ESTIMATION OF SINGLE-CELL PARAMETERS FROM A DISTRIBUTION OF BACTERIAL SIZE

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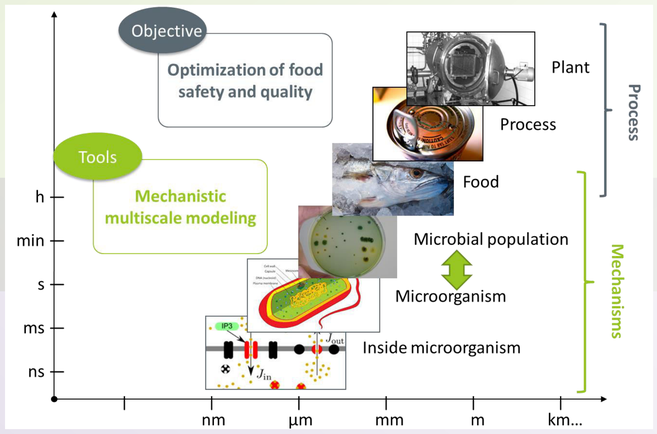
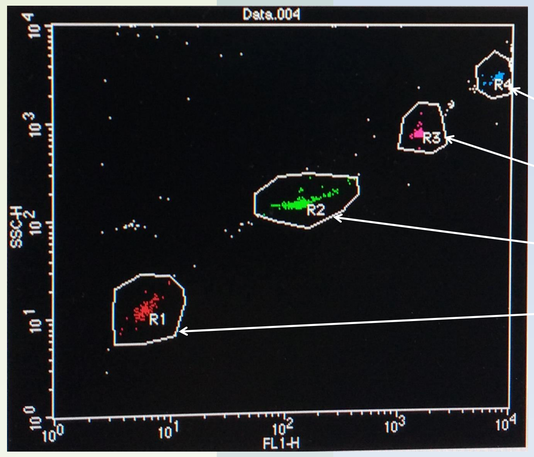
Motivation

- **Optimisation of antimicrobial treatments using Individual-based modelling (IBM)**
  - IBM is the natural mathematical formalisms to describe emergence and selection of antimicrobial resistance (AMR)
  - In IBM the essential first step is to describe division with simple equations
    ➔ Is size a good descriptor of division? [1]
  - IBM needs knowledge of individual parameters
    ➔ Can we extract individual parameters (like division size) from population statistics?
- **Application: controlling AMR in the food industry**



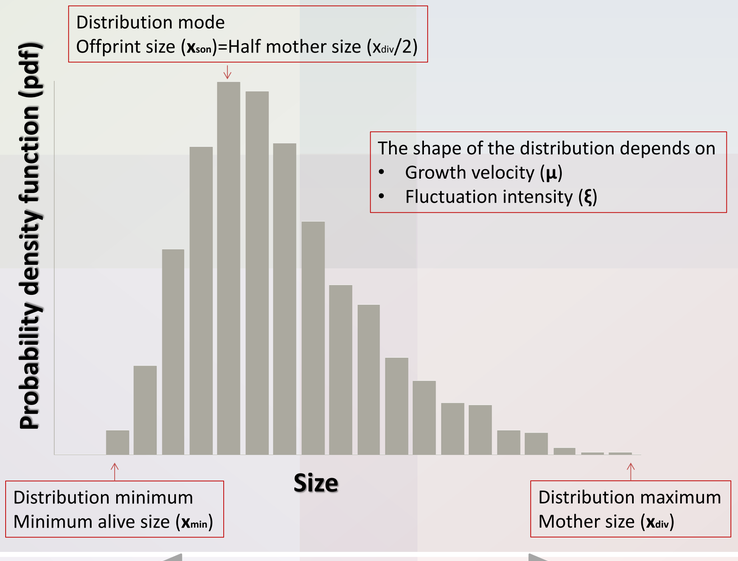


Experiments: Flow cytometry

- **Light scattering relates with cell size**
  - 0.2 µm (R4)
  - 0.5 µm (R3)
  - 1.0 µm (R2)
  - 2.0 µm (R1)

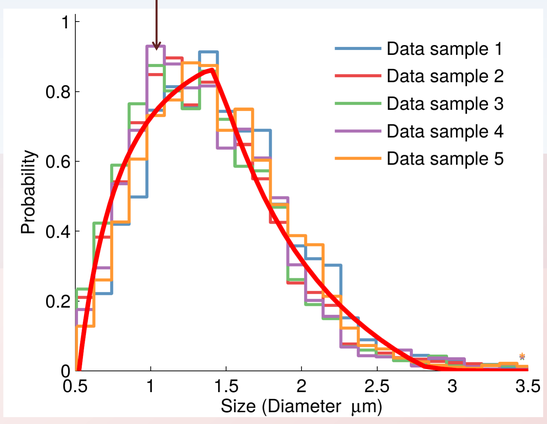
  Forward scatter (mainly for big cells)
  Side scatter (mainly for small cells)
  It requires a calibration with size reference beads [2]
- **Flow cytometry data provides population statistics**
  - Shape and time evolution of the probability density function
- **Theory is tested using size pdfs of *Pediococcus acidilactici*** at different times during the exponential phase (transparent histograms)

Population size distribution



Pediococcus data transparent histograms

Fokker-Plank model Continuous red line

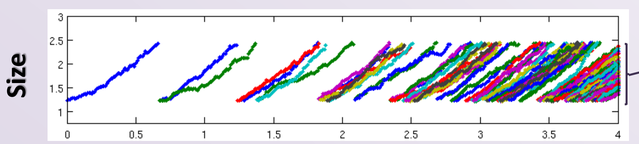


Model: Stochastic size growth

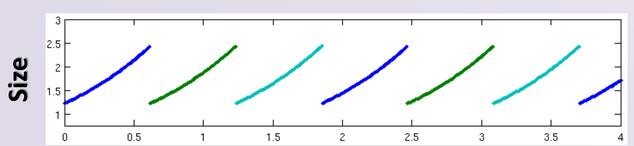
- **Assumption:** size is subject to a stochastic fluctuation δW characterized by a Wiener process [3]
- **Simulation using stochastic differential equations** (SDE)

$$\begin{aligned} &\text{Growth} && \text{if} \quad y = \log(\text{size}) && \delta y = \mu\delta t + \xi\delta W \\ &\text{Division} && \text{if} \quad y \geq y_{div} && y \longrightarrow y_{son}, y_{son} \text{ with } y_{son} = y_{div} - \log 2 \\ &\text{Death} && \text{if} \quad y \leq y_{min} && y \longrightarrow \emptyset \end{aligned}$$

- **Simulations starting from one bacteria**

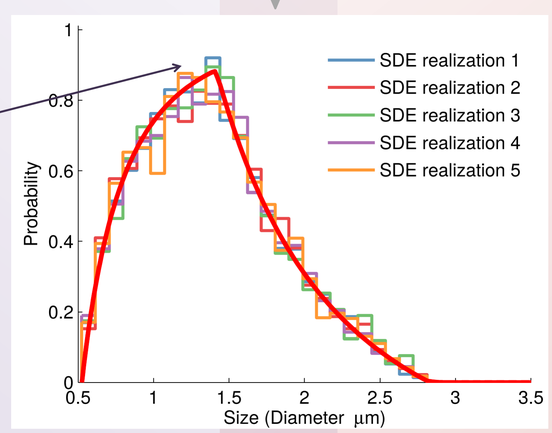


- **Comparison with deterministic simulations (ξ=0)**



Stochastic IBM Transparent histograms

Fokker-Plank model Continuous red line



Model: Fokker-Planck eq.

$$\begin{aligned} &\text{Probability population size (pdf)} && \frac{\partial F(t,y)}{\partial t} = -\frac{\partial J(t,y)}{\partial y} + B(t,y) + N(t,y) \\ &\text{Boundary conditions} && \forall t \quad F(t,y_{min}) = F(t,y_{max}) = 0 \\ &\text{Initial conditions} && \forall y \quad F(0,y) = \delta(y - y_{son}) \\ &\text{Fluxes} && J(t,y) = \mu F(t,y) - \frac{\xi^2}{2}\frac{\partial F(t,y)}{\partial y} \\ &\text{Division} && B(t,y) = -\frac{\partial J(t)}{\partial y}|_{y_{div}}\delta(y - y_{div}) + 2\frac{\partial J(t)}{\partial y}|_{y_{div}}\delta(y - y_{son}) \\ &\text{Normalization pdf} && N(t,y) = -F(t,y)\frac{\partial J(t)}{\partial y}|_{y_{div}} \end{aligned}$$

- **SDEs are transformed into a partial derivative equation**
  - allowing simulation of small and large populations
  - better estimations of the probability function
  - efficient calibrations and validations of the theory
- **Validation using *Pediococcus* data showing for example**
  - estimated growth velocity of the cell-size(µ=0.25 d^{-1}) coincides with population growth velocity (µ=0.24 d^{-1})

CONCLUSIONS:

The proposed model based on stochastic cell size growth shows promising features (efficient, simple) for individual-based modeling.

Single-cell parameters were recover from *Pediococcus* population statistics

Working now on extending the model to include a descriptor of antimicrobial resistance (probably stochastic membrane permeability)

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RESISTANCE

http://resistance.iim.csic.es/

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[1] Taheri-Araghi, et al. "Cell-size control and homeostasis in bacteria." Current Biology 25.3 (2015): 385-391

[2] Chandler, et al."A new microparticle size calibration standard for use in measuring smaller microparticles using a new flow cytometer." Journal of Thrombosis and Haemostasis 9.6 (2011): 1216-1224.

[3] Alonso, et al. "Modeling bacterial population growth from stochastic single-cell dynamics." Applied and environmental microbiology 80.17 (2014): 5241-5253.