Exploring Pathological T Cell-Neuron Functionality through the Modulation of CRAC Channel Dynamics: A Conductance-based Model

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Introduction/Background

Research Introduction

- Immune system: complex network of cells, tissues, and organs that protect the human body from infections and diseases
- Surface receptors of antigen-specific B and T lymphocytes bind to antigens → secretion of antibodies
- As Ca^{2+} concentration and influx increases, CRAC (Ca^{2+} release activated Ca^{2+} channel) channels on T cells modulate T cell depolarization and hyperpolarization rate during disease (neuro-immune interaction and apoptosis regulation)

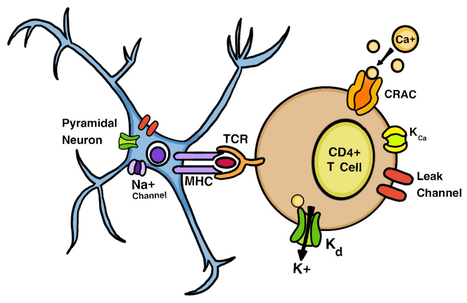


Figure 1: Illustration of Biological Basis for T Cell-Neuron Model

Literature Review

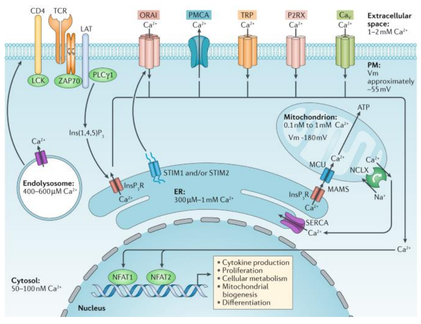


Image Credit: Mohamed Trebak & Jean-Pierre Kinet

- Intracellular calcium in CD4+ T cells have previously been modeled.
- ODE have potential to model neural-immune communication networks with calcium signaling by tracking movement of Ca^{2+} movement in neurons and T cells

Methodology

1. Establish the plausibility of modeling a generic pyramidal neuron and CD4+ T cell separately in response to injected current

- Two-cell, single compartment model developed in MATLAB: one neuron and one T cell
- Parameters for the neuron and T cell conductance and mechanism ion channels were taken from prior research (Prinz et al., 2003) and tuned to model the neuron-T-cell interaction.
- Ca^{2+} dependent channel CRAC (Calcium-release activated calcium channel, slow channel) for the T Cell was created based on a CaS channel created by Prinz et al.
- In addition, Leak, Kd, KCa, and NaV, channels for the neuron and T cell were modeled separately from (Ehling et al. 2016 and Eichinger et al 2018.). See Figure.
- The neuron cell consists of a Kd channel, a leak channel, and an NaV channel
- The T cell consists of channels CRAC (Calcium-release activated channel), KCa (Calcium-dependent potassium channel), Kd (potassium channel), and a leak channel.
- We passed current to both cells and ensured that Ca^{2+} change and action potentials (or spikes) are generated.

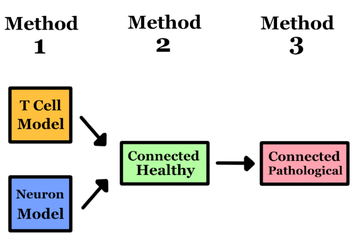


Figure 2: Pipeline of Methodology

2. Establish a biologically plausible two-cell network capturing CD4+ T-cell and pyramidal neural dynamics

- The neuron and T cell were connected via a generic glutamatergic chemical channel (Prinz et al., 2003, etc).
- Parameters (conductance, Ca^{2+} influx, tau (in milliseconds)) for the generic calcium mechanisms were slightly adjusted to correctly model the dynamics, meaning that Ca^{2+} dependent activity by the T Cell and Na+ driven spikes were produced.
- Conductance for all major channels were re-tuned to make sure the dynamics are well specified.

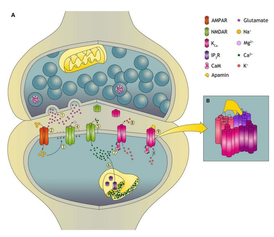
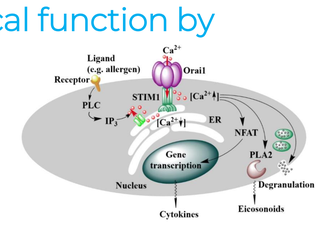


Image Credit: Amalia Dolga

3. Rescuing network dynamics from pathological function by modulating CRAC currents

- As current was passed to the system, Ca^{2+} changes were tracked
- Maximum conductance of the CRAC channel was changed to alter Ca^{2+} levels→ simulates infection conditions
- We found that Ca^{2+} levels could be adjusted to 10 times the "healthy" model parameter before the model was disrupted (broken down and no longer producing any dynamics).



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Results

Part 1: Model of T Cell and Neurons Separately

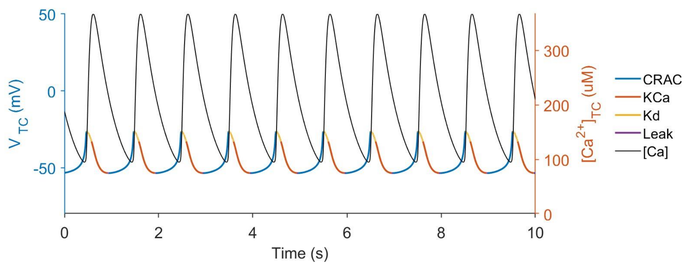

Figure 3: Individual T Cell Depolarization and Hyperpolarization Plot - Ca^{2+} Driven

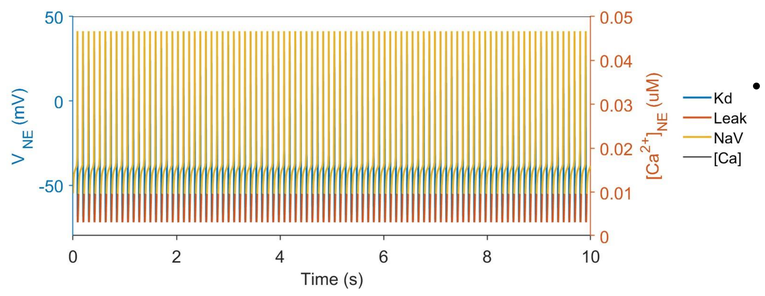

Figure 4: Individual Neuron Firing Plot - Na+ Driven

- Successful model: Action potentials produced by the neuron cell and hyperpolarization and depolarization dynamics occurred in the T cell.
- T cell hyperpolarization and depolarization are solely Ca^{2+} driven while the neuron cell spikes are Na+ driven.
- Could be observed that the CRAC cell is a much slower and more selective channel than the Na+ channel (Ehling et al. 2016)

Part 2: Connected Generic Model of the Neural-Immune System

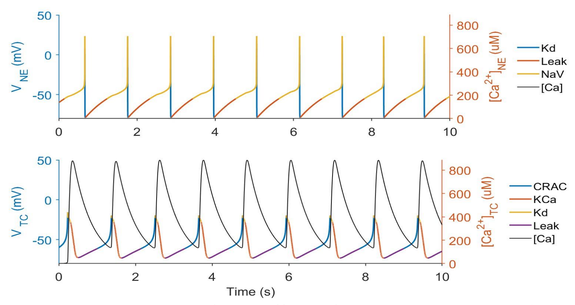

Figure 5: Connected T Cell and Neuron Dynamics - Healthy Model

- The T cell and neuron voltage are changing individually. Both exist in the presence of calcium dynamics, but the neuron has no Ca^{2+} sensitive channels.
- T cell depolarization and hyperpolarization are solely Ca^{2+} driven while neuron cell spikes are Na+ based

Part 3: Pathological Condition of the System: T Cell Hyperactivity

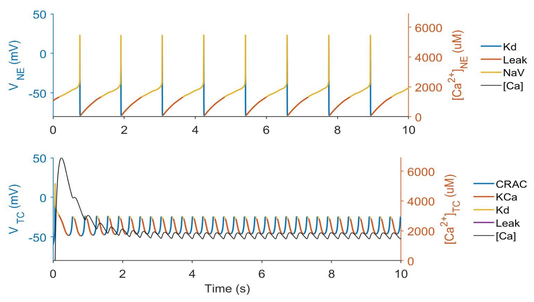

Figure 6: Connected T Cell and Neuron Dynamics - Pathological Model

- Pathological model created by increasing the Ca^{2+} channel to 10 times the "healthy" model parameter shows overapid depolarization and hyperpolarization of the T-cell
- Hyperactivity by T-cells cause apoptosis
- Observed increase in hyperpolarization and depolarization rate of T cell (pathologically increased voltage in T cells) when Ca^{2+} increases during infection

Discussion/Conclusions

Model Analysis

- Our model simulates the effects of Ca^{2+} imbalance in T cells during pathogenic infection through the voltage changes within the neuron vs T cell system
- Model was a glutamatergic interaction via Ca^{2+} imbalance and MHC (major histocompatibility complex) + TCR (T cell receptor) interaction
- Accurate T cell and neuron spikes dependent on the CRAC and Na channels validate the results of our model.
- Pathological conditions in comparison with a healthy generic model were simulated to determine the effects of Ca^{2+} influx on the depolarization and hyperpolarization rate of T cells
  - Over-excited spikes in the T cell prove that Ca^{2+} influx and imbalance increase during infections which result in apoptosis
- Results show the importance of CRAC in altering the depolarization and hyperpolarization rate of T cells based on Ca^{2+} influx
  - suggest that CRAC channel could be a potential drug-target for pathogenic infections involving the neural-immune network, given CRAC drives pathological behavior

Discussion & Improvements

- Model could be improved through incorporation of other channels involved in the glutamatergic system (Ex. Including NaV and KCa channels for both cells)
- Substitution of TCR-MHC interaction for the glutamatergic connection used in this model could improve the results
- Altering the CRAC differential equation instead of using the generic CaS equations could have also improved the results of the model. Further, the model could be tuned to humans more explicitly instead of approximating as we did here.

Future Research

- Further research could assure the importance of the CRAC channel in the neural-immune interaction
- In vitro and in vivo studied on the CRAC channel could validate this identified target

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