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A MULTI-SCALE EPIDEMIC MODEL OF ENTERIC INFECTION WITH HETEROGENEOUS SHEDDING RESULTING FROM HOST-MICROBIOTA-PATHOGEN INTERACTIONS

Simon Labarthe¹, Béatrice Laroche², Bastien Polizzi³, Florian Patout⁴, Magali Ribot⁵

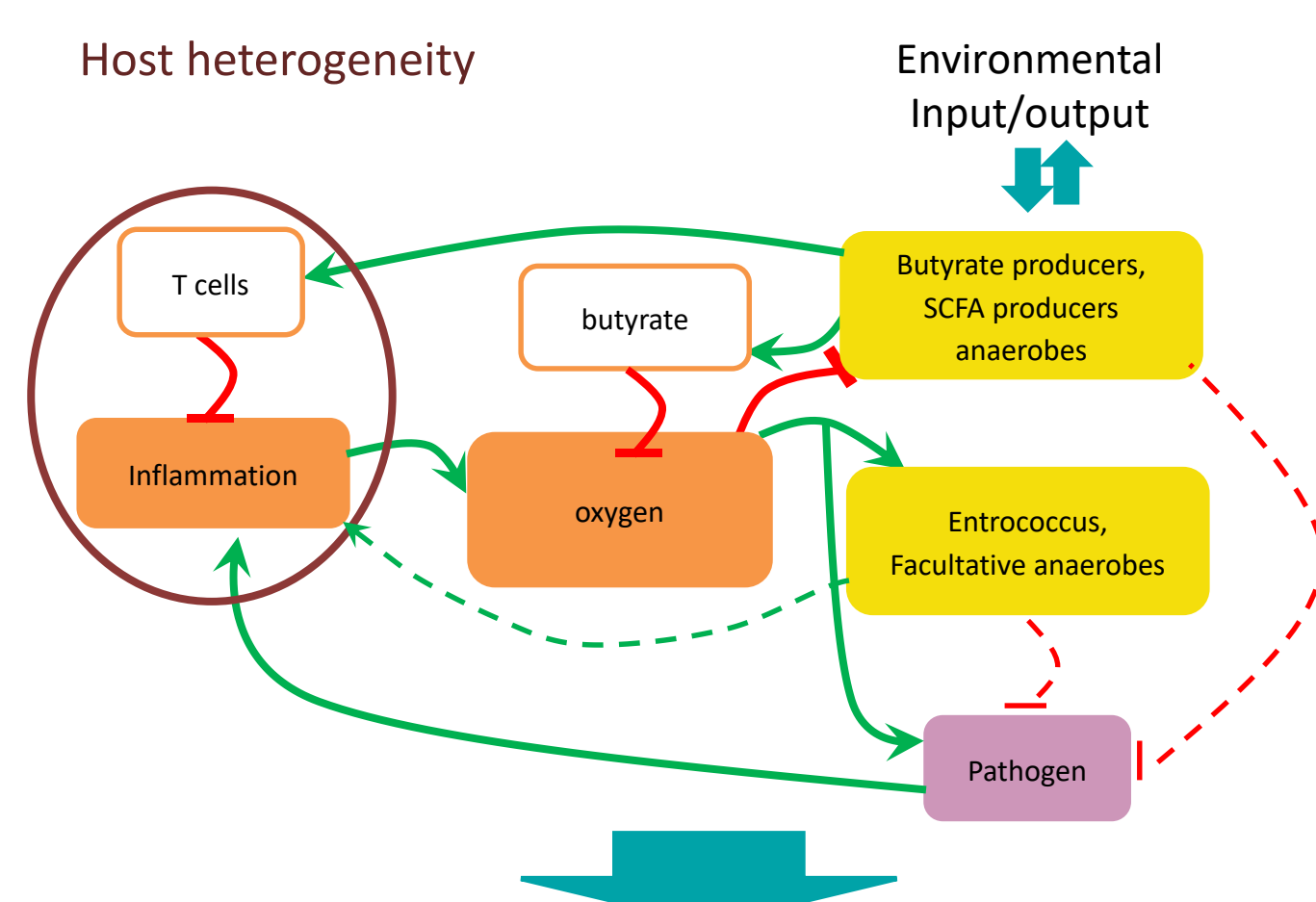
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Motivation: Enteric pathogens colonize the digestive tract of farm livestock, such as chickens or pigs and potentially infect food products, which results in a threat for human health and important economic losses. It has been shown that the ability to excrete the pathogen in the environment and contaminate other animals is variable. This heterogeneity in pathogen carriage and shedding results from interactions between the host's immune response, the pathogen and the commensal intestinal microbiota and plays an important role in epidemic propagation and control. The objective here is to propose a theoretical model of pathogen excretion and transmission linking within and between host dynamic.

Reference: Labarthe, S., Laroche, B., Nguyen, T. N. T., Polizzi, B., Patout, F., Ribot, M., & Stegmaier, T. (2020). A multi-scale epidemic model of salmonella infection with heterogeneous shedding. *ESAIM: Proceedings and Surveys*, 67, 261-284.

Simplified within host Dynamic

Inspired by a complex mechanisms proposed in *Byndloss et al. Science 2017*



Modelling hypotheses

niche competition (vicinity of intestinal wall) between pathogen (p) and local microbiota (b)

$$\begin{aligned} p' &= -\mu_0 p b \\ b' &= \mu_0 p b \end{aligned} \quad p + b = K$$

Inflammation signal (d) triggered by pathogen

$$d' = \frac{1}{\tau} \left(-d + C_2 \frac{p^n}{p^n + p_*^n} \right)$$

d more harmful for b than for p ,
 b limited by the environment

$$\mu_0 = \mu \left(1 - \frac{\alpha}{\mu} b - \frac{C_1}{\mu} d \right)$$

τ small (QSA) and **elimination of b** , setting $A = \alpha K - \mu$ and $C = C_1 C_2$

$$p' = p(K - p) \left(A - \alpha p + C \frac{p^n}{p^n + p_*^n} \right)$$

2 to 5 steady states (including 0 and K) according to parameter values,
 $p = 0$ **unstable** $\Leftrightarrow A > 0$

Noisy dynamic

$$dP = F(P)dt + \sigma dB$$

with

$$F(p) = \begin{cases} p(K - p) \left(A - \alpha p + C \frac{p^n}{p^n + p_*^n} \right), & \text{if } p \in [0, K], \\ 0, & \text{otherwise.} \end{cases}$$

(other possible choices for the noise: $\sigma p dB$ or $\sigma p(K - p)dB$)

Population level Dynamic

Pathogen load distribution without transmission

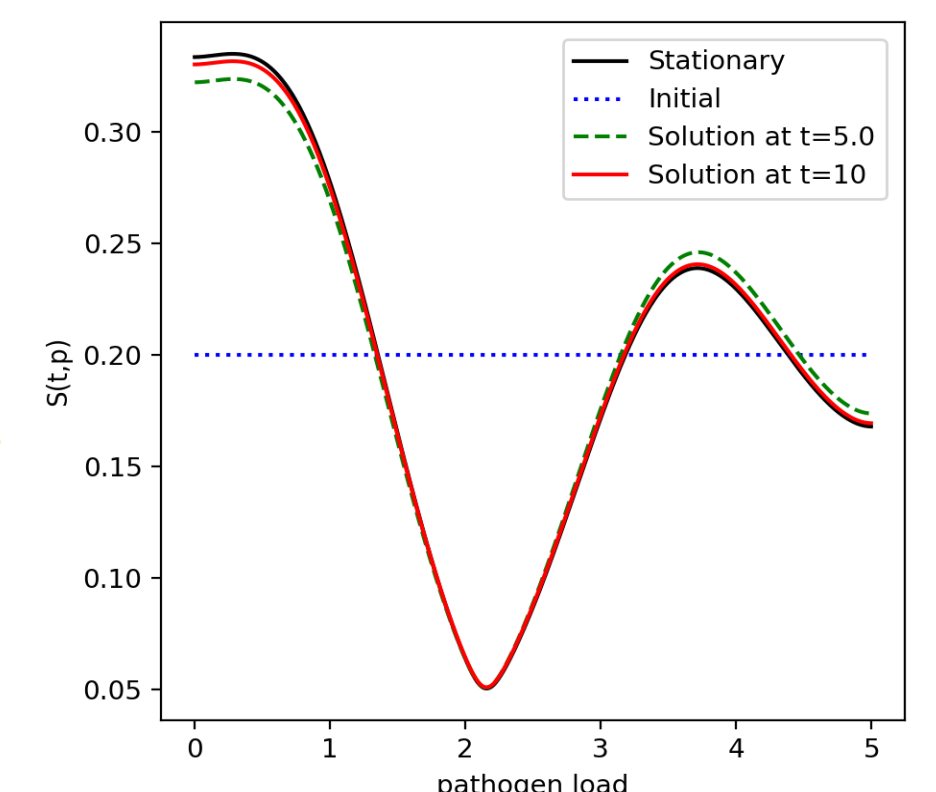
Parameter choice $\rightarrow A > 0$, 5 steady states, 2 stable positive values for p
forward Kolmogorov equation of SDE \rightarrow structured population model
 $s(t, p)$ population density of individuals with pathogen load p at time t

$$\partial_t s(t, p) = -\partial_p (F(p)s(t, p)) + \frac{\sigma^2}{2} \partial_{pp}^2 s(t, p),$$

$$\partial_p s(\cdot, 0) = \partial_p s(\cdot, K) = 0,$$

$$s(0, \cdot) = s_{\text{ini}}(\cdot) \in L^2(0, K), \quad \int_0^K s_{\text{ini}}(p) dp = N$$

Bi-modal distribution featuring low and high shedder phenotypes



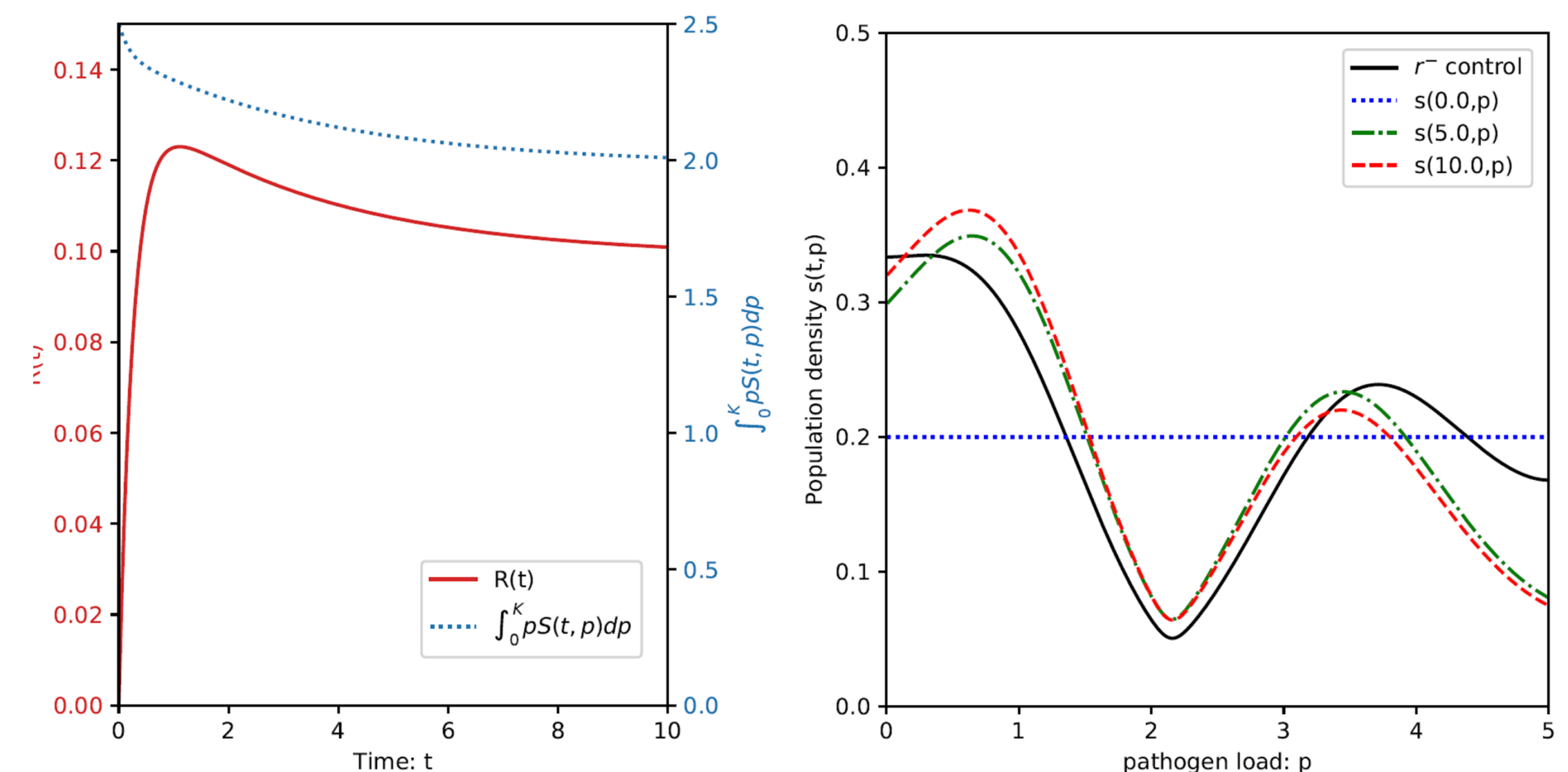
Adding between host transmission through an environmental reservoir

$$\partial_t s(t, p) = -\partial_p \left((F(p) + \beta_{\text{in}}(p)r(t) - \beta_{\text{ex}}(p))s(t, p) \right) + \frac{\sigma^2}{2} \partial_{pp}^2 s(t, p) \quad \beta_{\text{ex}}(p) = \beta_{\text{ex}} p \quad \beta_{\text{in}}(p) = \beta_{\text{in}}(K - p)$$

$$\frac{dr(t)}{dt} = -\left(\gamma + \int_0^K s(t, p)\beta_{\text{in}}(p)dp \right) r(t) + \int_0^K s(t, p)\beta_{\text{ex}}(p)dp$$

$$\sigma^2 \partial_{pp} s(t, K) + \beta_{\text{ex}}(K)s(t, K) = \sigma^2 \partial_{pp} s(t, 0) - \beta_{\text{in}}(0)r(t)s(t, 0) = 0$$

$$s(0, \cdot) = s_{\text{ini}}(\cdot) \in H^1(0, K), \quad \int_0^K s_{\text{ini}}(p)dp = N, \quad r(0) = r_{\text{ini}} \in \mathbb{R}^+$$

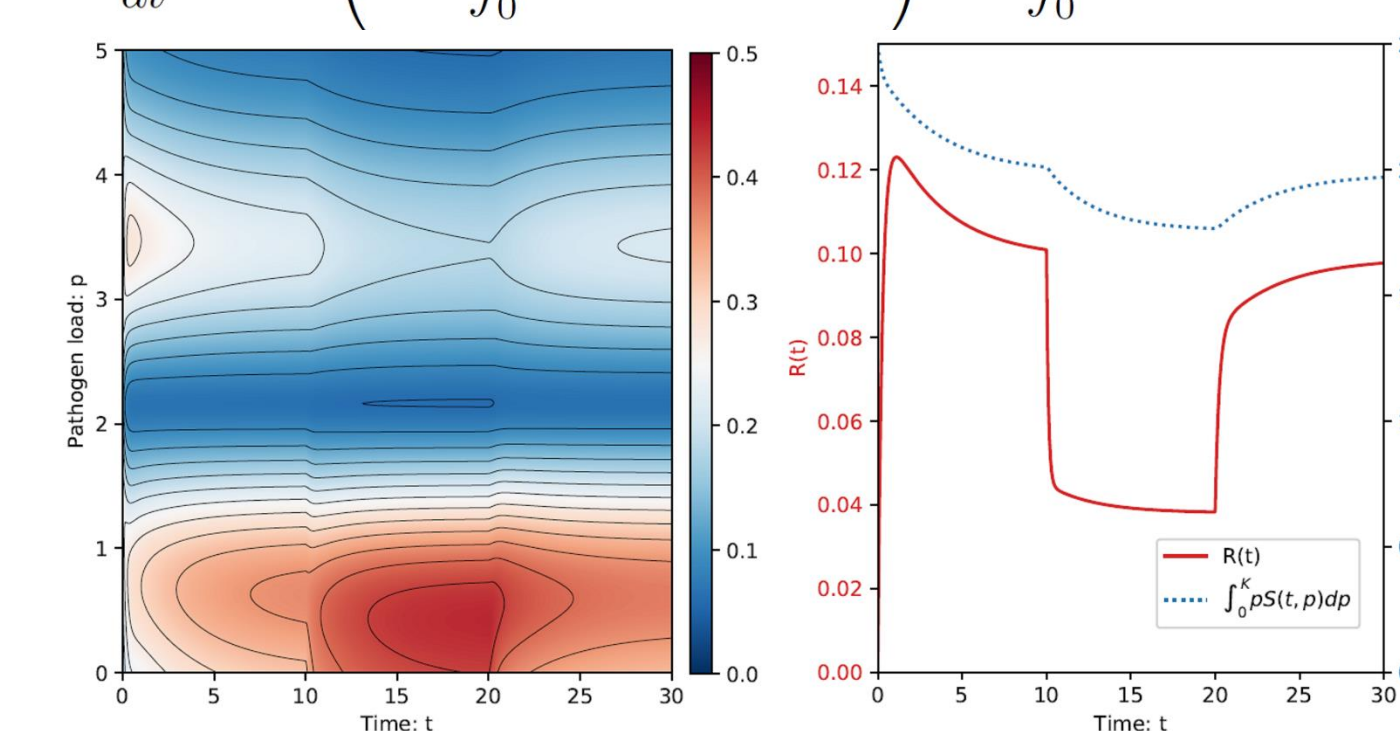


Control strategies

Environmental Cleaning

Cleaning= extra mortality term in the reservoir dynamic

$$\frac{dr(t)}{dt} = -\left(\gamma + \int_0^K s(t, p)\beta_{\text{in}}(p)dp \right) r + \int_0^K s(t, p)\beta_{\text{ex}}(p)dp - C(t, r)$$



For both control simulations

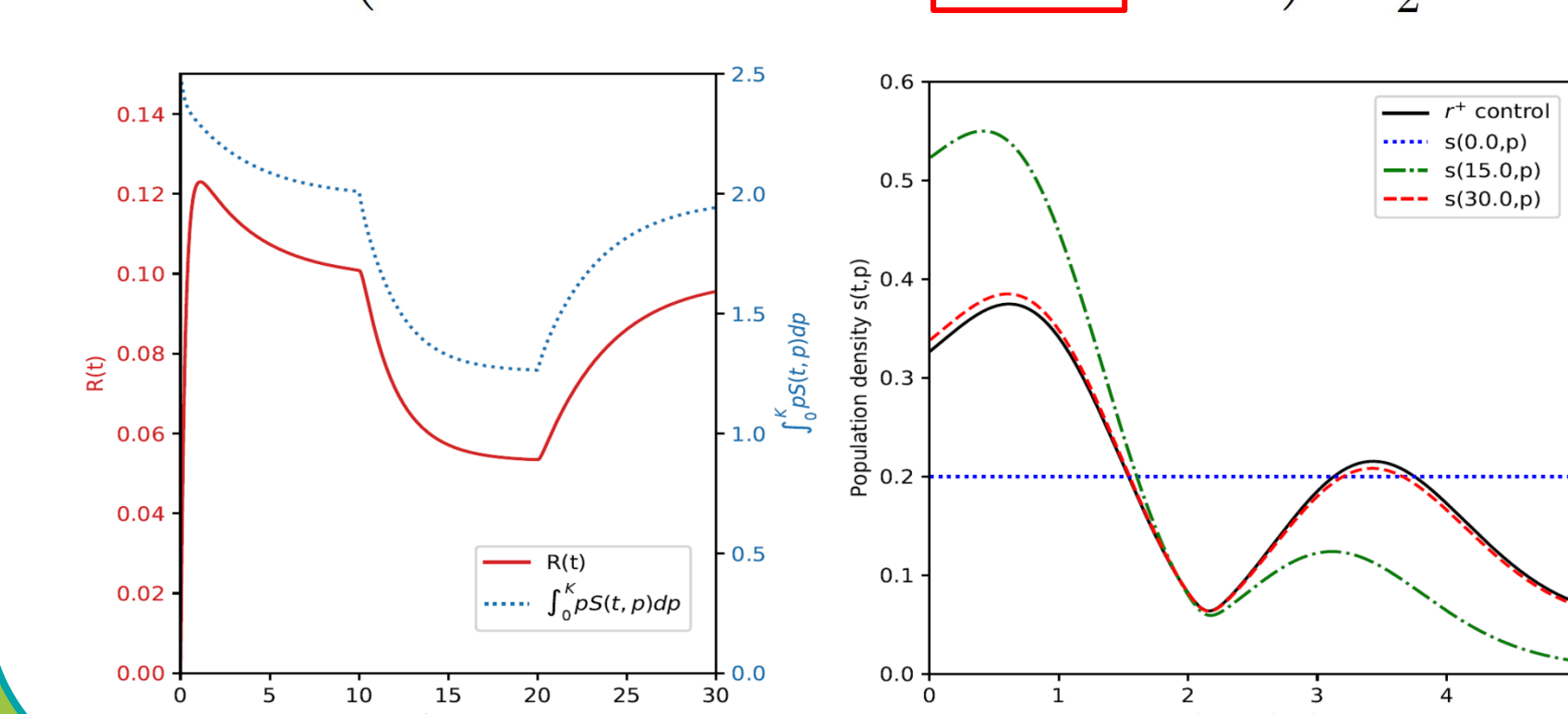
- the impact of cleaning or drug administration results in an extra mortality term proportional to the reservoir load or the pathogen load.

- The control is active between 10 and 20 days

Antimicrobial drug treatment

Treatment=extra mortality term in the pathogen load drift

$$\partial_t s(t, p) = -\partial_p \left((F(p) + \beta_{\text{in}}(p)r - \beta_{\text{ex}}(p) - T(t, p))s(t, p) \right) + \frac{\sigma^2}{2} \partial_{pp}^2 s(t, p)$$



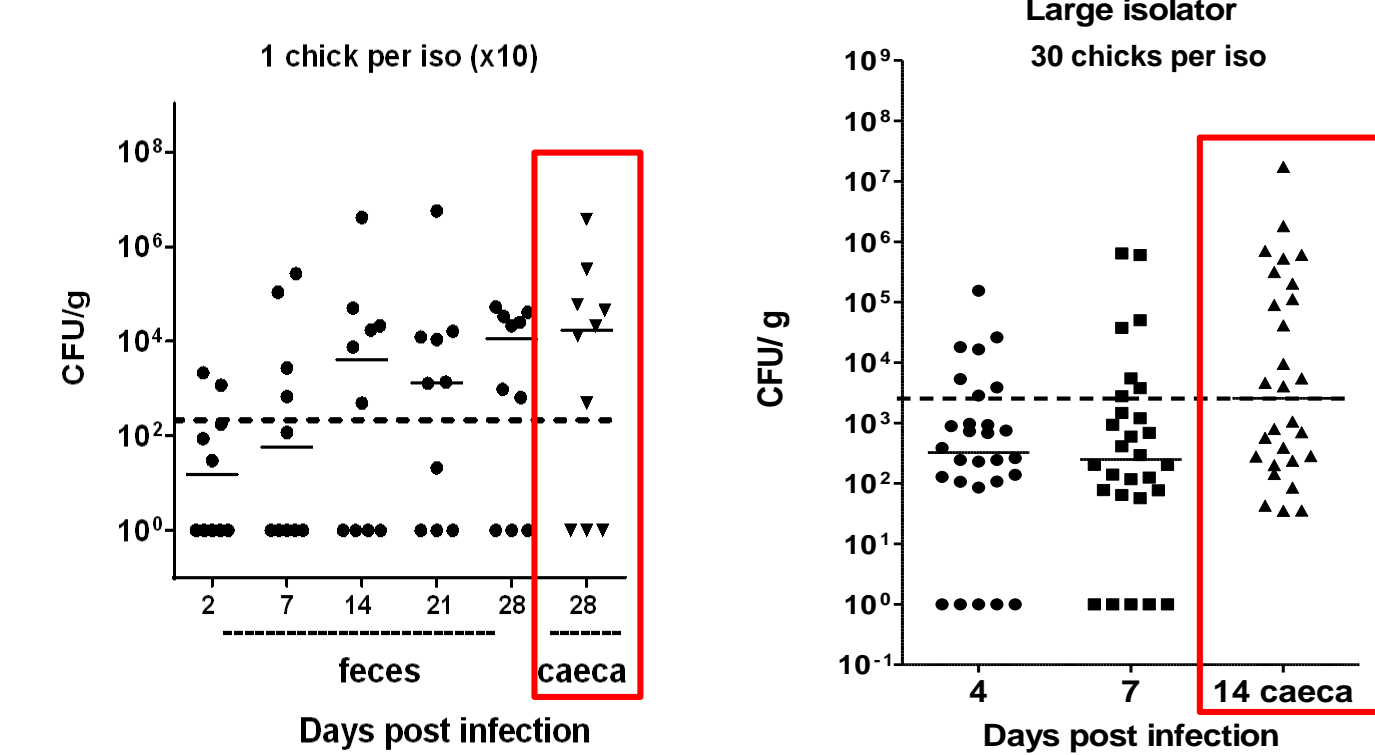
- The two controls induce a decrease in high-shedder frequency and an increase in low shedders, however the drug treatment seems much more efficient and leads to a substantial reduction of the pathogen load in the population

- When the control stops, the pathogen load distribution goes back to its stable, bimodal shape.

Discussion and perspective

- First simplistic theoretic model to link within host microbiota dynamic and between host epidemic transmission in the context of heterogeneous shedding
- In the near future, fit the pathogen load pdf with experimental data on poultry and pig, eg

Menanteau et al.
Environmental microbiology (2018)



- The model should be made more realistic:
 - Include host heterogeneity
 - Include age (education of immune system)
 - Offer a more complex description of the microbiota

This could open the way to alternative treatments of animal disease triggered towards the development of probiotics.