Finite Difference Model Representing Cell Distribution in Monolayer

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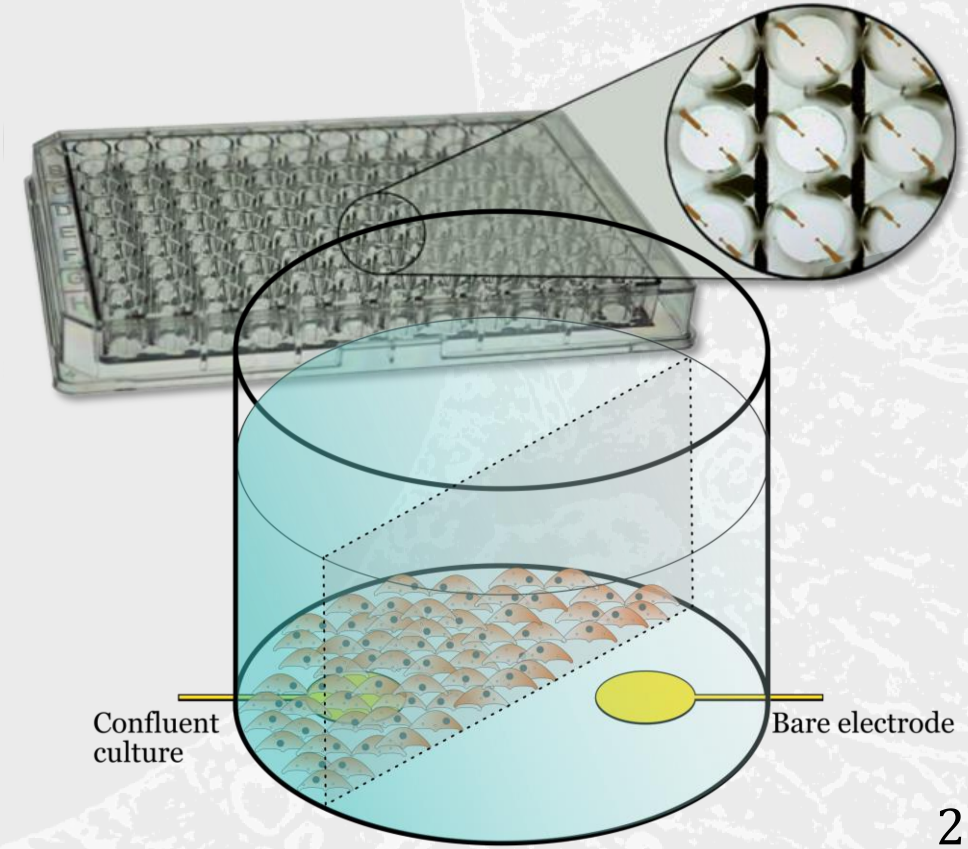
Objective

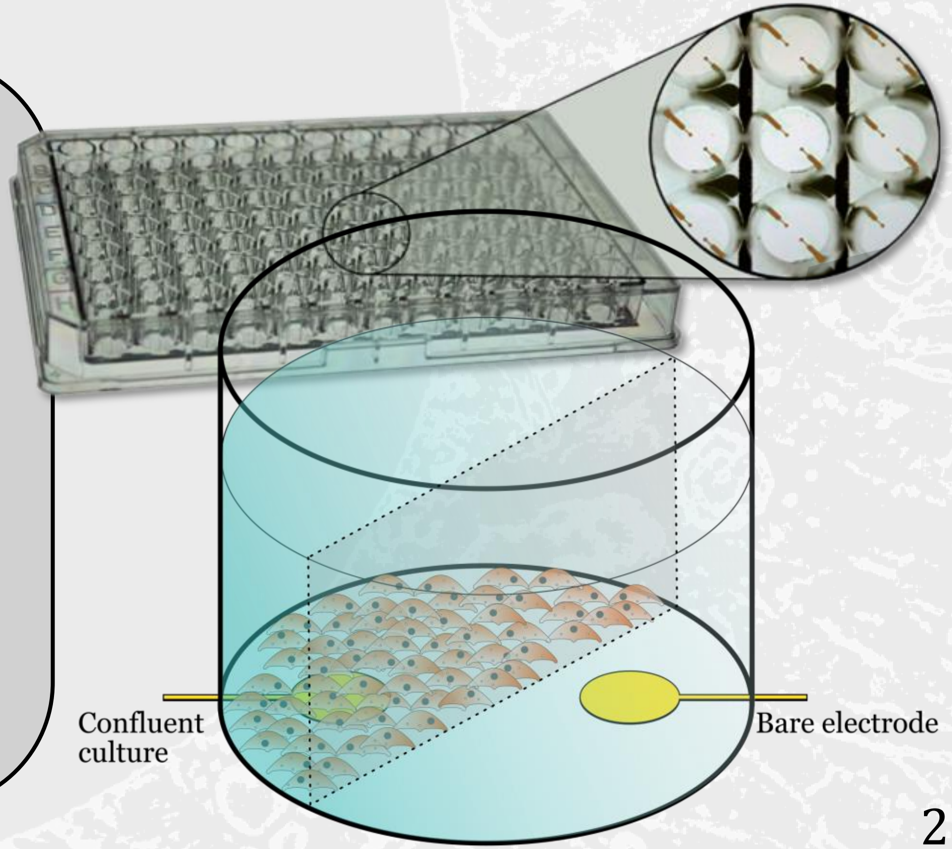
To estimate the electrode cell density only by its spectral impedance.



Objective

To estimate the electrode cell density only by its spectral impedance.

1. Develop a numerical culture model for the contribution of each cell.
2. Reobtain analytical model estimation for the same parameters (GK model: [α, Rb & Cm]).
3. Simulate non-confluent culture states (Random placement and Wound & Healing processes).
4. Compare experimental data to every simulation finding the closest cell density.

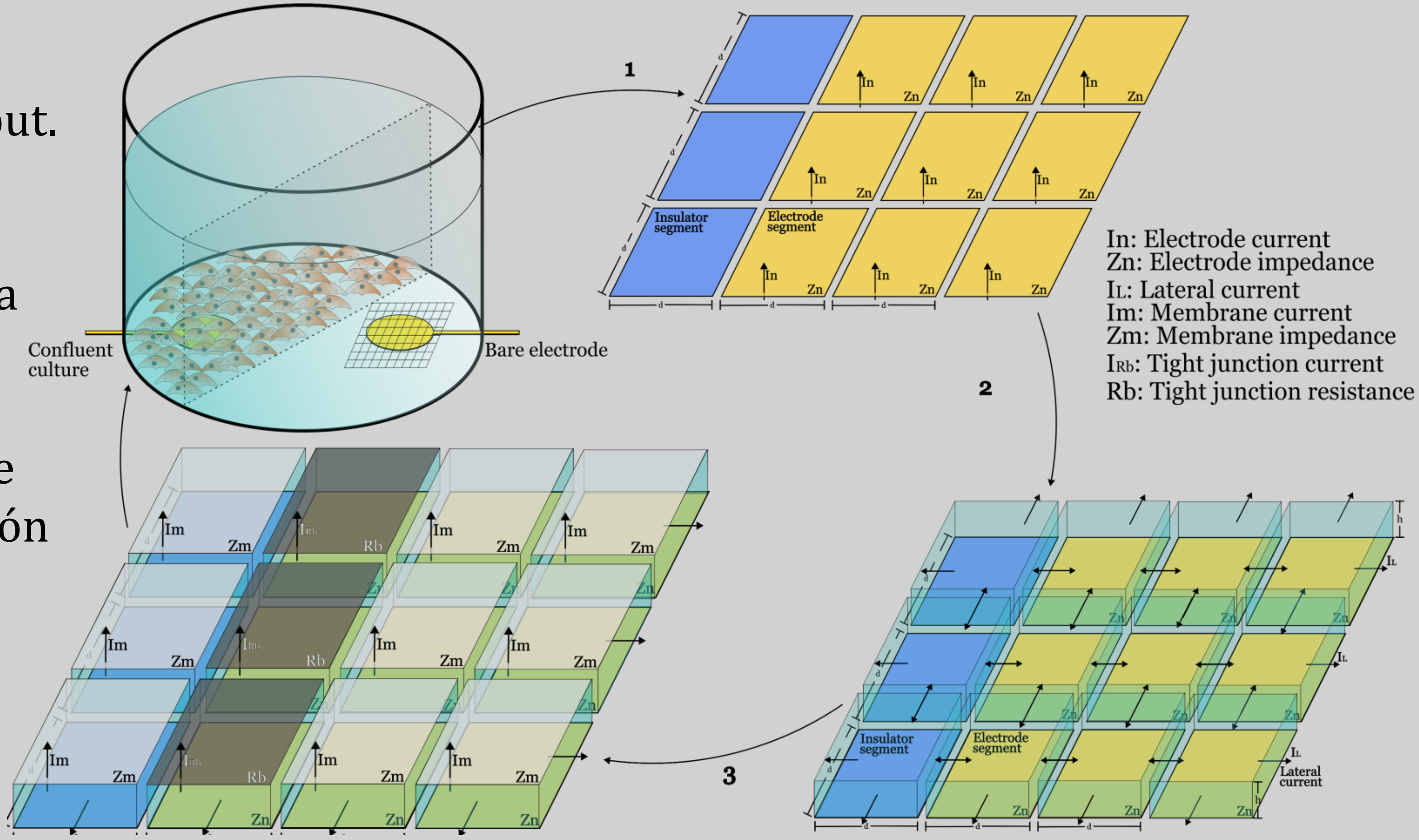


Designing a numerical model

1. Tile the substrate surface.
   a. Electrode tiles, current input.
   b. Insulator tiles.

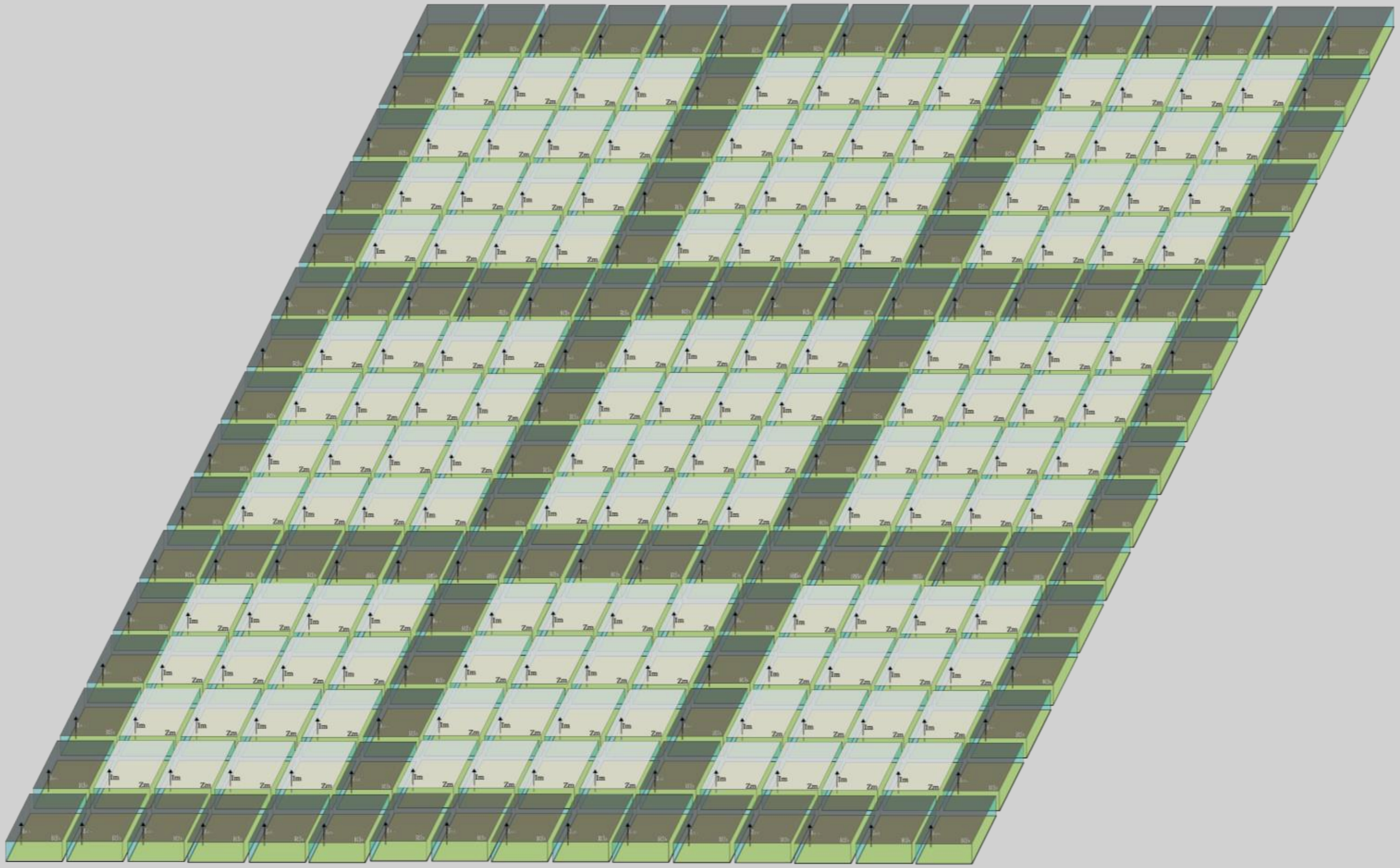
2. Neighboring tiles connected via eletrolyte (ρ).

3. Each tile covered by membrane (capacitive) or intercelular unión (resistive).



Building a culture

Each cell is an n by n tile matrix of membrane tiles surrounded by a ring of intecelular tiles.



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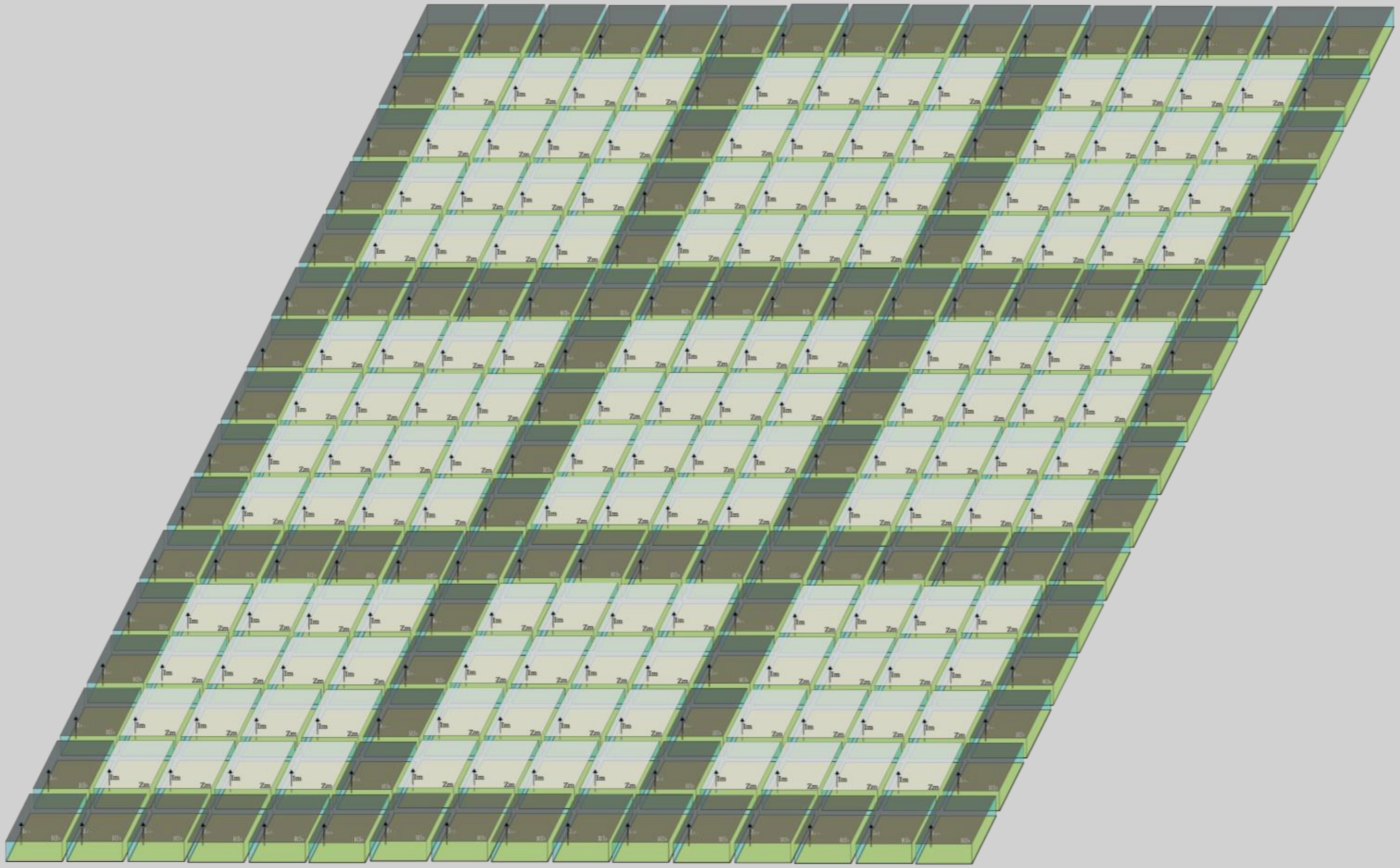
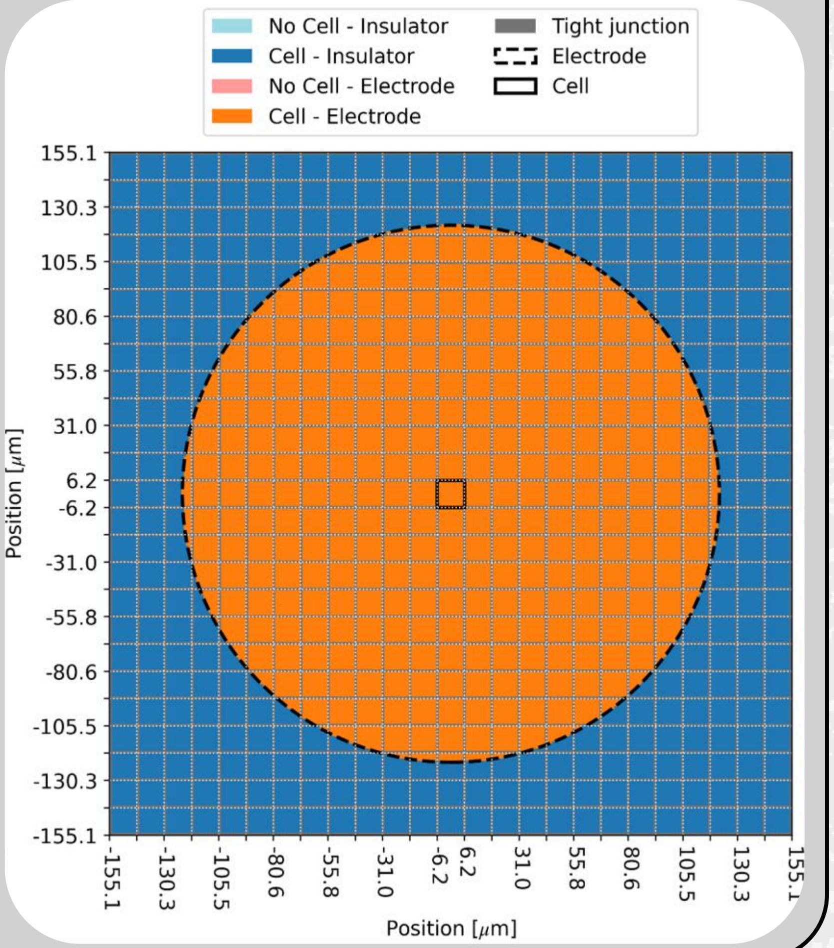
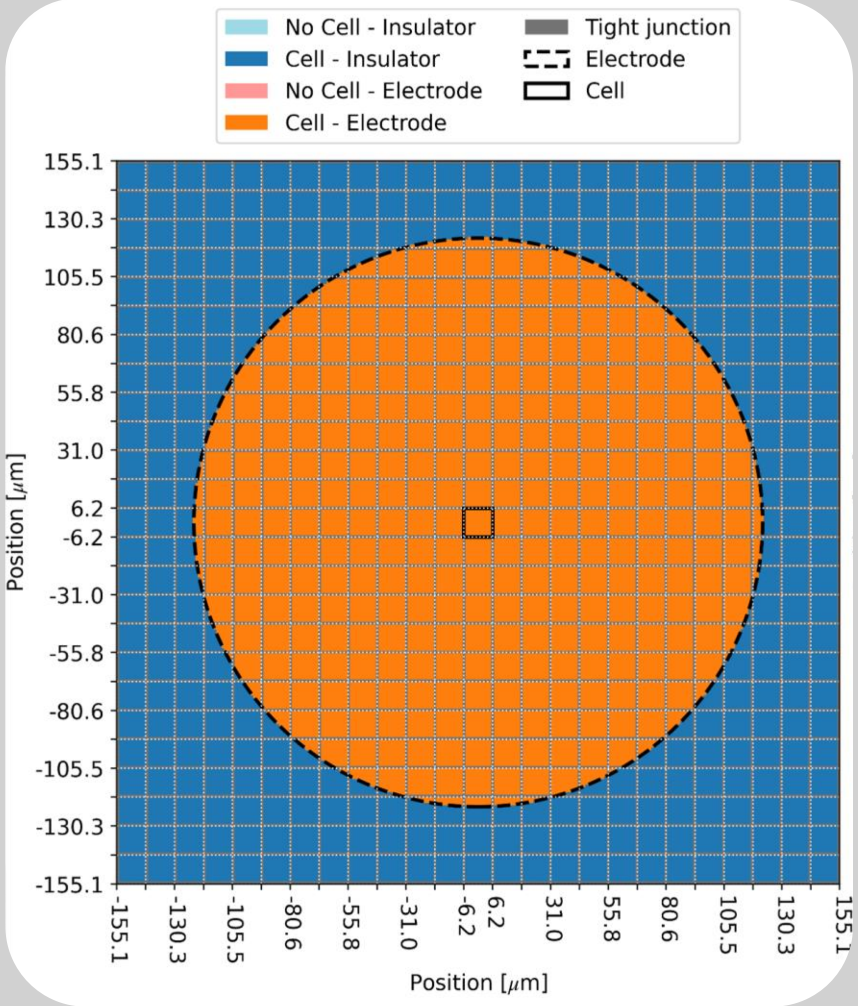




Confluent cultures

Fixed parameters:
- Cell size.
- Electrode size.
- Electrode impedance Zn.

Model parameters:
- α (~height culture).
- Rb (Intercelular resistance).
- Cm (membrane capacitance).



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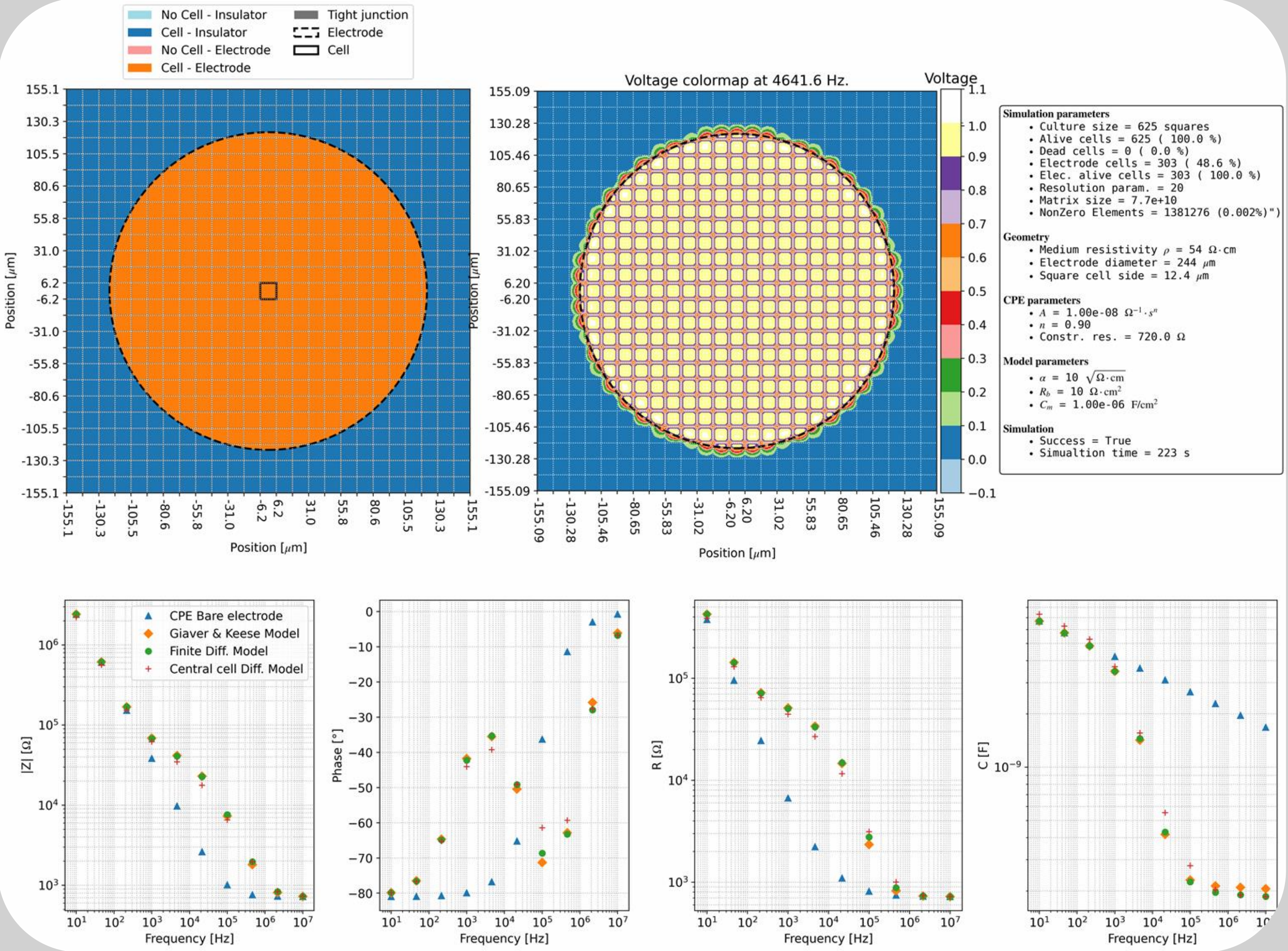
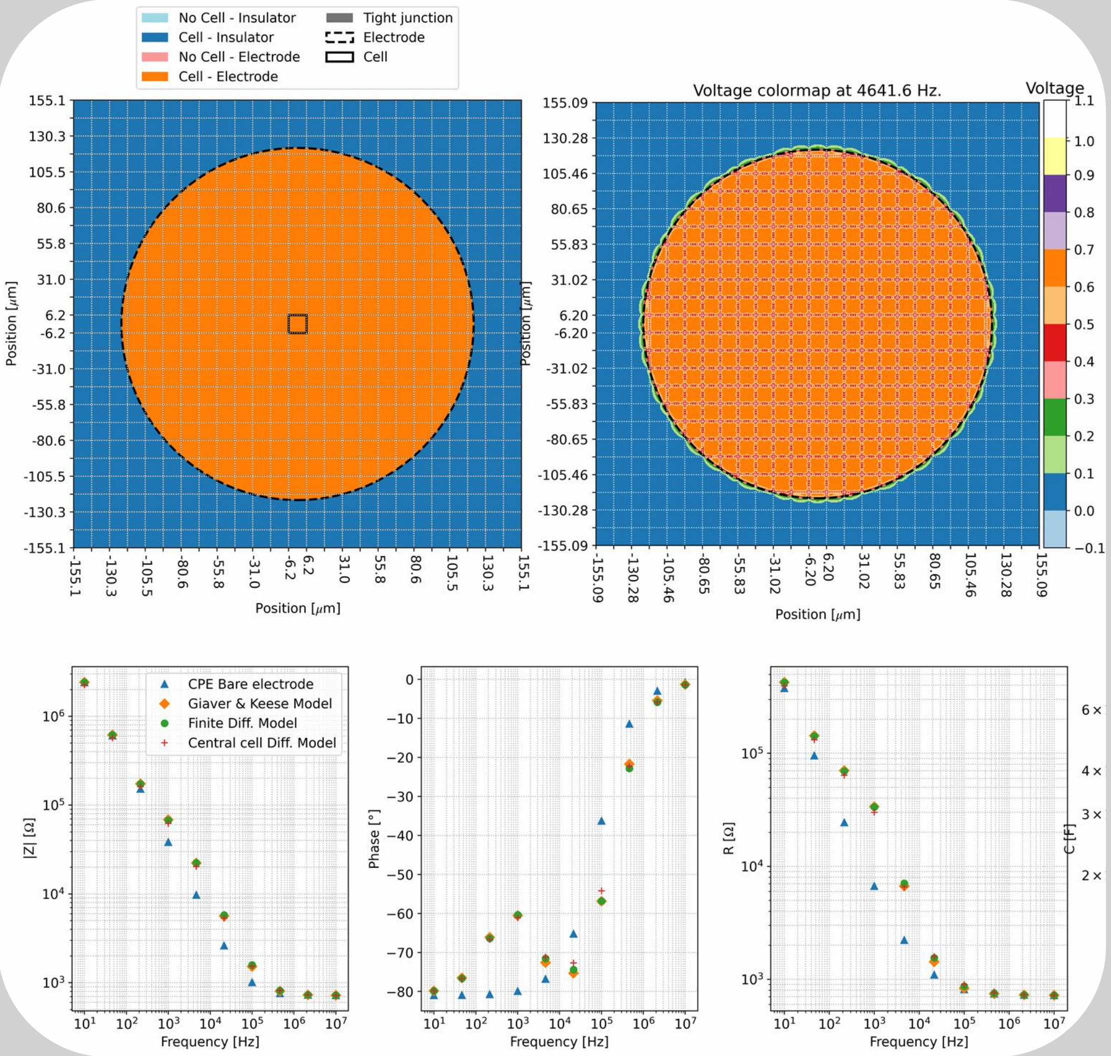
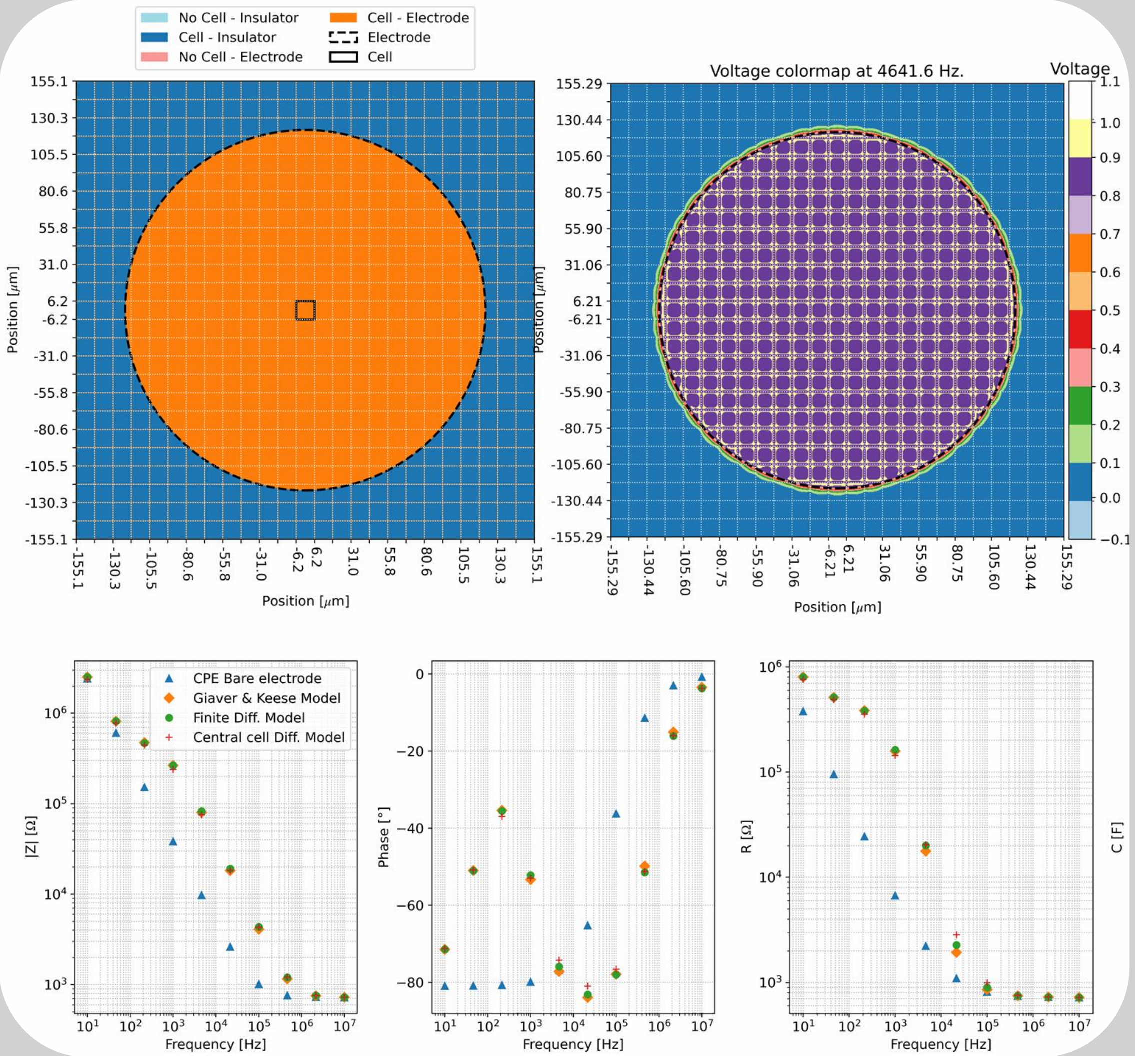


Non-confluent cultures

Random cell placement



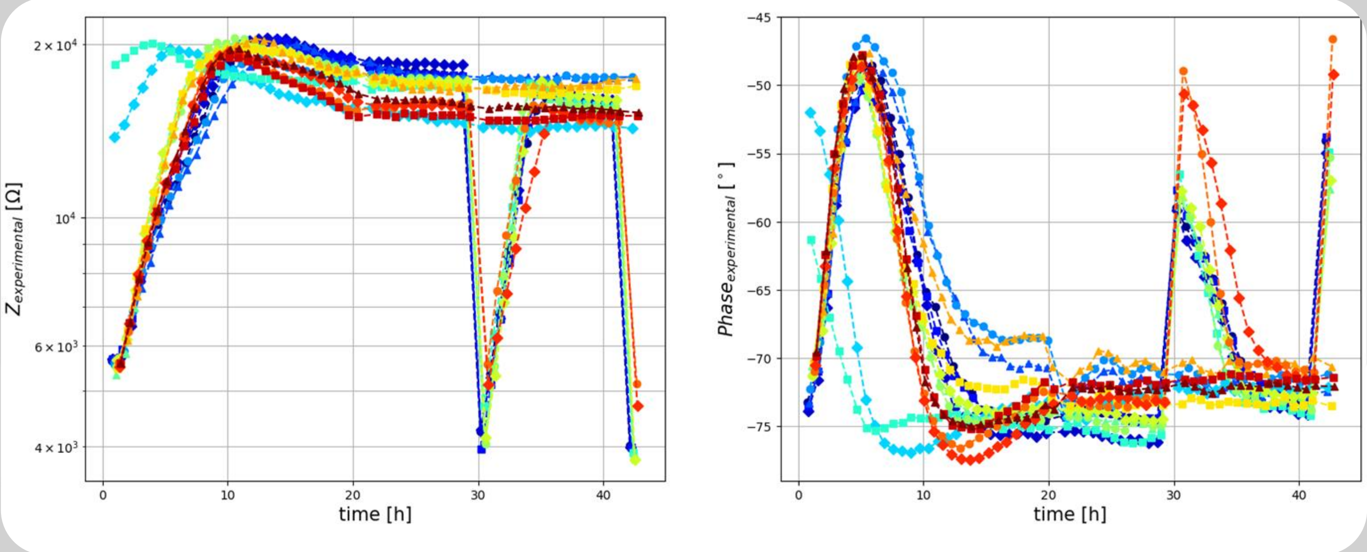
Wound and Healing concentrical



Experimental data clasification

1. The algorithm finds the best α, Rb & Cm for each culture.

2. Later it searches from the best simulations from the selected α, Rb & Cm for each experimental point.



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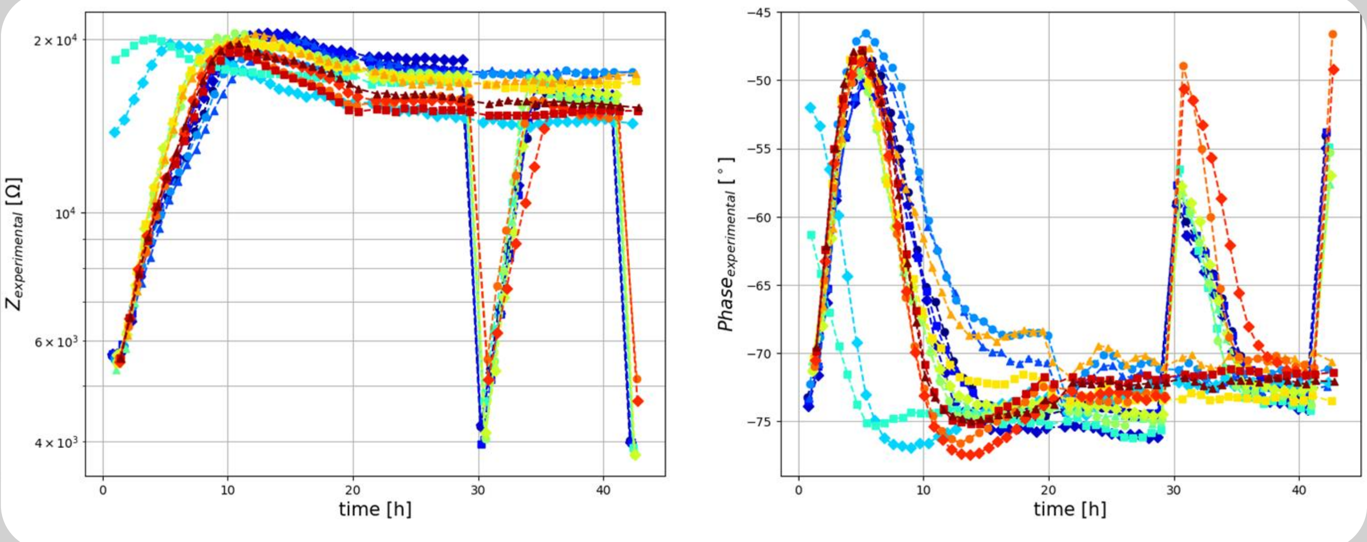
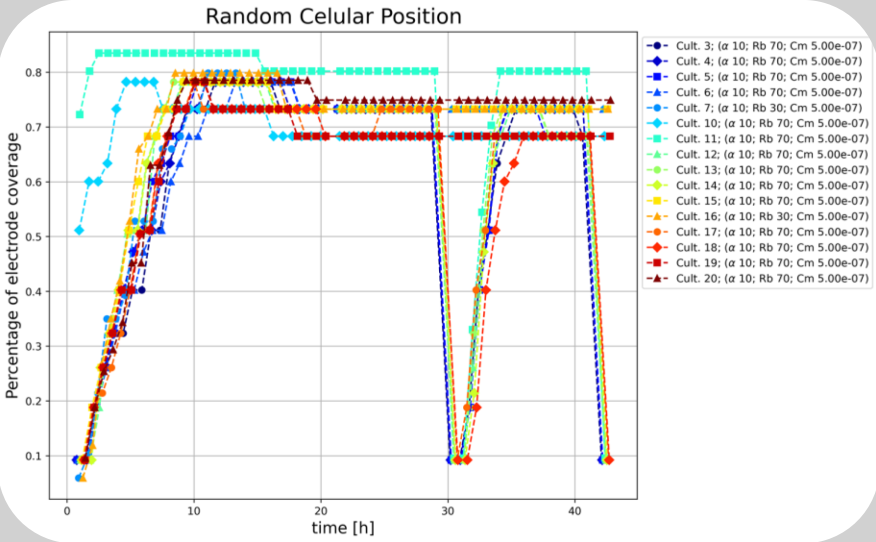
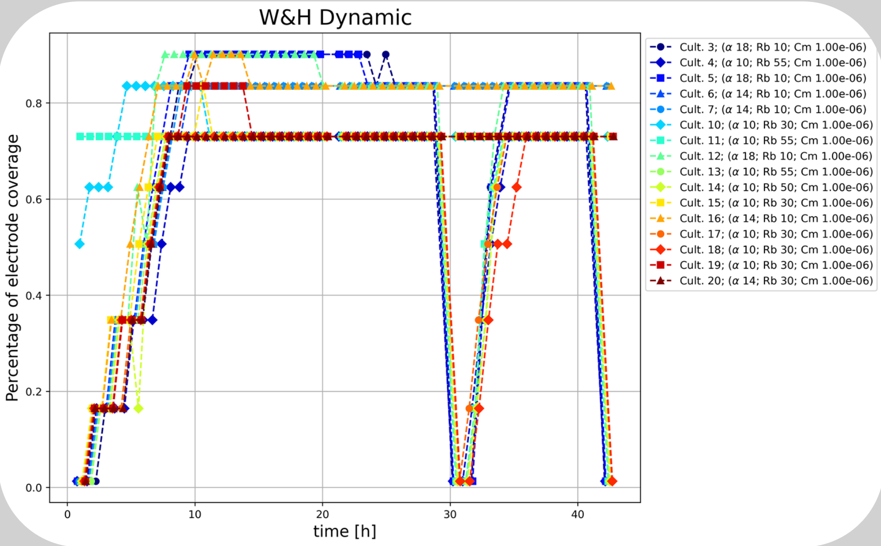
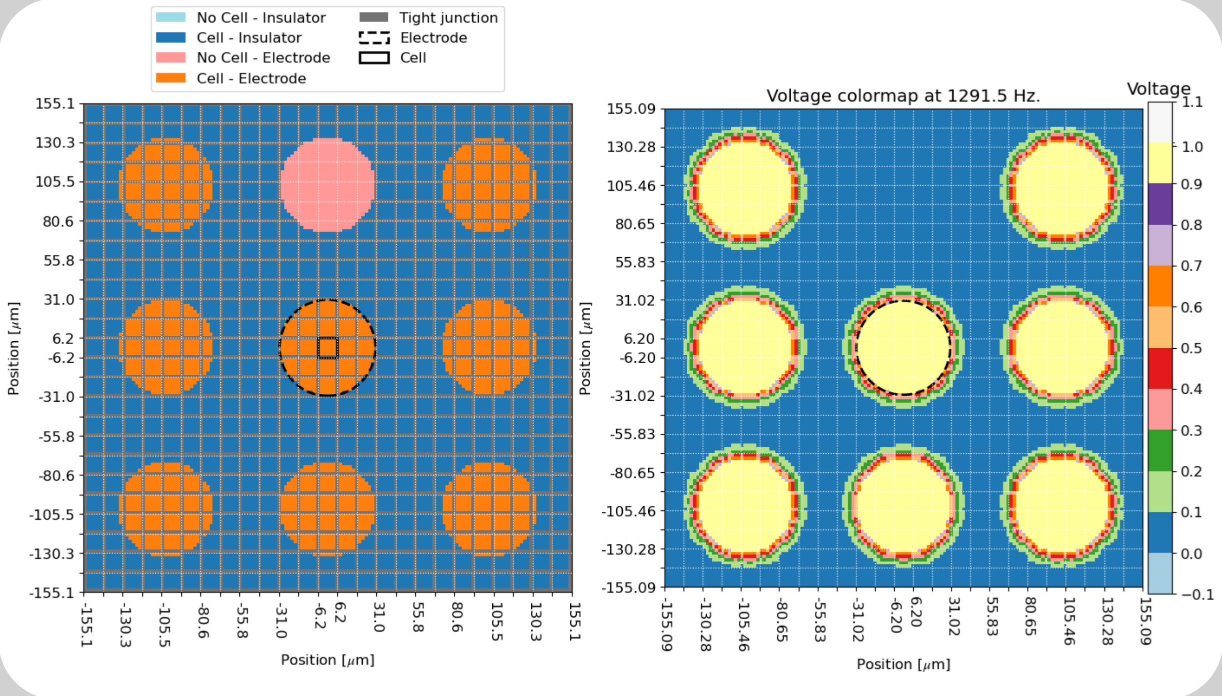






Continuation

Test different electrode arrays



Continuation

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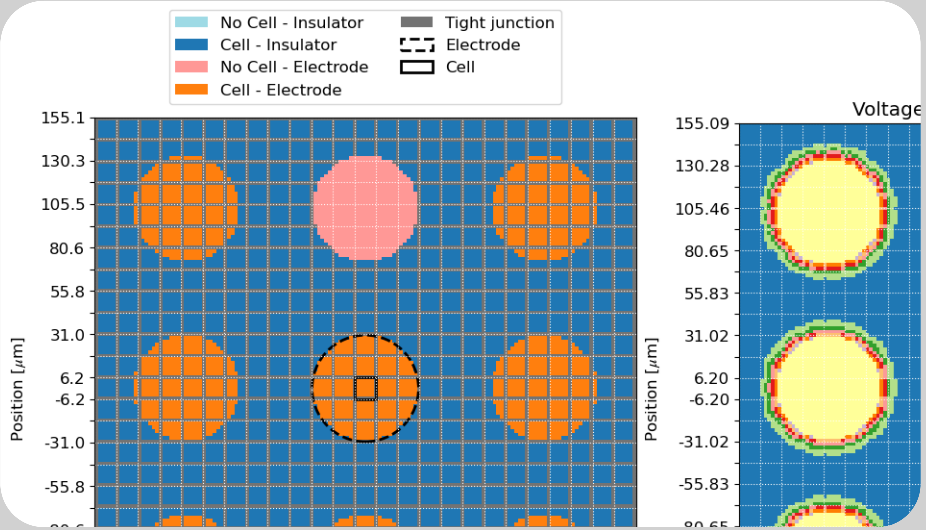
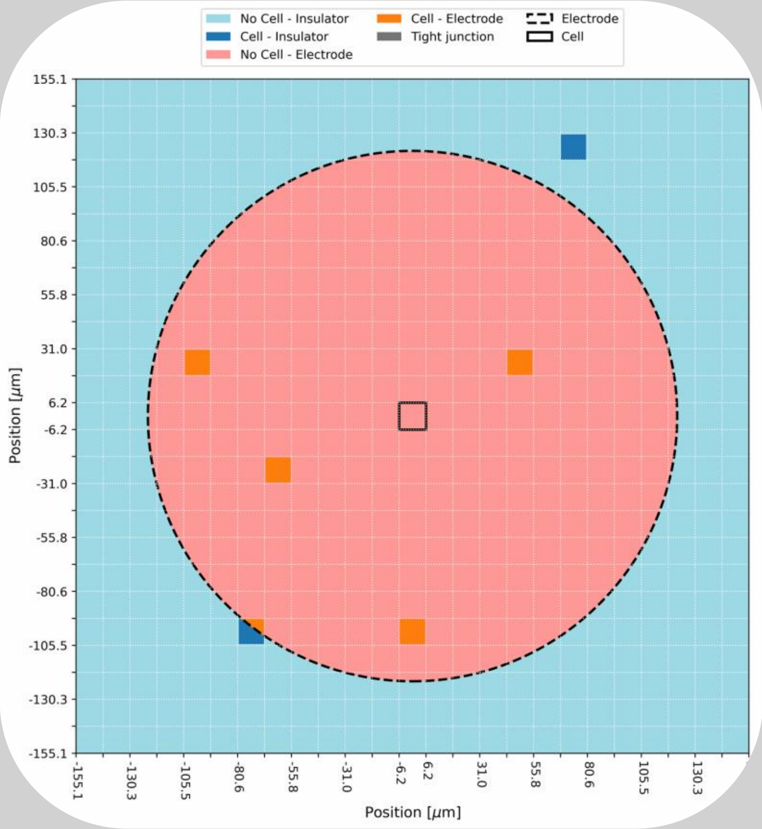


Simulate cell divition evolution



Continuation

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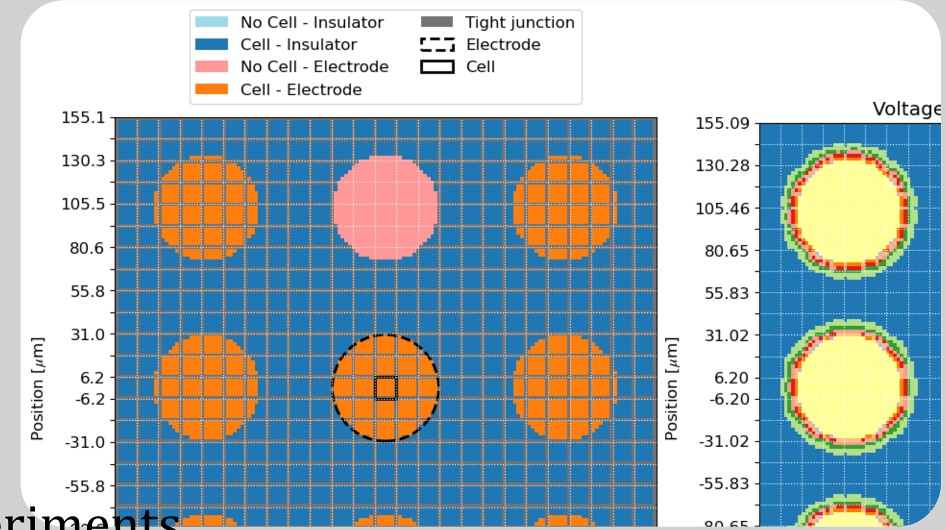
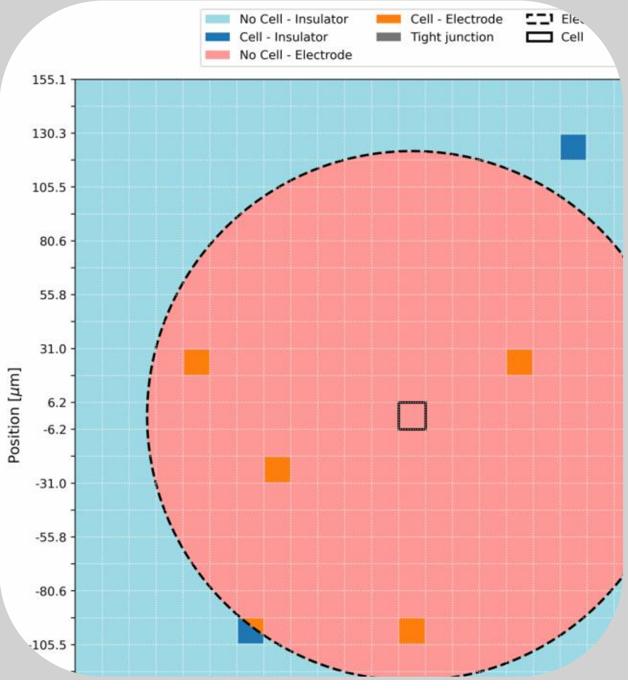
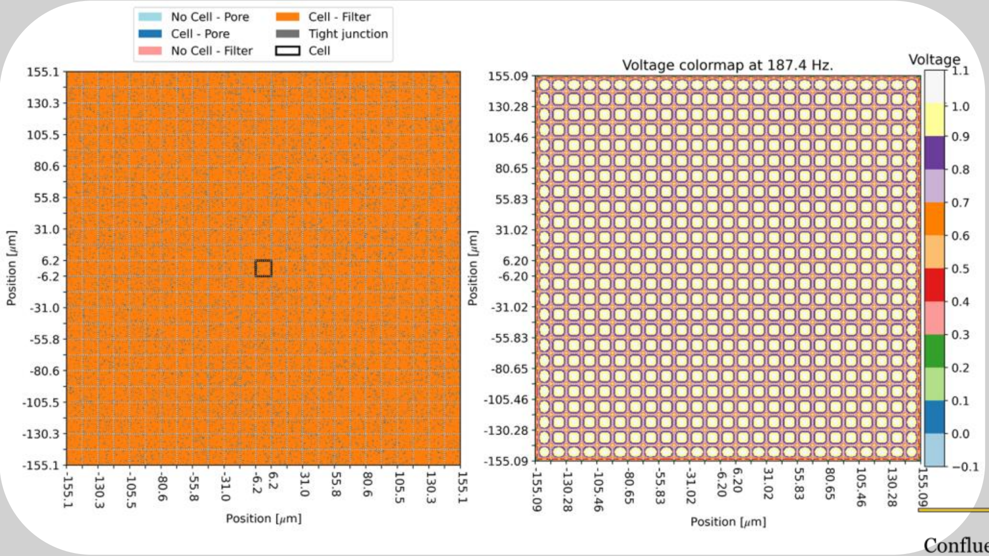
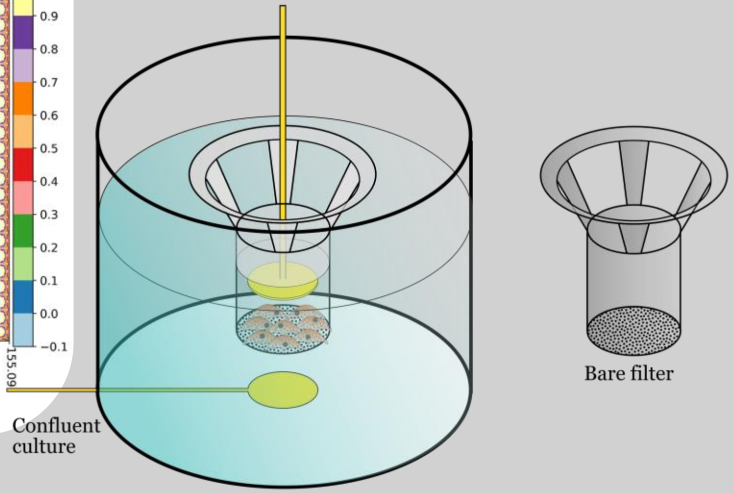


Simulate cell divition



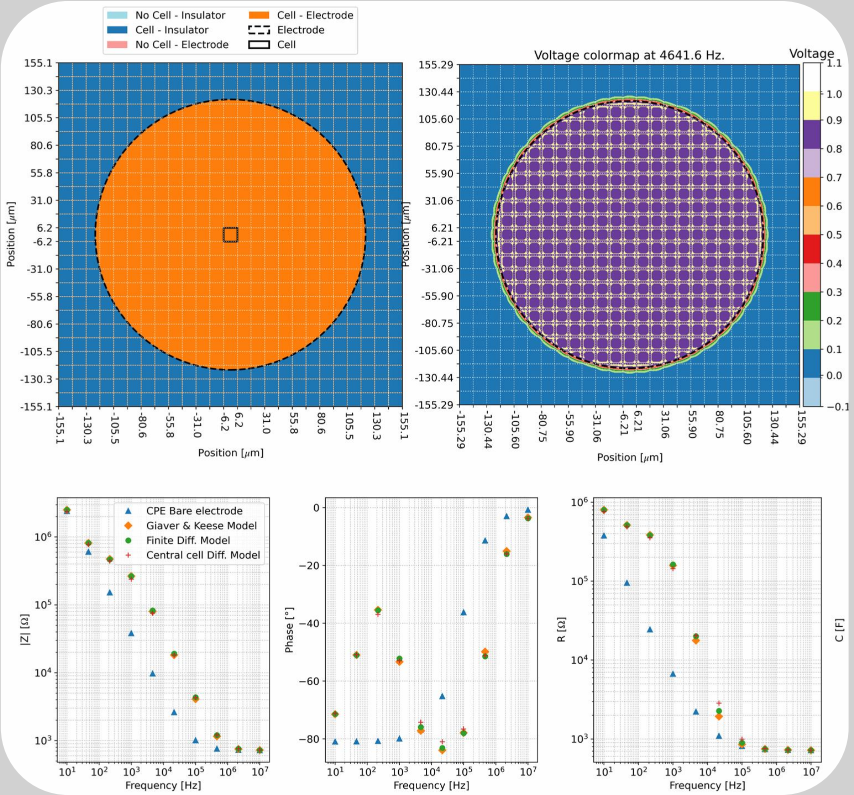
Adapt software for filter experiments

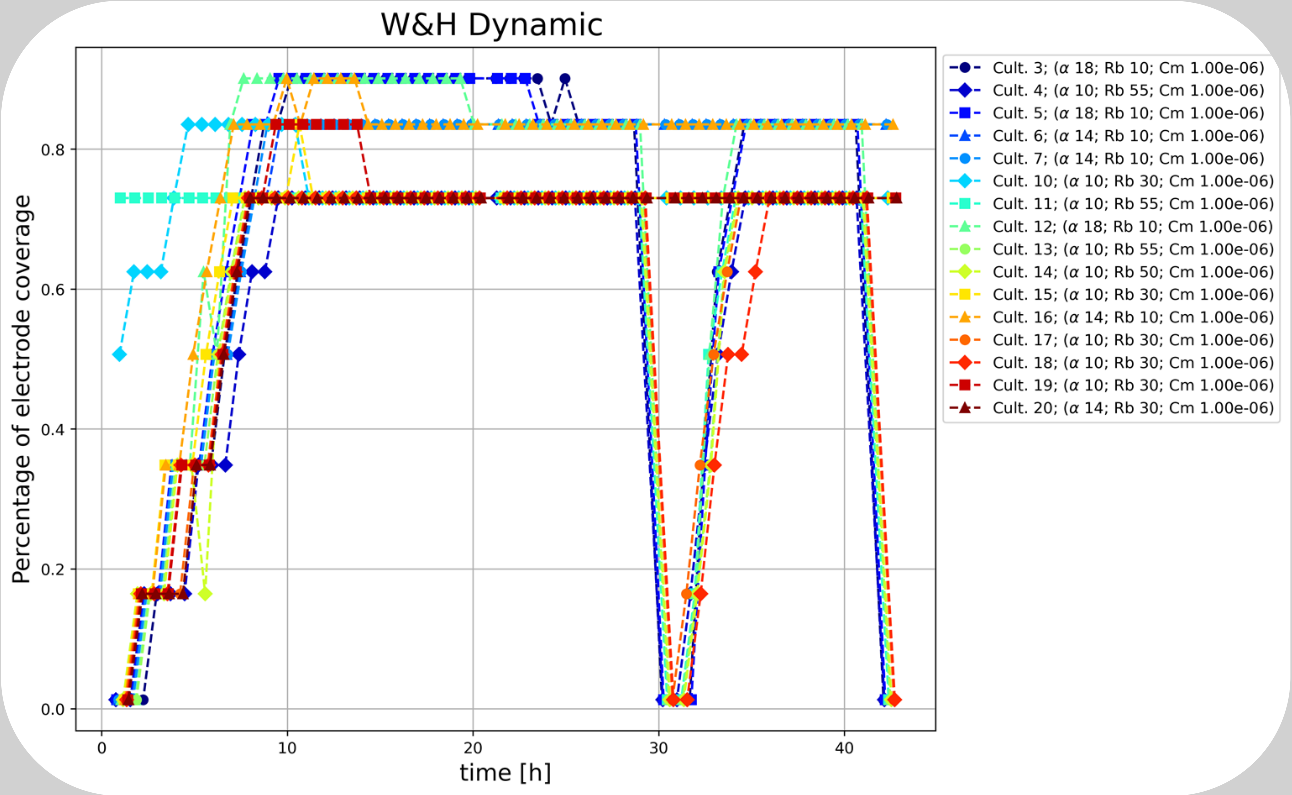




Resume up to the moment

- The number of cells above the electrode and insulator can be estimated at any moment of the measurement.

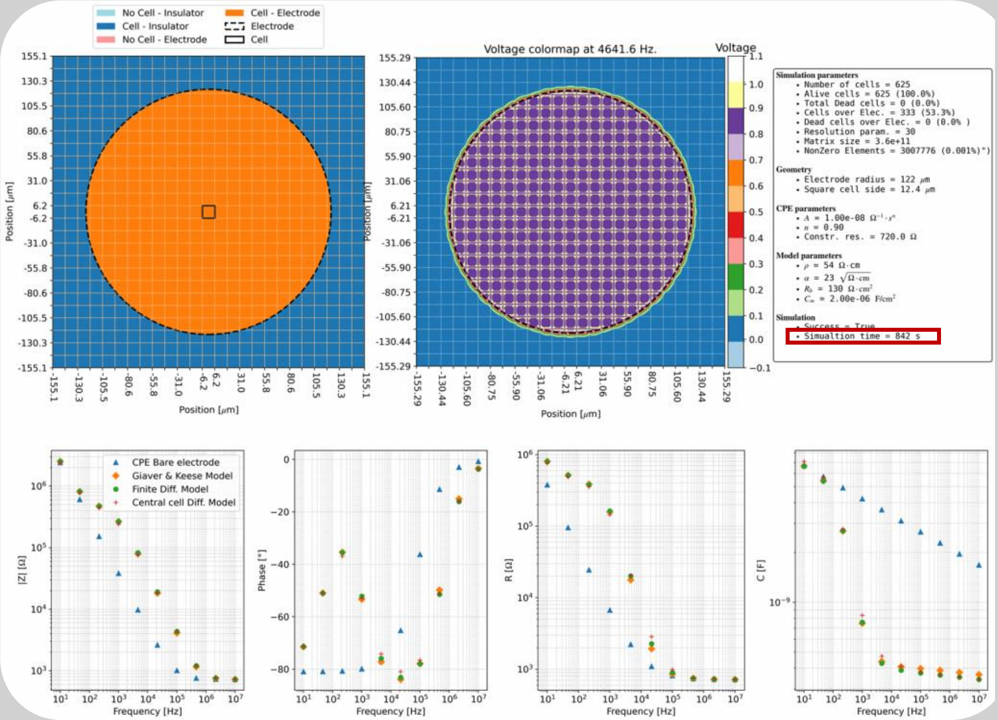




Resume up to the moment

- The number of cells above the electrode and insulator can be estimated at any moment of the measurement.

- Simulations are determined by the cell line and electrode in use and made in anticipation.

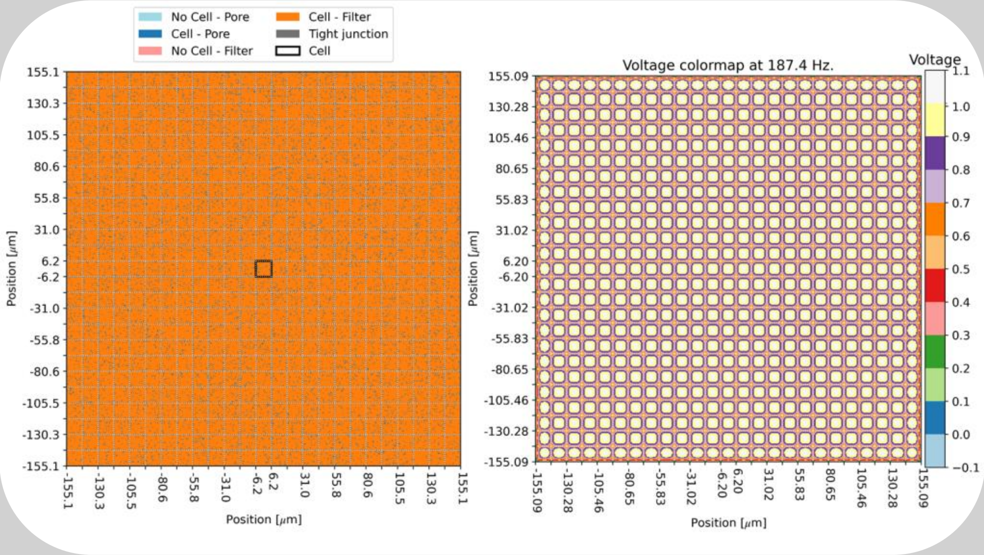


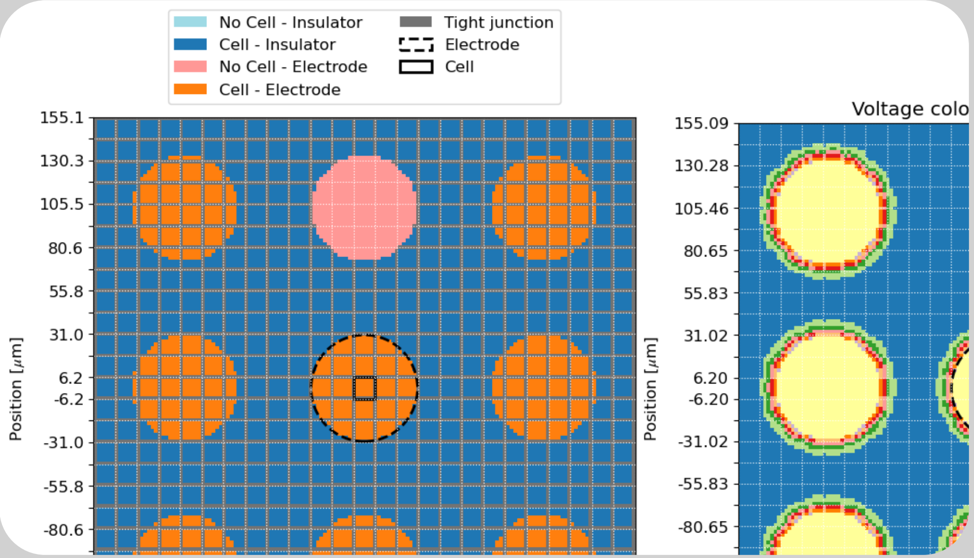
Resume up to the moment

- The number of cells above the electrode and insulator can be estimated at any moment of the measurement.

- Simulations are determined by the cell line and electrode in use and made in anticipation.

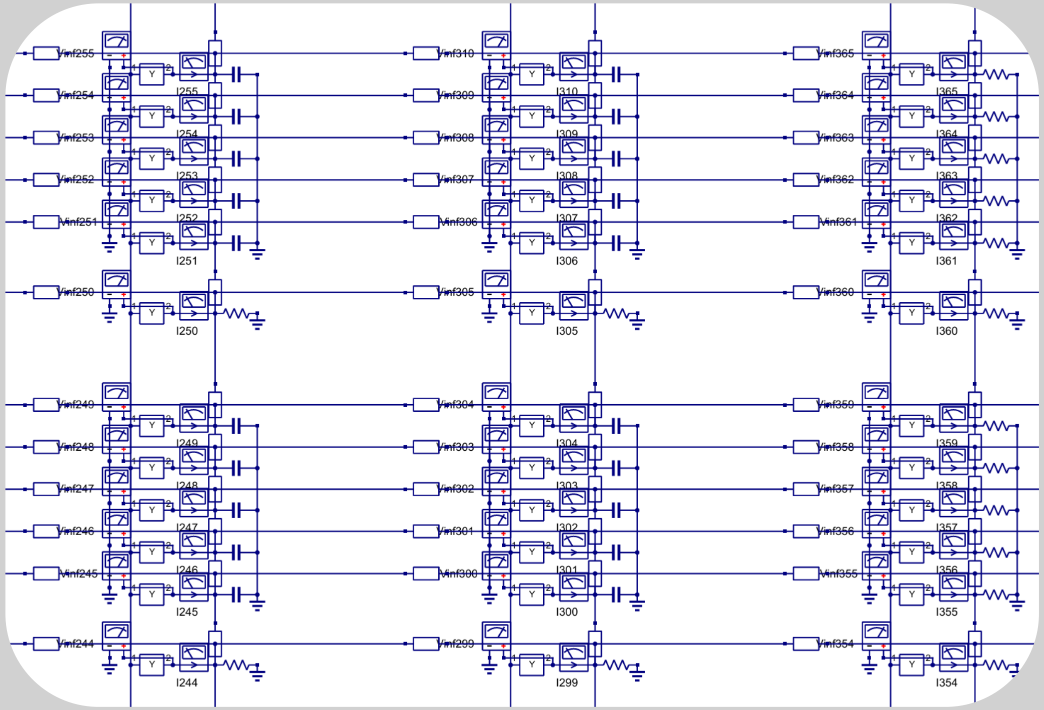
- The simulation can be adapted to different electrode shapes or substrates.

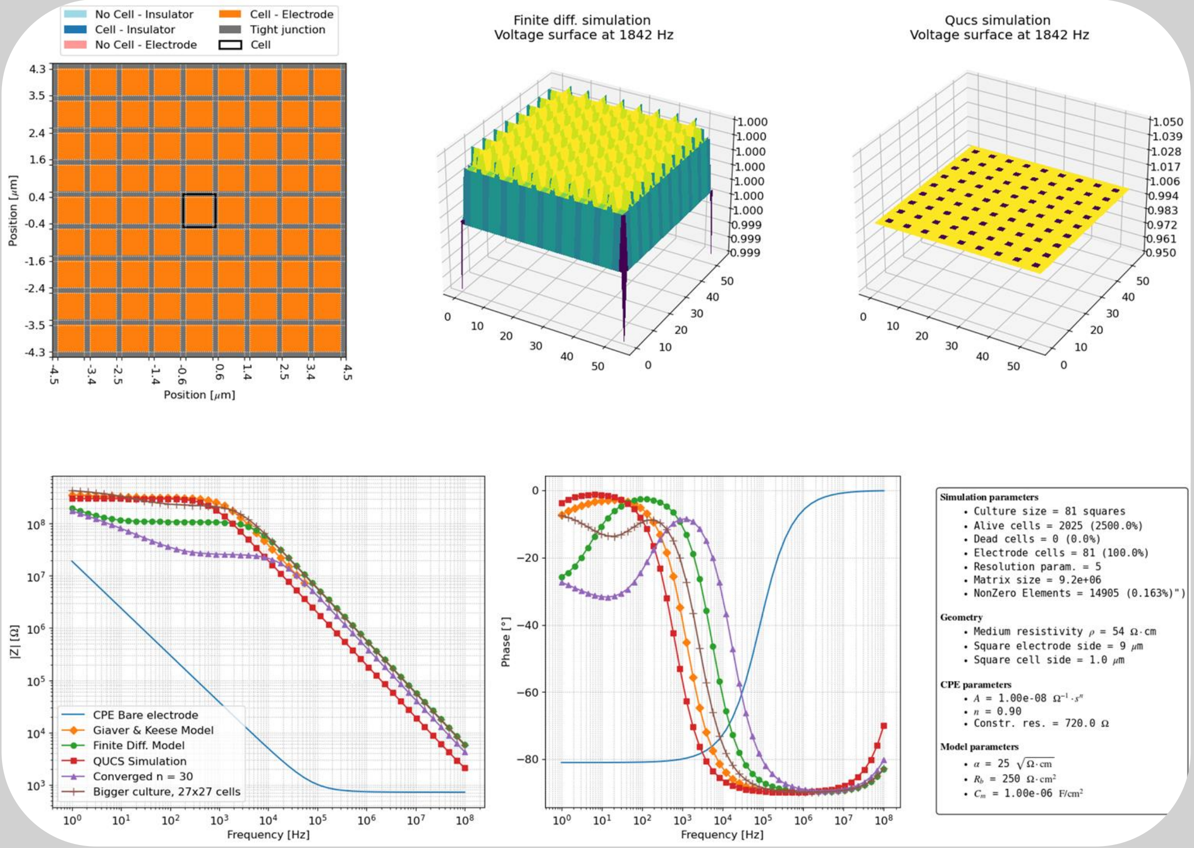




Thank you
Muchas gracias
Danke schön

Validation

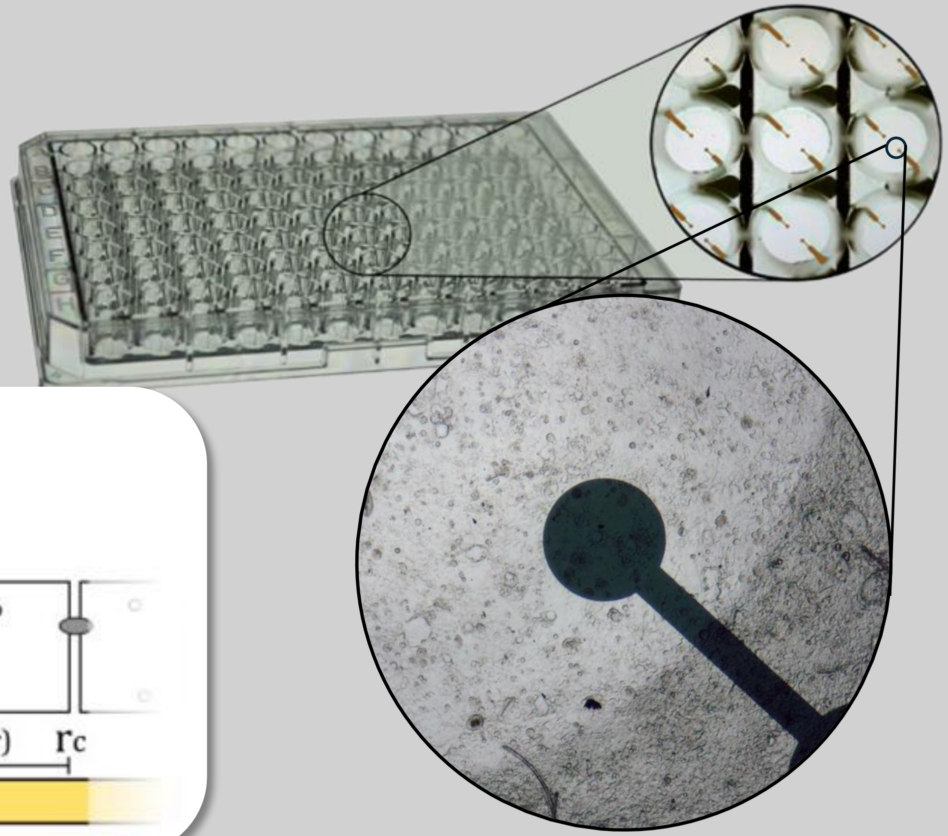


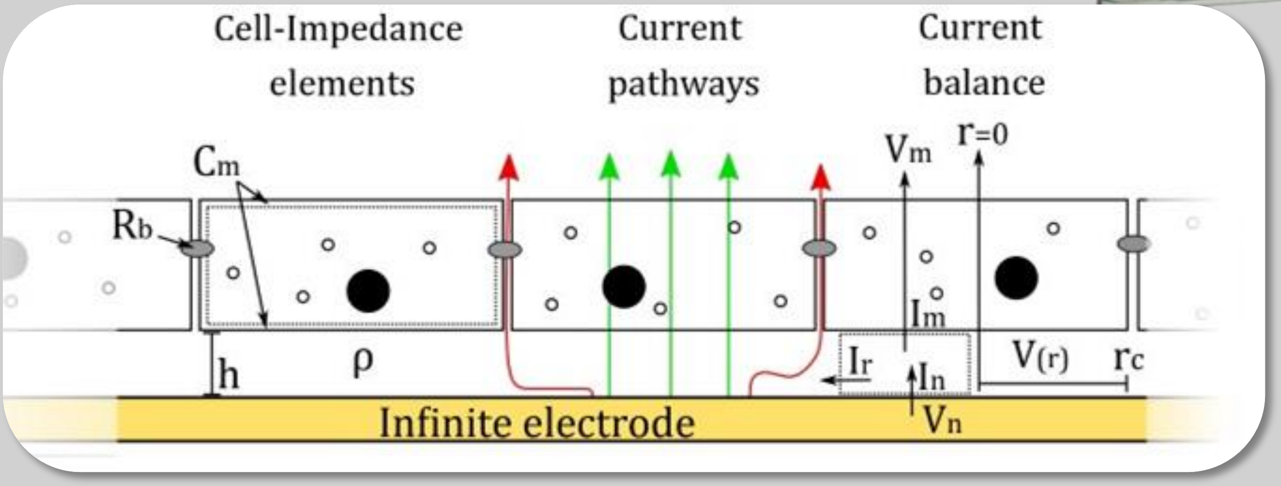

No Cell - Insulator
Cell - Insulator
No Cell - Electrode
Cell - Electrode
Tight junction
Cell
Position [μm]
Finite diff. simulation
Voltage surface at 1842 Hz
Qucs simulation
Voltage surface at 1842 Hz
|Z| [Ω]
Frequency [Hz]
CPE Bare electrode
Giaver & Keese Model
Finite Diff. Model
QUCS Simulation
Converged n = 30
Bigger culture, 27x27 cells
Phase [°]
Simulation parameters
• Culture size = 81 squares
• Alive cells = 2025 (2500.0%)
• Dead cells = 0 (0.0%)
• Electrode cells = 81 (100.0%)
• Resolution param. = 5
• Matrix size = 9.2e+06
• NonZero Elements = 14905 (0.163%)")
Geometry
• Medium resistivity ρ = 54 Ω·cm
• Square electrode side = 9 μm
• Square cell side = 1.0 μm
CPE parameters
• A = 1.00e-08 $\Omega^{-1} \cdot s^n$
• n = 0.90
• Constr. res. = 720.0 Ω
Model parameters
• α = 25 $\sqrt{\Omega \cdot cm}$
• R_b = 250 $\Omega \cdot cm^2$
• C_m = 1.00e-06 F/cm^2

Modelo de Giaver & Keese

- Mediante un modelo es posible estimar parámetros biofísicos subcelulares.

- Se modela un cultivo infinito sobre un electrodo infinito



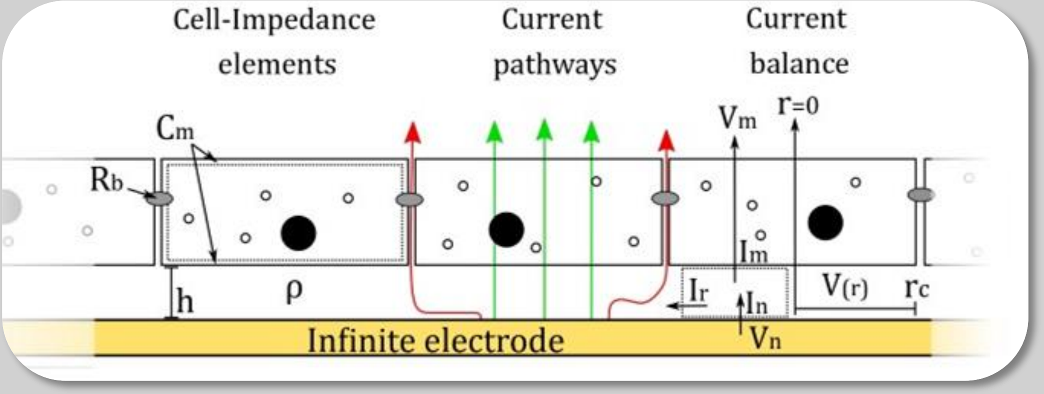


$$\frac{1}{Z_{cov}} = \frac{1}{Z_n(Z_n + Z_m)}\left[Z_n + \frac{Z_m}{\frac{\gamma r_c}{2}\frac{I_0(\gamma r_c)}{I_1(\gamma r_c)} + R_b\left(\frac{1}{Z_n} + \frac{1}{Z_m}\right)}\right]$$

$$\alpha = r_c\sqrt{\frac{\rho}{h}}.$$

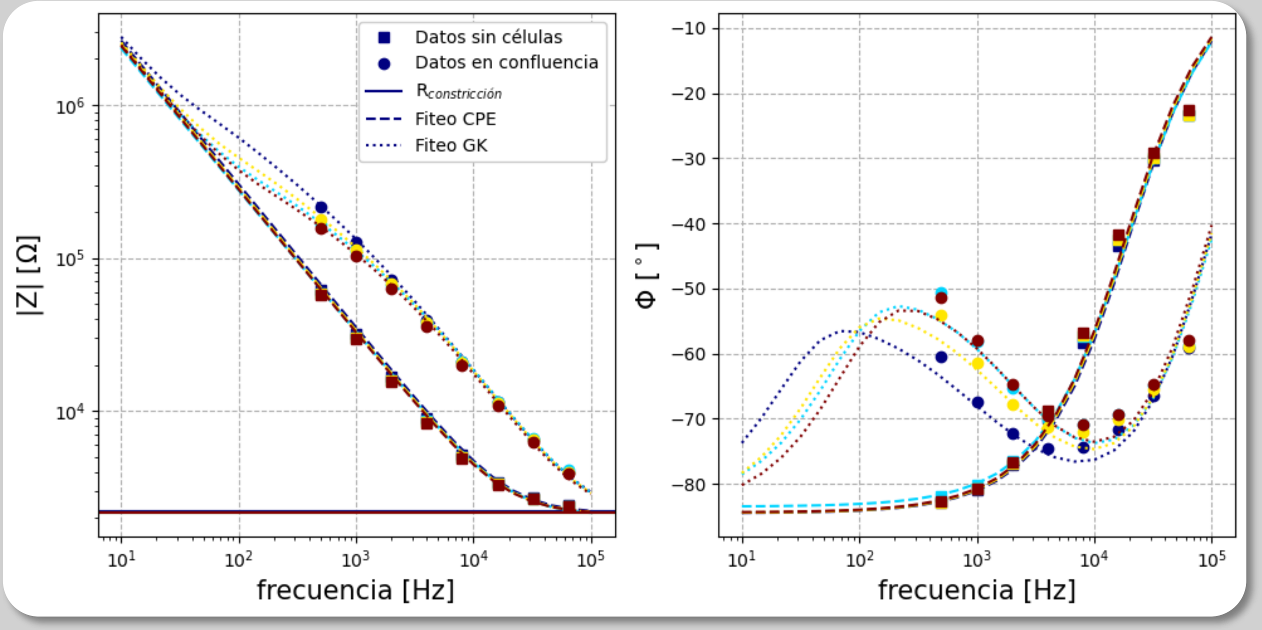
$$Z_m = -\frac{i}{2\pi f \frac{C_m}{2}}.$$

Modelo de Giaver & Keese



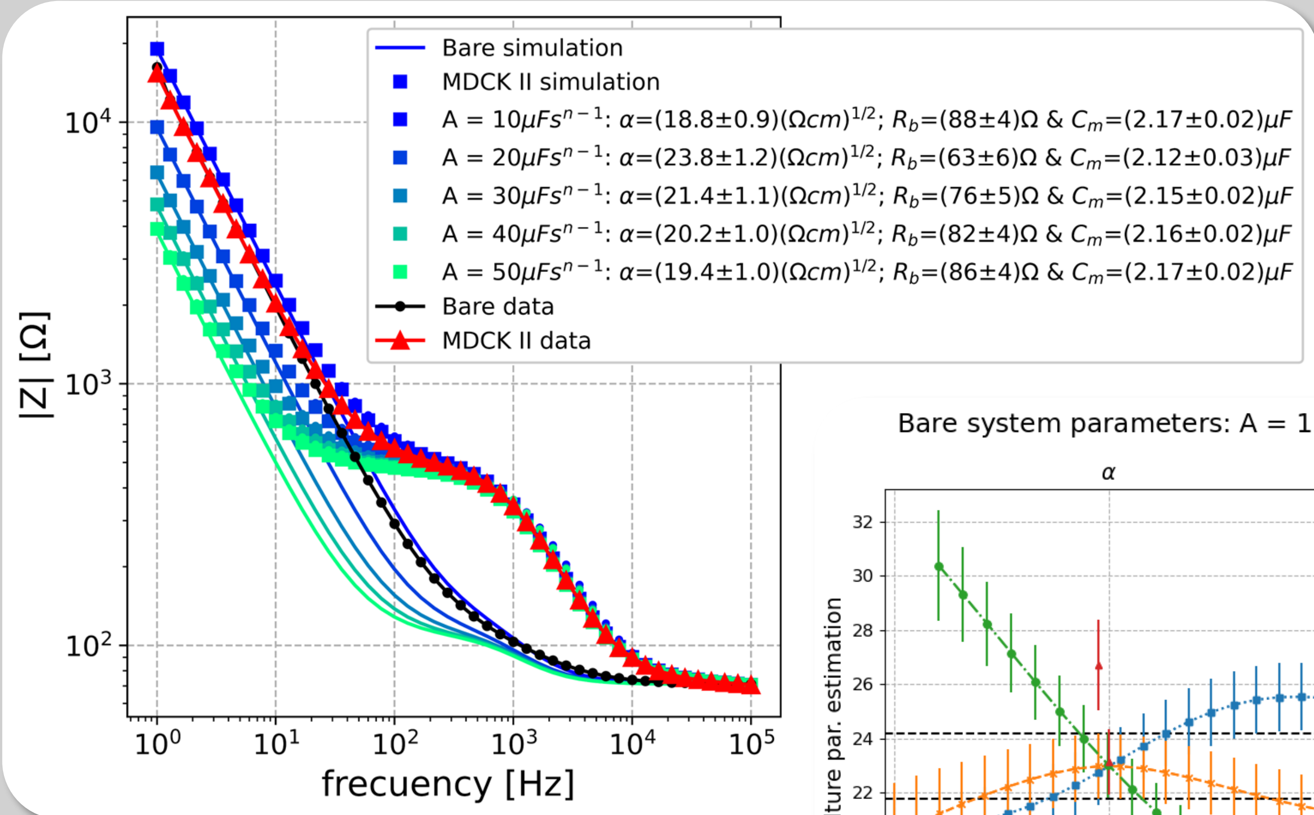
$$Z_{cov} = Z\left(Z_n, \rho, r_c, C_m, R_b, \alpha\right)$$

$$\rightarrow Z_{cov} = Z\left(C_m, R_b, \alpha\right)$$

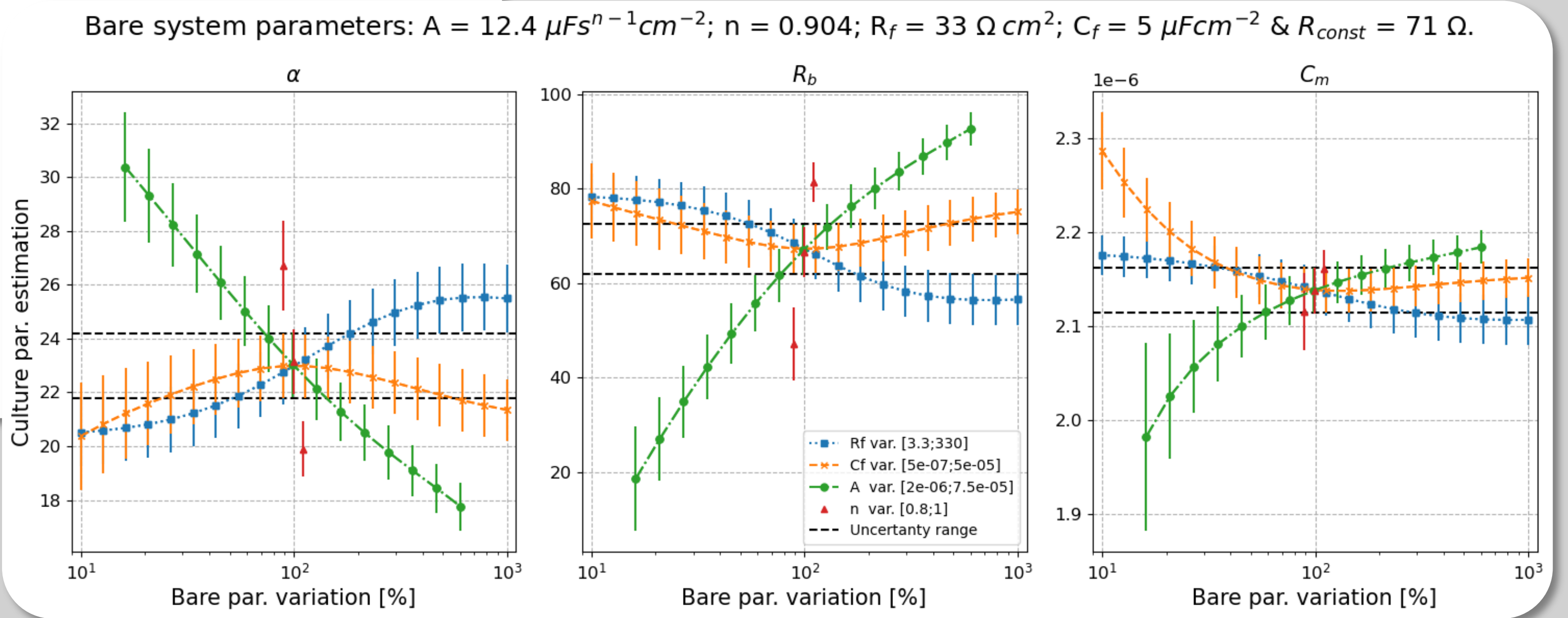


α = 22±8 [√Ωcm]
Rb = 21±5 [Ωcm^2]
Cm = 4.79±0.04 [$\mu F/cm^2$]

Dependencia del modelo al sistema de bioimpedancia



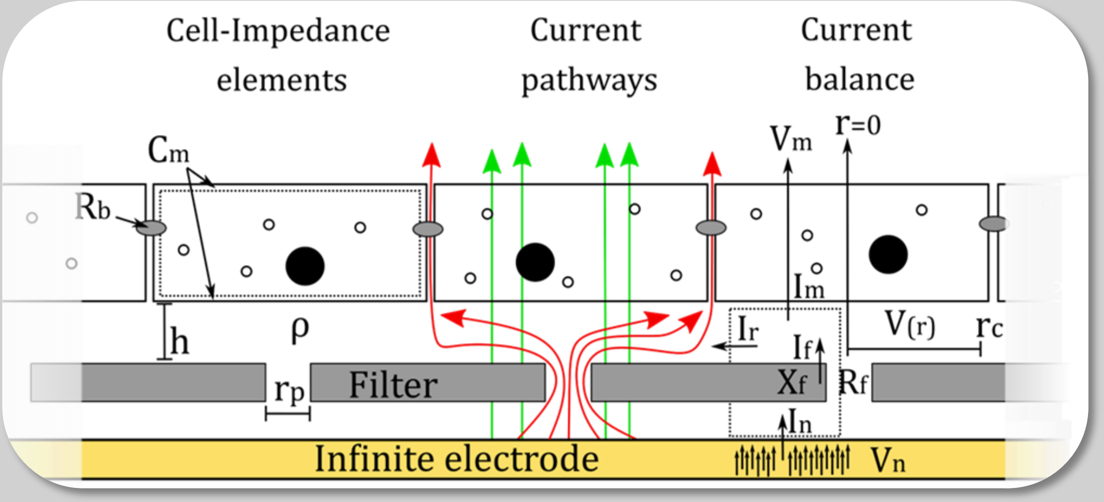
Para comparar parámetros biofísicos de cultivos monitoreados en distintos sistemas, la impedancia basal (sin células) debe ser igual



Modelo One Pore

- Se desarrolló un modelo considerando información de los filtros usados agregando 3 parámetros.

- Es necesario conocer los parámetros del filtro previamente a realizar la estimación del cultivo.



$$\frac{1}{Z_{cov}} = \frac{1}{r_c^2}\left\{\left[\frac{r_p^2}{\widetilde{Z_n^1}+Z_m} - \frac{2\widetilde{C_1}r_p}{\widetilde{Z_n^1}\gamma_1}I_1(\gamma_1 r_p)\right] + \left[\frac{(r_c^2-r_p^2)}{\widetilde{Z_n^2}+Z_m}\dots - \frac{2}{\widetilde{Z_n^2}}\frac{\widetilde{C_2}}{\gamma_2}\left[r_c I_1(\gamma_2 r_c) - r_p I_1(\gamma_2 r_p)\right] + \frac{2}{\widetilde{Z_n^2}}\frac{\widetilde{C_3}}{\gamma_2}\left[r_c K_1(\gamma_2 r_c) - r_p K_1(\gamma_2 r_p)\right]\right]\right\}.$$

where $\widetilde{C_i} = \frac{C_i}{V_n - V_m}$.

$$\begin{pmatrix} C_1 \\ C_2 \\ C_3 \end{pmatrix} = \frac{\left(V_m - \frac{\beta_2}{\gamma_2^2}\right)\begin{pmatrix} K_0(\gamma_2 r_p)\gamma_2 I_1(\gamma_2 r_p) + I_0(\gamma_2 r_p)\gamma_2 K_1(\gamma_2 r_p) \\ K_0(\gamma_2 r_p)\gamma_1 I_1(\gamma_1 r_p) + I_0(\gamma_1 r_p)\gamma_2 K_1(\gamma_2 r_p) \\ -I_0(\gamma_2 r_p)\gamma_1 I_1(\gamma_1 r_p) + I_0(\gamma_1 r_p)\gamma_2 I_1(\gamma_2 r_p) \end{pmatrix}}{\left[I_0(\gamma_2 r_c) + \frac{2hR_b\gamma_2}{r_c\rho}I_1(\gamma_2 r_c)\right]\left(I_0(\gamma_1 r_p)\gamma_2 K_1(\gamma_2 r_p) + K_0(\gamma_2 r_p)\gamma_1 I_1(\gamma_1 r_p)\right) + \left[K_0(\gamma_2 r_c) - \frac{2hR_b\gamma_2}{r_c\rho}K_1(\gamma_2 r_c)\right]\left(-I_0(\gamma_2 r_p)\gamma_1 I_1(\gamma_1 r_p) + I_0(\gamma_1 r_p)\gamma_2 I_1(\gamma_2 r_p)\right)}$$