CENTER FOR
COMPLEXITY
& BIOSYSTEMS
University of Milan

ISSUE #7 / DECEMBER, 2018
NEWSLETTER

COMPLEXITYBIOSYSTEMS.IT
COMPLEXITY@UNIMI.IT

Complexity in emergent facts between Big Data and AI

LUCIANO PILOTTI
University of Milan

The main difference between the past and the future of human action and decision-making is an emerging fact. Until recently, our future was a sort of extrapolation of the past in a linear, deterministic and mono-dimensional form, with a strong, positivistic distinction between the observer and the observed object. Nowadays, we are in the middle of an evolutionary transformation: our future – from medicine to transport, from art to economy, from territory to energy, from new technologies to nutrition, from communication to politics – will increasingly depend on Big Data and artificial intelligence (AI). The huge amount of data that we produce yearly would correspond to about one million times the information contained in the largest library in the world – the Washington Congress' library with 38 millions of books, 3.6 millions of recordings, 14 millions of photographs, 5.5 millions of maps, 7.1 millions of records and 70 millions manuscripts – and to one million times the verbal or written information that the inhabitants of the planet transfer each year.

Big Data allow to draw this evolutionary transformation of growing interdependence between environment (both physical and cultural), demography, science, technology and nature, and also between production, consumption and purchases. We can use this immense knowledge to explore the mutual influences among these different areas of action in a transition from physical to cognitive productivity in different fields:

- new information technologies, collective behavior and governance;
- industrial automation, economy, labor and society;
- natural intelligence, artificial intelligence and our decision-making abilities at individual/ community/organizational level;
- environment and health;
- computation, creativity and intuition;
- democracy and governance systems.

In medicine, for example, the project called "Precision Medicine Initiative" – confirmed by the former US President Obama with an investment of 215 million dollars – will apply Big Data analysis to decrypt the genetic traits of millions of people. Thus, opening the way to a medicine that is not only more predictive but also more interactive and participatory, with a bottom-up sharing network of available data. Biotechnology and bioinformatics data can be used to customize prevention, diagnosis and therapy for each individual. In fact, today it is possible to strengthen our immune system against specific types of tumor degeneration, urging specific antigens and obtaining highly-specialized vaccines.

We are creating a health ecosystem that links prevention, healthcare, pharmacological and surgical intervention to the cure. A healthcare system that extends the doctor-patient relationship to also include the environment (like hospitals). In addition, the integration between new biomaterials and biopharmaceuticals printed in 3D, artificial intelligence in support to medical decision, telemedicine and nanorobots, becomes the key to look at the future with unimaginable health solutions (even in remote) based on Big Data and AI.

Hence, Big Data are the core expression of a new transformative paradigm that will guide us in a future of a multi-layered and asymmetric globalization of science, society, economy, technology, and environment. Which may bring great opportunities but, maybe, also more inequalities. Thus, we will have to protect ourselves from data corporation – like Google, Amazon, Apple or Facebook – and their monopolistic approaches, since Big Data have to remain public. Such a task will require appropriate laws and rules from governments, aimed to maintain the public ownership of data of urban flows, consumption, mobility, energy, health, climate change and entertainment.

ComplexData is committed to this knowledge frontier and human behavior in the service of a new well-being and a new responsibility towards a shared governance of accessible and distributed resources, tangible and intangible, visible and invisible.

When complexity produces innovation: the spinoff Complexdata

The Center for Complexity & Biosystems of the University of Milan has embarked on a new journey: using the experience and the know-how of its members to find innovative solutions to data intense problems. To chase such a goal, on June 2018 two CC&B members, Caterina La Porta and Stefano Zapperi, together with Luciano Pilotti, professor of innovation management and corporate ecology, and other colleagues from CC&B working in computer science and applied mathematics, founded the spin-off COMPLEXDATA SRL (www.complexdata.it).
One of the main drives beyond the launch of this spin-off is to explore and develop potential applications of the research performed at the CC&B. Thus, COMPLEXDATA will provide tailored innovative solutions to data-based problem for private, public, institutional and non-profit organizations.
The fast-growing importance of Big Data is a challenge that requires new and innovative approaches. For instance, conventional visualization and analytical tools are unfit to deal with huge datasets because of their sheer size while, in biomedicine, researchers are hindered in their attempts to compare data from different sources since even slight differences in protocols and experimental may hide biological signals below confounding noise. Moreover, algorithm and computational methods can be of great help in many fields, from geolocalisation to the design of new molecules, from multiscale materials modelling to the optimisation of management strategies. By combining computer science, system biology, theoretical biophysics and materials science, the CC&B developed a wide range of proficiencies in various quantitative analysis tools.
COMPLEXDATA aims to draw from this expertise in order to face the aforementioned challenges. Its highly multidisciplinary approach is demonstrated by the curricula of the founding partners: Paolo Boldi and Sebastiano Vigna are both professors of computer science at the University of Milan, while Vittorio Loreto is the director of the SONY Computer Science Lab in Paris and professor of physics of complex systems at Sapienza University of Rome. On the mathematical front there are Giacomo Aletti and Alessandra Micheletti, professors of probability and mathematical statistics, and Giovanni Naldi professor of numerical analysis. Given the entrepreneurial nature of this project, the involvement of a researcher in economics like Luigi Orsi, together with Pilotti's experience in management and innovation, integrates the skill sets that COMPLEXDATA can provide to its clients.
COMPLEXDATA's first product is ARIADNE, an innovative platform that allows to evaluate the risk of metastasis formation by analysing gene expression of individual patients. The first step of this evaluation process consists in the integration and homogenisation of gene expression data (even from different sources). Then, using method based on artificial intelligence, it will be possible to identify the biological networks that are more or less activated; this information, combined with previous results from specific tumours, will allow researchers to quantify the risk of metastasis associated with each patient. Thanks to this project – which also involved two CC&B postdoc researchers, Maria Rita Fumagalli and Francesc Font Clos – COMPLEXDATA arrived at the semi-final of Bio-Upper in July 2018 and won the Startup 4.0 Special Award during the Start Cup Lombardia 2018 competition, held in October. A promising start for this new adventure in the field of complexity.

Cooperation between CC&B and the Weizmann Institute: the Disorder project

The foreign affair offices of Italy and Israel have recently assigned a cooperation grant to Stefano Zapperi from CC&B and Itamar Procaccia from the Weizmann Institute of Science. The goal of the project is to employ the machinery of statistical and nonlinear physics to pinpoint the mathematical underlying laws that result in the complex responses of disordered solids. Disordered amorphous solids appear in many forms, soft materials like foams and gels, hard materials like silica glass and metallic glasses and granular frictional matter like sand piles or assemblies of rice. All these materials act as solids under small strains, but they yield and flow under large strains, often catastrophically. The project will try to shed a new light on the phenomenon of mechanical yield and on the magnetic properties of amorphous solids in the bulk and in thin films, including the possible development of new memory devices. The cooperation between the CC&B and Weizmann will be developed through mutual visits of the PI's and of young collaborators, the exchange of software and the sharing of computer facilities. The joint effort is expected to lead to synergism that will enhance the capabilities of both groups and expose the early stage researchers to a bigger world of ideas and opportunities.

Quantitative dynamics of cell migration

Cells can collectively flow like a fluid but when their density increase they tend to crowd, slow down and finally arrest. This process of cell jamming could have a functional biological role and understanding how it works may shed light on a broad range of important problems, like embryogenesis, wound healing and cancer invasion. Here we showed that when a jammed cellular layer is wounded it rapidly reverts to a flowing state, and we measured several physical parameters that characterise this transition.
We studied a large set of cell layers using different cell types, which were scratched to provoke wounds. We recorded time-lapse images of the wounding process and analysed them with a specific technique that allowed us to estimate some parameters of cells movement. Then, we performed extensive numerical simulations of an active particle model where cells move due to self-propulsive active forces and interact with each other by aligning their velocities and forming adhesive contacts. Finally, we compared the simulated results with experimental

measurements, thus inferring the best biophysical parameters describing each experiment.
Taken together, our results show that scratch induced unjamming is a generic feature of cell monolayers formed by epithelial, endothelial or cancer cells. Our quantitative understanding of how key biophysical parameters conjure together to determine the collective cellular behaviour could be important to design possible interventions to promote or inhibit cell migration.

Paper references

From jamming to collective cell migration through a boundary induced transition
Soft Matter 14, 3774-3782 (2018)
O. Chepizhko, M. C. Lionetti, C. Malinverno, C. Giampietro, G. Scita, S. Zapperi, C. A. M. La Porta

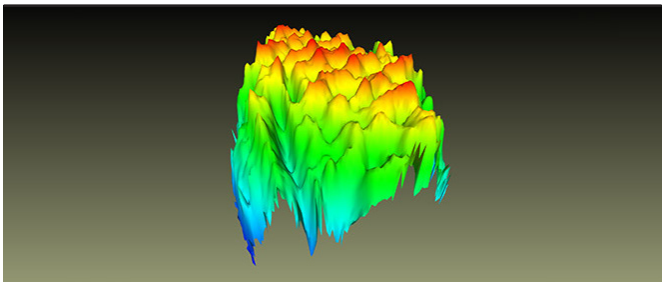
A study on twins confirms that obesity is more a matter of environment and life style, than of genes

Environment and lifestyle are more important than genetic background in the development of obesity. This is the main conclusion of a study published on Physiological Measurement by a group of researchers from the Center for Complexity and Biosystems (CC&B) of the University of Milan.
Obesity is a serious health problem, especially in developed countries. Some studies suggest that it might have a genetic origin but such explanation seems to account for only 5% of the severely obese cases. In particular, genetic contributions do not account for most variations of the body mass index between individuals, which are thus likely to be due to lifestyle and environmental factors. However, the effective relevance of the genetic background is still unclear.
"In a previous study, we identified a genetic signature that catches different features of a complex trait such as obesity, from inflammation to cancer, from mood to reproductive disorders", explains Francesc Font-Clos, post-doc researcher at the CC&B and leading author of the study. "Thus, we wanted to see if the 38 genes that constitute that genetic signature could help us to investigate a possible involvement of the genetic background in the development of obesity."
Font-Clos and his colleagues compared this list of genes with those reported in other studies being associated with variations in the body mass index (BMI). They did that by using a previously developed algorithm – which allowed them to improve the efficacy of their analysis – on more than six hundred samples from a UK database of twins, since the analysis of twin pairs with different BMI offers a very good opportunity to shed some light about the role of genetic background in obesity.
Their approach was the same used to analyse collective data on Google: they tried to combine and analyse all the available transcriptomes published in the public repositories. By doing so, they had the clear advantage of having more data, thus making it easier to discriminate the noise from the real signal.
"Our method is strongly interdisciplinary, based on the rapid development of complex network theory, which represents the foundation of new and promising disciplines like network physiology and network medicine", adds Font-Clos.
The results of this analysis show that the 38 genes that constitute the genetic signature of obesity are strongly correlated with both the body mass index and fat mass. A particularly interesting observation was made on pairs of monozygotic twins, who are genetically identical. CC&B researchers found that the obesity signature is not related to these twins' genetic background but to variations of their body mass index. Which means that the signature is associated with obesity rather than with any underlying genetic differences in the subjects, and that variations in body mass index between a subject and its monozygotic twin should be due exclusively to environmental factors and lifestyle.
"Our results highlight the important role of the environment instead of the genetic background, since they confirmed that obesity is linked to a non-correct behaviour and life-style", concludes 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. "Obesity is not due to the inheritance of some unlucky genes; it is not a matter of bad luck but a condition that can be reversed." It is thus important to study it in a broader context, where many external and internal factors cooperate.

Paper references

Gene expression signature of obesity in monozygotic twins
Physiol. Meas
Francesc Font-Clos, Stefano Zapperi and Caterina A. M. La Porta (2018)
DOI 10.1088/1361-6579/aab85a

Scientists mapped the hybrid cells that may lead to metastasis



A group of researchers from the University of Milan drew a map of the transitions that can lead tumour cells to become metastatic. Such an outcome provides useful information about the characteristics of cells during these transitions and allows researchers to visualise the activity of the genes involved. The authors of the study are part of the Centre for Complexity and Biosystems (CC&B) and their research was published on PNAS.
Our skin, as well as the inner and outer surfaces of our organs, are made of epithelial cells, which are closely connected to each other and pressed together in adherent layers that restrain their mobility. In some cases, this kind of cells can lose their features and transform into mesenchymal cells, which are less connected among them and can migrate easily. This happens during embryo development, when mesenchymal stem cells may then differentiate into bone, muscle, cartilage and fat cells, or during wound healing. But such a process is

also particularly relevant for cancer: almost 80% of human malignant tumours originates from epithelial cells that have become extremely aggressive and have invaded other tissues.

"We know from previous studies that the transition from epithelial to mesenchymal cells is a complex process, during which cells pass through intermediate states with mixed traits," explains Francesc Font-Clos, post-doc researcher at the CC&B and first author of the study. "For instance, they can combine a high mobility with adherent properties, which allow them to easily invade other tissues and then colonize them".

Cells with these hybrid traits are often unstable and their variations are determined by several genetic, physical and environmental factors. To study such a complex biological network, researchers from the CC&B used a mathematical model to simulate the transition from epithelial to mesenchymal cells, including the intermediate states. By doing so, they managed to produce a two-dimensional map that represents this transition as a rugged landscape with fractal-like features: different kinds of cells have their own positions in this landscape.

The researchers then analysed the expression of large set of genes from different kind of tissues, finding that the map obtained from experimental data is similar to the one simulated with their model. They located the genetic signatures of epithelial and mesenchymal cells, which represent the two stable and well-defined extremes of the transition; between them, they observed several hybrid states, with their own genetic characteristics, that are particularly prone to external perturbations. This strong kind of plasticity is often associated with the highly aggressive behaviour of tumour cells.

"It is also interesting to note that the fractal-like traits of our landscape are similar to those that can be observed in studies on disordered solids and glassy materials, showing that there are some common physical traits in the transition dynamics in organic and inorganic systems", said Stefano Zapperi, professor at the Department of Physics, who also contributed to the work.

The methodology developed by the CC&B researchers is not just a way to visualise the possible conformations assumed by those hybrid cells that could become malignant, but may also provide the possibility to measure the gene activity correlated to these intermediate states and facilitate the analysis of large set of sequencing data.

"Tumours are heterogeneous and the analysis of single cells that we carried out in this study sheds new light on the cancer development", concluded 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. "In particular, it helps us to understand the appearance of metastasis. In fact, we know that metastasis could come out after many years and in sites not related to the primary tumour. With our approach, we could literally see how this transformation occurs and describe a new method using network science on single cells to detangle tumour heterogeneity in view of personalized medicine".

Paper references

Topography of epithelial-mesenchymal plasticity
PNAS 115, 5902 (2018)
Francesc Font-Clos, Stefano Zapperi and Caterina A. M. La Porta

>>> UPCOMING EVENTS

6-19 December 2018

Prof. Eytan Domany

Weizmann Institute of Science

Prof. Eytan Domany from the Weizmann Institute of Science (Israel) will spend two weeks at the Center for Complexity and Biosystems. The visit is co-funded by the visiting scientist program of the Physics Department and by CC&B. Eytan Domany received his Ph D in statistical physics from Cornell University. After a few years at the University of Washington he joined the Weizmann Institute of Science in Israel, where he served as Head of the Department of Physics of Complex Systems, Chair of the Council of Professors and of the Institute's Scientific Council, was Head of the Kahn Center for Systems Biology and Henry J Leir Professorial Chair. His research interests have shifted years ago from statistical physics to bioinformatics and computational and systems biology, with a special focus on applications to experimentally and clinically motivated problems.

SEMINARS

Alessia Prato
Bristol Composite Institute, Bristol University, UK

Characterization of challenging materials: what a change in mechanical behaviour can imply

December 10th 2018
12.30 — Aula Caldirola

Eytan Domany
Weizmann Institute of Science, Israel

How to give talks

December 17th 2018
11.30 — Aula Polvani

Eytan Domany

Pathway-based personalized analysis of cancer

December 18th 2018
11.30 — Aula Caldirola

Itamar Procaccia
Weizmann Institute of Science, Israel

Catastrophic failure of amorphous materials
This is a Physics Colloquium organized by the Physics Ph. D. School

January 22th 2018
14.30 — Aula A

Andrea Mezzadri
Catholic University, Milan

Social Entrepreuriship

February 8th 2018

CC&B is a Coordinated Research Center at the University of Milan
Research within CC&B is supported by the European Research Council

UNIVERSITÀ DEGLI STUDI DI MILANO

erc
European Research Council
Established by the European Commission