How Can a Digital Twin Help Achieve Technical Efficiency? An Application to the French Medical Genomics Pilot Sequencing Platform Auragen

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Objective

Within the French Genomics Medicine Plan *(PFMG-2025)*, two multi-site medical genomic laboratories *(LBMMS)* have been launched to develop high-throughput genomic sequencing *[1]*. These two LBMMS, called AURAGEN and SeqOIA, are each composed on a sequencing facility, calculation, and archiving infrastructures. An operational chain of genomic sequencing configuration and supervision makes possible to manage targeted patients for rare diseases and cancers. The aim of this study is to develop a digital twin which can be used as an organizational analysis tool, to support decision-making helping to improve the performance of such platforms.

Methods

The model

- A hybrid Discrete-event simulation *(DES)* and Agent-Based *(the patient and the sample)* Modelling simulation *(ABM)* model was developed *[2,3]*. The first step towards building the model consisted in mapping the different steps of the process, identifying the actors and resources involved at each step and linking the activities to each other.
- Sample agents' flowchart model the LBMMS process with 3 main steps: sequencing and bioinformatics analysis, interpretation of sequencing's results, and an additional step to handle the various errors that could occur in the sequencing.
- Each state of the chart triggers DES micro-processes detailing the operations performed on patients and samples *(cf. Figures 1a and 1b)*.
- A set of rules was developed to model the flow management of samples and files in the LBMMS. Priority rules are coded using AnyLogic 'queue' blocks.
- The model was tested, validated, and sensitivity analyses were performed.

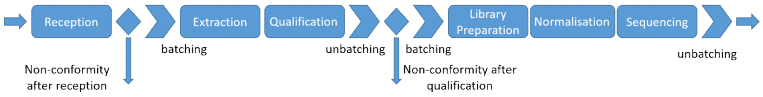

Figure 1a: Schematic DES diagram of the sequencing process

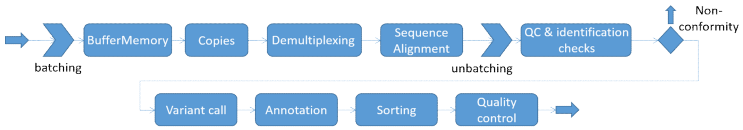

Figure 1b: Schematic DES diagram of the bio-informatics analysis process

The input

- The inputs used for the simulation are the laboratory usage data: the number of received prescriptions and received samples to calculate the admission rate of patients. Operation and waiting times have been evaluated on site.

The experiments

- *Validation*: we set the arrival rate of patients in the PFMG to match the volume of samples arriving on the platform each week *(200 rare disease samples and 10 cancer files)*.
- *Sensitivity analysis*: we set the arrival time between 1.43 and 4.05 patients per hours, with a step equals to 0.24 *(i.e. 8.3 files / week)*. These arrival times correspond to the reception of between 150 to 425 samples / week.
- *Ramp-up experiments [4]*: A stable phase of 365 days using the validation arrival rate; A linear arrival rate augmentation for a fixed period of 547 days; A final stable phase at the final arrival rate between 225 and 400 samples / week.

Results

The validation experiment

- The mean file lead time is 45.24 days *(sigma = 0.4)*, which is close to the treatment times of the laboratory. At several steps, the technicians occupation rate appears to be lower in the validation experiment than what they are in reality *(genotyping, preparation of libraries, etc.)*, showing that adjustments are still required.

The sensitivity analysis

- As expected, the technicians' occupation rate increases with the patient's arrival rate. A bottleneck appears to occur between the extraction and qualification steps *(cf. Figure 2)*. The performance indicators are negatively impacted by the saturation of the technicians' workflow, with a decrease in global number of files completed as the lead times go up *(cf. Figure 3)*.

The ramp-up experiment

- Performance indicators evolve as in the sensitivity analysis experiment, which would indicate that the laboratory evolves at near maximum capacity in terms of human resources. Ramp-up's performance indicators are presented in *Figure 4*.

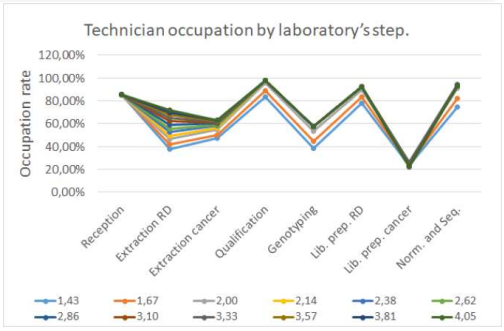

Figure 2: Sensitivity analysis (human resources occupation)

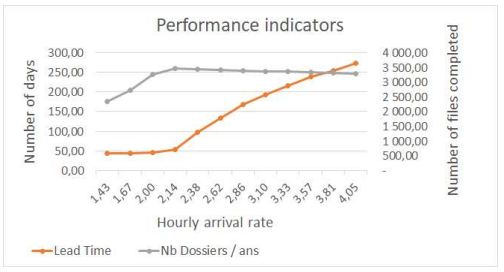

Figure 3: Sensitivity analysis (performance indicators)

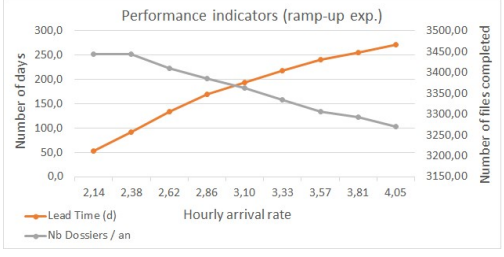

Figure 4: Ramp-up experiment (performance indicators)

Conclusions

- Further work is needed to bring the simulation model closer to the real system and better model the execution of each step. Additional experiments should be performed to test different scenarii of response to the ramp-up, like the addition of human and material resources. Modifications of the process are being implemented following technological evolutions, decreasing the time needed to perform different tasks, like the preparation of libraries, and increasing the technicians efficiency.

- Digital twin provides a decision-help to specify the total product function, to identify bottlenecks and additional resource requirements, to assess the impact of production planning modifications on performance indicators, and finally to achieve technical efficiency.

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