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& BIOSYSTEMS
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NEWSLETTER

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Cancer as an emerging complex phenomenon: the new frontiers of machine learning in biology

Tumors are highly complex systems. Unravelling the biological dynamics that regulate their insurgence and growth is a major objective in biomedicine, and machine learning could provide a valuable help in such a challenge.

Conventional strategies to study cancer usually try to characterize specific genetic/biological factors supposed to play a pivotal role in tumor progression with the aim of targeting them for possible therapeutic strategies. Tumors are, however, extremely heterogeneous and their growth depends on dynamical interactions among the cancer cells and between cells and the constantly changing microenvironment. All these interactive processes act together to control cell proliferation, apoptosis and migration. There is an increasing evidence pointing out that these interactions cannot be investigated only through biological experiments focusing on limited sets of genes, but require instead an integrative approach based on complex systems. It is thus necessary to study cancer as a systemic disease in which the cancer phenotype emerges from the collective properties of complex regulatory networks. On the other hand, the enormous magnitude of tumor heterogeneity within individual's primary or metastatic tumors and between patients has become particular relevant in view of a cancer precision medicine.

Therefore, nowadays there are two complementary aspects in tumors to detangle. At macroscopic level, it is important to identify the collective properties of tumors or subcategorize each tumor into different subclasses using the new tools of computational analysis and machine learning. At microscopic level, research should focus on the heterogeneity of the tumors, to better understand the fluctuations inside the system and identify the signals from the background noise. Disentangling these aspects will lead to models that we can use to investigate the effect on cancer of external perturbations, from nutrition to the immune system. This is the central issue that we address at CC&B.

Machine learning-based intelligent systems take an input feature matrix that includes characteristic values of designated positive and negative samples, and self-trains the prediction models in the system via learning the patterns in the feature matrix to ultimately address classification problems with respect to a data set. It is clear that since there is an increasing amount of data in biology and medicine, it is becoming important to develop new machine learning/data science methods and tools, and to apply them to important problems in medicine. While Deep learning has been applied to genomic medicine, its impact has not yet reached its full potential. The genome is not always predictive of the phenotype and this fact prevents important advances in medicine. Deep learning can bridge the genotype-phenotype divide, by incorporating an exponential growing amount of data and accounting for the multiple layers of complex biological processes that relate the genotype to the phenotype. In general, deep learning is successful in application where the humans are naturally adept, i.e. image, speech etc., but it is not intrinsically designed to understand the genome. To achieve these results, the interdisciplinary approach of CC&B provides a concrete answer to the language barriers between the different disciplines from physics and computer science to biology and biomedicine.

In this way, it would be possible to approach the study of heterogeneous and dynamic systems like cancers, by investigating the emergence of tumorous phenotype from the interactions and properties of complex biological networks.

Spotting the disease before it reveals its presence

A preclinical test that may open new perspectives in the diagnosis of neurological disorders. This is the result accomplished by a group of researchers from the Center of Complexity and Biosystems of the University of Milan, who just published their work on *Physical Review Applied*.

A vast class of incurable neurodegenerative disorders are characterized by the aggregation and deposition of aberrant proteins like the amyloid β peptide or the α-synuclein, considered to be a factor behind the development of Alzheimer's and Parkinson's diseases, respectively. Detecting the onset of such aggregations before the appearance of the symptoms of the disease is almost impossible nowadays, but some possible solutions have been proposed. One of the most promising ones is to take advantage of the same process that determines the spread of the diseases to amplify minute quantities of protein aggregates. By doing this, it would be possible to screen small biological samples for the presence of very low concentrations of aberrant aggregates, thus allowing preclinical diagnosis of neurodegenerative diseases.

Recent advances in microfluidic technology allow analysis of protein aggregation in very small samples but, in order to enable such diagnostic approach, it is necessary to find a way to minimize the risk of false positive or negative detections, which may easily occur when analysing small quantities of biological material.

And here is where the group of researchers from the Center of Complexity and Biosystems comes into play.

The authors of the study addressed the problem with a computational approach. Basically, they simulated the onset of protein aggregations in small samples, in order to study how this process fluctuates depending on the volume of the samples. By doing that, they managed to design and validate a preclinical screening test that will ultimately allow the determination of the exact number of aggregates within the analysed sample. Such a result will improve the precision and quality of protein aggregations detection, thus representing a first step towards the realization of *in vitro* tests for early diagnosis of neurodegenerative diseases.

"This is the first proof of concept *in silico* that could guide the development of a test *in vitro* to identify neurodegenerative disease before symptoms appear", said Caterina la Porta, biologist and leader of the research group.

Giulio Costantini, Zoe Budrikis,
Alessandro Taloni, Alexander K. Buell,
Stefano Zapperi, and Caterina A.M. La Porta
Fluctuations in Protein Aggregation: Design of Preclinical Screening for Early Diagnosis of Neurodegenerative Disease
Phys. Rev. Applied 6, 034012
Published 21 September 2016

Three questions to...
Giulio Costantini

Postdoctoral fellow at CC&B

What's your field of research?

My field of research and interest is centred on the complex system science, from behaviour of many materials showing a manifestation of complex phenomena to biology. Actually, my main focus is the study of the polymerization dynamics of amyloid β peptides and α-synuclein proteins. These proteins can create aggregates in the cells and many researches recently correlated this mechanism to the onset of important and terrible pathologies like Alzheimer's and Parkinson's diseases.

What are the main possible outcomes of your research and what impact could they have on therapies?

Many progresses have been done about the comprehension of how these neurodegenerative diseases evolve, but the way to an effective therapy is still long. Our contribution is to shed light on the polymerization kinetics that are strongly accelerated by the presence of pre-existing fibrils. This mechanism leads to an autocatalytic behaviour with an exponential proliferation of aggregates in the cells. Understanding how to decelerate or even stop this evolution could help the researchers to find new therapies for these neurodegenerative diseases.

How long is the way that leads from theoretic studies of protein aggregation to effective diagnostic tools?

As I said before, we are again far from having an effective therapy, but the way to create a tool for preclinical diagnosis is within our reach. A similar methodology already existed but it is used with prion disease and, unfortunately, it cannot be easily performed for the amyloid fibrils. Our idea, exposed in a recent publication, is to bypass the difficulties of the above methodology by using microfluidic technology supported by a model that quantifies possible errors due to false-positive and false-negative detection. Our results allow us to validate, in silico, a preclinical screening test and this is the first step to develop effective diagnostic tools for neurodegenerative diseases.

Starfish and sea urchins as inspirations for regenerative medicine

Living systems provide a formidable source of inspirations for the synthesis of new classes of materials. With this idea in mind, scientists from the Center of Complexity and Biosystems of the University of Milan developed a model that may pave the way for the design of bio-inspired materials. In fact, such a model would allow to explore the mechanical properties of a material before its production, by simulating them with a computer.

The structural and mechanical properties of animals mostly relies on collagen, which is one of the main structural protein of animal bodies and is present in tendons, cartilage, skin, bones, and many other tissues. Due to its mechanical proper-

ties, marine collage is a particularly promising material for the improvement or the replacement of biological tissues, and for application in regenerative medicine. This is why the researchers – whose results have been published on the *Journal of the Mechanical Behavior of Biomedical Materials* – focused their attention on the network of collagen molecules that constitutes the main component of the structure of three marine invertebrates: sea urchin, starfish and sea cucumber.
They analyse the elastic forces and the stiffening behaviour of these molecular networks. They found out that their mechanical properties are very similar to those of the collagen of mammalian origin, which confirmed that marine collagen might have a relevant use in biomedical applications. This experimental approach was followed by the development of a computational model that reproduce some key features of the experimental results and allow to simulate them. Such a model might thus represent the first step of the process necessary to synthetize a new materials, with specific mechanical features.

M. Ovaska et al.
Deformation and fracture of echinoderm collagen networks Journal of the Mechanical Behavior of Biomedical Materials
65, 42 (2017)

Three questions to...
Markus Ovaska

Ph. D. student at Aalto University

What's your field of research?
I am a physicist mainly doing research on how different materials deform and break, both experimentally and by doing simulations. I have previously studied materials such as metals, paper and wood, but this was my first experience with materials of animal origin.

What are the main possible outcomes of your research and what impact could they have on the production of new materials?
Characterizing the mechanical properties of collagen membranes, such as their stiffness and strength, is crucial before they can be used in any applications. We found the properties to resemble those of human skin, which suggest that the collagen membranes could be used in many biomedical applications. The numerical model we have developed allows us to better understand how the mechanical behaviour depends on structure, and this knowledge could be used to tune the production process of the membranes.

Animals provide a wide range of inspirations for scientists from different fields, from nanomedicine to material science. What are the animal models that you would be very excited to study?
It would be interesting to modify the model we have used here for animal-based fiber networks, and see how it could be applied to other fibrous materials, for instance paper. I also find it fascinating in general, how the mechanisms that have evolved naturally in animals can be used as a basis for models and applications in physics.

The Second Workshop of CC&B
October 5th, 2016

More than one year has passed since the foundation of the Center for Compexity and Biosystems. One year of rich and multidisciplinary explorations of the world of complex systems. Now, it is time again for the members of the Center to sum up what they did in the last year and to discuss future perspectives. The Second Workshop of CC&B will be the occasion for such discussion. It will be held on October 5th in the Sala Crociera Alta at the University of Milan, via Festa del Perdono 7, and will be open to everybody who wants to participate. We asked a few questions to Stefano Zapperi, coordinator of the Center, about this upcoming event.

What are the main goals accomplished in this first year of activity of the Center?
This first year of activity has been very rich. We formally started in April 2015, but things got into full swing only since September. During the course of the year, CC&B hosted a remarkable series of seminars by distinguished guests from all over the world. We learned about the latest development in individual and collective cell migration, quantitative image analysis, gene regulation, but also fracture and fluid flow. We held a stimulating series of journal clubs where young students and postdocs discussed their results. But most of all, we had incredible fun doing research with such an interdisciplinary approach.

Are there issues or weaknesses that still need to be solved?
While we made tremendous progress in integrating all our different backgrounds, from computer science to physics and biology, into a common interdisciplinary perspective, there is still work to do in this direction. The key issue is that the Center still lacks a common physical working space. We hope to solve this problem in the coming year.

In this workshop you will also discuss the future perspectives of the Center. Are they evolved since last year?
The core scientific ideas and motivations of the Center remain the same, but of course the specific problems we are studying are always progressing and changing.

Talking about the future, are there some topics that you and your colleagues would like to explore with your approach?
An important problem we are currently studying from a biological, bioinformatics and biophysical perspective is Progeria. We will have a long public discussion about it on October 5th. Jumping on a completely different subject, we are also exploring the biomechanical properties of carnivorous plants, again combining physics and biology. This issue is important since these plants can provide inspiration for new smart materials. A fascinating aspect of complex systems research is that it is not confined by narrow boundaries but can instead move across different disciplines.

Living with progeria

Getting very old at a very early age. This is what progeria is about. This genetic disorder has many forms – the most classic of which is Hutchinson-Gilford Progeria Syndrome – and is caused by a mutation in the gene called LMNA, responsible for the production of Lamin A, one of the main component of the cell nuclear structure. There is no cure for it. Children with progeria have a very short life expectancy and usually die from complications of atherosclerosis and hearth diseases. Such a disease is extremely rare: there are about 70 known cases all around the world, five of whom in Italy. And one of them is Sammy Basso.

Sammy will participate to the special event organized by the Center for Compexity and Biosystems on October 5th, just after the Center's second workshop. The event will be focused on progeria – one of the Center's lines of research is investigating the mechanisms underlying physiological and pathological changes provoked by this disease – and will see the participation of two eminent speakers.

One is Leslie Gordon, professor and researcher in medicine, and mother of a child affected by progeria, who died in 2014. Leslie co-founded The Progeria Research Foundation and participated to the study that identified the gene mutation associated to the onset of the disease, in 2003. She will talk about the scientific aspect of progeria and present the state-of-art of the research on this topic.

The second speaker will be Sammy himself. Sammy was born on December 1st, 1995 in Schio, and was diagnosed with progeria at the age of two. Since then, his parents Laura and Amerigo started to look for information on this rare disease and, in 2005, they founded an Association to spread information about it and to give their contribute to scientific research.

Progeria has a hard impact on the body, causing it to age at a rate eight to ten times faster than normal, but it does not affect the mind. And Sammy is a sound example of that. He is very active and curious; he participated, along with his parents, to several international meeting with other families and doctors; he enrolled to university to study biology, in order to know more about what was happening to his body; and he took an active role in the Association, by participating to different kinds of events to share his experience.

And this is what he will do at the event organised by the Center. Interviewed by the health and science journalist Roberta Villa, he will talk about himself. He will explain how he conceived the Association's logo, a salamander. He will tell about his US tour and his meeting with Avatar's director James Cameron and The Simpsons' creator Matt Groening. He will share his view about the Web and its potential role to raise awareness on topics like rare health disorders. Ultimately, he will talk about his life with such a disease.

To conclude the day dedicated to Sammy and to raising awareness around his rare disease, there will be a charity-evening event at Motosplash, in via Gardone 22, Milan, with a BBQ dinner, live music and a raffle, the proceeds from which will be entirely donated to the Italian Association Sammy Basso.

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

>>> UPCOMING EVENTS

WORKSHOPS

October 5th
9-17.30 — Sala Crociera Alta
via Festa del Perdono 7, Milano
Second CC&B Workshop

SEMINARS

November 17th
Herbert Levine
Rice University
Can theory help us understand cancer metastasis?

November 30th
h 12.00
Stephan Grill
Technische Universität Dresden
Biotechnology Center
Actomyosin Force Generation and Pattern Formation

>>> LATEST PUBLICATIONS

Looping probability of random heteropolymers helps to understand the scaling properties of biopolymers
Y. Zhan. L. Giorgetti, G. Tiana
Phys. Rev. E 94, 032402 (2016)

Bursts of activity in collective cell migration
Oleksandr Chepizhko, Costanza Giampietro, Eleonora Mastrapasqua, Mehdi Nourazar, Miriam Ascagni, Michela Sugni, Umberto Fascio, Livio Leggio, Chiara Malinverno, Giorgio Scita, Stéphane Santucci, Mikko J. Alava, Stefano Zapperi, and Caterina A. M. La Porta
PNAS, 2016
doi: 10.1073/pnas.1600503113