

ERCIM



NEWS

Special theme:

Digital Health



Editorial Information

ERCIM News is the magazine of ERCIM. Published quarterly, it reports on joint actions of the ERCIM partners, and aims to reflect the contribution made by ERCIM to the European Community in Information Technology and Applied Mathematics. Through short articles and news items, it provides a forum for the exchange of information between the institutes and also with the wider scientific community. This issue has a circulation of about 6,000 printed copies and is also available online.

ERCIM News is published by ERCIM EEIG
BP 93, F-06902 Sophia Antipolis Cedex, France
+33 4 9238 5010, contact@ercim.eu
Director: Philipp Hoschka, ISSN 0926-4981

Contributions

Contributions should be submitted to the local editor of your country

Copyright notice

All authors, as identified in each article, retain copyright of their work. ERCIM News is licensed under a Creative Commons Attribution 4.0 International License (CC-BY).

Advertising

For current advertising rates and conditions, see
<https://ercim-news.ercim.eu/> or contact peter.kunz@ercim.eu

ERCIM News online edition: ercim-news.ercim.eu/

Next issue:

October 2019, Special theme: Smart Things Everywhere

Subscription

Subscribe to ERCIM News by sending an email to en-subscriptions@ercim.eu or by filling out the form at the ERCIM News website: <https://ercim-news.ercim.eu/>

Editorial Board:

Central editor:
Peter Kunz, ERCIM office (peter.kunz@ercim.eu)

Local Editors:

Austria: Erwin Schoitsch (erwin.schoitsch@ait.ac.at)
Cyprus: Georgia Kapitsaki (gkapi@cs.ucy.ac.cy)
France: Christine Azevedo Coste (christine.azevedo@inria.fr)
Germany: Alexander Nouak (alexander.nouak@iuk.fraunhofer.de)
Greece: Lida Harami (lida@ics.forth.gr),
Athanasios Kalogeras (kalogeras@isi.gr)
Hungary: Andras Benczur (benczur@info.ilab.sztaki.hu)
Italy: Maurice ter Beek (maurice.terbeek@isti.cnr.it)
Luxembourg: Thomas Tamisier (thomas.tamisier@list.lu)
Norway: Monica Divitini, (divitini@ntnu.no)
Poland: Hung Son Nguyen (son@mimuw.edu.pl)
Portugal: José Borbinha (jlb@ist.utl.pt)
Sweden: Maria Rudenschöld (maria.rudenschold@ri.se)
Switzerland: Harry Rudin (hrudin@smile.ch)
The Netherlands: Annette Kik (Annette.Kik@cw.nl)
W3C: Marie-Claire Forgue (mcf@w3.org)

Cover illustration: source: Shutterstock.

SPECIAL THEME

The special theme Digital Health has been coordinated by Sara Colantonio (ISTI-CNR) and Nicholas Ayache (Inria)

Introduction to the special theme

4 The Digital Health Revolution

by Sara Colantonio (ISTI-CNR) and Nicholas Ayache (Inria)

6 Machine Learning Applied to Ultrasound Imaging – The Next Step in Democratising Medical Imaging

by Anne-Laure Rousseau (Assistance Publique - Hôpitaux de Paris)

7 Radiomics: How to Make Medical Images Speak?

by Fanny Orhac, Charles Bouveyron and Nicholas Ayache (Université Côte d'Azur, Inria)

9 Interpretable and Reliable Artificial Intelligence

Systems for Brain Diseases
by Olivier Colliot (CNRS)

10 Improving Cardiac Arrhythmia Therapy with Medical Imaging

by Maxime Sermesant (Inria and Université Côte d'Azur)

12 VoxLogicA: a Spatial-Logic Based Tool for Declarative Image Analysis

by Gina Belmonte (AOUS), Vincenzo Ciancia (ISTI-CNR), Diego Latella (ISTI-CNR) and Mieke Massink (ISTI-CNR)

13 New Directions for Recognizing Visual Patterns in Medical Imaging

by Alessia Amelio (University of Calabria, Italy), Lucio Amelio (independent researcher) and Radmila Janković (Mathematical Institute of the S.A.S.A., Serbia)

15 Radiomics to Support Precision Medicine in Oncology

by Sara Colantonio (ISTI-CNR), Andrea Barucci (IFAC-CNR) and Danila Germanese (ISTI-CNR)

16 Deep-Learning Based Analyses of Mammograms to Improve the Estimation of Breast Cancer Risk

by Francesca Lizzi (National Institute for Nuclear Physics, Scuola Normale Superiore, National Research Council, University of Pisa), Maria Evelina Fantacci (National Institute for Nuclear Physics, University of Pisa) and P. Oliva (National Institute for Nuclear Physics, University of Sassari)

18 Content-Based Analysis of Medical Image Data for Augmented Reality Based Health Applications

by Andrea Manno-Kovacs (MTA SZTAKI / PPKE ITK), Csaba Benedek (MTA SZTAKI) and Levente Kovács (MTA SZTAKI)

19 Artificial Intelligence: Understanding Diseases that People Cannot Understand?

by Marleen Balvert and Alexander Schönhuth (CWI)

- 20 The Genetic Diversity of Viruses on a Graphical Map: Discovery of Resistant and Virulent Strains**
by Alexander Schönhuth (CWI and Utrecht University) and Leen Stougie (CWI and VU Amsterdam)
- 22 Improved Antibody Optimisation for Tumour Analysis Through the Combination of Machine Learning with New Molecular Assay**
by Anna Fomitcheva Khartchenko (ETH Zurich, IBM Research – Zurich), Aditya Kashyap and Govind V. Kaigala (IBM Research – Zurich)
- 23 AI Enables Explainable Drug Sensitivity Screenings**
by Matteo Manica, Ali Oskooei, and Jannis Born (IBM Research)
- 25 Combining Predictive and Prescriptive Analytics to Improve Clinical Pathways**
by Christophe Ponsard and Renaud De Landtsheer (CETIC)
- 26 A Holistic Clinical Decision Support System for Diagnosis of Dementia**
by Mark van Gils (VTT)
- 28 Connecting People, Services, and Data for Continuity of Care**
by Fulvio Patara and Enrico Vicario (University of Florence)
- 29 High Quality Phenotypic Data and Machine Learning Beat a Generic Risk Score in the Prediction of Mortality in Acute Coronary Syndrome**
by Kari Antila (VTT), Niku Oksala (Tampere University Hospital) and Jussi A. Hernesniemi (Tampere University)
- 31 Digital Health Interoperability as a Tool Towards Citizen Empowerment**
by Dimitrios G. Katakakis and Angelina Kouroubali (FORTH-ICS)
- 32 Towards VNUMED for Healthcare Research Activities in Vietnam**
by Chau Vo, (Ho Chi Minh City University of Technology, Vietnam National University), Bao Ho (John von Neumann Institute, Vietnam National University) and Hung Son Nguyen, University of Warsaw
- 33 Empowering Distributed Analysis Across Federated Cohort Data Repositories Adhering to FAIR Principles**
by Artur Rocha, José Pedro Ornelas, João Correia Lopes, and Rui Camacho (INESC TEC)
- 35 SmartWork: Supporting Active and Healthy Ageing at Work for Office Workers**
by Otilia Kocsis, Nikos Fakotakis and Konstantinos Moustakas (University of Patras)

- 37 WellCo: Wellbeing and Health Virtual Coach**
by Vlad Manea (University of Copenhagen) and Katarzyna Wac (University of Copenhagen and University of Geneva)
- 39 A Personalisation Platform for Older Adults with Mild Cognitive Impairments**
by Marco Manca, Parvaneh Parvin, Fabio Paternò, Carmen Santoro and Eleonora Zedda (ISTI-CNR)
- 40 Technological Memory Aids for Neurodegenerative Diseases and the AuDi-o-Mentia Approach**
by Eleni Boumpa and Athanasios Kakarountas (University of Thessaly)
- 42 PAPAAYA: A Platform for Privacy Preserving Data Analytics**
by Eleonora Ciceri (MediaClinics Italia), Marco Mosconi (MediaClinics Italia), Melek Önen (EURECOM) and Orhan Ermis (EURECOM)
- 43 Resilient Network services for Critical mHealth Applications over 5G Mobile Network Technologies**
by Emmanouil G. Spanakis and Vangelis Sakkalis (FORTH-ICS)

RESEARCH AND INNOVATION

This section features news about research activities and innovative developments from European research institutes

- 46 A Contractarian Ethical Framework for Developing Autonomous Vehicles**
by Mihály Héder (MTA SZTAKI)
- 48 A Language for Graphs of Interlinked Arguments**
by Dimitra Zografistou, Giorgos Flouris, Theodore Patkos, and Dimitris Plexousakis (ICS-FORTH)
- 49 Distortion in Real-World Analytic Processes**
by Peter Kieseberg (St. Pölten University of Applied Sciences), Lukas Klausner (St. Pölten University of Applied Sciences) and Andreas Holzinger (Medical University Graz).

ANNOUNCEMENTS, IN BRIEF

- 45 ERCIM “Alain Bensoussan Fellowship Programme**
- 50 GATEKEEPER - Smart Living Homes for People at Health and Social Risks**
- 51 HORIZON 2020 Project Management**
- 51 In Memory of Cor Baayen**
- 51 Dagstuhl Seminars and Perspectives Workshops**

Introduction to the Special Theme

The Digital Health Revolution

by Sara Colantonio (ISTI-CNR) and Nicholas Ayache (Inria)

This special theme focuses on research advances and perspectives in digital health, offering a glimpse into the diverse range of topics and challenges that the research community is facing in the field.

The convergence of science and technology in our burgeoning digital era is driving a complete transformation of health, medicine and care paradigms, which aim to improve people's long-term wellbeing and quality of life. "Digital health" arises where value-based and system medicine meets digital innovations, harnessing the potential of new technologies to make the patient the point of care and modernise the delivery of health and care services.

Society's ageing population, the growing prevalence of chronic diseases and multimorbidities, and the shortage of clinicians and care personnel are big challenges for health and care systems. Society expects improved quality and experience of health services, integrated care systems, and greater equality of access to health and care [L1].

Digital health can offer solutions by leveraging recent advances in computing methodologies and engineering as well as capitalising on the fertile, multidisciplinary environment and the increasing availability of data. The combination of artificial intelligence and machine learning, big data analytics and computer vision techniques with multi-omics research, portable diagnostics, wearables and implantable sensors is helping us understand biological, social and environmental processes that underlie disease onset. Technologies such as mHealth (mobile health), augmented reality, robotics and 3D printing, may enable more precise diagnoses, interventions and personalised follow-up programmes, and help improve efficiency, resilience and sustainability of healthcare systems.

Digital health emerges as key to ensure the shift towards the 4P paradigm, which

aims at more predictive, preventative, personalised and participatory approaches to health and care [1]. However, its realisation requires vast amounts of curated and high-quality data, regulations for privacy, data ownership, security and liability issues, standardisation and interoperability. Trusted solutions should ensure reliability in handling patient safety.

This special theme features research, providing significant examples of the great potential of effective digital health systems, and a panorama of the impactful and vibrant community that is actively working in the field. The presented approaches target:

- clinicians and health professionals, to empower them through the provision of actionable insights for faster and more accurate diagnoses and prognoses, as well as for more precise, patient-tailored treatments, follow-ups and assistance.
- health and care platforms to ensure accessible, interoperable and sustainable systems.
- individuals, patients and informal caregivers, to make them active players in the management of health, via timely and targeted prevention and assistance strategies.

One of the well-established fields for digital health solutions is medical image analysis and understanding, whose recent advances is thrilling the research community. The recent successes of artificial intelligence in computer vision is promisingly heading towards systems that may reduce the workload of radiologists in intensive error-prone manual tasks, and exploit the rich content of imaging data into disease phenotypes for more accurate diagnoses. In her contribution, Anne-Laure Rousseau illustrates

the success of deep learning techniques in processing ultrasound imaging data to diagnose kidney diseases, and detect urinary track blocks as well as kidney cancer. She has gathered a multidisciplinary team of engineers and health professionals, NHance, to develop applications that may leverage the great potential of machine learning to overcome the current difficulties in ultrasound reading (p. 6).

The work by Orlhac et al. (p.7) introduces radiomics, an emerging discipline consisting of the extraction of a large number of quantitative parameters from medical images, whose mining may lead to predictive models for prognosis and therapy-response that support evidence-based clinical decision-making. In his work, Colliot (p. 9) discusses some of the most cogent issues pertaining to the interpretability and reliability of artificial intelligence algorithms when applied to medical image analyses. Sermesant illustrates how the rich and detailed information contained in magnetic resonance and computed tomography cardiac images may be used to reconstruct a 3D heart model to provide the physicians with visual data that may be navigated during an intervention and can even predict the result of an intervention (p. 10).

Belmonte et al. (p. 12) introduce a novel approach to medical image analysis based on the recent advances in spatial logics. VoxLogicA is the tool developed by the authors to process both 2D and 3D imaging data. The work by Amelio et al. addresses the problem of medical image registration to track the evolution of a disease over time (p. 13). The authors introduce a new similarity measure to register CT brain images and monitor the evolution of brain lesions.

Barucci et al. illustrate the potential of radiomic analyses to provide prognostic proxy data in the oncological domain (p. 15). The work by Lizzi et al. overviews deep-learning based analyses of mammographic images to assess the risk of breast cancer (p.16). Manno-Kovacs et al. explore the possibility of using augmented reality for the visualisation of 3D imaging data (p. 18).

Advances in artificial intelligence and machine learning are of great help to process multiomics data and, thus, gather an understanding of the processes that underlie disease onset and its response to therapy. In this context, the work by Balvert and Schönhuth (p. 19) presents a deep learning approach to unravel the complex architecture of serious diseases such as the Alzheimer's and amyotrophic lateral sclerosis. Schönhuth and Stougie address the problem of decoding the genetic diversity of viruses, in order to detect potential resistant and virulent strains through the construction of virus variation graphs (p. 20). Manica et al. explore deep learning architectures to predict drug sensitivity (p. 23). They adopt feature saliency techniques to explain the results provided by the network, thus identifying the genes involved. Instrumental to the histopathology analyses is the identification of the optimal stain of the specimen for the specific tissue under examination. Khartchenko et al. (p. 22) use machine learning to predict the quantity of stain in accordance to the quality of the resulting assay.

Supporting clinical decision making is a central idea of digital health, since it permits clinicians to provide evidence-based care for the patients and reduced treatment costs. Ponsard and De Landtsheer (p. 25) combine predictive and prescriptive analytics to optimise the organisation of care processes and the definition of clinical pathways. The work by van Gils combines data derived from various sources (imaging, lab data, neuropsychological tests) into a single tool that supports the differential diagnosis of dementia (p. 26).

Efficient and integrated ICT infrastructures have a crucial role to support clinical practice by delivering the right data and information at the right time to the right end-user (including citizens), thus breaking data isolation and fostering precision medicine and care. Much work has been done in the field, but some important issues remain open (e.g., data interoperability and curation) and new ones are emerging (e.g., integrating and managing citizens' generated data and granting them data access rights). Katehakis and Kourabali (p. 31) discuss the advances of the European Interoperability Framework developed in response to the needs and expectations that emerged from the last open consultation of the European Commission. Patara and Vicario present an adaptable Electronic Health Record (EHR) system (p. 28). Antila et al. (p. 29) demonstrate that the availability of data collected into EHRs may be successfully used to develop individuals' phenotypic models that may perform better than the risk scores currently in use in routine practice in mortality prediction. The work by Chou Vo et al. reports on recent advances in Vietnam in the deployment of hospital EHRs and their integration into a unified database, named VNUMED (p. 32). Rocha et al. debate the use of FAIR principles to tackle data integration and harmonisation while preserving privacy (p. 33).

For preventative strategies to have a long term impact, it is essential that individuals are empowered as active participants in their health management. This is an area that continues to be a focus in the digital transformation of health and care. Remote and self-monitoring systems are now being designed for work environments to sustain workability of the ageing workforce, as Kocsis and colleagues present in their contribution (p. 35). Their solution relies on a flexible and integrated worker-centric AI System to support health, emotional and cognitive monitoring as well as working task adaptation. User engagement remains a crucial feature to ensure the long-term impact of these personal applications. Manea and Wac (p. 37) describe their approach to engaging behavioural

change with a health and well-being personal virtual coach, developed in the WellCo project. Sustained quality of life and independence are the main goal of the contributions by Paternò and colleagues (p. 39) and Boumpa and Kakarountas (p. 40), who propose adaptable assistive technologies to support people affected by cognitive impairments.

The final two papers of the special theme propose approaches to important issues in digital health. Ciceri et al. tackle privacy preservation when developing and deploying data analytics tools, capitalising on a platform developed in the PAPAYA project (p. 42). Spanakis and Sakkalis propose resilient network services for ensuring the continuous availability of Internet connection to mHealth applications, thus safeguarding their reliability and acceptability (p. 43).

In conclusion, this special issue provides the readers with a vibrant illustration of a sample of the multi-disciplinary research activities which underpin the upcoming revolution of digital health.

Link:

[L1] <https://kwz.me/hyV>

Reference:

[1] M. Flores, G. Glusman, K. Brogaard, N.D. Price, L. Hood: "P4 medicine: how systems medicine will transform the healthcare sector and society", *Per Med.*, 10 (6) (2013), pp. 565-576.

Please contact:

Sara Colantonio, ISTI-CNR, Italy
sara.colantonio@isti.cnr.it

Nicholas Ayache, Inria, France
nicholas.ayache@inria.fr

Machine Learning Applied to Ultrasound Imaging – The Next Step in Democratising Medical Imaging

by Anne-Laure Rousseau (Assistance Publique - Hôpitaux de Paris)

Machine learning has made a remarkable entry into the world of healthcare, but there remain some concerns about this technology. According to journalists, a revolution is upon us: One day the first artificial intelligence robot receives its medical degree, the next, new algorithms have surpassed the skill of medical experts. It seems that any day now, medical doctors will be unemployed, superseded by the younger siblings of Siri. But having worked on both medical imaging and machine learning, I think the reality is different, and, at the risk of disappointing some physicians' colleagues who thought the holidays were close, there is still work for us doctors for many decades. The new technology, in fact, offers a great opportunity to enhance health services worldwide, if doctors and engineers collaborate better together.

The new techniques of computer vision can be seen as a modern form of automation [1]: after automating the legs (the physical work made possible with the motors), the hands (precision work made possible by robots in the industry), we automate the eyes (the detection of patterns in images). The computer vision algorithms are skilled at specific tasks: imagine having with you not one or two, but a thousand medical students who can quickly perform tasks that are not necessarily complex but very time consuming. This will change a lot of things: it will reduce the time necessary to complete an imaging exam but it will also change the very nature of these exams by changing the cost efficiency of certain procedures. It is the combination of the doctor and the machine that will create a revolution, not the machine alone.

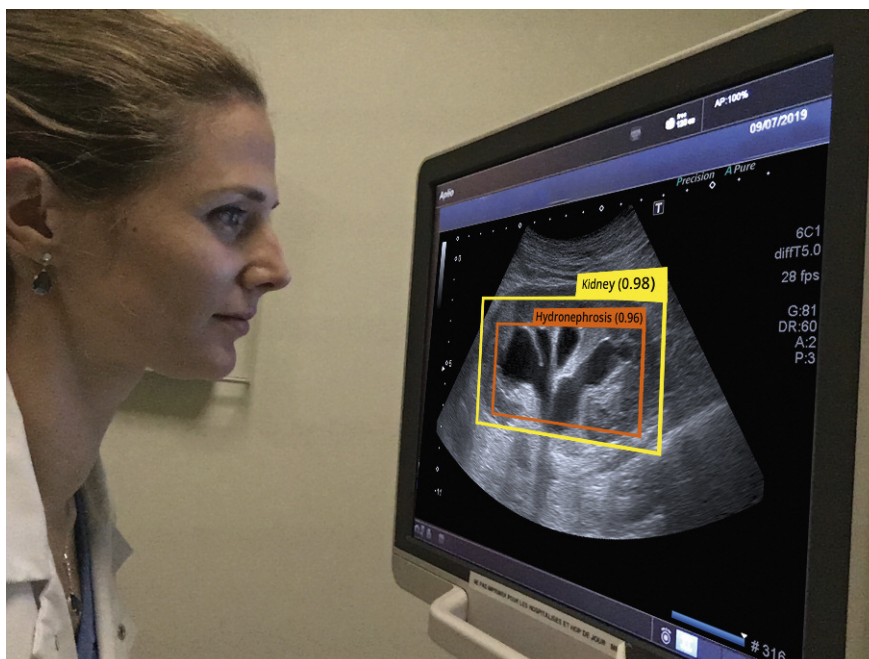
I gathered together a group of engineers and healthcare workers, the

NHance team [L1], to apply deep learning algorithms to ultrasound imaging. Ultrasound imaging has seen a most impressive growth in recent years and over 20 medical and surgical specialties have expressed interest in its use as a hand-carried ultrasound tool. According to WHO, two thirds of the world's population does not have access to medical imaging, and ultrasound associated with X-ray could cover 90 % of these needs. The decrease in hardware ultrasound prices allows its diffusion, and it is no longer access to equipment but the lack of training that limits its use [2].

Indeed, learning ultrasound is currently complex and not scalable. Machine learning could be particularly useful to alleviate the constraints of ultrasound, and further democratise medical imaging around the world.

Using algorithms to detect kidney diseases is one example of this. We trained our algorithms on 4,428 kidney images. To measure our model's performance we use the receiver operating characteristic curves (ROC). The areas under the ROC curves (AU-ROC) quantify the discrimination capabilities of the algorithms for the detection of a disease compared to the diagnosis made by NHance medical team. The higher the AU-ROC, the better the model is at distinguishing between patients with disease and no disease. The model whose predictions are 100% wrong has an AU-ROC of 0.0. On the contrary, an excellent classifier has an AU-ROC of around 1. In our study; the AU-ROC for differentiating normal kidneys from abnormal kidneys is 0.9.

We have trained algorithms to solve an emergency problem: for every acute renal failure, the physician needs to



This concept-image depicts how physicians could use deep learning algorithms in their future practice.

know if the urinary tract is blocked, and ultrasound is a good way to perform that diagnosis (a kidney state called hydronephrosis). AU-ROC for identifying hydronephrosis is 0.94 in our study.

We have trained our algorithms to detect kidney cancer. If kidney cancer is diagnosed when the patient has symptoms, such as blood in the urine or low back pain, it means in most cases that the cancer has already evolved and enlarged outside the kidney and it will be extremely difficult to cure, so highlighting a kidney cancer when it is asymptomatic can be a determinant factor for the patient. AU-ROC for identifying parenchymal lesion of the kidney is 0.94 in our study.

We have applied our research to other organs, such as the liver. The incidence of and mortality from liver diseases grows yearly. Our deep learning algorithms present an AU-ROC of 0.90 for

characterisation of a benign liver lesion and up to 0.90 for a malignant liver lesion. For medical experts, the AUROC for discriminating the malignant masses from benign masses was 0.724 (95 % CI, 0.566-0.883, $P = 0.048$) according to Hana Park et al.

These results are very encouraging and show that in the near future our algorithms could play an important role in assisting doctors with diagnoses. Our next step is to scale these results in collaboration with the Epione team led by Nicholas Ayache and Hervé Delingette at INRIA. We will work on all the abdominal organs in partnership with public assistance hospitals of Paris (APHP) that puts 1.3 million exams at our disposal for our project.

It's time to take cooperation between medical teams and engineering teams to the next level, in order to build better tools to enhance healthcare for everyone.

Link:

[L1] <http://www.nhance.ngo/>

References:

- [1] B. Evans: "10 Year Futures (Vs. What's Happening Now) [Internet], Andreesen Horowitz, 6 Dec 2017 <https://kwz.me/hy9>
- [2] C.L. Moore, J.A. Copel: "Point-of-Care Ultrasonography", *N. Engl. J. Med.* 24 Feb. 2011, 364(8):749-757. doi:10.1056/NEJMra0909487.
- [3] S. Shah, BA Bellows, AA Adedipe, JE Totten, BH Backlund, D Sajed: Perceived barriers in the use of ultrasound in developing countries, *Crit. Ultrasound J.* 19 June 2015; 7. doi: 10.1186/s13089-015-0028-2.

Please contact:

Anne-Laure Rousseau, President of the NGO NHance, European Hospital Georges Pompidou and Robert Debré Hospital, Paris, France
annelaure.rousseau@aphp.fr

Radiomics: How to Make Medical Images Speak?

by Fanny Orhac, Charles Bouveyron and Nicholas Ayache (Université Côte d'Azur, Inria)

Radiomics is the automatic extraction of numerous quantitative features from medical images and using these features to build, for instance, predictive models. It is anticipated that Radiomics enhanced by AI techniques will play a major role in patient management in a clinical setting. To illustrate developments in this field, we briefly present two ongoing projects in oncology.

Medical images are now routinely acquired during the care pathway and play an important role in patient management. However, medical images are still largely under-exploited, using mostly visual assessment and/or the measurement of very few quantitative features available in clinical practice. To extract more information from medical images, a new field, radiomics, has successfully developed since 2010, with almost 1000 publications now using "radiomics" in PubMed, more than 30 % of which were published during the first half of 2019. Just as "genomics", "proteomics" and "metabolomics" refer to the study of large sets of biological molecules, "radiomics" refers to the automatic extraction of large sets of quantitative features from medical images. Radiomic features can be derived from known mathematical expressions and reflect, for instance, the distribution of grey-levels, the shape of a volume of interest or the texture of the signal within

that volume. More recently, in addition of these handcrafted features, an infinite number of "deep features" can be extracted from intermediate layers of convolutional neural networks.

In oncology, encouraging results using radiomic features have been published to predict biological characteristics of lesions, patient response to therapy or overall survival, for several cancer types and imaging modalities (see Figure 1). In the coming years, radiomics enhanced by artificial intelligence techniques will certainly play a major role in patient management and in the development of 4P medicine (predictive, preventive, personalised and participatory).

Epione [L1] is a research team affiliated with Université Côte d'Azur, Inria (Sophia-Antipolis, France). The long-term goal of the team is to contribute to

the development of the e-patient (digital patient) for e-medicine (digital medicine). With the ongoing digital revolution in medicine and the need to analyse and interpret more and more high-dimensional data, the team has developed, for instance, a subspace discriminant analysis method which performs a class-specific variable selection through Bayesian sparsity, called sparse high-dimensional discriminant analysis (sHDDA) [1]. We demonstrated the interest of sHDDA for the radiomic analysis of computed tomography (CT) images to distinguish between lesion subtypes in lung cancer [1] or to identify triple-negative breast lesions based on positron emission tomography (PET) images [2]. Below we present two ongoing projects in radiomics in collaboration with clinical partnerships.

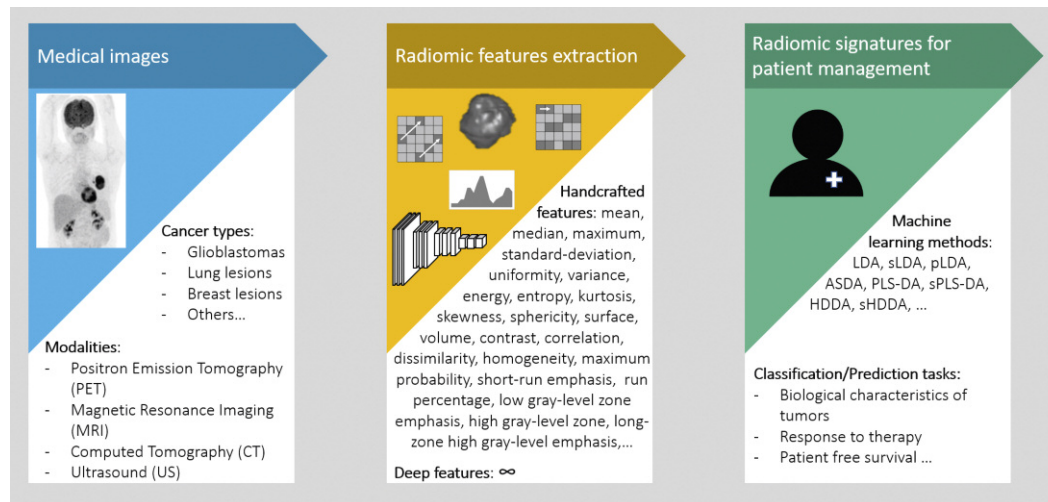


Figure 1: Process to obtain radiomic signatures in order to assist clinicians for patient management.

Management of glioblastomas

After an initial standard treatment, and in the case of clinically suspected recurrence, the differentiation between progression and radiation-induced necrosis for patients with a glioblastoma is often difficult based on magnetic resonance (MR) images. The use of PET images combined with a specific radiotracer (18F-FDOPA) improves the differential diagnosis but is still not completely accurate. In collaboration with Prof. J. Darcourt, Dr O. Humbert and Dr. F. Vandebos from the Centre Antoine Lacassagne [L2], we studied the relevance of radiomic features extracted from PET images to distinguish between progression and radiation-induced necrosis.

Using a retrospective cohort of 78 patients with a glioblastoma, we created parametric images resulting from the subtraction of two static PET scans performed 20 and 90 minutes after injection of the radiotracer (PET_{sub}=PET₉₀ – PET₂₀). Based on these new images and for each suspicious lesion, we extracted 43 radiomic features using LIFEx software [L3] including conventional features used in clinical practice, as well as histogram, shape and texture indices. We demonstrated that, thanks to a machine learning approach designed for low-sample size/high-dimensional data, the High-Dimensional Discriminant Analysis method (HDDA), it is possible to distinguish between progression and radiation necrosis with better performance than visual assessment [3]. In our cohort, the visual interpretation using the Lizarraga Scale led to a Youden Index ($Y = \text{Sensitivity} + \text{Specificity} - 1$) of 0.27 (Sensitivity = 97 %, Specificity =

30 %). Based on the radiomic analysis of the parametric images resulting from the evolution of radiotracer uptake, the Youden Index was 0.45 (Sensitivity = 65 %, Specificity = 80 %). Additional studies are ongoing to validate these results on an independent cohort and to test if including additional features extracted from MR images could further improve the performance.

Prediction of treatment response

In oncology, a major challenge for clinicians is to identify the right treatment for the right patient at the right time. To assist them in this task, our goal is to develop radiomic signatures to predict the patient's response to therapy. In collaboration with Dr T. Cassou Mounat, Dr A. Livartowski, and Dr M. Luporsi from Institut Curie [L4] and Dr. I. Buvat from Laboratoire IMIV [L5], we are focusing on two cancer types. In lung cancer, our objective is to combine radiomic features extracted from pre-treatment PET images in order to predict the response to chemotherapy. As nearly 50 % of patients do not respond positively, their early identification could allow clinicians to propose alternative therapies, such as immunotherapy, straight away. In breast cancer, we are developing a radiomic signature to predict the response to neoadjuvant chemotherapy. Indeed, a complete pathological response is only observed in about 20 % of patients while 10 % have stable or progressive disease after neoadjuvant chemotherapy. The early identification of non-responding patients or of tumours that will go on growing during chemotherapy would make it possible to adjust therapy at best without any loss of time.

Overall, the combination of radiomic analysis and modern machine learning approaches paves the way to better patient management thanks to a more extensive exploitation of medical images that are already currently acquired during the care pathway.

Links:

- [L1] <https://team.inria.fr/epione/en/>
- [L2] <https://kwz.me/hyf>
- [L3] <https://www.lifexsoft.org/>
- [L4] <https://institut-curie.org/>
- [L5] <http://www.imiv.fr>

References:

- [1] F. Orlhac, P.-A. Mattei, C. Bouveyron, N. Ayache: "Class-specific variable selection in high-dimensional discriminant analysis through Bayesian Sparsity", *J Chem*, 2019;33:e3097.
- [2] F. Orlhac, O. Humbert, T. Pourcher, L. Jing, J.-M. Guignonis, J. Darcourt, N. Ayache, C. Bouveyron: "Statistical analysis of PET radiomic features and metabolomic data: prediction of triple-negative breast cancer", *J Nucl Med*, 2018;59:1755.
- [3] F. Orlhac, A.-C. Rollet, C. Bouveyron, J. Darcourt, N. Ayache, O. Humbert: "Identification of a radiomic signature to distinguish recurrence from radiation-induced necrosis in treated glioblastomas using machine learning methods on dual-point 18F-FDOPA PET images", *J Nucl Med*, 2019;60:57.

Please contact:

Fanny Orlhac
 Université Côte d'Azur, Inria, France
orlhac@gmail.com

Interpretable and Reliable Artificial Intelligence Systems for Brain Diseases

by Olivier Colliot (CNRS)

In artificial intelligence for medicine, more interpretable and reliable systems are needed. Here, we report on recent advances toward these aims in the field of brain diseases.

As in different fields of medicine, AI holds great promise to assist clinicians in the management of neurological diseases. However, there is still an important gap to bridge between the design of such systems and their use in clinical routine. Two major components of this gap are interpretability and reliability.

“Interpretability”, the user’s ability to understand the output provided by an AI system, is important for the adoption of AI solutions by clinicians. To make AI systems more interpretable, different lines of work are being pursued. A first avenue is to explain the basis of a pre-

medical images of the patient. Recently, we proposed a system to predict brain images that are representative of different pathological characteristics in multiple sclerosis. In a first work [1], we designed a system that can predict a specific type of magnetic resonance image (MRI), called FLAIR, from other types of MR images. We showed that overall the predicted images did a good job of preserving the characteristics of the original image. We then applied an automatic segmentation algorithm and showed that its results on the predicted and original images are consistent.

acquire. The predicted image allows accurate quantification the amount and location of demyelinated areas. These results will need to be confirmed on larger, multicentric, datasets. By providing both the quantified outcome (demyelination) and the predicted image, our approach has the potential to be more interpretable for the clinician.

Naturally, reliability is a mandatory property of medical AI systems. Design of reliable systems involves many steps from evaluation of prototypes to certification of products. At the stage of academic research, an important compo-

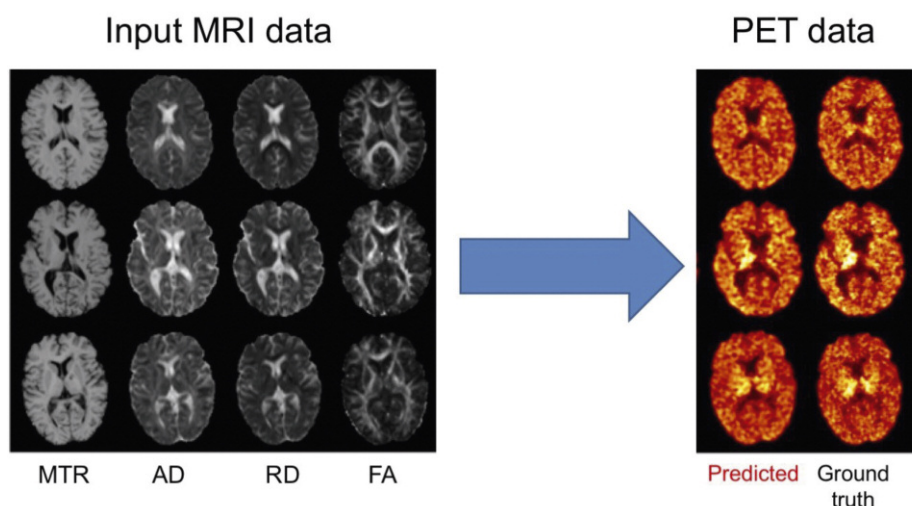


Figure 1: Prediction of myelin content, as defined from PET images, using multiple MRI modalities. On the left, input MRI modalities: magnetisation transfer ratio (MTR) and three measures computed from diffusion MRI, axial diffusivity (AD), radial diffusivity (RD) and fractional anisotropy (FA). On the right: predicted and ground truth PET data. The PET tracer is the Pittsburgh compound B (PiB) is used to measure myelin content in the white matter of the brain.

diction based on the input features. While this is relatively straightforward for linear models, it is more difficult for complex non-linear techniques such as deep neural networks, even though advances have recently been made in this area.

Another complementary way to make AI systems more interpretable is to predict not only a clinical outcome (e.g. diseased/healthy, lesional/non-lesional) but also different types of medical data and measurements characterising a patient. For instance, in Alzheimer’s disease, one may try not only to predict the future occurrence of dementia, but also the future value of cognitive scores or future

We further proposed an approach to predict myelin content from multiple MRI modalities (Figure 1) [2]. Myelin is a substance that wraps axons and increases the speed of transmission of information between neurons. Multiple sclerosis is characterised by the loss of myelin (demyelination) whose quantification is essential for tracking disease progression and assessing the effect of treatments. Myelin can be measured in vivo using positron emission tomography (PET) with specific tracers. However, PET is an expensive imaging modality and is not available in most centres. We showed that it is possible to synthesise PET images from multiple MR images, which are less expensive to

acquire. Replication is indeed a cornerstone of scientific progress in all areas of science. Such a process involves two related but distinct aspects: reproducibility, defined as the ability to reproduce results based on the same data, and replicability, the reproduction using different data.

In a recent work, we studied the problem of reproducibility of deep learning approaches for assisting diagnosis of Alzheimer’s disease from MRI data [3]. First, we reviewed existing studies and unveiled the existence of questionable practices in a substantial number of them. Specifically, among

the 32 studies, half of them potentially introduced data leakage (the use of some information from the test set during training). Data leakage was clear in six of them and possibly present in 10 others which had insufficient details about their validation procedure. This is a serious problem, particularly considering that all these studies have undergone peer-review. Given these defects in the validation procedure, it is unlikely that the very high performances reported in these studies would be replicated by others. Moreover, many of these works were not reproducible because the code and data were not made available.

We thus proposed a framework for reproducible experiments on machine learning for computer-aided diagnosis of AD [3]. The framework was composed of standardised data management tools for public data, image preprocessing pipelines, machine learning

models and validation procedure. It is open-source and available on github [L1]. We applied the framework to compare the performance of different convolutional neural networks and provide a baseline to which future works can be compared. We hope that this work will be useful to other researchers and pave the way to reproduce research in the field.

Link:

[L1] <https://github.com/aramis-lab/AD-ML>

References:

- [1] W. Wei, E. Poirion, B. Bodini, S. Durrleman, O. Colliot, B. Stankoff, N. Ayache: “Fluid-attenuated inversion recovery MRI synthesis from multisequence MRI using three-dimensional fully convolutional networks for multiple sclerosis”, *J Med Imaging* 6:27, 2019. DOI: 10.1117/1.JMI.6.1.014005, 2019

- [2] W. Wei, E. Poirion, B. Bodini, S. Durrleman, N. Ayache, B. Stankoff, O. Colliot: “Learning Myelin Content in Multiple Sclerosis from Multimodal MRI through Adversarial Training, in: *Proc. MICCAI - Medical Image Computing and Computer Assisted Intervention*, Springer, 2018.

- [3] J. Wen, E. Thibeau-Sutre, J. Samper-Gonzalez, A. Routier, S. Bottani, S. Durrleman, N. Burgos, O. Colliot: “Convolutional Neural Networks for Classification of Alzheimer’s Disease: Overview and Reproducible Evaluation”, 2019. ArXiv190407773 Cs Eess Stat.

Please contact:

Olivier Colliot
CNRS, Inria, Inserm, Sorbonne University, Brain and Spine Institute Paris, France
olivier.colliot@upmc.fr

Improving Cardiac Arrhythmia Therapy with Medical Imaging

by Maxime Sermesant (Inria and Université Côte d’Azur)

With medical imaging’s ability to provide a high level of detail about cardiac anatomy and pathology, it is high time for such information to be used during interventions. Technology to achieve this is now being made available to every cardiologist.

Ventricular fibrillation is a pathology in which cardiac electrophysiology, which controls the contraction of the heart, deteriorates into chaotic behaviour. The electric wave that has to activate each muscle fibre of the heart in a coordinated way becomes a storm that does not generate an effective contraction, a condition that is deadly within minutes without heart massage and defibrillator. This sudden death affects 400,000 people a year in Europe, which is more than the three most deadly cancers combined.

The occurrence of ventricular fibrillation depends largely on the extent of myocardial infarction: when it is not fatal, it produces damage that can cause arrhythmias years later, such as fibrillation or tachycardia. Traditionally these are treated by implanting a defibrillator, which will trigger an adequate electric shock in case of arrhythmia. But this

does not heal anything, represents a major intervention, and the electric shocks often affect the individual’s quality of life.

In recent years, another intervention has been developed, catheter ablation, which allows the cardiac cells responsible for arrhythmias to be burnt with a catheter. However, it is a complex procedure because the cardiologist only has access to a very compartmental vision of the heart during these interventions and must therefore exhaustively search for the right targets.

Medical imaging nowadays, however, makes it possible to obtain, in a non-invasive way, very detailed 3D information on the anatomy and the cardiac structure of these patients. Magnetic resonance imaging and computed tomography now have spatial resolutions of the order of a millimetre. But

these data are not currently available to the interventional cardiologist. The acquired images are interpreted by the radiologist and the cardiologist receives a report, but the 3D data cannot be used by the catheter systems.

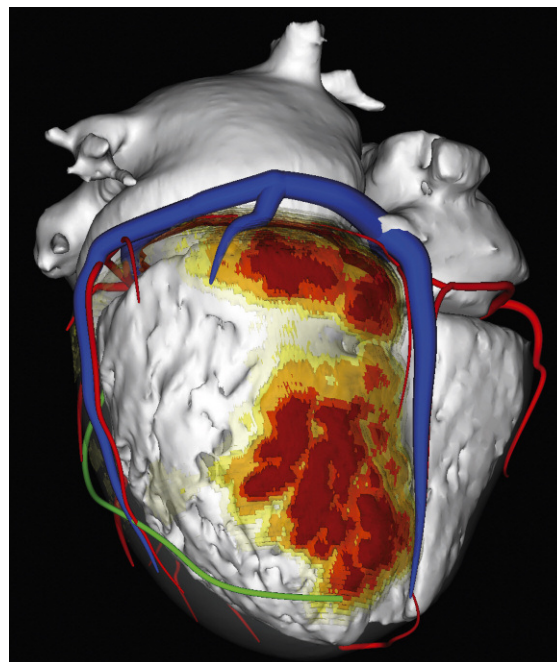
A new technology developed between Inria Sophia Antipolis and the IHU Liryc in Bordeaux makes it possible to extract the important information from the 3D images of the patient’s heart and to represent them in the form of meshes compatible with the interventional tools. The cardiologist can therefore manipulate his catheter while visualising the locations of the sensitive structures to avoid, and the areas to aim for. This accelerates the process, improves safety and increases the success rate [1]. This technology has been tested on hundreds of patients around the world and has been transferred to the start-up com-

pany inHEART, created in 2017 to commercialise this tool [L1].

However, to implement this technology, it was necessary to tackle various scientific and technical challenges:

- It is necessary to develop robust and fast image processing algorithms. Speed is required to integrate into the clinical workflow without adding additional time. Robustness is crucial for the results to be relevant even in difficult cases, for example if the image is of lower quality. The validation / correction step by the user must not take too much time compared to the time it would take to do everything manually, otherwise the algorithm loses its relevance.
- A key step is segmentation, which extracts important structures from the image. This is one of the major steps because the accuracy of the information provided to the cardiologist depends on it. The method used is based on deep learning [2] but allows the user to correct the result and validate it.
- It also requires image registration algorithms, which allow the matching of information from several modalities, such as MRI and CT. MRI can be used to image fibrosis and therefore the result of infarction, but not small structures such as coronaries, while CT does it very well. The ability to merge these modalities allows a more complete vision of the heart. Again, there are automatic techniques, but it is important to obtain the robustness necessary for clinical use, and that the user can guide the algorithm, including points of interest in each of the images.
- In addition, these algorithms must be integrated into software that can be used by a non-specialist, because in order to allow wide-scale use, the end-user must not be a specialist in medical imaging, nor a radiologist or a cardiologist. This is an ergonomic challenge so that the sequence of steps is natural [L2].
- Finally, we must develop an intuitive visualisation of the different meshes generated because they will be added to the substantial existing data that the cardiologist will have to interpret

Figure 1: 3D rendering of the cardiac atria and ventricles (white), veins (blue), coronaries (red), phrenic nerve (green) from CT and fibrosis quantification (yellow to red) from MRI. This detailed information provides structures to avoid (vessels, nerves) and areas to treat (fibrosis) when performing catheter ablation of arrhythmias.



during the intervention. We are not all equal in 3D visualisation, and the results must not be confusing, so it is important to interact with cardiologists to optimise this aspect.

On these different aspects, the contribution of computing is crucial, and the scientific challenge is notably to succeed in making the algorithms work on images coming from any hospital in the world, with different acquisition protocols and very variable image qualities.

A related area of research is the mathematical modelling of the heart, which could non-invasively predict ablation targets by simulating different electrical propagations and ablation strategies before the procedure. This is also part of the collaborative scientific program between IHU Liryc and Inria and is based on the image analysis outlined above. The challenge here is to succeed in quickly and robustly customising such mathematical models to a patient's images in order to generate the corresponding predictions [3].

Computer science allows this convergence of domains (imaging, modelling, catheters) and thus creates new and exciting possibilities for improving the success and safety of cardiac procedures.

Links:

- [L1] <https://www.inheart.fr>
- [L2] <https://kwz.me/hyw>

References:

- [1] S. Yamashita, H. Cochet, F. Sacher, S. Mahida, B. Berte, D. Hooks, J.-M. Sellal, N. Al Jefairi, A. Frontera, Y. Komatsu, H. Lim, S. Amraoui, A. Denis, N. Derval, M. Sermesant, F. Laurent, M. Hocini, M. Haissaguerre, M. Montaudon, P. Jais: "Impact of New Technologies and Approaches for Post-Myocardial Infarction Ventricular Tachycardia Ablation During Long-Term Follow-Up", *Circulation - Arrhythmia and Electrophysiology*, 9(7), 2016.
- [2] S. Jia, A. Despinasse, Z. Wang, H. Delingette, X. Pennec, P. Jaïs, H. Cochet, M. Sermesant: "Automatically Segmenting the Left Atrium from Cardiac Images Using Successive 3D U-Nets and a Contour Loss. In *Statistical Atlases and Computational Modeling of the Heart (STACOM)*", LNCS, Springer, 2018.
- [3] N. Cedilnik, J. Duchateau, R. Dubois, F. Sacher, P. Jaïs, H. Cochet, M. Sermesant: "Fast Personalized Electrophysiological Models from CT Images for Ventricular Tachycardia Ablation Planning", *EP-Europace*, 20, 2018.

Please contact:

Maxime Sermesant
Inria and Université Côte d'Azur,
France
+33 4 92 38 78 11
maxime.sermesant@inria.fr

VoxLogicA: a Spatial-Logic Based Tool for Declarative Image Analysis

by Gina Belmonte (AOUS), Vincenzo Ciancia (ISTI-CNR), Diego Latella (ISTI-CNR) and Mieke Massink (ISTI-CNR)

Glioblastomas are among the most common malignant intracranial tumours. Neuroimaging protocols are used before and after treatment to evaluate its effect and to monitor the evolution of the disease. In clinical studies and routine treatment, magnetic resonance images (MRI) are evaluated, largely manually, and based on qualitative criteria such as the presence of hyper-intense tissue in the image. VoxLogicA is an image analysis tool, designed to perform tasks such as identifying brain tumours in 3D magneto-resonance scans. The aim is to have a system that is portable, predictable and reproducible, and requires minimal computing expertise to operate.

VoxLogicA is a new tool to perform image analysis in a declarative way, based on the latest developments in the theory of spatial logics [L1]. The tool was developed as part of a collaboration between the "Formal Methods and Tools" group of ISTI-CNR and the Department of Medical Physics of the Azienda Ospedaliera Universitaria Senese (AOUS).

VoxLogicA can be used for 2D (general-purpose) imaging, and for analysing 3D medical images, which has so far been the most promising application scenario. VoxLogicA has been designed with an emphasis on simplicity, and with a focus on producing explainable and implementation-independent results. A VoxLogicA session consists of a textual

specification of image analysis, employing a combination of spatial features (distance between regions, or inter-reachability) with texture similarity, statistical, and imaging primitives.

VoxLogicA is publicly distributed, free and open source software (see link). At its heart lies a "model checker"; a very efficient computation engine for logical queries, exploiting advanced techniques, such as memoization and multi-threading, to deliver top-notch performance.

VoxLogicA sessions are written using a declarative logical language, "Image Query Language" (ImgQL), inspired by the very successful "Structured Query

Language" (SQL) for databases, but with strong mathematical foundations rooted in the area of spatial logics for topological (closure) spaces. When used in the context of medical imaging, this approach admits very concise, high level specifications (in the order of ten lines of text) that can delineate, with high accuracy, the contours of a glioblastoma tumour in a 3D Magneto-Resonance scan within eight seconds, on a standard laptop. In comparison, it takes an expert radiotherapist about half an hour to perform this task.

The same procedure has been applied to circa 200 cases (the well-known "Brain Tumour Segmentation (BraTS) challenge" dataset). Accuracy of the obtained results can be measured; the new procedure scores among the top-ranking methods of the BraTS challenge in 2017 - the state of the art in the field, dominated by machine-learning methods - and it is comparable to manual delineation by human experts. Figure 1 shows the results of segmentation of a tumour for one of those cases, where the top row shows the MRI image, the middle row the result of manual segmentation by independent experts, and the bottom row the result performed with VoxLogicA.

In the near future we plan to enhance this work, both in the direction of clinical case studies and to embrace other computational approaches that can be coordinated and harmonised using high-level logical specifications. Furthermore, the approach is very versatile, and its application is not limited to a single specific type of tumour or region in the body, paving the way for the analysis of other types of cancer and segmentation of various kinds of brain tissue such as white and grey matter.

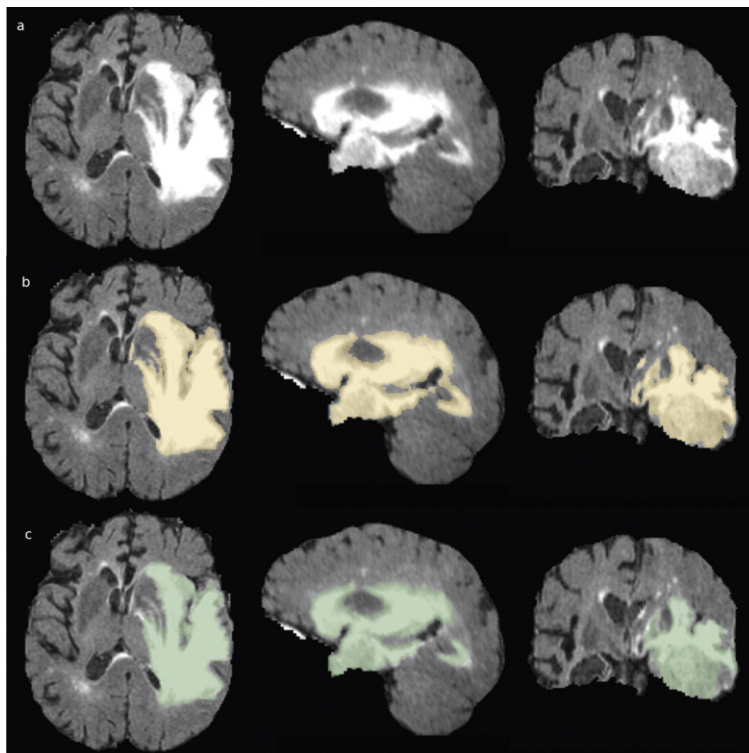


Figure 1: Results of segmentation of GTV for TCIA 471 patient: a) FLAIR acquisition b) Manual segmentation (BRATS 17 dataset) c) Segmentation result performed with VoxLogicA.

A recent publication introducing the tool and its application to glioblastoma segmentation can be found in [1]. The source code and binaries of VoxLogicA are available at the link below together with a simple example of a 2D background removal task, intended as a mini tutorial for the tool. The theoretical foundations of spatial model checking can be found in [2] and an earlier study on glioblastoma segmentation performed with the general purpose spatial-temporal model checker “topochecker” can be found in [3].

Link:
[L1] <https://kwz.me/hyy>

References:
[1] G. Belmonte, et al.: “VoxLogicA: a Spatial Model Checker for Declarative Image Analysis, TACAS 2019, LNCS 11427, pp. 281-298, 2019. DOI: 10.1007/978-3-030-17462-0_16
[2] V. Ciancia, et al.: “Model Checking Spatial Logics for Closure Spaces”, Logical Methods in Computer

Science Vol. 12, Nr. 4, 2016. DOI: 10.2168/LMCS-12(4:2)2016
[3] F. Banci Buonamici, et al.: “Spatial Logics and Model Checking for Medical Imaging”, STTT, Online first, 2019. DOI: 10.1007/s10009-019-00511-9

Please contact:
Vincenzo Ciancia
CNR-ISTI, Italy
vincenzo.ciancia@isti.cnr.it

New Directions for Recognizing Visual Patterns in Medical Imaging

by Alessia Amelio (University of Calabria, Italy), Lucio Amelio (independant researcher) and Radmila Janković (Mathematical Institute of the S.A.S.A., Serbia)

New study directions are focused on the extraction and recognition of visual patterns from different types of medical images.

Various methods have been developed to recognise visual patterns in medical imaging [1]. Some techniques are used for classification of medical images; the automatic recognition of the pathology associated with the given image. Others are adopted for clustering medical image repositories, whose aim is to detect the different pathologies characterising the image repository. Pattern recognition is also used for segmenting or clustering medical images in uniform regions which can correspond to high-risk areas. Finally, medical image registration exploits pattern recognition methods for comparing body part images captured in different conditions and detecting the

optimal alignment among them in order to monitor the evolution of the disease. All these approaches are important for multiple reasons: (i) quick identification of a given disease through visualisation and recognition of elements to further investigate with accurate medical exams, (ii) supporting the physician in the diagnosis process, and (iii) monitoring the patient’s conditions over time.

When it comes to medical image registration, different methods, based mainly on magnetic resonance (MR) images of the brain, have been proposed for monitoring the temporal evolution of a

stroke. These methods have limitations, however, given that acquisition costs are high and availability of MR imaging is sometimes low. Other studies are focused on monitoring the temporal evolution of a stroke in its acute phase.

To overcome these limitations, we propose a new system based on image registration techniques applied on computed tomography (CT) exams of the patient's brain for monitoring the temporal evolution of stroke lesions [2]. The system operates in two phases: (i) it evaluates past lesions which are not related to stroke through comparison of past CT exams with the most recent one related to stroke event; (ii) then it evaluates the trend of the lesion over time through comparison of recent CT exams related to the current stroke. Comparison of source and target CT exams is performed using image registration with a new introduced pattern-based similarity measure in 3D. The registration task aims to compute a transformation function maximizing the similarity between the source CT exam and a transformation of the target CT exam. The similarity function is a 3D extension of the “approximate average common submatrix” measure (A-ACSM). It computes the similarity between two CT exams as the average volume of the largest sub-cubes matching, to less than

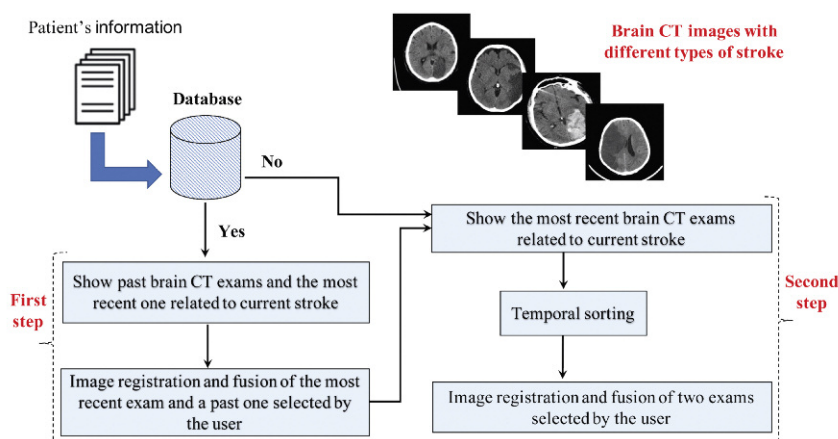


Figure 1: Flowchart of the proposed system [2].

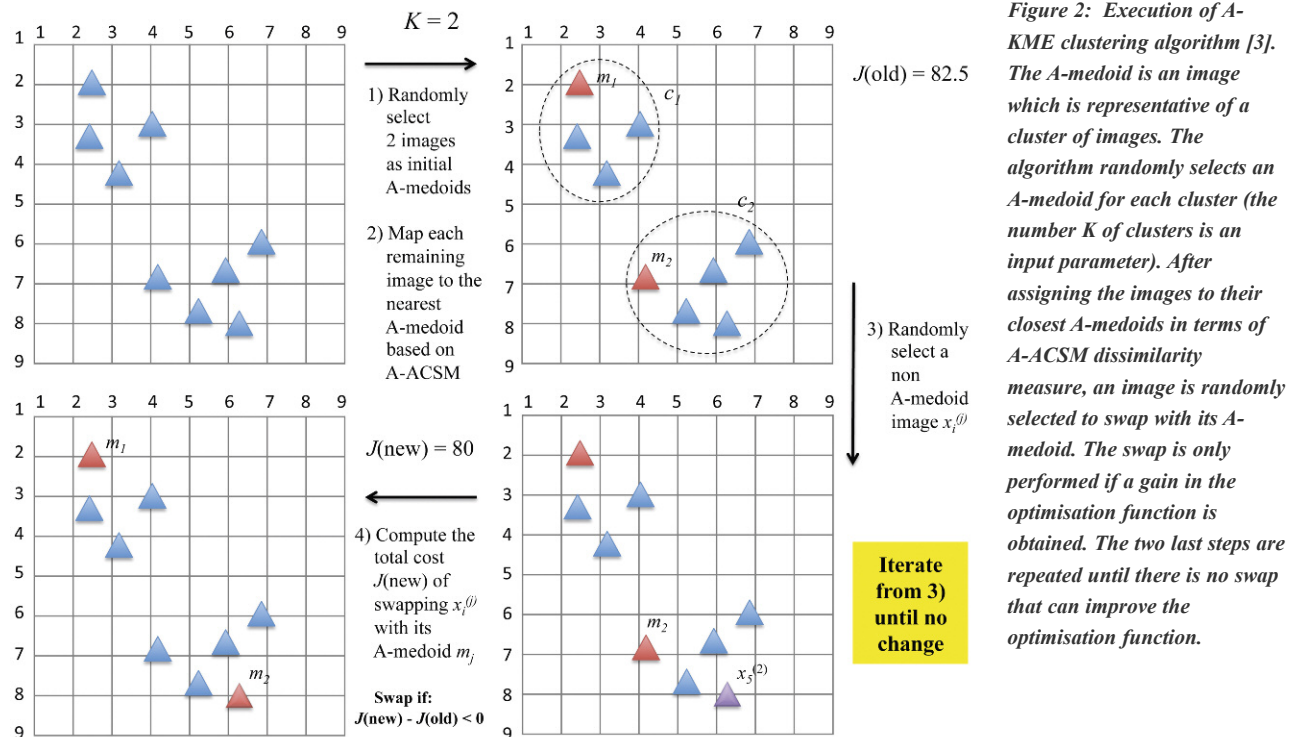


Figure 2: Execution of A-KME clustering algorithm [3]. The A-medoid is an image which is representative of a cluster of images. The algorithm randomly selects an A-medoid for each cluster (the number K of clusters is an input parameter). After assigning the images to their closest A-medoids in terms of A-ACSM dissimilarity measure, an image is randomly selected to swap with its A-medoid. The swap is only performed if a gain in the optimisation function is obtained. The two last steps are repeated until there is no swap that can improve the optimisation function.

a few voxels, in a neighbourhood in the two CT exams. The proposed system could provide substantial support to hospitals as well as industrial partners by monitoring the stroke for a period of time that is nominated by the physician. Since the new similarity measure in the image registration is robust to noise, comparison of CT exams is also more accurate than traditional registration methods. Figure 1 shows the flowchart of the proposed system.

In addition, we recently explored pattern recognition methods for clustering dermoscopic images of different types of skin lesions [3]. As yet, with the exception of melanoma images, the establishment of dermoscopic image repositories representing different pathologies has not been addressed in the literature. These methods can make the diagnosis process faster and more accurate, and support the design of interactive atlases, which can help physicians with a differential diagnosis. Accordingly, we exploited the 2D version of A-ACSM for clustering image repositories, and tested our approach on dermoscopic image databases. Specifically, A-ACSM computes the dissimilarity between two images starting from the average area of the largest square sub-matrices matching, to less than a few pixels, in the two images. The A-ACSM dissimilarity

measure is used in the optimisation function of a K-medoid-based clustering algorithm. The new clustering algorithm, called “approximate average common submatrix-based K-medoids” (A-KME), is run on a dermoscopic image repository with 12 skin diseases. Figure 2 shows the execution of the proposed A-KME algorithm.

At the end, we obtained very promising results in clustering dermoscopic image repositories versus competing methods.

The research directions about visual pattern recognition in the medical domain involved the University of Calabria, DIMES, and the Mathematical Institute of the Serbian Academy of Sciences and Arts, Serbia. Future work will investigate the use of A-KME algorithm on different types of medical images. The proposed system will also be extensively tested on different case studies and employed in real-life contexts.

References:

- [1] L. Amelio, A. Amelio: “Classification Methods in Image Analysis with a Special Focus on Medical Analytics”, Machine Learning Paradigms, Springer, 149, 31-69, 2019.
- [2] L. Amelio, A. Amelio: “CT image registration in acute stroke monitoring”, MIPRO, IEEE, 1527-1532, 2018.
- [3] L. Amelio, R. Janković, A. Amelio: “A New Dissimilarity Measure for Clustering with Application to Dermoscopic Images”, IISA, IEEE, 1-8, 2018.

Please contact:

Alessia Amelio, DIMES, University of Calabria, Rende, Italy
a.amelio@dimes.unical.it

Radiomics to Support Precision Medicine in Oncology

by Sara Colantonio (ISTI-CNR), Andrea Barucci (IFAC-CNR) and Danila Germanese (ISTI-CNR)

Precision health, the future of patient care, is dependent on artificial intelligence. Of the information contained in a digital medical image, visual analysis can only extract about 10%. Radiomics aims to extract an enormous wealth of quantitative data from biomedical images, which could not be processed through simple visual analysis, but is capable of providing more information on the underlying pathophysiological phenomena and biological processes within human body. The subsequent mining of these quantitative data can offer very useful information on the aggressiveness of the disease under investigation, opening at the tailoring of the therapies based on a patient's needs and at the monitoring of the response to care. Therefore, by using specific mathematical algorithms and artificial intelligence techniques, radiomics provides very powerful support for precision medicine, especially in oncology.

Solid tumours do not appear as a homogeneous entity, but are formed by multi-clonal populations of cancer cells that exhibit considerable spatial and temporal variability. Such variability can provide valuable information on both the aggressiveness and the probability of response to therapies (therapeutic response) of the tumour itself [1].

Needle biopsy is a commonly used tool in clinical practice, but it is an invasive procedure that does not allow detecting the entire range of potential biological variation within a tumour because of the limited number of locations where cancer cells are sampled (incomplete sampling). Clinical imaging, conversely, samples the entire tumour volume in a non-invasive way and allows phenotypic characteristics to be extracted from different spatial and temporal levels, from macro-lesions up to the cellular and genetic scale.

However, image characteristics are often visually evaluated and described by radiologists or clinicians, giving rise to a subjective description of tumour imaging phenotypes, with significant intra-and inter-observer variability [2]. Moreover, only about 10 % of the information contained in a digital medical image can usually be extracted by a visual analysis.

It was within this context that radiomics was born; the answer to the search for a quantitative, objective and reproducible information extraction method for biomedical images. Underpinning radiomics [3] is computer vision, but it also has deep roots in statistics, which are often underestimated. Radiomics can be defined as the omic discipline of clinical image analysis, whose results are intrinsically objective and repeatable. An example of a radiomic pipeline is shown in Figure 1.

Radiomics converts the intrinsic information within a digital image into a huge quantity of features (from a few dozen up to a few thousand) that are computed with specific mathematical algorithms. The evaluated features describe imaging parameters as intensity, shape, size, volume, textures, etc., related to the underlying tissue structures (e.g. the neoplasm and/or the surrounding healthy tissues).

By using appropriate data mining techniques (e.g. machine learning, deep learning), such features can be investigated, and the phenotypic and micro-environmental traits of a cancer tissue can be identified, enriching the data provided by laboratory tests and genomic or proteomic tests.

The identification of the “radiomic signature”, in combination with other omics data, can then be used for the

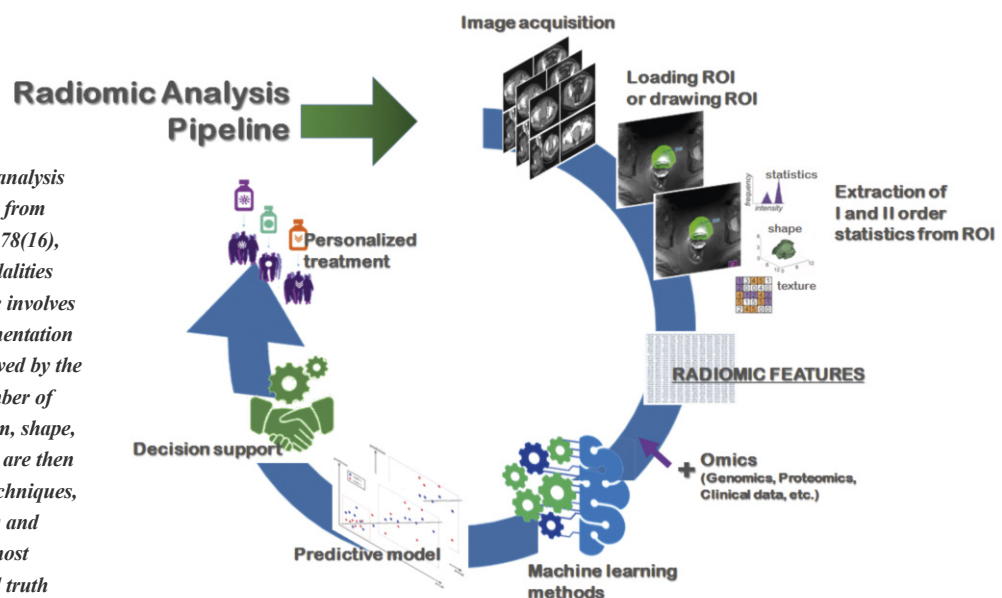


Figure 1: The pipeline of radiomic analysis toward precision medicine (inspired from Fig.2 of Nioche et al., Cancer Res., 78(16), 2018). For each of the imaging modalities (MRI, TC, PET, US), the first phase involves a semi-automatic or automatic segmentation of the relevant regions; this is followed by the automatic extraction of a large number of features (descriptive of the histogram, shape, texture and texture). These features are then processed with machine learning techniques, such as feature selection techniques and comparative analysis, to select the most robust ones that correlate to ground truth biomarkers (used in clinical practice).

development of diagnostic and prognostic models, describing phenotypic patterns connected to biological or clinical end points.

The availability of robust and validated quantitative biomarkers is fundamental to move precision medicine forward, and radiomics, in which imaging (and other) biomarkers are used to: (i) model the characteristics of each individual and the variability among individuals and (ii) predict the right treatment, for the right patient, at the right time, epitomises the research toward the implementation of personalised approaches.

Given that cancer has an intrinsically high intra- and inter-variability, owing to a range of internal and external factors, personalisation of the treatment becomes fundamental in oncology.

With this in mind, a multidisciplinary group of researchers from two CNR institutes, and clinicians from several hospitals and university centres, are combining their skills (including medical physics, biology, oncology, biomedical engineering, mathematics and

computer science) to investigate the radiomic signature for the grading of prostate cancer (PCa), as well as the use of inductive representation learning methods.

Our pilot study investigated the association between radiomic features extracted from multi-parametric magnetic resonance imaging (mp-MRI), the Prostate Imaging Reporting and Data System (PI-RADS) classification, and the tumour histologic subtypes (using the pathologist Gleason score grading system), in order to identify which of the mp-MRI derived radiomic features (signature) can distinguish high and low risk PCa, with the aim of integrating or replacing information obtained by solid biopsy.

Using a retrospective cohort of over 100 MRI patients, radiomic features (about 800) were evaluated on tumour areas segmented by the radiologists. A feed-forward method of selecting wrapper type features was used to select the four most relevant features. These were used to train (10-fold cross-validation) a narrow neural network able to predict Gleason score. Our method outper-

formed the majority of the works reported in literature based on standard machine learning techniques.

A descriptive paper was submitted to RSNA2020, another is undergoing submission to BIBE2019, while further data collection is underway.

References:

- [1] G. Lin, K. R. Keshari, and J. Mo Park: "Cancer Metabolism and Tumor Heterogeneity: Imaging Perspectives Using MR Imaging and Spectroscopy", *Contrast Media Mol Imaging* 2017.
- [2] S. Trattinig: "The Shift in Paradigm to Precision Medicine in Imaging: International Initiatives for the Promotion of Imaging Biomarkers", *Imaging Biomarkers*, 2017.
- [3] S. Rizzo et al.: "Radiomics: the facts and the challenges of image analysis", *European Radiology Experimental*, 2018.

Please contact:

Sara Colantonio, ISTI-CNR, Italy
sara.colantonio@isti.cnr.it

Deep-Learning Based Analyses of Mammograms to Improve the Estimation of Breast Cancer Risk

by Francesca Lizzi (National Institute for Nuclear Physics, Scuola Normale Superiore, National Research Council, University of Pisa), Maria Evelina Fantacci (National Institute for Nuclear Physics, University of Pisa) and P. Oliva (National Institute for Nuclear Physics, University of Sassari)

Breast cancer is the most commonly diagnosed cancer among women worldwide. Survival rates strongly depend on early diagnosis, and for this reason mammographic screening is performed in developed countries. New artificial intelligence-based techniques have the potential to include and quantify fibroglandular (or dense) parenchyma in breast cancer risk models.

Breast cancer is the most commonly diagnosed cancer among women worldwide. According to the latest American Cancer Statistics [1], breast cancer is the second leading cause of death among women, and one in eight women will develop the disease at some point in her life.

Although the incidence of breast cancer is increasing, mortality from this disease is decreasing. This is mainly due to the breast cancer screening programs in which women aged 45-74 are called to have a mammographic exam every two years. Although mammography is still the most widely used screening method,

it suffers from two inherent limitations: a low sensitivity (cancer detection rate) in women with dense breast parenchyma, and a low specificity, causing unnecessary recalls. The low sensitivity in women with dense breasts is caused by a "masking effect" of overlying breast parenchyma. Furthermore, the summation of normal breast parenchyma on the conventional mammography may occasionally simulate a cancer. In recent years, new imaging techniques have been developed: tomosynthesis, which can produce 3D and 2D synthetic images of the breast, new MRI techniques with contrast

medium and breast CT. However, thanks to screening programs, numerous mammographic images can be collected from hospitals to build large datasets on which it is possible to explore AI techniques.

In recent years, new methods for image analysis have been developed. In 2012, for the first time, ImageNet Large Scale Visual Recognition Competition (ILSVRC), the most important image classification challenge worldwide, was won by a deep learning-based classifier named AlexNet [1]. Starting from this result, the success of deep learning on

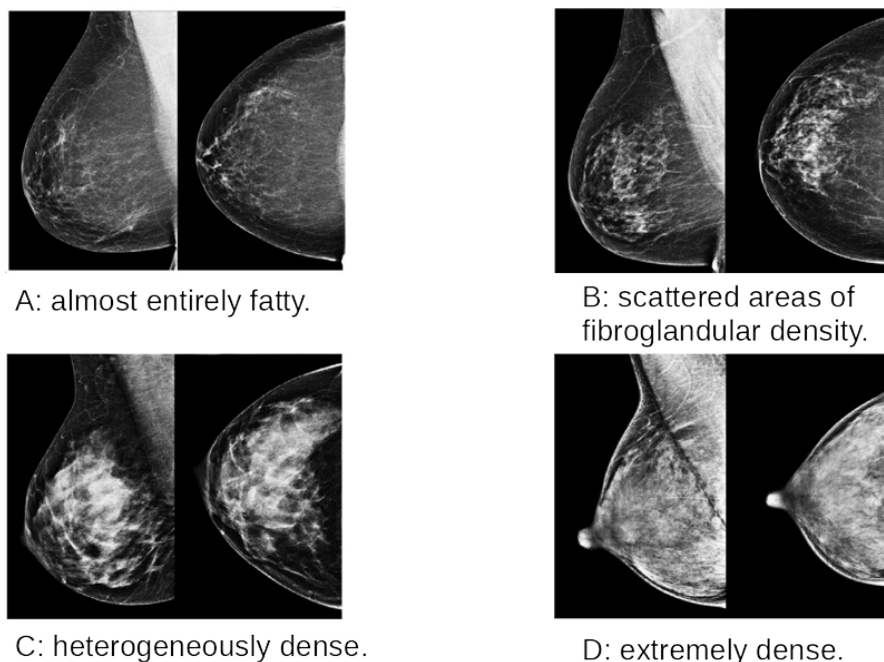


Figure 1: The four density classes are shown as reported in the BI-RADS Atlas. The classes are defined through textual description and examples and are named A, B, C and D in order of increasing density.

visual perception problems is inspiring much scientific work, not only on natural images, but on medical images too [2]. Deep learning-based techniques have the advantage of very high accuracy and predictive power at the expense of their interpretability. Furthermore, they usually need a huge amount of data and a large computational power to be trained.

At the Italian National Institute for Nuclear Physics (INFN), within the framework of a PhD in data science [L2] of Scuola Normale Superiore of Pisa, University of Pisa and the ISTI-CNR, we are working to apply deep learning models to find new image biomarkers extracted from screening mammograms that can help with early diagnosis of breast cancer.

Previously [3], we trained and evaluated a breast parenchyma classifier in the BI-RADS standard, which is made of four qualitative density classes (Figure 1), using a deep convolutional neural network and we obtained very good results compared to other work. Our research activities are continuing with a larger dataset and more ambitious objectives. We are collecting data from Tuscany screening programs and the ever-expanding dataset currently includes:

- 2,000 mammographic exams (8,000 images, four per subject) of healthy women labelled by the amount of fibroglandular tissue. These exams have been extracted from the Hospital of Pisa database.
- 500 screen-detected cases of cancer, 90 interval cancer cases and 270 control exams along with the histologic reports and a questionnaire with the known breast cancer risk factors, such as parity, height, weight and family history. It is possible to access all the mammograms prior to diagnosis for each woman. These exams have been extracted from the North-West Tuscany screening database.

The goal of our work is multi-fold and may be summarised as follows:

- to explore the robustness of deep learning algorithms with respect to the use of different mammographic systems, which usually result in different imaging properties.
- to define a deep learning model able to recognise the kind and nature of the malignant masses depicted in mammographic data based on the related histologic reports.
- to investigate the inclusion of the fibroglandular parenchyma in breast cancer risk models in order to increase the predictive power of current risk prediction models. In this respect, changes in dense parenchyma will be monitored over time

through image registration techniques, to understand how its variation may influence cancer risk. Furthermore, we will investigate the role of dense tissue in the onset of interval cancers and the correlation among both local and global fibroglandular tissue and other known risk factors so as to quantify the risk in developing a breast cancer.

Links:

[L1] <https://kwz.me/hy5>

[L2] <https://datasciencephd.eu/>

References:

- [1] Alex Krizhevsky et al.: “ImageNet classification with deep convolutional neural networks”, NIPS'12 Proceedings, 2012.
- [2] Geert Litjens et al.: “A survey on deep learning in medical image analysis”, Medical Image Analysis, 2017.
- [3] F. Lizzi et al.: “Residual Convolutional Neural Network for breast density classification”, BIOINFORMATICS Proceedings, 2019, ISBN: 978-989-758-353-7.

Please contact:

Francesca Lizzi, National Institute for Nuclear Physics, Scuola Normale Superiore, National Research Council, University of Pisa, Italy
francesca.lizzi@sns.it

Content-Based Analysis of Medical Image Data for Augmented Reality Based Health Applications

by Andrea Manno-Kovacs (MTA SZTAKI / PPKE ITK), Csaba Benedek (MTA SZTAKI) and Levente Kovács (MTA SZTAKI)

Novel 3D sensors and augmented reality-based visualisation technology are being integrated for innovative healthcare applications to improve the diagnostic process, strengthen the doctor-patient relationship and open new horizons in medical education. Our aim is to help doctors and patients explain and visualise medical status using computer vision and augmented reality.

Data from medical 3D sensors, such as computer tomography (CT) and magnetic resonance imaging (MRI), give 3D information as output, thereby creating the opportunity to model 3D objects (e.g., organs, tissues, lesions) existing inside the body. These quantitative imaging techniques play a major role in early diagnosis and make it possible to continuously monitor the patient. With the improvement of these sensors, a large amount of 3D data with high spatial resolution is acquired. Developing efficient processing methods for this diverse output is essential.

Our “Content Based Analysis of Medical Image Data” project, conducted with Pázmány Péter Catholic University, Faculty of Information Technology and Bionics (PPKE ITK) [L1], concentrated on the development of image processing algorithms for multimodal medical sensors (CT and MRI), applying content-based information, saliency models and fusing them with learning-based techniques. We developed fusion methods for efficient segmentation of medical data, by integrating the advantages of generative segmentation models, applying traditional, “handcrafted” features; and the currently preferred discriminative models using convolutional features. By fusing the two approaches, the drawbacks of the different models can be reduced, providing a robust performance on heterogeneous data, even with previously unseen data acquired by different scanners.

The fusion model [1] was introduced and evaluated for brain tumour segmentation on MRI volumes, using a novel combination of multiple MRI modalities and previously built healthy templates as a first step to highlight possible lesions. In the generative part of the proposed model, a colour- and spatial-based saliency model was applied, integrating a priori knowledge

on tumours and 3D information between neighbouring scan slices. The saliency-based output is then combined with convolutional neural networks to reduce the networks’ eventual overfitting which may result in weaker predictions for unseen cases. By introducing a proof-of-concept method for the fusion of deep learning techniques with saliency-based, handcrafted feature models, the fusion approach has good abstraction skills, yet can handle diverse cases for which the net was less trained.

In a similar manner, we also implemented a technique for liver segmenta-

tion in CT scans. First, a pre-processing was introduced using a bone mask to filter the abdominal region (this is important in the case of whole-body scans). Then a combination of region growing, and active contour methods was applied for liver region segmentation. This traditional feature-based technique was fused with a convolutional neural network’s prediction mask to increase segmentation accuracy (Figure 1).

The proposed techniques [2] have been successfully applied in the “zMed” project [L2], a four-year project run by Zinemath Zrt., the Machine Perception

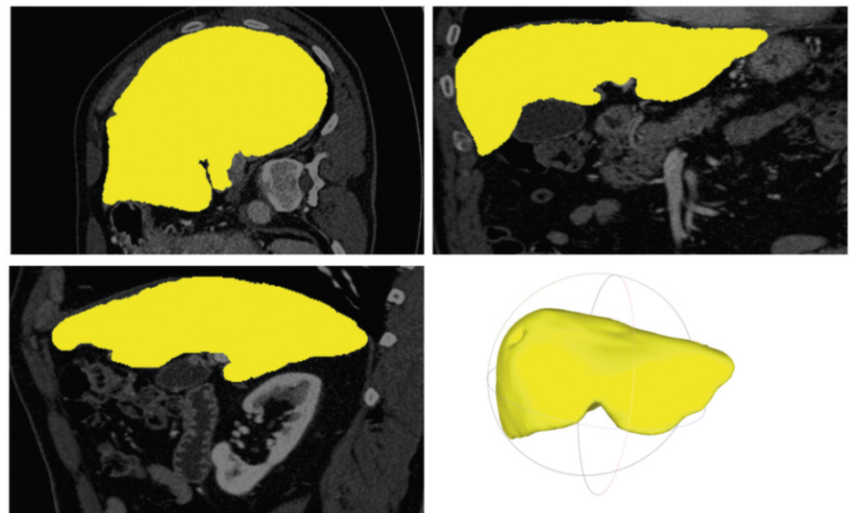


Figure 1: Liver segmentation and 3D modelling on CT data: Segmentation result in axial, coronal, sagittal view and the rendered 3D model of the liver.



Figure 2: The main motivations of the zMed project [L2].

Research Laboratory in the Institute for Computer Science and Control of the Hungarian Academy of Sciences (MTA SZTAKI) [L3] together with the University of Pécs (PTE). The Department of Radiology at PTE provides input data of different modalities (CT and MRI) for the segmentation algorithms, developed by the computer vision researchers of MTA SZTAKI. Based on these tools, Zinemath Zrt is developing a software package, which provides 3D imaging and visualisation technologies for unified visualisation of medical data and various sorts of spatial measurements in an augmented reality system. By creating a completely novel visualisation mode and exceeding the current display limits, the software package applies novel technologies, such as machine learning, augmented reality and 3D image processing approaches.

The developed software package is planned to be adaptable to multiple medical fields: medical education and training for future physicians, introducing the latest methods more actively; improving the doctor-patient relationship by providing explanations and visualisations of the illness; surgical planning and preparation in the pre-operative phase to reduce the planning time and contributing to a more precisely designed procedure (Figure 2).

This work was supported by the ÚNKP-18-4-PPKE-132 New National Excellence Program of the Hungarian Government, Ministry of Human Capacities, and the Hungarian Government, Ministry for National Economy (NGM), under grant number GINOP-2.2.1-15-2017-00083.

Links:

[L1]: <https://itk.ppke.hu/en>
[L2]: <http://zinemath.com/zmed/>
[L3]: <http://mplab.sztaki.hu>

References:

- [1] P. Takacs and A. Manno-Kovacs: "MRI Brain Tumor Segmentation Combining Saliency and Convolutional Network Features", Proc. of CBMI, 2018.
- [2] A. Kriston, et al.: "Segmentation of multiple organs in Computed Tomography and Magnetic Resonance Imaging measurements", 4th International Interdisciplinary 3D Conference, 2018.

Please contact:

Andrea Manno-Kovacs
MTA SZTAKI, MPLab
andrea.manno-kovacs@sztaki.mta.hu

Artificial Intelligence: Understanding Diseases that People Cannot Understand?

by Marleen Balvert and Alexander Schönhuth (CWI)

Many diseases that we cannot currently cure, such as cancer, Alzheimer's and amyotrophic lateral sclerosis (ALS), are caused by variations in the DNA sequence. It is often unknown which characteristics caused the disease. Knowing these would greatly help our understanding of the underlying disease mechanisms, and would boost drug development. At CWI we develop methods based on artificial intelligence (AI) to help find the genetic causes of disease, with promising first results.

Identifying disease-causing genetic characteristics starts with analysing datasets containing the genetic information of both healthy individuals and patients with a disease of interest. The data analysis provides direction to disease experts and lab researchers, who can experimentally test whether a genetic variant indeed causes disease. Validated disease-causing genetic variants provide insight into the cellular processes involved in disease, which is the starting point for drug development.

Today's predominant technique for analysing genome datasets, called genome-wide association studies (GWAS), ensures that cause (genetic variant) and effect (disease) can be linked in a way the human mind can grasp. GWAS examine each individual genetic variants for correlation with disease, following well-understood statistical principles. GWAS allows the researcher to easily interpret findings

and has been very successful: many potentially disease-causing variants have been detected for various diseases.

However, several diseases stubbornly resist such "human intelligence-based approaches", as their genetic architecture is difficult to unravel. One architectural feature that complicates analyses considerably is epistasis[1]: genetic variants do not necessarily just add up their effects to establish effects, but operate in terms of logical combinations. Consider, for example, three variants A, B and C, which establish the disease-causing effects if (and only if) A is not there, or B and C are both there. Such complex logical relationships reflect common biochemical gateways.

Analysing diseases with a more involved genetic architecture, such as cancer, type II diabetes or ALS, in terms of "human mind perceivable" approaches clearly has reached certain

limits. So, an immediate question is: if the human mind is struggling, can AI help out?

This motivated CWI researchers Marleen Balvert and Alexander Schönhuth to develop new, AI-based techniques for identifying complex combinations of genetic characteristics that are associated with disease. The challenge is twofold.

First, genome datasets contain millions of genetic variants for thousands or tens of thousands of individuals. Deep neural networks - currently established among the most successful classification techniques [2] - offer enhanced opportunities in processing large datasets. This motivated Balvert and Schönhuth to employ deep neural networks.

Second, deep neural networks have been predominantly developed for

image classification. Unlike image data - the structure of which can be grasped immediately - genetic data has a structure that is governed by the laws of evolution and reproduction. Arranging genetics data to act as input to deep neural networks therefore requires expert knowledge.

Together with ALS expert Jan Veldink from UMC Utrecht, Balvert and Schönhuth took on the challenge of developing a deep neural network to classify healthy individuals from ALS patients using data from over 11,000 people. The data were collected through Project MinE, a global genome data project that deals with ALS. Note that the CWI researchers were guided by the idea to design a general neural network architecture for diseases with a complex genetic architecture, so as to not necessarily specialise in a particular disease.

The team implemented a two-step procedure [3]. First, a relatively lightweight neural network identifies promoter regions - parts of the genome that initiate the reading of a gene - that are indicative of disease. Upon identifying several tens out of the 20,000 promoter regions an ultra-deep neural network predicts whether someone is affected by ALS based on the variants captured by the selected promoter regions.

If the neural network achieves good predictive performance, it has “learned” how to identify disease. The genetic architecture of the disease is thus captured by the wirings of the neural network.



CWI researchers are currently developing AI techniques to help identify the genetic characteristics that lead to disease. Picture: Shutterstock.

Balvert, Schönhuth and their team were intrigued and enthusiastic to observe that their networks achieved excellent performance in predicting ALS; ALS has been marked as a disease whose genetic architecture is most difficult to disentangle. The networks achieved 76 % prediction accuracy, surpassing the simpler, “human mind perceivable” approaches that achieved 64 % accuracy at best. Further improvements are still possible.

These highly encouraging results point out that AI can do an excellent job in understanding complex genetic disorders. However, we will encounter many further issues before AI will find its way into clinical practice. Most importantly, while AI can understand the genetic architecture of a disease, we are not able to fully disentangle the wirings a neural network uses for its predictions, and the human mind still has not been helped.

But there is hope: method development that aims at human understanding of AI is one of the most active areas of research of our times.

References:

- [1] V. Tam, et al.: “Benefits and limitations of genome-wide association studies”, *Nature Review Genetics*, 2019.
- [2] J. Schmidhuber: “Deep learning in neural networks: An overview”, *Neural networks* 61, 2015: 85-117.
- [3] B. Yin, et al.: “Using the structure of genome data in the design of deep neural networks for predicting amyotrophic lateral sclerosis from genotype”, *Bioinformatics (Proc. of ISMB/ECCB 2019)*, to appear.

Please contact:

Marleen Balvert, CWI, The Netherlands
m.balvert@cwi.nl

The Genetic Diversity of Viruses on a Graphical Map: Discovery of Resistant and Virulent Strains

by Alexander Schönhuth (CWI and Utrecht University) and Leen Stougie (CWI and VU Amsterdam)

Many life-threatening viruses populate their hosts with a cocktail of different strains, which may mutate insanely fast, protecting the virus from human immune response or medical treatment. Researchers at CWI have designed a method, named Virus-VariationGraph (Virus-VG) [3], that puts all strains onto a graphical map, which facilitates more reliable and convenient identification of potentially resistance-inducing or particularly lethal strains. □

Viruses, such as HIV, Ebola and Zika, populate their hosts as a viral quasi-species: a collection of genetically related mutant strains, which rapidly evolve by the accumulation of ever more

mutations as well as recombination among the strains. To determine the right treatment for infected people, it is crucial to draw a clear picture of the virus DNA that affects the patients [1].

The genome of an HIV strain, for example, consists of approximately 10,000 letters. While most virus strains generally share most letters, comparatively rare, but utterly relevant differ-

ences can decisively determine their clinically relevant properties, such as resistance to treatment, or their virulence. To draw a clear picture, it is necessary to, first, reconstruct the genomes of the different strains at full length, and second, to estimate the relative proportions of the strains that make up the viral quasispecies, the mix of strains affecting an individual patient.

Applying modern sequencing techniques to virus DNA extracted from infected people yields millions of sequence fragments, however, and not full-length genomes of strains. The task is now to assign the (many) fragments to different strains. Each genome then needs to be reconstructed at full length, and its relative abundance estimated within the mix of strain genomes. This procedure is commonly referred to as viral quasispecies assembly. It is important to note that virus reference genomes, which seem to promise orientation during the assembly process can considerably disturb this procedure, by introducing biases that can decisively hamper the assembly.

Viral quasispecies assembly is very challenging, particularly in the absence of reference genomes, and is not yet a fully resolved issue. Schönhuth, Stougie and their co-workers have recently taken big strides in this area.

Their idea was to put all fragments (or better: contigs, which are contiguous patches of fragments that together must stem from an identical strain; these can be reliably determined using other methods [2]) on a directed, graphical map. In such a map, full-length paths correspond to full-length genomes. Further, the relative abundance of a strain genome then relates to the relative number of fragments that make part of the path through this map. This graphical map then allows low-frequency strains - paths through the map that are supported by rather low amounts of fragments - to be conveniently highlighted. The identification of low-frequency strains is important in the analysis of viral quasispecies. When not subjected to a careful analysis, low-frequency strains tend to be neglected, and consequently such strains may induce resistance to treatment or emerge as particularly virulent after treatment.

Schönhuth, Stougie and co-workers have developed a method, Virus-

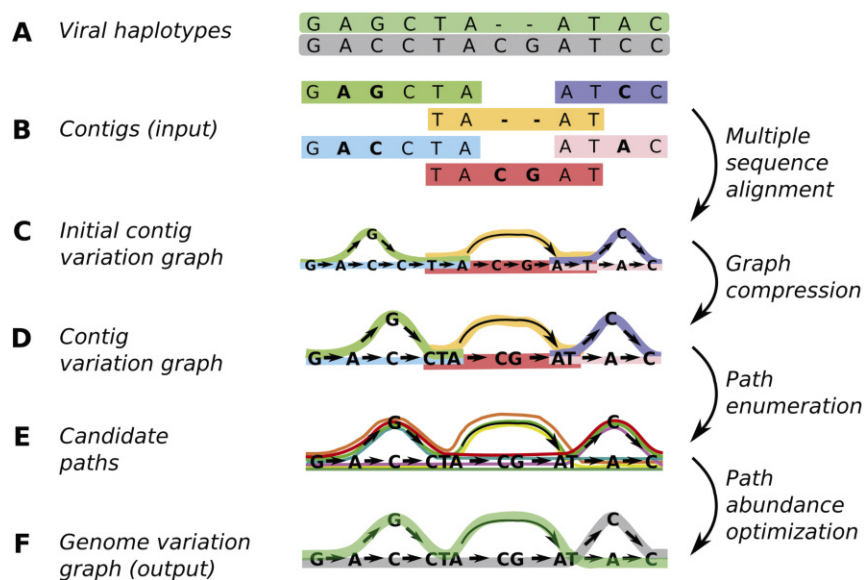


Figure 1: At CWI, researchers have developed Virus-VG, an algorithm that is more reliable and convenient to use for assembling viral quasispecies than earlier methods. Picture: CWI.

VariationGraph (Virus-VG) that implements these ideas. This was achieved through the construction of “variation graphs” from the input fragments (which are contigs, see above). Variation graphs have become popular recently in the analysis of genomes. The general idea is to transform a collection of related genomes into a variation graph, which allows for types of genome analyses that were hitherto unconceivable. Usually, however, variation graphs are constructed from full-length genomes, which prevents the use of variation graphs for viral quasispecies assembly.

Here, Schönhuth, Stougie and co-workers generalised the concept of variation graphs, which allowed them to be flexibly constructed from shorter sequence patches. They designed an optimisation problem whose solution consists of laying out the paths that correspond to strain genomes, and assigns relative abundances to those paths. See Figure 1 for an illustration of the steps.

They were able to demonstrate the advantages of the new graph-based approach over other viral quasispecies approaches (all of which use reference genomes), in various relevant aspects, such as strain coverage, length of genomes, and abundance estimates. This method seems especially beneficial for identifying low-frequency strains, which is of particular interest for the above-mentioned clinical reasons.

Overall, Schönhuth, Stougie and co-workers succeeded in providing the first solution to the viral quasispecies assembly problem that does not only yield the genomes of the strains at maximal length, but also reliably estimates their relative abundances, without making use of existing reference genomes. Virus-VG is publicly available at [L1].

Link:

[L1] <https://kwz.me/hy3>

References:

[1] S. Posada-Céspedes, D. Seifert and N. Beerenwinkel: “Recent advances in inferring viral diversity from high-throughput sequencing data”, *Virus research*, 239, 17-32, 2017.

[2] J. Baaijens, et al.: “Full-length de novo viral quasispecies assembly through variation graph construction”, *Bioinformatics*, btz443, <https://doi.org/10.1093/bioinformatics/btz443>, 2019

[3] J. Baaijens, A.Z. El Aabidine, E. Rivals, A. Schönhuth: "De novo assembly of viral quasispecies using overlap graphs", *Genome Research*, 27(5), 835-848, 2017.

Please contact:

Alexander Schönhuth.
CWI, Netherlands.
a.schoenhuth@cwi.nl

Improved Antibody Optimisation for Tumour Analysis Through the Combination of Machine Learning with New Molecular Assay

by Anna Fomitcheva Khartchenko (ETH Zurich, IBM Research – Zurich), Aditya Kashyap and Govind V. Kaigala (IBM Research – Zurich)

The role of a pathologist is critical to the cancer diagnosis workflow: they need to understand patient pathology and provide clinicians with insights through result interpretation. To do so, pathologists and their laboratory teams perform various investigations (assays) on a biopsy tissue. One of the most common tests is immunohistochemistry (IHC), which probes the expression levels for certain proteins that characterise the tissue, called biomarkers. This test enables sub-classification of the disease and is critical for the selection of a treatment modality. However, the number of biomarkers is constantly increasing, while the size of the biopsy is reducing due to early testing and more sensitive methods.

To reduce tissue consumption when performing these tests, our team implemented a variation of IHC that we termed micro-IHC (μ IHC). The rationale was to reduce the area stained on the tissue section only to a region of interest at the micrometre scale, for example a small portion of the tumour. To perform μ IHC we use a microfluidic probe (MFP), a liquid scanning probe, which is a device that locally deposits chemicals on specific regions of the tissue at the micrometre-length scale. This way, we perform not only local IHC staining but also can use several biomarkers on the same tissue section [1].

Using the capabilities of μ IHC, we envisioned its application in optimising antibody-antigen reaction, a critical step in quality control of the IHC test. Currently, new antibodies must be tested across a range of concentrations and incubation times with multiple tissue sections to test their specificity and sensitivity. This can consume a great number of valuable samples while providing only limited information. The high tissue consumption reduces the feasibility of optimising each batch of antibodies, although it is known that they can present variations in performance. These variations are amplified when more than one tissue section is used, which often come from different sources or are prepared differently.

In these circumstances, the use of μ IHC on a tissue section can generate an array with several conditions, limiting tissue consumption and equalising the whole downstream process. This potentially reduces the variability that is inherent when using different samples.

Defining “optimal” for a stain

With this methodology in hand we were faced with a rather tricky question: what is an “optimal” stain? We realised there is no straightforward answer, since the “optimal” stain varies depending on the tissue type. Take for example a common biomarker in breast cancer, HER2. The optimal stain in a healthy tissue would be “no stain”. Any stain that we observe is qualified as a false positive. However, in about 20 % of cases of breast cancer, the biomarker is present, producing a stain of varying intensities. “No stain” in this circumstance is regarded as a false negative, but even changes in stain intensity could misdirect the treatment provided by clinicians. Other staining artefacts, such as overstaining, can make the interpretation of the test more complex by masking the signal.

Using machine learning to obtain an optimal stain qualification

We asked several experts to classify our stains in “good”, “acceptable” and “not acceptable”. Nevertheless, we knew

that manual labour was not an efficient and scalable way to perform this (or any) optimisation. Therefore, we decided to use the capabilities of machine learning to generate a more objective way to score the tissues, using the references provided by the pathologists [2].

We imaged all tested conditions and proceeded to extract features based on intensity, texture and the Fourier transform. These features were used for two purposes. On one side, the algorithm had to understand what kind of tissue was being considered. As mentioned, the expected staining is not the same if we are analysing a healthy tissue over a tumour tissue, making tissue identification an important facet. To do so, we train a classifier method that can learn from labelled data, a Support Vector Machine, with sets of features until we identify a set that gives the best separation between the pre-defined classes. Once this is done, the images that were not used in the training are analysed and the algorithm predicts their probability of belonging to a certain tissue type.

On the other side, the algorithm analyses the contrast level between the different compartments observed in the cell by looking at the intensities of each region. This is necessary to understand

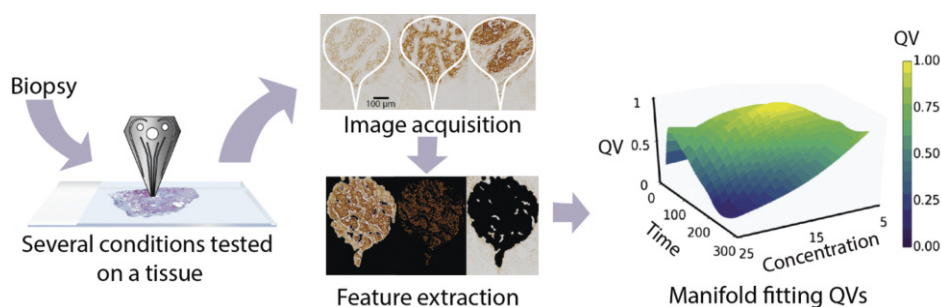


Figure 1: Schematic workflow for the processing of a tissue to obtain the quality value (QV) parameter manifold.

whether the stain, for the particular tissue type we are analysing, is a staining artefact. With all parts in place, the contrast level and the tissue type identifier are combined into an indicator, the “Quality Value” (QV), which gives the probability of a good quality stain ranging from 1 (best) to 0 (worst) depending on the tissue type (see Figure 1). We extracted the QVs from our analysed conditions and produced a manifold that provides essential information for optimal staining of a tissue for the patient.

Outlook

The information obtained from this study can be applied on biopsy samples

of individual patients to find the best staining conditions without consuming much of the sample. The remainder of the biopsy can then be used for other diagnostic tests. We believe that in this way the number of errors - defined as false positives and false negatives - caused by inadequate staining conditions may be reduced, however we are yet to decisively prove this. We hope to demonstrate such validation in future work.

We also believe the convergence of machine learning approaches with image processing and new implementations for performing biochemical assays on tissue sections will together lead to

more accurate tumour profiling and thereby a more reliable diagnosis.

References:

- [1] R. D. Lovchik, et al.: “Micro-immunohistochemistry using a microfluidic probe. Lab Chip 12”, 1040-1043 (2012).
- [2] N. M. Arar, et al.: “High-quality immunohistochemical stains through computational assay parameter optimization”, IEEE Trans. Biomed. Eng. pp, 1–1 (2019).

Please contact:

Govind V. Kaigala
IBM Research – Zurich, Switzerland
gov@zurich.ibm.com

AI Enables Explainable Drug Sensitivity Screenings

by Matteo Manica, Ali Oskooei, and Jannis Born (IBM Research)

Accelerating anticancer drug discovery is pivotal in improving therapies and patient prognosis in cancer medicine. Over the years, in-silico screening has greatly helped enhance the efficiency of the drug discovery process. Despite the advances in the field, there remains a need for explainable predictive models that can shed light onto the anticancer drug sensitivity problem. A team of scientists at the Computational Systems Biology group within IBM Research has now proposed a novel AI approach to bridge this gap.

Only 10–14 % of drug candidates entering clinical trials actually reach the market as medicine, with an estimated US \$2–3 billion price tag for each new treatment [1]. Despite enormous scientific and technological advances in recent years, serendipity still plays a major role in anticancer drug discovery without a systematic way to accumulate and leverage years of R&D to achieve higher success rates in the process. At the moment, a drug is usually designed by considering which protein target might induce signalling pathway cascades lethal for tumour cells. After this initial design phase, the efficacy of a compound on specific tumour types requires intensive experimental validation on cell lines. The costs of this experimental phase can be prohibitive and any solution that helps to decrease the number of required experimental assays can provide an incredible competitive advantage and reduce time to market.

In this context, IBM Research developed PaccMann [2,3], an in-silico platform for compound screening based on the most recent advances in AI for computational biochemistry. The model developed implements a holistic multi-

modal approach to drug sensitivity combining three key data modalities: anticancer compound structure in the form of SMILES, molecular profile of cell lines in the form of gene expression data and prior knowledge in the form of biomolecular interactions. PaccMann predicts drug sensitivity (IC₅₀) on drug-cell-pairs while highlighting the most informative genes and compound sub-structures using a novel contextual attention mechanism. Attention mechanisms have gained popularity in recent years, since they enable interpretable predictions by using specific layers that allow the model to focus and assign high attention weights to input features important for the task of interest.

PaccMann has been trained and validated on GDSC [L1], a public dataset of cell lines screened with a collection of compounds. The method outperforms a baseline based on molecular fingerprints and a wide selection of deep learning-based techniques in an extensive cross-validation benchmark. Specifically, PaccMann achieves high prediction performance ($R^2 = 0.86$ and $RMSE = 0.89$, see Figure 1), outperforming previously reported state-of-

the-art results for multimodal drug sensitivity prediction.

To showcase the explainability of PaccMann, its predictions on a Chronic Myelogenous Leukaemia (CML) cell line for two extremely similar anticancer compounds (Imatinib and Masitinib) have been analysed. The attention weights of the molecules are drastically different for the compounds' functional groups whereas the remaining regions are unaffected (see Figure 2, top). The localised discrepancy in attention centred at the different rings suggests that these substructures drive the sensitivity prediction for the two compounds on the CML cell line. On the gene attention level (see Figure 2, bottom) a set of genes has been detected as relevant. Interestingly, the DDR1 protein is a member of Receptor Tyrosine Kinases (RTKs), the same group of cell membrane receptors that both considered drugs inhibit. DDR1 as well as the other highlighted genes have been previously reported in cancer literature, especially in leukaemia. These findings indicate that the genes that were given the highest attention weights

are indeed crucial players in the progression and treatment of leukaemia.

To quantify the drug attention on a larger scale, a collection of screened drug-cell line pairs has been considered. For each drug, the pairwise distance matrix of all attention profiles was computed. Correlating the Frobenius distance of these matrices for each pair of drugs with their Tanimoto similarity (established index for evaluating drug simi-

ilarity based on fingerprints) revealed a Pearson coefficient of 0.64 ($p < 1e-50$). The fact that the attention similarity of any two drugs is highly correlated with their structural similarity demonstrates the model's ability to learn insights on compounds' structural properties. As a global analysis of the gene attention mechanism, a set of highly attended genes has been compiled by analysing all the cell lines. Pathway enrichment analysis [L2] on this set identified a sig-

nificant activation (adjusted $p < 0.004$) of the apoptosis signalling pathway [L3]. IC50 prediction is in essence connected to apoptosis (cell death) and the attention analysis suggests that the model is focused on genes connected to this process, thus confirming the validity of the attention mechanism.

PaccMann paves the way for future directions such as: drug repositioning applications as it enables drug sensitivity prediction for any given drug-cell line pair, or leveraging the model in combination with recent advances in small molecule generation using generative models and reinforcement learning to design novel disease-specific, or even patient-specific compounds. This opens up a scenario where personalised treatments and therapies can become a concrete option for patient care in cancer precision medicine.

An open source release of PaccMann and the related codebase can be accessed on GitHub [L4]. A version of the model has been trained on publicly available data for the prediction of drug sensitivity (IC50) and has been deployed on IBM Cloud [L5]. The model predicts drug response on a set of 970 cell lines generated from multiple cancer types given a compound in SMILES format.

Links:

- [L1] <https://www.cancerrxgene.org/>
- [L2] <http://amp.pharm.mssm.edu/Enrichr/>
- [L3] <http://pantherdb.org>
- [L4] <https://kwz.me/hyS>
- [L5]: <https://ibm.biz/paccmann-aas>

References:

- [1] G. Schneider: "Mind and Machine in Drug Design", Nature Machine Intelligence.
- [2] A. Oskoei, J. Born, M. Manica et al.: "PaccMann: Prediction of anti-cancer compound sensitivity with multi-modal attention-based neural networks", WMLMM, NeurIPS.
- [3] M. Manica, A. Oskoei, J. Born et al.: "Towards Explainable Anti-cancer Compound Sensitivity Prediction via Multimodal Attention-based Convolutional Encoders", WCB, ICML.

Please contact:

Matteo Manica
IBM Research, Switzerland
tte@zurich.ibm.com

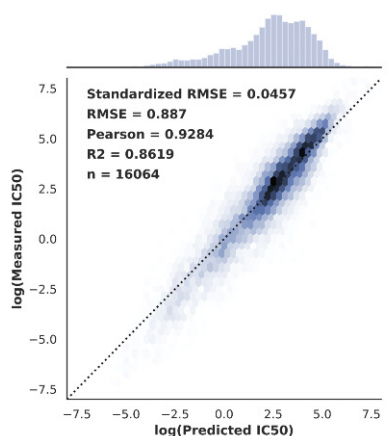


Figure 1: Performance of PaccMann on unseen drug-cell line pairs. Scatter plot of the correlation between true and predicted drug sensitivity by a late-fusion model ensemble on the cross-validation folds. RMSE refers to the plotted range, since the model was fitted in log space.

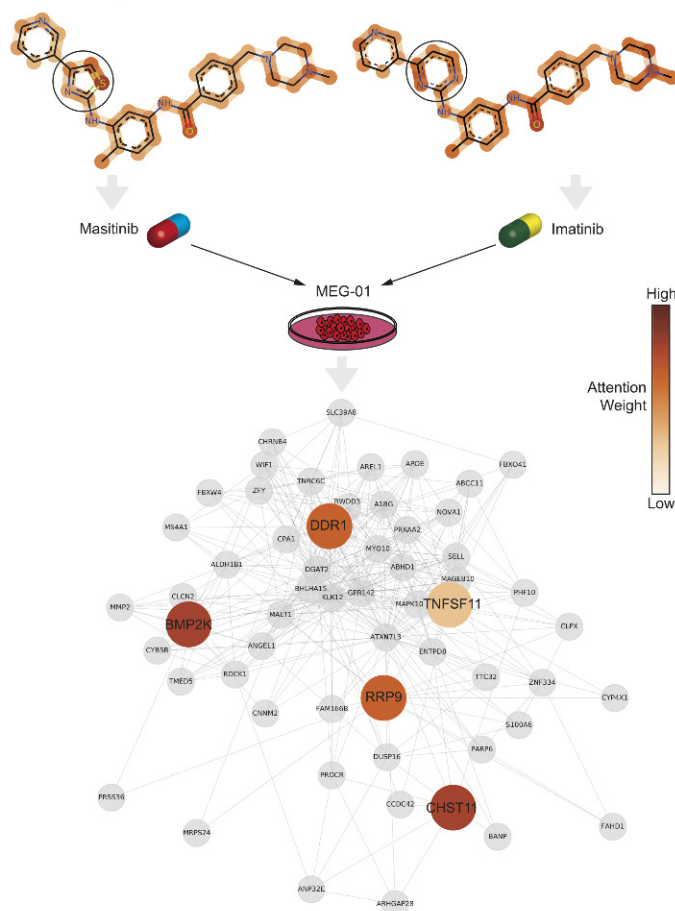


Figure 2: Neural attention on molecules and genes. Top: The molecular attention maps on the top demonstrate how the model's attention is shifted when the Thiazole group (Masitinib, left) is replaced by a Piperazine group (Imatinib, right). The change in attention across the two molecules is particularly concentrated around the affected rings, signifying that these functional groups play an important role in the mechanism of action for these Tyrosine-Kinase inhibitors when they act on a CML cell line. Bottom: The gene attention plot depicts the most attended genes of the CML cell line, all of which can be linked to leukemia.

Combining Predictive and Prescriptive Analytics to Improve Clinical Pathways

by Christophe Ponsard and Renaud De Landtsheer (GETIC)

Within a medical setting, clinical pathways enable efficient organisation of care processes, which benefit both the patient and hospital management. Digital health analytics plays a critical role in the successful deployment of clinical pathways. Two key aspects learned from our experience are the engineering of accurate workflow models and the use of online schedule optimisation, enforcing both care and resource constraints.

A clinical pathway is a multi-disciplinary view of the care process for a group of similar patients suffering from the same disease and with predictable evolution [1]. While scheduling the care for a single patient is straightforward, scheduling the care for a group of patients, and under limited resources is much more complex. Operating clinical pathways is very challenging because of the need to achieve the timely delivery of treatments like chemotherapy. It also requires a thorough knowledge of the history of each patient. Typical care quality indicators monitor the deviation from the ideal pathway and studies have stressed their correlation with cancer survival rate. Moreover, the actual workflow might be quite different from the defined workflow owing to adaptations resulting from a multidisciplinary context and the high level of personalisation.

Within the PIPAS project [L1], together with the Université catholique de Louvain, we have been engineering such a pathway. We started by developing a toolbox supporting the modelling and optimal scheduling of complex workflows [2]. To engineer medical process models, we defined and implemented different operators to combine/distinguish specific treatment for multipathology patients and to provide global or more focused viewpoints for specific agents (e.g. patient, nurse radiotherapist) or clinical departments.

Workflows of this kind need to be enacted precisely in order to ensure high quality of care to the pool of patients given the available resources (e.g. staff, beds, drug stocks). In order to orchestrate the work of an oncology day hospital, we developed an online scheduler dealing with the appointments and global nurse and room allocation [3]. Based on all the inputs illustrated in Figure 1, our tool provides

prescriptive analytics capabilities to the nurse in charge of setting appointments, i.e. it will help identify the next appointment date by looking at the time window allowed by the patient care indicator. It will also minimise

workload and triggers an alarm if insufficient resources are provisioned. Figure 2 shows how the scheduler can maintain a high care quality indicator (>90 %) until the service load becomes unmanageable.

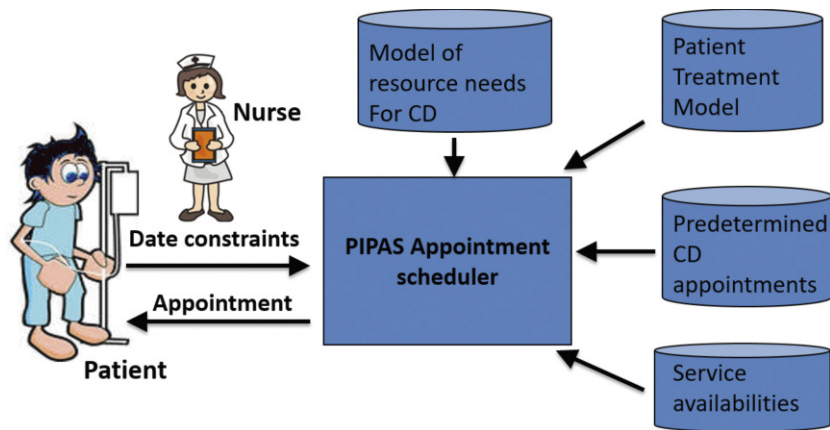


Figure 1: Prescriptive appointment scheduler.

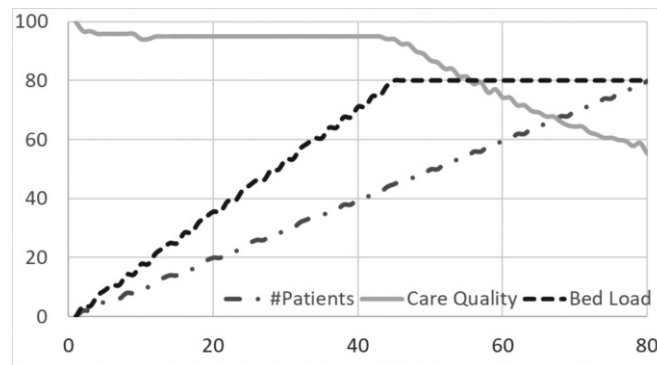


Figure 2: Simulation of service behaviour with increasing patient load until service saturation.

impacts on other patients by using a global view on the whole pool of known or even expected patients over their whole treatment period. Each deviation, such as a partial treatment or no show, is also immediately considered and recomputed using an efficient constraint local search engine called Oscar.CBLS [L2]. The scheduler also ensures a smoother repartition of the

The fact that the actual and theoretical workflows differ from one another, impacts the relevance of the proposed guidance. To address this risk, a reconciliation process analyses the path captured in patient health records to detect the presence of extra transitions, measure their relative frequencies and assess the global variability among patients. Predictive data analytics such

as data mining are used here. More specific techniques such as process mining can even help in inferring workflows from data. The result can then be used either to feed the tooling with a more accurate model or to reshape the organisation to enforce the wished workflow. This is our current progress and our next step is to start collecting and analysing data from our new Institute of Analytics for Health (INAH) in charge of providing an ethically controlled access to electronic health information based on the Walloon Health Network.

Links:

- [L1] <https://www.cetic.be/PIPAS-1169>
- [L2] <https://bitbucket.org/oscarlib/oscar>
- [L3] <https://www.cetic.be/INAH>

References:

- [1] H. Campbell and al.: “Integrated care pathways”, *British Medical Journal* pp. 133{137 (1998).
- [2] C. Damas, B. Lambeau, A. van Lamsweerde: “Transformation operators for easier engineering of medical process models”, *SEHC@ICSE*, 2013.

- [3] C. Ponsard and al.: “Quality of Care Driven Scheduling of Clinical Pathways Under Resource and Ethical Constraints”, *ICEIS (Revised Selected Papers) 2017*: 162-186.

Please contact:

Christophe Ponsard, CETIC, Belgium
+32 472 56 90 99
christophe.ponsard@cetic.be

A Holistic Clinical Decision Support System for Diagnosis of Dementia

by Mark van Gils (VTT)

Decision making for complex diseases requires efficient consideration of information from a large variety of very different data sources. We developed a machine-learning based decision support system for dementia diagnosis and evaluated it within four hospitals in Europe.

Clinical decision making is often fraught with difficulties related to extracting the right information from huge amounts of diverse data. Complex diseases are diseases in which diagnosis making is difficult. This may be, for instance, because symptoms are non-specific (different diseases cause similar symptoms), or there is high variability between individuals in how the disease manifests itself, or there is no objective gold standard regarding diagnosis.

An example of a complex disease is dementia. It is important to detect dementia as early as possible, before late-stage symptoms, such as severe memory problems become obvious, and there is no longer any room to improve quality of life. It is also important to discern between the different forms of dementia (differential diagnosis), in order to provide appropriate interventions. Different forms of dementia include Alzheimer’s disease (the most prominent form of dementia), vascular dementia, dementia with Lewy bodies, and frontotemporal dementia. To confuse the matter, healthy subjects may present with memory complaints similar to those of dementia patients.

Clinicians need to combine a wide range of data sources upon which to base deci-

sions. This information may range from imaging data (MRI, CT, and sometimes PET scans) to blood tests, genetic information, neuropsychological tests, text data from interviews and different -omics data. Additionally, data such as background information, as well as financial and feasibility constraints, need to be considered when deciding on appropriate interventions for an individual. The decision making also has a subjective component, based on personal experience. This complexity easily leads to less-than-optimal decision making, even if profound clinical expertise is available.

In addition to the complexity and diversity of the data, there are issues related to quality and availability. Not all data is available from all patients (different clinics have different resources, equipment and protocols), data quality may be less than optimal and the data may be in different formats and have different properties related to equipment and measurement environments. Clinical decision support systems (CDSS) based on principles of data-driven medicine potentially make the process more quantitative and objective. They thus may help to provide more confidence in the decision making for complex diseases.

In the EU-funded project VPH-DARE@IT [L1] a patient care platform was developed, and subsequently validated in the project PredictND [L2], that implements a CDSS integrating biomarkers from medical images, neuropsychological tests and other measurements. VTT and Combinostics Ltd. took care of the technical development, and clinical partners provided the needs and data for development and validation. The system helps form a multivariate integrated and easily understandable view of a patient’s status based on machine learning and data visualisation methods. It uses an approach where large multi-centre databases of previously diagnosed patients are used to build mathematical models of several dementing diseases, such as Alzheimer’s disease, frontotemporal dementia, vascular dementia and dementia with Lewy bodies. When a new patient arrives at a clinic, measurements are done, that are then compared with the disease models. The software architecture enables access to heterogeneous patient data from a large variety of data sources in different hospital settings.

The system’s analysis functionality has two main components: automatic segmentation and quantification of brain images and a supervised machine

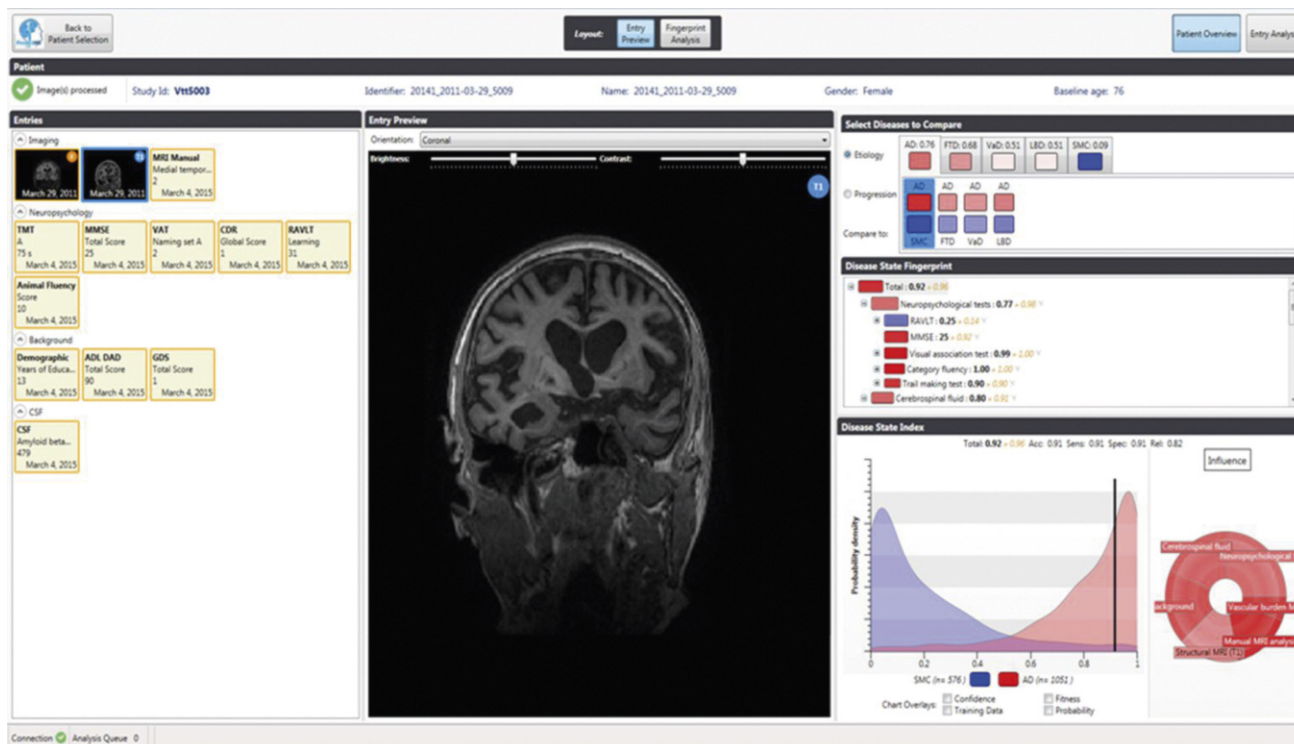


Figure 1: A screenshot of the decision support tool. On the left-hand side the different information sources are shown, including, in this example, MRI imaging data, neuropsychological test results, background information and cerebrospinal fluid (CSF) data. The middle panel shows the image analysis view which allows for automatic segmentation, quantification and visualisation of relevant parts of the brain. The right hand panel shows the multi-variate decision support functionality. At the top, the various forms of dementia that can be considered are shown, below is a “disease state fingerprint” indicating visually and quantitatively to which disease group this patient most likely belongs, together with the relative importance of the different variables. Finally, the raw data distributions of separate variables can be examined in the bottom right panel.

learning method for assessing and visualising the multi-variate state of patient with respect to the investigated diseases. First, fully automated image processing methods derive volumetric measures from brain MR images. Second, the quantified imaging data are combined with all other available data, including demographic information, neuropsychological test results, blood test analysis, CSF (cerebrospinal fluid) analysis and the patient’s genetic profile. A machine-learning paradigm, the Disease State Fingerprint [1], takes all patient data and compares it to previously diagnosed patients, providing an index of similarity with each disease profile. Moreover, it provides an interactive visual representation of the multi-variate patient state, allowing the clinician to understand which variables contribute to the decision suggestion, and how each contributes (Figure 1). It can show the overall “disease probability”, but also allows the user to zoom in to the distributions at detailed feature level to show, for instance, how the current patient’s measurements compare to the different disease-related distributions in the database. The methods work with interval, ordinal as well as nominal data,

and have been designed from the ground up to handle issues that are important in clinical decision making. These include dealing with missing data (“incomplete input vectors”) and the demand for explainability of classification results (“non black-box functioning”).

The methods have been shown, using cross-validation, to reach a classification accuracy of 82 % when discriminating patients between five different memory problems [2]. The clinical decision support tool using these methods was validated with 800 prospective patients, to examine how it performs, both quantitatively and from a usability perspective, with real users at four memory clinics across Europe (Finland, Denmark, The Netherlands and Italy) [3]. The results of this study showed that addition of the CDSS to the existing clinical process affected the diagnosis and increased clinicians’ confidence in the diagnosis indicating that CDSSs could aid clinicians in the differential diagnosis of dementia.

This work has been co-funded by the EC under Grant Agreements 601055 (VPH-DARE@IT) and 611005 (PredictND).

Links:

- [L1] www.vph-dare.eu
- [L2] www.predictnd.eu

References:

- [1] J. Mattila, J. Koikkalainen et al.: “Disease State Fingerprint for Evaluating the State of Alzheimer’s Disease in Patients”, *J Alzheimers Dis*, vol 27, pp. 163-176, 2011.
- [2] A. Tolonen, H. Rhodius-Meester et al.: “Data-Driven Differential Diagnosis of Dementia Using Multiclass Disease State Index Classifier”, *Frontiers in Aging Neuroscience*, vol. 10, , pp. 111, 2018.
- [3] M. Bruun, Marie; K.S. Frederiksen et al.: “Impact of a Clinical Decision Support Tool on Dementia Diagnostics in Memory Clinics: The PredictND Validation Study”, *Current Alzheimer Research*, vol. 16, pp. 91-101, 2019.

Please contact:

Mark van Gils
 VTT Technical Research Centre of Finland Ltd., Finland
 tel. +358 20 722 3342
mark.vangils@vtt.fi

Connecting People, Services, and Data for Continuity of Care

by Fulvio Patara and Enrico Vicario (University of Florence)

The RACE project (Research on Evidence-based Appropriateness in Cardiology) exploits innovative infrastructures and integrated software services with the aim of “providing the right care, to the right subject, at the right time, by the right provider, in the right health facility”.

Appropriateness in medicine is the proper or correct use of health services, products and resources [1]. To evaluate and support appropriateness, ICT plays a crucial role, offering a growing ecosystem of medical diagnostic and health monitoring devices, communication networks, health information systems, and medical data analytics. In this scenario, data and service integration is key to overcoming issues resulting from heterogeneous insular systems (i.e., information silos) and data with high complexity in terms of volume, variety, variability, velocity, and veracity.

The RACE project [L1] fits into this context with the challenging goal of designing and developing a hardware/software architecture for effective implementation of more personalised, preventive, participatory, and predictive models of continuity of care (i.e., P4-medicine) from hospital to home. A prototype of the overall architecture has been tested over a concrete operative scenario, demonstrating its applicability in the remote monitoring of patients with chronic moderate heart failure (NYHA class II-III). We illustrate here some core concepts of the proposed

architecture, focusing on the specific contribution of the University of Florence in the design and engineering of Empedocle [2], an Electronic Health Record (EHR) system characterised by adaptability and changeability as primary requirements.

The RACE architecture for continuity of care

RACE is an architecture-driven project for remote patient monitoring whose components can be organised in three main layers, as shown in Figure 1.

Feeder layer – This level is characterised by HW/SW systems used by healthcare professionals within clinical settings, or by non-professionals in non-clinical environments, for tracking the state of a patient across time. On the one hand, EHR systems serve as a key instrument for recording, retrieving and manipulating repositories of health information in computer-processable form within clinical environments. On the other hand, remote monitoring devices comprise a primary source of information for health status monitoring of patients in non-clinical settings (e.g., home), particularly in the management

of chronic diseases. They typically require sensors to measure specific physiological parameters (e.g., blood pressure, heart rate, pulse oximetry) and wirelessly communicate to a gateway connected to the Internet, so as to feed the architecture with acquired data. Mobile health applications running on portable devices can integrate raw sensor data with higher information provided by non-professionals in order to support patient self-management by improving treatment adherence and offering automated medication reminders and alerts on out-of-range measurements.

Integration layer – Continuity of care gives emphasis to the semantic interoperability between multiple sources of information deployed on different settings. To ensure a real integration of data (produced by the feeder layer) and services (exposed by the healthcare analytics layer), the proposed architecture exploits a middleware integration platform for implementing loosely-coupled publish-subscribe communications between independently deployed and heterogeneous systems over a bus-like infrastructure. All moved clinical events

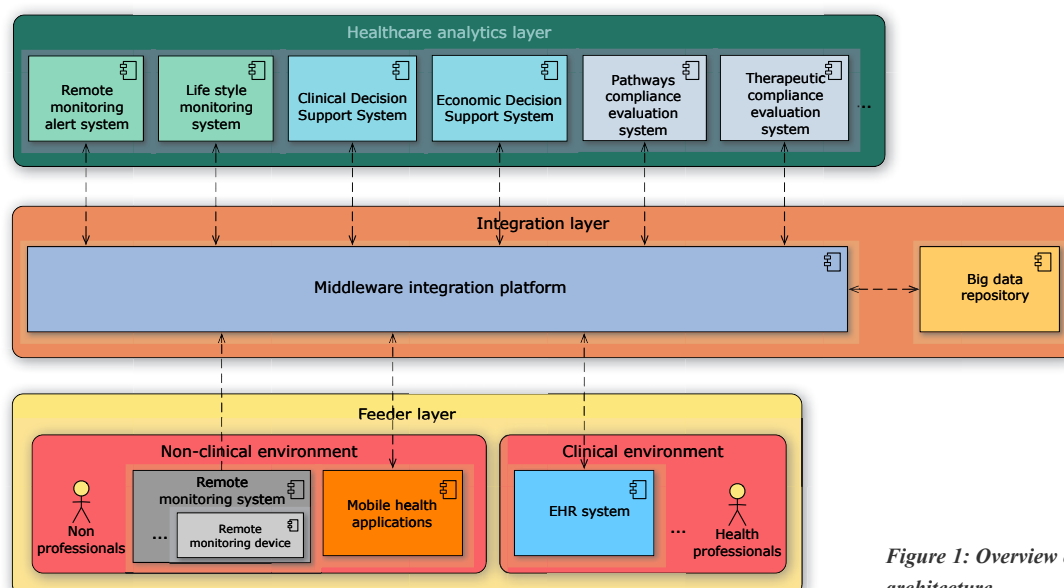


Figure 1: Overview of the RACE architecture.

are stored in a centralised big data repository that contains the full medical history about patients.

Healthcare analytics layer – A variety of data analytics systems are built on top of this architecture with the aim of processing historical records or new information stored in the big data repository for real-time and ex-post analytics uses. They are organised in three main categories based on their specific goals. Monitoring systems examine sensed data and generate personalised reminders for patients, and alarms for healthcare professionals in the case of adverse measurements. Decision Support Systems (DSS) assist clinical decision-making tasks (i.e., clinical DSS), as well as giving economic indicators to compare the costs and health outcomes of alternative care pathways (i.e., economic DSS). Finally, compliance evaluation systems evaluate the appropriateness of therapeutic treatment choices and care pathways.

Empedocle in action: an adaptable EHR system for continuity of care

The integration of multiple sources of structured information and the involvement of a variety of actors with different expertise emphasise the responsibility of EHR systems, which become key components in driving the patient to specific care pathways and, subsequently, in remotely monitoring the evolution of the patient's health status. In this context, we have developed the Empedocle EHR

system [2], a J2EE web-application that exploits a two-level meta-modelling architecture based on the Reflection architectural pattern [3] to combine the expected commodity level of any EHR system with some specific requirements posed by a real operative scenario of continuity of care, as: agile adaptability of the EHR data structure to different organisational contexts; interoperability of data and services across the platform; usability by users with different specialty expertise.

In such a scenario, Empedocle becomes a powerful real-time monitoring dashboard, offering to health professionals an effective alternative to in-clinic follow-ups, achieved by the integration of remote monitoring data in the local adaptable EHR. Moreover, the service orchestration capabilities offered by the integration platform enable several existing services to work together for enriching the EHR with higher-level knowledge (e.g., diagnostic investigations, drug interactions, contraindications, etc. as recommended by clinical guidelines implemented by the clinical DSS). Given the variety of skills involved in the process, connecting data with guidelines represents a key aspect for improving patient safety, reducing clinical risk, and evaluating the appropriateness of care.

The RACE Consortium

RACE was co-funded by Tuscany Region (Italy) in the POR FESR 2014-

2020 program from June 2015 to September 2018, and composed by industrial partners (i.e., GPI Group, Codices, Kell, Medilog, Spinekey, TD Nuove Tecnologie), public health institutes (i.e., G.Monasterio Foundation, Institute of Clinical Physiology of Pisa, Careggi University Hospital) and universities (i.e., University of Florence, Sant'Anna School of Advanced Studies).

Links:

[L1]: <https://stlab.dinfo.unifi.it/race-project>

References:

- [1] Canadian Medical Association. "Appropriateness in Health Care", 2015.
- [2] F. Patara, and E. Vicario: "An adaptable patient-centric electronic health record system for personalized home care", in Proc. ISMICT, 2014.
- [3] F. Buschmann et al.: "Pattern-oriented Software Architecture: A System of Patterns", 1996.

Please contact:

Fulvio Patara
University of Florence, Italy
fulvio.patara@unifi.it

Enrico Vicario
University of Florence, Italy
enrico.vicario@unifi.it

High Quality Phenotypic Data and Machine Learning Beat a Generic Risk Score in the Prediction of Mortality in Acute Coronary Syndrome

by Kari Antila (VTT), Niku Oksala (Tampere University Hospital) and Jussi A. Hernesniemi (Tampere University)

We set out to find out if models developed with a hospital's own data beat a current state-of-the art risk predictor for mortality in acute coronary syndrome. Our data of 9,066 patients was collected and integrated from operational clinical electronic health records. Our best classifier, XGBoost, achieved a performance of AUC 0.890 and beat the current generic gold standard, GRACE (AUC 0.822).

The use of electronic health records (EHRs) as a source of "big data" in cardiovascular research is attracting interest and investments. Integrating EHRs from multiple sources can potentially provide huge data sets for analysis. Another potentially very effective

approach is to focus more on data quality instead of quantity. We evaluated the applicability of large-scale data integration from multiple electronic sources to produce extensive and high quality cardiovascular (CVD) phenotype data for survival analysis and the

possible benefit of using novel machine learning [1]. For this purpose, we integrated clinical data recorded by treating physicians with other EHR data of all consecutive acute coronary syndrome (ACS) patients diagnosed invasively by

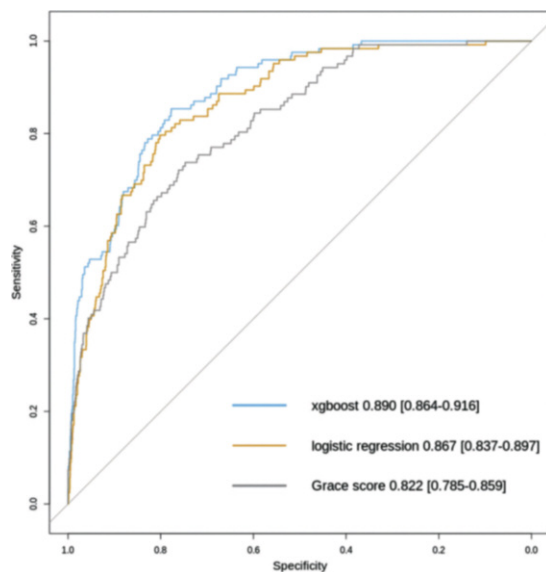


Figure 1: Comparison of model performance by receiving operating characteristic curves for different risk prediction models for six month mortality among patients undergoing coronary angiography in Tays Heart Hospital for acute coronary syndrome during years 2015 and 2016 (n = 1722 with n = 122 fatalities during a six-month follow-up).

coronary angiography over a 10-year period (2007 -2017).

To achieve this, we generated high quality phenotype data for a retrospective analysis of 9,066 consecutive patients (95% of all patients) undergoing coronary angiography for their first episode of ACS in a single tertiary care centre. Our main outcome was six-month mortality. Using regression analysis and machine learning method extreme gradient boosting (XGBoost) [2], multivariable risk prediction models were developed in a separate training set (patients treated in 2007-2014 and 2017, n=7151) and validated and compared to the Global Registry of Acute Coronary Events (GRACE) [3] score in a validation set (patients treated in 2015-2016, n=1771) with the full GRACE score data available.

In the entire study population, overall six-month mortality was 7.3 % (n=660). Many of the same variables were associated highly significantly with six-month mortality in both the regression and XGBoost analyses, indicating good data quality in the training set. Observing the performance of these methods in the validation set revealed that xgboost had the best predictive performance (AUC 0.890) when compared to logistic regression model (AUC 0.871, $p=0.012$ for difference in AUCs) and compared to the GRACE score (AUC 0.822, $p<0.00001$ for difference in AUCs) (Figure 1).

These results show that clinical data as recorded by physicians during treatment and conventional EHR data can be combined to produce extensive CVD phenotype data that works effectively in the prediction of mortality after ACS. The use of a machine learning algorithm such as gradient boosting leads to a more accurate prediction of mortality when compared to conventional regression analysis. The use of CVD phenotype data, either by conventional logistic regression or by machine learning, leads to significantly more accurate results when compared to the highly validated GRACE score specifically designed for the prediction of six-month mortality after admission for ACS. In conclusion, the use of both high quality phenotypic data and novel machine learning significantly improves prediction of mortality in ACS over the traditional GRACE score.

This study was part of the MADDEC (Mass Data in Detection and prediction of serious adverse Events in Cardiovascular diseases) project supported by Business Finland research funding (Grant no. 4197/31/2015) as apart of a collaboration between Tays Heart Hospital, University of Tampere, VTT Technical Research Centre Finland Ltd, GE Healthcare Finland Ltd, Fimlab laboratories Ltd, Bittium Ltd and Politechinco di Milano.

References:

- [1] J.A. Hernesniemi, S. Mahdiani, J.A.T. Tynkkynen, et al.: “ Extensive phenotype data and machine learning in prediction of mortality in acute coronary syndrome – the MADDEC study”, 2019. *Annals of Medicine*.
<https://doi.org/10.1080/07853890.2019.1596302>
- [2] T. Cheng, C. Guestrin: “XGBoost: A Scalable Tree Boosting System”, *KDD '16*, 2016.
<https://doi.org/10.1145/2939672.2939785>
- [3] K. Fox, J.M. Gore, K. Eagle, et al. : “Rationale and design of the grace (global registry of acute coronary events) project: A multinational registry of patients hospitalized with acute coronary syndromes”, *Am Heart J* 141:190–199, 2001.
<https://doi.org/10.1067/mhj.2001.112404>

Please contact:

Kari Antila
VTT Technical Research Centre of Finland Ltd
+358 40 834 7509

Digital Health Interoperability as a Tool Towards Citizen Empowerment

by Dimitrios G. Katehakis and Angelina Kouroubali (FORTH-ICS)

When interoperability policies and consistent implementations are in place, digital tools for citizen empowerment can be developed and used to provide information that would otherwise be unavailable to citizens.

The volume of data, the variety of data types, the increasing wealth of knowledge, and the ability to track disease and co-morbidities from start to finish already overpower the ability of humans to make informed decision about health and healthcare [1]. Single, personalised, user-friendly electronic health records for individuals are important enablers in achieving better health services and better patient outcomes. However, one of the greatest challenges in the digital era is providing people with seamless access to their health data within and across different health systems. Digital solutions for healthcare are still not as interoperable as expected and the secure sharing of information is limited. Even though the involved stakeholders have implemented a big number of digital projects in the past twenty years in the EU, most information is still in healthcare provider silos, rendering digital transformation for citizen empowerment difficult to realise.

In 2017, in an open consultation conducted by the Commission, the majority of respondents (93 %) either agreed (29 %) or strongly agreed (64 %) with the statement that “Citizens should be able to manage their own health data.” More than 80 % of respondents believed that sharing data could improve treatment, diagnosis and prevention of diseases across the EU. A large majority of respon-

dents (almost 60 %) identified the heterogeneity of electronic health records as one of the main barriers for exchange of health data in Europe [L1]. There is evident public demand for secure access to health data across the EU.

Although individuals have the right to, and desire for, access their personal data, including health data, most cannot yet access or securely share their health data seamlessly across the units of their national healthcare system.

In an effort to guarantee the secure and free flow of data within the EU for public administrations, businesses and citizens, the new European Interoperability Framework (EIF) was announced in 2017 [L2]. The new EIF provides guidance to public administrations, through a set of recommendations on interoperability governance, streamline processes for end-to-end digital services, cross-organisational relationships, and new legislation in support of interoperability. The new EIF can be adapted to support the eHealth domain in Europe, as a common framework for managing interoperability in the context of the eHealth digital services transformation at national level.

Within national health systems, interoperability should occur at all four levels: legal, organisational, semantic and tech-

nical. Legal interoperability ensures that organisations operating under different policies, legal frameworks and strategies can work together. Organisational interoperability refers to the way in which public administrations align their responsibilities, business processes and expectations to achieve mutually beneficial goals. Semantic interoperability refers to both the meaning of data and the exact format of the information specified for exchange. Technical interoperability covers the applications and infrastructures linking systems and services, including interface specifications [2], data presentation and secure communication protocols.

In order to secure citizens’ access to and sharing of health data, the EU is moving towards the development of specifications for a European exchange format, based on open standards, taking into consideration the potential use of data for research and other purposes. The recommendation on a European EHR exchange format sets out a framework to achieve secure, interoperable, cross-border access to, and exchange of, electronic health data in the EU [L3]. The aim is to deliver the right data, at the right time, for citizens and healthcare providers, and allow for the secure access, sharing and exchange of EHRs. The baseline includes electronic patient summaries, prescriptions and dispensa-

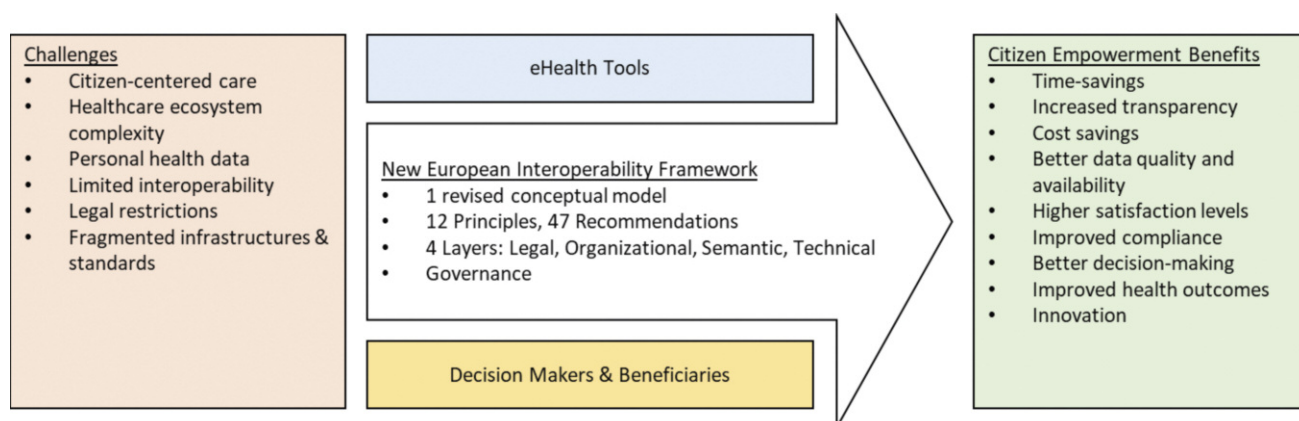


Figure 1: The New European Interoperability Framework as a facilitator of digital transformation for citizen empowerment [1].

tions, laboratory reports, medical images and reports, and hospital discharge reports, in alignment with established priorities at a European level.

By making the citizens as patients the point-of-care, digital health solutions, on the one hand, target clinician empowerment with actionable insights for faster and accurate diagnoses and prognoses for patient-tailored treatments, follow-ups and assistance, and, on the other hand, they assist individuals to be active players in their health management, with timely and targeted prevention and assistance strategies. The comprehensive vision focuses on making diseases, such as cancer [3], more preventable and treatment outcome more predictable, effective and personalised.

In order to achieve this vision, within national health systems, a roadmap for the development and maintenance of

national specifications needs to be in place. National, reusable interoperability specifications, compatible with the corresponding European ones, developed through open and transparent processes also need to be in place, together with mechanisms and tools for compliance control, testing and certification. Prerequisites for enabling data reuse and workflow automation include well-defined use cases, agreed terminology, and reliable clinical content.

Appropriate governance and legislation are important to ensure the consistent application of eHealth interoperability and that all involved parties, including health organisations and solution providers, will comply with it.

Links:

[L1] <https://kwz.me/hy6>

[L2] https://ec.europa.eu/isa2/eif_en

[L3] <https://kwz.me/hy7>

References:

- [1] A. Kouroubali, D. Katakis: “The new European interoperability framework as a facilitator of digital transformation for citizen empowerment”, *Journal of Biomedical Informatics*, 94, 103166, 2019.
- [2] D. G. Katakis, et al.: “Integrated care solutions for the citizen: Personal health record functional models to support interoperability”, *EJBI*, 13(1), 41-56, 2017.
- [3] A. Kouroubali, et al.: “An Integrated Approach Towards Developing Quality Mobile Health Apps for Cancer”, in *Mobile Health Applications for Quality Healthcare Delivery*, pp. 46-71, IGI Global, 2019.

Please contact:

Dimitrios G. Katakis
FORTH-ICS, Greece
+30 2810 391589
katakis@ics.forth.gr

Towards VNUMED for Healthcare Research Activities in Vietnam

by Chau Vo, (Ho Chi Minh City University of Technology, Vietnam National University), Bao Ho (John von Neumann Institute, Vietnam National University) and Hung Son Nguyen, University of Warsaw

Inspired by MIMIC-III [1], VNUMED is a unified intermediate database of electronic medical records that is being developed in Vietnam. Its purpose is to gather medical records from hospitals, which can be used to support medical research.

Recent legislation mandates that every hospital in Vietnam must support electronic medical records [2]. This is also encouraged by today's Industry 4.0. To achieve this, a digital transformation of the medical field is required. This means electronic medical records must be established, in addition to the existing information system in each hospital. This came into effect in all hospitals under the Ministry of Health on March 1st, 2019, and all hospitals in Vietnam are required to have electronic medical records by the end of 2030. As a result, a huge number of electronic medical records are being generated and will be available in every hospital very soon. Compiling them thus lays the foundations for medical case-based research both within medicine and related fields.

Although new legislation [2] requires that we apply standardised technologies

across hospitals [3], existing hospital information systems in Vietnam are very diverse, owing largely to differences in long-term investments in information technology among hospitals. Consequently, the development of electronic records has been a priority for some hospitals but not others. As outlined below, this presents huge challenges when it comes to using existing electronic medical records with external processing tools with the aim of gathering data to be used in research.

Firstly, the content of an electronic medical record needs to be well defined so that all the necessary details are available for reference in current treatment procedures and future processes. Traditionally, in Vietnam, like many other countries, hospitals have relied on paper medical records. Transferring all information from paper to electronic medical records is extremely difficult

because of problems associated with understanding hand-writing, time pressure, computer skills, etc. In addition, records must be integrative so that not only their textual content but also their images and time series from medical tests are included.

To achieve this task, as part of our initial phase we investigated the use of the database MIMIC-III to support VNUMED. MIMIC-III is a popular database which is well processed and widely used, and we are considering both its database schema and practical applications for VNUMED. Such a choice also makes VNUMED independent of any electronic medical record type in any existing hospital information system in Vietnam. Furthermore, practical applications can then be constructed on VNUMED, hopefully like those on MIMIC-III.

Secondly, transferring electronic medical records in different hospital information systems into VNUMED is a big challenge, stemming not only from diverse information technologies, but also policies and connections between various organisations in medical and non-medical fields. This is a complex problem that relates to human as well as technical issues. Data integration always presents its own problems, but this situation is unique in that we are dealing with highly sensitive data relating to many patients and organisations.

Thirdly, such sensitive data must be well protected. In MIMIC-III, the rule-based de-identification method was used. For English data similar to those in MIMIC-III, other more effectively well-defined de-identification methods might offer potential. In our case, both English and Vietnamese data exist in VNUMED, thus, de-identification on VNUMED needs to be developed from scratch. Without an effective data protection scheme, VNUMED cannot be formed – and even if realised, VNUMED cannot be available for external research communities.

Last, but not least, once VNUMED gets started, post processing issues on VNUMED need to be taken into account for maintenance and general use. The first relates mainly to the internal development of VNUMED while the latter to external human users and application programs potential for VNUMED. Moreover, user-related policies need to be obtained for the latter.

Development of VNUMED is expected to be done step by step and every difficult aspect will be tackled as it arises. As soon as VNUMED is available, it will benefit researchers in a range of medical and non-medical fields. During the development of VNUMED, we are taking into consideration a range of possible uses, including electronic medical record visualisation, clinical text analysis, drug utilisation, disease diagnosis, etc. We anticipate that this work will contribute to the health and well-being of the Vietnamese people, and the international community.

In short, an intermediate database of electronic Vietnamese medical records, VNUMED, is being developed to provide valuable data for medical research. Many challenges lie ahead of

VNUMED and we would appreciate any input and different perspectives that might help us achieve our goals.

This database is being built under a five-year research project funded by Vietnam National University at Ho Chi Minh City and the FIRST project of Ministry of Science and Technology, Vietnam.

References:

- [1] A. E.W. Johnson, et al.: “MIMIC-III, a freely accessible critical care database”, *Sci. Data* 3:160035, 2016. doi: 10.1038/sdata.2016.35
- [2] Ministry of Health, Vietnam, Circular No. 46/2018/TT-BYT: “Regulations on Electronic Medical Records”, December 28, 2018.
- [3] T. Benson and G. Grieve: “Principles of Health Interoperability: SNOMED CT, HL7 and FHIR” (3rd Edition), Springer, 2016. ISBN 978-3-319-30370-3 (eBook).

Please contact:

Hung Son Nguyen
University of Warsaw
son@mimuw.edu.pl

Empowering Distributed Analysis Across Federated Cohort Data Repositories Adhering to FAIR Principles

by Artur Rocha, José Pedro Ornelas, João Correia Lopes, and Rui Camacho (INESC TEC)

Novel data collection tools, methods and new techniques in biotechnology can facilitate improved health strategies that are customised to each individual. One key challenge to achieve this is to take advantage of the massive volumes of personal anonymous data, relating each profile to health and disease, while accounting for high diversity in individuals, populations and environments. These data must be analysed in unison to achieve statistical power, but presently cohort data repositories are scattered, hard to search and integrate, and data protection and governance rules discourage central pooling.

In order to tackle data integration and harmonization challenges while preserving privacy, we adopted an approach based on an open, scalable data platform for cohorts, researchers and networks. It incorporates the FAIR principles (Findable, Accessible, Interoperable, Reusable) [1] for optimal reuse of existing data, and builds on maturing federated technologies [L1][L3], where sensitive data is kept locally with only aggregate results being shared and integrated [3], in line

with key ELSI (Ethical, Legal and Societal Issues) and governance guidelines.

Since the measurement and observation methods used by cohorts to collect exposures and outcomes are often highly heterogeneous, using these data in a combined analysis requires that data descriptions are mapped onto subsets of research-ready core variables, and it must be clear if measurements are similar enough to be integratively

analysed. The implemented platform not only facilitates the process of duly curating cohort data, but also helps preserve knowledge about the original methods used in the scope of each data collection event, thus providing valuable insight and a systematic framework to decide if and how data can be made interoperable [2]. Although expert knowledge is key to drive the harmonisation process, to some extent data harmonisation procedures are also supported in the scope of the platform.

Physically, the deployed platform maps down to a network of distributed data nodes, each of them in full control over their local users and study data, while the software allows data managers to curate, describe and publish metadata about selected datasets. New datasets can also be derived according to agreed harmonisation dictionaries.

From a high-level perspective, data nodes can be organised in large-scale, dynamically-configured networks, with the potential to be used in different setups. In a federated setting, the network can take form by simply interconnecting data nodes that collaborate towards a common goal, such as taking part in a network of cohorts or large harmonisation studies. Since each of the nodes includes all the functionality to operate on its own, including a public catalogue, one of the nodes can also undertake the role of gateway to other nodes, allowing more centralised governance policies to be implemented (e.g. a common catalogue entry point).

Each data node is composed of four separate software components acting together, whose purpose is as follows:

- The Data Repository is the central data storage component at each data node. All data operations take place here;
- The Study Manager is where the studies' metadata is structured, characterised and eventually published;
- A Catalogue provides browsing and querying capabilities over the published metadata;
- An Authentication Server that centralises the authentication process for each data node and provides an interface to manage users, groups and their interrelationships, as well as a role-based access control to the remaining components of the system.

One of the projects implementing this approach is “RECAP Preterm – Research on European Children and Adults Born Preterm” [L4], a project having received funding from the European Union's Horizon 2020 research and innovation programme (grant agreement No 733280) under the “networking and optimising the use of population and patient cohorts at EU level” topic of the “personalised medicine” call. RECAP Preterm includes 20 partners [L5] and is coordinated by TNO (NL, ERCIM member), having

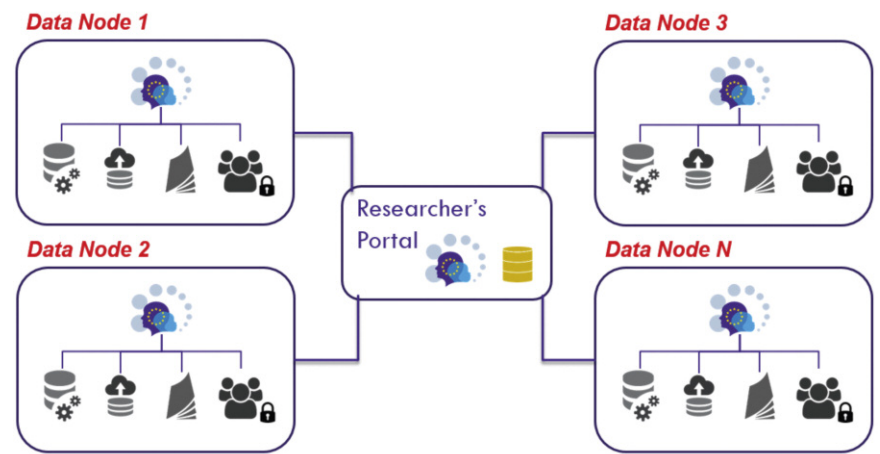


Figure 1: High-level view of the infrastructure used in RECAP Preterm.

INESC TEC as leader of the work package responsible for implementing the data infrastructure. The project's overall goal is to improve the health, development and quality of life of children and adults born very preterm (VPT) or with a very low birth weight (VLBW). In order to achieve this goal, data from European cohort studies and around the world will be combined, allowing researchers to evaluate changes in outcomes over time while providing important information on how the evolution in care and survival of such high risk babies has changed their developmental outcomes and quality of life. Figure 1 presents a high-level view of RECAP Preterm network of data nodes [L6] that is being used to study developmental outcomes as well as more effective, evidence-based, personalised interventions and prevention.

Also using a similar approach, the recently started EUCAN-Connect [L7] is a project having received funding from the European Union's Horizon 2020 research and innovation programme (Grant Agreement No 824989) under the topic: “International flagship collaboration with Canada for human data storage, integration and sharing to enable personalised medicine approaches”. EUCAN-Connect, led by UMCG (NL) has 13 partners [L8] and aims to promote collaborative and multidisciplinary research in high-value cohort and molecular data on a large scale in order to improve statistical power with the aims of making new discoveries about the factors that impact human life course and facilitating their translation into personalised diagnostics, treatment and prevention policies.

The outcome of this work will be a FAIR-compliant, federated network of data nodes to make cohort data findable, accessible, interoperable and reusable and enable large-scale pooled analyses with privacy-protecting features [L3] that account for ethical, legal and societal implications.

Links:

- [L1] <https://www.obiba.org/>
- [L2] <https://kwz.me/hyA>
- [L3] <http://www.datashield.ac.uk/>
- [L4] <https://recap-preterm.eu/>
- [L5] <https://kwz.me/hyD>
- [L6] <https://recap-preterm.inesctec.pt>
- [L7] <https://www.eucanconnect.eu/>
- [L8] <https://kwz.me/hyF>

References:

- [1] M.D. Wilkinson, et al.: “The FAIR Guiding Principles for scientific data management and stewardship”, *Scientific Data* 3 (2016).
- [2] I. Fortier, et al.: “Maelstrom Research guidelines for rigorous retrospective data harmonization”, *International Journal of Epidemiology* 46.1 (2017): 103-105.
- [3] A. Gaye, et al.: “DataSHIELD: taking the analysis to the data, not the data to the analysis”, *International Journal of Epidemiology* 43.6 (2014): 1929-1944.

Please contact:

Artur Rocha, INESC TEC, Portugal
artur.rocha@inesctec.pt

SmartWork: Supporting Active and Healthy Ageing at Work for Office Workers

by Otilia Kocsis, Nikos Fakotakis and Konstantinos Moustakas (University of Patras)

SmartWork is a European project addressing a key challenge facing today's older generation, as they are living and working longer than their predecessors: the design and realisation of age-friendly living and working spaces. SmartWork is building a worker-centric AI system to support active and healthy ageing at work for older office workers. In SmartWork modelling of work ability, defined as the ability of an individual to balance work with other aspects of their life, will account for both the resources of the individual and factors related to work and the environment outside of work.

The ageing population presents a huge challenge for governments worldwide, which are looking for strategies to effectively increase the participation of older workers in the labour force and reduce the rates of early retirement and labour market exit (e.g. retirement age was recently raised to 67 in many EU countries). Despite these efforts, in Europe early retirement rates remain high, with the EU-28 employment rate of 55-64 year olds recorded at only 55.3 % in 2016. The prevalence of chronic health conditions in people aged 50+ is very high, with every second person having hypertension and/or another chronic disease, and multimorbidity rates of 65 %

for people aged 65+ [1]. The majority of aging workers who do choose to remain in the workforce, however, indicate that they plan to work past their traditional retirement age, due to the reduced value of their retirement portfolios/income.

“Work ability” has been developed as an important multi-factorial concept that can be used to identify workers at risk of an imbalance between health, personal resources and work demands [2]. An individual’s work ability is determined by his or her perception of the demands at work and their ability to cope with them. The current challenge

in using the concept is to establish adequate tools to evaluate and measure work ability continuously, in order to capture the changing and evolving functional and cognitive capacities of the worker in various contexts.

The SmartWork project [L1], which started in 2019 and will finish in 2021, aims at building a worker-centric AI system for work ability sustainability for office workers, which integrates unobtrusive sensing and modelling of the worker’s state with a suite of novel services for context and worker-aware adaptive work support. The monitoring of health, behaviour, cognitive and

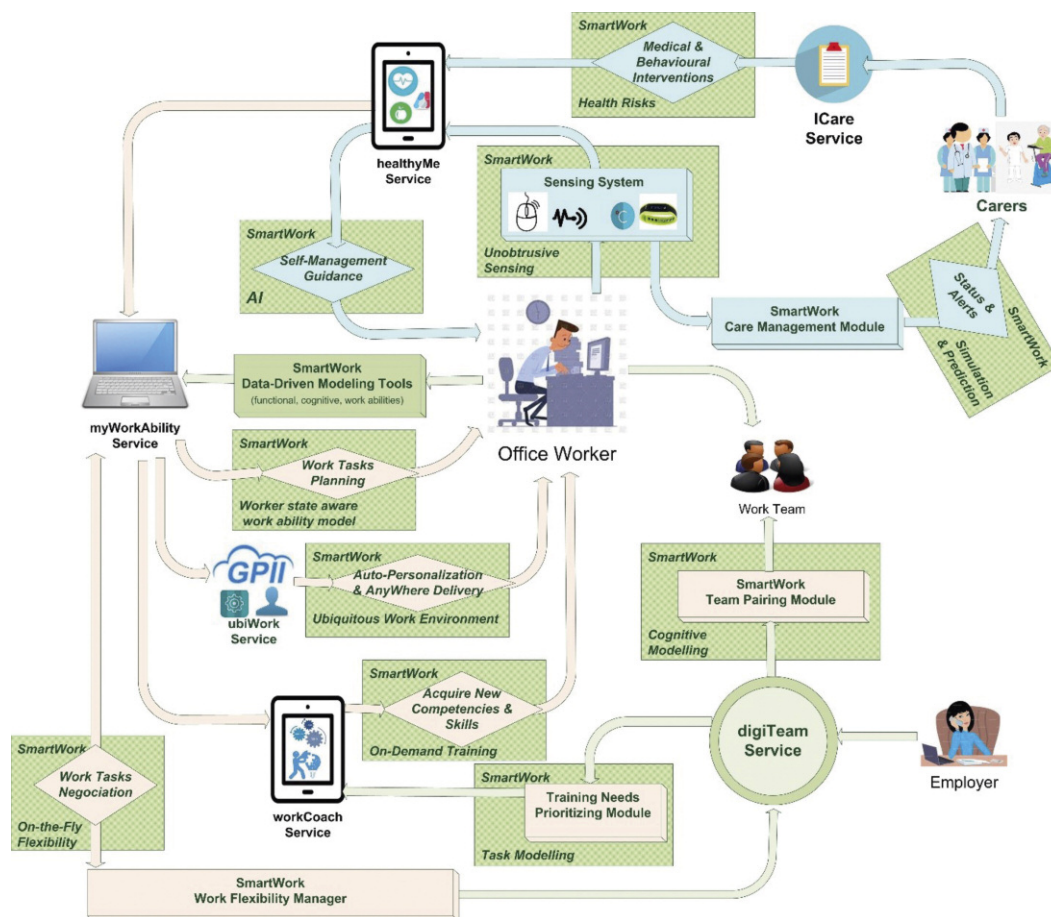


Figure 1: Generic architecture of the SmartWork suite of novel services.

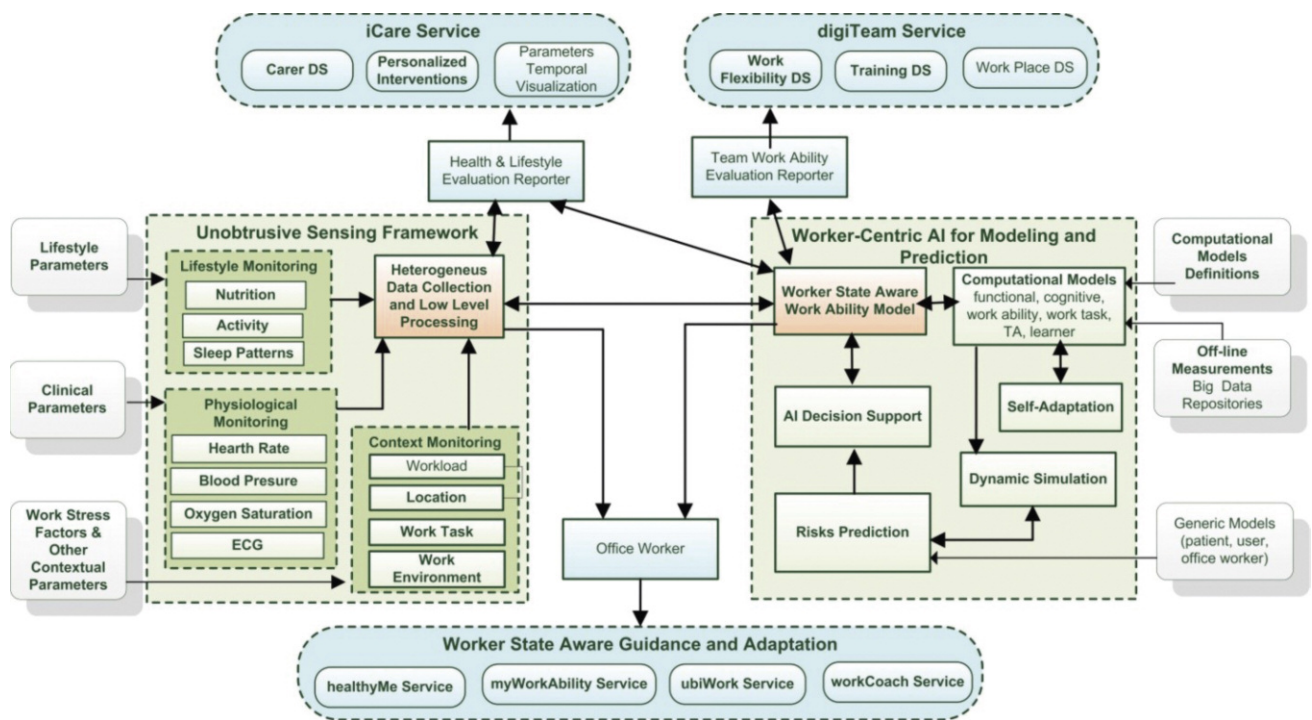


Figure 2: Conceptual architecture of the multi-dimensional modelling framework.

emotional status of the worker enables the functional and cognitive decline risk assessment. The holistic approach for work ability modelling captures the attitudes and abilities of the ageing worker and enables decision support for personalised interventions for maintenance/improvement of work ability. The evolving work requirements are translated into required abilities and capabilities, and the adaptive work environment supports the older office worker with optimised services for on-the-fly work flexibility coordination, seamless transfer of the work environment between different devices and different environments (e.g. home, office), and on-demand personalised training. The SmartWork services and module (Figure 1) also empower the employer with decision support tools for efficient task completion and work team optimisation. Formal or informal carers are enabled to continuously monitor the overall health status, behavioural attitudes and risks for the people they care for, and adapt health and lifestyle interventions to the evolving worker's status.

University of Patras (Greece) is joining forces with the Roessingh Research and Development (the Netherlands) and Linköping University (Sweden) to implement the modelling of work ability in SmartWork, which will

account for both the resources of the individual and factors related to work and the environment outside of work. The modelling of work ability will consider:

- generic user models (groups of users),
- personalised patient models,
- personalised emotion and stress models of the office worker,
- personalised cognitive models,
- contextual work tasks modelling,
- work motivation and values.

Continuous assessment of the various dimensions of work ability is facilitated through the continuous unobtrusive monitoring of the health, behaviour and emotional status of the office worker (Figure 2). AI tools for prediction and risk assessment will allow for dimension specific decision support and intervention, such as on-the-fly flexible work management, coping with stress at work, on-demand training, including memory training.

Spark Works ITC Ltd (United Kingdom) will join efforts with Instituto Pedro Nunes (Portugal) for the implementation of the Unobtrusive Sensing Framework, while Byte SA (Greece) together with Raising the Floor International (Switzerland) will implement the Ubiquitous Work Environment and Work Flexibility

tools. The European Connected Health Alliance (Ireland) is facilitating multi-stakeholder connections around the SmartWork system. In the final six months, the SmartWork system will be evaluated at two pilot sites, namely at Cáritas Diocesana de Coimbra (Portugal) and at the Center for Assisted Living Technology Health and Care, Aarhus Municipality (Denmark). This is the final step towards large-scale pilot validation and preparation for the SmartWork system to enter the market, potentially benefiting a large number of office workers, employers and formal and informal health carers.

Link:

[L1] www.smartworkproject.eu

References:

- [1] M. Dyakova, A. Clarke, and H. Fraser: "Innovating care for people with multiple chronic conditions in Europe project evaluation", *European Journal of Public Health* 26, 1, 2016.
- [2] K. Tuomi, et al.: "Promotion of work ability, the quality of work and retirement", *Occup Med* 51, 2001.

Please contact:

Otilia Kocsis
University of Patras, Greece
okocsis@bok.gr

WellCo: Wellbeing and Health Virtual Coach

by Vlad Manea (University of Copenhagen) and Katarzyna Wac (University of Copenhagen and University of Geneva)

WellCo is a European H2020 project that aims to design and evaluate an engaging virtual coach to help older adults make positive behavioural choices that benefit their long-term health, wellbeing, and quality of life in physical, psychological and social interaction domains.

Populations are growing, and the average human lifespan is increasing. Poor lifestyle choices may develop over a long period, resulting in chronic disease such as cardiovascular disease or diabetes later in life [1]. At the same time, ever-sophisticated wearable activity trackers and mobile applications enable the assessment of the individual's daily habits and risk factors which impact their long-term health.

The WellCo European H2020 project (2017-2021), delivers a radical new information and communication tech-

nology solution in the provision of personalised advice, guidance, and follow-up for its users. Its goal is to encourage people to adopt healthier habits that help them maintain or improve their physical, cognitive, mental, and social well-being for as long as possible. Advice is given through behaviour change interventions tailored explicitly to each user. These interventions range from setting social goals to recommending activities around the seven areas defined in WellCo: cognitive stimulation, leisure and entertainment, supporting groups, physical activity, health status, nutrition, and tips (Figure 1). The behaviour change concept leverages the Behaviour Change Wheel model [2].

nology of experiencing particular diseases. This assessment takes into account the user's profile, context, socio-economic status, health, and mental state. These characteristics are derived from data obtained from the user's activities of daily life (ADL) in which wearable sensors are seamlessly integrated (Figure 2), as well as from the user's mood, leveraging affective computing via visual and speech emotion recognition.

The virtual coach developed in WellCo provides guidance and follow-up. It is

an individual with particular preconditions (e.g. family history) or behavioural patterns (e.g. smoking) leading to the development of chronic diseases, such as cardiovascular disease or diabetes. The risk awareness tool also uses behaviour and risk patterns extracted from the individual's electronic health records (EHR). The theoretical foundations for the risk awareness tool are derived from the state of the art in preventive medicine. These are meta-analysis-driven, focusing on evidence-based disease risk models, including recent epidemiological findings. The

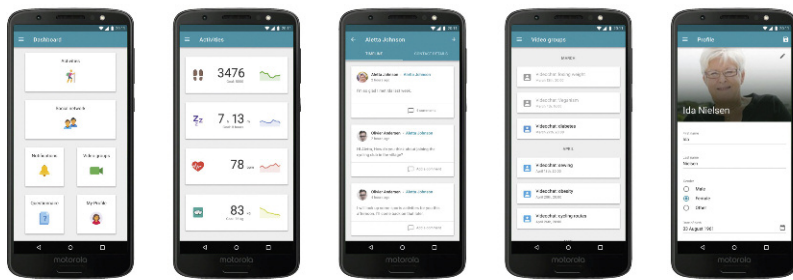


Figure 1: Prototype of the WellCo mobile application with information about activities, social network, video conversations, and user profile.



Figure 2: WellCo dashboard and two models of wearable device compatible with WellCo.

nologies (ICT) based solution in the provision of personalised advice, guidance, and follow-up for its users. Its goal is to encourage people to adopt healthier habits that help them maintain or improve their physical, cognitive, mental, and social well-being for as long as possible. Advice is given through behaviour change interventions tailored explicitly to each user. These interventions range from setting social goals to recommending activities around the seven areas defined in WellCo: cognitive stimulation, leisure and entertainment, supporting groups, physical activity, health status, nutrition, and tips (Figure 1). The behaviour change concept leverages the Behaviour Change Wheel model [2].

WellCo provides recommendations and goals after assessing the user's proba-

an affective-aware and always active service. The coach interacts through speech with the user to: 1) act as the virtual interface between the user and the platform (managing the flow of all user-platform and platform-user interactions, and: 2) empower users in the behaviour change process (through stimulation activities tailored to their current mood). A multidisciplinary team of experts, as well as the user's caregivers, continuously support the service. They provide their clinical evidence (expert-related outcomes) and personal knowledge about the user and the user's behaviours (observer-related outcomes) [3] to ensure the effectiveness and accuracy of the interventions.

The main technology-driven innovation of the WellCo solution is the health risk awareness tool. It assesses the risks of

output of the risk awareness tool includes: 1) relative risk, 2) modifiable risk (the risk that can be altered by behaviour), and 3) absolute risk (the probability of a given disease expression). The application of the risk awareness tool is vital in providing the individual, via the virtual coach, different future "if-else" scenarios for modifiable risks (Figure 3). They quantify how the user's health risk changes in response to changes in lifestyle.

WellCo is based on a co-design process where end-users play a crucial role. This means that end-users are involved right from the project's conception, and contribute at every step of the prototype's development, starting with a mock-up development, via an initial proof of concept with the users, and continuing with three incremental pro-

totypes to ensure a valid and effective service integration and validation.

The expected outcomes of WellCo may be categorised as short-term (feeling motivated to change one’s habits), intermediate (e.g. changing attitudes, norms and behaviours; translating good intentions into practical actions), and long-term (initiating and maintaining positive habits, changing activities and improving health status and quality of life over the long term). To demonstrate the health behaviour change process, long-term trials have just started (mid-2019) in several European countries, including Italy, Spain, and Denmark, with the participation of public health and social care organisations (Italy and Spain) and research organisations (Denmark).

The project involves eight European partners: HI-Iberia (Spain, the coordinator), Fondazione Bruno Kessler (Italy), Institut Jozef Stefan (Slovenia), Gerencia de Servicios Sociales de Castilla y León (Spain), ConnectedCare Services B.V. (The Netherlands), Monsenso (Denmark), Syddansk Universitet (Denmark), and Københavns Universitet (Denmark).

Links:

- [L1] <http://wellco-project.eu/>
- [L2] <http://qualityoflifetechnologies.org>

References:

- [1] M. Naghavi et al.: “Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016,” *Lancet*, vol. 390, no. 10100, pp. 1151–1210, Sep. 2017.
- [2] S. Michie, M. M. van Stralen, and R. West: “The behaviour change wheel: A new method for characterising and designing behaviour change interventions,” *Implement. Sci.*, vol. 6, no. 1, p. 42, Dec. 2011.
- [3] N. E. Mayo, et al.: “Montreal Accord on patient-reported outcomes use series—paper 2: terminology proposed to measure what matters in health,” *J. Clin. Epidemiol.*, Apr. 2017.

Please contact:

Vlad Manea, QoL Lab, University of Copenhagen, Denmark
 manea@di.ku.dk

Globorisk Lab

Risk of Cardiovascular Disease: lab input, tabular output.

Scenario 1: If the person continues like this...

The person's initial risk (denoted with I) is 10%. If the person continue like this, in 10 years, the alternative risk (denoted with A) will change by 5% to 15.

Risk of Initial Scenario



Risk of Alternative Scenario



▶ Complete Risk Tabke

Scenario 2: Quitting smoking...

The person's initial risk (denoted with I) is 10%. If in 10 years the person quit smoking, the alternative risk (denoted with A) will change by -2% to 8.

Risk of Initial Scenario



Risk of Alternative Scenario



▼ Complete Risk Tabke

		DENMARK																																												
		Women						Men																																						
		Non-diabetic			Diabetic			Non-diabetic			Diabetic																																			
Age	SBP	Non-smoker	Smoker	Non-smoker	Smoker	Non-smoker	Smoker	Non-smoker	Smoker	Non-smoker	Smoker	Non-smoker	Smoker																																	
70-74	180	10	11	12	13	14	16	17	18	20	21	22	24	26	28	30	33	36	38	40	43	44	45	46	47	13	14	15	16	18	15	16	17	19	20	20	21	23	25	27	22	24	26	28	31	
	160	8	9	10	11	12	13	14	16	17	18	19	21	22	24	27	29	31	33	35	38	39	40	41	42	10	11	12	13	14	12	13	14	15	16	15	17	18	19	21	18	19	21	22	24	
	140	6	7	8	8	10	10	11	12	13	14	15	16	17	19	21	23	25	26	28	28	29	30	31	32	8	8	9	10	11	9	10	11	11	12	12	13	14	15	17	14	15	16	18	19	
65-69	180	5	6	7	8	8	9	10	12	13	15	13	14	16	18	20	22	24	27	30	33	38	39	40	41	43	10	11	11	13	10	11	13	14	16	13	15	16	18	20	17	19	21	23	26	
	160	4	4	5	6	6	7	8	9	10	11	10	11	12	14	15	17	19	21	23	26	27	28	29	30	32	6	7	8	8	10	8	9	10	11	12	10	11	12	14	16	13	14	16	18	20
	140	3	3	4	4	5	5	6	7	7	8	7	8	9	10	12	13	14	16	18	20	21	22	23	24	26	4	5	6	6	7	6	7	8	9	10	7	8	9	11	12	10	11	12	14	15
60-64	180	3	3	4	4	5	5	6	7	8	9	8	9	10	12	14	15	17	20	23	26	27	28	29	30	32	6	6	8	9	10	8	9	11	13	15	10	11	13	15	18	14	16	19	22	25
	160	2	3	3	3	4	4	5	6	7	8	6	7	8	9	10	11	13	15	17	20	21	22	23	24	26	4	5	6	6	8	6	7	8	9	11	7	9	10	12	13	11	12	14	17	19
	140	2	2	2	3	3	3	4	4	5	6	4	5	6	7	8	8	10	11	13	15	16	17	18	19	21	3	3	4	4	5	4	5	6	7	9	5	6	7	9	10	8	9	11	12	14
55-59	180	2	2	3	3	4	4	5	6	7	8	6	7	8	10	12	13	15	18	21	25	26	27	28	29	31	4	5	7	8	9	7	9	11	13	15	9	10	12	15	18	14	16	20	23	28
	160	1	2	2	3	3	3	4	5	6	7	4	5	6	7	9	9	11	13	16	19	20	21	22	23	25	3	4	5	6	7	5	6	8	9	11	6	7	9	11	13	10	12	14	17	20
	140	1	1	2	2	2	2	3	4	5	6	3	4	4	5	6	7	8	10	12	14	15	16	17	18	20	2	3	3	4	5	4	5	6	7	8	4	5	6	8	9	7	9	10	13	15
50-54	180	2	2	3	3	4	4	5	7	8	10	5	6	8	10	12	13	16	19	23	28	29	30	31	32	34	4	4	6	7	9	6	8	10	12	15	7	9	11	14	17	13	16	19	24	29
	160	1	2	2	3	3	3	4	5	6	7	4	5	6	7	9	9	11	14	17	21	22	23	24	25	27	3	3	4	5	6	5	6	8	10	12	9	11	14	17	21					
	140	1	1	1	2	2	2	3	4	5	6	3	4	4	5	6	6	8	10	12	14	15	16	17	18	20	2	2	3	3	4	3	4	5	6	8	4	4	6	7	9	6	8	10	12	15
45-49	180	1	2	2	3	3	3	4	5	7	9	4	5	6	8	10	10	13	17	21	26	27	28	29	30	32	3	3	4	6	7	5	7	9	11	14	6	8	10	12	16	11	15	19	23	29
	160	1	1	1	2	2	2	3	4	5	6	3	4	4	6	7	7	9	12	15	19	20	21	22	23	25	2	2	3	4	5	4	5	6	8	10	8	10	13	17	21					
	140	1	1	1	1	2	2	2	3	4	5	2	3	4	5	6	5	6	8	10	13	14	15	16	17	19	1	2	2	3	4	3	4	5	6	8	6	7	9	12	15					
40-44	180	1	1	1	1	1	1	1	2	2	3	1	2	2	3	3	3	4	6	7	9	11	12	13	14	16	1	1	1	2	2	2	2	3	4	5	2	2	3	4	5	4	5	6	8	10
	160	1	1	1	1	1	1	1	2	2	3	1	2	2	3	3	3	4	5	7	9	12	13	14	15	17	1	1	1	2	2	2	2	3	4	5	2	2	3	4	5	3	4	5	6	8
	140	1	1	1	1	1	1	1	2	2	2	1	1	1	2	2	2	3	4	5	6	7	8	9	10	11	1	1	1	2	2	2	2	3	4	4	2	2	3	4	4	3	4	5	6	7

Scenario 3: A change in systolic blood pressure...

The person's initial risk (denoted with I) is 10%. If in 10 years the systolic blood pressure is changed by 20.099999999999857 mm Hg, the alternative risk (denoted with A) will change by -2% to 8.

Risk of Initial Scenario



Risk of Alternative Scenario



Figure 3: WellCo risk assessment scenarios: 1. “if the person continues like this...”, 2. if they quit smoking, and 3. if their blood pressure decreases.

A Personalisation Platform for Older Adults with Mild Cognitive Impairments

by Marco Manca, Parvaneh Parvin, Fabio Paternò, Carmen Santoro and Eleonora Zedda (ISTI-CNR)

The AAL PETAL project has developed a platform for personalising remote assistance of older adults with mild cognitive impairments. The platform is targeted at caregivers without programming knowledge in order to help seniors in their daily activities at home.

ICT technologies have great potential to help prolong the time elderly people can live independently in their preferred environment. However, several barriers exist when it comes to seniors actually using existing technologies: older adults may have different needs and attitudes to younger generations - for example, attitudes towards technology, physical or cognitive limitations, and interests. Furthermore, the needs of elderly people are not static; they are likely to evolve over time depending on variables such as evolving health conditions and preferences. Thus, the personalisa-

tion of ICT-based support is a fundamental challenge.

In the AAL PETAL project [L1] at the HIIS Laboratory of CNR-ISTI [L2] we are developing a platform for personalising remote assistance of older adults with mild cognitive impairments, with a particular focus on the support of lighting systems in order to provide orientation over time and in space. This category of users suffers from cognitive issues, such as the tendency to forget tasks/events and/or other issues such as cardiovascular issues, reduced sight,

and irregular eating habits, often associated with increased risk of social isolation and depression. The platform monitors the user's environment and behaviour, and personalises applications and control devices to better support seniors in their daily lives. Thus it exploits smart objects, such as lights, to provide appropriate activation or relaxation stimuli, and it generates alerts and reminders for physical and social activities, orientation over time and space, and sleep quality.

The user or caregiver can set the device to control lights and other digital devices when relevant events occur. In this way it is possible to personalise control of the lights and other digital appliances, to set personalised warning messages to be issued in risky situations, and persuasive messages to encourage healthier habits (e.g., more physical activity). The possible personalisations are expressed in terms of simple trigger-action rules [1, 2, 3]. Triggers represent situations or events that might be useful for caregivers to know: e.g. health/cognitive/emotional status, cognitive/physical/social activity, especially when the caregiver is not present (remote monitoring). The information associated with triggers is derived from various sensors (e.g. motion, proximity, lights, noise, respiration, heart). Actions represent what the technological equipment within the home could do: control appliances (e.g. switch on/off lights, close/open doors, play tv/radio), send reminders, send alarms, provide information about the user's needs. Personalised rules that can be obtained with this approach include:

- When the user leaves the house and rain is forecast, a phone alert can suggest taking the umbrella;
- A message can be sent to the caregiver when the user leaves home during the night;
- When a caregiver sends a message "where?", an automatic answer provides the user's location;



Figure 1: An example of home involved in the trials.



Figure 2: Sensors and Objects in the Trials.

- If a user has not done the planned cognitive exercises, a blink of the light acts as a reminder to continue this activity;
- If the user is close to the living room and time is 4 pm, turn on the TV.

We have organised trials in homes with older adults with mild cognitive impairments, distributed across various European countries (Figure 1 shows one home involved in the trials). Figure 2 shows the types of sensors, objects, and devices we use in such trials. Each user has a tablet, and a smartwatch. We have selected a smartwatch that, in addition to detecting physiological parameters such as heart rate and step counter, is able to connect and communicate at the same time through Bluetooth and Wi-Fi. This is exploited to obtain indoor positioning with the support of proximity beacons. For light, we use the GREAT luminaire (designed by Bartenbach, a company involved in the PETAL project), which aims to provide health-stimulating, biorhythm-stabilising, high-quality light for high visual demands, and creates an activating or calming room ambiance with different light scenes. The extremely high light intensity (1000 lx at eye level) of the

GREAT luminaire leads to effects comparable with classic light therapy within five hours of use. It compensates missing daylight and provides distributed light within a whole room of about 16 m². In addition, we use various types of Philips Hue lights to support similar effects in other parts of the home. Other sensors detect gas, smoke, humidity, use of objects, whether windows or doors are open and so on. The platform is also connected with an app developed by Ideable (a Spanish company involved in the PETAL project), which supports serious games for cognitive stimulation in order to allow caregivers to define rules depending on the user's cognitive and emotional state or depending on the training results.

Supporting this technology is a personalisation platform that includes a middleware (context manager) to gather raw information from the various sensors and convert it into data that can be analysed in terms of logical events and conditions. In this way, when the personalisation rules are created by the user or caregiver, it is possible to detect dynamically when they should be triggered and the consequent actions performed.

Links:

- [L1] <http://www.aal-petal.eu/>
 [L2] <https://giove.isti.cnr.it/lab/home>

References:

- [1] G. Ghiani, et al.: "Personalization of Context-dependent Applications through Trigger-Action Rules", *ACM Transactions on Computer-Human Interaction*, Vol.24, Issue 2, Article N.14, April 2017.
 [2] H. Huang, M. Cakmak: "Supporting mental model accuracy in trigger-action programming", in *Proc. of UbiComp '15*. ACM, New York, NY, USA, 215-225. DOI: <http://dx.doi.org/10.1145/2750858.2805830>
 [3] B. Ur, et al.: "Practical trigger-action programming in the smart home", *CHI 2014*: 803-812, 2014.

Please contact:

Fabio Paternò, ISTI-CNR, Italy
 +39 050 315 3066
fabio.paterno@isti.cnr.it

Technological Memory Aids for Neurodegenerative Diseases and the AuDi-o-Mentia Approach

by Eleni Boumpa and Athanasios Kakarountas (University of Thessaly)

Rates of dementia are increasing, putting pressure on national health systems. Digital health can help both patients and national health systems in a range of ways. One technology that is being developed is AuDi-o-Mentia, an acoustic memory aid to help people in the early stages of dementia.

The progress and the use of modern technologies and digital services have changed the way people monitor health and well-being. The ability to access personal data for remote monitoring and self-management can greatly improve healthcare.

Broadly speaking, there are two aspects to digital health: the perspective of the patient, and that of the state. For the patient, digital health represents personalised and higher quality care that adapts to their needs. For the state, digital health can reduce inefficiencies in healthcare provision and costs in national health systems. Thus, digital

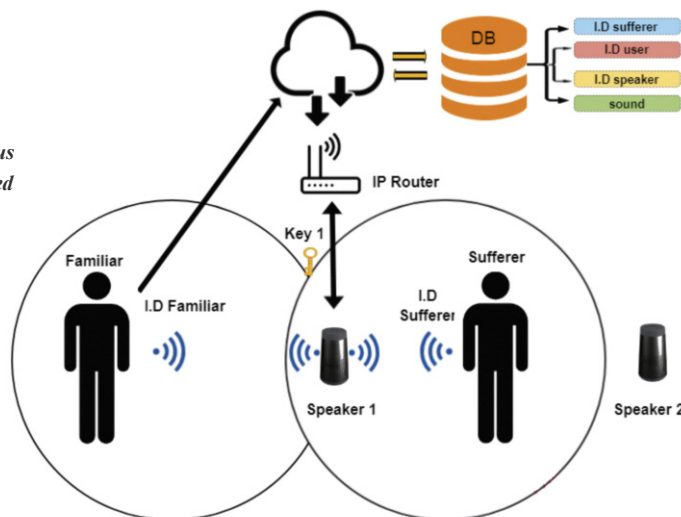
health has resulted in a significant increase in the quality of life of patients, as well as a significant positive effect on the global economy.

The rise of digital health raises the urgent need for technology to support "smart care" in the home environment, enabling people to live independently, for longer, in their preferred environment, whilst offering their physicians and carers resources and tools to manage their patients effectively and efficiently.

Many factors contribute to the development of neurodegenerative diseases,

which mainly affect people over the age of 60. Some of the most common neurodegenerative diseases include dementia (with its most well-known form being Alzheimer's disease), Parkinson's disease, and epilepsy. Several digital health systems have been proposed to support people suffering from neurodegenerative diseases, with an emphasis on dementia, since it is the most common neurodegenerative disease. The total population with dementia is projected to reach 82 million in 2030 and 152 million by 2050 [L1]. The increasing prevalence of this disease is putting pressure on national health systems worldwide.

Figure 1: Detection of a familiar person and reproduction of the associated acoustic stimulus at the smart speaker located closest to the sufferer.



Just like other digital health systems, the goal of proposed digital health systems in the area of dementia is to provide personalised care for patients and their relatives and/or caregivers, to monitor their mental health and well-being, and to give feedback on their health condition to their doctors. The proposed systems are mainly focused on either the early diagnosis of dementia symptoms or the provision of services to support the sufferers. Thus, these proposed systems can assist people in their daily lives, monitor their mood, guide them in their daily routine, supervise them when they leave their home environment, give them reminders (for example, to take their medication), and help them maintain active social lives and avoid becoming isolated because of their disease.

A promising technology for people suffering from dementia, and their relatives, is the AuDi-o-Mentia project [L2]. AuDi-o-Mentia is a home assistive system that works with the use of sound stimuli. The sound stimulus was selected because is beneficial for the sufferers and help them recall their identity, with better results than those produced by other stimuli, like an optical stimulus [1, 2]. Since this was proved by professionals (i.e., neurologists), exploiting music-therapy sessions, there was the need for an implementation that would be easily integrated in homes. AuDi-o-Mentia's function is to reproduce a distinctive sound representing each of the familiar faces of the sufferers, in order to provide them with an additional stimulus to recognise their loved ones. Whenever one of the familiar faces enters the suf-

ferer's home, the associated characteristic sound will be produced. The user selects the sound that represents each familiar, since the user has different memories from each person [3]. Alternatively, a caregiver may create the appropriate acoustic stimuli associations with the sufferer's familiar people, exploiting music therapy techniques.

AuDi-o-Mentia is based on the basic rules of music therapy, aiming to stimulate the auditory memory, which is statistically one of the last parts of memory that will be affected by a degenerative disease. It is a universal system, independent of age, gender, nationality or economic status. The concept itself is based on distributed smart speakers at the sufferer's home and the stimulation of memory depending of the identity of the visitor. The system is transparent to the sufferer, avoiding any confusion. The interface is based on the identification of the visitor (exploiting RFID, or ID detection via WiFi or Bluetooth) by the system and the acoustic stimulation. Thus, the interaction is made physical and no special training is required. This makes it suitable for people suffering from degenerative diseases and simple enough for caregivers to use.

In summary, digital health is the key to providing personalised health services and confronting many challenges facing national health systems. Smart technology is expected to provide novel solutions to sufferers and new tools to caregivers. It is the role of researchers to creatively apply technologies and knowledge to form new solutions for our fellow humans.

Links:

- [L1] <https://kwz.me/hy8>
- [L2] <https://audiomentia.com/>

References:

- [1] McDermott, et al.: "The importance of music for people with dementia: The perspectives of people with dementia, family carers, staff and music therapists", *Aging Ment. Health* 2014, 18, 706-716.
- [2] Holmes, et al.: "Keep music live: Music and the alleviation of apathy in dementia subjects", *Int. Psychogeriatr.* 2006, 18, 623-630.
- [3] E. Boumpa, et al.: "An Acoustic-Based Smart Home System for People Suffering from Dementia", *Technologies* 7.1 (2019): 29.

Please contact:

Eleni Boumpa, Athanasios Kakarountas,
University of Thessaly, Lamia, Greece
eboumpa@uth.gr, kakarountas@uth.gr

PAPAYA: A Platform for Privacy Preserving Data Analytics

by Eleonora Ciceri (MediaClinics Italia), Marco Mosconi (MediaClinics Italia), Melek Önen (EURECOM) and Orhan Ermis (EURECOM)

The PAPAYA project is developing a dedicated platform to address privacy concerns when data analytics tasks are performed by untrusted data processors. This platform regrouping will allow stakeholders to ensure their clients' privacy and comply with the General Data Protection Regulation (GDPR) [L1] while extracting valuable and meaningful information from the analysed data. PAPAYA targets two digital health use cases, namely arrhythmia detection and stress detection, whereby patients' data are protected through dedicated privacy enhancing technologies.

Recent advances in information technology make it easy for businesses and other organisations to collect large amounts of data and use data analytics techniques to derive valuable information and improve predictions. The information obtained, however, is usually sensitive, and may endanger the privacy of data subjects. Whilst the General Data Protection Regulation (GDPR) necessitates a technological means to protect privacy, it is vital that this is achieved in a way that still allows healthcare stakeholders to extract meaningful information and make good predictions (e.g., about diseases). The PAPAYA project aims to provide solutions that minimise privacy risks while increasing trust in third-party data processors and the utility of the underlying analytics.

The newly developed PAPAYA platform will integrate several privacy-preserving data analytics modules, ensuring compliance with the GDPR. The project considers different settings involving various actors (single/multiple data sources, queriers) and ensuring different privacy levels. The project will facilitate user experience for data subjects while providing transparency and control measures.

The PAPAYA project focuses on three main data analytics techniques, namely, neural networks (training and classification), clustering, and basic statistics (counting) and aims at developing their privacy-preserving variants while optimising the resulting performance overhead and assuring an acceptable utility/accuracy. More specifically, privacy-preserving neural networks (inspired by the architecture of neurons in human brains) learn prediction models about a certain characteristic/capability using some test datasets and

further apply this model over new data to make accurate predictions while keeping the input data confidential. On the other hand, privacy-preserving clustering algorithms allow data owners to group similar (but confidential) data objects in clusters. Finally, privacy-preserving counting primitives enable parties to encrypt one or several datasets related to individuals and further count the number of individuals in the set. The main cryptographic tools that will be

cases and the underlying PAPAYA solutions are summarised below.

Privacy-preserving arrhythmia detection

This use case targets scenarios whereby patients need to perform cardiac parameters analyses with the goal of verifying the presence/absence of arrhythmia. The patient wears a device that collects his/her ECG data for a fixed amount of time (e.g., 24 hours). Once the patient

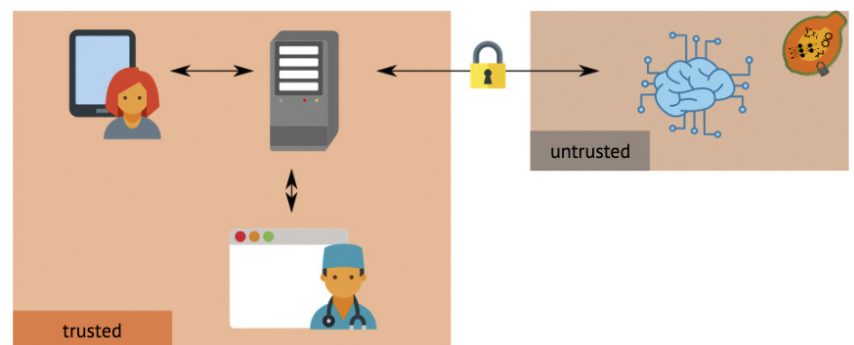


Figure 1: A patient's ECG data are collected by a pharmacist, sent to a trusted cloud, protected and submitted to the PAPAYA platform to predict arrhythmia. The detected arrhythmia are used by a cardiologist to redact the patient's report.

used to design these new solutions are homomorphic encryption, secure multiparty computation, differential privacy and functional encryption.

Privacy-preserving neural networks for two digital health use cases

The PAPAYA project defines two digital health use cases, namely privacy-preserving arrhythmia detection and privacy-preserving stress detection. While both use cases rely on neural networks, the former (arrhythmia detection) only considers the classification phase and the latter (stress detection) involves multiple data sources, such as hospitals, that collaboratively train a stress detection neural network model. Both use

returns the device to the pharmacy, the ECG data are protected and submitted to the PAPAYA platform, as illustrated in Figure 1. The data are then analysed to predict whether the patient suffers from arrhythmia.

The project aims to develop a privacy-preserving classification solution whereby the neural network model is executed over confidential data. These solutions use advanced cryptographic schemes such as homomorphic encryption [1] or secure multiparty computation [2]. The main challenge in using such tools is the complexity of the neural network in terms of size and the underlying operations. Therefore,

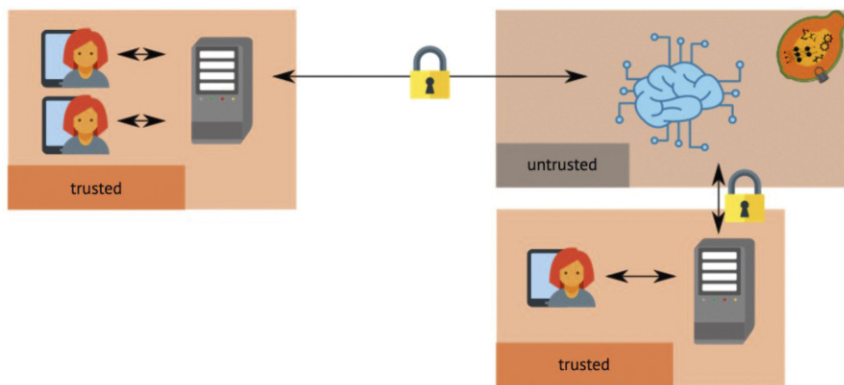


Figure 2: Health-related parameters are collected from workers, aggregated locally and outsourced to train a collaborative model, which can be later used to perform real-time detection of stress and anxiety conditions.

PAPAYA will use these advanced cryptographic tools once the original neural network is modified in order to make it compatible with the actual cryptographic tool (for example, complex operations are approximated to low degree polynomials). This modified neural network will still maintain a good level of accuracy.

Privacy-preserving stress management

This use case targets workers who suffer from stress. It would be very helpful to have an automatic solution that would help anxious and stressed people to recognise symptoms at their onset and suggest mitigation strategies to help the person take preventative action and keep stress levels in check. To this end, sensitive health data from IoT sensors are collected by multiple

sources and used to train a collaborative model via the PAPAYA platform as shown in Figure 2, with the goal of automatically detecting stress conditions in workers.

As a potential solution for this use case, we are studying the problem of privacy-preserving collaborative training based on differential privacy [3] involving many data owners who need to jointly construct a neural network model. Differential privacy prevents participants' individual datasets from being leaked, but allows the joint model to be computed.

This project is a joint work of the PAPAYA project consortium. The PAPAYA project is funded by the H2020 Framework of the European Commission under grant agreement no. 786767. In this

project, six renowned research institutions and industrial players with balanced expertise in all technical aspects of both applied cryptography, privacy and machine learning are working together to address the challenges of the project: EURECOM (project coordinator), Atos Spain, IBM Research Israel, Karlstad University Sweden, MediaClinics Italia and Orange France.

Link:

[L1] <https://kwz.me/hyK>

References:

- [1] R. Rivest, L. Adleman and M. L. Dertouzos: "On data banks and privacy homomorphisms," *Foundations of secure computation*, pp. 169--180, 1978.
- [2] A. Chi-Chih Yao: "Protocols for secure computations" (extended abstract), in *23rd Annual Symposium on Foundations of Computer Science, Chicago, Illinois, USA, 1982*, p.160–164, n.a., 1982. IEEE Computer Society.
- [3] C. Dwork: "Differential privacy", in *Proc. of the 33rd International Conference on Automata, Languages and Programming - Volume Part II, ICALP'06*, pages 1–12, Springer, 2006.

Please contact:

Orhan Ermis
EURECOM, France
orhan.ermis@eurecom.fr

Resilient Network Services for Critical mHealth Applications over 5G Mobile Network Technologies

by Emmanouil G. Spanakis and Vangelis Sakkalis (FORTH-ICS)

DAPHNE is aiming to develop a resilient networking service for critical related applications, as a novel approach for next generation mHealth information exchange. Our goal is to provide in-transit persistent information storage, allowing the uninterrupted provision of crucial services. Our system will overcome network instabilities, capacity efficiency problems, incompatibilities, or even absence of end-to-end homogeneous connectivity, with an emphasis on future networks and services (i.e. 5G). We aim to provide a set of tools for the appropriate management of communication networks during their design time and avoid the "build it first, manage later" paradigm.

Future mHealth informatics rely on innovative technologies and systems for transparent and continuous collection of evidence-based medical information at anytime, anywhere, regardless of coverage and availability of communication means. Such an emerging critical infra-

structure is influenced by factors such as biomedical and clinical incentives, advances in mobile telecommunications, information technology developments, and the socioeconomic environment. This cross dependency has led to concerns about reliability and resilience

of current network deployments, hence it is imperative that communication networks be designed to adequately respond to failures, especially in cloud, mobile and Internet Of Things (IoT) / Web Of Things (WoT) environments that have traditional boundaries.

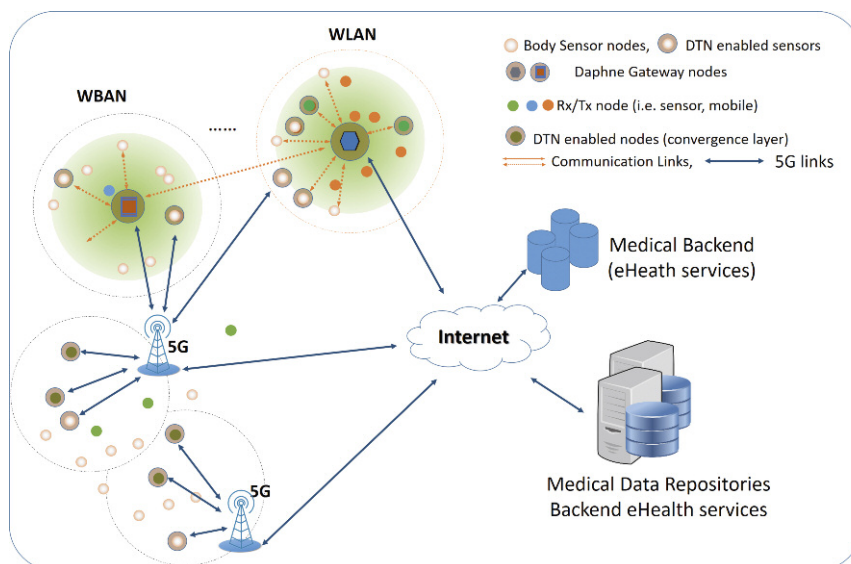


Figure 1: Daphne mHealth service network.

New community-based arrangements and novel technologies can empower individuals to be active participants in their health maintenance by enabling them to self-regulate and control their wellness and make better lifestyle decisions using community-based resources and services. Mobile sensing technology and health systems, responsive to individual profiles, supported by intelligent networking infrastructures and combined with cloud/IoT computing can expand innovation for new types of interoperable services that are consumer oriented and community based. This could fuel a paradigm shift in the way health care can be, or should be, provided and received, while reducing the burden on exhausted health and social care systems [1].

Crucial innovation is needed to make and deploy large scale ICT that facilitates end-user services that are usable, trusted, accepted and enjoyed. This will require multi-domain, multilevel, trans-disciplinary work that is grounded in theory and matched by business ability to bring innovation to the market. Importantly, it must be driven by the needs, expectations and capabilities of individuals and healthcare professionals. Communication networks are one of the most important critical infrastructures underpinning this system, since many other critical infrastructures depend on them in order to function. The heavy reliance on communication networks has led to concerns about reliability and resilience; hence, it is imperative that such networks are designed to

adequately respond to failures and attacks, especially in environments that have traditional boundaries. The goal is to form services at scale, establishing a layer of trust among entities in order to share/collaborate/communicate while minimising the likelihood of failure.

The fifth generation of mobile technology (5G) is positioned to address the demands and business context of 2020 and beyond. It is expected to enable a fully mobile and connected society and to empower socio-economic transformations in countless ways, many of which are unimagined today, such as facilitating productivity, sustainability and well-being. The meaning of 5G, and the ways it will affect electronic health services, is still a subject of discussion in the industry. However, the softwarisation of networks is expected to shape its design, operation and management. Right now there is a growing density/volume of traffic and a rapidly growing need for connectivity. To facilitate this, a multi-layer densification is required, as well as a broad range of use cases and business models, in order for vendors to avoid the “build it first, manage it later” paradigm. In this project our goal is to extend the performance envelope of 5G networks including embedded flexibility, a high level of convergence and access in a highly heterogeneous environment (characterised by the existence of multiple types of access technologies, multi-layer networks, multiple types of devices, multiple types of user interactions, etc).

DAPHNE is implemented around a bundle protocol (BP) (IETF RFC 4838 and RFC 5050) adapted to 5G network stack implemented around a convergence layer (CL). Data packets are encapsulated in the BP and can transparently travel across regions with different network protocol stacks. Our convergence layer implementations may include HTTP, TCP, UDP, Ethernet, BT & BLE, AX.25, RS232, IEEE 802.11x, 802.15.4, LR-WPAN, 5G and other. In our reference implementation, we created a “dntunnel proxy” forming a DTN tunnel over a heterogeneous 5G network that can sustain any delay or disruption, thanks to the in-network storage of our designed architecture.

Daphne [L1], implements a resilient service for critical to support mHealth services enabling personalisation, patient inclusion and empowerment with the expectation that such systems will enhance traditional care in a crisis and provide provision in a variety of situations, where remote consultation and monitoring can be implemented despite the lack of end-to-end connectivity (Figure 1) [2]. In this scenario we envision next generation personal health systems and pervasive mobile monitoring to empower individuals in well-being and disease prevention, and chronic disease management. IoMT and Personal Health Systems covering well-being, prevention of specific diseases or follow-up and management of existing chronic diseases can enhance patient empowerment and self-care management.

DAPHNE is focusing on the underline cyber-physical ecosystem of interconnected sensors and actuators to regulate this networking ecosystem, formed by a collection of biomedical sensors, wearable medical devices, control/sink nodes (mobile phones) and gateways supporting underline critical healthcare service and enable intelligent decision making. These proposed technologies for the underlying architecture, embrace remote monitoring, sensor data collection, remote patient monitoring, extraction of health related features for detection of risks/ alarming and/or alerting, personalized feedback and recommendation services for the patient or informal caregiver. The growing developments in the IoMT, including smart connected technology, can be used for

smart and uninterrupted data collection in order to benefit healthcare and its data-processing abilities, timely decision-making and the overall goal for better patient outcomes (i.e. remote healthcare and monitoring, better drug management through smart devices and actuators, adjustment of therapies and treatment plans, medical device monitoring and control, management of devices within critical healthcare infrastructures). The ability to resiliently provide in-transit persistent information storage will allow the uninterruptible provision of crucial e-Health services, overcoming network instabilities, incompatibilities, or even absence, for a long duration. In our implementation we support application scenarios for: Heterogeneous networks, Harsh intermittent connectivity, Extremely large delays and, Severe disruptions. Our focus is on the integration of a prototype proxy implementation adapted for mHealth requirements and future internet services through emerging

telecommunication converging networks (i.e. 5G) [3]. We analyze the vulnerabilities from a fault tolerant perspective, while taking into account the autonomic principles and we propose a self-healing based framework for 5G networks to ensure availability of services and resources. We will emphasise the problem of reliable system operation with extremely low power consumption and discontinuous connectivity, which are typical for continuous monitoring of people. The goal is to study network failures making them imperceptible by providing service continuity and by minimising congestion.

This project has received funding from the Hellenic Foundation for Research and Innovation (HFRI) and the General Secretariat for Research and Technology (GSRT), under grant agreement No 1337.

Link:

[L1]: <https://daphne.ics.forth.gr/>

References:

[1] E.G.Spanakis et al.: “Technology-Based Innovations to Foster Personalized Healthy Lifestyles and Well-Being: A Targeted Review”, *J Med Internet Res* 2016;18(6):e128, DOI: 10.2196/jmir.4863, PMID: 27342137.

[2] E.G. Spanakis, A.G. Voyiatzis: “DAPHNE: A Disruption-Tolerant Application Proxy for e-Health Network Environments”, 3rd International Conference on Wireless Mobile Communication and Healthcare, Paris, France, November 21-23, 2012.

[3] E.G. Spanakis: “Internet of Medical Things for Healthcare in Smart Monitoring and Diverse Networking Environments”, *EMBC* 2018.

Please contact:

Emmanouil G. Spanakis,
FORTH-ICS, Greece
spanakis@ics.forth.gr

ERCIM “Alain Bensoussan” Fellowship Programme

The ERCIM postdoctoral fellowship programme is open to young researchers from all over the world. It focuses on a broad range of fields in Computer Science and Applied Mathematics. The fellowship scheme also helps young scientists to improve their knowledge of European research structures and networks and to gain more insight into the working conditions of leading European research institu-

tions. The fellowships are of 12 months duration (with a possible extension), spent in one of the ERCIM member institutes. Fellows can apply for second year in a different institute.

Why to apply for an ERCIM Fellowship?

The Fellowship Programme enables bright young scientists from all over the world to work on a challenging problem as fellows of leading European research centers. An ERCIM Fellowship helps widen the network of personal relations and understanding among scientists. The programme offers the opportunity to ERCIM fellows:

- to work with internationally recognized experts;
- to improve their knowledge about European research structures and networks;
- to become familiarized with working conditions in leading European research centres;
- to promote cross-fertilization and cooperation, through the fellowships, between research groups working in similar areas in different laboratories.

Deadlines for applications are currently 30 April and 30 September each year.

Since its inception in 1991, over 500 fellows have passed through the programme. In 2005 the Fellowship Programme was named in honour of Alain Bensoussan, former president of Inria, one of the three ERCIM founding institutes.

<https://fellowship.ercim.eu>

“

The ERCIM Postdoc was a great opportunity! I moved to another country, I met new people and I worked in machine learning applied to industry. This definitely changed my career. Thanks a lot!



Rita Duarte PIMENTEL
Former ERCIM Fellow



“

It was a holistic experience, and the realization of the experience and knowledge I gained only grows each time I look back on it. ERCIM fellowship is a unique opportunity that needs to be grasped, that shapes your future and can give you experiences that will inspire you for many years.



Naveed Anwar BHATTI
Former ERCIM Fellow



A Contractarian Ethical Framework for Developing Autonomous Vehicles

by Mihály Héder(MTA SZTAKI)

The way forward for autonomous vehicle ethics does not revolve around solving old moral dilemmas, but on agreeing on new rules.

Contractarian ethical frameworks claim that the norms we accept as good or proper are mere results of social compromise that is ultimately driven by the self-interest of the involved parties. This position is in contrast with other paradigms around the foundations of ethics, for instance virtues or divine commands.

We are under no obligation to subscribe to one single, exclusive ethical paradigm for all purposes and aspects of our lives. One could apply a particular approach to autonomous cars while allowing others in other domains as long as they can be made compatible.

We believe that a contractarian approach should be taken in the context of autonomous cars, and also that if we are to ever enjoy a serious diffusion of fully autonomous cars it will happen based on the grounds of compromise - or it won't happen at all.

From this it follows that the decisions required during autonomous car development are to be found at the intersection of what is generally considered to constitute acceptable vehicle behaviour as applies to all road users - if such an intersection exists at all. This means that the industry involved in defining such behaviour should simply make proposals and ask for a compromise rather than chasing for moral truths.

The case of autonomous cars should be easier than other social issues, too, because any person can conceivably take on the identity of any type of road user in a particular situation. An individual may be a pedestrian in the morning, a bicycle rider during the day and a passenger in the evening e.g. in an autonomous cab. With other issues our identities tend to be more entrenched.

Let us take most basic autonomous vehicle related ethical dilemma to illustrate the approach. The autonomous car finds itself in an emergency situation in which it can either hit and kill a group of pedestrians or swerve and sacrifice its passengers [1]. There appears to be no other option. This thought experiment has been advanced with a variety of discriminating factors like the number of casualties in pedestrians/passengers, age, gender, various forms of social role of the involved people, etc.

The example reveals the very high dependence on both our and the car's epistemic facilities in evaluating such situations.

In reality the car cannot be certain what kind of objects it has detected as the Arizona Uber incident in which a cyclist died illustrated. Worse still, it has only a partial appraisal of the

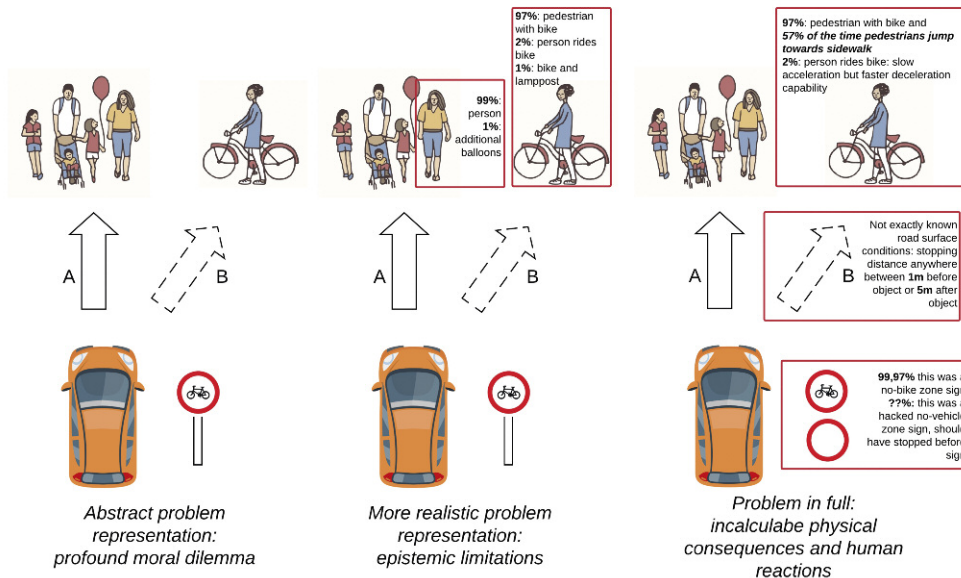


Figure 1: The epistemic constraints of the autonomous car limit the scope of design-time moral investigations.

uncertainty of the object categorisation itself. Also, it has been shown that the neural networks - the technology that performs the identification - can be tricked [2] (the resilience of neural networks to such attacks is a research subject at our department). The uncertainty attached to such situations means that the ethical dilemma itself is only known probabilistically.

At any rate, we are not expecting moral agency from the car itself. Instead these decisions are supposed to be made design-time. Here is where the fallacy of our epistemic facilities come into play. When asked in an experiment a large majority of subjects will say that the vehicle should sacrifice one to save many. But such preventive action has the non-trivial consequence that this known vehicle behaviour allows for malicious actors to trick cars into killing people - by actually jumping in front of a car or even without if the object detection can be tricked. Or, the pedestrian might jump away but the vehicle happens to swerve in the same direction, causing the very tragedy it tried to prevent. When presenting such scenarios to subjects they often backtrack on their previous opinions. Nontrivial consequences are one reason why surveys like the Moral Machine [3] are flawed.

Let us instead entertain a typically contractarian proposal: the autonomous car shall brake intensely in such situations but it will never swerve. This proposal has the marks of good rule-based systems: it is both simple to implement and to understand and results in predictable behaviour.

Such a proposal, as long as we think in the context of the current traffic conditions, would result in tragic casualties in some individual cases, which might have arguably been prevented by a human driver. However, the simplicity of such a self-preserving rule will allow those very conditions to be changed so that the situation won't arise.

The contractarian approach is rational because it does not attempt to solve moral value dilemmas that have proven to be intractable over the last couple of hundred years. It also accounts for the unimaginability of future situations that is the reality of design-time work. What it does instead is come

up with a simple set of rules design-time, asking for the consent of all road users, and thereby in run-time it allows for more control of the situations that impact humans by virtue of being easily predictable. This also allows an evolution of the overall attitude of human road users towards autonomous vehicles in yet unforeseen ways to manage their presence in their own self-interest.

Finally, in order for the contractarian approach to work it needs to stick to its principles - beyond simplicity and intelligibility, those behaviour patterns should be well-known or even advertised; it should be accepted if not with full consensus but at least with compromise; and these behaviour patterns should be guaranteed to operate consistently as much as possible. About a hundred years ago, when the automobile was a novelty, pedestrians needed to vacate some parts of the streets in ways they were not required to in the age of horse carriages - but in return they got traffic lights. At a red light, drivers stop even if there is absolutely no traffic for kilometres: the contract is binding and ensures safety by not allowing any self-judged overruling.

This work was supported by the Bolyai scholarship of the Hungarian Academy of Sciences and by the ÚNKP-18-4 New National Excellence Program of the Ministry of Human Capacities.

References:

- [1] P. Lin: "Why Ethics Matters for Autonomous Cars", M. Maurer et al. (Hrsg.), *Autonomes Fahren*, DOI 10.1007/978-3-662-45854-9_4, 2015.
- [2] A. Nguyen, J. Yosinski, J. Clune: "Deep Neural Networks are Easily Fooled: High Confidence Predictions for Unrecognizable Images", in *Computer Vision and Pattern Recognition (CVPR '15)*, IEEE, 2015.
- [3] E. Awad, et al.: "The Moral Machine experiment", *Nature*, 563 (7729), 59, 2018.

Please contact:

Mihály Héder,
 mihaly.heder@sztaki.mta.hu
<https://www.sztaki.hu/en/science/departments/hbit>

A Language for Graphs of Interlinked Arguments

by Dimitra Zografistou, Giorgos Flouris, Theodore Patkos, and Dimitris Plexousakis (ICS-FORTH)

ArgQL is a high-level declarative language, aimed to query data which are structured as a graph of interconnected arguments. It provides specially designed constructs and terminology that generate queries relevant to the domain of interest that are both easy to express and understand.

The recent advances in the technologies of Web 2.0 changed the role of its users from passive information consumers to active creators of digital content. Web became a universal terrain, wherein humans accommodate their inherent need for communication and self-expression. From a scientific point of view, this new era was accompanied by numerous new challenges. Navigation in dialogues and investigation of the informational requirements is one such challenge, which constitutes a pristine and until recently, almost untouched area. The process of human argumentation, in contrast, has been a longstanding subject of theoretical studies.

Computational argumentation is a branch of AI and it offers more accurate and realistic reasoning methods by transferring the cognitive behaviour of people when arguing into its computational models. An extensive overview in the area led us to the observation that it also defines solid and discrete constructs that structure a dialogue. This observation motivated us to develop ArgQL (Argumentation Query Language) [1, 2], a novel, high-level declarative query language that will allow for the navigation and information identification in a graph of interconnected arguments, structured in the principles of argumentation. ArgQL constitutes an initial effort to understand the informational and theoretical requirements during this process. The most significant contribution lies in its potential to provide a querying mechanism, focused on the internal structures of arguments and their interactions, isolating the process from technical details related to the traditional languages. Its need is highlighted by the complexity of constructing SPARQL queries, even for simple statements, like “How an argument with a given conclusion is attacked?” in the argumentation domain. Instead, ArgQL generates quite elegant and representative queries, easy to both express and understand.

ArgQL was designed to cover several predefined informational requirements, which can be categorised as follows:

- Individual arguments identification: We provide features that allow to add constraints to the argument’s internal structure, based on particular values.
- Correlated arguments identification: ArgQL also allows constraints to be expressed on an argument’s content with regard to other arguments, such as: search for pairs of arguments with commonalities in their content.
- Argument relations extraction: ArgQL offers built-in keywords that allow express restrictions to be expressed about the relations between arguments.
- Dialogue traversing and sub-dialogues identification: Expressions used for navigating across the relation between arguments are also provided.

In Figure 1, we show an example of the target data. In the left part, we show the data structures in the lowest level, consisting of arguments and two types of relations between propositions, conflicts and equivalences, while the right depicts their abstract view, in which data form a graph of interlinked arguments.

Figure 2 shows two examples of ArgQL, along with an intuitive description of the requirements captured by each.

As a first step, we formally define a data model based on the prevailing concepts in the area of computational argumentation. Afterwards, we define the language specifications in terms of its syntax, as well as its formal semantics that show how the different keywords and expressions are evaluated against the proposed data model. For query execution, we propose a methodology to translate ArgQL into already well-known storage schemes and in particular the RDF/SPARQL language. The methodology includes the mapping between the data models and the translation between the query languages. The correctness of the translation has been formally proven. We have implemented ArgQL and have also developed an endpoint, wherein queries can be executed against real datasets. The performance of the translation is experimentally evaluated on these datasets. Despite its theoretical correctness, the proposed translation revealed some issues at implementation time, which concerned particular query cases. To address those issues, we suggest a set of optimisations, which result in shorter and, therefore, more effective queries.

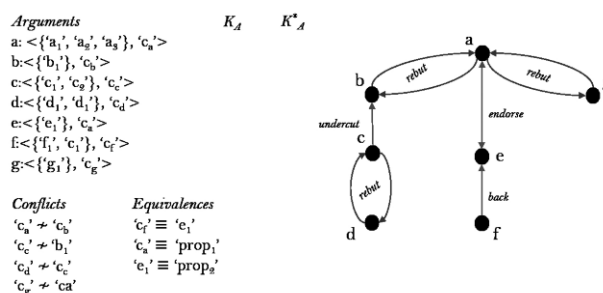


Figure 1: Example of target data.

```

"Find pairs of arguments with intersected premisses, that is, arguments with at least one common premiss."
Q match ?arg1: <?pr1, ?c1>, ?arg2: <?pr2[.?pr1], ?c2>
return ?arg1, ?arg2

"Find all those arguments that attack arguments with conclusion 'c1'".
Q match ?arg1 attack ?arg2: <?pr, 'c1'>
return ?arg1
    
```

Figure 2: Two examples of ArgQL.

References:

- [1] D. Zografistou, G. Flouris, D. Plexousakis: “Argql: A declarative language for querying argumentative dialogues”, in International Joint Conference on Rules and Reasoning (pp. 230-237), Springer, 2017.
- [2] D. Zografistou, et al.: “Implementing the ArgQL Query”, Computational Models of Argument, Proc. of COMMA 2018, 305, p.241, 2018.

Please contact:

Dimitra Zografistou, ICS-FORTH, Greece,
+30 2810 391683, dzograf@ics.forth.gr

Distortion in Real-World Analytic Processes

by Peter Kieseberg (St. Pölten University of Applied Sciences), Lukas Klausner (St. Pölten University of Applied Sciences) and Andreas Holzinger (Medical University Graz).

In discussions on the General Data Protection Regulation (GDPR), anonymisation and deletion are frequently mentioned as suitable technical and organisational methods (TOMs) for privacy protection. The major problem of distortion in machine learning environments, as well as related issues with respect to privacy, are rarely mentioned. The Big Data Analytics project addresses these issues.

People are becoming increasingly aware of the issue of data protection, a concern that is in part driven by the use of personal information in novel business models. The essential legal basis for considering the protection of personal data in Europe has been created in recent years with the General Data Protection Regulation (GDPR). The data protection efforts are confronted with a multitude of interests in research [1] and business [2], which are based on the provision of often sensitive and personal data. We analysed the major challenges in the practical handling of such data processing applications, in particular the challenges they pose to innovation and growth of domestic companies, with particular emphasis on the following areas (see also summary in Figure 1):

- **Anonymisation:** For data processing applications to be usable, it is essential, particularly in the area of machine learning, that the obtained results are of high quality. Classical anonymisation methods generally distort the results quite strongly [3]. Mere pseudonymisation, typically used up to now as a replacement, can no longer be used as a privacy protection measure, since the GDPR explicitly stipulates that these methods are not sufficiently effective. At present, however, there is no large-scale study on these effects which considers different types of information. Also, the approaches to mitigate this distortion are currently still mostly proofs of concept and purely academic. Concrete methods are needed to reduce this distortion and to deal with the resulting effects.
- **Transparency:** The GDPR prescribes transparency in data processing, i. e., the fact that a data subject has the right to receive information about the data stored about them at any time, and to know how it is used. At present, no practical methods exist to create this transparency whilst avoiding possible data leaks. Furthermore, the commonly used mechanisms currently in use are not designed to ensure transparency in the context of complex evaluations using machine learning algorithms. Guaranteeing transparency is also an important prerequisite for the deletion of personal information as well as for ensuring responsibility and reproducibility.

- **Deletion:** An important aspect of the GDPR is informational self-determination: This includes the right to subsequent withdrawal of consent and, ultimately, the right to data deletion. Processes must accommodate this right; therefore, methods for the unrecoverable deletion of data from complex data-processing systems are needed, a fact which stands in direct opposition to the design criteria that have been employed since the advent of computing. Deletion as a whole is also a problem with respect to explainability and retraceability, thus opening up a substantial new research field on these topics.
- **Data security:** The GDPR not only prescribes privacy protection of personal data, but also data security. Various solutions already exist for this; the challenge does not lie in the technical research but in the concrete application and budgetary framework conditions.
- **Informed consent:** Consent is another essential component of the GDPR. Henceforth, users will have to be asked much more clearly for their consent to using their data for more explicitly specified purposes. The academic and legal worlds have already made many suggestions in this area, so, in principle, this problem can be considered solved.
- **Fingerprinting:** Often data is willingly shared with other institutions, especially in the area of data-driven research, where specialised expertise by external experts and/or scientists is required. When several external data recipients are in the possession of data, it is important to be able to detect a leaking party beyond doubt. Fingerprinting provides this feature, but most mechanisms currently in use are unable to detect a leak based on just a single leaked record.

Within the framework of the Big Data Analytics project, methods for solving these challenges will be analysed, with

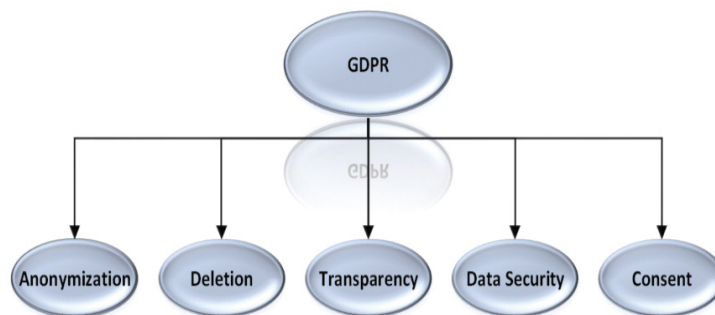


Figure 1: Important aspects of data science affected by the GDPR.

the aim of coming up with practical solutions, i. e., the problems will be defined from the point of view of concrete users instead of using generic machine learning algorithms on generic research data. In our testbed, we will implement several anonymisation concepts based on k-anonymity and related criteria, as well as several generalisation paradigms (full domain, subtree, sibling) combined with suppression. Our partners from various data-driven business areas (e. g. medical, IT security, telecommunications) provide complete use cases, combining real-life data with the respective machine learning workflows. These use cases will be subjected to the different anonymisation strategies, thus allowing the actual distortion introduced by them to be meas-

ured. This distortion will be evaluated with respect to the use cases' quality requirements.

In summary, this project addresses the question of whether the distortion introduced through anonymisation hampers machine learning in various application domains, and which techniques seem to be most promising for distortion-reduced privacy-aware machine learning.

References:

- [1] O. Nyrén; M. Stenbeck, H. Grönberg: "The European Parliament proposal for the new EU General Data Protection Regulation May Severely Restrict European Epidemiological Research", in: *European Journal of Epidemiology* 29 (4), S. 227–230, 2014.
DOI: 10.1007/s10654-014-9909-0, <https://kwz.me/hyj>
- [2] S. Ciriani: "The Economic Impact of the European Reform of Data Protection", in *Communications & Strategies* 97 (1), 41–58, SSRN: 26740102015.
- [3] B. Malle, et al.: "The right to be forgotten: towards machine learning on perturbed knowledge bases", in *Proc. of ARES 2016*, pp. 251-266, Springer, 2016.
DOI: 10.1007/978-3-319-45507-5_17

Please contact:

Peter Kieseberg
St. Pölten University of Applied Sciences, Austria
peter.kieseberg@fhstp.ac.at

New Project

GATEKEEPER - Smart Living Homes for People at Health and Social Risks

European citizens are living longer and this is putting pressure on European Healthcare to detect conditions and risks early, and to manage them properly. There are multiple efforts to address this with a common focus on digital transformation. ERCIM will be part of the 42 month duration GATEKEEPER EU H2020 project to create an open source hub for connecting healthcare providers, businesses, entrepreneurs, elderly citizens and the communities they live in. The aim is to provide a framework for creating and exploiting combined digital solutions for personalised early detection and interventions, and to demonstrate the value across eight regional communities from seven EU member states. The technical underpinnings include the Web of Things for integrating a variety of sensor technologies along with FHIR and SAREF for e-health records and semantic models. W3C/ERCIM will contribute its experience with developing Web technology standards in relation to the Web of Things and semantic interoperability, and will seek to exploit the work on open markets of services as the basis for future standardisation.

Link: <http://www.gatekeeper-project.eu/>

Please contact: Dave Raggett, W3C, dsr@w3.org.

15th EUROPEAN COMPUTER SCIENCE SUMMIT

www.informatics-europe.org/ecss
#ECSS_2019

ECSS 2019

Rome - Italy
28-30 OCTOBER



Organized by



In partnership with

- Pontifical Lateran University
- "Sapienza" University of Rome
- University of Rome "Tor Vergata"
- University of Rome "Tre"

ECSS is the forum to debate the trends and issues that impact the future of Informatics in Europe.

Join leading decision makers and hear from renowned speakers about the challenges and opportunities for Informatics research and education in an increasingly interconnected world.

Keynote Speakers:

- **Tony Belpaeme**, Ghent University
- **Virginia Dignum**, Umeå University
- **Mireille Hildebrandt**, Vrije Universiteit Brussel
- **Paola Inverardi**, University of L'Aquila
- **Bernd Stahl**, De Montfort University

Events:

- **Leaders Workshop**
- **WIRE Workshop**
- **Keynotes and Panel on Social Responsibility of Informatics**
- **Informatics Europe - ERCIM Awards Session**
- **Informatics Europe Sessions**
- **Talent Gap Workshop**



SCHLOSS DAGSTUHL
Leibniz-Zentrum für Informatik

Call for Proposals

Dagstuhl Seminars and Perspectives

Workshops

Schloss Dagstuhl – Leibniz-Zentrum für Informatik is accepting proposals for scientific seminars/workshops in all areas of computer science, in particular also in connection with other fields.

If accepted the event will be hosted in the seclusion of Dagstuhl's well known, own, dedicated facilities in Wadern on the western fringe of Germany. Moreover, the Dagstuhl office will assume most of the organisational/administrative work, and the Dagstuhl scientific staff will support the organizers in preparing, running, and documenting the event. Thanks to subsidies the costs are very low for participants.

Dagstuhl events are typically proposed by a group of three to four outstanding researchers of different affiliations. This organizer team should represent a range of research communities and reflect Dagstuhl's international orientation. More information, in particular, details about event form and setup as well as the proposal form and the proposing process can be found on

<https://www.dagstuhl.de/dsproposal>

Schloss Dagstuhl – Leibniz-Zentrum für Informatik is funded by the German federal and state government. It pursues a mission of furthering world class research in computer science by facilitating communication and interaction between researchers.

Important Dates

- Proposal submission: October 15 to November 1, 2019
- Notification: February 2020
- Seminar dates: Between September 2020 and August 2021 (tentative).

In Memory of Cor Baayen



Photo: CWI

It is with great sadness that we learned that Cor Baayen, first president and co-founder of ERCIM, passed away on Wednesday, 22 May 2019. Baayen served as ERCIM president from 1991 to 1994. He was scientific director of CWI from 1980 to 1994. During this period, he played a key role in shaping computer science as a distinct scientific field. Under his leadership CWI

transformed from a mathematical institute to a centre of expertise for both mathematics and computer science. Together with Alain Bensoussan from Inria and Gerhard Seegmüller from the former GMD, he founded ERCIM in 1989 with the aim of building a European scientific community in information technology.

Baayen started his first tenure at CWI in 1959, when it was still named Mathematisch Centrum (MC). He was appointed leader of the pure mathematics group at MC in 1965, as well as professor of mathematics at the Vrije Universiteit in Amsterdam. When Baayen became scientific director in 1980, he immediately had to deal with diminishing funds for academic research. One of the most notable strategies to secure MC's future, was to incorporate the institute in the first Dutch national ICT funding scheme. This fitted perfectly with a broadening of the institute's focus towards computer science. A milestone in this transformation is the renaming of the institute to CWI (Centrum voor Wiskunde en Informatica, comprising informatics) in 1983.

Cor Baayen will be remembered as one of the founders of ERCIM. The consortium grew out to become Europe's most ambitious association in this field, with currently 16 member institutes. ERCIM honours Baayen's legacy with its annual Cor Baayen Young Researcher Award for promising young researchers in computer science or applied mathematics.

HORIZON 2020 Project Management

A European project can be a richly rewarding tool for pushing your research or innovation activities to the state-of-the-art and beyond. Through ERCIM, our member institutes have participated in more than 90 projects funded by the European Commission in the ICT domain, by carrying out joint research activities while the ERCIM Office successfully manages the complexity of the project administration, finances and outreach. The ERCIM Office has recognized expertise in a full range of services, including identification of funding opportunities, recruitment of project partners, proposal writing and project negotiation, contractual and consortium management, communications and systems support, organization of events, from team meetings to large-scale workshops and conferences, support for the dissemination of results.

How does it work in practice?

Contact the ERCIM Office to present your project idea and a panel of experts will review your idea and provide recommendations. If the ERCIM Office expresses its interest to participate, it will assist the project consortium either as project coordinator or project partner.

Please contact:

Peter Kunz, ERCIM Office, peter.kunz@ercim.eu



Consiglio Nazionale delle Ricerche
Area della Ricerca CNR di Pisa
Via G. Moruzzi 1, 56124 Pisa, Italy
www.iit.cnr.it



Norwegian University of Science and Technology
Faculty of Information Technology, Mathematics and Electrical Engineering, N 7491 Trondheim, Norway
<http://www.ntnu.no/>



Centrum Wiskunde & Informatica

Centrum Wiskunde & Informatica
Science Park 123,
NL-1098 XG Amsterdam, The Netherlands
www.cwi.nl



RISE SICS
Box 1263,
SE-164 29 Kista, Sweden
<http://www.sics.se/>



Fonds National de la
Recherche Luxembourg

Fonds National de la Recherche
6, rue Antoine de Saint-Exupéry, B.P. 1777
L-1017 Luxembourg-Kirchberg
www.fnrl.lu



SBA Research gGmbH
Favoritenstraße 16, 1040 Wien
www.sba-research.org/



Foundation for Research and Technology – Hellas
Institute of Computer Science
P.O. Box 1385, GR-71110 Heraklion, Crete, Greece
www.ics.forth.gr



Magyar Tudományos Akadémia
Számítástechnikai és Automatizálási Kutató Intézet
P.O. Box 63, H-1518 Budapest, Hungary
www.sztaki.hu/



Fraunhofer ICT Group
Anna-Louisa-Karsch-Str. 2
10178 Berlin, Germany
www.iuk.fraunhofer.de



TNO
PO Box 96829
2509 JE DEN HAAG
www.tno.nl



INESC
c/o INESC Porto, Campus da FEUP,
Rua Dr. Roberto Frias, n° 378,
4200-465 Porto, Portugal
www.inesc.pt



University of Cyprus
P.O. Box 20537
1678 Nicosia, Cyprus
www.cs.ucy.ac.cy/



Institut National de Recherche en Informatique
et en Automatique
B.P. 105, F-78153 Le Chesnay, France
www.inria.fr



University of Warsaw
Faculty of Mathematics, Informatics and Mechanics
Banacha 2, 02-097 Warsaw, Poland
www.mimuw.edu.pl/



I.S.I. – Industrial Systems Institute
Patras Science Park building
Platani, Patras, Greece, GR-26504
www.isi.gr



VTT Technical Research Centre of Finland Ltd
PO Box 1000
FIN-02044 VTT, Finland
www.vttresearch.com