

Bacterial morphology-based pharmacokinetic-pharmacodynamic models of carbapenem-exposed Gram-negative bacteria

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Background and Aims

- Timelapse microscopy can assess antibiotic effect on individual cells with frequent measurements of cell shape and morphology
- Some Gram-negative bacteria change shape when exposed to certain antibiotics
- Filamentous bacteria have links to resistance/regrowth (1,2)

Aims:

- Develop framework for analyzing timelapse microscopy images
- Quantify changes in bacterial counts and morphology using PKPD modelling of *P. aeruginosa* + meropenem (PA+MEM) and *E. coli* + ertapenem (EC+ETP)

CellProfiler Image Analysis

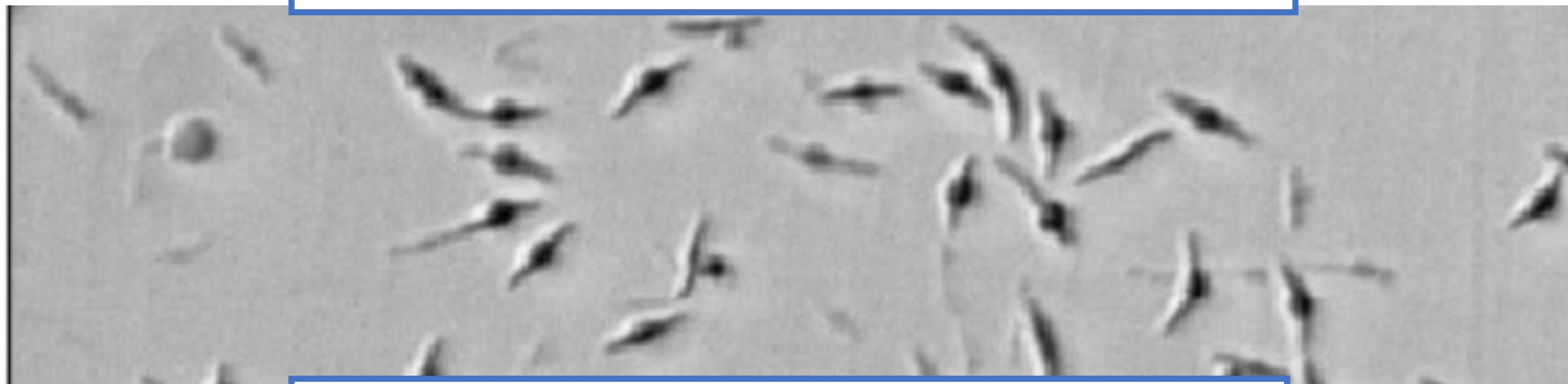
Count and measure bacteria from raw images.

Datasets

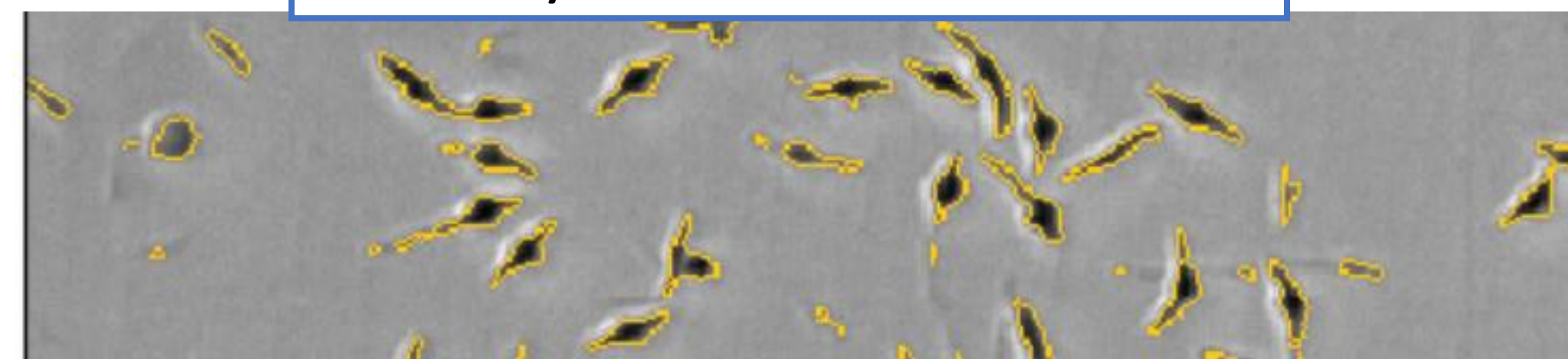
PA+MEM (0-16xMIC)

EC+ETP (0-16xMIC)

Raw images



Identify and measure bacteria



Classify bacteria

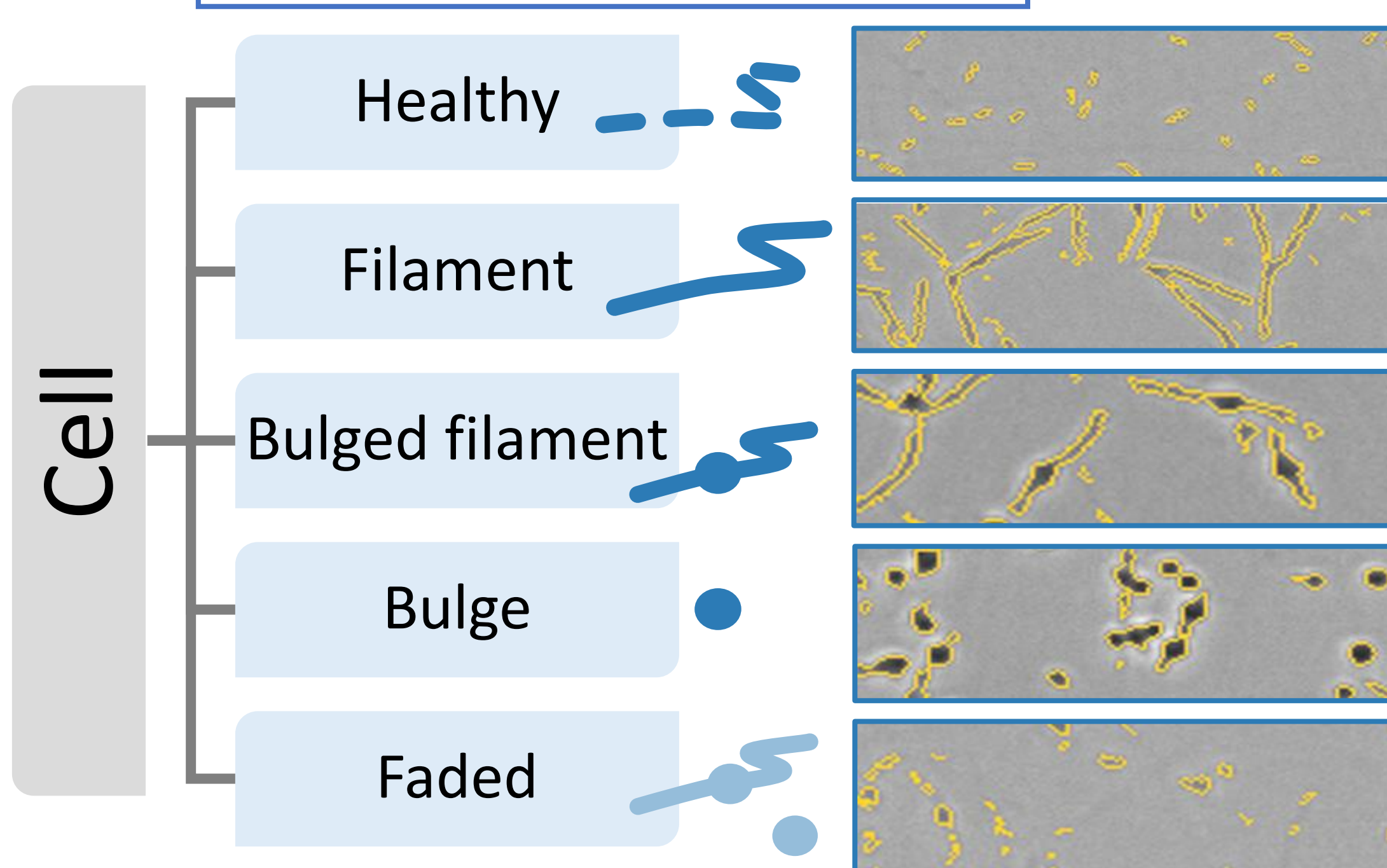
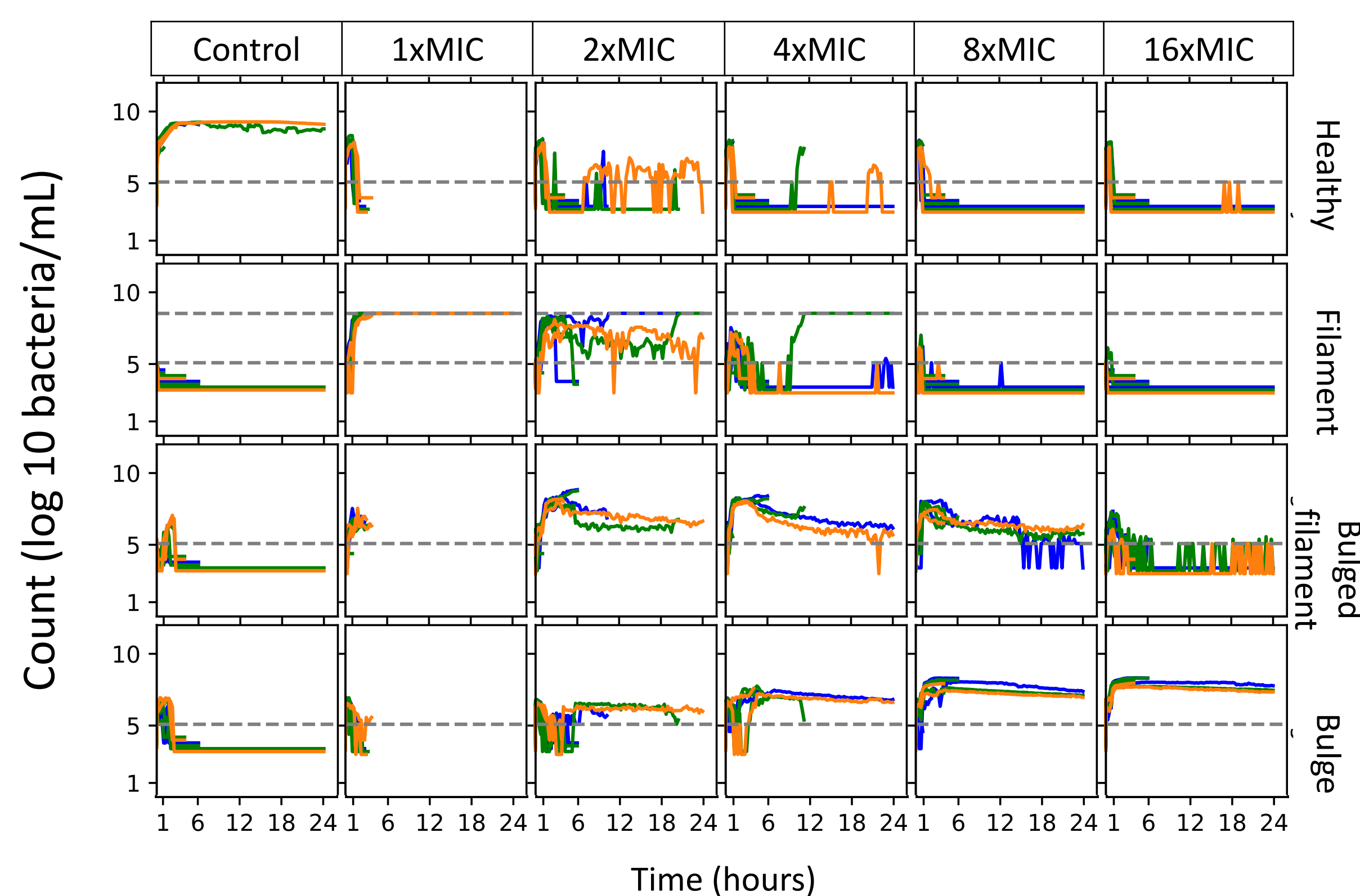
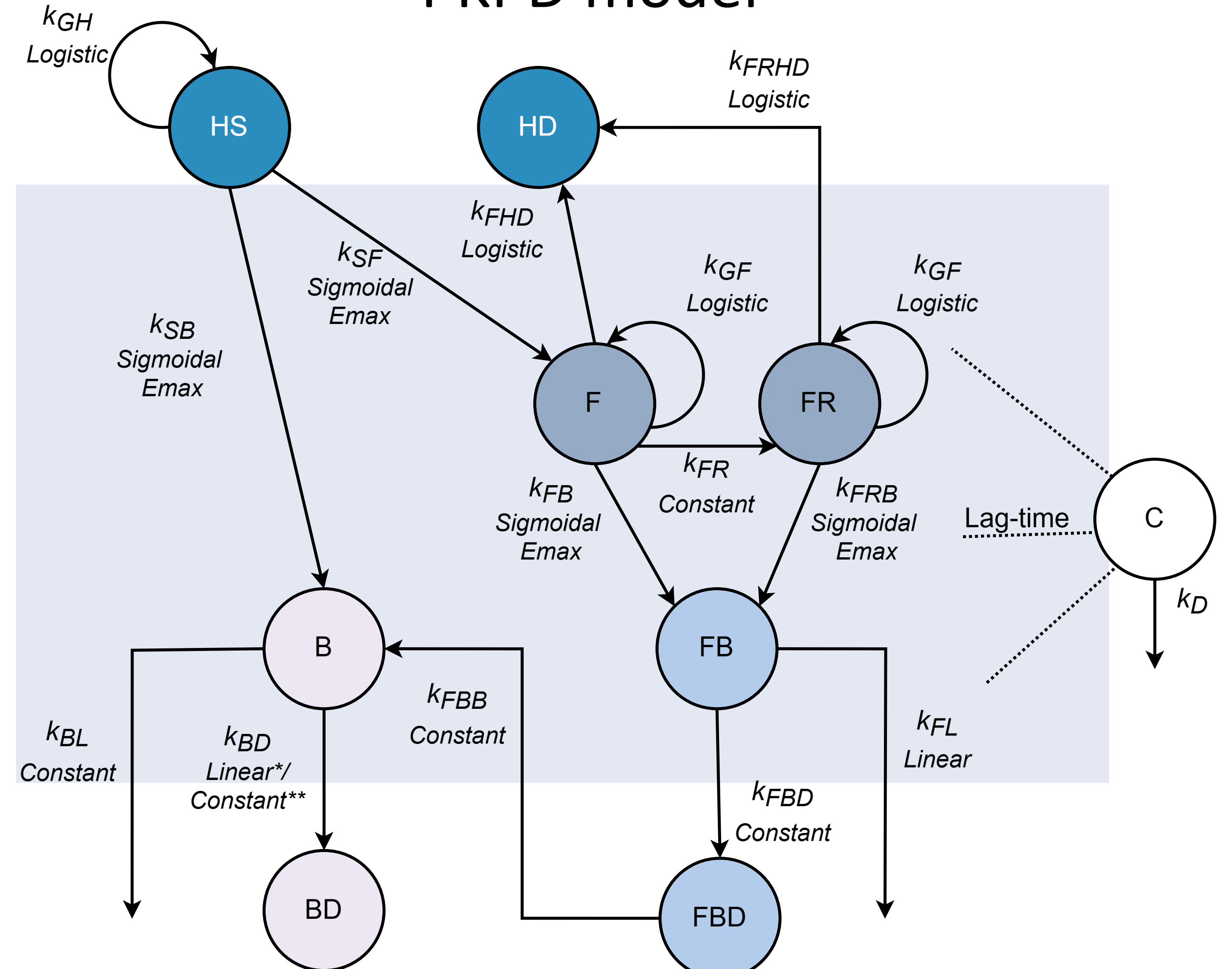


Image bacterial counts



We acknowledge the help from Dr. Carolina Wählby and Dr. Petter Ranefall from the SciLifeLab in developing the CellProfiler pipeline. Additionally, we acknowledge Wanchana Ungphakorn from Medical Sciences at Uppsala University for help in collecting data.

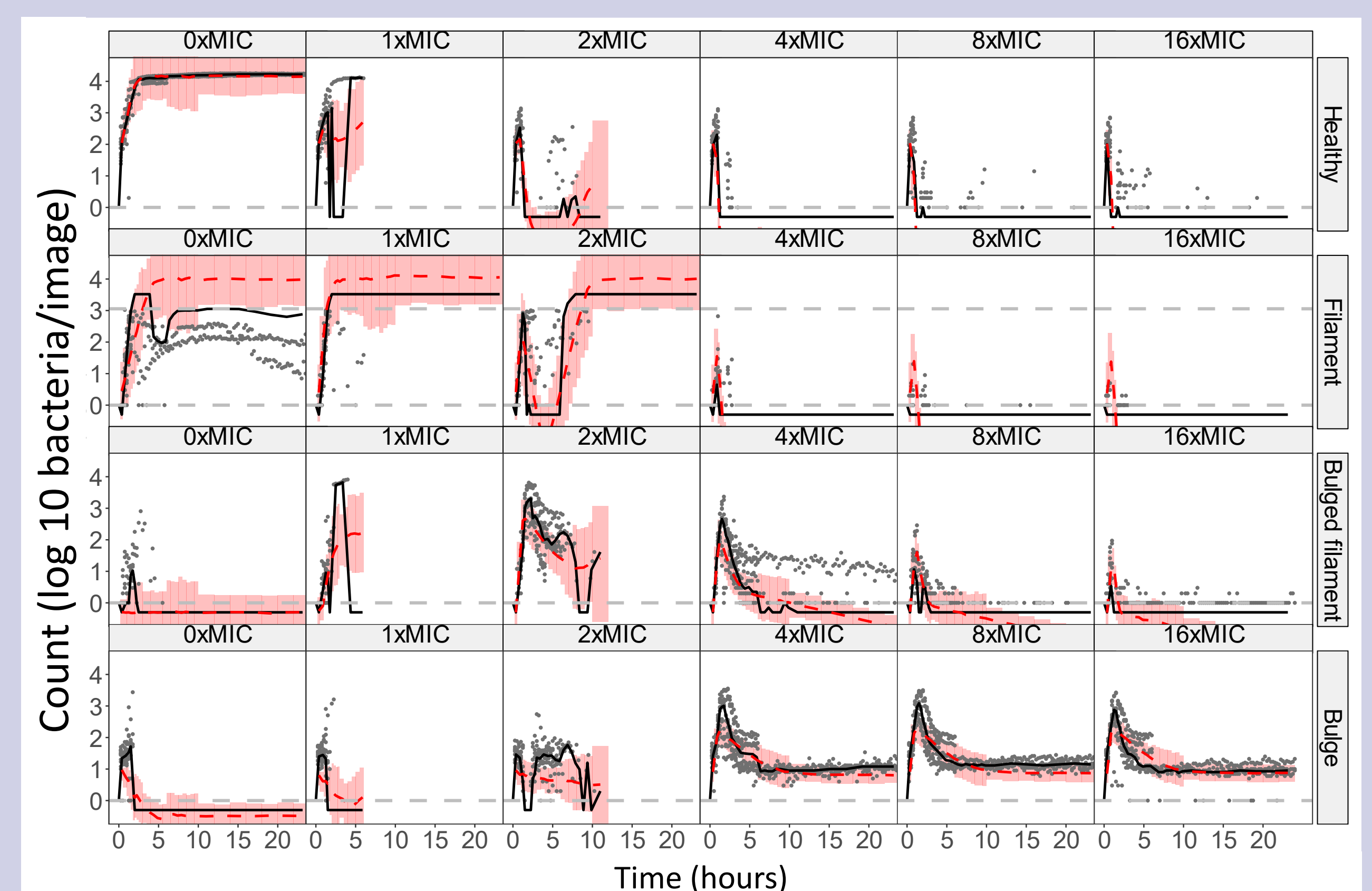
PKPD model



Drug concentration loss according to previous models (3,4). All rates in blue box except k_{BL} , k_{GF} are concentration dependent. H = rod-shaped. F = filament. B = bulge. R = resistant. D = dormant.
*Only PA+MEM. **Only EC+ETP

Visual Predictive Checks

PKPD model evaluation. ECOLI+ERT VPCs as an example.



The red area: 95% CI for the simulated median, grey points: observations, red dashed line: median of simulated counts (1000 simulations), black lines: median of observations. Grey dashed lines: limits of quantification.

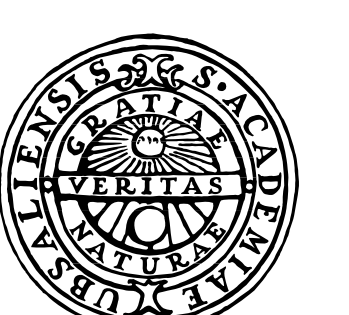
Conclusions

- The developed pipeline could identify, count, and measure bacteria
- ML models obtained moderate accuracy (87%)
- PKPD models describe count and morphology changes over time
- Method applicable to 2xGram-neg species + beta-lactam combinations
- Addition of morphology in antibiotic PKPD models could contribute to greater understanding of antibiotic/effect relationship

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References

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