KTH ROYAL INSTITUTE
OF TECHNOLOGY

Frontiers in Life Science Technology

Technologies for ageing and well-being

Time: 2015-12-03, 12:00-20:00

Place: Lecture Hall F1, KTH - Royal Institute of Technology, Stockholm, Sweden

Organizer: KTH Life Science Technology (LST) platform

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Technologies for ageing and well-being

Preliminary Program

12:00-12:10: Welcome

12:10-13:00: **Michael Miller**, Johns Hopkins University, *Computational Anatomy and Diffeomorphometry: 100 Years Since D'Arcy Thompson*
13:00-13:20: **Michael Malkoch**, KTH CHE, *Engineering Biomedical Patches for Bone Fracture Fixation Applications*
13:20-13:40: **Ina Schuppe Koistinen**, KTH BIO, *Swedish CArdioPulmonary bioImage Study (SCAPIS) Wellness Profiling*
13:40-14:00 **Wojciech Chacholski**, KTH SCI, Geometry of Data
14:00-14:20: **Wouter van der Wijngaart**, KTH EE, *Medical Microfluidic Technologies*
14:20-14:40: **Arvind Kumar**, KTH CSC, *And control will set you free: Future brain stimulation technology for changing the disease related brain activity*

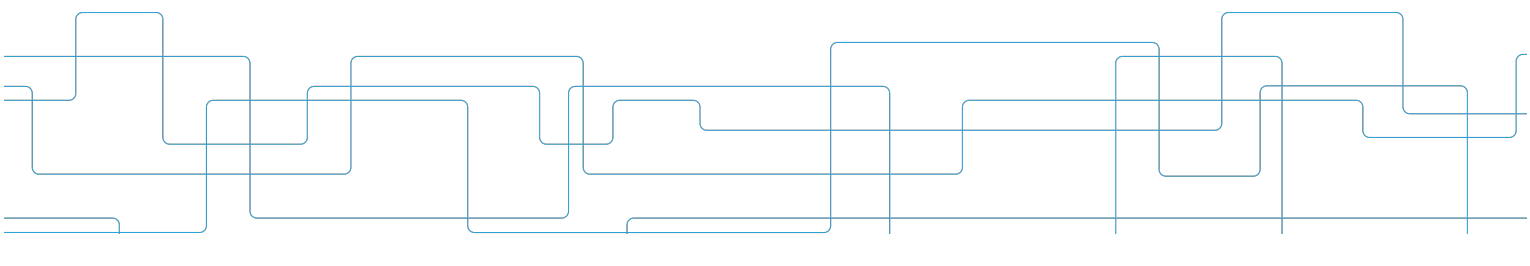
14:40-15:15: Coffee break & poster session

15:15-15:45: **Bodil Lidström**, Swedish eHealth Agency, *Possibilities and challenges for the elderly in the Digital world*
15:45-16:05: **Hedvig Kjellström**, KTH CSC, *To interact with robots in human environments*
16:05-16:25: **Britt Östlund**, KTH STH, *Why ageing is innovative!*
16:25-16:45: **Mario Romero**, KTH CSC, *Mixed-Reality Technology and Whole-Body Interaction for Active Lifestyles*

16:45-17:15: Coffee break & poster session

17:15-18:00: **Henrik Hautop Lund**, Technical University of Denmark, *Playful Prevention and Rehabilitation for Active Ageing - Effective games for health for the elderly*
18:00-18:10: Concluding remarks

18:10-20:00: Mingle and buffet dinner



Abstracts for Invited Speakers

Computational Anatomy and Diffeomorphometry: 100 Years Since D'Arcy Thompson

Michael Miller,

Johns Hopkins University

I will discuss the Computational Anatomy project, focussing on the metric construction of anatomical shape and form via diffeomorphic flow. The Euler-Lagrange equations for geodesics are discussed for shooting submanifolds: landmarks, surfaces and volumes. Shape momentum is derived along with statistical parametric models for encoding variations of human neuroanatomy. The spatial and temporal phenotypes of circuit neurodegeneration in Huntington and Alzheimer's disease based on 3T and high-field MRI will be described.

Possibilities and challenges for the elderly in the Digital world

Bodil Lidström

Swedish eHealth Agency

The elderly population is increasing, more vulnerable to illness and drug treatment and has a higher rate of hospitalization. At the same time the digital world is all around us and how can that be an advantage to the elderly population when it concerns health? The eHealth Agency is responsible for providing register and secures information to health care and pharmacies for the process of prescribing, collecting drug data and provides reports on drug sale and making a decision support system available to pharmacies for increased patient safety and better drug use. The development of digital information and tools can make elderly and relatives/caregiver more involved in the knowledgeable about the health of the elderly person. One challenge is to make laws and development synchronized another one is to make tools user friendly for the elderly

Playful Prevention and Rehabilitation for Active Ageing – Effective games for health for the elderly

Henrik Hautop Lund

Technical University of Denmark

Imagine a world where your play and playful creativity helps solving problems that we face in our daily lives in a globalized society. Play is life, a fundamental right and ability that fosters creativity, not only for children but also for elderly citizens. Though society has often viewed play as a childish and frivolous activity, we all engage in play over our entire lifespan, and engage in such play activities in which we forget about time and place just for the enjoyment and pleasure of play itself. The play activity provides life fulfilling enjoyment and meaning to the player. Play is, for everybody, a fundamental activity submitted to free will. In the act of playing, we manage our lives at our own choice, as we create the special form of lived life outside the "regular" life where (lust for) life and happiness as the essence of play rules.

With recent technology development, we become able to exploit robotics and modern artificial intelligence (AI) to create playware in the form of intelligent hardware and software that creates play and playful experiences for users of all ages. Such playware technology acts as a play force which inspires and motivates you to enter into a play dynamics, in which you forget about time and place, and simultaneously become highly creative and increase your skills - cognitive, physical, and social skills. The Playware ABC concept will allow you to develop life-changing solutions for anybody, anywhere, anytime through building bodies and brains to allow people to construct, combine and create.

As an example, the modular interactive tiles, Moto tiles, were developed as an alternative form of physical prevention and rehabilitation exercise to allow elderly to break away from monotonous treatment programs, and participate in an exercise that is fun and exciting, and therefore more motivating. The modular tiles can light up in different colors and can perceive the pressure when people press them with their hands or jump on them with their feet. Numerous games (exercises) are running on the tiles, and these games aim at providing high motivation for people to engage physically with the tiles. Therapists use the tiles to provide treatment for a large number of patients who receive hospital, municipality or home care, as well as for prevention and fitness training with elderly (e.g. balancing training as fall prevention). In Northern Europe, the modular tiles have been tested with cardiac patients, COPD patients and stroke patients in hospitals, rehab centres, elderly activity centers and in the private homes of elderly, and in rehabilitation of stroke patients in urban and rural Africa, e.g. for community-based rehabilitation. Scientific studies show that playing with the modular tiles has a large effect on the functional abilities of the elderly. The tests of effect show that training with the modular tiles provides improvements on a broad range of abilities including mobility, agility, balancing, strength and endurance. The playful training improves the abilities of the elderly in many areas of high importance for activities of daily living, in contrast to several other forms of training and exercise, which typically only improve a subpart of these abilities. It is shown that playful training can give significant effects with substantially less training sessions than what is needed with traditional training.

Videos: http://www.e-robot.dk/documentation.html
Effect study: http://online.liebertpub.com/doi/abs/10.1089/g4h.2014.0028
Web: http://www.mototiles.com

Abstracts for KTH Speakers

Engineering Biomedical Patches for Bone Fracture Fixation Applications

Michael Malkoch, KTH, School of Chemical Science and Engineering

Injuries are a permanent reminder that our human body is brittle by nature. Injuries range from simple skin tissue damage that can self-heal to more severe cases such as bone fractures. For the latter, those that are not disturbed during repair usually take about 12 weeks to heal. During this period the fractured bone gradually increases in strength. Unfortunately, fractured bone is typically defined by irreversible damage of the bone tissue and the local extra cellular matrix (ECM), which is unable to heal without medical intervention. High-risk groups include active children, athletes, individuals with chronic or cancer diseases and the elderly. Taking the growing population, especially the elderly, into consideration an increasing number of severe tissue damage cases can be foreseen worldwide.

This presentation will attempt to detail the current research activities in the field of tissue fixations with a special emphasis towards fiber reinforced adhesive patches (FRAPs) for bone fracture stabilization applications, Figure 1.

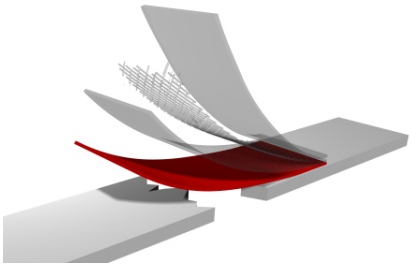


Figure 1. FRAP Methodologyology

Swedish CArdioPulmonary bioImage Study (SCAPIS) Wellness Profiling

Ina Schuppe Koistinen, Göran Bergström, Mathias Uhlén

In 2012, SCAPIS started at Sahlgrenska University Hospital and the University of Gothenburg in collaboration with the Swedish Heart-Lung foundation with the overall aim to improve early discovery and treatment of possible cardiovascular and lung disease. In total, 30 000 individuals between the age of 50 to 64 years undergo a very thorough health examination including imaging of the heart, blood vessels and lungs. The SCAPIS trial is designed as a prospective population study with a comprehensive base-line examination and follow up via registry data. However, the design has limitations since the time between data collection and development of clinical events can be long and a number of environmental exposures will change and make it difficult to study associations with disease. In SCAPIS Wellness Profiling we aim to overcome this limitation by performing continuous monitoring of biomarkers after the initial base-line examination.

The primary goal of the SCAPIS Wellness Profiling study is to develop a system for early detection of disease using continuous monitoring of critical biological parameters. To achieve this we will follow SCAPIS participants longitudinally after their baseline examination with frequent, repeated analyses of molecular markers in blood, urine and stool in combination with physical measurements and continuous monitoring of biological signals like sleep and activity. In the ongoing pilot study with approximately 100 individuals, we will first test the feasibility of the study procedure, develop the SCAPIS Wellness Profiling biobank and explore bioinformatics approaches for systems biology data integration. Proteomics (affinity proteomics, PEA, QPrEST), immunology (CyTOF), genetic (whole genome sequencing, RNA sequencing), metabolomics (plasma/urine) and microbiome analyses (16s RNA) will be used to understand the normal variation of molecular profiles in healthy individuals over time with the goal to facilitate a molecular definition of health.

Geometry of Data

Wojciech Chacholski, School of Engineering Sciences, KTH

Because of progress in technology and growing access to information more and more data (both numerical and categorical) is being collected. We face more and more situations in which standard methods of data analysis are no longer informative enough. For such data sets one approach is to use geometry. In this talk I will illustrate on several examples how topology is used for preprocessing and visualisation. I will also mention what mathematical problems arise in this context.

Medical Microfluidic Technologie

Wouter van der Wijngaart, School of Electrical Engineering, KTH

The talk will show some of our latest developments within micro- and nanosystems for medical diagnostics and therapy. Three specific examples will be described: a point-of-care sensing technology for the detection of Influenza directly from patient breath, using electrostatic aerosol droplet precipitation in combination with a digital ELISA assay; implantable microscale pharmaceutical factories for localized chemotherapy, based on polymer bead encapsulated genetically modified cells; and microfluidic synthetic paper, a new porous substrate material for enabling higher sensitive dipstick diagnostic tests.

And control will set you free: Future brain stimulation technology for changing the disease related brain activity

Arvind Kumar, School of Computer Science and Communication, KTH

Independent of their genetic, biochemical, and/or pyhsiological origins, behavioural symptoms of many brain disease (such as Epilepsy, Parkinson's disease, schizophrenia) are causally associated with changes in the electrical activity of the brain. When the disease-related activity is restored to normal levels, symptoms of the disease are also alleviated. This is best observed in the case of Parkinson's disease, for which deep brain stimulation (DBS) has become an established therapeutic intervention.

The success of DBS in PD suggests that by carefully controlling the brain activity dynamics, symptoms of a number other brain diseases could also be alleviated. However, most conventional methods to change/control the brain activity dynamics are very crude. Not only that the brain stimulation parameters have be determined heuristically, but these parameters also have to be adjusted regularly for optimal performance. Moreover, these stimulations systems overstimulate the brain and often result in undesired side-effects. That is, we are not really exploring the full potential of brain stimulation paradigms.

I will describe recent progress in mathematical modelling the brain network activity and how it can be used to devise more effective brain stimulation protocols. Specifically, I will describe a closed-loop stimulation strategy that uses minimal stimulation to not only change the brain activity state to normal levels but also recovers the network computations lost due to the disease condition. This closed-loop stimulation removes many manual fine tuning steps. But the future is more promising — we are developing mathematical models to devise stimulation protocols that 'shape the brain networks' and thereby remove the need for the external controllers to recover the healthy state of the brain activity.

To interact with robots in human environments

Hedvig Kjellström, School of Computer Science and Communication, KTH

I will talk about our research in human-robot interaction. We study the modeling and perception of human kinematics for human-robot interaction. This incorporates to develop algorithms to model humans with the same representation models as robots, and to measure the kinematic parameters through physical interaction. We also do research about social robotics, *i.e.*, robots that can collaborate with humans in human environments, and also function as interaction partners and mediate tele-interaction with other humans.

Why Ageing is Innovative!

Britt Östlund, School of Technology and Health, KTH

Increasing older populations are the most profound social change of our time. Usually we see them as receivers of our technological solutions or as test persons in research. But what with the older people as resources for innovation? The presenter has more than 25 years of experience of developing technology and design for and with older people. She will point out the main challenges of aging in our time, why technology is highly relevant to meet their needs and demands and why they are innovative.

Mixed-Reality Technology and Whole-Body Interaction for Active Lifestyles

Mario Romero, School of Computer Science and Communication, KTH

Recent advancements in mixed-reality commercial technology including the Oculus Rift, Google Cardboard, Google Tango, and Microsoft Hololens explore whole-body immersive interaction with virtual environments in novel and exciting ways. Many of these technologies are new and have not been tested for their long-term impact on the human body and mind. In this talk I will present the state-of-the-art landscape in mixed-reality whole-body interaction through a survey of the field and through a number of projects at KTH. I will conclude with a number of concrete opportunities to collaborate across disciplines to understand the long-term positive and negative impacts of these new technologies.

Abstracts for Poster Presentations

1. Development Of Perfusion Process For Pluripotent Cells In Electrospun Scaffold-Based Mini-Bioreactor Suitable For Cell-Based Therapy

Mattias Leino[1], Husnah Hussein[1], Carolina Åstrand[1], Atefeh Shokri[1], Otto Pintor Galego[1], Lubna Al-Khalili[1], Ye Zhang[1], Brendan Robb[2], Nanayaa Bates[2], Rob McKean[2], Per Stobbe[3], Christian Krause[4], Veronique Chotteau[1]
[1]School of Biotechnology, KTH; [2]The Electrospinning Company Ltd, Harwell Oxford, UK;[3]Stobbe Tech A/S, Holte, Denmark; [4]Presens Precision, Regensburg, Germany

Today's research in stem cell-based therapy focuses on identifying the appropriate cells with the targeted properties of biological efficacy, differentiation, phenotype and safety. Many methods for expanding stem cells and protocols to direct differentiation rely on static culture protocols in tissue culture plates. This is usually labour intensive, inefficient and, importantly, lacking reproducibility. To meet the demand of health care addressing life-threatening diseases by cell therapy, new methods and equipment to increase the manufacturing capability of these cells under controlled conditions are urgently needed. Our goal is to create a new perfusion bioreactor supporting cultivation of human stem cells adhering to electrospun nanofiber scaffolds of biocompatible and biodegradable polymers. In the present study, we aim to first establish a robust culture protocol for maintaining and differentiating pluripotent stem cells on scaffolds under static conditions then apply this to our scale-down mini-bioreactors. Thus far we show that pluripotent stem cells readily proliferate in our scaffolds while maintaining their pluripotency. By applying a Dual SMAD neural differentiation protocol to hiPS grown on scaffolds we could detect an induction of the neural progenitor marker Pax6 indicating that the scaffolds can support differentiation into neural lineages.

2. Long-Term Storage Of Nanolitre And Picolitre Liquid Volumes In Polymer Microfluidic Devices

Maoxiang Guo, School Of Electrical Engineering, KTH

We introduce uncomplicated nanolitre (23 nL) and picolitre (3.5 pL) liquid volume encapsulation in Off-Stoichiometry Thiol-Ene-Epoxy polymer (OSTEmer™322) wells using spontaneous room-temperature bonding of gold films to thiol and thioether groups present on the surface of the polymer for leak free sealing. Liquid encapsulation and storage on microsystems has been previously demonstrated in the μL range. However, the problem that suffers from liquid loss over time [1] has been emerged. Hence only metallic sealing materials should be considered for long-term storage.
Here we perform a transfer-bonding of a 100 nm thin Au-film from an oxidized Si handle-wafer to liquid-filled pL- and nL-well arrays in an intermediately cured OSTEmer™322 substrate. Au and OSTEmer™322 bonded spontaneously. nL-wells can be filled by pipetting, whereas transfer bonding of Au on top of pL-wells is performed during liquid submersion of the substrate [2] to avoid evaporation. The proposed method of liquid encapsulation could potentially be applied to long-term pre-store of liquid in bio-arrays of nL/pL-wells of OSTEmer™322 polymer.

Reference
[1] C.A. Gutierrez, and E. Meng, Micromachines, 2, 356-268, 2011.
[2] Y. Okayama et al., J. Micromech. Microeng. 20, 095018, 2010.

3. Gold nanoparticle PCR for rapid and enhanced DNA detection in a vertical flow assay

Lara Lama, Jorge Dias, Lourdes Rivas, Jesper Gantelius and Helene Andersson Svahn
School of Biotechnology, KTH

Bacterial meningitis is a disease associated with high mortality within the first 24-48 h after the onset of symptoms. When analysing patient samples for bacterial diseases, a polymerase chain reaction (PCR) can be used to amplify a specific common part of the bacterial DNA for detection. The DNA strand used in this work is a part of

Neisseria meningiditis, which can be used to diagnose patients with bacterial meningitis.

In order to improve the limit of detection and shorten the assay time the PCR primers are modified with gold nanoparticles (AuNPs) and used to amplify the target DNA. An advantage of the AuNPs is that it is possible to minimize non-specific interactions using ultrasound probe sonication. Ultrasonication yields large enough forces upon the AuNPs to separate them thus giving a higher number of target DNA-AuNPs that can hybridize with a printed capture DNA strand. A capture DNA strand complementary to the target DNA is printed on a porous nitrocellulose membrane. By applying the target DNAAuNPs in a vertical flow setup it is possible achieve a colorimetric detection with the advantage of the characteristics of the AuNPs [1]. The colorimetric detection along with the vertical flow setup gives a possibility for detection within a few minutes and can additionally be used in low resource facilities.

[1] Chinnasamy, Thiruppathiraja, et al. "Point-of-care vertical flow allergen microarray assay: proof of concept." Clinical chemistry 60.9 (2014): 1209-1216

4. Mechanisms of fluorescence decays of colloidal CdSe-CdS/ZnS quantum dots unraveled by time-resolved fluorescence measurement

Hao Xu, Volodymyr Chmyrov, Jerker Widengren, Hjalmar Brismar and Ying Fu
School of Engineering Sciences, KTH

Colloidal quantum dots (QDs) have been extensively studied [1-2], developed and utilized for many applications in many fields including biomedicine and optoelectronics. Extensive reviews about various aspects of QDs can be found readily in the literature. Though the fundamental photophysics behind the superb and unique optical properties of these QDs is well understood, a quantitative match between theory and experiment is limited. One major issue is about the time-resolved fluorescence decay spectrum.
By narrowing the detection bandpass and increasing the signal-to-noise ratio in measuring the time-resolved fluorescence decay spectrum of colloidal CdSe–CdS/ZnS quantum dots (QDs), we show that directly after the photoexcitation, the fluorescence decay spectrum is characterized by a single exponential decay, which represents the energy relaxation of the photogenerated exciton from its initial high-energy state to the ground exciton state. The fluorescence decay spectrum of long decay time is in the form of b/t^2 , where b is the radiative recombination time of the ground-state exciton and t is the decay time. Our findings provide us with a direct and quantitative link between fluorescence decay measurement data and fundamental photophysics of QD exciton, thereby leading to a novel way of applying colloidal QDs to study microscopic, physical and chemical processes in many fields including biomedicine.

Reference:
O. Chen, J. Zhao, V. P. Chauhan, J. Cui, C. Wong, D. K. Harris, H. Wei, H. S. Han, D. Fukumura, R. K. Jain and M. G. Bawendi, Nat. Mater., 2013, 12, 445–451
L. Li, Y. Chen, G. Tian, V. Akpe, H. Xu, L. M. Gan, S. Skrtic, Y. Luo, H. Brismar and Y. Fu, J. Phys. Chem. C, 2014, 118, 10424–10433

5. Software Tool for Fetal Heart Rate Signal Analysis

Ke Lu[1*], Farhad Abtahi[1], Lennart Nordström[2], Pelle Lindqvist[3] and Kaj Lindecrantz[1, 3]
[1]School of technology and health, KTH; [2]Department of Women's and Children's Health, Karolinska Institute; [3]Department of Clinical Science, Intervention and Technology (CLINTEC), Karolinska Institute

Cardiotocography (CTG) is the most common method for assessment of fetal wellbeing during labor. It is based on recording and analysis of fetal heart rate (FHR) and uterine contraction signals. Proper FHR trace is an indicator of sufficient oxygen supply and normal control functionality of central nervous system. Hence, the FHR analysis is an essential diagnose method for early detection of complications during labor and potential need for interventions. A software tool is developed to extract several interested features of FHR traces for evaluating the ability of different types of analysis to predict hypoxia risks. The software can process CTG traces extracted from Milou system, *MEDEXA Diagnostisk Service AB*. The system used at Karolinska University Hospitals includes 40,000 recordings from deliveries with extensive outcome variables e.g. lactate concentration, pH, Apgar score, neonatal death. General features, acceleration and deceleration features and variation features can be extracted by the tool with novel methods. The extracted features will be compared with outcome variables to seek for correlations. Current focus is on studies of the variation and deceleration trends in selected cases with increased lactate level in serial scalp blood sampling.

6. How do persons with Mild Acquired Cognitive Impairment use e-services and social media? Results from a Swedish national survey

Aboozar Eghdam, MSc[1], Aniko Bartfai, PhD[2], Christian Oldenburg, MSc[2], Sabine Koch, PhD[1]
[1]Health Informatics Centre (HIC), Department of Learning, Informatics, Management and Ethics (LIME), Karolinska Institutet; [2]Division of Rehabilitation Medicine, Department of Clinical Sciences Danderyds Hospital, Karolinska Institutet,

Mild acquired cognitive impairment (MACI) is a term used to describe a sub-group of persons with mild/moderate cognitive impairment who are expected to reach a stable cognitive level over time. Persons with MACI can have multiple cognitive and/or mild physical disabilities and need rehabilitation to improve their lost skills. One tactic that can be considered for further developing treatment of MACI is the use of Information and communication technology (ICT) and e-services. The main channel to receive and use e-services ubiquitously as a technology-based self-services is the Internet. Previously we have conducted and analyzed the identified tools using an analytical framework based on and a sub-set of common and important problems created by MACI experts in Sweden. A systematic literature review about available assistive ICT tools for

persons with MACI indicated a lack of knowledge about how they use existing technology today in addition to absence of evidence about which self-regulating tools support them in their life. The purpose of the current study was to investigate which e-services persons with MACI use and to analyze their attitudes towards supporting technology in general.

The principal method of data collection was a postal self-administered survey which was created in Swedish language and validated through MACI experts in Sweden based on categories of the International Classification of Functioning, Disability and Health (ICF). The paper based questionnaire mostly included close-endedquestions regarding the participants' demographic information and experience with e-services. To estimate the degree and type of impairments, the Cognitive Failure Questionnaire (CFQ) was added, measuring cognitive difficulties in performance of everyday tasks. The CFQ scores range from 0 to 100 (mild to severe). Two pilot tests were conducted with persons with MACI to measure the performance time and comprehensibility of the questions. Moreover, the questionnaire was approved by the Swedish Brain Injury Association (Hjärnkraft), to be sent as a postal survey to 600 members anonymously and randomly in Sweden.

During the enrolment period (June 2014/January 2015), 397 out of 600 persons (66%) replied to the invitation and 282 (47%) were interested and able to participate in the survey. Considering the estimated population size (about 70000 registered annually), the confidence level for this study was about 90% based on "The OpenEpi Collection of Epidemiologic Calculators". Firstly, a descriptive analysis was performed to understand the study population and determine normality within the subject data gathered from multiple choice and close-ended questions. Secondly, a qualitative content analysis approach was used to analyze the data collected from a few open-ended questions regarding the participants' positive and negative sentiments toward using e-services. Based on the respondents' CFQ scores (mean = 45 ± 18), they were suffering from mild/moderate cognitive impairments which acquired mostly from traumatic brain injuries. In addition to cognitive failure levels and demographic information, the results revealed numerous statistical data about use of e-services followed by their purpose of use, limitation and difficulties while being used by persons with MACI. Considering the responses, the majority (89%) were interested in using e-services in different categories and the most popular and essential category for the respondents was communication services and social media (59%). The analysis is still ongoing to find a relation between the cognitive failure level and use of e-services in addition to the participants' attitudes toward using e-service and social media.

This study is the first of its own kind to show persons with MACI use of e-services. So far, the results of this survey demonstrated that the majority of persons with MACI have a positive attitude towards using e-services to achieve a more self-regulating life and most likely would be able to use the e-services on their own. The results showed that areas such as banking and social interaction services are the most important aspects of this technology for this group. However, further studies are needed on utilizing these identified aspects for this group to support them with their chronic condition.

References

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Meijer W, Ragetlie P. Empowering the Patient with ICT-tools: The Unfulfilled Promise. The Journal on Information Technology in Healthcare. 2007;5(5):313-23.
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Eghdam A, Scholl J, Bartfai A, Koch S. Information and communication technology to support self-management of patients with mild acquired cognitive impairments: systematic review. Journal of medical Internet research. 2012;14(6).
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Broadbent DE, Cooper PF, FitzGerald P, Parkes KR. The cognitive failures questionnaire (CFQ) and its correlates. British Journal of Clinical Psychology. 1982;21(1):1-16.

7. MaRaCluster: A Fragment Rarity Metric for Clustering Fragment Spectra in Shotgun Proteomics

Matthew The, Lukas Käll
School of Biotechnology, KTH

Shotgun proteomics experiments generate large amounts of fragment spectra as primary data, normally with high redundancy between and within experiments. Here, we have devised a clustering technique to identify fragment spectra stemming from the same species of peptide. This is a powerful alternative method to traditional search engines for analyzing spectra, specifically useful for larger scale mass spectrometry studies. As an aid in this process, we propose a distance calculation relying on the rarity of experimental fragment peaks, following the intuition that peaks shared by only a few spectra offer more evidence than peaks shared by a large number of spectra. We used this distance calculation and a complete-linkage scheme to cluster data from a recent large scale mass spectrometry-based study. The clusterings produced by our method have up to 40% more identified peptides for their consensus spectra compared to the previous state-of-the-art method. We see that our method would advance the construction of spectral libraries, as well as serving as a tool for mining large sets of fragment spectra. The source code and Ubuntu binary packages are available from https://github.com/statisticalbiotechnology/maracluster, under Apache 2.0 license.

8. Identification of protein markers for cellular proliferation using a cell model for malignant transformation

Lovisa Åkesson, Frida Danielsson, Emma Lundberg
School of Biotechnology, KTH

Increased proliferation ability is one of several traits cancer cells acquire during development into malignant tumor-forming cells.1 The use of protein proliferation markers in cancer prognostics could hence give access to valuable information about the invasiveness and treatability of various types of cancer. In this study, an attempt to identify novel proliferation markers using an isogenic four-stage cell model for cancer malignancy was made. Based on data from RNA sequencing of these cells2, 200

differentially expressed genes were immunostained to identify proteins showing an increased expression in cells with a high proliferation activity. Image analysis of the stainings revealed over 100 upregulated proteins and among these, three distinct expression patterns could be observed; increased expression in all metastasizing cells, expression in a greater number of malignant cells or translocations between the two cell lines. The 22 most promising proteins were selected based on the expression profiles, and they are to be further evaluated by cell cycle dependency experiments together with IHC of cancerous tissue to reveal which ones that potentially could serve as a proliferation marker in the future.

1 Hanahan D, Weinberg R a, Francisco S. The Hallmarks of Cancer. Cell. 2000;100:57–70.
2 Danielsson F, et al. Majority of differentially expressed genes are down-regulated during malignant transformation in a four-stage model. Proc Natl Acad Sci U S A. 2013;110(17):6853–8.

9. Scalable detection of multiple poultry pathogens by droplet microfluidics

Prem Kumar Periyannan Rajeswari, Lovisa Söderberg, Haakan N. Joensson, Helene Andersson Svahn
School of Biotechnology, KTH

We report the development of an integrated droplet microfluidics platform for sensitive and multiplex detection of genetic biomarkers associated with common poultry pathogens using Luminex xMAP technology. The integration of xMAP microsphere technology with droplet microfluidics will enable highly multiplex detection of nucleic acid biomarkers by using distinct fluorescent-coded beads with unique capture probes to capture the target DNA. It will also enable detection of low prevalent targets in the sample, since, compartmentalization of single DNA fragments in individual droplets enables droplet PCR to overcome preferential amplification biases of traditional PCR amplification techniques.

In the present study, a multi-parallel droplet PCR amplification approach is used for detection of some of the most common poultry pathogens: avian influenza virus (AIV), Newcastle disease virus (NDV), infectious laryngotracheitis virus (ILTV), *Campylobacter* and *Salmonella*. The system is highly sensitive and even at low target concentration (33 pM), the hybridization signal could be clearly detected in the Luminex instrument. Currently, the multi-parallel droplet PCR assay for detection of AIV and NDV DNA biomarker is being optimized. In future, ILTV, salmonella and campylobacter targets will be added to the detection panel. The presented technique could be potentially used for detecting broad range of pathogens and it could be easily scaled up to add new targets to the detection panel.

10. A Printer-Free, Vertical Flow Based, Colorimetric Planar Bead Array for Point of Care Applications

Gustav Svedberg, Jesper Gantelius and Helene Andersson Svahn
School of Biotechnology, KTH

Massively multiplexed protein arrays are difficult to produce at present because individually printing tens of thousands of proteins is very time consuming. To address this issue, we present a novel planar bead array setup that allows for rapid production of highly multiplexed protein arrays that can be run and analysed quickly and with low equipment requirements for use in a point of care setting.

Populations of thiolated 100 µm silica beads are fluorescently barcoded by surface coating with different concentrations of 5 fluorophores. Each population is then coated with a different antibody. All the bead populations are mixed together, deposited in a single step on a microperforated adhesive tape membrane and fluorescently imaged. The end user flows sample and a colorimetric detection reagent through the membrane using a syringe pump. The detection reagent turns the beads red if they have bound their target and this signal can be detected using a USB microscope.

Clear signal has been achieved at protein concentrations down to 100 ng/ml.

Because the bead coating reactions can all be done in parallel, massively multiplexed arrays can be produced using this method that would take prohibitively long to produce using conventional array printing methods. Additionally, the low equipment requirements and rapid assay run time means the assay can bring this multiplexing potential to the point of care or low resource settings.

11. A rapid paper-based reverse phase vertical flow serum microarray for screening of 900 samples simultaneously

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Reverse phase microarrays are useful tools for affinity-based detection in hundreds of samples simultaneously. However, current methods typically require long assay times and fluorescent detection. Here we describe a paper-based Vertical Flow Microarray (VFM) assay as a rapid 2-minute colorimetric alternative for reverse phase microarray analysis. The VFM platform was optimized for detection of IgE giving a detection limit of 1.9 µg/mL in whole serum. Optimized conditions were then used to screen 113 serum samples simultaneously for hyper IgE syndrome (hIgE), a rare primary immunodeficiency characterized by elevated levels of IgE. The same subset of samples were then analysed with a conventional planar nitrocellulose microarray with fluorescent detection for head-to-head testing. Both assays found elevated levels in three out of four patients and no control samples showed elevated levels of IgE. The comparative experiments showed a very good correlation between the two assays, as determined from a linear correlation study (Pearson's r=0.76), however the conventional assay

time was two and half hour compared to the 2-minute VFM assay. Similar performance, assay-time reduction and reproducibility (CV = 13%) thereby demonstrating the applicability of the VFM platform for high throughput reverse phase screening in 880 samples.

12. Computationally Guided Drug Discovery of Ligand-Gated Ion Channel Family

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Ligand-gated ion channels (LGICs) convert chemical signal into ion fluxes through plasma membranes. They are important drug targets including anesthetics and benzodiazepines. However the gating mechanism of these channels is not well understood. A well-defined gating mechanism will enable "targeted design" for neurological diseases associated with LGICs. Computational predictions of gating pathways rely on high-resolution structural data. Within the last 5 years numerous structures of different LGICs were published in several different conformations. However which state (open, close or desensitized) these structures represent is not clear.
We present here a principal component analysis (PCA) of the high-resolution structure ensemble of LGICs. Using PCA we wereable to assign crystal structures to probable states. In addition we were able to predict a probable gating mechanism. Using several microsecond long molecular dynamics simulations we are currently sampling the principal component space and analyzing the gating motions. The fully explored gating path will then be used to assess the druggability. This ensemble study will serve as a guide to future drug discovery studies on LGICs.

13. An engineered affibody molecule with pH-dependent binding to FcRn mediates extended circulatory half-life of a fusion protein

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One of the central questions in biopharmaceutical development is how to extend circulation residence time of protein-based drugs to improve afficacy and patient comfort. Human serum albumin (HSA) and IgG are two proteins with naturally long serum half-life due to FcRn-mediated rescue from degradation in cells in contact with blood. Here, we describe development and characterization of affibody molecules that can hitchhike on the FcRn rescue system. We find that fusion of the generated FcRn-bind affibody molecules to a model protein, already engineered for increased half-life by inclusion of an albumin binding domain, leads to a close to 200% further increase in circulation residence time in mice. Such affibody may have general usage as fusion partners to biopharmaceuticals for extending their circulation residence times.

14. Tuning microfluidic cell culture conditions for droplet based screening by metabolite profiling

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We investigate the impact of droplet culture conditions on cell metabolic state by determining key metabolite concentrations in *S. cerevisiae* cultures in different microfluidic droplet culture formats. Control of culture conditions is critical for single cell or single clone screening in droplets, such as directed evolution of yeast, as cell metabolic state directly affects production yields from cell factories. Here we analyze glucose, pyruvate, ethanol and glycerol, central metabolites in yeast glucose dissimilation to establish culture formats for screening of respiring as well as fermenting yeast. Metabolite profiling provides a more nuanced estimate of cell state compared to proliferation studies alone. We show that the choice of droplet incubation format impacts cell proliferation and metabolite production. The standard syringe incubation of droplets exhibited metabolite profiles similar to oxygen limited cultures whereas the metabolite profiles of cells cultured in the alternative wide tube droplet incubation format resemble those from aerobic culture. Furthermore, we demonstrate retained droplet stability and size in the new better oxygenated droplet incubation format.

15. Augmented Reality (AR) in Health Care Education : Current focus rational use of antibiotics, potential use physical activity in patients with dementia

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AR combines computer-generated information with the real physical environment through an interface to provide a powerful, contextual and situated-learning experience. AR has the following characteristics: (1) Provides users with an authentic and situated experience, when connected with the surrounding real-world environment; (2) Enhances the physical environment around users with virtual information that becomes interactive and digital; and (3) Shows users an indirect view of their surroundings and enhances users' senses through virtual information.

AR in health care education
Within health care education, AR has been used across a range of subject such as: laparoscopic surgery (Botden, Hingh, & Jakimowicz, 2009; Leblanc et al., 2010; Volonté et al., 2011), forensic medicine (Albrecht et al., 2014), inguinal canal anatomy (Sakellariou, Ward, Charissis, Chanock, & Anderson, 2009), disease outbreak (Rosenbaum, Klopfer, & Perry, 2007), clinical breast examination (Kotranza, Lind, & Lok, 2012), cardiologic data (Lamounier, Bucioli, Cardoso, Andrade, & Soares, 2010), and life support training (Pretto, Manssour, Lopes, Silva, & Pinho, 2009). The research is broad covering user acceptance, system development and testing, to studying learning effects. In our pre-integrative review, we found that most papers claimed that AR is of value in learning in the health care field. However, few papers mentioned using a learning theory to guide the design or application of AR for health care education. Instead, the traditional learning strategy, "see one, do one, and teach one," was used to apply the new technology. AR in combination with mobile technology has the potential to transform health care education, yet lacks an effective framework for guiding the design, development, and application of such tools. We have designed a theory-driven framework consisting of three hierarchical layers: the foundation, the function, and the outcome layers. Three learning theories— situated, experiential, and transformative learning — provide foundational support based on differing views of the relationships among learning, practice, and the environment. The function layer depends upon the learners' personal paradigms and indicates how health care learning could be achieved with MARE (Mobile Augmented Reality Education). The outcome layer analyzes different learning abilities, from knowledge to the practice level, to clarify learning objectives and expectations and to avoid teaching pitched at the wrong level. Suggestions for learning activities and the requirements of the learning environment form the foundation for AR to fill the gap between learning outcomes and medical learners' personal paradigms.

Global health threat (1) — increasing prevalence of antibiotic resistance
The growing public health threat of increasing antimicrobial resistance (AMR) is quickly becoming a worldwide problem (WHO, 2014)). The increase in AMR is reducing the efficacy of antimicrobial agents on common infections which become harder to treat and resulting in lethal strains of bacteriua like Staphylococcus aureus (Spellberg et al., 2011). Every year almost 19,000Americans die from an infection by Staphylococcus aureus. Should resistance to antibiotics continue to increase, AMR would result in 10 million people dying every year costing up to 100 trillion USD by 2050 (O'Neill, 2014).

Global health threat (2) – increasing prevalence of dementia
Recent statistics revealed that the estimated worldwide prevalence of dementia will increase from 35.6 million in 2010 to approximately 115.4 million by 2050 more than seventy percent of whom will live in low- and middle-income countries (Alzheimer's Disease International, 2009).

More than 9 million people in China suffer from some form of dementia, the highest in any country (Chan et al., 2013). This is a great challenge in China where the population is rapidly aging in combination with the one-child policy and continued urbanization (WHO, 2011).

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16. Numerical study of hydrodynamics in wave bioreactors

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Culture of mammalian cells in wave bioreactors is nowadays widely used. However, the optimal hydrodynamic operation conditions have not been systematically investigated.

Computation Fluid Dynamics is considered an efficient tool for predicting the fluid behavior. In this study, we perform detailed numerical simulations employing Ansys-FLUENT to characterize the flow conditions in 10L cellbag of a wave bioreactor. In order to study the influence of the rocking motion intensity, we examine three rocking angles and three rocking speeds typical of real applications. The liquid-gas interface and fluid velocity are investigated at different stages during the rocking cycle. We calculate the shear stress from the velocity fields obtained from unsteady numerical simulations. Moreover, we document the spatial variations of the shear stress levels at different operating conditions.

Our detailed results extend the knowledge of shear stress and oxygen transfer in wave bioreactors and guide for selecting favorable hydrodynamic conditions.

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17. Long-range inhibition mediated by Martinotti cells causes surround suppression and promotes saliency in an attractor network model

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Although the importance of long-range connections for cortical information processing has been acknowledged for a long time, most studies focused on the long-range interactions between excitatory cortical neurons. Inhibitory interneurons play an important role in cortical computation and have thus far been studied mainly with respect to their local synaptic interactions within the cortical microcircuitry. A recent study showed that long-range excitatory connections onto Martinotti cells mediate surround suppression. Here we have extended our previously reported attractor network of pyramidal and Martinotti cells by introducing long-range connections targeting Martinotti cells. We have demonstrated how the network with Martinotti cell-mediated long-range inhibition gives rise to surround suppression and also promotes saliency of locations at which simple non-uniformities in the stimulus field are introduced. Furthermore, our analysis suggests that the presynaptic dynamics of Martinotti cells is only ancillary to its orientation tuning property in enabling the network with saliency detection. Lastly, we have also implemented a disinhibitory pathway mediated by another interneuron type (VIP interneurons), which inhibits Martinotti cells and abolishes surround suppression.

18. Tensor voting for inference of orientation information from DTI data

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Among the various diffusion MRI techniques diffusion tensor imaging (DTI) is still most commonly used in clinical practice in order to investigate connectivity and fibre anatomy in the human brain. Besides its apparent advantages of a short acquisition time and noise robustness compared to other techniques, it suffers from its major weakness of assuming a single fibre model in each voxel. This constitutes a problem for DTI fibre tracking algorithms in regions with crossing fibres. Methods approaching this problem in a postprocessing step employ diffusion-like techniques to correct directional information in those regions.

We show an approach based on the perceptual grouping technique tensor voting, which uses the information from single fibre voxels to interpolate orientation distributions in multi fibre voxels. Based on a new way of sampling the employed voting fields and the idea of clustering the received tensor votes, it is possible to resolve multiple fibre orientations in each voxel. To appropriately account for the locality of DTI data, we use a small neighbourhood for distributing information at a time, but apply the algorithm iteratively to ensure closing larger gaps.

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