The EPSRC and DoHSC Future Vaccines Manufacturing Research Hub:

Modelling tools to understand the dynamics of vaccines manufacturing and supply chains in developing countries

Professor Harris Makatsoris

25/06/2019

www.cranfield.ac.uk

Introduction to the Imperial Future Vaccine Manufacturing Research Hub

Cranfield Manufacturing

Imperial College London

The University of Nottingham

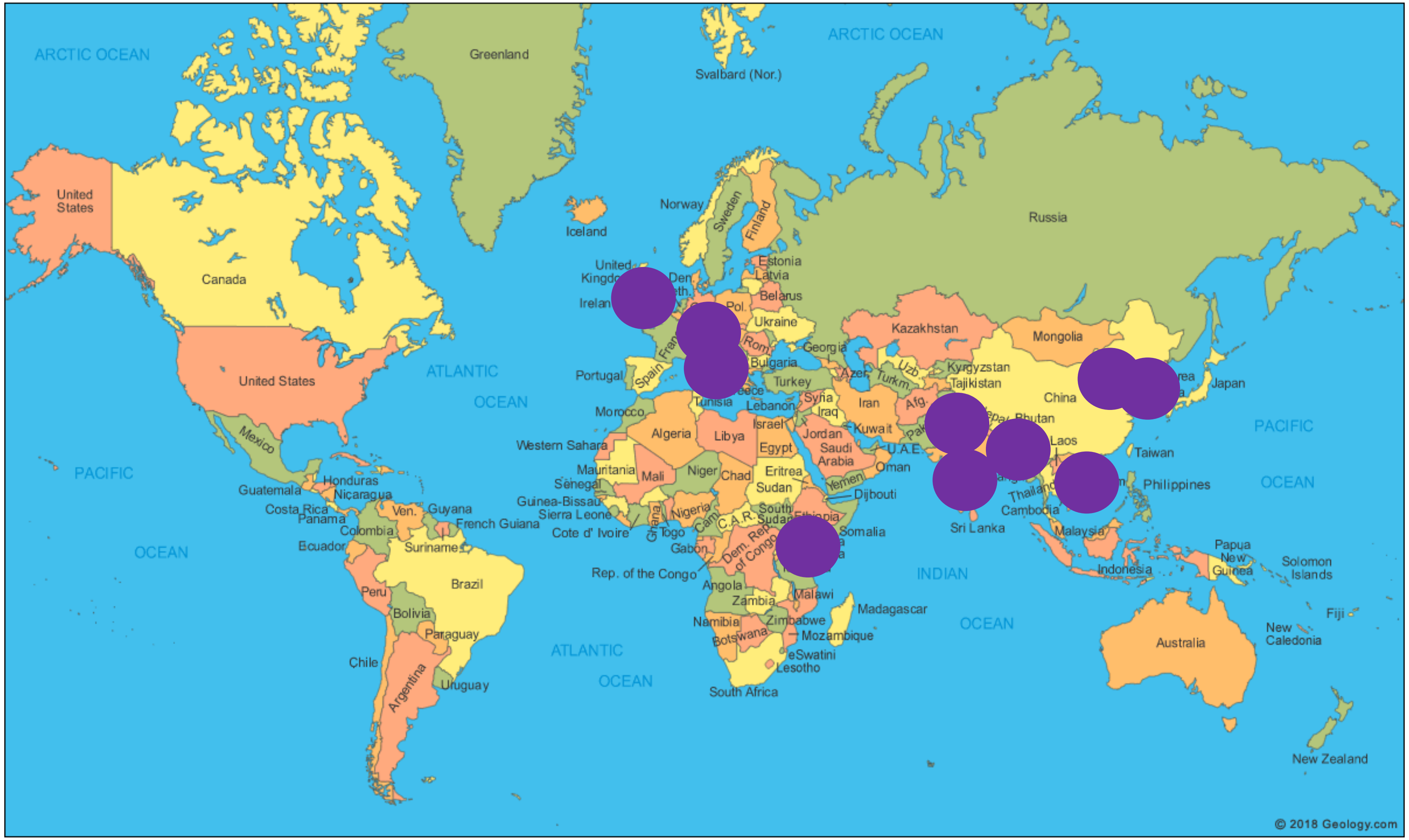
University of Bristol

NHS Blood and Transplant

Cranfield University

cpi

NIBSC
Confidence in Biological Medicines



University of Leeds

Biological E. Limited
Celebrating Life Every Day

MINHAI

Hissen
艾美汉信疫苗（大连）有限公司

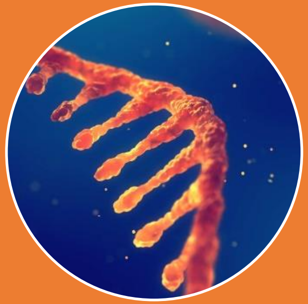
gsk

incepta

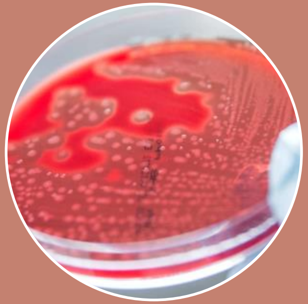
VABIOTECH

dcvmn
Developing Countries Vaccine Manufacturers Network

What the Future Vaccine Manufacturing Research Hub is about



Life Sciences



Immunology

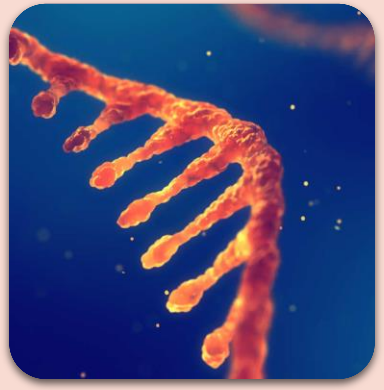
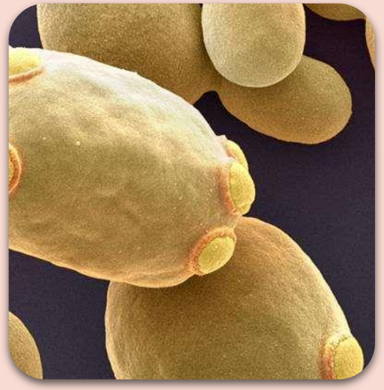
Engineering

- How to design production systems that can produce **tens of thousands of new doses within weeks** of a new threat being identified
- How to improve the way vaccines are **manufactured, stabilised** and **stored** so that **existing and new diseases** can be **prevented effectively**, and **costs reduced**

Goal: advancing the manufacture and deployment of cost effective vaccines

EPSRC Engineering and Physical Sciences Research Council
Department of Health & Social Care
Imperial College London

The Hub's vaccine technology platforms

RNA	Yeast	Baculovirus	GMMA
Rapid	Easy scale-up and high yield	Thermostable	Easy scale-up
Low cost	Low risk of contamination	Rapid	Mature
Synthetic and cell-free	Human glycosylation challenging	Feasible scale-up	Slow
Immature		Technologically complex	Purification challenging

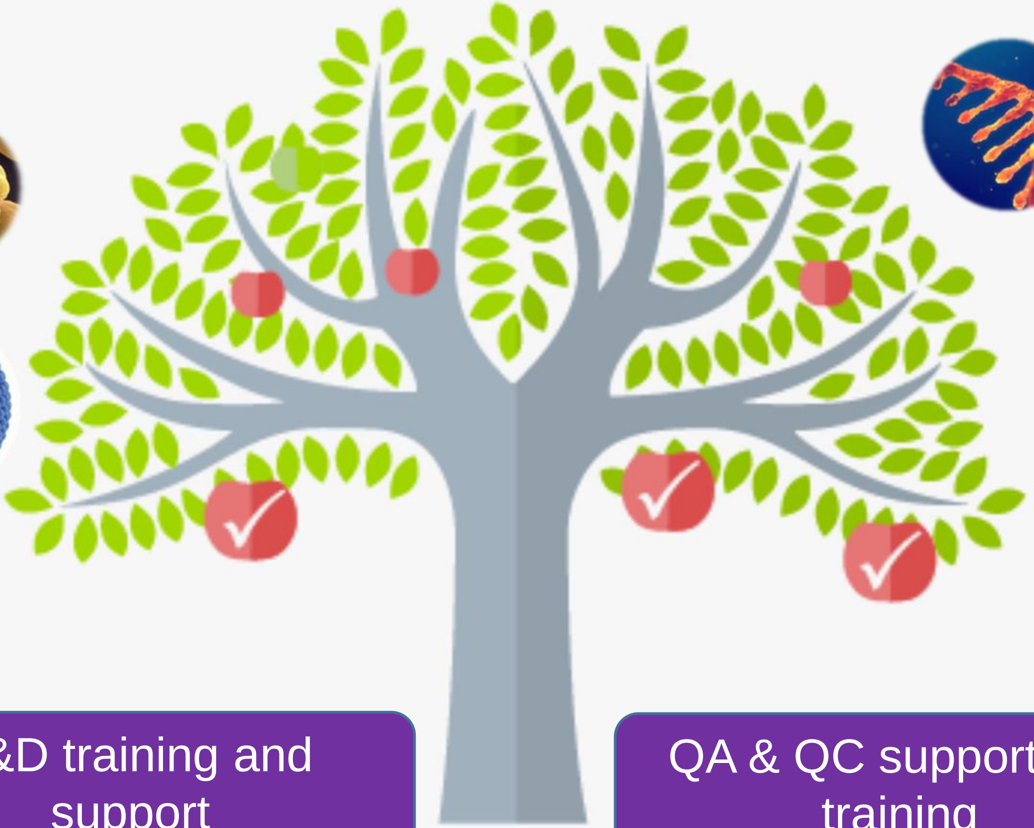
Decreasing risk →

Collaboration and Technology Transfer opportunities

Hissen
艾美汉信疫苗（大连）有限公司
Aimei Hissen Vaccine (Dalian) Co., Ltd.

incepta

gsk



VABIOTECH
For a Healthier life

Formulation for heat stabilisation

Vaccine specific modelling and decisional tools

Process optimisation of manufacturing platforms

R&D training and support

QA & QC support and training

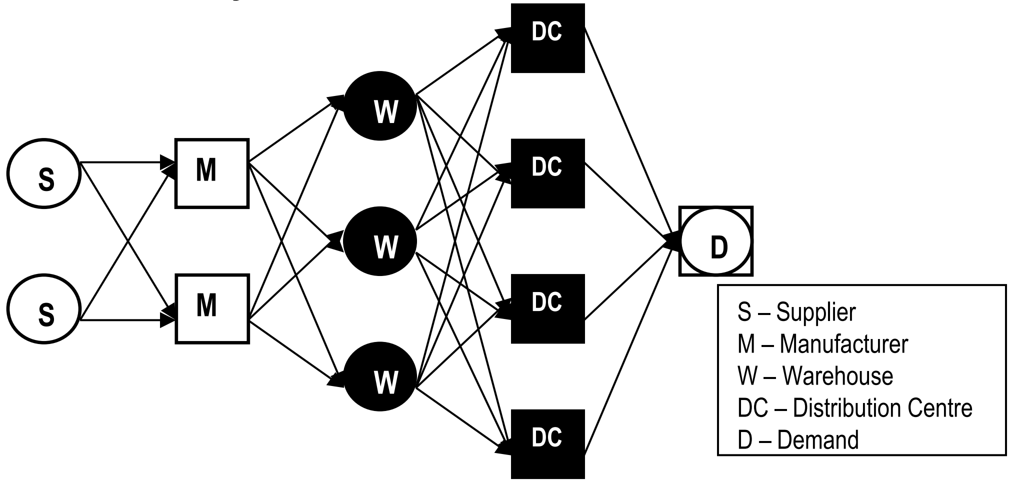
NIBSC
Confidence in Biological Medicines

Imperial College London | The University of Nottingham | University of BRISTOL | NHS Blood and Transplant | Cranfield University | cpi

Training researchers from Incepta in Bangladesh, in Dr Karen Polizzi's labs at Imperial College London

Supply chain management for Vaccines Manufacturers

- What is a Supply Chain?
  - The alignment of firms' activities to bring products or services to market
  - Linked by counter-current flow of material and information

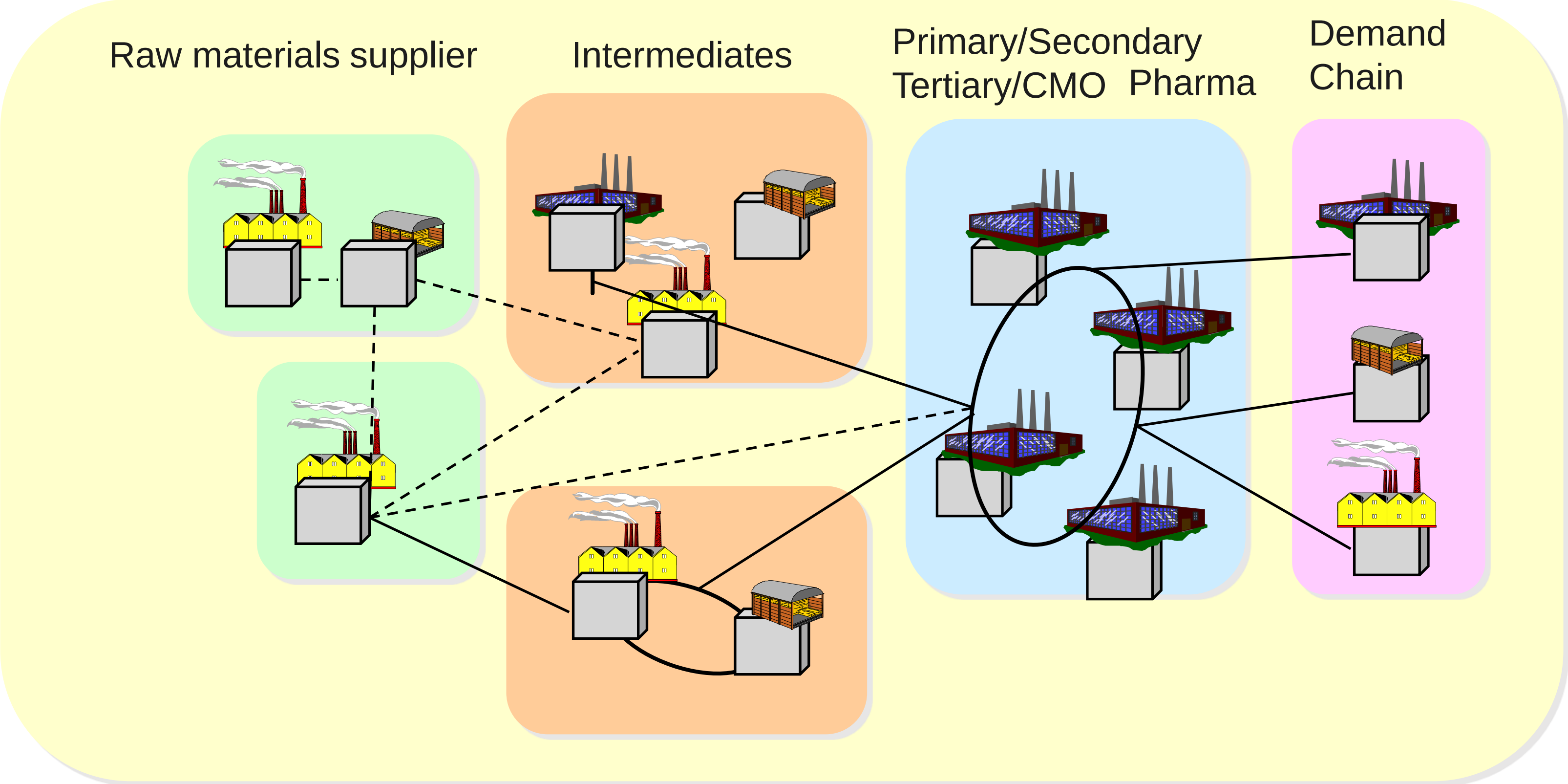


Supply Chain Management
"The systemic, strategic coordination of the traditional business functions and the tactics across these business functions within a particular company and across businesses within the supply chain, for the purposes of improving the long- term performance of the individual companies and the supply chain as a whole."

- Supply chain configuration drives opportunity, operational and financial performance:
  - centralised vs decentralised
  - shipment of bulk or fully-filled vaccines to clinics/local fill-finish plants
  - Quality of Service metrics

From serial supply chains to collaborative value networks

Mass vaccination or rapid response to outbreaks translates to Quality of Service by design which in turn requires agile and interconnected supply networks

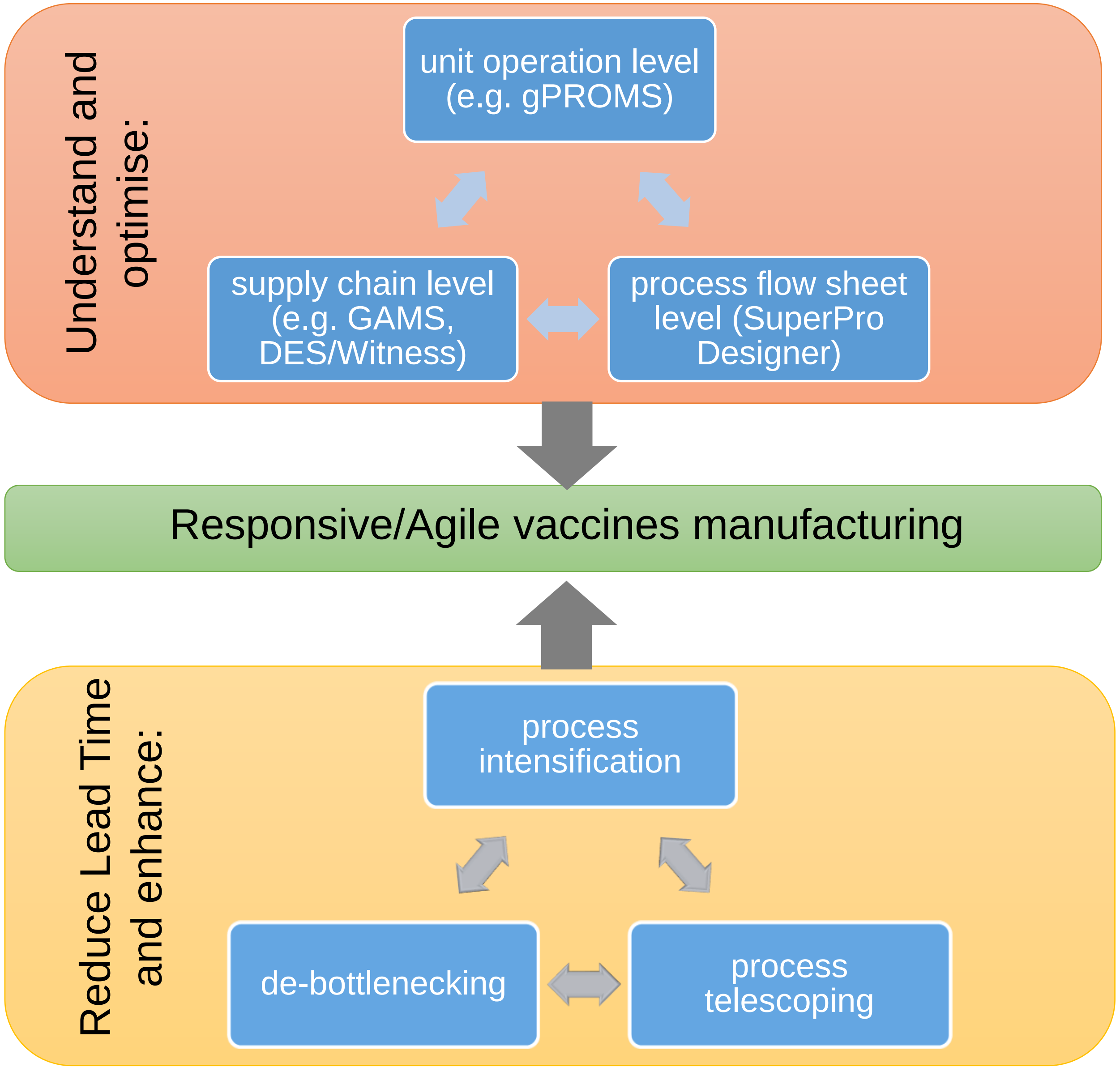


Makatsoris, H. (2004) et. al. in: Chang, Y., Makatsoris, H., & Richards, H., Evolution of supply chain management: Symbiosis of adaptive value networks and ICT (pp. 483-514), Boston: Kluwer Academic Publisher and **Makatsoris H. et. al. (2004)** INT. J. COMPUTER INTEGRATED MANUFACTURING, Taylor and Francis, VOL. 17, NO. 8, 679–69

Whole systems design for operational performance and agile response

- Product: host cell, vector optimisation → improve productivity & quality
- Manufacturing: downstream separations, formulation, fill-to-finish

Two key components we are concerned with



Department of Health & Social Care

EPSRC Engineering and Physical Sciences Research Council

Imperial College London

Working together

▪LMIC capabilities

- 90% LMIC production: attenuated & inactivated bacterial/virus
- 10% LMIC vaccines: mostly conjugates

Our capabilities

- modelling, optimising vaccine manufacturing to reduce costs
- model existing LMIC partner capabilities and alternatives

Collaboration

- whole process design & optimisation, process intensification
- improve responsiveness, operational flexibility, efficiency, reduce costs

Understanding and decision support through models

Operations Planning

- Balance capacity/supply constraints with demand
- Task coordination (scheduling)
- Plan inventory with uncertain demand
- Optimal setup configuration

Execution Control

- Manage complex operation profiles
- Handle a range of process parameters collectively with optimal control
- Handle uncertainty in measurements
- Inventory control and tracking

Design and Configuration

- Design/assess participation in the distribution chain
- Design and evaluate business models
- Optimise service levels subject to forecasts
- Scenario analysis/anticipate response to outbreaks
- Bioprocess design and delivery spec (packaging)

Regulatory & Compliance

- Enhanced process understanding
- Tracking and Monitoring
- Documentation/information exchange for audits
- Coordinate through regulatory diversity

Key benefits

- Increase manufacturing capacity
- Reduced labour costs
- Set optimal inventory levels and investigate response to outbreaks, rapidly
- Reduce CapEx and possibly footprint
- Design flexibility/agile operations
- Speed to market
- Improved quality through the application of QbD & PAT
- Assess the effectiveness of continuous manufacturing

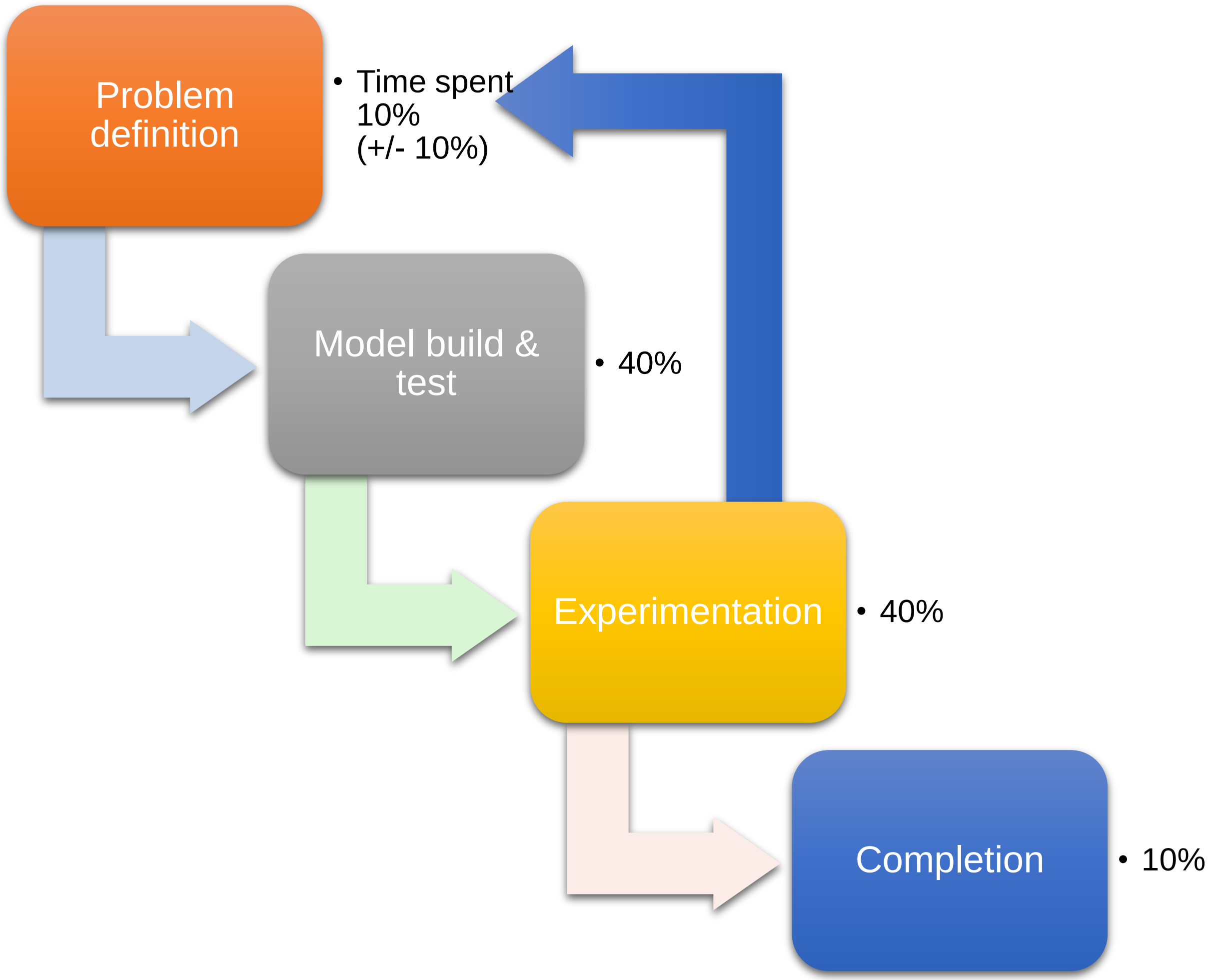
https://biopharma-asia.com/featured-article/challenges-development-continuous-processes-vaccines/

Some evaluation metrics we use in the Hub

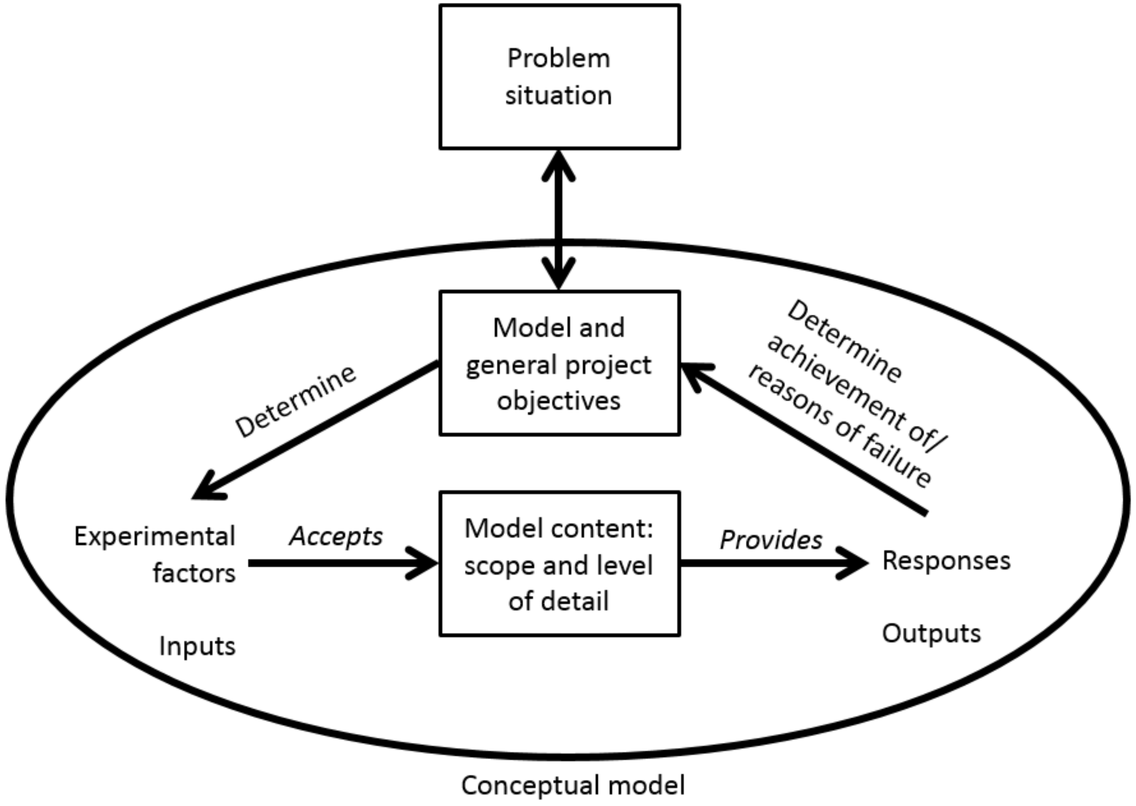
Speed	~100,000 vaccine doses, weeks after threat antigen identification
Cost	low cost, below 1 $/dose
Flexibility	on-demand production of a wide range of vaccine types (viral and bacterial)
Technological complexity	low technological complexity for implementation in developing countries
Technology readiness	mature technologies with established manufacturing processes
Ease of scale-up or -out	highly scalable upstream and downstream processes
Thermo-stability of product	vaccines stable at 40°C for at least 6 months

Modelling workflows for decision support

Modelling study project management



Conceptual model



5 key activities in Conceptual Modelling

1. Understanding the problem domain
2. Determining the modelling and general project objectives
3. Identifying the model outputs (responses)
4. Identifying model inputs (experimental factors)
5. Determining the model content (scope and level of detail), identifying and assumptions and simplifications

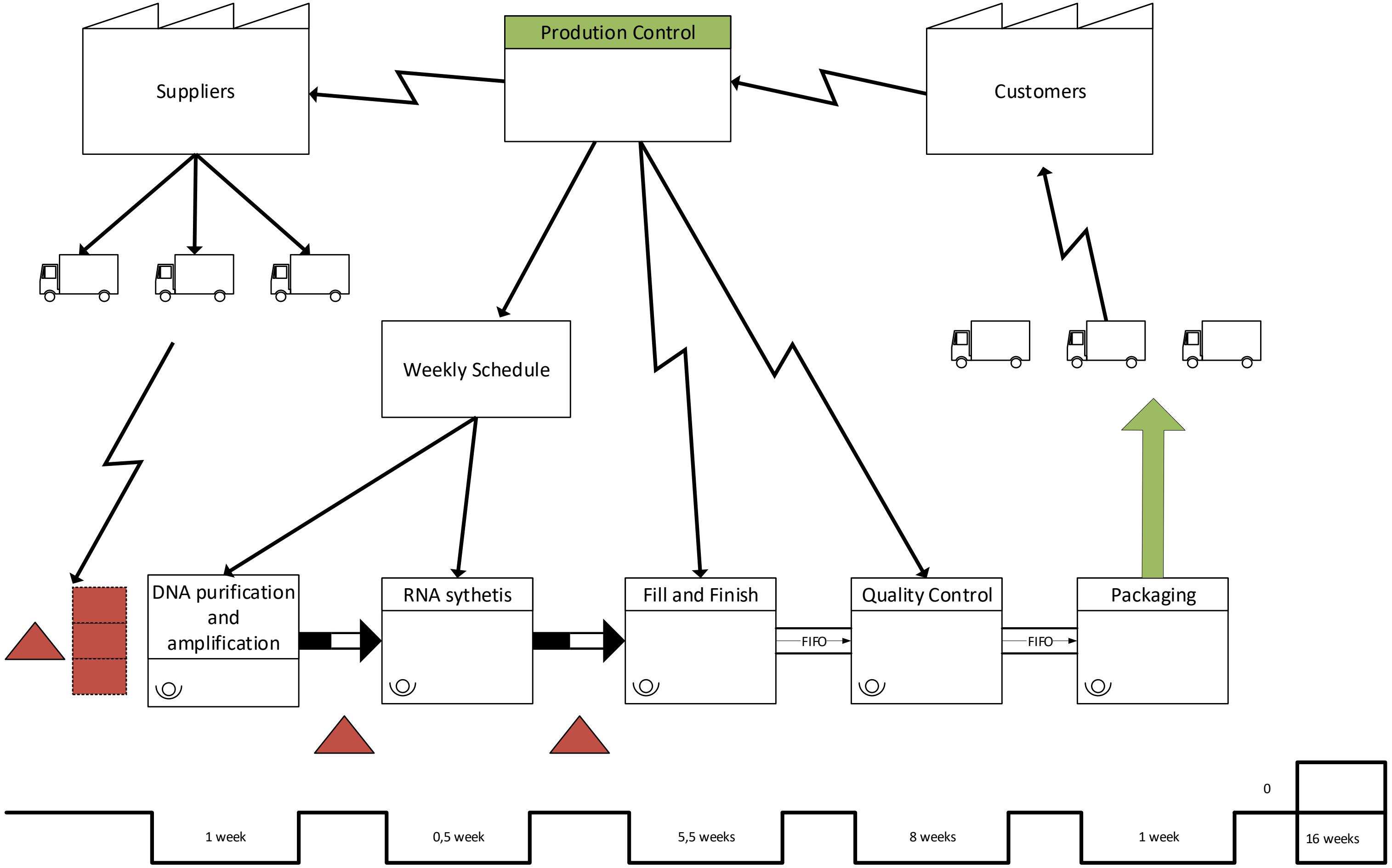
Robinson (2004)

Process Mapping

The Supplier, Input, Process, Output, Customer model is a systematic framework that helps capture and summarise one or more processes in table form.

Suppliers	Inputs	Process	Outputs	Demand
Raw Materials	BoM	**V**alue **S**tream **M**apping	Production quantities	Patients
	MPS		Costs	Hospital Trusts
	Cycle Times		Inventory	Governments
	Quantities		Productivity	Other stakeholders
	Arrival Times		Lead time	
	Costs			
	Quantities			

Value stream mapping: where material, energy, time, money go to?



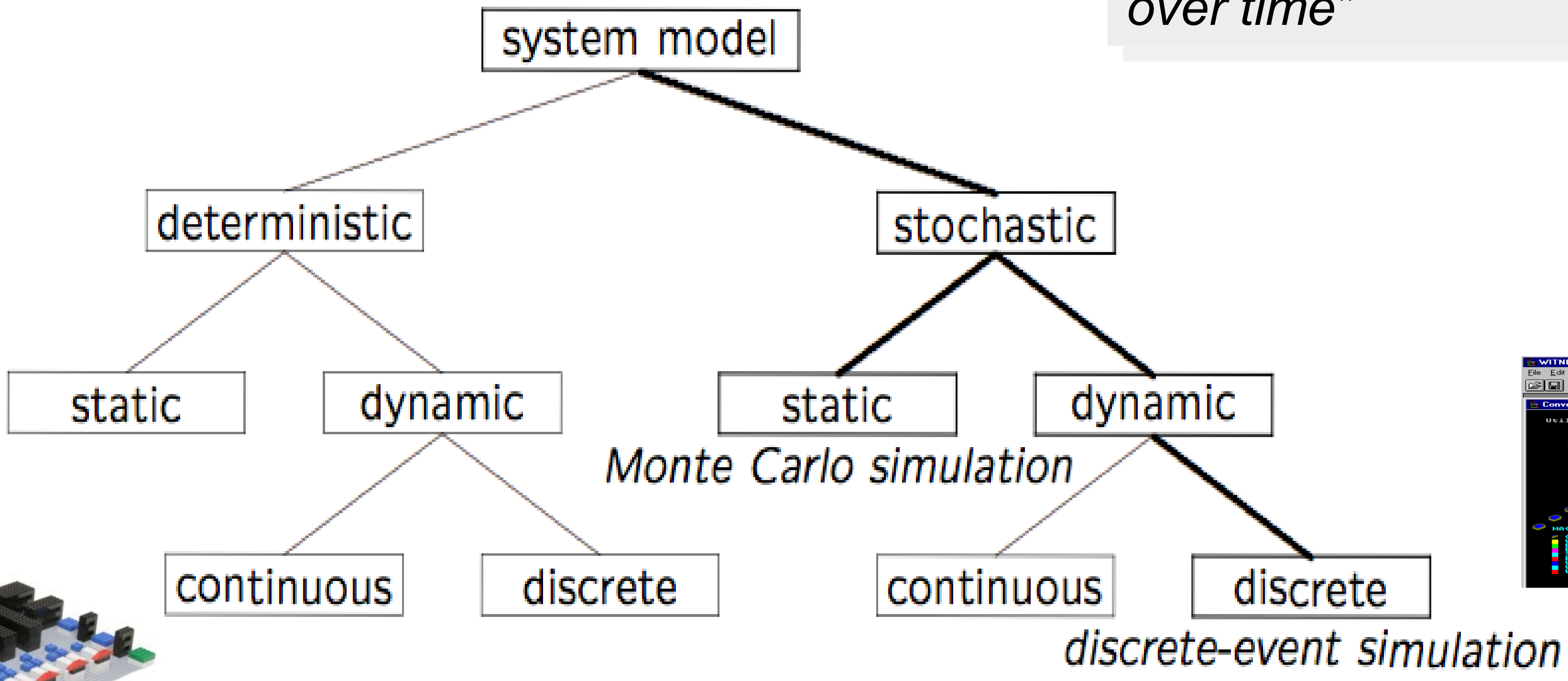
Some relevant modelling approaches

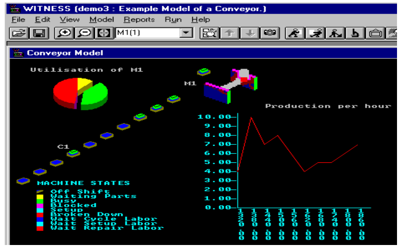
Discrete event simulation

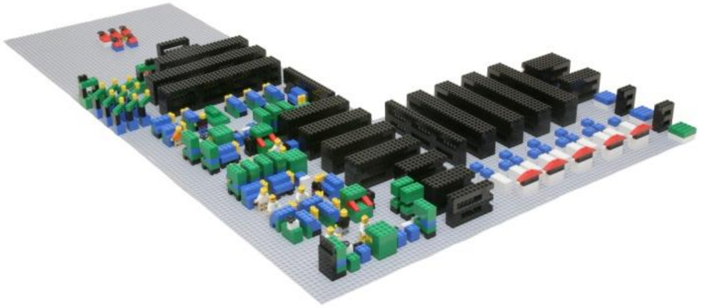
Mathematical models

System dynamics simulation

"The use of computers to perform calculations which will predict the performance of a system or sub-system over time"



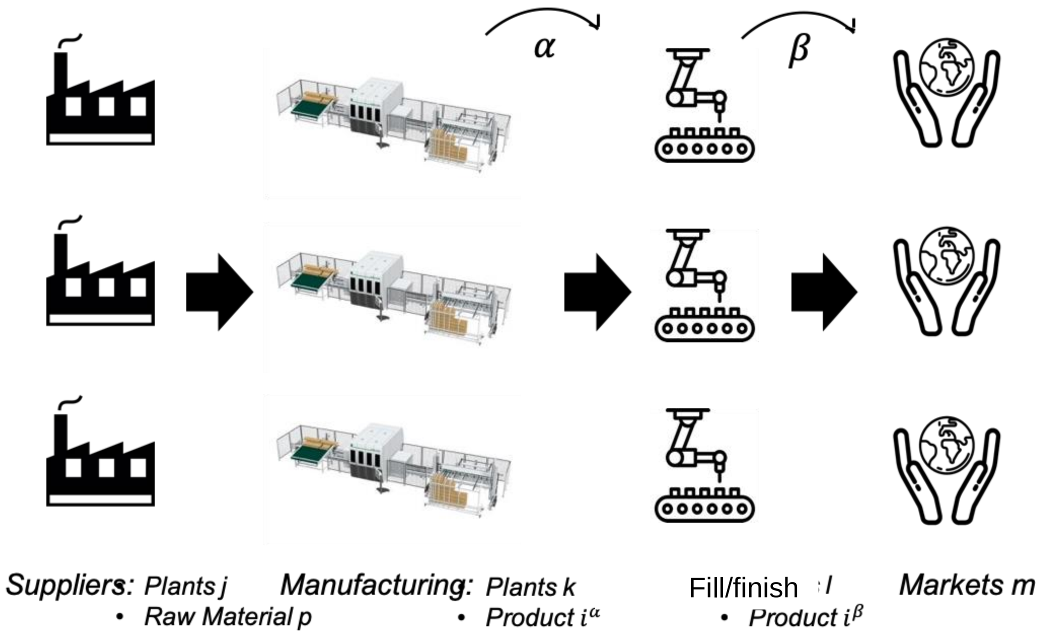


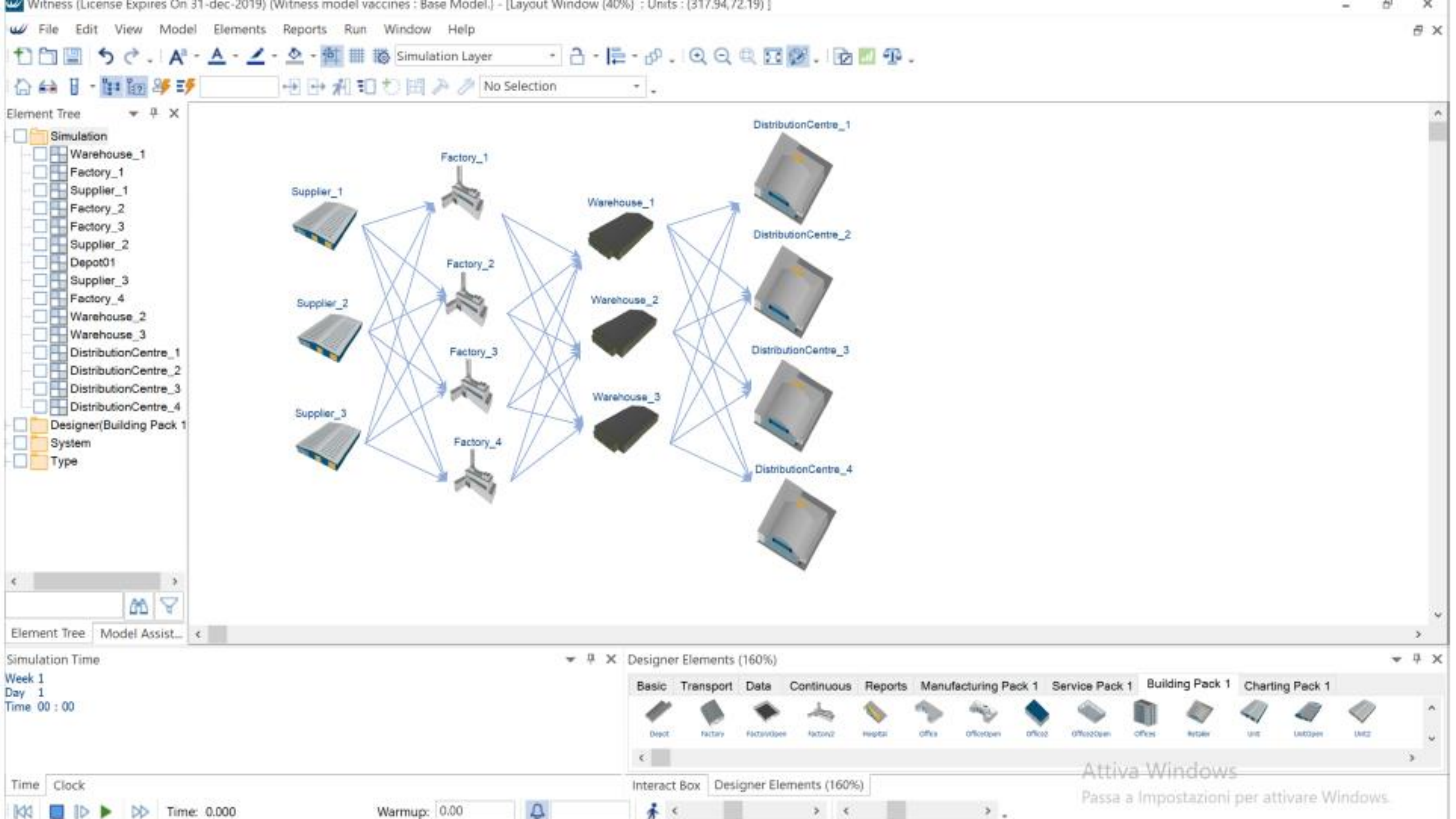


Discrete Event Simulation

- *Discrete-Event Simulation (DES)*
- It is simulation involving events (arrival, departure, cycle times, lead times, setups, breakdowns and other inputs) that occur at discrete points in time.

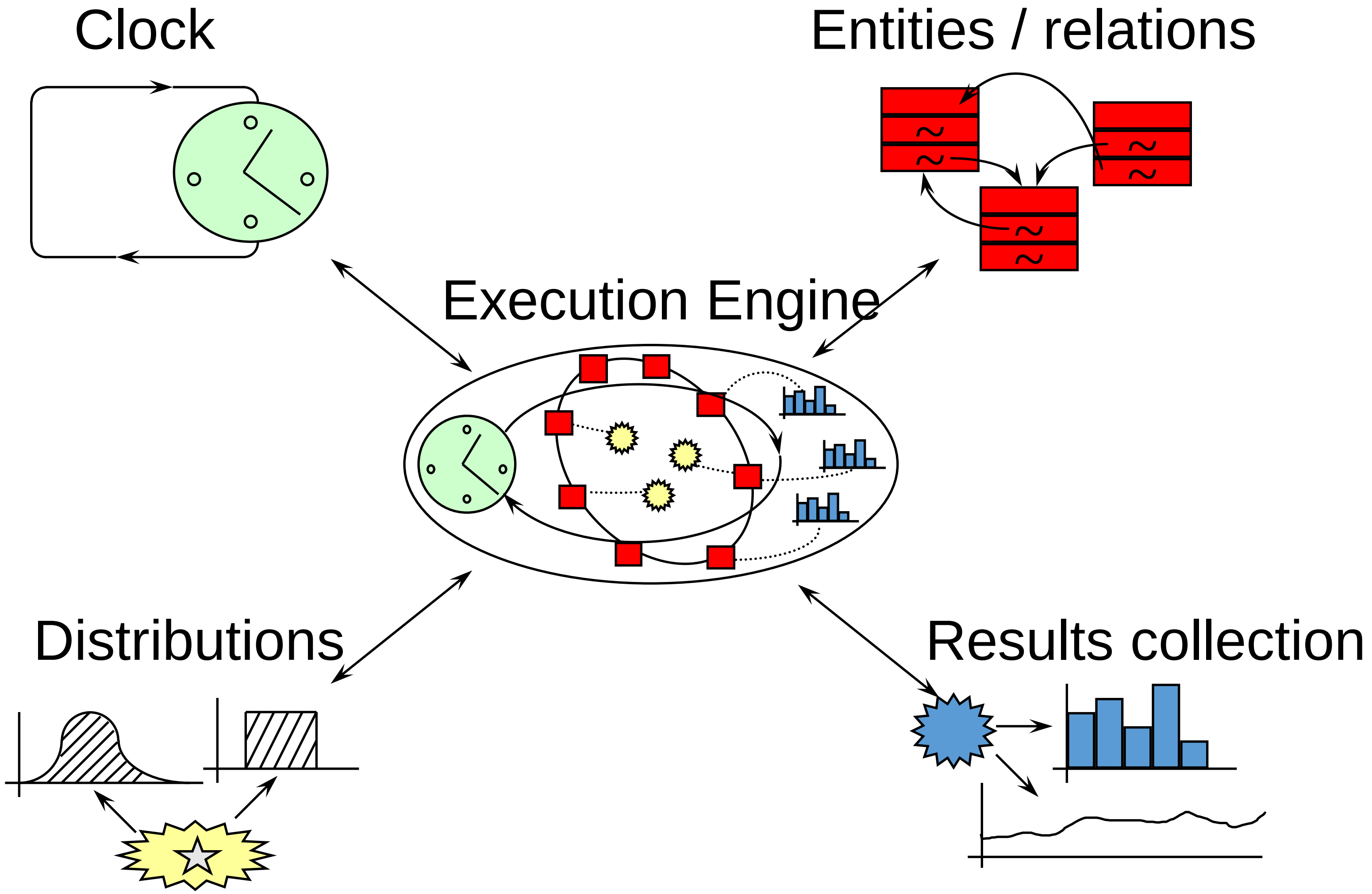
- Flexibility
- What if scenarios Experimentation
- Various levels of detail and granularity
- Dynamic assessment of the manufacturing process
- Ease of scalability
- Stochastic by default
- Intuitive and easy to prepare





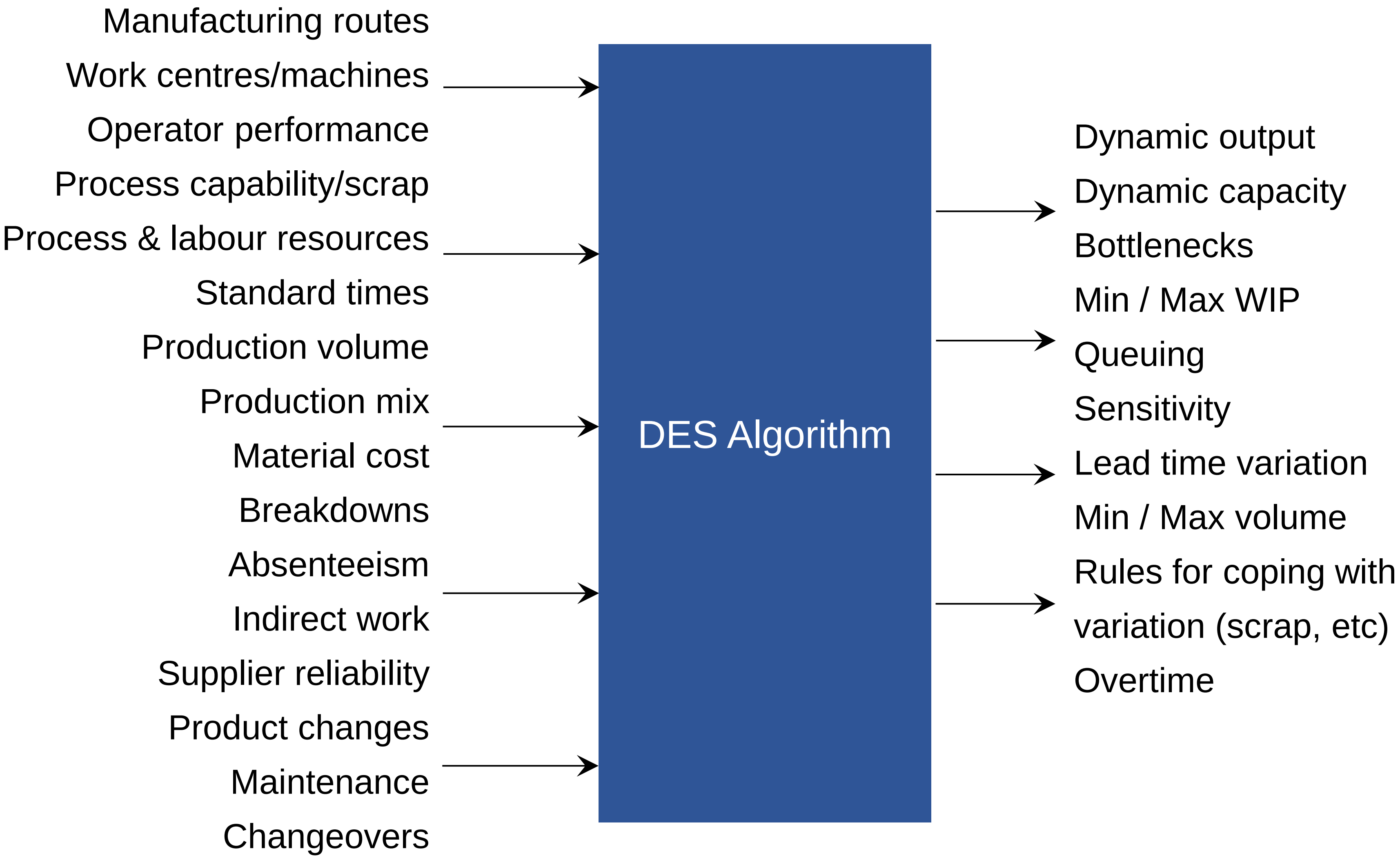
Witness (License Expires On 31-dec-2019) (Witness model vaccines : Base Model.) - [Layout Window (40%) : Units : (317.94,72.19)]
File Edit View Model Elements Reports Run Window Help
Simulation Layer
No Selection
Element Tree
Simulation
Warehouse_1
Factory_1
Supplier_1
Factory_2
Factory_3
Supplier_2
Depot01
Supplier_3
Factory_4
Warehouse_2
Warehouse_3
DistributionCentre_1
DistributionCentre_2
DistributionCentre_3
DistributionCentre_4
Designer(Building Pack 1
System
Type
Supplier_1
Supplier_2
Supplier_3
Factory_1
Factory_2
Factory_3
Factory_4
Warehouse_1
Warehouse_2
Warehouse_3
DistributionCentre_1
DistributionCentre_2
DistributionCentre_3
DistributionCentre_4
Element Tree
Model Assist...
Simulation Time
Week 1
Day 1
Time 00 : 00
Designer Elements (160%)
Basic
Transport
Data
Continuous
Reports
Manufacturing Pack 1
Service Pack 1
Building Pack 1
Charting Pack 1
Time
Clock
Time: 0.000
Warmup: 0.00
Interact Box
Designer Elements (160%)
Attiva Windows
Passa a Impostazioni per attivare Windows.

Structure of simulation algorithm

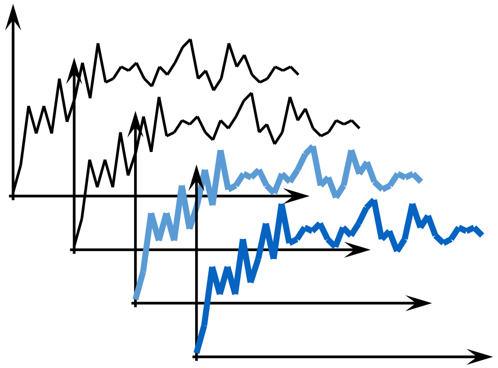


Adapted from Kreutzer

Typical outputs: more than a spreadsheet!



Multiple replications and batching



Either: repeat simulation run ~5 times

Run-in may take a long time

Random numbers may be difficult to modify

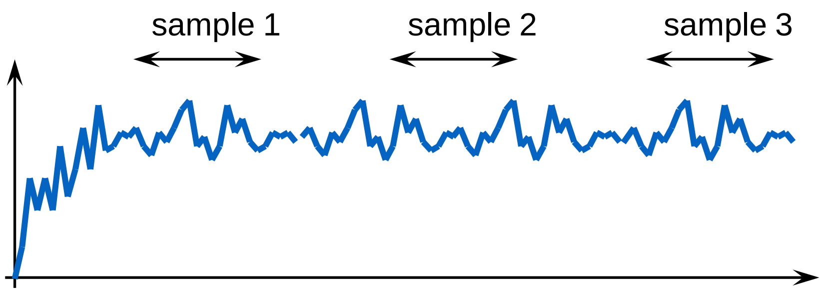
Possibly some software specific problems

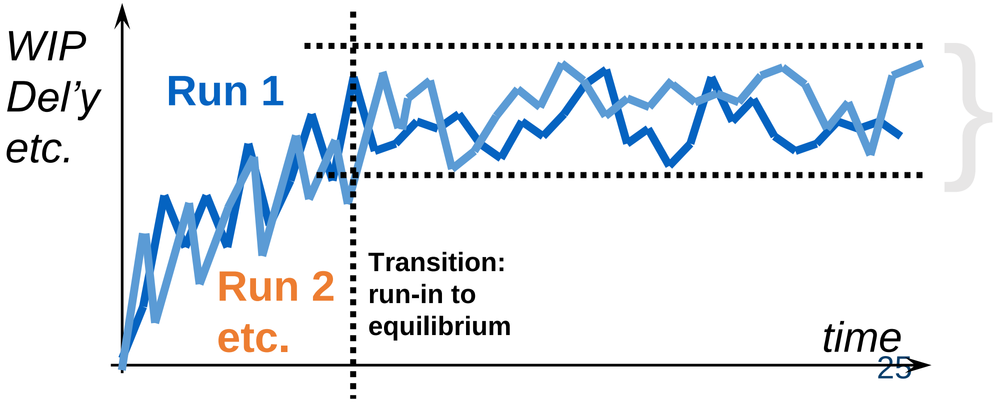
Or: perform one simulation run and use *independent* intervals.

Need to ensure samples are independent

Run may not last that long

Cannot save time by using several computers





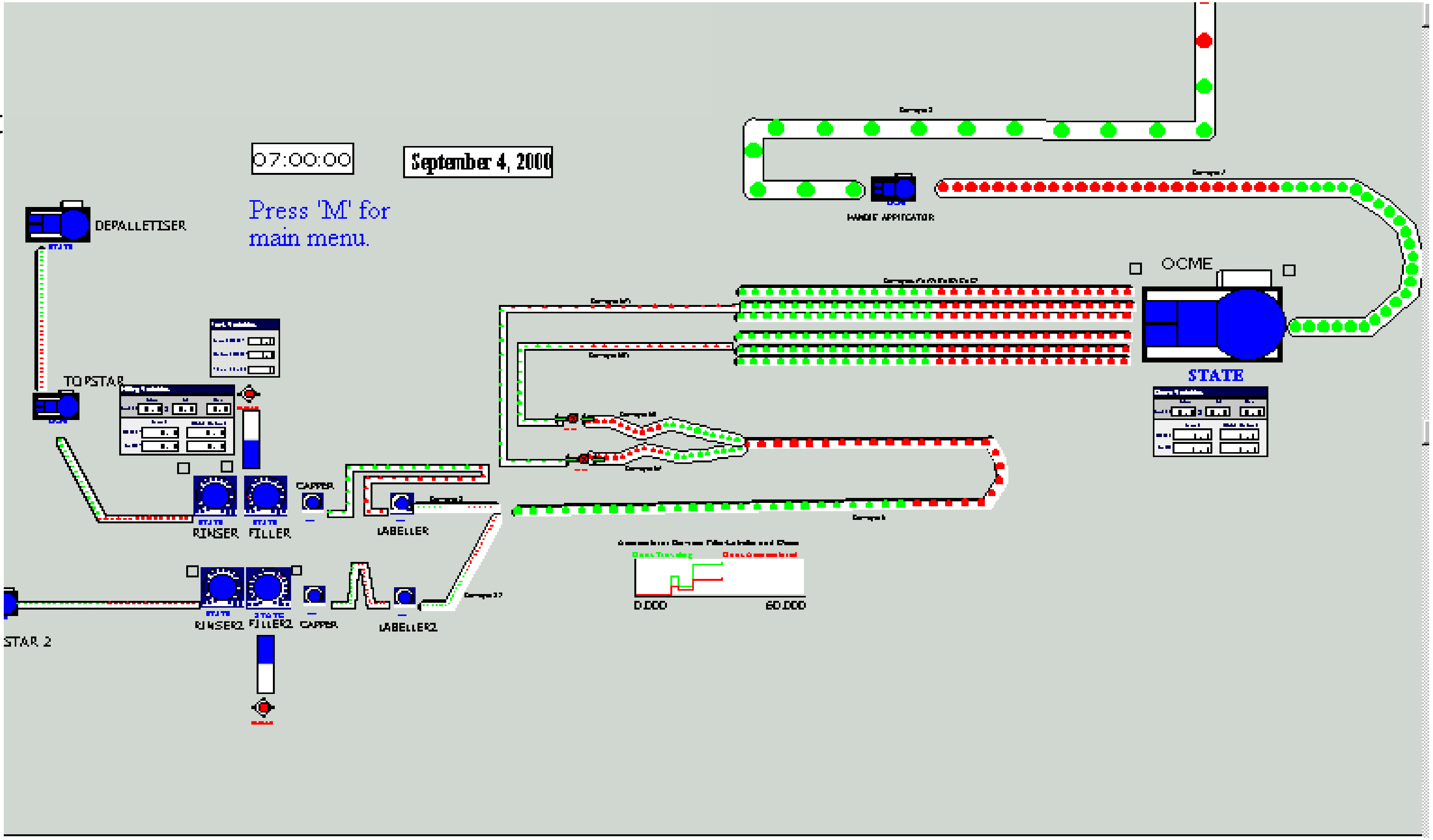
Likely operating range

Provides average and range of variation over time

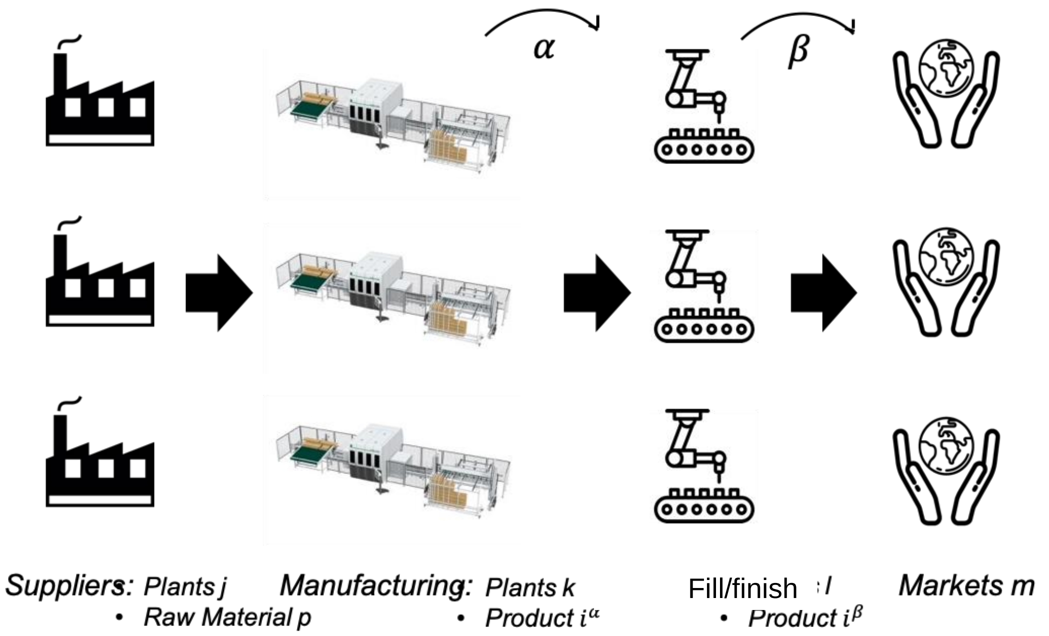
Fill line example

Purpose to:

Optimise throughput



Mathematical modelling for network flow problems: Variables and determining their relationship



$$\boldsymbol{min\, C = LC + TC + PC + IC}$$

$$LC = \sum_{p\in\hat{P}}\sum_{j\in\hat{J}}\sum_{t\in\hat{T}}\left(a^{p}_{jt}\tau^{p}_{pj}Q^{p}_{pjt}\right) + \sum_{i\in\hat{I}}\sum_{k\in\hat{K}}\sum_{t\in\hat{T}}\left(a^{\alpha}_{kt}\tau^{\alpha}_{ik}Q^{\alpha}_{ikt}\right) + \sum_{i\in\hat{I}}\sum_{l\in\hat{L}}\sum_{t\in\hat{T}}\left(a^{\beta}_{lt}\tau^{\beta}_{il}Q^{\beta}_{ilt}\right)$$

$$PC = \sum_{p\in\hat{P}}\sum_{j\in\hat{J}}\sum_{t\in\hat{T}}\left(q^{p}_{pjt}Q^{p}_{pjt}\right) + \sum_{i\in\hat{I}}\sum_{k\in\hat{K}}\sum_{t\in\hat{T}}\left(q^{\alpha}_{ikt}Q^{\alpha}_{ikt}\right) + \sum_{i\in\hat{I}}\sum_{l\in\hat{L}}\sum_{t\in\hat{T}}\left(q^{\beta}_{ilt}Q^{\beta}_{ilt}\right) + \sum_{i\in\hat{I}}\sum_{k\in\hat{K}}\sum_{t\in\hat{T}} Ca_{ik}Q^{\alpha}_{ikt}B'^{\alpha}_{ikt} + \sum_{i\in\hat{I}}\sum_{l\in\hat{L}}\sum_{t\in\hat{T}} Ca_{il}Q^{\beta}_{ilt}B'^{\beta}_{ilt}$$

$$TC = \sum_{p\in\hat{P}}\sum_{j\in\hat{J}}\sum_{k\in\hat{K}}\sum_{g\in\hat{G}}\sum_{t\in\hat{T}}\left(w^{p}_{pjkgt}W^{p}_{pjkgt} + x_{pjkgt}X_{pjkgt}\right) + \sum_{i\in\hat{I}}\sum_{k\in\hat{K}}\sum_{l\in\hat{L}}\sum_{g\in\hat{G}}\sum_{t\in\hat{T}}\left(w^{\alpha}_{iklgt}W^{\alpha}_{iklgt} + y_{iklgt}Y_{iklgt}\right) + \sum_{i\in\hat{I}}\sum_{l\in\hat{L}}\sum_{m\in\hat{M}}\sum_{g\in\hat{G}}\sum_{t\in\hat{T}}\left(w^{\beta}_{ilmgt}W^{\beta}_{ilmgt} + z_{ilmgt}Z_{ilmgt}\right)$$

$$IC = \sum_{p\in\hat{P}}\sum_{j\in\hat{J}}\sum_{t\in\hat{T}}\left(h^{p}_{pjt}I^{p}_{pjt}\right) + \sum_{k\in\hat{K}}\sum_{i\in\hat{I}}\sum_{t\in\hat{T}}\left(h^{\alpha}_{ikt}I^{\alpha}_{ikt}\right) + \sum_{l\in\hat{L}}\sum_{i\in\hat{I}}\sum_{t\in\hat{T}}\left(h^{\beta}_{lit}I^{\beta}_{lit}\right)$$

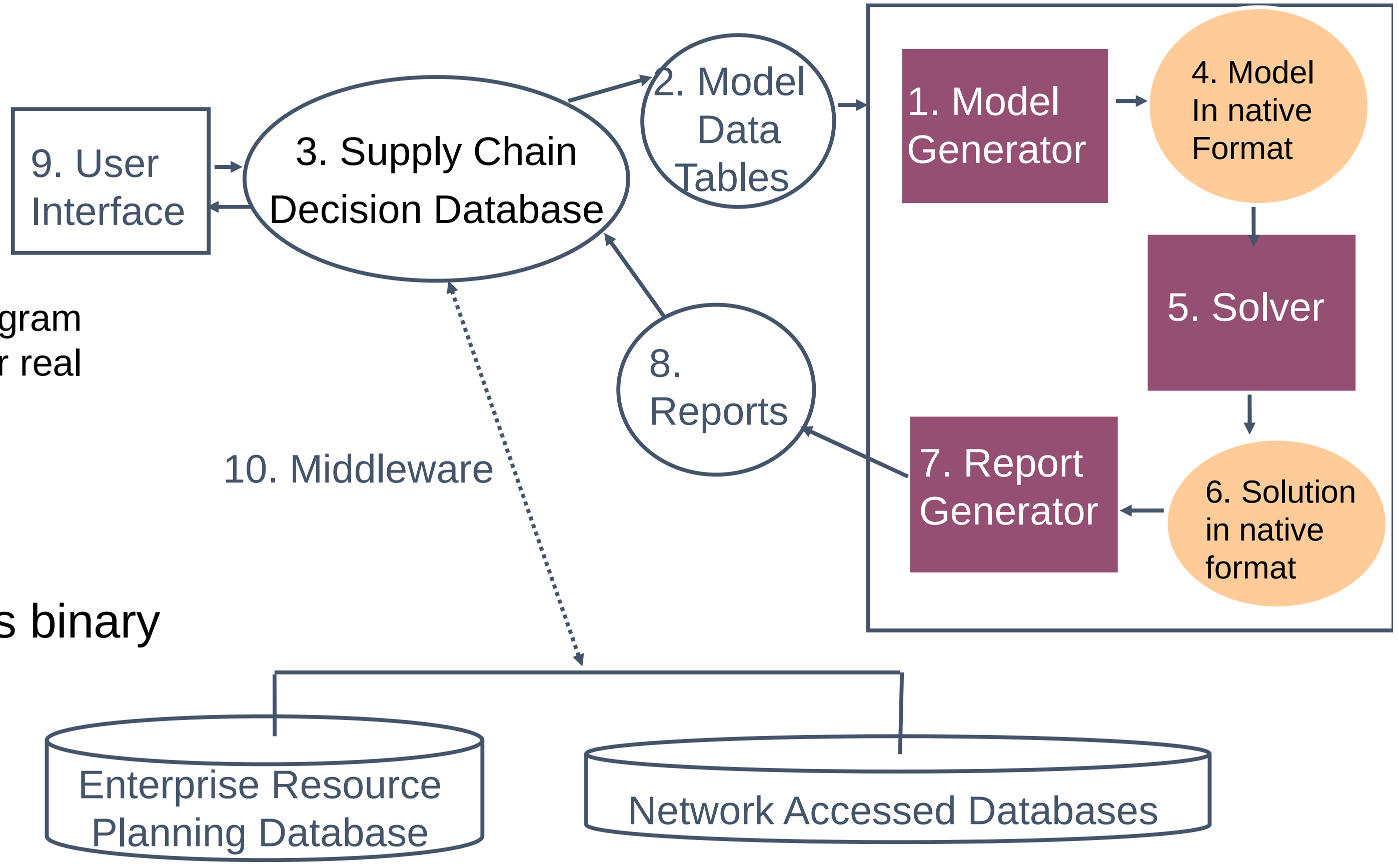
LC: Labour Cost, TC: Trasportation Cost, PC: Production Cost, IC: Inventory Cost

Solving mathematical optimisation models

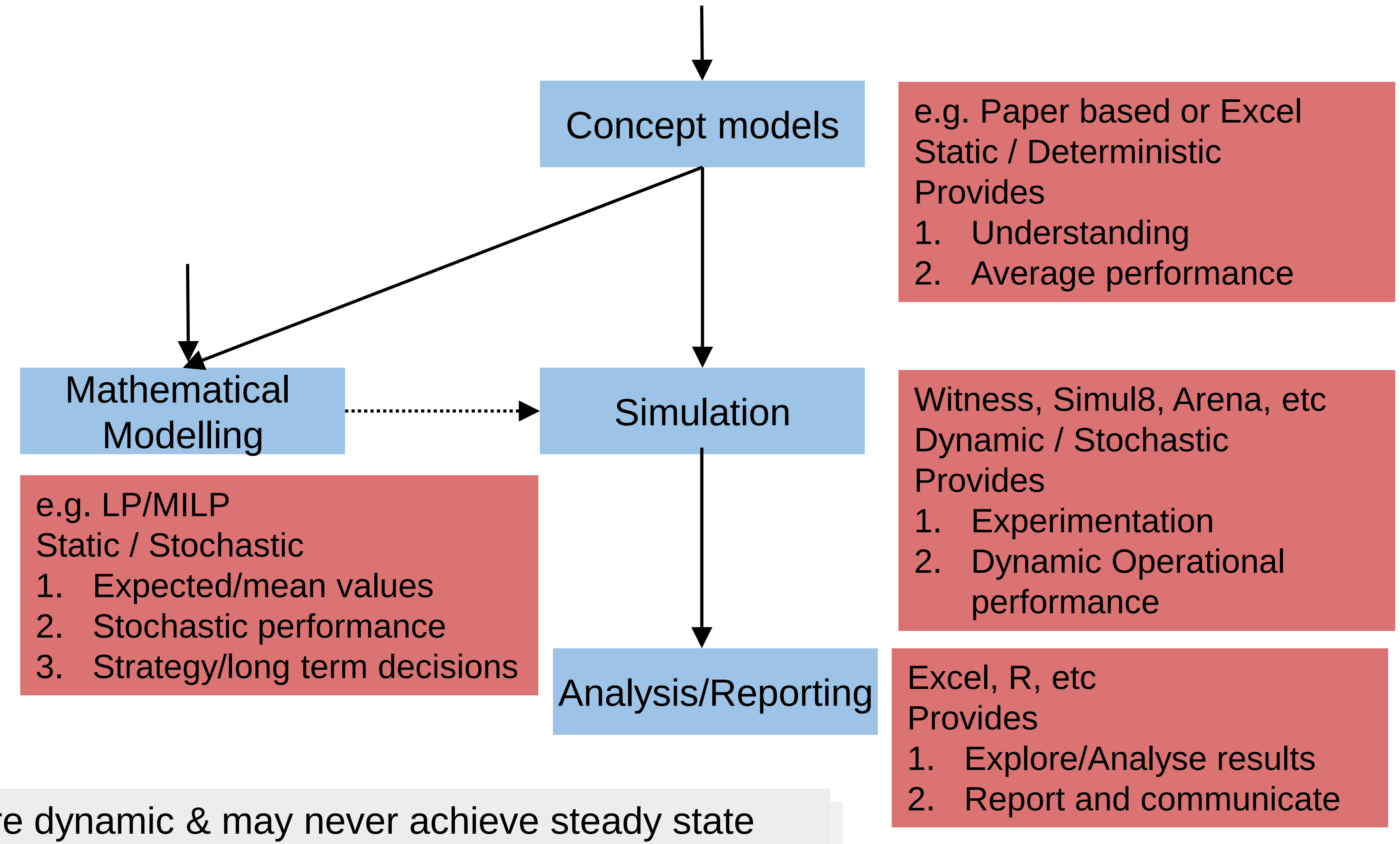
Mixed Integer Linear Programming (MILP)

A MILP problem is a mathematical optimisation or feasibility program in which some or all of the variables are restricted to be integer or real numbers

- Suitable for real-world problems
- Different available solvers
- Discrete and logical constraints are declared as binary variables

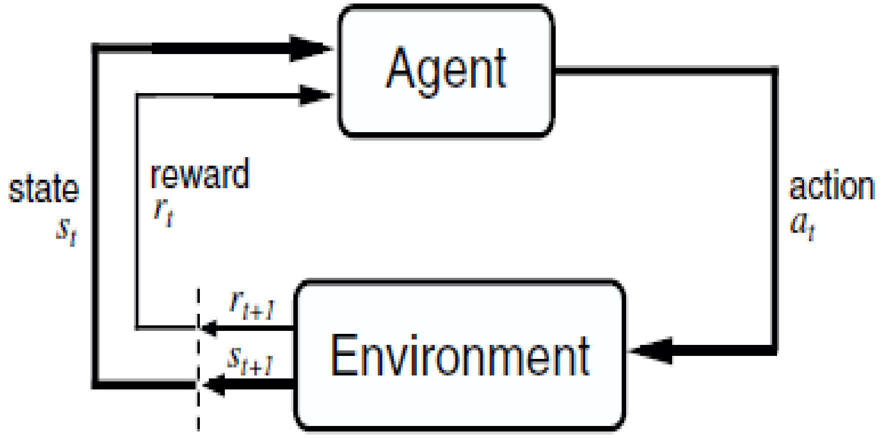


Usage of tools available



Real systems are dynamic & may never achieve steady state but we frequently analyse them making the assumption they will!

Pushing the envelope: SC design using AI / Reinforcement Learning (Rl)



What is RL?

- Goal oriented learning
- Requires no prior knowledge of environment
- Learns directly from experiencing the environment without explicit instructions

History of interaction:
$(s_t, a_t, r_{t+1}, s_{t+1}, a_{t+1}, r_{t+2}, s_{t+2}, a_{t+2} \dots)$

Information from each interaction (episode):
$(s_t a_t, r_{t+1}, s_{t+1})$

Agent attempts to maximise expected rewards:
$R_t = r_{t+1} + r_{t+2} + r_{t+3} + \dots + r_{t+k+1}$

Initialize Q (s,a) arbitrarily
Repeat (for each episode):
Initialize s
Repeat (for each step of episode):
Choose a from s using policy derived from Q (e.g. ϵ-greedy)
Take action a, observe r, s'
$Q(s,a) \leftarrow Q(s,a) + \alpha\,[r + \gamma\, max_{a'}(s',a') - Q(s,a)\,]$
$s \leftarrow s'$;
Until s is terminal

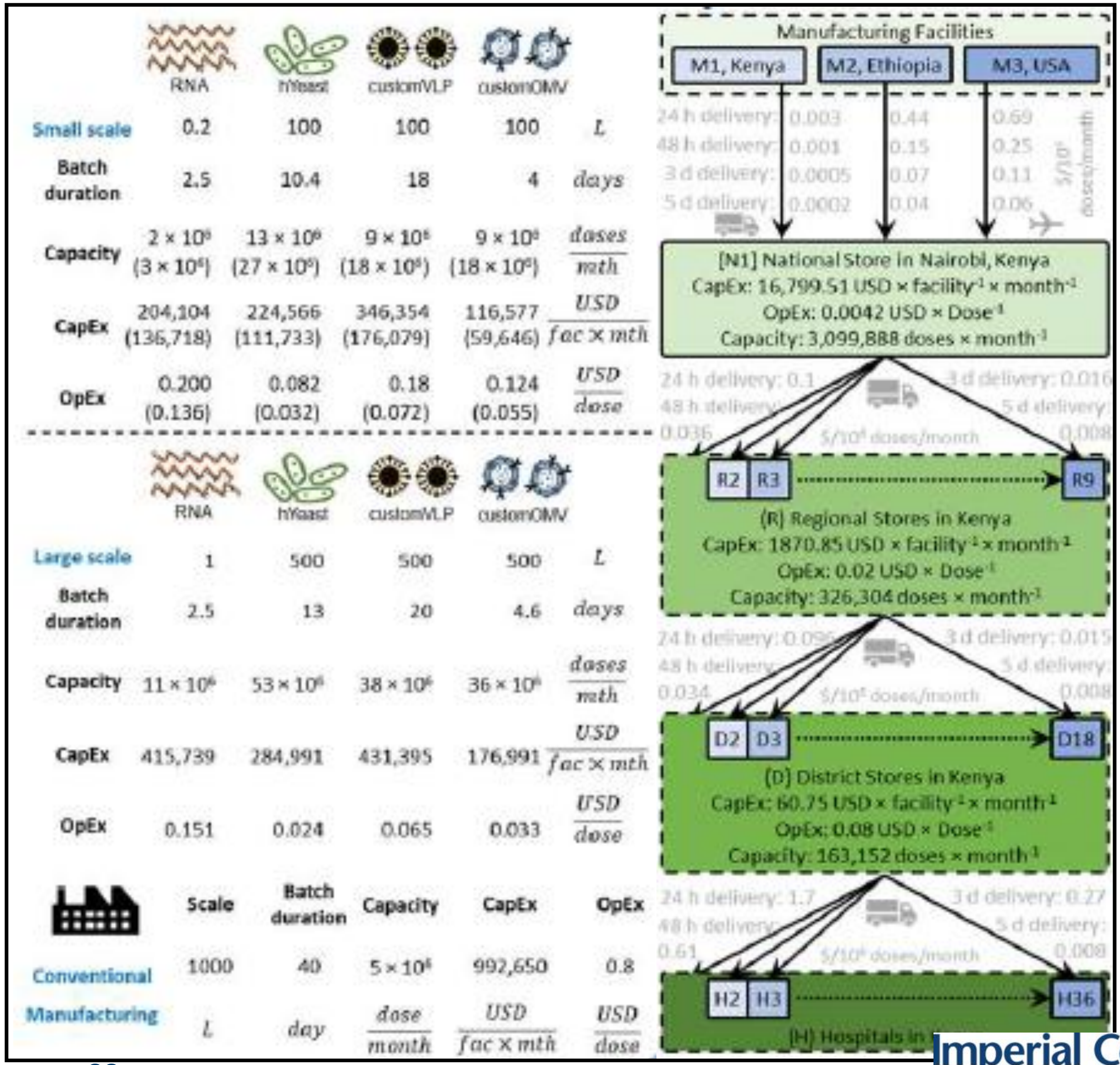
Mumith, J.A., et. al., (2014), *ATE*, *65*(1), pp.588-596; Mumith, J.A., et. al., (2015), *IJLCT*, p.ctv023

Case study: Impact of Novel Manufacturing Techniques on the Kenyan Supply Chain

www.cranfield.ac.uk

Supply chain modelling case introduction

- Kenyan vaccine supply chain optimization model results
- Mixed Integer Linear Programming (MILP) problem comparing our 4 manufacturing platforms
- Conventional vs intensification for distributed manufacturing
- 3 storage levels considered
- Choice of manufacturing facilities in Kenya, Ethiopia and USA
- Objective: Maximise Profit



Z Kis, M Papathanasiou, R Calvo-Serrano, C Kontoravdi, N Shah. JAMP. Submitted Mar 2019.

How the MILP model looks like

$\max NPV = \sum_v \sum_d \sum_h \sum_j \sum_t SINH_{vdhjt} \cdot Revenue - TCM_m - TCS_S - TCT_T$	E1
$s.t$	
$TC_m = \sum_m CCM_m \cdot E1_m + \sum_{vmt} FIN_{vmt} \cdot COM_m$	E2
$TC_S = \sum_n CCN_n \cdot E2_n + \sum_r CCR_r \cdot E3_r + \sum_d CCD_d \cdot E4_d + \sum_{vnt} CON_n \cdot FIN_{vnt} + \sum_{vrt} COR_r \cdot FIN_{vrt} + \sum_{vdt} COD_d \cdot FIN_{vnt}$	E3
$TC_T = \sum_{vmnjt} Y1_{vmnjt} \cdot TT_j \cdot U1_{mnj} + \sum_{vnrjt} Y2_{vnrjt} \cdot TT_j \cdot U2_{nrj} + \sum_{vrdjt} Y3_{vrdjt} \cdot TT_j \cdot U3_{rdj} + \sum_{vdhjt} Y4_{vdhjt} \cdot TT_j \cdot U4_{dhj}$	E4
$FINM_{vmt} = FOUTM_{vmt+TM}$,$FINN_{vnt} = FOUTN_{vnt+TSN}$,$FINR_{vrt} = FOUTR_{vrt+TSR}$, $FIND_{vdt} = FOUTD_{vdt+TSD}$	E5
$SINN_{vmnjt} = SOUTM_{vmnjt+TT_j}$, $SINR_{vrnjt} = SOUTN_{vnrjt+TT_j}$, $SIND_{vdrjt} = SOUTR_{vrdjt+TT_j}$,$SINH_{vdhjt} = SOUTD_{vdhjt+TT_j}$	E6
$\sum_v FINM_{vmt} \leq CAPMM_{mt}$,$\sum_v FINN_{vnt} \leq CAPMN_{nt}$ $\sum_v FINR_{vrt} \leq CAPMR_{rt}$, $\sum_v FIND_{vdt} \leq CAPMD_{dt}$	E7
$X1_{mn} \leq E1_m$, $X1_{mn} \leq E2_n$, $X2_{nr} \leq E2_n$, $X2_{nr} \leq E3_r$, $X3_{rd} \leq E3_r$, $X3_{rd} \leq E4_d$, $X4_{dh} \leq E4_d$	E8
$Y1_{vmnjt} \leq X1_{mn}$, $Y2_{vnrjt} \leq X2_{nr}$, $Y3_{vrdjt} \leq X3_{rd}$, $Y4_{vdhjt} \leq X4_{dh}$	E9
$\sum_j Y1_{vmnjt} \leq 1$,$\sum_j Y2_{vnrjt} \leq 1$,$\sum_j Y3_{vrdjt} \leq 1$, $\sum_j Y4_{vdhjt} \leq 1$	E10
$S^{min} \cdot Y1_{vmnjt} \leq SOUT_{vmnjt} \leq S^{max} \cdot Y1_{vmnjt}$, $S^{min} \cdot Y2_{vnrjt} \leq SOUT_{vnrjt} \leq S^{max} \cdot Y2_{vnrjt}$, $S^{min} \cdot Y3_{vrdjt} \leq SOUT_{vrdjt} \leq S^{max} \cdot Y3_{vrdjt}$, $S^{min} \cdot Y4_{vdhjt} \leq SOUT_{vdhjt} \leq S^{max} \cdot Y4_{vdhjt}$	E11

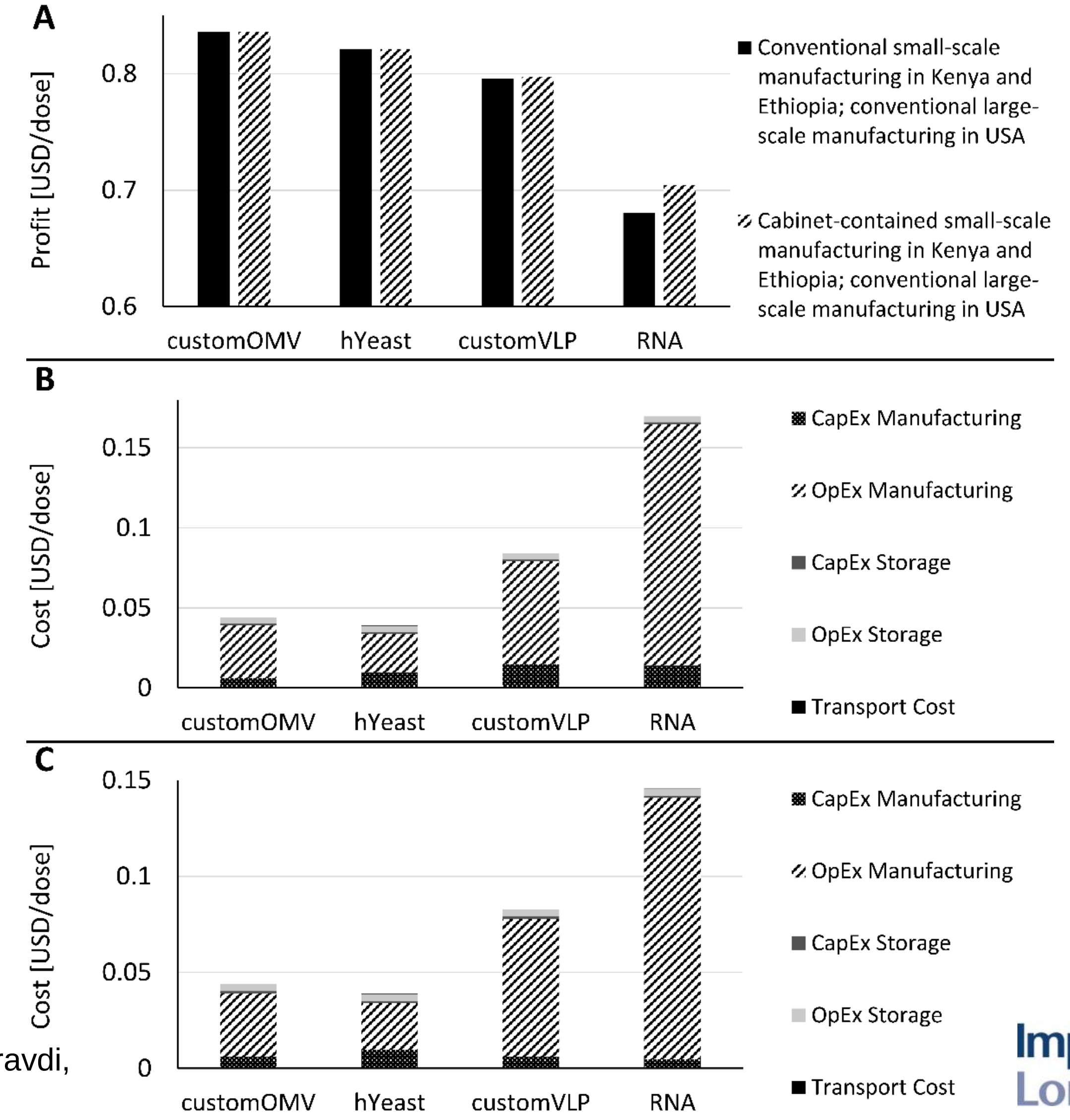
Supply chain modelling results

- Kenyan vaccine supply chain optimization model results.

A. Supply chain profitability: centralized large-scale vs intensified local manufacturing. Revenue = 1 USD/dose.

B. Cost categories for optimal supply chain configuration showed by solid black bars in part A.

C. Cost categories for optimal supply chain configuration showed by stripped bars in part A.



Z Kis, M Papathanasiou, R Calvo-Serrano, C Kontoravdi, N Shah. JAMP. Submitted Mar 2019.

Cranfield Manufacturing
Department of Health & Social Care
EPSRC Engineering and Physical Sciences Research Council
Imperial College London

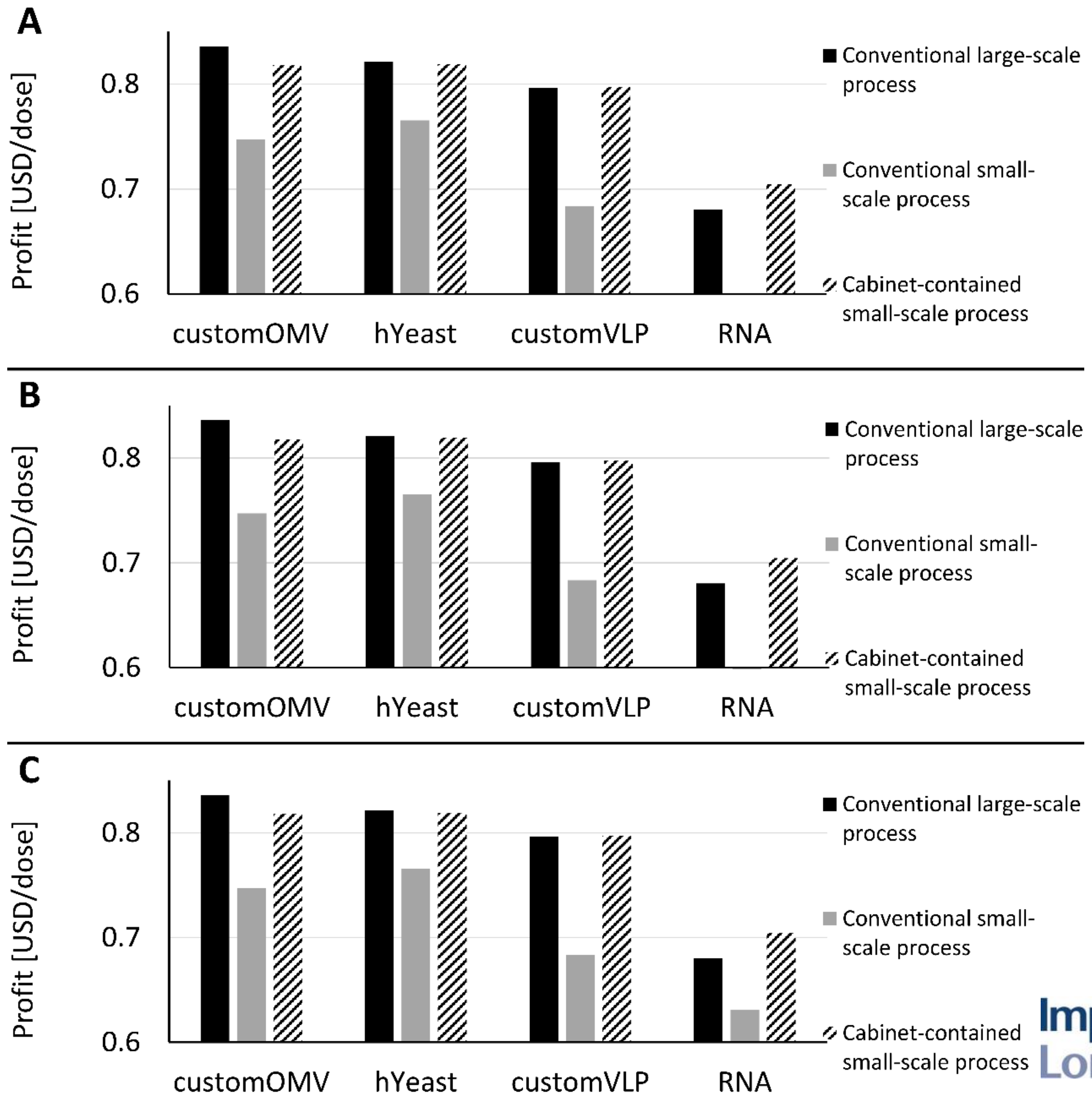
Supply chain modelling results

- The effect of facility location on cost per dose.

A. Facilities in USA only.

B. Facilities in Kenya only.

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



Z Kis, M Papathanasiou, R Calvo-Serrano, C Kontoravdi, N Shah. JAMP. Submitted Mar 2019.

Department of Health & Social Care
EPSRC Engineering and Physical Sciences Research Council
Imperial College London

Comparison: emerging vs conventional technologies

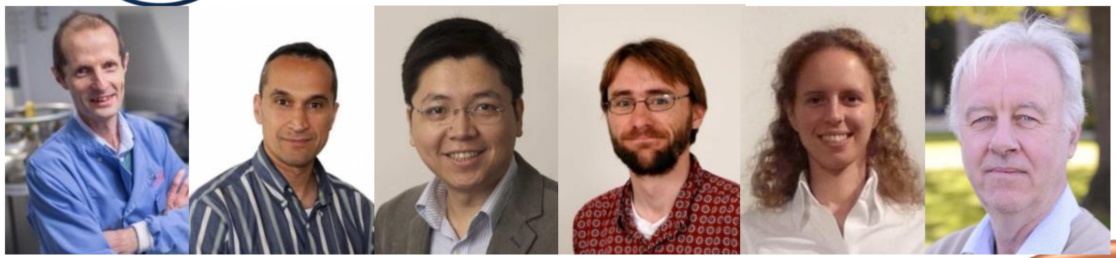
Metric	Emerging platform-based production	Conventional production
Speed*	weeks	years
Cost per dose	below 1 USD/dose	variable
Capital investment	tens of million USD	hundreds of million USD
Flexibility	wide product range	single product
Scalability	Scale-up and -out	Scale-up
Thermostability**	without cold chain	With cold chain

* speed for producing ~100,000 doses of a new vaccine after antigen identification

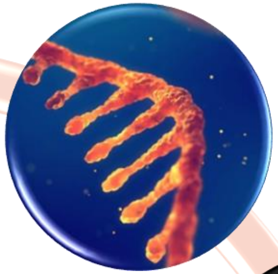
** thermostability of the product

Department of Health & Social Care
EPSRC Engineering and Physical Sciences Research Council
Imperial College London
Cranfield Manufacturing

Working together with stakeholders

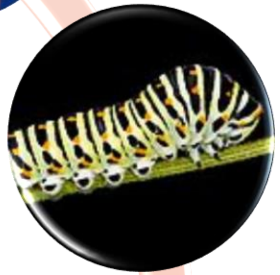


FVMR Hub



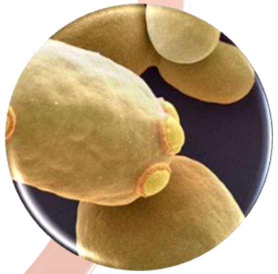
RNA in Uganda

Ebola, Marburg, Influenza, Rift Valley Fever, Lassa Fever



Baculovirus in Vietnam

Influenza



Yeast in Bangladesh

Human Papillomavirus, Rabies, Chikungunya

dcvmn
Developing Countries Vaccine Manufacturers Network

Further expansion and reach

Biological E. Limited
Celebrating Life Every Day

MINHAI

Adaptive, Modular, Responsive to Disease X.

Working together

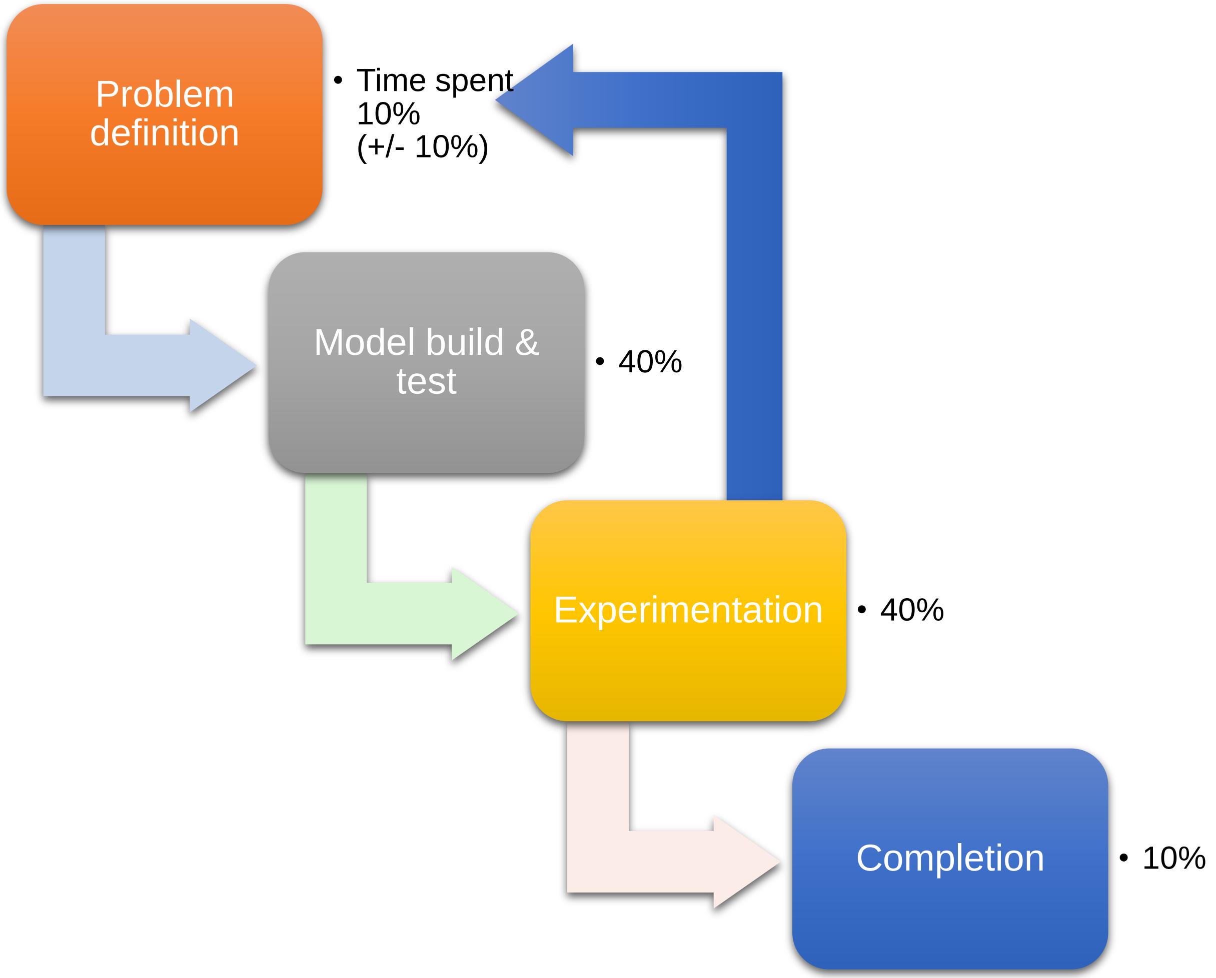
It is in our remit to work together with industry

Engage in confidential or collaborative projects demonstrating value

We use industrial strength tools to model and analyse cases

We use established project methodologies

1. Project initiation
2. Model build, verification and validation
3. Experimentation and analysis
4. Solution deployment/Implementation



Get in touch with me directly or Dr Ben Pierce b.pierce@imperial.ac.uk, our Hub's Manager

Thank you

/in/makatsoris

@mcharrismak

h.makatsoris@cranfield.ac.uk

https://www.cranfield.ac.uk/people/professor-harris-makatsoris-14023921