Cancer, Systems and Complexity

Lake Como School of Advanced Studies

Home

Workshop and School on Cancer, Systems and Complexity

September 28 – October 2, 2014

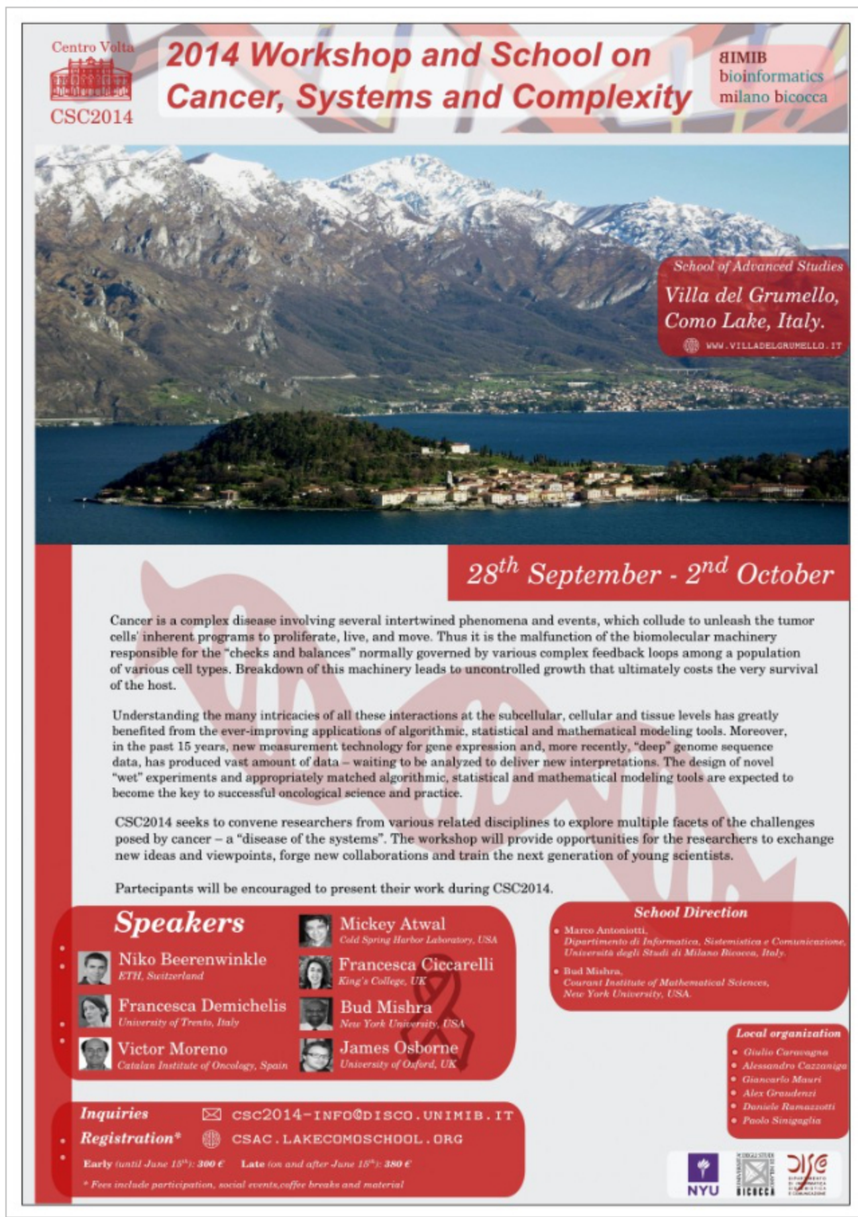
The 2015 edition of this school can be found at CEAC.lakecomoschool.org

Cancer is a complex disease involving several intertwined phenomena and events, which collude to unleash the tumor cells' inherent programs to proliferate, live, and move. Thus it is the malfunction of the biomolecular machinery responsible for the "*checks and balances*," normally governed by various complex feedback loops among a population of various cell types. Breakdown of this machinery leads to uncontrolled growth that ultimately costs the very survival of the host.

Understanding the many intricacies of all these interactions at the subcellular, cellular and tissue levels has greatly benefitted from the ever-improving applications of *algorithmic, statistical and mathematical modeling tools*. Moreover, in the past 15 years, new measurement technology for gene expression and, more recently, *"deep" genome sequence data*, has produced vast amount of data – waiting to be analyzed to deliver new interpretations. The design of novel "wet" experiments and appropriately matched algorithmic, statistical and mathematical modeling tools are expected to become the key to successful oncological science and practice.

The Workshop and School on Cancer, Systems and Complexity seeks to convene researchers from various related disciplines to explore multiple facets of the challenges posed by cancer – a "*disease of the systems*." The workshop will provide opportunities for the researchers to exchange new ideas and viewpoints, forge new collaborations and train the next generation of young scientists.

Participants interested in presenting their work are invited to submit a short abstract (1 page) to <csc2014-info [[a]] lists2.disco.unimib.it> with title and authors. Presentation sessions will be organized on the basis of the submission numbers.



Speakers

Gurinder Singh "Mickey" Atwal (Cold Spring Harbor Lab, U.S.A.)

Short bio

Fueled by massive amounts of data generated from DNA sequencing technologies, the Atwal Lab is currently focused on population genetics, cancer biology and high-performance computing. We often tackle scientific questions computationally by invoking theoretical concepts from statistical physics and machine learning.

A common thread in our research is the quest to understand collective biological phenomena from the perspective of the physical sciences. To this end, we develop and deploy mathematical and computational tools to address quantitative principles governing the behavior of many-body biological systems, ranging from molecular interactions in a single eukaryotic cell to the evolution of the species Homo sapiens.Our fantastic team of lab members and collaborators consists of physicists, biologists, mathematicians and computer scientists and we work closely with experimentalists and clinicians both here at Cold Spring Harbor Laboratory and around the world. For more details feel free to browse through our website.

Niko Beerenwinkel, ETH (Zurich, Switzerland)

Short Bio

Niko Beerenwinkel was born in Düsseldorf, Germany. He studied mathematics, biology, and computer science, and received his Diploma degree in Mathematics from the University of Bonn in 1999 and his PhD in Computer Science from Saarland University in 2004. He was a postdoctoral researcher at the University of California at Berkeley (2004-2006) and at Harvard University (2006-2007) before joining ETH Zurich as assistant professor of computational biology.

Niko Beerenwinkel's research is at the interface of mathematics, statistics, and computer science with biology and medicine. His interests range from mathematical foundations of biostatistical models to clinical applications. Current research topics include haplotype inference from ultra-deep sequencing data, somatic evolution of cancer, reconstruction of signaling pathways from RNAi screens, HIV drug resistance, graphical models, and algebraic statistics.

He has authored over 50 research articles in the areas of computational biology, bioinformatics, biostatistics, virology, and cancer biology. His honors include the Otto Hahn Medal of the Max Planck Society and the Emmy Noether Fellowship of the German National Science Foundation.

Lecture outline

Cancer evolution is a stochastic evolutionary process characterized by the accumulation of mutations and responsible for tumor growth, clinical progression, immune escape, and drug resistance development. Evolutionary theory can be used to describe the dynamics of tumor cell populations and to make inference about the evolutionary history of a tumor from molecular profiling data. We discuss recent approaches to modeling the evolution of cancer, including population genetics models of tumorigenesis, phylogenetic methods of intra-tumor subclonal diversity, and probabilistic graphical models of tumor progression. Evolutionary modeling will play an increasingly important prognostic role in predicting disease progression and the outcome of medical interventions, such as targeted therapy.

Charles Cantor, Agena Biosciences, Sequenom, Retrotope (San Diego, USA)

Short Bio

Charles Cantor is currently affiliated with Agena BioSciences Inc., Sequenom Inc. and Retrotope Inc. He is Professor Emeritus, Biomedical Engineering
Professor of Pharmacology, School of Medicine at Boston University, and former director of the DoE Human Genome Project. Charles Cantor's research is focused on identifying biological problems that are resistant to conventional analytical approaches and then developing new methodologies or techniques for solving these problems. His laboratory has developed methods for separating large DNA molecules, for studying structural relationships in complex assemblies of proteins and nucleic acids, and for sensitive detection of proteins and nucleic acids in a variety of settings. His current interests include the development of new methods for faster DNA sequencing, the development of new variations and analogs of the polymerase chain reaction, the development of bacterial strains suitable for environmental detoxification, and the discovery of human genes associated with sense and taste. He is also interested in exploring the possible use of biological molecules for applications in nanoengineering and microrobotics, and in making detectors capable of recognizing specific single molecules.

Francesca Ciccarelli, King's College (London, U.K.)

Short bio

Francesca Ciccarelli graduated in pharmaceutical chemistry at the University of Bologna and was trained as a computational biologist at the EMBL-Heidelberg. Her early work focused on DNA and sequence analysis and phylogenetic reconstructions. In 2005, she started her group at the European Institute on Oncology in Milan with the aim to elucidate the role of mutations in the development of cancer. Her group applies a combination of experimental and in silico approaches and pursues two main lines of investigation. The first aims at characterizing the systems-level properties of cancer genes and to use them to identify novel targets for therapy. The second line involves extensive cancer genome sequencing to characterize the evolution of cancer clones. In 2014, she moved to London as an Associate Professor at the King's College School of Medicine.

Lecture Outline

In my lectures I will discuss on the recent advances in on our understanding of cancer genetics and evolution. I will start by reviewing the accumulating evidence of cancer heterogeneity in terms of acquired genetic mutations and genomic rearrangements. I will then describe the impact of these novel results on our modelling of cancer networks. Finally, I will describe how the characterization of cancer driver genes in terms of network can help in identifying cancer-specific targets to be used in therapy.

Francesca Demichelis, Università degli Studi di Trento (Trento, Italy)

Short Bio

Dr Demichelis trained as a physicist at the University of Trento, Italy, and at the Imperial College of Science, Technology and Medicine in London, UK. She then obtained a PhD from the International School in Information and Telecommunication at the University of Trento where she worked on integrated and automated analyses to finally model in situ protein expression data from large scale tumour samples collections. She was then a postdoctoral fellow at the Harvard Medical School in Boston working on the characterization of the genomic landscape of solid tumours using high-density oligonucleotide platforms data and computational genomic approaches.In 2007, she joined Weill Cornell Medical College as Instructor and Institute Fellow in Computational Biomedicine and later joined the Faculty as Assistant Professor in Pathology and Laboratory Medicine in 2008. Since 2011 she is Assistant Professor at the Centre for Integrative Biology at the University of Trento where she directs the Laboratory of Computational Oncology with focus on the understanding of clonality and evolution to identify tumour driver events and on bridging germline polymorphisms and somatic aberrations to dissect tumour subclasses. She is the recipient of multiple awards including the New Investigator Award from the U.S. Department of Defense and the Prostate Cancer Foundation Competitive Award. She is co-recipient of the first American Association for Cancer Research (AACR) Team Science Award.

Lecture outline

Approaches to infer tumor evolution from single base level data will be presented and discussed in the context of the identification of driver events that are key in tumor progression both at gene and pathway levels. In addition, examples of tumor dynamics based in circulating DNA (plasma) from advanced patients will be presented.

Bhubaneswar Mishra, Courant Institute of Mathematical Sciences (New York University New York, NY, U.S.A.)

Short Bio

Professor of Computer Science & Mathematics, Courant Institute, New York University; Principal Investigator, NYU/Courant Bioinformatics Group; Principal Investigator, SEI/CMU/NYU Center for Malicious Behavior and Model Checking; Professor of Cell Biology, NYU School of Medicine, New York University; Qiß Visiting Scholar Simons Center for Quantitative Biology, Cold Spring Harbor Laboratory; Adjunct Professor Department of Human Genetics, Mt. Sinai School of Medicine; Adjunct Professor Tata Institute of Fundamental Research

Lecture outlines

Cancer: From Endless Complexity to Simplicity (Introductory Lecture)

Cancer biologists have been celebrating the powers of reductionist molecular biology and its major successes for four decades. Many of those who have participated in cancer research during this period have witnessed wild fluctuations from times where endless inexplicable phenomenology reigned supreme to periods of reductionist triumphalism. However, the advent of massive amounts of -omics data in recent years has tampered that enthusiasm and is pointing to a move back to confronting the endless complexity of this disease. We will discuss how this summer school may help us to create a roadmap for the next generation of analysis. Such a roadmap can be built on statistical inference from data, philosophical models of causality, mathematical basis of phenomenological models, bio-chemical frameworks for mechanistic models, logical approaches based on model checking and control-theoretic approaches to therapy design.

Causality and Cancer: Multiple Facets: (Sept 30 Lecture)

Existing techniques to reconstruct tree or DAG models of progression for accumulative processes such as cancer, seek to estimate causation by combining correlation and a frequentist notion of temporal priority. In these lectures we define a novel theoretical framework to reconstruct such models based on the probabilistic notion of causation defined by Suppes, and extended by Skyrm, Dupre and Cartwright. This view of causality differs fundamentally from that based on correlation. We consider a general reconstruction setting complicated by the presence of noise in the data, owing to the intrinsic variability of biological processes as well as experimental or measurement errors. Our analysis suggests the applicability of the method on small datasets of real patients.

Victor Moreno, ICO (Barcelona, Spain)

Short bio

Dr. Moreno is Professor of Preventive Medicine and Director of the Cancer Prevention and Control Program at the Catalan Institute of Oncology-IDIBELL in Barcelona, Spain. He has been long experience in genetic and molecular epidemiology studies on CRC. He has designed and conducted several case-control studies on CRC and contributed to the identification of genetic susceptibility loci, and molecular mechanisms involved in CRC etiology and progression. He leads the Unit of Biomarkers and Susceptibility at ICO, with strong expertise in biostatistics and bioinformatics. His team has experience both in the design of epidemiological and clinical studies and in the analysis of omics data. In his most recent project, COLONOMICS, (www.colonomics.org) tumors and adjacent normal mucosa from a sample of 100 CRC patients have been extensively characterized at molecular level (gene expression, micro-RNA expression, methylation, genetic variation, CNVs and somatic mutations in exome). Also samples of normal mucosa from 50 healthy donors have been analyzed. This resource is the bases for diagnostic and prognostic biomarker discovery and to elucidate the mechanisms involved using systems biology approaches.
Websites:

http://www.icoprevencio.cat/en/programa-biomarcadors

http://www.colonomics.org

Lecture outline

Transcriptional regulatory programs of normal and tumor colon cells

Dysregulation of transcriptional programs leads to cell malfunctioning and can have an impact in cancer development. Within the COLONOMICS study (www.colonomics.org) we have characterized global differences between transcriptional regulatory programs of normal and tumor cells of the colon. Expression array data (Affymetrix Human Genome U219) from 100 samples of colon tumor and their paired adjacent normal mucosa were used to reconstruct transcriptional networks. ARACNe algorithm was used to infer a consensus network for each cell type. Networks were compared regarding topology parameters and identified well-connected clusters, which were characterized by functional enrichment. ENCODE ChIP-Seq data curated in the hmChIP database was used for in silico validation of the most prominent transcription factors. A large loss of transcriptional interactions in the tumor network was observed, together with a subgroup of emergent or up-regulated transcription factors related to relevant colon cancer mechanisms. In a second analysis, microRNA data has been related to gene expression data to identify specific relevant regulatory clusters.

James Osborne, CS Department,University of Oxford, (Oxford, U.K.)

Short bio

I am running a workshop on Cell Based and Individual Based Modelling (CBIBM) as part of the 2014 International Conference on Computational Science, 10th-12th June 2014, Cairns Australia. For more information and to submit a paper or abract for a talk go here.

A recent poster I presented at the "Workshop on Mechanics and Growth of Tissues: from Development to Cancer" in paris in January 2014 is available here.

In 2000-2004 I completed an undergraduate degree in Mathematics at New College. From there I went to the Life Sciences interface Doctoal Training Centre (LSI DTC) to begin my DPhil studies. For research component of my DPhil I was based in the Computational Biology Group under the supervision of Jonathan Whiteley, my thesis was entitled "Numerical and Computational Methods for Simulating Multiphase Models of Tissue Growth".

From 2008-2011 I was working as a Post Doctoral Research Assitant, in the Computational Biology Group, looking at "Computational Approaches to Multiscale Modelling in Systems Biology" as part of the Oxford Centre for Integrative Systems Biology (OCISB). Between 2009 ans 2013 I returned to the DTC (www.dtc.ox.ac.uk) as an Associate Director with my time split between research and the DTC.

Since 2011 I have been a Senior Researcher in the Computational Biology Group and lead the cell based modeling group.

Since July 2013 I have been working at Microsoft Research Cambridge as part of the Biological Computation Group in the Computational Science Laboratory.

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Program

Plenary sessions will involve lectures and tutorials held by the invited speakers. The preliminary scheduled can be found in the table below. Outlines of the lectures can be found at this **page**.

Students and researchers are invited to submit an abstract describing their research (at this email address: <csc2014-info [[a]] lists2.disco.unimib.it>). According to the number of requests either a poster session or a short-talk session will involve the last day of the school.

	Sunday Sept 28	Monday Sept 29	Tuesday Sept 30	Wednesday Oct 1	Thursday Oct 2	
9:00-9:45	-	Victor Moreno	Bud Mishra	Mike Atwal	Francesca Ciccarelli	9:00-9:45
9:45-10:30	-		Charles Cantor			9:45-10:30
10:30-10:45	-	Coffee Break	Coffee Break	Coffee Break	Coffee Break	10:30-10:45
10:45-11:30	-	Victor Moreno	Niko Beerenwinkel	Francesca Ciccarelli	Participants' presentations: Cecilia Dalla Valle, Laura Curti, Baltazar Aguda, Giusy Pisignano, Riccardo Colombo	10:45-11:30
11:30-12:15	-					11:30-12:15
12:15-13:00	-	Welcome from the Rector of University of Milan-Bicocca, prof. Cristina Messa	Participants' presentations: Daniele Ramazzotti, Paola Lecca	Participants' presentations: Justin Jee, Davide Cittaro		12:15-13:00
13:00 – 14:30	-	Lunch	Lunch	Lunch	Lunch	13:00 – 14:30
14:30 – 15:15	-	Francesca Demichelis	Mike Atwal	James Osborne	Panel Discussion on "Future of Oncotherapeutics" led by Bud Mishra	14:30 – 15:15
15:15-16:00	Registration					15:15-16:00
16:00-16:15	Registration	Coffee Break	Coffee Break	Coffee Break	-	16:00-16:15
16:15-17:00	Bud Mishra: Introductory Lecture	Niko Beerenwinkel	Francesca Demichelis	James Osborne	-	16:15-17:00
17:00-17:45					-	17:00-17:45
18:00-19:30	Cocktail buffet					18:00-19:30
20:30 - late night			Social dinner at "Il solito posto", via Lambertenghi, 9, 22100 Como (Co)			20:30 - late night

Participants' abstracts

All presentations are limited to **15 minutes** plus 5 minutes for questions (see the program at this link).

Baltazar Aguda

Title: Feedback Loops Between Oncogenes & Tumor Suppressor Genes and their Control

Speaker: Baltazar D. Aguda, PhD (DiseasePathways, LLC, Bethesda, MD, USA)

Abstract: Interactions between oncogenes (such as Myc and Ras) and tumor suppressor genes (such as p53 and Ink4a) normally form negative feedback loops. Cancer stem cells may arise when certain steps in these interactions are perturbed. I will first give an overview of the Myc-p53 interactions in glioblastoma and the Ras-Ink4a interactions in pancreatic cancer. A qualitative network model of the Myc-p53 system is then discussed, including an illustration of how the system becomes unstable and how it can be controlled.

Key References:

Qualitative network modeling of the Myc-p53 control system of cell proliferation and differentiation. Aguda BD, Kim Y, Kim HS, Friedman A, Fine HA. Biophys J. 2011 Nov 2;101(9):2082-91.

Aguda BD., "The Significance of the Feedback Loops between KRas and Ink4a in Pancreatic Cancer," in Molecular Diagnostics and Therapy of Pancreatic Cancer (Ed Asfar Azmi). Elsevier Academic Press (2014). http://store.elsevier.com/Molecular-Diagnostics-and-Treatment-of-Pancreatic-Cancer/Asfar-Azmi/isbn-9780124081031/

Davide Cittaro

Title: Full deconvolution of clonal populations in recurrent hematological cancer using Gaussian Mixture Model

Authors: Davide Cittaro, Dejan Lazarevic, Cristina Toffalori, Elia Stupka, Luca Vago

Abstract: We performed Whole Exome Sequencing on five samples collected in eight years during the disease history of in a single patient with hematological cancer (Acute Lymphoblastic Leukemia, Remission and therapy-related Myelodysplastic Syndrome at three different time-points). We identified a joint set of 1201 variants that were present at least in one stage of the disease, for which we calculated allele frequencies corrected by the estimate of tumor purity. These were used to train a set of Gaussian Mixture Models (GMM) allowing for increasing number of classes. We selected the best model using Akaike Information Criterion (AIC) and assigned each mutation to a specific GMM clone. We calculated mutational signatures of each GMM clone according to the procedure proposed by Alexandrov [1] and estimated distance between them. We identified a single clone common to all relapses but not LLA, we built parent/child relationships with other clones using distance among signatures. Our analysis reveals a branching evolution of clones that putatively diverge in response to the clinical treatment. We show GMM is an effective and unbiased technique that can be applied to deconvolve clonal populations in cancer data only using allele frequencies. Clones can be then characterized by their mutational landscape, this information is sufficient to build clonal relationships when studying the evolution of the disease.

References:

1. Alexandrov, L. B. et al. Signatures of mutational processes in human cancer. Nature 500, 415–421 (2013).

Riccardo Colombo

Title: Definition of a computational pipeline for multi level metabolic analysis.

Abstract: Design principles of metabolism have been investigated exploiting several computational frameworks. Among these, constraint-based methods, and in particular Flux Balance Analysis (FBA), have proven to be useful and accurate to calculate the flux of metabolites through reactions of a metabolic network. Despite of this, constraint-based methods alone have not been able to explain mechanics of events and their temporal evolution, suggesting that other in silico methods should be applied. Due to the complex nature of biologic processes, in silico methods should consider multiple approaches to investigate systems. Multi level analysis is to- day a hot research topic in different areas, such as the theoretical formalization of the method and the development of computational tools for the integration of different modeling perspectives. For this reason we are developing a compu- tational pipeline able to perform analyses exploiting, one after the other, three main modeling frameworks for biological systems: constraint-based analysis, network analysis and mechanism-based analysis. Results emerging from the performed analyses will give a synoptic vision of the different properties of the system. In order to validate the developed method and the computational pipeline proposed, we defined a core model of the cellular metabolism in yeast [1]. The first section of the pipeline is a constraint-based analysis performed via FBA techniques maximizing or minimizing a certain physiological aspect; crucial for this task is the optimization of the objective function achieved exploiting ensemble approaches and genetic algorithms. The second part combines results from FBA with network analysis in order to highlight emergent and general properties of the system. In this context we developed a hierarchical clustering analysis exploiting a dendrogram to illustrate how solutions obtained with the genetic algorithm cluster together. Moreover we integrated in this step a visualization of the fluxes on the network and its topological analysis exploiting Cytoscape and the CyFluxViz plug in .The last part, currently under implementation, is devoted to the retrieval of kinetic constants from fluxes and to the mechanistic simulation of the system in order to allow further investigations using methods such as parameter sweep and sensitivity analysis. On the whole, the main goal of this multiple analyses is gaining, from each ex- plored model formalization (constraint-based, network-based and mechanism-based), a different kind of information in order to widen the knowledge on the system under evaluation.

References:

[1] Damiani C., et al. "An ensemble evolutionary constraint-based approach to under- stand the emergence of metabolic phenotypes." Natural Computing 13.3 (2014): 321- 331.

Laura Curti

Authors: Laura Curti, Domenico Albino, Cecilia Dallavalle, Carlo V. Catapano and Giuseppina M. Carbone. Institute of Oncology Research (IOR) and Oncology Institute of Southern Switzerland (IOSI), Bellinzona, 6500 Switzerland.

Abstract: The ETS transcription factor ERG controls multiple epigenetic effectors in prostate tumors Cancer of the prostate is a leading cause of cancer death worldwide. About 50-00 % of prostate cancers harbor ETS gene rearrangements, the most frequent being the TMPRSS2-ERG gene fusion. However, the role of ERG in prostate cancer progression is still debated. Oncogenic activity of translocated ERG may involve broad transcriptional and epigenetic reprogramming in fully transformed cells. We showed previously that ERG induces directly the expression of the histone methyltransferase EZH2, which is highly expressed in advanced and metastatic prostate cancers and promotes epigenetic gene silencing and dedifferentiation. In line with this finding, we reported that another epigenetic effector, UHRF1, was overexpressed in prostate tumors and contributed to epigenetic silencing of tumor suppressor, tissue-specific differentiation and androgen-regulated genes. UHRF1 expression was frequently associated with EZH2 upregulation and negatively correlated with expression of several tumor suppressor genes. We found that overexpression of UHRF1 was associated with ERG expression in prostate tumors. Consistently, expression of ERG in ERG negative LNCaP cells induced UHRF1 mRNA and protein level. We identify an ETS binding site in the UHRF1 promoter and demonstrated selective binding of ERG by chromatin immunoprecipitation. Thus, UHRF1 is an additional relevant target of ERG with a potentially important role in prostate tumorigenesis. This study uncovers novel epigenetic mechanisms by which ERG fusion can lead to prostate cancer progression.

Cecilia Dalla Valle

Title: MicroRNA-424 promotes transformation and stemness and is associated with aggressive prostate tumors.

Authors: Cecilia Dallavalle, Domenico Albino, Gianluca Civenni, Paola Ostano, Laura Curti, Giovanna Chiorino, Carlo V.Catapano, Giuseppina M. R. Carbone. Institute of Oncology Research (IOR), Bellinzona, Switzerland; Laboratory of Cancer Genomics, Fondazione Edo ed Elvo Tempia, Biella, Italy

Abstract: MicroRNAs play important roles in cell proliferation, differentiation and self-renewal regulating gene expression at a post-transcriptional level. To understand mechanisms controlling prostate epithelial cell differentiation and transformation, we profiled microRNA (miRNAs) expression in tissue samples of human primary prostate tumors (n=45) and normal prostate (n=21). miR-424 was significantly over-expressed in tumors compared to normal prostate and more robustly upregulated in a subgroup of tumors characterized by reduced level of ESE3 and aggressive features (ESE3low tumours). Consistently, miR-424 was at the top list of the miRNA overexpressed in prostate epithelial cells with stable ESE3 knockdown (PrEcESE3kd). Notably, prostate tumours with high miR-424 expression were enriched of epithelial-to-mesenchymal transition (EMT) and cancer stem cell (CSC) transcriptional features, reminiscent of the presence of similar features in ESE3low tumours. MiR-424 was upregulated broadly in other epithelial cancers including gastric, lung and breast cancer. Next, we showed by chromatin-immunoprecipitation (ChIP) that ESE3/EHF directly controlled miR-424 by binding to an ETS binding site in the pri-miRNA promoter and repressing its transcription. Consistent with an oncogenic role of miR-424, inhibition of miR-424 with an antimiR reduced anchorage-independent growth and cell migration. In contrast, stable expression of miR-424 increased anchorage-independent growth and cell migration in cells with low endogenous level of miR-424. Modulation of miR-424 expression affected cancer stem cell properties reducing in vitro prostatonospheres formation and the fraction of CD44high/CD24low cells. Furthermore, inhibition of miR-424 in metastatic prostate cancer cells reduced tumor initiation and metastatic spread in vivo. Collectively, these results show for the first time the activation and oncogenic properties of miR-424 in prostate tumors. Targeting miR-424 may be a valid approach to revert stemness in prostate tumours.

Justin Jee

Title: Causes and Effects in Analyses of Mutation Rates

Abstract: Mutation is one of the fundamental driving forces of cancer. But are mutations random, spontaneous events, or are they facilitated by stresses, such as carcinogens? I will review mathematics and experiments devised by Luria and Delbrück to answer this question. I will describe experiments I have done using *E. coli* as a model system and point out how biological irregularities can be incorporated into the Luria-Delbrück model. In particular, I will focus on the case study of antibiotic resistance in bacteria, which can arise spontaneously but is also "encouraged" by exposure to antibiotics themselves. Finally, I will discuss how high-throughput sequencing might be used to calculate, in an unbiased way, mutation rates for cells grown under different conditions, as well as the implications of such a method for cancer research.

Paola Lecca

Title: TO-DAG: a new graph-based timed model for cumulative cancer progression

Authors: Paola Lecca, Nicola Andrea Casiraghi, Francesca Demichelis

Abstract: The order and the timing at which the somatic alterations occur during cancer progression reveal important information on the underlying biological process with implications for diagnosis, prognosis and treatment. As latest high-throughput technologies provide base level resolution data, the cancer research community gains access to unprecedented comprehensive datasets of genomic alterations in human cancers and prompt to the development of computational models able to capture the process of mutation accumulation with as little assumption as possible. We present a novel computational method named "Timed Oncogenetic Directed Acyclic Graph" (TO-DAG) that infers the graph of the causal dependencies and the waiting times among mutational events from cross-sectional data of genomic alterations in independent human tumor samples. TO-DAG can process very large datasets, does not require a priori assumptions about the order and the timing of mutation event, overcomes the limitations of stochastic memoryless process based methods and allows for computation of conditional probability of multiple events (i.e. it is not limited to pairwise dependencies). Namely, TO-DAG computes the probability of occurrence of each alteration in a pathway as the probability that the alteration occurs when all alterations prior to it have occurred therefore inferring pathways of causal dependencies among genetic alterations reflecting more closely the real non-memoryless dynamics of the mutation accumulation during cancer formation. Once the causal structure of the graph is inferred, the waiting times of the mutation events are estimated as stochastic function of their conditional probability. We present the performance on synthetic data and the networks of causal relationships inferred among mutations affecting genes in prostate cancer [1] and in melanoma [2] and discuss them in the light of current knowledge in the genomics of those tumors.

References:

[1] C. E. Barbieri, S. C. Baca, M.S. Lawrence,F. Demichelis, M. Blattner, J. P. Theurillat, et al. (2012). Exome sequencing identifies recurrent SPOP, FOXA1 and MED12 mutations in prostate cancer. Nat Genet, 2012, 44 (6), 685-689.

[2] M. Berger,E. Hodis,Y. L. Deribe, M. S. Lawrence, A. Protopopov, E. Ivanova, E., *et al.*, Melanoma sequencing reveals frequent PREX2 mutations. Nature 2012 (485).

Giusy Pisignano

Title: Non-coding RNA-based regulation of gene expression in normal and cancer cells

Authors: Giuseppina Pisignano, Sara Napoli, Ramon Garcia-Escudero, Giuseppina M. Carbone, Carlo V. Catapano

Abstract: A variety of epigenetic events, such as DNA methylation, histone modifications and chromatin remodelling, take place during initiation and progression of human cancers. Transcriptional silencing of tumor suppressor genes, like the E-cadherin encoding gene (CDH1), is very frequent in human cancers. Loss of E-cadherin expression triggers epithelial-to-mesenchymal transition (EMT) and acquisition of tumor-initiating properties in epithelial cells. Reduced expression of E-cadherin is associated with tumor progression and poor clinical outcome in many epithelial cancers. However, what drives transcriptional silencing of tumor suppressor genes, like CDH1, is still an open question. Emerging evidence suggest that long non-coding RNAs (lncRNAs) are important players in epigenetic mechanisms and may have relevant roles in transcriptional reprogramming and tumorigenesis. In this study, we investigated the role of promoter-associated lncRNAs (paRNAs) in transcriptional silencing of tumor suppressor genes. paRNAs are defined as lncRNAs originating within a few hundred bases of transcription start sites of a protein-coding gene and have been proposed to act as docking elements for recruitment of epigenetic regulators to the neighbouring gene. We found that bidirectional transcription from distinct initiation sites in the CDH1 promoter generated sense (S) and antisense (AS) paRNAs. The level of S and AS paRNAs dictated the chromatin state and transcriptional activity of the gene. Both in human tumors and cell line models the prevalence of S-paRNAs and low AS/S ratio were associated with low CDH1 expression. The S-paRNA coordinated transcriptional gene silencing by recruiting Argonaute1 and the H3K9 histone methyltransferase SUV39H1 to the CDH1 promoter. Consistently, siRNA-mediated depletion of S-paRNA reactivated CDH1 transcription in low CDH1 expressing cancer cells. This resulted in profound inhibition of cell proliferation and clonogenic capacity. This study reveals a complex RNA-based regulatory network that relies on sequence-specific interactions of paRNAs with Argonauter1 and epigenetic effectors to coordinate transcriptional gene silencing. These findings give also a new prospective and insights into the mechanisms of gene regulation identifying paRNAs as relevant elements in these processes and potential targets for gene modulation strategies.

Daniele Ramazzotti

Title: inferring causal models of cancer progression with cross-sectional data

Comprehensive knowledge of cancer progression is of vital importance for diagnostics, prognostics and the development of targeted therapies. Towards this goal, a huge amount of genomic information has been collected in the last couple of decades from tumor samples. From this information, a set of specific driver events (e.g., genetic mutations, CNVs, etc.) has been identified as relevant in each specific progression. However, despite this flood of information, relatively little is known about the dynamics of cancer progression and the order in which these driving events are likely to occur. The main reason for this state of affairs is that information is usually obtained only at one (or a few) points in time (i.e. cross-sectional data), rather than over the course of the disease. It is an important challenge to extract the essential dynamic information from the available static data. In this presentation, I will describe a novel algorithm for inferring cancer progression from cross-sectional data named CAPRI (CAncer PRogression Inference), which combines insights from several fields, including algorithms in machine learning, theory of causality, and cancer biology.

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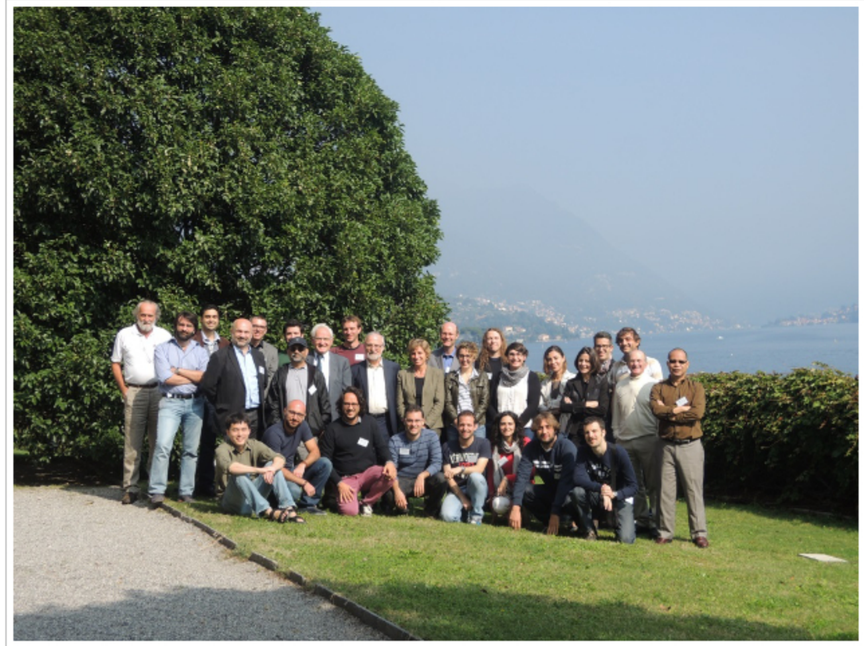
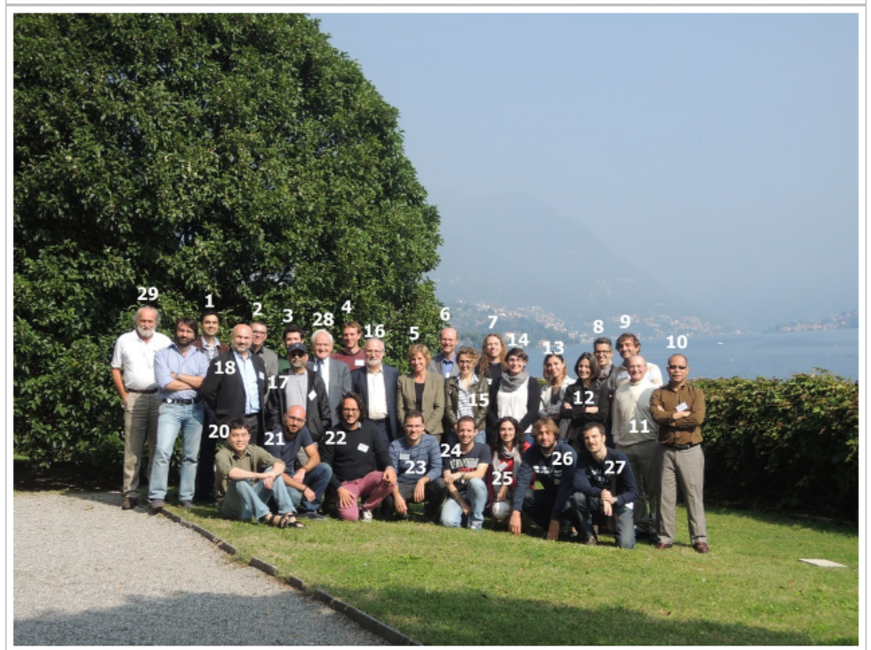
Participants





1 Mickey Atwal **2** Niko Beerenwinkel **3** Brian Lang **4** Jonas Behr **5** Cristina Messa **6** Victor Moreno **7** Marco Nobile **8** Matteo Cereda **9** Alex Graudenzi **10** Baltazar Aguda **11** Charles Cantor **12** Francesca Demichelis **13** Giuseppina Pisignano **14** Laura Curti **15** Francesca Ciccarelli **16** Giancarlo Mauri **17** Bud Mishra **18** Marco Antoniotti **19** Davide Cittaro **20** Justin Jee **21** Bachir Balech **22** Giulio Caravagna **23** Daniele Ramazzotti **24** Riccardo Colombo **25** Cecilia Dallavalle **26** Andrea Citrolo **27** Riccardo Vicedomini **28** Giulio Casati (Centro Volta) **29** Federico Codelli Canobbio (Centro Volta)

Registration

Registration fees include participation to the school, social events, coffe breaks and school material.

Regular registration (after August 31st, 2014): **380.00 EUR** VAT 22% included

One-day registration: **90.00 EUR** VAT 22% included (per day)

Personal information (required)

Name

Surname

Institution

Street

Postal code

Town

State/Province

Country

Phone

Email

Registration fee (VAT 22% included)

○ € 380,00 registration fee ○ € 90,00 one-day registration fee

Payment information (required)

Payment option

○ by credit card online ○ by bank transfer

*For credit card payment click the "pay now" button at the bottom of this page.

*For bank transfer: make it out to Centro Volta, ref. "Cancer, Systems and Complexity" drawn on Banca di Credito Cooperativo Alta Brianza – Alzate Brianza, Como, Via Rubini 3, 22100 Como – IBAN: IT 67 B 08329 10900 000000300918 – BIC: ICRAITRR950

Type of document

○ receipt ○ invoice

Invoice to be sent to:

VAT id/Fiscal code

Indicate both if different: they are mandatory to issue invoices.

Accomodation at the Guesthouse of Villa del Grumello:

○ yes ○ no

Please note: accommodation has to be paid onsite. Please check the accommodation page for details.

☐ By submitting this registration form you authorise Centro di Cultura Scientifica "Alessandro Volta" to include your personal data on its mailing list for the distribution of information material. In accordance with the Law 196/2003, you may have access to these details at any time and request their modification and cancellation.

Send

CSAC Registration fee - VAT 22% included

Full school - 380 €

Pay Now

Accommodations

The first registrants may ask to be hosted directly at the Guesthouse of Villa Del Grumello (in a shared accommodation) for an additional cost of 37.00 EUR V.A.T. included, per night up to capacity (10 places).

The accommodation can be paid on site at the check out – accommodation is available from September 28th to October 3rd (departure date), 2014.

The list of local hotels can be downloaded here: hotel list with details. For any help or additional information: please contact the Organizing Secretariat (email: alessandra.cazzaniga@centrovolta.it)

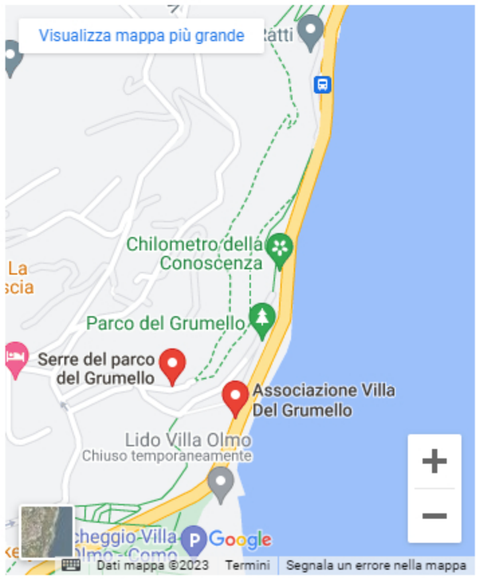
Cancer, Systems and Complexity

Lake Como School of Advanced Studies

Venue

The School on Cancer, Systems and Complexity will be held at Villa del Grumello.

Directions at this **link**



View larger map

Organization

ORGANIZERS

- Marco Antoniotti, Dipartimento di Informatica, Sistemistica e Comunicazione, Università degli Studi di Milano Bicocca, Milan, Italy.
- Bud Mishra, Courant Institute of Mathematical Sciences, NYU, New York, USA.

LOCAL ORGANIZATION

- Giulio Caravagna
- Alex Graudenzi
- Giancarlo Mauri
- Daniele Ramazzotti

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