Models of Brain Activity After Injury due to Repeated Subconcussive Impacts

CS 302 Modeling Complex Systems (Final Project)

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1 Intro

Subconcussive impacts are less severe head impacts that do not cause a concussion. A growing body of research suggests that repeated subconcussive impacts can cause severe brain injury and related neurological deficits (Daneshvar et al., 2015). This is a concern because impacts at these subconcussive levels are common in sports and military activities (Goldstein et al., 2014).

Because of how common and dangerous repeated subconcssive impacts are, current research is focused on understanding the mechanism of brain injury caused by subconcussive impacts and how this injury can impair brain function. For example, research suggests that Chronic Traumatic Encephalopathy (CTE), a form of brain degeneration, is due to repeated subconcussive impacts, not concussions (Daneshvar et al., 2015). While susceptibility to CTE is linked to genetics (Abdolmohammadi et al., 2020), recent research has hypothesized that CTE actually spreads like a viral or bacterial infection in the brain (Alyenbaawi et al., 2020). Therefore, in severe forms of CTE, brain connections are highly disrupted (Fig. 1; Stern et al., 2011).

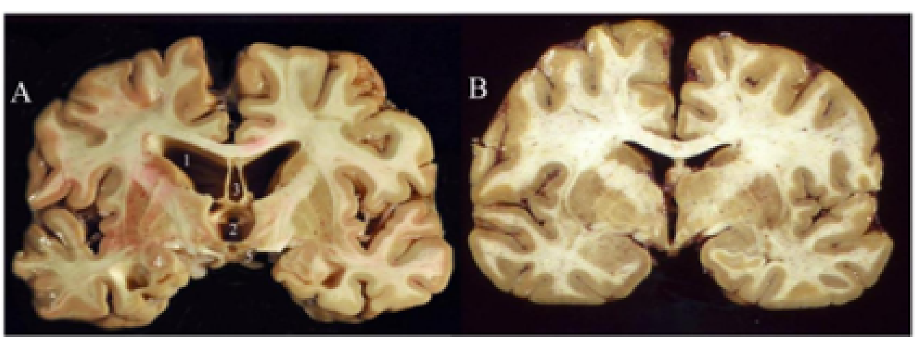


Figure 1: Comparison of a brain with severe CTE, where connections are highly disrupted, to a normal brain. Image from Stern et al. (2011).

In the normal brain, brain cells, known as neurons, carry out the functions of the brain. Neurons are connected by axons that send signals to other neurons. The majority of the brain's neurons are excitatory, responsible for sending signals to other neurons, while the remaining neurons are inhibitory. Inhibitory are responsible for stopping signals by regulating the activity of excitatory neurons. When the neurons are performing these responsibilities of sending or stopping signals, they are referred to as "active". Otherwise, the neurons are "resting", waiting to act, or "refractory", recovering to the resting state after being active. This is a highly simplified description of how the normal brain functions, but it makes clear that disruptions to the balance of excitatory versus inhibitory neurons or to the neurons themselves have the potential to impair brain function.

While many techniques exist to study brain function, electroencephalography (EEG) is often used clinically because of it is noninvasive, affordable, convenient, and has high temporal resolution. EEG measures the electric impulses of neurons firing. When many cells synchronize their activity, patterns, each of which are characterized by frequency, occur in the data (Fig. 2). Changes in EEG have been used in the assessment of concussion (Moore et al., 2017). For an impaired brain, we might expect decreased amplitude of the EEG signal (Wilson et al., 2015).

In this project, our research question is whether complex modeling can be used to explore the effect of subconcussive impacts on brain function. To answer this question, we focused on two models: a three-dimensional (3D) cellular automata (CA) and an agent-based network (ABN) model. To enable comparisons between the models, the ABN was designed to resemble the CA and vice versa. Each model accounts for neuron type (i.e., inhibitory or refractory) and neuron state (e.g., active, resting, or refractory). We evaluate each model in cases with and without injury and compare to EEG data to assess their validity. The models are also compared to demonstrate the strengths and weaknesses of each approach.

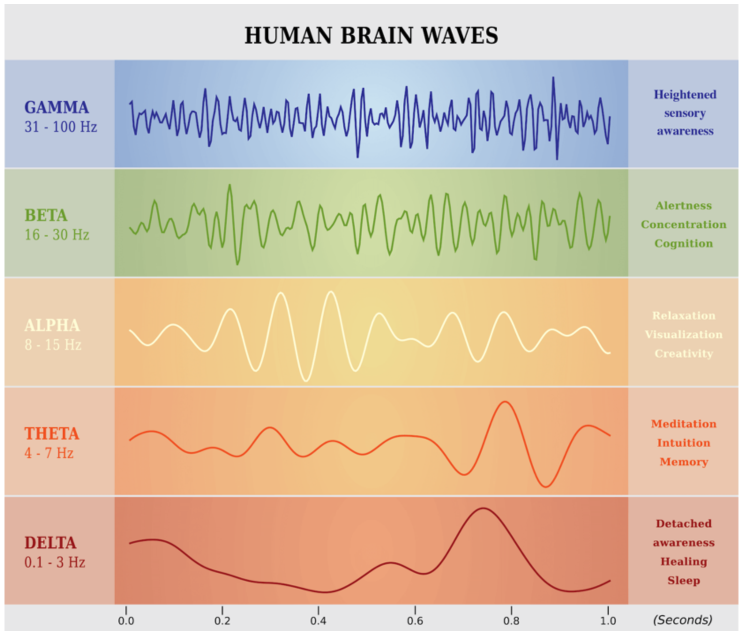


Figure 2: Example of brain waves that can be measured with EEG. Figure from Allen (2022).

2 Hypotheses

We hypothesize the following:

- We can model realistic (i.e., valid) brain activity using both CA and ABN models.
- The network model will produce more realistic (i.e., more valid) simulations of brain activity.
- A greater proportion of injured neurons (or more severely injured neurons) will decrease the proportion of active neurons in the brain.
- Injured neurons will have higher proportion of resting neurons than non-injured neurons.

3 General Assumptions

We made several assumptions that apply to both the CA and ABN models:

- **Type attributes**: The initial proportion of excitatory to inhibitory neurons is 70:30. Neuron type remains constant.

- Related work: Rubenstein and Merzenich [2003] reported that the brain is 80% excitatory and 20% inhibitory neurons. In a CA by Acedo et al. (2015), 30% of neurons were assigned as excitatory.

- **State attributes:** The initial proportion of active to resting neurons is 20:80.
  - Related work: Work by de Vries (2020) measured activity from 60,000 neurons in the mouse brain, which translates to approximately 10% of the brain.

- **Injury attribute**: A larger initial proportion of injured neurons represents a greater number of subconcussive injuries. Injury status remains constant: injured neurons remain injured.

- **Time**: Each time step is 0.005 seconds. Neuron state can change once per time step. Neuron state updates synchronously.
  - Related work: For neuron firing, frequencies from 40 to ¿200 Hz are considered realistic (Maex De Schutter, 2020)

- **System:** The system is closed: no new neurons are being created in the time period.

- **State transitions**:
  - To become active (or resting), a neuron must be connected to an active (or resting) neuron of the same type.
  - The probability of becoming active or resting is modified (increases or decreases) according to the fraction of neighbors of the same type and state.
  - The probability of becoming active or resting is modified (increases or decreases) according to the injury status of the neuron.
  - Neuron attributes (type, state, injury) are random (stochastic).
  - **Note 1:** The rates that neurons transition between states are assigned "logically" based on our modeling experience and the model performance. We describe these rates in more detail within the sections dedicated to each model.
  - **Note 2:** To keep both models from becoming overly complex, we assume that the state of the neurons only changes according to the corresponding transition rate, neigbhors, and injury status (as described above). No other attributes of the neurons are considered (e.g., region of the brain).

- **Scale**: The behavior of a group of neurons, or area of the brain, can be modeled the same as the behavior of a single neuron.

- **Note:** Based on this assumption, we will refer to the modeled elements interchangeably as "neurons", "cells", "nodes" (ABN), "cubes" (CA), and, more generally, "areas" or "regions" of the brain. Thus, because the number of neurons in the brain is approximately 10^11, each modeled element can represent millions of neurons.

- **Validity**: We assume EEG signals capture the fluctuations of the number of active neurons (Acedo, 2006).

4 Model 1: Cellular Automata

In work by Acedo et al. (2015), a network CA model was created that included both inhibitory and excitatory neurons and three states: active, resting, or refractory. The number of active neurons was used as a measure of brain activity. In this work, the behavior of the active neurons oscillated in a similar manner to EEG recordings. However, they report that 10^6 was the minimum number of "neurons" required in the model to achieve this realistic oscillatory behavior. Fraile et al. (2018) developed a much more simplified CA, which only included neuron state (active or inactive) for cells in a 1000 x 1000 grid. They also added defects (cells that are dead) to represent neuron injury. The interaction of neurons around the "boundaries" created by these defects was observed in terms of the fraction of active neurons and "transmission efficiency", or the amount of time required for two neuron groups to interact.

For developing our CA, we used the description of the CA model from Acedo et al. (2015) as a baseline and made several changes to both simplify the computational work required and incorporate brain injury. To evaluate the model behavior, we compared to the model to EEG data and calculated the proportion of active neurons over time for both total neurons and injured neurons.

Model-Specific Assumptions

The following assumptions applied to the CA model in addition to the assumptions listed in the General Assumptions section:

- Injury severity remains constant.
- The probability of an active neuron changing to refractory is not dependent on neuron neighbors or the neuron's own injury status.
- The probability of a refractory neuron returning to resting state is not dependent on neuron neighbors or the neuron's own injury status.
- Neurons should be as highly-connected as possible (within the limitations of the CA) to other neurons.

- The brain or region of the brain can be modeled with periodic boundary conditions. Although this is assumption is not spatially accurate, periodic boundary conditions may be a functionally-accurate representation of highly-connected areas of the brain.

System

- **Space**: The brain is represented as a three-dimensional space (10 x 10 x 10) divided into cubes, or "neurons".
- **Boundary conditions**: Periodic
- **Neighborhood**: Moore neighborhood, where each neuron has 26 neighbors).
- **Time**: The states associated with each neuron are updated after each time step for 100 total time steps (0.5 seconds).
- **Initial Conditions**:
  - A random fraction of all neurons are assigned as inhibitory (negative values). The remaining neurons are excitatory (positive values).
  - A random fraction of all neurons are assigned as active (double-digit values [resting value multiplied by a factor of 10]). The remaining neurons are resting (single-digit values).
  - A random fraction of all neurons are assigned as injured (values closer to zero). The remaining neurons are healthy (values further from zero).
  - **Example A**: A healthy excitatory neuron at rest is represented by the value 9, while a healthy inhibitory neuron at rest is represented by the value -9. If the healthy excitatory neuron is active, it is represented by the value of 90. If the healthy inhibitory neuron is active, it is represented by the value of -90.
  - **Example B**: A severely injured excitatory neuron at rest is represented by the value 1. A severely injured inhibitory neuron at rest is represented by the value -1. Furthermore, a dead excitatory or inhibitory neuron is represented by the value 0. If the severely injured excitatory neuron is active, it is represented by the value of 10. If the severely injured inhibitory neuron is active, it is represented by the value of -10.
- **Rules**:
  - Neurons become active based on three variables: (A) a probability, p_{alpha}, (B) the fraction of active neighbors of the same type, and (C) the neuron's own level of injury. Thus, a healthier neuron is more likely to become active, and a neuron connected to more active neurons of the same type is more likely to become active.

– Neurons become resting based on three variables: (A) a probability, p_{beta}, (B) the fraction of resting neighbors of the same type, and (C) the neuron's own level of injury. Thus, a more severely injured neuron is more likely to become resting, and a neuron connected to more resting neurons of the same type is more likely to become resting.

– Neurons change from active to refractory according to a probability, p_{delta}, which is not dependent on the surrounding neighbors. Refractory neurons are represented by decimal values (resting value divided by a factor of 10, or active value divided by a factor of 100).

– Likewise, neurons change from refractory to resting according to a probability, p_{gamma}, which is not dependent on the surrounding neighbors.

- **Note**: See Figure 3 for a visual representation of how the values were used to indicate the neuron type, state, and injury status.

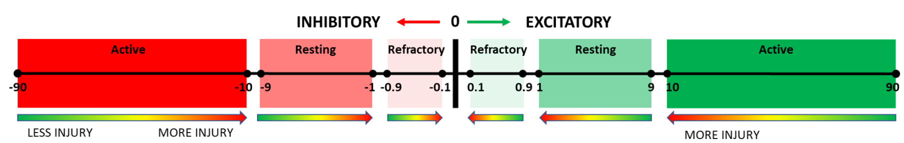


Figure 3: Representation of the values used in the CA to represent neuron type, state, and injury status.

Results - CA Model

For comparison to the ABN, we completed simulations for three different injury cases (no injury, 5% injury, and 10% injury) with p_{alpha} and p_{beta} values of 0.05, 0.10, 0.25, and 0.5. We used an injury severity level of 5. For each simulation, we performed 5 trials and calculated the average number of neurons of each type and state combination, fraction of active neurons out of the total neurons, and active injured neurons out of the total injured neurons (Appendix A). By comparing these results to EEG data, we determined that the most realistic values for p_{alpha} were between 0.25-0.50. Within this range, most values of p_{beta} produced realistic results for the number of excitatory active neurons, but the inhibitory active neurons were not realistic. At these values, the number of excitatory active neurons oscillates along a plateau and does not deplete within the 0.5 second window. This behavior is most similar to EEG data; the high frequency of oscillations is most representative of the gamma wave (Fig. 2). However, for all values, the number of inhibitory active neurons was depleted or nearly depleted, which is unrealistic.

Based on our simulations, we were able to partially address a few of the hypothesis.

- We were only able to partially model realistic brain activity using the CA model. The active inhibitory neurons were completely or nearly depleted in all simulations, which is not realistic (Figure 4).

- For the injury levels we tested, we did not see that a greater proportion of injured neurons substantially decreased the proportion of active neurons (or increased the proportion of resting neurons) in the brain (Figures 5 and 6).

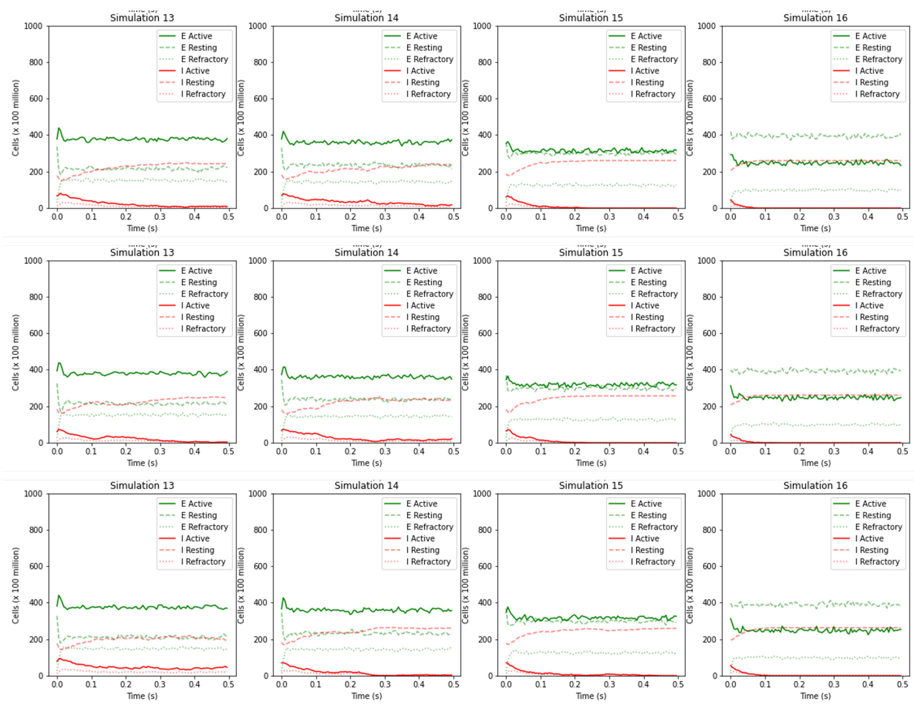


Figure 4: Selected CA simulation results. The rows from top to bottom represent no injury, 5% injury, and 10% injury cases. All simulations have $p_{alpha} = 0.5$.The columns correspond to a p_{beta} values of 0.05, 0.10, 0.25, and 0.50.

To achieve a more realistic result, we tried additional simulations with the same three injury cases, p_{alpha} of 0.50 and p_{beta} of 0.01 (Figure 7). The number of active inhibitory neurons still trends downward towards depletion. We also tried simulations with a large proportion (0.25) of "dead" neurons (Fig. 8). This increased injury severity did appear to decrease the number of active neurons over time, supporting our hypothesis. For future iterations of this CA model, we should revisit our calculations to improve the model's sensitivity to injury.

We did not test variations of p_{delta} and p_{gamma} for this analysis. However, in the realistic the simulations that we did test, we see that the number of

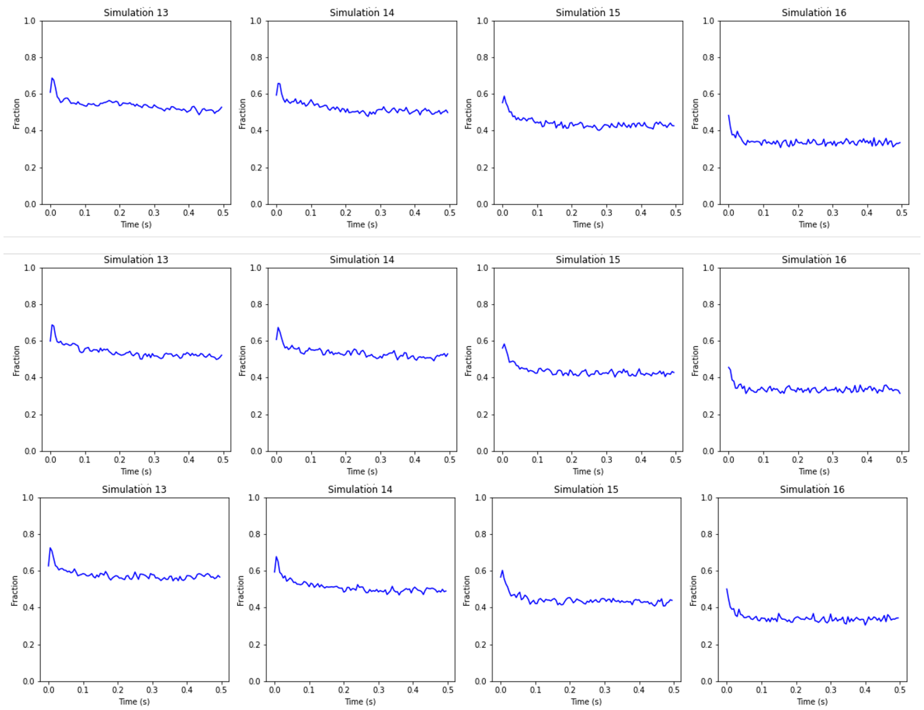


Figure 5: Fraction of active neurons out of total neurons for selected CA simulations. The rows from top to bottom include no injury, 5% injury, and 10% injury cases. All simulations have $p_{alpha} = 0.5$.The columns correspond to a p_{beta} values of 0.05, 0.10, 0.25, and 0.50.

refractory neurons does not ever become the majority state for either neuron type. This indicates that we do not have too high of a p_{delta}.

Due to one of the strengths of the CA being it's the spatial relationships within the model, future analysis can consider how the spatial distribution of activity in the brain changes around regions of the model with more injured neurons. Additionally, the CA model space was small (Fig. 9) in comparison to other published models (Acedo et al., 2015); however, it was challenging to complete the required number of simulations with a larger model due to time constraints. In the future, a larger model with more interactions may provide different results.

Colab Notebook

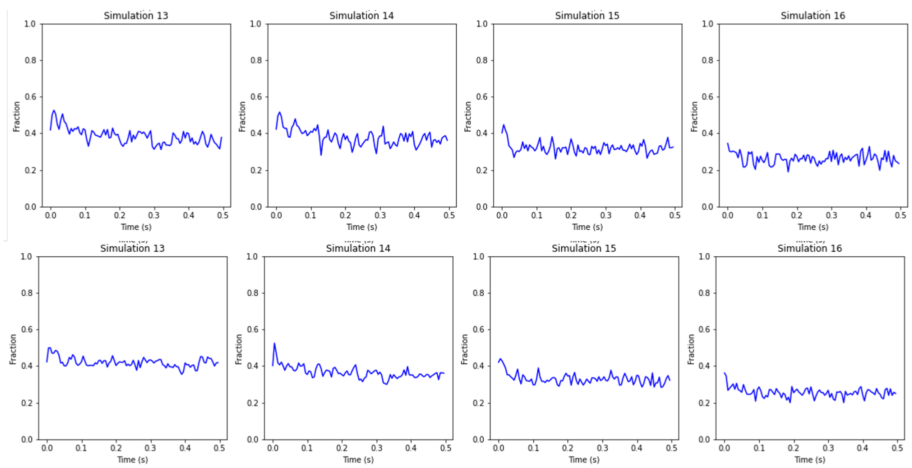


Figure 6: Fraction of active injured neurons out of total injured neurons for selected CA simulations. The first row includes 5% injury and the second row includes 10% injury cases. All simulations have $p_{alpha} = 0.5$.The columns correspond to a p_{beta} values of 0.05, 0.10, 0.25, and 0.50.

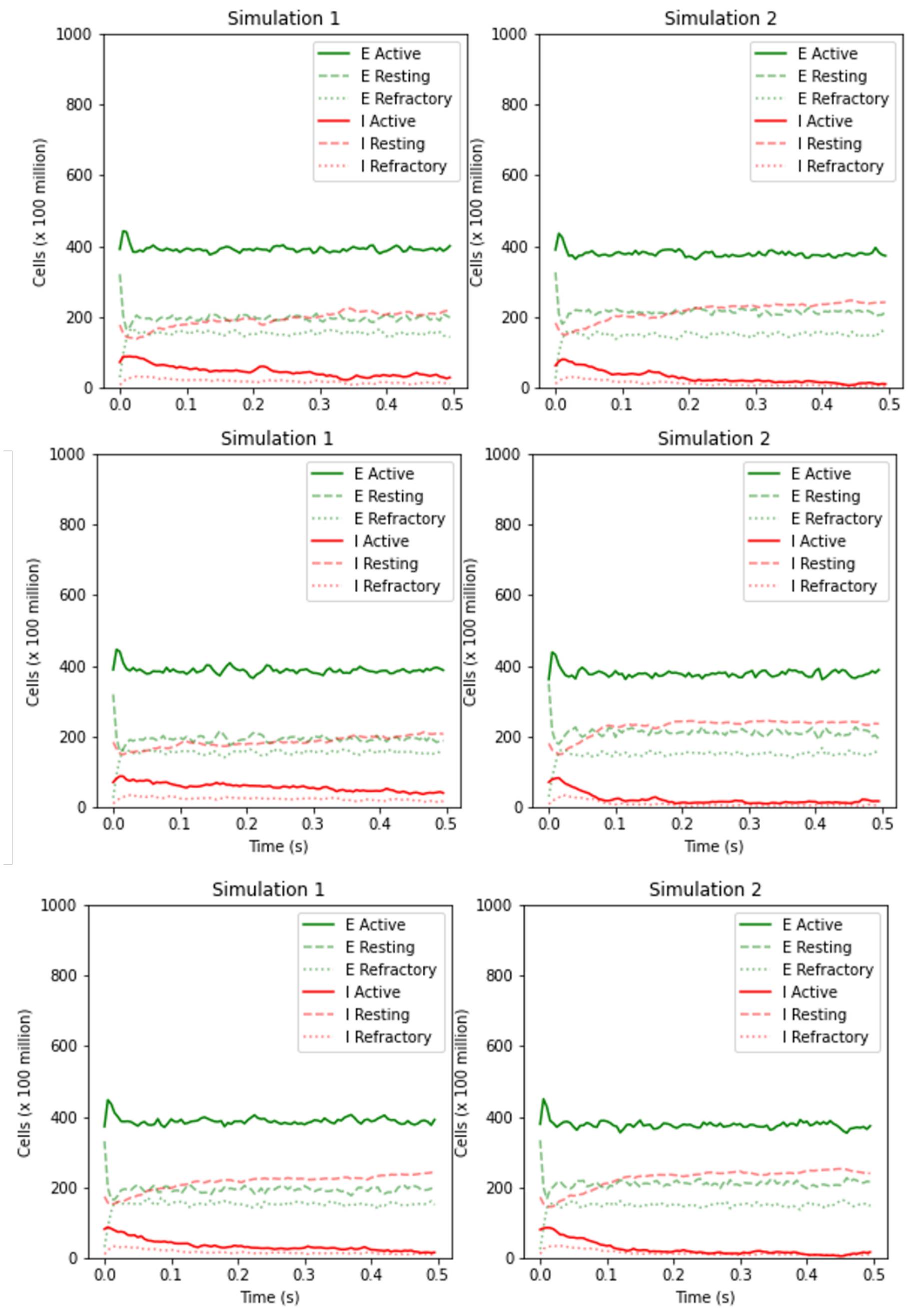


Figure 7: Selected CA simulation results for additional comparisons. The rows from top to bottom represent no injury, 5% injury, and 10% injury cases. All simulations have $p_{alpha} = 0.50$.The columns correspond to a p_{beta} values of 0.01 and 0.05.

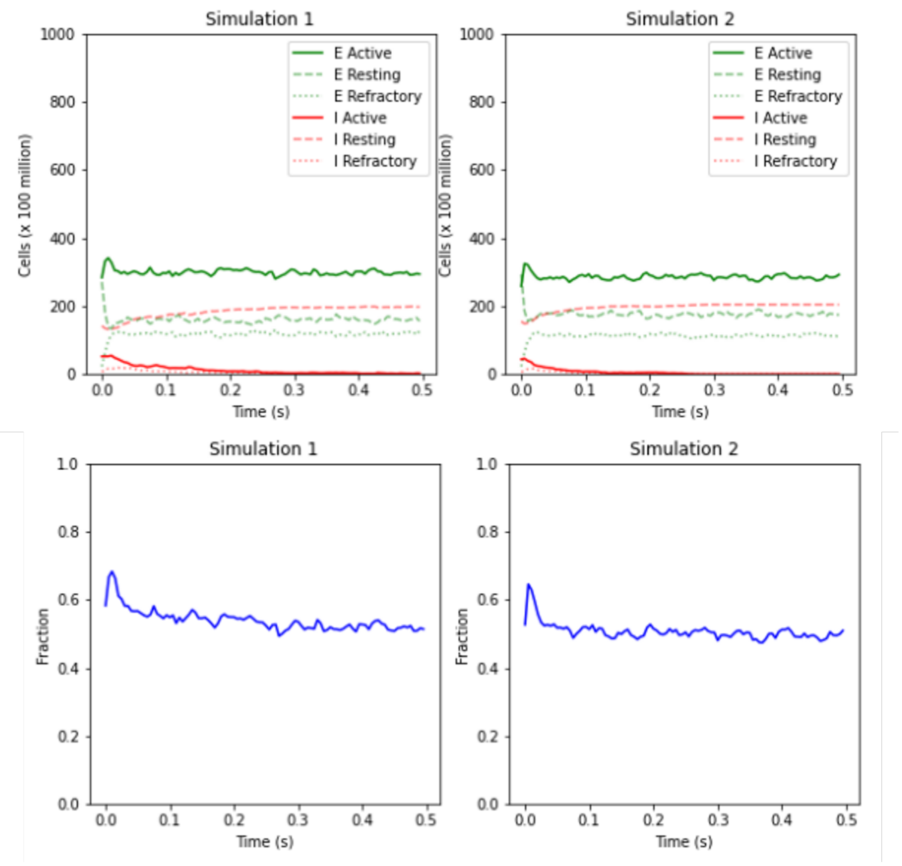


Figure 8: CA simulation for high-injury comparisons. All simulations were completed with 0.25 of the total neurons initialized as "dead". Top: The number of each neuron according to its type and state (dead neurons are excluded). Bottom: The fraction of active neurons out of the total neurons (dead neurons are included in the total). All simulations have $p_{alpha} = 0.50$.The columns correspond to a p_{beta} values of 0.01 and 0.05.

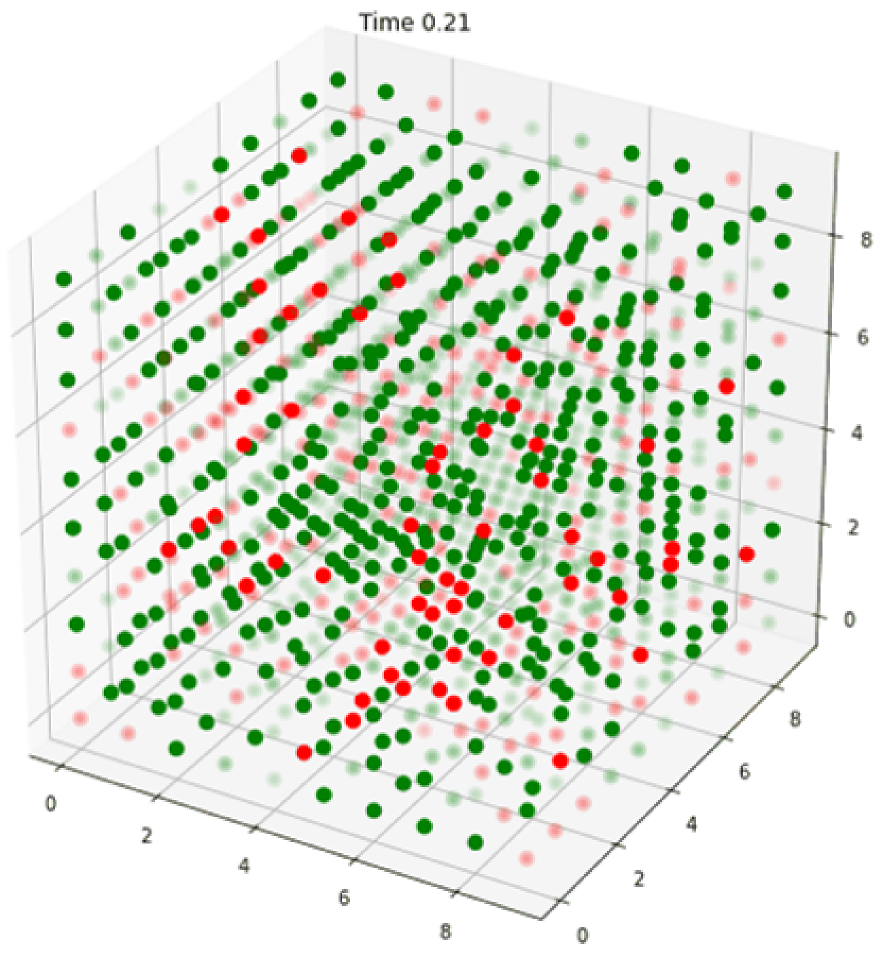


Figure 9: Example frame of the CA model. Excitatory neurons are represented by green circles, while inhibitory neurons are represented by red circles. The opaque circles represent active neurons. The more transparent circles represent resting or refractory neurons.

5 Model 2: Agent-based Network using a Brain Connectome

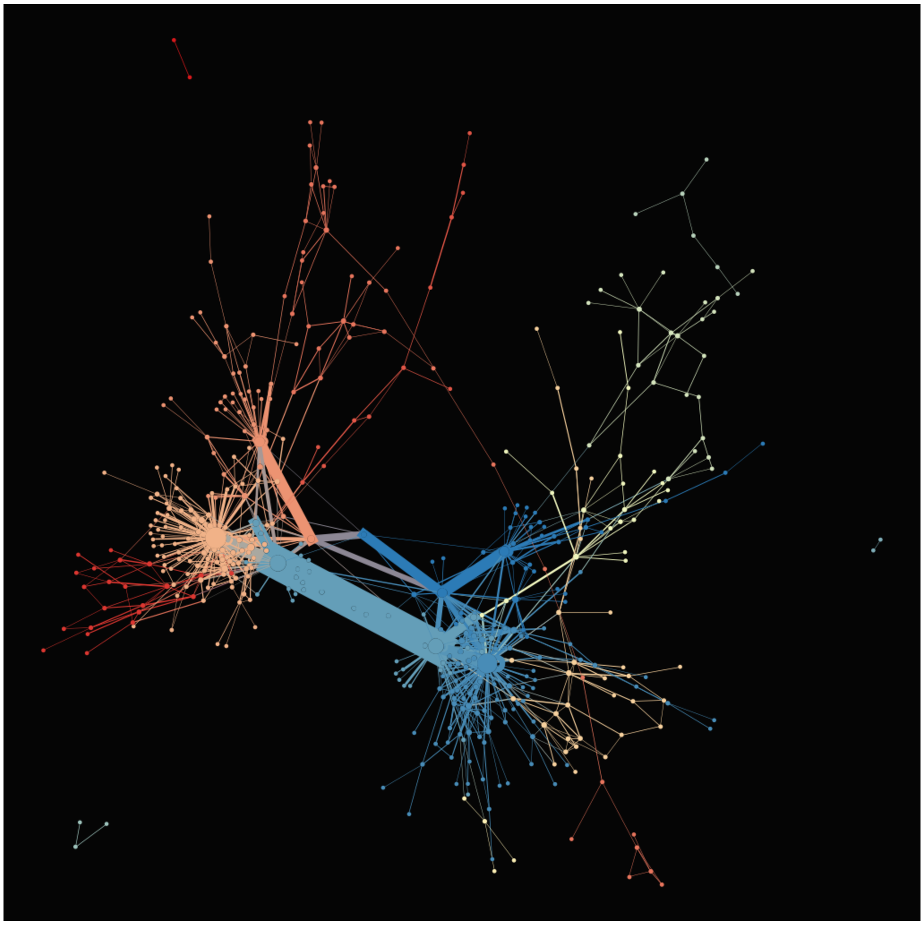


Figure 10: Budapest Conectome Network in Gephi 0.9

Our brain connectome data set was acquired from PIT Bioinformatics Group. The data is called "Budapest Reference Connectome version 3.0" and is a parameterizable consensus brain graph. It contains unified connectomes of 477 people (computed from MRI datasets of the Human Connectome Project) into a reference brain graph, which can be downloaded from PIT Bioinformatics Group or go to the next url: `https://pitgroup.org/connectome/?version=2`.

Our initial analysis has leveraged the default graph in version 3. It contains 480 Nodes and 1,000 Edges. The nodes represent areas of the brain and edges represent functional connectivity between nodes. The data set contains a weighted edge measure calculated by the formula n/L, where n is the number of tracks between the two regions, and L is the average length of those tracks). The data set is comprised of both female, male, resting state, healthy brains. The data is undirected.

Budapest Connectome in Gephi 0.9

Using the connectome above we generated a Gephi visual, figure 10 , where the Node size represents the number of degrees and the edges have a thickness related to their weight. Figure 19 , shows a degree distribution which reveals some nodes have many degrees and most nodes do not. This suggests a heterogeneous network where there is a large diversity of node degrees. This is shown again as a log-log plot in figure 20 suggesting a scale free network following an approximate power law function for for some portion of the plot. This Gephi analysis allowed us to quickly analyze various characteristics of the connectome before we started the analysis in python using Networkx. While we did not use community detection in this paper for our analysis overall, it would be interesting to use this data in future analyses. Summarizing below is how we produced the Gephi network visual.

- Node size is scaled to degree ranking
- Edge width is scaled to weight derived from connectome data source
- Color scale is derived from modularity class; 16 communities, 1 resolution
- No filtering was used due to already working with a smaller, filtered data set of 480 nodes

Budapest Conectome in Networkx

The network model was set up similarly to the CA and utilized many of the same parameters and initial conditions.

Model-Specific Assumptions

The following assumptions applied to the ABN model in addition to the assumptions listed in the General Assumptions section:

- Used a binary approach to injuring a node to simplify the model. Either the node was injured or not injured. There was not a value or range associated with the injury to the node.
- Assumed no refractory periods in state attribute; assigned only Active and Rest states.
- Assumed no rewiring of nodes in the the brain after injury. We assumed this due to short time intervals, measured in seconds. Over longer periods of time, neurons are thought to be able to rewire to new neurons.

System

The ABN system is described below:

- **Space**: The connectome network used comprised of 480 nodes and 1,000 edges. Nodes in the network represent areas in the brain and their connections to other areas of the brain are represented by edges. The network was built using Python package Networkx and used a spring layout (Fruchterman-Reingold force-directed algorithm). The network is scale-free and follows a power law function. There are two hubs corresponding to the left and right side of the brain. See figure: 20.
- **Time**: The state (rest or active) attribute associated with each node are updated after each time step for 1000 total time steps. Each step is considered a very small period of time, with each node update occurring synchronously.
- **Attributes**: The following are the attributes assigned to the nodes to create an ABN model using the connectome data in networkx.
  - State : Active or Rest
  - Type : Inhibitory or Excitatory
  - Injured : Injured or Not Injured
- **Initial Conditions**:
  - A random fraction of 80% of nodes were set to be at rest, with the remaining 20% set to active
  - A random fraction of 30% of nodes were set to inhibitory, and the remaining 70% to excitatory
  - Two values were used for determining initial proportion of injured neurons: 0% (no injury) and 5%, as well as 10% modeling subconcussive injuries.
  - Beta initial values: A base value was used for beta, the likelihood of node changing from being active to being at rest. Four values of beta were used for different scenarios: 0.05, 0.1, 0.25, and 0.5

- Alpha initial values: As with beta, a base value for changing from rest to active, denoted as alpha, was changed depending on the scenario being run. Base values for alpha were the same as for beta: 0.05, 0.1, 0.25, and 0.5

- **Rules**:
  - There are 4 overall scenarios in the ABN model considered which consist of 2 attributes State/Injured: 1. Active/Not Injured, 2. Active/Injured, 3. Rest/Not Injured, 4. Rest/Injured. For every node, the scenarios were determined (1,2,3,4), then a neighbor sweep to analyze the neighborhood and change the nodes state depending on the variable rate assigned.
    - **Example 1:** If a node was Active/Injured (scenario 2) then the next step was a neighbor sweep to determine if the majority of the neighbor nodes had the opposite state (Rest) and shared the same type attribute (inhibitory or excitatory). If a majority event (the count of nodes meeting this criteria divided by all neighbors of the node was greater than 0.50) occurred then the node had a higher rate (xxbeta = 0.1) of moving to rest in the next time step. If a minority event occurred, then the node had smaller rate of returning to rest (beta = 0.05) in the next time step.
    - **Example 2:** If a node was Rest/Injured (scenario 4) then the next step was a neighbor sweep to determine if the majority of the neighbor nodes had the opposite state (Active) and shared the same type attribute (inhibitory or excitatory). If a majority event (the count of nodes meeting this criteria divided by all neighbors of the node was greater than 0.50) occurred then the node had a higher rate (alpha = 0.050) of moving to rest in the next time step. If a minority event occurred, then the node had smaller rate of returning to rest (xxalpha = 0.025) in the next time step.
    - Since each attribute is binary and a node or neuron must fall in one of the states at all times, the groups can be understood in a way similar to the states of an SIS model. In particular, the number of resting nodes = total nodes - number of active nodes, and the number of inhibitory nodes = total nodes - number of excitatory nodes at all time steps in the simulations.
    - One key piece that makes this different from an SIS model is that the probabilities p_{alpha} and p_{beta} are not used to transfer a consistent proportion of neurons from one group to another. Rather, each node individually has a chance of changing groups, the specific probability of which is determined in part by its neighbors. This means that we instead have a proportion of neurons that change groups at each time step which is drawn

from a normal distribution of probabilities centered at either p_{alpha} or p_{beta}, depending on the scenario.

  – In every scenario, a majority rate was assigned a greater rate than the minority rate.
  – Active/Injured minority rate is greater than the Resting/Injured minority rate.
  – Active/Injured majority rate is greater than the Resting/Injured majority rate.
  – Active/Injured majority rate was set to the highest possible rate. Meaning when nodes were active, and surrounding neighbors were at rest, and type of nodes were the same, they changed states at the fastest rate.
  – Injured nodes are more likely than non-injured nodes to be at rest; they are twice as likely to change from active to resting and half as likely to change from resting to active than their non-injured counterparts.
  – A node will only change states if it has at least one neighboring neuron of a different state (active or resting) but same type (inhibitory or excitatory)
  – For further information of rates used in this study, see appendix figures: ABN Model Rate Values, ABN Model Scenario Rate Matrix (22, 23).

For each of the 32 combinations of parameters outlined above, 5 trials of the model were run, and the results for each of the four node conditions were averaged at each timestep and plotted against each other. The 32 corresponding plots are included in the appendix.

Results- ABN Model

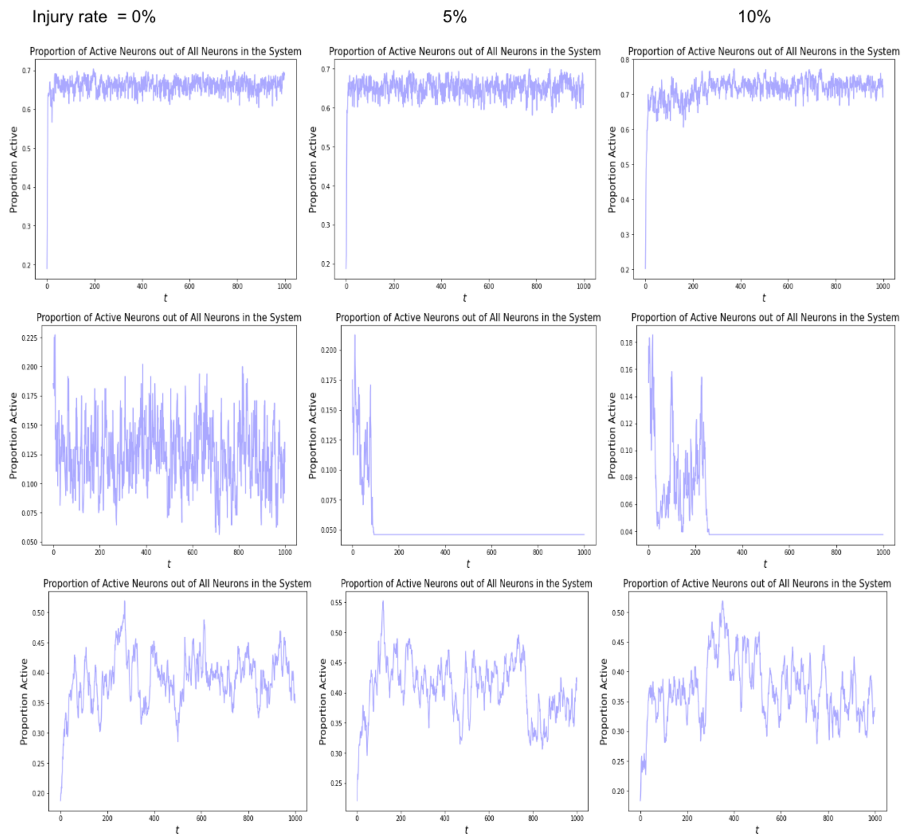
In order to allow for reasonable comparison to the CA model above, simulations were completed for different values of the following parameters: injury cases (0%, 5%, and 10% neurons injured), p_{alpha} (0.05, 0.10, 0.25, 0.50), and p_{beta} (0.05, 0.10, 0.25, 0.50). This resulted in a total of $3 * 4 * 4 = 48$ simulations, or cases. For each of these simulations, 5 trials were conducted, and the results of these trials were averaged across each time step. The full results of all of these simulations can be found in Appendix B.

Using this model, we were able to address our hypotheses as they related to the ABN. We can first address the following hypothesis as stated above:

- A greater proportion of injured neurons . . . will decrease the proportion of active neurons in the brain.

There does appear to be some evidence to support this hypothesis, although it does not appear to hold in all of the simulations and combinations of parameters.

Included below are some chosen plots to help illustrate these results. The full set of plots showing proportions of active neurons for all simulations can be found in Appendix B (Figures 27, 28, and 29).



In the above figure, injury rates are held constant in each column, and values of p_{alpha} and p_{beta} are held constant in each row. For the first row, we have $p_{alpha} = 0.5$ and $p_{beta} = 0.25$; in the second, $p_{alpha} = 0.25$ and $p_{beta} = 0.5$; and in the third, $p_{alpha} = 0.1$ and $p_{beta} = 0.1$.

As we can see in these plots, there isn't much of a noticeable difference in the end final proportion of active neurons for varying injury rates. Looking at the first row, the results are nearly identical for injury rates of 0% and 5%, both hovering around roughly 0.65. The proportion for the 10% injury rate is a bit higher at around 0.70, but still fairly close, and not enough to provide evidence of a difference in the overall proportions when we vary the injury rate.

We do see a bit of a difference in the second and third rows of the figure which does potentially align with our aforementioned hypothesis. In the second row, we can see that the 0% injury hovers around a proportion of roughly 0.125, the 5% injury around 0.05, and the 10% injury around roughly 0.04. Similarly, the third row shows the 0% injury simulation hovering around 0.38, the 5% injury rate around 0.38 as well, and the 10% injury rate a little lower at around

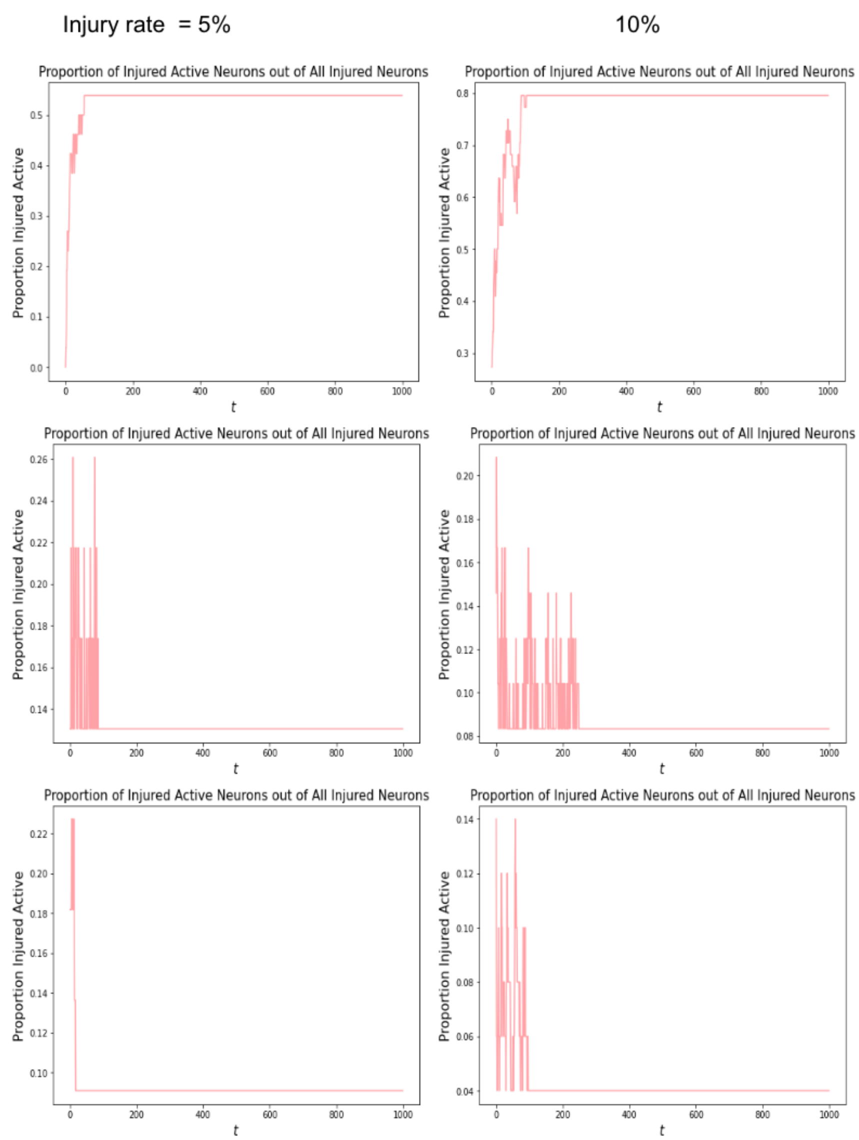
0.35.

While the first row in this figure does not seem to provide evidence to support our hypothesis, the latter two rows do, with the total proportion of active nodes staying roughly the same or showing a slight decrease as the proportion of injured neurons increases. As such, there does appear to be some validity to our hypothesis, but further investigation would be needed in order to make a definitive claim; in particular, more research should be done on the accuracy of the p_{alpha} and p_{beta} values, and additional simulations run which hone in on these different quantities. The results shown here, however, could provide a basis for that type of work to be conducted due to the evidence in support of our hypothesis.

Finally, we can address the last hypothesis that was presented:

- Injured neurons will have higher proportion of resting neurons than non-injured neurons.

As with the previous hypothesis, there was some variation in the results but did appear to be evidence to support our hypothesis, although it did not necessarily hold in every simulation. Shown below are some chosen plots of the proportion of active nodes out of all injured nodes to help illustrate these results. All 16 of these plots are available in Appendix B (Figures 30 and 31).

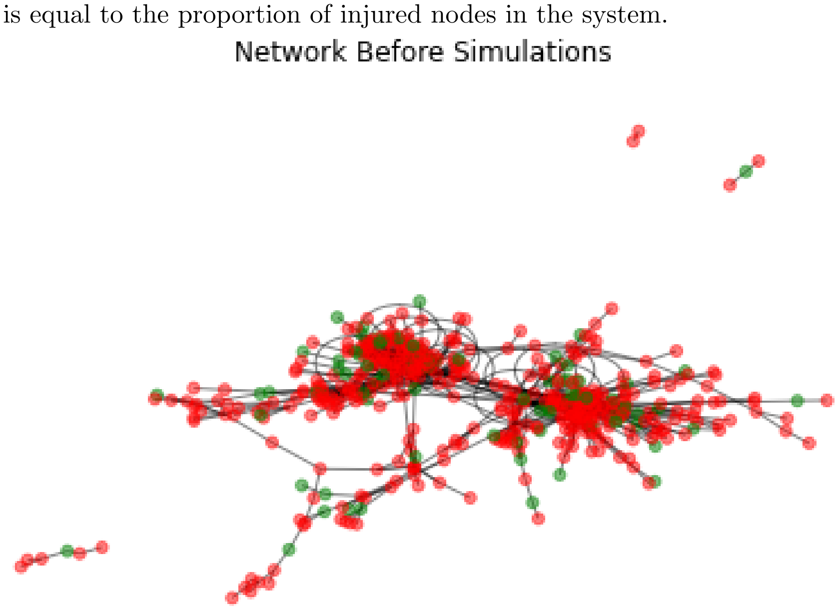


As before, the above figure shows p_{alpha} and p_{gamma} values being held constant in each row, and injury rates being held constant in each column. For the first row, we have $p_{alpha} = 0.25$ and $p_{beta} = 0.1$, for the second row $p_{alpha} = 0.25$ and $p_{beta} = 0.5$, and for the third $p_{alpha} = 0.1$ and $p_{beta} = 0.25$.

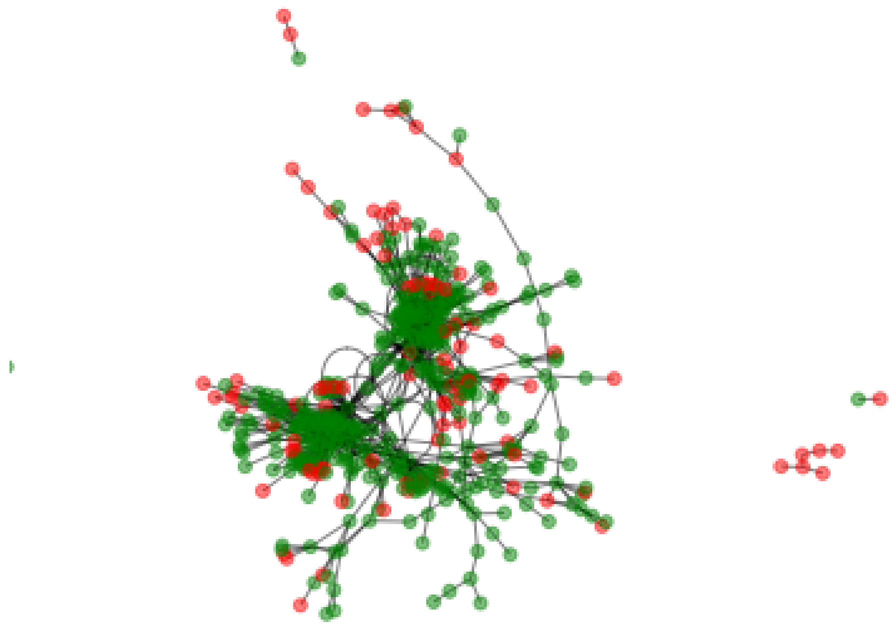
As with the results for the prior hypothesis, there is some evidence to support our claim, but it does not hold in every situation. For instance in the first row of the above figure, we actually see a slight increase in the proportion of active neurons out of all neurons that are injured, from a proportion of about 0.55 in the 5% injury simulation to about 0.8 in the 10% injury simulation. By contrast, the latter two rows show decreases that align with our hypothesis, from about 0.135 to about 0.08 in the second row, and from about 0.095 to about 0.04 in the third row.

This once again suggests that there is some evidence to support our hypothesis that the injured neurons have a higher proportion of resting neurons since we see the proportion of resting neurons (1 - the proportion of active neurons) increasing in many of these simulations when the injury rate is increased. As before, though, this result does not hold true across the board and appears dependent to a certain degree upon the values of p_{alpha} and p_{beta}. As such, further research would be needed to determine which of these values match the real world probabilities most closely, and more simulations would need to be run in order to hone in on these specific probabilities. These results shown here, however, do provide some basis for any future work of that type.

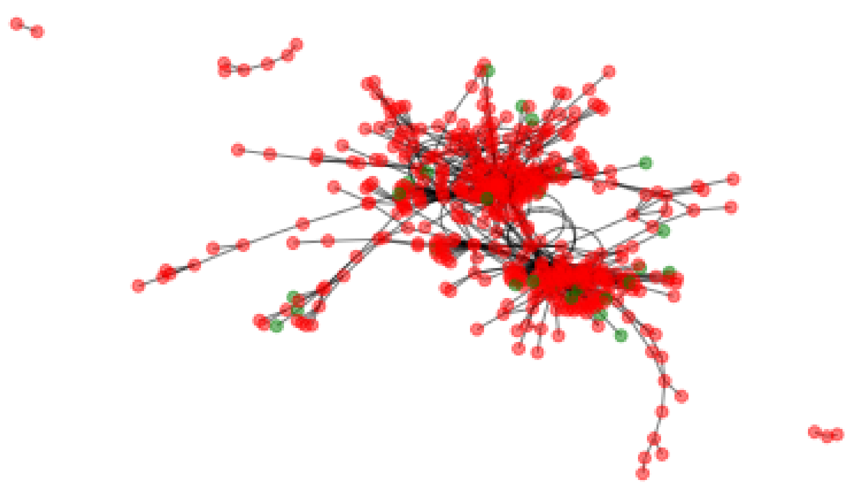
To visualize the changes to the network that are possible as a result of repeat injuries, we created visuals to help depict these changes on the network. Red nodes depicting rest states and green nodes depicting active states represent the changes from running the model before the simulation and running the model using a best and worse case scenarios. The best and worst case scenarios used our stochastic model applying the rates denoted in the titles. Based on the model, the best case scenario achieves more active nodes then the original scenario which set the initial conditions to 80% rest. Additionally, the model with the worst case scenarios of 10% injury visually confirms our hypothesis of what can happen when repeat injuries occur. Note that rho in the following figures is equal to the proportion of injured nodes in the system.



Network: Best case rho = 0.0, alpha=0.5   beta= 0.05



Network: Worst case rho = 0.1, alpha 0.05, beta = 0.5



Colab notebook for Agent Based Model

6 Model Comparison

A summary of the major similarities and differences between the simulations for the CA and ABN models is provided in Table 1. For both models, we considered the same time step size as well as the same proportions for number of neurons of each type, the initial states of the neurons, and the number of neurons injured. We also used the same probabilities for changing the states from resting to active and active to resting. For both models, the rates for transitioning between states were selected based on our modeling experience rather than real-life data from experiments.

While the CA was easy to specify and maintains spatial structures and relationships, it was challenging to keep track of the many different states and rules for the interactions between states. Additionally, the CA used periodic boundary conditions for simplicity, but that behavior may be less realistic than other types of boundary conditions. Conversely, the ABN easily tracked different states and interactions. Both models required only four or less rules, so a less complex approach is likely unrealistic. Both models were stochastic with several parameters and combinations of those parameters, making it necessary to use many simulations.

Due to mechanisms inherent in the nature of a standard CA and ABN model, the following is a detailed list in how the models systems and rules differed:

- **Injury Attributes / Level of injury**: The "level" of injury was assigned differently on the models. The CA model contained injury values assigned from -9 to 9 with negative values resulting in injury, with -9 being the highest injury. The ABN model did not assign a range of values, although this would be feasible. Instead, to simplify an already complicated model we used a binary approach, injured or not injured.

- **Space**: Space assumptions inherent in the model type chosen reflect different model topography. The ABN model leveraged an existing actual brain connectome to study the network that consisted of 480 nodes and 1000 edges. The CA model created the 3D spaced cube divided into smaller cubes representing cubes. In this sense, neurons were uniformly connected (every neuron has the same number of connections to other neurons. A Moore neighborhood was assumed and the CA was limited to 26 neighbors using periodic boundaries. Hence, every neuron has 26 neighbors (homogeneous connections). The ABN models neurons contained degree heterogeneity based on the number of edges connected to each degree varying substantially, with some having 1 neighbor and some having more than 100 neighbors. Hence, the neurons were not uniformly connected as they were in the CA model.

- **States Explored**: The CA model explored 3 states (Active, Refractory, Resting) while the ABN model focused on Active or Refractory to simplify an already complicated model. It would be feasible to add this element in future analyses fairly quickly.

Table 1: Comparison of CA and ABN.

Model 1: CA	**Both**	**Model 2: ABN**
Size: 1,000 cells	**Time step**: 0.005 seconds	**Size**: 480 nodes
States: active, resting, refractory	**Proportion inhibitory to excitatory**: 30:70	**Sates**: active, resting
Injury severity: range	**Proportion active to resting**: 20:80	**Injury severity**: binary value
Connectivity: 26 neighbors	**Fraction injured**: 0 or 0.05	**Connectivity**: up to 100 degrees
	Probability resting to active: 0.05 to 0.50	
	Probability active to resting: 0.05 to 0.50	

7 Future Analysis

State Transition Rates

As stated previously for this model to reflect the most accurate network trends, more information about the correct rates needs to be studied. Our research was not able to explore this further and with our main focus on the application of complex modeling capabilities in neural science.

Adaptive Rewiring

Our research revealed common traits brain networks share and tend to exhibit. There is an opportunity to expand out model(s) to study these defining characteristics before and after injuries to the brain and over time from subconcussive injuries. The goal is to identify how the brain connectivity is altered, how it might rewire itself, the time needed to rewire, and provide some thresholds to what a new equilibrium may look like for a brain that has experienced subconcussive injuries. Injuries to the brain can also address effects on brain communities. There is a great opportunity to use complex models such as network graph theory to explore adaptive rewiring and its affects on typical characteristics of neural networks on brain connectomes. These common characteristics are:

- ‘Small world network’ architecture (Bassett and Bullmore, 2017)

- Skewed network distributions
- Clustering
- Giant Components
- Short average path lengths
- Expected weak edges and a smaller proportion of strong ones)
- See Reference: Szalkai et al, 2015.

Spatial Distribution

Because one of the strengths of the CA is the spatial relationships within the model, future analysis can consider how the spatial distribution of activity in the brain changes around regions of the model with more injured neurons. This could be especially useful for evaluating brain activity around injured neurons if the CA is made more specific to CTE, which can spread through connected neurons (Alyenbaawi et al., 2020)

8 Conclusions

- As expected, the results differed between the two modeling approaches.
- The agent-based model approach produced more realistic results for all conditions. For complex model involving many attributes on a neuron, using the ABN model proved to be an elegant solution.
- In both approaches, the 5% injury did not have substantial effect on the simulation. The fraction of active neurons did decrease with a large increase (10%) in the injured neurons, in general.
- The models could be improved by re-evaluation of the rules for updating neuron state as well as additional experimental or clinical brain data that could be used to inform variables (e.g., state transition rates). This would result in more accurate results.
- These models can be used to simulate subconcussive brain injuries, with the ABN yielding generally more realistic results.

9 References

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10 Colab Notebooks

11 Appendix A: CA Simulation Data

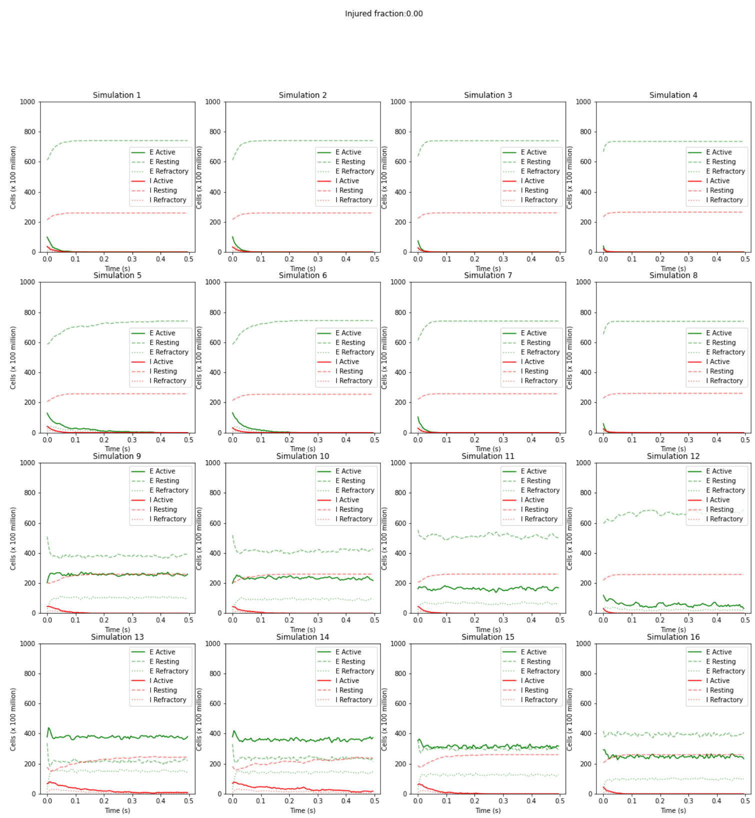

Figure 11: Averaged simulations for no injury case. Rows correspond to p_{alpha} values of 0.05, 0.10, 0.25, and 0.50 (top to bottom). Columns correspond to p_{beta} values of 0.05, 0.10, 0.25, 0.50 (left to right).

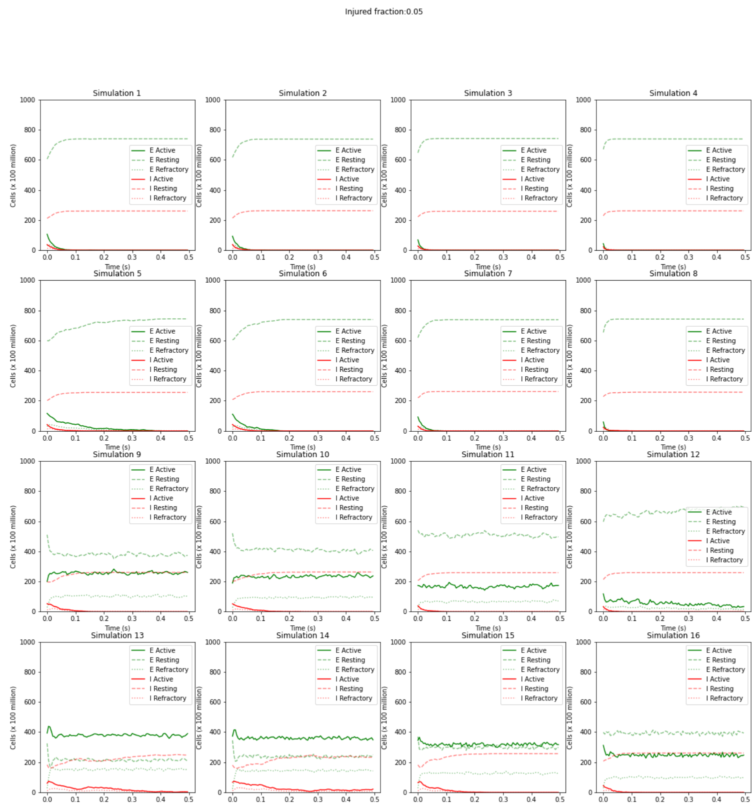

Figure 12: Averaged simulations for 5% injury case. Rows correspond to p_{alpha} values of 0.05, 0.10, 0.25, and 0.50 (top to bottom). Columns correspond to p_{beta} values of 0.05, 0.10, 0.25, 0.50 (left to right).

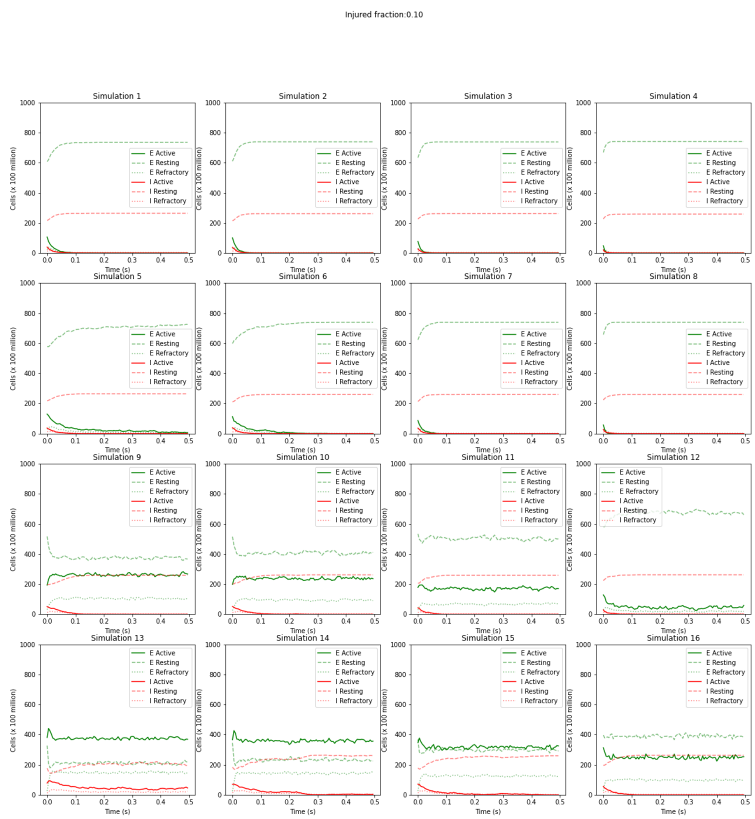

Figure 13: Averaged simulations for 10% injury case. Rows correspond to p_{alpha} values of 0.05, 0.10, 0.25, and 0.50 (top to bottom). Columns correspond to p_{beta} values of 0.05, 0.10, 0.25, 0.50 (left to right).

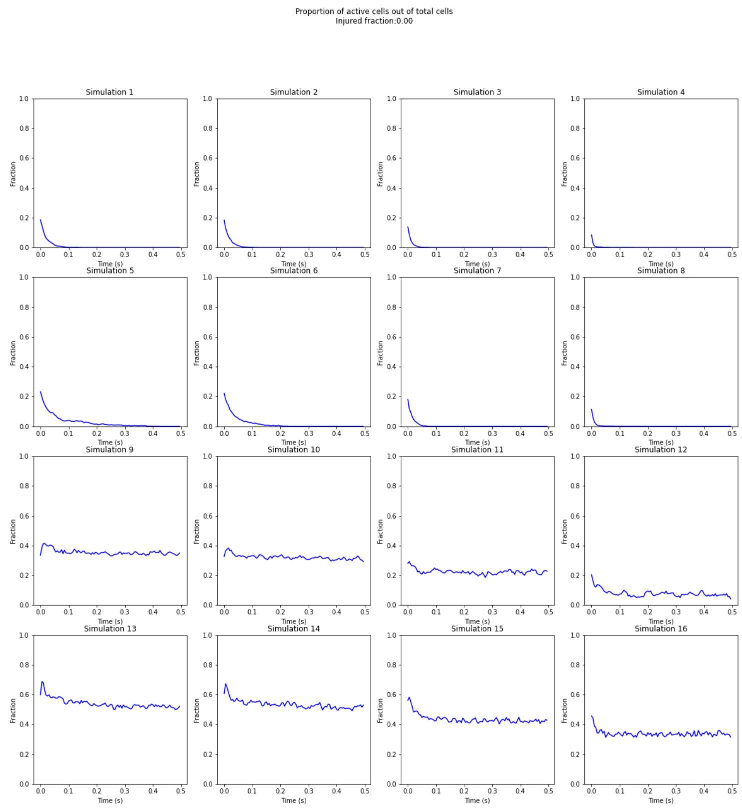

Figure 14: Fraction of active neurons out of total neurons for no injury case. Rows correspond to p_{alpha} values of 0.05, 0.10, 0.25, and 0.50 (top to bottom). Columns correspond to p_{beta} values of 0.05, 0.10, 0.25, 0.50 (left to right).

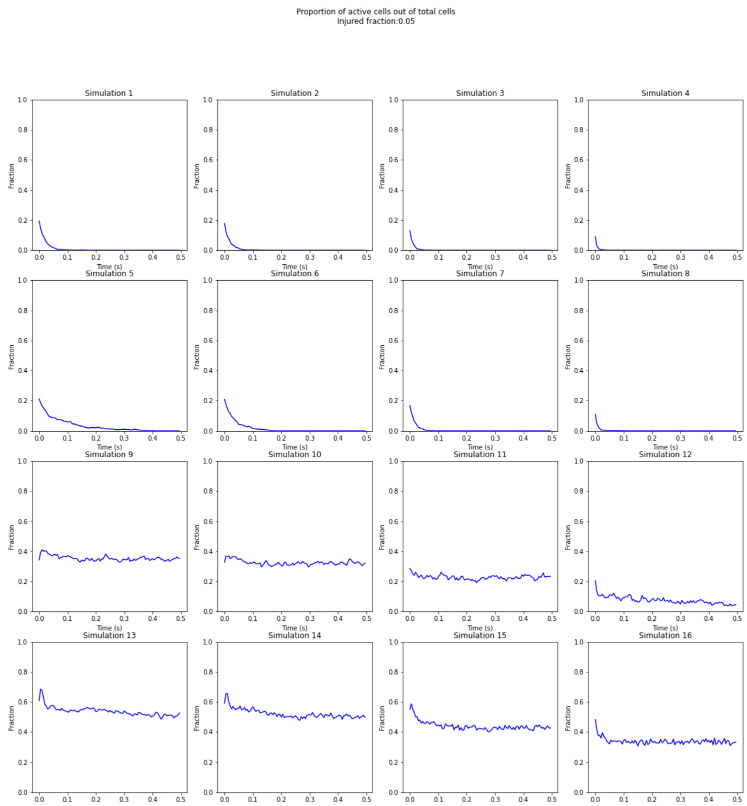

Figure 15: Fraction of active neurons out of total neurons for 5% injury case. Rows correspond to p_{alpha} values of 0.05, 0.10, 0.25, and 0.50 (top to bottom). Columns correspond to p_{beta} values of 0.05, 0.10, 0.25, 0.50 (left to right).

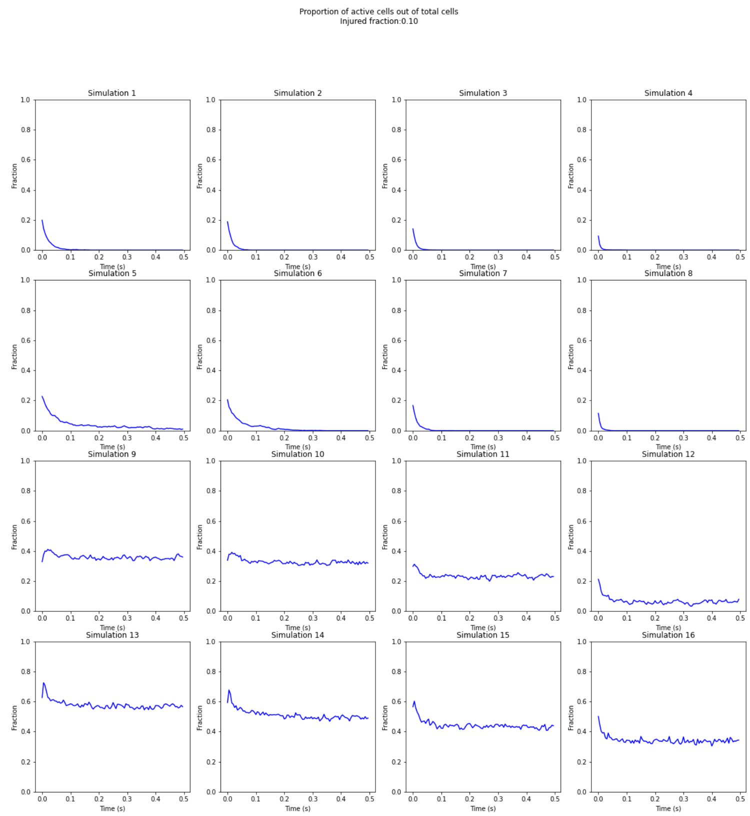

Figure 16: Fraction of active neurons out of total neurons for 10% injury case. Rows correspond to p_{alpha} values of 0.05, 0.10, 0.25, and 0.50 (top to bottom). Columns correspond to p_{beta} values of 0.05, 0.10, 0.25, 0.50 (left to right).

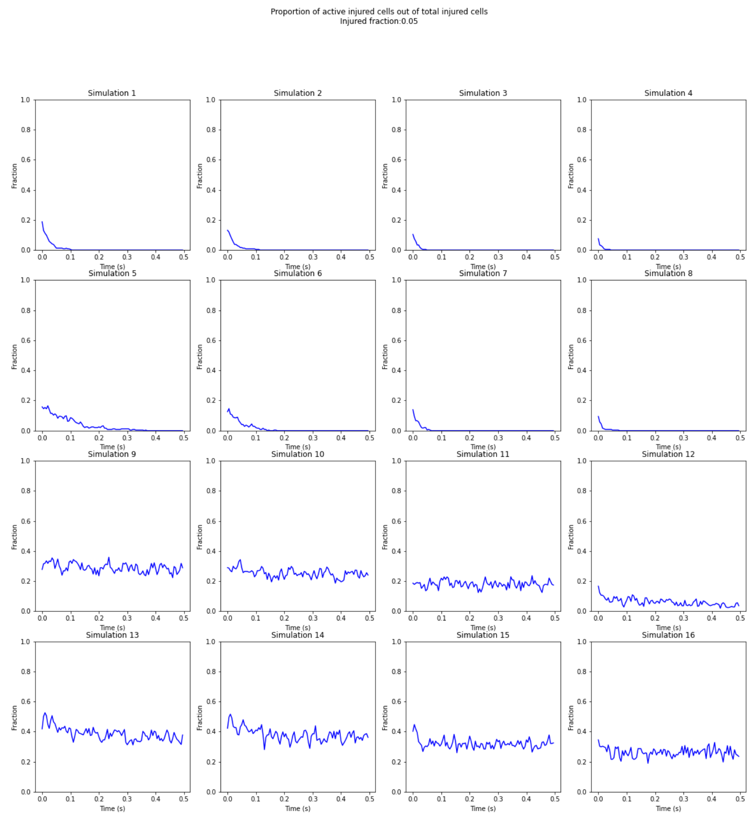

Figure 17: Fraction of active injured neurons out of total injured neurons for 5% injury case. Rows correspond to p_{alpha} values of 0.05, 0.10, 0.25, and 0.50 (top to bottom). Columns correspond to p_{beta} values of 0.05, 0.10, 0.25, 0.50 (left to right).

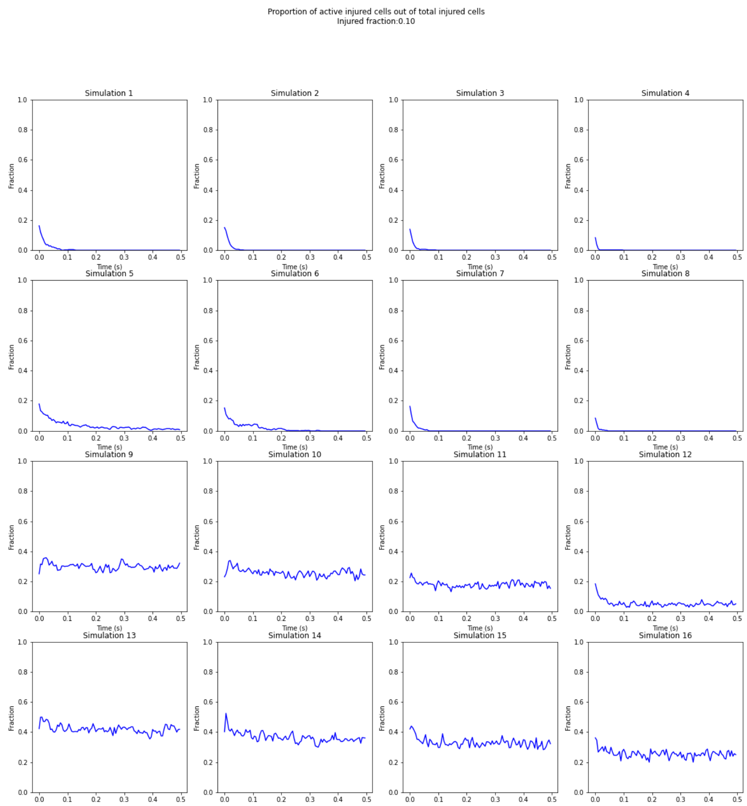

Figure 18: Fraction of active injured neurons out of total injured neurons for 10% injury case. Rows correspond to p_{alpha} values of 0.05, 0.10, 0.25, and 0.50 (top to bottom). Columns correspond to p_{beta} values of 0.05, 0.10, 0.25, 0.50 (left to right).

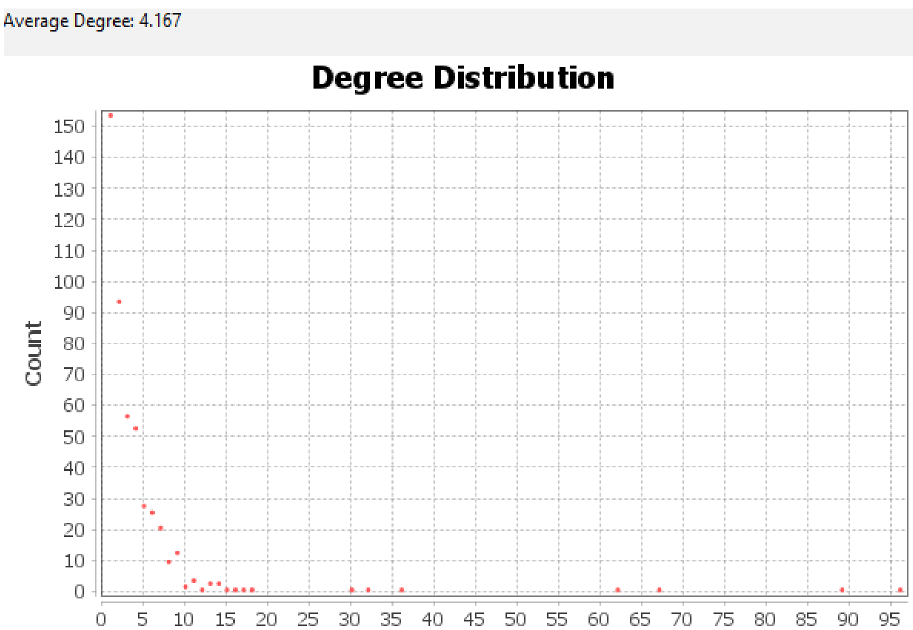

Figure 19: Budapest Conectome Degree Distribution in Gephi 0.9

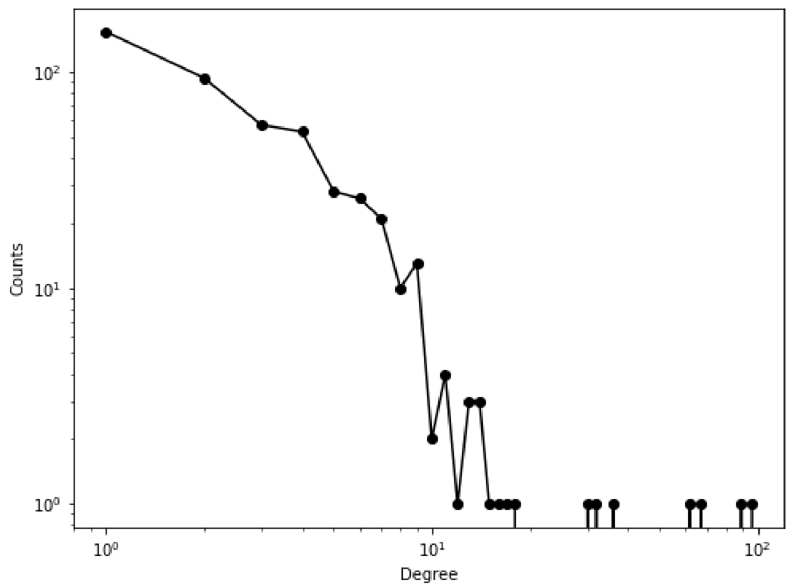

Figure 20: Budapest Conectome Degree Distribution Log Log in Networkx

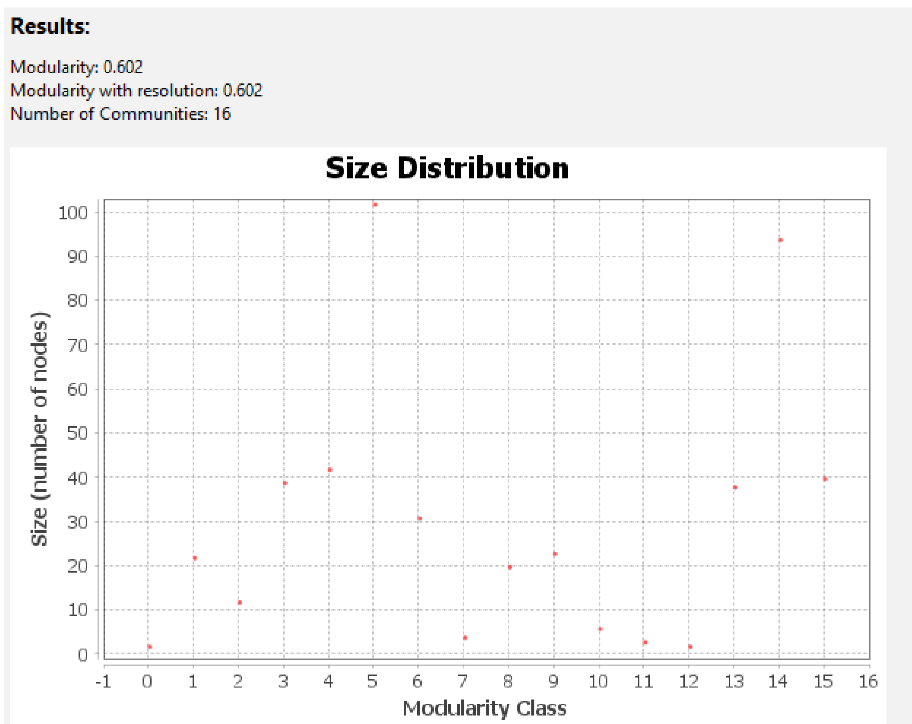

Figure 21: Budapest Conectome Community Detection- Gephi 0.9

12 Appendix B: ABN Simulation Data

Rate Logic	Values rate symbol	[0.05, 0.1, 0.25, 0.5) 0.05 used below	
beta	beta	base	0.050
	xbeta	1.5*beta	0.075
	xxbeta	2*beta	0.100
alpha	alpha	base	0.050
	xalpha	2*alpha	0.100
	xxalpha	1/2*alpha	0.025

Figure 22: ABN Model Rate Values

Scenario Rate Matrix

Scenarios	Event	Rate used	Prob of changing states (Active <>Rest)
Active/Not Injured	Minority	beta	0.050
	Majority	xbeta	0.075
Active/ Injured	Minority	xbeta	0.075
	Majority	xxbeta	0.100
Resting / Not Injured	Minority	alpha	0.050
	Majority	xalpha	0.100
Resting / Injured	Minority	xxalpha	0.025
	Majority	alpha	0.050

*where base alpha and base beta are 0.05

Figure 23: ABN Model Scenario Rate Matrix

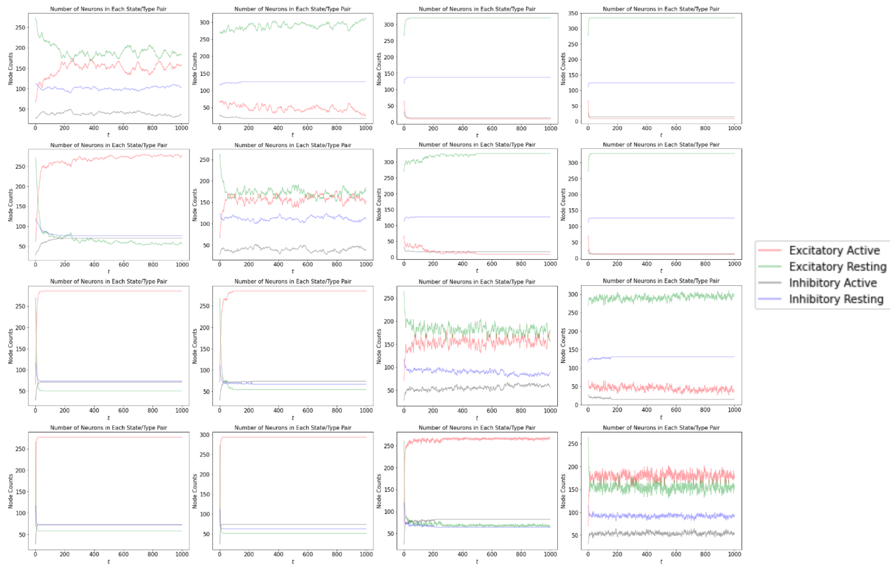

Figure 24: Fraction of the four classifications of neurons for 0% injury case. Rows correspond to p_{alpha} values of 0.05, 0.10, 0.25, and 0.50 (top to bottom). Columns correspond to p_{beta} values of 0.05, 0.10, 0.25, 0.50 (left to right).

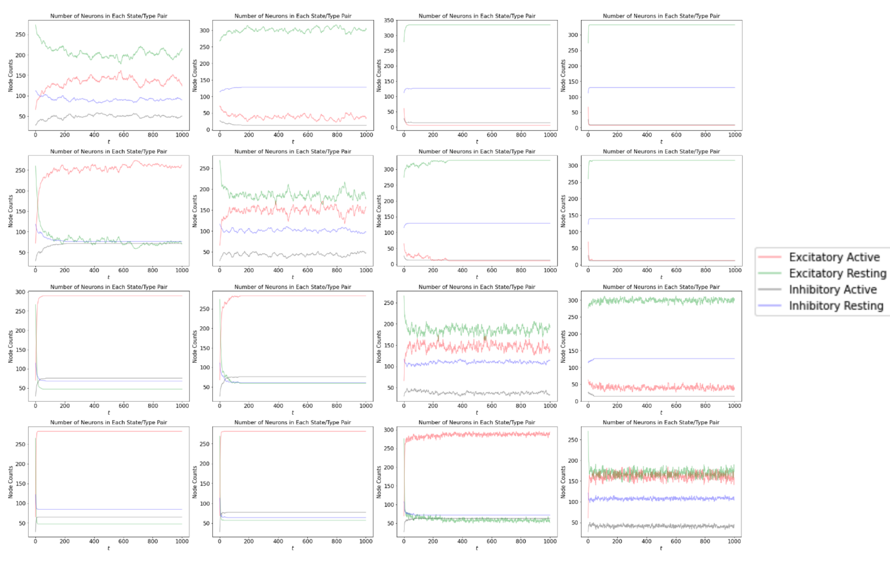

Figure 25: Fraction of the four classifications of neurons for 5% injury case. Rows correspond to p_{alpha} values of 0.05, 0.10, 0.25, and 0.50 (top to bottom). Columns correspond to p_{beta} values of 0.05, 0.10, 0.25, 0.50 (left to right).

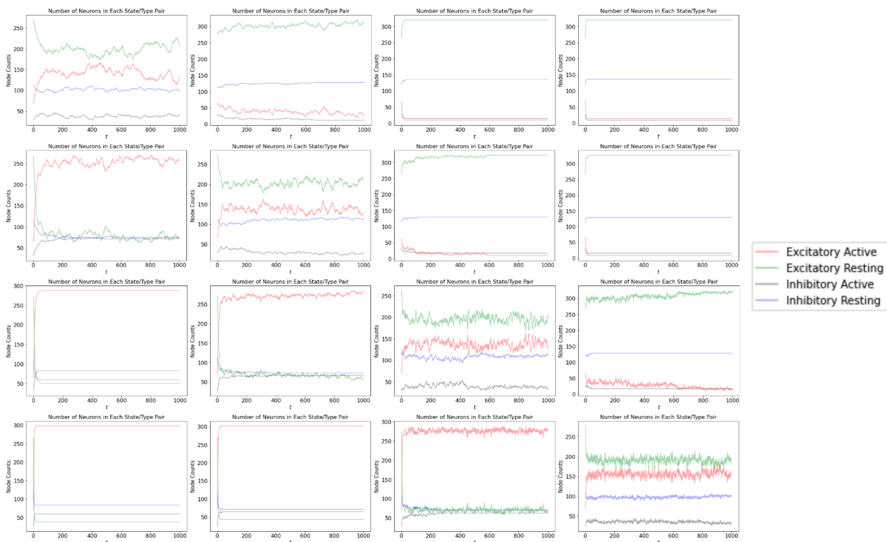

Figure 26: Fraction of the four classifications of neurons for 10% injury case. Rows correspond to p_{alpha} values of 0.05, 0.10, 0.25, and 0.50 (top to bottom). Columns correspond to p_{beta} values of 0.05, 0.10, 0.25, 0.50 (left to right).

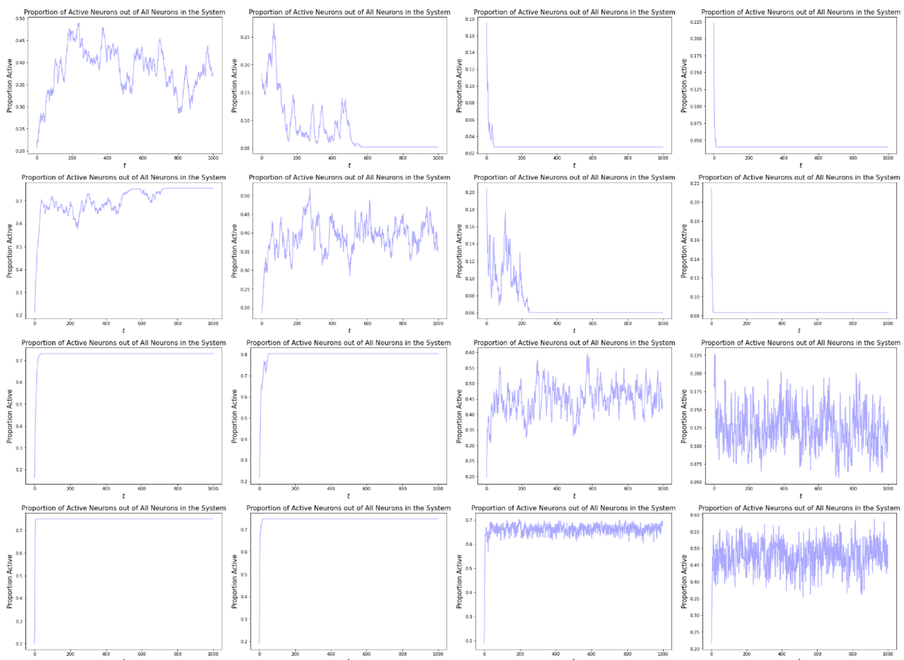

Figure 27: Proportion of active neurons out of all neurons in the system for 0% injury case. Rows correspond to p_{alpha} values of 0.05, 0.10, 0.25, and 0.50 (top to bottom). Columns correspond to p_{beta} values of 0.05, 0.10, 0.25, 0.50 (left to right).

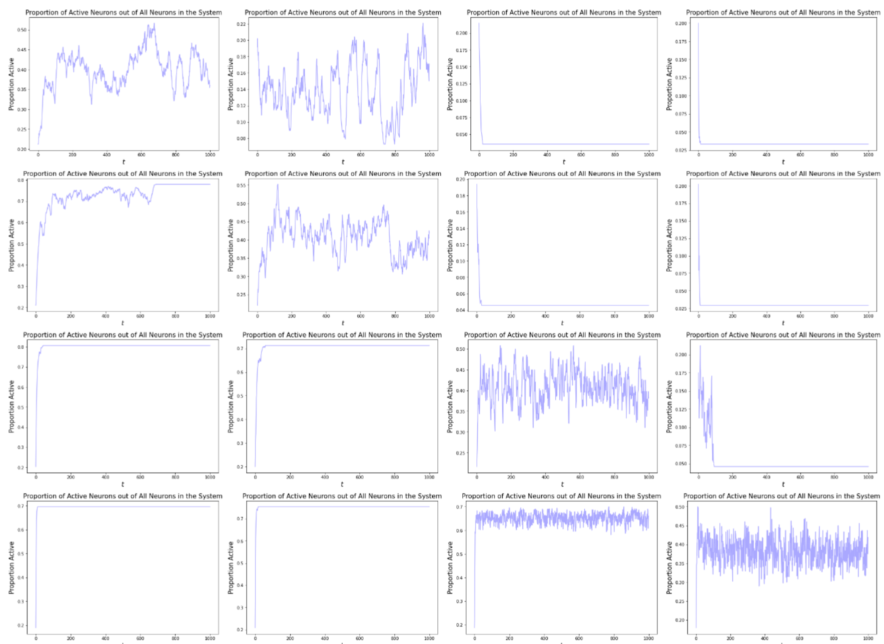

Figure 28: Proportion of active neurons out of all neurons in the system for 5% injury case. Rows correspond to p_{alpha} values of 0.05, 0.10, 0.25, and 0.50 (top to bottom). Columns correspond to p_{beta} values of 0.05, 0.10, 0.25, 0.50 (left to right).

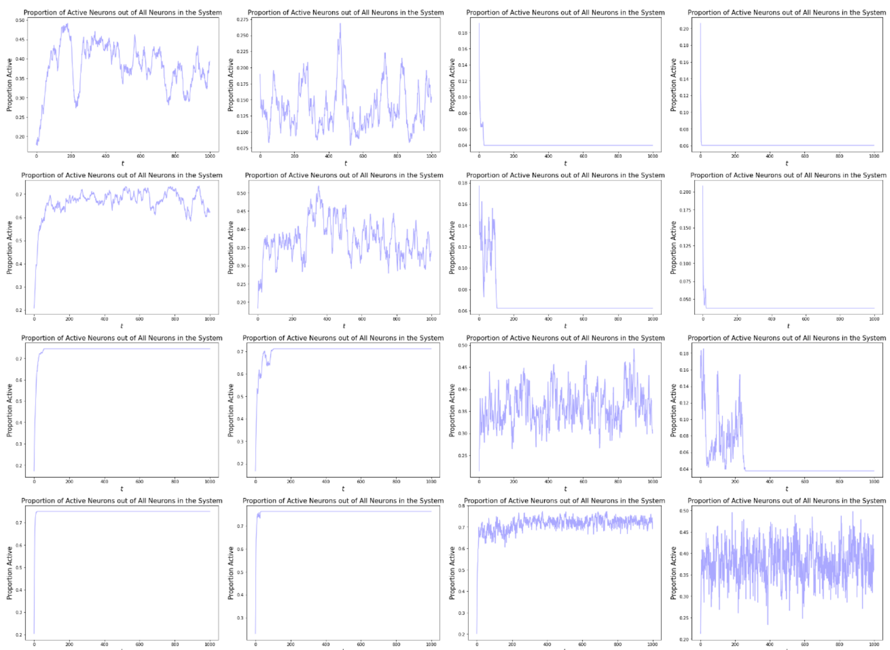

Figure 29: Proportion of active neurons out of all neurons in the system for 10% injury case. Rows correspond to p_{alpha} values of 0.05, 0.10, 0.25, and 0.50 (top to bottom). Columns correspond to p_{beta} values of 0.05, 0.10, 0.25, 0.50 (left to right).

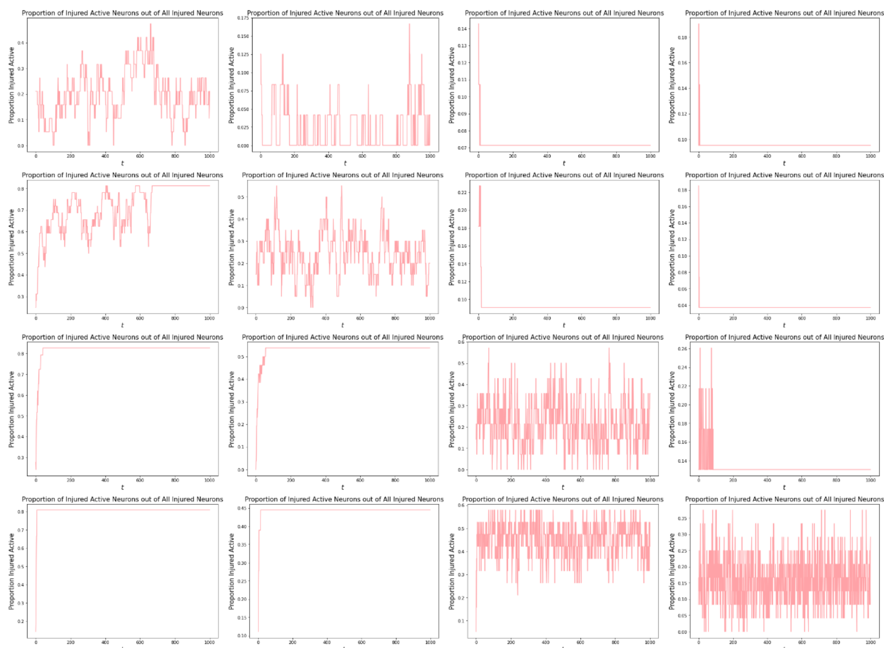

Figure 30: Proportion of injured active neurons out of all injured neurons in the system for 5% injury case. Rows correspond to p_{alpha} values of 0.05, 0.10, 0.25, and 0.50 (top to bottom). Columns correspond to p_{beta} values of 0.05, 0.10, 0.25, 0.50 (left to right).

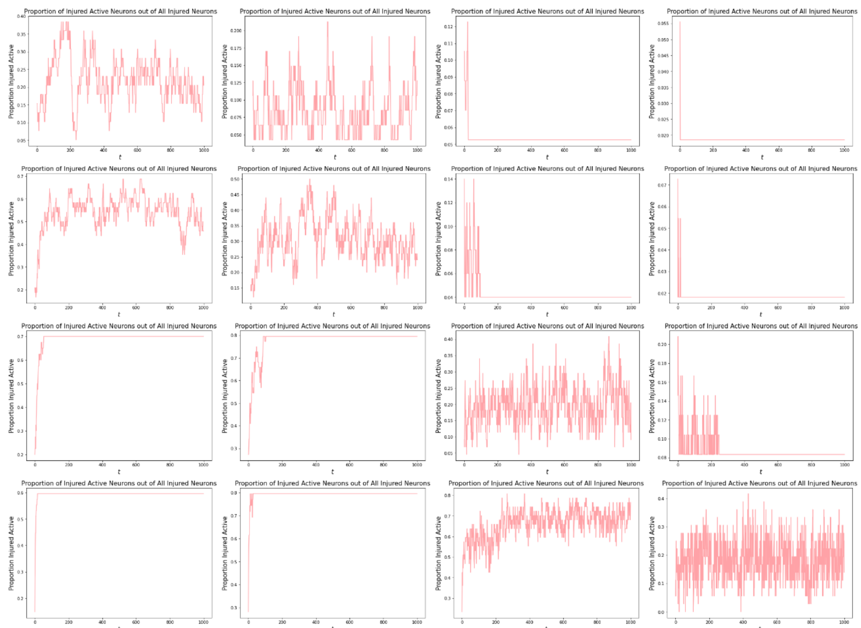

Figure 31: Proportion of injured active neurons out of all injured neurons in the system for 10% injury case. Rows correspond to p_{alpha} values of 0.05, 0.10, 0.25, and 0.50 (top to bottom). Columns correspond to p_{beta} values of 0.05, 0.10, 0.25, 0.50 (left to right).