EDITORS' CHOICE COMPUTER MODELING

Pairing the right ingredients for the perfect drug cocktail

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Developing new drugs is not the only way to make advances in disease treatment. In many cases, a combination of existing drug therapies is not only more effective than monotherapy but also requires lower doses—thus reducing side effects—and prevents the development of drug resistance. But there's a catch: exponential explosion. To consider the combination therapy of 10 drugs at four doses each, one million experiments would need to be conducted. This requires precious human samples, and all combinations must eventually be tested in people.

Existing computer models of combination drug therapy exclude the effects of drug interactions, are overly sensitive to noise in experimental data, and have too many free parameters. Therefore, Zimmer *et al.* developed and tested a mechanism-free mathematical model that uses limited experimental data to refine the list of promising drug combinations. To model antagonistic and synergistic interactions for three or more drugs, the investigators leveraged the assumption that a combination can be modeled from data on the effect of individual components and of all possible pairwise interactions, without needing to consider higher-order interactions. Their model requires dose-response curves for single drugs and pairwise combinations measured at a handful of concentrations. This new formula more accurately predicted the in vitro effects of triple-drug chemotherapy and of triple- and quadruple-antibiotic mixtures when compared with existing models, especially when antagonism was present. The remarkable performance implies that interactions between pairs are not affected by the presence of other drugs.

The model offers more than a prediction of combinatorial effects: By assessing the sensitivity of the results to reductions in model complexity, the model can also provide hypotheses about how drugs interact. This information may lead to improved drug combinations or more efficient therapies. Finding the minimum doses of medications required to achieve a targeted effect is also beneficial in decreasing side effects. This new computer model will help maximize the return on investments into our current drug arsenal by realizing the untapped potential of multidrug regimens.

A. Zimmer *et al.*, Prediction of multidimensional drug dose responses based on measurements of drug pairs. *Proc. Natl. Acad. Sci. U.S.A.* 10.1073/pnas.1606301113 (2016).[Full Text]