FULL PROPOSAL: Disorders of Cortical Dynamics (DeCoDe)

1. State of the art (with relevant references from major journals) (~ 1page) :

There is a growing realization in the neuroscience community that neurological conditions such as epilepsy, sleep disorders and coma are primarily system-level disorders of *dynamics* (Noble et al. 2024). Yet so far the clinical classification of brain states in sleep and coma has mostly relied on "surface" features of the EEG waveform that can be visually detected by neurophysiologists. In sleep, for instance, the identification of physiological vs pathological sleep onset is typically associated with the disappearance of the alpha rhythm, and deeper sleep stages with the appearance of spindles, K-complex or slow waves (Lacaux et al. 2024). Similarly in coma, classification of vegetative vs minimally-conscious states, as well as prognosis, rely traditionally on the observation of "malignant" EEG features, such as discontinuities, reduced amplitude and rhythmic or periodic discharges (Benghanem et al. 2022). However, such features are highly variable both intra and inter-individuals, and may only reflect the "tip-of-the-iceberg" of the underlying state of the system and they are not indicative of the mechanism underlying the transition between states. For instance, "benign" EEG that excludes any malignant feature still appears in 30% of bad-outcome patients (Fenter et al. 2023). Similarly, sleep researchers are starting to question the homogeneity of EEG appearance with sleep stages (Andrillon, 2023; Lacaux et al. 2024).

Project DECODE lies at the intersection of machine-learning, dynamical systems, and sleep and coma neurophysiology. The state of the art in this interdisciplinary perimeter is two-fold. First, recent years have seen a lot of applications of AI/machine learning to automatically detect/classify states of altered consciousness in coma or sleep (e.g. Ballanti et al. 2022). However, only a minority of these studies have focussed or even identified the need to model sleep and coma brain states as dynamical systems. Most AI diagnosis systems use clinical EEG features (e.g. burst suppression; Zheng et al. 2021) or learn these features with deep architectures (e.g. Pham et al. 2022) that are optimised to enhance the separability of the states, but not their internal dynamics.

Second, several studies have already applied insights from DST or statistical physics to understand brain dynamics and consciousness. One prominent example is to model resting-state networks as networks of connected nodes (Deco, Jirsa & McIntosh, 2011) with techniques to infer both network connectivity and node-level dynamics. These models, when fit to resting-state fMRI activity of vegetative vs minimally-conscious patients, show a poorer and less flexible repertoire of configurations (Demertzi et al., 2019); in sleep, they may also explain EEG slow waves (Massimini et al., 2024). However, the majority of these models postulate the explicit functional form of the model to fit it to data, but do not allow reconstructing this model in a purely data-driven manner. As such they do not e.g. easily allow comparing dynamical systems between individual patients or extract characteristic parameters that can serve as biomarkers for diagnosis.

In the field of AI, methods for the data-driven reconstruction of dynamical systems is a booming subfield of scientific machine learning (Brunton & Kutz, 2022). Moreover the understanding that latent dynamics of an inherently lower dimension determine the evolution of experimentally observed behaviour in complex systems has led to a proliferation of data-driven methods to aid meaningful model discovery. Of these, the Hankel alternate view of Koopman (HAVOK) framework (Brunton et al. 2017), provides reconstruction of the underlying state space, along with an approximate linear model purely from data. Sparse identification of nonlinear dynamics (SINDY; Brunton, Proctor & Kutz, 2016) enables the identification of a sparse set of governing equations directly from data. These methods though widely used in engineering contexts (Brunton & Kutz, 2022) have never been used to probe the neurophysiological measurements, particularly to learn and delineate the states of consciousness such as sleep and coma.

Simultaneously, dynamical mechanisms in the spectral domain, such as cross frequency coupling (Canolty et al. 2010) have been established as playing a causal role in the neural implementation of core cognitive processes. Evidence regarding the specific functional role of CFC points to a theory of communication through coherence (Fries 2015) between brain regions of interest, thereby coordinating their activity to generate and adapt behavior. Specifically, phase amplitude coupling (Koster, M., Gruber, T. 2022) has been identified as a common mechanism across neural scales and in various model organisms. In the context of sleep, slow cortical oscillations have been found to be dynamically coupled to spindles, with implications on memory related processes

(Latchoumane, C. F. V. et al. 2017, Purcell et al. 2017, Whitmore et al. 2022). Recent evidence also suggests LC-NE activity as a driving mechanism for transitions between NREM and REM stages of sleep (Osorio-Forero A et al. 2025), which further motivates this line of inquiry. Apart from the fact that sleep consists of multiple cyclic transitions between dynamically distinct regimes of neural activity, which is a natural platform to study internally driven transitions, disorders of sleep such as REM sleep Behavioral Disorders (RBD, Noh, T-G. et al. 2024) are recognized as precursors to neurodegenerative disorders. Presence or absence of markers associated with cognitive processes may be indicative of not only aberrations in the natural sequence of transitions in sleep disorders or the prevalent states of consciousness in comatose individuals, but also prognostic aspects and recovery (Zubler et al. 2016, Carrasco-Gomez et al. 2021). Such findings provide the necessary grounds for investigating the activity preceding and following transitions in states of consciousness in sleep and coma, from the context of established, neurocognitively interpretable dynamical mechanisms, using dynamical systems reconstruction.

2. Novelty of the project & Potential applications if any (~1/4 page):

Project DECODE lies at the intersection of AI and neuroscience, and proposes to leverage novel AI methods to infer normal and pathological dynamics from brain data in order to provide earlier and better diagnosis for two of the most important neurological diseases in both India and France: sleep disorders and coma. The novelty of our project lies in the thorough interdisciplinarity of its undertaking. We bring together dynamical insights from physics and cutting-edge modelling paradigms from machine learning to tackle pressing socially relevant problems in neurophysiology. This is enabled by an international collaboration between an Indian neuroscience lab and a French computational science team. We seek to hire relevant experts both at the postdoctoral and masters levels with relevant experiences in the physics of dynamical systems and experimental neurophysiology to accomplish this. The potential outcomes and applications of project DECODE are manifold.

Scientific: First, the project will change what we know of the neurophysiological processes that underlie altered states of consciousness such as sleep and coma (e.g. "can transitions between successive sleep stages be modelled as phase transitions or bifurcations of a dynamical system?"; "are the coma brain dynamics lower-dimensional than the healthy brain's dynamics?"). Second, it will introduce novel machine learning methods for analysing EEG data, and disseminate it with new open-source tools that simplify their use in the lab as well as the clinic (deliverables D1.2, D2.2, D3.2).

Clinical: The incidence of coma in the general population is estimated at 8.5 per 100,000 for traumatic causes (59% of which involve car accidents) and an additional 6 per 100,000 for non-traumatic causes (e.g. infection), per year (Masson et al. 2003). This represents more than 110,000 patients per year in Europe alone, 40% of whom will evolve to vegetative and minimally-conscious states, or death (Luaute et al. 2005). A national survey on coma epidemiology, evaluation, and therapy in India (Mahajan et al. 2024) has revealed less frequent usage of EEG for clinical evaluation. For the clinical practitioners, the methods being developed by this project could provide a quantitative basis for deciding the target and protocol of necessary interventions. For these patients and their family, our findings will provide new procedures for better informed diagnosis and more ethically-acceptable life-support decisions. Moreover, the novel insights gained from the analysis of neural activity associated with various stages of sleep will open avenues of characterizing sleep related disorders, and provide a common framework for modeling disorders of sleep and consciousness

Economic/technological: The machine learning procedures developed in the project have potential to improve the efficiency and effectiveness for health care services, and to be in high demand by patient families. They will be considered for IP protection and commercialization, using the maturation services of our host institution CNRS (CNRS Innovation), FEMTO-ST (FCInnov) and IITK (IIT Kanpur).

Societal: Beyond science, modelling the individual brain dynamics of patients will initiate a shift of paradigm from the typical application of AI for medical decision making, which tends to abstract individual diversity into broader statistical categories of patients with similar outcomes. This may have potentially important ethical and legal implications (e.g. "what is the status of a patient which can't pass clinical scales for consciousness, but whose brain nevertheless shows dynamical trajectories that resemble healthy controls"?).

3. Methodology including task calendar & Deliverables (~2 ½ pages) :

The intuition behind our methodology is, while dynamical system theory (DST) provides a powerful mathematical toolbox to analyse physiological systems, that toolbox gets richer the more is known about the system's behaviour. If all is known is a single high-dimensional measurement of the system (e.g. the EEG waveform of an individual coma patient), then the researcher is left with model-agnostic time-series methods (however sophisticated) such as the ones used so far in machine learning. If, on the other hand, the system is known by its full functional form (e.g. a system of ordinary differential equations ODEs, or as a network of coupled phase amplitude oscillators, with coupling functions inferred from the data), then DST offers tools not only to simulate arbitrarily large numbers of measurements from that system, but also to analytically study how they depend on its parameters in terms of phase transitions, bifurcations, fixed points, etc. Neurocognitive studies have provided grounding for the dynamical mechanisms involved in cognitive processes, and their neural implementation. Our rationale is to use DS reconstruction, fusing data driven and neurocognitively informed approaches, to progress along that continuum, abstracting away from the surface into depths where we can tap into the full power of DST to uncover otherwise unobserved properties of the underlying system. The research objectives are:

RO1: to evaluate the sensitivity of reconstructed DST parameters to the pre-existing clinical variables: do they correlate with coma severity and EEG malignancy, or with sleep stage dynamics?

RO2: to evaluate the capacity of reconstructed parameters to predict coma outcome and sleep stage classification, compared to other traditional predictors.

RO3: to look for novel mechanistic explanations for intra- and inter-individual EEG variability by measuring the similarity between the reconstructed systems between coma diagnostics and sleep stages.

Data: Our proposed data for this work are, for coma, a French internally-available dataset of 20min resting-state EEG (13 scalp electrodes) recorded in 181 post-cardiac-arrest comatose patients at the FEMTO-ST partner Hospital (GHU Paris), associated with neurological outcome (Coma Recovery Scale CRS-R at 7 days, Cerebral Performance Category, CPC at 3 months; Hermann et al. 2024); and for sleep, Indian experimental data to be collected in IITK of overnight sleep polysomnograms of healthy adults (scalp electrode EEG, ECG, EMG, EOG), with annotations of N1,N2,N3 and REM sleep stages, and various experimental manipulations of sleep conditions (light exposure, experimental stressors) such as those used in our previous work (Deshmukh and Ramakrishnan, 2024). . Both datasets will be shared across partners, so that methods developed on each side can be applied and compared on them.

Overall methodology: Given this available data, we propose three methodological routes (and work packages) towards our ROs, which exemplify 3 families of techniques that have recently emerged from the fields of neurocognition and physics-informed machine learning, and enables the exploration of complementary aspects of the reconstructed DS.

State space reconstruction (WP1) using a family of techniques which aim to approximate the relation between successive measurements of the system as a linear matrix operator A: $x_{k+1} \approx A.x_k$. This operator can be approximated, for instance, by the eigenmodes of a low-rank singular value decomposition (SVD) of the time delay matrix (Hankel alternate view of Koopman, HAVOK analysis; Brunton et al. 2017), or with variational autoencoders (VAE) trained on the delay embedding matrix (Raut et al. 2023). In the project, we transform the raw EEG time-series of each individual into a lower-dimensional trajectory in the state-space of a linear dynamical system that approximates the system's true dynamics (Pourdavood & Jacob 2024). To address the project's ROs, we will then analyse that trajectory instead of the original waveform to provide indicators of its complexity (e.g. its fractal dimension and Lyapunov exponents), and the transformation mapping (e.g. SVD matrix), to provide indicators of system dimensionality and topology (RO1,RO2). Finally, we will measure system similarity across coma diagnostics and sleep stages (RO3) based on how well the measurement of a system can be decoded from the embedded trajectory of another (Raut et al. 2023).

Phase amplitude coupling (PAC) (WP2) is a specific form of cross frequency coupling (CFC) (Canolty, Knight 2010) measured from neural oscillatory signals, which demonstrably plays a causal mechanistic role in the neural implementation of cognitive processes (Koster and Gruber, 2022). Recent advances in dimension reduction techniques to reconstruct phase amplitude dynamics (Yeldesbay et al, 2024, Soulat et al. 2022) have enabled the possibility of investigating EEG as a networked system of interacting oscillators in the lower dimensional space of phase and amplitude coordinates. The approach described in Yeldesbay et al. (2024) involves learning the functions that transform the signals from the space of electrodes to the space of interacting phase-amplitude oscillators, using parameterizations of the eigenfunctions of the associated Koopman operator. The resulting reconstructed dynamical system is a network of phase-amplitude oscillators with the interactions between them represented as coupling functions in phase and amplitude coordinates. The reconstructed dynamics simultaneously has reduced dimensions as well as neurocognitive interpretability (RO1). The approach will be applied on sleep data, motivated by findings such as the coupling of slow cortical oscillations to spindles through PAC, with implications on memory related processes (Latchoumane, C. F. V. et al. 2017, Purcell et al. 2017, Paller et al. 2022). The proposed methods would reveal the markers of neural activity which precede transitions in stages of sleep, to understand the driving mechanisms by which the transitions emerge. The insights gained from the dynamical characterization of transitions of sleep stages would not only provide a framework to assess deviations in sleep disorders, but also provide necessary grounding for the analysis and interpretation of clinical data in coma states (RO2,RO3), both within and across patients. Identifying dynamical signatures of core cognitive processes, such as attention and memory, in various stages of consciousness in sleep and coma, will provide a clear and well grounded path towards diagnostic as well as prognostic classification (RO3).

Finally, Symbolic regression (WP3), also known as the Sparse Identification of Non-linear Dynamics algorithm (SINDy; Brunton, Proctor & Kutz, 2016), attempts to directly write the differential equations of the system by approximating its vector field $dx/dt = f(x)$ by a large library of nonlinear basis functions (polynomial, trigonometric, etc.) that are linearly combined with regularised (LASSO) regression. In the project, we will use SINDy to learn the functional form $f(x)$ of each individual's time series. In addition to the high dimensional EEG, we also use SINDY to obtain governing equations of the latent low dimensional dynamics obtained in WP1. To address the project's ROs, we will then compare the parameters of each equation against clinical parameters and outcomes (RO1,RO2), as well as apply DST stability analysis on the obtained equations to look for common geometric and time-invariant properties across coma diagnostics and sleep stages (RO3).

References

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	1st year		2nd year	
	Months	Deliverables	Months	Deliverables
Objective 1 : Develop and validate algorithms for dynamical systems reconstruction from EEG Activities : a) Identify and select existing modules (e.g. yasa-python) for sleep stage classification as reference. b) Reconstruct and compare the dynamics observed in sleep stage transitions and coma states using methods in section 3. c) Validate developed methods on collected dataset.	1-12	Open repository with modules for each proposed work package.	12-24	Report on validation of developed algorithms on collected dataset, and documentation of modules.
Objective 2. : Collect EEG and physiological data from sleep study at IIT K Activities : a) Protocol design and pilot experiment b) Revision of protocols, ethical approval c) Revised study	6-12	Raw multimodal dataset of physiological measures - GSR, ECG, EOG - and EEG, from controlled sleep study	12-18	Preprocessed, annotated and anonymized dataset of sleep EEG and physiological measures, ready for analysis by developed algorithms.

Please indicate the approximate number of man–months in a year to be devoted to this project by each of the Principal and Joint Investigators. Please enclose a bar chart for the duration of each phase in which the project will be carried out.

	Man–months	
	1st year	2nd year
Indian Principal Collaborator	3 (25%)	3 (25%)
French Principal Collaborator	3 (25%)	3 (25%)

4. Complementarity Details:

a) Part of the project work, which will be conducted in each country.

Indian Side: Prof. Ramakrishnan's lab at IIT Kanpur brings their neurophysiological expertise. They will carry out both inhouse collection of healthy participant sleep EEG data and analyse both sleep and coma data sets using the methods described in section 3.

French Side: Dr. Aucouturier's group at FEMTO-ST will bring both their methodological expertise developing novel computational paradigms to model experimental neurophysiological data and their close association with hospitals in France. Thus they will bring access to a large Parisian coma database and implement the novel methods described earlier on both the coma data and the sleep measurements obtained from India.

b) Please clearly bring out the added value due to collaboration.

Both labs have started working on dynamical system reconstruction approaches, with complementary methods (French lab: HAVOC; Indian lab: PAC), and complementary neurological models (French lab: coma; Indian lab: sleep). The collaboration will allow to cross-fertilize methods and applications (HAVOC for sleep; PAC for coma), as well as jointly developing a new approach (SINDY). Doing so, both labs will multiply their expertise manifold, and increase the potential for a breakthrough impact of the project.

c) The infrastructure facilities related to the project activity available in the institutions, where the project work will be carried out.

The Indian lab has set up a well-equipped Sleep Station with a 32/64-channel EEG device, heart rate and skin conductance monitor, and a workstation for overnight data collection. The lab is temperature and humidity controlled, ensuring a stable environment for precise measurements of sleep-related neural and physiological signals. Additionally, IIT Kanpur offers High-Performance Computing (HPC) resources at subsidized costs, essential for time-intensive physiological data modeling. These computing resources will enable the efficient processing and analysis of large datasets and complex simulations, crucial for the project's research on neural dynamics during sleep.

The French lab has a in-house EEG lab (128-channel EEG device, autonomic electrophysiology, audiovisual stimulation hardware) fitted for cognitive neuroscience on healthy participants as well as, via our partner hospital institution GHU Paris, complete research access to patient data in the coma and epilepsy intensive care units.

(total ~1/2 page)

5. Indo-French training and Human Resource Development planned under the project (~3/4 page)

This project aims to foster cross-border collaboration and skill development in the field of neuroscience by leveraging the expertise and resources from both Indian and French institutions. The project will be spearheaded by Principal Investigators and postdoctoral associates from both sides, who will play a key role in shaping the direction of research and training initiatives. These PIs and postdocs will engage in research exchanges, visiting each other's labs to share research methodologies, discuss emerging ideas, and establish connections that will help strengthen the scientific collaboration between the two nations. This exchange will allow both groups to broaden their research perspectives and refine and develop approaches to understand the nature of dynamical systems that underpin neuroscience.

In addition to the postdoctoral exchanges, the project will also involve close mentorship of graduate students. One graduate student from the Indian team will be co-mentored by the French Principal Investigator (PI), and similarly, a graduate student from the French team will receive co-mentorship from the Indian PI. This model ensures that students gain exposure to different academic environments and research methodologies, enhancing their academic growth. As part of this exchange, the graduate students will have the opportunity to visit each other's labs during the grant period. These visits will not only support academic development but will also provide hands-on experience in cutting-edge research techniques that are critical to advancing their careers in the field.

Further, in the second year of the project, supported by CNRS, we plan to jointly organize a one-day workshop at IIT Kanpur, focused on dynamical systems approaches in neuroscience. The workshop will bring together leading researchers from India and France who are actively working in this field. The aim is to facilitate the exchange of knowledge and ideas while fostering stronger ties between researchers across the two countries.

The workshop will provide graduate and postgraduate students with both theoretical and practical training. Experts in the field will conduct tutorials, ranging from basic to advanced levels, ensuring that participants can engage with both the foundational concepts and the latest developments in the area of dynamical systems in neuroscience. In addition to the lectures, hands-on training will be provided in the

use of analytical tools necessary for exploring these complex systems. By providing students with access to world-class researchers and their tools, the workshop will serve as an invaluable resource in their educational journey.
Ultimately, this project aims to nurture the next generation of neuroscientists and researchers by fostering a rich, cross-cultural, and multidisciplinary exchange, equipping students and postdocs with the skills, knowledge, and networks needed to thrive in the global research community.

6. Knowhow of PIs supported by 5 papers for each PI, in the field of proposed project. (~1/4 page)

Indian side: • **Barack, D. L.**, Ludwig, V. U., Parodi, F., Ahmed, N., Brannon, E. M., Ramakrishnan, A., & Platt, M. L. (2024). Attention deficits linked with proclivity to explore while foraging. Proceedings of the Royal Society B. • **Sheng, F.**, Ramakrishnan, A., Seok, D., Zhao, W. J., Thelaus, S., Cen, P., & Platt, M. L. (2020). Decomposing loss aversion from gaze allocation and pupil dilation. Proceedings of the National Academy of Sciences, 117(21), 11356-11363. • **Ramakrishnan, A.**, Hayden, B. Y., & Platt, M. L. (2018). LFPs in the dACC encode reward but not time cost during foraging. Brain and Neuroscience Advances, 3, 2398212818817932. • **Ramakrishnan, A.**, Byun, Y. W., Rand, K., Pedersen, C., Lebedev, M. A., & Nicolelis, M. A. L. (2017). Cortical neurons multiplex reward-related signals along with sensory and motor information. Proceedings of the National Academy of Sciences, 114(24), E4841-E4850. • **Ramakrishnan, A.**, P. J., Pais-Vieira, M., Byun, Y. W., Zhuang, K. Z., Lebedev, M. A., & Nicolelis, M. A. L. (2015). Computing arm movements with a monkey brainet. Scientific Reports, 5, 10767.

French side: **Arias-Sarah, P.**, Bedoya, D., Daube, C., Aucouturier, J. J., Hall, L., & Johansson, P. (2024). Aligning the smiles of dating dyads causally increases attraction. *Proceedings of the National Academy of Sciences*, *121*(45), e2400369121.• **Adl Zarrabi, A**., Jeulin, M., Bardet, P., Commère, P., Naccache, L., Aucouturier, J. J. & Villain, M. (2024). A simple psychophysical procedure separates representational and noise components in impairments of speech prosody perception after right-hemisphere stroke. *Scientific Reports*, *14*(1), 15194. • **Benghanem, S.**, Guha, R., Pruvost-Robieux, E., Levi-Strauss, J., Joucla, C., Cariou, A. & Aucouturier, J. J. (2024). Cortical responses to looming sources are explained away by the auditory periphery. *Cortex*. • **Pruvost-Robieux, E.**, André-Obadia, N., Marchi, A., Sharshar, T., Liuni, M., Gavaret, M., & Aucouturier, J. J. (2022). It's not what you say, it's how you say it: A retrospective study of the impact of prosody on own-name P300 in comatose patients. *Clinical Neurophysiology*, *135*, 154-161. • **Goupil, L.**, Ponsot, E., Richardson, D., Reyes, G., & Aucouturier, J. J. (2021). Listeners' perceptions of the certainty and honesty of a speaker are associated with a common prosodic signature. *Nature communications*, *12*(1), 861

7. Five Indian and five French referees with their addresses including e-mails. ***You may also indicate name(s) of scientists to whom the proposal should not be sent, in your opinion, for reasons of conflict of interest.***

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