Handwriting Based Parkinson's Disease Diagnosis

Krithika Subramanian

Plano Senior High School

Purpose

This study aims to develop an inexpensive, accurate diagnosis of Parkinson's Disease via image processing and a machine learning framework

Contents

1. Abstract

Parkinson's Disease (PD) is a progressive neurodegenerative disorder that causes impaired balance, muscle stiffness, and uncontrollable tremors in the limbs. The earliest symptoms of PD include barely noticeable tremors and slower movements that gradually worsen over time. They are often dismissed in early stages, where medical treatment is more effective. Further, brain MRIs, specialized diagnoses, and treatment can cause the economic burden of PD to rise drastically with severity, reaching up to thousands of dollars.

This project aims to develop a cost-effective and reliable method for diagnosing PD through neural network processing techniques based on handwriting samples, as there is no specific lab or imaging test that provides a definitive diagnosis. The slight tremors and shaking of the hands and fingers suggestive of PD results in unsteady and smaller handwriting. The proposed procedure for diagnosis administers a drawing test of the Archimedes' spiral to the participants and utilizes a long short-term memory neural network to determine the likelihood of PD. To do this, the x and y coordinates of the participant will be continuously recorded while drawing, and data such as displacement, velocity, and acceleration of the writing will be calculated. With the processed image and derived data, an accurate prediction will be made on whether the participant has PD.

Future applications include implementing different tests, such as circles and cursive lettering, to improve predictions. Additionally, a graphics tablet could be used to obtain more raw data, such as pressure or angle of wrist, to develop a more informed diagnosis.

2. Introduction

2.1 Purpose

This study intends to develop a cost-effective, reliable form of diagnosing Parkinson's Disease. Neurodegenerative diseases like PD do not have specific lab or imaging tests like other diseases, so diagnosis takes time and is typically done by a specialized neurologist trained to analyze physical and neurological symptoms. Diagnosis is done clinically, using a patient's history, symptoms, and physical exams, but "pathological examination of the brains of patients with a clinical diagnosis of Parkinson's disease shows a different diagnosis in up to 35% of cases" (Schrag et al.).

Pen and paper tasks are helpful in PD diagnosis to analyze a patient's movements while writing. Specifically, the Archimedes' spiral demands a continuous movement that reveals abnormal frequencies and directions of tremors. However, doctors are only able to see the rendered spiral image, which does not provide an informed diagnosis, especially in early stages. While nuclear imaging dopamine transporter scans can support a PD diagnosis, they are not a definite determiner. Additionally, expensive imaging tests like brain MRIs or PET scans may help rule out other diseases, but are not helpful in pinpointing PD.

The purpose of this study is to develop an application capable of tracking a participant's movements as they draw an Archimedes' spiral and determine *x, y*, and velocity graphs for the writing. Then, a recurrent LSTM neural network will be applied to a spiral drawing dataset from the UCI Machine Learning Repository to determine the typical kinematics of healthy controls and PD patients. The potential of PD for the participants is predicted using this model and the derived data.

2.2 Goals/Hypothesis

This study involves the development of a novel machine learning method as participants undergo a standard clinical drawing test on a phone to track their writing and provide more data for diagnosis.

The project aims to create a cost-effective and accurate method to determine the velocity and acceleration of movements in clinical settings to better diagnose PD, while expanding current knowledge on the reliability of computerized medical technology.

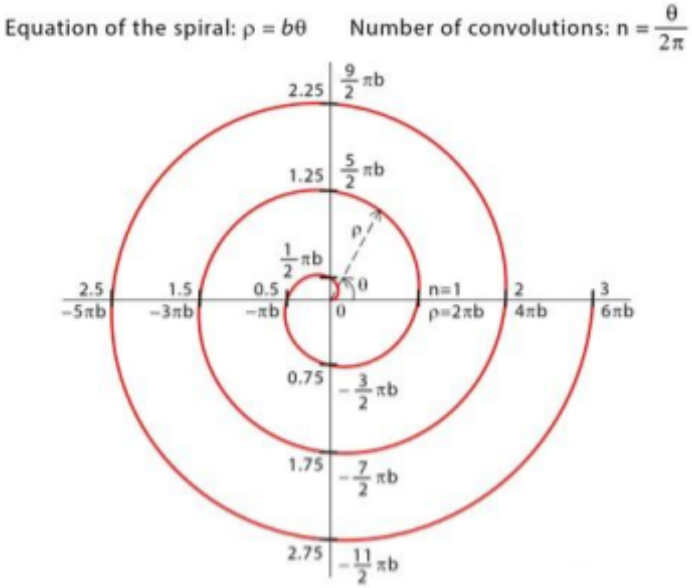
3. Review of Literature

3.1 Parkinson's Disease (PD)

Parkinson's Disease (PD) is a progressive synucleinopathic disease caused by a weakening of dopamine nerve cells in the brain that largely affects the aging population. Davie et al. expresses that "diagnosis of PD remains essentially a clinical one… it is important to recognize the early features together with symptoms and signs suggesting other causes of parkinsonism" (Davie et al., 2). Imaging tests rarely prove useful. Further, postmortem examinations show that 25% of supposed PD patients were subject to diagnostic error. Notably, however, a change in handwriting to a micrographic form is an early indicator of PD due to cardinal features of rest tremors, bradykinesia, limb rigidity, and postural instability. Early diagnosis is crucial, as mental and physical complications become exponentially more troublesome as the disease progresses.

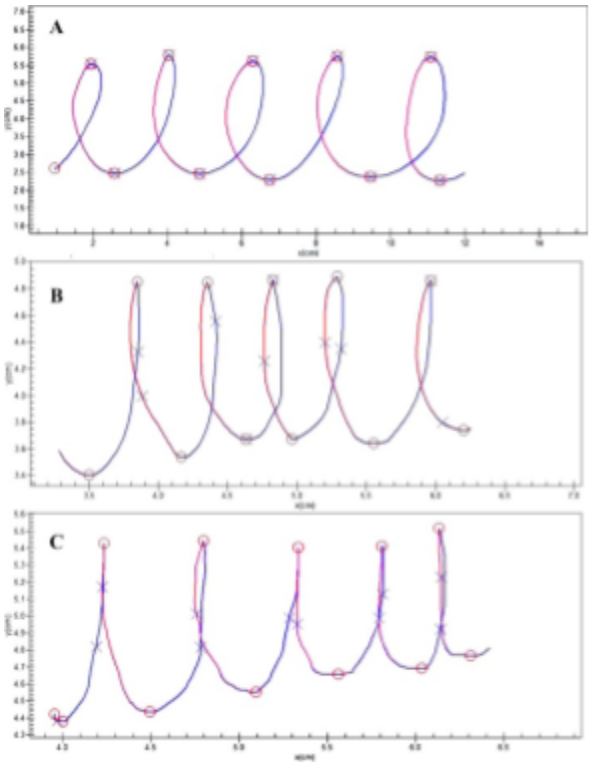
3.2 Handwriting Biomarker

Micrographia is an acquired medical phenomenon characterized by small, cramped, and unsteady handwriting, especially the progression to smaller writing. McLennan et al. states that abnormally small letter size is exhibited in PD patients up to 5% of the time *before* motor skills degenerate. Because handwriting requires the use of extended finger and wrist movements, the four cardinal features cause horizontal writing strokes to become shorter. Thomas et al. proposes that



Archimedes spiral with three convolutions (where ρ is radius and b is the distance between turnings). ScienceFacts.net

micrographia is thus a "presymptomatic neurobehavioral biomarker of PD". Micrographia is classified as consistent (letter size is overall reduced) and progressive (letter size reduces as writing progresses). Letters or drawing where consistent movement and contact with paper showcase this phenomenon. Specifically, drawings such as the Archimedes' spiral or cursive lettering (specifically linguistic units such as *e, l,* or *s*) are often used in clinical examinations. Thomas et al. suggests the use of digitized pens to gather kinematic data like velocity and acceleration of writing to support diagnoses. The following image displays a handwriting sample of a 5-gram repeated cursive *l*, where *A* represents a healthy control, *B* represents a PD patient taking the PD medication levodopa (*L*-dopa), and *C* represents a PD patient not taking *L*-dopa.



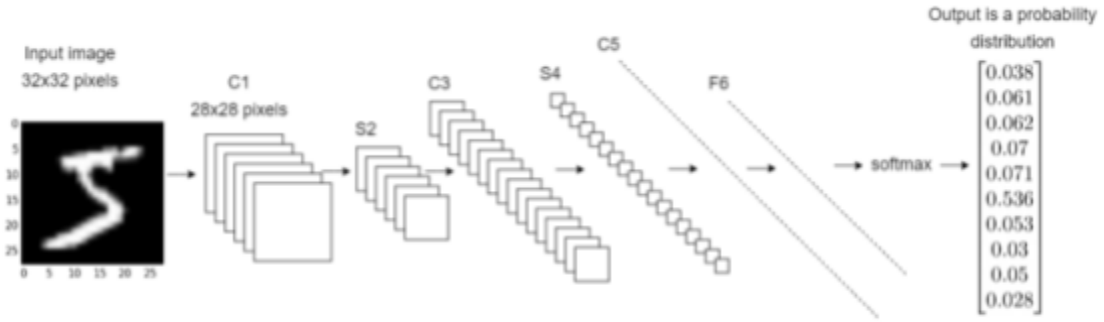
Thomas et. al.
"Handwriting Analysis in Parkinson's Disease"
A) Healthy control. **B)** PD patient on *L*-dopa, shows marked improvement in micrographia. **C)** PD patient off *L*-dopa, shows consistent horizontal micrographia.

3.3 CNN/RNN

Convolutional and Recurrent Neural Networks (CNN and RNN, respectively) are two classes of Artificial Neural Networks (ANN), which are algorithms modeled after neurons in the

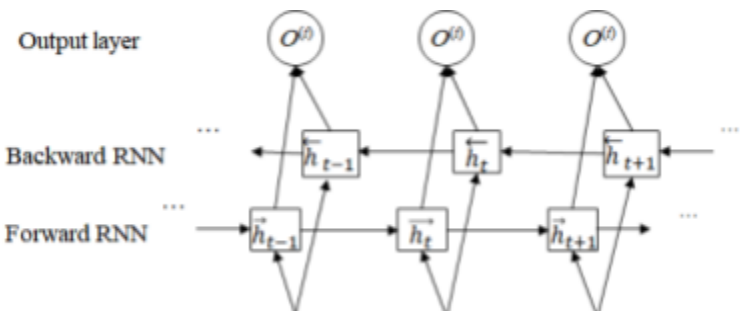
human brain that connect input and hidden layers to predict an output layer. They are primarily used in machine learning and data mining.

CNNs are designed for processing arrays of data and are incredibly useful in image classification applications. Special layers called convolutional layers detect patterns as simple as lines or gradients to complex objects like faces. Convolutional layers are stacked so the simplest features are processed first, before progressing to complex features. As a feed-forward network, CNNs do not move in cycles or loops; they progress forward through the layers. Feature extraction is done through kernel processing, where small matrices are processed in each convolutional layer, and the size of the map is reduced to speed up computation in the following pooling layer.



Wood, Thomas "CNN Layers Explained" deepai.org

In a study done by Diaz et al. a 1-dimensional CNN with stride 5 (with 8 filters) and stride 3 (with 16 filters) convolution kernels is used to analyze PD handwriting. The ReLU activation function is ideal to allow layers to build off each other, as "low-level features of the previous [layer] can be combined in several ways to obtain high level representations" (Diaz et al., 5). Further, Diaz et al. combined this CNN with a Bi-directional Gated Recurrent Unit (BiGRU), a type of RNN. RNNs are applicable for analyzing time-dependent vector sequence data, like speech recognition; bi-RNNs traverse through the



forward (positive) timesteps and the backward (negative) timesteps. For smaller datasets, GRUs are recommended as they use less memory. Diaz et al.'s study uses BiGRUs to read the input sequence (the x and y coordinate of the writing at each timestep) both in the forward direction and in the backward direction. The BiGRU uses sigmoid activation, a binary cross-entropy loss function (as determining PD or healthy control is a binary classification), and 10-fold cross validation. In an image created by Shi et al. when developing a sound recognition algorithm, $\vec{h}_t$ is defined as the hidden layer output of the RNN at time t. The input $x^{(t)}$ is fed to each hidden layer at every time for both the forward RNN and backward RNN, and the output $O^{(t)}$ is predicted for each layer.

3.4 Binary Classification

In statistics and machine learning, classification is an approach wherein algorithms learn from input data and sort them based on observations (classifications– data is sorted into "classes"). The mapping algorithm is called a classifier, and maps input data into specified categories (features) as predicted by the classification model. There are three types of classification: binary, multi-class, multi-label. Binary classification has two outcomes (true or false), multi-class classification has more than two outcomes (assigned to only one class), and multi-label classification conveys that each input is mapped to a set of labels.

Binary classification occurs when there are only two groups that elements in a set can be organized into. It is used in medical testing, like PD diagnoses, to determine if a patient has the disease or not. In reality, there are four outcomes (true positive, false positive, true negative, and false negative), while in classification models only a positive or negative outcome is exhibited as a prediction.

4. Method

4.1 Participants

Participants from a variety of age ranges were selected. One adolescent (17 years of age), one young adult (21 years of age), and two adults (45–55 years of age) were chosen to determine the accuracy of the program in determining PD likelihood. All participants in this study were healthy controls.

4.2 Design

The goals of the project were to develop algorithms that could determine if a patient had PD or not. To do this, a Long-Short Term Memory (LSTM) RNN model is developed from a dataset created through studies that recorded kinematic data on Archimedes' spirals drawn by healthy controls and PD patients. Once the model is trained to reasonable accuracy, it can be extracted to use for the developed application. The application utilizes the LSTM model and obtains raw data by asking the user to perform the typical clinical diagnosis test of drawing an Archimedes' spiral on a smartphone. It uses the raw and derived kinematic data as inputs in the developed model to predict the likelihood of the user having PD.

4.2.1 LSTM

LSTMs are ideal for time-series sequence prediction, making them extremely useful for analyzing kinematic data based on coordinate points recorded for each time stamp.

The UCI Machine Learning Repository hosts a Parkinson Disease Spiral Drawings Using Digitized Graphics Tablet Dataset compiled by Isenkul et al. and Erdogdu et al., which will be used for this study. The readable .csv files from the dataset will be loaded into memory and the relevant columns of data (the time series features of x, y, velocity) will be reviewed. A sequence length of 50 time steps is set.

Using TensorFlow, the LSTM generated is a many-to-one model, where three inputs are fed, and one label is outputted. As this is a binary classification problem, the ideal output will be a single number: 0 or 1 (healthy control or PD patient).

Since the proposed output is the probability of having PD, a sigmoid activation function, mathematically defined by $f(x) = \frac{1}{1+e^{-x}}$, is used. If $P(x) < 0.5$ the subject does not have PD, else if $P(x) > 0.5$ the subject does have PD. A reasonably accurate model will have probabilities extremely close to 0 or extremely close to 1.

Sigmoid activations are highly subject to the vanishing gradient problem, so a binary cross entropy loss function is necessary. It calculates how close or far the predicted probability is from the actual values of 0 or 1. Further, the typical Adam optimizer is used for faster computation time.

To train and test the model, 5-fold ($k = 5$) cross validation is used. The data is split into 5 folds, where the data is fit (trained) on $k - 1$ folds and the first group is held to be a test set. Each fold is run over 100 epochs.

The following graphs show examples of sample input from the dataset. For input C1, a healthy control, the model outputted a 0.00461945 probability of having PD. For input P23, a PD patient, the model outputted a 0.9989957 probability of having PD. It was concluded that the model was accurate.

The final model is converted into a TensorFlow Lite model to be used in a mobile application.

Sample Input for Healthy Control (C1 in Dataset)

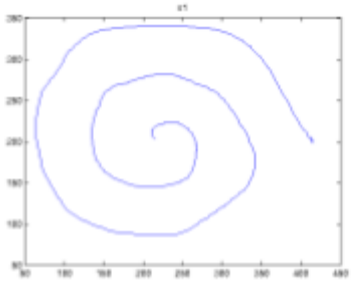
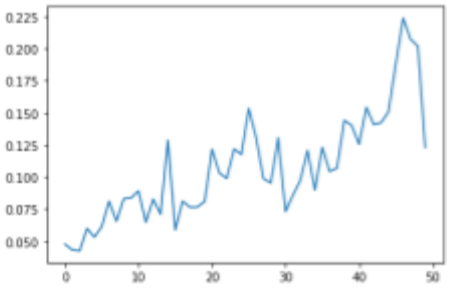
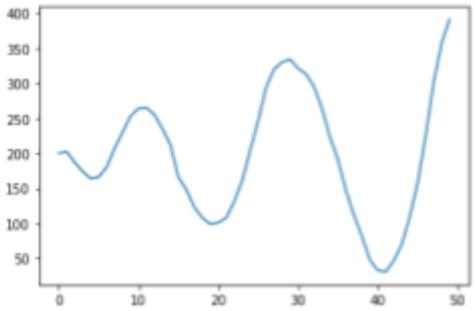


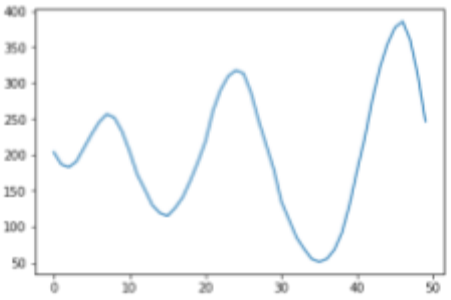
Image of Archimedes' Spiral



Velocity



x-values



y-values

Sample Input for PD Patient (P23 in Dataset)

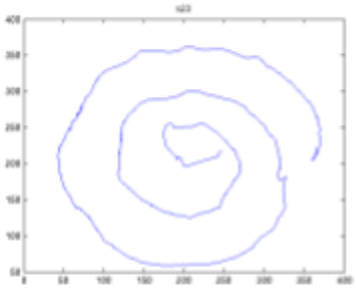
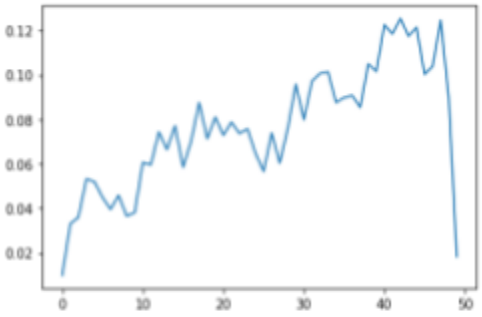
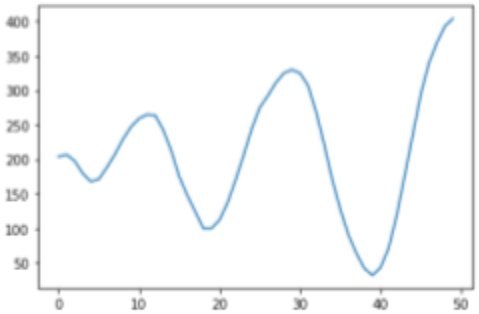


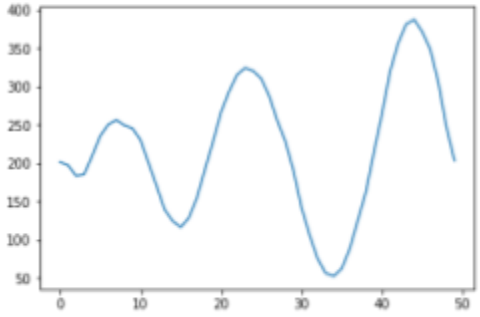
Image of Archimedes' Spiral



Velocity



x-values



y-values

4.2.2 Application

The purpose of the application is to use a user inputted Archimedes' spiral and determine if the user has PD.

The touchscreen is set to a drawing view with an outline of an Archimedes' spiral for a user to trace. The x and y coordinates of the user input are continuously recorded and stored in separate arrays.

The TensorFlow Lite LSTM model is loaded and encapsulated by an Interpreter. Like in the LSTM, sequence length is set to 50.

The x and y coordinates are compressed to match up with each time value of one second. Then, the velocity at each second is computed: $v = d/s$, where $d = \sqrt{(x_i - x_{i-1})^2 + (y_i - y_{i-1})^2}$ and s is the sequence index.

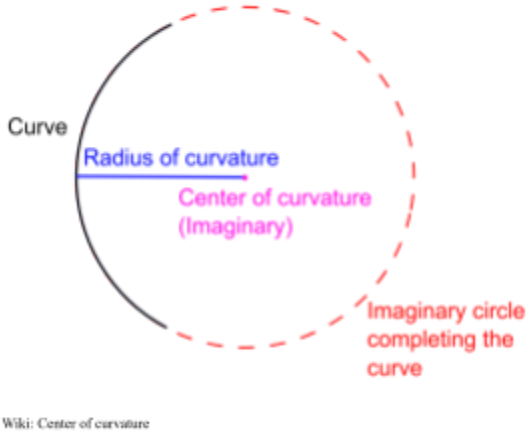
To aid the neural network, the local maxima (critical points) of the x coordinate graph is computed, since micrographia typically affects horizontal movement. Using this set of maxima, the manual risk is calculated. If the actual spacing of the peaks is greater than the average spacing, the manual risk for PD is true, since handwriting is computed to be unsteady. Or, if the actual and average spacing is consistently small, the manual risk for PD is true since handwriting is computed to be cramped.

x, y, and velocity are used as inputs for the TF Lite model, and the output is stored. The manual risk boolean and the model output is then used to calculate the risk percentage of PD, which is the final output seen by the user.

4.2.3 Modifications for Improvement

To further improve the application results, two more features were implemented: calculation of Gaussian curvature and identification of a Hausdorff space.

A radius of curvature of a curve is the approximate radius of a circle at any point, given there is a vector length of curvature. The radius of curvature is given by the equation $R = \frac{1}{|\kappa|}$, where $\kappa = \frac{d\theta}{ds} = \frac{d\theta}{\sqrt{(\frac{dx}{dt})^2+(\frac{dy}{dt})^2}}$, θ is the tangential angle, and s is the arc length. Given that $tan\theta = \frac{dy}{dx}$ the curvature of a planar curve can be further simplified to $\kappa = \frac{\frac{d^2y}{dx^2}}{[1+(\frac{dy}{dx})^2]^{3/2}}$.



Wiki: Center of curvature

Gaussian curvature is *intrinsic*, meaning the space around it is detectable. To incorporate calculation of the radius of curvature of each point on an Archimedes spiral, we first take a set of points. The angle and distance between the current coordinate and the subsequent coordinate in the set is calculated, as well as the derivative of the coordinates in the set. These values are used to calculate the varying radii of the spiral. A notable aspect of the Archimedes' spiral is that its turnings have constant separation distance, so the radius of the spiral and the rotation angle are linearly proportional. If the radius of curvature is increasing at a constant rate, the participant drawing should resemble an Archimedes' spiral.

Topological spaces are characterized by two sets of points that are "close", but the distance between them cannot be numerically measured. Hausdorff spaces are topological spaces wherein two distinct points have disjoint neighborhoods (in other words, two points x and y exist in a topological space S, where x is in a neighborhood U, y is in a neighborhood V, and

$U \cap V = \emptyset$).

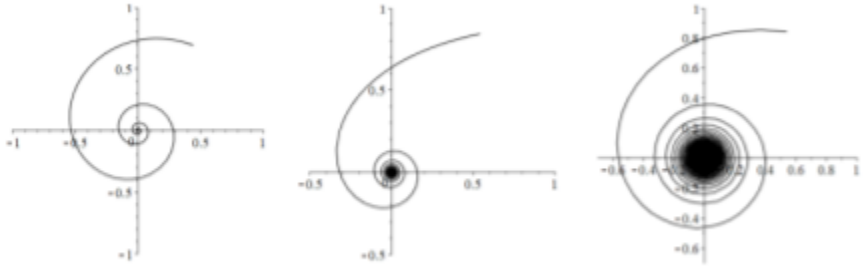


Figure 1: Three spirals: on the left, the *logarithmic spiral* with $\phi(x) = \exp(-x/5)$, in the centre a *hyperbolic spiral* with $\phi(x) = x^{-1}$, and on the right a *Lituus* with $\phi(x) = x^{-1/2}$.

These spirals have exponential winding functions and are characterized as Hausdorff spaces because of their nonconstant radii.

"*On Hölder solutions to the spiral winding problem*, Jonathan M. Fraser"

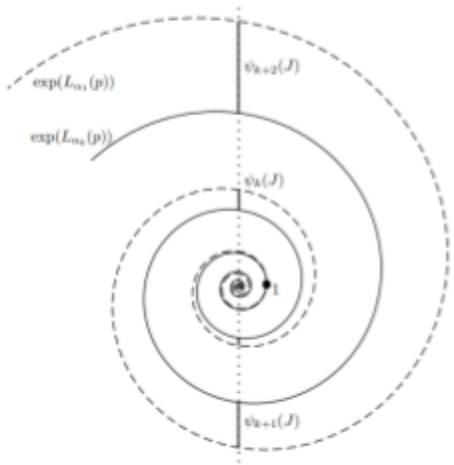


FIGURE 3. Two logarithmic spirals $(\exp(L_{\alpha_1}(p))$ and $\exp(L_{\alpha_2}(p))$, drawn with $p = 0$) and the increasing (in length) subintervals $\psi_k(J), \psi_{k+1}(J), \psi_{k+2}(J)$ of the imaginary axis.

This is a figure of two logarithmic spirals that exhibits how points on such a spiral exist in distinct neighborhoods.

"*Line, Spiral, Dense*, Neil Dobbs"

While Archimedes spirals are topological spaces, they are *not* Hausdorff spaces because the radial distances are constant. Therefore, the likelihood of a participant's drawing being a Hausdorff space can be determined because we can still calculate the spiral's theoretical Hausdorff dimensions. To do this, the largest theoretical Hausdorff distance is calculated given two sets of points A and B (this is the farthest distance that is possible to be traveled from a point in set A to a point in set B). Then, calculate whether all points in set A are within the Hausdorff distance of set B. In essence, this distance is the degree of "mismatch" between the sets, so for the farthest distance d, then every point of A must be within a distance d of some point of B and

vice versa. If the degree of mismatch is high (that is, the distances vary), it is likely that the shape drawn is a Hausdorff space and not an Archimedes spiral.

4.4 Materials

The software was developed for a Samsung S10 running Android 12.0.0 (Snow Cone), but will work on any Android 9.0.0 (Pie) or later device with a working touchscreen. Google Colaboratory was used to develop the machine learning model with pandas, Matplotlib, TensorFlow, and TensorFlow Lite as data analysis tools with a dataset sourced from the UCI Machine Learning Repository. A laptop running any OS (Linux was used) with at least 2 GB RAM and 1.5 GB available hard disk space capable of running Java IDE compatible with Android software, such as Eclipse or IntelliJ IDEA (IntelliJ IDEA was used) for developing the application.

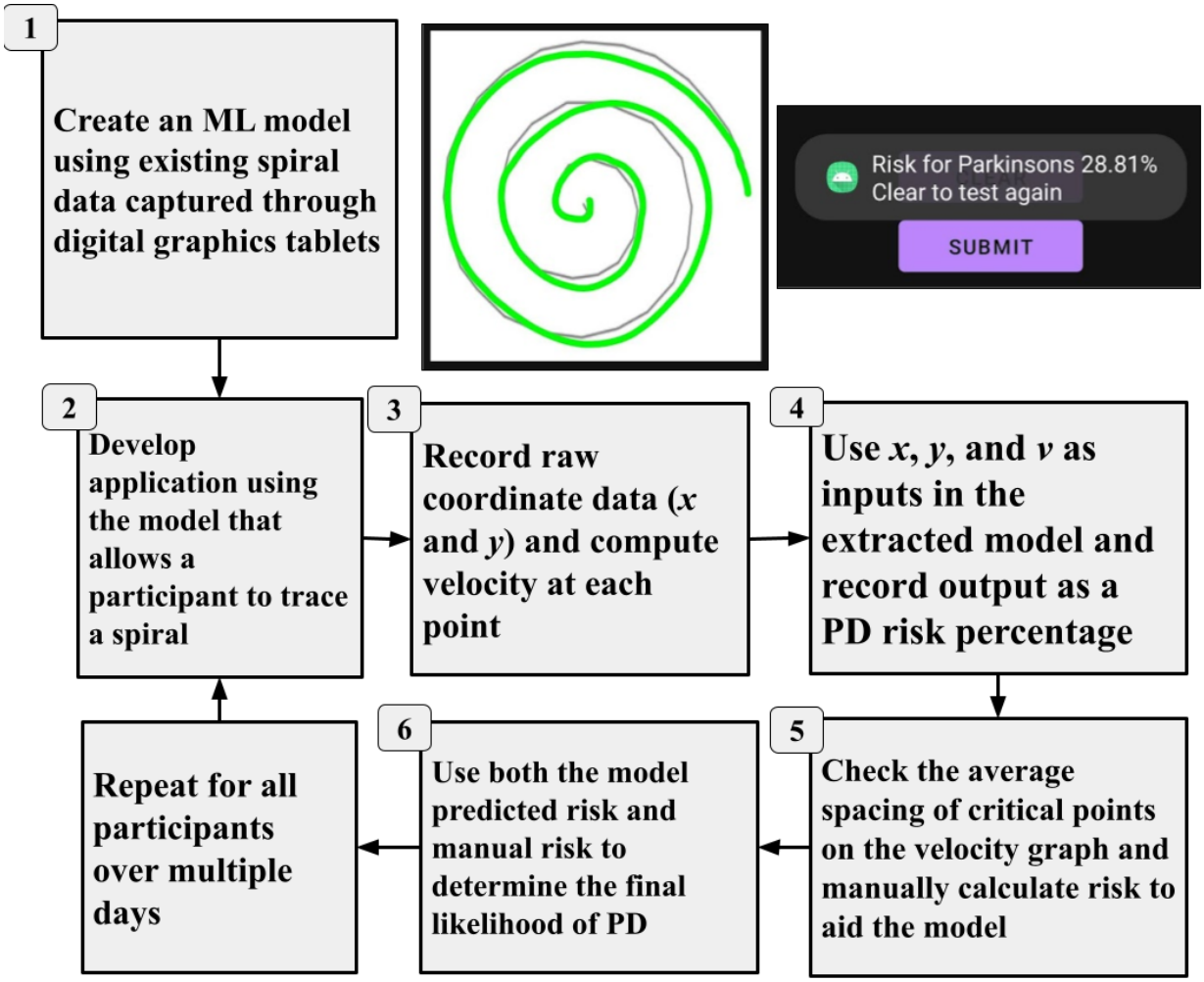
4.5 Procedure

1. Develop a classification model using Google Colaboratory and a dataset[1] with relevant PD diagnostic information (rendered spirals, x, y, and velocity from healthy controls and PD patients).
2. Develop an Android application using any Java IDE, TensorFlow Lite, and the developed model.
3. The application should allow a voluntary human subject to place their finger in the middle of the touchscreen and trace an Archimedes' spiral. The x and y coordinates of their finger will be continuously recorded for each second of drawing.
4. From the raw coordinate data, compute the velocity at each point (distance/current second) and the critical points on the velocity graph.
5. Use the *x, y, v* as inputs in the extracted model and record output as a PD risk percentage.

[1] UCI ML Repository: Parkinson Disease Spiral Drawings Using Digitized Graphics Tablet

6. Check the average spacing of the critical points and calculate manual risk of PD.
7. Use both the manual risk and the model predicted output to define a final risk percentage for PD and output the likelihood for having PD.
8. Repeat steps 2-7 over three days at the same time each day for each participant, resulting in three trials per subject. Make improvements based on application output.

4.6 Methodology Flow Chart



5. Results

5.1 Model Predictions

The following charts display model predictions of inputted data.

Model Predictions for Healthy Controls (HC)

Model Input (HC, Not At Risk)	PD Risk Prediction (%)	Model Accuracy
1	4.003294	Accurate
2	0.280085	Accurate
3	0.099063	Accurate
4	80.58306	Inaccurate
5	0.470314	Accurate
6	0.490854	Accurate
7	0.668898	Accurate
8	0.400429	Accurate
9	0.630435	Accurate
10	99.945045	Inaccurate
11	0.816167	Accurate
12	4.358224	Accurate
13	1.292497	Accurate
14	0.726658	Accurate

Model Predictions for Parkinson's Patients (PD)

Model Input (PD, At Risk)	PD Risk Prediction	Model Accuracy
15	99.92611	Accurate
16	99.99998	Accurate
17	98.27741	Accurate
18	70.898974	Accurate
19	99.92287	Accurate
20	99.99954	Accurate
21	99.99979	Accurate
22	96.375954	Accurate
23	99.74929	Accurate
24	99.99984	Accurate

25	99.99992	Accurate
26	99.58069	Accurate
27	99.989176	Accurate
28	99.99984	Accurate
29	99.99905	Accurate
30	99.35864	Accurate
31	99.993026	Accurate
32	99.999964	Accurate
33	99.99977	Accurate
34	93.759227	Accurate
35	99.99959	Accurate
36	99.998313	Accurate
37	99.96878	Accurate
38	99.991506	Accurate
39	99.999845	Accurate

Anomalies include inputs 4, 10, and 18, which will be analyzed in content area 6.

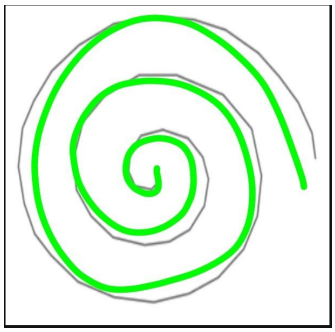
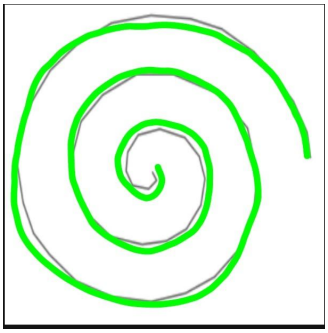
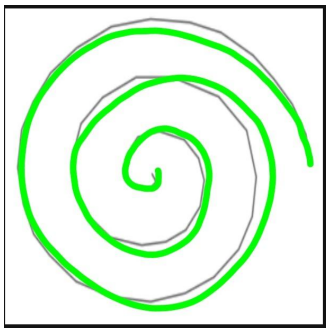
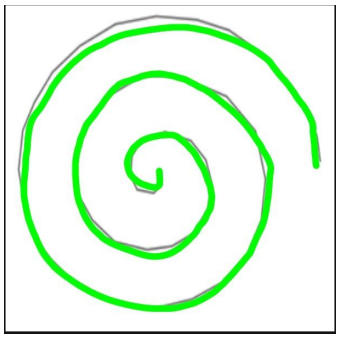
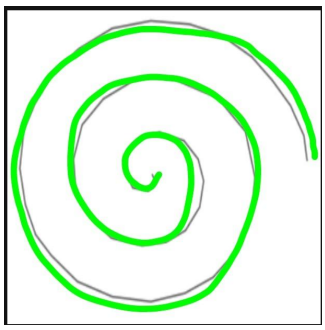
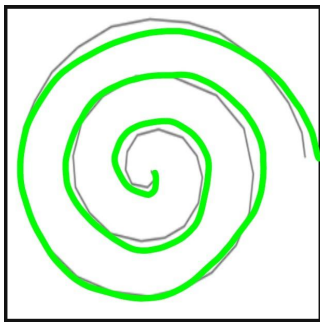
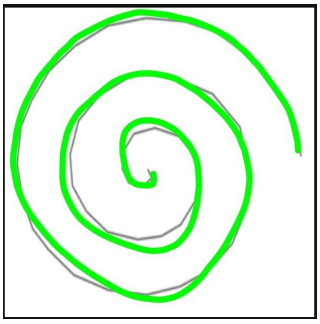
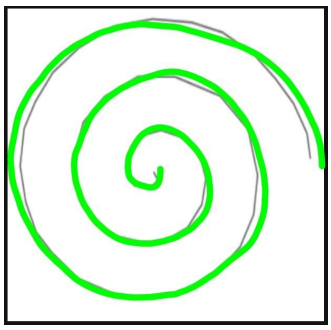
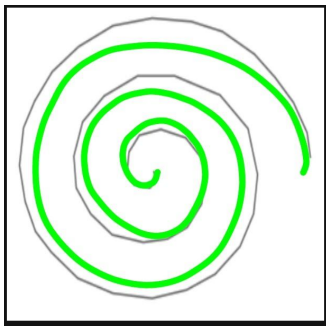
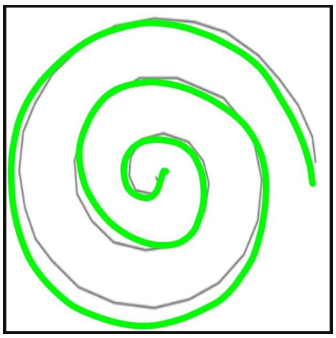
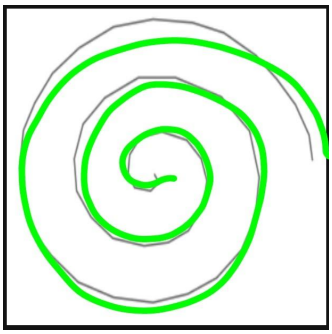
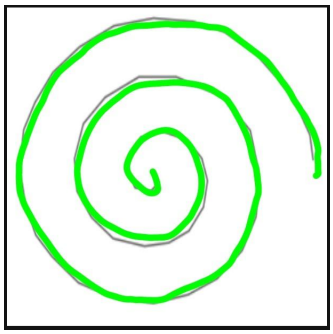
5.2 Application Data

The following charts and graphs display the data obtained from the application, from the participants described in content area 4.1.

Risk Percentage of PD, recorded for each subject and trial

Trial:	**01**	**02**	**03**
Subject 1 Age 17	0.01%	27.85%	28.81%
Subject 2 Age 21	29.74%	29.30%	28.39%
Subject 3 Age 48	27.66%	26.98%	29.54%
Subject 4 Age 55	0.01%	22.20%	29.08%

Rendered Archimedes' Spiral, recorded for each subject and trial

Subject 1 Age 17	 0.01	 27.85	 28.81
Subject 2 Age 21	 29.74	 29.30	 28.39
Subject 3 Age 48	 27.66	 26.98	 29.54
Subject 4 Age 55	 0.01	 22.20	 29.08

6. Discussion & Analysis

The LSTM model created for the application was reasonably accurate, and only three anomalies were identified. The model was inaccurate when attempting to identify if inputs 4 and 10 (both healthy controls) had PD. Further, although it was accurate in identifying that input 18 was that of a PD patient, the risk proportion was closer to 0.5 than 1. The model rendered data is shown below for these three inputs. The most probable cause for the model inaccuracies with input 4 and 10 is an unsteady velocity between data points. A typical velocity graph, seen in content area 4.2.1 displays that for a healthy control, velocity is generally increasing with smaller horizontal distances between peaks relative to a PD velocity graph. While input 10 is increasing, the central area presents an unnaturally steep increase in velocity.

Input 4 (HC) in Dataset

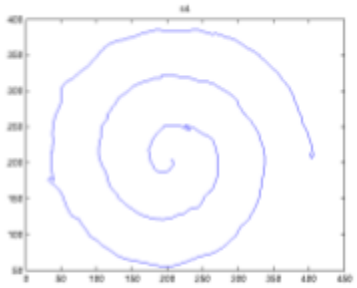
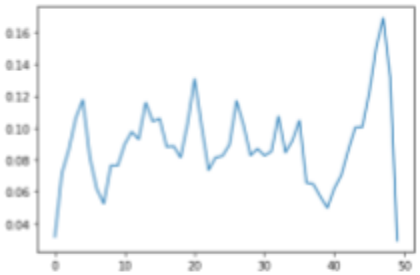
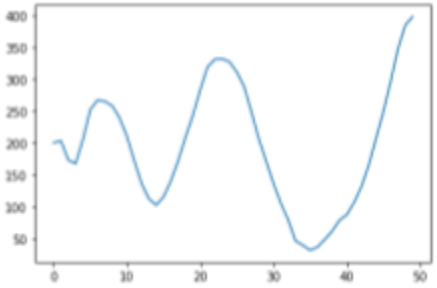


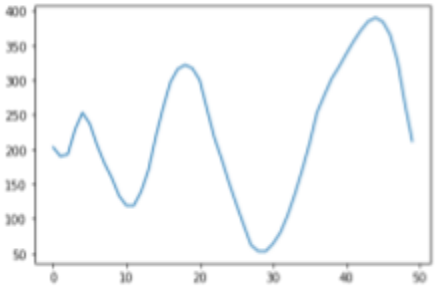
Image of Archimedes' Spiral



Velocity



x-values



y-values

Input 10 (HC) in Dataset

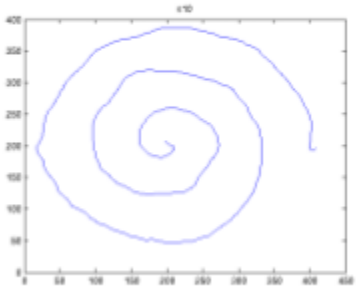
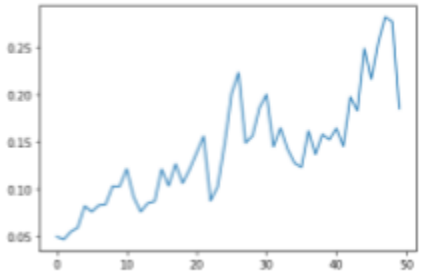
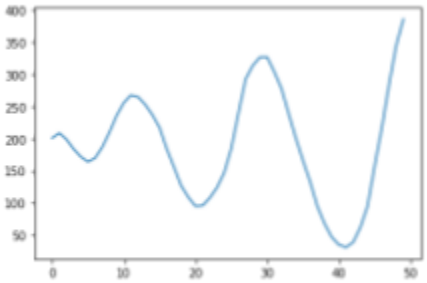


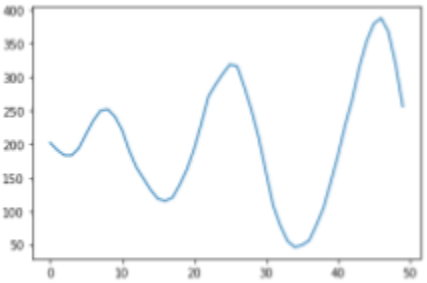
Image of Archimedes' Spiral



Velocity



x-values



y-values

Input 18 (PD) in Dataset

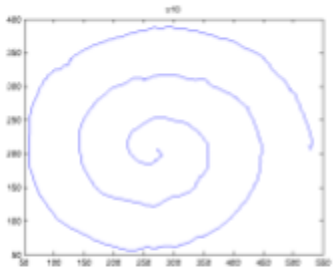
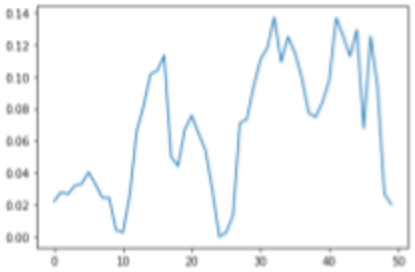
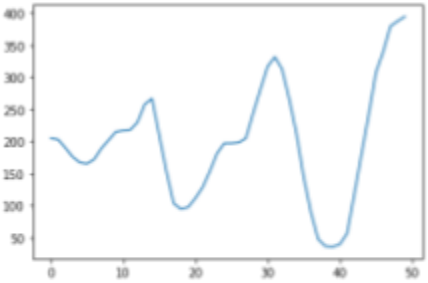


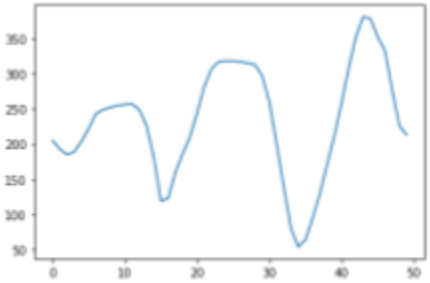
Image of Archimedes' Spiral



Velocity



x-values



y-values

Input 18 was correctly identified as a PD input, however the risk proportion was about 0.709, which indicates that the model was close to classifying the spiral as one drawn by an HC. Out of the 39 total inputs, 18 was unique in that while its graphs of *x*-values and *y*-values did have some clear peaks, there were also flattened, constant segments. Since the model was trained on a small set of data, these graphical anomalies could not be clearly classified, resulting in a risk proportion suggestive of PD, yet still closer to 0.5 than other PD inputs.

Ultimately, the velocity graphs contributed the most to imprecise model predictions. Thus, the developed application attempted to compensate for irregular velocity patterns through a manual risk identification process to aid the imported model. For most trials, the manual risk identification coupled with model predictions resulted in a reasonable PD risk percentage. However, two trials were distinctive: Subject 1, Trial 1 and Subject 4, Trial 1. Both of the established trials resulted in a very low risk percentage of 0.01%, meaning that both the manual risk and the model risk calculations were extremely low. While it may be rational to assume that 0.01% is the true risk percentage for those subjects, it remains a large deviation from other trials. It can be concluded that the LSTM model needs much improvement to reduce inaccuracies both in model input and in human input predictions.

These improvements include either utilizing a larger dataset or developing a GRU model that is more compatible with small datasets. Additionally, a CNN could be used to analyze rendered Archimedes' spirals while allowing an RNN to handle kinematic data. Such a conjunction would be beneficial, not only to improve predictions, but to compare with the original LSTM model. Furthermore, Thomas et al.'s novel use of digitized pen data could allow for more model inputs, like pressure, to further explore the nuanced differences between HC and PD handwriting.

7. Conclusion

Parkinson's Disease (PD) is a neurodegenerative disease caused by a loss and weakening of nerve cells in the area of the brain that produces the chemical dopamine. Most symptoms in early stages are dismissed, however, if left unnoticed, it can easily progress to much more severe stages of PD, where patients are unable to move without wheelchairs and have difficulty speaking. The cost of diagnosis and treatment, however, can rise to upwards of $50,000 USD, even with medical insurance.

The purpose of this study is to develop a cost-effective and reliable form of PD diagnosis in early stages. Currently, PD is diagnosed through clinical means which examine cardinal symptoms of rest tremors through handwritten tests like the Archimedes' spiral. The spiral demands a continuous extension of fingers and the wrist, so unsteady, micrographic handwriting is clearly visible. To aid clinical diagnosis, this study attempts to collect position and kinematic data via a LSTM Recurrent Neural Network loaded in a mobile application. The LSTM is trained on a dataset that provides useful position and kinematic data typical of healthy controls and PD patients. The application prototype will be tested on four subjects with three trials each (one trial each day), and the output will be examined to identify if there is a proper correlation based on their age and family history of neurodegenerative disorders.

Although the developed LSTM model had trouble identifying some model inputs, it was generally accurate, and it could be concluded that velocity data was the largest contributor to imprecise data. To rectify this issue, rather than solely importing the LSTM model to the application, a manual risk percentage calculation was implemented to ensure that the model had reasonable predictions. Even with manual risk, the model still presented extremely low values for two trials, relative to the other trials. Despite these problems, the developed application was

able to accurately conclude in all trials that participants had low risk for PD (were healthy controls).

In the future, different neural networks more suitable to image and small dataset analysis will be used, as well as more input labels like pressure and wrist angle. Participants that are confirmed to have PD must be tested to ensure that the application will be accurate not only for healthy controls, but for PD patients as well. Participants in higher age groups which are more susceptible to PD must also be tested.

This study hopes to prevent diagnostic errors by providing an inexpensive, accurate method to investigate the risk of a participant having Parkinson's Disease and encourages patients to seek diagnosis regardless of financial troubles and immediately take action to slow the progression of PD.

8. Future Research/Applications

In the future, research will be done to implement a model better suited for image processing, such as a CNN in conjunction with a less generalized RNN (GRUs are better suited for such a small dataset). A CNN would be used to analyze spiral images in the database, while a GRU would analyze time series data (x, y, kinematics). Additionally, comparisons could be made between LSTM and GRU models without convolution and those RNN models combined with CNNs. Age ranges more typical of PD (upwards of 60 years of age) must be tested to ensure the accuracy of the model, since current participants are all healthy and younger than 60 years of age and would not represent a likely PD patient. Further, more raw data can be collected with the use of a smart pen which can record pressure of pen tip and wrist (grip) angle to develop a more informed diagnosis, as described in Diaz et al.'s study.

This study will be useful in future applications to aid in clinical diagnostic tests for PD and develop more information on the accuracy of computerized medical technology.

Bibliography

Alty, J., Cosgrove, J., Thorpe, D., & Kempster, P. (2017). How to use pen and paper tasks to aid tremor diagnosis in the clinic. *Practical Neurology*, *17*(6), 456–463. https://doi.org/10.1136/practneurol-2017-001719

Studies the effect of essential, dystonic, and functional tremors on pen and paper tasks like handwriting, spirals, and line drawings written by PD patients.

Dahodwala, N., Li, P., Jahnke, J., Ladage, V. P., Pettit, A. R., Kandukuri, P. L., Bao, Y., Zamudio, J., Jalundhwala, Y. J., & Doshi, J. A. (2020). Burden of Parkinson's Disease by Severity: Health Care Costs in the U.S. Medicare Population. *Movement Disorders*, *36*(1), 133–142. https://doi.org/10.1002/mds.28265

Details the rising costs associated with PD, specifically in the US. Costs vary from as little as $400 to as high as $50,000 USD.

Davie, C. A. (2008). A review of Parkinson's disease. *British Medical Bulletin*, *86*(1), 109–127. https://doi.org/10.1093/bmb/ldn013

Description of the pathology, genetics, and clinical diagnosis of PD. Highlights clinical signs like a change of handwriting with micrographia.

Diaz, M., Moetesum, M., Siddiqi, I., & Vessio, G. (2021). Sequence-based dynamic handwriting analysis for Parkinson's disease detection with one-dimensional convolutions and BiGRUs. *Expert Systems with Applications*, *168*, 114405. PaHaW, NewHandPD. https://doi.org/10.1016/j.eswa.2020.114405

The study uses the combination of a 1D CNN and stacked BiGRUs to develop a binary classification model for PD diagnosis.

Erdogdu Sakar, B., Isenkul, M., Sakar, C.O., Sertbas, A., Gurgen, F., Delil, S., Apaydin, H., Kursun, O., 'Collection and Analysis of a Parkinson Speech Dataset with Multiple Types of Sound Recordings', IEEE Journal of Biomedical and Health Informatics, vol. 17(4), pp. 828-834, 2013. Provided data from the UCI ML Repository used.

Gil-Martín, M., Montero, J. M., & San-Segundo, R. (2019). Parkinson's Disease Detection from Drawing Movements Using Convolutional Neural Networks. *Electronics*, *8*(8), 907. https://doi.org/10.3390/electronics8080907

The use of a CNN to extract features from an Archimedean guided spiral and classification to connect convolutional layers.

Hochreiter, S., & Schmidhuber, J. (1997). Long Short-Term Memory. *Neural Computation*, *9*(8), 1735–1780. https://doi.org/10.1162/neco.1997.9.8.1735

Illustrates the use of LSTM models to fix the vanishing gradient and oscillating weight problems in typical RNN models.

Isenkul, Muhammed & Sakar, Betul & Kursun, O.. (2014). Improved Spiral Test Using Digitized Graphics Tablet for Monitoring Parkinson's Disease. 10.13140/RG.2.1.1898.6005. Provided data from the UCI ML Repository used. Shows the use of raw data (x, y, x, pressure, grip angle, and time) to derive kinematic data and create a dissimilarity acceleration histogram to view differences between healthy controls and PD patients.

Mayo Clinic. (2018). *Parkinson's disease - Diagnosis and treatment - Mayo Clinic*. Mayoclinic.org. https://www.mayoclinic.org/diseases-conditions/parkinsons-disease/diagnosis-treatment/drc-20376062

Explains different medications used in PD treatment, namely carbidopa-levodopa, that reduces the effects of PD symptoms like micrographia. The article emphasizes that imaging tests are not useful in PD diagnosis.

McLennan, J. E., Nakano, K., Tyler, H. R., & Schwab, R. S. (1972). Micrographia in Parkinson's disease. *Journal of the Neurological Sciences*, *15*(2), 141–152. https://doi.org/10.1016/0022-510x(72)90002-0

Description of progressive and consistent micrographia in Parkinson's disease patients. Concludes that use of PD drug levodopa results in significant increase in handwriting size.

Moore, K., & Williams, C. (n.d.). *Classification Problems | Brilliant Math & Science Wiki*. Brilliant.org. Retrieved November 30, 2022, from https://brilliant.org/wiki/classification/

Article that describes ML classification problems, classification algorithms, and specifically binary classification.

National Institute on Aging. (2022, April 14). *Parkinson's disease*. National Institute on Aging. https://www.nia.nih.gov/health/parkinsons-disease

Article that emphasizes the changes in cognition with the progression of PD. Severe memory and thinking problems can affect the accomplishment of writing tasks.

Saunders-Pullman, R., Derby, C., Stanley, K., Floyd, A., Bressman, S., Lipton, R. B., Deligtisch, A., Severt, L., Yu, Q., Kurtis, M., & Pullman, S. L. (2008). Validity of spiral analysis in early Parkinson's disease. *Movement Disorders*, *23*(4), 531–537. https://doi.org/10.1002/mds.21874

Explains the rationale behind the use of the Archimedes' spiral as a common clinical examination. The study proposes a digitized tablet to record the x, y, and pressure axes.

Schrag, A., Ben-Shlomo, Y., & Quinn, N. (2002). How valid is the clinical diagnosis of Parkinson's disease in the community? *Journal of Neurology, Neurosurgery & Psychiatry*, *73*(5), 529–534. https://doi.org/10.1136/jnnp.73.5.529

Showcases diagnostic errors present in the clinical diagnosis of PD, as PD is often confused with atypical parkinsonism, vascular parkinsonism, non-parkinsonian tremors, and other patients on anti-parkinsonian drugs.

Shi, L., Du, K., Zhang, C., Ma, H., & Yan, W. (2019). Lung Sound Recognition Algorithm Based on VGGish-BiGRU. *IEEE Access*, *7*, 139438–139449. https://doi.org/10.1109/access.2019.2943492

Shows structure of BiGRU.

Thomas, M., Lenka, A., & Kumar Pal, P. (2017). Handwriting Analysis in Parkinson's Disease: Current Status and Future Directions. *Movement Disorders Clinical Practice*, *4*(6), 806–818. https://doi.org/10.1002/mdc3.12552

Describes the use of digitized tablets to gain kinematic data on PD handwriting. Raises the limitation of reduced friction between smart pen and screen; digitization may not simulate writing properly.

Wood, T. (2019, May 17). *Convolutional Neural Networks*. DeepAI. https://deepai.org/machine-learning-glossary-and-terms/convolutional-neural-network

Article that explains what CNNs are, how convolutional layers are developed, activation functions, loss functions, and the applications of CNNs.

Acknowledgments

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