Multi-Scale Epidemic Model of Salmonella infection with Heterogeneous Shedding

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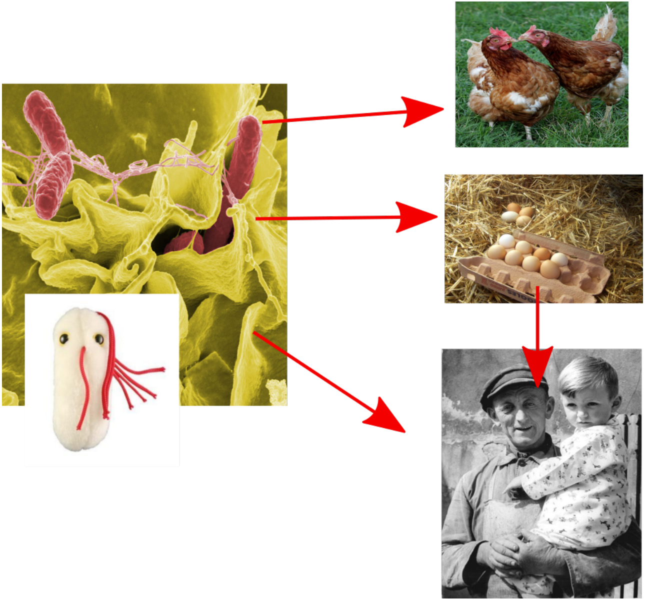
Salmonella



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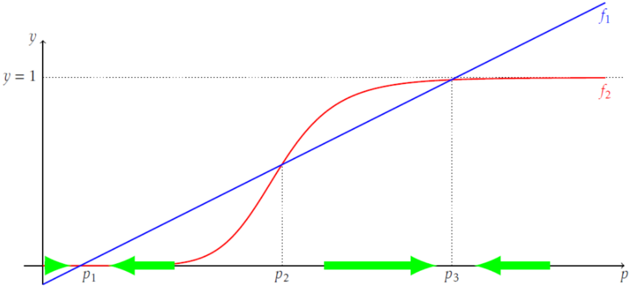
ODE model in the gut of a chicken

$$\begin{cases} \frac{dp}{dt} = p\,(K-p)\left(A - \alpha p + C\,\frac{p^n}{p^n + p_\star^n}\right) \\ p(0) = p_0 \end{cases}$$

Biological Interpretation of the different parameters

- p: concentration of pathogens in the host's gut.
- K: carrying capacity of the hosts gut.
- $p(K-p)$: logistic growth.
- $A - \alpha p$: interaction between the pathogen and the enviroment.
- $C\,\dfrac{p^n}{p^n + p_*^n}$: immune response of the host.

$$\frac{dp}{dt} = p\,(K-p)\left(A - \alpha p + C\frac{p^n}{p^n + p_\star^n}\right)$$



$$f_1(p) = \alpha \cdot p - A$$

$$f_2(p) = C \cdot \frac{p^n}{p^n + p_\star^n}$$

Figure: Three intermediate steady states. The steady points 0 and K are unstable.

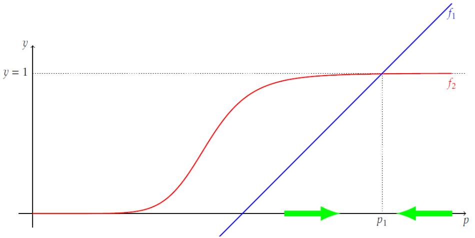


Figure: On stable steady state: p_1

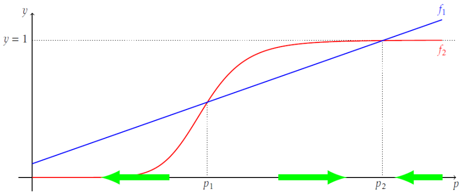


Figure: Two stable steady state: 0 and p_2

$$f_1(p) = \alpha \cdot p - A$$

$$f_2(p) = C \cdot \frac{p^n}{p^n + p_\star^n}$$

PDE MODEL

We get a PDE system

$$\begin{cases} \partial_t S = -\partial(F(p)S) + \dfrac{\sigma^2}{2}\partial_p^2 S \\ \partial_p S(t,0) = \partial_p S(t,K) = 0 \\ S(0,p) = S_0 \in H^1(0,K), \end{cases}$$

with the function F

$$F(P) = P(K-P)\left(A - \alpha P + C\frac{p^n}{p^n + p_\star^n}\right) \quad \text{if } 0 \le P \le K.$$

Theoretical results:

- Existence and uniqueness of solution of PDE model using Galerkin approximation.
- Existence of a steady state: $\bar{S}(p) = \exp\left(\frac{2}{\sigma^2}\int_0^p F(p') \cdot dp'\right)$.
- Exponential convergence to steady state.

Convergence rate to steady state

- **Define:** $G(t) := \left\| S(t,\cdot) - \bar{S}(\cdot) \right\|^2_{\mathcal{L}^2_V(]0,K[,e^V)} = \int_0^K \left(\frac{S(t,p)}{e^{-V(p)}} - 1 \right)^2 e^{-V(p)} \cdot dp,$
  with $V(p) = -\frac{2}{\sigma^2} \int_0^p F(p') \cdot dp'.$

- **Compute:**

$$G'(t) = \sigma^2 \int_0^K \left(\frac{S(t,p)}{e^{-V(p)}} - 1 \right) \partial_p \left[\partial_p S(t,p) + V'(p) S(t,p) \right] \cdot dp.$$

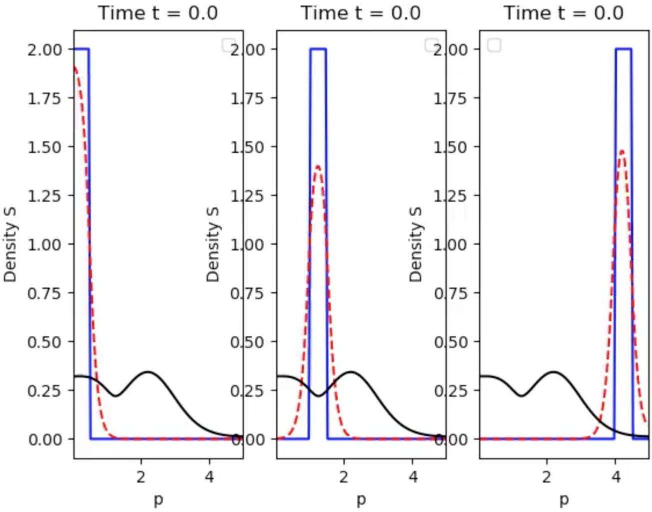
- **Integrate by part and use boundary condition**

$$G'(t) = -\sigma^2 \int_0^K \left| \partial_p \left(\frac{S(t,p)}{e^{-V(p)}} - 1 \right) \right|^2 \cdot dV(p)$$

- **Use Poincaré's inequality on a compact set:**
  ie: there exist $\kappa > 0$ such that $\kappa \int_0^K |u|^2 \cdot dV(p) \le \int_0^K \left| \partial_p u \right|^2 \cdot dV(p)$

- **Use Gronwall lemma:** $G(t) \le G(0) e^{-\sigma^2 \kappa t}$

Convergence of toward the steady state for different initial data



Reservoir variable

Reservoir variable

This leads to the following system :

$$\begin{cases} \partial_t S(t,p) = \partial_p^2 S(t,p) - \partial_p([F(p) + \beta_{in}(p)R - \beta_{ex}(p)]\, S(t,p)) \\ R'(t) = -\left(\gamma + \int_0^K S(t,p)\beta_{in}(p)dp\right) R + \int_0^K S(t,p)\beta_{ex}(p)dp. \end{cases}$$

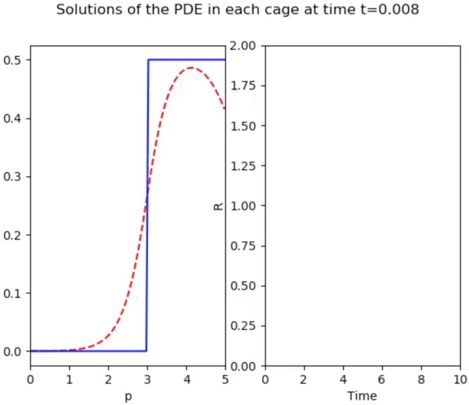
- R models the amount of excrement on the ground.
- β_{in} models the consumption of pathogen through excrement and β_{ex} the creation of pathogen through excrement.
- New boundary conditions

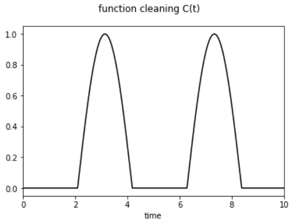
$$\partial_p S(t,K) = -\beta_{ex}(K)S(t,K),$$
$$\partial_p S(t,0) = \beta_{in}(0)R(0)S(t,0).$$

- Number of chicken constant.

Cleaning by acting on the reservoir R

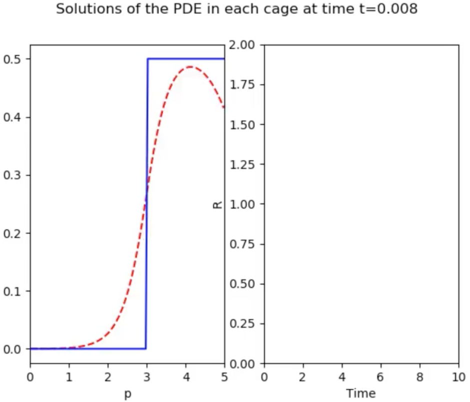
$$\begin{cases} \partial_t S = -\partial_p\Big(\big(F(p) + \beta_{in}(p)R - \beta_{ex}\big)S\Big) + \frac{\sigma^2}{2}\partial_p^2 S \\ \frac{dR}{dt} = -\left(\gamma + \int_0^K \beta_{in}(p)S(t,p)\cdot dp\right)R + \int_0^K \beta_{ex}S(t,p)\cdot dp - G(t)R. \end{cases}$$

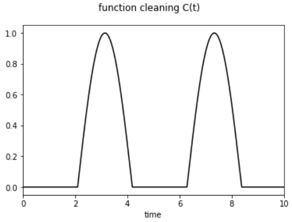




Treatment by acting on $S(t,p)$

$$\begin{cases} \partial_t S = -\partial_p \Big(\big(F(p) - G(t)p + \beta_{in}(p) R - \beta_{ex} \big) S \Big) + \frac{\sigma^2}{2} \partial_p^2 S \\ \frac{dR}{dt} = -\left(\gamma + \int_0^K \beta_{in}(p) S(t,p) \cdot dp \right) R + \int_0^K \beta_{ex} S(t,p) \cdot dp. \end{cases}$$





MULTIPLE CAGES

We introduce a finite number d of cages. $\mathbf{S}, \mathbf{R}$ are now vectors of $\mathbb{R}^d$:

$$\mathbf{S} := \begin{pmatrix} S_1 \\ S_2 \\ ... \\ S_d \end{pmatrix}, \quad \mathbf{R} := \begin{pmatrix} R_1 \\ R_2 \\ ... \\ R_d \end{pmatrix}$$

They verify a system of PDEs :

$$\begin{cases} \partial_t S(t,p) = \partial_p^2 S(t,p) - \partial_p([F(p) + \beta_{in}(p)R - \beta_{ex}(p)]\, S(t,p)) + TS, \\ R'(t) = -\left(\gamma + \int_0^K S(t,p)\beta_{in}(p)dp\right)R + \int_0^K S(t,p)\beta_{ex}(p)dp, \end{cases} \tag{1}$$

- T is a $d \times d$ transition matrix between cages.
- For $i \neq j$, $T_{i,j}$ is the amount of chicken of cage i moving to cage j. It is independent of p and t.

Transition matrix

The "conservation of chicken" law implies that

$$ {}^{\top}\begin{pmatrix} 1 \\ 1 \\ \vdots \\ 1 \end{pmatrix}_d T = 0. $$

In particular, 0 is an eigenvalue of T. Furthermore, T is diagonalizable and

$$ T = PDP^{-1}. $$

Let N be the population size

$$ N := \int_0^K S(t,p)dp. $$

can be explicitly computed since it verifies

$$ N'(t) = TN. \tag{2} $$

One deduce that

$$ N(t) = P\exp(tD)P^{-1}N(0). \tag{3} $$

A SPECIAL CASE

If the matrix T is the discrete Laplacian matrix :

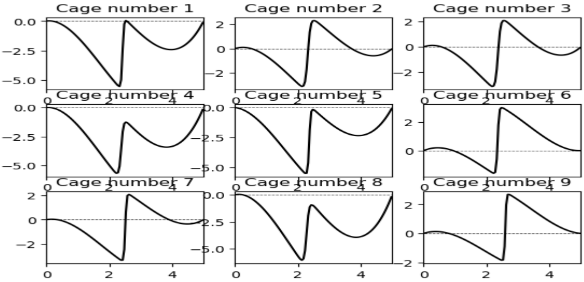
A MORE GENERIC CASE

The matrix T is no longer sparse, its coefficients are taken randomly :

Transfer of excrements

$$
\begin{cases}
\partial_t S(t,p) = \partial_p^2 S(t,p) - \partial_p([F(p) + \beta_{in}(p)R - \beta_{ex}(p)]\, S(t,p)) + TS \\
R'(t) = -\left(\gamma + \int_0^K S(t,p)\beta_{in}(p)dp\right)R + \int_0^K S(t,p)\beta_{ex}(p)dp + T_{ex}R.
\end{cases} \tag{4}
$$

$$
T_{ex} = \lambda_{ex} \begin{pmatrix} (d-1) & -1 & -1 & \dots & -1 \\ -1 & (d-1) & -1 & .. & -1 \\ \vdots & & \vdots & & \vdots \\ -1 & & .. & -1 & (d-1) \end{pmatrix}_d .
$$



Conclusion & Further Work

Dario Fo, *Morte accidentale di un anarchico, 1970* :
`"Siamo immersi nella merda fino al collo, é per questo che camminiamo a testa alta."`

Conclusions

- Theoretical and numerical results of convergence towards the stationary state without reservoir variable.
- The effect of more realistic models on is unclear.
- Attempt to model the cleaning and treatment:
  - Result are not satisfactory: pathogen load remain high
  - Objective: Study other modelling approach

Further Work

- Consider a structured model with space, *i.e.* $S(t,p,X)$ with $X \in \mathbb{R}^2$.