Physical modeling of the interaction between antibodies and bacteria in the gut

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Gut microbiota : friends and foes

About as many bacteria as human cells in a human body.

99% of these bacteria in the gut Sender et al. PLoS biology. 2016;14(8):e1002533.

Commensal bacteria:

help absorb nutrients and compete against pathogenic intruders.

Pathogenic bacteria

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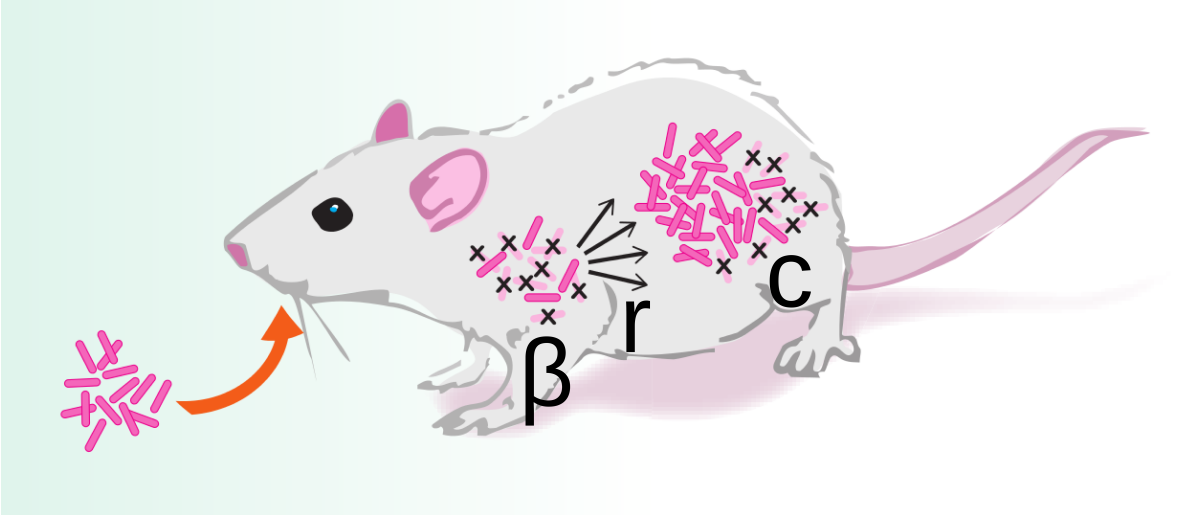
Inference: exploiting indirect data $\rightarrow$ Enchained growth
Mechanical modeling of the immune response
Evolutionary implications

Infection dynamics within a host



Indirect experimental data on mice gut colonization by salmonella

+

Stochastic models of infectious processes.

Analytical models using **branching processes**

Numerical simulations

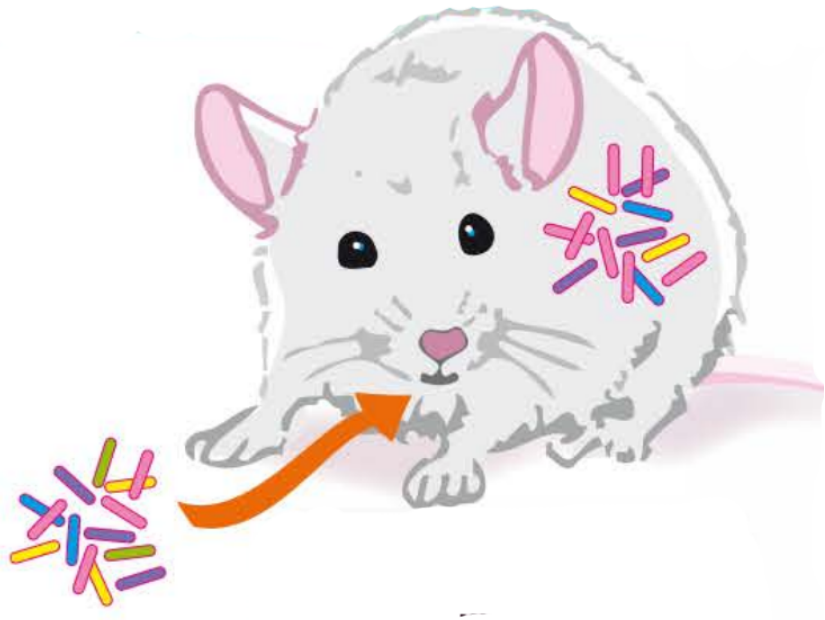
⇒

Infer biologically interesting parameters of the infection dynamics

and how they change depending on the conditions

Inferring what happened within the host using genetic tags: simple example

Example : Genetic tags with no fitness effect, of distribution known in the inoculum, and measured at the end of the experiment



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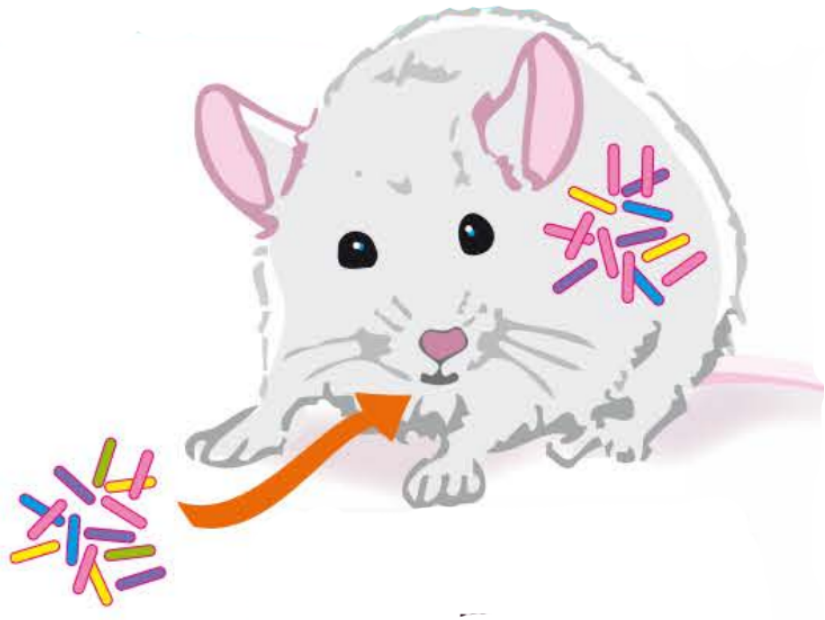
n_0 mean initial number of tagged bacteria in the inoculum

Probability β to establish.



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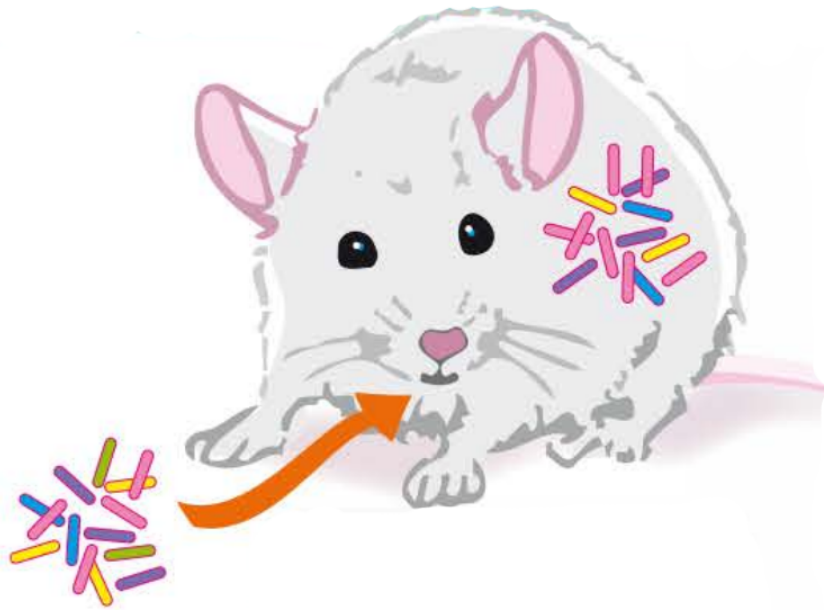
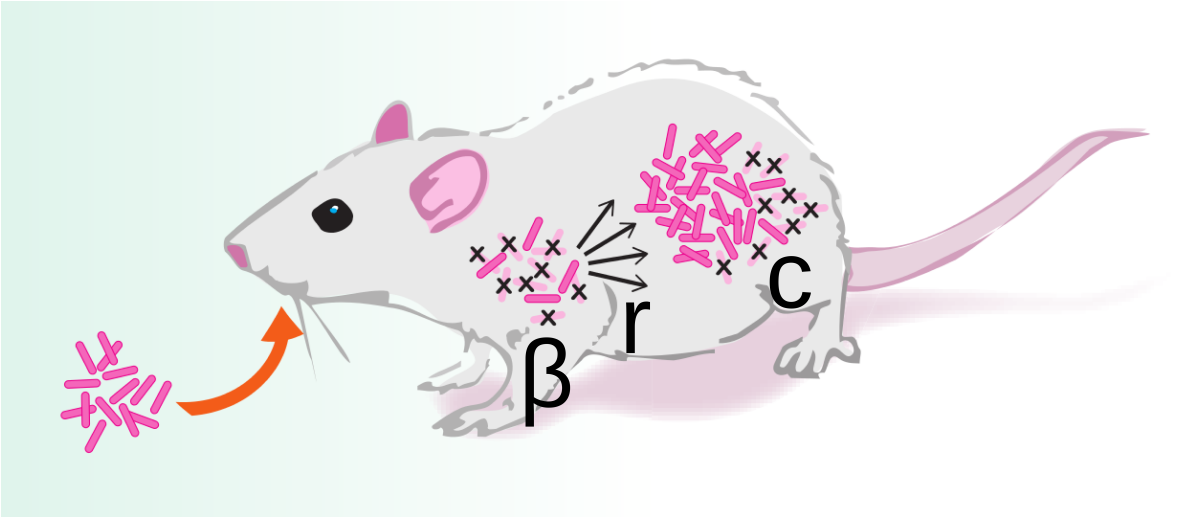


Probability to loose the tag: $\exp(-\beta n_0)$.

Inference



- More realistic models (bacterial loss; subpopulations; etc.)
- Distribution of genetic tags: which observable to use? tag loss? tag variance?
- Integration of other types of data

Mechanical aspects that make the immune response efficient

Experiments of *Salmonella* given orally to mice (Emma Slack group)
If mice vaccinated, don't get sick.
IgA main effector of the adaptive immune response in the gut.
IgA secretion is **protective. How?**
Do not kill bacteria nor prevent them from replicating.

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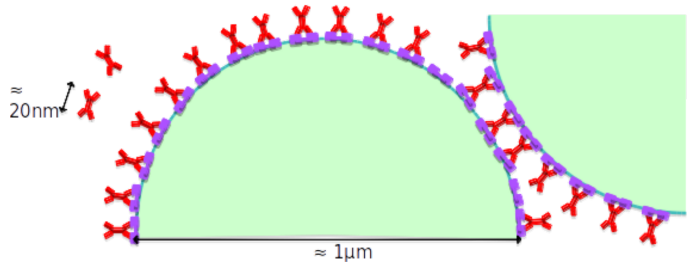
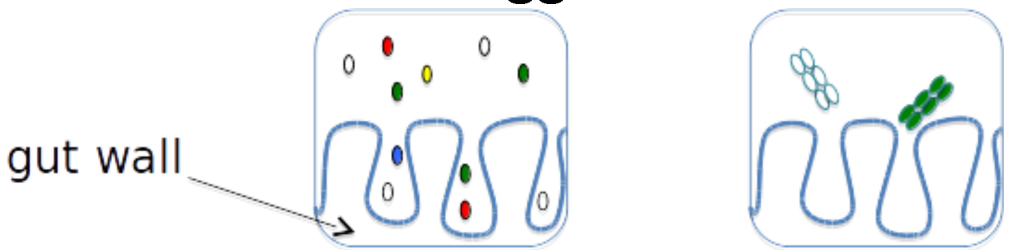


Classic idea: **agglutination**.



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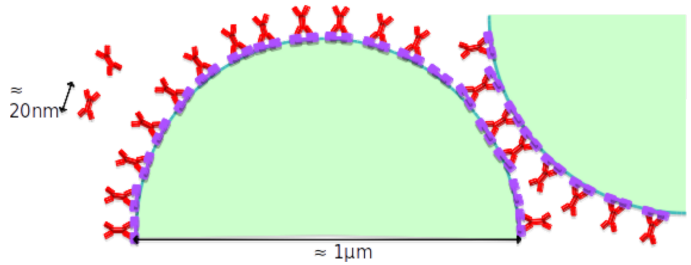

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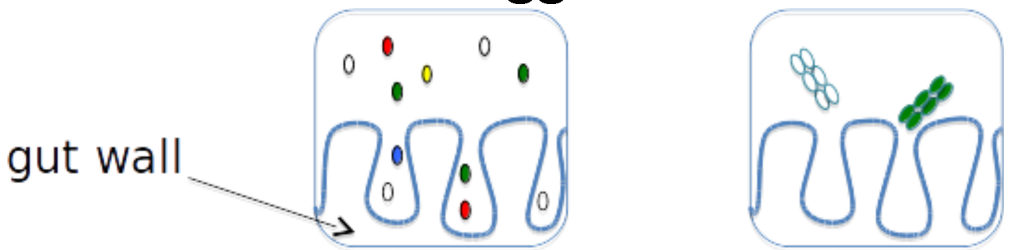
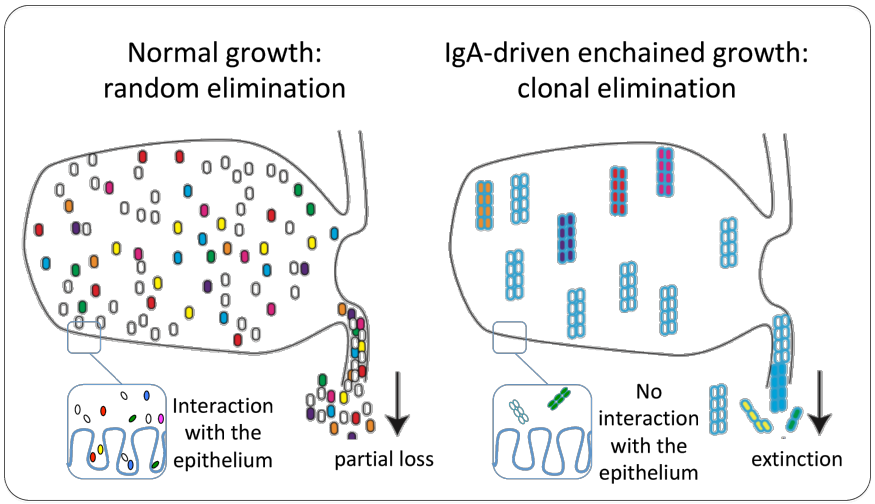
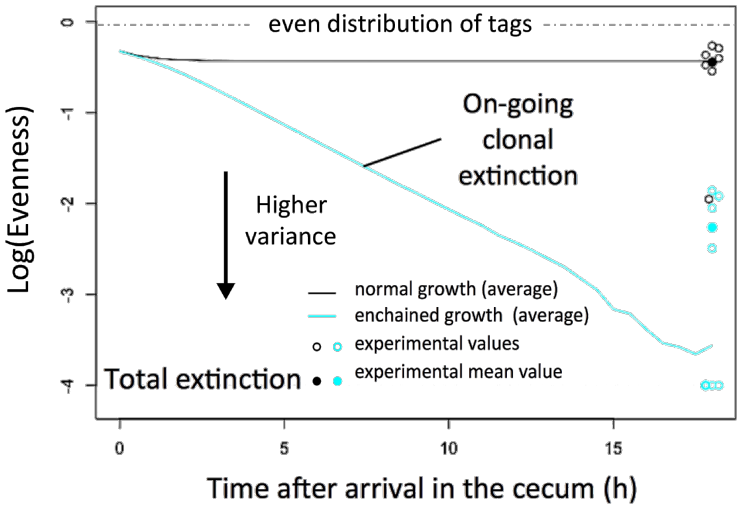


Not effective at realistic concentrations.

IgA protects by enchaining growing bacteria

We showed that actually, **IgA enchains daughter bacteria**.
Efficient at any bacterial concentrations
Decreases the bacterial genetic diversity





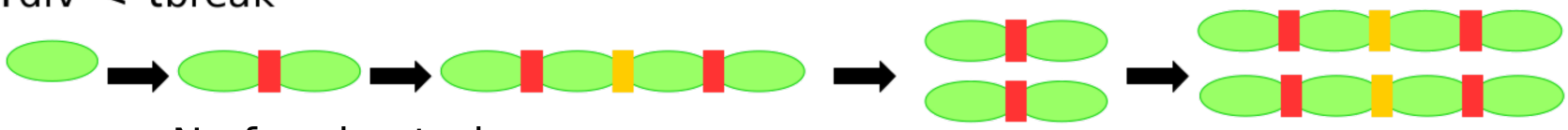
Moor Diard Sellin Felmy Wotzka Toska Bakkaren Arnoldini Bansept DalCo Voller Minola Fernandez-Rodriguez Agatic Barbieri Piccoli Casiraghi Corti Lanzavecchia Regoes Loverdo Stocker Brumley Hardt Slack. Nature 544, 498-502, (2017)

Enchained growth and cluster dislocation : a possible mechanism for microbiota homeostasis

Idea: the clusters do not grow indefinitely.
Link breaking could interplay with bacteria replication.

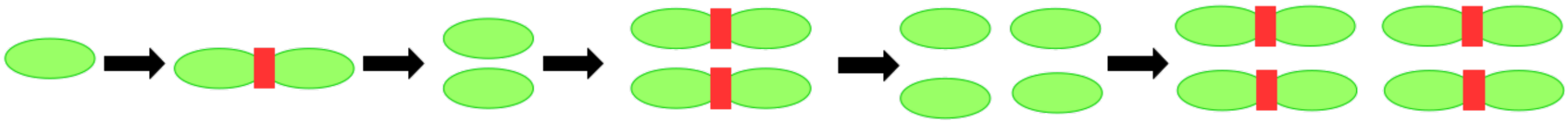
Division at τ_{div}, adhesion breaks at τ_{break}

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



No free bacteria

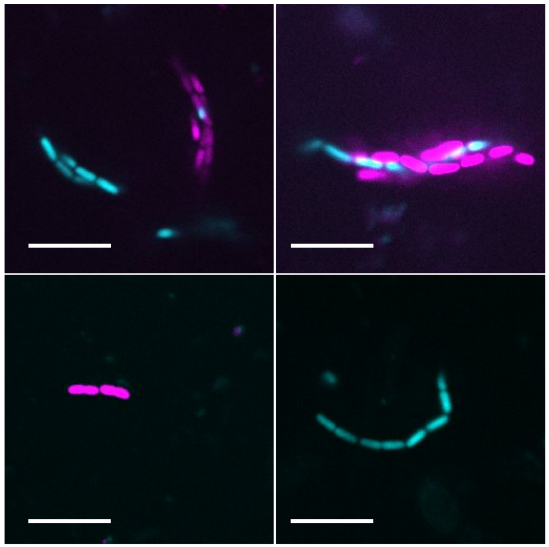
$T_{div} > \tau_{break}$



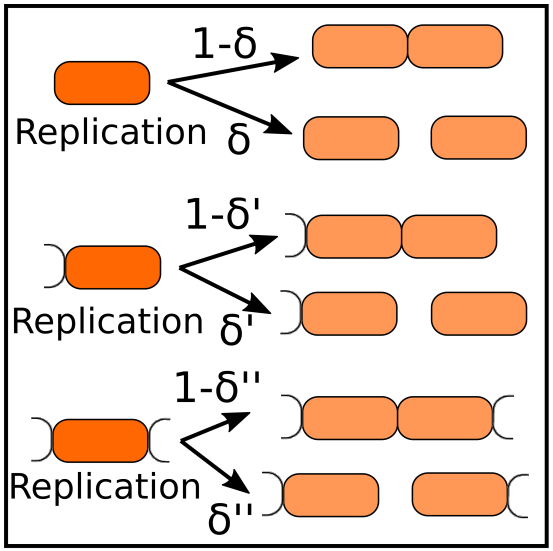
Free bacteria and 2-bacteria clusters

Does this conclusion hold for a more realistic model?
Comparison with experimental data?

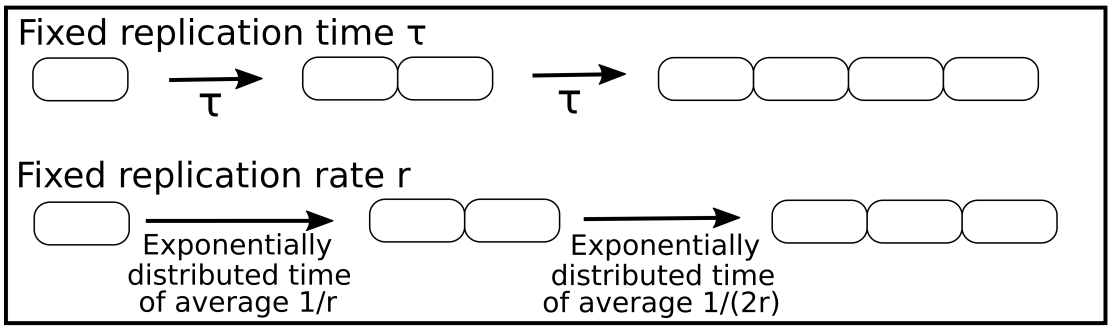
Model



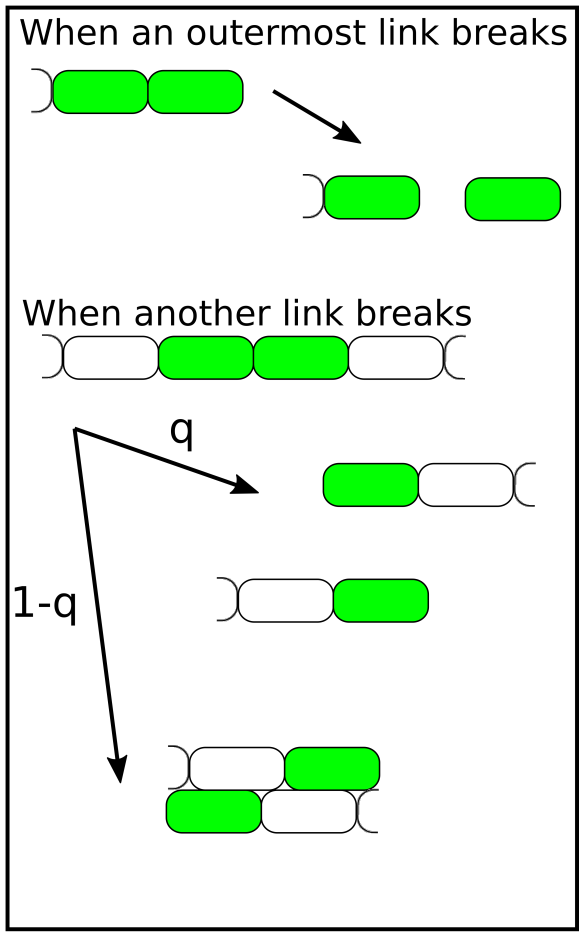
Cluster examples



Escape at replication



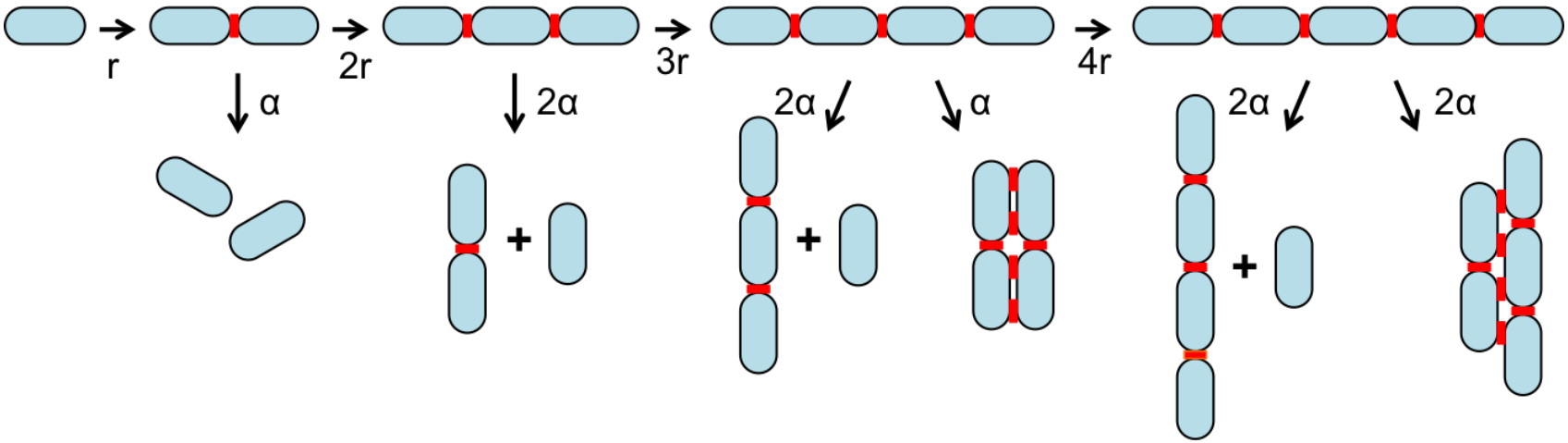
Replication at fixed time or fixed rate



Consequences of link breaking

All links break at the same rate vs. force-dependent breaking rate

Base model



Free bacteria

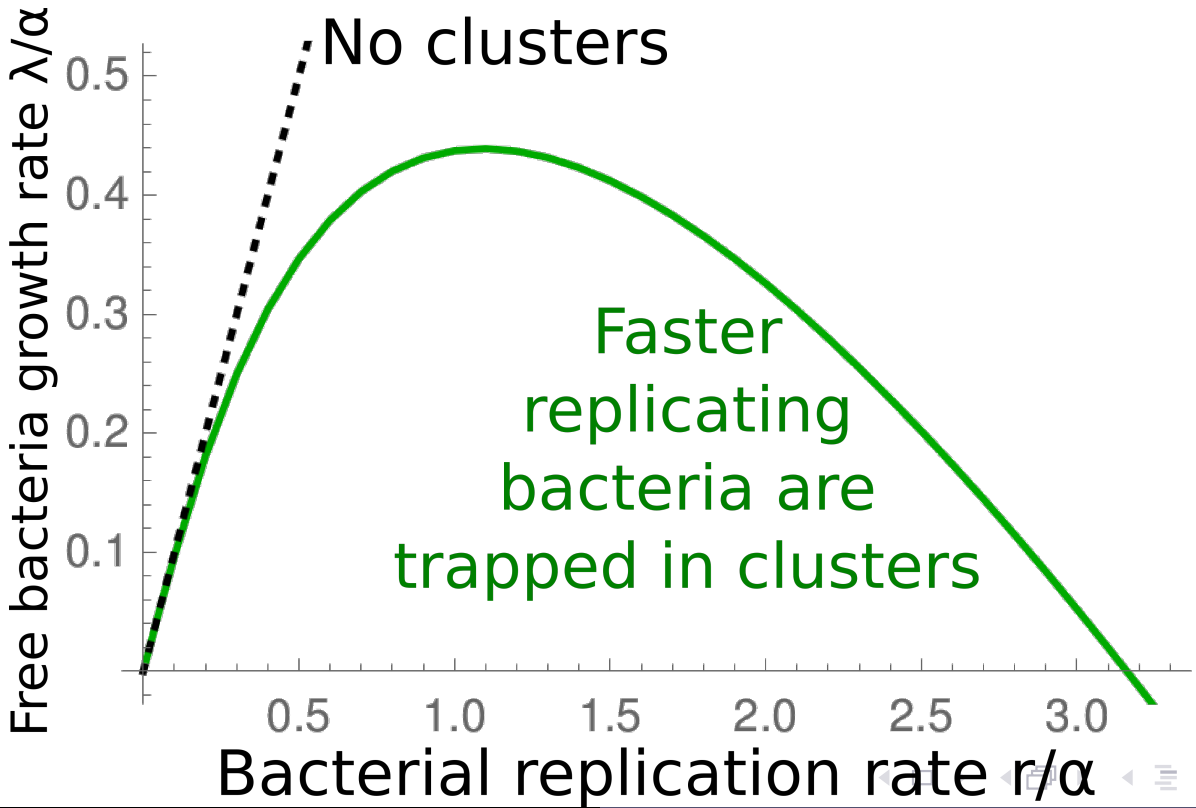
$$\frac{dn_1}{dt} = -rn_1 + \sum_{i=2}^{\infty} 2\alpha n_i$$

Linear clusters of length i

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

Clustering affects more the fast-replicating bacteria

Method: consider the system up to chain length n_{max} and solve numerically for the largest eigenvalue of the matrix such that $dN/dt = MN$ with $N = \{n_1, n_2, n_3, ..., n_{nmax}\}$



Chain length distribution

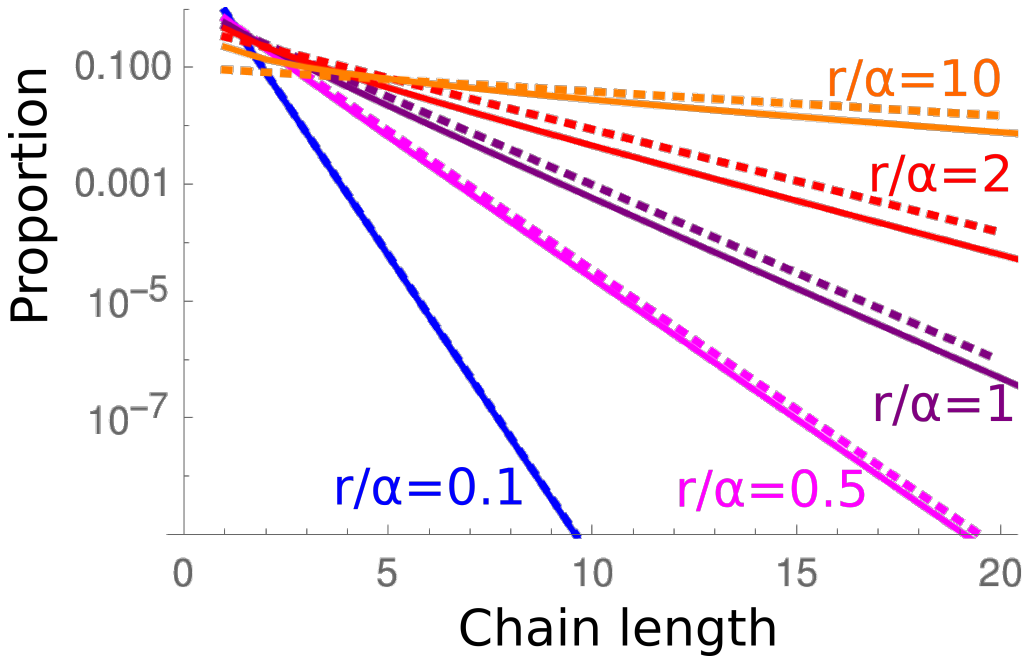
Analytical approximation: $\frac{dn_i}{dt} = rn_{i-1}(i-1) - irn_i - (i-1)n_i\alpha + 2\alpha n_{i+1}$

Steady state : $n_i \to Cp_i \exp(\lambda t)$ C a constant,

p_i the final proportion of chains of length i ($dp_i/dt = 0$), λ the long term growth rate

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

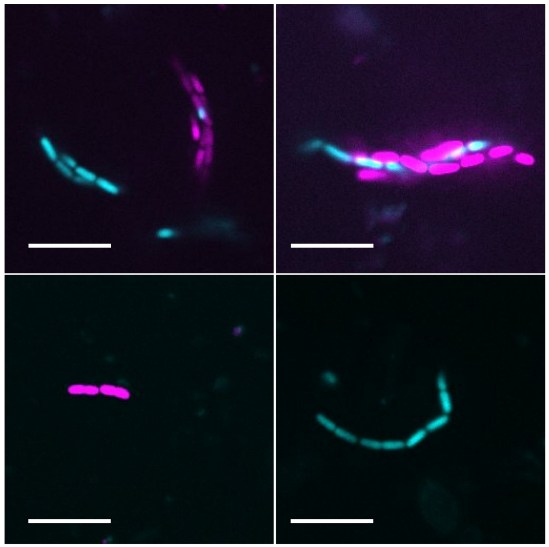
$$\text{large } i \Rightarrow rp_{i-1} \simeq (r+\alpha)p_i \Rightarrow p_i \simeq \left(1 - \frac{r}{r+\alpha}\right)\left(\frac{r}{r+\alpha}\right)^{i-1}$$



Numerical solution

Analytical approximation

Variants of the model



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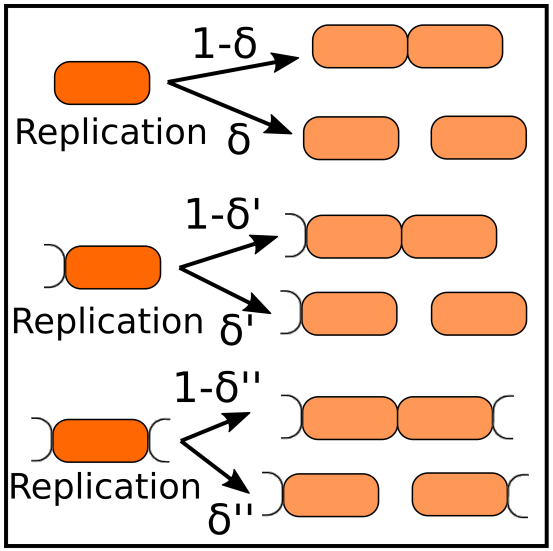

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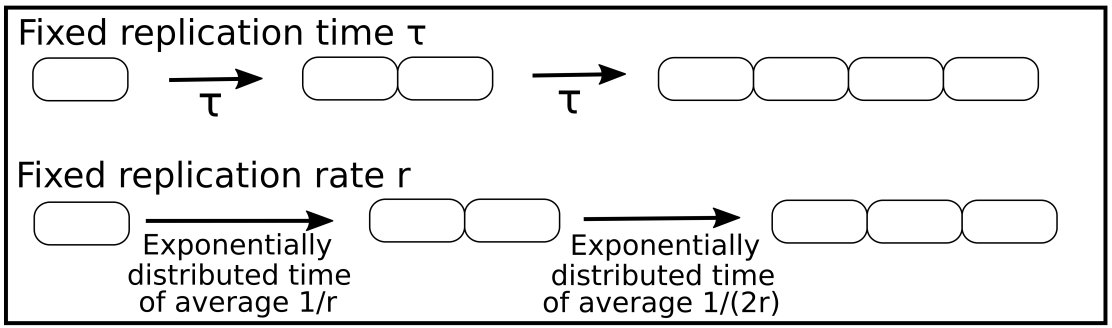

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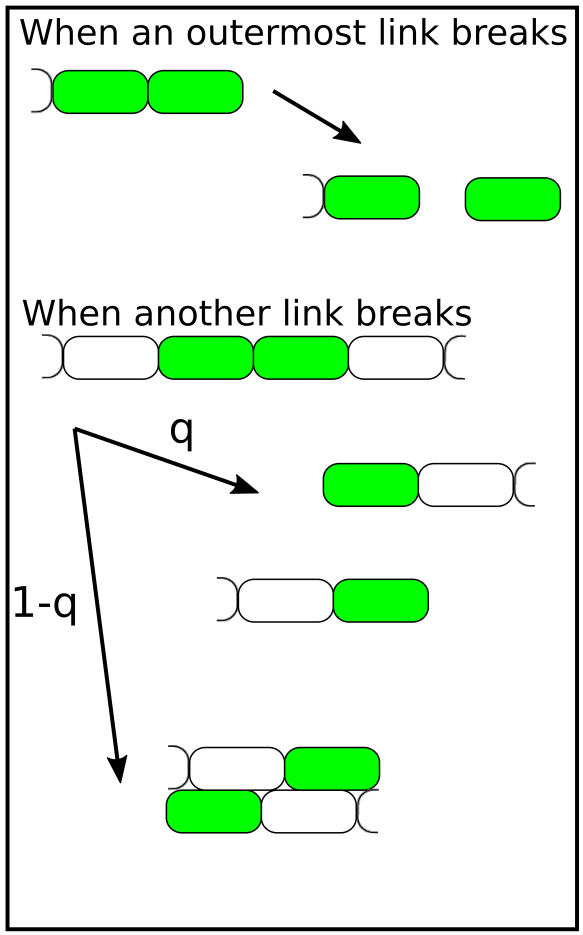

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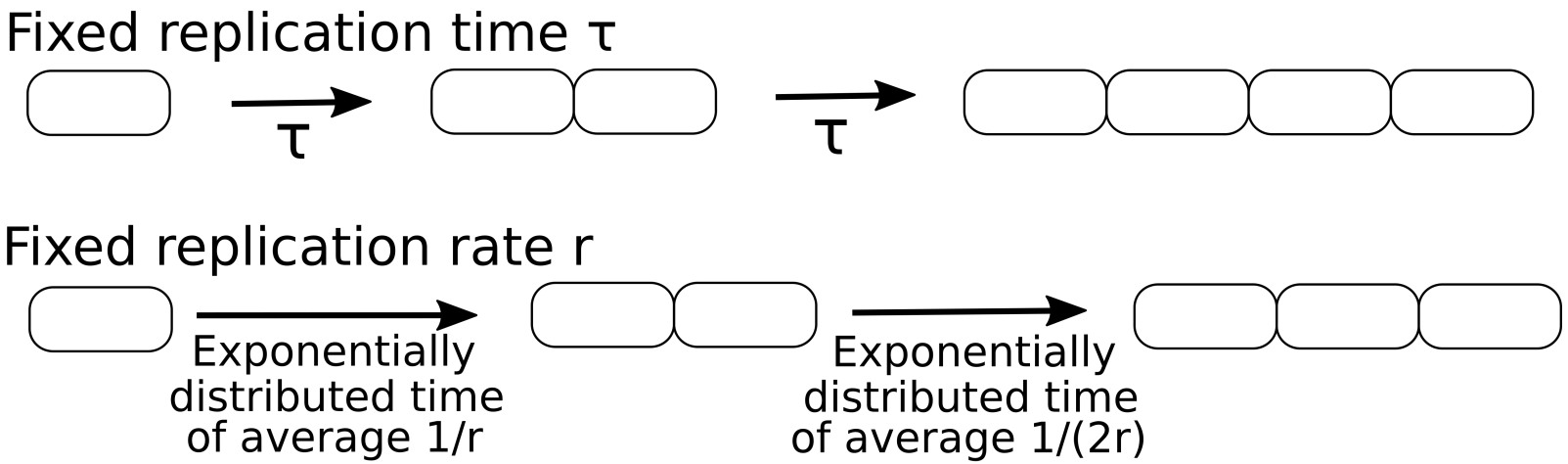
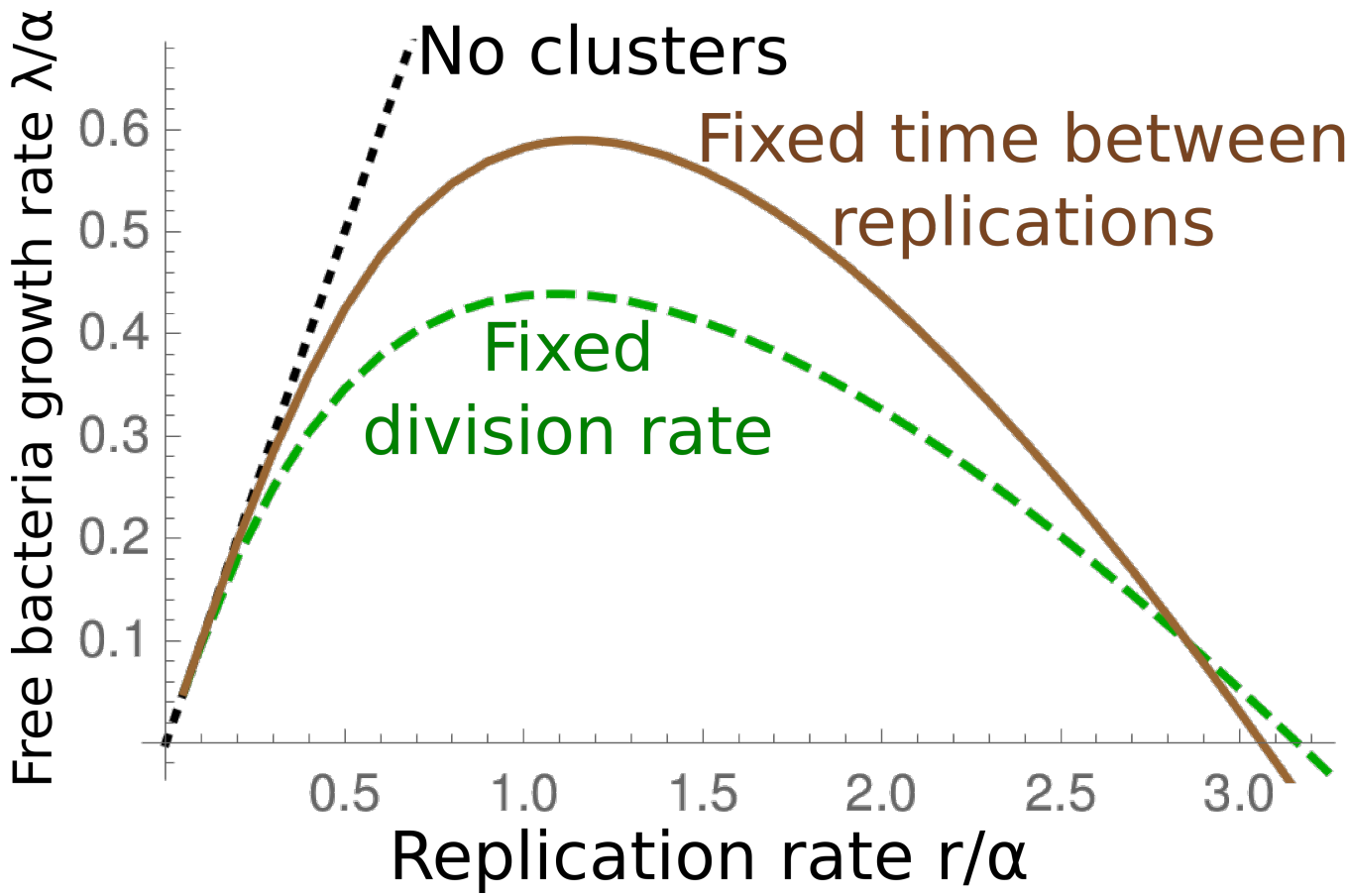
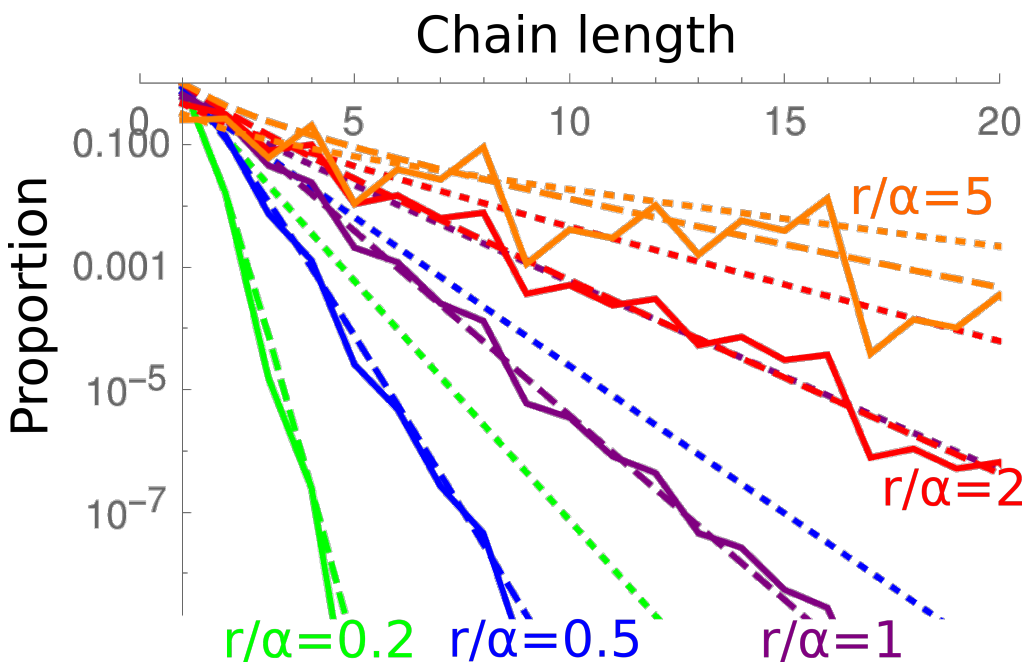
Bacteria replicate every τ



Little change on the dependence of the free bacteria growth rate on the bacterial replication rate



Different chain length distribution



Numerical solution

Analytical approximation

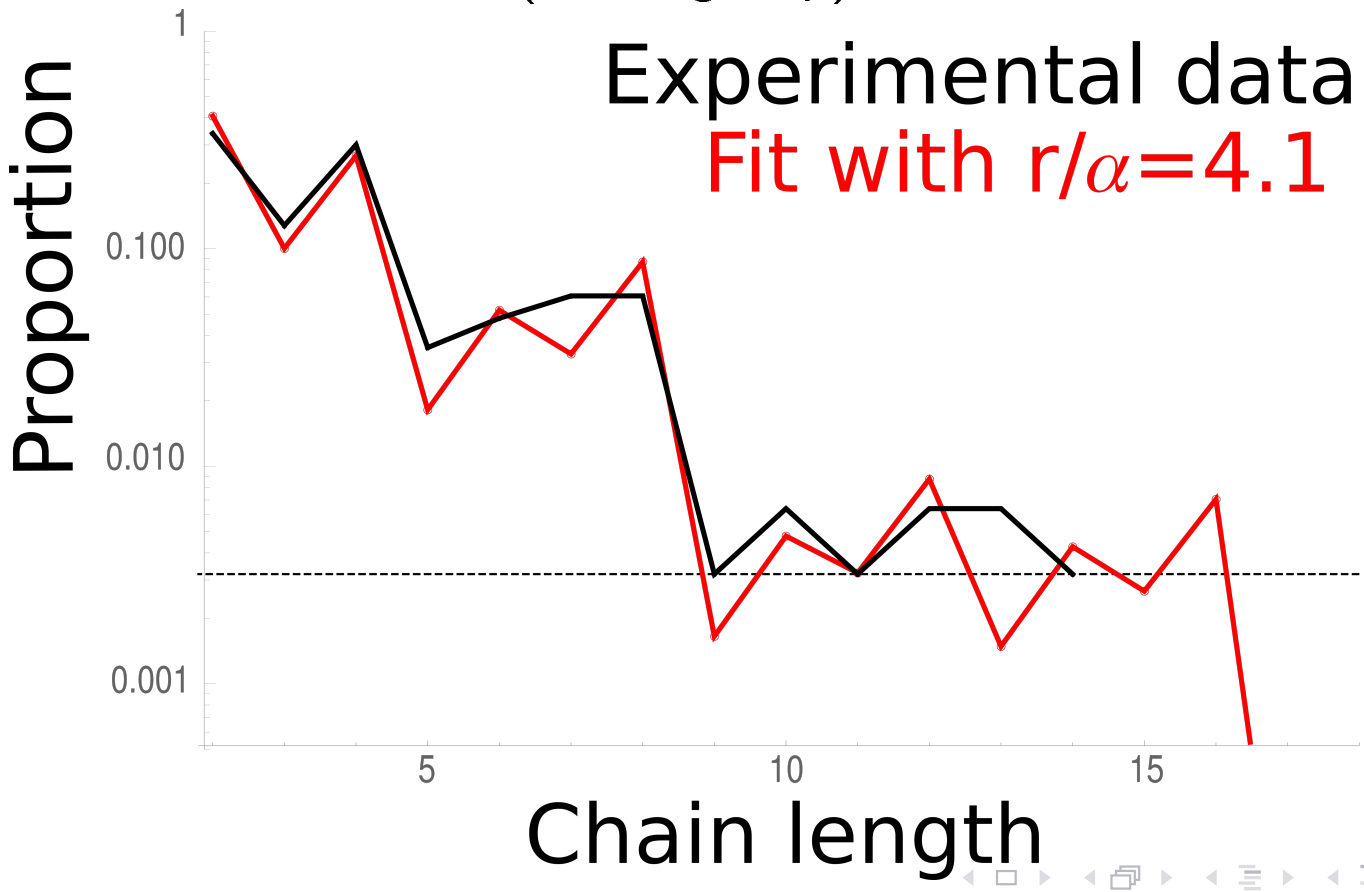
$p_i \propto i^{\frac{\alpha}{r_{eff}}-1} 2^{-2i\alpha/r_{eff}}$

Approximation for the base model

$p_i \propto (r/(r+\alpha))^i$

Fit to experimental data

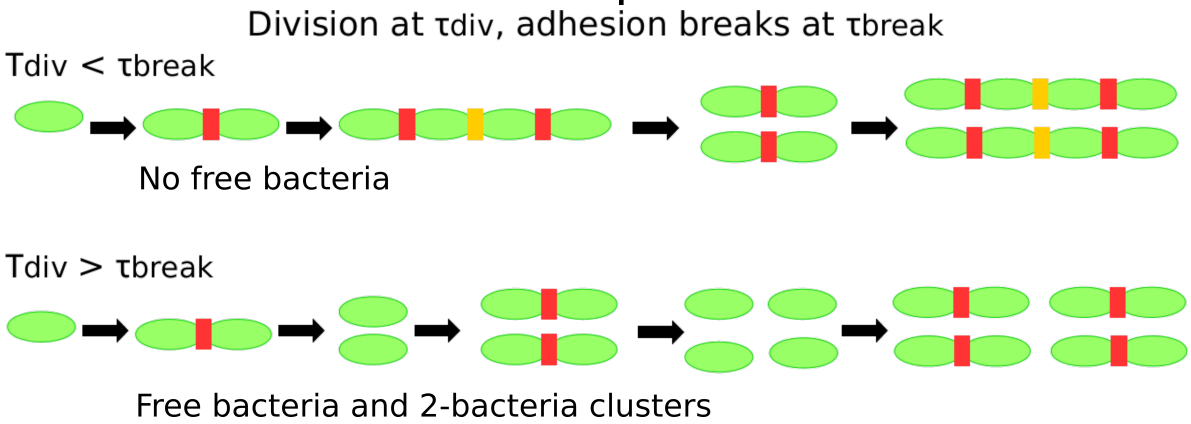
Length distribution of bacterial chains obtained from microscopy images of salmonella in diluted gut content from vaccinated mice (Slack group)



Enchained growth and cluster dislocation : a possible mechanism for microbiota homeostasis

The largest the replication rate, the more the effect of clustering on the free bacteria growth rate

Experimental chain length distribution compatible with fixed time between replications

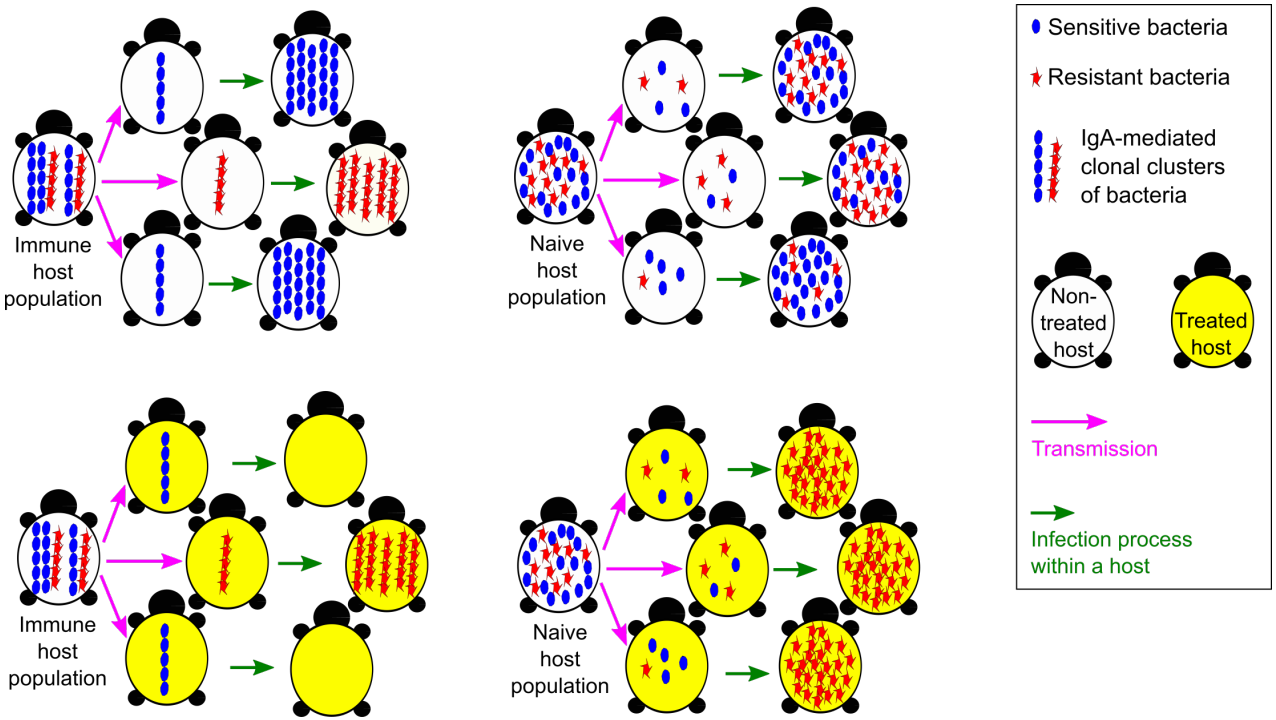


The immune system could produce IgA against all bacteria it has encountered, but only the fast-replicating ones affected

F.Bansept K.S.Moor M.Diard W-D.Hardt E.Slack C.Loverdo *(submitted)* BioRxiv:298059

Clustering decreases the probability of resistance emergence

Cross-scale model:
Deterministic within the hosts
Stochastic between the hosts, using branching processes



Florence Bansept, Loïc Marrec, Anne-Florence Bitbol, and Claude Loverdo, *Antibody-mediated bacteria cross-linking in the gut hinders the emergence of antibiotic resistance*, manuscript in preparation