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Project Summary: A Quantification Algorithm for Brain Connectedness

Overview

The primary objective of this project is to quantify the connectedness of individual brains. This will include improving upon existing quantification algorithms that calculate measures of small-worldness. Small-worldness is a measure to determine whether a given graph is a small-world network. Small-world networks are networks in which most nodes are not neighbors, but paths exist between nodes such that graph traversal is possible in a small number of steps. This project will utilize the concept of small-worldness to determine the level of connection in an individual brain. Existing literature proposes that brains are similar to small-world networks. This project will support that claim or provide evidence to the contrary. Once the brains have been measured, those measurements will be correlated with existing demographic information to determine whether more connected brains have certain properties, possibly higher IQs. All data for this project comes from the Human Connectome Project, which provides brain imaging and behavioral data for 1200 healthy adults. This project necessitates technical expertise in computer vision and graph theory and falls under the *NSF subtopic BM4 Noninvasive Imaging of Brain Function*.

Intellectual Merit

This Small Business Innovation Research Phase I project will develop a quantification algorithm for brain connectedness using Human Connectome Project data. The algorithm will compare the dense connectomes, or neural connection maps, of individuals. Similarity between the connectomes, represented as connectivity matrices, will be defined using belief propagation and algorithms described in “Algorithms for Graph Similarity and Subgraph Matching” by Koutra, Parikh, Ramdas, and Xiang. The primary technical hurdle of this proposal is defining and calculating dense connectome similarity, as this requires an algorithm efficient for large data sets but sensitive to subtle changes between matrices. The algorithm will be developed by combining existing algorithms in literature with modifications and improvements for efficiency and precision. After overcoming this hurdle, the primary work will be in comparing the connectedness measurements with behavioral data like stress, psychological well-being, and memory.

Broader Impact

This project will benefit neuroscience researchers. The quantification of brain connectedness may simplify comparisons between brains, which could enable researchers to better determine normal and abnormal brain traits. The quantification algorithm itself can be applied to other fields in which large datasets of small-world networks exist. The commercialization of this project will enable further scientific understanding of similarities between individuals’ brains and neural pathways.

A Quantification Algorithm for Brain Connectedness

Elevator Pitch

The primary customers for a quantification algorithm for brain connectedness are neuroscience researchers. There is currently no single algorithm that combines the precision of detecting subtle changes between a few data points with the efficiency to handle very large data sets. This innovation will allow neuroscience researchers to quantify brain connectedness in other data sets. The Human Connectome Project has detailed documentation on how they obtained their measurements. That documentation combined with this innovation will allow researchers to apply these exact techniques to any brains they want to analyze, which will be increasingly necessary as the field of neuroscience advances rapidly.

This innovation will enable researchers who work with the brain to better quantify and analyze it. Although there are many tools available for brain analysis, there is no one measure of connectedness. This measure will certainly not be comprehensive, but it can be used to quickly sort and classify brains. It will also enable researchers to determine simple connections between connectedness and behavioral traits, which will allow them to explore these relationships more deeply. The quantification algorithm differentiates itself from others in the field with its ability to handle large data sets and subtle differences between data points.

The primary work of this innovation will be developing the quantification algorithm. This will include improving upon existing quantification algorithms that calculate measures of small-worldness, which is a measure to determine whether a given graph is connected in a way that enables global traversal despite local disjointedness. This project will utilize the concept of small-worldness to determine the level of connection in an individual brain because many works in the literature claim that brains are small-world networks. This innovation will allow researchers to evaluate that claim. After the algorithm is developed and each brain is measured, those measurements will be correlated with existing demographic information to determine whether more connected brains have certain properties.

The secondary challenge of this innovation will be to efficiently compare the brain's quantified connectedness with every behavioral data point to determine where trends emerge. This combination of quantification and correlation will provide researchers with valuable information that does not currently exist. The largest impact of this innovation will be the algorithm, which can be applied to many different fields. All data for this project comes from the Human Connectome Project, which provides brain imaging and behavioral data for 1200 healthy adults. The Human Connectome Project's behavioral data includes information on individuals' stress, psychological well-being, memory, language comprehension, strength, and olfactory abilities.

Commercial Opportunity

It is clear that the market is ripe for an innovation to the MRI. Neurologists and neurosurgeons need to spend less time manually reviewing MRI results. Patients need to spend less time and money getting MRIs. There needs to be a way to reduce both the number of MRIs necessary and the amount of time spent analyzing one MRI. The clear solution is an algorithm that captures the important information from the MRI and leaves out the rest.

The quantification algorithm is a novel innovation in the neurology industry. It has no potential competitors. It aims to augment, not replace, the MRI. The algorithm is a low-risk innovation because it does not threaten any existing product. Its only weakness is that certain neuroscientists, neurologists, or neurosurgeons may try to overfit the data, which is a risk with any data analytics tool. The algorithm will be sold with clear instructions on how to avoid overfitting data.

The cost to produce the quantification algorithm is low. The project will need one software developer to develop and implement the quantification algorithm. All of the data used to build and verify the algorithm is freely available so there is no development cost for data access. The only development cost for the quantification algorithm is the cost of the software developer.

The quantification algorithm is available at a cost comparable to a single MRI. Neurologists, neurosurgeons, and neuroscientists will pay a one-time licensing fee of $2,611 to use the quantification algorithm. This one-time fee is equivalent to the average cost of an MRI in the United States. The fee will cover the use of the algorithm and documentation detailing how to properly use the algorithm. The fee will be charged per institution so one practice with multiple neurologists or neurosurgeons can share a license and one university with many neuroscientists and researchers can share a license. The algorithm is a low-cost product with a low development cost and will likely have a high adoption rate.

The MRI is the most frequently used brain imaging tool today. It is extremely valuable because it provides insight into the brain that is otherwise unattainable. This value is revealed in the high cost of an MRI. In addition to paying for the MRI itself, patients who receive MRIs must take at least half a day off of work to get the MRI, which is a burden for many individuals. Compounding this burden is the fact that many patients must get multiple MRIs over long time periods to monitor their progress and to determine if there are any changes in their brains. These factors make MRIs expensive and inefficient.

I propose a quantification algorithm to solve this problem. The algorithm will produce a standardized set of metrics to measure brain connectivity. With this information, neurologists and neurosurgeons can quickly and easily assess patients. These metrics will reduce the time spent evaluating each MRI. The algorithm can also act predictively once data tracking brain changes over time is obtained. The change data can be analyzed to construct predictive functions that can estimate how an individual's metrics will change over time. This analysis will reduce the number of MRIs an individual will have to get over his or her lifetime.

The modest cost of $2,611 per license will encourage neurology professionals to adopt this technology. The low cost also means that academic researchers will adopt this technology because cost will not be a barrier. If six licenses are sold, the development cost will be covered if the software developer is paid twenty dollars per hour. This is assuming that development will take eighteen weeks, which is a reasonable amount of time to develop and test the algorithm. It is almost certain that at least six licenses will be purchased, as there are over 26,000 neurologists in the United States alone.

The quantification algorithm is a novel and important innovation. With its low cost and ease of use, the algorithm is accessible to anyone working with the human brain. This quantification algorithm lays the foundation for future work that aims to enhance our understanding of the brain.

Societal Impact

I propose a quantification algorithm to measure brain connectivity because it is clear that there is a societal need for a brain measurement tool. This algorithm can measure both anatomical and functional connectivity. Anatomical connectivity refers to the physical links between brain regions in the form of neural pathways or blood vessels and can be seen with normal MRIs. Functional connectivity refers to activation patterns that are related across brain regions and can be seen with functional MRIs. Knowledge of both forms of connectivity is crucial for overall understanding of the brain.

This quantification algorithm will improve understanding of the brain, which is extremely complex and difficult to measure. Although there are many different brain imaging methods, there are few other ways to analyze brains. The field of neuroscience is lacking standardized metrics to measure and quantify brains. This lack of metrics has prevented the field from moving forward. If an algorithm for calculating brain measurement metrics were established, the analysis of brains would be much easier and more consistent.

An algorithm that measures brain connectivity is especially helpful for those who may be suffering from neurological disorders.Current diagnostic methods are effective, but inefficient. Individuals at risk for multiple sclerosis, for example, must receive an MRI every eighteen months. A neurologist then manually reviews the MRI and calls the patient with the results. The MRI itself takes close to four hours and the neurosurgeon may not complete the manual review for several business days. The process for diagnosing other neurological diseases is similarly inefficient.

A brain connectivity quantification algorithm will increase diagnostic efficiency by reducing the quantity of manual MRI reviews. Neurologists and their technicians must manually review many MRI results. This time-consuming process takes away from their time to see patients and to stay informed about new developments in the field. These doctors and technicians would benefit from an innovation that reduced the time necessary to review MRI results. If a tool could reduce MRI results to several comprehensive metrics, neurologists would have more time to spend with their patients. Such a tool could even improve diagnostic accuracy.

This quantification algorithm will introduce a standardized set of brain connectivity metrics, which will enable researchers who work with the brain to better quantify, analyze, and understand the brain. Although there are many tools available for brain analysis, there is no standardized set of measures for connectivity. This set of measures will simplify analysis of the brain. Instead of manually reviewing MRI results, a neurologist could compare the metrics to normalized values and use that comparison to construct a diagnosis. The metrics will drastically reduce the time spent on diagnosis because the manual review of the MRI results will no longer be necessary.

The quantification algorithm can be applied to any datasets that contain information about brains changing over time so the metrics can also be predictive. The change in metrics over time can then be calculated. Analysis of these changes over time will result in functions that can predict how an individual's metrics will change over time. This analysis could eliminate the need for MRIs every eighteen months to track changes in the brain. Instead, the predictive functions will have a confidence percentage for a certain amount of time and once that confidence drops below a certain threshold, the patient would have to return for an MRI. These predictive functions will drastically reduce the amount of time and money spent on MRIs.

The quantification algorithm aims to augment understanding of the MRI. The MRI is a powerful and valuable brain imaging tool, without which MRI we would not have insight into the structure and function of the brain. MRI images require training to understand and seem obtuse to those new to the field. The quantification algorithm bridges the gap between image and information, which is beneficial to not only researchers and doctors, but also to students.

Students will benefit from the simplicity and accessibility of the quantification algorithm. It can be difficult and time-consuming for students to learn how to analyze MRIs. The connectivity metrics produced by the quantification algorithm are well-defined and well-documented. The documentation that accompanies the quantification algorithm explains exactly how each connectivity metric is calculated. Additionally, the documentation explains how to properly interpret the metrics. Students can use the algorithm and documentation to enhance their study of MRIs.

The quantification algorithm for brain connectivity is valuable for neurologists, neuroscientists, neurosurgeons, and students. Neurologists and neurosurgeons benefit from spending less time on MRIs and more time with patients. Neuroscientists benefit from having more time to read scientific literature and work on research problems. Students benefit from having a lower learning curve. The quantification algorithm for brain connectivity distills an MRI into key metrics about brain connectivity, which is a necessary and welcome innovation in the field of neuroscience.

Technical Discussion and R&D Plan

The core technical component of the quantification algorithm is the development of the algorithm itself. The development of the algorithm includes identifying the best metrics to use in the quantification algorithm and improving the efficiency of the calculations in the algorithm. Many existing algorithms and techniques can be used to improve the aid in the development of the quantification algorithm. Because this quantification algorithm is working with graph data, there are known methods to improve the efficiency of some of the components of this algorithm.

The key objectives to be accomplished during the Phase I research include formatting the connectome for use with the quantification algorithm, calculation of the number of neighbors of each node in each connectome, calculation of the number of connections between all neighbors of all nodes in all connectomes, and calculation of the minimum path length of each node in each connectome.

Formatting the connectome for use with the quantification algorithm involves reading in the connectome file and transforming a single long line of text into a two dimensional matrix. This step is necessary to be able to perform the following calculations on the connectome because the connectome is a graph that is represented by an adjacency matrix. This formatting renders the adjacency matrix in the algorithm for ease of use.

A large component of the quantification algorithm is calculating the number of neighbors of each node, or datapoint, in the connectome. The connectome is a matrix representing the functional connections between different physical regions in the brain. Each entry [i][j] in this matrix is an edge that represents the strength of the functional connection between physical region i and physical region j. These physical regions are referred to as nodes and the neighbors of node i are the nodes that are connected to node i by an edge. Finding neighbors is a common problem in graph theory. Because of this component's commonality, there are several existing algorithms to find the neighbors of a node. The simplest method to find neighbors is to count the number of non-zero entries in the current node's row in a matrix that represents the graph, commonly called an adjacency matrix. It is also possible to use a modified breadth-first search or depth-first search algorithm to find neighbors.

After finding the number of neighbors of each node in the connectome, it is necessary to calculate the number of connections among those neighbors. The number of connections can be calculated using a similar method as the above algorithm to find neighbors. It is necessary to compare every neighbor with every other neighbor and count the neighbor of edges between all of these pairs. This metric is then divided by the number of neighbors and the result is averaged across all nodes.

The combination of the aforementioned components is the clustering coefficient, which measures the density of a node's connection. A densely connected node in this dataset indicates a physical region of the brain that is functionally connected to many other physical regions. This dense connection indicates functional importance of that physical region. In brains, nearly all physical regions are functionally important, which means most nodes in the connectomes are densely connected. This dense connection is one of the two major components of the quantification algorithm.

The second primary technical component of the quantification algorithm is the minimum path length, which is the smallest number of edges that must be traversed to go from one node to the next. In this dataset, the minimum path length is the minimum number of functional connections between one physical region and another. For the quantification algorithm, the minimum path length must be calculated between every pair of physical regions. The average minimum path length is then calculated, completing the major technical components of the primary focus of the proposed Phase I project.

The secondary focus of the proposed Phase I project is the comparison of the results of the quantification algorithm with the behavioral data supplied by the Human Connectome Project. The quantification algorithm measures the connectedness of an individual's brain by calculating the small-world-ness measure defined by Mark D. Humphries and Kevin Gurney in "Network 'Small-World-Ness': A Quantitative Method for Determining Canonical Network Equivalence". By comparing this connectedness to behavioral data, it is possible to determine whether there is any correlation between the connectedness of a brain and the behavior of an individual.

The available behavioral data includes metrics on stress, intelligence, and sociability. Analysis of the correlation between these metrics and brain connectedness will lead to the development of models to predict behavior given an individual's connectome. This could lead to earlier diagnosis of intelligence or sociability disorders, like autism, and potentially to improved treatment of disorders based on analysis of how the connectome responds to specific treatments.

The commercial feasibility of the proposed project relies on the demand of neurologists and neuroscientists for the quantification algorithm. There are very few risks in bringing the quantification algorithm to market, other than a potential lack of demand. The determination of this demand is the key commercial objective of the proposed Phase I project. In order to determine the level of interest of neurology professionals, it is necessary to conduct market research and to ask actual professionals in the field about their needs. Market research, marketing strategy development, and marketing will be conducted throughout the lifetime of the proposed project.

The timeline for the proposed Phase I project is as follows.

- Week 1: Begin project
  - Read data documentation
  - Outline steps of algorithm
  - Conduct market research
- Week 3: Objective 1
  - Read in connectome files
  - Transform connectome string into two dimensional matrix
  - Continue market research
- Week 5: Objective 2
  - Write algorithm to find number of neighbors of each node in each connectome
  - Test algorithm on sample data and verify results
  - Interpret market research
- Week 7: Objective 3
  - Write algorithm to find number of edges between neighbors
  - Test algorithm on sample data and verify results
  - Refine market research and conduct more market research, if necessary
- Week 9: Complete Objective 2 and Objective 3
  - Perform neighbor algorithms on Human Connectome Project data
  - Improve efficiency of number of neighbors algorithm
  - Improve efficiency of number of edges between neighbors algorithm
  - Begin development of marketing strategy
- Week 11: Objective 4
  - Write algorithm to calculate the minimum path length for each node
  - Test algorithm on sample data and verify results
  - Continue marketing strategy development
- Week 13: Complete Objective 4
  - Perform path length algorithm on Human Connectome Project data
  - Improve efficiency of path length algorithm
  - Complete marketing strategy development
- Week 15: Combine Objectives 1 - 4
  - Write small-world-ness algorithm
  - Perform algorithm on Human Connectome Project data
- Week 17: Small-world-ness
  - Improve efficiency of small-world-ness algorithm
  - Obtain small-world-ness values for 820 subjects in Human Connectome Project
- Week 19: Behavioral data
  - Read in behavioral data
  - Calculate correlation between small-world-ness and behavioral data
- Week 21: Behavioral data analysis

Determine which behavioral variables are highly correlated with small-world-ness
Read documentation for highly correlated behavioral variables

Week 23: Interpretation

Interpret correlation between highly correlated behavioral variables and small-world-ness
Outline steps for developing predictive model of highly correlated behavioral variables given small-world-ness or connectome

Week 25: Completion

Evaluate project success
Create final report and presentation
Begin marketing as detailed in marketing strategy