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Review Article

Review of Machine Learning Technologies and Neural Networks in Drug Synergy Combination pharmacological research

Artur S. Ter-Levonian[1], Konstantin A. Koshechkin[1,2]

1 *I.M. Sechenov First Moscow State Medical University (Sechenov University), 8-2 Trubetskaya St., Moscow 119991, Russia*

2 *Scientific Centre for Expert Evaluation of Medicinal Products of the Ministry of Health of the Russian Federation, 8 Petrovsky Blvd, Moscow 103051, Russia*

Corresponding author: Konstantin A. Koshechkin (koshechkin@expmed.ru)

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Abstract

Introduction: Nowadays an increase in the amount of information creates the need to replace and update data processing technologies. One of the tasks of clinical pharmacology is to create the right combination of drugs for the treatment of a particular disease. It takes months and even years to create a treatment regimen. Using machine learning (in silico) allows predicting how to get the right combination of drugs and skip the experimental steps in a study that take a lot of time and financial expenses. Gradual preparation is needed for the Deep Learning of Drug Synergy, starting from creating a base of drugs, their characteristics and ways of interacting.

Aim: Our review aims to draw attention to the prospect of the introduction of Deep Learning technology to predict possible combinations of drugs for the treatment of various diseases.

Materials and methods: Literary review of articles based on the PUBMED project and related bibliographic resources over the past 5 years (2015–2019).

Results and discussion: In the analyzed articles, Machine or Deep Learning completed the assigned tasks. It was able to determine the most appropriate combinations for the treatment of certain diseases, select the necessary regimen and doses. In addition, using this technology, new combinations have been identified that may be further involved in preclinical studies.

Conclusions: From the analysis of the articles, we obtained evidence of the positive effects of Deep Learning to select "key" combinations for further stages of preclinical research.

Keywords

Deep Learning, drug synergy, informatics, machine learning, neural networks, preclinical study.

Introduction

Pharmacological research is required to develop and market a new, unique drug or a new combination of drugs (Friends of cancer research). They include proof of quality, efficacy, and safety. Studies are carried out at first in the experimental laboratory, then enter a phase of preclinical tests, and further clinical studies are carried out, which are some of the most costly stages of the life cycle, both in terms of finances and time (Koshechkin et al. 2015). One of the most important ways to increase the availability of modern, more efficient, and safer drugs for patients is the reduction of pharmacological research costs without reducing their quality.

Recent advances in technologies have uncovered tremendous therapeutic opportunities, rapidly transforming the field of medicine. For example, molecularly targeted agents aim to exploit key tumor-specific vulnerabilities (Day and Siu 2016) or gene-therapeutic drugs (Ma et al. 2020). While drug combination therapies are a well-established concept in cancer treatment, identifying novel synergistic combinations is challenging due to the size of combinatorial space. However, computational approaches have emerged as a time- and cost-efficient way to prioritize combinations to test, based on recently available large-scale combination screening data (Chen et al. 2017; Li et al. 2017; Jeon et al. 2018; Li et al. 2018).

One of the most advanced methods for optimizing pharmacological research is the introduction of technology for the collection of primary data in digital form. This allows the further use of Machine Learning systems based on Neural Networks for their analysis.

Machine Learning is a technology that allows the Artificial Intelligence to automatically self-study from previous experience without using programming (Expert System 2020; Obermeyer and Emanuel 2016).

Its application is found in almost all spheres of human life. For its operation, it is necessary to create a huge database, data in which are combined into clusters and have a cause-and-effect relationship with one another. Using the experience and knowledge of the scientific community about the methods of interaction and establishing dependencies between them makes it possible to get closer to the exact results of Deep Learning.

Neural Network is a series of algorithms whose purpose is to recognize the main relationships in a data set through a process that simulates the operation of the brain (Investopedia 2020).

Neural Networks can learn high-level features from data to the ensemble-based predictors. By combining deep learning-generated score with only two main ensemble-based functional features, we can achieve superior performance of various Machine Learning classifiers. The synergy of Deep Learning scores and integrated metrics derived from protein sequence conservation scores can allow us to improve treatment development. Machine Learning predictions are leveraged in molecular simulations, protein stability, and network-based analysis to obtain insights about molecular signatures and enhance efficiency (Agajanian et al. 2018; Deist et al. 2018; Agajanian et al. 2019).

While the development of Artificial Intelligence algorithms has been fast paced, the actual use of most Artificial Intelligence algorithms in biomedical engineering and clinical practice is still markedly below its conceivably broader potentials. This is partly because for any algorithm to be incorporated into existing workflows it has to stand the test of scientific validation, clinical and personal utility, application context, and is equitable as well. In this context, there is much to be gained by combining Artificial Intelligence and human intelligence (Sniecinski and Seghatchian 2018; Amisha et al. 2019; Dzobo et sl. 2020).

The aim of our review is to draw attention to the prospect of the introduction of Deep Learning technology to predict possible combinations of drugs for the treatment of various diseases. We tried to assess the feasibility of using digital systems for the collection of primary data and Machine Learning systems for pharmacological research. The evaluation of the software on the market in terms of its applicability to the collection of primary information in digital form during pharmacological studies was carried out. The prospect of using Machine Learning technology for processing the results of pharmacological research has been evaluated.

Materials and methods

A literature review was conducted using the PUBMED electronic database of articles. As part of this review, articles from the last 5 years were used (from 2015 to 2019). The writing of this article was motivated by the introduction of Machine Learning technology to the market and the need to automate pharmacological research to create treatment regimens for various diseases. We analyzed the currently existing processing systems for the drug data set. The following keywords were used to search for articles: “Machine Learning Drug Synergy Combination”, “Neural Network Drug Synergy Combination”, “Machine Learning Drug”, “Deep Learning Drug”, “Deep Synergy Drug”, “Drug Synergy Combination”, “Deep Learning”, “Machine Learning Prediction”, “Deep Learning Prediction”. The research was made using Microsoft Office software based on the Microsoft Windows 10 operating system.

Search strategy

For this review, we searched through the PubMed database. According to PubMed, for example, the first publication for the request “Machine Learning Drug Synergy Combination” was in 2014. Since then, the number of publications grew every year, with 7 publications in 2018 and 8 publications in 2019. And in total, the search returned 22 publications on this request. Upon the request “Neural Network Drug Synergy Combination”, PubMed provided a list of 10 publications, most of which related to

2016–2019 indicating a growing interest in Deep Learning technology to predict possible combinations of drugs for the treatment of various diseases. Only papers that reported results and outcomes were included in this review. We analyzed 238 unique articles, 8 of which were carried out as vivid examples of the use of this technology in the preclinical process.

Study selection

We have limited our review to articles that, in our opinion, are the most significant for assessing the predictive opportunities of neural networks. Only studies about market available systems for the prediction of possible combinations of drugs are included. All the systems are based on data from preclinical studies. All the results provided by systems based on Artificial Neural Network are complementary for major pharmacological studies and were created to speed up research and provide useful hints for scientists. No decisions are proposed to be made on Artificial Neural Network results only.

Results and discussion

Pharmacological studies have the most significant position in the life cycle of a drug. At this stage, researchers receive reliable confirmation of its efficacy and safety, which determines the very possibility of medical use of the drug. Studies determine the therapeutic dosage to avoid toxic effects and ensure maximum effectiveness.

Systems for collecting research results are in digital form on the media and communications market. Their functionality allows such devices, as graphic processing of images, selection of news feeds based on web surfing stories, voice search, etc., to work.

Machine Learning technology is used in several pilot projects in the field of medicine and health care, for example, in ultrasound diagnostics of myositis, using the classification method and ultra-precise Neural Networks, and showed positive results in identifying this nosology (Burlina et al. 2017).

Machine Learning will allow us to find the most beneficial combination for a particular disease. As well as a lower concentration of the drug in combination, which has a low threshold for the onset of toxic effects and has many adverse effects. This creates the opportunity to increase the concentration of those drugs in combination which do not have such high values of toxicity and adverse effects.

Firstly, it is necessary to enter parametric data (predictors of synergy), to create the right combination of drugs using Machine Learning. These are the general data about the drugs: name, chemical structure and substructural profile, pharmacological effects based on the mechanism of drug action, toxic and adverse effects, considering the concentration of injected drugs.

Secondly, the need to create a database of targets for the action of these drugs, violations of which are a trigger in the pathogenesis of diseases, and which will serve as the basis for calculating the minimum dose at which the pharmacological effect occurs, as well as the targets of action of drugs that are not part of the pathogenesis of the disease, but cause adverse effects. Equally important is a toxic dose – this is an amount of the drug the excess of which will cause a toxic effect. Combinations of synergistic drugs will have the same effects, but the dose of the combined drugs will differ from the doses of their components. This is due to the fact that preparations of synergistic action, but with different chemical structures, have different effect-concentration ratios. It is also important to determine the pharmacokinetic properties and methods of administration of drugs, as well as the ability of the drug to accumulate and cross the histohematogetic barriers. The simultaneous use of synergy predictors will allow us to refine our search queries for a combination.

New perspectives open up the use of digital information processing systems when conducting preclinical studies. Machine Learning ”Combination Synergy Estimation” (CoSynE) (Burlina et al. 2017) can predict new synergistic interactions of drugs, as well as reveal hidden antagonism of drugs used in the clinic. For this purpose, it is necessary to create a pool of drugs with known pharmacological effects of the action, taking into account their probable manifestations in the cohort. This is also significant in the practice of clinical pharmacology, where the selected combinations of pharmaceutical preparations are empirically approved without the involvement of computer simulation. To implement the principles of personalized medicine, combinations of different amounts of drugs in a certain dosage can be selected, each of which will be evaluated according to its adverse and toxic effects. In preclinical studies, it is important to note the absence of toxic effects and the desire to reduce adverse effects. It is worth remembering that when combining drugs, summations are not only pharmacological effects, but also side (and toxic) effects. The new system aims to quickly create combinations of drugs that can be effectively used in the human population.

CoSynE is a digital system that allows you to select a successful synergistic combination of antibacterial agents based on their chemical structure (substructural profile), mechanism of action, taking into account the MIC (minimum inhibitory concentration). The advantage of CoSynE is that there is no need to have experimental data on each preparation. The disadvantage of this system is the reluctance to use experimental data.

The study showed that the digital system helped to find 20 synergistic and 28 antagonistic antibiotic pairs among 153 pairs (13% synergy and 18% antagonism).

The INDIGO algorithm (INferring Drug Interactions using chemoGenomics and Orthology) was investigated to select a combination of antibacterial agents in order to overcome the resistance of bacterial cells (Chandrasekaran 2019). In addition to finding the best combination, this approach used the data from chemogenomics – a combination of different genes that determine resistance to antibiotics in bacteria.

This tool can accurately predict the activity of drug combinations, including synergy, where the activity of the combination is greater than the sum of the individual drugs. It also accurately predicts antagonism between drugs, where the activity of the combination is less. In addition, it also identifies the genes that control these drug responses.

Among the combinations, INDIGO identified a five-drug combination of tuberculosis drugs –Bedaquiline, Clofazimine, Rifampicin, Clarithromycin with the antimalarial drug P218 – as showing a strong likelihood of effectiveness against tuberculosis. A combination of antibiotics Moxifloxacin, Spectinomycin, two drugs that are typically antagonistic, can be made highly synergistic by the addition of a third drug – Clofazimine.

All three groupings were in the top .01% of synergistic combinations identified by INDIGO. Successful combinations identified by INDIGO, when tested in a lab setting, showed synergy in 88.8% of cases.

In the practice of treating oncological diseases, a group of US scientists created the NCI ALMANAC database (Holbeck et al. 2017; Xia et al. 2018) (NCI – A Large Matrix of Anti-Neoplastic Agent Combinations) – "A large matrix of combinations of antitumor agents", in order to create a combination of drugs with the best antitumor activity. The use of synergistic effects of chemotherapy drugs, which have different points of application of their action, will allow avoiding overdosing and toxic effects with their single use, as well as immunological and metabolic disorders. Tumor cells have high mutational variability, which may mean the ability to enhance resistance to a particular drug.

In that study, a total of 2620 drug combinations matrices of drug concentrations for 4×4 were screened in 60 cancer cell lines to generate 3.04 million data points for the NCI ALMANAC database. The authors confirmed in vitro a synergistic drug interaction flagged in the drug combinations high-throughput screening between the vinca alkaloid microtubule assembly inhibitor vinorelbine (Navelbine) tartrate and the epidermal growth factor receptor tyrosine kinase inhibitor gefitinib (Iressa) in the SK-MEL-5 melanoma cell line. 75% of the drug combinations examined on the screen are not currently in the clinical trial database. Selected synergistic drug interactions flagged in the drug combinations high-throughput screening were subsequently confirmed in vitro, evaluated mechanistically, and were shown to have greater than single-agent efficacy in mouse xenograft human cancer models. Enrollment is open for two clinical trials for drug combinations that were identified in the drug combinations high throughput screening. The NCI ALMANAC database, therefore, constitutes a valuable resource for selecting promising drug combinations for confirmation, mechanistic studies, and clinical translation.

A more up-to-date system was developed by UK scientists and is called DeepSynergy (Preuer et al. 2018). DeepSynergy is a means of finding new synergistic combinations of drugs. Researchers at the Institute of Bioinformatics (Austria) presented an application that can predict combinations of anticancer drugs for a specific cancer cell line using Machine Learning. For the example of this software, 39 cell lines, 14 experimental, and 24 approved anticancer drugs with different structures and targets of action were used. The results of this method showed high prognostic efficiency and an average Pearsen correlation coefficient when compared with other methods of Machine Learning. Indicators of synergy are estimated by the Loewe method, the values of which are between -327 and 179. When using them in practice, positive were the combinations, the values of which were higher than 30.

DeepSynergy uses chemical and genomic information as input information, a normalisation strategy to account for input data heterogeneity, and conical layers to model drug synergies. DeepSynergy was compared to other Machine Learning methods, such as Gradient Boosting Machines, Random Forests, Support Vector Machines, and Elastic Nets on the largest publicly available synergy data set with respect to mean squared error. DeepSynergy significantly outperformed the other methods with an improvement of 7.2% over the second best method to predict novel drug combinations within the space of explored drugs and cell lines. At this task, the mean Pearson correlation coefficient between the measured and the predicted values of DeepSynergy was 0.73. Applying DeepSynergy for the classification of these novel drug combinations resulted in high predictive performance of an AUC of 0.90. All compared methods exhibit low predictive performance when extrapolating to unexplored drugs or cell lines.

The purpose of the introduction of digital systems is to automate the processes of laboratory work. Digital systems replace paper protocols. Numerical data and parameters, as well as the contents of the protocols, must be entered into programs, such as Microsoft Excel, GraphPad Prism and others for analysis, but this process is lengthy and time consuming, therefore, using primary electronic documentation will allow you to preserve the original material, such as confirmation of this study, and instantly translate it into other programs for simultaneous analysis. There is also the possibility of indexing the contents of the protocols and accelerating the use of the received data.

Primary electronic laboratory protocols solve the problem of creating a primary substrate for an in-depth analysis through Neural Networks and Machine Learning. The use of this technique by the scientific community in its practice will allow us to accelerate the process of scientific research, as well as to predict the success of scientific work. This creates an opportunity to save financial resources. Another direction within the framework of this issue is the creation of an electronic indexing system not only for the titles of scientific articles, but their contents, which will be based on a specific programming language with many dictionaries and the creation of Big Data with the possibility of a meta-analysis of the results of scientific works. Compliance with laboratory information management requirements is required. For example, Principles of Good Laboratory Practice (GLP) contain principles for the study of drugs in non-clinical studies using computerized systems.

Since the ongoing research will focus on combinations of drugs with extensive clinical histories, according to the major guidelines, preclinical studies on toxic effects are not necessary. Since we will study the combinations with different effects, it is advisable to conduct them in vivo in order to confirm or adjust the dose of the drugs administered in one combination, their pharmacological, adverse and toxic effects at different doses.

In Russia, many companies are automating their laboratories, but there are many flaws in this process. Since companies employ personnel who lack adequate biological and medical background, the possibilities for reforming these programs are very limited. Digital systems for medical and pharmacological purposes should not only provide the possibility of their registration, but also further use for processing by applying complex mathematical formulas and involving medical statistics. The 1C program, which is widely used in the health care system; is limited to accounting tasks.

Conclusions

The introduction of Deep Learning with the use of various methods of classifying and clustering information will help to improve pharmaceutical production in the search for a suitable combination of drugs to treat various human pathologies. Also, this technology can become an auxiliary tool in the further study of the effects of drugs on the body and in the identification of new targets of their action.

Conflict of interests

The authors declare no conflict of interests.

References

- Agajanian S, Odeyemi O, Bischoff N, Ratra S, Verkhivker GM (2018) Machine learning classification and structure-functional analysis of cancer mutations reveal unique dynamic and network signatures of driver sites in oncogenes and tumor suppressor genes. Journal of Chemical Information and Modeling 58(10): 2131–2150. https://doi.org/10.1021/acs.jcim.8b00414 [PubMed]
- Agajanian S, Oluyemi O, Verkhivker GM (2019) Integration of random forest classifiers and deep convolutional neural networks for classification and biomolecular modeling of cancer driver mutations. Frontiers in Molecular Biosciences 6: 44. https://doi.org/10.3389/fmolb.2019.00044 [PubMed] [PMC]
- Amisha, Malik P, Pathania M, Rathaur VK (2019) Overview of artificial intelligence in medicine. Journal of Family Medicine and Primary Care 8(7): 2328–2331. https://doi.org/10.4103/jfmpc.jfmpc_440_19 [PubMed] [PMC]
- Burlina P, Billings S, Joshi N, Albayda J (2017) Automated diagnosis of myositis from muscle ultrasound: Exploring the use of machine learning and deep learning methods. PLoS One 12(8): e0184059. https://doi.org/10.1371/journal.pone.0184059 [PubMed] [PMC]
- Chandrasekaran S (2019) Predicting drug interactions from chemogenomics using INDIGO: Methods and Protocols, 219–231. https://doi.org/10.1007/978-1-4939-8891-4_13
- Chen G, Tsoi A, Xu H, Zheng WJ (2018) Predict effective drug combination by deep belief network and ontology fingerprints. Journal of Biomedical Informatics 85: 149–154. https://doi.org/10.1016/j.jbi.2018.07.024 [PubMed]
- Day D, Siu LL (2016) Approaches to modernize the combination drug development paradigm. Genome Medicine 8(1): 115. https://doi.org/10.1186/s13073-016-0369-x [PubMed] [PMC]
- Deist TM, Dankers FJWM, Valdes G, Wijsman R, Hsu IC, Oberije C, Lustberg T, van Soest J, Hoebers F, Jochems A, El Naqa I, Wee L, Morin O, Raleigh DR, Bots W, Kaanders JH, Belderbos J, Kwint M, Solberg T, Monshouwer R, Bussink J, Dekker A, Lambin P (2018) Machine learning algorithms for outcome prediction in (chemo)radiotherapy: An empirical comparison of classifiers. Medical Physics 45(7): 3449–3459. https://doi.org/10.1002/mp.12967 [PubMed] [PMC]
- Dzobo K, Adotey S, Thomford NE, Dzobo W (2020) Integrating artificial and human intelligence: a partnership for responsible innovation in biomedical engineering and medicine. OMICS: A Journal of Integrative Biology 24(5): 247–263. https://doi.org/10.1089/omi.2019.0038 [PubMed]
- Expert System (2020) What is machine learning? A definition – expert system. https://expertsystem.com/machine-learning-definition/
- Friends of cancer research: Opportunities for combination drug development: data sources and innovative strategies to assess contribution of components. https://www.focr.org/publications/opportunities-combination-drug-development-data-sources-and-innovative-strategies
- Holbeck SL, Camalier R, Crowell JA, Govindharajulu JP, Hollingshead M, Anderson LW, Polley E, Rubinstein L, Srivastava A, Wilsker D, Collins JM, Doroshow JH (2017) The national cancer institute ALMANAC: a comprehensive screening resource for the detection of anticancer drug pairs with enhanced therapeutic activity. Cancer Research 77(13): 3564–3576. https://doi.org/10.1158/0008-5472.CAN-17-0489 [PubMed] [PMC]
- Investopedia (2020) Neural network definition. https://www.investopedia.com/terms/n/neuralnetwork.asp
- Jeon M, Kim S, Park S, Lee H, Kang J (2018) In silico drug combination discovery for personalized cancer therapy. BMC Systems Biology 12(2): 16. https://doi.org/10.1186/s12918-018-0546-1 [PubMed] [PMC]
- Koshechkin KA, Olefir YuV, Merkulov VA (2015) Management of Information Support for the Life Cycle of Drugs. Concepts of Using Elements of CALS/PLM Technologies for Information support of the Drug Life Cycle. Moscow, 284 pp. [in Russian]
- Li H, Li T, Quang D, Guan Y (2018) Network propagation predicts drug synergy in cancers. Cancer Research 78(18): 5446–5457. https://doi.org/10.1158/0008-5472.CAN-18-0740 [PubMed]
- Li X, Xu Y, Cui H, Huang T, Wang D, Lian B, Li W, Qin G, Chen L, Xie L (2017) Prediction of synergistic anti-cancer drug combinations based on drug target network and drug induced gene expression profiles. Artificial Intelligence in Medicine 83: 35–43. https://doi.org/10.1016/j.artmed.2017.05.008 [PubMed]

- Ma CC, Wang ZL, Xu T, He ZY, Wei YQ (2020) The approved gene therapy drugs worldwide: from 1998 to 2019. Biotechnology Advances 40: 107502. https://doi.org/10.1016/j.biotechadv.2019.107502 [PubMed]
- Obermeyer Z, Emanuel EJ (2016) Predicting the future – big data, machine learning, and clinical medicine. The New England Journal of Medicine 375(13): 1216–1219. https://doi.org/10.1056/NEJMp1606181 [PubMed] [PMC]
- Preuer K, Lewis RPI, Hochreiter S, Bender A, Bulusu KC, Klambauer G (2018) DeepSynergy: predicting anti-cancer drug synergy with deep learning. Bioinformatics 34(9): 1538–1546. https://doi.org/10.1093/bioinformatics/btx806 [PubMed] [PMC]
- Sniecinski I, Seghatchian J (2018) Artificial intelligence: a joint narrative on potential use in pediatric stem and immune cell therapies and regenerative medicine. Transfusion and Apheresis Science 57(3): 422–424. https://doi.org/10.1016/j.transci.2018.05.004 [PubMed]
- Xia F, Shukla M, Brettin T, Garcia-Cardona C, Cohn J, Allen JE, Maslov S, Holbeck SL, Doroshow JH, Evrard YA, Stahlberg EA, Stevens RL (2018) Predicting tumor cell line response to drug pairs with deep learning. BMC Bioinformatics 19(S18): 486. https://doi.org/10.1186/s12859-018-2509-3 [PubMed] [PMC]

Author contributions

- **Artur S. Ter-Levonian,** student, Digital Health Institute, Department of Information and Internet Technologies, e-mail: terlevonian@gmail.com, **ORCID ID** https://orcid.org/0000-0001-6762-8482. The author contributed to the project validation plan, performed search and selection of the publications, validated the methodology, conducted the analytical assessments, interpreted the results, and wrote the manuscript. Both the authors have read and approved of the present manuscript.

- **Konstantin A. Koshechkin**, PhD, Assistant Professor , Digital Health Institute; Head of Information Technology Department, Centre for Expert Evaluation of Medicinal Products e-mail: koshechkin@expmed.ru, **ORCID ID** https://orcid.org/0000-0001-7309-2215. The author designed the study and analytical set-up, validated the methodology, interpreted the results, and wrote the manuscript. Both the authors have read and approved the present manuscript.