

# *Optimization of Manufacturing Operations using Discrete Event Simulation*

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# Why simulate your manufacturing operations?

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- Provides **insight** into
  - Complex interactions on plant
  - Dynamics of plant operation
  - Impact of proposed changes

- Which allows you to **set direction**
  - Doing the right project
  - Focusing energy and resources on the right improvements
  - Mitigating less obvious risks



# How can you simulate a biotech plant?

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- Biotech plants are generally characterised by
  - Batch processes
  - Supported by both batch and continuous operations
- Steady state approximation?
  - Simplify by making assumptions
    - Availability
    - Constraints
  - Over-design / Under-design?
- Dynamic model?
  - Needs flexibility
    - Batch vs. continuous
  - Needs detail to accurately reflect plant operation

# Example: Capacity simulation and debottlenecking



**The Advanced Biologics Centre**

# Example: Capacity simulation and debottlenecking

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- Situation
  - Multi-stream, multi-product contract manufacturing facility
  - Recently commissioned two new streams, each with 5000L gross microbial fermentation
  - Productivity not meeting flowsheet as quickly as planned
- Expectations
  - 14d cycle initially for a product expressed in pichia pastoris
  - Improving to 7d cycle with continuous improvement and further investment
- Reality
  - 19d cycle and experiencing unavailability for buffers

# Approach

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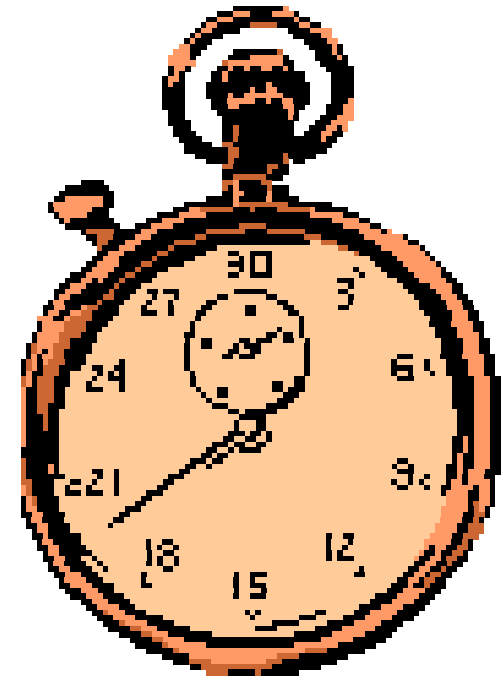
- Debottlenecking project initiated
- Decided to use a dynamic discrete event model to support prioritisation of possible solutions
  - Hardware
  - People & Resource
  - Systems & Procedures
- Selected BioPharm Services Ltd
  - Previous experience on site
  - Bringing biotech as well as simulation expertise
  - Customisable simulation software

biopharm  
SERVICES

# Tracking Time is Important

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- Processes are defined by time
  - Sequences of activities
  - Scheduling constraints
  - Complex dependencies
- Support operations driven by process
  - Batched
  - Continuous
- Shared equipment & utilities
  - Limited resources
  - Competition between process steps
  - Competition between streams



# Resources

## Batch

- Personnel
- Solution prep & hold
- CIP & SIP
- Parts washing
- Autoclaves



## Continuous

- Purified water
- WFI
- Clean steam
- Cooling



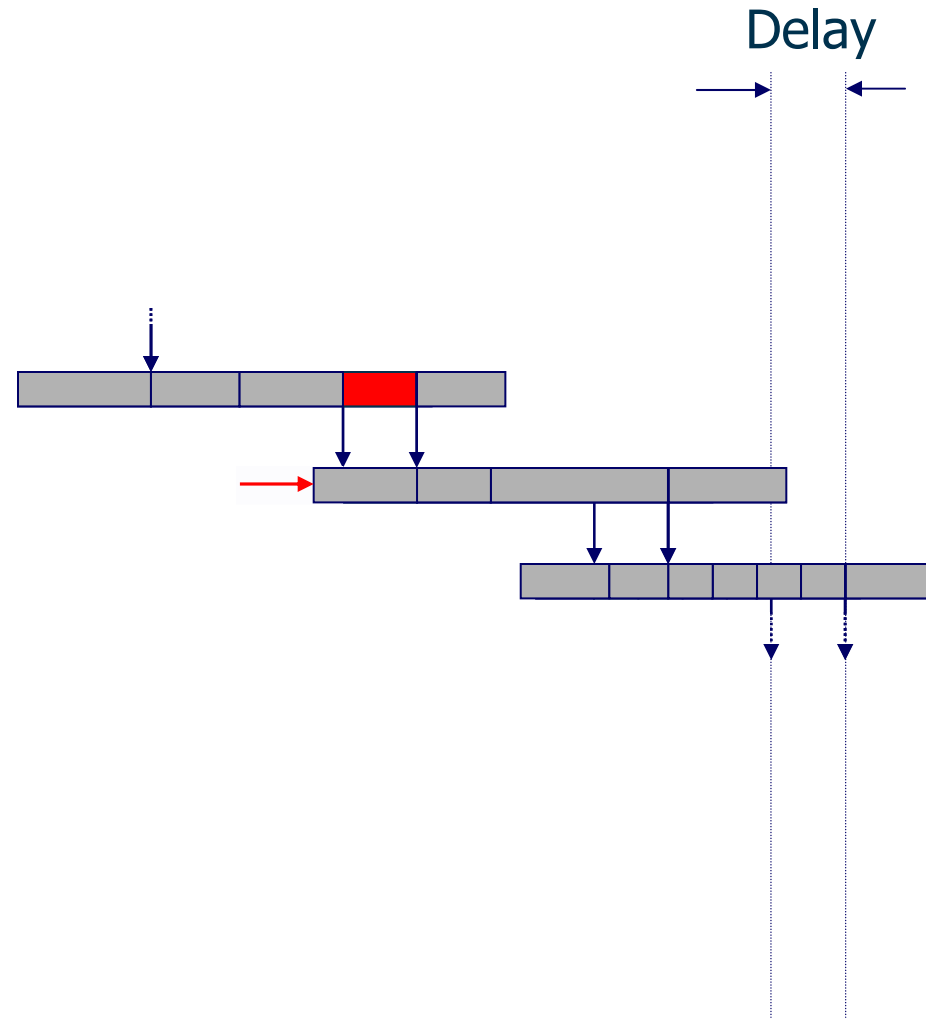
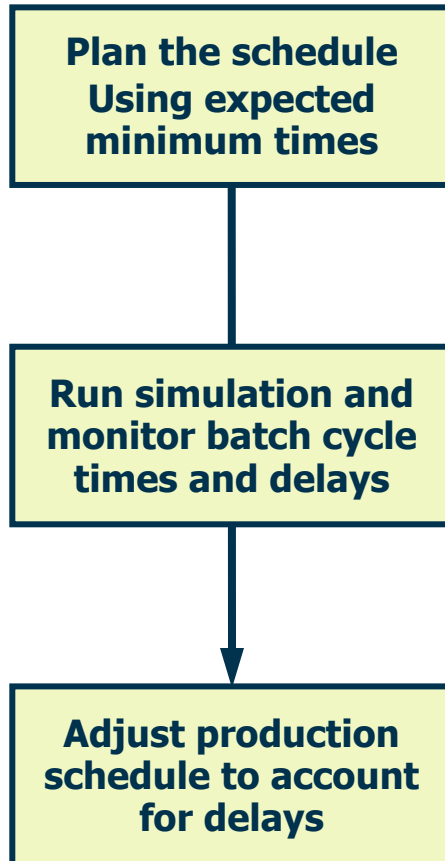
# Process Scheduler Tasks

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- Plans operations
  - Takes account of theoretical activities
  - Account for major process constraints
- Coordinate support activities
  - Media preparation
  - Buffer preparation
- Monitors delays
  - Adjust schedule
- React and reschedule for random events such as equipment break-down

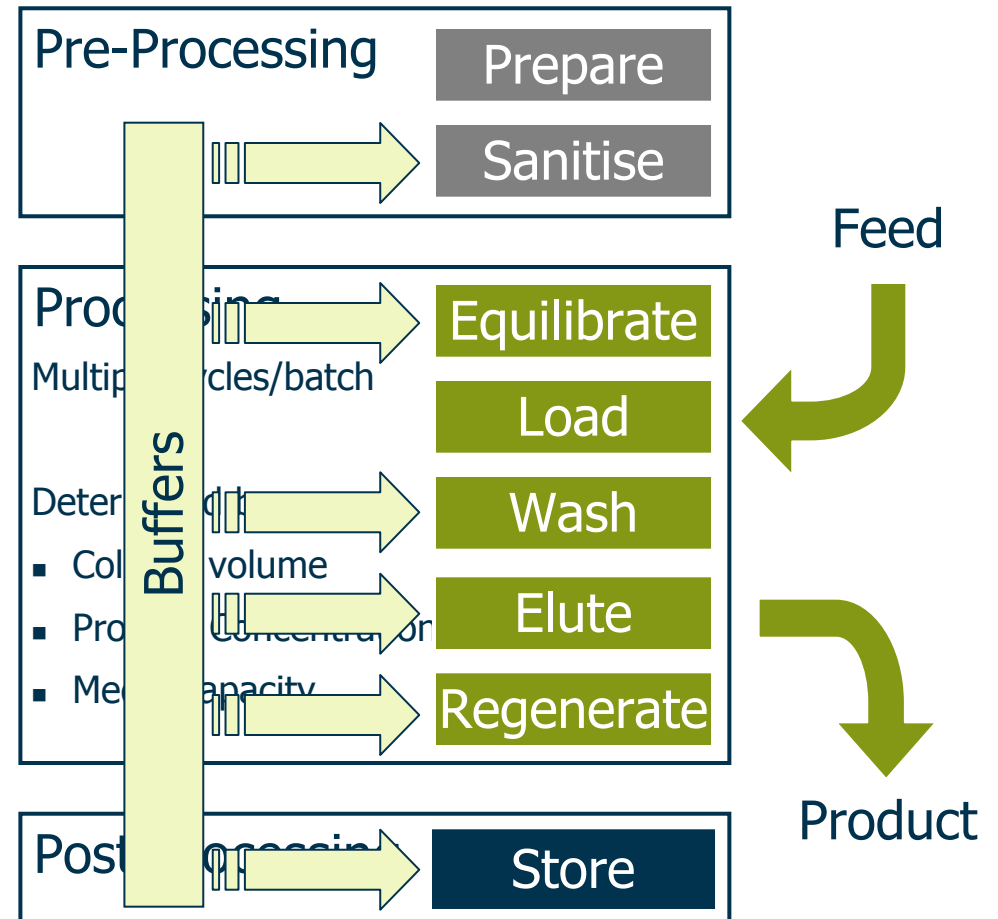


# Process Scheduler – Adaptive



# Unit Operations

- Part of sequence
  - Processes feed
  - Generates product
  - Linked to other operations
- Associated with:
  - Equipment
  - Personnel
  - Media/buffers
  - CIP
  - SIP



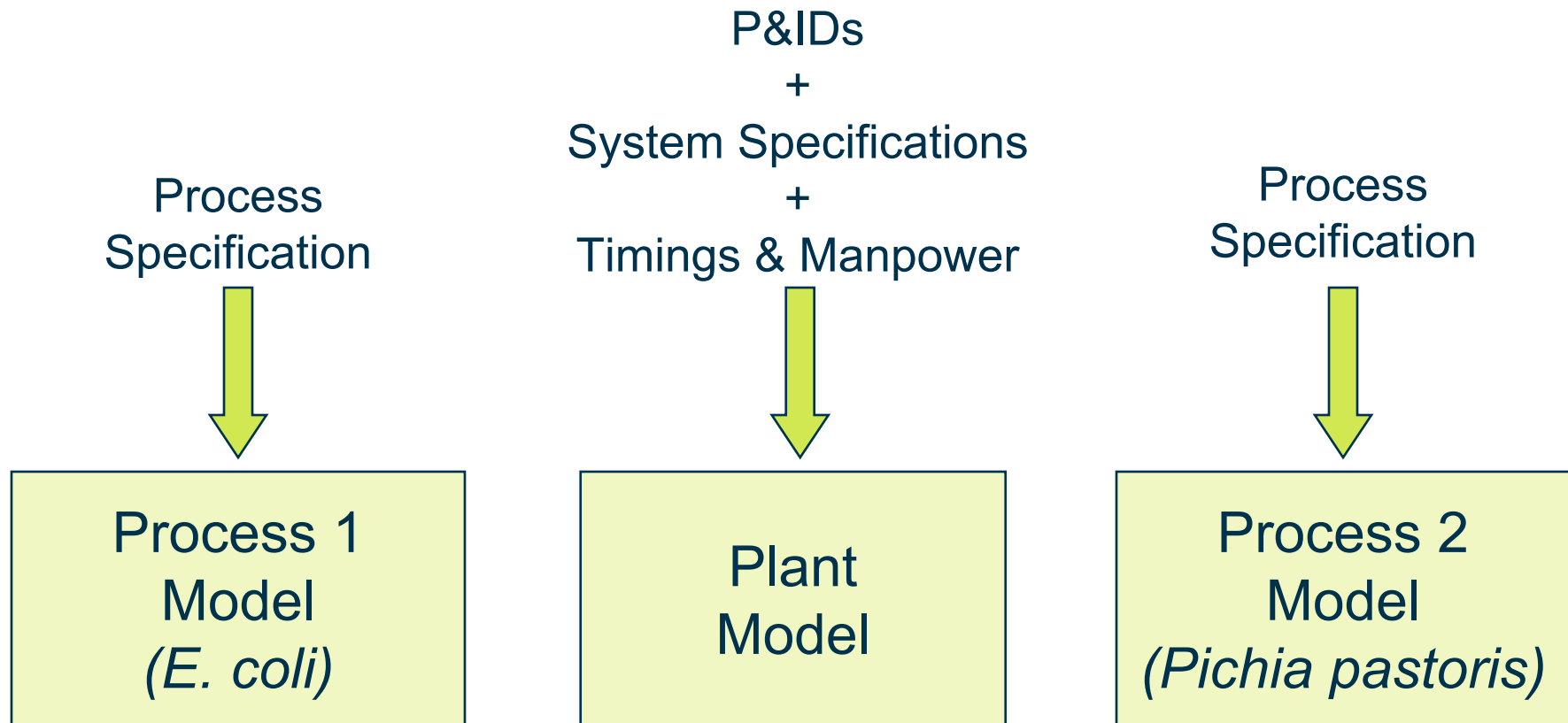
# The Database

- Simple list of steps that have to be carried out for each unit operation in a process (or CIP cycle...)
  - Quantities in / out
  - Buffers / utilities
  - Time
  - Personnel

Table	AIEX Column - rPA															Feed Range
Motor	Column:	E509	No.:	8												
Fieldr	Step	Step Type	Sub-Type	Sub-Type Row	Background Processing	Failure Probability	Failure Bypass	Feed Quantity (L.kg)	Waste Quantity (L.kg)	Time Limit (hr)	Time (hr)	Elapsed Time (hr)	Elapsed Sub-Op Time (hr)	Variable Duration	Personnel Allocation	
1	Setup				No						1.00	1.00	1.00		2	
2	Storage sol displacement	Utility	Pw	2	No			376.99	376.99		0.30	1.30	1.30		2	
3	Prime				No						1.00	2.30	2.30		2	
4	HETP	Buffer	[rPA] B2272D	65	No			301.59	301.59		0.50	2.80	2.80		3	
5	Flush	Utility	Pw	2	No			527.79	527.79		0.42	3.22	3.22		1	
6	Sanitisation	Buffer	[rPA] B2272J	70	No			301.59	301.59		1.00	4.22	4.22		1	
7	Pre-use wash	Utility	Pw	2	No			376.99	376.99		0.30	4.52	4.52		1	
8	Equilibration #1	Buffer	[rPA] B2272F	67	No			376.99	376.99		0.30	4.82	0.30		1	
9	Equilibration #2	Buffer	[rPA] B2272G	68	No			376.99	376.99		0.30	5.12	0.60		1	

# Model Build

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**4 weeks from initiation to first output**

# Model Output

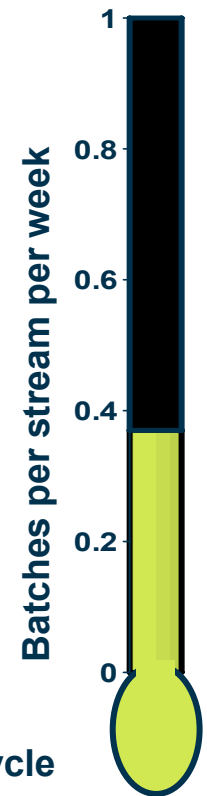
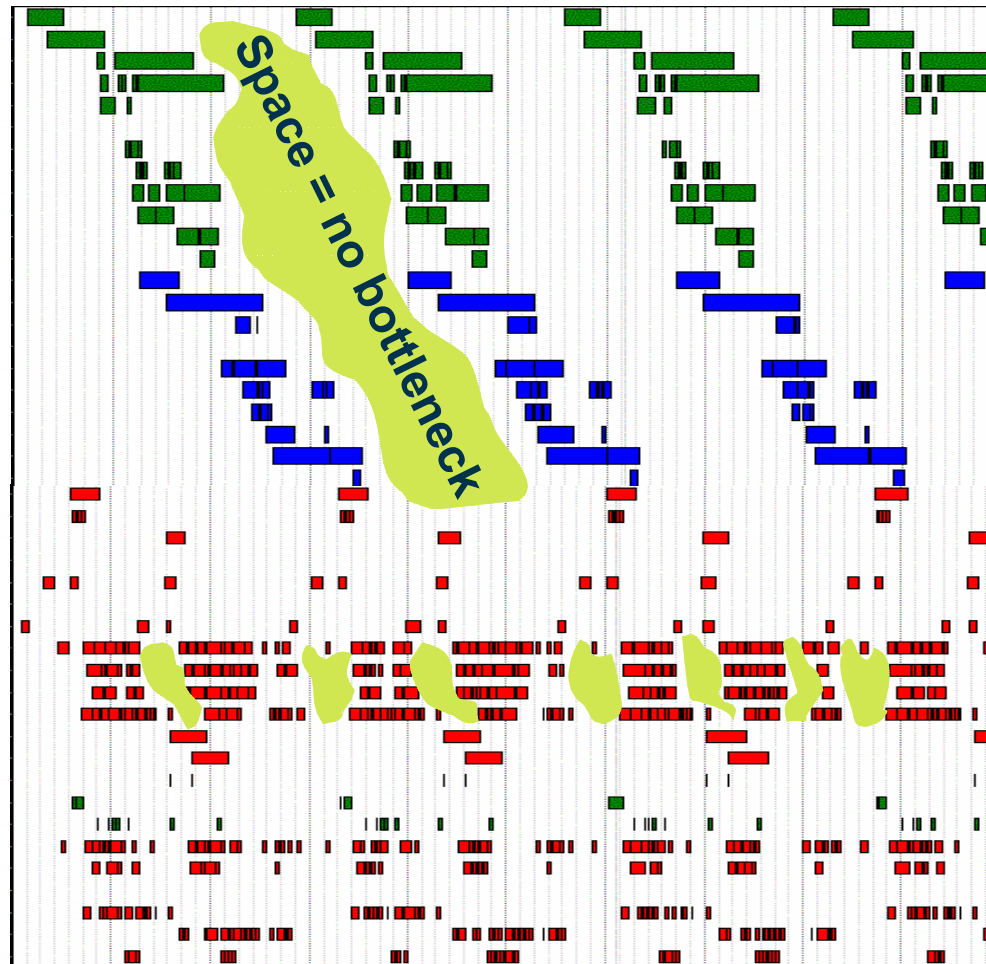
## Current Equipment & Resources

Process 1

Process 2

Buffer  
Prep

Vessels &  
Transfer  
Lines



19 day cycle

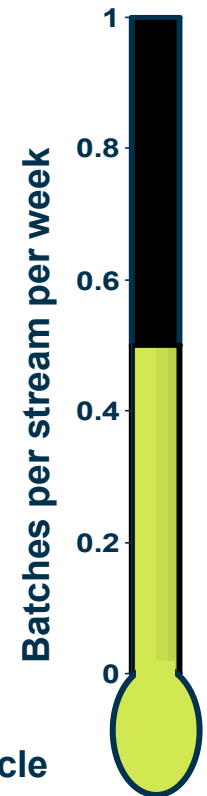
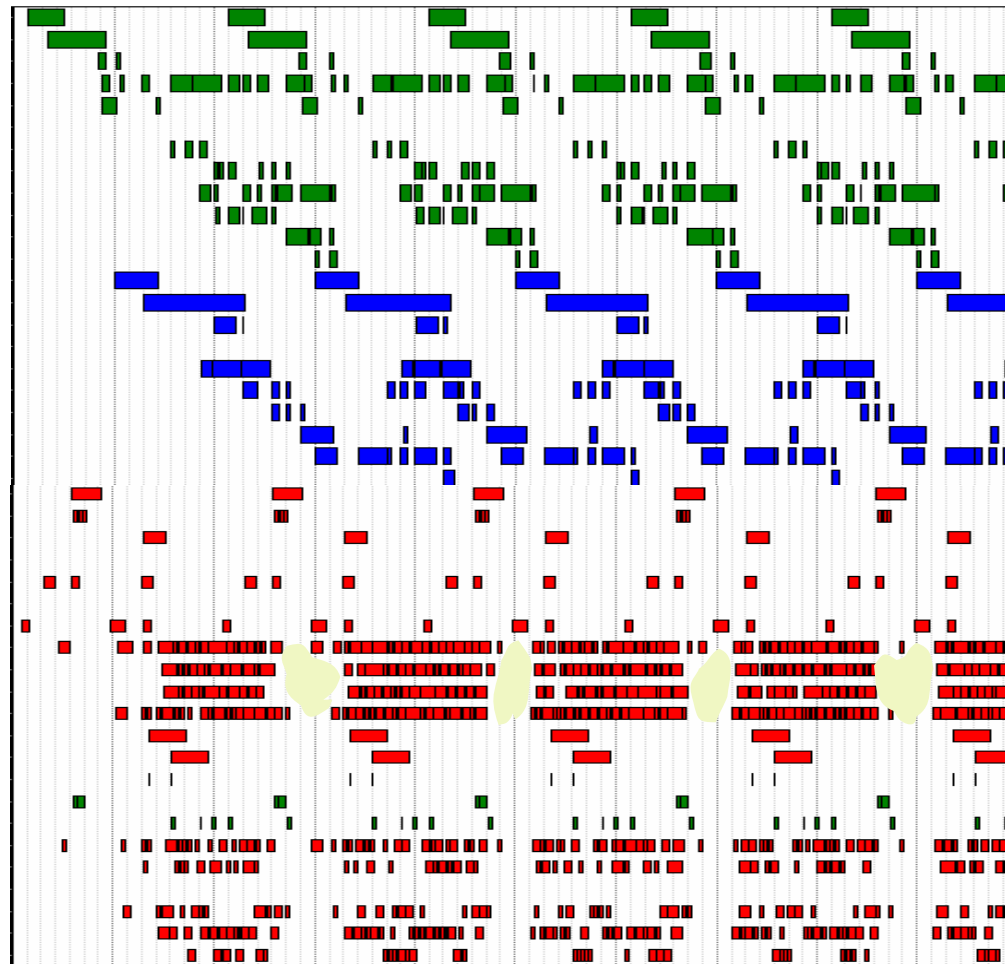
# Model Output Modified Work Patterns

Process 1

Process 2

Buffer  
Prep

Vessels &  
Transfer  
Lines



14 day cycle

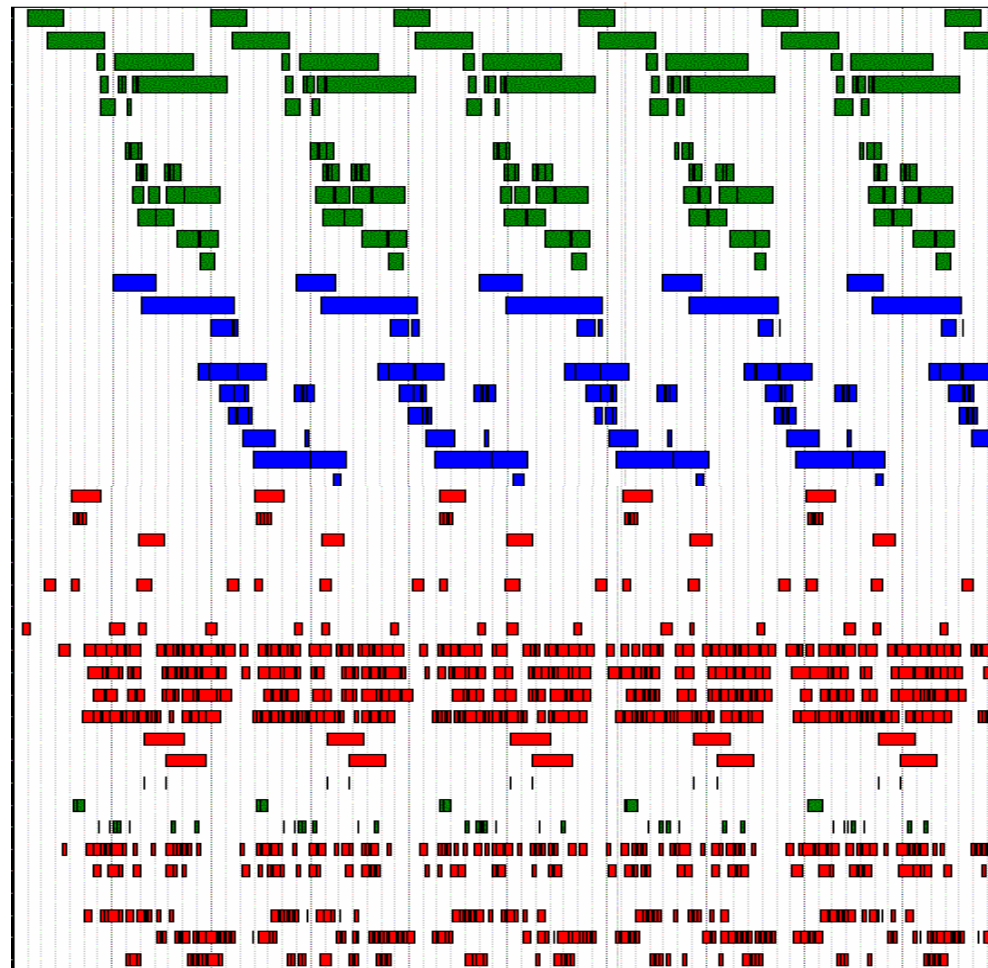
# Model Output Additional Manning

Process 1

Process 2

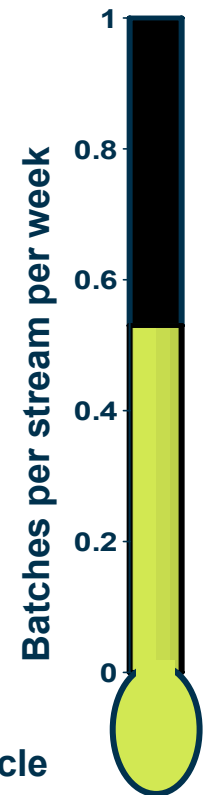
Buffer  
Prep

Vessels &  
Transfer  
Lines



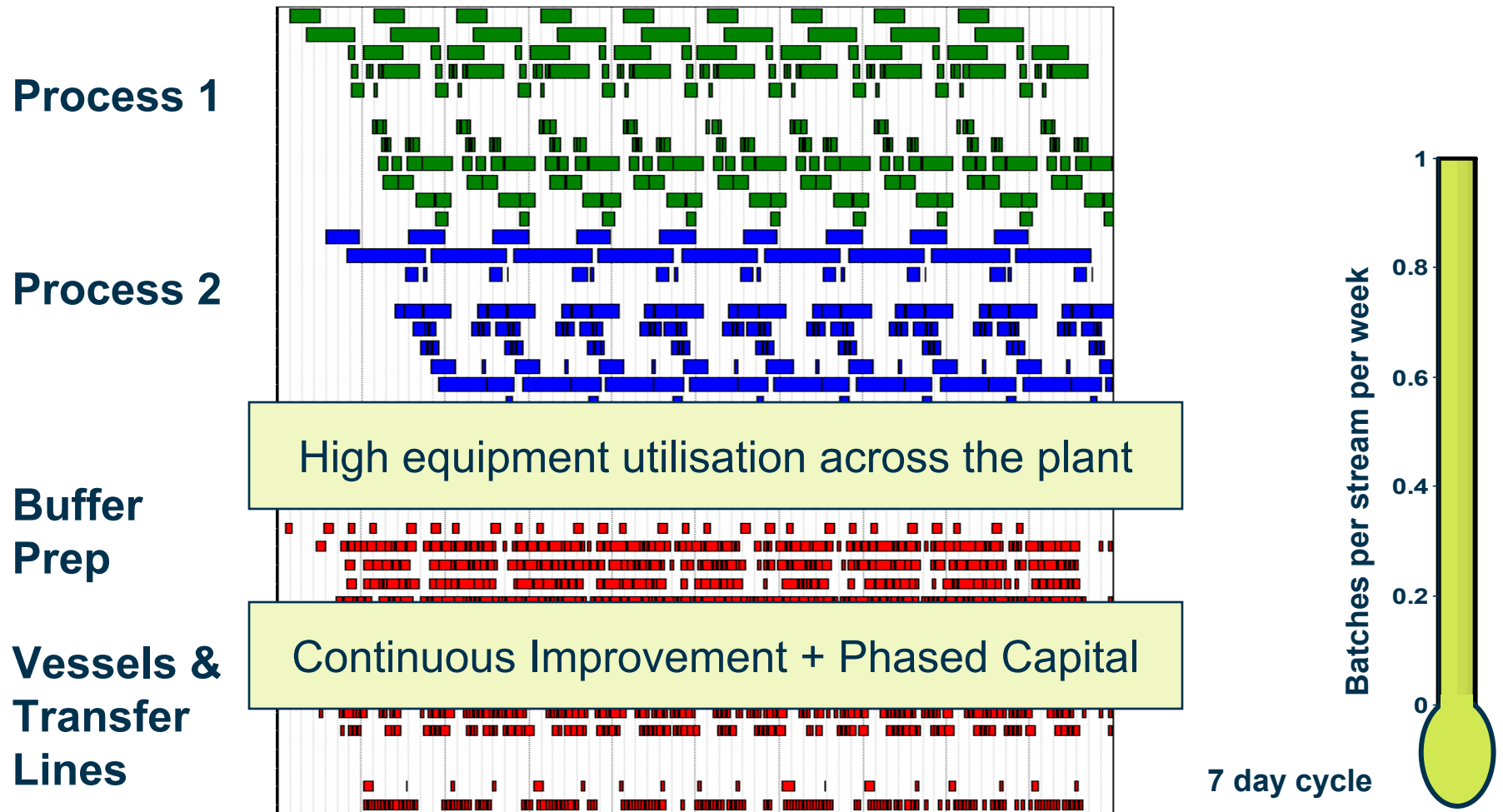
Bottleneck

13 day cycle



# Model Output

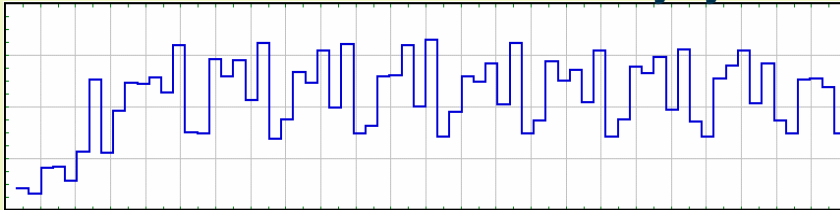
## Longer-term productivity goals



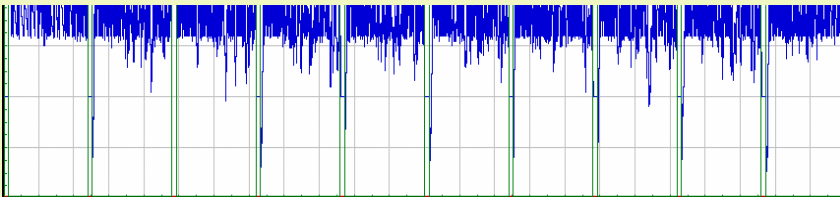
# Model Output Demand profiles

## Assessing utility capability

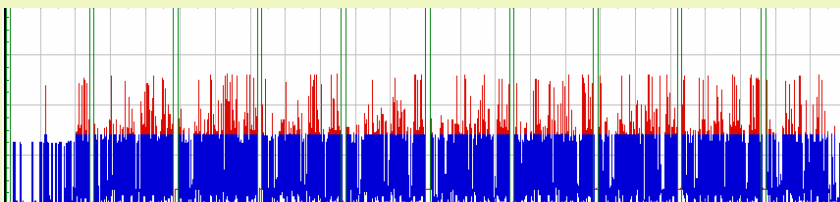
Purified Water Generation – 7 day cycle



Purified Water Storage – 7 day cycle

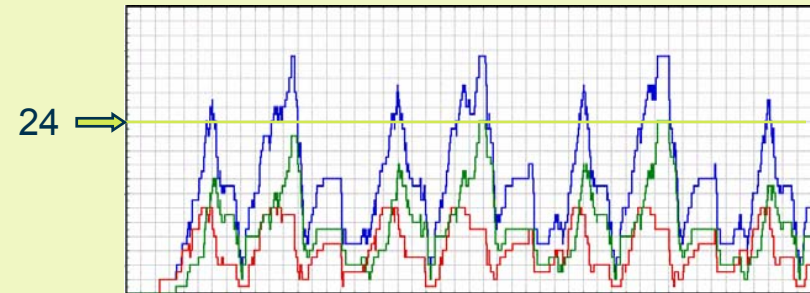


Purified Water Distribution – 7 day cycle

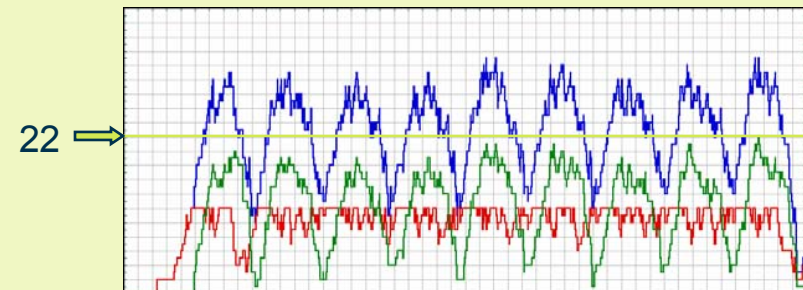


## Buffer scheduling controls buffer frame inventory

Bags in use – 19 day cycle



Bags in use – 7 day cycle

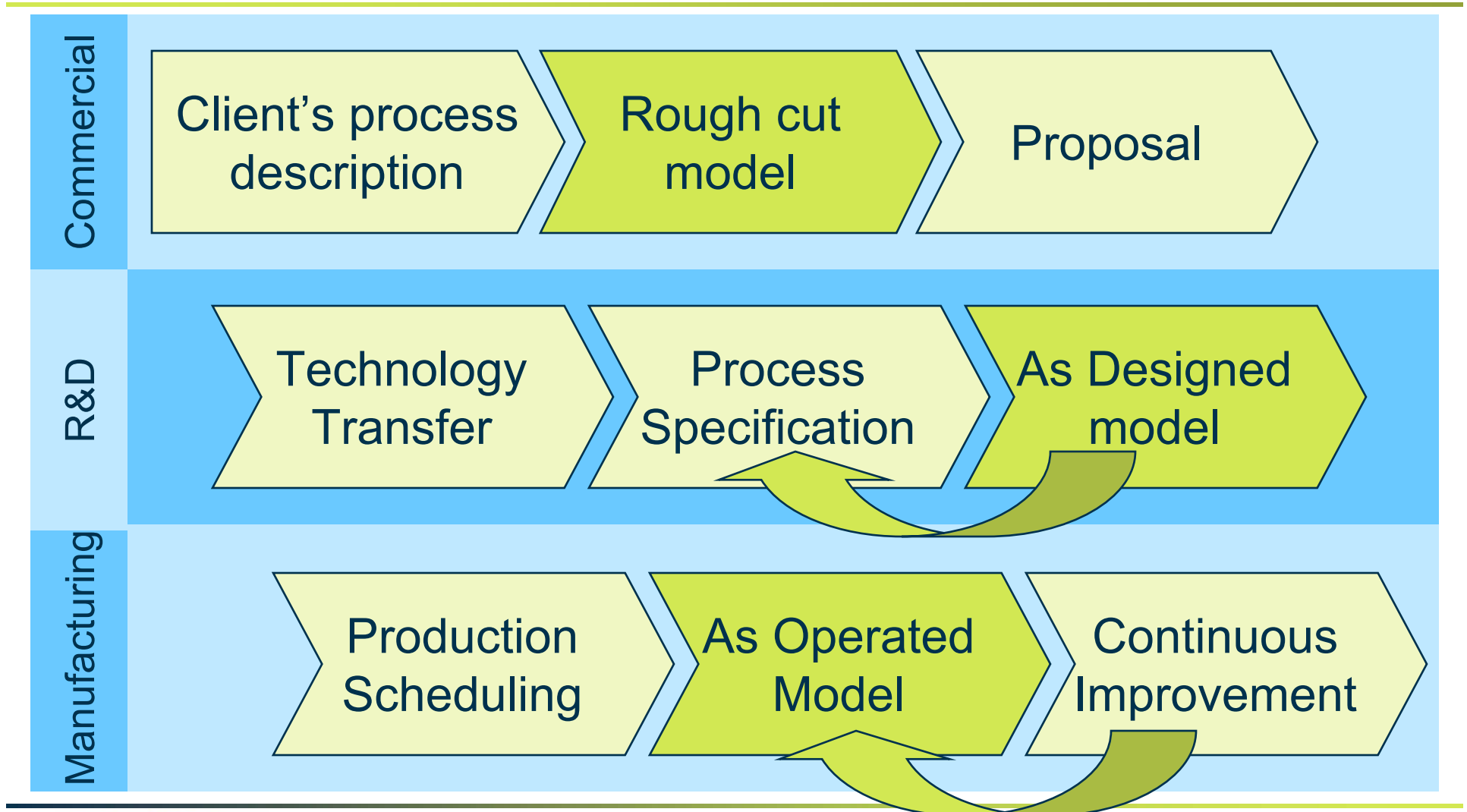


# Conclusions from Simulation

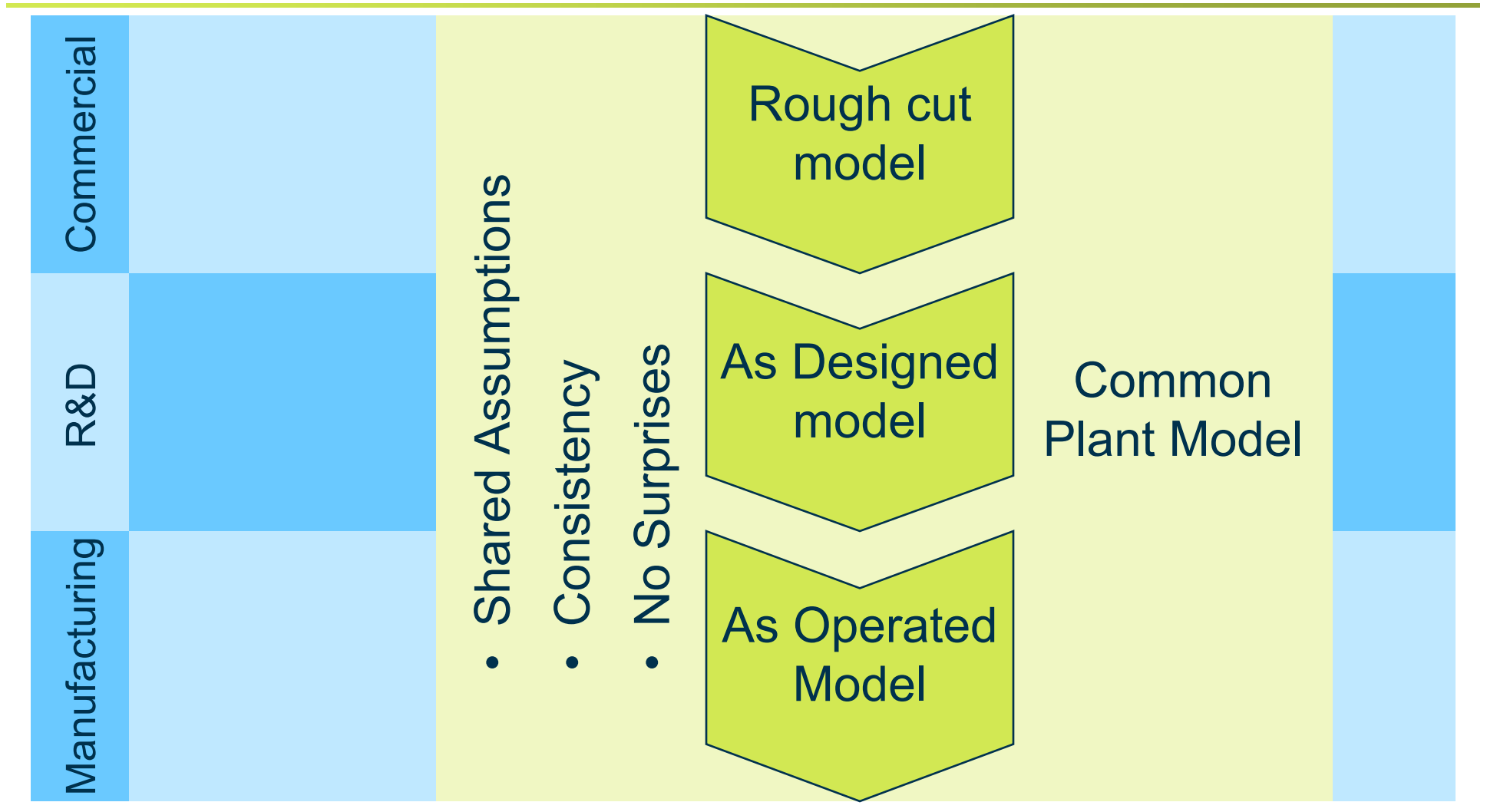
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- Buffer productivity was top priority
  - Improved work structure to ensure adequate resourcing
  - Streamline process to meet benchmark performance
- Manpower, work structuring and shift patterns
  - Matching supply profile of skilled resource to demand profile
- Can expect to improve productivity beyond flowsheet by continuous improvement alone
- Hardware demonstrated to be not an immediate bottleneck

# Integration with business processes



# Integration with business processes



# Summary

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- Simulation provides **Insight** into the complexities of biotech plants
- It helps to set **Direction** in projects and improvement programmes
- We have applied a Discrete Event dynamic model successfully for
  - Identifying productivity improvement targets
  - Prioritising capital improvements
  - Supporting New Product Introductions

# Thanks to...

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- Andrew Sinclair and James Savery
  - Helping us through building the model
  - Providing background material on discrete event simulation for this presentation
- Andrew Tidmarsh
  - In-house modelling expertise and analysis
- All of you for your attention

