-replicating bacteria are trapped. ***Does that hold with more realistic models?***

BASE MODEL:

- Fixed replication rate r
- Constant breaking rate α (scales time)
- When a longer chain breaks, rebind (q=0)
- No bacterial escape upon replication (δ=δ'=δ''=0)
- No loss (c=c'=0)

$$\frac{dn_1}{dt} = -rn_1 + \sum_{i=2}^{\infty} 2\alpha n_i$$

Replication

Break of a bigger chain extremity

For i>1:

$$\frac{dn_i}{dt} = rn_{i-1}(i-1) - irn_i - (i-1)n_i\alpha + 2\alpha n_{i+1}$$

Replication in a smaller chain

Replication

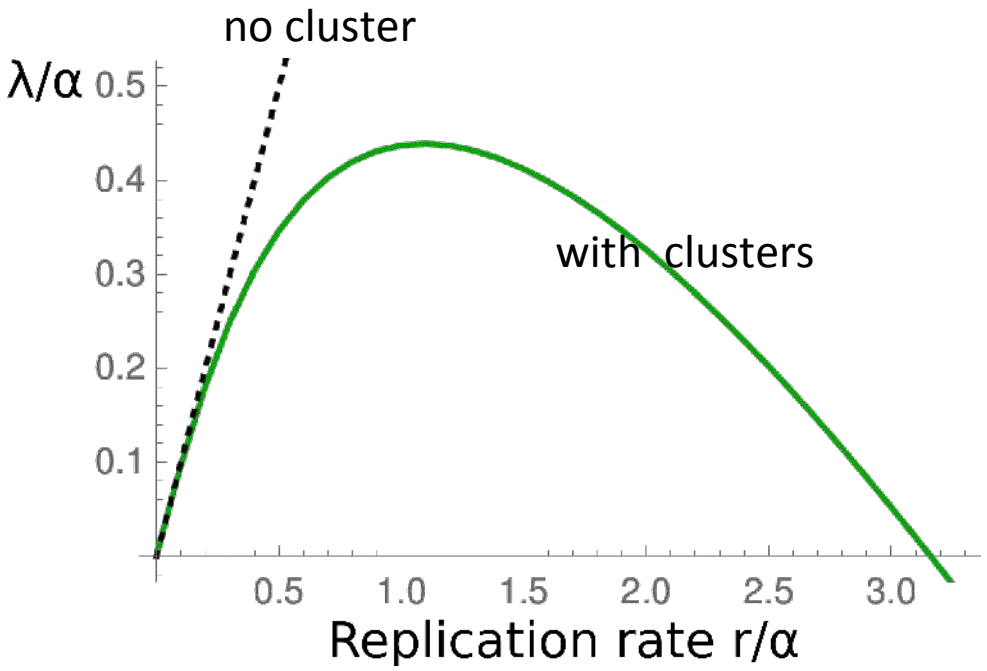
Break of one of the links

Break of a bigger chain extremity

BASE MODEL:

- Fixed replication rate r
- Constant breaking rate α (scales time)
- When a longer chain breaks, rebind (q=0)
- No bacterial escape upon replication (δ=δ'=δ''=0)
- No loss (c=c'=0)

Free bacteria growth rate



➢ **Fast-replicating bacteria are trapped !**

BASE MODEL:

- Fixed replication rate r
- Constant breaking rate α (scales time)
- When a longer chain breaks, rebind (q=0)
- No bacterial escape upon replication (δ=δ'=δ''=0)
- No loss (c=c'=0)

$$\frac{dn_i}{dt} = rn_{i-1}(i-1) - irn_i - (i-1)n_i\alpha + 2\alpha n_{i+1}$$

Long time limit: $n_i = Cp_i \exp(\lambda t)$

$$\lambda p_i = -irp_i + rp_{i-1}(i-1)p_i\alpha + 2\alpha p_{i+1}$$

For large i:

$$p_i \propto \frac{r}{r+\alpha} p_{i-1}$$

$$p_k = \left(1 - \frac{r}{r+\alpha}\right)\left(\frac{r}{r+\alpha}\right)^{k-1}$$

BASE MODEL:

- Fixed replication rate r
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- When a longer chain breaks, rebind (q=0)
- No bacterial escape upon replication (δ=δ'=δ''=0)
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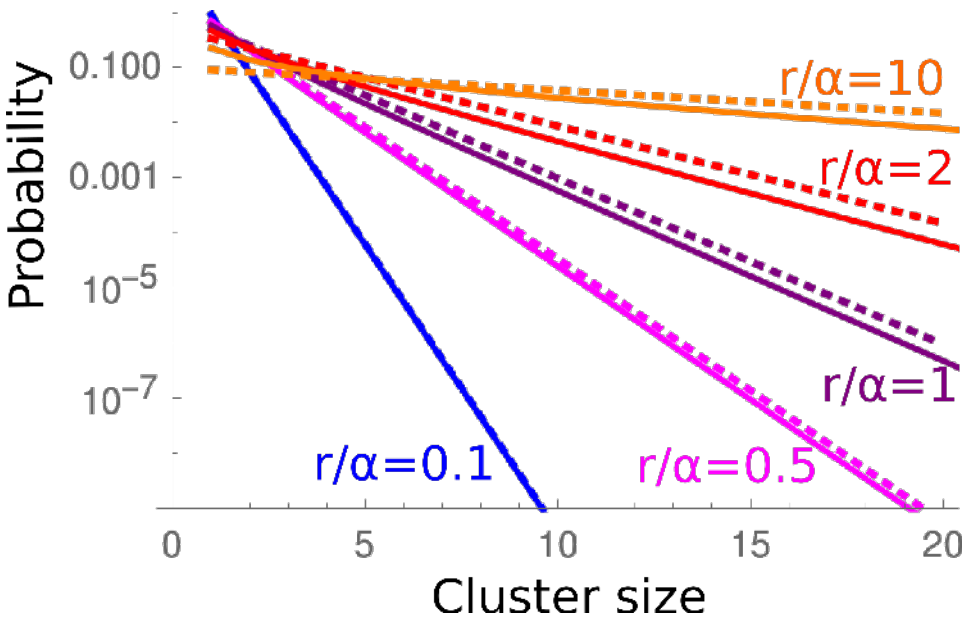


➢ **Faster-replicating bacteria make bigger clusters**

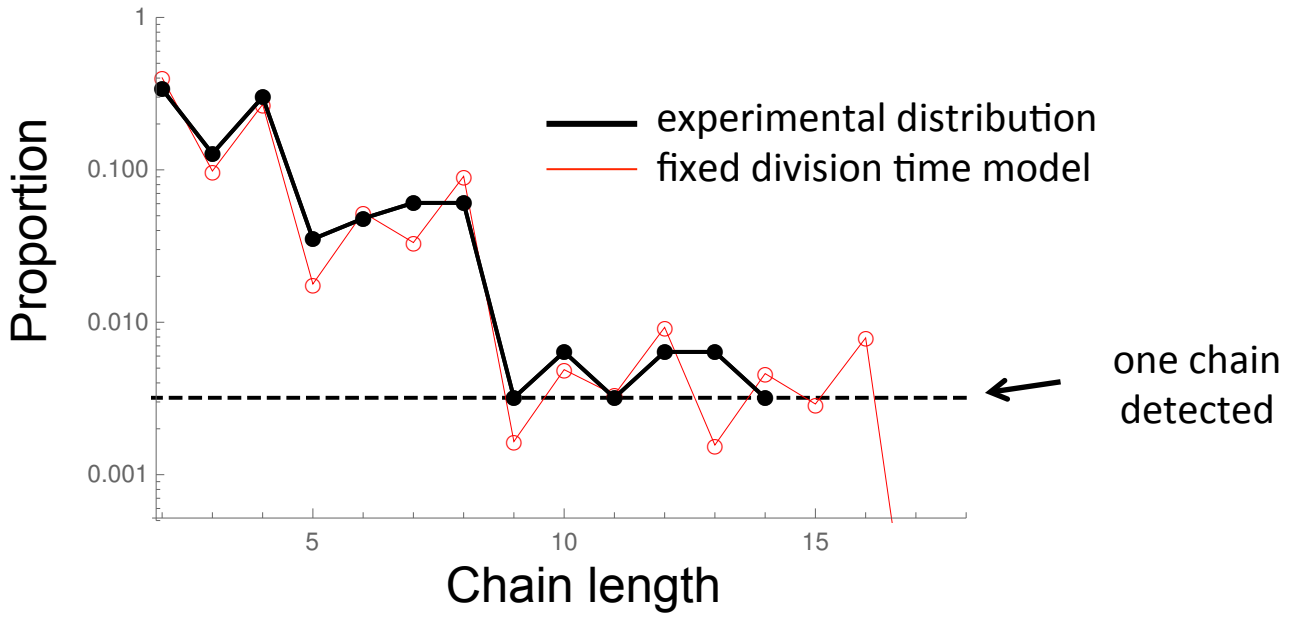
Variants of the base model:
- with escape
- fixed division time
- force-dependent breaking rates
- no recombination

- Except in a very specific case:

free bacteria growth rate < bacterial growth rate

- In most cases, non-monotonous

Experimental distribution?

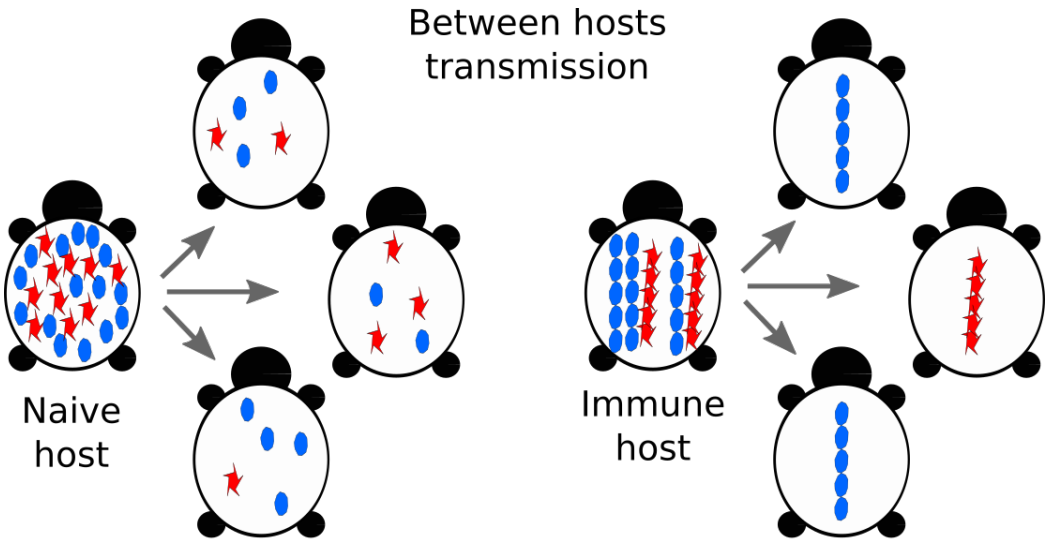


→ **A way for the immune system to regulate microbiota composition**

On the population level, what does it change?

If bacteria are transmitted via clonal clusters rather via random collections of sensitive/resistant bacteria, the probability that no resistant bacteria is transmitted is enhanced.

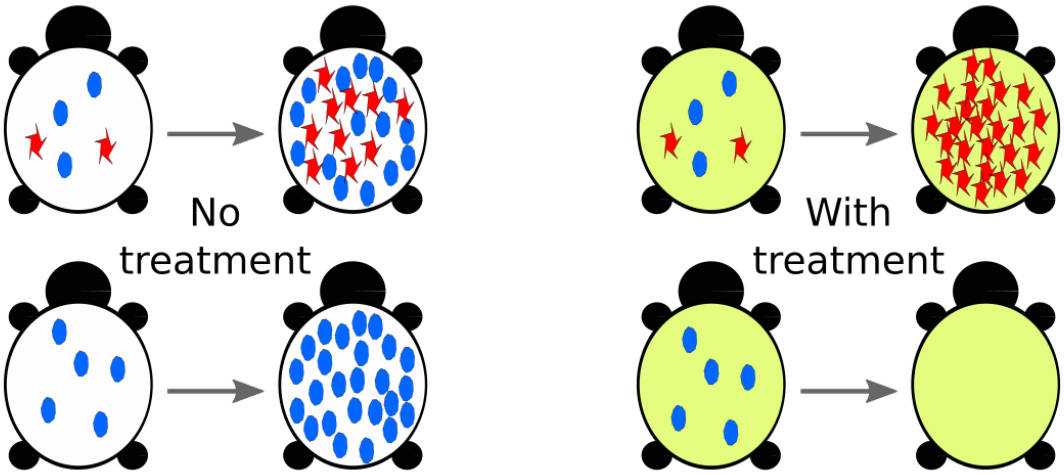
→ Simple cross-scale model



Simple model

- Stochastic between-host transmission (Poisson)
- Deterministic, exponential intra-host bacterial growth
- Each individual is infected with N bacteria and transmits sets of size N

Effect of the treatment:



Within host
outcome of infection

Simple cross-scale model

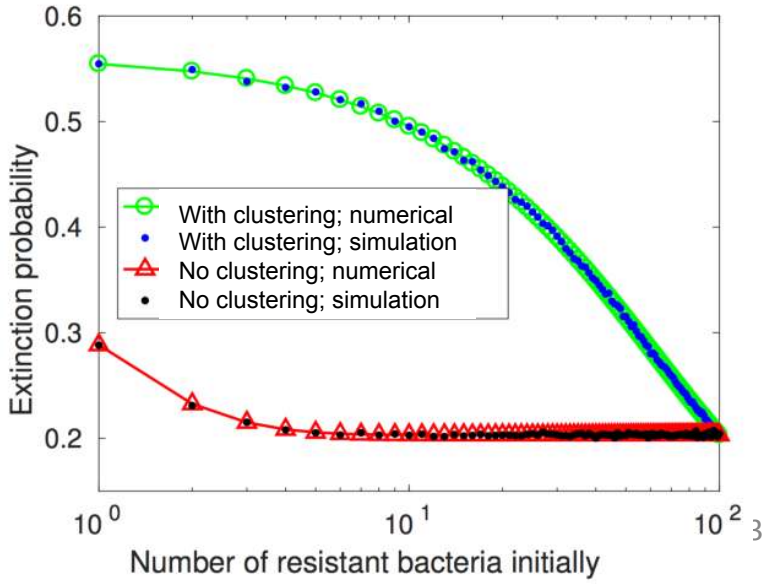
→ Write the generating functions of the branching process

$$g_n(z_0, z_1, ..., z_N) = \sum_{k_0=0}^{+\infty} \sum_{k_1=0}^{+\infty} ... \sum_{k_N=0}^{+\infty} p_n(k_0, k_1, ...k_N) z_0^{k_0} z_1^{k_1} ...z_N^{k_N}$$

Knowing there were n resistant initially, probability to transmit
- k_0 sets containing zero resistant bacteria
- ...
- k_N sets containing N resistant bacteria

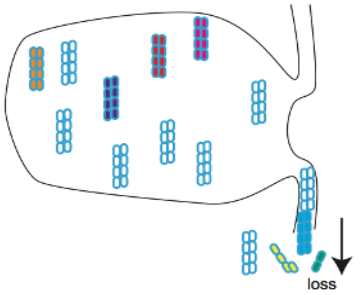
→ The fix points of the generating functions give the probabilities of extinction

$$\begin{cases} g_0(e_0, e_1, ..., e_N) = e_0 \\ g_1(e_0, e_1, ..., e_N) = e_1 \\ \quad ... \\ g_N(e_0, e_1, ..., e_N) = e_N \end{cases}$$

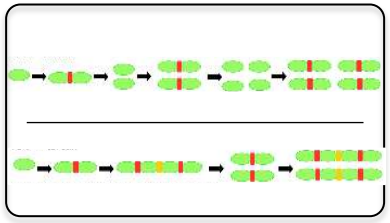


→ Extinction probability of the infection is increased !

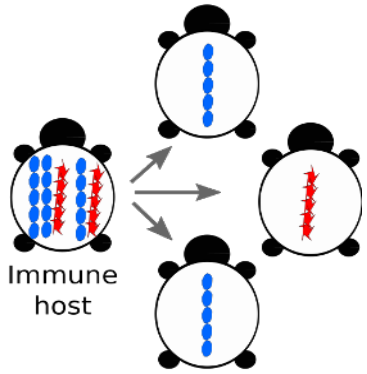
Summing up



→ A new idea in imunology : ***Enchained growth***
(element of proof: reduced diversity)



→ Consequence at the level of the host:
Discriminates against faster-growing bacteria



→ Consequence at the level of the host population:
Enhances extinction probability of the infection

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Thanks for your attention !