IBEC-VHIR INTERNATIONAL PhD PROGRAMME

Position

1. Project Title/ Job Position title:
   Exploring Biomedical Signals to Monitor Efficacy of Deep Brain Stimulation in Children with Drug-refractory Dystonia

2. Research project / Research Group description (max. 2.000 characters)

a. Research Project:

Dystonia is a rare, severe movement disorder in children caused by disruptions in the neuronal circuit connecting the basal ganglia, cerebellum, thalamus, and motor and somatosensory cortex. Dystonia in children is a feature of cerebral palsy and can result from various rare genetic disorders or acquired brain injuries to the developing brain [Pérez-Dueñas et al., 2022].

If left untreated, dystonia can severely impact children's lives, hindering daily activities such as walking, writing, eating, breathing, and communication, potentially leading to chronic pain, deformities and mental health challenges such as anxiety and depression [De Francesch et al., 2024].

In response to the lack of precision therapies, the Vall d'Hebron Paediatric Neurology team has developed an innovative deep brain stimulation (DBS) program for children with drug-resistant dystonia [Salazar-Villacorta et al., 2022]. At the moment, DBS has proven efficacy in up to 40 children (average age 12.8 years), with preliminary results showing a 40% motor improvement and a 28% reduction in disability scores, alongside improvements in quality of life, including reduced fatigue, anxiety, and stigmatization.

However, a significant number of DBS responders who experience improvement on quality of life do not exhibit a substantial reduction in dystonia severity as measured by the current rating scales [Candela et al., 2018]. These scales have severe limitations, as they rely on visual evaluations, which are subjective, time-consuming, and provide only a limited snapshot of symptoms that fluctuate with factors like stress or fatigue.

Therefore, measuring the severity of dystonia is critical for determining, evaluating, and optimizing DBS treatment. In this study, we will propose and use novel digital biomarkers of movement patterns extracted from biomedical signals for the assessment of children with dystonia at home. Collecting data of dystonic movements over an extended period in a familiar

environment would provide a more realistic and reliable assessment of dystonia. Our goals are: (1) to demonstrate the feasibility of collecting these unobtrusive measures in children with dystonia in a natural setting, and (2) to identify dystonia patterns, severity of movements, and outcome predictors for DBS response monitoring. The use of wearable devices and smartphones, with its built-in sensors, will be considered as simplified tools for measuring and monitoring at home.

b. Research Group Description:

VHIR: Therapeutics and Innovation in Pediatric Neurology and other Rare Paediatric Diseases.
Our research group focuses on rare paediatric neurological disorders, which require tailored approaches for diagnosis and treatment due to their rarity and complexity. We prioritize precise diagnosis, personalized care, and the development of biomarkers for early disease detection and monitoring.
In the last 5 years, Dr Pérez Dueñas has been a pioneer in developing the Spain's foremost Deep Brain Stimulation (DBS) program focusing on children with genetic disorders causing dystonia and other refractory motor problems. Our group leads this program and associated research, including a multicentre AES project examining precision use of DBS in rare diseases. We have treated over 40 children and adolescents with DBS, obtaining excellent clinical results. The results of our research on rare disease causing dystonia and DBS efficacy have been published in first decile journals, such as Mov Disord [Pérez-Dueñas et al., 2022], Dev Med Child Neurol [De Francesch et al., 2024] and J Neurosurg Pedi . [Candela et al., 2018].

IBEC: Biomedical Signal Processing and Interpretation (BIOSPIN) Group.
The group's research addresses the design and development of advanced signal processing techniques and the interpretation of biomedical signals to improve non-invasive monitoring, diagnosis, disease prevention and pathology treatment.
Our main objective is to improve diagnosis capability through the characterization of physiological phenomena and to enhance early detection of major neurological, cardiac and respiratory diseases and sleep disorders.
In the last 5 years, the BIOSPIN group has developed novel biomedical signal interpretation techniques to study neurological disorders, for the assessment of motor function, sleep quality, and new neurorehabilitation strategies.
This work of the BIOSPIN group was conducted in collaboration with the Institut Guttmann and the results led to relevant publications in Scientific Reports (Castillo-Escario 2021a), J of Neural Engineering (Castillo-Escario 2021b), and Sensors (Castillo-Escario 2021c).

References

- The Genetic Landscape of Complex Childhood-Onset Hyperkinetic Movement Disorders. **Pérez-Dueñas B**, Gorman K, Marcé-Grau A, Ortigoza-Escobar JD, Macaya A, Danti FR, Barwick K, Papandreou A, Ng J, Meyer E, Mohammad SS, Smith M, Muntoni F, Munot P, Uusimaa J, Vieira P, Sheridan E, Guerrini R, Cobben J, Yilmaz S, De Grandis E, Dale RC, Pons R, Peall KJ, Leuzzi V, Kurian MA. Mov Disord. 2022 Nov;37(11):2197-2209. doi: 10.1002/mds.29182.
- Natural history of SGCE-associated myoclonus dystonia in children and adolescents. De Francesch V, Cazurro-Gutiérrez A, Timmers ER, Español-Martín G, Ferrero-Turrión J, Gómez-

Andrés D, Marcé-Grau A, Dougherty-deMiguel L, González V, Moreno-Galdó A, Tijssen MAJ, **Pérez-Dueñas B**. Dev Med Child Neurol. 2024;00:1–10. DOI: 10.1111/dmcn.16214.

- Setting Up a Pediatric Deep Brain Stimulation Unit. J. Ferrero-Turrion, A. Salazar-Villacorta, A. Bescos, G. Español,L. Ispierto, R. Alvarez, M. Tardaguila, J. Muñoz, L. Ventura-Exposito, **B. Pérez-Dueñas.** Movement Disorders, Vol.37, Suppl.2, 2022. https://doi.org/10.1002/mds.29223.
- Frameless robot-assisted pallidal deep brain stimulation surgery in pediatric patients with movement disorders: precision and short-term clinical results. Candela S, Vanegas MI, Darling A, Ortigoza-Escobar JD, Alamar M, Muchart J, Climent A, Ferrer E, Rumià J, **Pérez-Dueñas B**. J Neurosurg Pediatr. 2018 Oct;22(4):416-425. doi: 10.3171/2018.5.PEDS1814.
- **Castillo-Escario, Y**., Kumru, H., Valls-Solé, J. García-Alen, L., Vidal, J., **Jané. R.** Assessment of trunk flexion in arm reaching tasks with electromyography and smartphone accelerometry in healthy human subjects. ***Scientific Reports*** 11**,** 5363 (**2021**). https://doi.org/10.1038/s41598-021-84789-3.
- **Castillo-Escario, Y.,** Kumru, H., Valls-Solé, J. García-Alen, L., **Jané. R.,** Vidal, J. Quantitative evaluation of trunk function and the StartReact effect during reaching in patients with cervical and thoracic spinal cord injury. **Journal of Neural Engineering**, Vol. 18, Num. 4, 0460d2 (**2021**). https://doi.org/10.1088/1741-2552/ac19d3
- **Castillo-Escario, Y.,** Kumru, H., Ferrer-Lluis, I., Vidal, J., **Jané. R.** Detection of sleep-disordered breathing in patients with spinal cord injury using a smartphone. **Sensors 2021** Oct 29;21(21):7182. doi: 10.3390/s21217182

3. Job position description

The PhD student will analyze **Digital Movement Patterns**, **Clinical Rating Scales**, and **CPK Biomarkers** to evaluate the severity of dystonia and assess the effectiveness of **Deep Brain Stimulation (DBS)** in treating movement disorders.

1. **Digital Movement Patterns (IBEC):** Using accelerometers and gyroscopes, we will track movement parameters such as speed, frequency, and direction. These digital sensors will provide detailed insights into patients' motor symptoms outside clinical settings, helping to assess movement patterns in real-life conditions. The objective will be to propose and analyse novel digital biomarkers to characterize and evaluate the movement patterns of children with dystonia in a program of deep brain stimulation.
2. **Clinical Rating Scales (VHIR):** The Burke-Fahn-Marsden Dystonia Rating Scale (BFM) and other validated clinical tools will be used to assess the severity of dystonia. These scales provide subjective assessments based on visual observations of a patient's symptoms and help measure the disability caused by movement disorders.
3. **CPK Biomarker (VHIR):** Creatine phosphokinase (CPK) levels will be measured to monitor muscle damage, as elevated CPK concentrations reflect muscle injury or abnormal activity. Tracking CPK levels will offer insights into disease progression and treatment response.

The PhD student will conduct a **construct validity analysis** to compare digital movement data, clinical ratings, and CPK biomarkers. The goal is to establish that digital tools correlate with clinical evaluations and biological markers, confirming their

reliability for monitoring dystonia and other movement disorders in a real-world setting.

Additionally, the student will assess the **efficacy of DBS** by comparing patient data during the **"ON"** (DBS active) and **"OFF"** (DBS inactive) states. Patients will be monitored for several hours in both conditions, capturing how DBS affects symptoms over time. Significant improvements in digital movement data and CPK levels in the ON state will demonstrate DBS effectiveness.

The research aims to validate digital, clinical, and biochemical biomarkers as reliable tools for remote, continuous monitoring of dystonia. If successful, this would facilitate more accessible, personalized patient care and improve the management of movement disorders outside clinical settings.

Group Leader at IBEC

1. Title: Professor, PhD
2. Full name: Raimon Jané Campos
3. Email: rjane@ibecbarcelona.eu
4. Research Group: Biomedical Signal Processing and Interpretation (BIOSPIN)

Group Leader at VHIR

1. Title: MD, PhD
2. Full name: Belén Pérez Dueñas
3. Email: belen.perez@vallhebron.cat
4. Research Group: Therapeutics and Innovation in Paediatric Neurology