Planning and scheduling under digital QC constraints – the case of the clinical trials

Jiaxu Liu, Brahim Benyahia*

Department of Chemical engineering, Loughborough University LE11 3TU The United Kingdom

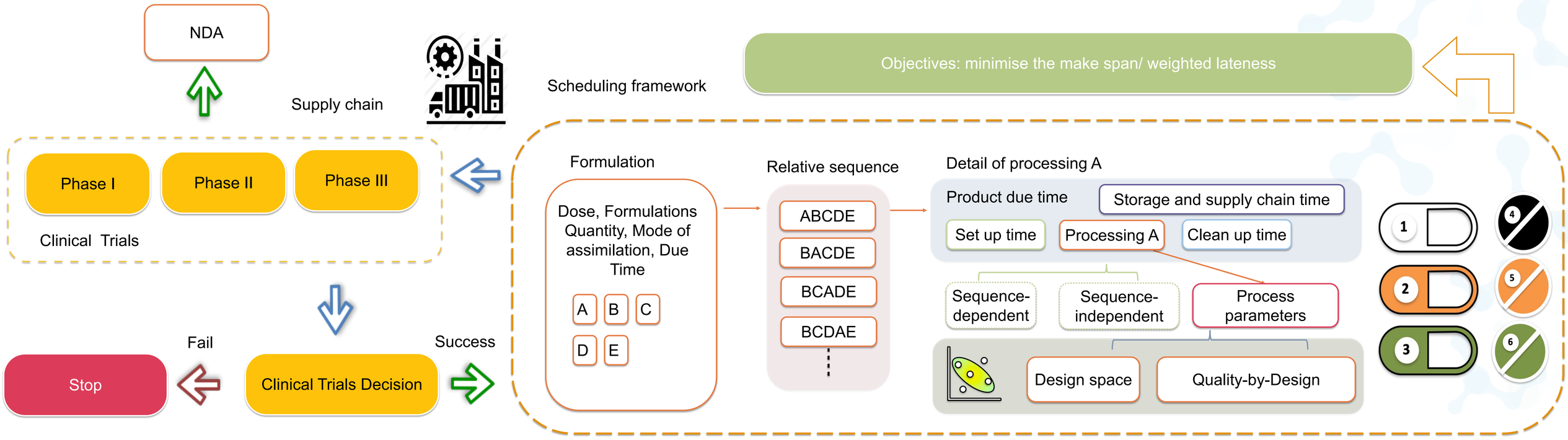
Email: b.benyahia@lboro.ac.uk, J.Liu2@lboro.ac.uk

1. Motivation and challenges

- **Efficient Resources Allocation:** Optimal allocation of resources, minimization of waste, and maximization of productivity leading to enhanced resilience and cost efficiency.
- **Optimized Inventory Management**: Effective planning and scheduling minimizes the risk of inventory shortages or surpluses, reducing associated costs.
- Incorporating quality constraints allows real time digital quality control
- Planning and scheduling may be a very complex multidimensional mixed integer nonlinear optimization problem.
- Effective planning and scheduling allows just in time production of different dose for clinical trials.

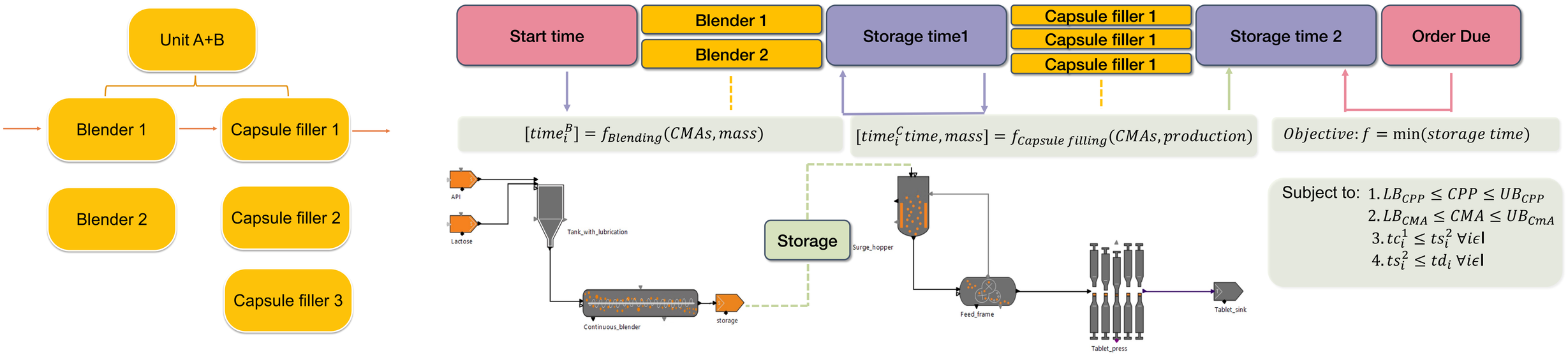
2. Use case

- A simple drug formulation (API + Excipient) is used to validate the proposed methodology
- A hypothetical demand signal with all required data (Dose, Formulations, Quantity, Mode of assimilation Due Time) are used to meet the clinical trials' needs. The digital optimization tool will deliver optimal production sequences. By manipulating CPPs, CMAs (from QbD), start time, and device choice, the cost function, here the storage time, is minimized while meeting the Digital QC requirements captured by the design space.



3. Case study

A Blending and capsule filling process



Subject to:
1. $LB_{CPP} \le CPP \le UB_{CPP}$
2. $LB_{CMA} \le CMA \le UB_{CmA}$
3. $tc_i^1 \le ts_i^2\ \forall i \epsilon I$
4. $ts_i^2 \le td_i\ \forall i \epsilon I$

$$Objective: f = \min \sum (t_{i,D} - f_{Blending}(Mass, production, Int_C) - f_{Cf/T}(production, Int_B) - t_{i,B})$$

Subject to:

Upper bounds and lower bounds:

$0 < t_{i,B}\ \forall i \epsilon I$
$0 < t_{i,C}\ \forall i \epsilon I$
$0 < Int_i^1 < 3\ \forall Int_i^1 \epsilon N_B$
$0 < Int_i^2 < 4\ \forall Int_i^2 \epsilon N_C$
$CPP_i^l \le CPP_i \le CPP_i^u$
$CMA_i^l \le CMA_i \le CMA_i^u$

Constraints:

$t_{i,B} + time_i^B \le t_{i,C}\ \forall i \epsilon I$
$t_{i,C} + time_i^C \le t_{i,d}\ \forall i \epsilon I$

Quality Constraints:

$CQA_i^l \le CQAi \le CQA_i^u$

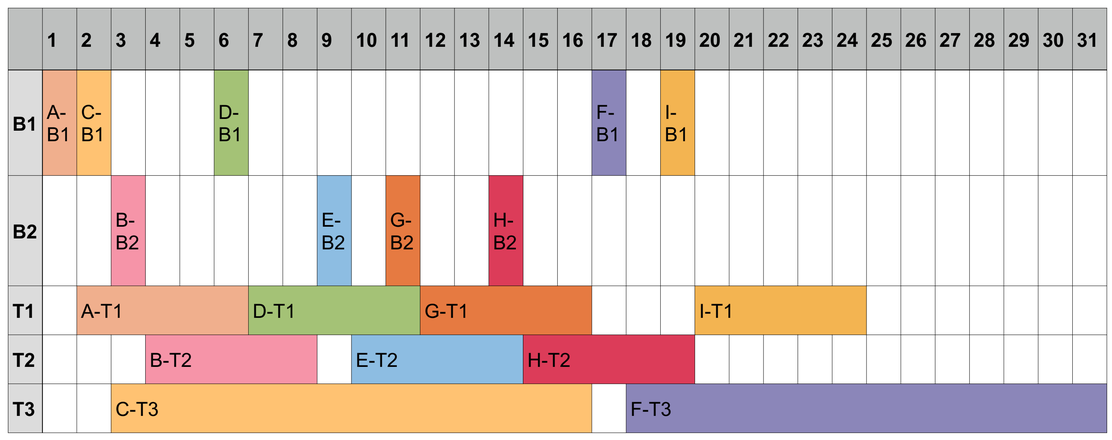
$t_{i,C}$ *Start time of capsule filling*
$t_{i,B}$ *Start time of Blending*
Int_i^1 *Capsule filler choice*
Int_i^2 *Blender choice*
$time_i^B$ *Blending time of order i*
$time_i^C$ *Capsule filling time of order i*
td_i *Order i due time*

Scheduling

Table 1 Demand profile

	A	B	C	D	E	F	G	H	I
API	0.05	0.07	0.09	0.11	0.13	0.15	0.17	0.19	0.21
Excipient	0.95	0.93	0.91	0.89	0.87	0.85	0.83	0.81	0.79
Production	50000	50000	50000	50000	50000	50000	50000	50000	50000
Demand Time	6	8	16	11	14	32	16	19	24

Table 2 Optimal schedule



An optimal scheduling was developed by minimizing the storage time

4. Conclusion and future work

- A framework for the planning and scheduling of clinical trials was proposed and validated based on hypothetical demand profiles. Compared to the current state of the art, the proposed methodology takes into consideration the Digital QC to guarantee built-in quality assurance.
- In future work, more complex and relevant drug formulations will be considered along with more effective global optimization stargies top enhance efficiency and accuracy.

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