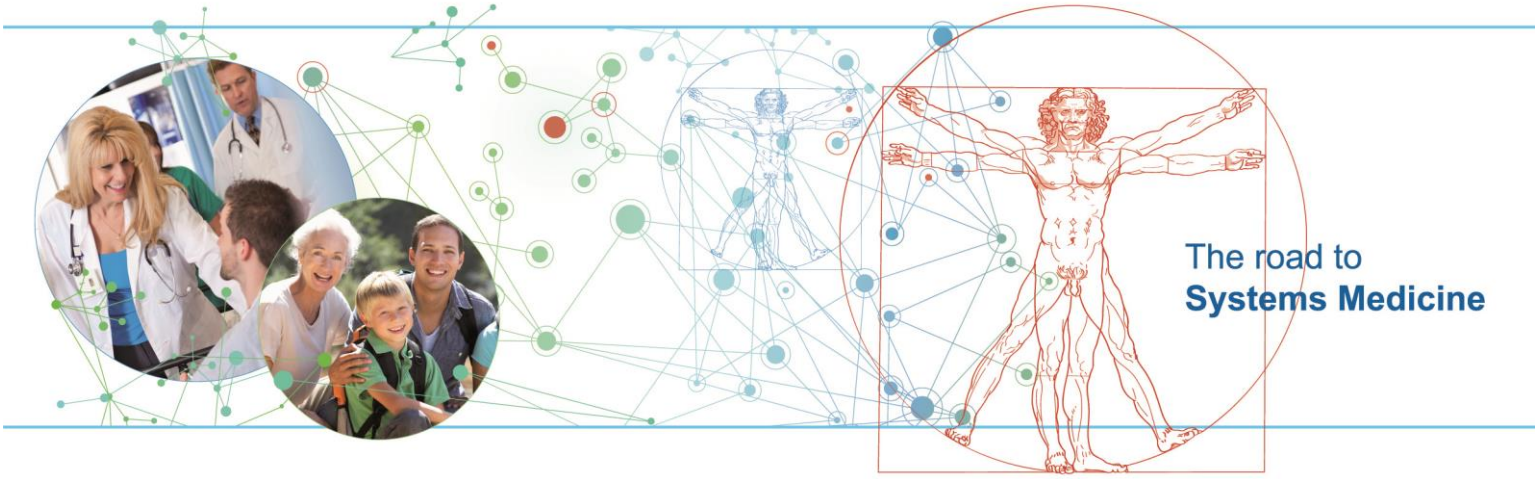
CASYM EUROPE

Coordinating Action Systems Medicine
Implementation of Systems Medicine across Europe

SEVENTH FRAMEWORK PROGRAMME



Plan for university SysMed undergraduate/ graduate education including pilot courses

CASyM training concept

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m.kirschner@fz-juelich.de

Authors
Damjana Rozman, Jure Acimovic, Charles Auffray, Maria Manuela Nogueira, Francis Levi, Jesper Tegner

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Contact information
Damjana Rozman
University of Ljubljana, Slovenia
damjana.rozman@mf.uni-lj.si

TABLE OF CONTENT

INTRODUCTION

Systems medicine has the potential to make medical care and practice more patient-centred, more (cost-) effective, more holistic (a more efficient integration of a variety of components), also achieving a better control of potential side effects. However, to develop and implement systems strategies in medicine, we do not only need medical literacy in basic scientists performing systems biology, but also trained and experienced clinical practitioners. What challenges do we have to meet on this way? By definition, systems medicine involves the implementation of systems biology approaches in medical concepts, research and practice. This could be achieved by iterative and reciprocal feedback between data-driven computational and mathematical models as well as model-driven translational and clinical investigations. Final outcomes could be examples of personalized medicine or the so- called 4P medicine (predictive, preventive, personalized and participatory).

Therefore, key components are e.g. the development of multidisciplinary training and professional dissemination of concepts, creating and shaping a sustainable European community of systems medicine. At the CASyM International Conference on Systems Biology (ICSB) 2013 training workshop and the Ljubljana CASyM course 2013, important issues have been discussed and goals have been defined: i) systems medicine should span all aspects of medical education as a framework for integration of all (pre-) clinical disciplines; ii) systems medicine-facilitated courses of “traditional” topics should aim at understanding complex topics with the help of dynamic systems approaches and (visualization-based) gadgets; iii) research physicians and clinical practitioners should be educated more thoroughly in statistics, bioinformatics, and -omics technologies, and should be open-minded for the use of systems biology modelling for medical purposes; and iv) software should be adapted for practical usage by clinicians.

Tasks we have to meet on the way to physicians with literacy in and probably affinity to systems medicine start during medical school. One possible choice is that medical education could be based on a 4-year graduation (Bachelor) focused on basic and natural sciences (in different proportions according to personal predispositions) followed by a 4-year medical degree (MD) in clinical medicine. This US type of curriculum could leave more space to hard sciences, seen as a good introduction to systems medicine, for a minority of specifically interested MDs. On the other hand, new concepts e.g. in Germany and Slovenia aim at a 6-year Master’s programme starting with clinical examples on the first day, focussing on “problem-orientated learning”, i.e. signs and symptoms, rather than patho-physiological systems (cancer, proliferation, inflammation etc.). Whether this is compatible with or in favour of systems medicine-oriented training might be doubted. In addition, many European countries face a shortage of physicians, especially in the field of general practitioners. This has motivated representatives of health insurance companies, political parties, and patient organisations to demand a faster and less “science-oriented” medical education. The desired result would be an increased output of practitioners that can recognize the most frequent signs and symptoms and prescribe a standardized, established and cost-effective therapy – if available. Moreover, the aforementioned shortage in physicians leads in many countries to i) a high and still increasing workload for physicians, and ii) a significant disparity between basic researchers and clinical practitioners in terms of income as well as the possibility to get tenured positions. Consequently, in many areas, it becomes increasingly difficult to find medical students or practitioners, which are willing and/or able to take an interest in or participate in new (scientific) developments. Very often, young clinicians that would be ideal candidates to become “systems physicians”, both as researchers and practitioners, are nowadays forced to and rewarded for fast, standardized and unquestioned application of (observational-) evidence-based medicine”.

In conclusion, besides the development of systems-medicine-facilitated courses of "traditional" and integrative topics, we should focus on two additional goals: i) to increase the awareness for the mid- and long-term benefits of this way among students, academic teachers, and clinicians, but also representatives of health insurance companies, political parties, and patient organisations; and ii) to give both medical students and young physicians a framework and protected area to train and participate both in the development and application of systems-based strategies. In the end, we absolutely need their positive input and enthusiasm.

Below we describe some of the education and training programmes in systems medicine which are in 2015 available in Europe and beyond. They are divided into master's and doctoral type of systems medicine education suitable also for lifelong training (Systems Medicine, 2016, Schmitz Ulf, Wolkenhauer Olaf (Eds.), ISBN 978-1-4939-3282-5).

Current state

Systems medicine at master's studies of medicine

Linköping University, Sweden — The medical curriculum of Linköping University currently includes a 1-hour introductory lecture in systems medicine during the fourth semester.

University of Ljubljana, Faculty of Medicine — The medical master's curriculum is composed of obligatory and elective courses that represent up to 10% per each study year (1 – 6). Details of the programme are described in the booklet o f uniform second level master's programme medicine that is available online (more information below). Several systems medicine quantitative and data oriented topics are already offered within the elective courses, each of 3 ECTS-credits, such as 'Application of physics and biophysics in diagnostics and treatment'; 'Mathematical principles in biochemistry'; 'Basics of computer based imaging methods in medicine'; 'E-learning and e-materials in medicine'; 'Health information practicum'; 'Molecular modelling in biochemistry'; 'Computer simulations of dynamical processes in biochemistry'; 'Application of bioinformatics tools in medicine'; 'Contemporary informatics in biomedicine'; 'Functional genomics in medicine', etc. Biophysics is offered in year 1 as an obligatory course while students are not offered mathematics. Students can also choose elective research projects which include systems medicine projects that can be performed also at another University, clinic or accredited research site. The current goal is to follow how many students are interested in education on the quantitative and systems approaches in medicine, and upon that decide whether to offer a "systems medicine elective course module" running from years 1 – 6.
More at: http://www.mf.uni-lj.si/media-library/2015/11/3a1169d4c1f6741d403d93e920fd0b75.pdf or http://www.mf.uni-lj.si/

Philipps-University Marburg, Germany — The Systems Biology Platform (www.i-lung.de) of the German Center for Lung Diseases is implementing a facultative curricular course in Systems Medicine for medical students and students in the Master's "human biology" programme. It will start in 2015 and grants 6 ECTS credit points. The course covers modules on clinical medicine & pathophysiology, molecular regulatory circuits & technology, as well as statistics, bioinformatics & modelling. In addition, the platform offers a clinician scientist programme for young physicians in cooperation with the University Medical Center Marburg. It provides training in systems medicine and free time for own research.

The Georgetown University Washington DC, USA — GUW offers a Dual Master's Degree Program (MD/MS) in Systems Medicine which seems to be the most comprehensive formal programme of systems medicine up to date. Medical students may choose to learning genomics, proteomics,

translational bioinformatics, metabolomics, systems biology, pharmacogenomics, epigenomics and biomedical informatics, all in the context of clinical decision making. In addition to course curriculum the students also experience a year-long practicum wherein they apply informatics methodologies to clinical data. While the experience is still nascent it appears that graduates are selecting careers in which these new systems medicine skills will be relevant. Further information is available at: https://gumc.georgetown.edu/spi/systemsmedicine.

Doctoral training towards MD/PhD title

The *University of Ljubljana* offers doctoral training to MDs within doctoral studies of Biomedicine, where MDs can choose courses for PhD in Basic Medicine or Clinical Medicine. This 3.5 year doctoral study since 2014 offers also a 10 ECTS module on Systems Medicine. Doctoral students could choose this module that includes lectures, hands-on computation tutorials and systems medicine project works that are graded.
More at: www.uni-lj.si/elektronske-knjige/02%20Biomedicina%20angl/Biomedicine.html#p=2

The *University College London* took the lead and is since 2013 already offering a systems biology course SysMIC (http://sysmic.ac.uk/home.html) to UK students of different Universities. They run a web-based training which offers multimedia content with guides for self-study and self-assessment. The courses had so far over 700 bioresearchers inscribed. This shows the growing awareness in life scientists about the need of systems skills. It is interesting to note that students funded by BBRSC (Biotechnology, Biological Science, Researching Council) in the field of life sciences are obliged to take this e-course. Several topics of the SysMIC course are relevant for systems medicine, especially all introduced mathematical concepts. What is missing is the disease-oriented problem work that could be introduced with the aid of CASyM partners.

The *Imperial College London* runs the STRATiGRAD PhD programme addressing the work at the interface of disciplines that collectively drive new discoveries at the systems level. Through the collaborative network of research organisations with common interests in the areas of stratified medicine, clinical diagnostics, prognostics and theranostic biomarker discovery, novel therapeutic development, etc., they train PhD students in the fields of molecular phenotyping, systems modelling and stratified medicine. The program applies e-training resources and computational/analytical infrastructures in systems biology at the Imperial College.
More at: https://www1.imperial.ac.uk/computationalsystemsmedicine/ or
http://www1.imperial.ac.uk/stratigrad/about/

The *Helmholtz Graduate School* "Molecular Cell Biology" is the collaboration between the Max Delbrück Center for Molecular Medicine (MDC) and the Humboldt-Universität zu Berlin (HU), Freie Universität Berlin and Charité-Universitätsmedizin Berlin Medical Faculty. The graduate school offers an interdisciplinary structured PhD research training and currently supports 350 PhD students. Research training is supplemented with lectures and workshops on methods and technologies, combined with soft skills courses in career development. The Graduate School applies the Credit Point System which helps the students to structure their training according to needs and interests. Students may choose to apply to international exchange programs, such as the MDC-NYU PhD Exchange Programme in Medical Systems Biology. The research offered at the MDC covers several multifactorial disease areas, such as Cardiovascular & Metabolic Research, Cancer Biology & Immunology, Neurobiology, Medical Systems Biology & Bioinformatics, etc.
More at: www.mdc-berlin.de/en/bimsb/phd_program/index.html

The *University College Dublin* has been running a Bioinformatics and Systems Biology structured PhD programme since 2009, with an emphasis on equipping its students with interdisciplinary 'wet' and

'dry' lab training. Research focuses on cancer and infection biology, and the programme is run in conjunction with collaborators at *Trinity College Dublin and the Royal College of Surgeons in Ireland.*
More at: http://bioinfo-casl.ucd.ie/PhD/

The PhD School at the *University of Milano Bicocca* offers PhD program in Biology and Biotechnology with curriculum in Systems and Synthetic Biology which deals with application of computational methodologies to the study of protein structure and function, metabolic and signal transduction pathways and to big –data.
More at: http://www.unimib.it/go/48774/Home/English/Research/Doctoral-Programs/Biology-and-Biotechnology

The *University of Turin* runs the PhD in Complex systems for the Life Sciences intended for Graduate Students in Biology, Mathematics, Chemistry, Physics, Medicine and Computer Science. Prospective students should have an excellent score in their previous classes, a strong undergraduate science background, a strong commitment to research and they should accept the challenge posed by a new interdisciplinary science. Indeed the present curriculum is specifically interested in recruiting students with broad scientific interests and a taste for collaboration. The curriculum is designed to offer scientific training, research projects and perspectives in the area of post-genomic biology by using combined computational, engineering and experimental approaches with theoretical modelling, rooted in theoretical physics and mathematics.
More at: http://en.unito.it/postdegree/phd/complex-systems-life-sciences

The *BioHealth Computing Consortium* (BioHC Consortium) linking together Public Universities, University Hospitals, Bioindustry Parks and Private Companies, to speed laboratory discoveries into solutions for patients offers (i) a 1-year Master Courses programme; and (ii) a 3 or 4 year PhD programme in the following areas: Clinical Research, Nano/Molecular Biotechnology, Environmental/Animal Health, and Computational Mathematics. This programme is connected with Erasmus Mundus Association and the European Scientific Institute (ESI), itself It was founded in 1994 at the initiative of CERN-based physicists and a group of European universities in order to develop high level training courses on technologies developed at CERN.
More at: http://biohealth-computing.org/

Warwick Medical School and Warwick Systems Biology Centre have joined forces to develop special training and research opportunities in Systems Medicine. The systems cancer chronotherapeutics team was created mid-2015, with four academic positions ranking from full to assistant professor, including two medical oncologists. Four lectures illustrating the relevance of systems medicine for oncology and chronotherapeutics are taught to medical students *MathSys* is a collaboration of three interdisciplinary research centres, each with their own excellent records of world-leading research involving application of mathematics to real-world problems: the Centre for Complexity Science; Warwick Systems Biology; and Warwick Infectious Disease Epidemiology Research (WIDER) centre. Funded by EPSRC, with support from MRC, 13 external partners (drawn from industry, finance and health) and the University of Warwick, the Centre will train a new generation of scientists needed to tackle the key global challenges facing science, business and society particularly where these involve complex, non-linear, uncertain and stochastic systems. Systems medicine represents an important issue addressed by the Centre.
More at: http://www2.warwick.ac.uk/fac/sci/systemsbiology

Systems medicine pilot workshop, courses, summer schools and tutorials

Workshops, courses, summer schools, etc. represent a crucial top-up to undergraduate and graduate education in systems medicine and offer as well opportunities for life long training in this area. The

benefit of these events is that they are timely constrained and can, due to participation of different tutors with different specialties offer up-to-date systems medicine approaches every year. CASyM was very active in organizing such training events that are briefly listed below. An important issue is accreditation of both ECTS for the formal education (undergraduate or PhD) as well as EACCME which brings continuous medical education (CME) credit points to medical doctors that need it to prolong their licenses. The CASyM training events are listed below and we will refer to some of them as well in the section of future plans.

CASyM: Modeling Tools for Pharmacokinetics and Systems Medicine — The event took place at Filderhalle Leinfelden-Echterdingen Convention and Conference Center, Leinfelden-Echterdingen, Germany located near the Stuttgart International Airport on May 18, 2014. The tutorial was adjoined to an international symposium "20th International Symposium on Microsomes and Drug Oxidations". The event consisted of 4-hands-on tutorials which were adapted for the beginner or advanced stage of trainees and had sufficient number of tutors to help trainees on the site. Attendees got hands-on experience in various mathematical and informatics approaches to medical relevant questions from 8 renowned European clinicians and scientists with following headlines:

- An introduction to physiology-based pharmacokinetic (PBPK) modeling
- Truly individualized systems medicine: a hands-on tutorial where participants will resolve paradoxes by using virtual twin / digital-me
- Systems cancer chronotherapeutics for the personalization of cancer treatments
- Feedback mechanisms and systems medicine: Modeling cholesterol homeostasis for drug discovery.

The event was accredited with 6 European CME credits (ECMEC) by the European Accreditation Council for Continuing Medical Education (EACCME).
The recorded tutorials are available at: http://videolectures.net/mdo2014_stuttgart/

The 1st SyBSyM Como School "Systems Biology and Systems Medicine: Precision Biotechnology and Therapies" — The School took place at the Lake Como School of Advanced Studies, Lake Como, Italy that is located near four international airports (two in Milano, one in Bergamo and one in Lugano, Switzerland) from September 21 till September 27, 2014. The Lake Como School of Advanced Studies is an international research facility that runs fellowships and short term programmes on a wide range of interdisciplinary subjects that share a common focus on complex systems. Tackling complex systems requires an interdisciplinary approach connecting various basic scientific fields in order to be able to adequately explain the ever increasing biological complexities. Systems biology and systems medicine are the emerging disciplines that integrate biomedicine (biology, molecular biology, biochemistry, medicine, etc.), mathematics (physics, statistics, computer science, etc.) and engineering. The use of high-throughput post-genomic experimental principles coupled with the theoretical framework of modelling biological processes represent the key tools for understanding pathogenesis, diagnosis and treatment options of complex human diseases.

The School introduced Systems Biology experimental and computational approaches that together enabled the participant to begin to tackle the complex networks of life, hands-on. Computable representations of systems biology/medicine integration are about to unleash revolutions in fundamental biology, predictable biotechnology and individualized medicine.

The school combined lectures on various topics ranging from a more fundamental introduction of computational models through systems biology approaches of studying cell homeostasis to tackling Parkinson's or fatty liver disease from a systemic approach. Participants were able to put some of the introduced topics of the morning lectures to practice in the afternoon's tutorials, where the first two dealt with more basic principles like flux balance analysis and dynamic models and the other two upgraded the models for pharmacokinetics and systems medicine/biology of a disease. Materials for the courses were available beforehand online. The 4 tutorials were adapted for the

beginner or advanced stage of trainees and had sufficient number of tutors to help trainees on the site.
In the light of the School's successful union of researchers from basic to translational aspects of systems medicine/biology, the Infrastructure for Systems Biology in Europe (more at: http://project.isbe.eu) and CASyM were also introduced to the participants to provide the necessary framework for future collaborations in order to further develop and strengthen systems biology/medicine in Europe and beyond.

CASyM: Systems approach to biological clocks and diseases —The event took place at the "Ecole Supérieure de Physique et Chimie Industrielles" (ESPCI) located in central Paris (France) on Wednesday, October 29, 2014. It was adjoined to the 44th congress of the French-speaking society of chronobiology (Société Francophone de Chronobiologie, SFC). It focused on systems medicine approaches to biological clocks and diseases. The program included an introduction to biological rhythms, followed by lectures on the circadian timing system - which governs the daily variations of the body and its control on cell cycle and cancer diseases. Successful systems medicine approaches in the field of circadian clocks and chronotherapeutics were detailed. The morning session included interactive hands-on tutorials where trainees were asked to bring their own laptops whereas the afternoon session consisted of scientific lectures. Materials for the courses were available beforehand online. This event was accredited with 6 (ECMEC) by the EACCME.

CASyM Summer School: Advanced Summer School in System Medicine: Implementation of System Medicine across Europe. A FEBS Advanced Lecture Course — In 2015, CASyM organized the first European Summer School in Systems Medicine taking place from 22- 26 June at the Djurönäset archipelago near Stockholm, Sweden. Participation of the Summer School was granted with 27 ECMEC by the EACCME. The Summer School programme (more information can be found: http://febscasymsummerschool.com/) was directed at both the next generation of clinicians as well as scientists and included activities starting from lectures in Systems Medicine approaches in a variety of fields to hands-on exercises in metabolic modelling or computational tissue engineering. A rich social programme accompanied the cutting-edge scientific programme. A total of 21 students and 18 invited lecturers/keynote speakers were attending the Summer School.

The 10th CFGBC Symposium with ISBE and CASyM workshops organized together with a Hands-on tutorial Systems Biology/Medicine —This event jointly organized by CASyM and ISBE took place in Ljubljana, Slovenia, from 30th June to 3rd July 2015 at the Faculty of Medicine, University of Ljubljana. The event was composed of a one day event attended by leading scientists from systems biology/medicine that were giving a joint effort inside ISBE and CASyM consortia to promote this new and exciting field in Europe and beyond, followed by 3 day hands-on tutorial Systems Biology/Medicine. The EACCME has granted 23 ECMEC to participants attending the workshops and the hands on tutorials. Additionally, University of Ljubljana has accredited the event: 5 ECTS for doctoral students, 3 ECTS for diploma and masters students (Subject: Functional Genomics in medicine). The meeting was attended by 94 participants from 9 countries. Unfortunately, we were unable to attract more than one MD but 14 tutorial participants were undergraduate students mostly from Faculty of Medicine (10) and Faculty of Chemistry and Chemical Technology, University of Ljubljana. The total number of tutorial participants was 22. 19 posters were presented at the poster session.

The event entitled "10th Centre for Functional Genomics and Bio-Chips (CFGBC) Symposium" at the Faculty of Medicine, University of Ljubljana, Slovenia, the second hands-on Systems Biology/Medicine tutorial was jointly organized by CASyM and ISBE. The 3-day tutorial focused on doctoral and post-doctoral students, medical doctors and medical professionals. The event hosted 5 tutorials and a lecture with topics ranging from personalized systems cancer chronotherapeutics to clinical next generation sequencing for diagnosis of rare diseases. Participants could solve systems

biology/medicine questions by using their own computers and academic software that was available for download. After a final and successful exam, participation in the event was granted 5 ECTS for doctoral students, 3 ECTS for diploma and master's students and 23 ECMEC for medical professionals (http://cfgbc.mf.uni-lj.si/events/seminars/2015SysBioMed).

PLAN FOR UNIVERSITY SYSMED UNDERGRADUATE/GRADUATE EDUCATION INCLUDING PILOT COURSES

Undergraduate systems medicine

Working in the systems medicine education and training area for over 4 years it became clear what is feasible and where are the major obstacles. There is an anonymous agreement that systems medicine training is a need, recognized both by students, trainers and the authorities. It is also clear that if medical students and young MDs are in question, the major depth are the communication and mathematical skills that would allow MDs to extract quickly and efficiently the enormous amount of already existing data for the benefit of patients. Despite this level of agreement for the needs, there is no agreement on the best practices and pathways to achieve the goal.

The reason lies in the generally fragmented approach in the European higher education, where even within a single country Universities teach similar subjects by different principles, and keep the decision autonomy. The Universities are independent in offering novel courses; accreditation for these is requested for Universities in countries that follow the Bologna process. So, despite the plan that CASyM could provide “the” curriculum for pan-European systems medicine education, this is in practical means not achievable within the current higher education system in Europe. However, some steps are achievable and have already been tested within the CASyM time course. Several medical schools in Europe teach subjects that are relevant for systems medicine, as described in the previous chapter. What is missing is to combine relevant subjects into modules that would receive the formal name of “systems medicine” module. If such modules are provided mostly by elective courses, we should promote that students receive the proper information regarding the systems medicine subjects.

In the future we should also seek to introducing novel formal systems medicine research and training networks through the Erasmus+ programme. One of the actions of Erasmus+ is also a joint doctorate. Here a group of Universities can decide to jointly propose a programme where students are flexible to perform their research and education within the network and they approve each other’s final degree. A successful example of this type was BioHC graduate school that was performed between Universities in Grenoble, Barcelona and Torino, and in association to ESI and CERN. The programme was accredited until 2015 and is now seeking for a novel accreditation. CASyM partners and associate partners collaborated in this master’s programme as partners and tutors by providing teaching research training and mentorship. It is envisioned that in the newly accredited programme will include as well University of Ljubljana as an additional CASyM partner.

Intensifying collaborations with other organizations and projects relevant for systems medicine education and training

An important step forward towards the pan-European Systems medicine perspective is planned by intensifying collaboration with organizations that join medical schools and medical students. The first is AMSE - Association of Medical Schools in Europe (http://www.amse-med.eu/). AMSE is a forum for European Faculties of Medicine to share experiences in the fields of education, research and management. AMSE seeks to stimulate co-operation between Medical Schools in Europe and to initiate and sustain relations with other professional, governmental and non-governmental organisations in education, research and health care. AMSE is thus an obvious partner that might be consulted to introduce the systems medicine concepts into the regular medical school association.

The second organization to consult is EMSA, the European Medical Student Association (http://emsa-europe.eu/). This is a network between European medical students that represents and voice the opinions of the medical students of Europe. They also act as a forum for medical students in Europe, to discuss topics related to the fields of medical education, medical ethics, and medical research. Students are interested to promote the highest standards in European medical education and ensure the quality of healthcare in Europe. EMSA aims to promote trainings, activities and projects related to health in Europe to the benefit of medical students and society.

Even if this was not planned in the initial CASyM training plan, it becomes obvious that we have to make strong contacts with these organizations to reach the pan-European systems medicine education goals particularly for medical students.

Other organisations/working groups/initiatives that should be contacted aimed at intensifying the collaboration are:

- The European Research Area (ERA) Steering Group on Human Resources and Mobility of Researchers (ERA SGHRM) chaired by Conor O'Carroll. Topics of interest include doctoral training and harmonisation of curriculum across the EU member states.
- The IMI (Innovative Medicines Initiative) Education and Training pillar, especially EMTRAIN.
  More at: http://www.emtrain.eu/index.php/about/imi
  EMTRAIN Coordinator and PharmaTrain Co-coordinator contact (Mike Hardman):
  http://www.emtrain.eu/index.php/component/contact/contact/1-mike-hardman

It is important to intensify collaborations as well with the ESFRI research infrastructures that lie in the heart of biomedical research. Relevant are collaborations with ELIXIR (data for life sciences) and the biobanking infrastructure BBMRI (http://bbmri-eric.eu/), as well as ISBE http://project.isbe.eu/, and some others in the Life Sciences field (https://ec.europa.eu/research/infrastructures/index_en.cfm?pg=esfri). Elixir that is getting more and more into the medical data management with intensified training of trainers on hacketons, workshops, etc., focusing also on e-education in biomedical data management strategies (https://www.elixir-europe.org/). ELIXIR accelerates its activities, including the education and training with major Horizon 2020 funding of the EXCELERATE project. The 'ELIXIR-EXCELERATE' project (http://ibmi.mf.uni-lj.si/en/node/222)aims to facilitate the integration of Europe's bioinformatics resources, supporting all sectors of life-science R&D. It will deliver excellence to ELIXIR's users by fast-tracking the development and deployment of essential data services. EXCLERATE funding will help ELIXIR coordinate and extend national and international data resources to ensure the delivery of world-leading life-science data services. It will support a pan-European training programme, anchored in national infrastructures, to increase bioinformatics capacity and competency. It will also provide efficiencies in management and operation throughout the infrastructure, which is distributed amongst 17 countries, many of which are also countries of CASyM.

Since an important pillar of all ESFRIs is the education and training component, this is also in the centre of the Horizon2020 project CORBELL https://news.embl.de/lab-matters/1504-elixir-corbel/. The project builds on existing efforts within the BioMedBridges project and others to develop the tools, services and data management required by cutting-edge European research projects. The ESFRI Biological and Medical Research Infrastructures (BMS RI) join scientific capabilities and shared services to transform the understanding of biological mechanisms and accelerate the translation of this knowledge into biological and health applications. The resources brought together by these infrastructures include physical biobank samples, imaging facilities and molecular screening centres. 'CORBEL' (Coordinated Research Infrastructures Building Enduring Life-science Services) aims to create a joint platform that will visibly reduce redundancy and simplify project management, transforming the ability of users to deliver advanced, cross-disciplinary research in Europe. CORBEL is coordinated by ELIXIR and the ESFRI Research Infrastructures involved are: BBMRI, EATRIS, ECRIN, EMBRC, EU-OPENSCREEN, Euro-BioImaging, INFRAFRONTIER, Instruct, ISBE and MIRRI. The CORBEL consortium thus includes all ESFRI research infrastructures in the life sciences.

Another foreseen collaboration is with FAIRDOM http://fair-dom.org/ that is a joint action of ERA-Net ERASysAPP and European Research Infrastructure ISBE to establish a data and model management service facility for Systems Biology, applicable also for the health research. The prime mission is to support researchers, students, trainers, funders and publishers by enabling Systems Biology projects to make their Data, Operating procedures and Models, Findable, Accessible, Interoperable and Reusable (FAIR). FAIRDOM builds on the outcomes of the previous successful SysMO-DB and SyBIT data management projects, uniting their tool and database development as well as their experience serving large systems biology projects (Working with stakeholders**:** funders, policy makers, research infrastructures, journals and standards initiatives to foster FAIR data and model management in Systems Biology).

Plan for graduate systems medicine education

Similarly as for undergraduate education also the doctoral education is dispersed in Europe. After discussing and testing several possibilities for systems medicine doctoral schools, three possibilities appeared as feasible for the future. Two of them were successfully tested within CASyM time frame.

(1) *Introducing (accredited or non-accredited) systems medicine concepts or subjects into the existing biomedical doctoral programmes* — An example is a 10 ECTS module of systems medicine at University of Ljubljana (see appendix for full programme). This has been performed for the first time last year and included multiple international professors and speakers, which should be also envisioned as a plan for the future. 5 ECTS have been provided by Prof. Dr. Gerold Baier from University College London who performed training of basic mathematical modelling for biomedical students who do usually not have strong mathematical backgrounds. The remaining 5 ECTS have been acquired during the SysBioMed workshop with multiple international CASyM and also ISBE speakers from academia, industry and clinical institutions.
On top of the workshop the students spent 3 days by hands on computation, solving relevant biomedical problems. The approach to provide to systems medicine students basics of modelling on top of top-edge systems medicine topics that can be translated to research or clinical practice should represent the future of doctoral systems medicine courses that can be adapted by multiple Universities throughout Europe.
More at: SysBioMed2015_book_of_abstracts

(2) *Introducing novel interdisciplinary systems medicine research training networks for doctoral students within the Marie Curie programmes* — A successful Marie Curie Initial training network (ITN) promoted by CASyM partners is Melplex that combines 15 research groups

and focuses to systems medicine approaches in treatment of malignant melanoma. CASyM members serve as partners as well as members of the Scientific Advisory Board. The students contributing to this systems medicine programme will perform research and PhD training in different countries at different Universities. In this model it is this not necessary to have a unified systems medicine formal training programme, but to have a research network where each provides an angle of the systems approach. The common events (systems medicine oriented workshops and tutorials) represent additional training templates within the Ph.D. programmes.

(3) *Establishing a formal systems medicine doctoral programme at individual Universities* — This option has not yet been tested within CASyM. Even if it initially looked appealing, the practice showed it is not so easy to establish a completely novel interdisciplinary doctoral programme at individual Universities. Even if this happens, there is no consensus list of subjects that are a "must" in teaching systems medicine. It is clear that doctoral students must be exposed to for them novel mathematical principles, including basics of modelling, ideally in the disease topic which is in the focus of their research. Such approach requires lots of individual work with students or at least work in small groups, which is not necessarily optimal from the financial perspective.

The role of CASyM and later of the European Association of Systems Medicine (EASyM) is/will be to promote interdisciplinary systems medicine concepts in medical undergraduate and graduate education. CASyM spreads the voice of importance of introducing more mathematical and informatics concepts into the biomedical curricula. CASyM became indeed a trademark for systems medicine education that is recognized widely in the biomedical community. EASyM can build on this reputation towards a sustainable support for promotion and realization of systems medicine education and training programmes and events.

Plan for tutorials, workshops and summer schools

During CASyM and beyond, within EASyM, this level of systems medicine education and training was the most visible, with most measurable success and the pan-European recognition. What we have not achieved so far and remains for the future is a larger number of applicants for the training events especially from the established medical doctors. The training events were so far organized adjoined to some medium-sized biomedical meetings that included both industries and clinics. However, to attract more MDs we need to propose systems medicine training events to large medical societies, such as the European Association for study of the Liver (EASL: http://www.easl.eu/), or similar. The EASL society yearly organizes the International Liver Congress with over 10 000 participants, mostly medical doctors. The plan and challenge now is to propose more disease oriented systems medicine tutorials and courses as satellites to big medical meetings and events, which can be realized in the EASyM era.

On top of that, the systems medicine tutorials and workshops adjoined to medium-sized meetings (as described above) should continue since they already have a tradition and raising reputation in the European biomedical community. Below is a list of all the future events foreseen to be organized/co-organized by CASyM. It is envisioned that these events will become traditional and supported in longer term also within the EASyM.

Planed CASyM training events

Event title	**Venue**	**Date**
SysmedIBD Spring School (Werner Mueller)	Venice	9–11 March 2016
Genome Medicine Summer school, TEAMING programme Artemida	Portorož	2-7 May 2016
Big Data for Healthy Living [Study Case: Obesity] and 2nd CASyM Summer School	Archamps	June/July 2016
BioHealthComputing introduction week	Archamps	August 2016
The 2nd SyBSyM Lake Como School: “Towards a Precision Medicine”	Lake Como	25-30 September 2016
CASyM Systems Medicine education and training workshop adjoined to the 1st Conference of the European Association of Systems Medicine	Berlin	26 October 2016
3rd CASyM/EASyM Winter/Spring School of Systems Medicine		Start in 2017

CONCLUSIONS AND PERSPECTIVES

Rather than providing a dry plan of systems medicine education and training CASyM decided for a practical approach by testing different systems medicine training approaches at different levels (undergraduate, graduate, life-long). It became clear that it will be impossible to propose or impose a systems medicine curriculum that could be accepted by all European Universities. An agreement is that a systems medicine curriculum should have theoretical (mathematics and informatics with modelling), experimental (biochemistry with molecular biology, etc.) and clinical (implementation for a particular disease area) components. If possible, the industrial component should also be included, especially where the systems medicine approaches can be used to propose novel disease markers, potential drug targets, improved therapies or better stratified patient groups.

CASyM will end in 2016 and will leave an important legacy in the European systems medicine education and training by education hundreds of young fellows in this exciting new interdisciplinary area. EASyM will start on this ground and should provide a sustainable promotion and support to the systems medicine education and training efforts in Europe. Systems medicine education and training is not the final goal. It is the path we need to walk also in the future, in collaboration with other organizations and projects relevant for the systems medicine training, to reach stratified or precision medicine and to teach young fellows how to apply data and mathematical tools to aid in medical decisions.

APPENDIX

UČNI NAČRT PREDMETA / COURSE SYLLABUS

Predmet: Sistemska medicina večfaktorskih bolezni
Course title: Systems medicine of multifactorial disorders

Študijski program in stopnja Study programme and level	Študijska smer Study field	Letnik Academic year	Semester Semester
Univerzitetni doktorski študij Biomedicina 3. stopnja **University Doctoral Studies of Biomedicine, 3rd level**	**Temeljna medicina** **Basic medicine**	**1** **1**	**1 - 2** **1 - 2**

Vrsta predmeta / Course type Temeljni predmet /basic subject

Univerzitetna koda predmeta / University course code: Nov modul /new module

Predavanja Lectures	Seminar Seminar	Vaje Tutorial	Klinične vaje work	Druge oblike študija	Samost. delo Individ. work	ECTS
25	**50**	**25**		**50**	**100**	**10**

Nosilec predmeta / Lecturer:

Prof. dr. Damjana Rozman

Osnovna znanja sistemske medicine/basic concepts of systems medicine
- Prof. dr. Damjana Rozman (funkcijska genomika, circadiani ritmi/ functional genomics, circadian rhythms)
-Prof. dr. Borut Peterlin, M.D. (medicinska genetika / medical genetics)
-Prof. dr. Vita Dolžan, M.D. (farmakogenomika/ pharmacogenomics)
-Prof. dr. Marko Goličnik (matematično modeliranje bioloških procesov / mathematical modeling of biological processes)
- Prof. dr. Jurij Stojan (kinetika encimskih reakcij in molekularno modeliranje / kinetics of enzyme reactions and molecular modeling)
-Doc dr. Lara Lusa (analiza »omskih« podatkov in statistika/ statistics, »ome« data analysis and statistics)
- Prof. dr. Janez Stare – podatkovne zbirke o boleznih (standardi, shranjevanje, zajemanje podatkov in rudarjenje / disease databases (standards, storage, retreival, mining)
- Prof. dr. Radovan Komel – pravni in etični vidiki, slovenska in EU zakonodaja (legal and ethical issues, Slovenian and EU legislation)

Specialna znanja o boleznih/Special disease aspects:
-Prof. dr. Tadej Battelino, M.D. (pediatrija, endokrinologija/ pediatrics, endocrinology)
- Prof. dr. Borut Peteriln, M.D. (nevrodegenerativne bolezni/neurodegenerative disorders)
- Prof. dr. Alojz Ihan (imunologija / immunology)
- Prof. dr. Daniel Petrovič (kardiologija / cardiology)
-Prof. dr. Janez Žgajnar, M.D. (onkologija/oncology)
-Prof. dr. Martina Tomori, M.D. (psihiatrija / psychiaty)

Vabljeni predavatelji iz tujine / Invited lecturers from foreign institutions

Jeziki / Languages:	**Predavanja / Lectures:**	**Slovensko ali angleško Slovene or English**
	Vaje / Tutorial:	**Slovene or English**

Pogoji za vključitev v delo oz. za opravljanje študijskih obveznosti:
Dokončan študij 2. bolonjske stopnje medicinskih, veterinarskih, farmacevtskih ali drugih sorodnih naravoslovnih znanosti (biokemija, biologija, biotehnologija, mikrobiologija, idr.). Z diferencialnimi izpiti tudi dokončan študij matematično-informatičnih ali tehniških znanosti (matematika, računalništvo, elektrotehnika, fizika, idr.)

Prerequisits:

Completed 2nd Bologna level of Medicine, Veterinary Medicine, Pharmacy or related natural sciences (Biochemistry, Biology, Biotechnology, Microbiology, etc.). With differential exams also completed studies of mathematical-informatic or technical sciences (mathematics, computer sciences, electrotechnics, physics, etc.).

Vsebina:
Predmet sestavljajo predavanja in praktično delo na projektu, ki zajema izbran klinični primer večfaktorske bolezni. **Primere bolezni bomo izbrali vsako leto glede na najnovejša znanstvena spoznanja in raziskovalni interes študijske skupine** (na primer metabolične, nevrodegenerativne, psihiatrične bolezni, rak, itd.). Predavanja bodo osvežila različne vidike izbranih večfaktorskih bolezni, s poudarkom na sistemskih pristopih po-genomske dobe, vključno z vidiki cirkadianega ritma. Znanje študentov bomo nadgradili s predavanji o računanju z velikimi skupinami podatkov, statistiko, modeliranjem podatkov in po-genomskimi zbirkami podatkov o boleznih (standardi, shranjevanje, zajemanje, rudarjenje). Študenti bodo pridobili tudi znanje o najnovejših mednarodnih prizadevanjih za

Content (Syllabus outline):
The course will consist of lectures and practical work on the project, focused on a chosen clinical example of multifactorial disorder. **Disease examples will be chosen each year based on most recent scientifc discoveries and research interests of the study group** (i.e.metabolic, neurodegenerative or psychiatric disorders, cancer, etc). Lectures will represent a refresher course covering different aspects of selected disorders, with particular emphasis on the systems approaches of the post-genome era, including the circadian aspects. Students' knowledge will be upgraded by courses of computation with large datasets, statistics, data modeling, post-genome disease databases (standards, storage, retreival, mining) and of up-to-date international efforts of post-genome data exchange. Students will get insight into

izmenjavo po-genomskih podatkov. Tako bomo osvetlili pomen globalnih genomskih raziskav za prediktivno in personalizirano (osebno) medicino, vključno s socialnimi vidiki uporabe novih tehnologij.

Specifični cilji projekta so:
1) Osvežiti biokemijske, patofiziološke, genetske, genomske, okoljske, itd. vidike izbranih večfaktorskih bolezni in pristopov zdravljenja v po-genomski dobi.
2) Pregledati osnovne pristope za matematično modeliranje stacionarnih oz. nestacionarnih kinetičnih procesov v bioloških sistemih.
3) Pregledati računske pristope za delo s podatki (programski jeziki, uporabnost, analiza »omskih« podatkov in statistka, itd.).
4) Spoznati za medicino pomembne po-genomske vire podatkov in podatkovne zbirke.
5)Spoznati osnove analize po-genomskih podatkov (testiranje hipotez, predikcijsko in opisno modeliranje, analiza in vrednotenje mrež, itd.).
6) Spoznati izzive in postopke translacije bazičnih genomskih raziskav v klinično medicino, s poudarkom na prediktivno in personalizirano medicino ter pomenom genomskih tehnologij za javno zdravje.

Poleg predavanj predmet temelji na mentorskem delu s posameznimi študenti ali pari študentov, ki bodo izvedli manjše projekte s področja podatkov sistemske medicine. Pri tem bodo združili biomedicinska, matematična in klinična znanja, da bi rešili praktične probleme. Primeri problemov so: integracija globalnih asociacijskih, ekspresijskih in proteomskih podatkov pri človeku in živalskih modelih večfaktorskih bolezni; simulacija majhne metabolične mreže človeške bolezni in ocena napovedne vrednosti, simulacija kronoterapije bolnikov z rakom, interpretacija podatkov sekvenciranja pacientov z večfaktorsko boleznijo, pogoji za translacijo genomskih raziskav v vsakdanjo klinično prakso in sistem javnega zdravstva, etc.

the role of global genome studies for the predictive personalized medicine, including teh social aspects of using novel technologies.

Specific aims of the course are:
1)To review biochemical, patophysiological, genetic, genomic, environmental, etc. aspects of chosen multifactorial diseases and treatment strategies in the post-genome era.
2) To review basic concepts for mathematical modelling of stacionary or non-stacionary kinetic processes in biological systems.
3) To review basic concepts of computational sciences (programme languages, applications, »ome« data analysis with statistics, etc.)
4) To get familiar with for medicine relevant post-genome data resources and data bases.
5) To review basic concepts of post-genome data analysis (hypothesis testing, predictive and descriptive modeling, networks and their analysis and evaluation, etc.).
6) To learn about challenges and procedures for translation of basic genome research into the clinical medicine, with special attention to predictive and personalized medicine and importance of novel technologies for public health.

In addition to lectures, the course will base on mentor-guided work with individual students or pairs of students who will carry-on small systems medicine projects. Within these projects they will combine the knowledge of biomedical, mathematical and clinical disciplines in order to solve practical problems. Examples of such problems are: integration of global association, expresison and proteome data of multi-factorial disorders in human and in animal models; simulation of a small human disease metabolic networks and assesment of prediction value; simulation of chronotherapy of cancer patients; interpretation of human genome sequencing data in diseased patients, rules and practices for translation of genome research into teh clinical practice and th esystem of public health, etc.

Praktično delo, pisno poročilo in ustni zagovor projekta bo ocenil mednarodni panel profesorjev.

Practical work, delivery of written report and oral defense of the project will be graded by the international panel of profesors.

Temeljni literatura in viri / Readings:

Modeliranje bioloških procesov /Modeling of biological processes: Behre J, de Figueiredo LF, Schuster S, Kaleta C. Detecting structural invariants in biological reaction networks. Methods Mol. Biol. (2012) 804:377-407.

Farmakogenetika/Pharmacogenetics: Maitland-van der Zee A.-H. (ur.), Dally A. K. (ur.). Pharmacogenetics and Individualized Therapy. John Wiley & Sons, Inc. Hoboken, NJ, 2012. ISBN-10: 047043354X (Izbrana poglaja/Selected chapters)

Imunologija/Immunology: Janeway CA, Travers P, Walport M, Shlomchik M. Immunobiology – The immune system in health and disease. Churchill Livingstone, Edinburgh 2010 (Izbrana poglavja / Selected chapters)

Viri iz sodobne mednarodne periodike.

Cilji in kompetence:

Študent podrobneje poglobi teoretične in spozna praktične vidike nekaterih »omskih« pristopov (analize transkriptoma, proteoma, metaboloma, interaktoma, itd.) in njihov naraščajoči pomen v medicini 21. stoletja. Spozna pomen bioinformatike pri shranjevanju in obdelavi velikega števila podatkov, ki jih proizvedejo tehnike mikromrež. V laboratoriju se seznani z infrastrukturo (opremo), ki je potrebna za globalne molekulske analize v medicini in kako se izvede eksperiment. Seznani se s koncepti prediktivne, personalizirane in translacijske medicine ter pomenom genomskih raziskav za javno zdravje.

Objectives and competences:

Student get an insight into the theory and practice of »omic« approaches (transcriptome analysis, proteome, metabolome, interactome, etc.) and their increasing importance for the 21st century medicine. She/he learns the importance of bioinformatics for storing and analysis the large amount of data arising form DNA microarray and other technologies. In laboratory student learns about equipment that is required for global molecular analyses in medicine, and how to perform an experiment. She/he also gets insight into the concepts of the predictive, personalized abd translational medicine and of the importance of post-genome research for public health.

Predvideni študijski rezultati:
Znanje in razumevanje: Praktično seznanjenje s sodobnimi tehnologijami pogenomskega obdobja, predvsem z uporabo mikromrež in nove generacije sekvenciranja ter s procesom translacije bazičnih po-genomskih spoznanj v klinično prakso in sistem javnega zdravstva.
Uporaba: Razumevanje tehnologij globalne molekulske analize (pato)fizioloških stanj in njihovo vpeljevanje v slovensko medicinsko prakso.
Refleksija: Povezovanje lastnega razumevanja teoretičnih osnov s praktičnim delom in pomen za nove pristope v medicini.
Prenosljive spretnosti: Podpora k reševanju kliničnih problemov.

Intended learning outcomes:
Knowledge and understanding: Practical learning of modern post-genome technologies, particular with DNA microarray technology and next generation sequencing and of the translation of basic post-genome knowledge into teh clinical practice and public health system,
Application: Understanding the technologies for global molecular analyses of (patho)physiological states and their incorporation into Slovenian medical practice.
Reflection: Integration of own understanding of theory with practical work and importance for new approaches in medicine.
Transfer competences: Support to solving clinical problems.

Metode poučevanja in učenja:
Interaktivna predavanja, seminarsko delo in izvedba poskusa v laboratoriju (seminarske vaje).

Learning and teaching methods:
Interactive lectures, seminar work , performance of experiment (tutorial).

Načini ocenjevanja:	Delež (v %) / Weight (in %)	**Assessment:**
Projekt		**Project**
	100%	

Reference nosilca / Lecturer's references:

D. Rozman:

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M. Goličnik

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STEERING COMMITTEE

The following officials, as part of the Scientific Steering Committee, are involved in the scientific coordination of CASyM:

Charles Auffray - European Institute for Systems Biology & Medicine - EISBM, France
Mikael Benson (Deputy Speaker) - Linköping University Hospital, Sweden
Rob Diemel - The Netherlands Organization for Health Research and Development, The Netherlands
David Harrison (Speaker) - University of St. Andrews, United Kingdom
Walter Kolch - University College Dublin, Ireland
Frank Laplace - Federal Ministry of Education and Research, Germany
Francis Lévi - Institut National de la Sante et de la Recherche Medicale, France
Damjana Rozman (Deputy Speaker) - University of Ljubljana, Faculty of Medicine, Slovenia
Johannes Schuchhardt - MicroDiscovery GmbH, Germany
Olaf Wolkenhauer - Dept. of Systems Biology & Bioinformatics University of Rostock, Germany

ADMINISTRATIVE OFFICE (COORDINATION)

Marc Kirschner - Project Management Jülich, Forschungszentrum Jülich GmbH, Germany


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