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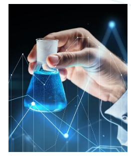
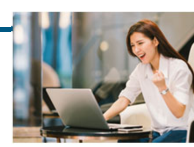


# Strategy of Experiments for Optimal Formulation

Mark J. Anderson, PE, CQE, MBA, Engineering Consultant
Stat-Ease, Inc., Minneapolis, MN
mark@statease.com

## Maximizing this educational opportunity



Welcome everyone!  To make the most from this webinar:

- Attendees on mute
- Chat addressed afterward
- Send further questions to mark@statease.com

PS  Presentation posted to www.statease.com/webinars/

*Please press the raise-hand button if you are with me.*

## Mixture Design*

Considerations:

- Factors are ingredients of a mixture.
- The response is a function of proportions, not amounts.

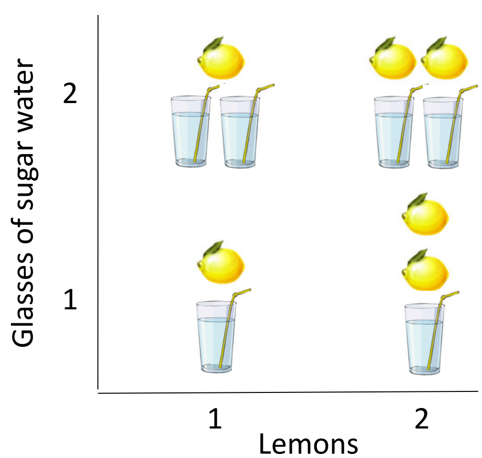
❖Given these two conditions, fixing the total (an equality constraint) facilitates mixture modeling as a function of component proportions.

*Let's try forcing a factorial design onto a mixture.*

*(Pioneered by Henry Scheffé, U Cal., 1957)

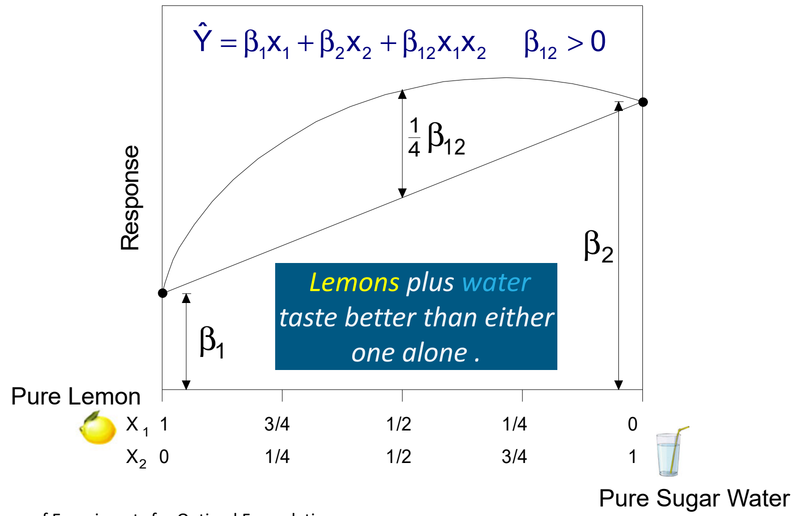


## Forcing (squeezing?) factorial design on a mixture: Lemonade



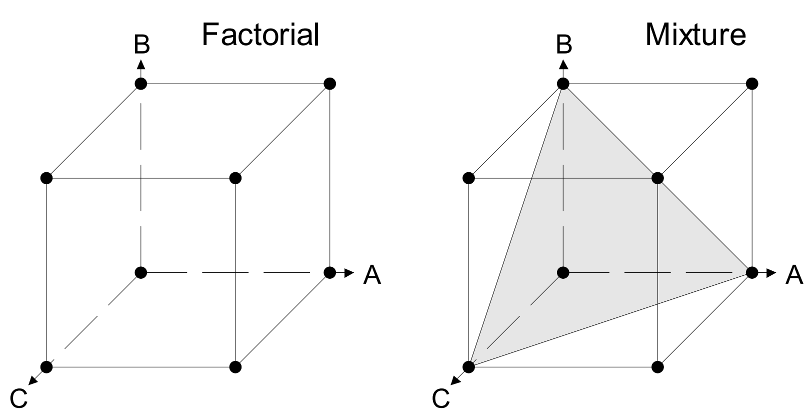
## Mixture Design and Modeling (sweet!)

Two components: Quadratic (synergistic)





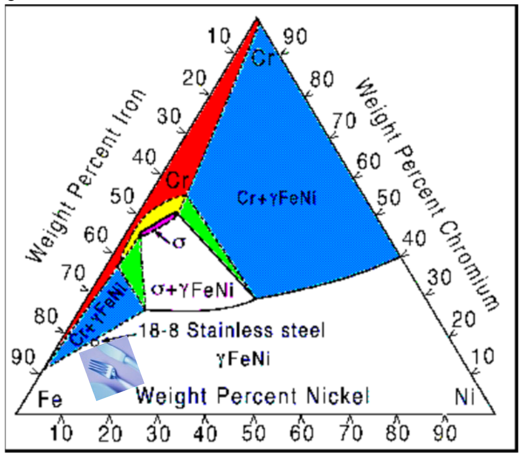

## Three-Component Mixture



# Ternary Diagram for Mixture Composition
(for example, stainless steel flatware)

$x_1 + x_2 + x_3 = 1$

$x_1$




$x_2$ $x_3$



# Mixture Case Study: Optimization

Keeping their total at 9%, three detergent components are varied:

A. Water, 3 - 5%
B. Alcohol, 2 - 4%
C. Urea, 2 - 4%

Goals for critical-to-quality responses:

1. Viscosity: 39-48 mPa-sec (cP), target 43
2. Turbidity: Minimize, <800 ideal, >900 unacceptable

*V22: Detergent tutorial*
*Rebuild, Analyze, Optimize, Overlay*

## A Fun At-Home Mixture Experiment

*Pound Cake (1/2)*

A kitchen scientist experimented on the main ingredients of pound cake: flour, butter, sugar and eggs. (In addition, they added a constant amount of milk for moisture and baking powder for tenderness. Via a "multicomponent" constraint, they incorporated two varieties of flour:

- Costly cake and
- Cheap all purpose

Here are the recipes for the top four tastiest cakes (rated by a panel):

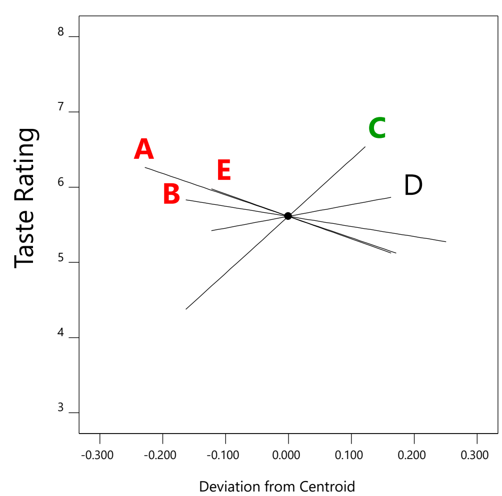
| Run | A:Cake fl... oz | B:AP flour oz | C:Sugar oz | D:Butter oz | E:Eggs oz | Color s=0 Rating | knife ... mm | Taste ... Rating |
|---|---|---|---|---|---|---|---|---|
| 24 | 3.0 | 0.0 | 5.0 | 5.0 | 3.0 | 7.6 | 64 | 7.1 |
| 5 | 2.0 | 2.0 | 5.0 | 4.0 | 3.0 | 7.1 | 60 | 6.8 |
| 19 | 0.0 | 3.0 | 5.0 | 4.0 | 4.0 | 8.4 | 64 | 6.8 |
| 7 | 0.0 | 5.0 | 5.0 | 3.0 | 3.0 | 6.9 | 58 | 6.6 |



## *Pound Cake (2/2)*

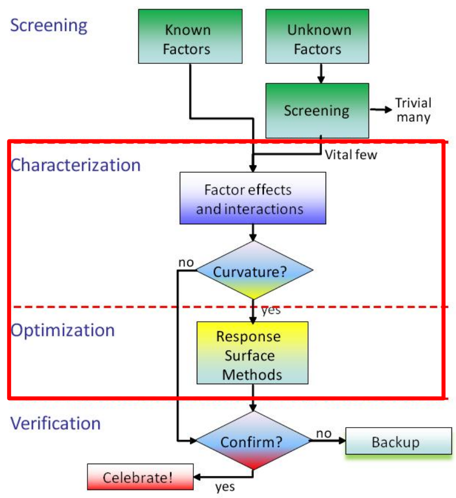
Only main-component effects emerged—a linear model. This "trace" plot tells the story: The tasters preferred more sugar (C) with less flour (A&B) and eggs (E).

PS Not only did this lead to a sweeter cake but seeing little advantage to the expensive flour by their aligned tracks, the new recipe reduced costs. ☺☺



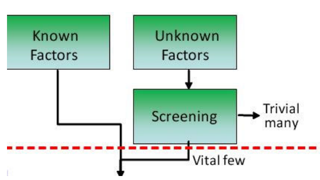
## Strategy of Experimentation on Mixtures
*(versus a process)*

*Adaptations*:
- *Components, not factors*
- *Characterization and optimization combined into one "nonlinear-blending" design*






## Mixture Screening
*An underutilized tool for formulation development*



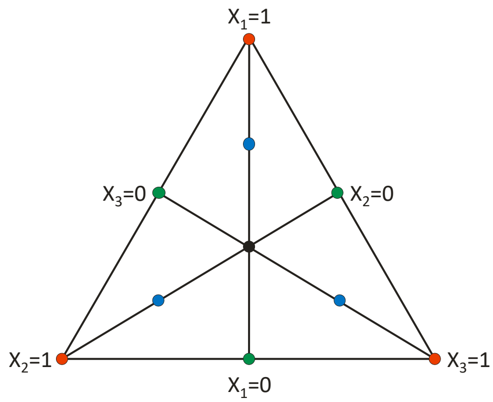

*When studying 6 or more components, consider an initial minimal-blend design (broad-and-shallow) with only the extreme combinations to screen these down.*

*Then do an in-depth optimization with just the vital few components.*

## Simplex Screening Designs

Pick (q + n), (2q + n) or (3q + n) design points, it's your option:

1. Vertices (q)
2. Axial check blends (q: optional points)
3. Overall centroid (replicated n times)
4. Constraint plane centroids (q: optional points)




*Along these tracks, each component goes from 0 to 1 while the proportions of the other components stay constant.*



## Simplex-Screening Design
*Success Story!*

Randy and his team at the U. S. Horticultural Research Lab in Ft Pierce, Florida ran a mixture-screening experiment on 8 growth regulators affecting shoot regeneration from a "Hamlin" sweet orange.* The screen identified two ingredients producing the greatest number—one (E: "ZR") being "extremely expensive" versus the other (A: "BA"), which costs "about 2,000x" less, yet "perfectly acceptable" being "only marginally less effective."

Citrus
Rebuild, Show Space Type, Reopen, Analyze, Trace

Randy Niedz & Terence Evens, "Mixture screening and mixture-amount designs to determine plant growth regulator effects on shoot regeneration from grapefruit (Citrus paradisi macf.) epicotyls," *In Vitro Cell.Dev.Biol.—Plant* (2011) 47:682–694.
*(Picture from https://minnetonkaorchards.com/hamlin-orange-tree/ )

## Extreme-Vertices Screening Designs
### For non-simplex constrained mixtures

Pick (2q + n) design points:

1. 2q vertices (for example 20 vertices for an experiment on 10 components).
   - Used to estimate linear effects.
2. Overall centroid (replicated n times; e.g., 5 times).
   - Provides a check for curvature.

*No worries,*
*Stat-Ease software will detect*
*if your constraints fit a simplex (or not).*



## Mixture-Screening Case Study

In this pioneering application of mixture screening,* chemists at Du Pont experimented on 8 ingredients 4 of which (underlined) were new. They hoped to identify components that would increase their critical-to-quality property and eliminate others to simplify their product recipe. They set up their design per the following ranges:

| | |
|---|---|
| .10 ≤ A (X1) ≤ .45 | .10 ≤ E (X5) ≤ .60 |
| .05 ≤ B (X2) ≤ .50 | .05 ≤ F (X6) ≤ .20 |
| 0 ≤ C (X3) ≤ .10 | 0 ≤ G (X7) ≤ .05 |
| 0 ≤ D (X4) ≤ .10 | 0 ≤ H (X8) ≤ .05 |

*Extreme*
*Rebuild, Analyze, Trace (spaghetti)*
*Go back to ANOVA & view gradients (shown next slide)*

*Snee and Marquardt, "Screening Concepts and Designs for Experiments with Mixtures," *Technometrics*, Vol. 18, No. 1, Feb 1976.

## Extreme-Vertices Screening

*Sort out components by their gradients*

| Component | Gradient in Reals | Component Effect | Gradient Std Error | Approx t for $H_0$ Gradient=0 | Prob > \|t\| | Gradient in Pseudo |
|---|---|---|---|---|---|---|
| **A-X1** | **-9.36** | -3.28 | 0.9743 | -9.61 | < 0.0001 | -6.55 |
| **B-X2** | **-6.24** | -2.81 | 0.8504 | -7.34 | < 0.0001 | -4.37 |
| C-X3 | 1.03 | 0.1031 | 2.73 | 0.3782 | 0.7114 | 0.7219 |
| D-X4 | -2.28 | -0.2279 | 2.78 | -0.8190 | 0.4276 | -1.60 |
| **E-X5** | **10.78** | 5.39 | 0.7881 | 13.67 | < 0.0001 | 7.54 |
| **F-X6** | **-3.42** | -0.5134 | 1.78 | -1.93 | 0.0762 | -2.40 |
| **G-X7** | **10.70** | 0.5351 | 5.25 | 2.04 | 0.0622 | 7.49 |
| **H-X8** | **19.26** | 0.9632 | 5.25 | 3.67 | 0.0028 | 13.48 |

*The chemists liked the positive impacts from new components G and H and added them to their mix. They rejected C and D. BTW, though existing ingredients A, B and F created negative effects, they were kept due to being cheap, but reduced in level.*

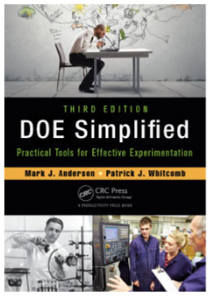


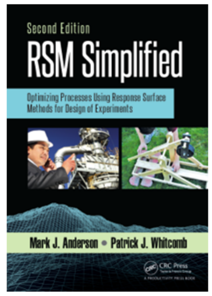
## This Webinar: What's In It for You

- By way of example, this presentation lays out a strategy for mixture design of experiments (DOE) that provides maximum efficiency and effectiveness for development of an ideal product recipe.
- It provides a sure path for converging on the 'sweet spot'—the most desirable combination of components.
- Learn how to screen down many ingredients to find the vital few and then discover their optimal formulation.

*Now you know!*

## References
*DOE/RSM/Formulation Simplified Series**





**Anderson, et al, Taylor & Francis, Productivity Press, New York, NY.*

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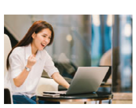
## Stat-Ease Training:
Sharpen Up Your DOE Skills

- Modern DOE for Process Optimization (public or private)
- Mixture Design for Optimal Formulations (public or private)
- Designed Experiments for Specific Industries (private only)

| Individuals | Teams (6+ people) |
|---|---|
| Improve your DOE skills | Choose your own date & time |
| Ideal for novice to advanced | Customize via select case studies |



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Mark J. Anderson, Engineering Consultant
Stat-Ease, Inc., Minneapolis, MN
mark@statease.com
www.linkedin.com/in/markstat/


*Stay on for some chat if you like.*