

Swiss Institute of Bioinformatics



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SIB | Swiss Institute of Bioinformatics

Quartier Sorge
Bâtiment Génopode
CH-1015 Lausanne
Switzerland
t +41 21 692 40 50
f +41 21 692 40 55

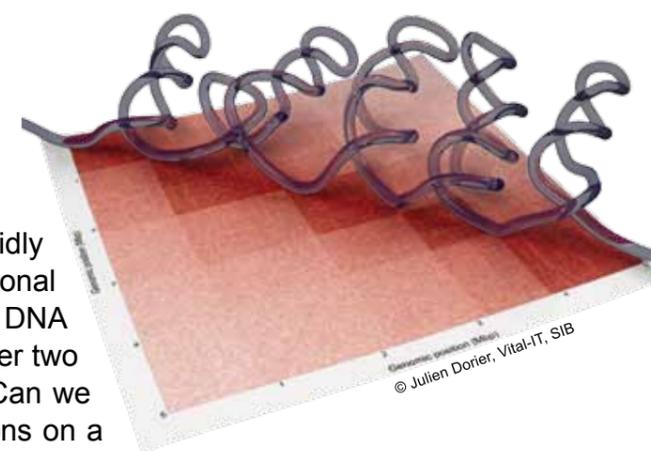
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Swiss Bioinformatics

SIB Newsletter – June 2015

EDITORIAL



MULTIDIMENSIONAL BIOINFORMATICS

This issue of *Swiss Bioinformatics* is dedicated to multidimensional bioinformatics, a fascinating and rapidly evolving field. When we talk about gene or protein sequences, we are in the realm of mono-dimensional bioinformatics, as both proteins and genes are chains of small molecules. When considering protein or DNA structures, or the nano-crystals that enable the amazing colour-changing of chameleons, we add a further two dimensions of complexity. And now, we are confronted with yet other dimensions and questions like “Can we predict how well a potential drug binds to its target structure?” or “Can we predict the effect of mutations on a protein’s structure?”.

In this SIB Newsletter, you will discover bioinformatics going well beyond 3D. When visualizing a heart beating or a tumour growing, time adds a fourth dimension. By adding biological functions to these images, measuring an organ’s sugar consumption or temperature for instance, we slip into a fifth dimension. Advanced bioinformatics tools enable the high-throughput extraction of over 400 quantitative features from medical images such as CT or PET scans, providing a comprehensive description of these five dimensions of, for example, a tumour. As bioinformatics is all about converting big data into smart data or knowledge, it is obvious that the data streams produced by multidimensional bioinformatics are highly challenging.

Multidimensional bioinformatics offers however amazing opportunities: from predicting the therapeutic effects of a molecule, as well as its potential side effects, to the assessment of the molecular and cellular characteristics of tumour biopsies. We wish you pleasant discoveries!

Ron Appel, Executive Director

ABOUT SIB

SIB Swiss Institute of Bioinformatics is an independent, not-for-profit foundation recognized of public utility. SIB helps shape the future of life sciences through excellence in bioinformatics, by providing life scientists and clinicians in academia and industry with world-class bioinformatics resources and services, and by leading and coordinating the field of bioinformatics in Switzerland. It has a long-standing tradition of producing state-of-the-art software and carefully annotated databases, such as UniProtKB/Swiss-Prot, the world’s most widely used source of information on proteins. SIB also provides leading educational services, data analysis support and bioinformatics research.

SIB includes 56 world-class research and service groups, which bring together more than 650 scientists in the fields of genomics, transcriptomics, proteomics, evolution, population genetics, systems biology, structural biology, biophysics and clinical bioinformatics, located in the Swiss cantons of Basel, Bern, Fribourg, Geneva, Ticino, Vaud and Zurich.

WHAT IS BIOINFORMATICS?

With the development of medical and life science technologies that produce gigantic quantities of data (“big data”), computing has become a central component of modern scientific research, applied sciences and personalized health.

Bioinformatics brings major advances in many different medical and life science areas, through the storage, analysis and effective use of “big data” produced by experimentation, as well as through the production of *in silico* data knowledge.



RESEARCH



CHANGING COLOUR, STAYING COOL

Michel Milinkovitch, Laboratory of Artificial and Natural Evolution, University of Geneva

SIB group leader Michel Milinkovitch and his team created a bit of a global buzz early this year with research they have carried out on chameleons.

Aware of the strong physical component which influences biological processes, Michel Milinkovitch uses techniques from the fields not only of biology but also of physics to understand them. A combination which has led to some surprising discoveries.

With the collaboration of the Quantum Materials Group led by Dirk van der Marel of the University of Geneva, Milinkovitch's lab demonstrated that chameleons carry two superimposed layers of iridophores. Iridophores are non-pigment cells full of guanine nanocrystals, which generate iridescent colours.

Techniques used in physics to understand biological processes

In chameleons, the two layers of iridophores are of a different nature, which is in itself an evolutionary novelty. The first iridophore layer is thick. It is located close to the surface of the reptile's skin and is full of nano-crystals neatly arranged in a triangular lattice. The second layer is situated deeper down in the dermis, and is full of larger, disorganized nano-crystals.

Colour changes on a chameleon's skin are caused by active tuning of the lattice within the superficial layer of iridophores, while the deeper layer reflects a large proportion of the sunlight's radiation energy, especially in the near-infrared range.

Chameleons are hence equipped with a surprising kit: two layers of iridophores which each serve a particular purpose. The first is involved in camouflage and social interactions, whereas the second protects the animal against overheating.

Publication:

Teyssier J et al. Photonic crystals cause active colour change in chameleons. *Nat Commun* 2015;6:6368 doi: 10.1038/ncomms7368.

www.isb-sib.ch/groups/geneva/anedc-milinkovitch.html

TWISTING CHROMATIN

Andrzej Stasiak, DNA and Chromosome Modelling Group, University of Lausanne

When a cell is not dividing, it is preparing to do so. During this part of the cell's cycle – known as interphase – the nucleus is busy transcribing and replicating DNA. For this to happen, the cell's chromosomes – generically known as chromatin – adopt a loose and seemingly disorganized structure giving the nucleus the overall aspect of a ball of string.

However, thanks to a high-throughput molecular biology technique known as 3C (Chromosome Conformation Capture), a closer look at the structure of chromosomes during interphase shows that their structure is far from disorganized. This technique is based on the proximity and frequency of chromatin contacts, and has revealed that a cell's chromatin is riddled with globular domains – or topological domains.

Chaos reveals logical structure thanks to molecular modelling

Until recently, no one knew how these domains were formed or what the nature of their structure was. This is what Andrzej Stasiak and his team set out to discover by designing a model which took into account two assumptions: 1) the boundaries of topological domains are attached to the nuclear matrix; 2) between the attachment points, chromatin fibres are supercoiled because of ongoing transcription.

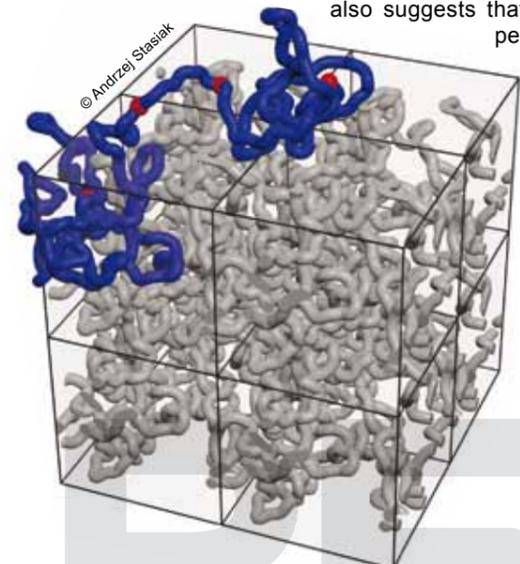
Once their modelled structure was designed, the researchers then sought to find out what 3C probing of their model would reveal. It turned out that this simple model reproduced very faithfully the experimental 3C data obtained for real chromosomes. So their model is not only good but

also suggests that supercoiling induced by transcription may well persist and have an organizing effect on chromosome structure.

Publication:

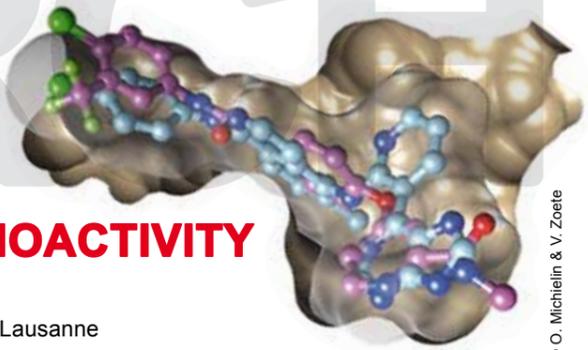
Benedetti F et al. Models that include supercoiling of topological domains reproduce several known features of interphase chromosomes. *Nucleic Acids Res* 2014;42:2848-55.

www.isb-sib.ch/groups/lausanne/dcm-stasiak.html



ON PREDICTING BIOACTIVITY

Olivier Michielin & Vincent Zoete, Molecular Modelling Group, University of Lausanne



Small molecules, such as metabolites, bind to their target proteins or other macromolecular entities thereby modulating their activity. Hence their name: bioactive molecules or, more generically, ligands. With the development of new technologies in the life sciences over the past years, researchers have managed to identify many ligands and their targets, which is the best way to explain the ligand's bioactivity.

Bearing this in mind, it is not difficult to understand that the more researchers know about bioactive molecules, the more they can use them or even tinker with them – by producing custom-made ligands, for instance – so that they have a chosen effect on their targets. This is the realm of computer-aided drug design, where complex software is developed to help scientists conceive drugs that will be able to act upon specific macromolecules involved in diseases, such as cancer or AIDS for instance.

SwissTargetPrediction: predicting interactions between bioactive small molecules and target proteins

So much has been discovered about the interactions between macromolecules and bioactive small molecules that they are now stored in libraries, or databases. Olivier Michielin and Vincent Zoete's team has used these particular libraries to develop software which is able to predict the interactions that could exist between an identified bioactive small molecule and possible target proteins, or even between a virtual ligand and unknown target proteins: SwissTargetPrediction. The team's approach is based on the assumption that if a small molecule resembles a ligand whose target is known and which has already been identified – both at the level of its chemical structure and also at the 3D level – there is a chance it will bind to the same target and hence present the same bioactivity. Such a tool is, unsurprisingly, of great help to the pharmaceutical industry since defining a ligand's possible bioactivity determines not only the positive effect it will have on a disease – opening the road to drug repurposing – but also the negative effect it could have on a patient by way of its side effects.

www.isb-sib.ch/groups/lausanne/mmg-michielin.html

www.swisstargetprediction.ch/

EXPLORING THE FIFTH DIMENSION

Osman Ratib, SIB Affiliate Group, Image Analysis and Visualization Tools

Osman Ratib is the initiator of a hugely successful open source platform for medical imagery known as OsiriX, based at the University Hospitals of Geneva. Although the beginnings of medical imagery in Geneva date back to the 1990s, it was in 2004 that Osman Ratib and Antoine Rosset, a radiologist in his team, began to develop this particular platform which is used today by clinicians all over the world. Recently, the OsiriX project agreed upon a collaboration with SIB for the development of clinical analytic tools to allow the integration of Big Omics Data with imagery data.

What exactly is OsiriX? OsiriX offers software that clinicians can use to visualize any part of the human body in 3D, right down to the molecular level. The program can generate interactive 3D images from different kinds of radiological images. It can also display the dynamic behaviour of human organs such as the heart by considering the temporal component – referred to as the fourth dimension. This is done through advanced processing and visualization techniques of different imaging modalities used in clinical practice.

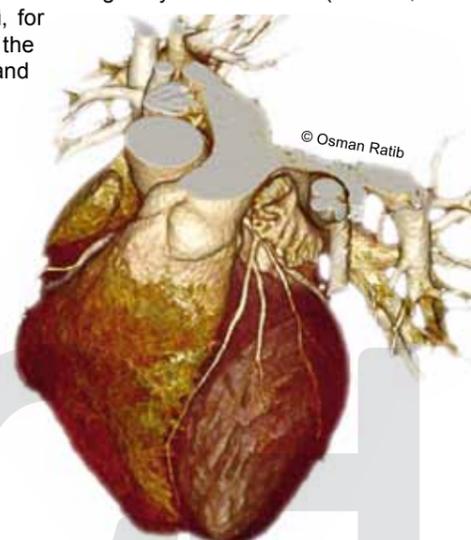
OsiriX: visualizing the effects of treatments

With such imaging techniques, clinicians are now able not only to visualize tumours, for example, but also how they evolve over time, and even their metabolic and biological functions, thus allowing to assess or even predict the effect medication could have on each individual patient. This ability to visualize the biological functions of living tissue is what Osman Ratib has coined the fifth dimension.

Consider, for instance, parameters such as temperature, or sugar intake of a given organ. When these are measured, they can be visualized in certain parts of the human body by applying a specific colour scale that represents their distribution. On images of a beating heart, for example, it is possible to distinguish parts in which cells have died following a myocardial infarct (in black, for example) from those that are still healthy (in red, for example). In this way, clinicians can actually visualize the effect of treatments which can save the viable tissue, and thus monitor the evolution of heart failure.

www.osirix-viewer.com/

foundation.osirixfoundation.com/



RESEARCH

POPULAR SCIENCE

SIB, 3D AND POPULAR SCIENCE

The field of bioinformatics is at the heart of drug design, and SIB is not only a pioneer in bioinformatics but also very active in developing software to assist researchers in designing molecules that could help in the treatment of diseases such as cancer. In 2014, SIB was granted funds by the Swiss National Science Foundation to create a workshop for students and laymen on the subject of Drug Design. Three SIB groups offered their expertise and support in the creation of this workshop: SIB's Training & Outreach Group led by Patricia Palagi, the Computational Structural Biology Group in Basel led by Torsten Schwede and, in particular, the Molecular Modelling Group led by Olivier Michielin and Vincent Zoete in Lausanne.

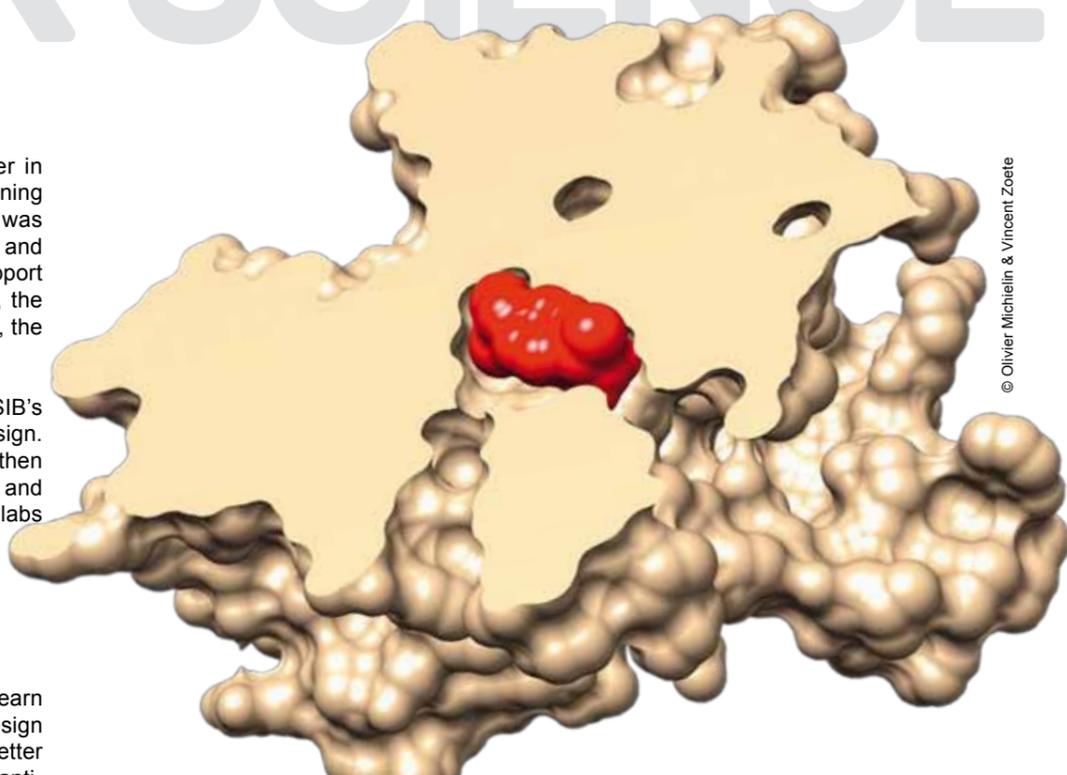
The workshop starts with a short film, produced by Studio KO graphic designers and SIB's Training & Outreach team. It presents the 3D structure of proteins and the realm of Drug Design. Key notions such as "targets", "ligands" and "docking" are explained. Students or visitors then move on to the workshop *per se* where they can learn the basics of how a drug is designed, and even discover bioinformatics tools developed by SIB which are used by researchers in their labs today, such as SwissDock, SwissTargetPrediction and SwissADME.



SIB workshop on drug design: huge success

There are two versions of the workshop. In the first, students learn how a drug against skin cancer is designed and can try to design their own, perhaps even with therapeutic properties that are better than those of existing drugs! In the second, they learn how an anti-inflammatory drug without gastrointestinal side effects is designed. 3D prints of the target protein and six potential drugs have been made use in the workshop so that students can actually "feel" the docking concept.

The workshop is very successful and has already been requested for all sorts of occasions: museum exhibitions, scientific employment forums, science fairs, public labs, open houses and so on.



© Olivier Michielin & Vincent Zoete

SIB's other popular science and educational sites
Virtual exhibition, Chromosome Walk:
www.chromosomewalk.ch

Workshops:
education.expsy.org/bioinformatique/

Online magazine:
www.proteinspotlight.org

The workshops are open to all and available at:
www.atelier-drug-design.ch

They can also be used by teachers for their classes. Or you can contact someone from SIB who will come and give the workshop:
info@atelier-drug-design.ch

NEWS IN BRIEF

ELIXIR, LATEST NEWS

ELIXIR is creating a highway for biological information at the European level, which integrates research data across Europe and provides services accessible to all, thus supporting life science research and its translation to medicine, agriculture, bioindustries and society. SIB is ELIXIR's Swiss Node and its biggest national Node.

ELIXIR has just been granted EU funds for two major projects. In the context of the CORBEL cluster project, ELIXIR will coordinate a €14.5 million grant over four years to establish and support a new model for biological and medical research in Europe by harmonizing user access to resources, unifying data management and creating common ethical and legal services. The objectives of the ELIXIR-EXCELERATE project, which has been granted €19 million over four years, are to build an adequate bioinformatics infrastructure in countries which need one, developing technical services for the European Life Science community, and laying the foundation for the sustainability of core resources. SIB is actively involved in the ELIXIR-EXCELERATE project, focusing on the promotion of excellence in data resource development and operation, the sustainability of core resources, as well as on training aspects.

SIB actively involved in a project to build a bioinformatics infrastructure at the European level

SIB hosted the recent ELIXIR Board meeting in Geneva on 13 and 14 April, turning the world famous Geneva's world famous fountain ELIXIR-orange. The ELIXIR Board meeting was attended by representatives from ELIXIR's 11 member countries and EMBL (European Molecular Biology Laboratory), four of ELIXIR's Observer countries and guests from several other countries working towards membership - a total of 23 countries were represented at the meeting in some capacity.

www.elixir-europe.org/about/elixir-switzerland



SIB DESIGNATED AS FAO REFERENCE CENTRE FOR BIOINFORMATICS

Earlier this year, the Food and Agriculture Organization of the United Nations (FAO) appointed SIB as the FAO Reference Centre for Bioinformatics. FAO fights hunger and poverty in the world by promoting food security and safety for all. SIB's collaboration involves the screening, monitoring and follow-up of zoonotic diseases – i.e. animal infectious diseases that can be transmitted to humans, such as avian influenza – but also animal diseases such as foot-and-mouth disease. SIB's expertise together with its state-of-the-art services led to the choice of the Institute. The bioinformatics tools that SIB has developed and is continuing to develop, in partnership with FAO, have improved not only the early detection of an infection, but also the alert system, by combining epidemiological and genetic information related to zoonotic diseases, as well as the analysis and modelling of the risks of pathogen emergence and spreading.

SIB's expertise and state-of-the-art services led to FAO's choice of the Institute

SIB also provides open-access databases – Viralzone, OpenFlu and OpenFMD – which give information on the pathogens' genome, their epidemiology, evolution and parenthood. These resources will help FAO address the many future challenges related to the management, sharing and analysis of epidemiological and genetic data.

2015 LEENAARDS AWARD WON BY TWO SIB GROUP LEADERS

Jacques Fellay who is head of the Host-Pathogen Genomics group in Lausanne and Evgeny Zdobnov who leads the Computational Evolutionary Genomics group in Geneva are directing one of the two projects which won this year's Leenaards Award for research in translational medicine. Viral genomes are a mirror image of human defence mechanisms against viral infection. Fellay and Zdobnov's research studies the impact that variations in the human genome have on the genomes of viruses – namely, HIV, Epstein-Barr and CMV. Such a combined approach allows them to detect the imprint of human genetic factors on mutations that the viruses accumulate, and how these variations influence the harshness of an infection.

SIB group leaders awarded for research on human genome and its effect on the genomes of viruses

Studying both the patients' genomes and the viruses' genomes concomitantly is a singularly innovative approach and has been made possible not only thanks to cutting-edge genomics and bioinformatics, but also by technological advances in the life sciences and the fact that their cost has diminished drastically in the past years. Discovering the parts of the human genome that play a key role in our defence against viruses, will help to elaborate novel diagnostic and therapeutic strategies.



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NEW MEMBERS

Andrzej Stasiak
DNA and Chromosome
Modelling Group,
University of Lausanne



Andrzej Stasiak leads a team that develops numerical simulations to shed light on how chromosomes are organized in yeasts and higher eukaryotes, such as humans. The group is particularly interested in understanding chromosome structure and organization during interphase – the longest cell cycle phase during which genes are expressed as the cell awaits cell division.

In 2012, thanks to a technique known as high-resolution 3C (Chromosome Conformation Capture), scientists discovered that the chromosomes of higher eukaryotes are composed of sequential blocks – or topological domains. However, it is not yet known how chromatic fibres are arranged in these blocks, or what mechanism is responsible for their formation.

Inspired by the fact that bacterial chromosomes are composed of supercoiled topological domains, the team performed Brownian dynamics simulations which revealed that transcription-induced supercoiling – i.e. supercoiling which occurs upon the transcription of DNA to RNA – explains the formation and all known properties of topological domains.

www.isb-sib.ch/groups/lausanne/dcm-stasiak.html

Maria Anisimova
Applied Computational
Genomics Team,
Zurich University of
Applied Sciences,
Wädenswil



Maria Anisimova leads a team which focuses on the theoretical and computational aspects of modelling the evolution and adaptation of a genome. Genomic data is not only growing continuously but is also becoming more and more complex. To address this growth and complexity, the team develops computational solutions whose focus is to be accurate, scalable and practical for a wide range of scientists in the analysis of evolution and selection patterns in large genomics data.

The team develops bioinformatics applications for real problems in the fields of biotechnology, medicine, ecology and agriculture, with the belief that evolutionary analyses of selective pressures in genomic data have high potential for applications since natural selection drives function conservation, adaptation to emerging pathogens and new environments, and plays a key role in immune and resistance systems.

www.isb-sib.ch/groups/wadenswil/acgt-anisimova.html

David Gfeller
Computational Cancer
Biology Group,
Ludwig Centre
for Cancer Research,
UNIL, Epalinges



Recent developments in immunotherapy are revolutionizing cancer treatments. With this in mind, David Gfeller and his team develop computational tools inspired by statistics, machine learning and modelling to understand the fundamental properties of tumours.

Tumours are characterized by changes at the genetic and epigenetic level. Though frequently detrimental to the patients, such changes provide a way of distinguishing cancer cells from normal cells. The immune system detects only a fraction of the proteins that are specifically expressed or mutated in cancer cells. This is because it can only detect proteins – or antigens – that are displayed on a cell's membrane, a process that is highly regulated in cells.

The aim of the tools developed by David Gfeller and his team is to determine how tumours are recognized by the immune system and predict which antigens have the greatest potential to elicit an immune response. Such antigens – together with immunotherapy drugs – could be used to redirect the immune system against cancer cells.

www.isb-sib.ch/groups/lausanne/ccb-gfeller.html

Ivo Kwee
Bioinformatics Core Unit,
Institute of Oncology
Research (IOR),
Bellinzona



Ivo Kwee leads a team whose research focuses on cancer bioinformatics. Their unit supports research groups within the IOR, offering computational and statistical services for genomic profiling, sequencing analysis, functional genomics, pharmacogenomics, and clinical study support.

Cancer is not caused by one sole gene but is the result of complex interactions between many genes. This is why it is important to go beyond single gene statistics and consider gene sets and interaction networks.

In this light, Ivo Kwee's team is currently developing a tool known as the Prize Collecting Steiner Tree (PCST) algorithm. The PCST finds locally correlated subnetworks within the larger genetic network, which may drive biological pathways that are at the heart of cancer. These are typically neighbourhoods with a concentration of genetic aberrations indicating a possible source for the development of the disease. The group also intends to integrate supplementary data such as copy number, methylation and expression in a single network.

www.isb-sib.ch/groups/bellinzona/bcu-kwee.html

NEWS IN BRIEF

ELIXIR / SIB INNOVATION AND SME FORUM – 9 JUNE 2015 IN BASEL

The ELIXIR / SIB Innovation and SME Forum "Data-driven innovation in the pharma and biotech industries" will take place in Basel on 9 June 2015 alongside the [BC]² Basel Computational Biology Conference.

The one-day event is aimed at the pharma and biotech companies that use public bioinformatics resources in their business. It is particularly relevant for large and small companies interested in:

- Using the free public tools, data resources and services that are available through SIB and ELIXIR partners,
- Hearing about successful examples of companies that are active in utilizing big data in their business,
- Networking and building collaborations with other companies and ELIXIR partners.

Pharma and biotech companies are invited to attend this event to find out how bioinformatics resources can support their research and development projects. Please join us on 9 June 2015 at the Congress Centre in Basel.

More information and registration at: www.bc2.ch/2015/elixir/

SIB PROFILE 2015, BRAND NEW

Last year, SIB decided to combine its annual report and institutional brochure, and published the first SIB Profile in the spring of 2014. This year, the SIB Profile 2015 was completely revamped, both with regard to its contents and its graphic design.

The publication is divided into two parts. The first is accessible to a wide audience and presents the field of bioinformatics as well as SIB's expertise. The second part describes briefly the research carried out by SIB's groups and is addressed to a more specialized audience.

Online copy:
www.isb-sib.ch/images/stories/Corporate/sib_profile_2015.pdf

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