Universidad de Málaga

Doctorado en Ingeniería de Telecomunicación
Departmento de Tecnología Electrónica
Escuela Técnica Superior de Ingeniería en Telecomunicaciones

Technology for processing saccadic electrooculograms in people with Spinocerebellar Ataxia type 2

PhD Thesis Dissertation

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March 11, 2022

UNIVERSIDAD DE MÁLAGA

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EDITA: Publicaciones y Divulgación Científica. Universidad de Málaga

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Realizada bajo la tutorización de Gonzalo Joya Caparrós y dirección de Gonzalo Joya Caparrós, Rodolfo Valentín García Bermúdez y Francisco García Lagos.

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Dedicatory

To my parents and my brother, for all the support through all these years.

To my wife, for being always there.

Acknowledgements

I'm at near the end of this long trip and I would like to give my most sincere and profound thanks to my directors of thesis Gonzalo, Rodolfo and Francisco. Without their patience, trust and understanding, this work would never have finished. Sharing a machine coffee at school with Gonzalo and chatting about artificial intelligence or Cuban literature, arguing with Rodolfo about microcontrollers and electronics, or how to design neuronal networks with Francisco. I had the privilege of working of all these years with them, and seeing now in perspective how they have influenced me as a scientist and as a person.

The second protagonists of this adventure are my mother Jacqueline and my father Roberto, the creators of the terrible for me *bad word* (euphemism to refer to finishing the doctoral thesis). They have been the true driving engine of this work and a large part of this I owe it to them. Only they know the great pressure I have suffered many times during these years to finish the work and always with words of encouragement managed to get a little more motivation in me until the goal was fulfilled.

My wife Sandra must be supported by these last 3 years of saccades and electrooculographic signals. I am eternally grateful for her love and understanding.

In the same way I would like to thank my brother Rodolfo Valentín, my grandmother Tata, my grandfather Tintin, my grandparents Antonio and Ofelia, my aunts Lily (Campaña and López), Tita, my cousins Lila and Norma, to Noel, and all the relatives who in one way or another have been worried about that this work is over.

To my partners Rocío Plaza and Ting Ting for understanding the importance of finishing the thesis and giving me the time I have needed to finish it. More than partners, they are the sisters that I never had.

My Spanish brother Carlos and my Spanish mother Beatriz. There is no way to thank you for the words and support actions in the darkest times when I felt more desperate, and welcome myself as one more at home.

I want to thank the Faculty of Information from the University of Holguín for always showing me your support and help at the beginning of this work. To my colleagues Michel Velázquez and Humberto Rodríguez, to my GPDB students who were then my colleagues and today friends who in one way or another participated in

this work as they are: Andrés Henríquez, Camilo Velázquez, Roberto Estrada, Abel Fernández and Alejandro Valdevila. From the faculty and university directive I would like to thank the professors in a special way Dr. Carmen Pino, Dr. Ana de Lourdes Torralbas and Dr. Matilde Riverón.

For the part of the Research and Rehabilitation Center of Hereditary Ataxies (CIRH) I would like to thank the doctors sincerely Luis Velázquez, Roberto Rodríguez and Jacqueline Medrano. First of all they are doing for the investigation of hereditary ataxies in Cuba and then for all the data support and documentation provided. Without them this research would not have been possible the way it is today.

Of all the people who supported me at the University of Holguín would like to make a special parenthesis with Professor Rosa Isabel Urquiza Salgado. Rosa is the person who always showed unconditional support and was a tireless driver for *her boys* the thesis will finish.

To always friends as Alejandro Ventura and Heiner Dalby, and others more recent but equally considered Abel Meneses and Judith Sanabria for being there for good and bad.

Finally, I have to thank my friend Yanet Conde for his review of the text in English and again to my mother to do the same with the Spanish part.

Institutionally, I want to thank the University of Holguín (UHO), to the Central University of Las Villas (UCLV), to the University of Havana (UH) and the University of Málaga (UM) for welcoming myself in the different stages of my life where I had to live or make stances on them, as well as the support given to this investigation. CIRAH for providing the data that served as the basis for this research. To the Spanish Agency for International Development Cooperation (AECID) to bear logistically a large part of this research with the scholarship that was granted to me in 2015.

Reconocimientos

Ya se acerca el fin de este largo viaje y quisiera comenzar dando mis agradecimientos más sinceros y profundos a mis directores de tesis Gonzalo, Rodolfo y Francisco. Sin su paciencia, confianza y comprensión este trabajo nunca se hubiera terminado. Compartiendo un café de máquina en la escuela con Gonzalo y charlando lo mismo de inteligencia artificial que de literatura cubana, discutiendo con Rodolfo sobre microcontroladores y electrónica, o cómo diseñar redes neuronales a medida con Francisco; me he dado de cuenta del privilegio que tenido todos estos años de contar con vosotros y viéndolo en perspectiva cómo me ha influido tanto como científico y como persona.

Los segundos protagonistas de esta aventura son mi madre Jacqueline y mi padre Roberto, los creadores de la tan terrible para mí *mala palabra* (eufemismo para referirse a terminar la tesis doctoral). Ellos han sido el verdadero motor impulsor de este trabajo y una gran parte de este se lo debo a ellos. Solo ellos saben la gran presión que he sufrido muchas veces durante estos años por terminar el trabajo y siempre con palabras de aliento lograron sacar un poquito más de motivación en mí hasta que el objetivo fue cumplido.

A mi esposa Sandra por soportar estos últimos 3 años de sácadas y señales electrooculográficas. Estoy eternamente agradecido por su amor y comprensión.

De la misma forma quisiera agradecer a mi hermano Rodolfo Valentín, a mi abuela Tata, a mi abuelo Tintin, a mis abuelos Antonio y Ofelia, a mis tías Lily (Campañá y López), a Tita, a mis primas Lila y Norma, a Noel, y a todas los familiares que de una u otra forma se han preocupado por que termine este trabajo.

A mis socias Rocío Plaza y Ting Ting por entender la importancia de terminar la tesis y brindarme el tiempo que he necesitado para terminarla. Más que socias, son las hermanas que nunca tuve.

A mi hermano español Carlos y mi madre española Beatriz. No hay forma de agradecerles las palabras y acciones de apoyo en los tiempos más oscuros cuando me sentí más desesperado, y acogerme como uno más en su casa.

Quiero agradecer a la Facultad de Informática de la Universidad de Holguín por mostrarme siempre su apoyo y ayuda en el inicio de este trabajo. A mis compañeros Michel Velázquez y Humberto Rodríguez, a mis estudiantes del GPDB que luego

fueron mis compañeros y hoy amigos que de una manera u otra participaron en este trabajo como son: Andrés Henríquez, Camilo Velázquez, Roberto Estrada, Abel Fernández y Alejandro Valdevila. De la directiva de la facultad y universidad quisiera agradecer de manera especial a las profesoras Dr. Carmen Pino, Dr. Ana de Lourdes Torralbas y Dr. Matilde Riverón.

Por la parte del Centro de Investigación y Rehabilitación de las Ataxias Hereditarias (CIRAH) quisiera agradecer de modo sincera a los doctores Luis Velázquez, Roberto Rodríguez y Jacqueline Medrano. Primero por todo lo que están haciendo por la investigación de las ataxias hereditarias en Cuba y luego por todo el apoyo de datos y documentación brindada. Sin ellos esta investigación no hubiera sido posible de la forma que es hoy.

De todas las personas que me apoyaron en la Universidad de Holguín quisiera hacer un paréntesis especial con la profesora Rosa Isabel Urquiza Salgado. Rosa es la persona que mostró siempre apoyo incondicional y fue una impulsora incansable para que *sus chicos* terminara la tesis.

A los amigos de siempre como Alejandro Ventura y Heiner Dalby, y a otros más recientes pero igual de considerados como Abel Meneses y Judith Sanabria por estar ahí para lo bueno y lo malo.

Finalmente, tengo que agradecer a mi amiga Yanet Conde por su revisión del texto en inglés y nuevamente a mi madre por hacer lo mismo con la parte de español.

Institucionalmente, quiero agradecer a la Universidad de Holguín (UHo), a la Universidad Central de Las Villas (UCLV), a la Universidad de La Habana (UH) y la Universidad de Málaga (UM) por acogerme en las distintas etapas de mi vida que me tocó vivir o realizar estancias en ellas, así como el apoyo brindado a esta investigación. Al CIRAH por proporcionar los datos que sirvieron como base a esta investigación. A la Agencia Española de Cooperación Internacional para el Desarrollo (AECID) por soportar logísticamente gran parte de esta investigación con la beca que se me otorgó en 2015.

Abstract

This work presents the development of a technology that processes human eye movement records fully automatically. It also has a strong focus on records of subjects suffering Spinocerebellar Ataxia type 2 (SCA2). The Spinocerebellar Ataxia type 2 (SCA2) is a disease which has a very high prevalence in my natal Cuba. Here, the Centre for the Research and Rehabilitation of Hereditary Ataxias (CIRAH) is the major institution in charge of the research on this disease and many other similar.

The process carried out nowadays by the Centre for the Research and Rehabilitation of Hereditary Ataxias (CIRAH) specialists to extract the relevant information from eye movement records is semiautomatic. Parts of the saccade identification process are performed by manually annotating where the saccade begins and where it ends, with the only criteria of the specialist's expertise. Moreover, it is used an old and expensive equipment which occasionally introduces power line noise to the signals.

Because of the current CIRAH situation regarding the processing of eye movement records, we set as major goals to design a fully automatic method to extract the relevant medical data from saccadic eye movement recordings, and to design and test a low-cost device to record eye movements for clinical purposes.

To accomplish the first goal, we study the current methods and techniques involved in saccadic eye movement processing. Then, we define a processing pipeline which comprises the following blocks: filtering, differentiation, segmentation and biomarkers extraction. For each one of these blocks, we devote at least a chapter (except filtering) where we analyze them in a deeper way. It is well established in the literature that for saccadic signals, the best way to keep the signal waveform is to employ a median filter to remove undesired noise, so it's unnecessary to devote an entire chapter to this matter. Regarding the differentiation chapter we evaluate 16 filters for the saccade identification task and for the biomarker computing task. The results allow to select the best filter for each of the tasks which improves the results of the next blocks.

Segmentation is the operation where we identify saccades from the rest of the events present in a saccadic eye movement signal. We approach this operation by evaluating two supervised machine learning techniques: Multilayer Perceptron (MLP)

and Random Forest (RF). The following chapter is devoted to picking which of the saccades are non spontaneous. These non spontaneous saccades are clinically useful because they follow a visual stimulus that allows to calculate biomarkers which are not computable from spontaneous saccades such as latency. For this specific task we also evaluate four supervised machine learning techniques: Support Vector Machines (SVM), K-Nearest Neighbors (KNN), Classification and Regression Trees (CART) and Naive Bayes. Also, we select which saccadic features are useful to separate non spontaneous saccades from spontaneous ones. Using data annotated by human experts a model is produced which learns from this expertise and replicates their behaviour without intersubject bias.

The output of the segmentation operation gives us the saccades from which we are going to extract the biomarkers data. In a separate chapter, we explain how to compute these biomarkers values accurately and how to present them into a report for the medical staff. This report will allow the specialists to decide based on specific criteria or their own statistical analysis.

To fulfill the second goal, we present the development of a low-cost equipment that uses electrooculography to record eye movements. The hardware part of this equipment is based on the OpenBCI Cyton board, but with our own custom firmware that we named *OpenEOG*. To record and visualize the signals obtained by the *OpenEOG* we developed a software called *Saccade Recorder*. The software includes a visual stimulator that allows us to record saccadic eye movements in a controlled way, in order to use them in clinical environments. The system was tested by analyzing the data recorded to 10 healthy volunteers and comparing them against data from professional equipments and results in literature.

Our work shows how a fully automatic method can extract the saccadic information required by professional medical doctors to help them study neurological diseases such as SCA2. Also, we have shown that implementing a low-cost eye movement recording system is possible.

Keywords

Eye Movements; Saccades; Electrooculography; Spinocerebellar Ataxia type 2; Numerical Differentiation; Saccade Identification; Saccadic Biomarkers Extraction; Machine Learning; Supervised Learning

Resumen

Título: Tecnología para el procesamiento de electrooculogramas sacádicos en personas con Ataxia Espinocerebelosa tipo 2.

Introducción

La Ataxia Espinocerebelosa de tipo 2 (SCA2, por sus siglas en inglés) es un subtipo muy común de las ataxias hereditarias. Las ataxias hereditarias a su vez son un grupo de desórdenes neurodegenerativos causadas por las afectaciones que incurren en el cerebelo y sus conexiones, la médula espinal, por los nervios periféricos y el tallo cerebral. Esta enfermedad es causada específicamente por la repetición patológica del trinucleótido CAG en la región que codifica el gen ATXN2 [1]. Es válido resaltar que el término *ataxia* no se refiere a una enfermedad en específico o un diagnóstico predeterminado, sino al símtoma resultante del estado patológico de la coordinación del movimiento. A menudo utilizamos el término *ataxia* para describir trastornos en la marcha caracterizados por la inestabilidad, descordinación e incremento de la base de soporte [2].

Cuba es el país con la mayor tasa de prevalencia de personas con ataxias hereditarias. Las SCA2 es la forma molecular más frecuente entre todas aquellas encontradas en Cuba, donde la mayor cantidad de pacientes que sufren la enfermedad se encuentran en la provincia de Holguín. En [3] se aprecia una tasa de prevalencia de 7.55 casos por cada 100000 habitantes y la prevalencia de portadores de la mutación a 36.2 casos por cada 100000 habitantes. La tasa de prevalencia en Holguín es la más alta reportada a nivel mundial [4, 5] alcanzando los 154.33 casos por cada 100000 habitantes en el municipio de Báguanos [3]. Estos datos de prevalencia justifican el enorme interés de la comunidad científica cubana en el estudio de esta enfermedad.

El estudio de los movimientos oculares son una valiosa fuente de información para médicos y científicos. En el caso de los neurólogos, el estudio del control de los movimientos oculares presenta una oportunidad única para entender las funciones cerebrales [6]. Los movimientos de persecución (siguen un objeto que se mueven a baja velocidad en la escena visual) y los movimientos sacádicos (movimiento rápido que

cambia el foco de la mirada hacia una nueva posición), entre otros, son necesarios para el seguimiento de objetos en movimiento, lo que los convierte en una gran herramienta para evaluar el desempeño de esta tarea [7]. Es un hecho científicamente establecido que las SCAs afectan los movimientos oculares, donde la SCA2 en particular se caracteriza por enlentecer los movimientos sacádicos [2].

El Centro para la Investigación y Rehabilitación de las Ataxias Hereditarias (CIRAH) está localizado en Holguín, Cuba. Este centro es considerado líder a nivel mundial en la investigación de la SCA2. Científicos del departamento de Neurofisiología Clínica del CIRAH llevan a cabo variados estudios para evaluar medicamentos y tratamientos para luchar contra la SCA2 y otras ataxias hereditarias. El análisis de los movimientos oculares es una tarea recurrente en estos estudios para identificar cambios relevantes en marcadores biológicos (biomarcadores) como la velocidad máxima sacádica y la latencia sacádica. Para registrar los movimientos oculares, en el CIRAH se utiliza el electronistagmógrafo Otoscreen, fabricado por la empresa alemana Jaeger-Toennies.

El Otoscreen incorpora una aplicación de software para registrar y procesar movimientos oculares utilizando una técnica denominada electroculografía. Las pruebas clínicas de electroculografía se realizan de la siguiente manera. Antes de empezar el registro se le ordena al sujeto que siga el estímulo visual que aparecerá y desaparecerá en cada lado del monitor; se sienta al sujeto frente a un monitor con la cabeza fijada a una distancia predeterminada y luego se conectan electrodos alrededor de los ojos. Capturar los movimientos oculares de manera controlada permite a los investigadores identificar cuáles de estos movimientos son respuesta al estímulo (no espontáneos) y cuáles no (espontáneos). Las sácadas no espontáneas son útiles para extraer los biomarcadores que son significativos para seguir la evolución de las ataxias hereditarias.

La utilización de este equipamiento por los especialistas del CIRAH ha producido una base de datos única de movimientos oculares, registrados utilizando protocolos diseñados con propósitos clínicos. Esta base de datos ha contribuido al desarrollo de diversos tratamientos y a la generación de una cantidad relevante de conocimiento científico de la SCA2. Sin embargo, el protocolo de procesamiento utilizado en la actualidad tiene problemas que dificultan estudios mejores y más avanzados debido a las siguientes condiciones:

- La tubería de procesamiento de señales utilizado por el equipo es desconocida.
- Muchas de las señales registradas son contaminadas con ruido.
- Los algoritmos no identifican todos los eventos de movimientos oculares válidos, o establecen el inicio o fin de la sácada en la muestra de tiempo errónea.
- No es posible adicionar nuevas características o elementos de procesamiento.

- El equipamiento no es portable y necesitan de técnicos altamente especializados para su operación.

Debido a estos problemas, el personal del CIRAH utiliza el Otoscreen solo para el registro de los movimientos. Entonces, los especialistas editan las señales y establecen los puntos de inicio y fin de los eventos relevantes como las sácadas. Luego de la anotación manual de las señales, se emplean métodos tradicionales de estadística comparativa utilizando los biomarcadores extraídos para confirmar o rechazar sus hipótesis. Esta aproximación presenta algunos problemas. Primero, la anotación manual introduce subjetividad al proceso en general, dificultando la reproducibilidad de la investigación. Este problema se incrementa aún mas debido a la falta de estandarización en las reglas para el establecimiento de los puntos de inicio y fin de las sácadas. Existen diversos artículos que utilizan diferentes métodos y umbrales en la literatura médica.

Segundo, el ruido presente en algunos registros dificulta el proceso de segmentación de la señal y el cálculo de algunos biomarcadores. Si adicionamos a esta situación que los métodos y algoritmos utilizados por el equipamiento son desconocidos, la incertidumbre introducida para análisis posteriores es significativa.

Tercero, la complejidad y no portabilidad del equipamiento afecta la capacidad de llegar a pacientes que viven en áreas remotas o de poca capacidad adquisitiva. Muchas de estas personas apenas poseen movilidad y el desplazamiento al CIRAH en varias ocasiones es altamente costoso o directamente inaccesible en algunos casos.

Debido a esta situación podemos establecer el siguiente problema: *la necesidad de una tecnología portable que sea capaz de procesar automáticamente movimientos oculares sacádicos en pacientes afectados por la SCA2 para evitar la subjetividad y extraer los biomarcadores necesarios para estudios clínicos de manera confiable.*

Para solucionar el problema nos hemos trazado los siguientes objetivos:

1. Desarrollar una metodología de procesamiento de electrooculogramas sacádicos que extraiga los biomarcadores clínicos de interés de manera completamente automática.

2. Diseñar y evaluar un equipamiento de bajo coste y portable que pueda reemplazar el Otoscreen en el CIRAH.

El equipo de medición debe ser capaz de registrar los movimientos oculares utilizando la electroculografía. Entonces, deberá identificar de forma totalmente automática la ocurrencia de sácadas (ignorando las espontáneas), utilizando técnicas de aprendizaje automático. De estas sácadas se extraerán biomarcadores relevantes

(velocidad máxima, latencia, duración y amplitud) y se exportarán a formatos estandarizados para su posterior análisis. Todo este proceso debe ser realizado de la manera más simple posible minimizando la interacción del especialista con la aplicación.

Estructura del documento

Hemos estructurado esta tesis en ocho capítulos con el siguiente orden:

Introducción: exponemos la motivación para el desarrollo de este trabajo, así como define el problema y los objetivos de la investigación.

Estado del Arte: describimos los métodos y técnicas utilizadas en el procesado de electrooculogramas. Primero se define el proceso de manera global y luego se detallan cada uno de sus etapas. Finalmente este capítulo presenta los fundamentos de las técnicas de inteligencia computacional utilizadas en nuestra investigación.

Diferenciación de electrooculogramas: evaluamos 16 métodos de diferenciación numérica para las tareas de identificación de sácadas y extracciom de biomarcadores. Para evaluar los métodos, diseñamos un experimento que compara todos ellos y analiza estadísticamente sus resultados. Finalmente, se selecciona el mejor método para cada una de las tareas propuestas. Los resultados de este capítulo fueron publicados en [8].

Identificación de sácadas: proponemos y evalúa un algoritmo de identificación de sácadas. Se exploran varias técnicas de aprendizaje automático como el Perceptron Multicapa y los Bosques Aleatorios (Random Forest en su denominación internacional) para identificar movimientos oculares sacádicos. Los resultados de este capítulo fueron publicados en [9].

Identificación de sácadas no espontáneas: desarrollamos un método que es capaz de discriminar entre sácadas útiles para el análisis clínico (no espontáneas) y cuáles no. Además, se seleccionan los biomarcadores más relevantes para clasificar sujetos sanos de sujetos con SCA2 utilizando técnicas de selección de atributos. Los resultados de este capítulo se publicaron en [10, 11].

Extracción de biomarcadores sacádicos: utilizamos los resultados obtenidos en los dos capítulos anteriores para extraer los datos requeridos por el personal médico para tomar decisiones clínicas. Mostramos el método utilizado para calcular de forma precisa cada uno de estos biomarcadores para la SCA2. Finalmente, presentamos el reporte que se le provee a los especialistas del CIRAH.

Equipamiento de registro OpenEOG: diseñamos y evaluamos un instrumento de medición de movimientos oculares de bajo coste y portable. Este equipo incluye los algoritmos desarrollados en este trabajo para automatizar la tubería de procesamiento.

Conclusiones: exponemos las principales contribuciones de este trabajo.

A continuación se resumirá el trabajo realizado en cada capítulo.

Estado del arte

Este capítulo se dedica a exponer los principales elementos de la literatura científica actual utilizados durante nuestra investigación. Primero se exponen los fundamentos biológicos de los movimientos oculares así como sus métodos de captura. Luego definimos una tubería de procesamiento de 6 etapas, detallando cada una de ellas. Los capítulos posteriores tratan con mayor profundidad los resultdos del desarrollo de cada una de las etapas y nuestros principales aportes.

Movimientos oculares

Los movimientos oculares son aquellos realizados por seres humanos y animales que garantizan una visión estable y clara de su ambiente. De acuerdo con [6] existen 7 tipos de movimientos oculares:

Vestibulares: mantienen imágenes en la retina de forma estable durante rotaciones breves de la cabeza.

Optocinéticcos: mantienen la imagen en la retina de forma estable durante rotaciones significativas de la cabeza.

Fijaciones: mantienen la imagen de un objeto estacionario en la fóvea.

Persecución suave: mantienen la imagen de un pequeño objeto en movimiento en la fóvea; o mantiene la imagen de un objeto pequeño o un objeto cercano durante un movimiento lineal con respuestas opticinéticas que ayudan a la estabilización de la mirada durante rotaciones significativas de la cabeza.

Fases rápidas de Nistagmos: reinician los ojos durante una larga rotación y redirigen la mirada hacia una nueva escena visual.

Vergencia: mueven los ojos en una dirección opuesta de forma que las imágenes de un objeto se localizan en ambas fóveas.

Sácadas: mueven las imágenes de objetos de interés a la fóvea.

Existen tres tecnologías fundamentales para el registro de movimientos oculares: la electroculografía, la lente de contacto escleral / bobina de búsqueda y la videooculografía.

La electroculografía es de las técnicas más utilizadas con fines clínicos, fue introducida en 1934 por Fenn y Hursh y se basa en la medición del potencial eléctrico que se genera en el área retina-córnea cuando ocurre una rotación ocular [12]. La principal ventaja de esta técnica es su baja invasividad (ayuda a la cooperación del paciente) y la posibilidad de registrar movimientos horizontales de hasta $\pm 40°$ con una resolución de $1°$ [6]. Es importante señalar que la señal resultante del registro con esta técnica se le denomina electrooculograma.

La lente de contacto escleral / bobina de búsqueda es una técnica introducida por Robinson en [13]. Esta técnica consiste en colocar una pequeña bobina de alambre embebida en una lente de contacto directamente en el ojo del sujeto. Esta es una técnica altamente invasiva con alta resolución espacial (menos de $1°$) y alta resolución temporal (menos de 1 ms). Sin embargo en muchos sujetos la aplicación de esta técnica presenta problemas con la tolerancia de las lentes de contacto que incluso llevan al desplazamiento de las lentes agregadas introduciendo errores en la señal de posición [14].

La videooculografía está basada en el procesamiento de las imágenes de los ojos capturadas con una cámara infraroja para determinar la posición horizontal y vertical de los ojos. Estas posiciones pueden ser convertidas a valores angulares utilizando procedimientos de calibración [15]. Actualmente es la técnica más empleada para el registro de movimientos oculares debido a su baja invasividad. Sin embargo, el enorme costo del equipamiento requerido para el registro de sácadas con fines clínicos es demasiado alto, generalmente mayor de 10 000 euros en la actualidad.

Los movimientos oculares y la SCA2

La disminución de la velocidad máxima sacádica es una de las características clínicas más comunes presentes en sujetos que sufren de SCA2. Esta situación se encuentra en el 98 % de los casos con SCA2. Esto permite confirmar la presencia de SCA2 utilizando este biomarcador [2]. Además de la SCA2, la velocidad máxima sacádica es útil para el estudio de otras enfermedades neurológicas como la distrofía miotónica y la degeneración olivopontocerebelosa. Las principales anomalías de la velocidad sacádica presentes en sujetos con SCA2 evidencian alteraciones cualitativas relacionadas con la morfología y amplitud del electrooculograma. Desde un punto de vista cualitativo se caracteriza por [2, 16]:

1. Enlentencimiento de la velocidad sacádica.

2. Incremento anormal de las latencias.

3. Dismetría sacádica. Desviación hipermétrica de los movimientos sacádicos para ángulos de estímulo de 10°, 20°, 30° y desviación hipométrica para 60°.

Las sácadas son consideradas lentas o rápidas cuando sus velocidades máximas se encuentran dentro o fuera del rango de la relación velocidad-amplitud. Existe un incremento de la latencia sacádica en 80 % de los sujetos con SCA2 que se expresa fisiológicamente en una demora de la iniciación de las sacádas. La dismetría sacádica, especialmente la hipermetría es un síntoma electrofisiológico tradicional de afectaciones cerebelares [2].

Procesado de electrooculogramas

Considerando que nuestro trabajo se relaciona con el procesamiento de electrooculogramas para el diagnóstico de enfermedades neurológicas como la SCA2, se hace necesario revisar cómo este proceso se realiza en la actualidad en el CIRAH. El resultado de este análisis nos ayudará a identificar qué partes del proceso pueden ser automatizados o mejorados.

El proceso de registro y análisis de electrooculogramas consiste básicamente en 3 etapas: registro, procesamiento y diagnóstico. La etapa de registro tiene como objetivo obtener las señales que se utilizarán como entrada en el resto del proceso. La etapa de procesado se enfoca en la manipulación de los registros obtenidos para extraer la información requerida por la etapa de diagnóstico. En general el procesamiento se puede separar a su vez en 4 sub-etapas: filtrado, diferenciación, segmentación y extracción de características. El diagnóstico es la última etapa y es el objetivo del proceso en general. Esta consiste en proporcionar al personal médico información cuantitativa interpretable que les permita tomar decisiones relacionadas con la evolución del paciente o la evaluación de tratamientos.

En la etapa de registro utilizamos los electrooculogramas obtenidos utilizando el Otoscreen en el CIRAH. Estas señales se registraron utilizando protocolos de medición de movimiento horizontales sacádicos con una frecuencia de muestreo de 200 Hz y un filtro de paso-alto de 100 Hz. Se utiliza una prueba de calibración horizontal para calcular el coeficiente que permita convertir de μV a posición angular en grados (°).

La etapa de filtrado se centra en reducir o eliminar, si es posible, los ruidos que puedan afectar el procesado de las señales. En los electrooculogramas nos encontramos de manera frecuente ruidos biológicos provocados por temblores y parpadeos, así como ruidos introducidos por el instrumento de medición como es el ruido de ancho de banda o el ruido de cuantificación causados por el proceso de conversión analógico a digital. Los temblores provocados por la enfermedad son visibles en la forma de onda de la señal como componentes de alta frecuencia y baja amplitud.

La presencia de ruido impulsivo debido a parpadeos es otro de los fenómenos típicos presentes en los electrooculogramas [17]. A este se le añade una componente de ruido alrededor de los 60 Hz que coinciden con la frecuencia de la línea eléctrica en Cuba.

Existen varias técnicas para eliminar los ruidos anteriormente mencionados. Entre éstos se encuentran los filtros de Respuesta Finita al Impulso (FIR) y Respuesta Infinita al Impulso (IIR) [18, 17], filtros de medianas [19, 17], filtros basados en la Transformada Discreta de Fourier (DWT) [20], y muchos otros más.

El estudio realizado por Juhola en [19] determinó que el filtro de medianas es adecuado para eliminar los ruidos presentes en las señales sacádicas debido a que disminuye el ruido sin afectar el valor de biomarcadores relevantes como la velocidad máxima sacádica.

Calcular el perfil de velocidad de un electrooculograma es un paso fundamental en varios algoritmos de procesamiento. Debido a la naturaleza discreta de estas señales, esta operación se realiza mediante el empleo de métodos de diferenciación numérica.

Utilizando los polinomios de interpolación de Lagrange se han desarrollado varios métodos de diferenciación conocidos comúnmente como métodos de la diferencia central. La diferencia central con 3 (Ecuación 1) y 5 (Ecuación 2) puntos han sido utilizados en electrooculogramas por Bahill y MacDonald en [21] y Niemenlehto en [22]. Este último método debe ser utilizado en serie con un filtro de paso-bajo para obtener los mejores resultados [23].

$$f'(x_0) = \frac{f(x_1) - f(x_{-1})}{2h} \tag{1}$$

$$f'(x_0) = \frac{f(x_{-2}) - 8f(x_{-1}) + 8f(x_1) - f(x_2)}{12h} \tag{2}$$

Inchingolo y Spanio también propusieron algoritmos basados en la diferencia central, declarados en su forma general en la Ecuación 3, donde f_s es la frecuencia de muestreo [24]. Además para una frecuencia de muestreo de 200 Hz determinaron que es apropiado el empleo de la diferencia central de 9 puntos y los coeficientes $a_1 = 0{,}8024$, $a_2 = -0{,}2022$, $a_3 = 0{,}03904$, $a_4 = -0{,}003732$ como se muestra en la Ecuación 4.

$$f'(x_0) = f_s \sum_{n=1}^{m} a_n \{f(x_n) - f(x_{-n})\} \tag{3}$$

$$f'(x_0) = 200 \sum_{n=1}^{4} a_n \{f(x_n) - f(x_{-n})\} \tag{4}$$

Además los métodos basados en la diferencia central, los investigadores han utilizado con éxito los diferenciadores Lanczos (también conocidos por Savitzky-Golay).

Su principal diferencia con respecto a los métodos basados en la diferencia central es que se emplea el ajuste de curvas en vez de la interpolación para la aproximación de la señal. En la Ecuación 5 se muestra un diferenciador Lanczos de 7 puntos [25].

$$f'(x_0) = \frac{-3f(x_{-3}) - 2f(x_{-2}) - f(x_{-1}) + f(x_1) + 2f(x_2) + 3f(x_3)}{28h} \tag{5}$$

La segmentación de los electrooculogramas se refiere al establecimiento de los puntos de inicio y fin de los eventos contenidos en ellos. Esta etapa se puede lograr de forma manual o de forma automática dependiendo de la aproximación elegida. La segmentación manual es realizada por expertos utilizando una interfaz gráfica. El problema principal con este método es la subjetividad, debido a que el criterio de anotación cambia de experto a experto. Sin embargo, la anotación manual permite corregir los errores producidos por los algoritmos automáticos, por ejemplo la eliminación de sácadas detectadas erróneamente.

La algoritmos de segmentación automática no sufren de la subjetividad presente en su contraparte manual debido a que se basan en reglas y umbrales previamente definidos. Aplicando los mismos parámetros y umbrales garantiza la uniformidad de criterios en la salida del proceso.

El problema de la segmentación automática de sácadas es tratado desde distintas aproximaciones. La aproximación más común emplea umbrales de velocidad. Estos métodos se basan en el principio de establecer los puntos de inicio y fin de sácadas, los cuáles ocurren cuando la velocidad instantánea excede un umbral predefinido [22, 24, 26, 27, 28]. Variaciones de estos métodos se han desarrollado utilizando los perfiles de aceleración y jerk, por ejemplo los algoritmos propuestos en [29].

Una vez que los electrooculogramas han sido segmentados, procedemos a extraer los biomarcadores a partir las sácadas y fijaciones identificadas. Estos biomarcadores poseen el significado clínico necesario para el diagnóstico y seguimiento de varias enfermedades neurológicas como la SCA2.

La duración y la velocidad máxima son dos de los biomarcadores más relevantes en el análisis de los movimientos oculares. Existe una relación directa entre ellos denominado *secuencia principal*, que han sido empleados por varios autores para caracterizar el comportamiento del sistema oculomotor [26, 30, 31, 32]. La velocidad máxima sacádica es considerado un biomarcador muy sensible y de alto valor endofenotípico para el diagnóstico de la SCA2 [4].

Diferenciación de electrooculogramas

En la literatura consultada hemos encontrado cuatro familias de métodos de diferenciación numérica basados en distintas aproximaciones matemáticas: Diferencia Cen-

tral (CD), Lanczos (L), Super Lanczos (SL) y Suave Robusto al Ruido (SNR). Los métodos basados en la Diferencia Central y Lanczos han sido utilizados para la diferenciación de electrooculogramas. Sin embargo, para el resto de los métodos no hemos encontrado aplicación directa en señales de movimientos oculares. Por lo que es muy interesante evaluar el rendimiento de los métodos como los Super Lanczos y los métodos Suave Robusto al Ruido para esta tarea en específico.

El objetivo de este capítulo es comparar los métodos de diferenciación numérica mencionados anteriormente para su aplicación en la identificación de sácadas y la extracción de biomarcadores sacádicos. Esta comparación debe ser basada en valores cuantitativos de los errores introducidos por cada uno de los algoritmos en las tareas referidas. Para medir el rendimiento de cada método, se utilizará un conjunto de señales sacádicas sintéticas con diferentes amplitudes de estimulación e imitando distintos estadios de pacientes (sano, enfermo con SCA2) al que se le ha adicionado una serie de ruidos previamente conocidos. Controlar el proceso de generación de las señales sintéticas nos permite contar con los datos exactos de la salida si fuese perfecta, soportando nuestro marco de comparación.

Para cumplir el objetivo trazado comparamos 16 métodos de diferenciación que pertenecen a las 4 familias introducidas previamente: Diferencia Central (CD3, CD5, CD7, CD9), Lanczos (L5, L7, L9, L11), Super Lanczos (SL7, SL9, SL11) y Suave Robusto al Ruido (SNR5, SNR7, SNR9, SNR11). Como se puede observar, a cada uno de los métodos se le añade un sufijo con la longitud del filtro correspondiente. Nuestro experimento compara el rendimiento utilizando 4 métricas distintas:

- Error Medio Cuadrático (MSE, Mean Square Error) entre la salida del método como señal aproximada y el perfil sintético de velocidad como señal exacta.
- Cantidad de sácadas no identificadas.
- Cantidad de sácadas erróneamente identificadas.
- Error absoluto introducido en el cálculo de los valores de los biomarcadores.

Finalmente, nuestro experimento queda estructurado de la siguiente manera:

1. Generar las señales sacádicas sintéticas utilizando parámetros característicos de los electrooculogramas para sujetos sanos y enfermos de SCA2. Obtenemos el Perfil de Velocidad Exacta (EVP) del cuál los registros sacádicos son generados.
2. Aplicar cada método de diferenciación a los electrooculogramas sintéticos con el ruido adicionado, resultando en los Perfiles de Velocidad Aproximados (AVP).
3. Para cada AVP:

a) Calcular el MSE entre el EVP y AVP. Analizar los resultados y eliminar los métodos con rendimiento significativamente inferior.

b) Identificar las sácadas utilizando el AVP y compararlo con las sácadas exactas identificadas utilizando el EVP. Comparamos el rendimiento del proceso de identificación utilizando las métricas de sácadas no identificadas y sácadas sobre identificadas (falsos positivos). Todas las sácadas correctamente identificadas utilizando el AVP son definidas como AS y su contrapartida exacta identificadas con el EVP se define como ES.

c) Para cada AS y su ES asociada se calculan los biomarcadores velocidad máxima, latencia y duración. Por cada par (ES, AS) y para cada biomarcador, se calcula el error utilizando el valor absoluto del biomarcador(ES) - biomarcador(AS).

4. Analizar estadísticamente los resultados de los pasos previos y determinar cuál método es el más adecuado para cada una de las diferentes tareas en el procesamiento de movimientos oculares sacádicos.

Las señales sintéticas fueron generadas utilizando el método descrito por Coughlin en [33]. Este método sigue el proceso inverso de la generación natural de las señales: primero se generan los perfiles de velocidad y luego se integran matemáticamente para obtener el perfil de posición. Los parámetros característicos empleados para generar las señales sintéticas son la velocidad máxima, latencia y duración que fueron obtenidos a partir del análisis estadístico realizado a registros de sujetos sanos y enfermos de SCA2.

Como primer resultado obtenido del experimento podemos señalar que los métodos de la Diferencia Central no son adecuados para nuestra tarea específica. El nivel de ruido introducido por este conjunto de métodos obstaculiza el procesado posterior de las señales. Para la tarea de identificación de sácadas el resto de los métodos se comportan razonablemente bien, con los métodos L9, L11, SL11 y SNR11 obteniendo puntuación perfecta.

Para cada biomarcador sacádico incluido en nuestro estudio, el experimento resulta en un conjunto único de métodos para cada uno de ellos. Respecto a la velocidad máxima sacádica se recomienda utilizar el método SL11. En el caso de la latencia sacádica se recomiendan cualquiera de los siguientes métodos: SNR11, SL11, SNR9. En el caso de la duración sacádica puede emplear los métodos L11 y L9.

Es importante señalar que algunos de los métodos con mejor rendimiento como el SL11, SNR9 y SNR11 no han sido previamente utilizados en electrooculogramas, siendo una contribución fundamental de este capítulo.

Identificación de sácadas

Las sácadas son un tipo de movimientos oculares rápidos que cambian la dirección de la mirada hacia una nueva localización. Los puntos sacádicos son aquellos donde inicia y termina la sácada, aunque no existe un criterio unificado donde ubicar estos. Actualmente la identificación de estos puntos es realizada por expertos manualmente o automáticamente utilizando algoritmos computacionales.

La identificación manual tiene como principal inconveniente la subjetividad introducida por el experto que realiza la selección de puntos. Esta subjetividad genera variabilidad entre la anotación efectuada por distintos expertos. En el caso de registros de sujetos enfermos, la dificultad de la anotación se incrementa debido a la presencia de ruidos y condiciones inherentes a la enfermedad.

Los métodos para la detección automática de puntos sacádicos son muy variados y de alguna forma formalizados en la taxonomía de Salvucci-Goldberg [34]. Entre los métodos incluidos en la taxonomía los más comunes son los basados en umbrales de velocidad. Estos métodos tienen como principal inconveniente que en registros de sujetos afectados por enfermedades neurológicas como la SCA2, la identificación de puntos sacádicos contiene alto niveles de error. Por otro lado, no existe un consenso en la literatura sobre los valores del umbral de velocidad empleado por estos métodos.

A partir de estas consideraciones, se deben explorar nuevos métodos para solucionar el problema de la identificación de saćadas. El aprendizaje automático, específicamente el aprendizaje supervisado, es una rama de la inteligencia artificial utilizada comúnmente en problemas de clasificación. Además, estas técnicas se emplean para clasificar patrones de señales de EOG [35, 36, 37]. En este capítulo proponemos dos métodos de clasificación para el problema de la clasificación de puntos sacádicos y no sacádicos en sujetos con SCA2 y analizamos su rendimiento. Los métodos analizados son el Perceptron Multicapa (MLP, por Multilayer Perceptron) y los Bosques Aleatorios (RF, por Random Forest).

Para la comparación de los métodos se diseñó un experimento que se describe a continuación:

Etapa I: se prepara el dataset con los vectores que se utilizarán en la siguiente etapa. Esta población de vectores se construye basada en las señales electrooculográficas segmentadas (sacádico o no sacádico) anotados en esta etapa.

Etapa II: selección de los datos de entrenamiento y validación teniendo en cuenta el balance de los casos más típicos.

Etapa III: entrenamiento y validación de ambos clasificadores, utilizando el modelo de partición por porcentaje para separar los datos de entrenamiento y validación.

En este experimento se utilizaron electrooculogramas obtenidos utilizando el Otoscreen y anotados mediante una aplicación de escritorio desarrollada por el autor.

La idea para las variables de entrada de un caso es seleccionar un patrón de puntos anterios y posteriores al punto que se está analizando en forma de ventana. Para construir los casos que conforman la población de datos, una ventana deslizante se mueve a través de cada uno de los puntos etiquetados utilizando la etiqueta del punto como la clase de salida del ejemplo.

Los resultados obtenidos de la validación de ambos métodos mostraron una exactitud superior al 92 %, por lo que los consideramos adecuados para la tarea en cuestión sin los inconvenientes que presentan los métodos tradicionales. Además, los resultados muestran un rendimiento ligeramente superior por parte de los Bosques Aleatorios sobre el Perceptron Multicapa.

Una de las ventajas fundamentales de los Bosques Aleatorios es que se podrían utilizar en un sistema de identificación de tiempo real debido a su rendimiento relacionado con la velocidad de entrenamiento y evaluación, además de por su exactitud.

Indentificación de sácadas no espontáneas

En el capítulo anterior se propuso un método que identifica movimientos oculares sacádicos utilizando una aproximación muestra-a-muestra. Este método nos permite discriminar si una muestra pertenece a un movimiento sacádico o no. En este capítulo utilizamos esta información pero para identificar cuáles de estos movimientos están relacionados con el estímulo (no espontáneos) y cuáles no, utilizando una aproximación basada en características. Además, evaluamos la utilización de algoritmos de aprendizaje automático teniendo en cuenta las fortalezas de las pruebas clínicas de electrooculografía para resolver la tarea propuesta. Nuestra aproximación utiliza señales de movimiento oculares horizontales y señal de estímulo, y no requiere de umbrales u otra entrada de usuario. Para ello, un nuevo conjunto de características fue seleccionado para entrenar los modelos teniendo en cuenta las características de movimientos sacádicos válidos.

Como modelo de clasificación evaluamos cuatro de ellos: Máquinas de Soporte Vectorial (SVM, por Support Vector Machines) [38], K-Vecinos más Cercanos (KNN, por K-Nearest Neighbors) [39], Árboles de Clasificación, Regresión (CART, por Classification and Regression Trees) [40] y Naive Bayes [41]. La selección de los métodos se realizó basada en la diferencia en los principios de funcionamiento de estos.

Para evaluar los algoritmos seleccionados diseñamos el siguiente experimento. La primera etapa consiste en detectar sácadas y anotarlas para construir el conjunto de datos que emplearemos en las siguientes etapas. Entonces, seleccionamos las mejores características a partir de las 10 consideradas inicialmente, para la tarea de clasifi-

cación de estadíos (enfermo de SCA2, sano) de pacientes. Una vez obtenido el mejor conjunto de características, procedemos a ajustar los parámetros de los modelos seleccionados para encontrar los más adecuados utilizando validación cruzada con 10 pliegues. Finalmente, comparamos el rendimiento de los modelos usando datos no empleados en el proceso de entrenamiento y validación cruzada empleando las métricas de exactitud, sensitividad y precisión.

Los modelos evaluados se entrenaron con un total de 8606 impulsos, 1797 sácadas válidas y 6809 sácadas inválidas. Para la etapa de evaluación externa (se utilizan impulsos no utilizados en el proceso de entrenamiento) se utilizaron 3797 impulsos, 704 impulsos sacádicos y 3093 no sacádicos.

La evaluación del rendimiento de los diferentes métodos se realizó utilizando Exactitud, Sensitividad y Precisión. La validación externa de los cuatro métodos resultó en exactitudes sobre el 95 %, sensitividad sobre el 92 % y precisión sobre el 83 %. Específicamente las Máquinas de Soporte Vectorial obtuvieron valores de rendimiento de 97 %, 96 % y 90 % de las tres métricas respectivamente. Estos resultados exceden de forma significativa las reportadas por la literatura en trabajos relacionados.

Extracción de biomarcadores sacádicos

El término *biomarcador* de acuerdo con [42] es *"una característica medida de forma objetiva y evaluado como un indicador de un proceso biológico normal, un proceso patogénico o una respuesta farmacéutica a la intervención terapéutica"*. Una definición más amplia fue desarrollada previamente por el Programa Internacional de Seguridad Química de la Organization Mundial de la Salud (WHO) en coordinación con las Naciones Unidas (UN) y la Organización Mundial del Trabajo (ILO) y establece que *"cualquier sustancia, estructura, o proceso que pueda ser medido en el cuerpo o su producto e influencia, o que pueda predecir la incidencia del resultado o de una enfermedad "* [43]. En resumen, los biomarcadores son características objetivas y medibles de los procesos biológicos [42].

Los perfiles de movimientos oculares por si mismos no son suficiente para extraer el conocimiento requerido por los estudios clínicos. Una vez que tenemos identificadas el conjunto de sácadas no espontáneas, podemos extraer de estas los biomarcadores de relevancia clínica. Existen varios biomarcadores sacádicos como son la *amplitud*, la *desviación*, la *latencia*, la *duración*, la *velocidad máxima* y muchos otros. Por ejemplo, en [44] se identificaron alteraciones en los tiempos de reacción (latencia sacádica) que están relacionadas con enfermedades neurodegenerativas como es el Alzheimer, el Parkinson, la Esclerosis Latetal Amiotrófica (ELA), por solo citar algunas. En sujetos con SCA2 se observan un decrecimiento tanto en la velocidad máxima sacádica como en la exactitud sacádica (*desviación*), y un incremento en la latencia sacádica [45].

A continuación definimos cada uno de estos biomarcadores:

Latencia: es un biomarcador temporal que representa el tiempo transcurrido entre el cambio de estímulo y el inicio de la sácada. Se representa en segundos.

Duración: es un biomarcador temporal que representa el tiempo transcurrido entre el inicio y fin de la sácada. Se representa en segundos.

Amplitud: es un biomarcador espacial que representa el desplazamiento angular realizado por los ojos entre el inicio y fin de la sácada. Se representa en grados.

Desviación: es un biomarcador espacial que representa la proporción entre la amplitud y el ángulo de estímulo.

Velocidad máxima: es un biomarcador cinético que representa la velocidad máxima alcanzada entre el inicio y fin de la sácada. Se representa en grados/segundo.

En este capítulo detallamos un procedimiento para calcular los biomarcadores anteriormente definidos a partir de sácadas previamente identificadas. Se provee una metodología basada en un modelo matemático continuo que evita el ruido presente en las señales y que son amplificados debido a la diferenciación numérica utilizada. Utilizando técnicas de optimización, se ajusta el modelo al vector de posición (porción del electrooculograma) donde se encuentra la sácada. Dado que nuestro modelo es diferenciable, se puede obtener el perfil de velocidad exacto mediante la evaluación de los parámetros ajustados en la derivada del modelo. Este perfil de velocidad ajustado nos permite establecer los puntos de inicio y fin de la sácada de manera más precisa, operación que es crítica para minimizar los errores en los valores de los biomarcadores.

Finalmente, se muestra un ejemplo de reporte que se le muestra al personal médico de forma que este pueda tomar decisiones clínicas informadas.

OpenEOG: Equipamiento de Medición

El objetivo fundamental de este capítulo es de diseñar un dispositivo capaz de registrar los movimientos oculares de forma controlada y extraer los biomarcadores de relevancia de forma que el personal médico pueda tomar decisiones clínicas. Además, este dispositivo debe ser capaz de reemplazar al Otoscreen utilizado actualmente en el CIRAH y ofrecer una mejora de sus prestaciones.

Proyectamos un costo de menos de 1000 euros por unidad, de esta forma el sistema de salud cubano puede permitirse varios de estos y dispersarlos en todo el territorio nacional. Esto debería aliviar la situación actual originada por solo tener un único equipo de este tipo en todo el país, forzando a los pacientes a moverse cientos de

kilómetros en condiciones difíciles para recibir atención. Además, consideramos razonable disponer de más de un dispositivo para realizar la misma tarea por razones de redundancia. En la acualidad, un fallo en el funcionamiento del Otoscreen implica que la investigación de estas enfermedades y la asistencia clinica a los pacientes quedan interrumpidas.

En este capítulo se discute el diseño de un dispositivo propio que capture los movimientos oculares utilizando la electrooculografía. Hemos denominado a este dispositivo como OpenEOG, y está basado en el hardware que provee el OpenBCI a través de la tarjeta Cyton. Primero definimos los requerimientos funcionales del sistema que guiarán el proceso de desarrollo. A continuación, se describe el hardware involucrado en nuestra solución y la interacción entre sus componentes. Además se explica el diseño de nuestra aplicación de control y la justificación de las tecnologías seleccionadas para su desarrollo.

El intrumento de medición que se obtiene por el trabajo de este capítulo posee características de frecuencia de muestreo, resolución del Convertidor Analógico a Digital (ADC), filtrado, entre otras, que se requieren para el registro de sácadas para aplicaciones clínicas como es el estudio de la SCA2. Desde una perspective económica, el instrumento logra el objetivo de costar menos de 1000 euros y el factor de forma de los componentes elegidos garantizan la portabilidad del mismo. La utilización de baterías evita situaciones de peligro para el sujeto, lo que contribuiría a su certificación como equipo médico.

El software incluido con el hardware ofrece una interfaz de usuario simple para el diseño de estudios de movimietos oculares y el registro de sus señales. Además, la arquitectura diseñada provee mecanismos de extensión que permiten añadir de forma simple nuevas características a la aplicación. Los archivos de salida de la aplicación ayudan al post-procesado de las señales debido al uso de formatos de archivo estandarizados. El firmware desarrollado para el OpenEOG permite controlar el proceso de registro haciéndolo más rápido y confiable.

Los datos sacádicos extraídos de nuestro equipamiento son similares a lo extraídos utilizando registros del Otoscreen, utilizando la secuencia principal como modelo de comparación. Además, para biomarcadores específicos como la latencia sacádica se presentan resultados similares a los reportados en la literatura. Por lo que consideramos que el instrumento puede realizar por lo menos las mismas tareas que realizaba el Otoscreen.

Conclusiones

En esta tesis se ha estudiado a fondo el procesamiento de los movimietos oculares y su relación con algunas enfermedades neurodegenerativas como la SCA2. Con este

estudio se establecen las etapas del procesamiento de electrooculogramas que son: el filtrado, la diferenciación, la segmentación y la extracción de características. Por lo que hemos enfocado todos los esfuerzos de este trabajo en el ajuste y optimización de cada una de estas etapas.

En la etapa de filtrado utilizamos el filtro de medianas, el más utilizado en la literatura para la eliminación de ruidos en señales de movimienos oculares sin comprometer la forma de onda de las señales.

En la etapa de diferenciación comparamos el rendimiento de 16 algoritmos específicamente para las tareas de identificación de sácadas y extracción de biomarcadores, lo que nos permitió determinar para cada tarea el conjunto óptimo de ellos.

En los capítulos de identificación de sácadas y clasificación de sácadas en espontáneas y no espontáneas se logró entrenar modelos supervisados con una exactitud superior al 90 % en todos los casos. Además, se realizó un proceso de selección de los mejores biomarcadores para la clasificación de estadios de pacientes. Estos algoritmos eliminan la subjetividad introducida por la segmentación manual realizada en la actualidad por el personal médico del CIRAH.

En el capítulo de extracción de biomarcadores se logra obtener una metodología para el cálculo de estos que minimiza los errores introducidos por las etapas anteriores del proceso, así como definir formalmente los más utilizados por el personal médico y su clasificación según categoría física de la propiedad de la señal con la que funciona.

Por último, se logró diseñar un instrumento de medición de los movimientos oculares que cumple con los requerimientos funcionales propuestos, así como las restricciones de costo y portabilidad. Los datos extraídos por el instrumento son similares a los extraídos por equipamiento profesional como el Otoscreen, por lo que se puede afirmar que pudiera ser su futuro reemplazo.

Todo lo anterior planteado nos lleva a concluir que los objetivos de esta tesis han sido cumplidos.

Contribuciones principales

- Se define la tubería de procesamiento de movimientos oculares sacádicos.

- Se seleccionan los mejores métodos de diferenciación numérica para las tareas de identificación de movimientos sacádicos y extracción de biomarcadores sacádicos.

- Se obtiene un modelo para la clasificación de puntos de un electrooculograma en punto sácadico o punto no sacádico.

- Se obtiene un modelo para la clasificación de sácadas en espontáneas y no espontáneas.

- Se obtiene el mejor conjunto de biomarcadores que separan a sujetos sanos de sujetos con SCA2.

- Se define un modelo matemático continuo para el cálculo de biomarcadores sacádicos robusto frente a los artefactos intintroducidos en las etapas previas del procesamiento.

- Se desarrolla un instrumento para la medición de los movimientos oculares sacádicos que integra todos los aportes de la tesis y los hace disponibles de forma simple al personal médico.

Publicaciones que avalan la tesis

- **Becerra-García, R.**, Joya-Caparrós, G., García-Bermúdez, R., Velázquez-Pérez, L., Rodríguez-Labrada, R., & Pino-Ávila, C. (2013). Saccadic Points Classification Using Multilayer Perceptron and Random Forest Classifiers in EOG Recordings of Patients with Ataxia SCA2. In I. Rojas, G. Joya, & J. Cabestany (Eds.), Advances in Computational Intelligence (pp. 115–123). Springer Berlin Heidelberg. Retrieved from

  `http://link.springer.com/chapter/10.1007/978-3-642-38682-4_14`.

- **Becerra-García, R.**, García-Bermúdez, R., Joya-Caparrós, G., García-Lagos, F., Fernández-Higuera, A., Velázquez-Rodríguez, C., Velázquez-Mariño, M. & Rodríguez-Labrada, R. (2015). Non Spontaneous Saccadic Movements Identification in Clinical Electrooculography Using Machine Learning. In I. Rojas, G. Joya, & A. Catala (Eds.), Advances in Computational Intelligence (Vol. 9095, pp. 56–68). Springer International Publishing.

  `https://doi.org/10.1007/978-3-319-19222-2`.

- **Becerra-García, R. A.**, García-Bermúdez, R. V., Joya-Caparrós, G., García-Lagos, F., Fernández-Higuera, A., Velázquez-Rodríguez, C., Velázquez-Mariño, M. & Rodríguez-Labrada, R. (2016). Data mining process for identification of non-spontaneous saccadic movements in clinical electrooculography. Neurocomputing, 250, 28–36.

  `https://doi.org/10.1016/j.neucom.2016.10.077`.

- **Becerra-García, R. A.**, García-Bermúdez, R., & Joya, G. (2021). Differentiation of saccadic eye movement signals. Sensors, 21(15), 1–12.
  https://doi.org/10.3390/s21155021.

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Chapter 1

Introduction

The Spinocerebellar Ataxia type 2 (SCA2) is a common subtype of hereditary ataxias. The hereditary ataxias are a heterogeneous group of neurodegenerative disorders caused by degeneration of cerebellum and its connections, spinal cord, peripheral nerves, and the brainstem. It is caused by the pathological repeat expansion of the trinucleotide CAG in the coding region of the ATXN2 gene [1]. The term ataxia does not refer to a specific disease nor a predetermined diagnosis, but the resulting symptom of a pathological state of the movement coordination. Often, we use the term to describe gait disorders characterized by instability, incoordination and increase of the support base [2].

Clinically, SCA2 is associated with gait ataxia, postural instability, dysmetria, cerebellar dysarthria, and dysdiachokinesia. These disorders can be accompanied by a slowing of horizontal saccadic eye movements and other less evident symptoms [46]. Unfortunately, there are no effective treatments available today to fight against the disease, and eventually people pass away because of their inability to perform critical biological functions such as feeding. However, there are some therapeutic strategies such as physical therapy and the use of some drugs that can improve the quality of life of the people suffering the disease [1].

Cuba is the country with the highest prevalence of people suffering from hereditary ataxias. The SCA2 is the most frequent molecular form found in Cuba, where the highest amount of sick people is in Holguin's province. In [3] a national rate of prevalence of 7.55 cases/100000 inhabitants and mutation carries a prevalence of 36.2 cases/100000 inhabitants. The prevalence of the disease in Holguin's is the highest worldwide [4, 5] reaching 154.33 cases/100000 inhabitants in the municipality of Báguanos [3]. The rate of prevalence of this molecular form is the second worldwide, only surpassed by the Spinocerebellar Ataxia type 3 (SCA3) [4, 47]. This prevalence statistics justifies the enormous interest in studying this disease by the Cuban scientific community.

Biological beings with visual capabilities perform eye movements as a response to some environmental stimulus. Its study is a valuable source of information for physicians and scientists. For neurologists, the study about the control of eye movements presents an unique opportunity to understand brain functions [6]. Also, these movements are important to identify a wide range of neurological disfunctions. Pursuit and saccadic movements, among others, are necessary to track moving objects, making them a great tool to test neurological tasks [7]. It is a scientific fact that several SCAs affect the human eye movements whereas the SCA2 provokes a slowdown in saccadic eye movement [2].

The Centre for the Research and Rehabilitation of Hereditary Ataxias (CIRAH) is located in Holguin, Cuba. The centre is a leading hub in the international research about SCA2. Besides its scientific duties, it is in charge of:

- A multifactorial neuro-rehabilitation program.
- Neurophysiologic characterization of somatic and autosomal systems.
- Identification of factors that change the starting age of the disease and its evolution course.
- Organization of a prenatal and presymptomatic diagnostic program for SCA2.
- Development of a cellular and transgenic model of the SCA2.

Scientists at the department of Clinical Neurophysiology in CIRAH carry out several studies to test drugs and treatments to fight against SCA2 and other hereditary ataxias. The analysis of saccadic eye movements is a recurrent task of these studies to identify changes in relevant biological markers (biomarkers) such as peak saccadic velocity and saccadic latency. They use the Otoscreen, an old electronystagmograph made by the German company Jaeger-Toennies to record eye movements.

Otoscreen has incorporated a software that records and processes several eye movement protocols using a technique called electrooculography. Clinical tests of electrooculography are setup as follows. Subjects with their head fixed are seated in front of a monitor at a previously set distance. After this, a set of electrodes is connected in the area around the eyes. Then, they are commanded to follow a visual stimulus which appears and disappears from one side to the other on the monitor. Capturing eye movements in these conditions using electrooculography allows researchers to identify which saccades respond to stimulus and which ones are spontaneous. Non spontaneous saccades are useful to extract biomarkers which are significant to follow the evolution of hereditary ataxias.

The usage of this equipment by CIRAH specialists produced an unique database of eye movements recorded using protocols designed for clinical and research purposes.

This database helps to develop several treatments and produces a large quantity of scientific knowledge on the subject. However, the current capture and processing protocol has some issues which difficults more advanced and reliable studies because of the following conditions:

- The signal processing pipeline used by the equipment is unknown.
- Many of the recorded signals are contaminated with noise.
- Algorithms do not identify all valid eye movement events, or establish the start (onset point) or the end (offset point) of the saccade at the wrong time sample.
- Adding extra features or processing elements is not possible.
- The equipment is not portable and needs highly specialized technicians to operate it.

Because of these issues, the staff of CIRAH uses the Otoscreen only for recording. Then, the specialists edit the signals and establish the onset and offset points of relevant events such as saccades. After the signal annotation, they use traditional comparative statistical methods using extracted biomarkers to confirm or reject their hypothesis. The current approach has several problems. First, manual annotation introduces subjectivity to the entire process, making reproducibility more unreliable. This problem increases because of the lack of standard rules for setting the onset and offset points of saccades. There are several articles using different methodologies and thresholds in the medical literature.

Second, the noise present in some records difficults the process of signal segmentation and some biomarkers calculation. If we add to this situation that the methods and algorithms used by the equipment are unknown, the uncertainty introduced to further analysis is significant.

Third, the complexity and non portability of the equipment affects the capacity of reaching people in remote areas and low income people. Many of these people can hardly move by themselves and the travel to CIRAH many times is not an option or is costly.

Due to this situation we can state the following problem: *the need for a new portable technology able to process automatically saccadic eye movements for subjects affected by SCA2 to avoid subjectivity and extract the biomarkers needed for clinical purposes in a reliable way.*

To solve this problem we set the following objectives:

1. Develop a fully automatic processing methodology for saccadic electrooculograms to extract the clinical biomarkers of interest.

2. Design and test a low cost and portable measurement equipment that can replace the Otoscreen at CIRAH.

The measurement equipment must be capable of recording the eye movements using electrooculography. Then, it must automatically identify the occurrence of saccades and dismiss the spontaneous ones using machine learning techniques and the resulting saccades to extract relevant biomarkers (such as saccadic peak velocity, latency, duration and amplitude) and exporting them to a standard format for further analysis. Also, the equipment must recommend the status of the subject using a previously trained model. All of this must be performed in the simplest way with minimal user (specialist) interaction.

1.1 Document structure

We structure this thesis in eight chapters outlined below:

Introduction: here we expose the motivation to develop this work, describe the problem and set the goals of our research.

State of the art: in this chapter we describe the methods and techniques used to process electrooculograms. First, the entire process is defined and then each of its steps is detailed. Finally, the chapter presents the fundamentals of the computing intelligence techniques used throughout the research.

Electrooculogram differentiation: in this chapter we evaluate 16 numerical differentiation methods for the tasks of saccade identification and biomarkers computing. To evaluate the methods, we design an experiment to compare them all and analyze its results statistically. Finally, we choose the best method for each of the proposed tasks. The results of this chapter are published in [8].

Saccade identification: in this chapter we propose and evaluate a saccades segmentation algorithm. We explore several machine learning techiques such as Multilayer Perceptron and Random Forest to identify saccadic eye movements. The results of this chapter are published in [9].

Non spontaneous saccades identification: in this chapter we develop a method to discriminate which saccades are useful from a clinical perspective and which not. Also, we select the most important biomarkers that separate healthy subjects from sick subjects using feature selection techniques. The results of this chapter are published in [10, 11].

Saccadic biomarker extraction: In this chapter we use the results from the previous two chapters to extract the relevant data required by medical staff to make clinical decisions. We show the method employed to compute accurately each of the relevant clinical biomarkers for the SCA2. Finally, we present the study report provided to the CIRAH specialists.

OpenEOG recording equipment: in this chapter we design a low cost and portable measurement instrument to capture eye movements. This equipment includes the algorithms developed in this report to automate the whole processing pipeline.

Conclusions: here we expose the main contributions of this work.

Chapter 2

State of the art

2.1 Eye Movements

Eye movements are those performed by humans and animals to guarantee a clear and stable sight of their environment. According to [6] there are 7 types of eye movements detailed below:

Vestibular: keeps images from the world in a stable form in the retina during brief head rotations.

Optokinetic: keeps images from the world in a stable form in the retina during substantial head rotations.

Visual fixation: keeps the image of a stationary object into the fovea.

Smooth pursuit: keeps the image of a small object in motion into the fovea; or keeps the image of a small or near object during a linear movement; with optokinetic answers to help the stabilization of the gaze during substantial head rotations.

Quick phases of Nystagmus: restarts the eyes during a long rotation and direct the gaze through a new visual scene.

Vergence: moves the eye in opposite directions in a way that images from an object are located or keeps in both foveas.

Saccades: moves images of object of interest into the fovea.

Eye movements recording technology

There are three main eye tracking methods: Electrooculography (EOG), Scleral Contact Lens/Search Coil (SCL/SC) and Video-oculography (VOG).

Table 2.1 presents a review of eye movement recording methods.

Table 2.1: Eye movement recording technologies

Method	Invasive	H. Accuracy	V. Accuracy	Resolution	Cost
Electrooculography (EOG)	Medium	$\approx 0.8°$ [48]	$\approx 2°$ [48]		Low
SCL/SC	High	$< 1°$ [14]	$< 1°$ [14]	< 1 ms	Medium
VOG	Low	$0.05°$ [49]	$0.05°$ [49]		High

Electrooculography

The EOG is one of the most used techniques to capture eye movements for clinical purposes. The functioning principle of this technique is based on the electrical potentials generated by the retina-cornea [12] (Figure 2.1).

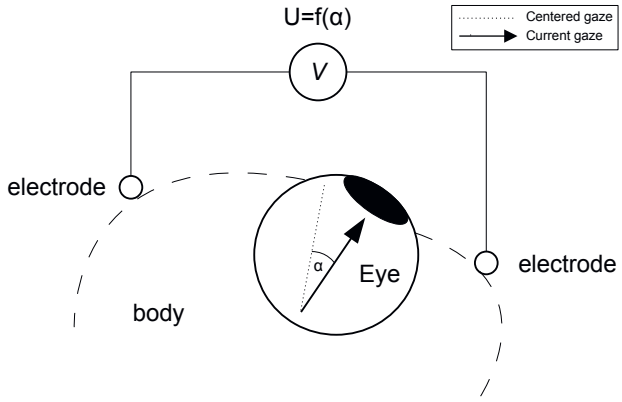

Figure 2.1: Functioning principle of the EOG technique. Based on [12]

Fenn and Hursh introduced the EOG technique in 1934, which measures the potential of the retina-cornea by placing electrodes in the skin around the eyes. This technique allows to extract the angular position of the eyes from the recorded potentials using calibration procedures [2]. It's important to notice that the illumination that receives the retina affects this potential, thus opening the possibility of applying this technique to measure the response of the eye to the light [50]. Because of this, we recommend maintaining the illumination conditions constant when we measure eye movements.

The main advantage of this technique is its low invasiveness (helping the cooperation of the subjects), and the possibility to record wide horizontal movements ($\pm 40°$) with a resolution of $1°$ [6].

The resulting signal of the electrooculography is named **electrooculogram**. We store this records in binary or text files depending on the equipment used for its capture. Otoscreen is the electronystamograph used at Centre for the Research and Rehabilitation of Hereditary Ataxias (CIRAH) to record electrooculograms. Otoscreen produces a simple American Standard Code for Information Interchange (ASCII) text format with a custom format and Comma-Separated Values (CSV) extension. The structure of these files is simple and separated by testing protocols (tests) making its parsing easier.

In the Department of Clinical Neurophysiology at CIRAH the specialists use predetermined protocols to capture saccadic, antisaccadic, smooth pursuit and many other eye movements. Each one of these protocols results in a set of signals (channels) with specific events contained that make up a test. During these protocols, the subject is placed at a predetermined distance from a monitor where the visual stimulus will appear. The specialists constrain the subject's head so that it faces the monitor and place the electrodes around the subject's eyes. Before the recordings start, they ask the subject to follow the visual stimulus (small white ball) that will appear on the monitor. The execution of the test consists of recording the subject's response to the successive visual stimuli [51].

Scleral Contact Lens / Search Coil

Robinson introduced the scleral search coil technique in [13]. The technique consists of placing a small coil of wire embedded in a contact lens on the subject's eye. This is a very invasive technique with a high spatial resolution (less than 1°) and high temporal resolution (less than 1 ms). However, many subjects have issues tolerating the contact coils. These issues sometimes lead to the slip of the lenses attached to the eye introducing errors at the position signal [14].

Video-oculography

Video-oculography is based on the processing images of the eye captured from an infrared video camera to determine the horizontal and vertical positions of the eyes. These positions can be converted into angular values using calibration procedures [15].

Today, this is the most used technique to record eye movements. Its low invasiveness makes it perfect to use it in almost every scenario. However, the current cost of the equipment needed to record saccades for clinical applications is fairly high, sometimes in a factor of ten thousand euros. This enormous cost is mainly because of the use of high resolution cameras that provide required sample rates. However, the cost of these cameras is dropping every day and in the future they will be the technology of choice to record eye movements for any purpose.

Eye movements and the Spinocerebellar Ataxia type 2 (SCA2)

The slowdown of saccades peak velocity is one of the most common clinical characteristics in subjects suffering from Spinocerebellar Ataxia type 2 (SCA2). We find this situation in 98% of subjects with SCA2, being mild in 32.12% of the cases, 13.19% moderate and 14% severe. This allows us to confirm SCA2 using this biomarker [2].

Saccadic peak velocity is a useful clinical tool to study other neurological pathologies such as myotonic dystrophy and olivopontocerebellar degeneration. The slowdown of this biomarker is caused by the affectation of the neural networks of the brain stem responsible of generating the saccadic pulse [2].

The main abnormalities in saccadic velocity present in subjects with SCA2 evidence qualitative alterations related to the morphology and amplitude of the electrooculogram. From the quantitative point of view it is characterized by [2, 16]:

1. Slowdown of saccadic velocity.
2. Abnormal increment of latencies.
3. Saccadic dysmetry. Hypermetric deviation of saccadic movements for stimulus angles of 10°, 20°, 30° and hypometric deviation for 60°.

Saccades are defined as slow or quick when their peak velocities are outside the standard range of the velocity-amplitude relation. There is an increase of saccadic latency in 80% of subjects suffering from SCA2; this is expressed physiologically in a delay at saccades initiation. Saccadic dysmetry, specially the hypermetry, is the traditional electrophysiologic sign of cerebellar affections [2].

2.2 Processing of electrooculograms

Considering that our work is concerned about the processing of electrooculograms to diagnose neurological diseases such as the SCA2, it is necessary to review how this process is performed nowadays at CIRAH. Analyzing how this processing is currently made by CIRAH specialists, allows identifying the parts of it that can be automated and improved.

The processes of record and analysis of electrooculograms consists of 3 stages: recording, processing and diagnosis (Figure 2.2). Recording, as the first stage, has the goal to get the signals that will be the input of the rest of the process. The processing stage is aimed at manipulating the obtained records to extract the necessary information. In general, we can establish the sub-stages of filtering, differentiation,

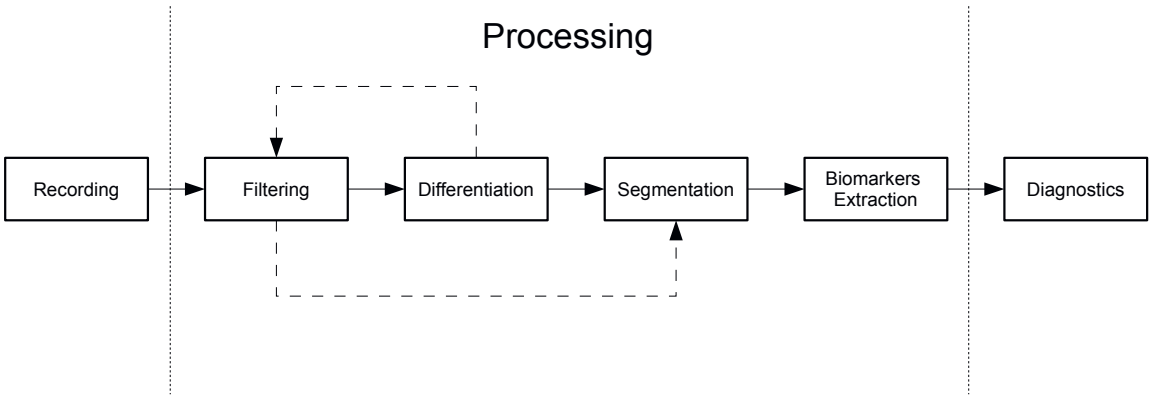

Figure 2.2: Diagram of the process of recording and analysis of electrooculograms.

segmentation, and extraction of characteristics, which are described in detail below. Diagnostics is the third and last stage, and it's the goal of the entire process. The diagnosis stage consists in providing the medical staff with interpretable quantitative data that can be used to make decisions regarding the subject's evolution or treatments.

In the following subsections we discuss each one of the processing sub-stages.

Recording

In this work we use electrooculograms recorded using the Otoscreen at CIRAH. These signals were recorded from horizontal saccadic movement protocols using a 200 Hz sampling frequency with a high-pass filter of 100 Hz. A typical study consists of a set of protocols listed below:

1. Horizontal calibration test (30°)
2. Vertical calibration test (20°)
3. Saccadic test 10°
4. Saccadic test 10° (Replica)
5. Saccadic test 20°
6. Saccadic test 20° (Replica)
7. Saccadic test 30°
8. Saccadic test 30° (Replica)

9. Saccadic test 60°
10. Saccadic test 60° (Replica)
11. Random saccadic test 60°
12. Random saccadic test 60° (Replica)
13. Horizontal calibration test (30°)

Horizontal calibration test is used to calculate a value that allows to convert μV recorded using Otoscreen Analog to Digital Converter (ADC) to angular position in degrees (°). The rest of the tests contains events with relevant clinical information.

Sometimes the baseline of the signal suffers a deviation due to the bad placement of electrodes and other setup defects. This problem occurred mainly in the tests at 10° (Figure 2.3).

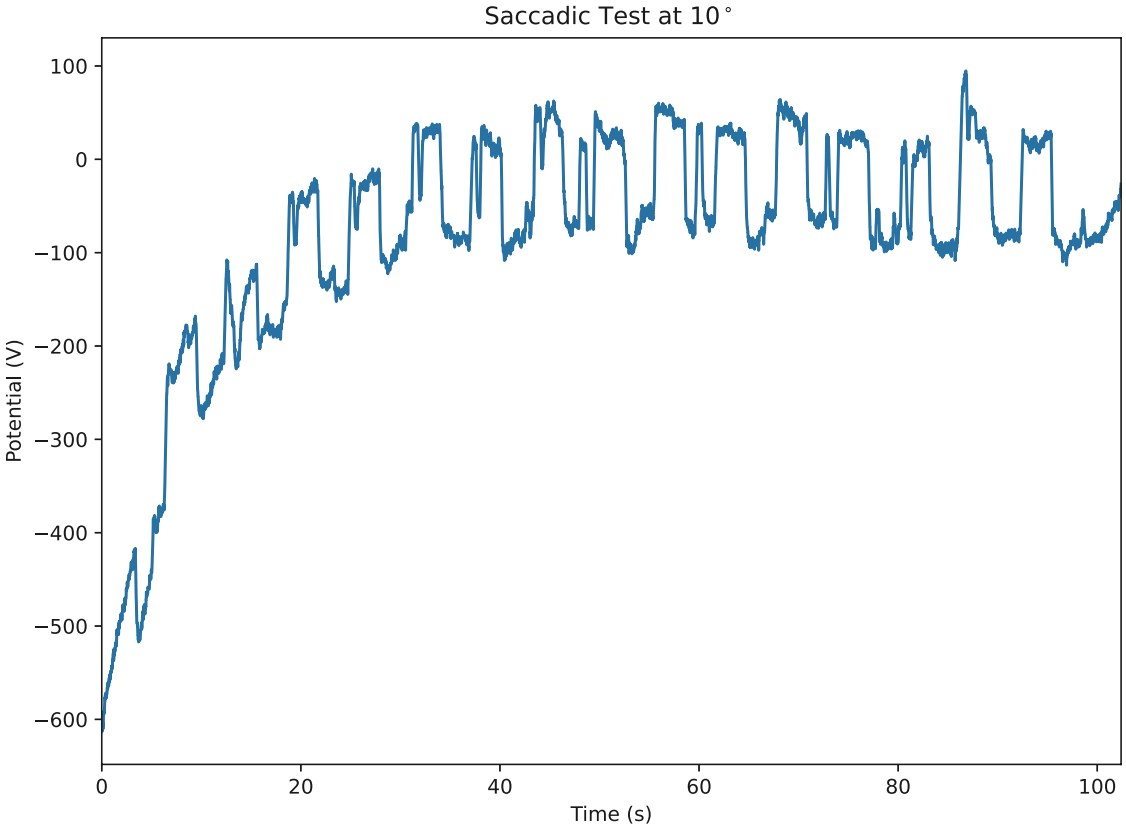

Figure 2.3: Saccadic signal at 10° with a deviated baseline

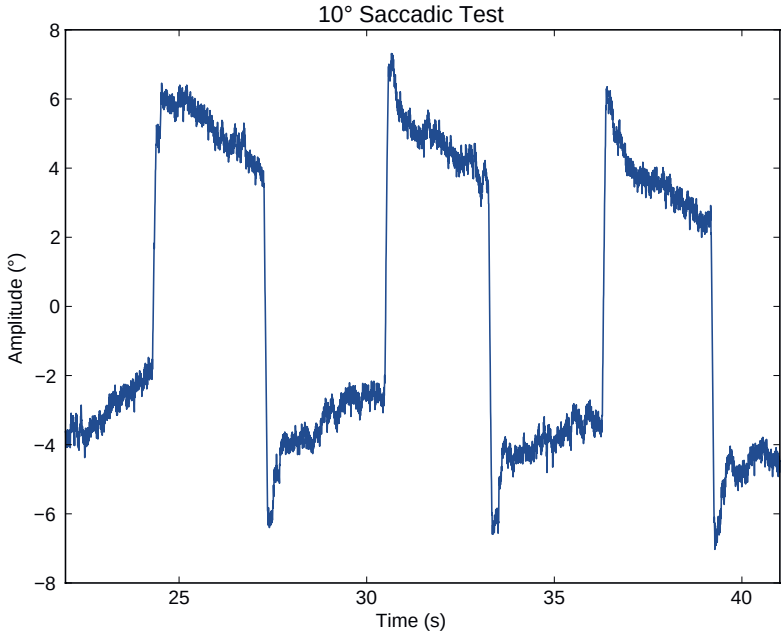

Figure 2.4: Unfiltered saccadic signal at 10° of a subject with SCA2

The correction of the baseline drift is a problem that has been studied in Electrocardiography (ECG) signals. Discrete Wavelete Transform (DWT) is the most common technique employed to tackle the problem. Following [52, 53, 54], we decompose the signal using the DWT seven times and then use the 7th approximation as correction signal. Other authors like Sayadi and Shamsollahi select the level of decomposition following spectral criteria [55]. Finally, the approximation signal is resampled to match the same amount of samples of the original signal and then subtracted from the original.

Filtering

Often the electrooculograms present several kinds of noises which prevents their adequate processing. The biological noise provoked by tremors and blinks, the bandwidth noise related to the measurement equipments and the quantification noise caused by the process of analog-to-digital conversion process, appear in signals recorded to subjects suffering from SCA2 at CIRAH. The tremors provoked by the disease are visible in a form of a high frequency and low amplitude noise as shown in Figure 2.4.

The presence of impulsive noise is due to eye blinks, which is a typical phenomenon present in electrooculograms [17] as observed in second and third saccade in Figure

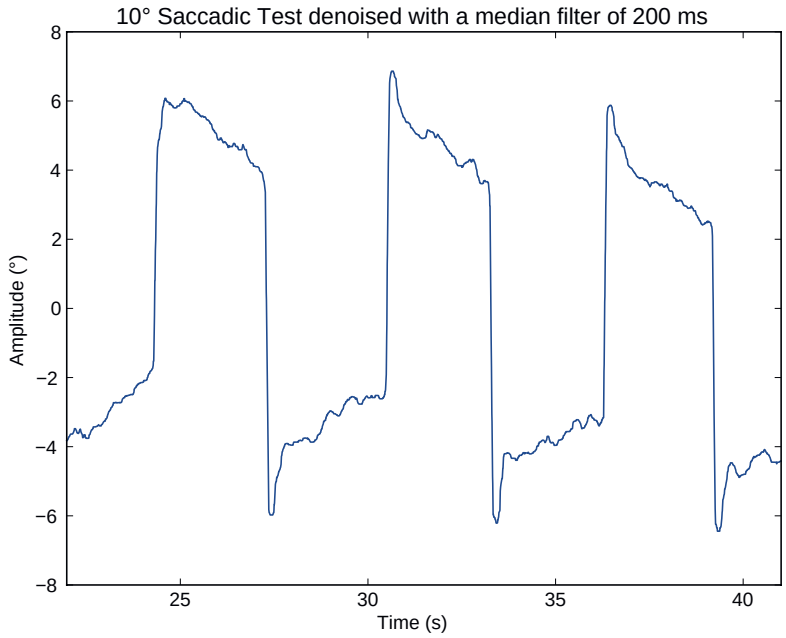

Figure 2.5: Filtered saccadic signal at 10° of a subject suffering from SCA2 using a median filter of 200 ms.

2.4. Also, there is some electrical noise provoked by the power grid which has a component around 60 Hz which matches with the frequency of the Cuban system.

There are several filtering techniques used to remove the aforementioned noises. Among those filters are the Finite Impulse Response (FIR) and the Infinite Impulse Response (IIR) [18, 17] filters, median filters [19, 17], filters based on the DWT [20], and many others.

The study performed by Juhola in [19] determined that the median filter is adequate to denoise saccadic signals because it is able to attenuate the noise without affecting important biomarkers such as saccadic peak velocity. This filter slides a window of $m = 2k + 1$ consecutive samples $x_{i-k}, \ldots, x_i, \ldots, x_{i+k}$ through an input signal and outputs a denoised version of it:

$$y_i = median\{x_j | j = i - k, \ldots, i + k\} \tag{2.1}$$

Differentiation

Computing the velocity profile is an esential part of several electrooculograms processing algorithms. Due to the discrete nature of these signals, this operation is per-

formed using methods of numerical differentiation. According to [56] the derivative of a function f in x_0 is:

$$f'(x_0) = \lim_{h \to 0} = \frac{f(x_0 + h) - f(x_0)}{h} \tag{2.2}$$

Using Lagrange's interpolation polynomials, several methods of numerical differentiation were developed and named *central difference* methods. For instance, equations 2.3 and 2.4 represent central different methods with 3 and 5 points respectively, where x_0 is the target sample and h the time between samples (sampling interval). Central difference with 3 points was used in electrooculograms by Bahill and McDonald in [21] and Niemenlehto in [22]. This last method must be used in serial order with a lowpass filter to obtain better results [23].

$$f'(x_0) = \frac{f(x_1) - f(x_{-1})}{2h} \tag{2.3}$$

$$f'(x_0) = \frac{f(x_{-2}) - 8f(x_{-1}) + 8f(x_1) - f(x_2)}{12h} \tag{2.4}$$

Inchingolo and Spanio also proposed algorithms based on central difference methods, declared in its general form in Equation 2.5, where f_s is the sampling frequency [24]. Also, for a sampling frequency of 200 Hz they determined that the appropiated method is a central difference method with 9 points and coefficients $a_1 = 0.8024$, $a_2 = -0.2022$, $a_3 = 0.03904$, $a_4 = -0.003732$ as shown in Equation 2.6.

$$f'(x_0) = f_s \sum_{n=1}^{m} a_n \{f(x_n) - f(x_{-n})\} \tag{2.5}$$

$$f'(x_0) = 200 \sum_{n=1}^{4} a_n \{f(x_n) - f(x_{-n})\} \tag{2.6}$$

Besides central difference methods, researchers have been using the Lanczos differentiators a.k.a Savitzky-Golay with success. Their main difference from central difference methods is that they employed curve fit instead of interpolation for signal approximation. In Equation 2.7 we show a Lanczos differentiator with 7 points [25].

$$f'(x_0) = \frac{-3f(x_{-3}) - 2f(x_{-2}) - f(x_{-1}) + f(x_1) + 2f(x_2) + 3f(x_3)}{28h} \tag{2.7}$$

Figure 2.6(b) shows a velocity profile of a saccadic signal computed using the Lanczos with 7 points methods as declared in Equation 2.7. To achieve an adequate performance at processing, the employment of differentiators must guarantee that the method does not afect the morphology of the velocity profile in a significative way and keeps the spectral information that it contains.

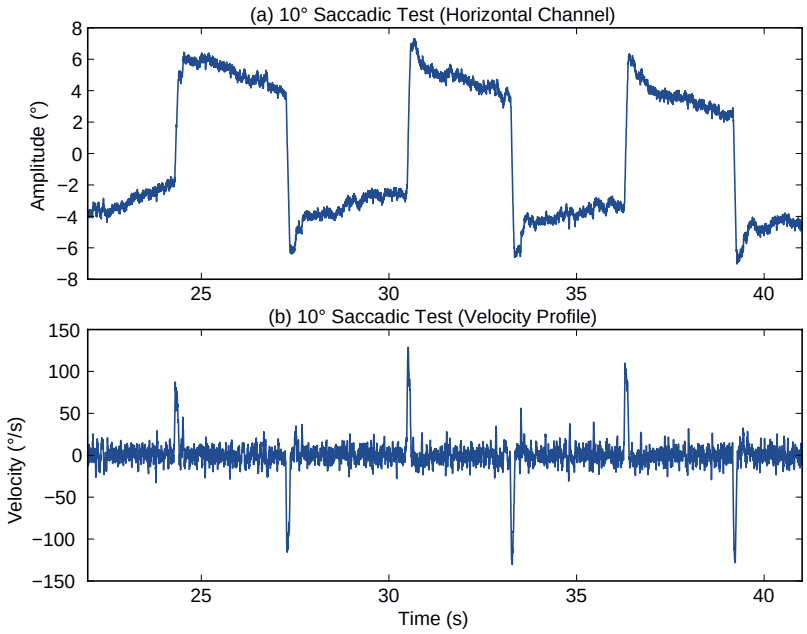

Figure 2.6: Computation of the velocity of a saccadic signal with 10° stimuli. (a) Horizontal channel (b) Horizontal channel velocity.

Segmentation

The segmentation of electrooculograms refers to the establishment of onset and offset points of events contained in them. This can be achieved manually or automatically depending on the approach selected.

Manual segmentation is usually performed by experts using visual user interfaces. The main issue with this approach is its subjetivity, because the annotation criteria differs from expert to expert. However, manual segmentation allows us to correct errors produced by automatic algorithms, for instance the removal of saccades wrongly detected.

Automatic segmentation algorithms do not suffer from the subjectivity present in the manual approach because they are based on rules and thresholds previously defined. Applying the same parameters and thresholds guarantee the uniformity of criteria in the output of the process.

Saccadic tests are the most common performed by CIRAH staff. *Saccades* and *fixations* are the relevant events identified in these kinds of signals. From these events we can extract important biomarkers required for the research of the SCA2.

To identify fixations the most common algorithms use dispersion criterias. In [57]

they compared 4 techniques to solve this problem as shown below:

Distance dispersion: based on that the distance between each point of the fixation with respect to the others cannot exceed a predetermined threshold d_{max}.

Centroid-Distance: also known as Anliker centroid-distance method, states that M from the N points of the fixation cannot be further away than a threshold c_{max} from the centroid of the points [58].

Variance-position: an alternative of the method Centroid-Distance with restrictions. States that the standard deviation of the distances to the centroid of the points cannot exceed the threshold σ_{max} [58].

Identification by dispersion threshold: proposed by Salvucci, states that the maximal horizontal distance plus the maximal vertical distance of the points of a fixation should be less than a predetermined threshold m_{max} [34].

In [34], it is proposed a taxonomy (known as Salvucci-Goldberg) which organizes the different methods for the identification of fixations according to the way temporal and spatial data is employed as shown in Table 2.2.

I-VT: (Identification by Velocity Thresholds) separates saccadic points from fixation points according to its instant velocity.

I-HMM: (Identification by Hidden Markov Models) uses probabilistic analysis to determine the most common identifications for a given protocol.

I-DT: (Identification by Dispersion Threshold) uses the idea that the low velocity of fixation points tend to be grouped closely.

I-MST: (Identification by Minimal Spanning Trees) uses a tree that connects a set of points in which the total length of the segment is minimized.

I-AOI: (Identification by Areas of Interest) identifies fixations located in predetermined areas. These areas are rectangular regions of interest representing units of information in the visual stimuli.

The problem with automatic segmentation of saccades has been tackled from dissimilar approaches. The most common approach employed velocity thresholds. These methods are based on the principle that onset and offset saccade points occur when the instant velocity exceeds or falls to a predetermined threshold [22, 24, 26, 27, 28]. Variations of these methods have been developed using the acceleration and jerk profiles, for example the algorithm proposed in [29].

Criteria		Representative Algorithms				
		I-VT	**I-HMM**	**I-DT**	**I-MST**	**I-AOI**
Spatial	Based on velocity	X	X			
	Based on dispersion			X	X	
	Based on area					X
Temporal	Sensible to duration			X		X
	Locally adaptive		X	X	X	

Table 2.2: Salvucci-Goldberg taxonomy [34]

Another approach to automatic detection is the use of the statistical properties of the signal. Keegan et al. proposed the use of a sliding window of 3 parts. In this window, if the mean of the difference of the absolute deviation between the first and last part of the window are below a predetermined threshold, and the mean of the central part has a value close to the mean of the edge parts; then we can establish that a saccade occurs near the central part [59].

Niemenlehto and Juhola use the technique of Cell Averaging of Constant False Alarm Rate (CFAR) for saccades identification. The principle behind this technique is the use of an adaptive detection threshold that fits the different characteristics of each signal [60].

Also, Juhola et al. use regular grammars [61] and syntactic analysis [62], a rare approach for saccade identification. These methods are based on the segmentation of the signal in symbols which are used by pattern recognition algorithms.

Tigges et al. proposed the use of a classifier based on an Artificial Neural Network (ANN) in signals with low level of noise. Using a retropropagated neural network with prototypes of patterns as input, a vector list of relevant features for saccade identification is obtained as a result [63].

It is important to point out that it's assumed that saccades occurred between fixations and viceversa as result of stimulation protocols. Because of this many authors use saccade identification methods to detect fixations and fixation detection methods to detect saccades.

Biomarkers extraction

Once the electrooculogram is segmented, we proceed to extract biomarkers from identified saccades and fixations. These biomarkers have the clinical meaning needed to diagnose and follow several neurological diseases such as SCA2.

The duration and peak velocity are two of the most relevant biomarkers in the

analysis of eye movements. There is a direct relation between them named *main sequence*, which has been employed by several authors to characterize the behaviour of the oculomotor system [26, 30, 31, 32]. Saccadic peak velocity is considered a very sensible and high value endophenotypic diagnostic biomarker of SCA2 [4].

Among the main alterations found in subjects with SCA2 there is the slowdown of saccadic peak velocity, the abnormal increase of saccadic latency, saccadic hypermetric deviation for stimulus of 10°, 20° and 30°, and saccadic hypometric deviation for stimulus of 60° [4].

The features used by CIRAH scientists for their research are:

Saccadic latency: time between the start of the stimulus and the saccade onset. Its value is expressed in milliseconds (ms).

Saccadic peak velocity: maximal velocity reached during the saccade. Its value is expressed in degrees per second ($^\circ/s$).

Saccadic duration: time between saccade onset and offset. Its value is expressed in milliseconds (ms).

Saccadic amplitude: difference between minimal and maximal angle reached during the saccade. Its value is expressed in degrees (°).

Saccadic deviation: rate between the amplitude of the saccade and stimulus amplitude. If the value is more than 1.0 the saccade is considered hypermetric, or hypometric if the value is less than 1.0.

Saccadic direction: enumeration with two possible values: *Left* or *Right*. If the angular position grows over time it is considered a *Right* saccade, or a *Left* saccade if the position decreases over time.

2.3 Conclusions

In this chapter we have started by studying the biological principles of human eye movements and how they are affected by neurological diseases. We have described the different eye movements and how saccades are affected by the SCA2. Also, we have studied 4 methods for recording eye movements and analyzed their strengths and weaknesses.

We also analyzed several methods and techniques involved in the processing of saccadic eye movements. Because of this analysis we have identified a processing pipeline for saccadic eye movements which comprises 4 steps: filtering, differentiation, segmentation and biomarkers extraction. Each of these steps was described and the methods currently used to approach them were presented.

Chapter 3

Electrooculogram differentiation

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3.1 Introduction

Eye movements are those performed by the eyes as a response to some environmental stimulus. For neurologists, the study of the control of eye movements presents an opportunity to understand the human brain [64]. Besides, these movements have a very useful role because they can identify disfunctions caused by several neurological diseases such as Spinocerebellar Ataxia type 2 (SCA2). Also, pursuit and saccadic movements are necessary to track objects in motion and provide a tool to explore neural functions [65].

Electrooculography (EOG) is a technique used to capture eye movements in clinical research. It's based on the measurement of potential generated in the retina-cornea area of the ocular system [12]. This technique was introduced by Fenn and Hursh in 1934 and uses superficial electrodes around the skin of the eyes. The resulting potential signal is called an **electrooculogram** and can be translated later into an angular movement signal using calibration methods.

Saccades are abrupt eye movements performed to move images of objects of interest to the fovea. Diseases such as Spinocerebellar Ataxias affect the performing of the saccadic system. For example, SCA2 provokes slowdowns in the saccadic movements [66]. Numerically, a saccade is a vector of contiguous eye positions that belongs to an electrooculogram (measured in angular degrees).

The velocity profile of an electrooculogram is a vector of instantaneous velocity points associated to the position vector of the electrooculogram. Getting this velocity profile is one step of saccade identification algorithms. For instance, one of the classic papers in saccade identification recommends to always use velocity as the

criteria to identify onset and offset saccade points [27]. This profile allows us to compute relevant biomarkers such as peak velocity, latency and duration. We compute the instantaneous velocity profile of an electrooculogram by the differentiation of its values.

Given the discrete nature of the electrooculograms, there is a requirement to use numerical differentiation methods to get the velocity profiles. These methods always introduce a level of noise to their output (velocity profile), even when the position profile is noise free.

Thus, Figure 3.1 shows how from an electrooculogram with almost no noise the output of the differentiation method presents high level of noise. Figure 3.1(a) shows a very clean position signal of a saccadic electrooculogram. In Figure 3.1 (b) and (c) we show noisy velocity profiles computed from the position signal using a central difference of 3 and 5 points, respectively. The noise of the output affects the identification of the position of the onset and offset points of a saccade. This situation leads to errors in the calculation process of important biomarkers such as maximum velocity, latency and duration of saccades.

In the literature reviewed we found four numerical differentiation method families based on different mathematical approaches: Central Difference, Lanczos, Super Lanczos and Smooth Noise Robust. Methods such as Central Difference and Lanczos have been used to differentiate electrooculograms. However, for the rest of the methods we have found no usage for these signals. It is very interest to evaluate the performance of methods such as Super Lanczos and Smooth Noise Robust for our specific tasks.

Researchers use central difference methods with acceptable results when the signal is noise free [67, 22]. However, Figure 3.1 shows the undesired effects of the noise in the differentiation output of these methods. Note how a minor noise in the movement signals produces a very noisy differentiated signal. Also, filtering the signal before differentiation does not improve the output of the process.

The signals captured using devices like electronystagmographers or eye trackers produce electrooculograms which may include several noises such as tremors (biological), power line noise, digitalization noise (Analog to Digital Converter (ADC)), and others. Using these position signals we can not get the associated exact velocity profile because of the included noise, hence it is impossible to have a framework to evaluate the performance of the numerical differentiators.

The goal of this work is to compare numerical differentiation methods available in literature for their application in saccadic identification and biomarker extraction tasks. This comparison has to be based on quantitative values of the errors introduced in the referred tasks. To measure the performance of each method, we will use a set of synthetic saccadic signals at different amplitudes and subject statuses (healthy or sick with SCA2) with added noise. These signals allow to know the exact values of

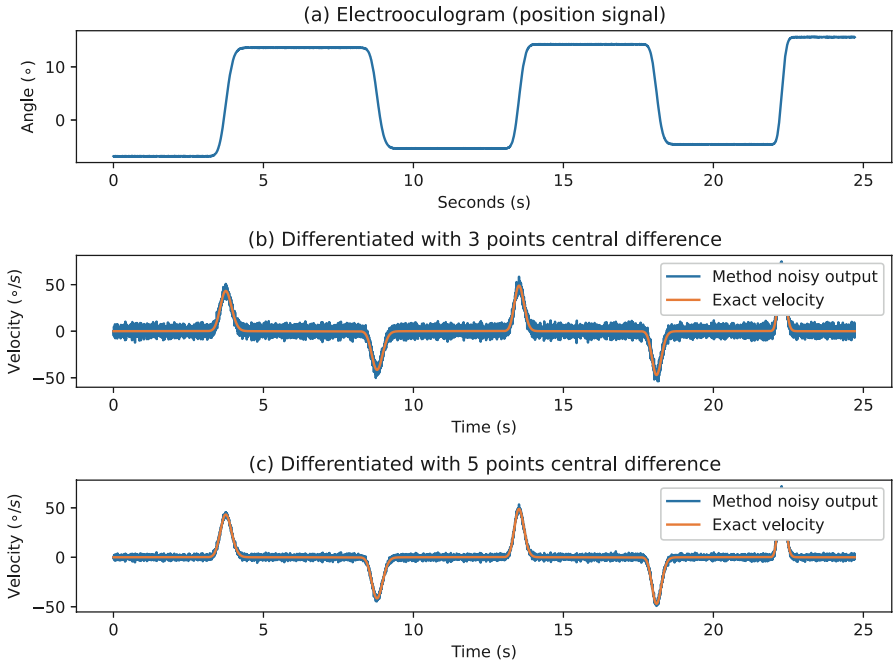

Figure 3.1: Example of an electrooculogram differentiated using the central difference of 3 and 5 points.

the errors introduced because the exact values of the biomarkers associated with these signals are also known.

In summary, we consider that this work presents two major contributions: (a) We find the best method to differentiate saccadic electrooculograms, (b) we provide the implementation of these methods for free at a GitHub repository.

The rest of this chapter is organized as follows: In Material and Methods section we describe the experiment designed to compare the differentiation methods. The Discussion section shows an analysis of the designed experiment results. Finally, the Conclusions section summarizes the main ideas and findings of this work.

3.2 Material and Methods

Numerical differentiation

The derivative of a function f in x_0 is defined in the Equation 1 [56]:

$$f'(x_0) = \lim_{h \to 0} = \frac{f(x_0 + h) - f(x_0)}{h} \tag{3.1}$$

Using Lagrange's interpolation polynomials, we can develop several differentiation methods based on central difference. Equation 3.2 represents the general form of the central difference methods.

$$f'(x_0) \approx \frac{1}{h} \sum_{k=1}^{(N-1)/2} a_k (f_k - f_{-k}) \tag{3.2}$$

In this equation x_0 is the point where the instant velocity is calculated, $f_{\pm k}$ represents $f(x_0 \pm kh)$, h is the time interval between samples, and a_k are the parameters to be determined.

The 3-point central difference was proposed by Bahill and McDonald in [67] and Niemenlehto in [22] to differentiate eye movement signals. This last method has to be used with a low-pass filter to get reliable results [21].

Inchingolo and Spanio proposed in [24] an algorithm to calculate the velocity profile of eye movement signals that is a particularization of the nine-points central difference. This method is described by Equation 3.3 where f_s is the sampling frequency. In the particular case of signals sampled at 200Hz, authors found that the best coefficients are $a_1 = 0,8024$, $a_2 = -0,2022$, $a_3 = 0,03904$ and $a_4 = -0,003732$.

$$f'(x_0) = f_s \sum_{k=1}^{4} a_k (f_k - f_{-k}) \tag{3.3}$$

Analog to central difference methods, the Lanczos methods have been developed as a particular set of Savitzky-Golay [25] differentiation filters. The fundamental difference regarding their predecessors is that they use curve fitting strategies instead of interpolation, making them more noise robust. Lanczos differentiators work as follows: for a fixed h step and sample $f(x)$ at odd N points around a central point x_0, we construct the polynomial shown in Equation 3.4 minimizing the cost function shown in Equation 3.5 with respect to unknown coefficients a_j [68].

$$P_M(x) = \sum_{j=0}^{M} a_j x^j \tag{3.4}$$

$$Z = \sum_{k=-(N-1)/2}^{(N-1)/2} (f_k - P_M(x_k))^2 \tag{3.5}$$

After the polynomial is computed, $f'(x_0)$ can be estimated as:

$$f'(x_0) = P'_M(x_0) \tag{3.6}$$

We call Lanczos differentiators to the filters built using $M = 2$ and Super Lanczos when $M = 4$.

One last family to be considered is the Smooth Noise-Robust methods [68]. They make up a variation of Lanczos family, and they are described in Equations 3.7 and 3.8

$$f'(x_0) \approx \frac{1}{h}\sum_{k=1}^{M} c_k(f_k - f_{-k}) \tag{3.7}$$

$$c_k = \frac{1}{2^{2m+1}}\left[\binom{2m}{m-k+1} - \binom{2m}{m-k-1}\right], m = \frac{N-3}{2}, M = \frac{N-1}{2} \tag{3.8}$$

where N is the filter length, as in the previous equations.

Experiment design

With the goal to choose the fittest numerical differentiation method for saccadic electrooculograms, an experiment was designed. In this experiment we compare 16 methods belonging to four families: Central Difference (CD3, CD5, CD7, CD9), Lanczos (L5, L7, L9, L11), Super-Lanczos (SL7, SL9, SL11), Smooth Noise-Robust (SNR5, SNR7, SNR9, SNR11). Each number attached as a suffix to the method name means the length of the corresponding filter.

Our experiment compares the performance of the differentiation methods using 4 different metrics:

- Mean Square Error (MSE) between the output of the method as approximated signal and the synthetic real velocity profiles as the exact signal.
- Misidentified saccades
- Over-identified saccades
- Absolute error introduced in the biomarkers values

The Mean Square Error (MSE) is computed from the output of the differentiation methods with respect to the exact velocity profile of synthesized signals. This metric gives a quantitative value, which describes similarity or, in contrast, the level of error/distortion between the signals. Formally, the operation is defined as follows: given two discrete signals x and y of finite length, $x = \{x_i | i = 1, 2, \ldots, n\}$ and $y = \{y_i | i = 1, 2, \ldots, n\}$, where n is the number of samples of the signals, and x_i and y_i are the value of the i-th samples of x and y respectively, the Mean Square Error between both signals is described in Equation 3.9.

$$MSE(x, y) = \frac{1}{n}\sum_{i=1}^{n}(x_i - y_i)^2 \tag{3.9}$$

To get saccadic biomarkers, first we need to identify the saccades. We can evaluate the performance of the differentiation methods by obtaining the number of saccades that are misidentified or over-identified using a simple velocity threshold algorithm with the output (velocity profile) of each method. For this algorithm we are going to use the same velocity threshold employed to generate the synthetic signals as onset and offset threshold.

There are many biomarkers used to study SCA2. Among the most common and relevant are the *Latency*, *Duration* and *Peak Velocity*. Latency is the time between the visual stimulus starts and the response of the subject. The duration of the saccade is the time between its start and its end. The Peak Velocity is, from our experience, the most important biomarker to diagnose SCA2 and is the maximal velocity reached during the saccade.

The designed experiment is structured as follows:

1. Generate synthetic saccadic records using characteristics parameters got from electrooculograms of healthy and SCA2-sick subjects. We get the exact velocity profile (EVP) from which the saccadic records are generated.

2. Apply each differentiation method to the synthetic electrooculograms with noise added, resulting in the approximate velocity profiles (AVP).

3. For each AVP:

    a) Compute the MSE between the EVP and AVP. Analyze the results and drop methods with significant poor performance.

    b) Identify saccades using the AVP and compare against the exact saccades identified using the EVP. We compare the performance of the identification process using misidentified and over-identified saccade metrics. All the saccades correctly identified using the AVP are defined as AS and their corresponding exact counterparts identified using the EVP are defined as ES.

    c) For each AS and their associated ES we compute the biomarkers peak velocity, latency and duration. For each pair (ES, AS) and for each biomarker, we compute the error using the absolute value of biomarker(ES) - biomarker(AS).

4. Analyze statistically the results yielded by the previous step and determine which methods to use for the different tasks in saccadic eye movements processing.

Class	20°	30°	60°	Total
Healthy	20	20	20	60
SCA2-Sick	20	20	20	60
Total	40	40	40	120

Table 3.1: Records distribution per subject status and angle.

Building synthetic saccadic signals dataset

The set of saccade signals employed for the comparison was generated synthetically using the method described by Coughlin in [33]. This algorithm follows an inverse process regarding the natural generation of the signals: first the velocity profiles are generated and then they are integrated to get the position profiles. The characteristic parameters used to generate the synthetic velocity profiles were maximum velocity, latency and duration got from a statistical analysis performed to healthy and SCA2-sick subjects.

To make the signals as real as possible, a set of noises found in real electrooculograms was added. Specifically, sinusoidal interference of 60 Hz simulating noise introduced by the industrial network, white noise, which has a uniform spectral distribution and color noise between 3 and 7 Hz. The color noise was found when performing the spectral analysis of records of people with the disease.

With the goal to get reliable statistic results, a set of 120 signals are generated and distributed, as shown in Table 3.1. Each of these signals contains a set of 20 saccades, making 2400 saccades in the full dataset. Here the saccades are generated from stimulation angles of 20, 30 and 60 degrees as found in real clinical electrooculograms.

The signals were generated with a sampling frequency equal to $1000Hz$. However, to mimic the characteristics of the real signals, we need to re-sample the synthetic signals to a sampling frequency of $200Hz$. To accomplish this we use the function *decimate*[1] of the SciPy library [69]. This function downsamples the signal after applying an 8th Order Chebyshev antialiasing filter. It is important to note that all the calculations of the experiment are performed using the $200Hz$ re-sampled signals.

[1] https://docs.scipy.org/doc/scipy/reference/generated/scipy.signal.decimate.html

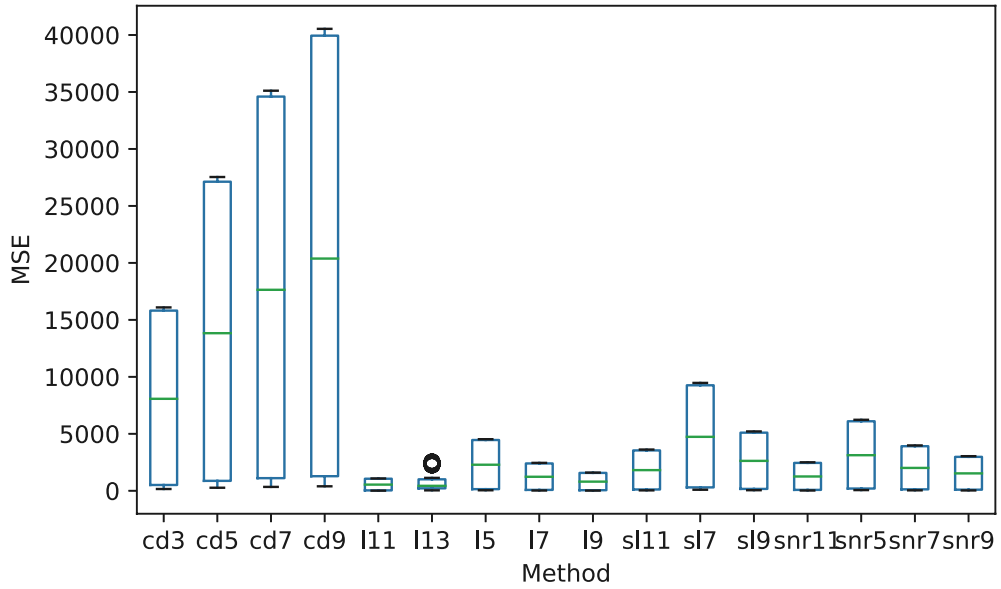

Figure 3.2: Errors introduced by differentiation methods measured using the MSE

3.3 Result analysis

MSE

To compare the signal waveform errors introduced by the differentiation algorithm, we built the box plot shown in Figure 3.2. In this plot we can notice how the central difference methods introduce errors higher than the rest in several orders of magnitude.

Figure 3.3 shows an example of the poor performance of the central difference method against the worst performed of the rest. In the figure it is also noticeable the error of the peak velocity introduced by the noise. Also, this noise is present in the regions near the points of saccade onset and offset, hindering the saccade's correct identification.

This low performance can be explained because of the instability inherent to numerical differentiation methods added to the principle of interpretation used by the central difference methods [56]. For these reasons these methods will be dropped for further analysis and focus our efforts in more adequate candidates for the tasks.

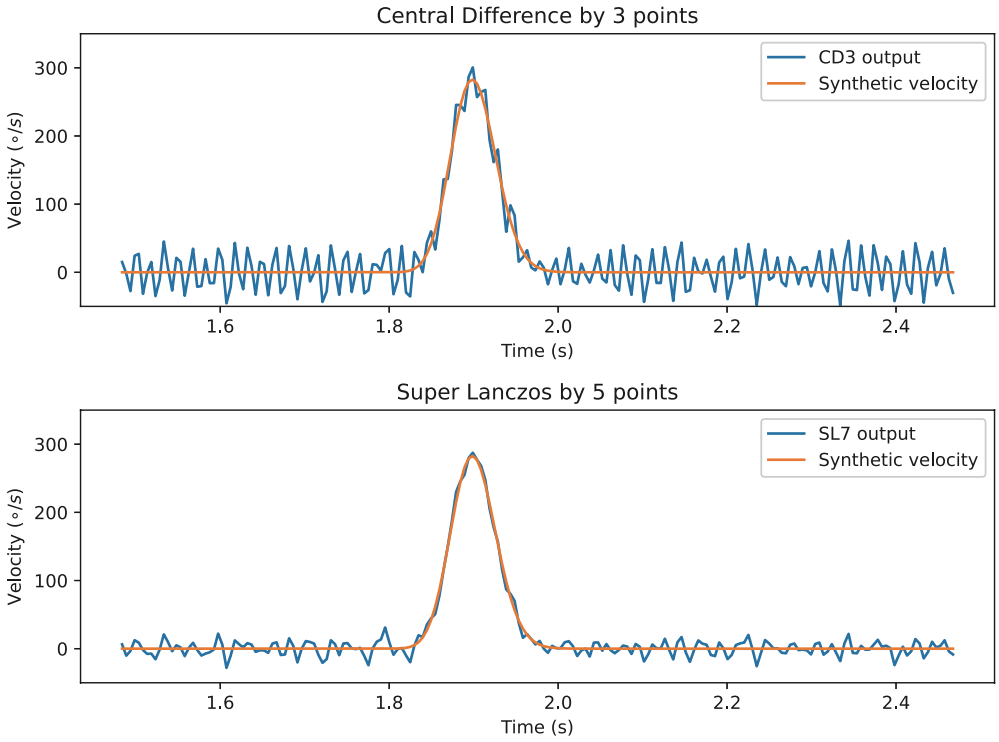

Figure 3.3: Comparison between the best central difference method and the worst of the rest of the families. The signal is from a healthy synthetic signal with saccades of 20°.

Saccade identification task

The previous step to biomarker computing is identifying the saccades from which these biomarkers are going to be extracted. We are going to use a simple velocity based saccade identification detailed by Algorithm 1. In this algorithm we use the output of the differentiation methods as V. For the occurrence threshold O_t we select the threshold used to generate the synthesized signals, and to set the onset and offset points of the saccades we use $P_t = 20°/s$ [70, 71]. The step h is equal to 0.05 seconds because the signals are sampled using a $200Hz$ frequency.

We use two metrics to measure the performance of the identification algorithms: unidentified saccades and over-identified saccades. Unidentified saccades are the amount of saccades that should have been identified by the algorithm and were not. Over-identified saccades are the amount of saccades detected as false positives by the algorithm. Figure 3.4 shows the errors introduced by using the output of the differentiation method as the output for the identification algorithm.

Algorithm 1: Velocity threshold saccade identification algorithm

Input: V computed velocities, O_t occurrence velocity threshold, P_t onset and offset velocity threshold, D_t minimal duration threshold, h sampling step

```
begin
    V ⟵ abs(V);
    last ⟵ length(V);
    index ⟵ 0;
    while index < last do
        if V_index > O_t then
            onset ⟵ index;
            while onset > 0 and V_onset−1 ≥ P_t do
                onset ⟵ onset − 1;
            end
            offset ⟵ index;
            while offset < last and V_offset+1 ≥ P_t do
                offset ⟵ offset + 1;
            end
            duration ⟵ (offset − onset) ∗ h;
            if duration >= D_t then
                yield Saccade (onset, offset)
            end
        end
    end
end
```

The performance of the analyzed methods is very satisfactory. From 2400 saccades the worst method (snr5) misidentified only 20 saccades, less than 1%. And more importantly, four methods show a perfect score. It is also noticeable that all the 11 points methods are in the set of perfect score.

Biomarkers calculations

The goal of the research regarding eye movements is to extract relevant knowledge which allows to diagnose and follow neurological diseases. This relevant knowledge is presented very often as biomarkers, hence the importance of their computing method. In this work we analyse how the differentiation methods impact on the values of saccadic biomarkers relevant to the research of SCA2 such as *Peak Velocity*, *Latency*

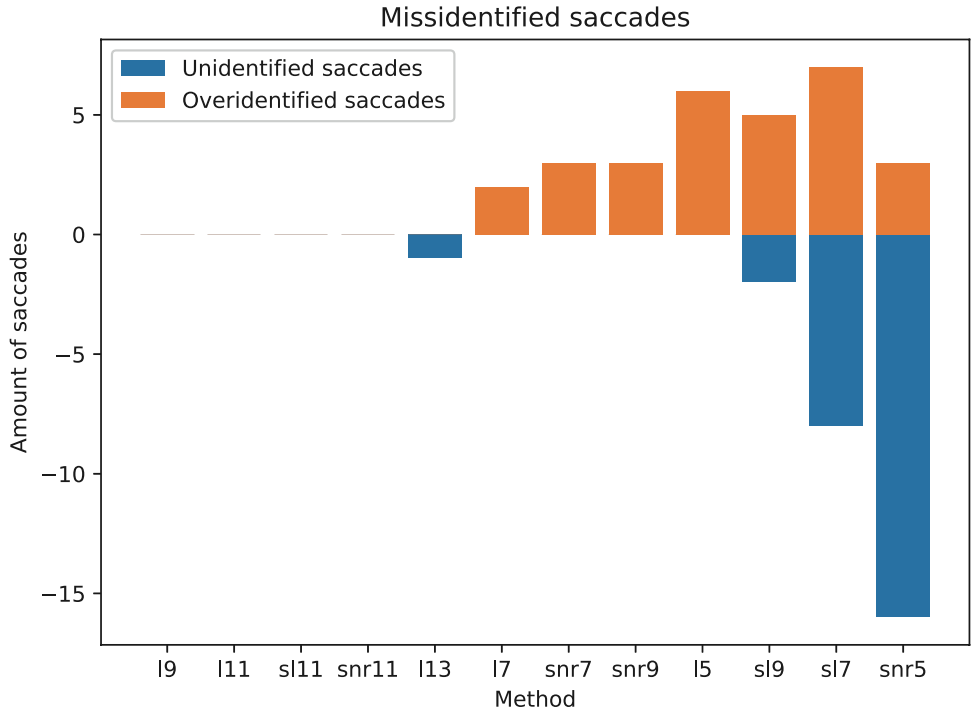

Figure 3.4: Number of misidentified saccades by the different methods

and *Duration*.

To make a complete interpretation of the results got by the application of the proposed methods, a comparative analysis using the Friedman statistical test was performed. This is a non-parametric statistical test equivalent to Analysis of Variance (ANOVA) with repeated measures, which determines if there are significant differences between the results of a set of methods over the same datasets [72]. Applying the Friedman test to the result yielded by each biomarker allows to determine that for each of the biomarkers there are significant differences among their means.

Now, to determine which of the methods are fit to compute each of the saccadic biomarkers, we applied a post-hoc Wilcoxon signed-ranked test pairing the method with lower error with the rest [73]. Each of the tests determines if there is significant differences between the pairs of biomarker means. In Table 3.2 the methods highlighted in bold belong to a cluster of methods in which the null hypothesis of Wilcoxon was accepted, meaning that the errors introduced by these methods have the same distribution.

In Table 3.2 we show the results obtained by the use of the proposed differentiation methods.

Rank	Peak Velocity ($^\circ/s$) Method	Error ± Std	Latency (s) Method	Error ± Std	Duration (s) Method	Error ± Std
1	**sl11**	2.1375 ± 2.2142	**snr11**	0.0045 ± 0.0080	**l11**	0.0079 ± 0.0065
2	sl9	3.8759 ± 4.3384	l11	0.0045 ± 0.0042	snr11	0.0084 ± 0.0135
3	l5	4.1076 ± 3.4649	l9	0.0047 ± 0.0064	**l9**	0.0085 ± 0.0115
4	sl7	4.4216 ± 5.2121	**sl11**	0.0049 ± 0.0104	sl11	0.0098 ± 0.0186
5	snr7	4.5968 ± 3.9061	**snr9**	0.0051 ± 0.0098	snr9	0.0100 ± 0.0175
6	snr9	5.1840 ± 4.4540	l13	0.0065 ± 0.0048	l13	0.0129 ± 0.0094
7	snr5	5.7055 ± 5.3013	l7	0.0067 ± 0.0116	l7	0.0141 ± 0.0235
8	snr11	6.0861 ± 5.4302	l5	0.0069 ± 0.0138	l5	0.0143 ± 0.0266
9	l7	6.4026 ± 5.5485	snr7	0.0076 ± 0.0150	snr7	0.0161 ± 0.0299
10	l9	9.4111 ± 9.0850	sl9	0.0128 ± 0.0259	sl9	0.0274 ± 0.0510
11	l11	13.3196 ± 13.4722	sl7	0.0145 ± 0.0299	sl7	0.0314 ± 0.0581
12	l13	29.6168 ± 26.0764	snr5	0.0147 ± 0.0283	snr5	0.0324 ± 0.0568

Table 3.2: Errors introduced by differentiation methods in saccadic biomarker computing. Methods highlighted in blue for each task are those that show no significant difference with the first ranked using Wilcoxon post-hoc method.

Table 3.2 shows that for the saccadic peak velocity, the Super Lanczos Method with 11 points is the most fit for the task. This could mean that **sl11** can better keep the waveform of the differentiated signal around the point of maximal velocity (middle of the saccade). Further study is required.

Regarding saccadic latency, Table 3.2 shows 3 methods with the best performance: Smooth Noise Robust with 11 points, Super Lanczos with 11 points and Smooth Noise Robust with 9 points. These results are related to how well the saccade onsets are positioned, explaining how these methods affect the samples near to the start of the saccade.

In the case of saccadic duration, the Lanczos with 11 and 9 points have the best performance. Like saccadic duration they are affected by the position of the saccadic onset, but are also affected by the saccadic offset position. The errors of the duration can be explained by the performance of the algorithms around the samples near the start and finish of the saccade.

Figure 3.5 shows the analyzed performance described in previous paragraphs in a more visual form.

It is interesting to notice how the best methods nominally always have 11 points. This could mean that 11 is the right size for the differentiation filters applied to signals with $200Hz$ of sampling rate, or at least with the characteristics of saccadic signals similar to the ones synthesized in this work. To confirm this theory, more study is required in this regard.

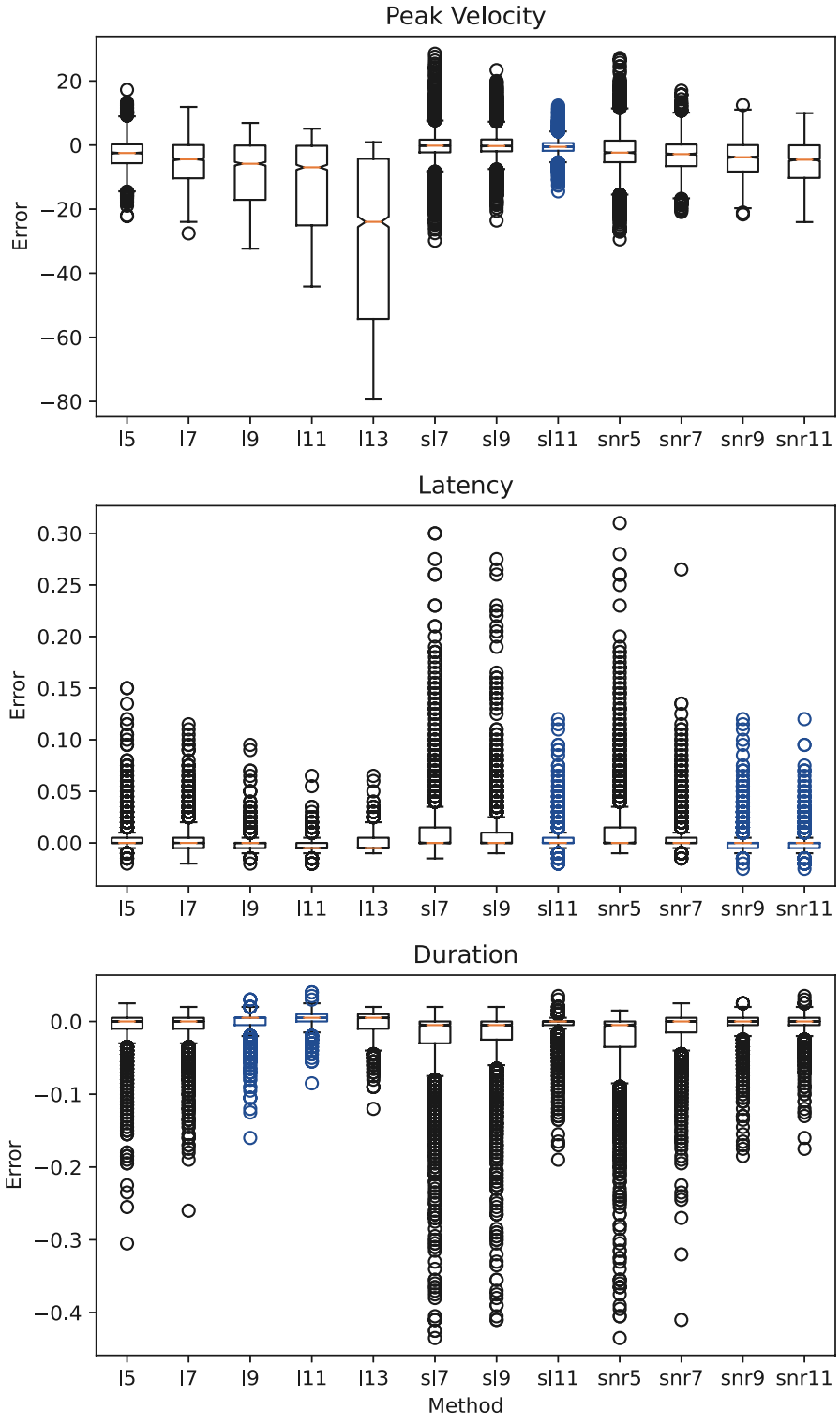

Figure 3.5: Biomarker computing errors box plot by method. Methods highlighted in blue for each task are those that show no significant difference with the first ranked using Wilcoxon post-hoc method.

3.4 Conclusions

In this chapter we have evaluated 16 numerical differentiation methods of 4 different families: Central Difference (cd), Lanczos (l), Super Lanczos (sl) and Smooth Noise Robust (snr) for saccadic signals differentiation of subjects suffering from SCA2. First, we presented a review of the methods traditionally used for our specific task and others used in other areas of knowledge. We designed an experiment to compare the methods numerically using quality and error metrics.

Our first conclusion from our experiment is that the central difference methods are not adequate for our specific task. The level of noise introduced by these sets of methods hinders the further processing of the signals. For the saccade identification task all the methods perform reasonably well, with the methods *l9*, *l11*, *sl11* and *snr11* getting perfect score.

For each saccadic biomarker included in our study, the experiment results in a unique set of methods fit to compute each one of them. With saccadic peak velocity, we recommend using the *sl11* method. For saccadic latency computation we recommend the use of these methods: *snr11*, *sl11*, *snr9*. For saccadic duration you can use the *l11* or the *l9* methods.

It is important to remark that some high performing methods like *sl11*, *snr9* and *snr11* were not used previously with electrooculograms, being a key contribution of this chapter.

Chapter 4

Saccade identification

4.1 Introduction

Saccades are a kind of eye movements; according to [74] these are rapid jerk-like movements of the eyes that direct the gaze to a new location, and ballistic movements in the sense of their duration. Saccadic points are those where the saccade begins and ends, but there is no unified criterium about where exactly a saccade does. Currently the identification of these points is performed by experts manually in the area or automatically by computational algorithms.

Identification by manual means has drawbacks such as the subjectivity introduced by the expert which makes the points selection. This subjectivity generates variability between the identification performed by various of these experts. In the case of signals recorded to sick subjects, the difficulties of manual identification rises due the presence of noises and conditions inherent of the disease.

The way of detecting saccadic points by computational methods is very varied and somehow formalized by the taxonomy of Salvucci-Goldberg [34]. Among the methods described by the taxonomy the most common ones are those based on velocity thresholds. These methods have as main drawback that for subjects affected severely by neurological diseases such as Spinocerebellar Ataxia type 2 (SCA2), the identification of saccadic points is very inaccurate. Besides there is no consensus in the literature about what value should take the velocity threshold used by these methods. There is a serious lack of research about the other methods proposed in the taxonomy, but presumably there is a notable difference in the results yielded by them and those yielded by velocity thresholds based methods.

From saccadic points and the corresponding signal channel, is possible to calculate saccadic features such as maximum velocity, latency, duration and the amplitude. These features have proven to be useful in the research of many neurological diseases

due the contrast of the behaviour of these features between patients and healtly individuals, as well as between patients of different diseases. For instance, saccadic velocity is significantly slower in subjects with SCA2 than in control subjects or subjects with other ataxias like SCA1 or SCA3 [75]. Also, the calculation of these features supports drug clinical trials and other kind of efforts to improve living conditions of subjects suffering this disease [76].

Latency, duration and amplitude are features very susceptible to the position of the saccadic points. So, the variability obtained by the methods currently employed have a negative impact on the utility of final data. On the other hand, the variability caused by the currently employed methods has a negative consequence on the interpretation of these features by experts, leading to misdiagnosis.

From this considerations, new methods have to be explored to solve the problem of identification of saccadic points. Here we propose two methods based on computational intelligence, capable of learning from a set of examples. Machine Learning, specifically the supervised learning is a branch of Artificial Intelligence often used to solve classification problems. Also these techniques are used in the task of classifying Electrooculography (EOG) signal patterns [35, 36, 37]. In this chapter we apply two different techniques of supervised learning to attack the problem of the saccadic and non-saccadic point classification in subjects with SCA2, and analize their performance. We aim to obtain results with high accuracy without the drawbacks present in traditional identification mechanisms.

The rest of this chapter is organized as follows: In section 2 we describe the designed experiments and available data. Section 3 is devoted to analize and comment the results. Finally, section 4 summarizes the main conclusions and future work lines.

An experiment was designed to apply two machine learning techniques: Multilayer Perceptron (MLP) and Random Forest (RF), to clasify a velocity saccadic pattern dataset. The experiment was separated in several stages as shown in Figure 4.1. The work performed in each stage is described more deeply in the followings sections.

In summary, each stage describes:

Stage I: Provide a set of cases that will conform the population used by the next stage. This population is builded based of EOG segmented data (saccadic or non-saccadic) created in this stage.

Stage II: Selection of training and validation data taking into account to balance the most typical cases.

Stage III: Training and validation of both classifiers, using percentage split scheme to separate training data and validation data.

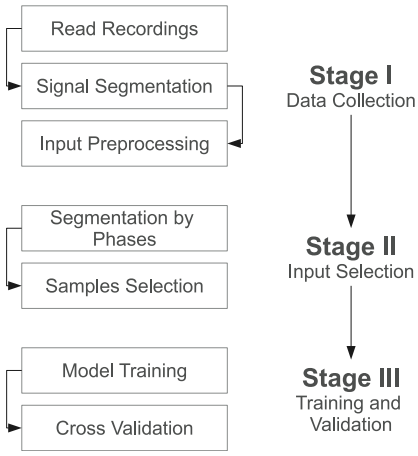

Figure 4.1: Experiment main flow. Each stage is separated in a sequence of ordered steps.

4.2 Data Collection

The data was recorded using the Otoscreen electronystamograph at a sampling rate of 204.8 Hz with a bandwith of 0.02 to 70 Hz (analogic filtering). Specifically, 60 degrees saccadic signals were selected due to its difference between healthy and sick subjects. Researchers from the Centre for the Research and Rehabilitation of Hereditary Ataxias (CIRAH) provide us about 30 records of sick subjects, many of them in very bad shape. After the analysis of these records, only six of them meets good quality requirements to train classifiers.

For signal segmentation purposes, a desktop application was developed capable to mark different types of segments as shown in Figure 4.2.

All the programming was done in Python language using NumPy and SciPy open source libraries for numerical calulations, and PySide Qt bindings for graphical user interface. The application uses **python-eog** for reading and writing the data managed by the user interface, developed by the authors too.

Even when the application is capable to tag many ocular events, in selected test only saccades, fixations and noise are relevant. For practical reasons we only need to discriminate saccades and non-saccades, thus, our task becomes a binary classification problem.

Many classical algorithms used to detect saccadic eye movements use a velocity threshold to set the initial and ending points of a single saccade. Even when they not agreed in a threshold value, there is a consensus about that the main criterion is the velocity. Thus, it seems reasonable to think that the pattern of velocities preceding and after a certain point in the signal determines if they are inside or outside of a

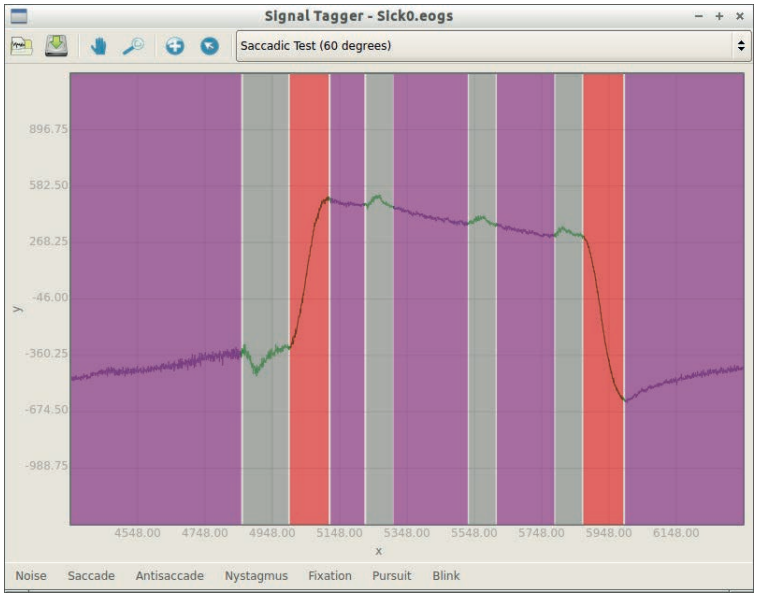

Figure 4.2: Signal editor main window. Pink segments mean *fixations*, gray segments mean *noise* and red segments mean *saccades*.

certain event as shown in Figure 4.3.

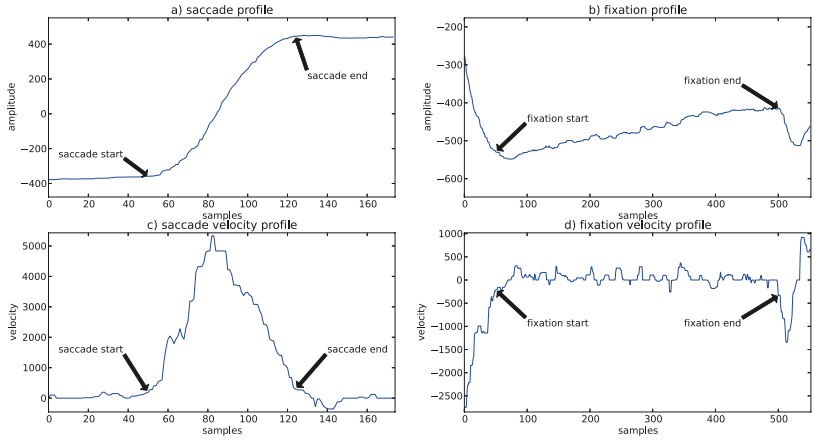

Figure 4.3: **a)** Time signal of a sample saccade, **b)** Time signal of a sample fixation, **c)** Velocity profile of a), **d)** Velocity profile of b).

The idea for input variables of a single case, was get the pattern of velocities before and after the target point, in a window fashion way. To build the cases population, an sliding window runs through each tagged point in selected records, using this tag

as the classification class. If this tag is a saccade we mark the sample as a saccadic point, if the tag is fixation or noise we mark the sample as non-saccadic point.

Filtering is, very often, the preprocessing part of signal analysis. For velocity profile calculations the input signal is first filtered using a median filter with a window size of 53.71 ms. After filtering, the velocity profile is calculated using a central difference by eight points method, which has proven to be adequate to signal sampled by 200 Hz [24]. Finally, new filtering is carried out to eliminate differentiation noise.

This aggresive filtering is posible because we are interested only in the relationship between the samples in velocity profile, not the waveform itself.

4.3 Input Selection

Once gathered instances population, we proceed to select the samples used for training and validation purposes. Is very important to provide a balanced set of input cases to the classifier in order to achieve better classification performance.

First, the number of cases used for training and validation process selected was 5000. The first half of them was devoted to saccade points and the another half to non saccadic points. The set of non-saccadic points was divided in fixation and noise ponits in equal proportions.

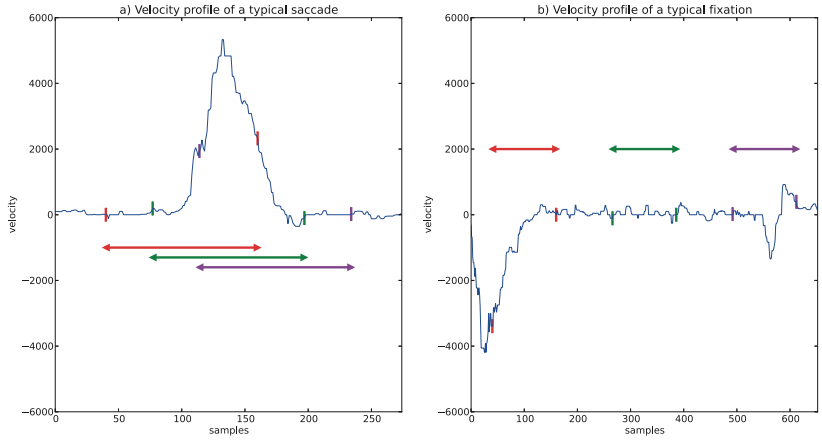

Figure 4.4: Example of windows of points at beginning, middle and ending of an event. *Red* range means a window of a point at beginning of the saccade in a) and fixation in b). *Green* range means a window of a point at middle of the saccade in a) and fixation in b). *Magenta* range means a window of a point at ending of the saccade in a) and fixation in b).

In Figure 4.4 is showed how different points belonging to the same saccade have a significative different window of velocities. That's mean that a point at beginning of the saccade usually have different window pattern than a point at the end of the saccade.

To get even more balanced set of data, was selected the same proportion of beginning, middle and end points of each class. As results of this input selection strategy, the samples count per class lays out in Table 4.1.

Table 4.1: Distribution of input samples per zone in the event and per event itself

	Saccade	**Non-Saccade**		**Total**
		Fixation	**Noise**	
Start	833	417	417	1667
Middle	834	416	416	1666
End	833	417	417	1667
Total	2500	1250	1250	*5000*

4.4 Training and Validation

The goal of our training is to predict whether a sample belongs to a saccade. Weka [77] is the software package used for training the selected data and validate the resulting models.

Previous experiments carried out by the authors indicate that the optimum input features count for the Multilayer Perceptron (MLP) and Random Forest (RF) input is of 121 components.

Multilayer Perceptron:

MLPs are a kind of feedforward Artificial Neural Network (ANN) which consists in multiples layers of nodes in a directed graph, where each layer is fully connected to the next. Except for the input nodes, each node is a processing element with a nonlinear activation function.

The MLP classifier was trained with a topology of 121 nodes in input layer, 61 sigmoid nodes in the hidden layer and 1 linear node in the output layer. The network use backpropagation as training algorithm with a learning rate of 0.3 and a momentum of 0.2. 500 epochs were used to train this model.

Random Forests:

RF is a ensemble of decision trees proposed by Leo Breiman[78]. The idea is based on building a forest of N decision trees, where in each trees we select M input cases in a random way using the same statistical distribution. Breiman in his paper proposes the use of Random Trees in the ensemble. In this type of trees, the split of features in each node is selected randomly from the K best splits.

Weka uses the algorithm proposed by Breiman. In our case we used the default values used in the package. This mean that our model will generate an ensemble of 10 Random Tree. For each tree the random split has 8 features.

The classification is made by the vote of each tree in the ensemble and selecting the most popular class among them.

The speed and accuracy of RFs make them a very good choice for problems related to computer vision. So we expect very good results from them, because the problem we are treating is in some extent a computer vision problem.

The training process uses 5000 examples distributed as shown in Table 4.1. The training were evaluated using cross-validation with 5 folds. Finally we test the trained model against 5000 new examples not present in training data.

4.5 Results

The validation process performed by weka states the following results:

Table 4.2: Validation results for both classifiers, in training and validation data. **TP** are True Positive cases, **FP** are False Positive cases, **TN** are True Negative cases and **FN** are False Negative cases.

Classifier	TP	FP	TN	FN
MLP Training Cross-validation	2325	177	2323	175
MLP Real Validation	2291	182	2318	209
RF Training Cross-validation	2375	166	2334	125
RF Real Validation	2387	182	2318	113

In Table 4.2 *Training Cross-validation* stands for the results obtained in the training process, and *Real Validation* stands for the results obtained in the test process (patterns not used in the training process).

Is a common practice in comparison of several classifiers to use metrics like sensitivity, specificity and accuracy. These metrics are derived from results shown in Table 4.2 and describe proportions between right and wrong predicted cases.

Sensitivity yields how good the model can predict possitive examples described by equation 5.5, in this case saccade points.

$$Sensitivity = \frac{TP}{FN + TP} * 100 \tag{4.1}$$

Specificity is the proportion on correct prediction on negative cases described by equation 4.2, in this case non-saccade points.

$$Specificity = \frac{TN}{TN + FP} * 100 \tag{4.2}$$

Accuracy is the proportion of right predicted cases, described by equation 4.3.

$$Accuracy = \frac{TN + TP}{TN + FP + FN + TP} * 100 \tag{4.3}$$

Table 4.3 shows that both methods perform very well and very similar for the proposed task. However, these results also shows that the Random Forest performs slightly better than the Multilayer Perceptron.

Table 4.3: Performance metrics comparison between MLP and RF classifiers in training and validation data

Classifier	Sensitivity	Specificity	Accuracy
MLP Training Cross-validation	93.00 %	92.92 %	92.96 %
MLP Real Validation	91.64 %	92.72 %	92.18 %
RF Training Cross-validation	95.00 %	93.36 %	94.18 %
RF Real Validation	95.48 %	92.72 %	94.10 %

4.6 Conclusions

This chapter presented a comparative between two machine learning techniques (MLP and RF) to solve saccade and non-saccade point classification problem of EOG signals measured to subjects with SCA2.

The results obtained by the validation of both methods shown an accuracy above 92 percent. So, they are suitable to solve the proposed task without the drawbacks present in traditional methods. Also, this results stated a slightly better performance for RF than MLP.

The RF classifier could be used to build a pseudo-realtime identification system due its performance in relation to training speed, and for its accuracy.

Chapter 5

Non spontaneous saccades identification

5.1 Introduction

The alteration of eye movements is one of the symptoms of many neurological diseases like Parkinsons syndrome, spinocerebellar ataxias or the Niemann-Pick disease [79]. Specifically in the Spinocerebellar Ataxia type 2 (SCA2) this alteration is an important clinical marker present in more than 90% of patients [1].

There are several kind of eye movements such as saccades, fixations and pursuits. Among them, saccades are critical to follow and evaluate subjects with SCA2. For instance, SCA2 patients have significantly slower saccades and with larger latencies than healthy subjects [1]. The analysis of this kind of movement is very often used in the researches conducted by the medical community, hence its importance.

A technique to measure eye movements called electrooculography consists in capturing the electrical potential of the eyes to calculate its magnitude and direction. This technique is widely used in electrophysiologic tests [80]. The resulting signals of this recording process are named electrooculograms [81].

There exists several methods and algorithms for identifying saccades in electrooculograms, the vast majority of them based on kinetic thresholds [24, 28, 29, 34], using supervised learning [63, 81], unsupervised learning [82] or other novel approachs [83, 84] like particle filters [85]. These methods were designed to work in a not constrained scheme having advantages in a lot of scenarios. They are usually evaluated against data from healthy subjects where the differences between saccadic and non saccadic movements are very evident. However, in electrooculography clinical tests these methods try to detect as many saccades as posible, not distinguishing which of them are spontaneous and which not.

In a previous work [9], we proposed a method that identifies saccadic movements using a sample-to-sample approach. This method allows us to discriminate whether a sample belong to a saccadic movement or not. Now, in this work we have the task of identifying which of these movements are stimuli related using a feature-based approach.

Here we set out to evaluate the use of machine learning algorithms taking into account the strengths of clinical tests of electrooculography to solve the proposed task. Our approach have to use only horizontal movement signals and stimulus signals, and do not require the use of thresholds or any other user input. To do so, a new set of features were selected to train the models taking into account characteristics of valid saccadic movements.

To identify the ocurrence of saccadic movements we use an impulse detection method based on velocity thresholds. These thresholds are calculated adaptively with a modified version of the method proposed in [83]. Our algorithm uses a classification model to solve the presented task, so we evaluate four of them: Support Vector Machines (SVM) [38], K-Nearest Neighbors (KNN) [39], Classification and Regression Trees (CART) [40] and Naive Bayes [41]. The performance of the classification models were measured, obtaining very good results ($> 98\%$ accuracy) in all of them.

5.2 Material and Methods

To test the selected algorithms an experiment was designed. The first step was detect potential impulses and annotating them to build a labeled dataset. Then, we select the best features among the 10 considered at first. Once we have the best set of features, we proceed to tune the parameters of the selected models to find the fittest ones for the task at hand, using 10-fold cross-validation. Finally, we analyze and compare the performance of the models against new examples using the metrics accuracy, sensitivity and precision.

The electrooculograms were recorded using the OtoScreen electronystamography device at a sampling rate of 200 Hz with a bandwith of 0.02 to 70 Hz. Records of 12 sick subjects with SCA2 were used to build a dataset with features extracted from signal impulses. Each one of the records have at least tests of 10°, 20° and 30° of visual stimulation. Typically saccadic tests have at least one horizontal channel and one stimulus signal (Fig. 5.1).

IPython notebooks [86] were used in conjunction with the Python language scientific facilities: NumPy [87], SciPy [88], Pandas [89], Matplotlib [90] and Scikit-Learn [91] for running the experiments. The intention behind using Python powered technologies is that the resulting algorithm (including trained models) will be used at NSEog, a processing platform developed by the authors.

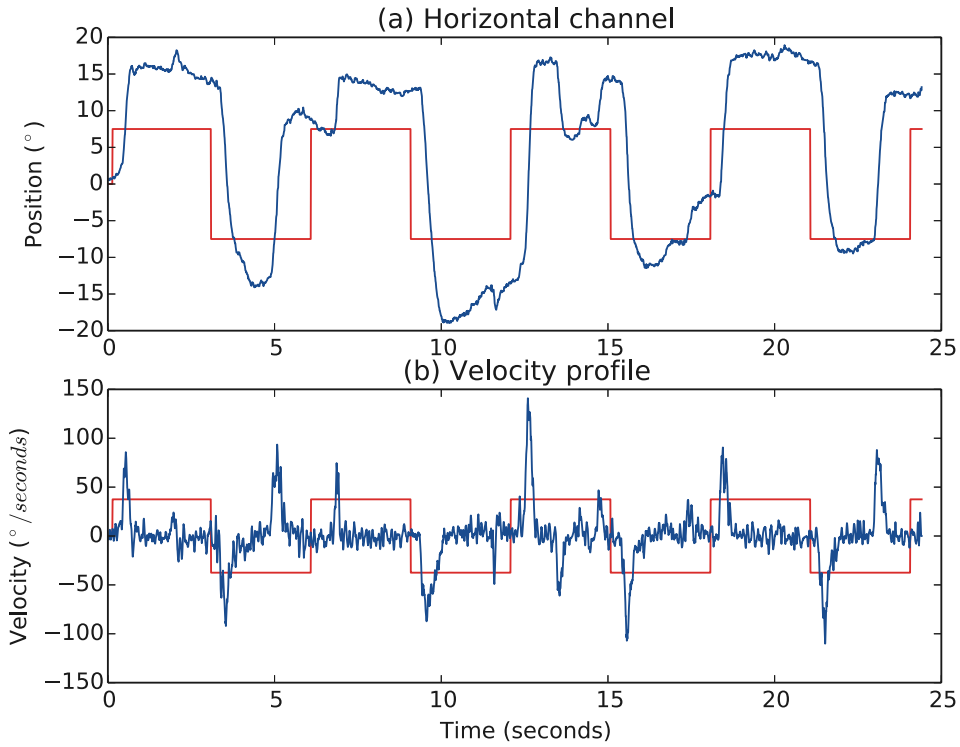

Figure 5.1: Typical electrooculography signal with 30° stimulus angle of a subject suffering SCA2. Red signals are the scaled stimuli signals. Blue signals are the horizontal channel (a) and its velocity profile (b) respectively.

Signals preprocessing

Before the identification of potentially saccadic impulses, two common tasks need to be performed: denoising and differentiation. Noise removal is a very important matter in order to eliminate non desired spectral components produced by equipment malfunction, poor analog filtering or biological artifacts. Differentiation allows to obtain the velocity profile used later by the algorithm.

Median filter (Equation 5.1) has proven to be very robust in eliminating high frequency signal noise while preserving sharp edges. An study carried out in [19] demonstrated that this kind of filters is appropiate for eye movements signals. To eliminate non desired noise present in the signals used in the experiment, we use a median filter with a window size of 9 samples (approximately 45 milliseconds) obtaining very good results. This is accomplished using the **medfilt** function of SciPy.

$$y_i = median\{x_j | j = i - k, \ldots, j + k\} \tag{5.1}$$

Due to the discrete nature of these signals, numerical differentiation is employed to calculate the velocity profiles. According [92], Lanczos differentiators (Equation 5.2) with 11 points ($N = 11$) have good performance for signals with the same characteristics as the ones used in this experiment.

$$f'(x^*) \approx \frac{3}{h} \sum_{k=1}^{m} k \frac{f_k - f_{-k}}{m(m+1)(2m+1)}, \quad m = \frac{N-1}{2} \tag{5.2}$$

We implemented the rutine of a Lanczos 11 differentiator which have the following formula:

$$f'(x^*) \approx \frac{f_1 - f_{-1} + 2(f_2 - f_{-2}) + 3(f_3 - f_{-3}) + 4(f_4 - f_{-4}) + 5(f_5 - f_{-5})}{110h} \tag{5.3}$$

Detection of impulses

Saccadic movements are represented as impulses in a velocity graph (Fig. 5.1b). Typically, this movements can be easily detected by its contrast in magnitude and shape with other movements such as fixations and microsaccades. However, for the same stimulus angle the range of values of true saccadic impulses vary from subject to subject. This situation is tied greatly on the degree of affectation present in the subject [93].

One of the critical parts of the algorithm is the detection of velocities impulses which can potentially be saccades. For that matter, a threshold is needed to know when the velocity has reached a certain value that can be considered as a saccade candidate. Due to the inter-subject variability explained before, this threshold should not be fixed a priori. Also should be large enough to ignore in most cases other movements like microsaccades and fixations, and not too large to miss valid saccadic movements.

To detect impulses we developed the algorithm described in Algorithm 2, which is a modification to the method introduced by Nyström and Holmqvist in [83]. The algorithm uses the absolute values of the *velocities* samples to calculate the approximation of the initial threshold (*last threshold*). This initial threshold is calculated by adding σ times the standard deviation of the *velocities* to its mean. Then, iteratively it adjusts the *last threshold* with the same formula using only *selected samples* of velocities below the previous threshold. The stop condition happens when the difference between the current threshold and the last one is less or equal than one degree. The value of the resulting threshold is represented graphically by the red line in Fig. 5.2.

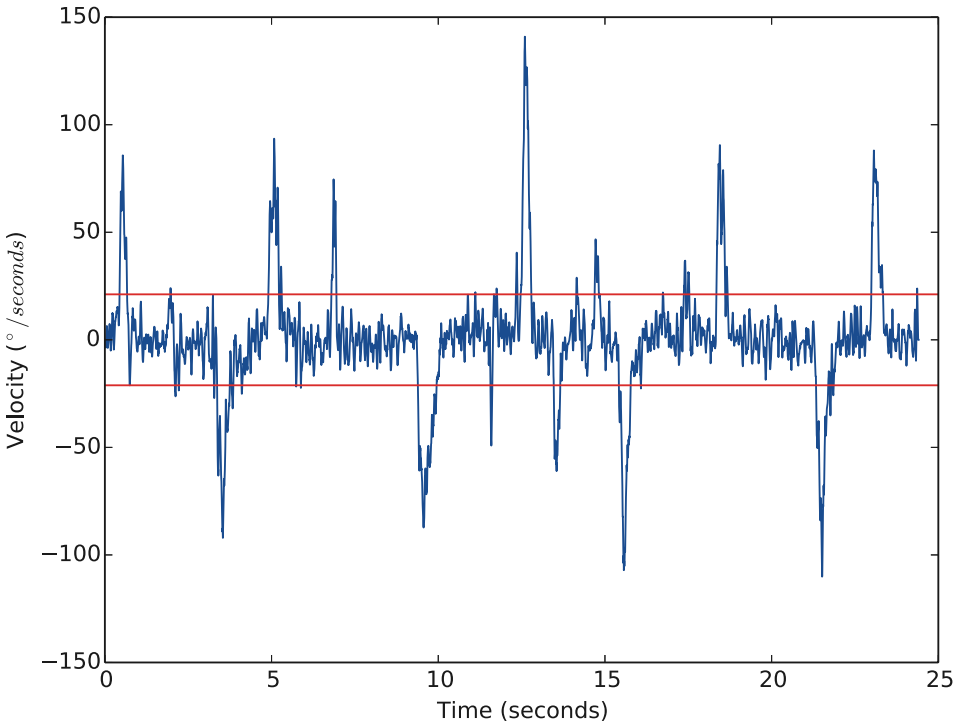

Figure 5.2: Threshold estimated in a 30° stimulus angle test of a subject with SCA2.

Algorithm 2: Modified version of Nyström and Holmqvist [83] threshold estimation algorithm

Input : velocity profile (Array of degree/seconds samples)
Input : σ (Safety margin)
Output: Threshold estimation
begin
  velocities $\longleftarrow$ `Abs`(velocity profile);
  last threshold $\longleftarrow$ `Mean`(velocities) + σ * `Std`(velocities);
  current threshold $\longleftarrow$ 0;
  while `Abs`(last threshold- current threshold) $>$ 1 **do**
    selected samples $\longleftarrow$ samples from velocities below last threshold;
    current threshold $\longleftarrow$ last threshold;
    last threshold $\longleftarrow$ = `Mean`(selected samples) + σ * `Std`(selected samples);
  return last threshold;

The original algorithm requires the initial threshold as input. This adds a little subjectivity to the main process, because to obtain good detection results this value must be variable and set by the user. The noise levels present on the signals and the degree of affectation of the subject have great influence on this issue. The proposed modification consists in calculate the initial threshold in a adaptive way using all velocity samples, so eliminating the subjectivity of the original approach. Using the new approach on signals recorded to subjects with SCA2 in different stages seems to be adecuate to the task at hand.

The safety margin ($\sigma = 6$) employed by [83] ignores too many valid saccadic movements in lower angle tests for subjects with SCA2. A value of $\sigma = 3$ seems to be adequate for most cases at the expense of the detection of more non valid impulses. Even when has a penalty in runtime performance, the final accuracy of the method should not decrease significantly. Due the amplitude of this new impulses the classification model should avoid them.

Finally, we detect the impulses individually by finding a group of samples grouped together that exceeds the calculated threshold. The principle behind this algorithm is looping through the signal to find velocities above the threshold. When we encounter with one of these points, we move to the left and to the right until the velocity is zero or cross it. This approach allows further refinement of the saccade start and ending points because the impulses usually get more samples beyond the real saccade limits. If the length of a detected impulse is not greater than 10 samples, then it is discarded to avoid very small invalid movements. A typical output of this method is represented in Fig. 5.3.

Data mining process

Because we are using Python technologies, Scikit-Learn was selected as machine learning library, hence we are constrained to a restricted set of models implemented in it. The main policy of model selection was family representation, meaning that we try to choose methods with different working principles. So we evaluate four different models: SVM, KNN, CART and Naive Bayes.

Feature selection

Once we have the saccadic impulses candidates, we need to know if they are saccades and if they are related to the stimulus. For this reason, the strategy behind our approach uses features used by human intuition to solve this task. To take advantage of the characteristics of the clinical tests, a set of 9 features was selected. These features are from spatial, temporal or kinetic nature.

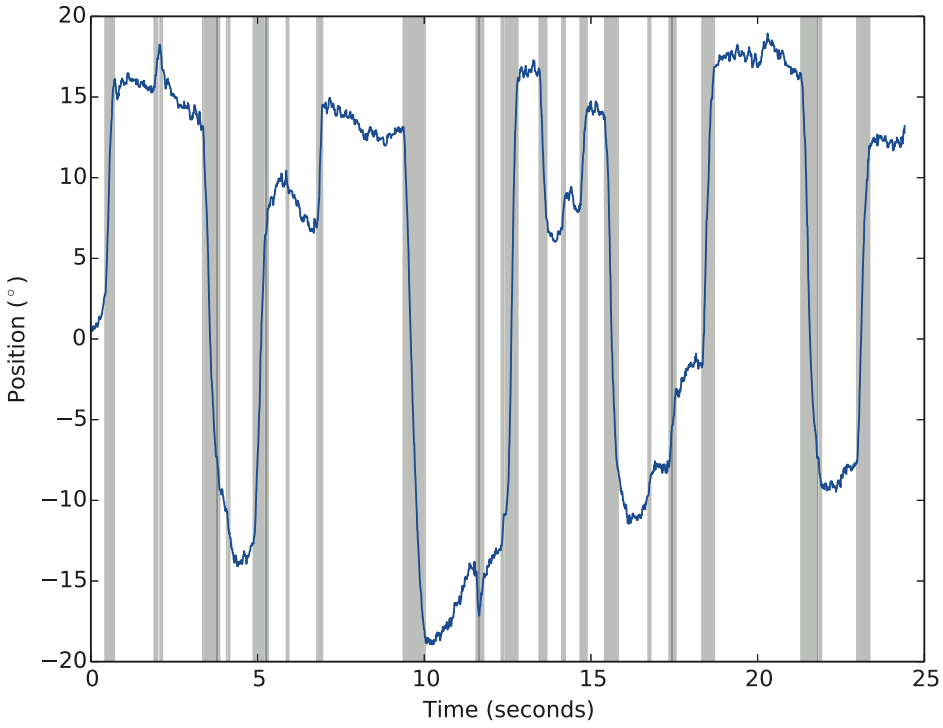

Figure 5.3: Identified impulses in the same signal used in Figure 5.2

We have selected four spatial features: **angle** $(10, 20, 30)$, **amplitude** $(°)$, **deviation** $(0..2)$ and **end relative position** $(0..1)$. The **angle** represents the amplitude of the stimulus and can take only three values. This feature was selected to specify the small differences between the saccadic movements resulting from using different angles of stimulation. The **amplitude** feature is the difference between the maximum position value and the minimum position value in the impulse in degrees. Used commonly by the medical community, the **deviation** is specified by the relation **amplitude** over **angle**. The **end relative position** takes values between 0 (left side) and 1 (right side), representing in which side of the stimulus the impulse ends.

As an important note, we have removed the **direction** feature employed in previous works [10]. Is evident that movements against the stimulus direction are not valid, so we choose to set this kind of impulses as not valid ones. This variation leads to a simpler and better model, adding only a line of code in the identification algorithm.

We have the **absolute latency** (ms) and **normalized latency** $(0..1)$ as temporal features. The **absolute latency** is the time between the start of the stimulus transi-

tion and the maximal velocity point of the impulse in milliseconds. The **normalized latency** is a version of the absolute latency with values between 0 and 1. The value 0 means that the maximal velocity is in the start of the fixation window, and the value 1 means that the maximal velocity is at the end of the fixation window.

Finally, we selected three kinetic features: **maximum velocity** ($^\circ/s$), **maximum acceleration** ($^\circ/s^2$) and **maximum jerk** ($^\circ/s^3$). These features were calculated using the first, second and third derivatives respectively of the horizontal channel signal. The method employed to calculate the numerical derivatives was the one specified in the Equation 5.3.

Using the features previously selected, a dataset of signal impulses was created. To build this dataset, a human specialist aided by the NSEog classified the detected impulses in valid and non valid saccades (Figure 5.4). As results, 1797 valid saccades and 6809 not valid impulses were obtained, resulting in 8606 instances.

SVMs are a set of supervised learning methods very effective in high dimensional spaces [38]. There are also very versatile supporting a set of kernel functions. Scikit-Learn implements four kernel functions: linear $\langle x, x' \rangle$, polynomial $(\gamma \langle x, x' \rangle + r)^d$, rbf $e^{-\gamma |x - x'|^2}$ and sigmoid $tanh(\gamma \langle x, x' \rangle + r)$. Results from preliminary experiments showed that for the proposed task, the rbf kernel function have the best performance compared with the others. Further study are necessary to fine tune the parameter γ of this kernel.

KNN is a type of instance-based learning which can be used for supervised or unsupervised learning. Instead of creating a generalizing function, it stores all the data inside the models using different data structures like Ball Trees or KD Trees. The principle behind the algorithm is to find a number of training samples nearest to the analized point and predict the label from it [39]. To train our model we tried several numbers of neighbors starting from 2, giving the best results when this value is equal to 3. The data structure used is determined automatically by the Scikit-Learn implementation using optimization techniques.

Decision trees are nonparametric supervised learning techniques. This algorithm requires little preprocessing and its runtime performance is good enough to handle real time tasks. This method split the data trying to infere decision rules which can be used to clasify instances. Scikit-Learn uses an optimized version of the CART tree that support classification and regression [40]. The implementation used here do not require any parameter by default.

Naive Bayes is a probabilistic supervised classifier based on the Bayes' theorem, where strong statistical inference is assumed. The classifier is highly scalable that requires a linear number of parameters in the learning problem [41].

As validation scheme we use an stratified 10-fold cross validation to evaluate internally the models. The metrics employed to measure the performance were accuracy (Equation 5.4), sensitivity (Equation 5.5) and precision (Equation 5.6) [94]. The ac-

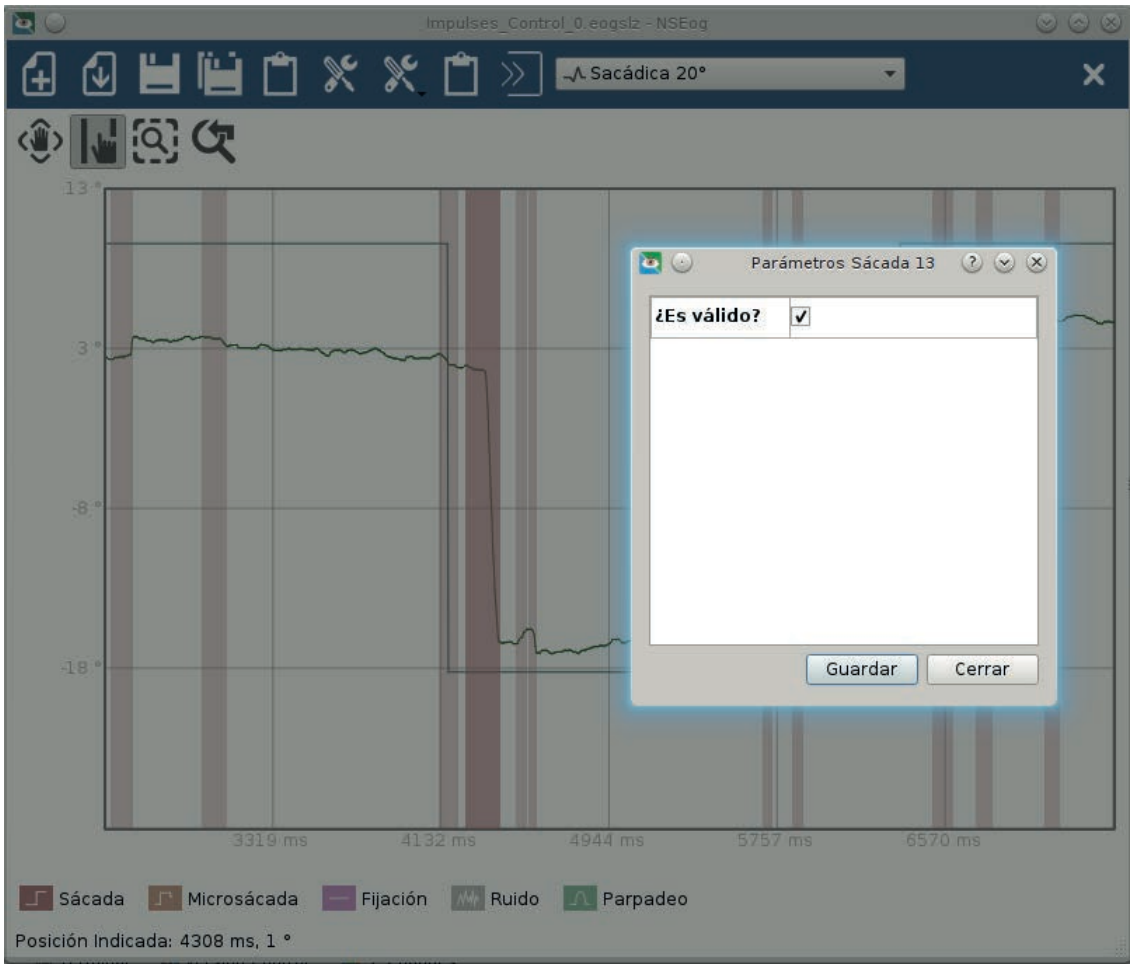

Figure 5.4: Impulses annotation with the NSEog platform.

curacy gives a general quality measure of the performance of the models, while the sensitivity and the precision allow to know how well the model predict or miss predict valid saccadic movements. In the following equations, TP (true positives), TN (true negatives), FP (false positives) and FN (false negatives) are the items from the confusion matrix used to compute involved metrics.

$$Accuracy = \frac{TP + TN}{TP + FP + TN + FN} \tag{5.4}$$

$$Sensitivity = \frac{TP}{TP + FN} \tag{5.5}$$

$$Precision = \frac{TP}{TP + FP} \tag{5.6}$$

The whole dataset was adjusted by removing the mean and scaled to unit variance. This technique is critical to obtain good results in the training of the RBF kernel version of SVM. These scales was saved along with the model for further use by the algorithm.

To compare the real performance of the models, the Friedman's nonparametric statistical test was used as recommended in [95]. In this step we use records not used in the training phase. Each metric were analyzed by separate and the statistical calculations were performed using the Keel tool [96].

The resulting classification algorithm is very simple and flexible. It consists in the evaluation of the features calculated from impulses detected in the signal by the supervised model. This approach allows the parallelization of the algorithm and even swap the model if needed. Due the use of the proposed impulse detection algorithm, the need for parameters managed by the user is eliminated.

5.3 Results

The evaluated models were trained with 8606 impulses, 1797 valid saccades and 6809 invalid ones. Using 10-fold cross validation the internal performance of the trained process was measured with the metrics accuracy, sensitivity and precision. Table 5.1 shows results above .97 of accuracy, .94 of sensitivity and .90 of precision in all cases.

Table 5.1: 10-fold cross validation results

Model	**Acc.**	**Rec.**	**Pre.**
SVM	0.9833	0.9750	0.9467
KNN	0.9796	0.9666	0.9376
CART	0.9769	0.9449	0.9445
Naive Bayes	0.9747	0.9817	0.9056

To perform a more objective evaluation, the algorithm was tested against records obtained from five new subjects not used in the training phase. A total of 3797 impulses were evaluated this time, 704 real saccadic impulses and 3093 not saccadic.

Results obtained analysing the performance individually by stimulus angle seems to favor slightly the SVM model (Table 5.2). However, doing the same analysis using independent subject records shows a more erratic behaviour (Table 5.3). Because of this situation, the Friedman's nonparametric statistical test was employed to compare the performance of the four models. Each record was considered as an individual dataset and each of the three performance metrics was analyzed independently using the data in Table 5.3. Results obtained by this method show that there are no significant differences in the performance of these models for a significance level of $p = 0.10$.

Table 5.2: External validation results by stimulus amplitude

	SVM			KNN			CART			Naive Bayes		
Angle	**Acc.**	**Rec.**	**Pre.**	**Acc.**	**Rec.**	**Pre.**	**Acc.**	**Rec.**	**Pre.**	**Acc.**	**Rec.**	**Pre.**
10	.9765	.9703	.9051	.9659	.9449	.8745	.9636	.9237	.8790	.9575	.9661	.8261
20	.9858	.9837	.9377	.9844	.9837	.9305	.9822	.9633	.9365	.9780	.9837	.8993
30	.9720	.9686	.9038	.9646	.9686	.8745	.9674	.9462	.9017	.9543	.9686	.8372
Mean	.9780	.9742	.9155	.9716	.9657	.8932	.9711	.9444	.9058	.9633	.9728	.8542
Std	.0070	.0082	.0192	.0111	.0195	.0323	.0098	.0198	.0290	.0128	.0095	.0394

Table 5.3: External validation results by subject record

	SVM			KNN			CART			Naive Bayes		
Subject	**Acc.**	**Rec.**	**Pre.**	**Acc.**	**Rec.**	**Pre.**	**Acc.**	**Rec.**	**Pre.**	**Acc.**	**Rec.**	**Pre.**
1	.9881	.9877	.9699	.9881	.9877	.9699	.9796	.9693	.9576	.9881	.9755	.9815
2	.9862	.9935	.9107	.9724	.9610	.8506	.9845	.9870	.9048	.9535	.9935	.7427
3	.9871	.9754	.9444	.9794	.9590	.9141	.9704	.8852	.9231	.9717	.9836	.8571
4	.9799	.9420	.9559	.9784	.9348	.9556	.9741	.9130	.9545	.9756	.9420	.9353
5	.9410	.9685	.8039	.9392	.9843	.7911	.9358	.9528	.7961	.9375	.9685	.7935
Mean	.9765	.9734	.9170	.9715	.9654	.8962	.9689	.9415	.9072	.9653	.9726	.8620
Std	.0201	.0201	.0669	.0189	.0215	.0748	.0193	.0417	.0659	.0199	.0195	.0982

Literature about the task proposed in this work is scarce and no methods to specifically solve it were found. However, similar works reported a sensitivity of .89 for 10° recordings on healthy subjects [84] and .80 of sensitivity on subjects with Obstructive Sleep Apnea Syndrome (OSAS) [97]. Other related research conducted by Tigges et al. shows an accuracy of .92 [63]. Taking into account that we are dealing with signals recorded to subjects which suffers a very severe neurological disorder, results shown in Table 5.2 and Table 5.3 are better than the others presented in the literature.

5.4 Conclusions

In this work we have described a procedure to indentify spontaneous saccades from a set of detected impulses in electrooculography signals. To detect the impulses we made a modification to the algorithm proposed in [83], which consists in adaptively calculate the initial thresholds. This new algorithm avoids the need of thresholds or any other user input and works very well for noisy signals like the ones recorded to subjects with SCA2, which is a difficult task.

To clasify we used and compared four machine learning paradigms: SVM, KNN, CART and Naive Bayes. The procedure has been applied to a database of eye movements recorded to subjects suffering spinocerebellar ataxias. The evaluation of the

performance of the different paradigms were carried out using metrics such as Accuracy, Sensitivity and Precision. The four used paradigms achieved an accuracy above 95%, a sensitivity above 92% and a precision above 83% by external validation (using patterns not used for training). Specifically for SVM the performance obtained was always above 97%, 96% and 90% for the three metrics respectively. These results exceed widely the reported by the literature in related works.

Chapter 6

Saccadic biomarker extraction

The term **biomarker** according [42] is *"a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention"*. A more broad definition was developed previously by the International Programme on Chemical Safety led by the World Health Organization (WHO) in coordination with the United Nations and the International Labor Organization and states that a **biomarker** is *"any substance, structure, or process that can be measured in the body or its products and influence or predict the indicence of outcome or disease"* [43]. Summarizing, **biomarkers** are objective and quantifiable characteristics of biological processes [42].

Raw eye movement profiles by themselves aren't enough to extract useful knowledge for clinical studies. Once we have identified a set of non spontaneous saccades, we can extract relevant biomarkers from them. There are several saccadic biomarkers such as *amplitude*, *deviation*, *latency*, *duration*, *peak velocity* and many others. For instance, [44] identified alterations in reaction times (saccadic latency) linked to many neurodegenerative diseases such as Alzheimer's disease, mild cognitive impairment, Parkinson's disease, amyotrophic lateral sclerosis, frontotemporal dementia and vascular cognitive impairment. With subjects suffering Spinocerebellar Ataxia type 2 (SCA2), they showed a decrease in saccade peak velocity and saccade accuracy (deviation) and an increase in saccadic latency [45].

In this chapter we describe the biomarkers relevant to the study of the SCA2 and the method used to extract them. Also, we explain several implementation details used to optimize the accuracy and performance for the calculations of the biomarkers.

6.1 Description

We can classify saccadic biomarkers according to the properties of the electrooculogram signals that it bases them from. There are temporal biomarkers, spatial biomarkers, and kinetic biomarkers. Temporal biomarkers such as *latency* and *duration* are measured in time units like seconds. Spatial biomarkers such as *amplitude* and *deviation* are measured in angular units as degrees. Kinetic biomarkers such as the *peak velocity* are measured in degrees/second units.

Temporal biomarkers

Temporal biomarkers are those measured in time units such as seconds or milliseconds. These biomarkers are related to the index of time where the saccade starts (onset) and ends (offset). Here we have temporal biomarkers: the latency and the duration. The latency is the time between the change of stimulus and the onset of the saccade. Duration is the time between the saccade onset and saccade offset.

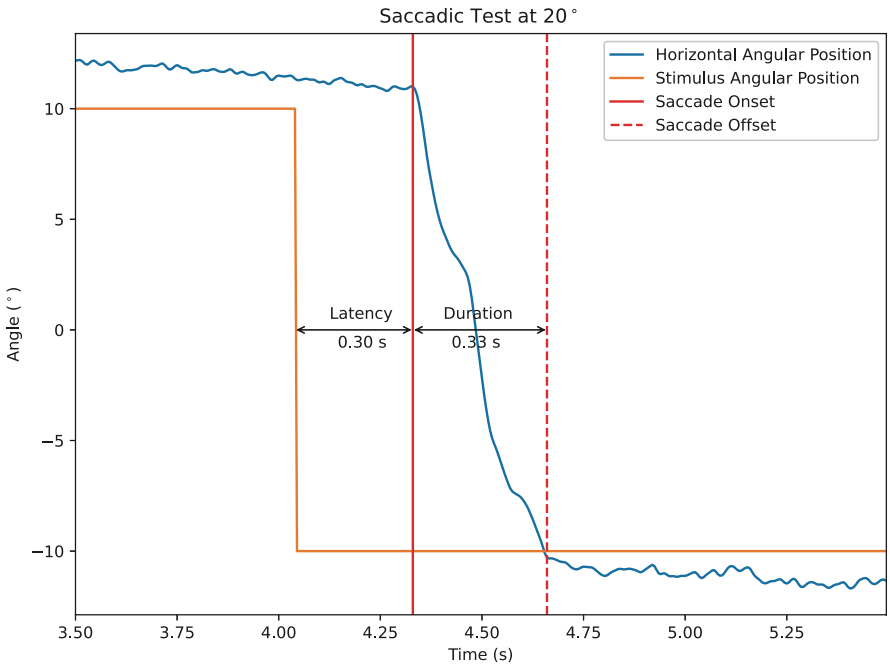

Figure 6.1: Temporal biomarkers visual representation.

Figure 6.1 shows how the latency and duration are directly related to the onset and offset of the saccade, respectively. Hence, the right positioning of these points is critical to calculate accurately these biomarkers.

Spatial biomarkers

Spatial biomarkers are those measured in position and longitudinal units such as angular degrees. In our research we have two spatial features: amplitude and deviation. The amplitude is the angular displacement performed by the human eyes between the saccade onset and offset. Deviation is the ratio between the amplitude and the stimulus angle.

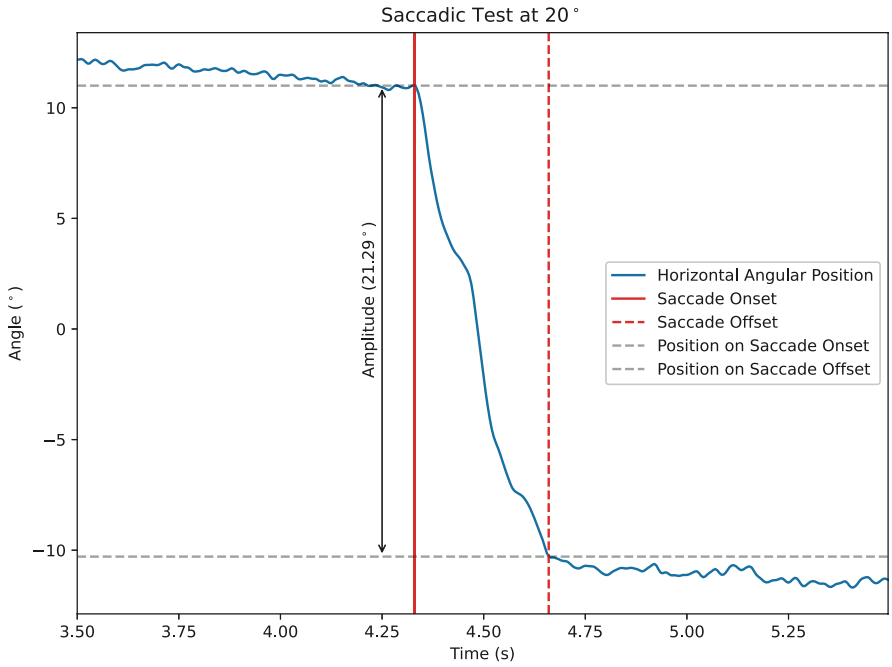

Figure 6.2: Spatial biomarkers visual representation.

In Figure 6.2, we can appreciate visually how to compute the amplitude with respect on saccade onset and offset points. The deviation of this saccade is equal to 1.09, so the saccade is hypermetric. If deviation is less than 1, we consider that the saccade is hypometric.

Kinetic biomarkers

We can consider several kinetic biomarkers such as average velocity, peak velocity, peak acceleration and many others. However, in the study of SCA2, the researchers consider that the most important saccadic biomarker is the peak velocity. Peak velocity is measured in angular degrees per second ($^\circ/s$).

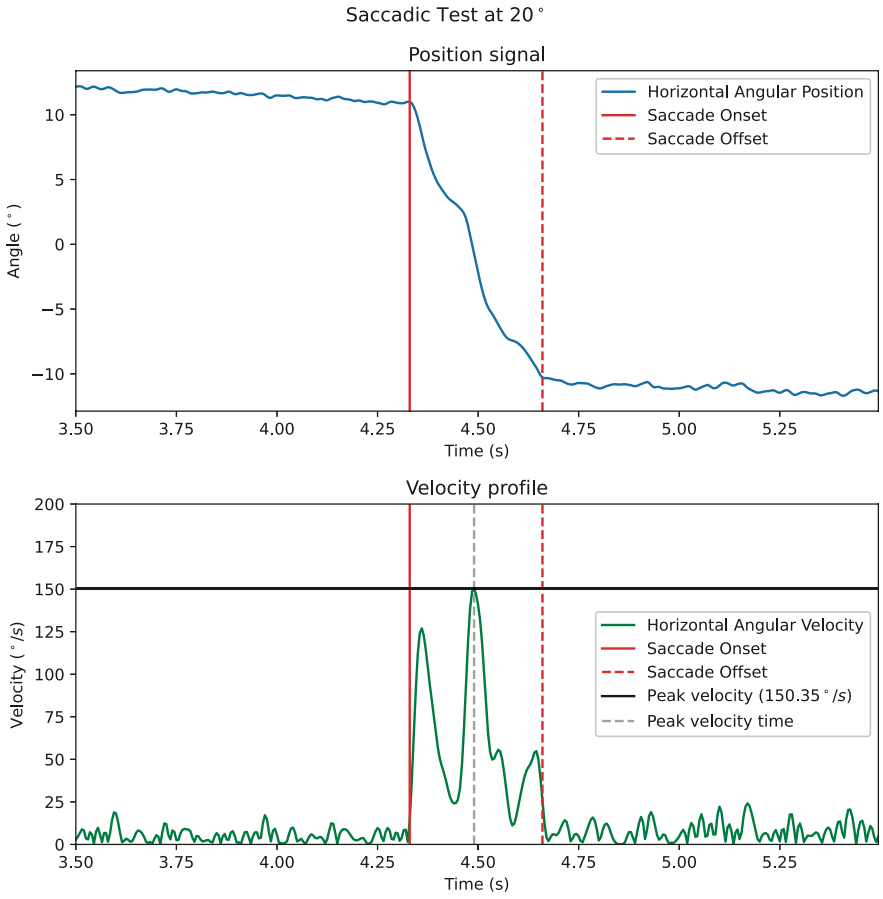

Figure 6.3: Kinetic biomarkers visual representation.

Peak velocity is the highest velocity achieved between the onset and offset of the saccade as shown in Figure 6.3. In contrast with the other biomarkers, peak velocity is more robust to errors in the saccade onset and offset points. The robustness of this biomarker is because of that its value is almost never near the starting and ending of the saccade.

6.2 Computing methodology

As mentioned in previous sections, the most relevant saccadic biomarkers for the study of the SCA2 are latency, duration, amplitude, deviation, and peak velocity. Almost all these biomarkers, except for the peak velocity, are strongly related to the positioning of the onset and offset saccade points. Because of this relation, the

well establishing of saccade onset and offset points is critical to minimize the errors in biomarkers computing. The major obstacle to define the right saccade points is the noise present in their neighborhood. So, in this section we are going to define a method to calculate all the biomarkers as accurate as possible.

Historically, the eye movement researchers have proposed several continuous mathematical models to describe the behaviour of a saccade. Curve fitting, differential equations, probabilistic models, and several other approaches are used to model human saccadic eye movements. In our work we are going to use a curve composed by the sum of a sigmoid and two gauss terms as described in Equation 6.1. Using an approximated continuous mathematical model solves the problem of the noise near the saccade edge points, hence the rationale of our approach.

In the step of biomarker calculation, we assume that an approximation of the saccade onset and offset point have been identified using the algorithms discussed in previous chapters. To get the vector of data that we are going to fit to the Equation 6.1 we use twice of the samples that the saccade contains centered in the middle of the saccade. This way we assure to get enough points in the neighborhood of the saccade edge points which are critical for the next steps.

$$y(x) = \frac{a}{e^{\frac{b-x}{c}} + 1} + a_1 e^{\frac{-(b_1-x)^2}{c_1^2}} + a_2 e^{\frac{-(b_2-x)^2}{c_2^2}} + d \tag{6.1}$$

Velázquez in [98] demonstrated the validity of the Equation 6.1 to model saccade position profiles. The first element of the equation is a sigmoid which models the main (step like) waveform of the saccade. The following two gauss terms model the possible undershot and overshot artifacts near the onset and offset of the saccade, respectively.

The velocity profile of the saccade is a requirement to set its onset and offset points. For that reason we have differentiated the Equation 6.1 getting the formula described in Equation 6.2. This derived formula allows us to get approximated noise free velocity profiles where we can use simple threshold based criteria to establish onset and offset saccade points more accurately.

$$y'(x) = \frac{ae^{\frac{b-x}{c}}}{c(e^{\frac{b-x}{c}} + 1)^2} + \frac{2a_1(b_1 - x)e^{-\frac{(b_1-x)^2}{c_1^2}}}{c_1^2} + \frac{2a_2(b_2 - x)e^{-\frac{(b_2-x)^2}{c_2^2}}}{c_2^2} \tag{6.2}$$

To fit the Equation 6.1 to the saccade data we use the *scipy.optimize.minimize* [1] method of the SciPy library, specifically using the *Powell* method. Figure 6.4a shows how well the saccade profile is fitted to the curve resulting in an Root Mean Square Error (RMSE) of $\approx 0.0005°$. With the goal of obtaining high quality fits, we set a

[1] https://docs.scipy.org/doc/scipy/reference/generated/scipy.optimize.minimize.html

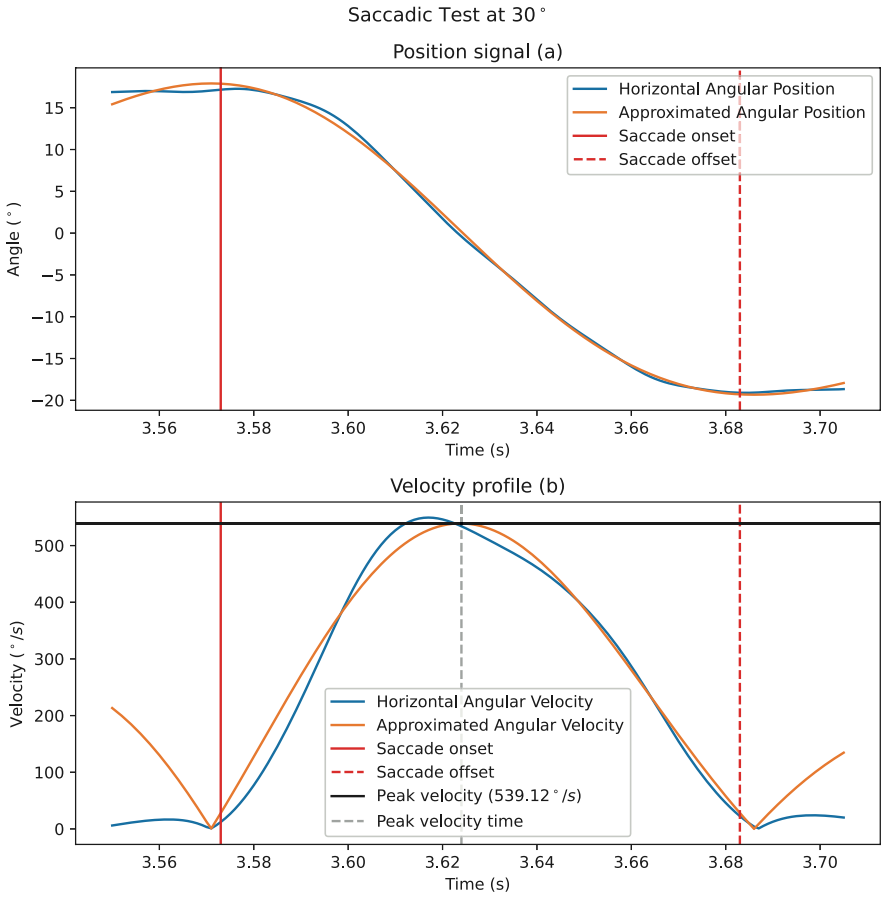

Figure 6.4: Equation 6.1 and Equation 6.2 fitted curve respectively.

maximum RMSE error of 1°. Testing the procedure on 20 healthy subjects using 4 different stimulation angles (10, 20, 30, 60) we get 1420 saccades with an average RMSE of $0.16 \pm 0.23°$.

Once the position profile is fitted, we get the velocity profile by evaluating the parameters returned by the optimization process against Equation 6.2. Then we use this velocity profile to set the saccade onset and offset points. To set the saccade points, we use a velocity based algorithm with a threshold of $30°/s$ as recommended by [83, 84, 99]. This means that we set the saccade onset point when the velocity is equal or greater than $30°/s$, and set the offset point when the velocity is lesser than $30°/s$. Figure 6.4b shows the saccade limits detected by this algorithm in the red vertical lines.

Having the saccade onset and offset point set, we can use the following terms to calculate the values of the biomarkers using the formulas described in Table 6.1:

Table 6.1: Biomarkers calculation formulas

Biomarker	Formula
Latency	$(Saccade_{onset} - Stimulus_{transition}) * SamplingInterval$
Duration	$(Saccade_{offset} - Saccade_{onset}) * SamplingInterval$
Amplitude	$abs(Y[Saccade_{offset}] - Y[Saccade_{onset}])$
Deviation	$Amplitude/Stimulus_{angle}$
Peak Velocity	$max(Y[Saccade_{onset} : Saccade_{offset}])$

$SamplingInterval$ Time between samples in seconds.

$Stimulus_{transition}$ Last sample index where the stimulus has changed prior the saccade onset.

$Stimulus_{angle}$ Swept angle by the visual stimulus.

$Saccade_{onset}$ Sample index where the saccade starts.

$Saccade_{offset}$ Sample index where the saccade ends.

Y Vector of angular positions in degrees (°).

We apply this methodology to each saccade found in previous steps of the eye movement processing pipeline. Our methodology allow to get accurate biomarkers values avoiding the handicap of noisy signals.

6.3 Saccadic study report

One goal of this work is to provide relevant data to the Centre for the Research and Rehabilitation of Hereditary Ataxias (CIRAH) researchers for making clinical decisions. This data should be in a simple to read and process format, allowing the specialist to perform their own transformations and statistics to it. For this reason we have designed a report that contains all the raw biomarkers values in a Microsoft Excel document, as well as a basic statistic overview of all data aggregated by stimulus angle.

Having the raw biomarkers values allows to perform comparative statistics, very useful in clinical trials and for evaluating subject evolution. Also, getting an overview of the aggregated data provides a fast way to assess the condition of the subject being studied.

Our typical study contains 4 saccadic tests with angles of 10, 20, 30 and 60°. Here, our report will contain 5 Microsoft Excel sheets (in a single file): Overview, 10, 20, 30, 60. The first one is a table with basic descriptive statistics in the format detailed

Table 6.2: Example of saccadic study report overview

Angle	Count	Latency Mean	Latency Std	...	Peak Velocity Mean	Peak Velocity Std
10	18	0.0683	0.0378	...	291.0136	29.9925
20	19	0.1098	0.0373	...	447.2520	44.8831
30	19	0.1312	0.0453	...	527.7312	38.8707
60	19	0.1078	0.0398	...	515.2895	35.1437

Table 6.3: Example of saccadic study report for a 10° angle

Index	Latency	Duration	Amplitude	Deviation	Peak Velocity
1	0.139	0.079	22.0232	1.1012	471.3344
2	0.097	0.084	22.3945	1.1197	487.7787
...	...	...	...	...	...
19	0.069	0.078	20.3711	1.0186	460.3557

in Table 6.2. Also, in Table 6.3 we show an example of the format used to provide the biomarkers data computed for a specific angle.

6.4 Conclusions

In this chapter we have detailed a procedure to compute saccadic biomarkers from previously identified saccades. We provided a methodology based on a mathematical continuous model to avoid the noise present in the signals which is amplified by the numerical differentiation. Using optimization routines, we fit the model to the position vector of the saccades. Due that our model is differentiable, we can get an exact velocity profile by evaluating the fitted parameters against the derivative of the model. The fitted velocity profile allows to set the saccade onset and offset points, operation critical to get accurate biomarkers values.

Also, we have detailed how we set the saccade onset and offset points and the formulas used to compute the biomarkers values. Finally, we have designed a report that aggregates all the biomarkers data extracted from the saccades in a format which can be used by the CIRAH staff to make decisions.

Chapter 7

OpenEOG recording equipment

7.1 Introduction

The Centre for the Research and Rehabilitation of Hereditary Ataxias (CIRAH) is a leading institution in the international research about the Spinocerebellar Ataxia type 2 (SCA2). In this center, its researchers study eye movements to diagnose and follow subjects suffering this horrible disease.

The fundamental goal of this chapter is to design a device capable of recording eye movements in a controlled environment and extract relevant biomarkers that allow doctors to make clinical decisions. Also, the device could replace the Otoscreen electronystagmographer used at CIRAH and improve its capabilities.

We project a cost of less than €1000 per unit, so the Cuban health care system could be able to gain several devices and spread them across the national territory. This should relieve the current situation originated from having only one device in the entire country, forcing patients to move hundreds of kms in hard conditions to receive treatment. It is always a good idea to have over one device able to perform the same task because of redundancy reasons. This means that if this device stop to work, the research of these diseases suffers a notable hit.

Also, the CIRAH researchers processed the signals captured with the Otoscreen using third-party applications to fulfill their specific needs. For this reason, another goal of our project is to include these specific needs in the software of our equipment as an added value.

In this chapter we discuss the design of our own device to capture eye movements using electrooculography. This device that we named OpenEOG, is based on the hardware that is provided by the OpenBCI Cyton board. First, we start by stating the functional requirements of the system that will guide the design process. Then, we describe the hardware involved in our solution and the interaction between its

components. Later, we explain our method in the design of our control software and the rationale behind the technologies selected for its development. This chapter completes by declaring the key contributions and conclusions achieved in our work.

7.2 Functional requirements

As stated at the introduction, there is a need for an instrument able of measuring eye movements that replace Otoscreen at CIRAH. However, to use it in a clinical environment, the device must have a set of additional features which are detailed below.

The International Society for Clinical Electrophysiology of Vision (ISCEV)[1] establishes several standards on how to use the different techniques employed to capture eye movements. Among them, there is one for electrooculography which was published the last time by Constable et al.[100] in 2017. This standard, for saccade recording, recommends using sampling rates greater or equal than 1 kHz for each channel to avoid the loss of information. They also recommend that the amplifier should use a 0.1 Hz high-pass filter to remove baseline drifts and 30 Hz low-pass filter to reduce noise.

Regarding to the angular accuracy required, we base our requirement in the results got by researchers using the same technique in similar recording conditions. For example, in [101] they achieve angular accuracies of $\approx 0.75°$ and $\approx 1.38°$ for the horizontal and vertical channel respectively and in [33] a horizontal accuracy of $\approx 1°$ is reported.

From an economic perspective, the equipment should have an unit cost low enough that countries in development like Cuba can afford several of them. Having several units will allow to perform studies across the country, improving the research process of several neurological diseases such as the SCA2. Also, we are targeting to reuse components such as PC and displays available in public health institutions, diminishing even further the cost per unit and have availability of replacement components. In our case adding up the price of the acquisition board at 500 USD, the range from 300 EUR to 400 EUR of a suitable computer, and the range from 100 EUR to 200 EUR of a suitable monitor we think we can achieve a total unit cost less than 1000 EUR.

Portability is another key design goal of our work. Making the equipment as portable as possible allows its use in primary public health attention, hence reaching more patients. The reusability mentioned before helps in this goal by allowing the use of equipment already present in public health institutions. For that reason we want the device can be carried using a small luggage such as a backpack.

[1] https://iscev.wildapricot.org/

The major goal of our work is to support the research related to the SCA2 carried out by CIRAH researchers. To fulfill this goal, we need to implement the processing protocol proposed by them. So, our equipment must be able to process the signals and to output the biomarkers relevant for the study of SCA2 as requested by the CIRAH staff.

Taking into consideration the needs exposed above, we state the following functional requirements:

1. Record saccadic eye movements.
2. Sampling frequency $\geq$ 1 kHz, with a high-pass filter of 0.1 Hz and a low-pass filter of 30 Hz.
3. Angular accuracy $\approx 1°$.
4. Affordable for countries in development like Cuba. Less than €1000 per unit.
5. Portable. Work with different computers and monitors and transportable in a backpack.
6. Implement the processing protocol proposed in this work to retrieve the significant clinical biomarkers for medical purposes.

7.3 Device components

OpenEOG is composed of 3 major components as shown in Figure 7.1: the acquisition board (OpenBCI Cyton), the Stimuli Display and the Control PC. The acquisition board converts electrical signals to their digital form and send it to the Control PC using a custom firmware. The role of the Stimuli Display is to show the visual stimulus generated from the Control PC. Both components are coordinated by the Control PC running the *SaccRec* (our recording application) software.

The capture of eye movement in a controlled way requires a physical setup. First, we seat the subject in front of the stimulus monitor and we fix its skull to prevent head rotational movements. Then, we connect the electrodes to the subject face, as shown in Figure 7.2. The red electrodes measure the horizontal angular movement, the blue electrodes measure the vertical angular movement, and the green electrode is used as a reference for the adquisition process.

Before the recording process starts, the operator explains to the subject what she/he has to do. The task comprises following a small circle on the screen with its gaze.

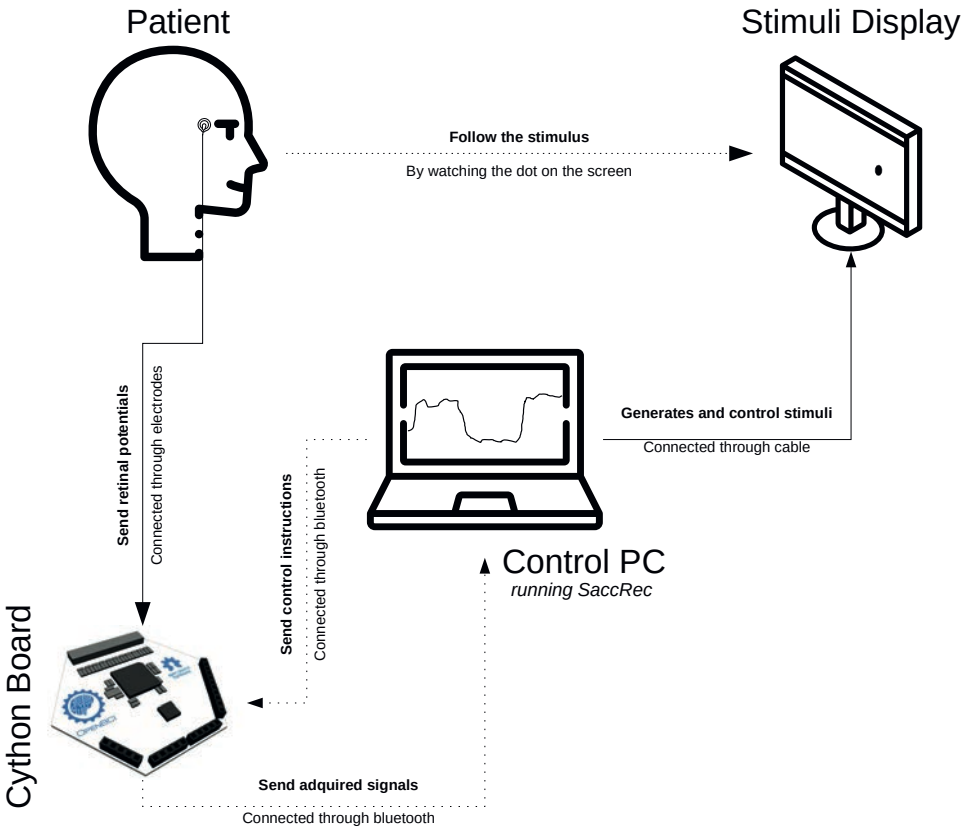

Figure 7.1: Main equipment schema.

Finally, we perform the main loop of the recording process as follows. First, the Control PC generates the stimulus to show it on the Stimuli Display. The following of the stimulus on the screen provokes that the subject move their eyes (see Figure 7.3) generating the electrical potentials around them. These potentials are then captured by the Cyton Board and sent to the Control PC for further processing.

In a horizontal saccade test, the stimulus comprises a small circle appearing on the left side of the Stimuli Display; it stays in the same position during the fixation duration and then changes its position abruptly to the right side (see Figure 7.3). Running this procedure back and forth allows to measure saccades in a controlled way.

The Control PC is the coordinator of the entire process. This component is responsible of generate the visual stimulus and send it to the Stimuli Display. Also have to record the signals sent by the Acquisition Board, show it to the specialist in real time and store it in persistent memory.

In Figures 7.4 and 7.5 respectively, we show the prototype built and how it is

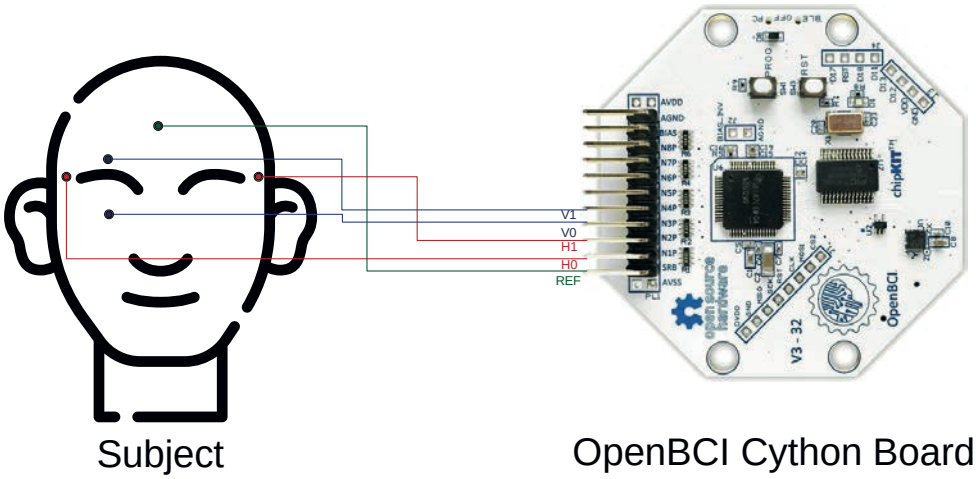

Figure 7.2: Electrodes disposition

connected to the subject.

Hardware components

Acquisition Board

OpenBCI is a US based company which develops and sells open hardware for Brain-Computer Interface (BCI). Their primary focus is on electroencephalography equipment. It was funded by the Defense Advanced Research Projects Agency (DARPA) because an award granted in 2013 with an amount of $99,724.00 under the umbrella of the Small Business Innovation Research (SBIR) program [2].

Among their major products are a set of affordable bio-sensing boards with included open source software and SDK. These boards are listed below:

Ganglion Board: with a cost of $249.99[3] and 4 channels use the MCP3912 chip [4]. The chip includes 4 synchronous sampling 24-bit Delta-Sigma A/D converters [102].

Cyton Biosensing Board: with a cost of $499.99 and 8 channels uses the chip ADS1299 from Texas Instruments [103].

[2]https://www.sbir.gov/sbirsearch/detail/408117
[3]The prices of OpenBCI products were consulted on August 2020
[4]https://www.microchip.com/wwwproducts/en/MCP3912

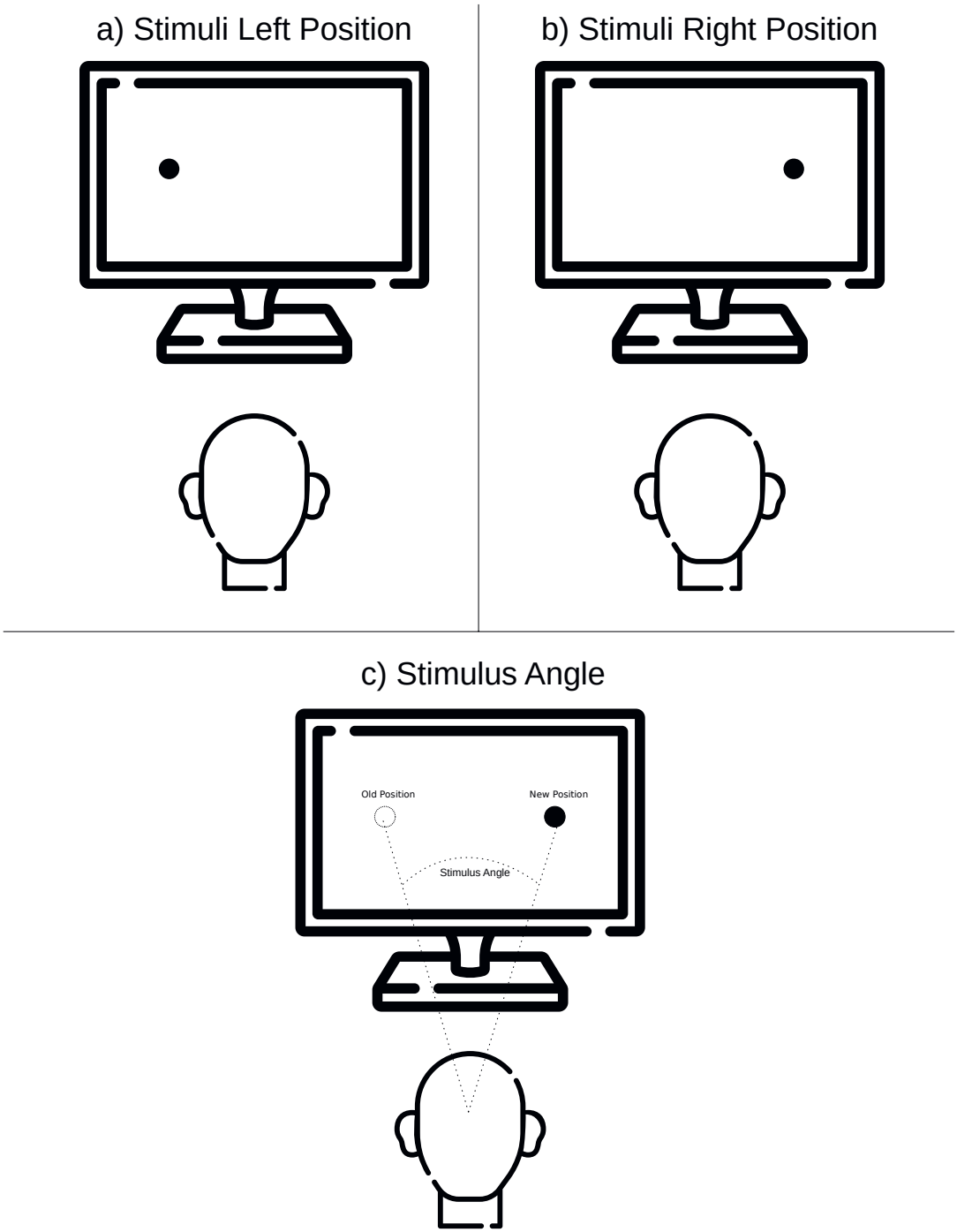

Figure 7.3: Stimuli generation

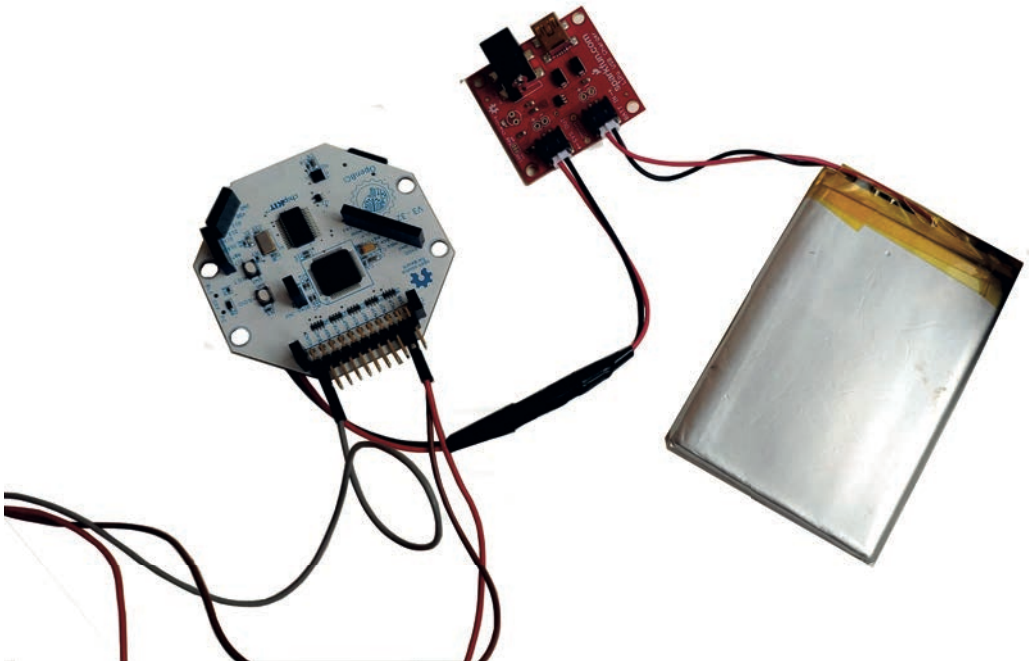

Figure 7.4: OpenEOG physical prototype

Cyton + Daisy Biosensing Boards: with a cost of $949.99 and 16 channels uses also the chip ADS1299 [103].

According [104] the Cyton board is comparable to the 25 times more expensive G.Tec bio-amplifier. This board has 8 channels, surpassing our current need of 5 channels to capture eye movements. Also, can sample rates above 1 kHz, much more than our initial requirements. For these reasons, the Cyton board fits our needs of data acquisition with the minimum price tag.

Stimuli Display

To show the visual stimulus to the subject, a computer display or a TV is required. Our instrument does not require any specific type or brand as long as is large enough to achieve the desired angular movement and can be used with the Control PC.

The angles of stimulation used by CIRAH staff range from 10° to 60°, being 30° the most common. In saccadic tests, the desired angular movement is generated by the control of the distance between the points on the Stimulus Screen and the distance between the subject to the Stimulus Screen (Figure 7.3).

Figure 7.5: OpenEOG subject setup example

The flexibility of using any brand or type of display minimizes the cost of the overall system. This is because we can reuse the equipment already present in clinics and hospitals in Cuba.

Control PC

As mentioned before, the Control PC is the center of the complete process. It is the coordinator that send the stimulus and captures the signals synchronously. Any desktop or laptop computer of the last decade capable of running the GNU/Linux operating system should be capable to fulfill the job. This allows also to reuse the equipment present in the different health institutions of Cuba. However, due the complexity of the setup is recommended to provide along with the Acquisition Board a computer already tested and configured for the task in question.

A very low end mobile system was tested as a Control PC successfully. This system is an EVO Ultrathin Laptop with the following hardware included:

- Intel Celeron N4000 (2 Cores, No hyperthreading, 1.6 GHz to 2.48 GHz (Turbo Boost), 4 Mb Cache, 6W)
- 3 Gb DDR3L-1600 SDRAM
- 32 Gb eMMC Flash
- Intel HD Graphics

Software

The hardware that conform our equipment is useless without a software able to use it and control it. To complete the equipment, we develop a software application capable of control the entire process of recording the eye movements and their later processing. This software fulfilled the last functional requirement stated in this chapter regarding the processing protocol proposed by the CIRAH staff.

Also, we like to support more hardware and processing methods in the future to support not only the SCA2 research. For this reason, we are proposing a modular architecture based on clean abstractions of each of the core functionality provided by our software. These core functionalities are listed below:

- Recording from external Analog to Digital Converter (ADC).
- Generate stimulus from templates.
- Process the recorded signals.

- Store the signals into persistent storage.

The software application that we develop which implements these functionalities is named **SaccRec**. SaccRec is a short name for Saccade Recorder, which refers to a central task in our project. So, from now on is how we will refer to our software product.

Technology and Environment

To build our application, we need to select a set of technologies which fit to the design goals proposed. We evaluate these technologies according to their affordability, performance, correctness and usability. Regarding the affordability, we employ Open Source technologies as much as we can, hence the cost of the development process and the final product was decreased significantly.

A **GNU/Linux** operating system (OS) was used to develop and deploy our solution, specifically the **Ubuntu** distribution. Linux based OSs are very customizable due that the kernel is Open Source. Even allowing to customize core functionalities such as process schedulers, which allow the development of preemptive kernels helping heavy IO applications in real-time contexts. In our setup that means lower latencies between the stimulus and the recording process, and prioritizing recording which diminish the chances of loosing samples by the Control PC. For applications like the ones we develop, is more interactive (lower latencies) that it's competition (Microsoft Windows 10) [105].

Another important advantage of using **GNU/Linux** distro is that we can pick our desktop environment or not use them and open directly to our application. These feature allows prevent the use of our Control PC for other tasks rather than be the instrument that runs our software. Also, using this feature disallows user access to the file system, protecting the recorded data from human error and malpractice.

To build **SaccRec** we choose the *Python* programming language. This a multiparadigm language very popular for develop scientific applications and artificial intelligence research. In Python occurs a very positive phenomenon regarding scientific and numerical computing. Contrasting other programming languages communities, Python community has focused on the development of two libraries for scientific computing: **NumPy** [106] and **SciPy** [69]. This situation makes these libraries very accurate and robust. Both libraries are released under Berkeley Software Distribution (BSD)[5] license of 3 clauses [107].

From conception they have been growing in functionality contesting today their commercial counterparts such as Matlab in many scenarios. NumPy provides routines to manipulate large arrays and matrixes of numerical data. SciPy extends NumPy

[5]The BSD license is an Open Source license

Table 7.1: Technologies employed

Technology	Version	Role
Ubuntu GNU/Linux	20.04	Operating system
Python	3.8	Programming language
NumPy	1.19.2	Numerical computing and vector algebra
SciPy	1.5.2	Scientific computing and optimization
Numba	0.51.2	Numerical computing acceleration
Scikit-Learn	0.23.2	Machine learning
Qt	5.15	GUI Toolkit
PyQt5	5.15.1	Qt toolkit bindings

functionality with an extensive collection of optimization algorithms, mathematical transforms, signal processing routines, statistics and many more [108].

On top of these two, a set of complementary libraries were developed conforming to the Python scientific computing ecosystem. Among the libraries in the Python scientific ecosystem we make use of the **scikit-learn** [109, 110] for machine learning and **Numba** [111] for numerical computing acceleration. These libraries are very important for processing the acquired signals.

As our software application requires interaction with a human specialist, the development of a desktop application is recommended. The basic building block of a desktop application is the Graphical User Interface (GUI) library or toolkit. In GNU/Linux there are several GUI toolkits, among the most popular are GTK and Qt. According to our research Qt is fit for the task at hand.

Qt provides a cross platform framework to create desktop, mobile and embedded applications [112]. It has a shared interface, platform independent from in memory character representation to multithreaded graphical applications [113]. Even when Qt has parts released under closed source licenses, for non-commercial applications is released under the GNU Lesser General Public License (LGPL) version 3 which is our case [114]. Qt, specifically its fifth version, can be used from the Python language using the PyQt5 bindings. These bindings are developed commercially by Riverbank Computing but released under the General Public License version 3 (GPLv3).

Summarizing, to build the desktop application we use the technologies listed in Table 7.1.

User interface

Facilitating the interaction with our system is one of our design goals. So we create a simple process which involves the following steps:

1. Record setup.
2. Signals recording.

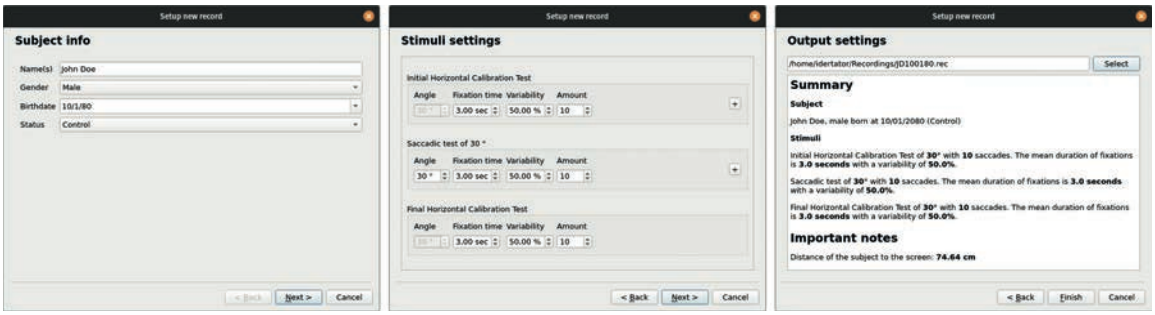

Figure 7.6: Protocol recording setup wizard

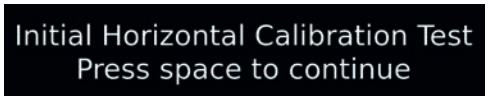

Figure 7.7: Test about to start prompt

3. Saccadic record generation.

The first step is the one involving the most user interaction. It designed to be used by a specialist and comprises three simple steps. These steps are implemented by using a wizard window of 3 pages as shown in Figure 7.6. In these interfaces the specialist set the subject relevant information, the stimulus settings for each test and the output file.

Once finished the wizard the second step will start prompting a message for the patient in the Stimulus Screen notifying the test is about to start. An example of this message is shown in Figure 7.7. When the specialist press the Space key the recording of signals starts and shows them on the SaccRec main window like the one shown in Figure 7.8. This prompt will show before each test, giving the specialist time to check if the setup stills correct and give some rest to the subject.

Monitoring the recording of signals in real-time will allow to assess if the process needs to be stopped because of equipment malfunction or bad test setup. In case of something wrong is happening, the specialist may choose to stop the process, preventing the subject from additional discomfort.

Finally, when the recording process is over, a dialog window will show to the specialist asking if he or she want to generate a saccadic report. This report is a Microsoft Excel (xls) file containing relevant saccadic statistics for diagnostics. The process is fully automatic and does not require additional user input.

A settings window is provided to establish important parameters such as OpenBCI port and channels, stimulus customization and screen size. The case of screen size is very important because it allows to use a wide variety of monitors and televisions with our software. The rest of the user interfaces are presented in Appendix A.

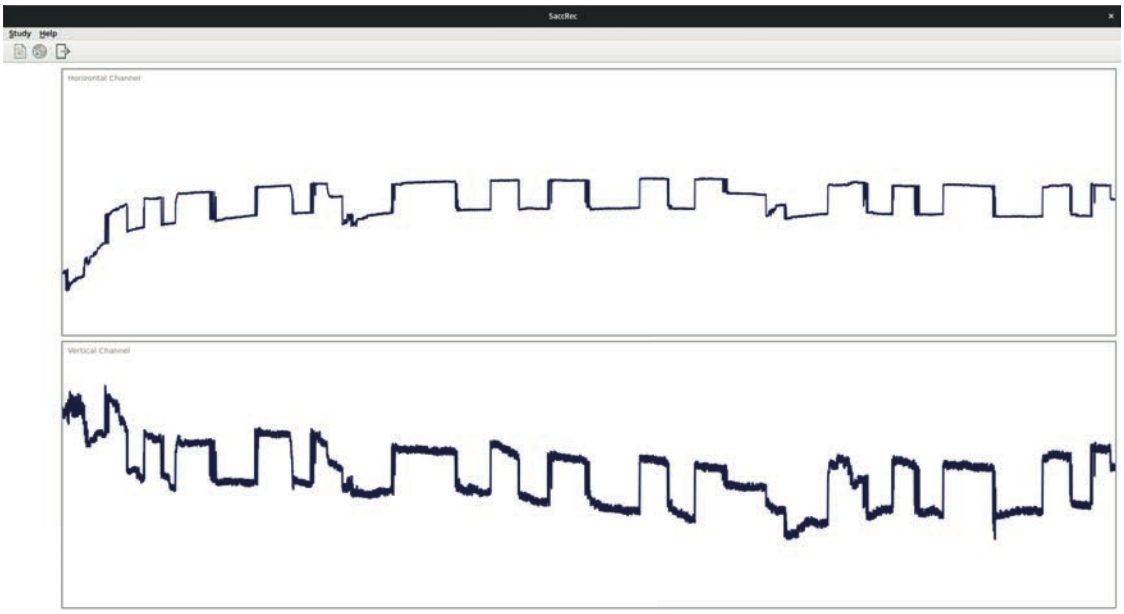

Figure 7.8: Monitoring signal recording in realtime

Record format

Once the signals are in the Control PC, they need to be stored for further research. For that reason, an efficient and simple file format is required. To fulfill this goal, we design a format which uses the **Zip** archive as the format file system. We use the extension *.rec* to identify our recording files from the *.zip* regular files.

To store the signal arrays in a compact and efficient manner, we rely on the NumPy compressed vector format[6]. This format is widely used by the Python scientific community and has an easy interface for reading and writing these files.

Each record had the file structure described in Figure 7.9:

As described in Figure 7.9 each record file includes a manifest in a JavaScript Object Notation (JSON)[7] format. This file contains all the relevant information about the accompanying record such as record date, subject information, hardware configuration and tests setup. An example of this file is listed in Appendix B.

Using JSON format allows for adding additional features to the format in the future without compromising compatibility in an easy and safe manner. Also facilitates the implementation of libraries that manipulate the file format in third party programming languages because of the format standardization.

[6]This archive is mostly known for the *.npz* extension

[7]JavaScript Object Notation is a human readable and commonly used information exchange text format.

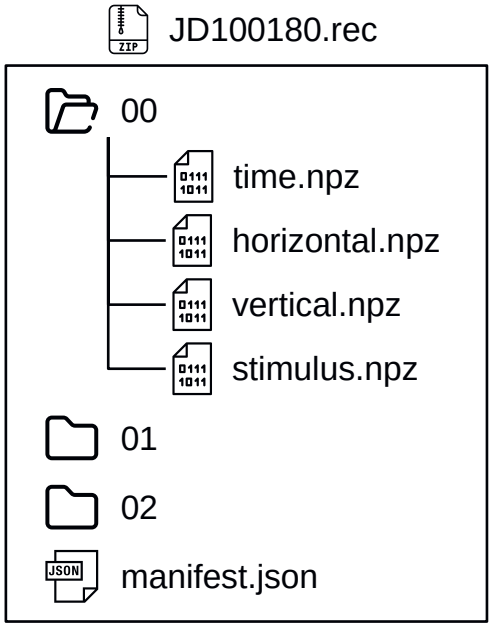

Figure 7.9: Record format file system structure

The record is separated in tests, having each test its own stimulus configuration. Signal channels recorded for each of these tests are stored in a separate folder which name is the index of the test declared in the manifest with two digits zero padding. Inside these folders there are typically four files containing each one a test signal in the NumPy array format as shown in Figure 7.9. This is a convenient way to manipulate these files because can be loaded into memory on demand, saving memory when processing them.

Firmware

The OpenBCI Cyton board includes a recording software that uses a firmware which latest version 3.1.2 was released the 14 of September 2018. This firmware is an open source and developed mainly by OpenBCI developers at GitHub [8]. This firmware is very well documented at CytonSDK [9].

The default Cyton board firmware can get generic Electroencephalography (EEG), Electrocardiography (ECG), Electromyography (EMG) and many other bio-signal recordings. However, EOG requires synchronism between the recording and visual stimulus with the smallest latency possible. To accomplish this, we can improve the

[8] https://github.com/OpenBCI/OpenBCI_Cyton_Library
[9] https://docs.openbci.com/docs/02Cyton/CytonSDK

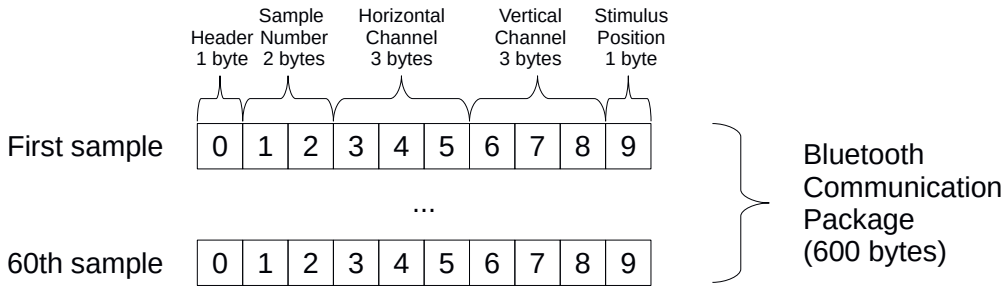

Figure 7.10: Communication sample and package description

recording process by optimizing the storage and communication process for the two only channels used in EOG and removing the support for unused features such as the attachable Daisy Board, Wi-Fi, Bluetooth Low Energy (BLE) and the included Accelerometer.

To take advantage to the most of the features offered by the Cyton board for the process of eye movement recording, we developed a custom firmware for the OpenEOG. For the developing of this firmware we take an iterative approach starting from the default Cyton board firmware. First, we remove all the unnecessary functionality mentioned before. Then, we add and test features specific for EOG recording needed by *SaccRec* optimizing the recording and communication process.

Once cleaned the code of unnecessary features, we separate the functionality in individual C++ classes, grouping them by functional responsibility. This separation improves the code readability and maintainability.

We first focus on optimizing the communication between the OpenEOG hardware and the Control PC. The default Cyton board uses 33 bytes per sample due to the usage of the 24 bit 8 channels. This sample size allows a Bluetooth communication with a sampling rate of maximum 250 Hz because of hardware limitations. These samples are sent one by one using the Bluetooth serial communication.

Figure 7.10 shows how we organized our samples. Each sample has 1 byte header, 2 bytes sample number, 3 bytes horizontal channel value, 3 bytes vertical channel value and 1 byte stimulus position. The total size of a sample is 10 bytes, 23 byte less than the default firmware sample. Also, in contrast with default Cyton firmware, we sent batches of 60 samples instead of sample by sample. Using batches optimizes the usage of the Bluetooth serial port. Also, reducing over 3 times the sample size theoretically allows us to send data at rates up to 750 samples per second. The use of higher sampling frequency allows us to have better previews of the signals currently recording.

One requirement of our design is that the signals were sampled at 1 kHz. As explained before, sending all this data by Bluetooth communication is not workable.

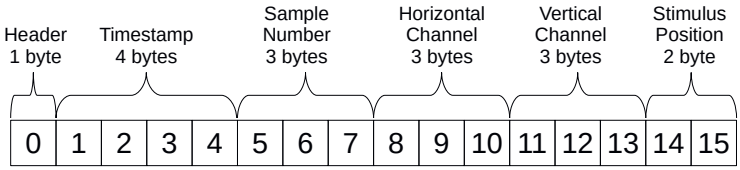

Figure 7.11: Sample description per byte for the SD file storage

The Cyton board includes a SDCard port that allows to store data internally at much higher rates than Bluetooth can handle. The default Cyton firmware uses an ASCII file format in which the samples are encoded to hexadecimal numbers and separated by commas. This feature makes the files stored in the SD a little larger than necessary and makes storing heavier because of the conversion and serialization processes.

In our OpenEOG firmware we used a binary format where each sample is 16 bytes only, as shown in Figure 7.11. Our sample size is at least 4 times smaller than the default Cyton firmware which, length can be up to 73 bytes per sample. Also, in our case there is no serialization conversion required, so the process is lighter and faster. These make the sample lost less probable than in the default firmware.

To allow a fluid and comprehensive interaction with the *SaccRec* we define a set of commands specifically for the EOG recording process defined below:

v Soft reset. Restarts the recording machinery and return hardware info.

O Set stimulus position. Includes a 1 byte parameter with the position of the stimulus.

N Set channel numbers. Includes two 1 byte parameters with the channel numbers (from 1 to 8) for horizontal and vertical channels respectively.

(Start recording a new test.

) Finish recording a stop the current test.

x Config channel. Includes a 9 bytes parameter with internal channel config. The same as in Cyton default firmware.

S Creates and open a file in the SDCard returning its filename.

j Closes SDCard opened file.

_ Reset SDCard current filename number to 0.

The symbiosis between the SaccRec and the OpenEOG firmware, due all the custom features developed for them, makes the process of eye movement recording more efficient and customizable. The OpenEOG firmware is released under the *MIT License* and available at GitHub.

7.4 Validation

The last step in the design of our equipment is to know if the data measured by our equipment is reliable. In order to do so we are going to compare saccadic biomarkers extracted from data recorded using the OpenEOG against data recorded using the Otoscreen and also compare our results against recent literature. We compare the saccadic information extracted from 10 control subjects previously recorded using the Otoscreen and 10 control subjects recorded with the OpenEOG.

To fullfill with the ethics in biomedical research, we have designed an informed consent that complies with current Spanish legislation. We deliver for each one volunteer the research data sheet and also they all sign the informed consent.

The first tool that we are going to use is the main sequence. The main sequence is an old concept which describes the relationship between the amplitude, peak velocity and duration of primate saccades [115]. This concept was first introduced by Bahill et al. in [26] and was inspired by the homonym astronomical term.

A good deal of different math curves have been used to model the data behind the main sequence. From the early days the relationship between the amplitude and duration was modeled using a linear model and the relationship between amplitude and peak velocity as a kind of non-linear model [26]. In Figure 7.12(a) we can appreciate how the linear model (Equation 7.1) still the best fit for the case amplitude vs duration.

$$V_{peak}(A, B) = A * x + B \tag{7.1}$$

To describe the main sequence between amplitude and peak velocity several curves have been used such as square root, fixed square root, power low, exponential, log-log, sigmoid, and many others [116]. For our data the model better fitted was the log-log which is described in the Equation 7.2.

$$V_{peak}(A, B) = e^{A*log(x)+B} \tag{7.2}$$

In both models (linear and log-log) the parameters A and B describe the behaviour of the models. As we can see in Figure 7.12 the numerical values of the parameters A and B, and the curves that they describe are fairly similar. The difference that we see can be explained due to subject variability, ADC (16 bit for Otoscreen and 24 bit

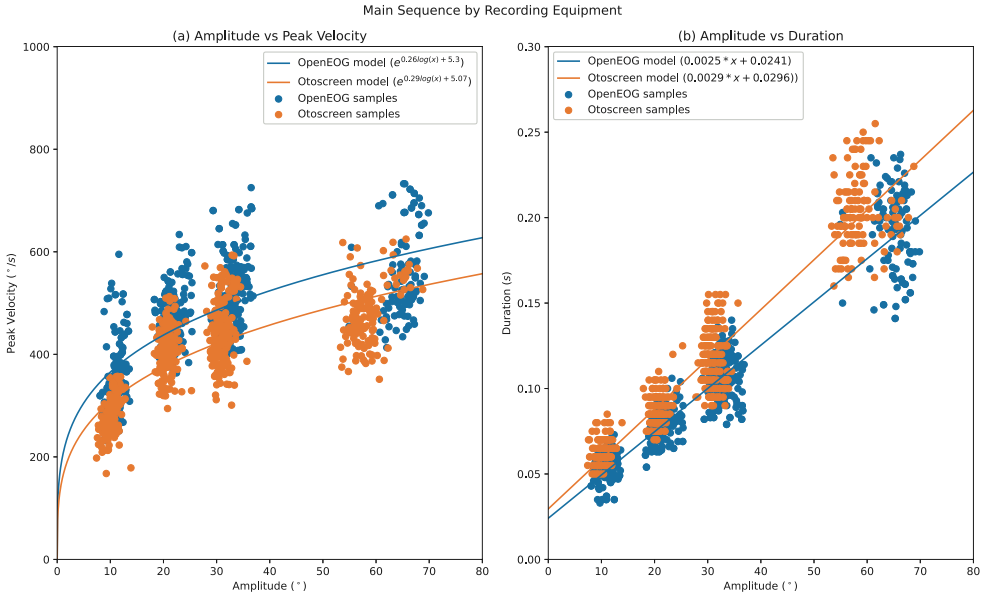

Figure 7.12: Main sequence of amplitude vs peak velocity and amplitude vs duration for Otoscreen and OpenEOG

for OpenEOG), filters and sampling rate difference (200 Hz for Otoscreen and 1000 Hz for OpenEOG).

Regarding the saccadic latency the Figure 7.13(a) shows means between 100 and 150 milliseconds. These results are near or in the range with recent results found in the literature such as [117] ($\leq 140ms$), [118] ($220.40 \pm 43.16ms$) and [119] ($\approx 169ms$). The rest of the Figure 7.13 subfigures shows the range of the values of the remaining biomarkers (duration, amplitude and peak velocity) which behaviour was modeled by the main sequence presented in Figure 7.12.

7.5 Conclusions

In this chapter we have designed, implemented and validated an instrument to measure saccadic eye movements. We have to start by identifying minimal requirements that are required for clinical applications, specifically to diagnose and follow people suffering the SCA2. Then, we select the hardware necessary to build the instrument and define the interactions between their components. Finally, we design and implement the software that makes use of the hardware to accomplish the proposed goal.

Our instrument possesses the features of sampling frequency, ADC resolution,

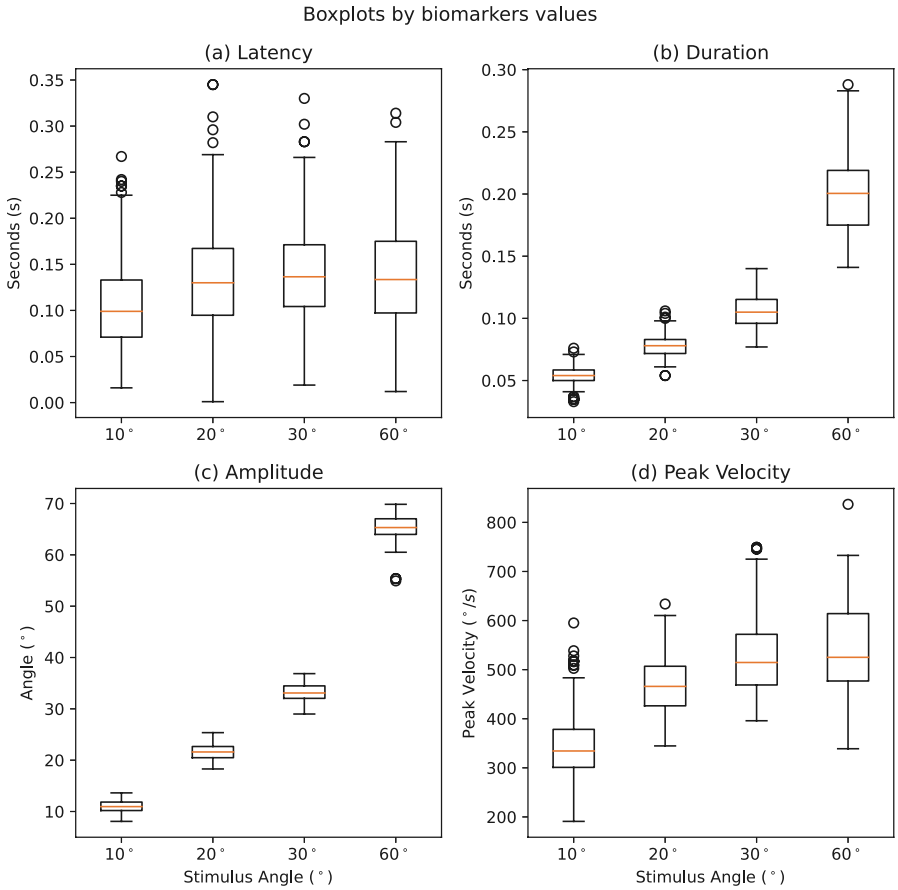

Figure 7.13: Distribution of values by each one of the relevant biomarkers

filtering, among others, required to record saccades for clinical applications such as the study of the SCA2. From an economic perspective, the instrument achieves the goal to cost under €1000 being affordable for Cuban public health system. The form factor of the components involved guarantees the portability hence the mobility of the equipment. Using batteries avoids possible hazardous situations for the subject and eases the certification process as medical equipment.

The software included with the hardware offers an easy and intuitive user interface to design eye movement studies and record eye movement signals. Also, the designed architecture provides interfaces to extend the capabilities of the software platform. Our output files ease the post processing of the signals by using standardized information exchange formats. The OpenEOG firmware allows to control the recording process and making it faster, reliable and customizable.

The saccadic data extracted from our equipment yielded results similar to the

data extracted from the Otoscreen using main sequence models. Also, with specific biomarkers such as latency presents values similar to the ones reported in the scientific literature.

For all the reasons previously stated, the instrument can perform the same tasks of Otoscreen regarding the eye movement studies for the SCA2 and even improving some of its features.

Chapter 8

Conclusions

In this thesis we have studied the recording and processing of saccadic eye movements. From the study of the processing techniques we have identified and established a processing pipeline which comprises 4 steps: filtering, differentiation, segmentation and biomarkers extraction. We have focused the signal processing part of our work on implementing and fine tuning each of these steps.

For the filtering step we have used the median filter as recommended in literature. We have empirically observed through our entire research how this filter can remove the main noise of the signals without compromising their waveform or relevant features for saccadic processing.

Differentiation is a very important step in the processing pipeline because it allows to get the velocity profile needed by the following steps. The performance of this step will affect a critical task as saccade identification. For this reason we have designed an experiment where we compare 16 differentiation filters against synthetic saccadic records. Results of this experiment shows how the Lanczos filters for 9 (*l9*) and 11 (*l11*) points, Super Lanczos filter for 11 points (*sl11*) and Smooth Noise Robust filter for 11 (*snr11*) points are adequate for the saccade identification task. Also, to compute each biomarker values there is a set of unique differentiation methods fit for the task: for peak velocity we recommend the *sl11*, for latency we recommend the Smooth Noise Robust of 9 (*snr9*) and 11 (*snr11*) points or the *sl11*, and for duration we recommend *l9* or *l11*. It is noticeable how the methods with 11 points are present in all methods set, so 11 must be the right filter size to perform this operation. Our principal contribution regarding the differentiation of these signals is that we have introduced high performance methods such as *snr9*, *snr11* and *sl11*, not used before in this domain.

Regarding saccade identification we used a supervised machine learning approach where we evaluate point by point if the sample belongs to a saccade or not. We have trained and evaluated two different models, the Multilayer Perceptron (MLP)

and the Random Forest (RF), using human annotated saccades. Both methods show very good accuracies above 92% so they are adequate to identify saccades. However, we recommend the use of RF model due to its superior performance in training and runtime evaluation, making it even suitable for real-time identification.

From the set of saccades got by the identification step, not all of them have clinical value. For medical research, the useful saccades are those which respond to a visual stimulus (non spontaneous). So we have trained and evaluated 4 machine learning models that use different paradigms to separate non spontaneous saccades from the rest. The evaluated models are Support Vector Machines (SVM), K-Nearest Neighbors (KNN), Classification and Regression Trees (CART) and Naive Bayes. All the models achieved accuracies above 95%, sensitivities above 92% and precision above 83% using external validation. Specifically, for the SVM the performance got was above 97%, 96% and 90% respectively for the previously mentioned metrics.

Using these supervised machine learning techniques against data annotated by human experts allows us to model all their collective knowledge. Using these models against new data avoids the bias and subjectivity inherently present in human experts, hence favoring the objective identification of clinical relevant saccades.

The last step of the processing pipeline is the biomarkers extraction. This step provides the medical staff with the required information to make decisions which may regard clinical trials or subject evolution. The most relevant saccadic biomarkers to study the Spinocerebellar Ataxia type 2 (SCA2) and other neurological diseases are *latency*, *duration*, *amplitude*, *deviation* and *peak velocity*. In our work we show our methodology to compute these biomarkers accurately. This methodology involves optimization techniques to fit the saccade discrete data to a continuous mathematical model. We use a novel differentiable formula which uses a sigmoid to model the saccade general waveform and two gauss sums terms to model the artifacts present near the saccade onset and offset points. The evaluation of the fitted parameters into the differentiated formula allows to get and exact and noise free velocity profile. This allows us to establish the saccade onset and offset points very accurately, which is critical to compute the saccadic biomarkers with the lowest possible error. Finally, we designed a report aimed at medical staff to ease it decision making.

The second major goal of this thesis is to design and test a portable low-cost system for recording saccadic eye movements. The emphasis in the low-cost part is because we want to use this system in developing countries such as Cuba. First, we identified the requirements to capture saccadic movements for clinical researches. Then we selected the hardware and software components that comprise our system.

We select the OpenBCI Cyton board as our acquisition hardware. In this board we can use the Electrooculography (EOG) technique to measure eye movements. This board also possesses features such as sampling frequency, Analog to Digital Converter (ADC) resolution, filtering, among others, to record saccades for clinical applications

regarding diseases such as SCA2. From an economic perspective, this board fills our low-cost requirements because its cost is under €750, which we can consider affordable for our proposed audience. The form factor of this board guarantees the portability of the equipment, hence its mobility. Using batteries instead of the power line, the board could avoid possible hazardous situations for the subject.

To optimize the performance of the OpenBCI Cyton board, specifically for the recording of saccadic eye movements, we implement a custom firmware that we named OpenEOG and released with an open source license in GitHub. This firmware is based on the default Cyton board firmware but with features focused on saccadic signal acquisition. To visualize and control the recording process performed by the OpenEOG we have designed and implemented a software application named *Saccade Recorder* using the Python programming language. This application provides an easy and intuitive interface to design eye movements studies and to record the signals generated by its application. The symbiotic relationship between the OpenEOG firmware and the *Saccade Recorder* allows full control of the recording process making it faster, reliable and customizable.

For testing the validity of the system, we recorded a study of 10 healthy volunteers which involves stimulation angles of 10, 20, 30 and 60°. Then we compared the saccadic biomarker results against 10 records from healthy subjects recorded using the Otoscreen (professional electronystagmographer). The results using main sequence models yielded very similar results for both equipments. Also, with specific biomarkers such as latency, our results are like those found in the literature. For all these reasons, we can state that our system performs at least at the same level as the Otoscreen.

The work performed in this thesis produced a method for processing the saccadic eye movement signals with no human interaction. This method produces in one click all the information required by a medical research to make clinical decisions. Using the method could favor future interlaboratory exchange of information because of its objectiveness.

Also, our proposed recording system can be used in developing countries to carry out researches regarding different neurological diseases such as SCA2. Due to the openness of our work, third parties can improve it or use it for other purposes.

8.1 Future work

Having established the method of saccade identification and biomarker extraction, it open the door to automate more complicated tasks such as subject status classification. Nowadays, is trivial to classify subjects suffering SCA2 from healthy subjects using the biomarkers extracted in our work. However, when we add the presymp-

tomatic status to the mix, it is very hard to discern them from healthy subjects. This is an open problem that may be tackled using the data resulted from our method. However, further study is required.

Regarding our recording system, we can add the support for more eye movement tests such as the Smooth Pursuit test or the Antisaccade test. These tests may even provide useful information to the problem of subject status classification. Our current design is extensible enough to implement these tests.

Appendix A

Software Interfaces

Figure A.1: SaccRec main window. This is the screen shown when the program starts.

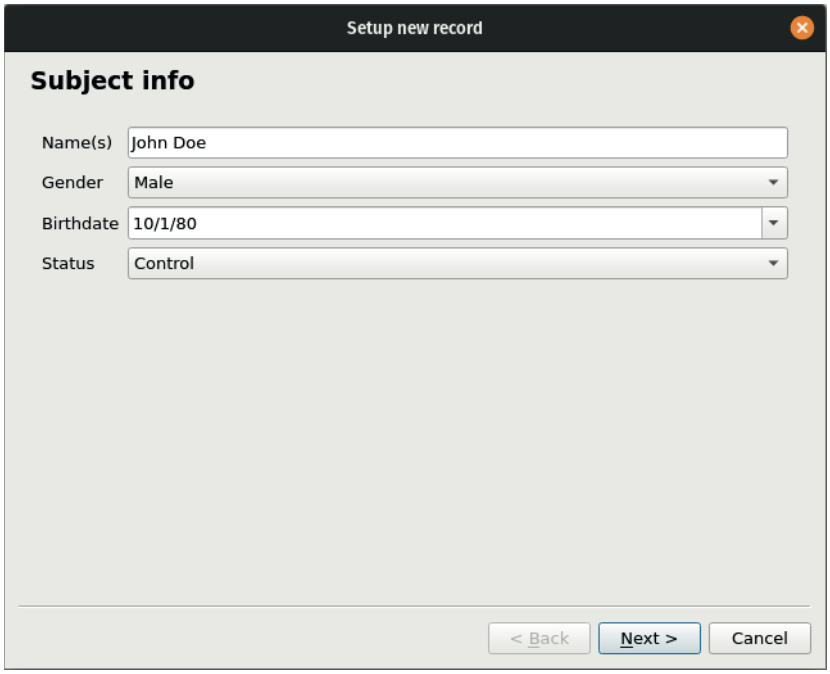

Figure A.2: Subject info page. Used to input the required data of the subject to which the record belongs. This is the first page of the recording wizard.

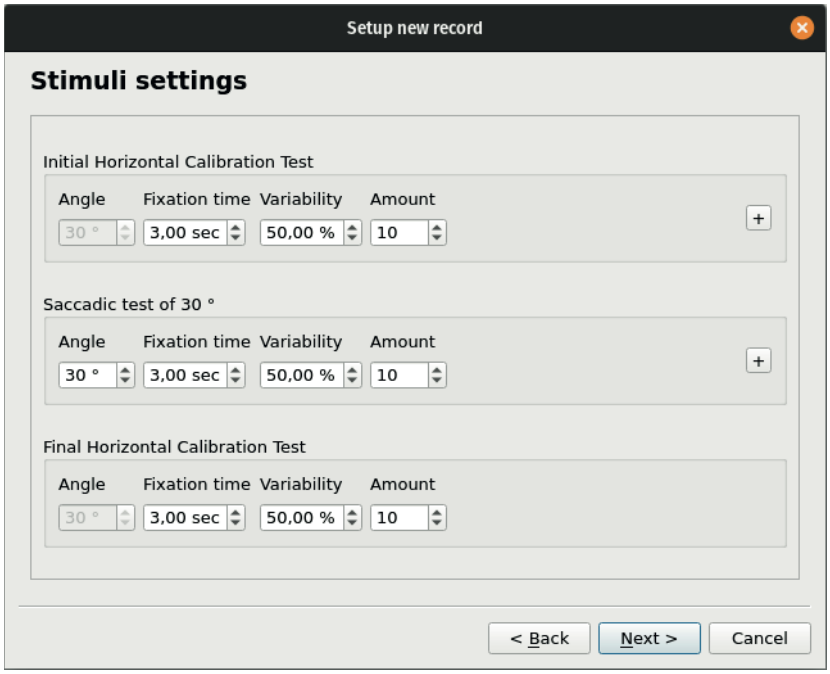

Figure A.3: Stimuli settings page. In this wizard page we setup the visual stimuli protocol that are going to be presented to the subject.

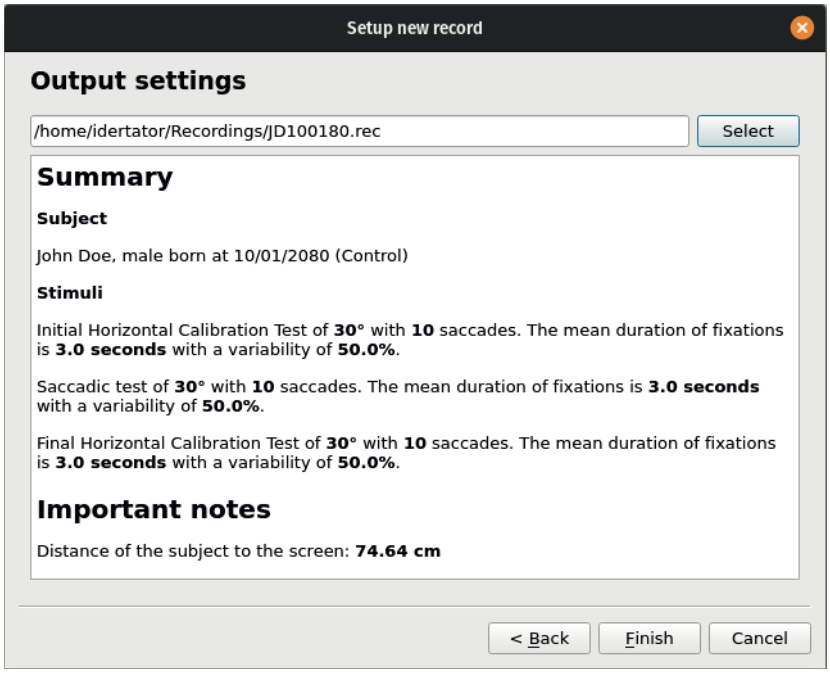

Figure A.4: Output settings page. This is a last page of the wizard that shows a summary of the recording process about to start and lets us to select where to put our record file.

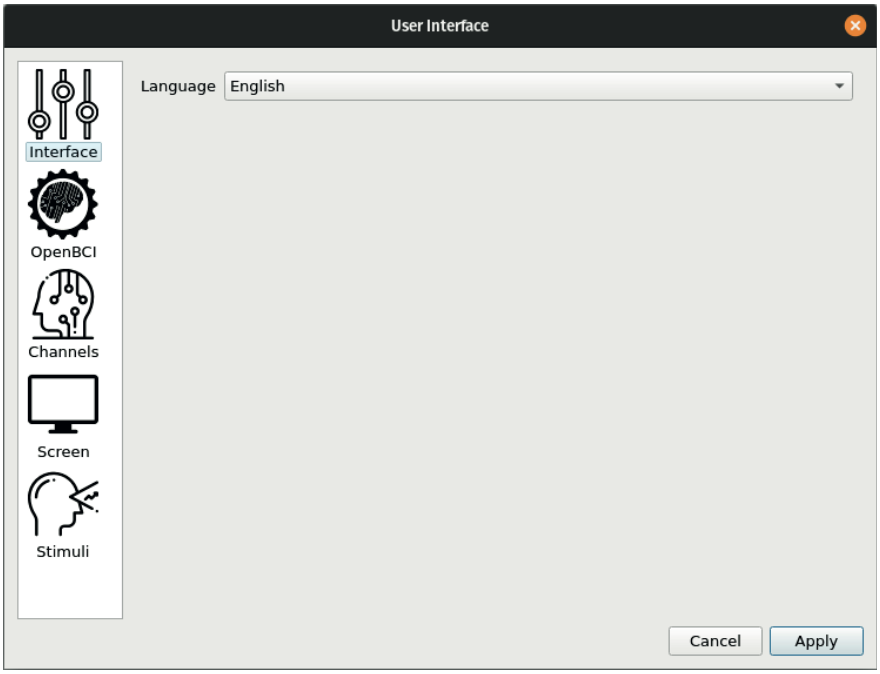

Figure A.5: User interface settings panel. This panel allows to set the user interface language.

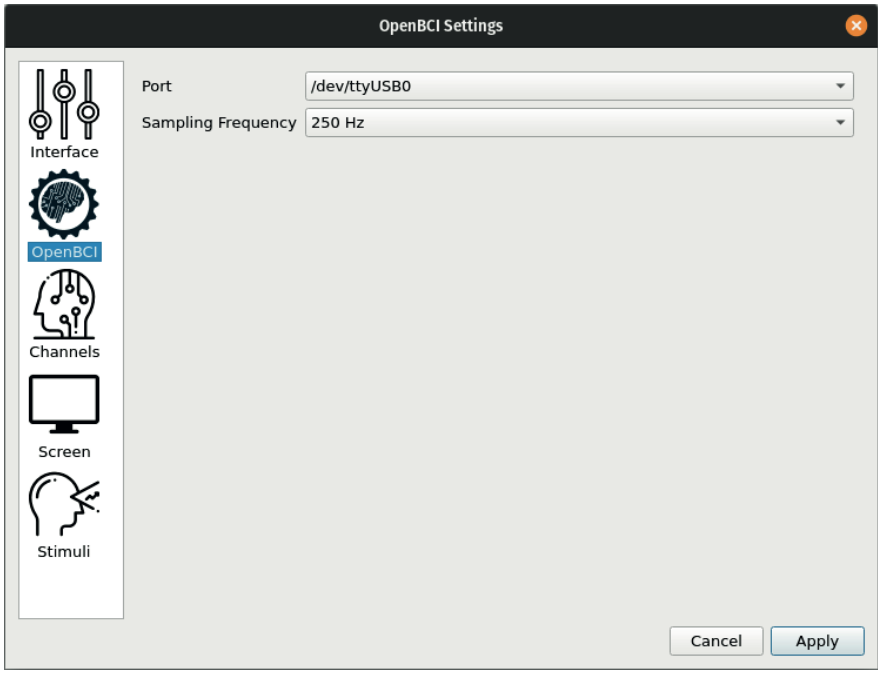

Figure A.6: OpenBCI settings panel. This panel allows to define the communication parameters with the OpenBCI card.

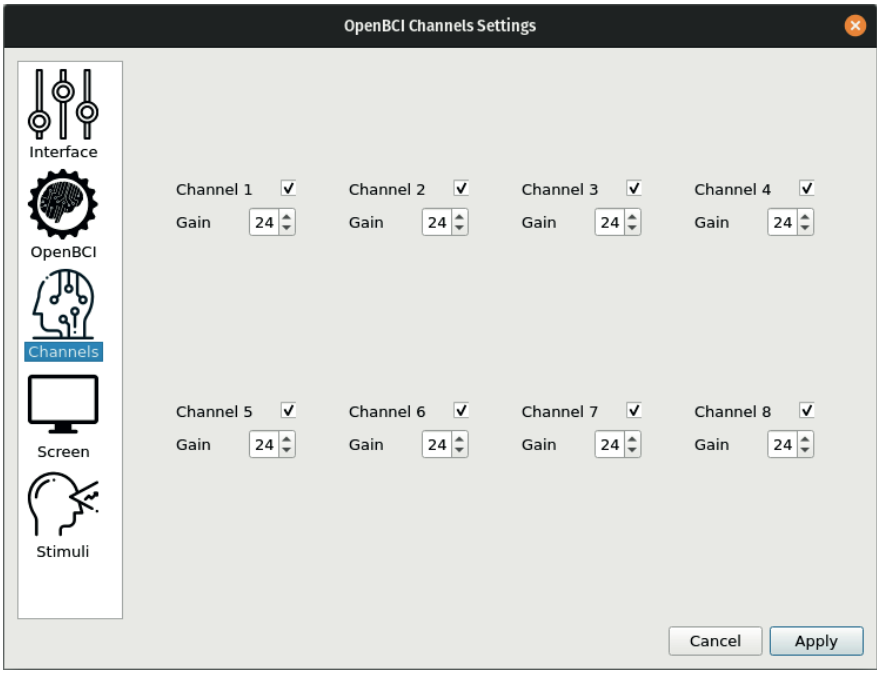

Figure A.7: OpenBCI channels settings panel. This panel allows us to select which channels to use for the recording process.

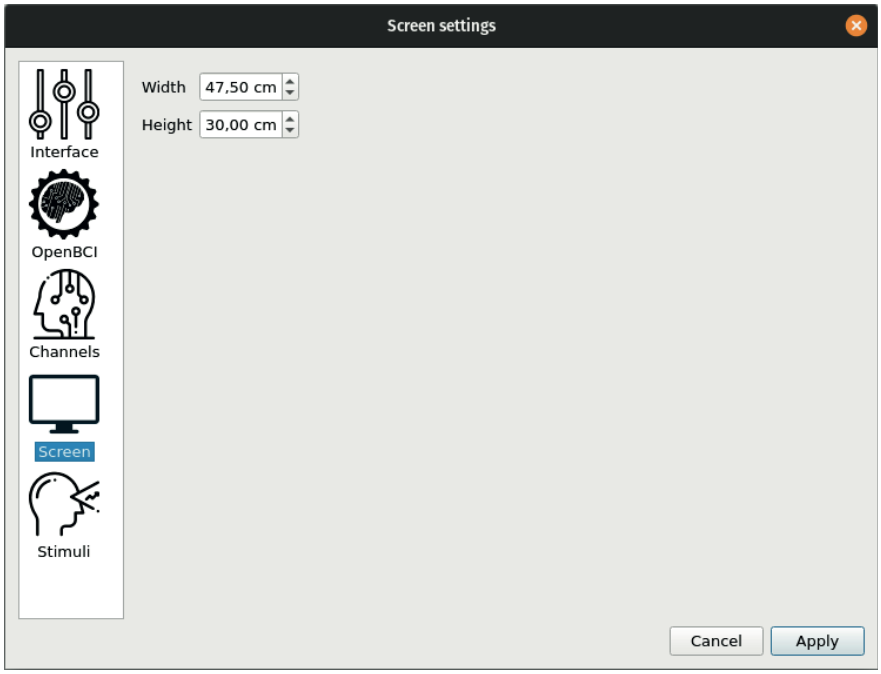

Figure A.8: Screen settings panel. This panel allows to set the size of the screen used for visual stimuli.

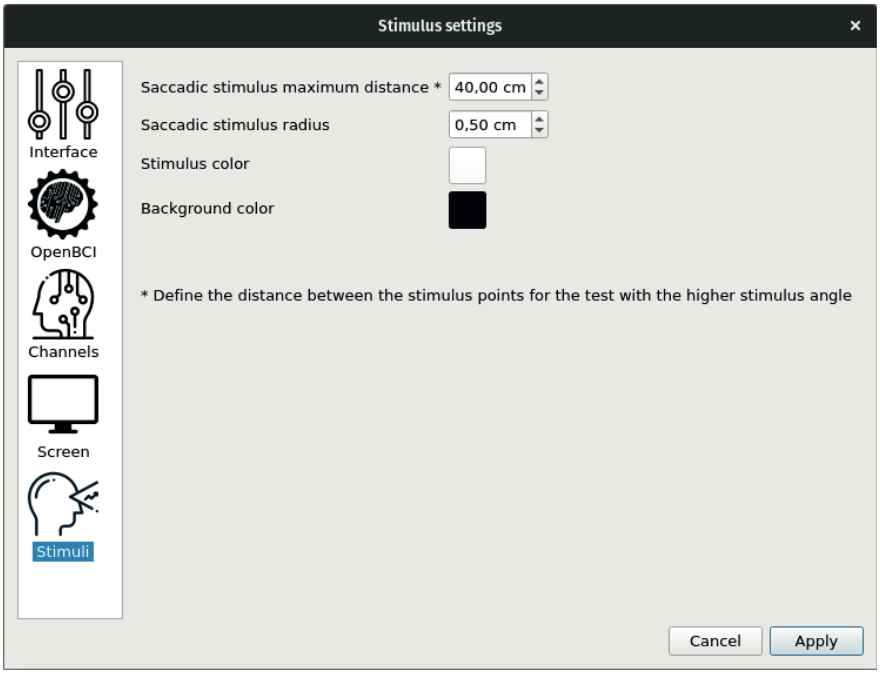

Figure A.9: Stimuli settings panel. This panel allows to set some visual stimuli parameters.

Appendix B

Manifest file example

The file format developed to store our recordings is a Zip file package (with .rec extension) that includes several serialized NumPy arrays and a manifest which describes the contained data. The manifest file is included on the root of the Zip file.

The following text is an example of a manifest file. This manifest uses the JSON (JavaScript Object Notation) syntax, which allows that included data are readable by humans and easily parsable by computers. Among the metadata included are those related to the subject from which the signals are recorded, the hardware used, the visual stimuli protocol employed and the signals themself.

```
{
    "version": 1,
    "record": {
        "datetime": "14/09/2020 11:13"
    },
    "subject": {
        "full_name": "John Doe",
        "gender": 1,
        "borndate": "10/01/2080",
        "status": 1
    },
    "hardware": {
        "sample_rate": 250,
        "channels": [
            {
                "index": 0,
                "active": true,
                "gain": 24
```


```
            },
            {
                "index": 1,
                "active": true,
                "gain": 24
            },
            {
                "index": 2,
                "active": true,
                "gain": 24
            },
            {
                "index": 3,
                "active": true,
                "gain": 24
            },
            {
                "index": 4,
                "active": true,
                "gain": 24
            },
            {
                "index": 5,
                "active": true,
                "gain": 24
            },
            {
                "index": 6,
                "active": true,
                "gain": 24
            },
            {
                "index": 7,
                "active": true,
                "gain": 24
            }
        ]
    },
    "tests": [
        {
```


```
            "properties": {
                "angle": 30,
                "fixation_duration": 3.0,
                "fixation_variability": 50.0,
                "saccades_count": 10,
                "test_name": "Initial Horizontal Calibration Test"
            },
            "stimulus": "00/stimulus.npz",
            "time": "00/time.npz",
            "horizontal": "00/horizontal.npz",
            "vertical": "00/vertical.npz"
        },
        {
            "properties": {
                "angle": 30,
                "fixation_duration": 3.0,
                "fixation_variability": 50.0,
                "saccades_count": 10,
                "test_name": "Saccadic test of 30 \u00b0"
            },
            "stimulus": "01/stimulus.npz",
            "time": "01/time.npz",
            "horizontal": "01/horizontal.npz",
            "vertical": "01/vertical.npz"
        },
        {
            "properties": {
                "angle": 30,
                "fixation_duration": 3.0,
                "fixation_variability": 50.0,
                "saccades_count": 10,
                "test_name": "Final Horizontal Calibration Test"
            },
            "stimulus": "02/stimulus.npz",
            "time": "02/time.npz",
            "horizontal": "02/horizontal.npz",
            "vertical": "02/vertical.npz"
        }
    ]
}
```


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Acronyms

ADC Analog to Digital Converter. 16, 26, 75, 83, 84, 88

ANN Artificial Neural Network. 22, 44

ANOVA Analysis of Variance. 35

ASCII American Standard Code for Information Interchange. 13, 82

CART Classification and Regression Trees. x, 48, 52, 54, 56, 57, 88

CFAR Cell Averaging of Constant False Alarm Rate. 22

CIRAH Centre for the Research and Rehabilitation of Hereditary Ataxias. ix, 6–9, 13–15, 17, 20, 23, 41, 65–69, 75

CSV Comma-Separated Values. 13

DWT Discrete Wavelete Transform. 17, 18

ECG Electrocardiography. 17, 80

EEG Electroencephalography. 80

EMG Electromyography. 80

EOG Electrooculography. 1, 11, 12, 25, 40, 46, 80–82, 88

FIR Finite Impulse Response. 18

IIR Infinite Impulse Response. 18

JSON JavaScript Object Notation. 79

KNN K-Nearest Neighbors. x, 48, 52, 54, 56, 57, 88

MLP Multilayer Perceptron. ix, 4, 40, 44–46, 87

MSE Mean Square Error. 1, 29, 30, 32

RF Random Forest. x, 4, 40, 44–46, 88

RMSE Root Mean Square Error. 63, 64

SCA2 Spinocerebellar Ataxia type 2. ix, x, 1, 2, 5–7, 9, 14, 17, 18, 20, 22, 23, 25, 26, 30, 31, 34, 39, 40, 46–49, 52, 57, 59, 61, 62, 67–69, 84–86, 88, 89

SCL/SC Scleral Contact Lens/Search Coil. 11, 12

SVM Support Vector Machines. x, 48, 52, 54, 56–58, 88

VOG Video-oculography. 11, 12