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NEWSLETTER

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Optimizing Complexity

Life is hardly ever questioned, and when it is the case, the minimal change to the closest maximum is clearly chosen. New solutions are more and more requested in this direction: they should be personalized, not adding disturbance, be fast, and possibly cheap. We know it, humans tend to keep their life simple. Our web apps solve a lot of our daily requests by finding solutions to an increasing number of our problem. Sometimes these same apps try to get ahead of us with various suggestions. But how can the algorithm behind the app solve efficiently our problem? To answer this question, we will consider here some scientific aspects involved with respect to the amount and complexity of the data needed to solve the problem. The web gives us access to a huge amount of data, and, in addition, every app continuously requests strategic data to rise our satisfaction.

A first key point is the reinforced learning. An algorithm is trained as a lab rat, so that situations that are liked by the customers are rewarded positively, and, conversely, discharged solutions will be penalized. In other words, reinforcement learning is a learning training method based on rewarding desired behaviors and/or punishing undesired ones. In general, a reinforcement learning agent is able to perceive and interpret its environment, take actions and learn through trial and error.

A second point is the collaborative impact of decisions on the algorithm. In fact, a personalized algorithm should have learned from the choices made by all the people that are similar (in some sense) to the querying person. From this point of view, negative reward in a transaction might be a good indicator for a possible solution for a person with a different view. In the context of book selling, it is of great interest to understand which group of people rates high or low a best seller. This second point introduces the last topic: the concept of similarity or closeness. During the cold phase, when a new user is seen by the algorithm, the solutions will be probably given according to the choices of the majority, or clustering will be made on collected socio-demographic data. As the users start to interact with the app, the first mechanism of reinforced learning will help also in moving the user closer to his true neighbors. In the example above, the neighbors are those who like your favorite books with high probability. Even if the neighbors are not known by you, they will help you find the best choice with their choices. Here, the complexity of the problem reduced by finding the community of people acting like you, so that solutions that will be proposed are likely to immediately and emotionally satisfy the request, saving human time, energy and intelligence. Moreover, the exploitation of a local optimum is balanced with an exploration in search of better solutions. When you sell books, this means that it is convenient to propose sometimes new books even if they are not positively rated by the querying neighbors

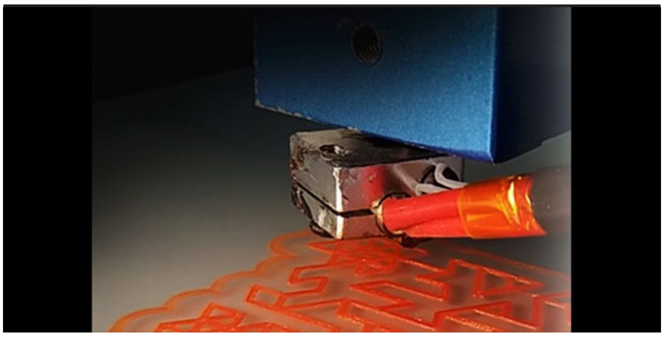
As Shakespeare wrote, "All that glisters is not gold" (*Merchant of Venice*, Act II Scene 7) or, at least, is not gold in all the fields. I started using the web since the beginning with the promise of an augmented knowledge of the way of thinking of people far from my convictions. The result now is alarming: in different situations we see people clustering on opposite positions who absolutely fail to understand the right and legitimate reasons of the other part. The support to the beliefs is continuously reinforced by the amount of data (positively rewarded choices) of the social neighbors taken as the whole truth. This fact simply reflects the dynamics of the algorithms present in the other fields. It responds to the fact that when we interface with some news, we want to satisfy our curiosity without being questioned too much. The maximum reward is to come out with as much knowledge as possible and less changes to do in our way of thinking or in our life. As an example, some analysis of the sentiments in different Twitter discussions shows long-term constant mean with local fluctuations due to reinforcement mechanisms. Strong polarization is often the final scenario of this game, both in beliefs and in the understanding and the respect of others' beliefs, the opposite of the promise of the nascent web. It is not important, from this point of view, on which side of the discussion you are, the conclusion is anyway tragically true.

The paradox is in the fact that complexity is managed with a schematic reduction where both critical and complex thinking cannot find their place. Complexity's acceptance is then not only the source of new biological life, but it might be also the antidote to a sick society, if new generations will face the reality in its entirety. Educational emergency can be faced only by adult people who are not afraid of complexity, and who are used to put themselves under discussion to find the best even with a long-term solution. With such people complexity is never a source of fear or something to keep far, even in the scientific environment.

Innovation at CC&B

Three projects submitted by CC&B researchers together with the spinoff COMPLEXDATA have been selected by Fondazione Unimi in the framework of the calls Seed4Innovation and Seed-4InnovationP. The Brain2Voice project use artificial intelligence to translate brain signals into language. The Mowi project proposes to develop a biosensor to detect the presence of fungi in grapes using bio-engineered yeast. Finally, the Metamech (http://metamech.design) project uses artificial intelligence for the automatic design of 3D printed mechanical actuators. These projects will complement the portfolio of products of COMPLEXDATA that has already developed ARIADNE (www.ariadneweb.it), a platform to predict the risk of aggressiveness of breast cancer. ARIADNE is protected by an international patent and cleared all the steps to obtain a CE Mark.

Designing 3D printed actuators by artificial intelligence



Mechanical metamaterials actuators achieve pre-determined input-output operations exploiting architectural features encoded within a single 3D printed element, thus removing the need of assembling different structural components. Actuators are currently used in many applications from machines to robots. A team of researchers from the Center for Complexity and Biosystems of the University of Milan used artificial intelligence (AI) to design metamaterial actuators with high efficiency, surpassing traditional human design. Their work was published in Nature Communications.

Designing materials with tailored mechanical properties and functionality still remains a great scientific and technological challenge, with huge potential for engineering applications and societal gains. A revolutionary approach of recent years has been to focus on materials that are structured on the macroscale producing mechanical metamaterials, a novel class of artificial materials engineered to have exceptional properties and responses that are difficult to find in conventional materials. These peculiar properties find natural applications in industrial design, as architectural motifs or reinforcement patterns for textiles, beams and other structures. The increased focus on metamaterials is stimulated by the recent advances in digital manufacturing technologies, such as 3D printing, which enable an easier design of such material structures with the removal of many of the constraints in scale and geometry at low cost. In metamaterials actuators constituent cells work together in a well-defined order to obtain a desired macroscopic movement. Current design strategies for metamaterial structures and machines are essentially based on manual operations, but CC&B researchers showed that AI can improve considerably the design process.

"We combined different computational algorithms to be able to optimize the response of the actuator and then compared the efficiency with human designed actuators. Machine design always beats human design!" explains Silvia Bonfanti, postdoctoral fellow at the Department of Physics and first author of the paper, "We have also tested that the predicted structures could be 3D printed and confirmed their high efficiency" adds Roberto Guerra, researcher at the Department of Physics and co-author of the paper. "The algorithm we devised has practical applications for human-machine interactions as interactive/responsive components and we are currently pursuing a commercialization strategy thanks to the support of the European Research Council" concludes Stefano Zapperi, professor of theoretical physics of matter the Department of Physics, who coordinated the study.

The work is supported by the proof of concept grant METADESIGN from the European Research Council.
https://metamech.design

Link to the paper:
https://www.nature.com/articles/s41467-020-17947-2

Three questions to...
Roberto Guerra
Researcher at CC&B

Can you describe your current research activities?
Presently I'm investigating how friction and dissipative phenomena arise from contacting atoms and molecules in relative motion. While macroscopic systems tend to simply generate heat in the presence of motion, things become less intuitive at the nanoscale, where the geometry of atomic patterns makes the frictional response strongly non linear, thus interesting.

What you think are the key challenges in your research field?
Most of the effort is dedicated to the attempt of quantitatively predicting the macroscopic response of a material, just by studying its microscopic details. This in practice requires designing a hierarchic set of approximations capable of squeezing extremely complex quantum-mechanical calculations into much simplified, but effective, models. The possibility of automatize such process is today a big challenge, aided by new tools such as machine-learning techniques.

Does your work have potential industrial applications?
It does, especially considering the growing need of new materials with targeted properties. Only by understanding the physics of the materials can allow us to optimize and push their characteristics to the limit. Cyclic economy and sustainable industry will require fundamental advancements in this respect, and research must provide the new ingredients for the future.

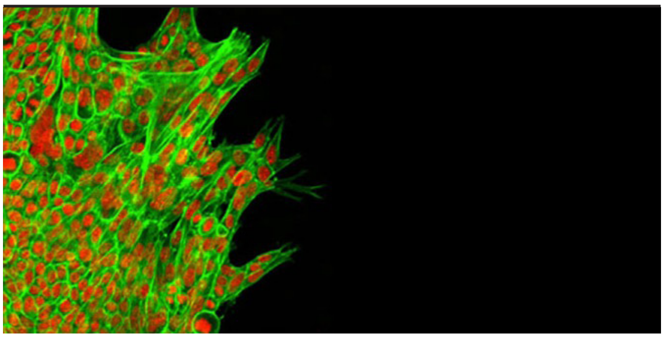
How circulating tumor cells spread through the body: a humanoid digital model

Cancer deaths are mainly due to metastasis, occurring when cancer cells detach from the primary tumor and colonize distant organs. But which organs are most likely to be colonized? And why? According to a time honored biological hypothesis, the answer depends on the compatibility between the cancer cells ("the seed") and the target organ microenvironment ("the soil"). Yet, to be able to colonize an organ, cancer cells should first reach it through the circulatory (and/or lymphatic) system. Hence, fluid dynamics should also account for the observed metastatic distributions. A precise quantification of the weight of physical and biological contributions to metastatic patterns is still missing.

To solve this longstanding issue, Francesc Font-Clos, Stefano Zapperi & Caterina AM la Porta from the Center for Complexity and Biosystems of the University of Milan constructed a high resolution humanoid computational model of the circulatory system allowing for a virtual 3D simulation of circulating tumor cells as they migrate from a primary tumor and colonize distant organs. Combining simulations with the analysis of thousands of autopsies, they disentangle the contributions of flow effects from those of "seed and soil" compatibility in explaining the spatial distribution of cancer metastasis. "It has been a real challenge to reconstruct the humanoid model from a complete 3D scan of a human body" said Francesc Font-Clos, "but with this model we can finally provide quantitative estimates of the relevance of each of the two effects" added Stefano Zapperi. "Our results highlight the importance of physical forces in understanding cancer metastasis", concludes Caterina la Porta, "and open interesting application even beyond cancer".

The paper is published in ***iScience***.
https://www.sciencedirect.com/science/article/pii/S2589004220302583

Mechanical control of breast cancer metastasis



Cancer metastasis occurs when cancer cells detach from the primary tumor and disseminate through the body either as single cells or collectively. In a paper just published in Nature Cell Biology, researchers from the Center for Complexity and Biosystems (CC&B) of the University of Milan, together with international collaborators from Radboud University Nijmagen and the Universities of Leipzig and Dresden, showed that in breast cancer the switch between single and collective cell migration can be controlled by a series of physical and biochemical factors including the stiffness of the extracellular matrix and the stability of cell-cell junctions.

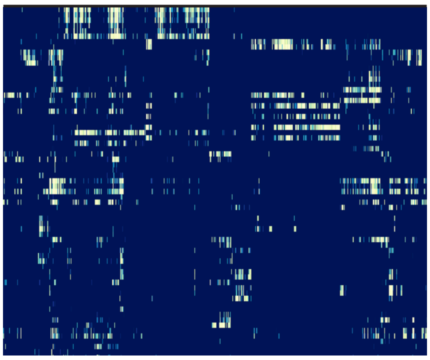
To identify the critical factors contributing to breast cancer dissemination, the authors of the paper combined experiments in vitro, in 3D spheroids, and in vivo, in mice, with quantitative image analysis and computational models. The main result is that the dissemination of tumor cells is crucially dependent by E-cadherin which plays a fundamental role as adhesion molecule. However, changing the stiffness of the microenvironment (e.g. the density of the collagen matrix surrounding the cells) the authors are also able to induce a switch in the mode of cell migration. These intriguing results are also commented by the authors in Nature Reviews Physics.

"Being able to identify the control parameters of breast cancer dissemination is of crucial importance in order to fight metastasis, which is the main causes of death in cancer patients" says Caterina La Porta professor of general pathology at the Department of Environmental Science and Policy and CC&B of the University of Milan. "It is remarkable that concept and ideas routinely used in physics to describe phase transformation in materials find such a direct application in the behavior of cancer cells", concludes Stefano Zapperi professor of theoretical physics of matter at the department of physics and at CC&B of the University of Milan.

References:
O. Ilina et al. ***Nature Cell Biology 2020***
doi: 10.1038/s41556-020-0552-6
https://www.nature.com/articles/s41556-020-0552-6

C. A.M. La Porta and Stefano Zapperi, ***Nature Reviews Physics 2020***
doi: 10.1038/s42254-020-0213-5
https://www.nature.com/articles/s42254-020-0213-5

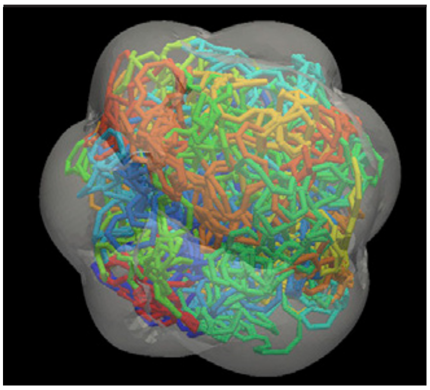
SARS-CoV2 and immune recognition



The response to SARS-CoV-2 infection differs from person to person, with some patients developing more severe symptoms than others. The reasons for the observed differences in the severity of the Covid-19 disease are mostly still unknown. In a paper published by Cell Systems, two researchers from the Center for Complexity and Biosystems of the University of Milan, Caterina La Porta and Stefano Zapperi, showed that the immune recognition of SARS-CoV-2 differs widely among individuals and could thus explain why we may respond differently to the virus.
When a cell is infected by a virus, it exposes on its surface fragments of the viral proteins, or peptides, in association with HLA molecules. There are two classes of HLA molecules: class I and class II. HLA class I molecules are exposed on the surface of all the nucleated cells and trigger the activation of T cells which then destroy the infected cell. HLA molecules differ from individual to individual and so does their ability to bind viral fragments and expose them on the cell surface. In their work, the authors used artificial neural networks to analyze the binding of SARS-CoV-2 peptides with HLA class I molecules. In this way, they identified two sets of HLA molecules present in specific human populations: the first set displays weak binding with SARS-Cov-2 peptides, while the second shows strong binding and T cell propensity. Stefano Zapperi, professor at the Department of Physics, explains "artificial neural networks are able to analyze massive amounts of experimental data accumulated over the years on HLA binding affinities to produce new predictions for SARSCoV-2." "Our work offers a useful support to identify the individual susceptibility to COVID-19 and illustrates a mechanism underlying variations in the immune response to SARS-CoV-2" continues Caterina La Porta, professor of General Pathology at the Department of Environmental Science, that then concludes, "this paper opens interesting perspectives for a pre-screening of the population to develop preventive strategies".

The paper is published in ***Cell Systems***.
https://www.sciencedirect. com/science/article/abs/pii/S2405471220302957

Nuclear alteration in progeria are due to mechanics



In a paper just published in the Biophysical Journal, researchers from the Center for Complexity & Biosystems clarified why the morphology of the cell nucleus is altered in progeria patients, who suffer from accelerated ageing due to a mutation in the lamin A gene, yielding an altered form of the protein, named progerin. The study was coordinated by Caterina La Porta, Professor of General Pathology and group leader of the Oncolab group at the Department of Environmental Science and Policy of the University of Milan and by Stefano Zapperi professor of Theoretical Physics of Matter at the Department of Physics "Aldo Pontremoli". The first authors are Maria Chiara Lionetti who carried out this study during her PhD thesis, performing all the experiments on a newly developed cellular model of progeria, and Silvia Bonfanti, a postdoctoral fellow who carried out numerical simulations of nuclear mechanics. "Our study combining quantitative cell biology and simulations of computational models provides a clear understanding of the mechanisms underlying morphological nuclear alteration in progeria. In particular, we showed that the presence of a small amount of progerin is able to change the mechanical interactions between the nuclear shell and cytoskeletal/chromatin tethers, affecting the mechanical properties of the nucleus and chromatin organization," said Stefano Zapperi. "We decided to study this pathology," explains Caterina La Porta, "because we were intrigued by the fact that progerin is also expressed in cancer, the core research field of my group. We understood that in order to clarify the role of progerin in tumors, we should first explain its behaviour in progeria. There is a paradox here, since progeria is associated with accelerated aging, while tumor cells are in principle never aging". She then concludes "Now that we have a clearer picture of progeria, we are starting to understand the role of progerin in tumor cells". These results will be described in a forthcoming paper.

The paper is published in the ***Biophysical Journal***.
https://www.sciencedirect.com/science/article/abs/pii/S0006349520303015

>>> UPCOMING SEMINARS

CC&B is continuing its virtual seminar series.
Details can be found in the website
https://sites.google.com/view/virtualseminarsoncomplexity

Previous seminars are available in the CC&B youtube channel:
https://www.youtube.com/channel/UC1l6ERTZiw0FX2PNizixwUg

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