2017

A YEAR IN REVIEW

IFOM
FIRC INSTITUTE OF MOLECULAR ONCOLOGY

Table of contents

About IFOM Review

The idea of publishing an annual report for the institute has been in the air for a very long time. However, we did not like producing every year a cold document highlighting our own results with plain scientific data.

Thus, we came to the conclusion that it would have been better to receive a sincere and frank opinion on our work from external colleagues and collect these commentaries in an editorial product.

Therefore, we consider the IFOM Review a chance for reflection on the progress of knowledge, moving from IFOM activities and results.

A special thanks goes to the authors who generously spent their time and energy to share their views on the progress and perspectives of our research.

Marco Foiani

Francesco Blasi

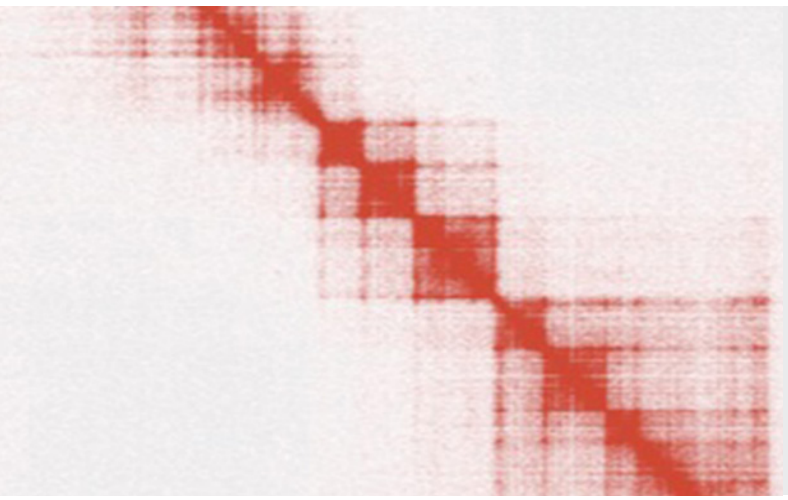
The authors:

Marco Foiani
Scientific Director

Prof. Foiani has a Ph.D. in Molecular Biology from the University of Milan (Italy).
Since 2002, Prof. Foiani, who is also Head of the Genome Integrity Laboratory at IFOM since its establishment, is Full Professor in Molecular Biology at the University of Milan.
His research interest focuses on the regulatory mechanisms that control genome integrity. Particularly, his work has contributed to elucidate the cellular mechanisms causing genome instability in cancer cells and chromosome abnormalities in certain human syndromes leading to cancer predisposition. Prof. Foiani has more than 80 papers published in international scientific journals.
Since 2008 Prof. Marco Foiani is the Scientific Director of IFOM.
Prof. Foiani was honored with internationally recognized memberships and awards, such as: the European Molecular Biology Organization membership; the Academia Europaea membership; the New York Academy of Sciences membership; the Italian Society of Genetics (AGI) membership; the Italian Society of Biophisics and Molecular Biology (SIBBM) membership; the Award from the Italian Society for Biophysics and Molecular Biology (SIBBM); the Biotec Award promoted by Amgen and Dompé; the "Chiara D'Onofrio" Prize from the Italian Federation of Life Sciences.
He was the founder in 2009 of the European Nanomedicine Foundation (CEN) and vice-president up to 2011.
He is also member of the Scientific Advisory Board of AIRC, the Italian Cancer Research Association, member of the editorial board of Cell and editor and reviewer for top impact factor scientific journals.

Francesco Blasi
IFOM Deputy Director

Francesco Blasi born in Naples, October 19, 1937.
MD from Naples University Medical School, then two post-Docs at the Max Planck Institut fuer Biophysik (Frankfurt, Germany) and NIH (National Institute of Arthritis and Metabolic Diseases) Bethesda, MD (U.S.A.).
In 1970 back in Italy at the CNR Research Center in the Naples University Medical School, then in 1980 Full Professor at the II Faculty of Medicine of the University of Naples.
Subsequently, Professor at the University of Copenhagen, Denmark and finally in Milano since 1992.
Is at IFOM since 2004, Director of research program Transcriptional Regulation in Development and Cancer.
From 2007 to 2011 coordinates the Molecular Oncology PhD program of SEMM. In 2011 becomes Deputy Director for Science of IFOM.
Has previously been Director of the International Institute of Genetics and Biophysics of CNR in Naples (1980-1983), of the Molecular and Cellular Biology Center in Copenhagen (Denmark), (1988- 1992), and of the Department of Cellular Biology and Functional Genomics (1998-2006) at DIBIT, Ospedale San Raffaele.
In 1979 is elected member of EMBO, the prestigious European Molecular Biology Organization, and 1991-1993 of its Council. Since 1992 is a member of Academia Europaea.
Has received national and international prizes and is Author of over 270 research articles in prestigious international Journals, including Nature and Cell.
Has been a member of the Advisory Board of AIRC, Associazione Italiana per la Ricerca sul Cancro, and of the Board of EMBO Journal.



Capturing 3D-DNA structure from compositions in diamond shape

Commentary on Forcato et al. “Comparison of computational methods for Hi-C data analysis”, Nat Methods. 2017 Jul;14(7):679-685.

by Silvio Bicciato

By the early 1920s, the Dutch artist Piet Mondrian started creating diamond-shaped paintings by rotating square canvases 45 degrees. In the diamond compositions, rectangular modules, enclosed by grid lines, are gathered into larger groups or clusters of modules that are delineated by lines of varying width and weight. The density of the clustering ranges from individual modules, which give the feeling of a constricted space, to groups of multiple modules, hinting to a more open and empty area. A century after Composition in Diamond Shape, Mondrian could have been be the inspired author of the lozenge grid-composition map that, in these days, scientists use to quantify genome-wide interactions detected from Hi-C data.

Hi-C is the latest of a set of experimental techniques based on chromosome conformation capture (3C1) that have been developed to probe the spatial organization of genomes and investigate how higher-order chromatin structures affect genome functionality. In Hi-C, the three-dimensional spatial proximity of potentially any pair of genomic loci is first traduced into biochemical events and then quantified as interaction frequencies using high-throughput sequencing. Hi-C read-out consists in hundreds of millions, or even billions, of read-pairs generated as the result of the ligation of pairs of DNA fragments that are close to each other in the three-dimensional genome space. These read-pairs are processed to generate the final result, i.e. a diamond-shaped, squared interaction map where each bin accounts for the number of contacts observed between two genomic regions as a proxy of their spatial adjacency.

When my former post-docs Mattia Forcato and Francesco Ferrari first showed me an Hi-C contact matrix I found myself eye-scanning the picture collecting and measuring the weight of each rectangle to extract some underlying structures and relationships, as it was an abstract painting. At that time, they were both working in the lab of Peter Park at the Harvard Medical School in Boston on computational methods to efficiently analyze and interpret the enormous

amount of genomic information contained in Hi-C interaction maps. The bioinformatics analysis of this data requires complex software pipelines that pre-process the sequence reads, generate and normalize the interaction maps, extract the patterns buried in the contact matrices, and finally associate signal intensities to different chromatin or chromosome structures. As in a Mondrian's painting, Hi-C contact maps manifest the presence of hierarchical patterns with different densities, reflecting chromatin or chromosome interactions at different scale lengths. The largest motifs are checkerboard-like sequential patterns of high and low interaction frequency, commonly associated to a bipartition of the genome in two sets of loci, named genomic compartments, characterized by enriched interactions within each set and depleted interactions between sets. The square patterns with distinct borders along the main diagonal are indicative of groups of genomic loci that tend to interact more with each other than with loci in other genomic regions and that, in metazoan genomes, are named Topologically Associating Domains (TADs). At a much finer scale, signal spikes account for local contact enrichments and may manifest the presence of point interactions e.g. between regulatory regions, as in the case of promoters and enhancers.

In the last few years, numerous algorithms have been developed to capture and extract these signal patterns and understanding the principles and usage of these computational tools is becoming increasingly important to support the interpretation of chromatin interaction maps2. Indeed, if on one side ultra-deep sequencing allows now producing high-resolution pictures of the 3D genome architecture, on the other the availability of reliable computational approaches for pattern identification and extraction is an essential prerequisite for capturing the actual, structural information encoded in the data.

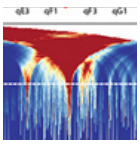
The work of Forcato et al. builds on the methodological imperative to quantitatively assess how the various methods for the analysis of Hi-C data perform relative to one another and how the adoption of one computational strategy impacts the identification of chromatin structures. Specifically, they compared the performances of thirteen methods for the identification of topological domains and chromatin interactions from Hi-C data. Given the scarcity of validated empirical evidences for chromatin architecture to calculate comparison statistics, the study design is based on a quite impressive large set of experimental and simulated data that have been used to quantitatively estimate reproducibility, accuracy, and precision of the various methods. Surprisingly, the comparison evidences that no algorithm prevails the others in the precise identification of chromatin structures and that, irrespectively of the data resolution, the choice of the method severely influences the quantity and characteristics of the identified interactions. Algorithms for the identification of TADs appear to be more stable and reproducible than methods to call point interactions. In particular, the latter suffer of poor reproducibility, with few interactions detected in one sample conserved in other replicates of the same cell type. Although striking, this disappointing result may be partly ascribed to the characteristics of the analyzed samples that, being ensembles of cells in different states, are not necessarily identical in terms of chromatin contacts, as postulated in the study design. Despite their limited reproducibility, most detected interactions are of biological significance, as testified by the significant proportion of cis promoter-enhancer looping interactions and by the very small number of biologically improbable contacts. Finally, the set of results generated by this comparison constitutes a precious resource by itself, comprising an extensive summary of chromatin structures, as TADs and point interactions, in human embryonic stem cells, in fetal lung fibroblasts, in lymphoblastoid cell lines and in fruit fly embryos, that is currently available through Hi-C public data browsers.

Chromosome conformation capture-based techniques is already one of the most powerful tools to unveil not only the 3D genome architecture but also aberrations in chromatin organization that can eventually trigger events leading to genetic disorders and cancer. Ultimately, it is appealing to envision that these techniques might, in the near future, represent a centerpiece

Capturing 3D-DNA structure from compositions in diamond shape
by Silvio Bicciato

in the process to rationally identify genomic regions worthy of synthetic editing for biomedical applications. However, to uncover novel exciting aspects of the 3D genome architecture and of its dynamics, it is indispensable that researchers can count on rigorous and robust computational approaches to analyze DNA interaction data as algorithms may be efficient in discerning real structures, but equally so at extracting patterns when they are entirely absent. Similar to Mondrian's diamond compositions, where essential geometrical elements are instrumental to perceive an underlying structure in the world, the repertoire of patterns in interaction maps is instrumental to fully access the still secret essence of the DNA molecule, provided that we are confident in extracting the subtle relationships they encode.

Comparison of computational methods for Hi-C data analysis
Hi-C is a genome-wide sequencing technique used to investigate 3D chromatin conformation inside the nucleus. Computational methods are required to analyze Hi-C data and identify chromatin interactions and topologically associating domains (TADs) from genome-wide contact probability maps. We quantitatively compared the performance of 13 algorithms in their analyses of Hi-C data from six landmark studies and simulations. This comparison revealed differences in the performance of methods for chromatin interaction identification, but more comparable results for TAD detection between algorithms.
[PMID 28604721]



Computational genomics
Francesco Ferrari

Capturing 3D-DNA structure from compositions in diamond shape

The author:

Silvio Bicciato

Silvio Bicciato obtained his PhD in Chemical Engineering from the University of Padova working on an automatic system for the control of biopolymer synthesis. He then joined the Bioinformatics and Metabolic Engineering Laboratory of G.N. Stephanopoulos at MIT (Cambridge, USA) where, as a post-doctoral associate, he started working on the design and application of database-mining algorithms and bioinformatics tools for the analysis of microarray gene expression data. After three years at MIT, he moved back to University of Padova where he established a research group of bioinformatics and functional genomics. In 2008, he moved to the University of Modena and Reggio Emilia where he created the Bioinformatics Lab at the Center for Genome Research, an interdisciplinary group comprising computer scientists, molecular biologists, statisticians, biotechnologists, and engineers that cooperate to the generations of the bioinformatics tools required by new technologies for genomics. His principal research interest is the design and application of computational and bioinformatics methods for the analysis of genomic data coming from high-throughput technologies and the modeling of complex biological systemsSilvio Bicciato obtained his PhD in Chemical Engineering from the University of Padova working on an automatic system for the control of biopolymer synthesis. He then joined the Bioinformatics and Metabolic Engineering Laboratory of G.N. Stephanopoulos at MIT (Cambridge, USA) where, as a post-doctoral associate, he started working on the design and application of database-mining algorithms and bioinformatics tools for the analysis of microarray gene expression data. After three years at MIT, he moved back to University of Padova where he established a research group of bioinformatics and functional genomics. In 2008, he moved to the University of Modena and Reggio Emilia where he created the Bioinformatics Lab at the Center for Genome Research, an interdisciplinary group comprising computer scientists, molecular biologists, statisticians, biotechnologists, and engineers that cooperate to the generations of the bioinformatics tools required by new technologies for genomics. His principal research interest is the design and application of computational and bioinformatics methods for the analysis of genomic data coming from high-throughput technologies and the modeling of complex biological systems

The new challenges in IFOM

by Tomas Lindahl

More than fifteen years after the start of its scientific activities, IFOM has established itself on the national and international scene as a consolidated reality in the field of molecular oncology. If the first years of IFOM were mainly characterized by fundamental research activities, over the years the research strands have increasingly provided ideas to start translational programs in order to have a concrete impact on the patient and thus close the cycle with the Civil Society. In this way, IFOM has established - in partnership with the European Institute of Oncology - an integrated system of highly specialized realities (Cogentech, TTFactor) that are not easily found in the Italian scene.

This experience in molecular oncology is now facing a new challenge: the progressive aging of the population both in Italy and in Europe. This demographic phenomenon is reflected in research, as it is increasingly evident that cancer and aging are closely linked. This represents a great opportunity for IFOM thanks also to the network of high-quality international partnerships woven over the years that can allow the Institute to face this challenge in an innovative and effective way.

What is the current state of affairs and how are the outlooks in molecular oncologies outlined? What are the consequences of the aging population in terms of chronic diseases? These are the questions IFOM is approaching.

2017 also saw the extension of IFOM's internationalization activities with the signing of the Memorandum of Understanding with the University of Shenzhen, in China, which soon followed the creation of the "Shenzhen University-IFOM Center for Genome Stability and Aging" aimed at carrying out research on the topic of genomic instability and its impact on aging in order to develop new therapeutic and diagnostic tools to reduce the risk and impact of aging-related diseases.

Among the various collaborations at national level, I particularly highlight the one activated with the Monzino Cardiology Center with the aim of improving the knowledge of the role of DNA repair mechanisms following mechanical perturbations or pathological affections involving cardiomyocytes derived from patients' iPS cells and / or derived from experimental animal models. Other important academic agreements have been signed with the University of Padua and the University of Trieste for an organic collaboration with the two scientists Stefano Piccolo and Giannino Del Sal of the respective

universities respectively on the topic of crosstalk and on the metabolism of cancer cells and oncogenic signaling.

Scientific productivity was confirmed to be high with 134 articles published in scientific journals with impact factor, for a total IF of 1397 and an average IF for publication of 10.42.

The calendar of events of international importance organized by IFOM has also been very varied.

I consider two events particularly successful:

- The ATW 2017 Ataxia-Telangiecatasia Workshop, organized by Marco Foiani and by Vincenzo Costanzo, focusing on the theme of Ataxia-Telangiectasia whose function is crucial to prevent not only neurodegenerative processes, but also the onset of cancer and premature aging.

- The 19th International Conference on Lymphatic Tissues and germinal centers in immune reactions, organized by Stefano Casola in collaboration with Dr. Sidonia del Fagarasan, Riken Institute, Yokohama, in Japan. It was held in Venice and focused on understanding the mechanisms underlying the immune system for the study of leukemia and lymphomas.

Varied and eclectic is also the calendar of popular events planned and organized by IFOM throughout the year, with talk shows and conferences during scientific festivals and the European night of researchers, involving researchers alongside scientific journalists.

The media coverage of IFOM grew in 2017 by counting overo 1000 media services, in the press, on television, in radios and on the web, potentially reaching an audience of 3.6 million citizens.

The subject most covered by the media is the dissemination of the scientific results of IFOM, but also the Institute itself, as an exponent of the scientific community and as an actor of the territory, the human factor and the stories of researchers, and dissemination activities of the YouScientist department. This is certainly a positive sign: it means that there is interest for science also in traditional media and this can have a successful impact on the education of citizens to the value of science.

Equally important is the dissemination activity of YouScientist, the outreach branch of IFOM: dozens of activities and thousands of students and teachers involved. Every year Youscientist contributes with original projects to the deepening of scientific themes with an accessible language and with engaging ways, such as the publication of the e-book “The ten hallmarks of cancer”, a scientific essay that tells about the ten characteristics of cancer cells.

The new challenges in IFOM
The author:

Tomas Lindahl

Emeritus Director of Cancer Research UK, Clare Hall Laboratories

Tomas Lindahl completed medical studies at the Karolinska Institute in Stockholm and has consistently been active in research. He worked as a post-doctoral fellow on nucleic acid biochemistry with J. Fresco at Princeton and G. Edelman at Rockefeller University, joining the faculty of the Karolinska Institute in 1969.

He became Professor of Medical Chemistry at the University of Gothenburg in 1978. In 1981 he was appointed Head of the Mutagenesis Laboratory at the ICRF Mill Hill Laboratories in London. From 1984 to 2006 he was Director of the Clare Hall Laboratories at ICRF and Cancer Research UK, also serving as Deputy Director of Research. Amongst many distinctions, Tomas Lindahl is a member of EMBO, a fellow of the Royal Swedish Academy of Sciences, and the Royal Society, London.

He was the Royal Society Croonian Lecturer in 1996 and received a Royal Medal in 2007, INSERM Prix Etranger in 2009, and the Copley Medal in 2010 of the Royal Society. He has received honorary doctorates from the Universities of Gothenburg, Oslo, Sheffield, and Sussex. He is now Emeritus Director of Cancer Research UK, Clare Hall Laboratories, and involved in various scientific activities.

Visiting Professor of the Chinese Academy of Science 2009 - 2012

2010 - Scientific Advisor, Beijing Inst. of Genomics2010

2010 - Scientific Advisory Board, IFOM Milan

2010 - Scientific Advisory Board, Cancer and Ageing Centre, University of Nice, France

2010 - Hon. Professor in Medical Oncology, University of Sheffield.

From 2010 he is President of the IFOM Scientific Adivisory Board

In 2015 he awarded the Nobel Prize in Chemistry

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Corporate profile

IFOM, the FIRC Institute of Molecular Oncology, is an Italian highly technology, non-profit research centre supported by FIRC, the Italian Foundation for Cancer Research. Research conducted at IFOM aims to understand the molecular processes responsible for the onset and development of cancer.

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Concept:
Leonardo Biondi

Editor:
Elena Bauer

Editorial project management:
Elena Bauer, Leonardo Biondi

Editorial supervision:
Francesco Blasi

Design project:
Deborah Agostini

Authors:
Silvio Bicciato, Tomas Lindahl

Photo credits:
D. Agostini, Fotolia, C. Villa

Testata registrata al Tribunale di Milano Reg. N. 36 del 14 febbraio 2014

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