BIOPHYSICAL MODELING OF AN ENTIRE STOMACH: Are we missing something?

FIU Engineering & Computing — Biomedical Engineering

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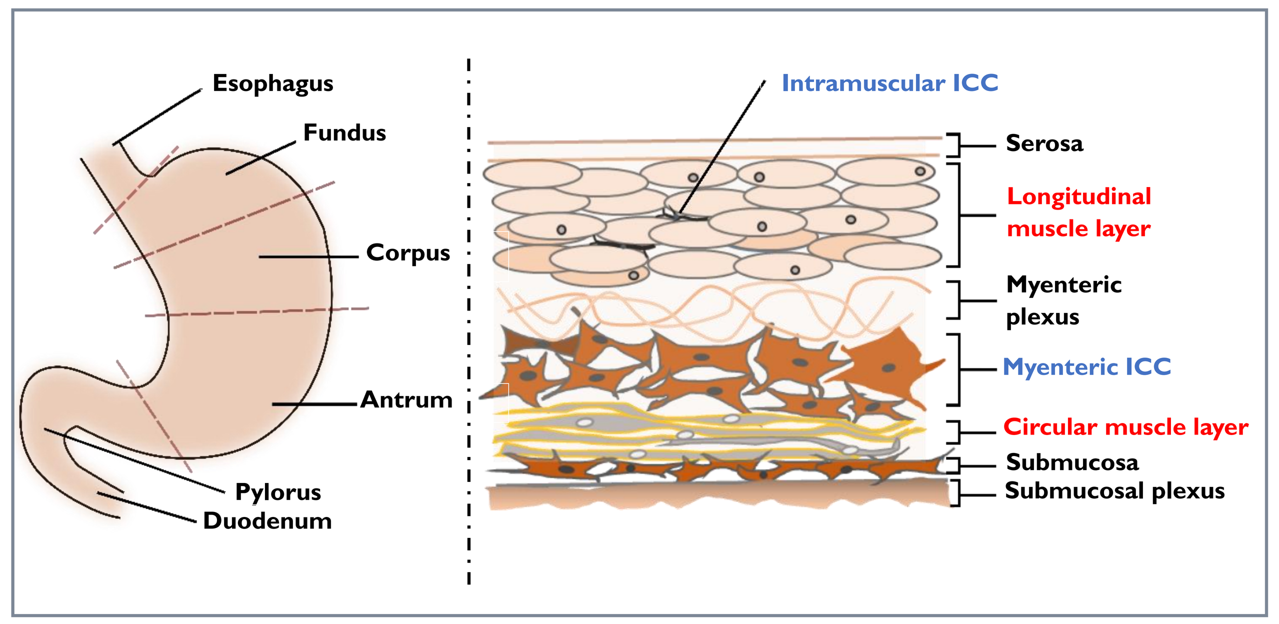
Introduction

Significance: Impairment in gastric motility, such as gastroparesis, can occur under diseases such as diabetes mellitus. Understanding the mechanisms of generation of the electrical slow-wave that produces gastric motility may allow improvements in gastric pacemaking neurotechnology.

Background & Objective:

- Slow-wave in the stomach originates in the mid-corpus and spreads through the antrum to the pyloric sphincter.
- Disruption of the slow wave impairs gastric motility.
- Biophysical modeling of the stomach wall may allow understanding of slow-wave anomalies such as **functional uncoupling**
- **Different groups have mathematically modeled the slow wave in portions of the stomach wall [1, 2]**

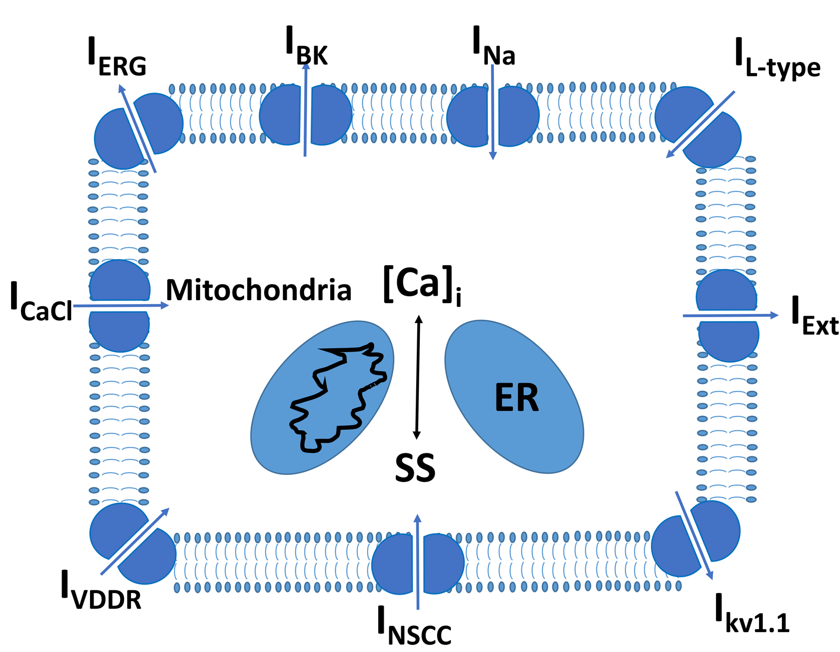
This study endeavors to model the slow wave along the entire length of the stomach wall and examine the role of gap junctions and biochemical coupling in maintaining the slow-wave.



Representation of the stomach anatomy and its different layers

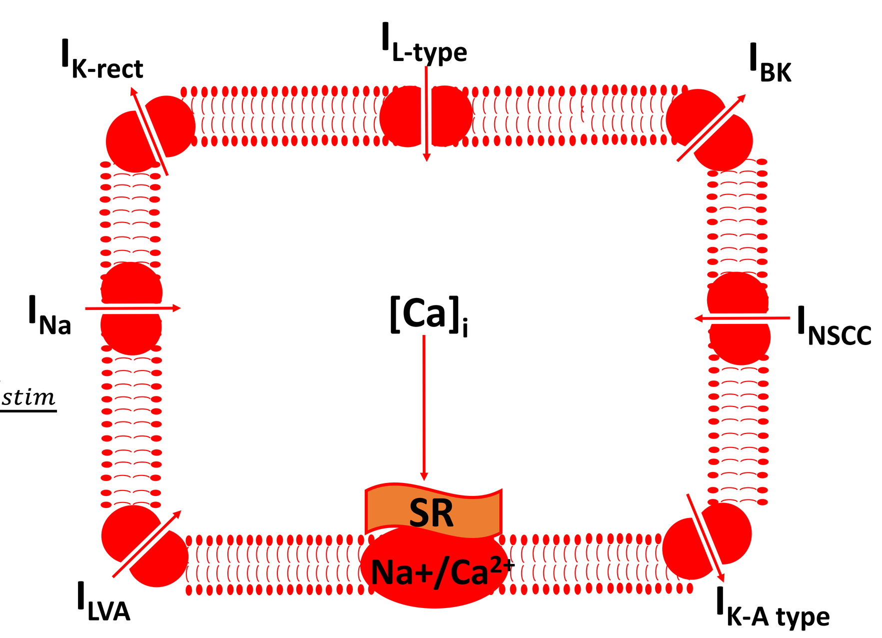
Method

The model consists of Interstitial cells of Cajal (ICC) connected with each other through gap junctions and smooth muscle (SM) cells connected in the same way. Each ICC cell is again connected to corresponding SM cell through gap junction.



ICC cell membrane potential modeled by Peng Du[2]

$$\frac{dV_{m(ICC)}}{dt} = -\frac{\sum I_{Ion,ICC}}{C_{m,ICC}}$$



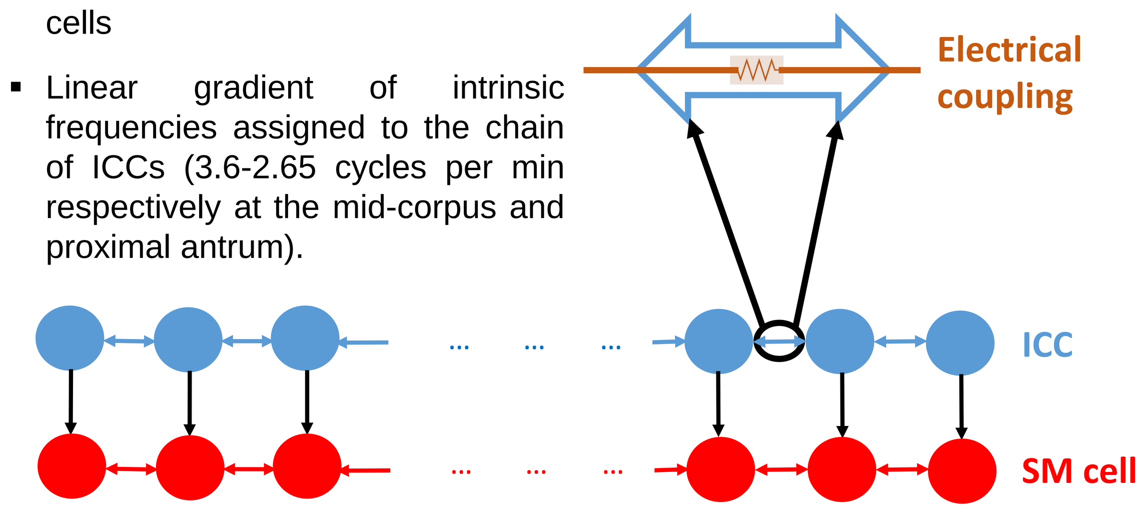
Smooth muscle cell membrane potential modeled by Corrias and Buist[3]

$$\frac{dV_{m(SMC)}}{dt} = -\frac{\sum I_{Ion,SMC} - I_{stim}}{C_{m,SMC}}$$

Method (cont.)

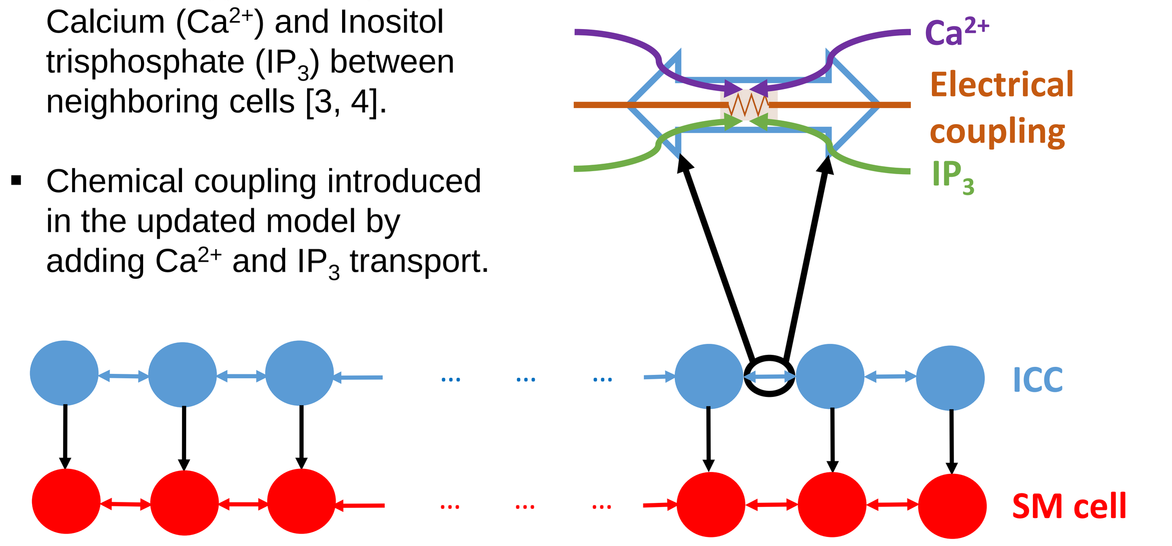
Initial Network Model

- Simulations conducted over a 2-D model of 28 ICC cells and 28 SM cells
- Linear gradient of intrinsic frequencies assigned to the chain of ICCs (3.6-2.65 cycles per min respectively at the mid-corpus and proximal antrum).



Updated Network Model

- Studies suggest transport of Calcium (Ca^{2+}) and Inositol trisphosphate (IP_3) between neighboring cells [3, 4].
- Chemical coupling introduced in the updated model by adding Ca^{2+} and IP_3 transport.



Assumptions:

- ❑ Functionality of myenteric ICC and intramuscular ICC incorporated in generic ICC
- ❑ The coupling strength between ICC cells and also between ICC to corresponding SM cells are assumed constant.

Data Analysis:

- ❑ Lag measured between the initiation of membrane potential of the first and the last SM cells of the network.
- ❑ Delta lag is defined as the difference in consecutive lags.
- ❑ In steady state, delta lag should be zero which is represented by a horizontal black solid line.
- ❑ In multivariate sensitivity analysis, green blocks represent entrainment and red blocks represent absence of it.

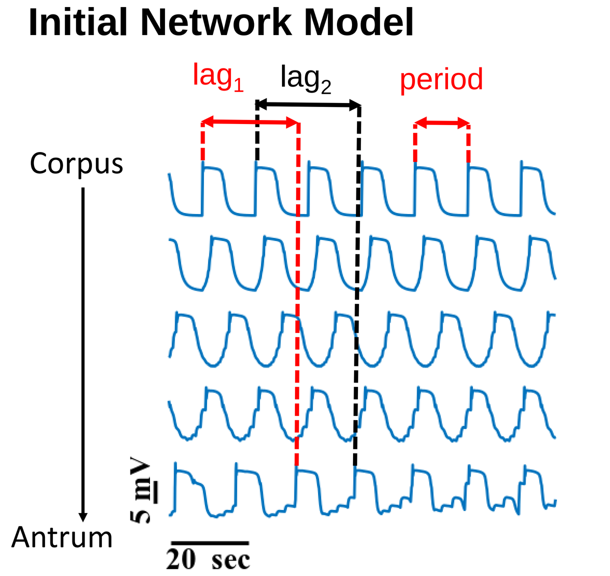
Symbols:

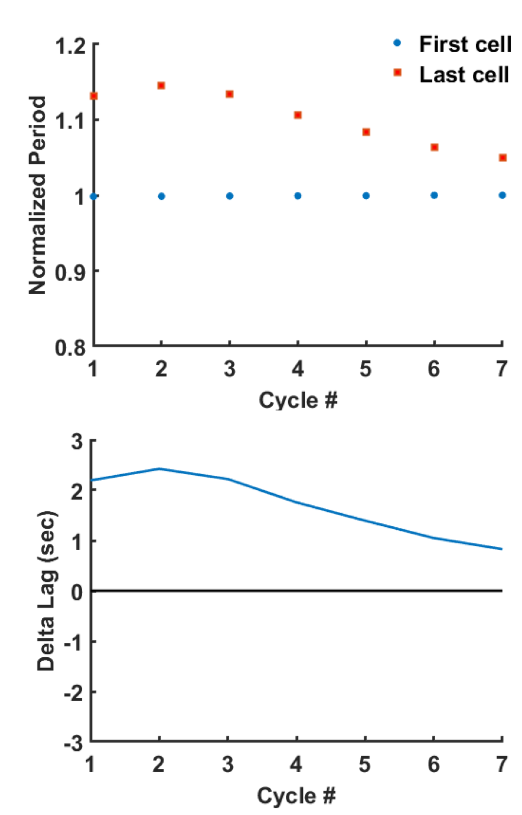
I_{L-Type}	L-type calcium current	I_{NSCC}	Non-selective cation channel current	I_{LVA}	Low voltage activated calcium current calcium current	SR	Sarcoplasmic reticulum
SS	Submembrane space	I_{K_rect}	Delayed rectifier potassium current			**β**	**proportional to intrinsic frequency**
ER	Endoplasmic reticulum	I_{VDDR}	Dihydropyridine-resistant Ca^{2+} current	$I_{K-A\ type}$	A-type potassium channel current	I_{stim}	stimulus current supplied to SM cell by ICC cell
I_{kv11}, I_{ERG},		I_{Na}	Sodium channel current	$C_{m,ICC}$	Membrane capacitance of ICC	$C_{m,SMC}$	Membrane capacitance of SM cell
I_{BK}, I_{kb}	Potassium channel currents	I_{CaCl}	Chloride channel current	Na^+/Ca^{2+}	Na^+ and Ca^{2+} ion exchange pump	g_{coup}	gap junction strength between ICC and SM cell

Results

Electro-chemical Coupling is needed for Entrainment

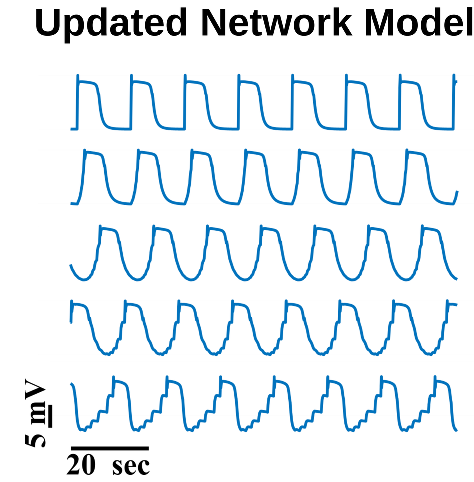
Initial Network Model

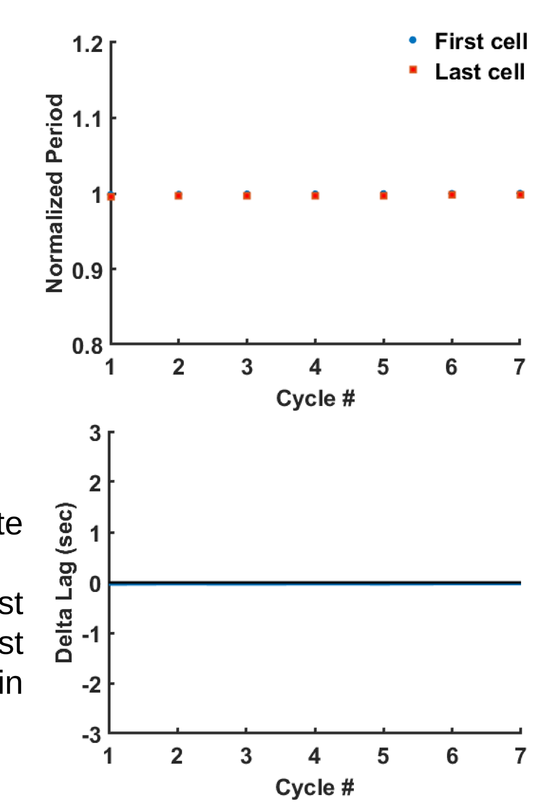




- The last cell is oscillating at a different frequency than the first cell.
- Normalized periods are different and Delta lag is not zero indicating absence of entrainment in the network

Updated Network Model

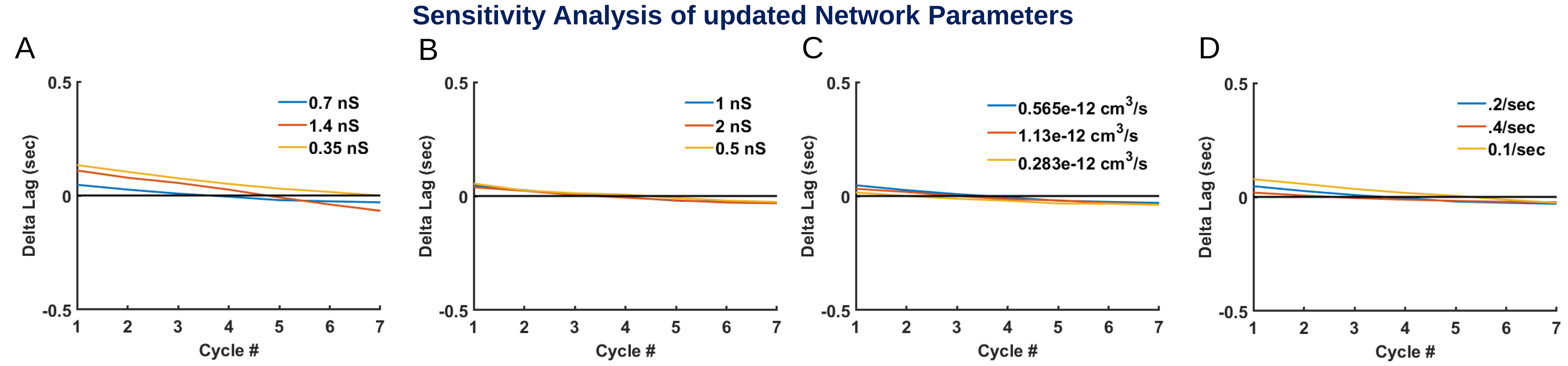




- All cells in the chain oscillate at same frequency.
- Normalized periods are almost same and Delta lag is almost zero indicating entrainment in the network

Key note : Only electrical coupling is not sufficient for network entrainment, chemical coupling is required along side with it.

Sensitivity Analysis of updated Network Parameters



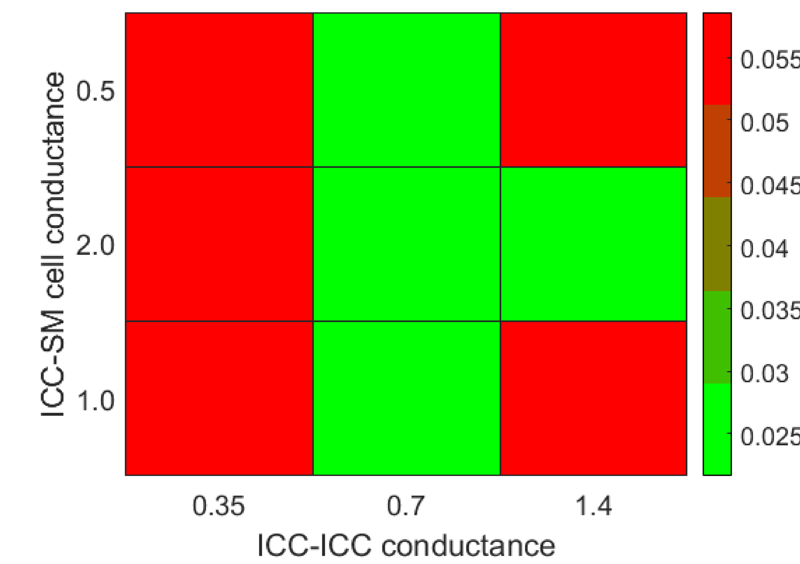
(A) ICC-ICC conductivity (B) ICC-SM cell conductivity (C) Ca^{2+} permeability (D) IP_3 permeability

Key note : Entrainment appears to be more sensitive to ICC-ICC conductivity and IP_3 permeability.

Results (cont.)

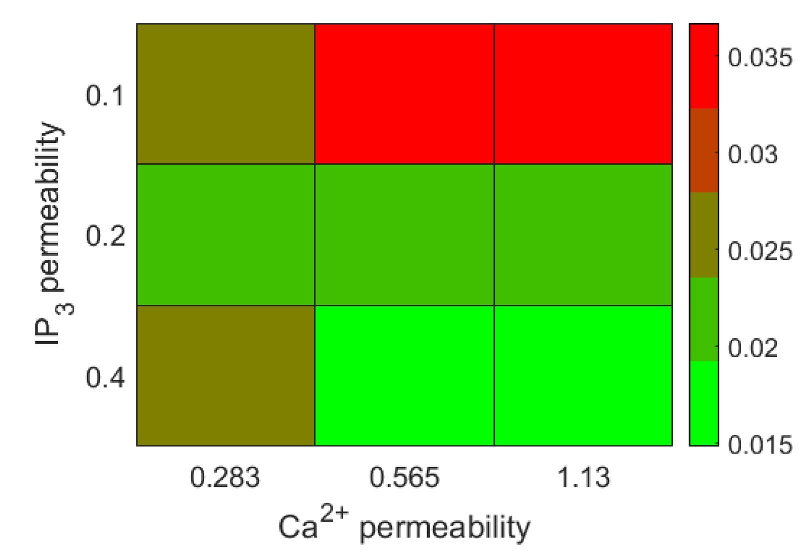
Multi-variable sensitivity Analysis

Two variable sensitivity analysis for ICC-ICC conductance and ICC-SM cell conductance



- ICC-ICC conductivity has more influence on attaining system entrainment between two electrical conductivities. .

Two variable sensitivity analysis for Ca^{2+} and IP_3 permeability across gap junctions



- Higher values of Ca^{2+} and IP_3 permeability appear to be necessary to attain entrainment

Conclusions

Our model qualitatively match the experimental recordings from the lower-mid corpus to the proximal antrum of the cat [5].

Mere electrical coupling may not be sufficient for creating entrainment along the entire length of the stomach. Ca^{2+} and IP_3 transport may play an important role in coordinating the activity that drives gastric motility.

Summary & Future Works

I. Simultaneous action of electrical and chemical coupling may play an important role in coordinating the activity that drives gastric motility.

II. Global sensitivity analysis of gap junction parameters need to be done in a wider range to completely quantify their effect in the network behavior.

III. Network's behavior in response to external perturbations (excitatory neurotransmitter or gap junction blocker) needs to be assessed and compared with experimental data.

References

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