The role of feedback in maintaining robustness and modulation across scales:

Insights from cellular and network neurophysiology

Julie Dethier

Supervised by Professor Rodolphe Sepulchre

Systems and Modeling Research Unit
Department of Electrical Engineering and Computer Science
Faculty of Applied Sciences
University of Liège, Belgium

A thesis submitted for the degree of
Doctor of Philosophy in Engineering Sciences

August 2015

The present dissertation has been supervised by

Prof. R. Sepulchre	University of Liège, Belgium

The present dissertation has been evaluated by the members of the Jury (sorted by alphabetical order):

Prof. R. Bogacz		University of Oxford, UK
Prof. J.-M. Goaillard		University of Aix-Marseille, France
Prof. G. Kerschen	(Chair)	University of Liège, Belgium
Prof. P. Maquet		University of Liège, Belgium
Prof. R. Sepulchre	(Advisor)	University of Liège, Belgium
Prof. V. Seutin		University of Liège, Belgium

The research described in the present dissertation was financially supported by the Belgian F.R.S.-FNRS (National Fund for Scientific Research), and by the Belgian Network DYSCO (Dynamical Systems, Control, and Optimization), funded by the Interuniversity Attraction Poles Programme initiated by the Belgian Science Policy Office.

Abstract

The brain is a complex system made of many components acting at very different resolution levels, from the microsecond and nanometer scales with ion channels to hours and brain-wide scale with proteins. The brain dynamics and functions emerge from the interactions between these resolution levels. Mathematical modeling is a powerful ally to uncover some of the brain organizing principles and mechanisms. From this perspective, the question of which cellular details must be retained at the network level is largely open.

Motifs simplify systems by approximating the wiring diagram and by taking advantage of the timescale separation between processes. Yet, motifs study each resolution level separately and neglect couplings between levels. This approach falls short of system-level questions and multiresolution intrinsic properties.

The present dissertation aims at narrowing the gap by looking at the *interplay between resolution levels*. We propose to extract essential elements, in the form of feedback loops, to be maintained from one resolution to the next in the hope of a better understanding of brain functions and diseases. The focus is on the spatiotemporal upscaling from the neuron to the network level and, in particular, on the maintenance of modulation and robustness properties across scales. This approach is used in a two-neuron network and is extended to a prospective multiresolution excitability framework. The main contributions of this dissertation are the following.

We identify the key role of *a cellular feedback loop for network oscillation robustness and modulation*. Rhythms are crucial in the brain functioning but much awaits to be understood regarding their control, regulation, and function. In a mutually-inhibitory network, we isolate an essential cellular property—a positive feedback loop in the slow timescale—to be retained at the network level to ensure modulation and robustness of network oscillations.

We highlight the peculiar role that *a cellular feedback loop can play for the regulation of network switches*. We identify that a cellular positive feedback loop brings localization properties, both temporally and spatially, to network oscillations. The emerging picture suggests a basal ganglia network model valid both in healthy movement-related oscillations and in parkinsonian conditions.

Multiresolution excitability emerges due to localization properties of excitable systems: different excitability resolution windows can be superposed and interact, generating multiresolution systems. In each window, the system is characterized via its transfer properties and input-output behavior. Signal processing properties appear in these multiresolution systems and endow multiresolution objects with gating and multiplex signaling capabilities.

In conclusion, the present dissertation provides novel insights on the importance of the interplay between cellular and network levels. This multiresolution motif perspective is thought to be general and not specific to neuroscience. Finally, exploiting the concept in multiresolution technologies is suggested.

Résumé

Le cerveau est un système complexe composé d'éléments actifs à des niveaux de résolution très différents, de la microseconde et nanomètre avec les canaux ioniques, à l'heure et l'échelle du cerveau avec les protéines. La dynamique et les fonctions du cerveau émergent des interactions entre les différents niveaux de résolution. La modélisation mathématique est un allié puissant pour dévoiler certains des principes organisationnels et mécanismes cérébraux. Dans ce contexte, la question de savoir quels détails cellulaires doivent être conservés au niveau du réseau reste largement ouverte.

Les motifs décomplexifient les systèmes en simplifiant le schéma de connexion et en exploitant la séparation des échelles de temps entre processus. Cependant, les motifs étudient chaque niveau séparément et négligent les couplages entre niveaux. Cette approche passe à coté des questions systémiques et des propriétés intrinsèques de multirésolution.

Cette thèse a pour but de rapprocher les deux domaines en étudiant les *interactions entre niveaux de résolution*. Nous proposons d'extraire les éléments principaux, sous la forme de boucles de feedback, à maintenir d'une résolution à la suivante dans l'espoir d'une meilleure compréhension des functions et maladies cérébrales.

L'accent est placé sur le changement d'échelle spatiotemporelle, du niveau neuronal au niveau réseau, et en particulier sur le maintien des propriétés de modulation et de robustesse à travers les échelles. Cette approche est utilisée dans le cas particulier d'un réseau de deux neurones et est étendue à un cadre théorique plus spéculatif d'excitabilité multirésolution. Les principales contributions de cette thèse sont les suivantes.

Nous identifions le rôle clé joué par *une boucle de feedback cellulaire pour la modulation et la robustesse des oscillations réseaux*. Les rythmes sont cruciaux pour le fonctionnement du cerveau mais leurs contrôles, régulations, et fonctions sont loin d'être compris. Dans un réseau avec inhibition mutuelle, nous isolons une propriété cellulaire essentielle—une boucle de feedback positive dans l'échelle lente—à maintenir au niveau réseau afin d'assurer des oscillations réseaux modulables et robustes.

Nous soulignons le rôle particulier qu'*une boucle de feedback cellulaire peut jouer dans la régulation des interrupteurs réseaux*. Nous identifions qu'une boucle de feedback positive apporte des propriétés de localisation, à la fois temporellement et spatialement, aux oscillations réseaux. Ces propriétés suggèrent un nouveau modèle réseau des ganglions de la base, valide dans l'état sain pour les oscillations liées au mouvement ainsi que dans l'état parkinsonien.

L'*excitabilité multirésolution* émerge dû aux propriétés de localisation des systèmes excitables : des fenêtres d'excitabilité de résolution différente sont superposées et interagissent, créant des systèmes multirésolutions. Dans chaque

fenêtre, le système est caractérisé par ses propriétés de transfert et par son comportement entrée-sortie. Des propriétés de traitement du signal apparaissent dans ces systèmes multirésolutions et dotent les objets multirésolutions de capacités de blocage et de multiplexage des signaux.

En résumé, cette thèse offre un nouvel aperçu de l'importance du couplage entre le niveau cellulaire et réseau. Le concept de motif multirésolution semble être général et non limité aux neurosciences. Enfin, l'exploitation du concept en technologies multirésolutions est suggérée.

Acknowledgements

A doctoral dissertation is a personal journey. However, this journey would have been impossible without the help and support from many people to whom I would like to express my sincere gratitude.

First and foremost, I heartily thank my advisor, Rodolphe Sepulchre, for his scientific enthusiasm and his ever pertinent guidance. I am very grateful to Rodolphe for his precious advice and support, both scientifically and personally. His permanent optimism and his passion for novelty in research succeeded in providing me with the motivation and self-confidence necessary to accomplish this journey. I am especially appreciative of the stimulating international work environment he established in Liège and Cambridge and his support and encouragements for my research stay in Princeton.

I am also indebted to my (former and present) colleagues. Many thanks to my friends and colleagues at the University of Liège. I enjoyed very much working and exchanging with them in a pleasant and friendly atmosphere. Special thanks go to Guillaume Drion for his sound advice and suggestions throughout this journey. I am also grateful to the team at Cambridge University for their warm welcome, help, and support during my research stays. Finally, I want to thank the team at Princeton University and especially Prof. Naomi Leonard for her guidance and the exciting work environment I benefited from during this past year.

I wish to express my sincere appreciation to the members of the Jury for devoting time and interest to the reading and evaluation of this manuscript. The members of the thesis committee are also acknowledged for their advices during the progress of this work.

I gratefully acknowledge the financial support from the Belgian National Fund for Scientific Research (FNRS), Wallonie-Bruxelles International, the Lear Foundation, and the Belgian Network DYSCO (Dynamical Systems, Control, and Optimization), funded by the Interuniversity Attraction Poles Programme, initiated by the Belgian State, Science Policy Office.

Last, but not least, my enormous gratitude goes to my family and friends. I owe my parents many thanks for their unconditional support and love which consistently pushed me to challenge myself. I am grateful to my sisters and family-in-law for helping me to disconnect from research when needed and offering me so many pleasant moments. I want to thank my friends, especially the ones who shared this journey with me at the University, for cheering me up when I needed so. Finally, my deepest gratitude goes to my loving, supportive, encouraging, and patient husband Thomas, whose faithful support has been, by far, the most precious encouragement. Having him by my side encourages me to undertake the most ambitious of the projects. Thank you.

Contents