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Real-time antimicrobial sensing – closing the loop on precision antimicrobial therapy

28th European Congress of Clinical Microbiology and Infectious Diseases, Madrid, Spain

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Real time monitoring and closed-loop control

Declaration

- No conflicts to declare

Individualized antimicrobial therapy

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- Challenges
- Antimicrobial biosensors
- Closed loop control
- New PK-PD targets
- Integrated systems

Dosing is a dynamic process

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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

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Laboratory

Checked in

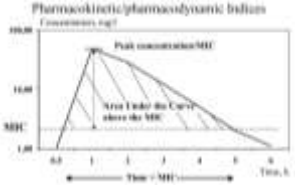
Spun

Analysed

Reported

Reviewed by prescriber

Interpreted



Dose adjustment

Challenges with drug monitoring

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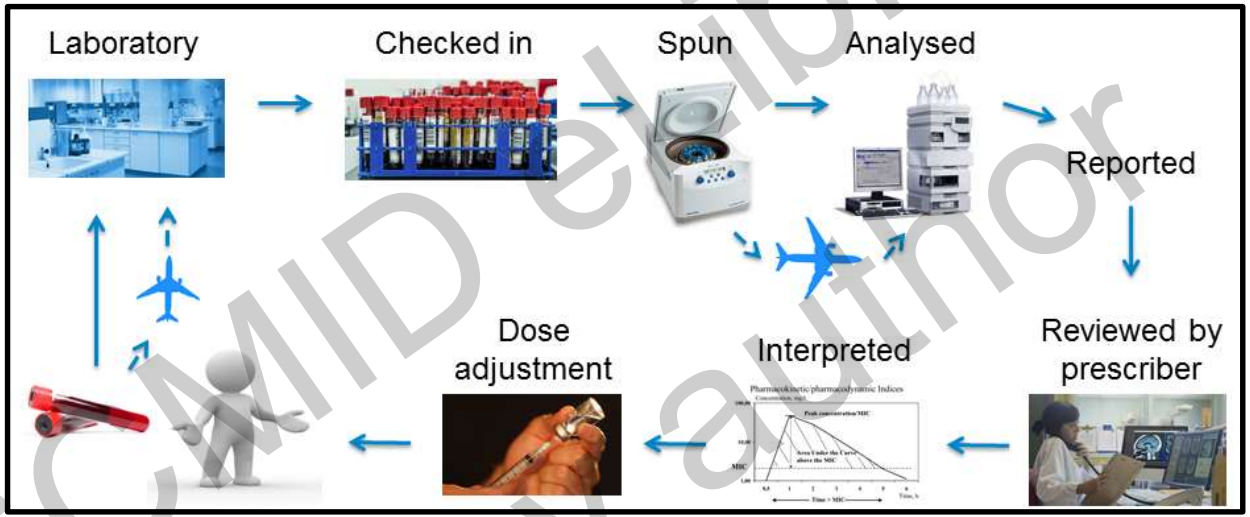
Risk of exposure to HCW's

Valid assay

Stability of drug



Equipment / staff costs

Timing samples

Delays in reporting

Population level estimates

Expertise to interpret

Can technology improve the way we dose antibiotics?

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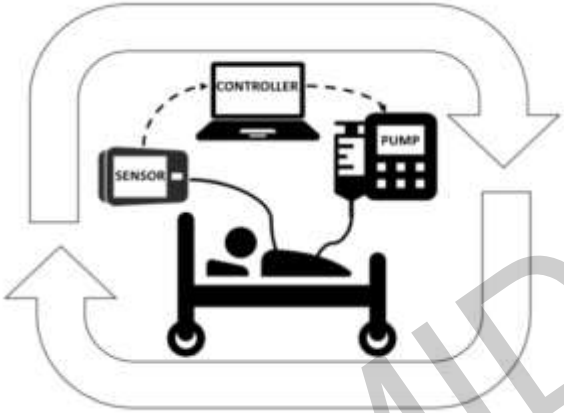

Closed-loop control for precision antimicrobial delivery.

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

Rawson, O'Hare, et al, JAC; 2018

Electrochemical Biosensors

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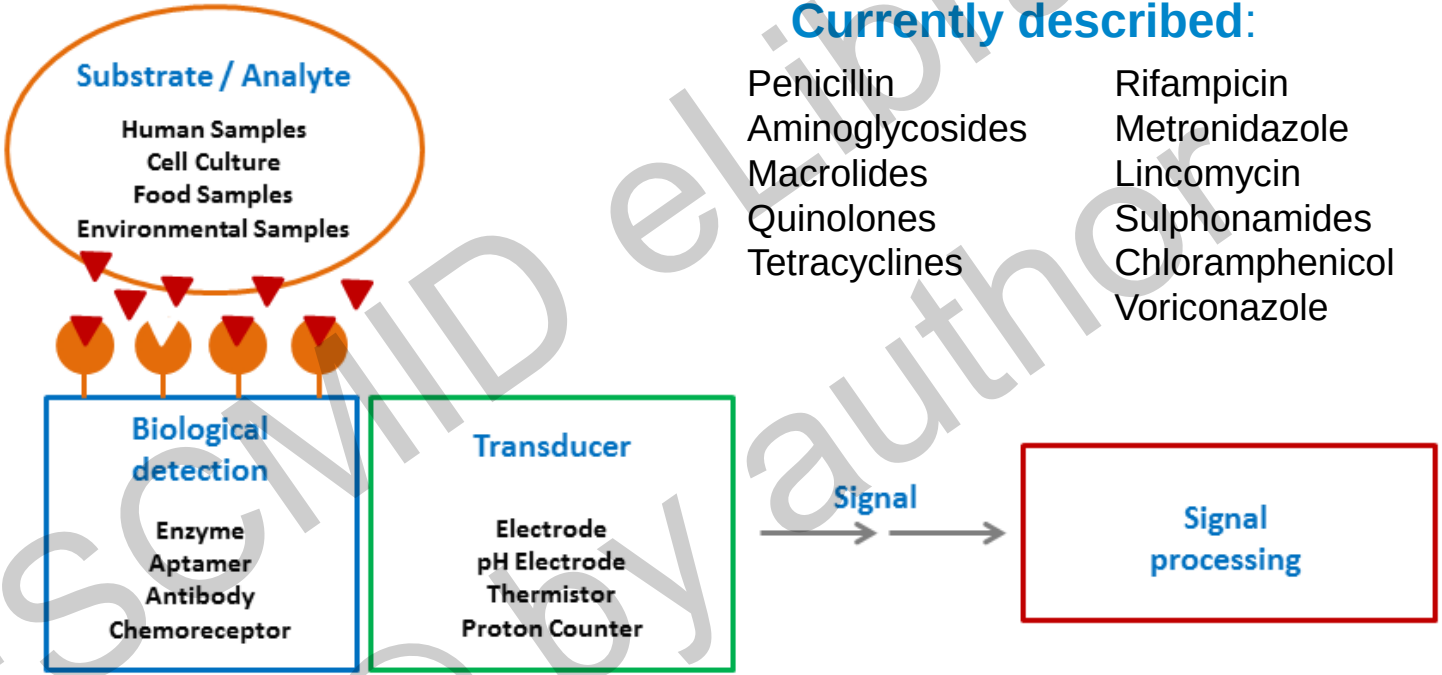

Currently described:

Penicillin
Aminoglycosides
Macrolides
Quinolones
Tetracyclines
Rifampicin
Metronidazole
Lincomycin
Sulphonamides
Chloramphenicol
Voriconazole

Rawson, O'Hare et al, JAC; 2018

Aptamer biosensors

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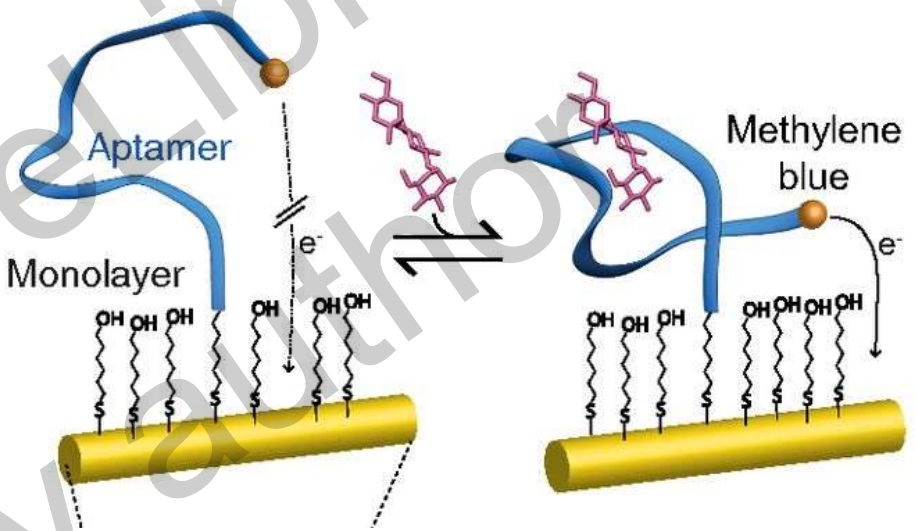
- Single stranded DNA or RNA sequences
- Bind to specific target molecules
- Selected by *systematic evolution of ligands by exponential enrichment* (**SELEX**)



Invasive drug monitoring

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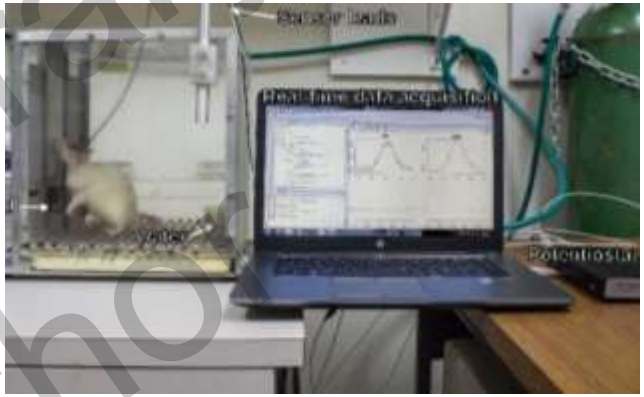
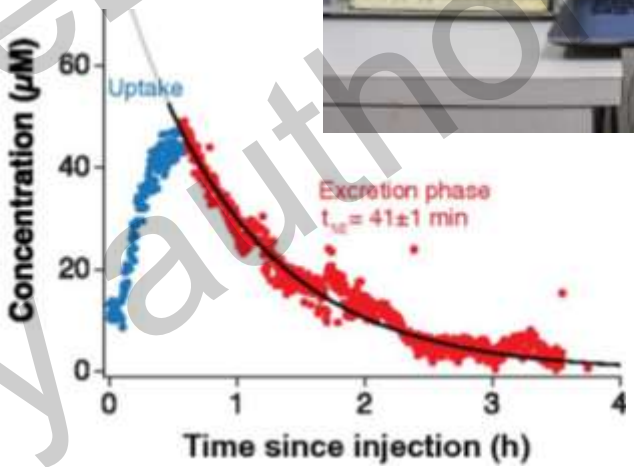
- Aptamer biosensor
- Central venous insertion
- Monitor in ambulatory animals
- Challenges:
  - Acceptability outside of ICU
  - Venous thrombosis
  - Bleeding





Figures from Arroyo-Currás et al, PNAS; 2017

Arroyo-Currás et al, PNAS; 2017, Ferguson et al, Sci Trans Med; 2013

Minimally invasive monitoring

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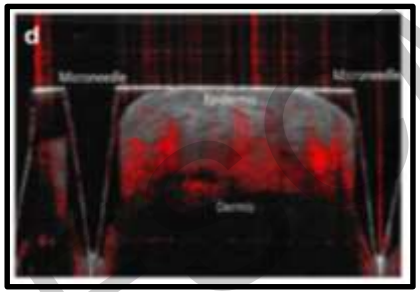
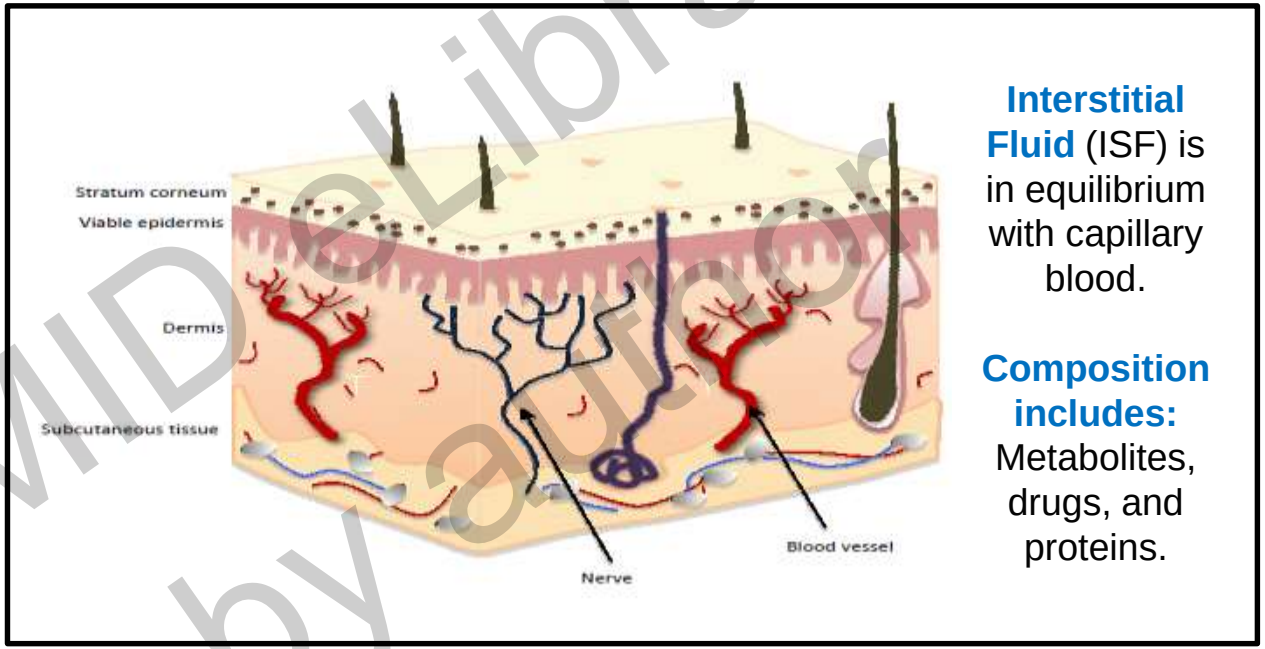
Microneedle array





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

Composition includes: Metabolites, drugs, and proteins.

Rawson, O'Hare et al, JAC; 2018; Rawson, Sharma et al, Electrochem Comms; 2017

Microneedle based sensing

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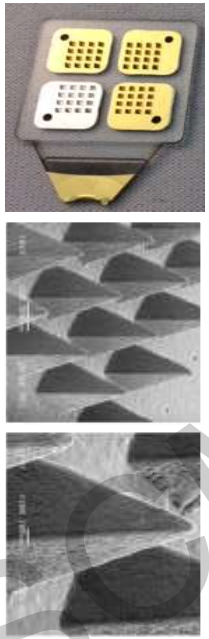

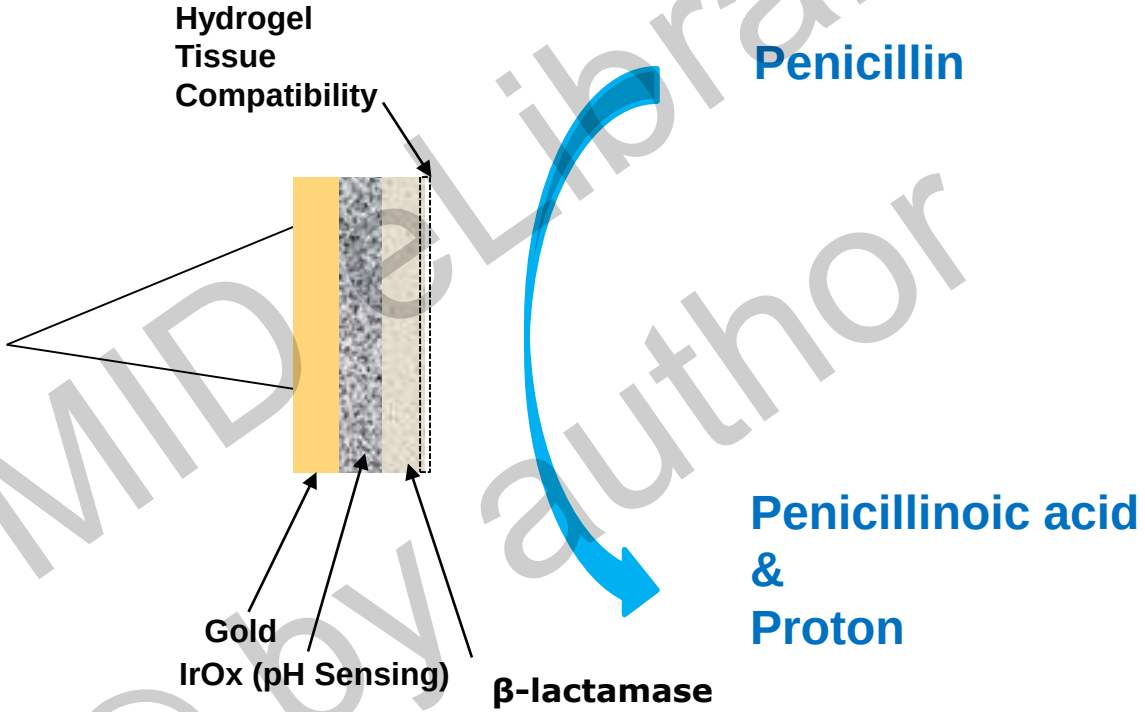

Rawson, Sharma et al. Electrochemistry Communications; 2017

In-vivo monitoring

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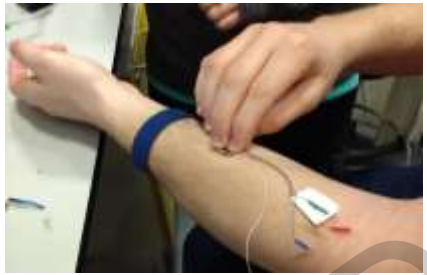
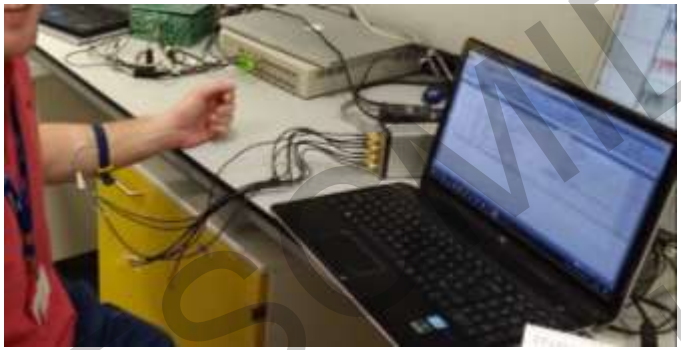
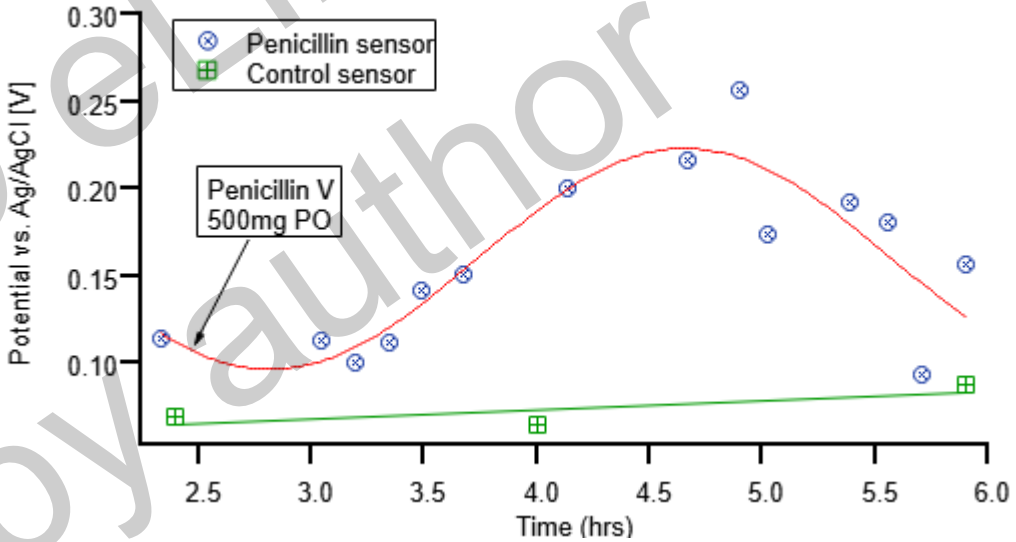




***In-vivo* results during penicillin-V dosing**



Rawson, et al, 2018

MISBLA study – April 2018

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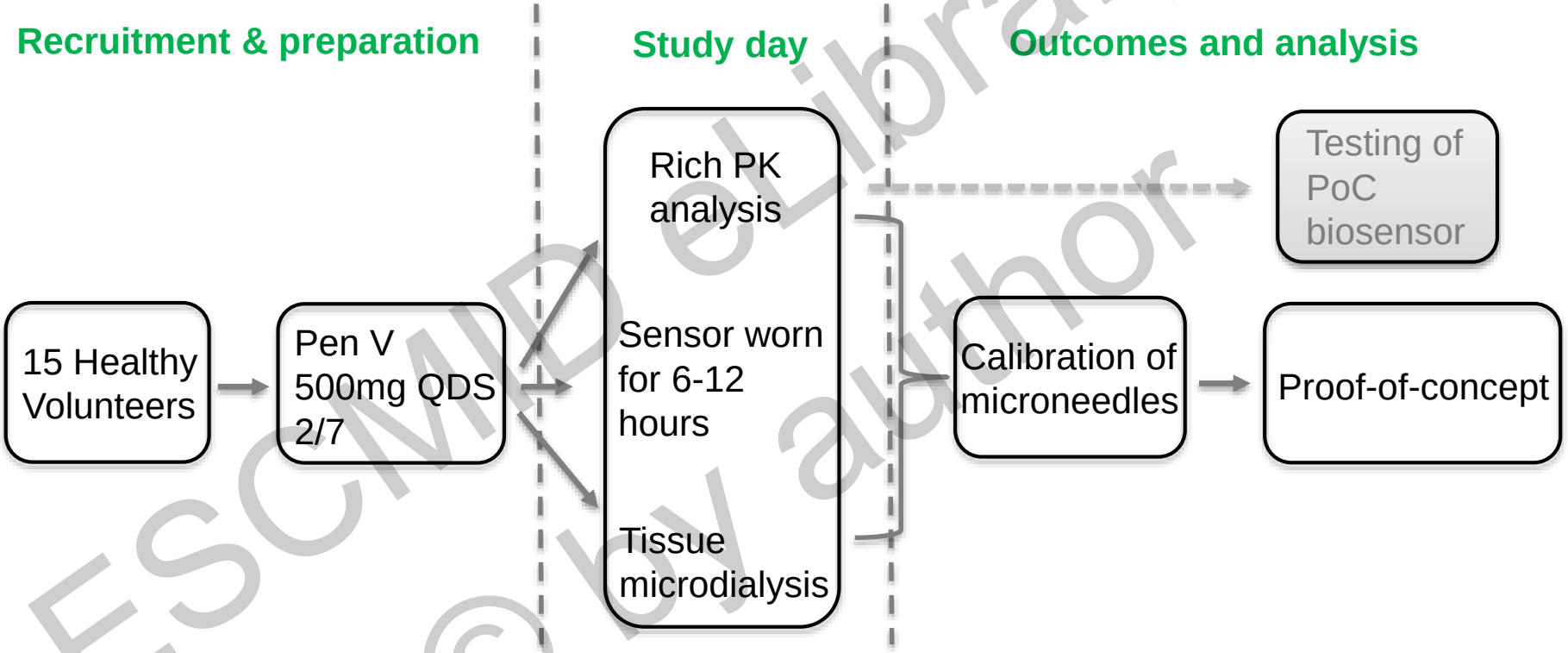

Closed-loop control

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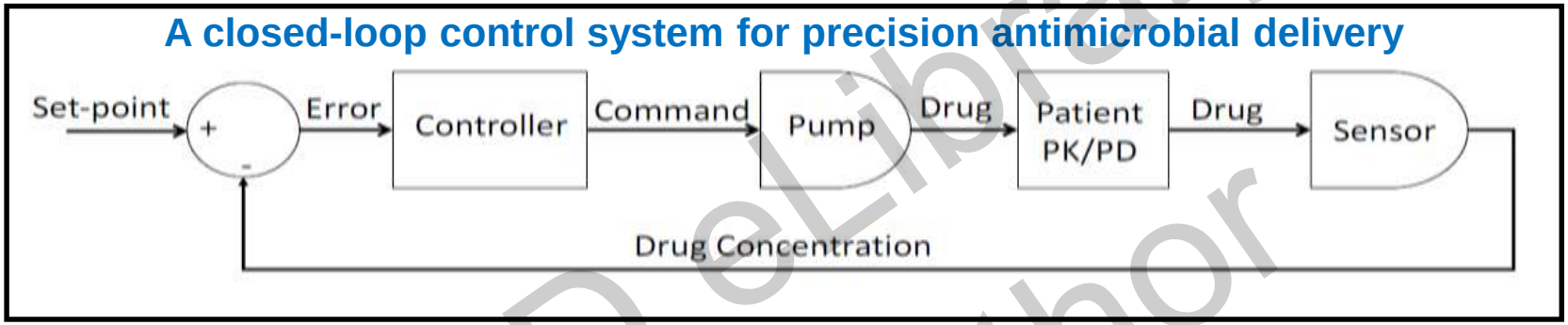
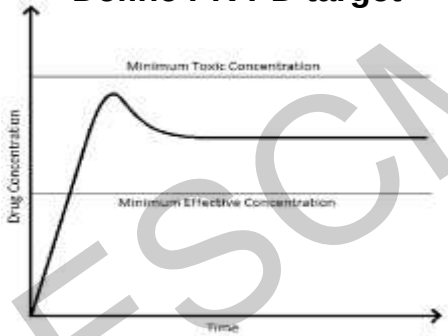
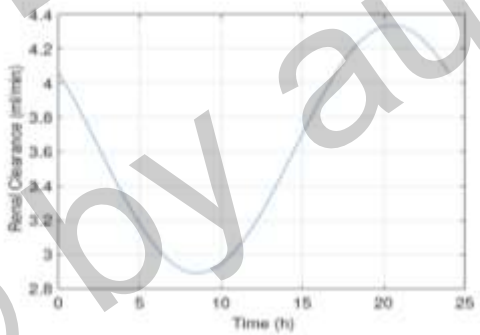


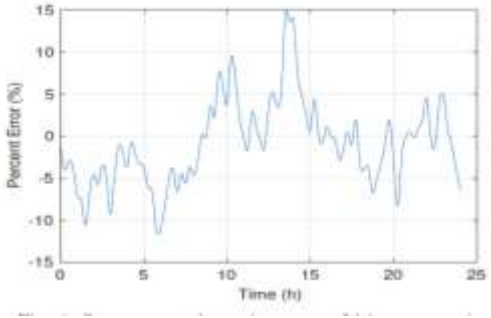
Define PK-PD target



Variation in CL



Sensor error



Rawson, O'Hare, et al. JAC; 2018; Herrero, Rawson, et al. TBME; 2017; Phillip, Rawson, et al; JHI (Supp 1); 2016

Closed-loop control

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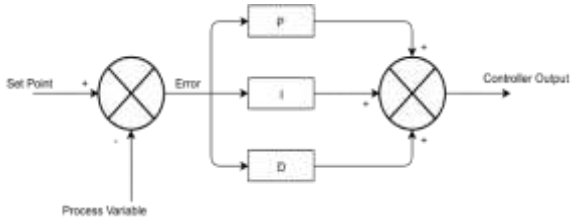
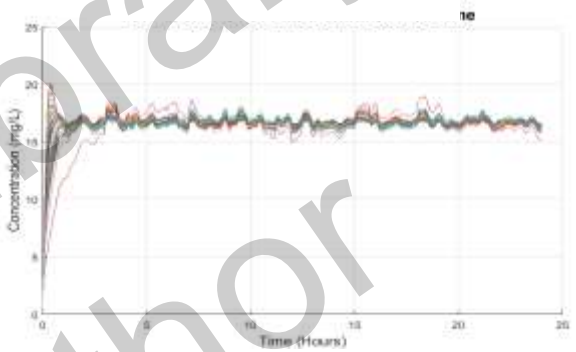
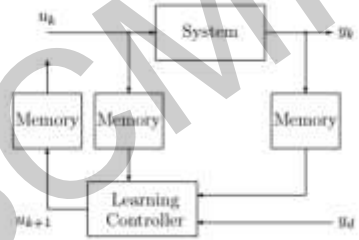
Continuous infusions – PID controller



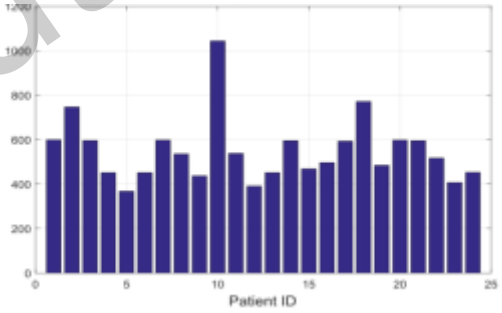
$$PID\ Controller\ Output\ = Kp * Error + Kd * \frac{dError}{dt} + Ki * \int Error$$



Intermittent infusions – ILC controller



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



Rawson, O'Hare, et al. JAC; 2018; Herrero, Rawson, et al. TBME; 2017; Phillip, Rawson, et al; JHI (Supp 1); 2016

PK-PD targets for therapy

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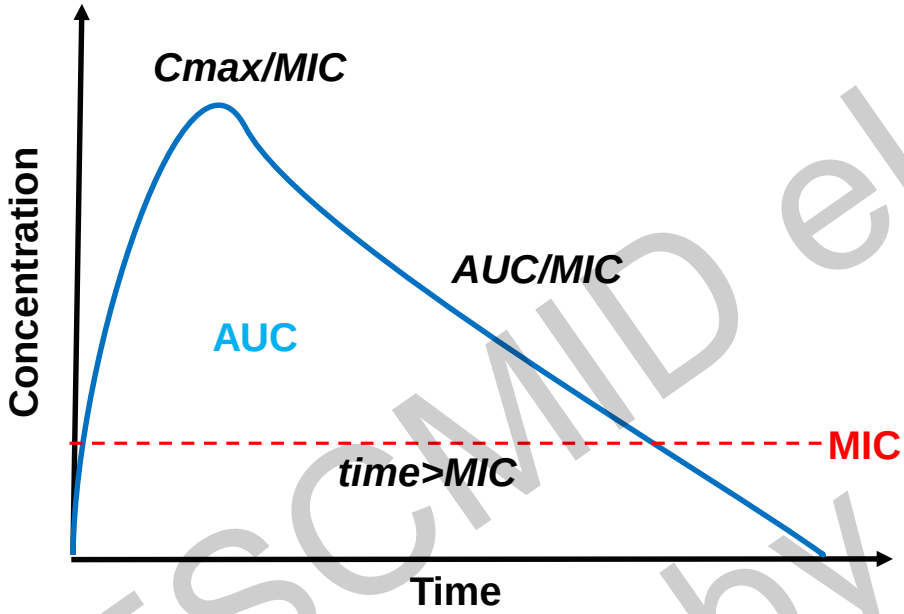

MIC gold standard

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

Use in empirical therapy?

Link with rapid diagnostics?

Are there alternatives / adjuncts?

- Kill curves
- AUC:EC_{50}

Mueller et al, AAC 2004; Ramos-Martin et al, JAC 2016; Rawson et al, TDM 2018

Can CRP predict vancomycin PD?

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Vancomycin PK

$$\frac{dX(1)}{dt} = R(1) + X(2) \cdot Kpc - X(1) \cdot \left(\frac{SCL}{V}\right) - X(1) \cdot Kcp$$

$$\frac{dX(2)}{dt} = X(1) \cdot Kcp - X(2) \cdot Kpc$$

C-reactive protein

$$\frac{dX(3)}{dt} = \left(KCRPp \cdot X(3) \cdot \left[1 - \frac{X(3)}{POPmax}\right]\right) - \left(\frac{KCRPi \cdot X(3) \cdot \left[\frac{X(1)}{V}\right]^H}{EC50^H \cdot \left[\frac{X(1)}{V}\right]^H}\right)$$

Pmetrics™

Individual AUC:EC$_{50}$

- Potential to provide *in-vivo* host and organism response data.
- May be useful adjunct to MIC
- Role during empirical phase for truly individualised therapy?
- Role of other markers, such as procalcitonin?

Ramos-Martin, et al. JAC; 2016, Rawson, Charani et al, TDM; 2018

Intelligent use of data

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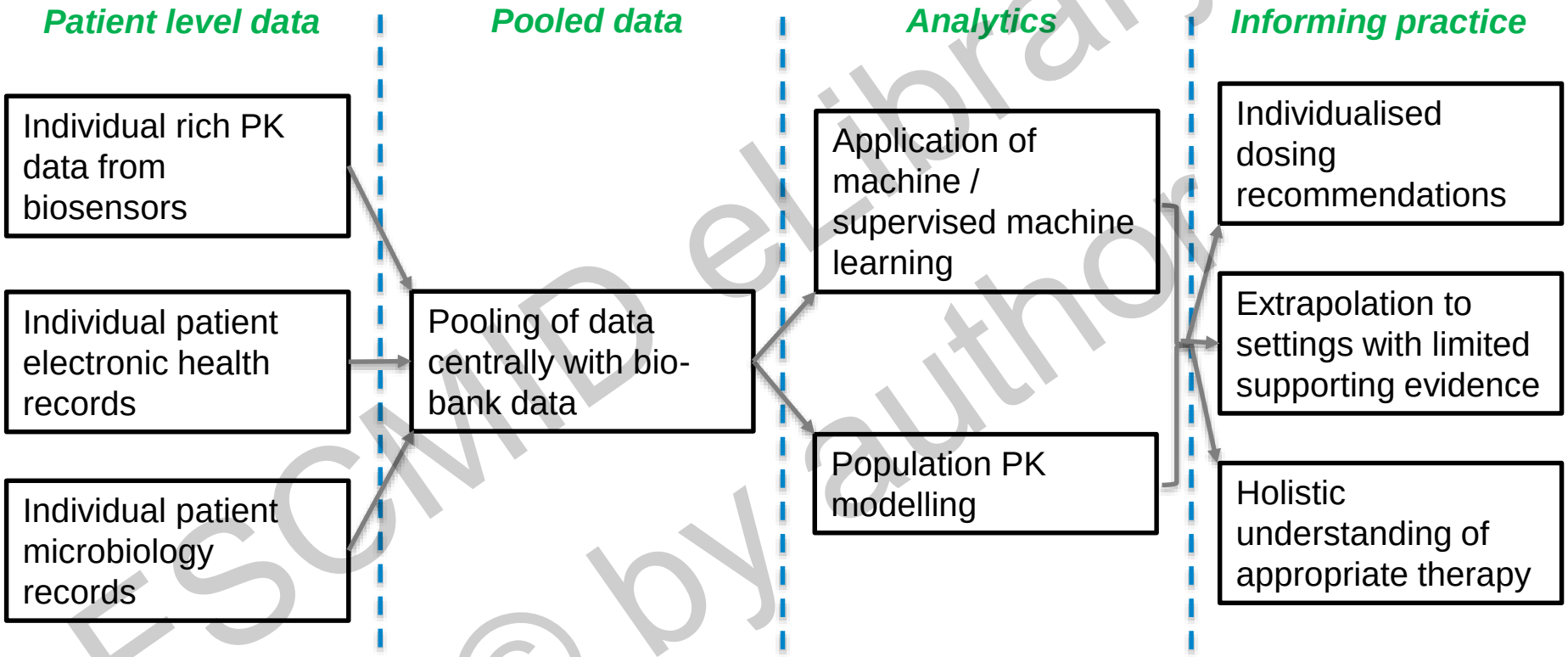

Integrated platforms

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Requirements

- Low cost
- Low power
- Ease of use
- Integrated with other CDSS
- Low maintenance
- Reliable / Valid

Integrated dose optimization platforms

Deliverables

- Dynamic dosing
- Multiple compartments
- Minimally invasive
- Missing gap in “appropriateness”
- Targeted agents

Summary

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- (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.

Acknowledgements

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EMBRACE

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MÉRIEUX RESEARCH GRANTS

Imperial Biomedical Research Centre

Imperial College London

epic impoc
enhanced, personalised and integrated care for infection management at point of care

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