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Computational Intelligence in biomedicine: Some contributions

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Abstract. The commodification of healthcare has led to an increasing demand for personalization of patients' treatments. Meeting this demand requires not only the commitment of abundant resources, but also a sophisticated management of information systems, leading to initiatives such as the standardization of electronic health records. As these become mainstream, the amount of medical data available for analysis and knowledge extraction will increase exponentially. This is coupled with a surge in novel techniques for the non-invasive measurement and acquisition of medically-relevant data, in various forms including signals and image. The resulting vast amount of information - notwithstanding issues of standardization and availability - is a valuable asset for the Computational Intelligence community. Tapping into this data source, biomedical applications of CI are already experimenting an extraordinary growth. At ESANN, the special session "Computational Intelligence in Biomedicine" reflects some of the main emerging themes in the field. This brief tutorial prefaces the session, summarizing some of the contributions, while also providing some pointers to opportunities and challenges for CI in biomedical research.

1 Introduction

We can trace back the origins of modern science to the figure of the French philosopher René Descartes and his groundbreaking Discourse on the Method [1]. Those of us working in the field of Computational Intelligence (CI) still dwell in the shadow he casts when delving into concepts such as projective spaces, distances, manifolds and the like. These all draw from Descartes' seminal studies on geometry [2], with Cartesian coordinates still deeply ingrained in the most basic levels of our scientific reasoning.

It may then come as a surprise that one of the philosopher's foremost interests was rather less abstract in nature: the pursuance of medical knowledge and human health. One of the staunchest early defendants of Descartes' new philosophy was precisely a medical doctor: Hendrik de Roy. Through the delivery of a notable and controversial series of lectures at the University of Utretch, in

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the Netherlands, on the subjects of physiology and the science of health [3], he arguably ignited the great debate of the $XVII^{th}$ Century that built the foundations of modern medical science as we know it today: A medical science grounded in experimental enquiry and reasoning.

We must leap no less than three centuries forward to find a formalization of the concept of Evidence-Based Medicine (EBM). Not even forty years have past since Scottish Professor Archie Cochrane laid out the foundations of EBM [4]. EBM would have certainly been sanctioned by rationalists such as Descartes or de Roy, as it means to provide "healthcare practice that is based on integrating knowledge gained from the best available research evidence, clinical expertise, and patients' values and circumstances" [5]. Its practice, even if contested from some quarters, has become so widespread and relevant to medical science that it has merited being shortlisted as the 8^{th} most relevant medical milestone since 1840 by the prestigious British Medical Journal (BMJ) [6], just behind the oral contraceptive pill and ahead of medical imaging, even as it includes, for instance, X-rays.

The practice of EBM requires health management to be based on objective findings, whose generality is well established, rather than on beliefs or subjective assessment. Nothing surprising here. Unfortunately, while the practice of EBM should concern the use of quantitative information, in concert with other available sources of knowledge -doing so in a sensible manner that suits the diverse real clinical context-, it has also been accused of being somehow soul-less and algorithmic, that is, of certain dehumanization. This perception may have to do with the fact that, fuelled by the rapidly increasing development of data acquisition and processing techniques, the medical field faces information overload and plenty of data management-related stress, which can take the focus off the patient as an individual and towards medical signals and statistical items.

While this might be seen as a concern, it may also be seen as an open field of opportunity for data mining and for the CI techniques usually associated with them. Information technologies play such a central rôle in current medical research and the delivery of healthcare that they came in 9^{th} place, just behind EBM, in the same BMJ poll.

Perhaps paradoxically, data processing is set to be the means to reverse the perception of dehumanization in healthcare. An example of this is pharmacogenomics. Rapid advances not just in systems biology but also in Information and Communication Technologies, including wireless processing, mobile communications, the world-wide web and algorithmic advances in CI itself, generated the so-called 4P agenda of preventive, predictive, personalised and participatory healthcare [7]. Importantly, this agenda is not just driven by a commodification of healthcare made possible by technological advances, but by a yet more powerful factor - the fact that healthcare is only sustainable in the mid-term if costs per person are substantially reduced. And this means caring for people while they are healthy, with an emphasis on preventive care, keeping people out of hospitals, with care in the home a priority, and following-up chronic disease with ambulatory measurements that, by issues both of expediency and ethics,

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need to be processed locally using automatic processing defined by CI methods. Alerts and advice are then generated and transmitted in a minimally invasive way, yet with life-saving potential, and an essential rôle in moderating the current trajectory of rapidly spiralling healthcare costs.

The 4P agenda will impact on routine care practices over the next two decades. Therefore, as we feed-forward into this century we see a step-change in the need and use of evidence base in the delivery of healthcare, where networked hospital systems generate data at a faster rate than we can turn over for direct patient care and the advent of human genome decoding in minutes rather than days will unleash a deluge of data at a much faster rate than we can extract useful information from it. The twin developments of EBM and data-rich environments provide fertile soil for the development of CI-based knowledge engineering.

Against this setting, we thought it appropriate to set up an ESANN special session on CI in Biomedicine. In this brief paper we assess the field of new opportunities that opens for CI techniques in their application to an area that is likely to increasingly demand them as tools of medical knowledge extraction. In fact, this field of application has become so broad that a tutorial such as this cannot even come close to cover its manifold facets. We therefore focus on some contributions provided by the papers accepted for the session as part of the 18^{th} European Symposium on Artificial Neural Networks.

2 Opportunities and challenges for data mining and CI in biomedical research

Over the last decade, biomedicine has become a data-intensive field of research in which new data acquisition techniques appear at a staggering pace. Nature recently devoted the cover of one of its latest issues [8] to advances in cancer research, one of the most active biomedical areas. Even within the very narrow context of just this journal issue and research field, several next-generation sequencing approaches were introduced with the specific target of monitoring genetic changes in tumour cells. Elsewhere [9], state-of-the art data acquisition was combined with advanced CI techniques, in the form of Bayesian mixture models applied to identify single-nucleotide variants in the human genome.

The increasing reliance on microarrays data in genomics, and on protein chips and tissue arrays in proteonomics, add to the wealth of information about active metabolic pathways that is available also from (f)MRI, PET, micro CT and MR spectroscopy. This, an already complex and diverse picture, is further complicated by the heterogeneity of the available medical evidence, which extends to expert data, for instance, on disease heterogeneity, especially in the composition of cancer samples, along with clinical indicators that are often systemic in nature. These indicators are often expressed with discrete data, in contrast to numeric physiological measurements. The development of high-throughput genomic technologies is forcing an in-depth re-evaluation of not only the standards of data handling and processing, but also igniting discussion about biomedical

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data accessibility on the web [10] or in collaborative grids [11].

A further challenge stems from the need for interpretation by the clinician, explanation to the patient, and regulatory pressures for validation and pharmacovigilance. They all make it important to express the operation of analytical models in clear-cut Boolean terms, with filters for patients whose risk-benefit balance lies in favour, or against, particular therapeutic choices [12]. In this respect, there has been, in recent years, plenty of interest in the use of rule extraction from CI models in biomedical research, much of it related to the analysis of cancer data (see, for instance, [13, 14])

3 CI in biomedicine: contributions to the ESANN 2010 special session

3.1 CI for dimensionality reduction in biomedical problems

Medicine has for long been a niche for statisticians. The central rôle played by statistics in medical science has been long acknowledged, and its aims include the monitoring and surveillance of health; the detection, prevention, and analysis of causes of disease; and the evaluation of treatments for disease [15]. The challenge of managing the complexity of biomedical data invites us to go one step further than traditional statistics and resort to knowledge discovery and data mining in order to implement data pre-processing strategies.

One of main and most common challenges posed by biomedical data is the *curse of dimensionality* [16]. Often, these types of data are not acquired with the specific purpose of data-based modelling, and one of the negative consequences of this is the not too uncommon situation in which only few data records and of large dimensionality are available for analysis. In no other fields is this more obvious than in those of the *-omics* family, with the development of high-throughput genomic and proteomic technologies [10]. Very few standard statistical methods (and the same can be said for CI techniques) scale well for small data sets of very large dimensionality. Limitations on data availability mean that the high-dimensional spaces where data reside are inherently sparse, which entails unexpected geometrical properties and problems with the use of standard metrics [17].

The problem of data high dimensionality is also one of model transparency. Indeed, amongst the drawbacks affecting the application of CI methods in the biomedical field (especially in everyday clinical environments) is the usually limited interpretability of the results they yield. This is, needless to say, a sensitive issue in the medical ambit, and one that should not be underestimated: even the best efforts put in state-of-the-art data modelling methods can be rendered useless by lack of translation into usable medical knowledge.

One way of increasing model transparency is by explaining the operation of CI methods using rule extraction techniques, as mentioned in the introduction. Alternatively, dimensionality reduction (DR) can ease the interpretation of results [18]. DR methods can be categorized according to different criteria. There

exist linear and nonlinear DR methods [17]. There are methods of Feature Selection (FS) that aim to single out one or several parsimonious subsets of attributes that are optimal according to a given criterion (for classification, prediction, error minimization, etc.), and there are methods of Feature Extraction (FE) that combine the available data in different ways to generate a new, smaller sets of features to substitute the original ones. All these approaches have advantages and limitations whose description is beyond this tutorial.

Methods of FS and FE for DR are discussed in [19] in the context of a problem of diagnosis of human brain tumors. It is argued here that, although Principal Component Analysis is a very common FE technique of choice in such context, it does unfortunately suffer from limitations, including one of interpretability. That situation makes it worth pursuing the development and use of better targeted FE techniques. The proposed Spectral Prototype Extraction method is developed within a robust variational Bayesian framework that does not sacrifice interpretability, while being suited to the specific characteristics of spectral data.

A different approach to DR is found in [20] and [21]. Here, high-dimensional data are approximated using low-dimensional manifold representations. These representations do not only simplify the interpretation of results *per se*, but are meant to provide the means for the visual display of data and results, together with information on the grouping structure of data. Visualization is an extremely powerful tool to gain exploratory insight into data. A Bayesian model of the manifold learning family, similar to the one used in [19], is applied in [20] to analyze electromyographic (EMG) data recordings corresponding to stroke patients undergoing rehabilitation therapy. This is a constrained Hidden Markov Model suited to the analysis of multivariate time series such as the EMG signal at hand that behaves robustly in the presence of noise. A more traditional Self-Organizing Map (SOM) model is used in [21] to analyze both physiological variables and treatment characteristics in patients undergoing chronic renal failure. SOM is used for qualitative knowledge extraction through visualization in a first stage of the analyses.

3.2 CI in biomedical pharma

Clinical decision support systems have used CI methods since the end of the fifties [22]. By 1995, more than 1,000 citations of artificial neural networks could be found in the biomedical literature [23]. Today, a basic search on a medical database such as PUBMED offers more than 17,000 results. However, this number is substantially lower when the search also involves the term "drug monitoring". To be more precise, a PUBMED search involving "neural networks" *and* "drug monitoring" only returns 18 results, an all of them quite recent (only 2 results if the search is further restricted to the terms "artificial neural networks" *and* "drug monitoring").

All of this comes to show that the application of neural networks has only very recently (as compared to other biomedical applications) emerged as a suitable tool for therapeutic drug monitoring (TDM), becoming a promising and

expanding field from both the theoretical and practical point of view.

The relevance of computer-based data analysis in the pharmaceutical sciences has sharply increased due to the availability of vast amounts of data providing information about treatments and response to treatments. CI methods can help to extract information from these data, thus providing clinicians with efficient decision support tools. There are many drugs whose effect is uncertain, especially those with narrow therapeutic ranges that are strongly dependent on patients' characteristics. In those cases, any aid to gauge the adequate dosages to be administered is crucial in order to avoid overdoses (likely intoxications) or underdoses (no relevant effect of the drug on the state of the patient).

Recently, important advances in dosage formulations, TDM, and the emerging role of combined therapies have resulted in a substantial improvement in patients' quality of life. Nevertheless, the increasing amounts of collected data, and the nonlinear nature of the underlying pharmacokinetic and pharmacodynamic processes justify the development of mathematical models capable of predicting concentrations of a given administered drug, and then adjusting the optimal dosage.

Physical models of drug absorption and distribution, Bayesian forecasting, neural and kernel methods have all been used to predict blood concentrations [24]. Also, very recently, there have been a few attempts [25, 26], based on Reinforcement Learning, to find optimal policies (medical protocols of drug prescription) in order to achieve a certain goal (usually defined by means of a certain patient's state). In our special session, Sun and colleagues [27] propose Gaussian Processes (GPs) with different covariance functions as predictors of the permeability coefficients of Human, Pig, Rodent and Silastic membranes. That is not just a difficult problem but also a very relevant one in the framework of biomedical pharma, since the delivery of drugs by means of skin patches has become relatively commonplace over the last years. Achieved results show that GPs perform better than quantitative structure-activity relationship (QSARs) predictors, especially when *Matérn* and *neural network* covariance functions are used.

All in all, and although the application of CI methods to Biomedical Pharma has already yielded some satisfactory results, there is still a long way to go in this area of research, in which a strong flow of activity is to be expected over the next years.

3.3 CI for cancer and survival analysis

The introduction of the on-line software package Adjuvant! [28] ignited an interest by clinicians in web-based decision support systems, especially for breast cancer. There is a substantial history of neural network algorithms for failure time data, also known as survival models, dating back to work by the originators of Adjuvant! [29]. However, the actual decision support package is not a data-driven model, more so one based on results from meta-analysis calibrated to a specific US data set and externally validated on data colleted for the British Columbia Cancer Agency in Vancouver.

The challenge in the field is to produce flexible models that can robustely fit data without the need for proportionality assumptions about the hazard, and in the presence of time dependent effects and subtle interactions between covariates. This need arises because standard medical statistical models typically rely on these assumptions, or hand-crafted parametric solutions to get around them. In particular, the non-linearity inherent in medical data has led to the categorization of crucial prognostic indicators, such as histological stage, damaging their robustness [30].

A central feature of survival models for cancer is the need to accurately reflect the presence of typically right-censored data, that is to say information about a lower-bound on the possible event date. An example would be where a patient dies of an unrelated cause to the cancer, which prevents information about cancer recurrence from being available after that date.

Several different modelling strategies have been derived which deal with censorship, the detail of which is outside the scope of this brief tutorial paper - more detail may be found in [31]. There methods are typically to model the cumulative probabilities for the risk of the event of interest occurring after any given year, akin to directly modelling survival [32, 33] and also modelling the condition probability of the event occurring during a discrete time interval, conditional on it not having occurred prior to the start of that interval. This is known as hazard modelling and was initially published with the Partial Logistic artificial Neural Network (PLANN) [34]. Other approaches include rigorous Bayesian frameworks applied to neural network achitectures, typically the Multi-Layer Perceptron [35, 36]. These approaches straddle conventional statistics and machine learning.

All of these models need to balance flexibility with good generalisation capabilities to discriminate between patient cohorts at significantly different risk of mortality or recurrence. This requires the application of complexity control framworks, of which the above Bayesian approaches are an example, and the evidence approximation with Automatic Relevance Determination(ARD) is another [37].

Further, analytical models need to be integrated into clinical interfaces that are meaningful to clinicians, and efforts have been made to group patients by risk and to explain the groupings using low-order Boolean rules, both for the purpose of validating the operation of the neural network against expert clinical knowledge and to simplify the prognostic model, replacing the analytical black-box structure with a prognostic rule tree [37, 38, 39].

Some of these methods have been extended further to model more than one competing risk, for instance local vs, distal recurrence of the tumour, when only time-to-first-event is possible and the hazard predictions for all risks must add strictly to unity, which can be ensured for instance using the well-known soft-max activation function and making a clear correspondence with the objective functions for statistical survival analysis [40].

More recently, attention has turned to applying kernel methods to survival [41], including the Support Vector Machine. This is a relatively new field that

seeks to exploit the remarkable discrimination ability of methods from computational learning theory, while making them applicable to failure time data with censorship. A good example of the state-of-the-art in this field is the last paper in this special session by Van Belle and colleagues [43].

4 Conclusions

Dimensionality reduction, pharmacogenomics and survival analysis illustrate three application areas of considerable potential for computational intelligence in biomedicine. While there are substantial advances in all of these areas published in the scientific literature, particular examples of which feature in this special session, still these fields are in their relative infancy, with much further work to be done. Some directions for further improvement are robustness in generalization, increase specificity of outcome prediction, implement scalability to large-scale data sets and also to combining together in a single overarching model different signal modalities, for instance numeric data derived from physiological measurements, together with categorical variables indicating clinical status and ordinal variables from demographics.

Overall, computational intelligence in biomedicine is a growth area for research, feeding on increasing volumes of data. It remains for the community of researchers to integrate with each other and with the clinical and IT sectors, to develop new machine learning models, to validated them appropriately e.g. using the frameworks detailed in [44] and find ways to translate the research into seamless interfaces to routine clinical practice.

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