IJMPR 2024, 8(12), 56-66

International Journal of Modern Pharmaceutical Research

www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Review Article

SJIF Impact Factor: 6.669

ARTIFICIAL INTELLIGENCE (AI) IN DRUG DISCOVERY AND DEVELOPMENT: AN IN-DEPTH REVIEW

Kommu Pradeep[*1] and Madhu Gudipati[2]

[1]Assistant Professor, Faculty of Health Sciences, Villa College, Male, Maldives.
[2]Department of Pharmaceutics, KITS College of Pharmacy for Women, Divili, Tirupathi (V), Peddapuram (MD), Kakinada-533433, Andhra Pradesh, India.

Article Received on: 19/10/2024
Article Revised on: 08/11/2024
Article Accepted on: 28/11/2024

***Corresponding Author**
Kommu Pradeep
Assistant Professor, Faculty of Health Sciences, Villa College, Male, Maldives.

ABSTRACT
Artificial Intelligence (AI) is rapidly advancing in the pharmaceutical industry and healthcare systems, demonstrating significant potential across various domains. AI has shown its utility in drug discovery, continuous manufacturing, dosage form design, quality control, drug delivery formulation, polypharmacology, hospital pharmacy, and more. Notably, de novo design has facilitated the development of innovative drug molecules with optimized qualities. This review explores various AI tools and their applications in the pharmaceutical sector, highlighting how AI is being integrated into healthcare systems and its potential benefits for society. Additionally, it addresses the challenges and obstacles associated with implementing AI in the pharmaceutical industry.

KEYWORDS: Artificial intelligence, drug discovery, artificial neural network, robotics, nanomedicine.

INTRODUCTION

Artificial intelligence (AI) has captured public interest with promises of improved quality and decreased cost of care.[1] Reports of suggested benefits in the media come in various forms, some overinflating and some under appreciating the technology's capabilities.[2] Although there has been a recent resurgence of this discussion in the media, AI is not a new phenomenon. The term *artificial intelligence* was first used in 1956 and use of AI grew substantially in the 1970s due to increased availability of computing resources, resulting in the first phase of healthcare interest in AI.[3] However, limited computational power, small data sets, and modest results led to stagnant interest in and growth of AI in healthcare.[4] Now, recent advances in data availability, electronic health record (EHR) adoption, and processing power have paved the way for resurgence of AI adoption in healthcare.[5] Although there are plenty of challenges ahead Topol has written an excellent review of the use of AI in the broader medical field, including a realistic assessment of how much farther the science has to advance before it makes a large impact on patient care. Specific to medication management, AI is already being actively used in research, patient-facing applications, and inventory management.[6,7]

Artificial Intelligence (AI) is a stream of science related to intelligent machine learning, mainly intelligent computer programs, which provides results in the similar way to human attention process.[8] This process generally comprises obtaining data, developing efficient systems for the uses of obtained data, illustrating definite or approximate conclusions and self-corrections/adjustments.[9] In general, AI is used for analyzing the machine learning to imitate the cognitive tasks of individuals. AI technology is exercised to perform more accurate analyses as well as to attain useful interpretation.[10] In this perspective, various useful statistical models as well as computational intelligence are combined in the AI technology. The progress and innovation of AI applications are often associated to the fear of unemployment threat. However, almost all advancements in the applications of AI technology are being celebrated on account of the confidence, which enormously contributes its efficacy to the industry.[11]

Recently, AI technology becomes a very fundamental part of industry for the useful applications in many technical and research fields.[10,11] The emergent initiative of accepting the applications of AI technology in pharmacy including drug discovery, drug delivery formulation development and other healthcare applications have already been shifted from hype to hope.[12,13]

Milestones in AI: The first use of the phrase- 'Artificial Intelligence' was appeared in 1956. However, the concept of AI was employed since 1950 with the uses of problem-solving as well as symbolic methodologies. Important milestones in the area of the AI uses are presented in Table 1.

Table 1: Important milestones in the area of the AI uses.	
Year	**Events**
1943	Walter Pitts and Warren McCulloch proved that logical operations like "and", "or" or "not" can be done by neurons connected in a network
1956	The term 'artificial intelligence' was first appeared.
1958	Frank Rosenblatt created neuronal networks called Perceptrons which can transmit information in one direction.
1974	Initiation of "First AI Winter".
1986	Georey Hinton promoted Back propagation algorithm design which is widely used in deep learning.
1987	Initiation of "AI winter".
1997	Garry Kasparov (Russian grandmaster) was defeated by IBM Deep blue.
2013	Google carried out efficient research on pictures by utilizing the British technology.
2016	In this year, the Go Champion Lee Sedol was defeated by Google DeepMind, software Alpha Go.

Classification of AI: AI can be classified into two different ways: according to calibre and their presence (Fig 1).[14,15] According to their ability, AI can be categorized as:

i) *Artificial Narrow Intelligence (ANI) or Weak AI:* It performs a narrow range task, *i.e.*, facial identification, steering a car, practicing chess, traffic signalling, *etc*.

ii) *Artificial General Intelligence (AGI) or Strong AI:* It performs all the things as humans and also known as human level AI. It can simplify human intellectual abilities and able to do unfamiliar task.

iii) *Artificial Super Intelligence (ASI):* It is smarter than humans and has much more activity than humans drawing, mathematics, space, *etc*.

According to their presence and not yet present, AI can be classified as follows:

i) *Type 1:* It is used for narrow purpose applications, which cannot use past experiences as it has no memory system. It is known as reactive machine. There are some examples of this memory, such as a IBM chess program, which can recognize the checkers on the chess playing board and capable of making predictions.

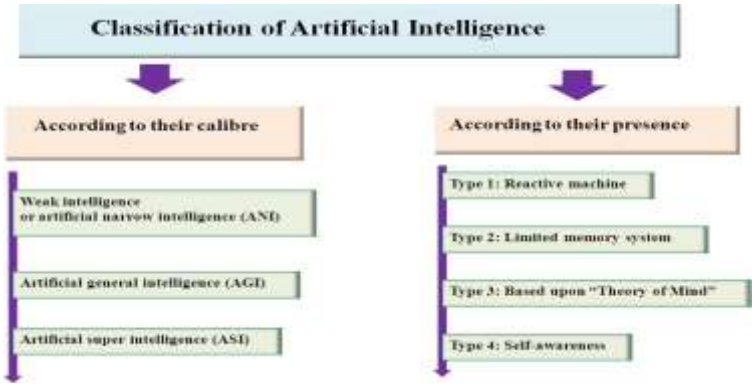

Fig 1: Classification of artificial intelligence.

ii) *Type 2:* It has limited memory system, which can apply the previous experiences for solving different problems. In automatic vehicles, this system is capable of making decisions there are some recorded observations, which are used to record further actions, but these records are not stored permanently.

iii) *Type 3:* It is based upon "Theory of Mind". It means that the decisions that human beings make are impinged by their individual thinking, intentions and desires. This system is non-existing AI.

iv) *Type 4:* It has self-awareness, *i.e.*, the sense of self and consciousness. This system is also non-existing AI.

Neural networks and ANNs: The learning algorithm of neural networks (from input data) takes two different forms mainly. The classes of neural networks are as follows (Fig 2):.[16,17]

i) *Unsupervised learning:* Here the neural network is submitted with input data having recognised pattern. It is used for organizational purpose. The unsupervised learning algorithm uses 'Self Organizing Map' or 'Kohonen'.[16] This is known as very useful modeling for the searching of relationships amongst the complex data sets.

ii) *Supervised learning:* This kind of neural network is illustrated with the sequences of harmonizing inputs and outputs. It is used for learning relationship-connection between the inputs and the outputs. It shows its usefulness in formulation to measure the cause and effects linking between input-output. It is the most frequently employed ANNs and is entirely linked with

the back propagation learning rule. This learning algorithm is known as the outstanding methodology for the prediction as well as classification jobs.[16]

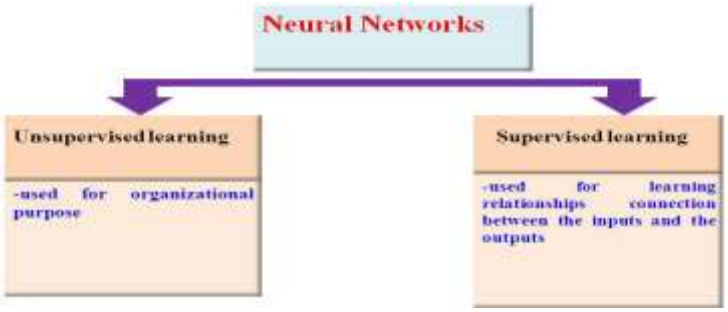

Fig 2: Classification of neural networks.

AI in the lifecycle of pharmaceutical products

Involvement of AI in the development of a pharmaceutical product from the bench to the bedside can be imagined given that it can aid rational drug design[18]; assist in decision making; determine the right therapy for a patient, including personalized medicines; and manage the clinical data generated and use it for future drug development.[19] E-VAI is an analytical and decision- making AI platform developed by Eularis, which uses ML algorithms along with an easy-to-use user interface to create analytical roadmaps based on competitors, key stakeholders, and currently held market share to predict key drivers in sales of pharmaceuticals[20], thus helping marketing executives to allocate resources for maximum market share gain, reversing poor sales and enabled them to anticipate where to make investments. Different applications of AI in drug discovery and development are summarized in Fig 3.

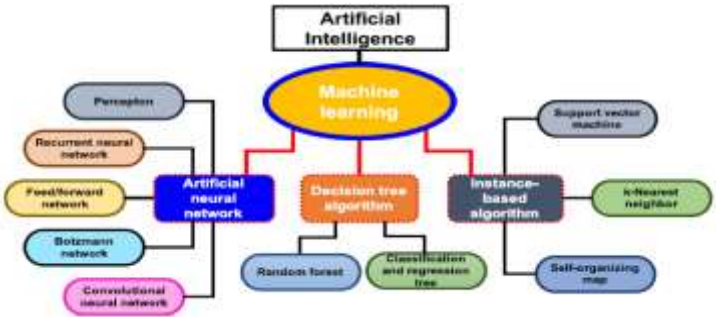

Fig 3: Different applications of AI in drug discovery and development

AI in drug discovery: The vast chemical space, comprising >1060 molecules, fosters the development of a large number of drug molecules.[21] However, the lack of advanced technologies limits the drug development process, making it a time-consuming and expensive task, which can be addressed by using AI.[22] AI can recognize hit and lead compounds, and provide a quicker validation of the drug target and optimization of the drug structure design.[21,23] Different applications of AI in drug discovery are depicted in Fig 4, 5.

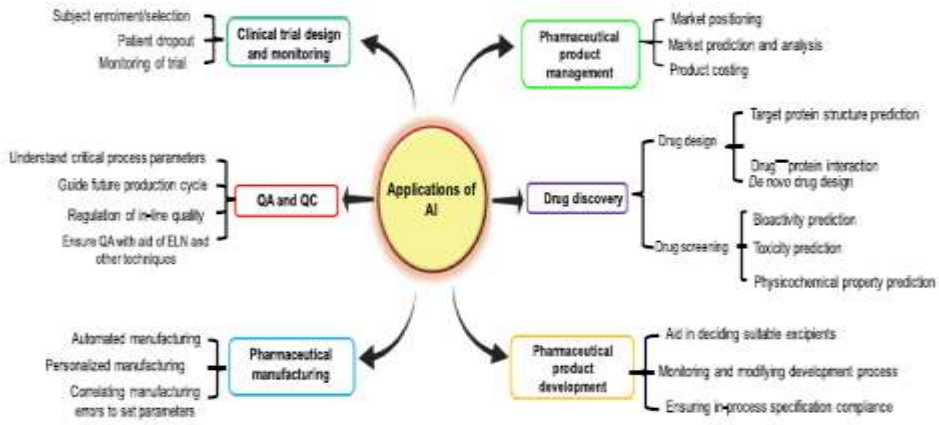

Fig 4: Applications of artificial intelligence (AI) in different subfields of the pharmaceutical industry, from drug discovery to pharmaceutical product management.

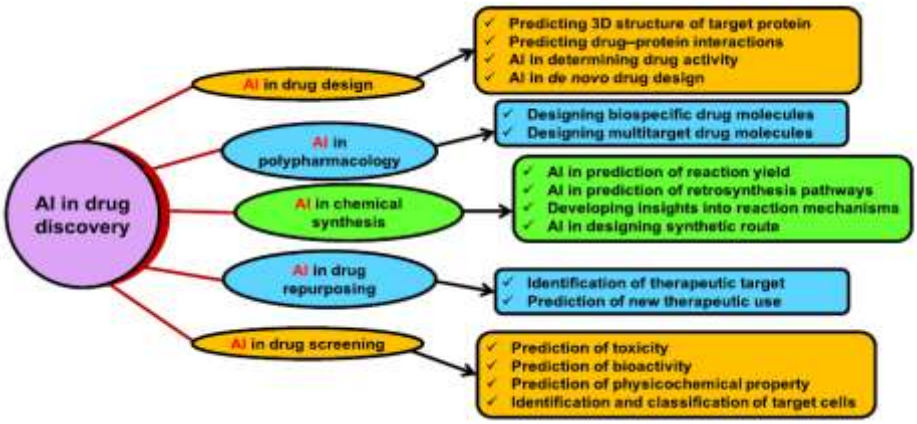

Fig 5: Role of artificial intelligence (AI) in drug discovery. AI can be used effectively in different parts of drug discovery, including drug design, chemical synthesis, drug screening, polypharmacology, and drug repurposing.

Table 2: Examples of AI tools used in drug discovery.

Examples of AI tools used in drug discovery			
Tools	**Details**	**Website URL**	**Refs**
DeepChem	MLP model that uses a python-based AI system to find a suitable candidate in drug discovery	https://github.com/deepchem/deepchem	[21]
DeepTox	Software that predicts the toxicity of total of 12 000 drugs	www.bioinf.jku.at/research/DeepTox	[22]
DeepNeuralNetQSAR	Python-based system driven by computational tools that aid detection of the molecular activity of compounds	https://github.com/Merck/DeepNeuralNet-QSAR	[23]
ORGANIC	A molecular generation tool that helps to create molecules with desired properties	https://github.com/aspuru-guzik-group/ORGANIC	[24]
PotentialNet	Uses NNs to predict binding affinity of ligands	https://pubs.acs.org/doi/full/10.1021/acscentsci.8b00507	[25]
Hit Dexter	ML technique to predict molecules that might respond to biochemical assays	http://hitdexter2.zbh.uni-hamburg.de	
DeltaVina	A scoring function for rescoring drug–ligand binding affinity	https://github.com/chengwang88/deltavina	
Neural graph fingerprint	Helps to predict properties of novel molecules	https://github.com/HIPS/neural-fingerprint	
AlphaFold	Predicts 3D structures of proteins	https://deepmind.com/blog/alphafold	
Chemputer	Helps to report procedure for chemical synthesis in standardized format	https://zenodo.org/record/1481731	

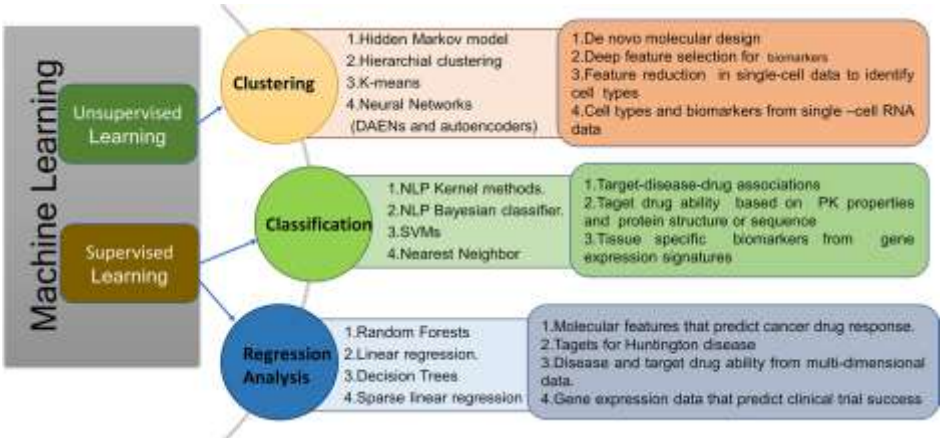

Fig 6: Applications of AI in Drug discovery depicts the Machine learning mechanisms.

Generative adversarial networks (GANs) are capable for the designing of drug molecules. The technology can prepare photo-realistic pictures from the text representation. In a work, employed GAN for suggesting compounds having anticancer characteristics.[25,28] Imagination or creations of new data can also be done by this technology based on the real data. Next generation AI is not dependent on the learning from large data sets.

The new AI technology is capable to handle all the problems that are difficult to solve previously.[24] The scientists and researchers are assisted by this new technology in the identification and selection of promising chemical agents on the basis of their efficacy, safety and selection of patients to the clinical trials.[27,24] Therefore, AI is helpful in drug delivery because of its capability of prioritising the molecules according to the simplicity of syntheses or development of useful tools, which have been proved effectual for the most favourable synthetic technique.[25] A list of important AI-based computer-assisted tools used in drug discovery is presented in Table 3.

Table 3: List of important AI-based computer-assisted tools used in drug discovery.

Table 3: List of important AI-based computer-assisted tools used in drug discovery.		
AI-based computer-assisted tools used in drug discovery	**Websites**	**Descriptions**
Chemputer	https://zenodo.org/record/1481731	More standardized set-up for reporting chemical synthesis
ODDT	https://github.com/oddt/oddt	For use in chemo informatics and molecular modelling
ORGANIC	https://github.com/aspuru-guzik-group/ORGANIC	Molecular generation tool to create molecules with desired characteristics
Deep Chem	https://github.com/deepchem/deepchem	A python-based AI tool for drug discovery predictions
Deep Neural Net-QSAR	https://github.com/Merck/DeepNeuralNet-QSAR	Predictions of molecular activity
Neural Graph Fingerprints	https://github.com/HIPS/neural-fingerprint	Property prediction of novel molecules
Hit Dexter	http://hitdexter2.zbh.uni-hamburg.de	Machine learning models for the prediction of molecules, which might respond to biochemical assays
NNScore	http://rocce-vm0.ucsd.edu/data/sw/hosted/nnscore/	Analysis of neural network-based scoring function for protein–ligand interactions
DeepTox	www.bioinf.jku.at/research/DeepTox	Prediction of toxicity and biocompatibility
Potential Net	https://pubs.acs.org/doi/full/10.1021/acscentsci.8b00507	Ligand-binding affinity prediction based on a graph convolutional neural network
REINVENT	https://github.com/MarcusOlivecrona/REINVENT	Molecular *de novo* design using RNN and reinforcement learning
DeltaVina	https://github.com/chengwang88/deltavina	A scoring function for rescoring protein–ligand binding affinity
Alpha Fold	https://deepmind.com/blog/alphafold	Prediction of protein 3D structure prediction

In a work of development of albumin-loaded chitosan nanoparticles, ANN modeling was employed for the analyses of the impacts of various independable variables (factors) on the dependable variables (responses) like albumin loading efficiency and cytotoxicity profile.[29] A 3 layer feed forward back propagation-based ANN modeling was studied for the development of nano-particles of tri-block poly(lactide)–poly(ethylene glycol)– poly(lactide) copolymer.[30] In this work, on the basis of correlation coefficient (*R2*) and mean squared error (MSE) values, the best analytical model for prediction was chosen for training, test as well as data validation analysis. Amongst all the investigated variables, the concentration of polymer in the copolymer-based nano-particle formulation was revealed as the most impacted factor. On the basis of central composite design (spherical), the formulation development of polymer-lipid hybrid nanoparticles of verapamil HCl was carried out, where the impacts of various formulation factors were analyzed. The multi-objective optimization of polymer-lipid hybrid nanoparticles of verapamil HCl was carried out employing the validated ANNs and continuous genetic algorithms and the analyses results indicated the better analytical capability of ANN model.[31] Some recent researches on the uses of AI technology in the formulation development of various kinds of drug delivery systems are also presented in Table 3.

Table 4: Some recent researches on the uses of AI in the development of drug delivery systems.

Table 4: Some recent researches on the uses of AI in the development of drug delivery systems.		
Drug delivery systems	**AI approaches used**	**References**
Ibuprofen-sustained release from tablets based on different cellulose derivatives	Adaptive neural-fuzzy inference system	Rebouh *et al.* (2019)[32]
Novel granulated pellet-containing tablets and traditional pellet-containing tablets	ANNs	Huang *et al*. (2015)[33]
Ultrasonic release of drug from liposomes	ANNs	Moussa *et al*. (2017)[34]
Doxycycline hydroxypropyl-β-cyclodextrin inclusion complex	RSM, ANN and support vector machine (SVM) modeling	Wang *et al*. (2013)[35]
Oral disintegrating tablets	ANN and DNN	Han *et al.* (2018)[36]
Agar nanospheres of Bupropion	Genetic algorithm, ANN and RSM	Zaki *et al*. (2015)[37]
Ophthalmic flexible nano-liposomes of pilocarpine HCl	RSM and ANN	Zhao *et al*. (2018)[38]
Floating tablets of rosiglitazone maleate	ANNs	Güler *et al*. (2017)[39]
Nifedipine osmotic release tablets	Mechanistic gastrointestinal simulation and ANN	Ilić *et al.* (2014)[40]
Gelatin nanoparticles of diclofenac sodium	Central composite design and ANNs	Koletti *et al*. (2020)[41]
Hydroxyapatite (HAp)-ciprofloxacin bone-implants	Quality by Design (QbD) and 23 factorial design	Nayak *et al.* (2011)[42]
Alginate-PVP K 30 microbeads of diclofenac sodium	Central composite design and RSM	Nayak *et al.* (2011)[43]
Timolol-loaded ultradeformable nanoliposome formulations	ANN and multiple linear regression (MLR) analysis	León Blanco *et al.* (2018)[44]
Transferosomal gel for transdermal insulin delivery	23 factorial design and RSM	Malakar *et al*. (2012)[45]
Besifloxacin HCl loaded liposomal gel	32 full factorial design and RSM	Bhattacharjee *et al*. (2020)[46]
Transferosomal gel for transdermal delivery of risperidone	Central composite design and RSM	Das *et al.* (2017)[47]
Multiple-unit pellet system of prednisone	Box–Behnken design, RSM and ANN	Manda *et al.* (2019)[48]
pH-dependent mesalamine matrix tablets	ANN, multi-layer perception (MLP) algorithm and RMSE	Khan *et al.* (2020)[49]
Voriconazole loaded nanostructured lipid carriers based topical delivery system	Box–Behnken design and QbD	Waghule *et al.* (2019)[50]
Calcium alginate-gum Arabic beads of glibenclamide	Central composite design and RSM	Nayak *et al.* (2012)[51]
Modified starch (cationized)-alginate beads of aceclofenac	Central composite design and RSM	Malakar *et al.* (2013)[52]
Oil-entrapped sterculia gum-alginate beads ofaceclofenac	32 factorial design and RSM	Guru *et al*. (2013)[53]
HAp-ofloxacin bone implants	32 factorial design and RSM	Nayak *et al*. (2013)[54]
Transferosomal gel for transdermal delivery of risperidone	Central composite design and RSM	Das *et al.* (2017)[55]
Pioglitazone-loaded jackfruit seed starch-alginate beads	32 factorial design and RSM	Nayak *et al*. (2013)[56]
Ionotropically-gelled mucoadhesive beads for oral metformin HCl delivery	32 factorial design and RSM	Nayak and Pal (2013)[57]
Oral disintegrating tablet formulations	ANN and DNN	Han *et al.* (2018)[58]
Sustained release matrix formulations of salbutamol sulfate	ANN	Chaibva *et al.* (2010)[59]
Jackfruit seed starch-alginate	32 factorial design and RSM	Nayak and Pal (2013)[60]

mucoadhesive beads of metformin HCl		
Jackfruit seed starch-pectin mucoadhesive beads of metformin HCl	32 factorial design and RSM	Nayak and Pal (2013)[61]
Emulsion-gelled floating beads of diclofenac sodium	23 factorial design and RSM	Nayak *et al.* (2013)[62]
Aceclofenac-loaded pectinate-poly (vinyl pyrrolidone) beads	32 factorial design and RSM	Nayak *et al.* (2013)[62]
Floating capsules containing alginate-based beads of salbutamol sulfate	32 factorial design and RSM	Malakar *et al.* (2014)[63]
Granulated pellet-containing tablets and traditional pellet-containing tablets	ANN	Huang *et al.* (2015)[64]

Deep models

For decades, most neural network models had only 1 or 2 hidden layers (Fig 7). Attempts to increase the number of layers (and therefore the power of the models) wound up with the extra layers learning nothing meaningful and all of the real learning being done in the final, hidden layer.[65] This had become such an impediment that most of the field had moved on to other machine learning algorithms by the mid 1990s. However, in 2006 a breakthrough allowed for meaningful learning in multiple layers of a neural network (Fig 8), and this opened whole new avenues for experimentation and development.[66] After just a few years, neural networks with many hidden layers, called deep models, deep architectures, or deep learning, had become the dominant approach in several scientific domains, such as computer vision and speech recognition.[67] It turns out that the same key ideas had been previously described as early as 1965 but were not given a catchy name and were not widely known within the machine-learning community.[68]

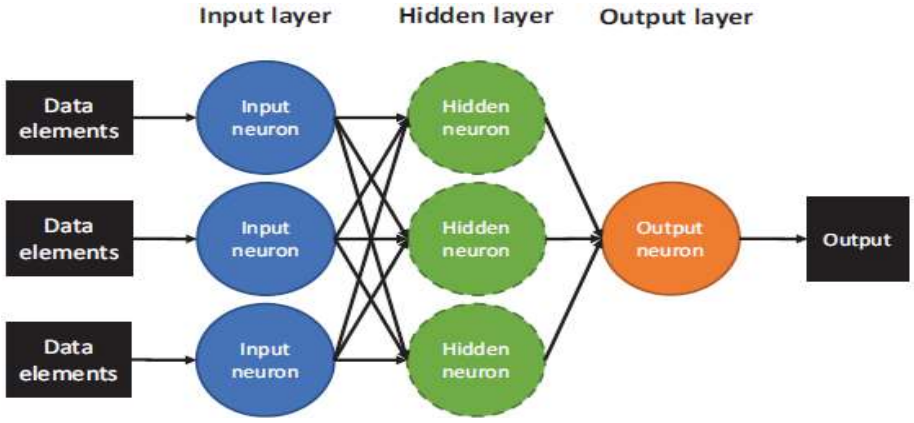

Fig 7: Example of a neural network. A neural network connects several "neurons" (linear models) together, where the outputs form one layer become the inputs for the next. The input layer processes the raw data inputs and then passes the results to the next layer (hidden layer) for additional processing, with the results then passed to the output neuron to obtain the final result.

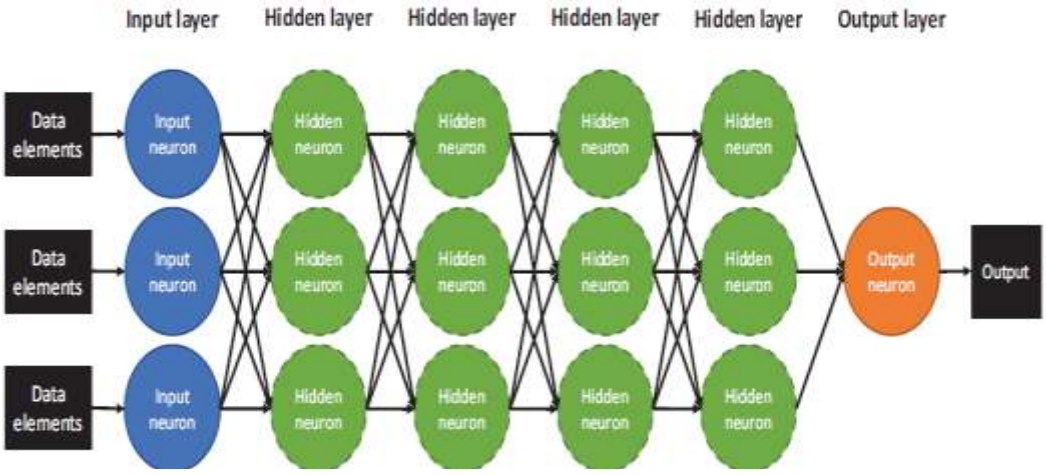

Fig 8: Example of a deep neural network, a subtype of neural networks with multiple hidden layers between the input and output layers. The outputs from one layer of neurons becomes the inputs for the next layer of neurons.

Specific innovations in deep architectures have been responsible for leaps forward in supervised, semi supervised, unsupervised, and reinforcement learning. Deep architectures have the same drawbacks as shallow neural networks but even more so; they require even larger data sets, and it can be even more difficult to visualize and interpret what the network has learned. Nevertheless, the leap in predictive accuracy made possible by deep learning is what has powered the current explosion of interest in machine learning and AI. Deep learning also excels at discovering and modelling very complex hidden variables that we are not able to measure directly. It has been applied to EHR data for predicting in-hospital mortality, 30-day unplanned readmission, prolonged length of stay, and final discharge diagnoses.[69] Other examples include interpreting radiology images[70], predicting acute kidney injury, 26 detecting diabetic retinopathy from images[71], medication adherence using video to confirm medication ingestion[72] and drug discovery.[73,74] Hierarchically, a deep learning model is a specific type of neural network model, which is in turn a subset of all models used in machine learning, which is a sub discipline of the AI field (Fig 9).

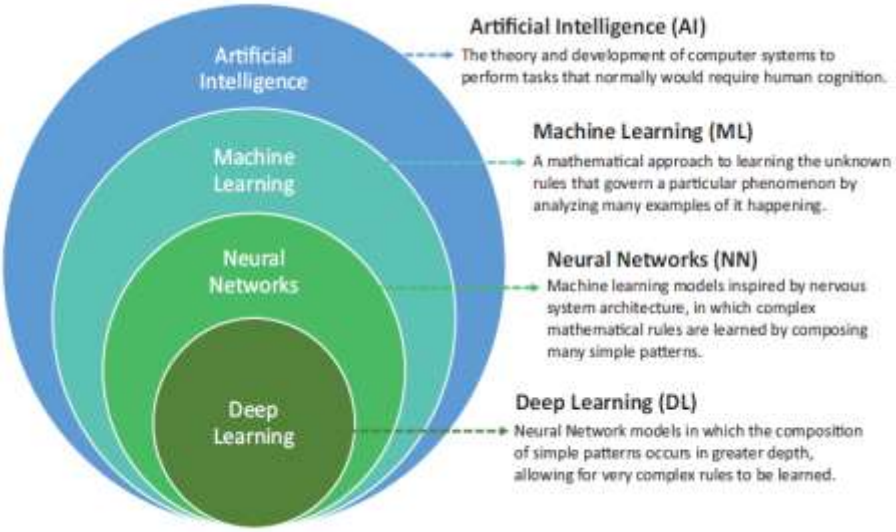

Fig 9: How deep learning fits into the hierarchy of artificial intelligence (AI). Deep learning models represent a specific subset of neural network models, which are in turn a subset of all models used in machine learning, which is a sub-discipline of the AI field.

CONCLUSION AND FUTURE DIRECTIONS

The AI technology is utilized in pharmaceutical industries including ML algorithms and deep learning techniques in daily life. ML techniques in drug development regions and health service centers have encountered numerous conflicts, especially in image analysis and omics data. In medical science, ML models predict the trained data in a known framework i.e., the compound structure can perform alternative tools like PPT inhibitors, macrocycles with traditional algorithms. Additionally, deep learning models can be considered the chemical structures and QSAR models from pharmaceutical data which was pertinent for molecules with appropriate properties, because to the forward success rate in clinical trials. AI technology has taken a forward step in entering into computer-aided drug development to retrieve the powerful capabilities in data mining.[74]

Some issues still existed i.e.,

1. The performance of deep learning methods can directly influence the innovation of datamining because multiple deep neural networks are effectively trained on a large volume of data. The main aim is to tackle the transfer learning automatic problem.
2. “Black-Box” model became confused in deep learning concepts. The Local Interpretable Model-Explanations (LIME) is an example of a counterfactual probe. LIME was utilized to unlock the black-box model. Here, restricted data was mandatory to explain through deep learning models.[65] However, revealing data by deep learning techniques perform only in the initial stages.
3. Many parameters are adjusted during the training period of neural networks but some theoretical and practical frameworks are out of reach to optimize these models.

Future directions

Web innovation was integrated with medical science to improve predictive power in decision- making and deep learning algorithms about biomarkers, side effects in therapies, therapeutic benefits. In clinical trials, success is achieved through the utilization of particular applications. So, motivation is performed for future investment in pharmaceutical companies. In the future, drug discovery and development, looking forward to covering all aspects by AI technology. Automated AI needs to coordinate theoretical results such as chemistry information, omics data, and medical data for emerging. Also, we are anticipating that more confirmations should be rebuilt for the medication revelation campaign.

REFERENCES

1. Forbes Media LLC. Ai and healthcare: a giant opportunity. https://www.forbes.com/ sites/insights-intelai/2019/02/11/ ai-and-healthcare-a-giantopportunity/# 11059a8d4c68. Published, February 11, 2019; Accessed September 2019.
2. Chen JH, Asch SM. Machine learning and prediction in medicine — beyond the peak of inflated expectations. *N Engl J Med;* 2017; 376(26): 2507-2509.
3. Patel VL, Shortliffe EH, Stefanelli M, et al. The coming of age of artificial intelligence in medicine. *Artif Intell Med;* 2009; 46(1): 5-17.
4. Kulikowski CA. Beginnings of artificial intelligence in medicine (AIM): computational artifice assisting scientific inquiry and clinical art – with reflections on present aim challenges. *Yearb Med Inform*, 2019; 28(1): 249-256.
5. Morris KC, Schlenoff C, Srinivasan V. A remarkable resurgence of artificial intelligence and its impact on automation and autonomy. *IEEE Trans Autom Sci Eng;* 2017; 14(2): 407-409.
6. Stead WW. Clinical implications and challenges of artificial intelligence and deep learning. *JAMA;* 2018; 320(11): 1107-1108.
7. Topol EJ. High-performance medicine: the convergence of human and artificial intelligence. *Nat Med;* 2019; 25(1): 44-56.
8. Mak KK, Pichika MR. Artificial intelligence in drug development: Present status and future prospects. Drug Discov Today, 2019; 24(3): 773-80.
9. Hassanzadeh P, Atyabi F, Dinarvand R. The significance of artificial intelligence in drug delivery system design. Adv Drug Deliv Rev; 2019; 151: 169-90.
10. Russel S, Dewey D, Tegmark M. Research priorities for robust and beneficial artificial intelligence. AI Mag; 2015; 36(4): 105-14.
11. Duch W, Setiono R, Zurada JM. Computational intelligence methods for rule-based data understanding. Proc IEEE; 2004; 92(5): 771-805.
12. Dasta JF. Application of artificial intelligence to pharmacy and medicine. Hosp Pharm; 1992; 27(4): 319-22.
13. Jiang F, Jiang Y, Zhi H. Artificial intelligence in healthcare: Past, present and future. Stroke Vasc Neurol, 2017; 2(4): 230-43.
14. Cherkasov A, Hilpert K, Jenssen H, Fjell CD, Waldbrook M, Mullaly SC, *et al*. Use of artificial intelligence in the design of small peptide antibiotics effective against a broad spectrum of highly antibiotic resistant superbugs. ACS Chem Biol; 2009; 4(1): 65-74.
15. Haykin S. Neural Networks: A Comprehensive Foundation, 1st ed. Prentice- Hall PTR. NJ, United State, 1998.
16. Agatonovic-Kustrin S, Beresford R. Basic concepts of artificial neural network (ANN) modeling and its application in pharmaceutical research. J Pharm Biomed Anal, 2000; 22(5): 717-27.
17. Mayr A, Klambauer G, Unterthiner T, Hochreither S. Deep Tox: Toxicity prediction using Deep Learning. Front Environ Sci; 2016; 3: 80.
18. Duch, W. et al. (2007) Artificial intelligence approaches for rational drug design and discovery. Curr. Pharm. Des; 13: 1497–1508.
19. Blasiak, A. et al. (2020) CURATE. AI: optimizing personalized medicine with artificial intelligence. SLAS Technol, 2020; 25: 95–105.
20. Baronzio, G. et al. (2015) Overview of methods for overcoming hindrance to drug delivery to tumors, with special attention to tumor interstitial fluid. Front. Oncol, 2015; 5: 165.
21. Mak, K.-K. and Pichika, M.R. (2019) Artificial intelligence in drug development: present status and future prospects. Drug Discovery Today, 2019; 24: 773–780.
22. Sellwood, M.A. et al. (2018) Artificial intelligence in drug discovery. Fut. Sci; 2018; 10: 2025–2028.
23. Vyas, M. et al. (2018) Artificial intelligence: the beginning of a new era in pharmacy profession. Asian J. Pharm; 2018; 12: 72–76.
24. Silver D, Schrittwieser J, Simonyan K. Mastering the game of Go without human knowledge. Nature, 2017; 550(7676): 354-9.
25. Lakdawala AS, Okafo G, Baldoni J, Palovich M, Sikosek T, Sahni V. Adapting drug discovery to artificial intelligence. Drug Target Rev; 2018; 50-2.
26. Yildirim O, Gottwald M, Schüler P, Michel MC. Opportunities and challenges for drug development: public–private partnerships, adaptive designs and big data. Front Pharmacol, 2016; 7: 461.
27. Mak KK, Pichika MR. Artificial intelligence in drug development: Present status and future prospects. Drug Discov Today, 2019; 24(3): 773-80.
28. Kadurin A, Nikolenko S, Khrabrov K, Aliper A, Zhavoronkov A. druGAN: An advanced generative adversarial autoencoder model for *de novo* generation of new molecules with desired molecular properties *in silico*. Mol Pharm, 2017; 14(9): 3098-104.
29. Baharifar H, Amani A. Size, loading efficiency and cytotoxicity of albumin-loaded chitosan nanoparticles: An artificial neural networks study. J Pharm Sci; 2017; 106(1): 411-7.
30. Asadi H, Rostamizadeh K, Salari D, Hamidi M. 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, 2011; 28(5): 406-16.
31. Li Y, Abbaspour MR, Grootendorst PV, Rauth AM, Wu XY. Optimization of controlled release nanoparticle formulation of verapamil hydrochloride using artificial neural networks with genetic algorithm and response surface methodology. Eur J Pharm Biopharm, 2015; 94: 170-9.
32. Rebouh S, Lefnaoui S, Bouhedda M, Yahoum MM, Hanini S. Neuro-fuzzy modeling of ibuprofen-sustained release from tablets based on different

cellulose derivatives. Drug Deliv Transl Res; 2019; 9(1): 162-77.
33. Huang Y, Yao Q, Zhu C, Zhang X, Qin L, Wang Q. Comparison of novel granulated pellet-containing tablets and traditional pellet-containing tablets by artificial neural networks. Pharm Dev Technol, 2015; 20(6): 670-5.
34. Moussa HG, Husseini GA, Abel-Jabbar N, Ahmad SE. Use of model predictive control and artificial neural networks to optimize the ultrasonic release of a model drug from liposomes. IEEE Transact Nano bio sci; 2017; 16(3): 149-56.
35. Wang Z, He Z, Zhang L, Zhang H, Zhang M, Wen X. Optimization of a doxycycline hydroxypropyl-β-cyclodextrin inclusion complex based on computational modeling. Acta Pharm Sin B; 2013; 3(2): 130-9.
36. Han R, Yang Y, Li X, Ouyang D. Predicting oral disintegrating tablet formulations by neural network techniques. Asian J Pharm Sci; 2018; 13(4): 336-42.
37. Zaki MR, Varshosaz J, Fathi M. Preparation of agar nanospheres: Comparison of response surface and artificial neural network modeling by a genetic algorithm approach. Carbohydr Polym, 2015; 122: 314-20.
38. Zhao F, Lu J, Jin X, Wang Z, Sun Y, Gao D, *et al*. Comparison of response surface methodology and artificial neural network to optimize novel ophthalmic flexible nano-liposomes: Characterization, evaluation, *in vivo* pharmacokinetics and molecular dynamics simulation. Colloids Surf B Biointerf, 2018; 172: 288-97.
39. Güler GK, Eroğlu H. Development and formulation of floating tablet formulation containing rosiglitazone maleate using artificial neural network. J Drug Deliv Sci Technol, 2017; 29: 385-97.
40. Ilić M, Đuriš J, Kovačević I, Ibrić S, Parojčić J. *In vitro-in silico-in vivo* drug absorption model development based on mechanistic gastrointestinal simulation and artificial neural networks: Nifedipine osmotic release tablets case study. Eur J Pharm Sci; 2014; 62: 212-8.
41. Koletti AE, Tsarouchi E, Kapourani A, Kontogiannopoulos KN, Assimopoulou AN, Barmpalexis P. Gelatinnanoparticles for NSAID systemic administration: Quality by design and artificial neural networks implementation. Int J Pharm, 2020; 578: 1-14.
42. Nayak AK, Laha B, Sen KK. Development of hydroxyapatite-ciprofloxacin bone-implants using >> Quality by Design<<. Acta Pharm, 2011; 61(1): 25-36.
43. Nayak AK, Khatua S, Hasnain MS, Sen KK. Development of alginate-PVP K 30 microbeads for controlled diclofenac sodium delivery using central composite design. DARU J Pharm Sci; 2011; 19(5): 356-66.
44. León BJM, González RPL, Arroyo GCM, Cózar-Bernal MJ, Calle SM, Canca OD, *et al*. Artificial neural networks as alternative tool for minimizing error predictions in manufacturing ultradeformable nanoliposome formulations. Drug DevInd Pharm, 2018; 44(1): 135-43.
45. Malakar J, Sen SO, Nayak AK, Sen K K. Preparation, optimization and evaluation of transferosomal gel for transdermal insulin delivery. Saudi Pharm J; 2012; 20(4): 355-63.
46. Bhattacharjee A, Das PJ, Dey S, Nayak AK, Roy PK, Chakrabarti S, *et al*. Development and optimization of besifloxacin hydrochloride loaded liposomal gel prepared by thin film hydration method using 32 full factorial design. Colloids Surf, A: Physicochem Eng Asp; 2020; 585: 124071.
47. Das B, Sen SO, Maji, Nayak AK, Sen K K. Transferosomal gel for transdermal delivery of risperidone: Formulation optimization and *ex vivo* permeation. J Drug Deliv Sci Technol, 2017; 38: 59-71.
48. Manda A, Walker RB, Khamanga SMM. An artificial neural network approach to predict the effects of formulation and process variables on prednisone release from a multipartite system. Pharmaceutics, 2019; 11(3): 109.
49. Khan AM, Hanif M, Bukhari NI, Shamim R, Rasool F, Rasul S, *et al*. Artificial neural network (ANN) approach to predict an optimized pH-dependent mesalamine matrix tablet. Drug Des Devel Ther, 2020; 14: 2435-48.
50. Waghule T, Rapalli VK, Singhvi G, Manchanda P, Hans N, Dubey SK, *et al*. Voriconazole loaded nanostructured lipid carriers based topical delivery system: QbD based designing, characterization, *in-vitro* and *ex-vivo* evaluation. J Drug Deliv Sci Technol, 2019; 52: 303-15.
51. Nayak AK, Das B, Maji R. Calcium alginate/gum Arabic beads containing glibenclamide: Development and *in vitro* characterization. Int J Biol Macromol, 2012; 51(5): 1070-8.
52. Malakar J, Nayak AK, Das A. Modified starch (cationized)-alginate beads containing aceclofenac: Formulation optimization using central composite design. Stärke, 2013; 65(7-8): 603-12.
53. Guru PR, Nayak AK, Sahu RK. Oil-entrapped sterculia gum-alginate buoyant systems ofaceclofenac: Development and *in vitro* evaluation. Colloids Surf B: Biointerf, 2013; 104: 268-75.
54. Nayak AK, Hasnain MS, Malakar J. Development and optimization of hydroxyapatite-ofloxacin implants for possible bone-implantable delivery in osteomyelitis treatment. Curr Drug Deliv, 2013; 10(2): 241-50.
55. Nayak AK, Pal D, Hasnain MS. Development, optimization and *in vitro-in vivo* evaluation of pioglitazone-loaded jackfruit seed starch-alginate beads. Curr Drug Deliv, 2013; 10(5): 608-19.
56. Nayak AK, Pal D. Ionotropically-gelled mucoadhesive beads for oral metformin HCl delivery: Formulation, optimization and antidiabetic evaluation. J Sci Ind Res; 2013; 72: 15-22.

57. Han R, Yang Y, Li X, Ouyang D. Predicting oral disintegrating tablet formulations by neural network techniques. Asian J Pharm Sci; 2018; 13(4): 336-42.
58. Chaibva F, Burton M, Walker RB. Optimization of salbutamol sulfate dissolution from sustained release matrix formulations using an artificial neural network. Pharmaceutics, 2010; 2(2): 182-98.
59. Nayak AK, Pal D. Formulation optimization of jackfruit seed starch-alginate mucoadhesive beads of metformin HCl. Int J Biol Macromol, 2013; 59: 264-72.
60. Nayak AK, Pal D. Blends of jackfruit seed starch-pectin in the development of mucoadhesive beads containing metformin HCl. Int J Biol Macromol, 2013; 62: 137-45.
61. Nayak AK, Pal D, Malakar J. Development, optimization and evaluation of emulsion-gelledfloating beads using natural polysaccharide-blendfor controlled drug release. Polym Eng Sci; 2013; 53(2): 338-50.
62. Nayak AK, Kalia S, Hasnain MS. Optimization of aceclofenac-loaded pectinate-poly (vinyl pyrrolidone) beads by response surface methodology. Int J Biol Macromol, 2013; 62: 194-202.
63. Malakar J, Dutta P, Purokayastha SD, Dey S, Nayak AK. Floating capsules containing alginate-based beads of salbutamol sulfate: *In vitro-in vivo* evaluations. Int J Biol Macromol, 2014; 64: 181-9.
64. Huang Y, Yao Q, Zhu C, Zhang X, Qin L, Wang Q, *et al*. Comparison of novel granulated pellet-containing tablets and traditional pellet-containing tablets by artificial neural networks. Pharm Dev Technol, 2015; 20(6): 670-5.
65. Tishby N, Zaslavsky N (2015) Deep learning and the information bottleneck principle. In: 2015 IEEE Information Theory Workshop (ITW). IEEE, 1–5.
66. Hinton GE, Salakhutdinov RR. Reducing the dimensionality of data with neural networks. *Science*, 2006; 313(5786): 504-507.
67. LeCun Y, Bengio Y, Hinton G. Deep learning. *Nature*, 2015; 521(7553): 436-444.
68. Schmidhuber J. Deep learning in neural networks: an overview. *Neural Netw;* 2015; 61: 85-117.
69. Rajkomar A, Oren E, Chen K, et al. Scalable and accurate deep learning with electronic health records. *NPJ Digit Med;* 2018; 1: 18.
70. McBee MP, Awan OA, Colucci AT, et al. Deep learning in radiology. *Acad Radiol*, 2018; 25(11): 1472-1480.
71. Gulshan V, Peng L, Coram M, et al. Development and validation of a deep learning algorithm for detection of diabetic retinopathy in retinal fundus photographs. *JAMA;* 2016; 316(22): 2402-2410.
72. Labovitz DL, Shafner L, Reyes Gil M, et al. Using artificial intelligence to reduce the risk of nonadherence in patients on anticoagulation therapy. *Stroke*, 2017; 48(5): 1416-1419.
73. Lavecchia A. Deep learning in drug discovery: Opportunities, challenges and future prospects. *Drug Discov Today*, 2019.
74. Schneider G. Automating drug discovery. *Nat Rev Drug Discov;* 2018; 17(2): 97-113.