CENTER FOR
COMPLEXITY
& BIOSYSTEMS
University of Milan

ISSUE #10 / JANUARY, 2022
NEWSLETTER

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CATERINA LA PORTA
CC&B founding member

Developing a personalized agriculture inspired by personalized medicine.

I study the root of pathologies, trying to identify the critical pathways involved and use this information to develop targets for therapeutic purposes. In collaboration with Stefano Zapperi and Francesc Font Clos, I used this philosophy to develop ARIADNE, a platform that predicts the risk to develop an aggressive tumor from a patient with a triple negative breast cancer. ARIADNE uses the transcriptome obtained from a bioptic sample of a given patient which corresponds to the expression of 20000 genes representing the unique phenotype of that particular subject. Using a complex network analysis assisted by AI, ARIADNE is able to calculate the risk that the patient in question will develop an aggressive phenotype. The strength of this platform is the ability to perform a deep and detailed analysis of a very complex dataset with the possibility to transfer the technique also to other kinds of tumors. Developing such a tool was only possible thanks to the interdisciplinary approach of the team blending together biomedicine (myself), complex systems (Stefano Zapperi) and data science (Francesc Font Clos).

Nowadays, agriculture is becoming more digitalized. The possibility to detect as soon as possible when plants become infected by pathogens is becoming an urgent need, as also reflected by the priorities set by the EU. Downy mildew of vine is a fungal disease caused by the mycete *Plasmopara viticola*. It is one of the most serious pathologies to damage vineyards as it affects almost all the herbaceous organs of the plant also penetrating into tissues. This kind of attack leads to a reduction of the photosynthetic activity with a consequent lower yield both in quantitative and qualitative terms. Consequences to which infected plants are subjected are not only related to the year in which it is manifested, but they could also compromise the following years as the fungus reduces nutritional reserves of the vine, leading to a loss of vigor which will be recovered only with time, therefore conditioning the productivity for the years to come. Using the same strategy and philosophy used for ARIADNE, the same CC&B team with the help of Paolo Boldi, a computer scientist also member of the CC&B, developed an integrated platform (MoWi) to fight this pathology. MoWi is able to identify the part of the field that has a higher risk to support the growth of Downy mildew. The platform combines AI and other innovative algorithms, with an APP that from a simple picture of a leaf can tell if it is affected by the pathogens, and a biological sensor that uses a biological and sustainable strategy to kill the pathogen when is identified.
The strength of this strategy is the possibility of using an integrative approach to reduce the amount of chemicals needed to fight this pathogen and produce a high quality wines. As for the case of ARIADNE, we can envisage that the same strategy can be transferred to other diseases relevant for agriculture. I think that the capability to mix different expertise and to address with a fresh and unbiases view different scientific topic is the strength of our team.

Extracting information from brain signals

High density electroencephalography (hdEEG) provides an accessible but indirect tool to record brain activity in real time. While the recorded signals encode a large amount of information, it is not straightforward to interpret them. This would be extremely useful for several potential applications such as disease diagnosis and monitoring. Researchers at the Center for Complexity and Biosystemts of the University of Milan, coordinated by Caterina La Porta from the Department of Environmental Science and Policy, have devised a new method to visualize and analyze hdEEG recordings based on a multilayer network representation. The work was just published in the journal Frontiers in Network Physiology.

A network representation provides an intuitive picture of the spatial connectivity underlying an hdEEG recording. In order to minimize the information lost in the network projection, CC&B researchers have constructed an algorithm that creates a network while maximizing the information content. The algorithm was then tested on hdEEG signals recorded during sleep in individuals with mental health issues by researchers at the Department of Health Sciences of University of Milan who collaborated to this research. The work also involved researchers at the Physics Department "Aldo Pontremoli" and at the Department of Biomedical and Clinical Sciences 'Luigi Sacco' of the University of Milan.

"By computing a set of statistical indicators of the network topology, we were able to reveal significant differences between patients with mood disorder and healthy subjects," explains Stefano Zapperi who coauthored the study. "The analysis also indicates that patients display a highly correlated activity in some regions of the brain", adds Caterina La Porta, "a very important result, because we could use our algorithm to identify patients directly from non-invasive hdEEG recordings with potential applications of the method also to other pathological conditions."

Font-Clos, F., Spelta, B., D'Agostino, A., Donati, F., Sarasso, S., Canevini, M.P., Zapperi, S. and La Porta, C.A., 2021. Information optimized multilayer network representation of high density electroencephalogram recordings. *Frontiers in Network Physiology*, p.8.

Predicting the risk of metastasis in breast cancer patients

COMPLEXDATA

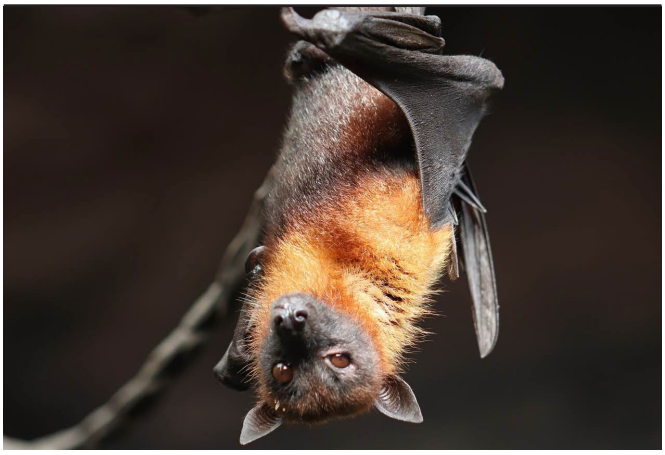
Predicting the metastasis risk in patients with a primary breast cancer tumor is of fundamental importance to decide the best therapeutic strategy in the framework of personalized medicine. Researchers from the Center for Complexity and Biosystems at the University of Milan lead by Caterina La Porta introduced and validated ARIADNE, a general algorithmic strategy to assess the risk of metastasis in patients with triple negativebreast cancer. The results are published in Cell Systems.

Triple negative breast cancer is a subtype of breast cancer with poorer prognosis with respect to the other subtypes and no specific therapeutic strategy. It is therefore of great importance to identify as soon as possible the patients with the highest risk to develop metastasis and those with lower risk
ARIADNE is able to identify patients whose tumor cells are more aggressive since they are in a hybrid state, in between the highly motile "mesenchymal" state and the more tissue-like "epithelial" state. "These hybrid cells are expected to be more aggressive and drive metastasis," explains Caterina La Porta who coordinated the study "but it is not easy to identify them from the biopsy of a patient."
ARIADNE uses a sophisticated algorithm that maps gene expression data obtained from the biopsy into the states of a computational model epithelial-mesenchymal network. "Using this mapping, it was possible to stratify patients according to their prognosis, as we showed by validating the strategy with three independent cohorts of triple negative breast cancer patients" concludes Caterina La Porta.

ARIADNE will be commercialized by Complexdata S.R.L a spinoff of the University of Milan. Complexdata cleared all the steps to obtain the CE Mark for ARIADNE as a type 2 medical device. ARIADNE provides a prognostic tool that could be applied to other biologically relevant pathways, in order to estimate the metastatic risk for other breast cancer subtypes or other tumor types.

Font-Clos, F., Zapperi, S. and La Porta, C.A., 2021. Classification of triple-negative breast cancers through a Boolean network model of the epithelial-mesenchymal transition. *Cell Systems, 12*(5), pp.457-462.

How bats coexist with viruses



How can bats coexist with viruses, including various types of coronavirus, without suffering from the diseases? Researchers at the Center for Complexity & Biosystems of the University of Milan investigated this interesting issue and found that the success in keeping viruses at bay stem from the variations of body temperature characteristic of bats.

Bats are represented by more than 1400 species, about one fourth of all existing mammal species, populating every kind of habitat and being the only mammals capable of sustained fight. Some species of bats are capable of hibernating during the winter season when the temperature decreases, prey are scarce and food requirements can easily exceed available resources. During the day, most bats decrease their activity and enter in torpor in order to hunt at dawn when the external temperature is lower and food is more abundant.

In a paper just published in the Journal of Royal Society Interface, CC&B researchers lead by Caterina La Porta, professor of general patology at the Department of Environemntal Science and Policy and Stefano Zapperi, professor at the department of physics, show that the peculiar variations in the bats body temperature are at the core of their unconventional coexistence with viruses. Using a minimal model of virus-host interaction and analysing experimental data from the literature, the researchers were able to evaluate the contribution of daily torpor in the maintenance of chronic viral infections in bats.

"We showed that daily torpor also contributes to a reduction of the immune response, preventing the risks correlated to a sustained chronic in inflammation" explains Caterina La Porta. "Our model for the interaction between virus and immune response displays interesting mathematical features showing a non-chaotic quasiperiodic attractor which makes the system more robust against perturbations in the sleep/wake cycle," concludes Stefano Zapperi.

READ THE PAPER

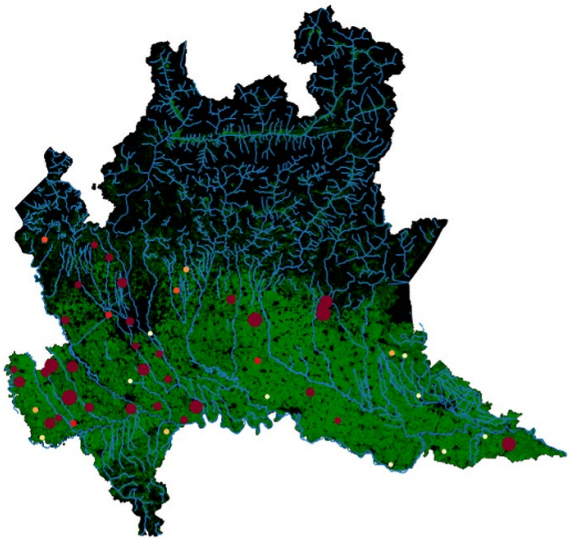
Fumagalli Maria Rita, Zapperi Stefano and La Porta Caterina A. M. 2021 Role of body temperature variations in bat immune response to viral infections J. R. Soc. Interface.182021021120210211 https://royalsocietypublishing.org/doi/10.1098/rsif.2021.0211

Synergistic effect of pollutants in Lombardy waters: an interdisciplinary analysis with Big Data and biological sensors

The 2030 Agenda, which invites us to study environmental balances with a systemic approach, underlines the strong links between the health of aquatic ecosystems and our individual and collective well-being. In particular territories, such as Lombardy, it is of crucial importance not only to monitor the state of water pollution, but also the sources of emerging risk in order to identify new strategies for intervention, prevention and change of production processes. The scientific journal Scientific Reports has published the results of a research developed by the interdisciplinary working group of the Department of Environmental Sciences and Policies and the Department of Physics of the University of Milan coordinated by Prof. Caterina La Porta from CC&B and Prof. Stefano Bocchi. The researchers, starting from geolocalized data of ARPA related to pollutants present in the waters of the Lombardy Region, were able to identify the most likely combinations (cocktails) of pollutants (generally of agricultural origin), some of which are no longer allowed, others still widely used as, for example, glyphosate. To better study the impact of these pollutant cocktails, the unicellular alga C. reinhardtii was used as a biosensor. Increasing doses of the cocktail revealed states of bioindicator stress with the progressive appearance of palmelloid neoformations.

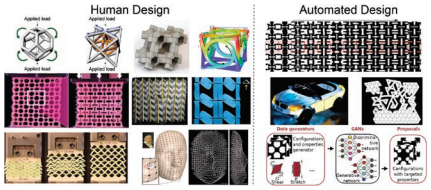
"This work uses a rigorous and quantitative approach," explains Caterina La Porta professor of general pathology and digital health expert, "which provides a strategy that can be used on a larger scale to study the synergistic impact of pollutants on the environment." Stefano Bocchi adds "These studies, developed at a territorial scale on the dynamics of ecosystems, allow us to investigate the many and complex challenges of the great One Health theme of the health of the planet, a front of innovation that pushes us to overcome disciplinary limits to adequately address increasingly complex issues."

La Porta, C.A.M., Fumagalli, M.R., Gomarasca, S., Lionetti, M. C., Zapperi, S., Bocchi, S. Synergistic effects of contaminants in Lombardy waters. *Sci Rep* 11, 13888 (2021). https://doi.org/10.1038/s41598-021-93321-6



Digital materials design

Designing materials with tailored structural or functional properties is a fundamental goal of materials science and engineering. A vast research activity is currently devoted to achieving metamaterials with superior properties and optimized functionalities by carefully fine tuning both the microstructure and geometry of the material. CC&B researchers have discussed the impact of digital technologies materials by providing in a recent perspective article that was highlighted on the cover



of APL Materials. The paper reports on recent progress obtained by combining numerical simulations, optimization techniques, artificial intelligence, and additive manufacturing methods and highlight promising research lines. The exploration of the space of possible material microstructures and geometries is reminiscent of the process of biological evolution in which traits are explored and selected according to their fitness. Biomimetic materials have long profited from adapting features of biological systems to the design of new materials and structures. Combining biomimetic approaches with digital simulation and optimization and with high throughput fabrication and characterization techniques may provide a step change in the evolutionary development of new materials.

Bonfanti, S., Guerra, R., Zaiser, M. and Zapperi, S., 2021. Digital strategies for structured and architected materials design. *APL Materials*, *9*(2), p.020904.

Three questions to...
Marianna Dourou

Postdoctoral Researcher

What is your research background?
I studied Biology (University of Patras, Patras, Greece) because I was always fascinated by the research conducted to benefit the environment. Considering the opportunities in several fields of biology, I became enthusiastic about the numerous uses of microbes. Therefore, during my Master's and my Ph.D. (University of Patras), the research focused on Applied Microbiology and Biotechnology. Specifically, I have worked on the aerobic or anaerobic bioconversion of organic wastes to high added-value compounds, using heterotrophs (i.e., yeasts and fungi) and autotrophs (i.e., microalgae). All of my research activities have been performed under the principles of circular bio-economy and sustainability, using low-cost and energy-saving technologies able to be scaled up and adopted by the agriculture or aquaculture sector.

Why did you decide to join the CC&B?
Currently, I have decided to shift my research interests a little and observe biology and microbiology under the viewpoint of dynamic systems, expanding my knowledge of cellular processes. After reading about the "Center for Complexity and Biosystems" and the recently published research articles, I immediately felt that the Center's ideas and purposes would help me explore and better understand complex phenomena and microbes' interactions with other living organisms. In addition, the idea of working in such a multidisciplinary group intrigues me.

What will be the subject of your future research?
As a Postdoc fellow at the Department of Environmental Science and Policy at the University of Milan and a member of Professor C. La Porta's group, I will work in the framework of the research project entitled "Digital monitoring of wine grapes: Precision Farming". The growing need to minimize chemicals in the vineyards using new, environmentally friendly approaches is a facing fact. My research will focus on using a biological-based method against the grape's pathogen fungus *Plasmopara viticola* without negatively affecting the quality characteristics of the wine. It is our belief that under this point of view and after optimizing the suggesting technology, the agriculture sector can become more sustainable shortly.

Three questions to...
Marco Zanchi

Ph.D. student

You just graduated in physics. What was the subject of your master thesis?
During my master thesis I have focused on the understanding of the mechanical properties of two-dimensional silica glasses by neural networks. Glasses are very complex and disordered materials preventing a straightforward comprehension of the relationship between their structural features and their mechanical behavior. These relationships can be understood by neural networks, which allow us to predict the mechanical behavior of silica simply from its atomic configuration. However, the model produced is a 'black-box' and we are not able to understand how and why the neural network is able to make the predictions. In order to solve this issue, I have applied neural networks interpretation methods which provide an insight into the decision process made by the AI algorithm. This has allowed to interpret the silica atomic structural features which cause that mechanical response

You are now enrolled in a Ph.D. in environmental sciences. What do you bring from your physics background in this new field?
During my training in physics, I have learnt how to build models to solve complex problems with a quantitative approach mainly supported by mathematical and programming skills. In addition, during my master's degree I have faced many problems from other disciplines as biology, finance and data analysis and proposed solutions inspired by physics. So, I think that my physical background can help me to propose quantitative approaches to efficiently solve problems in the field of environmental sciences.

What are the industrial applications of your Ph.D. projects?
My Ph.D. focuses on building intelligent sensors to detect and counter the infestation of Peronospora on vineyards. At the present, Peronospora has been fought using chemical insecticides, which can pollute the grounds and the waters. So, my project aims to provide an optimized and efficient way to help industries and farmers guaranteeing an eco-sustainable approach.

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

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