Multiscale modelling and optimisation of antimicrobial resistance dynamics

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1 Motivation

- The fast increase in bacterial resistance to current antimicrobials (*Antimicrobial Resistance* or AMR) poses a paramount economic and health concern that seems far from being solved.
- Recent studies [1] estimate 1,27 million the number of deaths worldwide that are directly attributable to AMR only in 2019.
- Understanding the main mechanisms involved in the emergence, selection, and spread of AMR is critical to determine the optimal therapies to deal with this undesirable phenomenon.

2 Objectives

- To explore the state-of-the-art mathematical modelling techniques for the study of the emergence, selection and spread of AMR within bacterial populations.
- To develop operational mechanistic models of AMR for model-based optimisation of disinfection therapies.
- To experimentally validate the developed models using real-life data obtained through flow cytometry [2] and morbidostat [3].

3 Mathematical modelling of AMR

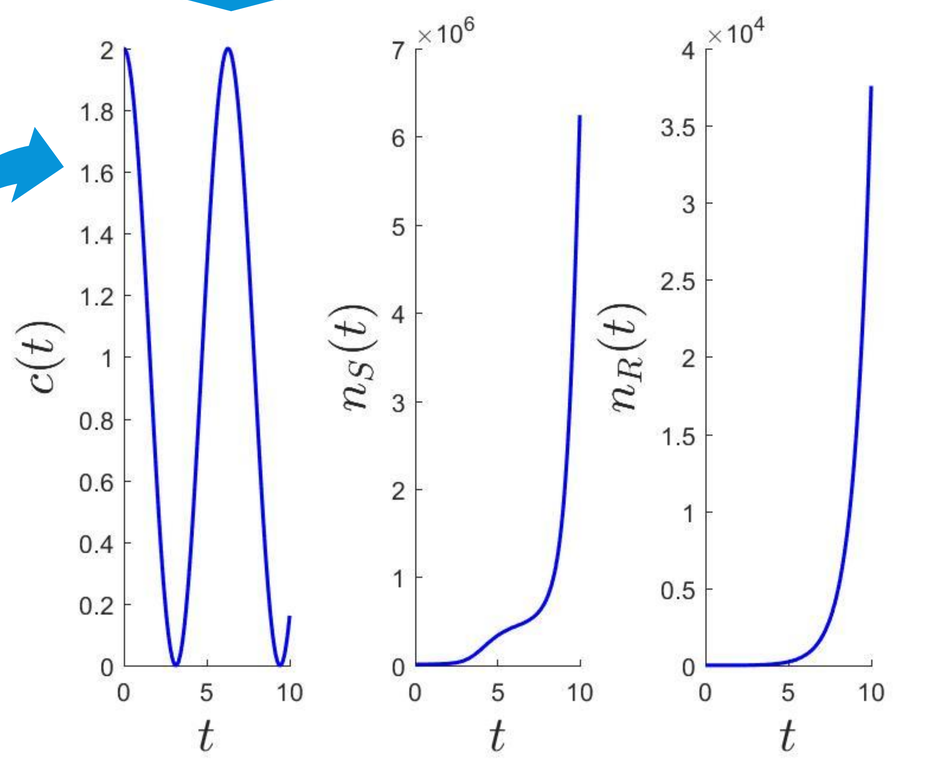
- Three different approaches: population-based (*macroscale*), individual-based (*microscale*) and *mesoscale* modelling [4].
- *Macroscale* models describe the properties of the bacterial population as a whole, while *microscale* models consider the differences between bacteria.
- *Macroscale* models are too simplistic to properly describe the dynamics of AMR, while *microscale* models are too complex for real-life monitoring and optimisation tasks.
- *Mesoscale* models describe average properties of the bacterial population, combining advantages of the other two techniques.

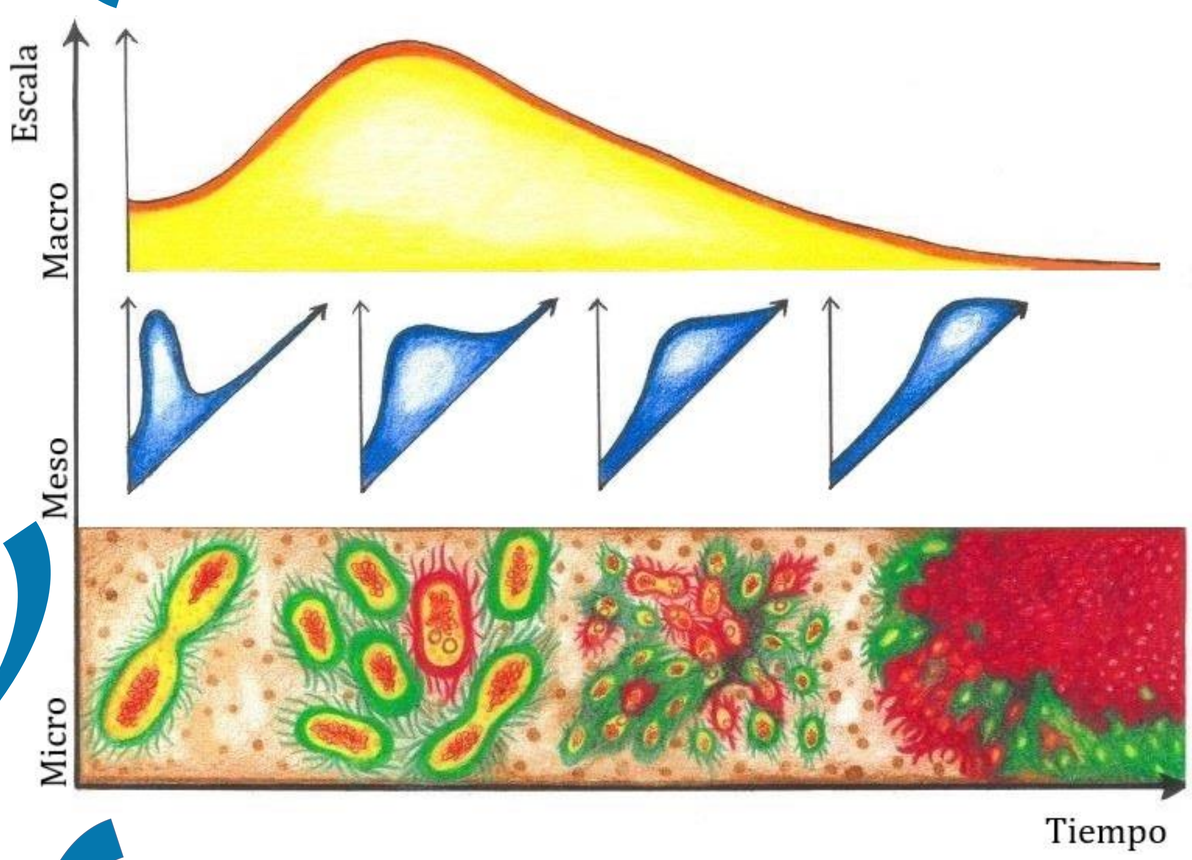
MACROSCALE

Normally given in terms of Ordinary Differential Equations (ODEs)

$$\frac{dn_S}{dt}(t) = \Big((1-\mu)b_S\big(c(t)\big) - d_S\big(c(t)\big)\Big)n_S(t)$$

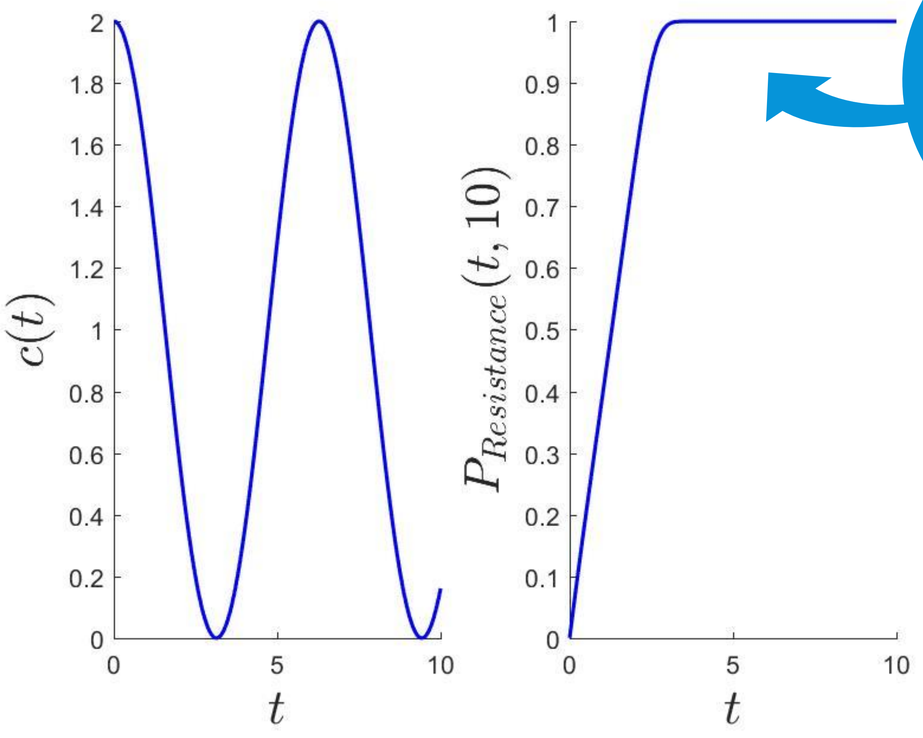
$$\frac{dn_R}{dt}(t) = \mu b_S\big(c(t)\big)n_S(t) + (b_R - d_R)n_R(t)$$





MESOSCALE

Normally given in terms of probability distributions

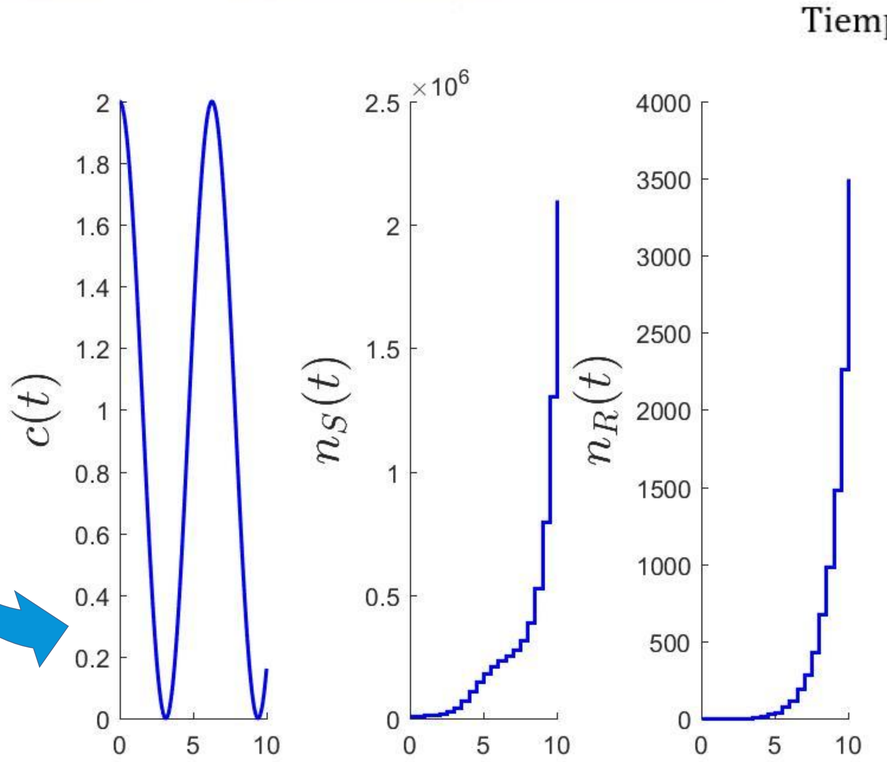


$$P_{extintion}(t,T) = 1 - \frac{(b_R - d_R)}{b_R - d_R e^{-(b_R - d_R)(T-t)}}$$

$$P_{Resistance}(T) = 1 - e^{\int_0^T \mu b_S\left(c(t)\right)n_S(t)\left(1-P_{extintion}(t,T)\right)dt}$$

MICROSCALE

Normally given in terms of stochastic processes



$$S \xrightarrow{(1-\mu)b_S} S + S \qquad S \xrightarrow{\mu b_S} S + R$$

$$S \xrightarrow{d_S} \emptyset \qquad R \xrightarrow{d_R} \emptyset$$

[1] Murray, C. L. J., Ikuta, K. S., Sharara, F., Swetschinski, L., Gisela, R. A., Naghavi, M. and col. (2022) *Global burden of bacterial antimicrobial resistance in 2019: A systematic analysis.* The Lancet, 399 (10325):629-655.

[2] Adan A., Alizada G., Kiraz Y., Baran Y. and Nalbant, A. (2017) *Flow cytometry: basic principles and applications.* Crit. Rev. Biotechnol. 37(2):163-176.

[3] Pedreira, A., Vázquez, J. A. and García, M. R. (2021) *Morbidostato: un sistema de cultivo continuo para el estudio evolutivo de poblaciones bacterianas sometidas a estrés por compuestos antimicrobianos.* XXVIII Cong. Soc. Esp. Microbiol.

[4] Martínez-López, N., Vilas, C. and R. García, M. (2021) *Comparativa entre modelos estocásticos de crecimiento bacteriano a distintas escalas*. XLII JJAA. Servizo de Publicacións da UDC, 442–44.

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