Optimal Purification Decisions for Engineer-to-Order Proteins at Aldevron

POMS Applied Research Challenge

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Joint work with

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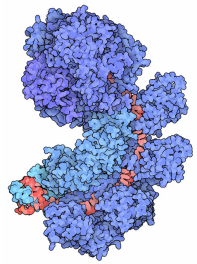
Background in Biomanufacturing

- Biomanufacturing: Manufacturing methods to produce biologicals.
  - Vaccines, hormones, proteins, insulin, tissues, etc.
  - Treatment of cancer, autoimmune diseases, strokes, blood diseases, etc.
- Key facts (Pharmaceutical Research and Manufacturers of America, 2015)
  - Over 7000 drugs in R&D. 325 million patients worldwide.
  - 83% survival gains in cancer patients since 1990.
  - Global biopharmaceutical market value of $197 billion.



Project Overview

- Collaboration with Aldevron, since February 2013.

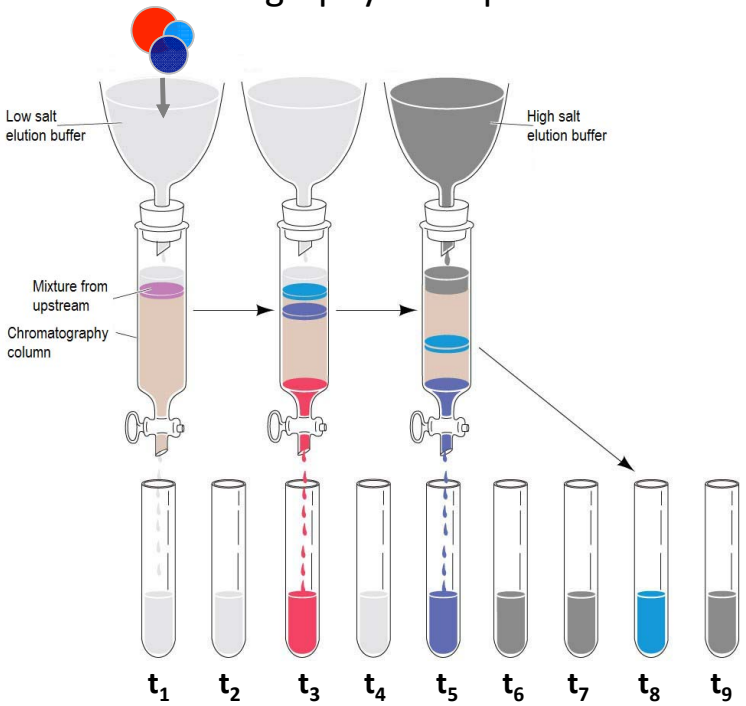
- Research objectives: Develop tools and models to reduce risks and costs in protein purification operations.

Protein purification is a common industry challenge.

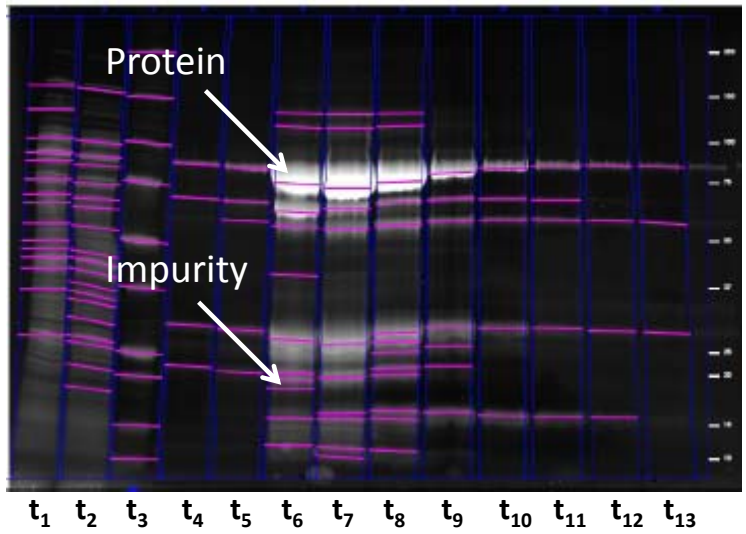
> *"Every protein is unique and has its own purification challenges – many of which cannot be predicted". Bitesizebio Blog, 2016.*
>
> *"Many mistakes are made because we don't have the right analytics". Technology Review, 2012.*

Protein Purification

Chromatography Principles

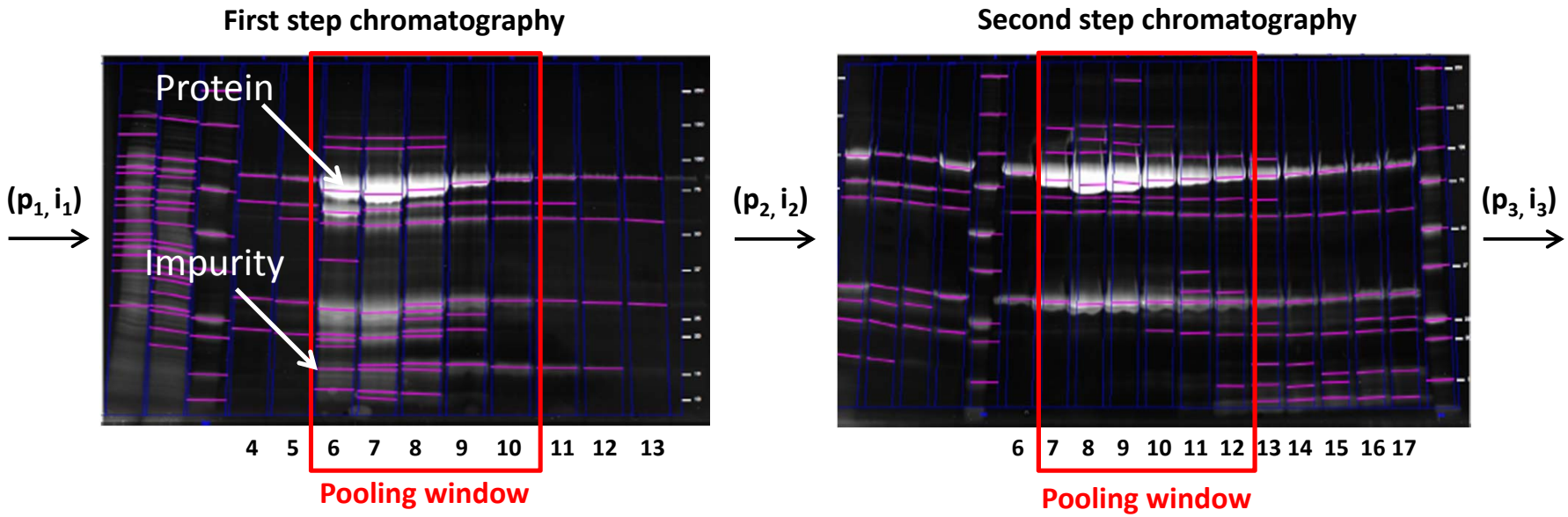


Chromatography Data



- **Objective** Separate proteins from impurities.
  - Exploit the size, molecular charge, hydrophobicity of the molecules.

What is the Problem?



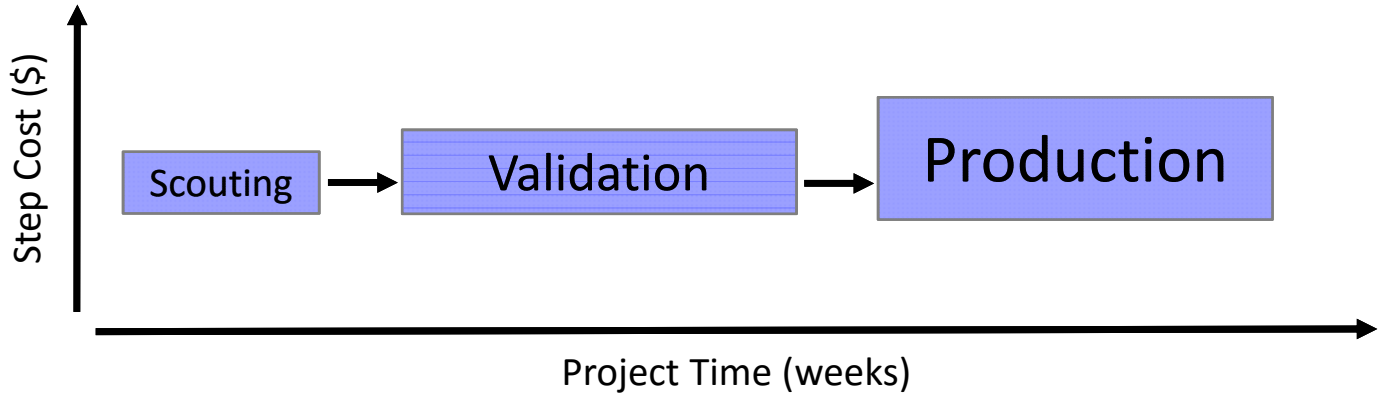
$$\text{Purity requirement} \geq 85\%,\ \text{Purity} = \frac{\text{protein (mg)}}{\text{protein (mg)} + \text{impurity (mg)}}$$

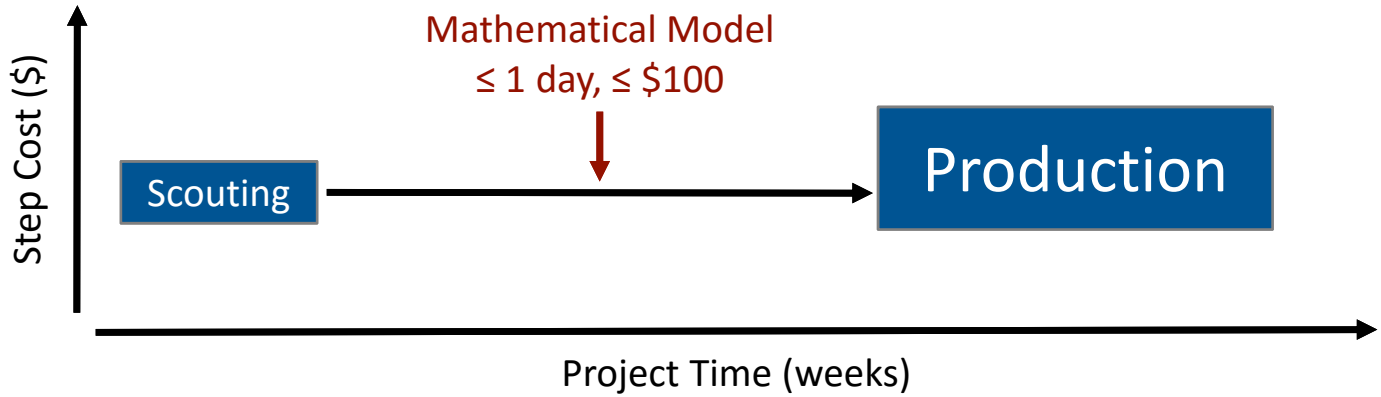
Yield requirement ≥ 8 mg protein.

What are the Challenges?

- Each protein is an **engineer-to-order** product
- **Strict production requirements** on purity and yield
- **Yield and quality trade-offs**
- **Uncertainty** in chromatography outcomes
- **Interlinked decisions** with 2 to 6 purification steps in series

Current Practice and Contributions





- Research impact: Replacing validation runs with a mathematical model enables to save up to 30% of the manufacturing lead time and costs.

Research Questions

- What is the best purification strategy? Room for improvement in practice?
- How to identify a "bad" starting material?
- How to identify a "good" batch leading to *guaranteed* purity and yield?

The Model

- Decision Epochs: Beginning of chromatography step t, $t \in \{1, \ldots, T-1\}$.
- State Space
  - p_t denotes the amount of proteins of interest available in the batch at the beginning of t^{th} chromatography step.
  - i_t denotes the amount of impurity at the beginning of t^{th} step.
- Actions: w_t denotes choosing the pooling window w_t to run the purification step t. Action S denotes stopping the process.
- State transitions estimated from scouting data.

Costs and Rewards

- Financial implications of the final batch

$$\text{Costs and rewards} = \begin{cases} \text{Penalty for failure} & \text{if purity not met,} \\ \text{No extra revenue} & \text{if purity met \& excess yield,} \\ \text{Penalty for shortage} & \text{if purity met \& yield shortage.} \end{cases}$$

- High operating cost at each step.

Dynamic Programming Formulation

- Finite horizon Markov decision model

$\mathscr{V}_t(p_t, i_t)$ for $t = \{1, \ldots, T-1\}$,

$$\mathscr{V}_t(p_t, i_t) = \max_{w_t \in W_t} \left\{ r_S(p_t, i_t), -c_t + \mathbb{E}\, \mathscr{V}_{t+1}(\theta_t p_t, \psi_t i_t | w_t) \right\},$$

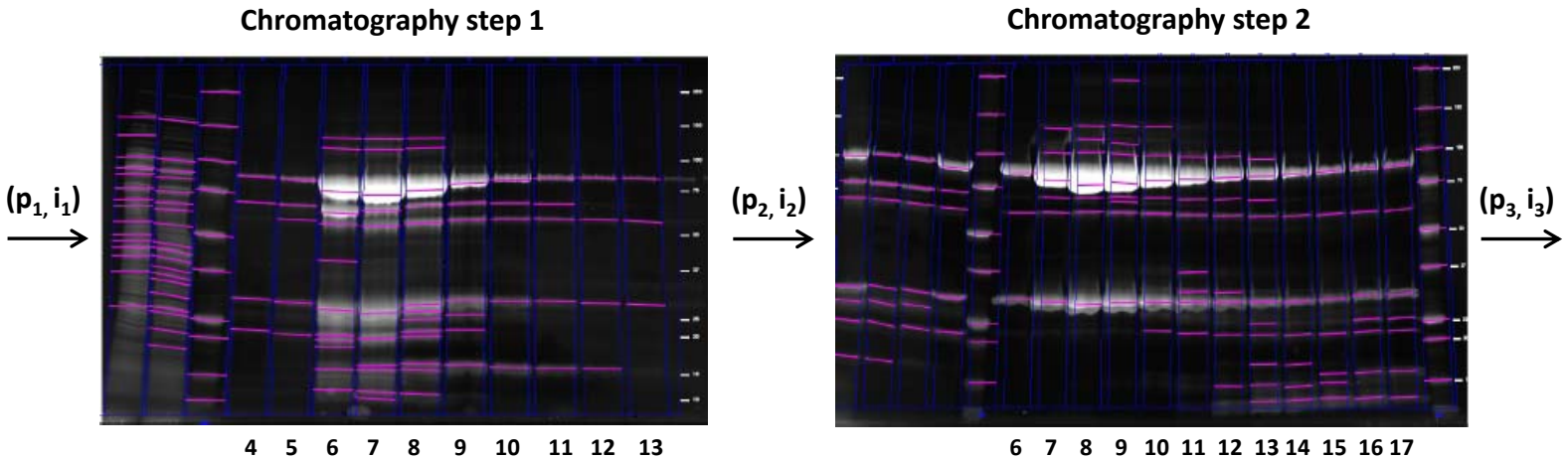
$$\mathscr{V}_T(p_T, i_T) = r_S(p_T, i_T),$$

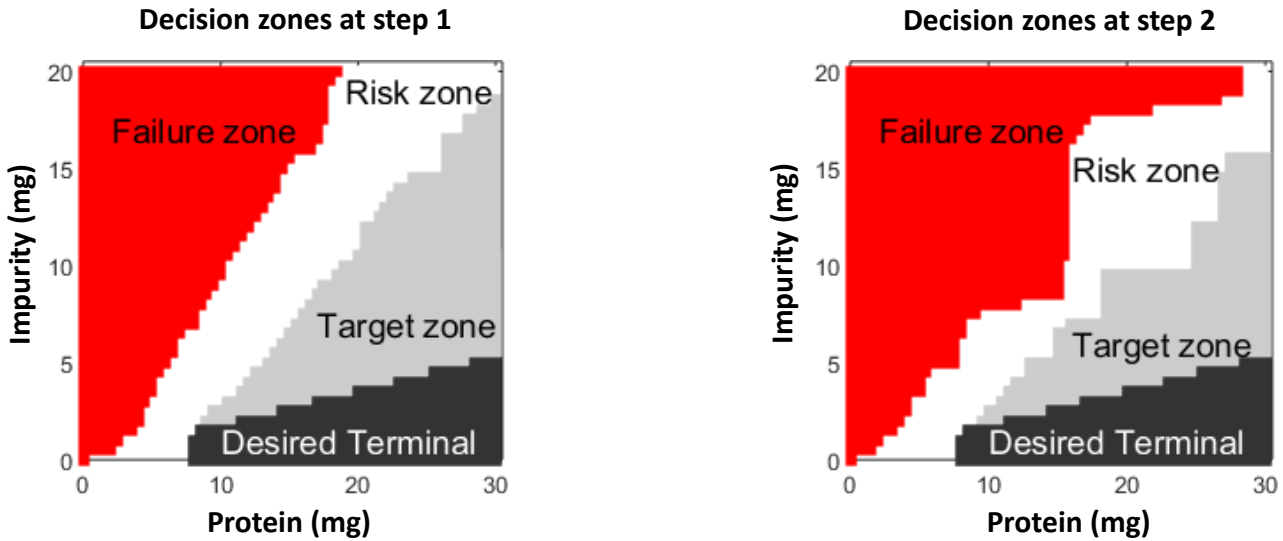
where,

$$\mathbb{E}\, \mathscr{V}_{t+1}(p_t \theta_t, \psi_t i_t | w_t) = \int_{\psi^l_{w_t}}^{\psi^u_{w_t}} \int_{\theta^l_{w_t}}^{\theta^u_{w_t}} f_t(\theta_t | w_t) g_t(\psi_t | w_t) \mathscr{V}_{t+1}(\theta_t p_t, \psi_t i_t) \mathrm{d}\theta \mathrm{d}\psi.$$

Objective is to maximize the expected profit.

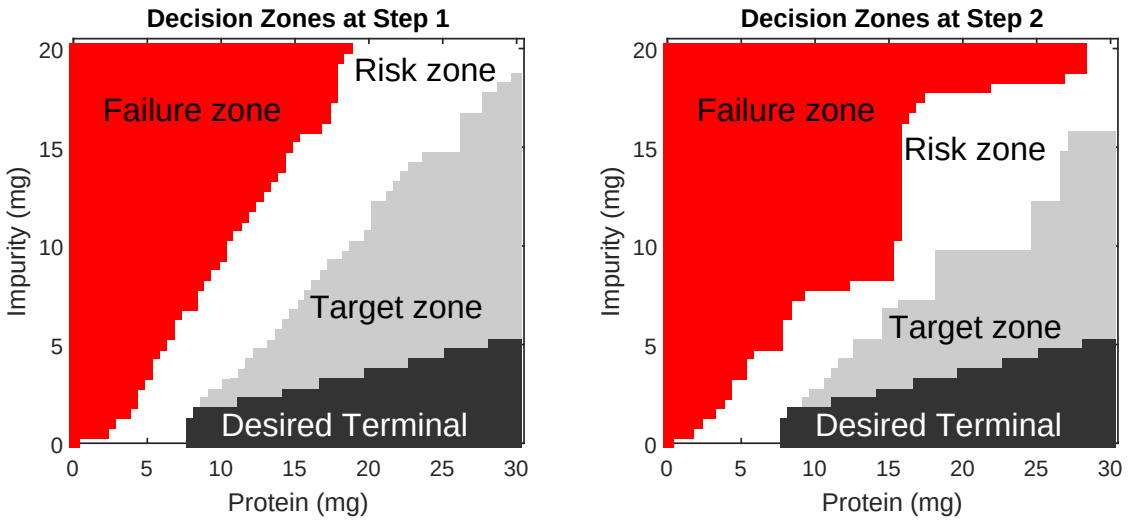
Overview of Analysis & Insights





- New decision making framework for practitioners: Decision-zones. Decision-zones provide important managerial insights and guidelines.

Failure Zone: What is a "bad" batch?

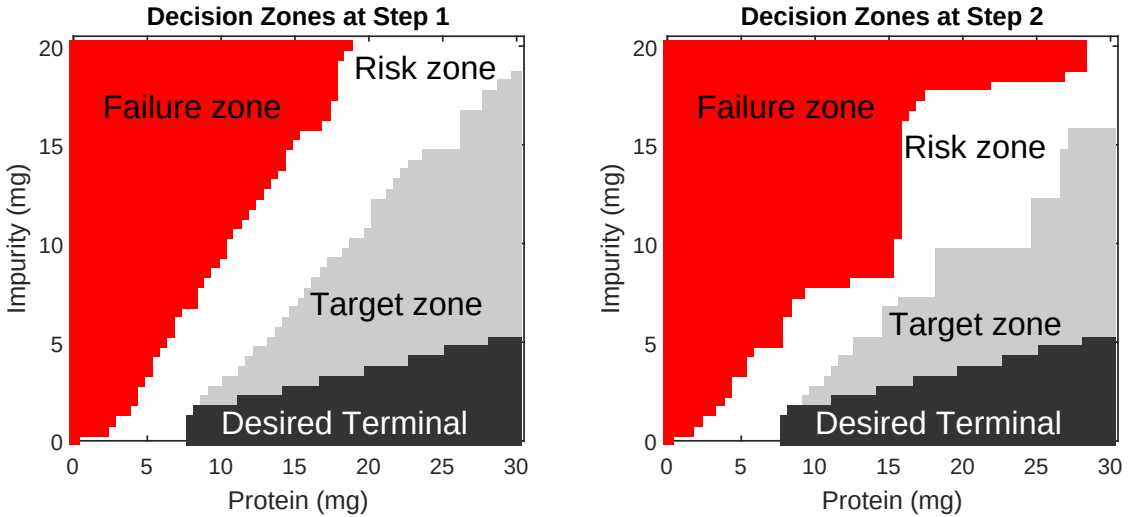


The biomanufacturer has no financial incentives for performing purification.

Theorem 1 (Failure Zone $\mathbb{F}_t$)

The optimal policy has the property that for some (p'_t, i'_t)*, the optimal action is to abandon the purification* $a^*_t(p'_t, i'_t) = S$ *for all states in* $\mathbb{F}_t = \{(p_t, i_t) \in \mathscr{P} \times \mathscr{I} : p_t \leq p'_t \text{ and } i_t \geq i'_t\}$*.* $\mathbb{F}_t$ *is the failure zone at* $t \in \mathscr{T}$*.*

Target Zone: What is a "good" batch?

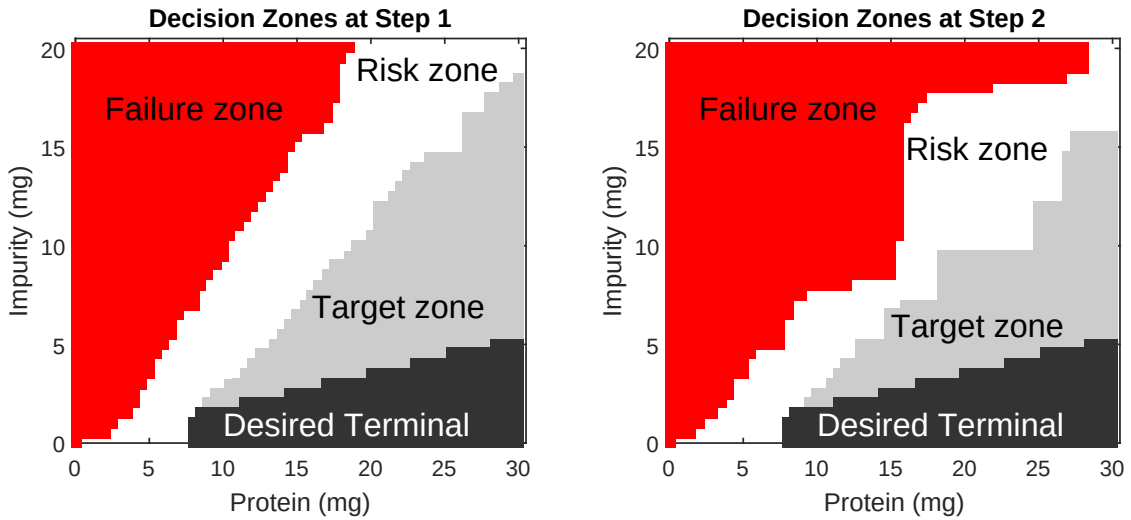


The biomanufacturer can *always* guarantee that there exists at least one purification policy that meets both the purity and yield requirements.

Theorem 2 (Target Zone $\mathbb{T}_t$)

$$\mathbb{T}_T = \left\{(p_T, i_T) : p_T \geq p_d,\, i_T \leq \frac{1-\gamma_d}{\gamma_d} p_T\right\},\ \mathbb{T}_t = \bigcup_{w \in \mathcal{W}_t} J_t^w(\mathbb{T}_{t+1}).$$

Structural Analysis of the Optimal Policy



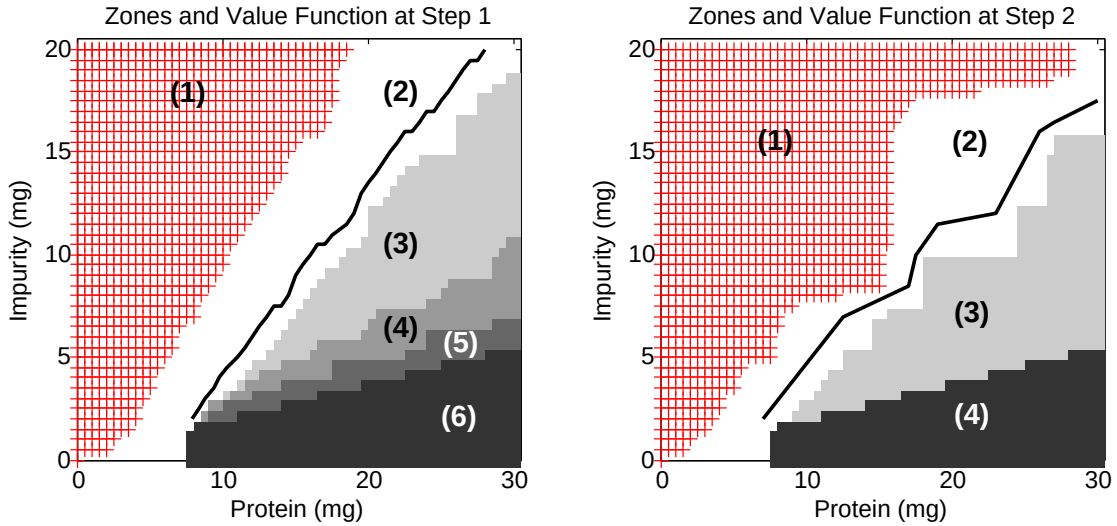
Rule of thumbs based on the decision zones.

Theorem 3 (Zone-based Decision Making)

The optimal policy has the property that for some (p_t, i_t) at step t,

- *If $(p_t, i_t) \in \mathbb{F}_t$, then the optimal action is to abandon the purification.*
- *If $(p_t, i_t) \in \mathbb{T}_t$, then choose w_t to keep the state within the target zone.*
- *If $(p_t, i_t) \in \mathbb{R}_t$, then choose w_t to meet purity with minimal yield losses.*

Implementation at Aldevron: An Example



	Region	Range of $\mathbb{E}\mathscr{V}_t(p_t, i_t)$	Business Implications
Step 1	(1)	$\mathbb{E}\mathscr{V}_1(p_1, i_1) = -48$	Failure Zone: Stop and scrap.
	(2)	$-48 < \mathbb{E}\mathscr{V}_1(p_1, i_1) < 10$	Risk zone: High potential losses.
	(3)	$\mathbb{E}\mathscr{V}_1(p_1, i_1) = 10$	Target Zone: Meet purity and yield in two steps.
	(4)	$10 < \mathbb{E}\mathscr{V}_1(p_1, i_1) < 25$	Target Zone: One step with lost sales.
	(5)	$\mathbb{E}\mathscr{V}_1(p_1, i_1) = 25$	Target Zone: Meet purity and yield in one step.
	(6)	$\mathbb{E}\mathscr{V}_1(p_1, i_1) = 40$	Terminal state: Stop.

Improvement in expected profit ranges between 18% to 25% compared to the current practice.

Implementation at Aldevron

- Project timeline, 2013 - 2016.

Timeline	Tasks
February 2013 - February 2014	Problem definition and modeling
February 2014 - June 2014	Data collection and model revisions
June 2014 - September 2014	Industry test runs
October 2014 - October 2015	Implementation and actual use
Since October 2015	Model and implementation enhancements (ongoing work)
Throughout the project	Weekly company visits, working group sessions, biotech conferences

- Implementation since October 2014: 20% improvement in expected profit and purification lead time on average, due to
  - Formal assessment of the starting material,
  - Reducing the number of validation runs,
  - Process economics taken into consideration.
- Scientists using the Java tool for modeling and implementation.

Conclusions

- OR/MS tools to complement biomanufacturing and life sciences.
  - End game is to drive down the health care costs.
  - Positive impact on Aldevron is passed along to Aldevron's clients.
- Tools and models are scalable to global pharmaceutical practices.
  - Global biopharmaceutical market value is $197 billion with 14% compound annual growth rate, accounting for 20% of the total global pharmaceutical market (BioPharm 2016).

Media Coverage and Industry Collaboration

- Madison biotech supplier goes lean to stave off foreign competitors, Xconomy (2014).
- Company Feature: Aldevron, Wisconsin Economic Development Corporation (2014).
- M&SOM student paper competition finalists, INFORMS (2015).
- Four researchers receive Marie Curie grant at TU/e, Eindhovens Dagblad (2016).
- When to stop the fermentation, Industrial Engineer, IIE (2016).
- Aldevron collaborates with UW-Madison, BioForward (2016).

Thank You. Any Questions?

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References

- Optimal Condition-Based Harvesting Policies for Biomanufacturing Operations with Failure Risks, *IIE Transactions*, 2016.
- Optimal Purification Decisions for Engineered Proteins. Under revision at *Operations Research* (Finalist at M&SOM student paper competition).
- Engineer-to-Order Proteins with Process Trade-offs: How Much to Produce and Waste? Under revision at *M&SOM*.