Application of Artificial intelligence in medicine A Deep Learning Approach to Antibiotic Discovery

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***Abstract*—In this report, we discuss the application of artificial intelligence to discover the new antibiotic - Halicin. Halicin is found to inhibit Mycobacterium tuberculosis, Carbapenem-resistant Enterobacteriaceae, Acinetobacter baumannii, and P. aeruginosa. Halicin complexes with iron in solution, thereby dissipates the transmembrane pH potential of the pathogens and thus kills the pathogens. We could expect more potential drugs to be discovered.**

***Index Terms*—Artificial intelligence, deep learning, antibiotic**

I. Introduction

One survey company drilled into what AI means to various people, one of two operating perspectives is usually at play. [1] First perspective is that AI is coming to take our jobs. People fear that AI will gain awareness of itself and begin to act with its own survival and interests in mind. Second perspective on AI says that the technology will enhance humanity. AI would make smarter decisions than us in diverse fields.

However, to most of the engineers, AI isn't either of those things. Since AI is just rule-based system, it only completes specific tasks. It is still a long way from delivering on the more extravagant claims that some have made for it. We won't need to worry about AI taking away our jobs or even invading our world. But we also cannot expect AI to solve all of our problems. What we have to do now is understanding it and benefiting from it.

Hence, in this report, I would like to introduce applications of AI in Medicine. Hope the medical students to better understand the future trends.

II. Application of artificial intelligence in medicine

Figure 1 shows the number of publications in healthcare industry in the last 20 years. [2] We could found growing research interest in the application of AI in the biomedicine area. Among them, four aspects are particularly prominent: machine learning, intelligent robots, image recognition, and expert system.

Machine learning is an algorithm automatically learns through the input data and builds a model based on the input data to accurately predict new data. For example, machine learning are used in predicting idiopathic peptic ulcer rebleeding and severe hand-foot-mouth disease with better sensitivity and specificity. [3] However, the black box problem of machine learning needs to be resolved. Black box means that machine learning hides its internal structure from the user.

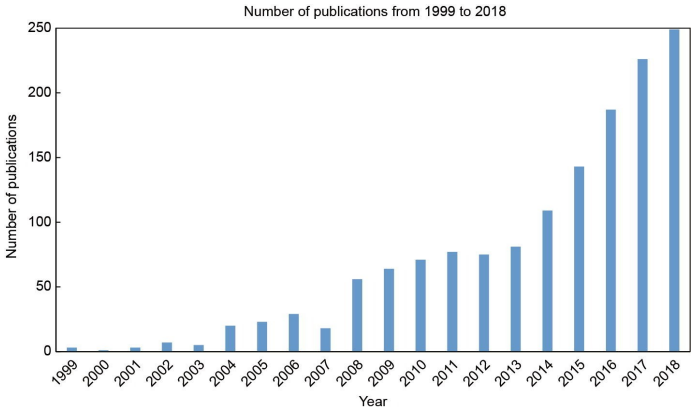

Figure 1. The number of publications in healthcare industry in the last 20 years.

By resolving the problem, the accuracy and computing power of machine learning can be improved and its application range can be expanded.

III. Antibiotic discovery

Last year, a research team in MIT used deep learning approaches to predict molecules with antibacterial activity. [4] We all know that discovering new antibiotics becomes more and more difficult. Two reasons account for this problem. Antibiotic-resistant pathogens and lack of economic incentives. However, in this study, we see a ray of hope

Modern approaches to antibiotic discovery often include screening large chemical libraries for those that elicit a phenotype of interest. These screens, which are upper bound by hundreds of thousands to a few million molecules, are expensive, time consuming, and can fail to capture an expansive breadth of chemical space. In contrast, machine learning approaches afford the opportunity to rapidly and inexpensively explore vast chemical spaces in silico. The differences between two ways is showed in Figure 4

In this paper, they constructed a deep neural network model by building a molecular representation based on a specific property, in their case the inhibition of the growth of E. coli, and using a directed message passing approach. They first trained their neural network model using a collection of 2,335 diverse molecules for those that inhibited the growth of E. coli. They optimized the model by augmenting with a set of molecular features, hyperparameter optimization, and

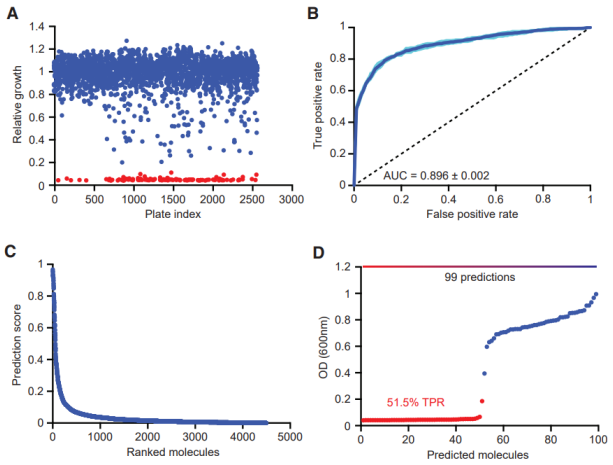

Figure 2.
(A) screening data for growth inhibition of E. coli by 2,560 molecules within the FDA-approved drug library supplemented with a natural product collection.
(B) ROC-AUC plot evaluating model performance after training.
(C) Rank-ordered prediction scores of Drug Repurposing Hub molecules that were not present in the training dataset.
(D) The top 99 predictions from the data shown in (C) were curated for empirical testing for growth inhibition of E. coli.

ensemble methods. Next, they applied the model to multiple chemical libraries to identify potential compounds with activity against E. coli. For example, Drug Repurposing Hub with 6111 molecules. After ranking the candidates according to the model's predicted score, they selected a list of promising candidates. Among these 99 candidates from Drug Repurposing Hub, 51 molecules were validated as true positives based on a cut-off of OD600 <0.2. The last step, they considered the toxicity, clinical phase of the molecule. Finally, one molecule qualified all the strict conditions. That was Halicin. Figure 2 shows some details of the process.

Originally, Halicin is researched for the treatment of diabetes, but development was not continued for this application due to poor results in testing. And know, this deep learning model found its potential to inhibit the pathogen. The structure of Halicin is showed in figure 3. Its MIC against E. coli is about 2ug/ml. And it is a bactericidal antibiotics. It functions through an uncommon mechanism of action, thus, few chances for bacteria to become Halicin-resistant. Halicin could inhibit Mycobacterium tuberculosis, Carbapenem-resistant Enterobacteriaceae (CRE), Acinetobacter baumannii, and P. aeruginosa. These pathogens are regarded by the WHO as the bacteria that most urgently require new treatments. Figure 2 shows MIC of halicin against these pathogens.

This paper also tried to realize the mechanism of Halicin. They first observed in RNA sequencing that a rapid downregulation of genes involved in cell motility across all concentrations, and upregulation of genes required for iron homeostasis at sublethal concentrations. This means that Halicin probably destroys the proton motive force, which results in the death of

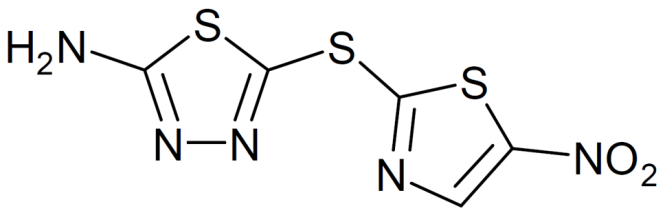

Figure 3. Sturcture of Halicin

cell.

They further verified this hypothesis. They found that the potency of Halicin decreased as pH increased. And they also applied disc3 to Halicin experiment. And thet conclude that, Halicin complexes with iron insolution, thereby dissipates the transmembrane pH potential.

It is worth mentioning that this molecule is similar to the one of Daptomycin. However, Daptomycin-resistant pathogens like S. aureus didn't confer cross-resistance to Halicin.

IV. Conclusion and Discussion

The development of new approaches that can substantially decrease the cost and increase the rate of antibiotic discovery is essential. And Halicin is the world's first new class of antibiotics to be discovered from scratch using artificial intelligence. There are more potential drugs in other chemical libraries waiting for us to do more experiment. However, although this approach seems successful, we still need to emphasize on that maching lerning is imperfect. We still need plenty of approaches to construct an appropriate experimental designs for antibiotic discovery.

Acknowledgment

The pictures in this report are from [2], [3], [4]. Thanks to these predecessors' research, which allows us to better understand the cross-field integration of medicine and computer science.

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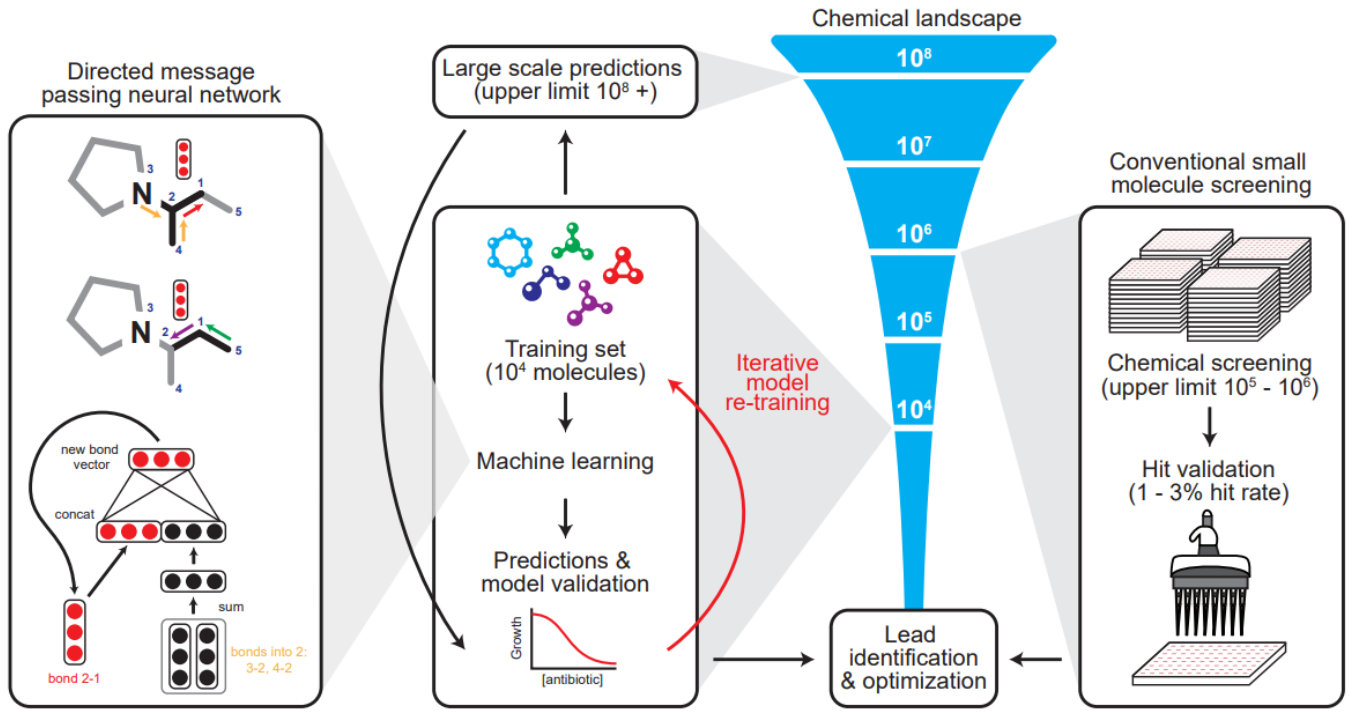

Figure 4. Conventional ways to find drugs are expensive and time consuming. However, with the aid of maching learning, we could capture an expansive breadth of chemical space.

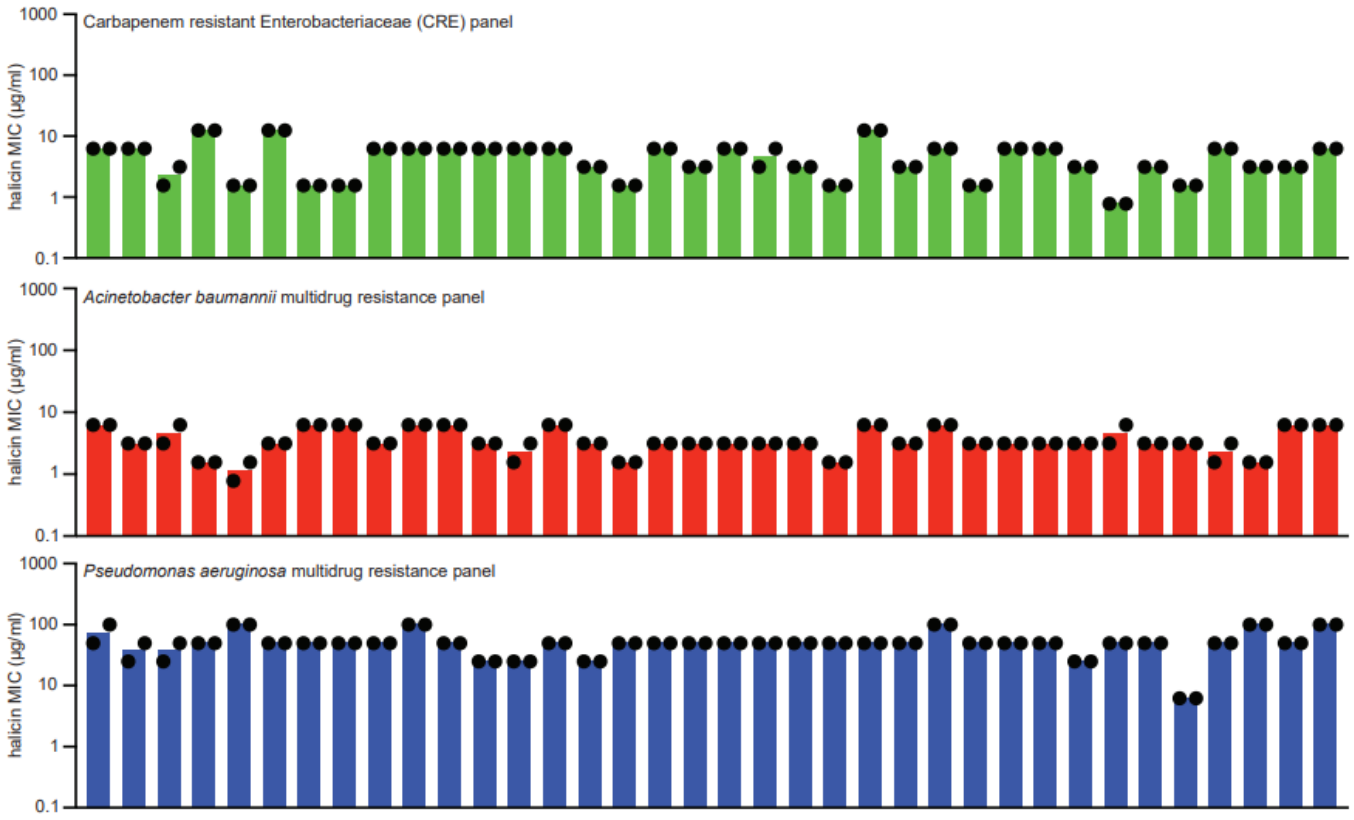

Figure 5. MIC of halicin against 36-strain panels of CRE isolates (green), A. baumannii isolates (red), and P. aeruginosa isolates (blue). Experiments were conducted with two biological replicates.