Developing a computational model of heterogeneous pancreatic islet cell interactions

Logan Barrios (IPHY), Pedro Lemos (CS), Zachary Caterer (ChBE)

Richard Benninger (Bioengineering, Anschutz) and Stephen Kissler (CS)

The Understanding of the Pancreas

Project Motivation and Goals

Model Development

Experimental Validation

Model Analysis

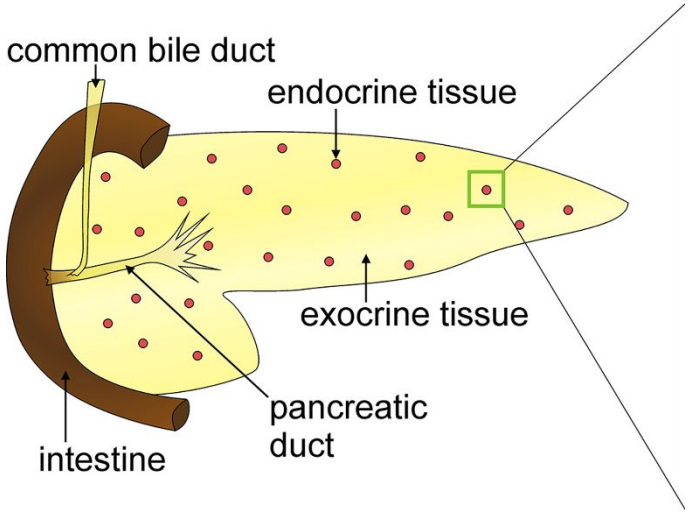
Conclusions and Future Directions

The Diabetes Epidemic

- In 2021, 537 million adults worldwide had a form of diabetes
- Diabetes is characterized by high blood glucose as a result of insufficient secretion of insulin
  - Type 1 Diabetes
  - Type 2 Diabetes
- Improvements needed to make more sustainable interventions and work towards a cure

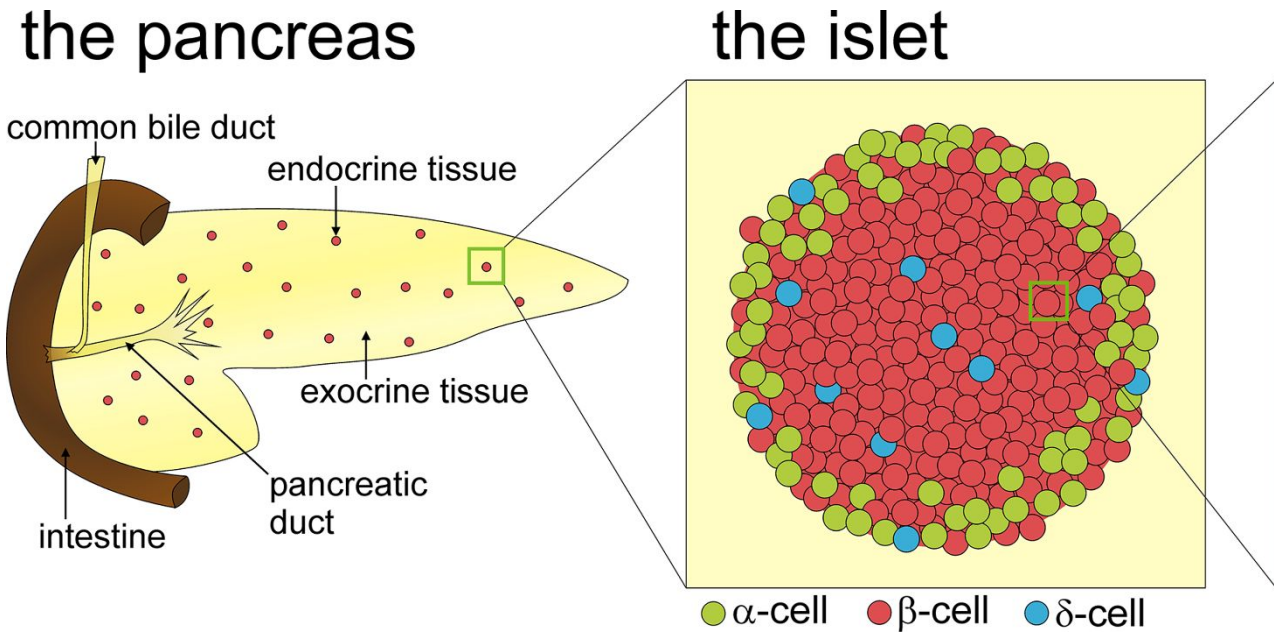
Understanding the pancreas

the pancreas



MacDonald, et al. PLoS Biol **(2006)**.

Understanding the pancreas



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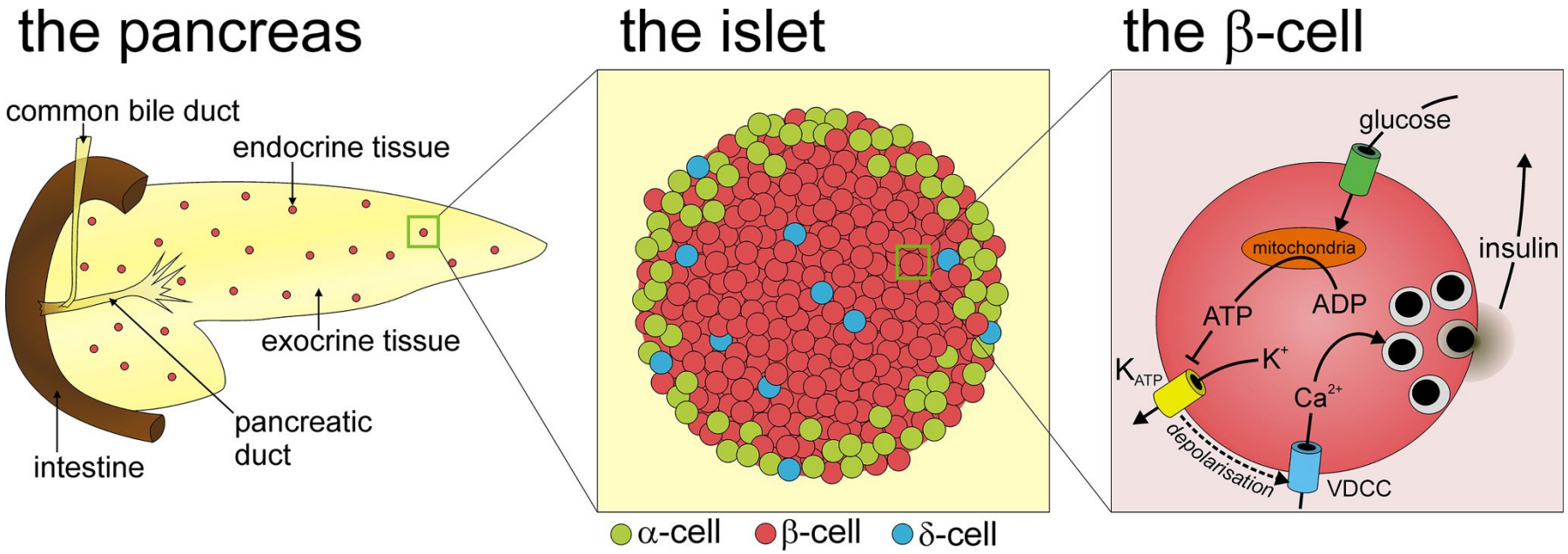

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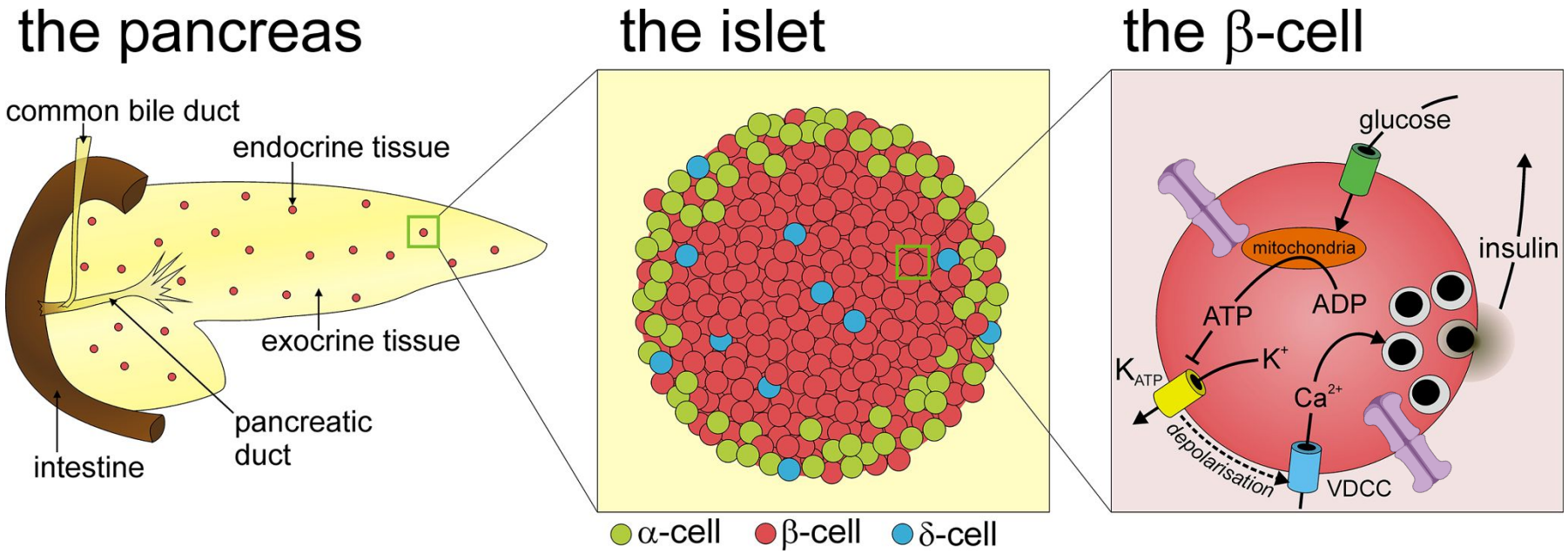

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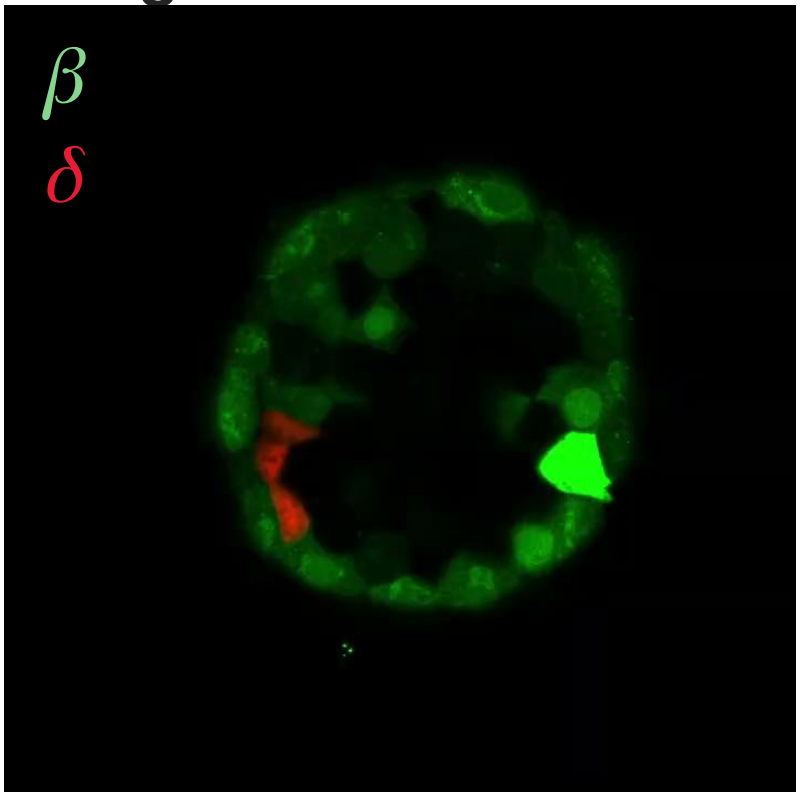
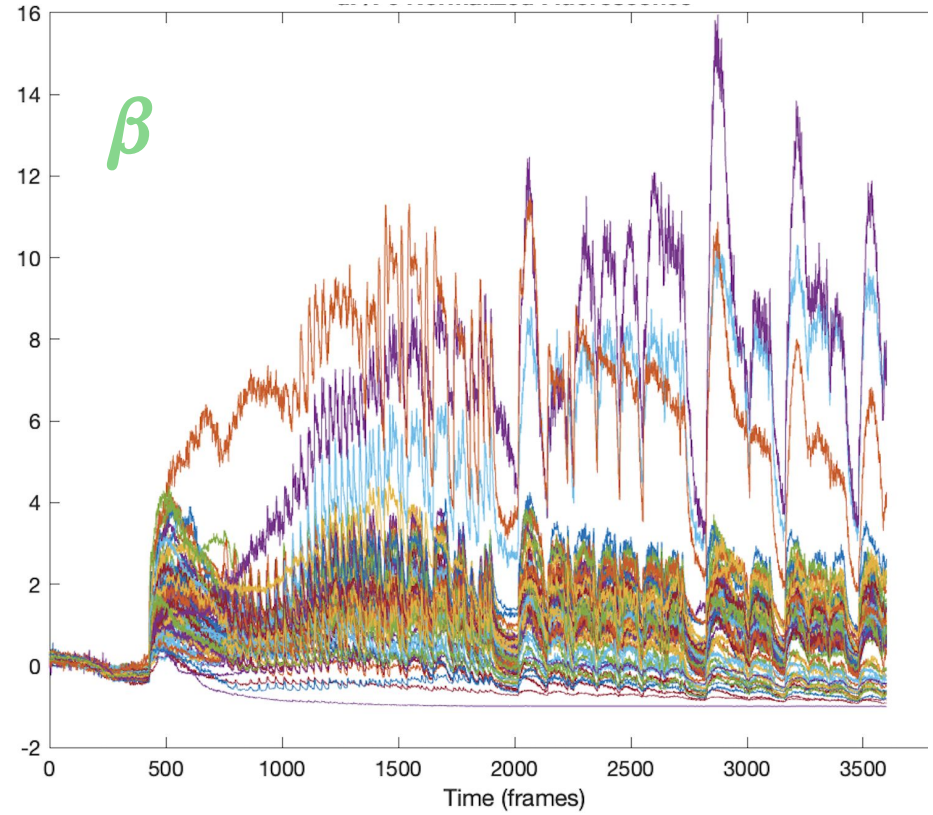
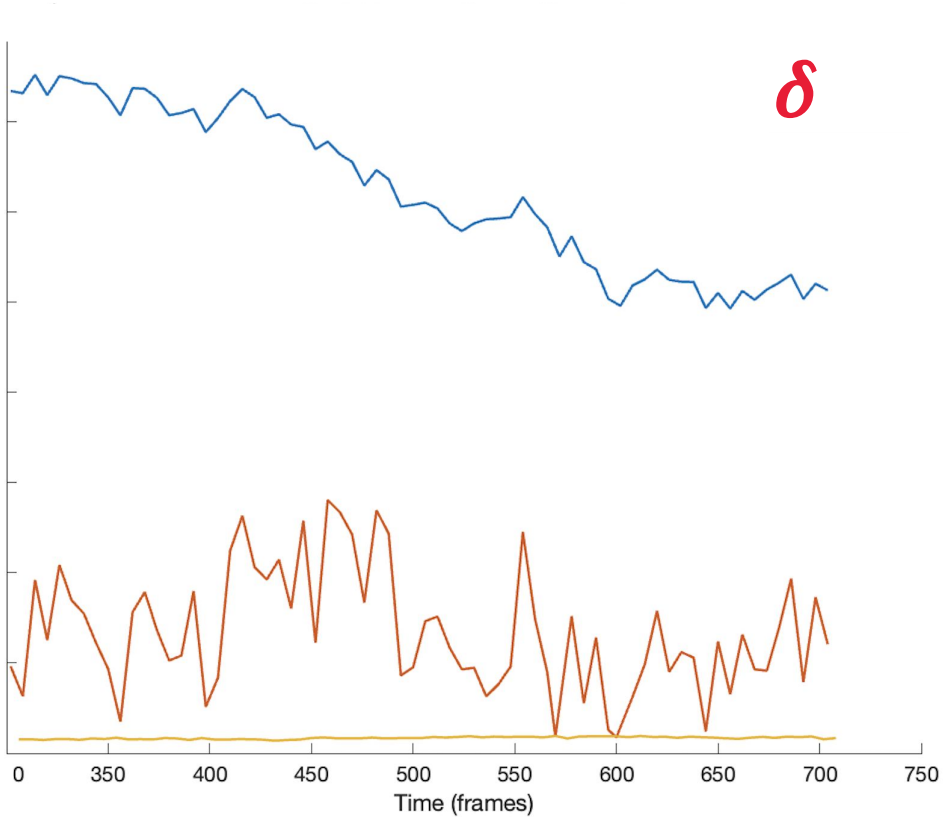
How this electrical coupling with other pancreatic cells, particularly delta cells, impacts the metabolic process is still being studied



Delta cell heterogeneity impact on insulin response





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Goals of our project

- Develop a Scalable Islet Model
- Implement Electrical Coupling Mechanisms
- Refine Electrophysiology Modeling
- Integrate Experimental Data
- Enhance Model Visualization

Understanding of the Pancreas

Project Motivation and Goals

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Single Cell Beta (β) & Delta (δ) Model

Single beta (β) cell model

$$C_m \frac{dV}{dt} = -\sum_k I_k(t)$$

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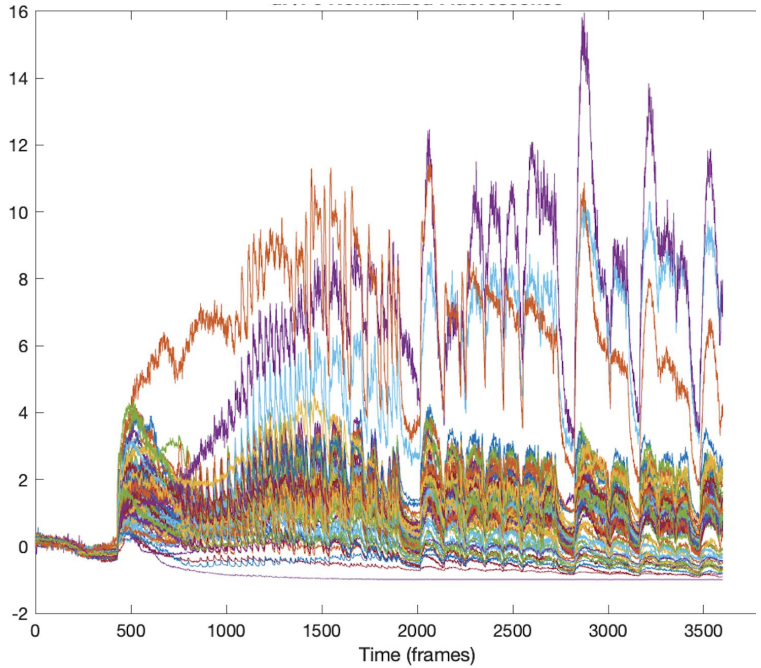
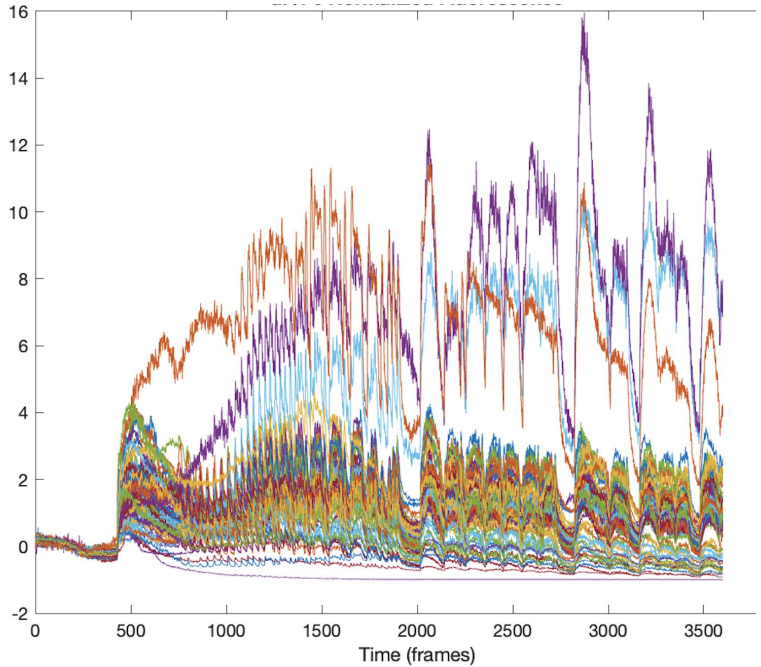


Single Cell Beta (β) & Delta (δ) Model

Single beta (β) cell model

$$C_m \frac{dV}{dt} = -\sum_k I_k(t)$$

$$\sum_k I_k(t) = I_{Ca} + I_K + I_{leak} + I_{K(Ca)} + I_{KATP}$$



- Adapted from "The Phantom Burster Model for Pancreatic Beta-Cells", Biophysical Journal, vol. 79, pp. 2880-2892, 2000

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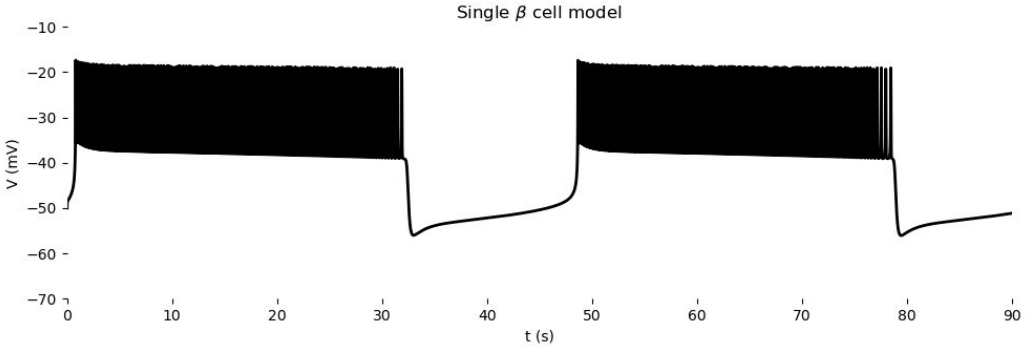

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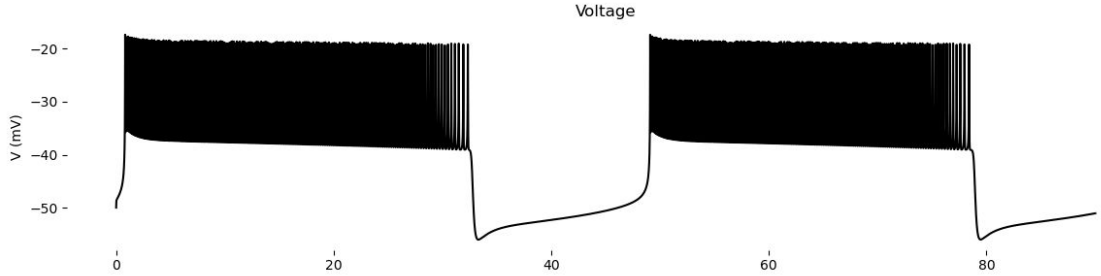

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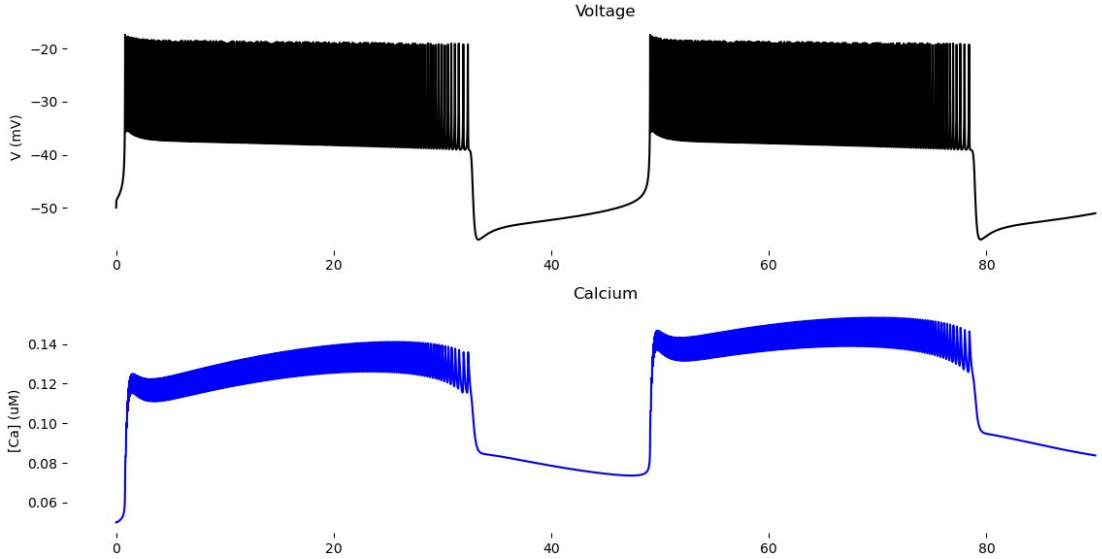

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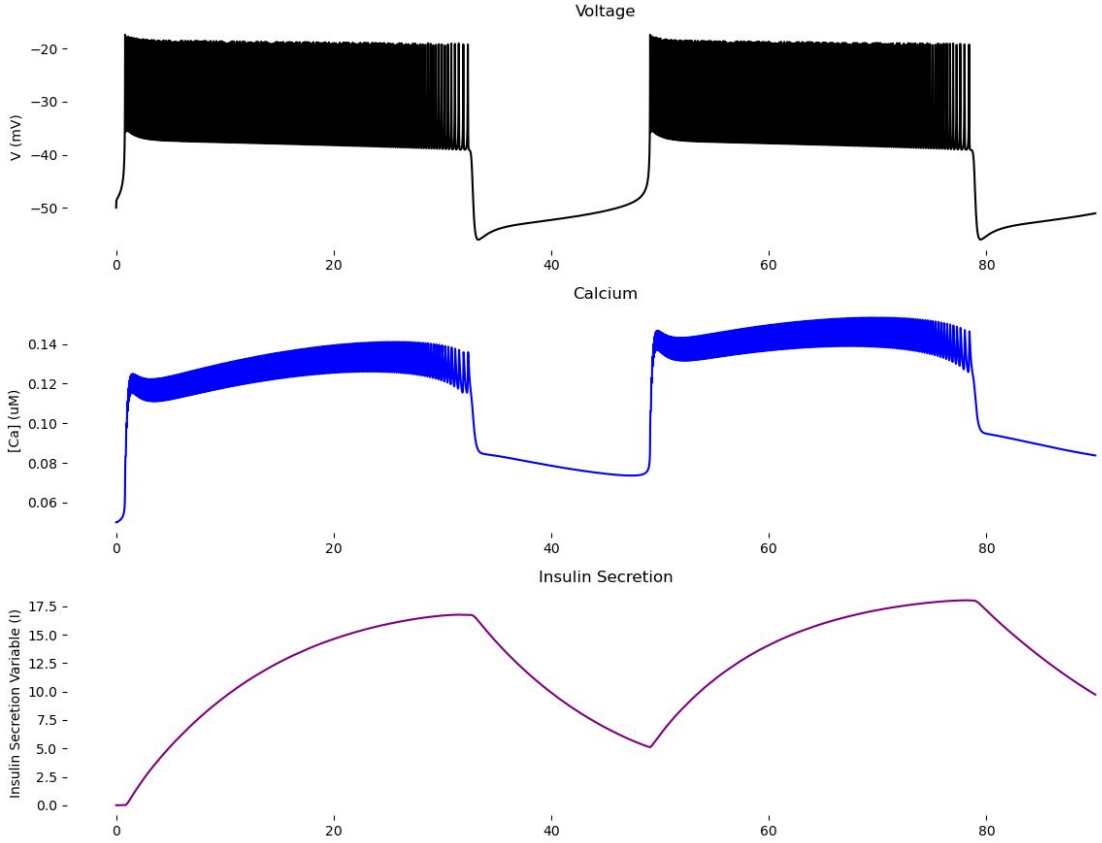

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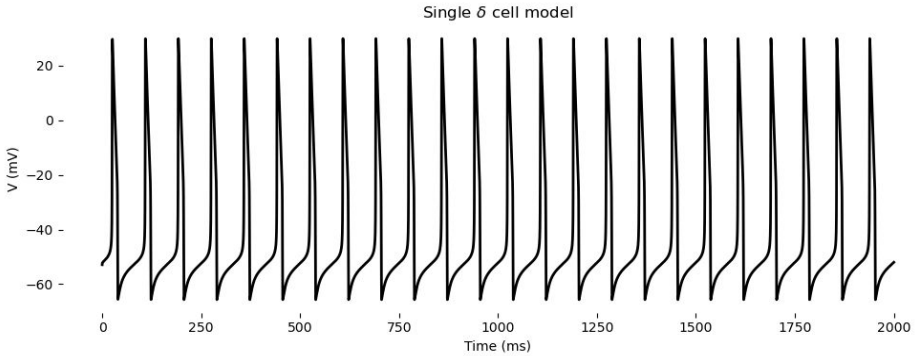

$$\sum_k I_k(t) = -(I_{CaL} + I_{CaT} + I_{CaN} + I_{Na} + I_{Kdr} + I_{KATP} + I_{Ka} + I_{leak})$$

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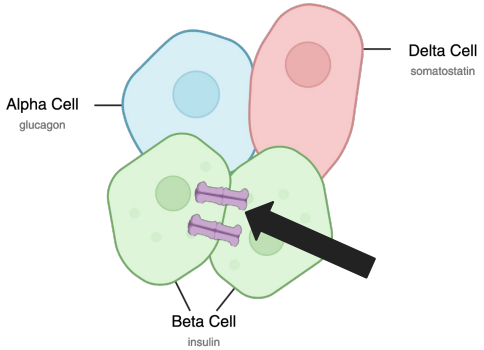
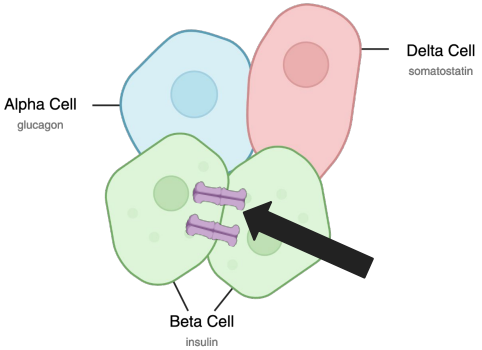
Coupled Beta Cell Model (Beta (β) - Beta (β))



Coupled Beta Cell Model (Beta (β) - Beta (β))

$$C_m \frac{dV}{dt} = -\sum_k I_k(t) + I_{GJ}$$



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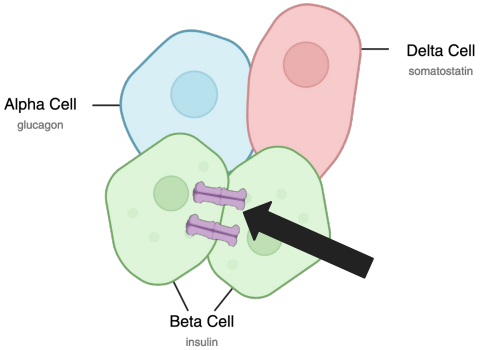
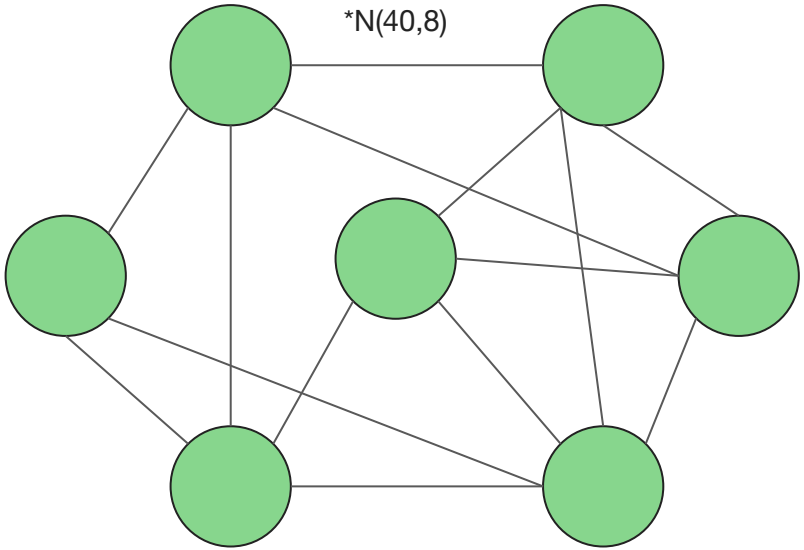


$$C_m \frac{dV}{dt} = -\sum_k I_k(t) \boxed{+ I_{GJ}}$$

* Gap junction coupling between beta cells

Beta cells coupled to 1 to 5 other beta cells

Synchrony improves insulin release



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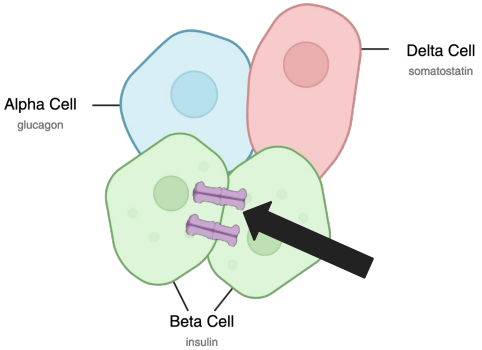

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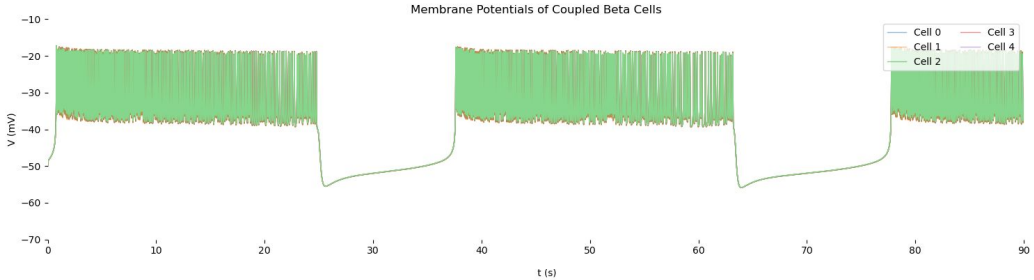

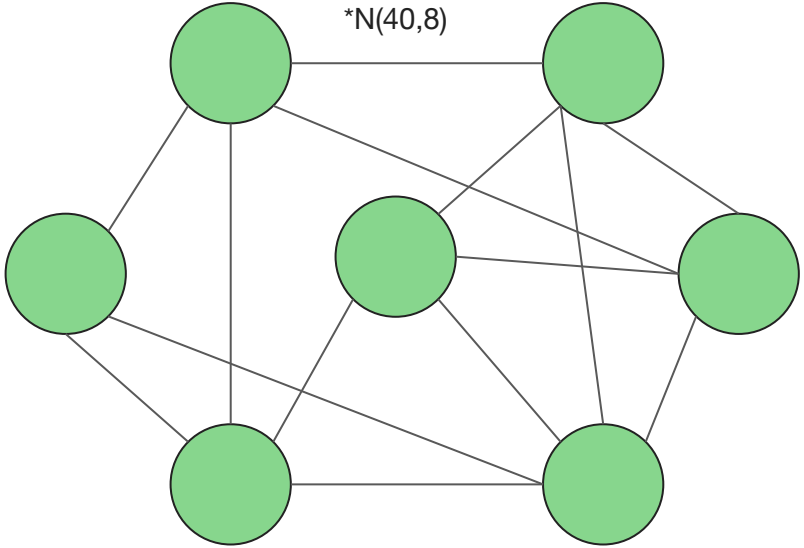

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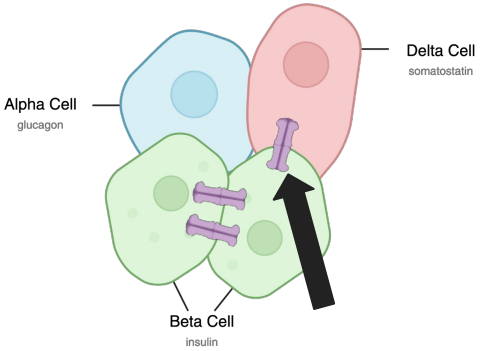

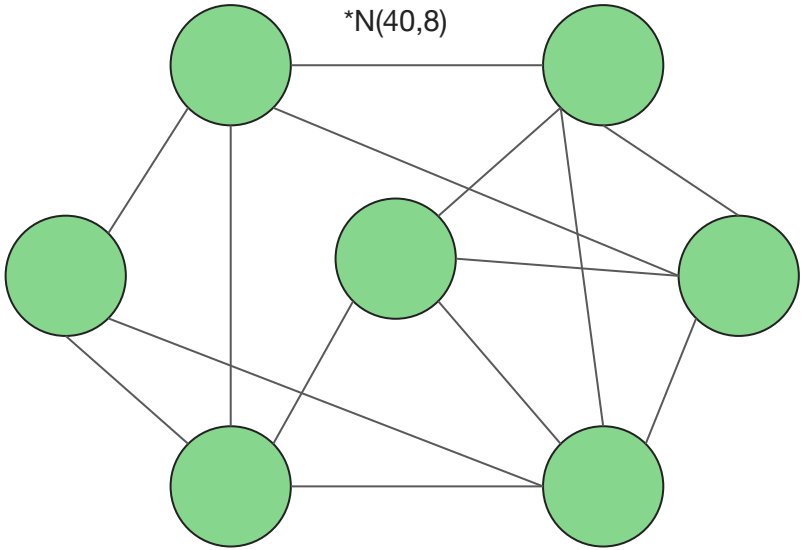

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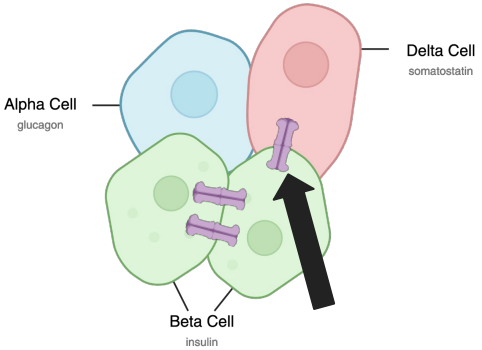
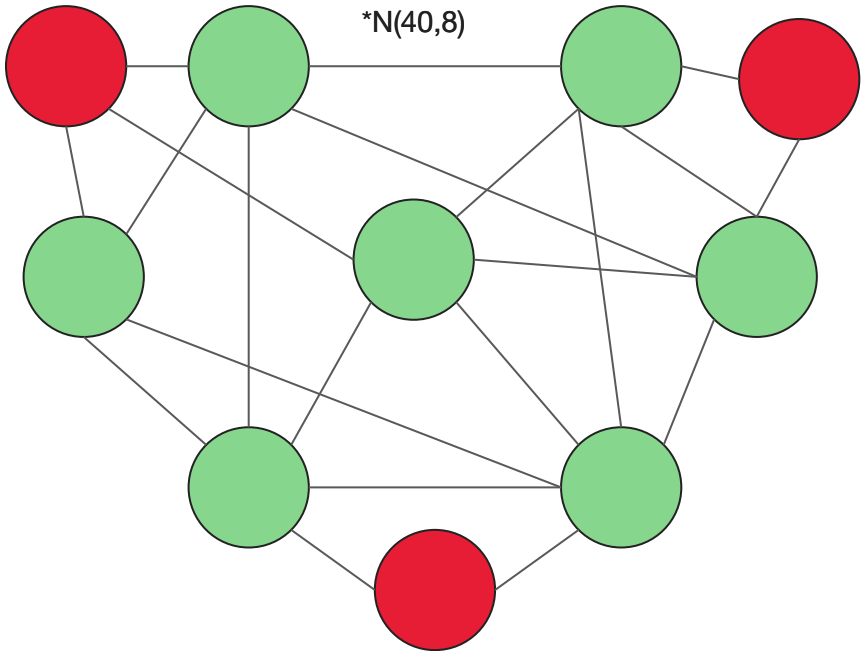
Delta cells modulate beta cell activity via paracrine somatostatin signaling





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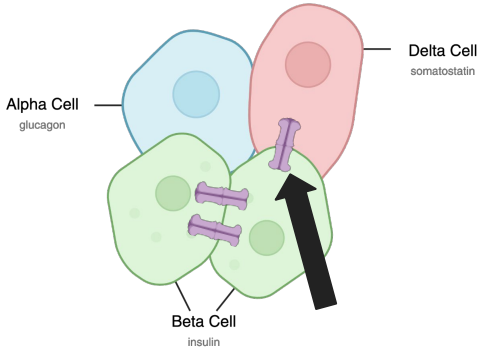

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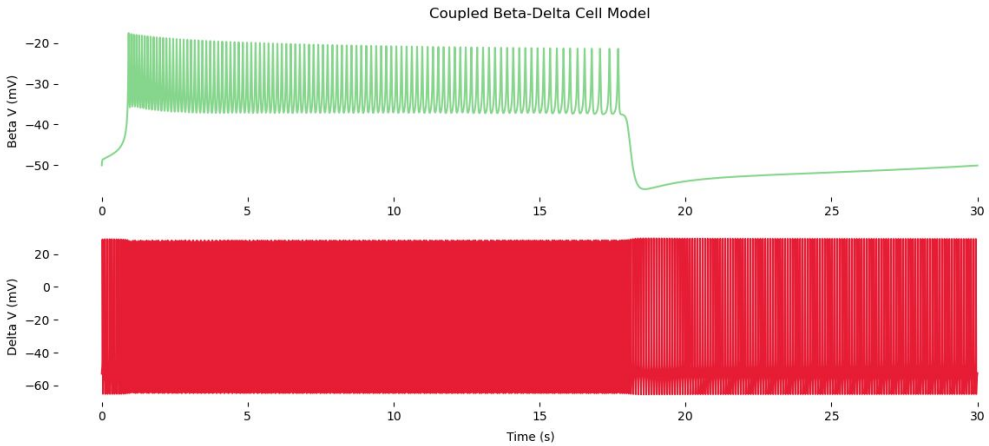

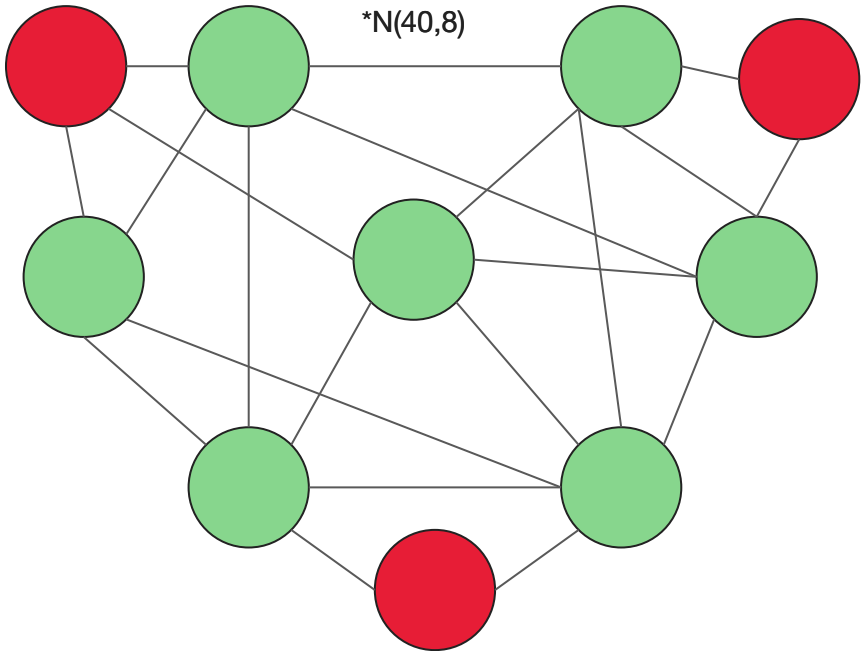

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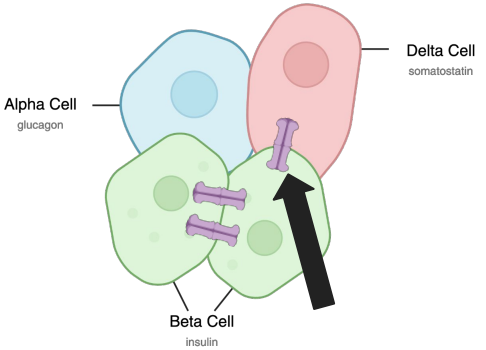

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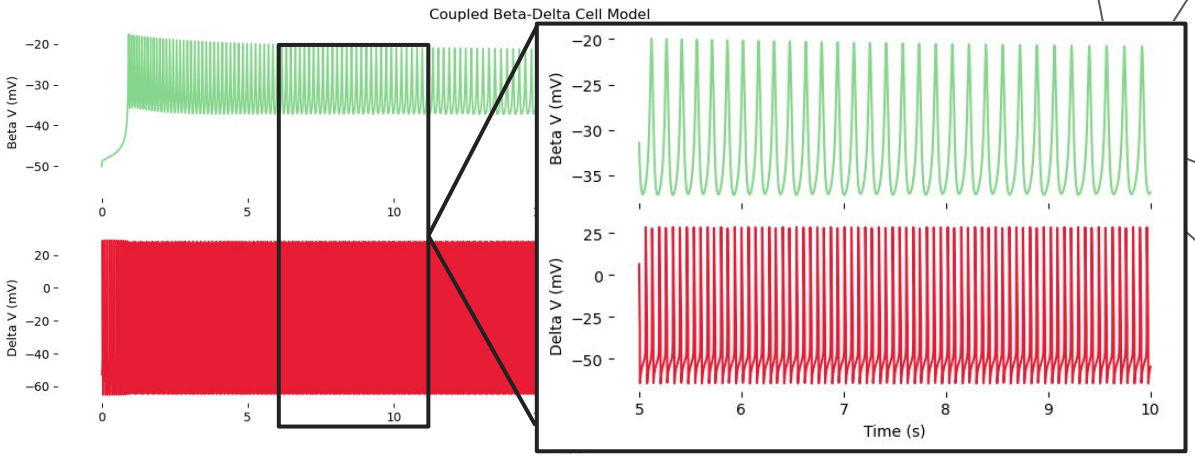

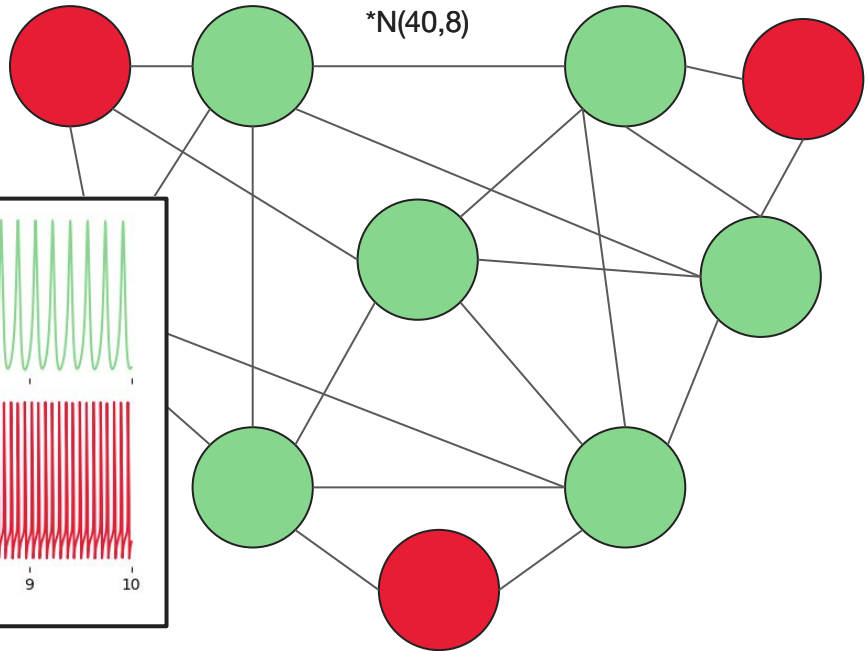

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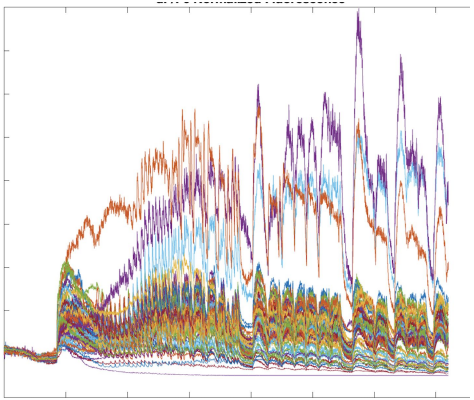
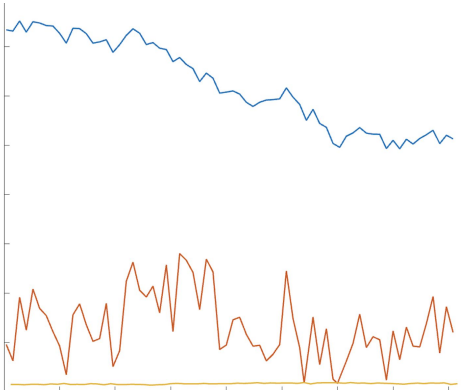
Experimental validation of our model

wild type

Gap Junction KO





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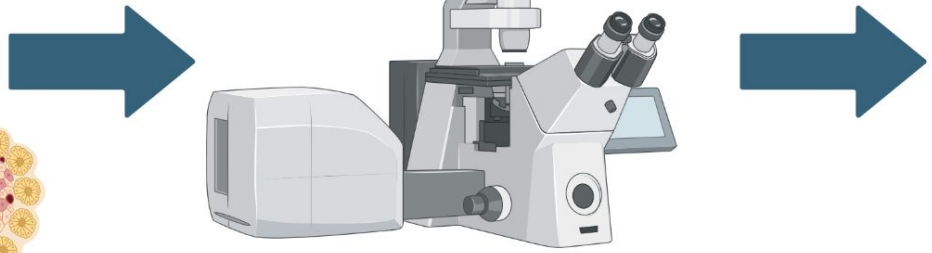
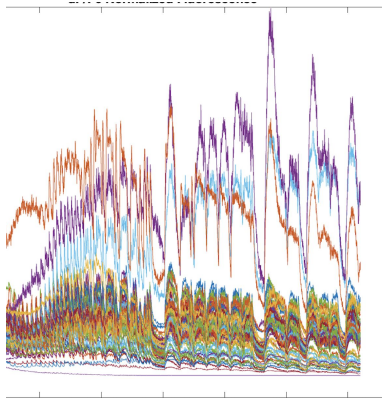
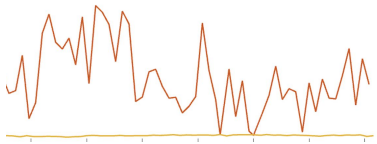
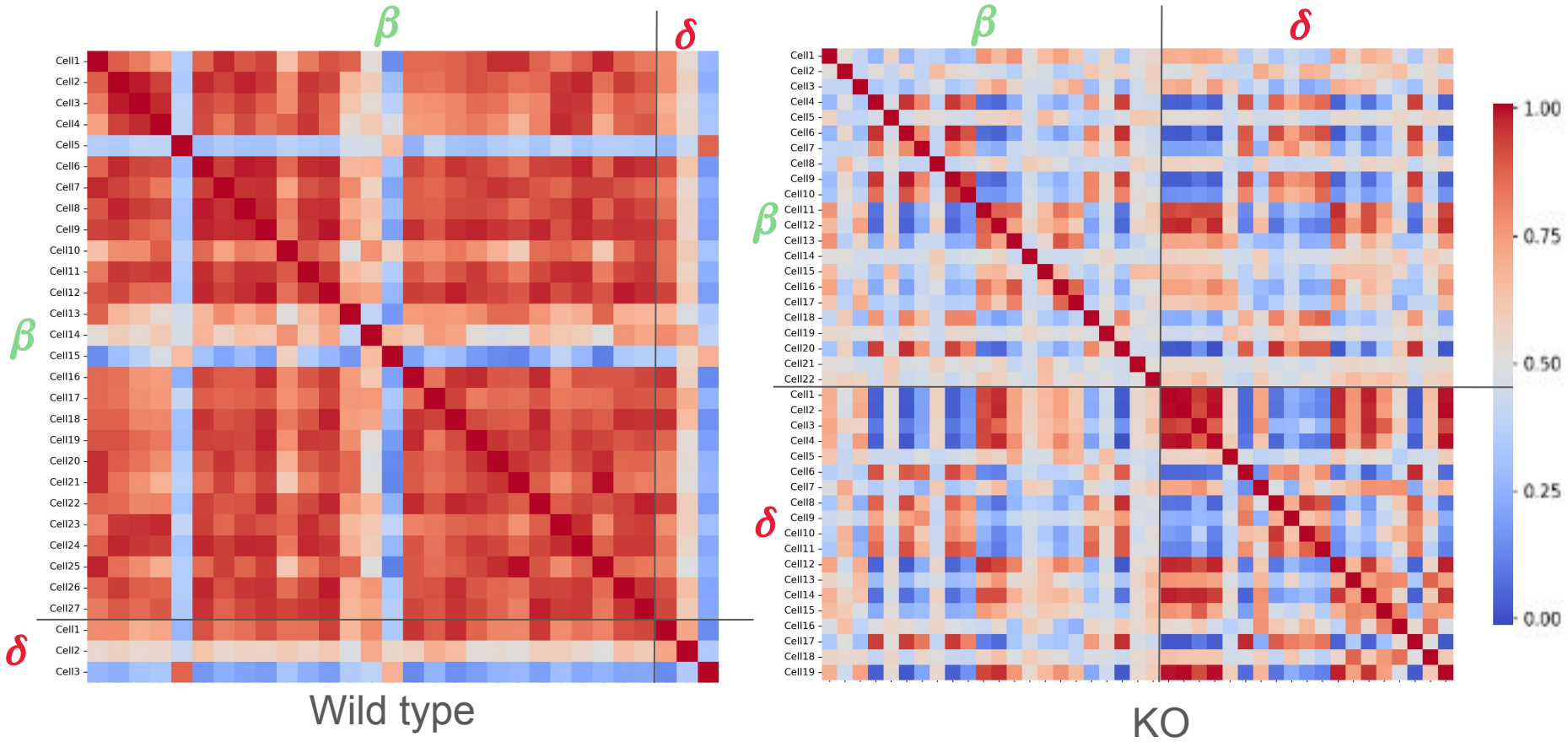






Wild type pancreatic islet cells experience more synchronization and heterogeneity



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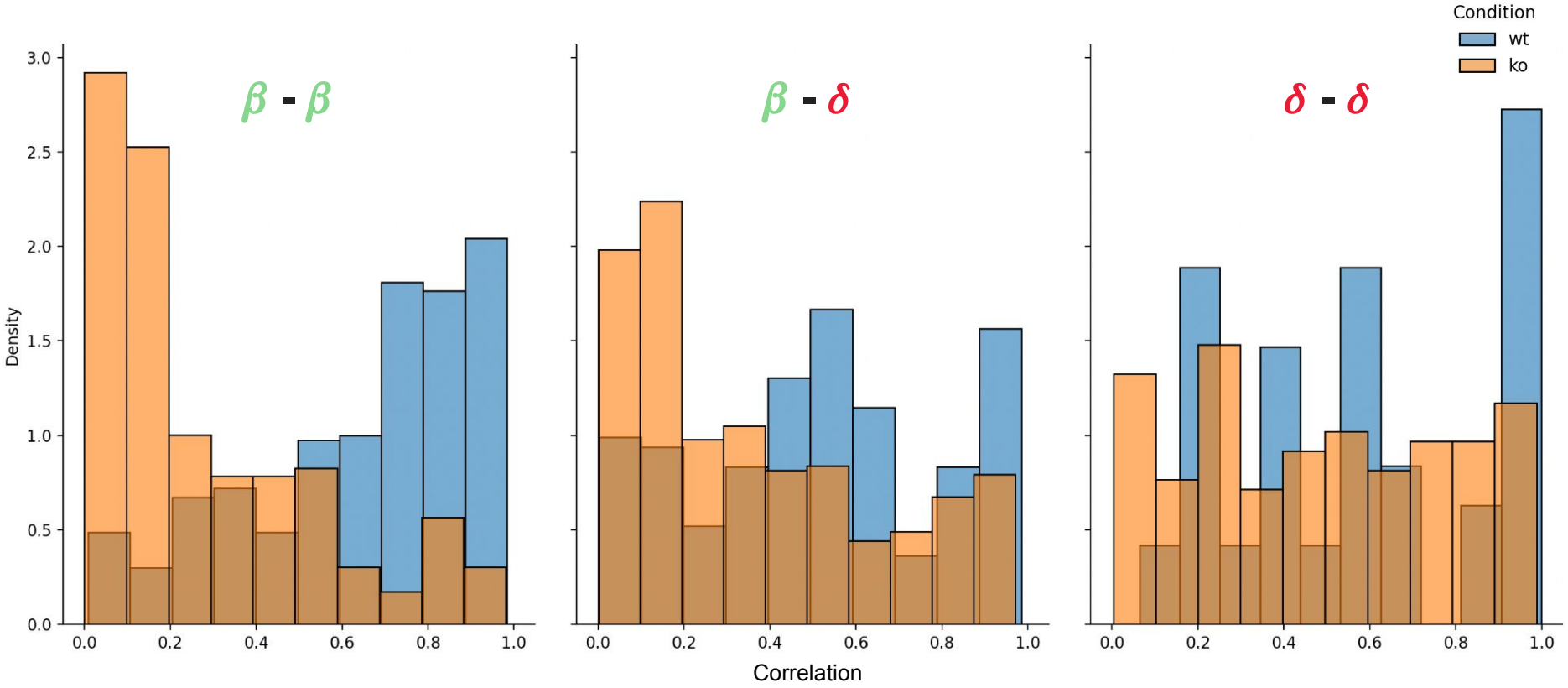

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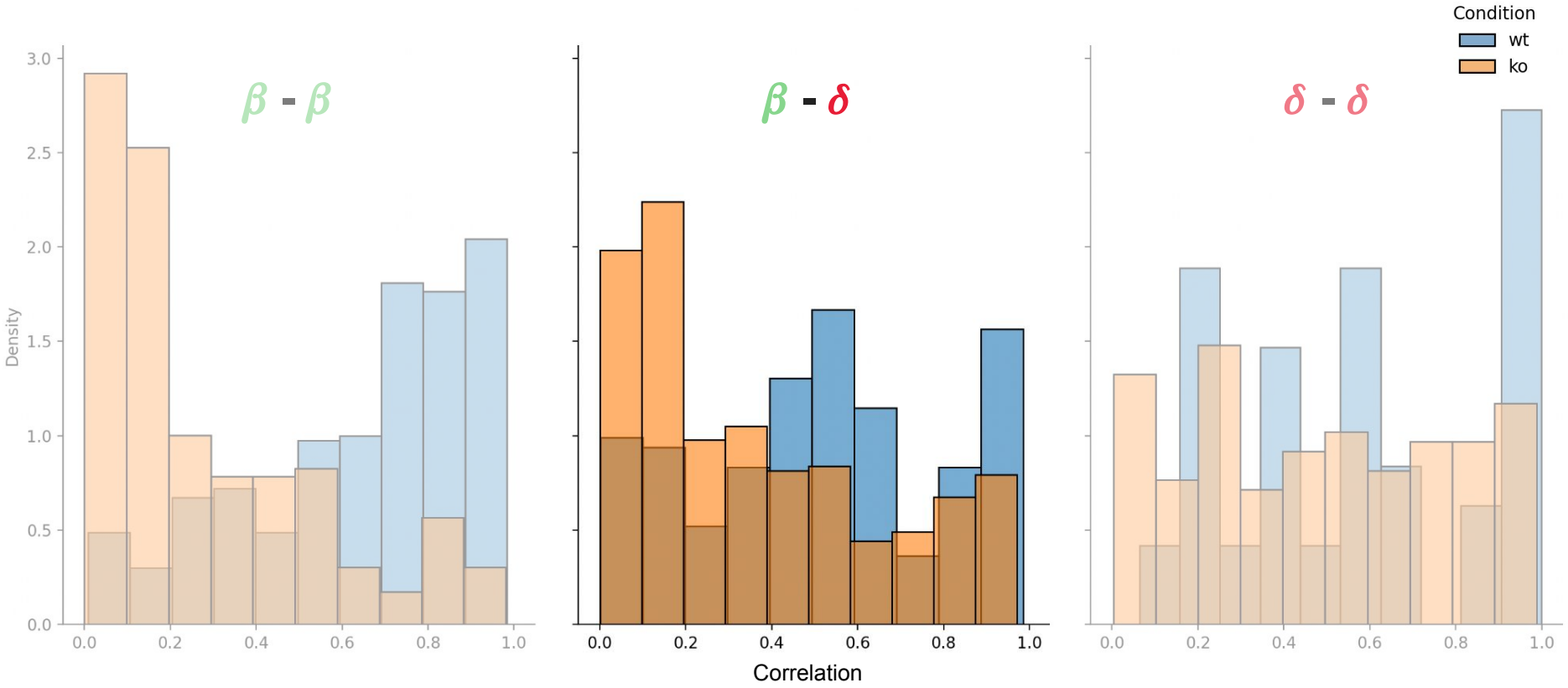

In the second phase of insulin secretion, we need to model gap junction coupling preserving synchronization and heterogeneity.

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Inferring Coupling Dynamics from Data

Inferring Coupling Dynamics from Data

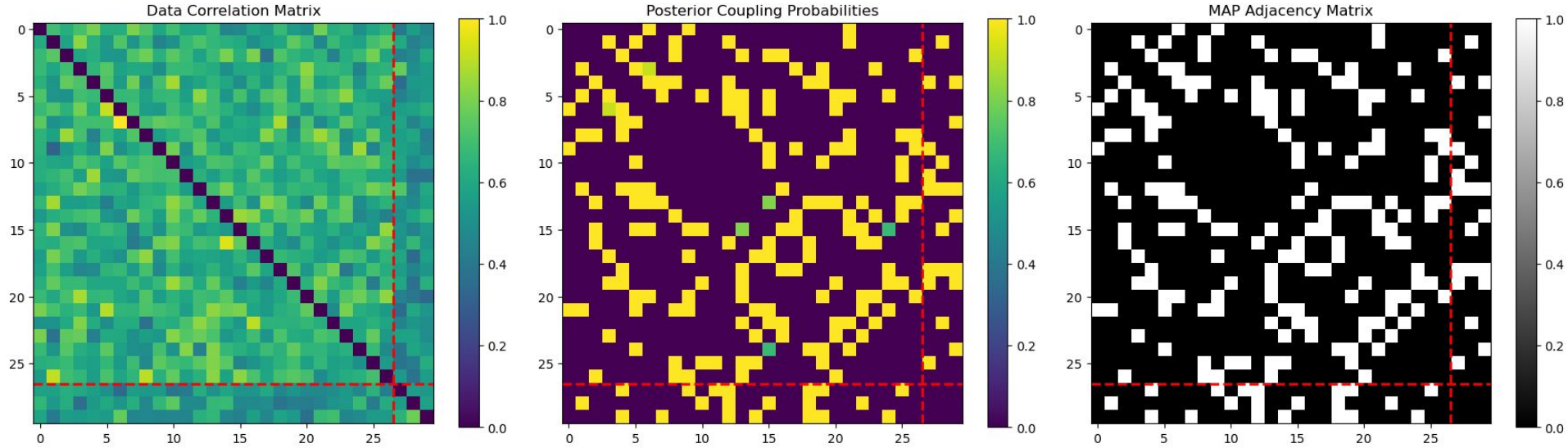
```
A ← random_adjacency_matrix()

for j = 1, ..., N do
    A_new ← propose_adjacency_matrix(A)
    V_sim ← simulate_voltage_dynamics(A_new)
    C_sim ← compute_correlation_matrix(V_sim)

    if error(C_sim, C_obs) < error(C_sim_prev, C_obs) then
        A ← A_new
        C_sim_prev ← C_sim
    else
        reject()

return A
```

Inferring Coupling Dynamics from Data



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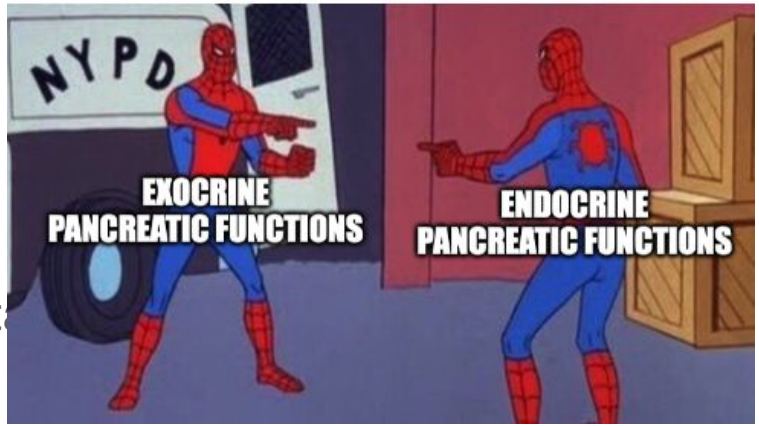
Conclusions and Future Directions

- Our model captures cell coupling and heterogeneity
- Incorporate statistical inference to determine coupling dynamics that optimize hormonal secretion pathways (e.g., insulin, somatostatin)
- Expand to a 3D islet model using imaging data to better reflect physiological structure
- Validate model predictions experimentally
- Long-term goal: guide therapeutic strategies to restore healthy islet communication in diabetes.



Acknowledgments

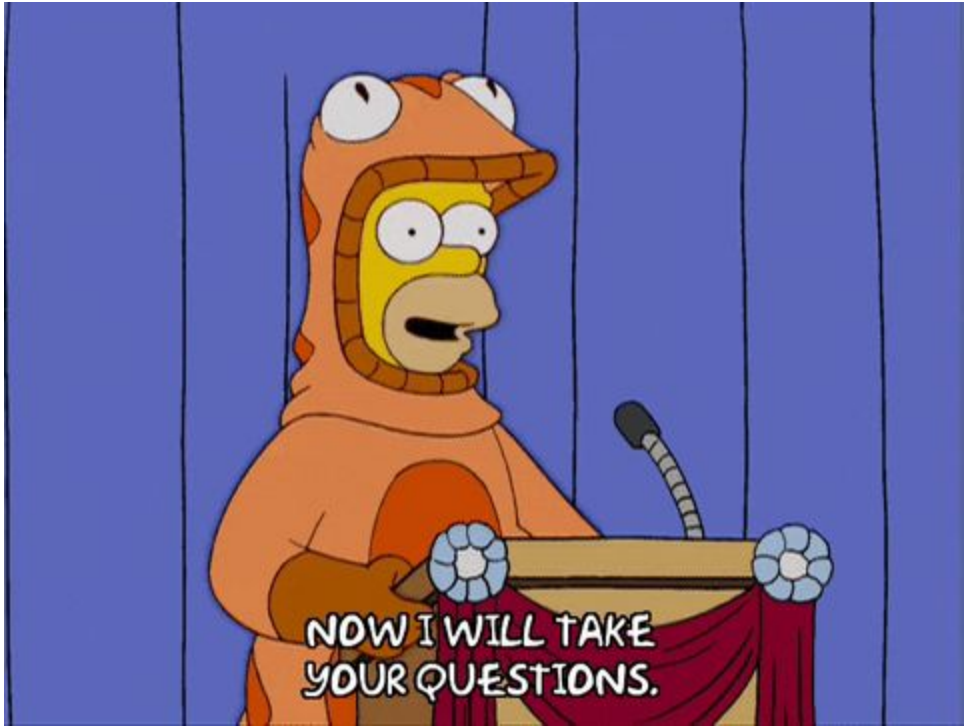
Dr. Richard Benninger

Dr. Stephen Kissler

Carissa Birznieks

Claire Levitt

Jennifer Briggs


NOW I WILL TAKE
YOUR QUESTIONS.