The problem and potential solution of combining drugs

January 10 2017

Drugs are combined in endless ways—chemotherapy and anti-nausea pills; Advil and multivitamins; blood pressure medication and anti-depressants. Include treatments such as the herbs and acupuncture of traditional Chinese medicine, and the number of arrangements increases further.

How do all of these things work together? Could they work together better? Does this improvement change for different patients?

To begin answering those questions, a team of scientists published a paper summarizing how to best model the variables of drug combinations to determine ideal dose and efficacy. The results were published in *IEEE/CAA Journal of Automatica Sinica* (*JAS*).

"The ultimate purpose of drug combination is the precision medication [for] the patients. Precision medicine is a rather new concept... the studies of transformation from theory to practice are still in progress," said Prof. Xianting Ding and Boqian Wang, researchers at the School of Biomedical Engineering at the Shanghai Jiao Tong University. "We hope that our work can guide the determination of algorithms and their parameters when we optimize drug combinations for patients."

The researchers found that the common method of modeling the relationship between the efficacy and dose of the drugs based on experimental observations worked, but only up to a point.

As the number of variables increases, the interaction prediction becomes significantly less accurate. With more variables, the algorithm is less able to separate out random errors, which muddies the results. This lapse is called overfitting.

"The danger of overfitting in modeling can be very serious in drug combination optimization as it directly leads to errors in fitting the dose-efficacy function," said Wang. "Such errors will bring about mistakes in the results of optimization, thus causing improper treatments [for] the patients."

The scientists cross-validated their analysis by examining the effect of eight chemotherapeutic drugs on three lung cancer cell lines, with the goal of seeing how different types of drugs might work to kill different types of cancer cells at the same time. A total of 59 combinations were tested, with three different doses from each drug. They also examined extracts commonly used in traditional Chinese medicine, and their effects on lung cancer cell lines.

The researchers found that, especially in combinations with more than six drugs, models with only observations for two variables work best. Anything higher increases the risk of overfitting.

"These algorithms can be used to optimize almost all kinds of drug combinations, even combinations of biological molecules like growth factors," Wang said.

More information: B. Q. Wang, X. T. Ding and F. Y. Wang. "Determination of polynomial degree in the regression of drug combinations," *IEEE/CAA Journal of Automatica Sinica*, vol. 4, no. 1, pp. 26-32, Jan. 2017.

Provided by Chinese Association of Automation