Response Surface Methodology

BIOE 498/598

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Optimizing with Continuous Factors

- With *discrete* factors we can choose the optimal factor settings by examining the coefficients.
- With *continuous* factors the optimal factor settings are usually not among the levels tested in the experimental design.
- RSM uses numerical optimization to find the ideal factor settings.

The Problem with First Order Models

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Maximizing the response y implies $x_1 \to \infty$ and $x_2 \to -\infty$.

The Problem with Two-Way Interaction Models

Adding a two-way interaction (TWI) doesn't help.

$$\begin{aligned} y &= \beta_1 x_1 + \beta_2 x_2 + \beta_{12} x_1 x_2 \\ &= 2.3 x_1 - 1.4 x_2 - 0.5 x_1 x_2 \end{aligned}$$

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If $x_2 < 4.6$, then set $x_1 = \infty$. Otherwise, $x_1 = -\infty$.

FO and TWI models are not realistic

No one believes that the response will increase indefinitely by increasing a factor with a positive effect.

The diminishing returns we see in real life are not reflected by FO models since they lack *curvature*.

TWI models curve, but they do not diminish as the magnitude of each factor increases.

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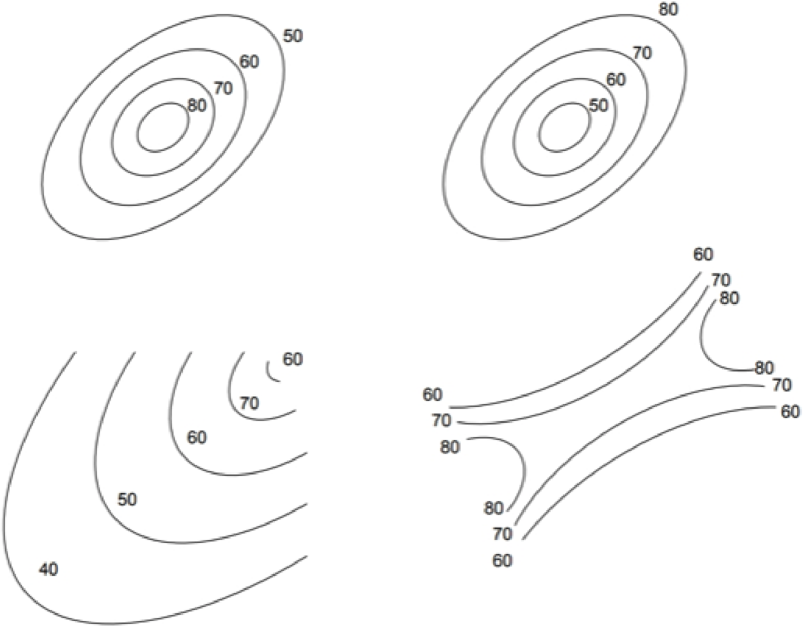
We are not claiming that f is quadratic. Rather, we claim that a second-order approximation is “good enough" over our domain of interest.

Surfaces that can be approximated with quadratics



Approximating f with a general quadratic

Let's find the second-order Taylor series of $f(x_1, x_2)$ centered at zero:

$$f(x_1, x_2) \approx f|_0 + \left.\frac{\partial f}{\partial x_1}\right|_0 x_1 + \left.\frac{\partial f}{\partial x_2}\right|_0 x_2 + \frac{1}{2}\left.\frac{\partial f}{\partial x_1 \partial x_2}\right|_0 x_1 x_2 \\ + \frac{1}{2}\left.\frac{\partial^2 f}{\partial x_1^2}\right|_0 x_1^2 + \frac{1}{2}\left.\frac{\partial^2 f}{\partial x_2^2}\right|_0 x_2^2$$

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Since the function f and its derivatives are unknown, we fit the parameters β with a linear model.

Approximating f with a general quadratic (continued)

In general we will have k factors and the quadratic approximation will be

$$y = \beta_0 + \sum_{i=1}^{k} \beta_i x_i + \sum_{j=1}^{k} \sum_{i=1}^{j} \beta_{ij} x_i x_j + \sum_{i=1}^{k} \beta_{ii} x_i^2$$

This model has $1 + k(k-1)/2 + k$ parameters, so response surface designs must have at least this many runs.

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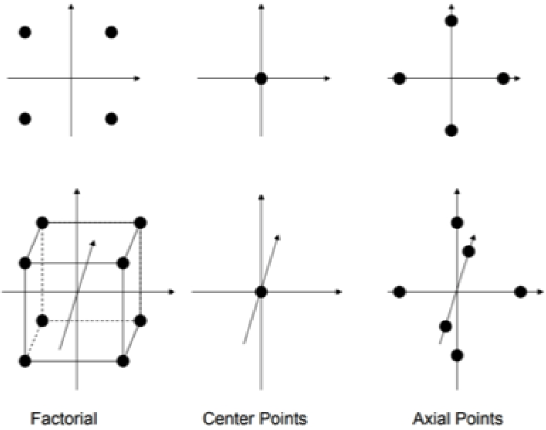
Additionally, we cannot use 2^k factorial (or fractional) designs since two levels for each factor **will not allow us to estimate curvature**. A 3^k factorial design would work, but a *central composite design* is better.

The Central Composite Design (CCD)



1. A 2^k factorial or a Resolution V 2^{k-p} fractional design allow estimation of the FO and TWI terms.
2. The axial points estimate the pure quadratic (PQ) terms.
3. Replicated center points estimate the model's precision.

Uncertainty in the design space

Factorial models are most precise at the center of the design space.

The variance in the model's predictions increases as the *radius* (the distance from the center point) increases.

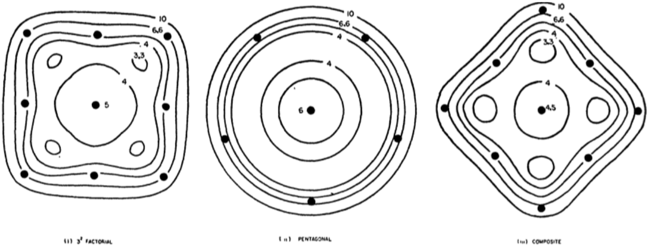
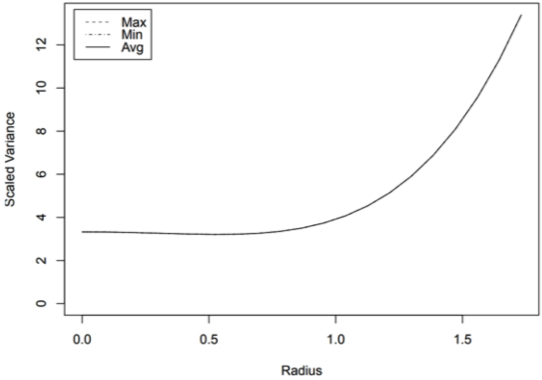


FIG. 2. Variance contours for some 2 dimensional designs

Image from Box and Hunter 1957.

Uniform Precision in CCD



A model has *uniform precision* if the variance at radius$= 1$ is the same as the variance at the center.

Choosing the correct number of center points in a CCD ensures uniform precision.

Correct number of center points (Box and Hunter 1957)

factors (k)	2	3	4	5	$5-1$	6
factorial points	4	8	16	32	16	64
axial points	4	6	8	10	10	12
center points	5	6	7	10	6	15
α	1.414	1.682	2.000	2.378	2.000	2.828

factors (k)	$6-1$	7	$7-1$	8	$8-1$	$8-2$
factorial points	32	128	64	256	128	64
axial points	12	14	14	16	16	16
center points	9	21	14	28	20	13
α	2.378	3.364	2.828	4.000	3.364	2.828

Rotatable Designs

Ideally, the change in precision should be independent of the direction we move away from the center. Designs where the variance only depends on the radius are called *rotatable designs*.

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Each factor in the CCD will be set at five levels:

$$-\alpha \quad -1 \quad 0 \quad 1 \quad \alpha$$

We make a CCD rotatable by choosing α, the distance to the axial points. If a design has F factorial runs, we set

$$\alpha = \sqrt[4]{F}$$

This means the coded units in a CCD have meaning!

Coding the CCD

Let's say we're designing a combination screening of three drugs. The absolute widest concentration range we can use for drug A is $[-3.2, 1.0]$ on a $\log_{10}$-μM scale. What are the five levels assuming a full-factorial CCD?

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$$\begin{aligned} \mathsf{A} &= \text{center}(\mathsf{A}) + \frac{\text{range}(\mathsf{A})}{2\alpha}[\text{code}] \\ &= -1.1 + \frac{1 - (-3.2)}{2(1.68)}[\text{code}] \end{aligned}$$

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code:	$-\alpha$	-1	0	1	α
$\log_{10}$-μM:	-3.2	-2.4	-1.1	0.2	1.0