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NEWSLETTER

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Geometry, the master of mechanics

Seeing my work appear in the blackboard of the sitcom The Big Bang Theory was undoubtedly the most unexpected event in my academic career to-date. I have no clue what inspired them to choose that piece of work but, perhaps inadvertently, they managed to capture a central theme of my academic research, and the reason that I had been looking forward so much to working in the CC&B group.

The central themes of my research up to that point in time, and the underlying concepts of that blackboard, are the ideas of structural hierarchy and bio-mimicry. Hierarchical structures, to me, are defined by their use of elements that have an internal, non-trivial, sub-structure with a much smaller characteristic length-scale. The original inspiration for the research of hierarchical structures was the observation that many natural structures are constructed this way, and that these naturally occurring geometries use material in a remarkably efficient manner.

Perhaps my favourite example of hierarchy in nature is trabecular, or "spongy", bone. This bone, found at the joints of many mammals, has been analysed in depth and the scaling of strength and weight has been found to have unusual and advantageous properties. Even more intriguingly, it has been observed that the geometry exhibits some degree of self-similarity — the structure looks the same regardless of how much you zoom in, self-similar in this case implies a degree of hierarchy. Starting from the assumption that self-similarity and efficiency were related, we tried to optimise slender hierarchical structures to suppress buckling as much as possible (using a given volume of material), with considerable success. Later, we found that this design philosophy is beneficial, not just under axial load, but in many loading conditions or environments: in pressure bearing structure, two-dimensional plates under applied moments, metamaterials under (almost) arbitrary applied stresses, creating flaw tolerance, and even when considering adhesion, hierarchy can be beneficial.

I believe this work is part of a wider theme, the idea that geometry and function have an intimate link. The term "designer material" has been coined recently referring to materials where the internal geometry is chosen to generate mechanical properties most fitting the chosen application. This could involve suppressing fracture, energy damping or maximising stiffness while minimising weight; each of these applications could require a completely different architecture, but in each case, geometry is the master of mechanics. An exciting development in this direction has been the advent of digital manufacturing (particularly additive manufacturing and laser cutting), which allows for complex geometries with numerous length-scales to be fabricated quickly and inexpensively. This gives the designer freedom to fabricate and test novel geometries that would previously have only been appropriate for theoretical studies.

This link between geometry and mechanics has inspired me to start studying kirigami (paper-cutting), origami (paper-folding) and rigidity theory. One interest that I have in this direction is how small changes in geometry can have a huge impact on a structure's — or meta-material's — response to mechanical stimuli. Most recently, I've been fascinated by the idea of elastic instability being used as a route to beneficial properties: in a rather unexpected twist, the phenomenon I had been trying so hard to suppress for so long, is exactly that which I'm now trying to utilise.

The possible link between cholesterol and neurodegenerative disorders

A prolonged decrease in the cholesterol content of cell membranes may provoke an abnormal accumulation of proteins. And that, in turns, might lay the ground for the insurgence of a neurodegenerative disease. This is the striking result of a study carried out on cultured cells by a group of scientists from the University of Milan, led by Caterina La Porta.

With cardiovascular diseases being the first cause of death worldwide, reducing cholesterol levels in the blood is one of the primary strategy against circulatory problems. And statins have proven very effective in doing that. But what happens when such a decrease occurs not in the blood, but in the cellular membranes? Cholesterol is known to play a crucial role in regulating the properties of cell membranes, affecting their fluidity and rigidity. Hence, by regulating its biosynthesis it would be possible to affect the form and function of all the membranes within the cell.

La Porta and her colleagues combined biological experiments and mathematical simulations in order to provide an answer to this question. They tested three different statins – SIM, rosuvastatin and PRA – and betulin, an inhibitor of two proteins that controls cholesterol concentration, on cultured cells. Their results, published on *Scientific Reports*, show that depleting cholesterol, both through statins or betulin, induced the aggregation of a protein called neuroserpin.

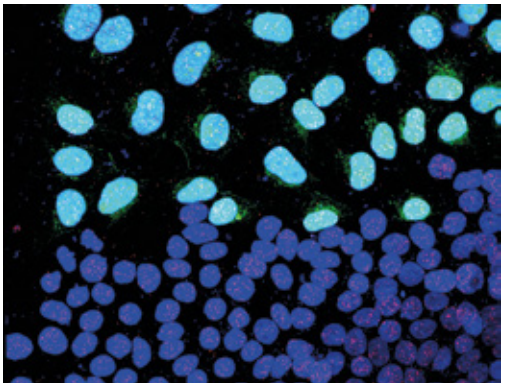
Neuroserpin is quite an important protein, for it plays a relevant role in brain development and neuronal survival. Mutations in the gene coding for neuroserpin produce abnormal versions of this protein, which may attach to one another forming anomalous aggregations within neurons. These clumps, in turns, provoke a progressive disorder of the nervous system called FENIB, which stands for "Familial encephalopathy with neuroserpin inclusion bodies", an extremely rare neurodegenerative disease characterized by dementia and seizures.

However, the experiments carried out by La Porta and her colleagues were performed on cultured cells with no mutations on the neuroserpin gene. Meaning that a chronic exposure to substances that decrease cholesterol levels in the cell membranes led to a dramatic increase in neuroserpin aggregates, regardless of genetics.

To elucidate the mechanism underlying this observation, the researchers developed a simple mathematical model, which they used to test a specific hypothesis. As mentioned before, cholesterol has an effect on some properties of cell membranes and its depletion could impair the formation of small cellular structures called vesicles, which are used to transport materials within the cells. According to the researchers' model, it is possible that small changes of key membrane parameters, induced by prolonged low levels of cholesterol, will result in a net impairment of vesicle formation, which in turns may lead to neuroserpin aggregation. Even in the absence of deleterious mutations that are known to induce aggregation of this protein. Taken together, these results suggest that long-term treatment with statins may affect intracellular trafficking in a way to enhance neuroserpin aggregation. Which does not mean that taking statins will eventually result in the onset of a serious neurodegenerative disorder such as FENIB. Further studies are necessary to clarify this point. However, protein aggregations are not a physiological phenomenon and, besides, neuroserpin is not the only protein that may be affected. "We focused our attention on neuroserpin but the alteration of the cell membranes and the intracellular transport system might provoke the aggregation of other proteins," say Caterina La Porta. "Moreover, neuroserpin aggregation has been also associated with other neurodegenerative diseases that are more common than the very rare FENIB, for instance Alzheimer's disease".

While we know that lowering cholesterol levels in the blood may reduce the risk of cardiovascular events, the consequences of chronic cholesterol depletion on the cell membranes were still unclear.

"What we have demonstrated in this paper is that neuroserpin without mutation can aggregate under specific environmental conditions, such as cholesterol impairment," concludes La Porta. "However, further studies will be needed to better understand the interplay between cholesterol, cell membranes properties and protein aggregations".



C. Giampietro, M. C. Lionetti, G. Costantini, F. Mutti, S. Zapperi & C. A. M. La Porta
Scientific Reports 7, Article number: 43669 (2017)

Link to the original paper in *Scientific Reports*:
www.nature.com/articles/srep43669

Three questions to... **Costanza Giampietro**

Researcher at ETH Zurich

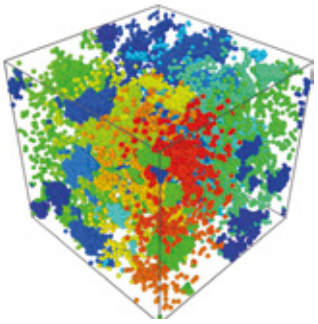
What's your field of research?

My field of research is vascular biology, my specific expertise are endothelial cell biology, cell-cell junction organization and signalling. I worked as PostDoc in the group of Elisabetta Dejana at IFOM, in Milan, for more than 10 years and I was a member of the Centre for Complexity and Biosystem at the University of Milan. Here I collaborated with Caterina La Porta on her research project about the role of cholesterol in neuroserpin aggregation. I recently joined the Laboratory of Thermodynamics in Emerging Technologies run by Aldo Ferrari at the ETH in Zurich. Here I share my knowledge and experience in vascular biology with physics, engineers, medical doctors and chemists working on the Zurich Heart project.

What are the main possible outcomes of your research and what impact could they have on biological and medical research?
More than 20 million people worldwide suffer from heart failure. Mechanical circulatory supports, such as implantable mechanical pumps, are viable solutions for patients, especially given the low number of available donor hearts for transplants. Artificial hearts suitable for long-term use are a promising alternative, and this is what we are working on in the Zurich Heart project.

The activity of biological systems is based on a complex intersection of different mechanisms and dynamics, from physiological functions to molecular interactions. What are the main challenges for a researcher aiming to study such systems?
Biological systems are complex. The project I'm actually working on is multidisciplinary and it requires the cooperation of different expertise in all of the necessary technical fields: this is challenging for a researcher. You need to find a "common language" to be understood outside your discipline, you have to communicate in a different way. This requires a lot of motivation, but it is also the most satisfactory aspect: to be able to work at high level and, at the same time, to address all the individual aspects of the problem.

Direct observation of percolation in the yielding transition of colloidal glasses



When strained beyond the linear regime, soft colloidal glasses yield to steady-state plastic flow in a way that is similar to the deformation of conventional amorphous solids. Plasticity in amorphous materials is associated with irreversible rearrangements of localized and highly strained zones, but the microscopic origin of yielding and plastic flow in soft glassy materials is still unclear.
To study how these rearrangements grow and organize in the transient state across yielding, an international team joining CC&B members lead by Stefano Zapperi and experimentalists from the University of Amsterdam combined confocal microscopy experiments on three-dimensional hard-sphere colloidal glasses with atomistic simulations of metallic glasses and mesoscopic modelling.
The researchers identified growing clusters of non-affine deformation percolating at yielding, which indicate that percolation of highly non-affine particles is the hallmark of the yielding transition in disordered glassy systems. This result seems to show a universal critical transition at the yielding of glasses and raises interesting questions on the most appropriate coarse-grained description of the yielding of amorphous solids. The work is part of the SIZEFFECTS ERC project and was published in one of the most prestigious physics journal: Physical Review Letters.

A. Ghosh, Z. Budrikis, V. Chikkadi,
A. L. Sellerio, S. Zapperi, and P. Schall
Phys. Rev. Lett. 118, 148001 (2017)

Direct link to the article:
https://journals.aps.org/prl/abstract/10.1103/PhysRevLett.118.148001

Three questions to...
Zoe Budrikis

Postdoc @ISI Foundation

What's your field of research?
I get to work on a wide variety of topics, which I enjoy. The overarching theme is using theoretical and numerical models to understand mechanical properties of complex materials, whether it's plastic deformation of amorphous materials, deposition of graphene on patterned substrates, aggregation of misfolded proteins, or behaviour of living cells.

What are the main possible outcomes of your research and what impact could they have on the production of new materials?
It's important to deeply understand the physics of materials if we want to engineer new design solutions – in that sense, my research is a building block for all kinds of materials development. For example, my work on plastic deformation in amorphous materials contributes towards understanding bulk metallic glasses, which have potential for everything from sport equipment to surgical implants.

How do different materials behave when pressed or strained? Do they deform in different ways?
That's one of the interesting aspects of my research into materials deformation – what behaviours are system-specific, and what are universal? Recently, in collaboration with a research group in Nuremberg, Germany, we've used simulations to demonstrate conclusively that you can summarize the plastic yielding transition for amorphous materials using a few numbers (scaling exponents) that are the same whether you stretch a sample, or shear it, or bend it, or even indent it. This is quite remarkable, because stress fields within an amorphous material are strongly direction-dependent, and the scaling exponents we find reflect this fact, but in the end universality still holds.

Complexity in cancer stem cells and tumour evolution: toward precision medicine

Understanding how tumours grow and develop is a key objective in cancer research. In a review published on ***Seminars in Cancer Biology***, Caterina La Porta and Stefano Zapperi, from the Center for Complexity and Biosystems of the University of Milan, discussed recent advances on the plasticity of cancer stem cells and highlighted their relevance for the understanding of the metastatic process, which, in turns, is crucial to guide therapeutic interventions.

Two main models have been used to describe this tumour growth: according to the stochastic clonal evolution model, most neoplasms arise from a single cell of origin, and cancer progression results from acquired genetic variability within the original clone allowing sequential selection of more aggressive sublines. On the other hand, the cancer stem cell (CSC) theory states that cancer cells are not all the same but are organised in a hierarchical structure, with a few of them acting as stem cells that reproduce themselves and sustain the cancer. Which means that a good way to get rid of a tumour would be targeting these CSCs with specific drugs and prevent them from nurturing the neoplasm.

The question of how tumours evolve, either stochastically or hierarchically, is at the core of an intense scientific debate. However, according to La Porta and Zapperi, the idea that only two possible scenarios are possible for cancer development appears too simple, as proved by contrasting results that appeared regularly in scientific literature. Results that could be explained with the discovery the depletion of cancer stem cells leads the other cancer cells to switch back into the cancer stem cell phenotype. This phenotypic plasticity could be either driven by genetic mutations or regulated by epigenetic factors.

Moreover, this plasticity has important implications for metastasis since migrating cells do not need to be cancer stem cells in order to seed a metastasis. In fact, the migrating cell could be a cancer cell that would automatically switch into a CSC once it has spread far enough from the primary tumour, thus triggering a new metastatic cycle. The phenotypic switch may be triggered by a depletion in the number of CSCs, but also by the surrounding microenvironment, as proved by the exposure of cancer cells to transforming growth factor beta (TGF-β), or repeated hypoxia/reoxygenation cycles.

La Porta and Zapperi also discussed the interplay between the CSCs niche and the immune system, in the light of the phenotypic switching mechanisms. A relationship that might be interesting to investigate, as it could provide information and ideas for new immune therapies aimed to influence the cancer microenvironment.

It is clear that the phenotypic switch in CSCs pose a challenge to existing therapeutic strategies. However, it also opens possible new avenues. Instead of directly targeting CSCs, a more successful strategy might be to prevent cancer cells from switching back into a pluripotent state. To this end, a possible future scenario might be to understand by microarray analysis the complex network of miRNAs produced by each tumour and study, with the aid of computational analysis, its possible impact on the plasticity of the cells.

Direct link to the article:
http://www.sciencedirect.com/science/article/pii/S1044579X17300251

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

CC&B third annual workshop

On October 9th, at the University of Milan, the Center for Complexity and Biosystems (CC&B) will hold its third annual workshop. The event, open to everybody who wants to participate, will represent an opportunity for the members of the Center to sum up what they did in the past year and to discuss future perspectives.

CC&B members will present the most recent advancements of their research and confront themselves with international guests who developed innovative ideas in similar scientific fields. As it happened in the previous editions, the CC&B annual meeting aims to bring together experts from different disciplines, accordingly to its highly interdisciplinary approach in scientific research. Furthermore, there will also be room to discuss the state of Italian research, with a particular focus on the conditions that young researchers have to face in order to find chances and support to carry out their work.

The workshop will be held in the eminent venue of the Sala Napoleonica of the University of Milan, in Via Sant'Antonio 12, beginning at 10 am. Stefano Zapperi, head of the CC&B, will open the event, while other CC&B members, Caterina La Porta, Guido Tiana and Sebastiano Vigna, will present their work. Four guests will be joining them with their talks: Ira Skvortsova, from the Innsbruck Medical University, Aldo Ferrari from the ETH in Zürich, Daniela Paolotti, from the ISI Foundation in Turin, and Luca Carra, scientific journalist from the Zadig agency, in Milan.

>>> UPCOMING EVENTS

SEMINARS

Michele Bellesi
Università Politecnica delle Marche
Sleep and synapses

June 21st 2017
12.30 — BS Room
via Celoria 26, Milano

SUMMER SCHOOL

Second Lake Como School on Advances in Complex Systems

June 3–7, 2017
Villa del Grumello, Como, Italy

designed by dndg.