AAPG2025	PROPHECY	PRME
Coordinated by :	Noura DRIDI (FEMTO-ST Institute)	48m
H.14 : Interfaces : mathématiques, sciences du numérique – biologie, santé		

PROPHECY : Prognostics of Fast and Slow Dynamics in Cancer and Coma

I. Pre-proposal's context, positioning and objective(s)

Non-linear dynamical systems, defined in the form of ordinary or partial differential equations, are ubiquitous in the human body and subserve essential aspects of physiological function in e.g. nervous, cardiovascular, or metabolic systems. While a vast literature in biomedical engineering has proposed methodologies for obtaining estimates of the parameters of dynamical systems from experimental data (for a review, Marmarelis, 2004), these techniques leave out a large class of problems which involve slow drifting systems in which the slow dynamics cannot simply be dismissed (e.g. high-passed) as undesirable because it is, on the contrary, "the very important phenomenon that one desires to analyse" (Chelidze & Cusumano, 2006). Such non-stationary systems occur in normal physiological function (e.g. slow autonomous nervous system influences on fast cardiovascular dynamics) but also, and perhaps most critically, in evolving diseases. The biggest challenge facing medical prognostication is indeed to track the evolution of the slowly evolving "hidden" pathological state using only measurements from a fast subsystem, such as the blood-flow driven metabolism (on a timescale of seconds) around a cancerous tumour growing on a timescale of months, or the fast resting-state oscillations of cortical activity (on a timescale of milliseconds) in a comatose brain recovering from cardiac arrest on a timescale of days.

Project's objectives and research hypotheses: Originating from a research team with a historical background in machinery condition monitoring (a field that is essentially constructed on the idea of non-stationarity), project PROPHECY aims to develop **new computational methods for the data-driven estimation and prognostics of non-stationary "fast/slow" systems in human physiology**, with a view to improve both biological understanding and clinical prognostics for two of our modern societies's most important pathologies: breast cancer and coma after cardiac arrest.

To do so, project PROPHECY has a three-fold theoretical and methodological *parti-pris.* First, we propose to model the disease process in the form of a non-stationary dynamical system that has **coupled, hierarchical dynamics consisting of fast/physiological and slow/pathological subsystems**:

$$\dot{x} = f(x, \theta)$$
$$\dot{\theta} = \epsilon . g(\theta, x)$$

where *x*, evolving according to its vector field *f*, is the fast, directly observable state; θ, evolving with *g,* is the slow dynamic variable on the parameters of *f,* and $0 < \varepsilon \ll 1$ is a time-scale constant making *g* slow compared to *f* (see Chelidze & Cusumano, 2006 for a similar formulation in the field of industrial health monitoring). Second, instead of relying on traditional system identification methods, we propose to capitalise on recent advances in the field of **physics-informed machine learning** (PI-ML, Karniadakis et al. 2021) which allow not only to learn system parameters, but also if needed the system's governing equations from experimental data (SINDY; Brunton et al. 2016). Third, in order to deliver the project's clinical objectives of improving medical prognostics and decision-making, we propose to develop methods that not only provide point estimate, but also **uncertainty quantification** on the system's future evolution - an important emerging theme in PI-ML (e.g. Hirsch et al. 2022).

Position of the project in relation to the state of the art: Project PROPHECY lies at the intersection of dynamical-system theory, machine learning, and cancer and coma physiology. The project goes beyond the state-of-the-art of this interdisciplinary perimeter in two major ways. First, while recent years have seen lots of applications of machine learning to automatically detect/predict the evolution of cancer (e.g. in our own work, Zuluaga-Gomez et al. 2021) or coma (Ballanti et al. 2022), they have done so mostly by considering "surface" features of physiological measurements.

For instance, in coma, prognostication relies traditionally on the detection of so-called "malignant" features, such as discontinuities, reduced amplitude or periodic discharges, in recordings of the patient's electroencephalogram/EEG (e.g. Benghanem et al. 2022). However, such surface features are typically highly variable both intra- and inter-individuals, and may only reflect the "tip-of-the-iceberg" of the underlying state of the system. For instance, "benign" EEG that excludes any malignant feature still appears in a vexing 30% of bad-outcome coma patients (Fenter et al. 2023). Our proposal departs from this approach by, first, learning the parameters of a dynamical system that explains the temporal dynamics of data and, then, **doing prognostics on these underlying parameters rather than on the measurement of the system**. Second, while recent advances in PI-ML have provided new methods to learn the parameters of dynamical systems from experimental data (e.g. PINNs for the thermal modelling of breast cancer - Perez-Raya & Kandlikar, 2023 ; PL-RNNs for the modelling of resting-state brain dynamics - Chen et al. 2024), they have remained focussed on modelling a single problem-specific timescale, typically learned from a low-rank transformation of the delay-embedding matrix of the measurement data (Raut et al. 2023) - i.e. what we call here the 'fast' subsystem. Our proposal departs from this approach by developing methods capable of **tracking** not/only the dynamics at the system's mesoscopic timescale, but also **the distortions that occur in this 'fast' vector field as a result of the underlying slowly evolving pathological *g*-process.**

Methodology to reach the scientific objectives of the project:

***Data-driven dynamical system modelling* -** Project PROPHECY proposes two PI-ML methodological routes towards our research objectives, which let us explore complementary aspects of our research questions depending on whether the fast subsystem has known functional form, or not. In breast cancer, we aim to model how tumour growth impacts the propagation of blood flow-driven heat in the human breast, with a view to develop a portable medical device for thermal imaging (Ketfi et al. 2024). Heat transfer in the breast is governed by a known partial differential equation (PDE), the so-called bio-heat equation (Pennes, 1948), which we propose to model with **physics-informed neural networks** (PINNs; Perez-Raya & Kandlikar, 2023). In coma, we aim to model how the gradual metabolic recovery or collapse of synapses impacts the resting-state brain oscillations post cardiac arrest. Although the modelling of cortical dynamics of (healthy) EEG activity is the subject of intense research effort (e.g. Deco, Jirsa & McIntosh, 2011), there is no accepted functional form for the *f*-subsystem, and we propose to use **symbolic regression** (SINDY; Brunton et al. 2016), in conjunction with nonlinear embedding models such as auto-encoders (VAE) or long short-term memory models (LSTM), to automatically learn this functional form from data.

Slow-subsystem modelling - To learn slow drifting dynamics on the fast subsystem's parameters, we will scaffold from simple to more complex methodologies. As a first step, we will use piecewise stationary methods (i.e. PINNs and SINDY) to infer *f*-parameters on successive time windows, and model the resulting time series of parameters as a **stochastic process** (e.g., extended Gamma process; Al Masry et al. 2021). To force the algorithms to identify successive dynamical systems into the same state-space, we will investigate the use of loss-functions that are grouped over successive inferences (e.g. group sparsity norms, Schaeffer et al. 2013). As a second step, we will develop methods that jointly estimate the fast and slow dynamics, for instance by **incorporating parameters of the stochastic process or the complete coupled *f*/*g* dynamics into the cost function** of the PINN/SINDY learning algorithms (Voina et al. 2024).

***Uncertainty quantification* -** Our clinical objective of improving medical decision-making requires to compute not only point estimates of the system's future trajectory (e.g. tumour size in one month), but uncertainty/confidence intervals on these estimates. In our project, uncertainties may hold both, and cumulatively, on *f*- and *g*-parameters. To model them, we will investigate **ensemble methods**, where uncertainty is quantified from the standard deviation of predictions of multiple models

learned on the same data (Lakshminarayanan et al. 2017); and **Bayesian extensions** of PINNs and SINDY which learn distributions over weights or equation coefficients (Hirsch et al. 2022; Dridi et al. 2024).

Experimental data for our project comes from three different sources. First, c**omputer simulations** of the system will be used as a benchmark to develop our algorithms. For cancer data, the propagation of blood flow-driven heat in the human breast (f-system), and how it depends on tumour growth (g-system), will be simulated with Computational Fluid Dynamics (CFD) software (COMSOL Multiphysics®). For coma data, although the system's PDE/ODE is unknown, we will simulate it for evaluation with a mean field model (bursting Liley model, Ruijter et al. 2017), where the g-process is modelled by a decrease of synaptic recovery time constants. Second (for cancer only), **phantom devices** will be used to test the methods' robustness to sensor and experimental noise. We will expand on our recently built prototype of augmented-bra with thermal sensors (Ketfi et al. 2024), and develop a silicon phantom device with a controllable thermal source mimicking tumour growth. Finally, we will use **clinical data** from two clinical trials already ongoing at our partner institutions (cancer: Hôpital Nord-Franche Comté - collaborator C. Devalland, M.D.; coma: APHP Cochin Hôspital - collaborator S. Benghanem, M.D., Ph.D). We already own datasets include single-shot recordings of N=30 cancer patients and matched controls wearing a thermal imaging device, and N=181 post-cardiac-arrest comatose patients with 20min resting-state EEG (Benghanem et al. 2022), which will allow working on *f*-process modelling immediately. To allow modelling the *g*-process, project PROPHECY will collect two additional cohorts of patients with longitudinal recordings (monthly recordings for 6-12 months for cancer; continuous 24h recordings for 4-7 days for coma), as well as prognostic benchmarks (tumour MRI for cancer; recovery scale CRS-R and biomarkers for coma). Ethical approvals for both trials were obtained prior to this submission.

Added-value of ANR funding: Project PROPHECY originates from a research team (DATA-PHM, Dept. of Automation & Robotics, FEMTO-ST Institute) with a 15-year background in machinery condition monitoring, which was recently joined by a CNRS researcher in Neuroscience (JJ.A, 2022) and a lecturer in Applied Maths (coordinator N.D, 2023). This original mix of skills opens an unprecedented opportunity to repurpose the team's expertise and address what we consider is a critical scientific obstacle in medical prognostics. The added-value of the project is to kick-start this new activity (which comes in complement to the team's other existing activities), by supporting the entry-cost into a new research community and funding PhD co-supervisions that our existing funding in e.g. industrial prognostics would not otherwise allow.

Ability of the project to address the chosen research theme: Project PROPHECY is perfectly aligned with the objectives of Axe H.14: it mobilises **mathematical** (dynamical system theory) and **computational** (machine learning) insights to propose a **new model** (coupled fast/slow dynamics) and **new data-driven methods** to estimate its parameters from experimental data. Doing so, it aims to accelerate research in a key domain of **health science** (medical prognostics), with a particular focus on 2 of our modern societies' most prevalent pathologies: breast cancer and coma after cardiac arrest. To do so, the project aims to both **evaluate our new proposed methodologies** with simulated data and phantom devices, and to **validate them with clinical data** obtained from ongoing clinical trials. Among the proposed challenges of Axe H.14, project PROPHECY directly contributes to *modélisation de processus biologiques et physiologiques; approches prédictives des comportements quantitatifs des systèmes; simulation numérique* and *approches d'apprentissage automatique.*

II. Partnership (team)

Project PROPHECY is a PRME proposal originated from the DATA-PHM team, one of the 3 research teams of the Dept. of Automation & Robotics, FEMTO-ST Institute in Besançon.

The project's **scientific coordinator**, **Noura Dridi** (PhD Telecom-Sud Paris, 2012), is an Assistant Professor of Applied Mathematics at the SUPMICROTECH engineering school, as well as incoming **co-director of the DATA-PHM research team**. Her research experience includes PI-ML and dynamical systems identification, with applications to ocean surface dynamics and biological heat propagation, as well as uncertainty quantification in Bayesian neural networks for renewable energy prognostics. In PROPHECY, beyond project coordination, Dridi will be research lead for uncertainty quantification (**Involvement: 50%)**.


Research team: Zeina Al Masry **(Involvement: 50%)** and JJ Aucouturier **(Involvement: 50%)**, both permanent researchers in the DATA-PHM team, will be the project's research leads for cancer and coma, respectively. • **Al Masry** (PhD Université de Pau, 2016) is an Assistant Professor of Applied Maths at SUPMICROTECH. Her research expertise includes applied probability and stochastic processes for industrial process monitoring and cancer diagnosis. She was the recent coordinator of a Swiss-French Interregional project on thermal monitoring of breast cancer, which provided pilot data for the current proposal. • **Aucouturier** (PhD Université Paris VI, 2006) is a CNRS senior researcher (Directeur de recherche) in computer science and neuroscience, and co-director (with coordinator Dridi) of the DATA-PHM research team. Aucouturier's expertise includes signal processing and machine learning approaches for neurology, for which he notably received funding from ERC (Stg CREAM 2014-2019, PoC ACTIVATE 2020-2021). He is the recent coordinator of ANR Sounds4Coma (2022-2025), which provided pilot data for the current proposal. Within the DATA-PHM team, the project will also benefit from punctual expertise from Prof. **Noureddine Zehrouni** (Prof. SUPMICROTECH, Industrial Prognostics & Health Management), Dr **Moncef Soualhi** (Assistant Professor UFC, Machine learning) and **Patrick Nectoux** (Ingénieur de recherche CNRS, Instrumentation & phantom devices).


Clinical collaborators: In addition to the above permanent members, project PROPHECY will also benefit from expertise by two of the team's clinical collaborators. **Christine Devalland**, M.D. (left), is a cancer specialist at Hopital Nord Franche-Comté, where she heads the Dept of Pathology and Cytology. Devalland is clinical lead on the project's cancer clinical trial. **Sarah Benghanem, M.D., PhD** (right) is an intensivist at APHP Cochin Hosp. in Paris, and an associated member of the DATA-PHM team. Benghanem is an expert in coma prognostication after cardiac arrest, and is clinical lead on the project's coma clinical trial.

III. References:

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