CENTER FOR
COMPLEXITY
& BIOSYSTEMS
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NEWSLETTER

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*CC&B founding member*

## Is traditional biology ending?

I was trained as a traditional biologist. I use molecular biology, cutting and sewing genes, and practice cell biology by growing cells, studying their growth *in vitro* and, more interesting for me, observing cells with the microscope. I was never fascinated by molecular biology too much. I understand its role and importance, but I always considered it limited by the fact that we are using models, studying single genes and avoiding the surrounding complex network inside the cell. I thought that studying cell biochemistry was more interesting for a person like me, who is always curious and forward-looking. I studied the signal transduction pathways in tumors and in particular a kinase, PKC, for many years using cells and animal models.

But I was not satisfied.

I always had in my mind the idea that I was missing something, for PKC was just a small part within the whole world of the cell. It is not surprising, thus, that I was captivated by the study of complex systems since I first approached them about 10 years ago. I was enchanted by the idea of investigating them trying to discover their emerging properties. This is also why I like to look at the cell with the microscope and discover their crucial properties. A cell is an entire world that we have the incredible possibility to observe and analyze during its life, a complex system from which we try to extrapolate a series of quantitative properties. Thus, in the past 10-12 years, I have studied collective cell migration, the plasticity of tumor cells, and the mechanical properties of insectivorous plants using a mix between computational analysis, quantitative biology and advanced microscopy. From this perspective, molecular biology is just one of the tools that allows me to construct a model to be studied further with a quantitative approach. The cell biology approach that I am pursuing now is completely different from the one I used in the past. These days – now that our last paper on insectivorous plants was successfully published in PNAS after at least three years of intense work with an incredible interdisciplinary team – I started thinking about the future of biology and its different disciplines (biochemistry, physiology, botany... etc.). Being a general pathologist, I am very happy to have the opportunity to join this community since this discipline's perspective is quite broad. A general pathologist is someone that has to be interdisciplinary in order to properly understand the roots of diseases. I think that traditional biology is dying, and we should teach to our new generation of students a different – and interdisciplinary – way to approach science, stressing the novel job opportunities it may offer. Many of my former students are doing highly interdisciplinary jobs, which are very different from those that traditional biologists do. I think that this was possible because of the experience they had in my lab, an experience rich in complexity, full of discussions with many people with different expertise. I believe that we as part of the scientific community, have to understand and join together all these little pieces of science published and collected during the last fifty years. We do not need to publish 100 papers per year but instead we should focus on fewer papers of higher quality containing some innovative ideas.

How to do this?

I have some thoughts but I think that the scientific community should discuss all together what to do. I am beginning to plan what I will do in the next ten years. The field of "Big Data" is already old and we often analyze huge amount of data without discovering something really new and understanding their deeper meaning. Complexdata, the spinoff that I founded and serve as CEO, represents the path I want to take to give a new impulse to science and, on the other hand, to help young scientists to find a nice and exciting job. Follow me in the coming years and you will see.


## The CC&B spin-off selected as an example of creative innovation

COMPLEXDATA

COMPLEXDATA participated to the "Genio e impresa" initiative, a project by Assolombarda in collaboration with the Lombardy Region, the Innovation Lab of the Politecnico di Milano and MEET (an international centre for digital culture), launched on July 2nd at Palazzo Gio Ponti in Milan.

The spin-off – founded in June 2018 by CC&B members Caterina La Porta and Stefano Zapperi, together with Luciano Pilotti and others colleagues from the University of Milan – participated to the initiative with ARIADNE, a platform based on artificial intelligence, capable of predicting the score of aggressiveness of breast cancer starting from a biopsy.

Inspired by the historical interaction between Leonardo Da Vinci and Lodovico il Moro, "Genio e impresa" includes several initiatives like a multimedia exhibit or a treasure hunt to discover places connected to Leonardo and innovation. 130 companies responded to a call launched by Assolombarda at the beginning of the year, and only twenty out of them were selected by the Politecnico di Milano. COMPLEXDATA was one of them, together with Pirelli, Montedison, Solvay and many other renowned examples of innovation in Lombardy.

The CC&B spin-off had its own place in the exhibit, which told the story of how Caterina La Porta and Stefano Zapperi developed the idea of the ARIADNE platform. The exhibition started on July 8th and ended in September 15th; it told the story of how Caterina and Stefano met, and how they developed the first spark of the idea of ARIADNE, showing how an interdisciplinary team and a scientific couple is the core secret of innovation.

ARIADNE won other prices, as it was among the semi-finalists of Bio-Upper in July 2018, semi-finalist at the GSVC competition, won the Startup 4.0 Special Award during the Start Cup Lombardia 2018 competition, and won G-Factor, the accelerator of Fondazione Golinelli for 2019.

«It has been a great honour to have been selected among 130 participants and it was really incredible to listen to our story at the exposition»", commented Caterina. «We love to work together and find solutions to complex problems thinking on their impact on society», concluded Stefano.

## Three questions to...
## **Simone Milan**

**What was your field of research at CC&B?**
My research fields were bioinformatics and biomechanics. In particular, I was involved in two projects. The first one was related to metabolic networks and is still in progress in the lab. The second project was the investigation of leaf closures in carnivorous plants of the Droseraceae family using a biophysical approach to understand the processes behind the movement. Learning from the plants, we were able to create new meta-materials with unique bending properties.

**What are the possible outcomes of your research?**
A possible outcome for this research is, for example, the creation by 3D-printing of particular plastic materials called metamaterials, with an internal structure inspired by the cells' organization in the leaf. This material is able to imitate the trap movements when a force is applied on its surface, and responds to it in an asymmetrical way, like the trap that can only bend in one direction. Possible examples of application of this material are mechanical actuators with possible uses in soft robotics and reconfigurable materials. The advantage offered from this material is, for example, the capability to deal with delicate samples like living matter.

**What is your current research activity about?**
In the last few months after the completion of my master degree in Molecular Biotechnology and Bioinformatics, I started working for a digital consulting company. In particular, I deal with Big Data ingestion, storage and subsequent analysis. In my job, I use the latest technologies to write the most efficient codes able to perform advanced IT tasks. I find this experience very interesting because it is very different from my previous research and it gives me the possibility to learn and use new advanced programming languages.

## How glasses break

Glass represents the quintessential brittle material, shattering in pieces with little deformation. Yet at the nanoscale, silica glass becomes ductile and deforms plastically like metals. Researchers at the Center for Complexity and Biosystems investigated such a behaviour – which was observed experimentally

in amorphous silica nanofibers but still unclear in its origins – by extensive atomistic simulations, and published their results in Nano Letters.

Led by Stefano Zapperi, the group showed that the observed small sample size enhanced ductility is primarily due to diffuse damage accumulation. For larger samples, however, damage coalesce in extended cracks leading to brittle catastrophic failure. Surface effects such as boundary fluidization also contribute to ductility at room temperature by promoting necking, but are not the main driver of the transition. Understanding the brittle to ductile transition in glasses is important to better control the mechanical properties of glass nanofibers for a variety of applications.

**Damage Accumulation in Silica Glass Nanofibers**
Silvia Bonfanti, Ezequiel E. Ferrero, Alessandro L. Sellerio, Roberto Guerra, and Stefano Zapperi, *Nano Letters 18, 4100 (2018)*
https://pubs.acs.org/doi/10.1021/acs.nanolett.8b00469

## Scientists revealed a weak spot of the Huntington's disease

Researchers have found that aberrant protein aggregates responsible for Huntington's disease have some weak spots that could be exploited to hinder the development of this pathology. The study, published on *Scientific Report*, has been conducted by scientists of the Centre for Complexity and Biosystems (CC&B) of the University of Milan, in collaboration with colleagues from Penn State University.

Huntington's disease is a genetic neurodegenerative disorder caused by the production of an abnormal version of a protein, huntingtin, which is involved in several cellular processes. Mutated huntingtin tends to form aberrant aggregates – like those characteristic of other neurodegenerative disorders – that, as the disease advances, interfere with neuron functions and can also be toxic to certain cell types in the brain.

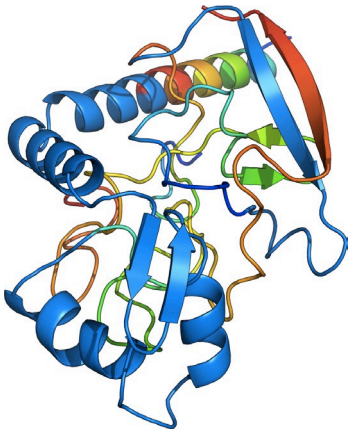
Recent studies have shown that in Parkinson's and Alzheimer's diseases the formation of these lethal protein aggregates can be transmitted to neighbouring cells, with potential prion-like infection and propagation as in the mad cow disease; these aberrant proteins can also induce their normal counterparts to change their structure assuming the aberrant one. Basically, they are capable of "infecting" the normal proteins, thus spreading the mutated conformation. Recently, it has been found that something similar occurs also in the Huntington's disease but the biological dynamics that leads to the formation of heterogeneous aggregates – i.e. those formed by both normal and mutated huntingtin – have never been studied so far, since most of the research focused on homogeneous aggregates of aberrant huntingtin.

CC&B researchers used their consolidated multidisciplinary approach to study the formation of heterogeneous aggregates of huntingtin, combining computational models and biological experiments. As a first step, they run a particular type of computational simulation that allowed them to investigate protein structures and their possible interactions. In this way, they identified a possible aggregation mechanism through which a single mutated huntingtin can bind to its normal counterparts, and some elements of the protein structure that trigger the aggregation process. After that, they verified their computational results in the laboratory, by adding mutated huntingtin in cell cultures that only possesses normal huntingtin, and analysing them with a special microscopic technique that allowed them to observe the co-localization and likely formation of heterogeneous aggregates of the two protein versions.

«Once we managed to identify the configurations that characterized the aggregates, we could understand which were the most promising molecular targets to destabilize these abnormal protein agglomerations», explained Silvia Bonfanti, post-doctoral researcher at CC&B and first author of the study.

«The identification of these possible "weak spots" in the structure of toxic aggregates of huntingtin could allow the development of drugs capable of hindering their formation, or at least of slowing it down, thus impeding the progress of the disease», added Caterina La Porta, professor of General Pathology at the Department of Environmental Sciences and Policy of the University of Milan and coordinator of the research.

**Molecular mechanisms of heterogeneous oligomerization of huntingtin proteins**
S. Bonfanti, M. C. Lionetti, M. R. Fumagalli, V. R. Chirasani, G. Tiana, N. V. Dokholyan, S. Zapperi & C. A. M. La Porta
*Scientific Reports 9, 7615 (2019)*



## Untangling how carnivorous plants catch their preys, helps design new materials

Carnivorous plants can be a source of inspiration for new materials with specific mechanical properties, according to researchers from the Centre for Complexity and Biosystems (CC&B) of the University of Milan. In a paper recently published on *PNAS* – and selected for the journal's cover – they analysed the mechanics by which one of these plants, *Drosera capensis*, folds its leaves around insects trapped on their sticky surface in order to digest them.

Carnivorous plants have fascinated scientists – including Charles Darwin, who wrote a book on the subject – for a long time, but most of the research activity focused on the biochemistry behind their leaf's movements. This allowed to identify a bunch of molecules, including plant growth hormones, that

are triggered by the presence of a prey and, in turns, can induce leaf closure. However, how mechanical forces actually carry out such a process in *Drosera capensis* is still unknown. Other carnivorous plants actuate their capture mechanisms by storing elastic energy that is then released through an extremely rapid movement, but that is not the way *D. capensis* acts: its leaves close on much slower time scales (from twenty minutes to up to three hours), thus suggesting a different self-shaping mechanism. Researchers from CC&B studied this mechanism by using milk drops of different volumes to simulate different preys landing on the plant surface, and then quantified the mechanical dynamics of the closure process by applying a counteracting force at the tip of a leaf until it is open. They combined these experiments with a detailed analysis of leaves' geometric and elastic properties, in order to build a reliable model of their mechanical behaviour, and with an examination of their microstructural features and biochemical signals.

Their results showed that the bending of *D. capensis* leaves is encoded in their cellular architecture, which is able to convert specific biochemical signals into an asymmetric response, which in turns triggers the closure movement.

«I happened to read carefully what Darwin wrote on carnivorous plants and was fascinated by how nature could create such a sophisticated machinery» said Caterina La Porta, professor of General Pathology at the Department of Environmental Science and Policy and one of the two lead authors of the study. «As a general pathologist, I want to understand the roots of biological processes. Understanding carnivorous plants


has been a tremendous challenge that helped me better clarify how different organisms combine mechanics and biochemistry to achieve their goals»

«The mechanism underlying the movements in carnivorous plants could provide inspiration in the design of bio-inspired materials with advanced functionalities», said Stefano Zapperi, professor of Theoretical Physics at the Department of Physics of the University of Milan, the second leading author of the paper. «In fact, in this study we managed to design a metamaterial structure that responds asymmetrically to a symmetric mechanical stimulus, following our experiments on *Drosera capensis*».

A similar strategy can be exploited to design other shapechanging metamaterials – i.e., artificial materials with properties usually not available in nature – that could find possible applications as components in soft robotics and provides examples of bio-inspired design.

**Metamaterial architecture from a self-shaping carnivorous plant**
C. A. M. La Porta et al.,
*PNAS 116, 18777-18782 (2019)*

## Stefano Zapperi won the Humboldt Research Award

The year 2019 marks the 250th anniversary of the birth of the great naturalist and explorer Alexander von Humboldt. In the same year, I had the great honour of receiving the Humboldt Research Award by the German foundation established in Humboldt name a few years after his death.

When accepting the award in Bamberg last March, I committed to spend a period of one year in Germany collaborating with German scientists. The planned collaboration is starting this fall and is bringing me to Munich and Fürth. I will split my time between two important German institutions, the Ludwig-Maximilian University (LMU) of Munich and the Friedrich-Alexander-Universität (FAU) Erlangen-Nürnberg.

At LMU, I will be hosted by the Arnold Sommerfeld Center for Theoretical Physics and in particular by the group of Erwin Frey, who is an expert in statistical physics and theoretical biophysics. At FAU, I will stay at the Institute of Materials Simulation in the Department of Materials Science lead by Michael Zaiser, a renowned expert in the mechanics of crystalline and amorphous materials. I will thus continue working both on biophysics and materials with the chance to interact closely with some leading researchers in both field. I expect that this year in Germany will be extremely valuable not only for myself but will provide opportunities for research interactions to the whole group at CC&B as well.

## >>> UPCOMING EVENTS

**Eytan Domany will receive the Rita Levi Montalcini Prize.**
He will be hosted for an extended stay at CC&B by Caterina La Porta.

**5 November 2019**
Rome

**CC&B Workshop at LMU**

**2 December 2019**
IBZ – Munich, Germany

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