

Minimal-PBPK urinary model and framework for investigation of nitrofurantoin, ciprofloxacin and fosfomycin effect on *Escherichia coli* in microfluidic-based hollow fiber infection model

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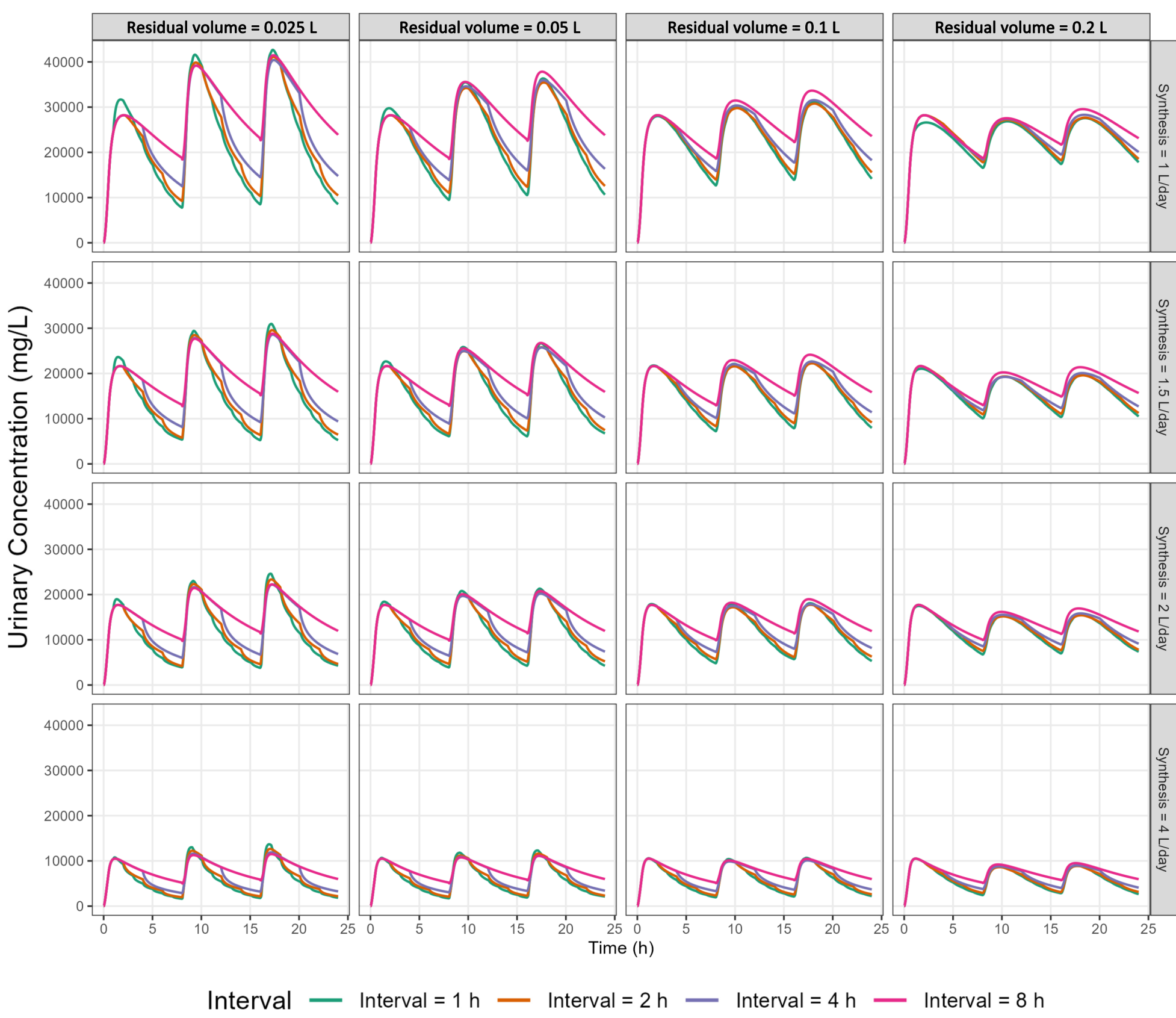
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To tackle antimicrobial resistance (AMR) global rise [1] and hurdles faced in research and development of anti-infective therapeutics, reflected in a marked slowdown in the discovery of novel-class antibiotics [2], the **NCCR AntiResist initiative** argues that **physiologically relevant assays**, those that reproduce in vivo-like conditions, represent an **underexplored** but **promising strategy** to accelerate the discovery of effective antimicrobial interventions [3].

This poster presents an exploratory work on **urinary volume profiles**, their impact on **prediction** of drug urinary concentration, and results from **microfluidic-based hollow fiber infection model** [4] **recapitulating urinary-relevant exposures** in synthetic urine[5].

We aimed at:

- Exploring physiology-based model structures describing the urine **voiding mechanism**, impactful parameters such as **volume synthesis speed**, **voiding interval** and **minimal residual volume**
- Describing *E. coli* **behaviour**, its growth and killing kinetics in **µHFIM experiments**.



Impact of a shift in the urinary parameters on the profiles of fosfomycin urinary concentrations. Residual urinary volume range from 25 to 200 mL (vertical), urinary synthesis range from 1 to 4 L/day (horizontal). Micturition interval range from every 1 to 4 hours (colors)

Scenario	Reported metrics	Predicted metrics
Ciprofloxacin IV 400 mg q12h (urine production 1.5 L/day, 50 mL residual urine, micturition every 4 h)	Cmax: 367 [242–650] mg/L (0–2 h) Cmax: 394 [162–681] mg/L (2–4 h) (Observations corresponding to 500 mg oral) Ref:[6]	Cmax: 480.22 mg/L Tmax: 1.42 h
Nitrofurantoin 100 mg q12h (urine production 2 L/day, 50 mL residual urine, micturition every 4 h)	AUC: 943.49 [228.2–2212.0] mg·h/L Cmax: 94.1 [40.1–209.4] mg/L Tmax: 5.1 [3.3–5.5] h Ref:[8]	AUC: 1084 mg·h/L Cmax: 63.8 mg/L Tmax: 4.5 h
Nitrofurantoin 50 mg q6h (urine production 2 L/day, 50 mL residual urine, micturition every 4 h)	AUC: 855.95 [378.6–2098.9] mg·h/L Cmax: 94.4 [26.8–176.3] mg/L Tmax: 6.8 [1.8–8.1] h Ref:[8]	AUC: 1076 mg·h/L Cmax: 49.1 mg/L Tmax: 4.5 h
Fosfomycin 8 g q8h (urine production 1.5 L/day, 50 mL residual urine, micturition every 4 h)	Cmax: 17.4 [9.1–23.6] g/L Tmax: 2 h (Digitalised values from plot) Ref:[7]	Cmax: 21.63 g/L Tmax: 1.68 h

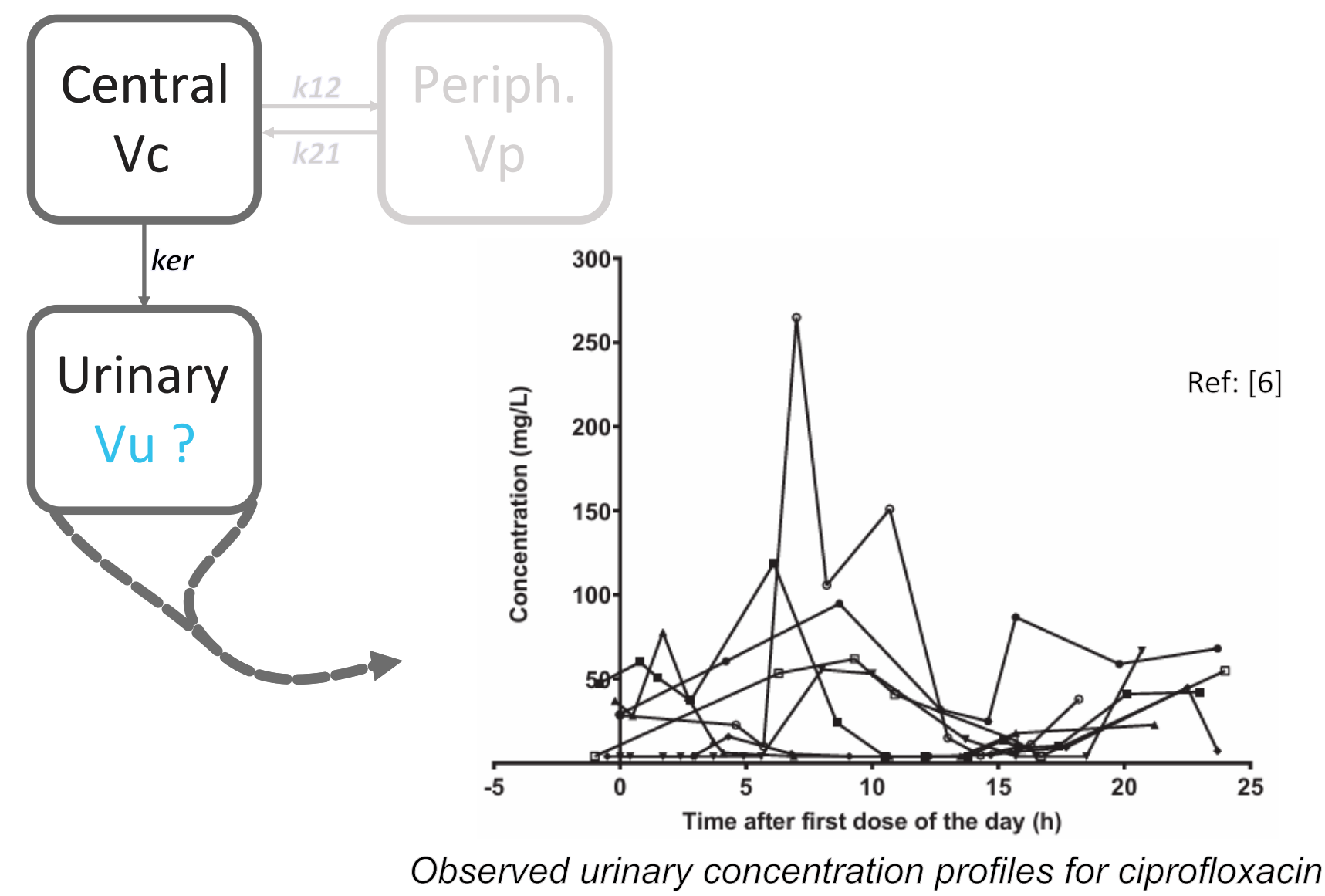
On a clinical side:

Increased urine production accelerates urinary drug dilution.
Incomplete bladder emptying attenuates magnitude of urinary concentrations.
Longer urinary retention promotes drug accumulation and increases overall urinary exposure rather than maximal concentration.

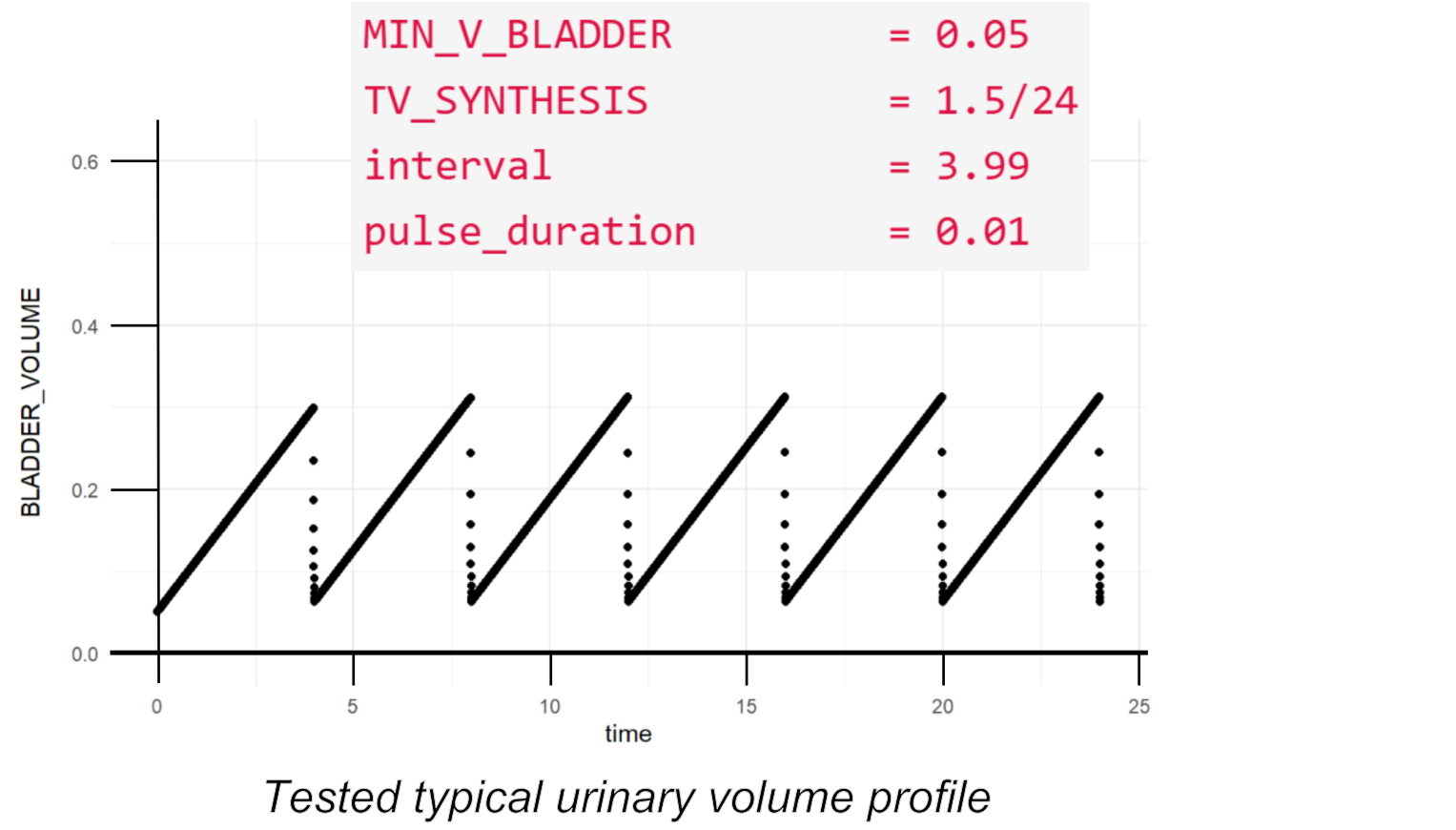
How to **balance** out **drug exposure** and **bacterial flushing**?

Sensitivity and summary metrics comparison analysis

Typical profile method



Published PK models or NCA [4,5] provide **plasma profiles** and **renally excreted amount/fraction** in patients, while **urine volume** show **high variability**, and **reliable literature** data for urinary concentrations **is lacking**

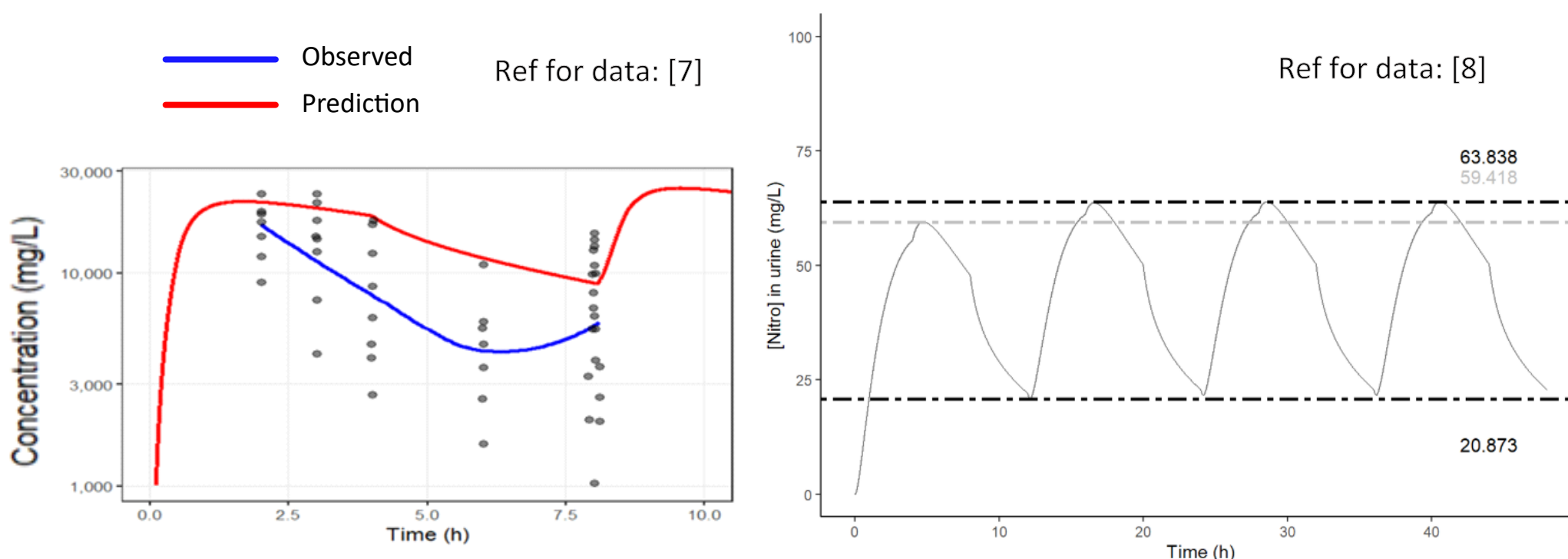


$\text{dxdt_BLADDER} = \text{ker} \cdot \text{CENT} - \text{k_purge} \cdot \text{BLADDER} \cdot (\text{BLADDER_VOLUME} - \text{MIN_V_BLADDER}) / \text{BLADDER_VOLUME};$
 $\text{dxdt_BLADDER_VOLUME} = \text{ksyn} - \text{k_purge} \cdot (\text{BLADDER_VOLUME} - \text{MIN_V_BLADDER});$

A priori or **informed parameter values** describing volume synthesis speed, voiding interval and minimal residual volume, were used to simulate urine filling cycle.

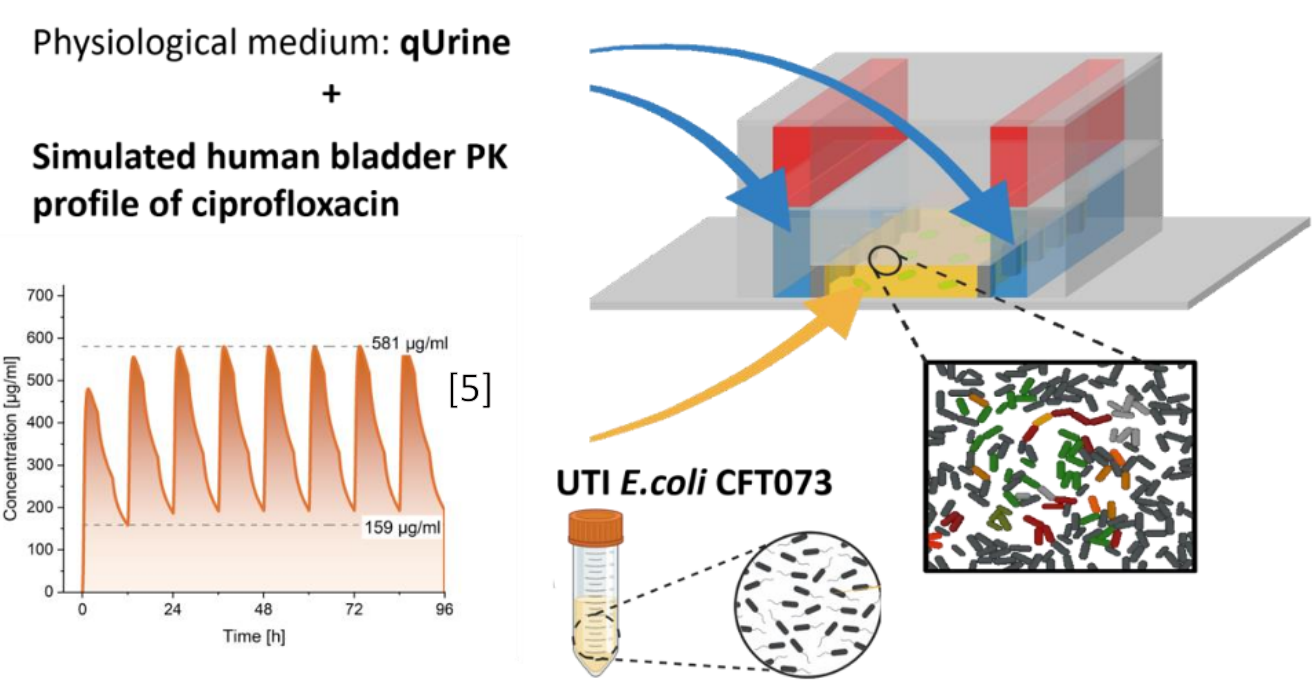
```
if(NEWIND <= 1 || EVID==55) {  
  self.mevent( TIME + interval, 44);  
  self.mevent( TIME + interval + pulse_duration, 55);  
  double k_purge = 0;  
}  
if(EVID==44) k_purge = 300;
```

acknowledgment: Kyle Baron



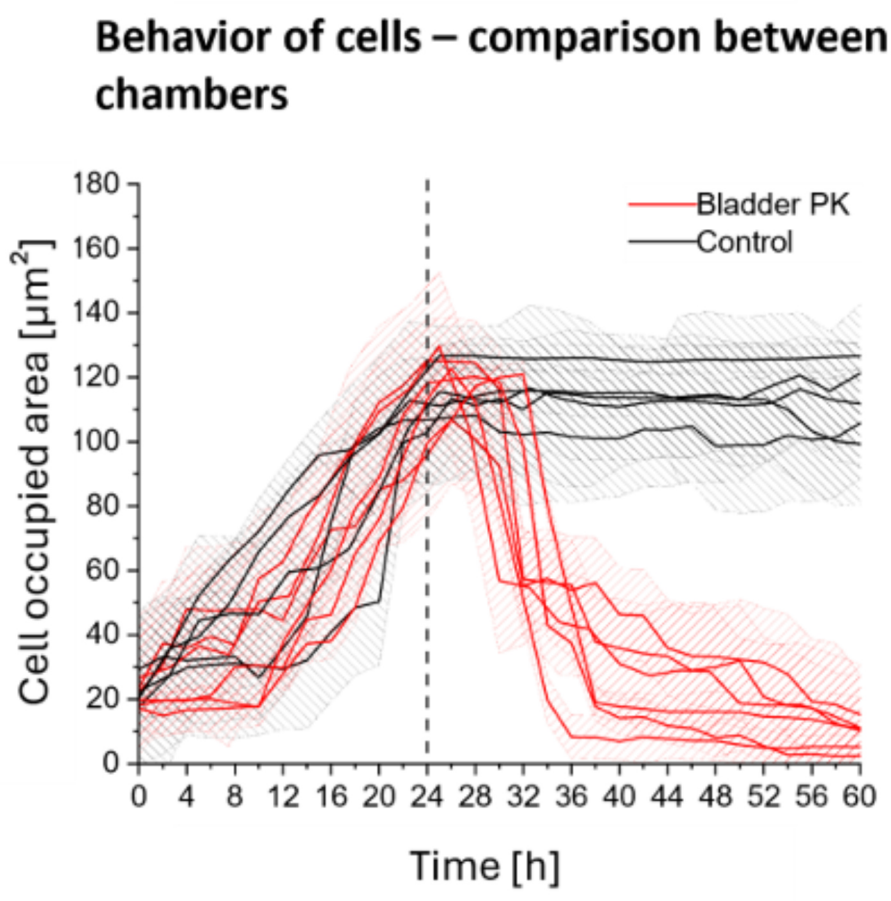
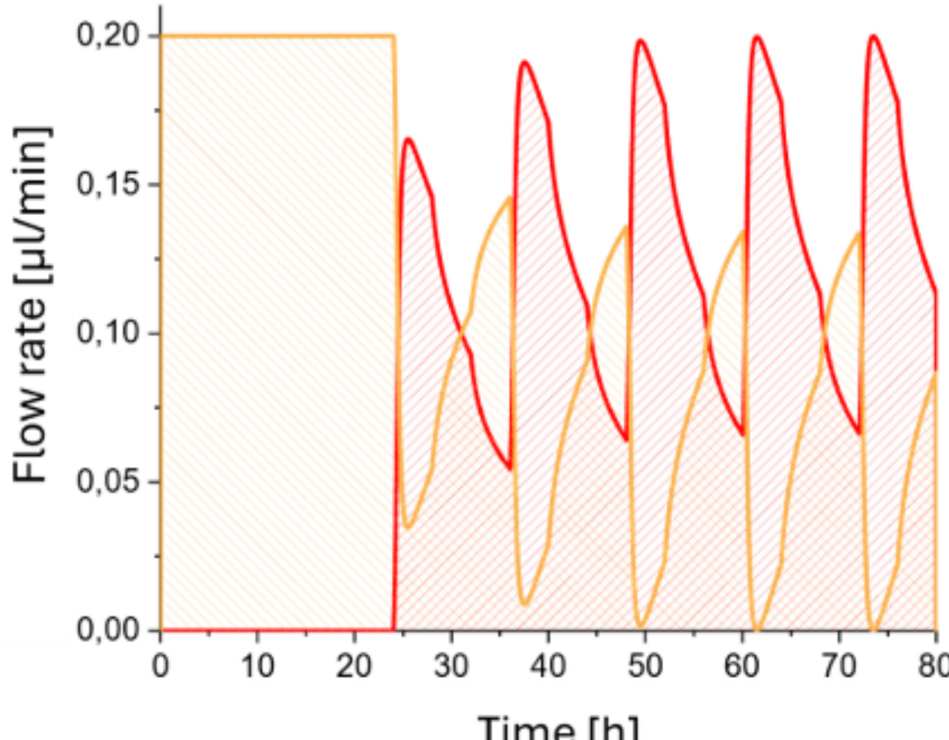
Partial voiding cycle for urine and drug in urine were used to simulate typical profiles

Microfluidic-based hollow fiber (µHFIM) [4]



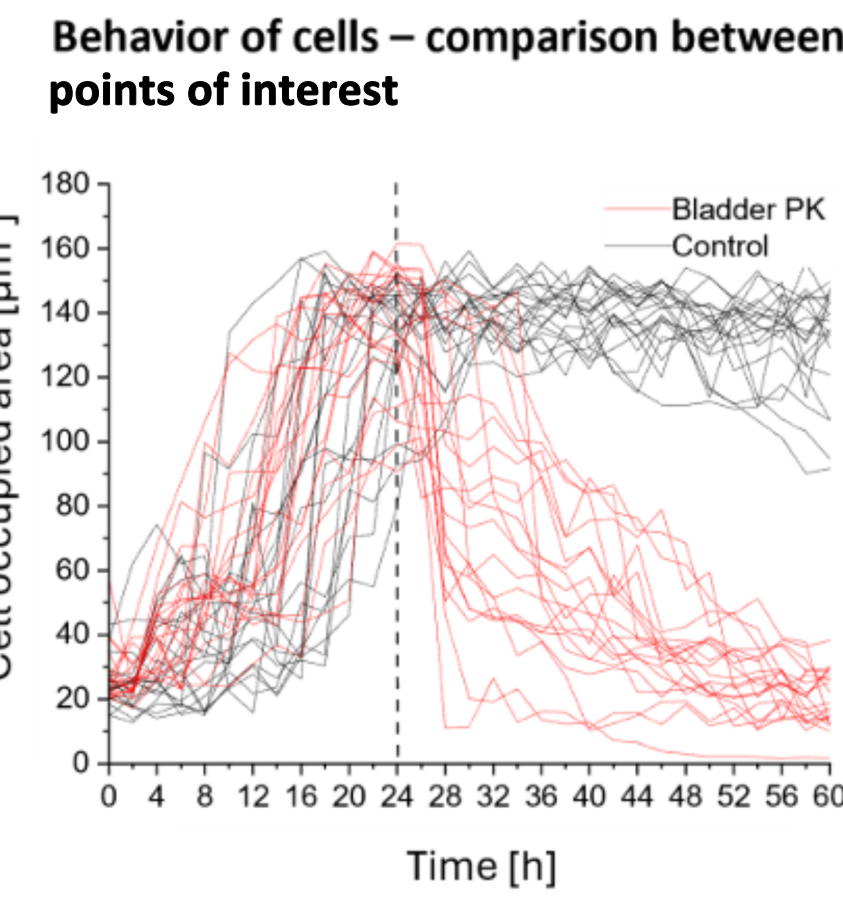
The **µHFIM** combines precise **fluidic control** with a tissue-mimicking **growth environment** and high-resolution time lapse **microscopy** in a compact setup.

Time-varying antibiotic concentrations are continuously supplied through adjacent side channels without washing out the bacteria, allowing the realistic simulation of **complex pharmacokinetic profiles** over several days.



Simulated profiles are used in **microfluidic-based hollow fiber** to evaluate bacteria growth and drug efficacy in **physiologically-relevant concentration ranges** using synthetic urine as media (qUrine)

The **high concentration** exposure of ciprofloxacin in synthetic urine, compared to plasma, **exhibited rapid and pronounced bacterial killing** with no regrowth, whereas the untreated control showed growth throughout the experiment.



This **simulation framework** shows potential for predicting urinary concentration profiles by integrating urine synthesis rate, residual urinary volume, and micturition interval with published pharmacokinetic data.

Mimicking the profile in an experimental setting demonstrated the **suitability of axenic models** for **replicating complex drug profiles** and showed that **in vivo urinary persistence is unlikely to be solely attributable to insufficient drug exposure in urine itself**.

This work lays the groundwork for **investigating bacterial persistence and translatability of bladder-mimicking in vitro experiments**.

Work is already going **further**, aiming to:

- Compare** the results in µHFIM to hollow-fiber model.
- Build up** on this work to **design experiments** in bladder-mimicking **tissue** model.
- Characterise** the **relevance of urine and plasma PK** on bacterial persistency in UTIs.

List of references

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