

The Applications of Genetic Algorithms in Medicine

Ali Ghaehri¹, Saeed Shoar², Mohammad Naderan³ and Sayed Shahabuddin Hoseini^{4*}

¹Department of Management and Economy, Science and Research Branch, Azad University, Tehran, Iran

²Department of Surgery, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran

³School of Medicine Tehran University of Medical Sciences, Tehran, Iran

⁴Hannover Medical School, Germany

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ABSTRACT

A great wealth of information is hidden amid medical research data that in some cases cannot be easily analyzed, if at all, using classical statistical methods. Inspired by nature, metaheuristic algorithms have been developed to offer optimal or near-optimal solutions to complex data analysis and decision-making tasks in a reasonable time. Due to their powerful features, metaheuristic algorithms have frequently been used in other fields of sciences. In medicine, however, the use of these algorithms are not known by physicians who may well benefit by applying them to solve complex medical problems. Therefore, in this paper, we introduce the genetic algorithm and its applications in medicine. The use of the genetic algorithm has promising implications in various medical specialties including radiology, radiotherapy, oncology, pediatrics, cardiology, endocrinology, surgery, obstetrics and gynecology, pulmonology, infectious diseases, orthopedics, rehabilitation medicine, neurology, pharmacotherapy, and health care management. This review introduces the applications of the genetic algorithm in disease screening, diagnosis, treatment planning, pharmacovigilance, prognosis, and health care management, and enables physicians to envision possible applications of this metaheuristic method in their medical career.

There is no doubt that computers have revolutionized our everyday life. They are vastly used and have benefited nearly all fields of science from aerospace and astronomy to biology, chemistry, physics, mathematics, geography, archeology, engineering, and social sciences.

In medicine, electronic chips and computers are the backbones of a lot of imaging, diagnostic, monitoring, and therapeutic devices. These devices, which are composed of several different hardware components, are managed and controlled by software, which in turn are based on algorithms. An algorithm is a set of well-described rules and instructions that define a sequence of operations. Metaheuristic methods are algorithms that can more quickly solve complex problems, or they can find an approximate solution when classical methods are not able to find an exact one.¹

Several metaheuristic algorithms for finding an optimal or near-optimal solution exist. These include the ant colony (inspired by ants behavior),² artificial bee colony (based on bees behavior),³ Grey Wolf Optimizer (inspired by grey wolves behavior),⁴ artificial neural networks (derived from the neural systems),⁵ simulated annealing,⁶ river formation

dynamics (based on the process of river formation),⁷ artificial immune systems (based on immune system function),⁸ and genetic algorithm (inspired by genetic mechanisms).⁹ Metaheuristic approaches have been frequently used in other fields of science where complex problems need to be solved, or optimal decisions should be made. In medicine, although valuable work has been done, the power of these potent algorithms for offering solutions to the countless complex problems physicians encounter every day has not been fully exploited.

In this paper, we introduce the genetic algorithm (GA) as one of these metaheuristics and review some of its applications in medicine.

The genetic algorithm

A GA is a metaheuristic method, inspired by the laws of genetics, trying to find useful solutions to complex problems. In this method, first some random solutions (individuals) are generated each containing several properties (chromosomes). Based on the laws of genetics, cross-over and mutations occur in chromosomes to produce a second generation of individuals with more diverse properties.

Crossover and mutation are the two most central methods for diversifying individuals. In crossover,

*Corresponding author: ✉shahab337@yahoo.com

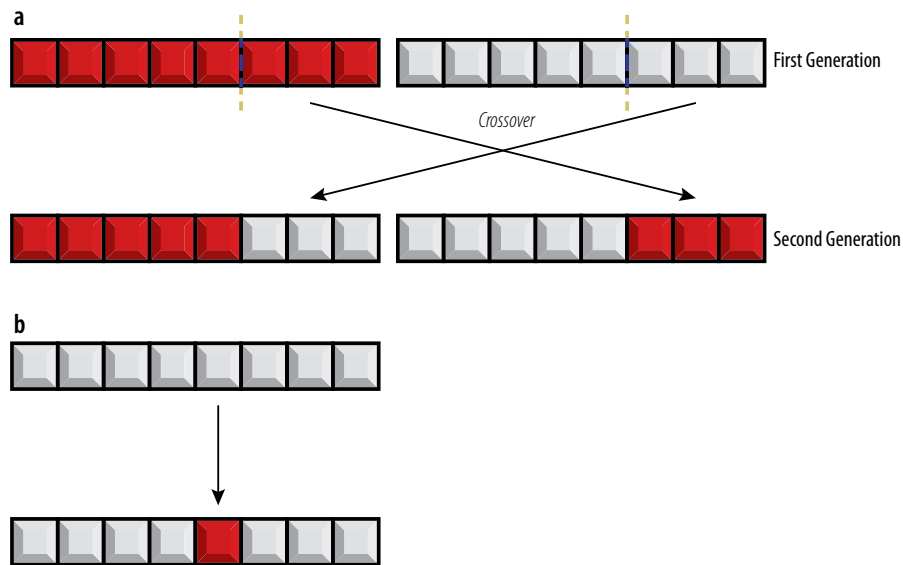


Figure 1: Methods to induce diversity in the population of individuals (candidate solutions). **(a)** During crossover, one part of a chromosome is exchanged by another fragment of another chromosome. **(b)** During mutations, one or more datasets on a chromosome are converted to different ones. These alterations will generate new individuals whose fittest (more optimal solutions) will survive.

two chromosomes are chosen. Then a crossover point along each chromosome is chosen followed by the exchange of the values up to the crossover point between the two chromosomes [Figure 1]. These two newly-generated chromosomes produce new offspring. The process of crossover will be iterated over and over until the desired diversity of individuals (i.e. solutions) is made. The mutation also generates new configurations by applying random changes in different chromosomes.¹⁰ One of the simplest mutation methods has been depicted in Figure 1.

In a GA, the possibility of reproduction depends on the fitness of individuals. The better chromosomes they have (i.e., those with better characteristics), the more likely they are to be selected for breeding the next generation. There are several selection methods; however, the aim of all is to assign fitness values to individuals based on a fitness function and to select the fittest. Genetic alterations in chromosomes will happen via crossover and mutations to produce another generation. This iterative process will continue until the fittest individual (the optimal solution) is formed or the maximum number of generations is reached.^{9,11}

It is worth noting that GAs are different from the derivative-based, optimization algorithms. First of all, GAs search a population of points in the solution space in each iteration while classical derivative-

based methods search only a single point. Moreover, GAs select the next population using probabilistic transition rules and random number generators while derivative-based algorithms use deterministic transition rules for selecting the next point in the sequence.^{11,12}

In the following, we introduce some of the applications of GAs in a variety of medical disciplines.

Radiology

Imaging techniques in radiology generate a large amount of data that needs to be analyzed and interpreted by radiologists in a relatively short time. Computer-aided detection and diagnosis are rapidly growing interdisciplinary technologies that aim to assist radiologists in faster and more accurate image analysis by detection, segmentation, and classification of normal and pathological patterns found on various imaging modalities. These include X-rays, magnetic resonance imaging (MRI), compute tomography (CT) scan, and ultrasound.¹³

In machine vision, an image of scenery (such as organs of the human body in radiology images) is acquired, processed, and interpreted. The boundaries (shape) and sizes of objects within the images need to be determined to assess the objects in more detail. Therefore, the process of edge detection becomes one of the integral parts of automatic image processing

techniques.¹⁴ Several researchers have used the GAs for edge detection of images acquired using different imaging modalities including MRI, CT, and ultrasound.¹⁴⁻¹⁶

Screening mammography is the gold standard for detection of breast cancer; however, due to its failure rate,^{17,18} researchers have tried to apply computational tools to improve the sensitivity of the system. In fact, the majority of the applications of GAs in radiology were performed on breast cancer screening primarily using mammography.

Karnan and Thangavel¹⁹ applied the GA to detect microcalcifications in mammograms suggesting of breast cancer. In their method, after enhancement and normalization of the mammograms, the border of breast and the nipple position was detected by the GA. Using the border and the nipple position of the right and left breasts as a reference, the mammogram images were aligned and subtracted from each other to find the asymmetry image suggestive of breast cancer. The Az value, which is the area under the receiver operating characteristic (ROC) curve, has been used as a useful measure for assessing the diagnostic performance of a system.²⁰ The Az value for their proposed algorithm was about 0.9.¹⁹

In another study, Pereira et al,²¹ applied a set of computational tools for mammogram segmentation to improve the detection of breast cancer. An algorithm was first designed to eliminate artifacts followed by denoising and image enhancement. Consecutively, combining wavelet analysis and the GA allowed detection and segmentation of suspicious areas with 95% sensitivity. GAs have also been successfully used for classification and detection of clustered microcalcifications in digital mammograms.²²⁻²⁴

In machine learning, feature selection is the process of selecting a subset of relevant features to construct a model by removing variables with little or no analytical value. Feature selection is important since choosing irrelevant features would increase the time, cost, and complexity of computation and reduce the accuracy of the model.²⁵ Besides, reducing the number of features would avoid the problem of over-fitting, reduce the chance of failure upon missing data, and allow for a better explanation and generalization of the model.²⁶

GAs have been applied for feature selection in studies aiming to identify a region of interest in mammograms as normal or containing a mass,²⁷ and

to differentiate benign and malignant breast tumors in ultrasound images.²⁵

de Carvalho Filho et al,²⁸ developed a GA for automatic detection and classification of solitary lung nodules. The designed algorithm could detect lung nodules with about 86% sensitivity, 98% specificity, and 98% accuracy.

Image registration or fusion is the process of optimal aligning of two or more images into one coordinate system. Precise integration of images becomes crucial when valuable information is embedded within several images acquired under different conditions (viewpoint, sensor, or time).²⁹ GAs have successfully been used to align MRI and CT scan images in several studies.^{30,31} In another study, positron emission tomography (PET) images were fused with MRI images by a GA to generate colored breast cancer images.³²

Precise tumor staging is an important part of designing a treatment plan. Accurate tumor size and volume determination using non-invasive imaging studies becomes essential for tumor staging. Zhou et al,³³ developed a system for extraction of tongue carcinoma from head and neck MRIs. A GA was applied for segmentation of images followed by an artificial neural network (ANN)-based symmetry-detection algorithm to reduce the number of false positive results. This approach was able to extract tongue carcinoma from an MRI with high accuracy and minimal user-dependency.

Oncology

Screening tests offer a valuable opportunity for early cancer detection, which if followed by proper treatment could improve the survival rate of patients.

To develop a non-invasive technique for cervical cancer detection, Duraipandian et al,³⁴ acquired Raman spectra from the cervical area via colposcopy. The biomolecular information generated via the Raman spectroscopy was analyzed by a GA-partial least square-discriminant analysis system to differentiate between a normal and dysplastic cervix. Partial least square (PLS) is a statistical method aiming to find a linear regression model between a dependent variable and some predictor variables.³⁵ This system was able to differentiate dysplasia from a normal cervix with 72% sensitivity and 90% specificity.³⁴

The advent of DNA microarrays has paved the way for massive gene expression profiling that could

revolutionize the field of molecular diagnostics and prognosis. However, generation of large sets of data poses statistical and analytical challenges necessitating the need to find key predictive genes.³⁶ Due to the inherent capability of GAs to search and find the optimal solution among large and complex possible solutions with multiple simultaneous interactions, they have been applied to analyze microarray data from several cancer cell lines.³⁶ Dolled-Filhart et al,³⁷ generated microarray data by staining breast cancer tissues with several antibodies specific for various markers to find a minimum set of biomarkers with maximum classification and prognostication values in breast cancer patients. The data analyzed using GAs showed that three markers with available antibodies could define a population of patients with more than a 95% five-year survival rate.

Tan et al,³⁸ conducted a study to investigate the relationship between soil trace elements and cervical cancer mortality in China. A combination of GA and PLS was used to choose five out of 25 trace elements. Then a least square support vector machine (LSSVM) model was developed. LSSVM is a method used in machine learning to infer a function from or find a pattern in training data.³⁹ The results showed that a combination of GA-PLS and LSSVM could predict the mortality of cervical cancer based on trace elements.³⁸

One of the important and informative factors influencing the choice of an appropriate therapeutic approach for cancer patients is determination of the disease prognosis. In a retrospective study on more than 200 patients, Bozcuk et al,⁴⁰ compared the performance of four different data mining methods to determine the outcome of cancer patients not being in terminal stages after hospitalization. In comparison to other methods, GA selected the least number of explanatory variables (lactate dehydrogenase and the reason for admission) to predict the outcome of patients.

Cardiology

GAs have been used in different fields of cardiovascular medicine. Atherosclerotic plaques are hallmarks of most myocardial infarctions and strokes. Determination of plaque mechanical properties such as elasticity would enable physicians to locate better and map vulnerable or unstable plaques. Khalil et al,⁴¹ used a system involving GAs

for parameter estimation necessary for accurate elasticity quantification to determine tissue elasticity. This system is superior to gradient-based methods used for parameter estimation of the inefficiency of gradient-based techniques for inhomogeneous solution spaces containing several local minima and requirement for substantial computational time limits their application.⁴¹

The field of biomarker discovery and clinical proteomics is rapidly growing in medical diagnosis, prognosis, and disease follow-up. Advanced technologies such as mass spectrometry can generate readouts of thousands of proteins from patient samples; however, the cost and complexity of such techniques on the one hand and computational and statistical methods for analysis, on the other hand, necessitates the selection of a few, relevant markers for clinical assay development. Zhou et al,⁴² employed an improved version of the GA supported by a recursive local floating enhancement technique to predict the risk of a major adverse cardiac event (MACE). This technique was able to select a panel of seven proteins including myeloperoxidase to predict the risk of MACE with 77% accuracy, which outperformed over several current methods.

Logistic regression models have been frequently used in diagnosing diseases. Due to its outstanding performance, a GA has been used to select the best variables for a logistic regression system aiming to model the presence of myocardial infarction in patients with chest pain. The GA-based method was superior in variable selection to other traditional methods.²⁶

One of the key elements in the automatic interpretation of the electrocardiogram (ECG) is the detection of QRS complexes that would allow assessment of heart rate variability and other relevant diagnostic parameters. Tu et al,⁴³ introduced a simple and effective GA to detect QRS complexes. Then, p-waves and f-waves, which happen in normal ECG and after atrial fibrillation, respectively, were successfully extracted from patient databases. Such algorithms could allow comprehensive research into ECG details.

Endocrinology

Hypoglycemia is the most common complication of insulin therapy in patients with type 1 diabetes mellitus (T1DM). Hypoglycemia can induce alterations in the patterns of electroencephalograms

(EEGs). Nguyen et al,⁴⁴ combined ANNs, GAs, and Levenberg-Marquardt (LM) training techniques to detect hypoglycemia based on EEG signals. ANN was used to model the relationship between blood glucose and EEG signals. For training ANN, the global search ability of GA and the local search capability of LM were combined. Data from four EEG parameters derived from two EEG channels were used by the analyzing system to detect hypoglycemia with 75% sensitivity and 60% specificity. In another paper, a GA-based multiple regression with fuzzy inference system was developed to detect non-invasive episodes of nocturnal hypoglycemia in children with T1DM. Using heart rate and corrected QT interval, hypoglycemia was detected with a sensitivity of 75% and specificity of over 50%.⁴⁵

Obstetrics and gynecology

The differentiation between normal and prolonged delivery allows obstetricians to determine the optimal timing for interventions, if necessary, during childbirth. One of the parameters that can help to forecast the delivery time and segregate normal versus prolonged labor is the time to reach full cervical dilation. Hoh et al,⁴⁶ applied a three-parameter logistic model using GA or the Newton-Raphson (NR) method to predict the time to reach full cervical dilation. The GA-based algorithm outperformed the NR method by more accurately predicting the time to full cervical dilation.

A Pap smear is a cytology test for detection of precancerous and cancerous cervical changes. In this method, 20 features of cells are assessed to describe them as normal or abnormal or, more specifically, categorize them into seven classes. Marinakis et al,⁴⁷ generated a hybrid model that took advantage of the feature-selection capability of GAs to reduce the complexity of features necessary for a nearest neighbor algorithm for classification of Pap smear results. The new method outperformed several other previously used approaches by accurately classifying the Pap smear results.

GAs have also been applied in prenatal diagnosis. One of the fetal features that can complicate delivery is fetal macrosomia. In an attempt to differentiate the large-for-gestational-age (LGA) from the appropriate-for-gestational-age (AGA) infants, amniotic fluid from the second trimester was evaluated by capillary electrophoresis. Bayesian

statistics was applied for data analysis. A GA was used to select the suitable wavelets (variables) of the electropherogram to minimize the computation time required for the Bayesian computation. This system was able to differentiate LGA from AGA using only two wavelets, one of albumin and the other of a negatively-charged unknown small molecule with 100% sensitivity and 98% specificity.⁴⁸

The prediction of fetal weight before delivery can reduce the potential problems associated with low-birth-weight infants. Yu et al,⁴⁹ introduced fuzzy logic into the support vector regression (FSVR) to estimate the fetal weight. GAs were used to generate an evolutionary FSVR to select the optimal features for the FSVR system. This outperformed a back-propagation neural network by achieving the lowest mean absolute percent error (6.6%) and the highest correlation coefficient (0.902) between the estimated and the actual fetal birth weight.

Pediatrics

Cardiotocography is a cheap and non-invasive technique to assess the fetal heart rate and uterine contractions to determine fetal well-being. Ocak⁵⁰ applied a GA to select the optimal features of cardiotocogram recordings for a support vector machine (SVM) classifier. The results showed that the new system classified fetal health status as normal or abnormal with 99.3% and 100% accuracy, which was superior to an ANN algorithm designed for the same purpose.

Autism is a neurodevelopmental disease that appears in early childhood and is characterized by impaired social functioning and verbal and non-verbal communications and repetitive behavior. To recognize autism based on the microarray gene expression data, Latkowski and Osowski⁵¹ used GAs to select the most relevant genes associated with the disease. Frequently selected genes include RMI1, NRIP1, TOP1, ZFH3, CEP350, NFYA, PSENEN, ANP32A, SEMA4C, and SP1. These genes provided an input for an ensemble of classifiers including SVM and random forest classifiers. The introduced system recognized autism with 96% sensitivity and 83% specificity.⁵¹

Acute lymphoblastic leukemia (ALL) is the most common type of leukemia in children and has many subtypes. Analysis of gene expression data derived from tumor cells can help classifying cancers. Due to the enormous size of information generated from

microarray gene expression profiling, Lin et al,⁵² used a GA to select the most relevant genes needed for ALL classification. Silhouette statistics was applied as a discriminant function to differentiate between six ALL subtypes. The proposed technique reached a 100% classification accuracy and used fewer discriminating genes compared to other methods.

Aneuploidy is a condition where one or a few chromosomes in the nucleus of a cell are above or below the normal chromosomal number of a species. Conventional chromosomal studies on amniocentesis samples are performed for definite diagnosis of fetal aneuploidy yet the rather long required time for these techniques necessitates the development of faster diagnostic tests. To this end, the proteomic profile of the amniotic fluid specimens was identified via mass spectrometry and the generated data was assessed by a GA. The proposed method could detect aneuploidy with 100% sensitivity, 72%–96% specificity, 11%–50% positive predictive value and 100% negative predictive value.⁵³

Surgery

ANNs are powerful mathematical algorithms capable of predicting the behavior of systems. Due to the predictive value of ANNs, a GA-based ANN (GANN) was developed to predict the outcomes after surgery for patients with non-small cell lung cancer (NSCLC). The GA was applied to help optimization not to fall into local minima. The GANN model could predict the outcome of NSCLC patients more accurately and significantly better than logistic regression. Besides, the inclusion of tumor size in calculations significantly improved prediction outcomes.⁵⁴

As populations age, the number of geriatric patients needing cardiac surgeries increases. Due to the high prevalence of comorbid conditions in elderly, proper prognostication of postoperative morbidity and mortality would be informative, precluding overestimation of risk and denial of surgery for patients deserving it, which could happen with some prediction models. Applying a GA, Lee et al,⁵⁵ showed that a short length of stay after cardiac surgery was correlated with younger age, no preoperative use of beta blockers, shorter cross-clamp time, and absence of congestive heart failure.

Pulmonology

In pulmonology, auscultation is the most common

diagnostic method that can differentiate lung diseases and guide the diagnostic approach toward more specific techniques. To automate lung sound diagnosis, a hybrid GANN was designed. The GA was applied to optimize the ANN training parameters and reduce the computation time. The new system could classify the lung sounds into normal, wheeze, and crackle.⁵⁶

Assessment of the partial pressure of carbon dioxide in the arterial blood (PaCO_2) is important in the management of critically ill patients. To avoid difficulties associated with arterial blood sampling, non-invasive methods for predicting PaCO_2 such as assessment of exhaled carbon dioxide at end-expiration (PetCO_2) could be applied in normal individuals; however, their use in sicker persons might be biased and less helpful. Engoren et al,⁵⁷ designed a GA to predict the PaCO_2 using 11 variables from capnography of non-intubated patients in the emergency department. The proposed system could improve the precision and bias of PaCO_2 prediction.

Infectious diseases

Tuberculosis is a possible lethal infectious disease not only in developing countries but also in developed nations after the emergence of human immunodeficiency virus (HIV). To predict the diagnosis (tuberculosis vs. non-tuberculosis patients), 38 parameters composed of examination parameters and laboratory data were used to design an ANN trained by a GA. The classification accuracy of the system was about 95%, which was higher than the results obtained by other algorithms.⁵⁸

Highly active antiretroviral therapy (HAART), an integral part of the treatment modalities against HIV, is composed of a combination of several antiretroviral medications aiming to decrease the replication of the virus. Since long-term HAART treatment needs patient compliance and might be associated with some side effects, structured treatment interruption has been proposed to reduce not only side effects, but also the selection pressure on the virus that could lead to the emergence of resistant particles. Therefore, Castiglione et al,⁵⁹ devised a GA-based system to choose the best HAART treatment schedule to control HIV and help the immune system to reconstitute. A virtual model of the immune system was used to assess the effects of anti-HIV drugs on virtual patients.^{59,60} The new structured interruption schedule could

achieve therapeutic results and protection against an opportunistic infection comparable to a full-length treatment.⁶¹

Radiotherapy

Intensity modulated radiotherapy (IMRT) was developed to transfer an accurate dose of radiation to a target such as the brain, prostate, or head and neck. Planning IMRT involves selection of 5–10 angles for wavelet projection and determining the radiation dose. The application of GA could improve the selection of gantry angles in a reasonable time frame.⁶² Similar GA-based irradiation planning has been applied for patients with other types of cancer including pancreatic,⁶³ rhabdomyosarcoma, and brain tumors.⁶⁴ GAs have also been successfully used to optimize the design of stereotactic radiosurgery, and radiotherapy treatment plans.⁶⁵

Rehabilitation medicine

As the need for physical rehabilitation increases, novel treatment equipment and techniques have to be developed and tested. Refinement of these new methods needs changing various parameters and testing of the resultant techniques on individuals, which is time-consuming and costly. Development of musculoskeletal models enables computer simulation of movements to assess the effect of new modifications on the efficiency of training. Pei et al,⁶⁶ developed a robotic technique for physiotherapy of the lower limb. A GA was applied to generate custom-made treatment plans for each patient.

In another paper, a therapeutic robot was designed for lower limb exercise. The system that consisted of an ANN and a GA was capable of learning the actions of a physiotherapist for each patient and mimicked its behavior in the absence of a therapist.⁶⁷

Orthopedics

Biomedical engineering has offered great solutions to the field of orthopedic surgery. Total hip arthroplasty (THA) has improved the management of various disabling hip joint diseases. Yet, failure of the femoral stem of a THA can compromise the success of treatment. Ishida et al,⁶⁸ reported the use of a GA in designing an optimized geometry of the femoral stem component. GAs have also been exploited to select the best design of tibial locking screws to reduce the probability of screw breakage

or loosening.⁶⁹ In another report, a combination of ANNs and GAs was applied to design spinal pedicle screws used for fixation of spinal fractures. The hybrid algorithm was able to design screws with a higher fatigue life and ideal pullout and bending characteristics.⁷⁰

Scoliosis is a three-dimensional deformity of spinal axis curves. The progression of the disease, which only happens in a small percentage of patients, is monitored by serial X-rays over time. Since frequent exposure to X-rays might increase the chance of cancer, it is desirable to assess the disease development using harmless methods. Jaremko et al,⁷¹ developed a GA-based ANN algorithm to estimate the angle of spinal axis deformity from indices of trunk surface deformity. The hybrid system was able to determine the angle deformity within 5% accuracy in more than two third of patients.

Neurology

Multiple sclerosis (MS) is a debilitating inflammatory disease of the neural system characterized by the formation of white matter scars otherwise known as plaques. Computer-assisted diagnosis has been applied for detection of pathologic features in these patients. In one study, a GA was developed to detect the MS lesions of brain MRIs. The similarity index of lesions determined by the GA and by a radiologist was 87%.⁷²

The EEG is a useful diagnostic method to detect the abnormal brain electrical discharges occurring during a seizure. To design an automated system for detection of abnormal EEG signals, several learning algorithms (LM, Quickprop, Delta-bar delta, and Momentum and Conjugate gradient) were used to train an ANN for EEG-based classification of epileptic versus healthy individuals. A GA was used to find the optimal parameters for and architecture of the ANN. The results demonstrated that the LM method combined with the GA was the best algorithm for training the ANN, which reached a general success of 96.5% in its performance.⁷³

Several reports have suggested that mitochondrial dysfunction plays an important role in Parkinson's disease. Since mitochondrial genetics has its idiosyncrasies, a simple comparison of mitochondrial mutations between healthy and disease conditions might not be so informative. Therefore, Smigrodzki et al,⁷⁴ devised a GA to detect biologically important patterns of mitochondrial mutations in Parkinson's

patients. The proposed system was able to diagnose Parkinson's disease with 100% accuracy based on mutational patterns in mitochondrial DNA.

Pharmacotherapy

Pharmacovigilance, the study of safety and adverse effects of drugs, is not only an integral part of currently-used drug assessment; it is also a crucial element in the evaluation of novel investigational medicines. The clinical judgment of a pharmacotherapist to attribute an observed adverse effect to a drug is valuable yet implicit while algorithms can make a less arbitrary and more objective evaluation. Koh et al,⁷⁵ developed a GA-based quantitative system for the evaluation of adverse drug reactions. The new scoring system was able to determine a probability of the causality of an adverse drug reaction to a suspected drug with about 84% sensitivity and 71% specificity.

Tacrolimus is an immunosuppressive agent used to prevent rejection after organ transplantation. The drug has highly variable pharmacokinetics and a narrow therapeutic window making its blood level control an essential and difficult task. In an attempt to predict the blood concentration of tacrolimus in liver-transplanted patients, an ANN algorithm was developed. A GA was used to choose the best set of clinically significant candidate variables. For validation, predicted results were compared to observed figures. The ANN was able to predict the blood level of tacrolimus, with 84% of data sets being within a clinically acceptable range of 3 ng/ml of the observed data.⁷⁶

Studies have shown that poor pharmacokinetics and lack of efficiency account for more than 50% of failures in the process of drug development. The traditional assessment of the efficacy and pharmacokinetics of novel investigational agents in animal models is a costly and time-consuming process. Therefore, computational methods have evolved to generate quantitative structure-pharmacokinetic relationship (QSPKR) models for rapid in silico screening of novel potential drugs.

Zandkarimi et al,⁷⁷ applied a GA to select the most suitable characteristics out of more than 1480 descriptors of alkaloid drugs. These sets of characteristics were then extracted from known drugs for training an ANN to generate QSPKR prediction models. The new system was able to predict the volume of distribution, clearance, and

plasma protein binding of alkaloid drugs with an acceptable efficiency.

Health care management

Proper management of monetary resources and personnel is an integral part of health systems all over the world. One of the important elements of hospital management which can improve patient servicing, satisfaction, and cost-effectiveness ratios is efficient scheduling of patients admission. A mathematical model was developed and optimized using a GA to improve the patient scheduling in an ophthalmology hospital. The new algorithm was superior to the traditional "first come, first serve" model in that it shortened the waiting list, lowered the vacancy rate of hospital beds, reduced the preoperative waiting time for patients, and increased the number of patients discharged from the hospital.⁷⁸ Another report showed that a combination of GA and particle swarm optimization, another powerful metaheuristic algorithm, was able to improve patient scheduling, reduce time wastage, and increase patient satisfaction.⁷⁹

In clinical laboratories, regular rotation of staff based on their skills through different facilities is fundamental for maintaining job skills and competence. GAs have been applied to improve staff rotation scheduling in a clinical laboratory. In one report, the GA-based software was capable of planning the rotation of staff effectively, ensuring maintenance of techniques and skills, saving time and the cost necessary for the scheduling process, and it was associated with the satisfaction of responsible supervisory personnel.⁸⁰

CONCLUSION

In this paper, we introduced GAs and some of their applications in various fields of medicine. Although GAs and some other metaheuristics are inspired by biology, the experts of other fields of science are more aware of them and these methods are frequently used to solve complex problems. Due to the inherent complexity of medicine, optimization methods could be of great value for physicians and medical researchers. The lack of an efficient interaction between computer scientists and physicians on the one hand and the unfamiliarity of complex mathematical formulas among the medical professions on the other is responsible for

this situation. Therefore, improving the interaction and understanding between physicians, computer scientists, and engineers, which could happen via joint journal clubs or attendance of physicians ground rounds and case report presentations, could solve the problem. Besides, improvement of interdisciplinary courses and efficient involvement of engineering researchers in health care environments and hospitals could offer new solutions for medical problems and new ideas for non-medical researchers.

Disclosure

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REFERENCES

- Osman IH, Kelly JP. Meta-heuristics: an overview. *Meta-Heuristics*: Springer; 1996. p. 1-21.
- Dorigo M, Stützle T. The ant colony optimization metaheuristic: Algorithms, applications, and advances. *Handbook of metaheuristics*: Springer; 2003. p. 250-285.
- Karaboga D, Basturk B. A powerful and efficient algorithm for numerical function optimization: artificial bee colony (ABC) algorithm. *J Glob Optim* 2007;39:459-471.
- Mirjalili S, Mirjalili SM, Lewis A. Grey wolf optimizer. *Adv Eng Softw* 2014;69:46-61.
- Potvin J-Y, Smith KA. Artificial Neural Networks for Combinatorial Optimization. *Handbook of metaheuristics*: Springer; 2003. p. 429-455.
- Henderson D, Jacobson SH, Johnson AW. The theory and practice of simulated annealing. *Handbook of metaheuristics*: Springer; 2003. p. 287-319.
- Rabanal P, Rodríguez I, Rubio F. Using river formation dynamics to design heuristic algorithms. *Unconventional Computation*: Springer; 2007. p. 163-177.
- De Castro LN, Timmis J. Artificial immune systems: a new computational intelligence approach: Springer; 2002.
- Reeves C. Genetic algorithms. *Handbook of metaheuristics*: Springer; 2003. p. 55-82.
- Hasancebi O, Erbatur F. Evaluation of crossover techniques in genetic algorithm based optimum structural design. *Comput Struc* 2000;78:435-448.
- MathWorks. Genetic Algorithm. Available from: <http://www.mathworks.in/help/gads/what-is-the-genetic-algorithm.html>.
- Krishnakumar K, Goldberg DE. Control-System Optimization Using Genetic Algorithms. *J Guid Control Dyn* 1992;15:735-740.
- Shiraishi J, Li Q, Appelbaum D, Doi K. Computer-aided diagnosis and artificial intelligence in clinical imaging. *Semin Nucl Med* 2011 Nov;41(6):449-462.
- Gudmundsson M, El-Kwae EA, Kabuka MR. Edge detection in medical images using a genetic algorithm. *IEEE Trans Med Imaging* 1998 Jun;17(3):469-474.
- Bhandarkar SM, Zhang YQ, Potter WD. An Edge-Detection Technique Using Genetic Algorithm-Based Optimization. *Pattern Recognit* 1994;27:1159-1180.
- Karnan M, Thangavel K. Automatic detection of the breast border and nipple position on digital mammograms using genetic algorithm for asymmetry approach to detection of microcalcifications. *Comput Methods Programs Biomed* 2007 Jul;87(1):12-20.
- Beam CA, Layde PM, Sullivan DC. Variability in the interpretation of screening mammograms by US radiologists. Findings from a national sample. *Arch Intern Med* 1996 Jan;156(2):209-213.
- Elmore JG, Wells CK, Lee CH, Howard DH, Feinstein AR. Variability in radiologists' interpretations of mammograms. *N Engl J Med* 1994 Dec;331(22):1493-1499.
- Karnan M, Thangavel K. Automatic detection of the breast border and nipple position on digital mammograms using genetic algorithm for asymmetry approach to detection of microcalcifications. *Comput Methods Programs Biomed* 2007 Jul;87(1):12-20.
- Bushberg JT, Boone JM. *Image Quality. The essential physics of medical imaging*. second ed: Lippincott Williams & Wilkins; 2011.
- Pereira DC, Ramos RP, do Nascimento MZ. Segmentation and detection of breast cancer in mammograms combining wavelet analysis and genetic algorithm. *Comput Methods Programs Biomed* 2014 Apr;114(1):88-101.
- Jiang J, Yao B, Wason AM. A genetic algorithm design for microcalcification detection and classification in digital mammograms. *Comput Med Imaging Graph* 2007 Jan;31(1):49-61.
- Bevilacqua A, Campanini R, Lanconelli N. A distributed genetic algorithm for parameters optimization to detect micro calcifications in digital mammograms. *Applications of Evolutionary Computing. Proceedings 2001;2037:278-287*.
- Yao B, Jiang JM, Peng YH. A CBR driven genetic algorithm for microcalcification cluster detection. *Engineering Knowledge in the Age of the Semantic Web. Proceedings 2004;3257:494-496*.
- Wu WJ, Lin SW, Moon WK. Combining support vector machine with genetic algorithm to classify ultrasound breast tumor images. *Comput Med Imaging Graph* 2012 Dec;36(8):627-633.
- Vinterbo S, Ohno-Machado L. A genetic algorithm to select variables in logistic regression: example in the domain of myocardial infarction. *Proc AMIA Symp* 1999;984-988.
- Sahiner B, Chan HP, Wei D, Petrick N, Helvie MA, Adler DD, et al. Image feature selection by a genetic algorithm: application to classification of mass and normal breast tissue. *Med Phys* 1996 Oct;23(10):1671-1684.
- de Carvalho Filho AO, de Sampaio WB, Silva AC, de Paiva AC, Nunes RA, Gattass M. Automatic detection of solitary lung nodules using quality threshold clustering, genetic algorithm and diversity index. *Artif Intell Med* 2014 Mar;60(3):165-177.
- Oliveira FP, Tavares JM. Medical image registration: a review. *Comput Methods Biomech Biomed Engin* 2014;17(2):73-93.
- Valsecchi A, Damas S, Santamaria J, eds. An image registration approach using genetic algorithms. *Evolutionary Computation (CEC), 2012 IEEE Congress on; 2012: IEEE*.
- Fan Y, Jiang TZ, Evans DJ. Medical image registration using parallel genetic algorithms. *Applications of Evolutionary Computing. Proceedings 2002;2279:304-314*.
- Baum KG, Schmidt E, Rafferty K, Krol A, Helguera M. Evaluation of novel genetic algorithm generated schemes for positron emission tomography (PET)/magnetic resonance imaging (MRI) image fusion. *J Digit Imaging* 2011 Dec;24(6):1031-1043.
- Zhou J, Krishnan S, Chong V, Huang J, eds. Extraction of tongue carcinoma using genetic algorithm-induced fuzzy clustering and artificial neural network from MR images. *Engineering in Medicine and Biology Society, 2004 IEMBS'04 26th Annual International Conference of the IEEE; 2004: IEEE*.
- Duraipandian S, Zheng W, Ng J, Low JJ, Ilancheran A, Huang Z. In vivo diagnosis of cervical precancer using Raman spectroscopy and genetic algorithm techniques. *Analyst* 2011 Oct;136(20):4328-4336.

35. Wold S, Sjostrom M, Eriksson L. PLS-regression: a basic tool of chemometrics. *Chemom Intell Lab Syst* 2001;58:109-130.
36. Ooi CH, Tan P. Genetic algorithms applied to multi-class prediction for the analysis of gene expression data. *Bioinformatics* 2003 Jan;19(1):37-44.
37. Dolled-Filhart M, Rydén L, Cregger M, Jirström K, Harigopal M, Camp RL, et al. Classification of breast cancer using genetic algorithms and tissue microarrays. *Clin Cancer Res* 2006 Nov;12(21):6459-6468.
38. Tan C, Chen H, Wu T, Xia C. Modeling the relationship between cervical cancer mortality and trace elements based on genetic algorithm-partial least squares and support vector machines. *Biol Trace Elem Res* 2011 Apr;140(1):24-34.
39. van Gestel T, Suykens JA, Baesens B, et al. Benchmarking least squares support vector machine classifiers. *Mach Learn* 2004;54:5-32.
40. Bozcuk H, Bilge U, Koyuncu E, Gulkesen H. An application of a genetic algorithm in conjunction with other data mining methods for estimating outcome after hospitalization in cancer patients. *Med Sci Monit* 2004 Jun;10(6):CR246-CR251.
41. Khalil AS, Bouma BE, Kaazempur Mofrad MR. A combined FEM/genetic algorithm for vascular soft tissue elasticity estimation. *Cardiovasc Eng* 2006 Sep;6(3):93-102.
42. Zhou X, Wang H, Wang J, Wang Y, Hoehn G, Azok J, et al. Identification of biomarkers for risk stratification of cardiovascular events using genetic algorithm with recursive local floating search. *Proteomics* 2009 Apr;9(8):2286-2294.
43. Tu C, Zeng Y, Yang X. A new approach to detect QRS complexes based on a histogram and genetic algorithm. *J Med Eng Technol* 2005 Jul-Aug;29(4):176-180.
44. Nguyen LB, Nguyen AV, Ling SH, Nguyen HT. Combining genetic algorithm and Levenberg-Marquardt algorithm in training neural network for hypoglycemia detection using EEG signals. *Conf Proc IEEE Eng Med Biol Soc.* 2013;2013:5386-5389.
45. Ling SS, Nguyen HT. Genetic-algorithm-based multiple regression with fuzzy inference system for detection of nocturnal hypoglycemic episodes. *IEEE Trans Inf Technol Biomed* 2011 Mar;15(2):308-315.
46. Hoh JK, Cha KJ, Park MI, Ting Lee ML, Park YS. Estimating time to full uterine cervical dilation using genetic algorithm. *Kaohsiung J Med Sci* 2012 Aug;28(8):423-428.
47. Marinakis Y, Dounias G, Jantzen J. Pap smear diagnosis using a hybrid intelligent scheme focusing on genetic algorithm based feature selection and nearest neighbor classification. *Comput Biol Med* 2009 Jan;39(1):69-78.
48. Boisvert MR, Koski KG, Burns DH, Skinner CD. Early prediction of macrosomia based on an analysis of second trimester amniotic fluid by capillary electrophoresis. *Biomark Med* 2012 Oct;6(5):655-662.
49. Yu J, Wang Y, Chen P. Fetal weight estimation using the evolutionary fuzzy support vector regression for low-birth-weight fetuses. *IEEE Trans Inf Technol Biomed* 2009 Jan;13(1):57-66.
50. Ocak H. A medical decision support system based on support vector machines and the genetic algorithm for the evaluation of fetal well-being. *J Med Syst* 2013 Apr;37(2):9913.
51. Latkowski T, Osowski S. Computerized system for recognition of autism on the basis of gene expression microarray data. *Comput Biol Med* 2015 Jan;56:82-88.
52. Lin TC, Liu RS, Chao YT, Chen SY. Classifying subtypes of acute lymphoblastic leukemia using silhouette statistics and genetic algorithms. *Gene* 2013 Apr;518(1):159-163.
53. Wang TH, Chang YL, Peng HH, Wang ST, Lu HW, Teng SH, et al. Rapid detection of fetal aneuploidy using proteomics approaches on amniotic fluid supernatant. *Prenat Diagn* 2005 Jul;25(7):559-566.
54. Jefferson MF, Pendleton N, Lucas SB, Horan MA. Comparison of a genetic algorithm neural network with logistic regression for predicting outcome after surgery for patients with nonsmall cell lung carcinoma. *Cancer* 1997 Apr;79(7):1338-1342.
55. Lee J, Govindan S, Celi LA, Khabbaz KR, Subramaniam B. Customized Prediction of Short Length of Stay Following Elective Cardiac Surgery in Elderly Patients Using a Genetic Algorithm. *World J Cardiovasc Surg* 2013 Sep;3(5):163-170.
56. Güler I, Polat H, Ergün U. Combining neural network and genetic algorithm for prediction of lung sounds. *J Med Syst* 2005 Jun;29(3):217-231.
57. Engoren M, Plewa M, O'Hara D, Kline JA. Evaluation of capnography using a genetic algorithm to predict PaCO₂. *Chest* 2005 Feb;127(2):579-584.
58. Elveren E, Yumuşak N. Tuberculosis disease diagnosis using artificial neural network trained with genetic algorithm. *J Med Syst* 2011 Jun;35(3):329-332.
59. Castiglione F, Poccia F, D'Offizi G, Bernaschi M. Mutation, fitness, viral diversity, and predictive markers of disease progression in a computational model of HIV type 1 infection. *AIDS Res Hum Retroviruses* 2004 Dec;20(12):1314-1323.
60. Bernaschi M, Castiglione F. Design and implementation of an immune system simulator. *Comput Biol Med* 2001 Sep;31(5):303-331.
61. Castiglione F, Pappalardo F, Bernaschi M, Motta S. Optimization of HAART with genetic algorithms and agent-based models of HIV infection. *Bioinformatics* 2007 Dec;23(24):3350-3355.
62. Nazareth DP, Brunner S, Jones MD, Malhotra HK, Bakhtiari M. Optimization of beam angles for intensity modulated radiation therapy treatment planning using genetic algorithm on a distributed computing platform. *J Med Phys* 2009 Jul;34(3):129-132.
63. Ezzell GA, Gaspar L. Application of a genetic algorithm to optimizing radiation therapy treatment plans for pancreatic carcinoma. *Med Dosim* 2000;25(2):93-97.
64. Wu X, Zhu Y. A mixed-encoding genetic algorithm with beam constraint for conformal radiotherapy treatment planning. *Med Phys* 2000 Nov;27(11):2508-2516.
65. Yu Y, Schell MC, Zhang JB. Decision theoretic steering and genetic algorithm optimization: application to stereotactic radiosurgery treatment planning. *Med Phys* 1997 Nov;24(11):1742-1750.
66. Pei Y, Kim Y, Obinata G, Hase K, Stefanov D. Trajectory planning of a robot for lower limb rehabilitation. *Conf Proc IEEE Eng Med Biol Soc.* 2011;2011:1259-1263.
67. Aminiazar W, Najafi F, Nekoui MA. Optimized intelligent control of a 2-degree of freedom robot for rehabilitation of lower limbs using neural network and genetic algorithm. *J Neuroeng Rehabil* 2013;10:96.
68. Ishida T, Nishimura I, Tanino H, Higa M, Ito H, Mitamura Y. Use of a genetic algorithm for multiobjective design optimization of the femoral stem of a cemented total hip arthroplasty. *Artif Organs* 2011 Apr;35(4):404-410.
69. Hsu CC, Chao CK, Wang JL, Lin J. Multiobjective optimization of tibial locking screw design using a genetic algorithm: Evaluation of mechanical performance. *J Orthop Res* 2006 May;24(5):908-916.
70. Amaritsakul Y, Chao CK, Lin J. Multiobjective optimization design of spinal pedicle screws using neural networks and genetic algorithm: mathematical models and mechanical validation. *Comput Math Methods Med* 2013;2013:462875.
71. Jaremko JL, Poncet P, Ronsky J, Harder J, Dansereau J, Labelle H, et al. Genetic algorithm-neural network estimation of Cobb angle from torso asymmetry in scoliosis. *J Biomech Eng* 2002 Oct;124(5):496-503.
72. Khotanlou H, Afrasiabi M. Feature Selection in Order to Extract Multiple Sclerosis Lesions Automatically in 3D Brain Magnetic Resonance Images Using Combination of

- Support Vector Machine and Genetic Algorithm. *J Med Signals Sens* 2012 Oct;2(4):211-218.
73. Koçer S, Canal MR. Classifying epilepsy diseases using artificial neural networks and genetic algorithm. *J Med Syst* 2011 Aug;35(4):489-498.
 74. Smigrodzki R, Goertzel B, Pennachin C, Coelho L, Prodocimi F, Parker WD Jr. Genetic algorithm for analysis of mutations in Parkinson's disease. *Artif Intell Med* 2005 Nov;35(3):227-241.
 75. Koh Y, Yap CW, Li SC. A quantitative approach of using genetic algorithm in designing a probability scoring system of an adverse drug reaction assessment system. *Int J Med Inform* 2008 Jun;77(6):421-430.
 76. Chen HY, Chen TC, Min DI, Fischer GW, Wu YM. Prediction of tacrolimus blood levels by using the neural network with genetic algorithm in liver transplantation patients. *Ther Drug Monit* 1999 Feb;21(1):50-56.
 77. Zandkarimi M, Shafiei M, Hadizadeh F, Darbandi MA, Tabrizian K. Prediction of pharmacokinetic parameters using a genetic algorithm combined with an artificial neural network for a series of alkaloid drugs. *Sci Pharm* 2014 Mar;82(1):53-70.
 78. Zhang LM, Chang HY, Xu RT. The Patient Admission Scheduling of an Ophthalmic Hospital Using Genetic Algorithm. *Adv Mat Res* 2013;756:1423-1432.
 79. Du G, Jiang Z, Yao Y, Diao X. Clinical pathways scheduling using hybrid genetic algorithm. *J Med Syst* 2013 Jun;37(3):9945.
 80. Boyd JC, Savory J. Genetic algorithm for scheduling of laboratory personnel. *Clin Chem* 2001 Jan;47(1):118-123.