TECHNION |

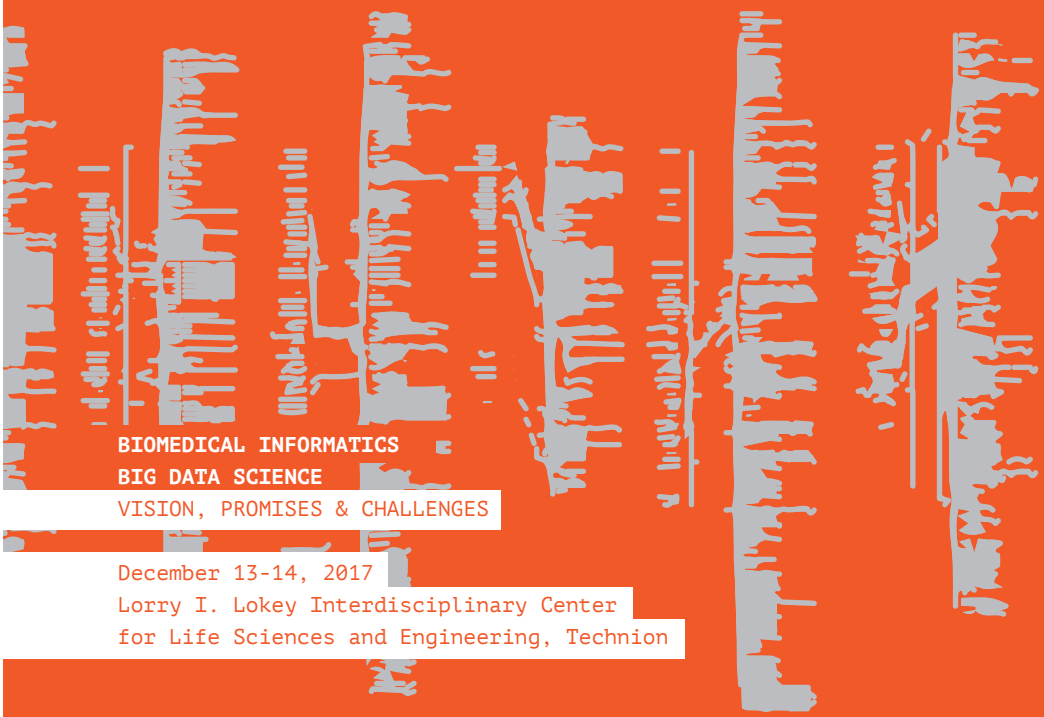
Lorry I. Lokey Interdisciplinary Center
for Life Sciences and Engineering

Biomedical Informatics

Big Data Science Conference

Vision, Promises
& Challenges

Dec. 13-14, 2017



BIOMEDICAL INFORMATICS
BIG DATA SCIENCE
VISION, PROMISES & CHALLENGES

December 13-14, 2017
Lorry I. Lokey Interdisciplinary Center
for Life Sciences and Engineering, Technion

/ Technion is ready for Biomedical Informatics

I would like to welcome all participants to the conference on "Big Data Science: Vision, Promises and Challenges." This conference is a timely one. No doubt we are at the beginning of an exciting era of biomedical research during which Biomedical informatics is emerging as a leading field that studies and pursues the effective implementation of biomedical data and medical information.

The buzzword is indeed "big data" which may comprise millions of digitized medical records, or populations' records of digitized body temperatures, pulse rates or blood pressures, or hormonal levels and many more. Once processed and analyzed these big data may provide new insights and understandings that will have substantial impact on both basic research and clinical sciences. Internet of things, limitless data storage capacities and inexpensive powerful computing capabilities, the technologies that are shaping the fourth industrial revolution, provide clinicians and basic researchers alike with new tools to improve health care services.

Biomedical informatics is an interdisciplinary area that relies on collaborations between mathematicians, computer scientists, life scientists and medical scientists, areas that must converge to enable the vision of moving from the laboratory bench to the bedside. The Technion is uniquely prepared to meet this challenge, in addition to excellent research in engineering, and natural and exact sciences, it has its own Faculty of Medicine, the Ruth and Bruce Rappaport Faculty of Medicine, with its affiliated hospitals and an excellent Faculty of Biology.

I am certain that this conference will chart the scopes of knowledge of this fascinating area, foster the creation of a motivated Technion community of researchers, and will encourage collaborations across the participating disciplines.

Prof. Peretz Lavie
President
Technion - Israel Institute of Technology

ORGANIZING COMMITTEE

Roy Kishony, Technion

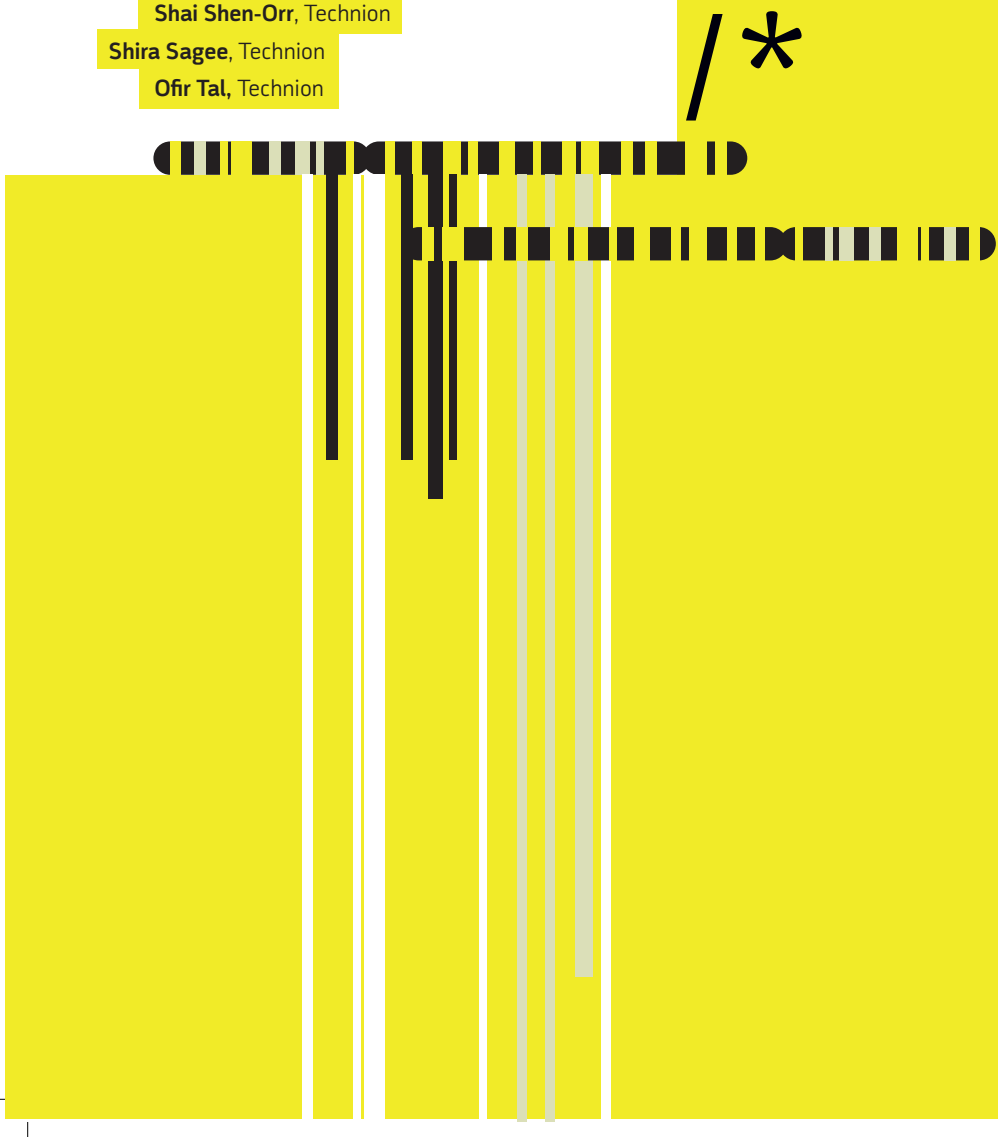
Kira Radinsky, Technion

Eran Segal, Weizmann Institute

Shai Shen-Orr, Technion

Shira Sagee, Technion

Ofir Tal, Technion



/ Welcome

We would like to welcome all of our guests, invited speakers and participants to the "Biomedical Informatics – Big Data Science - Vision, Promises & Challenges" Conference.

This meeting was made possible due to the generosity of and vision of Yad Hanadiv Foundation – we are fortunate to have their support.

Biomedical informatics is becoming a central focus across academic research centers, medical institutions and data-science industry and entrepreneurs. The application of machine learning approaches to large volumes of medical data, information, and knowledge is driving discovery at the interface of basic research and biomedicine. These approaches allow testing basic science hypotheses directly in patients and can even generate new hypotheses that traverse from basic research to human health. Indeed, as both medical research and healthcare become increasingly dependent on big data, biomedical informatics is promising to impact major biomedical questions and challenges from infectious diseases through genetic disorders to cancer. Inherently though, progress in this field requires interdisciplinarity across basic research in Biology, Computer Science and Medicine intertwined with collaborations with healthcare providers, industry leaders, entrepreneurs and even governmental agencies.

The aim of the conference is to bring together key innovators in these disciplines to showcase current approaches and breakthroughs and brainstorm future research directions and discovery paradigms. We are happy to see the interest of a large and diversified audience and hope that in the spirit of the Hanukkah holiday and its celebration of light the meeting will help bridge across disciplines and spark innovative projects illuminating major biomedical challenges with the light of big data.

We hope you will enjoy the meeting and have a pleasant stay in the Technion, in Haifa and in Israel.

Prof. Roy Kishony
On behalf of the organizing committee

Wednesday December 13, 2017

08:30-9:00 WELCOME RECEPTION

09:00-9:05 *Welcome:* **Roy Kishony**

09:05-9:15 *Opening greetings:* **Prof. Peretz Lavie,** President of the Technion

09:15-10:15 *Keynote:* **Jonathan Adiri**
The Era of Permanent Revolution

SESSION 1 MEDICAL INFORMATICS - FINDING TREASURE

10:30-10:50 **Amos Tanay**
Probabilistic modelling of complex and sparse medical records

10:50-11:10 **Kira Radinsky**
Predicting the future in medicine using data science

11:10-11:30 **Nigam Shah**
Building a machine learning health system

11:30-12:00 COFFEE BREAK

SESSION 2 HIGH-RES POPULATION STUDIES

12:00-12:20 **Hannah Bayer**
The HUMAN Project - Using big data to understand the human condition

12:20-12:40 **Soren Brunak**
Disease trajectories from population-wide data in the context of underdiagnosed disease

12:40-13:00 **Eran Segal**
Personalizing treatments using microbiome and clinical data

13:00-15:00 LUNCH BREAK & POSTER PRESENTATION I

SESSION 3 RESEARCH NUGGETS

15:00-15:20 **Roy Kishony**
Understanding, Predicting and Manipulating the Evolution of Antibiotic Resistance

15:20-15:40 **Shai Shen-Orr**
Moving Systems Immunology Beyond High bandwidth Measurements

15:40-16:00 **Ze'ev Ronai**
Microbiome - Immune system interactions in melanoma development

16:00-16:20 **Irit Hochberg**
Using MDclone medical database query to explore the effect of albumin and insulin type on inpatient hypoglycemia

16:30-17:00 CANDLE LIGHTING

17:30-22:00 *Speaker tour:* Beit She'arim tour and Dinner

Thursday December 14, 2017

08:30-9:00	GATHERING
09:00-10:00	*Keynote:* **John Wilbanks** Participant-centered design for ethical precision medicine
SESSION 4	**MEDICAL INFORMATICS - FROM THE PROVIDER PERSPECTIVE**
10:00-10:20	**Ran Balicer** Data-driven care: Innovation in Practice?
10:20-10:40	**Varda Shalev** Personalized medicine from theory to practice
10:40-11:00	**Eric Kirkendall** From Theory to Practice: Informatics Research in the Modern Clinical Setting
11:00-11:30	COFFEE BREAK
SESSION 5	**SYSTEMS BIOLOGY AND GENOMICS**
11:30-11:50	**Uri Alon** Evolutionary tradeoffs and the geometry of large scale biological datasets
11:50-12:10	**Joel Dudley** Moving from Precision Medicine to Next Generation Healthcare
12:10-12:30	**Jaroslaw Meller** LINCS Cellular Perturbation Signatures as a Resource for Precision Medicine
13:00-15:00	LUNCH & POSTER SESSION II
SESSION 6	**AUGMENTING THE HUMAN**
15:00-15:20	**Michal Rosen-Zvi** Helping physicians with specialized advisors - from HIV to Breast Cancer
15:20-15:40	**Elad Yom-Tov** Can Internet search engines guide you to better health?
15:40-16:00	**Jonathan Laserson** Zeroing in on Radiology
16:00-16:15	WINNING POSTER ANNOUNCEMENT
16:15-17:15	*Keynote:* **Isaac Kohane** What does it mean to be a doctor in the era of superhuman artificial intelligence?
17:15-17:30	*Concluding remarks:* **Roy Kishony**

/* The Era of Permanent Revolution

Jonathan Adiri
Founder, CEO - Healthy.io

On June 1997 in Mid Town Manhattan, Gary Kasparov capitulated to IBM's Deep Blue. 20 years later (and 30 years before the earliest prediction on record), in the Chinese city of Whuzhen, Ke Jie, the world champion in the ancient game of GO (10^127 possible moves) surrendered to Google's Alpha Go.

In his lecture, the Era of Permanent Revolution, Yonatan draws on his extensive statecraft and serial entrepreneurship to demonstrate how the rules of the game have been redrawn due to the exponential nature of technological growth and an inverse parallel cost curve. Who was the Greek immigrant that is perhaps the most influential individual on this acceleration? How did car thieves bring about breakthroughs in molecular biology and how on earth can taxi medallions predict the future of mobility?

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/* Probabilistic Modelling of Complex and Sparse Medical Records

Amos Tanay
Weizmann Institute of Science, Rehovot, Israel

Extensive clinical datasets derived from electronic health records (EHR) provide numerous opportunities for retrospective studies on common disease. But in order to maximize the power of EHR-based research, it is essential to develop integrative computational models for multi-variate distributions of laboratory measurements, diagnoses and medications, taking into account extremely high levels of missing data, uneven temporal sampling, and a myriad of biases and noise sources. We shall present our ongoing effort to develop such computational models, and discuss applications of our methodologies to de-identified data that we study in collaboration with Clalit Health Services. Metrics for evaluation of our models, in particular given multi-disease prediction tasks, will be discussed.

*/

/* Predicting the Future in Medicine Using Data Science

Kira Radinsky
eBay Director of Data Science & Visiting Professor Technion

Our world faces increasingly complex challenges: we destabilized the climate, haven't beaten all diseases, and haven't spread the values of democracy and freedom to large parts of the globe, where violence and riots reign supreme. The world must be fixed in our generation - everyone would agree. But in order to take action, build a plan, we need to see the complete picture, and empower decision makers with tools to make those changes. This decade, we have finally reached a critical amount of data to facilitate the creation of such tools.

My work is inspired by Mark Twain's quote, who once said: "The past does not repeat itself, but it rhymes." Although future events have unique circumstances, they typically follow familiar past patterns. Over the past few years, I devoted my life to development of prediction techniques. My system inferred that Cholera outbreaks in land-locked areas are more likely to occur following storms, especially when preceded by a long drought. Another inference is that genocide events tend to occur following events where local opinion makers describe minority groups as pests. These types of patterns are composed of several abstractions, over variable-term temporal extents and selected from a large number of possible causes. The algorithms I developed deal with the complexity of discovering such patterns.

Large-scale digital histories, social and real-time media, and human web behavior are harvested and augmented with human knowledge mined from the web to afford real-time estimations of likelihoods of fu-

ture events. Most recently, these algorithms have accurately predicted the first Cholera outbreak reported in Cuba in fifty years. These types of actionable predictions, that enable preventative measures, have drawn the attention of a UN genocide-prevention organization and the Gates foundations and illustrate the vast potential for real impact on the state of humanity.

In the last few years I have been focusing on applying similar techniques for the healthcare and Pharma, leveraging large amount of data obtained from both medical records, EMR and other medical research results data in a quest to create an AI system for automated medical research and breakthroughs.

*/

/* Building a Machine Learning Health System

Nigam Shah
Associate Professor of Medicine,
Stanford University, USA

In the era of Electronic Health Records, it is possible to examine the outcomes of decisions made by doctors during clinical practice to identify patterns of care - generating evidence from the collective experience of patients. We will discuss methods that transform unstructured EHR data into a de-identified, temporally ordered, patient-feature matrix. We will review use-cases, which use the resulting de-identified data, to discover hidden trends, build predictive models, and drive comparative effectiveness studies in a learning health system.

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/* The HUMAN Project - Using Big Data to Understand the Human Condition */

Hannah Bayer
Chief Scientist, The Human Project
Research Associate Professor of Decision Sciences, New York University, USA

Until now, most large-scale studies of humans have either focused on very specific domains of inquiry or have relied on between-subjects approaches. While these previous studies have been invaluable for revealing important biological factors in cardiac health or social factors in retirement choices, no single repository contains anything like a complete record of the health, education, genetics, environmental, and lifestyle profiles of a large group of individuals at the within-subject level. This seems critical today because emerging evidence about the dynamic interplay between biology, behavior, and the environment point to a pressing need for just the kind of large-scale, long-term synoptic dataset that does not yet exist at the within-subject level. At the same time that the need for such a dataset is becoming clear, there is also growing evidence that just such a synoptic dataset may now be obtainable - at least at moderate scale - using contemporary big data approaches. The HUMAN Project (THP) is an effort to accomplish these goals by aggregating data from 4000 New York City households in all five boroughs (roughly 10,000 individuals) whose biology and behavior will be measured using an unprecedented array of modalities over 20 years. This study will offer both synoptic and granular views of how human health and behavior co-evolve over the life cycle and why they evolve differently for different people. In turn, we argue that this will allow for new discovery-based scientific approaches, rooted in big data analytics, to improving the health and quality of human life, particularly in urban contexts.

*/

/* Disease Trajectories from Population-Wide Data in the Context Underdiagnosed Disease

Soren Brunak
University of Copenhagen, Danemark

Multi-step disease trajectories are key to the understanding of human disease progression patterns and their underlying molecular level etiologies. The number of protein coding genes is small and many genes are presumably impacting more than one disease. The talk will present approaches to the identification of frequent disease trajectories from population-wide healthcare data comprising millions of patients and corresponding strategies for linking disease co-occurrences to genomic individuality. An additional opportunity provided by redefining phenotypes as longitudinal patterns is to assess the validity of diagnoses (mis- and over-diagnosis), or alternatively suggest missing diagnoses (under-diagnosis), from their temporal context. We use COPD as a case and demonstrate how we can identify and impute likely under-diagnosed patients in this manner. Such a diagnosis "clean-up" effort is also relevant in conventional case-control studies where false negative and false positive individuals bring down the statistical power or the predictive performance of machine learning algorithms.

*/

/* Personalizing Treatments Using Microbiome and Clinical Data

Eran Segal
Weizmann Institute of Science, Rehovot, Israel

Accumulating evidence supports a causal role for the human gut microbiome in obesity, diabetes, metabolic disorders, cardiovascular disease, and numerous other conditions, including cancer. Here, I will present our research on the role of the human microbiome in health and disease, aimed at developing personalized medicine approaches that combine human genetics, microbiome, and nutrition.

In one project, we set out to understand personal variation in the glycemic response to food, tackling the subject of personalization of human nutrition, a poorly studied topic that is critical for human health and to billions of people predisposed to, or suffering from, obesity, T2D and related co-morbidities. We assembled a 1,000 person cohort and measured blood glucose response to >50,000 meals, lifestyle, medical and food frequency questionnaires, blood tests, genetics, and gut microbiome. We showed that blood glucose responses to meals greatly vary between people even when consuming identical foods; devised the first algorithm for accurately predicting personalized glucose responses to food based on clinical and microbiome data; and showed that personalized diets based on our algorithm successfully balanced blood glucose levels in prediabetic individuals. These results suggest that personalized diets may successfully modify elevated postprandial blood glucose and its metabolic consequences.

I will also present our studies of the mechanisms driving recurrent post-dieting obesity in which we identified an intestinal microbiome signature that persists after successful dieting of obese mice.

This microbiome signature contributes to faster weight regain and metabolic aberrations upon re-exposure to obesity-promoting conditions and transmits the accelerated weight regain phenotype upon inter-animal transfer. These results thus highlight a possible microbiome contribution to accelerated post-dieting weight regain, and suggest that microbiome-targeting approaches may help to diagnose and treat this common disorder.

Finally, we studied the relative contribution of host genetics and environmental factors in shaping human gut microbiome composition. To this end, we examined genotype and microbiome data in over 1,000 healthy individuals from several distinct ancestral origins who share a relatively common environment, and demonstrated that the gut microbiome is not significantly associated with genetic ancestry. In contrast, we find significant similarities in the microbiome composition of genetically unrelated individuals who share a household, and show that over 20% of the gut microbiome variance can be explained via environmental factors related to diet, drugs and anthropometric measurements. We define the term biome-explainability as the variance of a host phenotype explained by the microbiome after accounting for the contribution of human genetics. Consistent with our finding that microbiome and host genetics are largely independent, we find significant biome-explainability levels of 24%-36% for several human traits and disease risk factors. We also successfully replicated our results in an independent Dutch cohort. Overall, our results suggest that human microbiome composition is dominated by environmental factors rather than by host genetics.

*/

/* Understanding, Predicting and Manipulating the Evolution of Antibiotic Resistance

Roy Kishony
Director, Lorry I. Lokey Interdisciplinary Center for Life Sciences and Engineering, Technion - Israel Institute of Technology, Haifa

Antibiotic resistance is growing as a major public health concern. Understanding the evolutionary paths leading to antibiotic resistance is key for our ability to predict and control drug resistance. I will describe a series of experimental-theoretical methodologies that allow us to follow the evolution of antibiotic resistance in the lab and in the clinic. I will then describe new ways by which we can combine drugs to slow down and even reverse the evolution of antibiotic resistance. Together, these studies lay down foundations for genome-based anticipatory diagnostics of microbial infections to guide more resilient patient-specific multi-drug treatments

*/

/* Moving Systems Immunology Beyond High bandwidth Measurements

Shai Shen-Orr
Dept. of Immunology, Faculty of Medicine,
Technion - Israel Institute of Technology, Haifa

Protective immunity is not the end outcome of any single cell, but rather draws on functionality elicited by many cell types communicating between one another. Recent technological advances allow us to probe the immune system at high resolution and explore its variation between individuals. Such information is already being used to identify diagnostic biomarkers and new cell subsets. However, the question remains how we move from just a high dimensional data pile to truly thinking about immunity as a system which can be modeled such that we can intelligently reason on system-level effects of perturbations.

Here, I will describe our ongoing efforts to build a system level cell-centered view of genomic data, and its integration with knowledge in the primary immunology literature. By mining the primary literature, we compile a global high-resolution directed cell- cytokine interaction network together with how it varies across diseases, tissues and other conditions. This literature-reported evidence can be computationally analyzed to build disease-specific interaction networks, unveil disease/drug similarities, predict novel cell-cytokine interactions and interpret experimental data. Data and knowledge put together in this cell-centered framework establish a means to 'connect the dots' across immunology as well as systematic de novo hypotheses generation. */

/* Microbiome - Immune System Interactions in Melanoma Development */

Ze'ev Ronai
Professor, Rappaport Faculty of Medicine, Technion
Co-Director Technion Integrated Cancer Center (TICC)

Studies with the ubiquitin ligase RNF5 revealed that it plays a role in fine tuning of gut microbiome and immune checkpoint activity.

Mapping the select populations of phyla that are responsible for tumor rejection phenotype in the RNF5 KO mice, and their implications for the control of immune checkpoint activity will be discussed.

/* A Pioneering Study Using MDclone, a New Medical Database Query System, to Assess the Effect of Low Albumin and Insulin Type on Hypoglycemia Events in Hospitalized Patients

Irit Hochberg
Institute of Endocrinology, Diabetes and Metabolism, Rambam Healthcare campus, Haifa, Israel

For a clinician-researcher, there are many barriers between a research question and the actual querying of medical data. Most clinicians have no database management system programming skills, and rely on IT personal to retrieve the data. Regulatory processes are long and there is a concern about patient privacy.

Rambam Healthcare Campus is the first site introducing the novel MDclone big data query system that solves many of these barriers. The system allows retrieval of a wide range of variables from a defined timeframe around an index event. Further privacy can be gained by generating synthetic patient populations that are statistically identical to the original population and can give valid results when analyzed. Querying synthetic data omits the need for regulatory approval and omits the risk to patient privacy. Our preliminary studies have suggested that results from synthetic data are similar to those of real data.

We used MDclone to query the effect of low albumin on events of hypoglycemia (dangerously low glucose levels) in hospitalized patients when using either of two types of insulin. We retrospectively retrieved

data of all adult patients hospitalized in Rambam Healthcare Campus between 2012-2016 who were treated with these insulins and had at least one albumin blood test while hospitalized. For each patient we recorded the lowest glucose value measured around the date of lowest albumin. We compared the occurrence of glucose under 70 under the two types of insulin, taking into account additional known risk factors for hypoglycemia. A total of 4820 patients met the inclusion criteria, and there was an inverse correlation between albumin level and risk of hypoglycemia. A multivariate model demonstrated a significantly higher risk of hypoglycemia in patients with low levels of albumin that were treated with one of the insulins compared to the other. For normal range albumin levels, risk of hypoglycemia was similar between the two types of insulin. An identical analysis using synthetic data gave similar results.

In summary, MDclone provides a clinician-friendly process for complex queries on a big dataset and opens new possibilities for clinicians to ask clinically important questions that can improve patient care. Using synthetic data can provide access to database queries while maintaining full patient privacy. This pioneering study using MDclone suggests that a specific insulin type may be less safe in patients with low albumin and it may be advisable to consider avoiding it in such patients.

*/

/* Participant-Centered Design for Ethical Precision Medicine

John Wilbanks
Sage Bionetworks, Chief Commons Officer

Mobile technologies have the potential to revolutionize both the way in which individuals monitor their health as well as the way researchers are able to collect frequent, yet sparse data on participants in clinical studies. In order for data from these devices to have maximal impact in a research setting however, the development of systems to collect, manage, and broadly share these data is essential. Possibly more important are the social constructs on which these systems need to be built to allow maximal utility to come from these data while minimizing adverse impact on individual participants. More specifically, the union of these systems and constructs must be an ecosystem build upon trust. We will present one such ecosystem focused on putting the participant at the center of the data collection: specifically by acknowledging possible risks to both individual participants as well as sub-populations of participants, providing opt-in settings for broad data sharing, and the development of an open research ecosystem built upon a social contract between researchers and research participants. A case study of one such mHealth study, leveraging Apple's ResearchKit framework, will be presented and discussed.

*/

/* Data-Driven Innovation in Health Policy and Healthcare Practice */

Ran Balicer
MD, PhD, MPH
Director, Clalit Research Institute & Director, Health Policy Planning, Clalit Health Services, Israel

We live in an era of ensuing prevalence rates of non-communicable disease, which pose an increasing risk to the financial sustainability of health systems worldwide. It has been suggested that a paradigm shift is required if we are to properly deal with these challenges, transforming our healthcare system to one which can bridge the silos of care provision in a patient-centered approach, move from reactive therapeutic to proactive preventive care, and abandon our paternalistic narrative to a participatory and engaging patient-physician relationship.

It has been realized in recent years that a key driving force and a pre-requisite for these changes is the availability and intelligent integrated use of data and information technology. Clalit is Israel's largest healthcare organization which serves as insurer/payer and integrated care provider for over half of the Israeli population – over 4.3 million people. Clalit has been leading innovative interventions using clinical data to drive people-centered targeted and effective care models, for chronic disease prevention and control. Clalit actively pursues a paradigm shift to properly deal with these challenges, using IT, data and advanced analytics to transform its healthcare system to one which can bridge the silos of care provision in a patient-centered approach, and move from reactive therapeutic to proactive preventive care.

In this presentation we will review the driving forces and the need for such disruptive innovations, and detail specific examples that allowed for reducing healthcare disparities, preventing avoidable readmissions, and improving control of key chronic diseases.

*/

/* Personalized Medicine from Theory to Practice

Varda Shalev
MD, PhD, MPH
Director, Institute for Health, Research and Innovation,
Maccabi Health Care Services, Israel

Big data and machine learning are changing the world of medicine and ushering in a new era of personalized medicine, early detection and prevention of diseases and increased accuracy in diagnosis.
The Maccabi and Morris Kahn Research and Innovation Institute is leading innovative database, clinical and genetic based studies. A new prediction tool for colorectal cancer (CRC) has already been implemented in Maccabi Healthcare Service. This tool was developed in cooperation with Medial-CS's big data and machine learning experts, and calculates the risk of CRC from routine blood tests, long before anemia is apparent. This has created a unique opportunity to identify cases long before symptoms appear.

Similar studies are currently underway in the Institute, utilizing structured as well as unstructured data, including free text, patients' voice records and imaging. By harnessing new big data resources and tools, we can develop innovative solutions and practical tools to improve the quality of life of patients and the health of the general population. */

/* From Theory to Practice: Informatics Research in the Modern Clinical Setting

Eric Kirkendall
MD, MBI, FAAP
Associate Chief Medical Information Officer
Associate Professor | Biomedical Informatics | Hospital Medicine,
Cincinnati Children's Hospital Medical Center, USA

In the United States, federal government incentives and other factors have dramatically shifted the digital landscape in medicine. Similar changes are occurring in many other parts of the developed world. Accelerated digitization of clinical systems has provided an abundance of new opportunities for health informatics researchers, but it has also surfaced new challenges. Informatics research that integrates with or affects clinical workflows can be particularly difficult. In this presentation we will discuss some of these opportunities and challenges, highlighting a few research projects that demonstrate both successes and lessons learned.

*/

/* Evolutionary Tradeoffs And the Geometry of Large Scale Biological Datasets

Uri Alon
Department of Molecular Cell Biology,
Weizmann Institute of Science, Rehovot, Israel

Organisms, tissues and molecules often need to perform multiple tasks. But usually no phenotype can be optimal at all tasks at once. This leads to a fundamental tradeoff. We study this using the concept of Pareto optimality from engineering and economics. Tradeoffs lead to an unexpected simplicity in the range of optimal phenotypes- they fall on low dimensional shapes in trait space such as lines, triangles and tetrahedrons. At the vertices of these polygons are phenotypes that specialize at a single task. We demonstrate this using data from animal and fossil morphology, bacterial gene expression and other biological systems.

*/

/* Moving from Precision Medicine to Next Generation Healthcare

Joel Dudley
The Institute for Next Generation Healthcare,
Icahn School of Medicine at Mount Sinai, USA

The convergence of innovations in clinical, molecular, digital, and artificial intelligence domains is creating opportunities to go beyond making legacy medicine more precise. There is now an unprecedented opportunity to define the next generation of healthcare and fundamentally revisit our definitions and understanding of health and disease. This talk will cover projects and initiatives to envision, implement, and evaluate Next Generation Healthcare models in the largest health system in New York State.

*/

/* LINCS Cellular Perturbation Signatures as a Resource for Precision Medicine

Jaroslaw Meller
University of Cincinnati & Cincinnati Children's Hospital Medical Center, LINCS Data Coordination and Integration Center, USA

The Library of Integrated Network-based Cellular Signatures (LINCS) builds on the Connectivity Map project and arguably represents the most ambitious effort to systematically characterize RNA and protein level signatures of cellular perturbations to date (http://www.lincsproject.org/). As part of this effort, the BD2K-LINCS Data Coordination and Integration Center (http://lincs-dcic.org/) enables data harmonization, visualization and interpretation, while developing high capacity integrated knowledge environment and scalable tools to facilitate interaction with the LINCS data cube that consists of tens of thousands of small molecule and gene knockdown signatures as well as other types of data in multiple cell lines. Several applications of LINCS for drug repurposing, target identification, and loss/gain of function prediction are presented to illustrate the use of LINCS data sets, tools and related resources as a resource for systems biology and precision medicine. */

/* Helping Physicians with Specialized Advisors - from HIV to Breast Cancer

Michal Rosen-Zvi
Director, Healthcare informatics, IBM Research
Haifa Research Labs, Israel

This talk is about deriving evidence from Real World Data (RWD) – health-related records of individuals – a valuable complementary approach to the well-designed clinical trials. According to a recent paper in the New England Journal of Medicine, Real World Evidence (RWE) refers to information on health care that is derived from multiple sources outside typical clinical research settings, including electronic health records, claims and billing data, product and disease registries, and data gathered through personal devices and health applications. The talk share success stories and addresses open challenges associated with the generation of RWE. It will include a review of two concrete examples of leveraging RWE to generate physicians' advisors: an HIV expert assistance and radiologist assistant.

*/

/* Can Internet Search Engines Guide You to Better Health?

Elad Yom – Tov
Microsoft Research, Israel

The vast majority of Internet users in the US begin their search for medical information on general purpose search engines. Thus, it is important that search engines provide authoritative information which can be understood by their users, helping them reach their health goals. In my talk I will show how the medical condition people experience affects their search behavior, why their demographics matter, and what they understand at the end of their search process.

I will further demonstrate how simple interventions during this process can help guide people to better health outcomes.

*/

/* Zeroing in on Radiology */

Jonathan Laserson
Zebra Medical Vision LTD

Massive amounts of clinical data are starting to become available for analysis as data-hungry machine learning algorithms enter the medical domain. At Zebra Medical Vision, we have access to millions of X-ray scans, as well as their accompanied anonymized textual reports written by hospital radiologists. Can this data be used to teach an algorithm to identify significant clinical findings from these cans? Obtaining "clean" training labels through visual inspection by radiologists can be a slow and expensive process, and thus this approach is unscalable when dealing with such large-scale data. As a cheaper and more efficient alternative, we extract the labels from the noisy, free-form, textual reports. We will show how this approach can be used to train a deep learning network that identifies dozens of potential findings from a chest X-ray scan, and see how it compares to the alternative approach of using only "clean" visually-validated labels (but less data).

*/

/* What Does it Mean to Be a Doctor in an Era of Superhuman Artificial Intelligence?

Isaac Kohane
MD, PhD
Marion V. Nelson Professor & Chair,
Department of Biomedical Informatics,
Harvard Medical School, USA

There is hardly a medical data science startup business plan or academic data science department description that does not include the two words "Artificial Intelligence." Academic health centers and entire health systems are making or considering making industrial alliances to apply AI techniques to our data to improve care, improve cost-efficacy and advance science. However, this is not the first hype cycle for AI in Medicine. When I was a graduate student in the 1980's, there was a ferment very similar to the one now. However, I am more optimistic that AI will have a bigger impact on medicine today than it did 30 years ago. Of course there are overblown claims for AI in medicine, which I will address, but there are some fundamental shifts in the role of the physician that are being driven by AI. It will determine a new set of patient relationships and different models of reimbursement. Some of the paths along this way will be particularly tumultuous, and I will identify technologies and regulatory frameworks that will be decisive. In the context of the more recent advances I will also point out how the very high stakes (financial and knowledge-control) are very much still in play. I will conclude with what I believe to be the central role that biomedical informaticians can play in leading and safely implementing AI in Medicine.

*/

/* POSTERS

/* Evolution and Diversification of CRISPR-Cas Systems in Microbial Communities

Dina Berenbaum
Faculty of Biology,
Technion - Israel Institute of Technology, Haifa

Roy Kishony
Faculty of Biology,
Technion - Israel Institute of Technology, Haifa

Diverse microbial communities are critical for human health and must resist phage invasions to survive. CRISPR-Cas, a bacterial adaptive immune system, constitutes one of their most essential defenses against phages. By computationally analyzing an existing CRISPR database, we reveal spacer origin and CRISPR array evolution. We are also devising an experimental “CRISPR fishing” method for high-throughput sequencing of the entire repertoire of CRISPR arrays in a microbial community.

*/

/* # Modeling of Functional Genetic Alterations in Cancer Reveals Overlooked Candidate Drivers

Nadav Brandes
School of Computer Science and Engineering,
The Hebrew University of Jerusalem, Israel

Michal Linial
Department of Biological Chemistry,
The Alexander Silberman Institute of Life Sciences,
The Hebrew University of Jerusalem, Israel

We developed a computational framework for detecting cancer driver genes from cancer genomic data. Instead of looking at the density of mutations, we examine their expected effect on gene function, using a machine-learning prediction model. For each gene, we compare the distribution of observed effect scores with the distribution expected by random, and report genes showing a significant bias. We detected 593 genes enriched with harmful mutations that overwhelmingly overlap with known drivers.

*/

/* A Predictive Tool for Characterizing and Visualizing Populations Under Counterfactual Treatment Assignment

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The task of identifying and characterizing population segments for which one treatment is preferable over another is inherent to the work of medical informatics and market researchers. Employing real-world evidence for such tasks proves to be challenging, mainly due to the non-random nature of treatment assignment. Here, we present a novel causal pipeline, that enables the introduction of many candidate variables into the analysis, resulting in a small set of causal effect modifiers.

*/

/* # A Model for Early Detection of Cancer Risk Based on Routine Check-Up Data

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We analyzed medical records of 20,000 individuals who had one or more annual routine checkups over the past 17 years from the Tel Aviv Medical Center Inflammation Survey cohort and identified those who developed cancer later. We used a random-forest model of survival trees for left-truncated and right-censored data to predict future cancer diagnosis, and achieved an AUC of 0.67. Further improvements can lead to a means for early identification of persons at high risk for developing cancer.

*/

/*

Immune Cellular Homeostasis is Determined by Genetic Variants of Cellular Production and Turnover

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The immune system is one of the major life-sustaining systems in advanced organisms, employing dozens if not hundreds of distinct cell types, each with their own function, to orchestrate defense mechanisms. Immune cells are maintained in homeostasis, a balanced stoichiometry which is altered during disease. Baseline variation in cellular homeostasis exists between individuals and contributes to differences in immune response and is due both to environmental and complex genetic factors, but mapping those factors remains a big challenge. To identify genetic factors effecting individual level differences in baseline cellular immune homeostasis we coupled a highly genetically diverse set of mouse models, the Collaborative Cross, which allows for high resolution genetic mapping; with mass-cytometry (CyTOF) a high dimensional single cell profiling technology. We analyzed the data from CC mice bone marrow using high resolution clustering and identified a large number of genes that enriched for cell death and survival properties, which is further supported by differences in proliferation rates in dividing cells between mice. Our work shows that cellular homeostasis is a complex trait whose maintenance and fine tuning is performed through a delicate balance of genetic variants of cell production and turnover.

*/

/* # Annotated and Public TCRs In 587 Human Repertoires: a Big Data Study in Immunology

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T cells recognize a wide diversity of pathogens by a diverse set of T cell receptors (TCR). In this study, we analyze sharing of TCRs between individuals. The analysis is based on a data set of TCR repertoires sequenced from a cohort of 587 healthy volunteers. This is one of the biggest data sets of human TCR repertoires ever studied. We study sharing patterns between members of the cohort, and describe a scaling law for this sharing. We also focus on comparing sharing between men and women.

*/

/* Molecular Fate of Tumor Infiltrating Lymphocytes in Melanoma Cancer Revealed by RNA-Seq

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Tumor infiltrating lymphocytes (TILs) are heterogeneous populations of immune cells with potential anti-tumor reactivity. Their recognition and reactivity with autologous tumor is associated with increased secretion of IFN-γ. In the clinic, TILs are used for a therapeutic strategy of adoptive cell transfer (ACT) in which these TILs are isolated from the patient tumor, expanded ex-vivo and administered back to the patient. Despite the encouraging results obtained from the use of ACT in stage IV metastatic melanoma patients, and despite extensive research efforts, little is known about the cellular interactions and the mechanisms determine TIL reactivity. co-culturing reactive vs. non-reactive TILs with melanoma cells, following RNA-seq and systems biology strategies analysis revealed a set of genes (cytokines and TFs) and key molecular pathways which significantly distinguish between reactive and non-reactive TILs. Investigating the changes of several selected genes in the protein level using intracellular multi-color flow cytometry suggest positive correlation between the RNA and protein levels.

Our studies may shed light on the molecular mechanisms that control TIL reactivity, improve the clinical efficacy of TILs and assist with selecting TILs with potential reactivity.

*/

/* Deep Sequencing Platform to Characterize Non-Canonical DNA Structures */

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Longs non-coding RNAs (lncRNAs) have gained widespread attention as transcriptional regulators. While lncRNA association with chromatin is pervasive, it is unclear how they target specific genomic loci. One intriguing, yet controversial mode of targeting loci is the formation of non-canonical RNA/DNA structures such as triplexes or G-quadruplexes (GQ) that are based on Hoogsteen hydrogen bonds. Despite extensive research, evidence for such interactions in vivo is circumstantial. Thus, their existence and potential function remains debated.
To systematically screen the vast sequence space of Hoogsteen configurations, we developed two sequencing approaches to characterize non-canonical structures in vitro and in vivo. We designed libraries (1x104 -2x106 variants) of short, single-stranded oligos (20-40 nt) with putative triplex and GQ-forming sequences. These oligos were synthesized with a pre-set mix of bases of known proportions of specific nucleotides at particular positions. Following transfection of the libraries (in vivo) or incubation with dsDNA (in vitro), a subset of oligos binds DNA, is selectively enriched (Triplex-Seq) or ligated to genomic loci in close proximity (Triloci-Seq), and subsequently analyzed using deep sequencing.

*/

/*

Our Triplex-Seq datasets indicate that transfected libraries were strongly enriched for guanines and thymines while depleted for adenines; consistent with triplex or GQ interactions. To identify genomic target sites for the enriched oligos, we currently employ Triloci-Seq and aim to determine the genomic locations of such interactions. We hope that these results, together with complementary in vitro Triplex-Seq data, which refine the sequence context for non-canonical DNA structures, will establish a powerful tool to further explore non-canonical nucleic acid interactions and provide a platform to study how lncRNAs bind genomic loci, and may reveal an underlying code for such interactions.

*/

/* # A Goal-Based Decision-Support System for Patients with Multi Morbidities

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Clinical practice guidelines address a single morbidity but chronic patients often suffer from multiple morbidities. We are developing a goal-based decision-support system that utilizes drug mechanisms of action to combine knowledge from computer-interpretable guidelines and drug ontologies with patient data. This enables detecting interactions and planning non-contradicting therapies. Our algorithm uses patterns to check consistency and respond to diagnoses, enquiries and adverse events.

*/

/* Meta-Analysis of Vaginal Microbiome Data Provides New Insights into Preterm Birth

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Preterm birth is a birth of an infant before 37 weeks of pregnancy. We present the first meta-analysis of vaginal microbiome in preterm birth. We were able to gain new insights into the vaginal microbiome state in preterm birth patients, such as a higher variance in the abundance, especially during the first trimester. Our analysis revealed significant microbial genera more prevalent in preterm birth patients in the first trimester, including known and novel associations.

*/

/* # A Computational Model of the Inter-Cellular Immune Network Reveals Novel Signaling Targets

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Inter-cellular communication is central to immune system functionali-ty. Though these complex signaling interactions are highly studied, the information is not readily accessible, yielding inefficient progress pre-dominantly along consensus knowledge. This problem is intensified by the recent entrance of high dimensional measurement technologies, which challenge human capacity to reason over data. We built im-muneXpresso, a Text Mining engine, that structures and standardizes knowledge of immune inter-cellular communication. We applied it to PubMed to identify relations between 310 cell types and 140 signaling molecules across thousands of diseases. Leveraging the breadth of this network, we predict and experimentally verify novel cell-cytokine inter-actions, as well as build a global immune-centric view of diseases whose architecture we use to predict new cytokine-disease associations. This standardized knowledgebase offers new directions for immuno-therapy and rationalized interpretation of immune data, paving the way to model-driven systems immunology science.

*/

/* Inferring Metabolic Dependencies in Cancer

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Alterations in metabolic activity in tumors provide novel means to selectively target cancer cells. By using large-scale screening projects data of cancer cell lines, we find that metabolic gene essentiality is highly dependent on nutrient availability in the micro-environment. To derive a mechanistic understanding of metabolic gene dependencies throughout cell lines, we find molecular signatures predictive of dependency in metabolic enzyme-coding genes. Then, to predict gene essentiality in tumors we search for metabolic signatures in tumor data combining TCGA data and a metabolic network model.

*/

/* # Understanding the Role of Specific Immune Cell Populations in IBD Pathophysiology

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The exact pathogenesis of IBD is not completely understood, but probably involves dysfunction of the reciprocal interaction network among the immune cells in the intestine, which are normally responsible for homeostasis maintenance. Intestinal immune dysfunction causes enhanced recruitment of leukocytes from the peripheral blood into the inflamed area, and the interplay between these two immune compartments is of major importance. We analyzed paired intestinal biopsies and blood samples, and using immune-phenotyping techniques combined with computational methodologies built a high-resolution comprehensive screening of immune cell distribution in normal and inflamed intestine along the gut, in addition to its reflection in the peripheral blood. We found different cell content in each immune compartment, and constructed an immune cell map which characterize normal and pathology conditions. Overall, this profiling system generates a novel understanding level of IBD pathophysiologic mechanisms, and may accelerate finding of new targets or pathways for therapy.

*/

/* Alignment of Single-Cell Based Developmental Trajectories

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High dimensional single cell measurements can be used to generate detailed trajectories of biological dynamics, such as differentiation or development, as a function of time. Here we present cellAlign, an algorithm for comparing time series dynamics of high-dimensional single-cell data. Application of cellAlign on single-cell RNA sequencing and mass cytometry data reveals inter-species similarities and differences along parallel differentiation processes in human and mouse. */

/* PROMO: an Interactive Tool for Analyzing Large High-Throughput Genomic Datasets

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Modern genomic datasets may include thousands of samples, each measured by several high-throughput technologies and described by extensive clinical information. PROMO (Profiler of Multi-Omics data) is an interactive Matlab-based tool for visualizing and analyzing large multi-label multi-omic datasets, applying unsupervised analysis on both samples and features and utilizing various popular statistical tests including survival analysis. Special features include multi-omic dataset integration.

*/

/* Found in Translation: a Statistical Model for Improved Translation from Mouse to Human Inference

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Despite their essentiality to clinical research, mice have substantial differences from humans. There are numerous examples of successful therapeutic experiments in mice that later failed in human clinical trials. As such, there is an urgent need to develop methodologies for improving cross-species translational research. Here we present FIT (Found in Translation) a novel data driven statistical methodology that given a mouse gene expression experiment predicts the genes that are relevant to the parallel human condition. FIT leverages a comprehensive collection of dozens of mouse and human datasets that were manually assembled from the public domain, to allows a more informative translation process on any given mouse gene expression experiment. We applied FIT on mouse expression data from 25 different diseases and validated its results by comparing the predictions to the human gene expression. We show that it improves the ortholog overlap between the species in 78% of the diseases.

*/

/* ALICE: Bacterial Phenotype Prediction via Genome Feature Mining and ML

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Rapid genome-based diagnostics of antimicrobial resistance are increasingly in demand. Today, projects in the field use confirmed QTL catalogs for AMR prediction, measured in Minimum Inhibitory Concentration. However, it is unclear how inclusive current catalogs are. Here, we use custom models for different types of genomic changes to find MIC correlated k-mers. An ML regression model is fit upon these k-mers, producing a resistance model. We aim our methods for a future of use in the clinic.

*/

/* Inferring Meta-Lab States for Analysis of Multivariate Lab Records and Imputation of Missing Data in Electronic Health Records

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Lab tests recorded in EHRs have complex distributions and many missing values. The missing data is biased by linkage between disease state and ascertainment rate. We developed an approach that covers the multivariate test space by dense array of linked compact clusters. Our Bayesian model assumes prior distributions on missing data derived from empirical test distributions and literature. We demonstrate our approach on records of 4M individuals from the Clalit Healthcare system.

*/

/* # Crowdsourcing Patient-Reported Outcomes for Evidence-Based Medicine: a Case of Lower Back Pain

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Evidence is lacking for effectiveness of treatments for most medical conditions. We examined a consumer-based social network that collects patients' treatment ratings as a potential source of evidence for treatments for lower back pain. Acknowledging the potential biases of this data set, we used propensity score matching and generalized linear regression to account for confounding variables. Our results are comparable to those reported by evidence-based studies but also point to new evidence.

*/

/* # High Resolution Longitudinal Immune Profiling Reveals Immunosenescence Dynamics and Attractor States

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Immune response changes with age. Here, we used multiple 'omics' technologies to comprehensively capture population-level and subject-level changes in the human immune system in a cohort of over one hundred humans of different ages that were sampled longitudinally over the course of seven years. For a subset of features, we observe a non-linear baseline dependent rate, which yields a dynamic convergence of the feature to an attractor state around which it continues to fluctuate. Individual older adults show a large variability in the chronological age in which they reach the attractor state of a feature, allowing ordering of events describing immunological break-down. We also describe a high dimension trajectory of immune-aging consist of large number of immune features, which can describe a person immune-status better than his age. Taken together, this unique dataset allows to map the landscape of immunological aging and identify an older adult homeostatic immune state.

*/

/* Creating Ethnicity-Specific Reference Intervals for Diagnostic Tests from EHR Data

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Clinical diagnostic tests' reference intervals are an essential component of medical decision-making. Clinical laboratories not always set their own reference intervals to accommodate variation in local population and instrumentation, as this approach is costly and can be biased.

We also showed the EHR-based population-specific reference intervals are significantly more predictive of associated clinical outcomes. */

/* Deciphering the Neuro-Immune Network and its Effects on Immune Responses

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Protective immunity is a complex response to sensed threats and as such is modulated by the sensory systems of the brain. Immune cells express on their surface a broad array of receptors that are activated by different neurotransmitters, neuropeptides and endocrine hormones. Here we assembled a neuro-immune interaction network analyzing public murine gene expression data of over 100 immune cell types in 24 different tissues. We identify the landscape of neurotransmitter receptors on immune cells at high resolution and show that about a quarter of neurotransmitter dependent signaling are deferentially expressed between different immune states as well as lineage specific signaling. These findings suggest that signaling network between the brain and immune system in the periphery is more intricate than has been described to date. Our result allows for fine-grained understanding of neural signaling effects in immune-mediated diseases and suggest target receptors with tissue specific effect for pharmacological applications.

*/

/* # Single-Cell-Like Clustering by Long-Read, Single-Molecule Epigenetic Profiling

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We present a long-read, single-molecule mapping technology that generates hybrid genetic/epigenetic profiles of native chromosomal DNA. The genome-wide distribution of 5-hydroxymethylcytosine (5-hmC) in human peripheral blood cells correlates well with 5-hmC sequencing. However, the long read length of 100 kbp-1Mbp produces 5-hmC profiles across variable genomic regions that failed to show-up in the sequencing data.

*/

/* A Quantitative View of Tissue Specificity of Molecular Pathways in Humans

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We analyzed RNA sequencing data to learn about molecular pathways in the context of human tissues. We gained a quantitative view by creating a scoring method that measures the tissue associations of pathways. This allowed us to identify pathways that were up or down-regulated in specific tissues and to illuminate pathway-based differences between tissues. This can shed light on disease etiology, tissue-specific effects of drugs, and contribute to drug repurposing efforts.

*/

/* # A Model-Driven Methodology for Exploring Complex Disease Comorbidities Applied to Autism Spectrum Disorder and Inflammatory Bowel Disease

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We propose a model-driven methodology, based on stochastic Petri nets, to explore shared etiologies of comorbid diseases at the molecular pathway level. The method compares the phenotypic effects of perturbation of the autophagy network known to be involved in the autism spectrum disorder and inflammatory bowel disease comorbidities to predict new roles for mutations in comorbid conditions. Our method suggests three new disease-related roles for LoF mutations, which can be tested experimentally. */

/* A Novel System for Rapid Natural Language Processing in Healthcare: Fall Information Extraction Case Study

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We report one of the first systems called NimbleMiner that combine word embeddings with machine learning for the analysis of narrative clinical notes (n= 1,149,586 notes from homecare settings). NimbleMiner outperformed other systems aimed at fall information extraction. Our approach can be implemented rapidly without the need in large labeled datasets necessary for machine learning. Our system can be potentially used by almost any clinician without special training in health informatics.

*/

/* # Alternative Splicing Analysis of *Eosinophilic Esophagitis* Using High-Depth RNA-seq

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Inflammation of the esophagus in response to food allergens can cause lifelong impairment and suffering. To better understand the genomic profile of the disease, we analyzed alternative splicing in esophageal biopsies from 5 disease and 7 control patients using high-depth RNA-seq. We identified 119 differentially spliced exons in diseased tissue corresponding to 65 unique genes and enrichment for E-cadherin interactors, which form an important pathway governing epithelial barrier function.

*/

/* Evolution and Transmission in the Human Gut Microbiota

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The gut microbiota has been linked to multiple aspects of human physiology and health, but the means by which bacteria are acquired by the host and how they evolve within the host remains largely unknown. Here, we analyze individuals that each have multiple samples and find that the number of synonymous DNA sequence changes between strains of the same species extracted from distinct samples of the same individual strongly correlates with the time between their collection, suggesting that this number can serve as a "metagenomic clock" to estimate the time that passed between strains within or between individuals. Applying this clock to over 4,300 metagenomic samples from 10 countries, we obtain insights into the evolution and transmission histories of the 40 most highly abundant gut microbial species, accounting for over 95% of total abundance. Notably, we estimate that most of these strains have a last common ancestor less than 1000 years ago even when considering samples from different continents.

*/

/*

Genomic Proof of Probiotic Transmission from Capsule to Blood in Patients with *Lactobacillus Rhamnosus GG* Bacteremia

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Probiotic supplements are increasingly administered to hospitalized patients, yet recent studies suggest the possibility of adverse effects, including bacteremia. To determine whether bacteremia originated from probiotic capsules, we focused on 6 patients with lactobacillus bacteremia and compared whole-genome sequencing of isolates from their blood with isolates from probiotic products that they were given. We found that blood isolates were nearly identical to the probiotic isolates and both shared mutations distancing them from the closest available reference genome. Moreover, the minute genetic diversity among blood isolates mirrored preexisting genetic heterogeneity found in isolates from the probiotic product. These results establish that bacteremia in these patients originated from the bacteria of the probiotic capsule. Few blood-exclusive mutations, not found even in deep sequencing of the capsule, raise the possibility of bacterial adaptation to survival in the human host. Whole-genome transmission tracing can be applied to reveal the exact source of pathogenic infections.

*/

/* Long-Range Intercellular Communication in Collective Cell Migration

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Cell imaging has entered the “big data” era with high-content data and complex dynamic patterns that are inaccessible by eye. One example is emergence of collective cell behavior. By designing new analytical methods we discovered how local mechanical fluctuations induce long-range inter-cellular communication in migrating monolayers of epithelial cells, fine-tuning of contractility-mediating pathways is requires to compromise between motility forces and restriction of cell-cell communication.

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