



The significance of artificial intelligence in drug delivery system design

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ABSTRACT

Over the last decade, increasing interest has been attracted towards the application of artificial intelligence (AI) technology for analyzing and interpreting the biological or genetic information, accelerated drug discovery, and identification of the selective small-molecule modulators or rare molecules and prediction of their behavior. Application of the automated workflows and databases for rapid analysis of the huge amounts of data and artificial neural networks (ANNs) for development of the novel hypotheses and treatment strategies, prediction of disease progression, and evaluation of the pharmacological profiles of drug candidates may significantly improve treatment outcomes. Target fishing (TF) by rapid prediction or identification of the biological targets might be of great help for linking targets to the novel compounds. AI and TF methods in association with human expertise may indeed revolutionize the current theranostic strategies, meanwhile, validation approaches are necessary to overcome the potential challenges and ensure higher accuracy. In this review, the significance of AI and TF in the development of drugs and delivery systems and the potential challenging issues have been highlighted.

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1. Introduction

Over the last decades, development of the innovative systems for targeted delivery of therapeutics with maximal efficiency and minimal side effects has attracted a growing interest [1–3]. Controlled drug delivery and overcoming the challenges associated with conventional drug delivery systems including the systemic toxicity, narrow therapeutic index, and dose adjustment in long-term therapy have been the focus of intense research [2,3]. Application of the micro-fabrication technology for production of the implantable microchips appears promising for controlled delivery of drugs [4]. Microfabricated drug delivery systems including the drug reservoirs with a variety of geometries or capacities and capable of opening on command, provide continuous or pulsatile drug delivery [5–7]. Using this type of multifunctional and sophisticated devices for controlled drug release, a variety of challenges associated with traditional delivery systems have been addressed [8]. For controlled and targeted delivery of therapeutics, application of the implantable drug delivery systems (Fig. 1) with ability of automatic adjustment of drug concentration and timing of drug release is a promising approach for improving the efficiency, safety, and patients' compliance [9]. This would be particularly important in chronic diseases which require timely treatment and regular monitoring.

Designing the implantable drug delivery systems necessitates consideration of a number of points such as dose adjustment, targeted delivery, sustained release, and intelligent control system [9]. Neural networks, fuzzy logic, integrators, and differentiators have been applied for designing the control systems [10,11]. Methods of drug delivery include the focused ultrasound, micro-pump mechanism, and targeted delivery by microrobots [12–14]. For creation of the micro- or nanoparticles for drug delivery, application of the microfluidic platforms is a promising approach [15,16]. Using the microfluidic technology enables the development of smart drug delivery systems, e.g., Janus micro- or nanoparticles capable of delivery of multiple drugs [17,18]. For programmed drug delivery, electronic components, wireless communication hardware, and power supply have been embedded in a microchip implant (MicroCHIPS, Inc.) (Fig. 2) followed by a pulsatile release for about six months [19].

In first clinical trial, implantable microchips have been applied in osteoporotic patients for drug delivery [20]. Controlled insulin delivery

and continuous monitoring of glucose may significantly reduce the complications of diabetes. In this context, integration of glucose sensors, insulin delivery system, mathematical models and control algorithms is helpful. Integrating the insulin pump, dose calculator, and glucose meter into a device, an automated system has been provided for monitoring of glucose and delivery of insulin [3,21]. In designing intelligent delivery systems, on-demand adjustment of dose or rate of drug release, targeted delivery, and stability of pharmaceuticals should be taken into account [22]. Regarding the self-monitoring delivery systems, appropriate algorithms should be applied to control the amount and timing of drug release [3].

Information technology, wireless communication, and artificial neural networks (ANNs) contribute to the creation of smart drug delivery systems that might be useful for overcoming the limitations of conventional treatment strategies [2,3]. Wireless communication provides more flexibility for controlled drug delivery devices. The units receive the instructions from the external sources, send data to the monitors, and regulate drug release [3]. ANNs containing the interconnected processing elements which are created via simulating the network of model neurons, have been applied to develop software for mimicking the biological processes, generating the control algorithms, pharmacodynamic/pharmacokinetic modeling, controlled drug delivery, and evaluating the effectiveness of treatment strategies [3,23–29]. Using machine learning approaches for predicting ligand-based targets has resulted in the emergence of target fishing (TF) in which ligand datasets, target proteins, and relationship between the ligands and targets could be used to predict protein targets of novel compounds with biological activities [28,29]. Indeed, application of high technologies is necessary for development of the next generations of drugs and innovative delivery systems. This review highlights the significance of artificial intelligence (AI) and TF in designing of drugs and delivery systems and the potential challenging issues.

2. Artificial intelligence: the general aspects

Ideally, the term AI is applied to demonstrate the ability of a machine to mimic the cognitive functions of humans [30]. Creation of the novel generation of information, acquiring a higher degree of precision, automated simulations and predictions, continuous performance, and early detection or monitoring of a variety of disorders are the main advantages of AI [30–32]. In general, AI algorithms are used for more accurate analysis, interpretation, or management of data or complex functions [30]. In this context, statistical pattern recognition methods, computational intelligence, biological-based approaches (e.g., neural networks), and probability theories are integrated in AI [31,32]. AI tools enable the prediction of *in vivo* response, pharmacokinetics of novel therapeutics including their quantitative structure-property relationship (QSPR) or quantitative structure-activity relationship (QSAR), appropriate dosing, and skin- or blood-brain barrier permeability [33–43]. Based on the importance of prediction of the pharmacokinetic profiles of drug candidates, application of *in silico* tools may result in the increased efficiency and cost reduction in drug research projects [44]. In this context, machine learning techniques including the support vector machine, Gaussian process, random forest, k nearest neighbor, classification and regression tree, or Naive Bayes Classifier would be useful [44].

AI implicates a variety of approaches including those inspired by the biological processes [32,34]. Besides the pattern recognition, clustering, data modeling, and function approximation, ANNs are able to create

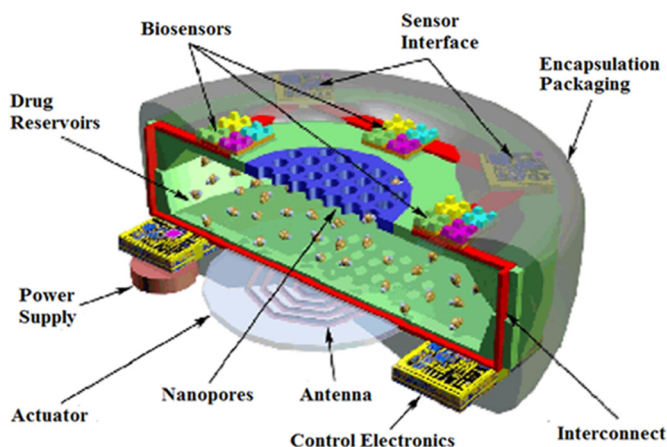


Fig. 1. Implantable drug delivery system. Adapted from Ref. [9].

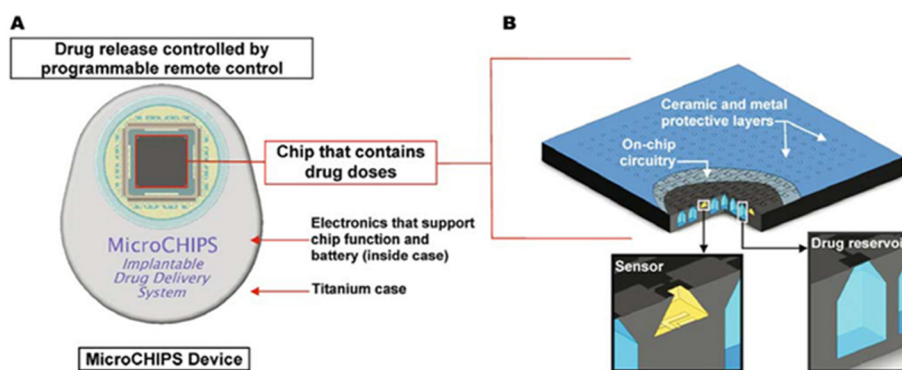


Fig. 2. Microchip-based device for electronically-controlled drug release. A: implantable microchip-based device (MicroCHIPS, Inc.) for controlled drug release. The microchip has been mounted on a biocompatible case including the electronic components, antenna, and power source for wireless communication. B: reservoir array for sensor applications or drug delivery. Each reservoir on the microchip has been filled with 25 μg leuprolide. Drug can be released from the implantable and programmable device at weekly or monthly intervals of time. Adapted from Ref. [19].

nonlinear input-output mappings, select the optimal gradient conditions in chromatography, analyze the multivariate nonlinear relationships in pharmaceutical research, design the pre-formulations, and predict the behavior of drugs [23–28,45,46]. Neural network modeling is a promising approach for describing the molecular structure of organic compounds and prediction of their physicochemical characteristics [47]. Processing elements called as the artificial neurons or nodes are the building components of ANNs [22,23]. Number of nodes in the input and output layers is determined using the number of independent and dependent variables, respectively [24,25]. Number of hidden layers and nodes in each layer depend on the complexity of problems [30–33]. In many of the ANN models, only one hidden layer is included, meanwhile, more than one hidden layer are used for modeling the complex problems [31,32]. Noteworthy, small number of hidden layers and nodes disrupts the learning capability of ANN models and large number of them results in overfitting [22–33,45]. Based on their functions, ANN models are classified into the associating, feature-extracting, or non-adaptive networks [31,32]. Since the relationship between the formulation and process factors and release profiles of controlled-release drug delivery systems is not linear, associating networks are preferred for development and optimization of the controlled release formulations [22–33]. ANNs are usually characterized by their architectures [25]. Using specific network topologies, it has been tried to enhance the robustness of traditional architectures [25,26]. There are two types of neural networks including the static and dynamic networks. The major difference between these networks is determined by the mechanism of signal transmission through the network [25,26]. In the static networks, outputs are calculated based on their connection with feedforward inputs [25,26]. Among various types of the static networks, multilayer perceptron (MLP) network (Fig. 3) is the most commonly applied network which maps the input data sets [47,48].

In MLP learning algorithm, the relationship between the inputs and outputs has been demonstrated as follows:

$$y_i = f_o \left[\sum_{o=1}^{N_o} b_o + \sum_{h=1}^{N_h} W_{ho} \cdot f_h \left(b_h + \sum_{i=1}^{N_i} W_{ih} x_i \right) \right]$$

(x_i , y_i : the primary input and output, w_{ih} , w_{ho} ($i = 1, 2, \dots, N_i$, $o = 1, 2, \dots, N_o$): weights of connections between the input and hidden units, and hidden and output units, respectively, b_o , b_h : biases of the output and hidden units, $f_o(\cdot)$, $f_h(\cdot)$: output and hidden functions, respectively), [48].

This neural network architecture includes multiple layers of nodes and each layer is fully connected to the next one leading to the recognition of particular elements [47,48]. MLP has been used for designing controlled release formulations, prediction of drug dissolution profile, and optimizing the formulations and drug release profile [49–51]. Due to the inner connectedness, dynamic networks are usually referred

as recurrent networks and various processing elements provide the flexibility [52]. In dynamic neural networks, past information is used to predict the present and future states of a system. This might be useful for characterizing or modeling drug release from controlled release formulations [53,54].

ANNs are trained to perform highly-specific tasks [26]. For training an ANN model, experimental data are usually categorized into the test, training, and validation sets [26,28]. Robust data sets are preferred for training ANN models and obtaining more reliable results [26,28,45]. In supervised training, ANN model is presented with input/output data sets [28]. In unsupervised training, inputs, but not desired outputs, are provided in the network [24–28]. In order to estimate minimum mean square error (MSE), training and validation procedures are applied for calculation of the optimum weights and biases [45]. Upon the integration of searching algorithms such as the genetic algorithms (GAs), trained ANN models have been used for optimizing the formulations including the controlled release ones [33–35]. ANNs in combination with GAs have been used for optimizing the method of detection of similar biophenols in blood [34,35,55].

Over the last decade, increasing interest has been attracted towards the realization of quality by design principles [56,57]. Response surface methodology (RSM) and ANN models have demonstrated significant sensitivity to the organization of experimental data sets [56]. Meanwhile, ANN-based models have shown superior predictive power than RSM and provided higher robustness for determination of the process design space and optimizing controlled release formulations [56,57].

Besides applications in genomics, proteomics, data modeling, development of the pharmaceutical products, and prediction of the bioavailability and behavior of drugs, ANNs have been suggested as reliable

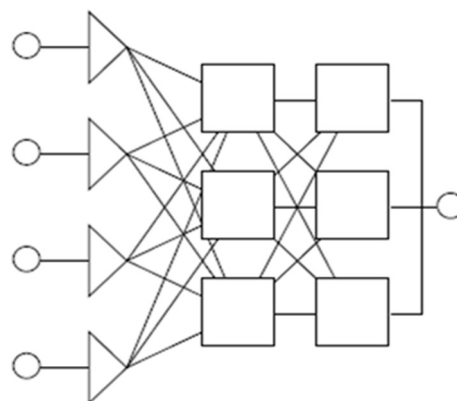


Fig. 3. Illustration of the multilayer perceptron network architecture. Adapted from Ref. [63].

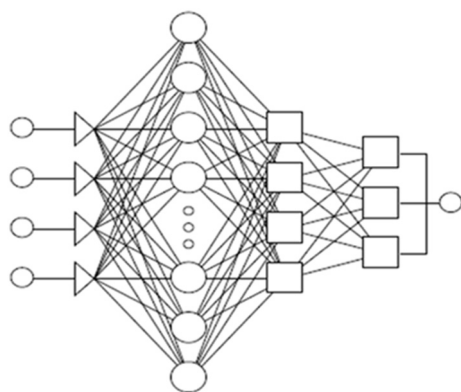


Fig. 4. An example of the generalized regression neural network architecture. Adapted from Ref. [211].

tools for capturing cause-and-effect relationships and prediction of *in vitro* and *in vivo* data (IVIVC) correlations [58–62]. IVIVC in association with ANNs provide the possibility for interpolation of the pharmacokinetic parameters and constructing complex relationships [62]. However, ANNs may not be useful for identifying the mechanism of correlation between the variables [63]. Following the development of IVIVC for modeling the sustained release paracetamol matrix tablet formulations, it was found that data generated by generalized regression neural network (GRNN) analysis, as a non-linear modeling tool (Fig. 4), were closer to those observed *in vivo* [64]. This indicates the suitable predictability of GRNN analysis and its ability for generalizing the complex relationships between the input and output parameters, compensation of differences in the kinetics of drug release under different conditions, and reliable estimation of drug behavior *in vivo* [64].

For development of the effective IVIVC, the ability of ANN models for incorporating a large number of variables and relationships without predefined model structure or assumptions might be of great significance [65]. The equation of GRNN is presented as follows:

$$\hat{y} = \frac{\sum_{i=1}^n y_i \exp(-D(x, x_i))}{\sum_{i=1}^n \exp(-D(x, x_i))} \quad D(x, x_i) = \sum_{j=1}^p [x_j - x_{ij} / \sigma_j]^2$$

(D : Distance between the point of prediction and training sample which is applied to clarify the mechanism by which training samples represent the prediction position (using σ as smoothness parameter), [65].

Using GRNN in a compressed multiunit particle system has provided the possibility to optimize the formulation and drug release profile [66]. This network type has been useful in prediction of drug dissolution profile [49,51]. Moreover, ANNs are promising tools for modeling the agglomeration processes [67].

2.1. AI for biomedical applications

Application of AI strategies provides promising opportunities for biomedical applications including the early diagnosis of a variety of disorders, prediction of signaling and metabolic pathways and patients' responses to therapies, and offering personalized treatment options [68–80]. In comparison to the common methods, confidence level for predictions made by ANNs may reach $\geq 90\%$ [75–80]. Such a predictive power might be a key step in development of the individualized treatment strategies [78,80]. ANN models help to predict the effects of drugs in individual patients [81]. In asthmatic patients receiving the monodisperse aerosols of salbutamol sulphate, ANNs have been applied for modeling the relationships between the *in vitro* data and *in vivo*

effects, prediction of aerosol behavior, and estimation of lung deposition of aerosol [81]. ANNs have also been used to create models capable of prediction the relative lung bioavailability of salbutamol and evaluation of IVIVC for different dry powder inhaler formulations [58].

An anesthetic agent administration and control system has been designed using a qualitative modeling and simulation methodology and fuzzy inductive reasoning which provide a suitable control performance of the anesthetic agent delivery system and enable development of a qualitative model for prediction of patient's behavior [82].

Continuous glucose sensing with insulin pump technology running on fuzzy logic rules is a promising approach for development of the closed-loop artificial pancreas [21]. ANNs have been applied for glyce-mic regulation and identification of patient dynamics [83,84]. AI tools are also helpful for rapid detection, classification, and quantification of pain, selecting the optimal treatment, and individualized therapy [85–88] that might be of great significance for reducing pain-induced pathological lesions.

Increasing the prevalence of obesity worldwide appears quite concerning. Since conventional treatment strategies are associated with a number of limitations [89–92], AI techniques provide the possibilities to predict the obesity and identify the genetic risk variants and relationship between the obesity-related disorders [93]. Fuzzy logic models have been applied to better understand the causes of obesity, prevent the disease or reduce its mortality and morbidity, and improve patient's quality of life [93].

Based on the significance of determining skin permeability of drugs, ANNs have been applied for modeling the process of skin transport and prediction of skin permeability with a reasonable accuracy [94–98] that may facilitate rational drug design. Using ANN analysis, an *in silico* method has been developed to predict the absorption of cosmetic products, physicochemical properties of vehicles, and human skin permeability coefficient [99]. This might be a promising approach for risk evaluation of the cosmetic ingredients.

AI techniques provide novel insights into the biophysics of cancer and enable prediction of cancer pathways [100,101]. An AI model has been applied to predict the risk of lymph node metastasis in patients with colorectal cancer and determine the necessity for further surgery following the endoscopic resection of tumor [102]. In this respect, unnecessary surgical procedures can be avoided.

Using the complex network approaches, it would be possible to assess the evolution of diseases, identify the factors implicated in the metabolic pathways, and process huge amounts of data related to the interactions between a variety of drugs, metabolites, and enzymes [103,104]. This might be of great significance in the development of more efficient therapeutics.

2.2. The role of AI in the advancement of tissue engineering

Tissue engineering (TE) in which a variety of strategies have been employed for development of substitutes for lost or damaged tissues, drug screening, and evaluation of the pharmacological profiles of drugs, is faced with several challenging issues [105–108]. Besides the modeling approaches and robotic techniques for manufacturing high-performance products and improved regeneration of tissues, ANNs have been used for prediction of TE strategies and their outcomes and generating TE schemes [105,109,110] that may result in more effective performance of TE projects with reduced failures and costs and improved therapeutic efficiency. AI has been suggested as a powerful tool for engineering tissues or precision biomaterials with high accuracy, and optimizing treatment protocols for individual patients [110–113] that might be of key importance in regenerative medicine.

2.3. Integration of AI and nanotechnology

AI programs can be used for accelerating and optimizing the nanofabrication process. A variety of methods such as decision tree or

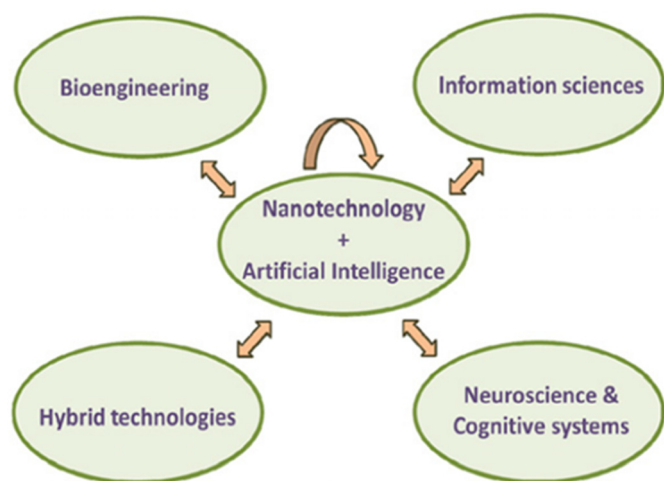


Fig. 5. A variety of scientific fields can be affected by the convergence of artificial intelligence and nanotechnology. Adapted from Ref. [115].

Bayesian network have been used for data mining, clustering, classification, or prediction [114]. Integration of AI and nanotechnology affects a variety of scientific fields (Fig. 5) that may result in the development of smarter technologies [115].

AI techniques have been used for solving the problems of nanotechnology including those related to designing of nanosystems, nanocomputing, and nanoscale simulation for which AI strategies provide novel designing principles, reduced computation time, efficient parameter estimation and system simulation, or interpretation of the experimental findings [115].

AI paradigms provide the possibility to overcome the physical limitations of nanotechnology and produce nanoarchitectures with increased computing power [114]. Scanning probe microscopy (SPM) is a useful tool for imaging sample-probe interactions, characterizing sample topography, or identifying the location of nanoparticles [116,117], meanwhile, signal interpretation is quite challenging [118]. Application of AI strategies provides a range of possibilities to address potential challenges, acquire a deeper knowledge about the interactions between the probes and samples, estimate the dielectric constants of samples and sample-tip distance, and more accurate image analysis [115]. In order to better clarify material properties, functional recognition imaging (SPM approach) has been represented in which the principal component analysis (PCA) and ANNs are used for simplification of the input data, reduction of the number of independent variables, extracting the relevant information from datasets, and faster problem solving [119]. Besides application for development of smarter sensors, AI tools have been used for categorization of the structural features of nanomaterials and assessment of their impact on the biological systems [120,121].

In nanomedicine, ANNs have been employed for modeling or analysis of the process of nanoparticle preparation leading to significant reduction of efforts, time, and costs [122–125]. QSPR modeling methods have been used for modeling the phase behavior of amphiphilic nanoparticles [126]. Using ANNs, a mathematical model has been developed for predicting the particle size and polydispersity index (PDI) of polymeric nanoparticles prepared by emulsification solvent evaporation method [127]. ANN model was built using the experimental datasets for covering all of the polymer properties which affect particle size and PDI of nanoparticles. The input layer of ANN model consisted of five factors; viscosity of polymer solutions, contact angle between water and polymer film, interfacial tension between water and ethyl acetate polymer solutions, poly(vinyl alcohol) concentration, and solvent to water ratio. Output layer included two responses; particle size and PDI of nanoparticles. Feedforward neural network with backpropagation learning algorithm was applied for model training.

Based on the results, concentration of poly(vinyl acetate) was the most important factor which affected nanoparticle size followed by interfacial tension, solvent to water ratio, viscosity, and contact angle. Furthermore, concentration of poly(vinyl acetate) showed the highest impact on PDI followed by the viscosity, interfacial tension, contact angle, and solvent to water ratio [127]. Moreover, ANNs have been constructed for prediction of the particle size and entrapment efficiency of noscapine-loaded poly(ethylene glycol)/polylactide (PEG/PLA) nanoparticles using various factors including the polymer to drug ratio, number of blocks, and molecular weight of polymer. Polymer to drug ratio and molecular weight of polymer showed the most dominant effects on the entrapment efficiency and particle size, respectively [128].

The ability of trained ANNs for prediction of the entrapment efficiency and particle size of nanoparticles might be of great significance in the development of more efficient nanotherapeutics [122–125]. For theranostic applications, determining optimal physicochemical properties of nanoparticles and providing maximal accumulation at target site are of critical importance [124,125]. In order to target the diseased microvasculature, ANNs have been applied to predict the optimal particle size and number of nanoparticles adhering to the vessel walls [129]. For structural characterization of the nanoparticle clusters and obtaining the unbiased cluster configurations, GA provides a deeper knowledge about the optimal arrangement of particles [130,131]. GA provides the possibilities to investigate the lattice structures and acquire optimal parameters for electron microscope imaging, nanooptics, or nanofabrication processes [115,132–134].

Carbon nanotubes (CNTs) with suitable stability, thermo-electrical conductivity, and mechanical properties have been extensively used in theranostic settings [135–142]. ANNs facilitate detection of organic compounds by CNTs [143]. Application of ANN models with higher computational abilities than common numerical models, has led to more accurate determination of the physical properties of quantum dot semiconductor optical amplifiers [144]. In designing the nanosystems, ANNs have been applied to identify the relationships between the input variables and output response. Furthermore, ANNs models are able to predict outputs [145].

AI techniques and paradigms are useful for easy simulations at nanoscale and development of nanodevices including the nanocomputers for performing complex tasks such as sensory information processing [115,146–148].

Noteworthy, interaction between the AI and nanotechnology is bidirectional. For instance, application of the nanotechnology-based quantum or DNA computing has provided solutions for a variety of problems [149,150]. Nanocomputing devices including the bio-inspired ones execute machine learning paradigms [151] that might be of key importance for solving the complex analytical problems.

3. Application of AI approaches for development of drugs and delivery systems

In modern drug discovery, creating the molecule libraries, identifying novel drug candidates with optimal properties, predicting the biological functions of proteins, and deep learning play critical roles [152–158]. In biopharmaceutical companies, using AI platforms for analyzing the biological data, identifying drug targets, and searching for a variety of pharmaceuticals might result in more effective drug discovery [159]. In the early phase of drug discovery, elimination of the inactive or toxic compounds is of critical significance [69,71]. Besides fast filtering or virtual screening methods, machine learning classification methods have been applied for screening and classification of drugs or nondrug collections and prediction of toxicities [160,161]. Support vector machines implicating the molecular structure descriptors and heuristic method have been used for prediction of the activity of enzyme inhibitors or rate-limited drug absorption [162,163]. In a QSAR study, 1,4-dihydropyridine calcium channel antagonists have been screened by least squares support vector machine [164]. Machine learning methods

enable prediction of target-drug interactions that might be of key importance in identification of the novel drugs or targets [165]. Among the supervised learning algorithms, regularized least squares classifier has been suggested as an efficient algorithm for prediction of drug-target interactions [165,166]. Furthermore, semi-supervised link prediction classifier has shown high performance in predicting drug-target interactions [167]. Gaussian interaction profile kernel and regularized least squares have suitable predictive performance, meanwhile, combination of Gaussian interaction profile kernels and genomic and chemical kernels has provided better predictive power [168]. During a variety of experimental procedures, findings obtained from optimal ANN-based models have been in good agreement with experimental data [169] indicating the suitable power of ANNs for being applied as the alternative of complex equations. Using ANNs, it would be possible to model the complex biological data and nonlinear systems, solve the problems of multivariate and multi-response systems, predict the secondary structures of proteins, and classify cancers [46,170–172]. Furthermore, ANNs have been applied for modeling the reaction rates such as the conversion rates of the oxidation reaction and prediction of the behavior of semibatch reactors in a series of experimental conditions [173]. Development of deep neural network models provides the possibility to predict the pharmacological profiles of drugs including their mechanisms of action and indications [69,152]. Besides providing predictive solubility models, undirected graph recursive neural networks method (a variant of recurrent neural network) is able to model drug-induced liver injuries [174].

AI approaches may also be applied to develop the predictive models, identify the biomarkers, construct correlations between the gene expression profile and clinical phenotype, and facilitate the personalized therapies [175–177]. Besides application in the early-stage drug discovery or design, AI techniques have been employed for rapid identification of the bioactive molecules among millions of compounds, assessment of the kinetic curves and data parameters in the chemical reactions, and guiding the traditional experiments [178] that may significantly save time and costs. Moreover, machine learning methods help to model the metabolism of drugs including their interactions with metabolic enzymes or relationships between the chemical structures of drugs and their biological fates, and metabolic endpoints [179] that may result in more accurate prediction of metabolic fates and potential toxicities of new drug candidates. In order to classify drug candidates as substrates of cytochrome P450, an ANN model has enabled development of an automated algorithm for evaluation of the metabolic transformations of compounds [180].

3.1. Peptide synthesis

Remarkable advances in biotechnology and peptide synthesis have provided the possibilities to benefit from the pharmacological effects of peptides. In this context, a variety of peptides have been synthesized and subjected to the screening procedures and analysis of the biological data by QSAR models [181]. An ANN method has been proposed for evaluation of the organ-targeting peptides which were selected from a random phage-peptide library using phage display technique [181]. Trained neural network included a multilayer system of fully connected neurons capable of mapping input dataset to the corresponding output dataset. Training and test sets statistics demonstrated the suitability of ANN models for selecting organ-targeting peptides from large peptide libraries [181]. ANNs have also been applied for accurate prediction of peptide binding to human leukocyte antigens and targets of immune responses [182].

3.2. Identifying novel antimycobacterial drugs

In recent years, virtual screening techniques for identifying new antimycobacterial drugs has attracted a growing interest [183]. In an attempt to reduce the risk of multidrug-resistant tuberculosis and identify

more efficient antimycobacterial drugs, an ANN model has been developed for introducing efficient descriptors for drug design [183]. For constructing the model, feedforward network was trained for performing a nonlinear regression between the minimum inhibitory concentrations and clustered descriptors. Several structure databases were analyzed using the cheminformatics tools capable of identifying the molecules as candidates for experimental assays [183]. In order to identify the effective compounds against the mycobacterium tuberculosis, a database consisting of various antimycobacterial agents was created followed by evaluation of the molecular descriptors. The model predicted the minimum inhibitory concentration with $MSE = 0.0002$ and $R^2 = 0.98$ [183].

3.3. Predicting the effectiveness of drug dosing and delivery methods

A data-driven predictive system has been developed using a machine learning framework capable of modeling the pathogen-drug dynamics and predicting the effectiveness of dosing patterns and drug delivery methods [184]. The method was experimentally validated for cell-drug interaction using metronidazole and *Giardia lamblia* and an accuracy of 85% was obtained for system performance [184].

3.4. Rapid identification of the bioactive agents and monitoring of drug release

Because of their capability of pattern recognition, modeling, and predictions, ANNs can be applied in pharmaceutical research areas including the modeling or development of drugs, optimization of their pharmacological profiles, and prediction of the structure and function of proteins [185]. In this context, ANNs have been applied for detection of amino acids with similar structures and determining concentrations of chiral samples or enantiomeric excess [46,185]. For quantification of two forms of ranitidine-HCl, ANNs have enabled rapid identification of the form 1 in a multi-component tablet [186]. An ANN model has been applied for simultaneous spectrophotometric estimation of the selective serotonin reuptake inhibitors, sertraline and fluoxetine, in the biological fluids and pharmaceutical formulations [187]. Three-layer feedforward neural networks using the backpropagation algorithm have been used for constructing and testing the models. Calculated relative standard deviation for fluoxetine and sertraline (1.06 and 1.33, respectively) in tablet samples revealed a good agreement between the predicted and experimental values [187] indicating the suitability of the combination of ANN models and spectrophotometric methods for determination of components in the pharmaceutical formulations. This kind of method can be a suitable alternative to the expensive and time-consuming chromatographic methods.

In general, the process of drug delivery system design is associated with several challenges such as predicting the relationship between the formulation parameters and response or treatment outcome, and occurrence of the unexpected phenomena [188]. Based on drug-carrying ability of erythrocytes, microchips are promising tools for monitoring the controlled delivery of antithrombotic drugs and targeting thrombi leading to the reduced risk of stroke or other life-threatening conditions [189]. For automated management of the arterial and venous circulation, fuzzy logic-based automated drug delivery system has been designed and validated [190]. Fuzzy decision analysis and fuzzy hemodynamic management modules were used to assess patient's condition and regulate arterial and pulmonary pressures and cardiac output, respectively. The system provided a faster response and more effective hemodynamic regulation [190]. Application of the supervisory-fuzzy rule-based adaptive control system is a promising approach for multiple drug hemodynamic control [191]. In this context, a control device applying an expert-system approach for two input-two output system has been designed by a mathematical model of the hemodynamic response [191]. Infusion rates of dopamine and sodium nitroprusside were considered as inputs and controlled variables included the cardiac output and mean arterial pressure. Dual mode control structure

included the coarse and fine control modes to ensure sufficient drug delivery. Based on the findings, hemodynamic variables were maintained within the limits [191].

Fuzzy control drug delivery systems are usually designed via application of the experts' knowledge without implication of the explicit mathematical models [190,191]. In pigs, mean arterial pressure has been successfully controlled by real-time fuzzy controller [192] suggesting the usefulness of fuzzy controller in the management of arterial pressure in the clinical settings. Regarding the modeling of bimodal drug delivery, MLP feedforward network has been applied for modeling the effects of causal factors on *in vitro* release profile of theophylline [193]. Besides the experimental datasets, several training algorithms were applied for training of ANN which contained a single hidden layer with four nodes. Assessment of the performance and prediction ability of the training algorithms represented the gradient descent backpropagation algorithms as the best training algorithms for modeling and prediction of drug release profiles [193]. Implementation of batch backpropagation revealed that enhancement of coating levels and reduction of the amount of chitosan-pectin complex result in the retarded drug release. As compared to another causal factor, coating weight gain, chitosan-pectin in the coating solution played a more influential role in determining dissolution profiles [193].

In order to provide suitable matrix erosion and bioadhesivity for an intravaginal drug delivery device, ANN models and molecular mechanics simulations have been applied for development of the bioadhesive intravaginal drug delivery devices for controlled delivery of therapeutics against the vaginal infections [194].

Using ANNs, physicochemical phenomena controlling the diffusion coefficients of loaded drugs in delivery systems and the most influential variable/s on diffusivity can be identified [195]. An ANN model has been developed to analyze the quantitative relationships between the physiological variables and release profile from a controlled drug delivery system including an intravaginal gel-type formulation for preventing the sexually transmitted diseases [195]. The effects of extrinsic/intrinsic and formulation variables on the diffusivity of sodium dodecyl sulphate were evaluated by ANNs. Based on the release profile of drug, a non-linear relationship between the physiological/formulation variables and diffusivity was found [195]. In comparison to the formulation or extrinsic variables, the secretion rate and pH of the vaginal fluid played more influential roles in determining the diffusion coefficient of sodium dodecyl sulphate from the delivery system and vaginal fluid pH was the most dominant factor in determining the diffusion coefficient of drug [195]. Furthermore, conditions of the external exposure proved to be more significant than the effects of formulation variables on the diffusion coefficient of drug. ANN tool helped to successfully predict the effects of intrinsic variables on drug release profile [195].

Using an ANN model, the release of doxorubicin from Pluronic P-105 micelles has been modeled [196]. The model revealed that more efficient drug delivery would occur at low frequencies and copolymer concentrations and enhanced power density, while, thermal effects do not play an important role [196]. ANNs by providing accurate predictions and optimizing the operating conditions, have been represented as reliable tools for modeling and prediction of the acoustic release of drugs from the polymeric micelles and optimizing the ultrasound application for targeted drug release [196,197].

ANNs applied to IVIVC (ANN-IVIVC) may overcome a variety of problems associated with classical regression methods [58–62]. Regarding the extended-release formulations, the abilities of a number of ANN configurations for determining IVIVC have been demonstrated [62]. Assessment of the predictive power of ANNs revealed that many of the network configurations successfully predicted mean plasma concentration profile. In this context, ANN-IVIVC has been proposed as a reliable tool for establishment of complex relationships and interpolation of pharmacokinetic parameters [62].

Dynamic lipolysis model (DLM) is useful for assessment of the novel lipid-based formulations and prediction of their behavior *in vivo* [198].

Using the combination of neuro-fuzzy networks and DLM enables prediction of the plasma concentration profiles of drugs [198]. The ability of DLM for simulation of the absorption of probucol from lipid-based formulations has been assessed by neuro-fuzzy networks [198]. Based on the findings, the rate and extent of probucol release from the oil formulation were significantly lower than those of self-emulsifying drug delivery system. Adaptive neuro-fuzzy modeling along with IVIVC tool showed efficient predictive performance as well as the potential to create complex relationships and interpolate pharmacokinetic parameters [198]. These findings represent the suitability of the combination of DLM, adaptive neuro-fuzzy modeler, and IVIVC tool for prediction of the behavior of lipid-based formulations.

As a complementary tool to the conventional methods, ANN can be used for assessment of the controlled drug release [50,63]. Mathematical models have been used for simulating the release profiles of rhodium (II) butyrate complexes and hydrocortisone from bioceramic and biodegradable matrices, respectively [50]. Drug loading, saturation solubility, and diffusion coefficient were predicted with a relative error of <1% suggesting the usefulness of ANN models for predicting the experimental conditions and providing controlled drug release for biodegradable polymers or bioceramic matrices [50].

Based on an intelligent modeling tool, generalized fuzzy neural network, an adaptive modeling and control scheme has been presented for automated drug delivery and regulation of the post-surgical blood pressure [199]. Following training, the model was evaluated for online adaptive control of the system. The adaptive controller implicated a feedforward generalized fuzzy neural network with a linear feedback loop capable of achieving a real-time control. Simulation studies showed the abilities of adaptive fuzzy neural method for modeling system uncertainties and nonlinearities and estimation of the effects of drug on blood pressure [199]. Following evaluation of the fuzzy logic ability to adapt the parameters of pharmacodynamic and pharmacokinetic model-based controller for delivery of pancuronium, practicality of the approach for acquiring a deeper knowledge about the characteristics of individual response to drugs has been verified [200].

A trained ANN model along with pharmacokinetic simulations have been used for designing controlled release dosage forms [201]. Formulation factors and cumulative percentage of drug released at various time points were selected as inputs and outputs, respectively [201]. ANN models may also be applied in the pre-formulation stage of controlled release oral dosage forms [50,63]. Using CAD/Chem software, an ANN model has been constructed to predict physicochemical properties of the controlled release matrix tablets [202]. Glass transition temperatures, moisture content of polymers, water-uptake profile, and viscosities of hydrophilic polymers have been accurately predicted by the model [202] suggesting the usefulness of trained ANN models for acquiring more accurate information in the pre-formulation stage.

3.5. Optimizing drug release from matrix tablets

AI methods may be applied to optimize drug release from the matrix tablets prepared by direct compression method [54,203]. Dynamic and static ANNs have been developed for modeling the dissolution profiles of various types of matrix tablets [203]. GA optimizer tool or Monte Carlo simulations were used for optimization of ANNs. Elman dynamic neural networks and decision trees accurately predicted dissolution profiles from the lipid and hydrophilic matrix tablet formulations with controlled release profiles [203]. In comparison to the most frequently used static network, MLP, Elman neural networks proved to be more successful for modeling of drug release profiles in different types of matrix tablets [203]. Using MLP with feedforward backpropagation method, metformin HCl sustained release matrix tablets with optimized *in vitro* release profile have been developed [204]. Input and output variables were applied for network training and leave-one-out method was used for model validation using several trial formulations in which the slope and R^2 values were assessed to identify the final optimized

model. Difference and similarity factors demonstrated no difference between MLP-predicted and experimentally observed drug release profile for optimal formulation [204] indicating the method suitability for modeling and optimization of the sustained release tablet formulations. In order to predict formulations of sustained-release tablets, solubility and ratios of hydroxypropyl methylcellulose/dextrin for several tablet formulations and their accumulation and *in vitro* release at various sampling times have been used as ANN model input and output, respectively [205]. ANNs have also been utilized for development of the controlled release tablets of carvedilol and no significant difference was observed between the experimental values and ANN-based predictions [206]. Moreover, ANNs have been applied for selecting the most appropriate formulation and processing variables for predicting the dissolution profiles of enteric-coated sustained release minitables [207].

In order to develop controlled-release formulations with suitable dissolution profiles and bioavailability and predict their *in vitro* and *in vivo* behaviors, pharmacokinetic simulations and ANNs have been employed and a good agreement was found between ANN-predicted and experimental findings [201] indicating the usefulness of ANN models for development of formulations with suitable physicochemical properties. A trained ANN model has been used to predict optimal compositions of tablet formulations based on the proper dissolution-time profiles *in vitro* and release profiles *in vivo* [201]. In sucrose esters matrix tablets, ANNs have enabled prediction and control of drug release and provided a deeper knowledge about the system [208]. Self-organizing map (an ANN type) and MLP networks facilitated evaluation of the interactions between the variables and prediction of drug release characteristics, respectively [208]. Furthermore, data clustering by self-organizing map ANNs helped to identify the correlations between the input and output variables. Based on the findings, sucrose esters, tensile strength, and tablet volume, but not tablet porosity, showed the highest impacts on drug release behavior [208]. In this respect, MLP and self-organizing map neural network approach have been suggested as suitable tools for optimizing multivariate systems and modeling the controlled release formulations [208].

Using an ANN model, formulation and release profile of time-dependent tablets have been optimized [209]. Backpropagation neural network technique was applied for modeling and optimizing of tablets. In the optimized formulation, drug release data were close to ANN-predicted release pattern [209] suggesting the usefulness of ANN-based methods for designing and optimizing complex dosage forms.

3.6. Making correlation between the formulation factors and release profiles

Besides prediction of dissolution and release profiles, ANNs are useful for optimizing modified-release products including the solid dosage forms [49,210,211]. GRNNs and connectionist models help to predict drug stability and release profile [63,65,211,212]. Using ANNs, a semi-empirical mathematical model capable of predicting the released drug amount from solid lipid extrudates has been developed [213]. System inputs included the diameter and length of the extrudates and dissolution times and the amount of released diprophylline was considered as output. Using the modified Weibull equation, it has been revealed that enhancement of the extrudate diameter results in reduced release rate [213]. ANNs have also been used to design the optimal formulations of sustained release dosage forms and predict their dissolution profiles [214]. GRNN has been applied for designing the extended-release aspirin tablets [215]. In order to obtain optimal aspirin tablets, optimized GRNN model has been applied for prediction of formulation characteristics and process factors. Based on the difference and similarity factors (f_1 and f_2), there was no difference between GRNN-predicted and experimentally-observed drug release profiles [216] indicating the suitability of GRNN for modeling extended-release tablets. Using MLP neural network and backpropagation algorithm, diclofenac sodium extended-release tablets have been optimized [217]. The amounts of

Carbopol® 71G and Kollidon® K-25 were selected as network inputs and *in vitro* dissolution time profiles were considered as outputs. Calculated similarity and difference factors revealed no difference between the experimental and predicted drug release profiles indicating the suitability of MLP for prediction of drug release and its applicability for modeling and optimizing sustained-release tablet formulations [217]. Dynamic neural networks capable of modeling dissolution profiles and more precise prediction of drug release profile (as compared to MLP and static networks), have been applied for modeling the release of diclofenac sodium from polyethylene oxide controlled release matrix tablets [54]. Networks with different topologies were established for obtaining accurate prediction of release profiles from the test formulations. Compression force and polymer fraction were demonstrated as the most dominant factors on drug release profile [54]. Furthermore, polyethylene oxides with high molecular weights proved to be more suitable for development of the controlled release dosage forms. Similarity and difference factors demonstrated the ability of dynamic networks for accurate predictions [54]. GRNN has been applied for development of multiunit particulate system for controlled delivery of diclofenac sodium, modeling the effects of causal factors on the release profile of drug from compressed matrix pellets, and obtaining the optimal formulation [66]. Correlation plots of the obtained and predicted values of drug release demonstrated the suitability of GRNN model ($R^2 \sim 0.98$). Furthermore, the percentage of polymer was recognized as the controlling factor of drug release from the compressed matrix pellets [66].

Combination of RSM and ANN methods has been used to optimize the formulation of isradipine-contained osmotic tablets [218]. Difference between the predicted and observed dissolution profiles of the optimized formulation was within the experimental error limits. Furthermore, calculated similarity and difference factors revealed no difference between the predicted and experimental drug release profiles [218], indicating the suitability of ANN models for obtaining suitable dissolution profiles and development of the controlled release formulations. For optimizing salbutamol sulfate osmotic pump tablets, an ANN model has been developed in which the causal factors included the amounts of hydroxypropylmethylcellulose, polyethylene glycol 1500 in coating solution, and coat weight. The average drug release rate and correlation coefficient of the amount of drug released were considered as the response variables [219]. Using trained ANN model, optimal formulation factors were acquired. Following the preparation and *in vitro* test of the optimized formulation, the release rate and correlation coefficient of the optimized formulation showed a good agreement with predicted effects [219]. ANN and design expert system have been applied for preparing glipizide push-pull osmotic pump tablets. Besides performing dissolution testing, the range of formulation factors and procedure were optimized by ANN [220]. ANNs have also been employed to optimize nimodipine zero-order release matrix tablet formulation [221]. For all responses, feedforward backpropagation ANN demonstrated better fit than multiple linear regression (MLR) models. Furthermore, estimation of the similarity factor confirmed the ability of ANNs to increase prediction efficiency [221].

In order to improve the accuracy of ANN models in pharmaceutical research area, software for parameter optimization has been developed which enables estimation of suitable ANN parameters that might be of great significance for development of the optimal formulations including the sustained release tablets [222]. Short half-life of melatonin, an effective agent against the sleep disorders, necessitates development of the extended-release tablets. Meanwhile, mimicking the plasma levels of melatonin appears quite challenging [223]. An ANN model has been applied to optimize melatonin release from hydrophilic polymer matrices. The model proved to be useful for optimizing the composition of extended-release melatonin tablets with suitable dissolution profiles [223]. ANN models have also been employed to predict the response variables, release parameters, and plasma concentrations of theophylline tablets. Findings demonstrated a good agreement between

ANN-predicted and experimental values [224,225]. Using ANNs, a comparative analysis of the release profiles and mucoadhesivity of buccal tablets of propranolol hydrochloride was performed and the polymers for optimized formulation were identified [226]. For obtaining increased mucoadhesion, polymers were selected by screening procedure and application of *feedforward* backpropagation ANN model. MLP network accurately identified the most significant input variables and suitable polymers for optimizing multipolymeric propranolol buccal tablets. PEG exhibited the most significant effect on the mucoadhesivity and mean dissolution time. MSE of 0.002 demonstrated high efficiency of the trained model and a comprehensive knowledge was obtained about the behavior of polymeric matrix tablets [226] that might be helpful for optimizing multipolymer drug delivery systems. Using several ANN software programs for prediction of dissolution profiles of controlled-release tablets, the best overall prediction has been shown by NeuralShell2 [51].

3.6.1. Beads, pellets, and microspheres

Several ANN models have also been developed to predict dissolution profiles of controlled release particulates including the beads, pellets, and microspheres [227–233]. A model constructed by CAD/Chem software has been applied for modeling the effects of formulation variables and process on the release profile of verapamil from the multiparticulate beads. Drug release data of the optimized formulations were in good agreement with those predicted by ANN model [227]. An ANN model has been used for assessment of the impact of process parameters on the entrapment of papain in cross-linked alginate beads leading to the improved stability and site-specific delivery [228]. Using optimal conditions, the neural network was constructed for prediction of the experimental matrix. Dissolution studies in the pH range similar to those in human gastrointestinal tract showed that alginate beads can be applied for delivery of papain to the small intestine. Accelerated and long-term stability evaluations revealed a significant improvement in the shelf-life of papain entrapped in alginate beads [228], indicating the usefulness of method for development of the stable beads capable of site-specific drug delivery.

ANNs provide useful information about the pellet properties and identify the relationships between the formulation characteristics, pelletization mechanisms, and key process variables [229]. Using neuro-fuzzy systems for prediction of the aspect ratio of pellets and characterizing preparation parameters [229] might be a promising approach for further formulation procedures. Using MLP neural network, dissolution profile of matrix-controlled release theophylline pellets has been predicted. High f_2 values (> 60) indicated the similarity of ANN-predicted dissolution profiles and those obtained from the experiments [49]. Regarding the granulated pellet-containing tablets, pellet size, Eudragit FS 30D, hardness of tablets, and coating weight gain have been identified as influential factors for evaluation of tablet properties including the release behavior. High correlation coefficients between ANN-predicted and experimental values demonstrated the suitable prediction power of ANNs [230].

Aspirin-loaded calcium alginate floating microspheres have been optimized by ANNs and RSM in which the amounts of formulation materials and release and floating rate of microspheres were used as inputs and outputs, respectively. As compared to RSM, ANNs more accurately predicted *in vitro* drug release profile [231]. In the formulation of verapamil hydrochloride-loaded polymer microspheres, pH of the external aqueous phase has been shown as the major determinant of incorporation efficiency and drug release behavior [232]. ANN and factorial analysis as multivariate methods were applied for assessing the impact of combined effects of external phase pH and other parameters, initial drug loading, and polymer concentration on the properties of polymer microspheres. Besides better fitting abilities, ANN model demonstrated less biased and more precise predictability than factorial analysis [232]. In this context, ANN models have been successfully applied for multivariate modeling of the release or encapsulation of ionizable drugs

from hydrophobic polymer microspheres. For preparation of the acrylic microspheres for controlled drug release, an ANN model has been developed for evaluation of the effects of preparative variables during the solvent evaporation method [233]. Input variables included the ratio of polymers, stirring rate, and concentration of dispersing agent. Size of the microspheres and $T_{63.2\%}$ were selected as response variables. ANN model showed higher predictability than MLR [233], suggesting that for evaluation of the formulation and process parameters, ANN models are suitable alternatives to the conventional regression methods.

3.6.2. Solid dispersions

Preparation of the solid dispersions is a promising approach for improvement of drug solubility [234]. Combination of ANNs and mixture experimental design has been applied for development the solid dispersions [234]. For improving the dissolution rate of carbamazepine, carbamazepine-Soluplus®-poloxamer 188 solid dispersions were prepared by solvent casting method. The effect of solid dispersion composition on dissolution rate of carbamazepine was assessed by three-layer feedforward MLP network and mixture experimental design. The relationship between the components of solid dispersion and percentage of released drug was well described by the mixture experimental design and ANN model, meanwhile, MLP network demonstrated better predictability than the mixture experimental design [234]. For preparation of PVP/PEG mixtures as carriers for development of drug solid dispersions, a feedforward backpropagation ANN with logistic sigmoid activation function has been applied to make correlation between the factors and dissolution characteristics and optimize dissolution rate [235]. ANNs demonstrated suitable prediction power and the prepared solid dispersions showed long-term physical stability [235]. Nimodipine-PEG solid dispersion has been used for development of the effervescent controlled-release floating tablet formulations [236]. Combination of the experimental design and machine learning algorithms including the genetic programming and ANN demonstrated suitable prediction power during the optimization process. Furthermore, simultaneous erosion and swelling were identified as the major mechanisms of the release of active ingredients [236].

3.6.3. Implants

For management of the postsurgical problems associated with cochlear implantation, coating of the cochlear implants has been suggested for topical delivery of drugs against the inflammation or infections [237]. An ANN model has been applied for prediction of the formulation parameters and release profile of dexamethasone from the cochlear implant coatings [237]. For obtaining an appropriate drug release profile, the ability of ANN model to determine the optimal levels of formulation parameters, was evaluated. Besides providing shorter formulation design process, drug release profile from the implant device was accurately modeled by ANN model and the results were so close to the experimentally obtained values indicating the model effectiveness [237].

3.6.4. Liposomes

Over the last decade, application of the echogenic liposomes for delivery of the chemotherapeutics has attracted a growing interest [238,239]. Since multiple drug resistance can be overcome by controlled drug release, ANN-based model predictive controller has been proposed for constant release of the chemotherapeutic agent and maintaining an appropriate concentration at tumor site [238] that may reduce the risk of multidrug resistance and shorten treatment duration. In order to design and optimize formulation parameters of leuprolide acetate-loaded liposomes, ANNs and MLR method have been compared [239]. For determining optimal ANN structure, various training sessions were carried out with different number of nodes in hidden layer. Nonlinear differential transfer functions was applied for predicting the percentage of drug entrapment in liposomal formulations. Based on the findings,

application of the feedforward backpropagation network and MLR is a promising approach for predicting appropriate composition for a specific response and acquiring a deeper knowledge about the effects of formulation parameters and preparation process on the product properties [239]. Comparison of the predicted and experimental data revealed no statistically significant difference. Furthermore, optimal ANN showed higher predictive power than MLR method because of the lower values of normalized error and higher precision level [239].

3.6.5. Transdermal formulations

An ANN model has been developed for optimizing transdermal ketoprofen hydrogel [240]. Optimal values of the response variables were applied for optimizing gel composition. The results obtained from the optimal formulation showed a suitable agreement with those predicted by ANN model [240]. For transdermal delivery of melatonin, ANNs and RSM have been applied for optimizing the vehicle composition [241]. Transdermal route was selected to prevent the remarkable hepato-gastrointestinal first-pass metabolism of melatonin and maintain its steady-state plasma concentrations for appropriate time periods. Since melatonin is unable to pass through the dense lipophilic matrix of stratum corneum, several solvents and their mixtures were used for enhancement of melatonin flux and reduction of lag time [241]. Multi-layer feed forward backpropagation network was developed for identifying the best solvent mixtures for a particular response and assessment of the inter-relativity between the responses. Experimental findings were comparable to the predicted ones [241]. Integrating the neural networks, GAs, and theory-based quantitative structure-property relationship models, a screening algorithm has been developed to identify the chemical penetration enhancers for transdermal drug delivery [242]. Besides assessment of melatonin permeability, enhancers were evaluated for their toxicity. Results demonstrated the suitability of algorithm for development of the skin permeation enhancers with improved performance [242].

Regarding the potential of neural network-based intelligent learning system for prediction of the release profiles of drugs, an experimental study regarding the transdermal iontophoresis has been conducted to assess the usefulness of a neural network model, Gaussian mixture model (GMM), for modeling and prediction of drug release profiles [243]. Using face-centered central composite design (CCD) approach, several tests were systematically designed for simultaneous evaluation of the effects of process variables during iontophoresis. Combination of GMM and face-centered CCD has been suggested as a useful intelligent learning system for prediction of the release profiles of drugs [243].

3.6.6. Hydrodynamically balanced systems, suppositories, pulmonary delivery

ANNs have been applied as modeling tools for predicting the release profiles of drugs from hydrodynamically balanced systems [244]. Based on the chemical structure of drugs and formulation description, ANNs helped to accurately predict the release profiles of various drugs and identify the key variables affecting drug release [244]. An ANN approach along with modeling and simulation of the compartment-based models have been applied for assessment of differences between the slower and faster release of paracetamol from the layered excipient suppositories [245]. It has been revealed that the extent of drug absorption is enhanced by absorption-increasing effect of mono-di-glycerides and liver bypass mechanism [245]. For designing the pulmonary drug delivery systems, two-layer perceptron feedforward backpropagation ANNs have been successfully used for simulating aerosol behavior [246].

3.6.7. Controlled-release formulations

Application of ANNs and fuzzy logic algorithm for designing of sustained release formulations helps to analysis the effects of formulation components on the release characteristics and optimize drug formulations [51,204,207,209]. In this context, controlled release formulations of clopidogrel have been developed using fuzzy logic

algorithm and ANN analysis for determining the effects of tablet components on the release characteristics [247]. Following development of the complex dosage forms and designing controlled-release formulations by pharmacokinetics simulations and ANNs, a good agreement has been found between the experimental findings and ANNs-based predictions [201,206].

Based on the content of separate components in colloidal delivery systems and nature of co-surfactants, GAs and ANNs can be used to predict the phase behavior of this type of delivery systems [248]. GA and a supervised ANN have been used for selecting the key molecular descriptors and making correlation between the selected descriptors and weight ratio of the system components and phase behavior, respectively [248]. Findings have shown the influential role of the chemical compositions, molecular volume, lipophilic-hydrophilic balance, length of the hydrocarbon chain, and hydrocarbon volume of co-surfactants. The genetic neural network model predicted the phase behavior of the colloidal delivery systems with high accuracy [248], suggesting the suitability of this approach for evaluation of the co-surfactants in pharmaceutical formulations.

3.6.8. Emulsions

Appropriate preparation of the emulsions necessitates a high level of expertise and technical knowledge. Based on the limitations of RSM including the poor estimation of the optimal emulsions [249], ANNs capable of optimizing and modeling the complex relationships between the formulation parameters and their effects on the quality of final product, have been applied for preparation of the stable emulsions [249]. In a study conducted by Kumar et al., ANNs have been used for formulating stable oil-in-water emulsion and optimizing the concentration of a fatty alcohol [250]. Input data included the variables of lauryl alcohol concentrations and time, and zeta potential, particle size, viscosity, and conductance were considered as outputs. Based on the validation experiments, ANN-predicted values were in good agreement with experimental data [250]. ANNs have also shown promising accuracy in prediction of the microemulsion type from its composition [251]. Using the combination of evolutionary ANNs and GA, internal structures and types of microemulsions have been predicted with high accuracy [251]. An ANN model has been developed to predict stable microemulsion formulation containing isoniazid and rifampicin for oral delivery [252]. Data from several pseudoternary phase triangles containing the mixture of surfactants and oil component were applied for training, testing, and validation of the ANN model. Using the radial basis function network architecture, weight ratios of the individual components were consistent with observed phase behavior. The obtained microemulsion formulation with improved stability was capable of targeted delivery of both antituberculous drugs during the continuation phase suggesting the formulation effectiveness to overcome the problems associated with combination of drugs with different solubilities [252].

3.6.9. Microparticles

In order to overcome dissolution rate-limiting step, benzimidazole chitosan microparticles have been prepared by coacervation method followed by application of an ANN model for optimizing the formulation [253]. Multi-response optimization was applied for obtaining the maximal yield, encapsulation efficiency, and dissolution rate, and the minimal size. ANN-predicted optimum values were in agreement with experimental findings indicating appropriateness of ANNs for development of the optimal benzimidazole chitosan microparticles [253]. Using ANNs capable of being trained online, an adaptive drug delivery system has been developed for more efficient treatment of infectious diseases [254].

3.6.10. Nanomaterials

Evaluation of the parameters which affect nanoparticle size, loading efficiency, or cytotoxicity might be helpful for designing more efficient drug delivery systems [18,126,127]. ANNs have been applied to predict

the physicochemical properties of nanoparticles with theranostic importance against a variety of disorders [255–261], analysis complex nonlinear relationships and factors affecting the stability or size of nanoparticles, or design the models for identifying the relationships between the factors affecting the development of controlled-release drug delivery systems [262–267]. Besides demonstrating input-output interactions, ANNs can be used for modeling and identification of key parameters which affect the size of nanoparticles in a multidimensional space [266,267]. For preparation of the biodegradable nanoparticles of tri-block poly(lactide)–poly(ethylene glycol)–poly (lactide) (PLA–PEG–PLA) copolymer as drug carrier, an ANN model has been developed for identifying the factors affecting the nanoparticle size [268]. Three-layer feedforward backpropagation ANN was applied for modeling the preparation of nanoparticles and the best predictive model was selected based on the appropriate R^2 and MSE values for training, test, and validation data. Among the processing factors, polymer concentration was found to be the most influencing factor [268]. For optimizing the formulation of polymer–lipid hybrid nanoparticles for controlled delivery of verapamil hydrochloride and assessment of the effects of formulation factors, optimization and modeling were performed based on the spherical central composite design [269]. Multi-objective optimization of nanoparticles was performed using the validated ANN models and continuous GAs. The obtained nanoparticles showed suitable properties such as drug loading efficiency of 92% and mean particle size of ~100 nm which are desirable for lymphatic transport after oral administration. Predicted response variables were in good agreement with experimental findings. Comparing the predictive performance of ANN models and RSM revealed the better generalization and recognition ability of ANNs [269]. Combining factorial design, ANN, and continuous GAs is a promising approach for multi-objective optimization and modeling of nanoformulations with suitable properties [269,270]. Using ANN, formulation parameters of chitosan–tripolyphosphate nanoparticles have been optimized in order to control nanoparticle size and improve the process yield at a novel pH [270]. Multilayer feedforward backpropagation neural network was applied for modeling the complex nonlinear relationship between the inputs and outputs and presenting outputs as 3D graphs. ANN architecture included three layers and trial and error approach was carried out for modeling. Various training parameters were used for obtaining appropriate predictive network and two approaches were applied to prevent over training of network. Concentration of sodium tripolyphosphate was found to have the greatest impact on the particle size and yield. Furthermore, successful interaction of chitosan and sodium 2q nanoparticle formation was confirmed by differential scanning calorimetry and Fourier transform-infrared spectroscopy indicating the ability of ANNs to predict size and yield of nanoparticles and identification of the influential factors [270]. In this respect, multivariate trained models capable of providing a deeper knowledge about the parameters affecting the physicochemical properties of nanoparticles and predicting or optimizing the processing conditions are promising tools for obtaining improved theranostic outcomes [270].

Regarding the albumin-loaded chitosan nanoparticles prepared by polyelectrolyte complexation technique, ANNs have been applied for simultaneous determination of the effects of independent variables on dependent ones [271]. Based on the findings, material concentrations are the most important factors affecting dependent variables, i.e., loading efficiency and cytotoxicity. In this sense, optimizing independent variables is necessary for obtaining suitable nanoparticles [271]. ANN models have also been applied for constructing a correlation between the entrapment efficiency of solid lipid or polymeric nanoparticles and prediction of the binding energy of drugs [170].

In order to overcome the problems associated with the application of nanoemulsions, ANNs have been applied for modeling the experimentally obtained data, evaluation of the factors which affect the cytotoxicity of nanoemulsion, and obtaining stable nanoemulsion system with reduced cytotoxicity [272]. Based on model findings, surfactant and oil

concentrations were the dominant factors affecting the nanoemulsion stability and cytotoxicity, respectively. In this context, ANNs have been shown as promising tools for describing the effects of nanoemulsion ingredients on the stability and cell viability [272]. ANN models are also helpful for identification of the key factors affecting the particle size of Nano emulsions [273]. An ANN model capable of modeling the formulation and processing experimental data related to budesonide nanoemulsion, has identified the parameters which affect the particle size. Total amount of energy used during the nanoemulsion preparation was recognized as the main factor affecting the particle size of nanoemulsion [273].

Because of the multivariate nature, development of drug loaded nanospheres is an expensive and time-consuming process [274]. ANN and GA have been used to simulate and optimize the fabrication process of agar nanospheres. GA and ANN proved to be more efficient tools than RSM for modeling and optimizing the manufacturing process of bupropione-loaded agar nanospheres and estimation of their physicochemical properties [274].

In designing the efficient nanoformulations, controlled release profile and targeted delivery are the essential factors which should be taken into account [127,128]. In this sense, designing the functional and specific linkers which affect the stability, release profile, and efficiency of nanotherapeutics [275,276] might be of critical importance. Application of advanced linker technologies including the simulation and modeling techniques, web-based systems, GAs, or GA/fuzzy hybrid algorithms helps to identify suitable linker candidates and develop novel linker-drug conjugates with enhanced efficiency and reduced toxicity [276–278].

Using ANNs, formulation of the nanoparticulate fingolimod delivery system has been optimized [279]. The amounts of polyvinyl alcohol, poly(3-hydroxybutyrate-co-3-hydroxyvalerate), and fingolimod, and time of drug release have been considered as input values. Output data included the polydispersity index, particle size, entrapment efficacy, loading capacity, and percentage of drug release from nanoparticles. Feedforward backpropagation was applied to assess the effect of time on the percentage of drug release and the optimal formulation was selected by Levenberg–Marquardt algorithm which showed less prediction error than other training algorithms [279].

4. Application of nanorobots for drug delivery

Development of the micro- and nano-electromechanical systems has provided the possibility of fabricating implantable robots for performing a variety of tasks including the controlled delivery of drugs or genes [280,281]. Because of the remarkable advances in nanotechnology, increasing interest has been attracted towards the development of nanorobots which are integrated with internal or external power supply, sensors, and AI [282,283]. These smart structures are capable of information processing, signaling, sensing, actuation, communication, performing the biological tasks at cellular levels, and localized delivery of drugs leading to the improved efficiency and reduced side effects of the conventional therapeutics [282–284]. Nanorobots hold great promise for detection of toxic agents and theranostic applications [285–288]. Bionanorobot rule structure includes the navigation rules, collision avoidance, target identification rule, detection and attachment rule, drug delivery rule, mission complete rule, and activation of flush-out mode leading to the excretion of bionanorobots [281,283,285,287]. In molecular manufacturing automation, application of AI provides the possibility to control the behavior or motion of nanorobots [289,290]. Using the simulation and modeling techniques, collaborative and autonomous behaviors of nanorobots or nanorobotic-based drug delivery systems have been effectively simulated [291]. Following the intravenous injection, bionanorobots are released into the bloodstream and their swarming and swimming behaviors are facilitated by bio-actuation mechanisms [292,293]. Swimming microrobots for controlled delivery of drugs, transient microrobot

system for targeted drug delivery using touch- or nano-communication frameworks, or wirelessly-controlled and deeply penetrable microrobots have been suggested as novel forms of controlled-release drug delivery systems for targeted therapy in a variety of disorders particularly the chronic ones [281,285,294–296] that would be of great value in personalized medicine.

Magnetic microrobots can be used for ocular drug delivery [297]. Wireless positioning and manipulation of drug delivery into the eye is a promising approach for targeted therapy with minimal invasiveness. Meanwhile, several issues have remained challenging including those related to the fabrication process, controlling interactions with complex biological environments, and biocompatibility [297]. Appropriate path planning is of critical importance for precise targeting and controlled drug delivery [298]. Besides simulation of the dynamic environments including the obstacles with different sizes and shapes, simulated annealing or a variety of algorithms such as the heuristic search, path planner, or swarm intelligence-based algorithms have been applied for detection of collisions, path planning and optimizing, target finding, or solving the problems associated with path finding [284,299–302]. Quorum sensing technique has been employed to improve path finding efficiency [303]. Furthermore, a novel technique which has been inspired by the bacterial foraging technique, has been represented for optimizing robot path planning and finding the shortest path towards the target [304]. An area coverage approach based on the genetic algorithm has also been proposed which is characterized by the combination of online and offline path planning for coping with environmental uncertainties and overcoming the obstacles during drug delivery [305]. Turning angles and lengths of paths should be assessed to find the shortest and collision-free path [305]. This might optimize energy consumption of robots which consist of micro-sensing, micro-actuating, and micro-control units, drug reservoir, and energy source for targeted drug delivery within certain periods of time [290,293,305]. Under the guidance of microcontrollers, microrobot moves towards the target followed by drug release. Because of the reusability, robots are able to bring back other drug reservoirs to the target site (Fig. 6), [305].

The entrapped drug is released from nanorobot via manipulation of the physiological conditions, however, any unexpected alteration of pH or temperature may negatively affect drug release profile [305]. In this respect, designing the externally-controlled nanomachines might be more appropriate for controlled drug delivery [306].

Magnetoelectric nanorobots are promising nanodevices for drug delivery. Locomotion of these nanocarriers is controlled by magnetic fields and their cargos are released in controlled and site-specific fashion [307]. For increased drug loading, nanowires have been pretreated with polydopamine leading to drug adsorption onto the surface of nanorobot [306–308]. Magnetic resonance imaging (MRI)-based drug delivery systems containing MRI propulsion and tracking modules, controller, and drug-loaded nanocapsules enhance the efficiency of therapeutics agents and reduce their side effects [309]. Application of the nanorobotic system guided by MRI enables real-time monitoring of nanocapsules by an active targeting mechanism [309]. Following surface modification, metallic nanoshells, quantum dots, gold nanoparticles, or CNTs have been used as carrier modules of MRI-guided nanorobots [310,311]. Meanwhile, application of the appropriate algorithms to control these nanocarriers against the environmental perturbations and providing 3D navigation path for enhanced targeting accuracy are necessary [312,313].

DNA nanorobots for biosensing, triggering apoptosis, or drug delivery, have been activated by external nucleic acids capable of interaction with their complementary counterparts on nanorobots [314–316]. Application of ANNs for prediction and optimizing the performance of nanorobots embedded with biosensors and transducers, is a promising approach for detection of tumor cells and targeted drug delivery (Fig. 7), [65,317] that might be of critical significance in cancer therapy and reduced adverse drug reaction. Detection of β -catenin and

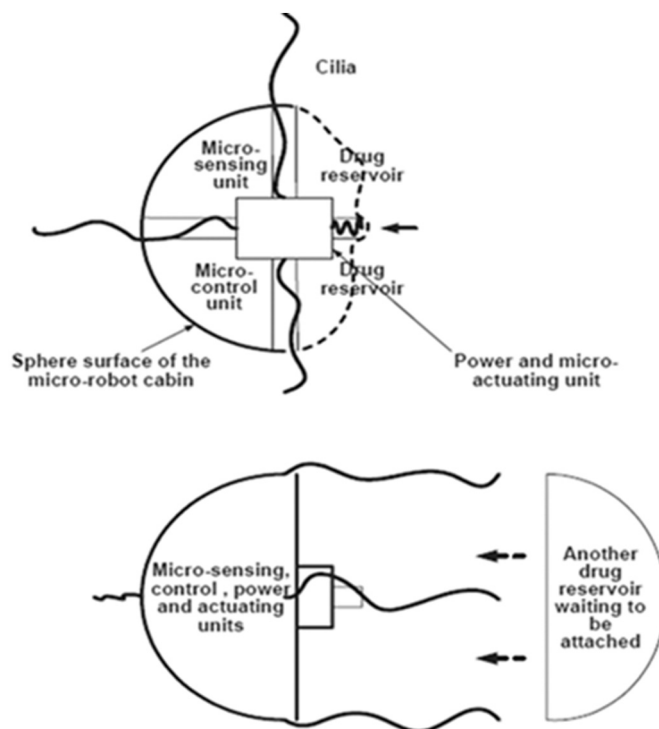


Fig. 6. Schematic illustration of drug release from a microrobot. The robot consists of micro-sensing, micro-actuating, and micro-control units, and drug reservoir for targeted drug delivery within certain periods of time. Under the guidance of microcontrollers, microrobot moves towards the target followed by drug release. Because of the reusability, microrobot is able to bring back another drug reservoir to the target site. Adapted from Ref. [305].

E-cadherin by these nanorobots facilitates target identification and localized delivery of therapeutics [293,318–322].

Nanorobots may also be applied for controlled delivery of genes and overcoming the challenging issues associated with non-specific gene delivery methods [323]. Moreover, nanorobots provide longer residence time for anticancer agents [324,325]. Controlled drug delivery and capability of nanorobots to carry drug combinations may provide pharmacological synergism and reduced drug resistance that might be of great significance in treating various cancer types [325,326]. For instance, combination of cyclosporine and doxorubicin has been shown to eradicate both leukemia and lymphoma [326,327]. For travelling towards the cancer cells, bionanorobots should face an unstructured and cluttered environment in the bloodstream [328]. This necessitates application of the suitable controllers and sensors for finding the right trajectory, overcoming the obstacles, discrimination of tumor cells (via detection of any difference between the temperature or electromagnetic field of the healthy and tumor cells), and delivery of the appropriate amount of drug [298,328].

Following determination of the concentration of glycoprotein molecules on the surface of cancer cells, cancer type can be identified by bionanorobots [298]. For instance, increased levels of CA19-9 and CA125 biomarkers indicate the presence of lymphoma and leukemia, respectively. Meanwhile, both of these markers are expressed in the aforementioned cancer types [298,319]. In fuzzy logic decision-making system which can be applied for navigation, overcoming the obstacles, preventing the collisions with other bionanorobots, tumor diagnosis, recognizing the disease stage, handling the uncertainties and noise, or delivery of the appropriate drug dosage [298,319], sensitivity and concentration of CA19-9 and CA125 biomarkers have been considered as determining variables for discrimination of tumor cells [298]. Because of the uncertainties associated with marker concentrations, application of Mamdani fuzzy logic with flexible structure has been suggested for tumor diagnosis [329]. Mamdani approach provides the possibility to

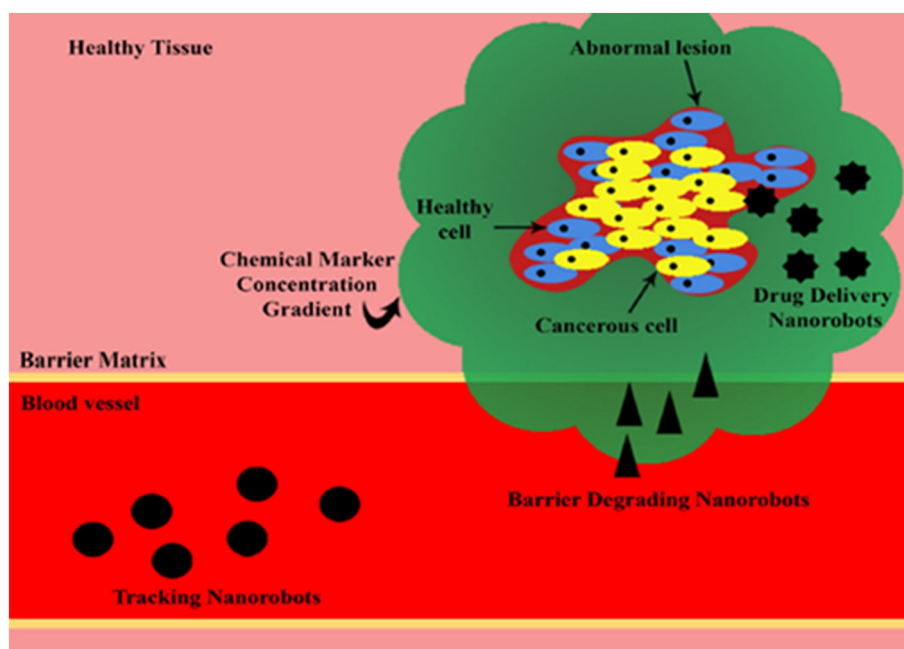


Fig. 7. Schematic illustration of targeted drug delivery using the nanorobots. Nanorobots embedded with biosensors and transducers can be applied for detection of tumor cells and targeted drug delivery. Adapted from Ref. [291].

incorporate the uncertainties into the rule-based system or model the uncertainties associated with navigation of bionanorobots or drug delivery process [329]. Reduced processing time and power consumption are other beneficial aspects of Mamdani fuzzy logic which provide increased execution time for bionanorobots [329]. After tumor diagnosis, drug dosage for intracellular delivery should be determined. Application of Takagi-Sugeno fuzzy model provides the possibilities of linear mappings and obtaining the effective dose for intracellular delivery [330]. Following attachment to the tumor cell surface and drug injection by nanocannula, mission complete rule guides the bionanorobot towards the excretory system [298].

In recent years, increasing interest has been attracted towards the development of medical capsule robots, the micro-systems capable of autonomous operation within the body for theranostic applications, monitoring disease progression, and drug delivery [331–334]. Meanwhile, the commercially available capsule robots do not execute the algorithms for optimized drug delivery that may be due to the absence of an active position control or real-time localization [335]. In this respect, integration of a holding mechanism inside the capsule or application of three-axis Helmholtz coil capsule capable of rotational movement, magnetic locomotion system, or reed switch have been proposed for targeted drug delivery [336–339]. For rapid development of the medical capsule robots and intelligent drug delivery in a targeted manner, drug delivery capsules have been designed based on the combination of multiple functionalities, an intelligent scheduler, and coil-magnet-piston mechanism for controlled drug release. The magnetic force and drug release profile have been modeled followed by experimental verification [340].

5. The significance of target fishing

Identification of the molecular targets might be of critical significance in the process of drug design. Target fishing (TF) by which the targets, mechanisms of action, or side effects of therapeutics are predicted, plays an important role in modern drug discovery [341,342]. In this context, algorithms of machine learning and cheminformatics toolkits provide a deeper knowledge about the structures of complex compounds and designing novel drug candidates against the complex diseases [341–344]. TF by exploring the mechanisms of action of small

molecules, identifying their target proteins, and speeding up the development process [345,346] may significantly reduce experimental costs.

In drug discovery, bridging the biological and chemical space might be quite important [347]. 2 and 3D descriptors can be applied to predict the targets of ligand probes considering their similarities to the reference molecules. In this context, high affinity binding of diethylstilbestrol to the estrogen receptors has been revealed [347]. TF which is based on the computational-, genomics-, and proteomics-based methods, is a promising approach for assessment of drug polypharmacology and molecular similarities [348–350]. Using a large-scale TF approach based on the similarity rankings with data fusion, drug-relevant targets and potential toxicities have been predicted indicating the significance of ligand-based TF in drug discovery [351]. Furthermore, search for the similarity of bioactivity profiles has been performed for identification of the targets for uncharacterized compounds, suggesting the novel targets for old therapeutics, and prediction of the polypharmacological profiles of various compounds, adverse effects, or novel therapeutic indications [352–354]. Considering the similarities between the ligands, the relationships between loperamide, methadone, and emetine with neurokinin, muscarinic, and adrenergic receptors (NK₂, M₃, α_2 , respectively) have been successfully characterized [355]. Using the similarity search methods, the inhibitors of DNA methyltransferase and anti-thrombotic activity of the anti-diabetic drug, glibenclamide, have been identified [356,357]. Furthermore, side-effect similarities and network analysis have enabled identification of the novel drug targets [358]. Application of phenotypic side-effect similarities followed by *in vitro* binding assay is a promising approach for characterizing unexpected relationships between drugs [359].

Chemoproteomic technologies have provided the possibilities to investigate the mechanisms of action of a variety of drugs or bioactive small molecules and characterize drug-induced alterations in protein expression [360]. Integrating the platforms of chemical proteomics into the initial stages of the process of drug discovery facilitates identification of the novel target proteins [361]. Chemoproteomic fishing has enabled identification of the modulators of brain glycogen phosphorylase which regulates the metabolism of glucose [362]. Chemoproteomics has also been applied to characterize the properties of calixarene derivatives and their interactions with identified biomolecular targets, and targets of bioactive small molecules [363,364]. It

has been revealed that bioactive compounds exert their pharmacological effects via modulation of various targets which could be unrelated by structure, function, or sequence [364].

In the cellular environment, application of the photoaffinity probes based on the carbene precursor, diazirine, has facilitated identification of target proteins and interactome mapping [365]. For rationalizing the cytotoxic effects of aryl-aminopyridine derivatives against various cancer cell lines, screening compound libraries against targets has been performed considering the best correlation between *in vitro* cytotoxicity and docking scores [366]. Based on the docking results, the modes of action of aminopyridine derivatives implicate disturbance of the cell cycle and signaling pathways via inhibition of various kinases. Furthermore, non-specific inhibition of tyrosine and cyclin-dependent kinases has resulted in the cytotoxic effects [366]. These types of findings can be utilized for modification of compounds and development of drugs capable of targeting the proteins implicated in the survival and proliferation of cancer cells.

TF using the cross-docking approach can be performed for identification of the novel protein–drug interactions. This might be useful for explaining various types of side effects or suggesting new modes of action [367]. For instance, peroxisome proliferator-activated receptor- γ has been predicted as a target of ethacrynic acid that may justify the hyperglycemia induced by this diuretic. The novel repositioning opportunities of drugs or potential mechanisms of adverse reactions can be predicted by cross-docking [367].

For investigating the effects and mechanisms of action of natural products in treatment of atherosclerosis, sepsis, or migraine, TF has been performed to identify the candidate targets and target-compound interactions [368–370]. Capsaicin has shown therapeutic potentials against a variety of disorders [371–375]. In order to better understand the mechanisms of action of this alkaloid, its potential targets have been predicted by PharmMapper followed by confirming via molecular docking and chemical protein interactome. Based on the findings, capsaicin is a potent inhibitor of the isoenzymes of carbonic anhydrase [376]. A pharmacophore-based TF approach has been employed to predict the targets of isoquinoline alkaloids with protective effects against the inflammation, pain, infections, or cancer [377]. TF approaches have also been applied to predict the potential targets and molecular mechanisms of the flavonoid, baicalein. It was shown that baicalein remarkably reduce the generation of intracellular nitric oxide and reactive oxygen species and exhibit protective effects against the neurotoxicity induced by N-methyl-D-aspartic acid receptors indicating the antiparkinsonian effect of this flavonoid [378]. Furthermore, chemical proteomics strategies can be used for identification of the binding partners of natural products including the antibacterial and cytotoxic agents [379]. For target identification of the electrophilic natural products, activity-based protein profiling (ABPP) is a promising approach [380]. Competitive ABPP has been applied for development of the inhibitors of serine hydrolase with therapeutic potentials against a variety of disorders [380–382]. Meanwhile, indirect nature of the most of the identification approaches and non-specific binding of some proteins are challenging issues in chemical proteomics that necessitates application of the advanced quantitative proteomics techniques and suitable linkers [275,276].

Regarding the special types of diseases in which the conventional drugs could be associated with serious side effects, identification of new macromolecular targets may provide therapeutics with increased activities and reduced side effects. Molecular modeling has enabled identification of the potential targets for novel anti-leishmanial agents [383]. Following TF study, 4-phenyl-1,3-thiazol-2-amines have been represented as suitable scaffolds for designing the selective anti-leishmanial drugs with improved activities [383]. TF tools have also proved to be useful for predicting targets for anti-tuberculosis drugs. DNA gyrase and RNA polymerase have been successfully predicted as targets of the antibacterial agent, CBR-2092 [384,385]. In difficult-to-treat diseases such as Chagas disease in which the currently available

drugs are associated with numerous side effects and low efficiency, identifying the novel molecular targets and development of their inhibitors provide improved therapeutic outcome [386]. The effects and mechanism of action of the antidepressant, sertraline, against the various strains of *Trypanosoma cruzi* have been investigated by TF. Chemogenomics strategy was used to identify several similar targets in the parasite. Based on the findings, sertraline with multi-target characteristics affects the bioenergetic metabolism of *Trypanosoma cruzi* [387].

In general, TF methods are based on the screening procedures including the machine learning algorithms, selection of the reference ligands, and determining the appropriateness of targets [341,388]. For target ranking or prioritization, various TF methods including those based on the ranking perceptrons algorithms and support vector machines have been applied [388,389]. Using network-based inference method, montelukast has been identified as the inhibitor of *dipeptidyl peptidase-4* [390]. Furthermore, polypharmacological profiles of ketocozazole, diclofenac, itraconazole, and simvastatin on the estrogen receptors have been evaluated [390].

Based on the necessity of validating the prediction and classification methods, machine learning methods have been used for cross-validation [391,392]. Retrospective analysis can also be used for validation of some TF methods [393]. Ligand-centric and target-centric methods can be used for predicting the activity of test ligands against the corresponding targets. Target-centric methods are usually based on the multi-target QSAR models or unsupervised learning approaches and numerous targets have been considered by ligand-centric methods [394–399]. In a study conducted by Peón et al., the methods of ligand-centric target predictions have been systematically validated using various clinically-used drugs and novel estimates regarding the polypharmacological profiles of drugs have been obtained [400]. Meanwhile, experimental confirmation appears more appropriate for validation of the predictive methods [184,197,238]. Over the last decade, parallel screening has been suggested as a promising approach for rational TF and pharmacological profiling of the chemicals [401,402].

6. Challenging issues and the potential solutions

The emergence of state-of-the-art and high-performance techniques and remarkable advances in computer science have provided the opportunities for improving drug screening strategies and development of advanced drug delivery platforms such as feedback-controlled, programmable, and microchip-based systems [1–5]. Meanwhile, a variety of issues have remained challenging [1–5,188,328]. Regarding the implantable drug delivery systems, size of drug reservoir, delivery efficiency, biocompatibility, providing appropriate concentrations of drugs, long-term operability, or potential risks associated with inappropriate design are challenging issues [4,5,9,12,14,19]. In this respect, application of safe biomaterials and specifically designed drug delivery devices with predictable drug release profile provides sustained and homogenous drug concentrations leading to the increased patient adherence to treatment [9,12]. Furthermore, miniaturization design of actuator provides larger drug reservoir without enhancing the overall volume of device [14].

Fabrication of the fully operational nanorobots for theranostic applications and targeted drug delivery appear quite difficult [283,285,288]. This necessitates acquiring a deeper knowledge about the biological processes, interactions of nanorobots within the body and their mechanisms of movement in liquid environments, application of the appropriate algorithms for controlling against the environmental perturbations, designing cores capable of recognizing the cells and molecular cues, size reduction, appropriate power supply, propulsion, actuation, sensing, system integration, control of the navigation and release of payloads, and path planning for controlled delivery of drugs, minimized consumption of energy, and optimized heat dissipation [280–282,285]. In cancer theranostics, high responsiveness and targeted movement of nanorobots, cell recognition and attachment, and payload delivery are

of critical importance [280–282]. Because of the uncertainties, sensor noise, or unknown parameters, nanorobots may fail to effectively determine drug dosage for delivery and differentiate healthy and cancer cells or tumor cell types [300,305]. In design process of nanorobots, alterations in cancer cells and environmental factors, heterogeneity of tumors, noise or uncertainty should be taken into account [285,288,290]. Since several factors, but not a fixed value, are usually considered for dose calculation of anticancer drugs, development of decision-making systems capable of managing the uncertainties appears necessary [290,293,298]. Moreover, inappropriate theranostic activity of nanorobot does not result in tumor eradication or even causes adverse events [288,290]. In general, application of the robust strategies and bio-inspired approaches might be helpful for designing efficient nanorobots with improved biocompatibility and reduced safety concerns [285,288]. Furthermore, development of effective communication between these automated nanomachines with coordinated movements, application of simulation techniques to acquire a deeper knowledge about the interactions of bionanorobots and predict their characteristics and dynamics within the body are necessary [307,313,316]. Regarding the capsule robots, suitable power backup, locomotion, space for drug reservoirs, mechanisms of anchoring, control over the profiles of drug release, incorporation of bi-directional communication systems, telemetry, image sensing, capacity of drug storage, theranostic activity, controlled drug release, clinical efficiency of delivered drugs, safety issues, and high costs have remained as challenging issues [310,334]. Advances in miniaturization techniques and electronics facilitate development of theranostic nanobots capable of traveling through the circulatory system [315,316]. AI tools can be applied for solving a variety of problems including the nanotechnology-related ones, performing computations and sophisticated tasks, data interpretation, and drug design with reduced side effects [24,30]. Successful AI-based procedures result in the development of stable, functional, and biocompatible drug delivery systems capable of overcoming a variety of limitations, accurate dosing, and targeted drug delivery with minimal safety concerns [24,26,30]. ANNs as highly adaptive nonlinear optimization algorithms along with other machine learning techniques including the genetic programming, fuzzy logic, or decision tree can be applied for overcoming the challenging issues in the field of modern drug discovery [24–26]. ANNs have attracted a growing interest in various scientific fields including the pharmaceutical industry that might be due to their capability of nonlinear data modeling, solving the complex problems, analyzing the large and multivariate data sets, making predictions, modeling and optimizing the formulation process, designing controlled release drug delivery system and classifying the associated problems, simulation of protein-protein or small molecule-protein interactions, and simultaneous prediction of multiple biological activities and *in vivo* toxicity [24,34,37,45,46]. ANN-based methods minimize the number of experiments and costs, optimize drug release profile, or estimate pharmacodynamic and pharmacokinetic profiles of drugs. In cancer therapy, application of fuzzy logic-based intelligent system is useful for theranostic applications, improved drug delivery efficiency and navigation of bionanorobots, and reduced false-positive rates [21,84,190,198,200]. Despite the advantages of AI tools such as rapid and continuous performance of a variety of tasks (e.g. designing of bionanorobots and controlled drug delivery) [24–26], AI strategies can be associated with several problems such as high costs of maintenance, repair, frequent upgrading of software, lost code recovery, and system reinstating, lack of common sense, creativity, judgment, or appropriate response to the altering environment, reflection of data inaccuracy in the obtained results, risk of data loss, or ethical concerns [24,26,30]. ANN models may not be useful for clarification of the mechanism of correlation between the variables [25]. Furthermore, obtaining a reliable ANN model is time-consuming and necessitates application of a large amount of data and sample size for development of more accurate models [33–35]. In general, constructing an ANN model with

proper topology is difficult [25,47], meanwhile, development of more powerful software packages might be helpful [45].

Lack of rational interpretation of the biological events may negatively affect the performance and reliability of AI techniques [69,152,174]. Meanwhile, problems like the incorrect model validation, overtraining, or overfitting can be overcome using the methods such as training with dropout techniques, early stopping, or Bayesian regularization which enable the development of robust models with high prediction capabilities [30,34]. Furthermore, sophisticated methods including the prediction-driven matched molecular pairs method help to evaluate the importance of network weights and facilitate model interpretation [23,25,47].

Despite the applicability of ANNs for modeling the complex datasets and generating the predictable models regarding the clinical response to drug products, selection of appropriate algorithms or datasets in ANNs-based drug research efforts can be quite challenging [103]. In this context, effective annotation of datasets, application of the proper methods for more accurate quantification of uncertainties and errors in the experimental protocols, model checkers for validating the performance of AI systems, computational approaches for prediction of the biological characteristics of molecules, optimization algorithms for enhancement of the computational efficiency and site-specific drug delivery, individualized dosing, and risk management shorten the relatively long distance towards the regulatory approval and commercialization of AI-related products [189,201].

In general, ANN models along with the conventional methods facilitate development and optimization of controlled release drug delivery systems and evaluation of the effects of process and formulation variables on delivery system [42,45]. Despite the capability of machine learning-based models for speeding up the process of drug discovery, rational drug design, target prediction, and development of safer drugs [45,46], integration of the experimental procedures and *in silico* simulations and development of interpretable machine learning models are necessary to reduce the rates of false negative or positive predictions [153,155]. Finally, application of high-performance nanocomputers might be useful for implementing AI paradigms [115].

7. Conclusion

Enormous amount of time and costs in drug research and development necessitate application of more innovative techniques and strategies. AI technologies offer tremendous opportunities for analyzing the massive amounts of multivariate data, solving the complex problems associated with designing of functional drug delivery systems, making more accurate decisions, classification and modeling of diseases, accelerated drug discovery, identifying biomarkers, drug targets, potential drug candidates and their pharmacological properties, novel indications for existing therapeutics, relationships between the formulations and processing variables, and physiological or pathophysiological pathways, optimizing dose ratio, and predicting the bioactivities and interactions of drugs, molecular behavior, disease status, cellular response, efficiency of drug combinations, and treatment outcomes. Besides designing the novel therapeutics with desired properties, application of AI-powered platforms for matching patients with the most relevant clinical trials may significantly reduce errors and improve cost-effectiveness. Analyzing large-scale molecular information and data connections provide new insights into the molecular mechanisms of diseases and factors affecting cell or tissue function leading to the development of more effective drugs or delivery systems. In this respect, AI would be one of the key elements of drug development process and personalized medicine.

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Declaration of interest

Authors declare that they have no conflicts of interest.

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References

- [1] P. Tangri, S. Khurana, Pulsatile drug delivery systems: methods and advances, *Int. J. Drug Formul. Res.* 2 (2011) 100–111.
- [2] M. Alessandra, D.D. Maria, L. Giulia, Oral pulsatile delivery: rationale and chronopharmaceutical formulations, *Int. J. Pharm.* 398 (2010) 1–8.
- [3] Mark Staples, Karen Daniel, Michael J. Cima, Robert Langer, Application of micro- and nano-electromechanical devices to drug delivery, *Pharm. Res.* 23 (2006) 847–863.
- [4] K.B. Sutradhar, C.D. Sumi, Implantable microchip: the futuristic controlled drug delivery system, *Drug Deliv.* 23 (2016) 1–11.
- [5] J.T. Santini Jr., A.C. Richards, R.A. Scheidt, M.J. Cima, R. Langer, Microchips as implantable drug delivery devices, *Ang. Chem. Int. Ed.* 39 (2000) 2396–2407.
- [6] A.C.R. Grayson, R.S. Shawgo, Y. Li, M.J. Cima, Electronic MEMS for triggered delivery, *Adv. Drug Del. Rev.* 56 (2004) 173–184.
- [7] Y. Li, H.L.H. Duc, B. Tyler, T. Williams, M. Tupper, R. Langer, H. Brem, M.J. Cima, In vivo delivery of BCNU from a MEMS device to a tumor model, *J. Control. Release* 106 (2005) 138–145.
- [8] H. Zhang, J.K. Jackson, M. Chiao, Microfabricated drug delivery devices: design, fabrication, and applications, *Adv. Funct. Mater.* 27 (2017) 1–31.
- [9] Kritika Ramesh, Shagun Gupta, Suhaib Ahmed, Vipin Kakkar, A comprehensive study on design trends and future scope of implantable drug delivery systems, *Int. J. Biosci. Biotech* 8 (2016) 11–20.
- [10] K.Y. Zhu, H. Zheng, D.G. Zhan, A computerized drug delivery control system for regulation of blood pressure, *Int. J. Intel. Comput. Med. Sci. Image Proc.* 2 (2007) 1–13.
- [11] P.L. Huang, P.H. Kuo, Y.J. Huang, A controlled-release drug delivery system on a chip using electrolysis, *IEEE Transact. Indust. Elect.* 59 (2012) 1578–1587.
- [12] N. Rainee, D.G. Hall, F.A. Mirand, RF telemetry system for an implantable bio-MEMS sensor, *Proc. Microwave Symp. Digest* 3 (2004) 1433–1436.
- [13] Y. Chahibi, M. Pierobon, O.S. Song, A molecular communication system model for particulate drug delivery systems, *IEEE Trans. Biomed. Eng.* 60 (2013) 3468–3483.
- [14] L. Cao, S. Mantell, D. Polla, Design and simulation of an implantable medical drug delivery system using microelectromechanical systems technology, *Sensors Actuators A* 94 (1–2) (2001) 117–125.
- [15] D. Liu, H. Zhang, F. Fontana, J.T. Hirvonen, H. Santos, Microfluidic-assisted fabrication of carriers for controlled drug delivery, *Lab Chip* 17 (2017) 1856–1883.
- [16] S. Damiatil, U.G. Kompella, S.A. Damiatil, R. Kodzius, Microfluidic devices for drug delivery systems and drug screening, *Genes* 103 (2018) 1–24.
- [17] T. Nisizako, Recent advances in microfluidic production of Janus droplets and particles, *Curr. Opin. Colloid Interface Sci.* 25 (2016) 1–12.
- [18] U. Xie, Z.G. She, S. Wang, G. Sharma, J.W. Smith, One-step fabrication of polymeric janus nanoparticles for drug delivery, *Langmuir* 28 (2012) 4459–4463.
- [19] J.H. Prescott, S. Lipka, S. Baldwin, N.F. Sheppard Jr., J.M. Maloney, J. Coppeta, B. Yomtov, M.A. Staples, J.T. Santini Jr., Chronic, programmed polypeptide delivery from an implanted, multireservoir microchip device, *Nat. Biotech.* 24 (2006) 437–438.
- [20] R. Farra, N.F. Sheppard, L. McCabe, et al., First-in-human testing of a wirelessly controlled drug delivery microchip, *Sci Transl Med* 4 (2012) 1–10.
- [21] P. Grant, A new approach to diabetic control: fuzzy logic and insulin pump technology, *Med. Eng. Phys.* 29 (2007) 824–827.
- [22] Shah Nihar, Patel Nishith, K.R. Patel, A sequential review on intelligent drug delivery system, *J. Pharm. Sci. Biosci. Res.* 3 (2013) 158–162.
- [23] E. Murttoniemi, P. Merkk, P. Kinnunen, K. Leivisk, J. Yliuusi, Effect of neural network topology and training end point in modelling the fluidized bed granulation process, *Int. J. Pharm.* 110 (1994) 101–108.
- [24] A.S. Achanta, J.G. Kowalski, C.T. Rhodes, Artificial neural networks: implications for pharmaceutical sciences, *Drug Dev. Ind. Pharm.* 21 (1995) 119–155.
- [25] S. Agatonovic-Kustrin, R. Beresford, Basic concepts of artificial neural network (ANN) modeling and its application in pharmaceutical research, *J. Pharmaceut. Biomed. Anal.* 22 (2000) 717–727.
- [26] K. Takayama, M. Fujikawa, T. Nagai, Artificial neural network as a novel method to optimize pharmaceutical formulations, *Pharm. Res.* 16 (1999) 1–6.
- [27] J.L.P. Soh, F. Chen, C.V. Liew, D. Shi, P.W.S. Heng, A novel preformulation tool to group microcrystalline celluloses using artificial neural network and data clustering, *Pharm. Res.* 21 (2004) 2360–2368.
- [28] A. Heller, Integrated medical feedback systems for drug delivery, *Am. Inst. Chem. Eng. J.* 51 (2005) 1054–1066.
- [29] A. Sherriff, J. Ott, Artificial neural networks as statistical tools in epidemiological studies: analysis of risk factors for early infant wheeze, *Paediatr. Perinat. Epidemiol.* 18 (6) (2004) 456–463.
- [30] Stuart Russel, Daniel Dewey, Max Tegmark, Research priorities for robust and beneficial artificial intelligence, *AI Mag.* 36 (2015) 105–114.
- [31] T. Hastie, R. Tibshirani, J. Friedman, *The Elements of Statistical Learning*, Springer, 2001.
- [32] W. Duch, R. Setiono, J.M. Zurada, Computational intelligence methods for understanding of data, *Proc. IEEE* 92 (5) (2004) 771–805.
- [33] Wen-Jin Xu, Ning Li, Chong-kai Gao, Preparation of controlled porosity osmotic pump tablets for salivary acid and optimization of the formulation using an artificial neural network method, *Acta Pharmaceutica Sinica B* 1 (2011) 64–70.
- [34] J.V. Gobburu, E.P. Chen, Artificial neural networks as a novel approach to integrated pharmacokinetic-pharmacodynamic analysis, *J. Pharm. Sci.* 85 (1996) 505–510.
- [35] P. Paixão, L.S.F. Gouveia, J.A.G. Morais, Prediction of the in vitro intrinsic clearance determined in suspensions of human hepatocytes by using artificial neural networks, *Eur. J. Pharm. Sci.* 39 (2010) 310–321.
- [36] J.V. Gobburu, W.H. Shelper, Quantitative structure pharmacokinetic relationships (QSPR) of beta blockers derived using neural networks, *J. Pharm. Sci.* 84 (1995) 862–865.
- [37] M. Koba, Application of artificial neural networks for the prediction of antitumor activity of a series of acridinone derivatives, *Med. Chem.* 8 (2012) 309–319.
- [38] Y. Uesawa, K. Mohri, M. Kawase, M. Ishihara, H. Sakagami, Quantitative structure-activity relationship (QSAR) analysis of tumor-specificity of 1,2,3,4-tetrahydroisoquinoline derivatives, *Anticancer Res.* 31 (2011) 4231–4238.
- [39] A. Yan, X. Chen, R. Zhang, M. Liu, Z. Hu, B.T. Fan, Predicting the standard enthalpy (ΔH°) and entropy (S°) of alkanes by artificial neural networks, *SAR. QSAR. Environ. Res.* 11 (2000) 235–244.
- [40] G. Espinosa, D. Yaffe, Y. Cohen, A. Arenas, F. Giralt, Neural network based quantitative structural property relations (QSPRs) for predicting boiling points of aliphatic hydrocarbons, *J. Chem. Inform. Comput. Sci.* 40 (2000) 859–879.
- [41] A. Moon, T. Smith, A preliminary evaluation of neural network analysis for pharmacodynamic modeling of the dosing of the hydroxymethylglutaryl coenzyme A-reductase inhibitors simvastatin and atorvastatin, *Clin. Ther.* 24 (2002) 653–661.
- [42] T. Degim, J. Hadgraft, S. Ilbasmi, Y. Ozkan, Prediction of skin penetration using artificial neural network (ANN) modeling, *J. Pharm. Sci.* 92 (2003) 656–664.
- [43] Z. Wang, A. Yan, J. Li, In silico prediction of blood brain barrier permeability: a support vector machine model, *Int. Res. App. Bioinform. Comput. Biol. Environ. Sci.* (2011) 155–171.
- [44] Yojiro Sakiyama, The use of machine learning and nonlinear statistical tools for ADME prediction, *Expert Opin. Drug Metab. Toxicol.* 5 (2009) 149–162.
- [45] Y. Sun, Y. Peng, Y. Chen, A.J. Shukla, Application of artificial neural networks in the design of controlled release drug delivery systems, *Adv. Drug Deliv. Rev.* 55 (2003) 1201–1215.
- [46] V. Sutariya, A. Groshev, P. Sadana, D. Bhatia, Y. Pathak, Artificial neural network in drug delivery and pharmaceutical research, *Open Bioinf. J.* 7 (2013) 49–62.
- [47] J. Taskinen, J. Yliuusi, Prediction of physicochemical properties based on neural network modeling, *Adv. Drug Deliv. Rev.* 55 (2003) 1163–1183.
- [48] J. Zhang, K.F. Man, Time series prediction using recurrent neural network in multi-dimension embedding phase space, *IEEE Syst. Man Cybern. Soc.* 2 (1998) 11–14.
- [49] K.K. Peh, C.P. Lim, S.S. Quek, K.H. Khoh, Use of artificial neural networks to predict drug dissolution profiles and evaluation of network performance using similarity factor, *Pharm. Res.* 17 (2000) 1384–1389.
- [50] M.A.A. Reis, R.D. Sinisterra, J.C. Belchior, An alternative approach based on artificial neural networks to study controlled drug release, *J. Pharm. Sci.* 93 (2004) 418–430.
- [51] D. Zupancic Bozic, F. Vrečer, F. Kozjek, Optimization of diclofenac sodium dissolution from sustained release formulations using an artificial neural network, *Eur. J. Pharm. Sci.* 5 (1997) 163–169.
- [52] R.B. Panerai, M. Chacon, R. Pereira, D.H. Evans, Neural network modeling of dynamic cerebral autoregulation: assessment and comparison with established methods, *Med. Eng. Phys.* 26 (2004) 43–52.
- [53] S. Haykin, *Neural Networks—A Comprehensive Foundation*, Prentice-Hall, New Jersey, 1999.
- [54] Jelena Petrovic, Svetlana Ibric, Gabriele Betz Jelena Parojic, Zorica Duric, Application of dynamic neural networks in the modeling of drug release from polyethylene oxide matrix tablets, *Eur. J. Pharm. Sci.* 38 (2009) 172–180.
- [55] G. Chen, J. Li, S. Zhang, C. Song, G. Li, Z. Sun, et al., Sensitive and efficient method to systematically detect two biophenols in medicinal herb, herbal products and rat plasma based on thorough study of derivatization and its convenient application to pharmacokinetics with semi-automated device, *J. Chromatogr. A* 1249 (2012) 190–200.
- [56] T. Sovány, Z. Tislér, K. Kristó, A. Kelemen, G. Regdon Jr., Estimation of design space for an extrusion-spheronization process using response surface methodology and artificial neural network modeling, *Eur. J. Pharm. Biopharm.* 106 (2016) 79–87.
- [57] A.S. Hussain, X.Q. Yu, R.D. Johnson, Application of neural computing in pharmaceutical product development, *Pharm. Res.* 8 (1991) 1248–1252.
- [58] M. de Matas, Q. Shao, C.H. Richardson, H. Chrystyn, Evaluation of *in vitro* *in vivo* correlations for dry powder inhaler delivery using artificial neural networks, *Eur. J. Pharm. Sci.* 33 (2008) 80–90.
- [59] M.E. Brier, J.M. Zurada, G.R. Aronoff, Neural network predicted peak and trough gentamicin concentrations, *Pharm. Res.* 12 (3) (1995) 406–412.
- [60] P. Veng-Pedersen, N.B. Modi, Application of neural networks to pharmacodynamics, *J. Pharm. Sci.* 82 (9) (1993) 918–926.
- [61] J.V.S. Gobburu, W.H. Shelper, Quantitative structure pharmacokinetic relationships (QSPR) of beta blockers derived using neural networks, *J. Pharm. Sci.* 84 (7) (1995) 862–865.
- [62] J.A. Dowell, A. Hussain, J. Devane, D. Young, Artificial neural networks applied to the *in vitro* *in vivo* correlation of an extended-release formulation: initial trials and experience, *J. Pharm. Sci.* 88 (1999) 154–160.
- [63] M. Raffenia, M. Amiri, M. Janmaleki, A. Sadeghian, Application of artificial neural networks in controlled drug delivery systems, *Appl. Artif. Intellig.* 24 (2010) 807–820.
- [64] Jelena Parojic, Svetlana Ibric, Zorica Djuric, Milica Jovanovic, Owen I. Corrigan, An investigation into the usefulness of generalized regression neural network analysis

- in the development of level A in vitro–in vivo correlation, *Eur. J. Pharm. Sci.* 30 (2007) 264–272.
- [65] D.F. Specht, A general regression neural network, *IEEE Trans. Neural Netw.* 2 (1991) 568–576.
- [66] B. Ivic, S. Ibric, G. Betz, Z. Djuric, Optimization of drug release from compressed multi unit particle system (MUPS) using generalized regression neural network (GRNN), *Arch. Pharm. Res.* 33 (2010) 103–113.
- [67] Yasmine Korteby, Yassine Mahdi, Amel Azizou, Kamel Daoud, Geza Regdon, Implementation of an artificial neural network as a PAT tool for the prediction of temperature distribution within a pharmaceutical fluidized bed granulator, *Eur. J. Pharm. Sci.* 88 (2016) 219–232.
- [68] Babak Bostan, Russell Greiner, Duane Szafran, Lu. Paul, Predicting homologous signaling pathways using machine learning, *Bioinformatics* 25 (2009) 2913–2920.
- [69] H. Chen, O. Engkvist, Y. Wang, M. Olivecrona, T. Blaschke, The rise of deep learning in drug discovery, *Drug Discov. Today* 23 (2018) 1241–1250.
- [70] A.W. Przybyszewski, M. Kon, S. Szlufik, A. Szymanski, P. Habela, D.M. Koziorowski, Multimodal learning and intelligent prediction of symptom development in individual Parkinson's patients, *Sensors* 16 (1498) (2016) 1–15.
- [71] D. Romeo-Guitart, J. Forés, M. Herrando-Grabulosa, R. Valls, T. Leiva-Rodríguez, E. Galea, et al., Neuroprotective drug for nerve trauma revealed using artificial intelligence, *Sci. Rep.* 8 (1879) (2018) 1–15.
- [72] M.H. Bahari, M. Mahmoudi, A. Azemi, M.M. Mirsalehi, M. Khademi, Early diagnosis of systemic lupus erythematosus using ANN models of dsDNA binding antibody sequence data, *Bioinformatics* 5 (2010) 58–61.
- [73] S.M. Pedersen, J.S. Jorgensen, J.B. Pedersen, Use of neural networks to diagnose acute myocardial infarction. II. A clinical application, *Clin. Chem.* 42 (1996) 613–617.
- [74] X. Deng, K. Li, S. Liu, Preliminary study on application of artificial neural network to the diagnosis of Alzheimer's disease with magnetic resonance imaging, *Chin. Med. J.* 112 (1999) 232–237.
- [75] K. Rudzki, M. Hartleb, T. Sadowski, J. Rudzka, Focal liver disease: neural network-aided diagnosis based on clinical and laboratory data, *Gastroenterol. Clin. Biol.* 21 (1997) 98–102.
- [76] M.G. Penedo, M.J. Carreira, A. Mosquera, D. Cabello, Computer-aided diagnosis: a neural-network-based approach to lung nodule detection, *IEEE. Trans. Med. Imag.* 17 (Dec 1998) 872–880.
- [77] G. Mello, E. Parretti, A. Ognibene, F. Mecacci, R. Cioni, G. Scarselli, G. Messeri, Prediction of the development of pregnancy-induced hypertensive disorders in high-risk pregnant women by artificial neural networks, *Clin. Chem. Lab Med.* 39 (Sep 2001) 801–805.
- [78] H. Hirose, T. Takayama, S. Hozawa, T. Hibi, I. Saito, Prediction of metabolic syndrome using artificial neural network system based on clinical data including insulin resistance index and serum adiponectin, *Comput. Biol. Med.* 41 (2011) 1051–1056.
- [79] J.E. Arle, K. Perrine, O. Devinsky, W.K. Doyle, Neural network analysis of preoperative variables and outcome in epilepsy surgery, *J. Neurosurg.* 90 (1999) 998–1004.
- [80] P. Schmid, M.B. Wischniewsky, O. Sezer, R. Bohm, K. Possinger, Prediction of response to hormonal treatment in metastatic breast cancer, *Oncology* 63 (2002) 309–316.
- [81] M. de Matas, M.F. Qun Shao, S. Biddiscombe, H. Meah, O.S. Chrystyn, Predicting the clinical effect of a short acting bronchodilator in individual patients using artificial neural networks, *Eur. J. Pharm. Sci.* 41 (2010) 707–715.
- [82] A. Nebot, F.E. Cellier, D.A. Linkens, Synthesis of an anaesthetic agent administration system using fuzzy inductive reasoning, *Artif. Intel Med.* 8 (1996) 147–166.
- [83] J. Fernandez de Canete, S. Gonzalez-Perez, J.C. Ramos-Diaz, Artificial neural networks for closed loop control of in silico and ad hoc type 1 diabetes, *Comput. Method Program Biomed.* 106 (2012) 55–66.
- [84] M.S. Ibbini, M.A. Masadeh, A fuzzy logic based closed-loop control system for blood glucose level regulation in diabetics, *J. Med. Eng. Technol.* 29 (2005) 64–69.
- [85] H.T. Alexander, Mark J. Molinaro, Jasmine F. Jethwa, Susana G. Sotocinal, Juan C. Prieto, Martin A. Styner, et al., A deep neural network to assess spontaneous pain from mouse facial expressions, *Mol. Pain* 14 (2018) 1–9.
- [86] Monika Salgueiro, Xabier Basogain, Antonio Collado, Xavier Torres, Juan Bilbao, Francisco Doñate, et al., An artificial neural network approach for predicting functional outcome in fibromyalgia syndrome after multidisciplinary pain program, *Pain Med.* 14 (2013) 1450–1460.
- [87] John D. Piette, Sarah L. Krein, Dana Striplin, Nicolle Marinec, Robert D. Kerns, Karen B. Farris, et al., Patient-centered pain care using artificial intelligence and mobile health tools: protocol for a randomized study funded by the US department of veterans affairs health services research and development program, *JMIR Res. Protoc.* 5 (2016), e53. <https://doi.org/10.2196/resprot.4995>.
- [88] P. Hassanzadeh, A. Ahmadiani, Inflammatory pain induces neuronal alterations in NO and JNK dependent manners, *Daru J. Pharm. Sci.* 15 (2007) 183–187.
- [89] P. Hassanzadeh, A quick look at obesity: The enemy within, *Gastroenterol. Hepatol. Bed Bench* 4 (2011) 186–191.
- [90] Casimiro Aday Curbelo Montañez, Paul Fergus, Abir Hussain, Dhiya Al-Jumeily, Basma Abdulaimma, Jade Hind, et al., Machine learning approaches for the prediction of obesity using publicly available genetic profiles, *Int. Joint Conf. Neural Networks* (2017) 2743–2750, <https://doi.org/10.1109/IJCNN.2017.7966194>.
- [91] I.K. Valavanis, S.G. Mougialakou, K.A. Grimaldi, K.S. Nikita, A multifactorial analysis of obesity as CVD risk factor: use of neural network based methods in a nutrigenetics context, *BMC Bioinform.* 11 (2010) 453.
- [92] S.J. Lewis, et al., Associations between an obesity related genetic variant (FTO rs939609) and prostate cancer risk, *PLoS One* 5 (10) (2010) 3–9.
- [93] S. Bouharati, M. Bounechada, A. Djoudi, D. Harzallah, F. Alleg, Prevention of obesity using artificial intelligence techniques, *Int. J. Sci. Eng. Invest.* 1 (2012) 146–150.
- [94] F. Yamashita, M. Hashida, Mechanistic and empirical modeling of skin permeation of drugs, *Adv. Drug Deliv. Rev.* 55 (2003) 1185–1199.
- [95] G.L. Flynn (Ed.), *Physicochemical Determinants of Skin Absorption (Principles of Route to Route Extrapolation for Risk Assessment)*, Elsevier Science, New York, 1990.
- [96] L. Holmstrom, P. Koistinen, Using additive noise in backpropagation training, *IEEE. Trans. Neural. Netw.* 3 (1992) 24–38.
- [97] X.C. Fu, X.W. Ma, W.Q. Liang, Prediction of skin permeability using an artificial neural network, *Die Pharm.* 57 (2002) 655–656.
- [98] W.J. Pugh, I.T. Degim, J. Hadgraft, Epidermal permeability penetrant structure relationships: 4. QSAR of permeant diffusion across human stratum corneum in terms of molecular weight, H-bonding and electronic charge, *Int. J. Pharm.* 197 (2000) 203–211.
- [99] T. Atobe, M. Mori, F. Yamashita, M. Hashida, H. Kouzuki, Artificial neural network analysis for predicting human percutaneous absorption taking account of vehicle properties, *J. Toxicol. Sci.* 40 (2015) 277–294.
- [100] Daniel Lobo, Maria Lobikin, Michael Levin, Discovering novel phenotypes with automatically inferred dynamic models: a partial melanocyte conversion in *Xenopus*, *Sci. Rep.* 7 (2017) 41339, <https://doi.org/10.1038/SREP41339>.
- [101] Dmitry Rykunov, Noam D. Beckmann, Hui Li, Andrew Uzilov, Eric E. Schadt, Boris Reva, A new molecular signature method for prediction of driver cancer pathways from transcriptional data, *Nucl. Acids Res.* 44 (2016) e110.
- [102] K. Ichimasa, S.E. Kudo, Y. Mori, M. Misawa, S. Matsudaira, et al., Artificial intelligence may help in predicting the need for additional surgery after endoscopic resection of T1 colorectal cancer, *Endoscopy* 50 (2018) 230–240.
- [103] Marcos Martínez-Romero, José M. Vázquez-Naya, Juan R. Rabuñal, Salvador Pita-Fernández, Ramiro Macenlle, Javier Castro-Alvarino, et al., Artificial intelligence techniques for colorectal cancer drug metabolism: ontologies and complex networks, *Curr. Drug Metabol.* 11 (2010) 347–368.
- [104] P. Hassanzadeh, Colorectal cancer and NF- κ B signaling pathway, *Gastroenterol. Hepatol. Bed Bench* 4 (2011) 127–132.
- [105] P. Hassanzadeh, F. Atyabi, R. Dinavand, Tissue engineering: still facing a long way ahead, *J. Control Release* 279 (2018) 181–197.
- [106] G.V. Novakovic, T. Eschenhagen, C. Mummery, Myocardial tissue engineering: in vitro models, *Cold Spring Harb. Perspect. Med.* 4 (2014) a014076.
- [107] M.A. Knight, G.R. Evans, Tissue engineering: progress and challenges, *Plast. Reconstr. Surg.* 114 (2004) 26E–37E.
- [108] P. Hassanzadeh, Tissue engineering and growth factors: updated evidence, *Biomed. Rev.* 23 (2012) 19–35.
- [109] J. Xu, H. Ge, X. Zhou, J. Yan, Q. Chi, Z. Zhang, Prediction of vascular tissue engineering results with artificial neural networks, *J. Biomed. Inform.* 38 (2005) 417–421.
- [110] J. Xu, H. Ge, X. Zhou, D. Yang, Tissue engineering scheming by artificial intelligence, *Int. J. Artif. Organs.* 28 (2005) 74–78.
- [111] J. Xu, X. Zhou, D. Yang, H. Ge, Q. Wang, K. Tu, et al., Applying informatics in tissue engineering, *Methods Inf. Med.* 44 (1) (2005) 38–43.
- [112] B.A. Aguado, J.C. Grim, A.M. Rosales, J.J. Watson-Capps, K.S. Anseth, Engineering precision biomaterials for personalized medicine, *Sci. Transl. Med.* 10 (2018) 1–7.
- [113] A. Zarrinpar, D.-K. Lee, A. Silva, N. Datta, T. Kee, C. Eriksen, K. Weigle, V. Agopian, F. Kaldas, D. Farmer, S.E. Wang, R. Busuttill, C.-M. Ho, D. Ho, Individualizing liver transplant immunosuppression using a phenotypic personalized medicine platform, *Sci. Transl. Med.* 8 (2016) 333–349.
- [114] D.Q. Ly, L. Paramonov, C. Davidson, J. Ramsden, H. Wright, N. Holliman, et al., *Nanotechnol. Percept.* 7, 2011 199–217.
- [115] G.M. Sacha, P. Varona, Artificial intelligence in nanotechnology, *Nanotechnology* 24 (2013) 1–13.
- [116] R.S. Becker, J.A. Golovchenko, B.S. Swartzentruber, *Nature*, 325, 1987 419–421.
- [117] J.A. Dagata, J. Schneir, H.H. Harary, C.J. Evans, M.T. Postek, J. Bennett, *Appl. Phys. Lett.* 56, 1990 2001–2003.
- [118] R. Miotto, F.D. Kiss, A.C. Ferraz, *Nanotechnology*, 23, 2012 485202.
- [119] M.P. Nikiforov, V.V. Reukov, G.L. Thompson, A.A. Vertegel, S. Guo, S.V. Kalinin, S. Jesse, *Nanotechnology*, 20, 2009 405708.
- [120] F.F. Gonzalez-Navarro, M. Stilianova-Stoytcheva, L. Renteria-Gutierrez, L.A. Belanche-Muñoz, B.L. Flores-Rios, J.E. Ibarra-Esquer, Glucose oxidase biosensor modeling and predictors optimization by machine learning methods, *Sensors* 16 (2016) 1–13.
- [121] M.A. Al-Khedher, C. Pezeszki, J.L. McHale, F.J. Knorr, *Nanotechnology*, 18, 2007 355703.
- [122] D. Fourches, D. Pu, C. Tassa, R. Weissleder, S.Y. Shaw, R.J. Mumper, A. Tropsha, *ACS Nano*, 4, 2010 5703–5712.
- [123] V. Epa, F.R. Burden, C. Tassa, R. Weissleder, S. Shaw, D.A. Winkler, *Nano Lett.* 12, 2012 5808–5812.
- [124] L. Brannon-Peppas, J.O. Blanchette, *Adv. Drug Deliv. Rev.* 56, 2004 1649–1659.
- [125] P. Zargoulidis, E. Chatzaki, K. Porpodis, K. Domvri, W. Hohenforst-Schmidt, E.P. Goldberg, N. Karamanos, K. Zargoulidis, *Int. J. Nanomed.* 7, 2012 1551–1572.
- [126] T.C. Le, X. Mulet, F.R. Burden, D.A. Winkler, Predicting the complex phase behavior of self-assembling drug delivery nanoparticles, *Mol. Pharm.* 10 (2013) 1368–1377.
- [127] John Youshia, Mohamed Ehab Ali, Alf Lamprecht, Artificial neural network based particle size prediction of polymeric nanoparticles, *Eur. J. Pharm. Biopharm.* 119 (2017) 333–342.
- [128] K.S. Shalaby, M.E. Soliman, L. Casettari, G. Bonacucina, M. Cespi, G.F. Palmieri, et al., Determination of factors controlling the particle size and entrapment efficiency of niosomes in PEG/PLA nanoparticles using artificial neural networks, *Int. J. Nanomed.* 9 (2014) 4953–4964.
- [129] D.P. Boso, S.Y. Lee, M. Ferrari, B.A. Schrefler, P. Decuzzi, Optimizing particle size for targeting diseased microvasculature: from experiments to artificial neural networks, *Int. J. Nanomed.* 6 (2011) 1517–1526.

- [130] N. Dugan, S. Erkoc, Genetic algorithm application to the structural properties of Si-Ge mixed clusters, *Mater. Manuf. Process.* 24 (2009) 250–254.
- [131] N. Dugan, S. Erkoc, *Comput. Mater. Sci.* 50, 2011 2950–2954.
- [132] P.Y. Chen, C.H. Chen, J.S. Wu, H.C. Wen, W.P. Wang, Optimal design of integrally gated CNT field-emission devices using a genetic algorithm, *Nanotechnology* 18 (2007) 395203 <https://doi.org/10.1088/0957-4484/18/39/395203>.
- [133] P. Ginzburg, N. Berkovitch, A. Nevet, I. Shor, M. Orenstein, Resonances on-demand for plasmonic nano-particles, *Nano Lett.* 11 (2011) 2329–2333.
- [134] C. Forestiere, M. Donelli, G.F. Walsh, E. Zeni, G. Miano, Negro L. Dal, Particle-swarm optimization of broadband nanoplasmonic arrays, *Opt. Lett.* 35 (2010) 133–135.
- [135] A.A. Bhirde, V. Patel, J. Gavard, G.F. Zhang, A.A. Sousa, A. Masedunskas, et al., Targeted killing of cancer cells in vivo and in vitro with EGF-directed carbon nanotube-based drug delivery, *ACS Nano* 3 (2009) 307–316.
- [136] G. Cellot, F.M. Toma, Z.K. Varley, J. Laishram, A. Villari, M. Quintana, et al., Carbon nanotube scaffolds tune synaptic strength in cultured neural circuits: novel frontiers in nanomaterial-tissue interactions, *J. Neurosci.* 31 (2011) 12945–12953.
- [137] Parichehr Hassanzadeh, Elham Arbabi, Fatemeh Rostami, Fatemeh Atyabi, Rassoul Dinarvand, Carbon nanotubes prolong the regulatory action of nerve growth factor on the endocannabinoid signaling, *Physiol. Pharmacol.* 19 (2015) 167–176.
- [138] Parichehr Hassanzadeh, Elham Arbabi, Fatemeh Atyabi, Rassoul Dinarvand, Carbon nanotube-anandamide complex exhibits sustained protective effects in an in vitro model of stroke, *Physiol. Pharmacol.* 20 (2016) 12–23.
- [139] Parichehr Hassanzadeh, Elham Arbabi, Fatemeh Atyabi, Rassoul Dinarvand, Application of carbon nanotubes as the carriers of the cannabinoid, 2-arachidonoylglycerol: towards a novel treatment strategy in colitis, *Life Sci.* 179 (2017) 66–72.
- [140] Parichehr Hassanzadeh, Elham Arbabi, Fatemeh Atyabi, Rassoul Dinarvand, Nerve growth factor-carbon nanotube complex exerts prolonged protective effects in an in vitro model of ischemic stroke, *Life Sci.* 179 (2017) 15–22.
- [141] P. Hassanzadeh, E. Arbabi, F. Atyabi, R. Dinarvand, Carbon nanotubes provide longer lasting gastroprotective effects for anandamide in stress-induced gastric ulcer in rat, *Physiol. Pharmacol.* 22 (2018) 38–47.
- [142] P. Hassanzadeh, F. Atyabi, R. Dinarvand, Application of carbon nanotubes for controlled release of growth factors or endocannabinoids: a breakthrough in biomedicine, *Biomed. Rev.* 27 (2016) 19–27.
- [143] M. Penza, G. Cassano, P. Aversa, A. Cusano, A. Cutolo, M. Giordano, et al., Carbon nanotube acoustic and optical sensors for volatile organic compound detection, *Nanotechnology* 16 (2005) 2536–2547.
- [144] J.I. Ababneh, O. Qasaimeh, *IEEE Trans. Electron Devices*, 53, 2006 1543–1550.
- [145] C.E. Kim, H. Soo Shin, P. Moon, H. Jae Kim, I. Yun, Modeling of In_2O_3 -10 wt% ZnO thin film properties for transparent conductive oxide using neural networks, *Curr. Appl. Phys.* 9 (2009) 1407–1410.
- [146] J. Arlat, Z. Kalbarczyk, T. Nanya, *IEEE Secur. Priv. Mag.* 10, 2012 69–72.
- [147] G.Y. Tseng, J.C. Ellenbogen, *Science*, 294, 2001 1293.
- [148] M.A. Uusitalo, J. Pelttonen, T. Ryhanen, *J. Comput. Theor. Nanosci.* 8, 2011 1347–1363.
- [149] T.D. Ladd, F. Jelezko, R. Laflamme, Y. Nakamura, C. Monroe, J.L. O'Brien, *Nature*, 464, 2010 45–53.
- [150] P.C. Maurer, et al., *Science*, 336, 2012 1283–1286.
- [151] J.M. Wing, Computational thinking and thinking about computing, *Phil. Trans. R. Soc. A* 366 (2008) 3717–3725.
- [152] A. Aliper, et al., Deep learning applications for predicting pharmacological properties of drugs and drug repurposing using transcriptomic data, *Mol. Pharm.* 13 (2016) 2524–2530.
- [153] L. Zhang, J. Tan, D. Han, H. Zhu, From machine learning to deep learning: progress in machine intelligence for rational drug discovery, *Drug Discov Today* 22 (2017) 1680–1685.
- [154] M.H.S. Segler, et al., Generating Focussed Molecule Libraries for Drug Discovery with Recurrent Neural Networks, 1701, 2017 01329.
- [155] T.B. Hughes, et al., Modeling epoxidation of drug-like molecules with a deep machine learning network, *ACS Central Sci.* 1 (2015) 168–180.
- [156] A. Ahmadiani, P. Hassanzadeh, M. Aleboeyeh, Development of tolerance to anti-inflammatory effect of morphine, *Arch. Iran Med.* 6 (2003) 307–309.
- [157] M.D. Wang, H.R. Hassanzadeh, DeeperBind: Enhancing Prediction of Sequence Specificities of DNA Binding Proteins, 1611, 2017 05777.
- [158] B. Alipanahi, et al., Predicting the sequence specificities of DNA- and RNA-binding proteins by deep learning, *Nat. Biotechnol.* 33 (2015) 831–838.
- [159] N. Fleming, Computer-calculated compounds, *Nature* 557 (2018) S55–S57.
- [160] C.Y. Zhao, H.X. Zhang, X.Y. Zhang, M.C. Liu, Z.D. Hu, B.T. Fan, Application of support vector machine (SVM) for prediction toxic activity of different data sets, *Toxicology* 217 (2–3) (2006) 105–119.
- [161] Selcuk Korkmaz, Gokmen Zararsiz, Dincer Goksuluk, Drug/nondrug classification using support vector machines with various feature selection strategies, *Comput. Meth. Prog. Biomed.* 117 (2014) 51–60.
- [162] V.V. Zernov, K.V. Balakin, A.A. Ivaschenko, N.P. Savchuk, I.V. Pletnev, Drug discovery using support vector machines. The case studies of drug-likeness, agrochemical-likeness, and enzyme inhibition predictions, *J. Chem. Inf. Comput. Sci.* 43 (6) (2003) 2048–2056.
- [163] H.X. Liu, R.J. Hu, R.S. Zhang, X.J. Yao, M.C. Liu, Z.D. Hu, et al., The prediction of human oral absorption for diffusion rate-limited drugs based on heuristic method and support vector machine, *J. Comput. Aided Mol. Des.* 19 (1) (2005) 33–46.
- [164] X. Yao, H. Liu, R. Zhang, M. Liu, Z. Hu, A. Panaye, et al., QSAR and classification study of 1,4-dihydropyridine calcium channel antagonists based on least squares support vector machines, *Mol. Pharm.* 2 (5) (2005) 348–356.
- [165] T. van Laarhoven, E. Marchiori, Predicting drug-target interactions for new drug compounds using a weighted nearest neighbor profile, *PLoS ONE* 8 (2013), e66952.
- [166] Qifan Kuang, Yizhou Li, Yiming Wu, Rong Li, Yongcheng Dong, Yan Li, et al., A kernel matrix dimension reduction method for predicting drug-target interaction, *Chemoset. Intell. Lab Syst.* 162 (2017) 104–110.
- [167] Z. Xia, L.-Y. Wu, X. Zhou, S.T.C. Wong, Semi-supervised drug-protein interaction prediction from heterogeneous biological spaces, *BMC Syst. Biol.* 4 (2010).
- [168] T. van Laarhoven, S.B. Nabuurs, E. Marchiori, Gaussian Interaction Profile Kernels for Predicting Drug-Target Interaction, 27, 2011 3036–3043.
- [169] P. Valeh-e-Sheyda, F. Yaripour, G. Moradi, M. Saber, Application of artificial neural networks for estimation of the reaction rate in methanol dehydration, *Ind. Eng. Chem. Res.* 49 (2010) 4620–4626.
- [170] A.A. Metwally, R.M. Hathout, Computer-assisted drug formulation design: novel approach in drug delivery, *Mol. Pharm.* 12 (2015) 2800–2810.
- [171] G.M. Sacha, F.B. Rodriguez, P. Varona, An inverse problem solution for undetermined electrostatic force microscopy setups using neural networks, *Nanotechnology* 20 (8) (2009) 085702.
- [172] B. Xu, Z. Shen, X. Ni, J. Wang, J. Lu, Determination of elastic properties of a film-substrate system by using the neural networks, *Appl. Phys. Lett.* 85 (2004) 6161.
- [173] E.J. Molga, B.A.A. Van Woezik, K.R. Westerterp, Neural networks for modelling of chemical reaction systems with complex kinetics: oxidation of 2-octanol with nitric acid, *Chem. Eng. Process.* 39 (2000) 323–334.
- [174] Y. Xu, et al., Deep learning for drug-induced liver injury, *J. Chem. Inf. Model.* 55 (2015) 2085–2093.
- [175] V.V. Solov'yev, A.A. Salamov, C.B. Lawrence, Predicting internal exons by oligonucleotide composition and discriminant analysis of spliceable open reading frames, *Nucl. Acid Res.* 22 (1994) 5156–5163.
- [176] B. Rost, C. Sander, Prediction of protein secondary structure at better than 70% accuracy, *J. Mol. Biol.* 232 (1993) 584–599.
- [177] E. Mjolsness, D. DeCoste, Machine learning for science: state of the art and future prospects, *Science* 293 (2001) 2051–2055.
- [178] M. Danishuddin, A.U. Khan, Structure based virtual screening to discover putative drug candidates: necessary considerations and successful case studies, *Methods* 71 (2015) 135–145.
- [179] T. Fox, J.M. Kriegel, Machine learning techniques for *in silico* modeling of drug metabolism, *Curr. Top. Med. Chem.* 6 (2006) 1579–1591.
- [180] D. Korolev, K.V. Balakin, Y. Nikolsky, E. Kirillov, Y.A. Ivanenkov, N.P. Savchuk, et al., Modeling of human cytochrome P450-mediated drug metabolism using unsupervised machine learning approach, *J. Med. Chem.* 46 (2003) 3631–3643.
- [181] Eunkyoung Jung, Junhyoung Kim, Seung-Hoon Choi, Minkyung Kim, Hokyung Rhee, Jae-Min Shin, et al., Artificial neural network study on organ-targeting peptides, *J. Comput. Aided Mol. Des.* 24 (2010) 49–56.
- [182] G.L. Zhang, A.M. Khan, K.N. Srinivasan, J.T. August, V. Brusic, Neural models for predicting viral vaccine targets, *J. Bioinform. Comput. Biol.* 3 (2005) 1207–1225.
- [183] Soroush Sardari, Houshmand Kohanzad, Ghazaleh Ghavami, Artificial neural network modeling of antimycobacterial chemical space to introduce efficient descriptors employed for drug design, *Chemoset. Intell. Lab. Syst.* 130 (2014) 151–158.
- [184] Y.Y. Li, S.C. Lenaghan, M. Zhang, A data-driven predictive approach for drug delivery using machine learning techniques, *PLoS ONE* 7 (2012) 1–11.
- [185] M. Hasani, M. Moloudi, F. Emami, Spectrophotometric resolution of ternary mixtures of tryptophan, tyrosine, and histidine with the aid of principal component-artificial neural network models, *Anal. Biochem.* 370 (2007) 68–76.
- [186] S. Agatonovic-Kustrin, V. Wu, T. Rades, D. Saville, I.G. Tucker, Ranitidine hydrochloride X-ray assay using a neural network, *J. Pharm. Biomed. Anal.* 22 (2000) 985–992.
- [187] H.R. Akbari Hasanjani, M.R. Sohrabi, Artificial neural networks (ANN) for the simultaneous spectrophotometric determination of fluoxetine and sertraline in pharmaceutical formulations and biological fluid, *Iran J. Pharm. Res.* 16 (2017) 478–489.
- [188] Oktay Yildirim, Matthias Gottwald, Peter Schüler, Martin C. Michel, Opportunities and challenges for drug development: public-private partnerships, adaptive designs and big data, *Front. Pharmacol.* 7 (2016) 461.
- [189] A. Rode, S. Sharma, K. Hatware, Artificial intelligence: microchip based drug delivery through resealed erythrocytes, *Biochem. Ind. J.* 11 (2017) 1–9.
- [190] J.W. Huang, R.J. Roy, Multiple-drug hemodynamic control using fuzzy decision theory, *IEEE Transact. Biomed. Eng.* 45 (1998) 213–228.
- [191] C.M. Held, R.J. Roy, Multiple drug hemodynamic control by means of a supervisory-fuzzy rule-based adaptive control system: validation on a model, *IEEE Trans. Biomed. Eng.* 42 (1995) 371–385.
- [192] H. Ying, L.C. Sheppard, Real-time expert-system-based fuzzy control of mean arterial pressure in pigs with sodium nitroprusside infusion, *Med. Prog. Technol.* 16 (1–2) (1990) 69–76.
- [193] A. Ghaffari, H. Abdollahi, M.R. Khoshayand, I. Soltani Bozchalooi, A. Dadgar, M. Rafiee-Tehrani, Performance comparison of neural network training algorithms in modeling of bimodal drug delivery, *Int. J. Pharm.* 327 (2006) 126–138.
- [194] V.M.K. Ndesendo, V. Pillay, Y.E. Choonara, L.C. du Toit, P. Kumar, E. Buchmann, et al., Optimization of a polymer composite employing molecular mechanic simulations and artificial neural networks for a novel intravaginal bioadhesive drug delivery device, *Pharm. Develop. Tech.* 17 (2012) 407–420.
- [195] Yuyung Lee, Alok Khemka, Jin-Wook Yoo, Chi H. Lee, Assessment of diffusion coefficient from mucoadhesive barrier devices using artificial neural networks, *Int. J. Pharm.* 351 (2008) 119–126.
- [196] G.A. Hussein, N.M. Abdel-Jabbar, F.S. Mjalli, W.G. Pitt, Modeling and sensitivity analysis of acoustic release of doxorubicin from unstabilized pluronic P105 using an artificial neural network model, *Technol. Cancer Res. Treat.* 6 (2007) 49–56.
- [197] G.A. Hussein, F.S. Mjalli, W.G. Pitt, N. Bdel-Jabbar, Using artificial neural networks and model predictive control to optimize acoustically assisted Doxorubicin release from polymeric micelles, *Technol. Cancer Res.* 8 (6) (2009) 479–488.

- [198] D.G. Fatouros, F.S. Nielsen, D. Douroumis, L.J. Hadjileontiadis, A. Mullertz, In vitro–in vivo correlations of self-emulsifying drug delivery systems combining the dynamic lipolysis model and neuro-fuzzy networks, *Eur. J. Pharm. Biopharm.* 69 (2008) 887–898.
- [199] Gao Yang, Meng Joo Er, An intelligent adaptive control scheme for postsurgical blood pressure regulation, *IEEE Trans. Neural Networks* 16 (2005) 475–483.
- [200] S.E. Kern, J.O. Johnson, D.R. Westenskow, Fuzzy logic for model adaptation of a pharmacokinetic-based closed loop delivery system for pancuronium, *Artif. Intel. Med.* 11 (1997) 9–31.
- [201] Y. Chen, T.W. McCall, A.R. Baichwal, M.C. Meyer, The application of an artificial neural network and pharmacokinetic simulations in the design of controlled-release dosage forms, *J. Control. Release* 59 (1999) 33–41.
- [202] N.K. Ebube, G. Owusu-Ababio, C.M. Adeyeye, Preformulation studies and characterization of the physicochemical properties of amorphous polymers using artificial neural networks, *Int. J. Pharm.* 196 (2000) 27–35.
- [203] J. Petrovic, S. Ibric, G. Betz, Z. Đurić, Optimization of matrix tablets controlled drug release using Elman dynamic neural networks and decision trees, *Int. J. Pharm.* 428 (2012) 57–67.
- [204] U. Mandal, V. Gowda, A. Ghosh, A. Bose, U. Bhaumik, B. Chatterjee, et al., Optimization of metformin HCl 500 mg sustained release matrix tablets using artificial neural network (ANN) based on multilayer perceptrons (MLP) model, *Chem. Pharm. Bull.* 56 (2008) 150–155.
- [205] X.H. Wei, J.J. Wu, W.Q. Liang, Application of an artificial neural network in the design of sustained-release dosage forms, *Yao Xue Xue Bao* 36 (9) (2001) 690–694.
- [206] E. Aktas, H. Eroglu, U. Kockan, L. Onur, Systematic development of pH-independent controlled release tablets of carvedilol using central composite design and artificial neural networks, *Drug Dev. Ind. Pharm.* 39 (2013) 1207–1216.
- [207] M.M. Leane, I. Cumming, O.I. Corrigan, The use of artificial neural networks for the selection of most appropriate formulation and processing variables in order to predict the in vitro dissolution of sustained release minitables, *AAPS Pharm. Sci. Tech.* 4 (2003) 1–12.
- [208] K. Chansanroj, J. Petrovic, S. Ibric, G. Betz, Drug release control and system understanding of sucrose esters matrix tablets by artificial neural networks, *Eur. J. Pharm. Sci.* 44 (2011) 321–331.
- [209] H. Xie, Y. Gan, S. Ma, Optimization and evaluation of time-dependent tablets comprising an immediate and sustained release profile using artificial neural network, *Drug Develop. Ind. Pharm.* 34 (2008) 363–372.
- [210] A.S. Hussain, P. Shivanand, R.D. Johnson, Application of neural computing in pharmaceutical product development: computer aided formulation design, *Drug Dev. Ind. Pharm.* 20 (1994) 1739–1752.
- [211] S. Ibric, J. Djurić, J. Parojčić, Z. Djurić, Artificial neural networks in evaluation and optimization of modified release solid dosage forms, *Pharmaceutics* 4 (2012) 531–550.
- [212] S. Ibric, M. Jovanovic, Z. Djurić, J. Parojčić, L. Solomun, B. Lucic, Generalized regression neural networks in prediction of drug stability, *J. Pharm. Pharmacol.* 59 (2007) 745–750.
- [213] Sinan Gures, Aleksander Mendyk, Renata Jachowicz, Przemysław Dorozynski, Peter Kleinebudde, Application of artificial neural networks (ANNs) and genetic programming (GP) for prediction of drug release from solid lipid matrices, *Int. J. Pharm.* 436 (2012) 877–879.
- [214] S. Ibric, M. Jovanović, Z. Djurić, J. Parojčić, S.D. Petrović, L.J. Solomun, B. Stupar, Artificial neural networks in the modeling and optimization of aspirin extended release tablets with Eudragit L 100 as matrix substance, *AAPS Pharm. Sci. Tech.* 4 (2003) 62–70.
- [215] N.A. Peppas, Analysis of Fickian and non-Fickian drug release from polymers, *Pharm. Acta Helv.* 60 (1985) 110–111.
- [216] S. Ibric, M. Jovanovic, Z. Djurić, J. Parojčić, L. Solomun, The application of generalized regression neural network in the modeling and optimization of aspirin extended release tablets with Eudragit® RS PO as matrix substance, *J. Control. Release* 82 (2002) 213–222.
- [217] I. Branka, I. Svetlana, C. Nebojsa, P. Aleksandra, T. Svetlana, D. Zorica, Application of design of experiments and multilayer perceptrons neural network in the optimization of diclofenac sodium extended release tablets with Carbopol® 71G, *Chem. Pharm. Bull.* 58 (7) (2010) 947–949.
- [218] Alpesh Patel, Tarak Mehta, Mukesh Patel, Kanu Patel, Natvarlal Patel, Design porosity osmotic tablet for delivering low and pH-dependent soluble drug using an artificial neural network, *Curr. Drug Deliv.* 9 (2012) 459–467.
- [219] T. Wu, W. Pan, J. Chen, R. Zhang, Formulation optimization technique based on artificial neural network in salbutamol sulfate osmotic pump tablets, *Drug Dev. Ind. Pharm.* 26 (2000) 211–215.
- [220] Z.H. Zhang, Y. Wang, W.F. Wu, X. Zhao, X.C. Sun, H.Q. Wang, Development of glipizide push-pull osmotic pump controlled release tablets by using expert system and artificial neural network, *Yao Xue Xue Bao* 47 (12) (2012 Dec) 1687–1695.
- [221] Panagiotis Barmplexis, Feras Imad Kanaze, Kyriakos Kachrimanis, Emanouil Georgarakis, Artificial neural networks in the optimization of a nimodipine controlled release tablet formulation, *Eur. J. Pharm. Biopharm.* 74 (2010) 316–323.
- [222] X.Y. Zhang, D.W. Chen, J. Jin, W. Lu, Artificial neural network parameters optimization software and its application in the design of sustained release tablets, *Yao Xue Xue Bao* 44 (10) (2009 Oct) 1159–1164.
- [223] D. Martarelli, L. Casetelli, K.S. Shalaby, M.E. Soliman, M. Cespi, G. Bonacucina, et al., Optimization of melatonin dissolution from extended release matrices using artificial neural networking, *Curr. Drug Deliv.* 13 (4) (2016) 565–573.
- [224] K. Takayama, A. Morva, M. Fujikawa, Y. Hattori, Y. Obata, T. Nagai, Formula optimization of theophylline controlled release tablet based on artificial neural networks, *J. Control. Release* 68 (2000) 175–186.
- [225] K. Takayama, M. Fujikawa, Y. Obata, M. Morishita, Neural network based optimization of drug formulations, *Adv. Drug Deliv. Rev.* 55 (2003) 1217–1231.
- [226] A.P. Munasur, V. Pillay, Y.E. Choonara, I. Mackraj, T. Govender, Comparing the mucoadhesivity and drug release mechanisms of various polymer-containing propranolol buccal tablets, *Drug Develop. Indust. Pharm.* 34 (2008) 189–198.
- [227] S. Vaithiyalingam, M.A. Khan, Optimization and characterization of controlled release multi-particulate beads formulated with a customized cellulose acetate butyrate dispersion, *Int. J. Pharm.* 234 (2002) 179–193.
- [228] M.G. Sankalia, R.C. Mashru, J.M. Sankalia, V.B. Sutariya, Papain entrapment in alginate beads for stability improvement and site-specific delivery: physicochemical characterization and factorial optimization using neural network modeling, *AAPS Pharm. Sci. Tech.* 6 (2005) E209–E222.
- [229] Aleksander Mendyk, Peter Kleinebudde, Markus Thommes, Angelina Yoo, Jakub Szlek, Renata Jachowicz, Analysis of pellet properties with use of artificial neural networks, *Eur. J. Pharm. Sci.* 41 (2010) 421–429.
- [230] Y. Huang, Q. Yao, C. Zhu, X. Zhang, L. Qin, Q. Wang, et al., Comparison of novel granulated pellet-containing tablets and traditional pellet-containing tablets by artificial neural networks, *Pharm. Dev. Technol.* 20 (2015) 670–675.
- [231] A.Y. Zhang, T.Y. Fan, Optimization of calcium alginate floating microspheres loading aspirin by artificial neural networks and response surface methodology, *Beijing Da Xue Xue Bao* 42 (2) (2010) 197–201.
- [232] H.I. Labouta, L.K. El-khordagui, A.M. Molokhia, G.M. Ghaly, Multivariate modeling of encapsulation and release of an ionizable drug from polymer microspheres, *J. Pharm. Sci.* 98 (2009) 4603–4615.
- [233] N. Yuksel, M. Turkoglu, T. Baykara, Modelling of the solvent evaporation method for the preparation of controlled release acrylic microspheres using neural networks, *J. Microencapsul.* 17 (2000) 541–551.
- [234] Djordje P. Medarevic, Peter Kleinebudde, Jelena Djuris, Zorica Djuric, Svetlana Ibric, Combined application of mixture experimental design and artificial neural networks in the solid dispersion development, *Drug Dev. Ind. Pharm.* (2015) 1–14, <https://doi.org/10.3109/03639045.2015.1054831>.
- [235] P. Barmplexis, I. Koutsidis, E. Karavas, D. Louk, Development of PVP/PEG mixtures as appropriate carriers for the preparation of drug solid dispersions by melt mixing technique and optimization of dissolution using artificial neural networks, *Eur. J. Pharm. Biopharm.* 85 (2013) 1219–1231.
- [236] P. Barmplexis, K. Kachrimanis, E. Georgarakis, Solid dispersions in the development of a nimodipine floating tablet formulation and optimization by artificial neural networks and genetic programming, *Eur. J. Pharm. Biopharm.* 77 (2011) 122–131.
- [237] Pedram Nemati, Mohammad Imani, Farhid Farahmandghavi, Hamid Mirzadeh, Ehsan Marzban-Rad, Ali Motie Nasrabadi, Artificial neural networks for bilateral prediction of formulation parameters and drug release profiles from cochlear implant coatings fabricated as porous monolithic devices based on silicone rubber, *J. Pharm. Pharmacol.* 66 (2013) 624–638.
- [238] H.G. Moussa, G.A. Hussein, N. Abel-Jabbar, S.E. Ahmad, Use of model predictive control and artificial neural networks to optimize the ultrasonic release of a model drug from liposomes, *IEEE Transact. Nanobiosci.* (2017) 149–156.
- [239] N. Arulsudar, N. Subramanian, R.S.R. Murthy, Comparison of artificial neural network and multiple linear regression in the optimization of formulation parameters of leuprolide acetate loaded liposomes, *J. Pharm. Pharmaceut. Sci.* 8 (2005) 243–258.
- [240] K. Takayama, J. Takahara, M. Fujikawa, H. Ichikawa, T. Nagai, Formula optimization based on artificial neural networks in transdermal drug delivery, *J. Control. Release* 62 (1999) 161–170.
- [241] K.K. Kandimala, N. Kanikannan, M. Singh, Optimization of a vehicle mixture for the transdermal delivery of melatonin using artificial neural networks and response surface method, *J. Control Release* 61 (1999) 71–82.
- [242] S.S. Godavarthy, K.M. Yerramsetty, V.K. Rachakonda, B.J. Neely, S.V. Madhally, R.L. Robinson Jr, et al., Design of improved permeation enhancers for transdermal drug delivery, *J. Pharm. Sci.* 98 (2009) 4085–4099.
- [243] C.P. Lim, S.S. Quek, K.K. Peh, Prediction of drug release profiles using an intelligent learning system: an experimental study in transdermal iontophoresis, *J. Pharm. Biomed. Anal.* 31 (2003) 159–168.
- [244] A. Mendyk, R. Jachowicz, P. Dorozynski, Artificial neural networks in the modeling of drugs release profiles from hydrodynamically balanced systems, *Acta Pol. Pharm.* 63 (1) (2006) 75–80.
- [245] A. Belic, I. Grabnar, R. Karba, A. Mrhar, Pathways of paracetamol absorption from layered excipient suppositories: artificial intelligence approach, *Eur. J. Drug Metab. Pharmacokinet.* 28 (1) (2003) 31–40.
- [246] C.I. Richardson, D.J. Barlow, Neural network computer simulation of medical aerosols, *J. Pharm. Pharmacol.* 48 (1996) 581–591.
- [247] C. Tan, I.T. Degim, Development of sustained release formulation of an antithrombotic drug and application of fuzzy logic, *Pharm. Develop. Technol.* 17 (2012) 242–250.
- [248] S. Agatovic-Kustrin, R.G. Alany, Role of genetic algorithms and artificial neural networks in predicting the phase behavior of colloidal delivery systems, *Pharm. Res.* 18 (7) (2001) 1049–1055.
- [249] A. Miwa, T. Yajima, H. Ikuta, K. Makado, Prediction of suitable amounts of water in fluidized bed granulation of pharmaceutical formulations using corresponding values of components, *Int. J. Pharm.* 352 (2008) 202–208.
- [250] K.J. Kumar, G.M. Panpalia, S. Priyadarshini, Application of artificial neural networks in optimizing the fatty alcohol concentration in the formulation of an O/W emulsion, *Acta Pharm.* 61 (2011) 249–256.
- [251] F. Podlogar, R. Šibanc, M. Gašperlin, Evolutionary artificial neural networks as tools for predicting the internal structure of microemulsions, *J. Pharm. Pharmaceut. Sci.* 11 (2008) 67–76.

- [252] S. Agatonovic-Kustrin, B.D. Glass, M.H. Wisch, R.G. Alany, Prediction of a stable microemulsion formulation for the oral delivery of a combination of antitubercular drugs using ANN methodology, *Pharm. Res.* 20 (2003) 1760–1765.
- [253] D. Leonardi, C.J. Salomón, M.C. Lamas, A.C. Olivieri, Development of novel formulations for Chagas' disease: optimization of benzimidazole chitosan microparticles based on artificial neural networks, *Int. J. Pharm.* 367 (2009) 140–147.
- [254] Radhakant Padhi Jayender R. Bhardhwaj, An adaptive drug delivery design using neural networks for effective treatment of infectious diseases: a simulation study, *Comput. Method Program Biomed.* 94 (2009) 207–222.
- [255] K. McNamara, S.A.M. Tofail, Nanoparticles in biomedical applications, *Adv. Phys.* 2 (2017) 54–88.
- [256] M. Bououdina, S. Rashdan, J.L. Bobet, Y. Ichiyanagi, Nanomaterials for biomedical applications: synthesis, characterization, and applications, *J. Nanomater.* (2013) 1–4.
- [257] P. Hassanzadeh, Nanopharmaceuticals: innovative theranostics for the neurological disorders, *Biomed. Rev.* 25 (2014) 25–34.
- [258] Parichehr Hassanzadeh, Fatemeh Atyabi, Rassoul Dinarvand, Nanoencapsulation: a promising strategy for biomedical applications of ferulic acid, *Biomed. Rev.* 28 (2017) 26–34.
- [259] Parichehr Hassanzadeh, Fatemeh Atyabi, Rassoul Dinarvand, Ahmad-Reza Dehpour, Morteza Azhdarzadeh, Meshkat Dinarvand, Application of nanostructured lipid carriers: the prolonged protective effects for sesamol in in vitro and in vivo models of ischemic stroke via activation of PI3K signalling pathway, *DARU J. Pharm. Sci.* 25 (2017) 25.
- [260] P. Hassanzadeh, E. Arbabi, F. Atyabi, R. Dinarvand, Ferulic acid-loaded nanostructured lipid carriers: a promising nanoformulation against the ischemic neural injuries, *Life Sci.* 193 (2018) 64–76.
- [261] Parichehr Hassanzadeh, Elham Arbabi, Fatemeh Rostami, Fatemeh Atyabi, Rassoul Dinarvand, Aerosol delivery of ferulic acid-loaded nanostructured lipid carriers: a promising treatment approach against the respiratory disorders, *Physiol. Pharmacol.* 21 (2017) 331–342.
- [262] N. Rizkalla, P. Hildgen, *Drug Dev. Indust. Pharm.* 31, 2005 1019–1033.
- [263] H. Asadi, K. Rostamizadeh, D. Salari, M. Hamidi, *J. Microencapsul.* 28, 2011 406–416.
- [264] A. Mendyk, P. Kleinebudde, M. Thommes, A. Yoo, J. Szlek, R. Jachowicz, *Eur. J. Pharm. Sci.* 41, 2010 421–429.
- [265] A. Amani, P. York, H. Chrystyn, B.J. Clark, D.Q. Do, *Eur. J. Pharm. Sci. Official J.* 35, 2008 42–51.
- [266] Parichehr Hassanzadeh, Fatemeh Atyabi, Rassoul Dinarvand, Application of modeling and nanotechnology-based approaches: the emergence of breakthroughs in theranostics of central nervous system disorders, *Life Sci.* 182 (2017) 93–103.
- [267] Y. Sun, Y. Peng, Y. Chen, A.J. Shukla, *Adv. Drug Deliv. Rev.* 55, 2003 1201–1215.
- [268] H. Asadi, K. Rostamizadeh, D. Salari, M. Hamidi, Preparation of biodegradable nanoparticles of tri-block PLA-PEG-PLA copolymer and determination of factors controlling the particle size using artificial neural network, *J. Microencapsul.* 28 (5) (2011) 406–416.
- [269] Y. Li, M.R. Abbaspour, P.V. Grootendorst, A.M. Rauth, X.Y. Wu, Optimization of controlled release nanoparticle formulation of verapamil hydrochloride using artificial neural networks with genetic algorithm and response surface methodology, *Eur. J. Pharm. Biopharm.* 94 (2015) 170–179.
- [270] A. Rania, Rania A.H. Ishak, Sherif Fahmy, Samar Mansour, Ahmed S. Geneidi, Chitosan-tripolyphosphate nanoparticles: optimization of formulation parameters for improving process yield at a novel pH using artificial neural networks, *Int. J. Biol. Macromol.* 86 (2016) 50–58.
- [271] H. Baharifar, A. Amani, Size, loading efficiency, and cytotoxicity of albumin-loaded chitosan nanoparticles: an artificial neural networks study, *J. Pharm. Sci.* 106 (2017) 411–417.
- [272] N. Seyedhassantehrani, R. Karimi, G. Tavoosidana, A. Amani, Concurrent study of stability and cytotoxicity of a novel nanoemulsion system - an artificial neural networks approach, *Pharm. Dev. Technol.* 22 (2017) 383–389.
- [273] Amir Amani, Peter York, Henry Chrystyn, Brian J. Clark, QDo. Duong, Determination of factors controlling the particle size in nanoemulsions using artificial neural networks, *Eur. J. Pharm. Sci.* 35 (2008) 42–51.
- [274] M.R. Zaki, J. Varshosaz, M. Fathi, Preparation of agar nanospheres: comparison of response surface and artificial neural network modeling by a genetic algorithm approach, *Carbohydr. Polym.* 122 (2015) 314–320.
- [275] Martin Pabst, William McDowell, Anaïs Manin, Andrew Kyle, Nicolas Camper, Elena De Juan, et al., Modulation of drug-linker design to enhance in vivo potency of homogeneous antibody-drug conjugates, *J. Control. Release* 253 (2017) 160–164.
- [276] Parichehr Hassanzadeh, Fatemeh Atyabi, Rassoul Dinarvand, Linkers: the key elements for the creation of efficient nanotherapeutics, *J. Control. Release* 270 (2018) 260–267.
- [277] Jianhua Zhang, Jun Yun, Zhigang Shang, Xiaohui Zhang, Borong Pan, Design and optimization of a linker for fusion protein construction, *Prog. Nat. Sci.* 19 (2009) 1197–1200.
- [278] C. Manion, R. Arlitt, M. Campbell, I. Tumer, R. Stone, A. Greaney, Automated design of flexible linkers, *Dalton Transact.* 1 (2015) 1–8.
- [279] Shadab Shahsavari, Leila Rezaie Shirmard, Mohsen Amini, Farid Abedin Dokoosh, Application of artificial neural networks in the design and optimization of a nanoparticulate Fingolimod delivery system based on biodegradable poly(3-hydroxybutyrate-co-3-hydroxyvalerate), *J. Pharm. Sci.* 106 (2017) 176–182.
- [280] D. Lixin, Z. Li, J.B. Dominik, J.N. Bradley, G. Detlev, Hybrid nanorobotic approaches for fabricating NEMS from 3D helical nanostructures, *Proc. IEEE Int. Conf. Robotics Autom* 2006, pp. 1396–1401.
- [281] Parichehr Hassanzadeh, Fatemeh Atyabi, Rassoul Dinarvand, Creation of nanorobots: both state-of-the-science and state-of-the-art, *Biomed. Rev.* 27 (2016) 37–44.
- [282] M. Hamdi, A. Ferreira, Multiscale design and modeling of protein-based nanomechanisms for nanorobotics, *Int. J. Robot. Res.* 28 (4) (2009) 436–449.
- [283] A. Robert, Current status of nanomedicine and medical nanorobotics, *J. Comput. Theor. Nanosci.* 2 (2005) 1–25.
- [284] A. Banharnsakun, T. Achalakul, R.C. Batra, Drug delivery based on swarm microrobots, *Int. J. Comput. Intel Appl.* 15 (2016) 1–25.
- [285] G.M. Patel, G.C. Patel, R.B. Patel, J.K. Patel, M. Patel, Nanorobot: a versatile tool in nanomedicine, *J. Drug Target* 14 (2006) 63–67.
- [286] P. Couvreur, C. Vauthier, Nanotechnology: intelligent design to treat complex disease, *Pharm. Res.* 23 (2006) 1417–1450.
- [287] A. Cavalcanti, B. Shirinzadeh, L.C. Kretly, Medical nanorobotics for diabetes control, *Nanomed* 4 (2008) 127–138.
- [288] Y. Saadeh, D. Vyas, Nanorobotic applications in medicine: current proposals and designs, *Am. J. Robot Surg.* 1 (2014) 4–11.
- [289] T. Toth-Fejel, Agents, assemblers, and ANTS: scheduling assembly with market and biological software mechanisms, *Nanotechnology* 11 (2000) 133–137.
- [290] A. Cavalcanti, R.A. Freitas, Nanorobotics control design: a collective behavior approach for medicine, *IEEE Transact. Nanobiosci.* 4 (2005) 133–140.
- [291] M. Ntika, P. Kefalas, I. Stamatopoulou, Formal modelling and simulation of a multi-agent nano-robotics drug delivery system, *Scal Comput.* 15 (2014) 217–230.
- [292] W. Zhou, L.Z. Wang, Three-Dimensional Nanoarchitectures Designing Next Generation Devices, Springer, New York, 2011.
- [293] A. Cavalcanti, D. Shirinzadeh, A. Freitas, T. Hogg, Nanorobot architecture for medical target identification, *Nanotechnology* 19 (2008) 1–15.
- [294] H. Li, J. Tan, M. Zhang, Dynamics modeling and analysis of a swimming microrobot for controlled drug delivery, *IEEE Trans. Autom. Sci. Eng.* 6 (2008) 220–227.
- [295] Y. Chen, P. Kosmas, P.S. Anwar, A touch-communication framework for drug delivery based on a transient microbot system, *IEEE Transact. NanoBiosci.* 14 (2015) 397–408.
- [296] Y. Chen, P. Kosmas, R. Wang, Conceptual design and simulations of a nano-communication model for drug delivery based on a transient microbot system, *Proceedings of 8th European Conference on Antennas and Propagation (EuCAP)*, The Hague 2014, pp. 63–67.
- [297] S. Fusco, F. Ullrich, J. Pokki, G. Chatzipirpiridis, B. Özkale, K.M. Sivaraman, et al., Microrobots: a new era in ocular drug delivery, *Expert Opin. Drug Deliv.* 11 (2014) 1815–1826.
- [298] Mark Fletcher, Mohammad Biglarbegian, Suresh Neethirajan, Intelligent system design for bionanorobots in drug delivery, *Cancer Nano* 4 (2013) 117–125.
- [299] N. Ganganath, C.-T. Cheng, C.K. Tse, An ACO-based off-line path planner for nonholonomic mobile robots, *Proc. IEEE Int. Symp. Circuits and Systems* 2014, pp. 1038–1041.
- [300] Y. Zhang, D.-W. Gong, J.-H. Zhang, Robot path planning in uncertain environment using multi-objective particle swarm optimization, *Neurocomputing* 103 (2013) 172–185.
- [301] M. Brand, M. Masuda, N. Wehner, X.-H. Yu, Ant colony optimization algorithm for robot path planning, *Proc. 2010 Int. Conf. Computer Design and Applications* 2010, pp. 436–440.
- [302] K.H.S. Hla, Y. Choi, J.S. Park, Obstacle avoidance algorithm for collective movement in nanorobots, *Int. J. Comput. Sci. Netw. Secur.* 8 (2008) 302–309.
- [303] S. Chandrasekarn, D.F. Hough, Swarm intelligence for cooperation of bio-nano robots using quorum sensing, *Proc. BioMicro and Nanosystems Conf.* (2006) 15–18.
- [304] A. Hossain, I. Ferdous, Autonomous robot path planning in dynamic environment using a new optimization technique inspired by bacterial foraging technique, *Robot. Auton. Syst.* 64 (2015) 137–141.
- [305] WeiMin Tao, Mingjun Zhang, A genetic algorithm-based area coverage approach for controlled drug delivery using microrobots, *Nanomedicine* 1 (2005) 91–100.
- [306] M.B. Somanna, Nanobots: the future of medical treatments, *Int. J. Sci. Tech Res.* 4 (2015) 276–278.
- [307] X.Z. Chen, M. Hoop, N. Shamsudhin, T. Huang, B. Özkale, Q. Li, et al., Hybrid magnetoelectric nanowires for nanorobotic applications: fabrication, magnetoelectric coupling, and magnetically assisted in vitro targeted drug delivery, *Adv. Mater.* (2017) 1–7.
- [308] Y.S. Lee, J.Y. Bae, H.Y. Koo, Y.B. Lee, W.S. Choi, A remote-controlled generation of gold/polydopamine (core@shell) nanoparticles via physical-chemical stimuli of polydopamine/gold composites, *Sci. Rep.* 6 (2016), 22650.
- [309] P. Vartholomeos, M. Fruchard, A. Ferreira, C. Mavroidis, MRI-guided nanorobotic systems for therapeutic and diagnostic applications, *Ann. Rev. Biomed. Eng.* 13 (2011) 157–184.
- [310] F. Carpi, C. Pappone, Magnetic manoeuvring of endoscopic capsules by means of a robotic navigation system, *IEEE Trans. Biomed. Eng.* 62 (2008) 546–549.
- [311] C. Sun, J.S.H. Lee, M. Zhang, Magnetic nanoparticles in MRI imaging and drug delivery, *Adv. Drug Deliv. Rev.* 60 (2008) 1252–1265.
- [312] C. Hill, A. Amodeo, J.V. Joseph, H.R. Patel, Nano- and microrobotics: How far is the reality? *Expert Rev. Anticancer Ther.* 8 (2008) 1891–1897.
- [313] S. Martel, O. Felfoul, M. Mohammadi, J.B. Mathieu, Interventional procedure based on nanorobots propelled and steered by flagellated magnetotactic bacteria for direct targeting of tumors in the human body, *Conf Proc IEEE Eng Med Biol Soc* (2008) 2497–2500.
- [314] E. Torelli, M. Marini, S. Palmano, L. Piantanida, C. Polano, A. Scarpellini, et al., A DNA origami nanorobot controlled by nucleic acid hybridization, *Small* 10 (2014) 2918–2926.
- [315] S.M. Douglas, I. Bachelet, G.M. Church, A logic-gated nanorobot for targeted transport of molecular payloads, *Science* 335 (2012) 831–834.

- [316] Jinglin Fu, Hao Yan, Controlled drug release by a nanorobot, *Nat. Biotech.* 30 (2012) 407–408.
- [317] Parichehr Hassanzadeh, New perspectives in biosensor technology, *Gastroenterol. Hepatol. Bed Bench.* 3 (3) (2010) 105–107.
- [318] Z. Zhang, Z. Li, W. Yu, K. Li, Z. Xie, Development of a biomedical micro/nano robot for drug delivery, *J. Nanosci. Nanotechnol.* 15 (4) (2015 Apr) 3126–3129.
- [319] G. Cerofolini, P. Amato, M. Asserini, G. Mauri, A surveillance system for early-stage diagnosis of endogenous diseases by swarms of nanobots, *Adv. Sci. Lett.* 3 (2010) 345–352.
- [320] P. Hassanzadeh, I. Fullwood, S. Sothi, D. Aldulaimi, Cancer nanotechnology, *Gastroenterol. Hepatol. Bed Bench* 4 (2011) 63–69.
- [321] G.V. da Silva Luz, K.V.G. Barros, F.V.C. de Araújo, G.B. da Silva, P.A.F. da Silva, R.C.I. Condori, et al., Nanorobotics in drug delivery systems for treatment of cancer: a review, *J. Mater. Sci. Eng. A* 6 (2016) 167–180.
- [322] M. Ntika, P. Kefalas, I. Stamatopoulou, Formal modelling and simulation of a multi-agent nano-robotics drug delivery system, *Scal Comput.* 15 (2014) 217–230.
- [323] A. Pedram, H.N. Pishkenari, Smart micro/nano-robotic systems for gene delivery, *Curr. Gene Ther.* 17 (2017) 73–79.
- [324] I. Lagzi, Chemical robotics—chemotactic drug carriers, *Open Med.* 8 (2013) 377–382.
- [325] X. Xu, K. Kim, D. Fan, Tunable release of multiplex biochemicals by plasmonically active rotary nanomotors, *Angew. Chem.* 54 (2015) 2525–2529.
- [326] C. Xia, P.G. Smith, Drug efflux transporters and multidrug resistance in acute leukemia: therapeutic impact and novel approaches to mediation, *Mol. Pharmacol.* 82 (2012) 1008–1021.
- [327] S. Karan, D.D. Majumder, Molecular machinery—a nanorobotics control system design for cancer drug delivery, *Int. Conf. Rec. Trend Info Syst.* (2011) 197–202.
- [328] S.C. Lenaghan, Y. Wang, N. Xi, T. Fukuda, T. Tarn, W.R. Hamel, M. Zhang, Grand challenges in bioengineered nanorobotics for cancer therapy, *IEEE Trans. Biomed. Eng.* 60 (2013) 667–673.
- [329] J. Matthias, S. Agnes, B. Jörn, H. Rainer, F.E.N.S. Gabriele, L. Bernhard, S. Olaf, Design and implementation of a control system reflecting the level of analgesia during general anesthesia, *Biomed. Eng.* 58 (2012) 1–11.
- [330] J.M. Garibaldi, S.M. Zhou, X.Y. Wang, R.I. John, I.O. Ellis, Incorporation of expert variability into breast cancer treatment recommendation in designing clinical protocol guided fuzzy rule system models, *J. Biomed. Inform.* 45 (2012) 447–459.
- [331] A. Connor, Location, location, location: gastrointestinal delivery site and its impact on absorption, *Ther. Deliv.* 3 (5) (2012) 575.
- [332] F. Munoz, G. Alici, W. Li, A review of drug delivery systems for capsule endoscopy, *Adv. Drug Deliv. Rev.* 71 (2014) 77–85.
- [333] N.K. Shah, B. Rane, N. Gujarathi, Developments in colon specific drug delivery systems – a review, *Pharm. Sci. Monitor* 5 (2) (2014) 95–110.
- [334] S.S. Mapara, V.B. Patravale, Medical capsule robots: a renaissance for diagnostics, drug delivery and surgical treatment, *J. Control. Release* 261 (2017) 337–351.
- [335] I. Wilding, The enterion capsule: a novel technology for understanding the biopharmaceutical complexity of new molecular entities (NMEs), *Drug Deliv. Technol.* 1 (1) (2001) 8–11.
- [336] S.P. Woods, T.G. Constantinou, Wireless capsule endoscope for targeted drug delivery: mechanics and design considerations, *IEEE Trans. Biomed. Eng.* 60 (4) (2013) 945–953.
- [337] S.H. Kim, K. Ishiyama, Magnetic robot and manipulation for active-locomotion with targeted drug release, *IEEE/ASME Trans. Mechatron.* 19 (5) (2014) 1651–1659.
- [338] S. Yim, M. Sitti, Shape-programmable soft capsule robots for semi-implantable drug delivery, *IEEE Trans. Robot.* 28 (5) (2012) 1198–1202.
- [339] W. Yu, R. Rahimi, M. Ochoa, R. Pinal, B. Ziaie, A smart capsule with GI-tract-location-specific payload release, *IEEE Trans. Biomed. Eng.* 62 (9) (2015) 2289–2295.
- [340] Marco Beccani, Gregorio Aiello, Nikolaos Gkotsis, Hakan Tunc, Addisu Taddese, Ekawahyu Susilo, et al., Component based design of a drug delivery capsule robot, *Sensors Actuators A* 245 (2016) 180–188.
- [341] Avid M. Afzal, Hamse Y. Mussa, Richard E. Turner, Andreas Bender, Robert C. Glen, A multi-label approach to target prediction taking ligand promiscuity into account, *J. Cheminform.* 7 (2015) 1–14.
- [342] Lirong Wang, Xiang-Qun Xie, Computational target fishing: what should chemogenomics researchers expect for the future of in silico drug design and discovery? *Future Med. Chem.* 6 (2014) 247–249.
- [343] F. Iorio, R. Bosotti, E. Scacheri, V. Belcastro, P. Mithbaokar, R. Ferriero, et al., Discovery of drug mode of action and drug repositioning from transcriptional responses, *Proc. Natl. Acad. Sci. U.S.A.* 107 (2010) 14621–14626.
- [344] B.F. Begam, J.S. Kumar, A study on cheminformatics and its applications on modern drug discovery, *Proc. Eng.* 38 (2012) 1264–1275.
- [345] B. Lomenick, R.W. Olsen, J. Huang, Identification of direct protein targets of small molecules, *ACS Chem. Biol.* 6 (2011) 34–46.
- [346] Sudeep Pushpakom, Francesco Iorio, A. Patrick, K. Jane Escott Eyers, Shirley Hopper, Andrew Wells, Andrew Doig, et al., Drug repositioning: progress, challenges and recommendations, *Nat. Rev. Drug Discov.* 18 (2019) 41–58.
- [347] James H. Nettles, Jeremy L. Jenkins, Andreas Bender, Zhan Deng, John W. Davies, Meir Glick, Bridging chemical and biological space: “Target fishing” using 2D and 3D molecular descriptors, *J. Med. Chem.* 49 (2006) 6802–6810.
- [348] R. Chaudhari, Z. Tan, B. Huang, S. Zhang, Computational polypharmacology: a new paradigm for drug discovery, *Expert Opin. Drug Discov.* 12 (3) (2017) 279–291.
- [349] Jeremy L. Jenkins, Andreas Bender, John W. Davies, In Silico Target Fishing: predicting Biological Targets from Chemical Structure, 3, 2006 413–421.
- [350] Oscar Méndez-Lucio, J. Jesús Naveja, Hugo Vite-Caritino, Fernando Daniel Prieto-Martínez, José Luis Medina-Franco, One drug for multiple targets: a computational perspective, *J. Mex. Chem. Soc.* 60 (2016) 168–181.
- [351] Xian Liu, Yuan Xu, Shanshan Li, Yulan Wang, Jianlong Peng, Cheng Luo, et al., In Silico target fishing: addressing a “Big Data” problem by ligand-based similarity rankings with data fusion, *J. Cheminform.* 6 (2014) 1–15.
- [352] Tiejun Cheng, Qingliang Li, Yanli Wang, Stephen H. Bryant, Identifying compound-target associations by combining bioactivity profile similarity search and public databases mining, *J. Chem. Inf. Model.* 51 (2011) 2440–2448.
- [353] M.D.M. Abdulhameed, S. Chaudhury, N. Singh, H. Sun, A. Wallqvist, G.J. Tawa, Exploring polypharmacology using a ROCS-based target fishing approach, *J. Chem. Inf. Model.* 52 (2012) 492–505.
- [354] M. Sirota, J.T. Dudley, J. Kim, A.P. Chiang, A.A. Morgan, A. Sweet-Cordero, et al., Discovery and preclinical validation of drug indications using compendia of public gene expression data, *Sci. Transl. Med.* 3 (2011) 96ra77.
- [355] M.J. Keiser, B.L. Roth, B.N. Armbruster, P. Ernsberger, J.J. Irwin, B.K. Shoichet, Relating protein pharmacology by ligand chemistry, *Nat. Biotechnol.* 25 (2007) 197–206.
- [356] O. Méndez-Lucio, J. Tran, J.L. Medina-Franco, N. Meurice, M. Muller, Toward drug repurposing in epigenetics: olsalazine as a hypomethylating compound active in a cellular context, *ChemMedChem* 9 (2014) 560–565.
- [357] H.J. Ting, F.T. Khasawneh, Glybenclamide: an antidiabetic with in vivo antithrombotic activity, *Eur. J. Pharmacol.* 649 (2010) 249–254.
- [358] M. Campillos, M. Kuhn, A.-C. Gavin, L.J. Jensen, P. Bork, Drug target identification using side-effect similarity, *Science* 321 (2008) 263–266.
- [359] M. Campillos, M. Kuhn, A.-C. Gavin, L.J. Jensen, P. Bork, Drug target identification using side-effect similarity, *Science* 321 (2008) 263–266.
- [360] Marcus Bantscheff, Gerard Drewes, Chemoproteomic approaches to drug target identification and drug profiling, *Bioorg. Med. Chem.* 20 (2012) 1973–1978.
- [361] Raymond E. Moellering, Benjamin F. Cravatt, How chemoproteomics can enable drug discovery and development, *Chem. Biol.* 19 (2012) 11–22.
- [362] F. Del Gaudio, F. Pollastro, M. Mozzicafreddo, R. Riccio, A. Minassi, M.C. Monti, Chemoproteomic fishing identifies arzanol as a positive modulator of brain glycogen phosphorylase, *Chem. Commun. (Camb.)* 54 (2018) 12863–12866.
- [363] Stefano Thomason, Carmen Talotta, Carmine Gaeta, Luigi Margarucci, Maria Chiara Monti, Agostino Casapullo, et al., Biomolecular fishing for calixarene partners by a chemoproteomic approach, *Angew. Chem. Int. Ed.* 54 (2015) 15405–15409.
- [364] L. Raj, T. Ide, A.U. Gurkar, M. Foley, M. Schenone, X. Li, et al., Selective killing of cancer cells by a small molecule targeting the stress response to ROS, *Nature*. 475 (2011) 231–234.
- [365] James R. Hill, Avril A.B. Robertson, Fishing for drug targets: a focus on diazirine photoaffinity probe synthesis, *J. Med. Chem.* 61 (2018) 6945–6963.
- [366] Slavica Eric, Song Ke, Teresa Barata, Tom Solmajer, Jelena Antić Stanković, Zorica Juranic, et al., Target fishing and docking studies of the novel derivatives of aryl-aminopyridines with potential anticancer activity, *Bioorg. Med. Chem.* 20 (2012) 5220–5228.
- [367] Hitesh Patel, Xavier Lucas, Igor Bendik, Stefan Ginther, Irmgard Merfort, Target fishing by cross-docking to explain polypharmacological effects, *Chem. Med. Chem.* 10 (2015) 1209–1217.
- [368] Jianyong Zhang, Rixin Liang, Lan Wang, Bin Yang, Effects and mechanisms of Danshen-Shanzha herb-pair for atherosclerosis treatment using network pharmacology and experimental pharmacology, *J. Ethnopharmacol.* 229 (2019) 104–114.
- [369] S.T. Ma, C.T. Feng, G.L. Dai, Y. Song, G.L. Zhou, X.L. Zhang, et al., In silico target fishing for the potential bioactive components contained in Huanglian Jiedu Tang (HLJDD) and elucidating molecular mechanisms for the treatment of sepsis, *Chin. J. Nat. Med.* 13 (2015) 30–40.
- [370] Benoit Leclerc, Priscilla Wu, Integrating system biology tools to decipher the mechanisms of action of herbal medicine, *MOJ Proteom. Bioinform.* 7 (1) (2018) 38–41.
- [371] M. De Lourdes Reyes-Escogido, E.G. Gonzalez-Mondragon, E. Vazquez-Tzompantzi, Chemical and pharmacological aspects of capsaicin, *Molecules* 16 (2011) 1253–1270.
- [372] J. Szolcsanyi, Forty years in capsaicin research for sensory pharmacology and physiology, *Neuropeptides* 38 (2004) 377–384.
- [373] I. D’iaz-Laviada, N. Rodríguez-Henche, The potential antitumor effects of capsaicin, *Prog. Drug Res.* 68 (2014) 181–208.
- [374] Victor Fattori, Miriam S.N. Hohmann, Ana C. Rossaneis, Felipe A. Pinho-Ribeiro, Waldiceu A. Verri Jr, Capsaicin: current understanding of its mechanisms and therapy of pain and other pre-clinical and clinical Uses, *Molecules* 21 (2016) 1–33.
- [375] L. Van Gerven, B. Steelant, Y.A. Alpizar, K. Talavera, P.W. Hellings, Therapeutic effect of capsaicin nasal treatment in patients with mixed rhinitis unresponsive to intranasal steroids, *Allergy* 73 (2018) 248–250.
- [376] Xuan-yi Ye, Qing-zhi Ling, Shao-jun Chen, Identification of a potential target of capsaicin by computational target fishing, *Evid Based Complement. Alternat Med.* 2015 (2015) 1–6.
- [377] Qifang Lei, Haibo Liu, Yong Peng, Peigen Xiao, In silico target fishing and pharmacological profiling for the isoquinoline alkaloids of *Macleaya cordata* (Bo Luo Hui), *Chin. Med.* 10 (2015) 1–20.
- [378] Li Gao, Jian-Song Fang, Xiao-Yu Bai, Dan Zhou, Yi-Tao Wang, Ai-Lin Liu, et al., In silico target fishing for the potential targets and molecular mechanisms of baicalein as an antiparkinsonian agent: discovery of the protective effects on NMDA receptor-mediated neurotoxicity, *Chem. Biol. Drug Des.* 81 (2013) 675–687.
- [379] M.H. Wright, S.A. Sieber, Chemical proteomics approaches for identifying the cellular targets of natural products, *Nat. Prod. Rep.* 33 (2016) 681–708.
- [380] N.A. Thornberry, A.E. Weber, Discovery of JANUVIA (Sitagliptin), a selective dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes, *Curr. Top. Med. Chem.* 7 (2007) 557–568.
- [381] R.H. Nelson, J.M. Miles, The use of orlistat in the treatment of obesity, dyslipidaemia and Type 2 diabetes, *Exp. Opin. Pharmacother.* 6 (2005) 2483–2491.

- [382] A.F. Kluge, R.C. Petter, Acylating drugs: redesigning natural covalent inhibitors, *Curr. Opin. Chem. Biol.* 14 (2010) 421–427.
- [383] C.A. Rodrigues, P.F. dos Santos, M.O.L. da Costa, T.F.A. Pavani, P. Xander, Geraldo MM, et al. 4-Phenyl-1,3-thiazole-2-amines as scaffolds for new antileishmanial agents, *J. Venom. Animals Toxins Trop. Dis.* 24 (2018) 1–10.
- [384] Philip Prathipati, Ngai Ling Ma, Ujjini H. Manjunatha, Andreas Bender, Fishing the target of antitubercular compounds: in silico target deconvolution model development and validation, *J. Proteome Res.* 8 (2009) 2788–2798.
- [385] A. Bender, D.W. Young, J.L. Jenkins, M. Serrano, D. Mikhailov, P.A. Clemons, J.W. Davies, Chemogenomic data analysis: prediction of small-molecule targets and the advent of biological fingerprint, *Comb. Chem. High Throughput Screen* 10 (2007) 719–731.
- [386] E.M. Cortés-Ruiz, O. Palomino-Hernández, K.D. Rodríguez-Hernández, B. Espinoza, J.L. Medina-Franco, Computational methods to discover compounds for the treatment of chagas disease, *Adv. Protein Chem. Struct. Biol.* 113 (2018) 119–142.
- [387] Daiane Dias Ferreira, Juliana Tonini Mesquita, Thais Alves da Costa Silva, Maiara Maria Romanelli, Denise da Gama Jaen Batista, Cristiane França da Silva, et al., Efficacy of sertraline against *Trypanosoma cruzi*: an in vitro and in silico study, *J. Ven. Animals Toxins Trop. Dis.* 24 (2018) 1–12.
- [388] Adrià Cereto-Massagué, María José Ojeda, Cristina Valls, Miquel Mulero, Gerard Pujadas, Santiago Garcia-Vallve, Tools for in silico target fishing, *Methods* 71 (2015) 98–103.
- [389] Nikil Wale, George Karypis, Target fishing for chemical compounds using target-ligand activity data and ranking based methods, *J. Chem. Inf. Model* 49 (2009) 2190–2201.
- [390] F. Cheng, C. Liu, J. Jiang, W. Lu, W. Li, G. Liu, et al., Prediction of drug-target interactions and drug repositioning via network-based inference, *PLoS Comput. Biol.* 8 (2012), e1002503.
- [391] T. van Laarhoven, S.B. Nabuurs, E. Marchiori, Gaussian interaction profile kernels for predicting drug-target interaction, *Bioinformatics* 27 (2011) 3036–3043.
- [392] X. Liu, I. Vogt, T. Haque, M. Campillos, HitPick: a web server for hit identification and target prediction of chemical screenings, *Bioinformatics* 29 (2013) 1910–1912.
- [393] D. Gfeller, A. Grosdidier, M. Wirth, A. Daina, O. Michielin, V. Zoete, SwissTargetPrediction: a web server for target prediction of bioactive small molecules, *Nucl. Acids Res.* 42 (2014) W32–W38.
- [394] H. Yu, J. Chen, X. Xu, Y. Li, H. Zhao, Y. Fang, et al., A systematic prediction of multiple drug-target interactions from chemical, genomic, and pharmacological data, *PLoS ONE* 7 (2012), e37608.
- [395] T. van Laarhoven, S.B. Nabuurs, E. Marchiori, Gaussian interaction profile kernels for predicting drug-target interaction, *Bioinformatics* 27 (2011) 3036–3043.
- [396] A. Koutsoukas, R. Lowe, Y. Kalantarmotamedi, H.Y. Mussa, W. Klaffke, J.B.O. Mitchell, et al., In silico target predictions: defining a benchmarking dataset and comparison of performance of the multiclass Naïve Bayes and Parzen-Rosenblatt window, *J. Chem. Inf. Model.* 53 (2013) 1957–1966.
- [397] M.J. Keiser, V. Setola, J.J. Irwin, C. Laggner, A.I. Abbas, S.J. Hufeisen, et al., Predicting new molecular targets for known drugs, *Nature* 462 (2009) 175–181.
- [398] A. Peón, C.C. Dang, P.J. Ballester, How reliable are ligand-centric methods for target fishing? *Front. Chem.* 4 (2016) 1–10.
- [399] F. Nigsch, A. Bender, J.L. Jenkins, J.B.O. Mitchell, Ligand-target prediction using Winnow and naïve Bayesian algorithms and the implications of overall performance statistics, *J. Chem. Inf. Model.* 48 (2008) 2313–2325.
- [400] Antonio Peón, Stefan Naulaerts, Pedro J. Ballester, Predicting the reliability of drug target interaction predictions with maximum coverage of target space, *Sci Rep* 7 (2017) 1–11.
- [401] Theodora M. Steindl, Daniela Schuster, Christian Laggner, Thierry Langer, Parallel screening: a novel concept in pharmacophore modeling and virtual screening, *J. Chem. Inf. Model.* 46 (2006) 2146–2157.
- [402] Judith M. Rollinger, Daniela Schuster, Birgit Danzl, Stefan Schwaiger, Patrick Markt, Michaela Schmidtke, et al., In silico target fishing for rationalized ligand discovery exemplified on constituents of *Ruta graveolens*, *Planta Med.* 75 (2009) 195–204.