Closed loop infection control using biocompatible wound dressings

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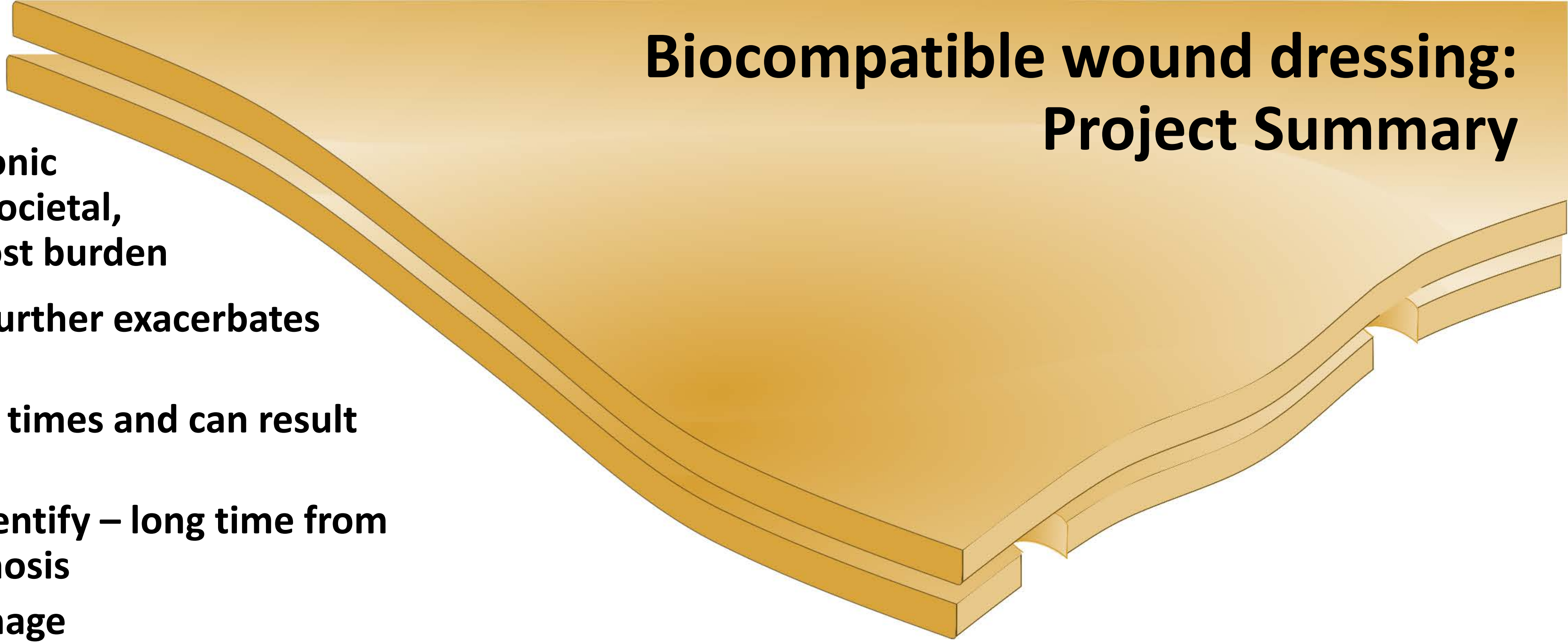
Biocompatible wound dressing: Project Summary



- Healing times for chronic wounds represent a societal, NHS and individual cost burden
- Infection of wounds further exacerbates the problem:
    - Increases healing times and can result in amputation
    - Challenging to identify – long time from infection to diagnosis
    - Expensive to manage
    - Comorbidities – e.g. Type II diabetes

- Our project aims to address these chronic wound challenges through the creation of:
    - A biocompatible polymer which PROMOTES wound healing
    - A SENSOR system which operates in a CLOSED LOOP manner to release silver to kill bacteria as soon as they are detected

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Production and Purification of P(3HO-*co*-3HD)

Seed Culture

15L Fermentation

70L Fermentation

Soxhlet Extraction

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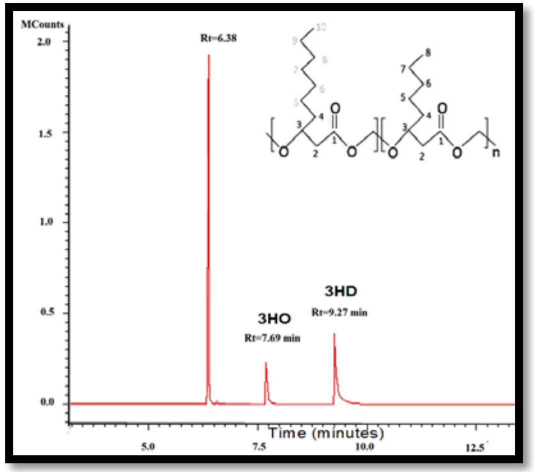
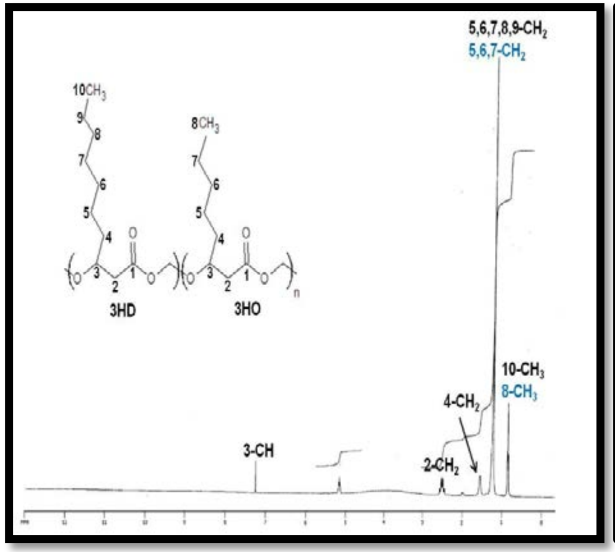
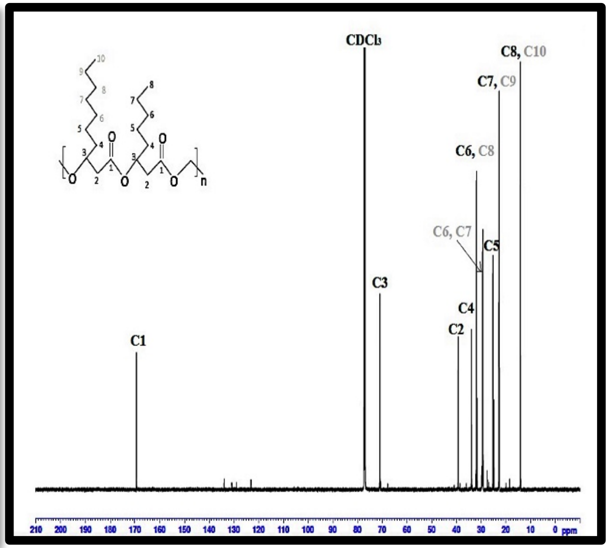
Characterisation of the Biocompatible Polymer

Gas Chromatography Mass Spectrometry



Nuclear Magnetic Resonance (NMR)





Molecular weight (kDa)

PHA	Molecular weight (KDa)
P(3HO-3HD)	377±24

Thermal Properties (Differential Scanning Calorimetry)

PHA	Tg (°C)	Tm (°C)
P(3HO-3HD)	-42.0	57.4

Mechanical Properties (Tensile testing)

PHA	σ_U, (MPa)	E (MPa)	ε_b (%)
P(3HO-3HD)	10.4	8.7	440

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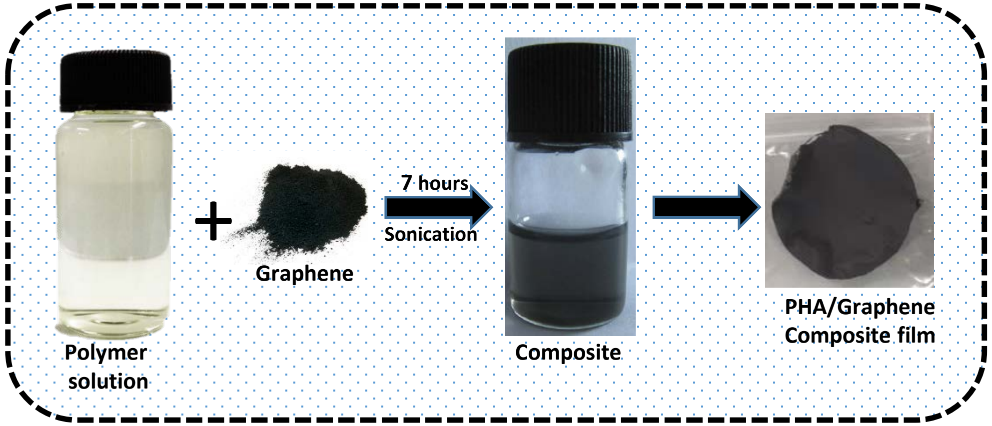
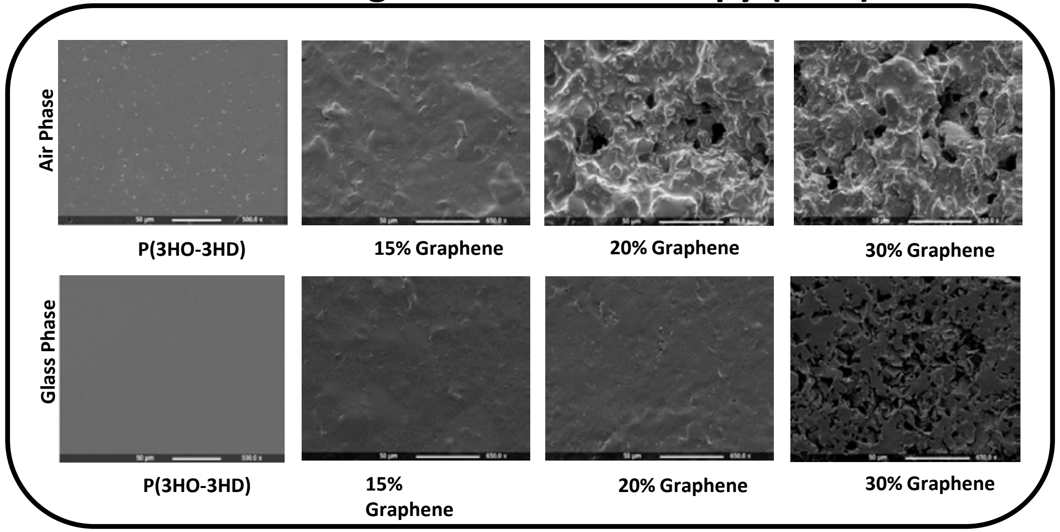
The Biocompatible Polymer Based PHA/Graphene Sensor

Production of P(3HO-3HD)/Graphene composite films



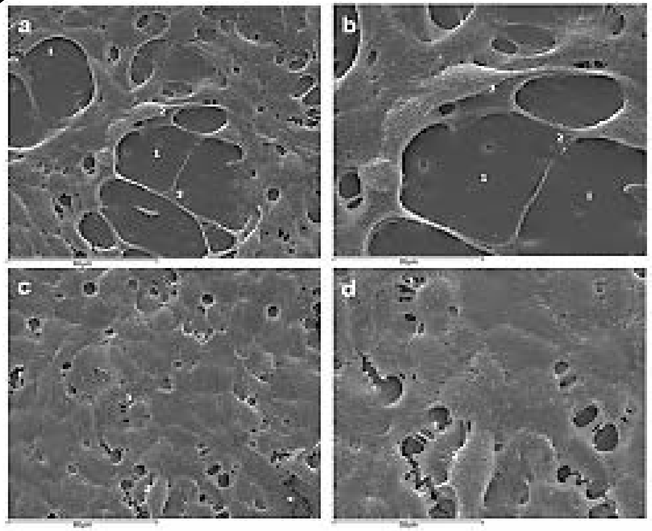
Scanning Electron Microscopy (SEM)



Water contact angle

PHA	Air Phase	Glass Phase
P(3HO-3HD)	87.7	98
15% Graphene	72.2	90.6
20% Graphene	70.6	95.5
30% Graphene	82	86.6

Biocompatibility studies



SEM images of the seeded HaCaT cells on PHA films: (a-b) Day 1 (c-d) Day 4 Confluent growth of the cells were observed on Day 4

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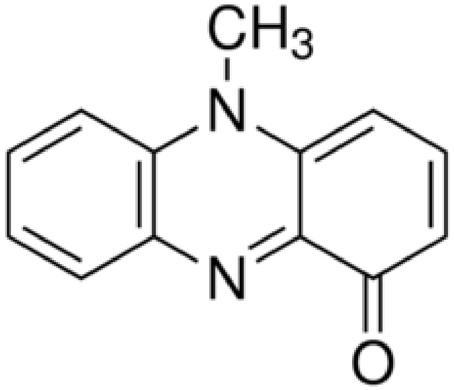
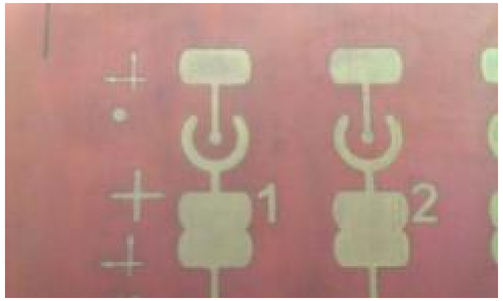
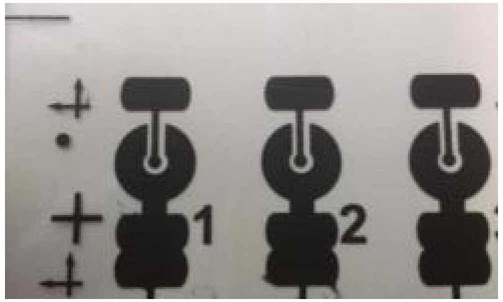
Detection and Killing of *P. aeruginosa*



- *P. aeruginosa* produces pyocyanin:
  - Redox active secondary metabolite
  - Related to quorum sensing network



- Biopolymer graphene composite to create a sensing surface:
  - Able to detect the presence of pyocyanin produced by *P. aeruginosa*



- Screen printed layer provides drug deliver and supporting electrodes:
  - Printed silver for electrochemical release of ions to kill silver
- LEARNING ALGORITHM closes the loop:
  - Predicts the concentration of sliver required to kill *P. aeruginosa*

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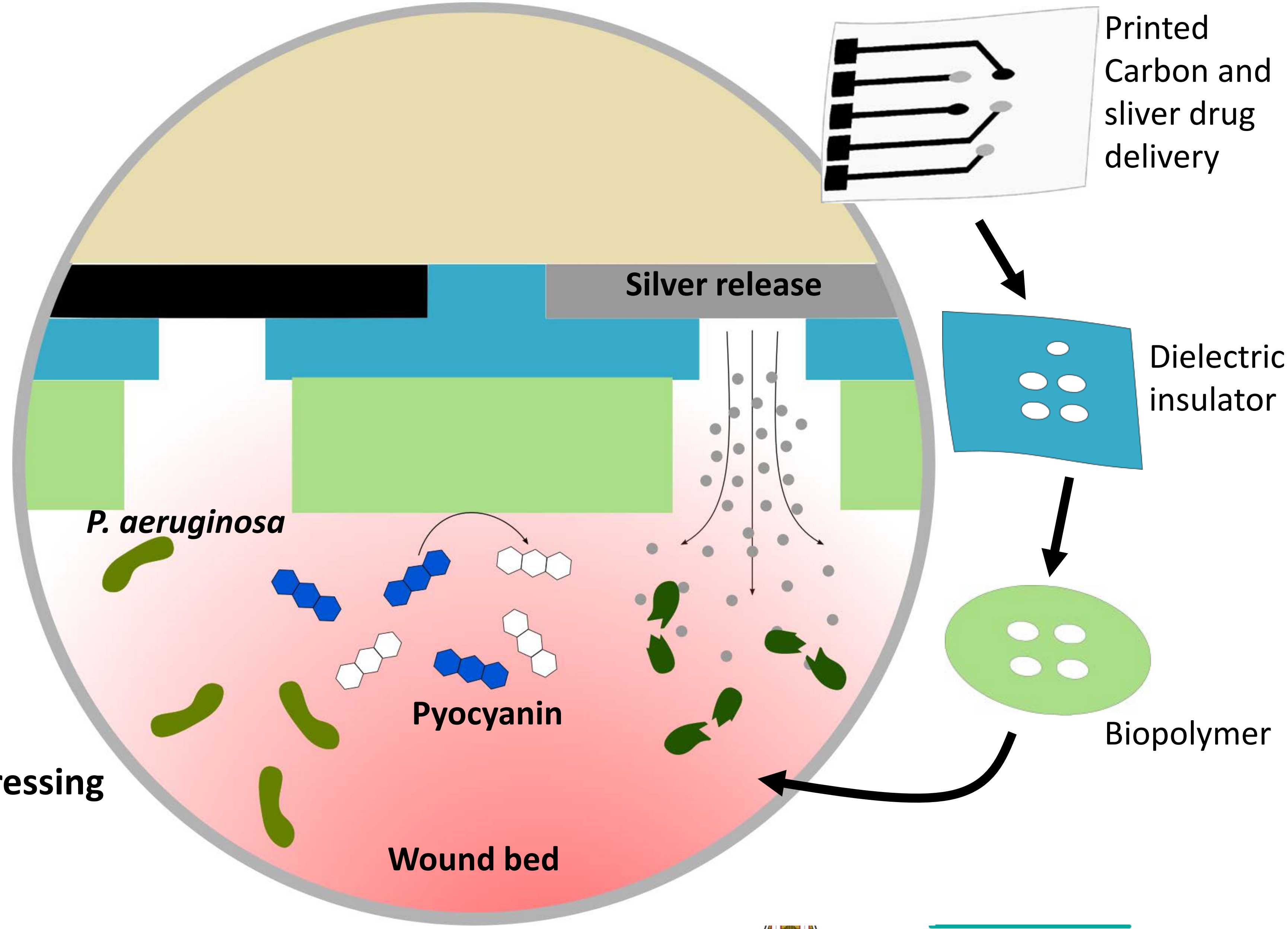
Design Summary

1. Screen printed drug delivery substrate – carbon and sliver on flexible substrate.

2. Biocompatible biopolymer dressing and sensor substrate.

3. Close loop algorithm used in conjunction with electrochemical dressing to detect *P. aeruginosa*.



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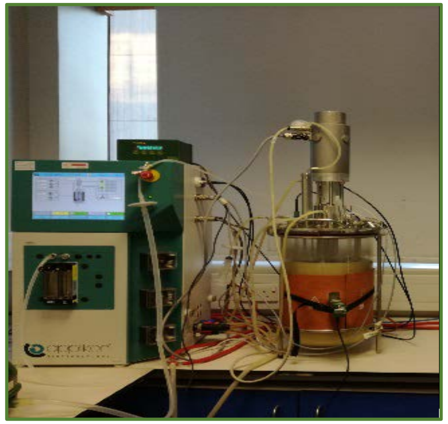
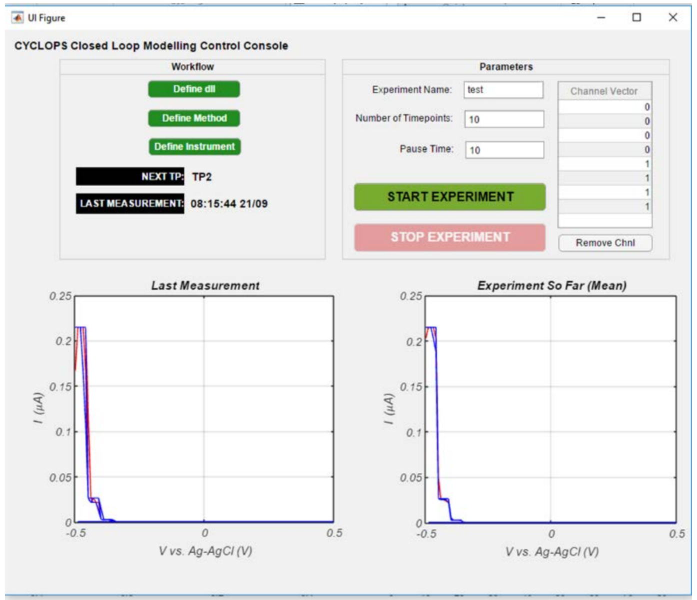
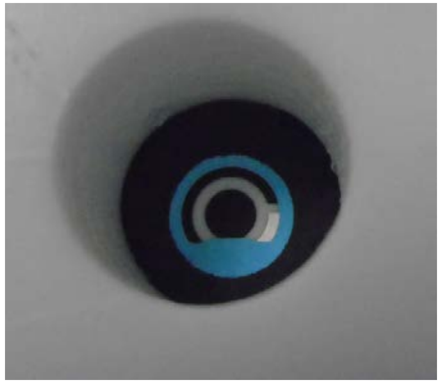
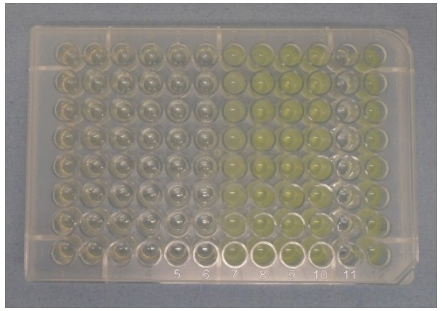
Experimental Setup

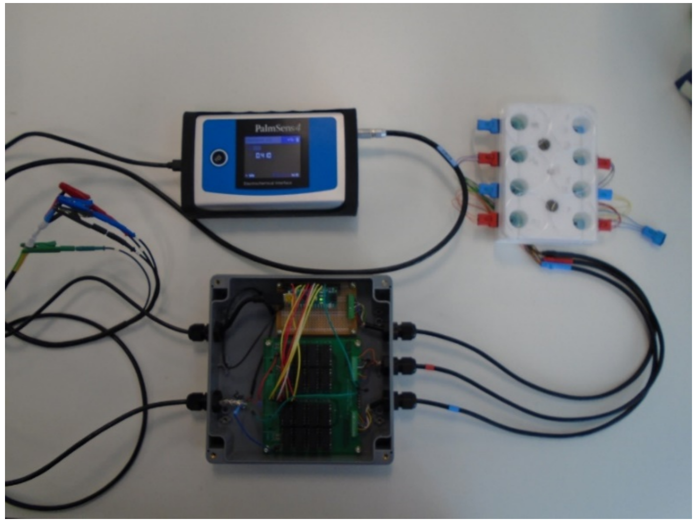
- **Biopolymer with functionalised graphene**
- **Test chambers constructed from PTFE with polymer/electrode at the bottom**
- **MATLAB control of potentiostat instrument**
- **Close loop algorithm to predict presence of *P. aeruginosa* and release of silver, implemented in Matlab**
- **Silver toxicity measurements performed with *P. aeruginosa***











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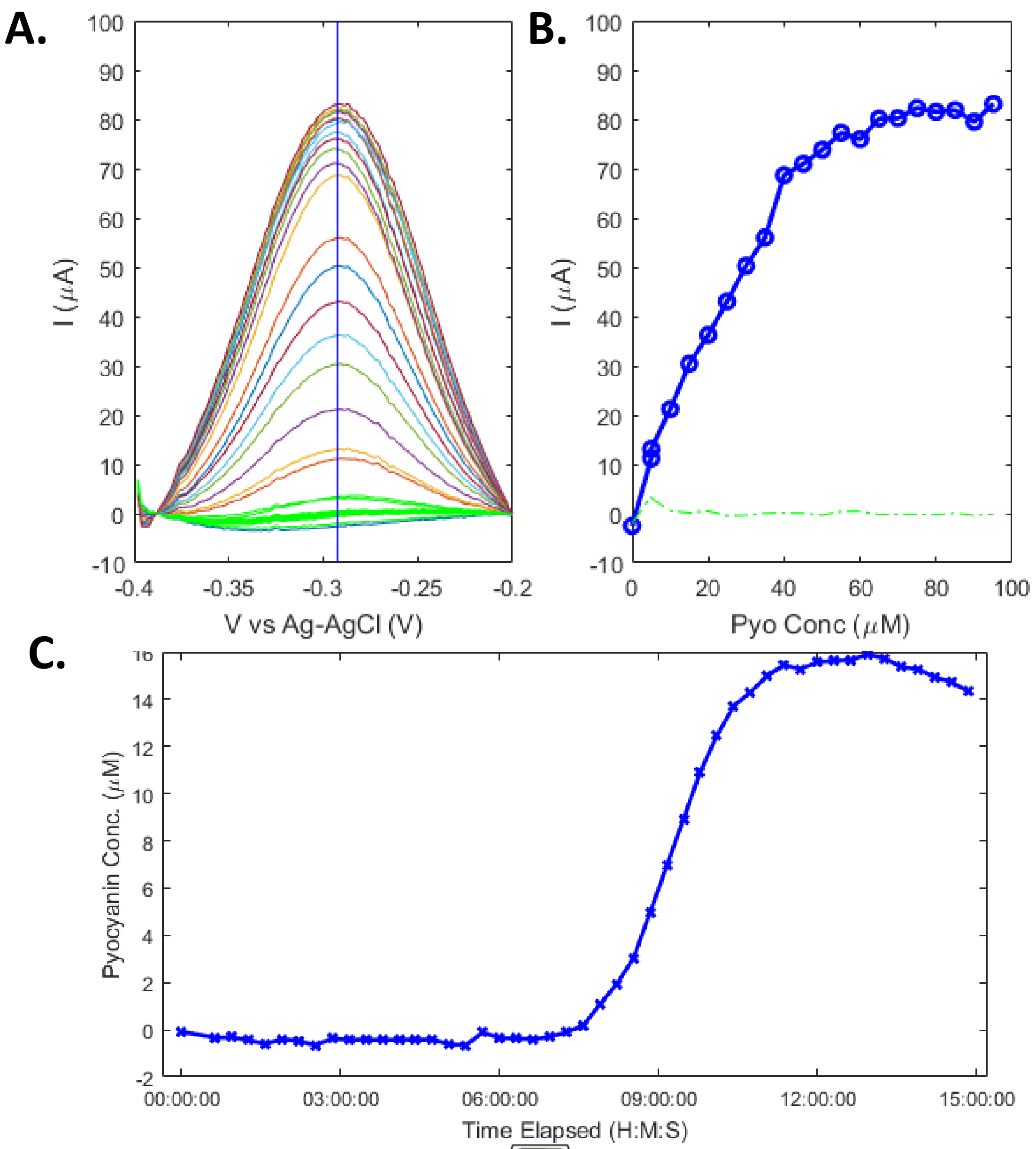
Baseline measurement with graphene electrodes

- **Baseline measurements performed with graphene electrodes**

- **Standard curve shows that pure pyocyanin can be detected biologically relevant levels (A & B)**

- ***P. aeruginosa* PA 14 shows production of pyocyanin during growth (C)**



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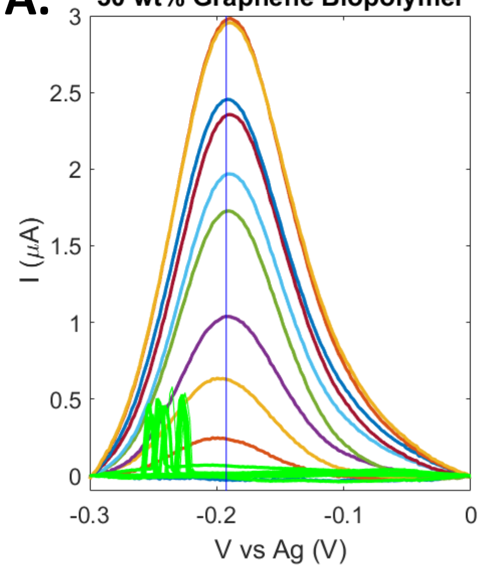
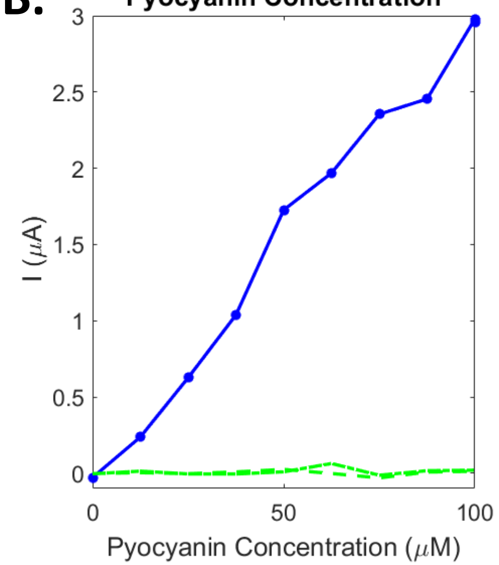
Detection of pyocyanin using biopolymer

- Redox peaks characteristic of pyocyanin were observed when the biopolymer itself was used as the electrode.
- Standard curve – measurement of biopolymer strip demonstrates ability to detect pyocyanin (A & B).
- Raises the prospect of developing a biocompatible electrode sensor for wound infection.
- Overnight culture of *P. aeruginosa* PA14 measured with biopolymer (C).

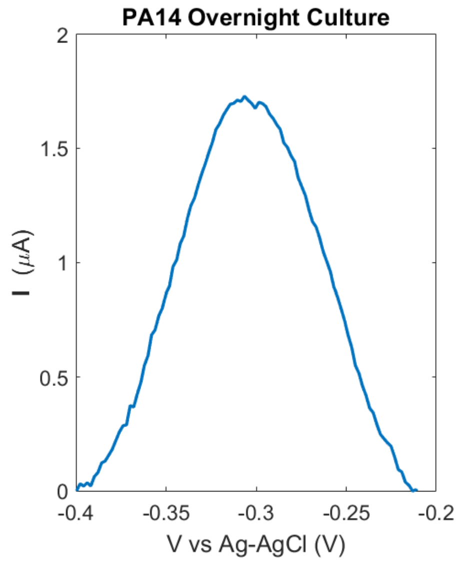
A.



B.



C.



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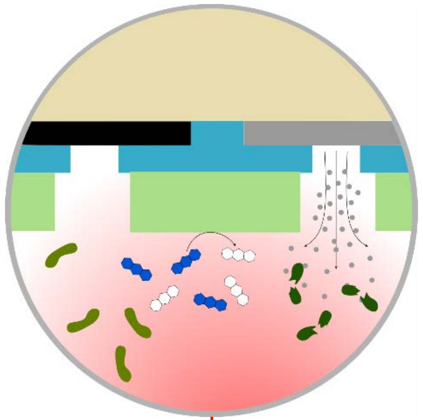
Prediction Algorithm: model training



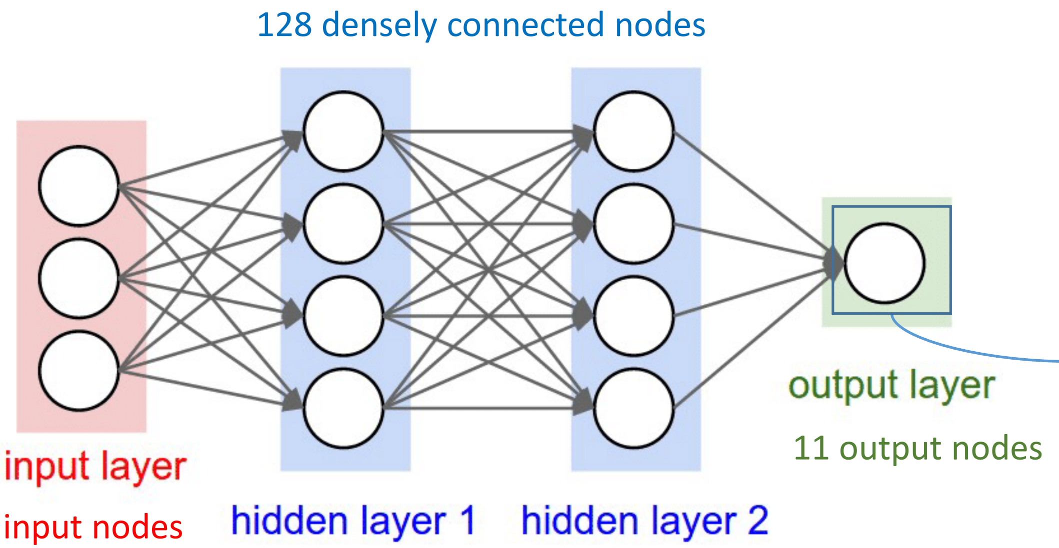
Model

$$\frac{d[\mathrm{LasR}]}{dt} = -k_R[\mathrm{LasR}] + V_R\frac{[\mathrm{LasR}][\mathrm{3oxo\text{-}C12\text{-}HSL}]}{K_R + [\mathrm{LasR}][\mathrm{3oxo\text{-}C12\text{-}HSL}]} + R_0$$

$$\frac{d[\mathrm{3oxo\text{-}C12\text{-}HSL}]}{dt} = V_A\frac{[\mathrm{LasR}][\mathrm{3oxo\text{-}C12\text{-}HSL}]}{K_A + [\mathrm{LasR}][\mathrm{3oxo\text{-}C12\text{-}HSL}]} + A_0 - k_A[\mathrm{3oxo\text{-}C12\text{-}HSL}] - \frac{\delta}{\rho}\left([\mathrm{3oxo\text{-}C12\text{-}HSL}] - [\mathrm{3oxo\text{-}C12\text{-}HSL}]_{\mathrm{ext}}\right)$$

$$\frac{d[\mathrm{3oxo\text{-}C12\text{-}HSL}]_{\mathrm{ext}}}{dt} = -k_E[\mathrm{3oxo\text{-}C12\text{-}HSL}]_{\mathrm{ext}} + \frac{\delta}{1-\rho}\left([\mathrm{3oxo\text{-}C12\text{-}HSL}] - [\mathrm{3oxo\text{-}C12\text{-}HSL}]_{\mathrm{ext}}\right)$$

Simulated measurement date used to train the deep learning neural network



Uncertainty In the model

Estimated Uncertainty

$$k_R = 0.7(1+\delta_1)$$
$$k_A = 0.02(1+\delta_2)$$
$$k_E = 0.1(1+\delta_3)$$
$$V_R = 2.0(1+\delta_4)$$
$$V_A = 2.0(1+\delta_5)$$
$$K_R = 2.0(1+\delta_6)$$
$$K_A = 1.0(1+\delta_7)$$
$$R_0 = 0.05(1+\delta_8)$$
$$A_0 = 0.05(1+\delta_9)$$
$$\delta = 0.8(1+\delta_{10})$$
$$\rho = 0.2(1+\delta_{11})$$

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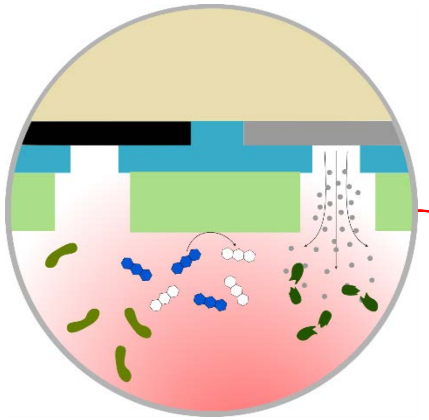
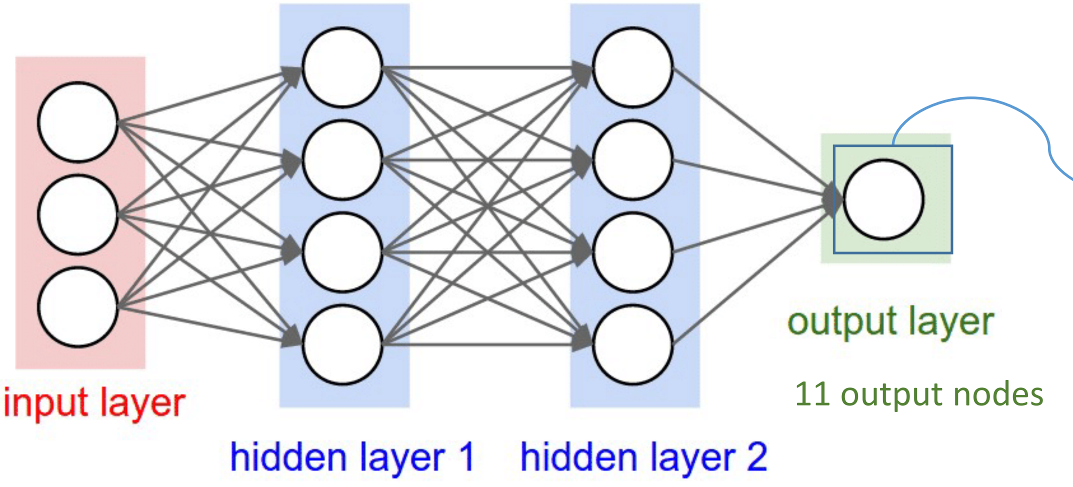
Prediction Algorithm: toxic level prediction



Stochastic model generates simulated noisy measurement



Estimated Uncertainty

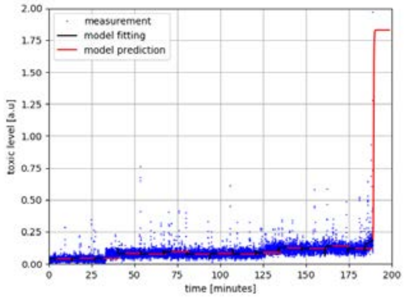
$$
\begin{aligned}
k_R &= 0.7(1+\delta_1)\\
k_A &= 0.02(1+\delta_2)\\
k_E &= 0.1(1+\delta_3)\\
V_R &= 2.0(1+\delta_4)\\
V_A &= 2.0(1+\delta_5)\\
K_R &= 2.0(1+\delta_6)\\
K_A &= 1.0(1+\delta_7)\\
R_0 &= 0.05(1+\delta_8)\\
A_0 &= 0.05(1+\delta_9)\\
\delta &= 0.8(1+\delta_{10})\\
\rho &= 0.2(1+\delta_{11})
\end{aligned}
$$

Update Uncertainty

$$
\frac{d[\mathrm{LasR}]}{dt} = -k_R[\mathrm{LasR}] + V_R\frac{[\mathrm{LasR}][\mathrm{3oxo\text{-}C12\text{-}HSL}]}{K_R + [\mathrm{LasR}][\mathrm{3oxo\text{-}C12\text{-}HSL}]} + R_0
$$

$$
\frac{d[\mathrm{3oxo\text{-}C12\text{-}HSL}]}{dt} = V_A\frac{[\mathrm{LasR}][\mathrm{3oxo\text{-}C12\text{-}HSL}]}{K_A + [\mathrm{LasR}][\mathrm{3oxo\text{-}C12\text{-}HSL}]} + A_0 - k_A[\mathrm{3oxo\text{-}C12\text{-}HSL}] - \frac{\delta}{\rho}\left([\mathrm{3oxo\text{-}C12\text{-}HSL}] - [\mathrm{3oxo\text{-}C12\text{-}HSL}]_{\mathrm{ext}}\right)
$$

$$
\frac{d[\mathrm{3oxo\text{-}C12\text{-}HSL}]_{\mathrm{ext}}}{dt} = -k_E[\mathrm{3oxo\text{-}C12\text{-}HSL}]_{\mathrm{ext}} + \frac{\delta}{1-\rho}\left([\mathrm{3oxo\text{-}C12\text{-}HSL}] - [\mathrm{3oxo\text{-}C12\text{-}HSL}]_{\mathrm{ext}}\right)
$$



Toxic level prediction

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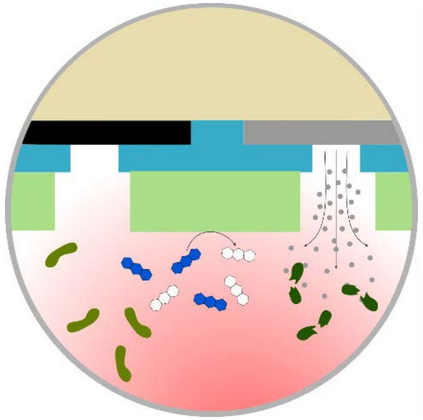
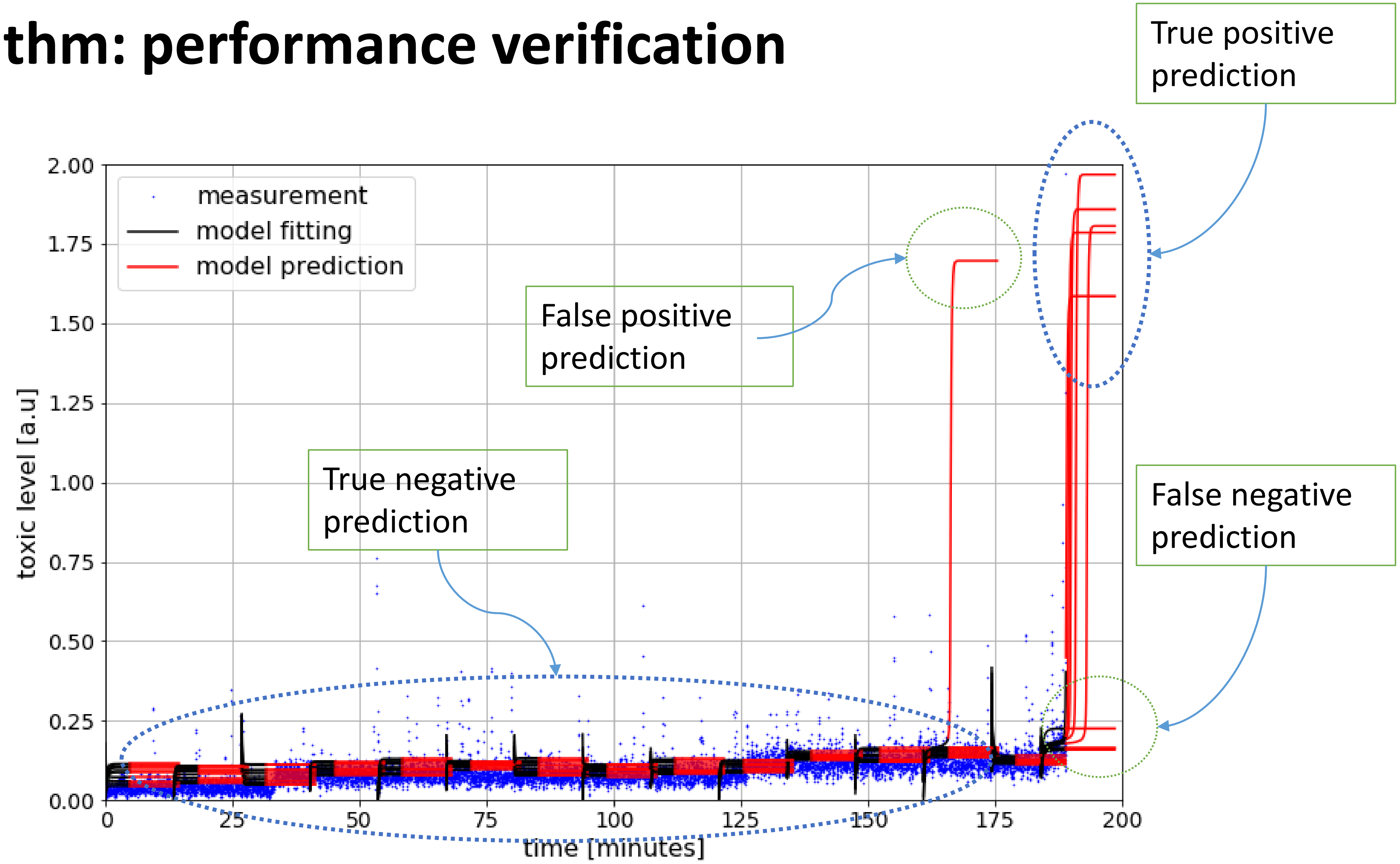
Prediction Algorithm: performance verification



Stochastic model generates simulated noisy measurement



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Current Project Summary

Achievements

- Biopolymer graphene composite
- Detection of purified pyocyanin with biopolymer
- Detection of pyocyanin produced by *P. aeruginosa*
- Electrochemical release of silver ions
- Prediction algorithm for detection developed

Next Steps

- Real time detection of *P. aeruginosa* using biopolymer in assembly
- Automated release of silver ions to kill *P. aeruginosa* using prediction algorithm

Challenges

- Wound bed microbiome and pathogens beyond *P. aeruginosa*
- Release of other antimicrobial drugs

Publication Draft

- Closed loop detection and killing of *P. aeruginosa* with a biocompatible wound dressing.
- Target journal: Advanced functional materials

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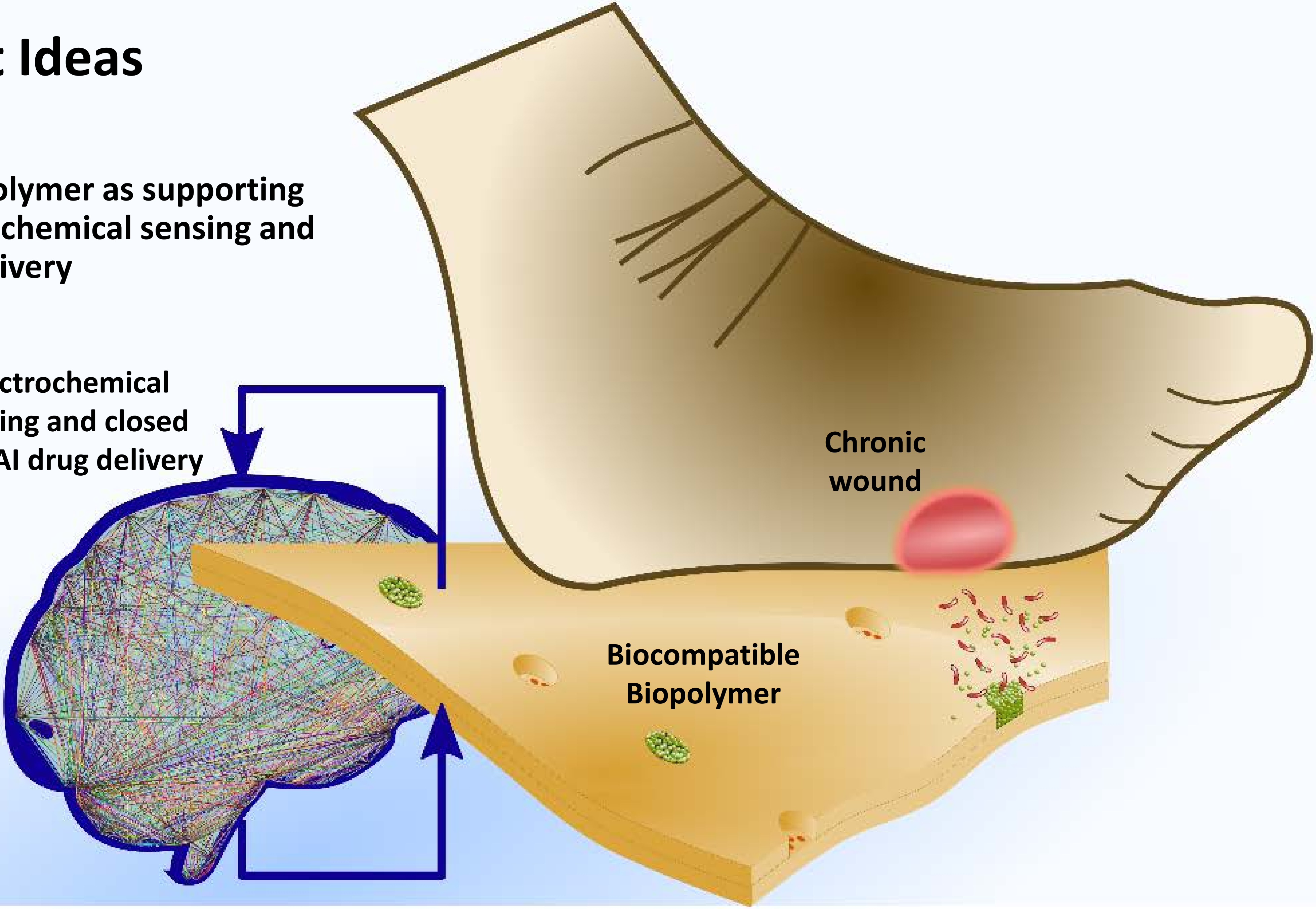
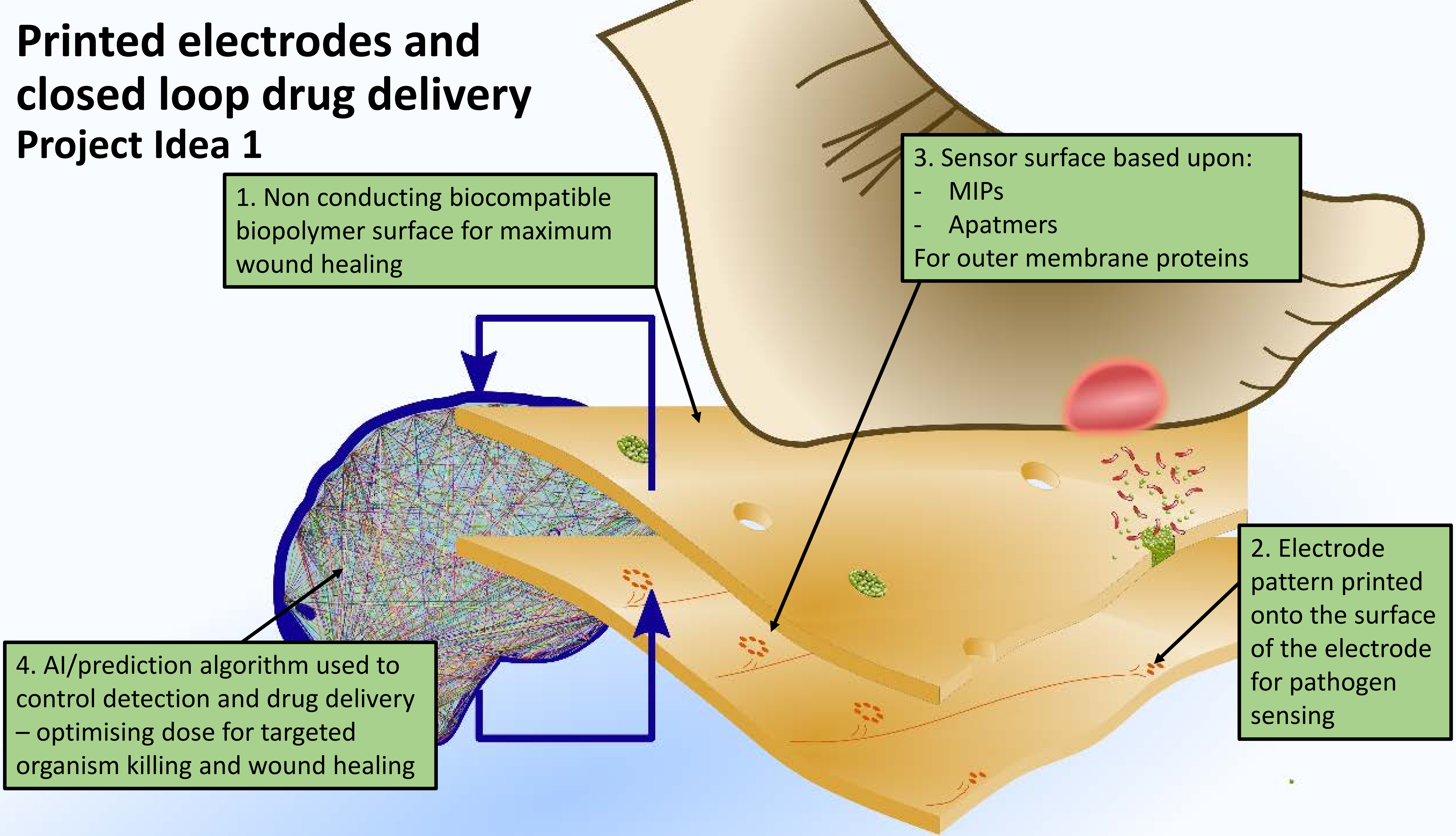
Future Project Ideas

- Biocompatible biopolymer as supporting substrate for electrochemical sensing and closed loop drug delivery

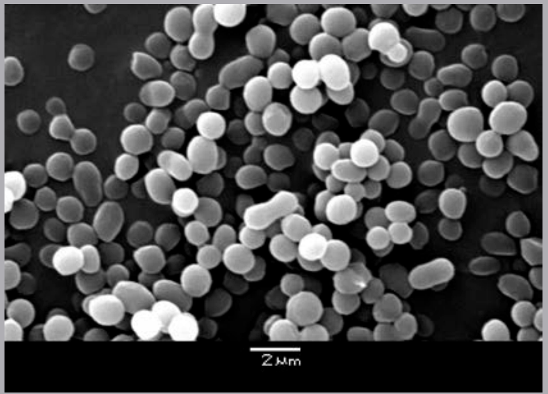


Printed electrodes and closed loop drug delivery

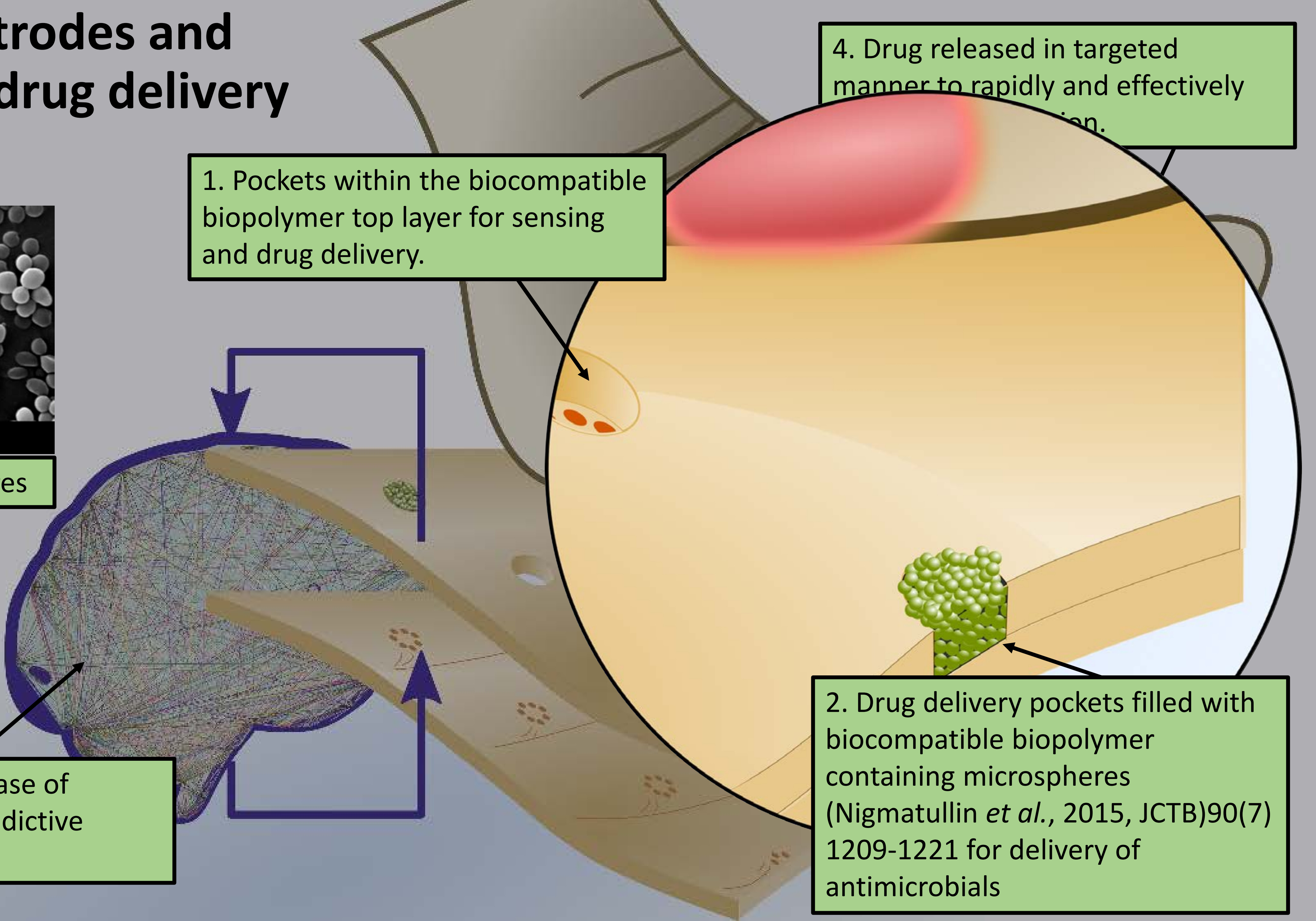
Project Idea 1



Printed electrodes and closed loop drug delivery
Project Idea 2



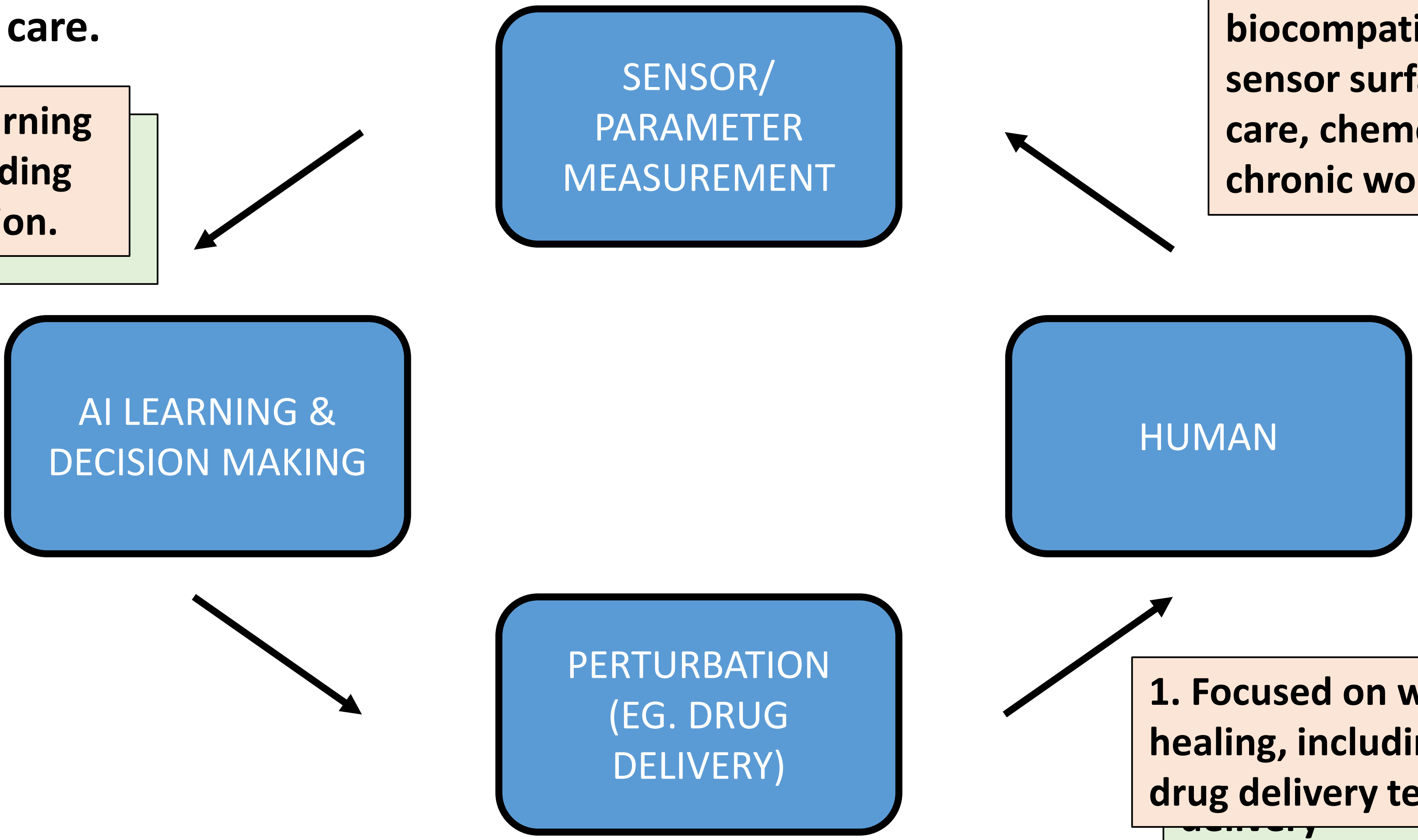
PHA-based microspheres



Thoughts on Platform Grant

Theme suggestions with a focus on chronic wound care.

3. Integrated learning algorithms including infection detection.



2. Imprinted biocompatible polymer sensor surfaces for critical care, chemotherapy and chronic wound care.

1. Focused on wound healing, including novel drug delivery technique.

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Project Stakeholders

CYCLOPS Network

Clinical Advisory Board

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Dr Jochen Salber
General Surgeon
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