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WARWICK BUSINESS SCHOOL
THE UNIVERSITY OF WARWICK

For the Problem Solvers

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Dynamic Scheduling Policies for Continuous Bioprocesses

Agenda

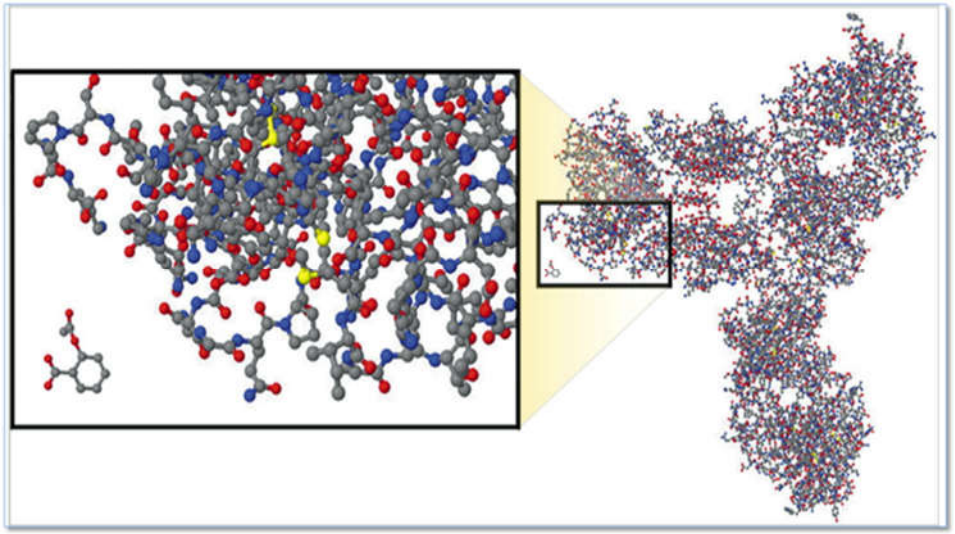
- Background on Biopharmaceutical Manufacturing
- Problem Description
- Hyper-heuristic Framework
- Scheduling Policies
- Results
- Conclusions

Biopharmaceutical Manufacturing

Background

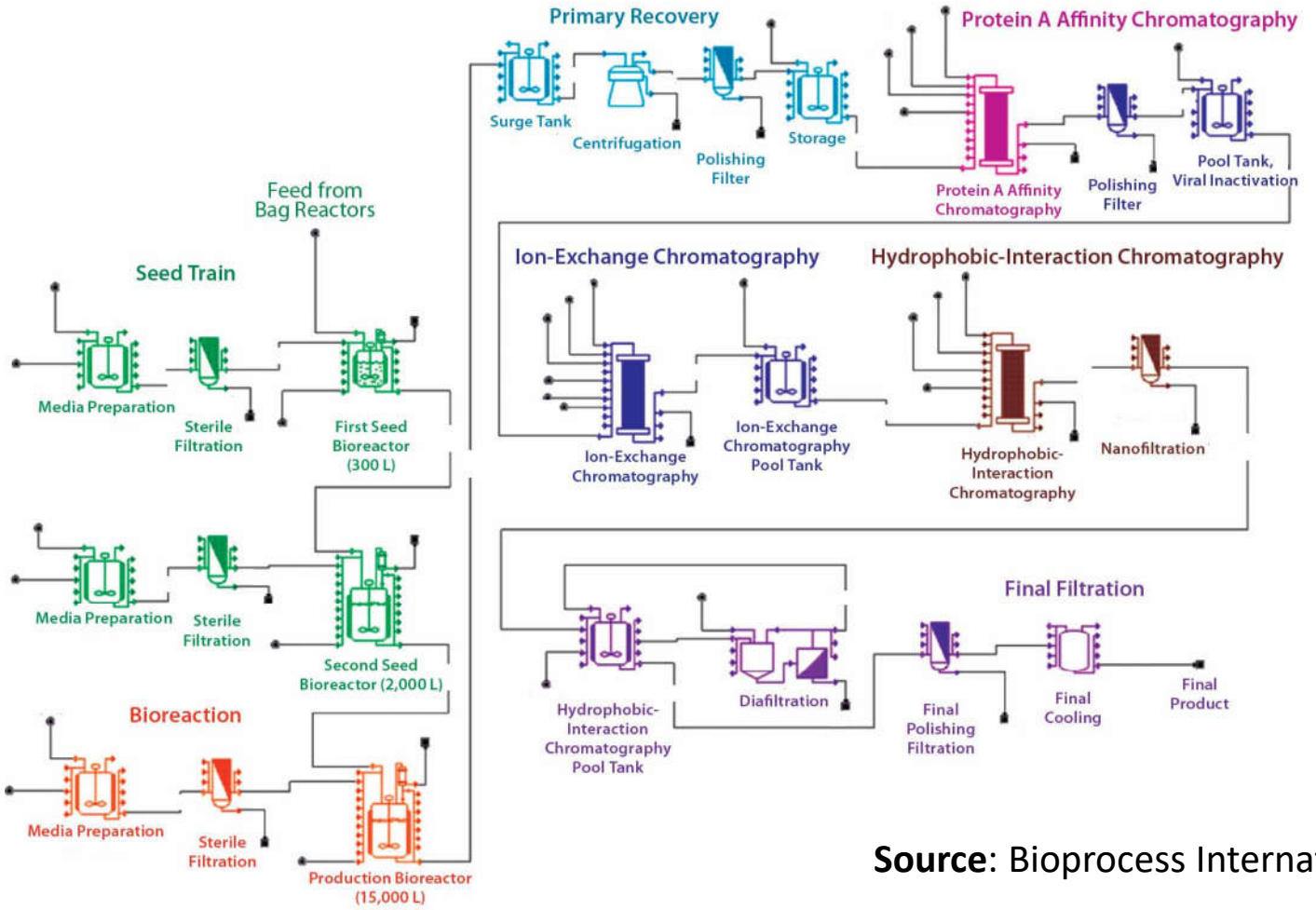
Biopharmaceuticals are complex biological drugs

- Examples include monoclonal antibodies (mAbs)
  - Bevacizumab (Avastin®) to treat AMD
  - Trastuzumab (Herceptin®) for breast cancer treatment
- Several orders more complex and expensive than chemically synthesized pharmaceuticals



Molecular complexity: Aspirin vs. mAb

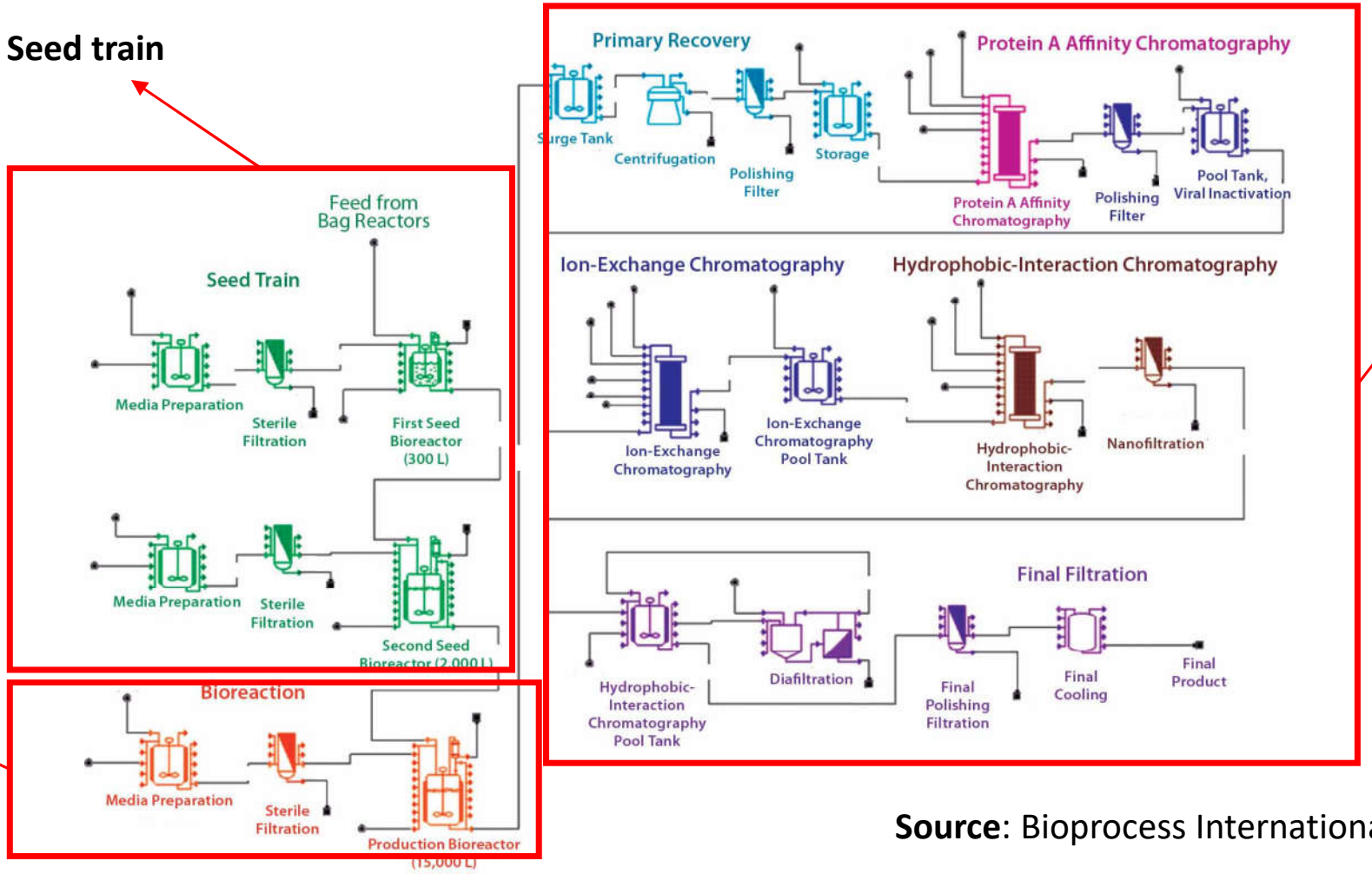
mAb manufacturing process



Source: Bioprocess International

mAb manufacturing process

Seed train

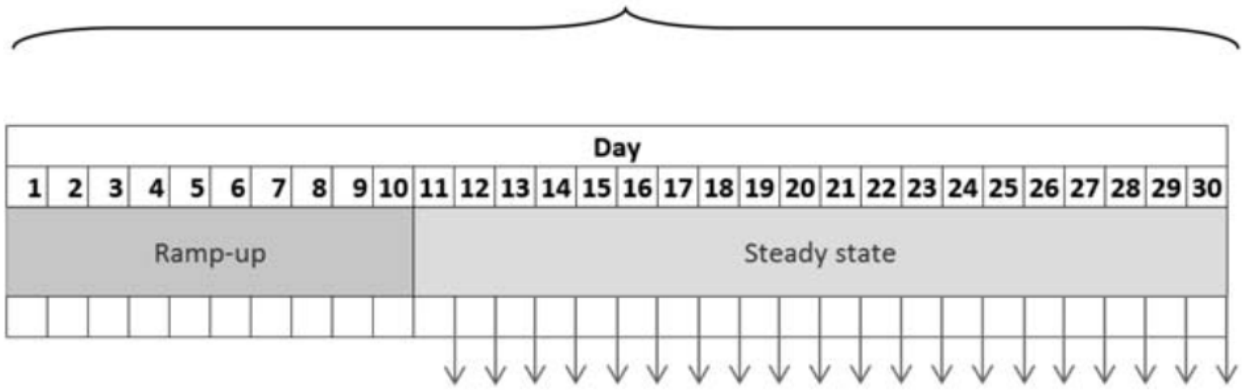


USP: upstream processing

DSP: downstream processing

Source: Bioprocess International

Semi-continuous perfusion USP



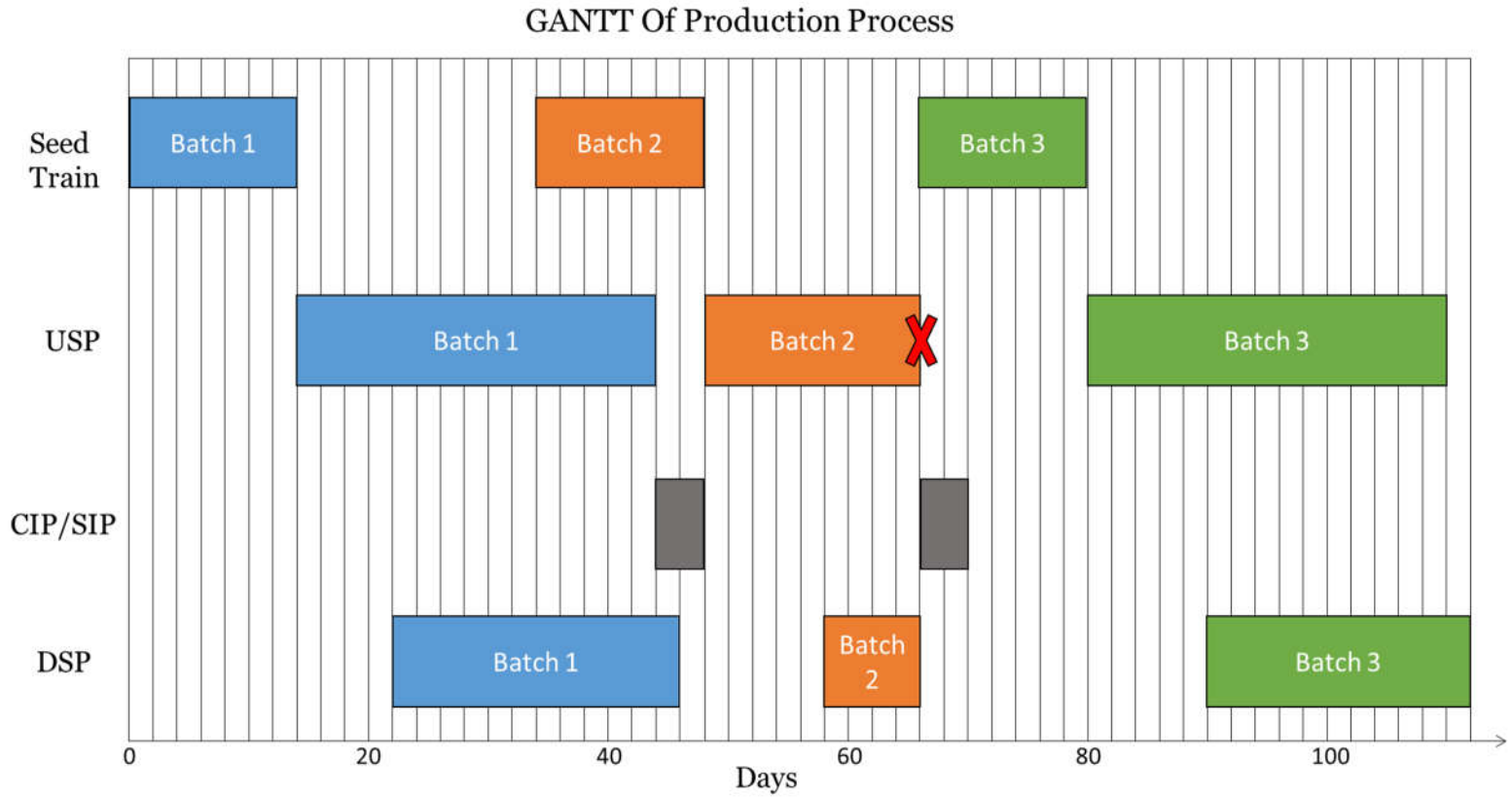
Continuously harvest, recover, capture and freeze

Pool harvests for DSP immediately, at a later date, in a different facility, or split up.

Source: Siganporia et al. (2014)

Impact of process failure

Failure probability increases with run time.



Problem Description

Stochastic economic lot scheduling (SELSP)

- Stochastic and uncertain demand
- Expected demand is stationary
- Discrete time-periods of one day
- USP is semi-continuous
  - We want to choose a good run time
- Random process failure
  - Cell culture contamination leads to batch termination
  - ATF filter failure causes a delay of one day
- No preventative maintenance

Case study

- Three products
- Seven year planning period
- Failure rates for cell culture and ATF filter
  - 10% and 2% respectively in 60 days
- Sequence-independent setup
- Maximum shelf-life of two years
- Unmet demand (backlog) accrues daily penalty cost
- Backlog decays over time

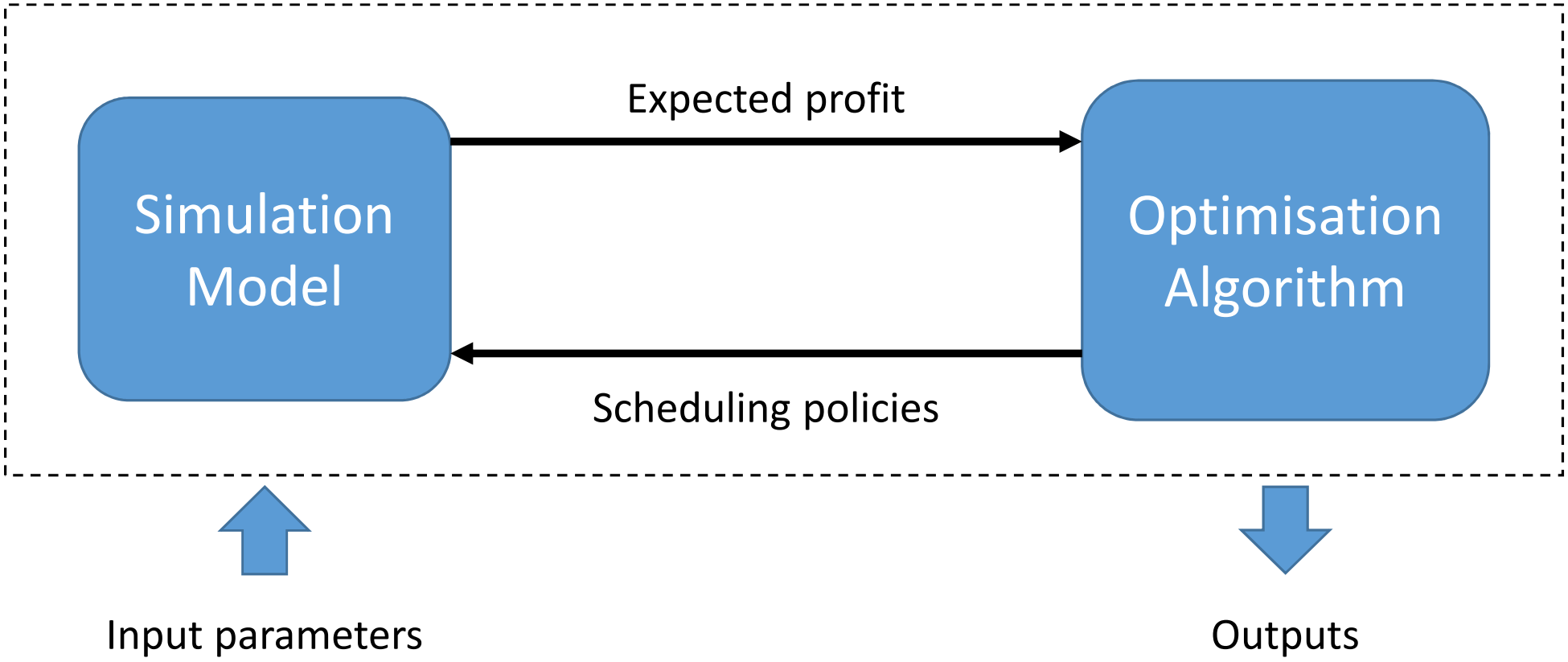
Modelling framework

Hyper-heuristic tool

Components of hyper-heuristic

- Bioprocess model(s)
- Simulation engine
- Scheduling policies or heuristic(s)
- Optimisation algorithm(s)

Hyper-heuristic framework



Scheduling policies

- Base stock policies
  - Simple – BSP1
  - Can-order – BSP2
  - Forecasting – BSP3
- ‘Standard’ policies
  - Heuristically chosen – BSP0
  - Fixed cycle – FCP
- Decisions made at end of batch, at failure event or in idle time(s)
- BSP0, BSP1, and BSP2 adapted from Löhndorf and Minner (2013)

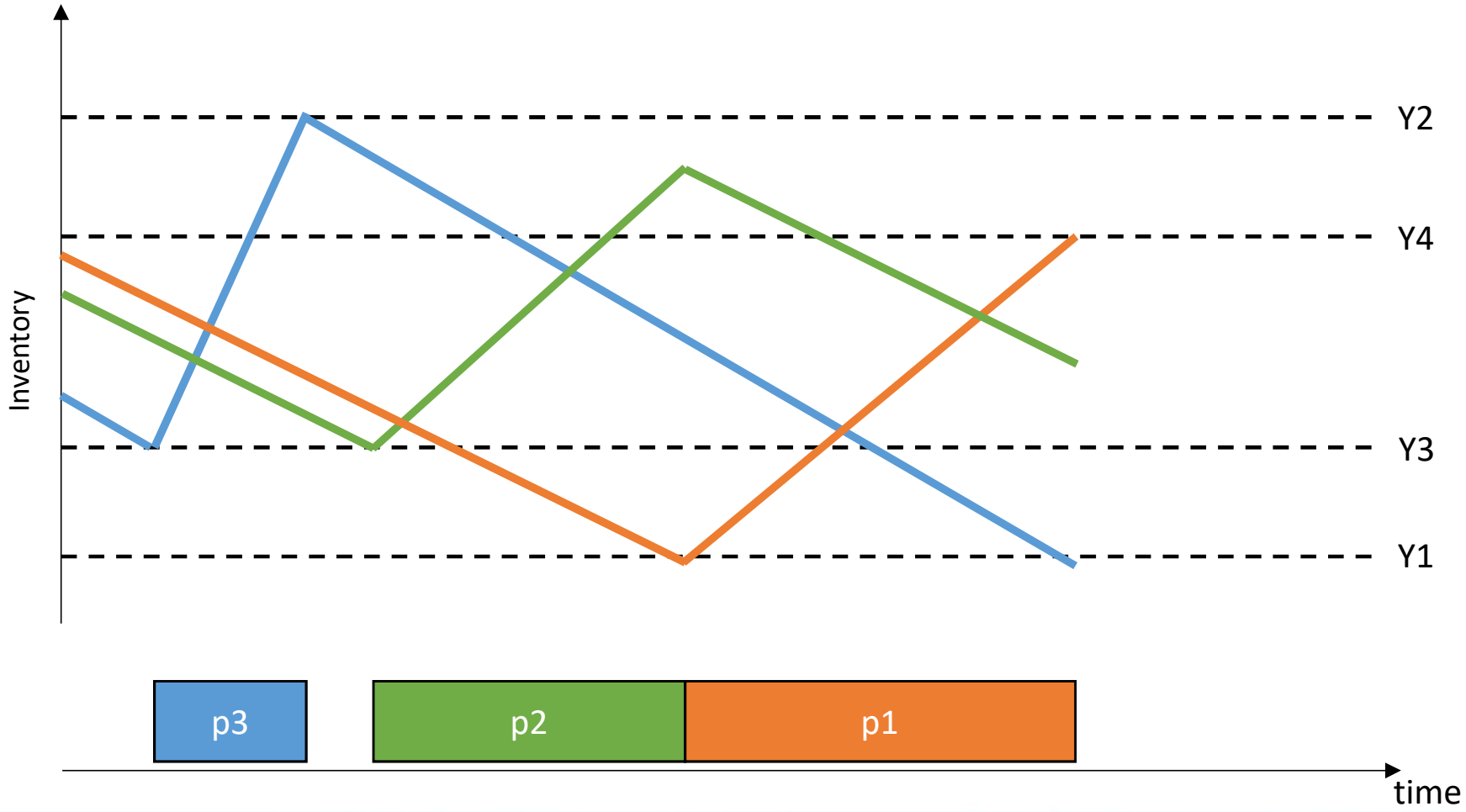
BSP0 and BSP1

- Based on typical (s,S) inventory policy
- Parameters are:
  - Y1 – reorder point
  - Y2 – order-up-to level
- BSP0 parameters chosen based on a common cycle time using Doll & Whybark Heuristic (Doll & Whybark, 1973).

BSP2

- Parameters are:
  - Y1 – reorder point
  - Y2 – order-up-to level
  - Y3 – can-order point
  - Y4 – can-order-up-to level
- Provides scope to interrupt campaigns to changeover to different product

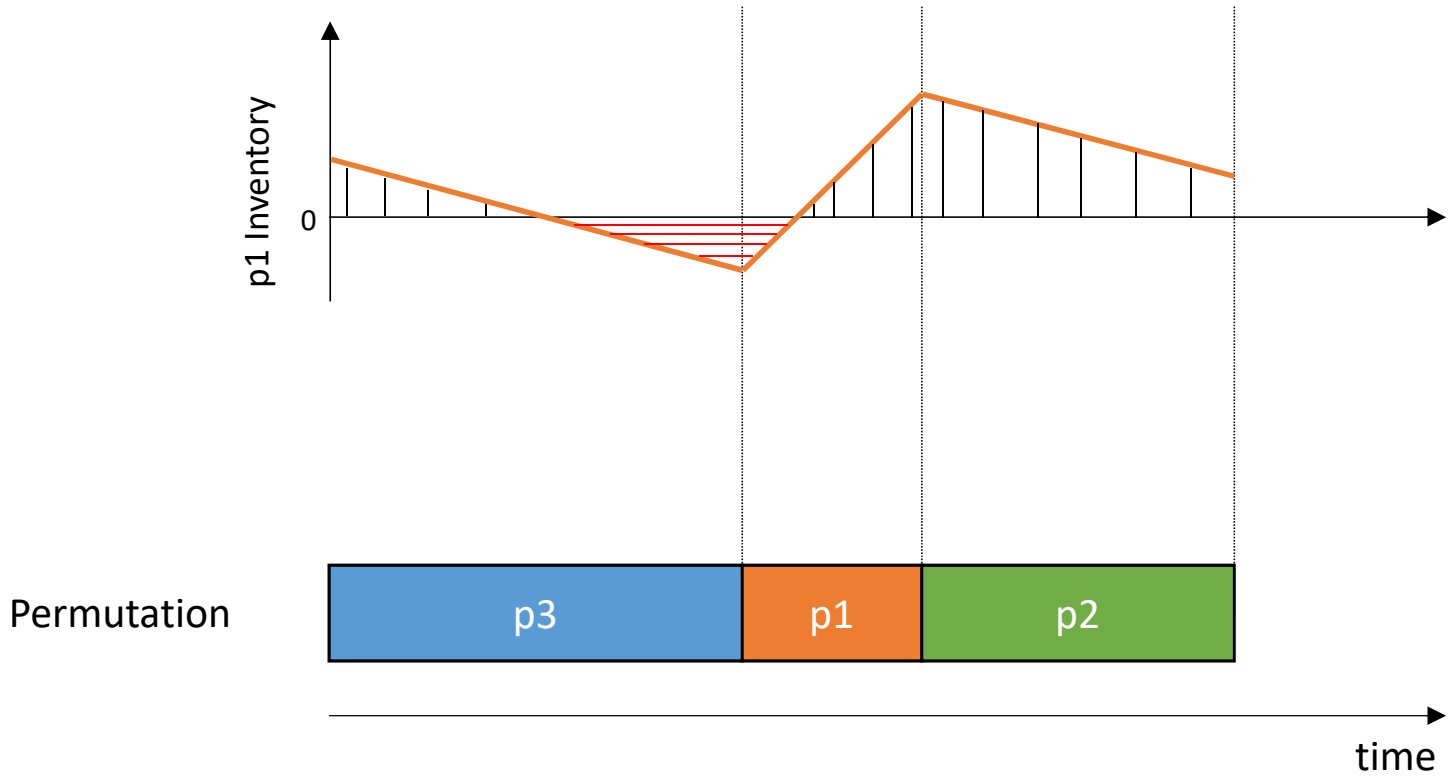
BSP2: Interruption rule(s)



BSP3

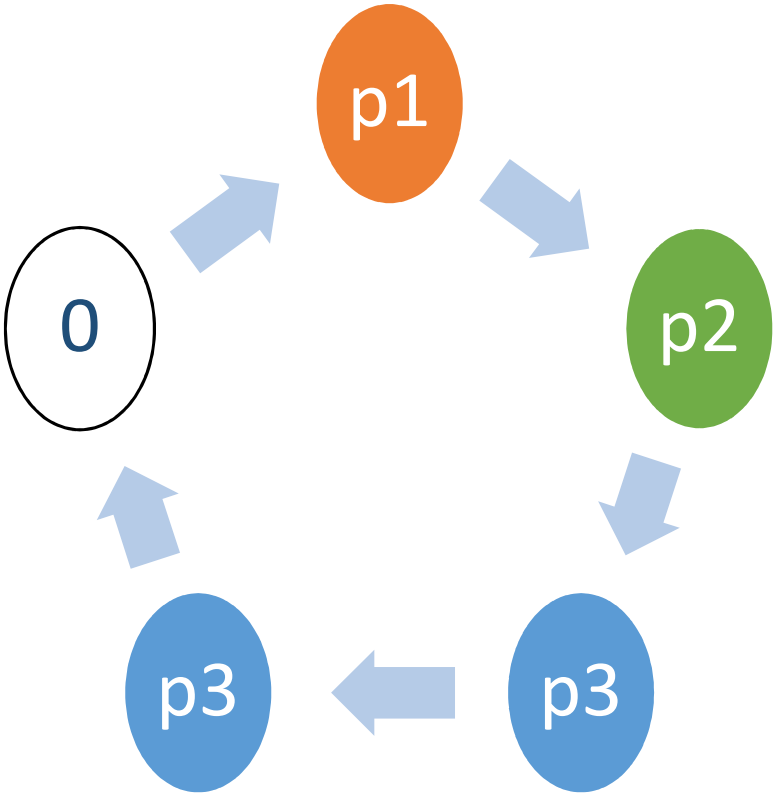
- Single parameter is:
  - Y5 – reorder point
- Look-ahead heuristic:
  - Enumerates all permutation of batches
  - Generates piecewise linear approximation of inventory levels
  - Based on this, estimates holding and backlogging costs
- Novel contribution

BSP3: Look-ahead heuristic estimation



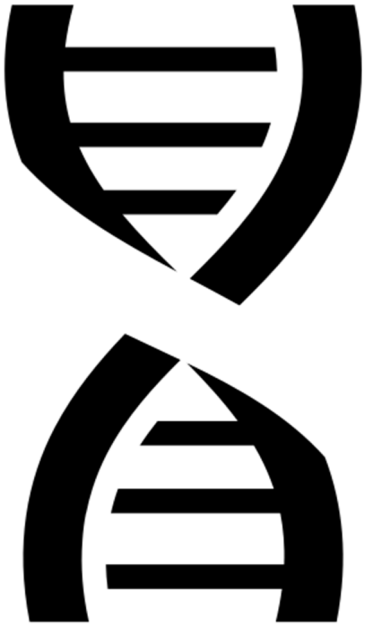
FCP

- Parameter for policy is a fixed sequence of batches.
- Idle times
  - Directly encoded
  - End when any product's run out time falls below 90 days
- Moves to next batch in sequence after failure



Genetic algorithm

- 200 generations
- Population of 30
- Elites of six
- Crossover
  - Two-point for FCP
  - Uniform for BSPs
- Mutation
  - Shift for sequences
  - Gaussian for real-valued
  - Random walk for run times



Results

Tuning and comparison of scheduling policy rules

Set of experiments

- Scheduling policies tuned with fixed `standard' run time of 60 days
  - Policies suffixed with 'A'
  - BSP0 run time is 60 days too
- Scheduling policies and run times tuned
  - Policies suffixed with 'B'
- Robustness tests

Policies with ‘standard’ run times

	BSP0	FCPA	BSP1A	BSP2A	BSP3A
Profit	179015 ± 21	186499 ± 19	189589 ± 2	189651 ± 5	**189711 ± 2**
Revenue	214690 ± 18	221684 ± 29	222908 ± 7	222996 ± 6	**223075 ± 8**
Total costs	35676 ± 6	35185 ± 40	**33319 ± 7**	33345 ± 6	33363 ± 8
Changeover costs	**478.0 ± 0.2**	1111 ± 14	1133 ± 0	1053 ± 4	1150 ± 1
Seed costs	**179 ± 0**	186 ± 0	181 ± 0	182 ± 0	182 ± 0

*All in RMU.

Policies with ‘standard’ run times

- The tuned base stock policies are superior
  - BSP0 <BSP1A < BSP2A < BSP3A

- Changeover costs are a main difference between BSP0 and others
  - Indicates campaigns of multiple batches
  - Especially as number of batches started is similar

Policies with optimised run times

	FCPB	*BSP3A*	BSP1B	BSP2B	BSP3B
Profit	186471 ± 175	*189711 ± 2*	189972 ± 6	190016 ± 14	**190125 ± 2**
Revenue	221402 ± 99	*223075 ± 8*	223101 ± 9	223123 ± 9	**223240 ± 7**
Total costs	34931 ± 121	*33363 ± 8*	33129 ± 7	**33107 ± 10**	**33116 ± 7**
Changeover costs	1113 ± 23	***1150 ± 1***	1211 ± 4	**1151 ± 6**	1250 ± 2

*All in RMU.

Policies with optimised run times

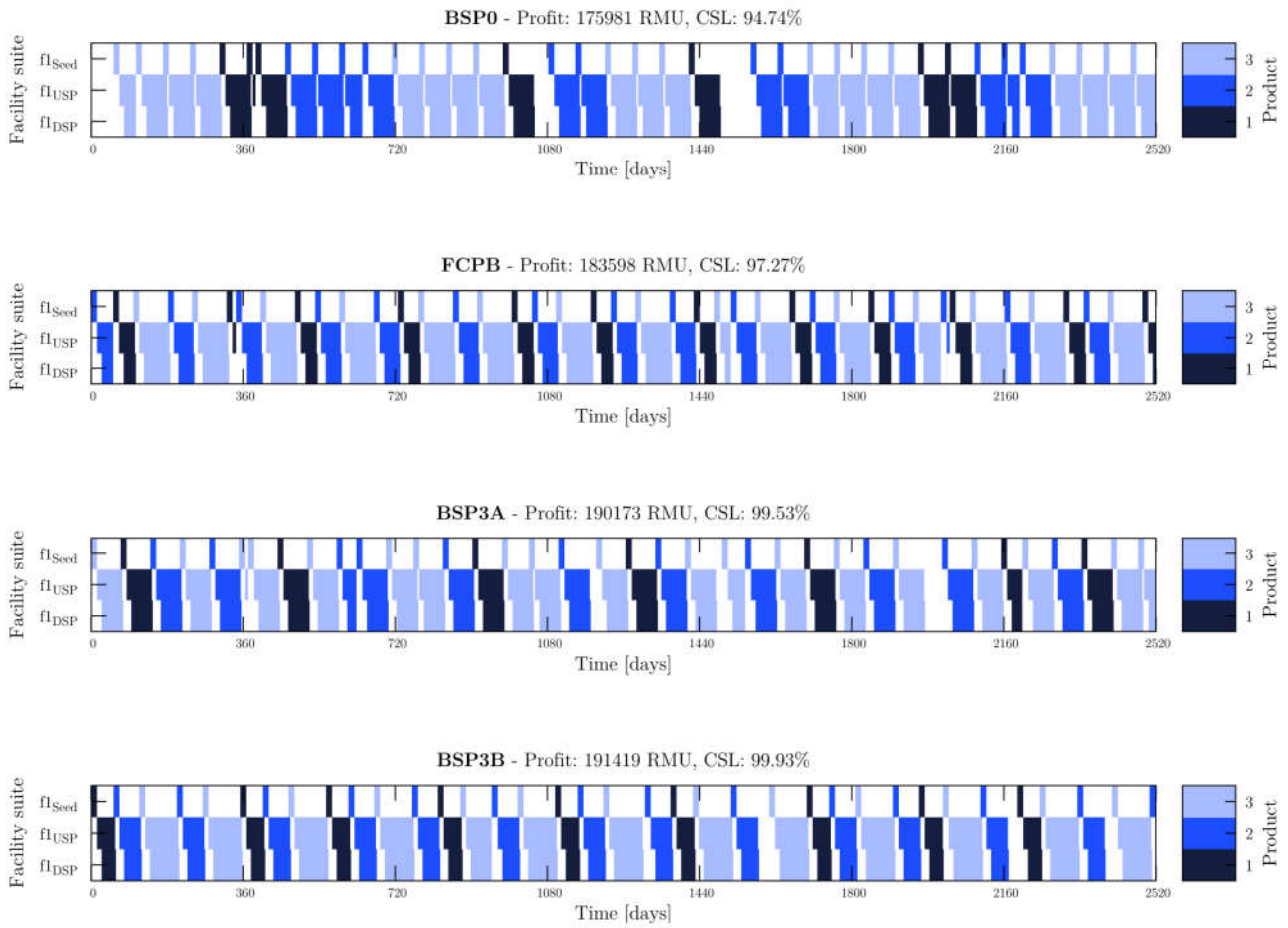
- The standard fixed cycle policy does not improve performance
  - So still worse than all base stock policies
- However, for others, optimised run times improves performance
  - The worst ‘B’ is better than the best ‘A’
- Optimised run times generally diverge from standard
- Best solutions do not schedule p1 and p2 all in one batch

Optimised process run times

	p1	p2	p3
‘Standard’	60	60	60
FCPB	38	47	72
BSP1B	47	58	65
BSP2B	43	59	74
BSP3B	43	51	79

*Run times in days.

Example facility GANTT charts

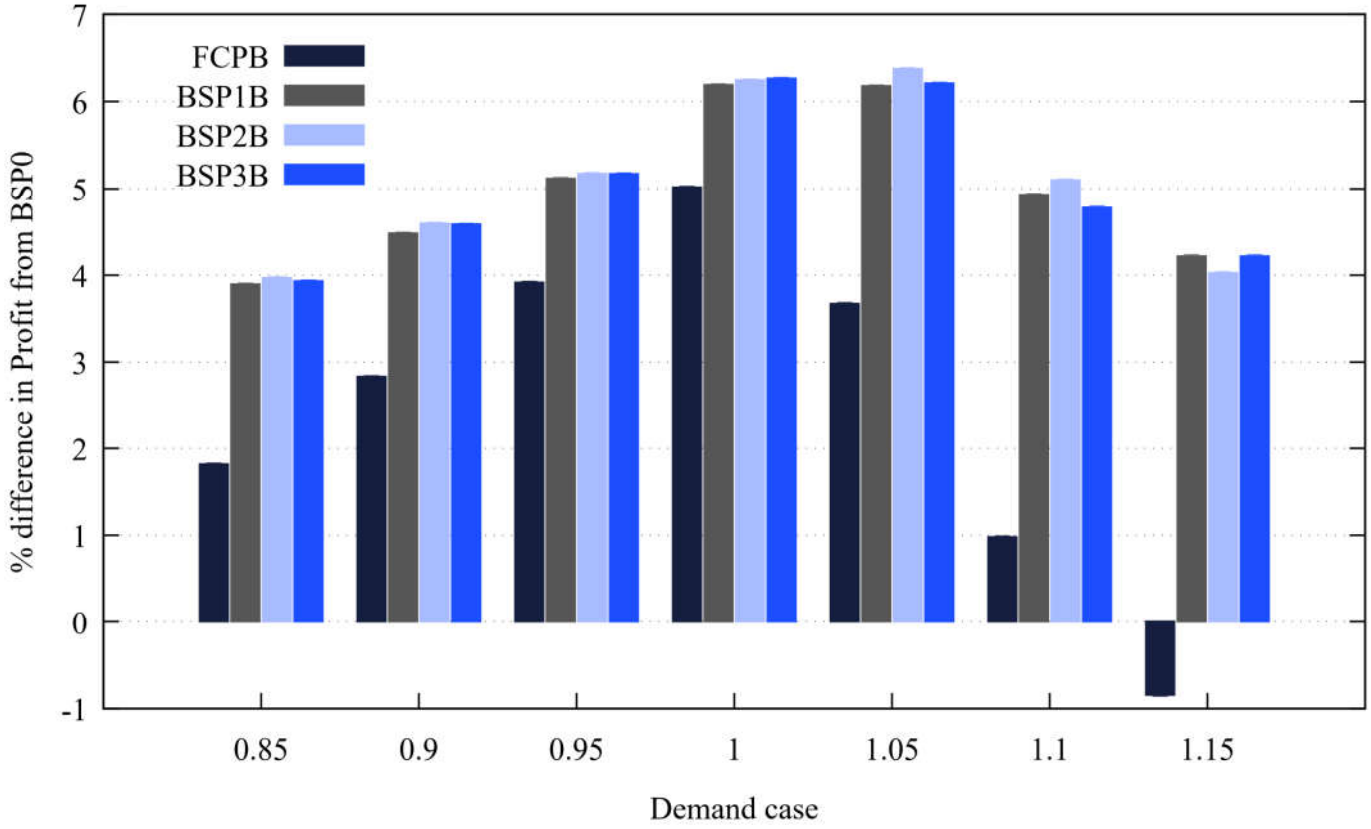


What do we see from the schedules?

- Best rule for each policy type shown
- Only BSP0 schedules long campaigns
- FCPB and BSP3B don’t schedule multi-batch campaigns at all

Robustness check

The observed demand distribution may differ from forecast(s).



Summary

- Developed a custom object-oriented simulation model
- Demonstrated benefit of tuning:
  - Inventory parameters
  - Process run times
- Recommendation to evaluate policies at different demand scales
- Decision-maker's preference for multi-batch campaigns may affect policy selection

Thank you.

Questions?