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A PROCESS SIMULATION MODEL FOR A HISTOPATHOLOGY LABORATORY

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ABSTRACT

Currently, although simulation models considering pathology departments exist, either in isolation or as part of a larger hospital model, they generally do not consider the individual steps within the histopathology process itself, instead adopting a high-level view of the histopathology laboratory. This prevents the study of policies that can improve efficiency, reduce the laboratory turnaround time (TAT), and/or reduce the staffing costs required to achieve a certain level of laboratory throughput. In this paper, we consider a discrete-event simulation model for a histopathology department at a hospital in the East of England, UK. Our model captures the histopathology department with a higher level of detail than currently exists in the literature, and address some specific simulation challenges that arise from such a modeling approach. We then demonstrate how our simulation model can be used to answer various management questions regarding staffing levels, TAT and the trade-offs between them.

1 INTRODUCTION

In the United Kingdom, capacity for histopathology requests has failed to keep up with growing demand; a report by Cancer Research UK (2016) showed an average yearly increase of 4.5% for histopathology requests but only 1.2–3% for consultant pathologists. One critical role of histopathologists is cancer screening, as malignancy typically creates noticeable changes in tissue appearance when viewed under a microscope. Despite this, in 2022/3, only 70.2% of NHS England patients requiring a cancer diagnosis received one within four weeks of referral (NHS England 2023). This combination of limited throughput capacity and increasing future demand highlights the need to maximize the efficiency of current histopathology resources. Other applications of histopathology include the diagnosis and grading of rejection in transplanted organs, the study of various diseases, and the posthumous diagnosis of myocardial infarction (Underwood 2016; Pai and Jairath 2019; Fishbein, Maclean, and Maroko 1978).

An important part of histopathology is the preparation of the tissue samples themselves, in the form of stained glass slides. This involves several stages in sequence, and various types of machine and staff resources. Therefore, it is important to have sufficiently detailed model to identify and reduce inefficiencies within and between stages. For example, Leeftink et al. (2016) used a five-stage model and found that performing tissue processing during the day, instead of only at night (except for priority specimens), had a significant effect on turnaround time (TAT), especially for small specimens. Brown (2004) found that a large portion of delays in their studied histopathology service were the result of staff scheduling; for example, tasks received at the end of the day would not be completed until the next day, with the largest non-value-added delays found in the reception and reporting stages.

On the other hand, the models of Leeftink et al. (2016) and Brown (2004) are not simulation models, and simulation models of histopathology processes in the literature generally do not capture individual processing steps in a high level of detail. For example, Burns, Konda, and Alvarado (2020) considered a Mohs surgery process; however, the pathology part of the process was reduced to only two seize-delay-

release blocks (one for the entirety of the laboratory work and one for analysis of the prepared sample). Similarly, Pongjetanapong et al. (2018) considered a cytology laboratory, but focused on the roles of pathologists, including non-clinical tasks such as meetings and teaching work, rather than on tasks related to slide preparation. This highlights the need for detailed models that can be used to effectively manage histopathology departments, with a focus on lab technician roles.

1.1 Contributions of This Paper

In this paper, we focus on the histopathology laboratory at Addenbrooke's Hospital, Cambridge, UK. Based on log records of histopathology requests and their progression through the various stages of the lab, the lab's standard operating procedure documents, and interviews with lab staff, a process model was created for estimating key performance indicators of the lab, which can be compared against guidelines set by the Royal College of Pathologists (RCPath). This was used to create a discrete-event simulation (DES) model for the lab, allowing for the estimation of various key performance indicators (KPIs) under various conditions. This, in turn, allows for the effect of various changes (e.g., staffing levels and scheduling) to be evaluated and compared. The development of the DES model revealed multiple challenges that were not considered in previous histopathology simulation models, which we address in this paper:

1. Staff members would often be required to perform tasks while not directly acting upon a specimen; e.g, returning to their "base" station after delivering a batch of specimens. (Section 4.2)
2. It is necessary to batch specimens based on their internal properties, e.g. the number of wax blocks produced by each specimen. An example of this is the batching of specimens for processing machine loading, where each processing machine has a fixed capacity of blocks. (Section 4.3)
3. Tasks may be gated with multiple trigger types; for example, processing machine runs can be started either at the end of a working day or when a full processing machine load is consolidated. (Section 4.3)
4. For short-term forecasting, we want to be able to start the simulation from a non-empty state, using data from the actual specimens currently within the histopathology department. The state of the specimens in the real system will be used to initialize the state of the corresponding specimens in the simulation model. (Section 4.5)
5. We want to be able to analyze certain sections of the simulation in isolation in addition to end-to-end analysis. For example, we may wish to estimate the hypothetical throughput of a histopathology stage in the absence of upstream bottlenecks. (Section 5.2)

1.2 Organization

The remainder of this paper is organized as follows. In Section 2, we provide a brief overview of histopathology in general, as well as previous efforts to build simulation models for histopathology. A summary of efforts to bring digital solutions to Addenbrooke's Hospital Histopathology laboratory in general is also provided. In Section 3, we provide an outline of the overall process flow in the histopathology laboratory and describe each high-level step in the process. Section 4 then describes the simulation model in detail, focusing on specific simulation challenges associated with the histopathology process. Section 5 demonstrates how our simulation model can be used to in scenario analysis to solve various management questions. Finally, concluding remarks are presented in Section 6.

2 BACKGROUND

Histopathology is the microscopic study of tissue samples, particularly for the study and diagnosis of disease. Although a number of histopathological processes exist for various purposes, for simplicity, we shall focus in this paper on routine Hematoxylin and Eosin (H&E) staining, which is by far the most common type of staining process in histopathology, whereas other stain types are typically requested only

after H&E staining is found to be insufficient for a particular specimen (King and King 1986). A typical pathway for a histopathology requests is as follows:

1. A specimen arrives at the lab's reception.
2. The specimen is cut into smaller pieces if necessary and the pieces are placed into small plastic cassettes.
3. The samples (in cassettes) are then chemically processed. Bone samples must first go through a process of decalcification.
4. Each sample is then embedded in paraffin wax, creating one wax block per cassette.
5. Slices are produced from each block using a microtome, and affixed to glass slides.
6. The slides are stained, labeled, and (depending on the laboratory) digitally scanned.
7. Histopathologists study the slides to generate the final report.

The above steps are explained in more detail in Section 3, focusing on routine H&E requests at the histopathology laboratory at Addenbrooke's Hospital.

The Royal College of Pathologists (RCPath) oversees the training of pathologists within the United Kingdom. RCPath has also published guidelines regarding the turnaround times (TAT) of histopathology requests — with the exclusion of some exceptional cases (Royal College of Pathologists 2013):

- 80% of cases should be reported within 7 calendar days.
- 90% of cases should be reported within 10 calendar days.

In the above guidelines, "reported" refers to the generation of a final local pathological report; cases referred for an external opinion are excluded. Additionally, the concept of a **lab TAT** was also included in our simulation outputs; this is the time from specimen reception to the completion of digital scanning and corresponds to the concept of "intradepartmental" TAT defined in Leeftink et al. (2016).

2.1 Discrete Event Simulation for Pathology

Although discrete event simulation (DES) models are commonly used to optimize processes, staffing, etc. in healthcare settings (Liu et al. 2020), few studies have focused on laboratory processes within the histopathology department.

Pongjetanapong et al. (2019) used a DES model (Pongjetanapong et al. 2018) to explore trade-offs between staffing levels and TAT in a pathology lab. It was found that even at the same average staffing level, measured as full-time equivalents (FTE), changing the staff schedule can significantly reduce TAT. Moreover, it was found that at a certain staffing threshold (dependent on the model parameters), a small increase in staffing can have a disproportionate effect on reducing TAT. However, the authors focus primarily on the roles of pathologists (including non-clinical roles) in a cytology setting, rather than that of lab technicians with respect to the preparation of slide images.

Burns, Konda, and Alvarado (2020) considered a DES model for a Mohs surgical clinic, where each layer of removed skin needs to be inspected for cancer. The simulation was implemented in Arena, with processes for skin excision, pathology technician work, sample analysis, and skin repair. If a positive result is returned, the patient undergoes an additional round of skin removal, thus creating a conditional loop in the modeled process. For optimization purposes, a weighted score was used based on throughput, patient waiting time, and staff overtime. It was found that the optimal scheduling strategy for Mohs surgery depended on both the number of patients and the weights used by the clinic to produce the combined score. However, a key limitation of this study was that the entire "pathology technician work" step was reduced to a single Process block, thus abstracting away the complexities of the histopathology process. Furthermore, due to the unique time requirements of Mohs surgery, the histopathology processes involved are very different than those for routine H&E staining and analysis.

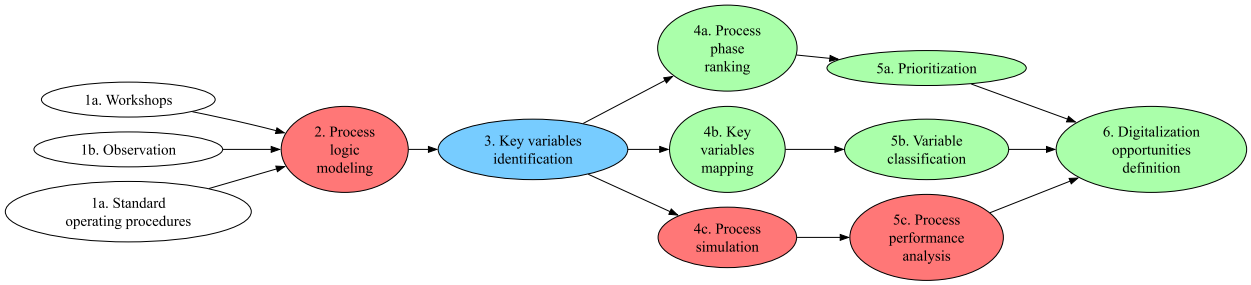

Figure 1: Research process steps for defining digitalization opportunities in a healthcare setting, as identified by Moretti et al. (2023). For the histopathology department considered in this paper, the steps in green were described in detail by Moretti et al. (2023), while the step in blue was covered by Mukherjee et al. (2023). Steps in red are addressed in the current paper.

2.2 Previous Studies at Addenbrooke's Hospital Histopathology

In Moretti et al. (2023), we identified a number of research process steps for bringing digital solutions to the histopathology lab. These steps and their dependencies are shown in Figure 1, with the steps covered in Moretti et al. (2023) highlighted in green. Notably, Steps 2 (Process logic modeling), 4c (Process simulation), and 5c (Process performance analysis) were not considered. In Mukherjee et al. (2023), process identification yielded a series of steps for the routine histopathology process, but these steps were not modeled in sufficient detail to complete Step 2 in full. Therefore, we shall aim to address these missing steps (highlighted in red in Fig 1) in the current paper.

As part of Step 3, a set of key performance indicators (KPIs) were identified in Mukherjee et al. (2023) for different aspects of a potential hospital digital twin, namely the Fabric, Process, Resources, and Supply Chain aspects. As this paper focuses on the Process aspect, we shall focus on the KPIs relevant to that aspect, especially throughput and TAT.

3 PROCESS IDENTIFICATION

As shown in Figure1, prerequisites for process logic modeling included workshops, lab observations, and the review of standard operating procedure (SOP) documents provided by the histopathology lab. Based on the information gathered in these steps, the following process stages were identified:

1. **Specimen Reception:** specimens are received and sorted by specialization and priority. They are then booked into the system and patient information cross-checked. Certain specimens may require additional investigation time due to missing or incorrect information.
2. **Cut-up:** specimens are cut and inserted into plastic cassettes ("blocks") for later embedding. Simple biopsies are handled by biomedical staff (BMS), whereas other cases are handled by one specialist and one cut-up assistant. Note, however, that our current model only considers the availability of cut-up assistants.
3. **Processing**
   (a) **Decalcification:** for some specimens, decalcification is required to make the sample soft enough for microtomy. For some cases, an acid bath inside an oven is sufficient, whereas bone marrow specimens are placed in a bone station which add agitation.
   (b) **Processing machine:** each block undergoes a series of chemical treatments in a processing machine. The duration depends on the type of specimen, thus only specimens sharing the same processing regimen can be batched.
   (c) **Embedding and trimming:** the blocks are embedded in paraffin wax and excess wax is trimmed.

4. **Microtomy:** slices are taken from each block and affixed to glass slides. A temporary label is affixed to each slide; this is required as the permanent label can only be applied after staining.
5. **Staining:** the glass slides are stained using H&E and a coverslip applied. For mega-sized slides, the coverslipping step is manual; for regular slides, both staining and coverslipping is performed by machine.
6. **Labelling:** permanent labels are affixed to each slide. This stage is handled by the microtomy staff.
7. **Scanning:** slides are batched and scanned.
8. **Block and quality check:** each specimen is checked to ensure all required blocks and slides have been stained and scanned; each slide is also checked for quality.
9. **Reporting:** a pathologist reviews the slide scans and prepares a diagnostic report.

The high-level process is entirely linear, with each specimen completing each of the nine stages in sequence. For the purpose of defining KPIs, we shall consider all nine steps for the **overall** TAT and throughput, and the first eight steps only for **lab** TAT and throughput.

4 SIMULATION MODEL

In this paper, a DES model was created in Arena (Kelton et al. 2024) to estimate key performance indicators (KPIs) of the histopathology lab. Specimen arrivals were modeled as two time-inhomogeneous Poisson processes, for cancer and non-cancer specimens, respectively, with hourly rates — this is accomplished by random filtering of ordinary Poisson processes. Staffing levels were set on a half-hourly basis using Arena's Schedule module, whereas machine resources were assumed to be constant. Finally, triangular distributions were estimated for each task in the simulation model, except for certain machine tasks of fixed duration, e.g. processing machine programs. These durations are based on information gathered from SOP documents and interviewing lab staff.

For organization purposes, a submodel was created for each stage of the histopathology process. Additional submodels were used for initializing the machine resource levels, updating the arrival rate of specimens every hour, assigning the initial attribute values of each specimen, preloading the simulation state with specimens already in progress, recording the number of specimens completed each day. Further details of key parts of our simulation model are described below.

4.1 Specimen Attributes and Object Hierarchy

In our simulation model, each specimen yields a number of blocks, which each in turn yields a number of slides. However, we enforce the policy that all assets from the same specimen are moved between stages together; thus all delivery steps in our simulation model act only at the specimen level. Key specimen attributes in our simulation model include the following:

- **isCancerPathway**: yes or no; affects probability distribution of the Priority attribute value.
- **SpecimenID**: unique integer for each specimen.
- **isInternal**: yes or no; affects branching routes and task durations in the Specimen Reception stage. Yes for specimens from Addenbrooke's Hospital and the nearby Royal Papworth Hospital, which uses a compatible electronic health record system.
- **Priority**: urgent specimens are not batched during delivery between stages, and use a shorter machine program in the Processing stage.
- **Cutup Type**: three types; affects what staff type performs the cut-up and what block types are produced.
- **Block Type**: three types; affects the number of blocks produced per specimen.
- **NumBlocks**: number of blocks produced from a specimen; affects microtomy duration.
- **TotalSlides**: the total number of slides produced from a specimen; computed by aggregating slide counts for each block produced from the specimen.

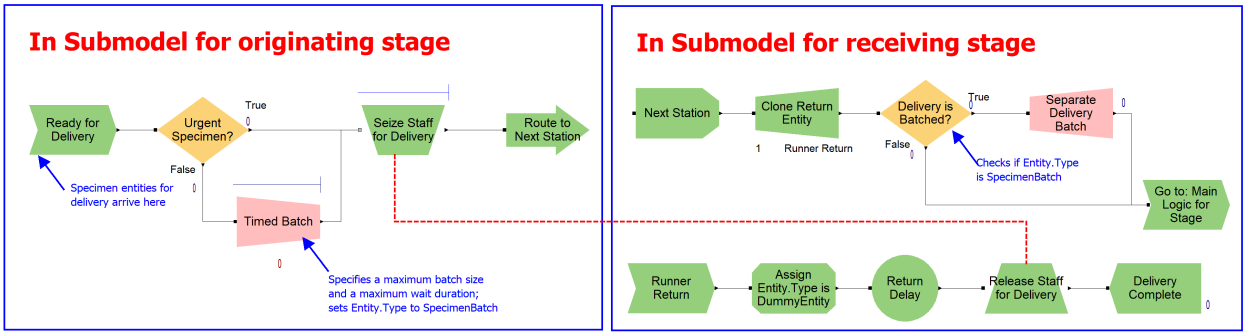

Figure 2: Arena simulation blocks for delivering specimens between process stages, using an Adjustable Batch with a time limit.

Other attributes include start and end timestamps for each stage of the histopathology process.

4.2 Specimen Delivery Between Stages

In general, specimens are delivered between stages by a staff member from the first stage. To model the round trip of these staff, a Clone module is used to generate a "Runner Return" task for the runner staff, while the specimen continues processing in the new stage. Additionally, non-urgent specimens are conditionally batched (using an Adjustable Batch module), with a maximum wait time for forming a batch. On the other hand, urgent specimens are delivered individually to avoid batching delays. A graphical representation of the runner logic is shown in Figure 2.

4.3 Time-Triggered Batch Jobs

The histopathology process contains two lengthy machine tasks, namely decalcification (bone station variant) and processing machine runs. In both cases, the machine (a bone station or processing machine) used in the task accepts batches of blocks; however, policy states that blocks belonging to the same specimen should not be split between multiple batches. Additionally, only specimens requiring the same processing machine program (urgent, small surgical blocks, large surgical blocks, or megas) can be batched at the processing machine step.

Completed batches are held until the end of the day, while any remaining specimens at the end of the day are also placed into a (partial) batch. Finally, all batches are released for machine loading at the end of the working day. However, completed **urgent** specimen batches do not wait for this end-of-day signal and are loaded immediately. (Note that this applies to the processing machine step only as urgent specimens never require decalcification.)

The process logic for batching specimens for processing machine loading is shown in Figure 3. Firstly, Hold queues are used to hold specimens for batching, with one queue per processing machine program. Specimens are removed from these Hold queues using the logic in the bottom box; additionally, any specimens still in the Hold queues at the end of the working day are also placed in an appropriate end-of-day batch. Finally, all specimen batches are forwarded to the "Processing Machine Job" label to initiate machine loading (after a final hold for an end-of-day time Signal in the case of non-urgent specimens).

An explanation of the bottom box in Figure 3 is as follows. One Batcher entity is created for each processing machine queue. The Batcher entity waits until the total number of blocks for the queued specimens exceed the set limit (either the machine capacity or a lower limit for urgent specimens); this is done using the **SAQUE** Arena function (sum of attribute of queue elements). The Batcher entity then enters a loop that removes specimens from the processing machine queue until the queue is empty or the next specimen contains too many blocks to fit in the current batch:

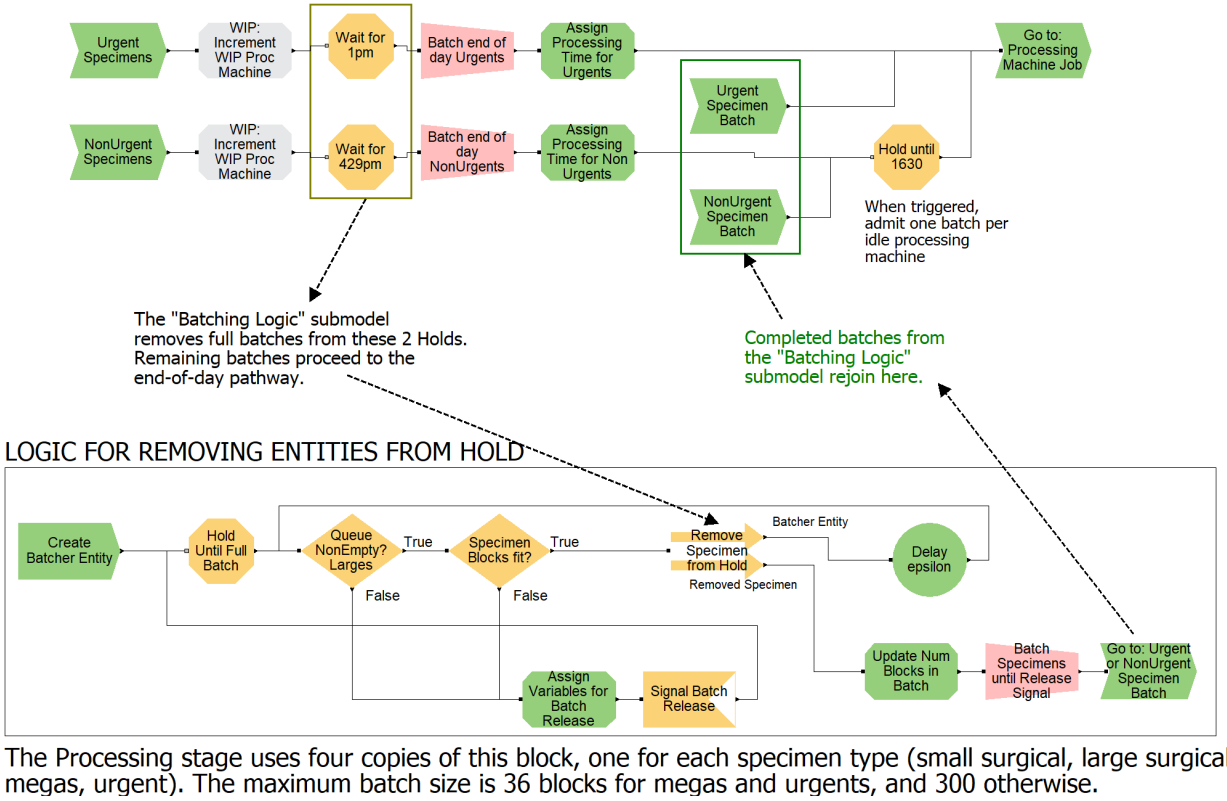

Figure 3: Arena simulation blocks for creating specimen batches to load in a processing machine (subject to the maximum block capacity), forming part of the Processing stage.

- The current batch size is stored in a variable.
- The number of blocks in the specimen at the head of the queue can be obtained using the **AQUE** Arena function with a 1 in the position argument and "**NSYM**(NumBlocks)" in the attribute argument.
- The sum of the two values above are compared against the batching limit.

Note that upon each removal of a specimen from the processing machine queue, an arbitrarily small delay (e.g., 10 microseconds) is added to the Batcher entity path. This ensures that the bottom path from the Remove block, which updates the current batch size and enqueues the specimen for the actual batch creation step (pink node labeled "Batch until Release Signal"), executes before the next iteration of the Batcher entity loop (dotted box).

Finally, if either exit condition of the Batcher entity loop (dotted box) is triggered, a Signal is triggered to released the batched specimens from the "Batch until Release Signal" node, and the current batch size variable is reset to zero.

4.4 Specimen Task Durations Based on the Number of Blocks or Slides

For certain tasks, while the task itself is modeled at the specimen level, the task duration depends on the number of blocks or slides belonging to that specimen. One example of this is slide labeling, where each slide requires several seconds and the total time to label all slides for a specimen must be derived. This is shown in Figure 4. Firstly, an entity is created for each slide belonging to the specimen, by creating "TotalSlides - 1" additional copies. Then, the labeling duration is sampled from a random distribution for each individual slide. Finally, the slides are collated (using the specimen ID for matching) and the total labeling duration is computed using the **SAG** Arena function (sum of attribute of group's entities).

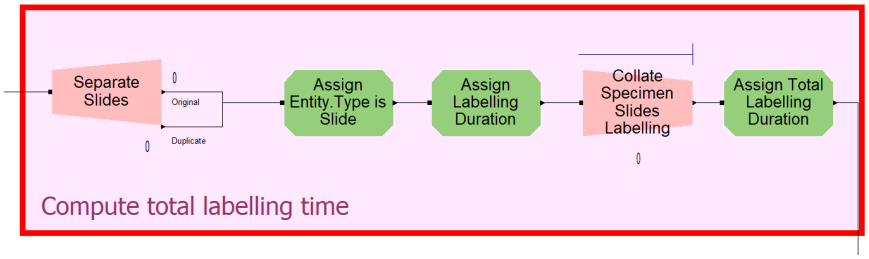

Figure 4: Arena simulation blocks for computing the total labeling duration, part of the Labeling stage.

4.5 Hot Start

To bootstrap a non-empty initial simulation state, specimens can be injected at the beginning of each stage, with attribute values read from an Excel workbook (with one sheet per stage). For scenarios where exact timestamps of completed stages are not available for hot-start specimens, one strategy we adopted was to use optimistic estimates based on assuming no queueing delays between tasks, whereas the usual distributions were applied to estimate the durations of completed tasks.

5 SCENARIO ANALYSIS

5.1 Effect of Additional Staffing on Lab TAT

We consider the effect of adding one staff member to the simulation model on the mean lab TAT, based on the type of staff member added. Note that staff roles in the simulation model mostly correspond to the process stages outlined in Section 3; however, cut-up may be performed by a biomedical staff (BMS) or a cut-up assistant depending on the type of cut-up, and slide labeling is performed by microtomy staff. For consistency, it is assumed that the extra staff member works from 9am to 5pm in all scenarios with a lunch break from 12:30pm to 1:30pm.

The mean lab TAT for each scenario is shown in Figure 5. Additionally, 95% confidence intervals for each mean are shown based on the results of ten simulation runs each. It is demonstrated that assigning the extra staff member to Microtomy results in the largest reduction in lab TAT, and in fact the only statistically significant reduction in lab TAT based on the confidence intervals. This example shows that our simulation model is effective at identifying the best use of limited staff resources.

5.2 Isolating a Sequence of Steps

A question received from Addenbrooke's Hospital's histopathology lab was "How many hours will it take processing staff to embed N wax blocks"? This required isolating the sequence of steps in the histopathology process related to block embedding, by adding temporary insertion and exit points for the simulation (as shown in Figure 6) and disabling regular specimen arrivals to the system. In Figure 6, the role of the "Embedding Entry Analysis" submodel is to insert N wax blocks into the system at time 0, and the role of the "Quick Exit" submodel is to immediately discard any arriving wax blocks. Since the simulation halts automatically when all entities have left the system, the final state of the simulation clock is the number of hours required for all N wax blocks to be processed, thus answering the question posed.

Finally, for the purpose of this scenario, staff shifts are ignored and the number of processing staff is held constant. This means that the simulation result defines a lower bound on the time required to complete the task (in the full model delays are caused by upstream bottlenecks, staff scheduling, and additional tasks assigned to processing staff), and its expected value is simply Nt/m where m is the number of processing staff and t is the mean time to embed each individual block. However, the *distribution* of this time value depends on the distribution of the time required to embed each individual wax block.

Figure 5: Mean lab TAT for various scenarios, in which each scenario other than the base scenario contains one additional staff member of the specified type. Error bars represent the 95% confidence interval of the mean based on ten simulation runs.

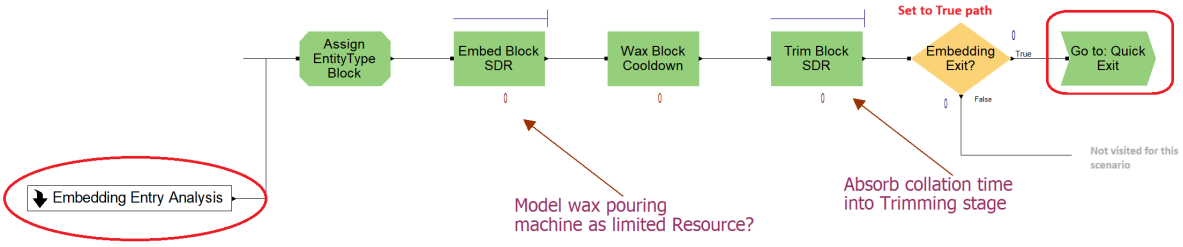

Figure 6: Part of the process logic for the Processing stage, showing the sequence of steps related to wax block embedding and the additional nodes (circled in red) added to isolate these steps for scenario analysis.

Figure 7 shows the results for $N = 400$ blocks, for two to five processing staff, with a total of 500 simulation replications for each histogram. The results are consistent with a single staff being able to process 40 blocks in one hour, or each block requiring an average of 90 seconds of staff time, as configured in our model's simulation parameters (60 seconds for embedding and 30 seconds for trimming excess wax from the block). The embedding times in all four cases are consistent with a normal distribution (Shapiro-Wilk test with $p > 0.05$).

6 CONCLUDING REMARKS

In this paper, we present a simulation model for a histopathology department, based on that of Addenbrooke's Hospital in Cambridge, UK. The simulation model adopted a detailed view of laboratory tasks not previously

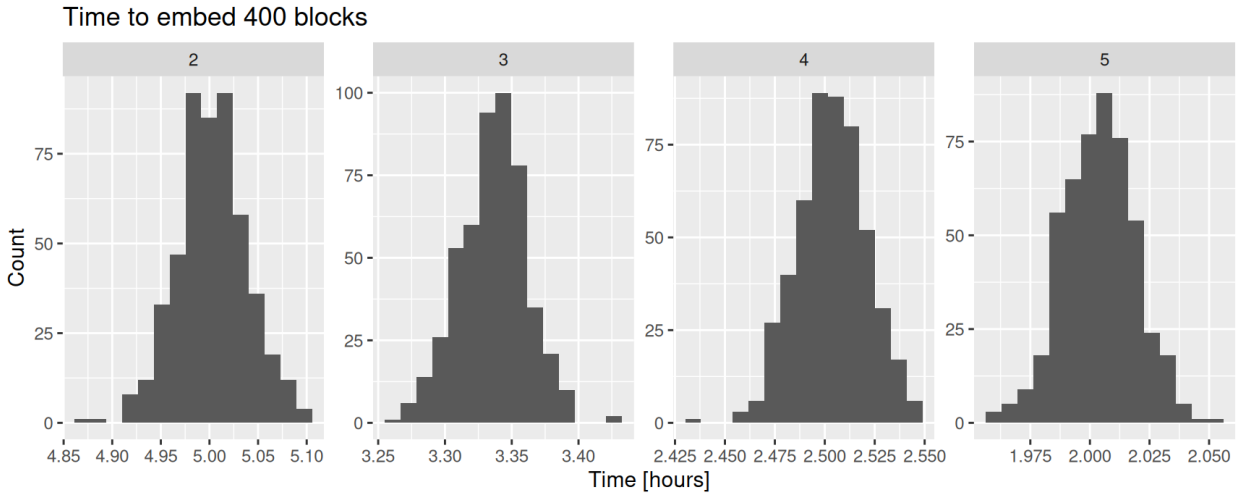

Figure 7: Time to embed 400 wax blocks, with respect to the number of processing staff (shown in the subplot title bars). "Count" represents the number of simulation results within each bin of the histogram, out of 500 replications total for each scenario.

seen in the literature, particularly in the preparation of routine H&E stained slides for pathological analysis. This allows the model to more effectively address questions related to resource management within the histopathology lab. The methodology in this paper also compliments an earlier paper (Moretti et al. 2023) on digitization opportunities in the histopathology department by considering research process steps (as outlined in Figure 1) described in the earlier paper but not addressed therein.

The more detailed view of laboratory processes in this study also led to various simulation challenges, which this paper addresses. One of the more difficult stages to model was the Processing stage, due to the need for batching specimens based on their number of blocks, waiting until a specific time to load the batches into processing machines, and the creation of end-of-day partial batches. The solutions presented in this paper may prove useful in the creation of other simulation models with similar batching-related modeling challenges.

One shortcoming of the current simulation model implementation in Arena is the limited ability to execute the same model with different parameter settings. While Arena's Process Analyzer is useful in some cases where a small number of non-array variables need to be changed between different scenarios, it does not provide a good interface for modifying array values, e.g. defining changing staffing levels over the course of a day. In fact, to produce Figure 5 in this paper, a separate copy of the simulation model was created for each scenario, despite the only difference being the filename used for the input parameter Excel file.

Another limitation of Arena that required a workaround when building our simulation model is that Arena is not object-oriented, meaning that it is difficult to define a composition relationship between specimen, blocks, and slides in our model. In contrast, in an object-oriented model, a specimen can contain a list of blocks that persist in memory when the blocks are batched, and are only disposed of when the parent specimen is itself disposed. Thus, Block entities are only created once, any task that operates at the block level can directly access a specimen's blocks. In contrast, Arena requires multiple Separate and Batch logic blocks to switch between the specimen/wax block/slide level, and blocks/slides are lost upon batching.

Finally, future work to improve the simulation model may include the following:

- Specimen arrivals are currently modeled using time-varying Poisson processes; in reality, they are delivered to reception in batches by couriers. More detailed analysis of the specimen arrival process

in the future may involve combining the current histopathology lab model with a specimen logistics model to create a *federated* simulation model with multiple sub-units.

- Specializations are currently ignored; for example, different tissue types may require different staff, particularly at the Cut-up and Reporting stages. Note that, as previously stated in Section 3, the currently modeling of the Cut-up stage does not consider the role of specialists at all.
- Specimen priority is not fully implemented in the current model, while some logic associated with urgent specimens exist, most task queues in the simulation model are simple first-in-first-out (FIFO) queues. Changing the queue disciplines to priority-based may improve modeling accuracy.

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