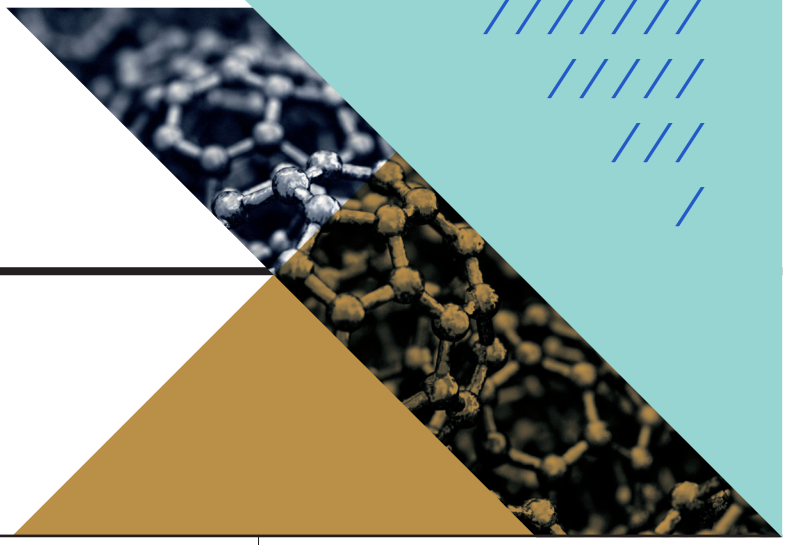
CENTER FOR
COMPLEXITY
& BIOSYSTEMS
University of Milan

COMPLEXITYBIOSYSTEMS.IT
COMPLEXITY@UNIMI.IT

ISSUE #1 / MAY, 2016
NEWSLETTER



Editorial

STEFANO ZAPPERI
CC&B Coordinator

It is already one year since the Center for Complexity and Biosystems (CC&B) started its activities at the University of Milan. A very exciting year, I would say. The center was created with colleagues from the departments of Physics, Biosciences and Computer Sciences, to overcome traditional disciplinary barriers posed by academic departments. We wanted to establish a new forum to tackle fundamental problems at the frontiers of science through an interdisciplinary approach based on complex systems. Science in general, and biomedical research in particular, is more and more driven by an unprecedented amount of data. However, extracting useful knowledge from this data requires novel quantitative analysis methods and theoretical models. CC&B has three legs that combine the main expertise needed to address this task: biologists lead by Caterina La Porta bring their knowledge of cell biology and biomedical research; computer scientists lead by Sebastiano Vigna and Paolo Boldi are expert in large scale data analytics and network theory; and physicists like myself and Guido Tiana know how to devise statistical and computational models of complex systems and materials. I am proud to say that in its first year of activity, the CC&B has already produced impressive scientific results. Let me mention here the complex regulation of cancer stem cells by microRNA discovered in melanoma by Caterina's team in an interdisciplinary work in collaboration with Cornell University. This work is important because it reveals fundamental problems in the eradication of cancer stem cells, which are at the root of tumor growth. Another important interdisciplinary work combing physics and biology, also lead by Caterina, clarified how cells change their shape: this was shown to be possible thanks to the flow of water through the membrane. In the field of materials science, my group, in collaboration with the University of Barcelona, established how spherical colloidal crystal shells deform and fail; an issue of relevance for the fabrication of new functionalized self-assembled materials. Last but not least, Sebastiano Vigna was in the news for his new algorithm to generate random numbers. You can read more about it in this newsletter. These examples provide only a glimpse of the extremely exciting activities currently underway at CC&B. In the coming newsletters, we will keep you updated on the progresses we are making on frontiers problems such as the analysis of big data in cancer, the mechanics of the cell and of bio-inspired materials, and complex processes taking place in proteins. The CC&B relies strongly on the interactions with colleagues from all around the world and in the past months we hosted a large number of seminars, and organized workshops and schools on a wide variety of interdisciplinary themes. These events are crucial to create a stimulating training environment for the real backbone of the center: the many young students and postdocs who work with us on these fascinating topics. You will hear their voices in these periodic newsletters, starting in this issue from Maria Chiara Lionetti. To conclude, I wish to thank the European Research Council who provides crucial funding for my research activities within the CC&B.

Using algorithms to unveil complexity

INTERVIEW WITH
SEBASTIANO VIGNA
CC&B founding member

The Center for Complexity and Biosystems (CC&B) consists of three thematic areas: Physics & Materials, Biosystems, and Computer Science. We had the pleasure to speak with Sebastiano Vigna, Head of the LAW (Laboratory for Web Algorithmics) and member of CC&B.

Professor Vigna, what are the main activities of the Computer Science group? The generation of pseudorandom numbers, such as the xorshift128+ algorithm of your own invention, had a certain prominence in the media.
The new algorithm for the generation of pseudorandom numbers has had a certain prominence, but actually it is not the focus of our research activities. Above all, we analyze very large networks. We have created algorithms that compress the networks, even of the size of Facebook, in a relatively small space, so that you can manipulate them on a single workstation. We have also algorithms that identify the most important nodes or the distribution of the distances with respect to the individual nodes. In general, we are able to represent the data sets in a very efficient way. In 2011, for example, we measured the entire graph of Facebook and the average distance between its users. It was a giant version of the Milgram experiment.

How can we determine if a system is complex or not?
The difference is not so much in the definition, but rather in the methodological approach. When you speak about complex networks, for a mathematician they are known as graphs. In our case, the studied object is so huge that an explicit description is not useful. With an experimental scientific approach, we construct a model based on existing networks and we try to make some predictions about its evolution. Thus, a system is complex when you cannot study it with mathematical tools, but it requires a more experimental approach. That means we must consider it as a physical object with an independent existence from us. This involves a certain loss of precision, but we are satisfied of the approximation that we can get.

How interact with each other the three CC&B research groups?
It is very important to have a multidisciplinary approach because each group makes available its own skills. In this way, you can progress beyond the limits of each branch of knowledge. The collaboration is not always trivial since the same problem can be explained and taken up in a different way from a biologist rather than a computer scientist. It is therefore necessary to have a common language. This is really exciting because the Physics & Materials and Biosystems groups will have access to our complex computational experiments, while the Computer Science group will work on material objects or living beings.

What kind of data are those analyzed by CC&B?
The CC&B is primarily concerned with biological data, which are more difficult to obtain than the social ones, generated daily by billions of individuals through photos, posts, smartphones, and credit cards. In biology, unfortunately, it is all a bit more complicated. For example, it is very difficult to have access to the data about the characteristics of cancer cells. Samples are often made of a few hundred patients. In social networks, instead, data abounds, but most is proprietary. Therefore, a typical problem of complex networks is the difficulty to obtain or access data.

Finally, what are the services and tools offered by CC&B?
With regard to my group, you can access to our websites [1][2], where there are several Java algorithms with an open-source license. This software is all available, documented and online. In any case, you can write us for the most complex problems.

Three questions to... Maria Chiara Lionetti

Ph. D. student at CC&B

What's your field of research?
I'm a cell biologist and a PhD student of environmental science, with a specific focus in complexity and biosystems. Our group is interested in several debated biological topics among which cancer, cancer physics, neurodegenerative diseases and cell division. The main topic of my research is progeria, a rare fatal genetic disorder that belongs to the family of laminopathies.

What are the main possible outcomes of your research and what impact could they have on therapies?
Our group do basic research, thus our aim is to investigate and better understand the mechanisms underlying physiological and pathological phenomena, in their complexity. Progeria is a controversial disease. The progeria gene was discovered only in 2003 and still much remains to be clarified about its function. In order to investigate it, we are using innovative molecular biology and cell biology approaches, combined with bioinformatics and phylogenetic studies. The complexity of such a topic makes it difficult to predict the possible outcomes of my research and, most of all, its impact on future applications. Although we are far from finding a resolving therapy, I'm confident that our scientific contribution could uncover an important missing piece of the puzzle.

How is to work in such a multidisciplinary team, with biologists, physicists and informatics cooperating on the same topics?
It's inspiring. Each member of the group offers his own skills and experience to others, thus resulting in a continuous exchange of ideas. This approach allows each of us to have a broader view of the issue, considering aspects that could have been ignored. I think that exploiting different individual skills and knowledge and taking advantages of them for the same purpose, is the best strategy to achieve excellent results.

Striking ALS before its triggering

A DISCUSSION WITH
PROF. NIKOLAY DOKHOLIAN
(UNC Chapel Hill, USA)
Visiting scientist at CC&B (February 2016)

The amyotrophic lateral sclerosis is a neurodegenerative disorder that hits the motor neurons responsible for voluntary movements, causing gradually worsening weakness and resulting in difficulty speaking, swallowing, and eventually breathing. Also called Lou Gehrig's disease, by the name of the renowned baseball player who was diagnosed with ALS in 1939 at the age of 36, is a rare and mysterious disease, difficult to diagnose, whose causes are mainly unknown (only 5–10% of cases are familiar) and whose incidence is 1.5 – 2.4 cases out of 100,000 persons each year. It usually begins around the age of 60 (or before in its inherited form) and quickly progress, leading most patients to death within three to four years.

There is no known cure for it. Only support therapies to improve quality and length of life as much as possible. However, research continues exploring the complex mechanisms underlying this disease.

A series of genes involved in the familiar form have been identified. Among them is SOD1, a gene that produces the Cu-Zn superoxide dismutase enzyme, which is associated with around 20% of inherited ALS cases. The enzyme protects the body from oxidative stress by neutralizing free radicals. Several SOD1 mutations are known and one of them could lead to a toxic accumulation of this protein, which in turns could contribute in triggering ALS. Several research groups are focusing their attention on this enzyme; among them, there is the one led by **Nikolay Dokholyan**, professor of biochemistry and biophysics at the University of North Carolina at Chapel Hill.

Dokholyan's team is studying the mechanisms behind SOD1 anomalous aggregation and its consequences. They are especially interested in the early stages of the diseases, since it is when the protein is still soluble and thus more sensitive to therapeutic interventions. Dokholyan presented the last results they obtained in a seminar in Milan on February 23rd, organized by the Center for Complexity and Biosystems.

"Our hypotheses is that some mutations may induce structural changes in SOD1 that promote the protein transition from its native state into soluble, potentially toxic misfolded species", explains Dokholyan. An ideal therapeutic strategy would be to interfere with those processes that facilitate the formation or soluble SOD1 or the deleterious interactions that lead to its toxic aggregation. However, in order to do so it is necessary to have detailed structural and mechanistic insight that is not yet available. "That's where our multidisciplinary approach comes into play", continues Dokholyan. Its lab uses a unique combination of biophysics, biochemistry, and structural and computational biology to uncover mechanisms of protein misfolding and aggregation. "We put the biological rules of the game into computers and then use computational biology to produce hypotheses, which we can later test with experiments. It's not different than designing planes. This way, we can design proteins that nature hadn't had before".

The final goal? To develop drugs able to stabilize SOD1 structure, preventing the formation of toxic aggregates. "But it's still a long way," warns Dokholyan. "Right now, we have some prototypes of drugs that we developed on specific cell lines but we still need to test them on living organisms, starting with mice and dogs".

SOD1 is not the only gene associated with ALS. Many others have been found, but even in those cases it seems that SOD1 aggregated and misfolded form is present. "Even though there are multiple pathways in the origins of this disease, it is possible that they converge", concludes Dokholyan. "And it's possible that SOD1 is playing the role of the killer in that stage".

A video interview with Prof. Dokholian is available at complexitybiosystems.it/en/videos

>>>> UPCOMING EVENTS

SEMINARS

May 23rd
12.30 — G22 room
Roberto Buccione
(Scientific Editor EMBO Molecular Medicine EMBO Press)
The transparent editorial process, data reproducibility and research integrity at EMBO Press
14.30 — G22 room
Meeting with PhD and Post-Doc about publishing and alternative careers

May 27th
12.30 — BS room
Xavier Trepat
(University of Barcelona)
Mechanical guidance of collective cell migration and invasion

JOURNAL CLUBS

May 9th
12.30 — room 9
Maria Chiara Lionetti
The CRISP-CAS9 system

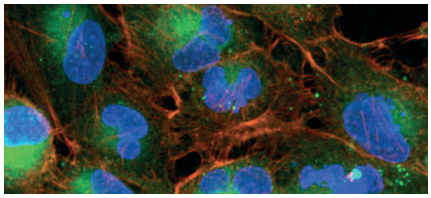
May 18th
12.30 — BS room
Enrico Ragni *(INGM)*
Human mesenchymal stem cells: from potency definition to clinical applications

→ Positions available:
If you are interested in joining CC&B as a Ph. D. student or postdoctoral fellow contact us at **complexity@unimi.it** and include your CV and a motivation letter!

Why cancer stem cells can not be eradicated

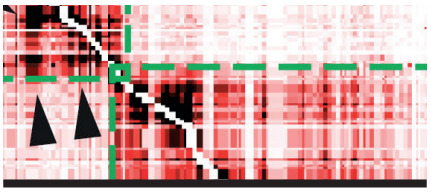
Two main hypothesis have been put forward to explain cancer origin: according to the traditional view all cells are tumorigenic and can sustain tumor growth, while according to the hierarchical model this is only possible for a small population of cancer stem cells.

In a paper just published in Nature Scientific Report, an international team lead by Caterina La Porta from CC&B including researchers from Cornell University and the Weizmann Institute of Science demonstrate that all cancer cells can switch into cancer stem cells by activating a complex network of micro-RNAs, small non-coding RNA molecules regulating a vast number of stem cell factors. This transformation does not occur randomly, but only when the number of cancer stem cells goes below a critical threshold, thus providing a mechanism to maintain a constant cancer stem cell fraction inside the tumor. This discovery has profound implications for therapeutic strategies but also for our understanding of stem cells. Eliminating cancer stem cells from the tumor would become impossible because their disappearance would trigger the switch of other cancer cells.



A. L. Sellerio, E. Ciusani , N. Bossel Ben-Moshe, S. Coco, A. Piccinini, C. R. Myers, J. P. Sethna, C. Giampietro, S. Zapperi & C. A. M. La Porta
Overshoot during phenotypic switching of cancer cell populations.
Nature Scientific Report, 5, 15464 (2015)
www.nature.com/articles/srep15464

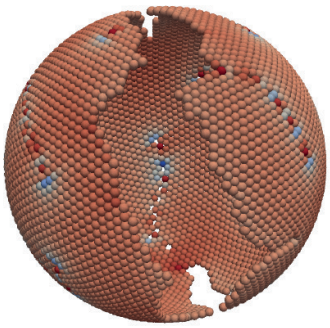
CC&B is a Coordinated Research Center at the University of Milan
Research within CC& B is supported by the European Research Council
CC&B cooperates with the ISI Foundation www.isi.it



New insights on chromatin organization

Along the research line on the structural properties of chromatin, members of CC&B lead by Guido Tiana have recently published an article on Biophysical Journal focused on the conformational fluctuations of interphasic chromatin. The dynamics of the chromatin fibre of mouse embryonic stem cells is studied making use of a physical polymeric model based on experimental data. The result is that the chromatin fiber within TADs can easily fluctuate between several conformational states, which are hierarchically organized and are not separated by important free energy barriers, and that this is facilitated by the fact that the chromatin fiber within TADs is close to the onset of the coil-globule transition. Making use of live-cell experiments to measure the dynamics of the chromatin fiber in mouse embryonic stem cells, in combination with dynamical simulations, we predict that conformational changes within one TAD are likely to occur on timescales that are much shorter than the duration of one cell cycle. This suggests that genes and their regulatory elements may come together and disassociate several times during a cell cycle. These results have important implications for transcriptional regulation as they support the concept of highly dynamic interactions driven by a complex interplay between site-specific interactions and the intrinsic biophysical properties of the chromatin fiber.

Guido Tiana, Assaf Amitai, Tim Pollex, Tristan Piolot, David Holcman, Edith Heard, Luca Giorgetti
Structural Fluctuations of the Chromatin Fiber within Topologically Associating Domains
Biophysical Journal, 110, 1234 (2016)
www.cell.com/biophysj/fulltext/S0006-3495(16)00146-6



Failure of spherical colloidal crystals

It is not possible to place a crystal on a sphere, as it is apparent by looking at a soccer ball. In that case, one has to introduce in the hexagonal crystals 12 extra pentagons, representing the topological defects of the crystal. Understanding the mechanical stability of spherical crystalline shells when they are deformed is of fundamental importance because these structures are at the forefront in the drive to fabricate new functionalized self-assembled materials.

In paper published in PNAS, CC&B scientists Carlotta Negri, Alessandro Sellerio and Stefano Zapperi show how topological defects help curved crystals to adapt their shape when the sphere is squeezed. The same defects, however, represent the weakest spot where fracture initiates when the sphere is inflated. The work, in collaboration with the University of Barcelona, is based on extensive numerical simulations of interacting colloidal particles confined to a surface. The results highlight the fundamental role played by geometrically necessary crystal defects in controlling mechanical stability and plastic rearrangements of the shell.

Carlotta Negri, Alessandro L. Sellerio, Stefano Zapperi, and M. Carmen Miguel
Deformation and failure of curved colloidal crystal shells
PNAS 2015 ; published ahead of print November 9, 2015, doi:10.1073/pnas.1518258112
Available on: www.pnas.org