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PN Relay 2.020

Executive summary

When a peripheral nerve is damaged due to mechanical injury, inflammation or various pathologies, the signal conduction from our brain to nerves and muscles is entirely or partially impaired, with resulting disabilities. Although scientists have made remarkable progress in many respects, there is still no effective system able to provide an effective solution at the moment.

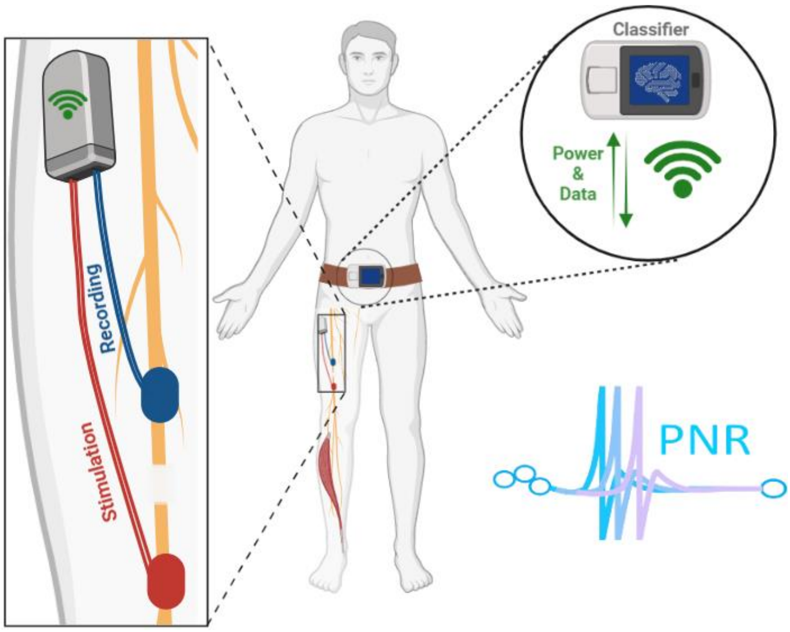
The aim of PNRelay 2.020 is to design an implantable neural interface used to replace or empower specific functions of the nervous system by extracting information from the signal upstream the damaged site and then selectively converting it into the desired stimulus for the neuromotor system.

The team identified four main fields of interest: safe implantation, optimization of the electrode used for signal recording, minimization of heating release from the circuitry, and signal processing reliability. First, we devised an ad-hoc biocompatible encapsulation meant to contain the electronic board. Secondly, 3D CAD simulations have been used to test the implanted cuff electrode on the nerve to assess the cuff selectivity and optimize its sensitivity. Then, a wired power transfer approach has been preferred for the implanted device to reduce overheating of surrounding tissues. Hence, the original printed board circuit has been modified accordingly. Finally, bandpass and adaptive noise cancelling filters can effectively reduce the multiple sources of noise the signal may embed. Support vector machines and artificial neural networks may recognize the type of stimulated movement from the input signal.

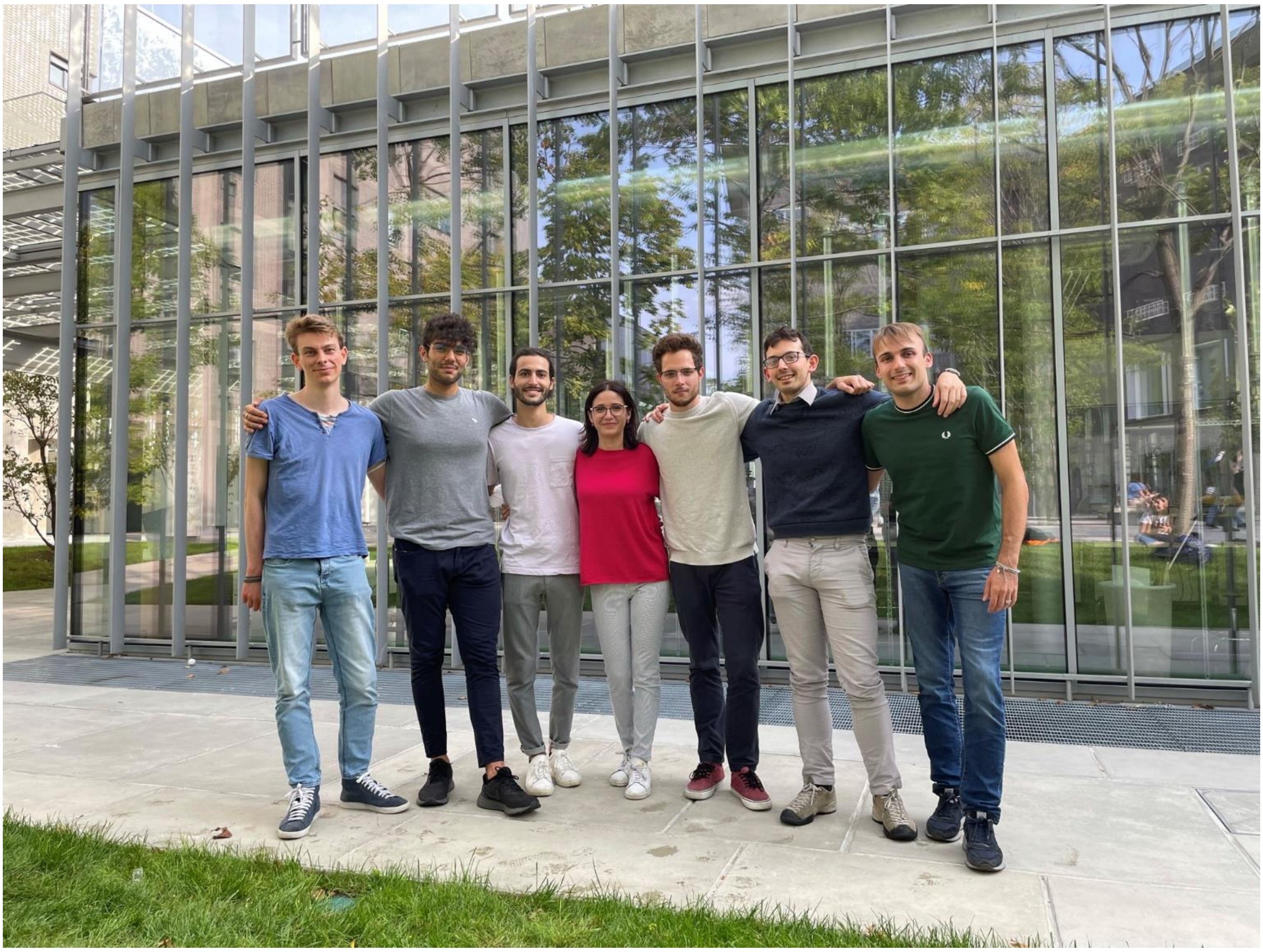
After having analyzed all the regulatory constraints and bureaucratic paths towards commercialization, we believe that this kind of device has an excellent future perspective. The innovativeness in its field of application has the potential to bring a tangible advantage to the whole society.

Key Words

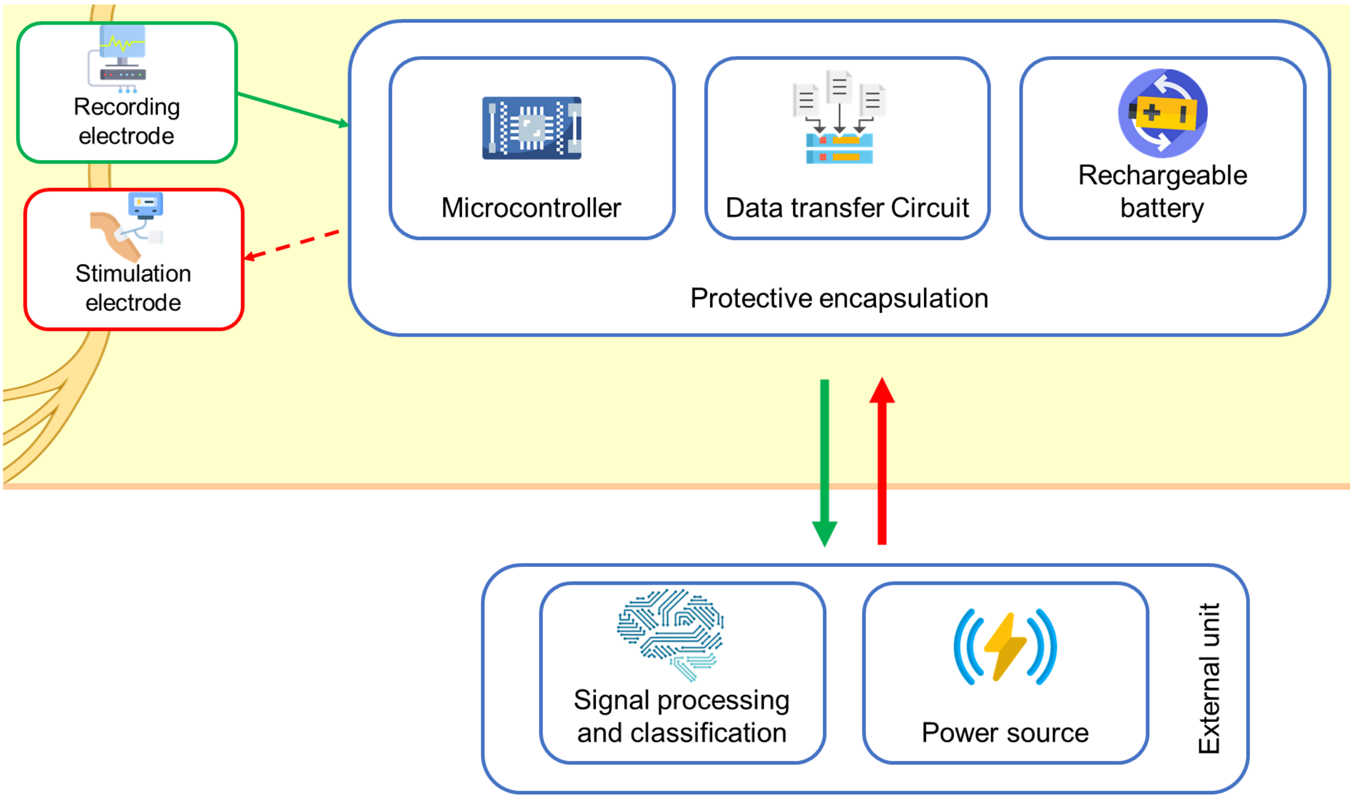
Peripheral Nerve Injuries, Implantable active device, Electroneurographic signal processing, Cuff Electrode, Pattern Recognition.



Fig, 1: Overview of the PNR system. Created with Biorender.com



Fig, 2: The PNR 2.020 team at Politecnico di Milano, during the final stages of the project.



Fig, 3: Outline of the core elements of the PNR 2.020 device. This illustration has been designed using resources from Flaticon.com

Project description written by the Principal Academic Tutor

Peripheral neuropathies affect 2%–3% of the world population and seriously interfere with the quality of life. Among these, mechanical nerve injuries are frequent, occurring in about 2.8% of trauma patients. The nerve regeneration is usually unsatisfactory, especially after severe injuries. So far, there is no technique to guarantee the total recovery and normalization of the nerve function, despite several possible procedures used, ranging from surgical (e.g., nerve grafting and conduit) to non-surgical interventions (e.g., medications, physiotherapy). New therapies are therefore mandatory based on new technologies that are able to (i) restore the nerve function; (ii) preserve the distal stump of the nerve; (iii) keep the denervated muscles functionally active; (iv) promote nerve regeneration.

Peripheral Nerve Interfaces (PNIs) are implantable devices used to monitor and modulate peripheral nerve (PN) activity. Most of the existing PNIs focus on the stimulation of the nerve to restore sensory feedback in assistive devices. Nowadays, PNIs integrating both stimulation and recording capabilities are not available due to the complexity of nerve injury physiology.

By leveraging on multidisciplinary competencies, the "Peripheral Nerve Bypass Nanotechnology for Neuroprosthetic Applications (PNRelay 2.020)" project has focused on the design of a fully implantable and highly compact neural interface to sense PN activity. The main goal is that of developing a device implanted on an interrupted nerve to electrically connect and stimulate the proximal and distal portions via bidirectional (internal-external) communication with other sub-systems. This device will prevent distal nerve stump degeneration and provide functional recovery.

The main results achieved during the project are:

1. Development of machine learning-based classification algorithms to recover the information encoded in PN signals and translate them into actuation signals for neuroprostheses.
2. Definition of the experimental protocol to encapsulate an electronic implantable device with a biocompatible material.
3. Analysis and design of wireless/wired technologies to power the PNI.

The development of the implantable neural interface device has benefitted from the competencies of external institutions that are at the forefront in the creation of innovative neuro-technologies to enable the communication between the nervous system and electronic devices for research tools and medical devices and from Neurologist/Neurophysiologist to support an approach suitable to be transferred to a translational research setting, thus allowing for a quick clinical application.

Team description by skill

Andrea Bezze and **Mariachiara Arminio** are **Biomedical Engineering** students.
They tackled the system biocompatibility issues, finding the practically adoptable solutions in establishing a connection between the implanted board and the external world, thus defining the optimal encapsulation protocol.

Francesco Strata and **Francesco Gabriele** are **Electronic** and **Physics engineering** students, respectively.
Starting from the power supply requirements, they developed a wired-based power approach which allows to fully satisfy the energy demand, without running into overheating issues.

Federico Ettori and Daniele Mocci are **Physics engineering** students.
They analyzed a set of provided signals, finding both the most suitable digital pre-processing techniques and the best performing data classification algorithm.

Nazareno Sacchi is a **Nanotechnologies for ICT** student.
He dealt with CAD simulation with the aim of optimizing the electrode sensitivity, performing signal localization at the nerve level.
As Team Controller, he timed the activity to follow the schedule, connecting the team member and the academic tutors.

Goal

The objective of PNRelay 2.020 is the design of a complete system for the measurement of the signal that runs in the sciatic nerve portion upstream of a lesion, its processing aimed at understanding the carried information (e.g. the movement to be performed) and the stimulation of the lower limb muscles to complete the task. Due to the ambitiousness of this vision, it is necessary to adopt an iterative design process with progressive improvement and integration of new elements. Notably, our team focused on signal recording and processing, leaving the stimulation part to future studies. Moreover, the overall aim was to optimize the design of the device for preclinical trials (i.e. animal tests), which represent a key step towards human implantation and the place on the market. We defined four main goals:

1. the design of a biocompatible encapsulation for the device to properly interface with the host organism
2. the evaluation of wired and wireless power transfer approaches and the implementation of the most suitable one
3. the study of pre-processing and classification techniques to analyze electroneurographic (ENG) signals
4. the identification of the optimal size and geometry for the electrode to maximize sensitivity

Understanding the problem

Peripheral nerve lesions can seriously menace quality of life, and permanent disability is the most threatening perspective due to the loss of sensory or motor function. The solution to this problem requires an implantable device for signal recording and subsequent nerve stimulation. As the literature has vastly addressed this second aspect, the team focused on studying the problems related to the first issue.

- The **biocompatible encapsulation** of the implantable components must be stable for the entire period of the experimentation. However, adverse tissue reactions increase the risk of failure. Furthermore, encapsulation should reduce the discomfort and prevent infiltration, which can damage the electronics. Hence, geometry, material and encapsulation procedure must meet these requirements.

- The **power supply and transfer** systems should be non-invasive, reliable, and safe. The most challenging task is to prevent the overheating of surrounding tissues while ensuring a sufficient and stable power supply for a proper interval of time. The NGNI Lab developed an integrated circuit (IC) for data recording. However, its wireless power transfer module dissipates too much heat. A wired approach would solve this issue but would require a new chip design.

- Biological and instrumental interference may corrupt the recorded **ENG signal.** Therefore, a pre-processing step should remove the noise and preserve the meaningful information. A classifier must process the signal features to detect the movement to be performed with adequate accuracy (or other rating scales).

- Electrodes must be minimally invasive. Extraneural cuffs meet this requirement but have a poor resolution if the contact array geometry is not well designed. **Computational models** can simplify design optimization and provide additional information through localization algorithms.

Exploring the opportunities

After analyzing materials and geometries in the literature, we selected a spiral cuff electrode made of polydimethylsiloxane. Considering data and power transfer, the inductive coupling, although potentially less invasive and more suitable for the market, is not feasible yet due to technological limitations related to bit rate and tissue overheating. Hence, different wired solutions have been developed using conductive *Huber needles*, permanent transcutaneous connectors or temporary transdermal modules. The encapsulation design was inspired by *port-a-caths*. We considered using modified commercial devices or manufacturing a silicone case with the same geometry. The solutions have been compared based on their non-invasiveness, power transfer efficiency (heat generation), ease of manufacturing, and cost. Various filters were studied to remove signal interference. The processed signals were used to test artificial intelligence classifiers (support vector machine and artificial neural network) to detect the signal type: proprioception, touch, nociception. A final issue is identifying the fastest approach to simulate such a complex system as a neural interface.

Generating a solution

The final solution includes a silicone case with a transcutaneous connector. The system will include a cuff electrode wrapped around the sciatic nerve and connected to the electronic board. The wires transfer data and power between the IC and the external unit through an Invilog connector. The unit supplies power and processes the data with the classification algorithm. The connector has a limited extracutaneous extension and the complementary connector should be inserted only when recharging or acquiring data. Encapsulation will be achieved using mould casting.

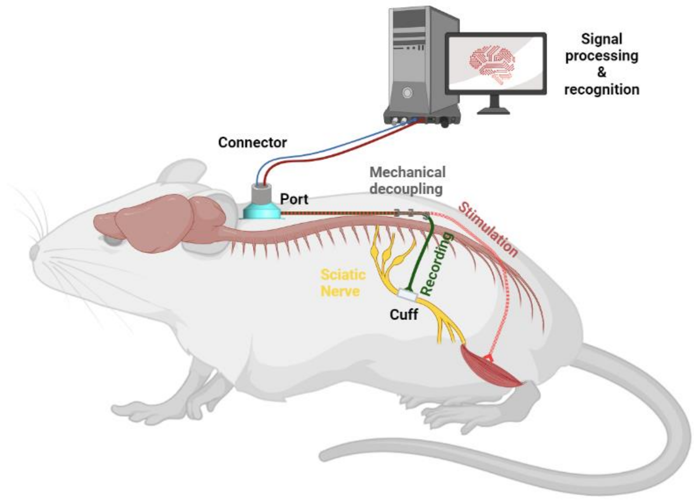
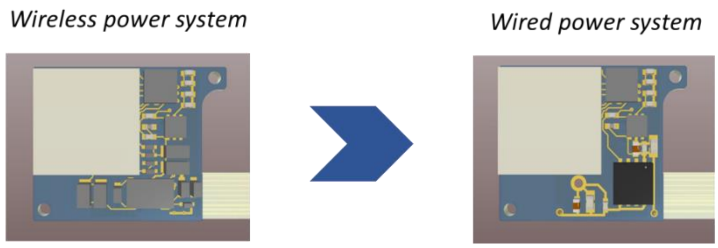


Fig. 4: Sketch of the final prototype. Created with BioRender.com

The NGNI Lab system involves wireless communication. Hence, we re-designed the chip to be compatible with a wired approach without compromising the other features of the system. This solution should cause no heating issues and ensure a stable power supply. The design may be an effective ready-to-use solution for preclinical trials.



Fig, 5: Comparison between the original NGNI Lab system (on the left) and the new modified version (on the right).

Using data collected by NewCastle University, we studied signal processing and classification algorithms. Firstly, more information can be extracted by utilizing all electrode signals and diversifying the typology of calculated features. Moreover, an Adaptive Noise Canceling filter can enhance the performance. Nevertheless, its implementation represents the main time bottleneck of the algorithm. Considering the classifiers, both algorithms can reach very high accuracy for all three rats.

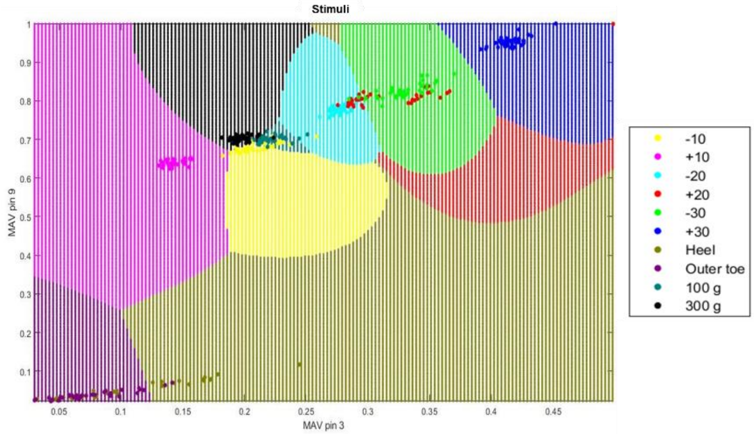


Fig. 6: Projection of the features hyper-plane onto 2 axes corresponding to Mean Absolute Value (MAV) for electrode 3 and 9

COMSOL® simulations showed that longer or thicker electrodes do not increase the sensitivity, while a 1 mm internode configuration can reduce the magnitude potential on the electrodes by three times. This arrangement makes the patterns similar to one another: information about different velocities or axons localization is harder to extract or lost. Therefore, the closer the cuff is to the nerve, the better signal recording is.

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