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Reflections on Biomedical Informatics: From Cybernetics to Genomic Medicine and Nanomedicine

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Abstract. Expanding on our previous analysis of Biomedical Informatics (BMI), the present perspective ranges from cybernetics to nanomedicine, based on its scientific, historical, philosophical, theoretical, experimental, and technological aspects as they affect systems developments, simulation and modelling, education, and the impact on healthcare. We then suggest that BMI is still searching for strong basic scientific principles around which it can crystallize. As -omic biological knowledge increasingly impacts the future of medicine, ubiquitous computing and informatics become even more essential, not only for the technological infrastructure, but as a part of the scientific enterprise itself. The Virtual Physiological Human and investigations into nanomedicine will surely produce yet more unpredictable opportunities, leading to significant changes in biomedical research and practice. As a discipline involved in making such advances possible, BMI is likely to need to re-define itself and extend its research horizons to meet the new challenges.
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1. Introduction

Several analyses of the current scientific status of Medical Informatics (MI), Bioinformatics (BI), and Biomedical Informatics (BMI), that has evolved over the last few years from the convergence between MI and BI, have been published over the last decade [1][2]. The authors of this paper have earlier contributed to this debate [3][4].

MI researchers have sometimes stated they encounter difficulties in receiving the scientific recognition that they think the discipline deserves [4]. In some cases, MI has been considered a pure engineering discipline, focusing on the technology related to health care. Could this situation be only circumstantial or might it reflect a trend that may become further accentuated? What could be the future of MI and BI? Will they merge into BMI or will they remain independent?

2. Proposal for a more systematic analysis of MI, BI, and BMI

In a series of various papers, the authors have analysed the scientific status of these three disciplines [3][4], using as a framework various ideas from the philosophy of science. We extend these ideas below, following various directions.

2.1.Historical

One of the goals of cybernetics was to study the components of what can be referred to as “human information systems”. In contrast, MI has not made this a main concern.

Instead, MI has been primarily involved in designing and developing applications for patient care, with computational methods for basic research on human physiology and pathology rarely impinging on its central agenda. BI, on the contrary, when faced with new challenges in the analysis of complex gene networks and pathways, or the influence of the environment in genetics, is connecting to the emerging subfield of "systems biology. In the process, some of the original ideas and methods from cybernetics are being re-introduced, and re-thought in the context of the latest experimental paradigms in biology. The emergence of nanobiotechnology promises to accelerate this trend, possibly catalyzing a new "nanocybernetics". Researchers such as Benenson, at Harvard University [5] propose to adapt the concept of Wiener's automata to the biomolecular world, as with an automaton built to recognize the characteristic molecular complexity of cancer cells and destroy them while leaving normal cells intact. In this sense, traditional biological research carried out "in vivo", "in vitro", and recently "in silico", can be carried out "in info".

2.2. A brief analysis from the philosophy of science

In one of our recent papers [3], we compare MI and BI based on ideas from major philosophers of science. This use is different from recent work that introduces philosophical ideas at the heart of BMI. Ontologies introduce informatics methods for creating a shared consensus about the concepts that underlie a specific domain [6]. While ontologies provide new approaches to knowledge engineering [7], they still must demonstrate that they can advance the scientific theories supporting MI. Some philosophical arguments are pertinent in considering this issue. For instance:

a) An ontology, itself, cannot be the scientific basis for triggering a paradigm shift. Kuhn suggested that a paradigm shift provoked a change in the underlying ontology [8]. An example comes from physics —a field where this kind of philosophical analysis has been carried out for well over a century. It was relativity theory that changed the meaning of the concepts "light" and "time". Without the theory, no ontology could have been developed to anticipate the new meanings of these two concepts.

b) The history of informatics and "preinformatics" disciplines illustrate some examples that should not be forgotten when attempting to redefine biomedical fields, such as physiology. Let us take an example. Recent efforts suggest the development of a broad, universal biomedical ontology, from scratch. At its core, "concepts", as used by original ontologists such as Gruber [6], would be changed to "entities". Also proposed is a new usage of the term "process", based on ideas of energy exchange and transformation. These "entities" and "processes" are then proposed to be used in redefining physiology, based on ontological assumptions. From an informatics perspective, this approach looks interesting, but from a physiological perspective they harken back to the "pre-cybernetics" period before the 1940's. One of the main achievements of cybernetics researchers was to show that physiology involves exchanges of information (with signalling in organisms) rather than simply the exchange of energy. Wiener himself considered the human body as an entire "message" [9]. The greatest drawback of returning to a strictly thermodynamical, or "energy-based" approach in physiological ontologies, as suggested above, is that it cannot represent the many information-based physiological processes that we find within organisms, such as signal messaging, feedback loops within their nervous systems and the homeostatic processes which are so pervasive at many physiological levels. .

c) Ontologists are currently taking holistic or top-down approaches in building biomedical ontologies [10]. From such a perspective, concepts (or entities) and relations (or processes) are being made explicit in computer representations. It can be argued that ontologies should be also generated using a bottom-up approach, scaling findings up from the molecular level, and both approaches, top-down and bottom-up, then combined. While building generic ontologies top-down from scratch may prove useful in describing human-designed and controlled systems and tasks such as database integration, the uncertainty and incompleteness surrounding our knowledge of continuously evolving groups of organisms in complex environments should make us very cautious in thinking of them as an a-priori valid scientific basis for deducing possible consequences about living systems.

d) More traditional ontologists such as Hartmann, or the Nobel laureate Konrad Lorenz [11] pointed out that integrative approaches in biology —and medicine— failed in their day, because they did not to consider different conceptual levels. According to Lorenz, it is not possible to deduce structure at higher levels based on characteristics of those from lower levels. This can be easily understood from an example from physics, where Einstein's theory of relativity applies and is adequate to explain phenomena at interplanetary distances, whereas quantum mechanics is needed at the atomic level. Neither can be deduced from the other and, even more fundamentally, both cannot hold true at the same time —they depend on the questions posed within their own specific experimental designs. Physicists continue to seek a new, integrated, unified theory to reconcile them. In biomedicine, terms that appear superficially alike, or even identical, frequently have very different meanings for a molecular biologist, a pathologist or an internist. Using a reductionist approach we cannot build up physiology simply from molecular biology, pathology from physiology, or public health from pathology. Similarly, the environment produces very different effects at the biochemical and the population level. Attempts to create extended ontologies that cover all levels of biomedicine, from atoms to populations, must consider such constraints and their implicit limitations for both knowledge- and software-engineering purposes.

2.3. Theoretical foundations

MI researchers have obtained outstanding results in theoretical research, related —as stated above— to topics such as natural language processing, uncertainty management, or image processing. But none of these or other advances has been strong enough to establish a scientific basis for the independent recognition of the discipline. Major challenges that are information-centered, such as understanding how consciousness works in humans, or how information is coded in the brain, have remained completely outside the mainstream of BMI. While these two challenges should indeed be primarily addressed by neuroscientists, cognitive scientists or neuro-informaticians, one might argue that a widely "integrating" field such as BMI should also consider such problems as part of its scope. They might indeed provide some of the underlying theory that the discipline needs to advance scientifically, and lead to external recognition. Insights into how brain function affects information processing would also have a deep impact in clinical medicine —especially on psychiatry, neurology, and on sensory integration and feedback for healthy subjects also.

There are areas whose research outcomes will be central to BMI. For instance, representing and modelling genotype-phenotype data and their interaction with the environment (and nutrition) is a major challenge where researchers from systems biology are focusing efforts and extending both computational as well as biological modelling. It presents an excellent opportunity for BMI researchers to participate.

2.4. Experimental research

Since the 1960s, researchers have applied a variety of techniques and tools (e.g., statistics, pattern recognition, and machine learning) to discover knowledge such as clinical prediction rules from large databases. In doing this, researchers wanted to avoid biases in the knowledge acquisition process from one or more experts. Yet, regrettably, few of these systems are actually used routinely to support medical practice. In many ways, data mining is an example of how difficult it is to encourage interactions between BMI researchers and professionals from other related areas. Biomedical statistics has developed for more than five decades, with significant impact on epidemiology and public health, but relatively little interaction with BMI. More vigorous exchanges could create a synergy, improving not only medical data analysis but also more efficient and deep knowledge integration and experimentation, facilitating the acceptance of project outcomes by medical practitioners.

2.5. Simulation

Researchers aim to predict cell behaviour by creating models that include cell features [12] as well as environmental data. Computers help to simulate the dynamic changes of cellular metabolism [13]. Virtual simulations use for this purpose data from the different "omics" projects that have proliferated over the last few years. At a higher level, BMI researchers have built disease models for over three decades. An early example is the CASNET expert system which incorporated a causal model, linking observations and pathophysiological states of the eye diseases comprising glaucoma [14]. More recently, complex simulations can reproduce pulmonary diseases using the Virtual Lung or cardiac physiology. By increasing the complexity and expanding the limits of specific simulations, researchers have proposed the development of an ambitious project, the Virtual Physiological Human (VPH) [15]. This project aims to integrate partial simulations from different systems —e.g., cardiac, lung, kidney, and others—, organs, and cells, into a whole simulation of the entire body. In the VPH, an integrated virtual human model would facilitate navigation, representation and simulation of physiological processes and, finally, carry out "in silico" experiments that can be used for testing diagnostic devices or new drugs.

Contrasting the Visible Human Project [16] and the VPH the former had as goal to build a 3-D anatomical representation of the human while the VPH aims to build a 3-D simulation of the physiological body, including metabolic pathways, biochemical reactions, electrical signaling and regulation processes, among others. While this is one of the most challenging programs that BMI researchers can address, we should keep in mind the difficulties mentioned above about jumping between the different biomedical "levels", from molecular biology to cells, from cells to tissue in systems and organs, from these to whole organisms, and from individuals to populations. Our knowledge here has significant gaps which must be filled before the VPH can be completed. Despite this, it is one of the most challenging ideas proposed during the last years, though considerably more ambitious in scale, and less clearly realizable than the Human Genome Project (HGP).

2.6. Training and education

The introduction of the technologies and new subfields such as, for instance, nanotechnology, molecular automata, or complex simulation models, will require a background that is different from that provided by the current curricula predominant in BI or MI. Since the areas of convergence are larger and quite different, new methods of modelling, analysis, and interpretation will be needed, overlapping with engineering, cognitive science, operations research, and most of the basic sciences. How good should BMI professionals be as mathematicians, physicists, or chemists? How good should they be in biological bench research? How can they possibly find the time to master the multiple disciplines and integrate the knowledge this entails? How can they compete with the specialists in increasingly narrow –omics subspecialties, and how with those in the increasingly important and related environmental and public health ones? In short, is there a good "complementarily symbiotic niche" to these other disciplines that can be designed for the biomedical informatician?

2.7. Impact in healthcare: Genomic medicine and nanomedicine, just two more "paradigm shifts"?

The success of the HGP and other *omic*s-related projects has introduced new approaches to basic medical science and healthcare, generically labelled as *Genomic Medicine*. Diseases such as cancer, a plethora of rare diseases, and many others are now being explained from different perspectives, including genetic information.

For Genomic Medicine to become real, in Europe, the European Commission has funded initiatives, such as the INFOBIOMED network of excellence and the ACGT (advanced Clinico-Genomic Trials) project, to develop methodologies for integrated analysis of biomedical information in clinical trials. In this scenario, many collaborative actions are being proposed. For instance, building biobanks that will gather clinical and genomic data; providing clinical data to bioinformaticians that will test their metabolic pathway representations; building new biomedical ontologies, or introducing omics-based data models in innovative genomic-based electronic health records. The goal is not to "deconstruct" the components of clinical practice and provide the computer tools that are needed for health professionals, but to shift clinical practice towards new approaches, deeply anchored in basic science.

In 1959, the Nobel laureate Richard Feynman proposed that there were no scientific obstacles to avoid the manipulation of atoms [17]. In his visionary speech, he also anticipated uses that this new approach could have for biological research. A good 40+ years later, a new discipline, called "nanotechnology", is slowly arising.

As nanomedicine begins to define itself, an increasing rate of discoveries will ensue, promising to deliver new diagnostic and therapeutic methods for medicine. Bionanomachines can work in the tiny space of living cells and be tailored for medical applications. Complex molecules that seek out diseased or cancerous cells, sensors for diagnosing diseased states, replacement therapy using custom constructed molecules, may be able to treat different diseases and conditions, opening a new horizon for medicine [18]. In nanotechnology, nanoparticles and nanomaterials are built as biodetection agents for deoxyribonucleic acid and proteins. In addition, nanodevices, such as nanowires and nanotubes, can be combined with nanoarrays to create automated nanodetection platforms. Molecular imaging modalities based on quantum dots and magnetic nanoparticles introduce new methods to intracranial imaging.

Paradoxically, just as the term “genomic medicine” is beginning to enjoy some currency after the completion of the HGP, a new term, “nanomedicine”, comes calling at the door, claiming to be its newest, exciting frontier. Genomic medicine and nanomedicine, then have an incredible potential to transform biomedicine and healthcare but, whereas they promise to deliver methods and technologies far more ambitious, they still need the theoretical foundations that are the basis for solid scientific disciplines, suggesting a fruitful field where adventurous BMI researchers can explore with specialist colleagues in the fields needed to make concrete advances.

3.Conclusions

From a scientific perspective, it can be argued that there are no real paradigms or theories that crystallize BMI around one or a very few core principles. On the other hand, the discipline may have not promoted or encouraged sufficient debates about its underlying science. When a rare unanimity around certain issues, or “hot topics” arises among researchers, it can often lead to periods of great breakthroughs. Later, once this unanimity ceases, other issues substitute for the old ones, and a new cycle ensues.

As a final thought— while BMI has contributed to change the face of healthcare and improve the lives of people like few other scientific disciplines, it still needs the strength and self-confidence, which can be reflected in stimulating controversies characteristic of the more established sciences and their technologies.

References

[1] Kohane, I. Bioinformatics and Clinical Informatics: The Imperative to Collaborate. 2000. J Am Med Inform Assoc. 7, 5: 439-443.
[2] van Bemmel JH. Medical informatics, art or science? Methods Inf Med. 1996 Sep;35(3):157-72.
[3] Maojo, V. and Kulikowski, C. Medical Informatics and Bioinformatics: Integration, or Evolution through Scientific Crises? Methods Inf Med (in press)
[4] Maojo V, and Kulikowski CA. Bioinformatics and medical informatics: collaborations on the road to genomic medicine? J Am Med Inform Assoc 2003 Nov-Dec;10(6):515-22.
[5] Benenson, Y., Gil, B., Ben-Dor, U., Adar, R. & Shapiro, E. An autonomous molecular computer for logical control of gene expression. Nature 429, 423-429 (2004).
[6] Gruber, T.R. "A Translation Approach to Portable Ontology Specifications", Knowledge Acquisition, 1993 5(2), 199-220.
[7] Gómez-Pérez, A, Corcho, O and Fernandez, M. Ontological Engineering. Springer Verlag 2004.
[8] Kuhn, T. The Structure of Scientific Revolutions. 2nd Ed.. Chicago: Univ. of Chicago Press. 1970
[9] Wiener, N. The Human Use of Human Beings. Da Capo Press. 1988.
[10] Ceusters W, Smith B, Goldberg L. A terminological and ontological analysis of the NCI Thesaurus. Methods Inf Med. 2005;44(4):498-507.
[11] Lorenz, K. Behind the Mirror. Harvest/HBJ Book. 1978.
[12] Ishii N, Robert M, Nakayama Y, Kanai A, Tomita M. Toward large-scale modeling of the microbial cell for computer simulation. J Biotechnol. 2004 Sep 30;113(1-3):281-94. Review.
[13] Hunter PJ, Borg TK. Integration from proteins to organs: the Physiome Project.Nat Rev Mol Cell Biol. 2003 Mar;4(3):237-43. Review.
[14] Weiss,S., Kulikowski, C., Amarel, S., and Safir, A. A model-based method for computer-aided medical diagnosis, 1978. JArtif. Intell., 11, 145-172.
[15] http://cordis.europa.eu/ist/directorate_h/index.html
[16] Ackerman, M.J. The visible Human project, Proc IEEE. 1998. 86,3 :504-511.
[17] Feynman, R, There's Plenty of Room at the Bottom. Annual Meeting of the Am Phys Soc, 1959.
[18] Goodsell, D. Bionanotechnology: Lessons from Nature. Wiley, 2004.