

ESF Exploratory Workshop on Computational disease Modeling

A joint workshop ESF-CRM

Institut d'Estudis Catalans
September 24 to 26, 2008



Carrer del Carme, 47
08001 Barcelona
Contact phone number: 93 581 40 86 (CRM)
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<http://www.crm.cat/DISMOD>

Programme

(abstracts below)

Wednesday, September 24

14:00-14:30	Albert Compte	Welcome and introductory remarks. Brief presentation of ESF activities.
14:30-15:10	Mikael Benson	What do clinical researchers want from modelling and systems biology?
15:10-15:50	Jesper Tegnér	Bridging the gap – challenges and possibilities
15:50-16:20	Coffee Break	
16:20-17:00	Jean-Pierre Boissel	Systemic Physiopathology: why and how?
17:00-17:40	Gunnar Cedersund	Progress and challenges in systems biology studies of type II diabetes
17:40-18:20	Discussion: General objectives and challenges – Round table	
18:20-19:00	Cheese and wine reception	
20:00	Dinner	<i>Detailed information on the social activities is given below</i>

Thursday, September 25

9:00-9:40	Marta Cascante	A Systems Biology approach to multifactorial diseases
9:40-10:20	Zoltan Oltvai	Disease networks
10:20-10:50	Coffee Break	
10:50-11:30	Fazoil Ataullakhanov	Mathematical modeling of the metabolism and viability of red blood cells as a tool to study the mechanisms of hereditary hemolytic anemia.
11:30-12:10	Jörg Stelling	Robustness and intervention in cellular networks
12:10-12:40	Discussion: Focus on molecular pathways	
12:40-14:30	Lunch	
14:30-15:10	Charles Auffray	Combining transcriptome analysis, functional annotation and systemic modeling to decipher the cellular states of innate tumor drug responses
15:10-15:50	Gary An	An Agent-Based framework for Integrative Dynamic Representation of Biomedical Knowledge: Towards an Ecological Paradigm for Collaborative Research
15:50-16:20	Coffee Break	
16:20-17:00	Johan Björkegren	The nature of atherosclerosis – are networks and modelling feasible to learn more?
17:00-17:40	Randall Thomas	Collaborative multi-scale modeling of blood pressure regulation and fluid homeostasis
17:40-18:10	Discussion: Multilevel integration	
19:00-21:00	Guided tour around the Barcelona Gothic Quarter	
21:00	Dinner (approximate time as dinner will begin when participants arrive from their tour)	

Friday, September 26

9:00-9:40	Pablo Villoslada	Computational modelling of the immune system for understanding autoimmune diseases and immunotherapies
9:40-10:20	Boris Gutkin	Computational Models of nicotine Addiction: from circuit dynamics to behavior
10:20-10:50	Coffee Break	
10:50-11:30	Klaas Enno Stephan	Towards neurocomputational models for investigating and diagnosing psychiatric diseases

11:30-12:10	Albert Compte	A systemic modeling approach to the pathophysiology of atherosclerosis
12:10-12:40	Discussion: Focus on cellular population modeling	
12:40-14:30	Lunch	
14:30-15:10	Gilles Clermont	Biological variability and in silico design of interventional clinical trials
15:10-15:50	Gustavo Deco	Statistical Fluctuations in Attractor Networks Related to Schizophrenia
15:50-16:20	Coffee Break	
16:20-17:00	Ricard Solé	Cancer as a critical system: catastrophes and breakpoints in genetically unstable tumors
17:00-17:40	Mats Gyllenberg	Evolutionary aspects of human diseases
17:40-18:10	Discussion: Focus on systemic and abstract modeling	
18:10-19:30	Final discussions and follow up activities	
21:00	Dinner	

Practical information

Lecture room: The Workshop will take place in the "Nicolau d'Olwer" conference room at the Institut d'Estudis Catalans, IEC, in downtown Barcelona. See map and directions at the end of the document.

Address:

Institut d'Estudis Catalans (IEC)
 C. del Carme, 47
 08001 Barcelona
 Tel.: + 34 93 270 16 20
<http://www.iec.cat>

CRM Administration: The CRM will provide Administration assistance at the IEC during the Workshop. If you need assistance at other times please call Ms. Neus Portet at the CRM at 935814086 (office hours).

Lodging arrangements: Lodging arrangements have been made at:

Residència d'Investigadors
 C. Hospital, 64
 08001 Barcelona
 Phone: + 34-93443 86 10

A list with the participants and their lodging arrangements is posted on the Workshop's web page. Please, check yours and contact us as soon as possible if you need to make any changes.

Details for reimbursements: Please, make sure to give us the documents/information below so that we can prepare your payment/reimbursement:

Copy of passport
Full personal address
Copy of airplane ticket (in case you have bought it yourself)
Full bank information

Breaks: Coffee and cookies will be served during the morning and afternoon breaks.

Meals: For practical reasons we have arranged fixed menus with the different restaurants. If a participant has dietary special needs she/he can talk to the Secretary to arrange it accordingly.

Daily social programme

Wednesday, September 24

- Cheese and wine reception: at the IEC at the end of the last afternoon's session.
- Dinner: At the Gran Cafè restaurant (C. Avinyó, 9) at 21:00. The restaurant is located at walking distance from both the IEC and the Residència d'Investigadors. Participants will meet at the Residència d'Investigadors reception hall at 20:35 to walk together to the Restaurant at that time. If you wish to go by yourself check the map provided or ask the Secretary for directions.

Thursday, September 25

- Lunch: At the Antic Forn restaurant at 13:00 (carrer Pintor Fortuny 28). See map below.
- Guided visit through the Barcelona Gothic Quarter: the visit will begin at 19:00 (sharp) from the IEC front door and walk through the Gothic Quarter to the restaurant where dinner will be served. The group will leave exactly at 19:00, so please make sure to be there on time. Comfortable shoes are highly recommended. Inform the CRM Secretary if you are not going to attend.
- Dinner: At the Chipiron restaurant (Moll Espanya, 5-6) at 21:00 (approximate time). Ask the Secretary for directions if you intend to go by yourself.

Friday, September 26

- Lunch: At the Antic Forn restaurant at 13:00 (carrer Pintor Fortuny 28). See map below.
- Dinner: At the La Provença restaurant (C. Provença, 242) at 21:00. The Restaurant is located at about ½ hour walking distance from both the IEC and the Residència d'Investigadors. Participants will meet at the Residència d'Investigadors reception hall at 20:25 to go together to the Restaurant. If you wish to go by yourself check the map provided or ask the Secretary for

directions. You can take public transportation to go there. Take the FGC train from "Plaça Catalunya" to "Provença" station.

Note on the social activities:

The CRM Secretary can give you a copy of the menus to be served. Talk to the CRM Secretary if you wish to bring a companion or have dietary special requirements.

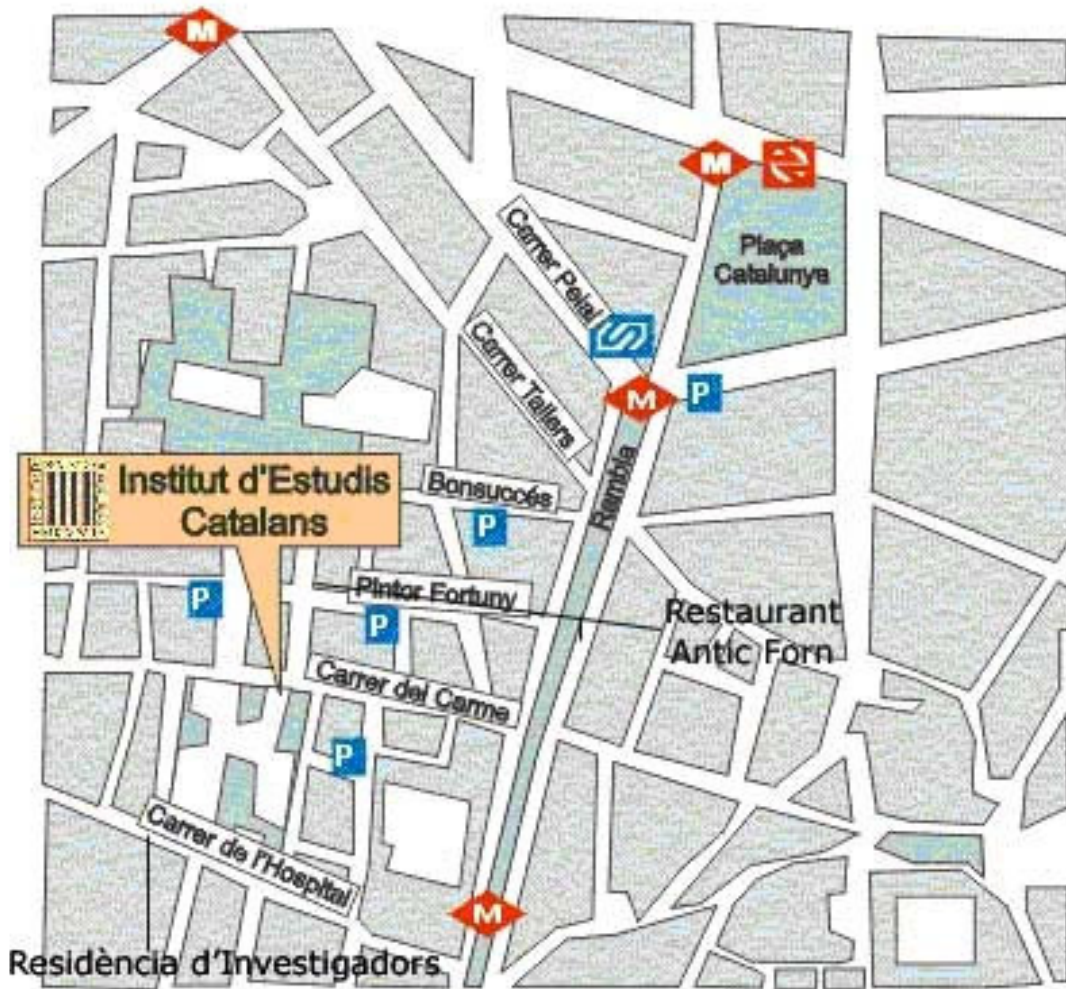
Picture: A group picture will be taken on Thursday, September 25 before the morning coffee break. The picture will be posted on the Workshop's web page.

Questionnaire: Following the directions of the CRM Governing Board, we give a questionnaire to all the people participating in activities at the CRM in order to assess their level of satisfaction. The questionnaire is anonymous and not mandatory, but we would greatly appreciate it if you could answer the questions and return it to us before you leave. Thank you for your cooperation.

List of participants:

An, Gary	Northwestern University Feinberg School of Medicine
Ataullakhanov, Fazoil I.	National Hematology Research Center
Auffray, Charles	CNRS
Benson, Mikael	Göteborgs University
Björkegren, Johan	Karolinska Institute
Boissel, Jean-Pierre	Université de Lyon
Cascante, Marta	Universitat de Barcelona
Cedersund, Gunnar	Fraunhofer-Chalmers Centre for Industrial Mathematics
Clermont, Gilles	University of Pittsburgh
Compte Braquets, Albert	Hospital Clínic - IDIBAPS
Deco, Gustavo	Universitat Pompeu Fabra
	Département d'Etudes Cognitives (DEC) at Ecole Normale Supérieure (ENS)
Gutkin, Boris S.	University of Helsinki
Gyllenberg, Mats	SCAIF
Oltvai, Zoltan N.	Universitat Pompeu Fabra
Solé, Ricard	ETH Zürich
Stelling, Jörg	University of Zürich
Stephan, Klaas Enno	Linköping University
Tegner, Jesper	IBISC
Thomas, Randall S.	Universidad de Navarra
Villoslada, Pablo	

Map showing the Institut d'Estudis Catalans, Residència d'Investigadors and the Restaurant where lunch will be served.



Abstracts (ordered alphabetically)

Gary An

Title

An Agent-Based framework for Integrative Dynamic Representation of Biomedical Knowledge: Towards an Ecological Paradigm for Collaborative Research."

Abstract

The hierarchical structure of biological systems is well recognized. The existence of these hierarchies presents significant challenges for the translation of mechanistic research results from one organizational level to another. Furthermore, the research community itself remains relatively compartmentalized, leading to barriers to communication and adding an additional challenge to the synthesis of basic science data into a unified whole. There is a general need within the biomedical research community to be able to dynamically represent the state of its knowledge in order for it to "know what it knows." Agent Based Modeling (ABM) is a simulation technique that is well suited for the dynamic representation of researchers' conceptual models in order to facilitate the verification of those models. ABM maps well to the hierarchical organization of biological systems, and by utilizing the principles of population behavior provides a means of integration and translation of knowledge across organizational scales. A series of ABMs of acute inflammatory processes developed at multiple levels of resolution will be presented, extending from intracellular signaling leading up to simulated organ function and organ-organ interactions. These models can be viewed as dynamic representations of conceptual models at various scales, and can aid in the determination of the plausibility of those models: i.e. conceptual model verification. This process can facilitate the translation of biomedical knowledge both "vertically" across these scales and "horizontally" across the research community, creating a community-wide "knowledge ecology" and aiding in the evolution of community knowledge.

Fazoil I. Ataullakhanov

Title

Mathematical modeling of the metabolism and viability of red blood cells as a tool to study the mechanisms of hereditary hemolytic anemia.

Abstract

In my lecture I will address several questions that pertain to modelling of different diseases:

1. What is a disease from the mathematical point of view?
2. Complex and simple models: how do they relate to each other?
3. Why so many enzymes have redundant activities in the cell?

In answering these questions I will use the results of my lab's research of erythrocyte's metabolism as an example. Many of the hereditary hemolytic anemia are caused by a paradoxically small (5-10 fold) decrease in the activities of certain erythrocyte enzymes. The impact of these small changes is surprising because in healthy red blood cells the activities of many enzymes often exceed what is required for a normal metabolic flux by 10^3 - 10^4 times. It would seem that the residual activity of these enzymes should still be enough for normal functioning of the metabolic pathways, but this is not the case and such patients have usually a high rate of the erythrocytes death. Furthermore, there is no correlation between the level of enzyme activity in the patient's blood and the severity of anemia.

To try to understand this paradox we used a simple mathematical model of a chain metabolic pathway and found that the 10-fold decrease in the activity of an enzyme that has a 10^4 -fold excess in its activity in normal metabolism, should not have affected the metabolic flux. We then used a rather complex mathematical model, which included all major metabolic networks that are important for erythrocyte's viability, and arrived at the same conclusion. With these models we calculated a threshold activity of some of these enzymes that would result in cell's death and found that it was $>10^3$ times lower than in patients blood. We then hypothesized that mutant form of an enzyme was less stable and this enzyme had a shorter lifetime. With this assumption, model results corresponded well with clinical data, and it helped us to explain why the severity of anemia does not depend on a mean enzyme activity in blood. The model predicted that it should correlate with the rate of enzyme inactivation. Consequently, it was found that the mutant forms of some of these enzymes had decreased resistance to different denaturants, in agreement with model's predictions.

Charles Auffray

Title

Combining transcriptome analysis, functional annotation and systemic modeling to decipher the cellular states of innate tumor drug responses

Abstract

I will use one of our landmark studies on cancer (Graudens et al. 2006) to illustrate the use of different types of mathematical tools at successive steps of an integrative systems biology research strategy. First, I will discuss how the iterative use of statistical power assessment enabled us to account for experimental and biological variations and limit false positive and negative results. Second, I will emphasize the use of a diacyclic graph representation of hierarchical functional relationships, combined with statistical enrichment analysis to identify relevant biological pathways involved. Third, I will discuss the initial steps taken in building SBM-encoded graphical representations of the cellular states characteristic of patients who respond or resist upon exposure to chemotherapy, as a basis for future kinetic modeling. Finally, recognizing that multi-scale integration from molecules to organs represents a major challenge in systems biology because the formal tools used at each biological level are often based on distinct or even incompatible principles, I will briefly introduce the mathematical and physical framework based on scale relativity theory that we have developed to overcome the anticipated limitations (Auffray and Nottale; Nottale and Auffray, 2008).

Refs: Graudens et al. (2006) *Genome Biol.* 7, R19. Auffray and Nottale; Nottale and Auffray (2008) *Prog. Biophys. Mol. Biol.* 97, 79-114 and 115-157.

Mikael Benson

Title

What do clinical researchers want from modelling and systems biology?

Abstract

Complex diseases like allergy, diabetes and cancer are each caused by altered interactions between multiple genes and environmental factors. On top of this complexity there are individual variations in both genetic and environmental factors. The causal role of such factors may change over time. Thus, two patients that appear to have the same disease may represent different pathogenic mechanisms. A common clinical consequence is variable response to treatment.

This causes both increased suffering and costs. Ideally, it would be possible for clinicians to personalize medication based on genomic or proteomic fingerprinting.

These problems are very difficult to address using "reductionist" approaches. Instead, combining high-throughput technologies, modelling and systems biology may lead to practical solutions to clinical problems. The talk will discuss examples of this, as well as problems, questions and future possibilities seen from a clinical researcher's perspective.

Johan Björkegren

Title

The nature of atherosclerosis – are networks and modelling feasible to learn more?

Abstract

In the era of functional genomics there is much hope that whole-genome data coupled to genetic screens of hundred thousands of single nucleotide polymorphisms will be helpful to dissect regulatory genes and interplay of pathways in networks leading to atherosclerosis. However, the flora of different cell types and mixture of reactive and causative molecular changes make this task challenging. What can we learn from profiling patients carrying the disease and what is the use of animal and cell model systems? Can computational modelling help to fill in the gaps?

Jean-Pierre Boissel

Title

Systemic Physiopathology: why and how?

Abstract

Systems biology has been devised to tackle the barrier of complexity in life science. Beyond the complexity issue, numerical modelling has been introduced in physiopathology and therapeutic research because of the decreasing innovation efficiency in therapeutics and the growing difficulties for physicians to make optimal treatment decision for a given patient through combining the many available modestly efficacious treatments. Altogether, these two worrying developments result in a lost of chance for patients when compared to the amount and quality of available knowledge. The ultimate goal of "in silico" models in physiopathology is to improve health. Through designing numerical models of a disease and running computer simulations, we expect a better understanding of the links between its various components, weighting the respective influence of its various factors, deciphering new and more relevant targets for innovative medicines and a quicker way of testing a new therapeutic intervention at the very beginning of its development, before a sizeable amount of resources has been invested (early proof of concept). Altogether, these developments should result in improving the way new therapies are discovered and in providing doctors with tools predicting the outcome of combining therapies. Also, following the introduction of a patient parameter values into the numerical models of his/her disease and of all the available therapies, a reasonable choice among all the alternatives and their combinations would be facilitated. Actually, in terms of complexity, physiopathology is far beyond system biology. Disease mechanisms are much more complex than anything else. The main reason is that a disease develops throughout a diversity of levels, from gene expression up to population, whereas system biology limits itself at a couple of levels, molecules and cell, sometimes a population of cells. The tissue level is seldom accounted for, and neither physiology

nor anatomy is paid attention to. Diseases encompass several piled up organisational levels of complex phenomenon, from genes to population. Time scales vary from nanosec to several decades, with for the former scale chemical interactions and evolution to clinical events for the later. In chronic diseases, such as cancer or atherosclerosis, the sequence of events at the molecule, cell, tissue and target organ levels takes decades to achieve in death or myocardial infarction. In addition, new knowledge is emerging at high rate: data from clinical research is coming in on top of evolving biological knowledge. This observation has three consequences: i) the ever extensive amount of knowledge one should incorporate in a numerical model of disease; ii) the need of a careful knowledge management tool; iii) models should be conceived flexible enough in order to integrate any new relevant knowledge. In addition, beyond pure science, numerical modelling of diseases is science applied to improving care to patients. As a consequence, the researcher should pay attention to both quality and transparency. For ethical reason, the former is compulsory, whereas the later is required by regulators. Actually, regulations are already mandatory, and one can bet they will be even more stringent in the future in order to protecting consumers. Models and processes which they are part of should comply with the regulations. All this makes modelling in physiopathology different. It explains why an appropriate strategy and relevant methodologies are needed.

Marta Cascante

Title

A Systems Biology approach to multifactorial diseases

Abstract

Several techniques as DNA sequencing, expression arrays, and proteomic and metabolomic experiments have provided us a large amount of new information that cannot be easily interpreted. The integration of all these *in vivo* information in models is likely to be the most interesting tool to understand and to complete an overview picture of the cellular processes. Metabolic profile is the end point of the signaling events, where changes caused by diseases may be reflected. Using data from the different -omics, incubation with ¹³C labeled substrates and isotopomer analysis in selected metabolite pools, and appropriate software developed in our laboratory to estimate dynamic flux distribution among the metabolic network we are able to identify the main steps that control a metabolic pathway, which may be used as new therapeutical targets. We are applying this approach to understand metabolic adaptations accompanying different multifactorial diseases as cancer, diabetes and chronic obstructive pulmonary disease (COPD). Applying these strategies we identify the maintenance of pentose phosphate cycle oxidative and nonoxidative unbalance to be critical for cancer cell survival and vulnerable to chemotherapeutic intervention. Additionally, we used Metabolic Control Analysis (MCA) to identify the main enzymes controlling ribose-5-P synthesis and to plan combined target strategies. Finally, we validated the obtained strategies using specific inhibitors. This strategy results of great interest in imminent applications for the study of other multifactorial diseases. In particular, we are applying this strategy to achieve a better understanding of glucose metabolic network to design interventions at a metabolic level in diabetes and COPD. This new principle for rational drug design originates from the integrative, systems biology approach of understanding cell function and opens new ways to develop novel treatments for diseases as diabetes or COPD.

This work was supported by funds of the Ministerio de Ciencia y Tecnologia of the Spanish Government (SAF2005-01627) and AGL2004-07579-C04-03/ALI); European Comission (FP6) BioBridge LSHG-CT-2006-037939; The ISCIII-RTICC (RD06/0020/0046) from the Spanish government and the European Union FEDER;

and the Comission d'Universitats i Recerca de la Generalitat de Catalunya (SGR00204).

Gunnar Cedersund

Title

Progress and challenges in systems biology studies of type II diabetes

Abstract

The first aspect of this talk deals with some important methodological challenges that most systems biology studies have to face. These challenges are due to the large complexity of the studied systems, especially with respect to the available information in the data. This problem implies that many model predictions are the result of arbitrary choices on large parameter manifolds, even though the imulation-data agreement is good. However, some model properties are not arbitrary, but can be uniquely identified also in over-parametrized models. We denote those properties core predictions, and look at two paths for their identification: one through model reduction and identifiability analysis, and one through modifications of global optimization algorithms.

The second aspect of the talk deals with type II diabetes. This disease is a systems property, and can not be understood as the malfunction of a single gene or interaction. For this reason, systems biology approaches are suitable, if not necessary. We will look at some recent developments in the characterization of the insulin signalling network, and see how modelling has been used to characterize some of its systems properties, such as overall time-scales, the relative contribution of feedbacks etc.

I will also talk about the recent developments towards a hierarchical model for glucose homeostasis, which attempts to integrate insights and models on the cellular and organ levels, into models and insights on the whole-body level, the level where the disease occurs.

Gilles Clermont

Title

Biological variability and in silico design of interventional clinical trials

Abstract

Appropriate characterization of inter-individual variability poses serious challenges to the design of reliable simulations of clinical trials. The objectives of this lecture are to explore quantitative approaches to this characterization and to present recent clinically relevant implementations illustrating such approaches.

Albert Compte

Title

A systemic modeling approach to the pathophysiology of atherosclerosis

Abstract

Experimental methods have made great progress recently but they are still inadequate to achieve a complete mechanistic understanding of complex diseases. Computational methods can be useful to integrate data from different levels and formulate distinct mechanistic alternatives.

We will present here a computational approach to atherogenesis in the arterial wall. The model is defined based on the known interactions between relevant molecules and cells during atherogenesis, leaving the kinetic parameters undefined. The model is then constrained based on available lesion data from a mouse model of atherosclerosis (Skogsberg et al., PLoS Genetics, 2008). Using optimization algorithms and simulation power, we address how much these constraints specify model behavior and mechanisms, and how this modeling approach can integrate gene data from this mouse model.

Gustavo Deco

Title

Statistical Fluctuations in Attractor Networks Related to Schizophrenia

Abstract

We present a hypothesis of how the positive, negative, and cognitive symptoms of schizophrenia could be related to alterations in the stability of cortical networks which lead to a reduced signal- to-noise ratio. We analyze using integrateand- fire simulations of attractor networks how some of the symptoms of schizophrenia could be related to a reduced depth of basins of attraction, produced by for example a decrease in the NMDA receptor conductances, and to statistical fluctuations caused by stochastic spike firing of neurons.

Both of these processes contribute to instability in short term memory, attentional, and semantic neuronal networks.

Boris Gutkin

Title

Computational Models of nicotine Addiction: from circuit dynamics to behavior

Abstract

Smoking, a compulsive behavior that can be characterised as addiction, remains a salient public health problem. Nicotine is the major addictive substance in tobacco smoke. While much is known about nicotine's molecular targets as well as its effects at the receptor, cellular and behavioural levels, the precise mechanisms by which such effects are linked remain elusive. We take a neurodynamical perspective on the problem developing two complimentary modelling approaches.

The first is a hypothetical model of nicotine self-administration that combines a set of neural circuits at the molecular, cellular and system levels and accounts for several neurobiological and behavioural processes leading to nicotine addiction. We propose that combining changes in the nicotinic receptor response at the dopaminergic neurons in the ventral tegmental area (VTA), with dopamine-gated learning in action- selection circuits, suffices to capture the acquisition of nicotine self-administration. We show that an opponent process enhanced by persistent nicotine taking renders self-administration rigid and habitual by inhibiting the learning process, resulting in long-term impairments in the absence of drug.

Secondly we tackle the mechanisms by which nicotine usurps dopaminergic signalling in the (VTA). We build and analyse a circuit level model of the VTA, that also includes major aspects of nicotinic acetylcholine receptors, such as relative distributions on various cell types, affinity, sensitisation and inactivation. We show how nicotine leads to a persistent increase in dopamine output. We further show how the in vivo and in vitro data, to this date contradictory with each other, can be reconciled.

Mats Gyllenberg

Title

Evolutionary aspects of human diseases

Abstract

Infectious agents such as bacteria, virus and macro parasites evolve by natural selection like all other living organisms. In this talk I present a mathematical framework for dealing with evolution of diseases and host-parasite co-evolution.

Zoltan N. Oltvai

Title

Disease networks

Abstract

Most diseases are the consequences of the breakdown of cellular processes, but the relationships among genetic/epigenetic defects, the molecular interaction networks underlying them, and the disease phenotypes remain poorly understood. In my talk I will describe our recent, network analysis-based approach to understand relationships among diseases and their pathogenesis.

Ricard Solé

Title

Cancer as a critical system: catastrophes and breakpoints in genetically unstable tumors.

Jörg Stelling

Title

Robustness and intervention in cellular networks

Abstract

Robustness, the ability to maintain performance in the face of perturbations and uncertainty, is a key property of living systems. Its molecular and cellular basis, however, have only recently begun to be understood because it is intimately linked to cellular complexity. Considering robustness in cell biology and its implications for basic science as well as for drug discovery requires a systems (theory) perspective and new methods for development and analysis of mathematical models for biological networks.

Mathematical modeling and systems analysis face challenges when applied to biological networks due to the networks' complexity and because often our knowledge on them is highly incomplete. Comparative methods that investigate several different circuit designs and / or possible hypotheses on network function can help in facing these challenges. Here, we employ (global) sensitivity analysis of mathematical models for the circadian clock to investigate circuit design principles and their relation to robustness and possible interventions. For the example of the target of rapamycin (TOR) signaling pathway, methods for reverse-engineering that are based on ensembles of structurally different models will be discussed. These case studies show that, in perspective, robustness may be a key to understand

cellular complexity, to elucidate general design principles of cellular networks, and to devise new intervention strategies for biomedical applications.

Klaas Enno Stephan

Title

Towards neurocomputational models for investigating and diagnosing psychiatric diseases

Abstract

This presentation will outline a research program that combines neuroimaging, electrophysiology, biophysical modeling and pharmacological manipulations to establish model-based indices of neurophysiological processes as diagnostic markers for psychiatric diseases. The modeling approach rests on Dynamic Causal Modeling (DCM), a framework for analyzing effective connectivity in the human brain, which characterizes mechanisms in non-linear neural systems perturbed by experimentally designed inputs. After briefly reviewing current pathophysiological concepts of psychiatric diseases (particularly with regard to schizophrenia) and the conceptual foundations of DCM, some (very preliminary) results from ongoing validation studies will be presented. These studies are performed in rodents and designed to test whether currently available DCMs are capable of correctly inferring the state of specific neurophysiological processes, i.e. spike-frequency adaptation and specific forms of short-term synaptic plasticity, from measured responses of larger neuronal populations.

Jesper Tegnér

Title

Bridging the gap – challenges and possibilities

Abstract

Can we find the dynamical core in a system without having a detailed molecular representation of all the events in the system? Is there room for compression when analyzing biological systems underlying complex diseases?

I will talk about the gap between detailed quantitative models vs more abstract representations of the phenomena of interest. The cell-cycle will be used as an initial example. The talk will motivate the need for abstract modelling and I will provide an overview of different types of network modelling, data-integration techniques and ensemble simulations.

Stephen Randall Thomas

Title

Collaborative multi-scale modeling of blood pressure regulation and fluid homeostasis

Abstract

I will present the SAPHIR project, a multi-resolution core modeling environment (CME) in the spirit of the IUPS Physiome, with implementation of a prototype core model based on a modular implementation of the classic systems model by Guyton et al. (1972 Ann. Rev. Physiol. 34:13-44) and its extension by Ikeda et al. (1979

Annals Biomed. Engin. 7:135-166). This core model targets short- and long-term regulation of blood pressure and homeostasis of body fluids and major solutes. The aim is to provide a collaborative modeling environment enabling plug-and-play construction of integrated systems models with lumped-parameter sub-models at the organ/tissue level yet also allowing focus on cell- or molecular-level detailed models embedded in the larger core model. Detailed extensions are under development for heart, kidney, and lung. Thus, in silico exploration of gene-to-organ-to-organism scenarios is possible while keeping computation time manageable.

Pablo Villoslada

Title

Computational modelling of the immune system for understanding autoimmune diseases and immunotherapies

Abstract

Autoimmunity is a common dysfunction of the immune system that is dependent on fundamental properties that underpin the organization of the immune system. We have modeled the human immune system using a System Dynamics framework and stochastic differential equations to demonstrate that autoimmunity can arise through a failure in the mechanisms controlling peripheral immune tolerance. Our analysis shows that by fine-tuning the parameters regulating the negative feedback between effector and regulatory T-cells, the immune system can generate the characteristic relapsing-remitting dynamics of autoimmune diseases. Such autoimmune dynamics are obtained in a range of parameters close to the normal functioning of the immune system. We also found some unexpected behaviors and for instance, therapies aimed at modulating the activity of T_e or T_r might have the opposite effects under certain circumstances. In addition, stochastic simulations of the immune system show that the timing at which relapses appear is highly unpredictable. Finally, we introduced targeted perturbations into the model that mimicked immunotherapies to modulate effector and regulatory populations. We demonstrate that the effects of such therapies are highly dependent on the timing and/or dose, and on the underlying dynamic of the immune system. This would imply that personalized immunotherapies must be developed, focused on obtaining healthier dynamics in the control module of peripheral tolerance rather than in keeping the absolute number of T-cells within specific ranges.

Special notes

- September 24: Barcelona holiday: La Mercè

On September 24 the city of Barcelona celebrates the festivity of "La Mercè". There are many activities organised through the city. You can check them at <http://www.bcn.cat/english/ihome.htm> and at the leaflet that you will find in your folder.

Please, note that it is a holiday and therefore shops and offices will be closed on that day.

Some suggestions for activities organised around the "La Mercè" holiday

- Concert "Mozart a París III. París"

By: Orquestra simfònica de Barcelona i Nacional de Catalunya

Director: Christian Zacharias

Place: Auditori de Barcelona - Sala 1 Pau Casals

Day: Saturday at 19:00 and Sunday at 11:00 h

More information: <http://www.obc.cat> <http://www.auditori.org/>

Performing:

Mozart: "Simfonia núm. 31, KV 297, París"

Haydn: "Concert per a trompeta i orquestra"

Mozart: "Rondó per a violí i orquestra"

Ravel: "Ma mère l'oye"

- MERCÈ 2008: Cosmocaixa Open house day

More information: <http://www.bcn.cat/merce>

<http://www.cosmocaixa.com/>

Show: "Eisntein, the atomic and the relative" by the Zahir Circo,

Day: Saturday at 19:00. Free

More information: <http://www.lacaixa.es/obrasocial>

<http://www.cosmocaixa.com/>

Exhibition: 'Amazònia de sol a sol'

More information: <http://www.cosmocaixa.com/>

- MERCÈ 2008: "Nits de Ramadà. Nit Magrebina"

Place: Passeig Lluís Companys

Day: Friday, Saturday and Sunday from 18:00

More information: <http://www.bcn.cat/merce>

- Exhibition "Alphonse Mucha (1860 - 1939) seduction, modernity and utopia"

Place: CaixaForum Centre Social i Cultural

More information: <http://www.lacaixa.es/ObraSocial>

- MERCÈ 2008: "Sky's party"

Place: Parc del Fòrum

Day: Saturday and Sunday from 10:00 to 20:00

More information: <http://www.bcn.cat/merce>

- Modern Musiques: Concert "Whiskyns's"

Place: L'Auditori de Barcelona - Sala 3 Tete Montoliu

Day: Saturday at 22:00

More information: <http://www.auditori.org/>

Pick pocketing is, unfortunately, not uncommon in the tourist sites of the city of Barcelona. Keep your belongings well protected at all times.

Institut d'Estudis Catalans: You can find information about the institution and its historic building at:

<http://www.iec.cat/gc/ViewPage.action?siteNodeId=926&languageId=5&contentId=3062>

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