PN RELAY

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Executive Summary:

Physiological mobility and sensitivity can be lost during life due to physical trauma or other adverse medical conditions that damage the nervous system leading to permanent disabilities. The objective of the project is to target this problem developing a new peripheral nerve interface, capable of conveying information between brain and organs. This kind of medical devices generally record the electrical stimulus travelling within the nerve, analyze it and finally artificially stimulate the nerve below the injury to replicate the natural response of the body.

Although a few partial solutions are described in the literature, no complete device currently exists for human subjects, especially for the recording section. Following extensive analysis of the background literature, PN Relay proposed a full-stack system for electroneurographic recording. The design includes a minimally invasive cuff-electrode collecting the signal at a decade of locations on the nerve surface and feeding an implanted classifier. The electrode and the processing units are wholly implantable and able of sending the classification output outside, with a sustainable data rate and limited overheating. Once transmitted externally, the results of the classifier could be potentially used to drive an actuator.

A strategy for reaching the market within five years has been drafted, together with the design of a first prototype, that would be hopefully realized and tested by the end of 2020. The feasibility of the project requires meaningful collaborations with research groups and companies in the sector and few of them have been already concluded. Entering the market as a first mover in recording interfaces, the device could have multiple applications, not only in peripheral nerve bypass nanotechnology, but even for functional electrical stimulation, brain-computer interfaces and bionic prostheses control.

Our vision is to disrupt the whole rehabilitation process for millions of patients, enabling the chronic application of selective recording from the central and peripheral nervous system.

Key Words:
Peripheral Nerve Injuries, Bypass Nanotechnology, Cuff Electrode, Wireless Powering, Pattern Recognition, Neural Network

Fig. 1: The team in London to attend the conference "SMR Bioelectronic medicines: Past, Present and Future" on October 2nd, 2019.

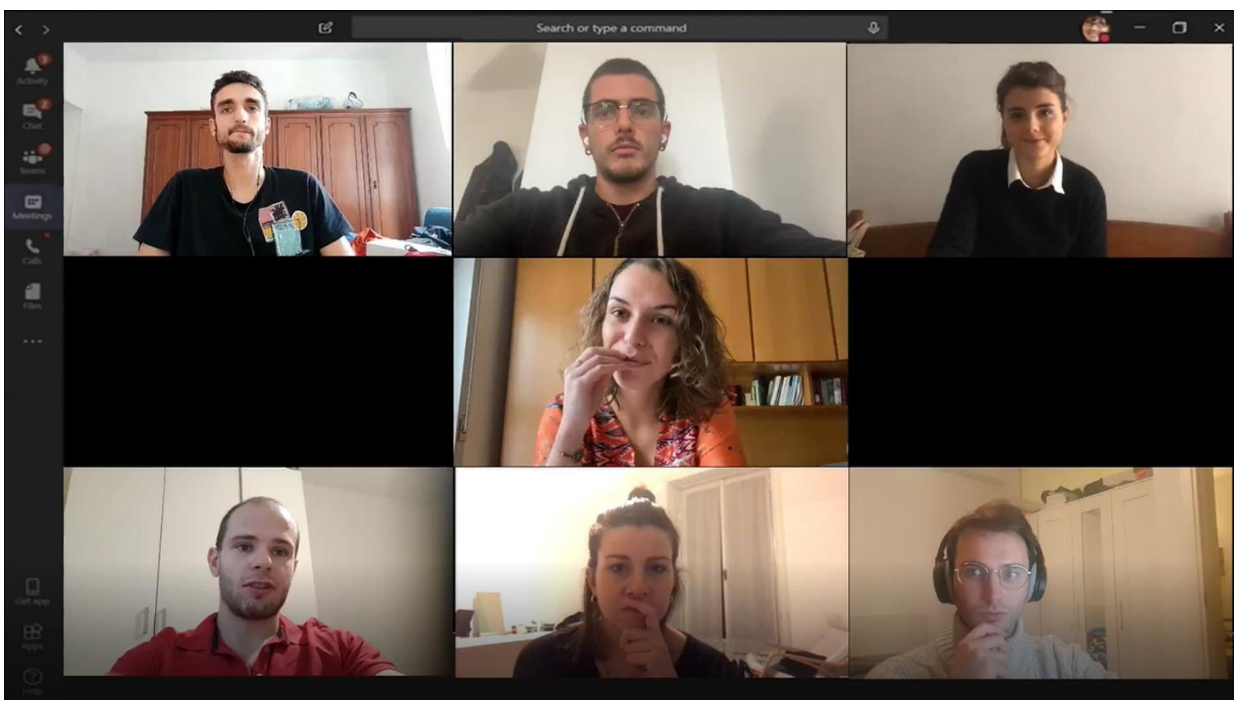

Fig. 2: The team at work on Teams Platform, during the worldwide pandemic COVID-19.

Project description written by the Principal Academic Tutor:

Peripheral nerve (PN) disorders affect over one million people worldwide every year. Although clinical and preclinical research has achieved remarkable progresses in biological and cellular strategies for reconstruction of PN injuries, a satisfactory functional recovery has not been guaranteed yet and, therefore, better approaches must be developed.

The main objective of the "**Peripheral Nerve Bypass Nanotechnology for Neuroprosthetic Applications** (PN Relay)**"** project consists in the development of a fully implantable and highly compact neural interface to sense PN activity for humans, thus allowing for a preclinical study in neuroscience experiments.

The main requirements for the device are wireless bidirectional data communication and configurability of recording and stimulating settings. The envisioned system must be powered through the skin and must be suitable for chronical implants.

The main goals and challenges pursued in the project are:

1. Design of an innovative wrapping cuff electrode for sensing weak PN signals. Its key aspects must be flexible mechanical structure and biocompatibility.
2. Design of an electronic circuit for signal conditioning of the neural interface system to record and reliably relay neural signals.
3. Development of classification algorithms to recover the information encoded in PN signals and translate them into actuation signals for neuroprostheses.
4. Evaluate the efficiency of appropriate schemes for extra-body relaying PN signals (e.g., digital vs. analog modulations).
5. Evaluate suitable technologies for transcutaneous power transfer, i.e. wireless vs. wired.

The development of the implantable neural interface device has benefitted from the competences of external institutions that are in 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.

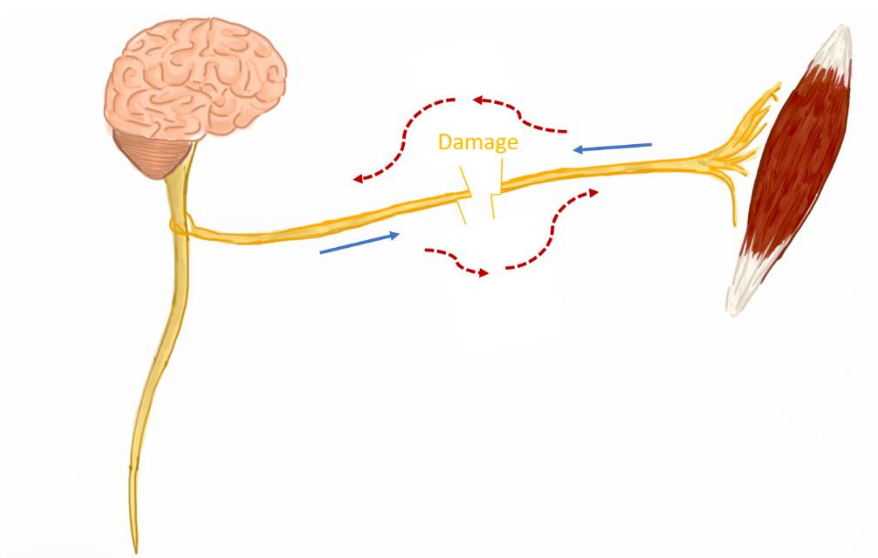

Fig. 3: Peripheral neuropathies affect peripheral nerves.
The damage prevents the transmission of the natural electrical signal (blue line) that is flowing from the brain to the periphery, or the other way around, from the periphery to the brain. The idea of the project is to bypass the lesion (red dashed line), evoking the natural response that is missing in peripheral neuropathy.

Team description by skill:

Federica Camossi is a Biomedical Engineer.
She focused on all the bio-interface aspects, defining requirements and specifications for this part. She also proposed an innovative design for signal transmission and power source in the physical prototype.
Stefano Crotti is a Physicist.
He worked on the classification algorithm, applying digital signal processing and statistical learning techniques.
Fabiana Del Bono is a Biomedical Engineer.
She analysed the European regulations for the requirements definition and the feasibility study. Also, she defined specifications for the electronic circuit and contributed to dimension the amplification chain.
Gabriele Gatani is a Nanotechnology Engineer.
He studied the feasibility of the proposed design, investigating the materials chosen for their bio-properties. He also evaluated possible fabrication methodologies for the prototype.
Beatrice Federici is a Biomedical Engineer.
She contributed to the development of the classification algorithm by processing real electroneurographic signals. As Team Controller, she monitored the working progress to stay on schedule and she acted as connection between the team and the academic tutors.
Stefano Panaro is an Electronic Engineer.
He focuses his attention on the electronic circuit design and the requirements analysis.
Federico Vismarra is a Physics Engineer.
He focuses his attention on the power supply requirements and wireless communication protocols. He has also analyzed the economic aspect and defined the business model of the future product.

Goals:

The final goal of **PN Relay** project is to design and optimize a medical device aimed at bypassing the damaged portion of a peripheral nerve and restore the mobility lost due to physical trauma (Fig.3). More precisely, the system aims at **1)** recording the signal above the damaged portion of the sciatic nerve with a cuff electrode; **2)** classifying which stimulus has generated such signal and **3)** stimulate the natural response, that cannot be elicited naturally due to the nerve damage. At the moment there are no nerve bypass devices in clinics. However, research in this area has been expanding rapidly over the last decades. The main limitations of these works is that they focus on the optimization of a single element of the system rather than the development of the whole set-up or the surgical procedure. This causes that these studies leave aside some technical issues that arise when the elements are assembled together. As a multidisciplinary team, the primary goal of PN Relay is to identify the compatible cutting-edge technologies that have been proposed for the single elements and integrate them in a unique safe and functional device. The project has an invaluable potential and the results would represent a starting point to improve current strategies for Electroneurogram (ENG)-controlled robotic prostheses or neuro-prostheses. However, the final goal is highly complex and it would surely need great time and resources to be fully developed.
During this 1.5-yr project, we decided to focus on the development of the **1)** recording and **2)** classification sections of the bypass device, since the stimulation part has already been developed for few clinical applications with promising results.

Understanding the problem:

Nowadays it is not possible to find any complete system to bypass a peripheral nerve injury. Major issues arise with the development of the recording stage and, for that reason, our project focus mainly on this section. A schematic representation of the main components of a recording interface for peripheral nerve application is reported in Fig. 4.

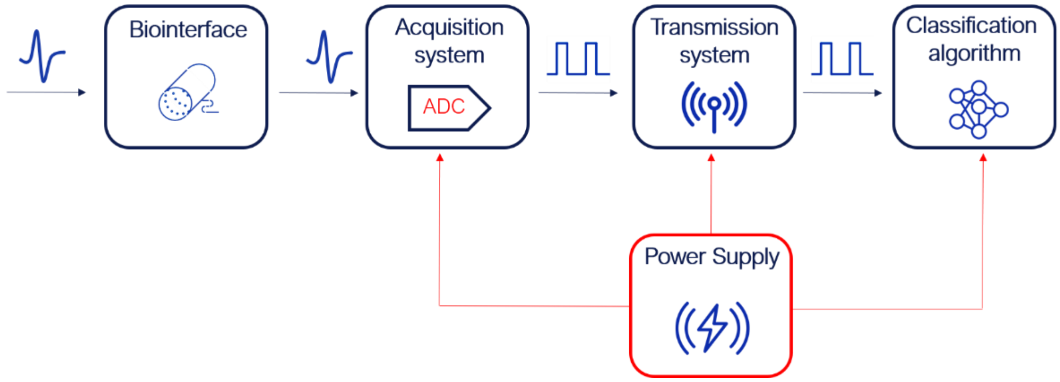

Fig. 4: Block diagram of the system architecture.
The signal is acquired by means of a bioelectrode and immediately digitalised in order to be processed by the electronics. The transmission of the digital signals out of the body can be accomplished before the classification step (as presented in this scheme) or after the classifier has processed the data within the body.

The problem of building the complete implantable system can be divided into three main sections:

- **Bio-interface:** the first section requires to choose an appropriate electrode to collect the nervous signal in the form of electric potential, to be handled by the electronic circuit. To gain the rapid approval by the Ministry of Health, we focused our attention on having the minimum risk of foreign body reaction and so the choice of low invasive extra-neural electrodes, or cuff. The main drawbacks are low sensitivity and selectivity, due to the higher distance from the signal source. Thus, a careful optimisation of the cuff geometry should be defined according also to the number of inputs required by the proposed classifier.
- **Acquisition system, Power supply and Transmission system:** the function of the implanted electronic circuit is to acquire the feeble signals coming from the cuff electrodes and convert them in low-noise, high-accuracy digital signals.
The main hardware constraint is given by biocompatibility: physical dimensions must be restrained, implanted battery must be avoided, and any wired connection between the implanted circuit and external devices must be discarded. Moreover, in order to be compliant with the medical regulation, it is necessary to limit the impact of the circuit on the biological tissue, keeping under control its inner temperature and the amount of radiation emitted by the wireless communication and power section. In order to satisfy all these requirements an integrated circuit might be preferable, although it comes at the cost of a higher initial investment.
- **Classification algorithm:** the classifier is a digital algorithm that takes as inputs the digital signals coming from the electronic circuit and gives as outputs the meaning of the associated signals. The main obstacle in designing the classifier is to combine the physical limitations (represented both by the low computational power available and the number of electrodes contacts) with the classification accuracy. The classifier can be implanted or placed on an external device in communication with the internal circuit. The second option eases the constraint on the physical dimensions, but requires a high bit rate communication section.

Exploring the opportunities:

To solve the presented problems, three different solution have been identified combining properly the cutting-edge technologies:

- **Solution 1:** the main goal of this solution is to minimize the implementation cost and time, choosing for the circuit some electronic elements already available on the market. The main drawbacks of the strategy are the big area and power requirements. The area occupation is minimized reducing the classifier inputs to 3, and the communication to an external device is simply implemented with a Bluetooth LE protocol (to be carefully designed to avoid biocompatibility problems). This solution considerably reduces both design and manufacturing costs but, implementing only three input channels, it also destroys the classifier accuracy, making the device almost useless.

-**Solution 2:** First of all, it is necessary to increase the number of classifier inputs (e.g. up to 8) to increase the classifier accuracy. Moreover, the electronic circuit is implemented with an ASIC (Application specific integrated circuit) to cope with the available area. It processes the signal and reduces efficiently the amount of noise injected. However, the increased number of acquired data cannot be physically transferred by a Bluetooth protocol not to have problems of high-power consumption and radiated emission. So, an inductive power link has been chosen for both communication and power section. This inductive link guarantees a much smaller bit rate, that could be achieved under sampling the input signals only in predefined time interval.

-**Solution 3:** this last solution allows to increase again the number of inputs with the use of a multi contacts electrode. The electronic circuit is again implemented with an ASIC to cope with the available area. However, the increased number of acquired data cannot be transferred to an external device by a wireless protocol thus it was decided to integrate even the Classifier section in the same implanted ASIC and transmit externally only the classification results. This optimizes the converter efficiency, doubling the battery life and decreasing of almost one order of magnitude the human tissue absorption but, on the other hand, doubles the complexity of the integrated circuit, consistently increasing both design and manufacturing cost.

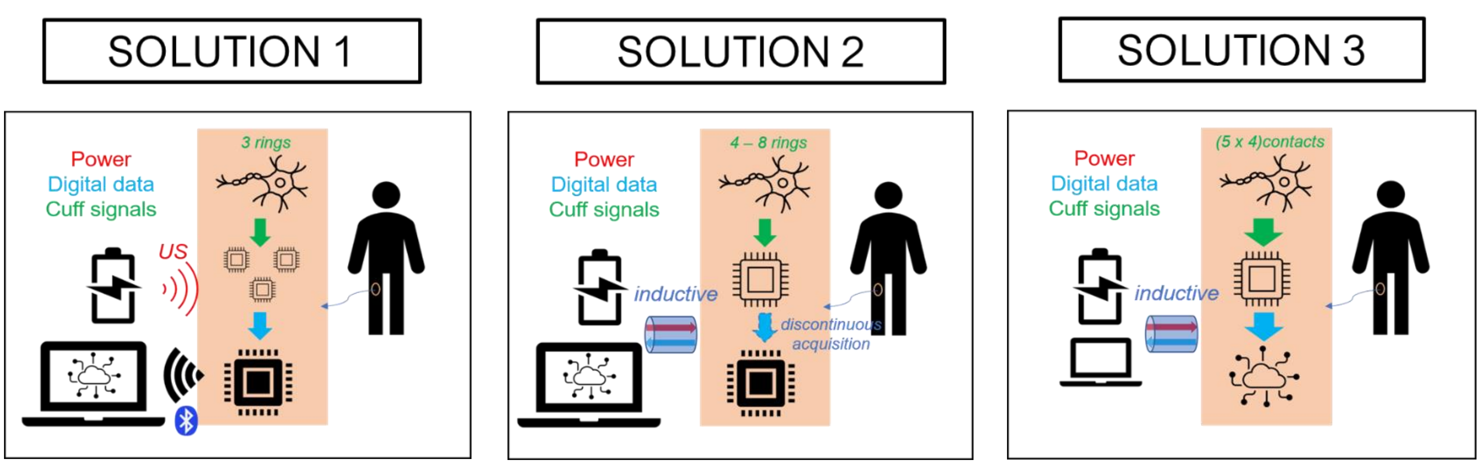

Fig. 5: Overview of the 3 possible solutions identified.

Generating a solution:

Due to the complexity of the Classifier section, to obtain meaningful results for an hospital application, it is necessary to opt for the solution providing the best trade-off between the maxima criteria, derived by grouping the different technical and economical requirements. The selected overall solution is the Solution 3.

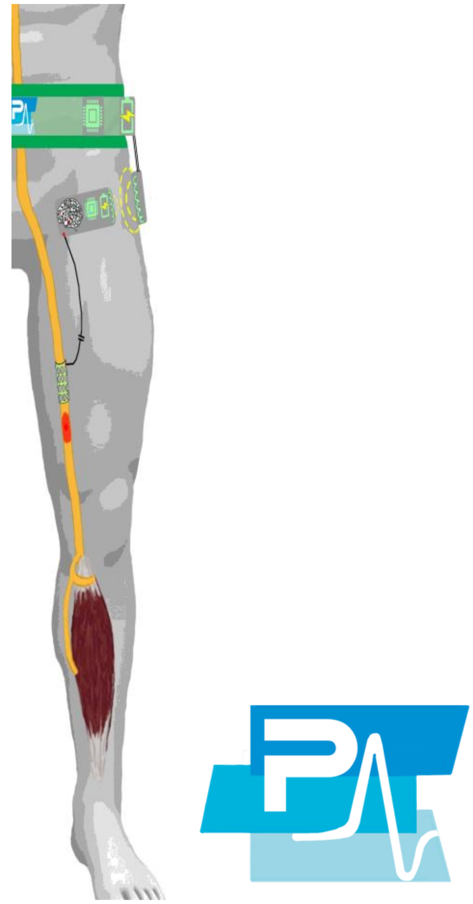

Fig. 6: Overview of the overall system.
Our idea is to record the electrical activity of the nerve above the lesion with a multi-contact electrode (e.g. 5 rings x 4 contacts for each ring). The recorded signal is transmitted to the implanted electronic interface, where it is digitalized and processed by a classifier which extracts the encoded sensory or motion information. The outputs of the classification are sent externally by an inductive coupling through the patient's skin.

During the project, a simplified animal prototype has also been designed to experimentally verify the feasibility of the realization of PN Relay's bypass technology, after which we might consider entering the market. To accelerate the realization, we decided to merge the team's technical knowledge with the expertise of key partners highlighted in Fig. 7.
With respect to the cuff electrode, we decided to acquire it from Wise Co., a specialized company for neuronal electrodes manufacturing. For the acquisition system, instead, a simplified electronic circuit was designed directly by our team, but the collaboration established with the Imperial College of London gave us the opportunity to introduce their newly developed circuit for neuronal interface in our prototype and speed up the pre-clinical trials. This partnership enabled us to focus more on the development of the power and communication sections, that were implemented with a transdermal port. We proposed the manufacturing process considering all the technical aspects. Finally, a classification algorithm able to discriminate between 3 classes of activities has been developed. It has been tested on the dataset used in **[5]** and it achieves results comparable with the state of the art of naturally-evoked ENG signal classification (Fig. 8).

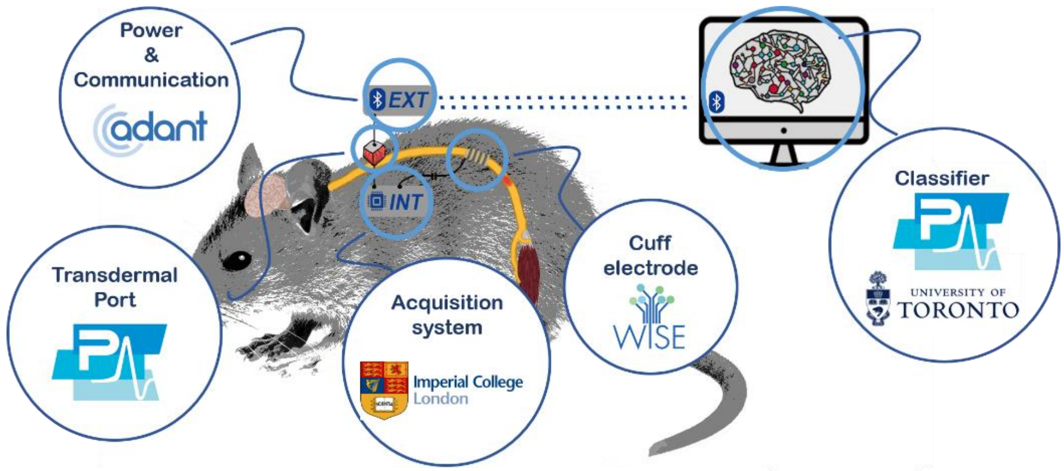

Fig. 7: Overview of the designed rat prototype with the network of partners the team managed to established during the project. Each one of them either granting us a specific component or sharing with us their knowledge about it.

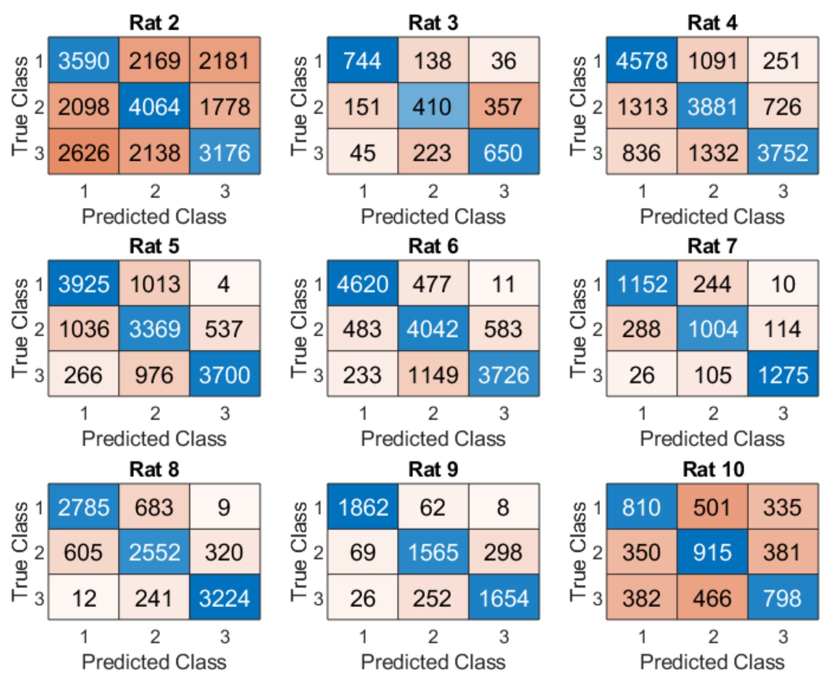

Fig. 8: Confusion matrices for the 3-class discrimination problem obtained by means of our algorithm. The misclassification rate is comparable with the results obtained by a state-of-the-art classifier for ENG signals. The algorithm uses few physically explainable features for the classification and it presents a low computational power consumption.

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Fig. 9: The team at Politecnico di Milano, after the Final Presentation of PN Relay Project on October 16th, 2020.