

# Individualized approaches to infection management

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# Individualized approaches to infection management

## Declaration

- No conflicts to declare

# Individualized antimicrobial therapy

- Challenges
  - Antimicrobial biosensors
  - Closed loop control & artificial intelligence
  - New PK-PD targets
  - Deployment in low resource settings
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# Dosing is a dynamic process

Race

Weight

Age

Gender



Medications

Comorbidities

**Inter-individual variability**

Circulatory  
changes

Organ support

Renal failure

Hepatic  
dysfunction

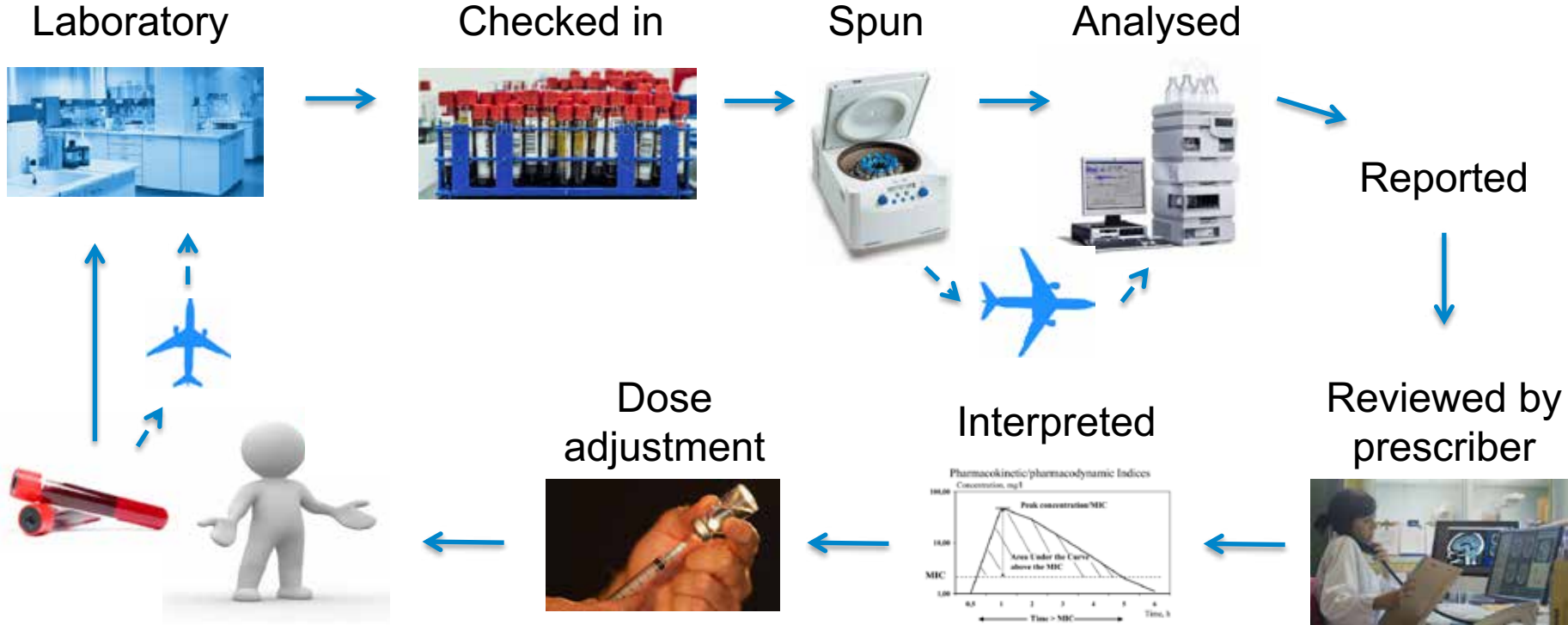


Clearance

Fluid balance

**Intra-individual variability**

# Current approach to drug monitoring



# Challenges with drug monitoring

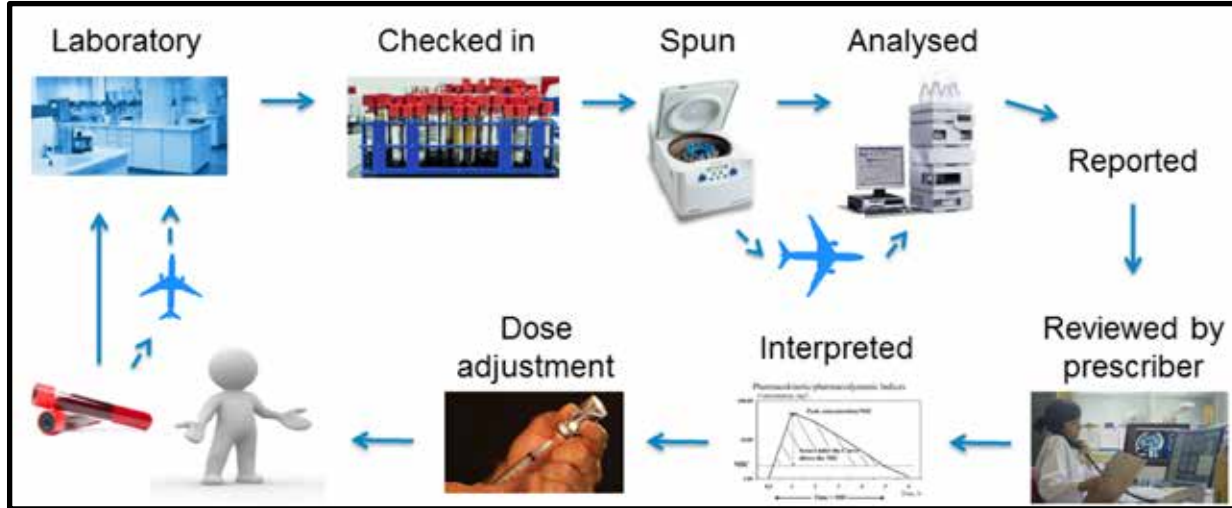
**Risk of exposure  
to HCW's**

**Valid assay**

**Stability of  
drug**

**Equipment /  
staff costs**

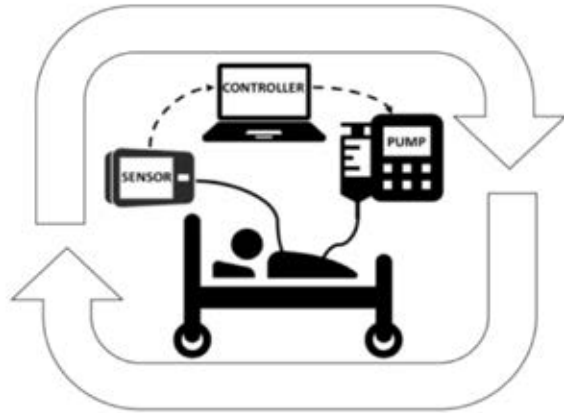
**Timing  
samples**



**Population level  
estimates**

**Expertise to  
interpret**

# Can technology improve the way we dose antibiotics?



## Closed-loop control for precision antimicrobial delivery.

Already validated in diabetes control through individualised insulin delivery and anaesthesia control intra-operatively

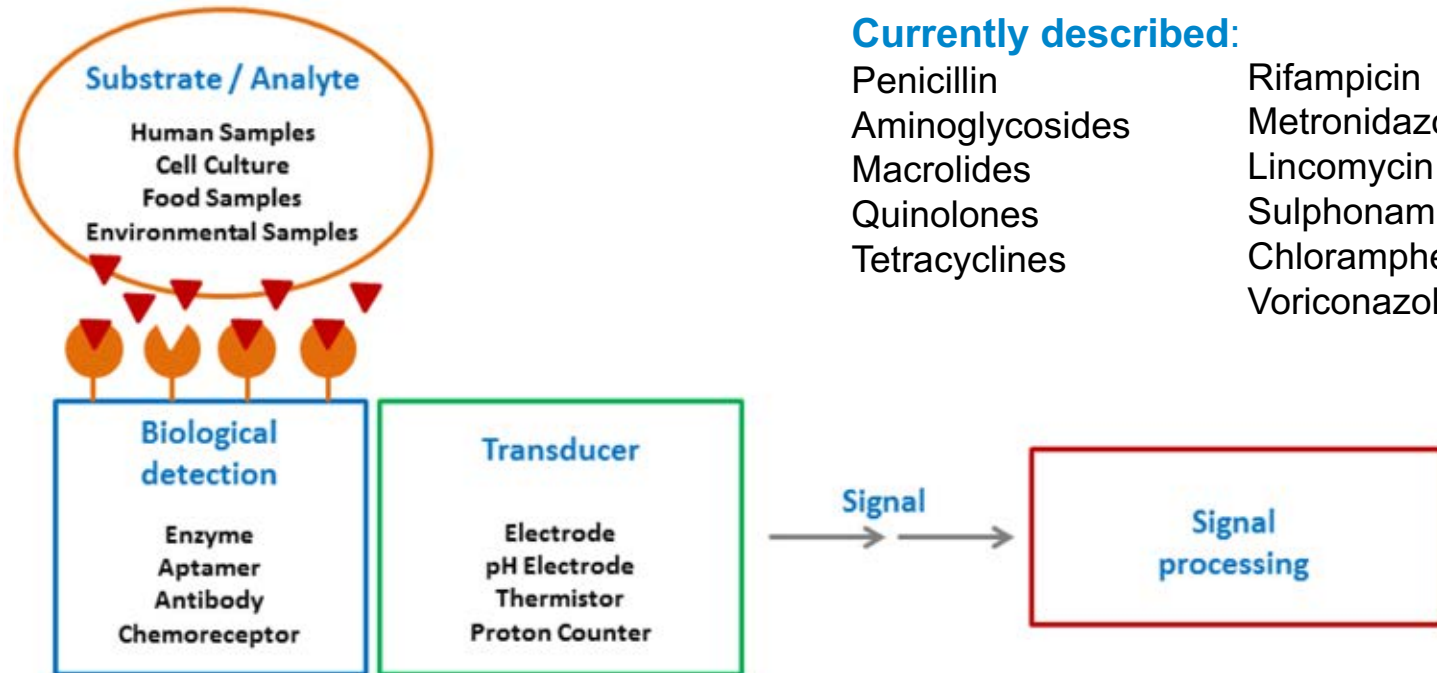
## Improved methods for drug monitoring required



Minimally invasive  
Point-of-care  
Continuous monitoring  
Broad range of agents



# Electrochemical Biosensors



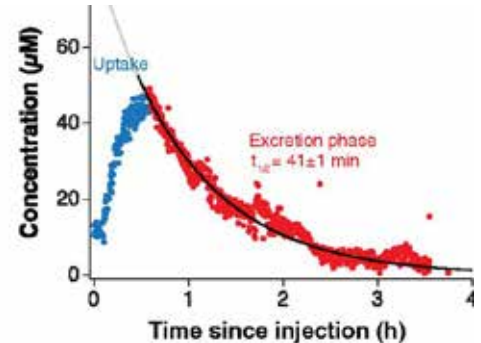
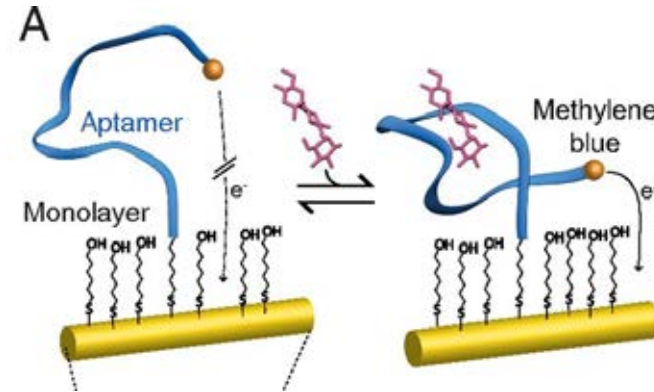
## Currently described:

|                 |                 |
|-----------------|-----------------|
| Penicillin      | Rifampicin      |
| Aminoglycosides | Metronidazole   |
| Macrolides      | Lincomycin      |
| Quinolones      | Sulphonamides   |
| Tetracyclines   | Chloramphenicol |
|                 | Voriconazole    |



# Invasive drug monitoring

- Aptamer biosensor
- Central venous insertion
- Monitor in ambulatory animals
- Potentially calibrationless
- Challenges:
  - Acceptability outside of ICU
  - Venous thrombosis
  - Bleeding

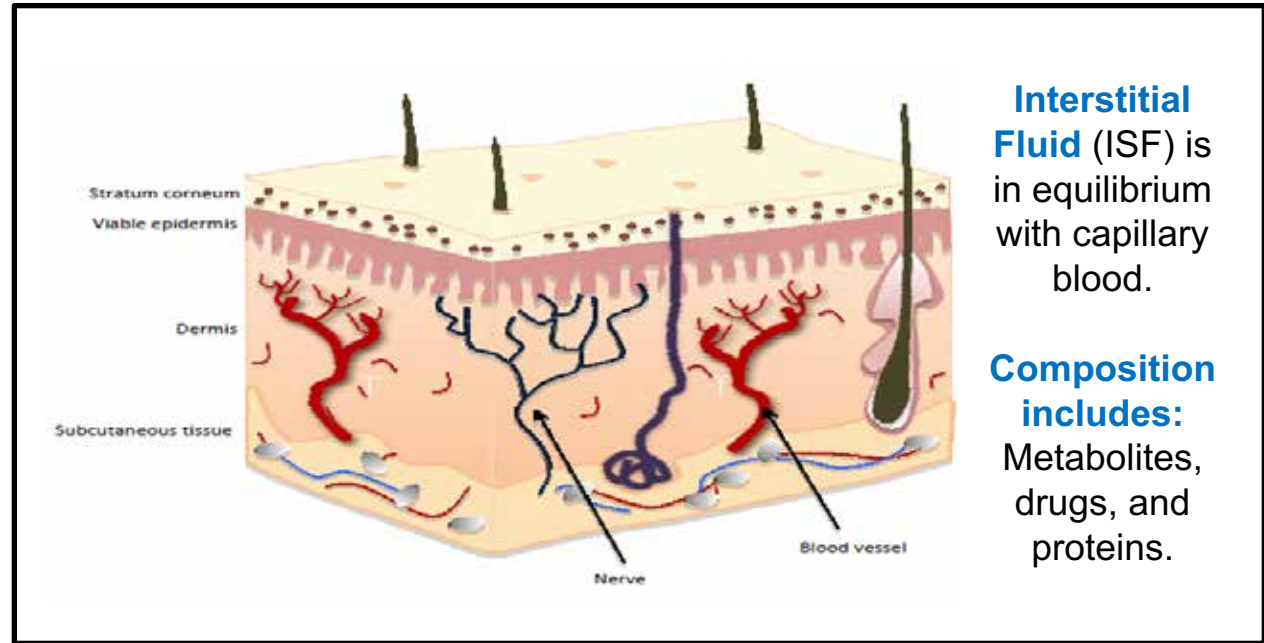
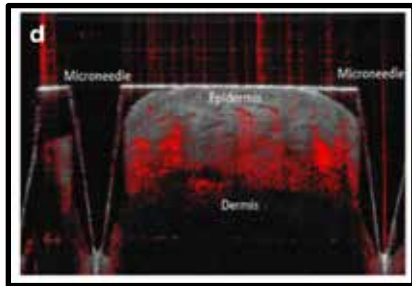


Figures from Arroyo-Currás et al, PNAS; 2017

# Minimally invasive monitoring



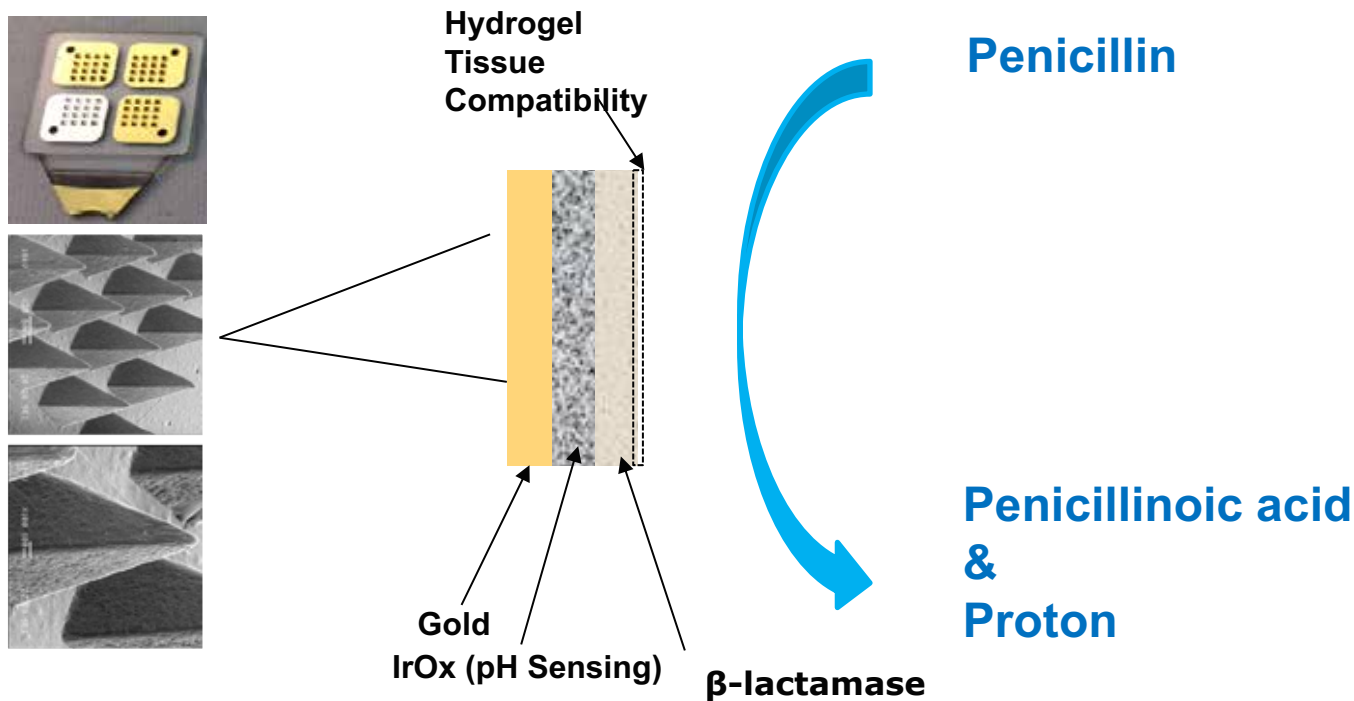
*Microneedle array*



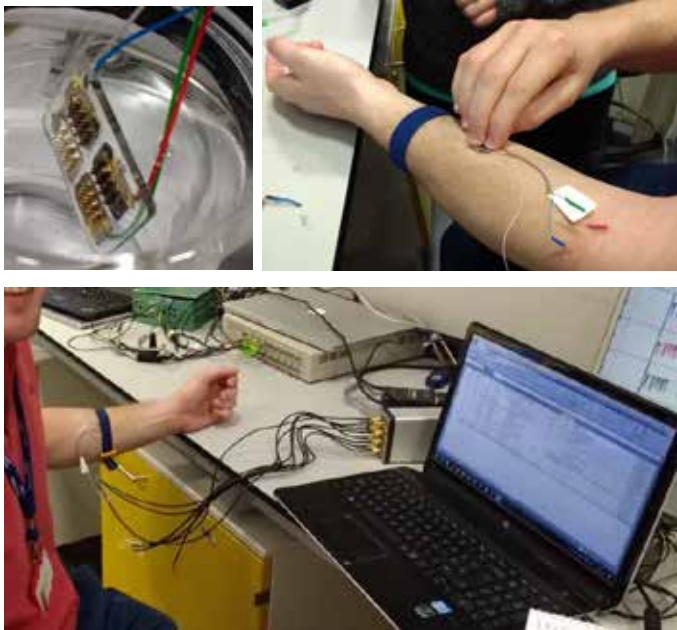
**Interstitial Fluid (ISF)** is in equilibrium with capillary blood.

**Composition includes:**  
Metabolites, drugs, and proteins.

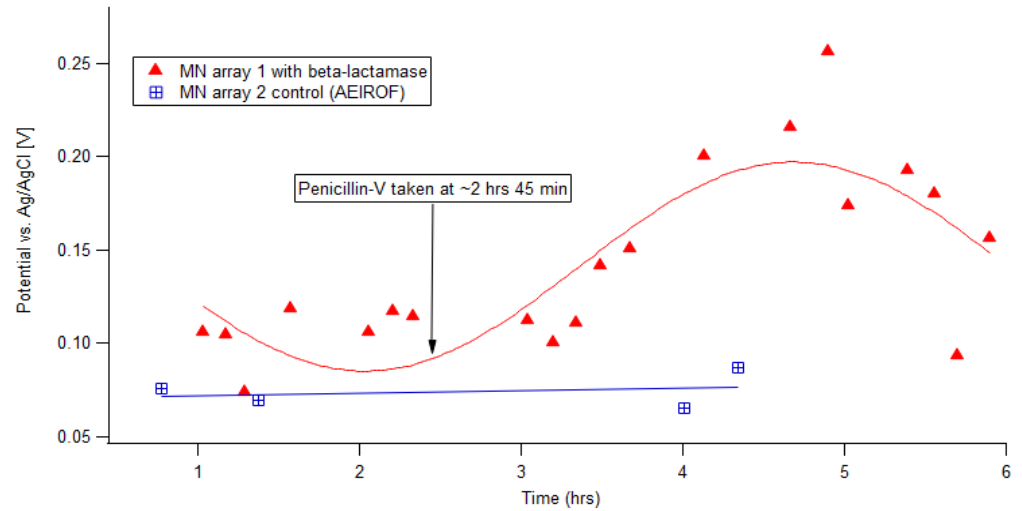
# Microneedle based sensing



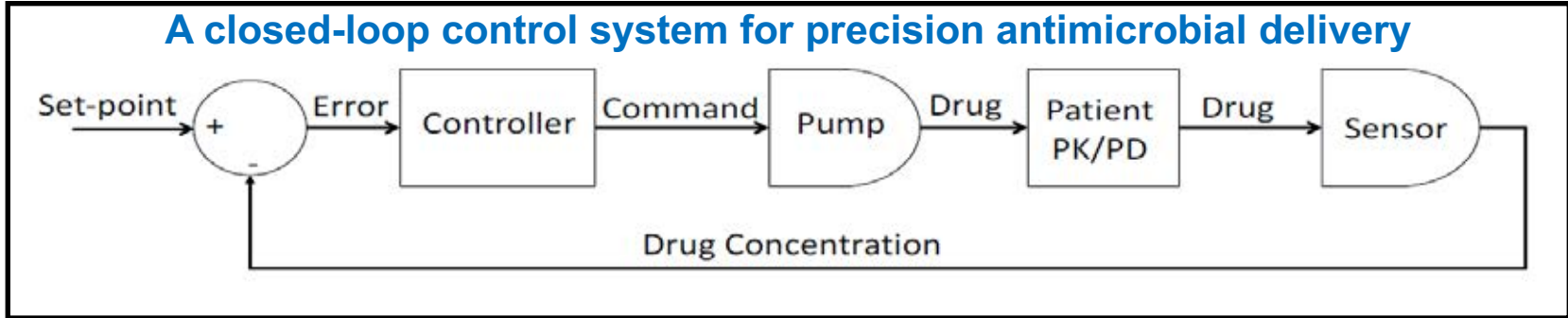
# In-vivo monitoring



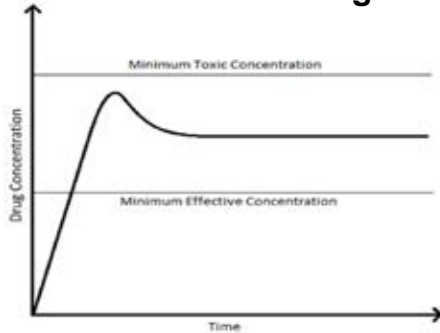
### *In-vivo* results during penicillin-V dosing



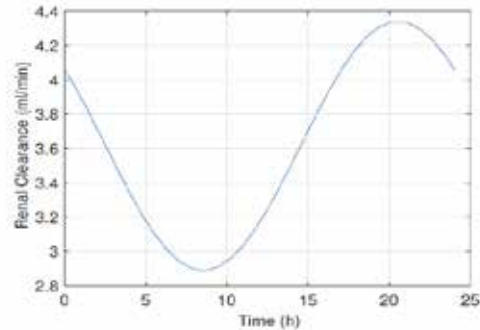
# Closed-loop control



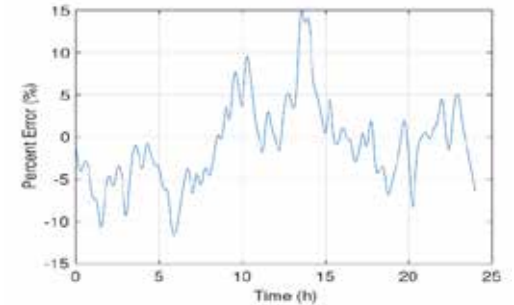
**Define PK-PD target**



**Variation in CL**

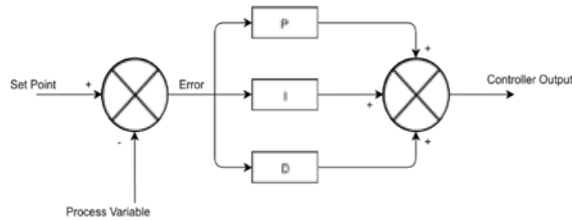


**Sensor error**

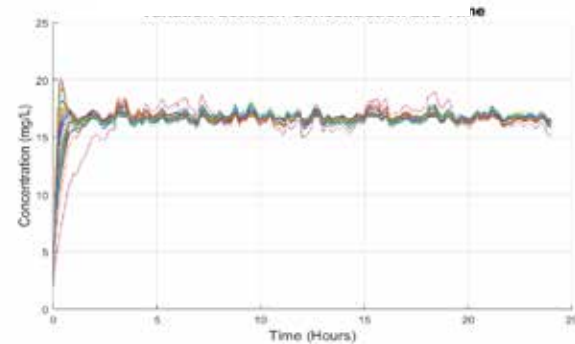


# Closed-loop control

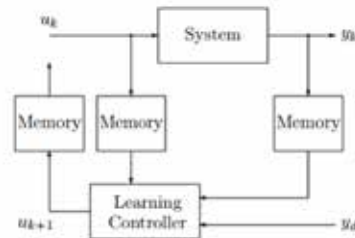
## Continuous infusions – PID controller



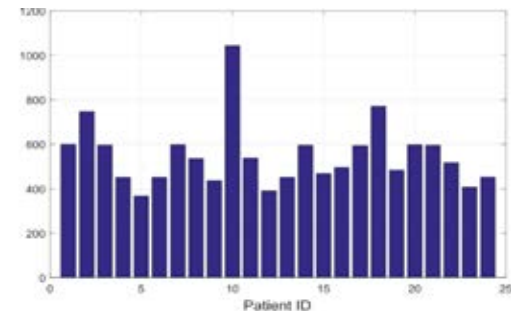
$$PID \text{ Controller Output} = K_p * Error + K_d * \frac{dError}{dt} + K_i * \int Error$$



## Intermittent infusions – ILC controller



$$ILC \text{ Output} = U_{k+1}(t) = U_k(t) + \gamma e_k(t+1)$$



# Intelligent use of data

## *Patient level data*

Individual rich PK data from biosensors

Individual patient electronic health records

Individual patient microbiology records

## *Pooled data*

Pooling of data centrally with bio-bank data

## *Analytics*

Application of machine / supervised machine learning

Population PK modelling

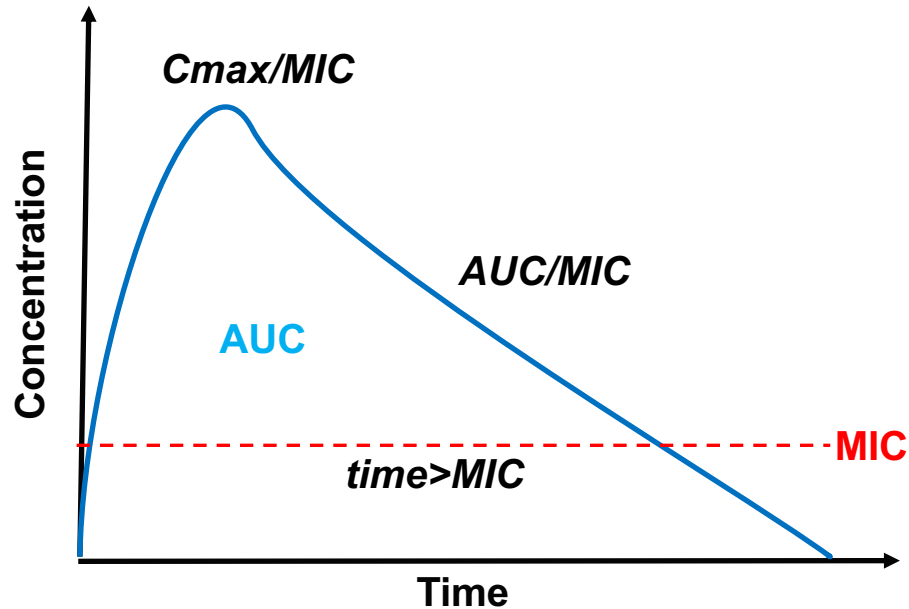
## *Informing practice*

Individualised dosing recommendations

Extrapolation to settings with limited supporting evidence

Holistic understanding of appropriate therapy

# PK-PD targets for therapy



## MIC gold standard

- *In-vitro*, static measure
- Ignores host factors

Use in empirical therapy?

Link with rapid diagnostics?

## Are there alternatives?

- Kill curves
- $AUC:EC_{50}$



# Low resource settings



# Summary

- (Dynamic) dose optimization important consideration of appropriate antimicrobial therapy.
  - Current approaches have a number of problems.
  - Technology offers a new frontier to improve antimicrobial drug monitoring.
  - Development must focus on acceptability across care settings.
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# Acknowledgements



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