Informatics and Medicine
From Molecules to Populations


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Summary
Objectives: To clarify challenges and research topics for informatics in health and to describe new approaches for interdisciplinary collaboration and education.
Methods: Research challenges and possible solutions were elaborated by scientists of two universities using an interdisciplinary approach, in a series of meetings over several months.
Results and Conclusion: In order to translate scientific results from bench to bedside and further into an evidence-based and efficient health system, intensive collaboration is needed between experts from medicine, biology, informatics, engineering, public health, as well as social and economic sciences. Research challenges can be attributed to four areas: bioinformatics and systems biology, biomedical engineering and informatics, public health and individual healthcare, and public health informatics. In order to bridge existing gaps between different disciplines and cultures, we suggest focusing on interdisciplinary education, taking an integrative approach and starting interdisciplinary practice at early stages of education.

Keywords
Informatics, bioinformatics, health informatics, biomedical engineering, biomedical informatics, public health

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1. Introduction

Medicine and the whole health care domain are undergoing substantial changes. On the one hand, advances in molecular life sciences, biomedical sciences and engineering have significantly influenced diagnostic and therapeutic options. Molecular mechanisms of disease are being understood better than ever before, and disease patterns can be understood with increasing granularity down to the level of molecules. Therapeutic methods range from drug design and individualized therapy to image guided minimally invasive surgery. On the other hand, demographic and sociocultural changes, together with increasing costs of new diagnostic and therapeutic procedures, have put our health systems under severe pressure.

In this complex situation, a key role has emerged for informatics in health, in health technology and in related fields, including biomedical engineering, bioinformatics, biotechnology, pharmacology, management and also economics. Informatics is an underlying core element for these fields, providing scientific methodology, key applications, and the pioneering of new services. We believe that informatics will be the most important driver and mediator for innovation in all health-related scientific disciplines – with even more significant impact than previously seen in other fields, such as the automotive industry, e-commerce, or global logistics.

The focus of informatics is information: how it is discovered, created, identified, collected, structured, managed, preserved, accessed, processed, presented, and studied. This also includes how it is used in different environments with different information technologies, and how it is applied and changes over time. The successful use of informatics has to be based on intimate knowledge and interaction of scientific, technological and professional practice components. The term “informatics”, which was coined in 1957 [1], has been increasingly used across Europe during the last decades [2, 3] implying a meaning similar to “computer science” as denoted in many English speaking countries. In these countries, the term “informatics” was first used in the context of “medical informatics”. Biomedical informatics has been defined as “the scientific field that deals with biomedical information, data, and knowledge – their storage, retrieval, and optimal use for problem solving and decision making” [4]. For a discussion of terminology we refer to [4].

To face the challenges in medicine and in related fields, multidisciplinary collaboration between informatics, medicine, and many other fields has become essential. Experts from the areas of biology, medicine, public health, informatics, engineering, social and economic sciences need to cooperate. In this article, we aim at clarifying challenges and research topics. We suggest intensive collaboration, and we recommend to educate a new generation of experts with interdisciplinary knowledge and skills, who will be ready to work in a multidisciplinary environment and to think out of the box.

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In the following chapters, we will outline our vision of collaborative research and structured interdisciplinary education. In order to clarify needs, multidisciplinary working groups were established in 2006, involving researchers from the two Munich Universities and the Munich Helmholtz Center, representing five different faculties. In an iterative and interactive process, areas of collaboration were identified, and new perspectives on education were elaborated in 2006/7. Our central aim was to lay the foundation for a research-oriented interdisciplinary Graduate School which has been established in 2008.

2. The Overall Picture: Where Do We Stand and Where Do We Go

Progress in medicine, covering all areas from drug development to personalized diagnostics and therapeutics, reflects the success of the most challenging disciplines involved: molecular biology and informatics, science and technology. Digital data and information are key elements of a) basic and applied research in molecular life sciences, clinical, and population-based studies, b) biomedical engineering and informatics, c) medical care, d) organization and communication for efficient and seamless care, e) public health, health care management, and health economics.

Dramatic developments in molecular biology and their direct influence on the understanding of human diseases will have far-reaching consequences for the whole healthcare system, significantly influencing prevention, diagnosis, and therapy. Progress in biomedical engineering will result in new diagnostic (e.g. devices for home monitoring) and therapeutic options (e.g. image-guided minimally invasive surgery). Progress in biomedical informatics will result in new large-scale, pervasive and ubiquitous systems for human-computer interaction and transformation of scientific inquiry and technological development, finally realizing what Wiener proposed for cybernetics more than 50 years ago. An aging society on the one hand, and the need for affordable healthcare on the other, are more than enough reason that there is an urgent demand to translate the scientific progress into clinical practice and into new prevention strategies using tools from informatics, economics, and many other sciences and technologies.

A number of observable technical trends in computing and software technology will create significant impact on the handling and processing of huge amounts of complex information:

1) Computing power will continue to grow, permitting complex tasks to be solved such as local correlation of patient-related data as well as the systematic exploration of huge distributed data sets.
2) Broadband networks and reliable wireless roaming enable access to this computing power from everywhere and make high-volume data transfers and sharing of analytical and interpretative software tools possible – even in real time.
3) Powerful and reliable embedded systems will become increasingly networked and will be able to make use of their environment using a variety of data acquisition techniques based on complex sensors and large sensor networks.
4) Data volumes will continue to grow exponentially; database technology including integration and association methods will enable us to efficiently handle unprecedented volumes of complex data and to structure them into useful knowledge.
5) Multi-agent software systems have the potential of becoming more and more autonomous and federated, e.g. experimenting with becoming self-organizing when performing varying tasks, as well as self-administrating and self-healing. As a consequence, the ascription of responsibility and liability can become a significant challenge.
6) Service-oriented architectures (SOA) enable a much more flexible, integrated software environment; thanks to advances in middleware technology, access to data resources and software tools will become increasingly seamless, enabling complex tasks and workflows as required, e.g., for systems biology and for eHealth architectures.
7) The metaphor of new medical devices becoming intelligent ‘assistance systems’ is increasingly becoming accepted; unrealistic claims of full automation have been abandoned. Keeping humans in the loop and using their cognitive abilities will lead to a much higher acceptance of computer-aided systems in health than previous approaches.
8) Advanced knowledge management and the development of advanced semantic data models and inference methods will enable researchers to explore the medical knowledge in research and will support knowledge-driven discovery and interpretation of complex data sets (such as studies correlating individual genetic disposition, physiological data, and disease statistics).

In concrete terms, we anticipate the following benefits for health research and its translation into medicine from the above: items 1-3 will rapidly advance bioinformatics-based progress in data analysis and data mining and will also improve imaging technologies; they will make reliable health telematics and eHealth strategies possible; items 4 not only triggering the development of new (implantable, intelligent) devices providing direct feedback from biochemical or physiological data but also making devices possible that close the control loop, i.e. sense-compute-act, inside (or near) the patient. Software trends may lead to completely new devices – and it seems obvious that items 5 and 6 will enable eHealth systems via highly interactive advice loops. Item 6 will make it possible to identify, choose and manage approaches in prevention and healthcare that are cost-effective and that fit patients’ preferences; item 7 will guide the development strategies of new medical devices, from simple (in preventive applications) to complex (in the operating theatre); while item 8 will support basic and applied research with structured interfaces to medical knowledge.

These developments are of relevance not only at the scientific, but also at the indus-
trial and societal level. According to a study by the Boston Consulting Group [5], the three pillars of the health market, pharmaceutical industry, medical technology, and healthcare IT are growing by 5% to 12% per year, with growth rates increasing steadily. More specifically, the overall growth rate for medical technology is a sustained 5% per year, with the total worldwide market having grown from €24 bn in 1980 to €109 bn in 2004 and €133 bn in 2008 [6]. The healthcare-IT market (hardware, software and related services) is growing at a rate of 12% per year, with a total volume of €60 bn (predicted for 2008), up from €2.5 bn in 1980. In other words: in the last 25 years the proportion of spending on information technology has increased from 10% to almost 50%. We can anticipate long-term development that will lead to a complete information logistics chain ‘from single molecules to the entire human population’ (see Fig. 1).

From the perspective of the bio-sciences, medicine, and public health (upper part of Fig. 1), informatics plays a significant role as a critical enabler: Research in the field of molecular biology requires computational resources to make huge amounts of data generated at independent sites available and subject to multiple analyses. Not only do massive datasets of biological information need to be handled, but so much the analysis, experimental design and process-control for heterogeneous experimental systems ranging from nano- and cryo-technologies to the increasingly more precise atomic-level probes. Clinical research will not be restricted to small local patient groups, but is likely to be more frequently extended worldwide, increasing the quality and lowering the cost of studies. The integration of genetic information into clinical trials and into the clinical environment will change medicine, both in the area of clinical research and in clinical practice. The correlation of genomic variation with individual phenotypes will make it possible to better estimate risks, and success rates of therapies, leading to increasingly personalized medicine. Population-based studies are about to correlate genetic variation with clinically defined phenotypes taking into account environmental factors. Economic evidence finally enables society to rationally decide which innovations are acceptable under financial as well as legal/ethical constraints. In all of these domains, digital data must be stored, processed and analyzed, and information models need to be built. Integration and multidisciplinary collaboration are essential. Traditionally separate disciplines on both sides – informatics and medicine – need to collaborate and share information in a much more coherent way.

The lower part of Figure 1 shows the methodology and technology research areas relevant to the application domains mentioned above. Methodology and technology areas overlap, and their relationships to the application domains are not one-to-one but many-to-many. It is these areas that will most directly benefit from advances in informatics. They will enjoy the most rapid growth and create the highest demand for interdisciplinary experts. We would like to point out that this requires more than information logistics for communicating data between the application domains: these scientific results and concepts also need to be communicated between application domains and methodological research areas – which requires intensive cooperation between application domains, biomedical informatics and informatics. Moreover, prototype implementations have to be translated subsequently into the professional environment of the participating industrial and medical partners.

The importance of cooperation between disciplines, and the perspectives for the fields involved have been described before for a number of specific fields, e.g. for biomedical information in clinical trials and in public health [7, 8]. The need for tools and a new generation of information systems has been described and analyzed [9-11]. Synergy between medical informatics and bioinformatics was described in 2004 [12]. Several “Grand Challenges” articles have been published over the last decade [13-15], which emphasize interdisciplinary work. The need for translation is being addressed in the U.S. by the CTSA program [16]. In 2002 Kulikowski characterized challenges for medical informatics in relation to a spectrum from molecular medicine to public and global health [17]. To face these challenges and the challenges outlined by us, we argue in favor of intensive transdisciplinary co-
operation and true multidisciplinary education.

3. Areas for Collaboration and Cooperation

In recognition of the need for profiling and conceptual exchange, we have identified four areas for collaboration and cooperation which are closely intertwined. No order of importance implied, the priority areas for collaborative research and development, complemented by structured interdisciplinary education are:

- bioinformatics and systems biology
- informatics for biomedical engineering (BME)
- health informatics and eHealth
- public health informatics and public health

The goal of bioinformatics is to understand molecular mechanisms, their genetic framework for diseases and their responsiveness to therapy (e.g., expression analysis vs. tumor type) using advanced information technologies.

There are relevant informatics-related aspects of biomedical engineering and biomedical physics, such as bio-signal and image processing, robotics, sensors, biomedical imaging, modeling and simulation of biophysical processes, adaptation of models to treatment strategies, and also analysis of clinical outcomes.

eHealth covers the whole range of use of information and communication within the health sector, focusing on individual citizens and patients. eHealth is one of the core application areas of health informatics which addresses biomedical and health information discovery and management, technology, science and their social/ethical implications.

Public Health combines science and technologies directed to maintaining and improving the health of all people, emphasizing prevention and basic health needs of the population as a whole and managing care given the constraints of our health care systems. While health informatics is mainly oriented towards individual healthcare, public health informatics is mainly oriented towards population measures and health policy.

Aiming at an evidence-based and efficient health system, these areas will help to

- understand molecular mechanisms of disease based on biological networks and computational models, including visualizing disease with increasing granularity down to the molecular level,
- study and apply new fine-grained and translational insights into disease mechanisms for personalized medicine, including identifying personal risks and targeting preventive interventions (behavioral, social and medical),
- construct sensors and devices for research, diagnosis, treatment,
- improve communication and cooperation,
- gain and apply knowledge about genetic variation in the population,
- analyze and evaluate cost-effectiveness of health care interventions.

There is a need for a generation of scientists, who can combine knowledge and skills from the areas of medicine and informatics related to these areas. This would cover a multidisciplinary perspective from an understanding of basic research topics ("bench") to clinical medicine ("bedside") and to the societal environment, and conversely, from bedside to bench. The concept should involve clinical and epidemiological research, as well as engineering and informatics research.

Thus, in terms of Figure 1, both the horizontal and the vertical axis will be of relevance. Along with interdisciplinary education, interdisciplinary research areas will generate research topics for informatics, engineering, economics, statistics, and social sciences, and, conversely, benefit from this research. An example of how areas collaborate, and of how complementary domains may contribute to multidisciplinary areas of study and coursework is shown in Figure 2.

Our suggestion is to intensify collaboration and education in a multiaxial way between methodical "core" disciplines, i.e. biology, medicine, informatics, and engineering, and applied methodical disciplines, such as bioinformatics and health informatics. Figure 1 puts areas and disciplines which are primary research targets in
relation to applied methodical disciplines. Biomedical informatics can be described as a biomedical science, underlying and connecting these applied methodical disciplines (cf. [4]), while on the other hand drawing upon methodical core disciplines. Figure 2 illustrates this by showing examples of how applied and underlying basic methodical disciplines can cooperate with the application domains. In the following subsections, we will describe the four areas outlined in more detail, pointing out their relevance to health in general and their role for research and education. Besides describing interdisciplinary and translational research challenges, we will contribute to the discussion on education and collaboration [4, 18, 19, 20].

3.1 Bioinformatics and Systems Biology

3.1.1 Background and Motivation

With increasing amounts of human genomic information at hand, the challenge is to correlate medical phenotypic information with its genomic and epigenetic counterparts; in other words, with the genetic background of the patient and its environmental modifiers. The etiology of human diseases and their progression is often reflected by unexpected patterns of evidence at the molecular level. Monitoring such molecular states and predicting the outcomes of treatments will require intensive research employing many high-throughput technologies. These advanced methods generate complex data that are typically large in scale, high-dimensional and highly structured. The interpretation of data in the context of existing knowledge and the conversion of the results into meaningful and clinically actionable knowledge is of utmost importance to the progress of medical research.

Molecular data, in contrast to classical biochemical parameters, are not as directly interpreted clinically. Thus, therapeutic approaches must rely on medical records which are structured and administered in suitable, integrated databases. Research in the past has usually focused on the computational aspects of data analysis (efficiency), on scalability to large and highly structured databases, and on user/computational interfaces for data exploration. Other problems that have been studied include integrating data from heterogeneous sources, correlating phenomena from different views, detecting unusual subgroups, and probabilistic approaches to support medical decision-making or the design of mathematical models. One of the key problems is the organization of knowledge related to molecular disease mechanisms as well as clinical studies (e.g., probabilistic prognosis based on classification of tumor expression profiles). Research aims include discovering new biomarkers for diagnostic purposes, correlating these markers with the clinical course of disease, and choosing the “right” therapy for specific patient phenotypes.

While the bioinformatics groundwork must provide generic workflows for the implementation of such data collections and the tools to explore them, clinical and population genetics studies must generate the data required. Such an approach is often referred to as “personalized medicine”, which critically needs evaluation and feedback to experimental design to close the “bench to bedside and back” loop.

3.1.2 Research Challenges

The challenges are, on the one hand, the transformation of experimental or clinical data into suitable models (in the sense of the biology of the system), and on the other hand the professional implementation of these models in software systems that are accepted by medical staff. Indeed, available biological measurements (e.g., differential patterns of gene expression) and images in the context of medical knowledge generate information of a complexity far beyond what can currently be processed. To achieve sustained progress, it is also necessary to improve considerably on the underlying mathematical and biological models for processes at many different levels, including those for cellular compartments, whole cells and their development, organs, and their variation across animal models and human populations. More powerful hybrid models (combining discrete and continuous modeling techniques) must be developed and implemented. In particular, processes concerning several (temporal and spatial) orders of magnitude have to be represented. These challenges can be addressed only by interdisciplinary teams and research groups, since advanced methods from medicine, molecular and systems biology, bioinformatics, mathematics and computer science are required. One example is the study of genetic variations, such as SNPs (single nucleotide polymorphisms) as markers for individual susceptibility to certain diseases. The amount of data from genome-wide association studies with more than 1 million SNPs per person for thousands of individuals provides challenges for data management, biostatistics and bioinformatics. And, SNPs only provide a first, simplified set of associations which do not cover the many multiple gene interactions, alternative splicings, and effects within proteomes of different tissues and systems.

Dealing with the large data volumes to be generated by the many such new datasets is a key research area for he database and data management communities, where integration, handling of large and complex data, and security are essential. Moreover, semantic data modelling and reasoning across the semantic web – allowing the association of rich application-specific semantics with raw and derived data – is likely to become a central topic of research in the informatics community, extending translationally today’s methods.

Besides the modelling challenges arising from high-dimensional data, there is also a need to create and implement new IT concepts which allow a practical presentation as well as manipulation not only of complex data but also of complex concepts. A unifying methodological toolbox for specification and usage of high-dimensional and complex models is needed. On the statistical side, this includes models with many and high-dimensional covariates, specification of interaction structures and non-linear terms in functional form, or specification of additional information like prior distributions in Bayesian models.

A challenge for translating experimental approaches into clinical practice is the preclinical evaluation of safety and efficacy. Specific and economic delivery systems...
need to be developed for drugs, genes or cells. New bioimaging techniques are required to monitor effects at the molecular, cellular and organism level. Genomic, transcriptomic and proteomic approaches will identify novel targets for diagnosis and therapy and will also help to monitor consequences of therapeutic strategies at the molecular level. In a second and final step, candidate drugs or cell preparations must be prepared under GLP/GMP (Good Laboratory/Manufacturing Practice) conditions and a clinical evaluation must be undertaken in well defined groups of patients with a thorough monitoring of pharmacokinetics, cell traffic, clinical side effects and efficacy parameters.

3.1.3 New Perspectives in Systems Biology

The understanding of biological systems will be supported by formalized descriptions of interactions following the abstraction of input/output models and various alternative structural and functional assumptions about their internal composition. A wide range of complexity has to be investigated from simple “what if” models to complex networks of differential equations with stochastic effects, allowing for the prediction or at least rough estimation of systems behavior in yet unobserved states. Subsystems, their stability, and their interactions have to be characterized, modeled, and simulated. The parameter space of the possible states of any biological system is practically unlimited, but, on the other hand, highly restricted in “real life” by constraints as the result of evolution. We will never be able to span this space by experiments. However, if the parameters involved can be experimentally derived, models can be built and tested. Pioneering efforts in systems biology are introducing novel methodologies for the understanding and description of biological systems.

Bioinformatics has grown to an indispensable discipline driven by biological challenges. The understanding of the organism, its constituent components and their interactions is a prerequisite for the rational translation of biological knowledge into medicine. Within a few years, the availability of genomic and proteomic information has revolutionized the understanding of biology, but it is yet far from yielding mechanistic models of complex diseases, though new functional discoveries are made on an ongoing basis. It is not clear whether classical mechanistic reductionism will be able to describe the wide range of significant epigenetic effects critical in medicine.

Bioinformatics plays a key role in interdisciplinary education due to its profound experience serving as an interface between life sciences and informatics. However, the genome and proteome-based views in clinical research and medical diagnostics are still in their infancy and the recent progress in the application of different omics technologies is only beginning to influence medical research, diagnostics and therapy. Yet, the successes of genomics and functional genomics can be found in the field of model organisms, ranging from unicellular eukaryotes to model species with functional characteristics more directly related to those of human biology. Since bioinformatics spans biology, mathematics, and information technologies and their applications, it is ideally positioned to mediate the interdisciplinary connections between informatics and medicine. The transition, which is already taking place from the investigation of single genes to complex interactions, is being driven by research projects in many new areas involving bioinformatics, such as monitoring of metabolism in diabetes by high-throughput MS/MS and its correlation to susceptibility loci at the genomics level. Bioinformatics is closely related to biomedical engineering (e.g., molecular imaging), as well as to health informatics and eHealth (e.g., studies combining genetic and clinical data), public health informatics (e.g., new perspectives for epidemiological studies) and general informatics (e.g., handling of large and complex data volumes including the semantic web, distributed processing and knowledge representation, and the management of pervasively available data, which, despite attempts at de-identification, presents critical confidentiality and security challenges). All related areas will benefit from the research results of the adjacent areas and, conversely, generate research topics.

3.2 Informatics for Biomedical Engineering

3.2.1 Background and Motivation

Biomedical engineering (BME) is commonly defined as “a discipline that advances knowledge in engineering, biology and medicine, and improves human health through cross-disciplinary activities that integrate the engineering sciences with the biomedical sciences and clinical practice” [21]. Broadly speaking, BME is the application of engineering principles and techniques to a large number of medical fields, ranging from materials science for simple and complex artificial organs, by way of mechanical and electronic devices for drug delivery or life support functions, to the most complex machines for detecting and imaging the finest details of the human body [22]. The field deals with the design and use of all kinds of medical devices, including probes and sensors, as well as their integration within individual-level devices, or systems-level automation and information, and – often under-estimated – their integration with human perception and cognition [23].

As in many other engineering disciplines, in BME product innovation and development process efficiency are facilitated by informatics and technology. Virtually all medical devices crucially depend on sophisticated software for their operation. But powerful software tools are also a prerequisite for modeling, designing, testing, validating and producing them. Moreover, networking these devices, embedding them into the work flow of hospitals and integrating the data from a multitude of different classes of devices (in-house and outdoor) are just another few prominent applications of informatics and technology to BME. Closely related to BME, biomedical physics (BMP) deals with all applications of physics and physical methods in life sciences which are relevant to imaging technologies, modeling and simulation of biological processes, sensors, biosignal processing, robotics, and instrumentation.

The areas in which advanced informatics methods are particularly important for progress in BME and BMP are, for example: im-
aging with different modalities and interpretation of images, recording and analysis of biosignals, computer-aided medical procedures like surgery or endoscopy. Biomedical informatics researchers then use the output from such devices in the development of new cross-disciplinary computational models to characterize not only individuals, but populations of subjects or patients, and their correlation with clinical conditions and outcomes under health and disease, as is carried out through integrated imaging architectures based on semantic models such as the Foundational Model of Anatomy (FMA) and large-scale atlases of the brain and body [24-26].

Modern cross-sectional imaging modalities such as Multi-Detector row CT (MDCT) and Magnetic Resonance Imaging (MRI) provide imaging data with sub-millimeter isotropic voxels of large body parts, or even the whole body. Moreover, functional, metabolic and even molecular information can be obtained by tracer and optical techniques and combined with high-resolution morphological visualization in multimodality imaging. On the one hand, this results in an enormous amount of heterogeneous and multi-dimensional data on the human organism; on the other hand, the clinician then has to cope with this huge data volume. Therefore, support by adequate software tools for classification and mutual registration of these data as well as for the integration into complex clinical decision-making processes is urgently needed in order to fully exploit the potentials of modern imaging modalities. Promising results have been obtained with whole-body imaging, both in preventive care and in clinical application. Instead of diagnostic imaging targeted to particular organs and body parts, examinations tailored to specific disease entities and risk patterns can be set up. This approach takes into account the systemic nature of various diseases, such as diabetes mellitus, atherosclerosis, immunological and oncological diseases.

Advances in the areas of data and signal acquisition as well as software technologies have resulted in intelligent recording, processing, transfer and storage of a variety of biosignals, e.g. of neurophysiological, hemodynamic, and respiratory signals. In order to use these signals for monitoring purposes intraoperatively as well as during later treatment (in different clinical situations, i.e., intensive care unit, operating room or home care), relevant information has to be extracted from highly complex signals. For routine use in clinical practice the raw signals need to be analyzed, transformed and condensed into an easily-understandable form of an indicator and presented to the clinicians. This ambitious goal involves biomedical engineering, informatics and medicine with subtasks including signal recording and processing, information retrieval and machine learning as well as medical expertise. Specific characteristics of the individual patients or the time course of the indicator values are often neglected in this procedure, particularly since this information is often not sufficiently represented by the given example data. Tests must be performed in the clinical environment, to check the plausibility of the developed indicators.

As for computer-aided medical procedures, more and more open operations are being replaced by minimally invasive, image-guided therapeutic options. They include ablation of tumor tissue by radiofrequency energy, laser, microwaves, and cryoprobes as well as photons, particle ions and ultrasound energy (focused ultrasound). Extremely high precision in targeting the volume to be destroyed is imperative, and adjacent normal tissues must not be damaged. Therefore, online registration and correction have to be implemented in the guiding devices. Complex data management and integration issues arise, such as image fusion, real-time processing of large amounts of data, and process integration [27]. Endoscopy is another field where increasingly complex devices are transmitting online data from within the body, and where one would expect that optical technologies could be combined with nano-technologies, biosensors and maneuvering technologies. Embedding these devices into the clinical workflow and integrating and managing complex data will also be a challenge.

### 3.2.2 Research Challenges

As a consequence of the expected dominance of information and communication technologies and their theoretical and scientific foundation, a focus on research on the aspects of informatics-related BME and a closer coupling to biomedical informatics is needed. This will cover the design and optimization of algorithms, the study of their complexity, the integration of sensors of different reliabilities for on-line coupling of the system to a human, the need for data integration, real-time issues, among others. Education should cover the complete software development process, i.e. specification, verification and validation in the medical domain including all safety-related problems, integration of large distributed medical systems (including sub-systems and devices connected via wireless broadband networks), automatic adaptation and learning (e.g. for personalization), and information logistics, i.e. transparent and seamless bridging between and across different modalities.

From an applications point of view, this includes (in arbitrary order) the use of informatics methodologies for systems analysis, medical imaging and multi-modal data fusion, high-resolution image processing, physiological signal processing, as well as 3-D modeling, for tasks such as predicting tissue and tumor behavior. Concrete devices that profit from this research in a more or less generic way include multiphoton laser-scan scanning microscopes, (f)MRI scanners, X-ray machines, CT scanners, PET and ultrasonic scanners, as well as any combination of such devices.

Beyond the classical cutting-edge challenge of improving sensor resolution down to millimeter-size and lower, we are facing emerging challenges like cognitively adequate real-time visualization, picture archiving and communication (PACS) and content-based image retrieval (CBIR) [28], e.g., based on natural language interfaces.

As mentioned above, another emerging field that opens up completely new areas of exciting research for many years to come is molecular imaging, where biomarker probes are developed and validated to help visualize various targets, pathways, or systems in a living organism. Future medical applications include early detection of diseases, as well as the study of the effect of pharmaceuticals on an organism. Current
research challenges are the qualitative and quantitative assessment of the significance of observed changes for disease development. Simulation and modeling of the probe’s kinetic behavior yield new insights in complex biological processes, but pose many challenges in the areas of image generation algorithms and image processing. In vivo images will be correlated with microscopic images and high-throughput molecular analyses obtained from the very same neoplastic or non-neoplastic tissue to demonstrate sensitivity and specificity.

Among the research challenges resulting from embedding BME into health informatics is the handling of streaming data in addition to (conventional) persistent data. Tasks that can benefit from processing streaming data streams on-the-fly include traditional tasks such as bedside patient monitoring as well as new applications like mobile devices for monitoring patients at home or ad-hoc networks for data acquisition, data sharing, and data analysis, e.g., in the context of disaster management. Such processing may include alerting responsible physicians or an ambulance whenever certain vital signs reach critical values. It may also comprise filtering and delivering incoming information to relevant recipients among the physicians, authorities, and coordinators working at the scene of a disaster. Distributed sensor networks in general provide for monitoring, archiving, and presentation of corresponding data. Streaming applications will continue to gain importance since they allow quick reaction time to various kinds of events and are also able to efficiently process large volumes of data online.

3.3 Health Informatics and eHealth

3.3.1 Background and Motivation

Due to demographic development, sociocultural changes, increasing mobility of citizens, the globalization of markets, increasing costs of new examination and therapy methods, and the growing demands of the health services consumer, modern health systems are under significant pressure. There is a broad consent among stakeholders worldwide that eHealth is one of the most important tools for meeting the challenge. eHealth has been defined by the WHO as the use of information and communication technology (ICT) for health at the local site and from a distance [29]. The driving force behind eHealth from the citizens’ and patients’ perspective is the need for seamless, high quality, and efficient care, and the opportunity to empower citizens to manage their own health by improved access to knowledge and to personal medical data. On the level of healthcare systems, coordination of activities via information logistics is essential. Especially in the case of scarce resources, coordination and collaboration are necessary to bridge interfaces between all agents involved in healthcare delivery and prevention.

eHealth is already the third largest pillar of the healthcare industry (after pharmaceutical and medical devices industries), and its market is expected to grow to 5% of healthcare expenditure within the next ten years [30]. A large number of possible eHealth applications have shown their potential for various application scenarios, including: i) management of trauma, emergency and disaster, ii) prevention and self-management, iii) healthcare at home (e.g. tele-monitoring), iv) integrated care, v) surveillance and early warning.

All components of healthcare systems according to WHO, i.e., service delivery, financing, resource generation and stewardship [31], are likely to become the target of informatics applications and services in the following areas [32]: eCare, mainly addressing the delivery of health services from healthcare providers to persons facing a health problem, utilizing ICT for the delivery; eLearning, addressing professional education, but also the education of patients (especially for chronic conditions), and also the education of healthy citizens on prevention and lifestyle-related health threats; eSurveillance, supporting health reporting, acquisition and analyses of epidemiological data, including observation satellite data, for early warning on epidemics and public health development and monitoring; eGovernance/eAdministration, to streamline and enhance the efficiency of activities such as electronic reim-
bursement, checking of insurance status of patients, and decision-making of stakeholders; eResearch, aiming at the support of biomedical research in all its aspects, with electronic source data interchange and bridging clinical and research information systems being the major challenge. The increasing importance of information technology in medicine has been described recently [33]. Studies evaluating the impact of informatics on medical care have been carried out [34, 35], demonstrating positive effects on access to care, on preventive health, and on surveillance and monitoring.

3.3.2 Research Challenges

For more than a decade, advances in informatics and in health informatics have broadened the scope of information systems and have contributed to the comprehensive scope of eHealth. Hospitals, regions, and countries are being networked, health care professionals’ decisions are being supported by information systems and knowledge bases, patients and citizens are being empowered, and concepts of ubiquitous computing are being transformed into real systems. Electronic patient records and health records are being implemented more widely. Many old challenges still exist, however, and new ones add to the complexity of the emerging picture [36-38].

Further research is needed on architectures, interoperability, ontologies, and standards. In order to build modular, dynamically adapting systems that can guarantee adequate quality of service, research should focus on distributed information systems and databases, on interoperability on the technical and semantic level, but also on the organizational and political level. eHealth requires data integration and the handling of large and complex data volumes, especially when existing islands of information are to be combined, and when genomic data are to be added to the electronic health records. Moreover, functional and process integration is needed. Service-oriented architectures (SOAs), which are a current informatics research topic, provide a means for enabling the integration of heterogeneous information systems on a global
scale via loosely coupled subsystems, while at the same time preserving their local autonomy. Maturing standards are supporting communication and cooperation [39], but for knowledge management and for developing the full potential of decision support, further research on their underlying semantics and ontologies is essential.

Often seen as a major barrier in gaining broad acceptance of eHealth among professionals and citizens, the need for safe storage and communication of confidential data requires research on innovative combinations of technologies and their smooth incorporation into the eHealth infrastructure and processes. Current security research topics in the database domain comprise efficient and secure execution of workflows and fine-grained access control, e.g., as needed in the context of patient empowerment. Incorporation of current informatics research topics is a relevant option. These include concepts such as k-anonymity or new approaches following the Heisenberg principle, as well as research on trusted pseudonymity services that are resistant to unauthorized access, taking into account that most security-critical incidents are due to human error or neglect. At present there are no guaranteed methods for securing the privacy of health (or other) information on systems, and the resulting lack of trust presents a major challenge to widespread voluntary adoption of these systems for health-and-security critical information.

Acceptance research, impact research and human factors analyses are needed. The factors contributing to the acceptance of new, eHealth-enhanced, services and workflows among professionals, patients and citizens have to be researched and related to specific impacts, such as the time-saving factor, the costs-savings potential, and improved medical service quality. In spite of promising perspectives, it has become increasingly clear over the last few years that cost savings and improvements in medical quality, e.g. by decision support and guidelines, are difficult to achieve and hard to verify. Moreover, failures are not uncommon and even adverse consequences were observed. Failure analyses and evaluations have shown the need for advances in human factors analyses, cognitive science, and change management involving health risks under the wide range of uncertainty characteristic of these problems [40]. Research on workflows and related socio-technical aspects is essential in order to build successful, effective, and efficient eHealth services, with a focus on patients and health care professionals as well as on organizations on the intra- and cross-enterprise level. Innovative methods and systems for information logistics and information management, including risk management, are needed.

For the management of eHealth services, considerable research on logistic and economic models is necessary in order to support informed decision making for investors in this fragmented market.

For full deployment of eHealth services, existing regulations and legal frameworks have to be revised. Research is needed on how to break down the requirements of eHealth service categories with their specific technological, organizational, social and political constraints into broader workable principles that can form the core of amendments and extensions to existing acts and rules, while at the same time covering emerging technologies as widely as possible.

Digital data have become a core element of research, knowledge generation and knowledge management. Data organization has become critical due to the known complexity of clinical data as well as the increasing volume of genomic data and its availability through public databases. Various types of information (literature, clinical guidelines, clinical pathways) are publicly available and appropriate to support evidence-based medicine (EBM). Biomedical informatics methods are needed to find new ways to synthesize information and knowledge from diverse data sources and to carry out coordinated research efforts that span multiple institutions [9-17]. A common vision is the integration of various data sources and types into a comprehensive infrastructure in order to accelerate the complete translational cycle, from genomic, molecular, and clinical data collection, to individualized and tailored treatment, and further to evaluation, and new hypotheses. Three perspectives need to be combined to support both high-quality patient care, and clinical as well as translational research from bench to bedside to bench:

1) Information flow needs to be adapted to the work practice of healthcare professionals, providing access to data from different sources and locations, including imaging devices, biosignals, text, and molecular data. Decisions need to be based on comprehensive data and on the best available evidence. Among the challenges are seamless integration at the semantic and ontological level, data security, workflow management, and knowledge management which supports evidence-based medicine.

2) Clinical trials need to be supported by sophisticated systems which are in compliance with regulatory requirements. The interchange of clinical trial data and semantic interoperability with clinical systems will improve recruitment, follow-up, scheduling, adverse event reporting, and individual feedback to patients, but requires research and development efforts. Among the challenges are issues such as access right management, de- and re-identification of patient data, pseudonymization, separation of personal and research data, informational self-determination (patient view), and intellectual property rights (IPR) (researcher view), as well as their close relationships to legal issues.

3) Systematic tissue collection has to be combined with use of molecular-based technologies. Tissue, serum, and body fluid banks provide access to biomedical phenotype data which needs to be combined with higher clinical data.

Health informatics is a discipline which focuses on the complete spectrum of applied informatics in medicine and health, so interrelationships and overlaps exist with all three other areas, as well as with informatics as the underlying core discipline. As in the other three areas, knowledge discovery, data integration, data visualization and data management are essential for analyzing different biomedical data (e.g., gene expression, sequence, signal transduction pathways, gene signature, clinical data, imaging data, sensor data) and for integrating a wide variety of data on all levels of research,
health care, and prevention. Scientific challenges such as limitations of today’s early ontological efforts are accompanied by technological challenges like, for instance, difficulties with multimodal data fusion and network security. With public health it shares the ubiquitous problems of defining health risk and hazard for individuals as opposed to groups, and related challenges in accounting for genetic versus environmental factors.

3.4 Public Health, Life Sciences, and Public Health Informatics

3.4.1 Background and Motivation

Improving human health is one of the key goals of society from a global perspective. In particular, demographic changes represent an extraordinary challenge with the rapidly growing number of elderly people requiring adequate healthcare. However, the financial resources for large-scale social coverage are decreasing, and it appears unavoidable that decisions in the healthcare systems of developed nations will be determined by the effectiveness of all medical services and their cost-effectiveness. In an aging society, effective prevention is therefore of the highest priority, in particular for those chronic diseases that are becoming a major burden to societies, in conjunction with the rapidly declining number of younger people who are active members of the work force. It is mandatory to obtain a better understanding of the determinants underlying those diseases that can develop even at a young age, and, more importantly, to develop new measures to mitigate or control them. And, learning about the cost-effectiveness of such new prevention strategies is essential [41, 42]. Efficient prevention strategies need to be embedded into innovative solutions for healthcare, which will become available through progress in biomedicine and information technologies.

Genome research and genetic medicine are core disciplines driving technological progress in medicine. A basic requirement for successful applications in healthcare is knowledge about the genetic variation in the entire population. In addition, population-wide patterns of metabolic states, images, and disease phenotypes in general, are required to study disease predisposition, disease course and treatments in the context of different lifestyles and environments on a population level. We must also understand the economic boundary conditions under which novel technologies can be developed and implemented in the healthcare system. Information technology is central to such applications – in order to improve targeted diagnosis and treatment, and also for developing new forms of early intervention. This leads to new challenges on how health issues are communicated and how increasing management needs can be met. A high degree of multidisciplinarity is required, including input from clinical and genetic medicine, epidemiology, health economics and the public area for providing and developing new strategies and putting them into action.

At present, the incidence and prevalence of several important chronic disorders is increasing. This applies, e.g., to obesity and metabolic disorders such as diabetes, to allergies, and to neurological disorders such as dementia. In addition, the high load of cancer morbidity and mortality is especially burdensome. The prevention and control of such conditions pose specific challenges for public health and related basic, clinical and population sciences. Many of these diseases are a consequence of an aging population in combination with sedentary lifestyles, characterized by hypernutrition and a lack of exercise.

There are two levels of interaction with populations in the context of future healthcare systems: i) recording and describing disease and disease courses in targeted populations, and ii) choosing, implementing, and evaluating treatments and prevention strategies. The first level includes the assessment of comprehensive biomarker profiles derived from genomic applications. The second level includes intervention studies, interactive counselling and the implementation of lifestyle modifications. For both levels there will be overlaps with bioinformatics and with the health informatics activities.

Extensive databases and information platforms combined with powerful profiling technologies will enable the development of new health care tools with manifold applications, for instance, to identify population groups at risk, to detect environmental cancerogenic factors, to design cancer prevention campaigns, and to establish public information centers.

3.4.2 Research Challenges

With the wealth of genomic information and high-throughput profiling technologies for a wide range of biological organisms and systems, medical research is able for the first time to define on a molecular basis the susceptibility, course and outcome of disease within the context of different environments and treatments. For metabolic disorders for instance, diet and food components are prime environmental factors that interact with the genome, transcriptome, proteome and metabolome. This life-long interaction defines the health or disease state of an organism. Profiling technologies are also used in cancer and age-related neurological disorders to guide clinical sciences in developing evidence-based recommendations and health-promoting strategies. Hence, this research area needs to focus on i) developing new health-care supporting tools (e.g. tele-monitoring devices) to allow the assessment and reporting of health-related parameters in targeted populations; ii) developing new avenues of interaction between healthcare providers and customers in order to obtain high levels of information and to ensure consent on a population level; iii) developing the information/communications technology structure for study centers in the area of nutrition and chronic diseases; iv) developing web-based information and interactive counselling tools for prevention and the promotion of healthy lifestyles.

Epidemiological study platforms with biobanks form a good example for the need of combining advanced methods from epidemiology, genetics, clinical medicine, bioinformatics, and informatics. Pseudonymization services are necessary, and phenotype data need to be managed together with data from genetic and molecular studies. The genetic and molecular data are high-dimensional and pose the challenge of
integrating data coming from different sources and different experimental techniques. Current databases contain 1 billion datasets and more, while an increase with a factor of ten is realistic within the next few years.

Research in health economics is needed. The care of chronically ill people may significantly benefit from technical devices that support monitoring of functioning and of clinical parameters, as well as preventive and treatment interventions (e.g., by increasing adherence to in-time and in-dose drug treatment) or that are endowed with emergency help capabilities. The question of how effectively health can be improved, and with what cost-effectiveness this can be accomplished, is of relevance to public health and to social security systems. Evaluations of various types of health care interventions regarding medical and economic criteria, and studies on the optimization of health care management are a highly relevant research focus in this context.

In summary, challenges in public health informatics and life sciences are closely related to all other areas, e.g. the challenge of integrating genetic and telemetry data into epidemiological studies, and of building eResearch and eHealth infrastructures. At the same time, relevant aspects of current informatics research need to be addressed, such as the handling of large and complex data sets, integration, ontologies, and security concepts.

4. Interdisciplinary Collaboration and Education

Our suggestion is to strengthen collaboration and structured interdisciplinary education in the four priority areas encompassing medicine, informatics, bioinformatics, biology and system biology, engineering, health informatics and public health. As mentioned before, each of these disciplines has developed its own domestic culture. These cultures have proven to be highly resilient to change and, for many reasons, have resisted, to a large extent, all attempts to become integrated. In some disciplines, subcultures have emerged that obstruct communication even between members of the same discipline, e.g. between clinical and basic medical research.

In our opinion, it is only through a change in the attitude of scientists that these cultures will merge, and this change will come about only in new generations of scientists that are educated in (at least) two of these cultures. Moreover, while the scientific core of each discipline will remain stable, interdisciplinary education is needed to provide a firm structure for permanent and effective exchange of people and ideas. This will encourage the networking of practicing scientists and engineers or technologists, and, in a very natural way, also encourage more integration with industry.

The fact that scientists and students are obliged to act and to learn together across disciplines will also refute the entrenched belief that integration is not feasible. In other words, historical structures need to be rethought: an innovative type of education is needed that will have structural impact, not by trying to dilute the disciplines or research areas, but by providing its scholars with an interwoven approach to applying informatics in health. While excelling in their “home disciplines”, members of such a school can also serve as “boundary-breaking” agents to other research areas and thus empower innovation. In our opinion, this concept will offer a high potential for substantial and sustainable change in these structures because of its long-term bottom-up approach.

In the traditional university system, there has been a cultural gap between classical natural sciences (e.g., chemistry, biology, physics) and engineering and informatics. While the former are primarily dedicated to basic research, engineers and informaticians consider themselves closer to technological applications, which frequently results in gaps or avoidable discontinuities between discovery, invention, innovation, and widespread technology adoption. It would be desirable to overcome such gaps or discontinuities, to translate research results into applications, and to take steps that would encourage various disciplines to work together much more closely. From our perspective, the most effective way of changing the patterns of scientific education is to address the level where teaching and research meet: MSc and PhD programs. Accordingly, the operational objectives of such programs would be:

i) to coordinate and combine advanced courses and research training for advanced students in medicine, science and engineering/informatics thereby promoting their interaction across disciplines;

ii) to create added value for individual key research areas through structural provisions, e.g., definition of joint research projects, focused and targeted workshops;

iii) to foster links at the institutional and personal levels;

iv) to encourage project-oriented teamwork at a high scientific level, covering different research cultures.

All students in such a program should receive true interdisciplinary tuition in at least two previously distinct fields while performing their research work.

5. Conclusion

The relevance of informatics in health has continuously grown over the last decade. We have outlined the urgent need to translate scientific progress into clinical practice and into new prevention strategies. In order to handle the massive complexity of medicine and health care, and to build affordable and efficient health care systems, true multidisciplinary collaboration has become essential over a broad spectrum of disciplines. In our opinion, the ‘top-down’ approach of defining joint research programs which try to combine scientists from applied sciences, engineering and life sciences in order to achieve progress in health has not always lived up to its promise. Our suggestion is to take an integrative approach by starting interdisciplinary practice at early stages of education, and to build common ground early and in a structured way. It is only through having experts in one scientific discipline who have a profound understanding of the other disciplines’ terminology and scientific culture, that true interdisciplinary
arity can develop, which is exactly what is now needed for our health care systems.

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