Simulation based Decision Support System for Pharmaceutical Quality Control Laboratory

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Abstract—A simulation based decision support system was developed with the aim of assisting laboratory managers in the tasks of resource planning and scheduling. Implemented as a discrete-event simulation model of a Quality Control Laboratory, this decision support tool was employed on a simulation study as a benchmarking platform to gather insight on the estimated performance of a new, state of the art facility. Estimated metrics such as sample time in system, analytical staff and equipment scheduled utilization rates were computed and analysed under alternative Governance Model scenarios, as to propose the best solution to be implemented in practice.

I. INTRODUCTION

The pharmaceutical industry is undergoing times of upheaval. Recent disruptive trends, such as rising R&D costs, shortening of drug patent lives and increasing regulatory scrutiny levels, have brought unprecedented challenges upon the industry. This conjuncture, in addition to the desire of reducing the time-to-market of new drugs, has prompted companies to pursue new standards of operational excellence.

To this end, organizations are adhering to the paradigm shift spurred on by the extension of the fourth industrial revolution to the pharmaceutical realm - Pharma 4.0 - an archetype of Industry 4.0 that promises to introduce a productivity leap across the industry’s key focus areas - drug discovery, development, manufacturing and marketing.

In the strive towards process optimization, Quality Control Laboratories (QCLs) have been identified as bottlenecks; logistics and manufacturing operations have commanded the attention of planners, who neglected the the relationship between drug manufacturing and Quality Control (QC). One of the main detracting factors to the integration of these two operational services is the contrast between the complexity of the analytical procedures and the basic tools employed by QCL managers, planning and sequencing their execution list, with ample room for improvement. In order to plan and schedule QCL resources efficiently, a robust computerized solution is required to minimize the time spent by supervisors and provide flexibility to react to the schedule changes and optimize the overall lab performance [1].

A. Related Work

The first applications of system modelling and simulation to QCLs date back to the early 1980s. In 1984 Janse and Kateman [2] developed a model of a small water quality monitoring laboratory and recognized the use of queueing theory based simulation to emulate QCL as a viable approach to investigate organizational features which could increase operational efficiency and be extended to other analytical domains. Later in the same decade, Klaessens et al. [3] presented a decision support system that combined historical data and a rule-based framework compiled from expert knowledge to derive, test and compare laboratory organizational structures. Additionally, the authors identified key QCL simulation model components and studied the impact of two key model parameters on the system’s performance: maximum allowed queue size per equipment and centralized vs. decentralized scheduling of analytical work.

II. QUALITY CONTROL LABORATORY MANAGEMENT

Quality Control Laboratories are a key unit of Contract Development and Manufacturing Organizations (CDMOs), assisting a wide range of services: drug manufacturing, development and validation of new analytical methods, particle engineering, scale-up of chemical processes and drug formulation studies. Despite its notorious significance, there is a industry-wide tendency to regard QC as a support service, instead of the primary importance status it merits.

Planning focuses on long-term decision making, based on expected demand levels, assessing whether the installed capacity is capable of meeting forecasts and, if necessary, procure the necessary resources ahead of time. In the short-term, as the planning horizon draws closer to the present date, more information is gradually made available; scheduling algorithms are employed to allocate specific jobs to machines and personnel, as well as sequencing their execution list, according a set of predetermined objectives. However, given the basic tools employed by QCL managers, planning and scheduling of QC work remains a manual, time consuming task, with ample room for improvement. In order to plan and schedule QCL resources efficiently, a robust computerized solution is required to minimize the time spent by supervisors and provide flexibility to react to the schedule changes and optimize the overall lab performance [1].

In this spirit, a data-driven decision support system was implemented in the form of discrete event simulation model of a QCL, developed with the aim of assisting laboratory managers in the tasks of resource planning and scheduling. Considering a new, state of the art facility as a case study, crucial workflows were modelled and vectors for improvement pinpointed. A simulation study was conducted to gather insight into the expected performance of the future laboratory, using the model as a testing platform to benchmark alternative Governance Models, scheduling heuristics and resource allocation policies.
The most comprehensive study in this field was conducted by Costigliola [4], who developed a simulation model of a QCL operating under a pharmaceutical CDMO that represents in detail the entire analytical work flow. This work again reinstated discrete event simulation as a viable means to emulate the operation of QC laboratories and. Having used Simio, the author created an expandable object library that was adapted and extended to meet the specifications of the QCL considered in this work.

B. Proposed Solution and Expected Benefits

The laboratory considered in this case study is still in the design phase. Typically, planning and scheduling tasks are approached in hierarchical fashion, with long-term planning taking precedence over short-term scheduling. However, given that the system is still under design, the planning and scheduling problems can benefit from being solved simultaneously in one model [5]. This methodology allows for scheduling constraints dependent on the planning guidelines (such as the number of analytical equipment and staff members) to be accounted for in the design stage, easing the task of identifying bottlenecks and addressing them at their root cause.

The proposed solution consists of a robust computerized tool, in the form of a discrete-event simulation model of the new QCL being designed. The model acts as a decision support system, assisting laboratory managers in the tasks of resource planning and scheduling of analytical work. Through the integration of the strategic (planning) and operational (scheduling) tasks into a coupled problem, the simulation model was used to compare and propose laboratory Governance Models (GMs) - the set of administrative guidelines according to which the laboratory operates, covering topics such as analyst staff work schedules, analytical samples’ priority levels and allocation of certain equipments to specific tasks - based on multi-criteria objectives, such as minimizing the sample time in system while ensuring that the analysts’ scheduled utilization level remains within specific intervals.

III. MODELLING QUALITY CONTROL WORKFLOWS

Ensuring that the simulation tool under development accurately emulates the real system is of fundamental importance. In order to fulfill this requirement, the design process was preceded by an information gathering stage, during which a well-founded conceptual vision of the system is acquired. As to expand the understanding of this system, a detailed description of the QC related workflows, as well as the context in which they occur, was sought. Doing so will allowed for schedulable tasks to be identified, in addition to uncovering vectors for improvement whose potential is not presently explored.

A. Analytical Work Overview

The diversity of analytical techniques employed in the pharmaceutical industry escalates the overall complexity of QC analysis. For the purpose of this project, the six most frequently performed analytical techniques were considered (listed below); they account for the critical mass of analytical work to be carried out in the QCL considered in this study.

- Differential Scanning Calorimetry (DSC)
- Gas Cromatography (GC)
- Karl Fischer Titration (KF)
- High Performance Liquid Cromatography (HPLC)
- Particle Size Analysis (PSA)
- X-Ray Powder Diffraction (XRPD)

The following work types were considered in this study:

- Raw Material (RM) tests
- Intermediate (IN) Product tests
- Final Product (FP) tests
- In-process Control (IPC) tests
- Change of Line (COL) tests
- Product Stability tests
- Fast Analysis (FA) and Miscellaneous tests

Samples compete for the same resources (analysts and equipment) and, depending on the type, have different validity and priority degrees. Given the characteristic slow response times of QCLs, delays in the analytical process increase the storage period and might lead to the degradation of the sample’s proprieties, impose setbacks on manufacturing batches and postpone the release of final products.

B. Process Modelling

The development of a useful planning and scheduling platform ought to be based on a set of consensual ground rules, agreed upon by the project stakeholders, developers and end users alike, that realistically captures all assumptions and requirements of the modelled processes.

Workflow and process modelling aims to capture and translate the conjunction of ongoing activities at a given organization, facilitating the understanding of key operational dependencies and levels of interaction across and within departments. This practice can act as the foundation to model and visualize current processes (as-is scope), allowing for vectors of improvement to be identified in the pursuit of improved, target processes (to-be scope).

With the aim of mitigating the imprecise nature of written prose, it is preferable to adopt the framework set by a standard graphical language, such as Business Process Modelling Notation (BPMN). BPMN is a flowcharting technique that further expands its reach by targeting both technical and business users, making use of a technical yet intuitive notation, capable of representing complex process semantics. This propriety has allowed for BPMN to be adopted across several industries, including the health and pharmaceutical sectors ([6], [7]), becoming one of the business modelling tools of choice when it comes to bridging the communication gap between process design, implementation and monitoring.

A comprehensive overview of BPMN can be found in [8].

Each sample type has its own associated workflow. In this article, the cases of IPC and product stability are presented in detailed fashion; These examples were chosen to showcase the contrasting dynamics of QC related tasks performed in QCL, as well as the intricate network of information and
material flow between the operational and support services found in pharmaceutical CDMO. The generic analysis workflow was also modelled in BPMN.

1) In-Process Control: Series of checks performed during production, in order to monitor and, if necessary, to adjust the process to ensure that the product conforms to its specifications. Samples intended for testing are collected from an ongoing production batch at predefined times and stages, identified as crucial points of the manufacturing procedure at which the product properties should conform to acceptable tolerance ranges. Following their retrieval and proper packaging, the samples are transported to the QCL, where they are to be processed. Once the sample arrives at the laboratory, the analyst registers this event by recording the sample Date Received timestamp under the appropriate database field and proceeds to prepare the sample and the equipment for the required analytical tests. Once the analysis has been conducted the result is verified by the analytical chemist and the result is passed on onto the production overseer. IPC workflow in BPMN notation is presented in figure 1.

Samples and the analytical methods according to which they ought to be analysed are allocated into the existing database when a planned order is assigned the ongoing process status. At this stage, a communication bridge is established between the production and QCL personnel, to keep track of the production batch and corresponding IPC samples status. Presently, such communication bridge is kept over telephone or e-mail. As a vector for improvement, the events of an order entering the ongoing process status and the collection of samples at the manufacturing line should trigger notifications, delivered to the QC laboratory through an organization-wide information system, allowing the required preparations to be conducted before the sample arrives and keep the analytical staff informed of potential delays on the production side.

2) Product Stability: Product stability tests are commissioned by the QC office. Upon receiving the product, a sample is retrieved and placed under the specified conditions for the prescribed exposure time. Once the exposure period has ended, the sample is ready to be tested within a certain time frame. Following the analysis, the stability study report is filled in with the results and sent to the QC office for approval and archiving purposes. Product stability analysis workflow in BPMN notation is presented in figure 2. The relatively large time frame during which the sample ought to be processed when compared to other samples types, along with the low priority assigned to stability tests often leads to these samples being pushed back in favour of higher priority work. A structured scheduling algorithm should take advantage of downtime opportunities to expedite stability tests, reducing the current average processing time of this sample type.

3) Generic Analysis: Samples must be prepared before being processed. Additionally, the equipment must be configured before conducting the analysis; this requires the analyst to calibrate the parameters according to information specified in the analytical method and, in the case of equipment requiring their suitability to be validated, to allocate the solutions used for this purpose. This step, confined to GCs and HPLCs, can be rather time-consuming, but does not require the analyst to be present during its execution. Once the system’s suitability has been checked by the analyst, the equipment is deemed available to analyse samples according to the ratified method. After the analysis has finished, the analyst must disassemble the equipment, collect the sample and process the results. This task is carried out at data processing workstations, and may involve hand and computer-assisted calculations. A representation of the generic analytical workflow in BPMN notation in Figure 3.

IV. QUALITY CONTROL LABORATORY SIMULATION MODEL

A. Simulation Study Scope

To cope with time-varying QC services, facility managers face the challenges of assembling a team composed of the appropriate number of analysts - working under adequate schedules - and ensuring that the available equipment pool

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Fig. 1. BPMN representation of In-Process Control Workflow

Fig. 2. BPMN representation of Product Stability Analysis Workflow

Fig. 3. BPMN representation of the Generic Analysis Workflow
is sufficient to process pending orders in a timely manner. Quality Control services at the CDMO considered in this study are arranged in branches, following an organizational structure that mimics the segmentation between four key operational areas. In the interest of preserving the identity of each branch, they are referred to as branches A, B, C and S in the context of this work. Undeterred by the fact that the pool of resources could theoretically be shared between branches, they operate contiguously under proprietary resource allocation policies. This structured self-governing regime fails to capitalize on possible fruitful benefits that a free-for-all approach could entail. Seizing the opportunity presented by the new facility, project stakeholders expressed the desire to compare the performance of the system under these two governance models (structured vs. free-for-all).

A scenario-based approach was devised to assess the impact of (1) breakdown by branches, (2) varying analyst schedule configurations (3) high-level sample allocation and scheduling policies on system performance.

The review of related work conducted in the context of this study divulged Discrete Event Systems (DES) as the state of the art paradigm for modelling and simulation of QC laboratories; being suitable to emulate the underlying dynamics and processing logic of the laboratory considered in this work, a DES paradigm was adopted. The discrete event simulation paradigm implemented in software packages such as Simio revolves around the definition of entities, that flow through the system along steps of an underlying logic framework. Entities are treated as objects that seize the capacity of resources for given periods of time, as they undergo some process. Under this object-oriented architecture, and in the context of QC laboratories, samples are modelled as entities, with equipment and analysts being treated as resources. Relevant model parameters include:

1) Demand Forecasting and Sample Arrival Rate: In the context of pharmaceutical QC labs, the demand for analytical work can be quantified as the time-varying volume of incoming samples. Project stakeholders expressed the desire to consider the scenario in which the new facility would receive a volume of samples similar to the total registered over the previous year across the laboratories whose services will be merged. Under this request, it is expected that new facility should be able to cope with a workload level akin to that of the last 12 months, allowing for the remaining capacity to be evaluated.

A data-driven sample generation framework was developed for simulation purposes. Raw data was extracted from the existing Laboratory Information Management System (LIMS) and processed to generate a set of samples with analogous incidence of sample types, analytical techniques and methods. The relative frequency of each occurring combination of analytical tests performed on unique samples was computed as the first step in the development of said framework. This routine was extended to all sample types, with detailed results for IPC being presented as a Pareto chart in Figure 4. The relative frequency effectively traduces the empirical probability of a given unique sample of type \( t \) being subjected to a specific mix of analytical tests, \( a \), from amongst the set of occurring possible combinations for that sample type, \( \{ A_t \} \). This probability can be expressed as:

\[
P(A_t = a \mid T = t)
\]

Having mapped the sets of analytical tests to be performed on individual samples of each sample type based on the underlying empirical distribution, the second stage of the sample generation engine covers the assignment of methods to each technique. A similar approach was followed: the relative frequency of each recorded method \( (m \in M) \) per sample type \( (t) \leftrightarrow \text{analytical test } (a) \) pairings was computed, resulting in several lookup tables for the probabilities:

\[
P(M = m \mid \{ t, a \})
\]

Raw data extracted from LIMS was used as the basis to derive a model that accurately emulates the arrival of samples, considering important factors such as the effect of seasonality, the actual inter-arrival times between consecutive samples and whether the samples arrive one at the time or grouped in a batch (Table 1).

Clustering analysis was conducted to assess the impact of seasonality on the arrival rate of samples. The K-means algorithm was employed to group months of the year into sets of similar workload level, quantified by the number of samples received over the course of each period of days. This analysis was performed for each sample type, considering up three workload classes - low, moderate and high. The effect of seasonality on the volume of samples received per month was found to be prevalent across all types (Figure 5), implying that reducing the arrival rate of each type to a yearly summary measure would neglect important system dynamics.

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### TABLE I

<table>
<thead>
<tr>
<th>Sample Type</th>
<th>Grouping</th>
<th>Workload Pattern</th>
<th>Shift Pattern</th>
<th>Workload Level</th>
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<tr>
<td>Change of Line</td>
<td>Batch</td>
<td>7 days/week</td>
<td>24 hours/day</td>
<td>3</td>
</tr>
<tr>
<td>Fast Analysis</td>
<td>Single</td>
<td>Mon. – Fri.</td>
<td>24 hours/day</td>
<td>3</td>
</tr>
<tr>
<td>Final Product</td>
<td>Batch</td>
<td>Mon. – Fri.</td>
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<td>2</td>
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<td>Single</td>
<td>7 days/week</td>
<td>24 hours/day</td>
<td>1</td>
</tr>
<tr>
<td>In-process Control</td>
<td>Single</td>
<td>7 days/week</td>
<td>24 hours/day</td>
<td>3</td>
</tr>
<tr>
<td>Raw Materials</td>
<td>Batch</td>
<td>Mon. – Fri.</td>
<td>08:00h. – 17:00h.</td>
<td>3</td>
</tr>
<tr>
<td>Substrate</td>
<td>Batch</td>
<td>1 day/week</td>
<td>08:00h. – 17:00h.</td>
<td>2</td>
</tr>
</tbody>
</table>

Fig. 4. Relative Frequency of Occurring Combinations of Analytical Tests on IPC Samples
The Poisson process is suitable for cases where the arriving entities are independent and identically distributed (IID) exponential random variables, with its application to a given stochastic arrival process depending on the following requisites:

1) Entities arrive one at the time
2) \( N(t + s) - N(t) \), the number of arrivals in the time interval \([t, t + s]\), is independent of \( \{N(u), 0 \leq u \leq t\} \)
3) The distribution of \( N(t + s) - N(t) \) is independent of \( t \) for all \( t, s \geq 0 \)

Property 1. is verified by sample types that arrive one at the time, but needs to be adapted to fit the case of types whose arrival occurs in batches.

Property 2. requires the number of arrivals in a given time interval \([t, t + s]\) to be independent of the number of arrivals in the earlier time intervals \([0, t]\), which holds true for the QCL under consideration.

Precondition 3. however, requires the samples’ arrival rate to be independent of the time of day, day of the week and other time-related factors. The integrity of this property was evaluated at day of the week level. This analysis was conducted for each sample type, over each specific arrival window (see Table I), per monthly workload level; summary statistics for the number of samples received per week day were computed and the mean values found to be approximately equal, suggesting that the arrival rate is fairly constant over each 24-hour period and thus not dependent on the day of the week. Detailed results for IPC samples are presented in Figure 6.

A simple modification was introduced to the Poisson process formulation to allow an extension of this methodology to suit the arrival of batches. A compound Poisson process was employed, given that the inter-arrival times of successive batches are IID exponential random variables. In this case, the arrival event triggers the sampling of a second distribution, that maps the relative frequency of occurring batch sizes.

Having hypothesized on theoretical and empirical grounds that the arrival of samples (both singular entities and grouped in batches) follows a Poisson process with exponentially distributed inter-arrival times, the rate \( \lambda \) of each process (per sample type \( \leftrightarrow \) monthly workload level pairing) was estimated using the maximum likelihood estimator, as described in [9]. The “quality” of the parameters was evaluated by means of two heuristic procedures: Density-Histogram and \( Q = Q \& \ P = P \) probability plots, again following the methodology presented in [9]. Detailed results Change of Line (batch arrival) samples are presented in Figures 7-8.

For simulation purposes, the agglutination of the arrival process properties i. and ii. - the arrival window - was modelled as the activation period of the entity sources of each sample type. An illustration of the underlying logic process of the sample generator framework presented in Figure 9. Under this representation, \( \lambda_k \{l, m, h\} \) denotes the arrival rate of sample type \( k \) for months of low, moderate or high workload. This notation is extensible to the batch size \( B_k \). For illustrative purposes, under Figure 9, sample types \( \{1, n\} \) arrive as single entities, whereas samples of type \( i \) arrive grouped in batches.

2) Analyst Staff: Ensuring that the right number of analysts is allocated to meet the time-varying amount of incoming samples is of paramount importance. In practice, the basic demand forecasting techniques employed by laboratory managers to estimate the arrival of samples over a period of time tend to be inaccurate, resulting in either under or overstaffed analyst teams. Both scenarios lead to negative repercussions, such as contributing to longer sample time-in-system (analyst understaffing) or lower scheduled utilisation
of human resources (analyst overstaffing). At the CDMO considered in this study, three analyst work-shift variants - detailed in Table II - are presently employed.

The field Rotating Teams refers to the number of distinct analyst teams operating under each regime, that alternate to comply with the mandatory resting periods between extended shifts.

3) Analytical Equipment: Analytical equipment play a key role as one of the fundamental resources in QC laboratories. Drawing a parallel between classic manufacturing systems theory and QCL operations, a strong duality is discernible amidst job shop machines [10] and analytical equipment: each device serves its own designated purpose, in the form of the analytical test it was designed to perform; additionally, similar equipment tend to be grouped according to the specific analysis they execute.

Data concerning the processing times of sample preparation, equipment setup, analysis runtime and data processing activities gathered by Costigliola in [4] was retrieved and used in this work.

Fig. 8. COL Samples, High Monthly Workload: Batch Size Empirical Cumulative Distribution

<table>
<thead>
<tr>
<th>Work-shift</th>
<th>Weekdays</th>
<th>Hours</th>
<th>Rotating Teams</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>7 days/week</td>
<td>08:00 - 20:00</td>
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<td>08:00 - 08:00</td>
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</tr>
<tr>
<td>#2</td>
<td>Mon. – Fri.</td>
<td>08:00 - 17:00</td>
<td>2</td>
</tr>
<tr>
<td>17:00 - 24:00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#3</td>
<td>Mon. – Fri.</td>
<td>08:00 - 17:00</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

TABLE II

ANALYST WORK-SHIFTS VARIANTS

B. Model Framework Overview

The QCL simulation model framework developed by Costigliola, presented in [4], was adapted and expanded to fulfil the requirements of this work. Namely, the hierarchical model library, originally comprised by the generic sample and generic equipment archetypes, was complemented with the addition of the generic sample source, part of the sample generator framework.

The scope of the model covers the entire sample flow within the laboratory, across 3 relevant stages: (1) moment of arrival (event triggered by the sample generator framework), (2) allocation to an equipment of the appropriate variant required to perform the analytical test, according to the scheduling policy implemented at equipment group level and (3) the actual analytical workflow, consisting of the steps detailed in Figure 3. The high-level model flowchart is depicted in Figure 10, and two snapshots of the 3D visualization are presented in Figure 11.

The QCL simulation model considers two assumptions:

1) The couple sample ↔ analytical test(s) was treated as a single entity. In practice, this translates into each sample being separated into as many instances as the total number of analytical tests it must undergo, and each instance being processed by an equipment of the respective kind.

2) System suitability is valid for 24 hours; during this period, a given equipment remains suitable to process samples according to the validated method. Once it expires, or a sample with a different method is scheduled to the processed that particular equipment, the suitability run must be carried-out beforehand.
Assumption i. is justifiable on the basis that it is common practice for analysts to do the same in practice. As for assumption ii., the value of 24 hours was agreed with project stakeholders and deemed as a reasonable compromise.

Sample sequencing and scheduling policies were enforced at two distinct levels: global equipment group and individual equipment queue. At global group level, an heuristic allocation rule that aims to reduce the impact of system suitability on the sample’s time in system was implemented. This rule consists on scanning the equipment pool for devices whose last validated method matches that of the sample to be scheduled and, provided that such equipment exists and its queue contains less samples than the maximum number allowed, the sample is allocated to that equipment; if no match is found, the scope of the search algorithm is widened to available but invalidated equipment. If no such equipment is found, the incoming sample is retained at the equipment group buffer, awaiting a change of state that enables it to be assigned. At individual equipment level, the maximum queue size \(Q_{\text{max}}\) was regarded as a tunable simulation parameter.

Two sample priority levels were considered: high, awarded exclusively to IPC samples, and regular, attributed to the remaining sample types; this binary decision variable was used as the primary entity sequencing rule.

As for the allocation of analysts to specific samples, the two alternative governance model frameworks were compared. Under the structured organizational policy, the breakdown of sample types per QC branch, suggested by project stakeholders and presented in Table III, was followed. Under the the free-for-all paradigm, the entire analyst staff available at the laboratory at a given time is allowed to process every sample, regardless of its type.

### C. Model Performance Metrics

To assess the behaviour of the model and estimate the real-world performance of the new laboratory under varying governance models, a set of key QCL performance metrics was gathered and compared between simulation runs. The considered metrics are listed below:

**Time in System**: Translates the total time that takes to process a given sample, form the moment of its arrival at the QCL until the analysis and subsequent data processing has finished.

**Throughput rate**: A measure of the capacity of the QCL to process the incoming volume of samples; it is computed by diving the number of processed samples by the total number of incoming samples.

**Equipment usage rate**: A measure of the fraction of time a given equipment spent performing active work, computed over 24 hours a day, 7 days per week.

**Analyst scheduled utilization**: A measure of the fraction of time that the analysts spend working, calculated over the corresponding total shift-time for each employee.

### V. SIMULATION STUDY

Validation of input parameters was performed by comparing the number of incoming samples created by the sample generator framework with the historical data referent to the previous year. To achieve this goal, the number of generated samples was logged over 20-year-long simulation runs. Results are presented in Figure 12; to conceal the real number of received samples, the axis tick marks were wilfully removed. The upper and lower bounds of one standard deviation of the mean are also presented, to convey the extent of variability between simulation runs. From the data presented in Figure 12, coupled with the goodness-of-fit tests that attest the decision of modelling the arrival of samples as Poisson processes, it is possible to conclude that the devised sample generator framework is capable of consistently creating accurate volumes of incoming samples, providing a solid foundation for simulation input data.

In order to compare Governance Models to be instilled at the new laboratory, a scenario-based approach was devised by assembling a set of alternative GMs, resulting from different configurations of the following model parameters:

1. Overall governance policy: structured vs. free-for-all
2. Total number of analysts and breakdown per work-shifts
3. Total number of devices per equipment variant
4. The maximum equipment queue size, \(Q_{\text{max}}\)

The results here presented stem from simulation runs spanning a period of 92 days, modelled as an hypothetical three month sequence of low-high-high workload levels, across all sample types.

**Time in System & Analyst Scheduled Utilization**

A benchmark of the average TiS registered under six alternative GMs is presented in Figure 14; for this comparison, three structured and three free-for-all GM were considered.

To allow for the effect of the governance policy to be considered independently of other parameters, the equipment
group scheduling rule was set as First in First Out for all six scenarios; moreover, the maximum equipment queue size was limited to two samples ($Q_{\text{max}} = 2$), and number of equipment available kept the same as currently planned in the rolling blueprint of the laboratory (Table IV). Additionally, the impact of scaling the number of analysts was assessed by comparing three tiers of employed staff.

For the purpose of assigning analysts to the existing work-shifts (Table II), information concerning the arrival regime of each sample type was considered in tandem with the sample types processed by each QC branch. Given that the sample types allocated to branch $A$ arrive continuously over 24 hours, analysts assigned to this branch should operate under work-shift #1. The type of work done by branches $B$ and $C$ does not require constant presence of analysts at the laboratory; therefore, analytical staff of these two branches was predominantly assigned to work-shift #2. Lastly, given its relatively lower priority, analysts performing stability work were appointed only to work-shift #3.

The mean relative time-savings achieved under free-for-all are presented in Table V. The allocation of analysts to work-shifts under each GM, along with the average scheduled utilization of employees, is detailed in Tables VI (structured GMs) and VII (free-for-all GMs). The field $\Sigma$ Analysts results from the rotating teams discussed in section IV-A.2.

- The two-tier sample priority policy results in In-process Control having the shortest TiS of all sample types; this imperative requisite, given the ties of IPC with manufacturing, was thus met. Under free-for-all guidelines all available analysts prioritize this type of work, reducing the overall time it takes to complete a production batch.
- The biggest reduction in TiS occurs in stability samples. Given the low priority of this type of work, it does not warrant a high number of dedicated analysts when a structured policy is considered. However, under free-for-all, provided that no higher priority samples are pending, analysts will leverage the opportunity to process stability samples, reducing the TiS of this sample type in around 80% and thus fulfilling another requisite expressed by project stakeholders.
- With the exception of GM #1, all five other GMs considered in this study result in scheduled utilization of the analyst staff under 70%, a requirement stated by project stakeholders. For the same volume of samples, increasing the number of analysts allows for lower TiS to be achieved, but reduces the scheduled utilization of human resources. This is understandable under the light that not all stages of the analysis workflow require the presence of the analyst; partial automation of the tasks that do require an analyst should be considered.
- Crucially, for the same number of analysts and available equipment, nearly every sample type is processed faster under free-for-all; The potential time-savings that can be achieved by transitioning to a free-for-all policy demonstrate that the performance of the laboratory can be improved through an organizational rearrangement, without the need to procure additional resources.

The results portrayed in Figure 14 can be interpreted as macro-level laboratory performance metrics. However, they

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**TABLE IV**

<table>
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<th>Equipment</th>
<th>DSC</th>
<th>GC</th>
<th>HPLC</th>
<th>KF</th>
<th>PSA</th>
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**TABLE V**

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<th>Sample Type</th>
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<th>GC</th>
<th>HPLC</th>
<th>KF</th>
<th>PSA</th>
<th>XRPD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>44</td>
<td>52</td>
<td>60</td>
<td>44</td>
<td>52</td>
<td>60</td>
</tr>
</tbody>
</table>

**TABLE VI**

<table>
<thead>
<tr>
<th>QC Branch</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>S</th>
<th>$\Sigma$ Analysts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6</td>
<td>1</td>
<td>6</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>2</td>
<td>6</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>2</td>
<td>6</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

**Fig. 13.** Comparison of Governance Model’s Mean Time in System, per Sample Type
fail to convey detailed insight into the TiS of each analytical test, a metric that warrants scrutiny as it can help to identify bottlenecks in the form of shortage of equipment of a given kind. Detailed results for analytical tests conducted on IPC samples are presented in Figure 14.

<table>
<thead>
<tr>
<th>Gov. Model</th>
<th>Work-Shift</th>
<th>Free-for-All</th>
<th>% Analysts</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>g1</td>
<td>8 (65.23%)</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>g2</td>
<td>n. a.</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>g3</td>
<td>12 (68.84%)</td>
<td>52</td>
</tr>
<tr>
<td>5</td>
<td>g2</td>
<td>n. a.</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>g3</td>
<td>12 (63.57%)</td>
<td>52</td>
</tr>
<tr>
<td>6</td>
<td>g1</td>
<td>12 (45.31%)</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>g2</td>
<td>n. a.</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>g3</td>
<td>12 (62.36%)</td>
<td>52</td>
</tr>
</tbody>
</table>

TABLE VII
Free-for-All Governance Models - Analytical Test Breakdown per Branch/Work-shift (Scheduled Utilization %)

Fig. 14. Comparison of Mean Time in System for IPC samples, per Analytical Test

The following conclusions can be drawn from the data presented in Figure 14:

- Equipment pools consisting of smaller number of equipment (PSA, DSC, KF, RX) benefit the most from operating under free-for-all. Since every analyst can process any sample, regardless of its type, a given equipment is less likely to be left idling while waiting for a designated analyst. If the laboratory managers decide to implement a structured governance policy, the planned equipment pool-sizes of PSA, DSC and KF should be increased.
- GC and HPLC tests are heavily conditioned by the need to perform system suitability runs before the analysis. This factor, combined with the large equipment pool-size of this two device variants, results in smaller benefits under a free-for-all governance policy. This is underlined by the fact that increasing the number of analysts results in small reductions of TiS.

Equipment Usage Rate

Detailed equipment usage rate statistics for the six considered GMs are presented in Table VIII, along with the maximum registered number of concurrent equipment in use during one simulation run.

<table>
<thead>
<tr>
<th>Gov. Model</th>
<th>DSC</th>
<th>GC</th>
<th>HPLC</th>
<th>KF</th>
<th>PSA</th>
<th>XRPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34.67 (3)</td>
<td>38.58 (34)</td>
<td>46.84 (57)</td>
<td>40.70 (4)</td>
<td>32.36 (12)</td>
<td>11.29 (1)</td>
</tr>
<tr>
<td>2</td>
<td>37.30 (3)</td>
<td>37.96 (35)</td>
<td>46.30 (56)</td>
<td>37.62 (4)</td>
<td>32.49 (12)</td>
<td>9.95 (1)</td>
</tr>
<tr>
<td>3</td>
<td>39.64 (3)</td>
<td>38.04 (35)</td>
<td>46.23 (57)</td>
<td>37.46 (4)</td>
<td>32.85 (12)</td>
<td>16.34 (1)</td>
</tr>
<tr>
<td>4</td>
<td>34.76 (3)</td>
<td>38.12 (35)</td>
<td>45.87 (54)</td>
<td>24.09 (4)</td>
<td>31.60 (12)</td>
<td>11.25 (1)</td>
</tr>
<tr>
<td>5</td>
<td>33.92 (3)</td>
<td>37.38 (35)</td>
<td>45.41 (53)</td>
<td>19.54 (4)</td>
<td>33.25 (12)</td>
<td>9.95 (1)</td>
</tr>
<tr>
<td>6</td>
<td>33.60 (3)</td>
<td>37.35 (35)</td>
<td>45.46 (51)</td>
<td>17.09 (4)</td>
<td>33.07 (12)</td>
<td>11.45 (1)</td>
</tr>
</tbody>
</table>

TABLE VIII
Equipment Usage Rate % (Maximum number of concurrent equipments in use)

HPLCs: At most, only 57 out of the total 100 HPLCs were used simultaneously, with this number dropping to 51 under GM #6. This value suggests that the initially planned capacity of 100 HPLCs was overestimated; average utilization is approximately 46%, a value that rises to 58.48% if only the 10 most used devices are considered.

GCs: Similar conclusions can be drawn for GCs as those stated for HPLC: out of the 50 devices planned to be installed, at most 35 were used concurrently. In the case of GCs, the 10 most used devices registered an utilization rate of 45.75%.

DSCs, KFs and PSAs: A similar pattern occurs for these three equipment variants: transitioning to a free-for-all governance policy reduces the equipment usage rate. This behaviour highlights what was stated when the utilization rate metric was introduced; since the analyst must interact with the equipment to start the analysis and collect the sample after it is finished, having a greater pool of analysts who can process a given sample reduces the time an equipment spends in idle state waiting to be tended by an analyst, increasing the time it is available for use.

XRPD: The single X-Ray device is deemed sufficient to cope with the volume of samples requiring this type of analytical test.

Sample Throughput

All six GM variants considered in the initial analysis achieved a throughput rate in excess of 98%; in practice, this implies that the laboratory was able to cope with the sequence of low-high-high monthly workloads without accumulating work-in-process at the end of the simulation run. The residual corresponds to the samples that were being processed / waiting in queue when the simulation was halted.

Equipment Queue Size

The impact of the maximum allowed equipment queue size, $Q_{max}$, was evaluated by comparing the average TiS...
between two GM variants that employ the same number of analysts: GM #2 (structured) and GM #5 (free-for-all).

Detailed analysis of the data presented in Figure 15 yields the following conclusions:

- Increasing $Q_{\text{max}}$ from 2 to 5 reduces the overall mean TiS across all sample types. The relative difference is more pronounced under the structured governance policy, which suggests that for GM#5 the TiS was already near the conceivable lower bound.
- Increasing $Q_{\text{max}}$ from 5 to 10, results in longer sample TiS; this trend is more noticeable for sample types that arrive grouped in batches (Change of Line, Final Product, Misc., Raw Materials and Stability), given that samples of the same batch are to be processed according to the same analytical method. In practice, it is more likely that the system suitability time window will expire before all samples placed in the queue of equipment with larger values of $Q_{\text{max}}$ can be processed; TiS will thus be higher for samples that have to wait for a second suitability run to be performed.

VI. CONCLUSIONS

The core goal of this project – developing a data-driven decision support system to assist Quality Control Laboratory managers in the tasks of resource planning and scheduling – was achieved through the implementation of a discrete-event simulation model. Said model was employed in the context of a real-world application, with a future state of the art facility currently under design posing as a case study. To ensure that the model provides a robust representation of the system under consideration, its behaviour was discussed with project stakeholders after each landmark development stage. Crucial workflows were modelled, ensuing vectors for improvement proposed, and a comprehensive simulation study was conducted to assess the impact of alternative Governance Models, scheduling heuristics and resource allocation policies on laboratory performance.

Through the approach of integrating strategic (planning) and operational (scheduling) constraints into the design stage of the laboratory, detailed considerations on the effect of model parameters on system performance were drawn and presented in Chapter V. As an overview, the factor with the highest impact on the considered performance metrics was found to be the high-level organizational policy; crucially, for the same allocated resources, free-for-all Governance Models resulted in lower values of sample Time in System. The time-savings when compared to a structure policy are substantial, amounting to 40% in the case of IPC samples, and 80% for stability work. Concerning the planned number of equipment to be installed at the new laboratory, the predicted capacity of HPLCs and GCs was found to be overestimated for the considered sample volume, but would provide ample room for increasing demand in the future; Increasing the size of the analyst staff contributed to lower sample Time in System, but the effect was not as pronounced as the shift resulting from changing the organizational policy. The effect of the maximum equipment queue size was found to be non-linear, with the Time in System increasing beyond a certain threshold.

In summary, the laboratory was found to be more responsive under a free-for-all framework, employing moderately sized equipment queues. An analyst staff in the range of 50 to 60 employees should be allocated to cope with short term demand for analytical work, resulting in analyst utilization levels in the interval of 50% to 70%, as requested by project stakeholders. It was also demonstrated that the performance of the laboratory can improve through an organizational shift free-for-all governance, without the need to procure additional resources.

REFERENCES