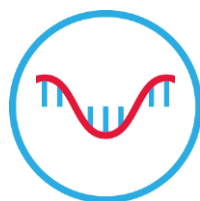


Let Models Speak: Machine Learning Process Models with Interpretable AI Agents

Gang Wang

Moderna, Inc.

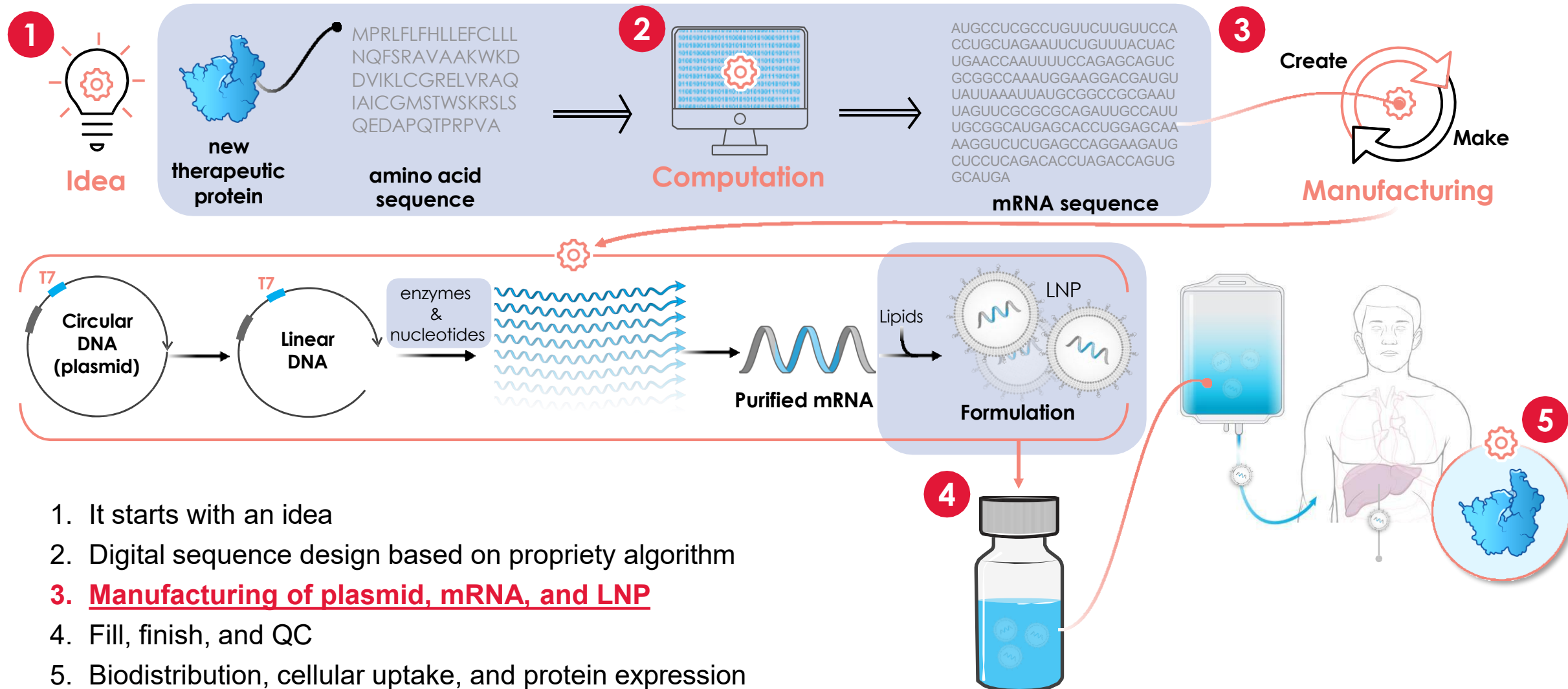


Disclosures

I am employee and stockholder of Moderna, Inc

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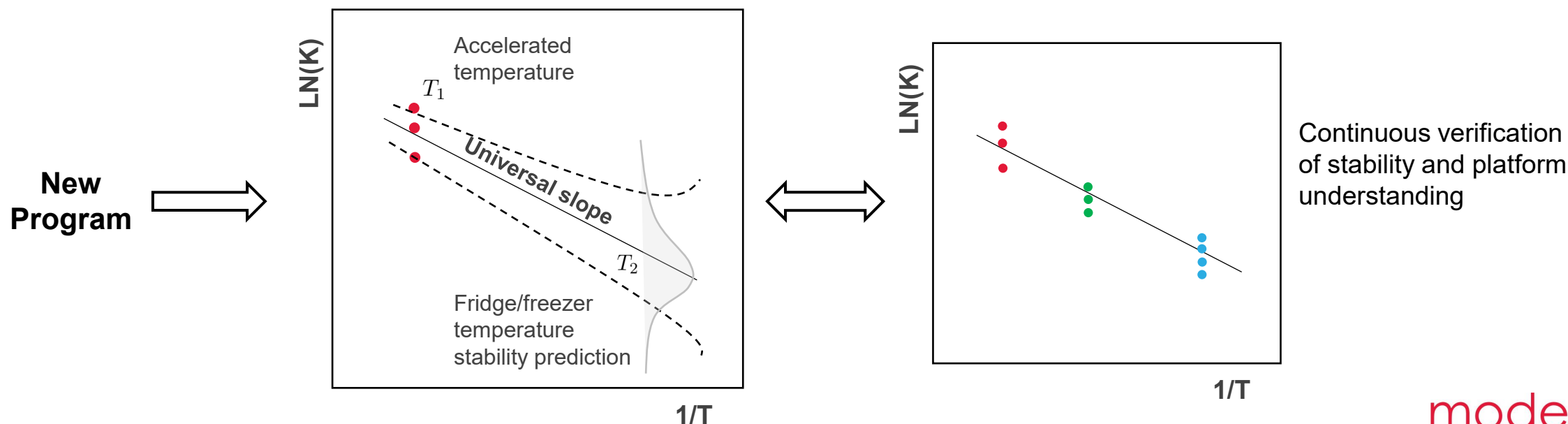
General mRNA overview



Problem statement

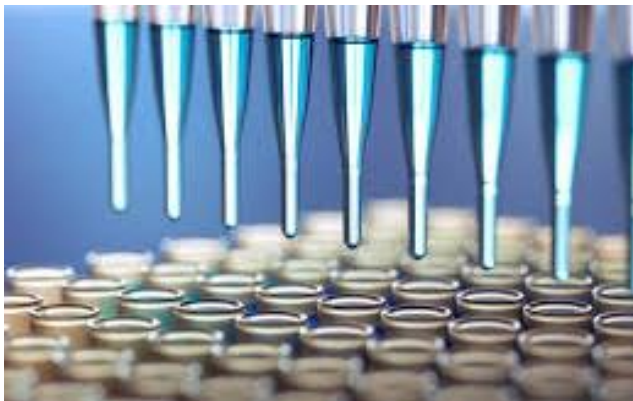
- How to use prior knowledge to accelerate process development and give confidence of quality for new drugs by **predicting** process outcome / manufacturability
 - Improved understanding and robustness during pharmaceutical development
 - Patients receive new drugs earlier
 - Feasibility: Large amount of data has been collected
- **This presentation: Interpretable ML consistent to mechanistic understanding and evidence-based reasoning**

Another example: Universal Arrhenius behavior to support accelerated stability study of mRNA
(Not in this presentation)



Goal: Utilize the pattern recognized in process data to accelerate process development of the next program

Digital apps



Automation

Home

DNA Synthesis

Preps

Batches

RNA Synthesis

Formulation

Robotics

Process

Matt Wilson

Yield Analytics

Showing 30000 Jobs

Q

Advanced

Download Data

Lot ID	Length	Targeted (mg)	Stage 1 Yield		Stage 2 Yield		Stage 3 Yield		Final Yield	QC'd Yield (mg)	Requested (mg)	Yield Fraction
12205741	1505	20	28.8mg (+4.0mg / +4%)	69%	26.0mg (+2.8mg / +10%)	78%	10.9mg (+0.3mg / -36%)	84%	6.4mg (+4.0mg / -47%)	100%	6.93	4 1.0x
			View		View	DA2885		View		View		
12207941	2072	25	23.4mg (+1.0mg / -7%)	79%	14.9mg (+1.0mg / -36%)	75%	8.5mg (+1.0mg / -43%)	65%	4.4mg (+1.4mg / -48%)	80%	5.23	4 1.0x
			View	LS3904								
12207911	1890	50	32.4mg (+1.0mg / -38%)	60%	22.6mg (+1.0mg / -30%)	55%	9.1mg (+1.0mg / -40%)	27%	8.9mg (+2.0mg / -7%)	45%	9.43	10 0.8x
			View	LS3334		View		View		View		
12205673	913	25	50.6mg (+2.0mg / +102%)		41.2mg (+1.0mg / -20%)	99%	30.7mg (+0.7mg / -34%)	100%	16.2mg (+0.7mg / -47%)	100%	20.9	5 0.8x
			View	LS3996		View		View		View		
12204231	1120	250	345.8mg (+9.0mg / +3%)	90%	185.2mg (+6.0mg / -47%)	80%	88.0mg (+1.0mg / -33%)	60%	54.4mg (+3.0mg / -36%)	84%	55.39	50 1.0x
			View	LS2728								
12240601	1814	10	7.0mg (+3.0mg / +30%)	37%	6.9mg (+0.0mg / -7%)	31%	2.9mg (+3.0mg / -58%)	6%	1.6mg (+1.0mg / -45%)	24%	1.86	2 0.8x
			View	DA2737		View		View		View		
1224061	613	25	23.0mg (+0.0mg / -0%)	83%	21.2mg (+0.0mg / -8%)	87%	14.2mg (+3.0mg / -33%)	88%	9.2mg (+0.0mg / -35%)	100%	9.4	5 1.0x
			View				View					

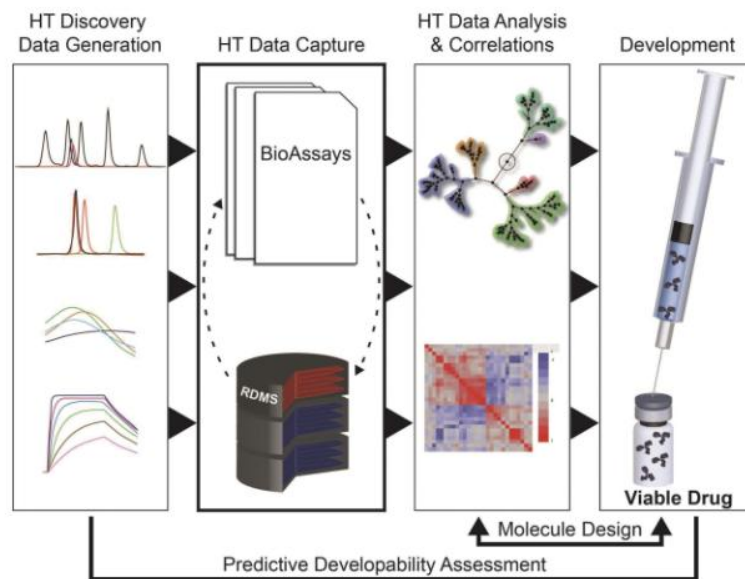
Scaled capacity from 40/month to up to 1000/month

[illegible][illegible]

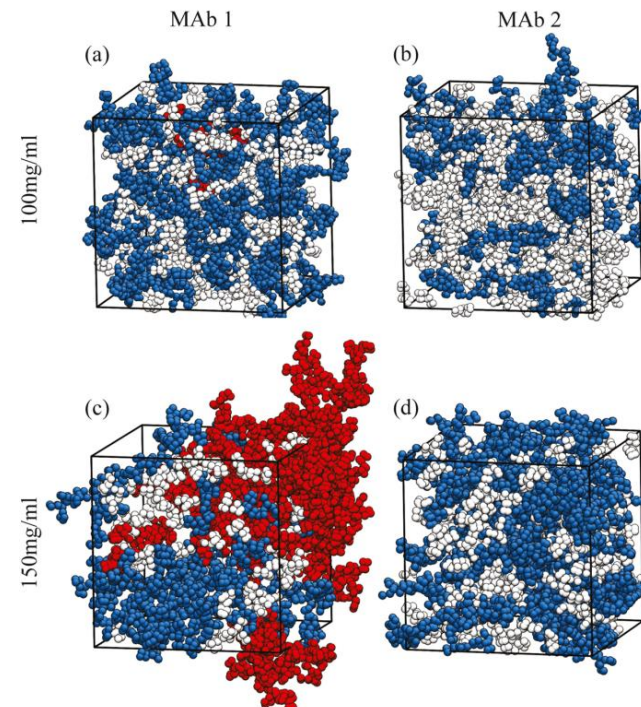
Extensive research has been done for mAbs on developability prediction

High-throughput | computational | machine learning

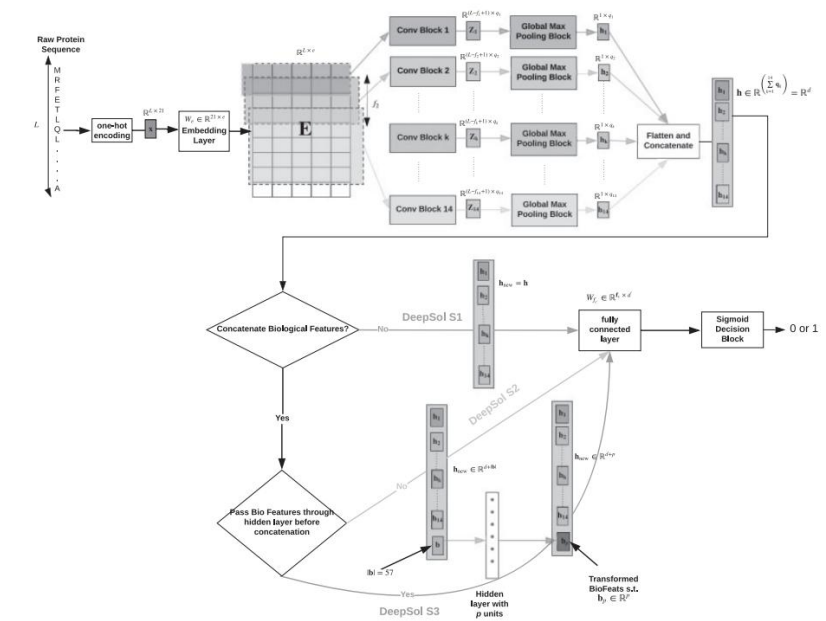
- First-principle computational molecular models are relatively mature for mAbs
- Hybrid approach is commonly used (HT + ML / MD + ML / ...)



Bailly *et al.* "Predicting antibody developability profiles through early stage discovery screening." *mAbs* (2020)



Wang *et al.* "Structure and relaxation in solutions of monoclonal antibodies." *Journal of Physical Chemistry B* (2018)



Khurana *et al.* "DeepSol: a deep learning framework for sequence-based protein solubility prediction." *Bioinformatics* (2018)

Scientific and regulatory challenges for ML predictive models

Model robustness, generalizability, and interpretability are strongly emphasized in the EMA draft reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle (2023).

2.4.1. Data acquisition and augmentation

*All efforts should be made to acquire a **balanced training set**, considering the potential need to over-sample rare populations.*

2.4.3. Model development

*Promote a development practice that favours **model generalisability and robustness** ... sensitivity analyses with stratification of training data on calendar time.*

2.4.4. Performance assessment

*Generalisability to data with different class proportions, and robustness in relation to **uncontrolled secular trends in data**.*

2.4.5. Interpretability

*Black box models may be acceptable in cases where developers substantiate that **transparent (i.e., interpretable) models** show unsatisfactory performance or robustness ... feature importance lists, SHAP and/or LIME analyses or similar explainability metrics ... attention plots ...*

- **Process evolution: How to transfer prior knowledge obtained from statistical learning models to updated processes?**
 - DoE with representative sequences for every process version?
- **Using statistical learning models for inference on a NEW product (i.e. NEW mRNA sequence)**
 - Statistical learning models have limited extrapolation capability: How to justify it is generalizable to a NEW sequence?
 - How to justify the prediction on a new product is an interpolation (input space or latent space) instead of extrapolation?
- **Model monitoring and update**
 - All parameters will likely change especially for deep learning models – How to interpret the parameter deltas?
 - Finetuning / incremental learning / federated learning on specific instrument?
- **Moderna's case study: Does interpretable ML (partially) solve these challenges?**

Develop an ML solution with interpretability to enable confidence and trust

Features of an interpretable ML solution for process development

- Glass-box model that can be inspected on inner workings
- Obeys structural knowledge of the domain, such as monotonicity, causality, structural constraints, additivity or physical constraints that come from domain knowledge
- Human-understandable reasoning process with actual data points / prior knowledge

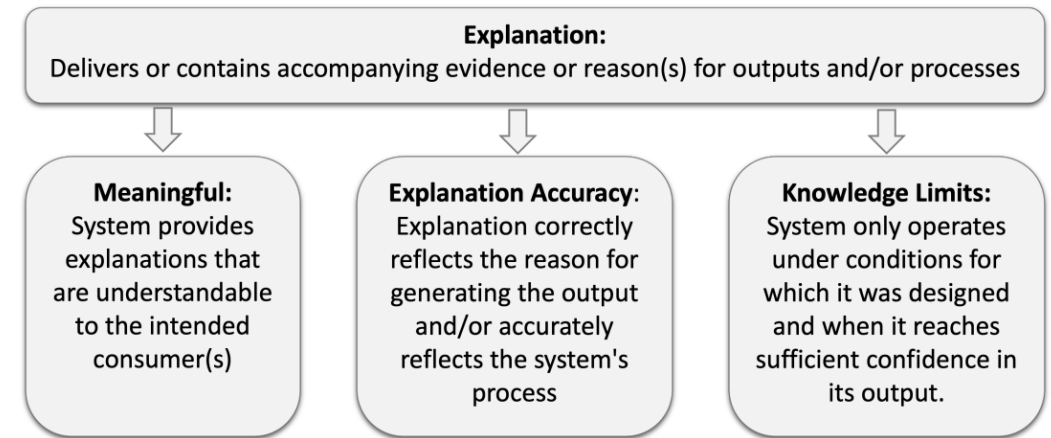
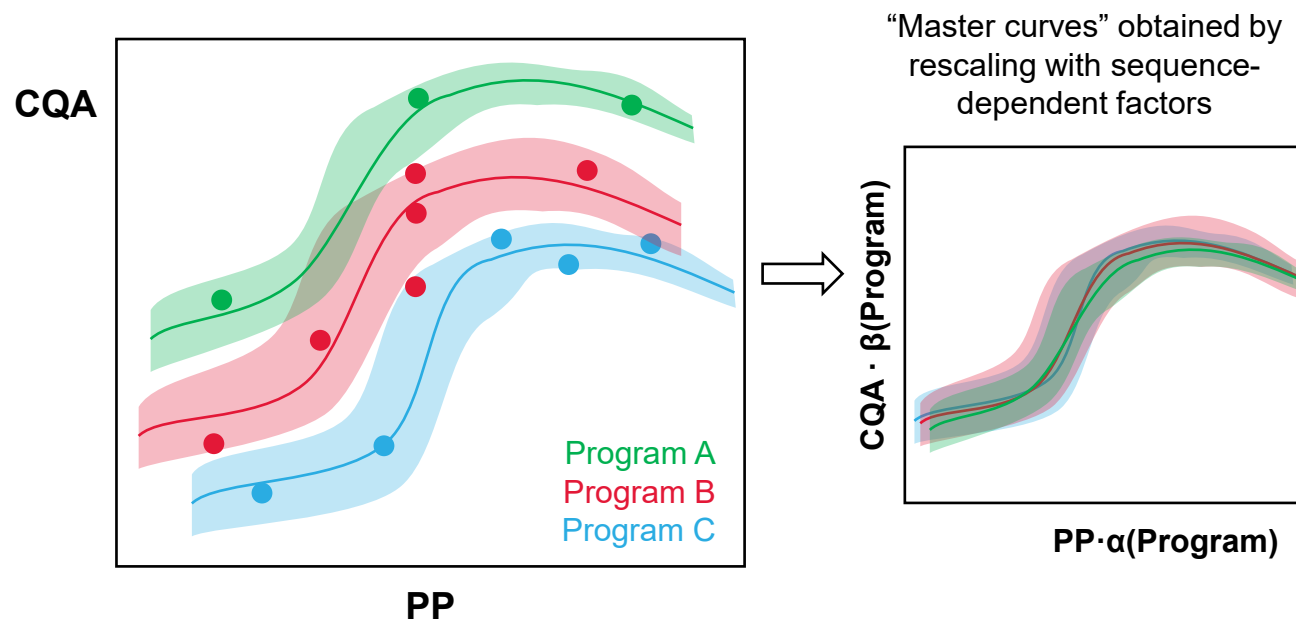


Fig. 4. Characteristics of trustworthy AI systems. Valid & Reliable is a necessary condition of trustworthiness and is shown as the base for other trustworthiness characteristics. Accountable & Transparent is shown as a vertical box because it relates to all other characteristics.

ML model needs to be **CONSTRAINED** by process understanding

- The correlation among performance, process, and sequence originates from physics: The response commonly has similar characteristics across different mRNA sequences
- The goal is to use ML to identify those universal characteristics between CQA, PP, and mRNA sequence

Constrained ML model to identify pattern and get interpretability



Some approaches

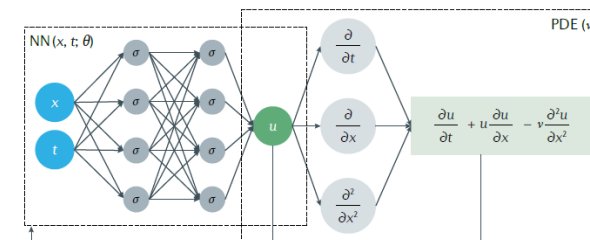
Constraining model form, such as generalized additive model (GAM)

$$y = \sum_{PP} f_i(x_i) + \sum_{Seq.} g_i(u_i)$$

Hybrid model (ML + mechanistic)

$$k_m \rightarrow Q \frac{\partial C_i}{\partial x} = l J_v C_i$$

Physics-informed neural networks (PINNs)



Accelerating Stability and Process Development using Universal, Sequence-Independent Correlation

CQAs of unit operation, or degradation rate

$$y = \mathcal{F}(x) + \mathcal{G}(z)$$

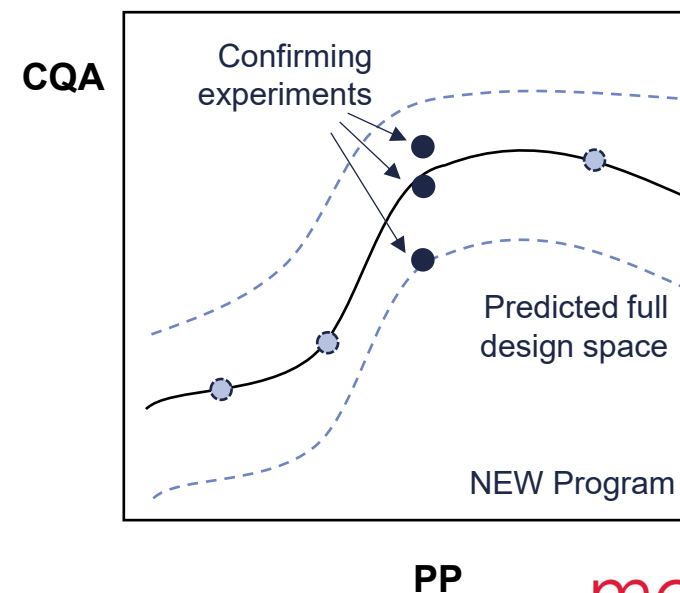
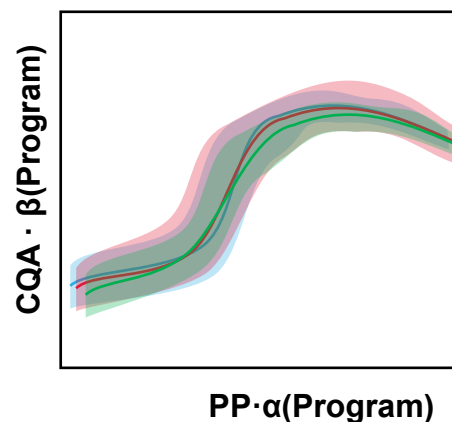
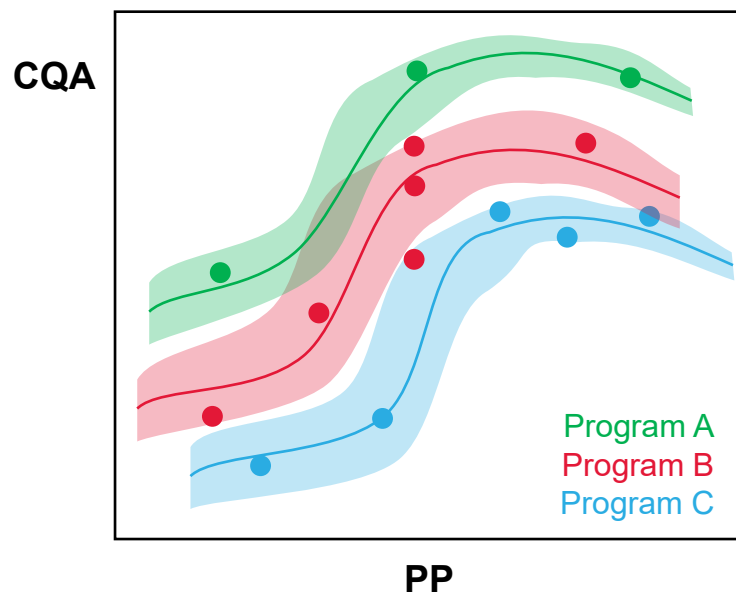
Decoupled relationship with sequence attributes

Universal correlation with process parameter or stability condition

Example: Arrhenius equation

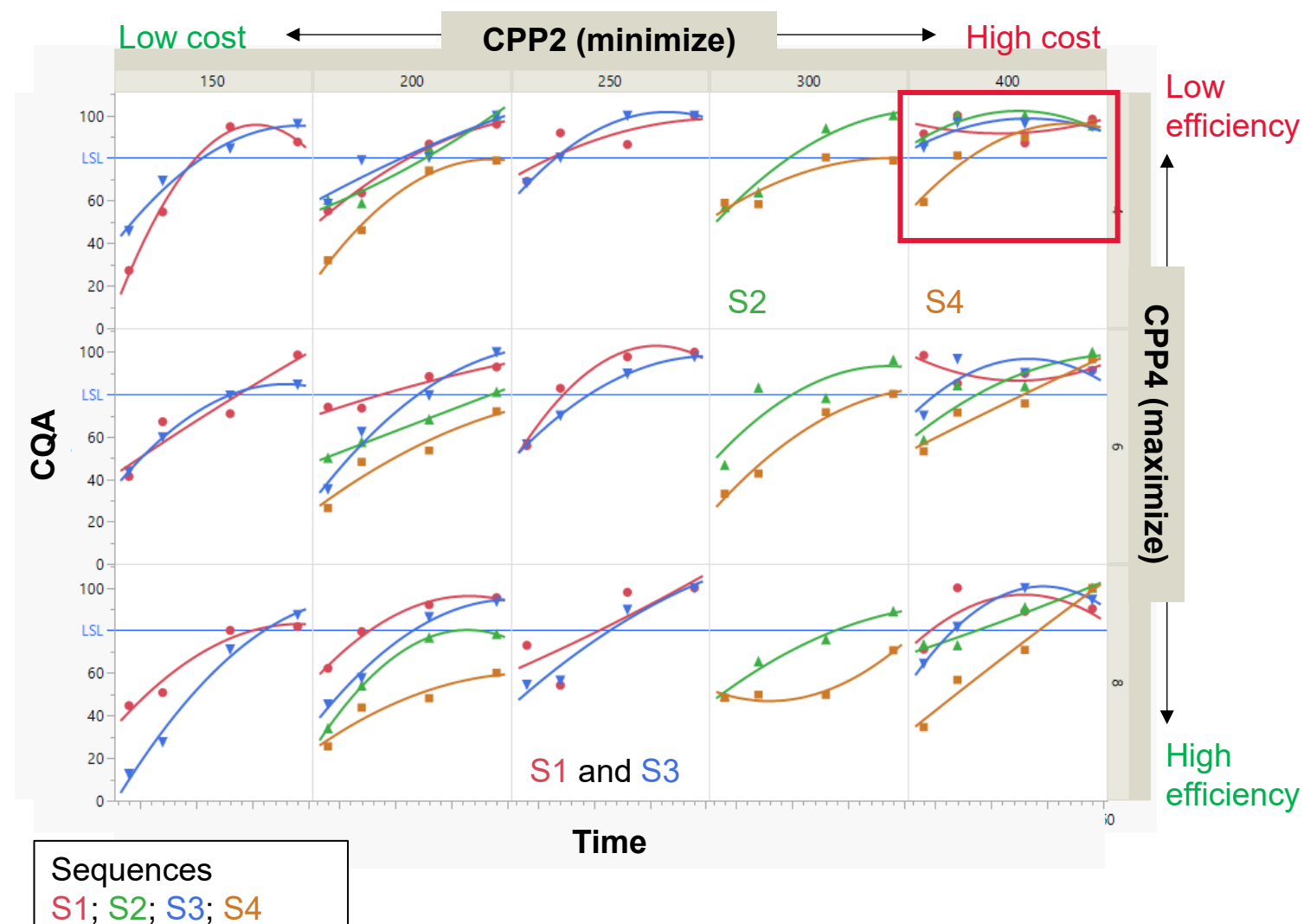
$$\ln k_{\text{Seq}} = -\frac{E_a}{R} \cdot \frac{1}{T} + \ln A_{\text{Seq}}$$

Universal correlation identified from process/stability data



Case study of a UnitOp (*in silico* simulated data)

How to predict the optimal process parameters for the next program?

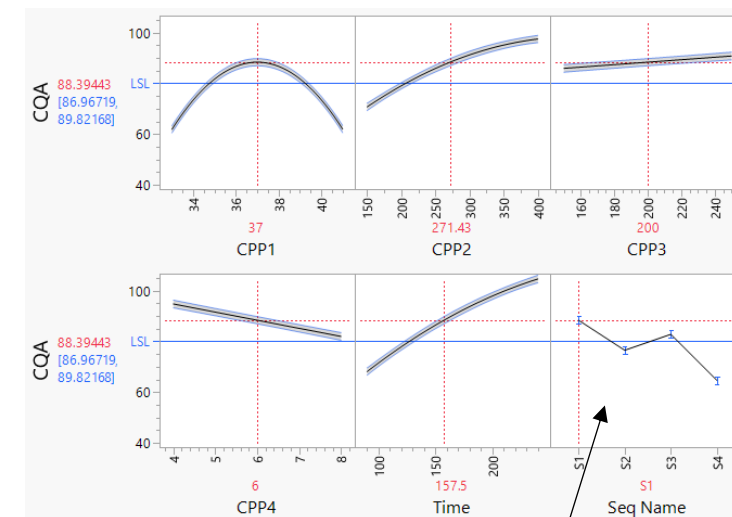


Strategy 1

Use single process parameter set for ALL sequences (conservative and maybe high cost)

Strategy 2

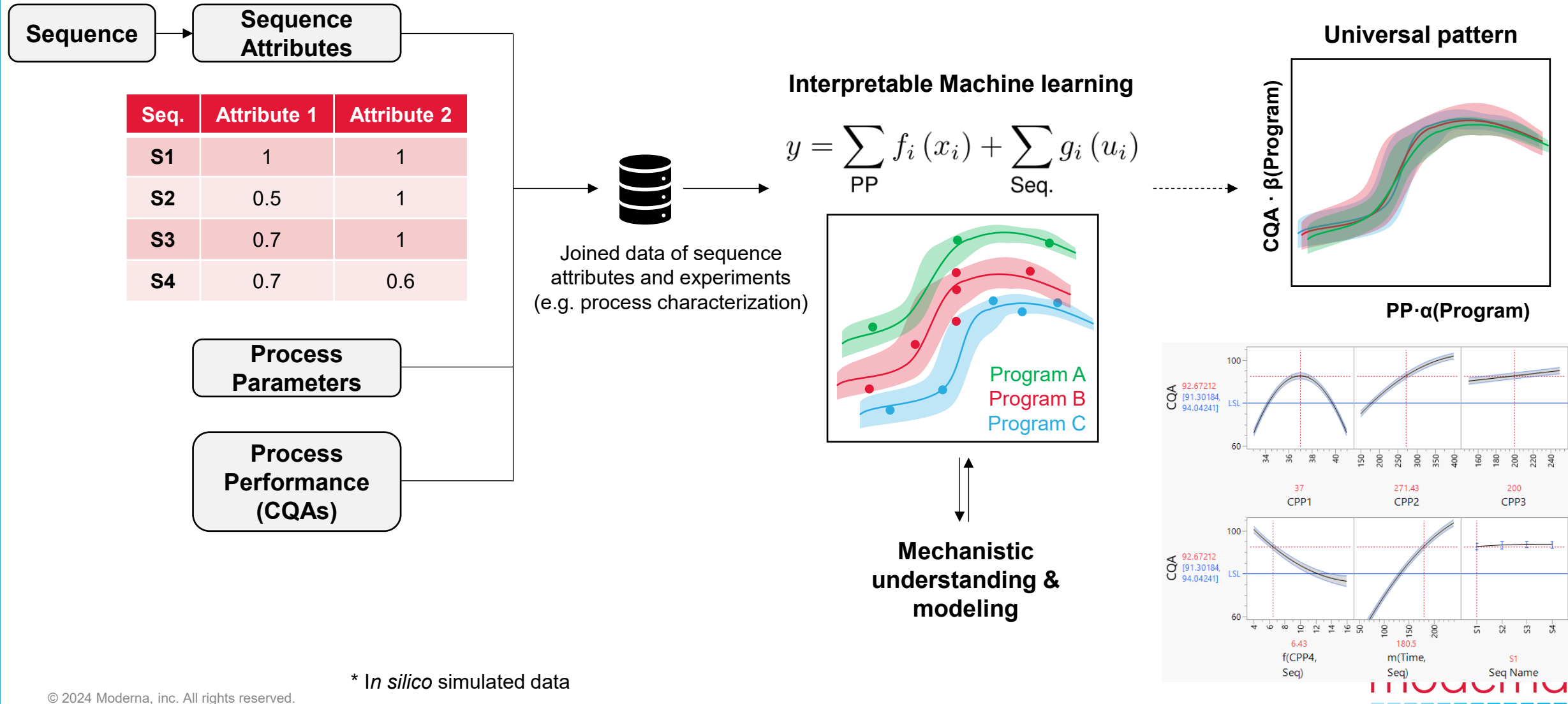
Use different process parameter set for each sequence (DoE needed every time)



Sequence impact is significant

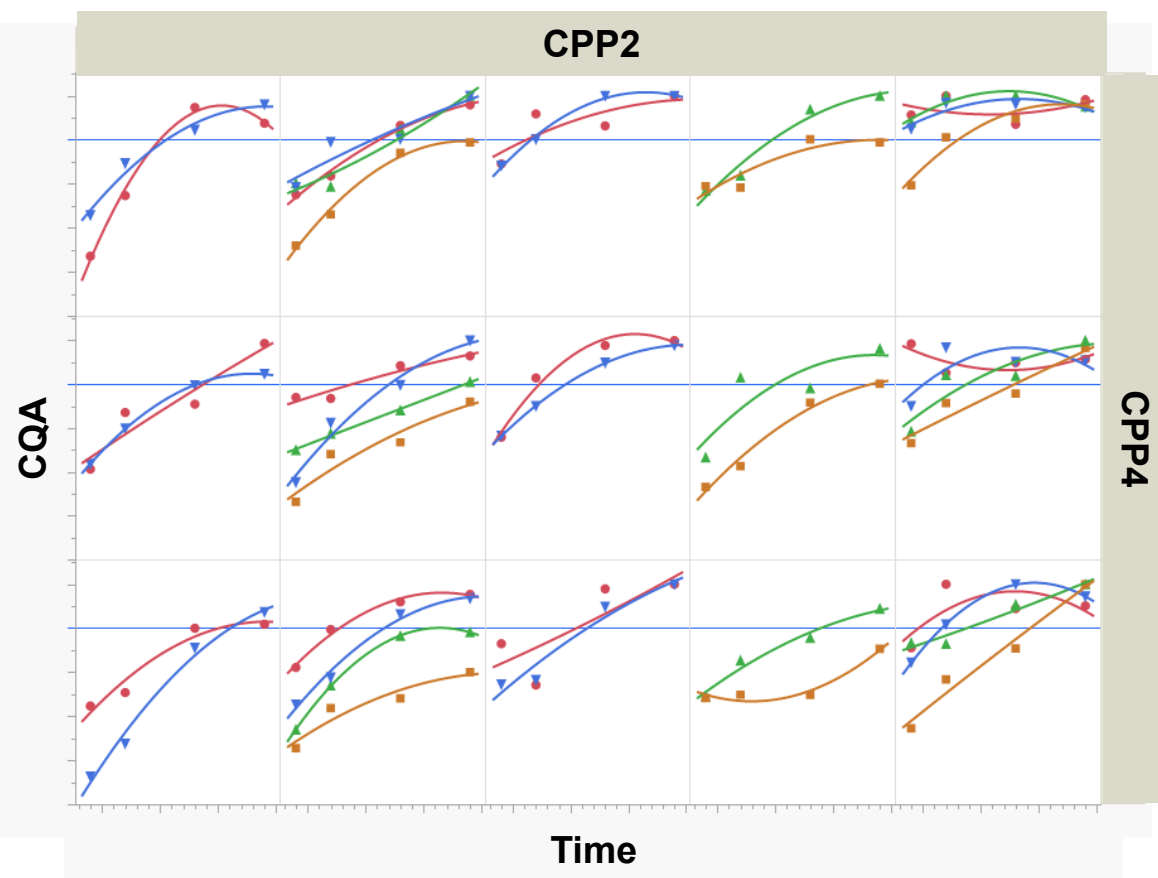
Using machine learning to identify correlation among manufacturability, sequence attributes, and process parameters

Master curves universal to all sequences obtained from machine learning and feature engineering

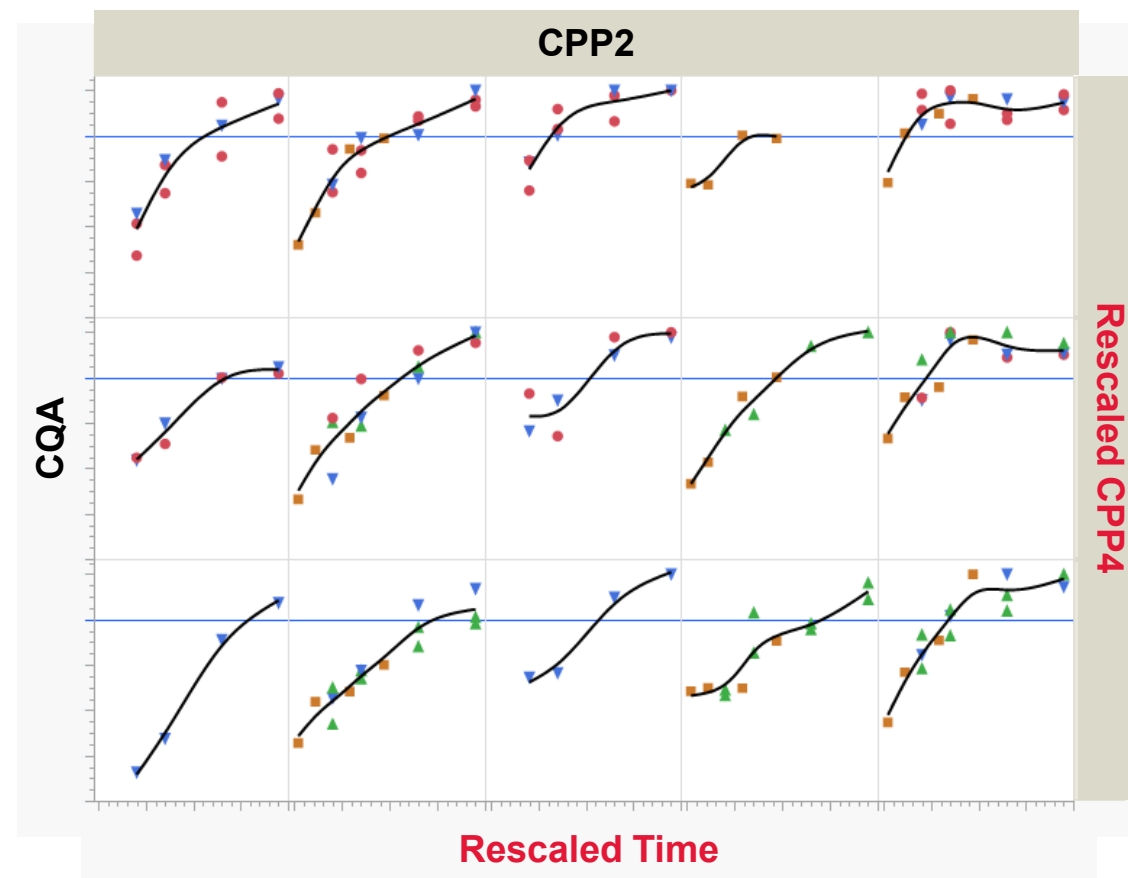


Justification of universality in CQA – CPP relationship across programs

CQA-CPP relationship is different for each sequence
How to predict the manufacturability of the next program?



However, there is universal pattern by rescaling process parameters with sequence attributes: All sequences overlap into one single master curve that represents process understanding.

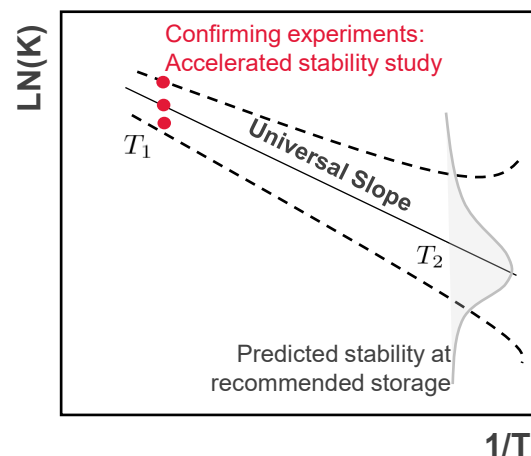
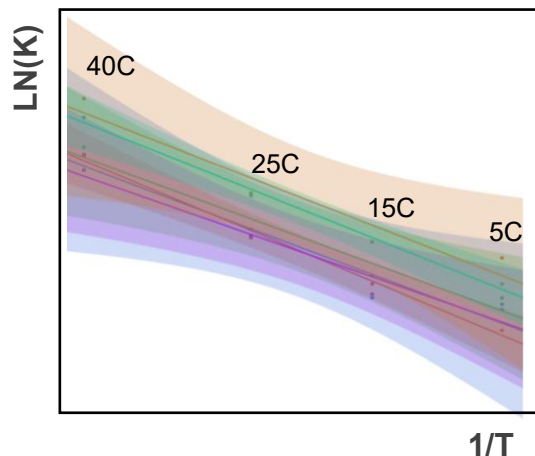


Platform Understanding Accelerates Stability & Process Development

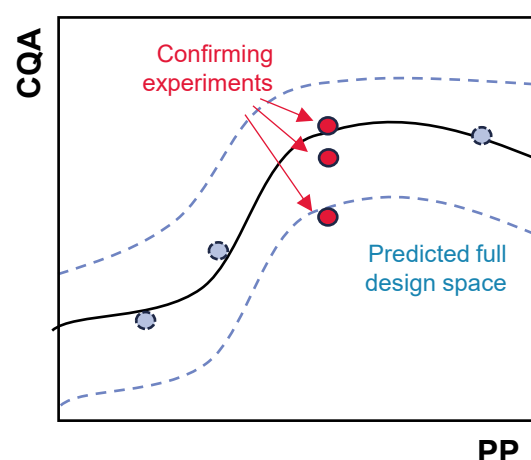
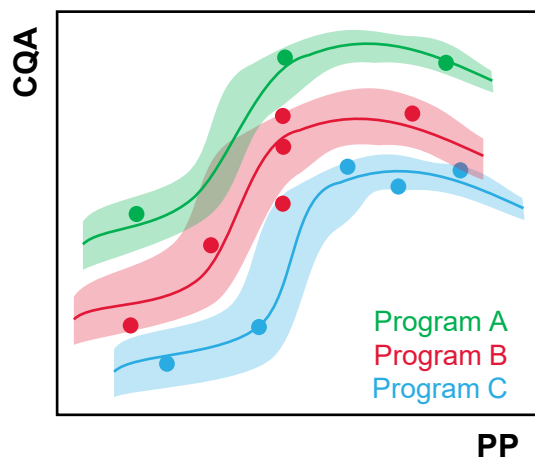
Universal correlation identified
from experimental data

Prediction with universal correlation
confirmed with fewer experiments

Stability correlation
using Arrhenius
behavior



Process performance
over characterized
design space



High Confidence in
Quality

Validation of
Model with
Even More Data

Prediction
Accelerates
Development

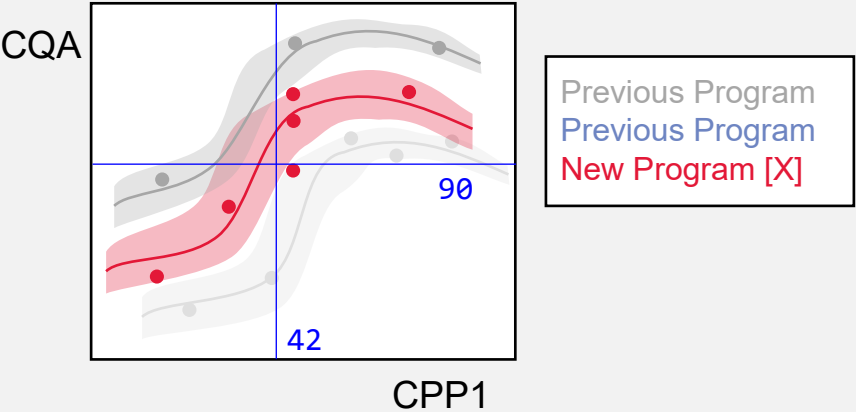
Next step: Build reasoning AI around the interpretable models

Task: Recommend an optimal process for new sequence [alpha] for program [X]. What is the optimal [CPP1] value for [UnitOpA]? We want to fix [CPP2] to 37 so that it is consistent with PAR we're used to, and because of upstream feed, [CPP3] is at least 100.

Result: The optimal [CPP1] for [UnitOpA] with given constraints is 42.

Justifications

A CQA model has been built for [UnitOpA] consistent with prior knowledge that has following response curve to each process parameters.

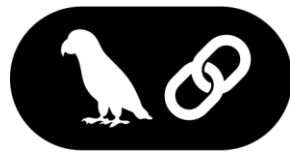


There are 100 historical data points with similar condition and 92% of them give good CQA results. The experiments are listed as follows and justify PAR for [CPP1] of 42 to 46.

Expt. ID	CPP1	CPP2	CPP3	CPP4	CQA
DH-1001	42	37	150	80	92
DH-2004	44	35	200	80	87
DH-9013	46	39	110	80	90
DH-2031	43	37	130	80	93

Open-source programming frameworks are ready for implementing an AI agent capable of:

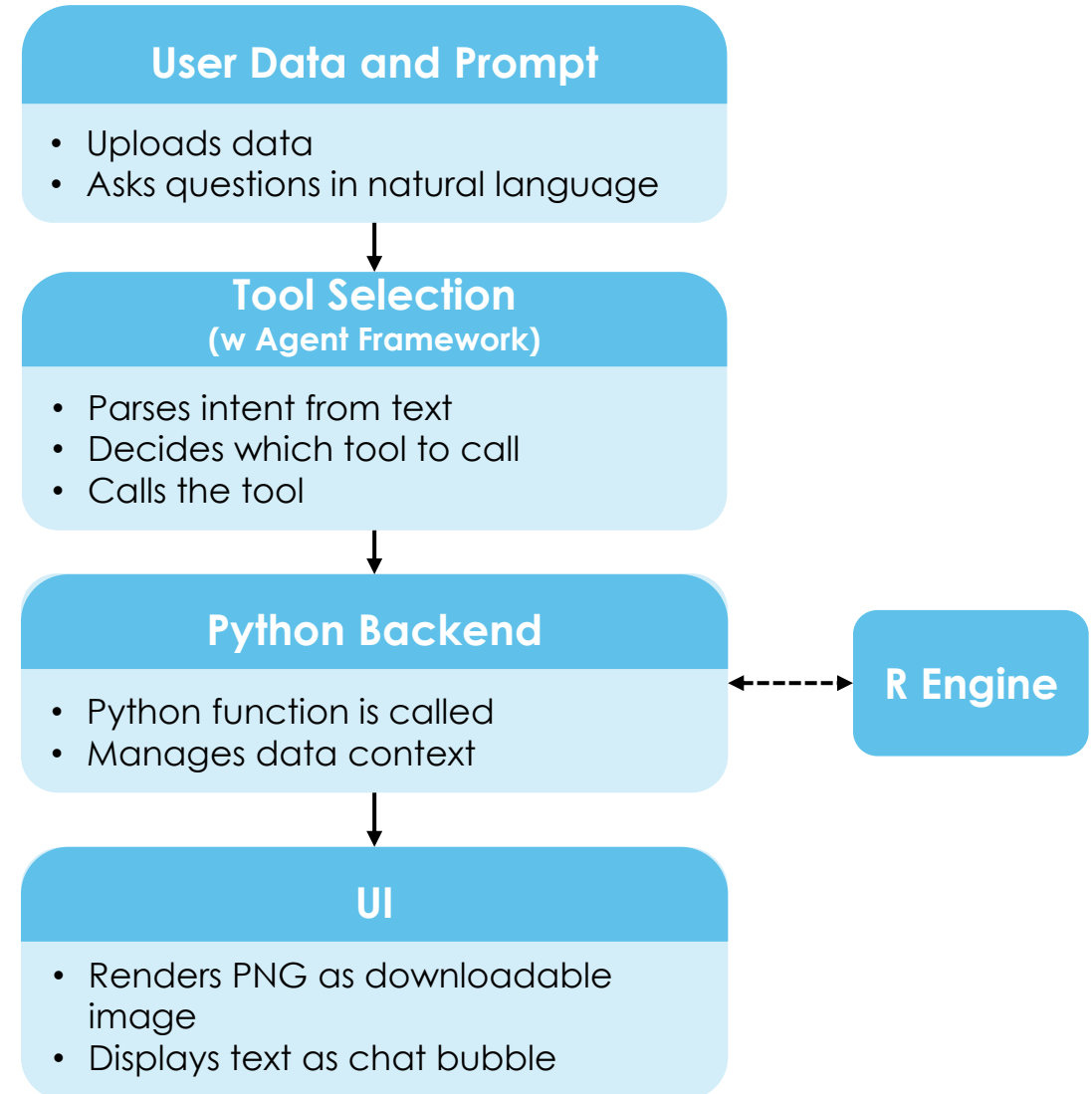
- Understanding user's natural language prompts
- **Select the right tools (program / code / script)**
 - The tool can either be analysis or database query
- **Execute the tools upon user provided data with arguments extracted from user's prompts**
- **Explain what it did**
- **Save a log**



LangChain



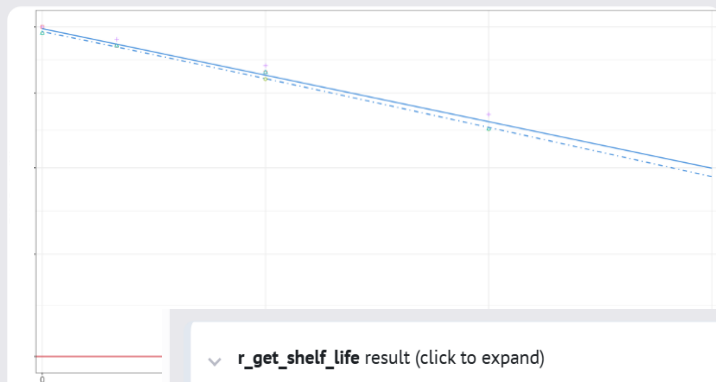
LlamaBot



Examples: Shelf-life calculation and control charting

Estimate the shelf life of [redacted] vs Time (month) of [redacted] at Temperature = [redacted], using log transform and LSL = [redacted]

r_get_shelf_life:

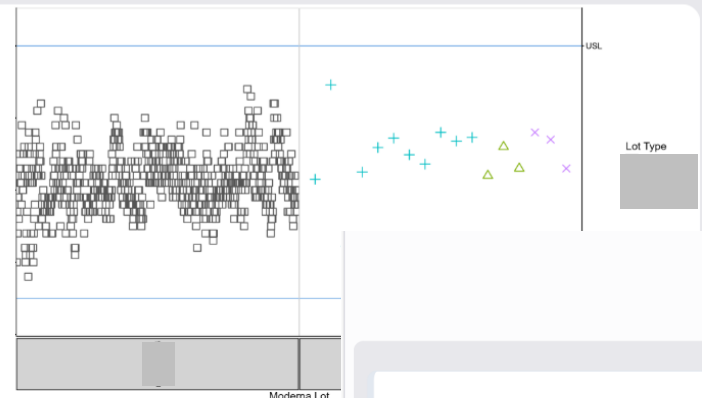


▼ r_get_shelf_life result (click to expand)

```
predicted_shelf_life: [redacted]
worst_lot: NA
final_model: [redacted]_model
n_lots: 4
expiry_limits: {'lower': [redacted], 'upper': 'nan'}
ci_method: mean
ci_level: 0.95
model_comparison_output: # A tibble: 4 x 4
  Model AICc delta weight
```

Type your message here, / for prompts

Create a faceted control chart of [redacted] vs Moderna Lot comparing all vaccines, facet by Vaccine, and make sure both facets use the same x-axis scale, color by and shape by Lot Type, add spec limits with [redacted]. Remove x axis labels



Are any of the points out of spec?

> write_and_execute_code_wrapper result (click to expand)

respond_to_user: No—there are 0 out-of-spec points.

- Using [redacted] measurements are in spec.
- By vaccine: [redacted] in spec.

Want me to annotate the control chart with an in-spec count per facet or highlight any points that would be OOS if limits changed?

Type your message here, / for prompts

Traceability is key: Log and export feature allows for human verification.

Explainable optimization algorithm for process development decisions

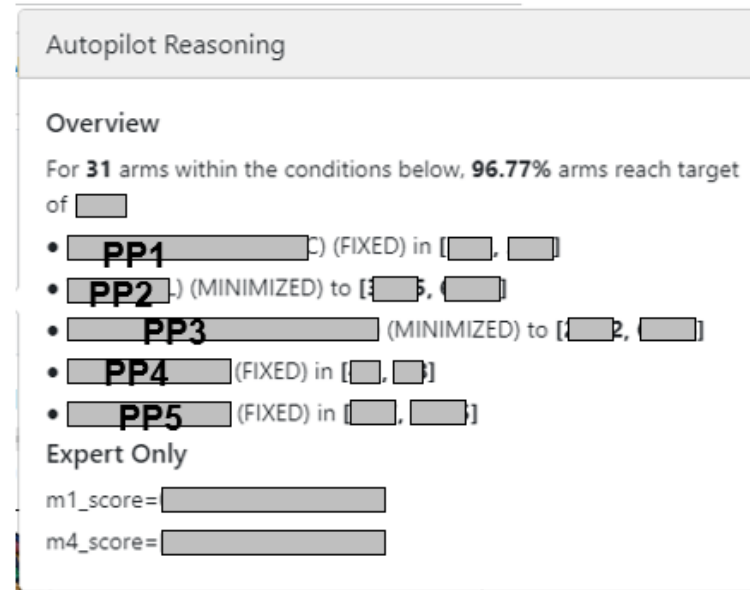
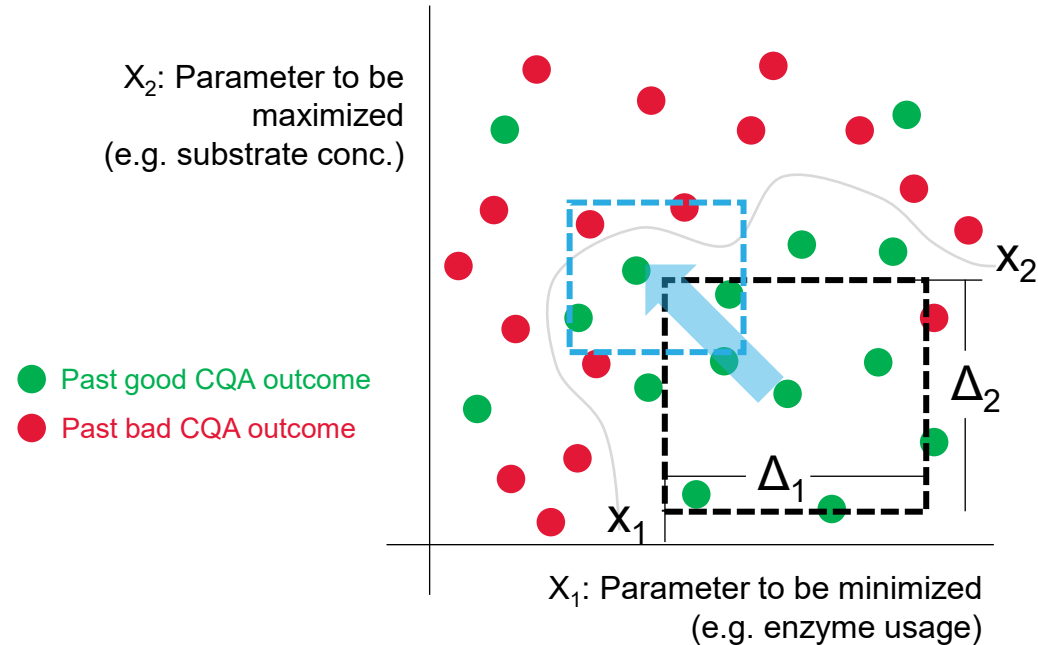
Weighted performance metrics

$$\begin{aligned} \min . \quad & -\lambda \cdot \text{Perf}(\mathbf{x}) \\ \text{s.t.} \quad & x_i \in \Gamma_i \end{aligned} \longrightarrow$$

Introducing weight representing prior evidence

$$\begin{aligned} \min . \quad & w_{\text{Evidence}} - \lambda \cdot \text{Perf}(\mathbf{x}) \\ \text{s.t.} \quad & x_i \in \Gamma_i \\ & \alpha D_i \leq \Delta_i \leq \beta D_i \end{aligned}$$

Soft constraint: The design space must enclose sufficient and confident good CQA outcome



Digital app giving reasoning of recommendation

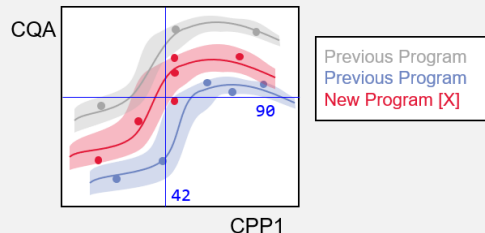
Vision: Transparent and human-understandable mathematical formulations and algorithms

Each output is from solving mathematical problems and users can see the inner working: “glass box”

Output of Interpretable AI

Result: The optimal [CPP1] for [UnitOpA] with given constraints is 42.

A CQA model has been built for [UnitOpA] consistent with prior knowledge that has following response curve to each process parameters.



Model is consistent to process understanding and universal to all sequences

There are 100 historical data points with similar condition and 92% of them give good CQA results. The experiments are listed as follows and justify PAR for [CPP1] of 42 to 46.

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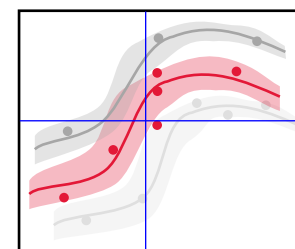
Algorithm needs to justify the recommendation using historical data (prior knowledge): “We’ve done this before”

Mathematical View

$$\min. \quad w_{\text{Evidence}} - \lambda \cdot \text{Perf}(\mathbf{x})$$

$$s.t. \quad x_i \in \Gamma_i$$

$$\alpha D_i \leq \Delta_i \leq \beta D_i$$



$$y = f(\mathbf{x})$$

$$y = f(x_1 | x_2, x_3, x_4, \dots, x_N)$$

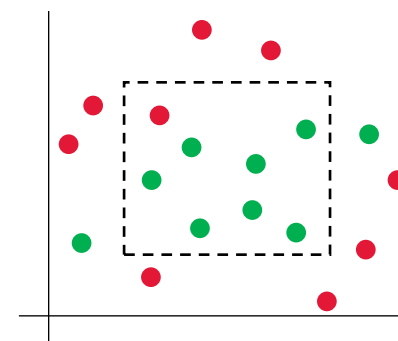
Algorithm View

Constrained Optimization Problem

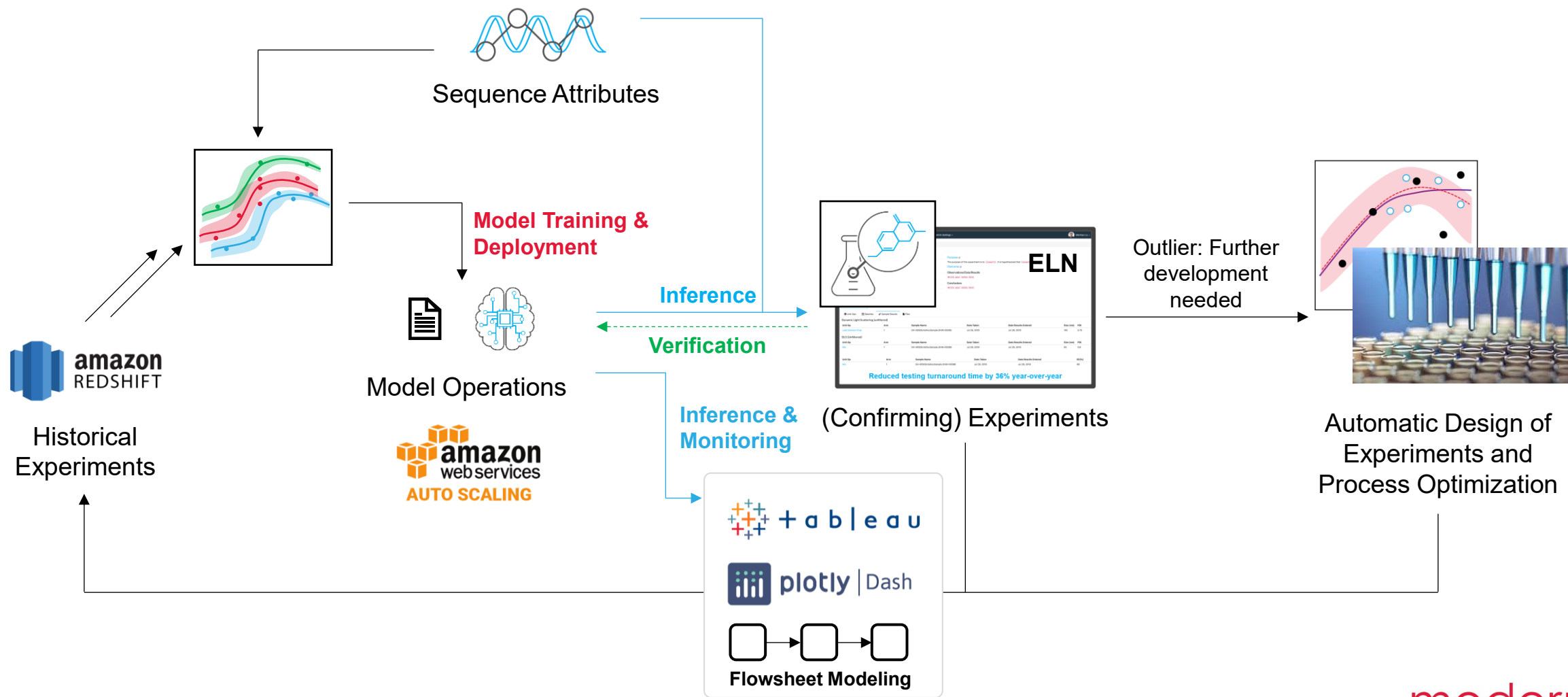
Individual Conditional Expectation Plots

Set Cover Problem (Mixed-Integer Programming)

↓ TRUST



Vision: Accelerated process development with ML-prediction, continuous experimental verification, and automatic design of experiments: Data based decision making for future products



Thank you