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Vaccine manufacturing and supply chain optimisation

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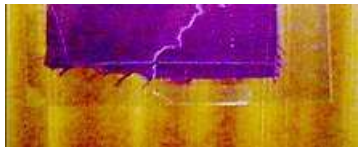
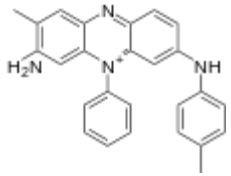
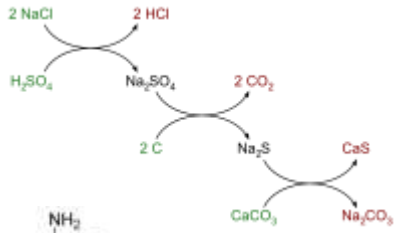
Context

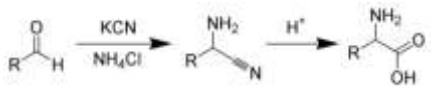
- ***Some milestones in synthetic chemistry***
- 1791: Leblanc process for soda ash
- 1850: Strecker synthesised amino acids
- 1856: Perkin synthesised mauvine

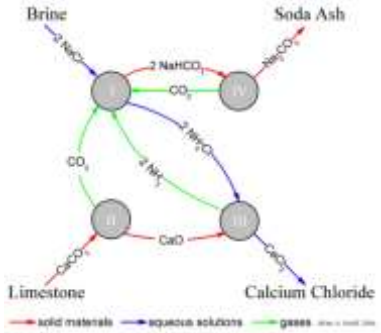


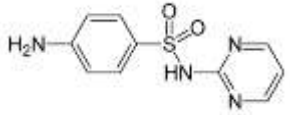


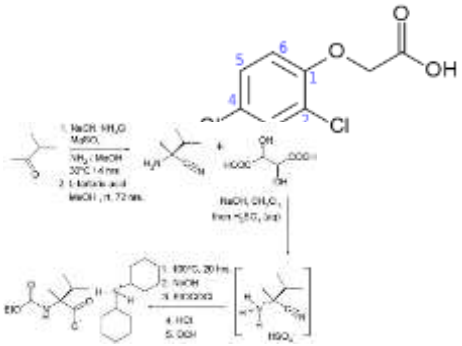
- 1863: UK Alkali act
- 1864: Solvay process
- 1892: Chlor-Alkali process
- 1925: Fischer–Tropsch process
- 1944: Woodward and Doering synthesis quinine
- 1940s: Sharpe and Dohme commercialise sulfa drugs
- 1946: 2-4-D herbicide developed at RRes
- 1963-date: asymmetric (amino acid) synthesis
- 2000s: DNA/RNA synthesis





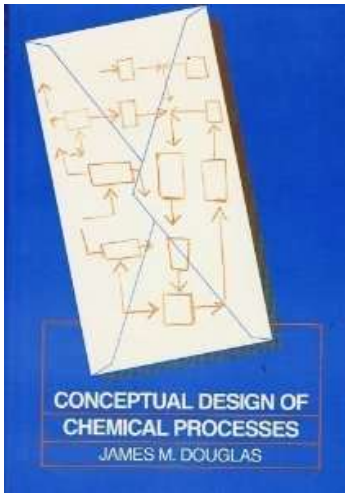


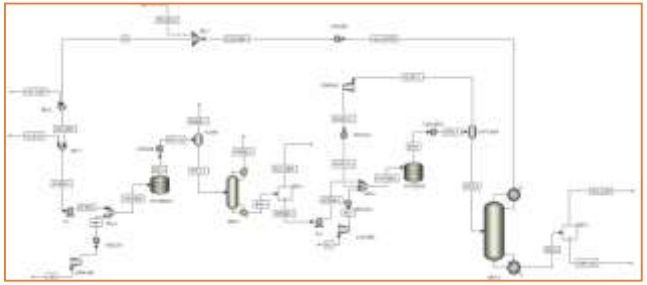


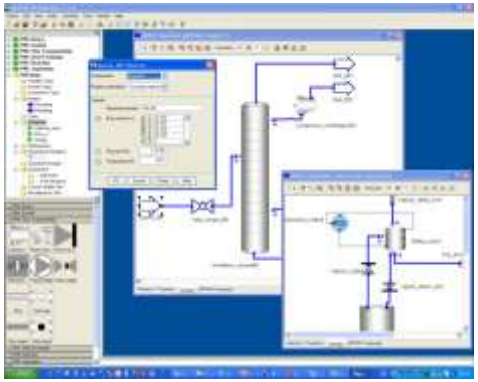


Process engineering

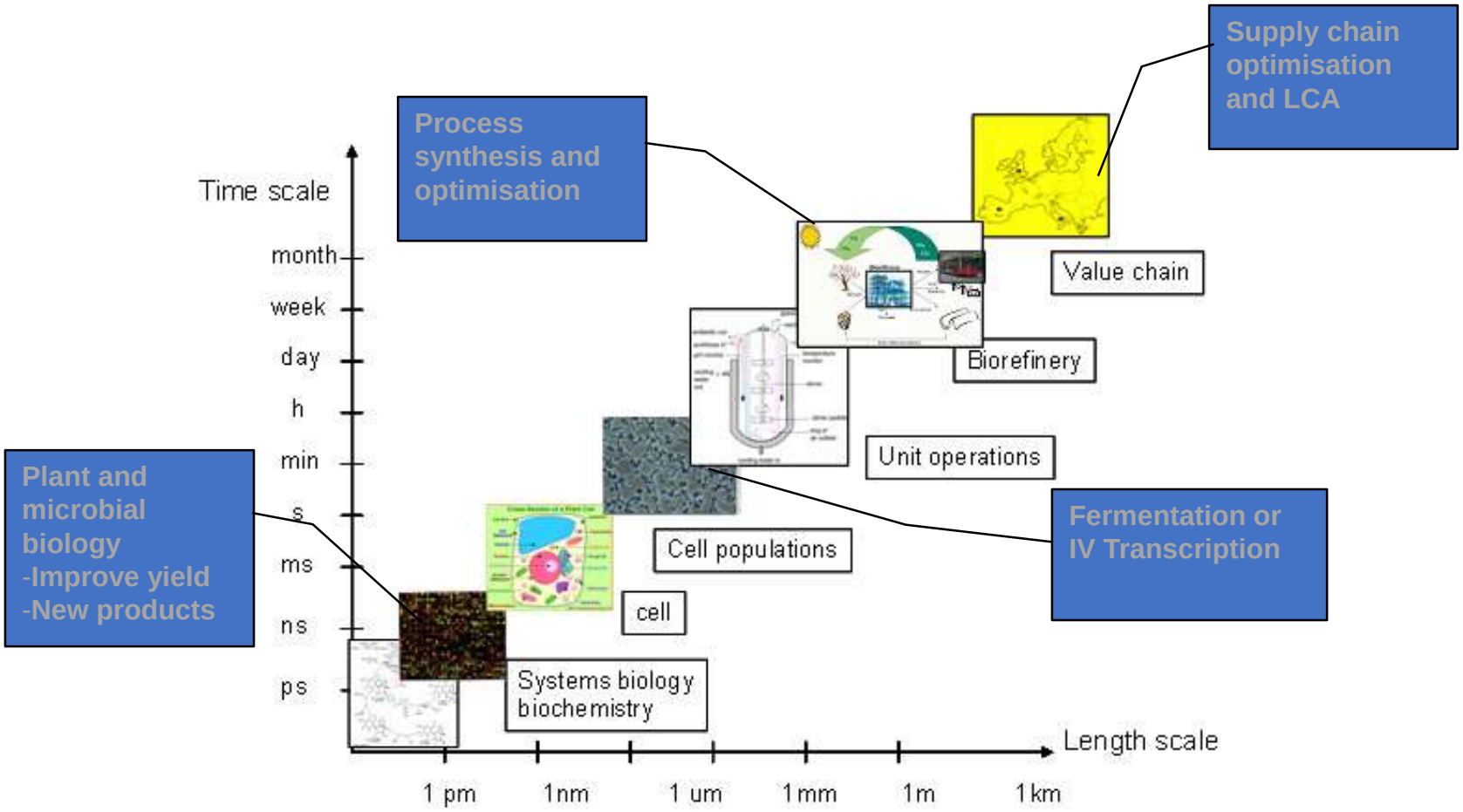
- 1888: George Davis (formerly an Alkali Act inspector) develops the concepts of Chemical Engineering and Unit Operations
- 1908: AIChE founded
- 1922: IChemE founded
- 1940s: biochemical engineering
- 1950s: transport phenomena, physical properties
- 1960s: **process systems engineering**
- 1970s: formal methods and tools for process design
- 1980s: rapid expansion of computer-aided chemical engineering
- 1990s: high throughput screening and miniaturisation/intensification
- 2000s: bio/info/nano
- Gentle pace -> rapid pace







PSE/Multiscale modelling in biotechnology



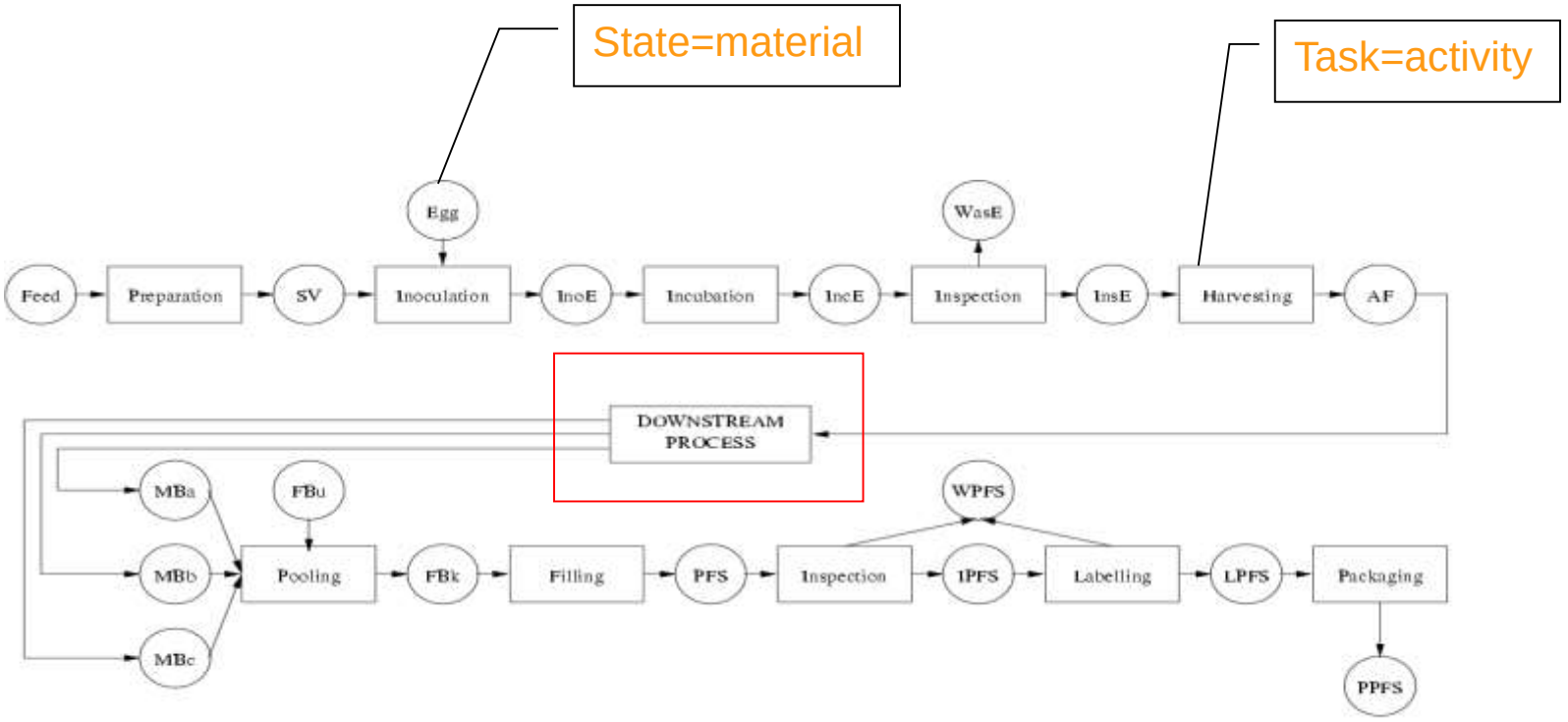
Problem #1 Scheduling a vaccine production facility

- To develop a model of the manufacturing process, with a view to
  - Understanding the process in more detail
  - Identify bottlenecks
  - Identify what constrains time to market
- Model determines the key decisions related to the system
  - Sequence
  - Size
  - Number of resources
  - Timing of the operations

Scheduling Characteristics

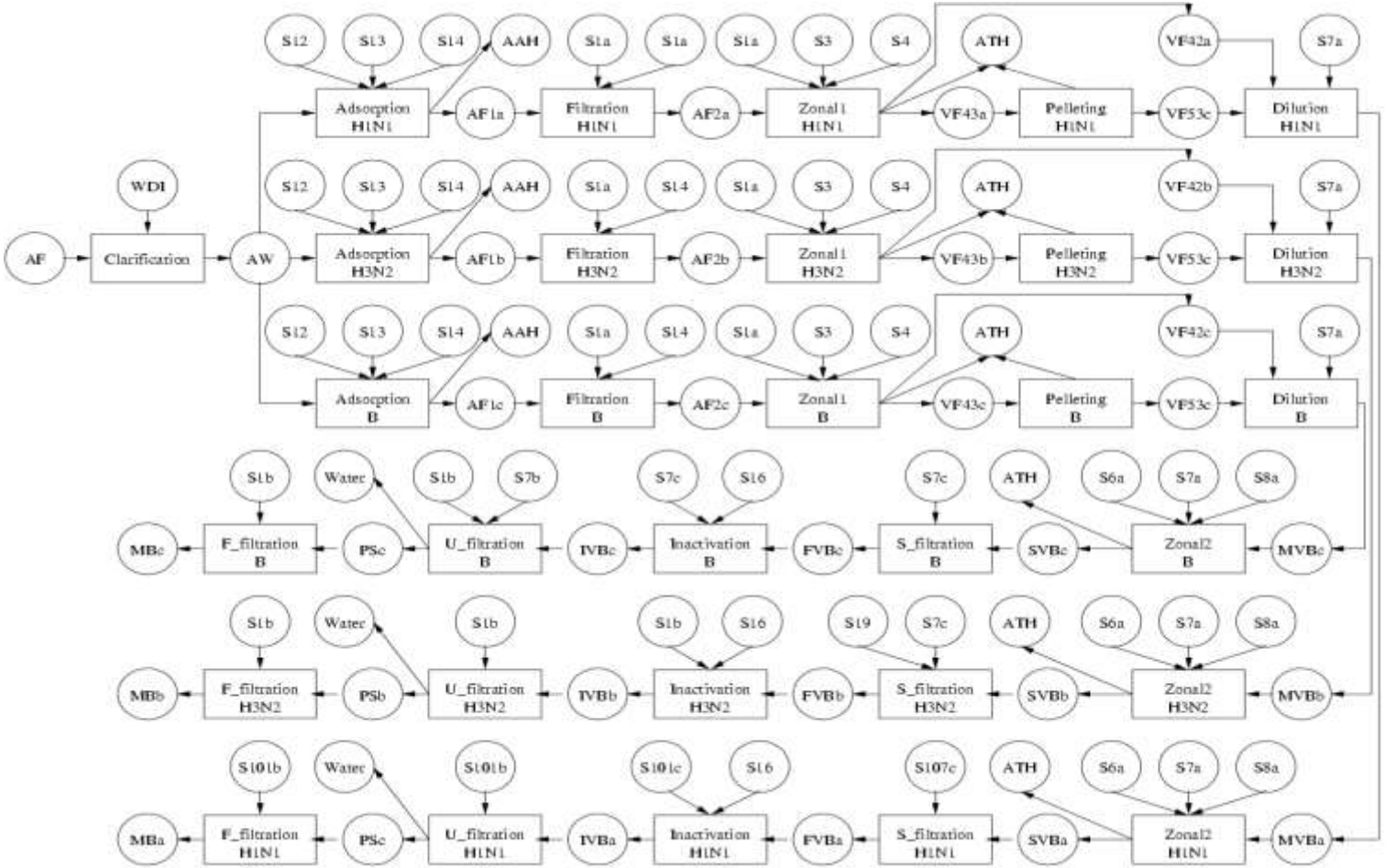
- An important aspect of process operations
- Generates a production plan over a set horizon
- Allocates equipment and resources so that
  - demands are met
  - equipment and resources are utilised efficiently
- May be used for the whole process or for individual stages

Debottlenecking an influenza facility



Rapidly growing demand
Limited time for manufacture (Apr onwards for NH)
Shortages occurring
How to increase production?

Downstream Process

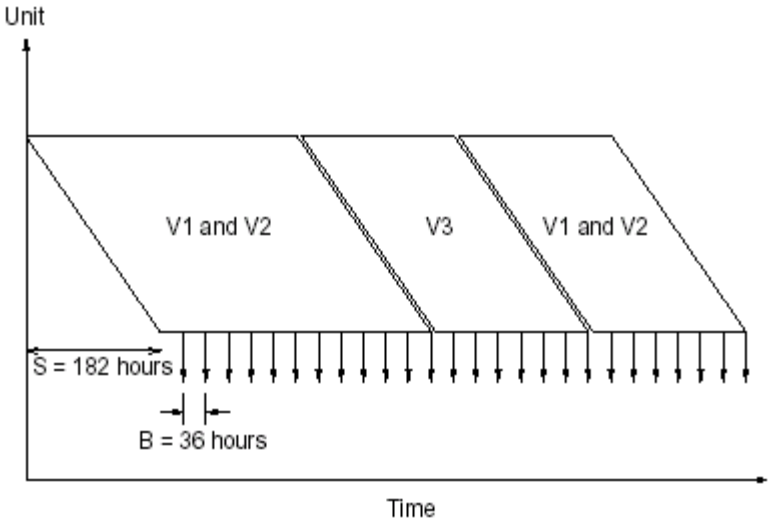


Solution Methodology

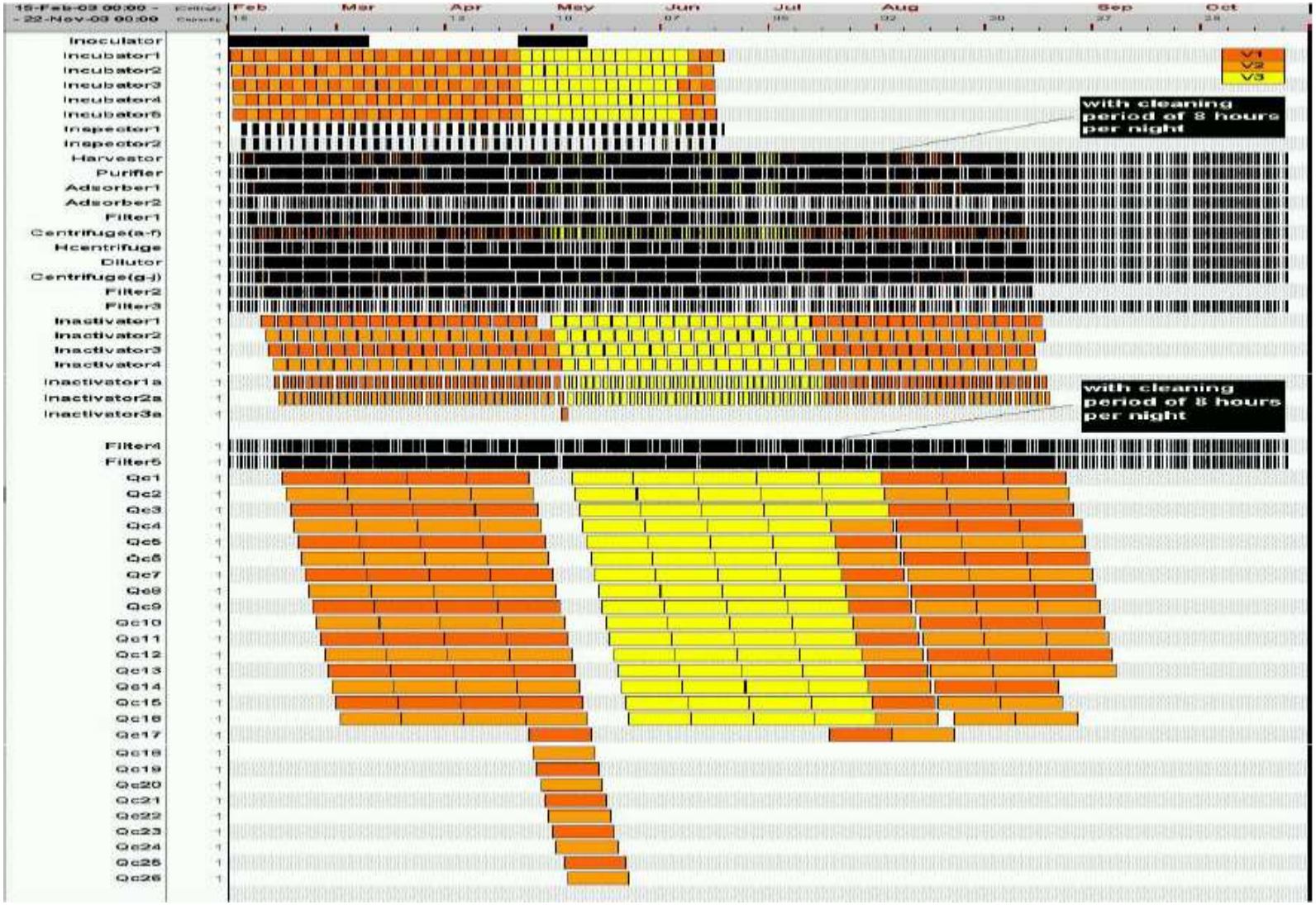
- Whole problem is too large to solve with optimisation
- Decompose upstream/downstream from packaging
- Use heuristics for upstream/downstream
- Use optimisation for packaging

Heuristic-Based Scheduling

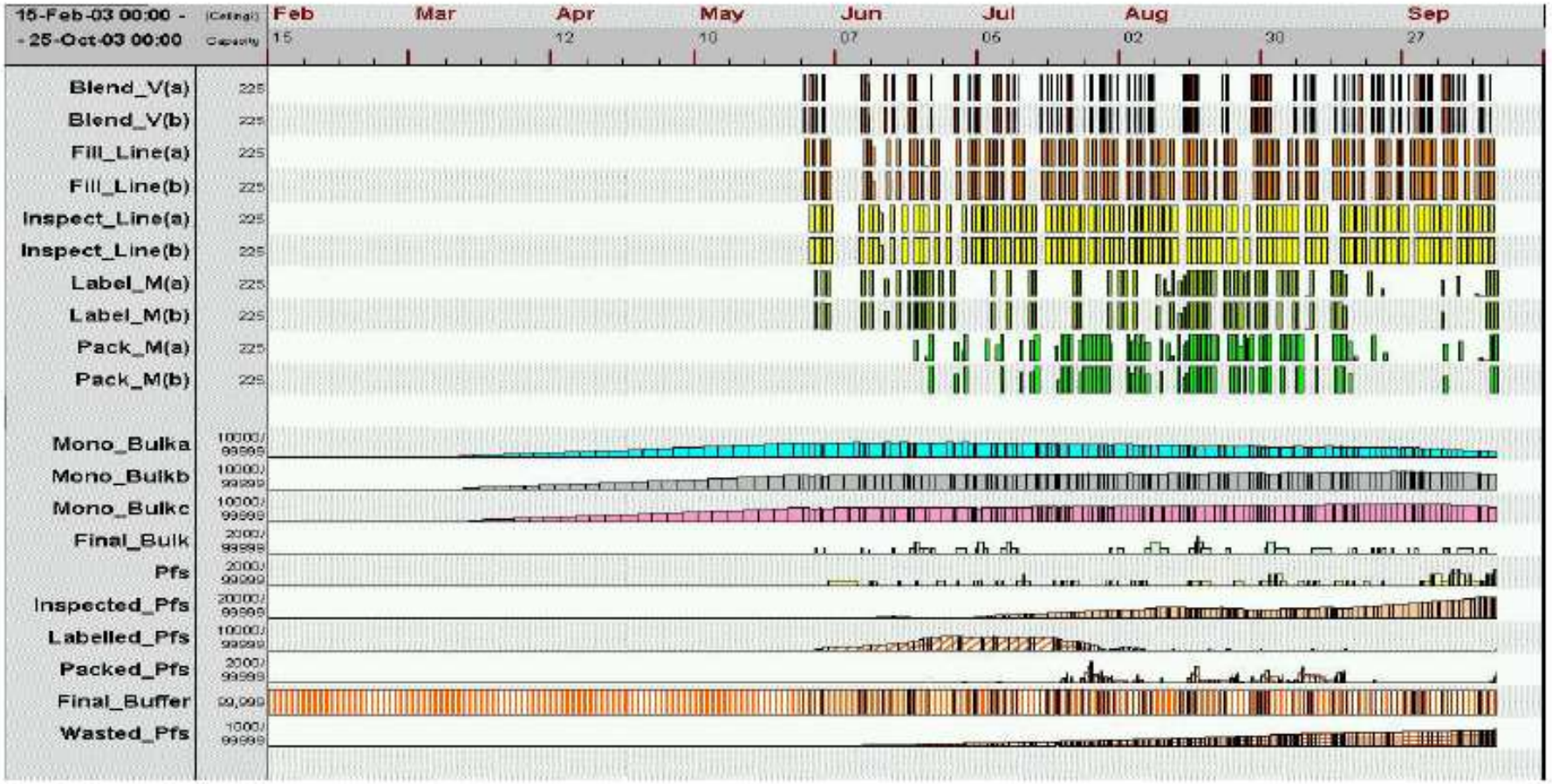
1. Determines earliest start time of the task, i.e. it may not start before the previous task has finished
2. Selects, from the list of suitable equipment items, an item using the following criteria:
   - assign a unit that has not been allocated any tasks
   - otherwise, assign the first unit that is able to start the task on time
   - otherwise, find a unit that has a suitable gap in its allocations
   - otherwise, select the unit that is available earliest



Gantt Chart – Upstream schedule optimisation



Downstream


15-Feb-03 00:00 -
- 25-Oct-03 00:00
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
15
12
10
07
05
02
30
27
Blend_V(a)
Blend_V(b)
Fill_Line(a)
Fill_Line(b)
Inspect_Line(a)
Inspect_Line(b)
Label_M(a)
Label_M(b)
Pack_M(a)
Pack_M(b)
Mono_Bulka
Mono_Bulkb
Mono_Bulkc
Final_Bulk
Pfs
Inspected_Pfs
Labelled_Pfs
Packed_Pfs
Final_Buffer
Wasted_Pfs

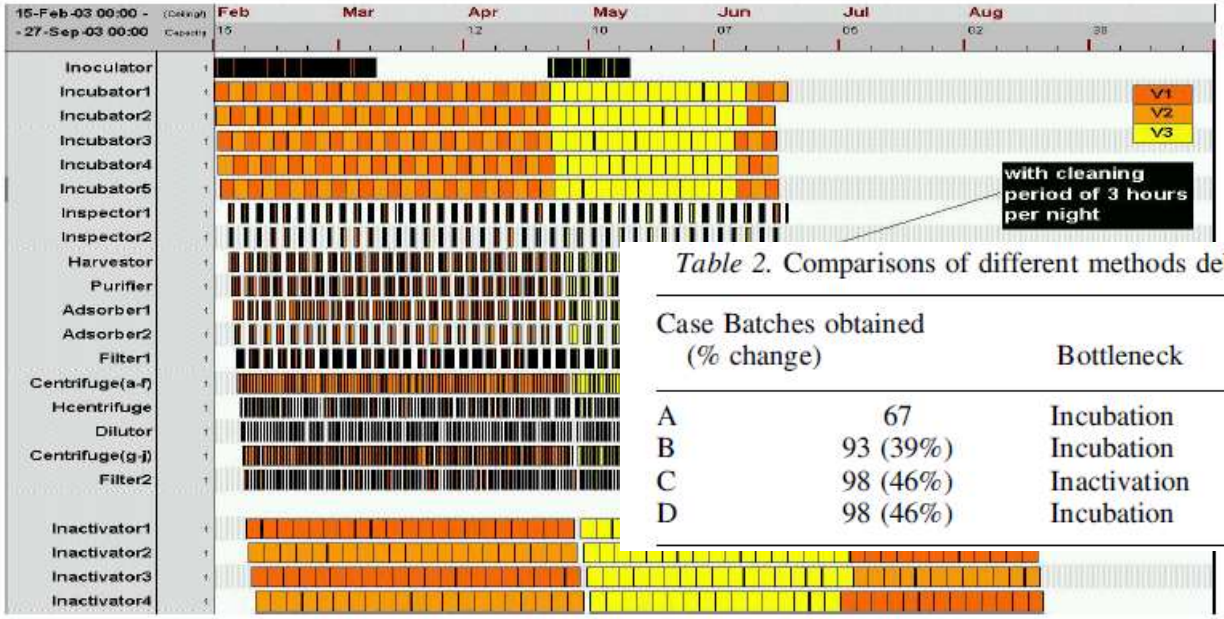
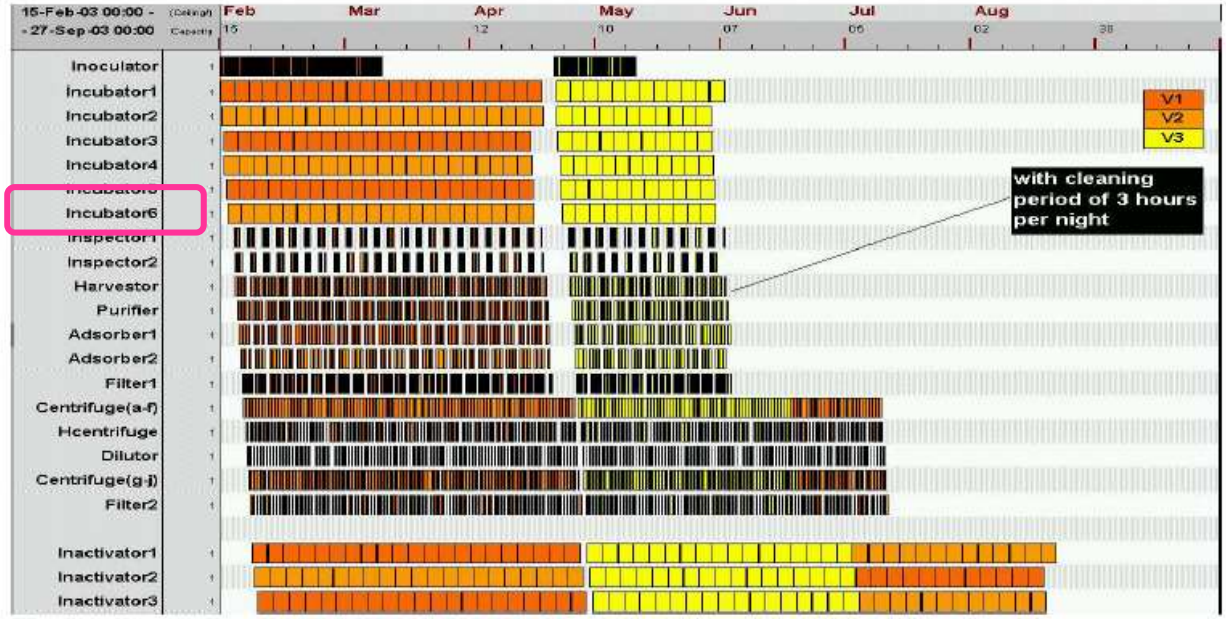


Table 2. Comparisons of different methods debottlenecking strategies.

Case	Batches obtained (% change)	Bottleneck	Customer service level
A	67	Incubation	93%
B	93 (39%)	Incubation	100%
C	98 (46%)	Inactivation	100%
D	98 (46%)	Incubation	100%

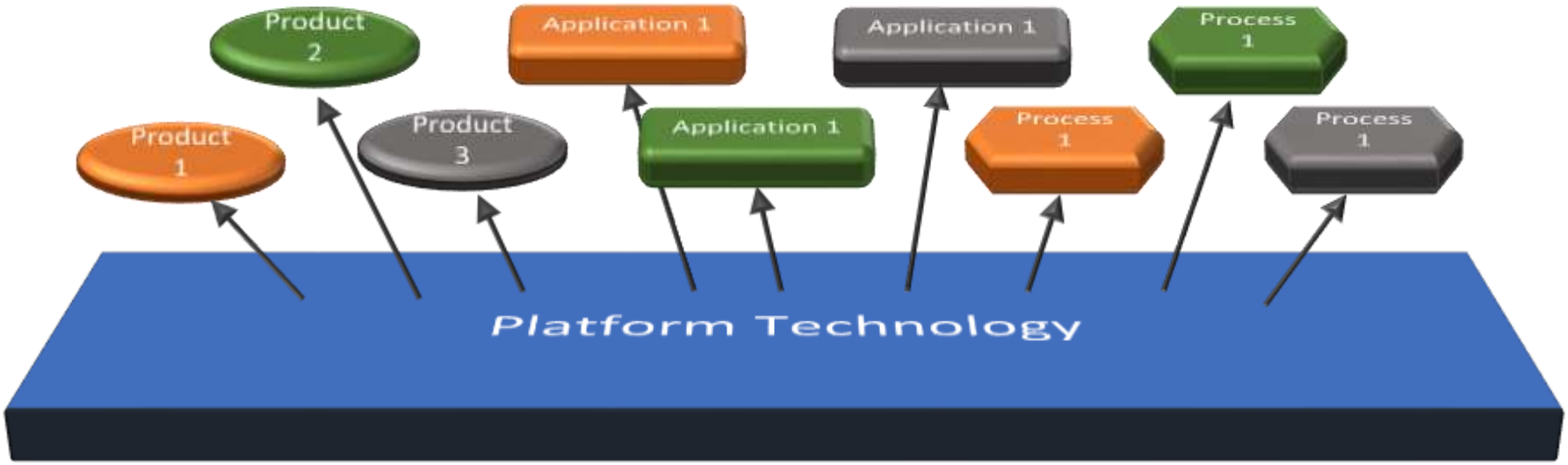
Fig. 7. Heuristic-Based Upstream-Downstream Schedule: Effects of Cleaning Times



Problem #2: process design and manufacturing optimisation

Platform technologies : What are the benefits?

A base technology which enables the development of a wide range of offspring products, applications, processes or technologies



Z. Kis, C. Kontoravdi, A. K. Dey, R. Shattock, N. Shah. Rapid development and deployment of high-volume vaccines for pandemic response. Journal of Advanced Manufacturing and Processing. 2020;e10060:1-10. https://doi.org/10.1002/amp2.10060. June 2020.

The synergy of physical and digital technologies will enable:

- Improved performance and efficiency of the production process
- Knowledge-rich regulatory submissions and platform "pre-qualification"
- Easier scale-up
- Easier technology transfer → distributed manufacturing

Rapid development & mass-production

Low cost manufacturing

Flexibility for wide range of vaccine types

Simple
Robust
Scalable

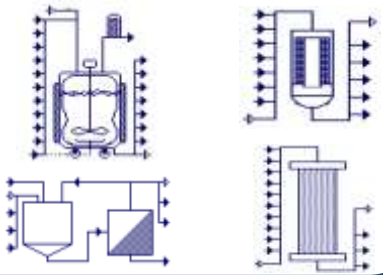
Vaccine product platforms

saRNA CustomVLP

hYeast CustomOMV

+

Bioprocessing modalities



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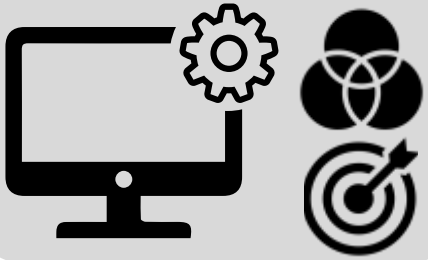
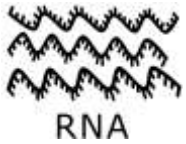
Computational modelling



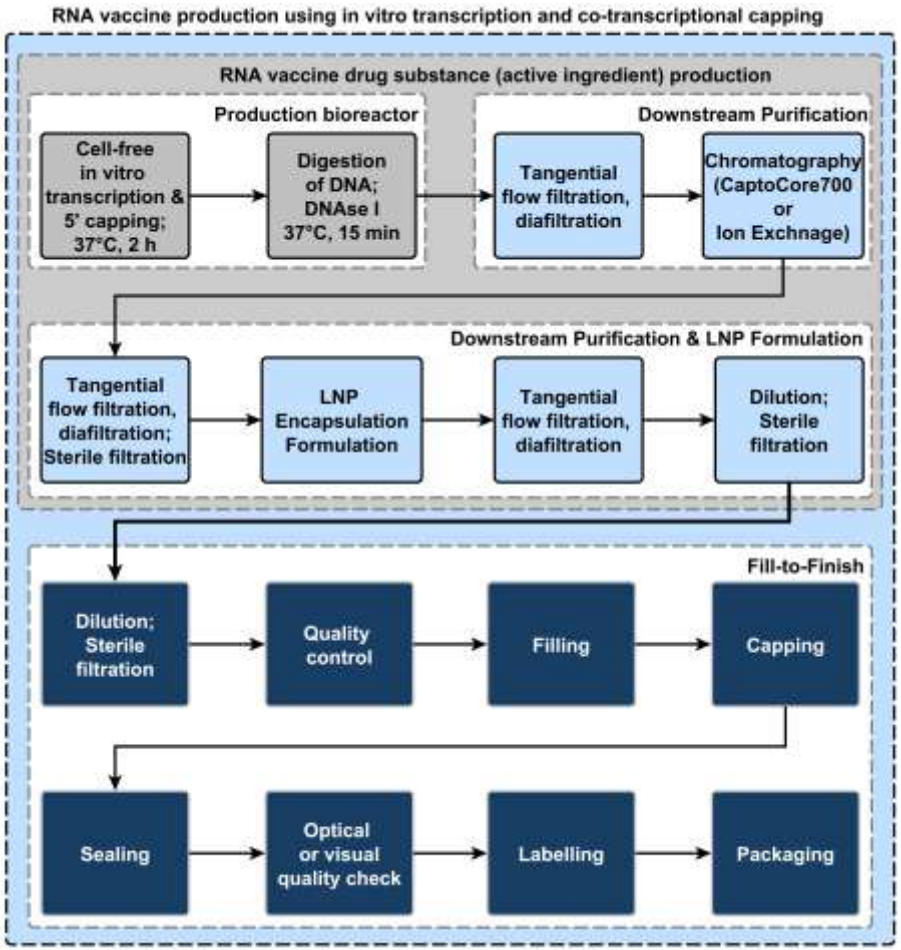
RNA vaccine production process

RNA vaccines

- RiboNucleic Acid, single stranded non-branching polymer, conveyer of genetic information
- ~10 kb self-amplifying RNA
- produced using the *in vitro* transcription
- cell-free production process
- Co-transcriptional 5' capping, e.g. using ARCA, CleanCap
- Amount per dose: 0.1 - 10 µg/dose



Kis Z, Kontoravdi C, Shattock R, Shah N. Resources, Production Scales and Time Required for Producing RNA Vaccines for the Global Pandemic Demand. Vaccines. 9(1), 3. 2021.



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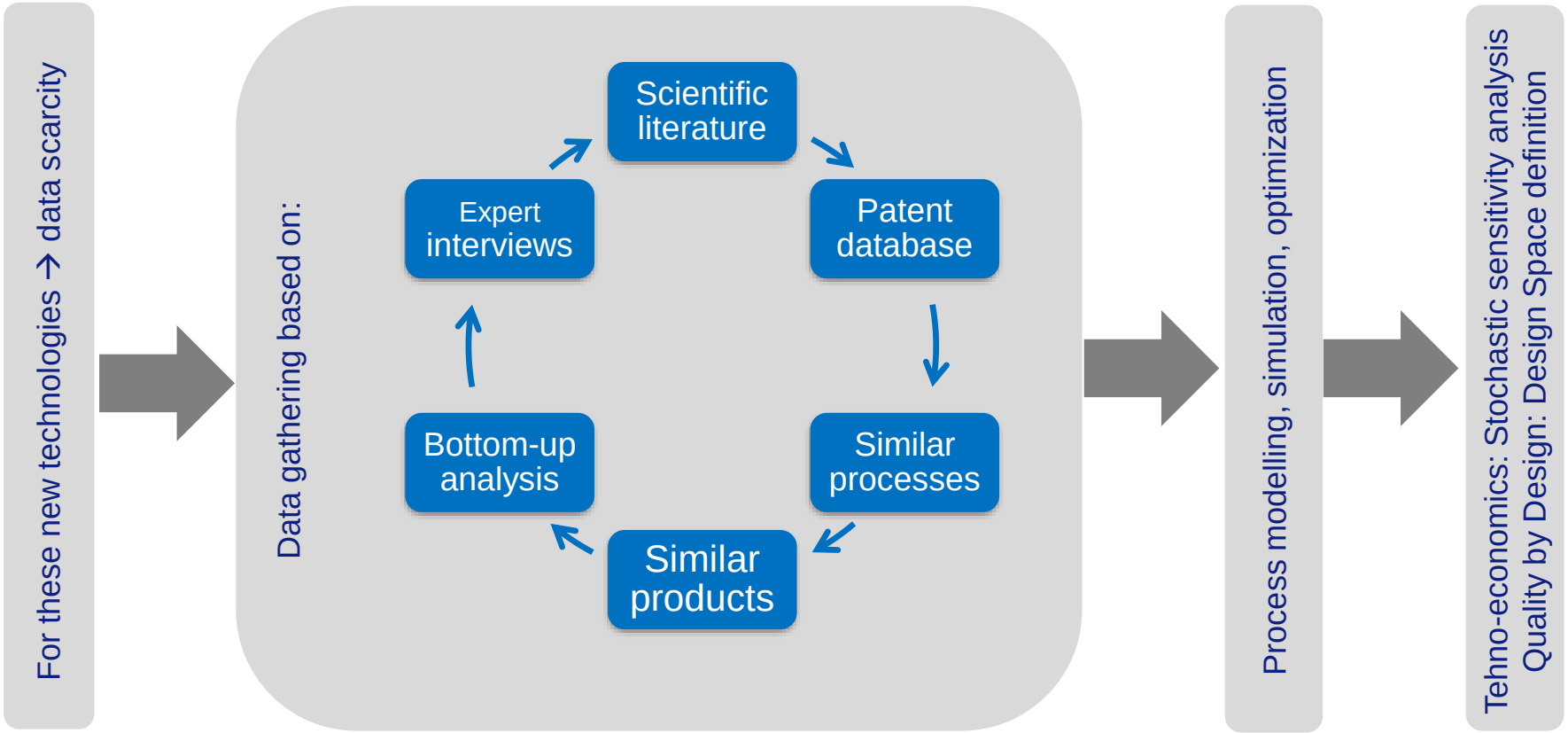
How can emerging technologies be assessed?



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Quality by Design

QbD is “a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management in order to ensure the quality of the product” - ICH Q8 (R2)

Endorsed by US Food and Drug Administration, European Medicines Agency and Pharmaceutical and Medical Devices Agency of Japan

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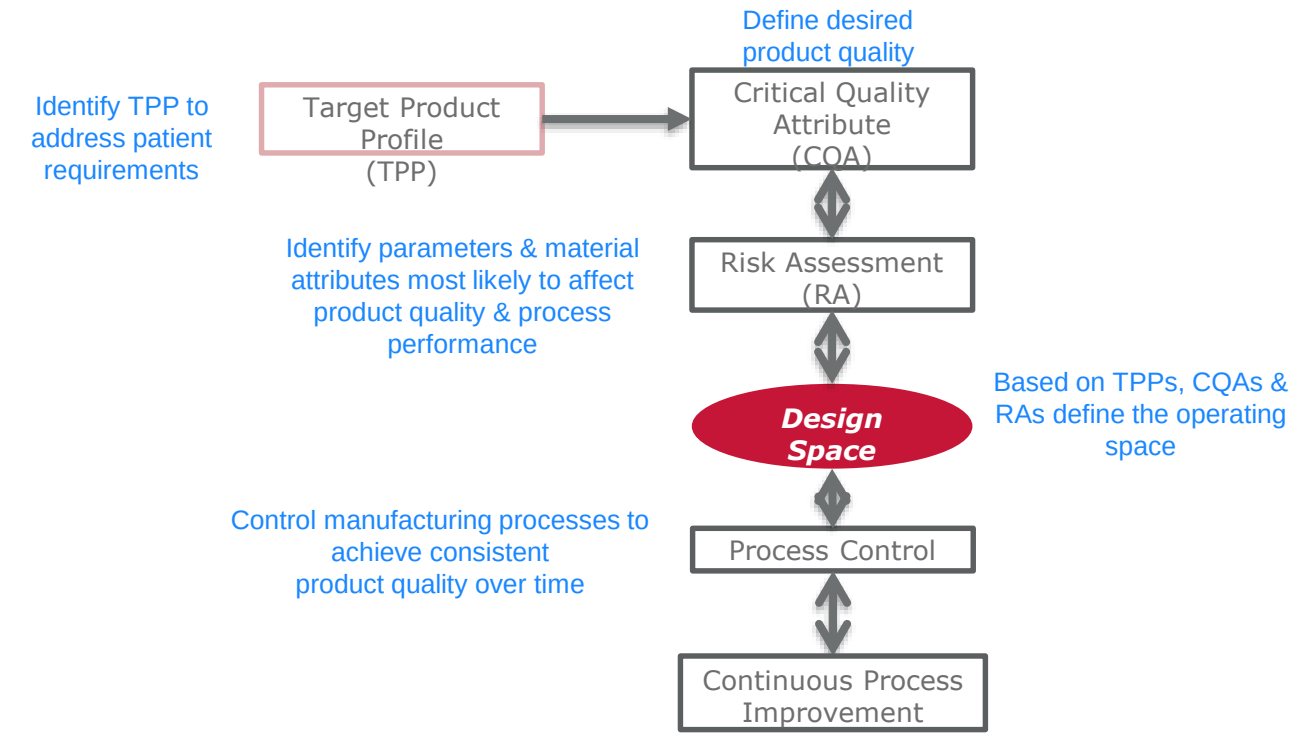
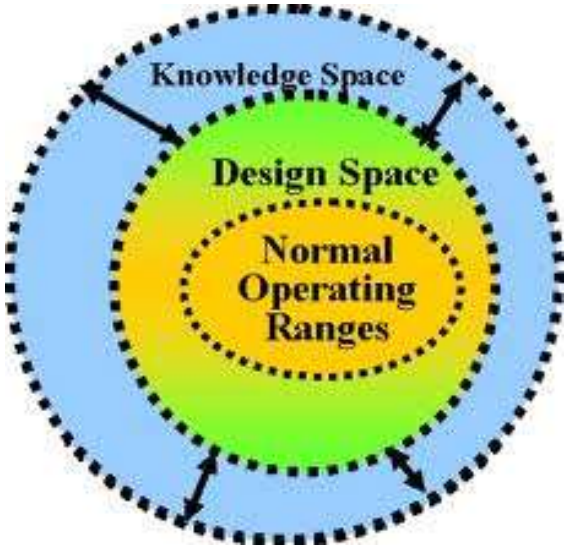
Quality by Design in practice



Slide courtesy of Dr. Maria Papathanasiou

Method development including QbD elements



The Method Operable Design Region (MODR) is the multivariate space of analytical procedure parameters that ensure the ATP is fulfilled and therefore provides the assurance of the quality of the measured value (USP <1220>)

S. Orlandini, S. Pinzauti, S. Furlanetto: *Anal. Bioanal. Chem*. 405 (2013) 443-450

L. Nompari, S. Orlandini, B. Pasquini, C. Campa, M. Rovini, M. Del Bubba, S. Furlanetto, "Quality by design approach in the development of an ultra-high-performance liquid chromatography method for Bexsero meningococcal group B vaccine", *Talanta, 178 (2018) 552-562*

https://cdn.ymaws.com/www.casss.org/resource/resmgr/nlab/032021_lebrun_pierre_slides.pdf

Slide courtesy of Dr. Cristiana Campa

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Impact quantification

1. CQA listing
2. CQA prioritization (min - - -; max + + +)

QA	Safety	Efficacy
QA_1	0	+ + +
QA_2	0	+
QA_3	+ +	- -
QA_4	- -	+ +
QA_5	+ + +	0
QA_n	+ +	-

3. CPP listing
4. CPP prioritization (min - - -; max + + +)

PPs	CQA_1	CQA_2	CQA_3	CQA_4	CQA_5	CQA_n
PP_1	+ +	+ + +	- -	0	+	- - -
PP_2	- -	+	+ +	- -	-	0
PP_3	+ +	- - -	- -	+ +	-	+
PP_4	- -	+ +	Data analysis	0	0	+
PP_5	+ + +	0	- -	+ +	Data analysis	-
PP_n	+ +	-	+ + +	- -	+	0

- Predominantly based on clinical trial data
- e.g. if CQA_1 ↑, safety unchanged, efficacy ↑↑↑
- table above identifies correlation, direction and magnitude of change

- Predominantly based on production process data;
- Data analysis: Design of Experiment (DOE) can help to determine correlation, direction and magnitude of change;
- Obtain functions to describe the process

Impact quantification

QAs	Unit	Acceptance criteria	Impact Score - Safety[α]	Impact Score - Efficacy[α]	Uncertainty score - Safety[β]	Uncertainty score - Efficacy[β]	Severity Score – Safety[γ]	Severity Score – Efficacy[δ]	Max Severity	Classification[ε]
Amount of precipitate	g/L	<0.001	2	8	4	4	8	32	32	pCQA
RNA sequence integrity	kb (length)	>9	8	25	4	3	32	75	75	CQA
RNA sequence identity	%match	>99%	8	25	4	3	32	75	75	CQA
RNA yield	g/L	>1.5	2	8	3	3	6	24	24	CQA
5' capping efficiency	%	>85%	2	25	3	2	6	50	50	CQA
Residual host cell proteins (E. Coli)	g/L	<500 ng/mg RNA	2	2	3	3	6	6	6	QA
Residual host cell DNA (E. Coli)	g/L	<100 ng/mg RNA	8	2	3	3	24	6	24	QA
Residual template DNA	g/L	<50 ng/mg RNA	8	2	3	3	24	6	24	QA
Bacterial endotoxins	g/L	None	25	2	2	4	50	8	50	CQA[ω]
Bioburden	g/L	None	25	8	2	4	50	32	50	CQA[ω]
Post-filtration pH	/	±0.1	2	25	3	3	6	75	75	CQA[ω]
Salt concentration	mM	±0.1	2	8	3	3	6	24	24	QA

change

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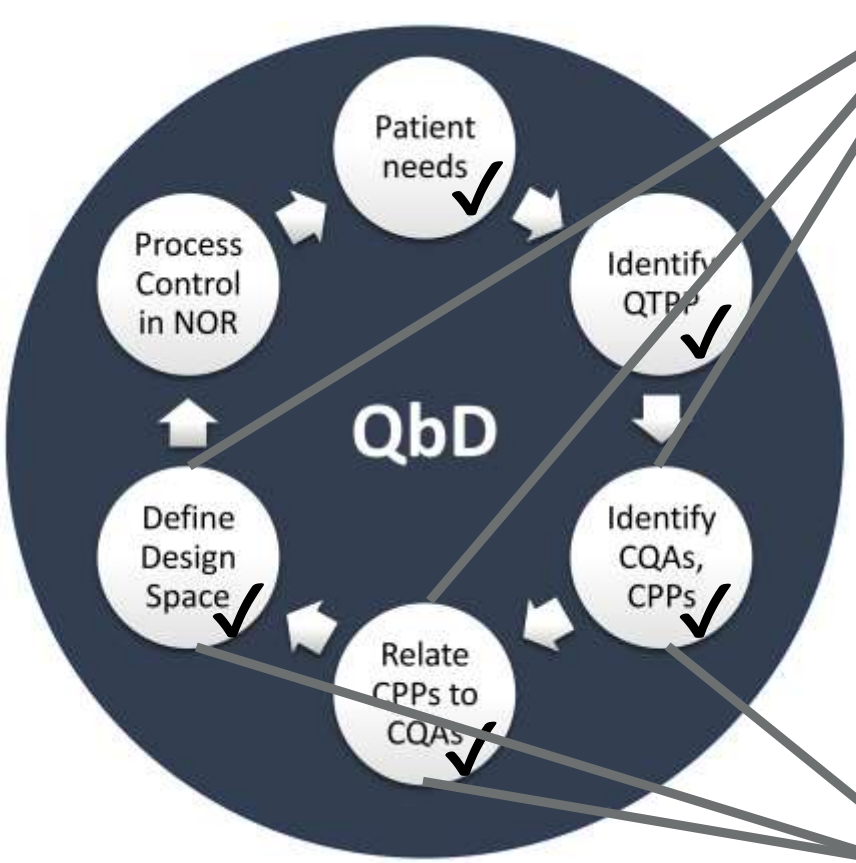
QbD for *in vitro* RNA synthesis

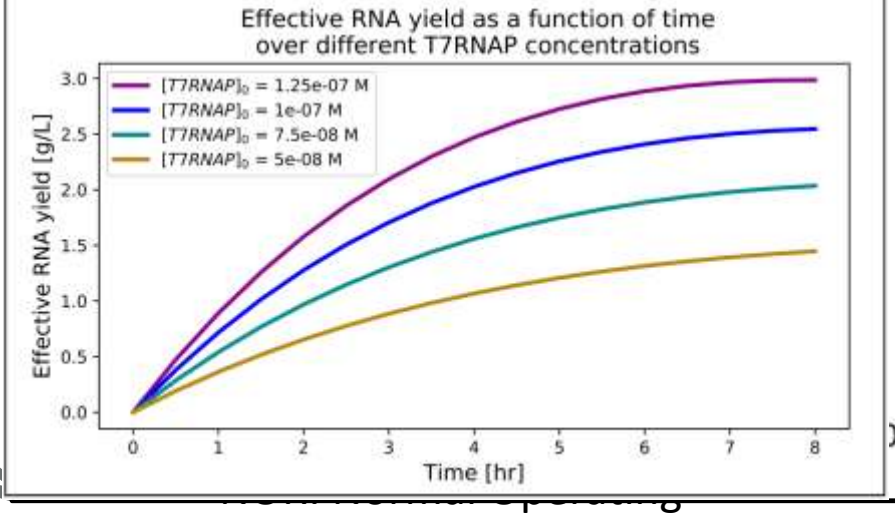


Mechanistic dynamic models, with predictive power

$$\frac{d[RNA_{effective}]}{dt} = V_{transcription} - V_{degradation} \quad [=]\frac{g}{L\,hr}$$

$$V_{transcription} = k_{app}[T7RNAP]\frac{[Mg^{2+}][MgNTP^{2-}]}{1 + K_1[Mg^{2+}] + K_2[MgNTP^{2-}]} \quad [=]\frac{g}{L\,hr}$$

$$V_{degradation} = \left(k_{ac}[H^+]^{n_{ac}} + k_{ba}[OH^-]^{n_{ba}} + k_{Mg}[Mg^{2+}]^{n_{Mg}}\right)[RNA_{effective}] \quad [=]\frac{g}{L\,hr}$$



Range, within the design space

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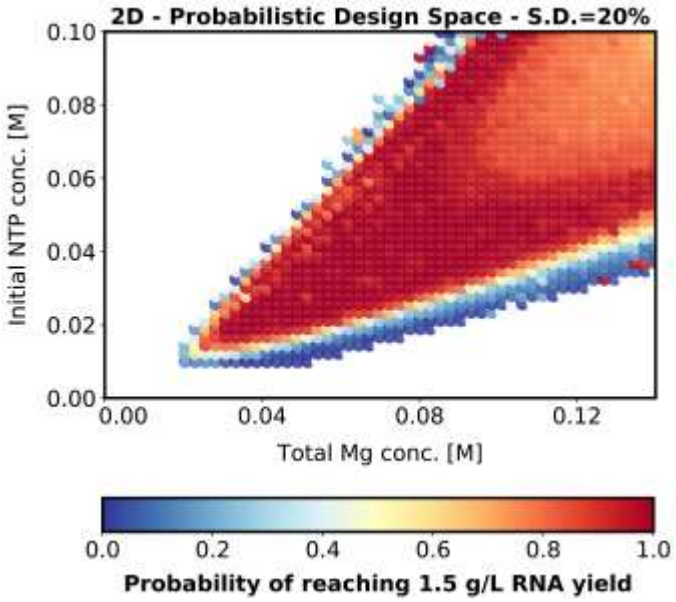
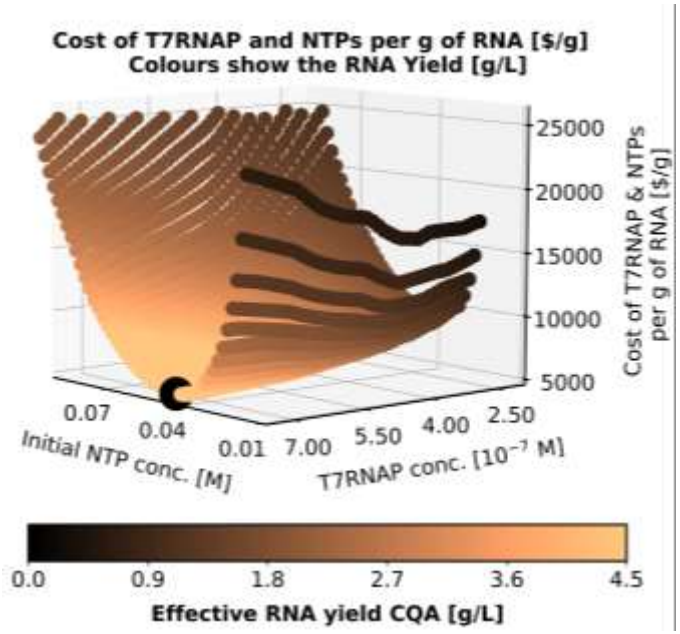
QbD for *in vitro* RNA synthesis



2-dimensional probabilistic design space. The probability of 20% standard deviation in the kinetic rate constant model parameters at a fixed 5×10^{-7} M T7RNAP concentration to give a 1.5 g/L RNA yield CQA is illustrated by the colour code.



Yield-cost-concentration plot showing RNA production yield and T7RNAP and NTP cost per g of RNA in function of T7RNAP and NTP concentrations at 85mM constant Mg^{2+} concentration.

Van de Berg et al., 2021. *NPJ Vaccines*. 6:65.

Strong relationship to original work in flexibility analysis at CMU in the 1980s/1990s (Grossmann et al.)

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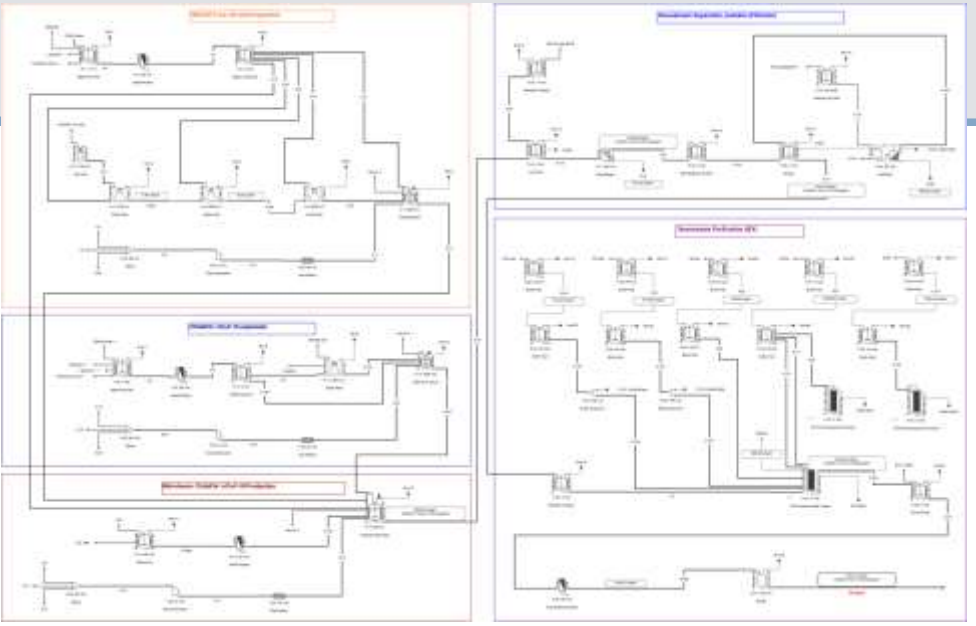
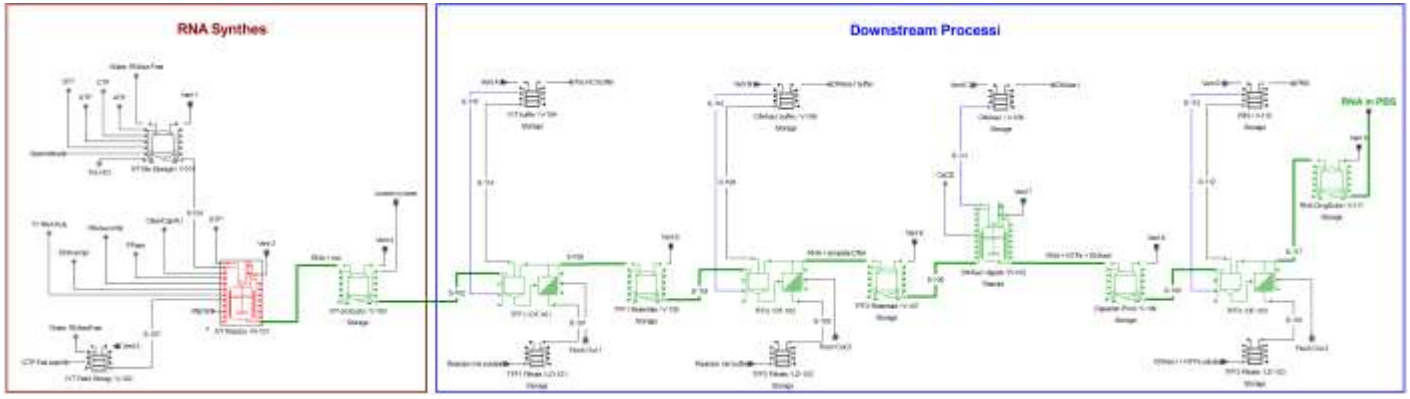
Viral vector vaccine platform



Versus…

RNA vaccine platform



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Main differences between two platforms

Viral vector vaccines

Produced in mammalian cells

Manufacturing process take 26-30 days

1500-3500 doses/L of culture

2000 L working bioreactor volume

Viral vectors have been used in gene therapy

Large manufacturing capacity globally

mRNA vaccines

Enzymatic (cell-free) synthesis

Manufacturing process takes 40-45 hours

Up to 2-3 million doses/L of culture

~30 L bioreactor volume

No previously licensed RNA vaccine

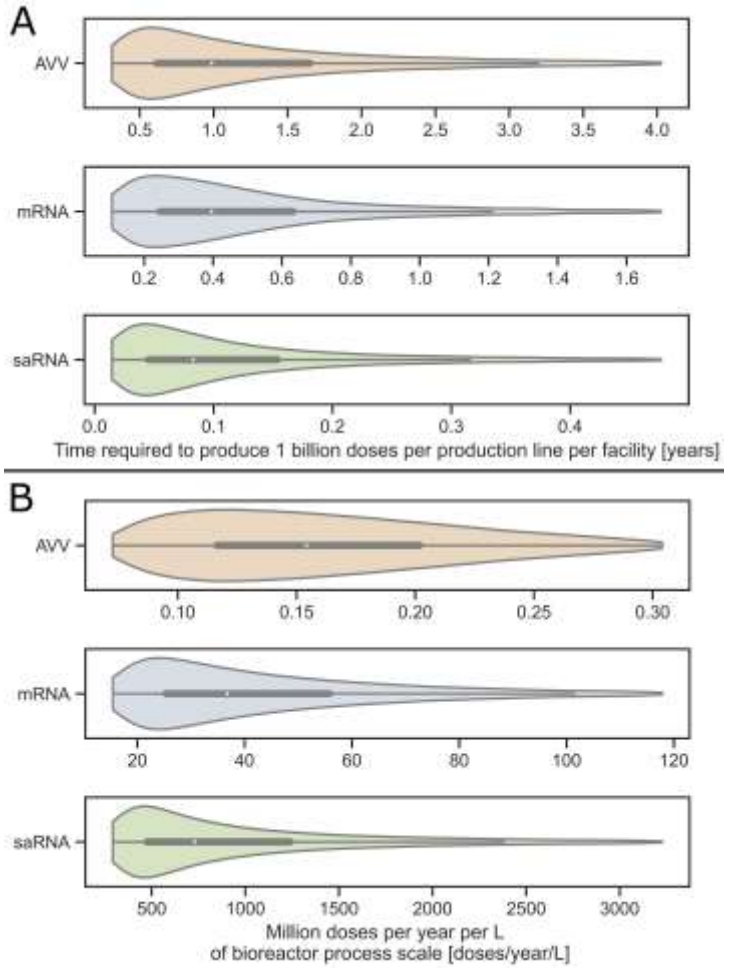
Formulated in lipid nanoparticles

- Require low temperatures to maintain stability

New process, new facilities

How fast can AVV and RNA vaccines be produced?

- Volumetric productivity: saRNA (731m doses/L of reaction mix/year) → mRNA (37 million doses/L of reaction mix/year) → AVV (154k doses/L of culture/year)
- RNA limitation: scale-out; limited facilities & experts, supply chain for RNA vaccine manufacture (this will change)
- AVV advantage: considerable manufacturing know-how worldwide

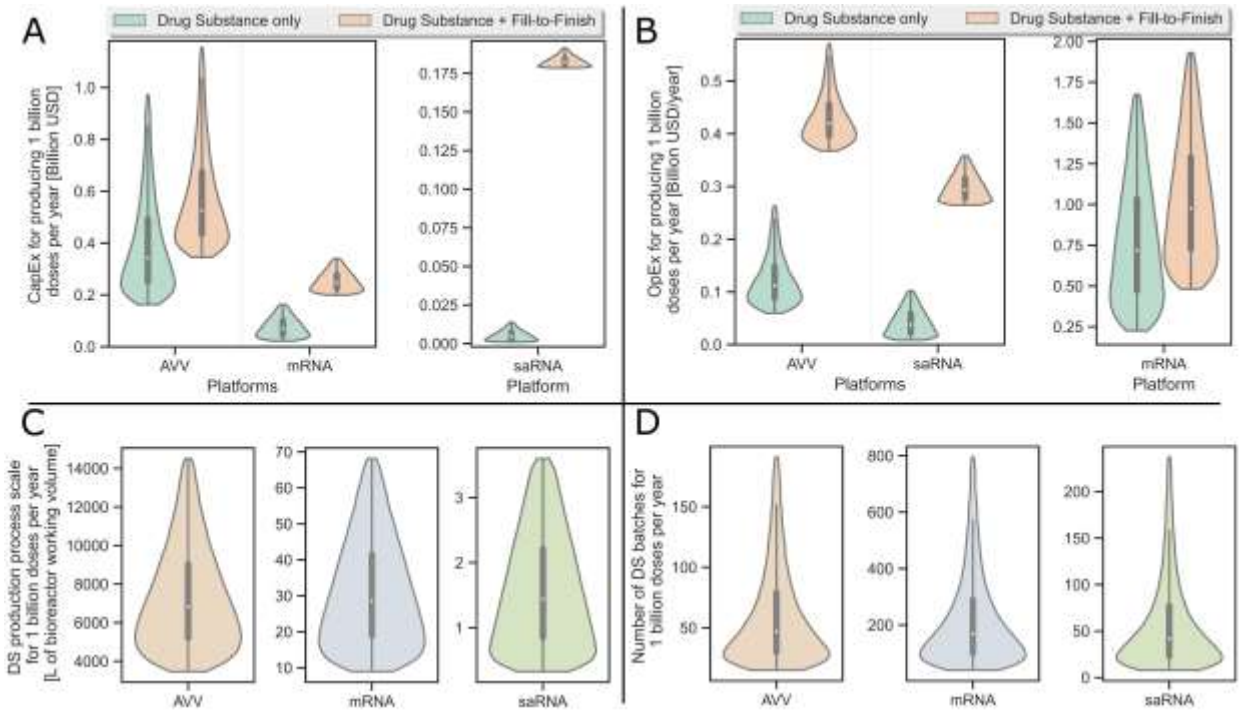


Zoltán Kis, Kyungjae Tak, Dauda Ibrahim, Maria Papathanasiou, Benoît Chachuat, Nilay Shah and Cleo Kontoravdi. Pandemic-response adenoviral vector and RNA vaccine manufacturing. Preprint at https://doi.org/10.1101/2021.08.20.21262370

What resources are required to mass-manufacture RNA and AVV vaccines?

Key Findings:

- RNA vaccine production has lower CapEx but higher OpEx compared to AVV vaccine production
- RNA vaccine production requires smaller facility footprint
- AVV vaccine production have higher fixed cost, thus it is more cost effective to maintain RNA vaccine production surge capacity



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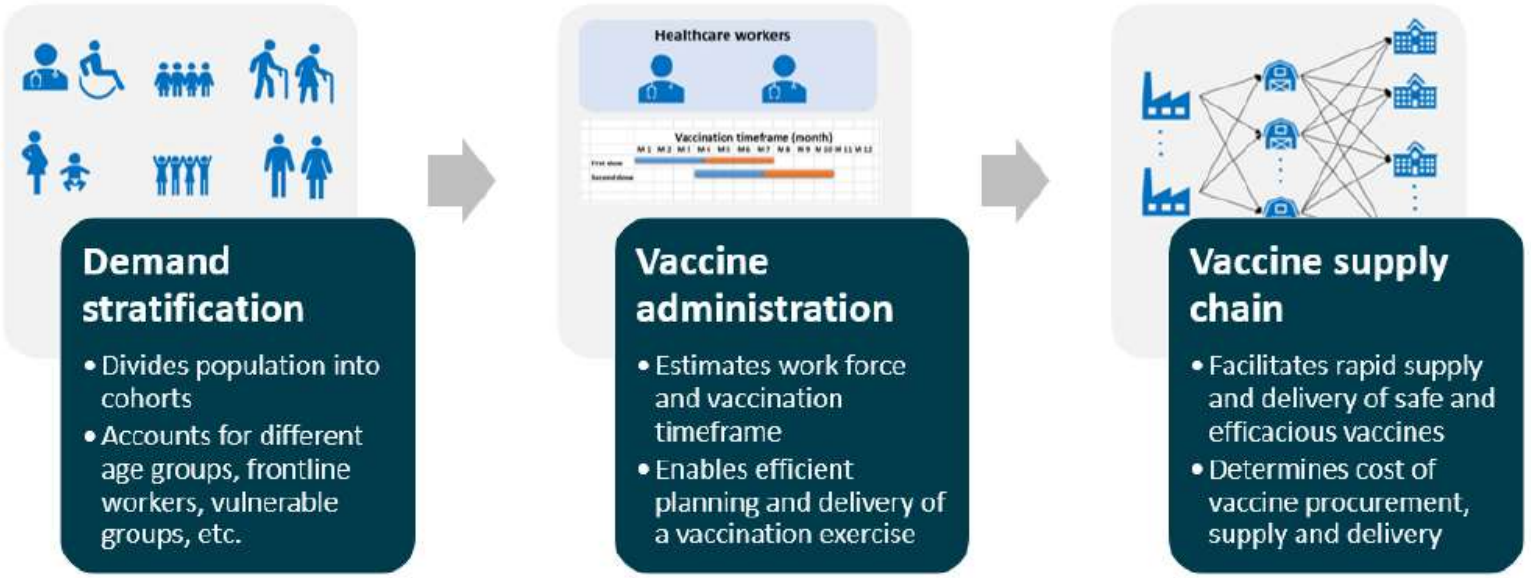
Vaccine supply chain optimisation

What does it take to sustain 500k doses/w in the UK?

Figure 7. Supply chain for the distribution and delivery of BNT162b2 SARS-CoV-2 vaccine candidate across the UK. No in-country vaccine manufacture and fill-finish facilities.

Methodology

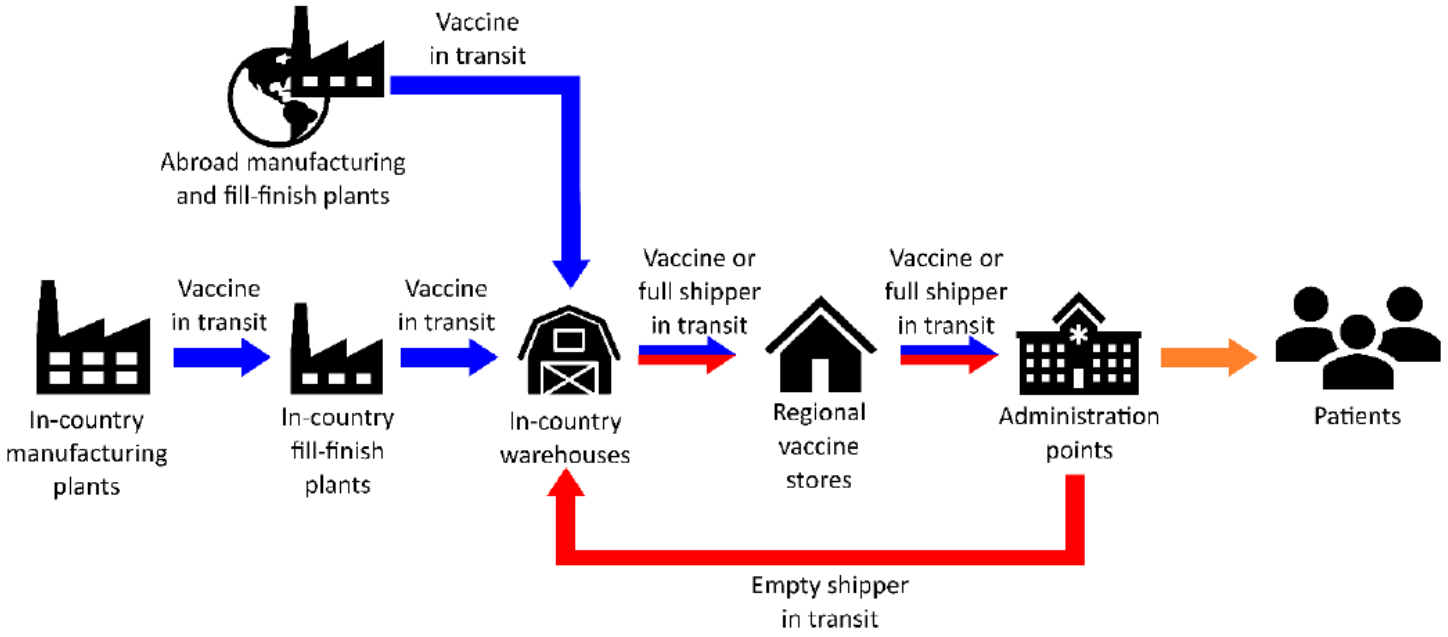


Data analysis

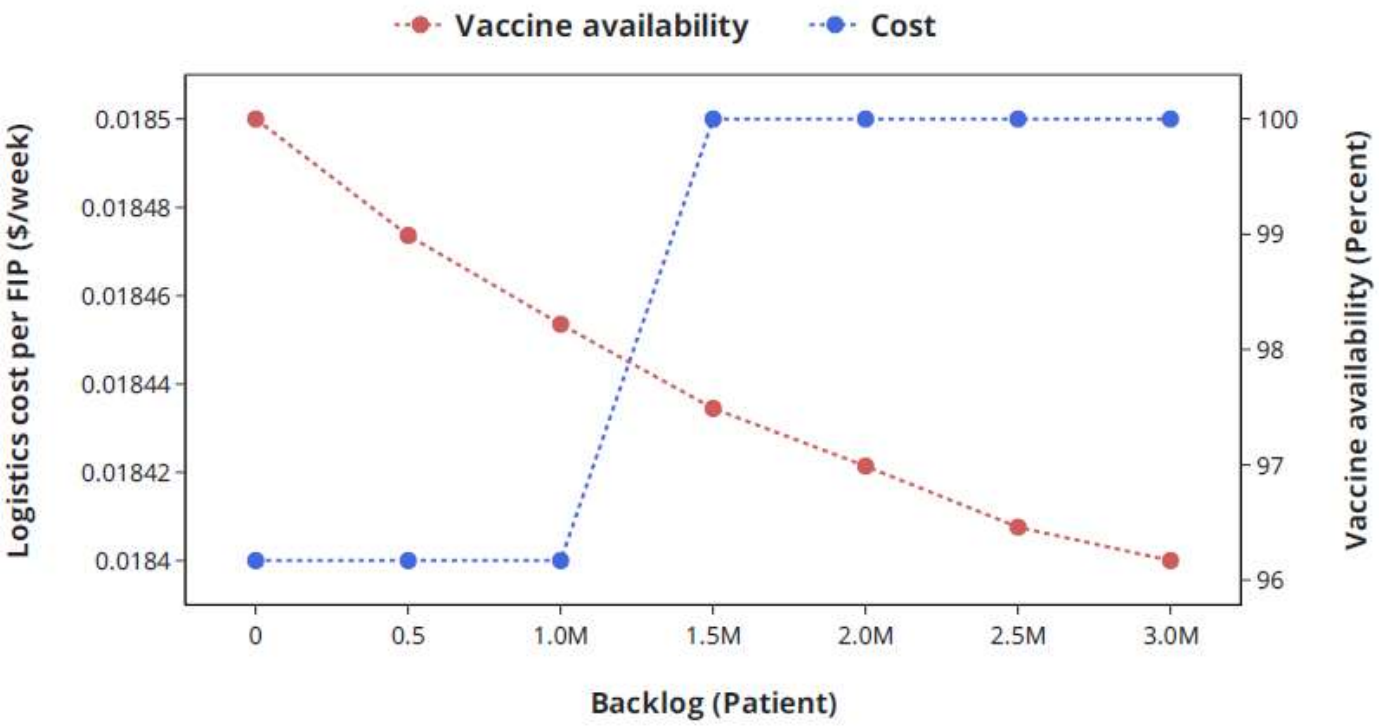
Data analysis

MILP model

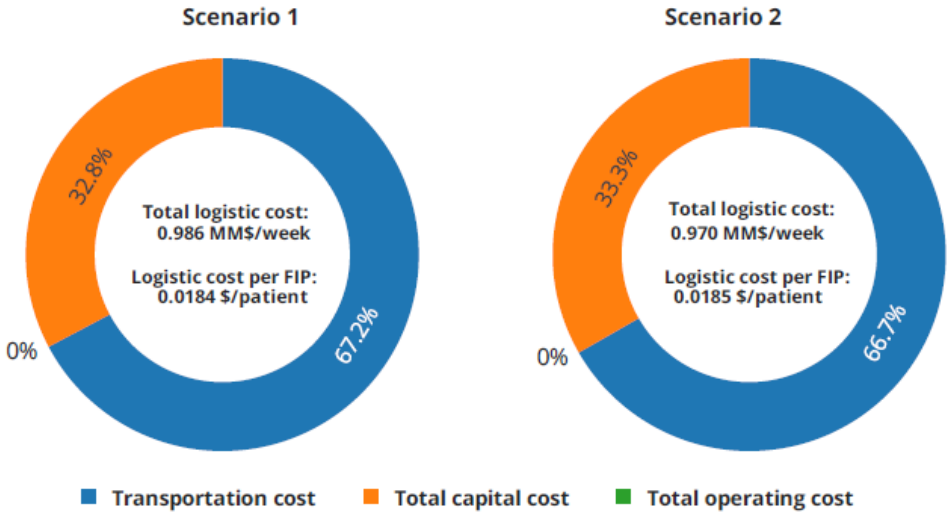
System model

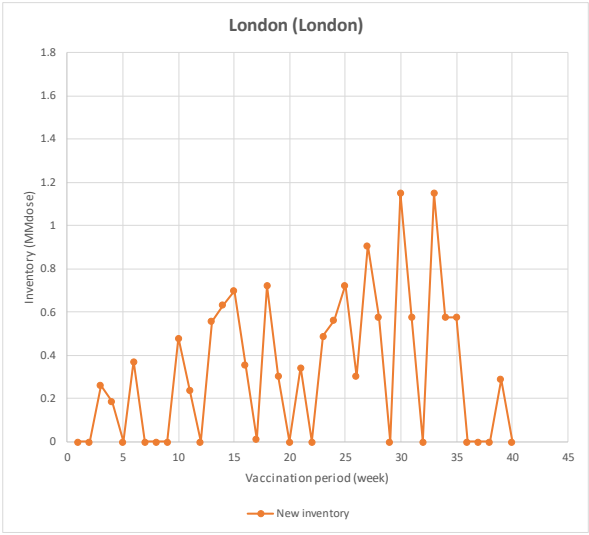


Trade-offs


Vaccine availability
Cost
Logistics cost per FIP ($/week)
0.0185
0.01848
0.01846
0.01844
0.01842
0.0184
100
99
98
97
96
Vaccine availability (Percent)
0
0.5
1.0M
1.5M
2.0M
2.5M
3.0M
Backlog (Patient)

Cost elements





4. Cost components

Item	Scenario 1	Scenario 2	Units
Cost of vaccine shipper	7.72	7.39	million USD
Cost of dry ice	20.30	19.90	million USD
Cost of vaccinating individuals	1.88	1.85	billion USD
Cost of vaccinating individuals at care home	24.10	24.10	million USD
Cost of vaccine procured	2.00	1.96	billion USD
Cost of quality control checks	59.90	58.70	million USD

Global supply chains versus local manufacture

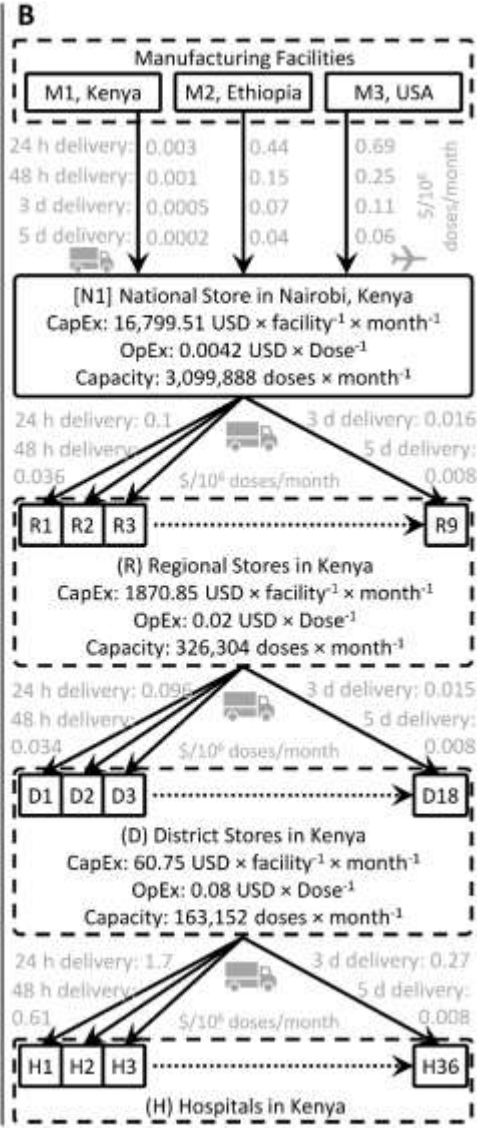
A

	RNA	hYeast	customVLP	customOMV	
Small scale	0.2	100	100	100	L
Batch duration	2.5	10.4	18	4	$days$
Capacity	2×10^6 (3×10^6)	13×10^6 (27×10^6)	9×10^6 (18×10^6)	9×10^6 (18×10^6)	$\frac{doses}{mth}$
CapEx	204,104 (136,718)	224,566 (111,733)	346,354 (176,079)	116,577 (59,646)	$\frac{USD}{fac \times mth}$
OpEx	0.200 (0.136)	0.082 (0.032)	0.18 (0.072)	0.124 (0.055)	$\frac{USD}{dose}$

	RNA	hYeast	customVLP	customOMV	
Large scale	1	500	500	500	L
Batch duration	2.5	13	20	4.6	$days$
Capacity	11×10^6	53×10^6	38×10^6	36×10^6	$\frac{doses}{mth}$
CapEx	415,739	284,991	431,395	176,991	$\frac{USD}{fac \times mth}$
OpEx	0.151	0.024	0.065	0.033	$\frac{USD}{dose}$

	Scale	Batch duration	Capacity	CapEx	OpEx
Conventional Manufacturing	1000 L	40 day	5×10^6 $\frac{dose}{month}$	992,650 $\frac{USD}{fac \times mth}$	0.8 $\frac{USD}{dose}$

B



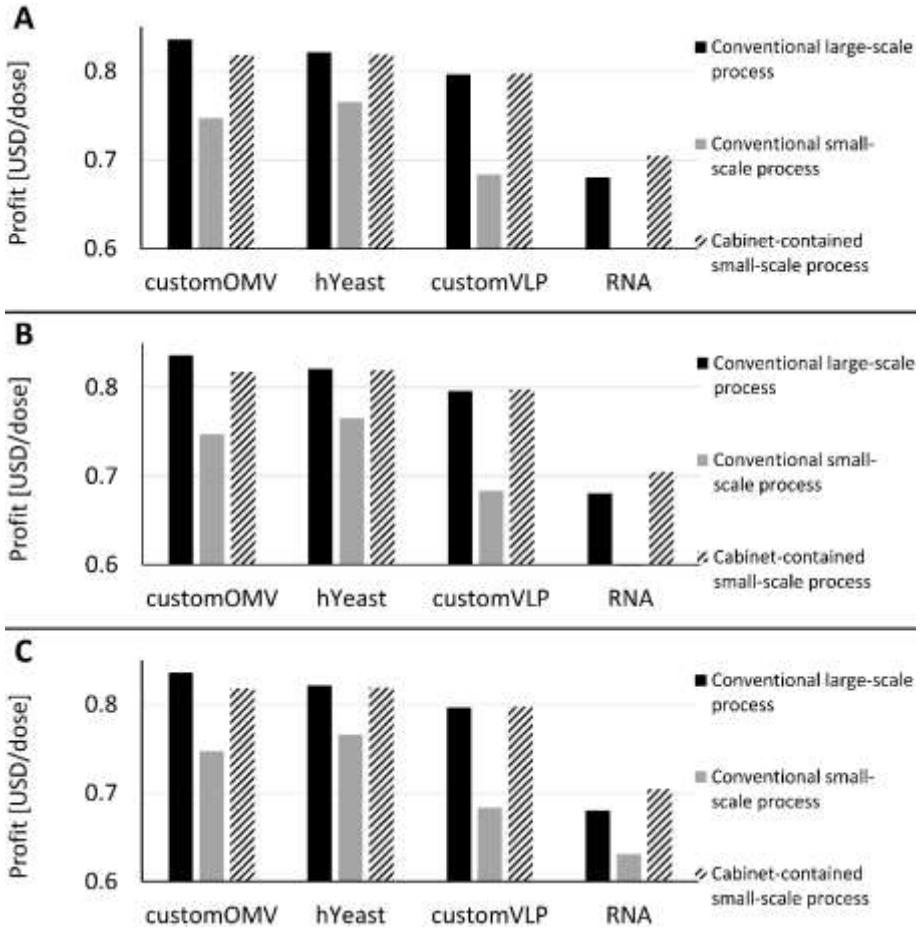
Centralized vs. distributed manufacturing

The effect of facility location on cost per dose.

A. Facilities in USA only.

B. Facilities in Kenya only.

C. Facilities at the location chosen by the model (i.e. USA, Kenya or Ethiopia).



New process technologies
Make in-country manufacture profitable

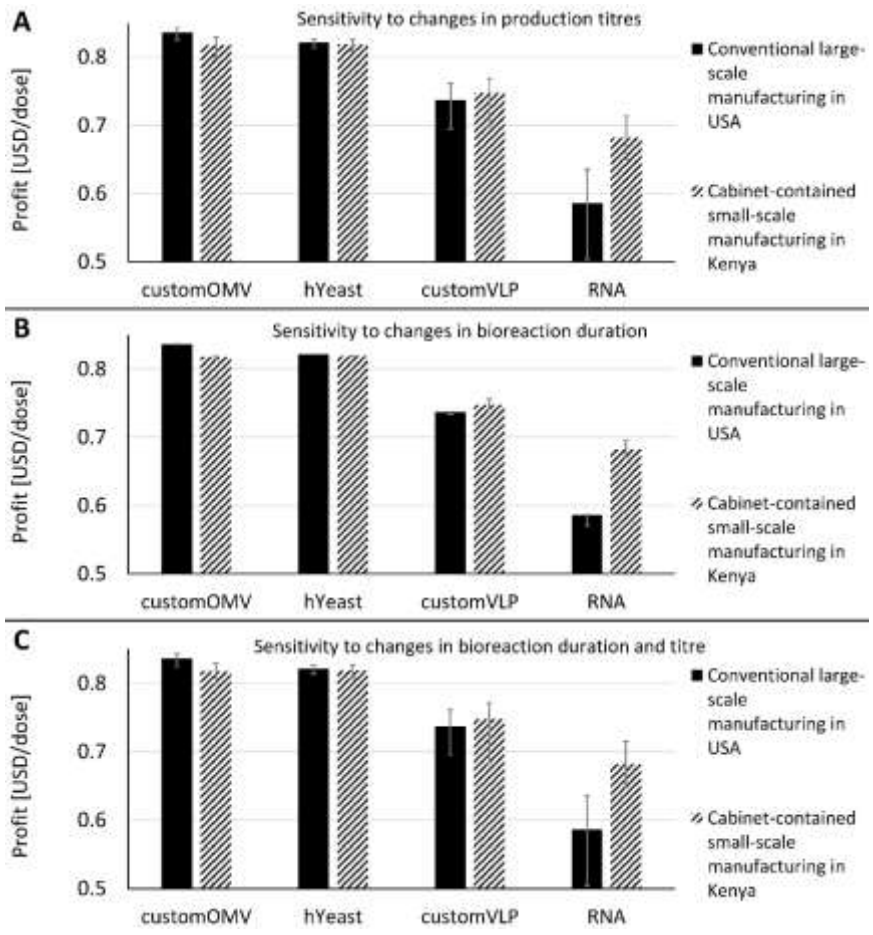
Sensitivity analysis

Sensitivity of profits (shown by error bars) to variations in production titer and in the duration of the fermentation or bioreaction:

A. The sensitivity of supply chain profits to variations of ±25% in the production titer.

B. The sensitivity of supply chain profits to variations of ±25% in the duration of the bottleneck bioreaction or fermentation operation.

C. The sensitivity of supply chain profits to ±25% simultaneous variations in production titers and in the duration of bioreaction or fermentation.



Conclusions

- Increasing integration between product design, process design, manufacturing and supply chain
- Innovations in any one area can strongly affect the other (e.g. heat-stable formulations)

- Rapid new developments in biotechnology -> need effective mechanisms to translate into manufacturing

- Manufacturing innovation can be supported by modelling
  - Generate early stage information:
    - Viability of process
    - Performance-limiting parameters
    - Understand risk and where to focus effort
  - Optimal integration of models and experiments in a synergistic cycle

- Outstanding opportunities for interdisciplinary collaboration!