Artificial Neural Networks and Predictive Medicine: a Revolutionary Paradigm Shift

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1. Introduction

Physicians every day try to accomplish their mission: to give the better care and assistance to their individual patients. They know perfectly that an individual subject is typically "unique". He or she has specific characteristics, qualities and features, different perceptions of risk value, different values scale, different familiar environments and social roles, all together interacting in a complex way. In other words no subject is equivalent to another, nor even mono-ovular twins.

But physician has to take decisions continuously, in front to every single individual, facing always with uncertainty. Will my diagnosis be confirmed later on? Will my treatment work in this patient? Will this patient follow my indications? These are questions that most physicians ask themselves every day.

Physicians know that an individual patient is not the average representative of the population. Rather he or she is a person with unique characteristics. What they not always know is that an intervention may be effective for a population but not necessarily for the individual patient. The recommendation of a guideline may not be right for a particular patient because it is not what he or she wants, and implementing the recommendation will not necessarily mean a favourable outcome.

The fundamental resource for them still remain their experience and their intelligence in using experience as a guide. In addition, increasing expectations of the highest quality of health care and the rapid growth of ever more detailed medical knowledge leave the physician without adequate time to devote to each patient – who all-too-often becomes a case or a file rather than being a person. So, for lack of time, most medical decisions must be based on rapid judgments of the "case" relying on the physician's unaided memory. Only in rare situations can a literature search or other extended investigations be undertaken to assure the doctor (and the patient) that the latest knowledge is being brought to bear on any particular malady. Continued training and recertification procedures encourage the physician to keep more of the relevant information constantly in mind, but fundamental limitations of human memory and recall coupled with the growth of available and accessible knowledge assures that most of what is known cannot be known by most individuals.

The spectacular development of information technology and molecular biology has increased exponentially the quantity of the information available for the busy physician. It is not unusual to have at hand, especially when faced with treatment planning for a chronic degenerative disorder, hundreds of different variables, consisting of clinical history data, objective findings, symptoms, multi-item scales of different meanings, laboratory examinations, etc. With the increased availability and use of functional genomics and digital imaging we now tentatively have at our disposition thousands of data per subject.

This creates a paradox: in comparison with 10-20 years ago we are now able to collect more data per subject than subjects per study.

2.The emergence of complexity in medicine

Non linearity, complexity, fuzzy interaction are emerging features of chronic degenerative diseases which account for most morbidity and mortality in western world. Unfortunately even the most powerful and well established statistical methods were developed in the first half of the past century when the scenario was dominated by acute infective diseases and the available information was much more simple, or at maximum "complicated" rather than "complex". comparison with today.

More features imply more information and potentially higher accuracy. Unfortunately more features we have, the more difficult information extraction is. In this high dimensional space, the hyper points corresponding to single individuals are sparse and the notion of proximity fails to retain its meaningfulness. For this reason clustering become extremely hard to be performed. In this situation we are dealing with flat, rectangular data set, a sort of telescope data set. This kind of data set are intractable from a traditional statistics point of view due to the fact that the excessive amount of degrees of freedom allows any kind of data interpolation most of the time meaningless.

A part from quantitative features, non linearity, complexity, fuzzy interaction are new emerging qualitative features of chronic degenerative diseases which account for most morbidity and mortality in western world. Unfortunately even the most powerful and well established statistical methods were developed in the first half of the past century when the scenario was dominated by acute infective diseases and the available information was much more simple, or at maximum "complicated" rather than "complex". comparison with today.

There is now the reason to ask a fundamental question: is the mathematics used in medicine what it should be given the complexity of the chronic degenerative diseases?

There are a number of different reasons to apply complex systems mathematics on predictive medicine and some of them are listed in the table 1.

Processes are based on complex networks of interacting genes and proteins.
Health status is the consequence of dynamic processes that regulate these networks
Non linear critical thresholds link to pathology
The predictions have to be applied at individual patient level.
Huge amount of data per subject hamper statistical tests

Table 1. Motivations to apply complex systems mathematics on predictive medicine

Complexity is based on small elementary units working together in small populations of synchronous processes. In a complex system each component changes, over time, losing its identity outside of the system. Complexity needs a different kind of mathematics, able to handle chaotic behaviour, non linear dynamics, and fractal geometry (Kaplan & Glass,1995; Goldberger, 1996).

Computational and mathematical medicine needs different statistical approaches, based on new mathematical and logic assumptions broadly belonging to complex theory setting allow to tame these intractable data sets. Seen in this perspective computer science is now playing the role which mathematics did from the seventeenth through the twentieth centuries: providing an orderly, formal framework and exploratory apparatus for knowledge progress.

Actually the coupling of computer science and these new theoretical bases coming from complex systems mathematics allows the creation of "intelligent" agents able to adapt themselves dynamically to problem of high complexity: the Artificial Neural Networks (ANNs).

3. Artificial Neural Networks

Artificial Neural Networks are adaptive models for the analysis of data which are inspired by the functioning processes of the human brain. They are systems which are able to modify their internal structure in relation to a function objective and are particularly suited for solving problems of the non linear type, being able to reconstruct the approximate rules that put a certain set of data - which describing the underlying problem with a particular target (specific diagnosis, outcome etc.).

They are particularly suited for solving problems of the non linear type, being able to reconstruct the approximate rules that put a certain set of data - which describes the problem being considered - with a set of data which provides the solution. For a detailed description of these models and tools we refer to recent reviews (Grossi & Buscema, 2007; Grossi & Buscema, 2006)

The base elements of the ANNs are the nodes, also called processing elements, and the connections. Each node has its own input, from which it receives communications from other nodes and/or from the environment and its own output, from which it communicates with other nodes or with the environment. Finally, each node has a function f through which it transforms its own global input into output (see figure 1).

Each connection is characterized by the strength with which pairs of nodes are excited or inhibited. Positive values indicate excitatory connections, the negative ones inhibitory connections.

The connections between the nodes can modify themselves over time. This dynamic starts a learning process in the entire ANNs. The way through which the nodes modify themselves is called "Law of Learning". The total dynamic of an ANNs is tied to time. In fact, for the ANNs to modify its own connections, the environment has to necessarily act on the ANNs more times. Data are the environment which acts on the ANNs.

The learning process is, therefore, one of the key mechanisms that characterize the ANNs, which are considered adaptive processing systems. The learning process is one way to adapt the connections of an ANNs to the data structure that make up the environment and, therefore, a way to "understand" the environment and the relations that characterize it.
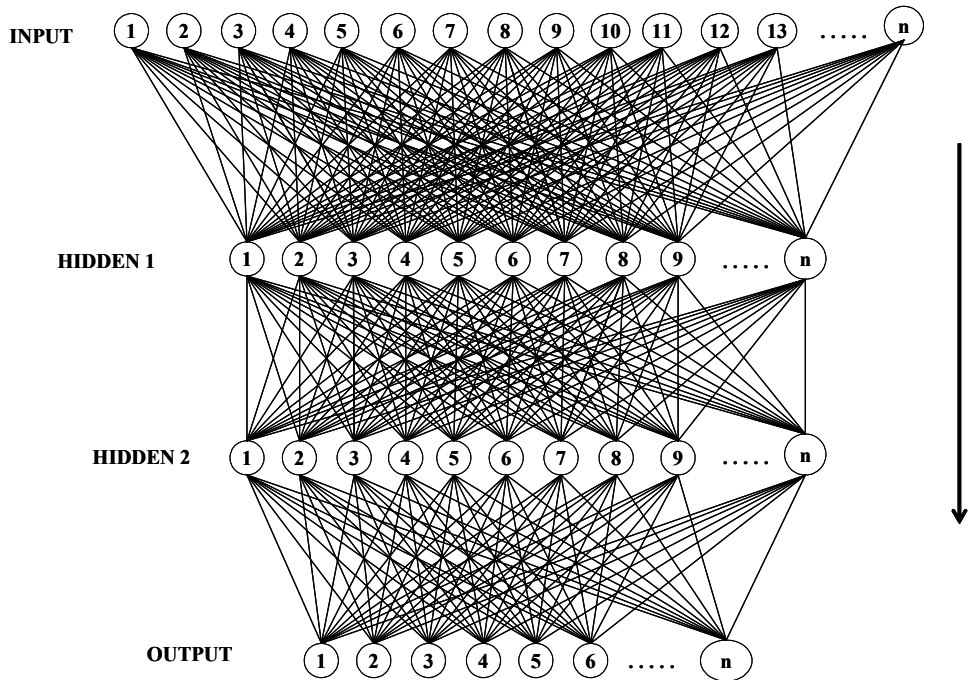
Fig. 1. Example of Supervised artificial neural network. The architecture is that of back propagation neural network with one layer of input nodes, corresponding to independent variables, two layers of hidden nodes allowing the integration of non linear functions, and one layer of output nodes corresponding to the target variables.

The raw indicate the direction of flow of data along the network.

4. Evolutionary algorithms

At variance with neural networks which are adaptive systems able to discover the optimal hidden rules explaining a certain data set, Evolutionary Algorithms (EA) are Artificial Adaptive Systems able to find optimal data when fixed rules or constraints have to be respected. They are in other words optimisation tools which become fundamental when the space of possible states in a dynamic system tends toward infinitum.

An EA for example can help to distribute the original sample in two or more sub-samples with the aim of obtaining the maximum performance possible from an ANN that is trained on the first sample and tested on the second. It is possible, in order to limit eventual optimistic polarizations in the evaluation of the performance, to invert the two samples and to consider the mean between the two approximations obtained as fitness of the algorithm and as an estimate of the model's quality.

Also the problem to select among the different variables available those most related to a particular outcome without the recur to linear correlation parameters can be approached with EA. When linear systems are used, an instrument exists, correlation index , which indicates the degree of relationship existing between the input and output variables of the

system, in this way suggesting which of the variables available to use to build a model of the problem. The problem of selecting a subset of variables on which to build the model for the process under examination stems from the fact that, when data are gathered to build the Data Base, the relationship between the collected variables and the function of the process being examined is not known. In this case the natural approach is to include all of the variables that may have a connection with the event being studied. The result of this approach is that often a series of variables which do not contain any information regarding the process being examined are present. These variables, inserted in the model, cause an increase of the noise and therefore a greater difficulty for the ANN to learn the data correctly.

The coupling of ANN and EA and brings to the concept of artificial organisms, able to optimize the classification performance and prediction ability.

Training & Testing and Input Selection which have been combine in a single system called TWIST (Buscema, 2007-2008) are example of such artificial organisms which are devoted to the problems above discussed respectively.

5. Basic philosophy of Artificial Neural Networks

The basic principle which is proposed in ANNs is very simple: all the biological signals from all the sources available are analyzed together -and not individually- both in time and space. The reason for such an approach is quite simple and self-explaining: the instant value of the system in any recording source depends, in fact, upon its previous and following values (how many, and in which amount for each previous state?), upon the previous and following values of all the other recording sources (how many, and in which amount for each previous state?).

In summary, the aim of the "analyzer" is not to analyze the language of each individual variable, but to evaluate the meta-language which considers the holistic contribution of all the recorded variables. We, in fact, believe that the equilibrium of each individual subject is defined by a specific background signal model, distributed in time and in the space. Such a model is a set of background invariant features able to specify the quality of the immune activity for example. The system that we propose to apply in this research context completely ignores the subject's contingent characteristics. It utilizes a recurrent procedure which squeezes at progressive steps the significant signal and progressively eliminates the non-significant noise.

6. The paradigm shifts of Artificial Neural Networks in predictive medicine

The use of ANNs and in particular Neural Networks are already emerging as new trends in medical statistics. Although these methods are not yet in widespread use, they have already had a clinical impact in specific areas, notably cervical cytology, x-Ray mammography and early detection of acute myocardial infarction where large-scale prospective multicenter studies have been carried out. Extensive reviews on this subject has been published (Lisboa, 2002).

There are in the literature many examples of successful application of ANN in outcome research.

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Our group has proved the usefulness of the added predictive value gained with the use of advanced artificial neural networks coupled with evolutionary algorithms in a number of medical fields, ranging from heart diseases, gastroenterology and neurology with special regard to Alzheimer disease, stroke and Amyotrophic Lateral Sclerosis (Street *et al.*, 2008; Grossi, 2006).

ANNs bring a number of revolutionary paradigm shifts which will have a strong impact in predictive medicine. They are listed in the table 2.

No limitation in the amount of data processed
No limitation in the different nature of data processed
No limitation in the degree of complexity of data processed
Bottom - up computation: models are data driven
Interactions among different factors are easily picked-up
Inference takes place at individual level
Internal validity of modelling ensured with validation protocols
Fuzzy logic allows to escape from the probability theory trap

Table 2. Paradigm shift introduced by ANNs in medicine

ANNs are able to reproduce the dynamical interaction of multiple factors simultaneously, allowing the study of complexity; this is very important for the researcher interested to deep the knowledge of a specific disease or to better understand the possible implications relative to strange associations among variables. This has to do to what is called "intelligent data mining". But one the other hand ANNs can also help medical doctors in making decisions under extreme uncertainty and to draw conclusions on individual basis and not as average trends. The modern patient wants to be treated as an individual person and not just as a statistics. Patients want to know their own risk, not just a parameter regarding a class of people similar to them just for some aspects. ANNs are very powerful in modelling at single individual level, and by combining several parallel ANNs trained on the same data set is possible to make multiple statistics on a single subject, allowing in this way the calculation of the confidence interval of the prediction estimate. Finally ANNs make possible to treat huge amount of information without squeezing arbitrarily the data and without loosing complexity. This contributes to a new holistic vision of the human subject contrasting the statistical reductionism, which tends to squeeze or even delete the single subject sacrificing him to his group of belongingness. A remarkable contribution to this individual approach comes from Fuzzy Logic, according to which there are no sharp limits between opposite things, like health and disease. This approach allows to partially escape from probability theory trap in situations where is fundamental to express a judgment based on a single case and favours a novel humanism directed to the management of the patient as individual subject.

7. The unfulfilled dream: prediction of individual response to treatments

Making predictions for specific outcomes (diagnosis, risk assessment, prognosis) represents a fascinating aspect of medical science. Different statistical approaches have been proposed to define models to identify factors that are predictive for the outcome of interest. Studies

have been performed to define the clinical and biological characteristics that could be helpful in predicting who will benefit from an anti-obesity drug for example, but results have been limited (Padwal *et al.*, 2003).

Traditional statistical approaches encounter problems when the data show big variability and not easily normalized for inherent nonlinearity. More-advanced analysis techniques, such as dynamic mathematical models, can be useful because they are particularly suitable for solving nonlinear problems frequently associated with complex biological systems.

Use of ANNs in biological systems has been proposed for different purposes, including studies on deoxyribonucleic acid sequencing (Parbhane *et al.*, 2000) and protein structure (Jagla & Schuchhardt, 2000).

ANNs have been used in different clinical settings to predict the effectiveness of instrumental evaluation (echocardiography, brain single photon emission computed tomography, lung scans, prostate biopsy) in increasing diagnostic sensitivity and specificity and in laboratory medicine in general (Tafeit & Reibnegger, 1999). Also, they have proven effective in identifying gastro-oesophageal refux patients on the sole basis of clinical data (Pace *et al.*, 2005). But the most promising application of ANNs relates to prediction of possible clinical outcomes with specific therapy. ANNs have proven effective in detecting responsiveness to methadone treatments of drug addicts (Massini & Shabtay, 1998), to pharmacological treatment in Alzheimer disease (Mecocci *et al.*, 2002), to clozapine in schizophrenic patients (Lin *et al.*, 2008) and in various fields of psychiatric research (Politi *et al.*, 1999).

The use of ANNs for predictive modelling in obesity dates back to a decade ago, where it was proposed to model the waist-hip ratio from 13 other health parameters (Abdel-Aal & Mangoud, 1997). Later, it has been proposed as a tool for body composition research (Linder et al., 2003).

One of the main factors preventing a more efficient use of new pharmacological treatments for chronic diseases like for example hypertension, cancer, Alzheimer disease or obesity is represented by the difficulty of predicting "a priori" the chance of response of the single patient to a specific drug. A major methodological setback in drawing inferences and making predictions from data collected in the real world setting, such as observational studies, is that variability in the underlying biological substrates of the studied population and the quality and content of medical intervention influence outcomes. Because there is no reason to believe that these, like other health factors, work together in a linear manner, the traditional statistical methods, based on the generalized linear model, have limited value in predicting outcomes such as responsiveness to a particular drug.

Most studies have shown that up to 50% of patients treated with new molecules given in monotherapy or as an adjunct to standard treatments may show an unsatisfactory response. As a matter of fact, when time comes for the physician to decide about type of treatment, there is very little evidence that can help her/him in drug treatment choice. Take for example obesity. Here only scanty data are available on predictive factors to the specific treatment, and attempts at developing models for predicting response to the drug by using traditional techniques of multiple regression have showed an unsatisfactory predictive capacity (i.e. inferior to 80% of total variance). (Hansen *et al.*, 2001; Hainer *et al.*, 2005). A possible explanation could be that obesity is a so-called complex disease, where different factors interact with multiple interactions among variables, positive and negative feedback loops, and non-linear system dynamics. Another good example is Alzheimer Disease.

Clinical trials have established the efficacy of cholinesterase inhibitor drugs (ChEI), such as tacrine, (Knopman *et al.*, 1996) donepezil, (Rogers *et al.*, 1998) and rivastigmine (Rösler *et al.*, 1999) based on improvement in cognitive aspects and in overall functioning using the Alzheimer's Disease Scale—Cognitive subscale (ADAS-Cog) and the Clinician's Interviewed Based Impression of Change (CIBIC), respectively. Although the mean score of treated patients in both scales was significantly higher than the placebo group, many subjects under active treatment showed little or no improvement (non-responders).

However it is not possible to estimate which patients are likely to respond to pharmacological therapy with ChEI. This prediction would be an important decision-making factor in improving the use of healthcare resources.

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A possible alternative approach to the solution of the problem is represented by the use of Neural Networks.

Although ANNs have been applied to various areas of medical research, they have not been employed intensively clinical pharmacology as they might deserve.

In our personal experience ANNs proved to be a useful method to discriminate between responders and non-responders, better than traditional statistical methods in our three experimental studies carried out with donepezil in Alzheimer disease and with sibutramine in obesity and with infliximab in Crohn disease.

In a paper published in 2002 (Mecocci, 2002) we have evaluated the accuracy of artificial neural networks compared with discriminant analysis in classifying positive and negative response to the cholinesterase inhibitor donepezil in a opportunistic group of 61 old patients of both genders affected by Alzheimer's disease (AD) patients in real world setting along three months follow-up.

Accuracy in detecting subjects sensitive (responders) or not (non responders) to therapy was based on the standard FDA criterion standard for evaluation of efficacy: the scores of Alzheimer's Disease Assessment Scale—Cognitive portion and Clinician's Interview Based Impression of Change—plus scales. In this study ANNs were more effective in discriminating between responders and nonresponders than other advanced statistical methods, particularly linear discriminant analysis. The total accuracy in predicting the outcome was 92.59%.

In a second study we evaluated the performance of ANN in predicting response to Sibutramine treatment in obese patients (Petroni *et al.*, in press). Out of 162 patients treated in an open-label multicentre study with 6-month Sibutramine 10 mg/day, increased to 15 mg/day if weight loss ≤ 5% after 3 months, we evaluated 92 obese subjects (10 M, 82 F, mean age 44.2 ± 12.4) with full data set available. Patients were considered responders if body weight loss was ≥ 5% at the end of the study. At descriptive analysis, non-responders (n=26) only differed from responders (n=66) in having significantly lower values of TSH and in having a more frequent history of previous dietary or pharmacological treatment for weight loss. Out of 84 baseline variables, after a preliminary analysis, 33 variables which

best discriminated between responders and non-responders were selected; a logistic regression (LR) was also performed on same variables. The overall mean accuracy of ANN detection of responders was 79.1%, being correctly recognised in 90.5%; predictive model could not be developed by LR . Among baseline predictive variables, those with the highest "input relevance" were: previous drug treatment, android fat distribution, alcohol consumption, HDL cholesterol, hypertension; variables that also significantly contributed to the model were: previous dietary treatment, pregnancies, abnormal lipid profile, physical activity, FT4, heart rate, diastolic blood pressure, obesity in siblings, previous smoking, triglycerides, age, basal energy expenditure, weight at 20 years, current smoking, TSH, creatinine. In Conclusion ANN proved to be a useful method to discriminate between responders and non-responders, better than traditional statistical methods.

Finally in a third study we evaluated the use of artificial neural networks in predicting response to infliximab treatment in patients with Crohn's disease(Kohn *et al.*, 2005).

In this pilot study , different ANN models were applied to a data sheet with demographic and clinical data from 76 patients with steroid resistant/dependant or fistulizing CD treated with Infliximab to compare accuracy in classifying responder and non responder subjects with that of linear discriminant analysis.

Eighty one outpatients with CD (31 men, 50 women; mean age± standard deviation 39.9 ± 15 range: 12-81) participating to an Italian Multicentric Study (Parbhane *et al.*, 2000), were enrolled in the study. All patients were treated, between April 1999 and December 2003, with a dose of Infliximab 5 mg/kg of body weight for luminal refractory (CDAI > 220–400) (43 patients), fistulizing CD (19 patients) or both of them (14 patients).

The final data sheet consisted of 45 independent variables related to the anagraphic and anamnestic data (sex, age at diagnosis, age at infusion, smoking habit, previous Crohn's related abdominal surgery [ileal or ileo-cecal resections] and concomitant treatments including immunomodulators and corticosteroids) and to clinical aspects (location of disease, perianal disease, type of fistulas, extraintestinal manifestations, clinical activity at the first infusion [CDAI], indication for treatment). Smokers were defined as those smoking a minimum of 5 cigarettes per day for at least 6 months before their first dose of Infliximab. Non smokers were defined as those who had never smoked before, those who had quit smoking at least 6 months before their first dose of Infliximab, or those who smoked fewer than 5 cigarettes per day. Concomitant immunosuppressive use was defined as initiation of methotrexate before their first Infliximab infusion or initiation of 6-mercaptopurine (6-MP) or azathioprine more than 3 months before their first Infliximab infusion.

Assessment of response was determined by clinical evaluation 12 weeks after the first infusion for all patients. Determination of response in patients with inflammatory CD was based on the Crohn's Disease Activity Index (CDAI). For clear - cut estimate clinical response was evaluated as complete response or partial / no response.

Complete response was defined as (a) clinical remission (CDAI < 150) in luminal refractory disease and (b) temporary closure of all draining fistulas at consecutive visits in the case of enterocutaneous and perianal fistulas; entero-enteric fistulas were evaluated by small bowel barium enema and vaginal-bladder fistula by lack of drainage at consecutive visits. For patients with both indications the outcome was evaluated independently for each indication.

Two different experiments were planned following an identical research protocol. The first one included all 45 independent variables including frequency and intensity Crohn disease symptoms, plus numerous other social and demographic characteristics, clinical features

and history. In the second experiment the IS system coupled to the T&T system automatically selected the most relevant variables and therefore 22 variables were included in the model.

Discriminant analysis was also performed on the same data sets to evaluate the predictive performance of this advanced statistical method by a statistician blinded to ANN results. Different models were assessed to optimise the predictive ability. In each experiment the sample was randomly divided into two sub-samples, one for the training phase and the other for the testing phase, with the same record distributions used for ANN validation.

ANNs reached an overall accuracy rate of 88% while LDA performance was only of 72%.

8. Conclusions

New mathematical laws coupled by computer programming allow today to perform predictions which till few years ago were considered impossible. The prediction of response to a specific treatment in individual patients with supervised artificial neural networks has been documented and validated extensively in the literature. Less experience exists in predicting major unwanted effects of a new drugs after the commercialisation. In doing this task a close cooperation between regulatory agency scientific team and bio mathematicians experts in the use of new generations artificial adaptive system has to be strongly recommended.

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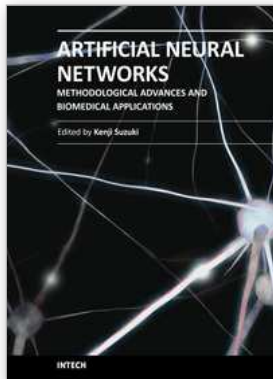
Artificial Neural Networks - Methodological Advances and Biomedical Applications

Edited by Prof. Kenji Suzuki

Artificial neural networks may probably be the single most successful technology in the last two decades which has been widely used in a large variety of applications in various areas. The purpose of this book is to provide recent advances of artificial neural networks in biomedical applications. The book begins with fundamentals of artificial neural networks, which cover an introduction, design, and optimization. Advanced architectures for biomedical applications, which offer improved performance and desirable properties, follow. Parts continue with biological applications such as gene, plant biology, and stem cell, medical applications such as skin diseases, sclerosis, anesthesia, and physiotherapy, and clinical and other applications such as clinical outcome, telecare, and pre-med student failure prediction. Thus, this book will be a fundamental source of recent advances and applications of artificial neural networks in biomedical areas. The target audience includes professors and students in engineering and medical schools, researchers and engineers in biomedical industries, medical doctors, and healthcare professionals.

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