9th CFGBC SYMPOSIUM

FROM ARRAYS AND SEQUENCING TO UNDERSTANDING DISEASE

and

ISBE WORKSHOP

SYSTEM BIOLOGY AND ITS IMPACT ON SCIENCE, ECONOMY, INDIVIDUALS AN-D SOCIETY

BOOK OF ABSTRACTS

October 17th 2014
Ljubljana, Slovenia

9th CFGBC Symposium

FROM ARRAYS AND SEQUENCING TO
UNDERSTANDING DISEASES

AND

ISBE Workshop

SYSTEM BIOLOGY AND ITS IMPACT ON SCIENCE,
ECONOMY, INDIVIDUALS AND SOCIETY

Organized by:

October 17, 2014
Ljubljana, Slovenia

9th CFGBC Symposium and ISBE Workshop
FROM ARRAYS AND SEQUENCING TO UNDERSTANDING DISEASES

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INTRODUCTION

Dear Colleagues,

The Organizing Committee from Faculty of Medicine at University of Ljubljana and from National Institute of Biology take a great pleasure in inviting you to the joint event of 9th CFGBC Symposium "**From Arrays and Sequencing to Understanding Diseases**" and the Infrastructure Systems Biology Europe (ISBE) workshop "**Systems biology and its impact on science, economy, individuals and society**".

The CFGBC symposium is a traditional yearly event where members of the Slovenian Consortium of Bio-Chips and international participants present their discoveries and promote further development of the functional genomics research in Slovenia. The topics of this year will be focused on systems biology, data management and functional genomics with aspects of translation into the clinical care or within the agri-food chain. The focus on systems and data approaches is an excellent stand for hosting this symposium at Faculty of Computer and Information sciences. The lectures, poster presentations and other discussions will provide some state of the art information in the above areas and how this is linked to the ESFRI infrastructures, in particularly the European Life sciences Infrastructure for Biological Information ELIXIR and previously mentioned ISBE.

The global post-genome efforts combined with in-depth computation, in particular bioinformatics and mathematical modelling, will be discussed within our symposium. Together with good data management strategies, this represents a modern approach for understanding the complexity of multifactorial events – from multifactorial diseases, to host-pathogen interactions and beyond, aimed at ameliorating disease prognosis and diagnosis as well as in providing templates for the design of better drugs.

We look forward to welcoming you to this scientific symposium in the new building of Faculty of Computer and Information Sciences, University of Ljubljana.

Prof. Dr. Damjana Rozman
Head of the Centre for Functional Genomics and Bio-Chips

Centre for Functional Genomics and Bio-Chips

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The Slovenian scientists joined the post-genome era by organizing a Slovenian Network for Functional Genomics that was formalized in December 2001 with the constitution of the Slovenian Consortium of Bio-Chips. This Consortium now includes 16 members and since June 16th 2005 performs its activities in the laboratories of the Centre for Functional Genomics and Bio-Chips (CFGBC) at Faculty of Medicine, University of Ljubljana. The infrastructure belonging to the Consortium is located at CFGBC being freely accessible to all members. A formal act "Regulations of the Activities of the CFGCB" was signed by all partners in November 2005. The boards of CFGBC, including the Management Board and the Scientific Board, have been established in January 2006. Since 2004 CFGBC is a part of the Network of Infrastructure Centres of University of Ljubljana (MRIC-UL).

CFGBC is a microarray and sequencing infrastructure of the Slovenian national importance. It represents an educational unit for Slovenian and international students of biomedical sciences who have functional genomics related subjects in their curricula or have to perform experiments within their undergraduate diplomas, doctoral theses or post-doctoral training. An important mission of CFGBC is promotion of post-genomic technologies and linking the CFGBC activities to major international efforts. This is achieved through the yearly CFGBC symposium, theoretical and practical seminars, guided tours for students and teachers/supervisors from high school to university level, and activities at international level. CFGBC members from different institutions are leaders of the Slovenian ESFRI (European Strategy Forum on Research Infrastructures) activities for biomedical sciences, particularly ELIXIR (Infrastructure for Biological Information), EATRIS (Infrastructure for Translational Medicine) and ISBE (Infrastructure Systems Biology Europe). ELIXIR Slovenia is hosted at Faculty of Medicine and includes activities of multiple institutions.

CFGBC hosts also multiple national and international health, agri-food and data sciences related projects where scientists from the Consortium co-ordinate activities or work as collaborators. In recent period, many CFGBC groups have oriented their research towards systems biology/medicine. These are novel interdisciplinary research fields that connect the biomedical (medicine, veterinary medicine, biology, biochemistry and molecular biology, etc.), mathematical (informatics, statistics, mathematics, physics, etc.) and engineering sciences. Systems biology/medicine apply quantitative and high-throughput post-genome experimental and theoretical approaches to allow a holistic view on biological processes. This is crucial for understanding, i.e. the pathogenesis of, complex human disorders, their prognosis and diagnosis, as well as in predictions of the treatment outcome, taking into account inter-individual variations. The European infrastructure for systems biology ISBE and its visions are described in more detail later in this book.

Organizational Scheme of CFGBC

http://cfgbc.mf.uni-lj.si/

ACADEMIA

University of Ljubljana

Faculty of Medicine
Faculty of Pharmacy
Biotechnical Faculty
Veterinary Faculty
Faculty of Comp. and Inf. Sci.
Faculty of Electrical Engineering

University of Nova Gorica

CLINICAL INSTITUTIONS

University Medical Centre Lj.
Institute of Oncology
Blood Transfusion Centre of Slo.
National Laboratory of Health, Environment and Food

RESEARCH INSTITUTES

National Institute of Biology
National Institute of Chemistry
Agricultural Institute of Slovenia
Jožef Stefan Institute

PHARMACEUTICAL INDUSTRY

Lek, d.d.

CFGBC is a consortium of 16 members from Academia, Research and Clinical Institutions and Industry, with a Management Board and a Scientific Advisory Committee.

Figure 1: Members of the Slovenian Consortium for Bio-Chips.

Synopsis of Elixir Slovenia

Prof. Dr. Damjana Rozman

Joining the pan-European efforts to establish and maintain sustainable research infrastructures is essential for small research communities as is Slovenia. We join ELIXIR as a national node, providing data resources, compute and training provision, and tools infrastructure for specific biological domains. Slovenian node will be represented by Centre for Functional Genomics and Bio-Chips (CFGBC, http://cfgbc.mf.uni-lj.si), a 16-member consortium of academia, research institutes, clinical institutes and pharmaceutical industry. Particular CFGBC members will be active within Elixir.si node as service providers: University of Ljubljana (UL), Faculties of Medicine, Computer and Information Science, Electrical Engineering and Biotechnical Faculty will represent the basis of e-infrastructure and help desk for genome and transcriptome data, by linking specialized data resources from biological domains (Biomedicine, Plant sciences, Animal genomics) to ELIXIR tools. This will be supported by National Institute of Biology (NIB) with expertise in plant sciences and computation, together with Jozef Stefan Institute (IJS), by National Institute of Chemistry (NIC) with expertise in cheminformatics and molecular modeling, and by biomedical data and sample resources from Oncological Institute (OI) and clinics from the University Medical Centre Ljubljana (UMCL). Pediatrics clinic from UMCL holds expertise also in lipid MS-based metabolomics. Other CFGBC members will at current stage remain Elixir users, with the potential to offer their expertise and services at a later time. The common goal of our node is to establish the basis of the mid-European ELIXIR interdisciplinary training center in Slovenia. The training efforts will be in concert with the recently funded ESFRI activity Infrastructure Systems Biology Europe (ISBE) and the Coordinated Action for Systems Medicine (CASyM), where partners of the Slovenian Elixir node are also involved, together with the Slovenian Ministry of Education & Research.

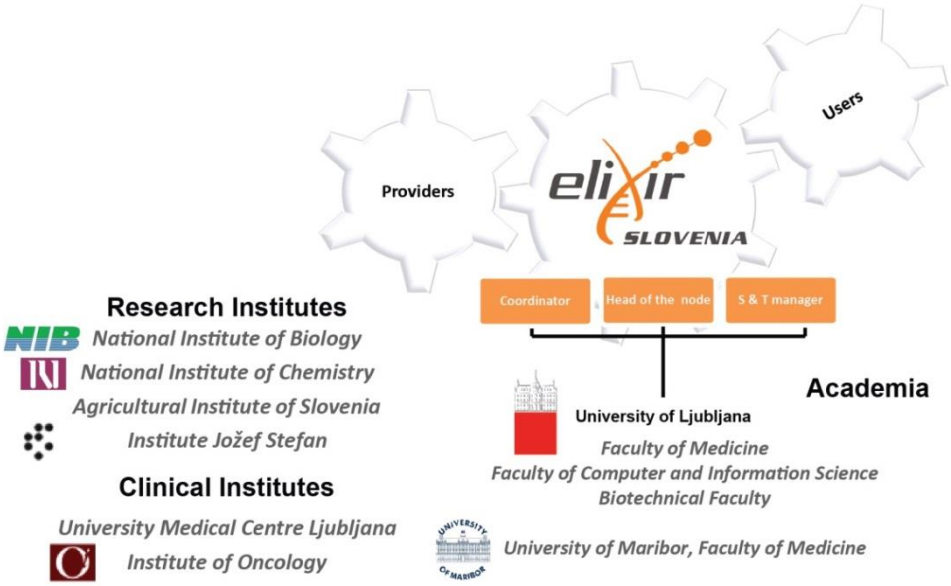

Figure 2: Particular Consortium members will provide e-infrastructure and help desk for genome and transcriptome data, expertise in plant sciences, computation, cheminformatics and molecular modelling, and biomedical sample resources; other Consortium members will represent ELIXIR users.

Project ISBE – Infrastructure for Systems Biology Europe

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The mission of ISBE is to establish, and enable access to an integrated, distributed infrastructure of state-of-the-art facilities for system biology across Europe, with a view to transforming our understanding of the life sciences, human health and the environment.

ISBE's vision is to enable European life scientists from all sectors to tackle complex biological problems from a systems perspective. ISBE will achieve this by establishing a distributed European-wide infrastructure, and providing the means for accessing these hubs of technological excellence in systems biology. The infrastructure will offer the best multidisciplinary research expertise, training, experimental and modelling facilities, repositories of data and models necessary for small to large scale systems biology research programmes. Facilitation of this integrated systemic approach to the study of biological processes will transform our basic knowledge of biological systems at many scales – from molecules to cells to whole organisms. Exploitation of which will result in applications in areas including bio-medicine, agricultural science and the environment; thus positively impacting future healthcare and bio-based technological development for the greater benefit of European industry, society and the overall economy.

Source: http://project.isbe.eu/

Improving translational research through EATRIS

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The concept of EATRIS (**European Advanced translational Research Infrastructure** http://www.eatris.eu/Home.aspx) is designed with the strategic objective to establish the infrastructure that will enable faster and more efficient transfer of knowledge from basic research laboratories into products and services in the field of biomedicine.

EATRIS consortium represents a distributed infrastructure that serves the development of the most advanced diagnostic methods and therapeutic approaches. The importance of highly specialized centers is in the standardization of procedures, harmonization of regulations and the introduction of safety standards including pre- and clinical research. EATRIS is designed as distributed infrastructure interconnecting research organizations, educational institutions and clinical departments, covering all stages of the research and development involving disease pathogenesis, design of diagnostic biomarkers, the synthesis of new molecules to Phase 1 clinical trial for new substances or diagnostic markers.

UL FFA has established the center infrastructure EATRIS-TRI.si, which currently has observer status in the EATRIS- ERIS. Full membership in EATRIS will allow faster development and implementation of the principles of applied strategies in the Slovenian area, which in turn will affect the competitiveness of the economy. Furthermore, the enforcement of the legal and professional standards in the field of applied biomedical example, the creation of spin-off companies.

Uvod

Dragi kolegi,

organizacijski odbor Medicinske fakultete Univerze v Ljubljani ter Nacionalnega inštituta za biologijo vas toplo pozdravlja na 9. simpoziju CFGBC "Od DNA mikromrež in sekvenciranja do razumevanja bolezni" ter na delavnici ISBE "Sistemska biologija in njen vpliv na znanost, gospodarstvo, posameznika in družbo kot celoto".

Na že tradicionalnem simpoziju CFGBC člani Slovenskega konzorcija za biočipe in mednarodni gostje vsako leto predstavijo zadnje raziskovalne dosežke in tako pripomorejo k razvoju področja funkcijske genomike v Sloveniji. Letos bo predvsem poudarjeno področje sistemske biologije, upravljanja s podatki ter funkcijske genomike s prenosom v kliniko ali agronomsko–prehrambno področje. Prav poudarek na sistemskem pristopu in obdelavi podatkov je idealna priložnost, da bo letošnji simpozij CFGBC gostila Fakulteta za računalništvo in informatiko. Najnovejše informacije s teh področij bodo podane preko predavanj in predstavitev posterjev, poudarjene pa bodo povezave z infrastrukturo ESFRI (European Life sciences Infrastructure for Biological Information ELIXIR ter ISBE).

Na simpoziju bodo predstavljeni predvsem post–genomski podatki v povezavi z bioinformatičnimi analizami in matematičnim modeliranjem. Skupaj z učinkovitim upravljanjem podatkov, taki pristopi predstavljajo moderen pristop k razumevanju zapletenih večfaktorskih dogodkov (od večfaktorskih bolezni do interakcij med gostiteljem in patogeni), s pomočjo katerega lahko izboljšamo prognozo in diagnozo bolezni ter pripomoremo k sintezi boljših zdravil.

Veseli nas, da vas lahko pozdravimo na tem znanstvenem simpoziju v novi zgradbi Fakultete za računalništvo in informatiko Univerze v Ljubljani.

Prof. Dr. Damjana Rozman
Vodja Centra za funkcijsko genomiko in biočipe

Center za funkcijsko genomiko in biočipe

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Slovenski znanstveniki so se post-genomskemu obdobju pridružili z organizacijo slovenske mreže za funkcijsko genomiko decembra 2001, ter z ustanovitvijo Slovenskega konzorcija za biočipe. Konzorcij vključuje 16 članov in od 16. junija 2005 opravlja svojo dejavnost v laboratorijih Centra za funkcijsko genomiko in bio-čipe (CFGBC) na Medicinski fakulteti Univerze v Ljubljani. Novembra 2005 so partnerji CFGBC podpisali "Pravilnik o dejavnosti CFGBC". Upravno telo CFGBC, vključno z upravnim in znanstvenim odborom, pa je bilo ustanovljeno januarja 2006. Od leta 2004 naprej je CFGBC tudi del mreže infrastrukturnih centrov Univerze v Ljubljani (MRIC/UL). Infrastruktura, ki se nahaja na CFGBC je del konzorcija in je prosto dostopna vsem članom.

CFGBC predstavlja infrastrukturni center nacionalnega pomena za tehnologijo DNA mikromrež in sekvenciranja. Deluje tudi kot izobraževalni center za slovenske in mednarodne študente biomedicinskih ved, kateri imajo v svojih učnih načrtih predmete povezane s funkcijsko genomiko ali morajo v sklopu diplomskega, doktorskega oziroma podoktorskega izobraževanja izvesti del raziskav z omenjenimi tehnologijami. Pomembno poslanstvo centra je promocija post-genomskih tehnologij in povezovanje njegovih aktivnosti z večjimi mednarodnimi pobudami. CFGBC to uresničuje z letnim simpozijem, teoretičnimi in praktičnimi seminarji, vodenimi ogledi za študente in profesorje od nivoja srednje šole pa do univerze ter aktivnostmi na mednarodnem nivoju. Člani CFGBC iz različnih institucij vodijo slovenske ESFRI (Evropski strateški forum za raziskovalno infrastrukturo) aktivnosti za biomedicinske vede, še posebej ELIXIR (Infrastruktura za biološke informacije), EATRIS (Infrastruktura za translacijsko medicino) in ISBE (Infrastruktura za sistemsko biologijo v Evropi). ELIXIR Slovenija gostuje na Medicinski fakulteti Univerze v Ljubljani in vključuje dejavnosti več institucij.

Na CFGBC se izvajajo tudi nacionalni in mednarodni projekti povezani z zdravjem, hrano in informatiko, kjer znanstveniki iz konzorcija usklajujejo aktivnosti oziroma delo kot sodelavci. V zadnjem času je več skupin znotraj CFGBC svoje raziskave usmerilo v sistemsko biologijo/medicino. Gre za novo interdisciplinarno vedo, ki povezujejo biomedicino (medicina, veterinarska medicina, biologija, biokemija in molekularna biologija, itd.), matematiko (informatika, statistika, matematika, fizika, itd.) in inženirstvo. V sistemski biologiji/medicini se uporabljajo kvantitativni in visokozmogljivi pogenomski eksperimentalni kot tudi teoretični pristopi za celovito razumevanje bioloških procesov. To je ključno za razumevanje npr. patogeneze kompleksnih človeških bolezni, njihove prognoze in diagnoze, pa tudi napovedovanje izida zdravljenja z upoštevanjem medosebnih razlik. Vizija Evropske infrastrukture za sistemsko biologijo v Evropi ISBE je predstavljena kasneje v tej knjigi.

Organizacijska shema CFGBC

http://cfgbc.mf.uni-lj.si/

AKADEMSKE INŠTITUCIJE

Univerza v Ljubljani

Fakulteta za medicino
Fakulteta za farmacijo
Biotehniška fakulteta
Veterinarskafakulteta
Fakult. za raču. in informatiko
Fakulteta za elektrotehniko

Univerza v Novi Gorici

KLINIČNE USTANOVE

Univerzitetni klinični center
Onkološki inštitut
Center za transfuzijo RS
Nacionalni laboratorij za zdravje, okolje in hrano

RAZISKOVALNE ORGANIZACIJE

Nacionalni inštitut za biologijo
Nacionalni inštitut za kemijo
Kmetijski inštitut Slovenije
Inštitut Jožef Stefan

FARMACEVTSKA INDUSTRIJA

Lek, d.d.

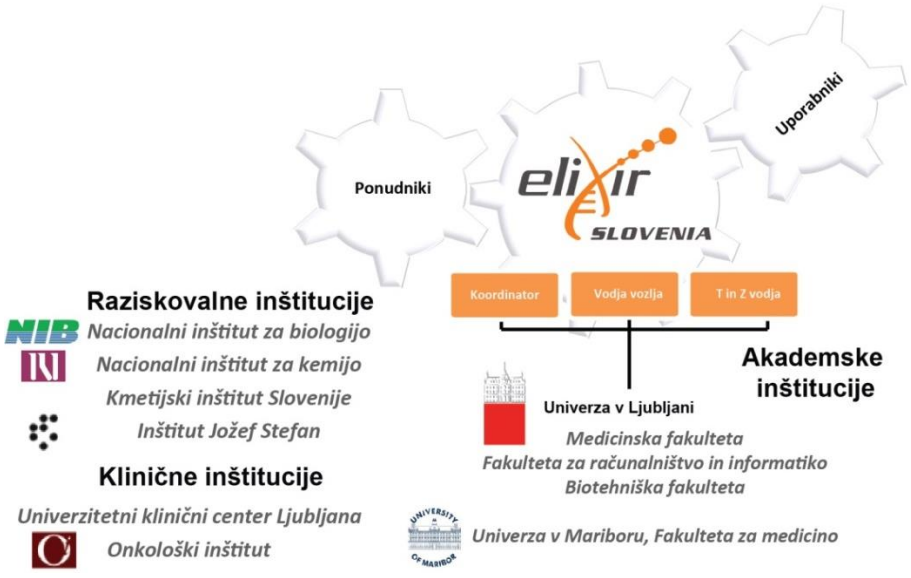
CFGBC sestavlja konzorcij 16 članov iz akademije, raziskovalnih in kličinih ustanov ter industrije s skupnim upravnim in znanstvenim odborom.

Slika 1: Člani Slovenskega konzorcija za biočipe.

Povzetek slovenske veje ELIXIR

Prof. Dr. Damjana Rozman

Za majhna raziskovalna območja, kakršna je Slovenija, je pomembna pridružitev vse-evropskim prizadevanjem za ustanovitev in vzdrževanje trajnostne raziskovalne infrastrukture. ELIXIR-ju se pridružujemo kot narodno vozlišče, ki zagotavlja vir podatkov, sredstva za računsko obdelavo in šolanje ter infrastrukturo za posamezna biološka področja. Slovensko vozlišče bo predstavljal Center za Funkcijsko Genomiko in Biočipe (CFGBC, http://cfgbc.mf.uni-lj.si), 16-članski konzorcij visokega šolstva, raziskovalnih in kliničnih ustanov ter farmacevtske industrije. Kot ponudniki storitev znotraj vozlišča Elixir.si bodo aktivni predvsem člani CFGBC: Univerza v Ljubljani (UL), Fakultete za medicino, računalništvo in informacijske vede, elektrotehniko in Biotehniška fakulteta bodo predstavljale osnovo e-infrastrukture in nudile pomoč pri genomskih in transkriptomskih analizah s povezovanjem posebnih podatkovnih virov iz bioloških področij (biomedicina, rastlinske vede, genomika živali) z ELIXIR-jevimi orodji. Podporo bo skupaj z Inštitutom Jožef Stefan (IJS) nudil tudi Nacionalni inštitut za biologijo (NIB) s strokovnim znanjem na področju rastlinskih ved in računanja, Kemijski inštitut (KI) s strokovnim znanjem kemoinformatike in molekularnega modeliranja, Onkološki inštitut (OI) z zagotavljanjem biomedicinskih podatkov in vzorcev ter Univerzitetni klinični center (UKC) s kliničnim delom. Na pediatrični kliniki UKC imajo ustrezno strokovno znanje tudi s področja lipidov in metabolomike s pomočjo masne spektrometrije. Ostali člani CFGBC bodo zaenkrat ostali uporabniki Elixir-ja, pri čemer bodo lahko svoje strokovno znanje nudili v prihodosti. Skupni cilj našega vozlišča je postaviti temelj ELIXIR-jevega srednjeevropskega interdisciplinarnega centra za šolanje v Sloveniji. Šolanje bo potekalo v sodelovanju z nedavno ustanovljenim ESFRI (European Strategy Forum on Research Infrastructures), ISBE (Infrastructure for Systems Biology) in CASyM (Coordinated Action for Systems Medicine), pri čemer bodo skupaj s slovenskim Ministrstvom za izobraževanje, znanost in šport udeleženi tudi slovenski partnerji vozlišča Elixir.



Slika 2: Določeni člani konzorcija bodo omogočili dostop do e-infrastrukture in uporabnikom nudili pomoč pri analizi genomskih in transkriptomskih podatkov, strokovno znanje iz področja rastlinskih tehnologij, znanje iz področja računanja, kemoinfomatike in modeliranja ter pridobivanja biomedicinskih virov informacij. Ostali člani konzorcija bodo uporabniki storitev infrastrukture ELIXIR.

Projekt ISBE – Infrastruktura za sistemsko biologijo Evrope

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Poslanstvo projekta ISBE je vzpostavitev in dostopnost povezane mreže infrastrukturnih središč po vsej Evropi, ki naj bi spreminjala naše razumevanje ved o življenju, našega zdravja in okolja.

Vizija projekta je omogočiti evropskim znanstvenikom z vseh področij ved o življenju raziskovanje zapletenih bioloških problemov iz sistemske perspektive. S tem projektom bo vzpostavljena dostopna mreža infrastrukturnih središč po vsej Evropi. Infrastrukturna središča bodo zagotavljala multidisciplinarno strokovno znanje, izobraževanje, možnosti za izvajanje poskusov in modeliranje, repozitorije podatkov ter modele, nujne za majhne ali velike programe sistemske biologije.

Z raziskavami bioloških procesov z uporabo nove infrastrukture bomo povečali naše temeljno znanje od ravni molekul in celic do celotnih organizmov. Uporaba infrastrukture bo vodila do novih aplikacij v biomedicini, kmetijstvu, okolju. Pozitivno bo vplivala na prihodnje zdravstveno varstvo in tehnološki razvoj, povezan z vedami o življenju, kar bodo občutili evropska družba, industrija in celotno gospodarstvo.

Vir: http://project.isbe.eu/

Uspešnejša translacija raziskovalnih rezultatov s pomočjo EATRISa

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Koncept EATRISa (**European Advanced Translational Research InfraStructure** http://www.eatris.eu/Home.aspx) je zasnovan s strateškim ciljem vzpostaviti infrastrukturo, ki bo omogočila hitrejši in učinkovitejši prenos spoznanj iz bazičnih raziskovalnih laboratorijev v proizvode in storitve na področju biomedicine.

EATRIS konzorcij prestavlja distribuiran infrastrukturni center, ki služi razvoju najsodobnejših diagnostičnih metod in terapevtskih pristopov. Pomen visoko specializiranih centrov je tudi v standardizaciji postopkov, harmonizaciji predpisov in v uvajanju visokih standardov varnosti na področju pred- in kliničnih raziskav. Koncept velike infrastrukture je zato izdelan multicentrično, povezuje raziskovalne organizacije, izobraževalne inštitucije in klinične oddelke, ki pokrivajo vse faze raziskav in razvoja od raziskav patogeneze bolezni, izdelave diagnostičnih bioloških označevalcev, preko sinteze novih molekul do 1. faze kliničnega testiranja bodisi novih učinkovin ali diagnostičnih markerjev.

Na Univerzi v Ljubljani, Fakulteti za farmacijo je vzpostavljen infrastrukturni center EATRIS-TRI.si, ki ima trenutno status opazovalca v EATRIS-ERIS. Polnopravno članstvo v EATRIS bo omogočilo hitrejšo uveljavitev principov razvojnih in aplikativnih strategij v slovenskem prostoru, kar bo posledično vplivalo na večjo konkurenčnost gospodarstva. Nadalje pa na uveljavitev pravnih in strokovnih standardov na področju aplikativne biomedicine npr. ustanavljanje spin-off podjetij in podpora srednje velikim podjetjem, gospodarskim središčem in centrom kompetenčnosti na tem in podpornih tehnoloških področjih.

PROGRAMME

08:00-08:45	**REGISTRATION**
08:45-09:00	**OPENING REMARKS: KRISTINA GRUDEN AND GUESTS**
09:00-09:30	**OPENING LECTURE** (CHAIRMAN: BRANE LESKOVŠEK)
	James Malone, *EMBL-EBI, Wellcome Trust Genome Campus, Hinxton, United Kingdom* Data Integration with Ontologies
09:30-10:40	**SESSION 1** (CO-CHAIRMEN: DAMJANA ROZMAN AND BORUT PETERLIN)
09:30-09:40	Brane Leskošek, *Faculty of Medicine, University of Ljubljana, Slovenia* ELIXIR Slovenia use-cases for life science community
09:40-09:50	Irena Mlinarič Raščan, *Faculty of Pharmacy, University of Ljubljana, Slovenia* Improving translational research through EATRIS
09:50-10:10	Jernej Kovač, *Children's Hospital, University Medical Centre Ljubljana, Slovenia* The analysis of the selected genes regulating reactive oxygen and nitrogen species equilibrium in patients with autistic spectrum disorder
10:10-10:30	Borut Peterlin, *Clinical Institute of Medical Genetics, University Medical Centre Ljubljana, Slovenia* Centre for Mendelian genomics: translation of genomic technologies into clinical care
10:30-10:40	ROCHE d.o.o. Commercial presentation
10:40-10:50	Kemomed d.o.o. Commercial presentation
10:50-11:20	**COFFEE BREAK AND POSTER SESSION I**
11:20-13:00	**SESSION 2** (CO-CHAIRMEN: BLAZ ZUPAN AND BRANKA JAVORNIK)
11:20-11:40	Tomaž Curk, *Faculty of Computer and Information Science, University of Ljubljana, Slovenia* Protein-RNA interactions: two sides of a story
11:40-12:00	Miha Moškon, *Faculty of Computer and Information Science, University of Ljubljana, Slovenia* Recent approaches for the modelling and computational design of biological information processing structures
12:00-12:20	Damjana Rozman, *CFGBC, Institute of Biochemistry, Faculty of Medicine, University of Ljubljana, Slovenia* Non-alcoholic (fatty) liver disease - from mathematical to mouse models
12:20-12:40	David Dobnik, *Department of Biotechnology and Systems Biology, National Institute of Biology, Ljubljana, Slovenia* Integration of microarrays, functional genomics and next-generation sequencing for ultimate understanding of plant pathogen interactions
12:40-13:00	Branka Javornik, *Biotechnical Faculty, University of Ljubljana, Slovenia* Genome sequencing of *Verticillium albo-atrum* patotypes to understand wilt disease in hop
13:00-13:05	**CLOSING REMARKS**
13:05-14:00	**POSTER SESSION II**
14:00-17:00	**ISBE WORKSHOP**

ABSTRACTS OF LECTURES

LECTURES

Data Integration with Ontologies

James Malone

EMBL-EBI, Wellcome Trust Genome Campus, Hinxton, United Kingdom

The advent of low cost technologies which can produce large and complex data sets presents a challenge in how a researcher integrates and analyses such data. Coupled with an increasing need to understand biomedical questions across many different omics levels, the role of data integration in biomedicine has never been more important. In this talk I will outline some of the approaches and technologies we use to tackle these challenges. This includes the use of bio-ontologies as a tool for annotation and integration and semantic web technologies to enable questions to be asked across multiple, heterogeneous data sources. Finally, I outline some of the challenges we face in the future with regards translating these approaches into fully fledged applications that can help advance bioinformatics into clinical and translational research.

ELIXIR Slovenia use-cases for life science community

Brane Leskošek

Faculty of Medicine, University of Ljubljana, Slovenia

ELIXIR (http://www.elixir-europe.org) is a sustainable European infrastructure for biological information, supporting life science research and its translation to medicine, agriculture, bioindustries and society. In ESFRI roadmap ELIXIR infrastructure is one of three top priority ESFRI projects and the only one from the field of life sciences. For the time being 17 European countries are partners in ELIXIR, among them is also ELIXIR Slovenia node (http://cfgbc.mf.uni-lj.si/elixir). ELIXIR Slovenia node is active in majority of Work Streams and Task Forces, especially in training (leading eLearning Task Force) and also in Cloud, AAI, Service Registry and Ontology Task Forces and Works Streams. University of Ljubljana, Faculty of Medicine coordinates ELIXIR Slovenia and brings together members from academia, research institutes, clinical institutes and pharmaceutical industry. ELIXIR Slovenia has, similar to some other EU examples, the ambition to connect overlapping activities between different European and national infrastructures and, where possible, integrate them under ELIXIR umbrella. ELIXIR Slovenia thus closely collaborate with other important European and national infrastructures like ESFRI infrastructure EATRIS (European Advanced Translational Research Infrastructure, Slovenia is also member of EATRIS), ARNES (Slovenian NREN = National Research and Educational Network; partner in GEANT), EGI (European Grid Infrastructure) and SLING (Slovenian Initiative for National Grid; part of EGI). Initial talks for collaboration with ESFRI infrastructures BBMRI (Biobanking and BioMolecular resources Research Infrastructure) and Euro-BioImaging (European Research Infrastructure for Imaging Technologies in Biological and Biomedical Sciences) are under way. In lecture, we will present the available and possible ELIXIR Slovenia use-cases, pilots and services.

Improving translational research through EATRIS

Prof. dr. Irena Mlinarič Raščan

Faculty of Pharmacy, University of Ljubljana, Slovenia

The concept of EATRIS (European Advanced translational Research Infrastructure http://www.eatris.eu/Home.aspx) is designed with the strategic objective to establish the infrastructure that will enable faster and more efficient transfer of knowledge from basic research laboratories into products and services in the field of biomedicine.

EATRIS consortium represents a distributed infrastructure that serves the development of the most advanced diagnostic methods and therapeutic approaches. The importance of highly specialized centers is in the standardization of procedures, harmonization of regulations and the introduction of safety standards including pre- and clinical research. EATRI is designed as distributed infrastructure interconnecting research organizations, educational institutions and clinical departments, covering all stages of the research and development involving disease pathogenesis, design of diagnostic biomarkers , the synthesis of new molecules to Phase 1 clinical trial for new substances or diagnostic markers.

UL FFA has established the center infrastructure EATRIS-TRI.si, which currently has observer status in the EATRIS- ERIS. Full membership in EATRIS will allow faster development and implementation of the principles of applied strategies in the Slovenian area, which in turn will affect the competitiveness of the economy. Furthermore, the enforcement of the legal and professional standards in the field of applied biomedical example. the creation of spin-off companies.

The analysis of the selected genes regulating reactive oxygen and nitrogen species equilibrium in patients with autistic spectrum disorder

Jernej Kovač[1], Katarina Trebušak Podkrajšek[1], Tadej Battelino[2,3]

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The difficulties in social interaction, communication and narrow set of interest coupled with stereotypical repetitive behaviour are characteristic for neurodevelopmental autistic spectrum disorder (ASD). The incidence of ASD is rising and reaching up to 1:88 children, usually diagnosed by the age of 3 years. The incidence in male population is up to five times higher than in female population.

The exact aetiology of ASD is unknown. The complex interaction between favourable genetic predisposition and the environmental factors is suspected to play a major role in ASD. One of these factors is oxidative stress – the state of lost equilibrium between anti-oxidative mechanisms of the cell and generation of reactive oxygen species. The uncontrolled accumulation of ROS leads to the generation of cytotoxic products, enzyme and DNA dysfunction causing a wide spectrum of diseases. The key ROS defence mechanisms are linked to superoxide dismutase enzymes (SOD), glutathione peroxidases (GPX) and glutathione-S-transferases (GST). A higher level of oxidative stress biomarkers was detected in ASD patients.

We analysed association of genetic variants with ASD in genes involved in ROS defence mechanisms (SOD, GPX, GST) and in selected genes involved in generation of ROS and cytotoxic products (NOS, GLO1 and HAGH). A total of 143 participants with ASD and 150 healthy controls were involved in the association analysis.

Using high resolution DNA melting analysis and selective DNA sequencing we identified 52 genetic variants. Genetic variants of SOD1 rs2234694 and rs36233090 were statistically significantly associated with ASD (OR=2.65; 95%CI=1.40 – 5.00; $p<0.01$) as well as genetic variants of GLO1 rs2736654 (OR=2.2; 95% CI=0.99 – 4.9; $p=0.045$) in rs1049346 (OR=1.5; 95% CI=1.10-2.20; $p<0.05$).

Our results indirectly confirm the contribution of oxidative stress in the aetiology of ASD. The functional analysis including the analysis of SOD1 and GLO1 enzyme activity as well as expression analysis in brain tissue of SAM patients is required to establish the exact mechanism of possible ROS involvement in the development of SAM.

Centre for Mendelian genomics: translation of genomic technologies into clinical care

Borut Peterlin, Aleš Maver

Clinical Institute of Medical Genetics, University Medical Centre Ljubljana, Slovenia

Advances in technologies for determination of genetic sequence now permits investigation of genetic information to single nucleotide resolution on the whole exome and genome scale. In light of significant genetic and phenotypic heterogeneity of human genetic diseases, these new approaches open the opportunity to significantly facilitate diagnosis in clinical genetics practice. To ensure the efficient and active translation of NGS into clinical practice, we have established a Centre for Mendelian genomics at the Clinical Institute of Medical Genetics in Ljubljana in 2013. Since the establishment, we have performed whole exome and clinical exome sequencing in 200 cases affected by a wide variety of disease groups, including neurological, cardiovascular, developmental and various other conditions. Depending on the disease group were able to identify causative alterations in up to 80% of patients, with mutation identification rates depending on the disease group. To maximize the diagnostic yield, we have implemented a tailored bioinformatics pipeline for identification of potentially causative single nucleotide variants, copy number variants and mitochondrial variation. Furthermore, we have implemented an innovative variant prioritization approach that combines pathogenicity properties of variants and their phenotypic consequences. Using these approaches, we have, in addition to genetic disorders, also investigated familial cases of complex disorders and have identified genes harboring rare and plausibly pathogenic variants potentially contributing to their development. In conclusion, we present our experience in translating new genomic technologies into diagnostics of patients with rare genetic disorders. We also present opportunities opened by novel approaches in deciphering genetic architecture of common complex disorders.

Protein-RNA interactions: two sides of a story

Tomaž Curk

Faculty of Computer and Information Science, University of Ljubljana, Slovenia

The field of RNA biology has witnessed enormous progress in recent years. The iCLIP [1] method for the identification of protein-RNA interaction sites on the RNA and the mRNA interactome capture [2] method for the identification of RNA-binding proteins are just two examples of experimental procedures, which yield a wealth of information on protein-RNA interactions in vivo.

We give an overview of current experimental methods for protein-RNA interaction site discovery. We present two recent computational approaches developed to identify interaction sites on RNA and proteins, respectively. We conclude with a discussion on current computational approaches that aim for a better understanding of the underlying mechanisms and roles of protein-RNA interactions by integrating interaction data on both players involved.

References:

1. Konig, J., Zarnack, K., Rot, G., Curk, T., Kayikci, M., Zupan, B., Turner, D. J., Luscombe, N. M., and Ule, J. (2010) iCLIP reveals the function of hnRNP particles in splicing at individual nucleotide resolution. Nat Struct Mol Biol, 17(7), 909–15.
2. Castello, A., Fischer, B., Eichelbaum, K., Horos, R., Beckmann, B. M., Strein, C., . . . Hentze, M. W. (2012) Insights into RNA biology from an atlas of mammalian mRNA-binding proteins. Cell, 149(6), 1393-406.

Recent approaches for the modelling and computational design of biological information processing structures

Miha Moškon, Miha Mraz

Faculty of Computer and Information Science, University of Ljubljana, Slovenia

We present some of the approaches that are directed towards the efficient modelling and computational design of biological systems with information processing capabilities. Firstly, we review the existent techniques used for the modelling of such systems. We further on present some of the metrics, i.e. measures that can be used to objectively evaluate the performance of modelled biological systems with information processing capabilities. These measures may be exploited to analyse the compatibility among the basic information processing structures and therefore automatize the modular design of more complex systems. However, the usability of such automatisation is conditioned with the efficient modelling techniques. One of the problems of conventional modelling approaches is their computational complexity, which becomes intractable even in relatively simple biological systems when we are dealing with multiple promoter binding sites on which transcription factors may bind. We present an adaptation of Stochastic Simulation Algorithm, which allows us to perform accurate simulations even for such systems. Another problem that may make the computational models inefficient, especially when the quantitative response is needed, is missing kinetic data. We propose to solve this problem with the quantitative fuzzy logic approach, which can be used in a combination with conventional modelling techniques only in the parts of the system were kinetic data are missing. Our lecture is therefore divided in four tightly related topics, i.e. review of existent modelling techniques, establishment of metrics for computational design of biological systems with information processing capabilities, stochastic modelling of gene regulatory networks with multiple promoter binding sites and quantitative fuzzy modelling of biological systems with unknown or uncertain kinetic data.

Non-alcoholic (fatty) liver disease - from mathematical to mouse models

Damjana Rozman

CFGBC, Institute of Biochemistry, Faculty of Medicine, University of Ljubljana, Slovenia

Background: Non-alcoholic (fatty) liver disease (NAFLD), the hepatic manifestation of the metabolic syndrome, is the most common chronic liver disease in western populations with a prevalence of 25-30%. It ranges from steatosis (NAFL), to steatohepatitis (NASH), and can progress to cirrhosis and hepatocellular carcinoma. Numerous metabolic pathways are involved in NAFLD pathogenesis (cell development, inflammation, fibrosis, endoplasmic reticulum stress, lipid and glucose metabolism, etc.), in addition to environmental factors and aberrant xenobiotic metabolism. The multifactorial nature of NAFLD suggests that it is a "network" disease.

Consequently: Only a few genes polymorphisms correlated with the disease and we cannot predict which patients will progress to later disease stages. Aims: To tackle the multifactorial nature of NAFLD and to address the role of cholesterol metabolism in development of NAFLD.

Results: We generated SteatoNet, a multi-pathway, multi-tissue model and in silico platform of hepatic metabolism and deregulations. SteatoNet bases on object-oriented modelling where objects correspond to functional entities, and features two novel hepatic modelling aspects: the interaction of hepatic metabolic pathways with extra-hepatic tissues and inclusion of transcriptional/post-transcriptional regulation. At normalised steady state the need for constraining kinetic parameters is circumvented. Validation/ identification of flux disturbances highlights the ability of SteatoNet to effectively describe biological behaviour. SteatoNet identifies crucial pathway branches (transport of glucose, lipids and ketone bodies) where changes in flux distribution drive the healthy liver towards hepatic steatosis, the primary stage of non-alcoholic fatty liver disease. Cholesterol metabolism and its transcription regulators were highlighted as novel steatosis factors. To investigate further the role of cholesterol metabolism we prepared a hepatocyte knockout (LKO) mouse of lanosterol 14α-demethylase (CYP51) from the part of cholesterol synthesis that is already committed to cholesterol. LKO mice developed hepatomegaly with oval cell proliferation, fibrosis and inflammation, but without steatosis. The key trigger were depleted cholesterol esters that provoked cell cycle arrest, senescence-associated secretory phenotype and ultimately the oval cell response, while elevated CYP51 substrates promoted the integrated stress response. In spite of the oval cell-driven fibrosis being histologically similar in both sexes, data indicated a female-biased down-regulation of primary metabolism pathways and a stronger immune response in males. Liver injury was ameliorated by dietary fats predominantly in females, whereas addition of cholesterol rectified fibrosis in both sexes.

Conclusions: The mathematical model Steatonet and the liver conditional knockout of Cyp51 from cholesterol synthesis show unequivocally that hepatic cholesterol metabolism is an independent factor in liver pathogenesis.

Integration of microarrays, functional genomics and next-generation sequencing for ultimate understanding of plant pathogen interactions

David Dobnik, Kristina Gruden

Department of Biotechnology and Systems Biology, National Institute of Biology, Ljubljana, Slovenia

Potato (*Solanum tuberosum* L.) is most widely grown tuber crop and the fourth most important food crop. It is challenged by changing environment and pathogens, one of them being the Potato virus Y^{NTN} (PVY^{NTN}). Understanding the biology of potato-PVY interaction, using systems biology tools, can contribute to plant breeding and development of efficient agricultural practices. Potato responds to pathogens by activating a variety of active and passive defence mechanisms which can be detected as a broad spectrum of physiological and histological changes. These responses were studied within our group on several levels. First of them was the transcriptomic level, where microarrays were used. We identified several differentially expressed genes and confirm their expression with real-time PCR. To functionally analyze the role of these genes in plants, we have used the approach of functional genomics to modify the expression of the selected genes. With the help of transgenic plants we were able to confirm/reject the role of selected genes in potato-PVY interaction. Furthermore, next-generation sequencing was performed to study the small RNAs that play an important role in regulation of mRNA levels and of translation. We identified differences in numbers of individual micro RNAs (miRNAs) present in different samples. Moreover, we identified several target genes of miRNAs. Finally, our goal is to integrate all the data together and feed it to the systems biology model of potato defence that we are developing.

Genome sequencing of *Verticillium albo-atrum* patotypes to understand wilt disease in hop

Jernej Jakše[1], Gregor Rot[2], Vid Jelen[1], Marko Flajšman[1], Sebastjan Radišek[3], Blaž Zupan[4], Bart PHJ Thomma[5], Branka Javornik[1]

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Introduction: The causative agent of the devastating wilt disease spreading through European hop gardens is a highly aggressive strain of *Verticillium albo-atrum*, a soil born vascular pathogen. Fungal isolates vary in aggressiveness and have been classified by pathogenicity tests into mild and lethal pathotypes. In general, the mild strain infection rarely causes death of the whole plant, whereas lethal strain infection causes very severe symptoms, with rapid plant withering and dieback. Lethal strains with increased virulence in hop were first reported in the UK in 1933, followed by outbreaks in Slovenia in 1997 and in Germany in 2005. Host resistance accompanied by phytosanitary measures is the most effective disease control, so understanding plant resistance mechanisms and the pathogen infection strategy could enhance resistance breeding. We have employed various research approaches to decipher hop resistance to *V. albo-atrum* and to search for virulence-associated factors that might explain the increased aggressiveness of *V.albo-atrum* strains. Here we present our fungal genomic results.

Results: Whole genomes of three mild and three lethal isolates were sequenced using Illumina technology. Five different insert size libraries (370 bp, 500-600 bp, 1Kb and 5Kb) were sequenced for the reference strain, producing over 93M reads. The other five strains were sequenced to a depth of 4.8 up to 11.5 M reads. For annotation of the transcribed part of the genome, 38.3 M RNA-seq reads were produced from one mild and one lethal transcriptome. De-novo assembly of the reference genome using CLC and SSPACE software and paired-end data information resulted in 439 contigs, with a total length of 35.6 Mb. Additional optical mapping of the reference genome showed ten molecules with a total length of 35.2 Mb. Reference mapping of the other five genomes revealed a 0.5 Mb genomic region common to all three lethal strains and absent in the mild strains. Gene prediction tools supported by Exonerate protein alignments and RNA-seq analysis resulted in 9858 gene models. Around 90 gene models were predicted in the lethal specific region, with additional evidence of a few regions being expressed but not predicted by the software tools. Masking of the assembled genome with RepBase models showed 1.53% of the genome to be associated with the repetitive type of DNA, whereas de-novo building of the models masked 5.86% of the genome. Currently, *V. albo-atrum* deletion mutants of several gene models from the lethal specific region, with the highest expression level in xylem, simulating medium and several in planta expressed fungal transcripts as detected by proteomic and transcriptomic analysis, are being generated and tested on hop plants for their impaired virulence.

Conclusion: We obtained a well assembled genome of *V. albo-atrum* and with population sequencing were able to find genome specific regions characteristic of aggressive strains. A survey of gene models in the lethal specific region enabled selection of candidate virulence-related genes.

ABSTRACTS OF POSTERS

POSTERS

GoMapMan: integration, consolidation and visualization of plant gene annotations within the MapMan ontology

Špela Baebler[1], Živa Ramšak[1], Ana Rotter[1], Matej Korbar[2], Igor Mozetič[2], Björn Usadel[3,4], Kristina Gruden[1]

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Introduction: Understanding the different aspects of plant biology using systems biology tools can contribute to crop plant breeding and development of efficient agricultural practices. However, the approach is hindered by lacking or dispersed crop-specific experimental data, functional annotations and visualization tools.

Results: Recently we have developed GoMapMan (http://www.gomapman.org), an open web-accessible resource for gene functional annotations in the plant sciences. It was developed to facilitate improvement, consolidation and visualisation of gene annotations across several plant species. GoMapMan is based on the MapMan ontology, organized in the form of a hierarchical tree of biological concepts, which describe gene functions. Currently, genes of the model species *Arabidopsis* and three crop species (potato, tomato and rice) are included. The main features of GoMapMan are 1) dynamic and interactive gene product annotation through various curation options, 2) consolidation of gene annotations for different plant species through the integration of orthologue group information, 3) traceability of gene ontology changes and annotations, 4) integration of external knowledge about genes from different public resources, and 5) providing gathered information to high-throughput analysis tools via dynamically generated export files.

Conclusions: Using GoMapMan, the knowledge on plant biology can be improved by translating existing knowledge from model to crop species and by easier data interpretation of crop experimental data.

Reference:

1. Ramšak Ž. et al. (2014) Nucleic Acids Res. 42:D1167–75.

Quantitative modelling of a 3-gene repressilator with uncertain kinetic data using fuzzy logic

Jure Bordon, Nikolaj Zimic, Miha Moškon, Miha Mraz

Faculty of Computer and Information Science, University of Ljubljana, Slovenia

Due to advances in synthetic and systems biology in the past ten years, modelling of biological systems has become an indispensable computational tool for design optimization of novel and analysis of existing biological systems. However, in order to construct a quantitative model of any biological system using conventional modelling techniques, accurate kinetic data that describe the system's dynamics are required. These data are often hard or impossible to obtain even with the help of parameter estimation techniques. With this poster we present a fuzzy logic modelling approach that can be used for quantitative modelling and can produce relevant simulation results when kinetic data are incomplete or only vaguely defined. In addition, our fuzzy logic approach can be used with existing state-of-the-art quantitative modelling techniques. Only the parts of the model where kinetic data are missing can be replaced by the fuzzy logic approach, while we can use existing approaches and retain their accuracy for other parts. We demonstrate the proposed approach using a case study model of a 3-gene repressilator.

Modeling the interfaces of protein-RNA interactions

Andrej Čopar, Tomaž Curk

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Protein-RNA interactions have an essential role in many cellular processes. Experimental determination of 3D molecular structure is a slow and difficult process. Consequently, computational methods, which successfully predict interaction sites and molecular conformations, are needed. We have defined a number of attributes to describe 3D properties of protein-RNA interactions using data from PDB database [1]. We have implemented a protein-RNA docking method that uses machine learning and an optimization algorithm to predict sites of protein-RNA interaction. The accuracy of the proposed algorithm is comparable to results of best existing methods [2].

References:

1. Protein Data Bank (2014), available at http://www.rcsb.org.
2. T. Puton, L. Koslowski, I. Tuszynska, K. Rother, J. M. Bujnicki, 2012 Computational methods for prediction of protein-RNA interactions, J Struct Biol 179, 261–68

a)

	Accuracy	Precision	Recall	AUC	MCC
Classification tree	0.916	0.973	0.936	0.854	0.420
Naive Bayes	0.862	0.900	0.946	0.825	0.343
Random forest	0.906	1.000	0.906	0.840	0.002
SVM	0.906	0.999	0.908	0.865	0.090
Majority	0.906	0.000	0.000	0.500	0.000

b)

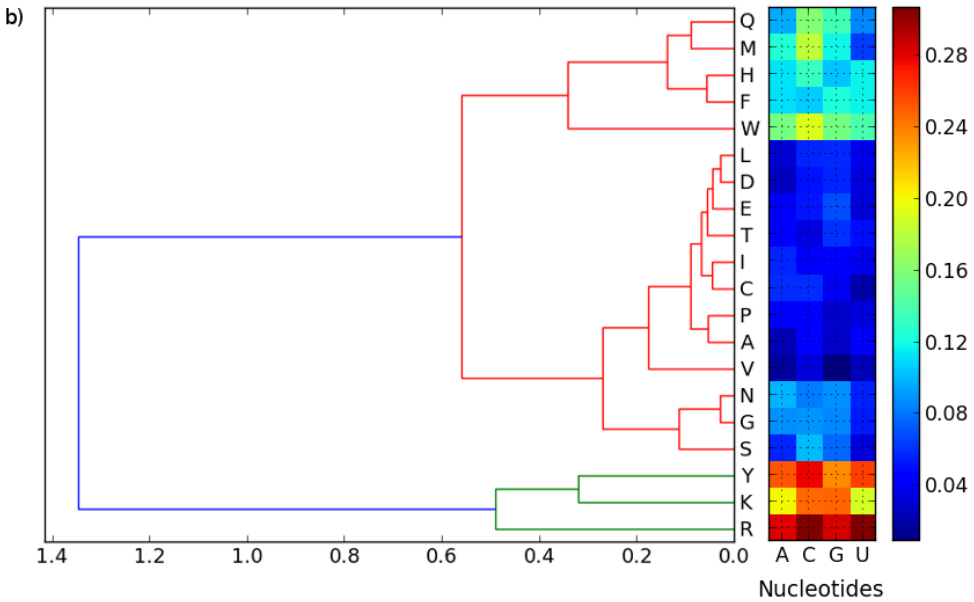

Figure 1: a) Predictive performance of different classifiers. b) Clustering of amino acid-nucleotide interaction frequency.

APOE genetic variants are associated with plasma lipid levels in patients with type 1 diabetes

Tinka Hovnik[1], Anja Švigelj[1], Gašper Klančar[1,2], Nataša Bratina[2], Tadej Battelino[2,3], Katarina Trebušak Podkrajšek[1]

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Introduction: Apolipoprotein E (APOE) genetic variants have a major influence on lipid metabolism and represent a risk factor for development of cardiovascular disease in patients with type 1 diabetes (T1D). The c.334T>C (rs429358) and c.472C>T (rs7412) polymorphisms in APOE gene determine 3 major alleles: e2, e3, e4 and 6 corresponding genotype combinations: e2/e2, e3/e2, e3/e3, e4/e3, e4/e2, e4/e4. Alleles encode 3 isoforms, which differ from each other by amino-acid substitutions at residues 112 and 158. The aim of this study was to determine the influence of APOE genetic variants on plasma concentrations of total cholesterol and triglycerides in patients with T1D.

Methods: The study population consisted of 260 unrelated children, adolescents and young adults with T1D (137 male and 123 female patients, median age 17.8 ± 4.4). Based on recommended limit lipid levels for T1D, the patients were divided into a group with elevated total cholesterol (> 4.4 mmol/L) or triglycerides (> 1.7 mmol/L) and a group with normal total cholesterol (< 4.4 mmol/L) or triglycerides (< 1.7 mmol/L). Independent t-test was performed to compare the continuous parameters. APOE genotyping was performed using TaqMan genotyping assays. Patients were compared on the basis of identified alleles, genotype combinations, basic clinical characteristics and plasma lipid levels.

Results: Patients with T1D with elevated levels of total cholesterol or triglycerides had higher body mass index and poor glycemic control, additionally; patients with elevated total cholesterol had higher body weight and increased diastolic blood pressure. In the study population the most common allele was e3 (84.8 %), the most common genotype combination was e3/e3 (71.5 %). Patients with T1D who are carriers of genotype combination e4/e3 have higher concentration of total plasma cholesterol.

Conclusion: We can conclude that elevated levels total plasma cholesterol in patients with T1D is significantly influenced by individual's genetic background and not only the environmental factors.

Familial defective apolipoprotein B-100: early recognition with genetic testing

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Background: Familial defective apolipoprotein B-100 (FDB) is an autosomal-dominantly inherited disorder caused mutations in the apolipoprotein (apo) B gene. FDB is most commonly caused by APOB-100 gene point mutation resulting in aminoacid change of glutamine to arginine at position 3527. A single amino acid substitution in apolipoprotein B diminishes the ability of low density lipoproteins to bind to the low density lipoprotein receptor. Low density lipoproteins accumulate in the plasma because their efficient receptor-mediated catabolism is disrupted. This leads to hypercholesterolemia and increased risk for cardiovascular diseases (CVD). The p.Arg3527Glu mutation have a wide geographic and population distribution among Caucasian patients. Its prevalence among European populations varies from 0.08 % to 1.4 %. To our knowledge, genetic background of FDB has not yet been studied in the Slovenian population.

Materials and Methods: Following clinical evaluation, p.Arg3527Glu mutation was analysed in a cohort of 102 paediatric patients recruited through nation-wide hypercholesterolemia screening, and 44 adult patients referred to specialised outpatient clinic due to full clinical presentation of hypercholesterolemia and manifestations of CVD.

Results: p.Arg3527Glu mutation was identified in 14 out of 102 paediatric and in 6 out of 44 adult patients.

Conclusions: Studied population represents two clinical extremes of the FDB, one with and one without manifestations of CVD. Similar frequencies of the mutation were detected in both studied groups, namely 13.7 % in paediatric and 13.6 % in adult patients. Therefore early definitive identification of FDB through paediatric hypercholesterolemia screening is crucial in enabling early treatment of high cholesterol levels enabling prevention of CVD.

Funding: (J3-4116) grant of the Slovenian Research Agency: Genetic and clinical characteristics of hypercholesterolemia in children and adolescents.

Timing of circadian genes in mammalian tissues - a modelling approach

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Circadian clocks are endogenous oscillators driving daily rhythms in physiology. The cell-autonomous clock is governed by a network of transcriptional feedback loops. Hundreds of clock-controlled genes (CCGs) regulate tissue specific functions. Transcriptome studies reveal that different organs feature substantially varying sets of CCGs with different peak phase distributions. To study the phase variability of CCGs in mammalian peripheral tissues, we developed a core clock model for mouse liver and adrenal gland based on expression profiles and promoters. We extended our core clock model to simulate profiles of other clock-controlled genes. We modelled specific rhythmic genes; variability in amplitude and phase of cytochromes P450 can be reproduced by our models with variations in the 'modulation factors' (Fig. 1). We used our extended model to simulate tissue-specific phase distributions by sampling the parameter space in a biologically plausible range. We compared the range of behaviour that could be expected for CCGs with particular regulatory regions to available ChIP-seq and transcriptome data. Much of the phase variability can be traced back to E-box and ROR-element regulations. We list candidates of additional co-regulatory transcription factors. Our modelling approach is particularly valuable to understand the mechanism of 12 h rhythms observed in about 1% of mouse liver genes. We show that multiplicative regulation by clock components generates harmonics.

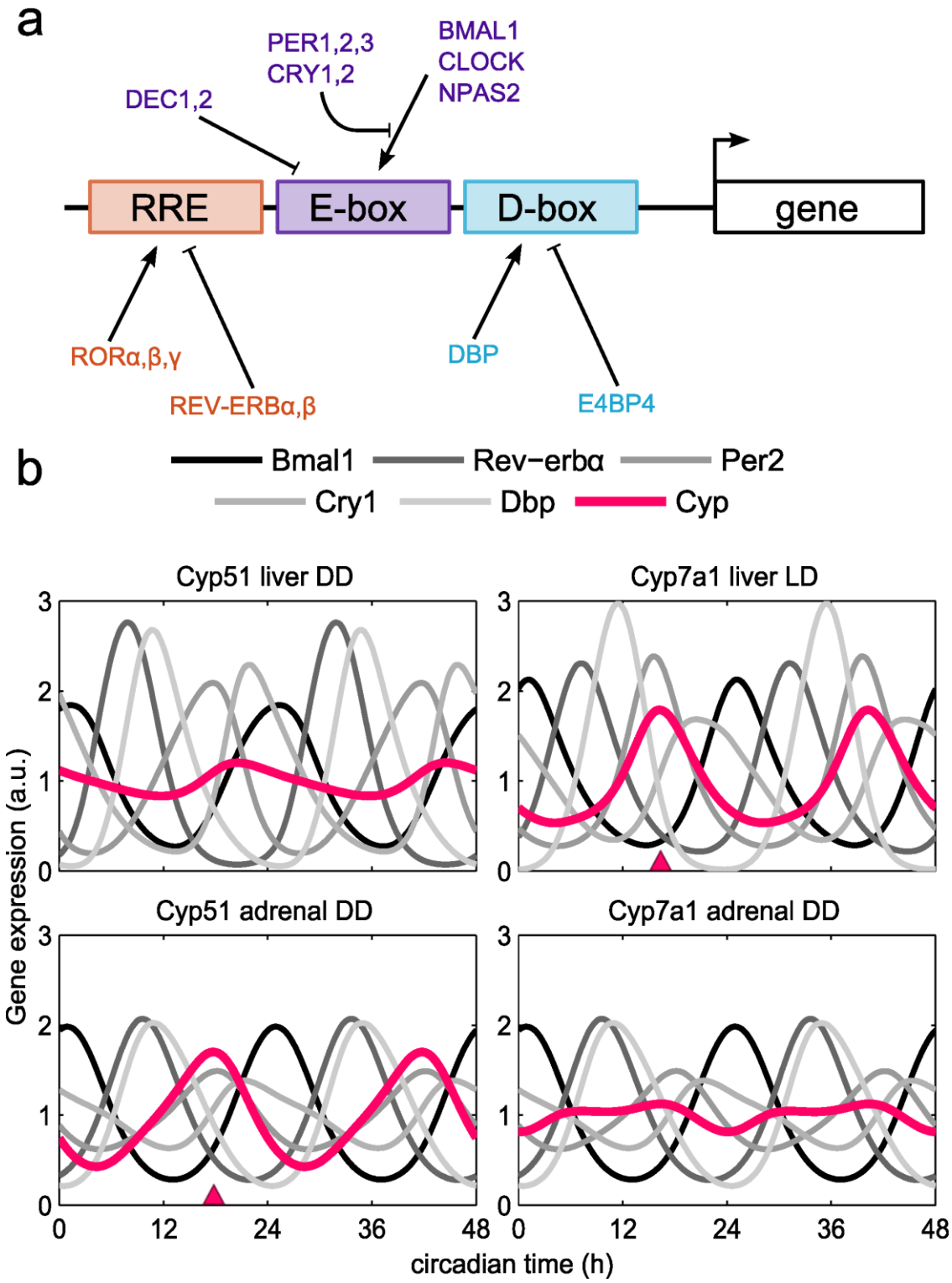

Figure 1: A – main circadian promoter elements: E-boxes, D-boxes, and RORE. B – *Cyp51* and *Cyp7a1*: triangles represent the observed experimental phase in case of rhythmic expression, and the thick line shows the simulated time-course. The gray curves show the 5 simulated core clock genes.

Circadian gene expression patterns on the periphery depend on mouse genotype

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Introduction: Biological clock is an important component in body homeostasis. However, it is not clear how the genetic background of each individual influences circadian expression and regulation. We addressed this question by investigating gene expression in liver and adrenal glands of inbreed mouse strains 129/SvPas plus C57BL/6J and pure C57BL/6J, in DD or LD conditions.

Methods: 24 h gene expression profiles were fitted using various trigonometric functions to obtain the circadian amplitudes and phases. Genome variation data files were downloaded from dbSNP database for the three 129 mouse strains and compared to the reference strain C57BL/6J.

Results: Robustness of circadian expression depends on genotype and tissue. In adrenal glands under LD many genes differ in circadian profiles between mouse strains. Steroidogenic genes (*Cyp11a1, Cyp17a1, Cyp21a1, Cyp51*) are phase-shifted between strains at least in one of the lightening conditions. The majority of steroidogenic and core clock genes are expressed at higher levels with higher amplitudes in 129/SvPas mixed strain, exceptions are *Arntl* and *Cry1*. Liver seems to maintain a more robust circadian regulation with fewer differences observed. Since the genomes of 129 and C57BL/6J mice are already sequenced we questioned whether the modified circadian expression derives from mutations in these genes or their regulatory regions. We identified 16.900 sequence variations in 193 selected genes. The majority of variations (> 97%) were discovered in intron and promoter regions. All three 129 strains have the same variations in coding regions of *Per3*, *Vipr2*, *Opmn4* and *Dusp4*. Nucleotide variations were also observed in intron and promoter regions of genes that showed differences in gene expression.

Conclusions: Light has greater impact on circadian expression of core clock and metabolic genes in the 129/SvPas background. Together with the genotype, the light influences primarily the amplitudes of core clock genes while the amplitudes and phases are affected in metabolic genes. 86% of analyzed genes in three different 129 strains harbor genetic variations compared to the reference strain C57BL/6J. The majority of these are in intron and promoter regions that could affect gene expression and thus also the circadian changes observed in our experiment. These findings might have important implications for understanding the genetic bases of the circadian rhythm differences in human individuals and their susceptibility to develop the clock-based diseases.

Low doses of insecticide coumaphos do not affect behaviour and hypothalamic gene expression in mice

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Coumaphos is an organophosphate insecticide widely used in beekeeping for the control of Varroa Jacobsoni infestation. Organophosphates are a group of chemicals that inhibit the activity of acetylcholinesterase, an enzyme that is important component of the nervous system. As acetylcholinesterases are also present and have important functions in mammals, organophosphates are at high doses also very harmful for domestic animals and humans. Acute effects of different organophosphorous compounds are well understood, but much less is known about potential long-term effects of exposure to low doses of organophosphorous compounds.

In the present study, potential influences of exposure to low concentration of coumaphos (1 mg/kg BW) on development and function of the central nervous system was studied in balb/c mouse strain. Mice were treated with coumaphos through drinking water from 60 days of age onwards. After two weeks from the start of the treatment, behaviour of mice (group continuously exposed to coumaphos and control group) was studied in standard behavioural tests modelling human psychiatric disorders. Anxiety like behaviours were tested in the elevated plus maze test (EPM), marble burying test and open field test (OFT). Social behaviour and social memory disorders were tested in the social recognition test while depression like behaviours were tested in the forced swim test (FST). After behavioural testing, mice were sacrificed and RNA was isolated from the hypothalamus of treated and control mice. RNA was subjected to microarray analyses using Affymetrix mouse genome microarrays.

The results of the study did not reveal any statistically significant differences in behavioural tests between the group exposed to the coumaphos and the control group. In EPM, OFT and social recognition tests, there were statistically significant differences between sexes, as expected. Hypothalamic gene expression results revealed statistically significant difference between the group exposed to coumaphos and the control group in the expression of only one gene (gpr88). The results of our study therefore suggest that prolonged exposure to low doses of coumaphos in adulthood probably does not have harmful effects on the brain function in mice.

Pathological Consequences of Reduced Cholesterol Synthesis in the Liver: Lessons from the Hepatocyte-Specific Knockout of Mouse *Cyp51*

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Background & Aims: Disturbed lipid homeostasis is a key factor of liver pathologies. To reveal the role of hepatic cholesterol synthesis we developed a mouse hepatocyte-specific knockout (LKO) of lanosterol 14α-demethylase (CYP51) catalyzing the rate-limiting step in the post-squalene cholesterol synthesis.

Methodology & Results: Morphology and histopathology of the LKO mice revealed prominent hepatomegaly with ductular reaction (oval cell proliferation), accompanied by fibrosis and inflammation, but without steatosis. Biochemical and expression profiling analyses together with dieting identified depleted hepatic cholesterol esters as the major cause for the observed pathologies. Increased hepatocyte cell cycle arrest and elevated senescence-associated secretory phenotype pathways reflected in strong ductular proliferation. Down-regulated bile acid synthesis changed composition of the bile, which might have hindered intestinal fat absorption as indicated by the slower weight gain and reduced fat depots of the LKOs. Accumulated CYP51 substrates contributed by promoting the integrated stress response, apoptosis and inflammation. Altogether, this resulted in periportal fibrosis that was histologically similar in both sexes. Nevertheless, the microarray data support a sex-related pathogenesis with a stronger activation of the immune-inflammatory system in males and a female-biased down-regulation of *Ppara*, *Adipor2*, *Esr1*, and amino acid metabolism pathways. Accordingly, dietary fats ameliorated liver injury predominantly in females, but caused hypocholesterolemia without hepatic improvement in the males. Supplementing high-fat diet with cholesterol ameliorated the phenotype in both sexes.

Conclusions: Hepatocyte loss of *Cyp51* in mice disrupted cholesterol synthesis and represents a novel sex-dependent determinant in driving liver pathologies. This defect in hepatic cholesterol synthesis leads in the mouse to some of the non-alcoholic steatohepatitis features like ductular reaction, inflammation and fibrosis.

Using OMICS approaches to study the interaction between potato, *Potato virus Y* and Colorado potato beetle

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Introduction: In the field, plants are challenged by more than one biotic stressor at the same time. In the present study, the molecular interactions between potato (*Solanum tuberosum* L.), Colorado potato beetle (*Leptinotarsa decemlineata* Say; CPB), and Potato virus Y^{NTN} (PVY^{NTN}) were investigated through analyses of gene expression in the potato leaves and the gut of the CPB larvae, and of the release of potato volatile compounds.

Results: CPB larval growth was enhanced when reared on secondary PVY-infected plants, which was associated with decreased accumulation of transcripts associated with the antinutritional properties of potato. RNAseq analysis of potato leaves suggests that in PVY-infected plants, the ethylene signalling pathway induction and induction of auxin response transcription factors was attenuated, while no differences were observed in jasmonic acid (JA) signalling pathway. Similarly to rearing on virus-infected plants, CPB larvae gained more weight when reared on plants silenced in the JA receptor gene (*coi1*). Although herbivore induced defence mechanism is regulated predominately by JA, transcriptional response in *coi1*-silenced plants only partly corresponds to the one observed in PVY-infected plants, confirming the role of other plant hormones in modulating response. Potato plant volatile release was profiled using a non-targeted GC-MS approach. The release of β-barbatene and benzyl alcohol was different in healthy and PVY-infected plants before CPB larvae infestation, implicating the importance of PVY^{NTN} infection in plant-to-plant communication. This was reflected in gene expression profiles of neighbouring plants showing different degree of defence response.

Conclusions: We showed that the ET, auxin and gibberellin signalling modules are important components that collectively regulate induced defences during CPB larvae infestation and PVY^{NTN} infection in potato plants. We have detected attenuation in production of antinutritive compounds but the extent of these changes could not explain the effect on larval growth completely. A second component, the increased nutritional value of PVY^{NTN}-infected plants, seems to contribute to the faster growth of larvae. We have also shown that the priming of infected plants can be effected which might have a broader agroecological implications.

Acknowledgements: We thank Daniel J. Palmer and Oxana Habuštová for providing CPB eggs, and Sabine Rosahl for providing the cv. 'Désirée' potato plants. We also thank Neža Turnšek, Lidija Matičič, Tina Demšar and Andrea Lehr for technical support in the laboratory. This study was supported financially by the Slovenian Research Agency Program P4-0165 and Project J4-4165, COST actions FA0806 and BM1006, and Ad futura grant (Slovene Human Resources Development and Scholarship Fund).

Multiscale stochastic simulation algorithm for complex gene regulatory networks

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Many biological systems presents a gene regulatory mechanism which comprises promotors where multiple transcription factors binding sites are aligned sequentially along the promotors region. Such promotors are common in virus genomes, such as in the Epstein-Barr Virus (EBV) and their gene expression can be dynamically very different to the gene expression regulated by a singular transcription factor binding site. This difference becomes even more evident when such gene expression is simulated in-silico using common modelling techniques for accurate calculation of all possible promotor states. The total number of these states in a promoter with multiple binding sites, can increases dramatically with the number of available binding sites. Hence, in order to apply a common modelling technique for such promotor's dynamic, it is imperative to select a strategy to avoid a possible exponential number of promotor states. Here we construct a simulation technique based on an adaptation of the Gillespie's stochastic simulation algorithm (SSA), that fits the accurate modelling of the Epstein-Barr gene regulatory network. With this technique we can easily avoid the computational explosion of the number of reactions needed to define the entire promotor's binding events reaction space. One can obtain such low computational complexity by nesting an independent SSA algorithm, which fires the promotor's binding reactions, inside the outermost SSA algorithm, which in turn fires the gene expression reactions, i.e. transcription, translation and degradation. We demonstrated the correctness of this technique on the gene regulatory network of the EBV genetic switch, where a total of 20 binding sites are present in the region of repeats on one of the promoters.

Analysis of candidate SNPs in selected segregation genes in gastric cancer

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Introduction: Gastric cancer is a common type of cancer; however the etiology of this heterogeneous disease is quite unknown. Carcinogenesis is very complex process involving genetic and epigenetic mechanisms. The main theme of novel genetic studies of gastric cancer is genomic instability which is broadly classified into microsatellite instability (MIN) and chromosomal instability (CIN) leading to aneuploidy. Kinases play pivotal roles throughout cellular division. From DNA damage and spindle assembly checkpoints before entering mitosis, to kinetochore and centrosome maturation and separation, to regulating the timing of entrance and exit of mitosis, mitotic kinases are essential for cellular integrity. Polymorphisms in genes which encode the mitotic kinases and/or their combinations may confer a higher relative contribution to the risk of developing cancer, but their lower penetrance makes identification more difficult.

Aim: We would like to determine the association of polymorphisms and gastric cancer risk. There is a critical lack of information on the genetic backgrounds of cancer patients in Slovenia. We wish to continue and expand our pilot studies on the effect of polymorphisms in segregation genes in gastric cancer patients.

Methods: We conducted a case-control study. The study included 164 patients with gastric cancer, which we collected in collaboration with the Department of Abdominal Surgery and the Department of Thoracic Surgery, University Medical Centre Ljubljana and Institute of Oncology Ljubljana. We used bioinformatics web tools in order to identify candidate SNPs in selected segregation genes, such as ZW10, CASC5, ESPL1 and TPX2. We performed SNP genotyping with TaqMan SNP assays.

Results and conclusion: We found statistically significance between the tumor and the control group in polymorphism rs1185333 on the gene CASC5 ($p = 0{,}022$). According to our results we assume, that the polymorphism rs1185333 could have an impact on the development of gastric cancer. Interestingly, rs1185333 is statistically significant only in male population. Polymorphisms related to gastric cancer may be useful as potential biomarkers which could be used for detection of gastric cancer in early stages and could thus improve the prognosis of patients suffering from this type of cancer.

Detecting components of ribonucleoprotein complexes

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Protein-RNA interactions greatly affect the regulation of gene expression and consequently their function. Complex ribonucleoprotein structures form when proteins interact with RNA. We have developed an algorithm, which uses iCLIP [1] data on cross-linked nucleotides, to identify individual proteins of a given ribonucleoprotein complex. The method has been validated using data on the spliceosomal complex [2], for which a number of components have been identified.

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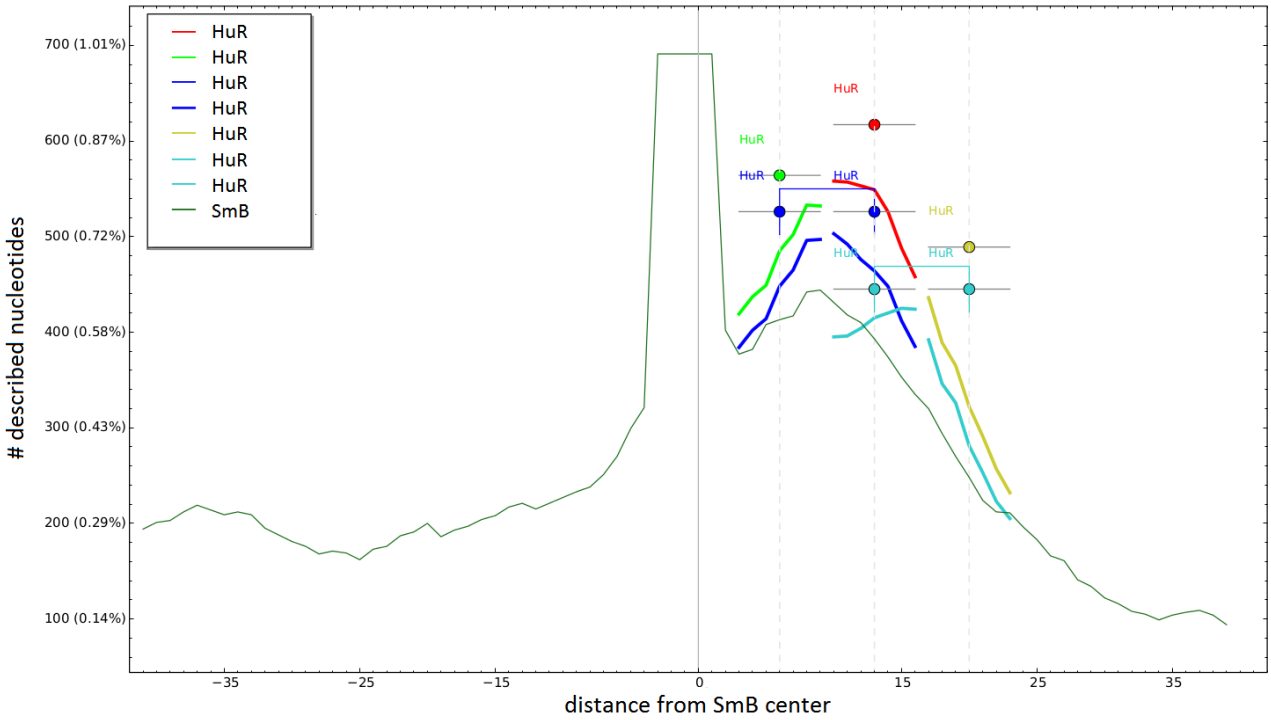

Figure 1: Example of a pattern identified by the algorithm, which indicates that protein HuR is associated with the SmB complex.

Integrative genome-wide analysis of protein-RNA interactions

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RNA binding proteins (RBPs) regulate post-transcriptional control of RNAs, such as splicing, polyadenylation and stabilization. Furthermore, their role has been confirmed in diseases such as cancer or neurodegeneration [1]. While existing protein-RNA interaction models assume prior knowledge on precise structural information on proteins and RNAs, we present an entirely data-driven approach for genome-wide prediction of RBP target sites, based on nonnegative matrix factorization[2,3]. We have developed an orthogonal matrix factorization (ONMF) algorithm, able to classify RNA-interacting nucleotides from 31 publicly available experiments for RBPs, obtained by CLIP, iCLIP[4], HITSCLIP and PARCLIP. The resulting model provides interpretable decompositions into clusters with highly correlated features. The model is able to discover patterns in various data sources: RNA sequence content, RNA structure, Gene Ontology terms and genomic features. As the data is being generated with an unprecedented pace, we expect efficient and flexible data-driven approaches to play a key role in discovering novel biological knowledge.

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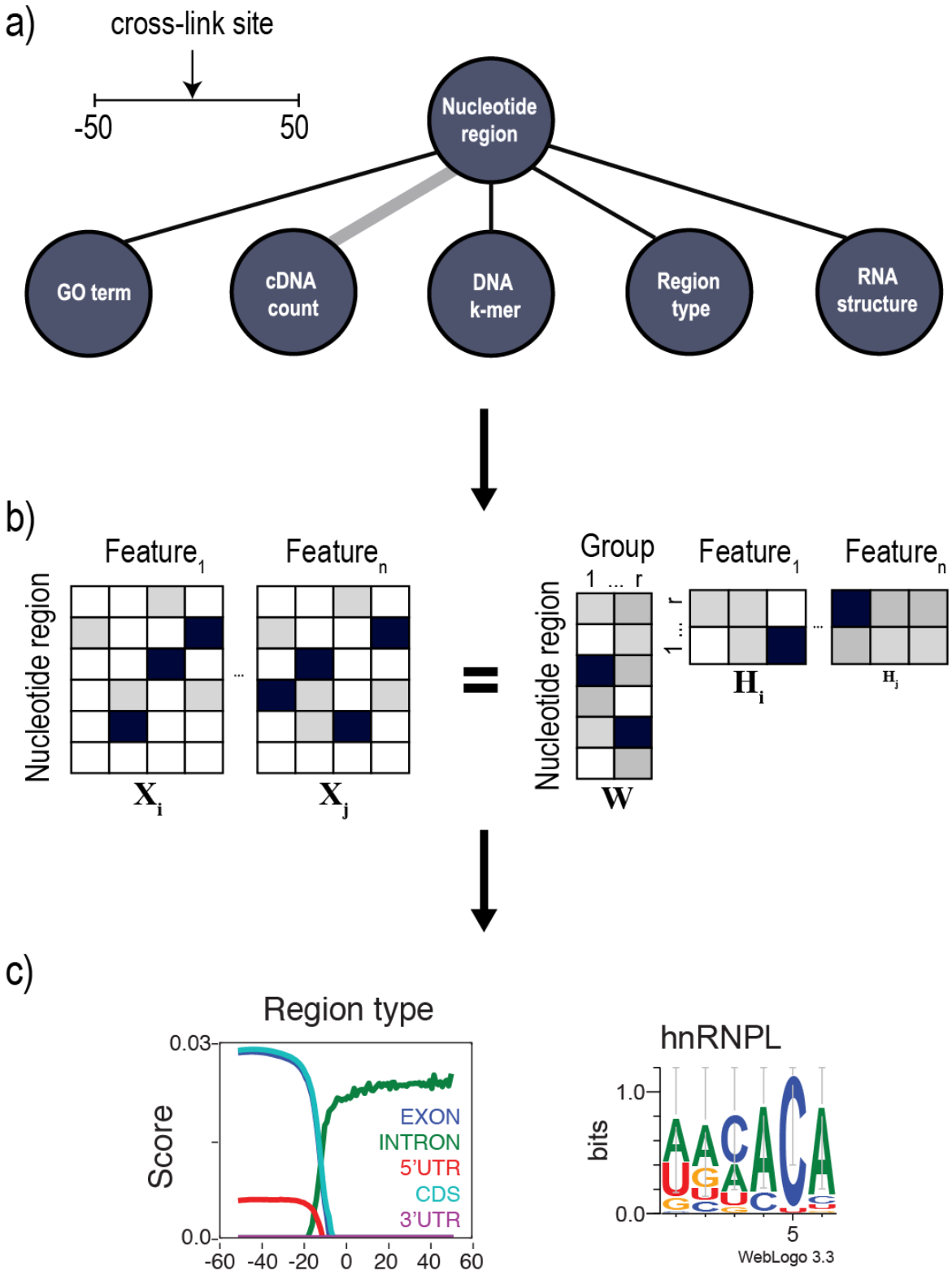

Figure 1: a) Cross-link sites are annotated using data sources listed b) Data is factorized with ONMF, and c) discovered patterns are visualized for each data source separately. Characteristic genomic features for cross-link sites can be extracted (left) and complex motifs derived from RNA sequence (right).

Gamma klotho, a novel marker and oncogene in a subset of triple negative breast cancer

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Introduction: The family of Klotho proteins consist of three members, alpha, beta and gamma klotho that are evolutionary conserved in vertebrates. They are type I transmembrane glycoproteins with extracellular region that contains beta-glycosidase-like domains. Intriguingly, the critical residues required for the potential enzymatic activity are not conserved implying that they serve other physiological functions. Recently, a groundbreaking discovery uncovered the biological function of alpha (KL) and beta klotho (KLB) as obligate co-receptors for the endocrine fibroblast growth factors (FGFs) that regulate bile acid, phosphate, and energy homeostasis. Further, recent studies suggested that klotho and beta klotho have tumor-suppressor function and are down-regulated in several cancers. Lately, a third member of the family was discovered and named gamma klotho (KLG). In contrast to alpha and beta klotho, gamma klotho has only one beta-glycosidase-like domain in its extracellular region. Our preliminary experiments show that KLG binds several FGF receptors and might be involved in FGF signaling. To investigate its potential role in cancer, we preformed gene expression analysis of paired (tumor and control) samples from 68 patients with breast cancer. Interestingly, we found that in contrast to alpha and beta klotho, gamma klotho is up-regulated in breast cancer, in particularly in a subtypes of the triple-negative breast cancer (TNBC) samples. The aim of this project was to examine the role of KLG in triple-negative breast cancer cells.

Results: To find appropriate model, we determine the expression levels of KLG in different breast cancer cell lines. KLG was not detected in any of the non-TNBC cell lines, but it was expressed in some TNBC cell lines with the highest level in HCC1395. To investigate the requirement of gamma klotho for proliferation and survival of breast cancer cells, we inhibited the expression of KLG by siRNA and assessed the effects by MTS/PMS, anchorage dependent and independent growth assay. KLG down-regulation significantly inhibited HCC1395 cell growth, whereas there was no effect on MDAMB-157 cells that don't express KLG. To understand the molecular mechanism of KLG function, we analyzed the effect of KLG silencing on the level of gene expression by DNA microarrays. Analysis revealed several potential pathways that might be modulated by KLG and are important in tumorigenesis, such as ubiquitination of proteins, cell signaling, modulation of extracellular matrix and cell adhesion.

Conclusion: Our results show that gamma klotho is expressed in a subset of TNBC cancer cells and is necessary for their survival. Triple-negative breast cancer (TNBC) is a very diverse group of breast cancer where no targeted therapy is available. Understanding the role of KLG can provide new insights in TNBC cancer development. More importantly, KLG might represent potential novel marker of TNBC subtype and drug target for TNBC therapy.

Global characterization of the most severe phenotypes of the *Cyp51* liver conditional knockout mice

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Background and aims: Lanosterol 14α-demethylase (CYP51) is a rate-limiting cytochrome P450 enzyme from the latter part of cholesterol biosynthesis, disruption of which causes embryonic lethality in mice. We have developed a *Cyp51* liver conditional knockout mice model, which lacks the *Cyp51* gene only in hepatocytes (LKO). From 380 mice that survived the weaning period, 19 (4 females, 15 males) were underdeveloped, with jaundice and hepatomegaly (runts). All were of the LKO genotype and represent predominantly males (3 : 1). Runts form a heterogeneous group with the most severe phenotypes. They were euthanized at 5 - 10 weeks of age. We aim to understand molecular mechanisms leading to their development and evaluate possible gender differences.

Methods: Liver sections were fixed in PFA, embedded in paraffin and stained for general histological evaluation (H&E), presence of fibrosis (Sirius Red), etc. Transcriptome analysis from frozen liver samples was carried out by Affymetrix GeneChip® Mouse Gene 2.0 ST Array on 6-7 week runts and 6 week old LKOs and LWTs. Expression of selected genes was confirmed by RT-qPCR.

Results: Runts did not gain much weight after the weaning period, had a hunched posture and jaundice. Their liver-to-body weight ratio is significantly higher compared to their siblings (6 week old LKO mice). Histology shows frequent apoptoses and mitoses. There is notable fibrosis around the periportal area and moderate to severe oval cell response. Most of these symptoms are to a lesser extent visible also in LKOs. Transcriptome analysis revealed 7585 differentially expressed genes between runts and 6 week LKOs and 8549 between runts and 6 week old LWTs. KEGG pathway enrichment analysis yielded 180 and 150 enriched pathways within the same comparison. Most deregulated are pathways of cancer, cell adhesion, immune response, and steroid biosynthesis. qPCR confirmed downregulation of *Cyp51* in runts and 6 week old LKOs in comparison to LWTs. Runts show a higher expression of *Pparγ* and reduced expression of several genes from the bile acid synthesis pathway (*Cyp27a1, Cyp8b1, Cyp7b1*) compared to 6 week LKOs.

Conclusion and perspectives: The functionality of *Cyp51* from cholesterol synthesis is essential for normal liver physiology. While we don't yet understand, why some mice with LKO genotype fail to develop normally, it seems that males are more affected than females. Transcriptome data analysis confirms activation of inflammatory processes and deregulated metabolism, together indicating declining liver functions.

Biomedical data fusion by simultaneous matrix tri-factorization

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Predictive biomedicine is challenged by the abundance of heterogeneous data sets and the construction of methods for their integration. Data fusion may provide substantial gains in accuracy. We have developed a general matrix factorization-based data fusion approach that can model any number of data sources that can be represented as matrices and, unlike existing data integration approaches, does not require their transformation into a common target space of, for example, genes, diseases or patients. The fusion is achieved by simultaneous tri-factorization of data matrices through the sharing of low-dimensional matrix factors between data sources.

We exemplify the utility of this approach in gene function prediction. The flexibility of our data fusion allows us to integrate data from diverse data sources that include gene expression profiles, known gene annotations, networks and literature data. In particular, we show that our approach can accurately predict Gene Ontology annotations in slime mold *D. discoideum* and recognize proteins of baker's yeast *S. cerevisiae* that participate in the ribosome or are located in the cell membrane. We also show that the accuracy of the approach benefits from the preservation of data structure. The predictive performance of our approach is superior to that of state-of-the-art approaches including methods that implement data integration through the construction of a single gene profile table (called early integration) or integration by the ensambling of diverse data models (kernel-based data fusion).

ISBE WORKSHOP

ISBE WORKSHOP

Mathematics+Biology=Systems Biology?

Prof. dr. Kristina Gruden

Of course this is perhaps an oversimplification. But it is true that only with interdisciplinarity in research we can address complex biological questions. Systems biology besides biology and mathematics entangles also chemistry, engineering and computers sciences. The aim of this lecture is to show why approaches like this are needed. If observed at molecular level, each cell consists of complex mixture of macromolecules and small molecules. A quantum leap forward in development of methodologies allowing exact quantification of different molecules per cell has been achieved in recent years. We are now aware of the fact that each cell consists of 30.000 genes, 300.000 different proteins; the diversity on the level of small metabolites is even higher. Millions of data points describing activity of the genes in different cells through time can be generated in the lab in less than a week. This information can only be digested with the help of mathematics and computer sciences. The ultimate goal of systems biology is thus to generate knowledge and understanding of biological system based on the experimental data collected. For example, a Virtual Human initiative has started which should allow for complete understanding of the way our body functions in development and disease. The road to this understanding is however still quite long, the intermediate success stories will however perhaps encompass development of new anticancer therapies or improved strategies for food production.

Mathematical modelling and systems biology

Prof. dr. Ales Belič

Transfer of property from biological systems into some abstract space is not a unique mapping, however, it can reveal some valuable information on original system functioning. Mathematical modelling is special mapping that transfers some properties of the biological system into mathematical form; however, non-uniqueness of mapping allows the same biological system to be described by many different mathematical forms, depending on what properties we want to map. The non-uniqueness of the mapping also requires very clear definition of modelling goals prior to the modelling start in order to prevent serious problems along the way. There are three major groups of modelling that can be applied. When general properties of the system need to be preserved and specific properties can be neglected theoretical modelling is used. Theoretical modelling tends to describe the process on basis of some generally acceptable rules or laws. The combination of all applicable mathematically formalised laws for all the objects of the system is called the model and describes the functioning of the system as a whole. When specific properties need to be described and general properties serve merely as a frame, the model is built using some statistical procedure that is applied to the measured data. This is called experimental modelling or identification. Such models have often problems of large scale generalisation of the relation since they have been built from a limited set of data. In practise we combine both procedures which is called combined modelling, since we lack the data for successful identification as well as the applicable laws are not fully specified. Biological systems are dynamic, which means that their states (quantities, concentrations, energy, etc.) cannot change in an infinitely short time and they depend on their previous values; therefore, some form of differential equations should be used to describe the systems. In the frame of systems biology the metabolic properties are mostly studied, therefore, chemical reactions, metabolites, enzymes, proteins, various types of RNA, DNA and small molecules form the set of system states. Measurements of the states in this case is rather limited, therefore, theoretical models of reactions are used as a backbone of the models. However, such combination is still not sufficient to uniquely set all the model parameters, therefore, some additional assumptions must be made. The model must be simplified down to only most necessary descriptions and natural limitations must be taken into account. Normalisation of states' values is also a very important procedure since some variables can be eliminated. Since metabolic system must operate in non-zero flux steady-state, the number of independent model parameters can be substantially reduced. The remaining independent parameters influences can be evaluated with model simulation studies. Since biological systems operate in closed loop conditions, all possible regulation mechanisms must be included. Feedback loop can substantially change the properties of the controlled system. The usefulness of the systems biology is currently limited to description of general properties of subjects while subject specific properties cannot be reliably described due to lack of measured data. In spite of such limitation they can serve as tools to better understand several processes and in planning of new treatment strategies of complex network diseases such as all forms of metabolic syndrome or various types of cancer. One additional problem with modelling is biological interpretation of the results. This is a reverse mapping from modelling and is also not unique, since several properties of the model come from mathematical limitations of the model and not from biological background of the model. Therefore modelling is placed somewhere between science and art and requires experiences as well as reasonable amount of common sense to correctly interpret the results.

Systems Biology in Europe

Assist. Prof. Ddr. Jure Ačimovič

Several Western European countries have identified systems biology (SB) as a major priority in the early part of the previous decade (Netherlands, UK, Austria, Germany, Sweden, Switzerland…) which has resulted in significant and directed investments in SB, in order to underpin and promote a tighter cooperation of large numbers of scientists from different disciplines. Support by national funders was often via the establishment of Centres of Excellence, together with directed funding for research programmes and training across the life sciences portfolio. Many of these funders have also been engaged in European-level support, notably via ERANets and similar, in FP6 and FP7.

In 2001, the German Federal Ministry of Education and Research (BMBF) started to support SB research on a nation-wide level. Since then, the BMBF continued its policy, setting up further national and international systems biology research consortia and has invested some 435 million € over the last 10 years in quite a high number of initiatives on Systems Biology, including FORSYS and the other 11 national initiatives in an international context.

In 2006, there has been the call of the BMBF "FORSYS – Research Units for Systems Biology", an initiative being embedded within the BMBF research support program "Biotechnology". A major objective of the "FORSYS-Research Units for Systems Biology" initiative is the development of interdisciplinary and collaborative research units for systems biology at German universities, non-profit research institutions, and industrial companies that will have a high impact on SB research in Germany. As a result of the FORSYS call, four FORSYS Centres located in Freiburg, Heidelberg, Magdeburg, and Potsdam, received a financial support of € 45 million € from the BMBF.

Besides the development of systems biology research units, FORSYS has boosted teaching activities in the FORSYS Centres. The importance of this goal is reflected by the fact that all FORSYS Centres have set up novel SB educational programs for master and bachelor students in the life sciences. Moreover, dedicated PhD programs have been established. These activities strongly account for BMBF's support of selected teaching and student exchange programs. For complete overview of SB educational programs in Germany see http://www.systembiologie.de/de/magazin, Issue 07, October 7, 2013).

There are 3 Government funded Research Councils in the UK (Biotechnology and Biological Research Council (BBSRC), Medical Research Council (MRC), and Engineering and Physical Sciences Research Council (EPSRC)) who support research in SB. Training /Education is presented by SysMIC (http://sysmic.ac.uk/) which provides a comprehensive online course in the interdisciplinary skills which are increasingly important to cutting edge biological research. SysMIC has been produced as a collaboration between University College London, the Open University, Birkbeck College and the University of Edinburgh. It has been supported by the BBSRC and is free for researchers with BBSRC funding. The course is open to all level researchers: from graduates beginning their career, to established researchers wishing to improve their skills. The courses include the necessary background for the mathematics covered and does not assume any previous experience in computer programming.

Therefore it is envisaged that also Slovenia starts funding SB projects and education to be able to compete with Western European countries. The future lies in the interdisciplinarity.

Synthetic Biology: Modular engineering of natural molecules and processed

Prof. dr. Roman Jerala

Modularity is extensively used in engineering for the rapid and cost effective construction of different devices and structures. In biological systems construction of complex devices requires large sets of orthogonal elements, which may be difficult to harvest from the nature. Nucleotide sequence provides a large and easily accessible combinatorial diversity that underlies programming in biological systems. Recognition code of the sequence-specific DNA binding proteins enables preparation of large number of orthogonal DNA binding proteins. Designable DNA-binding TALE domains can be used to construct genetic logical NOR gates and prepare all 16 two-input functional logic gates and more complex information processing circuits. In terms of the modular construction of molecular structures designable orthogonal coiled-coil dimers provide the basic building blocks based on the specificity of interactions between the segments of polypeptide chain. This principle allows the design of completely new modular protein folds, composed of a single polypeptide chain such as the tetrahedron, where the final structure can be encoded by the order of concatenated coiled-coil segments.

Virtual Liver Network - pan-German program of systems biology

Prof. dr. Damjana Rozman

Virtual Liver Network (VLN: http://www.virtual-liver.de/wordpress/en/) represents a major investment by the German Government and the Federal Ministry of Education and Research (BMBF) in the areas of systems biology and systems medicine. The five-year project that will be completed in March 2015, involves over 70 research groups from 41 academic, research and industrial institutions all over Germany and is worth 43 million EUR. VLN is a continuation of a previous all-German project HepatoSys, which shows that already 10 years ago Germany chose the interdisciplinary fields of systems biology and medicine as a strategic development target in the fields of medicine and life sciences. Why was the liver chosen for this? Liver represents the major metabolic factory of humans. Each day it processes over 10 000 different body and exogenous compounds and allows the body extract energy from food, builds new molecules and secrete harmful substances. Hepatic metabolism is crucial for drug development because it has a central role in the toxicity as well as efficacy of drugs. Exploring the liver and its functions is of great importance for medicine and the pharmaceutical industry.

VLN is a comprehensive program that deals with the major challenges of the post-genomic period of life sciences, namely how to interconnect large amounts of diverse biological data and create an added value from the integrated understanding. Integrating data from various resources is necessary to enable understanding the complexity of living organisms, including humans. This will contribute to improvements and more personalized approaches in diagnosis, prognosis and treatment of complex diseases, as well as a faster route to the development of more effective drugs. To achieve the objectives of the project VLN uses a number of mathematical approaches and models that go beyond the individual cell and are focused on modelling the whole body impairment. VLN also set a precedent of using different types and levels of modelling (Multi-scale modelling) and linking it with human physiology. At the same time, it is also developing tools and protocols that will be useful in other systems and will assist in the further use of modelling and simulation in modern medical practice. VLN represents a unique program that is building bridges between sub-cell research and clinical studies as well the path for the data flow. The ultimate goal of virtual liver network is not only to connect quantitative data from different levels of organization, but to establish a dynamic mathematical model from the subcellular level all the way up to the entire organ. The model will contain channels, networks and functions that are necessary for a detailed dynamic insight into the functioning of the liver, in the context of the function and anatomy of the organ in healthy conditions and in diseases. With the integrated approach VLN undoubtedly contributes to the development of new paradigms in biology and medicine of the post-genome era.

Can systems biology help agriculture?

Dr. Špela Baebler

Securing access to sufficient, safe and nutritious food for a growing world population is an enormous challenge. Due to land limitations it is expected that only 10% of increase can be achieved by agricultural land expansion, while the rest should be gained by improving the quality of production. Stress, drought, pathogen infection and herbivore attack, to mention only the most important ones, are the major factors determining yield and quality of crop production. It is estimated that insects alone can cause up to 80% loss in crop harvest yield and moderate drought conditions up to 30%. Moreover, impending climate changes might broaden the areas affected by specific pathogens, pests and detrimental environmental conditions. Chemical plant protection products are often not sufficiently effective against pests and can cause undesirable effects on the environment; therefore there is a need for safer alternatives.

The advances in molecular biology techniques have contributed to development to high-throughput »omics« technologies that asses the biological system on different levels. Data generation became easy, yet the approaches haven't resulted in any application in the agricultural practice. The reasons lie in the size and the complexity of plant genomes and variability of cellular components (e.g. large number of secondary metabolites) among plant species, cultivars and even ecotypes.

At National Institute of Biology major research efforts are focused to study the interaction of potato with its important pathogen, potato virus Y. Due to impending climate changes, the extent of the damage the virus is causing in sensitive potato cultivars is extending to large areas of Europe and North America. In our research, we are comparing resistant and sensitive potato plant responses using systems biology tools. In this way we have identified some of the previously unknown components of defence response which could contribute to plant efficient defence response and thus limitation of economic losses.

Source:

http://www.bbsrc.ac.uk/news/policy/2011/110111-f-systems-biology-agriculture.aspx

ISBE DELAVNICA

Matematika+biologija=sistemska biologija?

Prof. dr. Kristina Gruden

Seveda ni čisto tako enostavno. Res pa je, da samo s kombinacijo interdisciplinarnih pristopov lahko rešimo kompleksna biološka vprašanja. V sistemski biologiji se poleg biologije in matematike skrivajo in prepletajo še elementi kemije, inženirstva in računalništva. Namen tega predavanja pa je, da vam z biološkega vidika razložimo zakaj se biologija razvija v tako smer. Na molekularnem nivoju je vsaka celica višje razvitih organizmov sestavljena iz kompleksne mešanice makromolekul in malih molekul. Metodologije so na področju biologije izjemno napredovale, tako da lahko natančno določimo število različnih molekul za vsako celico posebej. Vemo na primer, da vsaka celica višje razvitih organizmov vsebuje približno 30.000 različnih genov, različnih proteinov do 300.000, ostalih malih molekul pa še nekajkrat več. V enem poskusu, ki poteka v laboratoriju nekaj dni, na relativno enostaven način pridobimo milijon podatkov o tem kako delujejo geni v različnih celicah v različnih časih. Takšnega obsega kompleksnosti pa ne moremo obvladovati brez matematike in računalništva. Namen sistemske biologije je torej, da iz velikega števila podatkov o organizmih sestavi razumevanje o delovanju le-teh. V sklopu aktivnosti povezanih s sistemsko biologijo se je začel projekt Virtualni človek, katerega končni namen je razumevanje nas samih. Seveda je pot do končnega cilja še zelo dolga, na vmesnih postankih pa bomo gotovo dobili odgovore na to, kako uspešneje zdraviti rakava obolenja ali kako pridelati več hrane na okolju prijazen način.

Matematično modeliranje in sistemska biologija

Prof. dr. Aleš Belič

Prenos lastnosti delovanja bioloških sistemov v nek abstrakni prostor sicer ni enolična preslikava, lahko pa veliko pove o načinu delovanja originalnega sistema. Matematično modeliranje je posebna preslikava, ki določene lastnosti biološkega sistema zapiše v matematični obliki. Ker ta preslikava ni enolična, pa lahko isti sistem opišemo z zelo različnimi matematičnimi formalizmi, odvisno od tega, katere lastnosti nas pri biološkem sistemu zanimajo. Prav zato je potrebno zelo dobro definirati cilj modeliranja že v naprej, sicer lahko zaidemo v težave. K modeliranju lahko pristopimo v grobem na tri načine. Kadar nas zanima splošno delovanje biološkega sistema iz konceptualnega vidika delovanja se največkrat odločimo za tako imenovano teoretično modeliranje, ki opiše sistem glede na poznane teoretične lastnosti posameznih gradnikov, model pa nato prikazuje delovanje sistema kot celote. Tovrstni modeli niso namenjeni opisovanju konkretnih osebkov, lahko pa dobro opišejo splošne lastnosti neke populacije. Kadar nas zanima delovanje konkretnega osebka navadno gradimo model na osnovi meritev na osebku in nato zgradimo relacije med vrednostmi meritev na osnovi nekih statističnih postopkov. Tovrstni modeli delovanje sistema opisujejo le na področjih delovanja, ki so bili zajeti z meritvami in za konkretne osebke, pri posplošitvah pa so manj uspešni. Ker običajno teorije ne poznamo dovolj dobro in nimamo dovolj podatkov se velikokrat zatečemo h kombinaciji obeh pristopov. Ker so biološki sistemi dinamični, kar pomeni, da se vrednosti njihovih stanj (količin, koncentracij, energije, itn.) ne morejo hipno spremeniti in so hkrati odvisna tudi od njihovih preteklih vrednosti, moramo načelno njihove lastnosti opisati z diferencialnimi enačbami. V okviru sistemske biologije večinoma opisujemo delovanje organizmov s stališča kemijskih reakcij med metaboliti, encimi, proteini, različnimi vrstami RNA, DNA in raznimi malimi molekulami. Meritve koncentracij omenjenih molekul večinoma ne zadoščajo za izgradnjo modelov, zato jih kombiniramo z znanjem o poznanih reakcijah, vendar tudi v tem primeru vseh parametrov modela ne moremo enolično določiti, zato se moramo zateči k določnim poenostavitvam in uporabiti naravne lastnosti tovrstnih sistemov. Zelo pomembna je normalizacija koncentracij/količin v modelu, ker se s tem znebimo določenega števila spremenljivk. Drugi pomemben korak pa je upoštevanje dejstva, da metabolno regulacijske mreže v telesu običajno prevajajo neke nenične vrednosti metabolnega pretoka v svojem ustaljenem stanju, kar močno zmanjša število neodvisnih parametrov modela in zato lahko preverimo njihov vpliv na delovanje sistema s simulacijo možnih situacij. Naslednje pomembno dejstvo pa je, da biološki sistemi vedno delujejo v pogojih zaprte povratne zanke, zato je nujno, da v modelih metabolnih poti upoštevamo možna regulatorna omrežja, ker lahko povratna zanka popolnoma spremeni naravo sistema, ki ga nadzira. Uporabnost modelov sistemske biologije pa je trenutno bolj ali manj omejena na opisovanje splošnih lastnosti organizma, medtem ko za prilagoditev modela na posebne lastnosti posameznega osebka nimamo dovolj ustreznih izmerjenih podatkov. Navkljub tej omejitvi pa so lahko izredno koristni pri razumevanju mehanizmov delovanja in pri načrtovanju strategij zdravlljenja ali pa razvoja novih zdravilnih učinkovin. Za ta namen je velikokrat potrebno razviti model poenostaviti do takšne mere, da prikazuje le bistvene lastnosti sistema glede na namen študije, sicer zaradi podrobnosti lahko izgubimo pregled nad celovitostjo delovanja sistema. Še večji problem kot prehod iz biološkega sistema v matematični zapis pa predstavlja transformacija rezultatov modeliranja in simulacije nazaj v biologijo. Tu moramo paziti, da neidealnosti, ki izvirajo iz lastnosti matematičnega zapisa ne poskušamo biološko interpretirati, ker nas to lahko zavede. Ravno zaradi neenoličnosti preslikave iz bioloških procesov v matematični zapis in nazaj je modeliranje nekje vmes med znanostjo in umetnostjo in zahteve veliko mero občutka in izkušenj pri uporabi.

Sistemska biologija v Evropi

Doc. ddr. Jure Ačimovič

Na začetku prejšnjega desetletja je večina zahodnoevropskih držav (Nizozemska, Velika Britanija, Avstrija, Nemčija, Švedska, Švica, ...) kot prednostno nalogo izpostavila sistemsko biologijo (v nadaljevanju SB). To je povzročilo znatna in usmerjena vlaganja v SB z željo podpreti in spodbuditi tesnejše sodelovanje velikega števila znanstvenikov iz različnih disciplin. SB so na nacionalnem nivoju podprli posredno z ustanovitvijo centrov odličnosti, skupaj z usmerjenim financiranjem v raziskovalne programe in usposabljanja iz celotnega področja ved o življenju. Veliko projektov je sodelovalo tudi na evropski ravni v okviru šestega in sedmega okvirnega program Evropske skupnosti za raziskave in tehnološki razvoj (npr. ERAnet).

Nemško zvezno ministrstvo za izobraževanje in raziskave (v nadaljevanju BMBF) je začelo podpirati raziskave SB na vsedržavni ravni. Od takrat je BMBF nadaljeval svojo politiko z vzpostavljanjem dodatnih nacionalnih in mednarodnih raziskovalnih konzorcijev SB. V zadnjih desetih letih je BMBF investiral približno 435 milijonov €. Veliko tega denarja je bilo namenjeno različnim pobudam SB vključno s FORSYS in ostalimi 11 nacionalnimi pobudami na mednarodni ravni.

BMBF je v letu 2006 izvedel razpis za "FORSYS - raziskovalne enote za sistemsko biologijo", iniciativo znotraj raziskovalnega podpornega programa "Biotehnologija". Glavni cilj pobude FORSYS je razvoj interdisciplinarnih in raziskovalnih enot za SB na nemških univerzah, nepridobitnih raziskovalnih ustanovah in industrijskih podjetjih, ki bodo imela velik vpliv na raziskave SB v Nemčiji. BMBF je s 45 milijoni € v okviru programa FORSYS finančno podprl štiri FORSYS centre (Freiburg, Heidelberg, Magdeburg in Potsdam).

Poleg prispevka k razvoju raziskovalnih enot SB je FORSYS tudi pospešil poučevanje SB v FORSYS centrih. To se odraža v dejstvu, da so vsi FORSYS centri ustanovili nove izobraževalne programe SB na dodiplomskem in podiplomskem nivoju. Te dejavnosti predstavljajo močno podporo BMBF v izbranih učnih programih in študentskih izmenjavah. Za popoln pregled izobraževalnih programov SB v Nemčiji glej: http://www.systembiologie.de/de/magazin, številka 07, 7. oktober 2013.

V Veliki Britaniji so trije raziskovalni sveti (Biotechnology and Biological Research Council (BBSRC), Medical Research Council (MRC), in Engineering and Physical Sciences Research Council (EPSRC)), ki so subvencionirani s strani države, in podpirajo SB. Primer usposabljanja/izobraževanja s SB predstavlja projekt SysMIC, ki zagotavlja celovit spletni (e-learning) tečaj interdisciplinarnih znanj, ki so vedno bolj pomembna za novodobne vrhunske biološke raziskave. SysMIC je nastal kot plod sodelovanja med University College London, Open University, Birkbeck College in University of Edinburgh. Tečaj je podpira BBSRC in je brezplačen za raziskovalce, ki jih BBSRC financira. Namenjen je raziskovalcem vseh ravni: od diplomantov, ki šele začenjajo s svojo kariero, do že uveljavljenih raziskovalcev, ki želijo izboljšati svoje znanje. Tečaj zajema potrebne osnove matematike in ne zahteva predznanja s področja računalniškega modeliranja.

Če želimo vstopiti v korak z zahodnoevropskimi državami, je za Slovenijo ključna podpora financiranja projektov in izobraževanja sistemske biologije. V interdisciplinarnosti je prihodnost.

Sintezna biologija: Modularni inženiring naravnih molekul in procesov

Prof. dr. Roman Jerala

V inženirstvu se za hitro in učinkovito gradnjo različnih naprav in objektov pogosto uporablja modularni princip. V bioloških sistemih, ki se morajo sestaviti samostojno je za gradnjo kompleksnih naprav nujen velik nabor ortogonalnih elementov, ki pa jih je težko pridobiti neposredno iz narave. Najboljšo osnovo za programiranja v bioloških sistemih predstavljajo nukleinska zaporedja, ki omogočajo lahko dostopno variabilnost ter izjemno raznolikost, saj se npr. 18 nukleotidov lahko uredi v več kot 60 milijard kombinacij. Z nedavnim odkritjem kode proteinov, ki so sestavljeni iz ponovljivih modulov in se specifično vežejo na določeno zaporedje DNA lahko pripravimo veliko ortogonalnih proteinov. Domene TALE, ki jih lahko dizajniramo za vezavno na izbrano zaporedje DNA, lahko uporabljamo za sestavljanje genetsko logičnih vrat NOR in pripravo vseh 16 dvovhodnih funkcionalnih logičnih operacij in bolj zapletenih vezij za procesiranje informacij.

Podobno lahko izkoristimo modularnost za pripravo novih molekulskih struktur na osnovi biopolimerov. V tem primeru lahko uporabimo kot peptidne ovite vijačnice, ki tvorijo dimere in predstavljajo osnovne strukturne gradnike na osnovi specifičnosti interakcij med segmenti polipeptidne verige. Tak princip omogoča oblikovanje popolnoma novih modularnih vzorcev zvitja proteinov. Te so sestavljene iz enojne polipeptidne verige iz katere smo sestavili tetraeder, v katerem končno zgradbo kodira razpored sestavljenih delov ovite vijačnice.

Virtualna mreža jeter – vsenemški program sistemske biologije

Prof. dr. Damjana Rozman

Virtualna mreža jeter (angl. Virtual Liver Network VLN, http://www.virtual-liver.de/wordpress/en/) predstavlja glavno investicijo nemške vlade in Zveznega ministrstva za izobraževanje in raziskave (BMBF) v področji sistemske biologije in sistemske medicine. Petletni projekt, v katerem sodeluje preko 70 raziskovalnih skupin iz 41 akademskih, raziskovalnih in industrijskih ustanov celotne Nemčije, je vreden 43 mio eur in se bo zaključil marca 2015. VLN je zrasel na predhodnem vse-nemškem projektu HepatoSys, kar kaže na to, da je Nemčija že pred 10 leti izbrala interdisciplinarni področji sistemske biologije in medicine kot strateška razvojna cilja na podočjih medicine in ved o življenju. Zakaj so prav jetra v središču zanimanja? Jetra so glavna metabolična tovarna človeka. Na dan predelajo preko 10 000 različnih telesnih in izventelesnih snovi in omogočajo telesu, da presnavlja hrano, gradi nove molekule in izloča telesu škodljive snovi. Presnova v jetrih je ključnega pomena tudi za razvoj zdravil, saj imajo centralno vlogo pri toksičnosti kot tudi učinovitosti zdravil. Raziskovanje jeter in njenih funkcij je tako velikega pomena za medicino in za farmacevtsko industrijo.

VLN je obsežen program, ki se ukvarja z glavnimi izzivi po-genomskega obdobja znanosti o življenju, in sicer kako med seboj povezati velike količine raznolikih bioloških podatkov in iz povezav ustvariti dodano vrednost celostnega razumevanja. Povezovanje podatkov različnih izvorov je nujno, saj bomo le tako lahko razumeli kompleksnost živih organizmov, vključno s človekom, kar bo pripomoglo k izboljšanim in personaliziranim pristopom diagnoze, prognoze in zdravljenja kompleksnih bolezni, kot tudi k hitrejši poti do razvoja učinkovitejših zdravil. Za dosego ciljev projekt VLN uporablja številne matematične pristope in modele, ki presegajo posamezno celico in so usmerjeni v modeliranje celotnega organa jeter. VLN tako predstavlja precedenčni primer uporabe različnih zvrsti in ravni modeliranja (angl. multi-scale modelling) enega organa in povezovanje le-tega s fiziologijo človeka. Sočasno s tem se razvijajo tudi orodja in protokoli, ki bodo uporabni za delo na drugih sistemih in bodo v pomoč pri nadaljnji uporabi modeliranja in simulacij v moderni medicinski praksi. VLN tako predstavlja edinstven program, ki postavlja mostove med sub-celičnim raziskovanjem in kliničnim študijami in gradi poti za pretok podatkov. Končni cilj virtualne mreže jeter je ne le povezati kvantitativne podatke različnih ravni organizacije, temveč vzpostaviti dinamični matematični model od subcelične ravni do celotnega organa. Model bo vseboval tiste poti, mreže in funkcije, katerih podrobosti so nujne za dinamični vpogled v delovanje jeter, v kontekstu funkcije in anatomije organa v zdravem stanju in pri boleznih. Z integriranim prostopom VLN nedvomno prispeva k razvoju novih paradigm v biologiji in medicini pogenomske dobe.

Ali sistemska biologija lahko pomaga kmetijstvu?

Dr. Špela Baebler

Zaradi naraščajoče populacije se v svetovnem merilu povečujejo potrebe po pridelavi hrane. Le majhen delež le-teh lahko dosežemo s povečanjem površin za gojenje rastlin, kar pomeni, da je potrebno izboljšati kvaliteto produkcije. Poleg tega bo potrebno zaradi klimatskih sprememb in novih povzročiteljev bolezni gojiti rastline, ki bodo na te spremembe prilagojene. Izboljšanje produkcije in prilagoditev rastlin na vse omenjene dejavnike je možna tako s klasičnim žlahtnjenjem kot z modernimi biotehnološkimi pristopi. Sistemska biologija lahko k temu pripomore s poglobljenim poznavanjem metabolizma rastlin in njihovega odgovora na različne dejavnike iz okolja. Pridobivanje podatkov z različnih bioloških nivojev je postalo z napredkom molekularno bioloških metod dokaj enostavno, vendar pa, v primerjavi z drugimi disciplinami, rastlinska biologija relativno zaostaja za drugimi področji in do sedaj pristopi sistemske biologije še niso bili uporabljeni za izboljšanje rastlin. Vzroki za to so veliki genomi in velika raznolikost posameznih komponent (npr. sekundarnih metabolitov) med različnimi vrstami in celo sortami ali ekotipi ene rastlinske vrste.

Na Nacionalnem inštitutu za biologijo se ukvarjamo z odnosom krompirja in pomembnega virusnega povzročitelja bolezni (PVY). Virus povzroča veliko gospodarsko škodo na občutljivih sortah krompirja in postaja zaradi klimatskih sprememb in širjenja prenašalcev ekonomsko pomemben na velikem delu Evrope in Severne Amerike. V naših raziskavah s sistemsko-biološkimi pristopi primerjamo, kako se na virus odzivajo občutljive in kako odporne sorte. Na ta način smo identificirali prej neznane komponente odziva na virus, ki lahko prispevajo k omejevanju virusa in s tem k zmanjšanju gospodarske škode, ki jo povzroča virus.

Viri (originalen angleški tekst)

http://www.bbsrc.ac.uk/news/policy/2011/110111-f-systems-biology-agriculture.aspx

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