CENTER FOR
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NEWSLETTER

GUIDO TIANA
CC&B Member

Picturing the genome in the cellular nucleus

The various genome projects started at the turn of the millennium provided the DNA sequences of several organisms. These sequences store much, but not all, of the information needed for the development of the organisms. For instance, small pieces of the genome – the genes – define the proteins needed by the organism, but not when and in what type of cells they must be produced. Cells have several ways to synthetize a given protein only when necessary, and some of them involve the spatial organisation of the genome within the cellular nucleus. An example is the approaching of a specific piece of the genome, called *enhancer*, to a gene is a widespread mechanism to activate that gene, and thus to produce the corresponding protein.

Having a picture of how chromosomes are spatially arranged within the nucleus can thus be very useful to understand how and when different genes are activated. And that, in turn, would help us to investigate the underlying molecular mechanism, and eventually to be able to control it. Unfortunately, there is no camera able to take high-resolution pictures of what is inside the cellular nucleus. However, there are different experimental techniques that can provide the necessary pieces of information. They range from fluorescence microscopy to biological assays capable of giving quantitative results about what piece of a chromosome is close in space to what other piece. Physical models can be used to turn these quantitative data into a picture of the chromosomes or, even better, into a movie, since chromosomes are definitely not static. From these models one can learn much more than what the raw data can teach.

At the Center for Complexity and Biosystems we have already studied polymeric models that describe both the structure and the dynamics of small chromosomal pieces. The goal now is to build a complete high-resolution model of the whole genome in the nucleus, in line with the available experimental data, and capable of describing both the structure and the dynamics of the chromosomes.

The problems associated with this task are multidisciplinary. One has to solve non-trivial physical issues related to the theory of complex polymers, and answer biophysical and biochemical questions about how to interpret the experimental data within a microscopic polymeric model. There are also problems involving computer science. The system is huge; if we want to reach the resolution of 10-kbase, we have to describe 10^5-10^6 genomic elements that move in the nucleus. Thus, to study their dynamics highly optimized algorithms are needed. Some aspects of the problem are typical of big-data analysis; for instance, experiments may provide the probability that each pair of genomic element is in contact. Since there are 10^{10}-10^{12} of such pairs, just storing all this information in a computer would require an amount of terabytes that are difficult to manage. It is thus necessary to use statistical methods in order to filter out unnecessary and redundant data. Finally, we expect the biological interpretation of the results of the model to be far from simple. In spite of all these problems, the availability of a simple physical model to describe the spatial arrangement of the chromosomes in the nucleus and their dynamics can open unprecedented improvements in understanding the mechanism of genetic control, and to exploit it.

How cancer cells move in our bodies

A group of cells migrating to a wounded area to repair it and a pack of cancer cells invading healthy tissues have something in common, for they move in similar ways. Most of all, their moving behaviour shows some resemblance with that of groups of animals and even humans, as well as that of inanimate objects. A group of international researchers, led by Caterina La Porta and Stefano Zapperi, from the Center of Complexity and Biosystems of the University of Milan, managed to identify the laws that regulate these cellular mass movements. A knowledge that may provide valuable information for several biomedical applications, from regenerative medicine to cancer therapy.

The researchers – whose results have been published – examined different kinds of collective cell migrations over different substrates and experimental conditions. Results obtained by experiments with living cells were then analysed in order to identify the statistical properties of these movements, which were then compared to computational simulation.

Collective cell migrations are driven by biological mechanisms within the cell as well as by external factors, mainly represented by the matrix that provides structural and biochemical support to the cells of a tissue. The main component of this matrix is collagen, which forms a network of fibers that ensure cell and tissue integrity by offering little resistance and high sensitivity to small deformations. When a single cell moves, its internal structure faces an internal stress, which may be transmitted through the matrix between neighbouring cells. This leads to the formation of real stress waves, which result in the intermittent burst of activity that the researchers observed and characterised from a mathematical point of view.

In fact, they found that these bursts are similar to those previously recorded in animal and even human mobility patterns, and are described by similar universal laws. Which means that living cells move and invade available spaces the same way inanimate particles do, as it occurs when a fluid fill an empty space.

They also found out that cell migration is highly affected by the structure and stiffness of the substrate over which they are moving. Migration is a key property of tumour cells and these findings implies that cancer cells use different internal mechanisms to move, depending on the environment. A fact that should be extremely relevant for the understanding of the metastatic processes.

O. Chepizhko, C. Giampietro, E. Mastrapasqua, M. Nourazar, M. Ascagni, M. Sugni, U. Fascio, L. Leggio, C. Malinverno, G. Scita, S. Santucci, M. J. Alava, S. Zapperi, C.A.M. La Porta
Bursts of activity in collective cell migration
PNAS 113, 11408–11413 *(2016)*

Three questions to...
Oleksandr Chepizhko

Postdoctoral fellow at Aalto University

What's your field of research?

My field of research is the physics of active matter. This is a new direction which covers the studies of biological and artificial objects that are able to move, converting inner source of energy into motion. In particular, we were analysing the results of experiments on collective cell migration. By comparing available data and computer simulations of simplified particle based models we were able to unravel properties of collective cell behaviour.

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

Better understanding of an important process of collective cell migration is the main outcome of our study. Particularly, we have found that during wound healing the motion of cells is not uniform but occurs in bursts that resemble avalanches. This burst-like behaviour happens when the material is pinned to substrate, stopped, and then suddenly released. Our studies are particularly important for further understanding of cancer metastasis. We develop a view from mechanical prospective on this process, which will be helpful for biomedical research and applications.

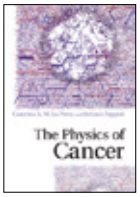
The relevance of your results is not restricted to biomedicine but goes beyond it, into the realm of complex behaviours and dynamics; are there some universal laws underlying all these phenomena?

Yes, the burst-like dynamics of the cell front propagation found by us in the wound healing experiments was shown to be quite universal among different species of cells placed on different substrates. We measured the size distributions of the bursts of cellular activity. We found that all of the distributions can fit onto one universal curve. Similar dynamics is well-known in non-biological systems, such as crack propagation in solids, liquid imbibition through porous material, etc. We see that the laws governing these distinct phenomena are very similar to each other. This suggests that further comparison of them may lead to fruitful research.

The Physics of Cancer

Recent years have witnessed an increasing number of theoretical and experimental contributions to cancer research from different fields of physics, from biomechanics and soft-condensed matter physics to the statistical mechanics of complex systems. All these contributions are reviewed in *The Physics of Cancer*, the first book devoted to the emerging interdisciplinary field of cancer physics, aimed at providing a sophisticated overview of the topic.

Systematically integrating approaches from physics and biology, it includes topics such as cancer initiation and progression, metastasis, angiogenesis, cancer stem cells, tumor immunology, cancer cell mechanics and migration. Biological hallmarks of cancer are presented in an intuitive yet comprehensive way, providing graduate-level students and researchers in physics with a thorough introduction to this important subject. The impact of the physical mechanisms of cancer are explained through analytical and computational models, making this an essential reference for cancer biologists interested in cutting-edge quantitative tools and approaches coming from physics.
Authored by Caterina La Porta and Stefano Zapperi, members of the Center for Complexity and Biosystems of the University of Milan, *The Physics of Cancer* is a book that provides a useful introduction to cancer for any student of biological physics, reviews the contributions of physics to cancer research, and includes mathematical and physical models for cancer research.



C. A. M. La Porta and S. Zapperi
The Physics of Cancer
Cambridge University Press, 2017

Scientific predictions in social contexts

Alessandro Vespignani, Professor of Physics, Computer Science and Health Sciences at Northeastern University, was interviewed during the Second Workshop of CC&B on October 5th, 2016. This article reports the content of the interview, which is also available as a video here: y2u.be/WnYKq_LlYJ0

When speaking of scientific predictions, the first thing that comes to our mind is weather forecast. But meteorological predictions are not the only ones science is capable of. Predictions in other fields of knowledge, especially those where human beings and their society are involved, are remarkably different from meteorological ones. The main difference being that the weather does not care about societal and cultural issues, and will follow its own course without being influenced by our actions and reactions.
For instance, when we try to foretell the spread of an epidemic within a population, we have to consider that people will change their own behaviour once they will be aware of the prediction. Individual reactions are not the only element that must be taken into account, since public health institutions will also take appropriate measures in order to face the epidemic threat and these will also impact on people's behaviour.
Clearly, all these factors influence the validity of a prediction, which will be restrained in its temporal span. After that, we will need to consider all the changes that have undergone within the society and integrate them in our model, in order to draw new predictions.
All complex systems are characterized by a certain degree of unpredictability, due to the renowned butterfly effect. Even weather forecast is not considered reliable beyond two weeks. When a social component is part of the system, as it occurs in the case of epidemics, the temporal span of a prediction depends on individual attitudes and how they change based on the information available.
When dealing with social systems, a big question mark is represented by the influence exercised by leaders over crowd behaviour, since they are often credited with playing a significant role in directing people's attitudes. However, in the last forty years complexity science taught us that a mastermind is not always necessary to understand (and thus predict) mass behavioural patterns. We all have this idea of the queen bee overseeing workers and soldiers within a strict hierarchical structure, but it turned out that there are some very complex and hierarchical behaviours that emerge in many social systems without being directed by some sort of leader. That is why it is said that complexity killed the myth of the queen bee.
This is a highly relevant point, for it means that many phenomena emerging from social aggregations may be understood by investigating the basic interactions between all the individual components of such systems.
Our dream is to build a computational infrastructure for pandemics and epidemics predictions, with the aim of forecasting when, where and how one of these threats will strike once it has started. It is important to point out that we cannot foretell what the next epidemic will be, but once we have some information on an infectious disease that is scattering somewhere in the world, we could try to predict its diffusion. In order to do that, we integrate demographic data at high resolution levels – there are databases, developed by NASA, that manage to infer population numbers on a grid of five square kilometres – with data about people's mobility, like all aircraft movements around the world or the different forms of transports and commuting, and infrastructures, like the number of hospital beds. All this information allows us to create a virtual world within a computer, where we then introduce a disease spreading pattern and simulate what happens. If we have a good knowledge of the disease initial conditions, we can elaborate its path through our virtual world, thus trying to predict how it will behave in reality.

>>>> UPCOMING EVENTS

SEMINARS

February, 2 2017
Micheal Pusch
Istituto di Biofisica, CNR, Genova
CLC chloride channels and transporters – from biophysics to human genetic diseases

February, 27 2017
Vincenzo Vitelli
Instituut-Lorentz for Theoretical Physics, Leiden University
Topological sound and odd viscosity in chiral active matter

When size matters

Things do not break always in the same way. And, when dealing with fractures, size matters. A one atom-thick sheet of graphene cracks differently from a bridge. The breaking of a bone is characterized by the formation of microscopic fractures, which is not what happened when a pane of glass falls apart. Every structure, from a thirty-storey building to the tiniest molecular machine, is exposed to external forces that may provoke deformations and breakings. Studying how different materials respond to such forces is a main goal within the field of engineering sciences.

A tough goal to achieve, for dealing with very small or very big objects makes it difficult – if not even impossible – for researchers to perform proper structural tests. Moreover, resistance tests carried out in the laboratory involve small size samples of a specific material, which will then be used to build much larger structures. And, when moving from tiny to bigger scales, many things change. It is, however, possible to simulate how a given material behaves in specific conditions by relying on physical and statistical models. Models that, in turn, require grounded theoretical basis about molecular interactions. But a general theory for materials' deformation and breaking is still missing.

That is where SIZEFFECTS comes into play.

SIZEFFECTS is a project headed by Stefano Zapperi who, in 2011, got an Advanced grant by the European Research Council to conduct his research.

Having always been fascinated by the way things break differently at different scales, Zapperi was not satisfied by models used by engineers to describe metals deformations, since they couldn't account for a particular phenomenon that is observed at a microscopic level: when exposed to external forces, very tiny objects – differently from larger ones – exhibit unpredictable bursts of deformation. According to Zapperi, in order to investigate these dynamics it is thus necessary to apply other theoretical models, like those developed within the field of physical statistics to study complex and disordered systems.

Understanding the properties of a complex system requires not only to know its individual components, but also their interactions. Because it is from such interactions that the macroscopic attributes that characterize the system emerge. In this particular case, by investigating the way these micro-components interact when exposed to an external force, Zapperi aims to identify the emerging properties of the system itself. From the small parts to the large architecture, also taking into account all the differences in each material behaviour according to the scale considered.

SIZEFFECTS first results seem to confirm the validity of this method: by studying the deformation of microscopic metallic columns exposed to pressure, Zapperi and his colleagues have found a general mechanism that, if confirmed by further experiments, could also prove useful to shed light on major deformations of the Earth crust like earthquakes.

Thanks to a multidisciplinary approach, the SIZEFFECTS project is making significant advances towards the development of a general theory for irreversible deformation and fracture.

erc European Research Council Established by the European Commission

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Second school on Advances in Complex Systems in Como

The Center for Complexity and Biosystems organises **the second school on Advances in Complex Systems in Como**. The first edition of the school took place in the summer of 2015 The scope of the school series is to present recent advances in complex systems discussing applications of statistical mechanics of non-equilibrium and disordered systems, theories of complex networks and other stochastic systems to different topics in materials science, social sciences, biology and biomedical research. The broad choice of interdisciplinary topics is designed to expose the students to some of the multiple facets of complex systems theory. The 2017 edition of the school will focus on **interdisciplinary approaches to tissue regeneration, chromatin conformations and telomeres, bio-inspired materials, protein aggregation and complex networks in health sciences**.

Lecturers: L. Amaral, M. Ben Amar, N. Dokholian, J. Griffith, J. Holly, S. Huang, M. Labouesse, T. Liedl, F. MacKintosh, L. Mirny, G. Tiana, J. Urbach, A. Vespignani

The school is open to **40** Ph. D. students or postdocs working in complex systems and related fields. All applicants have to fill out the application form, including a short CV with list of publications and the motivation for their participation to the School, before **March 1, 2017**.

The Complex Systems Society is funding **two fellowships** covering the registration fee to the School on Advances in Complex Systems. Perspective participants who wish to apply for a fellowship should indicate this in the application form. To receive a fellowship participants are requested to become members of the CSS. Selection will be based on the CV and the motivation letter of the applicants. Selected candidates will be expected to deliver a short talk at the school.

Application form:
acst.lakecomoschool.org/applications-deadlines/
Student application deadline:
March 1, 2017
Notification of acceptance:
March 30, 2017
Registration (only accepted students):
May 1, 2017
For further information:
acst.lakecomoschool.org

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