Centre d'Études Doctorales : Sciences et Techniques de l'Ingénieur

N° d'ordre /2020

SYNTHESE DE THESE DE DOCTORAT

Présentée par

Mlle: AOURAGHE IBTISSAME

Spécialité : Informatique et systèmes intelligents

Sujet de la thèse: Développement de méthodes de l'intelligence artificielle et de l'apprentissage automatique pour la détection précoce et la classification des pathologies neurodégénératives basé sur l'écriture manuscrite Arabe en ligne sur tablette graphique : Étude sur la population Marocaine bilingue.

Thèse présentée et soutenue le -------------------------------- devant le jury composé de :

Nom Prénom	Titre	Établissement	
Faouzi BELAHSEN	PES	Faculté de Médecine et de Pharmacie de Fès	Président
Emmanuel LE CLEZIO	PES	Université de Montpellier – France.	Rapporteur
Mohammed SABBANE	PES	Université des Sciences - Meknès	Rapporteur
Hassan QJIDAA	PES	Faculté des Sciences Dhar El Mehraz Fès	Rapporteur
Khadija LAHRECH	PH	École Nationale des Sciences Appliqués de Fès	Examinatrice
Saad BENNANI DOSSE	PES	École Nationale des Sciences Appliqués de Fès	Examinateur
Mostafa MRABTI Ghizlane KHAISSIDI	PES PH	École Nationale des Sciences Appliqués de Fès École Nationale des Sciences Appliqués de Fès	Directeurs de thèse

Laboratoire d'accueil : Laboratoire d'Informatique et de Physiques Interdisciplinaires.

Établissement : École Normale Supérieur de Fès.

I. Introduction

L'analyse de l'écriture manuscrite a été pendant longtemps focalisée sur le problème de la reconnaissance automatique du signal manuscrit. En effet, à ce jour, la reconnaissance automatique du signal manuscrit est une technologie réussie et mature [1] avec plusieurs résultats promoteurs dans plusieurs applications commerciales, particulièrement les banques et la poste pour le traitement des chèques et des adresses [2] [3], et ceci est dans le contexte de l'écriture manuscrite hors ligne, traitée comme une image (acquise sur feuille avec un simple stylo). En outre, dans le cadre de l'analyse de l'écriture manuscrite en ligne, cette nouvelle technologie est utilisée considérablement pour reconnaître des notes prises sur des smartphones, des tablettes ou des assistants numériques personnels PDA ('Personal Digital Assistant') [4].

Plus récemment, l'analyse de l'écriture manuscrite a migré vers le domaine de la santé. Innover dans ce domaine est devenue une stratégie clé vu le développement spectaculaire que les tablettes numériques graphiques ont connus ces derniers temps. En effet, ces tablettes permettent l'acquisition du tracé au cours du temps, tracé dit « en-ligne », riche en information cinématique du scripteur. Dans cette perspective, l'acquisition de l'écriture manuscrite sur une tablette graphique numérique est devenue un nouveau terrain de recherche porteur d'espoir dans le domaine de la santé et plus particulièrement dans la détection précoce des maladies neurodégénératives.

En fait, l'écriture manuscrite est une activité complexe et automatisée nécessitant un contrôle de la motricité fine. Elle implique des composants cognitifs, kinesthésiques, perceptuels-moteurs et une coordination neuromusculaire spécifique [5]. Une fois qu'un sujet a appris à écrire, l'échange (feedback) entre la perception visuelle et le contrôle musculaire requis pour écrire devient automatique, entraînant des mouvements extrêmement rapides, ce qui signifie qu'un programme de contrôle moteur s'est à ce stade développé dans le cerveau. Ainsi, la détérioration de cette faculté de haut niveau, aussi petite soit-elle, peut être le signe d'une détérioration ou d'un dysfonctionnement de ce programme moteur fin, dû au vieillissement ou à une pathologie. En conséquence, il peut être un biomarqueur important pour la détection et l'évaluation des pathologies neurologiques.

Plusieurs travaux de la littérature ont étudié le lien entre la détérioration de l'écriture manuscrite et des pathologies telles que la maladie de Parkinson [6][7][8][9][10][11][12], la maladie de Huntington [13], la schizophrénie [14], la sclérose en plaques [15][16], la maladie d'Alzheimer [15][16] et d'autres problèmes de santé tels que la dépression [17][18], l'anxiété et le stress [18].

Cette analyse en ligne de l'écriture manuscrite fournit des informations dynamiques invisibles mais précieuses sur la manière dont le manuscrit est réalisé.

Dans cette thèse, nous nous sommes intéressé à analyser l'écriture manuscrite en ligne des patients atteints de la maladie de Parkinson. La maladie de Parkinson (MP) est une maladie dégénérative à long terme caractérisée par la destruction progressive des neurones dopaminergiques de la substance compacte dans le mésencéphale. Cette destruction de ces neurones entraîne une diminution de la dopamine, qui est le neurotransmetteur responsable du contrôle et de la régulation des mouvements de l'organisme. Cela entraîne des tremblements corporels, des mouvements lents, une hypertonie et des problèmes d'équilibre [19]. La maladie de Parkinson affecte le plus souvent les individus âgés, et touche annuellement des milliers de personnes dans le monde. Or, les critères permettant de porter un diagnostic précoce et fiable de cette maladie reste difficile et limité à l'heure actuelle vu que les symptômes, aux premiers stades, peuvent passer inaperçus. En effet, les signes avant-coureurs les plus fréquemment observés évoluent silencieusement et n'apparaissent que 5 à 10 ans après le début de la maladie avec 50 à 60% de dégénérescence des neurones dopaminergiques [19]. De ce fait, la détection de cette maladie à un stade précoce est cruciale pour contrôler son évolution et par conséquent. Ceci explique que toute étude qui sera orientée dans ce sens, aura une valeur scientifique précieuse, et tout résultat qui en découle pourrait contribuer considérablement à l'amélioration de la qualité de vie des patients, ce qui permettra un accompagnement plus rapide et augmentera les chances de succès du traitement.

D'autre part, l'exploitation des paramètres cinématiques de l'écriture manuscrite constitue un enjeu majeur et primordial pour la détermination de l'ensemble des attributs portant l'information diagnostique de cette pathologie.

Notre projet de détection de pathologies à travers l'analyse de l'écriture manuscrite en ligne s'inscrit dans le cadre d'une collaboration entre notre Laboratoire d'Informatique et de Physique Interdisciplinaire (LIPI) et le service de neurologie au CHU Hassan II de Fès. Toute l'équipe a montré sa motivation pour relever le défi et chercher de nouveaux moyens diagnostiques simples et innovants pour la détection précoce des pathologies neurodégénératives en se basant sur l'analyse de l'écriture manuscrite chez la population Marocaine.

Cette étude comprend principalement deux phases:

- Phase d’acquisition des données d’écriture au sein du Centre Hospitalier Universitaire Hassan II à Fès permettant de construire une base de données d’une population bilingue/monolingue.
- Phase d’extraction, d’analyse des paramètres descriptifs, et de classification des données de l’écriture manuscrite acquises de sujets contrôles et de patients atteints des pathologies neurodégénératives.

Cette thèse se concentre uniquement sur l'écriture manuscrite en ligne pour les personnes atteintes de la maladie de Parkinson.

II. Protocole d’acquisition de l’écriture manuscrite en ligne et construction de la base de données marocaine

Dans la littérature, plusieurs études ont été menées sur l'analyse de l'écriture manuscrite en ligne afin de détecter des pathologies neurodégénératives. Ces études concernaient principalement les langues latines. À notre connaissance, il n’existe pas de base de données publique sur la langue Arabe. Notre projet concerne particulièrement une population marocaine bilingue, dont la langue maternelle est l'Arabe. Pour mener à bien cette étude, nous avons procédé à l'acquisition et à la construction de notre propre base de données d'écriture manuscrite en ligne.

L'acquisition des données se fait au sein du service de neurologie du Centre Hospitalier Hassan II de Fès. Le projet ENEMAR (**É**tude **N**eurologique de l’**É**criture des **MAR**ocains) concerne les pathologies neurodégénératives, à savoir la maladie de Parkinson, la maladie d'Alzheimer et les troubles cognitifs légers. Dans le cadre de ce projet, trois méthodes sont acquises: l'écriture manuscrite en ligne, la parole et la marche. Cette thèse se concentre uniquement sur l'écriture manuscrite en ligne pour les personnes atteintes de la maladie de Parkinson.

a. Population cible

Le projet ENEMAR cible quatre catégories de profils cognitifs:

- **Groupe «Maladie de Parkinson: MP»:** Cette catégorie comprend les patients atteints de la maladie de Parkinson (MP). Pour quantifier la progression de la maladie de Parkinson et l'efficacité du traitement, tous les patients ont été diagnostiqués sur la base de l'échelle unifiée d'évaluation de la maladie de Parkinson (UPDRS) [20]. L'état cognitif de chaque patient est évalué par un bilan neuropsychologique complet. Ainsi, pour évaluer particulièrement son niveau cognitif et mental, un test MMSE (Mini-Mental State Examination) est utilisé.

- **Groupe «Maladie d'Alzheimer: MA»:** Ce groupe comprend les patients atteints de la maladie d'Alzheimer (MA), leur état cognitif est évalué par un test. Ces patients sont diagnostiqués par un gériatre ou un neurologue sur la base des critères du Manuel diagnostique et statistique des troubles mentaux, 4e édition (DMS-IV ou V) [DSM-IV, DSM-V] [21].
- **Groupe «Troubles cognitifs légers: MCI»:** Ce groupe est formé de patients diagnostiqués avec un MCI par un gériatre ou un neurologue sur la base des critères de Petersen [22].
- **Groupe «sujets contrôles: SCs»:** Ce dernier groupe est composé de personnes qui ont réalisé une évaluation neuropsychologique complète pour s'assurer qu'elles ont un profil cognitif normal.

- L'UPDRS est une échelle qui permet une analyse générale de la situation du patient et de l'évolution de ses symptômes. Cette évaluation constitue un outil complet et flexible de suivi de la progression de la maladie de Parkinson et du niveau de perte d'autonomie du patient.
- Le MMSE est un test d'évaluation cognitive globale. Il consiste en un questionnaire en 30 points comprenant des questions pour évaluer les compétences: d'orientation spatio-temporelle; attention et calcul; apprentissage et transcription d'informations; langue et identification; et la praxis constructive (la capacité d'organiser une série de mouvements dans un but précis en reproduisant des formes géométriques).

b. Critères d'inclusion et d'exclusion

Pour le recrutement des participants, nous avons défini des critères d'inclusion et de non-inclusion, et évidemment chaque participant doit signer un formulaire de consentement pour participer à l'étude, parmi ces critères:

Critères d’inclusion:

- Accepter de participer librement à l’étude en signant un formulaire de consentement.
- Être un patient suivi en consultation neurologique au CHU HASSAN II Fès.
- Tous les patients ont passé un bilan cognitif complet leur permettant d’être inclus ou exclus de l’étude. Critères d’inclusion par groupe :

- Groupe 1: Sujets contrôles ayant un fonctionnement cognitif global normal.
- Groupe 2: Patients Parkinsoniens, MMSE entre 20 et 25, Échelle motrice UPDRS, bilan neuropsychologique complet.
- Groupe 3: Patients atteints d'Alzheimer débutant avec un MMSE entre 20 et 25.
- Groupe 4: Patients souffrant des Troubles Cognitifs Légers.

Critères de non-inclusion

- Patients ayant des troubles visuels ou auditifs leur empêchant de réaliser convenablement les tâches.
- Toute personne exclue par le test MMSE pour des raisons comme le traumatisme crânien, AVC, ou autre.
- Sujets sous régime de protection curatelle ou tutelle.

c. Matériel utilisé

L'acquisition de l'écriture manuscrite se fait sur une tablette graphique « WACOM Intuos Pro » à stylet créative (Figure 1).

Cette tablette est capable de détecter 2048 niveaux de sensibilité à la pression, avec une fréquence d'échantillonnage de 125 HZ permet aussi d'enregistrer au cours du temps les coordonnées du stylo. Le signal manuscrit correspondant associe à chaque point de la trajectoire une séquence de six valeurs numériques (T [n], X [n], Y [n], P [n], Θ [n], Φ [n]) qui représentent, respectivement, le temps, les positions cinématiques en X, en Y, la pression du stylet, l'altitude et l'azimut du stylet (voir Figure 2). Une feuille de papier est placée sur la tablette pour permettre un retour visuel de la trajectoire produite. La disposition du stylet est échantillonnée à une fréquence de 125 Hz. La résolution spatiale de la tablette est de 5080 pixels / pouce (dpi). Cette tablette permet de détecter les coordonnées du stylet même lorsqu'il est en air (jusqu'à 1.5 cm au-dessus de la tablette).

Cette tablette ne permet pas un retour visuel du tracé effectué mais permet de capturer les signaux à travers une feuille de papier posé sur elle ; avec un stylo spécial « Inking Pen » de Wacom (stylo à encre), la personne peut avoir un retour visuel du tracé qu'elle effectue sur le papier.

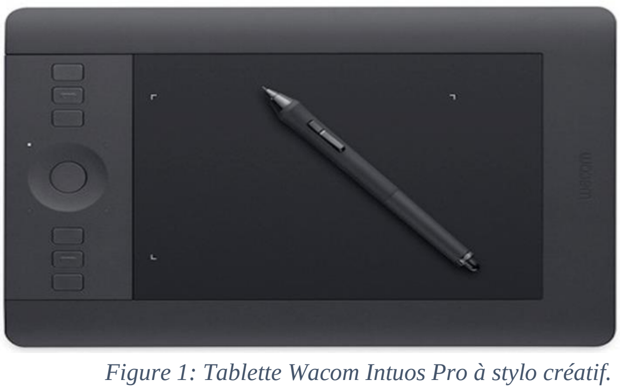


Figure 1: Tablette Wacom Intuos Pro à stylo créatif.

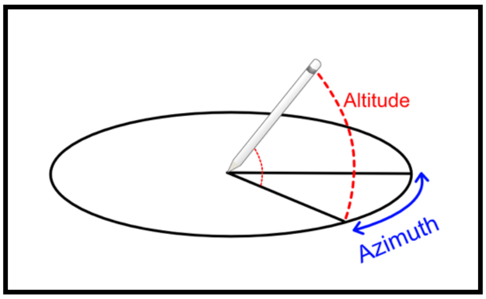


Figure 2:Angles azimut et altitude du stylet.

d. <u>Exercices proposés</u>

L'acquisition des données est en cours depuis quatre ans au sein du service de Neurologie du Centre Hospitalier Universitaire Hassan II-Fès.

Les participants volontaires sont invités à reproduire des écrits selon un protocole prédéfini. Les données sont recueillies de façon anonyme et confidentielle, et tous les participants ont le droit de se retirer de l'étude à n'importe quel moment.

Nous commençons par saisir les métadonnées concernant le participant sur l'interface d'un logiciel lié à la tablette. L'évaluation complète d'un patient dure une heure et trente minutes : Une heure pour le bilan neuropsychologique et trente minutes pour l'acquisition de l'écriture. Pour les sujets contrôles, nous leur faisons passer un bilan de 20 min afin de connaître leur profil cognitif pour s'assurer, entre autres, qu'ils ont un profil cognitif normal.

Tous les participants devaient suivre, dans l'ordre, un certain nombre de tâches, que nous leur avons présentées au fur et à mesure. Notre étude se compose de 3 exercices concernant l'Arabe, 3 exercices concernant le Français, et finalement 4 exercices de dessins. Le premier exercice consiste à recopier un texte imposé en Arabe et en Français (Figure 3). Le deuxième exercice consiste à écrire un texte libre aussi bien en Arabe et un texte libre en Français, suivis d'une série de quatre lettres «*llll* » cursives reliées entre elles à écrire quatre fois pour le Français, et une série de 4 lettres « ص » reliées entre elles quatre fois aussi pour l'Arabe. Le reste des exercices de dessins consiste à dessiner des cercles, une spirale, des allers-retours entre deux carreaux. Le modèle de la feuille d'acquisition est représenté dans la figure 3:

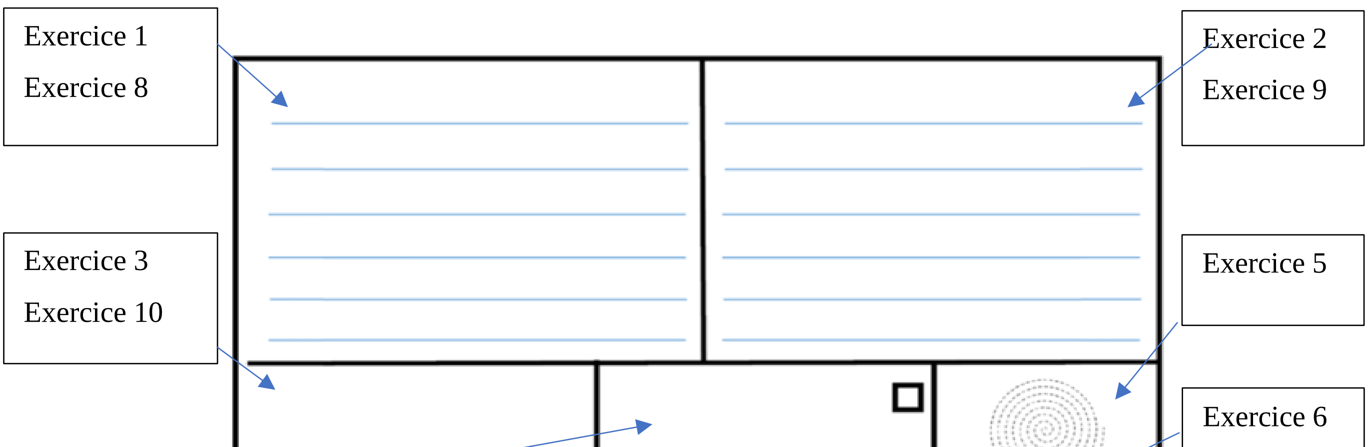


Figure 3: Exemple de feuille d'acquisition.

L'évaluation complète d'un participant prend en moyenne 90 minutes: une heure pour réaliser un bilan neuropsychologique (voir annexe) et 30 minutes pour acquérir les données d'écriture. Tous les participants sont revus deux fois s'ils sont d'accord. La première visite a lieu au mois M0, la seconde au mois M12 (12 mois plus tard) pour réacquérir leurs données d'écriture selon le même protocole. Ces données nous permettront de réaliser une étude longitudinale lors de la poursuite du projet ENEMAR.

Il est à noter que les travaux de cette thèse ont été réalisés uniquement sur les données acquises lors de la première session M0 (étude transversale).

La feuille (Figure 7) représentant les différents exercices proposés est placée sur la tablette pour acquisition. L'acquisition de l'écriture manuscrite consiste à effectuer trois tâches en arabe, trois tâches en français et quatre tâches de dessin.

Les tâches d'écriture dans l'ordre sont:

1. Texte arabe imposé (tâche 1);
2. Texte arabe libre (tâche 2);
3. Quatre séries cursives et continues de lettres arabes «صصصص» (Tâche 3);
4. Aller et retour entre deux carrés pendant 15 secondes (tâche 4);
5. Dessinez des cercles sur la circonférence d'un cercle pendant 15 secondes (tâche 5);
6. Archimède en spirale (tâche 6);
7. Placez le stylo au centre d'une croix pendant 15 secondes (Tâche 7);
8. Texte français imposé (tâche 8);
9. Texte français libre (tâche 9);
10. Quatre séries cursives et continues de boucles «llll» (tâche 10).

L'équipe a également mis en place un protocole dédié à la population analphabète.

e. Présentation des données acquises

À ce jour, nous avons acquis les données d'écriture manuscrite de 202 personnes. Parmi eux, il y a 137 sujets contrôles, 42 patients atteints de la maladie de Parkinson, 16 patients atteints de la maladie d'Alzheimer (MA) et 7 patients atteints de troubles cognitifs légers (MCI).

Dans la figure 9, nous représentons en camembert le pourcentage de femmes et d'hommes, et elle montre que 5% de la population acquise sont gauchers et 95% sont droitiers.

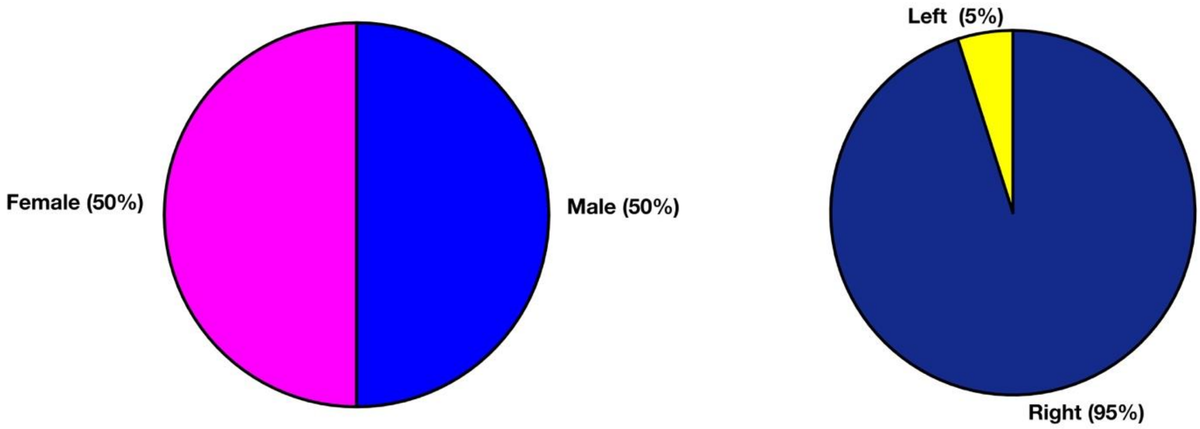


Figure 4: Représentation du sexe et de la préférence manuelle de la population étudiée.

La répartition de ces différentes données en fonction du profil cognitif des participants est présentée sur la figure 10.

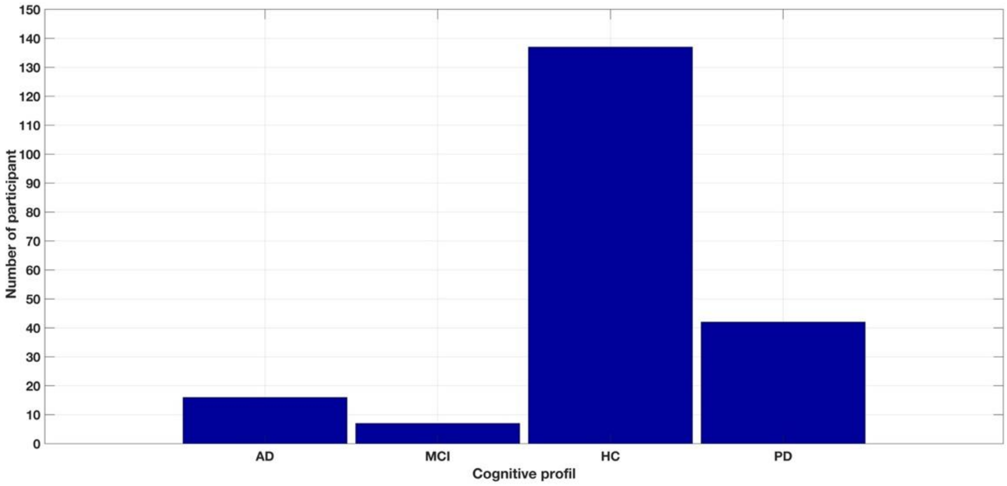


Figure 5: Histogramme du nombre de participants en fonction de leur profil cognitif.

La signification de chaque étiquette est la suivante:

- AD: patients atteints de la maladie d'Alzheimer;

- MCI: patients présentant une déficience cognitive légère;
- SC: personnes ayant un profil cognitif normal suite à une évaluation neuropsychologique;
- MP: patients atteints de la maladie de Parkinson.

Le tableau 1 montre le nombre exact de personnes différentes selon leur profil cognitif.

Table 1: Répartition exacte des différents profils cognitifs.

Profil cognitif	Effectif
AD	16
MCI	7
PD	42
SC	137

III. Apprentissage non supervisée pour la caractérisation de l'écriture manuscrite Arabe en ligne

a. Contexte

Dans cette partie, nous proposons de caractériser l'écriture manuscrite en ligne pour la détection précoce de la maladie de Parkinson. Ainsi, en utilisant les caractéristiques cinématiques, mécaniques et spatiales de l'écriture manuscrite, nous recherchons la caractérisation de la maladie de Parkinson. Cette étude décrit la phase d'acquisition de données qui est actuellement réalisée au sein du service neurologique du CHU Hassan II de Fès. À la suite de cette étude, nous avons proposé une approche basée sur des techniques d'apprentissage non supervisé pour analyser l'écriture en ligne de 34 patients atteints de la maladie de Parkinson et de 34 sujets contrôles selon des caractéristiques quantitatives et qualitatives. Sur la base de 230 caractéristiques calculées pour chaque participant, notre étude a permis de découvrir trois différents types de participants. Les résultats montrent que les complications de la motricité fine chez les patients atteints de la maladie de Parkinson se caractérisent notamment par une dégradation significative des caractéristiques cinématiques de l'écriture manuscrite [23].

b. Base de données utilisée

Appariés selon le niveau d’étude et l'âge, au total, 68 sujets (34 patients MP et 34 sujets contrôles) ont participé à ce travail. Les volontaires sont tous droitiers, ont achevé 6 années d'études et sont de langue maternelle Arabe. Tous les patients atteints de MP étaient sous traitements et ont pris le traitement 30 à 60 minutes avant la tâche d’écriture. Les métadonnées telles que l'âge, la fréquence hebdomadaire de l’écriture, le traitement, la profession, etc. ainsi que les données d’écriture manuscrite sont collectées de manière anonyme. Dans le tableau 2, nous présentons les données démographiques des populations étudiées.

Table 2: Données démographiques des populations étudiées.

	Mean Age (std)	MMSE Score	Mean UPDRS	Hoehn and Yahr stages
PD	55.10 (± 9.18)	28.5 (± 1.2)	12 (± 7.9)	2.16 (± 0.3)
SCs	53.10 (± 10.3)	30	-	-

c. <u>Exercice étudié</u>

L'analyse présentée dans cet article concerne le premier exercice Arabe du protocole [24] [25]. La tâche consiste à copier un texte imposé en Arabe fourni composé de six lignes. Un exemple du texte imposé est illustré à la Figure 6. La couleur bleue représente les vitesses faibles et la couleur rouge représente les vitesses élevées dans des plages de valeurs allant de 0 à 20 cm / s.

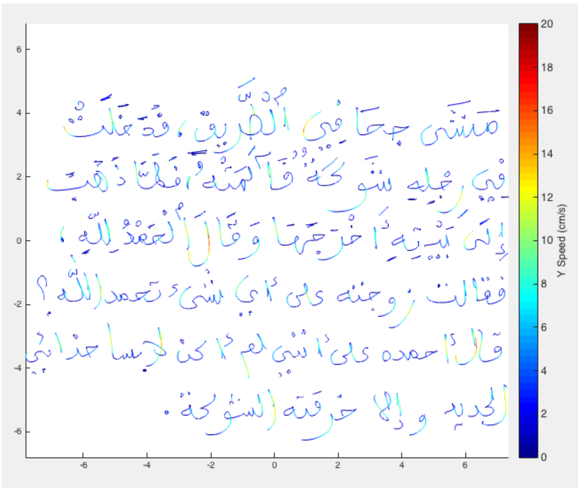


Figure 6: Visualisation des vitesses.

d. Paramètres calculés

La tablette Wacom génère, pour chaque point (n) de la trajectoire du stylet, X (n), Y (n), P (n). À partir de ces vecteurs, nous calculons de nouveaux paramètres qui peuvent être classés en trois catégories:

- Cinématique: vitesse horizontale et verticale, accélération, jerk, jerk normalisé, vitesse, changements du nombre de vitesse NCV, changements du nombre d'accélération NCA, etc.
- Spatial: hauteur des mots, longueur des espaces intra et inter-mots, complexité du stylet de trajectoire (lorsque le stylet est en l'air).
- Mécanique: pression, variation de pression.

Ainsi, certaines des fonctions statistiques sont calculées pour extraire des informations contenues dans les caractéristiques de l'écriture manuscrite, telles que: moyenne, écart type, maximum, minimum, quantiles Q1 et Q3, entropie, médiane, Kurtosis et Skewness. Sur la base de ces trois catégories, nous avons calculé 230 paramètres pour chaque participant.

e. Classification non-supervisée et visualisation des résultats

L'analyse en composantes principales (ACP) [26][27] est l'une des méthodes d'analyse de données multivariées les plus couramment utilisées. Elle permet d'explorer des ensembles de données multidimensionnels constitués de variables quantitatives à l'aide d'une transformation orthogonale. ACP a été utilisé pour visualiser la disposition des scripteurs sur la base des 230 paramètres.

La matrice de données (Scripteurs x Paramètres) (Échantillons x Variables) est convertie en une matrice de score, une matrice de chargement et une matrice résiduelle. La transformation convertit un ensemble de variables corrélées en un ensemble de variables non corrélées (composantes principales, CP). En tant que procédure statistique multivariée non supervisée, l'ACP est largement utilisée comme outil d'exploration des données. En particulier, en traçant les composantes principales, des groupes peuvent apparaître dans le graphique, qui indiquent des individus présentant des caractéristiques similaires. La matrice de données était composée des 68 individus en colonnes et 230 entités en lignes. Les deux premiers axes d'ACP récupèrent 98,73% d'inertie.

La figure 7 représente la visualisation ACP. Les participants sont colorés en fonction de leur profil cognitif. Les points rouges correspondent aux patients MP et les bleus correspondent aux sujets contrôles.

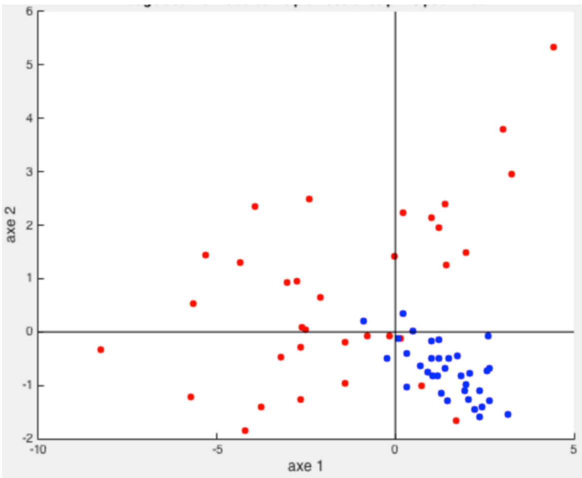


Figure 7: Projection ACP des individus. Points rouges: Parkinsoniens; Points bleus: sujets contrôles.

Dans ce travail, l'analyse de clustering est effectuée sur la base de caractéristiques où nous essayons de trouver des sous-groupes d'échantillons basés sur des caractéristiques calculées.

Selon la figure 7, la majorité des sujets contrôles sont pratiquement regroupés dans la même zone et les patients atteints de MP sont dispersés dans le reste de du graphe. Visuellement, on peut distinguer deux ou trois classes. Pour plus de précision, nous avons appliqué la méthode de regroupement des K-moyennes (K-means) [28] sur les deux premières composantes principales correspondant aux deux premiers axes. Afin de générer le nombre optimal de clusters, le critère Silhouette a été utilisé. Le critère Silhouette a généré un nombre optimal de trois clusters, qui sont déterminés très clairement dans la figure 8.

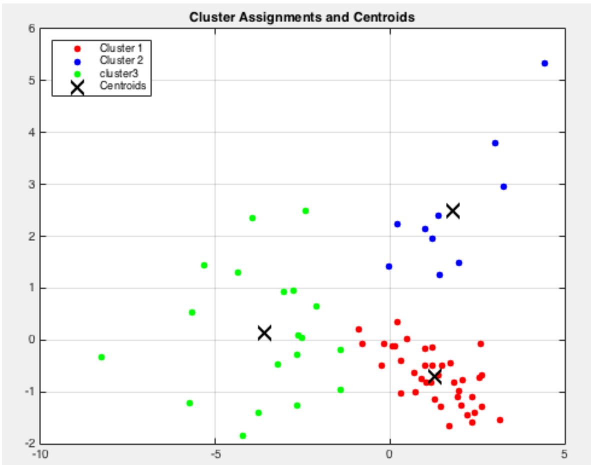


Figure 8: Projection ACP des trois classes générées par K-means sur les deux premières composantes principales.

Sur la figure 14, nous avons 3 groupes, les points en rouge sont principalement des sujets contrôles, les points en bleu et en vert sont constitués uniquement de patients MP.

f. Caractérisation des clusters obtenus

Le but de cette étape est de trouver les paramètres de l'écriture manuscrite caractérisant chaque cluster obtenu. Ainsi, une analyse ANOVA de la variance [29] est appliquée entre la variable quantitative l'écriture manuscrite qui est la réponse, et la variable de classe qui a le rôle de variable explicative.

- Cluster 1: La plupart des scripteurs de ce cluster sont des sujets contrôles, ils ont une vitesse, une accélération et un jerk très élevés. Ils ont également une pression moyenne. Ces scripteurs ont un niveau d'éducation moyen à élevé avec une fréquence d'écriture élevée.
- Cluster 2: Constitué uniquement de patients Parkinsoniens, ce cluster est caractérisé par une vitesse, une accélération et un jerk moyens. Les personnes appartenant à ce cluster ont également une pression moyenne. Tous ces scripteurs ont un niveau d'éducation élevé avec une fréquence d'écriture élevée.
- Cluster 3: Ce cluster est caractérisé par les caractéristiques cinématiques les plus basses, ainsi qu'une très faible pression. Ces scripteurs passent beaucoup de temps dans l'air, ils ont également un stade avancé de MP par rapport aux patients du cluster 2, selon leur score UPDRS.

Selon les résultats obtenus, les patients atteints de MP subissent des modifications principalement des paramètres cinématiques. Contrairement aux sujets contrôles, les patients atteints de MP se caractérisent par une lenteur significative de la vitesse, de l'accélération et du jerk.

IV. Apprentissage supervisé basée sur l'analyse globale de l'écriture manuscrite

a. Contexte

Dans cette étude, nous avons cherché à analyser l'écriture Arabe de 18 patients atteints de la maladie de Parkinson (MP) et de 18 sujets contrôles de même âge. Nous nous sommes concentrés sur la tâche de copier e texte imposé en Arabe. Pour chaque participant, nous avons calculé 528 caractéristiques, et le but de cette étude est de trouver un sous-ensemble de caractéristiques d'écriture manuscrite sélectionnées appropriées pour identifier efficacement les sujets atteints de MP. Les paramètres sélectionnés ont été injecté dans un classificateur de machine à vecteurs de support SVM avec noyau RBF, dont le but est d'identifier les sujets souffrant de MP. La robustesse de ce classificateur est mesurée à l'aide de trois matrices de performance, à savoir la précision, la sensibilité et la spécificité. Les résultats obtenus montrent une précision de classification globale de près de 80% [30].

b. <u>Base de données utilisée</u>

Dans ce travail, nous avons inclus 18 patients atteints de la maladie de Parkinson avec un âge moyen de 56 ans +/- 9 ans, et 18 sujets contrôles avec un âge moyen de 55 ans +/- 8 ans. Toutes ces personnes sont droitières et ont achevé au moins 6 années d'études. Les 36 personnes ont été invitées à copier un texte imposé en Arabe. Les patients atteints de MP ont été examinés uniquement dans leur état ON lorsqu'ils étaient sous traitement dopaminergique, c'est-à-dire 1 à 2 heures après la prise de leur dose régulière de médicament dopaminergique. Au moment de l'étude, leurs symptômes étaient gérés avec succès. Pour le recrutement des participants, nous avons défini des critères d'inclusion et de non-inclusion, et évidemment chaque participant doit signer un formulaire de consentement pour participer à l'étude, parmi les critères déjà mentionnés la partie II.

c. <u>Algorithme proposé</u>

Pour les 36 participants, l'étude suivante est limitée uniquement à l'exercice de copie de texte d'écriture en Arabe. Ainsi, pour chaque participant, nous avons calculé 528 caractéristiques. La sélection des fonctionnalités s'est faite en deux étapes; la première consiste à sélectionner un sous-ensemble à l'aide du test statistique de Mann-Whitney U (255 caractéristiques). La seconde, en utilisant l'algorithme Relieff, nous ordonnons ces caractéristiques des plus pertinentes aux moins pertinentes. Les caractéristiques finales les plus significatives ont été injectés à un classificateur de machine à vecteurs de support SVM avec noyau RBF, dont le but est d'identifier les sujets souffrant de MP. Voir la figure 9.

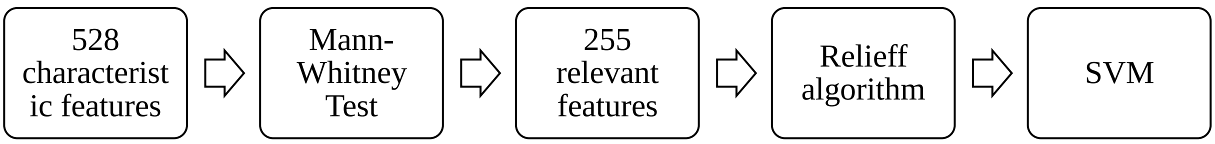


Figure 9: Approche suivie.

d. Calcul des paramètres

Nous avons calculé les caractéristiques qui peuvent être classées selon 3 catégories: cinématique, spatiaux et dynamique.

Les caractéristiques sont calculées selon des formules conventionnelles (voir chapitre 2), et sont généralement soit des vecteurs (V), soit des scalaires (S).

De plus, 30 mesures statistiques des caractéristiques vectorielles ont été calculées. Ceux-ci comprennent les minimum, les maximum, la robustesse des valeurs aberrantes (99e percentile - 1er percentile), la moyenne géométrique, la médiane, le mode, la moyenne, l'écart type, les moments statistiques (3, 4, 5, 6), les moyennes tronquées (5, 10, 20, 30, 40, 50), percentiles (1, 5, 10, 20, 30, 90, 95, 99), quartiles (25 / inférieur, 75 / supérieur) et kurtosis. Ces mesures statistiques peuvent être capables de donner une image fidèle sur la dynamique du scripteur. Nous avons donc 528 caractéristiques calculées dans l'air et en surface.

e. Sélection des paramètres pertinents

Pour conserver les caractéristiques les plus pertinentes et éliminer celles qui ne représentent pas de différence significative entre les patients atteints de la maladie de Parkinson et les sujets contrôles, nous avons appliqué le test statistique de Mann-Whitney [31] sur toutes les caractéristiques précédemment calculées. Ce test non paramétrique, qui sert de type de filtre avant l'étape de classification, a permis de comparer tous les paramètres des deux populations (Parkinson, sujets contrôles) et de sélectionner ceux qui représentent des différences statistiques significatives et discriminantes. Le choix de ce test est justifié par le fait que parmi les paramètres calculés il y a ceux qui ne suivent pas une loi normale (la normalité des paramètres est vérifiée par le test statistique Kolmogorov-Smirnov [32]). La sélection a été faite avec un risque d'erreur inférieur à 5%.

Pour mesurer la pertinence des 255 caractéristiques sélectionnées par le test statistique de Mann-Whitney, l'algorithme de sélection Relieff est implémenté [33]. Son rôle principal est de calculer une mesure de pertinence globale des caractéristiques en accumulant la différence de distance entre les exemples d'apprentissage choisis au hasard et leurs k plus proches voisins de la même classe et de l'autre classe. Elle constitue une technique de sélection automatique des paramètres qui adopte une approche aléatoire dans la recherche des attributs les plus corrélés à la classe prédite et à laquelle elle attribue des pondérations entre [-1,1] en fonction de leurs degrés de pertinence.

f. Classification SVM

Les 255 caractéristiques sélectionnées par le Mann-Whitney sont ensuite injectées dans le Relieff qui à son tour a attribué un poids à chaque attribut en fonction de son degré de pertinence. En plus de déterminer le sous-ensemble de caractéristiques qui fournissent une spécificité, une sensibilité et un taux de classification maximal, nous avons injecté ces paramètres dans une machine vectorielle de support d'algorithme d'apprentissage automatique supervisé (SVM) avec des noyaux RBF à fonction de base radiale non linéaire, dont le but est d'identifier les sujets souffrant de MP [34]. Tout d'abord, nous injectons le paramètre qui a le plus grand poids, puis nous injectons les deux premiers qui ont un poids maximum, jusqu'à ce que nous scrutions tous les 100 paramètres les plus pertinents donnés par le test Relieff. La figure 16 montre que la précision de classification la plus élevée de 85% a été obtenue pour 60 caractéristiques les plus pertinentes sélectionnées à l'aide de l'algorithme Relieff.

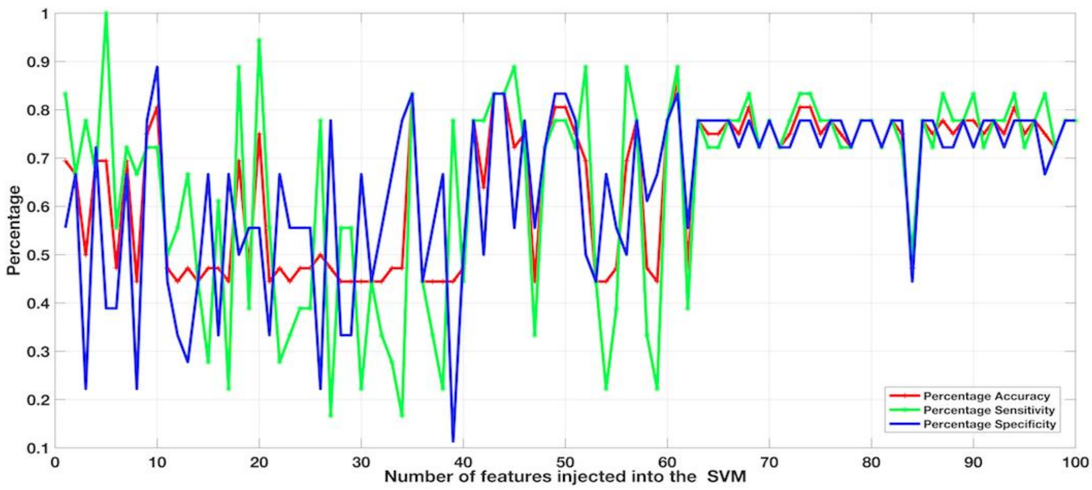


Figure 10: Sensibilité, spécificité et précision pour les 100 premiers paramètres les plus pertinents.

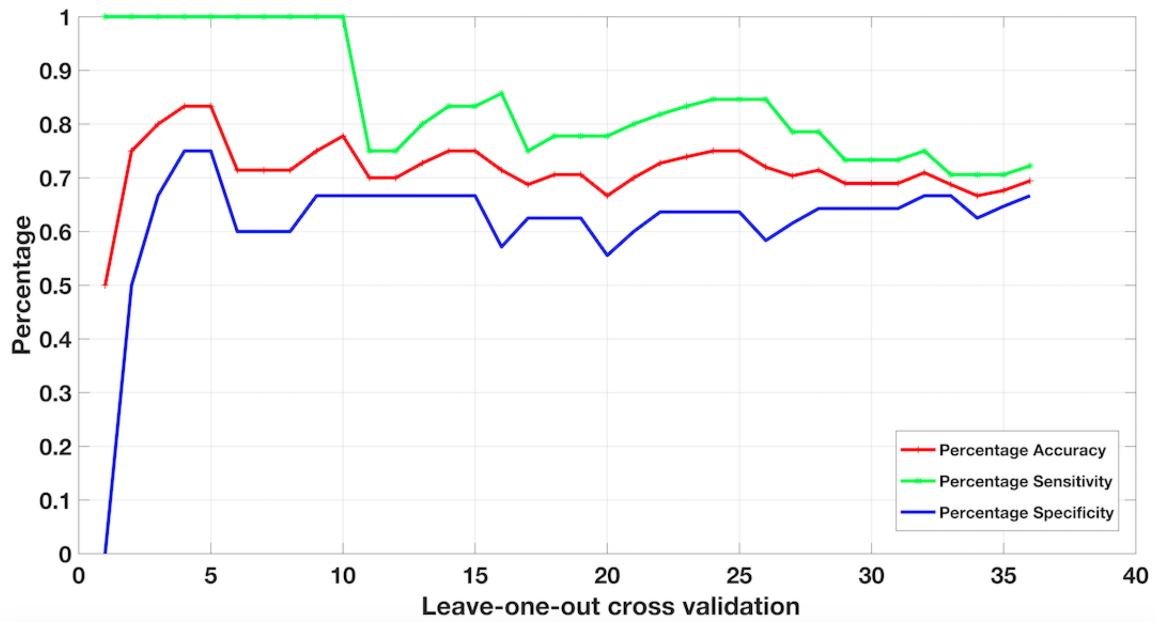


Figure 11: Résultats de la classification pour SVM.

V. Analyse profonde de l'écriture manuscrite en ligne: Étude comparative de différentes techniques d'apprentissage supervisé appliquées sur un texte segmenté

a. Contexte

Dans cette partie, nous proposons une nouvelle méthode pour détecter la maladie de Parkinson, basée sur la segmentation du texte manuscrit en lignes. En effet, nous proposons de comparer les patients atteints de la maladie de Parkinson et les sujets contrôles, sur la base de la dynamique complète des nouveaux paramètres temporels et spectraux. Trois classificateurs ont été utilisés, K-plus proches voisins (K-Nearest Neighbours), Machines à vecteurs de support (Support Vector Machine) et les Arbres de Décision (Decision Trees). Les performances de ces trois classificateurs ont été estimées à l'aide d'une validation croisée stratifiée imbriquée avec K=10 (10 Stratified Nested Cross-Validation). Tous les modèles de cette étude ont été évalués en utilisant la précision, la précision équilibrée, la sensibilité, la spécificité, le F-Score et le coefficient de corrélation de Matthews. Une précision de 92,86% a été obtenue avec le classificateur Arbres de Décision dans la dernière ligne. Les nouvelles catégories de paramètres temporels et spectraux ont donné les meilleures performances de classification par rapport aux caractéristiques statistiques de base [35].

b. Base de données utilisée

L'étude présentée a été menée sur 40 patients Parkinsoniens (21 femmes / 19 hommes) et 40 sujets contrôles (20 femmes / 20 hommes) appariés conformément à l'âge et au niveau intellectuel. Tous les participants sont de langue maternelle arabe, droitiers et ont au moins 6 ans d'études. Les 80 sujets ont été invités à copier un texte imposé en arabe selon notre protocole proposé [24] [36]. Tous les patients PD ont déjà pris le traitement (L-DOPA) 30 minutes à une heure avant l'exécution de la tâche d'écriture. Le tableau 3 présente les métadonnées démographiques et cliniques.

Table 3: Caractéristiques démographiques et cliniques des participants.

Cognitive Profile	Age		Score MMSE		Disease Duration		UPDRS		Hoehn and Yahr stages	
	Mean	Std	Mean	Std	Mean	Std	Mean	Std	Mean	Std
PD	54.3	9.49	28.15	1.14	8.10	4.03	11	7.66	2.08	0.60
SC	49.65	9.79	30	0	-	-	-	-	-	-

c. Segmentation de texte en lignes

Cet exercice est une tâche particulière qui englobe plusieurs spécificités de la langue arabe, et qui implique des efforts moteurs et cognitifs complexes des participants. En effet, de nombreuses irrégularités de mouvement telles que la perte de fluidité, les tremblements, l'hésitation, surviennent et augmentent au cours de l'exécution de la tâche temporelle. Par conséquent, l'analyse du manuscrit ligne par ligne pourrait révéler des informations plus pertinentes, et ainsi distinguer au mieux l'écriture des patients atteints de la MP de celle des SCs. En passant d'une ligne à une autre, cette nouvelle approche nous donnera la possibilité d'étudier la dégradation du l'écriture lors de l'exécution de la tâche.

Un retour de ligne peut être décrit avec une grande variation des coordonnées X et Y entre deux points successifs de la trajectoire numérisée du scripteur. Pour cela, nous avons calculé pour chaque point i de la trajectoire en surface: $\Delta_{xi}= x_{i+1} - x_i$ et $\Delta_{yi}= y_{i+1} - y_i$. Le calcul de ces deux variations en chaque point permet de déterminer les valeurs maximales pouvant correspondre à des sauts de ligne. Par conséquent, pour extraire les lignes, il faut spécifier un seuil adapté pour Δ_x et un autre pour Δ_y à partir duquel la variation calculée est directement associée à un saut de ligne. Le choix de ce seuil est important et doit être relatif à chaque personne, en fonction de la nature de son écriture.

La méthode de segmentation proposée est basée sur la génération de trois clusters en appliquant la méthode de classification non supervisée de partitionnement de données K-means [126] sur le vecteur Δ_x . Le cluster 1, le cluster 2, le cluster 3 incluent respectivement des variations petites, moyennes et grandes de Δ_x . Le seuil $threshold\_\Delta_x$ est choisi comme le minimum du Δ_x contenu dans le cluster 3 qui concerne les grandes variations. Cet algorithme est également appliqué au vecteur Δ_y pour déterminer le $threshold\_\Delta_y$. Ainsi, un saut de ligne est marqué une fois que la condition $\Delta_{xi} \geq threshold_{\Delta_x}$ et $\Delta_{yi} \geq threshold_{\Delta_y})$ est vérifiée.

Dans la figure 12 (a), nous présentons les coordonnées en surface avec la couleur bleue et les coordonnées en air avec la couleur rouge. Les coordonnées en surface correspondent au texte produit par le scripteur, et le tracé en rouge correspond aux mouvements en air effectués pendant la tâche de l'écriture. Afin de segmenter le texte manuscrit, nous avons éliminé les coordonnées en air. La figure 12 (b) montre uniquement le texte en surface. La figure 12 (c) représente le résultat obtenu après l'application de la méthode de segmentation en lignes.

Figure 12: Segmentation du texte en lignes individuelles.

d. Calcul des paramètres

Pour chaque point i du signal, et à partir des paramètres fournis par la tablette graphique, nous calculons les vecteurs de caractéristiques cinématiques, à savoir la vitesse, l'accélération et le jerk. Les nouveaux paramètres temporels et spectraux permettent de quantifier les variabilités inter-intra/patients. Ces techniques de traitement du signal (transformée en ondelettes discrète, transformée de Fourier rapide, filtre de Butterworth et filtre adaptatif) sont appliquées sur la vitesse, l'accélération et le jerk, puis la moyenne de chaque signal est calculée.

Au total, nous avons obtenu 67 paramètres pour chaque participant, et pour chaque élément étudié (Texte en entier ainsi que les lignes segmentées).

Nous évaluons la pertinence des paramètres calculés en utilisant le coefficient de corrélation de Pearson calculé entre le vecteur de paramètre et le vecteur étiquette. Ce score nous permettra de quantifier la capacité à séparer les patients Parkinsoniens des SCs. Dans la figure 13 utilisant des boîtes à moustaches, nous représentons la pertinence de chaque ligne segmentée, ainsi que la pertinence du texte en entier. Tous les participants ont écrit au moins 4 lignes. Dans le tableau 4, nous représentons la moyenne et le maximum du score de pertinence pour le texte avant segmentation et pour les quatre lignes.

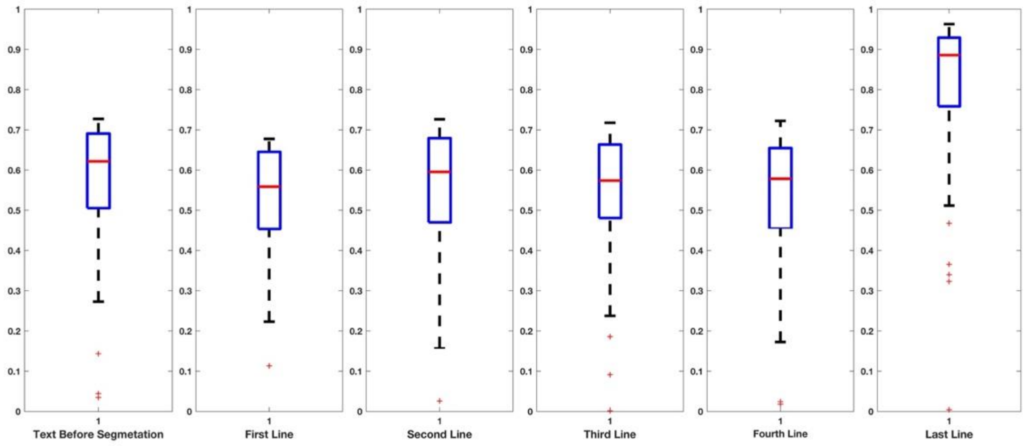


Figure 13: Pertinence des paramètres calculés sur les entités étudiées.

Table 4: Maximum et moyenne du score de pertinence.

Studied component	Max features' Relevance	Mean features' Relevance
Text before segmentation	0.72	0.57
Line 1	0.67	0.52
Line 2	0.72	0.55
Line 3	0.72	0.53
Line 4	0.72	0.53
Last line	0.96	0.81

Il est intéressant de noter qu'une grande différence est détectée entre la dernière ligne et les autres composants étudiés. Le score de pertinence atteint 0,96 dans la dernière ligne. L'analyse de la première ligne est effectuée afin de comparer les résultats obtenus avec ceux du texte avant segmentation et ceux de la dernière ligne. L'analyse de la première ligne est réalisée afin de montrer la dégradation de l'écriture manuscrite d'une ligne à l'autre jusqu'à la dernière ligne. Cette altération de l'écriture manuscrite pourrait être due à la fatigue qui se produit lors de la tâche l'écriture. C'est pourquoi les étapes de sélection et de classification se concentreront uniquement sur le texte avant la segmentation, la première et la dernière ligne.

e. Selection des paramètres pertinents

À partir de nombreux algorithmes de sélection de caractéristiques existant dans la littérature, nous utilisons dans ce travail la méthode de sélection de caractéristiques de redondance minimale - pertinence maximale (minimum Redundancy - Maximum Relevance mRMR) [37] appliqué pour classer les 67 paramètres.

f. Classification et validation

Trois classificateurs largement utilisés dans la littérature ont été appliqués dans ce travail: (1) K-Nearest Neighbours [38] [39], (2) Support Vector Machines with RBF kernel [40], et (3) Decision Trees (DT) [41]. Ces algorithmes sont adaptés au petit jeu de données utilisé dans notre cas et à la grande dimensionnalité des paramètre dans l'espace.

Les performances du processus de sélection du modèle ont été évaluées à l'aide d'une estimation sans biais en appliquant la validation croisée stratifiée imbriquée de 10 fois (K=10). Dans cette perspective, l'ensemble de données composé de 40 patients Parkinsoniens et 40 SCs est d'abord divisé en 10 sous-groupes externes. En outre, les données d'écriture correspondant aux 9 sous-groupes extérieurs sont partitionnées en 10 sous-groupes intérieurs. Une technique simple de validation croisée [42][43] est réalisée sur ces derniers pour connaître les hyper-paramètres optimaux de chaque classificateur. Ainsi, les classificateurs résultants ont été entraînés sur les sous-groupes intérieurs avec les valeurs d'hyper-paramètres optimisées et ont ensuite été testés sur le sous-groupe extérieur maintenu.

Cette procédure est répétée 10 fois, chaque sous-groupe extérieur étant utilisé une fois comme sous-groupe de test afin de garantir que toutes les données sont testées. En effet, les performances des modèles de prédiction générés ont été évaluées à l'aide de plusieurs taux statistiques dont la précision (Acc), la précision équilibrée (Acc_{bal}), la sensibilité (Sen), la spécificité (Spec), le F-Score et le coefficient de corrélation de Matthews (MCC) [44] [45].

g. Résultats et discussion

A ce niveau, l'apprentissage des trois classificateurs est effectué sur les différentes catégories de paramètres séparément, afin d'évaluer, dans la comparaison, la capacité de prédiction de chaque catégorie lors du processus de classification. La classification est également effectuée sur la combinaison des trois catégories de fonctionnalités avant et après la méthode de classement des paramètres mRMR de manière incrémentale, pour observer l'amélioration probable des mesures de performance en injectant un nombre réduit de fonctionnalités les plus adaptées. En effet, la sélection des sous-ensembles de paramètres optimaux est effectuée en injectant séquentiellement dans chaque classificateur les 67 paramètres classés en fonction de leurs scores mRMR. Cette procédure consiste à injecter dans chaque classificateur, le paramètre qui a le plus grand poids, puis les deux premiers qui ont un poids maximum, et ainsi de suite, jusqu'à ce que toutes les 67 paramètres soient injectés. Ces résultats sont obtenus sur le texte avant segmentation, première ligne et dernière ligne respectivement [35].

Le résultat le plus frappant à émerger est l'existence d'une augmentation significative des performances de classification entre la première et la dernière ligne pour tous les classificateurs considérés. La précision n'a atteint que 78,57% dans la première ligne alors qu'elle atteignait jusqu'à 92% dans la dernière ligne. Par ailleurs, le texte avant segmentation offre moins de puissance prédictive que celle de la dernière ligne, et une précision de 85,71% a été obtenue pour ce composant étudié. En revanche, les paramètres spectraux et temporels ont conduit à des taux de classification plus élevés par rapport aux paramètres statistiques de base souvent calculés dans la littérature. Il est également intéressant de noter que l'entraînement des modèles de prédiction basé sur les données combinées des trois catégories de paramètres avant sélection n'a conduit à aucune amélioration significative des performances. Néanmoins, la sélection basée sur l'injection séquentielle de caractéristiques classées en fonction des scores mRMR, a donné une augmentation remarquable des taux de classification dans tous les cas considérés. La meilleure précision atteinte pour le texte avant la segmentation était de 85,71% pour un sous-ensemble de 23 caractéristiques en utilisant le classificateur KNN. Concernant la première ligne, le classificateur DT offre une précision de 78,57% en injectant 40 fonctionnalités. De manière significative, la dernière ligne a donné les meilleures performances et atteint une précision maximale de 92,86% pour seulement 20 fonctionnalités en utilisant DT.

Dans l'ensemble, la segmentation du texte en lignes est une nouvelle approche qui nous a permis d'analyser le texte plus en profondeur. Les résultats obtenus mettent en évidence la méthode de segmentation proposée, compte tenu de l'amélioration des performances de classement de la première à la dernière ligne.

Cela peut être dû à des informations spécifiques, qui peuvent être impliquées dans la caractérisation de l'écriture manuscrite des sujets atteints de Parkinson, et qui peuvent être accentuées d'une ligne à l'autre ou peuvent également apparaître pour la première fois dans la dernière ligne. Ces altérations se manifestent fortement dans les caractéristiques de la dernière ligne. Ainsi, la dernière ligne discrimine au mieux les patients Parkinsoniens des SCs, ces résultats semblent bien étayés en obtenant la précision minimale de 92%[35]. Selon ces résultats, la méthode de classement des paramètres mRMR utilisée est intéressante car elle donne les sous-groupes optimaux de paramètres pour lesquels on obtient de meilleures performances de classement. En fait, les meilleures précisions sont atteintes avec l'injection séquentielle de caractéristiques en fonction des scores mRMR. Remarquablement, la dernière ligne a donné les meilleures performances et discrimine au mieux les patients Parkinsoniens des SCs. Ce résultat intéressant indique que la détérioration de la motricité et par conséquent la dégradation du matériel sont plus visibles dans la dernière ligne que dans les autres lignes. De manière pertinente, cela est en bon accord avec notre hypothèse concernant la fatigue survenant lors de l'écriture.

VI. Conclusions et perspectives

Dans cette thèse, nous proposons un nouveau paradigme pour étudier les changements de l'écriture en ligne dû au déclin cognitif associé à la maladie de Parkinson. Notre travail a abordé certaines limites majeures de l'état de l'art à savoir:

- C’est la première étude qui traite la langue arabe. La plupart des études menées sur la maladie de Parkinson, dans la littérature, concernaient principalement les langues latines.
- Nous sommes également la première équipe de recherche à avoir acquis le jeu de données d'écriture manuscrite en ligne arabe après avoir développé un protocole d'acquisition spécifique. Cette acquisition se fait sur une tablette graphique Wacom au service de neurologie du CHU HASSAN II de Fès. Les sujets qui ont participé à l'acquisition des données ont signé un formulaire de consentement et ont été examinés par l'équipe médicale.

- Toutes les études de la littérature se sont concentrées uniquement sur les lettres, les mots ou les phrases. Néanmoins, à notre connaissance, il s'agit de la première étude à traiter de l'analyse d'un texte composé de plusieurs lignes.
- La caractérisation de la population marocaine à partir des paramètres d'écriture qualitative et quantitative. En utilisant les techniques de l'apprentissage non supervisé, nous avons généré trois groupes de scripteurs, deux sous-groupes de patients atteints uniquement de la maladie de Parkinson et le troisième concerne des sujets contrôles. Le premier sous-groupe de patients atteints de la maladie de Parkinson est principalement caractérisé par un stade précoce de la MP selon le score UPDRS. Ce cluster est caractérisé par une vitesse, une accélération et un jerk moyens, avec une pression moyenne. Tous ces scripteur ont un niveau d'éducation élevé avec une fréquence d'écriture élevée. Cependant, le deuxième sous-groupe de patients atteints de la maladie de Parkinson est caractérisé par des valeurs de paramètres cinématiques les plus basses, ainsi que par une pression très basse. Ces scripteurs passent beaucoup de temps dans l'air, et selon leur score UPDRS, ils ont également un stade avancé de la maladie de Parkinson par rapport aux patients atteints de la maladie de Parkinson du premier sous-groupe. En revanche, le troisième sous-groupe concerne uniquement les sujets contrôles. Ils ont une vitesse, une accélération et un jerk très élevés. Ils ont également une pression moyenne. Ces participants ont un niveau d'éducation moyen à élevé avec une fréquence d'écriture élevée. En résumé, selon les résultats obtenus, les patients atteints de la maladie de Parkinson subissent des modifications principalement dans les paramètres cinématiques. Ainsi, les complications de la motricité fine chez les patients atteints de la maladie de Parkinson se traduisent principalement par une dégradation majeure des aspects cinématiques de l'écriture manuscrite. Contrairement aux sujets contrôles, les patients atteints de la maladie de Parkinson se caractérisent par une lenteur significative de la vitesse, de l'accélération et du jerk.
- Nous proposons également une analyse globale de l'écriture manuscrite en ligne. À partir d'un texte imposé composé de plusieurs lignes, nous étudions l'aspect global de l'écriture manuscrite. Le but de cette étude est de trouver, sur la base des caractéristiques statistiques de base souvent calculées dans la littérature, un sous-ensemble de caractéristiques d'écriture manuscrite sélectionnées qui identifient efficacement les Marocains atteints de la maladie de Parkinson. Pour chaque

participant, nous avons calculé 528 paramètres. À l'aide du test statistique Mann-Whitney et de l'algorithme Relieff, nous avons sélectionné les caractéristiques les plus pertinentes capables de discriminer au mieux les patients atteints de la maladie de Parkinson et les sujets contrôles. Ces fonctionnalités pertinentes ont été injectés à un classificateur de machine à vecteurs de support SVM avec noyau RBF. En effet, nous avons pu classer correctement près de 80% des sujets étudiés.

- Afin d'améliorer les performances de classification et de construire par la suite un système d'aide au diagnostic intelligent et autonome, nous proposons, en plus des paramètres statistiques de base souvent calculés dans la littérature, de nouvelles catégories de fonctionnalités pour analyser l'écriture des deux profils cognitifs étudiés en combinant entre la segmentation de l'écriture manuscrite en ligne et les algorithmes d'apprentissage automatique appliqués sur les nouveaux paramètres temporels et spectraux proposés.
- Sur la base de la segmentation du texte en lignes individuelles, nous étudions également de manière semi-globale, la dynamique complète de l'écriture manuscrite des profils cognitifs étudiés. La segmentation de texte est une nouvelle approche qui vise à analyser le texte plus profondément et à comparer la tâche de texte avant et après la segmentation de ligne, afin d'évaluer la dégradation dynamique complète de l'écriture manuscrite qui peut être plus perceptible lors de l'exécution de la tâche durant le temps. En passant d'une ligne à l'autre, cette approche inédite nous a donné la possibilité d'étudier la dégradation de l’écriture manuscrite reflétant la fatigue pathologique, qui est plus visible dans la dernière ligne du texte manuscrit. En outre, la dernière ligne a donné le meilleur résultat dans la classification, ainsi, elle distingue au mieux les patients atteints de la maladie de Parkinson des sujets contrôles.
- De plus, notre équipe scientifique a développé des méthodes de classification supervisée et non supervisée qui sont interprétables de bout en bout pour le corps professionnel de la santé. En effet, tous nos résultats et conclusions sont discutés et approuvés par tous les membres du projet ENEMAR avant publication.

Dans cette thèse, plusieurs contributions sont présentées. Cependant, il reste des découvertes potentiellement nouvelles dans le domaine de la détection précoce de la maladie de Parkinson qui peuvent encore être explorées. Par ailleurs, nos travaux ouvrent la porte à de nombreux travaux futurs, que ce soit à court, moyen ou long terme. Ces perspectives peuvent être divisées en deux parties principales:

1. L'objectif principal de ce projet est de développer un système d'aide au diagnostic intelligent pour détecter d'une manière précoce les différentes pathologies neurodégénératives. Ce système est une application Android permettant aux utilisateurs de s'auto-diagnostiquer afin de détecter les anomalies à un stade précoce et donc de consulter le médecin spécialiste pour un éventuel examen préventif avant toute détérioration majeure. Ce système est un outil peu coûteux pour la détection automatique des pathologies neurodégénératives.

Il est important de souligner que nos encadrants ont déjà recruté des doctorants que nous co-encadrons et qui sont en train de finaliser le Système d'Aide au Diagnostic en intégrant toutes les méthodes que nous avons développées et qui sont présentées dans cette thèse.

2. Le deuxième volet de ce projet est l'extension de la base de données d'écriture puis l'analyse de tous les autres exercices du protocole ainsi que des autres pathologies neurodégénératives pour lesquelles les données d'écriture sont déjà acquises comme la maladie d'Alzheimer et le MCI. Notre travail est également étendu à la schizophrénie et à d'autres maladies psychologiques. Ainsi, les travaux de cette deuxième partie du projet se déroulent comme suit:

- Nous sommes conscients que nos recherches peuvent présenter certaines limites telles que la taille de l'ensemble de données utilisé. A cet effet, l'acquisition des données est toujours réalisée au sein du service neurologique du Centre Hospitalier Universitaire Hassan II de Fès, afin d'élargir notre base de données.
- Étaler cette étude sur la langue française, et comparer les résultats entre ceux obtenus sur la langue arabe et ceux obtenus sur la langue française. En plus d'étendre cette analyse même aux exercices de dessin.
- Concernant l'aspect longitudinal, nous pouvons commencer à partir des résultats obtenus dans cette étude. En effet, la classification non-supervisée nous a montrée qu'il y avait certains sujets contrôles proches des patients débutants de la maladie de Parkinson ou même des patients parkinsoniens ayant un stade légers qui sont proches des parkinsoniens ayant un stade avancé. L'étude longitudinale sur la période comprise entre 12 mois (données disponibles dans notre base de données) est utile pour évaluer le pouvoir prédictif de notre approche en regardant le cas de sujets contrôles susceptibles de se convertir en Parkinsoniens, ou pour analyser l'évolution de la maladie de Parkinson du stade léger au stade avancé. L'un des

résultats de cette étude sera d'identifier les paramètres spatio-temporels prédictifs de la maladie de Parkinson à un stade très précoce.

Enfin, il est à noter que toutes les recherches menées sur l'écriture manuscrite seront étendues à la parole et à la marche avec un protocole spécifique pour chaque modalité. En effet, nous sommes en train de collecter une base de données des mêmes patients concernant la parole et la marche au service neurologique du CHU Hassan II Fès, et éventuellement de combiner nos résultats prometteurs avec ceux de la parole et de la marche afin de détecter la maladies neurodégénératives et psychologiques à un stade précoce.

VII. Références

[1] R. Plamondon and S. N. Srihari, "On-line and off-line handwriting recognition: A comprehensive survey," *IEEE Trans. Pattern Anal. Mach. Intell.*, vol. 22, no. 1, pp. 63–84, 2000.

[2] M. A. El-Yacoubi, M. Gilloux, and J. M. Bertille, "A statistical approach for phrase location and recognition within a text line: An application to street name recognition," *IEEE Trans. Pattern Anal. Mach. Intell.*, vol. 24, no. 2, pp. 172–188, 2002.

[3] B. Moysset *et al.*, "The A2iA Multi-lingual Text Recognition System at the Second Maurdor Evaluation," in *Proceedings of International Conference on Frontiers in Handwriting Recognition, ICFHR*, 2014, vol. 2014-Decem, pp. 297–302.

[4] H. Mouchère, C. Viard-Gaudin, R. Zanibbi, and U. Garain, "ICFHR2016 CROHME: Competition on recognition of online handwritten mathematical expressions," in *Proceedings of International Conference on Frontiers in Handwriting Recognition, ICFHR*, 2016, vol. 0, pp. 607–612.

[5] G. P. van Galen, "Handwriting: Issues for a psychomotor theory," *Hum. Mov. Sci.*, vol. 10, no. 2–3, pp. 165–191, 1991.

[6] H. L. Teulings and G. E. Stelmach, “Control of stroke size, peak acceleration, and stroke duration in Parkinsonian handwriting,” *Hum. Mov. Sci.*, vol. 10, no. 2–3, pp. 315–334, 1991.

[7] H. L. Teulings, J. L. Contreras-Vidal, G. E. Stelmach, and C. H. Adler, “Parkinsonism reduces coordination of fingers, wrist, and arm in fine motor control,” *Exp. Neurol.*, vol. 146, no. 1, pp. 159–170, Jul. 1997.

[8] J. Walton, “Handwriting changes due to aging and Parkinson’s syndrome,” *Forensic Sci. Int.*, vol. 88, no. 3, pp. 197–214, 1997.

[9] M. J. Slavin, J. G. Phillips, J. L. Bradshaw, K. A. Hall, and I. Presnell, “Consistency of handwriting movements in dementia of the Alzheimer’s type: A comparison with Huntington’s and Parkinson’s diseases,” *J. Int. Neuropsychol. Soc.*, vol. 5, no. 1, pp. 20–25, 1999.

[10] P. Drotár, J. Mekyska, Z. Smékal, I. Rektorová, L. Masarová, and M. Faundez-Zanuy, “Prediction potential of different handwriting tasks for diagnosis of Parkinson’s,” in *2013 E-Health and Bioengineering Conference, EHB 2013*, 2013, pp. 1–4.

[11] M. Thomas, A. Lenka, and P. Kumar Pal, “Handwriting Analysis in Parkinson’s Disease: Current Status and Future Directions,” *Mov. Disord. Clin. Pract.*, vol. 4, no. 6, pp. 806–818, 2017.

[12] M. Diaz, M. A. Ferrer, D. Impedovo, G. Pirlo, and G. Vessio, “Dynamically enhanced static handwriting representation for Parkinson’s disease detection,” *Pattern Recognit. Lett.*, vol. 128, pp. 204–210, 2019.

[13] J. G. Phillips, J. L. Bradshaw, E. Chiu, and J. A. Bradshaw, “Characteristics of handwriting of patients with huntington’s disease,” *Mov. Disord.*, vol. 9, no. 5, pp. 521–530, 1994.

[14] M. P. Caligiuri, H.-L. Teulings, C. E. Dean, A. B. Niculescu, and J. Lohr, “Handwriting movement analyses for monitoring drug-induced motor side

effects in schizophrenia patients treated with risperidone," *Hum. Mov. Sci.*, vol. 28, no. 5, pp. 633–642, 2009.

[15] D. Impedovo and G. Pirlo, "Dynamic Handwriting Analysis for the Assessment of Neurodegenerative Diseases: A Pattern Recognition Perspective," *IEEE Rev. Biomed. Eng.*, vol. 12, pp. 209–220, 2018.

[16] C. De Stefano, F. Fontanella, D. Impedovo, G. Pirlo, and A. Scotto di Freca, "Handwriting analysis to support neurodegenerative diseases diagnosis: A review," *Pattern Recognit. Lett.*, vol. 121, pp. 37–45, 2019.

[17] A. Schröter, R. Mergl, K. Bürger, H. Hampel, H. J. Möller, and U. Hegerl, "Kinematic analysis of handwriting movements in patients with Alzheimer's disease, mild cognitive impairment, depression and healthy subjects," *Dement. Geriatr. Cogn. Disord.*, vol. 15, no. 3, pp. 132–142, 2003.

[18] L. Likforman-Sulem, A. Esposito, M. Faundez-Zanuy, S. Clemencon, and G. Cordasco, "EMOTHAW: A Novel Database for Emotional State Recognition from Handwriting and Drawing," *IEEE Trans. Human-Machine Syst.*, vol. 47, no. 2, pp. 273–284, 2017.

[19] J. H. K. Man, L. Groenink, and M. Caiazzo, "Cell reprogramming approaches in gene- and cell-based therapies for Parkinson's disease," *J. Control. Release*, vol. 286, pp. 114–124, 2018.

[20] C. C. Goetz, "The Unified Parkinson's Disease Rating Scale (UPDRS): Status and recommendations," *Mov. Disord.*, vol. 18, no. 7, pp. 738–750, Jul. 2003.

[21] V. Del Barrio, "Diagnostic and statistical manual of mental disorders," *Curated Ref. Collect. Neurosci. Biobehav. Psychol.*, 2016.

[22] R. C. Petersen, G. E. Smith, S. C. Waring, R. J. Ivnik, E. G. Tangalos, and E. Kokmen, "Mild cognitive impairment: Clinical characterization and

outcome," *Arch. Neurol.*, vol. 56, no. 3, pp. 303–308, 1999.

[23] I. Aouraghe, A. Ammour, G. Khaissidi, M. Mrabti, G. Aboulem, and F. Belahsen, "Unsupervised learning for characterization of Arabic online handwriting of Parkinson's disease patients," *SN Appl. Sci.*, vol. 2, no. 2, p. 141, 2020.

[24] A. Ammour, I. Aouraghe, G. Khaissidi, M. Mrabti, G. Aboulem, and F. Belahsen, "A new semi-supervised approach for characterizing the Arabic on-line handwriting of Parkinson's disease patients," *Comput. Methods Programs Biomed.*, vol. 183, 2020.

[25] A. Ibtissame *et al.*, "Analyse automatique de l'écriture manuscrite en ligne pour la détection précoce des pathologies neurodégénératives," *Internet des objets*, vol. 17, no. 2, Jun. 2017.

[26] A. Tefas and I. Pitas, "Principal component analysis," *Intell. Syst.*, vol. 2, no. 1–3, pp. 37–52, 2016.

[27] M. C. Campbell *et al.*, "Principal component analysis of PiB distribution in Parkinson and Alzheimer diseases," *Neurology*, vol. 81, no. 6, pp. 520–527, 2013.

[28] J. A. Hartigan and M. A. Wong, "Algorithm AS 136: A K-Means Clustering Algorithm," *Appl. Stat.*, vol. 28, no. 1, p. 100, 1979.

[29] A. Cuevas, M. Febrero, and R. Fraiman, "An anova test for functional data," *Comput. Stat. Data Anal.*, vol. 47, no. 1, pp. 111–122, 2004.

[30] I. Aouraghe, M. Mrabti, A. Ammour, G. Aboulem, G. Khaissidi, and F. Belahsen, "Automatic analysis of Arabic online handwriting of patients with Parkinson's disease: Statistical study and classification," in *ACM International Conference Proceeding Series*, 2019.

[31] N. Nachar, "The Mann-Whitney U: A Test for Assessing Whether Two

Independent Samples Come from the Same Distribution," *Tutor. Quant. Methods Psychol.*, vol. 4, no. 1, pp. 13–20, 2008.

[32] M. Keita, "Introduction à la méthode statistique et probabiliste," 2016.

[33] R. P. L. DURGABAI and R. B. Y, "Feature Selection using ReliefF Algorithm," *Ijarcce*, vol. 3, no. 10, pp. 8215–8218, 2014.

[34] D. Ruppert, *The Elements of Statistical Learning: Data Mining, Inference, and Prediction*, vol. 99, no. 466. Springer Science & Business Media, 2004.

[35] I. Aouraghe, A. Alae, K. Ghizlane, M. Mrabti, G. Aboulem, and B. Faouzi, "A novel approach combining temporal and spectral features of Arabic online handwriting for Parkinson's disease prediction," *J. Neurosci. Methods*, vol. 339, p. 108727, 2020.

[36] P. Drotar, J. Mekyska, Z. Smekal, I. Rektorova, L. Masarova, and M. Faundez-Zanuy, "Contribution of different handwriting modalities to differential diagnosis of Parkinson's Disease," in *2015 IEEE International Symposium on Medical Measurements and Applications, MeMeA 2015 - Proceedings*, 2015, pp. 344–348.

[37] H. Peng, F. Long, and C. Ding, "Feature selection based on mutual information: Criteria of Max-Dependency, Max-Relevance, and Min-Redundancy," *IEEE Trans. Pattern Anal. Mach. Intell.*, vol. 27, no. 8, pp. 1226–1238, 2005.

[38] L. E. Peterson, "K-nearest neighbor," *Scholarpedia*, vol. 4, no. 2, p. 1883, 2009.

[39] R. Nisbet, G. Miner, and K. Yale, *Handbook of statistical analysis and data mining applications*. Academic Press, 2017.

[40] S. R. Sain and V. N. Vapnik, *The Nature of Statistical Learning Theory*,

vol. 38, no. 4. Springer science & business media, 1996.

[41] Y. Y. Song and Y. Lu, "Decision tree methods: applications for classification and prediction," *Shanghai Arch. Psychiatry*, vol. 27, no. 2, pp. 130–135, 2015.

[42] P. A. Robinson, "Understanding the molecular basis of Parkinsons disease, identification of biomarkers and routes to therapy," *Expert Rev. Proteomics*, vol. 7, no. 4, pp. 565–578, 2010.

[43] T. Fawcett, "An introduction to ROC analysis," *Pattern Recognit. Lett.*, vol. 27, no. 8, pp. 861–874, 2006.

[44] D. Chicco, "Ten quick tips for machine learning in computational biology," *BioData Min.*, vol. 10, no. 1, p. 35, 2017.

[45] D. Chicco and G. Jurman, "The advantages of the Matthews correlation coefficient (MCC) over F1 score and accuracy in binary classification evaluation," *BMC Genomics*, vol. 21, no. 1, p. 6, 2020.

Abstract

In this thesis, we present a new paradigm for characterizing Parkinson's disease through the analysis of online handwriting acquired on a digital graphic tablet based on techniques and methods of machine learning and artificial intelligence. The state of the art is extensively dominated by studies carried out on Latin languages, and limited only to letters, words or sentences. These studies have also focused only on the use of the basic statistical functions computed on the global kinematic, mechanical and spatial features of handwriting.

Our work addresses the major limitations as follows. First of all, we propose to conduct our study on an imposed Arabic text composed of several lines, acquired by our team in the neurological department of the University Hospital Center Hassan II Fez, based on a specific protocol proposed by our scientific and neurological team. In our own knowledge, this is the first study to deal with the Arabic language. Moreover, in order to characterize the handwriting of the Moroccan studied population, we start by an unsupervised learning to find automatically homogeneous clusters or groups of subjects and analyze the information contained in these clusters consisting of the two considered cognitive profiles (Parkinson's disease patients and Healthy controls). After this unsupervised characterization, we computed the basic statistical features often used in the literature, and based on the Support Vector Machine classifier, we achieved 80% overall classification accuracy.

With the aim of improving the classification performances, we developed a novel and original method based on the combination between the segmentation of the online handwriting text into individual lines and the machine learning algorithms applied on new proposed temporal and spectral features.

This new approach allowed us to study the full dynamics of handwriting, analyze the text more deeply, and evaluate the fatigue that may occur while writing from one line to another. Besides, instead of adopting only the basic statistical parameters often used in the literature, we propose a new type of temporal and spectral parameters. An accuracy of 92.86 % was obtained with Decision Trees classifier in the last line. The new categories of spectral and temporal features gave the best classification performances in comparison to the basic statistical ones.

Finally, it is worth mentioning that this thesis was carried out as part of the ENEMAR project (**É**tude **N**eurologique de l'**É**criture des **MAR**ocains) resulting from a collaboration between the research team of the Interdisciplinary Computer Science and Physics Laboratory of ENS-Fez and the neurology department of the HASSAN II University Hospital Center. This project was launched after the agreement of the ethics committee for biomedical research of the Faculty of Medicine and Pharmacy Fez under number **N ° 03/15; July 10, 2015; Fez, Morocco.** The objective of this project is to develop an intelligent and an early diagnosis aid system in order to detect the neurodegenerative pathologies (Parkinson's, Alzheimer's and mild cognitive impairment) for a bilingual Moroccan population. In this context, we acquired our own online handwriting dataset at the HASSAN II University Hospital Center in Fez following our specific protocol. All the subjects who participated in the data acquisition signed a consent form and were examined by the medical team.

Keywords: ***Machine learning, Clustering, Classification, Feature Extraction, Temporal and Spectral Features, Statistics, Stratified Nested Cross-validation, Database, Arabic Online Handwriting Analysis, Segmentation, Parkinson's disease, Neurodegenerative pathologies.***

Résumé

Dans cette thèse, nous présentons un nouveau paradigme pour la caractérisation et la détection précoce de la maladie de Parkinson à travers l'analyse de l'écriture manuscrite en ligne acquise sur une tablette graphique numérique. Cette étude est basée sur des techniques et des méthodes d'apprentissage automatique et d'intelligence artificielle. L'état de l'art est largement dominé par des études menées sur les langues latines, et limité uniquement aux lettres, mots ou phrases. Ces études se sont également concentrées uniquement sur l'utilisation des calculs statistiques de base appliqués sur les paramètres cinématiques, mécaniques et spatiaux globaux de l'écriture manuscrite.

Notre travail traite les principaux limitations et aspects qui ne sont pas encore abordés dans la littérature. Tout d'abord, nous proposons de mener notre étude sur un texte Arabe imposé composé de plusieurs lignes, acquis par notre équipe au service de neurologie du Centre Hospitalier Universitaire Hassan II Fès, suivant un protocole spécifique proposé par notre équipe de scientifiques et neurologues. À notre connaissance, il s'agit de la première étude portant sur la langue Arabe. Par ailleurs, afin de caractériser l'écriture manuscrite de la population marocaine étudiée, nous commençons par un apprentissage non supervisé pour générer automatiquement des clusters ou groupes de sujets homogènes et analyser les informations contenues dans ces clusters constitués des deux profils cognitifs considérés (patients atteints de la maladie de Parkinson et sujets contrôles). Après cette caractérisation non supervisée, nous avons calculé les caractéristiques statistiques de base utilisées dans la littérature, ensuite nous les avons injecté dans le classificateur Machine à Vecteur de Support. Cette approche nous a permis d'atteindre une précision de classification globale de 80%.

Dans le but d'améliorer les performances de classification et de développer un système automatique et intelligent de détection précoce des pathologies neurodégénératives, nous avons développé une nouvelle approche dont l'originalité porte sur l'extraction de nouveaux paramètres temporels et spectraux ainsi que sur la combinaison entre la segmentation du manuscrit en lignes individuelles et les algorithmes d'apprentissage automatique.

Cette nouvelle approche nous a permis d'étudier toute la dynamique de l'écriture manuscrite, d'analyser le texte plus en profondeur et d'évaluer la fatigue qui peut survenir lors de l'écriture d'une ligne à l'autre. Par ailleurs, au lieu de n'adopter que les paramètres statistiques de base souvent utilisés dans la littérature, nous proposons un nouveau type de paramètres temporels et spectraux. Une meilleure précision de 92,86% a été obtenue particulièrement sur la dernière ligne segmentée en se basant sur le classificateur Arbre de Décision. Les nouvelles catégories de paramètres spectraux et temporels ont donné les meilleures performances de classification par rapport aux paramètres statistiques de base utilisés dans la littérature.

Cette thèse a été réalisée dans le cadre du projet ENEMAR (Étude Neurologique de l'Écriture des MARocains) issu d'une collaboration entre l'équipe de recherche du Laboratoire Interdisciplinaire d'Informatique et de Physique de l'ENS-Fès et le service de neurologie du CHU HASSAN II. Ce projet a été lancé après l'accord du comité d'éthique de la recherche biomédicale de la Faculté de médecine et de pharmacie de Fès sous le numéro N ° 03/15; 10 juillet 2015; Fès, Maroc. L'objectif de ce projet est de développer un système d'aide au diagnostic intelligent et précoce afin de détecter les pathologies neurodégénératives (Parkinson, Alzheimer et troubles cognitifs légers) pour une population marocaine bilingue. Dans ce cadre, nous avons acquis notre propre base de données d'écriture manuscrite en ligne au CHU HASSAN II de Fès selon notre protocole spécifique. Tous les sujets qui ont participé à l'acquisition des données ont signé un formulaire de consentement et ont été examinés par l'équipe médicale.

Mots Clés: ***Apprentissage Automatique, Clustering, Classification, Extraction de Paramètres, Paramètres Temporels Et Spectraux, Statistiques, Validation Croisée Stratifiée Imbriquée, Base De Données, Analyse de l'Écriture Manuscrite Arabe En Ligne, Segmentation, Maladie De Parkinson, Pathologies Neurodégénératives.***

Acknowledgements

It is a moment of gratification and pride to look back with a sense of contentment at the long traveled path, to be able to recapture some of the fine moments, to be think of the infinite number of people, some who were with me from the beginning, some who joined me at different stages during this journey, whose kindness, love and blessings has brought me to this day. This PhD thesis is the output of the effort and support of several people to whom I am extremely grateful.

First and foremost, I bow my head with absolute respect and pleasantly convey my heartily thankfulness to my supervisors Professor Ghizlane Khaissidi and Professor Mostafa Mrabti, for having given me the opportunity to embark on this enriching journey, providing valuable advices, assistance and priceless guidance. I also thank them for awakening in me the sense and the passion for research. Both made me go further professionally and personally. I have found a teacher, a friend, an inspiration, a role model and a pillar of support in my two lovely supervisors. Many thanks for their warm support when I needed most. It has been a privilege to work under their direction. Hope to be able to work with them again in the near future.

I wish also to acknowledge Professor Faouzi Belahsen and Doctor Ghita Aboulem for facilitating my integration into the Neurological department team at the UHC Hassan II, Fez.

I am profoundly grateful for the hard work of my co-author Alae Ammour and his substantial contribution to uplift the studies presented in this thesis. I am delighted to have worked with you and I look forward to working with you again.

I would like to warmly thank all the members of our Interdisciplinary Computer Science and Physics Laboratory (LIPI) of ENS Fez, especially its Director Mr.Chenouni Driss for his warm support and welcome in his laboratory.

I wish to acknowledge the reviewers of this thesis for their time to review this thesis and their good advices of making it better.

My acknowledgement would be incomplete without thanking the biggest source of my strength, my family and friends. My deepest gratitude goes to my lovely parents for giving me everything, especially their education, their love, their unwavering support and their warm encouragement, without them, I wouldn't have got this far. Special and profound thanks to my two sisters and my brother in law Mrs. Hanae Aouraghe, Ms. Ilhame Aouraghe and Mr. Abdessalam Guenoun for always cheering me up.

Dedication

I dedicate this thesis to my beloved parents,
The reason of what I become today.
Thanks for your great support, continuous care and unconditional love.

To my sisters,
You have been my inspiration, and my soul mates.

To my dearest and most beloved best friend Amouna.
You are the treasure I got during this journey.

I love you all dearly.

Table of Contents

List of Figures

List of Tables

List of Acronyms

ACC: *Accuracy*
ALZ: *Alzheimer's disease*
ANOVA: *Analysis Of Variance*
BiSP: *Biometric Smart Pen*
CDT: *Clock Drawing Test*
CNN: *Convolutional Neural Network*
DAS: *Diagnosis Aid System*
DMS: *Diagnostic and Statistical Manual of Mental Disorders*
DT: *Decision Trees*
EMD: *Empirical Mode Decomposition*
ENEMAR: *Étude Neurologique de l'Écriture des MARocains*
FN: *False Negative*
FP: *False Positive*
HC: *Healthy Control*
HW: *Handwriting*
IMF: *Intrinsic Mode Functions*
KNN: *K-Nearest Neighbor*
LOOCV: *Leave-One-Out Cross-Validation*
MCC: *Matthews Correlation Coefficient*
MCI: *Mild Cognitive Impairments*
MMSE: *Mini Mental State Examination*
mRMR: *minimum Redundancy - Maximum Relevance*
NB: *Naïve Bayes*
NCA: *Number of Changes in Acceleration*
NCP: *Number of Changes in Pressure*
NCV: *Number of Changes in Velocity*
OPF: *Optimum-Path Forest*
PCA: *Principal Component Analysis*
PD: *Parkinson's Disease*
PDA: *Personal Digital Assistant*
PDQ: *Parkinson Disease Questionnaire*
RBF: *Radial Basis Function*
ROC: *Receiver Operating Characteristic*
SEN: *Sensitivity*
SPEC: *Specificity*
SVM: *Support Vector Machine*
TN: *True Negative*
TP: *True Positive*
UPDRS: *Unified Parkinson's Disease Rating Scale*

1. Chapter 1: General Introduction

1.1. Introduction

Handwriting analysis has long been focused on the problem of automatic recognition of the handwritten signal. Indeed, to date, the automatic recognition of the handwritten signal is a successful and a mature technology [1] with several results in commercial applications, in particular banks and post office for the processing of checks and addresses [2][3], in the context of offline handwriting (acquired on sheet with a simple pen). Moreover, in the context of online handwriting, this technology is used to recognize notes taken on smartphones, tablets or Personal Digital Assistant PDAs [4]. More recently, the analysis of handwriting has evolved into the field of health. Given the spectacular development of digital graphics tablets, innovation in the analysis of handwriting for medicine has become a promising field. These tablets allow the acquisition of the plot over time, called "online", rich in kinematic and mechanical information of the writer. In this perspective, the acquisition of handwriting on a digital graphic tablet has become a new hopeful area of research in healthy field and more particularly in the early detection of neurodegenerative diseases.

In fact, handwriting is a complex and automated activity requiring fine motor control. It involves cognitive, kinesthetic, perceptual-motor components, and specific neuromuscular coordination [5]. Once a subject has learned to write, the exchange (feedback) between visual perception and muscle control required to write becomes automatic, resulting in extremely rapid movements, which means that a motor control program is developed in the brain. Thus, the deterioration of this high-level faculty, no matter how small, can be a sign of a deterioration or dysfunction of this fine motor program, due generally to neurological pathologies. Accordingly it can be an important biomarker for the detection and the evaluation of these diseases.

Several works in the literature have studied the link between the deterioration of handwriting and pathologies such as Parkinson's disease [6][7][8][9][10][11][12], Huntington's disease [13], Schizophrenia [14], multiple sclerosis [15], Alzheimer's disease [16][17] and other health problems such as depression [18][19], anxiety and stress [19]. This online analysis of handwriting provides invisible but precious dynamic information on how the manuscript is performed.

In this thesis, we are interested to analyze the online handwriting of Parkinson's disease patients specifically Moroccan population and Arabic handwriting. Parkinson's disease (PD) is a long-term degenerative disorder characterized by the progressive destruction of dopaminergic neurons of the compact substance in the midbrain. This destruction of these neurons leads to a decrease in dopamine, which is the neurotransmitter responsible of the control and regulation of movements in the body. This results in body tremors, slow movements, hypertonia and balance problems [20]. Unfortunately, despite the great progress of medicine, an early and reliable diagnosis of PD is still difficult and remain limited until now. In fact, the most commonly observed warning signs evolve silently and only appear 5 to 10 years after the beginning of the disease with 50%–60% of the dopaminergic neurons degeneracy [20]. Thereby, the detection of this disease at an early stage is crucial in order to control its evolution and consequently, to improve the patients' quality of life, which will allow a faster support and increases the chances of successful treatment.

1.2. Handwriting as part of Parkinson's disease diagnosis

1.2.1. Contribution of this work

The main objective of this thesis is to characterize Parkinson's disease through the automatic analysis of online Arabic handwriting. This is a cross-sectional study considering two cognitive profiles: Healthy Controls (HCs), Parkinson's Disease patients (PD patients).

In our project, we propose a new paradigm to investigate the main limitations and aspects that are not yet addressed in the literature.

1. Studies carried out on neurodegenerative diseases particularly concern Latin languages. However, according to our own research, there are no studies conducted on the Arabic language. Thus, in this thesis we focused on Arabic online handwriting and Moroccan Parkinson's disease patients.
2. In the literature, the studies conducted in this topic were limited to letters, words or sentences only. To our own knowledge, this is the first study to deal with an imposed text composed of several lines.

3. Through the use of kinematic, mechanical and spatial features of handwriting, we aim to characterize Parkinson's disease. We offer unsupervised learning to find homogeneous clusters of subjects and we analyze the information contained in these clusters or groups according to cognitive profiles.
4. We propose a global analysis of online handwriting. Based on a text composed of several lines, we study the global aspect of handwriting. The goal of this study is to find, based on the basic statistical features often computed in the literature, a subset of selected handwriting features that effectively identify Moroccan people with Parkinson's disease.
5. Based on the text segmentation into individual lines, we develop a novel approach by combining between the segmentation of the online handwriting and the machine learning algorithms applied on new proposed temporal and spectral features.

   The text segmentation is a new approach that allowed us to study the full dynamics of handwriting, analyze the text more deeply, and quantify the fatigue that occurred while writing from one line to another. In addition to the computed statistical parameters, we propose a new type of temporal and spectral features extraction which gave the best classification performances in comparison to the basic statistical ones.
6. Our scientific team developed clustering and classification methods which are end-to-end interpretable for the medical professional. Indeed, all our results and conclusions are discussed and approved by all members of ENEMAR project before publication.
7. It is important to mention that the used online handwriting database is acquired by our own medical and scientific team at the HASSAN II University Hospital Center in Fez. All the subjects who participated in the data acquisition signed a consent form and were examined by the medical team.

This thesis was carried out as part of the ENEMAR project (**É**tude **N**eurologique de l'**E**criture des **MAR**ocains) resulting from a collaboration between the research team of the interdisciplinary computer science and physics laboratory (LIPI) of ENS-Fez and the neurology department of the HASSAN II University Hospital Center. This project was launched after the agreement of the ethics committee for biomedical research of the Faculty of Medicine and Pharmacy Fez under number **N ° 03/15; July 10, 2015; Fez, Morocco.** The objective of this project is to develop an intelligent and an early diagnosis aid system in order to detect the neurodegenerative pathologies (Parkinson's, Alzheimer's, mild cognitive disorders) for a bilingual Moroccan population. This project includes three modalities: Online handwriting, speech and gait.

1.2.2. Thesis organization

Chapter 2 presents the state of-the-art of online handwriting analysis for the early detection of Parkinson's disease. We explore new research axes on this thematic that have never been addressed before and that highlight the richness of the online handwriting signal of the Arabic language including all its specificities such as: cursive script and vocalization.

Chapter 3 treats in detail the acquisition protocol elaborated by our scientific and neurological team and describe our own handwriting database acquired at the Hassan II University Hospital Center in Fez.

Chapter 4 deals with the quantitative and qualitative characterization of online handwriting based on unsupervised machine learning techniques. This approach is explained in detail. Thus, this chapter highlights the major results obtained by exploiting K-means clustering. A visualization of the obtained clusters and identification of the most relevant features are carried out using the Principal Component Analysis (PCA).

Chapter 5 explores the supervised learning using Support Vector Machines (SVM) classifier. This classification method is conducted on the imposed Arabic text composed of several lines. The feature extraction is done using the basic statistical parameters allowing us to study the global aspect of online handwriting.

Chapter 6 represents a novel method to separate at best Parkinson’s disease patients from healthy controls. This original approach explores the full dynamics of acquired signals, it is based on the combination between the segmentation of the online handwriting text into individual lines and the machine learning algorithms applied on new proposed temporal and spectral features. The performances of the used classifiers were estimated using a stratified nested 10 cross-validation never used in the literature before. This chapter also highlights the classification performance improvements of our approach compared to those in the literature.

Finally, **Chapter 7** gives a global conclusion of all obtained results in this thesis and discusses the different perspectives of this project.

2. Chapter2: State of the art

2.1. Introduction

Parkinson's Disease (PD), first medically determined by James Parkinson in 1817, is the second most widespread degenerative neurological disease after Alzheimer's disease [21], it is a neurological disorder in the central nervous system. In 2015, this disease affected 6.9 million people globally and is expected to affect 14.2 million people by 2040 worldwide [22]. PD is characterized by the chronic and progressive destruction of dopaminergic neurons. PD dramatically affects the brain areas' structure and functions. Therefore, it causes a progressive decline of cognitive, functional and behavioral abilities. These changes in the brain result in the degradation of motor skills' performances [23].

At the moment when the first symptoms appear, it is estimated that 50% to 60% of the nerve cells of the substantia nigra are already destroyed [20]. Thus, when the symptoms appear, the disease has already on average 5 to 10 years of evolution [24]. Accordingly, early PD detection is still challenging.

Unfortunately, there is currently no cure for PD. Nevertheless, developing an early and reliable Diagnosis Aid System could strongly detect this pathology and help in the control of its evolution, consequently, in the improvement of the patients' quality of life.

Handwriting (HW) is a daily task which is a combination of cognitive, kinesthetic and perceptual-motor abilities. Thus, any change in the brain areas affects directly on the aspects of HW, and can be manifested by micrographia, slower movements, or tremors. These important HW's alterations could be considered as a prominent biomarker of PD [17][16].

For this purpose, identification of accurate biomarkers is the primary goal of research done on the analysis of online HW in order to early detect PD. Indeed, in the last few years there has been a growing interest concerning this subject, several studies were done on the analysis of online handwriting in order to detect neurodegenerative diseases. Studies conducted on PD can be classified into four categories:

1. Investigating the response to medication and their effects on handwriting in order to quantify the efficiency of treatment and monitor disease progression through the analysis of online handwriting [25] [26] [27] [28] [29] [30].
2. Studying the effect of practicing handwriting [31].

3. Examining changes in HW to better understand the brain body functional relationship [32] [33] [26] [34] [32] [35] [36].
4. Developing a Diagnosis Aid System (DAS) to investigate the adoption of online handwriting as a low-cost objective tool for automatic PD detection [37][38][39][10][40][41][42].

This chapter aims at presenting a review of the most related state of the art studies done on the analysis of online handwriting in order to assess and support the early identification of Parkinson's Disease. The most relevant handwriting tasks and computed features are also highlighted.

All the studies considered in this review, utilize digitizing tablet technology or Biometric Smart Pen for the online handwriting analysis.

2.2. Medical Diagnosis of Parkinson's Disease

Parkinson's disease is a degenerative pathology which is mainly characterized by a progressive destruction of dopaminergic neurons. Its progression can be described as follows[43]. At the start, the loss of cells happen in the substantia nigra due to unknown factors [44]. Then, it damages the dopamine pathway which generates an insufficient dopamine in these areas (See Figure 1). Unfortunately, before the first symptoms appear and before the medical diagnosis is made, more than half of these neurons have already disappeared.

However, some warning signs may exist, such as smell blindness, cramped handwriting, tremor, uncontrollable movements during sleep, voice changes, and stooped posture [45]. The identification of these signs is based on the retrospective declaration of the affected subjects or that of their relatives. The most observed signs are discreet; namely fatigue and concentration difficulties or very often a decrease in performances while performing daily tasks. In the initial stage, the most relevant motor symptoms can include but not by way of limitation to slowness of movement, postural instability, and tremor. Over time, these symptoms can unfortunately make the patient lose its mobility [46]. PD can also cause some mood disorders, such as depression as well as anxiety. Besides, in their early stages, more than a third of PD patients suffer from mood disorders.

Finally, the micrographia often appears before the other symptoms, but rarely noticed [43].

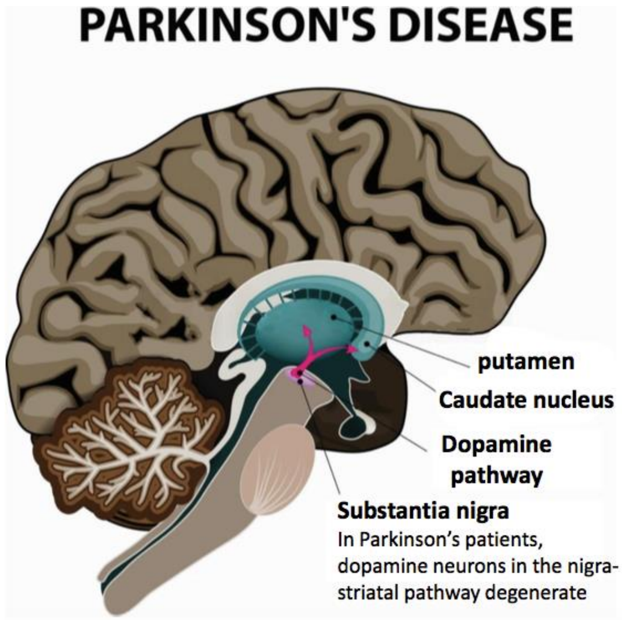


Figure 1: The progressive cells loss in the substantia nigra area destroying the dopamine pathway.

The diagnosis of PD is never obvious and requires expertise. Its purpose is to find out other possible explanations for the symptoms observed and to clarify whether it is PD itself or another pathology namely Parkinson's syndrome[47]. Making a successful clinical diagnosis of PD can be complicated. In fact, there's no test, such as a blood test, that can give a conclusive result. Instead, doctors must carefully analyze symptoms, family history and other factors to draw an accurate conclusion [48].

There are several scales for PD assessment, which have been methodologically validated. These are clinical scales which are not essential for diagnosis and monitoring, but which can be useful, even necessary during therapeutic evaluations.

These scales are divided into:

- **Global evaluation scale:** Hoehn and Yahr scale [49], allowing the classification of the disease in different stages.
- **Analytical assessment scales:** that quantify disability [50].

–**Functional scales:** that measure the consequences of PD on daily activities : Schwab and England scale[51], PDQ-39 (Parkinson Disease Questionnaire) [52] and its abridged version PDQ-8.

–**Multi-dimensional scales:** Unified Parkinson's Disease Rating Scale (UPDRS) which assesses the mental, behavioral and thymic state, the activities of daily life, the motor examination, the treatment's complications.

–The other scales of assessment mainly concern cognitive functions, mental state, motor fluctuations, dyskinesia, akinesia and tremor[53].

2.3. Parkinson's Disease: Motor skills and handwriting

In the literature, it has been shown that Parkinson's disease affects motor skills or motor functioning in the preclinical phase and before clinical diagnosis [54][55]. Handwriting has been used in two main settings to characterize Parkinson's disease: Offline handwriting and online handwriting. Several approaches have already been investigated in the offline domain [54] [55], for instance in [55], the authors have dealt with the problem of PD recognition by using computer vision techniques on an offline dataset consisting of spiral drawings images extracted from the handwriting of 37 PD patients and 18 healthy controls (HCs). Indeed, in [54] N. Zhi et al have worked on the offline historical signature samples of 12 PD patients.

Currently, several research studies have exploited the quick emergence of digital technologies to analyze writing disorders in patients with these kind of diseases. Most of these studies concerning the online handwriting acquisition are adopted. The major gain of the online handwriting is the ability to acquire and analyze the full dynamic of the handwriting based on the kinematic, mechanical and temporal features[56]. In fact, the dynamic parameters given by the online handwriting acquisition devices are: the position in x and y, time duration, pressure exerted on the surface tablet, pen's azimuth angel w.r.t the horizontal plane, and pen's altitude angel w.r.t the vertical axis [57]. The pen trajectory

Figure 2: On surface (Black color) and in air movements (Red color).

is recorded when the pen is on surface as well as when it is in air (see Figure 2) (maximal height is 1.5cm above the device).

2.4. Typical followed procedure

Most of the studies conducted on the dynamic analysis of handwriting for the detection of Parkinson's disease generally pursue a common experimental approach: Starting by data acquisition, then feature extraction and at the end data analysis (see Figure 3). These steps are addressed separately in the coming paragraphs.

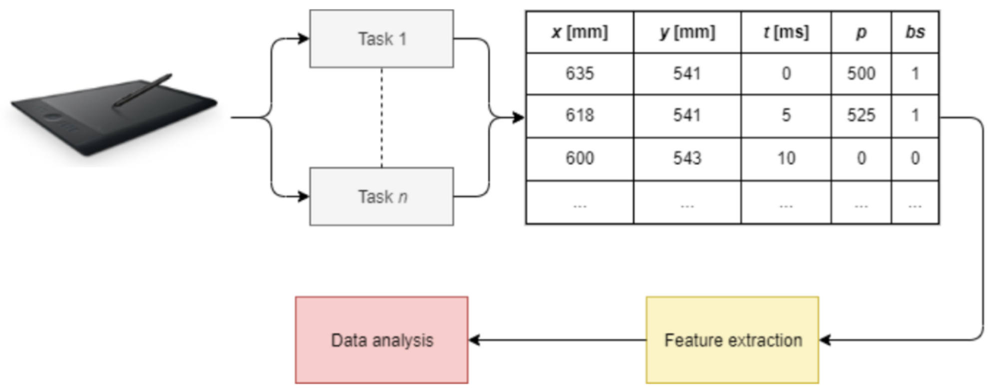


Figure 3: Flowchart of typical followed procedure of dynamic handwriting analysis (t represents timestamp, p represents pressure, and bs represents button status).

2.4.1. Data Acquisition

At this stage, the most essential steps concern the recruitment of participants, the choice of devices and the definition of the acquisition protocol. The currently available datasets concerning Parkinson’s disease are also represented.

2.4.1.1. Participant recruiting

Regarding the recruitment of participants, several criteria must be taken into account. The most important is to respect the parity of these criteria. The first important parity’s point to take into consideration is the cardinality of studied populations. Furthermore, not only the age parity is crucial, since handwriting alteration can be associated to age differences rather than underlying pathological conditions, but also the level of education (typically expressed in years) which can influence directly on handwriting even though the presence of cognitive decline [58]. In some works the handwriting frequency is also considered. The ON or OFF medication is another important aspect taken into consideration for PD patient. For instance, some studies were conducted on PD and dealt with patients under antiparkinsonian treatment [26][30]. These studies demonstrated that handwriting can significantly changes depending on the level of medical treatment.

Moreover, in order to take into consideration the disease severity, the UPDRS Unified Parkinson's Disease Rating Scale - (part V) score, relating to the Modified Hoehn and Yahr Scale, is a generally used as a rating scale for describing the patient's situation and quantifying the evolution of his symptoms during time [59]. This assessment provides a complete and flexible tool for monitoring the progression of Parkinson's disease and the patient's level of loss of autonomy.

Several studies use also the Mini-Mental State Examination score for the assessment of the cognitive profile of participants [60]. The MMSE is a global cognitive assessment test carried out first for all neurological examinations. It consists of a questionnaire of 30-point comprising questions to assess skills: spatiotemporal orientation, attention and calculation, learning and transcription of information, language and identification, and praxies constructive (the ability to organize a series of movements for a specific purpose by reproducing geometric shapes). It is also crucial to give close and thoughtful attention to participants who have visual problems, whether they have bring their eyeglasses or not so they can execute the handwriting tasks without difficulties. Therefore, any degradation of writing related to this problem and not to neurological problems should be eliminated.

The choice of healthy controls (HCs) group is principally done after passing a cognitive examination by specialists. Generally, elderly and young controls can be also considered; nevertheless an objective comparison should take into consideration demographic as well as educational characteristics.

2.4.1.2. Materials

There exists an extensive range of devices for acquiring online handwriting data. The most used devices are graphics tablet [57] and/or Biometric Smart Pens [61] (See Figure 4). The parameters given by these devices are usually the x- and y-coordinates of the trajectory made by the writer on the surface tablet or in the air, sampled time, angle's pen orientation (azimuth and altitude angle) and pressure exerted by the pen while writing.

In some devices, there exists a button status considered as a binary variable assigning 0 for pen-ups (in-air trajectory) and 1 for pen-downs (on-surface trajectory). To make writing conditions familiar and natural to participants, most of studies prefer to fix a sheet of paper on the tablet surface and write with an inking pen [32]. Recently, this field of research have known a new technology called Biometric Smart Pen (BiSP) [62][63]. These smart pens are electronic multi-sensorics systems which record and analyze handwriting as well as hand and finger movements whether on a paper pad or in air. Position, acceleration, pressure while writing and fingers pressure while holding the pen are captured. It is worth noting that thanks to these technological devices, the analysis of online handwriting is quite simple and non-invasive, it can be done only in the patient's home.

(a) *(b)*

Figure 4: (a)-Digitizing tablet; (b)-Biometric Smart Pen (BiCP).

It should be noted that elderly people can be unusual with technological apparatus: Thus, in order to make writing conditions as close as possible to the familiar ones, an effective option is to let them write with an inking pen on a sheet of paper fixed to the digitizer tablet [32]. On the contrary to other diagnostic techniques, namely medical imaging, data acquisition through these apparatus can be done even in the patient's home; furthermore, the handwriting task performance is quite simple and natural, moreover does not need timing or intensive repetitions.

2.4.1.3. Proposed task

The judicious choice of writing tasks is a fundamental step in the development and implementation of a Diagnostic Aid System based on online handwriting. The choice of proposed tasks is not done randomly, on the contrary, the scientific committees responsible for the careful choice of protocols generally choose tasks ranging from the simplest to the most complex exercises. Some tasks concern writing, and others concern drawing. Some are repetitive tasks and others are reflection tasks. In general, handwriting tasks existing in the literature can be classified into three categories: simple drawing, simple handwriting and complex tasks. More details about these categories are described in the table 1. It should be noted that, some preliminary tests can be necessary before the execution of the handwriting tasks so that the participant can be familiarized with the equipment.

<u>Simple drawing</u>: In the literature, there exist a wide number of simple drawing exercises. The most used ones are the spirals, meanders and circles. These tasks are very simple and easy to perform. These exercises are usually studied for assessing and evaluating tremor by analyzing the handwritten dimension, trajectory, and velocity [63][18][64][26][33][18][65].

<u>Simple Writing:</u> In general simple writing tasks consist of either a letter combination or words. So, these tasks contain one or more cursive, continuous and repetitive letters, for instance "lll" or "lele" [62][80][9][70][68]. These easy exercises are often used in the literature given their simplicity and their ability to minimizes the language comprehension skills and efforts. According to R.Plamondon [81], the letters "e" and "l" consist of ascendant and descendent traits defined by their velocity strokes. According to the Delta-Lognormal Kinematic Theory [81] of the handwriting process which "*describes a stroke velocity profile as the output of a system made up of two neuromuscular systems, one agonist (acting in the direction of the movement) and the other antagonist (acting in the opposite direction)*", the "e" and the "l" letters are composed of two velocity strokes. Furthermore, the use of "e" as well as "l" means the handwriting of the same character scaled in amplitude. Besides, short words and sentences have been also extensively used (See table 1). Commonly, words and sentences adopted in these exercises are chosen based on their simplicity in handwriting as well as their easy syntax. Some studies adopted sentences containing a common "core", for instance "The leveler leveled all levels" [82].

This approach is adopted to find out how a frequent pattern changes with or without a suffix or a prefix. In some works, they have considered also the letter “g”, by including words and sentences with up and down traits [37]. In fact, writing a sentence composed of several different words requires an immense degree of movement planification and simultaneous processing of neuro-motor programming load than a simple sequence of identical pattern. A handwritten sentence allows to better assess the motor-planning ability between letters. Actually, a pause or an hesitation between letters or words could indicate the necessity to re-plan the handwriting activity, whereas a fluid handwriting manner can point out the existence of an anticipated motor planning. Indeed, a sentence offers the capturing of a large number of in-air movements between characters and words [37], contrariwise a word can be written without lifting the pen tip from the digitizer tablet.

Complex Writing: These handwriting tasks involve several functions namely cognitive, motor and functional ones. In fact, Van Gemmert et al. [82] show that the handwriting of PD patients is more deteriorated when it comes to a secondary task realization in comparison with elderly or young controls. In [35], authors combined between handwriting, hearing and counting in the same time. In the handwriting analysis, some studies working more on Alzheimer’s Disease (AD) than PD, as AD is mainly characterized by cognitive deficiency, adopting functional handwriting tasks. For instance copying the details of a bank check into convenient fields. In this case, the patient should be capable to read from the source place, locate the objective position and finally write the imposed content there. Some literature works used the Clock Drawing Test (CDT) [83]. CDT allows to detect visual-spatial deterioration. This task as well as many other complex exercises, implicate several neuro-psychological capacities: auditory perception and memory, abstraction ability, visual perception and memory, visual-space functions, programming and execution abilities. Moreover, in [72][71], authors studied the restraint on time duration as well as the stroke dimension, in addition to the adoption of the visual feedback in order to reach specific targets while writing [84],[6]. In [69], the verbal feedback by reminding patients to write in a bigger manner, has also been considered.

Table 1: Tasks type.

Tasks	Type	Reference
Simple Drawing	Spiral drawing	[66][65][64]
	Meanders drawing	[67][64]
	Circles	[66][65]
	Horizontal straight lines	[65]
Simple Writing	Repetitive cursive letters	[28][68][69][70][71]
	Simple words	[72][37][38][39][10][73]
	Writing own name	[74][37][38][39][10][73]
	Simple sentences	[32]
	Handwritten signature	[37][38][39][10][73][34][30][75]
Complex Tasks	Adapt the drawing size to a displayed input	[76]
	Time constraints and stroke dimension	[72][71]
	Drawing Loops while counting	[35]
	Filling an example of bank checks	[32]
	Copying a text composed of several lines	[41][42][77][78][79]

2.4.1.4. Used Dataset

Unfortunately, there is a very reduced number of available datasets to explore. In table 2 we represent a detailed description of each dataset.

The "PaHaW" dataset which is an abbreviation of "The Parkinson's Disease Handwriting" database, is constituted of several handwriting samples of 37 PD patients and 38 age and gender matched HCs. Participants whose native language is Czech, were asked to perform eight HW exercises following a specific template:

- Drawing an Archimedean spiral;
- Writing in a cursive manner the characters "l", "le", and "les";

- Writing in a cursive way the words: “lektorka” (“female teacher” in Czech), “porovnat” (“to compare” in Czech), and “nepopadnout” (“to not catch” in Czech);
- And finally writing in a cursive manner the sentence “Tramvaj dnes už nepojede” (“The tram won’t go today” in Czech).

The principal characteristics of the selected tasks is their simplicity in writing as well as their manner to be written without lifting the ink pen above the white paper overlaid on the digitizer tablet.

Besides, there exist an original dataset called “HandPD” that contains static (offline) handwriting tasks of PD patients and HCs. Nonetheless, this dataset was extended for the online analysis under the name of “NewHandPD” using the BiSP smart pen. It encompasses handwriting data from 66 participants (31 PD patients and 35 HCs). In this new dataset, participants were requested to draw 10 tasks containing: 4 drawings of spirals, 4 drawing of meanders, 2 circled movements (one circle in the air and another on the paper). Furthermore, the drawn spirals are scanned and studied as images.

The ParkinsonHW dataset contains the handwriting data of 15 HCs and 62 PD patients. It encompasses three categories of handwriting: Static Spiral Test (SST), Dynamic Spiral Test (DST), and Stability Test on Certain Point (STCP). The drawn spirals by participants are all scanned and provided as images. First, concerning the SST test, the participant was invited to retrace three Archimedes spirals which appeared on the digitizer tablet. However, regarding the DST test, the participant was forced to memorize the pattern of the Archimedes spiral and to continue drawing it, since the sample of the Archimedes spiral appear and disappear after a time stamps. As to the STCP task, in order to quantify the patient’s hand stability or tremor, a red point appears in the screen of the graphic tablet, and participants were required to hold the pen on the point without touching the surface. At the date of writing of this thesis, Castrillón et al. [86] are developing a wide set of Parkinsonian handwritten patterns, containing samples from elderly and young HCs. Unfortunately, most research has been conducted on reduced sets of PD patients and HCs.

Recently, the EMOTHAW (EMOtion recognition from HAndWriting and draWing) was developed to examine emotional states. This dataset does not include PD patients, but the used exercises are typically adopted in studies dedicated to PD [19], however, this database could be useful for comparison aims.

Table 2: Available Datasets (PD = Parkinson's Disease, HCs = Healthy Controls)

Dataset	Groups	Material	Tasks	Country	Reference
PaHaW	37PD – 38 HCs	Wacom Intuos 4M	Spiral drawing, repetition of characters.	Czech Republic	[37]
NewHandPD	31PD – 35 HCs	Biometric Smart Pen	Spiral and meander drawing.	Brazil	[63]
ParkinsonHW	62PD – 15 HCs	Wacom Cintiq 12WX	Spiral drawing and stability test.	Italy	[85]
EMOTHAW	129 HCs	Wacom Intuos 4	Copying of: pentagons, house drawing; writing four words; loop drawing; Clock Drawing Test; writing of a sentence	Italy	[19]

2.4.2. Feature Extraction and Methods

The raw handwriting data acquired by the digitizer apparatus are generally enhanced using the well-known signal pre-processing techniques: Starting by filtering, reducing noise and smoothing the signal. These standard algorithms can be applied, nevertheless their adoption could lead to the loss of crucial information. For instance, the normalization of the signal duration can be done in order to obtain all S(n) sequences of the same length, this technique is often adopted in the verification of signatures [87]. Nonetheless, in the handwriting analysis for the early detection of neurodegenerative diseases, it could result to the loss of important information. Sometimes this information can be a discriminative feature, and can associated to the time spent in performing the handwriting task by the participant. Based on this interpretation, it is familiar to skip the pre-processing steps [88].

The horizontal and vertical coordinates of the handwritten trajectory are recorded by the digital apparatus. Those components of handwriting are divided into two categories of sequences: 0n-surface and in-air movements, according to their pressure values and sometime to their button status.

In the literature, a stroke is defined as a single continuous and linked trait of the handwritten trajectory, which means the on surface pattern made between two successive pen-lifts. Based on these parameters given by the digitizer device, various features could be computed:

- Kinematic features: Horizontal, vertical and tangential velocity, acceleration, and jerk, number of changes in velocity (NCV), and number of changes in acceleration (NCA). NCV and NCA are computed respectively as the number local extrema of tangential velocity and acceleration. These features are computed for on-surface and in-air movements. Displacement parameter stands for the trajectory made between two consecutive points during handwriting. It gives an accurate approximation of the handwritten pattern. Indeed, based on this displacement parameter, the velocity, acceleration and jerk features can be derived respectively as the as the first, second, and third derivatives of displacement. Similarly, these features are computed for both horizontal and vertical directions.
- Mechanical features: Typically based on the pressure parameter, several features can be computed, namely: Mean pressure, number of changes in pressure vector (NCP) which means the number of local extrema of tangential pressure, and relative NCP [37].
- Spatiotemporal features: Encompass stroke duration, size, speed, height and width. In addition to on-surface and in-air time, and their normalization and ratio. Total time spent in the handwriting of the entire task is also calculated.
- Entropy and energy features: These type of features are recently used in the literature, and computed for on-surface and in-air strokes. They allow to capture the fine movements irregularities and deteriorations [38]. This category of features include: Shannon and Rényi entropy [89]; signal-to-noise ratio (SNR) [90]; and Empirical Mode Decomposition (EMD) [91]. Empirical Mode Decomposition divides in an iterative manner the handwritten signal into nominal Intrinsic Mode Functions (IMFs) [92],

which are functions that respond to two conditions: (1) the computed number of extrema and the number of zero crossings are either equal or differ by maximum one, and (2) the average of their upper and lower envelopes is equal to zero.

Generally, in order to accurately interpret the obtained values and results, for each feature vector, statistical functions are computed. Namely mean, standard deviation, kurtosis, skewness, median, mode, moments, percentiles, etc. It is worth mentioning that before the classification step, the feature vectors are normalized accordingly to have zero as mean and one as variance.

- Model-based features: In [95] authors used a different approach to study the handwriting changes, based on the Kinematic Theory of Rapid Human Movements [93][94], namely sigma-lognormal $\sum\Lambda$ model. This model is highly recommended, given its reliable results in several studies, such as the verification of online signature [96], and the detection of graphomotor abilities in children [97]. The major benefit of this novel approach is that it relies on a physiological model of the production of human movement which results a better characterization of the invisible handwriting specificities of writers.
- Automatically learned features: Based on deep learning models, some recent studies [98] used the convolutional neural networks in order to automatically extract features from static images retrieved through information of online handwriting.

In Table 3 represents a detailed description of the most used features in the literature. In conclusion, all categories of features have led to successful results, both directly measured through devices or derived from them. In fact, the categories of kinematic and spatiotemporal features are capable to detect if the handwriting is fluent or there exist some abnormalities in it. Features automatically extracted through deep learnings techniques provide, in general, relevant and non-redundant information. In a very recent study [41], for the first time, authors have used the pen inclination features, reporting promising results.

Table 3: Most generally adopted features, similarly computed for both on-surface and in-air movements.

Features	Description	Observation
Device parameters		
Position	(X,Y) coordinates of the handwritten pattern.	They are adopted to derive the geometrical trajectory of HW.
Time Stamp	Sampled time information of handwritten pattern.	It is adopted to compute the temporal duration of the handwriting task.
Pen Pressure	Pressure exerted on the surface device.	Pressure reveals irregular values in PD patients due to cognitive and motor abnormalities.
Azimuth angle	Angle between the pen and the surface plane.	They are used for the first time in [41], and appear to discriminate between PD patients and HCs.
Altitude angle	Angle between the pen and the plane vertical to the surface.	
Button status	Indicates whether the pen is on-surface or in-air.	Separating between on-surface and in-air strokes, it shows how the two HW modalities carry on nonredundant information.
Kinematic		
Displacement	Trajectory while writing.	Commonly used to derive other kinematic features.
Velocity	Change rate of displacement w.r.t. time.	PD patients do not write with the same fluency as HCs. In fact, they have lower HW velocity, with repeated acceleration peaks, and higher wrist jerk values.
Acceleration	Change rate of velocity w.r.t. time.	
Jerk	Change rate of acceleration w.r.t. time.	
NCV/NCA	Number of local extrema of velocity and acceleration respectively.	Allow to detect the fluidity of the HW movement. Fine automated movements are characterized by smooth velocity and acceleration profiles.
Spatio-temporal		
Stroke length	The size of strokes' path .	Patients suffering from PD can have micrographia.
Stroke height/width	Strokes' height and width.	
Stroke duration	Duration of movement per stroke.	The mean time duration of a PD patient is generally longer than in that of a HCs.
Time	Time duration spent on-surface and in-air while writing.	

Features	Description	Observation
Entropy and energy		
Entropy	Features computed through the Entropy.	These measures allow to capture the randomness and abnormalities of fine motor control.
SNR	Features computed through the signal-to-noise ratio.	
EMD	Features computed through the empirical mode decomposition.	
Model-based		
sigma − lognormal ∑Λ-based	Features of the ∑Λ reconstruction of the handwritten trajectory.	Investigating the dynamics of handwriting while producing the writing activity.
Automatically extracted		
Deep-learning models	Features automatically extracted by deep learning techniques trained on static images of the dynamic information of handwriting.	Provide relevant and non-redundant information.

2.4.3. Data Classification and Analysis

This section is partitioned into two categories of studies: First we discuss studies based on statistical analysis, and second focus on classification studies. Generally, this is the last step, and its goal is to discover effective patterns able to support decision making.

In Table 4 we represent the major results of the statistical studies conducted on PD patients' handwriting. Overall, we can conclude that PD patients suffer from irregularities in motor activities. It is clear in their reduction in amplitude and dimension of strokes in so called-on micrographia. They also undergo slowness of movements, tremor, bradykinesia, rigidity and akinesia. It is worth noting that tasks described in table 4 are classified in an increasing order according to their complexity. However, in recent times, all the studies concentrate on the development of reliable computer aid systems able to detect Parkinson's disease at an early stage, based on algorithms of machine learning and statistical pattern recognition techniques.

2.4.3.1. Approaches using statistical tests

Based on statistical analysis, most of the literature studies focused on the investigation of the handwriting changes due to aging. For instance, the ANOVA analysis of variance is commonly used to quantify the group differences through the use of different computed features of handwriting.

The first row in Table 4 concerns studies conducted on simple drawing exercises or simple writing of sentences. The main finding of the studies is that patients suffering from PD have slower movement than HCs. For instance, in [32] participants were invited to perform handwriting on a paper fixed on the tablet, by writing their names and copying an imposed address. Statistical measures were computed for each task namely mean pressure and speed, the spatial and temporal features were also computed for each handwriting stroke. The obtained findings were successful are shown that those two exercises are efficient to differentiate between handwriting of PD patients and that of HCs. In fact, PD patients are characterized by a reduced length, width and height of strokes, and slower speed. Similarly, the same results were obtained for the studies of the second row. For example, in [36] authors analyzed various works conducted on handwriting of PD patients. These studies were conducted on digitizer tablets or simply with ordinary pencil-and-paper measures, besides their results show that kinematic and spatio-temporal features are discriminant between PD patients and HCs. Indeed, Letanneux et al [36] specially found that kinematic features namely velocity discriminates not only between handwriting of PD patients and that of HCs, but also between PD patients on and off medication. However, they found that features computed on dimension of handwritten strokes are not very efficient in the differentiation between the two cognitive profiles. Furthermore, authors propose the term “PD dysgraphia” which signify that deteriorations due to Parkinson’s disease can alter the handwriting kinematics and fluency without necessarily altering handwriting dimension. Thus, it is clear to say that dynamic and kinematic features are appropriate for the diagnosis and monitoring of PD, and also for investigating the effectiveness of a given medication.

In the third row of table 4, we represent studies that found high tremor and jerk in handwriting of PD patients while drawing circles and lines in various orientations. As for [68], the authors invited participants to draw circles, spirals, lines, repeated letters "elelelel" and finally to write a sentence. Authors were particularly interested in recording pen tip pattern while performing the handwriting tasks. The findings reveal that these type of exercises provide unbiased measures for tremor and micrographia of PD patients.

Table 4: Representation of statistical studies conducted on handwriting of PD patients.

References	Tasks	Results
[32]; [33]; [34]; [74]; [6]; [102]; [103];	Drawing meanders, circles, and spirals. Writing Sentences and names. Copying task.	Slower movements.
[26]; [32]; [33]; [34]; [35]; [36];	Drawing loops. Writing Sentences and names. Copying task.	Reduced size.
[33]; [68]; [82]; [103]; [104];	Drawing meanders, horizontal, straight forward and backward slanted lines, circles. Writing sentence.	High tremor and jerk in PD patients.
[69]; [84];	Drawing figure and writing "llll".	Visual feedback is important to PD patients in order to increase their stroke size.
[84]; [102];	Drawing figure. Drawing while adjusting the size based on visual information. Writing "llll" beneath different dimension and time conditions.	PD patient are barely able than HCs to adjust the dimension of their writing.
[25]; [27]; [28]; [29]; [30];	Drawing circles before and after treatment. Writing "llll", "eeee" and sentence before and after the treatment .	Treatment reduces main PD handwriting degradations.
[31];	Writing under visual and auditory feedback.	Training on writing a specific task can help PD patients to increase their handwriting size.

In addition, the visual feedback of handwriting is very helpful for PD patients to increase their stroke dimension as reported by Oliveira et al. [69] and Fucetola and Smith [84]. These studies which are the subject of the fourth line in table 4, asked their participants to draw a figure or to write “llll”. Although, it is worth noting that PD patients still less capable to adjust the dimension of their writing in comparison with HCs as described by Van Gemmert et al. [102] and Fucetola and Smith [84] (See the fifth row of table 4).

Concerning studies classified in the sixth row of table 4, they involve tasks conducted on PD patients before and after treatment. The participants were invited to draw circles and write “lll” and “eeee”. The main findings show that, thanks to medication, the handwriting alterations of PD patients are reduced and stabilized.

Finally, in the last row of table 4, Ziliotto et al. show that training on writing with visual and auditory feedback helps PD patients to stabilize and increase their handwriting dimension.

2.4.3.2. Approaches using classification

In recent times, all the studies concentrate on the development of reliable computer aid systems able to detect Parkinson’s disease at an early stage, based on algorithms of machine learning and statistical pattern recognition techniques [99]. A noticeable contribution to the use of machine learning algorithms to the automatic discrimination between PD patients and HCs was done by Drotár et al. Indeed, Drotár et al. propose a new PD on line handwriting dataset, containing handwriting data of both PD patients and HCs. Authors conducted several studies and experiments on their own dataset. This dataset contains drawing and writing tasks namely Archimedean spiral, repetitively writing simple syllables and words, and writing of a sentence. In fact, all their research works were conducted on this same dataset, i.e., PaHaW, which they made freely available. For example, in [37], in order to detect differences between PD patients and HCs, researchers used three classifiers: k-Nearest Neighbours (K-NN), AdaBoost and support vector machines (SVM), and found that SVM which was the best performing one. Authors adopted new features based on the pressure applied over the writing surface. The principal features computed through pressure vector, were the mean value of pressure exerted on the surface tablet while writing and the rate of pressure changes w.r.t time.

Based on the correlation coefficients, authors study the relationship between pressure and kinematic computed features.

Similarly, in another study, Drotár et al. propose in [38] new features in addition to the standard kinematic handwriting features. These new proposed features encompass entropy, signal energy, and empirical mode decomposition of the handwritten signals. In fact, it is shown that these novel measures can help at understanding the data. These features were computed only for on-surface strokes. The authors used two supervised learning classifiers namely support vector machines (SVM) and Naïve Bayes [38] trained on kinematic and spatiotemporal features. They found that SVM gave the best accuracy values in comparison with other standard approaches. These same authors, propose in [6] to compare the prediction potential of classifiers models trained on each task individually, then they trained the same classifiers by combining all tasks together. The findings show that the best accuracy was achieved by the fusion of all tasks. However, in [40] Drotár et al. sought to know to what extent classification performance can be ameliorated by taking into account on-surface movements and in the air movements, knowing that the two modalities seem to relate to non-redundant information. Accordingly, they found that in-air movements hide precious information than on-surface movements. These results were also confirmed in [39] by using several feature selection techniques.

It is worth noting that, the spiral task adopted by Drotár et al. did not achieve significant accuracy classification rate. This problem could be due to the adoption of measures dedicated only for handwriting. Alternately, using deep learning algorithms [12] [105] could help to overcome this problem by providing new features.

In a study proposed by Rosenblum et al. [32], participants were invited to write their name and copy an imposed address in a specific target. Based on the standard computed features of handwriting, they found that compared to HCs, PD patients have a reduced size stoke, exert less pressure, and need more time duration. Indeed, these computed features can help to accurately detect PD patients and HCs. Besides, Rosenblum et al. were interested to study the importance of in air movements merged with on-surface movements, given that these two modalities contain non-redundant information. As reported by the authors, in-air time express the action of planning the next movement, which can clearly give a sight of the cognitive capacities of the writer.

Some studies however used the technology of the electronic biosensor BiSP smart pen, such as Ünlü et al. [17]. Relying on the pressure information given by BiSP pen and the recorded tremor, authors obtained an 0.933 of area under the ROC curve. They showed that tremor is controlled while writing more than the pen tilt, that is to say that PD patients control their tremor while they are in movement better than permanent pressure.

Another study in Reference [63], used also the electronic biosensor BiSP smart pen. Pereira et al. proposed a dataset called "NewHandPD", consisting of handwriting data collected using the BiSP. This dataset compasses drawings of spirals and meanders. Each sensor of the used device provides the entire signal captured while performing the handwriting tasks sampled point by point; thus, it can be described subsequently as a time series. Pereira et al. adopted Convolutional Neural Network CNNs and meta-heuristic-based optimization algorithms to tune up the optimized network hyper-parameters considering their high capacity to learn without human intervention. Therefore, the major contribution of this study is the application of a deep learning-oriented approach to facilitate the diagnosis of PD as well as the design of a signal-based dataset. Similarly, in references [98][106], authors have extended the main finding of the previous study. In [106] CNNs were adopted to extract and learn features precisely from time-series-based images. Authors supposed that the texture-oriented features are capable to detect the tremors all along handwriting. Besides, in reference [98], authors used the recurrence plot technique in order to map the signals provided by the pen into static image domain. Then, these images are exploited to assign a CNN how to extract and lean relevant features.

In fact, a repetitive plot allows to visualize recurrent events of high dimensions by their projection on low-dimensional representations. Authors in [64] conducted a study on drawing Archimedes spiral in order to early detect and diagnose PD. San Luciano et al. found that in general, spatio-temporal features are significantly discriminant between PD patients and HCs. Unlike Drotár et al., San Luciano et al. showed that spiral task seem to be a pertinent quantitative biomarker for the early detection and diagnose of PD.

In [104], Kotsavasiloglou et al. invited their participants to draw a straight horizontal line on the digitizer tablet surface, while managing the pen's velocity as regular as possible. In fact, the authors proposed a new measure by normalizing the velocity variability. This new metric allow to quantify the variability of the pen speed while writing. Authors obtained a good classification accuracy using Bayesian classifier. It is worth mentioning that even if it is a simple drawing task, it gave the possibility to accurately detect differences between the two studied cognitive profiles, because the deficiency manifests itself independently of the complexity of the task. All of the previous studies considered the PD patients group as a single cluster having the same stage of the disease and sharing the same degree of its severity. In other words, they typically adopted the binary classification by discrimination HCs vs PD patients. In this context, Zham et al. investigated the relationship between computed features on the spiral drawing and the severity of the disease. In particular, they studied the correlation between speed, pressure and the disease severity. As a result, they found a strong correlation by merging the two features, in consequence, they found accurate differences between early and advanced stage of the disease. Unfortunately, this approach was not capable to find differences between low and medium or medium and high level of the disease. Promising results were found in [75], by using angular features and number of direction changes while drawing the spiral.

Impedovo et al. have also investigated this issue [107]. They applied a classification study on the PaHaW dataset, concentrating only on low and medium degree of the PD severity. They show that the performances of the supervised learning techniques significantly decrease when they use this subgroup, rather than using all the PD patients acquired in the dataset which have more severe stages. Another contribution of this work, is the combination of the different tasks altogether, by merging the features computed on each task into one unique high dimensional feature vector.

Several studies investigate the efficiency of deep learning techniques [12][100] given they automatic and accurate extraction of features. Generally, they use convolutional neural networks to feed the connected layers or only the standard classifiers. Unfortunately all the existing databases are small, however, various resampling methods are used to reach better and reliable performances of classification, namely the cross-validation technique and leave-one-out approach[101].

Similarly, Gallicchio et al. [95] adopted the application of deep learning techniques to early detect PD through on line handwriting by employing neural networks. These deep learning techniques were adopted in order to automatically extract relevant features without the human intervention from handwriting data of the ParkinsonHW dataset [108]. Successful results are reported in [108], where Mucha et al. suggest a new approach for computing kinematic features of PD patients relying on fractional derivatives of arbitrary order.

Authors in [109] improved the findings on the PaHaW dataset [38] by merging new features computed to velocity-based features with the classic ones. These features are computed through sigma-lognormal model, the Maxwell–Boltzmann distribution, and the Discrete Fourier Transform.

Similarly to the obtained results in [32][39], Jerkovic et al. [110] show that in air and on surface strokes contain relevant and non-redundant information. Indeed, the best achieved accuracy resulted by merging both in-air and on-surface features.

In [111], Loconsole et al. used new features computed on the gyroscope signal provided by the digitizer tablet. Regrettably, they used a very small number of participants.

In another study, authors propose to compute geometrical and nonlinear dynamic features combined to standard kinematic features [112]. Rios-Urrego et al. aim at finding the abnormalities and irregularities of handwriting, which generally increase as the disease advances.

Besides, Diaz et al. [12] introduced a new "dynamically enhanced" representation of handwriting consisting of artificially generating images by exploiting at the same time static and dynamic properties of handwriting. Particularly, authors propose a static description that merge dynamic information relying on drawing points of the pattern, rather than linking them, in order to extract spatio-temporal and kinematic information with its relative pen-ups. This novel approach outperformed the findings already obtained by separating static from dynamic handwriting on the PaHaW database.

Ribeiro et al. [100] concentrated on the investigation of tremor as it is the most commonly symptom of PD. Specifically, they introduce to study the temporal information from time signals acquired from handwriting tasks based on the gated recurrent units included in neural network architectures. Besides, authors also proposed the novel concept of "bag of samplings" as a representation of handwriting signals.

Finally, in Reference [41], Ammour et al. aim to use a clustering algorithm in order to analyze the intervention of several factors in the characterization of PD patients and HCs. These qualitative factors are: age, intellectual level, frequency of writing per week. Next, they used a semi-supervised approach on an Arabic imposed text. Authors computed the standard features in addition to new features calculated on pen inclination based on the azimuth and altitude angles provided by the digitizer tablet. The findings show three clusters: First cluster contains only PD patients, second one with mostly HCs, and the third one is a mixture between HCs with medium intellectual education level and PD patients with high intellectual level and writing frequency. This result indicates that education level may act as a resilience factor against the deterioration caused by neurodegeneration [58].

2.5. Future directions

All of these previous studies have confirmed that Parkinson's disease has a major impact on the deterioration of handwriting's components. In addition, the realization of a Diagnosis Aid System (DAS) based on online handwriting involves an interaction between several technical aspects related to the choice of exercises, the choice of relevant parameters, the choice of methods of features selection, and classification. However, there are some other demographic, educational and medical factors related to the patient that can have a significant impact on the handwriting process. All of these factors must be taken into consideration while processing and analyzing manuscripts. The estimation of the degree of influence pertinent to these factors in presence of the disease could contribute effectively to improve the envisaged DAS's performances. Currently, none of the previous studies has provided any metadata for such an analysis [16]. Moreover, the extraction of the discriminant information may also depend on the graphic characteristics of the writing which vary according to the country and the language. Related works conducted on Parkinson's disease were particularly concerned with the Latin languages, and have only focused on words or sentences. Nevertheless, according to our own research, there exists no study that was done on the Arabic language. Moreover, this is the first study to deal with the analysis of a text composed of several lines. In fact, the Arabic has a cursive script that is written horizontally from right to left. Vocalization is one of the unique characteristics of this language which applies short vowels to the letters.

Hence, one of the originalities of this thesis is that it aims to analyze and characterize the Arabic handwriting of Moroccan Parkinson's disease patients and healthy controls using qualitative and quantitative parameters.

First, based on an unsupervised learning, we propose to analyze all types of factors that can intervene in the characterization of the Moroccan population from the most relevant handwriting's descriptors. The generated subpopulations are characterized based on the set of selected features of each category, the cognitive profile, the age, the intellectual level as well as the frequency of writing per week. Thus, it becomes possible via a clustering approach to distinguish the aspects of deterioration of handwriting pertaining to these factors and to those of pathological conditions.

Secondly, we propose to analyze in a global way the handwriting of PD patients and that of healthy controls. Based on a set of computed features on the imposed text, we were able to find a subset of selected handwriting features suitable for efficiently identifying subjects with PD. The obtained results show almost 80% overall classification accuracy.

Moreover, we were interested to study the imposed text more deeply, in a semi-global way, in order to analyze and evaluate the full dynamic handwriting degradation that can be more noticeable during the time task execution. Thus, we propose a novel method to detect Parkinson's disease, based on the segmentation of the online handwritten text into lines. Indeed, we propose to compare Parkinson's disease patients and healthy controls, based on the full dynamics of new temporal and spectral features.

One of this thesis's originality is the calculation of new features based on the combination of temporal and spectral signal processing techniques specifically Discrete Wavelet Transform, Butter filter and Adaptive filter. To our own knowledge, this is the first study to deal with the segmentation of the manuscript text into lines. Our proposed method takes into consideration the handwriting specificities and aspects related to each scripter of all participants. The analysis carried out in this study mainly concern the text before segmentation, the first line and the last line. Passing from one line to another, this novel approach will give us the ability to study the HW degradation reflecting pathology fatigue. In fact, PD patients undergo a significant fatigue which directly influences their writings during the execution of the HW task [16]. Our work has led us to conclude that the last line has significant discrimination power in comparison with other lines.

In summary, our approach addresses some limitations of the literature, as follows:

- **At the level of the studied language:** This is the first study to deal with the Arabic language. Most of the studies in the literature concerned mainly the Latin languages.
- **At the level of the studied task:** All the studies in the literature have only focused on words or sentences. Nevertheless, this is the first study to deal with the analysis of a text composed of several lines.
- **At the level of the characterization of the studied population:** This is the first study which is based on the combination of qualitative and quantitative parameters for the characterization of the studied population, namely the Moroccan population.
- **At the level of the extraction of parameters:** We propose in this study a new categories of parameters to analyze the handwriting of PD patients and that of healthy controls by combining temporal and spectral features.
- **At the level of the fatigue detection:** The aim of the proposed segmentation method, is to study and compare the text task before and after line segmentation, in order to evaluate the full dynamic handwriting degradation that can be more noticeable during the time task execution. Passing from one line to another, this novel approach gave us the ability to study the HW degradation reflecting pathology fatigue, which is more noticeable in the last line of the handwritten text.

2.6. Conclusion

In conclusion, the field of handwriting analysis in order to diagnose Parkinson’s disease has experienced a plethora transformation after the introduction of kinematic and spatio-temporal analysis using the technology of digitizing tablets and smart pens BiSP.

Overall, on line handwriting can be considered as a good biomarker for the monitoring of PD. This chapter aimed at providing a clear overview of the various studies conducted on handwriting analysis in order to develop an early and reliable diagnosis aid system capable of monitoring and assessing PD, starting by handwriting data acquisition, feature extraction and data analysis and classification. The main findings to retain are: PD patients undergo several irregularities and abnormalities in their handwriting such as micrographia, jerking and slow movements.

Besides, we give a sight on the still opening issues in this research field that need to be addressed, because even if all the presented studies have proved the efficiency of online handwriting in the assessment of PD, they still confront various challenges.

For instance, the protocol definition is an open problem that requires to be investigated. Researches should find which task can be more accurate to discriminate at best between PD patients and HCs.

3. Chapter 3: Online Handwriting Acquisition and Moroccan Database Construction

3.1. Introduction

In the literature, several studies were conducted on the analysis of online handwriting in order to detect neurodegenerative pathologies. These studies mainly concerned Latin languages. To our own knowledge, there is no public database available on the Arabic language. Our project particularly concerns a bilingual Moroccan population, whose mother tongue is Arabic. In order to carry out this work, we proceeded with the acquisition and construction of our own online handwriting database.

Data acquisition is done within the neurological department of the Hassan II Hospital Center in Fez. The whole team showed their motivation to take up the challenge and look for new intelligent and innovative diagnostic tool for the early detection of neurodegenerative pathologies based on the analysis of online handwriting for the Moroccan population.

The ENEMAR project (**É**tude **N**eurologique de l'**É**criture des **MAR**ocains) concerns neurodegenerative pathologies, namely Parkinson's, Alzheimer's and mild cognitive disorders. As part of this project, three modalities are acquired: Online handwriting, speech and gait. This thesis focuses specifically on online Arabic handwriting for patients with Parkinson's disease.

The purpose of this chapter is to describe exhaustively the proposed protocol, then the current data acquisition phase, precisely carried out on the Moroccan population.

The inclusion and exclusion criteria, the used equipment, the proposed handwriting tasks as well as the data acquired are detailly represented.

3.2. Target population

The ENEMAR project targets four categories of cognitive profiles:

- **"Parkinson Disease: PD" group:** This category includes patients with Parkinson's disease (PD). To quantify the progression of Parkinson's disease and the effectiveness of treatment, all patients were diagnosed on the basis of the Unified Parkinson's Disease Rating Scale (UPDRS) [113]. The cognitive state of each patient is assessed through a complete neuropsychological assessment. Thus, to particularly assess one's cognitive and mental level, an MMSE (Mini-Mental State Examination) test is used.

- **"Alzheimer Disease: AD" group:** This group includes patients with Alzheimer's Disease (AD). These patients are diagnosed by a geriatrician or a neurologist based on the criteria of *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DMS-IV or V) [DSM-IV, DSM- V][114].
- **"Mild Cognitive Impairment: MCI" group:** This group is formed by patients who have been diagnosed with MCI by a geriatrician or a neurologist based on Petersen criteria[76].
- **"Healthy Controls : HC" group**: This last group is made up of people who have carried out a complete neuropsychological assessment to ensure that they have a normal cognitive profile.

The UPDRS is a scale which allows a general analysis of the patient's situation and the evolution of his symptoms. This assessment provides a complete and flexible tool for monitoring the progression of Parkinson's disease and the patient's level of autonomy loss.

The MMSE is a global cognitive assessment test. It consists of a 30-point questionnaire including questions to assess skills of: spatiotemporal orientation; attention and calculation; learning and information transcription; language and identification; and constructive praxis (the ability to organize a series of movements for a specific purpose by reproducing geometric shapes).

3.3. Inclusion and exclusion criteria

For the recruitment of participants, we have defined inclusion and non-inclusion criteria, and obviously each participant must sign a consent form to participate in the study, among these criteria:

<u>Inclusion criteria:</u>

- Agree to participate freely in the study by signing a consent form.
- To be a patient followed by neurological consultation at UHC HASSAN II Fez.
- All patients have had a complete cognitive assessment allowing them to be included or excluded from the study. Criteria for inclusion by group:

– Group1: Healthy Controls with normal cognitive functioning, MMSE (Mini Mental State Examination: Scale measuring the level of cognitive degradation) superior to 27.

– Group2: Parkinson’s patients, MMSE between 20 and 25, UPDRS motor scale, complete neuropsychological assessment.

– Group3: Alzheimer's patients starting with MMSE upper or equal to 20.

– Group4: Patients with Mild Cognitive Impairment (MCI), Petersen criterion.

<u>Exclusion criteria:</u>

- Patients with visual or hearing problems that prevent them from performing the tasks properly.
- Anyone excluded by the MMSE test for reasons such as head trauma, stroke, or other.
- Subjects under guardianship or trusteeship.

Volunteers are invited to reproduce written material according to a predefined protocol in Arabic and French [66]. Data is collected anonymously and confidentially, and all participants have the right to withdraw from the study at any time.

3.4. Materials

The manuscript is acquired using the "WACOM Intuos Pro Large with creative pen" graphics tablet (See figure 5). This tablet is capable of detecting 2048 levels of pressure sensitivity and makes it possible to record and digitize over time the trajectory of the writer on surface and in air, up to 1.5 cm above the tablet. The corresponding manuscript signal associates with each point of the trajectory a sequence of six numerical values (T[n], X[n], Y[n], P[n], ϴ[n], Φ[n]) which represent, respectively, the time, the kinematic positions in X, in Y, the pressure of the pen, the altitude and the azimuth of the pen (See figure 6). A sheet of paper is placed on the tablet to allow visual feedback of the produced trajectory by using the Wacom inking pen. The pen layout is sampled at a frequency of 125 Hz. The tablet's spatial resolution is 5080 pixel / inch (dpi).

Figure 5: Wacom Intuos Pro Large Creative Pen Tablet.

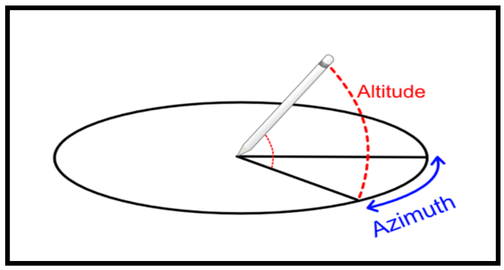


Figure 6: Azimuth and Altitude angles of the pen.

This Wacom Intuos Pro Large tablet is connected to a PC DELL PRECISION M6800 during the acquisition. However, it also offers the possibility of connecting via Bluetooth to a PC. The interface which made it possible to acquire the data was developed in Java within our laboratory. All calculations were made on Matlab 9.3.0 (R2017b) installed on a MacBook Pro using the macOS Sierra operating system version 10.12.6 (16G2136), with a 2.8 GHz speed processor Intel Core i7, and a 8 GB RAM.

3.5. Proposed tasks

The complete assessment of a participant takes on average 90 minutes: One hour to perform a neuropsychological assessment (see Annex), and 30 minutes to acquire the handwriting data. All participants are reviewed twice if they agree. The first visit takes place in month M_0, the second in month M_{12} (12 months later) to re-acquire their handwriting data according to the same protocol. Those data will allow us to make a longitudinal study during the continuation of the ENEMAR project.

It should be noted that the work of this thesis was carried out on the data acquired during the first M_0 Session (cross-sectional study).

The sheet (Figure 7) representing the different proposed exercises is placed on the tablet for acquisition. Acquiring handwriting involves performing three tasks in Arabic, three tasks in French and four drawing tasks.

The writing tasks in order are :

1. Imposed Arabic text **(Task 1);**
2. Free Arabic text **(Task 2);**
3. Four cursive and continuous series of Arabic letters **'صصصص' (Task 3);**
4. Back and forth between two square for 15 seconds **(Task 4);**
5. Draw circles on the circumference of a circle for 15 seconds **(Task 5);**
6. Spiral Archimedes **(Task 6);**
7. Place the pen in the center of a cross mark for 15 seconds **(Task 7);**
8. Imposed French text **(Task 8);**
9. Free French text **(Task 9);**
10. Four cursive and continuous series of loops *'llll'* **(Task 10).**

The team has also established a protocol dedicated to the illiterate population.

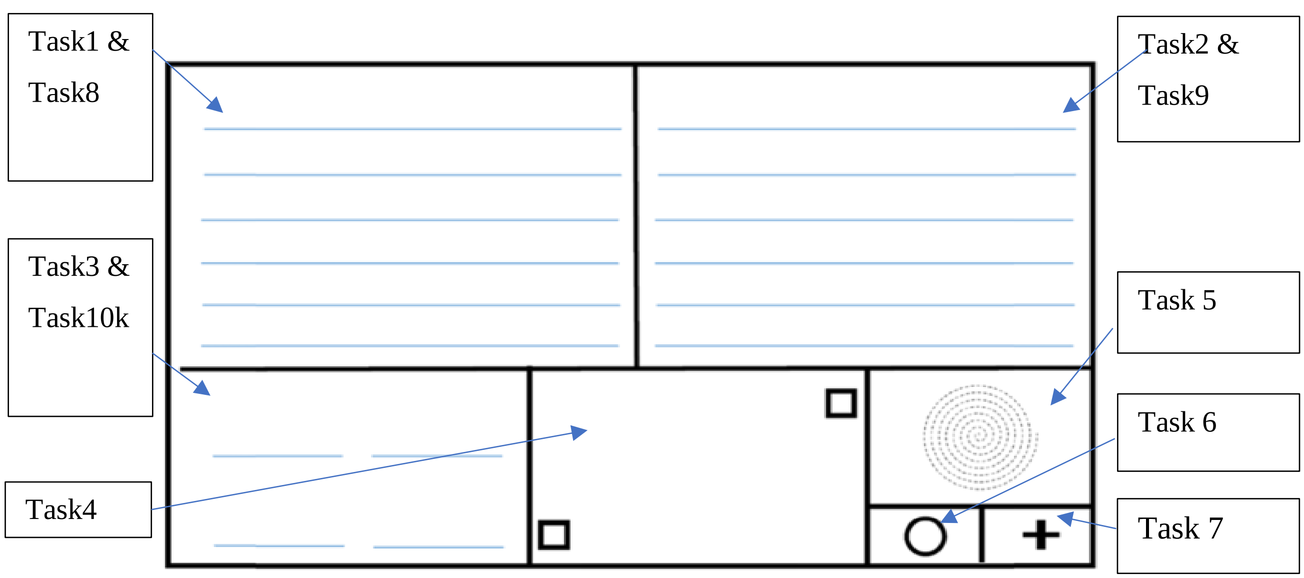


Figure 7: Acquisition sheet.

In tables 5 and 6, we represent the mean task durations of each exercise.

Table 5: Writing tasks durations.

	Arabic writing tasks			French writing tasks		
Task	Imposed Arabic text (Task 1)	Free Arabic text (Task 2)	Four series of letter ص (Task 3)	Imposed French text (Task 8)	Free French text (Task 9)	Four series of letter (Task 10)
Estimated duration	5mn	7mn	30s	5mn	7mn	30s
The durations of the writing tasks are not limited (values given are estimated approximated)						

Table 6: Drawing tasks durations.

	Drawing tasks			
Task	Back and forth Between two squares. (Task 4)	Circles superimposed. (Task 5)	Spiral Archimedes. (Task 6)	Place the pen in the center of a cross mark. (Task 7)
Limited duration	15s	15s	Estimated 30s	15s
The durations of the drawing tasks are imposed (Expect for Task 6).				

3.6. First meeting with the participant

During the first meeting with the participant, we follow a number of instructions and guidelines:

1. Explain the aim of the study and the investment that it requires of the participant.

2. Present the consent form to the participant and explain how to complete it (give each step if necessary) and sign it. Specify in all cases orally that:

- The data collected will be treated anonymously.
- Participants have the right to withdraw from the study at any time.
- His decision (accept or refuse) will not change his relationship with the hospital or the care provided by our service.
- He may have access to the total or personal data collected during the study.

3. Enter the participant's metadata on the software interface, starting with giving him an anonymous identifier consisting of an indicator of the linguistic profile followed by the first 2 letters of the name and then the first 2 letters of the first name, followed by his date of birth by separating the fields by line. Metadata is collected during an interview during the inclusion or the first evaluation visit. This interview will include the collection of demographic and medical data when it comes to a healthy control participant (not followed up in the hospital). For those followed in the hospital, metadata will be entered from the medical file. The interview must also include the collection of data concerning the languages used by the participant in order to determine the exercises corresponding to their linguistic profile.

NB: The linguistic profiles taken into consideration are as follows:

1. Arabic only.
2. French only.
3. Bilingual.
4. Illiterate.

4. If the participant is a healthy control participant, a self-questionnaire of "The Geriatric Depression Scale (GDS)" is used. The form must be introduced to the participant in the following manner while adapting it to their language:

“ I'm going to give you a quiz about your emotional state right now.

- Please fill it out as honestly as possible.

- There will be neither right nor wrong answers. For each sentence you must indicate whether it applies to your current situation or not. It may be that for some questions you have the feeling of being in the middle (neither yes or no). I advise you not to spend too much time thinking about the answer, generally it is the first answer that passes by your mind that will best match your current state.”

5. If the person is a healthy control, ask them if they would agree to perform a cognitive assessment. If this is the case, take his contact details, make an appointment for him to do so, preferably on a date of his choice. This should be introduced as follows:

“In this study we would like to analyze the way in which writing is associated with cognitive functions, i.e.: memory, language, and attention. Thus, a cognitive assessment is used. For hospital patients, this assessment is carried out as part of medical monitoring.

To those who are not followed in the hospital, we suggest that they carry out a completely free assessment. If you want, you can receive an oral feedback of the results at the end of the assessment. If the neuropsychologist identifies something abnormal, he will notify you. In all cases the results of this evaluation will be used anonymously. Would you agree to perform this cognitive assessment? ”

- If the participant accepts: “You should know that the assessment lasts about 1 hour, and if you do not live very far I suggest that you schedule an appointment to carry out the cognitive assessment. Otherwise we can see if the neuropsychologist is available immediately.”

- If the neuropsychologist is not available, make an appointment and / or suggest that the neuropsychologist call him in the coming days to arrange a new appointment.

6. Presentation of the equipment to be used.

7. Tell the person that he will have a series of exercises to do, which you will present to him as you go along, always in the same order as defined below.

3.7. Instructions given to perform the first studied task

Before acquiring the data, the participant fills out and signs the consent form placed on the Wacom Tablet with the appropriate stylus.

Task 1: Ask the person to copy on the left side of the acquisition sheet (See Figure7), a short story from Joha's adventures (imposed text). This imposed text is composed of 6 lines, 36 words, 201 characters (See Figure 8).

مَشَى جُحَا فِي الطَّرِيقِ، فَدَخَلَتْ فِي رِجْلِهِ شَوْكَةٌ فَآلَمَتْهُ
فَلَمَّا ذَهَبَ إِلَى بَيْتِهِ أَخْرَجَهَا، وقَالَ الْحَمْدُ لله
فقالت زوجته على أي شيء تحمد الله؟ قال أحمده على
أنني لم أكن لابسا حذائي الجديد وإلا خرقته الشوكة

Figure 8: Arabic imposed text.

The imposed text **(Task 1)** extracted from the story "Joha" was chosen because it is a simple text, without a significant syntactic and grammatical complexity. In addition, the text is not tragic things (which could destabilize the participant). Our work does not focus on the syntactic and grammatical levels of the text but on the analysis of graphics. This text was also chosen because its handwritten version contains a lot of shafts and legs, which some patients with fine motor skills have trouble performing [7]. In our own knowledge, the exercise of copying an imposed text has never been studied before for the analysis of the Arabic on line handwriting in order to detect Parkinson's Disease. On the other hand, it has been used in Alzheimer's Disease [88] using an Hebrew imposed text composed of 107 characters.

3.8. Presentation of acquired data

To date, we have acquired handwriting data from 202 people. Among them, there are 137 healthy controls, 42 Parkinson's disease patients, 16 Alzheimer's disease (AD) patients and 7 patients with Mild Cognitive Impairment (MCI).

In figure 9 we represent in camembert the percentage of women and men, and it shows that 5% of the acquired population are left-handed and 95% of it are right-handed.

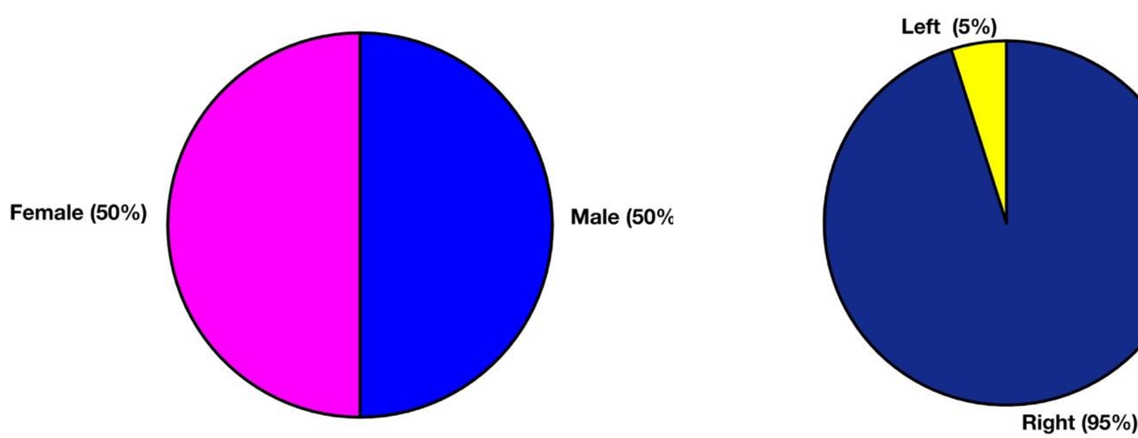


Figure 9 : Camembert representation of population's gender and handedness.

The distribution of these different data according to the cognitive profile of the participants is presented in Figure 10.

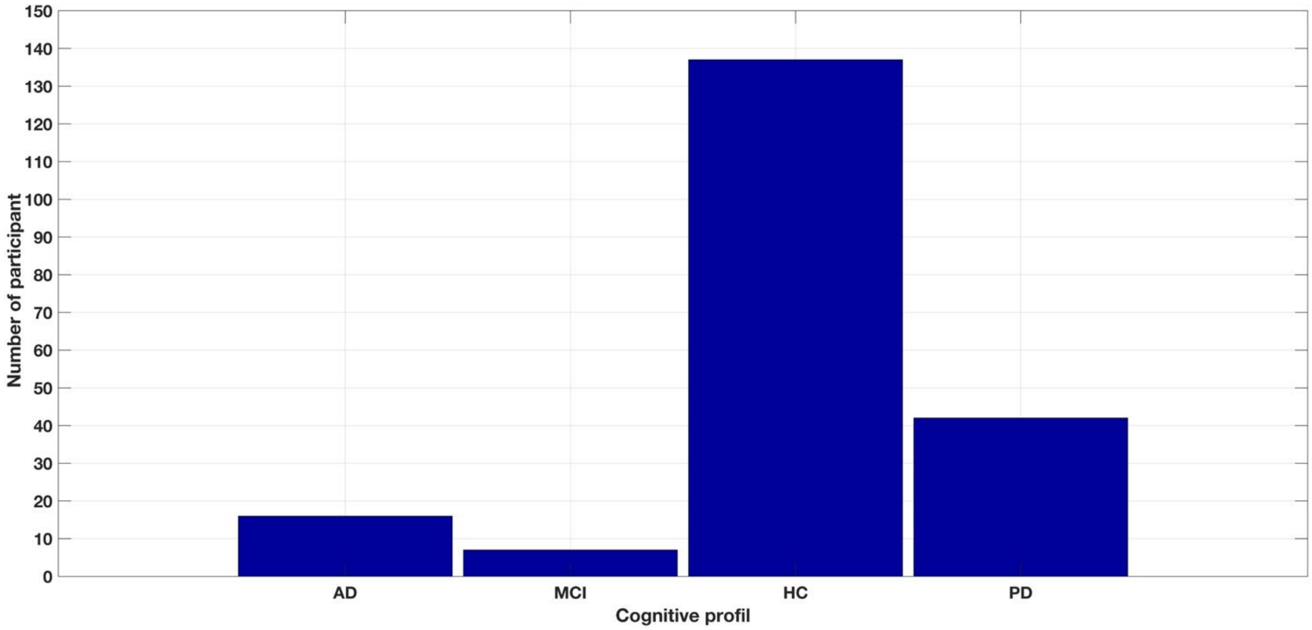


Figure 10: : Histogram of participants' number according to their cognitive profile.

The signification of each label is as follows:

- AD: Patients with Alzheimer's disease;
- MCI: Patients with mild cognitive impairment;
- HC: People with a normal cognitive profile following a neuropsychological assessment;
- PD: Patients with Parkinson's disease.

Table 7 shows the exact number of different people according to their cognitive profile.

Table 7: Exact distribution of the different cognitive profiles.

Cognitive profile	Number of persons
AD	16
MCI	7
PD	42
HC	137

The age distribution of participants according to cognitive profiles is given in Figure

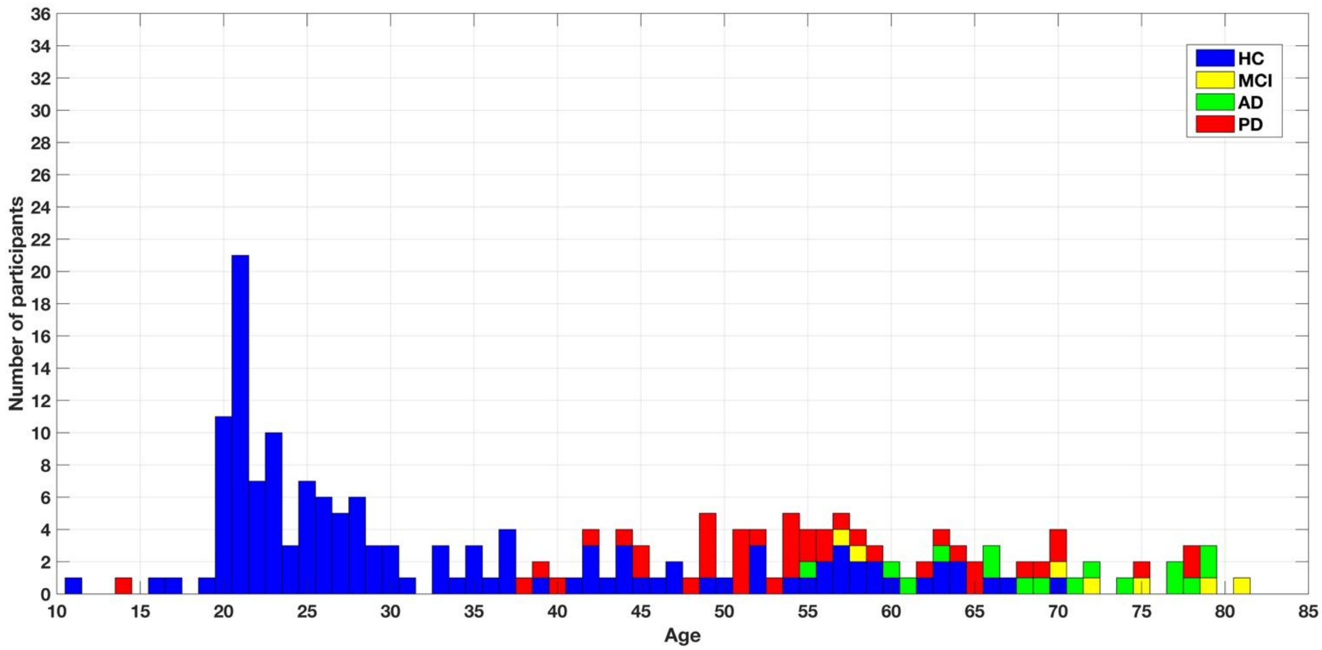


Figure 11: Age distribution of participants according to cognitive profiles.

11.

3.9. Conclusion

In this chapter, we have presented the statistics of the acquired handwriting data as well as the whole procedure from the recruitment of the participants to the acquisition of the data. After a selection of subjects according to the different inclusion criteria.

4. Chapter 4: Clustering And Unsupervised Learning For The Characterization Of Arabic Online Handwriting

4.1. Introduction

Handwriting (HW) is a complex activity requiring fine motor control, it is characterized by a major involvement of muscles and brain, and touches the deepest mechanisms of cognition and sensorimotor. The HW alteration is mostly due to neurodegenerative diseases such as Alzheimer [18][115][116], and Parkinson's Disease (PD) [38][73][79][88].

In fact, HW is a conventional and fine activity that requires learning, which can be different from one country to another, from one culture to another, and obviously from one language to another. The handwriting can be degraded with the age, the physical and mental state of the writer and according to the linguistic context or the task performed: Drafts, personal notes, private or official letters, thus the handwritten trace takes several different aspects.

The analysis of this handwritten trace is necessary and important to see how it changes or deteriorates through age, culture, language, and pathology. Moreover, several studies have been done on HW to develop a simple and early diagnosis of neurodegenerative pathologies. As a result, HW analysis has become a new and promising field of exploration for health researchers, especially in neurosciences. Starting from the fact that some changes in HW resulting from an irregular movement can be evocative of a disease. A degraded handwritten text could bring considerable diagnostic information on its author.

The real time acquisition of the HW from a digital tablet is called online handwriting. It allows to extract kinematic and spatio-temporal features while writing.

Based on a set of wisely elaborate HW exercises, the majority of the research studies conducted on this subject, have statistically proven that a strong relationship exists between the degradation of HW and neurodegenerative pathologies [20][32][39][105][117][118][119][120]. Thus, the early detection of these diseases based on online HW could be useful for helping to detect and control the progression of these pathologies.

In this paper we present a study that was conducted on online HW of PD patients. In fact, PD is a progressive nervous system disorder that affects movement. This disease results in a slow and progressive destruction of dopaminergic neurons [121][122]. The motor symptoms of this pathology are tremors, muscle rigidity, impossibility or slowing of movements, as well as the intellectual impairment symptoms such as deterioration of memory, hesitation, lack of attention[122]. The average age of onset of the disease is between 55 and 65 years, but there are early forms that begin around age 40, and late forms that begin after age 75.

4.2. Methods

4.2.1. Handwriting Acquisition Protocol

The HW acquisition is done in the neurology department at the UHC Fez. First, the participant sign freely a consent form before the execution of handwriting's tasks. For participants' recruitment, an inclusion and non-inclusion criteria were defined in a detailed manner in Chapter 3, among these criteria:

Inclusion criteria:

- Signing the consent form to participate freely in the study.
- The patient must be followed by neurological consultation at UHC HASSAN II Fez.
- A cognitive assessment is passed for all the participants.

Exclusion criteria:

- Participants suffering from visual or hearing problems.
- Each participant suffering from stroke or head trauma.
- Subjects under trusteeship or guardianship.

Participants are encouraged to reproduce a handwritten trace following the protocol in Arabic and French as well [41][66]. Data is acquired confidentially and anonymously. The Volunteers have indeed, the right to withdraw from the study at any moment.

4.2.2. Materials

Using the graphical tablet WACOM Intuos Pro Large with Inking Pen we collected the handwriting data of the participants in this study. This tablet is capable to detect 2048 of pressure levels, with a 125 Hz of sampling frequency. It records over time the coordinates (x (t), y (t)), pressure, as well as pen's inclination. For more details see chapter3.

4.2.3. Used Database

Matched according to level of education and age, altogether, 68 subjects (34 PD patients and 34 healthy controls (HCs)) participated in this work. The volunteers are all right-handed, completed 6 years of education, and native speakers of Arabic. All PD patients were on medication and took the treatment 30 to 60 minutes before the HW task. The metadata such as age, HW frequency per week, treatment, profession, etc.. as well as the HW data are collected anonymously. In table 8, we present the demographic data of the studied populations.

Table 8: Demographic Data of the studied population.

	Mean Age (std)	MMSE Score	Mean UPDRS	Hoehn and Yahr stages
PD	55.10 (± 9.18)	28.5 (± 1.2)	12 (± 7.9)	2.16 (± 0.3)
HCs	53.10 (± 10.3)	30	-	-

4.2.4. Handwriting Task

The analysis presented in this article concerns the first Arabic exercise of the protocol [41][66]. The task consist of copying a provided Arabic text consisting of six lines. An example of the imposed text is shown in Figure 12. The blue color represents the low speeds and the red color represents the high speeds in ranges from 0 to 20 cm/s.

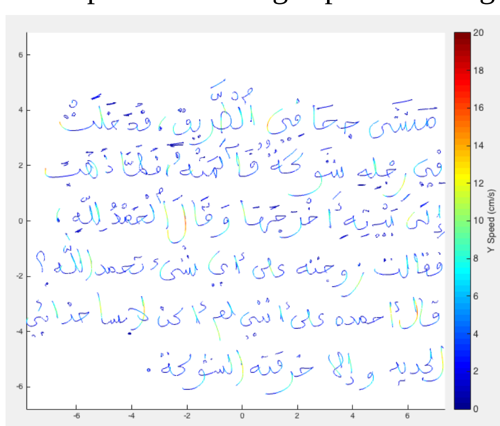


Figure 12: Visualization of the HW velocity. (change the visualization)

4.3. Feature Extraction

The Wacom tablet generates, for each point (n) of the pen trajectory, X(n), Y(n), P(n). From these vectors we compute new features that can be arranged in three categories:

Kinematics: Horizontal and vertical velocity, acceleration, jerk, normalized jerk, speed, changes in velocity number NCV, changes in acceleration number NCA, etc.

Spatial: Words height, length of intra and inter word spaces, complexity of the trajectory pen (when the stylus is in the air).

Mechanical: Pressure, pressure variation.

In the category of kinematic features, the horizontal and vertical velocities are estimated at each point n as follows [123]:

$$V_x(n) = \Delta x(n)/\Delta t(n) \; and \; V_y(n) = \Delta y(n)/\Delta t(n) \quad (1)$$

Where:

$$\Delta x(n) = x(n+1) - x(n-1), \Delta y(n) = y(n+1) - y(n-1) \; and \; \Delta t(n) = t(n+1) - t(n-1), \quad (2)$$

The accelerations (A_x and A_y) are calculated in the same way as a derivative of the velocity and the jerk (J_x and J_y) as a derivative of the acceleration as follows:

$$A_x(n) = \Delta V_x(n)/\Delta t(n) \;\; and \;\; A_y(n) = \Delta V_y(n)/\Delta t(n) \quad (3)$$

and

$$J_x(n) = \Delta A_x(n)/\Delta t(n) \;\; and \;\; J_y(n) = \Delta A_y(n)/\Delta t(n) \quad (4)$$

In the category of spatial parameters, the direction θ of the displacement of the stylus and the curvature $\emptyset$, are estimated locally on the plot as in [123]:

$$\cos\theta(n) = \Delta x(n)/\Delta s(n) \;\; \text{where } \Delta s(n) = \sqrt{\Delta_x(n)^2 + \Delta_y(n)^2} \quad (5)$$

and

$$\phi(n) = \theta(n+1) - \theta(n-1) \quad (6)$$

Thus, some of statistical functions are computed to extract information contained in HW features, such as: mean, standard deviation, maximum, minimum, quantiles Q1 and Q3, entropy, median, Kurtosis, and Skewness. Based on these three categories, we computed 230 statistical features for each participant.

4.4. Visualization and clustering

4.4.1. PCA Visualization

Principal Component Analysis (PCA) [124][125] is one of the most commonly used multivariate data analysis methods. It makes it possible to explore multidimensional datasets made up of quantitative variables using an orthogonal transformation. PCA was used to visualize the disposition of writers based on the 230 features.

The data matrix (Writers x Features) (Samples x Variables) is converted into a score matrix, a loading matrix and a residual matrix. The transformation converts a set of correlated variables into a set of uncorrelated variables (principal components, PCs). As a multivariate unsupervised statistical procedure, PCA is widely used as a data exploratory tool. In particular, by plotting the principal components (scores plot), clusters may appear in the graph, which are indicative of individuals with similar features (composition/spectrum). The data matrix was composed of the 68 individuals in columns and 230 features in rows. The first two PCA axes retrieve a 98.73% of inertia.

The figure 13 represents the visualization PCA. Writers are colored according to their group. Red dots correspond to PD patients and the blue ones correspond to HCs.

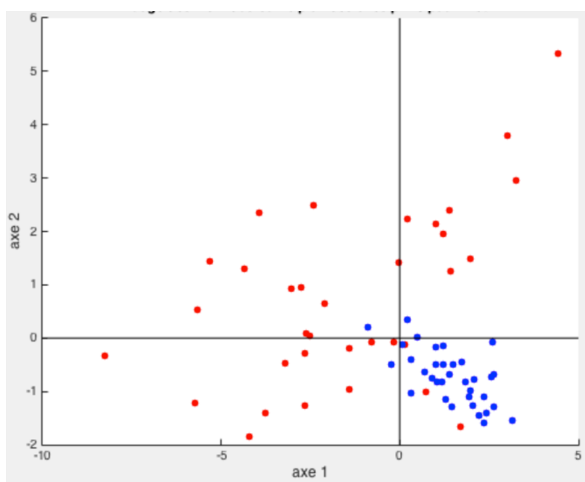


Figure 13: PCA projection of the computed features. Red color : PD patients. Blue color : HCs.

4.4.2. Clustering (Unsupervised learning)

In this section, we present an unsupervised learning approach to get an intuition about the structure of the data. It can be defined as a step of identifying subgroups in the data such that data points in the same subgroup (cluster) are very similar while data points in different clusters are very different. In other words, we try to find homogeneous subgroups within the data such that data points in each cluster are as similar as possible according to a similarity measure such as Euclidean-based distance or correlation-based distance. The decision of which similarity measure to use is application-specific.

In this work, clustering analysis is done on the basis of features where we try to find subgroups of samples based on computed features.

In the literature, one of the most used and efficient algorithm of clustering is K-means. It is an iterative algorithm that tries to partition the dataset into K pre-defined distinct non-overlapping subgroups (clusters) where each data point belongs to only one group. It tries to make the intra-cluster data points as similar as possible while also keeping the clusters as different (far) as possible. It assigns data points to a cluster such that the sum of the squared distance between the data points and the cluster's centroid (arithmetic mean of all the data points that belong to that cluster) is at the minimum. The less variation we have within clusters, the more homogeneous (similar) the data points are within the same cluster.

The way K-means algorithm works is as follows:

1. Specify number of clusters K.
2. Initialize centroids by first shuffling the dataset and then randomly selecting K data points for the centroids without replacement.
3. Keep iterating until there is no change to the centroids. i.e assignment of data points to clusters isn't changing.

- Compute the sum of the squared distance between data points and all centroids.
- Assign each data point to the closest cluster (centroid).
- Compute the centroids for the clusters by taking the average of the all data points that belong to each cluster.

The approach K-means follows to solve the problem is called **E**xpectation-**M**aximization. The **E**-step is assigning the data points to the closest cluster. The **M**-step is computing the centroid of each cluster.

The objective function is:

$$J = \sum_{i=1}^{m} \sum_{k=1}^{K} w_{ik} \left\| x^i - \mu_k \right\|^2 \tag{7}$$

where $w_{ik} = 1$ for data point x^i if it belongs to cluster k; otherwise, $w_{ik} = 0$. Also, μ_k is the centroid of x^i's cluster.

It's a minimization problem of two parts. We first minimize J w.r.t. w_{ik} and treat μ_k fixed. Then we minimize J w.r.t. μ_k and treat w_{ik} fixed. Technically speaking, we differentiate J w.r.t. w_{ik} first and update cluster assignments (*E-step*). Then we differentiate J w.r.t. μ_k and recompute the centroids after the cluster assignments from previous step (*M-step*). Therefore, E-step is:

$$\frac{\partial J}{\partial w_{ik}} = \sum_{i=1}^{m} \sum_{k=1}^{K} \left\| x^i - \mu_k \right\|^2 \quad (8)$$

$$w_{ik} = \begin{cases} 1 \; if \; k = argmin_j \left\| x^i - \mu_k \right\|^2 \\ \quad 0 \; otherwise. \end{cases} \quad (9)$$

In other words, assign the data point x^i to the closest cluster judged by its sum of squared distance from cluster's centroid.

And M-step is:

$$\frac{\partial J}{\partial \mu_k} = 2 \sum_{i=1}^{m} w_{ik}(x^i - \mu_k) = 0 \quad (10)$$

$$\mu_k = \frac{\sum_{i=1}^{m} w_{ik} \, x^i}{\sum_{i=1}^{m} w_{ik}} \quad (11)$$

Which translates to recomputing the centroid of each cluster to reflect the new assignments.

According to figure 13, the majority of the HCs are practically grouped in the same area, and the PD patients are scattered throughout the rest of the figure. Visually, we can distinguish two or three classes. For more precision, we applied the K-means clustering [126] method on the first two principal components corresponding to the first two axes.

In order to generate the optimal number of clusters, the Silhouette criterion was used. Silhouette analysis can be used to determine the degree of separation between clusters. For each sample:

- Compute the average distance from all data points in the same cluster (a^i).
- Compute the average distance from all data points in the closest cluster (b^i).
- Compute the coefficient:

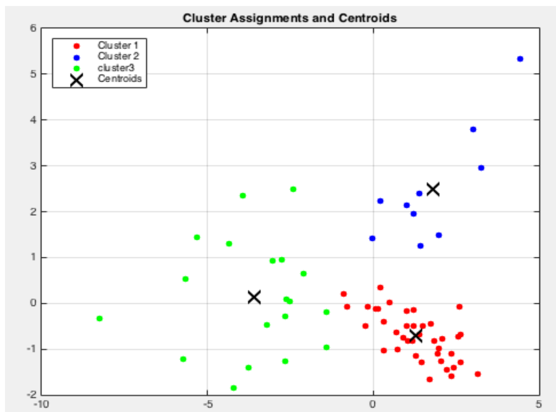
$$\frac{b^i - a^i}{\max(a^i, b^i)} \quad (12)$$

The coefficient can take values in the interval [-1, 1].

- If it is 0: The sample is very close to the neighboring clusters.
- If it is 1: The sample is far away from the neighboring clusters.
- If it is -1: The sample is assigned to the wrong clusters.

Therefore, we want the coefficients to be as big as possible and close to 1 to have a good clusters.

In our case, the Silhouette criterion generated an optimal number of three clusters, which are determined very clear in the figure 14.



In figure 14, we have 3 clusters, the dots in red are mainly HCs, the points in blue and green are both consisting only of PD patients.

Figure 14: PCA projection of the three classes generated by K-means over the first two principal components.

4.4.3. Characterization of obtained clusters

The aim of this step is to find the HW parameters characterizing each obtained cluster. Thus, a one-way analysis of variance [127] is applied between the HW quantitative variable which is the response, and the class variable which has the role of the explanatory variable.

Cluster 1 : The writers of this cluster are mostly HCs, they have a very high velocity, acceleration and jerk. They have also an average pressure. These writers have a medium to high educational level with a high HW frequency.

Cluster 2 : Consisting of only PD patients, this cluster is characterized by an average velocity, acceleration and jerk. The writers of this cluster have also an average pressure. All these writers have a high educational level with a high HW frequency.

Cluster 3 : This cluster is characterized by the lowest kinematic features, as well as a very low pressure. These writers spend a lot of time in air, they also have an advanced stage of PD compared to PD patients in cluster 2, according to their UPDRS score.

4.5. Discussion

Parkinson's Disease is the most widespread neurological pathology after Alzheimer. It's mainly characterized by a gradual and persistent loss of dopaminergic neurons, which affects some specific areas in the brain. This brain's deterioration causes an important decline of cognitive, functional and behavioral abilities of the affected subject. Thus, handwriting, which is a combination of motor and cognitive abilities, is also affected.

The written text seems to be better than the letters and sentences for the separation between PD patients and HCs. Indeed, a text makes it possible to record a large number of movements on tablet and in air for a prolonged time. These movements are associated, on the one hand, with the cursive writing of words and vowels applied to letters, and on the other hand with the raising of the pen between words, line breaks and vocalization. As a result, the features extracted on the digitized trajectory make it possible to describe more precisely the graphic motricity of the writer at the time of writing.

According to the obtained results, PD patients undergo alterations mostly in kinematic parameters. On the contrary of healthy controls, PD patients are characterized by a significant slowness in velocity, acceleration and jerk. We are aware that our research may have some limitations such as the size of the used database. For this purpose, the data acquisition is still carried out within the neurological department in order to enlarge our database.

4.6. Conclusion

Following this paper, we propose an unsupervised learning technique for characterizing the online handwriting of 34 Parkinson's Disease patients and 34 Healthy Controls according to quantitative and qualitative features. Based on 230 computed features, our study has uncovered three different types of writers. The complications of handwriting skills in Parkinson’s Disease patients are reflected by a considerable deterioration in kinematic aspects.

5. Chapter 5: Classification approach based on a global online handwriting analysis

5.1. Introduction

Handwriting is mainly characterized by a primary intervention of the muscles and the brain. This shows both the subtlety and the complexity of writing, which touches on the deepest mechanisms of sensorimotor and cognition.

The degradation of people's writing is mainly due to pathologies such as Alzheimer's, Parkinson's, Cancer, heart disease and potential psychiatric pathologies such as schizophrenia. In the case of neurodegenerative pathologies such as Parkinson's (PD), Alzheimer's (AD) and mild cognitive impairment (MCI), movement disorders are observed during writing [88][128]. Several research studies have exploited the quick emergence of digital technologies to analyze writing disorders in patients with these kind of diseases. The literature especially refers to the use of two fundamental technological approaches to writing analysis: one is called "Offline" where the manuscript is captured and processed as an image, while the "Online" handwriting allows the acquisition of the manuscript in real time from a graphics tablet that extracts kinematic and spatiotemporal parameters related to the interaction between the stylus and the surface of the tablet [1]. Most of online studies have worked on Latin-alphabet handwriting and have statistically proven the existence of a strong correlation between the degradation of writing and neurodegenerative diseases, which could be practically invested in order to diagnose and monitor the progression of these pathologies [40][70][129][130]. Parkinson's disease, Alzheimer's and MCI often affect older individuals and thousands of people worldwide annually [131]. However, the criteria for an early and reliable diagnosis of these diseases are limited at the moment because the symptoms, in the early stages, may go unnoticed, therefore the use of kinematic parameters of the handwriting could be a major key for the determination of all the attributes bearing the diagnostic information of these pathologies. In this context, a data acquisition is carried out within the neurology department at the University Hospital Center Hassan II of Fez, it contains 6 French and Arabic exercises (Latin and not Latin) and 4 drawings of bilingual Parkinson’s, Alzheimer’s and MCI disease patients. In this paper, we aimed to analyze the Arabic Handwriting of 18 Parkinson’s disease patients and 18 age matched healthy controls, and we focused only on one exercise which consist on copying an Arabic text. For each participant we have calculated 528 features, and the purpose of this study is to find a subset of handwriting features suitable for efficiently identifying subjects with PD. Feature selection was done in two stages; the first one selected a subset using statistical Mann-Whitney U test, and the second one selected the most relevant features of this subset by Relieff algorithm. The selected features were fed to a support vector machine classifier with RBF kernel, whose aim is to identify the subjects suffering from PD. The accuracy of the classification of PD was as high as 82%, with sensitivity and specificity equal to 100 % and 75% respectively. The reported results show that the proposed predictive model achieves medically relevant results in identifying subjects with PD.

5.2. Proposed methodology

5.2.1. Participants

In this work, we included 18 Parkinson's patients with an average age of 56 years +/- 9 years, and 18 control subjects with a mean age of 55 years +/- 8 years. All these people are right-handed and have completed at least 8 years of study (Middle school level). The 36 people were asked to copy a text imposed in Arabic [77]. PD patients were examined only in their ON-state while on dopaminergic medication, i.e. 1–2h after taking their regular dose of dopaminergic medication. At the time of the study, their symptoms were successfully managed and they had no analgesic treatment. For the recruitment of participants, we have defined inclusion and non-inclusion criteria, and obviously each participant must sign a consent form to participate in the study, among the criteria already mentioned in Chapter 3.

5.2.2. Proposed Algorithm

For 36 participants, and from 10 handwriting and drawing tasks, the following study is limited only on the copying Arabic handwriting text exercise. So, for each participant we have calculated 528 features. Feature selection was done in two stages; the first one consists on selecting a subset using statistical Mann-Whitney U test (255 features). The second, by using Relieff algorithm, we ordinate these features from the most to the least relevant ones. The final most significant features were fed to a support vector machine classifier with RBF kernel, whose aim is to identify the subjects suffering from PD. See Figure 15.

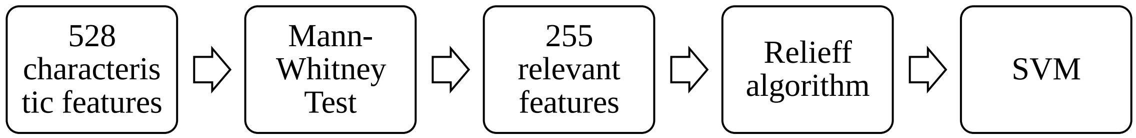


Figure 15: The followed approach in this study.

5.3. Features Selection

5.3.1. Computing characteristic features

For each point of the pen trajectory, the Wacom tablet generates X(n), Y(n), P(n) that represent the abscissa, the ordinate, and the stylus pressure, respectively. We deduce extracted features that can be classified according to 3 categories:

- **Kinematics:** velocity (in x, y, and module), acceleration (in x, y, and module), jerk or derivative of acceleration and normalized jerk (in x, y, and module), speed, number of changes in velocity NCV, number of changes in acceleration NCA, etc.
- **Spatials:** Direction, curvature, length of intra-word spaces, length of inter-word spaces, height of words, complexity of the trajectory of the pen (at the moment the pen is in the air).
- **Dynamics:** Pressure, pressure variation.

The features are calculated according to conventional formulas (See chapter 2), and are generally either vectors (V) or scalars (S).

Additionally, 30 statistical measures of the vector features were computed. These include minima, maxima, range, outlier robust range (percentile 99th - percentile 1st), geometrical mean, median, mode, mean, standard deviation, statistical moments (3, 4, 5, 6), trimmed means (5, 10, 20, 30, 40, 50), percentiles (1, 5, 10, 20, 30, 90, 95, 99), quartiles (25/lower, 75/upper), and kurtosis. This statistical measures are able to give a ground truth image on the dynamics of the writer. So we got 528 features calculated in air and on surface.

5.3.2. Mann-Whitney test

To keep the most relevant features and eliminate those that do not represent any significant difference between Parkinson's patients and control subjects, we applied the Mann-Whitney statistical test [132] on all features previously calculated. This non-parametric test, which serves as a filter type before the classification stage, made it possible to compare all the parameters from the two populations (Parkinson's, Control Subjects) and to select those that represent significant and discriminating statistical differences. The choice of this test is justified by the fact that among the calculated parameters there are those which do not follow a normal law (the normality of the parameters is verified by the Kolmogorov-Smirnov[133] statistical test). The selection was made with a risk of error of less than 5%.

5.3.3. Relieff Algorithm

To measure the relevance of the 255 features selected by the Mann-Whitney statistical test, the Relieff selection algorithm is implemented [134]. Its main role is to compute an overall relevance measure of characteristics by accumulating the difference in distances between randomly selected learning examples and their k nearest neighbors of the same class and the other class. It constitutes an automatic parameter selection technique that adopts a random approach in the search for the most correlated attributes to the predicted class and to which it assigns weights between [-1,1] according to their degrees of relevance.

5.4. Support Vector Machines Classification

The 255 features selected by the Mann-Whitney are injected afterwards into the Relieff which in turn has assigned a weight to each attribute according to its degree of relevance. Besides to determine the subset of characteristics that provide a specificity, sensitivity, and maximum classification rate, we have injected these parameters in supervised machine learning algorithm support vector machine (SVM) with non-linear radial basis function RBF kernels, whose aim is to identify the subjects suffering from PD [135].

The underlying idea of SVM classifiers is to calculate a maximal margin hyper plane that maximizes the margin which separates the two classes of data. To discriminate between two nonlinearly separable classes, the data is implicitly transformed to a larger space by means of a kernel function, where a separation hyper plane is easier to find. The new samples are ranked according to the side of the hyper plane where they belong, which amounts to seeing the sign of the decision function. For two-class support vector machine, we consider the following decision function [136]:

$$\boldsymbol{f(x) = sign[\omega^T g(x) + b]} \tag{13}$$

where ω is the d-dimensional weight vector and b is a bias. To obtain ω and b the following optimization problem with linear equality constraints is solved:

$$\text{Minimize}\textbf{:} \quad J(\omega, b, \xi) = \frac{1}{2}\omega^T\omega + \frac{\gamma}{2}\sum_{i=1}^{N}\xi_i{}^2 \tag{14}$$

$$\text{s.t} \quad y_i[\omega^T g(x_i) + b] = 1 - \xi_i\,, \quad i = 1,2,\ldots,N.$$

In this minimization problem, N is the number of samples in the training dataset, y_i is the target value of the training dataset, γ is the regularization hyperparameter and ξ_i the slack variable.

The Lagrangian is defined as:

$$\mathbf{L(\boldsymbol{\omega}, b, \boldsymbol{\alpha}_i, \boldsymbol{\xi}_i) = \frac{1}{2}\boldsymbol{\omega}^T\boldsymbol{\omega} + \frac{\boldsymbol{\gamma}}{2}\sum_{i=1}^{N}\boldsymbol{\xi}_i{}^2 - \sum_{i=1}^{N}\boldsymbol{\alpha}_i\,\{y_i[\boldsymbol{\omega}^T g(x_x) + b]\ + \boldsymbol{\xi}_i - 1\}} \tag{15}$$

where $\alpha_i \in \mathbb{R}$ is Lagrangian multiplier.

After solving (3), discriminant function of linear separating hyper plane is derived as:

$$\mathbf{f(x) = sign\left[\sum_{i=1}^{N}\boldsymbol{\alpha}_i y_i K(x, x_i) + b\right]} \tag{16}$$

Where $\mathrm{K}(\mathrm{x}, \mathrm{x_i})$ is a kernel function [16].

We use radial basis kernel function RBF, defined as:

$$\mathbf{K}(\mathbf{x}, \mathbf{x_i}) = \mathbf{e}^{\frac{-\|\mathbf{x}-\mathbf{x_i}\|}{2\sigma^2}} \tag{17}$$

The kernel parameter σ is referred to as the kernel width. In general, SVM requires the specification of several internal parameters, and SVMs are known to be sensitive to their values [135]. The performance of SVM with RBF kernel depends on kernel width (σ) and penalty parameter (γ), that were optimized using a grid search of possible values. Specifically, we searched over the grid (γ, σ) defined by the product of the sets $\gamma = [10^{-8}, 10^{-7}, \dots, 10^{7}, 10^{8}]$, $\sigma = [10^{-9}, 10^{-8}, \dots, 10^{8}, 10^{9}]$.

First, we inject the parameter that has the greatest weight, then we inject the first two that have a maximum weight, until we scan all the 100 most relevant parameters given by the Relieff test. The Figure 16 shows that the highest classification accuracy 85%, was achieved for 60 most relevant features selected using Relieff algorithm.

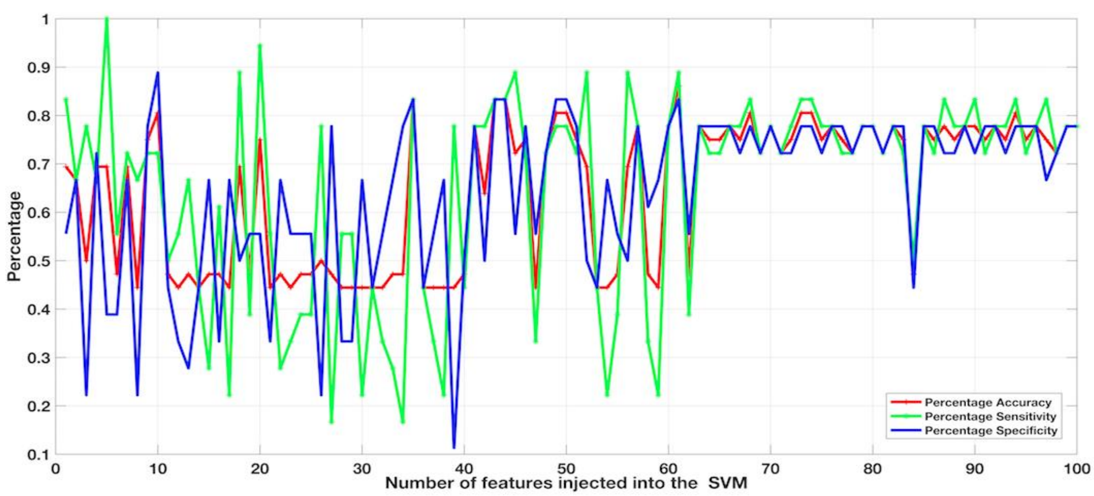


Figure 16: Sensitivity, Specificity, and Accuracy for the 100 most relevant features obtained after the Relieff algorithm application, and injected into the SVM.

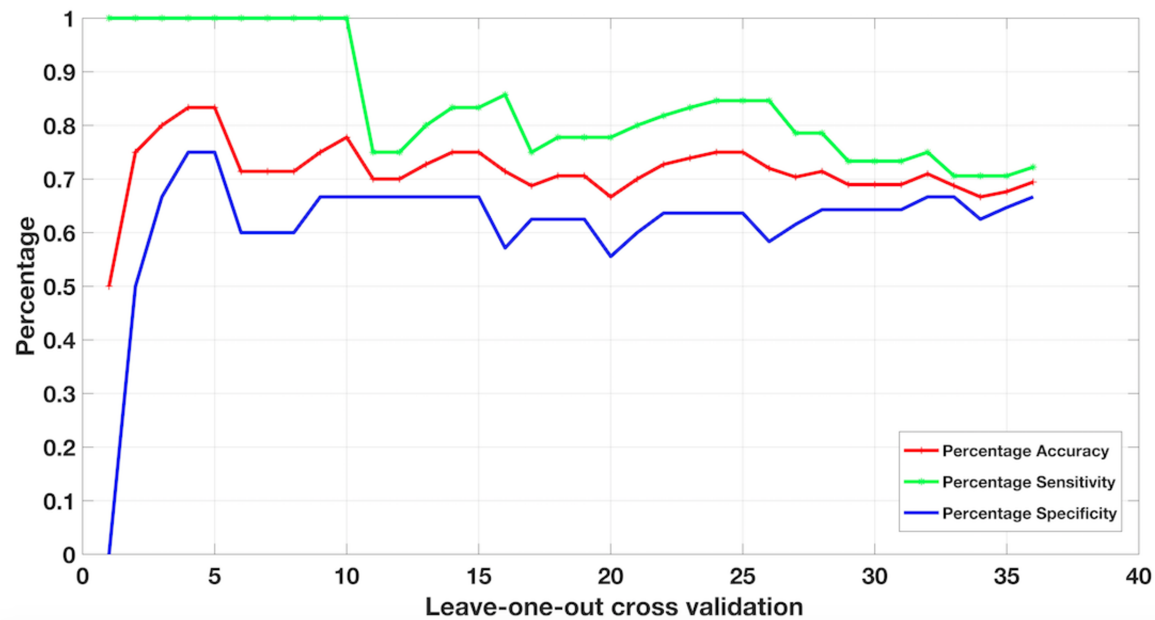


Figure 17: Classification results for the SVM classifier, with leave-one out approach.

5.5. Validation and Evaluation of SVM Classifier

Cross-Validation is a statistical method of evaluating and comparing learning algorithms by dividing data into two segments: one used to learn or train a model and the other used to validate the model. Classifier validation was conducted using the leave one-out approach validation (with k = 36). Leave-one-out cross-validation (LOOCV) is a special case of k-fold cross-validation where k equals the number of instances in the data. In other words, in each iteration nearly all the data except for a single observation are used for training and the model is tested on that single observation [137]. We can evaluate the quality of the prediction model provided by a classification method and measure its validity with the calculation of: Sensitivity, Specificity, and Precision [138]. Using a group of individuals who are already known to have the disease or not, we measure the ability of the test to predict the present of the disease (See table 9).

Table 9: Confusion matrix.

	Parkinson's Patients	Control Subjects
Detected Sick	TP	FP
Detected non sick	FN	TN

- TP (true positive): Represents the number of sick individuals who are found to be sick.
- FP (false positive): Represents the number of non-sick individuals who are found to be sick.
- FN (false negative): Represents the number of sick and detected non-sick individuals.
- TN (true negative): Represents the number of non-sick individuals and detected non-sick [138].

Sensitivity: Sensitivity is the probability that a test performed on a sick person is positive; in other words, that the model detects a patient knowing that the person is really sick. Sensitivity measures the ability of the model to detect patients. It is calculated as follows:

$$\boldsymbol{Sen} = \frac{\boldsymbol{VP}}{\boldsymbol{VP+FN}} \tag{18}$$

Specificity: Specificity is the probability that a test performed on a healthy person is negative; in other words, that the model detects a non-sick person knowing that the person is not sick. Specificity measures the ability of the model to detect non-patients. It is calculated as follows:

$$\boldsymbol{Spe} = \frac{\boldsymbol{VN}}{\boldsymbol{VN+FP}} \tag{19}$$

Accuracy: Represents the rate of elements that are well classified by the model. It is calculated as follows:

$$\boldsymbol{Acc} = \frac{\boldsymbol{VP+VN}}{\boldsymbol{VP+VN+FP+FN}} \tag{20}$$

5.6. Conclusion

The main objective of our study is to develop an automatic system for diagnosis of neurodegenerative diseases. In this paper, we are presenting a SVM classification method for Arabic online handwriting analysis of 18 Parkinson’s disease vs 18 healthy controls.

The proposed approach is applied to a copying Arabic handwriting text exercise. After the steps of extracting and selecting relevant parameters, we are using the SVM classification method. The obtained results show that the accuracy is upper than 80%. Future works are interesting to the other exercises and a comparison will be done between Arabic and French handwriting for Moroccan population.

6. Chapter 6: Deep Online Handwriting Analysis: Comparative Study Of Different Supervised Learning Techniques Applied On Segmented Text

6.1. Introduction

Parkinson's disease (PD) is a long-term degenerative disorder characterized by the progressive destruction of dopaminergic neurons of the compact substance in the midbrain. The loss of these neurons affects the brain area responsible for the production and release of the neurotransmitter called dopamine, which plays a primordial role in the control of body movements [21][23][139]. The symptoms of PD are mainly manifested by motor disorders including akinesia, bradykinesia, postural instability, and resting tremors. Unfortunately, the early clinical diagnosis tools of this disease remain limited until now, because these symptoms appear only 5 to 10 years after the onset of the disease [20] with 50% to 60% of the dopaminergic neurons degeneracy [24]. Thereby, early and reliable diagnosis of this pathology is crucial in order to control its evolution and consequently, to improve the patients' quality of life.

In this perspective, the acquisition of handwriting (HW) on a digital graphic tablet has become a new hopeful area of research in healthy field and more particularly in the early detection of neurodegenerative diseases. Indeed, handwriting is a complex activity requiring fine motor control. It involves cognitive, kinesthetic and perceptual-motor components, whose deterioration can be an important biomarker for the detection and the evaluation of these neurological pathologies [16][140].

In the literature, online HW analysis has been used in many studies of Alzheimer's disease [115][116][18] and Parkinson's disease [35][38][63][70][73][108][141][142]. This analysis provides invisible but precious dynamic information on how the manuscript is performed.

Several studies [119][120] [143] have shown that the automatic HW discrimination between affected subjects and healthy controls (HCs) can be achieved using the kinematic and mechanical HW features computed from simple or complex exercises performed on the graphic tablets. Indeed, both the PD motor symptoms (slowness and rigidity of movement.) and the PD cognitive symptoms (hesitations, lack of attention, slow thinking, memory and perception disorders.) influence directly on the HW intrinsic descriptor parameters. The severity of this deterioration can be noticeable according to the type and the complexity of the performed task.

Drotar et al. [39][10][40] calculated several HW kinematic features of 75 subjects (37 HCs and 38 PD patients). Applying the support vector machine (SVM), 85.16% of accuracy was achieved. Thus, in another study [37] the same authors compared three different models of machine learning, namely K-Nearest Neighbor (KNN), Adaboost ensemble model and SVM. This comparative study was applied by combining eight HW exercises. The classification accuracy achieved 81.3% with SVM classifier.

Using the same dataset, Impedovo [109] investigated a new different velocity-based signal processing techniques, namely the sigma log-normal model, the Maxwell-Boltzmann distribution, the Fourier and the Cepstrum transforms. The 37 PD patients and the 38 HCs completed 8 handwriting tasks, including writing and drawing tasks. Impedovo showed that combining new velocity-based features with classic features improves state of-the-art performance on the PaHaW dataset [38]. The final accuracy of 98.44% in the HC/PD classification on the freely available PaHaW dataset has been gained.

Another study based on the combination of spatio-temporal characteristics and mechanical characteristics computed from pressure, was conducted in [32]. The used dataset contains 20 HCs and 20 PD patients. The classification step is performed using the Linear Discriminant Analysis, the obtained results show a rate of 97.5% in the validation phase.

Pereira et al realized a study on a dataset containing only spiral drawings, collected from 55 participants including 37 PD patients and 18 HCs [54]. Three methods of supervised learning were applied, namely Optimum-Path Forest (OPF), SVM and Naive Bayes (NB). 78.9% of validation accuracy was obtained with NB classifier. In parallel, this same study was performed on a HandPD dataset regrouping spiral and meander drawings, collected from 18 HCs and 74 patients with PD [144]. The obtained validation accuracy is 67%.

In order to find simple and objective features for characterizing HW movements of HCs and PD patients, another clinical study was done on 20 HCs and 24 PD patients [104]. The volunteer participants draw simple horizontal lines. Based on the obtained signals, Kotsavasilogloua et al. computed various characteristics corresponding to the variability of pen velocity, the deviation from the horizontal plane and the entropy of trajectory. An average accuracy of 88.63% was obtained with the NB classifier.

In one of our previous work [79], we analyzed the online Arabic HW of 18 PD patients and 18 age-matched HCs. The study was conducted on the Arabic imposed text task. 528 features were computed for each participant. The selected relevant features were fed to SVM classifier with RBF kernel. The obtained findings show almost 80% of classification accuracy.

All of these studies have shown that PD has a direct impact on the degradation of the various HW's components. Therefore, the development of an intelligent Diagnosis Aid System based on online HW calls for an interaction between several technical aspects related to the choice of HW tasks, the choice of relevant features and the choice of selection and classification methods.

Related works conducted on Parkinson's disease were particularly concerned with the Latin languages. Nevertheless, according to our own research, there exists no study that was done on Arabic language. Thus, the proposed approach in this article concerns the analysis of Arabic online handwriting. The study was conducted on our own dataset elaborated within the neurological department of the UHC Hassan II of Fez. The acquisition protocol was defined by our interdisciplinary team of neurologists, neuropsychologists, graphologists and finally data scientists, after the ethical agreement (N° 03/15; July 10, 2015; Fez, Morocco) for the biomedical research of the FMPF.

One of this paper's originality is the calculation of new features based on the combination of temporal and spectral signal processing techniques specifically Discrete Wavelet Transform, Butter filter and Adaptive filter. To our own knowledge, this is the first study to deal with the segmentation of the manuscript text into lines. The aim of the segmentation, is to study and compare the text task before and after line segmentation, in order to evaluate the full dynamic handwriting degradation that can be more noticeable during the time task execution. The line segmentation method was developed using the unsupervised clustering K-means applied on the variation trajectory of both kinematic coordinates X and Y. Our proposed method takes into consideration the HW specificities and aspects related to each scripter of all participants. The obtained results were very satisfactory. The classification phase is based on the comparison of the three different machine learning methods, KNN, SVM and Decision Trees (DT). The KNN classifier gave the best accuracies on both training and testing datasets.

The analysis carried out in this study mainly concern the text before segmentation, the first line and the last line. Passing from one line to another, this novel approach will give us the ability to study the HW degradation reflecting pathology fatigue. In fact, PD patients undergo a significant fatigue which directly influences their writings during the execution of the HW task [145]. Our work has led us to conclude that the last line has significant discrimination power in comparison with other lines.

The rest of the paper is organized as follows: Section II, gives a brief overview of the studied dataset, equipment, handwritten imposed text task, and also describes the new proposed approach concerning the line segmentation as well as the preliminary analysis of computed features. The third section concerns the feature selection and classification. Training, validation and testing results are outlined in section IV. Eventually, our conclusions are drawn in the final section.

6.2. Materials and Methods

6.2.1. Dataset acquisition and description

The data collection was carried out within the neurological department of the Hospital Hassan II of Fez. The presented study was conducted on 40 PD patients (21 women / 19 men) and 40 HCs (20 women / 20 men) matched conforming to age and intellectual level. All participants are Arabic native speakers, right-handed, and have achieved at least 6 years of education. The 80 subjects were invited to copy an imposed text in Arabic according to our proposed protocol [41] [77]. All PD patients have already taken the treatment (L-DOPA) 30 minutes to one hour before the execution of the HW task. The stage of PD is quantified by the Unified Parkinson's Disease Rating Scale (UPDRS) [113]. A neuropsychologist assesses the cognitive state of each patient through a complete neuropsychological test. The HCs must have a score of Mini-Mental State Examination (MMSE) [146] upper or equal to 27. All participants verified the inclusion and exclusion criterion, and after receiving information on the study’s purpose and content they freely signed a consent form. The metadata, as well as the HW data, are collected anonymously. Table 10 shows the demographical and clinical metadata. The age distribution of the two participants group is presented in Figure 18.

The acquisition of HW is done using the graphic tablet "WACOM Intuos Pro Large" with the creative pen "Inking pen". The proposed protocol sheet is positioned on the tablet's surface to allow the visual feedback of the plot. The manuscript's digitization is recorded at a sampling frequency of 125 Hz and consists on associating at each point of the trajectory on surface or in air (1.5 cm above the tablet) a sequence of six values (T [n], X [n], Y [n], P [n], Θ [n], Φ [n]) which represent, time, kinematic coordinates in (X,Y), pressure pen (2048 levels), Azimuth angle, and Altitude angle respectively.

Table 10: Demographic and clinical characteristics of study participants.

Cognitive Profile	Age		Score MMSE		Disease Duration		UPDRS		Hoehn and Yahr stages	
	Mean	Std	Mean	Std	Mean	Std	Mean	Std	Mean	Std
PD	54.3	9.49	28.15	1.14	8.10	4.03	11	7.66	2.08	0.60
HC	49.65	9.79	30	0	-	-	-	-	-	-

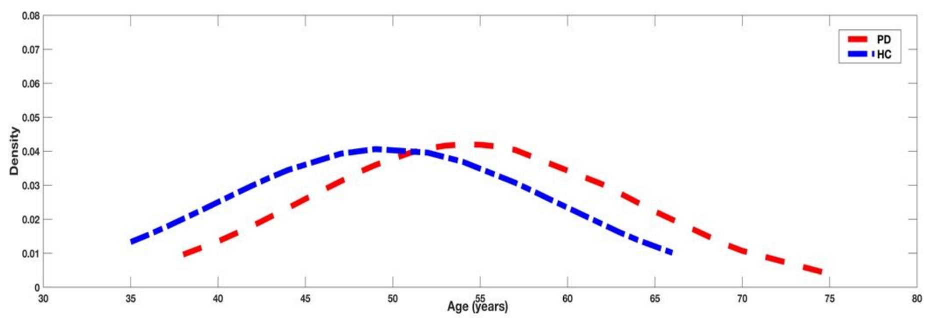


Figure 18: Age distribution of the two groups of subjects.

6.2.2. Segmentation proposed method

The analysis presented in this article concerns the first exercise of our proposed protocol [77][41] which consists on copying an imposed Arabic text. This exercise is a special task that encompasses several specificities of the Arabic language, and which involves complex motor and cognitive efforts of the participants. Indeed, many movement irregularities such as loss of fluidity, tremors, hesitation, occur and increase during the time task execution. Therefore, the analysis of the manuscript line by line could reveal more relevant information, and thus discriminate at best HW of PD patients from that of HCs. Passing from one line to another, this novel approach will give us the ability to study the HW degradation during the time task execution. For this purpose, and to segment text into lines, we developed the following algorithm represented in Figure 19.

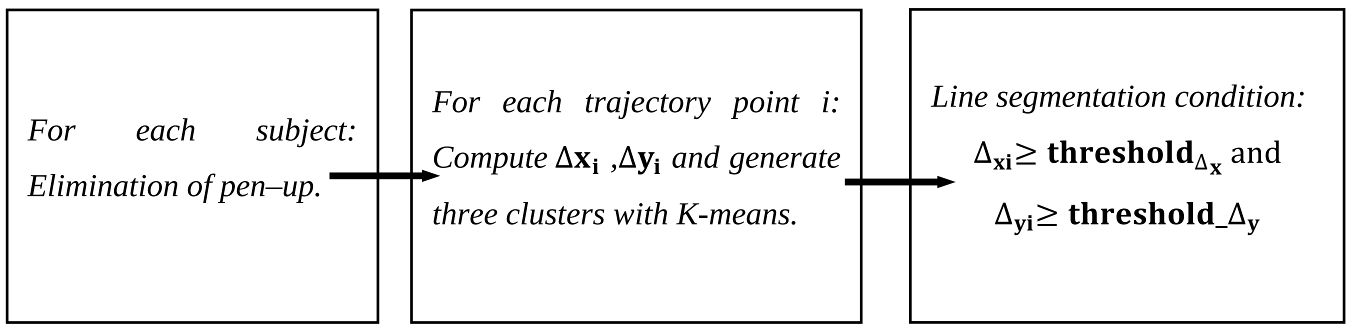
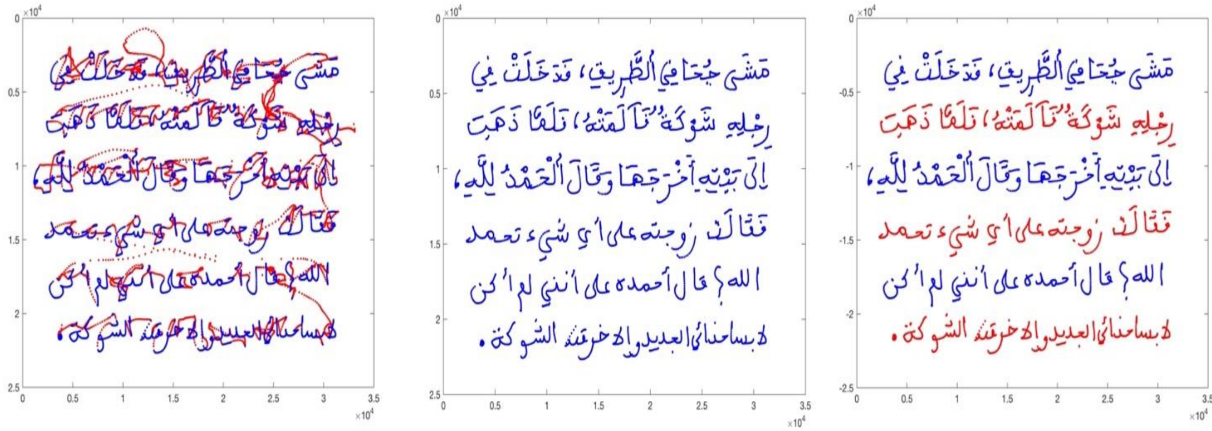


Figure 19: Flowchart of the segmentation proposed method.

A line return can be described with a large variation in the X and Y coordinates between two successive points of the writer's digitized trajectory. For this purpose, we have computed for each point i of the trajectory on surface: $\Delta_{xi}= x_{i+1} - x_i$ and $\Delta_{yi}= y_{i+1} - y_i$. The computation of these two variations at each point makes it possible to determine the maximum values that can correspond to line breaks. Therefore, to extract the lines, it is necessary to specify a suitable threshold for Δ_x and another for Δ_y from which the computed variation is directly associated with a line break. The choice of this threshold is important and must be relative to each person, depending on the nature of their HW. The proposed segmentation method on the segmentation algorithm is based on the generation of three clusters by applying the K-means [126] data partitioning method on the Δ_x vector. Cluster 1, cluster 2, cluster 3 include respectively small, medium and large variations of Δ_x. The threshold $threshold\_\Delta_x$ is chosen as the minimum of the Δ_x contained in cluster 3 which concerns the large variations. This algorithm is also applied to the vector Δ_y to determine the $threshold\_\Delta_y$. Thus, a line break is marked once the condition ($\Delta_{xi}\geq threshold_{\Delta_x}$ and $\Delta_{yi}\geq threshold_{\Delta_y}$) is verified. In Figure 20 (a) we present the on-surface coordinates with the blue color and the in-air coordinates with the red color. The on-surface coordinates correspond to the text produced by the writer, and the plot in red correspond to the in-air movements made during the HW task. In order to segment the handwritten text, we eliminated the in-air coordinates. Figure 20 (b) shows the text on the surface. Figure 20 (c) represents the result obtained after the application of this segmentation method into lines.



(a) *(b)* *(c)*

Figure 20: Text segmentation: (a) Handwritten text with in-air movement (Red color) and on-surface movements (Blue color); (b) Elimination of in-air movements; (c) Line text segmentation.

6.3. Temporal and spectral feature extraction

This section represents another originality of our paper, which is the calculation of new features in temporal and spectral domains. Each type of temporal or spectral feature specifically describes different aspects of the writer's behavior and interaction with the tablet during exercise execution. Therefore, the analysis and the interpretation of these aspects allow discovering hidden complexities of HW characteristics. Thus, for each point i of the HW signal, and from the parameters provided by the graphic tablet, we compute the vectors of kinematic features, namely velocity, acceleration and jerk.

Table 11 shows kinematic, mechanical, and temporal features. Those features are calculated for the entire text and also for each segmented line.

Table 11: List of computed features.

Feature	Description
Velocity Horizontal Vx, Vertical Vy, Norm Vr	Rate of change of pen's position with respect to time in mm/s.
Acceleration Horizontal Ax, Vertical Ay, Norm Ar	Rate of change of pen's velocity with respect to time in mm/s2.
Jerk Horizontal Jx, Vertical Jy, Norm Jr	Rate of change of pen's acceleration with respect to time in mm/s^3.
Pressure	The pressure exerted on the scripting tool during writing.
Total time	On-surface time.

The new temporal and spectral features are calculated on these parameters shown in table 12, and allow to quantify the inter-intrapatient variabilities. These signal processing techniques (Discrete Wavelet Transform, Fast Fourier Transform, Butter Filter and Adaptive Filter) are applied on signals velocity, acceleration, and jerk, then the mean of each signal is computed. Those proposed features are listed in table 12. In total, we obtained 67 features for each subject, and for his entire text and his segmented line.

We evaluate the relevance of the calculated features using the Pearson's correlation coefficient computed between the parameter vector and the response variable. This score will enable us to quantify the capacity to separate PD patients from HCs. In Figure 21 using Boxplots, we represent the relevance of each segmented line. All participants wrote at least 4 lines. In table 13 we represent the max and mean relevance score for the text before segmentation and for the four lines.

Table 12: Statistical, temporal and spectral features.

Statistical, temporal, and spectral Functions	Features	Number of features
Mean	Velocity (Vx,Vy,Vr), Acceleration (Ax,Ay,Ar), Jerk (Jx,Jy,Jr), Pression, Total time of each line.	11
Standard deviation	Velocity (Vx,Vy,Vr), Acceleration (Ax,Ay,Ar), Jerk (Jx,Jy,Jr), Pression, Total time of each line.	11
Shannon Entropy	Velocity (Vx,Vy,Vr), Acceleration (Ax,Ay,Ar), Jerk (Jx,Jy,Jr).	9
Discrete Wavelet Transform	Velocity (Vx,Vy,Vr), Acceleration (Ax,Ay,Ar), Jerk (Jx,Jy,Jr).	9
Fast Fourier Transform	Velocity (Vx,Vy,Vr), Acceleration (Ax,Ay,Ar), Jerk (Jx,Jy,Jr).	9
Butter Filter	Velocity (Vx,Vy,Vr), Acceleration (Ax,Ay,Ar), Jerk (Jx,Jy,Jr).	9
Adaptive Filter	Velocity (Vx,Vy,Vr), Acceleration (Ax,Ay,Ar), Jerk (Jx,Jy,Jr).	9

Table 13: Max and mean of relevance score.

Studied component	Max features' Relevance	Mean features' Relevance
Text before segmentation	0.72	0.57
Line 1	0.67	0.52
Line 2	0.72	0.55
Line 3	0.72	0.53
Line 4	0.72	0.53
Last line	0.96	0.81

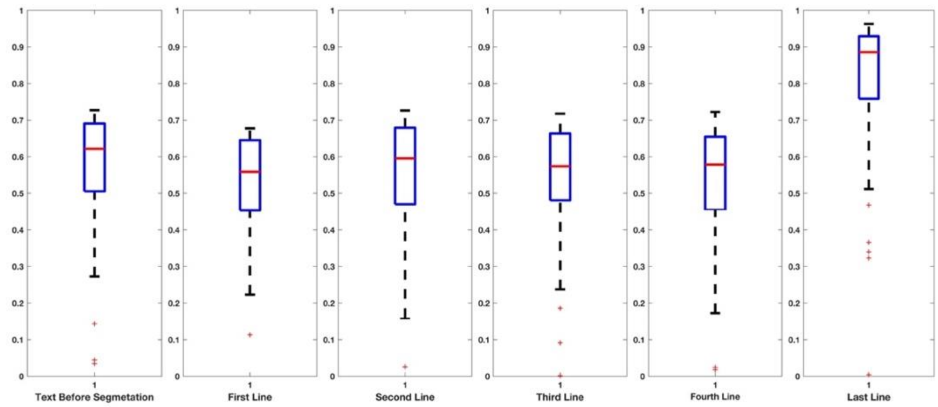


Figure 21: Features' relevance computed for each segmented line.

It is interesting to note that a big difference is detected between the last line and other studied components. The relevance score reached 0.96 in the last line. The analysis of the first line is conducted in order to compare the obtained results with those of the text before segmentation and those of the last line. The analysis of the first line is done in order to show the degradation of handwriting from one line to another until the last line. This handwriting alteration could be due to the fatigue which occur while handwriting. That's why selection and classification steps will be focused only on the text before segmentation, first line and last line. To better illustrate the obtained results concerning the feature relevance, we represent in the following table 14 some features whose correlation coefficient (CC) is greater or equal to 0.94 in the last line. These same features are also represented for the text before segmentation and the first line.

The table 14 shows a big difference between the HW of the HCs compared to that of the PD patients. This discrimination is very considerable in the last line. It is also essential to highlight the significant differences between the features means and standard deviations of the two studied populations. In this study, the obtained results are achieved through not only the implementation of signal processing advanced techniques but also by the application of these techniques on the automatically segmented text based on the K-means algorithm. Focusing on the analysis of the last line is an innovative solution that reveals very interesting and allows a better discrimination between HCs and affected subjects. In fact, the PD patients' last line undergo a significant degradation which is strongly manifested in the most relevant features.

Table 14: Ten kinematic features with the largest relevance in the last line ranked according to the Pearson's correlation coefficient.

Features, statistical function	Text before segmentation			First Line			Last Line		
	CC	PD Mean (std)	HC Mean (std)	CC	PD Mean (std)	HC Mean (std)	CC	PD Mean (std)	HC Mean (std)
Velocity Vx Entropy	0.72	6.34 (0.81)	7.59 (0.58)	0.65	6.30 (0.82)	7.32 (0.57)	0.96	5.25 (0.52)	7.76 (0.56)
Jerk Jx Entropy	0.62	10.49 (1.13)	11.72 (0.51)	0.45	9.43 (0.80)	9.99 (0.44)	0.95	7.44 (0.47)	9.60 (0.47)
Acceleration Ax Entropy	0.70	8.76 (1.26)	10.50 (0.72)	0.60	8.23 (1.02)	9.27 (0.56)	0.95	6.35 (0.63)	9.20 (0.64)
Velocity Vr Entropy	0.64	9.40 (1.13)	10.74 (0.64)	0.54	8.79 (0.93)	9.59 (0.51)	0.95	6.95 (0.56)	9.45 (0.56)
Jerk Jx Std	0.66	0.015 (0.008)	0.029 (0.009)	0.59	0.014 (0.008)	0.027 (0.01)	0.95	0.006 (0.001)	0.035 (0.006)
Jerk Jx Butterworth Filter	0.72	0.002 (0.001)	0.006 (0.001)	0.67	0.002 (0.001)	0.005 (0.001)	0.95	0.001 (0.001)	0.007 (0.001)
Velocity Vx Adaptive filter	0.04	-9.53e6 (0.002)	- 6.50e4 (0.01)	0.30	-0.005 (0.02)	0.016 (0.043)	0.95	-0.011 (0.019)	0.07 (0.015)
Velocity Vx Std	0.72	3.10 (1.43)	5.69 (1.42)	0.65	3.20 (1.64)	5.64 (1.59)	0.94	1.86 (1.44)	7.56 (1.30)
Acceleration Ax Butterworth Filter	0.72	0.02 (0.01)	0.04 (0.01)	0.67	0.022 (0.013)	0.044 (0.015)	0.94	0.011 (0.01)	0.05 (0.01)
Velocity Vx FFT	0.65	375.43 (113.09)	522.19 (81.80)	0.63	179.01 (51.37)	251.95 (49.44)	0.94	60.11 (50.14)	249.24 (42.85)

6.4. Feature selection and classification

6.4.1. Features Selection

Feature selection is a crucial step that precedes the classification stage, and allows to better understand data in machine learning [147]. This technique aims to select a subset of relevant features enabling to improve the classification performances and to reduce the dataset dimensionality. From plenty of feature selection algorithms existing in the literature, we use in this work the minimum redundancy - maximum relevance (mRMR) feature selection framework [148] applied to rank the 67 features.

Using Pearson's correlation coefficient, the feature relevance and redundancy are defined as:

$$Relevance\ (F, Y) = \frac{1}{|F|} \sum_{i \in F} |Corr(i, Y)| \tag{21}$$

$$Redundancy\ (F) = \frac{1}{|F|^2} \sum_{i,j \in F} |Corr(i, j)| \tag{22}$$

where F is a feature set, and $|Corr(i, Y)|$ (respectively $|Corr(i, j)|$) is the absolute value of Pearson's correlation coefficient computed between the i^{th} feature and the response variable Y (respectively between the i^{th} and the j^{th} features). The mRMR ranks features by minimizing redundancy between characteristics and maximizing their relevance with respect to the response variable y. This process is implemented by maximizing the operator ϕ:

$$\emptyset(Relevance, Redundancy) = Relevance - Redundancy \tag{23}$$

6.4.2. Classification and validation

Three widely used classifiers are applied in this work : (1) K-Nearest Neighbors [149] [150], (2) Support Vector Machines with RBF kernel [151], and (3) Decision Trees (DT) [152]. These algorithms are adapted to the small dataset used in our case and to the large dimensionality of space's parameter.

The mathematical approach concerning SVM classifier is detailed in chapter 4 section Support Vector Machines Classification. The hyperparameters of SVM classifier are optimized in a grid-search, the training of the model was performed by using the two hyperparameters C and γ, which represent respectively the kernel width and the penalty parameter. These latter were optimized up to powers of ten where $C \in \{10^{-3}, 10^{-2}, \dots, 10^{2}, 10^{3}\}$ and $\gamma \in \{10^{-3}, 10^{-2}, \dots, 10^{2}, 10^{3}\}$.

Concerning the k-Nearest neighbors (KNN) which is a simple and easy algorithm for solving problems related to pattern recognition, regression, and classification [153] [154]. The idea behind this algorithm is objects that are closest to each other belong to the same group posed by similar attributes [155]. It is categorized as supervised learning algorithm that performs its classification based on distance between classes in training data and testing data [156]. The similarity calculation is necessary for classification between the sample to be classified, and the training sample dataset obtains k nearest samples [154]. KNN relies on distance metric in identifying the k nearest neighbors from query points [155]. The purpose of distance metrics is to measure distance between new sample and existing samples in data set [157]. The K-Nearest Neighbors from training set are considered and take majority vote as the class and it should be in odd number to avoid ambiguity [158]. Label belonging to these neighbors is taken as reference and assigned as a class to the query point [156].

Figure 22 shows an example of KNN for given value K. Small positive value integer is used for the value of K [155], K=5 represents the classification of sample to nearest five neighbors [157]. Various formulas have been introduced to perform calculation and to find similarity classes in KNN algorithm; this includes Euclidean, Mahalanobis, City-block, Chebyshev, Minkowski, and standardized Euclidean [159]. Euclidean distance is the most common and popular distance calculation being used in KNN [155] [160] [161].

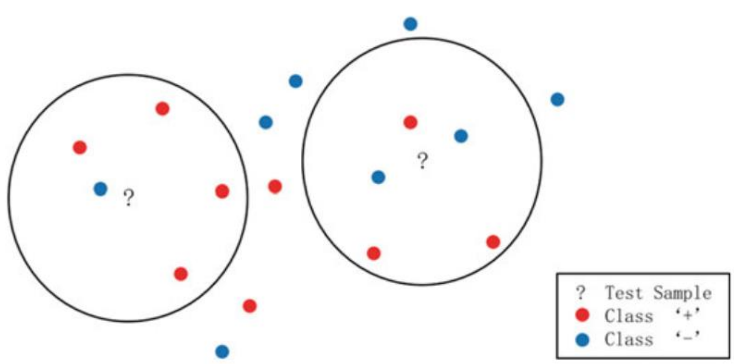


Figure 22: An example of kNN classification task with k = 5 Taken from [154].

In this work, we used the Euclidean distance to calculate the distance (d) of two points in Cartesian coordinates, since its highest accuracy in comparison with other six metrics [159]. The Euclidean distance is defined is as follows [157]:

$$\boldsymbol{d}(\boldsymbol{x},\boldsymbol{y}) = \sqrt{\sum_{\boldsymbol{i}=\boldsymbol{1}}^{\boldsymbol{n}}(\boldsymbol{x_i}-\boldsymbol{y_i})^{\boldsymbol{2}}} \tag{24}$$

Where:

- x train dataset.
- y query point or test dataset.
- n number of train set.

In general, KNN involves two main steps: (i) find the number of nearest neighbors; and (ii) classify the data point into appropriate class [158]. The detailed steps of kNN algorithm can be illustrated as in Algorithm 1 (See table 15).

Table 15: K-NN Algorithm steps.

Algorithm steps:	K-Nearest Neighbors Algorithm details
Step 1:	Determine the value of k.
Step 2:	Compute the distance between each record of the training set and the testing record.
Step 3:	Sort the neighbors in the increasing order of the distances.
Step 4:	Select the first k neighbors from the sorted list.
Step 5:	Check for the class, that majority of the neighbors belong to and assign that class to the training data.

In this work, the hyperparameters of each classifier are optimized in a grid-search. the KNN classifier was trained for the possible number of neighbors $K \in \{3,5,7,9\}$.

Finally, as for the Decision Trees classifier, we opt to use it because it is typically easy to interpret and fast to compute.

A classification tree aims at modeling the binary response variable Y by a vector of p predictor variables X = $X_1,\ldots,X_p$. Throughout the text, we encode “Parkinson” as 1 and “Healthy Control” as 0, so {HC, PD} becomes {0, 1}. Tree-based methods first partition the feature space X into a set of M rectangular regions R_m (m = 1,...,M) based on split rules, and then fit a (typically simple) model within each region $\{Y|X \in R_m\}$, e.g. a constant like the mode. In this section, we will closely follow the notation used by [162] to describe the partitioning algorithm, the parameter space and the optimization problem. As done by [162], we only consider tree models with two-way splits and with some maximum number of terminal nodes M_{max}. Throughout the text, we denote a classification tree with M terminal nodes by:

$$\theta = (v1, s1, \ldots, vM-1, sM-1). \tag{25}$$

Let $\{(x_i, y_i)\}$ for i=1 till N, denote the N observed predictor-response pairs in the dataset, where $y_i \in \{0, 1\}$ describes the response and $x_i = (x_{i1,\ldots,} \ x_{ip})^t$ represents the p associated predictor variables of i.

For each scripter, a probability estimate or score, S∈[0, 1], can be calculated based on the observed features x_i of the scripter. In the PD context, the probability of an instance being a PD is determined by a score function S(X, θ) which is based on all explanatory variables X and the chosen tree structure θ from **(1)**. The instances from class 0 (HC) are assumed to have a lower score than the instances from class 1 (PD). We define the score of instance i as:

$$\boldsymbol{s(x_i, \theta) = \sum_{m=1}^{|\theta|} \hat{p}_m I(x_i \in R_m)} \tag{26}$$

Where $|\theta|$ is the number of terminal nodes (i.e. regions R_m) and

$$\mathbf{\hat{p}_m = \frac{1}{N_m} \sum_{i:x_i \in R_m} I(y_i = 1)} \tag{27}$$

is the proportion of class 1 observations in node m which represents a region R_m with N_m observations.

It is obvious from (2) and (3) that the PD scores lie between zero and one. Note that a higher score indicates a higher likelihood of PD. These scores are often converted to predicted classes $\hat{y} \in \{0, 1\}$ by comparing them with a classification threshold t∈[0, 1]. All instances with a score S smaller than t are classified as non-PD, i.e. $S(x_i, \theta) \leq t \implies \hat{y}_i = 0$ whereas instances with S larger than t are classified as PD, i.e. $S(x_i, \theta) > t \implies \hat{y}_i = 1$.

The split criterion was tested for both Entropy and Gini index, and the maximum depth was optimized for {4,6,8,12}. It should be noted that for each type of studied component namely text before segmentation, first line and last line, we applied the three supervised learning algorithms.

The performances of the model selection process were evaluated using an unbiased estimation by applying the stratified nested 10-fold cross-validation. In this perspective, the dataset consisting of 40 PD patients and 40 HCs is first divided into 10 outer folds. Furthermore, the HW data corresponding to the 9 outer folds are partitioned into 10 inner folds. A simple cross-validation technique [137][138] is performed on these latter to find out the optimal hyperparameters of each classifier. Thus, the resulting classifiers were trained on the inner folds with the optimized hyperparameter values and were tested then on the held-out outer fold. This procedure is repeated 10 times, with each outer fold being used once as the testing fold in order to assure that all data are tested. Indeed, the performances of the generated prediction models were evaluated using several statistical rates including accuracy (Acc), balanced accuracy (Accbal), sensitivity (Sen), specificity (Spec), F-Score and Matthews Correlation Coefficient (MCC) [163]. The expression of each metric is described as follows:

$$Acc = \frac{TP+TN}{TP+TN+FP+FN} \tag{28}$$

Where TP denotes the actual positives that are correctly predicted positives, FN denotes the actual positives that are wrongly predicted negatives, TN denotes the actual negatives that are correctly predicted negatives, and finally the FP denotes the actual negatives that are wrongly predicted positives.

$$Sen = \frac{TP}{TP+FN} \tag{29}$$

$$Spec = \frac{TN}{TN+FP} \tag{30}$$

$$Acc_{bal} = \frac{Sen+Spec}{2} \tag{31}$$

$$MCC = \frac{TP\times TN-FP\times FN}{\sqrt{(TP+FP)(TP+FN)(TN+FP)(TN+FN)}} \tag{32}$$

$$F - Score = \frac{2 \times TP}{2 \times TP + FP + FN} \quad (33)$$

F-Score also known as F-measure in statistical analysis of binary classification. F-Score returns value between 0 and 1 where 1 indicates perfect predictions and 0 means worst predictions. MCC is used to measure a test's accuracy. MCC can have a value between -1 and 1, where 1 indicates perfect classification and -1 indicates perfect misclassification. MCC is the only binary classification rate that generates a high score only if the classifier is predicting correctly the negative and the positive elements [164].

6.5. Experimental results and discussion

At this level, the training of the three classifiers is performed on the different categories of features separately, in order to evaluate, in the comparison, the prediction capacity of each category at the classification process. The classification is also carried out on the combination of the three feature categories before and after the feature-ranking method mRMR in an incremental manner to observe the probable improvement of the performance metrics by injecting a reduced number of the most suitable features. Indeed, the selection of the optimal feature subsets is conducted by injecting sequentially into each classifier the 67 features ranked according to their mRMR scores. This procedure consist on injecting into each classifier, the feature that has the greatest weight, then the first two that have a maximum weight, and so forth, until all the 67 features are injected. The overall measurement classification results are summarized in table 16, 17 and 18. These findings are obtained on text before segmentation, first line, and last line respectively.

From these findings, the most striking result to emerge is the existence of a significant increase in classification performances between the first and the last line for all the considered classifiers. The accuracy has reached only 78.57% in the first line while it reached up to 92% in the last line. Besides, the text before segmentation provides less predictive power than that of the last line, and an accuracy of 85.71% was achieved for this studied component. In the other hand, the spectral and temporal features have led to higher classification rates compared to the basic statistical ones often computed in the literature. It is also worth noting that the prediction models training based on the combined data from the three categories of features before selection did not lead to any significant performances improvement. Nevertheless, the selection based on the sequential injection of features ranked according to the mRMR scores, gave a remarkable increase of the classification rates in all the considered cases. The best accuracy reached for the text before segmentation was 85.71% for a subset of 23 features by using KNN classifier. Concerning the first line, the DT classifier provides an accuracy of 78.57% by injecting 40 features. Significantly, the last line gave the best performances and reached a maximum precision of 92.86% for only 20 features by using DT.

Overall, the segmentation of the text into lines is a new approach that allowed us to analyze the text more deeply. The obtained results highlight the segmentation proposed method, given the improvement in classification performances from the first to the last line.

This may be due to specific information, which may be involved in the characterization of the handwriting of PD subjects, and which may be accentuated from one line to another or may also appear for the first time in the last line. These alterations are strongly manifest in features of the last line. Thus, the last line discriminates at best between PD patients and HCs, these findings appear to be well substantiated by obtaining the minimum accuracy of 92%. According to these findings, the used feature-ranking method mRMR is interesting because it gives the optimal subgroups of features

for which a better classification performances are obtained. In fact, the best accuracies are reached with the sequential injection of features according to the mRMR scores. Remarkably, the last line gave the best performances and discriminates at best between PD patients and HCs. This interesting result indicates that the deterioration of motor skills and consequently the HW degradation are more noticeable in the last line than in the other lines. Relevantly, this is in good agreement with our hypothesis concerning the fatigue occurring while writing.

Table 16: Classification results applied on Text Before Segmentation using stratified nested 10 cross-validation. S: Size of subset features, Acc(%): Accuracy, ACC_{bal}(%): Balanced accuracy, Sen(%): Sensitivity, Spec(%): Specificity, F-score, MCC: Matthews Correlation Coefficient.

Feature set TBS	Classifier	S	Hyperparameters	Acc	Acc_{bal}	Sen	Spec	F-score	MCC
Basic Statistical features	KNN	31	K=7	71.43	72.92	75.00	70.83	0.71	0.34
	SVM		$C = 1000$ $\gamma = 10$	58.93	61.46	56.67	66.25	0.58	0.19
	DT		MaxDepth =6 Split Criterion= Gdi	64.29	62.92	58.33	67.50	0.53	0.23
Temporal features	KNN	18	K=7	78.57	79.17	75.00	83.33	0.78	0.46
	SVM		$C = 0.1$ $\gamma = 1$	62.50	78.57	57.14	100	0.72	0.33
	DT		MaxDepth =6 Split Criterion= Entropy	71.43	70.83	66.67	75.00	0.66	0.37
Spectral features	KNN	18	K=9	72.62	78.93	83.61	74.25	0.65	0.42
	SVM		$C = 100$ $\gamma = 1$	71.43	80.00	60.00	100	0.75	0.48
	DT		MaxDepth =12 Split Criterion= Gdi	78.57	79.17	75.00	83.33	0.78	0.41
Basic Statistical + Temporal + Spectral	KNN	67	K=3	75.00	83.33	66.67	100	0.80	0.47
	SVM		$C = 100$ $\gamma = 10$	66.67	68.06	58.33	77.78	0.66	0.31
	DT		MaxDepth =8 Split Criterion= Entropy	76.19	76.39	77.78	75.00	0.74	0.40
Features + mRMR (Sequential Injection)	KNN	23	K=7	85.71	87.50	100	75.00	0.85	0.53
	SVM	32	$C = 10$ $\gamma = 10$	85.71	90.00	100	80.00	0.80	0.59
	DT	45	MaxDepth =4 Split Criterion= Entropy	85.71	87.50	100	75.00	0.85	0.53

Table 17: Classification results applied on the First Line using stratified nested 10 cross-validation. S: Size of subset features, Acc: Accuracy, ACC_{bal}: Balanced accuracy, Sen: Sensitivity, Spec: Specificity, F-score, MCC: Matthews Correlation Coefficient.

Feature set TBS	Classifier	S	Hyperparameters	Acc	Acc_{bal}	Sen	Spec	F-score	MCC
Basic Statistical features	KNN	31	K=5	59.64	60.83	66.67	55.00	0.59	0.13
	SVM		$C = 10\ \gamma = 10$	56.55	56.11	58.89	53.33	0.57	0.10
	DT		MaxDepth=12 Split Criterion=Gdi	57.14	58.33	50.00	66.67	0.57	0.16
Temporal features	KNN	18	K=5	66.07	69.17	63.33	75.00	0.73	0.27
	SVM		$C = 1000\ \gamma = 100$	57.14	75.00	100	40.00	0.44	0.30
	DT		MaxDepth =12 Split Criterion= Entropy	64.29	64.58	66.67	62.50	0.61	0.25
Spectral features	KNN	18	K=5	64.64	64.50	65.33	63.67	0.62	0.23
	SVM		$C = 1000\ \gamma = 100$	62.50	63.33	66.67	60.00	0.57	0.23
	DT		MaxDepth =12 Split Criterion= Entropy	67.66	69.26	71.30	67.22	0.62	0.27
Basic Statistical + Temporal + Spectral	KNN	67	K=7	71.43	70.83	75.00	66.67	0.75	0.32
	SVM		$C = 10\ \ \gamma = 10$	59.82	57.81	63.75	51.88	0.57	0.11
	DT		MaxDepth =8 Split Criterion= Entropy	71.43	75.42	67.50	83.33	0.75	0.40
Features + mRMR (Sequential Injection)	KNN	36	K=5	71.43	70.83	75.00	66.67	0.75	0.32
	SVM	29	$C = 10\ \gamma = 10$	68.30	71.67	79.17	64.17	0.66	0.33
	DT	40	MaxDepth =12 Split Criterion= Entropy	78.57	85.42	70.83	100	0.82	0.48

Table 18: Classification results applied on the Last Line using stratified nested 10 cross-validation. S: Size of subset features, Acc: Accuracy, ACC_{bal}: Balanced accuracy, Sen: Sensitivity, Spec: Specificity, F-score, MCC: Matthews Correlation Coefficient.

Feature set TBS	Classifier	S	Hyperparameters	Acc	Acc_{bal}	Sen	Spec	F-score	MCC
Basic Statistical features	KNN	31	K=5	80.36	86.67	100	73.33	0.73	0.53
	SVM		$C = 1\ \gamma = 0.001$	86.25	90.77	81.55	100	0.88	0.56
	DT		MaxDepth =4 Split Criterion=Entropy	85.71	89.00	78.00	100	0.87	0.57
Temporal features	KNN	18	K=7	80.36	85.42	100	70.83	0.76	0.50
	SVM		$C = 1\ \gamma = 0.001$	85.89	90.17	80.33	100	0.88	0.56
	DT		MaxDepth =6 Split Criterion=Gdi	89.73	91.88	83.75	100	0.90	0.59
Spectral features	KNN	18	K=7	87.50	90.00	100	80.00	0.85	0.58
	SVM		$C = 1\ \gamma = 0.001$	86.43	90.44	80.88	100	0.88	0.57
	DT		MaxDepth =4 Split Criterion=Gdi	87.50	90.00	80.00	100	0.88	0.58
Basic Statistical + Temporal + Spectral	KNN	67	K=5	85.71	90.00	100	80.00	0.83	0.59
	SVM		$C = 1\ \gamma = 0.001$	85.89	90.08	80.17	100	0.88	0.56
	DT		MaxDepth =4 Split Criterion=Entropy	85.71	89.00	78.00	100	0.87	0.57
Features + mRMR (Sequential Injection)	KNN	39	K=9	90.48	92.50	100	85.00	0.88	0.61
	SVM	17	$C = 1\ \gamma = 0.001$	87.50	90.00	80.00	100	0.88	0.58
	DT	20	MaxDepth =12 Split Criterion=Entropy	92.86	93.75	100	87.50	0.92	0.59

6.6. Conclusion

In this work, we have proposed a novel approach based on the text line segmentation by using the unsupervised clustering K-means. The purpose was to study and compare the text task before and after line segmentation in order to evaluate the dynamic handwriting degradation that may be more noticeable during the time task execution. Tree components were studied in this paper: text before segmentation, first segmented line and last segmented line. The obtained findings have highlighted the importance of not only the proposed segmentation method which allowed us to analyze the text more deeply, but also the combination of temporal and spectral signal processing techniques, given that these new proposed categories of features have led to higher classification rates compared to the basic statistical features often computed in the literature.

Overall, our work has led us to confirm the hypothesis concerning the fatigue occurring while writing in PD patients, since the last sentence discriminates at best between PD patients and HCs. These findings appear to be well substantiated by obtaining an accuracy of 92.86% in the last line. However, we aware that our research may have some limitations such as the size of the used dataset. For this purpose, the data acquisition is still carried out within the neurological department of the University Hospital Center Hassan II of Fez, in order to enlarge our dataset.

7. Chapter 7: General Conclusions and Perspectives

7.1. Conclusions

In this thesis, we propose a new paradigm to study anomalies in online handwriting due to the cognitive decline associated with Parkinson's disease. Our work has investigate the main limitations and aspects that are not yet addressed in the literature:

- This is the first study to deal with the Arabic language. Most of the studies carried out on neurodegenerative diseases, in the literature, concerned mainly the Latin languages. Thus, in this thesis we focused on Arabic online handwriting and Moroccan Parkinson’s disease patients.
- We are also the first research team that acquired the Arabic online handwriting dataset after developing a specific acquisition protocol. This acquisition is done on a graphical tablet Wacom at the neurological department of the HASSAN II University Hospital Center in Fez. The subjects who participated in the data acquisition signed a consent form and were examined by the medical team.
- All the studies in the literature have only focused on letters, words or sentences. Nevertheless, based on our own research, this is the first study to deal with the acquisition and the analysis of a text composed of several lines.
- We have realized the characterization of the Moroccan population based on the qualitative and quantitative handwriting features. Using the unsupervised learning, we generated three clusters of writers, two subgroups of only Parkinson’s disease patients, and the third one concern healthy controls. The first subgroup of Parkinson’s disease patients is mainly characterized by an early stage of the disease according to the UPDRS score. This cluster is characterized by an average velocity, acceleration and jerk, with an average pressure. All of these writers have a high educational level with a high handwriting frequency. However, the second subgroup of Parkinson’s disease patients is characterized by the lowest kinematic features, as well as a very low pressure. These writers spend a lot of time in air, they also have an advanced stage of PD compared to Parkinson’s disease patients in the first subgroup, according to their

UPDRS score. By contrast, the third subgroup concerns only healthy controls. They have a very high velocity, acceleration and jerk. They have also an average pressure. These writers have a medium to high educational level with a high handwriting frequency. In summary, according to the obtained results, Parkinson’s disease patients undergo alterations mostly in kinematic parameters. Thus, the complications of fine motor skills in Parkinson’s disease patients are mainly reflected by a major degradation in the kinematic aspects of handwriting. On the contrary of healthy controls, Parkinson’s disease patients are characterized by a significant slowness in velocity, acceleration and jerk.

- We also propose a global analysis of online handwriting using supervised learning. Based on an imposed text composed of several lines, we study the global aspect of handwriting. The goal of this study is to find, adopting the basic statistical features often computed in the literature, a subset of selected handwriting characteristics that effectively identify Moroccan people with Parkinson's disease. For each participant we have calculated 528 features. Using Mann-Whitney U statistical test and the Relieff algorithm, we selected the most relevant features able to discriminate at best between the Parkinson’s disease patients and healthy controls. These relevant features were fed to a support vector machine classifier with RBF kernel. Indeed, we were able to correctly classify almost 80% of the studied subjects.
- In order to improve the classification performances and subsequently build an intelligent and autonomous Diagnosis Aid System, we propose, in addition to the basic statistical parameters often computed in the literature, a new categories of features to analyze the handwriting of the two studied cognitive profiles by combining between the segmentation of the online handwriting and the machine learning algorithms applied on new proposed temporal and spectral features.
- Based on the text segmentation into individual lines, we also study the full dynamics of online handwritten manuscripts. The proposed segmentation

is a new approach that aims to analyze the text more deeply and to compare the text task before and after line segmentation. Passing from one line to another, this novel approach gave us the ability to study the HW degradation reflecting pathology fatigue, which is more noticeable in the last line of the handwritten text. Furthermore, the last line gave the best result in the classification, thus, it discriminates at best Parkinson's disease patients and healthy controls.

- In addition, our scientific team developed clustering and classification methods which are end-to-end interpretable for the medical professional. Indeed, all our results and conclusions are discussed and approved by all members of ENEMAR project before publication.

7.2. Perspectives

In this thesis, several contributions were presented. However, there remain potentially new findings in the area of the early detection of neurodegenerative pathologies, that can still be explored. Besides, our work opens the door to many future works, whether in the short, medium or long term. These perspectives contain two principal parts:

1. The main objective of this project is to develop an intelligent Diagnostic Aid System for different neurodegenerative pathologies. This system is an Android application allowing users to self-diagnose in order to detect anomalies at an early stage and therefore consult the specialist doctor for a possible preventive examination before any major deterioration. This system is a low-cost tool for automatic neurodegenerative pathologies detection.
   It is important to highlight that our supervisors have already recruited PhD students whom we co-supervise and who are in the process of finalizing the Diagnostic Aid System by integrating all the methods that we have developed and which are presented in this thesis.
2. The second current part of this project is the expansion of the handwriting database and then the analysis of all other protocol exercises as well as the other neurological pathologies for which data are already acquired such as Alzheimer's disease and MCI. Our work is also extended to Schizophrenia

and other psychological diseases. Thus, the work of this project's part proceeds as follows:

- We are aware that our research may have some limitations such as the size of the used dataset. For this purpose, the data acquisition is still carried out within the neurological department of the University Hospital Center Hassan II of Fez, in order to enlarge our dataset.
- We extend this study on the French language, and compare results between those obtained on the Arabic language and those obtained on the French language. As well as extend this analysis even to all other drawing exercises.
- Regarding the longitudinal aspect, we can start from the results obtained in our study. Indeed, clustering has shown us that there were some of the subjects with HCs close to beginner PD patients or even mild PD patients close to PD with advanced stage. The longitudinal study over the period of time between 12 months (data available in our database) is useful to assess the predictive power of our approach by looking at the case of HC subjects likely to convert to PD, or to analyze the evolution of light PD to advanced PD. One of the results of this study will be to identify the spatiotemporal parameters predictive of Parkinson's disease at a very early stage.

Finally, it is worth mentioning that all the research study conducted on handwriting will be extended to speech and gait with specific protocol for each modality. In fact, we are in the process of collecting a database of the same patients concerning the speech and the gait at the neurological department of the UHC Hassan II Fez, and eventually combining our promising results with those of speech and gait in order to detect the neurodegenerative and psychological diseases at an early stage.

8. Bibliography

[1]R. Plamondon and S. N. Srihari, "On-line and off-line handwriting recognition: A comprehensive survey," *IEEE Trans. Pattern Anal. Mach. Intell.*, vol. 22, no. 1, pp. 63–84, 2000.

[2]M. A. El-Yacoubi, M. Gilloux, and J. M. Bertille, "A statistical approach for phrase location and recognition within a text line: An application to street name recognition," *IEEE Trans. Pattern Anal. Mach. Intell.*, vol. 24, no. 2, pp. 172–188, 2002.

[3]B. Moysset *et al.*, "The A2iA Multi-lingual Text Recognition System at the Second Maurdor Evaluation," in *Proceedings of International Conference on Frontiers in Handwriting Recognition, ICFHR*, 2014, vol. 2014-Decem, pp. 297–302.

[4]H. Mouchère, C. Viard-Gaudin, R. Zanibbi, and U. Garain, "ICFHR2016 CROHME: Competition on recognition of online handwritten mathematical expressions," in *Proceedings of International Conference on Frontiers in Handwriting Recognition, ICFHR*, 2016, vol. 0, pp. 607–612.

[5]G. P. van Galen, "Handwriting: Issues for a psychomotor theory," *Hum. Mov. Sci.*, vol. 10, no. 2–3, pp. 165–191, 1991.

[6]H. L. Teulings and G. E. Stelmach, "Control of stroke size, peak acceleration, and stroke duration in Parkinsonian handwriting," *Hum. Mov. Sci.*, vol. 10, no. 2–3, pp. 315–334, 1991.

[7]H. L. Teulings, J. L. Contreras-Vidal, G. E. Stelmach, and C. H. Adler, "Parkinsonism reduces coordination of fingers, wrist, and arm in fine motor control," *Exp. Neurol.*, vol. 146, no. 1, pp. 159–170, Jul. 1997.

[8]J. Walton, "Handwriting changes due to aging and Parkinson's syndrome," *Forensic Sci. Int.*, vol. 88, no. 3, pp. 197–214, 1997.

[9]M. J. Slavin, J. G. Phillips, J. L. Bradshaw, K. A. Hall, and I. Presnell, "Consistency of handwriting movements in dementia of the Alzheimer's type: A comparison with Huntington's and Parkinson's diseases," *J. Int. Neuropsychol. Soc.*, vol. 5, no. 1, pp. 20–25, 1999.

[10] P. Drotár, J. Mekyska, Z. Smékal, I. Rektorová, L. Masarová, and M. Faundez-

Zanuy, “Prediction potential of different handwriting tasks for diagnosis of Parkinson’s,” in *2013 E-Health and Bioengineering Conference, EHB 2013*, 2013, pp. 1–4.

[11] M. Thomas, A. Lenka, and P. Kumar Pal, “Handwriting Analysis in Parkinson’s Disease: Current Status and Future Directions,” *Mov. Disord. Clin. Pract.*, vol. 4, no. 6, pp. 806–818, 2017.

[12] M. Diaz, M. A. Ferrer, D. Impedovo, G. Pirlo, and G. Vessio, “Dynamically enhanced static handwriting representation for Parkinson’s disease detection,” *Pattern Recognit. Lett.*, vol. 128, pp. 204–210, 2019.

[13] J. G. Phillips, J. L. Bradshaw, E. Chiu, and J. A. Bradshaw, “Characteristics of handwriting of patients with huntington’s disease,” *Mov. Disord.*, vol. 9, no. 5, pp. 521–530, 1994.

[14] M. P. Caligiuri, H.-L. Teulings, C. E. Dean, A. B. Niculescu, and J. Lohr, “Handwriting movement analyses for monitoring drug-induced motor side effects in schizophrenia patients treated with risperidone,” *Hum. Mov. Sci.*, vol. 28, no. 5, pp. 633–642, 2009.

[15] T. Schenk, E. U. Walther, and N. Mai, “Closed- and open-loop handwriting performance in patients with multiple sclerosis,” *Eur. J. Neurol.*, vol. 7, no. 3, pp. 269–279, 2000.

[16] D. Impedovo and G. Pirlo, “Dynamic Handwriting Analysis for the Assessment of Neurodegenerative Diseases: A Pattern Recognition Perspective,” *IEEE Rev. Biomed. Eng.*, vol. 12, pp. 209–220, 2018.

[17] C. De Stefano, F. Fontanella, D. Impedovo, G. Pirlo, and A. Scotto di Freca, “Handwriting analysis to support neurodegenerative diseases diagnosis: A review,” *Pattern Recognit. Lett.*, vol. 121, pp. 37–45, 2019.

[18] A. Schröter, R. Mergl, K. Bürger, H. Hampel, H. J. Möller, and U. Hegerl, “Kinematic analysis of handwriting movements in patients with Alzheimer’s disease, mild cognitive impairment, depression and healthy subjects,” *Dement. Geriatr. Cogn. Disord.*, vol. 15, no. 3, pp. 132–142, 2003.

[19] L. Likforman-Sulem, A. Esposito, M. Faundez-Zanuy, S. Clemencon, and G. Cordasco, “EMOTHAW: A Novel Database for Emotional State Recognition from Handwriting and Drawing,” *IEEE Trans. Human-Machine Syst.*, vol. 47, no. 2, pp. 273–

284, 2017.

[20] J. H. K. Man, L. Groenink, and M. Caiazzo, “Cell reprogramming approaches in gene- and cell-based therapies for Parkinson’s disease,” *J. Control. Release*, vol. 286, pp. 114–124, 2018.

[21] M. R. Cookson, “Parkinson’s disease,” in *Disease-Modifying Targets in Neurodegenerative Disorders: Paving the Way for Disease-Modifying Therapies*, Elsevier, 2017, pp. 157–174.

[22] E. R. Dorsey and B. R. Bloem, “The Parkinson pandemic - A call to action,” *JAMA Neurol.*, vol. 75, no. 1, pp. 9–10, 2018.

[23] B. Thomas and M. F. Beal, “Parkinson’s disease. Hum Mol Genet 16 Spec No.,” 2007.

[24] B. R. Haas, T. H. Stewart, and J. Zhang, “Premotor biomarkers for Parkinson’s disease - a promising direction of research,” *Translational Neurodegeneration*, vol. 1. 31-May-2012.

[25] P. C. Poluha, H. L. Teulings, and R. H. Brookshire, “Handwriting and speech changes across the levodopa cycle in Parkinson’s disease,” *Acta Psychol. (Amst).*, vol. 100, no. 1–2, pp. 71–84, 1998.

[26] T. E. Eichhorn *et al.*, “Computational analysis of open loop handwriting movements in Parkinson’s disease: A rapid method to detect dopamimetic effects,” *Mov. Disord.*, vol. 11, no. 3, pp. 289–297, 1996.

[27] J. L. Contreras-Vidal, P. Poluha, H. L. Teulings, and G. E. Stelmach, “Neural dynamics of short and medium-term motor control effects of levodopa therapy in Parkinson’s disease,” *Artif. Intell. Med.*, vol. 13, no. 1–2, pp. 57–79, 1998.

[28] W. G. K. Cobbah and M. C. Fairhurst, “Computer analysis of handwriting dynamics during dopamimetic tests in Parkinson’s disease,” in *Conference Proceedings of the EUROMICRO*, 2000, vol. 2, pp. 414–418.

[29] H. L. Teulings, J. L. Contreras-Vidal, G. E. Stelmach, and C. H. Adler, “Adaptation of handwriting size under distorted visual feedback in patients with Parkinson’s disease and elderly and young controls,” *J. Neurol. Neurosurg. Psychiatry*, vol. 72, no. 3, pp. 315–324, 2002.

[30] O. Tucha *et al.*, “Kinematic analysis of dopaminergic effects on skilled handwriting

movements in Parkinson's disease," *J. Neural Transm.*, vol. 113, no. 5, pp. 609–623, 2006.

[31] A. Ziliotto, M. G. Cersosimo, and F. E. Micheli, "Handwriting rehabilitation in parkinson disease: A pilot study," *Ann. Rehabil. Med.*, vol. 39, no. 4, pp. 586–591, 2015.

[32] S. Rosenblum, M. Samuel, S. Zlotnik, I. Erikh, and I. Schlesinger, "Handwriting as an objective tool for Parkinson's disease diagnosis," *J. Neurol.*, vol. 260, no. 9, pp. 2357–2361, 2013.

[33] J. G. Phillips, G. E. Stelmach, and N. Teasdale, "What can indices of handwriting quality tell us about Parkinsonian handwriting?," *Hum. Mov. Sci.*, vol. 10, no. 2–3, pp. 301–314, 1991.

[34] M. M. Ponsen, A. Daffertshofer, E. C. Wolters, P. J. Beek, and H. W. Berendse, "Impairment of complex upper limb motor function in de novo Parkinson's disease," *Park. Relat. Disord.*, vol. 14, no. 3, pp. 199–204, 2008.

[35] S. Broeder, E. Nackaerts, A. Nieuwboer, B. C. M. Smits-Engelsman, S. P. Swinnen, and E. Heremans, "The effects of dual tasking on handwriting in patients with Parkinson's disease," *Neuroscience*, vol. 263, pp. 193–202, 2014.

[36] A. Letanneux, J. Danna, J. L. Velay, F. Viallet, and S. Pinto, "From micrographia to Parkinson's disease dysgraphia," *Mov. Disord.*, vol. 29, no. 12, pp. 1467–1475, 2014.

[37] P. Drotár, J. Mekyska, I. Rektorová, L. Masarová, Z. Smékal, and M. Faundez-Zanuy, "Evaluation of handwriting kinematics and pressure for differential diagnosis of Parkinson's disease," *Artif. Intell. Med.*, vol. 67, pp. 39–46, 2016.

[38] P. Drotár, J. Mekyska, I. Rektorová, L. Masarová, Z. Smékal, and M. Faundez-Zanuy, "Decision support framework for Parkinson's disease based on novel handwriting markers," *IEEE Trans. Neural Syst. Rehabil. Eng.*, vol. 23, no. 3, pp. 508–516, 2015.

[39] P. Drotár, J. Mekyska, I. Rektorová, L. Masarová, Z. Smékal, and M. Faundez-Zanuy, "Analysis of in-air movement in handwriting: A novel marker for Parkinson's disease," *Comput. Methods Programs Biomed.*, vol. 117, no. 3, pp. 405–411, 2014.

[40] P. Drotár, J. Mekyska, I. Rektorová, L. Masarová, Z. Smékal, and M. Faundez-Zanuy, "A new modality for quantitative evaluation of Parkinson's disease: In-air movement," in *13th IEEE International Conference on BioInformatics and*

BioEngineering, IEEE BIBE 2013, 2013, pp. 1–4.

[41] A. Ammour, I. Aouraghe, G. Khaissidi, M. Mrabti, G. Aboulem, and F. Belahsen, "A new semi-supervised approach for characterizing the Arabic on-line handwriting of Parkinson's disease patients," *Comput. Methods Programs Biomed.*, vol. 183, 2020.

[42] I. Aouraghe, A. Alae, K. Ghizlane, M. Mrabti, G. Aboulem, and B. Faouzi, "A novel approach combining temporal and spectral features of Arabic online handwriting for Parkinson's disease prediction," *J. Neurosci. Methods*, vol. 339, p. 108727, 2020.

[43] H. Zhang, C. Song, A. S. Rathore, M. Huang, Y. Zhang, and W. Xu, "mHealth Technologies towards Parkinson's Disease Detection and Monitoring in Daily Life: A Comprehensive Review," *IEEE Rev. Biomed. Eng.*, pp. 1–1, 2020.

[44] A. J. Lees, "When did Ray Kennedy's Parkinson's disease begin?," *Mov. Disord.*, vol. 7, no. 2, pp. 110–116, 1992.

[45] S. Sharma *et al.*, "Biomarkers in Parkinson's disease (recent update)," *Neurochem. Int.*, vol. 63, no. 3, pp. 201–229, 2013.

[46] D. Porter, "Balancing contested meanings of creativity and pathology in Parkinson's Disease," in *Balancing the self*, Manchester University Press, 2020.

[47] F. Hopfner *et al.*, "Parkinson-Syndrome II," in *DGN-Kongress 2019*, 2019, p. 320.

[48] G. H. L. Roberts, S. A. Santorico, and R. A. Spritz, "The genetic architecture of vitiligo," *Pigment Cell Melanoma Res.*, vol. 33, no. 1, pp. 8–15, 2020.

[49] R. Bhidayasiri and D. Tarsy, "Parkinson's Disease: Hoehn and Yahr Scale," in *Current Clinical Neurology*, vol. 36, Springer, 2012, pp. 4–5.

[50] P. Martinez-Martin, L. Prieto, and M. J. Forjaz, "Longitudinal metric properties of disability rating scales for Parkinson's disease," *Value Heal.*, vol. 9, no. 6, pp. 386–393, 2006.

[51] G. T. Stebbins and C. G. Goetz, "Factor structure of the Unified Parkinson's Disease Rating Scale: Motor Examination section," *Mov. Disord.*, vol. 13, no. 4, pp. 633–636, 1998.

[52] C. Jenkinson, R. Fitzpatrick, V. Peto, R. Greenhall, and N. Hyman, "The Parkinson's disease questionnaire (PDQ-39): Development and validation of a Parkinson's disease summary index score," *Age Ageing*, vol. 26, no. 5, pp. 353–357, 1997.

[53] T. Witjas, E. Kaphan, and J. P. Azulay, “Non-motor fluctuations in Parkinson’s disease,” *Rev. Neurol. (Paris).*, vol. 163, no. 8–9, pp. 846–850, 2007.

[54] C. R. Pereira *et al.*, “A step towards the automated diagnosis of parkinson’s disease: Analyzing handwriting movements,” in *Proceedings - IEEE Symposium on Computer-Based Medical Systems*, 2015, vol. 2015-July, pp. 171–176.

[55] N. Zhi, B. K. Jaeger, A. Gouldstone, R. Sipahi, and S. Frank, “Toward Monitoring Parkinson’s Through Analysis of Static Handwriting Samples: A Quantitative Analytical Framework,” *IEEE J. Biomed. Heal. Informatics*, vol. 21, no. 2, pp. 488–495, 2017.

[56] C. C. Tappert, C. Y. Suen, and T. Wakahara, “The State of the Art in On-Line Handwriting Recognition,” *IEEE Trans. Pattern Anal. Mach. Intell.*, vol. 12, no. 8, pp. 787–808, 1990.

[57] W. Jackson and W. Jackson, “The Hardware of Digital Painting: Tablet and Stylus,” in *Digital Painting Techniques*, Springer, 2015, pp. 53–61.

[58] M. T. Angelillo, D. Impedovo, G. Pirlo, L. Sarcinella, and G. Vessio, “Handwriting dynamics as an indicator of cognitive reserve: An exploratory study,” in *Conference Proceedings - IEEE International Conference on Systems, Man and Cybernetics*, 2019, vol. 2019-Octob, pp. 835–840.

[59] P. Martínez-Martín *et al.*, “Parkinson’s disease severity levels and MDS-Unified Parkinson’s Disease Rating Scale,” *Park. Relat. Disord.*, vol. 21, no. 1, pp. 50–54, 2015.

[60] 重森健太 undefined, “認知症の早期評価を目的とした Mini-Mental State Examination の臨床活用に関する研究: 前頭前野の知見による Mini-Mental State Examination 因子構造の解明,” *Princ. Pract. Geriatr. psychiatry*, vol. 1, no. 813, pp. 1–12, 2011.

[61] M. Bashir and F. Kempf, “Advanced biometric pen system for recording and analyzing handwriting,” *J. Signal Process. Syst.*, vol. 68, no. 1, pp. 75–81, 2012.

[62] A. Ünlü, R. Brause, and K. Krakow, “Handwriting analysis for diagnosis and prognosis of Parkinson’s disease,” in *Lecture Notes in Computer Science (including subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics)*, 2006, vol. 4345 LNBI, pp. 441–450.

[63] C. R. Pereira, S. A. T. Weber, C. Hook, G. H. Rosa, and J. P. Papa, “Deep learning-aided Parkinson’s disease diagnosis from handwritten dynamics,” in *Proceedings - 2016*

29th SIBGRAPI Conference on Graphics, Patterns and Images, SIBGRAPI 2016, 2017, pp. 340–346.

[64] M. San Luciano *et al.*, "Digitized spiral drawing: A possible biomarker for early Parkinson's disease," *PLoS One*, vol. 11, no. 10, 2016.

[65] F. Costa, S. Marino, and A. Accardo, "Kinematic analysis of handwriting in parkinson disease," in *IGS2017: 18th Conference of the International Graphonomics Society*, 2017, pp. 135–138.

[66] A. Ibtissame *et al.*, "Analyse automatique de l'écriture manuscrite en ligne pour la détection précoce des pathologies neurodégénératives," *Internet des objets*, vol. 17, no. 2, Jun. 2017.

[67] S. L. Pullman, "Spiral analysis: A new technique for measuring tremor with a digitizing tablet," *Mov. Disord.*, vol. 13, no. SUPPL. 3, pp. 85–89, 1998.

[68] E. J. Smits *et al.*, "Standardized handwriting to assess bradykinesia, micrographia and tremor in Parkinson's disease," *PLoS One*, vol. 9, no. 5, 2014.

[69] R. M. Oliveira, J. M. Gurd, P. Nixon, J. C. Marshall, and R. E. Passingham, "Micrographia in Parkinson's disease: The effect of providing external cues," *J. Neurol. Neurosurg. Psychiatry*, vol. 63, no. 4, pp. 429–433, 1997.

[70] C. Bidet-Ildei, P. Pollak, S. Kandel, V. Fraix, and J. P. Orliaguet, "Handwriting in patients with Parkinson disease: Effect of l-dopa and stimulation of the sub-thalamic nucleus on motor anticipation," *Hum. Mov. Sci.*, vol. 30, no. 4, pp. 783–791, 2011.

[71] A. W. A. Van Gemmert, H. L. Teulings, and G. E. Stelmach, "Parkinsonian patients reduce their stroke size with increased processing demands," *Brain Cogn.*, vol. 47, no. 3, pp. 504–512, 2001.

[72] A. W. A. Van Gemmert, C. H. Adler, and G. E. Stelmach, "Parkinson's disease patients undershoot target size in handwriting and similar tasks," *J. Neurol. Neurosurg. Psychiatry*, vol. 74, no. 11, pp. 1502–1508, 2003.

[73] P. Drotar, J. Mekyska, Z. Smekal, I. Rektorova, L. Masarova, and M. Faundez-Zanuy, "Contribution of different handwriting modalities to differential diagnosis of Parkinson's Disease," in *2015 IEEE International Symposium on Medical Measurements and Applications, MeMeA 2015 - Proceedings*, 2015, pp. 344–348.

[74] M. P. Caligiuri, H. L. Teulings, J. V. Filoteo, D. Song, and J. B. Lohr, "Quantitative

measurement of handwriting in the assessment of drug-induced parkinsonism," *Hum. Mov. Sci.*, vol. 25, no. 4–5, pp. 510–522, 2006.

[75] P. Zham, S. P. Arjunan, S. Raghav, and D. K. Kumar, "Efficacy of Guided Spiral Drawing in the Classification of Parkinson's Disease," *IEEE J. Biomed. Heal. Informatics*, vol. 22, no. 5, pp. 1648–1652, 2018.

[76] R. C. Petersen, G. E. Smith, S. C. Waring, R. J. Ivnik, E. G. Tangalos, and E. Kokmen, "Mild cognitive impairment: Clinical characterization and outcome," *Arch. Neurol.*, vol. 56, no. 3, pp. 303–308, 1999.

[77] A. Ibtissame *et al.*, "Automatic analysis of on-line handwriting for the early detection of neurodegenerative pathologies," 2017.

[78] I. Aouraghe, A. Ammour, G. Khaissidi, M. Mrabti, G. Aboulem, and F. Belahsen, "Unsupervised learning for characterization of Arabic online handwriting of Parkinson's disease patients," *SN Appl. Sci.*, vol. 2, no. 2, p. 141, 2020.

[79] I. Aouraghe, M. Mrabti, A. Ammour, G. Aboulem, G. Khaissidi, and F. Belahsen, "Automatic analysis of Arabic online handwriting of patients with Parkinson's disease: Statistical study and classification," in *ACM International Conference Proceeding Series*, 2019.

[80] H. L. Teulings, J. L. Contreras-Vidal, G. E. Stelmach, and C. H. Adler, "Parkinsonism reduces coordination of fingers, wrist, and arm in fine motor control," *Exp. Neurol.*, vol. 146, no. 1, pp. 159–170, 1997.

[81] R. Plamondon, "Handwriting generation: the delta lognormal theory," in *Proceedings of the Fourth International Workshop on Frontiers in Handwriting Recognition*, 1994, vol. 1, no. 10.

[82] A. W. A. Van Gemmert, H. L. Teulings, and G. E. Stelmach, "The influence of mental and motor load on handwriting movements in Parkinsonian patients," *Acta Psychol. (Amst).*, vol. 100, no. 1–2, pp. 161–175, 1998.

[83] S. Borson, J. Scanlan, M. Brush, P. Vitaliano, and A. Dokmak, "The mini-cog: A cognitive 'vital signs' measure for dementia screening in multi-lingual elderly," *Int. J. Geriatr. Psychiatry*, vol. 15, no. 11, pp. 1021–1027, 2000.

[84] R. Fucetola and M. C. Smith, "Distorted visual feedback effects on drawing in Parkinson's disease," *Acta Psychol. (Amst).*, vol. 95, no. 3, pp. 255–266, 1997.

[85] D. Impedovo *et al.*, “Writing generation model for health care neuromuscular system investigation,” in *Lecture Notes in Computer Science (including subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics)*, 2014, vol. 8452 LNBI, pp. 137–148.

[86] K. Lopez De Ipina *et al.*, “Selection of entropy based features for the analysis of the Archimedes’ spiral applied to essential tremor,” in *IWOBI 2015 - 2015 International Work Conference on Bio-Inspired Intelligence: Intelligent Systems for Biodiversity Conservation, Proceedings*, 2015, pp. 157–162.

[87] D. Impedovo and G. Pirlo, “Automatic signature verification: The state of the art,” *IEEE Trans. Syst. Man Cybern. Part C Appl. Rev.*, vol. 38, no. 5, pp. 609–635, 2008.

[88] P. Werner, S. Rosenblum, G. Bar-On, J. Heinik, and A. Korczyn, “Handwriting process variables discriminating mild Alzheimer’s disease and mild cognitive impairment,” *Journals Gerontol. - Ser. B Psychol. Sci. Soc. Sci.*, vol. 61, no. 4, pp. P228–P236, Jul. 2006.

[89] L. Golshani, E. Pasha, and G. Yari, “Some properties of Rényi entropy and Rényi entropy rate,” *Inf. Sci. (Ny).*, vol. 179, no. 14, pp. 2426–2433, 2009.

[90] J. F. de Boer, B. Cense, B. H. Park, M. C. Pierce, G. J. Tearney, and B. E. Bouma, “Improved signal-to-noise ratio in spectral-domain compared with time-domain optical coherence tomography,” *Opt. Lett.*, vol. 28, no. 21, p. 2067, 2003.

[91] P. Flandrin, G. Rilling, and P. Gonçalvés, “Empirical mode decomposition as a filter bank,” *IEEE Signal Process. Lett.*, vol. 11, no. 2 PART I, pp. 112–114, 2004.

[92] A. Ayenu-Prah and N. Attoh-Okine, “A criterion for selecting relevant intrinsic mode functions in empirical mode decomposition,” *Adv. Adapt. Data Anal.*, vol. 2, no. 1, pp. 1–24, 2010.

[93] R. Plamondon, “A kinematic theory of rapid human movements: Part III. Kinetic outcomes,” *Biol. Cybern.*, vol. 78, no. 2, pp. 133–145, 1998.

[94] R. Plamondon, “A kinematic theory of rapid human movements - Part I. Movement representation and generation,” *Biol. Cybern.*, vol. 73, no. 1, p. 95, 1995.

[95] C. O’Reilly and R. Plamondon, “Development of a Sigma-Lognormal representation for on-line signatures,” *Pattern Recognit.*, vol. 42, no. 12, pp. 3324–3337, 2009.

[96] A. Fischer and R. Plamondon, “A Dissimilarity Measure for On-Line Signature Verification Based on the Sigma-Lognormal Model,” in *Biennial Conference of the International Graphonomics Society*, 2015, pp. 83–86.

[97] T. Duval, C. Rémi, R. Plamondon, J. Vaillant, and C. O’Reilly, “Combining sigma-lognormal modeling and classical features for analyzing graphomotor performances in kindergarten children,” *Hum. Mov. Sci.*, vol. 43, pp. 183–200, 2015.

[98] L. C. S. Afonso *et al.*, “A recurrence plot-based approach for Parkinson’s disease identification,” *Futur. Gener. Comput. Syst.*, vol. 94, pp. 282–292, 2019.

[99] C. Robert, *Machine Learning, a Probabilistic Perspective*, vol. 27, no. 2. MIT press, 2014.

[100] L. C. F. Ribeiro, L. C. S. Afonso, and J. P. Papa, “Bag of Samplings for computer-assisted Parkinson’s disease diagnosis based on Recurrent Neural Networks,” *Comput. Biol. Med.*, vol. 115, p. 103477, 2019.

[101] G. James, D. Witten, T. Hastie, and R. Tibshirani, *An introduction to Statistical Learning*, vol. 7, no. 10. New York : Springer, [2013] ©2013, 2000.

[102] A. W. A. Van Gemmert, H. L. Teulings, J. L. Contreras-Vidal, and G. E. Stelmach, “Parkinson’s disease and the control of size and speed in handwriting,” *Neuropsychologia*, vol. 37, no. 6, pp. 685–694, 1999.

[103] M. P. Broderick, A. W. A. Van Gemmert, H. A. Shill, and G. E. Stelmach, “Hypometria and bradykinesia during drawing movements in individuals with Parkinson’s disease,” *Exp. Brain Res.*, vol. 197, no. 3, pp. 223–233, 2009.

[104] C. Kotsavasiloglou, N. Kostikis, D. Hristu-Varsakelis, and M. Arnaoutoglou, “Machine learning-based classification of simple drawing movements in Parkinson’s disease,” *Biomed. Signal Process. Control*, vol. 31, pp. 174–180, 2017.

[105] M. Moetesum, I. Siddiqi, N. Vincent, and F. Cloppet, “Assessing visual attributes of handwriting for prediction of neurological disorders—A case study on Parkinson’s disease,” *Pattern Recognit. Lett.*, vol. 121, pp. 19–27, 2019.

[106] C. R. Pereira *et al.*, “Handwritten dynamics assessment through convolutional neural networks: An application to Parkinson’s disease identification,” *Artif. Intell. Med.*, vol. 87, pp. 67–77, 2018.

[107] G. Vessio, “Dynamic handwriting analysis for neurodegenerative disease

assessment: A literary review," *Appl. Sci.*, vol. 9, no. 21, p. 4666, 2019.

[108] M. E. Isenkul, B. E. Sakar, and O. Kursun, "Improved spiral test using digitized graphics tablet for monitoring Parkinson's disease," in *Improved spiral test using digitized graphics tablet for monitoring Parkinson's disease*, 2014, no. MAY 2014, pp. 171–175.

[109] D. Impedovo, "Velocity-Based Signal Features for the Assessment of Parkinsonian Handwriting," *IEEE Signal Process. Lett.*, vol. 26, no. 4, pp. 632–636, 2019.

[110] V. Miler Jerkovic, V. Kojic, N. Dragasevic Miskovic, T. Djukic, V. S. Kostic, and M. B. Popovic, "Analysis of on-surface and in-air movement in handwriting of subjects with Parkinson's disease and atypical parkinsonism," *Biomed. Tech.*, vol. 64, no. 2, pp. 187–194, 2019.

[111] C. Loconsole *et al.*, "A model-free technique based on computer vision and sEMG for classification in Parkinson's disease by using computer-assisted handwriting analysis," *Pattern Recognit. Lett.*, vol. 121, pp. 28–36, 2019.

[112] C. D. Rios-Urrego, J. C. Vásquez-Correa, J. F. Vargas-Bonilla, E. Nöth, F. Lopera, and J. R. Orozco-Arroyave, "Analysis and evaluation of handwriting in patients with Parkinson's disease using kinematic, geometrical, and non-linear features," *Comput. Methods Programs Biomed.*, vol. 173, pp. 43–52, 2019.

[113] C. C. Goetz, "The Unified Parkinson's Disease Rating Scale (UPDRS): Status and recommendations," *Mov. Disord.*, vol. 18, no. 7, pp. 738–750, Jul. 2003.

[114] V. Del Barrio, "Diagnostic and statistical manual of mental disorders," *Curated Ref. Collect. Neurosci. Biobehav. Psychol.*, 2016.

[115] E. Onofri *et al.*, "Dysgraphia in relation to cognitive performance in patients with Alzheimer's disease," *J. Intellect. Disabil. - Diagnosis Treat.*, vol. 1, no. 2, pp. 113–124, 2013.

[116] J. Garre-Olmo, M. Faúndez-Zanuy, K. López-de-Ipiña, L. Calvó-Perxas, and O. Turró-Garriga, "Kinematic and Pressure Features of Handwriting and Drawing: Preliminary Results Between Patients with Mild Cognitive Impairment, Alzheimer Disease and Healthy Controls," *Curr. Alzheimer Res.*, vol. 14, no. 9, pp. 960–968, 2017.

[117] K. Akyol, "A Study on the Diagnosis of Parkinson's Disease using Digitized Wacom Graphics Tablet Dataset," *Int. J. Inf. Technol. Comput. Sci.*, vol. 9, no. 12, pp.

45–51, 2017.

[118] J. Kawa, A. Bednorz, P. Stępień, J. Derejczyk, and M. Bugdol, "Spatial and dynamical handwriting analysis in mild cognitive impairment," *Comput. Biol. Med.*, vol. 82, pp. 21–28, 2017.

[119] S. Müller, O. Preische, P. Heymann, U. Elbing, and C. Laske, "Increased diagnostic accuracy of digital vs. conventional clock drawing test for discrimination of patients in the early course of Alzheimer's disease from cognitively healthy individuals," *Front. Aging Neurosci.*, vol. 9, no. APR, pp. 1463–1469, 2017.

[120] S. Müller, O. Preische, P. Heymann, U. Elbing, and C. Laske, "Increased diagnostic accuracy of digital vs. conventional clock drawing test for discrimination of patients in the early course of Alzheimer's disease from cognitively healthy individuals," *Front. Aging Neurosci.*, vol. 9, no. APR, p. 101, 2017.

[121] A. M. Lozano, J. Dostrovsky, R. Chen, and P. Ashby, "Deep brain stimulation for Parkinson's disease: Disrupting the disruption," *Lancet Neurol.*, vol. 1, no. 4, pp. 225–231, 2002.

[122] S. K. Kalia, T. Sankar, and A. M. Lozano, "Deep brain stimulation for Parkinson,s disease and other movement disorders," *Curr. Opin. Neurol.*, vol. 26, no. 4, pp. 374–380, 2013.

[123] I. Guyon, P. Albrecht, Y. Le Cun, J. Denker, and W. Hubbard, "Design of a neural network character recognizer for a touch terminal," *Pattern Recognit.*, vol. 24, no. 2, pp. 105–119, 1991.

[124] A. Tefas and I. Pitas, "Principal component analysis," *Intell. Syst.*, vol. 2, no. 1–3, pp. 37–52, 2016.

[125] M. C. Campbell *et al.*, "Principal component analysis of PiB distribution in Parkinson and Alzheimer diseases," *Neurology*, vol. 81, no. 6, pp. 520–527, 2013.

[126] J. A. Hartigan and M. A. Wong, "Algorithm AS 136: A K-Means Clustering Algorithm," *Appl. Stat.*, vol. 28, no. 1, p. 100, 1979.

[127] A. Cuevas, M. Febrero, and R. Fraiman, "An anova test for functional data," *Comput. Stat. Data Anal.*, vol. 47, no. 1, pp. 111–122, 2004.

[128] J. L. Contreras-Vidal, H. L. Teulings, and G. E. Stelmach, "Micrographia in parkinson's disease," *Neuroreport*, vol. 6, no. 15, pp. 2089–2092, 1995.

[129] N. Zhi, B. K. Jaeger, A. Gouldstone, S. Frank, and R. Sipahi, “Quantitative assessment of a therapeutic exercise in mitigating micrographia associated with Parkinson’s disease,” in *2014 IEEE Healthcare Innovation Conference, HIC 2014*, 2014, pp. 327–330.

[130] A. P. Accardo, M. Genna, and M. Borean, “Reprint of ‘Development, maturation and learning influence on handwriting kinematics,’” *Hum. Mov. Sci.*, vol. 32, no. 5, pp. 999–1009, 2013.

[131] A. Ramé, *La maladie de Parkinson*, no. 86. Elsevier Health Sciences, 2007.

[132] N. Nachar, “The Mann-Whitney U: A Test for Assessing Whether Two Independent Samples Come from the Same Distribution,” *Tutor. Quant. Methods Psychol.*, vol. 4, no. 1, pp. 13–20, 2008.

[133] M. Keita, “Introduction à la méthode statistique et probabiliste,” 2016.

[134] R. P. L. DURGABAI and R. B. Y, “Feature Selection using ReliefF Algorithm,” *Ijarcce*, vol. 3, no. 10, pp. 8215–8218, 2014.

[135] D. Ruppert, *The Elements of Statistical Learning: Data Mining, Inference, and Prediction*, vol. 99, no. 466. Springer Science & Business Media, 2004.

[136] J. A. K. Suykens and J. Vandewalle, “Least squares support vector machine classifiers,” *Neural Process. Lett.*, vol. 9, no. 3, pp. 293–300, 1999.

[137] S. Arlot and A. Celisse, “A survey of cross-validation procedures for model selection,” *Stat. Surv.*, vol. 4, pp. 40–79, 2010.

[138] T. Fawcett, “An introduction to ROC analysis,” *Pattern Recognit. Lett.*, vol. 27, no. 8, pp. 861–874, 2006.

[139] P. A. Robinson, “Understanding the molecular basis of Parkinsons disease, identification of biomarkers and routes to therapy,” *Expert Rev. Proteomics*, vol. 7, no. 4, pp. 565–578, 2010.

[140] C. De Stefano, F. Fontanella, D. Impedovo, G. Pirlo, and A. Scotto di Freca, “Handwriting analysis to support neurodegenerative diseases diagnosis: A review,” *Pattern Recognit. Lett.*, vol. 121, pp. 37–45, Apr. 2019.

[141] J. Jankovic, “Parkinson’s disease: clinical features and diagnosis,” *J. Neurol. Neurosurg. psychiatry*, vol. 79, no. 4, pp. 368–376, 2008.

[142] G. Pirlo, M. Diaz, M. A. Ferrer, D. Impedovo, F. Occhionero, and U. Zurlo, “Early

diagnosis of neurodegenerative diseases by handwritten signature analysis," in *Lecture Notes in Computer Science (including subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics)*, 2015, vol. 9281, pp. 290–297.

[143] T. D. Pham, "Pattern analysis of computer keystroke time series in healthy control and early-stage Parkinson's disease subjects using fuzzy recurrence and scalable recurrence network features," *J. Neurosci. Methods*, vol. 307, pp. 194–202, 2018.

[144] C. R. Pereira *et al.*, "A new computer vision-based approach to aid the diagnosis of Parkinson's disease," *Comput. Methods Programs Biomed.*, vol. 136, pp. 79–88, 2016.

[145] D. Impedovo, G. Pirlo, G. Vessio, and M. T. Angelillo, "A Handwriting-Based Protocol for Assessing Neurodegenerative Dementia," *Cognit. Comput.*, vol. 11, no. 4, pp. 576–586, 2019.

[146] M. F. Folstein, L. N. Robins, and J. E. Helzer, "The mini-mental state examination," *Arch. Gen. Psychiatry*, vol. 40, no. 7, p. 812, 1983.

[147] H. H. Hsu and C. W. Hsieh, "Feature selection via correlation coefficient clustering," *J. Softw.*, vol. 5, no. 12, pp. 1371–1377, 2010.

[148] H. Peng, F. Long, and C. Ding, "Feature selection based on mutual information: Criteria of Max-Dependency, Max-Relevance, and Min-Redundancy," *IEEE Trans. Pattern Anal. Mach. Intell.*, vol. 27, no. 8, pp. 1226–1238, 2005.

[149] L. E. Peterson, "K-nearest neighbor," *Scholarpedia*, vol. 4, no. 2, p. 1883, 2009.

[150] R. Nisbet, G. Miner, and K. Yale, *Handbook of statistical analysis and data mining applications*. Academic Press, 2017.

[151] S. R. Sain and V. N. Vapnik, *The Nature of Statistical Learning Theory*, vol. 38, no. 4. Springer science & business media, 1996.

[152] Y. Y. Song and Y. Lu, "Decision tree methods: applications for classification and prediction," *Shanghai Arch. Psychiatry*, vol. 27, no. 2, pp. 130–135, 2015.

[153] Y. Song, J. Liang, J. Lu, and X. Zhao, "An efficient instance selection algorithm for k nearest neighbor regression," *Neurocomputing*, vol. 251, pp. 26–34, 2017.

[154] S. Chen, "K-Nearest Neighbor Algorithm Optimization in Text Categorization," in *IOP Conference Series: Earth and Environmental Science*, 2018, vol. 108, no. 5, p. 52074.

[155] H. S. Khamis, "Application OF k-Nearest Nieghbour Classification In Medical Data

Mining In The Context Of Kenya," *Int. J. Inf. Commun. Technol. Res.*, vol. 4, no. December, 2014.

[156] A. Giri, M. V. V. Bhagavath, B. Pruthvi, and N. Dubey, "A Placement Prediction System using k-nearest neighbors classifier," in *Proceedings - 2016 2nd International Conference on Cognitive Computing and Information Processing, CCIP 2016*, 2016, pp. 1–4.

[157] N. E. Z. Md Isa, A. Amir, M. Z. Ilyas, and M. S. Razalli, "The Performance Analysis of K-Nearest Neighbors (K-NN) Algorithm for Motor Imagery Classification Based on EEG Signal," in *MATEC Web of Conferences*, 2017, vol. 140, p. 1024.

[158] A. Bablani, D. R. Edla, and S. Dodia, "Classification of EEG data using k-nearest neighbor approach for concealed information test," *Procedia Comput. Sci.*, vol. 143, pp. 242–249, 2018.

[159] K. Chomboon, P. Chujai, P. Teerarassammee, K. Kerdprasop, and N. Kerdprasop, "An Empirical Study of Distance Metrics for k-Nearest Neighbor Algorithm," in *Proceedings of the 3rd international conference on industrial application engineering*, 2015, pp. 280–285.

[160] M. A. jabbar, B. L. Deekshatulu, and P. Chandra, "Classification of Heart Disease Using K- Nearest Neighbor and Genetic Algorithm," *Procedia Technol.*, vol. 10, pp. 85–94, 2013.

[161] S. AhmedMedjahed, T. Ait Saadi, and A. Benyettou, "Breast Cancer Diagnosis by using k-Nearest Neighbor with Different Distances and Classification Rules," *Int. J. Comput. Appl.*, vol. 62, no. 1, pp. 1–5, 2013.

[162] T. Grubinger, A. Zeileis, and K. P. Pfeiffer, "Evtree: Evolutionary learning of globally optimal classification and regression trees in R," Working Papers in Economics and Statistics, 2014.

[163] D. Chicco and G. Jurman, "The advantages of the Matthews correlation coefficient (MCC) over F1 score and accuracy in binary classification evaluation," *BMC Genomics*, vol. 21, no. 1, p. 6, 2020.

[164] D. Chicco, "Ten quick tips for machine learning in computational biology," *BioData Min.*, vol. 10, no. 1, p. 35, 2017.

9. List of author's publications

9.1. Publications

[Aouraghe, I. et al., 2020] Aouraghe, I., Ammour, A., Khaissidi, G., Mrabti, M., Aboulem, G., & Belahsen, F. “A novel approach combining temporal and spectral features of Arabic online handwriting for Parkinson’s disease prediction.”, Elsevier, Journal of Neuroscience Methods, 108727, April 2020.

[Aouraghe, I. et al., 2020] Aouraghe, I., Ammour, A., Khaissidi, G., Mrabti, M., Aboulem, G., & Belahsen, F. “Unsupervised learning for characterization of Arabic online handwriting of Parkinson’s disease patients.”, Springer, SN Applied Sciences, 2(2), 141, January 2020.

[Ammour, A. et al, 2019] Ammour, A., Aouraghe, I., Khaissidi, G., Mrabti, M., Aboulem, G., & Belahsen, F. “A new semi-supervised approach for characterizing the Arabic on-line handwriting of Parkinson's disease patients.”, Elsevier, Computer Methods and Programs in Biomedicine, 183, 104979, July 2019.

[Aouraghe, I. et al., 2019] Aouraghe, I., Ammour, A., Khaissidi, G., Mrabti, M., Aboulem, G., & Belahsen, F. “Automatic analysis of Arabic online handwriting of patients with Parkinson's disease: statistical study and classification.”, Association for Computing Machinery, In Proceedings of the new challenges in data sciences: acts of the second conference of the Moroccan classification society (pp. 1-5), March 2019.

[Aboulem, G. et al., 2018] Aboulem, G., Aouraghe, I., Ammour, A., Khaissidi, G., Mrabti, M., El-Yacoubi M. A., Garcia-Salicetti, S., & Belahsen, F. “Étude de l’écriture manuscrite sur tablette graphique pour l’aide au diagnostic précoce des maladies neurodégénératives. Premiers résultats chez des patients parkinsoniens.”, Elsevier, Revue Neurologique, 174, pp S33, April 2018.

[Aouraghe, I. et al., 2018] Aouraghe, I., Ammour, A., Aboulem, G., Khaissidi, G., Mrabti, M., Faouzi, B., El-Yacoubi M. A., & Garcia-Salicetti, S. “Analyse automatique de l’écriture manuscrite en ligne pour la détection précoce des pathologies neurodégénératives.”, ISTE OpenScience, Information and Communication, Internet of Things, 1, June 2017.

9.2. Works presented at conferences or congresses

[Ammour, A., et al., 2020] Ammour, A., Aouraghe, I., Aboulem, G., Khaissidi, G., Mrabti, M., & Faouzi, B. “Prediction potential analysis of Arabic diacritics and punctuation marks in online handwriting: A new marker for Parkinson’s disease.”, WITS'20 - The 2020 International Conference on Wireless Technologies, embedded and Intelligent Systems, October 2020.

[Elghzizal, Y. et al., 2020] Elghzizal,Y., Khaissidi, G., Mrabti, M., Aouraghe, I., & Ammour, A. “A Supervised & semi supervised automatic detection of Parkinson diseases based on online spiral analysis.”, WITS'20 - The 2020 International Conference on Wireless Technologies, embedded and Intelligent Systems, October 2020.

[Aouraghe, I. et al., 2019] Aouraghe, I., Ammour, A., Khaissidi, G., Mrabti, M., Aboulem, G., & Belahsen, F. “Automatic analysis of Arabic online handwriting of patients with Parkinson's disease: statistical study and classification.”, Association for Computing Machinery, In Proceedings of the new challenges in data sciences: acts of the second conference of the Moroccan classification society (pp. 1-5), March 2019.

[Aboulem, G. et al., 2017] Aboulem, G., Aouraghe, I., Ammour, A., Khaissidi, G., Mrabti, M., Faouzi, B., El-Yacoubi M. A., & Garcia-Salicetti, S. « Étude de l’écriture manuscrite sur tablette graphique pour l’aide à la détection précoce des maladies neurodégénératives. Premiers résultats chez des patients parkinsoniens. » Journée de Neurologie de Langue Française 2018. Bordeaux. 10-13 April 2018.

[Ammour, A., et al., 2018] Ammour, A., Aouraghe, I., Aboulem, G., Khaissidi, G., Mrabti, M., & Faouzi, B. “Analyse automatique de l’écriture manuscrite en ligne pour la détection précoce des pathologies neurodégénératives.”, Journée Doctorale organisée par le Laboratoire d'Informatique et de Physique Interdisciplinaire - ENS-Fès, March 2018.

[Ammour, A., et al., 2017] Ammour, A., Aouraghe, I., Aboulem, G., Khaissidi, G., Mrabti, M., & Faouzi, B. “Détection de la maladie de Parkinson par l’analyse automatique de l’écriture manuscrite en ligne acquise sur tablette graphique.”, Conférence: 3ème Rencontre Nationale des Jeunes Chercheurs en Sciences de l’Ingénieur 2017 - FST-Fès. Premier prix du meilleur papier présenté oralement, November 2017.

[Aboulem, G. et al., 2017] Aboulem, G., Aouraghe, I., Ammour, A., Khaissidi, G., Mrabti, M., Faouzi, B., El-Yacoubi M. A., & Garcia-Salicetti, S. “Étude de l’écriture manuscrite sur tablette graphique pour la détection précoce des maladies neurodégénératives chez une population marocaine.”, Conférence : Le 3ème forum des doctorants à la faculté de Medecine de Fès. Troisième prix du meilleur court-métrage présentant le projet, December 2017.

[Aouraghe, I. et al., 2018] Aouraghe, I., Ammour, A., Aboulem, G., Khaissidi, G., Mrabti, M., Faouzi, B., El-Yacoubi M. A., & Garcia-Salicetti, S. “Analyse automatique de l’écriture manuscrite en ligne pour la détection précoce des pathologies neurodégénératives.”, ISTE OpenScience, Information and Communication, Internet of Things, 1, June 2017.