Modeling and Active Learning for Experiments with Quantitative-Sequence Factors

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Quantitative-Sequence (QS) factors:

- In modern scientific areas, there are non-traditional experiments considering both the quantities and sequences for arranging components, named as quantitative-sequence (QS) factors.
- Cancer Treatment – in vitro study:
  - Three anti-tumor drugs A, B and C were added in a sequence with different doses.
  - The percentage of tumor inhibition was measured six hours after administering the last drug.

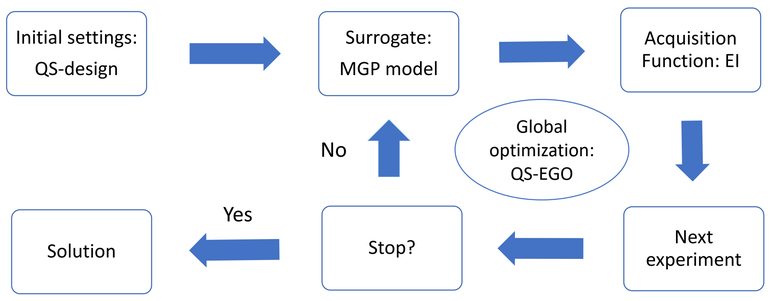
Run	Drug A		Drug B		Drug C		Response
	dosage	order	dosage	order	dosage	order	
1	3.75 μM	1	95 nM	2	0.16 μM	3	39.91
2	2.80 μM	1	70 nM	2	0.16 μM	3	30.00
3	3.75 μM	3	95 nM	1	0.16 μM	2	34.68

- Experiments with QS Inputs
  - Characteristics of Quantitative-Sequence (QS) factor:
    - Different drug dosage affects the response.
    - Different sequence order affects the response.
    - The QS factor is not purely continuous, not purely categorical and not purely ordinal.
  - Objectives:
    - To study the relationship between the response and the QS factor.
    - To optimize the dosage and the order in the sequence for each drug.
  - Challenges:
    - Numerous possibilities: for k components with s levels, $s^k \times k!$ possible runs.
    - A good design for QS input is not trivial.
    - A good statistical model for QS input is needed.

QS-learning

We propose an active learning approach (QS-learning) which includes

1. **MaGP**: a novel mapping-based additive Gaussian process model for prediction and uncertainty quantification,
2. **QS-EGO**: a sequential scheme using efficient global optimization algorithms,
3. **QS-design**: a new class of optimal experimental designs for collecting initial data points.



MaGP

- Consider the i^{th} input as $\mathbf{w}_i = (\mathbf{x}_i^{\mathrm{T}}, \mathbf{o}_i^{\mathrm{T}})^{\mathrm{T}}$ with $\mathbf{x}_i$ takes quantitative values and $\mathbf{o}_i$ is a vector containing the orders of the components in the arrangement sequence.
- For an experiment with n runs and k components, we model the output at $\mathbf{w} = (\mathbf{x}^{\mathrm{T}}, \mathbf{o}^{\mathrm{T}})^{\mathrm{T}}$ as

$$Y(\mathbf{w}) = \mu + \sum_{h=1}^{k} G_h(\mathbf{w}) + \epsilon,$$

where $G_1, \ldots, G_k$ are independent zero-mean GP with stationary covariance functions and $\epsilon \sim N(0, \tau^2)$ is a random error ($\tau^2 > 0$ for physical experiments and $\tau^2 = 0$ for computer experiments).

- G_h corresponds to the impact of h^{th} component with its covariance function ϕ_h as

$$\phi_h(\mathbf{w}_i, \mathbf{w}_j) = \sigma_h^2 \exp\Big\{ -\theta_h (x_{i,h} - x_{j,h})^2 \Big\} \exp\Big\{ -\sum_{l=1}^{t} (\tilde{o}_{i,h}^{(l)} - \tilde{o}_{j,h}^{(l)})^2 \Big\}$$

where σ_h^2 is the variance parameter and θ_h is the correlation parameter for the h^{th} component.

- We consider mapping the order o_h to a vector $(\tilde{o}_h^{(1)}, \ldots, \tilde{o}_h^{(t)})$. The t-dimensional mapping $(t = 1, \ldots, k-1)$ for the order of any component is defined as

$$\begin{matrix} c_1, \ldots, c_k \end{matrix} \begin{bmatrix} 1 \\ 2 \\ \vdots \\ k \end{bmatrix} \rightarrow \begin{matrix} \tilde{o}^{(1)} & \tilde{o}^{(2)} & \ldots & \tilde{o}^{(t)} \end{matrix} \begin{bmatrix} \delta_1^{(1)} & \delta_1^{(2)} & \ldots & \delta_1^{(t)} \\ \delta_2^{(1)} & \delta_2^{(2)} & \ldots & \delta_2^{(t)} \\ \vdots & \vdots & \vdots & \vdots \\ \delta_k^{(1)} & \delta_k^{(2)} & \ldots & \delta_k^{(t)} \end{bmatrix}_{k \times t},$$

where we set $\delta_l^{(j)} = 0$ for all $j \geq l$ to avoid over-parametrization.

QS-EGO

1. Step 1: Construct an optimal initial design for QS factors with n_0 runs $\mathbf{w}_1, \ldots, \mathbf{w}_{n_0}$, evaluate their responses $Y(\mathbf{w}_1), \ldots, Y(\mathbf{w}_{n_0})$, and fit the MaGP model based on these observations.
2. Step 2: Let the next design point $\mathbf{w}_{n+1}$ maximize the expected improvement $E[I(\mathbf{w}_{n+1})]$ and observe $Y(\mathbf{w}_{n+1})$. (We proposed an algorithm.)
   Here for a target input $\mathbf{w}_* = (\mathbf{x}_*, \mathbf{o}_*)$:

$$E[I(w^*)] = (y_{\min}^{(n)} - \widehat{Y}(\mathbf{w}_*)) \Phi\left(\frac{y_{\min}^{(n)} - \widehat{Y}(\mathbf{w}_*)}{s(\mathbf{w}_*)} \right) + s(\mathbf{w}_*) \varphi\left(\frac{y_{\min}^{(n)} - \widehat{Y}(\mathbf{w}_*)}{s(\mathbf{w}_*)} \right)$$

3. Step 3: Re-fit the MaGP model based on observations $(\mathbf{w}_1, y(\mathbf{w}_1)), \ldots, (\mathbf{w}_{n+1}, Y(\mathbf{w}_{n+1}))$.
4. Step 4: Repeat Step 2 and 3 until the stopping criterion is met or the maximum number of sequential runs is reached.

QS-design

1. We propose a new class of optimal designs for QS factors, named as QS-design, which achieves space-filling and pair-balanced properties.
2. We propose a general approach to construct QS-design with any run and factor sizes; and provide a deterministic algebraic construction for certain design sizes.
3. Denote the design for QS factors as $D = (X, O)$ where X is the quantitative part and O is the sequence part, both using components as columns.
4. Our key idea is to first construct a good design O, and then construct a good design X in combination with O to obtain the QS-design $D = (X, O)$.

A Real Combinatorial Drug Experiment on Lymphoma

Lymphoma is cancer that causes lymphocytes grow out of control.

- Real Data: a 24-run three-drug (A: paclitaxel, B: doxorubicin, C: mitoxantrone) experiment for Lymphoma cancer treatment. (Wang et al. 2020)
  - All six possible sequences of the three drugs were enumerated. For each sequence, two dose-levels for A (Level 0: 2.8 μM; Level 1: 3.75 μM) and B (Level 0: 70 nM; Level 1: 95 nM), and a fixed dose-level for C (0.16 μM) were considered.
  - We run the proposed QS-learning to see if we can use fewer runs to identify the optimal treatment in this experiment. We construct an 8-run QS-design to collect the initial data and the proposed QS-learning selects 7 sequential runs until the stopping rule is satisfied.
  - The true maximum response 47.18 has been found, along with the third and fourth largest responses 44.38 and 44.33.

X_A	O_A	X_B	O_B	O_C	Y
0	3	0	2	1	35.04
1	2	0	1	3	22.26
0	1	1	3	2	43.93
1	2	1	3	1	20.88
0	1	0	2	3	30.00
1	1	0	3	2	38.18
0	2	1	1	3	26.02
1	3	1	1	2	34.68

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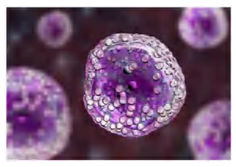
X_A	O_A	X_B	O_B	O_C	Y
1	2	1	1	3	17.08
1	1	1	2	3	39.91
1	2	0	3	1	31.40
1	1	0	2	3	44.33
1	1	1	3	2	44.38
1	3	1	2	1	37.37
0	1	0	3	2	47.18



Simulation Studies

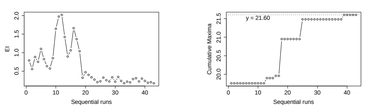
- Single Machine Scheduling Problem

$$R(\mathbf{x}) - C(\boldsymbol{\alpha}, \mathbf{x}) = w_0 \sum_{i=1}^{k} x_i - \sum_{h=1}^{k} w_h T^2(\alpha_h)$$

- Traveling Salesman Problem

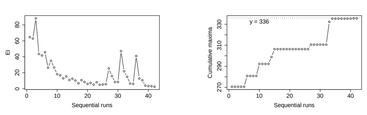
$$F(\mathbf{x}, \boldsymbol{\alpha}) = ka + e \sum_{i=1}^{k} x_i - bC(\mathbf{x}, \alpha_k) - f \sum_{j=1}^{k} T(\mathbf{x}, \alpha_j).$$

2d-MaGP model



Expected improvements Cumulative maximum responses

2d-MaGP model



Expected improvements Cumulative maximum responses

Conclusions

- In this work, we propose an active learning approach to identify optimal solutions for experiments with quantitative-sequence (QS) factors.
- Analyzing such experiments is challenging due to their semi-discrete and possibly very large solution spaces as well as complex input-output relationships.
- From our empirical results, the proposed QS-learning can provide desirable solutions within a few number of sequential runs.