Centre for Process Systems Engineering

PharmaSEL

Paper 483 at ESCAPE30

Nested Sampling Strategy for Bayesian Design Space Characterization

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Overview

Topics and Key Concepts

- **Design Spaces**
- Methods
- Results

- Process Flexibility
- Process Uncertainties
  - Noisy disturbances
  - Changes in processing requirements
  - Imperfect information
- Pharmaceutical Quality by Design

Overview

Topics and Key Concepts

- Design Spaces
- **Methods**
- Results

- Algorithm Classes
  - Design Centering
  - Sampling-based
- Uncertainty Quantification
  - Probabilistic
  - Set-based
- Bayesian Design Spaces

Overview

Topics and Key Concepts

- Design Spaces
- Methods
- **Results**

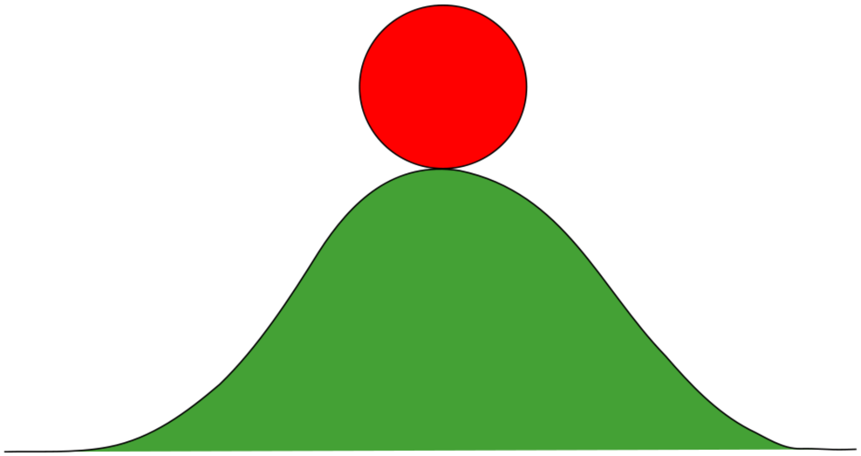
- Nested Sampling for Design Space
  - Outline
  - Comparison
- Improvements to NS for DS
  - Vectorization
  - Two-phase strategy
  - Dynamic Number of Live Points
- DEUS
  - Python implementation
  - Open-source

Flexibility

Process Flexibility

1. Process optimization → effective & efficient processes

Optimization Goal:
place ball at highest point



Optimal!

Flexibility

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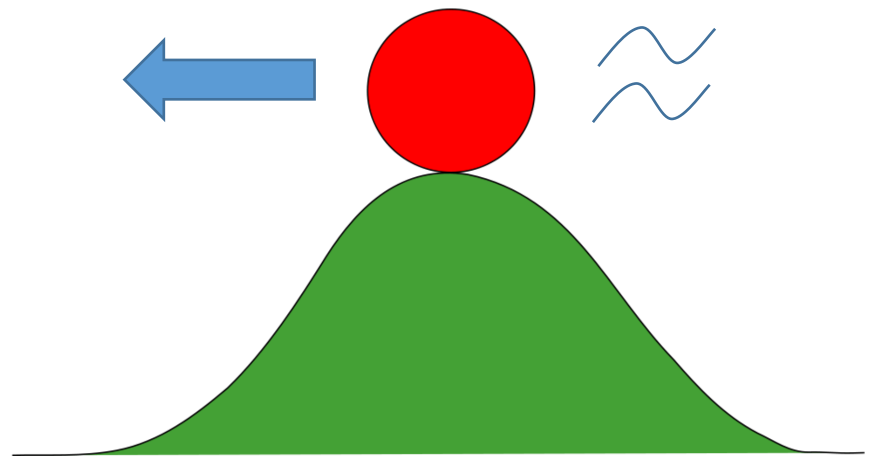

Optimal!
Stable?

Flexibility

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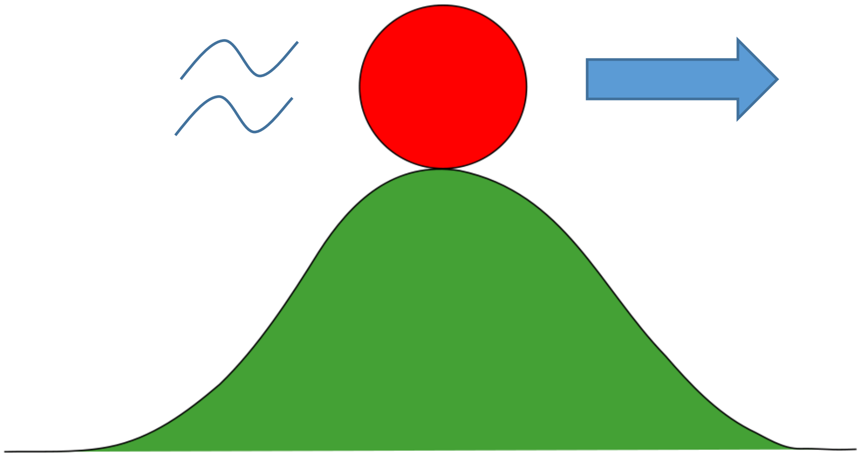


Optimal!
Stable?

Flexibility

Process Flexibility

1. Process optimization → effective & efficient processes

2. Understanding process **flexibility** is important!

Flexibility Analysis

"Is control needed to ensure feasibility given uncertainty?"

Optimization Goal
place ball at highest point

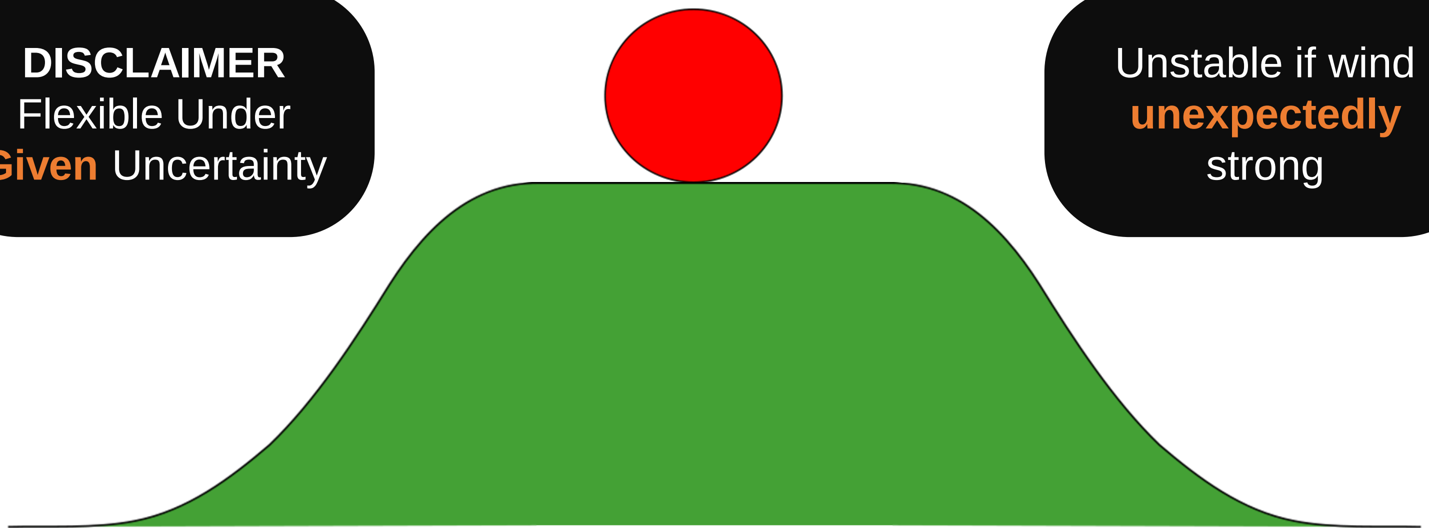
Optimal ≠ Stable

<u>Alternative Outcome</u>
Innately Flexible System

→

A *space* where goal achieved
Larger space → more flexible

DISCLAIMER
Flexible Under
Given Uncertainty



Unstable if wind
unexpectedly
strong

Optimal & **Stable Without Controls**

Design Space

Pharmaceutical Quality by Design

- Quality by Design
  - Set of guidelines for pharmaceutical process development
  - Promotes systematic, holistic approaches
- Design Space

"Multidimensional combination and interaction of input variables (material attributes) and process parameters that have been demonstrated to provide assurance of quality"

- Characterization offers **regulatory** flexibility
  - No re-approval for process changes within DS
  - Promote holistic process understanding

Design Space

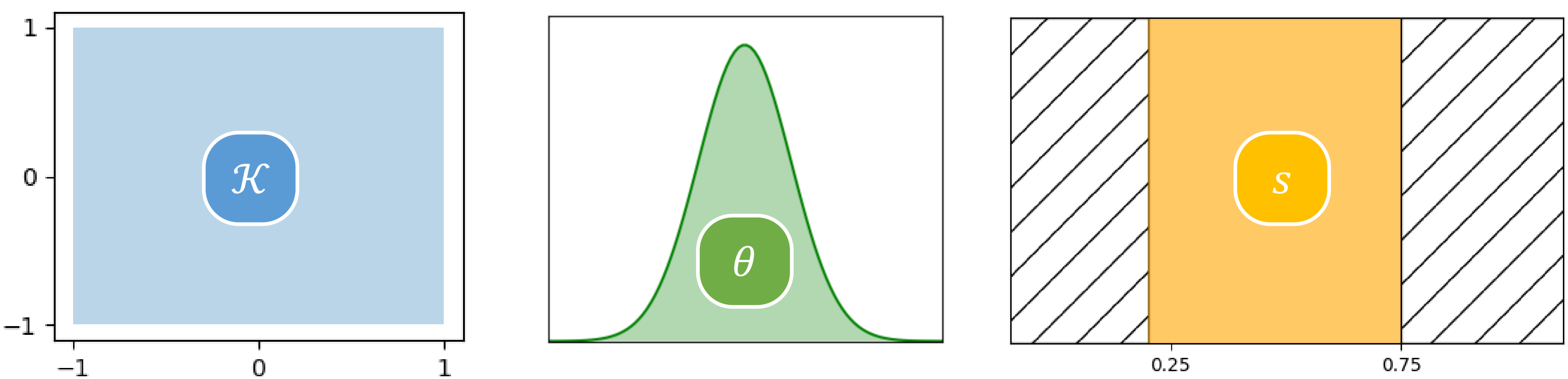
Illustrative Example

Design Variables
$\boldsymbol{d} \in \mathcal{K}$

Uncertain Variable
θ

→ **Model**
$\theta d_1^2 + d_2$ →

Critical Quality Attribute(s)
$0.20 \leq s \leq 0.75$



Design Space

Illustrative Example

Model

$\theta d_1^2 + d_2$

→

Nominal DS $\mathcal{D}_{\text{nom}}$

$\theta = \theta_{\text{nom}}$

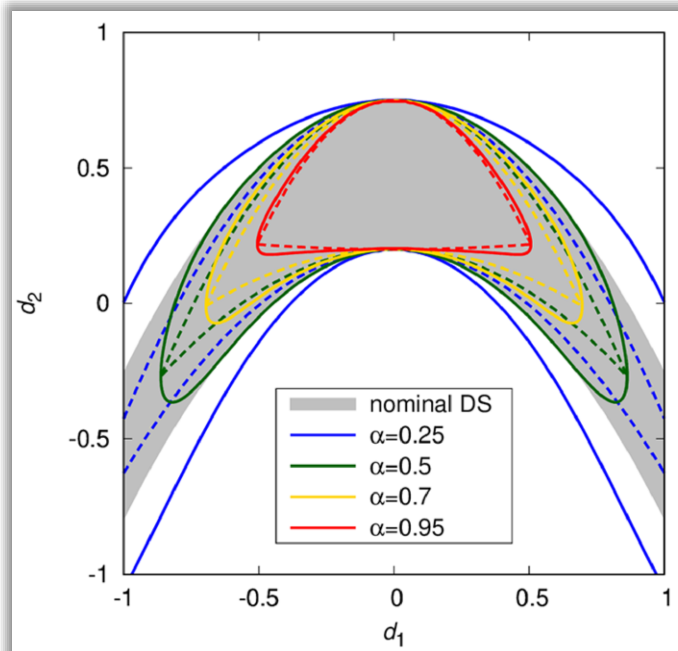
Bayesian DS $\mathcal{D}_{\alpha}$

$\theta \sim p(\theta)$

Robust DS $\widehat{\mathcal{D}}_{\alpha}$

$\theta \in \Theta$

→



Solid Lines : Bayesian

Dashed Lines : Robust

Design Space

Illustrative Example

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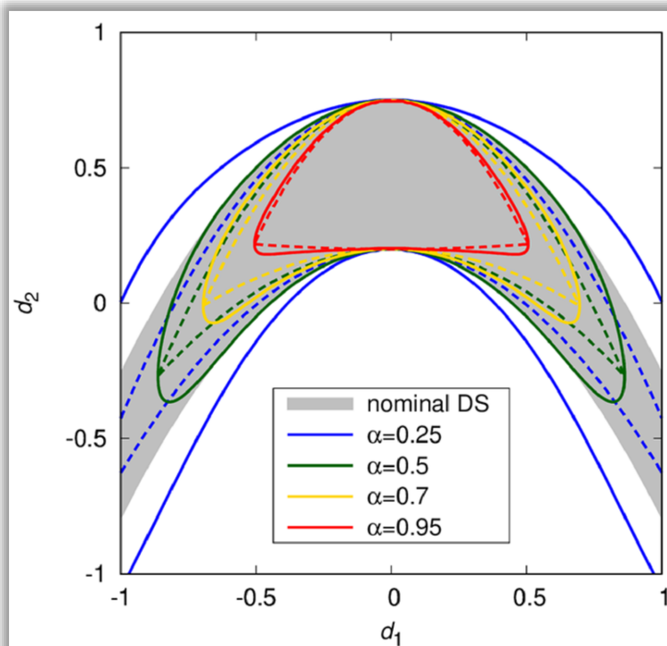

Solid Lines : Bayesian
Dashed Lines : Robust

- ❑ $\mathcal{D}_{\mathrm{nom}}$ excessively optimistic
- ❑ Often lead to false positives
- ❑ Unsuitable for strictly-regulated processes

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Design Space

Illustrative Example

Model

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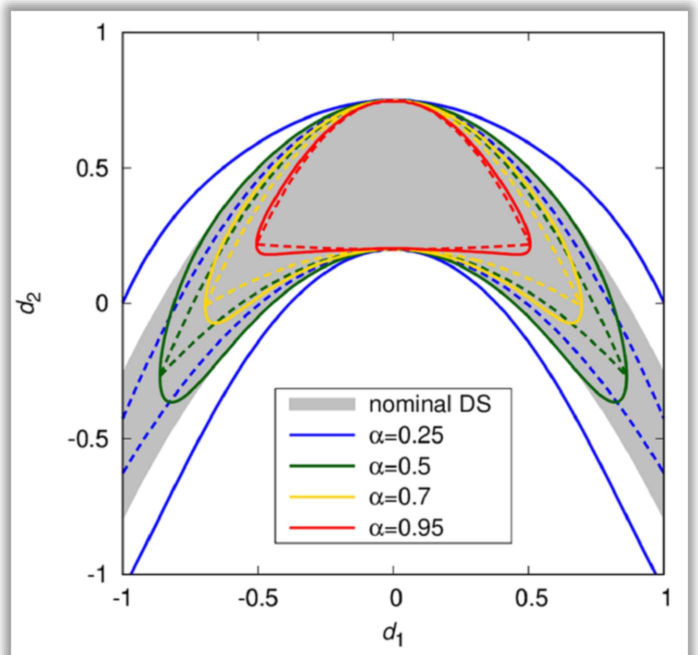

Solid Lines : Bayesian
Dashed Lines : Robust

- Reliability value α specifies attitude
- Treat θ as random variable
- Exploits information from probability density function $p(\theta)$

Design Space

Illustrative Example

Model

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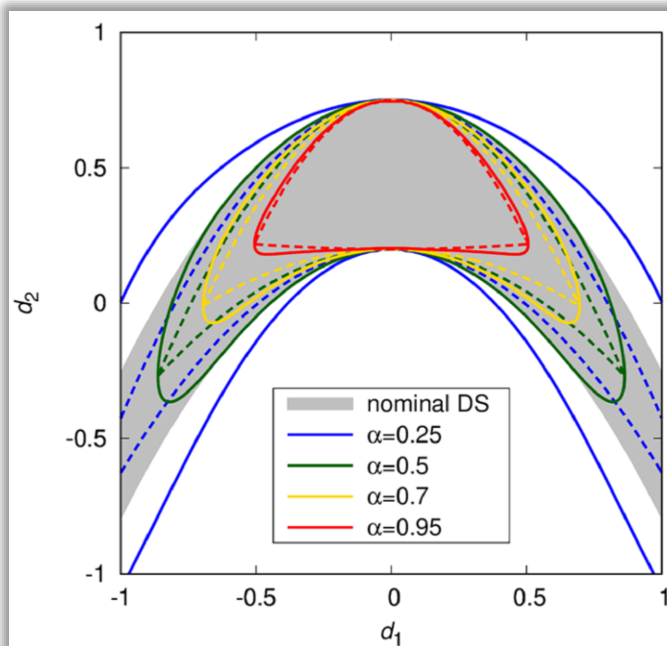
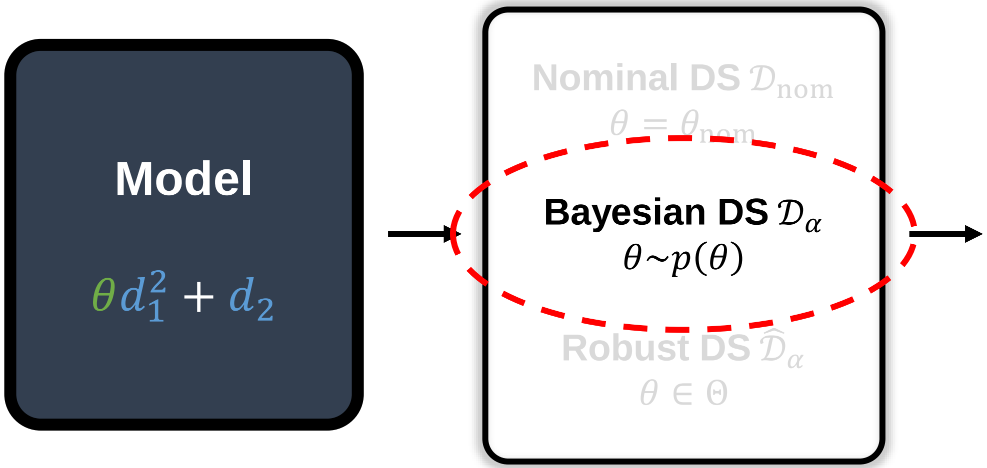


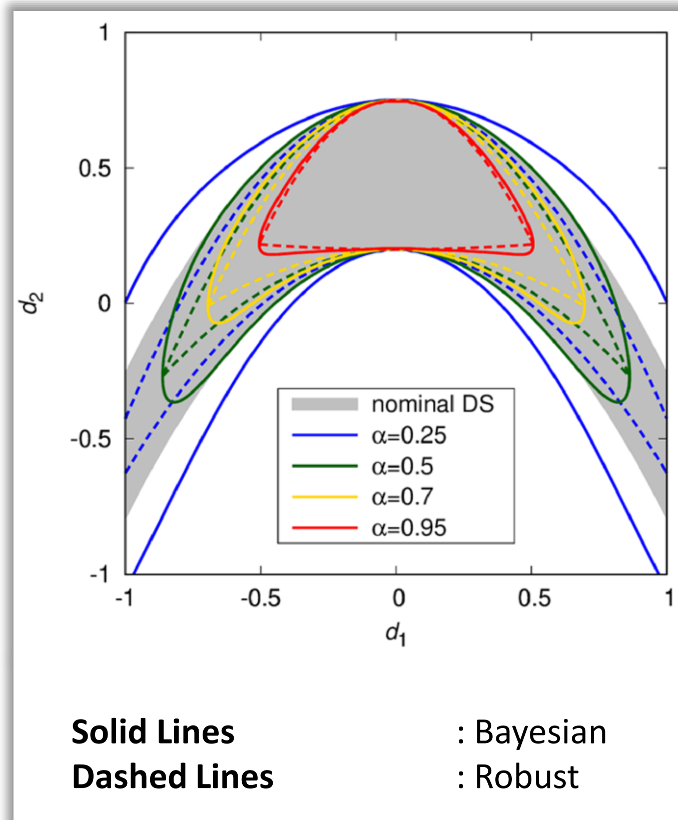
Solid Lines : Bayesian
Dashed Lines : Robust

- Treat θ as random variable bounded in Θ
- *Robust* towards all values within Θ
- Θ depends on α

Design Space

Illustrative Example





- ❑ Focus of this work
- ❑ Challenging and computationally costly
- ❑ Effective & efficient tools are needed

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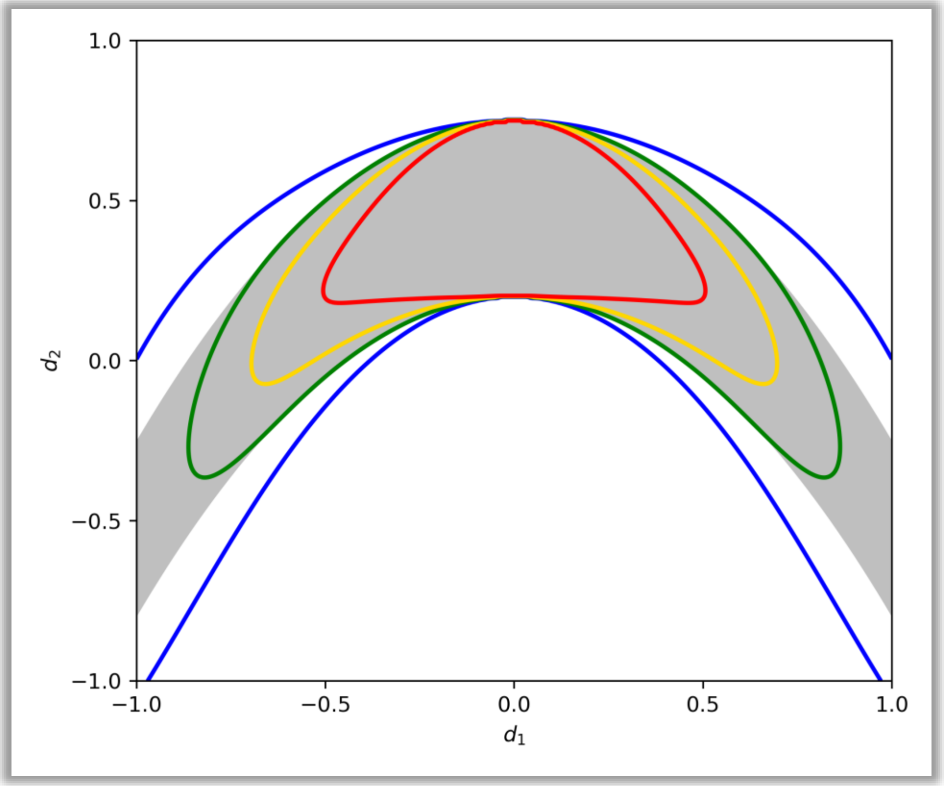
Methods

Numerical Strategies

- ❑ **Design-centering algorithms**

- ❑ **Sampling algorithms**



Methods

Numerical Strategies

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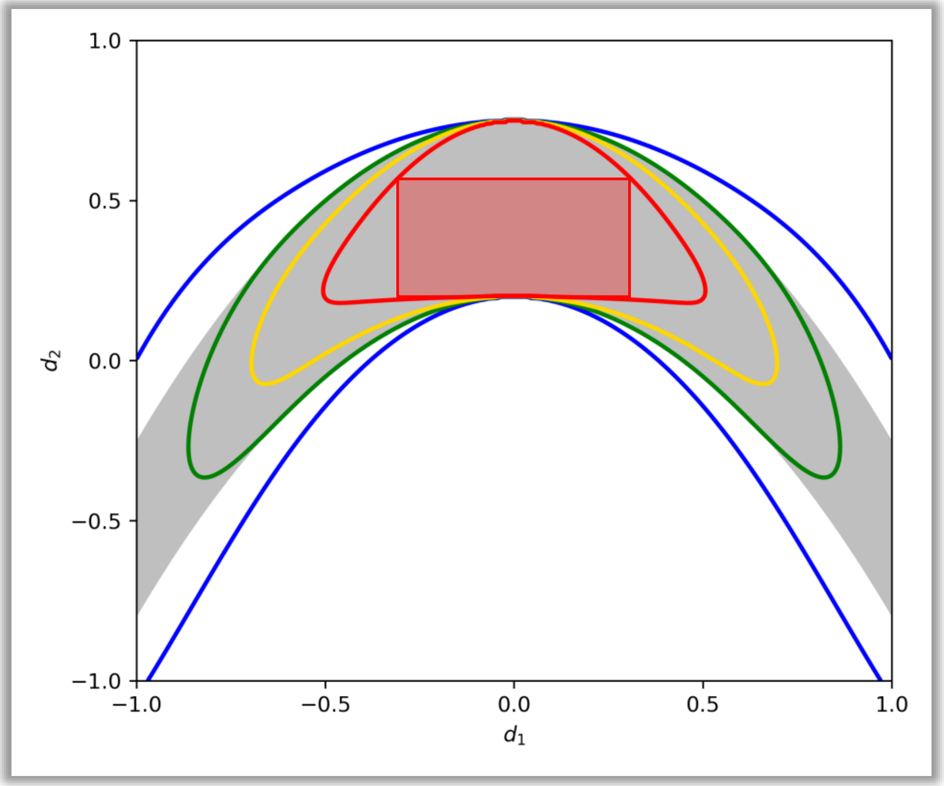

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Methods

Numerical Strategies

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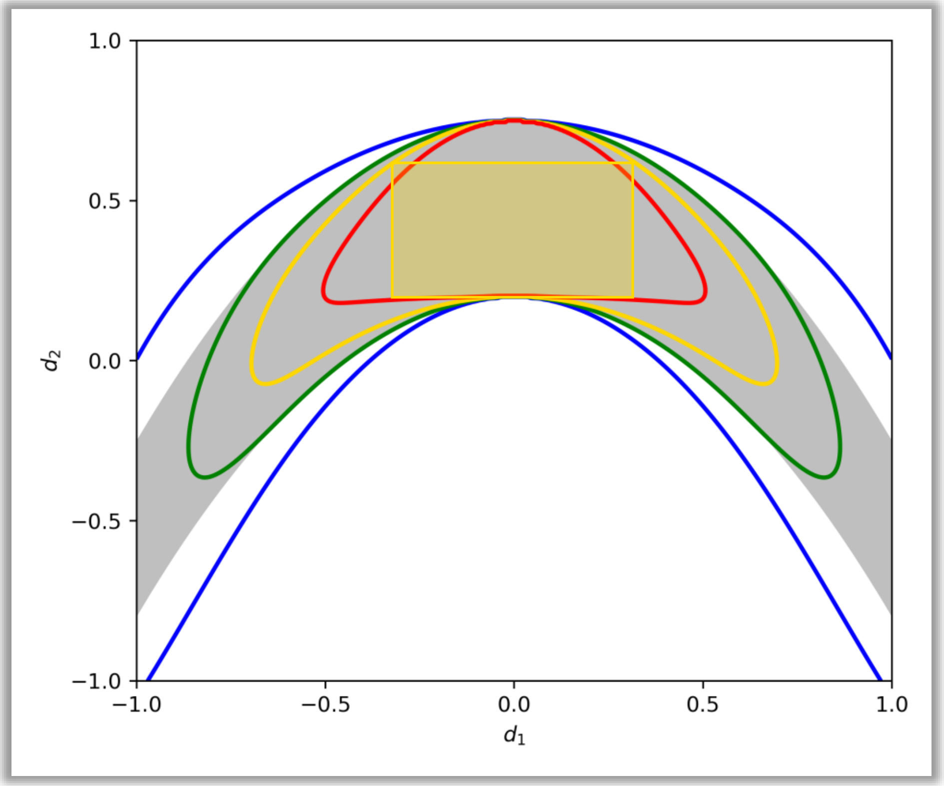

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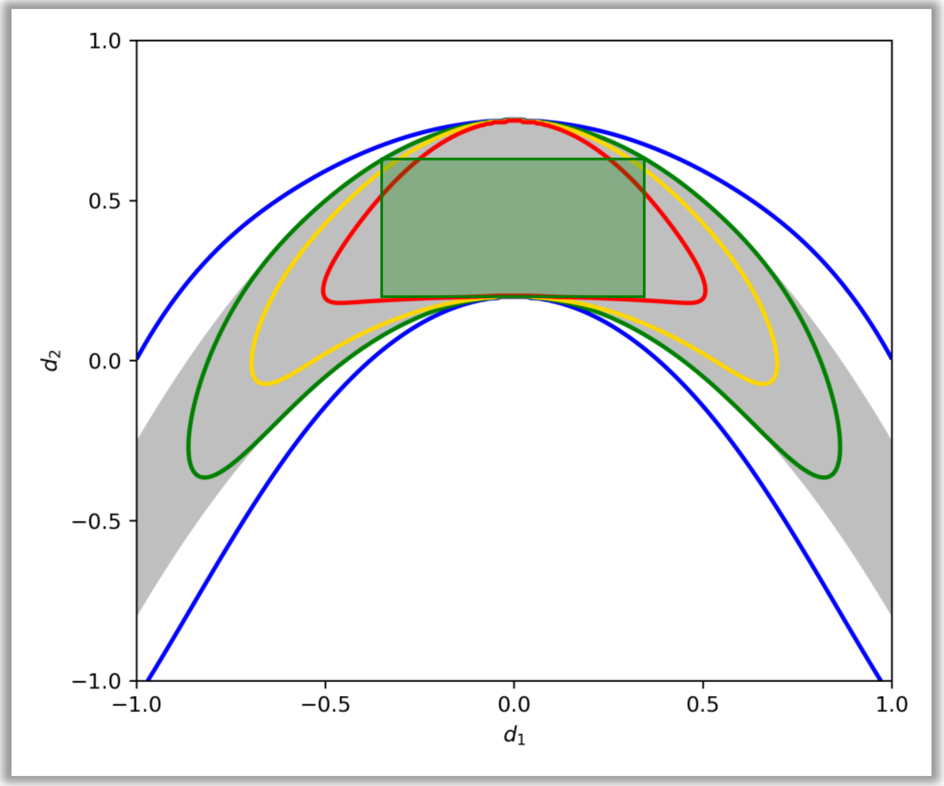

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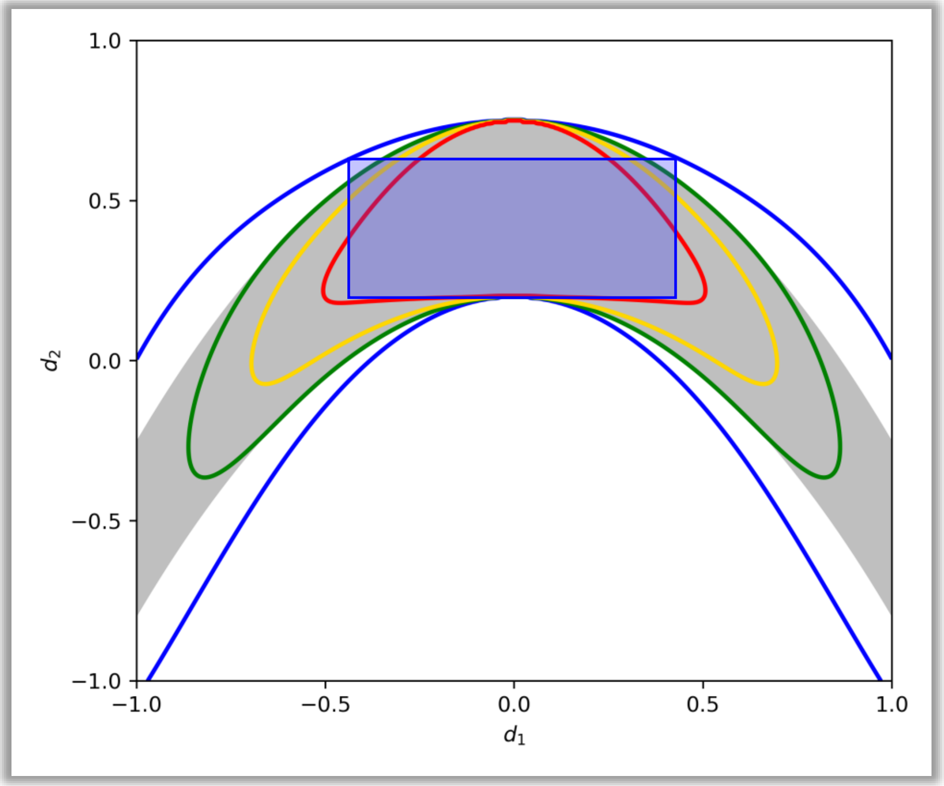


- ❑ Sampling algorithms

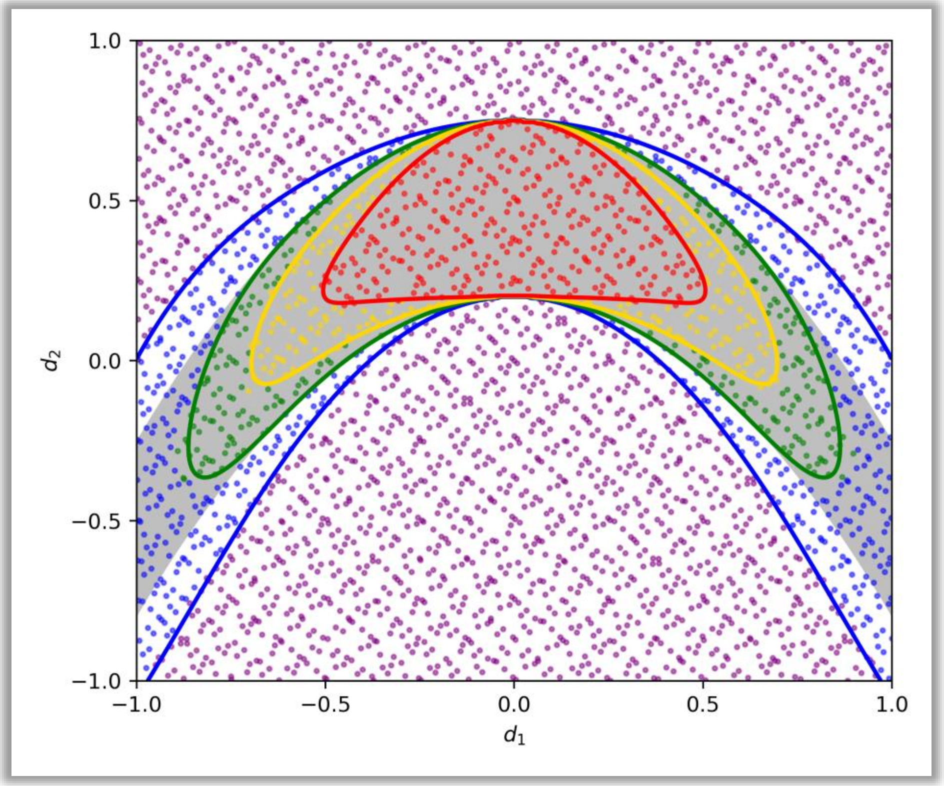
Methods

Numerical Strategies

- ❑ Design-centering algorithms

- ❑ **Sampling algorithms**

Sobol Sampling – Non Adaptive

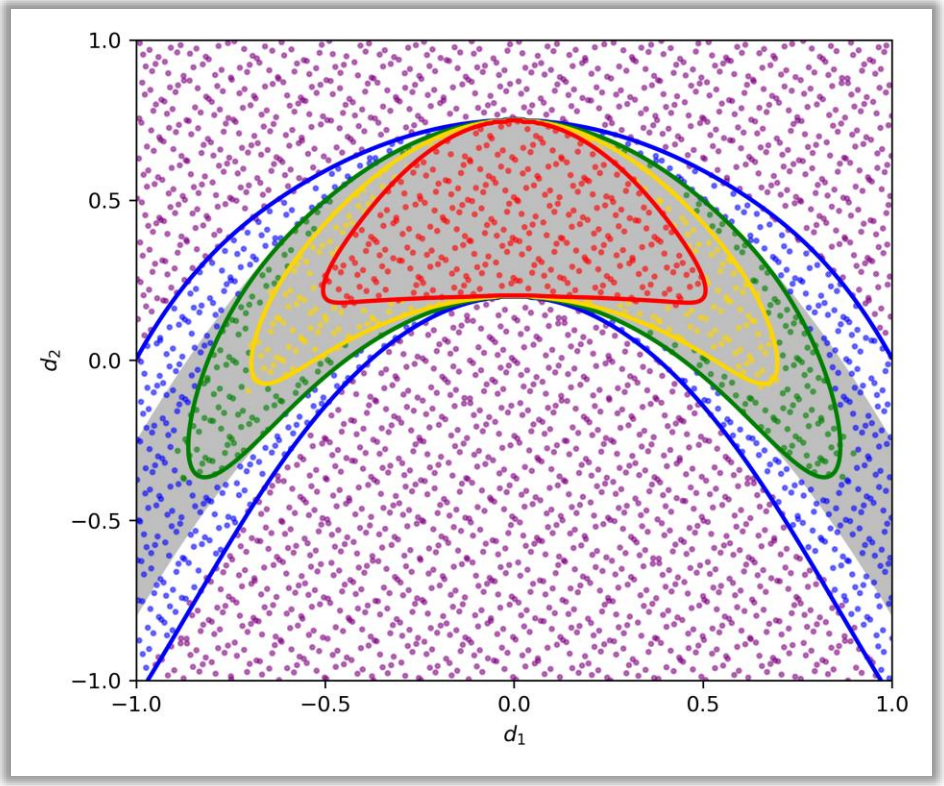


Methods

Numerical Strategies

- Design-centering algorithms

Effective!



- **Sampling algorithms**

Methods

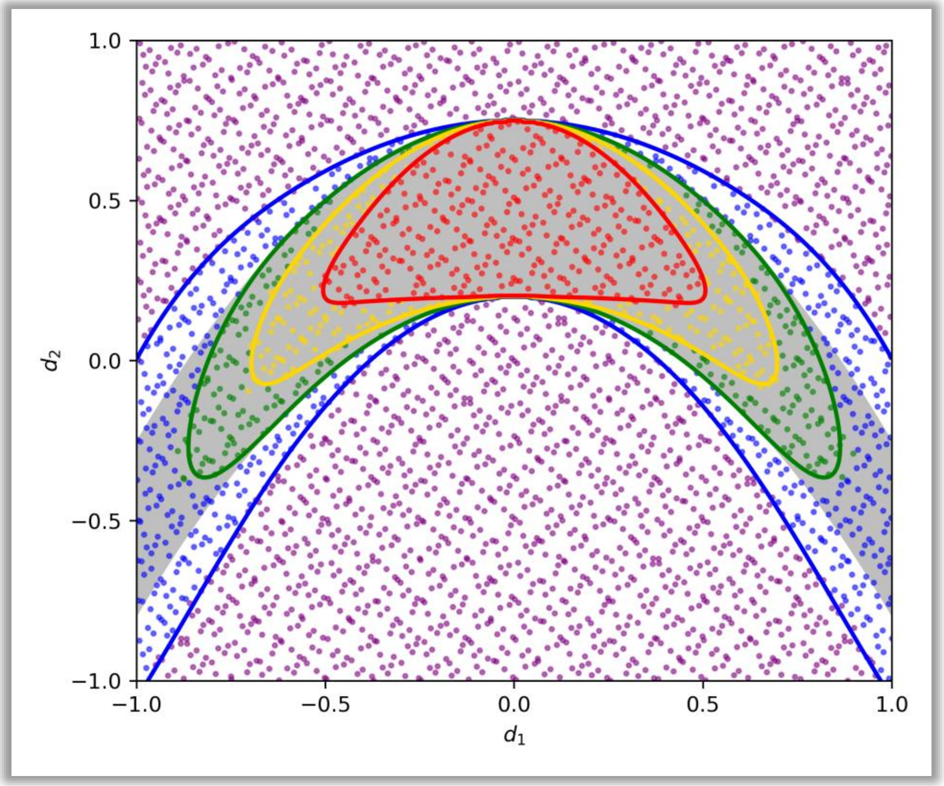
Numerical Strategies

- ❑ Design-centering algorithms

- ❑ **Sampling algorithms**

Each sample may require ~10^2 - 10^9 model runs

Effective, but too costly → 3,249 samples



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- ❑ Design-centering algorithms

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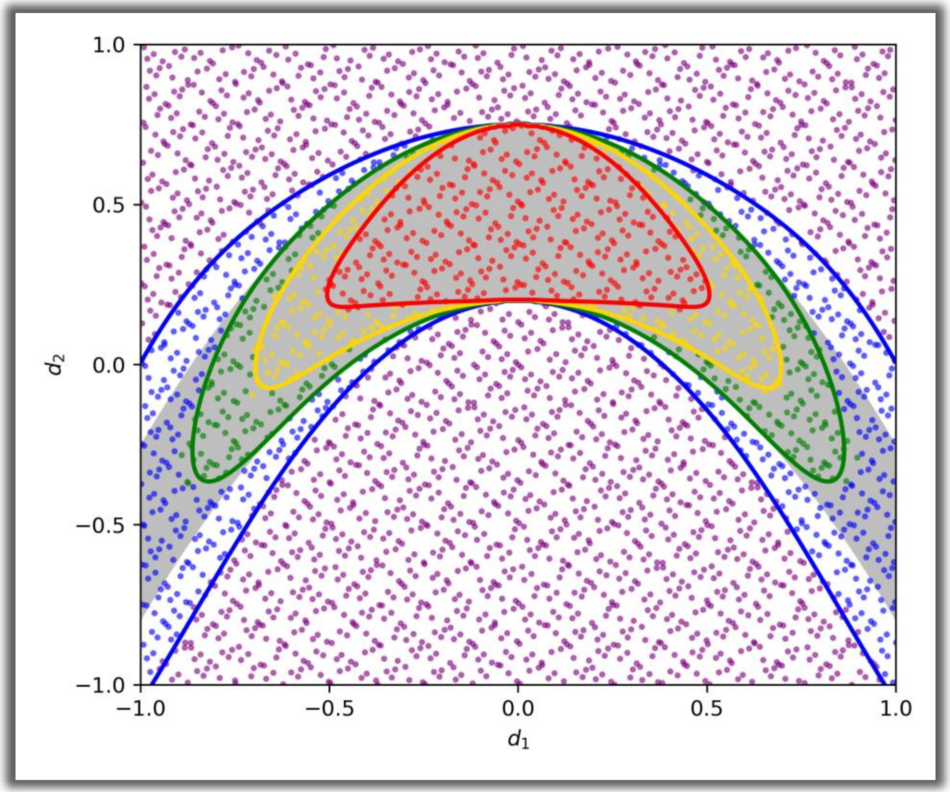
NESTED SAMPLING
For Design Space[1]

Samples **concentrate** towards target α



[1] Kennedy P. Kusumo, Lucian Gomoescu, Radoslav Paulen, Salvador García Muñoz, Constantinos C. Pantelides, Nilay Shah, and Benoît Chachuat *Industrial & Engineering Chemistry Research* **2020** *59* (6), 2396-2408 DOI: 10.1021/acs.iecr.9b05006

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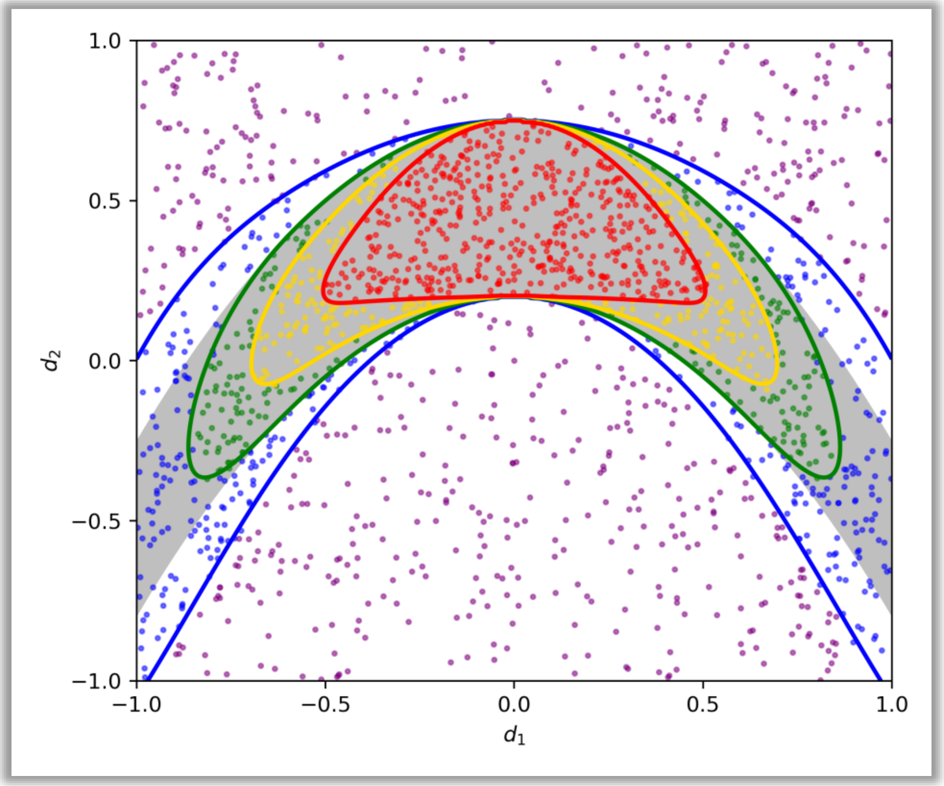

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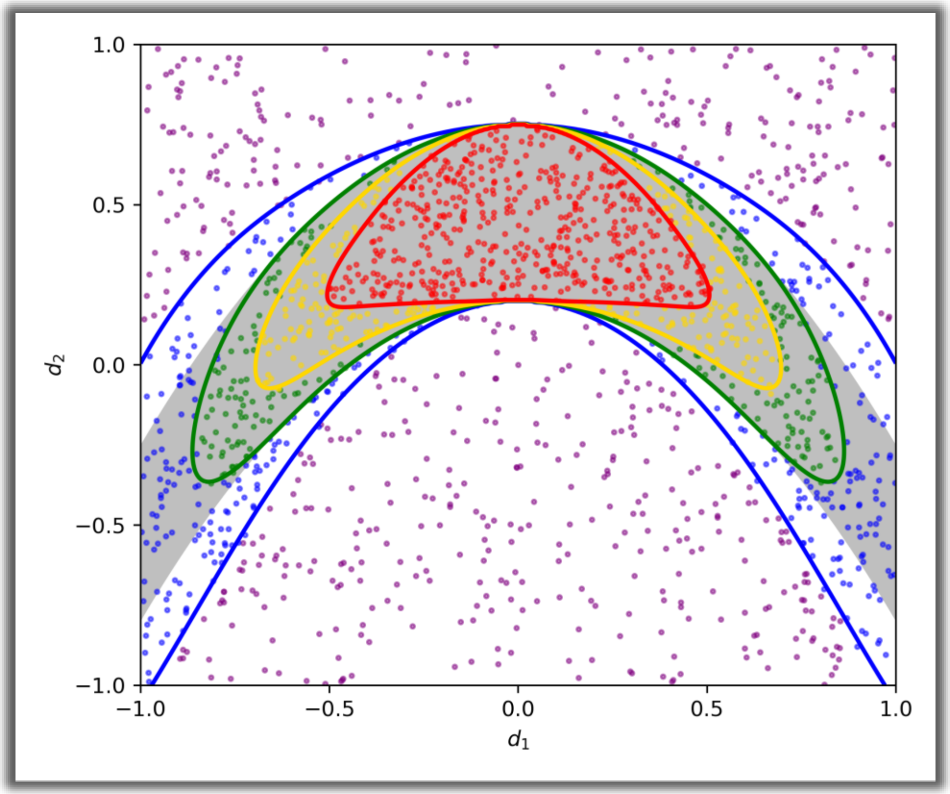
Methods

Nested Sampling



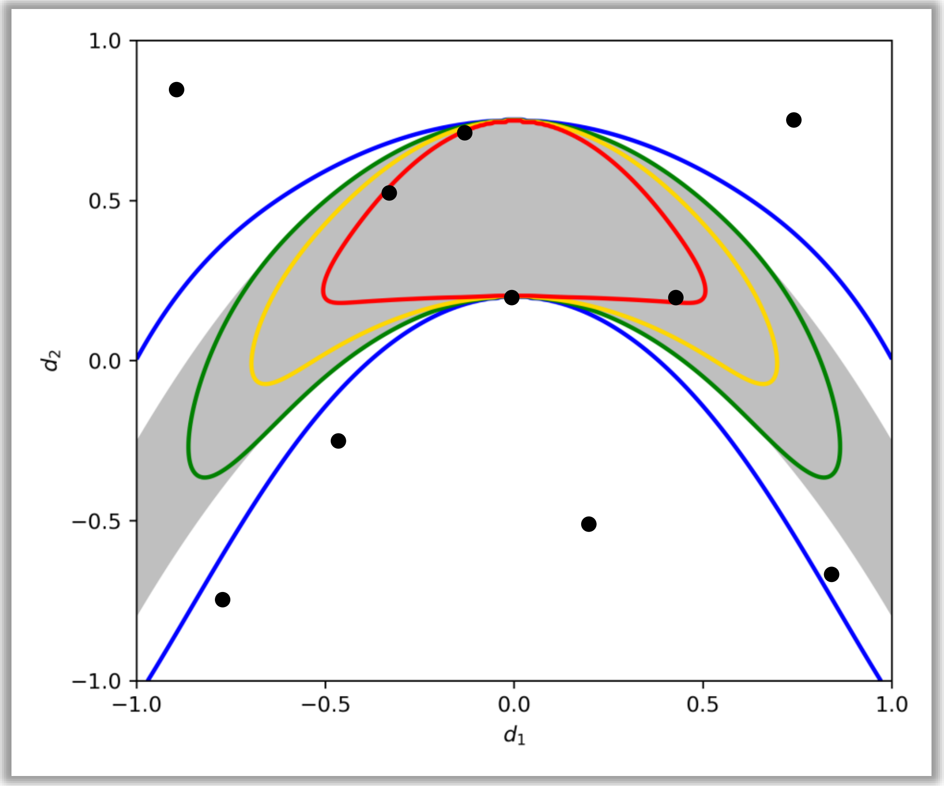
Outline

- ❑ Maintain constant no. of **live points**
- ❑ Iteratively replace with better points
- ❑ Many proposal schemes
- ❑ Chosen scheme[1]:
  - Uniform points in **enlarged** ellipsoid around live points
  - Enlargement factor of ellipsoid shrinks between iterations

[1] Feroz, F.; Hobson, M. P.; Bridges, M. MultiNest: an efficient and robust Bayesian inference tool for cosmology and particle physics. Mon. Not. R. Astron. Soc. 2009, 398, 1601−1614

Methods

Nested Sampling



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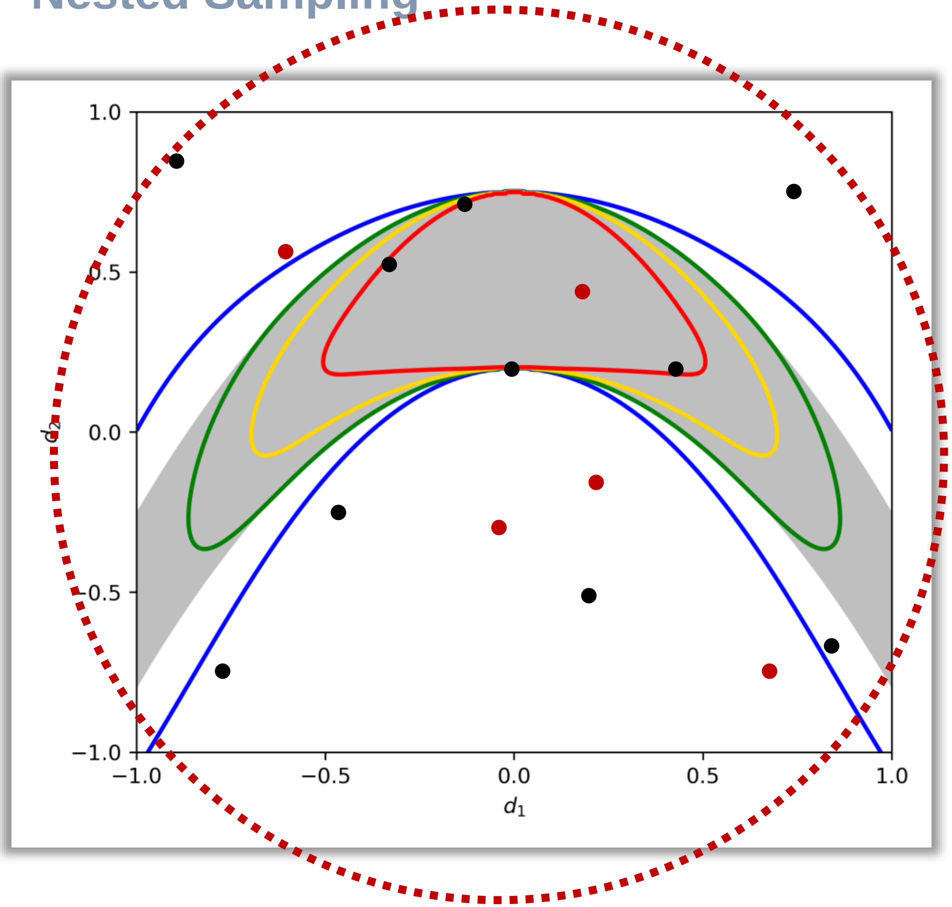

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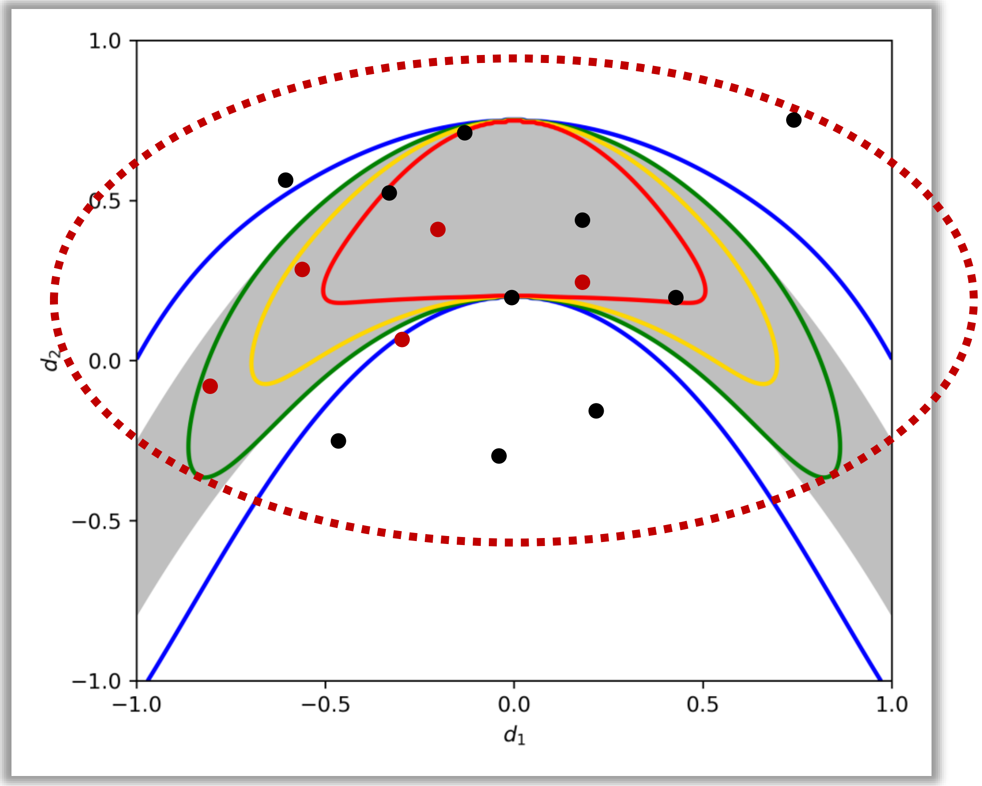

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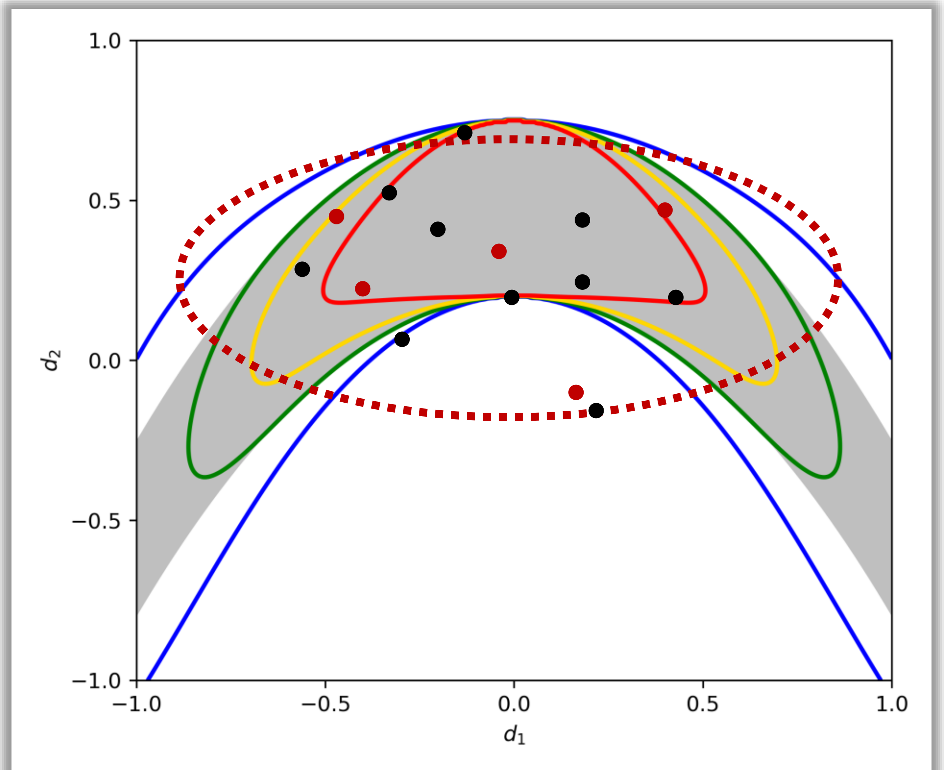

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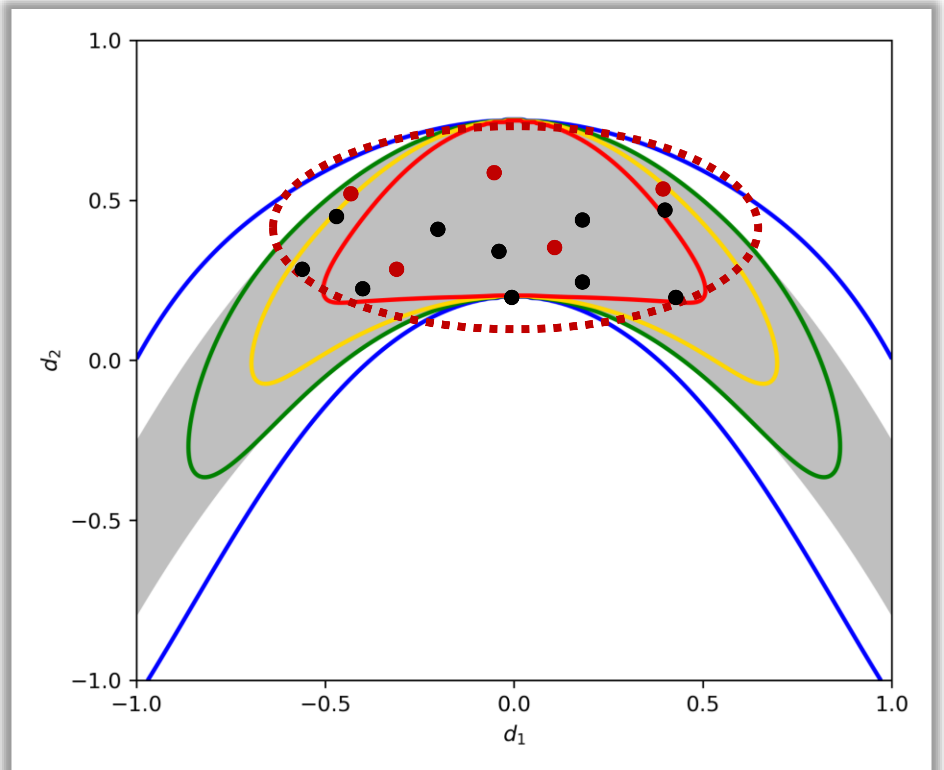

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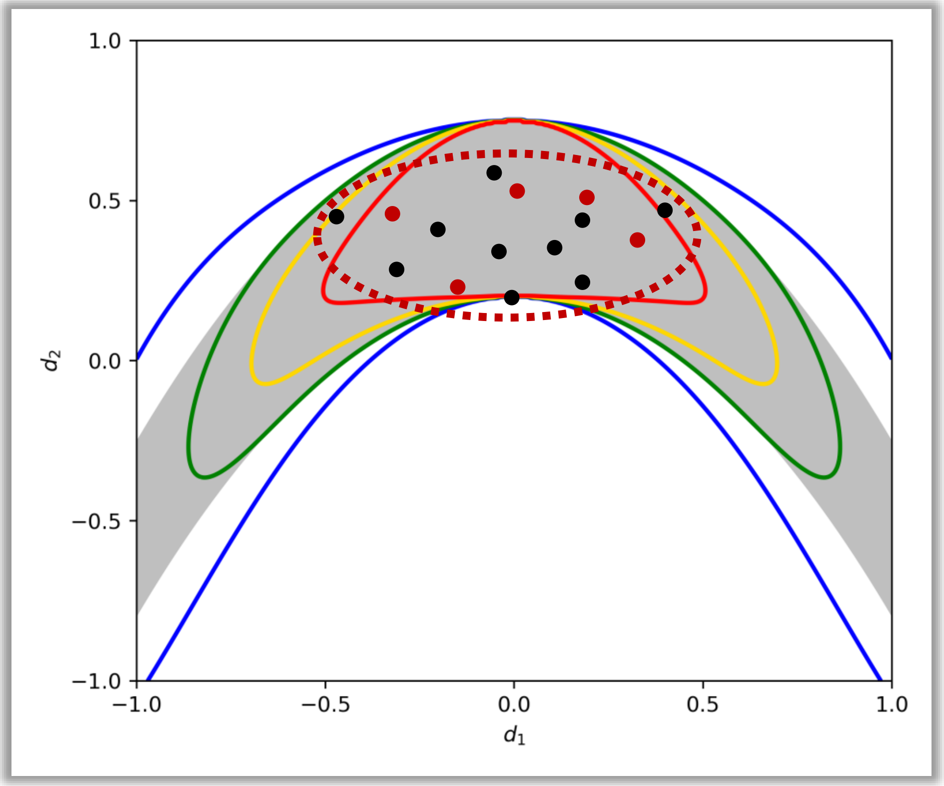

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Improvements

Three Ideas for Nested Sampling

I1: Two-phase nested sampling

- Draw samples from $\mathcal{D}_{\mathrm{nom}}$
- Initialize with $\mathcal{D}_{\mathrm{nom}}$ samples
- Less evaluations for *locating* $\mathcal{D}_{\alpha}$

I2: Dynamic number of live points

- $\uparrow N_{\mathrm{L}}$ over iterations
- Top-up live points
- Further concentrate samples in target $\mathcal{D}_{\alpha}$

I3: Vectorized function evaluations

- Do model runs in parallel
- Utilize multi-cores in CPUs

Improvements

Three Ideas for Nested Sampling

Reduced Evaluations

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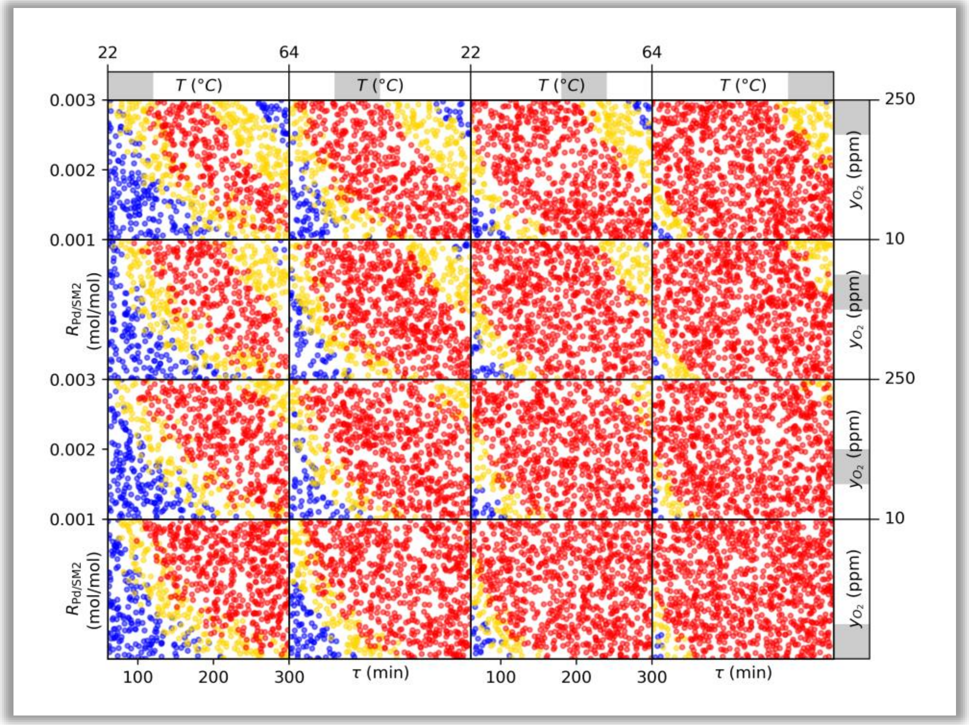
Time Savings

Original Strategy

Industrial Case Studies: Suzuki Coupling Reaction[1]

- Batch Reactor.
- 4-dimensional DS.
- 11 chemical reactions with 22 uncertain kinetic parameters.
- Two constraints:
  - Conversion of reactant
  - Concentration of impurity



112.4 CPU hrs
Manageable Cost

14.54×10^6
Model runs

[1] García-Muñoz, S.; Luciani, C. V.; Vaidyaraman, S.; Seibert, K. D. Definition of design spaces using mechanistic models and geometric projections of probability maps. Organic Process Research & Development 2015, 19, 1012–1023.

Improved Strategy

Industrial Case Studies: Suzuki Coupling Reaction[1]

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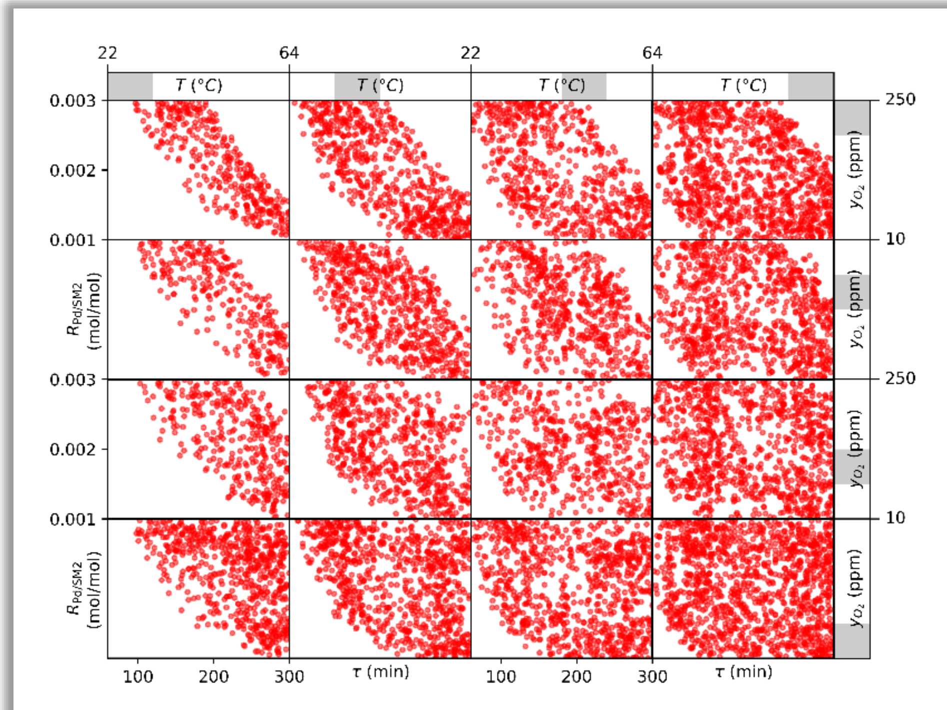

21.8 CPU hrs
Convenient Cost

11.80×10^6
Model runs

[1] García-Muñoz, S.; Luciani, C. V.; Vaidyaraman, S.; Seibert, K. D. Definition of design spaces using mechanistic models and geometric projections of probability maps. Organic Process Research & Development 2015, 19, 1012–1023.

Conclusion

Remarks

- A sampling-based approach: applicable to any model
- Three changes to NS for DS were proposed
- Compared to the original NS on the same industrial case study
  - Four-fold reduction in computation time
  - ~15% reduction in evaluations
- The changes proved to be improvements
  - Help solve problems previously too large

Implementation

DEUS: Python Package

- DEUS available on demand at: https://github.com/omega-icl/DEUS

Thank You!

Questions?

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