文献报告

Prediction of multidimensional drug dose responses based on measurements of drug pairs

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内容摘要

- 提出了一种的新的有效的数学模型dose model来预测multidrug combinations 组合药物的药效；

- 通过用dose model和已存在的三种其他方法bliss，Lserliss，regression来进行比较，用R^2来评价预测结果的好坏；

- 发现了组合药物中的一种继承制度来描述药物之前的协同作用或者抵抗作用等；

背景

- 组合药物的优点

  在最小的剂量下增加药效；
  减少副作用和毒性；
  最小化出现耐受的可能性；

- 组合药物的实验筛选是非常大的工作量，随着药物和剂量的变化呈指数增加

  D^N measurements for N drugs and D doses

- 现有的数学模型

  1、Bliss independent model（Bliss）

  g12=g1*g2
  ignore the synergism and antagonis

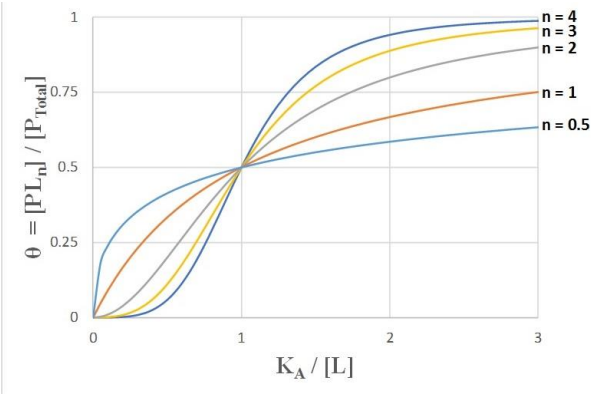
  2、machanism-independent model（Lserliss）
  for antibiotics by Wood et al.
  Lserliss-like formula example for triplet
  $g_{123} = g_{12}g_3 + g_{13}g_2 + g_{23}g_1 - 2g_1g_2g_3$.

  3、machine learning algorithms（Regression）

  use regression and require interation cycle can avoid local maxima

$$g_i = \frac{1}{1 + (D_i/D_{0_i})^{ni}}.$$

WIKI:Dose–response relationship



Wiki：Hill equation

注释：

dose–response curve

ni=Hill coefficient

D_0 = a halfway point D_0,
equal to the drug concentration of 50% effect

Model

$$g_{1\ldots n} = g_1(D_{1eff}) \cdot g_2(D_{2eff}) \cdots g_n(D_{neff})$$

$$D_{ieff} = D_i \prod_{j \neq i} \left(1 + a_{ij} \frac{D_{jeff}/D_{0j}}{1 + D_{jeff}/D_{0j}}\right)^{-1}.$$

Eg:对于两种药物组合 $g_{12} = g_1(D_{1eff}) g_2(D_{2eff})$.

$$D_{1eff} = \frac{D_1}{\left(1 + a_{12} \frac{D_{2eff}/D_{02}}{1 + D_{2eff}/D_{02}}\right)}; \quad D_{2eff} = \frac{D_2}{\left(1 + a_{21} \frac{D_{1eff}/D_{01}}{1 + D_{1eff}/D_{01}}\right)}.$$

Methods

Regression Model. Machine learning approaches often use regression models. A commonly used regression formula employs the variables $x_i = 0$ or 1 that denote the absence or presence of drug i in the mixture. The effect of the mixture g is described in the model as $\log(g) = \sum b_i x_i + \sum c_{ij} x_i x_j$. The parameters b_i and c_{ij} are fit from single and pair data. For triplets, the equivalent formula is $g_{123} = g_{12} g_{13} g_{23} / g_1 g_2 g_3$. For quadruplets, $g_{1234} = g_{12} g_{13} g_{14} g_{23} g_{24} g_{34} / (g_1 g_2 g_3 g_4)^2$.

Estimation of Model Parameters. We determine the values and confidence intervals of the model parameters (n_i, D_{0i}, and a_{ij}) using the MATLAB function "fit." We use the single-drug dose–response curve to estimate the values and uncertainty of n_i and D_{0i} for each drug. The interaction parameters a_{ij} are determined by the two-drug response matrix. In the process of fitting a_{ij}, we allow n_i and D_{0i} to change within their uncertainty estimated from the single-drug measurements.

Computation of Effective Doses in the Model. In the general case $a_{ij} \neq 0$, we determine the effective dose by numerically solving Eq. 2 using the MATLAB function "fmincon." When there exists a hierarchy between the drugs in the combination and $\{a_{ij} = 0 | a_{ji} = 0\}$, there is an analytic solution to Eq. 2 that one can use instead of a numerical solution

$$D_{1eff} = D_1; \; D_{ieff} = D_i \prod_{j \neq i} \left(1 + a_{ij} \frac{D_{jeff}/D_{0j}}{1 + D_{jeff}/D_{0j}}\right)^{-1}.$$

a quadratic number of measurements, $N \cdot D + cN(N-1)/2$, where c is ~10.

This means that forN = 6 drugs and D = 8 doses, we need only 198 measurements instead of $DN \approx 3 \cdot 105$.

For N = 10 drugs and D = 8 doses, we need only 530 measurements instead of ~109.

实验 1. 三种药物组合： doxorubicin, taxol, and cisplatin.(阿霉素, 紫杉酚, 顺铂 皆是肿瘤药物)

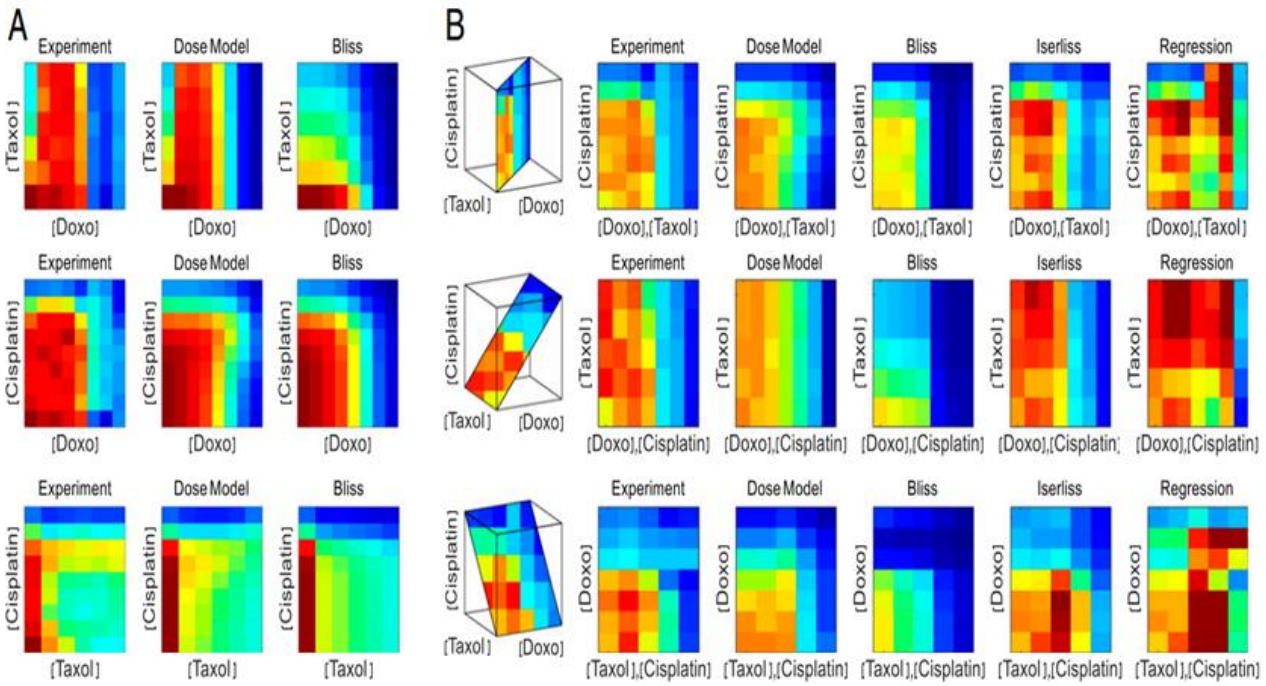


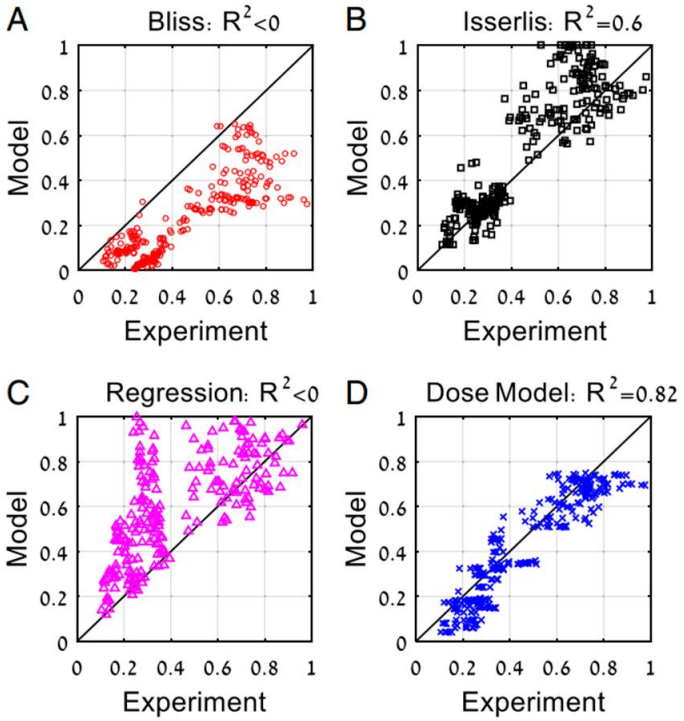
Fig. 1. Response matrix of three chemotherapy drugs at eight doses shows nonmonotonic behavior that is well captured by the dose model but not by other models. (*A*) Survival of A549 lung cancer cells when treated with the three pairs of drugs (taxol–doxorubicin, cisplatin–doxorubicin, cisplatin–taxol) at eight doses each: (*Left*) the measured response, (*Middle*) the predicted response using the present dose model, and (*Right*) the predicted response by Bliss independence. (*B*) Slices of the three-drug dose–response matrix. The first column is the measured response, followed by the prediction of the three drugs' interactions using different models. Note that the Isserlis and regression models apply only to triplets and above, not to pairs.

$R^2 = 1 - \sum(\text{Model} - \text{Experiment})/\text{var}(\text{Experiment})$ can yield negative values when the mean model prediction is different from the mean experimental measurement, indicating a very poor fit

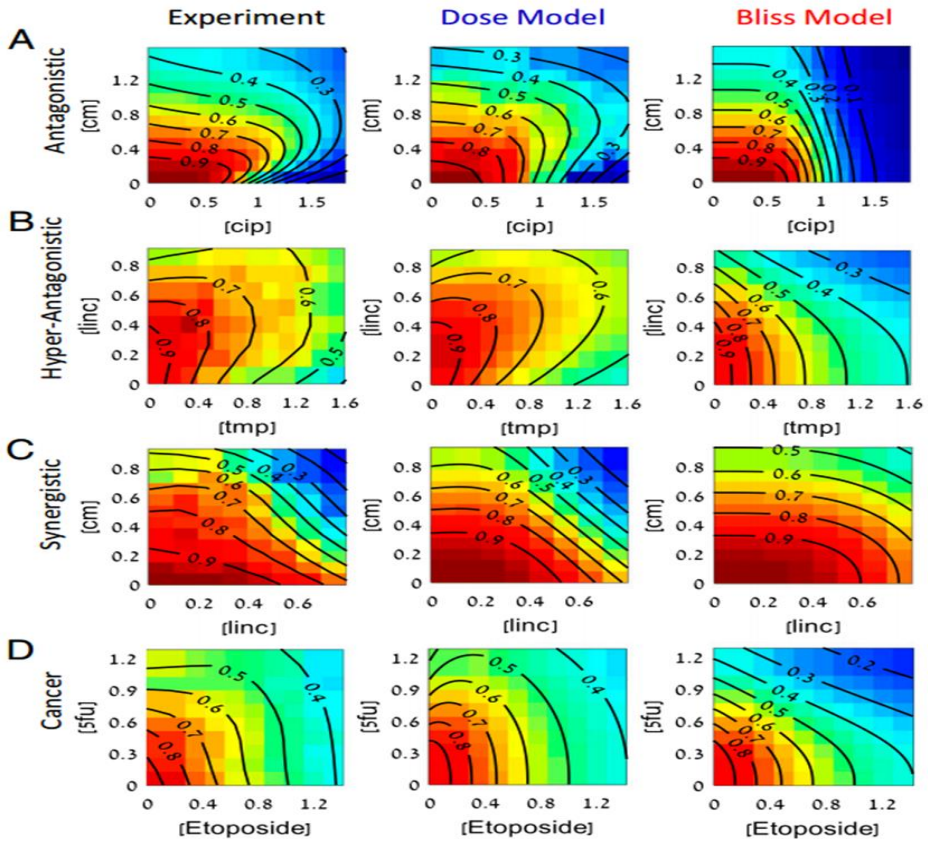
g123(D1, D2, D3) = g1(D1)g2(D2)g3(D3).

g123 = g12g3 +g13g2 + g23g1 − 2g1g2g3.

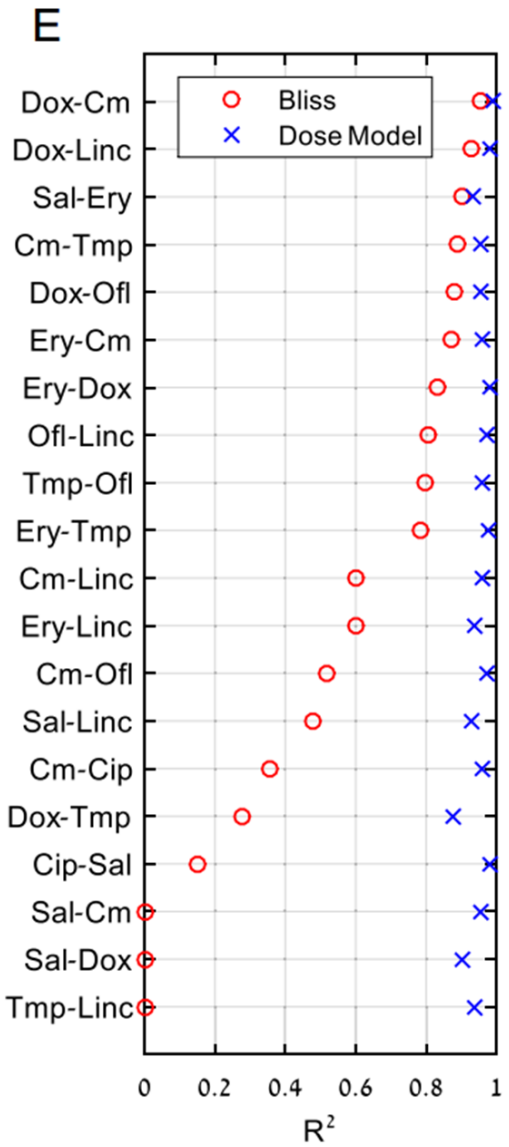
g123 = g12g13g23=g1g2g3 .



实验 2. Dose model在不同情况下的表现良好

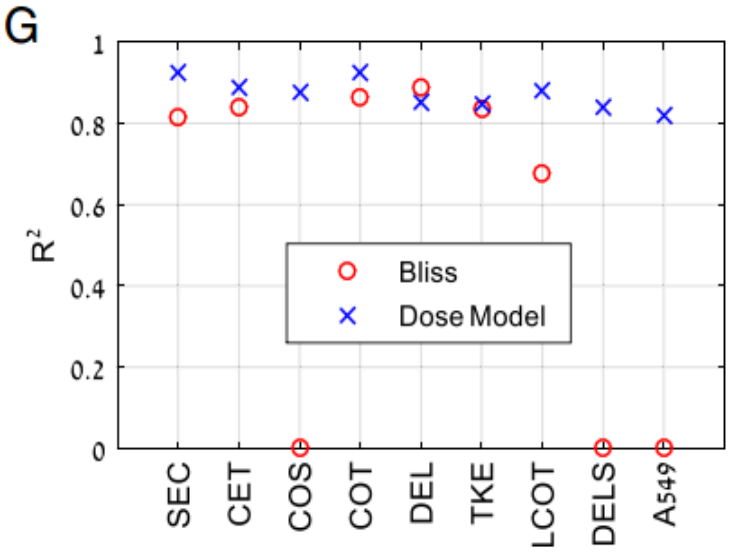


Cip, ciprofloxacin;环丙沙星
Cm, chloramphenicol;氯霉素
Dox, doxycycline;盐酸多西霉素
Ery, erythromycin; 红霉素
Linc, lincomycin;林可霉素
Ofl, ofloxacin;氧氟沙星
Sal, salicylate;水杨酸盐
Tet, tetracycline;四环素
Tmp, trimethoprim;甲氧苄啶　　皆是抗菌药物



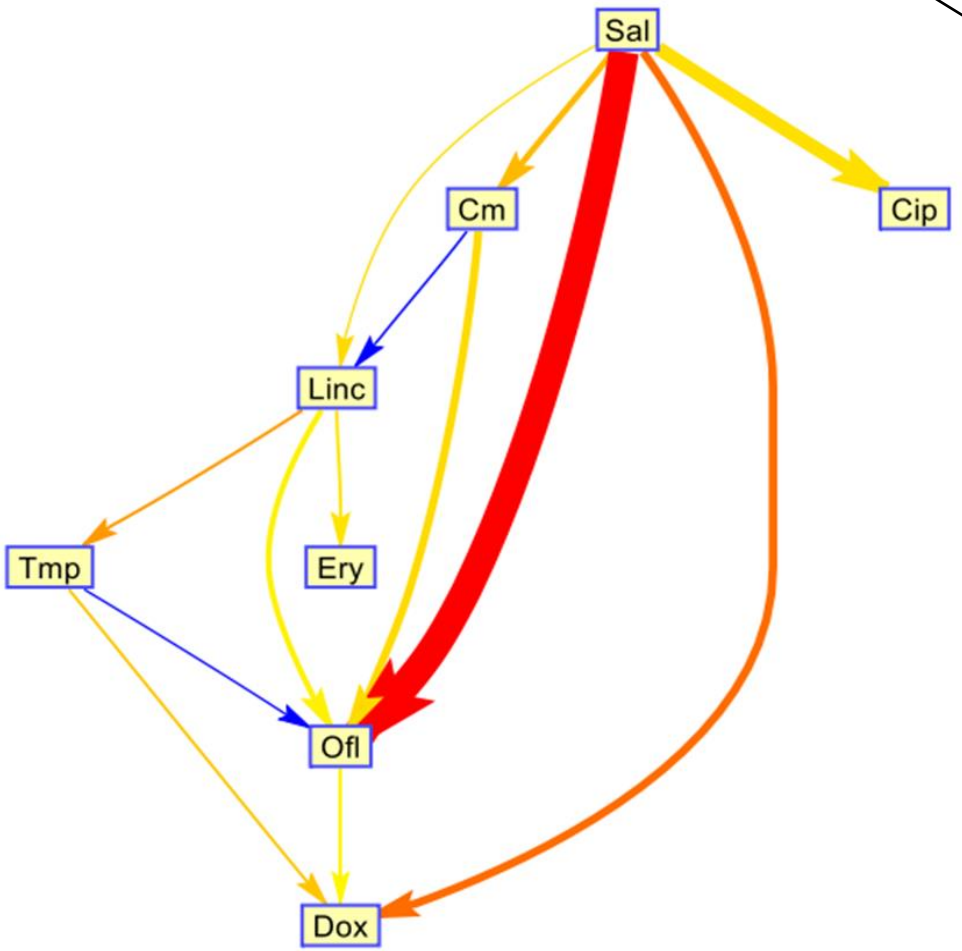
(A) Antagonistic
(B) hyperantagonistic,
(C) synergistic.
(D) Interactions of anticancer drug pairs

ALL well described by the model.



interaction

有助于研究细胞能量代谢的机制



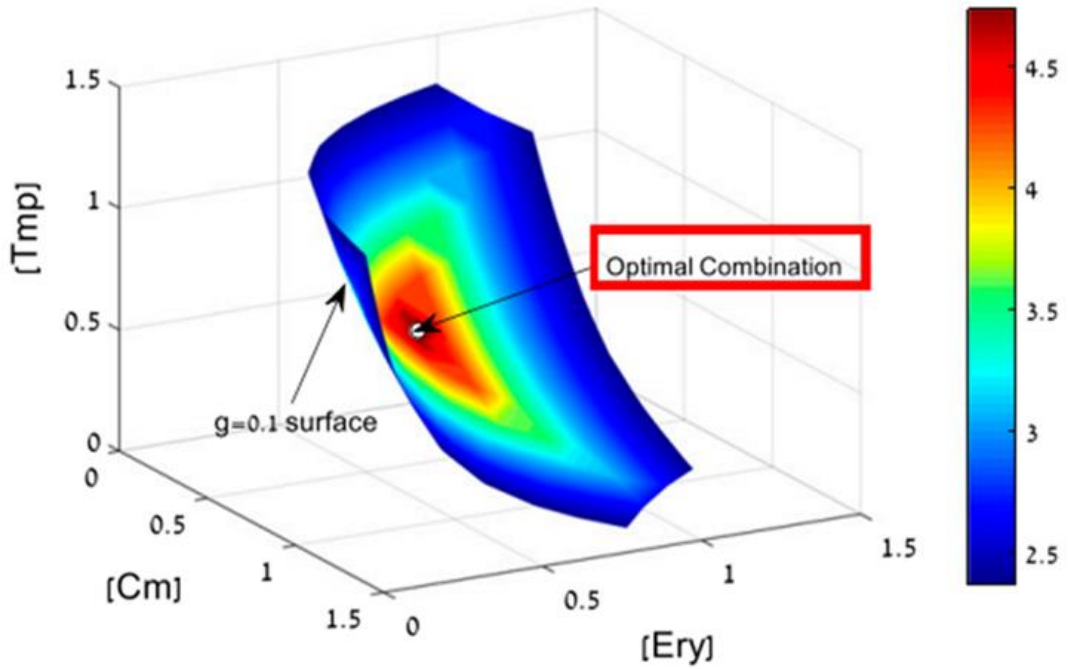
btained because we find that that these relations are transitive: If drug 1 affects drug 2 (1→2) and drug 2 affects drug 3 (2→3), then drug 1 will affect drug 3 (1→3) but not vice versa.

The direction of the interaction is transitive, but the absolute strength of the interaction is not always transitive. To quantify the strength of the hierarchy we use the goodness of fit (RMSE)(标准误差) difference in the case of a12 = 0 and a21 = 0

The strength of the interaction is indicated by the color of the arrow (red, strong antagonistic; blue, strong synergistic).
We plotted only interaction with nonnegligible hierarchy (ΔRMSE > 0.005%).(越大相互作用越强)

减少耐受

Assuming that side effects increase with drug doses, we can seek to minimize



（1）概括

这篇文章利用计算机辅助辅助组合药物设计，改进了Bliss independent model，提出了computation of model 来预测组合药物的效果。与早先的三种方法进行了比较，无论是在3种药物组合还是4种药物组合，均有更好的预测效果。

（2）启发

在药物设计研发中，构建合适的模型，会极大的减少工作量，提高效率，比如虚拟筛选时的SVM模型，并且在构建模型时，选取适合的特征，可以很好的优化模型的效果。

（3）改进

本文的模型虽然已经提高了效率，但是仍然需要实验测试两两药物组合的反应数据，这一点可能可以通过模型的改进来规避，及改进参数a

谢谢！