RIDC NeuroMat

Tenth Report of Activities

Jul 30, 2022 - Aug 31, 2023

Contents

1 Highlights of the period

- **Random Processes in the Brain: from experimental data to Math and back** was a thematic program held at the Institut Henri Poincaré, Paris, from February 27 to April 7, 2023. In this event, NeuroMat gathered a group of top scientists in the world to discuss the main lines of the NeuroMat project. The program featured a series of focused colloquia, convening experts from diverse fields to explore the intersections of neuroscience and mathematics. The "Structural Learning by the Brain" colloquium examined the brain's capacity for statistical inference and model selection, while the "Networks of Spiking Neurons" colloquium focused on collective phenomena in EEG and fMRI data. The IHP program not only advanced the frontiers of knowledge but also contributed to the global impact of the NeuroMat research agenda and its role in bridging mathematics and neuroscience at an international level.

- **Pathways to the 2023 IHP thematic program Random Processes in the Brain** was a preparatory process for the conference "Random Processes in the Brain: From Experimental Data to Math and Back" (see above). The goal of the preparatory process was to frame and pave research practices among the participants of the conference that eventually emerged during the actual conference. Ten webinars were organized in 2022 in the context of the Pathways series (the list of webinars and speakers can be seen in Annex 8).

- **Estimating the interaction graph of stochastic neuronal dynamics by observing only pairs of neurons**, by E De Santis, A Galves, G Nappo, M Piccioni, which appeared in *Stochastic Processes and their Applications* **vol. 149**, pp. 224-247 (2022), is a real step forward in the direction of making statistical model selection for systems of interacting point processes with memory of variable length used to model systems of spiking neurons. This paper is a major improvement of a previous article produced by the NeuroMat team (Duarte et al. 2019).

- **The Neuroscience Experiments System (NES)–A Software Tool to Manage Experimental Data and Its Provenance**, by M. Ruiz-Olazar, E. S. Rocha, C. D. Vargas and K. R. Braghetto, which appeared in *Frontiers in Neuroinformatics*, **vol. 15**, pp. 1-18 (2022), presented the open-source software NES that was developed by the NeuroMat team. The software enables researchers to efficiently perform the management of their experimental data in a secure and user-friendly environment, providing a unified repository for the experimental data of an entire research group and allowing for efficient data sharing.

- **Stochastic neuron model implementation in NEST using NESTML**, by R. O. Shimoura, C. A. P. Linssen, P. N. Babu, A. C. Roque, M. Diesmann and C. Pouzat, which was presented orally

at The virtual NEST Conference, June 15-16 2023, describes an implementation of the Galves-Löcherbach model in the NEST simulator. NEST is an established, open-source simulator for spiking neuronal networks, which can capture a high degree of detail of biological network structures while retaining high performance and scalability from laptops to supercomputers. The simulator is maintained by the NEST Initiative organization, of which Markus Diesmann, member of NeuroMat's International Advisory Board, is one of the directors. NEST is used by a large number of international researchers, which makes the implementation of the Galves-Löcherbach model in the simulator an important step towards making the model more accessible to the computational neuroscience community.

- **Construction of a robot arm to deliver transcranial magnetic stimulation (TMS) to specific cortical sites** (see Section 4.3.1). The major achievement in the period was the assembly of the robotic arm in accordance with the standards designed by the NeuroMat team. Details can be seen in the article TMS with fast and accurate electronic control: Measuring the orientation sensitivity of corticomotor pathways, by V. H. Souza, J. O. Nieminen, S. Tugin, L. M. Koponen, O. Baffa, R. J. Ilmoniemi, in *Brain Stimulation* **15**, pp. 306-315 (2022). Three camera systems (Polaris, Polhemus and Claron) were adapted to control the robot to record the position of the head and coil, and all the routines to interface the robotic arm with the InVesalius neuronavigator were developed and evaluated. TMS procedures, like motor mapping, can now be fully automated and performance tests are currently being done.

- **Technology transfer and dissemination related to the NeuroMat Parkinson Network (AMPARO)**. There have been around 80 publications on the AMPARO Facebook page, normally in video format. The initiative has also launched a podcast providing life histories and specialized information on Parkinson's Disease and wellbeing.

- **Five PhD students under the supervision of NeuroMat PIs** obtained their doctoral degree during the period assessed in this report. Details are provided in Annex 10.

2 RIDC NeuroMat Identification

RIDC: Research, Innovation and Dissemination Center for Neuromathematics (NeuroMat)

Grant number: 2013/07699-0

Host institution: Instituto de Matemática e Estatística da Universidade de São Paulo

Associated institutions: Aalto University; Centre National de la Recherche Scientifique - CNRS (Strasbourg); Faculdade Cásper Líbero; Forschungszentrum Jülich; Gran Sasso Science Institute (GSSI); IBM Thomas J. Watson Research Center; Instituto de Matemática Pura e Aplicada (IMPA); National Institute of Neurological Disorders and Stroke (NIH); New York University Shanghai; Universidad de Buenos

Aires; Universidad de la Republica; Universidad de San Andrés; Universidade Estadual de Campinas (UNICAMP); Universidade Federal do ABC (UFABC); Universidade Federal do Pará (UFPA); Universidade Federal de Pernambuco (UFPE); Universidade Federal do Rio de Janeiro (UFRJ); Universidade Federal do Rio Grande do Norte (UFRN); Universidade Federal do Rio Grande do Sul (UFRGS); Universidade Federal de São Carlos (UFSCar); Universidade Federal de São Paulo (UNIFESP); Università di Roma "La Sapienza"; Université Côte d'Azur; Université Paris 1 (Pantheon-Sorbonne); University of California, Berkeley.

Webpage: http://neuromat.numec.prp.usp.br

Principal Investigator/Center Director: Jefferson Antonio Galves

Vice Director: Pablo Augusto Ferrari

Co-Principal Investigators: Antônio Carlos Roque da Silva Filho; Claudia D. Vargas; Ernst Hamburger (*in memoriam*); Fernando da Paixão; Jorge Stolfi; Oswaldo Baffa Filho; Pablo Augusto Ferrari

Education and Knowledge Dissemination Coordinator: Fernando Jorge da Paixão Filho

Technology Transfer Coordinator: Antônio Carlos Roque da Silva Filho

RIDC Executive Manager:

System analyst:

Administrative assistant: Lourdes Vaz da Silva Netto - IME/USP

Manager of Education and Dissemination of Knowledge:

Manager of Technology Transfer:

The Research, Innovation and Dissemination Center for Neuromathematics (RIDC NeuroMat) is a center of mathematics which has as mission to develop the new mathematics needed to construct a Theory of the Brain accounting for the experimental data gathered by neuroscience research. Mathematician Antonio Galves coordinates this center. Hosted by the University of São Paulo, the RIDC NeuroMat was established in 2013, with support from the São Paulo Research Foundation (FAPESP), grant 2013/07699-0, which will last until July 2024.

The RIDC NeuroMat has an interdisciplinary team, bringing together researchers in mathematics, computer science, statistics, neuroscience, biology, physiotherapy, medicine, physics and communication, among other disciplines. RIDC NeuroMat leads a worldwide university network, with ramifications that sprawl to several high-level research institutions in Brazil, Latin America, the United States, Europe and China (Annex 1). Most research output has had co-authors from more than one country, thus contributing to put NeuroMat at the center of a blossoming international scientific cooperation around Neuromathematics.

Alongside a research team that focuses on the scientific challenges pertaining to Neuromathematics,

NeuroMat has active technology-transfer and dissemination teams. The technology-transfer effort is concentrated on devising tools for diagnosing and clinical guidelines for neurological conditions, and on developing free, open-source computational tools to manage and compile experimental and clinical data. This development team is part of a joint effort to create an international open database for neuroscientific data. The dissemination-team effort includes a nonstatic web portal (Creative Commons license), open multimedia productions and training projects with public-school teachers. A distinctive feature of this effort is that it relies on web-2.0 media tools as a means of communicating on-the-go scientific endeavors as well as involving a scientific and broad community around bridging the high-level science that this RIDC develops and general audiences.

Pablo Augusto Ferrari (UBA and USP), Antonio Carlos Roque da Silva Filho (USP), Fernando Jorge da Paixão Filho (UNICAMP), Ernst Wolfgang Hamburger (USP, *in memoriam*), Jorge Stolfi (UNICAMP), Claudia Domingues Vargas (UFRJ), and Oswaldo Baffa Filho (USP) remain co-principal investigators, along with PI Antonio Galves (USP). David Brillinger (UCBerkeley), Francesco Guerra (Universita di Roma "La Sapienza"), Leonard Cohen (National Institute of Neurological Disorders and Stroke), Markus Diesmann (Jülich Institute of Neuroscience and Medicine), and Wojciech Szpankowski (Purdue and NSF Center for Science of Information) take part in NeuroMat's International Advisory Board.

NeuroMat's main laboratory and offices are located on a three-story building, with approximately 1,000 square meters, at 1171 Prof. Luciano Gualberto Avenue, at USP's central campus, in São Paulo. NeuroMat's main building has recently gone through an extension (+175 square meters) and renovation to support new laboratory facilities; the construction cost was BRL R$ 1,603,339 and was fully covered by USP, MaCLinC grant (recipient: Antonio Galves). NeuroMat has set up three laboratory facilities: an EEG laboratory at its main building in São Paulo, and a Simulation Laboratory (SimLab) and a TMS experimental facility at the USP Ribeirão Preto campus. Multiuser experimental facilities in São Paulo and Ribeirão Preto are being planned. NeuroMat's administrative staff team is composed of one administrative assistant. This position is supported by USP.

3 Scientific report

3.1 Mission

The mission of NeuroMat is to develop the new mathematics which is deemed necessary to account for a Theory of the Brain, accounting for the full experimental data gathered by neuroscience research. The long-term objective is to understand and explain complex neuroscientific phenomena, with focus on plasticity mechanisms underlying learning and memory neurorehabilitation and rewiring. This Neuromathematics is envisioned, at this time, as conjoining probability theory, combinatorics, statistics, and neuroscience. This requires the definition of a full new class of mathematical models to describe and

explain in a parsimonious way the different scales of neural activity and the relationship between them. The construction of these models should occur together with the development of suitable statistical and computational methods, including model selection principles and results.

3.2 Executive summary

The main goal of NeuroMat is to build the new mathematical, statistical and computational framework which is necessary to address the challenges of neurobiology. Activities presented in this report strictly relate to the goals announced in the document submitted to FAPESP in November 2012, in the third and final step of the selection process. The general goals of this research project are the following:

- Development of new classes of stochastic processes which are necessary to model brain functioning;
- Development of the statistical tools required by this new class of stochastic processes.

Detailed progresses on these two goals were exhaustively reported in the documents "First Report of Activities 2013-2014", "Second Report of Activities 2014-2015", "Complementary Form 2013-2015", the Evaluation by FAPESP International Committee in November 2015, "Third Report of Activities 2015-2016," the "Complementary Form 2015-2017," "Fourth Report of Activities 2016-2017," the presentation "NeuroMat: first 5 next 6" to FAPESP's International Assessment Committee, the 2018 Statement of Impact (SoI), "Fifth Report of Activities 2017-2018," "Sixth Report of Activities January 2019-July 2019," "Seventh Report of Activities August 2019-October 2020," "Eighth Report of Activities November 2020-August 2021." "Ninth Report of Activities August 2021-July 2022." and "Complementary Form 2017-2022." These documents were carefully reviewed by FAPESP. The SoI is a summary of main activities and highlights our main achievements. This statement is still up-to-date and informs substantially this report, along with relevant parts of the document for the renewal of the RIDC NeuroMat by FAPESP, the "Project for the period 2018-2024".

The progresses achieved in the first term of the RIDC have opened up the path for a new stage of development. In spite of all the challenges posed by the COVID-19 pandemics, NeuroMat continued with the construction of innovative applications of the new stochastic models and statistical tools developed in the previous years, aiming at concrete questions of Neuromathematics and computational modeling in neurobiology, electroencephalographic recordings analysis, and neurorehabilitative therapy. Research highlights and corresponding published works are listed below, in the appropriate section. Since the "Ninth Report of Activities", the NeuroMat research team has:

- published 55 papers;
- submitted 12 online pre-prints;

- published 1 book;
- had 5 PhD dissertations concluded and 13 in progress;
- had 3 MA thesis concluded and 7 in progress.

NeuroMat scientific publications in the period being assessed in this report are listed on Annex 2. A full list of publications since the inception of NeuroMat can be viewed at NeuroMat's Google Scholar (https://goo.gl/LvZV4f). Citations to these publications across the years are available on Annex 3.

In parallel to the mathematical and theoretical biological developments which are necessary to foster the scientific project of NeuroMat, the RIDC has also sustained two laboratories. In April 2016, NeuroMat launched a new research facility: the NeuroMat Simulation Laboratory (SimLab). The simulation of large-scale network models remains a key activity to test analytical results, and the NeuroMat SimLab allows for such tests, providing the NeuroMat team with a new experimental tool to test and construct large-scale computational implementations of NeuroMat's newly developed models. The SimLab is installed at the Laboratory of Neural Systems (SisNe) of the Department of Physics of USP Ribeirão Preto, under the direction of NeuroMat PI and Technology transfer coordinator A. C. R. da Silva Filho (USP-Ribeirão Preto). In July 2017, NeuroMat launched an Electroencephalography Laboratory, with an EEG DC actiCHamp 128CH System. The creation of NeuroMat's EEG lab was made possible by the expansion of the building, through a grant from the University of São Paulo (value of support: BRL R$ 1,603,339). A TMS facility equipped with a robotic arm started operations in 2020 at the Biomagnetism Laboratory of the Department of Physics of USP Ribeirão Preto, under the direction of NeuroMat PI O. Baffa. Two multiuser experimental facilities equipped with high end equipment for data acquisition are being planned.

3.3 Research results highlights

There are two main axes in the NeuroMat research agenda, which follow:

- the development of a new class of stochastic processes aimed at a realistic description of nets of spiking neurons;
- the introduction of a new mathematical approach to address the classical conjecture that the brain retrieves statistical regularities from sequences of stimuli.

The first axis appears to be by now a well-established area of research in Probability Theory. For instance, according to Google Scholar, there have been around 120 papers with direct references to the paper (Galves and Löcherbach, 2013). Since 2021, there have been 39 publications with direct references to this paper.

The second research axis has evolved in 2022 into a new research program to look at the brain activity before and following the responses in the Goalkeeper's game. In this program, a comparison is made between the law of the EEG segments between successful predictions and prediction failures (Hernández et al. 2021). Thus, the correlation between the Beta band coefficients and successful predictions and failures of the goalkeeper are checked. The team conjectures that the Beta band coefficients will give us a good indication whenever a given segment of EEG is discrepant with respect to the law characteristic of that context and prediction.

In the same line of research, the dissertations by Paulo Roberto Cabral Passos and Fernando Araujo Najman have contributed new dimensions to the framework proposed by Duarte et al (2019). Passos' PhD dissertation has relied on the Goalkeeper Game. Experimental results and a new statistical analysis have shown evidences that besides the succession of contexts embedded in the sequence of stimuli the successive predictions made by the volunteers have an influence on the law of their reaction times. Najman's PhD dissertation has revisited data previously studied in Hernández et al (2021). Using a new statistical cluster analysis approach, it has found out that the brain encodes the sequence of stimuli through the regular, periodic structure embedded in the random sequence of stimuli generated by the ternary and quaternary context tree models.

A complete list of papers is available as Annex 2.

3.4 Scientific meetings organized by NeuroMat in the period

An important aspect of the work NeuroMat depends on fostering a tight relationship among members of the NeuroMat community worldwide. As emphasized in our interaction with FAPESP International Committee, we are especially aware of this challenge, and we have sustained partnerships among scientists from different parts of the world —of which the high rate of papers with co-authors from different countries is an evidence. The fostering of a tight community around Neuromathematics strongly meets the expectations of FAPESP's Committee.

A key part of the community-building entrepreneurship NeuroMat has sustained relates to organizing frequent conferences and meetings on topics pertaining to Neuromathematics. In the period covered by this report, we continued with this endeavor and were not stopped by the COVID-19 Pandemics. The meetings organized in the period are listed below.

During the period of activities being reported in this document, the NeuroMat team organized the "Pathways to the 2023 Institut Henri Poincaré (IHP) thematic program Random Processes in the Brain" series, in which ten seminars were organized. More details on these events are available as Annex 8.

The IHP's program "Random Processes in the Brain: From Experimental Data to Math and Back" was held from February 27 to April 7, 2023, in Paris. The event focused on understanding neuronal systems' stochastic interactions and learning by the brain.

Our three-month-long program was driven by the conviction that an understanding of the brain may only be achieved through the establishment of a strong connection between, on the one hand, fundamental mathematical research, and, on the other hand, neurobiological experiments (and vice versa), following the thought pattern: neurobiological question $\rightarrow$ mathematical model $\rightarrow$ new experimental protocol $\rightarrow$ data $\rightarrow$ model fitting to data $\rightarrow$ critique and evolution of the mathematical model.

The "Structural Learning by the Brain" colloquium, held from March 6 to 10, explored the brain's ability to perform statistical inference and model selection and had 93 registered attendees. The key question of this colloquium was: How does the brain engage in statistical inference to select one of the most suitable models in order to make predictions and be capable of acting in the world? The "Networks of Spiking Neurons" colloquium, from March 27 to 31, delved into neuron systems and collective phenomena observed in EEG and fMRI data and had 128 registered attendees. Public talks by Gilles Laurent and Olivier Faugeras engaged a wide audience, discussing brain dynamics and the role of mathematics. Two courses covered foundational neurobiology and probability theory, aiming to bridge knowledge gaps between disciplines.

With strong female participation, the IHP's program facilitated interactions, fostering new connections and discussions among diverse researchers. The program also provided a distinct chance to further strengthen the global reach of the NeuroMat research initiative.

4 Technology transfer report

The main focuses of this area have been the development of supporting tools for the diagnosis and neuro-rehabilitation research being conducted by the AMPARO and ABRAÇO initiatives on Parkinson's Disease and Brachial Plexus Injury, respectively. These tools are the Goalkeeper Game, a robot arm for accurate real-time positioning of a transcranial magnetic stimulator on the head, and the Neuroscience Experiments System (NES). Details and links to the GitHub pages of the software developed by NeuroMat can be seen at NeuroMat's Intellectual Property webpage.

An important milestone has been the publication of Ruiz-Olazar et al (2022). This article has rigorously presented the software tool to manage experimental data and its provenance developed by NeuroMat, the Neuroscience Experiments System (NES). NES enables researchers to efficiently perform the management of their experimental data in a secure and user-friendly environment, providing a unified repository for the experimental data of an entire research group. Furthermore, its modular software architecture is aligned with several initiatives of the neuroscience community and promotes standardized data formats for experiments and analysis reporting.

The highlight of the period was related to the robot arm development. The communication and closed-loop control systems were constructed, and now the robot can be instructed to move to a desired place on the scalp and apply the stimulation while keeping the coil on the same position even if the head moves.

4.1 Neuro-rehabilitation and diagnosis

4.1.1 ABRAÇO Initiative

NeuroMat's Brachial Plexus Injuries focus area is called ABRAÇO Initiative, or Ação NeuroMat para a Lesão do Plexo Braquial. The ABRAÇO website is the first worldwide platform devoted to this health condition and is aimed at being both a source of help and support for patients, caregivers, students and professionals, and a powerful scientific knowledge sharing platform.

4.1.1.1 Assessing plasticity associated to Brachial Plexus Injuries The team led by NeuroMat CO-PI Claudia Domingues Vargas (INDC/UFRJ) is using the Goalkeeper Game (Section 4.2.1) to study mechanisms of plasticity in the brain after a brachial plexus injury (TBPI) aiming at developing new tools to assess plastic changes in the brain induced by this traumatic injury. New evidence of these plastic changes were gathered recently by our team. The publication Plasticity of face–hand sensorimotor circuits after a traumatic brachial plexus injury, by F. F. Torres, B. L. Ramalho, M. R. Rodrigues, A. C. Schmaedeke, V. H. Moraes, K. T. Reilly, R. P. Carvalho, C. D. Vargas, in *Frontiers in Neuroscience* **17**:1221777 (2023), investigated bilateral changes in inhibitory circuits of the sensorimotor cortex after a traumatic brachial plexus injury. In the paper Upper limb joint coordination preserves hand kinematics

after a traumatic brachial plexus injury, by L. Lustosa, A.E. Lemos Silva, R.P. Carvalho and C. D. Vargas, which appeared in *Frontiers in Human Neuroscience* **16**:944638 (2023), the authors suggest that upper limb coordination is reorganized after a traumatic brachial plexus injury so as to preserve hand kinematics. In the motor context, prediction can be seen as an automatic process of choosing and implementing a next step in a sequence of events. Tests are being conducted with healthy human subjects playing the Goalkeeper Game to determine which parameters of the context tree generating stochastic sequences of events in the Goalkeeper Game are best associated with the optimal processing of sequences of motor events. Furthermore, data collection from patients with brachial plexus injury has already started in order to investigate how this injury interferes in the ability of these individuals to predict events compared with the healthy subjects. This important step to better understanding the prediction process after a brachial plexus injury could help in the development of new treatments for this injury. More specifically, the objective is to check the possibility of using the Goalkeeper Game as a tool for rehabilitation of brachial plexus injury patients.

4.1.1.2 New transcranial magnetic stimulation protocol This endeavor involves a collaboration between Neuromat CO-PI Oswaldo Baffa Filho (FFCLRP/USP), Neuromat CO-PI Claudia Domingues Vargas (INDC/UFRJ) and R. Ilnomiemi (Aalto) for the development of a closed-loop robotic system for the positioning of a transcranial magnetic stimulation (TMS) coil on a subject's scalp (see Section 4.3.1). Besides the technological aspects of this initiative, a team of researchers led by NeuroMat CO-PI Claudia Domingues Vargas (INDC/UFRJ) is developing a new protocol to test whether the primary motor cortex (M1) holds the memory of a sequence of TMS pulses driven by a stochastic chain. If so, it should be possible to recover in the motor evoked response (MEP) a signature of a sequence of TMS pulses applied in M1. In other words, can a sequence of TMS pulses generated by a stochastic chain be recovered on the MEP response? Having this answer, then it would be interesting to test if this recovered signature is affected by a brachial plexus lesion.

4.1.2 AMPARO Initiative

The NeuroMat focus area towards Parkinson's Disease is called AMPARO Initiative, or Rede de Apoio NeuroMat a Amigos e Pessoas com Doença de Parkinson. The AMPARO website is a reference source on Parkinson's disease in Brazil, providing scientific and practical information, case histories and questions and answers for people with Parkinson's disease, their relatives and caregivers.

4.1.2.1 A tool for early Parkinson's Disease diagnosis The team led by NeuroMat researcher Maria Elisa Pimentel Piemonte (FM-USP) is using the Goalkeeper Game (see Section 4.2.1) to study putative novel relationships between the main cardinal Parkinson's disease symptom, bradykinesia, and implicit probabilistic learning and lack of ability in automatic motor control. The objective is to develop a new

measure and typology to establish the limits between normal decline associated to aging process and abnormal alterations associated to the onset of the pathological process of Parkinson's disease. The clinical implication of this work is to offer a free and friendly test to early diagnosis of Parkinson's disease. The main step towards this goal in the period has been the development, in collaboration with J. G. Vivas Miranda (UFBA), of an index based on a two-dimensional movement analysis that uses kinematic gait variables to detect subtle alterations in gait and postural control in early stages of Parkinson's disease. Currently, in the clinical setting, these alterations can only be identified in moderate to advanced stages of the disease. The new index, which can be widely used in clinical practice, may open therapeutic windows for new interventions that can prevent falls and higher levels of disability in people with Parkinson's disease. Details can be seen in the article A non-expensive bidimensional assessment can detect subtle alterations in gait performance in people in the early stages of Parkinson's disease, by M. S. d'Alencar, G. V. Santos, A. F. Helene, A. C. Roque, J. G. V. Miranda, M. E. P. Piemonte, which appeared in *Frontiers in Neurology* **14**:1101650 (2023).

4.1.2.2 Collaborative network for Parkinson's disease clinical guideline

AMPARO Initiative organizes monthly meetings with NeuroMat members, professionals, patients and caregivers. The goal is to share knowledge towards the collaborative building of guidelines for Parkinson's disease in Brazil, especially for the public health system. In particular, in collaboration with national and international institutions, including the Movement Disorder Society, which is a global reference in Parkinson's disease,, AMPARO has offered four in-person training for professionals from Brazil and other American countries on optimal interdisciplinary care for people living with Parkinson's disease (see Annex 15).

4.2 Computational tools

4.2.1 Goalkeeper Game

NeuroMat researchers devised experimental protocols to test the performance of human subjects in identifying sequences of stimuli represented by context trees. An innovation spin-off from NeuroMat's research project is the "Goalkeeper Game". It is an online game with desktop and mobile device versions in which the player, taking the role of a goalkeeper in a penalty shootout, guesses the position in the goal where the ball will hit (left side, right side or center) after being kicked by the opponent. The game consists in a sequence of penalty kicks in which the ball positions are generated by a context tree model. As the player (the goalkeeper) succeeds in guessing the right sequence, the complexity of the context tree model increases and the game becomes more difficult. The goalkeeper game has potential to be used as diagnosis and rehabilitation tool in neurology, and the NeuroMat technology transfer team is currently testing its applicability in its two main clinical development fronts: Parkinson's Disease and Brachial Plexus Injuries (see Sections 4.1.2.1 and 4.1.1.1). The game is openly, freely available at:

game.numec.prp.usp.br and also at Apple Store and Google Play.

4.2.2 Neuroscience Experiments System

The Neuroscience Experiments System (NES) is a free software to manage data and metadata from neuroscience experiments. It integrates data records from different types such as clinical, electrophysiological, and behavioral. NES is currently being used by the teams involved in both ABRAÇO (Section 4.1.1) and AMPARO (Section 4.1.2) initiatives. NES is integrated to the Goalkeeper Game (Section 4.2.1) and to the NeuroMat Open Database (Section 4.2.3). The main functionalities, which include Electrophysiology and Export modules, were improved in the period, and modules that deal with data from machine learning tools are being developed. The development team of the Neuroscience Experiments System is led by the Associate Investigator K. R. Braghetto (IME/USP).

4.2.3 NeuroMat open database

The NeuroMat Open Database provides an open-access platform for sharing and searching data and metadata from neuroscience experiments. The platform is constituted by a web portal and a REST (Representational State Transfer) API (Application Programming Interface). The web portal was designed to have a user-friendly interface. The REST API is used to feed the open database with experimental data generated by NeuroMat's researchers. Currently, the API intermediates the receiving and retrieving of data from research laboratories that use NES (Section 4.2.2). It can be can easily adapted to receive (or transfer) data from (for) other client systems. The development team of the NeuroMat open database is led by K. R. Braghetto, and its source code is available at NeuroMat's GitHub portal.

4.3 Hardware tools

4.3.1 Closed-loop system of robotic stimulator positioning in the brain

The impact of transcranial magnetic stimulation (TMS) on the brain is remarkably precise; deviations of approximately 1 mm in positioning and a few degrees in coil angles can evoke significantly divergent responses. In addition, the patient or volunteer being awake throughout the procedure performs small involuntary movements, even with the head secured on a head strain. If the subject moves during stimulation, the stimulator must be repositioned. As a solution to this problem, robotic arms have been proposed to help position the TMS coil. Robotic positioning also enables the development of new methods for automated motor mapping. However, the combination of TMS and robotic arms is not yet commonly used by the clinical and scientific communities due to three main factors. The first is low portability, that is, the systems are fixed and cannot be transported between rooms and clinics. The second is the high cost of commercial equipment. And the third is that commercial navigation programs are closed systems, making it impossible for new tools to be developed to test different research protocols. A closed-loop system is a set of mechanical or electronic devices that automatically regulates a variable to

the desired state, without human interaction. Closed-loop systems are designed to automatically achieve and maintain the desired condition (exit condition), comparing it to its condition at the given moment (real condition). Since the last report, the team led by NeuroMat PI O. Baffa Filho and R. Ilmoniemi has completed the development of a novel methodology of an autonomous robotized multilocus TMS (mTMS) positioning system. The development of the mTMS stimulator continues at Aalto University and the postdoc Renan Matsuda spent one year in Helsinki working in this area also to ensure a smooth transfer of skills and technology from this group to Neuromat´s group. It is now possible to combine robotic positioning with mTMS electronic targeting, enabling the automation of TMS procedures, such as hotspot hunting and motor mapping. The robot control can accurately position the TMS coil on the target, and it can also follow the patient's head, performing an automated head move compensation. The robot control achieves superior accuracy than with manual positioning and comparable stability and accuracy to existing robotized TMS systems. The motor mapping experiment demonstrated the system's ability to perform high-density mappings in a fast and autonomous way. The new open-source platform for robotic control of mTMS transducer positioning represents an important step to increase the accuracy and reliability of TMS procedures. This platform facilitates the development of new tools and methods for brain investigation. The automation of mTMS procedures can bring more streamlined, safe, and reproducible applications in both clinical and research environments. For the next step, the real-time EMG and EEG analyses will be combined with the robot control, enabling coil positioning and targeting based on the physiological responses. This integration will, in turn, enable the development of new TMS protocols to test whether the primary motor cortex (M1) holds the memory of a sequence of TMS pulses driven by a stochastic chain.

The paper TMS with fast and accurate electronic control: Measuring the orientation sensitivity of corticomotor pathways, by V. H. Souza, J. O. Nieminen, S. Tugin, L. M. Koponen, O. Baffa, R. J. Ilmoniemi, in *Brain Stimulation* **15**, pp. 306-315 (2022) shows the importance to produce high-quality data of a fast and accurate positioning of the magnetic stimuli using the multilocus TMS device. Another published paper (Forearm and Hand Muscles Exhibit High Coactivation and Overlapping of Cortical Motor Representations, by G. P. Tardelli, V. H. Souza, R. H. Matsuda, M. A. C. Garcia, P. A. Novikov, M. A. Nazarova, O. Baffa, in *Brain Topography* **35**, pp. 322–336 (2022)) contributes to a more detailed cortical motor representation towards a synergistic, functional arrangement of M1. Understanding the muscle group coactivation may provide more accurate motor maps when delineating the eloquent brain tissue during pre-surgical planning. The paper MarLe: Markerless estimation of head pose for navigated transcranial magnetic stimulation, authored by R. H. Matsuda, V. H. Souza, P. N. Kirsten, R. J. Ilmoniemi, O. Baffa, published in *Physical and Engineering Sciences in Medicine* **46**, pp. 887–896 (2023), shows another important step to improve the coil positioning by using face fiducial marks to

guide the robotic arm. The Paper Real-time tractography-assisted neuronavigation for TMS, authored by D. B. Aydogan, V. H. Souza, R. H. Matsuda, P. Lioumis, R. J. Ilmoniemi, *bioRxiv* 2023.03.09.531565 (2023), demonstrates the incorporation of real-time tractography into the neuronavigation system, enabling the visualization of neural fiber networks at stimulation points. The combination of real-time tractography and TMS opens doors to the formulation of new protocols for defining the target brain areas for stimulation. This combination allows for a deeper understanding of brain connectivity, facilitating the training of machine learning models for target stimulation identification through the analysis of cerebral nerve fibers. This study has the potential to automate the positioning of the stimulator at the hotspot and to identify stimulation targets in neurological diseases with greater accuracy. This approach is being developed by master's degree student Lucas dos Santos Betioli, under the supervision of NeuroMat's PI Oswaldo Baffa and co-supervision of Renato Tinós (FFCLRP-USP), with collaboration from postdoctoral researcher Renan Matsuda.

5 Dissemination report

NeuroMat's dissemination activities have as a compass point working as a collaborative hub, developing web-2.0 media tools as a means of communicating on-the-go scientific endeavors as well as involving a scientific and broad community around the high-level science that this RIDC develops. Activities are envisioned to use innovative means to transform scientific culture, overcoming artificial field boundaries and contributing to foment an integrated and genuinely multidisciplinary approach to the study of the brain. These activities have seen a significant increase in production and viewers in the context of the pandemic.

NeuroMat's milestone dissemination activities include in the period of interest:

- the *A Matemática do Cérebro* podcast
- the Wikimedia Initiative
- Media Exposure
- Web resources: portal, Facebook page, dissemination blog
- NeuroCineMat
- the Introduction to Science Journalism course
- NeuroMat's science dashboard

5.1 The *A Matemática do Cérebro* podcast

The RIDC NeuroMat launched in August 2019 the podcast "A Matemática do Cérebro" – in Portuguese, Mathematics of the Brain. This resource is available on the most important podcast technologies and also hosted on its own website. The production of the podcast is led by NeuroMat director Antonio Galves and NeuroMat associate investigator Eduardo Vicente.

NeuroMat's podcast is aimed at covering three main topics: the model for systems of spiking neurons that the research team developed; the Statistician Brain conjecture; and pertaining institutional aspects of doing research in Brazil. The overall goal is to bring public awareness on work that is being done within the NeuroMat community.

NeuroMat podcasts have released 11 episodes, which have reached 1,144 plays on Spotify in the period of interest for this report.

5.2 The Wikimedia Initiative

NeuroMat's Wikipedia Initiative has become a strategic activity at the interface of communication and education. It has been recognized in Brazilian and foreign outlets as a "success case" of the use of Wikipedia and other collaborative projects as a means of scientific dissemination.

Main achievements on Wikipedia have been:

- 322 million content viewers in Wikimedia; and
- 193 thousand words added to Portuguese Wikipedia and related projects.

Moreover, NeuroMat has been engaged in uploading media files to the open repository Wikimedia Commons. In the period assessed by this report, 2,696 files had been uploaded by the NeuroMat team in this repository. These files have reached 2,227,669 views per month, on average (from 2019 to 2022).

In the period covered by this report, an on-wiki portal for the Wikimedia Initiative has been launched at: https://pt.wikipedia.org/wiki/WikipÃľdia:GLAM/CEPID_NeuroMat

The control panel of the NeuroMat Wikipedia Initiative is available at: https://outreachdashboard.wmflabs.org/campaigns/neuromat/programs.

5.3 Media Exposure

Activities from FAPESP'S RIDC NeuroMat were featured in around a hundred external media outlets since its inception in 2013. NeuroMat's media clipping for this year is attached to this report as Annex 4.

A highlight of the period were the interviews given by NeuroMat's Associate Investigator A. F. Helene (IB-USP) to the Hiperconectado program of the publich network television *TV Cultura*. The interviews, available on the network's Youtube channel (Interview 1, Interview 2) took place at the Museum of Veterinary Anatomy of USP. They were centered around aspects of the nervous system's organization, using the backdrop of the exhibition set up under the scope of NeuroMat in 2018.

5.4 Web resources: portal, Facebook page, dissemination blog

NeuroMat's web portal was launched in early February 2014, and is thought of as the main official reference of the RIDC. It provides robust updates on research, technology transfer and dissemination activities. Publications are in English and Portuguese. There have been 10 thousand pageviews in the period of interest of this report different users — around 66% of which did not come from Brazil.

NeuroMat's Facebook page was launched in September 2014 to serve as a reference space for the diverse community that is involved with and interested in Neuromathematics. Since its creation (9/20/2014), the page has reached 1,680 followers, as of July, 2023. Community growth has been organic.

Since April 2016, the NeuroMat dissemination team has maintained a blog on scientific challenges and activities pertaining to science communication, especially relying on web-2.0 platforms. The blog is called "Traço de Ciência".

Posts on this resource have been published continuously; a detailed report is provided on Annex 6.

References are:

- web portal: https://neuromat.numec.prp.usp.br
- Facebook page: https://www.facebook.com/neuromathematics
- ABRAÇO Facebook page: https://www.facebook.com/iniciativaabraco/
- blog: https://difusaoneuromat.wordpress.com

5.5 NeuroCineMat

The NeuroMat dissemination team has fully produced 401 movies. A full list is available on the NeuroMat Youtube channel. There has also been continuous streaming of activities on YouTube. A full list is available on:

https://www.youtube.com/user/neuromathematics

This material has been viewed on Youtube and Facebook 80,395 in the period of the interest of this report.

5.6 The Introduction to Science Journalism course

The NeuroMat dissemination team launched in 2021 an Introduction to Science Journalism course to contribute to capacity building of communications professionals who are interested in specializing in science coverage. The course strictly abides to curriculum expectations of the Mídia & Ciência call.

The course has been developed under the supervision of NeuroMat PI Fernando J. Paixão, supported by NeuroMat team members and FAPESP science-journalism fellows.

The course is available freely on Wikiversity:

https://pt.wikiversity.org/wiki/Introdução_ao_Jornalismo_Científico.

This course has become a major asset for FAPESP's journalism fellowships, for NeuroMat and for other scientific projects supported by FAPESP. Since 2017, 21 journalism fellows have been supervised by NeuroMat, most of them have gone through this course. At least seven people from other projects have taken the course, including fellows from the University of São Paulo Physics Department and Engineering School. Noteworthily, fellows have later engaged professionally with science communication, mostly on digital outlets, or joined an academic path about journalism and science.

5.7 NeuroMat's science dashboard

A new institutional academic profile was developed at RIDC NeuroMat, based on Wikidata. Wikidata is a platform inspired by the vision of the Semantic Web, which was designed to allow computers and people to interact over a network. The Semantic Web presents knowledge in a form that is more easily machine-processable, enables data to be linked from a source to any other source, and to be understood by computers. This provides the opportunity to create inference rules and to manage automated reasoning both between people and between machines, so they could perform increasingly sophisticated tasks

The option for a new development was justified due to the disadvantages of the most common platforms, for example using closed code and having limited functionalities for data visualization and scientometric consultation. In contrast, Wikidata is a collaborative technology, under a free license, which allows queries and visualizations based on inferences made by the users themselves.

The dashboard is available freely on NeuroMat's website:
https://vitrine.numec.prp.usp.br/. Three papers on the dashboard methodology have been submitted.

6 Annexes

Annex 1 - NeuroMat global network of scientific, institutional affiliations

Annex 2 - NeuroMat scientific publications

Annex 3 - NeuroMat Scientific Publications: Citations

Annex 4 - NeuroMat's media clipping

Annex 5 - Website's analytics

- Annex 5a - NeuroMat's web portal
- Annex 5b - NeuroMat's podcast web portal
- Annex 5c - Abraço's web portal
- Annex 5d - Rede AMPARO's web portal

Annex 6 - NeuroMat dissemination blog "Traço de Ciência"

Annex 7 - Scientific Missions

Annex 8 - Seminars

Annex 9 - Post-doctoral fellows

Annex 10 - PhD dissertations

Annex 11 - MSc dissertations

Annex 12 - Scientific Initiation

Annex 13 - Scientific Journalism

Annex 14 - Technical Training

Annex 15 - AMPARO Technical Training

Annex 16 - Reports from FAPESP scholarships

- Annex 16a – Arthur Lopes da Silva Valencio
- Annex 16b – Carolina Salles Carvalho
- Annex 16c – Karine Damásio Guimaraes
- Annex 16d – Isabela Tosta Ferreira
- Annex 16e – Isabela Tosta Ferreira
- Annex 16f – Eliezer Francisco de Santana Junior
  - Annex 16f – 1 Annex Plano de atividades e cronograma
  - Annex 16f – 2 Annex Anexos Relatório Científico
- Annex 16g – Eliezer Francisco de Santana Junior
- Annex 16h – Fernando Araujo Najman
- Annex 16i – Erika Guetti Suca
- Annex 16j – Erika Guetti Suca
- Annex 16k – Noslen Hernández González
- Annex 16l – Noslen Hernández González
- Annex 16m – Paulo Roberto Cabral Passos
  - Annex 16m – Anexo 1
  - Annex 16m – Anexo 2
  - Annex 16m – Anexo 3
- Annex 16n – Bia Ramalho dos Santos Lima
  - Annex 16n – Anexo 1
- Annex 16o – Kádmo de Souza Laxa
- Annex 16p – Flavio Roberto Rusch
- Annex 16q – Morgan André
- Annex 16r – Eduardo Janotti Cavalcante