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Application of kriging models for a drug combination experiment on lung cancer

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Combinatorial drugs have been widely applied in disease treatment, especially chemotherapy for cancer, due to its improved efficacy and reduced toxicity compared with individual drugs. The study of combinatorial drugs requires efficient experimental designs and proper follow-up statistical modeling techniques. Linear and nonlinear models are often used in the response surface modeling for such experiments. We propose the use of kriging models to better depict the response surfaces of combinatorial drugs. We illustrate our method via a drug combination experiment on lung cancer and further show how proper experimental designs can reduce the necessary run size. We demonstrate that only 27 runs are needed to predict all 512 runs in the original experiment and achieve better precision than existing analyses.

KEYWORDS
combinatorial drug, experimental design, Hill-based model, neural network, response surface model

1 | INTRODUCTION

Combination chemotherapy with multiple drugs has been widely applied in cancer therapy. Such combinatorial drugs can have enhanced efficacy and reduced toxicity.[1-3] Preclinical experiments in vitro are usually conducted to characterize the pathological mechanisms and find the optimal drug combinations. In the analyses of these experiments, different response surface modeling techniques have been used to quantify the dose-effect relationships. Response models that require less runs and have better predictive powers are preferred in practice.

Hill models based on ray designs[3] are popular for studying fixed-ratio combinations; however, for three or more drugs, Hill models are less applicable as there are too many ratios to be studied. Polynomial models accompanied by full or fractional factorial designs are often used in analyzing multiple drug combinations,[4] but the predicted responses from polynomial models are unbounded as the dose levels increase to infinity, which is an obvious deviation from the reality. Hill-based models[5] overcome these shortcomings by combining Hill and polynomial models together. However, the Hill-based model includes many parameters in a complex nonlinear formulation, and sometimes the optimization algorithm used in model estimation may fail to converge. Neural networks have also been applied to drug combination analyses.[6] However, neural networks involve many parameters and require a large amount of data to achieve accuracy and good predictions.

This paper explores the application of kriging models[7] to the analyses of drug combination experiments. Originally from geosciences, the kriging model is now widely used in deterministic computer experiments for optimization and sensitivity analysis.[8,9] Due to the existence of measurement errors in physical experiments, we add a noise term to the

original kriging model and apply it to the data from a three-drug combination experiment on lung cancer.[6] Kriging models are parsimonious and robust under various experimental designs and can efficiently identify drug interactions. Kriging models fitted with 27 design points can provide similar or even more accurate predictions than either polynomial or Hill-based models fitted with a 512-run full factorial design. These results demonstrate the superiority of the kriging models compared with other modeling techniques.

This paper is organized as follows. In Section 2, we briefly describe the kriging models, as well as the neural networks,[6] the polynomial models,[5] and the Hill-based models.[5] In Section 3, we compare these four response surface modeling techniques in analyzing a drug combination experiment on lung cancer.[6] Section 4 concludes and discusses some future research.

2 | RESPONSE SURFACE MODELING

2.1 | The kriging model

In a deterministic simulation, eg, a computer experiment, the key idea of the kriging model is to consider its responses (outputs) as realizations of a Gaussian process. Detailed introductions to the kriging model can be found in many existing literatures.[8-11] Compared with the universal kriging model, the ordinary kriging model often suffices and is commonly used in practice.[12] In this paper, we focus on the ordinary kriging model and all results can be easily generalized to the universal kriging model.

Because drug combination experiments have measurement errors, we consider an ordinary kriging model with a noise term, which is defined as

$$y(x) = \mu + Z(x) + \epsilon, \tag{1}$$

where μ is the trend parameter, $Z(x)$ is a stationary Gaussian process with zero mean and covariance function ϕ defined in (2), and $\epsilon \sim N(0, \tau^2)$ is a random error term and independent of $Z(x)$. The covariance function for $Z(x)$ is

$$\phi(x_i, x_j) = \text{Cov}\left(Z(x_i), Z(x_j)\right) = \sigma^2 \prod_{l=1}^{d} K(h_l; \theta_l), \tag{2}$$

where σ^2 is the variance parameter, $h_l = |x_{i,l} - x_{j,l}|$, $x_{i,l}$ and $x_{j,l}$ are the lth elements of the ith run x_i and the jth run x_j, d is the dimension of x (ie, number of drugs studied), and $K(h_l; \theta_l)$ is a chosen correlation function with positive parameter θ_l. Popular correlation functions include Gaussian and Matérn family correlations. The sample paths of $Z(x)$ with Gaussian correlation $K(h; \theta) = \exp(-h^2/(2\theta^2))$ have derivatives at all orders and are too smooth in some cases, which may result in nearly singular covariance matrices and thus cause numerical problems in model estimations.[13] The Matérn correlation function with parameter $\nu = 5/2$ is defined as

$$K(h; \theta) = \left(1 + \frac{\sqrt{5}h}{\theta} + \frac{5h^2}{3\theta^2}\right) \exp\left(-\frac{\sqrt{5}h}{\theta}\right). \tag{3}$$

The sample paths of $Z(x)$ with this Matérn correlation are twice differentiable and less smooth than that with the Gaussian correlation. Another choice is the Matérn correlation function with $\nu = 3/2$, which is $K(h; \theta) = (1 + \sqrt{3}h/\theta)\exp(-\sqrt{3}h/\theta)$. This leads to even rougher paths than correlation function (3). The Matérn correlation function with parameter $\nu = 5/2$ offers a good balance and is recommended in practice.[14] Figure 1 shows the Matérn correlation function (3) with different θ. The correlation decreases as the distance h increases. The larger the θ is, the slower the decreasing rate is. When θ is close to 0, identifiability problems may raise.[10]

Unknown parameters can be estimated by the maximum likelihood estimation (MLE) method. The best linear unbiased prediction at point x is given by

$$\hat{y}(x) = \hat{\mu} + \gamma^T C^{-1}(\mathbf{y} - \hat{\mu}), \tag{4}$$

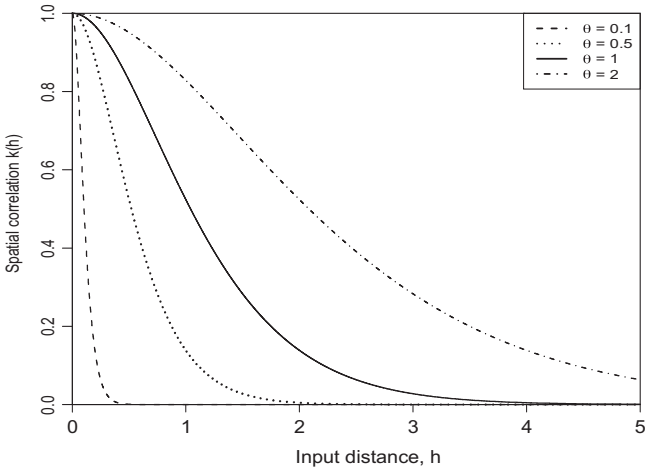

FIGURE 1 Examples of spatial correlation functions of Matérn family

where $\hat{\mu} = (\mathbf{1}^T C^{-1}\mathbf{1})^{-1}\mathbf{1}^T C^{-1}\mathbf{y}$ is the MLE of μ, $\mathbf{1}$ is a column of ones, $\gamma = (\phi(x, x_1), \ldots, \phi(x, x_n))^T$, $C = \Phi + \Delta$, Φ is the variance-covariance matrix $(\phi(x_i, x_j))_{1\leqslant i,j\leqslant n}$, and Δ is a diagonal matrix with diagonal elements τ^2. The predicted response at any point can be viewed as a weighted average of observed responses. When $\tau = 0$, the kriging model interpolates the observed data.

2.2 | Neural networks

Neural networks[15,16] are widely used in machine learning, pattern recognition, medical diagnosis, and many other areas. An (artificial) neural network is a multilayer model based on a collection of connected units called neurons. Neurons in each layer receive inputs from the last layer and produce outputs via a predefined activation function.

When analyzing the lung cancer drug combination experiment, Al-Shyoukh et al adopted a single (hidden) layer four-neuron multilayer perceptron (neural network),[6] which is shown in Figure 2. In this neural network model, for the jth hidden neuron ($j = 1, 2, 3, 4$), the most commonly used network activation function is

$$f^{(j)}(x) = \frac{1}{1 + e^{-\sum w_{i,j}x_{i,j}}},$$

where $w_{i,j}$ are parameters to be estimated, $x_{0,j} = 1$, and $x_{i,j}$ is the ith input value ($i = 1, 2, 3$). Here, the linear output $g(x) = \sum w'_j x'_j$ is adopted, where w'_j are parameters to be estimated, $x'_0 = 1$, and x'_j is the output from the jth hidden neuron ($j = 1, 2, 3, 4$). Neural networks can be estimated via resilient back-propagation method, and the R package "neuralnet"[17] is a current popular tool.

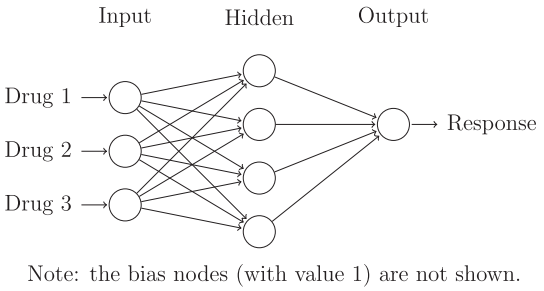

FIGURE 2 A multilayer perceptron with one hidden layer of four neurons

2.3 | Polynomial and Hill-based models

The polynomial model is a common analytic tool to study main effects and interactions. A second-order polynomial model for studying three drugs at dosages x_1, x_2, x_3 is defined as

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_1^2 + \beta_5 x_2^2 + \beta_6 x_3^2 + \beta_7 x_1 x_2 + \beta_8 x_1 x_3 + \beta_9 x_2 x_3 + \epsilon, \tag{5}$$

where y is the response, β_i are parameters to be estimated and $\epsilon \sim N(0, \sigma^2)$ is a random error. This model can be easily generated to accommodate more drugs.

In vivo system, the relationship between the drug dosage and its effect usually follows a sigmoidal curve.[3] Based on this, the Hill-based model,[5] which combines the polynomial model and Hill model, is proposed

$$y = \frac{1}{1 + \left(\frac{C}{IC_{50}(p)}\right)^{\gamma(p)}} + \epsilon, \tag{6}$$

where C is the total dosage of all drugs, p is a vector with each entry being the proportion of a drug, and $IC_{50}(p)$ and $\gamma(p)$ are two second-order polynomials of p. As an illustration, for three drugs with $p = (p_1, p_2, p_3)$,

$$IC_{50}(p) = a_0 + a_1 p_1 + a_2 p_2 + a_3 p_1^2 + a_4 p_2^2 + a_5 p_1 p_2,$$
$$\gamma(p) = b_0 + b_1 p_1 + b_2 p_2 + b_3 p_1^2 + b_4 p_2^2 + b_5 p_1 p_2,$$

where a_i and b_i are parameters to be estimated. Note that $p_1 + p_2 + p_3 = 1$; thus, $IC_{50}(p)$ and $\gamma(p)$ include only two independent entries of p. The $IC_{50}(p)$ measures the dosage of the drug combination, which yields 50% effect level, and $\gamma(p)$ measures the changing rate of the smooth curve. Hill-based models are able to characterize the interaction patterns for all drug combinations.[5]

3 | RESULTS

3.1 | A drug combination experiment on lung cancer

We focus on the data of a drug combination experiment on lung cancer.[6] The experiment studied three drugs, AG490 (A), U0126 (B), and indirubin-3′-monoxime (C), which are inhibitors targeting signaling pathways for cell survival and proliferation. A 512-run eight-level full factorial design (D_{full}) was applied to normal cells and lung cancer cells separately. The eight levels were the eight dosages listed in Table 1. The response variable was the total cellular adenosine triphosphate (ATP) level (standardized to 0 to 1 range) measured 72 hours after drug treatment. Cellular ATP is one of the most common and essential markers for live cells. Small ATP level indicates low cell activity. One purpose of this experiment was to characterize the response surface.

3.2 | Model fitting and comparison

We fit the kriging model in (1), the neural network shown in Figure 2, the polynomial model in (5), and the Hill-based model in (6) to the full data (D_{full}), as well as subsets of the data. Subsets are chosen according to three designs, ie, an 80-run random subdesign RD_{80}, a 27-run random subdesign RD_{27}, and a 27-run three-level full factorial design $D047$. In

TABLE 1 Dose levels for each drug in the combinatorial experiment on lung cancer

Drug	Dosage (μM)							
AG490 (A)	0	0.3	1	3	10	30	100	300
U0126 (B)	0	0.1	0.3	1	3	10	30	100
I-3-M (C)	0	0.3	1	3	10	30	100	300
Order of dosages	0	1	2	3	4	5	6	7

Abbreviations: I-3-M, indirubin-3′-monoxime.

TABLE 2 The "1000 · MSE (r)" for different models on normal cells

	D_{full}	RD_{80}	RD_{27}	$D047$
Kriging ($\tau = 10^{-4}$)	0(100.00%)	0.11(99.94%)	1.39(99.36%)	0.18(99.92%)
Kriging ($\tau = 10^{-3}$)	0(100.00%)	0.19(99.91%)	0.97(99.82%)	0.06(99.97%)
Kriging ($\tau = 10^{-2}$)	0(100.00%)	0.21(99.88%)	0.98(99.56%)	0.31(99.86%)
Neural network	0.21(99.89%)	1.24(99.39%)	3.58(98.35%)	6.78(96.95%)
Polynomial	0.48(99.75%)	1.16(99.42%)	3.65(98.39%)	1.12(99.49%)
Hill-based	0.89(99.10%)	1.07(99.49%)*	3.57(98.30%)*	3.30(98.39%)

TABLE 3 The "1000 · MSE (r)" for different models on cancer cells

	D_{full}	RD_{80}	RD_{27}	$D047$
Kriging ($\tau = 10^{-4}$)	0(100.00%)	0.20(99.92%)	2.06(99.16%)	0.49(99.82%)
Kriging ($\tau = 10^{-3}$)	0(100.00%)	0.26(99.89%)	2.36(99.04%)	0.15(99.94%)
Kriging ($\tau = 10^{-2}$)	0(100.00%)	0.37(99.78%)	1.84(99.23%)	1.08(99.65%)
Neural network	0.48(99.79%)	1.55(99.35%)	4.31(98.28%)	10.87(96.23%)
Polynomial	2.98(98.67%)	6.77(97.09%)	39.82(87.74%)	5.84(97.66%)
Hill-based	1.42(98.80%)	1.67(99.33%)*	4.99(97.93%)*	4.70(97.92%)

design $D047$, the three levels are the dosages with orders 0, 4, and 7 in Table 1. For fitting each model, the dosages for each factor are normalized to 0 to 1 range. We use each fitted model to predict the 512 responses for the full design D_{full}. We fit kriging models using the R package "DiceKriging"[10] with the Matérn correlation function (3). When analyzing drug combination experiments, the error term ($\epsilon \sim N(0, \tau^2)$) in (1) represents the measurement error or experiment error. Since the measurement was accurate to two decimal places in this study, we report results with three choices of $\tau = 0.0001$, $\tau = 0.001$, and $\tau = 0.01$.

Tables 2 and 3 show the mean squared error (MSE) and the correlation (r) between predicted and observed responses for normal and cancer cells, respectively. Results are shown in the format "1000·MSE (r)." The R package "neuralnet" for neural network yields slightly different results each time, so we run the command 100 times and take the average. Results for designs RD_{80} and RD_{27} are averages from 100 random designs. When fitting Hill-based models with RD_{80} and RD_{27}, the optimization algorithm fails to converge 6 and 35 times, respectively, so we mark the results with asterisks in the tables.

From Tables 2 and 3, kriging models always produce smaller MSEs and larger correlations between predicted and observed responses compared with other models. More excitingly, for both normal and cancer cells, kriging models fitted with the 27-run design $D047$ perform better than polynomial and Hill-based models fitted with the 512-run full design D_{full}, and neural networks fitted with 80-run random designs. Kriging models describe the dose-effect relationship precisely and hence can make good predictions with a small number of observations, which is a preferred feature by experimenters for saving time and expense. In contrast, neural networks do not work well with the three-level design $D047$.

Since kriging is an interpolation method, the prediction error using D_{full} is roughly zero as long as τ is small. Comparing the results using RD_{80}, RD_{27}, and $D047$, we see that different τ values lead to similar prediction accuracy here, considering the measurement error was around 0.01 in this experiment. In the following, we illustrate the results from $\tau = 0.01$.

Figures 3 and 4 show the scatter plots of predicted versus observed responses for all four models with design $D047$. Kriging models are the best in prediction for both normal and cancer cells. For polynomial models, several predicted responses are negative for both normal and cancer cells, which deviates from the fact that the ATP levels cannot be negative. Neural networks and Hill-based models perform poorly for both normal and cancer cells, probably because they require more observations to achieve accuracy.

Kriging models have the least number of parameters to be estimated. In this experiment, the kriging model only contains five parameters, compared with 21, 10, and 12 parameters for the neural network, polynomial, and Hill-based models,

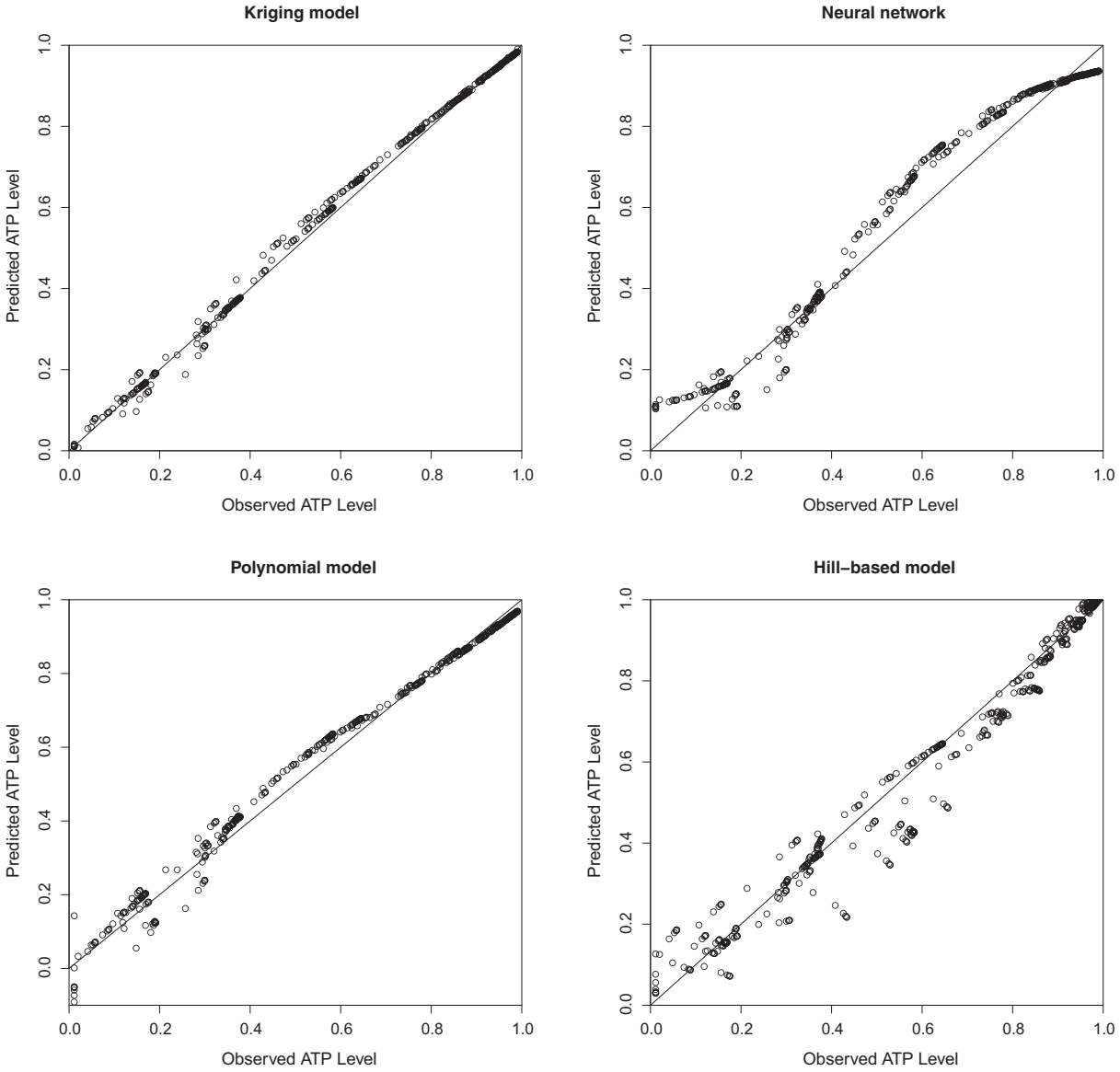

FIGURE 3 Scatter plots of predicted versus observed adenosine triphosphate (ATP) levels on normal cells using design $D047$

respectively. Kriging models are parsimonious and suitable for fitting high dimensional data, ie, data consisting of a large number of drugs. Table 4 shows the estimated parameters (or hyperparameters in some literature) and their standard errors (SEs) for kriging models accompanied by designs D_{full} and $D047$. Here, the SEs are estimated via a simulation approach.[10]

In order to study drug interactions, we investigate contour plots of effect levels predicted by kriging models using designs D_{full} and $D047$. Figures 5 and 6 report the contour plots on pairwise drug combinations with the third drug dosage fixed at 0 for two types of cells, respectively. Designs D_{full} and $D047$ provide similar contour plots, which implies that kriging models require few observations for detecting drug interactions. Two drugs are synergistic when they work cooperatively and antagonistic when they inhibit each other. From Figures 5 and 6, when both of the pairwise drugs are at low dosages, contours are nearly straight or slightly convex, which suggests no drug interactions or slight synergism. For the A/B and A/C plots, their contours show more synergism as dosages increase. In addition, comparing the A/C contour plots for both types of cells, we can find many pairwise drug combinations, which produce less than 0.1 effect level for cancer cells but more than 0.3 effect level for normal cells. These drug combinations can lead to potential treatments that can kill cancer cells effectively while protecting normal cells.

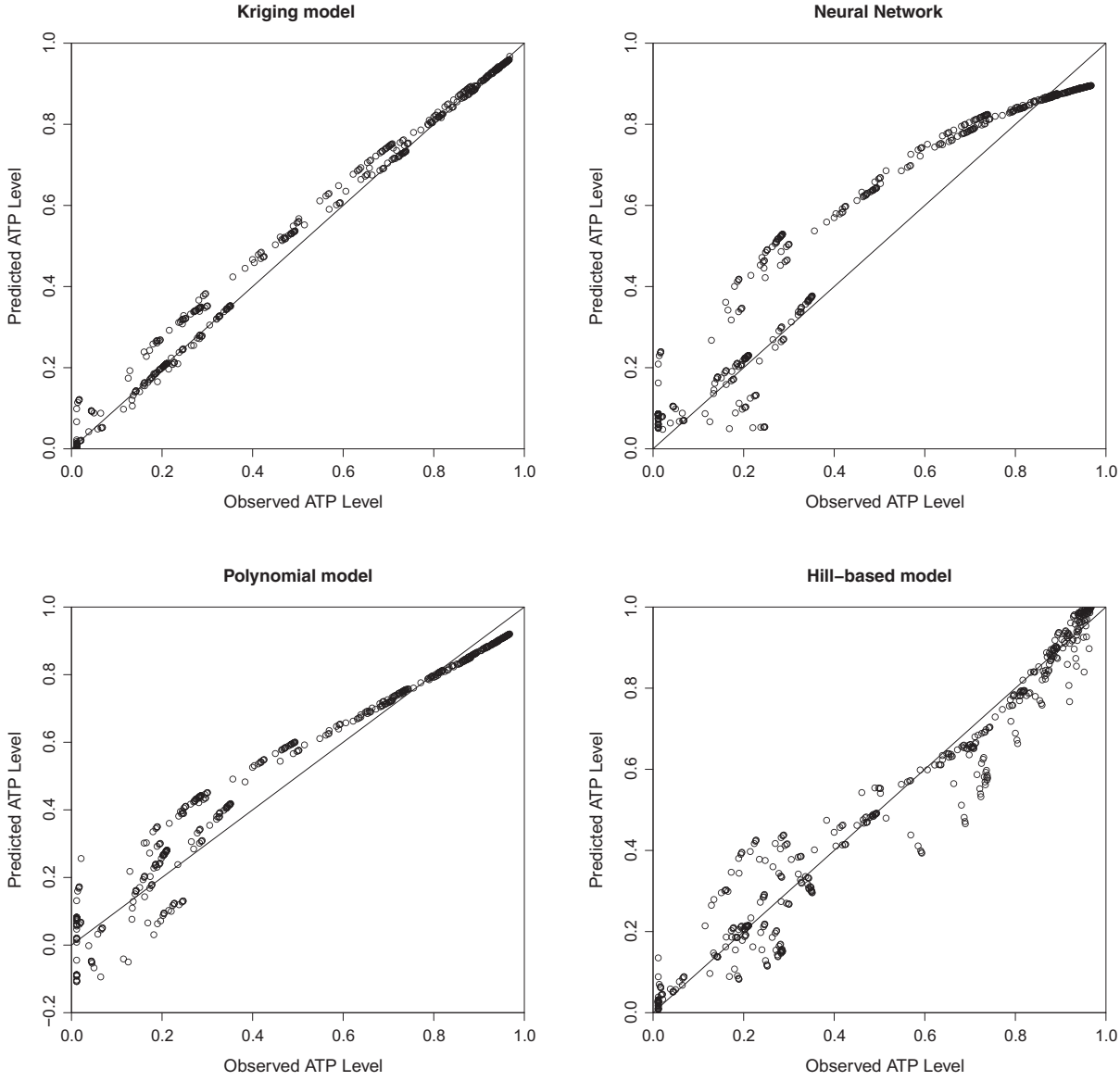

FIGURE 4 Scatter plots of predicted versus observed adenosine triphosphate (ATP) levels on cancer cells using design $D047$

TABLE 4 Estimations of parameters (and standard errors) in kriging models

Normal cells	θ_A	θ_B	θ_C	σ^2	μ
D_{full}	1.24(0.11)	2.00(0.04)	1.24(0.12)	0.26(0.04)	0.62(0.06)
$D047$	1.11(0.22)	1.89(0.26)	1.08(0.22)	0.24(0.05)	0.54(0.10)
Cancer cells	θ_A	θ_B	θ_C	σ^2	μ
D_{full}	0.98(0.11)	1.21(0.13)	0.52(0.06)	0.12(0.04)	0.39(0.04)
$D047$	0.83(0.20)	1.46(0.23)	0.41(0.10)	0.16(0.04)	0.37(0.06)

For a given fixed ratio of pairwise drugs, the Loewe interaction index (I) is widely used to study pairwise drug combinations[18,19]

$$I = \frac{C_{A,r}}{IC_{X,A}} + \frac{C_{B,r}}{IC_{X,B}}, \tag{7}$$

where X is the reference effect level; $IC_{X,A}$ and $IC_{X,B}$ are the respective dosages of drugs A and B to achieve X effect level when applied individually; r is the predetermined fixed ratio between drugs A and B; $C_{A,r}$ and $C_{B,r}$ are dosages of drugs A

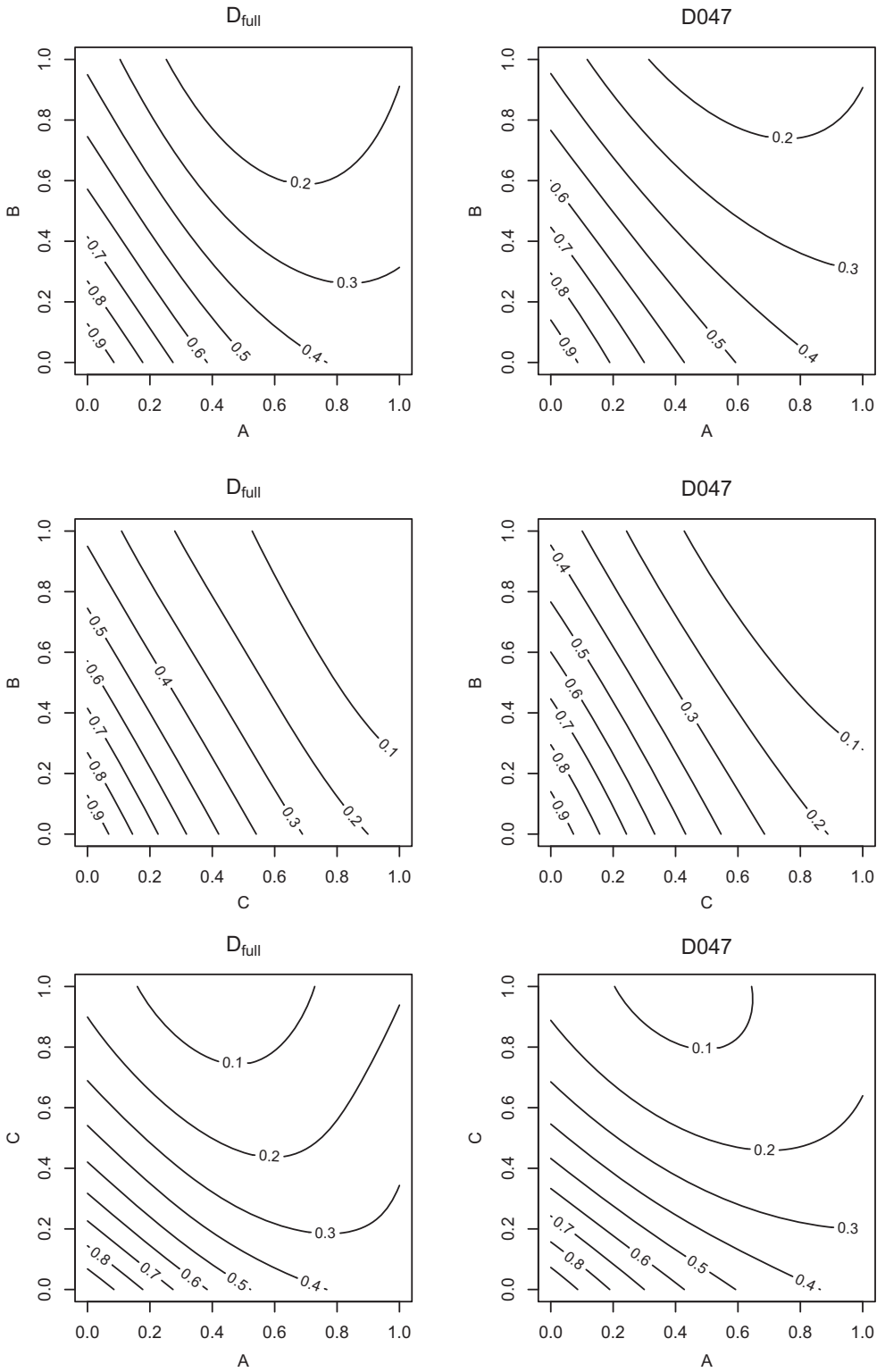

FIGURE 5 Contour plots of predicted adenosine triphosphate (ATP) levels via D_{full} and $D047$ under kriging models on normal cells

and B in the drug combination with fixed ratio r to result in X effect level, respectively. Given X and r, if $I = 1$, there is no interaction between drugs A and B (additive mixture); if $I < 1$, these two drugs work cooperatively (Loewe synergism), and if $I > 1$, the two drugs inhibit each other (Loewe antagonism).

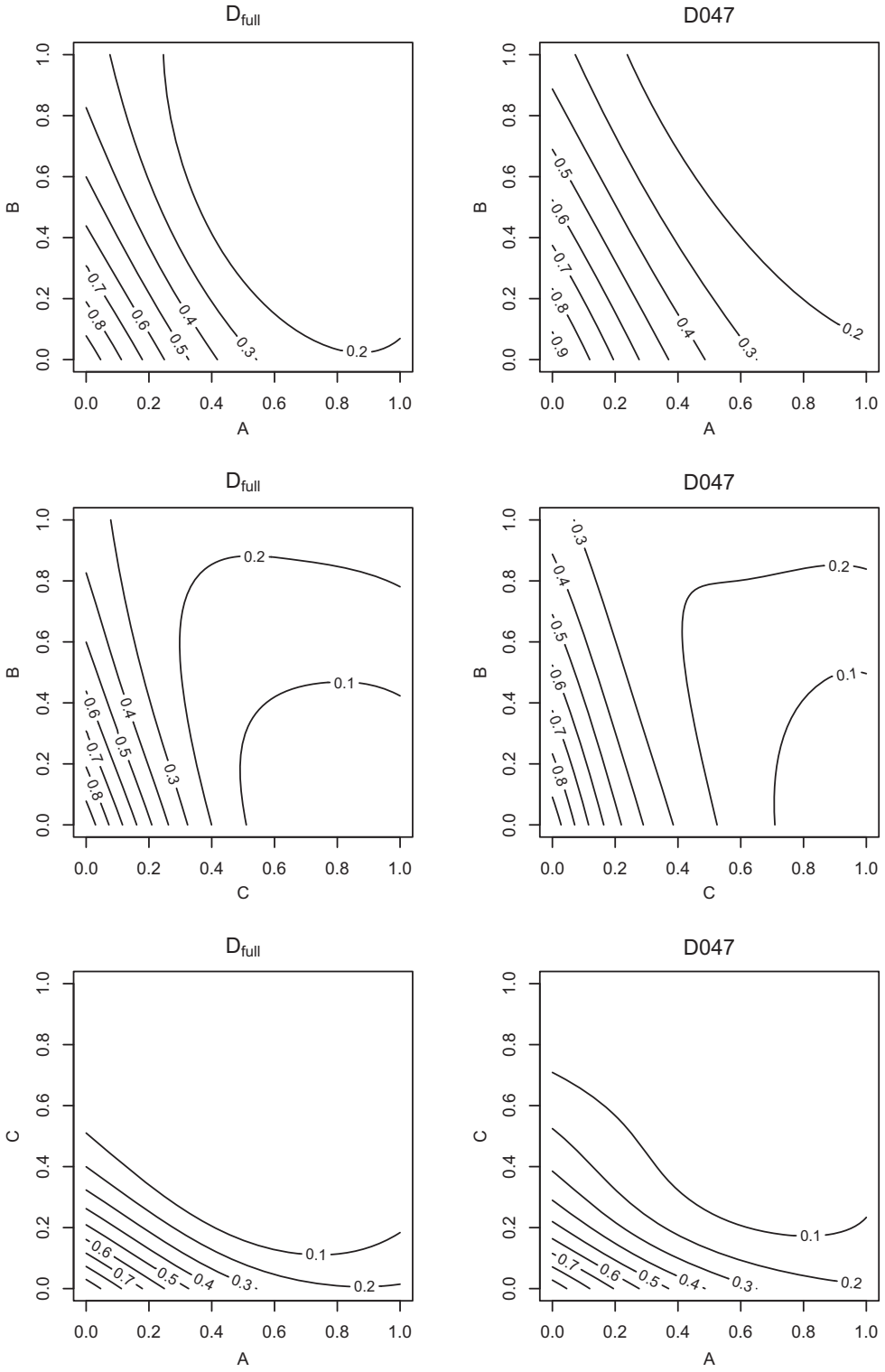

FIGURE 6 Contour plots of predicted adenosine triphosphate (ATP) levels via D_{full} and $D047$ under kriging models on cancer cells

On the basis of our fitted kriging models using designs D_{full} and $D047$, we show in Table 5 the Loewe interaction indexes (I) and their SEs at effect level $X = 0.5$ and fixed ratio $r = 1 : 1$. Both designs result in similar estimates of the Loewe interaction indexes. Design $D047$ has smaller number of runs and hence larger SEs, compared to D_{full}. From this table, pairwise drugs are nearly additive or slightly synergistic at effect level $X = 0.5$, which is consistent with the contour plots in Figures 5 and 6.

TABLE 5 Loewe interaction indexes (and standard errors) based on fitted kriging models

Normal Cells	A/B	A/C	B/C
D_{full}	0.964(0.015)	0.946(0.022)	1.010(0.013)
$D047$	0.986(0.066)	0.973(0.072)	1.031(0.068)
Cancer Cells	**A/B**	**A/C**	**B/C**
D_{full}	0.977(0.012)	0.997(0.009)	0.995(0.014)
$D047$	1.008(0.078)	0.965(0.037)	1.051(0.089)

4 | CONCLUSIONS AND DISCUSSIONS

In drug combination analyses, an accurate response surface model can not only provide desirable drug combinations, but also help characterizing their pathological mechanisms. In this paper, we have compared four types of response surface models along with four possible designs in analyzing a drug combination experiment.[6] We find that kriging models need the least number of runs and give the most accurate predictions. The 27-run design $D047$ is sufficient for fitting kriging models in this study. The choice of designs is not unique. For example, choosing a 27-run full factorial design with dosage orders 0, 5, and 7 provides similar results.

When fitting kriging models in this study, if we assume τ as a parameter to be estimated, its MLE is essentially (nearly) 0 up to some rounding error. However, we should not use $\tau = 0$ here for two reasons. First, when designs D_{full} and RD_{80} are used, $\tau = 0$ will lead to nearly singular covariance matrices and cause problems in model estimation, as the data points are too close to each other. Second, the kriging model with $\tau = 0$ will give zero response variance at all observed data points, which is not an appropriate assumption for drug combination experiments where experiment errors exist.

Due to the complexity of underlying biological systems, a systematic quantification of effects for multiple drugs is challenging, and thus, various models should be explored for such experiments. In such situations, space-filling designs are ideal due to their robustness.[20-24] Maximin distance designs are ideal for kriging models, as any unobserved point will not be too far from observed design points and thus the prediction error will not be too big. An interesting topic for the future research is how space-filling designs, especially maximin distance designs, perform under kriging models in drug combination studies.

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