Bridging the Gap between Mathematical Approaches and Biological Problems
Combler le fossé entre les approches mathématiques et problèmes biologiques
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LOÏS BOULLU, Université de Montréal
Building a model of delay-differential equations with state-dependent delay for megakaryopoiesis

Since the early work of M. C. Mackey and J. Bélair in the 80s [1], the intricate multiple feedbacks of megakariopoiesis (the process along which the platelets are produced) have been the source of many investigations in the field of delay differential equations.

In this talk I describe how an emphasis on TPO regulation and progenitor cells proliferation can lead to a model describing megakaryoiesis with system of delay differential equations, the delay being state-dependant and defined by threshold: using a tool from Smith [2], we transform this system into a fonctionnal differential equation with fixed delay, allowing us to explore wellposedness and fixed point stability.

1 Bélair J, Mackey M C (1987) "A model for the Regulation of Mammalian Platelet Production", Annals New York Academy of Sciences

2 Smith L H (1992) "Reduction of structured population models to threshold-type Differential equations and funtionnal differential equation : a case study" Mathematical Biosciences 113:1-23

ADÈLE BOURGEOIS, University of Ottawa
Overcompensatory dynamics in integrodifference equations

We consider integrodifference equations (IDEs), which are of the form

$$N_{t+1}(x) = \int K(x - y)F(N_t(y))dy,$$

where K is a probability distribution and F a growth function. It is already known that for monotone growth functions, solutions of the IDE will have spreading speeds and are sometimes in the form of travelling waves. We are interested in studying the case where F is a function with overcompensatory dynamics, i.e. p-point cycles can appear for certain parameter values, eventually leading into chaos. Such is the case for the Ricker function. This topic was first introduced in [Kot, 1992]. It was claimed that when F manifests a stable two-point cycle, the solution of the IDE alternates between two profiles, all the while moving with a certain spreading speed. However, simulations revealed that not only do the profiles alternate, but the solution is a succession of two travelling objects with different spreading speeds. Using the theory from [Weinberger, 1982], we can prove this and establish the theoretical formulas for the spreading speeds that exist within the different parts of the solution. Those results can then be compared with numerical simulations. The existence of successive travelling objects within a solution will also allow us to relate to the theory of dynamical stabilization in continuous systems.

[Kot, 1992] M.Kot. Discrete-time traveling waves: Ecological examples. *Journal of Mathematical Biology*, 30:413-436, 1986.

[Weinberger, 1982] H.F. Weinberger. Long-time behavior of a class of biological models. *SIAM Journal on Mathematical Analysis*, 13:353-396, 1982.

PAUL CISEK, University of Montreal
Inferring the dynamics of decision-making

During natural behavior, animals must continuously make decisions in a rapidly changing environment. Recent studies suggest that in such conditions, the brain simultaneously represents multiple potential actions that compete against each other within the same sensorimotor control circuits involved in execution. Here, I present analyses of neural spiking activity recorded from

the cerebral cortex of monkeys, while they decided between two reaching movements based on a changing stimulus indicating which is more likely to be rewarded. We represent the state of the system as an evolving trajectory in a very high-dimensional space where each axis corresponds to the activity of one neuron, and use dimensionality reduction to project this to a 9-dimensional space capturing most of the variance in the data. We find that during the process of deliberation, the neural state evolves upon a roughly two-dimensional "decision manifold" defined by orthogonal components related to sensory evidence and the growing urge to respond. The moment of commitment occurs when the neural state falls off the edge of this manifold into one of two orthogonal attractors that lead to the initiation of the movements. We find qualitatively different decision manifolds in different brain regions. For example, the manifold in premotor cortex is significantly curved while in primary motor cortex it is remarkably linear. We conjecture that the premotor cortex implements a non-linear recurrent attractor system in which the decision is made, and this is read-out by the primary motor cortex to initiate the chosen action.

ERIK COOK, McGill University
Temporal tuning of the nonlinear input/output properties of biological neurons

We applied a systems-identification approach to quantitatively describe the nonlinear behavior of biological neurons. Dendritic membrane potentials were recorded from pyramidal neurons in mouse prefrontal cortex in response to either small (subthreshold) or large (suprathreshold) white-noise current injections. Convolving the small current injection with a linear filter fully accounted for the dendritic membrane potential. The filters were relatively fast, with an initial exponential-like decay followed by an undershoot that produced a resonance. The large suprathreshold injections produced both somatic action potentials (spikes) and dendritic spike-like nonlinearities. Deconvolution was used to isolate the nonlinear components from the linear response. The results of the deconvolution revealed nonlinear inward current spikes, that when added to the white-noise current injection, accounted for all of the dendritic membrane potential. We modeled the isolated dendritic spikes using a second linear spike-filter followed by a static nonlinearity. When convolved with the large stimulus, the spike-filter/nonlinear cascade described both the dendritic spike amplitude and the time that each dendritic spike occurred. In comparison to the filters that described the linear membrane potential, the dendritic spike-filters were much faster. The shape of the spike-filter suggests that dendritic nonlinearities are tuned to the temporal properties of fast inward current events such as synaptic inputs.

ERIC CYTRYNBAUM, University of British Columbia
Modelling the biochemistry of spatiotemporal pattern formation in bacteria

The Min proteins, MinC, MinD and MinE, form an important spatial regulator of cell division in bacteria where they interact on the membrane to generate an oscillatory spatially alternating pole-to-pole localization. Spatial pattern formation has recently been reconstituted in vitro on flat supported membrane and in cell-shaped micro-fabricated chambers. Traveling waves and spiral waves on supported membrane and in vivo-like oscillations in cell-shaped chambers have been observed. In this talk, I will present the results of our recent work on modelling the biochemistry of this system. We have formulated a general model based on interactions that have been recently proposed in the literature and have used the available data to find optimal parameter values. By selectively removing terms and repeating the fitting procedure, we are able to test the importance of various biochemical interactions for fitting the data and gain insight into the geometry of the protein interactions. I will also describe the novel parameter fitting protocol which we developed for the problem at hand.

ELDON EMBERLY, Simon Fraser University
Operational principles of a molecular lawnmower

In many bacteria there is an active process that is responsible for the segregation of genetic material after replication. It is driven by a two protein system that functions like a molecular lawnmower; one protein acts as a substrate that gets processively removed by the other protein. Amazingly, recent experimental work has shown that this system can be reconstituted outside the cell, yielding a functional in vitro molecular machine. In this talk I will present a deterministic model for the in vitro system, showing how noise in the initial conditions is sufficient to lead to the spontaneous formation of a gradient in the substrate concentration that drives directed motion. Our model predicts that the system possesses an optimal speed that depends on the range of the force to the range of substrate removal. When we allow for the removed substrate to recover, two dynamical

regimes exist and we predict that it should be possible to observe persistent acceleration in one and the ability to stall the system in the other. We suggest experiments using the in vitro system that could test these predictions.

MARIE-JOSÉE FORTIN, University of Toronto
Spatial, directional, and spatio-temporal network algorithms in ecological studies

Given current climate and land use change, species movement in intensively human-modified landscapes is impeded by landscape cover types as well as the distances among remnant habitat patches. It is important to determine to what degree habitat patches scattered throughout the landscape may function as stepping stones facilitating dispersal among otherwise isolated habitat. To this end connectivity metrics can be used; however, such metrics do not account for species abundance and population dynamics that also affect species dispersal and persistence. Hence one needs to model the spatio-temporal dynamic of population dynamics (demography), dispersal (connectivity), and the directionally of species migration. Here I present how network theory (1) can be spatialized, (2) can account for the number of dispersing individuals and long-distance dispersal processes across generations, (3) can be directional, and (4) can measure spatio-temporal connectivity. I illustrate how these methods can be used to investigate species range expansion (Black Woodpecker, Spain), spread of vector-borne disease (Lyme disease, Ontario), and forest dynamics. I show that the loss of intermediate and large stepping-stone habitat patches can cause a sharp decline in the distance that can be traversed by species (critical spatial thresholds). Yet the presence of stepping-stone habitat is critical for short- and long-distance invasion of both the tick vector and the pathogen by mice and deer. Last, I show that the impact of land use changes on species dispersal can be modelled using novel spatio-temporal network algorithms.

PAUL FRANCOIS, McGill University
Phenotypic spandrel: absolute discrimination and ligand antagonism

Recent works in quantitative evolution have shown that biological structures are constrained by selected phenotypes in unexpected ways . This is also observed in simulations of gene network evolution, where complex realistic traits naturally appear even if they have not been explicitly selected . An important biological example is the absolute discrimination between different ligand "qualities", such as immune decisions based on binding times to T cell receptors (TCRs) or FcεRIs. In evolutionary simulations, the phenomenon of absolute discrimination is not achieved without detrimental ligand antagonism: a "dog in the manger" effect in which ligands unable to trigger response prevent agonists to do so. A priori it seems paradoxical to improve ligand discrimination in a context of increased ligand antagonism, and how such contradictory phenotypes can be disentangled is unclear. Here we establish for the first time a direct mathematical causal link between absolute discrimination and ligand antagonism. Inspired by the famous discussion by Gould and Lewontin, we thus qualify antagonism as a "phenotypic spandrel": a phenotype existing as a necessary by-product of another phenotype. We exhibit a general model for absolute discrimination, and further show how addition of proofreading steps inverts the expected hierarchy of antagonism without fully cancelling it. Phenotypic spandrels reveal the internal feedbacks and constraints structuring response in signalling pathways, in very similar way to symmetries structuring physical laws.

TARIK GOUHIER, Northeastern University
Ecosystem-based management in a complex and interconnected world

Ecosystem-based management has emerged as an important holistic approach for promoting the health, functioning, and resilience of exploited marine ecosystems. However, its application is fraught with difficulties due to the complex and interconnected nature of real systems. Here, I use a spatially-explicit predator-prey model to show that ecosystem-based management via reserve networks can achieve optimal results for trophically-coupled species when they undergo unpredictable dynamics but not when they reach a stable equilibrium. This "paradox of predictability" suggests that ecosystem-based management may be more broadly applicable in nature than previously thought.

To determine whether these results hold for more complex ecosystems that are coupled by both organisms and material, I develop a spatially-explicit meta-ecosystem model to understand how reciprocal feedbacks between local ecosystems affect the optimal allocation of reserves to manage an herbivorous fish-macroalgae-coral community. I show that there is a trade-off between local and regional conservation objectives when designing reserve networks: Small and aggregated reserves based on the extent of

dispersal maximize the abundance of corals and herbivores regionally, whereas large and isolated reserves always maximize the abundance of corals within reserves, regardless of the extent of dispersal. The existence of such "conservation traps", which arise from the fulfillment of population-level objectives within local reserves at the cost of community-level objectives at regional scales, suggests the importance of adopting a more holistic strategy to manage complex and interconnected ecosystems.

JANE HEFFERNAN, York University
Waning immunity and epidemiological outcomes

A goal in the control of infectious diseases is to generate herd immunity, the level of immunity needed in a population to effectively protect everyone (vaccinated and vaccinated). Immunity is generated from infection and vaccination, but immunity can also wane over time. We have studied the effects of waning immunity with changing demographics and seasonal forcing. An array of periodic solutions can be generated from such models, and chaos. We will discuss implications in mathematical modelling and public health control.

GARY HUANG, McGill University
Fractional differentiation in pyramidal neurons enable power-law adaptation to natural sensory stimuli

The understanding of how neural circuits perform key computations underlies the fundamental knowledge of how cellular machinery leads to neural network activity, which in turn determines perception/behavioral responses. Several studies have shown that neural coding strategies in many sensory systems are adapted to natural scene statistics to efficiently encode sensory stimuli as well as to maximize redundancy reduction in spatiotemporal correlations. Despite this, the molecular and/or computational mechanisms underlying such optimal adaptation remain elusive. Here we investigated how small conductance calcium-activated potassium (SK) channels contribute to optimizing neural coding and perception of natural second-order envelopes, which are found ubiquitously across sensory systems and carry important spatiotemporal information necessary for perception. In order to do so, we used the electrosensory system of the gymnotiform weakly-electric fish Apteronotus leptorhynchus as a model for its unique advantages for in vivo awake-behaving experiments. We recorded from sensory pyramidal neurons in the electrosensory lateral line lobe (ELL) in response to natural stimuli and demonstrated that these neurons perform fractional differentiation in order to give rise to power-law adaptation, leading to optimal encoding of a continuous range of envelope frequencies. Our results further reveal a novel function of SK channels in that they provide the fundamental bio-computational mechanism which enables optimal neural processing and behavioural perception to natural stimuli. The strong homology between SK channels and the weakly-electric fish to their mammalian counterparts suggest that it is very likely that our results will be generally applicable across systems and species.

ANMAR KHADRA, McGill University
Parabolic and irregular bursting in GnRH neurons: A modeling investigation

The release of gonadotropin-releasing hormone (GnRH) by synchronized GnRH neurons is required for fertility in all vertebrates of both sexes. The pulsatile release of this hormone has been hypothesized to depend on the intrinsic electrical activities of these neurons, which includes two endogenous modes of action potential burst firing: the parabolic and irregular bursting. The first mode is characterized by a slow wave in membrane potential that can underlie periodic clusters of action potentials with a spike-frequency that is parabolic (i.e., biphasic), whereas the second is characterized by clusters of action potentials that are separated by varying durations of interburst intervals and a relatively stable baseline potential. We have recently developed a stochastic Hodgkin-Huxley type model to explain how each mode of burst firing is produced based on differences in ion channel conductances. In this talk, I will present this model and demonstrate its agreement with experimental data. I will then show, using bifurcation analysis, that although the two modes of burst firing differ in their burst characteristics, they are both topologically equivalent, and that the latter exhibits more sensitivity to noise because it is closer to the firing threshold (a SNIC bifurcation).

LAURENT MACKAY, McGill University
Deciphering the allosteric modulation of the purinergic P2X receptors using Markov models

The family of Purinergic P2X receptors are ligand-gated cation channels which are affected by a number of allosteric modulators. Inducing conformational changes throughout the whole protein, allosteric modulators modify the efficacy and potency of a receptor's orthosteric ligands. We briefly review the literature of mathematical models of P2X receptors and develop modelling paradigms for allosteric modulation of orthosteric systems based on previous models of P2X receptors and the experimental protocols that they depend on. Furthermore, we analyze in detail allosteric modulation of P2X4 receptors by the pharmacological agent Ivermectin and present two plausible types of models. Using an MCMC methodology, we compare the models and the mechanisms by which they reproduce experimental data, concluding that sensitization and desensitization of receptors are not independent of each other, and that the later can occur subsequent to the former. To capture this behaviour, we develop a two layer Markov model that is more compatible with our understanding of allostery and experimentally observed data. Finally, we discuss the possibility that this two layered model represents a shared mechanism governing the dyanmics of all P2X receptors.

JUSTIN MARLEAU, Champlain College Saint-Lambert
From Mechanism To Model: Functional Forms in Nutrient Colimitation

The nutrient limitation status of primary producers and other organisms in ecosystems is of increasing importance as human activities continue to alter the relative abundances of nutrients in ecosystems. In recent studies, there has been growing evidence of multiple nutrients being limiting rather than just one, causing ecologists to search for mechanisms to explain these patterns and to try new functional forms in models to obtain nutrient colimitation. However, I will show in this lecture that how the mechanisms are translated into functional forms can result in large differences in ecosystem dynamics and functioning. This result suggests that greater care must be taken in the formulation of models such that they accurately reflect the mechanisms in the field.

CHRIS PACK, McGill University
Patterns of oscillations in the visual cortex

Electrical signals recorded from the brain are often observed to be oscillatory. Indeed the strongest known neurophysiological signal is the alpha oscillation, a 10 Hz signal that correlates in amplitude with visual stimulation and attentiveness. The role of oscillations at higher frequencies is hotly debated: Different models assign them different functions, such as object recognition, attention, interval timing, etc. Other models hypothesize that high-frequency oscillations are incidental consequences of brain connectivity, and that they have no function at all.

In this presentation I will focus on the beta oscillation, which corresponds to frequencies near 20 Hz. I will show that beta oscillations are a prominent feature of the monkey visual cortex, but that, when measured on a small spatial scale (hundreds of microns), they carry little information about visual stimuli or visually-guided behaviors. However, patterns of oscillations, distributed across several millimeters of visual cortex, exhibit interesting properties. In particular, I will show that beta oscillations frequently reorganize their relative phases to form a traveling wave of activity that sweeps across the cortical representation of visual space. This wave is triggered by eye movements, and it controls the timing of responses from individual neurons. I will speculate that these waves are responsible for some previously unexplained aspects of visual perception during eye movements.

PEDRO PERES-NETO, Université du Québec à Montréal
Spatial pattern detection in genetic data

Landscape genetics studies using neutral markers have focused on the relationship between gene flow and landscape features. Spatial patterns in the genetic distances among individuals may reflect spatially uneven patterns of gene flow caused by landscape features that influence movement and dispersal. We present a method for identifying spatial patterns in genetic data that adopts a regression framework where the predictors are generated using Moran's eigenvectors maps (MEM), a multivariate technique developed for spatial ecological analyses and recommended for genetic applications. Using simulated and real genetic data, we show that our MEMGENE method can recover patterns reflecting the landscape features that influenced gene flow. We developed the MEMGENE package for R in order to detect and visualize relatively weak or cryptic spatial genetic patterns

and aid researchers in generating hypotheses about the ecological processes that may underlie these patterns. MEMGENE provides a flexible set of R functions that can be used to modify the analysis.

GEOFF WILD, The University of Western Ontario
A simple method of modelling animal behaviour and an application

Evolutionary biologists are interested in understanding the adaptive significance of cooperation. I will briefly introduce a perturbation approach that can be used to model the evolution of social behaviours like cooperation. The approach, itself, is mathematically straightforward and is amenable to interpretation in terms of concepts familiar to biologists. I will apply the approach to study a particular question about competition and cooperative breeding in animals that has been of concern to biologists. I will demonstrate that competition within breeding groups may not be a hindrance to the emergence of cooperation, as previously thought. I will also show that, in a sense, competition within groups may actually correspond to a boon for cooperative breeding.