Title: Diagnostic and resolving For dereguLated complex sYstems: From aErospace safety to peRsonalised medicine-FLYER

Funding: Université Fédérale Toulouse Midi-Pyrénées, starting october 2019.

Supervisors: N. Davezac noelie.davezac@univ-tlse3.fr (UPS), J. Bordeneuve-Guibé joel.bordeneuve@isae-supaero.fr (ISAE-SUPAERO)

Specialty: Systems Engineering, Systems Biology

Keywords: System modelling, uncertain models, interconnected systems, reactive oxygen species, neurodegenerative diseases, ageing.

Abstract: System biology is a recent approach based on engineering sciences and tools to study complex biological systems. It is especially relevant for topics concerning personal medicine. The links made between systems engineering and diagnostic systems enable to list common knowledge necessary for their study: mathematics, system modelling (identification, estimation, optimization), control, computing, safety analysis.

Aerospace programs have always been an important field of application for engineering techniques. The innovative challenges have constantly forced engineers to develop new techniques for modelling dynamical systems, designing, developing and testing new equipments. The ever-growing complexity of the considered systems has highlighted new properties like robustness, predictability and reliability. Just as many electrical, mechanical, or hydraulic systems, bio-molecular systems are now considered by researchers as a set of non-linear dynamical interconnected subsystems, submitted to many uncertainties and stochastic behaviors. In particular, it is now admitted that the concepts of retroactivity, dynamic input/output response, or distributed systems are highly useful and suitable for modelling and analysing biological systems. Thus, employing an appropriate combination of tools from systems and control theory, mathematical biology, and experimental techniques, appears to be an interesting way of addressing and investigating new biological issues.

This thesis uses a system biology approach for the study of an optic neuropathy “Autosomal Dominant Optic Atrophy type 1” (DOA) and others diseases related to OPA1 gene disorders such as parkinsonism, ataxia, deafness, Behr syndrome, in order to predict pathology evolution and to give appropriated treatment for a specific patient. DOA is characterized by moderate to severe loss of visual acuity with insidious onset in early childhood associated with optic nerve atrophy. This complex pathology remains without effective treatment or predictive diagnosis to date.

The objective is to model the molecular mechanisms involved in DOA to predict pathology evolution considering individual patient’s factors such as modulator genes. In the future, personalised treatments will be proposed based on model analyses. A first thesis on this subject is successful (Merabet et al., 2017; Merabet et al., 2016 july 8-14; Millet A. et al., 2017) and allowed the first step of the model. This thesis received a thesis price from AFSEP (Association Française des Méthodes Séparatives). This first work paves the way for a second one based on the continuity of the work.

Laboratories: CRCA (CNRS UMR5169, Toulouse, France) Université Fédérale de Toulouse, and DCAS, ISAE-SUPAERO, Toulouse.

PhD director 1: The project will be coordinated by N. Davezac (PhD, HDR) at the Centre de Recherche sur la Cognition Animale (CNRS UMR5169, Toulouse, France). N. Davezac possesses a recognized expertise on proteomics, oxidative stress and genetic diseases (Davezac et al, 2004 Proteomics; Lipecka et al, 2006 JPET; Moriceau et al., 2009 J Immunol; Witko-Sarsat et al., 2010 J Exp Med; Colas et al, 2012

HMG; Bouayad et al., 2012 J Biol Chem) and acquired an expertise in oxidative metabolism (Millet et al, 2016; Merabet et al., 2017; Merabet et al., 2016 july 8-14; Millet A. et al., 2017). She patented novel findings in understanding DOA pathogenesis driving to a potential therapy: "Method, process and kit for prognosis of OPA1 gene or OPA1 gene product deficit induced diseases" (European Patent EP14305448 and International Patent PCT/EP2015/056814). The team has a long time expertise in the mitochondria field. They participated to the discovery of the first gene controlling mitochondrial dynamics (OPA1) involved in a neurodegenerative process (Dominant Optic Atrophy) (Delettre et al., 2000 Nat Genet.). Since then, the team has investigated at the molecular and cellular levels the functions of this protein (Olichon et al., 2003 JBC; Olichon et al., 2007 Cell Death Differ), and the consequences of its inactivation on DOA pathological mechanisms (Olichon et al., 2007 J Cell Physiol, Landes et al., 2010 Semin Cell Dev Biol).

PhD director 2: Joel Bordeneuve-Guibé is working in the Department of Aerospace Vehicles Design and Control of ISAE-Supaéro, which aims to develop methods, techniques and tools that make it possible to understand, analyze, evaluate, control and design, the functional and operational behavior and the performances of complex systems. Joel Bordeneuve-Guibé has a recognized expertise in modelization and control of complex dynamical systems (Y. Denieul et al, Journal of Aircraft, 2017; Y. Denieul et al, IFAC World Conference, 2017; J. Bordeneuve-Guibé et al, Journal Européen des Systèmes Automatisés, 2011 ; D. Alazard, et al, AIAA Guidance Navigation and Control Conference, 2013; J. Bordeneuve-Guibé et al, AIAA Guidance Navigation and Control Conference, 2014). More specifically, the relevant skills of the Control team of the Department mainly focuses are: (i) the modelling of complex dynamical systems, (ii) the development of control law design methods (multivariable, robust, self-scheduled, adaptive, non-linear) and their implementation within realistic applications (aircraft and space craft). Many research projects handled by the Control team are focused on the interdependence between the modelling process and the controller design: Indeed, the main challenge under consideration is to select the most appropriated model to solve a specific control problems. Especially when robustness analysis is considered, the model complexity should be strongly related to the analysis methods. A special attention is given to the multidisciplinary aspects: indeed in the case of complex systems, it is necessary to consider the optimality of the models for every subsystem and the interactions between them. Mastering the couplings between subsystems considered as elements of a whole physical system is a key problem addressed by several projects in the Control team. Model reduction techniques, extensively used in Aerospace control engineering, are also under study.

References:

- Merabet, N., Bordeneuve-Guibe, J., and Davezac, N. (2017). Modelling the redox imbalance in Dominant Optic Atrophy: the case of respiratory Complex I. IFAC-PapersOnLine 50.
- Merabet, N., Millet, A., Belenguer, P., Bordeneuve-Guibe, J., and Davezac, N. (2016 july 8-14). Mathematical modeling of redox imbalance in Dominant Optic Atrophy Type 1. SSBSS 2016 International Synthetic and Systems Biology Summer School, Volterra Italy.
- Millet A., M.N., Bertholet A., Daloyau M., Reynier P., G.A., Devin A., Wissinger B.,, and Bordeneuve-guibe J., B.P., Davezac N. (2017). Imbalance of the REDOX state in dominant Optic Atrophy: the way of mathematical modeling. Archives of the International Society of Antioxidants in Nutrition and Health 5, 21-24

Skills: The candidate is expected to do scientific research in the domain described, write a PhD thesis and publish research results in scientific journals. A strong background in systems engineering is needed, a culture in biological fields would be highly appreciated. Moreover, the candidate must be comfortable in programming languages such Matlab.

Applications: may be submitted electronically to noelie.davezac@univ-tlse3.fr and joel.bordeneuve@isae-supaero.fr and must include a cover letter, a curriculum vitae detailing educational background, research experience and up to three recommendation letters.