Introducing Kuhn et al.'s Paper "Informatics and Medicine: From Molecules to Populations" and Invited Papers on this Special Topic

Editorial

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Summary

Objective: To introduce the paper by Kuhn et al. "Informatics and Medicine: From Molecules to Populations" and the papers that follow on this special topic in this issue of *Methods of Information in Medicine*, which opens a debate on the Kuhn et al. paper's assertions by an international panel of invited researchers in biomedical informatics.

Method: An introductory summary and comparative review of the Kuhn et al. paper and the debate papers, with some personal observations.

Results: The Kuhn et al. paper makes a strong case for interdisciplinary education in biomedical informatics across institutions at the graduate level, which could be strengthened by analysis of previous relevant interdisciplinary experiences elsewhere, and the challenges they have faced, which point to more pervasive and earlier-stage needs for both education and practice bridging the research and healthcare communities.

Conclusions: The experts debating the Kuhn et al. paper strongly and broadly support the key recommendation of developing graduate education in biomedical informatics in a more comprehensive way, yet at the same time make some incisive comments about the limitations of the "positivistic" and excessively technological orientation of the paper, which could benefit from greater attention to the narrative and care-giving aspects of health practice, with more emphasis on its human and social aspects.

Keywords

Informatics, medicine, interdisciplinary education, molecules to populations, genotype to phenotype, clinome, narrative medicine, evidence-based medicine

Methods Inf Med 2008; 47: 279–282

Parallel rapid developments in both the science and technologies of biology and informatics are already strongly affecting the practice of medicine. They hold the promise of eventually revolutionizing our knowledge of how genetics, development, disease, and environment interact in affecting human health, and strongly impacting medical and healthcare practices. Recently, Professor Klaus Kuhn and colleagues at Munich Technical University, the Ludwig-Maximilians University and the Munich Helmholtz Center proposed the creation of "a research-oriented interdisciplinary Graduate School" [1] which has now been established. This issue of *Methods* publishes a paper by Kuhn et al. [1] laying out the rationale for such a Graduate School, arguing how informatics and medicine interact uniquely in the study of health and disease across a range of biological scales from molecules to populations, in a way that requires a much stronger interdisciplinary focus than current individual programs to prepare future leaders in the study of biomedical systems affecting all aspects of biomedical research, healthcare practice, and education. Because the importance of this initiative far transcends its immediate local and national contexts in Munich and Germany, the editor of *Methods* solicited comments on the paper from an international group of experts in biomedical and health informatics and related disciplines, with the goal of stimulating a lively debate on the challenges facing our field. I believe that our readers will agree they have succeeded in this. The paper with these commentaries [2] and one by the past editor of *Methods* and founder of the IMIA Yearbook [3] which follow that of Kuhn et al. include a wide range of reasoned arguments and original position statements which, while strongly endorsing the educational needs identified by Kuhn and his colleagues, also point out fundamental challenges that are very specific to the unusual combination of scientific, technological, personal and social problems characterizing biomedical informatics. Most importantly, these point to the ultimate objectives of managing difficult human health problems which are unlikely to yield to technological solutions alone, however effective these may prove for solving some of the better understood and constrained ones. The psychological, societal, and environmental components of health and disease are emphasized by several of the commentators, setting the stage for further debate and constructive suggestions. I appreciate the opportunity to contribute this Guest Editorial emphasizing some of the highlights of Kuhn et al.'s paper with those of the expert commentators in the light of some of my own observations and experiences [4].

What are the major points made by Kuhn et al. to support their thesis that interdisciplinarity is more needed than ever to make informatics effective in medicine? And, does the case for biomedical informatics go beyond what is needed for other similar interdisciplinary programs? The analytical foundation of the paper rests on a four-way breakdown of how informatics has an impact on: 1) basic (systems) biology; 2) biomedical engineering; 3) eHealth; and 4) public health, which is illustrated in figure 1 of [1]. This breakdown gives structure to the arguments of how informatics and its mathematical and computational underpinnings will increasingly help support the development of molecular medicine, clinical translational research, clinical medicine, seamless healthcare and public health (figure 2 in [1]). In defining "the overall picture" early in the paper, the authors identify eight major technical trends in computing and software technology which are likely to increase the ability of systems to handle the massive amounts of complex, structured information involved. These are then divided into groups in terms of their likely impact on advancing: 1) bioinformatics methods for research and increasing the reliability of remote telematics applications of eHealth, 2) clinical decision support for integrating the interpretation of complex and heterogenous data; 3) improvements in the opportunities for personalized prevention strategies; 4) effectiveness of the design of new medical devices; and 5) interface to the wealth of structured knowledge in the literature through the semantic web. The authors then argue for "structured interdisciplinary education" in four areas: bioinformatics and systems biology; informatics for biomedical engineering; health informatics and eHealth, and public health informatics and public health. The core of this paper details those aspects of each that the authors consider most valuable for such education, concluding with an observation that "traditional university systems tend to strengthen a 'cultural gap' between classical natural science (e.g. chemistry, biology, physics) and engineering and informatics" ([1], p 11). These in turn are considered to lead to discontinuities between "discovery, invention and innovation" and "widespread technology adoption", which could be overcome by "changing the patterns of scientific education at the MS and PhD levels where teaching and research meet". Implementation suggestions are to: 1) coordinate and combine courses across the disciplines; 2) encourage joint research projects and workshops to share experience; 3) foster links at the institutional and personal levels; and 4) encourage project-oriented teamwork spanning the differing research cultures at a high scientific level. The paper concludes by saying that doing this at early graduate school levels with "experts of one scientific discipline who have a profound understanding of the other disciplines' terminology and scientific culture" is a major need for healthcare systems. The case for breadth and heterogeneity of informatics problems and solutions across the spectrum from "molecules to populations" is certainly convincing. However, what is not addressed are whether there might be lessons to be learned from experiences in other interdisciplinary fields where informatics is critical – in ecological management, earth and environmental sciences where satellite images, GPS and advanced sensor arrays are affecting all sorts of natural, civil and military problems, or the political and economic sciences, where the web of online information has likewise changed the practices of political, legal, commercial and financial competition, for instance.

The commentaries in [2] touch on many difficult problems faced by biomedical informatics as it attempts to span the incredibly wide range of differing needs from basic biological research, through individual healthcare and consumer perspectives in a networked society, to understanding public health implications for various populations at risk. There is a pattern, however, to both the praise and criticisms made by the experts. No one disagrees that more interdisciplinary education is needed and that the graduate level is the realistic one at which to do this, once students have acquired enough background in two or more contributing disciplines. The commentators on the whole take a positive view of the Kuhn et al. paper, suggesting ways of amplifying its content or strengthening its arguments. What proves more controversial is the emphasis on technological solutions to research and healthcare problems argued in [1]. This tends to downplay the personal and social aspects of biomedical informatics which often are major barriers to improving healthcare, and several commentators emphasize this as a limitation. I will next highlight some of the major supporting and critical points made by each commentator, and conclude with a summary.

Russ Altman of Stanford University adds to Kuhn et al.'s analysis an emphasis on the "empowered, independent and thoroughly networked (health) consumer" [2], which has transformed the world of communication and social interaction so completely in the past decade. He argues that in the future this trend will have a strong effect on people increasingly making decisions on handling their own healthcare – which should dramatically change the concept and practice of medical and health education for practitioners and health consumers alike – and provide ample research opportunities for biomedical informatics and allied fields. Rudi Balling from the Braunschweig Helmholtz Center for Infection Control raises the vexing questions of the contrast between the "hard" vs. "soft" sciences in the cultures that make up biomedical informatics, and the difficulties of trying to overcome current disciplinary prejudices at the graduate level – he argues for the need to do this much earlier in the educational process, while recognizing the political and societal trends that work against it. His plea to "merge the coffeerooms" for students and faculty suggests that increasing understanding and respect among colleagues might be as necessary for finding constructive solutions within competitive environments as its more typical opposite.

James Brinkley from the University of Washington compares and contrasts the Munich proposal to some of the experiences at his university, noting that differences in terminology and practice in informatics between the US and Europe gives the latter a broader scope which could help unify practices across a broad range of biomedical applications. In addition, he points out that figure 2 should more generally show a full set of interconnections between core informatics competencies and the different levels of biomedical application, rather than the strictly horizontal ones, which are too restrictive.

Enrico Coeira of the University of New South Wales points to antecedents for the multilevel approach to informatics and medicine and then focuses on the barriers to adoption of IT in healthcare, which he posits are mainly of a social and not technological nature. He argues for the need to develop an understanding of the unexpected interactions between humans and technological artefacts which can help bridge the different social systems of bioscience, clinical medicine and the citizen. Fabrizio Consorti of La Sapienzia contrasts the technological and evidence-based medicine (EMB) perspective of the Kuhn et al. paper to the need for a narrative-based medicine (NBM) approach which is more typical of the practicing clinician's way of describing a patient's condition within the clinical context. He argues that considering EMB and NBM as "two different paired dimensions of medical knowledge"[2] will reduce the boundaries between knowledge management and e-learning.

Ali Dhansay from South Africa emphasizes the challenges for biomedical informatics in developing and "hybrid" countries like his own where interracial differences and endemic HIV/AIDS, malaria and tuberculosis have a major daily impact on the lives of people. He brings up a number of economic, ethical and practical issues that arise when one tries to make the scientific achievements in genomics and biomedicine more effective and accessible through informatics, while, however, creating new challenges in terms of anonymity and confidentiality. Antoine Geissbuhler of Geneva University and Hospitals argues that the "info-bio convergence" implicit in Kuhn et al.'s proposal is challenged by the need for semantic integration across very different domains, which will change the current emphasis on hypothesis-driven research towards more data-driven research in the future. This certainly will require more education and new models to encourage cross-disciplinary skills for the healthcare workforce under exceptionally difficult and complex social conditions. William Hersh of Oregon Health and Science University suggests that informatics has to go beyond computer science and embrace the human dimensions of information processing, and the need to identify the core competencies of a field which will continue to lead to a wide variety of very distinct career pathways. Yunkap Kwankam of WHO and the University of Yaounde raises the important issue of assessment of health informatics, which is underplayed in the Kuhn et al. paper. After pointing out the known financial benefits from programs that improve drinking water and sanitation worldwide, he argues that health informatics must demonstrate comparable or even greater benefits in order to obtain more adequate funding. He emphasizes the need to identify "communities of practice" that are effective in developing a "collective wisdom" that can help WHO and other organizations to include biomedical informatics in its "value chain"[2]. Nancy Lorenzi, from Vanderbilt University, and immediate Past President of IMIA, and developer of IMIA's Strategic Plan Towards IMIA 2015, comments that Kuhn at al's article supports the view that informatics is "the most important driver and mediator for innovation" [2] and that collaboration is essential to achieve this. Knowledge is seen as the core of innovation, which feeds into the major components of IMIA's Strategic Plan that are designed to integrate and connect the science with the practice of informatics in biomedicine and healthcare. Publications and electronic dissemination of information are identified as the major disseminators of knowledge, and the international interdisciplinary collaborations fostered by IMIA are seen as central to achieving the future goals for informatics and medicine as envisioned by Kuhn et al.'s paper. Fernando Martin-Sanchez from the Ministry of Science and Innovation in Madrid makes the point that nanomedicine and regenerative medicine present both opportunities and challenges for biomedical informatics. With a rapidly ageing population, many European (and other, mostly developed) countries are faced with urgent needs for management and prevention of chronic conditions in disproportionately large percentages of their populations. This will require imaginative and novel approaches to prevention and rehabilitation, including the incorporation of the latest developments in nanomaterials and artifacts for effective deployment. He lists EU initiatives, such as the ACTION-Grid which is to develop healthcare information systems based on the Grid capabilities and new technologies that support these novel directions. George Mihalas of Victor Babes University in Timisoara points to the difficulties that were faced by neuroinformatics in having an impact, and the need to connect to systems biology with projects like the Virtual Physiological Human and the Physiome Project – all of which will require educational components like AMIA's 10×10 to educate the workforce in informatics.Yuval Shahar of Ben Gurion University in Beer Sheva brings out a very essential point in Kuhn et al's paper: "only through experts in one discipline who profoundly understand the conceptual world of another discipline can true multidisciplinary research develop" – he argues for "boundary breaking agents" [2] as role models for students to meet during their training in order to foster true and productive interdisciplinarity. Using the specific example of developing a "smart medical home" Shahar says that only by combining the right bioengineering and medical informatics will this be achieved. He argues for tackling a number of grand challenges, including what he terms the "Human Clinome Project"[2] as a continuously changing library of declarative and procedural clinical knowledge that can be "represented and accessed by computational means". He points to preliminary successes in clinical guideline structuring and representation as precursors to this work. Two other challenges Shahar identifies are the management of patients, especially those with chronic disease, and with emphasis on the temporal aspects of their conditions and the need to define "clinarrays" of laboratory data (in analogy to microarrays) to suggest new ways for subtyping diseases. In addition, the need for decision support including genetic components is seen as a fertile area for engaging patients to take more responsibility for their own decisions while tying this to clinical workflows. Katsuhiko Takabayashi, from Chiba University emphasizes the role of clinical studies and appropriate security and confidentiality needed to safeguard the individual while yielding the knowledge that underlies how medical decisions are complemented by genetic data. But he warns that law and ethics are also important areas of study for biomedical informatics given their strong impact on people and how they handle health information. Finally, Gio Wiederhold from Stanford University gives a more detailed description of the interrelated roles of biomedical informatics, engineering, and software engineering (SWE). He recognizes the bureaucratic barriers to change, but indicates that practical problems of security, confidentiality, and limitations of the state-of-the-art in SWE, and economic considerations constrain the development of large and effective eHealth systems. He points out that the ratio of 25 : 7 : 1 between research projects, their practical implementation, and integration into practice has remained unchanged despite new initiatives such as Service-Oriented Architectures. His commentary touches on the social expectations which limit collaboration between the formal mathematically based disciplines and those of the biological world, where variability and ongoing experimentation is the norm, and concludes with an interesting comment on the nature of randomness in limiting what we can know about our own reasoning processes – suggesting the need for more research in this direction to help improve clinician-patient interactions.

The separate paper by Jan van Bemmel [3] provides an excellent summary of Kuhn et al.'s paper and draws parallels and contrasts to the experience at Erasmus University Medical Center in Rotterdam, and its pioneering development of a framework for interdisciplinary research in medical informatics. He quotes from Gilles Holst's "Ten Commandments" for encouraging productive research in a long-standing, highly successful industrial research lab (Philips Physics Research Lab in Eindhoven). These include the need for engaging competent scientists when young, without too much concern about their prior experience, giving them a lot of freedom, but expecting them to work hard and share their work through publications and discussions. Solving problems through multidisciplinary teams and encouraging the free movement from research to development, while being guided by academic insights as much as by market opportunities are also essential for success. Van Bemmel identifies a number of grand challenges which he ties to the adherence to these "commandments" and illustrates how they might be solved if there was more attention to aspects of human behavior that define needs not easily or necessarily satisfied by technological solutions alone. The cultural aspects of "overstretched expectations' is a concern raised to caution the readers about the need to realistically assess proposals such as the one in Kuhn et al.'s paper.

In summary, the paper "Informatics and Medicine: From Molecules to Populations" [1] has opened a timely debate through the Commentary papers [2, 3] on the nature of biomedical informatics and the challenges it faces, especially in education, in this era of translational and personalized medicine. They highlight the urgent need to improve our understanding of how structuring and managing information is central to understanding the roles of genomics and other -omics methods in contributing to the promotion of individual and group health as we attempt to map the complex pathways from genotype to phenotype [5]. Further considerations extending the scope of these commentaries might well ask whether and how the underlying basic sciences of information generation and processing in humans as well as machines is likely to be advanced by biomedical informatics, which is at the unique intersection of science, technology, and the practice of healthcare. Helping alleviate suffering draws on deep emotional sources of shared empathy, for which better cognitive and perceptual models are needed. And, to better understand how successful nursing and medicine can interact with the help of informatics in social situations and across different cultures [6], may well open a largely untapped and rich source of experience into how we can truly personalize healthcare in ways that we as individuals would wish it to be practiced when we ourselves need it the most.

On behalf of the editors and editorial board of this journal I am pleased to extend an invitation to all readers to contribute to this ongoing debate through Letters to the Editor which could be published in future editions of *Methods of Information in Medicine.* We look forward to your contributions.

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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, health informatics 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 information 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 interpretive 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 3-8 will help to provide large amounts of knowledge for the interpretation of complex data, to support decision-making and to allow for new prevention concepts; with item 4 not only triggerering 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 industrial 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).

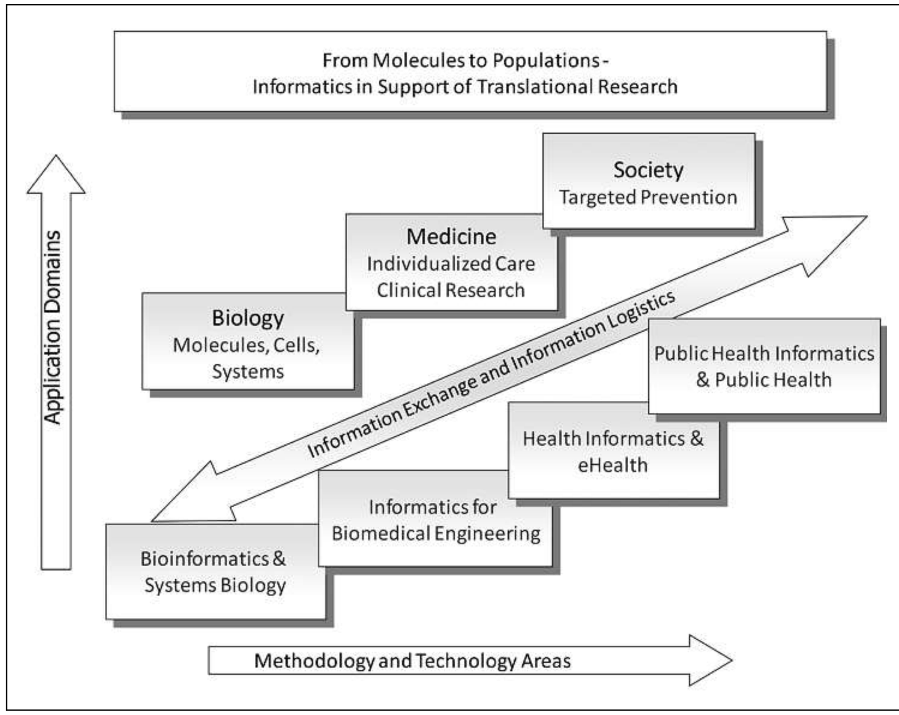

Fig. 1 Health and interrelations with informatics (for explanation see text)

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 must 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-

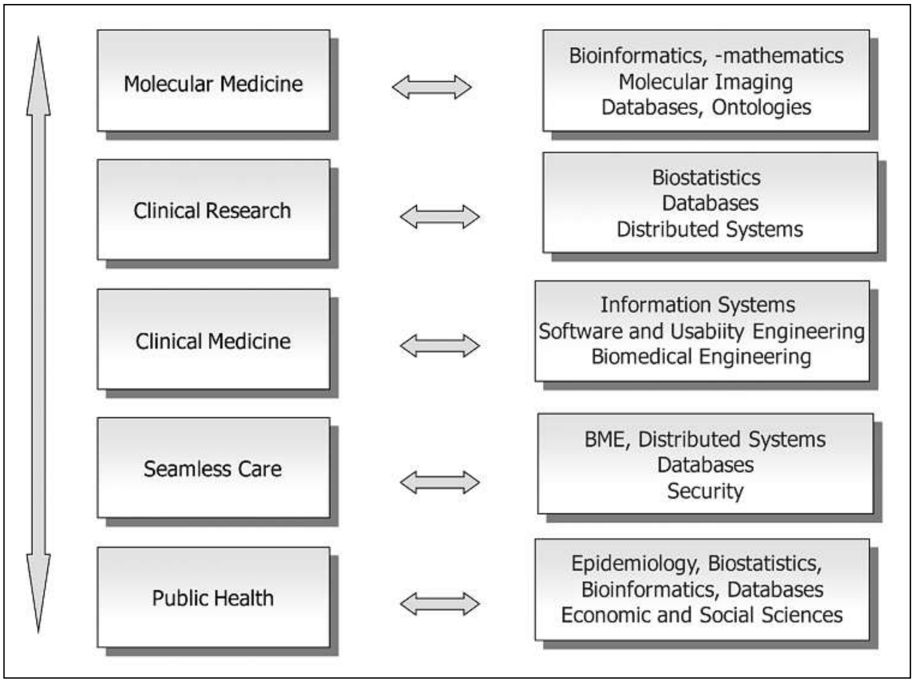

Fig. 2 Examples of multidisciplinary cooperation

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 pre-clinical 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: imaging 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 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 laserscanning 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 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 reimbursement, 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, transciptome, 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 interdisciplinarity can develop, which is exactly what is now needed for our health care systems.

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Commentaries on "Informatics and Medicine: From Molecules to Populations"

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Summary

Objective: To discuss interdisciplinary research and education in the context of informatics and medicine by commenting on the paper of Kuhn et al. "Informatics and Medicine: From Molecules to Populations".
Method: Inviting an international group of experts in biomedical and health informatics and related disciplines to comment on this paper.
Results and Conclusions: The commentaries include a wide range of reasoned arguments and original position statements which, while strongly endorsing the educational needs identified by Kuhn et al., also point out fundamental challenges that are very specific to the unusual combination of scientific, technological, personal and social problems characterizing biomedical informatics. They point to the ultimate objectives of managing difficult human health problems, which are unlikely to yield to technological solutions alone. The psychological, societal, and environmental components of health and disease are emphasized by several of the commentators, setting the stage for further debate and constructive suggestions.

Keywords
Medical informatics, biomedical informatics, health informatics, interdisciplinarity

Methods Inf Med 2008; 47: 296–317

With these comments on the paper "Informatics and Medicine: From Molecules to Populations", written by Prof. Klaus Kuhn and others [1], *Methods of Information in Medicine* wants to stimulate an urgently needed broad discussion for further interdisciplinary research and education of informatics and medicine, and beyond. An international group of experts in biomedical and health informatics and related disciplines have been invited by the editor of *Methods* to comment on this paper. Each of the invited commentaries forms one section of this paper.

1. Informatics for the "Networked" Generation (by Russ B. Altman)

The paper by Kuhn et al. [1] offers an exciting and comprehensive vision of how informatics can be a unifying force for integrative research in biology and medicine. They make a convincing case that the physical spectrum from atoms and molecules to populations and global health has a parallel "informatics spectrum" from bioinformatics to public health informatics. What can be added to their comprehensive and convincing analysis? I would like to stress one important emerging phenomenon: the empowered, independent, and thoroughly "networked" consumer.

Modern youth have access to technology that arguably makes their intellectual, social and economic development radically different from not only their parents, but from any generation of humans that have yet lived. Young adults have grown up in a world with routine access to information around the globe via the internet (news sites, blogs, wikis, chat rooms, social networking sites, and more). They have and expect rapid access to volumes of information that could hardly be imagined 25 years ago. They manage this information with novel strategies that emerge by necessity: some use fairly static trusted sources (in the form of blog sites, wikipedia or even traditional news agencies) to aggregate information and distill it to something more consumable. Others have increased their communication bandwidth through apparently constant, uninterrupted use of e-mail, instant messaging, and text messaging to create multiplexed conversations that allow them to "sense" their environment and make decisions about how to respond. Of course, most use combinations of these strategies. The revolutionary nature of these changes is clear to anyone who speaks to a young person: "Why do we even have libraries? What are newspapers for? Why would I use e-mail when I can 'text'? Why should I pay for music?"

What does this have to do with biology and medicine? I think we are already seeing changes in the fabrics of both disciplines that we can attribute to these trends. In science, there is great interest among young scientists in open access publications, open source software, and open data sharing. The traditional silos that provided protection and controlled access to information are not acceptable anymore. This creates not only major social and economic challenges (which I will not address here), but creates fascinating informatics research problems. Indeed, the availability of all these data sources creates a market for innovative informatics tools that can connect people to the information they want, when they want it, and in the (integrated) form they want it in. Research about how these tools should work will transcend any division between bioinformatics, engineering informatics, eHealth and public health informatics, because the best tools are likely to be general purpose.

In medicine, the effects of this transition are likely to have an even larger impact. Health care consumers are increasingly rejecting a model of parentalistic healthcare, where the physician is a parent-figure who makes independent decisions based on access to specialized information and as a proxy decision-maker for the patient. Consumers now have access to massive amounts of information on the web, and access to other consumers with similar health issues, and a willingness to share their experiences, treatments, and opinions. Even access to tests of potential medical relevance, such as large-scale genotyping of an individual's genome, is now available "direct to consumer" along with web resources to assist in the interpretation. The implications of all these activities for the informatics research agenda are tremendous: How can we support decision-making by healthcare consumers in partnership with their physician, as well as in partnership with their social network? How can we help them best use the network of health information and health providers to manage their health? How can we create methods for helping consumers gauge the credibility of an information source, and integrate information sources dynamically for a given health-related query? Finally, how can we ensure that the overall outcome of this new health-information economy is improved health?

One approach to these challenges may be to radically reconsider the structure of how we train scientists and medical students, and how we model the interaction between physicians and patients. In both cases, I think that the principles of informatics can be the actual basis of the "curriculum". We should acknowledge to young researchers and physicians-in-training that there is too much knowledge for them to master in their brains, and so we will present a framework for knowledge and information use that stresses how to gather, organize and use information in their professional life, with much less stress on large amounts of content. Through problem-based learning, and research projects, they will get experience collecting and using detailed information to solve problems, but the curriculum will be entirely about collecting and managing information for the purposes of research and providing healthcare.

For patients, we should acknowledge that health-related information is overwhelming, and their physician is a collaborator who will help them navigate through this information, formulate questions and potential actions, and help them make decisions about how to proceed. The primary physician will be a "general contractor" for health information, who will work with the patient to find "subcontractors" that can provide specialized services and information that the patient needs.

In summary, current trends indicate that an information-processing metaphor for scientists, healthcare providers and patients is a more realistic model as we move forward. If this is true, the research opportunities for bringing it to reality are extremely exciting.

2. Let´s Merge Coffeerooms (by Rudi Balling)

My first reaction to the article by Klaus A. Kuhn and his colleagues was asking myself, whether the first author was related to Thomas S. Kuhn, the author of the famous book "The Structure of Scientific Revolutions", published in 1962. In this book T. Kuhn describes the development of new paradigms in the course of the history of science stating: "*Conversions will occur a few at a time until, after the last holdouts have died, the whole profession will again be practicing under a single, but now a different, paradigm*" (p 151).

I think there is no doubt that we are currently in the midst of a scientific revolution. The question is which one: The revolution triggered by the progress in information and communication technology, where we have developments such as the Turing-machine, the invention of the transistor, integrated circuits and the computer? Or the revolution in genetics and genomics providing completely new insights into the complexity, emergence and regulation of biological systems?

The article by K. A. Kuhn et al. "Informatics and Medicine" reminds us that we are already at the next phase, which is characterized by the merger of these two fields and how they influence each other. The authors provide an impressive description of the "application space" of these new technologies and one wonders if their outline of the convergence of informatics and medicine is already an indicator of a 6th "Kondratieff-cycle".

Being excited and enthusiastic about the scientific and economic potential, or skeptic and reflective about the social and ethical risks involved is one side of the story. Equally interesting is the question of how we, as a scientific community, cope with the challenges of interdisciplinary research. Kuhn et al. argue for a strengthening of interdisciplinary collaboration and education.

It is much easier to talk about interdisciplinarity than to practice it. There is no doubt that, quoting Leland H. Hartwell [3]: "The next generation of students should learn how to look for amplifiers and logic circuits, as well as to describe and look for molecules and genes." But how do we teach the ability to work in an interdisciplinary environment? How should future curricula for biology and informatics look like? "Depth or breadths?"

Kuhn et al. describe the cultural gap between classical natural sciences (e.g. chemistry, biology, physics) and engineering and informatics. I spent some time during the last years in talking to engineers, physicists, mathematicians and computer science/informatics professionals trying to entice them for joint research programs tackling the complexity of biological systems. I had to learn that many of these colleagues were as scared of biology as biologists are often scared of mathematics. Nevertheless, the interest and the excitement to bridge the gap of disciplines and go beyond one's own "domestic culture" was enourmous.

It is not so long ago, that mathematicians, computer scientists and physicists were looked down upon by their colleagues if they devoted their research to biological problems. Apparently they didn't make it in their own hard and stringent discipline. This has changed. The grand challenges of the future have been recognized to lie, not exclusively but increasingly, in understanding the complexities of biological systems. And this is recognized by the best and the brightest in these "hard and stringent" disciplines.

My suggestion is to put the emphasis on our ability to talk with each other across the various disciplines. Talking to each other requires either the same language or at least some basic knowledge in the foreign language. Mathematics is THE language if we want to tackle the issue of predicting how biological systems will behave in case they are perturbed. Information science and technology could not exist witout mathematics at the heart of it.

I am not sure whether I agree with the suggestion made by Kuhn et al. that "… 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". I fully support their proposal to set up coordinated and combined courses and research training for advanced students in medicine, science and engineering/informatics. I am also a great fan defining joint research projects and workshops, to foster links at the institutional and personal level and to encourage team-work at a high scientific level.

I am worried that all of this will come will come too late. We need to start much earlier. There are a lot of complaints from our colleagues teaching first year biology about a declining level of the students profiency (and interest) in mathematics. At least in German highschools one can observe a dramatic degradation in the importance given to mathematics, physics and biology. Parents are more worried about getting their children through highschool at all, opening the doors to soft(er) disciplines and a lack of appreciation for a solid education in natural sciences.

Unfortunately this trend is amplified by many of our leading politicians. We are heading for a disaster, and our political leadership still braggs about how little they understand about mathematics and genetics. The waters might be muddy and the logic might be fuzzy, but the message is clear: Informatics and medicine will converge. Kuhn et al. give us a valuable orientation on how to structure the bewildering heterogeneity and opportunities of cooperation of these fields. As a first step I suggest to merge the coffeerooms for our students and faculties. Then all the rest will follow.

3. Towards Biomedical Informatics as a Scientific Field (by James F. Brinkley)

This paper by Kuhn et al. [1] is the result of a set of meetings among leaders of two universities in Munich, the goal being to implement an interdisciplinary graduate school in biomedical informatics. Members of the group, who are the authors of this paper, are generally the leaders of biomedical, technical and management departments at the two universities. Specific fields represented include medical informatics, bioinformatics and systems biology, robotics, computer architecture, software engineering, databases, algorithms, augmented reality, nuclear medicine, molecular biology, cardiovascular surgery, genetics, radiology, internal medicine, dermatology, orthopedics, biometry, and epidemiology. The particular list of fields is relevant because much of the paper can be seen as an attempt to discover and classify the common biomedical informatics activities already ongoing in these separate disciplines. In fact the recognition of this commonality, along with the increasing relevance of informatics to biomedicine, is undoubtedly the major impetus for the creation of the interdisciplinary graduate school. Such an endeavor is truly visionary, going far beyond most academic biomedical informatics programs, many of which are struggling to achieve departmental status, let alone the status of an entire graduate school. Yet the shear breadth of activities described in the paper makes it clear that there are enough biomedical research problems to justify the creation of an entire graduate school, so it is likely that this effort will not be the last of its kind.

In order to create a graduate school the many activities need to be organized into separate but overlapping units. In the US such units would be called departments. Thus, the four classifications in the paper suggest separate departments of bioinformatics and systems biology, bioengineering informatics, health informatics and eHealth, and public health informatics. This classification is similar to one that we use in our University of Washington (UW) Biomedical and Health Informatics graduate program (BHI): biology informatics, clinical informatics, and public health informatics. We never considered including bioengineering informatics in our program because the UW already has a very strong bioengineering department, many members of which are involved in some aspect of computing. On the other hand we do collaborate with faculty in bioengineering, bringing expertise in information and knowledge management, which the bioengineering faculty are generally not experts in. Thus, a case could certainly be made for including bioengineering informatics, especially if there is not already a separate bioengineering department.

One difference in terminology appears to come from the use of the term "bioinformatics". In the paper it is stated that "the goal of bioinformatics is to understand the molecular mechanisms, their genetic framework for diseases and their responsiveness to therapy…", yet many of the research problems described in section 3.1 involve correlating genotype with phenotype, which often means dealing with information at all structural levels ranging from genes to the whole organism. Although it is true that the common understanding of bioinformatics is that it deals with the molecular level, the need to correlate genotype with phenotype has led many researchers to move beyond the molecular level. With the completion of the various genome projects this migration will only become more prominent, and in fact several groups have attempted to extend the definition of bioinformatics to include all of basic biology, thereby automatically including such fields as physiological simulation and systems biology (which many would argue are the same thing). One reason we chose not to use the term "bioinformatics" in our program is to avoid this ambiguity.

A second difference in terminology is in the use of the word "informatics". In the introduction it is stated that the European use of this word corresponds more or less to the term "computer science" in English speaking countries. Yet the many research problems described in the paper go beyond what is generally taught in most US computer science departments, including activities like imaging, signal processing and computational modeling, which are generally taught in electrical engineering or bioengineering departments. Thus, the impression is that the use of the term "informatics" in the title of the paper implies all these activities applied to biomedicine. Such a broad definition is appealing because it helps to unify many activities under one umbrella – although such a unification would not occur in the US given our more narrow definition of computer science.

Given the broad definition of informatics as defined in the paper, it might be useful to list the informatics research issues that are described under the four categories. These issues include but are not limited to: signal and image processing, simulation and modeling, data and knowledge representation, data management and integration, visualization, information retrieval, and sociotechnical issues. As noted several times in the paper these informatics issues occur in many if not all of the four fields described in the paper, which is where the commonality of these fields is seen to lie. Thus, in some ways figure 2 is misleading: in fact arrows should be drawn between each box on the left side and every box on the right side, not just those on the same level.

This commonality leads to the notion that there is a core set of informatics methodologies that underlies all four of the areas. Thus, in the BMI program we would call the areas in the paper *application domains* (which in our case are basic biology, clinical medicine and public health), and we define core informatics domains as those areas that underlie biomedical informatics research in all the application domains. These areas are generally drawn from and include pre-requisites from underlying disciplines such as computer science or electrical engineering, but the courses that teach them are tailored to the biomedical domain. Thus, as the new graduate school is developed it might be worthwhile considering the addition of a unit that could teach these core informatics areas. Such a unit would formalize the commonality that is already evident in the descriptions seen in the paper, and would help transform the field of biomedical informatics from a collection of loosely connected application areas to a scientific or engineering field in its own right, with its own core principles and methodology distinct from any other field.

4. Systems Informatics and the Socio-technology of Bioscience (by Enrico Coiera)

The agenda of informatics researchers almost inevitably returns to technology, and for good reason. Information and communication systems are transforming our world in a powerful way. We would not be able to anticipate climate change without highly sophisticated computational models to alert us to its risks. We would not be able to more robustly deal with international financial shocks than we did in past centuries without the web of economic data shared by central banks globally. And we would not be able to anticipate the now palpable revolutions in systems biology and genome science that foreshadow truly personalised medicine, without IT. The human genome project after all, in the end hinged on computers to pull together shot-gunned genetic fragments into a plausible pastiche of a whole genome.

The technological challenge in bringing together systems biology and clinical medicine, what we now seem to be calling translational bioinformatics [4], is huge. This union "from cell to system" has been long anticipated, and Blois back in the 1980s already then wrote of the nature of 'vertical reasoning' that takes place in clinical decisions, from low-level biology through to clinical and organisational levels [5]. Kuhn and his colleagues paint us a broad and exciting picture of many of the information technology challenges that we face in that journey [1]. Not least of these is the huge representational and inferential challenges of build knowledge structures at different scales and expecting them all to effectively interact and generate meaningful information [6]. They also note in passing that humans themselves are part of the big picture, and that there are cultural barriers to be breached if we are to bring bioscientists and clinicians together.

I have said in the past that health informatics is "the study of how clinical knowledge is created, shaped, shared and applied. Ultimately, it is the study of how we organise ourselves to create and run healthcare organisation" [7]. In other words, we cannot separate the cognitive and the social from the technical, and this lesson is as true of the challenges for e-health at the clinical level as it will be for translational bioinformatics. Indeed, if we are to imagine an informatics which is all about integrating different biomedical, clinical and organisational systems – let us call it a systems informatics – then I want to argue again that we must put ourselves into the middle of that system as primary actors whose behaviour needs to be modelled, along with molecules and medicines.

At present the cross-systems informatics research agenda is driven largely by the technical challenges of information integration, and an analysis based upon an assumption about the way scientists "do things around here". In many ways the bioscience informatics agenda is where clinical informatics was in the eighties, where we used idealised models of what work should be, and were blind to how things actually were. The last 20 years have seen a growing sociotechnical critique, for example from influential commentators like Berg [8], who began to highlight how often seemingly well-designed IT failed when it was finally put into the clinical workplace, because it's designers fundamentally misunderstood how clinical work was done. The mantra of 're-engineering' clinical work for efficiency, and of clinicians and not technologists needing to change their attitudes was the initial informatics response to this clinical push-back.

But we now know a little better. Clinicians usually resist change for very good reasons – we still build systems that help administrators more than clinicians. We still build electronic record systems that on the face of it take longer to use than pen and paper, even if there is a big downstream payoff in safety, quality and efficiency. And we build systems that still ignore the fundamentally complex nature of healthcare. Clinical work is not like work in a factory, is not like a pilot's cockpit nor like a bank, and many of the models of workflow automation that work so well in other settings ill-fit clinical practice, which is fluid, multitasking, interrupt-driven [9], complex, and where treatment is often necessarily bespoke because of patient differences.

We should therefore already intuitively understand that bioscientists do more than analyse complex data sets. Before the experiment, before the analysis, there is a complex social process, in some way similar to the processes that clinicians undertake before a treatment plan is agreed upon. And once an analysis is done, its meaning is debated and shaped socially, because of the inherent ambiguity and incompleteness of our knowledge, and the various perspectives scientists bring to such discussions. For example, co-expression of cellular proteins does not strictly imply co-regulation or a causal relationship in biochemical processes. Scientists employ additional background knowledge to make assessments about the weight of evidence behind known relationships, or the likely causal relations that might be implied through associational studies. Whose background knowledge triumphs in a research team's debate is still no doubt often a tribal affair.

Latour has written vividly about such social aspects of science [10] and our new challenge is to embrace a richer sociotechnical agenda so that we can craft systems that truly link bench to bedside [11]. The 'secret' work that gives rise to bioscience data and its interpretation is something we really need to understand, because what bioscientists do today, clinicians will do tomorrow. The clinicians of the near future will be awash with genetic and biomarker data from their patients, and they will often have little concrete information to guide them to what they all really mean. As ever, we have much more data than we have knowledge about what those data might mean.

Socio-technical systems science has arisen in response to the challenges of understanding complex technical systems that are embedded in a human world [12]. It has arisen most strongly because the unexpected interactions between humans and artefacts often produce unanticipated errors, system failures, cost overruns and breakdowns. The socio-technical view attempts to understand the contribution of phenomena at the human social level to the performance of technical systems, and vice versa. It is thus the missing system in any bold re-conceptualisation of our field as a systems informatics. What is therefore needed is a way of describing events at the socio-technical level, connecting them to system behaviours and thence to artefact design. We need to get 'technical' about what we mean when we describe socio-technical events, 'technical' about what we want from system design, and we need to work both alongside technologists to shape technology, as well as with the processes, organizations and cultures within which they will be embedded [13].

Socio-technical systems thinking is an essential prerequisite to the process of developing new, safer and more effective ICT systems that span different social systems like bioscience, clinical medicine and the citizen. Each is its own universe, and technology will not 'normalise' these universes into one. Instead it must help bridge these universes, which are ever evolving, ever different, ever new.

5. Enhancing the "Human Factor" into the Framework (by Fabrizio Consorti)

Multidisciplinary integration at research and educational level is surely the right way to proceed and face the relevant challenges that the inner complexity of healthcare domain put forward, especially when the management of information is concerned. The paper of Klaus Kuhn and co-workers [1] represents a powerful effort toward a comprehensive framework for an inter-professional curriculum in health informatics. Nevertheless, to the taste of a physician – like I am – an essential ingredient is still scarce in the recipe, in its dual flavor of "caregiver" and "patient": the human factor.

In the paper, social sciences are quoted in conjunction with economics, ethics or with passive concepts like "acceptance" or "impact", along with functional expressions as "time-saving" or "cost-saving". Moreover, topics like the Internet or the web, intended as social environments, are never explicitly mentioned. Maybe these remarks come just from a wrong feeling, based on a misunderstanding of the sense of some sentences, but all the same it's a worth discussing the dimensions of the "human factor" in deeper details.

Multi-professionalism is not just a matter of exchange of competencies but mainly an encounter of professional paradigms, aimed at the definition of a common meta-paradigm, bridging cultural gaps. Mutual awareness of the different points of view is as important as the acknowledgment of the different, specific technical competencies. Then my contribution to the discussion will bring an up-to-date clinical point of view, by briefly summarizing the role of the web-based social cooperative environments in the evolution of current "master narratives" related to the healthcare domain. Concepts like wellness and illness, process of care, patient-caregiver relationship are changing in their social representation and ICT is a factor of the process. This trend will be framed in the context of the two conflicting paradigms of evidence-based medicine (EBM) and narrative-based medicine (NBM).

Narrative has always been the main way to communicate knowledge about facts in the world. Even scientific knowledge needs the support of narrative to be communicated: a scientific paper is the "story" of an experiment, even if it is expressed in a rather formalized structure. More specifically, narrative knowledge is focused about understanding the situation of a singular person through cognitive, symbolic and affective means. A master narrative (or meta-narrative) "is a global or totalizing cultural narrative schema which orders and explains knowledge and experience" [14]. It acts as an organizing principle which provides sense to every-day experience and synthesizes shared ideas in an archetypical way. Examples of master narratives are myths and popular tales, the narration of national historical events, masterpieces of literature. Personal identities too are narratively constituted [15], as complex networks made by self-narration and by the stories told by others about ourselves. In this context, identity is then a social construct and every mean affecting in some way socially shared narratives has a relevant consequence for everyone [16]. Technological innovations such as the Internet have increased the interconnectedness of groups. The web has contributed to the erosion of traditional community life by decreasing the importance of proximal, local sites of social influence with respect to the global community [17]. Basic concepts like health, illness and risk conditions are evolving in their meaning [18] and the evolution is strongly influenced not only by the great availability of healthcare-related information on the web but also by social environments like virtual communities [19, 20]. As a matter of fact, the largest part of knowledge present on the web – in forums and blogs – has a narrative format.

The term "narrative based medicine" was born by the end of nineties, in a series of papers on the British Medical Journal [21], based on an original book by Katrin Hunter [22]. NBM is a novel approach to medical practice, as a reaction to a technology-driven practice lacking empathy. It has been often opposed to the other raising professional paradigm of the evidence-based medicine (EBM), even if the competition has in fact no foundation, because NBM and EBM simply define two different, paired dimensions of medical knowledge.

However, since its more known definition by Sackett in 1996 [23] as "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients, integrating individual clinical expertise with the best available external clinical evidence" EBM produced an uninterrupted flow of discussion, which reveals how sensitive is the topic of representing medical knowledge among physicians.

EBM as intended nowadays would be virtually impossible without the availability of digital libraries. This last point, together with the diffusion of systems for at-distance learning based on a constructivist approach, highlights the importance of considering the ongoing shift from a static representation of knowledge as a "content" (accurate and universal representation of some prior reality) to a concept of knowledge as an enactment of "knowing" in a given context [24]. Focusing on the contextualized act of knowledge rather than on the content in fact strongly reduces the difference between "knowing" and "learning" and it blurs the boundaries between knowledge management systems and e-learning systems [25, 26].

Which consequences for research and education can we drive from all of these considerations?

1) There should be an explicit involvement of anthropology, sociology, social psychology and education sciences in the blend of multi-professionalism, for an effective curriculum and a creative research environment.
2) Attention should be devoted not only to technologic development (technology in itself is not inherently empowering) and to quantitative research aimed to maximize/minimize a parameter but also to qualitative research, aimed to "knowing", also in terms of personal commitment of the intended users of ICT systems.
3) From an educational point of view, a systemic approach should be adopted, always keeping in mind the whole while discussing the detail and highlighting the links and the relationships among dimensions and contexts.
4) A particular attention should be devoted to emerging topics for research and education like the management of narrative knowledge, also in considering that in a few years the generation of "digital natives" will be adult and will have an active role in society. For them, booking an appointment or accessing personal health data by the Internet will be just a routinary task, while probably they will be demanding for much more sophisticated possibilities of interaction.

6. Informatics and Medicine from a Developing World Perspective (by Ali Dhansay)

When I was invited to write a commentary on the paper by Kuhn et al. [1], I was uncertain since I saw myself as being 'informatics naïve'. On the other hand, I thought I could bring to the discussion a multidisciplinary medical background (pediatrics and child health with research experience in the same fields), as well as nutrition research and research management experience at a senior level in a developing country setting – South Africa. Some might argue, justifiably to my mind, that SA is a 'hybrid' of a developing (major part) and developed country, which lends itself to novel research opportunities and challenges. I consider the invitation as a learning (for myself in the area of informatics) and a sharing opportunity (from a South African, research and medical perspective).

6.1 Introduction

"*Knowledge of what is, does not directly open the door to what should be.*"– Albert Einstein

The above quote, in effect, exhorts one to move towards action, i.e. translating knowledge into outcomes beneficial for the health and well-being of populations [27, 28]. It captures the essence of what Kuhn and colleagues from two Munich universities and the Munich Heimholz Center have achieved, with the establishment of a 'research-oriented interdisciplinary Graduate School'. Their paper neatly captures the 'knowledge of what is', as well as the 'what should be' parts of the above quote. They have moved from theory to practice in a sense and should be commended for this. The bottom line, of course, will be the evaluation of whether the graduate school reached its intended goals – a keenly awaited result in light of the dearth of documentation of such experiences [29].

6.2 Interdisciplinary Research (IDR)

A definition of IDR is appropriate at this time: "Interdisciplinary research is a mode of research by teams or individuals that integrates information, data, techniques, tools, perspectives, concepts, and/or theories from two or more disciplines or bodies of specialized knowledge to advance fundamental understanding or to solve problems whose solutions are beyond the scope of a single discipline or area of research practice" [30].

"*It took an ex-physicist – Francis Crick – and a former ornithology student – James Watson – to crack the secret of life. They shared certain wanderlust, an indifference to boundaries.*"– Robert Wright

It is refreshing to see that informatics researchers are looking at concrete ways of contributing, nay, being part of the current movement towards translating knowledge to practice. The paper reflects, on one hand, the universal call for employing interdisciplinary research to tackle the complex nature of disease and ill health in today's globalized society, and on the other, seeks to specifically establish the role of informatics and its disciplines as part of this important challenge. There is no doubting the role of ID health research [30-35]. ID health research is based upon the recognition of diversity/differences, yet agreeing upon the ultimate objective of a unitary outcome, viz. improvement of health and well-being for individuals and populations. Interdisciplinary thinking is rapidly becoming an integral feature of research as a result of four powerful "drivers" [30]:

1) the inherent complexity of nature and society;
2) the desire to explore problems and questions that are not confined to a single discipline;
3) the need to solve societal problems;
4) the power of new technologies.

It is encouraging to note that Kuhn and colleagues have moved beyond the bedside, to the community and population level. The keywords that stand out in the paper are collaborative research and structured interdisciplinary education. While somewhat 'lost' within figure 1 and not repeated again in the text, the critical phrase 'Informatics in Support of Translational Research' captures the essence of their paper.

Kuhn et al. have also traversed the intersection of bioinformatics and medical informatics (biomedical informatics) [36-39] and cogently address the issues of public health informatics and public health, with prevention as an ultimate target. They present a practical framework of how informatics can act as driver/enabler/interlocker in the continuum from molecules to population via the fields of biosciences, medicine and public health. The authors call for collaborative research and structured interdisciplinary education in four priority areas: bioinformatics and systems biology; informatics for biomedical engineering; health informatics and e-Health; and public health informatics and public health.

6.3 The Challenges of IDR

When setting up their graduate school, one accepts that the authors would have taken into account the comments of the National Academy of Sciences [30] and others [40-43] regarding IDR, viz. (not in order of importance)

- need for structures to support interdisciplinary research;
- job opportunities for IDR;
- evaluation of IDR and scientists and outputs will need modification of the peer-review process to include researchers with interdisciplinary expertise in addition to researchers with expertise in the relevant disciplines;
- funders' views on IDR and its support;
- role of professional and academic societies;
- shortage of health workers and scientists/researchers in developing countries;
- the success of IDR groups depends on institutional commitment and leadership;
- promotion, tenure, and resource allocation;
- institutions are impeded by traditions and policies that govern hiring practices;
- the success of IDR groups depends on institutional commitment and research leadership;
- new modes of organization and a modified reward structure to facilitate interdisciplinary interactions;
- professional societies have the opportunity to facilitate IDR by producing state-of-the-art reports on recent research developments and on curriculum, assessment, and accreditation methods; enhancing personal interactions; building partnerships among societies; publishing interdisciplinary journals [44] and special editions of disciplinary journals and promoting mutual understanding of disciplinary methods, languages, and cultures;
- learning from collaborative interdisciplinary research partnerships among universities, industry, and government.

The above points immediately present a bigger challenge to researchers in developing countries, faced with problems of rudimentary health systems, poor infrastructure and human resources for health, and low spending on research and development. Table 1 and Figure 1 below illustrate the situation well.

6.4 IDR Leading to Translational Research

While the lack of funding, health infrastructure and resources can be seen as added impediments to IDR in developing countries, this makes it even more important to 'work smartly' in multidisciplinary and interdisciplinary collaborations than ever. Similarly, the need to fast track knowledge translation in these countries is just as urgent – interventions which are cost-effective need to be implemented. In this regard, the framework for the integration of informatics with health as presented by Kuhn et al. needs to be tested and implemented in developing country settings as a matter of urgency.

6.5 Context Is Important

While there are many similarities in health challenges facing developing countries compared to developed countries (e.g. health and nutrition transition to 'diseases of lifestyle'), there are also major differences, e.g. the massive burden of HIV and AIDS, tuberculosis and malaria in Africa. Health information systems are not efficient, impacting on resource allocation and evaluations of the health system. Developing countries including South Africa are experiencing severe shortages of health care personnel in the public sector to Europe and North America, as well as to the WHO! Poverty and inequity (in general and in health) are inexorably linked, and this is reflected in the not unexpected differentials in morbidity and mortality found in South Africa (skewed unfavorably towards blacks). Inequality and inequity at all levels and sectors present many challenges to the goal of improving the health of nations [45].

In South Africa, 93% of the majority black African population (80% of SA population) has no medical aid (insurance) and is dependent on the public health sector, while 58% of the minority white population (9% of SA population) has no private medical cover. These differences in health care financing are important in the context of funding of 'high tech' innovations. A recent survey of the role of genomics medicine in developing country contexts, which included South Africa, argues that there is a role for investing in genomic sciences in developing countries. They posit that investing in the field, identifying niche areas within it and within areas of local interest, and building life sciences-based capacity around such knowledge could contribute to improving local health, as well as potentially stimulating economic development. The role of private partnerships in this regard is also highlighted [46]

The area of personalized medicine was also mentioned by Kuhn et al. in the context of public health and genomics. Again, in the South African context, issues such as race and ethnicity and the medicalization of race are issues that numerically and ethically assume much greater importance than the BiDil debate in the USA [47]. These are fertile areas of potential research for interdisciplinary teams, including informaticians.

6.6 What Are the Implications of the Paper for Developing Countries?

1) There is a need to embrace the call for interdisciplinary research and education, and to highlight the role of informatics as an enabler in the whole process from bench to bedside to the community.
2) Collaboration with developing countries on an equal footing should be encouraged.
3) Realization that there are context-specific issues that have to be considered, e.g. local technological, funding, population dynamics. Recognition of diversity and differences.
4) Foster debate around ethics (of genomic medicine and personalized medicine), information access, education and social issues in developing country settings.
5) Personalized medicine also raises the question of identification of patients who are most likely to benefit.
6) Ensure partnerships with, for example private sector are conducted ethically and openly for the benefit of public health.

Table 1 Researchers and GERD in developing and developed countries

	World population	World researchers	World GDP	World GERD
Developing countries	79%	28%	42%	20%
Developed countries	21%	72%	58%	80%

GERD = gross expenditure on research and development

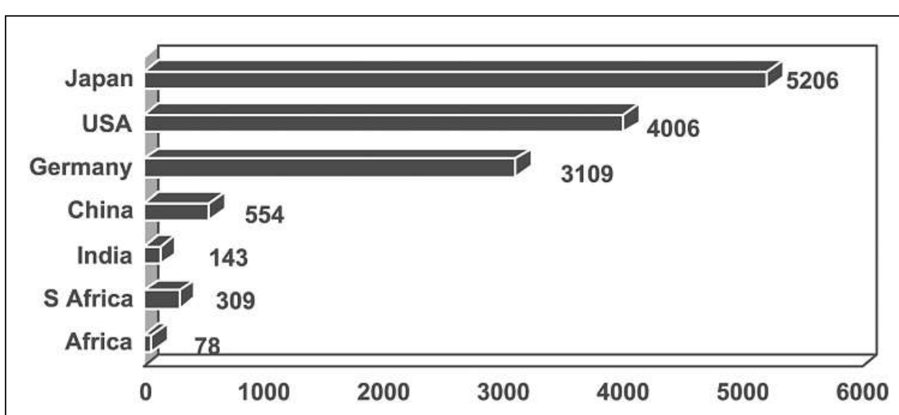

Fig. 1 Researchers per million inhabitants – year 2000 (source: National Research Foundation, South Africa)

6.7 Conclusion

One trusts that new synergies will be forged between the various disciplines, e.g. medical informatics and bioinformatics, based on the promise outlined in the paper by Kuhn et al. To quote the present director of the National Institutes of Health, Dr. E. A. Zerhouni: "It is the responsibility of all of us who are involved in health research to translate the remarkable scientific achievements/innovations we are witnessing into health gains for the nation" [28]. Of course, this should be extended to the global community, and especially the developing nations with their greater burden of disease.

The authors have taken a bold step in establishing the Graduate School in Munich – in effect demonstrating the move from theory to practice. To my mind, there is a dearth of information on such initiatives; little has been documented about how researchers experience interdisciplinary health research in practice. Furthermore, factors such as career path opportunities, reward and recognition, evaluation criteria, long-term future etc. are all important. It is therefore imperative that they document and share their experiences, which will be keenly awaited by the scientific, academic, medical, and informatics fraternity.

Both the medical and informatics communities need to extend the discourse initiated by Kuhn et al. to the challenges posed by developing country settings. It is only proper that those areas of the world most beset by ill health should be part of the move towards working smartly and in an interdisciplinary fashion. South Africa has the unenviable reputation of being the world leader in many disease areas such as HIV and AIDS, tuberculosis and fetal alcohol syndrome. With its diversity of populations (exemplified by its rainbow nation tag) and in burden of disease patterns, the country lends itself to opportunities for collaborative research on informatics and health between north and south [48, 49].

7. On Global Trends and Challenges (by Antoine Geissbuhler)

Enabling information and knowledge to flow and grow from molecular scale to patients and populations is one of our ambitious goals and grand challenges. This "info-bio convergence" has an enormous potential to improve our fundamental knowledge in life sciences, the ability to translate it into better and individualized patient care, and will open new ways of studying and steering our pressured health and healthcare systems. Further down the road, many foresee the additional convergence with nanotechnologies and cognitive sciences, thus realizing an unprecedented synergy of skills and knowledge [50].

Although the way seems clear and the future bright, there are many obstacles that need to be overcome, many of which lie partly within the scope of biomedical informatics, and most of which will require new forms of collaboration, of research, and probably of education.

We must be able to connect information from these various knowledge domains. Connectivity of the infrastructure from multiple, heterogeneous, and distributed resources is likely to evolve from the current data and computational grids. Connecting the physical and the information world will require new abilities to identify, track, and link objects from both worlds. But the main connection challenge will be the semantic integration of these mostly distinct domains, as exemplified by the IUPS Physiome Project [51].

With the advent of our knowledge society, we need to rethink the way we design research. Digging in the massive amount of data that is made available on the Web, will need new research paradigms, potentially moving away from hypothesis-driven research (whether in vivo, in vitro or in silico) into data-driven research [52]. At the same time, citizens of our knowledge society will have the opportunity to reshape the way their information can be used for research, potentially displacing the centers of knowledge production away from the academic environments [53]. Furthermore, the new interactions between humans and machines that are currently appearing will require new research disciplines, such as the Web science, coined by the Web inventor, Tim Berners-Lee [54].

In this interconnected, highly complex landscape, multidisciplinary collaboration will indeed be the rule for progress. A challenge will be to foster the right mix of hard sciences, life sciences and social sciences necessary to apprehend the problems at hand. The collaborative tools of the social Web will help to some extent, as will the knowledge engineering tools brought by informatics research. It is however likely that the current educational models will not be able to cope with the increased needs for cross-disciplinary skills and will have to be revisited.

Finally, we must realize that the knowledge society is becoming global, bringing new challenges and new opportunities. In order to limit the progress of the digital divide between those who have access to these new tools and those who don't, we will have to learn how to better share knowledge, and make it relevant to multiple contexts, in order to solve real and urgent problems, and in particular those of the health systems. For example, it is likely that biomedical informatics, e-health and telemedicine will enable new solutions for the current healthcare workforce crisis, helping to train, inform and support healthcare professionals and patients in the poorest and most remote parts of the world, where they are most needed [55].

Enthused by these new promises, we should always keep in mind that the overarching goal of our efforts, from fundamental research to the bedside activities, from molecules to populations, is to improve the health and quality of life of the people of the world.

8. From Molecules to Populations Is Only One Dimension of Health and Biomedical Informatics (by William Hersh)

The paper by Kuhn et al. [1] describing the spectrum of health and biomedical informatics provides an excellent elucidation of the subject domains that describe our field. But the subject domain is only one dimension of informatics, and other important dimensions must be described and explored. In my commentary, I will set forth my own view of informatics, health and biomedical informatics, and the dimensions that the field covers.

First, what exactly is informatics? The paper discusses this only briefly, noting but expressing some dissent the European view that informatics is fundamentally computer science. I am glad to see this view changing in Europe and beyond. My view of informatics is that it is fundamentally about information, in particular what humans do with it and how they apply technology to improve its use for improving the human condition. Informatics is an integrative discipline, drawing upon areas such as information and computational sciences, business and management, and other fields, but also deeply rooted in a subject domain. In the field of health and biomedical informatics, the subject domains range from biology to medicine to personal and public health.

All branches of health and biomedical informatics are heterogeneous yet have a common intellectual core. The bioinformatician who analyzes gene expression microarray data may seem to have little in common with the clinical informatician who is trying to reconcile with highly interrupted workflow of clinical care with collecting high-quality information that can be used not only for better patient care, but also to drive decision support systems and quality assessment. Likewise, a consumer health informatician might be focused on helping an individual maintain optimal health, while the public health informatician is likely to be focused on monitoring risk factors for disease in a community.

Yet all of these areas of health and biomedical informatics have common underlying themes. All are focused on the optimal collection and use of information. All would benefit from technology systems that have optimal usability, facilitate collection and use of high-quality data, and aim for interoperability based on the best standards. All require attention to the larger contexts and human organizations in which they are used, whether biomedical research organizations, health care delivery systems, or public health agencies.

The paper by Kuhn et al. acknowledges that all subject domains of biomedical informatics have related areas, whether the statistical methods of bioinformatics, the people and organizational issues of medical informatics, or the social and economic aspects of public health. I would argue that these related areas are not necessarily limited to any particular subject domain. Examples include the application of qualitative methods to bioinformatics [56] and the need to be cognizant of genomics (e.g., single-nucleotide polymorphisms or SNPs) and clinical data quality issues in genome-wide association studies [57].

It is thus imperative for us to move beyond arguing what adjective should precede informatics (e.g., bio-, medical, consumer health, etc.) and instead focus on the core attributes that unite all aspects of informatics and how we apply them in health and biomedical informatics. Our discipline is indeed interdisciplinary, and some of its key attributes reflect that. Informatics is integrative, drawing on computational and information sciences as well as business and management sciences, yet firmly rooted in a deep understanding of the discipline in which it is applied, be it biology, medicine, or health.

Our academic departments must recognize this fundamental undercurrent of all informatics. Our educational programs should teach from this perspective. Not every health and biomedical informatics department or degree program must cover the entire domain perspective, but they should perform their research, teaching, and service from the viewpoint of informatics. Likewise, their educational programs should recognize there is no single career pathway within the field. What an informatician does as a job is a function both of what he or she did before entering training and what knowledge and skills he or she gained from that training.

The 21st century provides exciting opportunities in health and biomedical informatics. Improvements in information technology provide us a growing ability to use information to improve human health at the personal, health care, and public health levels. This will require research and educational programs that acknowledge the core similarities across the subject domains of health and biomedical informatics and train new practitioners and academicians in this point of view.

9. The Value Chain "from Bench to Bedside" (by Yunkap Kwankam)

The paper of Dr. Klaus Kuhn et al. [1] is well documented (researched) and clearly written. It captures the essence of the broad spectrum of issues spanning the continuum from molecular genetics to public health policy. The fact that it elaborates on the quite intuitive value of interdisciplinary research in health informatics, is itself indicative of the imperviousness of the silos into which research has fallen. The reaffirmation is thus very welcome.

And although the consultation on creating the graduate program was local – limited to Germany – the challenges discussed cover a variety of socio-political and economic contexts, and thus the paper is of much broader relevance than to single a typology of health system context.

9.1 Assessment of Health Informatics

The paper mentions the importance of assessment and the dearth of robust methodologies for such assessments. This is the crux of the matter. Methodological improvements in the assessment of informatics are needed to convincingly chart influence pathways from health informatics interventions to health intermediate and final outcomes. This is the key to unlocking funding for the very promising research described and support for the marketing, deployment and use of the fruits of such research. Until the return on investment, or return on value, is demonstrated, the funding levels needed to sustain interdisciplinary efforts will continue to be a challenge and thus an inhibitor to the change in culture within disciplines that the paper calls for.

Funding for public health informatics is in competition with other priorities, and this competition is especially fierce in resource-challenged health systems. Health, as a production function, shows a number of variables, water and sanitation, for example, accounting for nearly 10% of the global burden of disease. A 2008 WHO report estimates the economic benefits of investing in drinking-water and sanitation in several forms: "health-care savings of US$ 7 billion a year for health agencies and US$ 340 million for individuals; 320 million productive days gained each year in the 15- to 59-year age group, an extra 272 million school attendance days a year, and an added 1.5 billion healthy days for children under five years of age, together representing productivity gains of US$ 9.9 billion a year; time savings resulting from more convenient drinking-water and sanitation services, totaling 20 billion working days a year, giving a productivity payback of some US$ 63 billion a year." [58]. The above figures are taken from a study which shows a total payback of US$ 84 billion a year from the US$ 11.3 billion per year investment needed to meet the drinking-water and sanitation target of the Millennium Development Goals [59].

Health informatics would need to show similar, or better benefits, in order to get a fare share of limited budgets.

9.2 Translating Knowledge into Policy and Action

The paper lays heavy emphasis on greater levels of sophistication in research for scientific discovery. However, one could argue that the weakest link in the research continuum from discovery to dissemination and deployment, is perhaps in the latter phases of this chain. Therefore, there needs to be a balance between efforts aimed at discovery and those targeted at the so called "know-do gap" – the gulf between what is known and what is done in policy and practice. Again, interdisciplinary training, which the paper advocates, would strengthen research into "technology enhanced knowledge translation" [60]. The field examines the role that ICT can play in the actions of individuals, as well as systemic factors that militate in favor of successful transformation of available information and knowledge into action. It also looks at what informatics tools need to be devised for capturing and sharing experiential (or tacit) knowledge, which unfortunately is compartmentalized in individuals. Can health informatics networks in support of communities of practice serve as a model for breaking down these silos, so as to promote sharing of available tacit knowledge? Can such networks improve the use of experiential knowledge on a systematic basis within health systems?

ICT can remove distance and time barriers to the flow of information and knowledge for health and help ensure that our collective knowledge is brought to bear effectively on health problems in individual countries, as well as globally. It would require a system where all decision-making in health is supported by an ICT-mediated knowledge-coupling system which builds on Weed's vision [61] as adapted by Kwankam et al. [62] and ensures that: a) all relevant options known to the health sciences are readily available for consideration; b) specific features of the situation at hand that bear on the discrimination among these options are taken into account; c) appropriate associations are made between the specific features of the situation and the many options; and d) the right technology is deployed and local capacity developed to permit access to the information.

9.3 Building on the Collective Wisdom

Several recent meetings have raised the issue of an international registry for informatics research/trials – to provide a repository of research information/experience and the potential to build on successes while learning from the errors of one and all.

The paper's broad scope also covers the role that informatics can play in empowering citizens to contribute to their health. The authors thus encourage one to hope that such thinking also offers an opportunity to focus less on health as the absence of disease, and the attendant emphasis on disease mechanisms, and more on the WHO vision of an ecological balance between the physical, mental and social dimensions of life.

The paper concludes that "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 inter-disciplinarity can develop ...". Such interdisciplinary understanding would greatly facilitate visualizing and understand the big picture. Then the boundary conditions that are necessary for information and knowledge exchange between disciplines, and between sub-disciplines within disciplines, in the value chain that leads from bench to improved health, may be better understood and managed.

10. Envisioning the Future – Informatics and Collaboration (by Nancy Lorenzi)

In Lewis Carroll's classic book, Alice in Wonderland [63], Alice comes to a fork in the road with two paths leading in different directions. Confronted by a Cheshire cat she asks: "Which path should I take." The response from the Cheshire cat is: "Well, that depends on where you want to end up?" Alice said she did not know. The Cheshire cat responds: "If you don't know where you want to go, it doesn't matter which path you take."

Without vision we are both unclear about our direction and at times have conflicting directions. This makes it difficult to formulate plans, objectives, goals, actions, and no way to measure results. Unless we know where we need to go, we cannot create the path to the future

The *Informatics and Medicine: From Molecules to Population* article presents an outstanding overview of the current progress in medicine, bioinformatics and biology informatics, biomedical engineering health informatics and eHealth, and public health, life sciences, public health, life sciences and public health informatics. This article will become an instant cornerstone classic article not only for its overview, but for its challenges and directions. Congratulations to the multiple authors for creating this article that is a world-wide guide.

I titled my commentary "Envisioning the Future – Informatics and Collaboration". The phrase "envisioning the future" characterizes the challenge that we face in achieving the overall picture painted in the vision the *Informatics and Medicine: From Molecules to Population* article creates. The sub-title "Informatics and Collaboration" not only supports that informatics will be "the most important driver and mediator for innovation" as stated in the article, but stresses that we need collaboration to be successful.

One organization that is prepared to support collaboration is the International Medical Informatics Association (IMIA). Three of IMIA's goals include:

- promote informatics in health care and research in health, bio and medical informatics;
- advance and nurture international cooperation;
- further the dissemination and exchange of knowledge, information and technology.

IMIA created a strategic plan (Towards IMIA 2015 [64-67]). Knowledge is the central core of IMIA's strategies, interactions and efforts. The plan next focuses on science, portraying IMIA members' connection and integration with the science and discovery of informatics. The next connection is the application of scientific discoveries, including the multiple questions and issues that are created and disseminated in informatics. This is followed by IMIA's impact, referring to the potential impact that IMIA and its members can have on governments, nations, outcomes, health professionals, and all other stakeholders. The last major focus represents IMIA's interactions with individuals, citizen organizations, personal health involvement, dissemination and acceptance, enabling personal responsibility, and public/personal health.

The second dimension of IMIA's Strategic Plan represents six key sectors that IMIA as an international association is prepared to facilitate or work with others to effectively address. The six sectors are:

1) health improvement;
2) research/science (including how we understand and create evidence to support health);
3) the behavioral responsibility (ethics) that refers to our ethical and social responsibility;
4) education (including best practices in educating ourselves and others);
5) the multiple types of relationships (communications and connections to build relationships among stakeholders); and
6) the equity of IMIA, our obligation to share, distribute and disseminate.

We stand at the crossroads of tomorrow, compelled to address the challenges outlined in the article and impact of our multiple efforts and the visions they enable.

Inherent in IMIA's role is to bring together, from a global perspective, scientists, researchers, users, vendors, developers, consultants and suppliers in an environment of cooperation and sharing to research and develop the concepts needed to support the organizations of the world seeking technology as transformational. Through its many publications (*Methods of Information in Medicine*, *International Journal of Medical Information* and *Yearbook of Medical Informatics*) and electronic communication mechanisms IMIA can be a major disseminator of the knowledge created. As an organization committed to promoting best practice in the use of information and communication technologies within biomedical informatics and in health and healthcare, IMIA will ensure that it uses and promotes best practice in its own use of technology as a transformational strategic asset.

We stand looking at the future portrayed by the *Informatics and Medicine* article. We have a vision. If we work independently toward various isolated goals we will lose the opportunity to work together to create the synergy needed for reaching the desired state. This is an excellent time for international cooperation.

11. Nanomedicine and Regenerative Medicine Pose New Challenges for Biomedical Informatics (by Fernando Martin-Sanchez)

The reading and study of the paper of Kuhn et al. [1] has represented a particularly motivating and scientifically enriching task. After several years of working on aspects related with the analysis and implementation of the synergy between medical informatics and bioinformatics, this document represents the most complete updated review of the research challenges in each of the four areas that are accepted as constituent of biomedical informatics (BMI). Furthermore, these four disciplines are not described independently, instead a thorough analysis of their mutual relations is provided. The analysis of the connections between BMI and biomedical engineering results especially interesting because this is a topic that has given rise to some controversial opinions in the past. The authors provide here a framework that can be very useful to facilitate a reciprocal collaboration between experts in both fields and to define some common ground (such as image processing or modeling and simulation of biological entities and processes).

It is also very valuable the effort made by the authors to provide a model for interdisciplinary education that it is clearly oriented towards facilitating translational research. I fully agree with their claim that the new generation of scientists should have to be exposed to (at least) two of the core disciplines at early stages of education. Furthermore, I believe that the integrative approach that has inspired the authors to design the new Graduate School will become a reference and will be followed by other academic centers.

Indeed, there is no a major criticism to the paper from my side, however, taking into account that several outstanding bioengineers have participated in the work leading to this paper, I believe that it would have been important to raise the issue of nanotechnology and regenerative medicine since they pose new challenges for BMI. It is not my intent to consider these issues in depth in this brief commentary. Rather, I will point out some considerations and let the reader become more informed and interested about these topics, particularly with reference to their complementarity with the paper authors' design of educational programs.

11.1 Nanomedicine and Regenerative Medicine Represent New Trends beyond Genomic Medicine

Although the paper only mentions nanotechnology on one occasion in section 2, nanomedicine and regenerative medicine are recognized to be among the most promising trends in medicine for the future. Nanomedicine is defined as the use of nanoscale tools and components for the diagnosis, prevention and treatment of diseases and for understanding their pathophysiology (European Science Foundation, Nov. 2005). Regenerative medicine seeks to develop functional cell, tissue, and organ substitutes to repair, replace or enhance biological function that has been lost due to congenital abnormalities, injury, disease, or aging (NIH Definition, NIBIB, June 2004).

Interestingly, while genomic medicine is based on the use of molecular information to design new approaches to promote health, and prevent, diagnose, cure and treat disease, nanomedicine and regenerative medicine go beyond that point, in the sense that they can entail an intervention on the biological structure of the human being. It is my belief that these two fields pose new challenges for informatics beyond those addressed under the realm of genomic medicine.

11.2 Impacts of these New Trends that Can Be Envisioned in Every Facet of Healthcare

Nowadays the number of clinical applications of nanotechnology is increasing with research at the nanoscale providing important information prior to clinical application. Just as mentioned above, we are likely to see nanomedicine impacting on areas such as biomedical research, prevention, diagnosis and therapy [68].

- Prevention and diagnosis – All the new advances in nanotechnology are encouraging the scientific community, especially in biomedicine, to use the 'nanoscope' that will allow them to see a new scale of genomic, phenotypic and environmental data to integrate with the information already available. As an example, the next generation of DNA sequencers makes use of beads and other nanotechnologies. Nanosensors and nanodevices will permit to assess the different positive and negative environmental factors that affect an individual's risk to suffer from a disease. New in vitro diagnostic tests and miniaturized imaging systems will provide more sensitive detection methods.
- Therapy – New nanostructures will be used as drugs. Novel methods of drug delivery systems consisting of anti-cancer products bound to nanoparticles such as buckyballs, nanocapsules and dendrimers are already a reality. Imaging techniques will be used to monitor drug release or for patient's follow-up. Stem cells may provide tissue for transplants in the context of degenerative diseases. Finally regenerative medicine will allow the manufacture of new artificial tissues or organs, or the use of nanotubes and nanofibers to build scaffolds where cells from different organs can grow.

Nevertheless, some of the recently developed nanoparticles may have negative side effects. For instance, an article in *Nature Nanotechnology* has recently reported that some forms of carbon nanotubes could be as harmful if inhaled in sufficient quantities [69]. This fact justifies the need of careful data handling in clinical trials in this area.

11.3 Nanoinformatics Could Represent a New Subdiscipline within Biomedical Informatics

Nanotechnology requires the contribution of informatics to process all the knowledge that is being generated at the nano level and to integrate it with the biomedical (phenotypic, genotypic and environmental) data. Nanomedicine gathers and deals with large volumes of complex data, linked with external sources and usually distributed in heterogeneous locations.

Nanoinformatics involves the research and development of effective tools/technologies for collecting, standardizing, sharing, analyzing and visualizing the vast amounts of data and information relevant to the nanoscale science in several areas such as literature, physico-chemical properties, biological and toxicological interactions and clinical effects [70].

Several requirements for BMI come from the need of improved tools for designing, modeling, and visualizing the new nanomaterials and scaffolds for tissue engineering. Also, new databases will have to be designed to store physical, chemical and biological properties of nanotechnology developments. Semantic interoperability will have to be granted not only between nano resources, but also between them and the existing medical terminology and coding systems. Biomedical informatics can support regenerative medicine through the application of tools and information systems to characterize the molecules involved in differentiation mechanisms, including growth factors, hormones, cytokines or integrins.

ACTION-Grid is a new research project funded by the European Commission (2008-2009) on healthcare information systems based on grid capabilities and nano/bio/medical informatics. This project, coordinated by Prof. Maojo from the Universidad Politécnica de Madrid and our own group has as its main objectives to analyze synergies between biomedical informatics and nanoinformatics and to combine these results with data from an inventory of grid/nano/bio/medical methods and services developed by the consortium [71].

11.4 In Conclusion

Nanomedicine and regenerative medicine open new avenues for research in biomedical informatics methods and tools. Just as the advances in "-omics" research brought about the connection of medical informatics with the molecular domain, is BMI ready now for addressing the nano world and expanding its scope down to the atomic level as shown in Figure 2?

None of my views expressed in this commentary should be interpreted as a critic to the paper by Kuhn et al. On the contrary, an educational program such as the one described in the paper by our colleagues from Munich, that is based on interdisciplinarity and with a clear translational vocation, is placed in the best position to face the new challenges related to information processing in medicine, whether they come from the side of nanotechnology or from any other new development that may arise in the future.

In this regard, a new generation of scientists knowledgeable about nanotechnology will be essential to manage this new information and efficiently integrate it with biomedical data from the atomic to the populational level to translate all these findings into better healthcare.

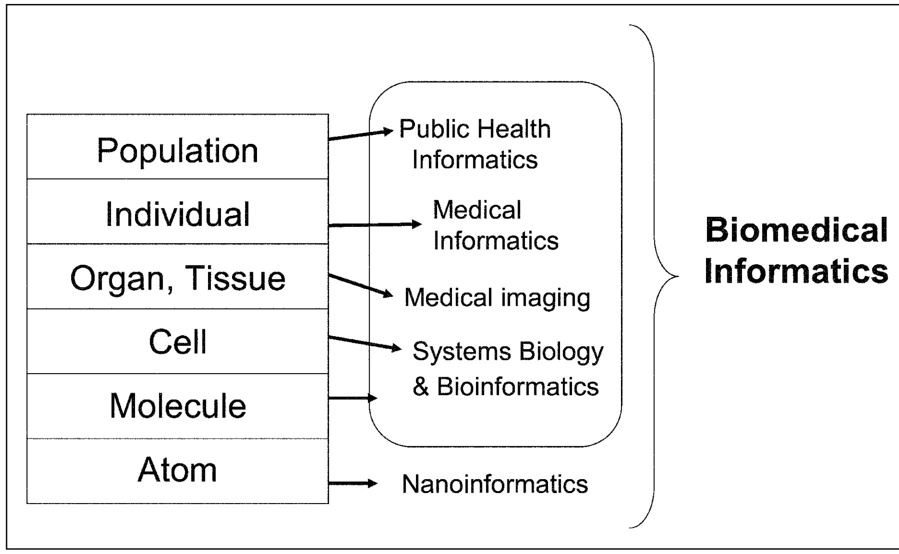

Fig. 2 Information and medicine: from atom to population

12. The Need to Create the Frame for Interdisciplinary Collaboration (by George Mihalas)

Biomedical informatics is today a field with one of the highest rates of development. New techniques or devices, new approach or methods, new applications or solutions are reported every day [1]. Such an avalanche of news needs a systematic work for classifying and stratifying all accumulated data and knowledge. The most natural approach in classification would start from the structural level of the studied system [72]. And this approach has been adopted also by Kuhn and his collaborators [1] who emphasized this view even in the title: "From Molecules to Population". Their excellent paper is fully comprehensive by counting all topics of research, brings some refinement in description and updates the actual trends. It is worth to make here some short comments concerning the research challenges on each level.

12.1 Bio-silico Interfacing

I would start my comments by noting the original approach in the second chapter "The Overall Picture: Where Do We Stand and Where Do We Go", with a detailed list of technical trends in computer science and adjacent domains which will bring a significant impact biomedical informatics. We can add here the interdisciplinary research (biophysics and computer science) on the direct information transfer between biological system and computers [73]. The potential applications are tremendous and still seem close to "science-fiction".

12.2 Neuroinformatics

During the nineties most prospective views about medical informatics research used to consider bioinformatics and neuroinformatics as most promising [74]. The previsions on bioinformatics turned out to be true. However, the chapters on neuroinformatics are now rarely present. The reason might be that the impact of neuroinformatics research would rather be on cognitive sciences than on medical sciences. And the same might be true about "affective computing" [75]. However, applications in neurosciences and psychology, with their "medical" shadows – neurology and psychiatry –, show that the connections to biomedical informatics are strong enough and the integrative view, which has been repeatedly mentioned by the authors, would become even more consistent by including these items too.

12.3 Simulations in System Biology and Virtual Physiological Human

Another welcomed feature in the article is the specific reference and the detailed presentation of "Informatics for Biomedical Engineering", a topic often left on a second place or treated superficially. The research challenges cover, indeed, several directions, requiring various tools. And when we talk about new informatics tools in cell biology we must mention the work of Masaru Tomita and his co-workers [76] on the "virtual cell" – a package for computer simulation of cellular processes, dedicated software developed for this purpose [77]. We can expect that specialized software or even new theoretical models will be developed for each level. On the next structural level we have to mention the Physiome Project, initiated by Peter Hunter [78], followed by the Europhysiome Project, and continued by the Virtual Physiological Human Project of the European Commission [79].

12.4 Integration and the Role of Professional Organizations

Various aspects of integration have been discussed in the paper and there are also several other studies dedicated to integration (refs. 9, 10, 12, 17, 37, 39 of [1]). The emphasis on integration is understandable: the properties of a level are different from a simple sum of the properties of lower component levels! Some recent events organized by the European Federation for Medical Informatics EFMI had topics dedicated to integration of biomedical information [80, 81].

Actually the integrative view supposes a quite complex approach and here it is the origin of the need to create the frame for interdisciplinary collaboration and provide an education which crosses the boundaries – as so well is presented in the paper in chapter 4. I fully share the view of the authors and do consider that biomedical and health informatics professional organizations, like EFMI or IMIA (International Medical Informatics Association) should get involved in creating the appropriate collaborative frame and contribute to educational programs, following the good example of the 10×10 program of the American Medical Informatics Association AMIA (ref. 18 of [1]).

13. The Need for a Human Clinome Project (by Yuval Shahar)

The "Molecules to Populations" paper by Kuhn et al. is a highly commendable effort at a through, in-depth analysis of the need for multidisciplinary collaboration in the 21st century between informatics, as an area of scientific endeavor, and several specific subareas of medicine and biology, as other such areas. I would like to comment on some of its key strengths as well as on several important key challenges to be faced that should be added to its research challenges list.

First, regarding the key strengths and main significance of the paper: I had found both the descriptive insights provided from this analysis, and the specific educational structural recommendations implied by these insights, to be quite invigorating, and potentially highly beneficial. In particular, the authors emphasize that only through experts in one discipline who profoundly understand the conceptual world of another discipline can true multidisciplinary research develop. This emphasis is very important, and is certainly evident to multidisciplinary researchers, but unfortunately is not as obvious to decision makers in education as one would like it to be. One often encounters the view that, for example, having a well trained computer scientist or informatician work with biologists or clinicians is sufficient for bringing about new breakthroughs in bioinformatics or medical informatics; similar views are often held in the case of other disciplines. But, as the authors point out, the various sub-cultures of the disciplines studied by Kuhn et al. have been highly resilient to change or to integration. Only by what the authors term "boundary breaking agents", i.e., personal examples of multidisciplinary researchers that the students meet during their training, can true interdisciplinary understanding and research exist.

A particularly good example out of the several potential interdisciplinary collaborations suggested by the authors, is, in my opinion, the need to strengthen the links among bioengineering and medical informatics. A specific example, not explicitly discussed by the authors but probably on their mind, is the possibility of developing a "smart medical home", which monitors its residents, alerts them or specific care centers when unusual patterns are detected (e.g., an elderly person falls, or seems to have a heart attack). Developing such a smart home requires understanding of both the multiple sophisticated (and possibly quite new) sensors involved, as well as development of intelligent computational methods for analyzing the huge volumes of data emerging from these sensors, and for continuously integrating these data with up-to-date clinical and epidemiological knowledge.

Second, regarding several of the areas I would like to see more strongly emphasized as part of the key research challenges, at least as a part of any interdisciplinary research program that includes as one of its components the area of medical informatics: I would like list three such challenges, although they are somewhat linked.

1) The first grand challenge for a multidisciplinary collaboration is the creation of a universal, formal, computationally accessible medical knowledge base. Much of the collaboration among areas such as clinical medicine, clinical research, public health, and medical informatics, can and should be distilled into a set of formal representations of declarative and procedural knowledge that would be stored in a universally accessible (to humans and machines) knowledge base. That is, insights regarding meaningful [declarative] patterns of both individual (clinical) or population (epidemiological) data, and, most importantly, the best state-of-the-art [procedural] methods, protocols, guidelines, and care plans, to deal with such patterns, can and should be organized, specified, stored, and maintained within a universally accessible digital library, using a machine-comprehensible format (including the use of a set of ontological and terminological standards) that supports maintenance, use, reuse, and sharing of the knowledge.

I call such a continuously changing library of declarative and procedural clinical knowledge "the Human Clinome Project", in homage to the Human Genome project – or perhaps it should be termed the Human Cli-Knowme project, since it would encompass all currently known declarative and procedural human knowledge that can be represented within and accessed by computational means.

A particular section of the Human Clinome project that I have in mind as a good specific starting point is a worldwide machine-comprehensible digital library of procedural knowledge, namely, clinical guidelines and their somewhat more rigorous version, clinical protocols. These guidelines have been shown to be highly beneficial with respect to both improving the quality of care [82] and reducing its cost; it is also clear that to be effective, the guidelines must be integrated within the clinician's workflow [83]. Free-text and even somewhat structured guideline libraries exist and are accessible through the World-Wide Web. However, to be truly effective, guidelines must be continuously updated and universally accessible in a machine-comprehensible way, so that they can be automatically applied to the relevant patient (or patient population). One such attempt at a digital guideline architecture is the DeGeL project [84], which includes a comprehensive methodology for specification, maintenance, search, retrieval, and application of clinical guidelines, using a hybrid methodology that support several intermediate formats on the way from a free-text-based representation to a completely formal, executable format. The collaborative methodology for guideline specification was recently evaluated in a multinational collaboration and found to be feasible [85]. Of course, many sub-parts of such an architecture require further research and enhancement; multiple researchers throughout the medical informatics community are working on various aspects of this challenging problem, such as how to expressively represent the guidelines, or how to automatically verify and validate the knowledge expressed within them.

Such a grand challenge would bring together many of the disciplines mentioned by the authors of Kuhn et al.'s paper, and enforce true collaboration to be successful.

2) Much of the declarative biomedical knowledge necessary for better management of patients, in particular, chronic patients (the care of which is responsible for about 80% of the health care costs in developed countries), such as might be part of the Human Clinome project, should be acquired from analysis of massive amounts of data of patients monitored longitudinally for significant amounts of time (i.e., often, many years), to mine meaningful patterns from the data, using pre-existing clinical knowledge. In other words, we need to continuously perform massive, distributed, intelligent temporal data mining. Indeed, it has been recently suggested, although without much emphasis on the temporal aspect, that "clinarrays" (influenced by microarrays) might be constructed from analyzing large amounts of population-based laboratory data, possibly correlating it with biological data, so as to suggest new ways for disease subtyping [86]. However, adding the temporal dimension as well as the effect of using existing medical ontologies and knowledge bases to better interpret the data would shift the emphasis towards a massive, large scale, continuous clinical trial that uses and reuses the world's increasingly voluminous electronic medical record data base. Needless to say, ontological and terminological standards are an absolute prerequisite in the case of accessing clinical data as they are in the case of accessing medical knowledge.

Such an analysis would better identify meaningful [temporal] patterns and associations within and among features of diseases such as diabetes, hypertension, cerebral stroke, AIDS, etc. The goal would be to discover the "natural" course of such diseases, to identify meaningful temporal clusters and patient types, to detect patterns predictive of certain intermediate and final outcomes, to improve best practice guidelines (i.e., affect also the procedural aspect of the Human Clinome library), and to enhance our epidemiological knowledge and preventive care understanding.

Such a challenge requires and fosters close collaboration among clinicians, epidemiologists, informaticians, mathematicians, computer scientists, biomedical engineers (consider the effect of a "smart medical home" technology on the source of data available for such a project), biologists, and other disciplines.

3) One aspect I would like to see better represented in the context of both individual and public health care (and it could be eventually part of the universal procedural knowledge base) is an emphasis on medical decision support that considers individual, customizable, patient preferences as an inherent part of each decision that might include an option for deliberative thinking.

Examples include genetic consultation (e.g., the value of early knowledge of potential serious disabilities of the baby, versus the risk of spontaneous abortion of a healthy baby), therapy of hypercholesterolemia, hypertension, and depression, oncological care (e.g., weighing the benefits and costs of surgery, chemotherapy, and irradiation), and many other situations that are not life-threatening in an immediate fashion, enable a certain amount of deliberation on the side of the patient and care provider, and might be potentially affected by patient preferences. Such an endeavor is not only useful; it is ethically imperative, even if some of the patients might elect to not use it, delegating the responsibility of deciding on the best course of action to their care provider [87].

Again, effective solution of such a challenging problem requires and fosters the collaboration and deep mutual understanding of care providers, decision analysts, game theorists, behavioral scientists, economists, computational scientists, and other medical, engineering, and computational disciplines. Typical challenging research tasks include finding and developing increasingly effective ways to elicit patient preferences [88], and efficiently integrating such preferences within the overall clinical and public health care workflow [89].

In summary, I welcome the discussion started by Kuhn et al. and its stimulating educational implications, while suggesting a particular set of challenges that we might focus on, especially in the area of enhancing our understanding of individual and population-based patient care.

14. Collaboration of Specialists Is more Practical than to Find a Genius (by Katsuhiko Takabayashi)

Current medical and health care domains can be divided into several fields from molecular medicine to public health and in each field informatics plays a significant role. Kuhn et al. described precisely each relationship and explained the importance of interdisciplinary collaboration and education in their review. Kuhn realized the substantial change from hospital information systems to electric health records (EHRs) in the early days with distinguished ability [90]. Here he classified informatics into four areas for corresponding medicine and health care; bioinformatics and systems biology, informatics for biomedical engineering, health informatics and eHealth, and public health informatics in order from the point of micro to the mass world. In fact it is incredible to do without informatics in all fields nowadays and he also provided their perspectives respectively.

As for bioinformatics and systems biology, there are large amounts of data in omic (genomics, transcriptomics, proteomics and phenomics) world [91, 92]. Because genomic and proteomic data will explode to astronomical numbers of information in the very near future, researchers cannot work without informatics to handle these data and to know their relations. Since even SNPs which just express point mutations exist in one million per person, or there are 22,000 genes and more than 100,000 proteomes, it is quite easy to imagine numerous combinations existing between them to be explored. Thus sophisticated and useful information technology and powerful software will contribute to a great progress in molecular medicine. Especially data mining techniques [93] will be very useful tools for translational research to connect omic data and clinical phenomenon or contribution to diagnosis and selection of treatment with omics data. Therefore we must provide suitable environments to use them [94]. As it will bring reasonable profits in this field, many industries will emerge to deal with them as venture companies as in Silicon valley.

Healthcare information is also a field for blue chip industries, because eHealth provides a large portion of healthcare expenditure [95] in this decade as Kuhn mentioned. Electronic medical records (EMRs) will certainly advance in the near future, and EHRs hold many dreams as integration of not only EMR but also with many other health areas or even other information not related to health. Some governments consider an electronic post office box or an ATM card system for the integration of pensions, EMR of several hospitals, health checkup data, health insurance and so on. This personal health records (PHR) concept [96] is also open to industries as well, and all data of one individual about not only PHR but also various information would be stored. Of course data of PHR must be strictly limited to personal use because it includes confidential information. However, when some common parts can be utilized as EHR in broad terms, it will be reutilized in many other ways apart from personal use. To achieve it, preparing the rules and guidelines such as access control [97] and protection systems of privacy as well as many sophisticated systems in compliance with regulatory requirements are crucial. Additionally even after de-identification, proprietary of the data to use is not clearly defined in law, though it is very important in the near future for transverse study. If someone would not accept one's data to be used for such a study, it will make some bias in results. Therefore all data should be enrolled for special studies, which is controversial in regard to individual rights.

As Kuhn emphasized, digital data have become a core element of research, knowledge generation and knowledge management. EMRs and EHRs are ultimate targets for automated research like text mining [98]. We would find drug interactions or potential effects and side effects quite easily from medical records with them. Sometimes we need the tools to transform original data into other expressions in order to use them more easily. For example, time-oriented clinical data such as laboratory findings or prescriptions will be perhaps transformed into other expressions for easy manipulation and accurate enhancement of clinical assessment such as temporal abstraction [99]. There are only few practical tools at the moment but we will obtain universal tools after trial and error in the future. Moreover, for these trials, we also need long data storage beyond facilities. With them we can complete one's whole life data for PHR and also to compare with or integrate with omic (genome or proteome) data, which will be a very strong method for translational studies. In these days retrospective studies are not well estimated in medical journals. However when we expect the effects or outcome of some treatment over the long term such as ten years or more, we have to wait for the results many years, and expected results would not be obtained because of changes of treatment or other circumstances in that period. From this point of view, the retrospective study is very important and efficient when informatics can provide enough huge data to be analyzed.

Public health informatics seems to have more weight than any informatics in other fields of medicine or health care, because the results of analysis of information in this field directly affects critical politics such as global warming, biofuels, or global food shortage, which relates to the fate of humanity. Since public health informatics should include all information comprehensively with absolute accuracy, it is expensive to create and maintain vital information. Even though, we cannot completely entrust industries with these works, because the results might be crucial in deciding our destiny.

Finally, in all informatics fields, data value increases when integrated under the guarantee of their credibility in quality and they are now showing their whole appearance as the name of truth in front of us by integrating. However they might be so huge like an ocean or a big forest. Unless we have strong tools to discover their relations and offer them before us, we cannot say that we can really see them, though it might be a vicious cycle between the data and data mining tools.

Kuhn mentioned how vital it is for generations of scientists who can combine knowledge and skills from both medicine and informatics and emphasized the importance of the interdisciplinary education in early phases as well as interdisciplinary collaboration. He started to strengthen the collaboration and structured interdisciplinary education in encompassing medicine, informatics, bioinformatics, biology and system biology, engineering, health informatics and public health in Munich. In eastern Asian countries like Japan, different environments from those of the European countries, most researches in clinical medicine have been proceeding in the departments of medical informatics at national university hospitals. They consist of medical doctors and specialists of informatics or computer sciences and there were few departments for bioinformatics in other faculties. This might mean that they are still in the course of western countries in the old days where bioinformatics was not independent of medical school, or it might be as a result of different historical perspectives. At any rate they can work together without any restraint in the hospital at the moment. Some engineering students work together with medical doctors in our department at the hospital. In other fields of medicine such as molecular medicine, however, specialists for informatics come from school of engineering or physics. In summary, in eastern Asia, there is no strict boundary between specialties originated from Meister system and they seem to have less difficulty to collaborate in clinical medicine. Nevertheless it is not ideal because this is not intended systematized interdisciplinary collaboration.

Even in medicine or in informatics, there are no specialists in all fields, and therefore we need teamwork collaboration between medical doctors and specialists for the informatics field and others in various fields if necessary. There are a few people who are familiar with both fields because of graduation from both medical school and faculty of engineering or physics. However they are rare cases and even if one knows well in both fields, he cannot surpass two specialists who collaborate well unless he is a real genius. There is a proverb in Japan that god gives us only one talent. According to this proverb and taking into account of the very small numbers of geniuses in the world, good and successful collaboration of specialists of different disciplines will be more practical than to find a genius. One of the purposes of multidisciplinary education is understanding one's colleagues' work as well as knowing the position of one's specialty comprehensively in the beginning of one's education. It is also important to learn about laws and ethics in the fields as general matters in this education. Thus I believe most importantly that a key to success to collaborate in information and medicine is mutual respectability and generosity to their colleagues in different discipline. This spirit will be cultivated in early interdisciplinary education that Kuhn proposed.

15. Strategic Thinking Is Needed, Cost when the Research Results Are Transferred to Practice Is an Issue to Be Addressed (by Gio Wiederhold)

The article by Kuhn et al. [1] is impressive in its comprehensiveness. It also is frightening. The number of problems that require research, the multi-disciplinary cooperations needed to be successful in the interaction of informatics and medicine, the difficulties of demonstrating effectiveness, and the barriers to beneficial implementations are shown to be massive. While there may indeed be an urgent need to transfer research results to practice, strategic thinking is needed as well, as has been shown in simpler settings [100]. Cost is one issue to be addressed. We expected in the past ratios of research projects efforts to practical implementation to integration into practice of 1 : 7 : 25 [101], and little has been changed to improve this ratio. Medical informatics will have to depend on progress in software engineering to create usable software. We expect that new initiatives cited, as service-oriented architectures, will improve software development, but an early reliance on a technology that is not yet mature is currently frustrating efforts at the US Veterans Health Administration systems to update their medical record system (VistA) [102]. It is purely a coincidence, but also an illustration, that other Vistas are encountering development and acceptance problems as well [103]. Medical informatics cannot supplant computer software engineering (SWE) efforts but must take care in understanding when and what to exploit as part of biomedical engineering (BME).

The total cost of software-based solutions in any setting has to be budgeted properly. Computer science education serves us poorly there. Software maintenance costs run at about 15% of prior software investment costs and are due primarily to keep the software up-to-date as the external world changes around us [104]. These maintenance costs over time exceed initial development costs, and after some further time, exceed the benefits that software provides. This fact is the major reason for closing down apparently successful medical informatics projects, often surprising and frustrating the participants. Unfortunately, we do not teach our SWE students how to plan for these costs, nor do we teach them how to assess the potential economic benefits of the software [105].

Replicating successful local systems has been difficult in the past and remains hard. Early systems were tied to obsolescing technology, but more recent systems, as seen at Vanderbilt and the Palo Alto Medical Foundation have not spawned successors either [106]. There is more involved than technology, leadership is certainly one issue.

The hard issues of economics are cited in the beginning and the end of the paper, but do not pervade the discussions. The growth of IT spending at 12% year is taken as indication of importance, but is also a rate which is unsustainable in relation to national expenses in any country, especially as the support base of working taxable individuals decreases [1, Sec. 2 and Sec. 3.4.1]. At the same time the industrial tax base is diminishing, as companies find ways to move their intellectual property and the profits derived from that IP to tax havens with no or small health care costs [107]. Given the high cost of implementation, it is important to focus on large and costly populations where actual cost reductions are possible, an issue not always covered by cost-effectiveness arguments. Some disease-based categories are well recognized now, as diabetes. However most diabetics present multiple problems, are seen in diverse settings, and their records at each site tend to be incomplete. For information integration there is a benefit in that members of that patient group tend to travel less, so that local and regional integration can proceed before national and global record integration is achieved, and economic benefits can be realized as well as improved care [108]. The same pattern holds for many of the elderly population, who require a substantial fraction of our health care services. Cost-effectiveness is stressed in the paper, but transfer to practice requires a cost-benefit as well. That benefits are hard to demonstrate is recognized in the paper, but must be sought.

Moving to the opposite direction, personalized diagnoses and therapies, is an extremely attractive goal. But given financial constraints, systems to bring research results will require very careful strategies. How does one conduct clinical trials to determine efficacy of personalized care protocols? Presenting findings to clinicians will require innovation. Phrasing findings in terms of statistical evidence based on similar populations, as done now for medical versus surgical treatment choices conveys little insight or trust. Can the findings be conveyed using a "mechanistic" metabolic model, showing affected pathways [1, Sect. 3.1.3]? How can we present patient-specific information from probes [1, Sect. 3.2.1]? And how should patients be informed of conditions for which no known intervention exists? In general unfettered access to the patients' own medical information has been shown to be beneficial, but customization has been recommended as well [109]. Any approach supporting personalized treatment decisions requires novel software, incorporating experience from many disciplines. Such software will require regular updating, since our knowledge is bound to change for many years to come. How will software be maintained when personalized experience differs? Who will maintain the software at a reasonable cost?

Cooperative approaches are recommended in Section 3. Bureaucrats indeed feel safer when topics and funding can be constrained to recognized disciplines. Only if scientists and the public experience benefits will existing regulations and legal frameworks that limit interdisciplinary work be removed [1, Sec. 3.3.2]. Practical and beneficial examples will be important. Figure 2 only links abstract concepts; lessons learned from actual projects are needed as well. The gap between the "bench" and "bedside' communities is recognized. Social expectations limit collaboration as well. There is a serious, but largely unrecognized gap between the mathematically-based disciplines, where proofs, once validated, should stand forever, and the biological disciplines, where experiments have to be repeated to cover ever more of the variations that the living world presents. Scientists have at times disparaged scientific approaches used by others as being either naïve or imprecise. Engendering sympathy to the problems that both communities face in their research is a prerequisite to achieve cooperation at the individual level, creating a model that can then move up the organizational ladders. My personal sense is that directives imposed from above, mandating cooperation, do not create effective long-term collaborations.

One barrier, recognized in the paper, to transition of research to practice are privacy concerns [110]. Expecting guaranteed methods for securing privacy is too much to ask for [1, Sec. 3.3.1]. Approaches as k-anonymity, while already problematic, assume that there is no external information that can be exploited by an intruder. Lack of trust and the resulting rules will continue to hinder beneficial applications of health care information systems [Ness]. Involuntary adoption of EHR, as implied here, will cause politicians and the administrating bureaucrats to mandate approaches to privacy protection that are based on worst case scenarios, and give little choice to the patients. Questions posed in motivating surveys often reveal a bias by the questioner. How questions are phrased makes a great deal of difference, i.e. asking "Are you concerned about others accessing your private medical records?" will elicit a different response than "Are you willing to share information from your medical records so that others with similar problems can benefit?". Some indication about patients' attitudes about privacy will be gleaned from the acceptance of web-based voluntary personal medical data systems, as Dossia, Google Health, and MS Healthvault. While all of these promise privacy, individual with deep concerns are sure not to participate. The immediate reason not to join is of course that with few participating health care providers the benefits of entering data and links are minimal.

In conclusion, even Norbert Wiener, cited in [1, Sect. 2], will probably agree that we don't have the capability to move most of our research results into practice, and not only because of economic constraints. Our genetic and environmental history, even if it could be fully captured, does not fully determine who we are. For instance, what our brains do with all the inputs is yet quite unknown, and randomness remains [111]. Research is required to open up possibilities. On the horizon are systems that help the clinicians and the patients to interact effectively, to which research into the issues listed in this paper will contribute.

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Medical Informatics Is Interdisciplinary *avant la Lettre*

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Summary

Objective: To discuss the elements of interdisciplinary research and to analyze its contribution to (bio)medical informatics.

Method: Commenting on 'Informatics and Medicine – From Molecules to Populations' from K. A. Kuhn et al. in this issue of *Methods of Information in Medicine*. Referring to examples of successfully established interdisciplinary research.

Results and Conclusions: Medical informatics is an interdisciplinary field *avant la lettre*. Experience with successful interdisciplinary research already exists for many decades: Interdisciplinary research is not a category of research but a consequence of addressing a complex problem in society, involving the collaboration between and methods drawn from multiple disciplines. Because research is people, personal interactions are critical for interdisciplinary research. Collaboration takes extra time to develop, to build consensus and to understand new methodologies, languages, and each other's culture. Interdisciplinary research requires leaders with vision and expressive skills. Effective scientific and institutional leadership is critical to the success of interdisciplinary groups. Interdisciplinarity begins in the classroom. Interdisciplinary research cannot be effective without interdisciplinary education. Researchers and teachers should immerse themselves in the culture of other disciplines, learning to explain their work in terms understood by people outside their own discipline. Teams that perform interdisciplinary research should promote collaboration, meet regularly, and recognize that it requires a commitment toward good communication and clear goals. Although much progress is achieved by interdisciplinary research, basic monodisciplinary research is still required to advance the frontiers of scientific knowledge, such as in physics or biology.

Keywords

Medical informatics, biomedical informatics, interdisciplinarity

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On several occasions researchers in (bio)medical informatics have presented their visions on the expected contributions of informatics to health care. Klaus Kuhn and his colleagues from two universities in Munich have added their views to the already existing body of opinions on this subject [1]. Probably, one of the very first workshops on the challenges in Medical Informatics took place during an early SCAMC congress in Baltimore, in 1984 [2, 3]. Since then, several meetings were held and articles published on the subject of the future direction of (bio)medical informatics, health informatics, nursing informatics and the like (e.g. [4]).

1. The Core Message of the Article

Kuhn et al. [1] observe substantial changes in health care. The main changes they see are the impact of molecular biology, contributions by engineering, design of new drugs, minimally invasive surgery, and sociocultural changes in the structure of health care provision. They notice a central role for informatics in all such domains, considering it to be the key element and the most important driving force for all developments. They conclude that there is a need to educate a new generation of experts who can work in a multidisciplinary team. Their common goal was to establish in 2008 a research-oriented Graduate School in Munich, supported by the two universities they represent.

Some elements for the future research that they envisage are the following: New systems for man-machine interaction along the lines predicted by Wiener in the 1950s; a systematic exploration of large databases of patient-related data; embedded systems for the acquisition of data from sensor networks; useful knowledge to be derived from large data sets; the realization of autonomous and self-healing software systems; seamless access to software and data by advances in middleware technology; intelligent medical assist devices, while keeping humans in the loop; knowledge-driven discovery and interpretation of complex biomedical data. In short, they foresee a complete information logistics chain, from single molecules to the entire human population.

To meet such challenges, multidisciplinary collaboration is a must. Four application domains are indicated by the authors: 1) bioinformatics and systems biology; 2) informatics and biomedical engineering; 3) health informatics and eHealth; and 4) public health informatics and public health. The article of Kuhn et al. [1] then enlarges on these four areas and makes suggestions for future research, such as the understanding of molecular mechanisms to get insight in the development of diseases; the translation of newly obtained knowledge for personalized health care; the construction of new sensors for data acquisition; the application of knowledge on genetic variation in the population; and the assessment of health care interventions. In pursuing this multidisciplinary research they hope to contribute to an evidence-based and efficient health system.

2. Commentary

First of all, I applaud the initiative of the colleagues in Munich to found this multidisciplinary Graduate School, for which apparently the agenda has been set in the document contained in their article. Their initiative is very far-reaching indeed, and covers virtually all the challenging developments we see in biomedicine, from biomolecular research up to the social aspects of health care. In a way, this plan is paralleled by many similar initiatives around the world. In my commentary I will make a few supporting and also some mildly critical remarks.

2.1 Graduate Schools

The idea of Graduate Schools is very timely and has proven to be highly beneficial for the advancement of science. Many researchers have noted that the future progress in science will come from research at the crossroads of different disciplines. Since the beginning of the 1990s, in the Netherlands we have also seen the establishment of many such schools. These schools are in principle multi-departmental research institutions. Many of them have an interdisciplinary character. The task of the schools is 1) the advancement of disciplinary or multidisciplinary research, and 2) education and training of young researchers at the MSc and PhD level. One of the schools in the biomedical domain, operational since the early 1990s, is the Netherlands Institute for Health Sciences (NIHES) at Erasmus Medical Center Rotterdam, where researchers in epidemiology, medical informatics, and public health research collaborate around major and challenging research projects and where both MSc and PhD students are trained [5]. NIHES has around 200 PhD students. It is hoped that the Munich initiative will be equally successful. It is our experience that both high-quality leadership and the ability to attract talented PhD students are key factors for success. I have no doubt that the colleagues in Munich are well aware of these factors.

2.2 Interdisciplinarity

As said, taking a multidisciplinary approach towards the solution of major scientific problems is often the right way to go. It should be mentioned at the same time, that fundamental monodisciplinary research is still of utmost importance, such as the research in the Large Hadron Collider in Geneva or the ITER project in Grenoble. Nevertheless, for large problems in society, such as the changing climate, the energy crisis, or the provision of advanced health care, a multidisciplinary approach is the proper direction to take.

A few years ago I was a member of a Committee on Interdisciplinary Research (IDR) of the National Academy of Sciences, the Institute of Medicine, and the National Academy of Engineering in the United States. The Committee consisted of researchers from a wide range of different disciplines, from the natural sciences to the social sciences and from engineering to philosophy and ethics. I was privileged to give input from medical informatics and also to provide a bridge to similar developments in Europe. For the results of this IDR Committee see [6], which also includes many references to interdisciplinary research. One of the results of the work of the Committee was a definition for this new type of research, which was phrased as follows:

'*Interdisciplinary research in science and engineering is a mode of research by teams or individuals that uses information, techniques, tools, perspectives, and/or theories from two or more established disciplines to solve problems whose solutions are beyond the scope of a single scientific discipline or area of scientific practice.*'

2.3 Early Initiative

When diving into the history of interdisciplinary research it is interesting to see that a very early initiative in this sense was taken in the 1930s by Gilles Holst at Philips Physics Research Laboratory near Eindhoven, the Netherlands. Hendrik Casimir, the famous Dutch physicist, who was for many years the Research Director of the Physics Research Lab, documented this pioneering initiative in a publication, in which he summarized Holst's principles in the form of 'Ten Commandments' [7]:

1) Engage competent scientists, if possible young, yet with academic research experience.
2) Do not pay too much attention to the details of their previous experience.
3) Give them a good deal of freedom and give a good deal of leeway to their particular idiosyncrasies.
4) Let them publish and take part in international scientific activities.
5) Steer a middle course between individualism and strict regimentation; base authority on real competence; in case of doubt prefer anarchy.
6) Do not divide a laboratory according to different disciplines but create multidisciplinary teams.
7) Give the research laboratories independence in choice of subjects but see to it that leaders and staff are thoroughly aware of their responsibility for the future of the company.
8) Do not try to run the research laboratories on a detailed budget system and never allow product divisions budgetary control over research projects.
9) Encourage transfer of competent senior people from the research laboratories to the development laboratories of product divisions.
10) In choosing research projects, be guided not only by market possibilities, but also by the state of development of academic science.

The history of the Philips Company was documented in 2001 in a book by Prof. Marc de Vries from Delft University of Technology [8]. From his book I cite the following observation: '*The fact that the Philips Research Lab survived until today, in contrast to the research labs of many of its competitors, is most probably rooted in its multidisciplinary character. The directors of this company always understood the importance of the collaboration between different disciplines. This was also reflected in the organization of the lab. The structure of the lab has always been project-oriented. On its new large research campus, which is now being realized south of Eindhoven, many disciplines will be present, including the social sciences, e.g., to conduct research for the realization of the intelligent home.*' This conclusion is a very stimulating one for the initiative phrased by the colleagues from Munich.

2.4 Recommendations

Coming back to the IDR Committee that I mentioned, I want to cite some of its main conclusions and recommendations, relevant and supportive for the Munich initiative and similar endeavors elsewhere [6]:

- Interdisciplinary research is not a category of research but a consequence of addressing a complex question, with methods drawn from multiple disciplines.
- Research is people, and personal interactions are critical to interdisciplinary research. Collaboration takes extra time to develop, to build consensus and understand new methodologies, language, and culture.
- Interdisciplinary research requires leaders with vision and 'expressive' skills. Effective scientific and institutional leadership are critical to the success of interdisciplinary groups.
- Interdisciplinarity begins in the classroom. Interdisciplinary research cannot be effective without interdisciplinary education.
- Researchers and teachers should immerse themselves in the culture of other disciplines, learning to explain their work in terms understood by people outside their own discipline.
- Teams that perform interdisciplinary research should promote collaboration, meet regularly, and recognize that it requires a commitment toward good communication and clear goals.

I dare to say that medical informatics is an interdisciplinary field *avant la lettre*. In our own institute in Rotterdam, we have research teams with very different backgrounds: physicists and medical doctors, engineers and informaticians, epidemiologists and biologists. For such teams, the recommendations by Holst and the ones from the US Committee on IDR are very relevant.

After the paragraphs above, much in support of the Munich initiative, I also take the opportunity to make some critical comments. These remarks pertain to the largely positivistic and technological approach that is described in [1] and the minimal description of the grand challenges in modern health care. Last, I want to mention some of the over-optimistic expectations of the past that – regretfully – were not fulfilled. The question then is, why was there a lack of success? This is most important, because people who do not know their history run the risk of repeating the errors of the past.

2.5 Technology-driven Approach

The type of research that is described in [1] to advance biomedicine is characterized by the authors as 'a complete logistics chain, from single molecules to the entire human population'. The way in which they want to accomplish this 'logistics chain' is summarized as exploration of large patient databases; acquisition of data from sensors; knowledge derivation from databases; self-healing software systems; seamless access to software and data; intelligent medical devices; and knowledge-driven discovery. This is, indeed, a long-term research agenda for a large institute, mainly oriented towards technology-driven research. And this is at the same time one of the 'mild' criticisms that I have about this proposal: the authors give the impression that they do not base their research agenda on needs in health care or society, but to start from possible contributions of technology.

Of course, all research in the natural and biomedical sciences is a compromise between needs and possibilities; the needs are the driving forces and the methods offered by science are the vehicles to reach the goals. I have the feeling that the balance in [1] is too much tilted towards technological possibilities, although even in this respect, much basic research is still to be done. Having said that, I am still missing a few areas of exciting 'technology-driven' research, such as imaging and image interpretation, a rapidly expanding field. Perhaps, this type of research is meant to have been incorporated in one of the areas that are mentioned, but I consider imaging and 4-D image processing, let alone image interpretation, both at the level of organs and cells, as a most important research field in itself. More examples can be given, but perhaps it is more appropriate to discuss some health care challenges themselves.

2.6 Health Care Grand Challenges

The field of (bio)medical informatics is at best an ancillary discipline, only existing for the benefit of health care. It is not an independent, 'stand-alone' domain, such as astronomy, geology or biology. Because medicine itself is a melting pot of many different disciplines, also medical informatics bears the same characteristics. As said, it is a multidisciplinary domain *avant la lettre*. For every different research challenge in medicine and health care, multidisciplinary research teams are composed to solve a specific problem. For the computer interpretation of medical images one needs different people than for the construction of electronic health records. For the development of modern hospital networks, giving seamless access to patient data, again different disciplines are required. For research on systems for intensive patient care, the team is again differently composed.

Thus, each research team is brought together in such a way that it can tackle the specific problem to be solved. The problems are most often not defined by the research teams themselves, but presented by health care in its widest sense. In this, typical diseases of modern society play a key role, such as cardiac and lung diseases, cancer, and – in general – the multiple diseases of the elderly, including stroke and Alzheimer's disease. Many chronic diseases, such as diabetes and hypertension, are caused by our lifestyle. But we should also not forget, that 'old' diseases, such as tuberculosis and many other infectious and viral diseases, such as HIV, can also be the consequence of human behavior, impure water sanitation, unhealthy food, smoking, unsafe personal behavior, global travel and sometimes also the mismanagement of antibiotics. Besides, there is a growing insight in the genetic causes of diseases. To enlarge the list of challenges a bit further, we see that modern societies are confronted with exponentially rising costs of health care and even in rich countries one is sometimes confronted with inequities in the distribution of medical services for different social groups. In addition, patients and consumer groups are, because of the Internet, increasingly involved in their own health care and want to have insight in the effectiveness and the quality of care. Lastly, in most countries, health care provision is very much scattered and improperly coordinated, even in countries with a prominent primary health care system. Implicitly and explicitly the article by Kuhn and colleagues addresses all these external factors on health and our health care system (the needs), but – as said – I have the impression that the balance is somewhat tilted towards potential technological possibilities instead of needs.

Finally, I would like to make a remark regarding lessons from the past. In the past, there have been several overoptimistic expectations regarding the contributions from medical technology to health care. I vividly remember the predictions in the 1970s on the impact of medical decision-support systems, expert systems etcetera on medical care. Well – to put it in a friendly way – their contributions were only very modest. The same applies to the overoptimistic expectations of the realization of electronic health records. All of this appears to be far more complex than ever expected, although the technology is widely available. Another example pertains to medical image processing. Image boundary detection in often noisy medical images appears to be extremely difficult. A last example is the processing of free text in medical records. Not only from the viewpoint of a natural language processing is this most difficult, but the nature and culture of medicine itself, with its many traditions and continuously changing knowledge, appears to be a hindrance to a generalized approach. This is not the proper place to discuss the reasons for these overstretched expectations, but it is most important to take this experience into account when setting the research agenda for the future.

3. Conclusion

I repeat that I am most impressed by the Munich initiative and therefore I congratulate the colleagues with the founding of their Graduate School. I have made some positive and some mildly critical remarks. Looking at their very comprehensive research agenda, I would like to phrase a very last remark in German: *In der Beschränkung zeigt sich der Meister* (In the restriction the master appears).

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