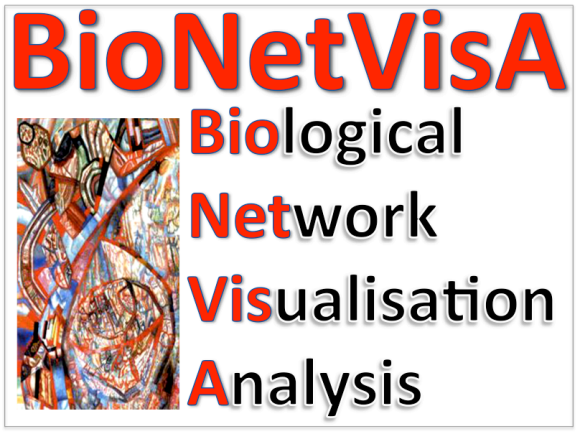

BioNetVisA workshop

From biological network reconstruction to data visualization and analysis in molecular biology and medicine

Singapore
25 November 2015

The **BioNetVisA** workshop will bring together different actors of network biology from database providers, networks creators, computational biologists, biotech companies involved in data analysis and modeling to experimental biologists, clinicians that use systems biology approaches. The participants will be exposed to the different paradigms of network biology and the latest achievements in the field.

The goal of **BioNetVisA** workshop is to build a discussion around various approaches for biological knowledge formalisation, data integration and analysis; compatibility between different methods and biological networks resources available the field; applicability for concrete research and clinical projects depending on scientific question and type of high-throughput data.

The **BioNetVisA** workshop aims at identifying bottlenecks and proposing short- and long-term objectives for the community as discussing questions about accessibility of available tools for wide range of user in every-day standalone application in biological and clinical labs. In addition, the possibilities for collective efforts by academic researchers, clinicians, biotech companies and future development directions in the field will be discussed during the round table panel.

Organizers

Inna Kuperstein (Institut Curie, France)

Emmanuel Barillot (Institut Curie, France)

Andrei Zinovyev (Institut Curie, France)

Hiroaki Kitano (Okinawa Institute of Science and Technology Graduate University, RIKEN Center for Integrative Medical Sciences, Japan)

Nicolas Le Novère (Babraham Institute, UK)

Robin Haw (Ontario Institute for Cancer Research, Canada)

Alfonso Valencia (Spanish National Bioinformatics Institute, Madrid, Stain)

Venue

Block MD7, Seminar Room M9 Yong Loo Lin School of Medicine National University of Singapore (NUS)

Web site
http://icsb15.apbionet.org/index.php/workshop/

http://sysbio.curie.fr/bionetvisa

Contact

bionetvisa@curie.fr

BioNetVisA workshop program

Session 1
Development of biological network databases and platforms

Chair: Deins Thieffry (IBENS, Ecole Normale Supérieure, Paris, France)

9.00-9.30

Garuda Platform and Its Applications in Biomedical Research
Yukiko Matsuoka (Systems Biology Institute, Tokyo, Japan)

9.30-10.00

PhysioDesigner: A versatile platform for multilevel modeling of physiological systems network
Yoshiyuki Asai (The Okinawa Institute of Science and Technology, Okinawa, Japan)

10.00-10.30

Studying cancer biology big data with Google Maps: NaviCell Web Service and Atlas of Cancer Signaling Network
Andrei Zinovyev (Institut Curie, Paris, France)

10.30-10.45 Break

10.45-11.05

SIGNOR: a database of causal relationships between biological entities
Livia Perfetto (University of Rome Tor Vergata, Rome, Italy)

11.05-11.55

Keynote lecture

Molecular networks as determinants of response and outcome
Lodewyk Wessels (Netherlands Cancer Institute, Amsterdam, Netherlands)

12.00-13.30 Lunch

Session 2
Data visualisation and analysis in the context of biological networks in research and medicine

Chair: Andrei Zinovyev (Institut Curie, Paris, France)

13.30-13.50

NetLand: A comprehensive tool for simulation and visualization of transcriptional network kinetics
Jie Zheng (Nanyang Technological University, Singapore)

13.50-14.10

Significant prognostic gene and interconnection network enrichment (SPGINE) analysis stratifies breast cancers into three reproducible subclasses determined by novel genetic grading signatures
Vladimir Kuznetsov (Bioinformatics Institute, Singapore)

14.10-14.30

Prediction of sensitivity to genotoxic drug by modeling cancer cell lines and patient omics data in the context of comprehensive DNA repair signaling network
Inna Kuperstein (Institut Curie, Paris, France)

14.30-14.50

Communities and Disease Comorbidities from Multiplex Biological Networks
Anaïs Baudot (CNRS-AMU, Marseilles, France)

14.50-15.00 Break

Session3
Modelling of biological networks
Chair: Lodewyk Wessels (Netherlands Cancer Institute, Amsterdam, Netherlands)

15.00-15.30

Predictive logical modelling of cell fate decision networks
Deins Thieffry (IBENS, Ecole Normale Supérieure, Paris, France)

15.30-15.50

Computing Life: Blue-print modelling and domino approach in design principle studies of Reactive Oxygen Species management
Alexey Kolodkin (University of Luxembourg, Luxembourg)

15.50-16.10

Multiscale model to recapitulate breast cancer invasion phenotypes
Arnau Montagud (Institut Curie, Paris, France)

16.10-17.00

Keynote lecture
Data-based modeling of signal-transcription network for cell fate control
Mariko Okada ((RIKEN Center for Integrative Medical Sciences Yokohama, Japan)

17.00-17.10 Break

17.10-17.50

Round table discussion

17.50-18.00

Conclusions

BioNetVisA workshop abstracts

Garuda Platform and Its Applications in Biomedical Research

Samik Ghosh[1], Yukiko Matsuoka[1], Hiroaki Kitano[1]

The Systems Biology Institute, Tokyo, Japan[1]

With the ever-increasing diversity of omics-scale experimental data, a key challenge is the ability to discover the right tools for a specific analysis and navigate through their specific formats. Garuda is an open, community-driven, platform that provides a framework to discover, connect & navigate through different applications in bio-medical research. We provide an overview of the Garuda platform, the community Garuda Alliance and a brief demonstration of the platform in action together with its various components. Further, we focus on case studies of the application of Garuda platform in different domains, from analysis of transcriptomics data, pathway and network biology driven analysis and outline current use cases in these scenarios. Further, we provide scenarios of application of Garuda platform in drug discovery, translational research as well as analysis of clinical data. We summarize with a vision on applications of Garuda across the different stages of research and analytics in biomedicine and the role of Garuda as an integration platform to connect, discover and navigate the complexity of biomedical data.

PhysioDesigner: A versatile platform for multilevel modeling of physiological systems network.

Yoshiyuki Asai[1], Takeshi Abe[1], Hiroaki Kitano[1,2]

Okinawa Institute of Science and Technology, Okinawa, Japan[1],
The Systems Biology Institute, Tokyo, Japan[2]

Integrated physiology and systems biology have been developing as new interdisciplinary scientific fields, in which the importance of multilevel modeling of physiological systems is rapidly increasing. To develop such models increasing in size and complexity, systematical supports from software is necessary. For example, SBML (http://sbml.org) is currently de facto standard to describe subcellular biochemical phenomena, and CellDesigner (http://www.celldesigner.org) is the most used software to edit and simulate SBML models. CellML (http://www.cellml.org) is for modeling of physiological system, among others.

In the same direction, we have been developing PhysioDesigner as a common platform on which users can develop multilevel models with interdisciplinary collaborations. PhysioDesigner enables users to build hierarchical multi-layer models. Each of models includes multiple modules representing a component of physiological functions. PhysioDesigner is freely available at http://physiodesigner.org. Models built on PhysioDesigner are written in PHML (Physiological Hierarchy Markup Language) format, which is an XML based specification to describe hierarchy of systems in comprehensive biological models, and which is a partially convertible with CellML.

In PHML, each of biological and physiological elements represented in a model is called a module, and structural and functional relationships among modules are defined by edges. A group of modules can be treated as a module at a higher level. By this recursive definition of the modules, a hierarchical structure found in the physiological systems is expressed in a model. Modules also form a big network representing functional connectivity among physiological functions. Each module is quantitatively characterized by several physical quantities, such as, states defining the system's dynamics, and variable and static parameters. Definition of the dynamics such as ordinary differential equations, or functions of physical-quantities are explicitly described by mathematical equations. Morphometric and time series data can be integrated to modules as well. It is possible to import a SBML model in a module. Such an SBML-PHML hybrid model can represent a multilevel biophysiological system incorporating different technologies.

Simulations can be performed by Flint, which can read not only PHML models, but also SBML and SBML-PHML hybridized models. There is also a cloud-based simulation service powered by Flint, called Flint K3, which is in-service at http://flintk3.org.

Studying cancer biology big data with Google Maps: NaviCell Web Service and Atlas of Cancer Signaling Network

Andrei Zinovyev[1], Inna Kuperstein[1], Emmanuel Barillot[1]

Institut Curie, Paris, France[1]

Computer-based technologies in geography allow navigating and comprehending large amounts of complex data. By analogy, it is tempting to chart a global map of molecular biology representing all available knowledge of known molecular mechanisms in a cell, and use it for visualizing and reasoning on the big biological data at different scales. We present a set of systems biology resources, including NaviCell Web Service and Atlas of Cancer Signaling Network (ACSN), which implements this task for the field of cancer biology. ACSN is a map of cancer biology browsable using Google Maps technology, organised in a form of “geography-like” map having a meaningfull and insightfull layout. It contains detailed description of the mechanisms implicated in cancer including DNA repair, Cell Survival, Apoptosis, Cell Cycle, EMT and Cell Motility together with their connections and cross-regulations. NaviCell Web Service is a tool for network-based visualization of``omics" data which implements several innovative data visual representation methods and tools for combining them together, using geographical map metaphor. All functions of NaviCell can be manipulated in several programming languages including Python and R: therefore, the tool can serve as an online front-end for many existing data analysis pipelines. We show various possibilities of visualization of different types of cancer-related data starting from simple gene lists to visualizations of whole transcriptomes or phosphoproteomic data. Data abstraction together with network abstraction methods used in this approach helps to smoothly zoom out and zoom into the details of molecular mechanisms involved in a specific cancer type or in a tumoral sample.

SIGNOR: a database of causal relationships between biological entities

Livia Perfetto, Leonardo Briganti, Alberto Calderone, Andrea Cerquone Perpetuini, Marta Iannuccelli, Francesca Langone, Luana Licata, Milica Marinkovic, Anna Mattioni, Theodora Pavlidou, Daniele Peluso, Lucia Lisa Petrilli, Stefano Pirrò, Elena Santonico, Filomena Spada, Luisa Castagnoli and Gianni Cesareni

Molecular Genetics Group, Department of Biology, Tor Vergata University, Rome, Italy

De novo network reconstruction, for large biochemical networks, is achieved by confronting the experimental data with an interaction subspace constrained by available literature evidence. SIGNOR (http://signor.uniroma2.it), the SIGnaling Network Open Resource is a new database designed to facilitate the storage and analysis of causal interactions, i.e. interactions where a source entity has an effect (up-regulation, down-regulation, etc.) on a target entity, and it is suitable to support such a strategy by providing a scaffold of prior experimental evidence.

An on-going curation effort in our group aims at making SIGNOR a prominent resource in the biological community by offering a comprehensive network of experimentally validated functional relationships between signalling proteins. At the time of writing, the core of SIGNOR is a collection of approximately 12000 manually-curated causal relationships between proteins and other biological entities that participate in signal transduction. Each relationship is linked to the literature reporting the experimental evidence and it is assigned a score. More than 4,900 modified residues causing a change in protein concentration or activity have been curated and linked to the modifying enzymes (about 351 human kinases and 94 phosphatases).

This wealth of structured information can be used to support experimental approaches based on multi-parametric analysis of cell systems after physiological or pathological perturbations.

Molecular networks as determinants of response and outcome

Lodewyk Wessels[1], Sander Canisius[1], Bram Thijssen[1], Kathy Jastrzebski[1], Roderick Beijersbergen[1]

The Netherlands Cancer Institute, Amsterdam, The Netherlands[1]

The exact mechanisms involved in tumor development and therapy response are still largely unclear. Here we report on two computational approaches we developed to systematically unravel these genetic interactions based on high throughput datasets and show these can be employed to predict response to anti-cancer agents.

In the first approach, we developed a computational approach to reliably detect molecular interactions (co-occurrences and mutually exclusivities) from somatic variant and copy number data. We show that the number of aberrations per gene and per sample have a major influence on the results and propose a null-model to correct for these effects. We demonstrate the approach on the TCGA and METABRIC breast cancer cohorts. We identify no co-occurring aberrations but multiple mutually exclusive interactions, that represent a global breast cancer interaction network, shedding new light on breast cancer development and subtyping. We also performed a pan-cancer interaction analysis which reveals cancer type independent interactions.

In the second approach we performed integration of multiple omics data sets to construct models of drug response in cancer cell lines. While many oncogenic drivers and drug resistance mechanisms have been discovered, it is generally unclear how these mechanisms interact to induce sensitivity or resistance in a cell line for a particular drug. We characterized 30 breast cancer cell lines at the DNA, RNA and protein level, and measured the response to various kinase inhibitors. We then constructed Bayesian models encompassing several of the important driver pathways and resistance mechanisms, and tested how well these models describe the available data. The models provide estimates of the relative contribution of each of the drivers and resistance mechanisms and allow estimation of latent variables such as ‘pathway activation’. We demonstrate the utility of the models by thoroughly analyzing which parts of the data cannot be explained even by fairly extensive models. This provides interesting new leads and narrows down which follow-up studies may be most fruitful to advance our understanding of drug response. The systematic, quantitative understanding of drug response gained from these models will contribute significantly towards precision medicine for individual cancer patients.

NetLand: A comprehensive tool for simulation and visualization of transcriptional network kinetics

Jing Guo[1], Feng Lin[1], Jie Zheng[1,2]

School of Computer Engineering, Nanyang Technological University, Singapore, Singapore[1]
Genome Institute of Singapore, Agency for Science, Technology, and Research, Biopolis, Singapore, Singapore[2]

Transcriptional regulation through a gene regulatory network (GRN) is a major force to change cellular states. During cell differentiation or reprogramming, changes in gene expression profiles are crucial. Thus kinetic models of GRNs have been used to study the determination of cell fates. *In silico* simulation is a common method to analyze the kinetic dynamics of a network, based on a mathematical model generated from the network structure. Through iterative comparisons with experimental results, the model is corrected and adapted, in order to make reliable predictions. For a comprehensive understanding of the modeled GRN, Waddington's epigenetic landscape is a powerful framework to analyze and visualize the global dynamics of the network. Based on the essential idea of Waddington's landscape, changes of cell fates are represented by state transitions overcoming energy barriers between attractors. Thus the quantified epigenetic landscape is the stage on which the play of cell fate decisions is choreographed according to regulatory constraint and stimulations analogous to physical forces.

NetLand is a software tool designed for studying GRN kinetics. It provides comprehensive methods for simulation and visualization of network dynamics. The biological influences in GRN can be converted into the Boolean logics (Boolean or multi-value model) and differential equations (ODE or SDE model). Through *in silico* simulation, the dynamics of the GRN can be visualized in multiple ways, e.g. the state transition graph of a Boolean network, trajectories of continuous models and Waddington's epigenetic landscape. NetLand can be applied to various fields of molecular and cell biology, including stem cell and cancer research.

Significant prognostic gene and interconnection network enrichment (SPGINE) analysis stratifies breast cancers into three reproducible subclasses determined by novel genetic grading signatures

Vladimir A. Kuznetsov[1, 2], Luay Aswad[1, 2], Efthimios Motakis[1], Zhiqun Tang[1], Ghim Siong Ow, Anna V. Ivshina[1]

[1]*Bioinformatics Institute, 30 Biopolis street, Singapore 138671*
[2]*School of Computing Engineering, Nanyang Technological University, Singapore 639798*

The Cox-proportional hazard *regression model* could build the prognostic gene classifiers in network analysis of gene expression data. In this work, we tested the hypothesis that gene expression patterns selected via significant prognostic gene and interconnection network enrichment (SPGINE) analyses, integrating with survival data can select the functional cell cycle gene modules predicting genetically distinct cancer sub-classes, differentiating by tumor aggressiveness, chromosome instability and pluripotent cells gene expression patterns.

Meta-analysis of publicly available microarray profiles and clinical data from 1317 breast cancer (BC) patients from 7 cohorts were carried out in this study. Based on the Cox proportional hazard survival model, we developed a prediction method of post-surgery breast cancer patient risk stratification and SPGINE analysis, providing novel prognostic classifiers and perspective biomarkers selection.

This method links the gene expression profiles of subjects' primary tumors with their survival data. Firstly, our one-dimensional data-driven grouping approach was used for the selection of survival-significant genes, stratifying BC patients into two disease development risk groups. The method also used the pair enrichment test to select a sub-set of top-level synergistically significant genes according to the log-rank statistics and subsequently, hypergeometric test (at FDR<1%) specified based on the number of links of individual genes with the other survival significant gene partners.

SPGINE tested the H0-hypothesis that the number of gene partners for a survival significant gene occurred in the expression dataset at random. SPGINE automatically selected the 10-gene prognostic classifier, stratifying the patients of several studied cohorts into three reproducible prognostic subgroups (PSGs). Subsequently, by comparing global gene expression profiles between the PSGs, SPGINE selected a small subset of differentially expressed genes (13-gene DEG classifier) significantly discriminating the PSGs. The genes of our classifiers provided a highly-interconnected regulatory network, enriched with periodically changed mitosis/ cycle genes. Most genes of both signatures showed pro-oncogene survival patterns and were involved in mitosis, chromosome assembly/rearrangement, and stem cell-like self-renewal processes. Univariate and multivariate analyses showed prediction significance and reproducibility of the classification models across the cohorts. Importantly, the classification, provided by our prognostic classifiers were strongly correlated with histologic and genetic low- and high- genetic grading systems of breast cancers, reported in our previous studies (Ivshina et al., 2005; 2006; Kuznetsov et al. 2006; Aswad, et al, 2015), and predicted the risks of distant metastasis. Our SPGINE analysis provides reproducible cell-cycle genes related molecular classification of the breast cancer patients. These findings could help to better understand molecular basis of BC classifications and provide novel specific genetic determinants for personalized patient's prognosis and BC therapeutic intervention.

Prediction of sensitivity to genotoxic drug by modeling cancer cell lines and patient omics data in the context of comprehensive DNA repair signaling network

Inna Kuperstein, Christophe Russo, David Cohen, Eric Bonnet, Eric Viara, Laurence Calzone, Hien-Anh Nguyen, Luca Grieco, Emmanuel Barillot and Andrei Zinovyev

Institut Curie, Paris, France, INSERM U90, Ecole des Mines ParisTech, Paris, France

Genomic instability is a cancer hallmark, perturbations in DNA repair are exploited in genotoxic treatments, but not always efficiently due to backup mechanisms in signaling. A signaling map was built in CellDesigner; structural analysis was done using BiNoM, followed by synthetic lethal combinations study by OCSANA algorithm and finalized by prioritizing gene intervention sets based on omics data. Atlas of Cancer Signaling Network (ACSN) is a resource of signaling maps and tools with web-based environment for map navigation, curation, and data visualisation.

A comprehensive map of DNA repair, from the ACSN collection, has been used for deciphering genetic interactions to overcome drug resistance by: 1) deriving a state transition graph from the map and retrieving all paths from a damaged DNA to the repaired DNA state; (2) applying an minimal cut sets algorithm for searching all sets of DNA repair genes whose concomitant invalidation would deregulate the overall efficiency of DNA repair machinery; (3) considering genes that regulate each state transition as potential target for interference. We have retrieved all possible gene sets whose knock-out halts DNA repair. Integrating expression and mutation data from drug resistant breast cancer cell lines and treatment resistant patients allowed prioritizing synthetically lethal gene sets and predicting specific intervention set for restoring sensitivity to genotoxic drugs in each case.

Our approach allows complementing genotoxic chemotherapy by targeting specifically cancer cells harboring certain DNA repair defects, providing a strategy to develop personalized cancer treatment strategies based on the extended cancer signaling in ACSN.

Communities and Disease Comorbidities from Multiplex Biological Networks

Anaïs Baudot[1], José-Luis Portero[1,2], Gilles Didier[1]

[1]I2M – CNRS-AMU, Marseilles, France, [2]Present address: Novo Nordisk Pharma SA, Madrid, Spain

Functional relationships between genes and proteins are numerous and diverse: protein-protein interaction or gene co-expression, for instance. Biological networks are thus intrinsically multiplex, i.e. they can be represented as a collection of networks sharing the same nodes (the genes/proteins), but encompassing interactions of different nature. One of the leading approaches to extract functional knowledge from biological networks is their clustering into communities – or functional modules – of tightly linked genes/proteins. But what is the best option to identify communities from multiple biological network sources?
We assess here classical approaches of network or community aggregations, and compare them to a multiplex-modularity approach that considers the multiplexity of biological network. By simulating random networks, we demonstrate that the multiplex-modularity method outperforms the aggregation approaches when network layers are incomplete or heterogeneous in density. Application to a multiplex biological network containing 4 layers of physical or functional interactions allows recovering communities more accurately annotated than their aggregated counterparts. Overall, the multiplex-modularity framework is better suited to combine different biological networks for community identification[1].

We recently identified overlaps between susceptibility genes[2] and deregulated genes[3] associated to diseases presenting direct or inverse comorbidities. Multiplex networks and communities allow to extend these analyses by considering the genes/proteins functional relationships potentially involved in disease comorbidities. We undertook a systematic study of communities enriched in diabetes and pancreatic/prostate cancer-related genes. This approach provides some molecular hypotheses, including a role for the anti-diabetic drug metformin, to better understand the relationships between these diseases that, at the epidemiological level, show direct and inverse comorbidities.

[1] Didier, Brun and Baudot. Submitted.
[2] Tabarés-Seisdedos et al. Lancet Oncol. 2011 Jun;12(6):604-8.
[3] Ibáñez et al. Plos Genetics 2014 Feb 20;10(2).

Predictive logical modelling of cell fate decision networks

Denis Thieffry[1]

Institut de Biologie de l'Ecole Normale Supérieure (IBENS), UMR CNRS 8197 - INSERM 1024, 46 rue d'Ulm, 75005 Paris, France[1]

Logical modelling constitutes a flexible framework to design predictive qualitative models, which can be readily analysed or simulated as such, and potentially used as scaffolds to build more quantitative (continuous or stochastic) models.

We use multi-valued decision diagrams to implement (multi-level) logical updating rules in the modelling software *GINsim*. This representation enabled the development of efficient algorithms for the identification of stable states, as well as to identify specific (positive or negative) regulatory circuits involved in specific dynamical properties (e.g., multiple attractors or sustained oscillations).

To cope with large molecular regulatory networks, we have further implemented a flexible reduction method, which preserves the dynamical attractors representing alternative cellular states.
This reduction method is complemented with a novel algorithm enabling the compression of state transition graphs into hierarchical graphs, yet emphasising the most important transitions associated with attractor reachability.

This approach will be illustrated through the modelling of regulatory networks controlling cell fate decisions in human cancer cells. In particular, I will show how it can be used to predict the effects of single and multiple drug applications, and thereby delineating synergistic drug effects.

Computing Life: Blue-print modelling and domino approach in design principle studies of Reactive Oxygen Species management

Alexey Kolodkin[1], Andrew Ignatenko[2], Bernhard Peters[2], Evangelos Simeonidis[1,"], Matteo Barberis[4], Nilgun Sahin[5], Rudi Balling[1] and Hans V. Westerhoff[4,5,6]

[1]*Luxembourg Centre for Systems Biomedicine, University of Luxembourg, LUXEMBOURG;*
[2]*Faculty of Science, Technology and Communication, University of Luxembourg, LUXEMBOURG;*
[3]*Institute for Systems Biology, USA;*
[4]*Synthetic Systems Biology, SILS, NISB, University of Amsterdam, THE NETHERLANDS;*
[5]*Molecular Cell Physiology, VU University Amsterdam, THE NETHERLANDS;*
[6]*Manchester Centre for Integrative Systems Biology, UK*

One of the goals of systems biology is to understand how biological function absent from macromolecules in isolation, emerges when they are components in a system. Millions of interactions in the living organism make the system too complex to be handled intuitively in a human brain or on the back of an envelope and require a computer replica of reality. A computer replica of the whole human body will ultimately lead to the Virtual Human model which is now anticipated for personalized medicine.

Here we discuss the application of two techniques which may be useful in building the Virtual Human model: a domino approach (building the model by adding modules incrementally, like domino tiles) and blueprint modelling (a generic "blueprint" can be parameterized for a particular instantiation). Both domino approach and blueprint modelling may be performed hand in hand with design principle studies aiming to identify how certain design features are responsible for a certain biological function. On the one hand, when using the domino approach, one can analyze the functional role of each domino module and check which new emergent properties are gained with the addition of an extra module. On the other hand, one can check which emergent properties are affected by a certain parameter set, e.g. attributed to healthy or diseased cell instantiations.

As an example of design principles study accompanied by blueprint modelling and domino approach, we have built a dynamic ODE-based Reactive Oxygen Species (ROS) management model. ROS management is associated with obesity, cancer, Parkinson's Disease (PD) and other systems biology diseases, which result from a persistent perturbation of the healthy functioning of intracellular and paracellular networks; by implication, each disease is caused by multiple malfunctions at various positions in the network. The converse implication is that different diseases may share the same molecular processes. Our model offers insight into the structure of the system of ROS management and allows the simulation of the disease-specific systemic response to oxidative stress and it can be used in the development of personalized medicine approaches.

Multiscale model to recapitulate breast cancer invasion phenotypes

Arnau Montagud[1,2,3], Margriet M Palm[4], Vanessa Benhamo[1,5], Laurence Calzone[1,2,3], Andrei Zinovyev[1,2,3], Dirk Drasdo[4], Anne Vincent-Salomon[1,5], Emmanuel Barillot[1,2,3]

Institut Curie, Paris, France[1], INSERM U900, Paris, France[2], Mines ParisTech, Paris, France[3], INRIA, Le Chesnay, France[4], INSERM U830, Paris, France[5]

Understanding tumour invasion mechanisms is crucial to improve prognosis and develop new cancer treatment strategies, but this is hindered by the lack of understanding of detailed molecular determinants of this process and their interactions leading to different ways cancer cells invade the surrounding tissues. Tumour invasion varies from individual to collective cell movement or if proteases facilitate their migration.

We devised a multi-scale mathematical model that incorporates information of a series of traits, cellular and environmental, that output in a set of invasion modes. For this, the model incorporates different intracellular and signalling pathways and the resulting influence network has been translated into a mathematical model using discrete logical modelling. We have taken advantage of continuous time Boolean modelling based on Markovian stochastic process defined on the model state transition graph to simulate intracellular molecular processes determining individual cellular properties. We have embedded this Boolean model in a lattice-free individual cell population model to cope with interaction between cells and microenvironment affecting cell properties, leading to various patterns of collective cell behaviour.

The model is now tuned to recapitulate major breast cancer invasion phenotypes such as mesenchymal single cell invasion, solid strand multicellular invasion and bulk growth tumour. Present work is part of a collaborative effort to model tumour invasion in order to identify treatment strategies and to understand underlying properties of metastasis.

Data-based modeling of signal-transcription network for cell fate control

Mariko Okada-Hatakeyama[1]

Laboratory for Integrated Cellular Systems, RIKEN Center for Integrative Medical Sciences (IMS), Japan[1]

Signal transduction network is a system to sense, sort and transfer a variety of extracellular information to transcription factors in the nucleus to regulate gene expression for cell determination. Interestingly, signaling pathways often control these processes in a nonlinear manner and, in some cases, analogous graded doses of extracellular stimuli promote digital activation of transcription factors. Time and space-resolved context-dependent network plays an essential function to realize these types of responses. In this talk, the data-based modeling, as one of the methods for heterogeneous data integration, to explain digital activation mechanisms of two transcription factors, c-Fos and NF-κB, will be explored.

We show that prolonged ERK activation along with c-fos mRNA transcription and c-Fos protein stabilization by ERK forms a feedforward AND gate loop for full activation of c-Fos in growth factor-stimulated breast cancer cells. In this system, duration of ERK activity is a critical factor to determine the c-Fos response. Our analysis shows that different growth factors initially activate similar signaling pathways but the transcription response cascades switches after the timing of c-Fos activation. On the other hand, in antigen-stimulated BCR response, NF-κB activity is controlled by two positive feedback loops within the signaling pathway, from TAK1 to IKK and from IKK to IKK, to produce a switch-like activation of NF-κB. These feedback loops contribute to determine the threshold for NF-κB-mediated B cell proliferation, suggesting that the mechanism is important for B cell lineage commitment.

Digital activation of transcription factors may be more beneficial in a noisy cellular environment and for accurate control of gene expression for cell fate decision. Our studies suggest that cellular complexity might arise from combinatorial regulation of binary states of transcription factors.