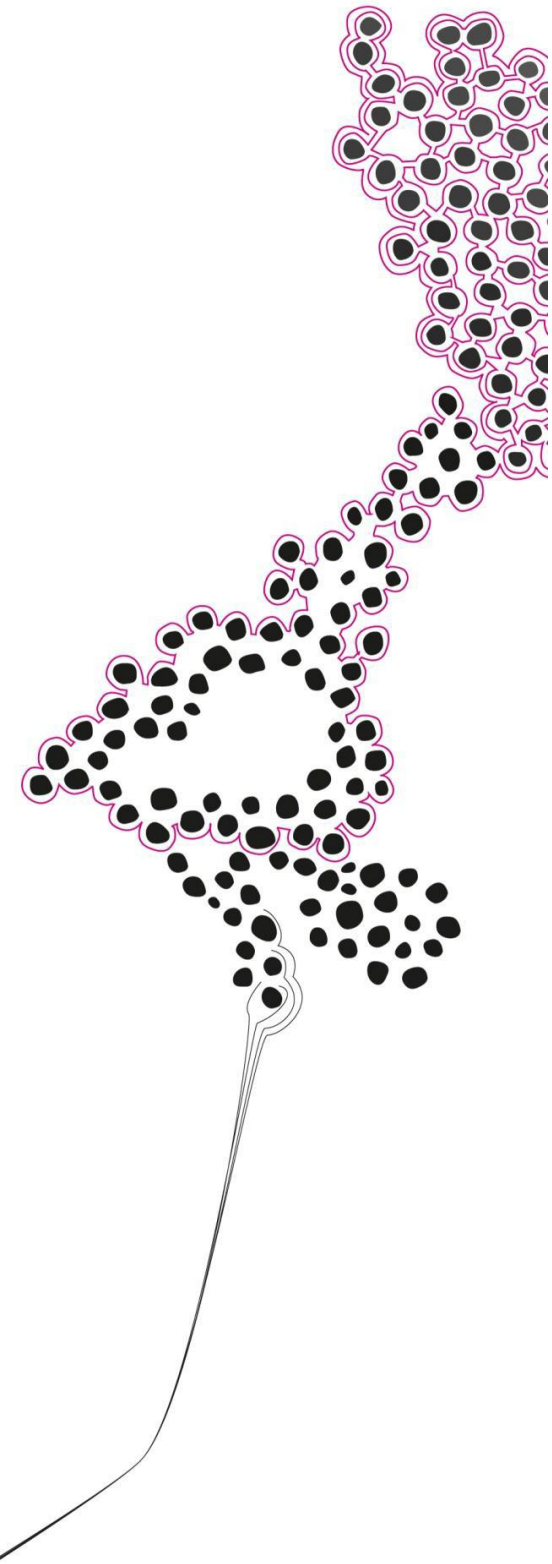

Simulating the histology laboratory

Evaluation of organizational interventions for the histology laboratory through the development of a generalizable Discrete-Event simulation model.

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UNIVERSITY OF TWENTE.

LABPON
Laboratorium Pathologie Oost-Nederland

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Management Summary

LabPON is an innovative and large-scale histopathological laboratory, with the mission to deliver fast, effective and good services to doctors and hospitals. In line with this mission, the organization strives to be progressive and innovative, which has led to the organization becoming a pioneer in the field and pushing the boundaries of the status quo. For example, LabPON is one of the first laboratories to have implemented the scanning of slides, enabling a fully digitized clinical workflow. With regards to logistics, several assessments and lean projects have been executed to improve the laboratory workflow. However, despite these projects and the application of several logistical principles, the management observes that inexplicable delays occur frequently. These delays can take up to several days, causing patients to have to wait for a diagnosis and delaying treatment.

Although the management had several ideas to solve the occurrence of delays, it became apparent that insufficient insight into the logistical process existed to substantiate implementation. For this reason, LabPON has requested the execution of the research delineated in the thesis. The objective of this study is therefor to provide insights into the logistical processes of the histology laboratory at LabPON, and to evaluate what organizational interventions are possible to reduce the process variability and throughput time.

To provide an insight into the laboratory, a context analysis has been performed followed by an in-depth data analysis. The data analysis revealed that long waiting times occur between embedding and sectioning. Roughly half the daily demand is found to enter the laboratory at 15:00, resulting in high work pressure at grossing in the afternoon and overloaded Express Tissue Processors at the beginning of the next day. In the morning, the batch resulting from the overnight VIP tissue processor combined with the overloaded Express tissue processors cause large buffers to form at embedding and sectioning, resulting in the observed high waiting times. In these buffers, assessments are processed in order of assessment number, with the exception of urgent specimens which are prioritized. As such, large specimens are often processed first as these generally have the lowest assessments numbers, causing the smaller group 2 and 3 assessments to be delayed most. However, despite efficient processing and prioritization in the aforementioned buffer, less than 20% of large specimen assessments finish processing in the laboratory within 2 workdays, making it difficult for the examining pathologist to finish the assessment within the Service Level Agreement (SLA) of 3 workdays. In summary, the strict SLA causes tension on the workflow of large specimens, as a result, 10% of the assessments cause persistent buffers to form, causing group 2 and 3 specimens (76% of assessments) to accumulate long waiting times in times of high demand.

Several organizational interventions have been proposed to reduce the process variability and throughput time. For the evaluation of these interventions, a simulation model is constructed. After verification and validation, the simulation was used to execute two experiments to evaluate the effects and possible interaction effects of the proposed interventions.

From the intervention analysis, it was concluded that to improve the throughput time and lower variability, the embedding and sectioning should be executed on arrival order of assessments instead of processing on order of assessment number. In other words, switching the processing order from First-In-First-Out (FIFO) on system level to sub-process level. Implementing this

intervention will help prevent persistent buffers from being created, eliminating the delays observed by management. This results in the reduction of average throughput time and variability for 90% of the assessments, exemplified with a reduction of 68 to 83% in average standard deviation depending on assessment group in the simulation. The trade-off for this intervention is a 6% increase in average throughput time for group 4 assessments, however with a 43% reduction of average standard deviation. As the strict SLA is already causing tension in the group 4 workflow, which will be further increased by the implementation of this intervention, it is suggested that the SLA for large specimens be increased to 4 workdays.

In closing, it can be concluded that the laboratory of LabPON operates in an efficient and effective manner, but attempts to make a small part of the assessments meet unrealistic throughput times cause buffers to be form which, in times of high demand, result in the delays observed by management.

Management Samenvatting

LabPON is een groot histopathologisch laboratorium in Hengelo waar de missie wordt nagestreefd om snelle, doelmatige en goede dienstverlening aan aanvragende artsen en ziekenhuizen te leveren. In lijn met deze missie, streeft de organisatie om de dienstverlening te verbeteren door een innovatieve en progressieve instelling, hierdoor is LabPON een voorloper binnen de sector. LabPON is het eerste laboratoria waarin digitale pathologie is geïmplementeerd, waarbij coupes via een scan worden gedigitaliseerd, waardoor pathologen kunnen werken via een compleet digitale klinische workflow.

Om de logistieke stroom van het laboratorium te verbeteren, heeft LabPON evaluaties en lean-projecten uitgevoerd. Echter, ondanks de uitvoering van evaluaties en de toepassing van verschillende lean principes, worden regelmatig onverwachte vertragingen waargenomen, waardoor casussen soms dagen later dan verwacht worden aangeleverd bij de patholoog. Patiënten moeten hierdoor onnodig lang wachten op diagnose, wat kan leiden tot vertraging in het zorgpad.

Hoewel binnen het laboratorium enkele ideeën zijn geformuleerd om de vertragingen te voorkomen, bleek onvoldoende inzicht te bestaan in de complexe logistieke processen om implementatie van deze ideeën te funderen. Om meer inzicht te krijgen in het logistieke proces en het effect van interventies is dit onderzoek opgezet. Het doel van dit onderzoek is om inzicht te verschaffen in de logistieke processen van het histologische laboratorium bij LabPON, alsmede het identificeren van mogelijke interventies en het evalueren van het effect op de procesvariabiliteit en doorlooptijd.

Om inzicht te geven in het laboratorium is een contextanalyse uitgevoegd, gevolgd door een grote data-analyse. Uit de data-analyse bleek dat lange wachttijden ontstaan tussen het inbedden en microtoom snijden. Tevens is opgemerkt dat ongeveer de helft van de dagelijks aangeleverde onderzoeken pas om 15:00 bij het laboratorium binnen komt, waardoor een hoge werkdruk wordt ervaren bij het uitsnijden in de namiddag, gevolgd door een overbelasting van de Express weefsel doorvoermachines in de volgende ochtend. In de ochtend ontstaan grote buffers bij het inbedden en microtoom snijden, deze ontstaan door samenloop van de grote batch afkomstig uit de VIP-doorvoermachine die 's nachts draait, en de overbelaste Express doorvoermachines. In deze buffers wordt materiaal verwerkt op volgorde van onderzoeknummer, met uitzondering van prioriteit casussen, waardoor grote onderzoeken vaak als eerste worden verwerkt omdat deze lagere onderzoeknummers hebben, gezien ze al langer in bewerking zijn. Hierdoor worden de kleinere onderzoeken van groep 2 en 3 materiaal het meest vertraagd. Ondanks de efficiënte verwerking en prioritering van groot materiaal in de eerdergenoemde buffer, is minder dan 20% van het groot materiaal binnen twee werkdagen klaar op het laboratorium, waardoor pathologen weinig tijd overhouden om onderzoeken te beoordelen en voltooien binnen de in de Service Level Agreement (SLA) gestelde tijd van 3 werkdagen. Samengevat ontstaat spanning op het logistieke verwerkingsproces van groot materiaal door de strenge SLA, hierdoor veroorzaakt 10% van de onderzoeken buffers in het systeem waardoor 76% van de onderzoeken (groep 2 & 3) wachttijden opbouwen.

Verschillende organisatorische interventies zijn voorgesteld om de procesvariabiliteit en de doorlooptijd te reduceren. Voor de evaluatie van deze interventies is een simulatiemodel ontwikkeld. Na verificatie en validatie van het simulatiemodel zijn twee experimenten uitgevoerd om de effecten en mogelijke interactie-effecten van de voorgestelde interventies te evalueren.

Uit de interventieanalyse is geconcludeerd dat om de doorlooptijd en de lagere variabiliteit te reduceren, het inbedden en microtoom snijden moet worden uitgevoerd op volgorde van aankomst in plaats van beoordelingsnummer. In andere woorden: het bij inbedden en snijden wisselen van werken op First-In-First-Out (FIFO) op laboratoriumniveau naar FIFO op proces niveau. Implementatie van deze interventie voorkomt de vorming van buffers waardoor onderzoeken langdurig vertraagd kunnen worden. Hierdoor zal de gemiddelde doorlooptijd en variabiliteit van 90% van de beoordelingen verminderen; de gemiddelde standaardafwijking daalde in de simulatie met 68% tot 83% afhankelijk van materiaalgroep. Hiertegenover staat dat de doorlooptijd van groot materiaal zal toenemen, volgens de simulatie met gemiddeld 6%, daarentegen verminderd de waargenomen gemiddelde standaardafwijking met 43%. Zoals eerder genoemd staat de bewerking van groot materiaal onder de huidige werkwijze al onder spanning door de strenge SLA, de toename van doorlooptijd door de interventie zal deze spanning verder doen toenemen. Daarom wordt voorgesteld de SLA voor groot materiaal te verhogen tot 4 werkdagen.

In conclusie kan worden gesteld dat het laboratorium van LabPON op een efficiënte en effectieve manier functioneert, maar dat buffers ontstaan door het streven om een klein deel van de onderzoeken een onrealistische doorlooptijd te laten halen. Hierdoor ontstaan wachtrijen welke, op momenten van drukte kunnen leiden tot de waargenomen vertragingen.

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Preface

Dear reader,

The thesis lying in front of you marks not only the fruition of a research project initiated in March 2017, but also of a far-off dream which began in September 2011, as it concludes after six beautiful years, my academic studies at the University of Twente. When I initially discovered this assignment, hidden away between many others, it immediately grasped my attention and felt like the right challenge; six months later I am happy to say this feeling was entirely valid.

During the six months over which this study has been conducted, I have encountered many exciting challenges and enjoyed a lot of freedom carrying out my research, which has allowed for the fulfilment of endless curiosity. For the trust and support in this endeavour within their organization, my gratitude goes out to Henk van der Veen and Jacqueline van Kesteren. Furthermore, I would like to thank everyone at LabPON who helped realize the completion of this thesis, whether it be by providing information, support, interesting discussions or otherwise. Special thanks go out to Edwin Mees, for all the help he provided in accessing and extracting relevant data from the database, which has been the backbone of this research. Also, I would like to sincerely thank Nardo Borgman and Gréanne Leeftink, for all the feedback, support and flexibility. You have been the best supervisors I could have hoped for.

Finally, my sincere gratitude to my friends and family for all the love, support and sincerity.

Eelco Markhorst

Enschede, September 2017

Glossary

CDF	Cumulative Density Function
DES	Discrete-Event Simulation
FIFO	First-In-First-Out
HE	Haematoxylin
Iprova	Document management portal of LabPON
Lab. throughput time	Time from accessioning until distribution of cases to pathologists
Large-grosser	Analyst capable of grossing large specimens
LIMS	Laboratory Information Management System
MU	Moveable Unit; an assessment in the simulation model
OFAT	One-Factor-At-a-Time
PathLab	Brower-based management portal that provides access to production data and throughput times
PDF	Probability Density Function
SLA	Service Level Agreement
Total Throughput Time	Time from accessioning until delivery of diagnosis to applicant
WIP	Work-in-Progress

Chapter 1. | Introduction

Chapter 1 provides a general introduction into the organization where the research is performed, the core business it is concerned with, and the intention behind the research.

1.1. LabPON

LabPON is a pathological laboratory which is established in Hengelo. With a yearly throughput of over 90.000 examinations each year it is one of the largest laboratories of the Netherlands. The catchment area of the laboratory covers the regions of Twente and the eastern Achterhoek (LabPON, 2017j).

The mission of LabPON is to deliver "fast, effective and good services to the requesting doctor and hospital" (LabPON, 2017g). In practice, this means the delivery of pathological examinations and diagnostics of the highest quality standard within three workdays, with an emphasis on error prevention.

At LabPON, three types of examinations are conducted: Histological; Cytological; and Molecular. This research will solely focus on the Histology department, where 55.000 examinations are handled every year.

As an organisation, LabPON strives to be progressive and innovative. For example, LabPON was one of the first in the world to implement a fully digitized histopathological clinical workflow, which allows pathologists to view and diagnose scanned slides digitally (LabPON, 2016). Another example is the execution of several lean projects to improve the process, which was included in workflow design during the construction of the current building.

Despite the application of several logistical principles, the management observes that inexplicable delays frequently occur. These delays can take up to several days, causing patients to have to wait for a diagnosis and delaying treatment, consequently causing a delay in the care pathway resulting in angered doctors and patients. For this reason, the organization has the idea that it has insufficient insight into its logistic processes and wishes to gain more knowledge. Therefore, LabPON has requested the execution of this research.

1.2. Pathology & Histology

The term Pathology comes from the ancient Greek words páthos (= suffering) & logia (= study of), and thus in literal terms means the study of suffering; these days it is defined as the study of disease. As a specialism of modern medicine, pathology is broadly concerned with the origin and progression of diseases (Cambridge Dictionary, 2017; LabPON, 2017i).

Histology is a subspecialty within pathology which is concerned with the study of disease within tissue; an example of such a disease is cancer. Histological assessments are an important diagnostic tool which reveals the nature and origin of a disease. As a result, it has a direct influence on the treatment a patient will receive. It is therefore a critical part of the care pathway for many diseases (LabPON, 2017c).

At the histology laboratory, tissue is received and through a complex process prepared into *slides* which can be assessed by pathologists. Although most of the submitted specimens are small, the size of the tissue received can vary from hardly visible to complete organs or even entire limbs (LabPON, 2017c).

All submitted specimens get processed in roughly the same way. The process is divided in the following sub-processes: Accessioning & Preparation; Grossing; Tissue Processing; Embedding; Microtomy Cutting; Staining; Scanning & Distribution. Besides the main process, other processes take place such as highly urgent Frozen Sections; Autopsies; and handling requests for advanced staining or from cytology. After the specimen has completed the process in the laboratory, it can be assessed by a pathologist for diagnosis (LabPON, 2017c).

1.3. Aim of the research

The aim of the research is to increase the insight into the logistical chain of the histology department at LabPON and to identify possible interventions to improve the process. As such, interventions are identified and further investigated to assess the effect on the throughput, robustness and quality of the system. For this purpose, a clear insight into the logistical chain and how it is influenced by different process parameters should be obtained. This overview of the process should help to identify potential problem areas and lead to proposals for the improvement of the logistical chain of the histology department.

With regards to academic contribution, the research aims to uncover methods that can be extrapolated to be applied in other histology laboratories. In the last ten years there has been an increase in the adoption of lean methodologies by histology laboratories. While general guidelines have been specified for lean implementation, a gap of literature still exists with regards to best practices in process design. Answering the questions posed in this thesis yields interesting results and could be used by other histology laboratories, ideally increasing histology laboratory throughput worldwide and leading to lower waiting times for histological diagnosis. Ultimately, this would result in less anxiety for patients and faster care pathways.

Chapter 2. | Problem context

The second chapter of this thesis presents the problem context and poses research questions that will be solved. For this purpose, first the problem cluster method is used to create an overview of the present problems, followed by the selection of core problems. From the selected core problems, a research question is formulated which is further split into research problems. Finally, the available data, the scope, and report structure are discussed.

2.1. Problem cluster

The problem context gives an overview of problems and remarkable features that are observed, combined with the expected relationships between these problems. The context is presented using a problem cluster method, the problem cluster is provided in Figure 1. The arrows within the problem cluster represent expected cause and effect relationships; problems that have no specified causes are called root problems and may be subject to further research. To ensure proper execution and depth of research, only a small number of root problems have been selected. As such, the selection of root problems principally defines the scope of the research (Heerkens & Winden, 2012).

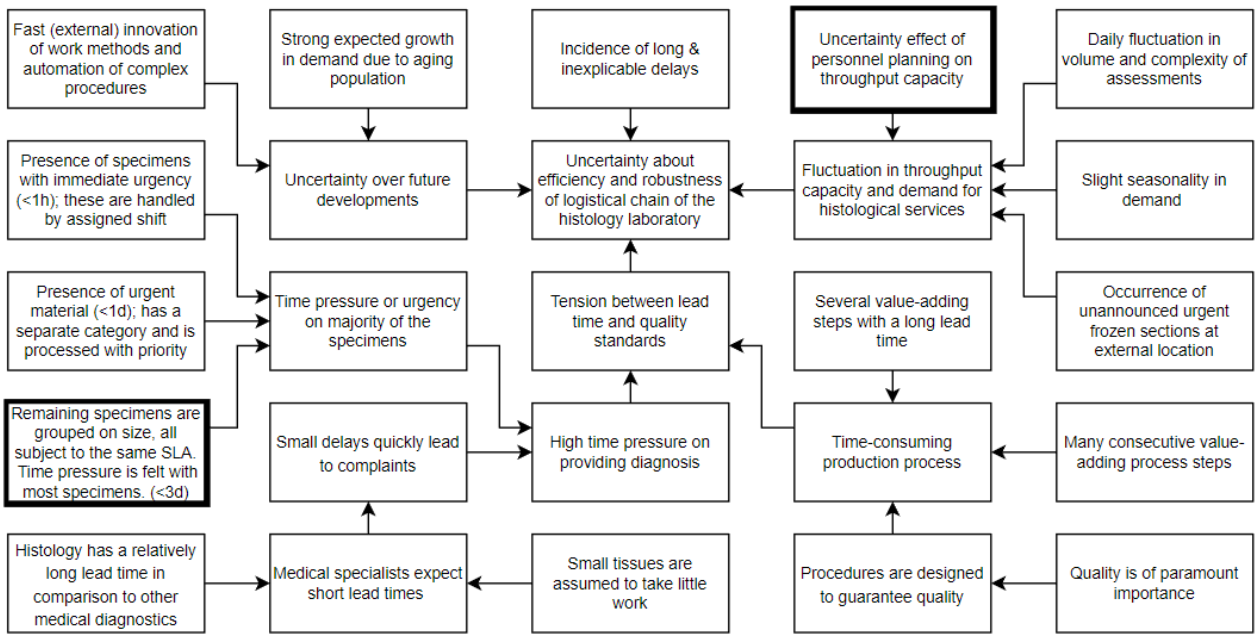


Figure 1 - Problem cluster of observed situation at LabPON

In consultation with the company supervisor, two core problems have been selected. The selected core problems are: the uncertainty of the effect of personnel planning on capacity, and the time pressure that is felt on most regular specimens.

The choice for looking at the uncertainty of personnel planning on capacity was made because using flexible shifts was explored shortly in 2016 during a pilot. Although the pilot was promising, a lot of uncertainty remained regarding the best way to implement the concept and the expected results. As such, implementation could not be substantiated.

The choice for the second core problem, the time pressure felt with group 2, 3 and 4 specimens, is made because LabPON wants to have more insight into the differences between the groups and suspects that improvements are possible in specimen planning.

2.2. Research question

Based on the selected core problems from the problem cluster, the following research question to be answered in this thesis has been formulated:

"What organizational interventions are possible to reduce the process variability and throughput time of the logistical process of the Histology Department of LabPON?"

To answer the research question in a proper and structured way, several research problems have to be answered. The following knowledge will be gathered to answer the research question:

1. How is the histological process at LabPON organized?
    - What steps does the histological process at LabPON include?
    - What types of specimens are in the histological process and how do they differ?
    - What resources are used in the histological process?
    - Which employees & stakeholders are involved in the histological process?
    - What are the Key Performance Indicators of the histological process?
2. What is the current performance of the histological process at LabPON?
    - How does LabPON perform in general?
    - How is the demand for histological services distributed?
    - What are the throughput times of the sub-processes?
    - What are the waiting times between the sub-processes?
3. What can be found in literature about the histological process from an operations management perspective?
    - What is known about histology throughput times?
    - What methods are used to improve the histological process?
    - How can the histological process be modelled?
4. What organizational interventions are possible at LabPON?
    - What are restrictions and limitations to possible interventions?
    - What interventions are possible according to literature?
    - What interventions are possible according to the stakeholders?
5. What organizational interventions are promising for LabPON?
    - What is the influence of interventions on the Key Performance Indicators?
    - Do the interventions have reciprocal interaction effects?
6. How can interventions be optimally implemented?
    - What methods can be used for successful implementation of interventions?
    - What implementation techniques are applicable?
    - How should the interventions be implemented at LabPON?

2.3. Research & thesis structure

The research and thesis are structured according to the Managerial Problem Solving Method (MPSM) in combination with sound simulation study design, as can be seen in Figure 2 (Heerkens & Winden, 2012; Law, 2007).

With regards to thesis structure, each chapter in this thesis corresponds to one of the research problems formulated in Paragraph 2.2. As such, all research problems will have been answered at the end of the thesis.

Managerial Problem Solving Method	Sound simulation study design
1. Global problem	1. Formulate problem & plan the study
2. Formulate problem approach	
3. Problem Analysis	2. Literature study 3. Collection of data 4. Analysis of data 5. Define model 6. Validate assumptions 7. Construct a simulation model 8. Validate simulation model
4. Formulation alternative solutions	9. Design experiments
5. Choice for solution	10. Analyse output data 11. Document, present and use results
6. Implementation	
7. Evaluation & feedback	(Heerkens, 2012; Law, 2007)

Figure 2 - Research approach

2.1. Scope

The scope of this research is limited to specifically the histology laboratory of LabPON. As such, cytology laboratory, molecular laboratory and the pathologists at LabPON are outside of the scope of this thesis. However, remarkable findings have been included in the recommendations for future research.

2.2. Data collection

At LabPON a Laboratory Information Management System (LIMS) is used to keep track of all specimens and store all relevant data (LabPON, 2016). All specimens that enter LabPON are registered in this system and labelled, after which the specimens can be accurately followed through the entire process. At each processing station, a barcode scanner is present which has been made essential to use for completion of the task through the design of the system. As such, large amounts of data are generated daily, which has resulted in the accumulation of a sizeable database of accurate and reliable data. This database is used for the retrieval of data, which is explained further in the chapter Data analysis.

Chapter 3. | Context of the histology laboratory

Chapter 3 provides an insight into the histology laboratory at LabPON. First the process overview is described, followed by an explanation of each sub-process. Next, the types of specimens and specimen groups are discussed, and why the nature of these specimens makes the histology laboratory unique. Finally, an overview of employees and resources is provided.

3.1. The histology laboratory

The histopathological at LabPON consists of several sequential steps which can be seen in Figure 3. The process is similar to histopathological processes at other histology laboratories in the Netherlands and around the world, except for the addition of the scanning step (Buesa, 2010; LabPON, 2017h; Leeftink et al., 2015). The scanning step is included at LabPON since it is one of the first organizations to implement digital pathology. Each step of the histopathological process will be shortly described in the following paragraphs.

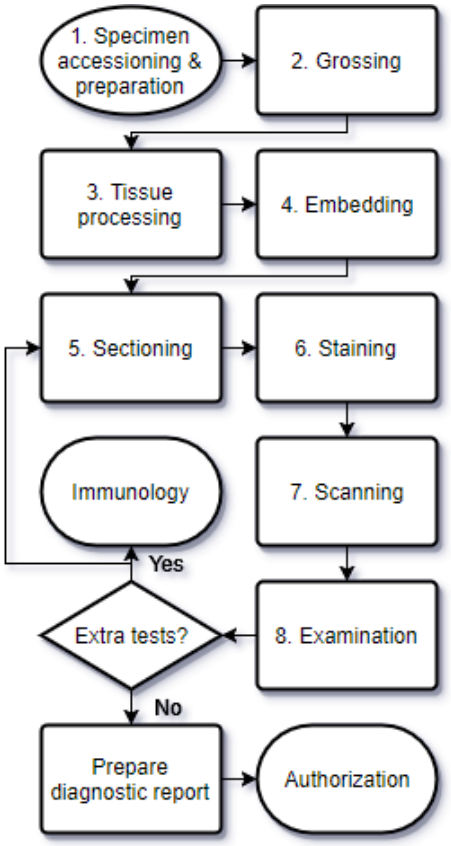


Figure 3 - Histopathology processes at LabPON

3.1.1. Accessioning & Preparation

During the accessioning process, specimens are formally received and entered into the LIMS. This happens at the laboratory, but also at two front offices located in the MST Enschede and ZGT Almelo. During this process, the specimens are also checked on faults at delivery, such as leakages or incomplete delivery.

Finally, a specimen is assigned a group number according to the nature of the material. The following group numbers are used:

Group 1. – Urgent specimens
Group 2. – Small specimens
Group 3. – Medium specimens
Group 4. – Large specimens

These groups will be further explained in 3.2.

Figure 4 - Accessioning of specimens (LabPON, 2017c)

After grouping the specimens, groups 1, 2 & 3 are moved to grossing. Group 4 specimens are moved through a hatch to the 'wet room', where the large specimens are cleaned, prepared and put on fresh formaldehyde for further fixation. The fixation of specimens takes a lot of time, which is dependent on the thickness of the material. At LabPON, the general rule used by analysts is that group 4

specimens need at least 12 hours to fixate before they are deemed ready for grossing. In special cases, such as an entire brain, this process can take up to 90 days.

3.1.2. Grossing

Figure 5 - Grossing of a specimen (LabPON, 2017c)

After specimens are properly fixated, they enter the grossing process. This process consists of two steps: the macroscopy and the cutting of material into cassettes.

During the macroscopy, the specimen is closely inspected and any remarkable features are noted in the LIMS using voice recognition software. The inspection also includes a check that the specimen fits the assessment description, in order to prevent any swaps from occuring.

After the macroscopy, the specimen is cut (if necessary) into pieces with a thickness of 2 to 3 milimeters and put in a small plastic cassette. The cassettes are color coded to match the assessment type and automatically printed by a cassette dispenser. When the grossing is complete the cassettes are moved to a formaldehyde resevoir for post-fixation and to await tissue processing. The post-fixation takes 1 hour for group 1 specimens, 2 hours for group 3 and 4 specimens, and is not required for group 2 specimens

At LabPON, this process is performed at six special tables called '*Uitsnij*' 1 through 6 (U1-U6). Following a lean implementation project the tables have each been assigned a main specimen type, in order to create a continuous parallel flow of different specimens. As such, group 1 specimens are grossed at U1; group 2 at U2; group 3 at U3; and group 4 at U 4 & 5. The U6 table has special features for handling radioactive materials, and as such is mostly used for special cases such as highly urgent specimens; fetuses; or specimens (often breast tissue) with a radioactive seed. When all specimens have been grossed at a specific table, other specimens will be collected to gross starting with group 1 specimens, followed by group 2 and group 3.

3.1.3. Tissue Processing

By this stage the specimen has been fixated, cut into small parts and put into cassettes. Nevertheless, the tissue still contains fluids and fats which makes the cutting of usable sections very difficult. The tissue is therefore processed to remove all fluids and fats to secure the tissue structure.

Figure 6 - Putting cassettes in the tissue processing machine (LabPON, 2017c)

This processing is done using either of two tissue processing machines: The VIP or the Sakura Express. The VIP is very good at removing all fats from the tissue and keeps the tissue in pristine condition, retaining the possibility to conduct all tests at a later stage in the

assessment. The downside however is that the VIP takes a long time for tissue processing, with an overnight program of 13 hours (LabPON, 2017b).

The Sakura express on the other hand is a machine capable of processing tissue in one or two hours. The express is also capable of rapid throughput tissue processing, making it possible enter up to 34 cassettes every twenty or thirty minutes during processing. At LabPON two expresses are installed, one of which runs the shorter program of 85 minutes, while the other runs longer program of 145 minutes (LabPON, 2017k). Although the expresses are very fast in processing, they are less suitable for removing fats and use more aggressive reagents, requiring different protocols to be used to conduct certain molecular tests at a later stage in the assessment. Since uniformity in protocols is desired for later assessments, only specimens that will not require molecular tests are processed using the Sakura Express (LabPON, 2017a).

3.1.4. Embedding

Figure 7 - Positioning tissue for embedding (LabPON, 2017c)

After the tissue has properly been processed it is ready to be embedded. During the embedding, the tissue is taken out of the cassette and put in a stainless-steel container. The positioning of the tissue is of great importance, as the side that faces down will later be cut and put on a slide. After positioning the tissue, a first fill of paraffin wax is put into the container. While the wax is setting, pressure is applied to ensure that the tissue sets properly on the bottom. Once the wax has set, the rest of the container is filled with paraffin and a coupling piece is pressed on top. This coupling piece is used to secure the tissue block to the microtome.

At the embedding stations, a fluctuation of supply is experienced due to the batch-driven nature of the preliminary tissue processing procedure. Currently, a peak of supply is experienced during the morning by the analysts. The cassettes are processed in order of assessment number in relation to the entire system (i.e. first-in-first-out (FIFO)).

3.1.5. Sectioning

When the tissue block has properly set and any overflow wax has been removed from the sides, the tissue is ready to be cut with a microtome. During sectioning, sections of the tissue are cut with a thickness of approximately 0,002mm. These sections are then laid upon a bath of water from where they are scooped onto glass slides. During this process it is important that all tissue is included in a section and that a satisfactory section is secured before all material is cut away, since the specimen is irreplaceable (Buesa, 2007a). The cutting of blocks at the microtomy station is, like embedding,

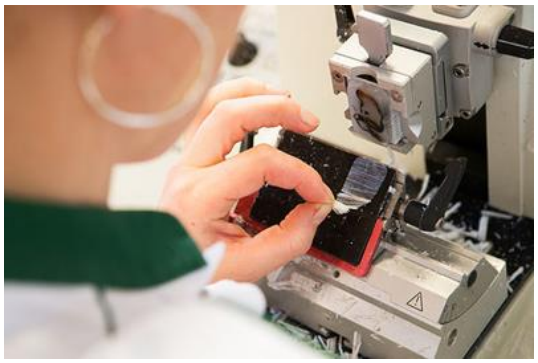


Figure 8 - Cutting a section of 0.002mm at the microtome (LabPON, 2017c)

processed in a FIFO manner in regard to the entire system. However, one microtomy station is dedicated as a fast-track for blocks for extra tests requested by pathologists.

3.1.6. Staining

Figure 9 - Slides after receiving a HE-stain (LabPON, 2017c)

After cutting the specimen onto slides colouring is applied. All assessments start with a standard chemical colouring called Haematoxylin (HE). After staining a cover is slipped onto the slide automatically sealing the stained tissue. After this process, the slide is essentially ready to be assessed by a pathologist.

Besides the standard HE stain, many different colourings are possible to show or highlight different aspects of the tissue. These additional stains can be chemical or immunological in nature and are requested by the pathologist if they are required for diagnosis.

At LabPON, a special shift exists for chemically staining slides. As such, one person is responsible for staining all slides during a day. This shift consists mostly of loading and unloading machines with slides & chemicals, as most of the staining is automated. For staining three different machines are used: one for HE-staining, one for frequently requested special stains, and one for less frequent stains. Some stains however still have to be conducted manually. Immunological staining is done by the immunology department of LabPON, this department is outside of the scope of this research.

3.1.7. Scanning & Distribution

After staining, the slides are essentially ready for assessment. However, LabPON has included one extra step in their histopathological process: LabPON is one of the first histology laboratories in the world to implement and explore digital pathology, where every slide is scanned using a special high-quality scanner. This results in digital images of the slides which range from 2 to 3 gigabytes in size and are suitable for diagnosis.

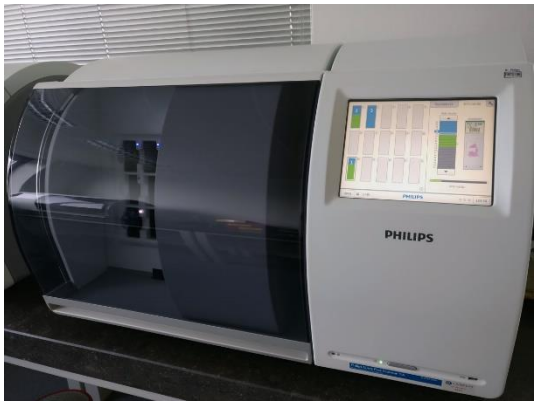


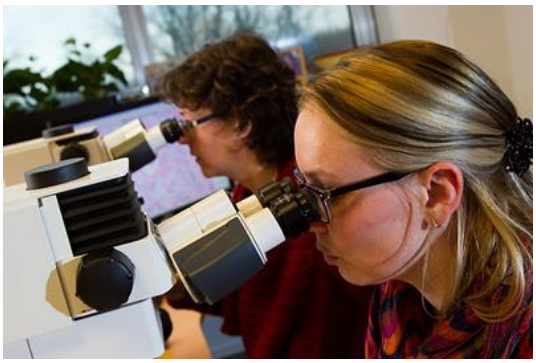
Figure 10 - Scanner used for digitalizing slides

In most cases scanned slides can completely replace physical slides. In few cases reviewing or rescanning the physical slides may be necessary due to limitations in scan procedure or quality of the scanned image (S. Roothaan, personal communication, 13-03-2017). However, the strive is to make the physical slides superfluous for pathologists in the diagnostic process.

After scanning, the slides are collected to be distributed to a pathologist. As soon as all slides of an assessment are present, it is assigned to a pathologist for examination and signed off as completed in the LIMS; this moment marks the end of the laboratory throughput time.

The distribution of assessments to pathologists essentially aims at providing each pathologist with a workload of at maximum seven or nine folders of twenty slides each day, depending on employment conditions. Any secondary activities which the pathologists must perform have been given a workload value expressed in folders, so that these can be considered in the distribution. In the distribution, specialisation is taken into account by assigning specific slides to the preferred pathologist as much as possible. As soon as a pathologist is assigned nine folders in workload for a day, no more work will be assigned for that day. In case all present pathologists have been assigned nine folders, the remaining folders will be assigned for the following day. Note that such a planning method, directly assigning a set number of folders to each pathologist each day, essentially creates a number of parallel single server queueing systems with equal arrival rates. This provides little flexibility in the process by not considering the actual current workload and processing speed of each pathologist. Although this is determined to be out of scope for this research, it is an opportunity for further research.

3.1.8. Examination



After all slides have been prepared, scanned and distributed, they are examined by a pathologist. If diagnosis is not yet possible with the regular HE-stain, additional staining or immunological tests are requested (LabPON, 2017h).

If diagnosis is possible, a report is made and sent to the requesting doctor, after which the assessment is authorised.

Figure 11 - Pathologist examining a slide
(LabPON, 2017c)

3.2. Specimens at the histology laboratory

3.2.1. Specimen types & groups

Many different types of specimens enter the histology laboratory at LabPON. The specimens range from very small biopsies to large specimens such as intestines and other parts of the body. Differences also exist in urgency, some specimens being extremely urgent and requiring immediate action, while others have little to no urgency. Using these characteristics, the specimens can be partitioned in different groups. As mentioned earlier, LabPON has divided the different specimens in the following four groups:

Group 1. – Urgent specimens
Group 2. – Small specimens
Group 3. – Medium specimens
Group 4. – Large specimens

Group 1 contains all specimens which are of an urgent nature, for which it is attempted to have the diagnosis ready the next working day. Most of the group 1 specimens are biopsies and specimens from oncological care pathways (LabPON, 2017d). These specimens are grossed at U1 and receive

preferential treatment throughout the process. After grossing they are put on post-fixation for at least one hour before being processed (LabPON, 2017a). Group 1 specimens, specifically lung and thin mamma biopsies, are also the only specimens which get processed in the day program of the VIP (LabPON, 2017a).

Group 2 specimens are classified as small materials. These include gastroenterological biopsies, skin biopsies or shaves, prostate biopsies, and other non-urgent biopsies (LabPON, 2017d). These are grossed at U2 and due to their small size require no extra fixation after arrival. As such, group 2 specimens can be processed in the express tissue processor as soon as they have been grossed.

Group 3 specimens consist of all non-complex medium sized specimens and small specimens which are not included in groups 1 and 2 (LabPON, 2017d). Some examples are curettage, cysts, haemorrhoids and nails. Specimens that are normally categorized as group 3 but are too complex are classified as group 4 specimens. The group 3 specimens are grossed at U3 and receive at least 2 hours of post-fixation before being processed after grossing (LabPON, 2017a).

Finally, group 4 includes all large specimens and the more complex medium sized specimens. It is a specimen group that consists of many types of different material, many of which are complex to process during grossing. Frequently seen submissions of group 4 specimens are mammas; prostates; intestines; and placentas. For illustration: these specimens are respectively mostly analysed for breast cancer; testicular cancer; colon cancer; and to monitor for abnormalities during pregnancy.

Due to the size of group 4 specimens, a long time is required for proper fixation of the tissue. For this purpose, all large specimens are left overnight on formaldehyde after being cleaned and cut open, so that the tissue can be properly infiltrated, fixated and cross-linked. After grossing, the material is post-fixated for two hours similar to group 3 material. The size of the tissue also causes it to contain more fat and moisture. Analysts therefore prefer to process group 4 specimens through the VIP tissue processors, since this ensures proper removal of fat and liquids which is beneficial for the quality of the final slides.

Furthermore, due to the complex nature of group 4 specimens, the material can only be grossed by pathologists or analysts that received additional education specifically for this purpose. In general, these analysts are often called Pathassers (short for Pathology Assistants), a term which is protected for analysts who have completed the corresponding course at the university of applied science. However, at LabPON some of the staff is trained internally, for this reason the unprotected title large-grosser is used.

Most of the group 4 material is grossed by the large-grossers at grossing station U4 and U5. The most complex specimens are left for pathologists, these come to the laboratory every day between 14:00 to 16:00 to gross these specimens, during which they receive assistance from the grossing analysts.

These different groups serve the purpose of splitting the received specimens into manageable streams of material, a purpose for which they seem to be properly defined. Each group has a set of

distinct features with regards to urgency, complexity and amount of work which make them suitable for further analysis. This distinction will therefore be used during the data analysis.

3.2.2. Influence of specimen properties on histology laboratory characteristics

A histology laboratory is unique in several ways. The specimens that get processed are usually solid in nature, heterogenous and irreplaceable. Because of this reason it is important that mistakes are avoided, since a damaged or unusable specimen can lead to an uncertain diagnosis. This is in contrast with other types of laboratories, where often liquid specimens are used which by its nature is more replaceable and thus more forgiving on additional required research or mistakes (Buesa, 2007a).

Because of the broad diversity in specimens and medical inquiries, the procedures within the histological laboratory are very diversified (Buesa, 2007a). The majority of the specimens in the laboratory get processed using the standard procedure of fixation on formalin, embedding in paraffin, followed by a HE-stain. But a large part of the specimens also require special treatments with a large array of exceptions and choices that are made by insight of the analyst or upon request by the pathologist. Because of this, complete standardisation of the process is difficult and is mainly focussed on procedural consistency (Buesa, 2007a).

Consequentially, histological laboratories currently have a relative low amount of automation compared to other medical laboratories. Because of the long throughput times of several steps, it is usual to group materials in batches. Recent innovations have started reducing the long throughput times with the goal of enabling continuous processing (Buesa, 2007a; Gabriele Halwachs-Baumann, 2010).

The amount of responsibility for choices during the process is high in the histological laboratory. The broad diversity in procedures and specimens requires the analysts to make process related choices at their own discretion at nearly every step. Examples are the selection of which part of the specimen to cut out during grossing; the amount of material per cassette; necessity of decalcifying and the duration thereof; the usage of either the VIP or the Express processing method; the material position during embedding; and the choice for which microtome section to put on a slide. All of these choices have a direct influence on the final product and as such can influence the diagnosis (Buesa, 2007a). In addition to the amount of choices, the pressure is high since mistakes are hard to detect and often cannot be repaired or fixed after completion of the process.

These characteristics create a production environment in which quality is of paramount importance, even more so than in other medical laboratories. The nature of material requires the histological laboratory to be very deliberate and secure in all processes, even though these are very diverse and often quite complex. The introduction of continuous processing has started to reduce the long throughput times in the histology laboratory, showing that shorter throughput times are possible and thus increasing pressure to reduce these throughput times. For much of the material however, utilizing continuous processing is detrimental to the quality and should therefore be considered cautiously.

3.3. Employees

At LabPON, various types of employees work together to fulfil all tasks in the histopathological process. The employees that are directly involved in the histopathological process are the pathologists; the (large-grossing) analysts; and the laboratory assistants. Indirect involvement in the histopathological process is performed by the management and supportive functions, which organize and facilitate the production process. The employees that are directly involved in the histopathological process are further discussed.

Pathologists are the medical specialists who are specialized in establishing diagnosis through microscopic inspection of tissue. They carry the highest authority with regards to knowledge about pathology and as such are closely involved with the design of the process. Besides diagnosing slides, the pathologists also gross the most complex specimens. For this purpose, three pathologists come to the laboratory every day between 14:00 and 16:00, with assistance from the large-grossers. This time-slot has been specifically selected since it does not interfere with continuous processing during the day and allows all complex cases to be included in the night-run of the VIP.

The analysts are the employees actively working with the specimens in the laboratory to create the slides for the pathologists. As the analysts are responsible for carrying out all process steps mentioned in the process description, they are capable of conducting a diverse number of procedures. This is also reflected in the regular planning, in which employees circulate between the procedures preventing monotonous work.

Within the group of analysts, a distinction can be made between the regular analysts and the large-grossing analysts. The grossing of large specimens is a complex task which is vital for setting the right diagnosis. As such, it can only be performed by pathologists and a small group of large-grossers who have completed an extra education focussed on this procedure.

Finally, the laboratory assistant is responsible for support tasks within the laboratory. These include cleaning of machines, keeping stock and ordering of the reagents, and managing the short-term archive.

The planning of analysts and lab-assistants is the responsibility of the head of the histology laboratory and in general is conducted by one of the analysts. Within the laboratory, a minimum occupancy rate of sixteen analysts is used as a rule of thumb to fill all shifts to produce consistently. However, in general eighteen to twenty analysts will be scheduled depending on expected demand. During planning, care is taken to ensure that all analysts circulate between the different tasks within the laboratory, the two main reasons for this are to keep the work from becoming monotonous and to protect employees from repetitive stress injuries to the wrists for which microtome cutting is notorious.

The offline scheduling (i.e. scheduling ahead of time) of analysts is based on a number of shifts that should be fulfilled which are scheduled through personal expertise of the scheduler. To be able to complete all tasks within the laboratory the following shifts are planned (LabPON, 2017e):

- U1; U2; U3 - Grossing of respectively group 1, 2 and 3 specimens
- N-shift - Grossing of group 4 specimens
- P-shift - Responsible for handling highly urgent frozen sections
- R-shift - Responsible for moving shifts from grossing through embedding
- Snij1-6 - Responsible for embedding and microtome cutting of tissue
- Snij-G - Responsible for cutting of special staining requests
- Snij-J - Responsible for embedding & cutting, afternoon backup for J-shift
- M-shift - Preparation of group 3 and 4 specimens for grossing
- G-shift - Responsible for chemical staining of slides
- J-shift - Responsible for scanning slides and distribution to pathologists
- Lab assistant - General cleaning and restocking reagents

All of the above shifts concern regular working hours, with the exception of the M-shift, which is only scheduled in the afternoon. To give a better overview of the number of employees involved with a certain task, Table 1 shows the simplified task groups and the number of employees generally involved with the task.

Table 1 - Number of employees per task

Task	Number of employees
Grossing small	3
Grossing large	2
Embedding & Sectioning	8
Staining	1
Scanning	1
P-shift; R-shift; Lab assistant	3
Total	18

For online scheduling (i.e. rescheduling during the workday), a coordinating analyst is present in both the grossing laboratory and the microtome laboratory. He/she determines whether real-time alterations to the employee schedule are necessary and how these can best be made. For example, the coordinating analyst in the microtome laboratory also determines the ratio of embedders to microtome cutters, this is done using a rule of thumb of one embedder per two cutters and balanced according to the amount of stock between embedding and cutting.

3.4. Resources

3.4.1. Transport

Transportation of the specimens from hospitals and clinics to the laboratory of LabPON is conducted by the internal transportation service. This transportation service is shared with LabMicta, another medical laboratory organization that is located in the same building with whom several overhead resources are shared. Currently, five vehicles are driving each day to collect all specimens. Since the transportation schedule has to match the necessitated arrival times for LabMicta and internal transportation times of the hospitals, it is difficult to change.

3.4.2. VIP Tissue processor

Two VIP Tissue processors (formally called the Thermo Shandon Excelcior) are present in the laboratory at LabPON. The VIPs are filled with racks which can fit up to 50 cassettes each, providing a capacity of 300 cassettes per VIP or 600 in total (LabPON, 2017b). Tissue processing using the VIP is done once a day in a single overnight program which results in quite a large batch. An exception is made for small urgent biopsies which may not be processed using the Sakura express, if present these are processed using an accelerated day program at 11:00. Once the tissue processing process is initiated it is completed autonomously and cannot be pre-empted.

3.4.3. Sakura Express rapid throughput tissue processor

The Sakura Tissue-Tek Xpress 120 is the rapid throughput tissue processor in use in the laboratory at LabPON. Two of these machines are available in the laboratory, one is used for the shorter program of 85 minutes and the other for the 145 minute program. The Sakura express processes tissue using four sequential steps, which are performed in different containers. As the cassettes move stepwise through the Sakura Express in 85 or 145 minutes, it is possible to insert new cassettes to be processed every twenty or thirty minutes. The last batch of the day is inserted at roughly 15:00 for the short program and 14:00 for long program. Once the process is initiated it is completed autonomously, however the batches do have to be removed after processing (LabPON, 2017k).

The capacity of the Sakura Express is two racks of 17 cassettes per processing step, providing a theoretical maximum throughput of 136 cassettes per respectively 85 or 145 minutes. However, analysts report that the processing time becomes slightly longer when the machines are used at full capacity because of waiting times for subsequent batches inside of the machines.

3.4.4. Embedding & microtomy stations

In the histology laboratory of LabPON, four embedding stations and eight microtomy stations are present. All stations require an analyst to continue processing and process one cassette at a time. Within the laboratory, two analysts are cutting slides at the microtome for each analyst that is embedding cassettes; this ratio resulted from experience of the coordinating analysts. As described above, under normal conditions up to eight people are scheduled for embedding and microtomy: snij1-6; snij G; and snij J.

Chapter 4. | Data analysis

This chapter describes the data analysis. The goal of this data analysis is to provide an insight into the performance of LabPON; the characteristics of the demand for histological assessments; the characteristics of the different sub-processes and the waiting times within the histological laboratory. This information provides a good understanding of the organisation and is used as an input to the modelling approach.

4.1. Key Performance Indicators

The prerequisite for a proper data analysis is clearly knowing what it is that needs to be measured. For this reason, the Key Performance Indicators (KPIs) of the histological process at LabPON will first be defined.

In a large collaborative effort, the Royal College of Pathologists in the United Kingdom assembled a list of proposed KPIs for Pathology services in order to create a national framework of standards for pathology laboratories. In this collaboration, seven categories of KPIs were proposed for the assessment of Pathology services (Helliwell & Liebmann, 2013):

1. Staffing
2. Training and education
3. Repertoire of test and integrity of reporting results of tests
4. Engagement with patients and users
5. Interpretative clinical advice and engagement with multidisciplinary teams
6. Timeliness of reports and clinical advice
7. External quality assurance

For the purpose of this research, the most relevant KPI category is the timeliness of reports and clinical advice. This KPI requires 80% of cases to be completed within seven calendar days, and 90% of cases to be completed within ten calendar days; cases requiring molecular tests or prolonged decalcification are excluded (Helliwell & Liebmann, 2013). The other KPIs are relevant for the histology laboratory, but are excluded from this analysis since the focus is on logistical performance. Of course, different norms may be present regarding waiting times between the United Kingdom and the Netherlands. However, a study regarding productivity standards of histology laboratories found the throughput time to be roughly equal worldwide, thus any differences in maximum accepted waiting times are likely to result from cultural differences rather than operational differences (Buesa, 2010).

The Service Level Agreement (SLA) of LabPON is much stricter, requiring 80% of the assessments to be completed within three working days for normal assessments, and five working days with additional tests (LabPON & MST, 2014). Since achieving this speed is part of the mission statement of LabPON, the throughput time specified in the SLA will be used as KPI for further analysis in this research.

Finally, one additional KPI should be noted as important for LabPON: the average cost per assessment. This KPI has no direct influence in the quality of the pathological services, and therefore not listed by the Royal College of Pathologists. However, it is important to include to balance with the other KPI and should be controlled for the prolonged wellbeing of the organisation.

In conclusion, seven categories of key performance indicators have been proposed by the royal college of pathologists from the United Kingdom to control the quality of histological assessments, and costs has been added from an organizational point of view. From the proposed KPIs, this research will solely focus on the throughput time KPI. Costs are included in the considerations, but will not be quantified as this research aims to increase throughput time through operational interventions under while capacity remains equal. The throughput time will be measured using the norm self-imposed by LabPON through the SLA: three workdays for regular assessments and five workdays for assessments with additional testing.

4.2. Data collection

Since LabPON is a production laboratory, it receives and generates large amounts of data in its daily operations. To properly store and keep track of this data, LabPON uses a *Laboratory Information Management System* (LIMS), mostly abbreviated to LMS (LabPON, 2016). Each research that is submitted to the laboratory is carefully documented in the LMS, with both clinical- and process data.

Most of the process data is registered using barcode scanners, which are present at each workstation in the laboratory. Each process is preceded by scanning the material that is to be processed, where necessary this action also supplies the required information or labels for the employee. This way, required information is always at hand and all submissions, cassettes, and slides are provided an identification code which is coupled to the respective research.

Because of the integration of the barcode scanner in the production process, the throughput time of different process steps can be accurately determined. With the aid of the system administrator, Edwin Mees, the process data of all histological assessments conducted in 2016 have been extracted from the database using a series of MySQL queries. This resulted in a number of very detailed datasets of sizeable format concerning the grossing, embedding and microtome cutting times.

Furthermore, the general assessment data was extracted from the browser-based management portal PathLab, which is powered by MagnaView. From this portal, a summary of all assessments of 2016 was extracted, matching the data that was extracted from the database using MySQL. Also, an overview of the weekly demand for histological assessments over the time period 2011 to 2017 was extracted.

Following the extraction of data from the system, the data has been cleaned of incomplete or corrupt entries. It was remarkable to see that the data was of high quality, requiring only little cleaning. This was expected as the scanning of material is strongly integrated in the production process, nevertheless this provides confidence in the correctness of the data. An overview of the retrieved datasets, size, timespan and retrieval information can be found in Table 2. Each graph and table

below will have included dataset(s) included in the annotation, along with the number of data rows and corresponding timespan.

Table 2 - Datasets and retrieval methods from LIMS

Dataset	N=	Timespan from	to	retrieved	Retrieval method
General production	92970	1-1-2016	31-12-2016	25-4-2017	PathLab
Submissions per week over 5 years	288	1-1-2013	9-5-2017	9-5-2017	PathLab
Grossing timestamps	81081	1-1-2016	31-12-2016	9-5-2017	MySQL query
Embedding timestamps	166447	1-1-2016	31-12-2016	9-5-2017	MySQL query
Microtome cutting timestamps	282933	1-1-2016	31-12-2016	3-7-2017	MySQL query

4.3. Throughput time LabPON

In Figure 12 and Figure 13 an overview is provided of the total throughput time of all histological assessments that have been conducted 2016. The total throughput time is defined here as the time from accessioning until delivery of diagnosis to applicant, thus includes the diagnosis by pathologists. Furthermore, a distinction has been made between assessments with and without additional tests, as this distinction is also made in the SLA: at least eighty percent of assessments without additional tests have to be completed within three workdays, compared to five workdays for assessments with additional tests (LabPON & MST, 2014). In the figures, assessments that do not meet the norm defined in the SLA are indicated with black.

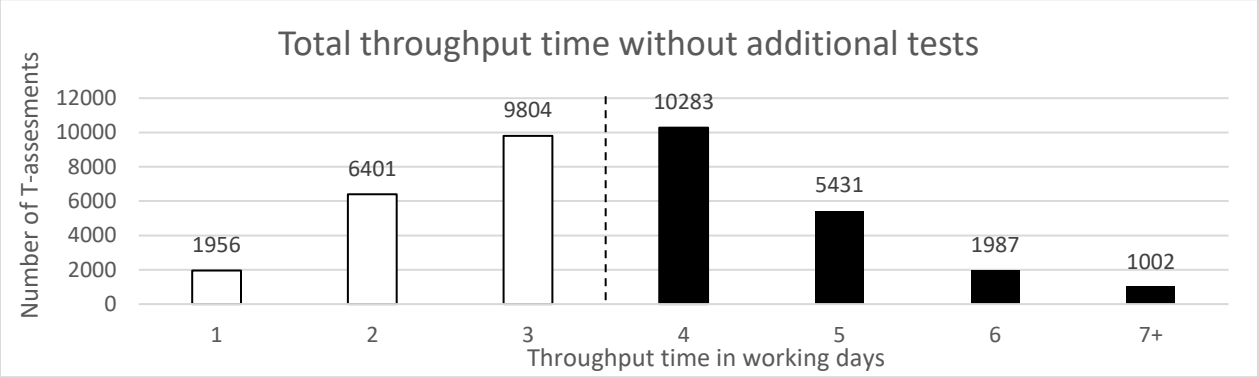


Figure 12 - Total throughput time without additional tests(General Production, N=36864, 1/1/2016-31/12/2016)

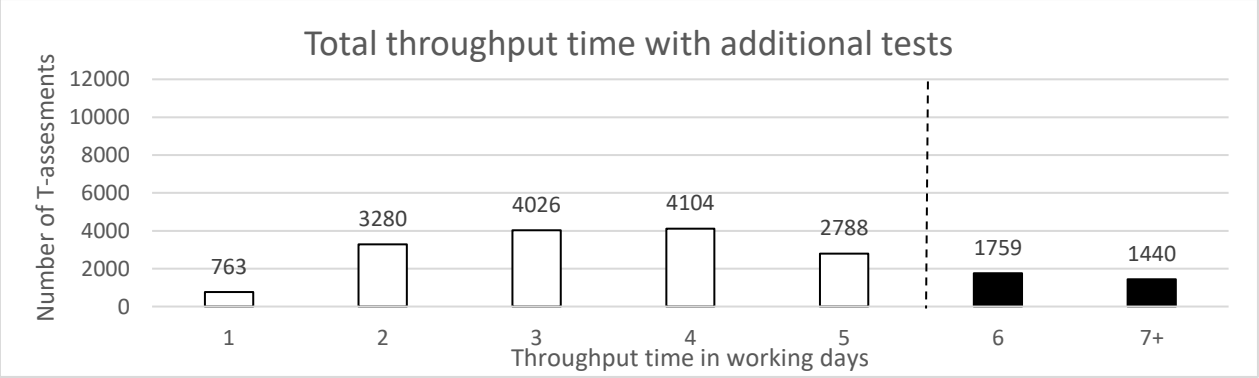


Figure 13 - Total throughput time with additional tests (General production, N=18160, 1/1/2016-31/12/2016)

The figures clearly show that the throughput time for assessments without additional tests as defined in the SLA is not met. For further specification Table 3 provides the percentage of total assessments completed after a given number of workdays. The table shows that only 49,3% of assessments without additional test are completed within three workdays, and even a SLA of 80% within four working days would not be met. This indicates that either something is wrong with the process, or the SLA is constructed in an unrealistic way.

Table 3 - Percentage of assessments completed after given number of workdays (General production; N=55024; 1/1/2016-31/12/2016)

Working days	1	2	3	4	5	6	7+
No additional test	5,3%	22,7%	49,3%	77,2%	91,9%	97,3%	100%
With additional test	4,2%	22,3%	44,4%	67,0%	82,4%	92,1%	100%
Total	**4,9%**	**22,5%**	**47,7%**	**73,8%**	**88,8%**	**95,6%**	**100%**

The previously presented throughput times are with regards to the entire process in LabPON. The scope of this research however is limited to the histology laboratory. Within the laboratory, meaning from accessioning until distribution to the pathologist, the aim is to have assessments completed in the laboratory within two workdays; leaving one workday for examination by pathologists. Figure 14 and Table 4 show the pecentage of assessments that are completed within a certain throughput time overall and per specimen group. It is striking to see that large differences in throughput times exist between the specimen groups. Over 80% of the urgent group 1 assessment are have completed the laboratory process within one day and the small group 2 specimens take just 1,5 workday. In contrast, it takes nearly three workdays to complete 80% of group 3 and group 4 material, making it nigh impossible to meet the SLA. For group 4 assessments the long throughput time is caused by the necessity of overnight fixation and overnight tissue processing. This process takes a minimum of 8 to 16 workhours (depending on the submission time of the assessment) before embedding, compared to a minimum of one to two hours for group 1 and 2 specimens. Group 3 assessments do not require overnight fixation and can be processed using rapid tissue processing. Rather, it is found that the high group 3 throughput time is caused by waiting times, this is discussed below and shown in Figure 18 and Figure 24. In conclusion it can be stated that lead time issues arise because of the group 3 and group 4 specimens, either because of the characteristics of the specimens or by design of the system. This will be discussed throughout the data analysis and in the theoretical framework.

Table 4 - Percentage of assessments completed in laboratory after given number of workdays (General production; N=55024; 1/1/2016-31/12/2016)

Workdays	N	0,5	1	1,5	2	2,5	3	3<
Group 1	7195	15%	84%	96%	99%	99%	100%	100%
Group 2	13402	2%	45%	85%	92%	94%	99%	100%
Group 3	27572	1%	5%	18%	40%	60%	88%	100%
Group 4	5616	3%	4%	5%	16%	52%	85%	100%
Overall	**53785**	**3%**	**25%**	**44%**	**59%**	**73%**	**92%**	**100%**

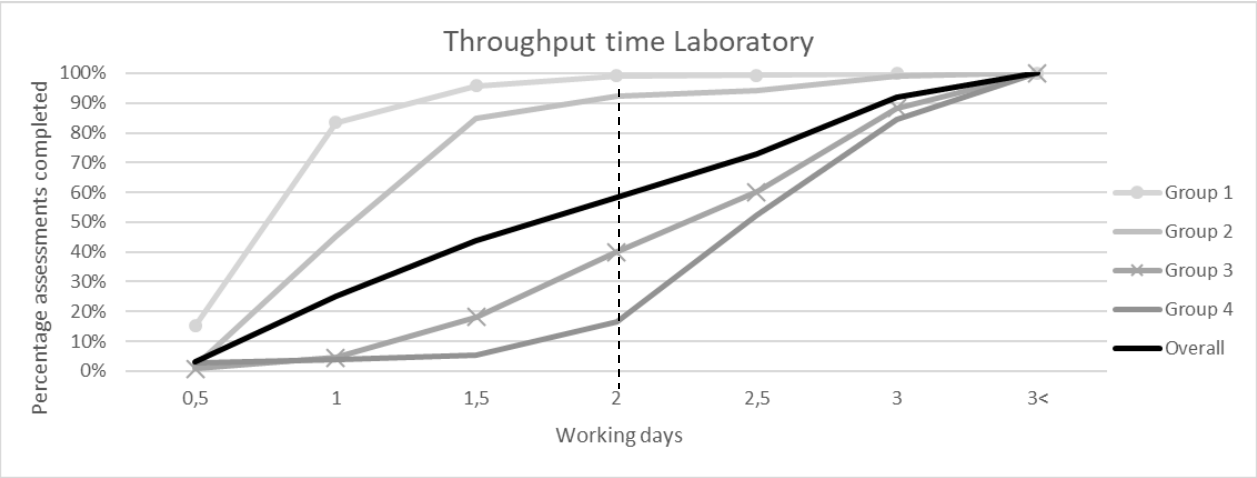


Figure 14 - Laboratory Throughput time per specimen group(General production; N=55024; 1/1/2016-31/12/2016)

4.4. Submission characteristics

4.4.1. Submissions per week

To investigate the seasonality of the demand for histological diagnostics, data on the number of weekly submissions over the past five years was extracted from PathLAB. This data was used to calculate the average number of assessments submitted each week, together with the standard deviation. In Figure 15, the historical average number of assessments is displayed together with one standard deviation difference of the mean. It should be noted that the sample size per week is rather small, with only five data points per week or n = 5. Therefor the standard error of the mean is quite high ($Standard\ Error = \frac{\sigma}{\sqrt{n}}$), as such the sample averages should be viewed as rough estimations of the true mean. Also, the true mean can be influenced by many factors, as such historic results are no guarantee for the future.

However, the values in Figure 15 show a clear fluctuation with clear drops in weeks 52 to 1; 18 to 19; 29 to 31 and smaller dips in weeks 9 and 42 to 43. Respectively, these drops correspond to Christmas & new year; the May holidays; the summer holidays; and the spring break.

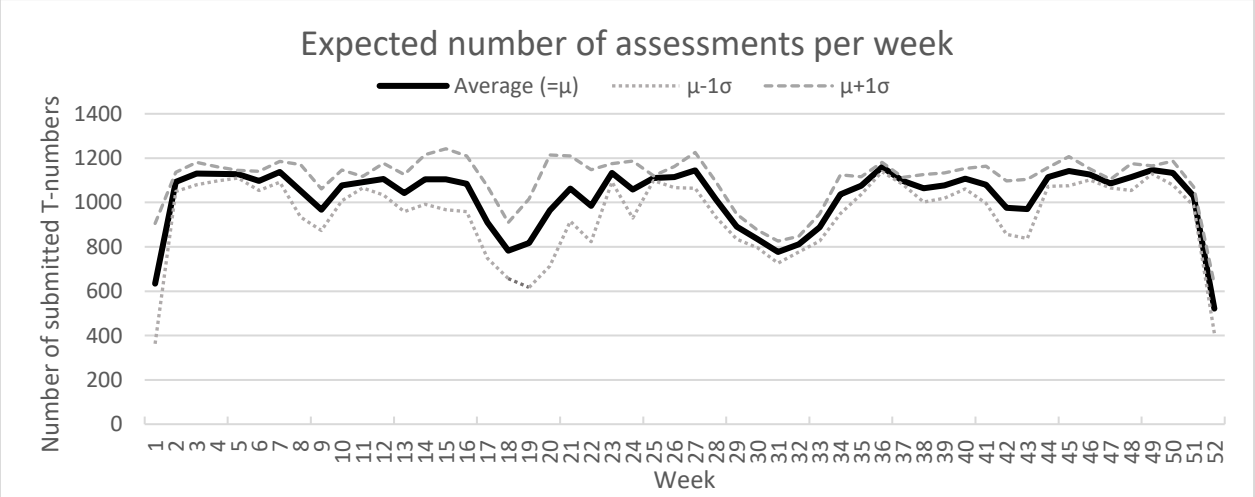


Figure 15 - Expected number of assessments per week based on five years of weekly data (Submissions per week over 5 years, N=228, 01/01/2013-14/05/2017)

4.4.2. Submissions per day

For the planning of staffing levels, it is important to know whether the day of the week affects the expected number of incoming submissions. To determine this, all submissions received in 2016 were grouped on the day of arrival; these data are shown in Table 5. These data have been corrected for the number of working days, in which the number of weekdays in 2016 and statutory holidays were included.

With the total number of submissions and number of weekdays, the average number of submissions per day has been determined. The average number of submissions per day over the entire year has been used as an index to compare the percentage difference of each day. The results show that the midweek is busiest, while Mondays and Friday are relatively slow. Although the differences do not seem that large compared to the index, the difference between the slowest and busiest day (e.g. Monday & Wednesday) amounts to 16,75%. Finally, it should be noted that during the validation of the data analysis, an analyst commented that although the shown data is very recognizable, the distribution has been different in the past due to differences in hospital schedules. As such the distribution of submission could easily change in the future as a result of changes at hospitals.

Table 5 - Submissions per weekday (General production; N=54602; 1/1/2016-31/12/2016)

Submitted T-nummers	Total	Monday	Tuesday	Wednesday	Thursday	Friday
Total number of assessments	54602	9514	11760	11558	11335	10435
Number of days in 2016	261	52	52	52	52	53
Number of holidays	6	3	0	1	1	1
Average assessments per day	214,0	194,2	226,2	226,6	222,3	200,7
Deviation from average	0%	-9,3%	5,7%	5,9%	3,9%	-6,2%

4.4.3. Submissions per hour

Accessioning is the process of formally receiving specimens in the laboratory and providing it with an identification number after which the process is started. For LabPON this process happens in three different places, at the laboratory and at the front offices in Enschede and Almelo. After accessioning at the front office, the specimens still have to be transported to the laboratory in Hengelo.

To provide insight in the arrival of specimens into the process, the total number of arrivals over 2016 per 10 minute interval has been plotted in Figure 16 and Figure 17. It is striking to see that the majority of specimens are accessioned at the front office between 12:00 and 14:00. According to the travel planning of the transport service, both front office shipments arrive at LabPON at 15:00 (LabPON, 2017f). This coincides with the peak load of accessioning at the laboratory. Since the cutting tables are cleaned from around 16:00 or 16:30 depending on analyst' working shift, just over one hour is available to process a large part of the specimens if it is desired to include material in the overnight VIP.

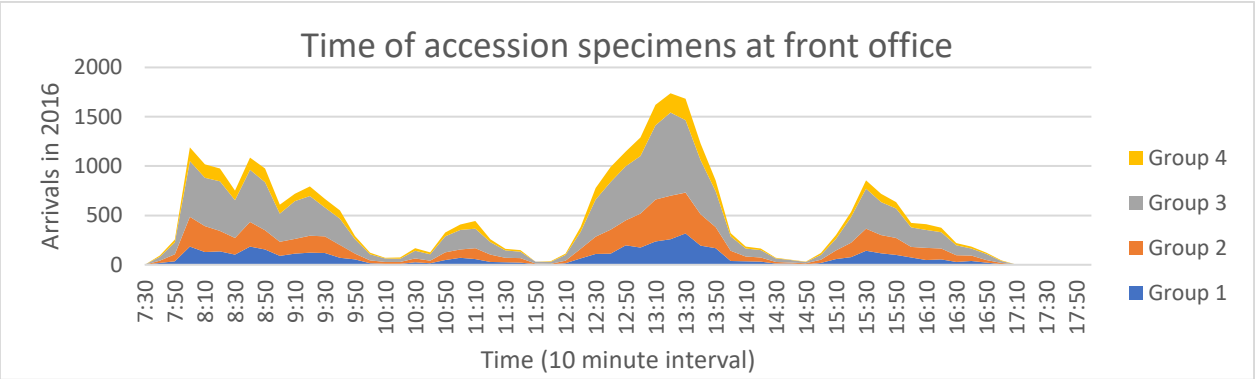


Figure 16 - Time of accession specimens at front office (General production; N=29974; 1/1/2016-31/12/2016)

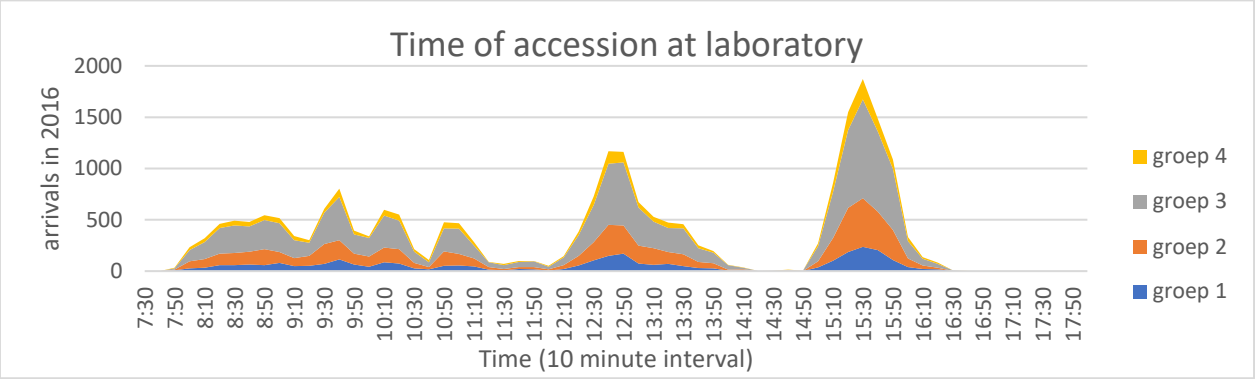


Figure 17 - Time of accession specimens at laboratory (General production; N=22957; 1/1/2016-31/12/2016)

The flow from accessioning to the grossing stations is shown in Figure 18. Because the process between accession and grossing includes fixation, which requires a large amount of time and continues outside working hours, we not only include working hours. The data has been split per specimen type, since the specimens are split on type upon arrival. Although not unexpected, the graph shows a very clear difference in the four specimen types. Approximately 85% of the urgent group 1 specimens arrive at the grossing station within the first day; it is expected that the remaining 15% require fixation or are delivered at the end of the day. Conversely, the large group 4 specimens spend a significant time fixating, which leads to hardly any specimens being grossed the first day. The increase around the 70 hour mark is likely to represent specimens that arrive late on Friday, which get stored over the weekend.

The findings in Figure 16 and Figure 17 seem to explain the large number group 2 and 3 specimens that are grossed the next workday, since the majority of specimens enter the process just a hour before cleaning begins. Consequently, the question arises how much of the specimens could be processed at grossing on the same day if grossing could continue longer at the end of the day. However, several analysts voiced concerns over the degree of fixation of material if it is grossed immediately, indicating that with insufficient fixation in formaldehyde the specimen can be too raw to gross properly (personal communication, 12-07-2017).

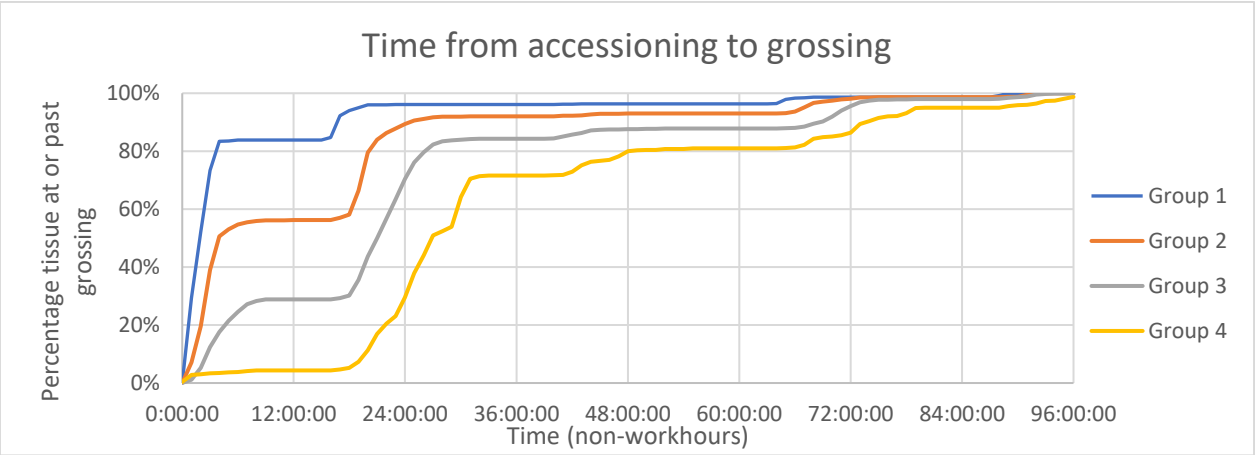


Figure 18 - Time from accessioning to grossing (General production & Grossing timestamps; N=125142; 1/1/2016-31/12/2016)

4.4.4. Submissions per location

The submissions to LabPON come from different locations, the distribution of specimen origin is valuable information for possible changes in delivery schedules. In the previous paragraph large peaks in accessioning time were visible for both the front offices and the laboratory, which indicates that it might be possible to improve in this area.

As can be seen in Table 6, most of the submissions come from the hospitals in the region, and nearly half of all submissions come through the front offices. The other category consists among others of the general practitioners' offices and outpatient clinics in the area.

Table 6 - Number of assessment submission per location (General production; N=54602; 1/1/2016-31/12/2016)

Location	Submissions over 2016
MST Enschede	17842
ZGT Almelo	13051
ZGT Hengelo	8458
SKB Winterswijk	7086
Other	8165
Total	**54602**

Regarding the delivery times of specimens from each location, the delivery timetable of LabPON provides an insight in the arrival distribution which can be seen in Table 7. A superscript annotation is given for each hospital location a vehicle has visited; E for Enschede, A for Almelo, H for Hengelo and W for Winterswijk.

Table 7 - Delivery vehicle arrival times at LabPON in Hengelo per location (LabPON, 2017f)

Arrival timeslot	Vehicle 1	Vehicle 2	Vehicle 3	Vehicle 4	Vehicle 5
9:00-11:30		9:05[A; H]	9:55		10:55[E]
11:30-13:30	12:20	12:15[A; H]	13:23	12:25[E; W]	11:30
13:30-15:30	15:00[E]	15:00[W]	14:50[A; H]		
15:30-17:30	17:35[E]	17:10	17:10	17:20	

Striking to see is that the deliveries from all hospitals are scheduled to arrive at roughly the same time in both the midday and afternoon. As mentioned earlier, LabPON shares its overhead with LabMicta, this includes the transportation of specimens. According to Tonny Smits of LabMicta, team leader of the transportation service, medical administration and reception, the midday shift is scheduled in favour of the laboratory process of LabMicta, such that as much of their material can be included in the LabMicta processing batch at 13:00. However, as seen in Figure 16 and Figure 17 this batch provides only a small peak in the production process.

The afternoon delivery around 15:00 however seems very troublesome for LabPON. All specimens from the front office peak between 12:10 and 14:10 in Figure 16 are delivered at 15:00, as such it coincides with the peak that occurs in Figure 17 after 15:00. Finally, the deliveries take about ten to fifteen minutes to arrive upstairs in the laboratory and from 16:00 to 16:30 analysts start cleaning the laboratory. Thus, it can be concluded that many specimens are delivered just one hour before the laboratory stops production. This results in a high work pressure at the end of the day at grossing, which continues to embedding and sectioning in the morning.

4.5. Throughput time laboratory processes

4.5.1. Method data analysis throughput times Grossing

For the analysis of grossing throughput times, a dataset of 81017 grossing records was used. For the analysis only consecutive activities which are conducted by the same analyst on the same table are included, since these give a realistic representation of the processing times. Furthermore, breaks have been filtered from the data of group 1, 2 and 3; for group 4 however, coffee breaks were unfortunately indistinguishable from regular processing time. The time difference between the activities is assumed to be equal to the grossing time. However, it is likely that analysts get distracted from grossing by small side activities such as ringing timers that require attention and people that come with inquiries; as such these times are included in the grossing time. For each of the group of specimens an overview was created of where the specimens are most often cut including average time per table, and an overview of the distribution of cutting times and time it takes before a certain percentage of specimens is processed. Since analysing the specimen groups per second resulted in a heavily fluctuating graph, the choice was made to group measurements together in five second intervals for group 1, 2 and 3, and twenty second intervals for group 4.

To illustrate the grossing times in the following analysis', two types of probability functions are used repeatedly: the probability density (PDF) and the cumulative density (CDF). These are shortly introduced in order to aid understanding of their meaning.

The PDF shows the chance of specimen processing being completed in a specific time interval. This way it provides an insight into how likely it is that an assessment is completed in a specific time interval.

The CDF shows the chance that a specimen will have completed processing in the given time or less. In other words, it shows what percentage of assessments that have been completed within a given time.

Finally, the analysis distinguishes between the different grossing tables. As explained in 3.1.2. these are named U1 through U6, short for 'Uitsnijtafel'.

4.5.2. Group 1 specimens

Group 1 specimens are classified as urgent and are prioritized within the laboratory. In general, these specimens are processed at the first grossing table, as is reflected in the findings Table 8. It is remarkable to see that the average processing time on grossing station Hist_Uitsnij 1 (U1) is higher than that of grossing station U2 and U3. Since other grossing stations also show higher average grossing times for their respective main material flow, it is assumed that people will engage more in small side activities when cutting routine work compared to when they are aiding with the processing of other specimen groups. In effect making the average times of U2 and U3 the average processing times when working uninterrupted, while U1 provides the realistic average processing time.

In Figure 19 the PDF and CDF per grossing table for the group 1 specimens are given. The graph shows a fast process with a relatively long tail, the mode is around just a single minute per cassette and 90% of group 1 cassettes completed within five minutes.

Table 8 - Processing location and times group 1 specimens (Grossing timestamps; N=14620; 1/1/2016-31/12/2016)

	Specimens processed	Average processing time
Group 1		
U1	8829	0:03:27
U2	2467	0:02:49
U3	2492	0:02:47
U4	313	0:02:28
U5	332	0:03:14
U6	187	0:16:24
Group 1 Total	**14620**	**0:03:22**

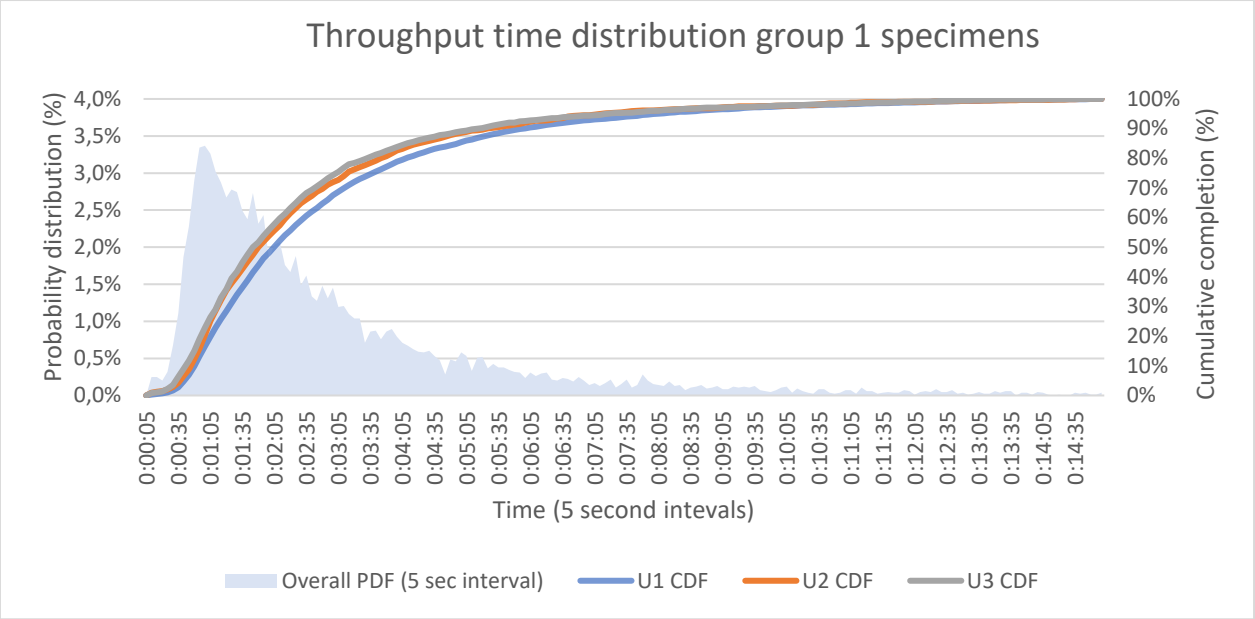


Figure 19 - Throughput time distribution group 1 specimens (Grossing timestamps; N=14620; 1/1/2016-31/12/2016)

4.5.3. Group 2 specimens

Group 2 specimens are small specimens and is generally processed at the second grossing table. Similar to group 1 specimens, In Figure 20, the PDF and CDF for the group 2 specimens are provided. The graph shows a fast process, with a mode around 1:10 per specimen and 90% of group 2 cassettes completed within four to five minutes.

Table 9 shows a longer average processing time on Hist_Uitsnij2 (U2), where the specimens are normally grossed. However, nearly 30% of the group 2 specimens are also grossed at the first grossing table. of it is also often processed at the first grossing table

In Figure 20, the PDF and CDF for the group 2 specimens are provided. The graph shows a fast process, with a mode around 1:10 per specimen and 90% of group 2 cassettes completed within four to five minutes.

Table 9 - Processing location and times group 2 specimens (Grossing timestamps; N=18661; 1/1/2016-31/12/2016)

	Specimens processed	Average processing time
Group 2		
U1	5465	0:02:32
U2	8448	0:03:06
U3	3525	0:02:36
U4	228	0:03:18
U5	257	0:04:29
U6	738	0:03:52
Group 2 Total	**18661**	**0:02:54**

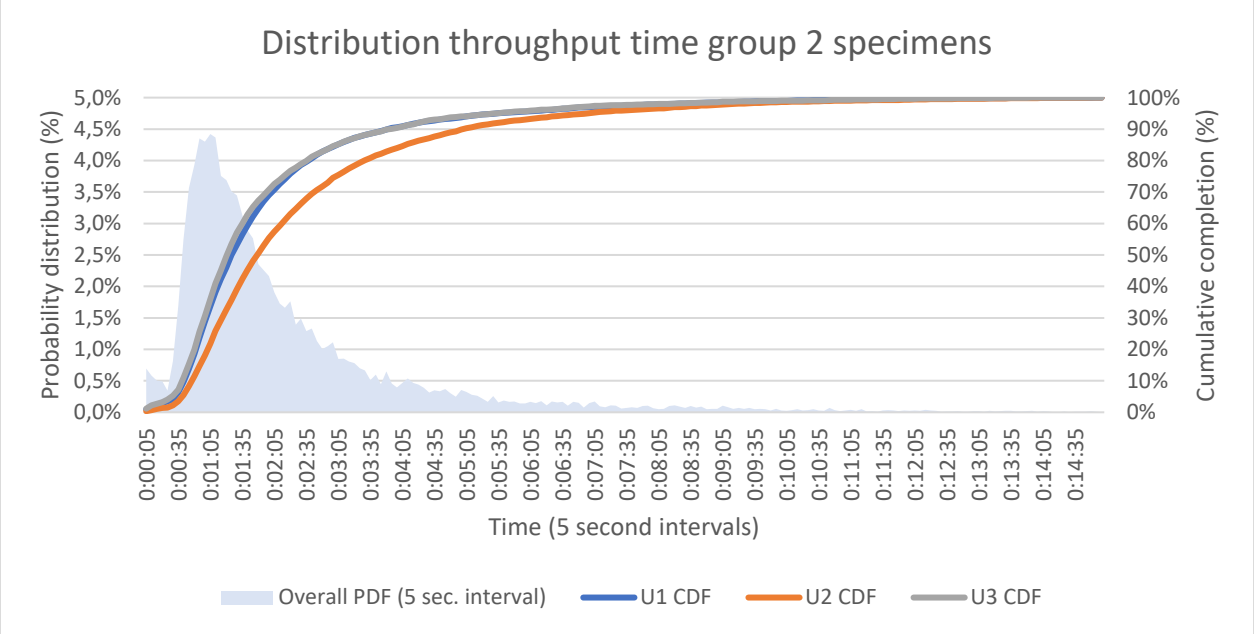


Figure 20 - Throughput time distribution group 2 specimens(Grossing timestamps; N=18661; 1/1/2016-31/12/2016)

4.5.4. Group 3 specimens

Group 3 specimens are the medium sized specimens and are generally processed at the third grossing station. However, Table 10 shows that over half the group 3 specimens are processed at either the first or second grossing stations. The processing time at each of the stations is surprisingly equal, providing an interesting example of the Law of Large Numbers, which states that the average of a large number of trials will approach the true expected value of said trial.

Table 10 - Processing location and times group 3 specimens (Grossing timestamps; N=33136; 1/1/2016-31/12/2016)

	Specimens processed	Average processing time
Group 3		
U1	7562	0:04:44
U2	8901	0:04:44
U3	12261	0:04:42
U4	1349	0:05:39
U5	1239	0:07:17
U6	1824	0:06:24
Group 3 Total	**33136**	**0:04:57**

In Figure 21, the PDF and CDF for the group 3 specimens are provided. The graph shows a slightly slower process, with a mode of 1:35; an overall average of 4:57 and 90% of group 3 cassettes completed after eight minutes.

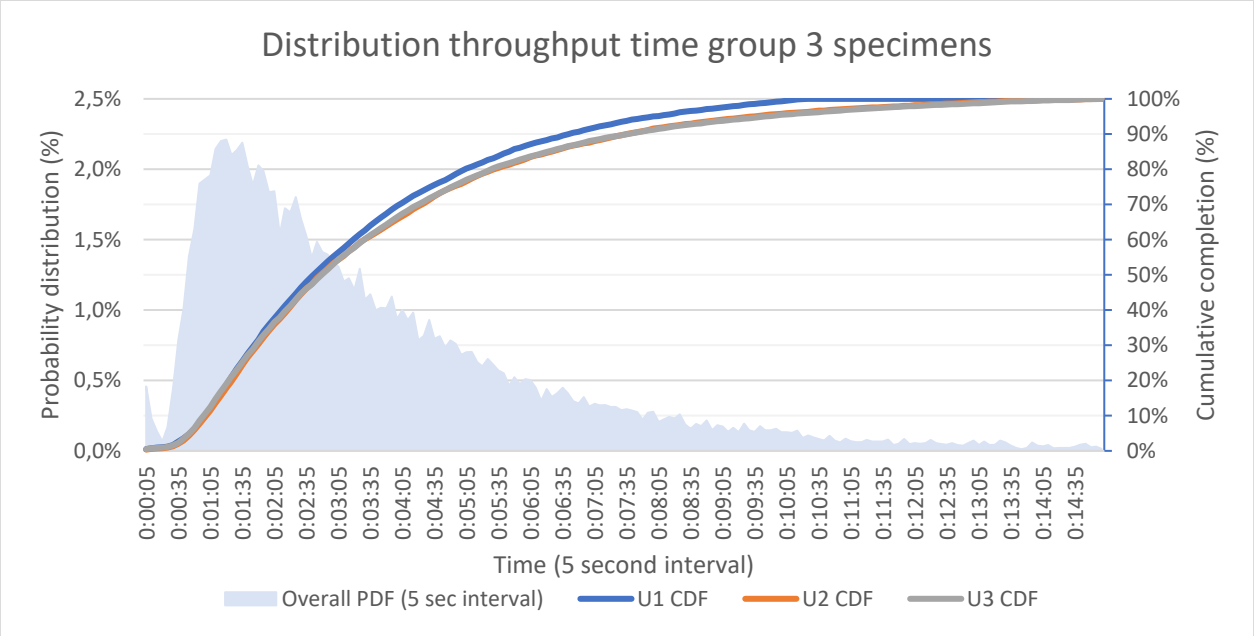


Figure 21 - Throughput time distribution group 3 specimens (Grossing timestamps; N=33136; 1/1/2016-31/12/2016)

4.5.5. Group 4 specimens

Group 4 specimens are the large sized specimens. These are generally grossed at the fourth and fifth grossing stations by the large-grossers, who have received special education for grossing such material. The more complex group 4 material is grossed by the Pathologists with assistance from the large-grossers. It can be remarked that the spread of grossing stations used is quite large, according to analysts this was due to pathologists starting grossing at whatever station is available. As expected, Table 11 shows that the average grossing time per specimen is higher than observed with group 1, 2 or 3 specimens. This is as expected since the material is much larger and complex than the smaller material, making it more laborious to process. Another remarkable feature is the peak in processing time for grossing station five. Inquiry of analysts for possible causes resulted in

the suggestion that this grossing station is often used for training purposes. Another potential cause that was suggested is that it could frequently be used for specimens that are more laborious to gross.

Table 11 - Processing location and times group 4 specimens (Grossing timestamps; N=8154; 1/1/2016-31/12/2016)

	Specimens processed	Average processing time
Group 4		
U1	575	0:11:08
U2	608	0:10:32
U3	563	0:09:54
U4	2908	0:21:04
U5	2332	0:26:38
U6	1168	0:19:23
Group 4 Total	**8154**	**0:20:10**

In Figure 22, the PDF and CDF of the group 4 specimens are provided. The graph shows a very wide and upredicatble spread of processing times. This graph indicates that the processing time of group 4 specimens is likely very dependent on the type of material which is being processed. Furthermore, the knack around the fourteen minute mark followed by the long tail indicates that although most of the material can be processed quite rapidly, there are several specimens which take a long time to process. These findings called for further investigation into the processing times of different specimens.

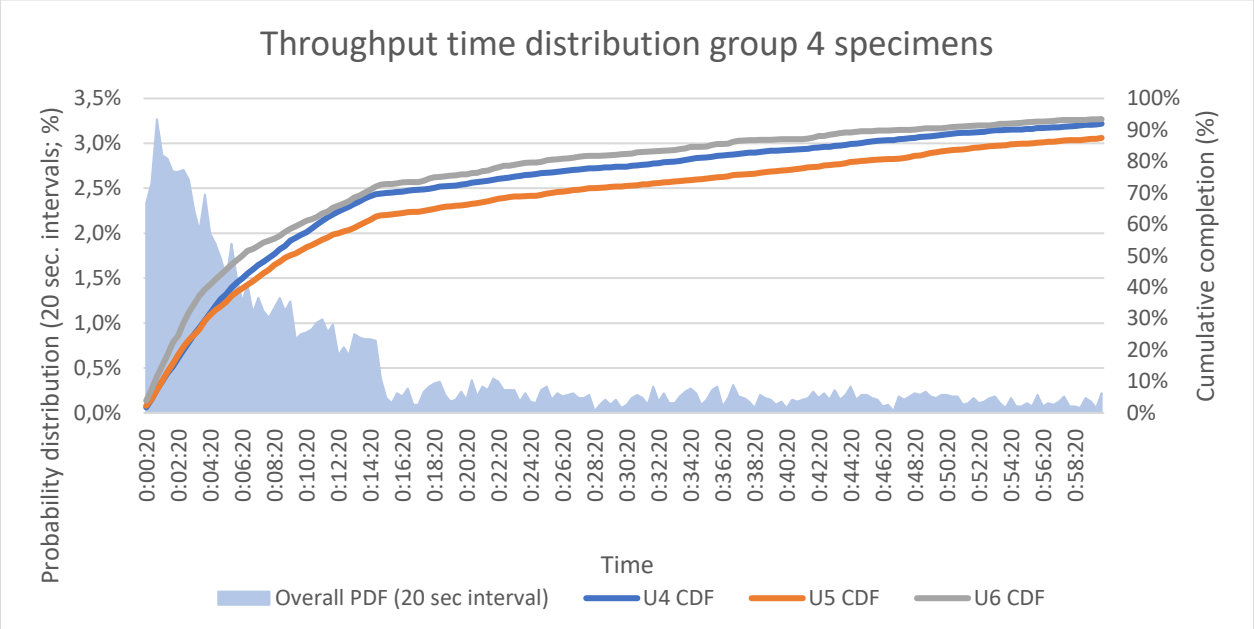


Figure 22 - Throughput time distribution group 4 specimens (Grossing timestamps; N=8154; 1/1/2016-31/12/2016)

In order to get a clear understanding of the workload caused by the different types of specimens, a scatter plots was created of the frequency with which a specimen is submitted versus the average processing time at the grossing station; the scatter plot can be found in Figure 23.

The scatter plot confirms the assumptions generated by the PDF and CDF plot of the processing times. A large spread is visible in the average processing time and frequency of different specimens. This allows for easy distinguishing of the specimens which are responsible for most of the workload. This led to the identification of five high-workload specimen types, which together are responsible for 53% of the total group 4 grossing workload; these types are:

- Colon resection – 18,9%of total workload
- Mamma – 14,3%of total workload
- Uterus – 8,9% of total workload
- Placenta – 6,7% of total workload
- Rectum resection – 4,3% of total workload

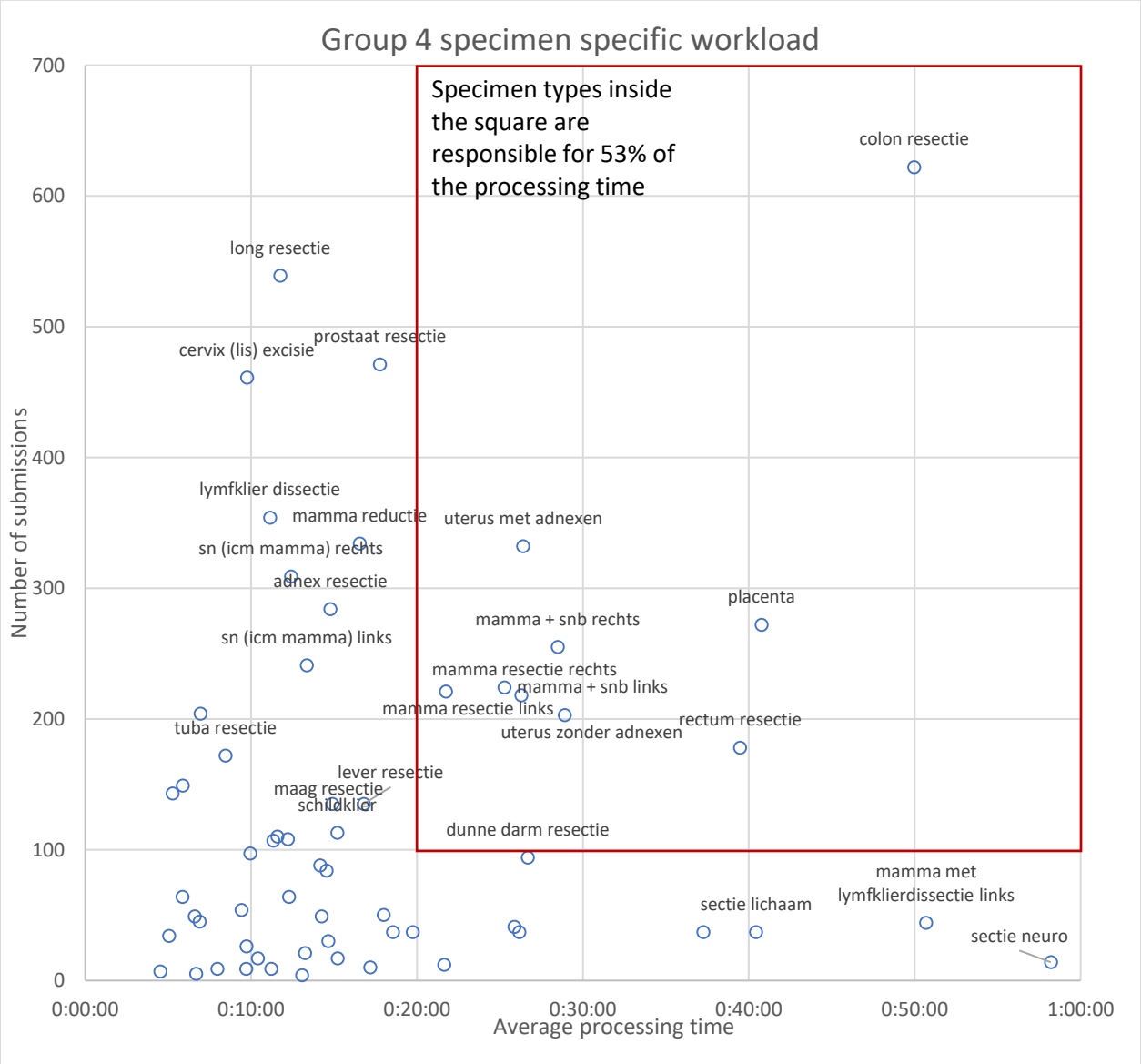


Figure 23 - Specimen specific workload of group 4 specimens in frequency vs. average processing time(Grossing timestamps; N=8154; 1/1/2016-31/12/2016)

The distinct differences in workload per specimen type could be used for workload balancing purposes, which could help with the daily fluctuation of demand shown earlier in Table 5. For this purpose, the findings are discussed with a pathologist with regards to medical urgency and potential for application in workload balancing. The discussion of these findings showed that routine placentas have little medical urgency compared to the other specimens, and could wait if that benefitted the throughput of the other specimens (S. Roothaan, personal communication, 24-07-2017).

4.5.6. Throughput time from grossing to embedding

Although the processing times of the individual grossing steps are interesting, they provide little information about the process as a whole. The total time it takes for an assessment to go from the grossing station to the embedding station is more interesting for this purpose. This process includes the processing of a specimen, the post-fixation of the cassettes, processing of the tissue, and additional waiting time before it is finally embedded. In Figure 24, the percentage of assessments that has arrived at embedding a given time after grossing is shown for each specimen group. It is striking to see that this is the only part in the process where the urgent group 1 material do not have the shortest throughput time. This is can be explained however, as group 1 material requires at least one hour post-fixation and is often processed through the overnight VIP, while group 2 specimens require no post-fixation and thus can be processed through the Express immediately after grossing.

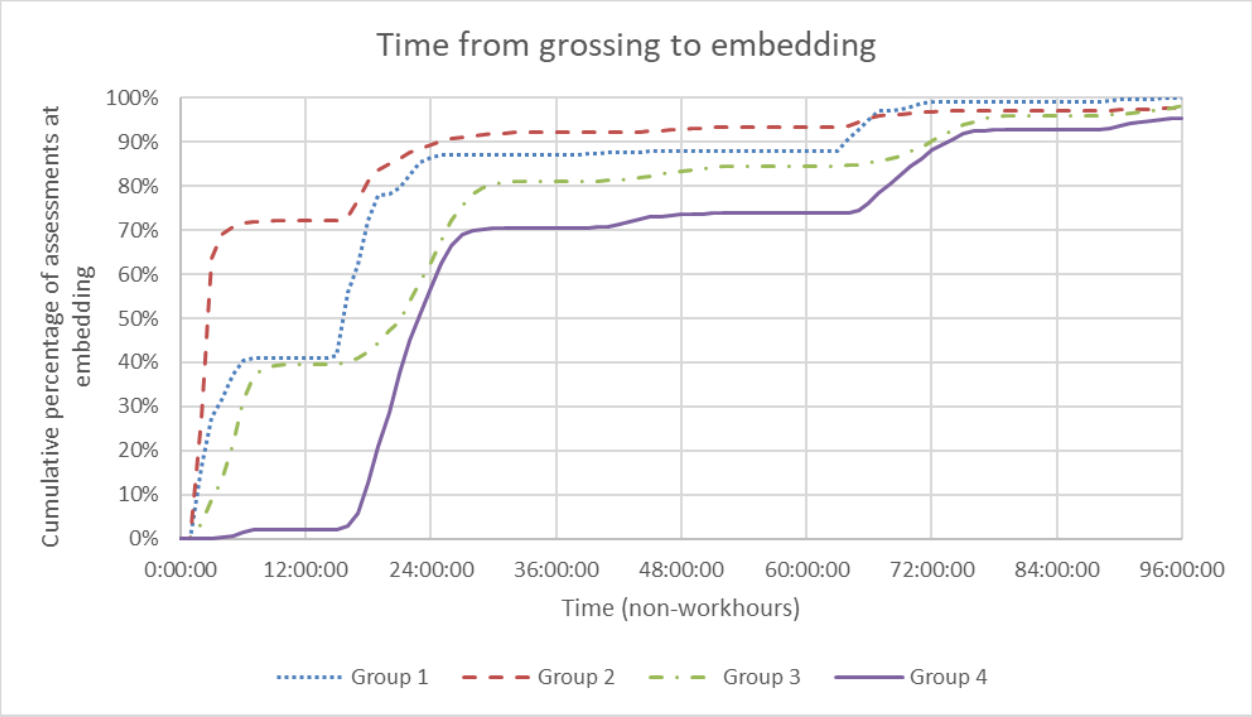


Figure 24 - Time from grossing to embedding (Grossing timestamps & Embedding timestamps; N=29856; 1/1/2016-31/12/2016)

The influence of the weekend is once again clearly visible, with an increase around the 70-hour mark of about 1/5th of the percentage of specimens that is not grossed within one day.

The group 4 material shows small bumps at the 40- and 90-hour marks, indicating that about 5% of the larger material takes two working days to get from grossing to embedding. According to analysts this occurs when material requires extra fixation after grossing, often caused by fatness of the tissue. Very rarely does it occur that there are more cassettes than the capacity of the VIP, in which case tissue is prioritized. Finally, the reason that the not all assessments have passed embedding within 96 hours after grossing is because of special procedures such as decalcification, which takes at least four days.

It is highly likely that the 28% of group 2 material that has to wait until the next day consists of the specimens delivered and grossed after 15:00, since the Sakura Express does not get filled after this time.

In conclusion, Figure 24 clearly shows the difference in processing time between usage of the VIP and Express tissue processing methods. Although some outliers can be seen in the graph, these are all accounted for by analysts for reasons required for quality. Extending working hours for additional Sakura express tissue processing runs would increase the number of cases processed the same day, as specimens from the 15:00 delivery could be included. However, unless processed immediately this would not benefit throughput times as it would only enlarge the batch that enters the system the next morning.

4.5.7. Throughput time Embedding

The throughput time per cassette of the embedding process as shown in Figure 25. On average, the duration of the embedding process is 1 minute and 13 seconds; the graph furthermore shows a mode at 40 seconds. A small tail is seen assumed to be caused by distractions and complex cases during embedding, however, a case taking longer than 3 minutes is rare.

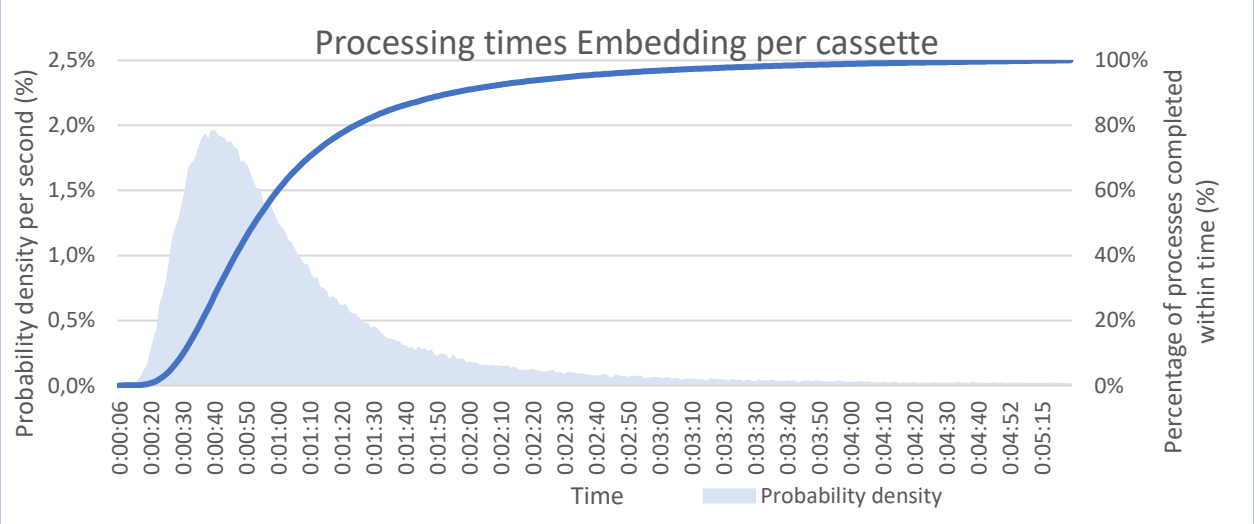


Figure 25 - Throughput time distribution embedding(Embedding timestamps; N=166447; 1/1/2016-31/12/2016)

Although the processing time of the embedding station is little noteworthy, the throughput time from embedding to microtome cutting seen in Figure 26 is remarkable as it shows a long "tail".

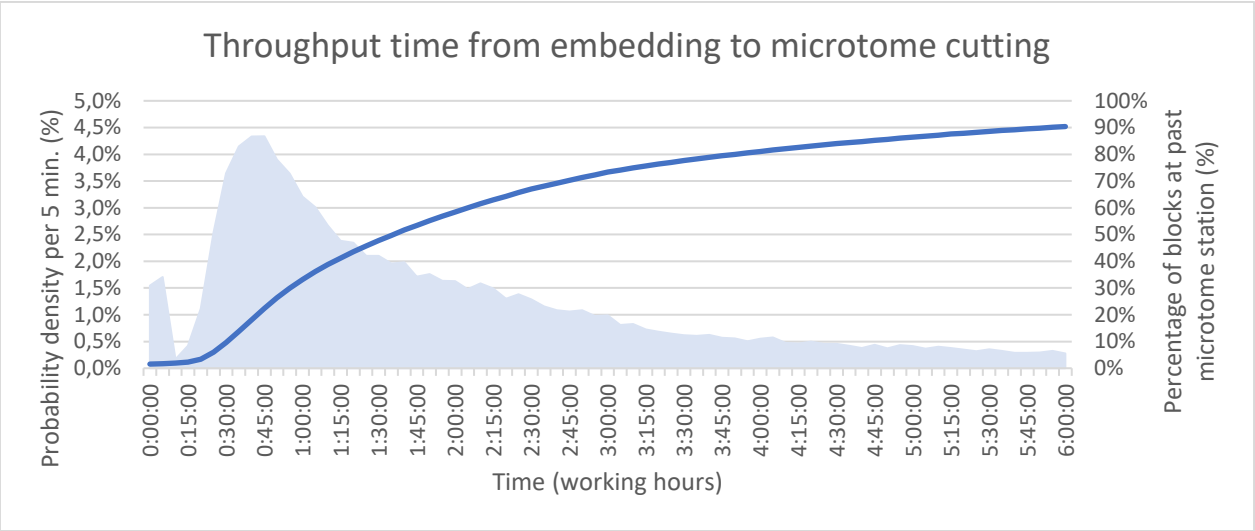


Figure 26 - Time from embedding to microtome cutting (Embedding timestamps & Microtome timestamps; N=47998; 1/1/2016-31/12/2016)

The probability density plot shows that most of the work has a high throughput rate. However, surprisingly only 90% of assessments start sectioning within six hours after embedding. This means that over 10% of material has to wait over six hours for no apparent reason, and indicates that a long "tail" of waiting times may be present. To further inspect this several calculations are conducted which can be found in Table 12. The large difference between average time and median time indicates a long-stretched right tail with blocks waiting for a large amount of time. Furthermore, 1,9% of assessments took over two days before being cut at the microtome after embedding, a waiting time equal to the laboratories internal throughput time aim, making the assessment nearly guaranteed to break the SLA.

Table 12 - Measures time from Embedding station to Cutting (Embedding timestamps & Microtome timestamps; N=47998; 1/1/2016-31/12/2016)

Time from Embedding to Microtome	#	%
Total assessments	53106	100%
Within 1 hour	16811	31,7%
Within 2 hours	30216	56,9%
Within 4 hours	42505	80,0%
Over one day	2837	5,3%
Over two days	600	1,1%
Peak CDF	0:40:00	-
Median time	2:02:34	-
Average time	11:39:57	-

The question remains what causes these waiting times. Part of the waiting times is likely to be caused by an imbalance in embedding and cutting capacity, which during times of peak pressure will create a large buffer of embedded cassettes awaiting cutting. Another possible explanation for this tail was provided by a coordinating analyst who mentioned that cassettes are handled FIFO according to cassette number instead of arrival time (personal communication, 19-07-2017). The FIFO method is utilized both at embedding and sectioning, this would negate the problem if all assessments arrived at embedding at the same time. However, as the assessments arrive using

continuous processing, assessments with a high assessment number can be embedded and followed by many assessments with lower assessment numbers, essentially locking the higher assessment number in the buffer between embedding and sectioning.

4.5.8. Throughput time Microtome Cutting

The microtome cutting processing time per block is shown in Figure 27 per second interval. The number of slides cut per block is variable with an average of 1,3 slides. The average cutting time is 2:44 with a standard deviation of 2:14; the mode of the cutting times is at 1:14. As the average cutting time is over twice the mode of the cutting time, it is clear that the right-side tail of the processing time has a large influence. This tail is likely caused by side activities such as distribution of new blocks to the different microtome stations, the melting of excess wax of newly embedded blocks, and interruptions by people walking in to request information. Although this tail is quite large, it is not necessarily a problem as people are likely performing other tasks during this time.

With regards to the internal rule-of-thumb of having one person embedding blocks for every two people cutting at the microtome, the ratio embedding speed to cutting speed is 1:13 to 2:44 resulting in a ratio of 1 embedder for every 2,25 people cutting. As such the rule-of-thumb is deemed close to reality and very useful, when in doubt preference should be given to microtome cutting.

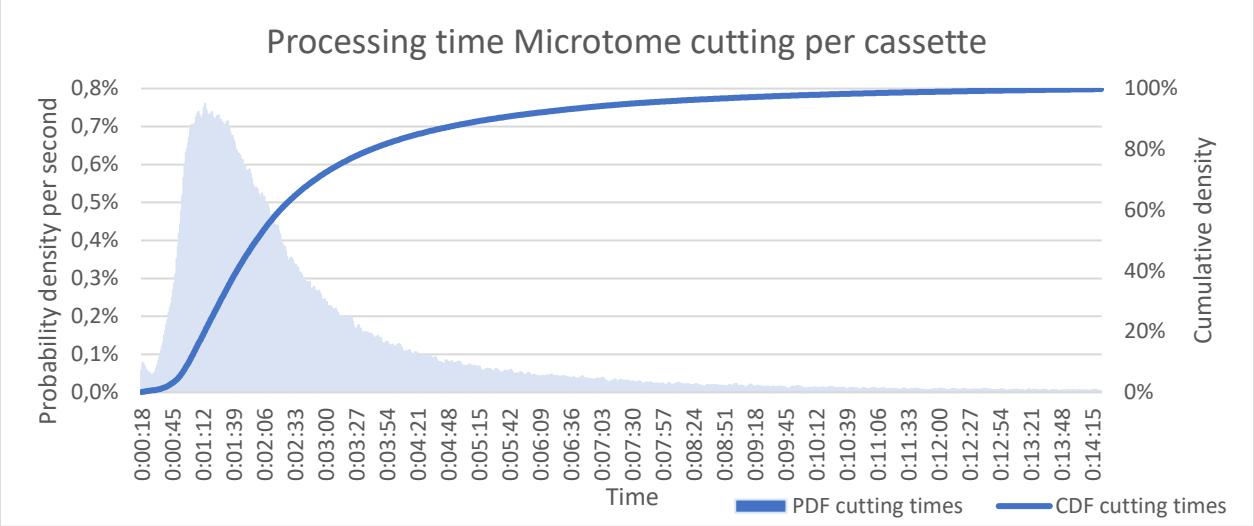


Figure 27 - Throughput time distribution embedding (Microtome timestamps; N=188163; 1/1/2016-31/12/2016)

4.5.9. Throughput time Staining & Scanning

The last step before being finished in the laboratory is the staining & scanning of the slides. Unlike the previous processing steps, the check-out from the laboratory only happens if all slides of an assessment are present. As such, Figure 28 shows the time from when the first slide of an assessment is cut at the microtome until the last slide is finished with scanning and the assessment is checked out. This process includes several consecutive steps: cutting, staining, cover slipping, scanning, assignment to a pathologist and check-out. The cumulative density function shows that 90% of assessments are checked out in just over four workhours after they have first been processed at microtome cutting. Considering the number of process steps that are involved and that all slides of an assessment must have finished processing, this can be considered good. The right tail of the PDF

is acceptable and is assumed to be caused primarily by larger assessments in which several slides traverse a longer production process due to differences in fatness of the tissue or other laborious characteristics. It is concluded that the staining and scanning process performs well and should not be changed.

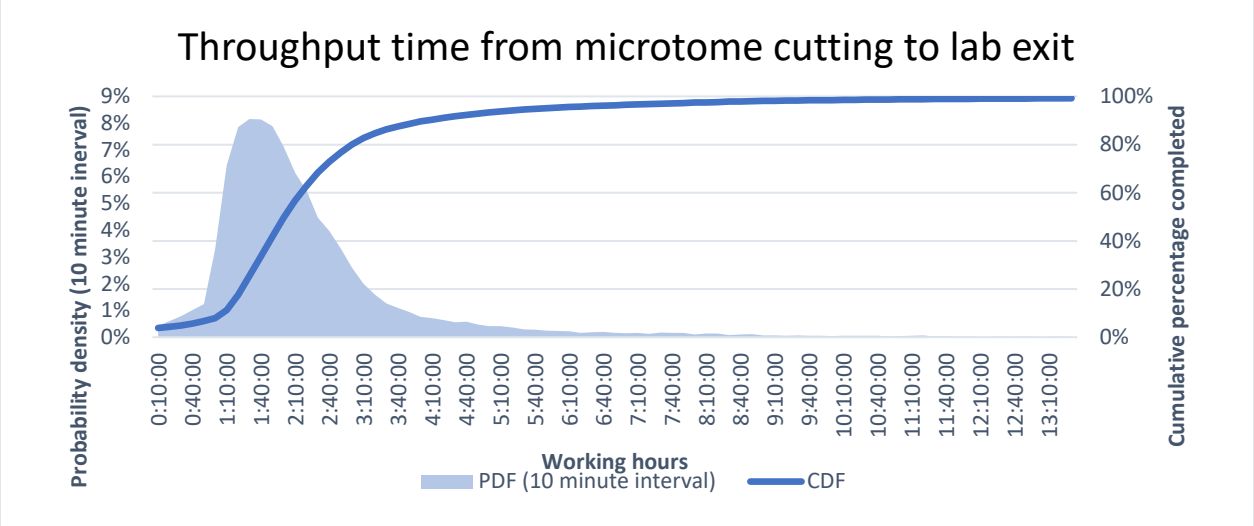


Figure 28 - Time from microtome cutting to laboratory exit (General production & Microtome timestamps; N=54756; 1/1/2016-31/12/2016)

4.6. Summary Data Analysis

In summary, it can be concluded that most processes at LabPON perform well, although measurement of throughput time using the lead time KPI would suggest otherwise. This is partly due to the strictness of the SLA, however also due to shortcomings of the measurement method, as it does not differentiate in the properties of specimens which is shown to have a big influence.

Slight variation exists in the demand for histological services both on weekly and daily basis, however this variation is quite predictable as it coincides with holidays and hospital planning. As noticed throughout the years, the latter can quickly change if a hospital reschedules their operating schedules, but will generally stay constant.

The main issue for the histology laboratory of LabPON are the large batch arrival moments caused by the coinciding delivery of approximately half of the daily demand at 15:00, and the batch resulting from the VIP tissue processor. It is suspected that a similar batching issue is also present in the transfer to pathologists, although this was not analysed due to it being out of scope for the research

Furthermore, long waiting times occur between embedding and microtome cutting. This is likely the result of the previously mentioned large batches caused by the VIPs in combination with the FIFO policy on system level (working on order of number i.e. registration time).

Finally, a small number of large specimen types are responsible for much of the workload in the system. It is suggested that placentas, which have a high workload and low medical urgency, can be used for workload balancing.

Chapter 5. | Theoretical framework

Chapter five provides relevant information from academic literature. First, the expected throughput times according to literature are determined and compared to the performance of LabPON. Special attention is given to Tissue Fixation of larger material, as this process is essential for quality but consumes large amounts of time. Next, the emergence continuous processing & lean methodologies within histology laboratories is described. Finally, an overview of Operation Research methodologies that can be applied is given, followed by further information about the chosen method.

5.1. Productivity standards for the Histology Laboratory

The throughput time of histological laboratory varies from several minutes (e.g. frozen sections) to several hours for the preparation of slides after receiving the material (Buesa, 2007a). Large tissue generally takes longer since it first has to fixate in formalin, a process which under normal circumstances takes at least eight hours, but for best results can be extended to 48 hours (Buesa, 2008; Buesa & Peshkov, 2012; Perry et al., 2016).

In 2010, R.J. Buesa has conducted a large-scale research to the throughput times of the different process steps in histological laboratories around the world (Buesa, 2010). The productivity standards established during this research can be found in Table 13, adapted to included only the averages over all laboratories and the average over large laboratories which are similar in size to LabPON.

Comparing LabPON to the productivity standards found by Buesa, it is found that LabPON no remarkably large differences are found. The following section refers to the findings found in the data analysis in Chapter 4.

Grossing and cassetting as described by Buesa are similar to the grossing of group 1, 2 or 3 specimens, and are both done by the same analyst during grossing at LabPON. According to the research, grossing on average takes 2:54 in large histology laboratories, followed by 1:56 for cassetting for a total of five minutes. As such, the average times at LabPON of around three minutes for group 1 and group 2 specimens and 4:44 for group 3 specimens are faster than average. The group 4 specimens are excluded from this assessment as Buesa focussed on the grossing of simple specimens.

Embedding at LabPON is conducted at a rate of 49,3 blocks per hour, very similar compared to 50 found by Buesa. Sectioning is conducted at a rate of 22 blocks per hour, which is slightly lower than the rate found by the study of 24 blocks per hour over all laboratories and 25 per hour at laboratories of similar size. Of course, it should be kept in mind that this figure included all general delays caused by small and often necessary side activities during microtomy cutting at LabPON which presented itself as a long but thin tail in the data analysis, such delays have not been included in the research of Buesa. If this tail of delays is disregarded, the mode of microtomy throughput times at 1:14 surrounded by a narrow peak of the microtomy time PDF suggest that an analyst at LabPON focussing solely at sectioning easily keeps up or even outperforms the productivity standard.

Table 13 - Productivity standards in histology laboratories; Adapted from (Buesa, 2010)

Human pathology: productivity by lab class

Task or aspect	Indicator	All labs	Lab classes (×1000 cases/y) ≥50
Grossing (cases/hour)	n labs	69	7
	Average	14	21
Blocks/case	n labs	196	16
	Average	3.2	2.4
Cassetting (cassettes/hour)	n labs	136	12
	Average	54	31
Embedding (blocks/hour)	n labs	168	12
	Average	50	50
Cutting: (blocks/hour)	n labs	174	13
	Average	24	25
Automated H&E (% of labs)	n labs	138	11
	%	51	91
Automated coverslipping (% of labs)	n labs	174	9
	%	43	78
HC (1 test every n cases)	n labs	145	12
	n cases	4.0	5.4
IHC (1 test every n cases)	n labs	137	14
	n cases	1.5	1.6
Staff available time (hour/day)	n labs	118	11
	Average	68	143
Time usage (%)	Average	74	92
Gross WFP (blocks/hour)	n labs	196	18
	Average	3.6	4.8
	Median	3.2	4.5
Total WFP (units/hour)	n labs	168	16
	Average	4.5	6.0
	Median	4.0	5.7

5.2. Tissue fixation

A critical step in the histological process is the fixation of tissue, which stops the decomposition of tissue and thus allows preservation of the specimen for diagnosis. The current method of fixation uses a fixing solution called Neutral Buffered Formalin (NBF), in which the active ingredient is formaldehyde (Buesa, 2008). When submerged in NBF, three processes are initiated: penetration of the tissue, binding of the tissue, and cross-linking proteins within the tissue. These processes take quite a long time, with penetration happening at a rate of about 1mm of tissue thickness per hour, followed by four hours until fixation and about 16 hours after penetration until complete cross-linking; complete binding of surgical specimens generally takes 24 to 48 hours (Buesa, 2008). Proper binding of the tissue however is essential for the histological quality, since insufficient fixation of the tissue causes difficulty with microtomy resulting in lower quality slides, as well as causing paraffin infiltration problems and negatively influencing subsequent tests (Buesa, 2008; Buesa & Peshkov, 2012).

It is possible to increase the rate of fixation in formalin by heating the fixation solution to 45°C, reducing the time for proper fixation of 3mm thick specimens from 48 to 10 hours (Buesa & Peshkov, 2012). However, warming the fixation solution introduces more fumes which are very harmful since

formaldehyde is toxic and a strong carcinogenic substance, thus strong ventilation would be required.

It should be noted that because of the strong carcinogenic nature of formaldehyde many attempts are made to find suitable substitutes for formalin. Although substitutes have been found this is determined to be out of scope for this research since, formalin still offers too many advantages (Buesa, 2008).

For LabPON using heated formaldehyde could provide an opportunity to drastically reduce the throughput time of group 4 material that is submitted to the laboratory early in the morning, as specimens could be ready for grossing the same day and potentially be included in the overnight VIP. This would reduce the throughput time for these specimens by a day.

5.3. Continuous throughput processing

Although many technological innovations were introduced in the histopathological laboratory during the previous century, the workflow of the conventional histopathological laboratory essentially stayed the same until the turn of the century (Buesa, 2007a; Vernon, 2005). All tissue was left to fixate on formaldehyde overnight, followed by grossing the next day before spending another night being processed in the tissue processor. As such, tissue was accumulated in large batches throughout the day, which had to be completely processed during the morning. This resulted in long turnaround times and skewed workloads throughout the day (Buesa, 2007a; Vernon, 2005).

Since 1997 however, continuous throughput rapid tissue processing machines have been in development, using common histologic reagents and microwave energy to rapidly process tissue (Morales et al., 2002). This allows tissue to be processed much faster allowing for tissue processing during the day, which has a large impact on the planning of the histological process (Buesa, 2007b; Morales et al., 2002). In modern days, the continuous throughput processing machines have been adapted by most histology laboratories and have revolutionized the workflow by making it possible to shorten turnaround times by up to one day (Vernon, 2005).

Leeftink et al. performed a study at the histology laboratory in the UMC Utrecht where continuous throughput processing was not yet implemented and all tissue was still processed overnight. During the study, a MILP model was constructed to test the influence of implementing continuous throughput processing; together with staggered shifting and earlier opening hours. The study showed that implementing continuous throughput processing by processing tissue during the day could decrease the turnaround time of the histology laboratory by up to 25% and level workload over the day (Leeftink et al., 2016b).

At LabPON, continuous throughput processing has been implemented using the Sakura Express tissue processing machines. As mentioned before these machines are used for most of the material, but are less suitable for fat material and require different protocols for molecular testing if used. For this reason, the overnight VIP is still used for the large group 4 cassettes which are often fat and some of the group 1 cassettes for homogeneity in molecular testing protocols. This essentially creates a hybrid between the conventional and modern laboratory. The strength and weaknesses of both

systems need to be kept in mind while planning the workflow, to have both systems complement each other and achieve the best results. Furthermore, a complete transfer to continuous throughput processing would be desirable in the future, provided that the technology can deliver the desired quality.

5.4. The lean laboratory

Like most healthcare organisations, medical laboratories have experienced strong pressures to increase productivity and lower costs during the previous decades due to increased demand caused by an aging society with continuously growing expectations of quality and speed, while financial conditions for healthcare systems mostly have remained equal or have even shrunk (Gabriele Halwachs-Baumann, 2010; Poksinska, 2010; Quetz, Dantas, Hirth, Brasil, & Juaçaba, 2015). In reaction to this challenge, many healthcare organisations have adopted a performance improvement methodology originally called the Toyota Production system, but is colloquially known as lean management (Poksinska, 2010).

In its core, the lean approach aims to seeks to find improvements within the framework of an organisations existing processes, in order increase customer value and reduce waste without requiring high investments (Poksinska, 2010). Waste in this context is defined as "anything that does not add value to the final product or service, in the eyes of the customer"; a general estimation is that waste accounts for 30% to 50% of healthcare spending (G Halwachs-Baumann, 2010). This waste can present in the form of over-production; waiting times; transport; over-processing; excess inventory; unnecessary movement; defects; and unused expertise (Symbol, 2017).

Lean thinking consists of the following five principles (Symbol, 2017):

1. Value – Identifying value for the customer
2. Value stream – Knowing how the value is created
3. Flow – Creating flow in the process by eliminating waste
4. Pull – Produce and supply based on demand
5. Perfection – Continuously striving for perfection in production

A literature review conducted by B. Poksinska found little evidence of the complete Lean philosophy being applied in the healthcare system. Rather, lean is often seen as a set of tools and techniques for improving processes, most often applied the healthcare context to understand the organisations processes, identifying the value stream and creating a continuous flow (Poksinska, 2010). As such, most healthcare organisations only implement the first three of the five lean principles. However, the lean methodology includes many more techniques which can be applied, such as Poka Yoke methods for mistake prevention, the 5S-system for an orderly and neat working environment, the creation of Standardized Operating Procedures (SOP), visual management, heijunka practices for levelling out the workload and continuous improvement by lowering work-in-progress (WIP) to identify problems (Symbol, 2017).

Several applications of lean methodology to histology laboratories have been found. These papers show that through value stream mapping and analysing and simplifying the movement patterns of

employees, lead times could be reduced from 9 to 5 days (Quetz et al., 2015). Another study showed that smart redesign of workstations could reduce travel outside an employees' optimal working space from 38% of procedures requiring travel to just 9%, as such drastically reducing analysts travel (Yerian, Seestadt, Gomez, & Marchant, 2012).

LabPON has already conducted several lean projects and has enjoyed the opportunity of designing the current laboratory during construction. Because of this, the laboratory layout has been designed around the workflow of the histology laboratory, which has eliminated most unnecessary movement wastes. With regards to implemented lean methodologies, the workload is levelled out in the grossing area in a way similar to heijunka practices. Also, visual management has been implemented by using colour coded cassettes and slides for specimens requiring specific treatment or priority status. Procedures have also been extensively described in Standardized Operating Procedures, and deviations from procedures or mistakes are tracked and analysed. Furthermore, time is made to properly clean and tidy the work environment every day. An effort is made to keep the work-in-progress low, although the data analysis showed waiting times indicating high WIP caused by batched arrivals. With regards to the pull principle, the presence of a specimen in the system inherently indicates customer demand. Since a specimen is required to start processing, LabPON will always process on customer demand. Additionally, this means that waste in the form of over-production and excess inventory are unlikely to occur at LabPON. Finally, an effort is made by the coordinating staff to continuously strive for better performance.

In conclusion, it seems that LabPON has implemented lean methodologies solidly as they have engaged in all five lean principles, which is rarely seen in literature (Poksinska, 2010). With regards to waste, the main forms to be aware of are waiting times; defects; and unused expertise.

5.5. Operations Research methods

5.5.1. Operations Research methods in general

Operations research is the scientific approach to decision making that seeks to design and operate a system as best as possible, under the condition of scarce resources (Winston, 2004). A system in this sense refers to an organization of interdependent components that work together to accomplish the goal of the system.

The scientific approach to operations research generally involves mathematical models, which is a mathematical representation of the reality which can be used to better understand a situation and can help to make better decisions. Of course, different questions require different approaches, as such many different models have been developed for use in operations research. Several examples of such methods are ((Mixed-)Integer) Linear Programming models; Network models; Game theory; Inventory models; Markov chains; Dynamic Programming models; Queueing models; Forecasting models; and Simulation models (Winston, 2004).

All the methods mentioned above have specific strengths and limitations. Therefore, it is important to select the right operations research method for the question at hand. In the next paragraph, the use of operations research methods in health care will be discussed as well as the reasoning behind

the choice of method. This information will be used to make a substantiated decision about the type of operations research method to use.

5.5.2. Operations Research in histology laboratories

Several papers can be found in the literature discussing the application of operations research methods and mathematical models in the context of histology. Although many papers discuss topics such as simulation or linear programming, most are aimed at the development of medical classification schemes and automation of diagnosis in light of the rapid development of digital pathology (Fine, 2014; Mangasarian, Street, & Wolberg, 1994). However, some papers are found that discuss the application of operations research methods to the histology laboratory.

The main contributor of operation research papers for histology laboratories is A.G. Leeftink et al., who published three papers concerning the reduction of turnaround times in the histology laboratory using MILP models. For this purpose, all three papers consider optimization of batch scheduling by implementing tissue processing during the day. Implementation of tissue processing during the day was found to significantly reduce the turnaround time by 20% to 25% while providing a more levelled workload distribution (Leeftink et al., 2015, 2016a, 2016b). One of the papers also considers staggered shifting and earlier opening hours: staggered shifting showed no significant benefit in turnaround time compared to the baseline; earlier opening hours combined with tissue processing during the day provided the best performance, but was not significantly different from just tissue processing during the day (Leeftink et al., 2016b). With regards to implications for this research, the findings confirm the decision of LabPON to have implemented continuous rapid processing, and provide interventions to be considered.

Another research evaluated the feasibility of implementing whole-slide imaging using business process modelling software. This model is limited to the embedding, sectioning and staining processes in the laboratory and its use is limited to the evaluation of turnaround time after the implementation of a whole-slide scanner. Furthermore, the paper is dated, as it concludes that implementation of whole-slide scanning is infeasible in reality, a statement which is refuted by the successful implementation of digital pathology at LabPON (McClintock, Lee, & Gilbertson, 2012).

A paper by Muirhead et al. (2010) describes the use of a top-down 'Pathology Economic Model Tool' to generate an insight in the workflow and cost distribution in pathology laboratories, allowing for a better understanding of cost driving factors to aid in cost effective decision making. In the research it was found that labour and overhead together contribute approximately 80% of the total cost for a single H&E stained slide (Muirhead, Aoun, Powell, Juncker, & Mollerup, 2010).

Finally, a paper of Laurence Brown (2004) is found about improving histopathology turnaround time using a process management approach. However, unfortunately no access could be gained.

In conclusion, several studies have been found in which operations research methods have been applied to the context of the histological laboratory. For analysis of interventions over the whole laboratory using an existing model, the MILP model developed by Leeftink is the most promising model. However, the MILP model considers a batching problem at a tactical level (Leeftink et al.,

2016a). As such, it is concluded that a gap in literature exists with regards to reducing variability and throughput time in the operational scheduling of the histology laboratory. In order to analyse the system on the intended level of depth, a mathematical model would quickly become too complex, especially to compare different proposed system designs accurately (Law, 2007). For this reason, the choice is made to focus on simulation models for modelling the laboratory.

5.5.3. Simulation methods in health care

For over 40 years the healthcare domain has been successfully analysed by the employment of simulation methods. Recently, the role of simulation modelling has become more important and recognized. As such, simulation modelling techniques are rapidly being adapted within the healthcare sector, which can be observed by the strong increase in health-care simulation papers that are released (Brailsford, Harper, Patel, & Pitt, 2009; Gunal, Pidd, & Günal, 2010; Marshall et al., 2015; Mielczarek, 2016).

The simulation methods that are used within healthcare are most commonly classified in four categories: Monte Carlo; discrete-event simulation; system dynamics; and agent-based simulation. The selection of a simulation method is mainly influenced by the area of the problem, in which the following distinct areas have been identified: health policy; healthcare system operation and improvements; forecasting; healthcare system design; and medical decision making. Nevertheless, other factors such as goals, time horizon of the research and amount of input data also influence choice for a model (Mielczarek, 2016).

Discrete-Event Simulation (DES) is the most commonly used simulation method for healthcare applications. It is the dominating method in the domain of healthcare system operations and improvements, as it is very supportive to the operational level of healthcare management. DES models simulate processes over a time period and follow the interaction of individual, dynamic objects with the system's resources, and are used to analyse queuing processes and networks of queues (Marshall et al., 2015). The time horizon of DES is most often short to medium term and the aggregation of data and formulas goes down to the patient level. Furthermore, the input data required needs to be very detailed to generate a valid simulation (Mielczarek, 2016).

Monte Carlo simulation is often applied in the evaluation of economic effectiveness of health policy and medical decisions, as well as forecasting economic and clinical indicators. Monte Carlo simulations try to estimate the distribution of output variables given a certain sampling of several probabilistic input variables. These kinds of simulations are often utilized for the tactical level of healthcare management, where they are utilized for managing risks. The aggregation of data and formulas goes down sub-group level and the simulations are aimed at a medium-term time horizon. Like DES, Monte Carlo simulations require a large amount of process data to be valid (Mielczarek, 2016).

System dynamics is a method that is often used in a higher, more aggregated and strategic level, and as such is mostly used to solve problems on the strategic level. It uses a set of stocks and flows to generate a holistic perspective of a system. System dynamics simulations require less input data

then its stochastic counterparts, however, appropriate calibration of key parameters is still of importance (Mielczarek, 2016).

Finally, agent-based systems have gained increased interest the past several years and are mostly applied to the spread of infectious diseases and epidemics. It is a bottom-up approach which simulates the interaction between different agents, each operating with an own set of rules. The agent-based systems are, like DES, supportive to the operational level and are used to study consequences at the collective level that are not directly predictable from the behaviour of individuals (Mielczarek, 2016).

In conclusion, it is clear that the different methods frequently used for healthcare operations modelling each have their distinct characteristics. DES is most commonly used and is strong in analysing queuing processes and networks of queues. Monte Carlo simulations are well suited for forecasting economic and clinical effectiveness of health policies and medical decisions. System dynamics is suited for generating high-level holistic system perspectives. And finally, agent-based systems are well suited for assessment of epidemics. As such Discrete-Event Simulation seems the most likely choice of method, which will be discussed in the following paragraph.

5.5.4. Choice of Method

For simulating the histology laboratory of LabPON the choice is made to use discrete-event simulation. This choice has been made because of the following reasons (Law, 2007; Mielczarek, 2016):

- It offers a flexible simulation, that can be easily adapted to compare different interventions
- It offers visual representation of the simulation, which helps people comprehend the model
- It has proved useful in many similar applications
- It can handle variability, uncertainty and complexity of dynamic systems
- The required data to build a valid DES model has become available through the data analysis

5.6. Discrete-Event Simulation

5.6.1. Simulation in general

Simulation is the technique of using computers to imitate real-world processes and systems by mathematical or logical relationships, in order to analyse and understand the behaviour of the corresponding system (Law, 2007). Since most real-world systems are too complex to be modelled in a completely realistic fashion, simulations are inherently abstractions of reality and are used to estimate the true characteristics of the system. As such, simulation finds its use in answering questions of what would happen if an intervention were to be implemented in a system, without causing disruptions in the actual system (Law, 2007).

Further advantages of simulation models include the following (Law, 2007):

- They are more capable of modelling complex systems than mathematical models
- They allow for estimation of system performance under a set of operating conditions

- Alternative proposed designs can easily be compared to each other
- It allows for high control over the experimental conditions
- It can be used for the study of a system over a long-time frame

According to Law, "Discrete-Event Simulation concerns the modelling of a system as it evolves over time by a representation in which the state variables change instantaneously at separate points in time. These points in time are the ones at which an event occurs, where an event is defined as an instantaneous occurrence that may change the state of the system."(Law, 2007). In simpler terms, it is the scheduling and chronological execution of different tasks, each of which influences the system. All laboratory tasks can be scheduled in this way, such as the arrival of a specimens from the hospital at 15:00; the completion of grossing, 4 minutes from the starting moment; and the ending of a workday for an analyst at 16:30. Modelling all events together creates a simulation model that yields an abstract rendering of reality.

5.7. Conclusion

In this literature study, topics are discussed that can be grouped in three different categories.

First off, productivity standards for histological laboratories according to literature are provided. These are used to compare and gauge the performance of LabPON. It was found that the histology laboratory at LabPON performs above the average productivity standards of all histology laboratories and on par with histology laboratories of similar size.

Secondly, methods and methodologies used to improve processes in the histological laboratory and healthcare systems in general were discussed, and compared to current application at LabPON. The first method discussed was accelerated fixation of tissue using heated formalin, which can reduce time until complete fixation; binding; and cross-linking for 3mm thick specimens from 48 to 10 hours. The second method was the implementation of continuous throughput rapid tissue processing and the subsequent paradigm shift it caused in the planning of histological processes. Finally, the application of lean methodologies was discussed, which LabPON has already largely implemented. With regards to types of waste, it is stated that the main concern of LabPON should be waiting times; defects during the process; and unused expertise.

Finally, operations research methods were described and the potential applications were explained. Following this explanation, it was found that although an operations research model of the histology laboratory at the tactical level regarding batching problems exists, no such model exists for the operational level. As such, a gap in literature was identified regarding an operational model of the histology laboratory aimed at reducing throughput time through the reduction of process variability; the decision was made to create an operations research model for this purpose.

Discrete-Event Simulation was chosen as a suitable method for modelling the laboratory. This choice was made because it is a powerful method which is easy for others to comprehend due to the visual representation and offers flexible simulation that can handle the variability, uncertainty and complexity of dynamic systems. As well as the fact that all required data necessary to build a valid DES model has become available through the data analysis.

Chapter 6. | Interventions

The sixth chapter of this thesis answers the question what organizational interventions are possible at LabPON. For this purpose, several interventions are suggested, these interventions come from a combination of findings in literature, stakeholders, and insights from the data analysis. Finally, a choice is made regarding which interventions are promising to further explore in this research.

6.1. Shift in personnel planning

The first two interventions are concerned with shifting the personnel planning for certain employees, in effect creating staggers employee shifts. Although the research of Leeftink et al. (2016b) also considered staggered shifting and found no significant effects, the interventions will be considered as LabPON operates in a different context, with a large part of the specimens arriving as a batch in the afternoon and the scanning of slides included in the process. Earlier opening hours as suggested by Leeftink et al. (2016b) will not be considered, because the reasoning behind this intervention was reducing waiting time between completion of overnight tissue processing and the start of the analysts; a period which is just 30 minutes at LabPON (LabPON, 2017b).

6.1.1. Later stop for completion of group 2 & additional express tissue processing runs

It has been observed that a large influx of specimens arrives at LabPON at 15:00 (page 23, Figure 16, Figure 17). After arrival, it takes about ten to fifteen minutes for specimens to arrive in the laboratory, leaving just over one hour to process all the specimens. This time is currently mainly used for the processing of the prioritized group 1 specimens. The waiting time analysis confirmed this by showing that just 55% of group 2 specimens are processed at grossing the same day it came into the laboratory (page 24, Figure 18). Furthermore, a shortage of capacity has been observed at the express processing machines in the morning leading to a bottleneck in the process flow.

These findings indicate that the express processing machines are flooded in the morning on a structural basis, because of the confluence of the specimen influx of the previous day which is largely processed in the morning, the cassettes that have been post-fixating overnight, and the new specimens. Thus, a solution is desirable to relieve the pressure no this bottleneck.

One method to do so is to reduce the pressure of the 15:00 specimen influx on the morning by completing a larger part of it on the day of arrival by having one or two analysts work later. This would allow for the grossing of more specimens and additional express tissue processing runs, providing extra daily tissue-processing capacity.

The specimens that should be grossed during this time are the group 2 specimens, since they can be grossed quickly and unlike group 3 cassettes do not require post-fixation. As such the completed cassettes can be included immediately in one of additional express tissue processing runs.

This intervention is expected to result in a more balanced workload during the morning, thus preventing unnecessary waiting times. Furthermore, the group 2 throughput time is expected to increase.

6.1.2. Shift in Staining & Scanning worktimes

Although the results of the data analysis concerning staining & scanning were positive with regards to throughput time, the management has remarked that many slides are left between cutting & staining at the end of the day. This means the slides must be stained and scanned during the morning, prior to distribution to the pathologists. As a result, the pathologists receive these slides roughly two hours into their workday. Many of these slides are routine HE-stained slides in response to which the pathologist might request additional special staining or immunological tests. Since these additional tests take time to prepare, it is beneficial to request these as early as possible in the day, to avoid a capacity overload at the end of the day at staining or immunology.

A possible intervention would be to shift the working hours of the scanning shift and having this employee also run the routine HE-staining during the later hours. This would result in all routine slides being finished at the end of the day, and thus available at the pathologists first thing in the morning. This enable pathologists to request special staining or immunological tests earlier in the day, thereby levelling the workload over the day. As a result, the peak pressure could be reduced for the immunology and the chemical staining station for additional stains.

6.2. Changing specimen delivery schedules

Earlier, an intervention is proposed to process the large specimen influx at 15:00 by extending working times to complete group 2 specimens. However, this intervention would not be necessary if no large influx of specimens occurred at 15:00. For this purpose, the specimen delivery schedules are inspected to see if intermittent deliveries might be possible. This will result in a better spread of submissions through the day, improving the work-balance over the day and reducing the specimen influx peak at 15:00.

6.3. Embedding and sectioning on arrival order

As observed in Paragraph 4.5.7. Figure 26, an unexpectedly large waiting time exists between the embedding and sectioning, with 20% of the material waiting over 4 hours before beginning sectioning after embedding, and 5,3% even waiting more than one workday. Which is a significant waiting time for two processes which are sequential and both take just over a minute per cassette.

The cause for this waiting time is hypothesised to be two-fold: an imbalance in embedding & cutting capacity and the handling of cassettes on a system FIFO with priority, where first the urgent material is handled, followed by the lowest research ID. As such an intervention should focus on balancing the capacity of the embedding & cutting stations and switch the processing selection method from selecting the lowest research ID to the earliest arrival at the embedding station or microtome, essentially implementing FIFO on process level with priority for urgent material.

In Paragraph 3.4.4. it is shown that in total twelve embedding and microtome stations are available, with a normal occupancy of up to eight analysts. As such, the capacity is not limited by the number of available stations but the number of analysts working. This allows for capacity balancing between the embedding stations and cutting stations by switching an analyst between embedding and cutting depending on the intermediate buffer. One way to implement this is by creating a small

transition buffer between the two processing steps with visual indicators to indicate which kind of processing capacity is required. If the buffer is nearly empty, the analyst will start embedding until the buffer is again sufficiently filled.

6.4. Workload balancing with large specimens

The large group 4 specimens have a relatively long processing time and need to be grossed by analysts that have been trained for cutting large specimens. Furthermore, due to the long fixation times, it is important that little delay is made with grossing to have an assessment meet the current SLA. Add to this the inherent variation in number of submissions of group 4 specimens and it becomes clear that it generates a sizeable amount of work pressure in the grossing room.

During the data analysis, it was observed a large variation existed in the workload in different specimens, as well as the frequency with which they are submitted. A further investigation was made into the high-workload high-frequency specimens and showed that the following categories are responsible for 53% of the workload:

- Colon resection
- Uterus resection
- Placenta
- Mamma's
- Rectum resection

Since these specimen types have such a large impact on the total workload for grossing of large specimens, the question was posed if any of these specimen types could be used for workload balancing. Meaning processing less of a specific specimen type during times of peak pressure, and processing those on days when fewer specimens are submitted.

A pathologist was asked to judge the medical urgency of the provided specimens and noted that routine placentas have lower medical urgency than the other specimen types, and might be used for such workload balancing purposes (S. Roothaan, personal communication, 24-07-2017).

Looking at the data it is found that the placentas represent 6,7% of the workload for grossing of large specimens. Looking back at the fluctuating demand, discussed in Paragraph 4.4.2. , it is found that the daily fluctuation of demand compared to the average is roughly similar.

As such a possible intervention would be to only process placentas on Mondays and Fridays, thereby reducing the workload during the midweek and balancing the load during the entire week. Implementing this strategy would increase the lead time of placentas by zero to three days, depending on day of submissions, while decreasing the lead time of all other specimens in the system as the workload and capacity usage is balanced throughout the week.

6.5. Shortening fixation time

Currently, when a large specimen arrives it is cleaned and put on new formaldehyde to fixate overnight. As such, all specimens first need to be handled at the laboratory before entering having

to wait overnight. For large specimens that arrive during the 12:30 shifts and 15:00 shifts this provides an efficient use of time, as the material is prepared and left to fixate outside of working hours. However, the specimens that arrive at the laboratory around 17:10 and 09:05, which contains all specimens from surgeries after 14:30 the previous day, do not get processed in the wet room the same day as excision. This delays fixation until the night of the day after the surgery. Consequently, it will arrive at the grossing station a full two days after the specimen was collected, after which it is required to wait for another overnight process in the VIP. For this material, shortening of the fixation process could yield a reduction of lead time of one day, by fixating the material during the day instead of including it in the overnight VIP run.

As the material is put in a container with formaldehyde right after surgery, the described specimens have had a minimum of 14 hours to fixate assuming the last excisions are made at 17:00 and they are processed at the histological laboratory at 07:00. Using the fixation times described in Paragraph 5.2 this would mean that the specimens are at least fixated to a depth of 10mm below the tissue surface. According to S. Roothaan, specimens can be grossed as soon as they are properly fixated, cross-linking does not have to be completed yet as this continues during post-fixation. As such, specimens could be grossed and lamellated into thin slices before finishing the cross-linking.

However, proper cross-linking needs to be ensured before processing the tissue through the VIP. It is uncertain if the current method of post-fixation would result in proper cross-linking. Therefore, it is suggested to use heated formaldehyde during post-fixation as described in 5.2, this would increase the rate of cross-linking nearly fivefold and allow for tissue processing through the VIP one day earlier.

6.6. Change in Service Level Agreement

The current Service Level Agreement (SLA) of LabPON is set up in a rather one-size-fits-all manner, with the promise to complete 80% of all examinations without additional tests within three working days and 80% of examinations with additional tests within five working days. Although such a SLA is clear-cut and easy to understand, it does not take the nature of the specimen in account. As a result, laborious large specimens that require a lot of time could be branded as too slow by the SLA, even though it was handled very efficiently. Conversely, an urgent small specimen that takes little to no work is can be handled with horrible efficiency and still be okay with regards to the SLA.

A fairer approach would be to change the SLA in a way that reflects the nature of the specimens. For example, one working day for urgent group 1 specimens; two working days for group 2 specimens; three working days for group 3 specimens; and 4 working days for group 4 specimens; with an additional two working days in case of special testing.

Of course, this intervention is a matter of problem solving by changing the measurement method. However, an argument can be made that it is unfair to both the customer and the system to present a SLA norm without keeping the nature of the specimen in mind. For the customer receives a less accurate expected response time than is known, and the system is unjustly reprimanded by the SLA for work that takes longer by nature.

6.7. Summary of interventions

Seven interventions have been proposed in this chapter. The first two interventions have been proposed by the management of LabPON and are shifting grossing worktimes and shifting staining and scanning worktimes. The first is aimed at allowing additional express tissue processing runs and more specimens of the afternoon delivery to be grossed, the second at having more assessments completed the same day, allowing more assessments to be on the desk of the pathologist first thing in the morning. The third intervention is changing the specimen delivery times, aimed at spreading out the specimen deliveries to the laboratory to reduce the arrival peaks. The fourth intervention is implementing embedding and sectioning on arrival order, which is aimed at reducing the waiting times observed between embedding and sectioning. The fifth intervention is workload balancing with large specimens, specifically placentas, reducing peak pressure on the system with the trade-off of having the less urgent placentas take zero to three workdays longer to process. The sixth intervention is from literature and concerns shortening the fixation time, aimed at reducing the throughput time of large specimens. Finally, the last proposed intervention is changing the SLA to reflect the actual workload for a specimen.

All these interventions have an influence on the production of the laboratory. However, the extent of the influence and possible side effects are hard to predict within a complex system such as the laboratory. To investigate the actual effect of the proposed interventions, they are modelled and evaluated in a discrete-event simulation model of the laboratory; this process is discussed in the following chapters.

Chapter 7. | Simulation

This chapter provides an insight in the development of the simulation model. The model is developed according to the simulation study design methodology by Law (2007), as stated in Chapter 2. First, the collection of data and the design of the model is described. Next, the simulation model is verified to match the conceptual design without errors or bugs remaining in the program. After the program is verified, pilot runs are conducted for validation of the model. Finally, experiments are designed for analysis of the different interventions.

7.1. Design of the model

The context of the histopathological process and laboratory is already described in Chapter 3. However, a simulation is always a simplified abstraction of reality, for this reason a conceptual model design is established here to aid in the structured development of the simulation model.

Law (2007) defines several activities which should be conducted during the conceptual design of a model, these activities comprise of:

- Gathering information about the system structure and operating procedures
- Collecting data to specify model parameters and input probabilities
- Keeping a document of written assumptions
- Choosing the level of model detail of the model, it should be noted that one-on-one correspondence between model and reality is not desirable
- Establishment of a simple model structure
- Regular interaction with the manager

It is apparent that a number of these activities are performed in earlier chapters of this thesis. Chapter 3 provides in-depth information about the system structure and operating procedures. For further information about the system, documents delineating standard operating procedures have been extracted from iProva (the document management portal of LabPON) during the design of the model. If uncertainty regarding the system still persisted, the questions were discussed with analysts in the laboratory. The data to specify the model parameters and input probabilities are analysed in Chapter 4. A transcript with written assumptions has been kept and can be found in the appendix.

A simple model structure has been established using the scope of the research as a guideline. As the scope of the research is limited to the histology laboratory, the histopathological process found earlier in Figure 3 is reduced to a process containing just the laboratory steps as seen in Figure 29.

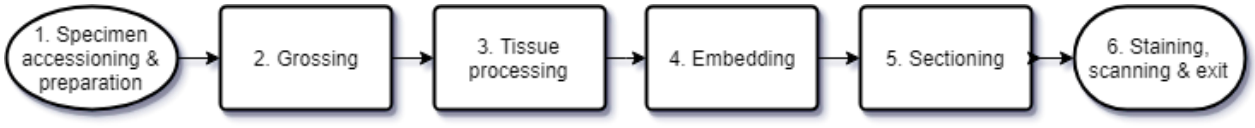


Figure 29 - Conceptual design of the simulation model

With regards to the level of detail, the choice is made to model each processing station on a level in which all activities conducted at that processing station are encompassed in the processing time of the station, similar to the level of the data analysis. This way, information found in the data analysis is usable in the simulation model to create a valid representation of the real situation, while still providing enough detail to investigate the research objectives. With regard to the staining & scanning procedures, the decision is made to merge the processes into a so called 'black box' approach, since the data analysis showed little reason to model the internal processes of these steps, and correctly doing so would be very difficult with the available data. This choice however does not affect the capability of the model to be used for effective decision making. Finally, the head of the histology department and the supervisor from the university have been involved during the design of the model.

In order to convey how the system of interest is modelled and to avoid communication errors, the assumptions made for the model are provided below (Law, 2007).

- Laboratory lead time is the time from arrival at the laboratory until distribution to the pathologist.
- Due to lack of information regarding assessment generation, it is assumed assessments are generated uniformly over the day between 08:00 and 16:00 by hospitals and GPs.
- All assessments coming from Front Offices have already been accessioned; all assessments from other sources still need to be accessioned.
- The demand and capacity per day is assumed to stay constant, to reduce complexity and enable clear examination of material flow within the laboratory.
- Non-standard procedures such as decalcification are assumed not to occur, as adding these procedures would make the model needlessly complex while providing little additional information regarding the flow of assessments.
- In consultation with the coordinating grossing analyst, fixation preparation is assumed to be normally distributed with an average of 5 minutes and a standard deviation of 4 minutes, with a lower bound of 1 minute and upper bound of 15 minutes. One hour overtime is allowed to ensure all large material that arrived at 15:00 is processed.
- It is assumed that the transportation service to the laboratory always arrives exactly on the scheduled time.
- Cassettes are processed at tissue processing in arrival order after they have finished post-fixation.
- For embedding and fixation, group 1 specimens are prioritized, the other specimens are processed on assessment number.
- The material is distributed according to the distribution found over 2016: 13,39% Group 1; 24,90% group 2; 51,38% group 3; 10,33% group 4.
- Fixated specimens are moved into the process once a day at 7:30; or an additional time at 14:00 if shortened fixation times are used.
- Staining, scanning and distribution to pathologists is assumed to be one process, as this is the same resolution as the processing times from the data analysis, which showed no reason to further simulate the individual parts.

The simulation model is designed in Technomatix Plant Simulation version 13.2 by Siemens PLM software (Siemens PLM software, 2017). An overview of the model can be seen in Figure 30, the model consists of an overview frame in which six different frame objects are embedded. In each of

these frames, a specific part of the production process of the histological laboratory is modelled. These parts correspond to the steps described in the conceptual model of the laboratory: Administration & preparation; grossing; tissue processing; embedding; sectioning; and staining & scanning.

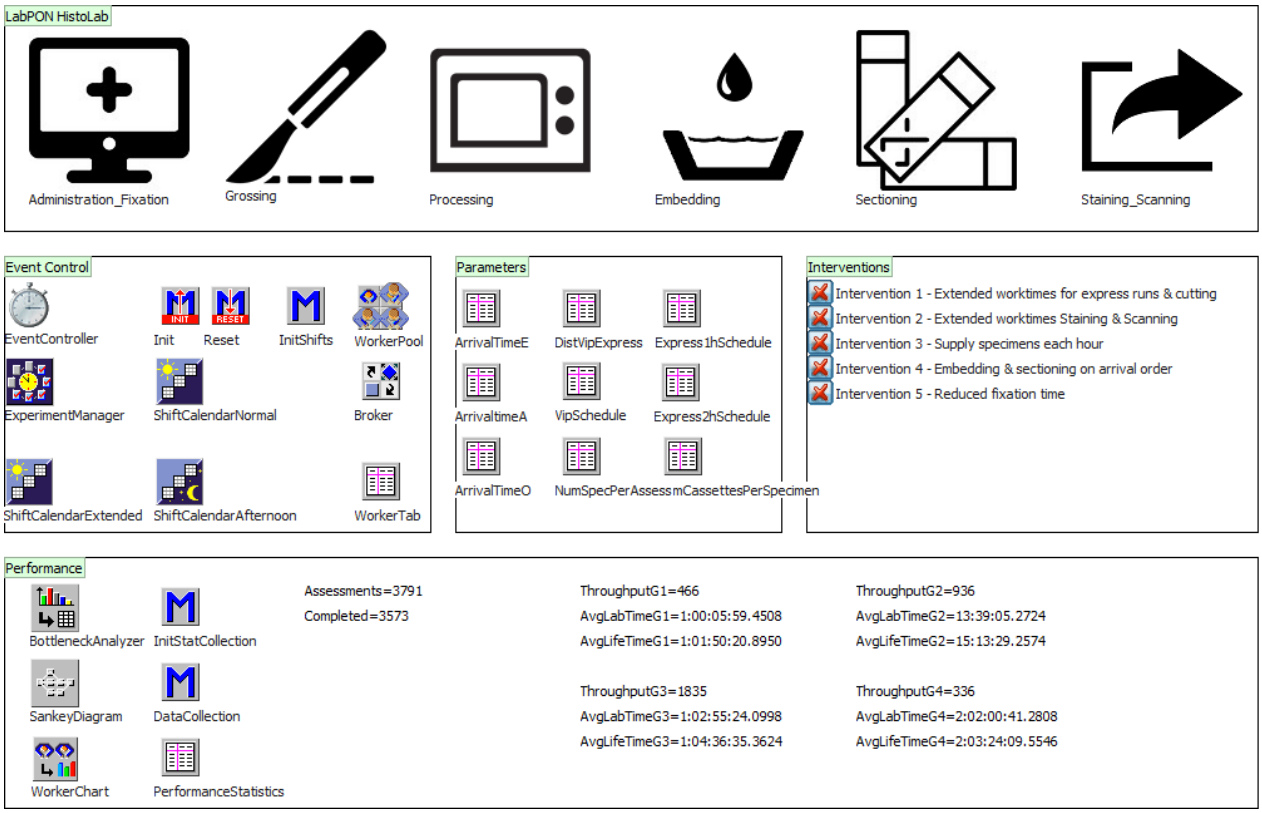


Figure 30 - Screen capture of the simulation model overview frame

For clarification of the inner workings of the model, each frame of the simulation model is shown and discussed in the Appendix C.

7.2. Model verification

Model verification is the process of making sure that a model behaves as expected, without errors or bugs. Law describes eight different techniques for verifying a simulation models (Law, 2007):

1. Debugging modules and subprograms during programming.
2. Having other people review the simulation model.
3. Running the simulation under various input parameters to check for predictable results.
4. Tracing contents of the event list, state variables or counters to check events for correct behaviour in specific events, by using breakpoints and forcing specific occurrence of events.
5. Running the model under simplified conditions for which the characteristics are known or can easily be computed.
6. Observing the animations for peculiarities.
7. computing sample mean and sample variance for simulation inputs for comparison.
8. Use programming provided by commercial simulation packages.

During programming these methods have all been applied, albeit with varying levels of intensity. Techniques 1, 3, 4 and 6 have been used constantly and intensively during programming, which led to many errors and bugs being found right away. Coding of methods has been done meticulously, checking the code for correctness and syntax every one to three lines written, and debugging each method before use. The debugging was primarily conducted using breakpoints to closely inspect the execution of methods and the changing of parameters. Each placed object has been inspected with a similar amount of care, using variable watches and animation inspection to find peculiarities in behaviour.

Plant Simulation offers many predefined objects that are useable in the construction of the general model. These predefined objects however are not sufficient for modelling all laboratory processes. The more complex laboratory processes are therefore modelled using programmable methods in conjunction with predefined objects. This approach offers more control and flexibility to correctly represent reality. Examples of such complex laboratory processes are the tissue processors, post-fixation, and the arrival of specimens in the laboratory.

The model has been reviewed by several people, these included the head of the histology department, a coordinating analyst the thesis supervisor, Wilte Barels (a master student working on a simulation research of the transport service for LabMicta & LabPON), and several students with knowledge of programming. These reviews have been conducted in an informal manner and often resulted in discussions offering new insights. The reviewers associated with LabPON generally agreed with the setup of the model and found no peculiarities, except for some minor comments which have been corrected.

Finally, each input variable has been carefully selected. Below, the origin and input will be shortly discussed of following input variables: the arrival times of specimens at the laboratory; the number of submitted assessments; the VIP and Express schedule; the number of workers; and the number of cassettes per assessment.

The arrival times of the specimens at the laboratory are extracted from the transportation schedule which is posted on the document management system Iprova. This schedule is provided earlier in Paragraph 4.4.3. , page 25, Table 7. For the number of assessments submitted, the average per day per location over 2016 is used. It should be noted that the number of submitted assessments is a constant input variable and as such limits the variability in the simulation model compared to the real-life system. The reason for this simplification of the abstract model is that the variability in real-life is currently countered through scheduling. Although a dynamic scheduling approach could be programmed in the simulation model, it is not specifically necessary for the intended purpose of the model. Nevertheless, this approach would make the model more complex, harder to validate and make results more difficult to interpret because of the noise caused by dynamic scheduling. For future work, the addition of a variable input should be considered.

The VIP and Express schedules are defined using the processing times provided in the machine manual documents hosted on Iprova. The VIP is scheduled to process a single large batch at 16:00 every day which finishes the following morning. The 1-hour express is stocked with new batches every 20 minutes from 07:00 until 15:00, with a processing time of 85 minutes the last batch is

finished at 16:25. The 2-hour express is stocked with new batches every 35 minutes from 07:00 until 13:25, with a processing time of 145 minutes the last batch is finished at 16:15.

The number of workers initiated in the simulation is based on the shifts defined by LabPON, these are described in Chapter 3. The number of employees used as input for the simulation model is provided in Table 14. The P-shift, R-shift and lab assistant have not been included in the simulation as these are supportive functions or not related to general production.

Table 14 - Number of employees per task in the simulation

Task	# employees
Grossing small	3
Grossing large	2
Embedding & Sectioning	8
Staining	1
Scanning	1
Total	15

To determine the number of specimens and cassettes present in each assessment. The percentages are extracted from the dataset used earlier in the data analysis. The exact percentages used as input can be found in the appendix. As an overview, Table 15 provides the observed averages number of cassettes and corresponding standard deviation, compared to the values generated in a simulation spanning 100 days. The values show that the generated number of cassettes per assessment in the simulation closely approximates the reality. The biggest deviation from reality is seen in the group 4 assessments, which are generated in the simulation with on average two cassettes less and a higher variation.

Table 15 - Number of cassettes in reality versus generated in simulation(General production; N=54602; 1/1/2016-31/12/2016)

Input cassettes	Observed average	Observed Std. Dev.	Sim. Average	Sim. Std. Dev.
Group 1	6,83	6,84	6,85	6,86
Group 2	3,01	3,02	3,24	3,63
Group 3	3,31	4,02	3,17	3,59
Group 4	16,19	7,78	13,97	11,02

7.3. Model validation

For the validation of the simulation model, Law (2007) proposes three validation methods: Output validation; face validation; and sensitivity analysis. The first two have been applied for the validation of the simulation model. Output validation consists of comparing the performance measure of the simulation model to those of the actual system to see if they are comparable. Face validation is the process of discussing the model with subject-matter experts to see if they agree that the output mimics reality (Law, 2007).

For the comparison of the simulation model to the existing system, performance measure data is taken from the data analysis and the simulation model. For the simulation to be considered valid, it is not necessary for the performance measures to be exactly equal. Rather, the simulation model

should approximate the existing system and be accurate enough to allow the intended experimentation to be conducted (Law, 2007).

To compare performance measures, a simulation run was executed of the current situation. The simulation consists of 25 observations and is compared to the actual laboratory performance over 2016, the results are shown in Table 16.

Table 16 - Performance measures actual system versus simulation (General production; N=29974; 1/1/2016-31/12/2016)

Specimen Group	Average laboratory TPT		Simulated performance (N=25)		Sim. Excl. outliers (N=21)	
	Workhours	Std. deviation	Average	Std. deviation	Average	Std. deviation
Group 1	6:05:04	2:44:07	7:47:27	4:49:10	6:17:18	0:50:00
Group 2	9:11:04	4:07:24	11:00:41	6:08:14	8:53:43	1:19:34
Group 3	17:23:00	5:49:30	13:38:13	3:57:17	12:12:58	0:55:23
Group 4	20:21:21	7:24:44	18:08:48	2:01:24	17:24:35	0:33:40

Comparison between the average laboratory throughput time (TPT) and the average simulated performance over 25 observations shows large differences, initially suggesting questionable validity of the model. However, the simulated performance shows remarkably large standards deviations in the faster group 1 and 2 specimen groups. Closer inspection of the individual observations reveals that this deviation is caused by four of the observations, in which the simulation got flooded leading to large queues with high throughput times of 20 up to 36 workhours. Analysts have indicated that such moments of peak pressure also occur in the laboratory. However, at such moments the (coordinating) analysts reportedly react by arranging for extra capacity and focus on smaller assessment first. This is unlike the simulation model, which has no similar reaction to peak pressure and will continue producing according to its programming. For this reason, the decision was made to exclude the four outliers from the comparison.

Comparison of the 21 included simulation observations to the average laboratory throughput time shows quite similar performance. The simulated averages of Group 1 and group 2 specimens both differ roughly three percent from the actual group 1 and 2 throughput times, as such they can be considered valid. For group 4 specimens, the actual throughput time is underestimated by roughly three hours or 16,9%. This difference is expected to be caused by absence of time-consuming non-standard procedures in the model such as decalcification, a process which often takes around three days to complete. The simulated throughput time of group 3 specimens is surprisingly low, differing more than five hours with the average of the actual system for a difference of 42,3%. A small part of this difference may be attributed to time-consuming non-standard procedures, the majority however seems to be caused by the inexplicable waiting time in the laboratory. Such waiting times are also shown in the data in Paragraph 4.5.6. and current findings might suggest that a majority of the cassettes waiting between embedding and sectioning as seen in Figure 26 could be group 3 specimens, as group 1,2 and 4 cassettes get priority.

With regards to validation of the model through discussion with subject-matter experts, the model has been discussed with the head of the laboratory and a coordinating analyst at LabPON. These

discussions resulted in generally positive feedback and a recognition of the actual system in the simulation model.

To summarize, the simulation model is a reasonably good approximation of the actual system and should be accurate enough for the intended experiments to be conducted. The simulation runs show that the current setup is prone to accumulating inventory between processing steps, which can cause throughput times to increase strongly. Coordinating analysts have remarked that they intervene during such periods by prioritising smaller assessments, which is likely the cause of the lower average throughput times for group 1 and group 2 specimens compared to the original simulation, and might also explain the difference in observed group 3 throughput times.

7.4. Simulation model settings

Simulation setup is an important factor for attaining usable results. To properly initialize the experiments, this paragraph discusses the characteristics of simulation model and corresponding settings.

With regards to termination characteristics, the simulation model is considered a non-terminating simulation under normal conditions, since there are no natural events that specify the end of a simulation run. An argument could be made that the simulation is terminating, since the laboratory is simulated to close outside of working hours. However, production does not shut down due to the utilization of overnight processing and fixation, which is a prerequisite of terminating simulations (Law, 2007).

The output of the simulation model can show transient behaviour or steady state behaviour. Transient meaning that the performance depends on initial conditions, while steady state does not depend on initial conditions (anymore). The simulation model of the laboratory shows steady-state behaviour. For a terminating steady-state model, the suggested output analysis method is the Replication/Deletion approach for the mean (Law, 2007). This versatile method provides reasonably good statistical performance, can be applied to all types of output parameters, and is usable for comparison of different system configurations. However, the method requires that only observations made after the warm-up period of the model are included in the analysis. Since the initial condition of the simulation model is an empty system, a warm-up period must be defined before statistics should be stored. In order to determine the correct length of this warm-up period, the Welch method is applied (Law, 2007).

The Welch method consists of making 5 or more independent replications of a simulation, with a simulation length sufficiently large to not be affected by the initial conditions. Over all replications, the mean of each observation is calculated in order to smooth the variability of individual simulations, finally a moving average is calculated over a length of 'w'. The resulting graph is shown in Figure 31, the output is relatively stable after roughly 1000 observations, indicating a warm-up period of six days in the simulation. This value is used in all following simulations.

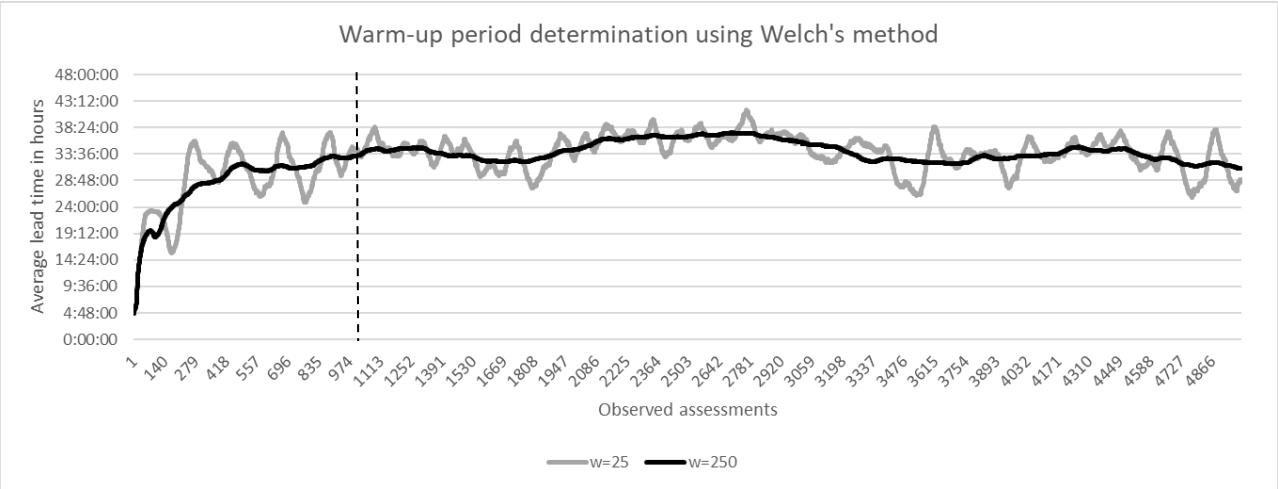


Figure 31 - Determination of warm-up period using Welch's method (base simulation, 5 replications, runtime 100 days)

It should be noted that due to the random nature of simulation, output generated by models only gives point estimates of the system performance. As such, multiple observations must be made to achieve an accurate result. Results are generally provided in 95% confidence interval, which states that with a confidence of 95% the true mean of the system lies within the interval.

Ideally, the confidence interval should be as small as possible. However, to achieve the smallest possible confidence interval an infinite number of replications should be executed. As limitations exist with regards to available processing time, a number of replications should be selected which is sufficiently small, relative to the average output of the experiment. One method to determine the number of replications per experiment is by use of the relative error formula. This formula is typically used for terminating simulations, but can also be applied to non-terminating simulations for estimating the necessary number of observations per experiment for a certain relative error rate. The following formula is used for calculating the relative error: (Law, 2007)

$$\frac{t_{n-1,1-\alpha/2}\frac{s}{\sqrt{n}}}{\overline{X}} < \gamma'$$

Estimating the number of replications necessary for a confidence interval of 95% (α=0.05) and a relative error of γ=0.10 using the data provided in model validation, it is found that 197 replications are necessary for the data excluding outliers to have a relative error of at maximum 10%, as seen in Table 17. Although using the data excluding outliers is not ideal, it is acceptable as a baseline since interventions which prevent such outliers may have a relative error within the bounds. For the simulation of the main effects, a larger number of iterations can be used as the number of experiments to conduct is smaller. For this purpose, the maximum number of replications feasible within acceptable processing time is selected. It is found that for eight experiments, 500 replications per experiment yields a total of 4000 replications with an expected processing time of about nine hours. The relative error achieved with these settings is smaller than 10% except for group 1 specimens, which show a 12,1% expected relative error for data including outliers, for the intended purpose this is deemed sufficient.

Table 17 - Relative error estimation on number of runs

Specimen Group	Relative error (α=0.05; n=197)		Relative error (α=0.05; n=500)	
	Data incl. outliers	Data excl. outliers	Data incl. outliers	Data excl. outliers
Group 1	19,4%	10,0%	12,1%	6,2%
Group 2	15,5%	8,9%	9,7%	5,6%
Group 3	10,0%	5,4%	6,3%	3,4%
Group 4	5,4%	3,0%	3,4%	1,9%

In summary, the simulation is a non-terminating steady state model which will be evaluated using a replication/deletion method. The warm-up period used for this evaluation is found to be 6 days using Welch's method. For setting the number of replications per experiment, the relative error formula is used; the replications per experiment is set to 197 for interaction effects and 500 for determining the main effects.

7.5. Implementation of interventions in the simulation

Following the interventions described in Chapter 6, a total of seven process interventions have been modelled in the simulation model. Two of the proposed interventions have not been specifically modelled, these are the workload balancing with large specimens and the changing of the SLA. The workload balancing with large specimens intervention has not been modelled since the model has been simplified with a constant supply of assessments. Changing the SLA intervention has not been modelled since it is not an operational process intervention. However, the intervention will be discussed using the results of the simulation to get an insight into the validity of the intervention and what values should be used for the SLA.

Table 18 shows the seven process interventions that are modelled and summarizes the implementation of the intervention in the simulation model. The interventions concerning a change in personnel planning have both been modelled with two variants: the first shifting the schedule one hour forward, and the second extending the extending the schedule by one hour. This choice was made for the evaluation of the interventions both with an unchanged capacity in available analyst workhours, as well as with a slightly increased analyst capacity. Since these interventions are mutually exclusive, they are indicated with the same intervention number with a varying suffix.

It should be noted that Intervention 4, the hourly arrival of specimens, is simulated as a lower bound as no explicit plan exists for lowering the time between specimen arrivals. As such this intervention is aimed at assessing the influence of deceasing the interarrival time of specimens at the laboratory.

Table 18 - Simulated process interventions

Intervention	Description	Implementation in simulation
1a	Shifted worktimes for grossing & express tissue processing	One-hour schedule shift for small grossing analysts & express tissue processing; from 07:30-16:30 to 08:30-17:30
1b	Extended worktimes for grossing & express tissue processing	One-hour schedule extension for small grossing analysts & express tissue processing from 07:30-16:30 to 07:30-17:30
2a	Shifted worktimes for staining & scanning	One-hour schedule shift for staining & scanning analysts; from 07:30-16:30 to 08:30-17:30
2b	Extended worktimes for staining & scanning	One-hour schedule extension for small grossing analysts & express tissue processing; from 07:30-16:30 to 07:30-17:30
3	Embedding & sectioning on arrival order	Sort arrivals in embedding on arrival order instead of assessment number; group 1 specimens still get priority
4	Hourly arrival of specimens at the laboratory	Arrival schedule specimens changed to once every hour
5	Reduced fixation time	Reduction of group 4 fixation time in preparation to 4 hours; fixated specimens enter grossing at 14:00.

7.6. Experimental design

To evaluate all interventions and their influence on the throughput time of the different assessments at LabPON, two experimental designs are constructed.

The first experimental design strategy used is the one-factor-at-a-time (OFAT) approach. This approach consists of selecting a baseline, in this case the current situation, and varying each factor over its range while keeping the other factors constant. This allows analysis of the direct effect of an intervention compared to the baseline, with a relatively limited number of runs (Montgomery, 2017).

The OFAT experimental design is shown in Table 19 and will be executed with a warm-up period of six days and 500 replications per experiment.

Table 19 - OFAT experimental design

Int. / Exp.	1a	1b	2a	2b	3	4	5
1 (Baseline)	-	-	-	-	-	-	-
2	+	-	-	-	-	-	-
3	-	+	-	-	-	-	-
4	-	-	+	-	-	-	-
5	-	-	-	+	-	-	-
6	-	-	-	-	+	-	-
7	-	-	-	-	-	+	-
8	-	-	-	-	-	-	+

A major disadvantage of the OFAT strategy is that it does not consider any possible interaction effects between the factors. The definition of interaction effects is the failure of one factor to produce the same effect on the response at different levels of other factors (Montgomery, 2017). For example, while stopping the grossing shift later might have benefits if most specimens are delivered at 15:00, it might not have any benefits if specimens are delivered equally over the day. To analyse these interaction effects, a factorial experiment is designed. In the factorial experimental design, factors are varied together instead of one at a time. Using this method, all possible combinations of levels and factors are observed, revealing all main effects and interaction effects in the system.

The second experimental design strategy is therefore a 2^k-factorial design, a design that simulates all combinations of factors over two levels. However, the risk with a factorial approach is that the number of experiments tends to grow very rapidly, doubling the amount of necessary experiments for each factor involved; for seven factors, this would result in 128 experiments and an expected computation time of three days. Therefore, the number of factors included in the factorial design is limited to only include process interventions which are considered most for implementation following the results of the OFAT simulation.

The 2^k-factorial experimental design is shown in Table 20 and will be executed with a warm-up period of six days and 197 replications per experiment to keep computation time within acceptable limits, while providing a sufficiently low relative error for simulations without outliers.

Table 20 - 2^k-factorial experimental design

Int. / Exp.	1a) Shift in Grossing & Processing	2a) Shift in staining & Scanning	3) Embedding on arrival order	4) Hourly delivery of specimens
1	+	+	+	+
2	+	+	+	-
3	+	+	-	+
4	+	+	-	-
5	+	-	+	+
6	+	-	+	-
7	+	-	-	+
8	+	-	-	-
9	-	+	+	+
10	-	+	+	-
11	-	+	-	+
12	-	+	-	-
13	-	-	+	+
14	-	-	+	-
15	-	-	-	+
16	-	-	-	-

Chapter 8. | Results

This chapter shows the results of the simulations. These results are generated as output of the experiment design described in the previous chapter. First, the OFAT experiment is discussed, showing what effect each individual intervention has on the model. Next, the results of the 2^k-factorial experiment are discussed to find the interaction effects between the interventions in the simulation.

8.1. Results One-Factor-At-a-Time simulation

The One-Factor-At-a-Time experimental design was run on a HP EliteBook 8560w with 4gb RAM, a 2.00GHz i7 processor, running a Windows 10 64-bit operating system. As specified in the experimental design, the simulation consisted of eight experiments, each consisting of 500 replications and simulating 100 workdays of laboratory operations. The simulation experiment was completed in just under eight and a half hours.

Figure 32 presents an overview of the 95% confidence intervals of the average throughput time per specimen group for each experiment. An intervention is significantly different if the confidence interval of the baseline and the intervention do not overlap. As the resolution of the overview is not sufficient for accurate evaluation, each specimen group will be evaluated individually below as well. However, from the overview it is apparent that most experiments show equal or slightly reduced average throughput times compared to the baseline. Most remarkable is intervention 3, the implementation embedding on arrival order, which shows a strong reduction of average throughput time for group 1, 2 and 3 specimens, while slightly increasing group 4 throughput time.

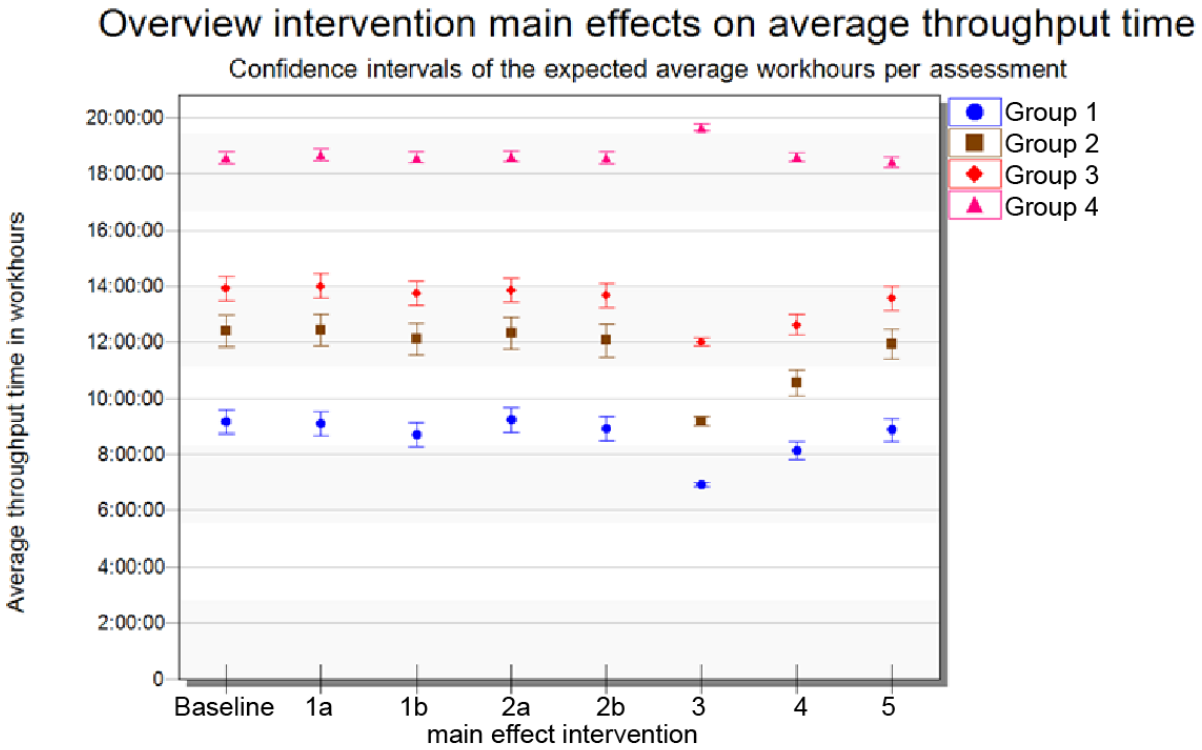


Figure 32 - Overview intervention effects in OFAT simulation

Table 21 - T-test p-values for each specimen group compared to baseline,† indicates significant difference from baseline (95%)

int. / T-test	1a	1b	2a	2b	3	4	5
Group 1	0.856	0.149	0.858	0.44	0†	0†	0.329
Group 2	0.907	0.509	0.881	0.439	0†	0†	0.255
Group 3	0.743	0.597	0.843	0.466	0†	0†	0.26
Group 4	0.512	0.977	0.776	0.926	0†	0.903	0.259

A student T-test is conducted to more accurately determine the significance of the differences between the intervention experiments and the baseline; the resulting p-values are shown in Table 21. Interventions that have a p-value of 0,05 or lower are said to significantly differ from the baseline with a probability of 95%. From the values, it becomes that apparent that intervention 3 (embedding on arrival order) and intervention 4 (hourly delivery of specimens) are the only interventions showing significant results.

A closer examination of the results of interventions 3 and 4 is given in Table 22 and Figure 33, and discussed below. Table 22 provides output values of interest per intervention for each specimen group, with the difference compared to the baseline in percentage. Figure 33 provides the corresponding confidence intervals for average throughput time per group, similar to Figure 32 but with higher resolution allowing for comparison.

Table 22 - OFAT simulation output values of interest per specimen group in workhours

Group 1	**Baseline**	**Intervention 3**		**Intervention 4**	
Observed average	9:10:23	6:55:49	-24%	8:09:08	-11%
Standard deviation	4:56:34	0:48:59	-83%	3:37:55	-27%
Observed minimum	6:25:23	6:26:49	0%	6:31:28	2%
Observed maximum	34:32:21	14:11:12	-59%	27:25:01	-21%
Group 2					
Observed average	12:23:23	9:11:09	-26%	10:33:23	-15%
Standard deviation	6:27:56	1:51:54	-71%	5:21:21	-17%
Observed minimum	7:15:41	7:10:44	-1%	6:33:45	-10%
Observed maximum	41:05:49	21:48:30	-47%	35:30:46	-14%
Group 3					
Observed average	13:54:45	12:00:02	-14%	12:37:25	-9%
Standard deviation	4:57:22	1:34:21	-68%	4:12:41	-15%
Observed minimum	10:15:33	10:11:15	-1%	9:44:41	-5%
Observed maximum	33:45:58	21:10:01	-37%	30:48:33	-9%
Group 4					
Observed average	18:35:13	19:39:01	6%	18:36:12	0%
Standard deviation	2:22:01	1:20:43	-43%	1:50:56	-22%
Observed minimum	16:47:23	17:47:01	6%	17:21:36	3%
Observed maximum	26:02:44	25:32:59	-2%	26:37:12	2%

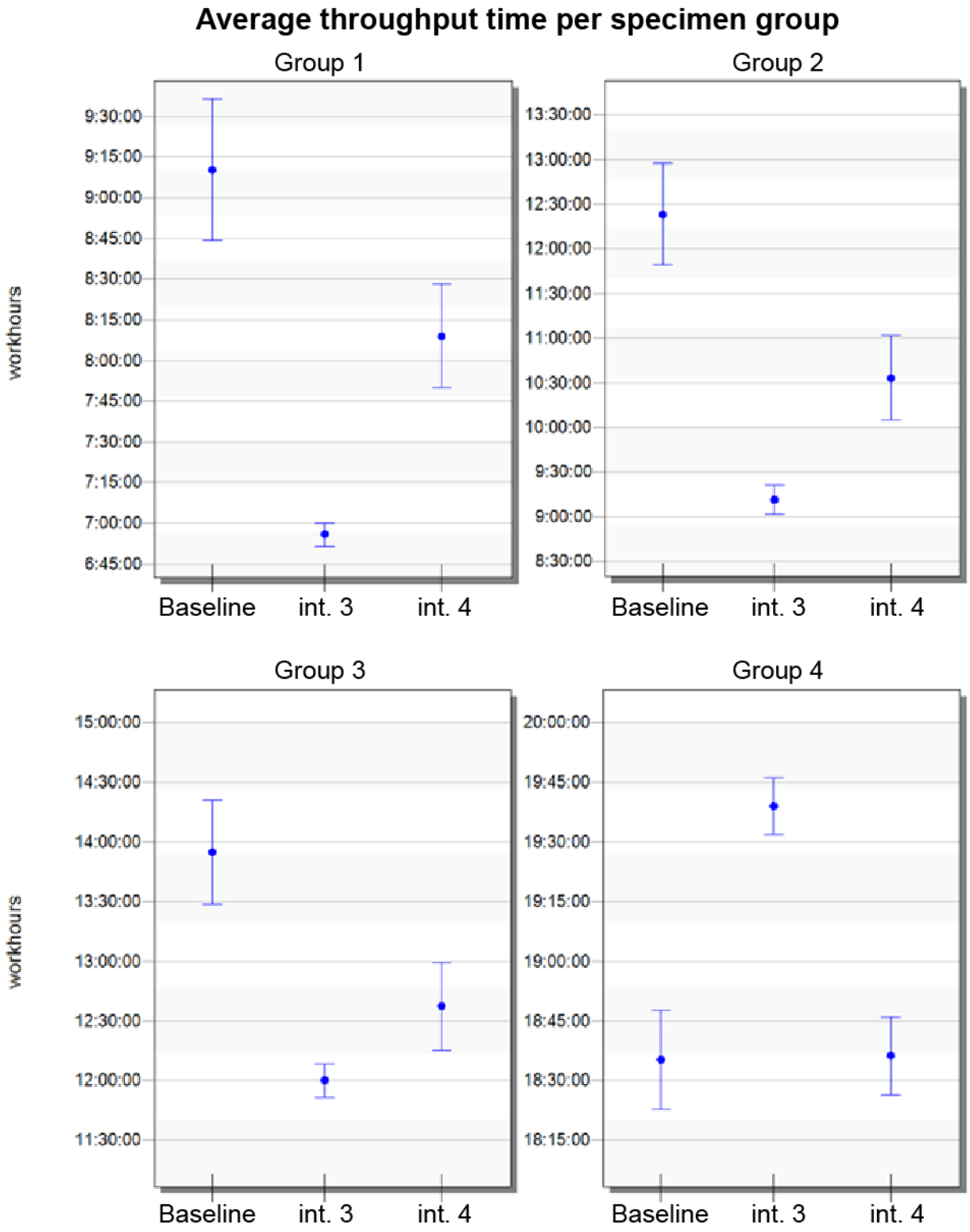


Figure 33 - OFAT simulation intervention effects of significant interventions

In Table 22, the group 1 baseline shows a large standard deviation, which is reflected in the maximum and minimum values observed. The maximum observed average throughput time is nearly four times as large as the average value, and over five time larger than the lowest observed value. This indicates large fluctuations in the average throughput time observed in the system. These fluctuations are not surprising, since during model validation the model showed a tendency to get flooded with assessments during moments of peak demand, causing waiting times to increase dramatically.

Comparing the baseline to the significant interventions, the observed minimum is roughly equal for all three experiments. This means that the three systems are capable of producing at the same rate when the system is not stressed. However, standard deviations observed with intervention 3 and 4 are both lower. Intervention 3 shows a drastic decrease in standard deviation of 83% with a corresponding decrease of 59% in the highest observed average. These findings suggest that implementing intervention 3 or intervention 4 increases the laboratories capability to handle fluctuations in demand for histological services. With intervention 3, embedding on arrival order, showing the most promising results.

The group 2 and group 3 specimens both show the similar responses to intervention 3 and 4 as the group 1 specimens. Both show a roughly equal observed minimum and drastic decreases in standard deviation with intervention 3, with the corresponding lower observed average throughput time per assessment and observed maximum. The decrease in percentage of standard deviation and observed maximum is slightly lower than in the group 1 specimens. This indicates that the intervention has the biggest impact on group 1 specimens, followed by group 2 specimens and relatively the smallest impact on group 3 specimens. This finding is unsurprising, as this is concurrent to the prioritization of specimens.

Another notable finding is that intervention 4, the hourly delivery of specimens, shows a reduction in the observed minimum average throughput time for specimens of group 2 and 3. This indicates that intervention 4 could also reduce the average throughput time per assessment for group 2 and 3, instead of just reducing system variability. To further investigate this finding, histograms of the 'observed average' output of intervention 3 and intervention 4 are compared. The group 3 output values of intervention 3 and 4, shown in Figure 34 and Figure 35, reveal that embedding on arrival negates very high outliers in average workhours for group 3 specimens, but when ignoring outliers has a higher throughput time than hourly delivery. As such, it can be concluded that hourly arrival of specimens at the laboratory can reduce the average throughput time for group 3 specimens, and embedding on arrival order prevents excessive queues.

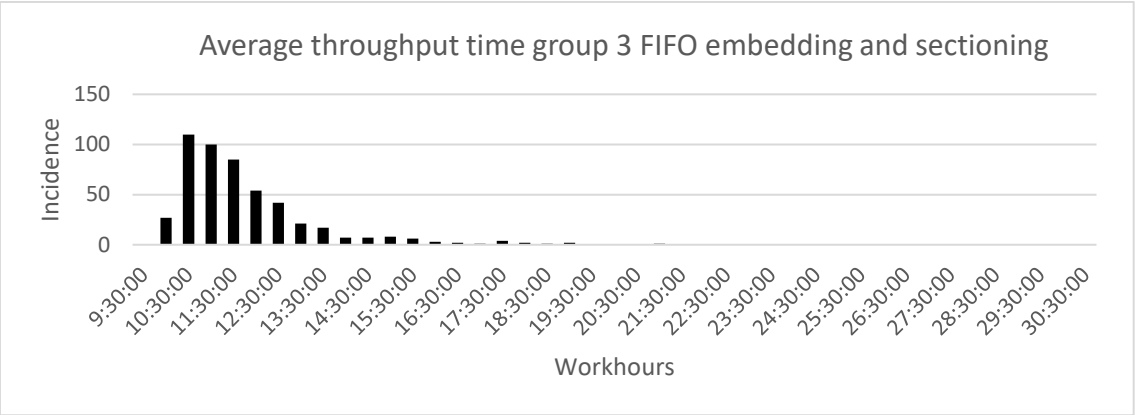


Figure 34 - Histogram OFAT simulation output values group 3 with embedding and sectioning on arrival order

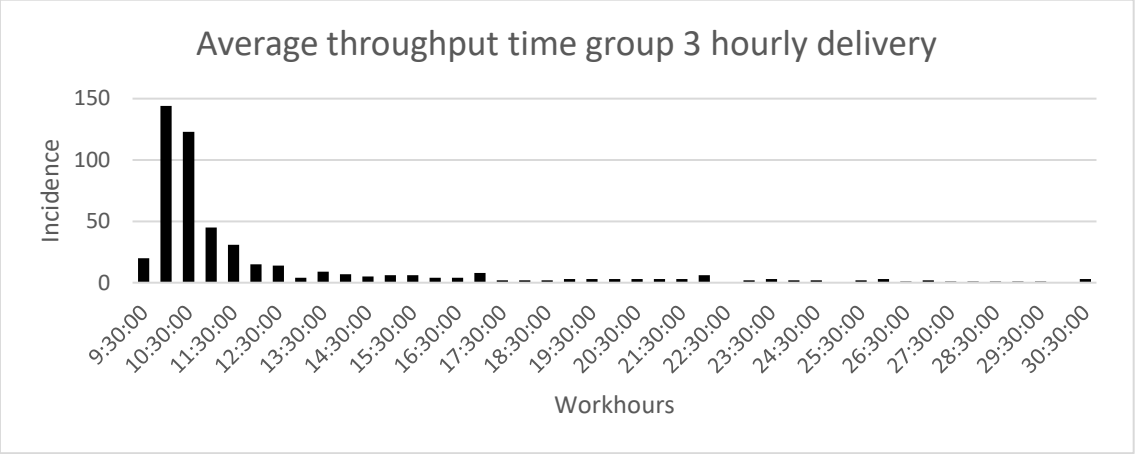


Figure 35 - Histogram OFAT simulation output values group 3 with hourly delivery of specimens

With regards to the first three specimen groups, Figure 33 shows a reduction of variability and average observed throughput time for both intervention 3 and 4 compared to the baseline. However, group 4 specimens present a trade-off for intervention 3, the implementation of embedding on arrival order increases the observed average throughput time for group 4 specimens by 6%, while decreasing the standard deviation by 43%. The explanation for this result is that the baseline first-in-first-out approach on research number at embedding favours group 4 specimens, as they have been in the system for two overnight processes by the time they arrive at the station. However, as group 4 specimens have been in the system for a long time already and still have to be examined by the pathologists, not prioritising the assessments would make it very likely for them to fall outside of SLA. This can be seen in the comparison between the histograms in Figure 36 and Figure 37, keeping in mind to be within the SLA the examination must be completed within 24 workhours including examination. Thus, it can be concluded that the pressure put on group 4 specimens by SLA is at the root of choices in the design of the system which result in the formation of queues, causing throughput times for the smaller specimen groups to increase rapidly and as such creating pressure on the system.

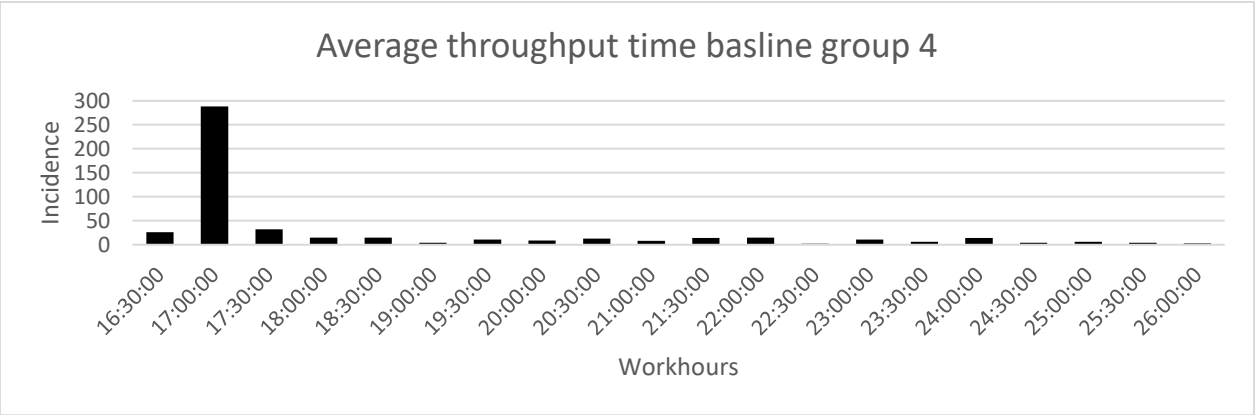


Figure 36 - Histogram OFAT simulation output values baseline group 4

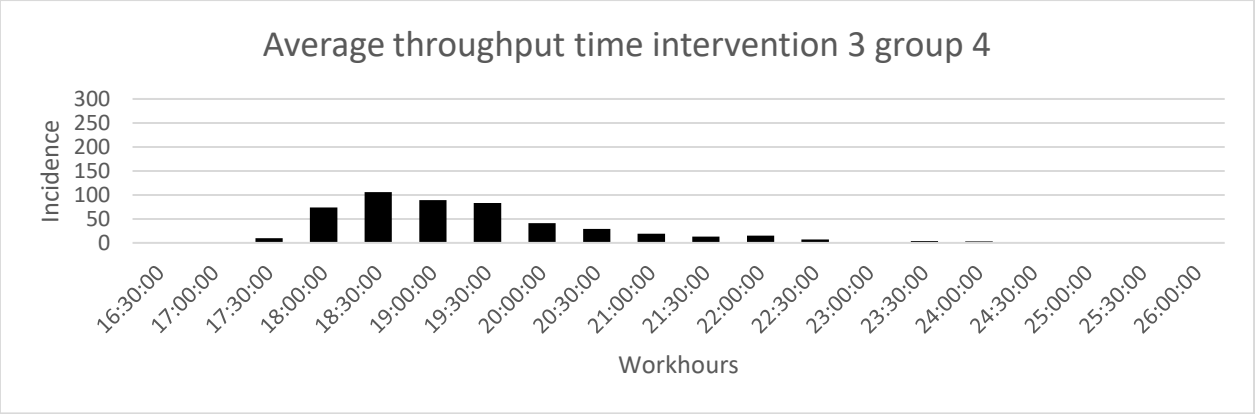


Figure 37 - Histogram OFAT simulation output values intervention 3 group 4

In summary, from the OFAT simulation it can be concluded that pressure on the system is created by sorting assessments first-in-first-out on a system level. This pressure can be alleviated by switching to sorting first-in-first-out on a process level. This will make the system less likely to buffer large queues which result in much wasted waiting time. The trade-off for this implementation is a 6% longer average throughput time for group 4 specimens, making it hard for those assessments to be completed within the current SLA. These findings support the intervention proposal of changing the SLA, as this will allow the pressure to be released of the system.

Furthermore, it was found that by having specimens arrive at the laboratory every hour, the throughput time of group 2 and group 3 specimens within the laboratory can be reduced. This does not necessarily mean that the transportation service should go to every hospital every hour, rather it advocates the distribution of transportation arrival times throughout the day.

The OFAT simulation however only gives an insight in direct effects of interventions on a system. To investigate for potential interaction effects between the interventions, the results of the 2^k-factorial simulation are discussed in the next paragraph.

8.2. Results 2^k-factorial simulation

The 2^k-factorial experimental design was run on a HP EliteBook 8560w with 4gb RAM, a 2.00GHz i7 processor, running a Windows 10 64-bit operating system. As specified in the experimental design, the simulation consisted of sixteen experiments, each consisting of 197 replications and simulating 106 workdays of laboratory operations with a warm-up period of 6 days per replication. The simulation experiment was completed in just over six and a half hours.

For reference, the experimental design constructed earlier is shown Table 23. The results of the 2^k-factorial simulation will first be compared on relative difference of average throughput time per specimen group between experiments. The comparison will first be made against the baseline, which has been simulated in experiment 16. Following the baseline-comparison, the results will be compared to the most notable intervention of the OFAT simulation: intervention 3 - embedding on arrival order, in the 2^k-factorial design this intervention is simulated by experiment 14.

Following the relative difference comparisons, the main-effects and interaction effect of each intervention are provided for each specimen group.

Table 23 - 2^k-factorial experimental design

Int. / Exp.	1a) Shift in Grossing & Processing	2a) Shift in staining & Scanning	3) Embedding on arrival order	4) Hourly delivery of specimens
1	+	+	+	+
2	+	+	+	-
3	+	+	-	+
4	+	+	-	-
5	+	-	+	+
6	+	-	+	-
7	+	-	-	+
8	+	-	-	-
9	-	+	+	+
10	-	+	+	-
11	-	+	-	+
12	-	+	-	-
13	-	-	+	+
14 (intervention 3)	-	-	+	-
15	-	-	-	+
16 (Baseline)	-	-	-	-

For the comparison of the sixteen different experiments, relative difference charts are used. These graphs provide an overview of the difference in percentages of a specific output value, in comparison to a specific experiment.

For this purpose, we start with a comparison with the current situation, provided in Figure 38. The deviation in percentages of the average throughput time per specimen group is shown in

comparison with experiment 16. To illustrate, as experiment 16 is compared with itself, all specimen groups show 0% difference.

From the graph, it is apparent that all combinations of interventions simulated provide a similar or worse performance for group 4 specimens, while improving performance for other specimen groups by varying degrees. The experiments with the best overall performance are 2, 6, 10 and 14, as these show the largest reductions of average throughput time for group 1, 2 and 3 assessments; referring back to the 2^k-factorial design, these experiments are all performed with embedding on arrival order and without hourly delivery of specimens. In case a worse performance in group 4 specimens is not allowed, experiment 15 provides the best performance; this experiment features hourly delivery.

Thus, from this graph it can be concluded that while embedding on arrival order and hourly delivery both improve performance individually, implementing them together creates an interaction effect which actually lowers the performance.

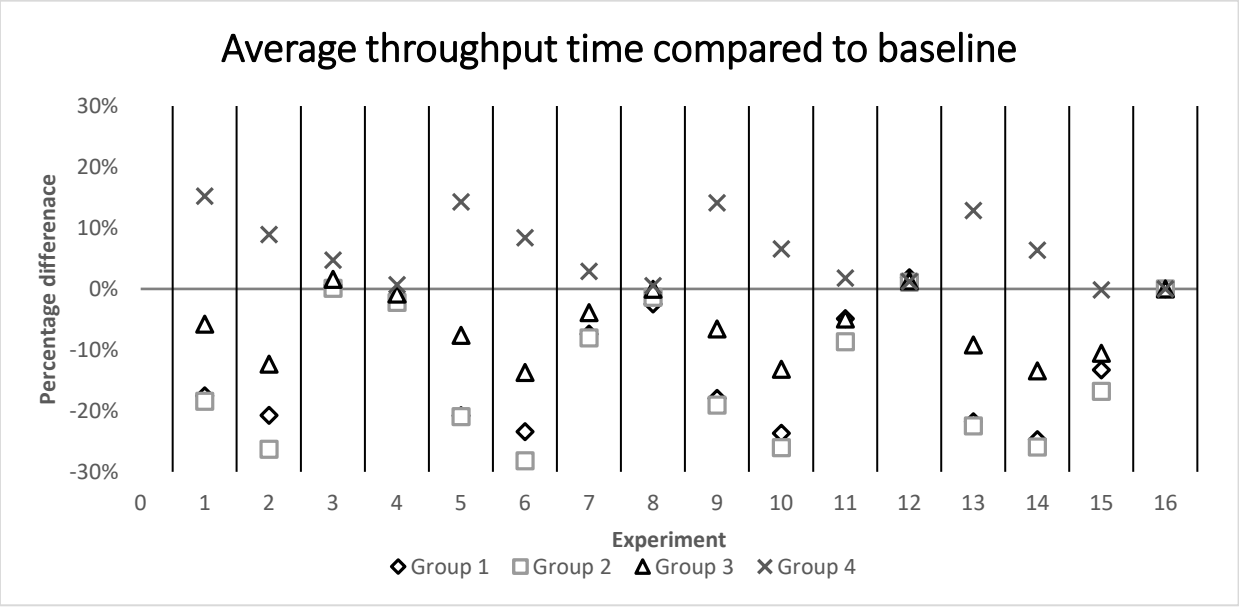


Figure 38 - Relative difference throughput time 2k-factorial experiments in comparison to baseline experiment 16

Besides average throughput time, the standard deviation is an output value of interest, as the simulation model has been shown to have a tendency for creating intractable queues resulting with large waiting times in several configurations.

In Figure 39, the relative differences in standard deviation are provided compared to the baseline experiment 16. The graph shows the standard deviation of nearly all experiments and groups are lower than the baseline standard deviation, with many showing a decrease over 50%. The previously mentioned experiments 2, 6, 10 and 14 show good performance, although experiment 1, 5, 9 and 13 seem to provide a rather low standard deviation as well.

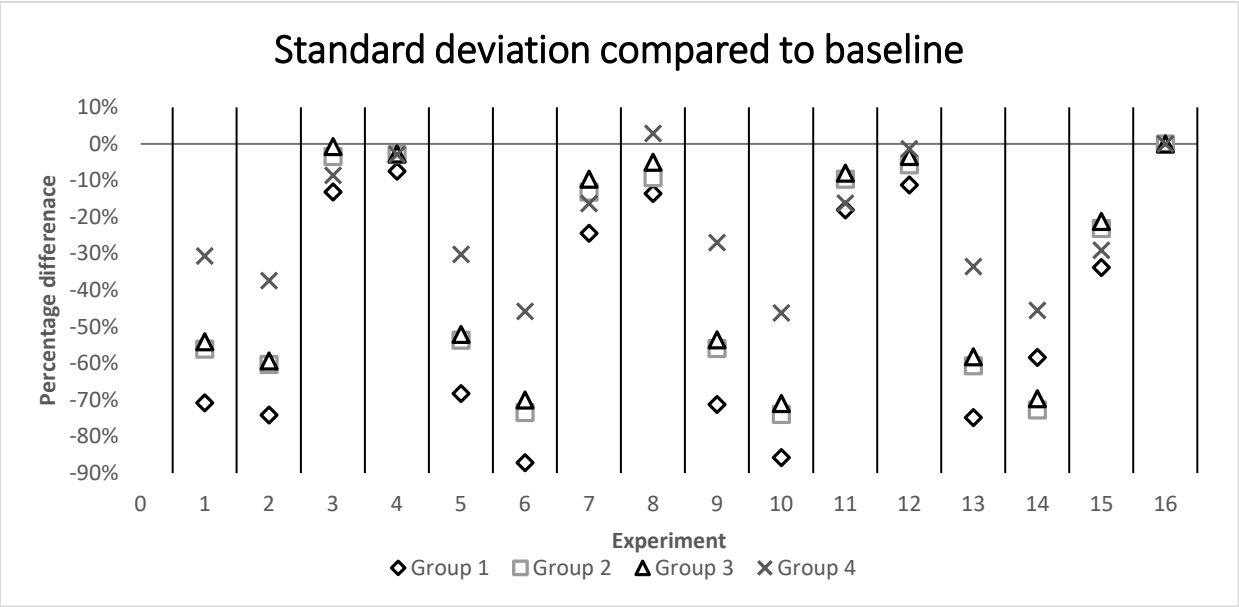


Figure 39 - Relative difference standard deviation 2k-factorial experiments in comparison to baseline experiment 16

During the OFAT simulation, intervention 3 was identified as a promising intervention for LabPON. To further explore this intervention, the relative difference of all 2^k-factorial experiments compared to the embedding on arrival order are given in Figure 40. Inspection of the experiments reveals experiment 6 and experiment 10 have equal results justifying further attention.

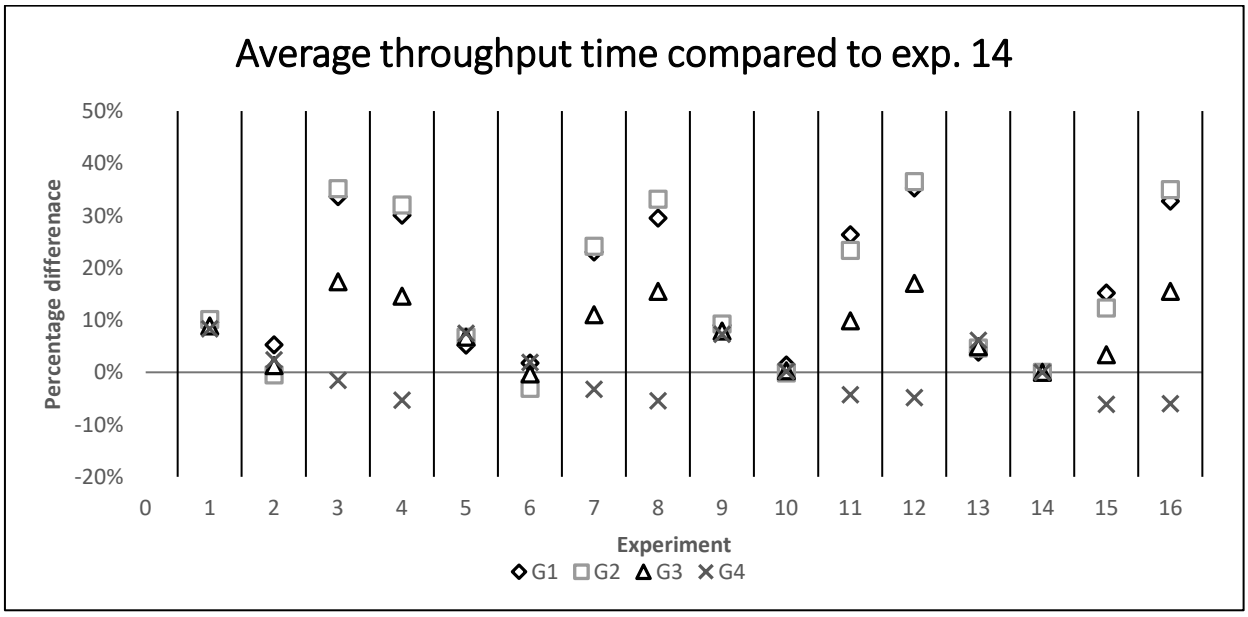


Figure 40 - Relative difference throughput time 2k-factorial experiments in comparison to intervention 3 (experiment 14)

Experiment 6 features embedding on arrival order and a shifted grossing and processing shift. The graph shows a slightly better performance with group 2 specimens, which have a 3% lower average throughput value compared to experiment 14. However, the group 1 and 4 specimens are 2% slower. With regards to standard deviation the experiments are nearly identical. Since group 2 specimens

are shown in the data analysis to be well within the SLA and are less urgent than group 1 specimens, experiment 6 seems less favourable then experiment 14.

Experiment 10 features embedding on arrival order and a shifted schedule for staining and scanning. It shows near identical average throughput time values to experiment 14. With regards to the standard deviation, as seen in Figure 41, experiment 10 shows a much lower observed standard deviation between replications for group 1 specimens. This is further investigated using histograms below.

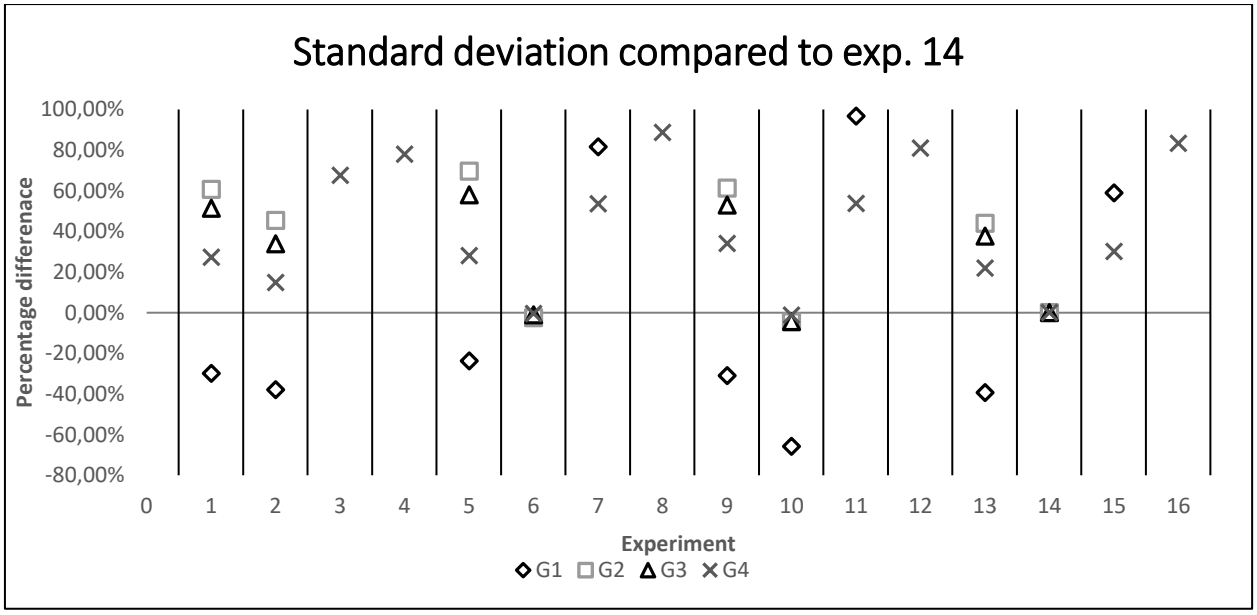


Figure 41 - Relative difference standard deviation 2k-factorial experiments in comparison to intervention 3 (experiment 14)

The histograms of the average throughput time output values of group 1 specimens per replication for experiment 10 and 14 are provided in Figure 42 and Figure 43. It is visible that experiment 14 shows lower possible average throughput times, but also more high outliers. As these large outliers are in reality prevented by intervention of coordinating analysts, it is expected that the system configuration used in experiment 14 will yield better results with regards to throughput time for urgent specimens. However, as more outliers are observed in experiment 14, high work pressure is expected to occur more frequently.

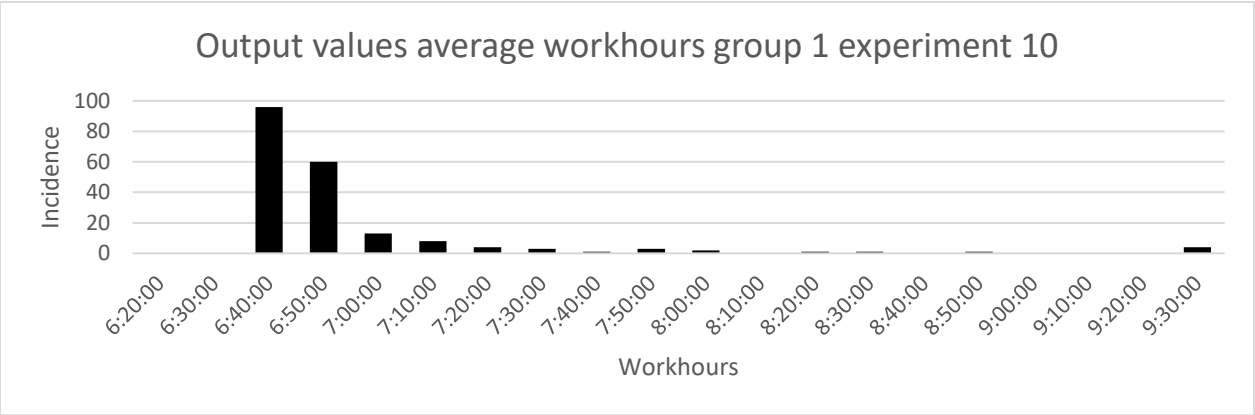


Figure 42 - Histogram average throughput time group 1 specimens 2k-factorial experiment 10

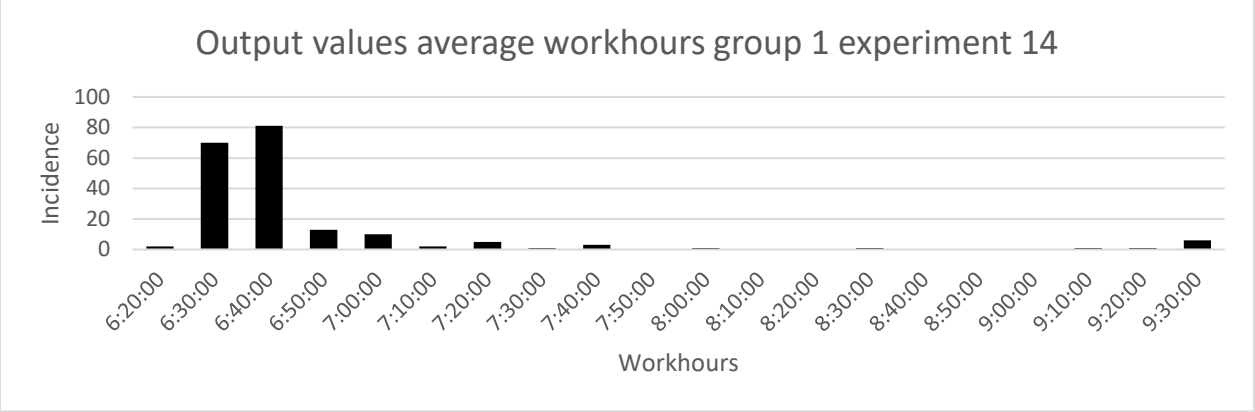


Figure 43 - Histogram average throughput time group 1 specimens 2k-factorial experiment 14

Finally, the expected main effects and two-factor interaction effects of each (combination of) intervention(s) are calculated using the 2^k-factorial design analysis (Law, 2007). The main effect shows the average change in the response after changing a single factor, this is taken as the average over all experiments in the current design. The two-factor interaction effects show the average change in response caused by a dependency between two factors together, in which case the factors are said to interact. The effects are presented in The main factor effects show a clear response with the implementation of intervention three, embedding on arrival order, which as seen earlier lowers the expected time of specimen groups 1, 2 and 3, while causing group 4 specimens to take longer. The interaction effects show few improvement effects, with factor combination 1x3 and 2x3 showing a small reduction of expected average throughput time. It should be noted that the calculation of main effects and interaction effects takes all experiments into account equally, as such experiments presenting large outliers are included and may cause a skewedness in the data. However, the effects still provide a proper insight into the effects caused by the different interventions and combinations thereof.

Table 24 and visualized in Figure 44.

The main factor effects show a clear response with the implementation of intervention three, embedding on arrival order, which as seen earlier lowers the expected time of specimen groups 1, 2 and 3, while causing group 4 specimens to take longer. The interaction effects show few improvement effects, with factor combination 1x3 and 2x3 showing a small reduction of expected average throughput time. It should be noted that the calculation of main effects and interaction effects takes all experiments into account equally, as such experiments presenting large outliers are included and may cause a skewedness in the data. However, the effects still provide a proper insight into the effects caused by the different interventions and combinations thereof.

Table 24 - Expected main & two-factor interaction effects on average throughput time in 2k-factorial experiment

	Expected main effect (minutes)				**Expected two-factor interactions (minutes)**					
	1	*2*	*3*	*4*	*1x2*	*1x3*	*1x4*	*2x3*	*2x4*	*3x4*
Group 1	7,3	20,4	-98,6	-5,4	-0,6	0,4	10,3	-5,4	12,1	25,2
Group 2	11,7	22,8	-141,8	-5,0	-0,8	-12,3	25,2	-8,3	18,8	52,8
Group 3	14,6	18,5	-67,2	5,6	-2,0	-8,4	18,0	-5,7	14,0	43,5
Group 4	18,0	11,1	104,4	46,1	-1,6	1,3	5,8	-3,1	5,4	27,0

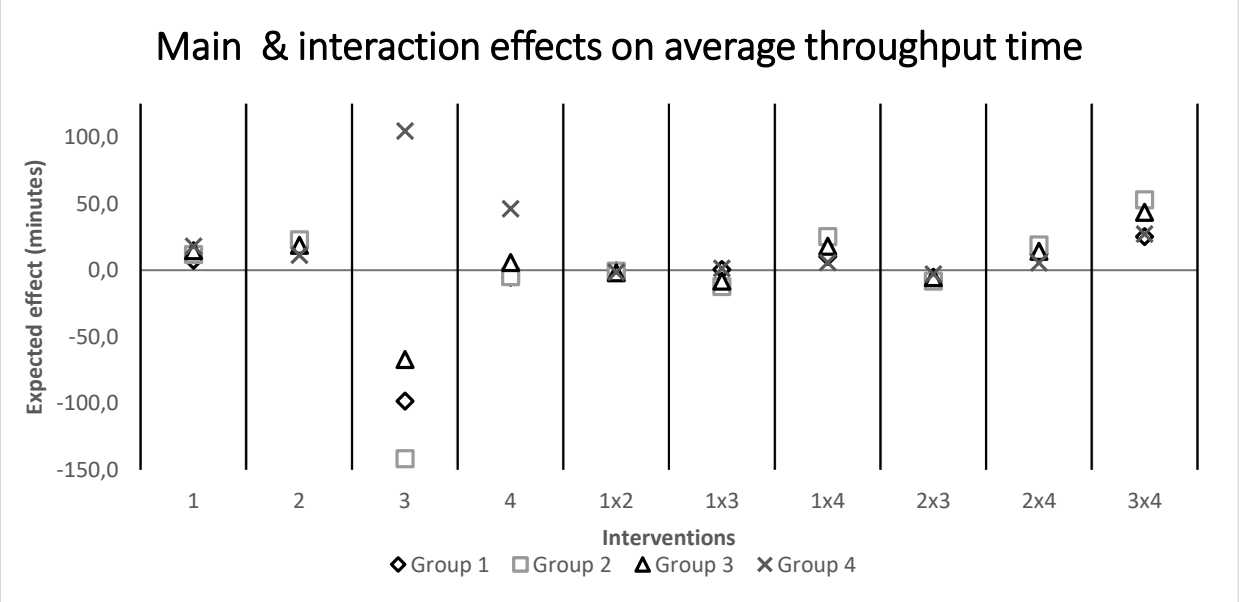


Figure 44 - Main & two-factor interaction effects on average throughput time in 2k-factorial experiment

8.3. Conclusion of simulation results

This chapter evaluated the simulation runs that were designed in Chapter seven. Two simulation experiments have been run: an One-Factor-At-a-Time simulation consisting of eight experiments with 500 replications each, and a 2^k-factorial design experiment of four factors, consisting of sixteen experiments run with 197 replications each.

The OFAT simulation showed that a pressure on the system is created by sorting assessments first-in-first-out on a system level. This pressure can be alleviated by switching to sorting first-in-first-out on a process level. This will make the system less likely to buffer large queues which result in

much wasted waiting time. The trade-off for this implementation is a longer average throughput time for group 4 specimens, making it very hard for those assessments to be completed within the current SLA. These findings support the intervention proposal of changing the SLA, as this will allow the pressure to be released of the system. Furthermore, it was found that by having specimens arrive at the laboratory every hour, the throughput time of group 2 and group 3 specimens within the laboratory can be reduced.

The 2^k-factorial simulation supported the findings of the first simulation, showing a significant main effect for the implementation of the third intervention: embedding on arrival order. With regards to interaction effects between embedding on arrival order and the other interventions, no significant beneficial interactions are discovered.

In conclusion, the results of the two simulations experiments encourage the implementation of embedding and sectioning on arrival order, that is switching from first-in-first-out processing on system level to first-in-first-out processing on process level. This will result in lower throughput times for group 1, 2 and 3 specimens which account of 90% of the assessments. As a trade-off, the throughput times of group 4 specimens will increase slightly.

As the strict SLA norm for group 4 specimens was found to be the cause of the pressure on the system, and the proposed intervention will slightly increase group 4 processing times, it is suggested to relax the SLA standard for the group 4 specimens to four days. This will relax the system and improve the throughput time and throughput consistency of the other specimen groups.

Chapter 9. | Conclusion & Discussion

This chapter summarizes and discusses the findings to conclude the thesis. The conclusion is structured using the research problems in Chapter 2. In the discussion, both the strengths and weaknesses of this thesis will be discussed, as well as the limitations that have been encountered during the execution of the research. Finally, recommendations for further research will be provided, both for LabPON and histology laboratories in general.

9.1. Conclusion

The goal of this research was to increase the insight into the logistical chain of the histology department at LabPON and to identify possible interventions to improve the process. To reach this goal, a problem cluster was constructed from which uncertainty of capacity effect of personnel planning and the time pressure felt on non-urgent specimens were selected as core problems. Based on the selected core problems, the following research question was formulated to be answered in this thesis:

"What organizational interventions are possible to reduce the process variability and throughput time of the logistical process of the Histology Department of LabPON?"

To answer this research question properly in a structured method, the following six research problems were identified that needed to be answered:

1. How is the histological process at LabPON organized?
2. What is the current performance of the histological process at LabPON?
3. What can be found in literature about the histological process from an operations management perspective?
4. What organizational interventions are possible at LabPON?
5. What organizational interventions are promising for LabPON?
6. How can interventions be optimally implemented?

Each research problem has been answered in a separate chapter, the findings for each research problem are summarized below.

The histological process at LabPON consists of eight consecutive steps: Accessioning & Preparation; Grossing; Tissue Processing; Embedding; Sectioning; Staining; Scanning & Distribution; and finally, examination. This process is similar to other histology laboratories except for scanning, which LabPON has implemented to facilitate digital pathology. The specimens that are submitted to the laboratory are divided into four different groups: Group 1 for urgent material; group 2 for small material; group 3 for medium material; and group 4 for large material. Except for the examination, all steps are performed by the analysts of the histology laboratory. Most tasks can be performed by all analysts, however some tasks such as grossing specimens require special training. The grossing of the most complex material and examination of slides is performed by the pathologists. Notable resources that are used during the histopathological process are the six grossing tables (U1-U6); the

two VIP and two Sakura express tissue processing machines; the four embedding stations and eight microtomes in the histology laboratory; the different colouring machines and the five slide scanners. Several KPIs were found for the histopathological process, of these KPIs throughput time was determined to be the focus for this research.

For the determination of the current performance, a large data analysis is performed. It is found that the performance compared to the SLA does not meet the specified standards, however, the individual processes at LabPON perform well suggesting that the SLA is too strict. Demand for histological services fluctuates both both on weekly and daily basis. Mondays and Fridays are found to have low demand, while Tuesday and Wednesday show high demand. The difference in demand between the slowest and busiest day is 17,75%. This variation is caused by operating schedules of hospitals and as such is rather constant, but can change quickly if hospital schedules are altered. Weekly demand variation is mainly impacted by holidays, which result in low demand. With regards to location, 85% of demand comes from the four hospitals. A total of 56,6% is currently handled through the front offices in MST Enschede and ZGT Almelo. The throughput times of the different sub-processes are determined. Large workload differences exist within the grossing of large specimens: a small number of large specimens types are responsible for over half the workload. Long waiting times occur between embedding and sectioning. This is caused by the combination of the large batch arrival of over half the daily specimens from hospitals at 15:00, combined with the overnight batch processing in the VIP. This batch arrival causes high workloads for grossing in the afternoon and overloaded Express tissue processors in the morning, causing buffers at embedding and sectioning, ultimately resulting in waiting time.

In the literature, it was found that the processing times of the distinct histological process steps are roughly equal around the world and mostly influenced by the size of a laboratory. Common methods used to improve or speed up the histological process are the implementation of continuous throughput tissue processing, adaptation of lean management, and the shortening of fixation times through heated fixation. Techniques to model the histological process have been described, Discrete-Event simulation was found to be the most suitable method for the current application.

With regards to what organizational interventions are possible at LabPON, interventions are formulated in response to the result of the data analysis, the findings in literature or suggestions by management or personnel; seven possible interventions are proposed:

Intervention 1 - Later stop for grossing & tissue processing of small specimens
Intervention 2 - Later stop for staining & scanning
Intervention 3 - Changing the specimen delivery schedule for more continuous delivery
Intervention 4 - Embedding and sectioning on arrival order
Intervention 5 - Workload balancing by processing placentas on slower days
Intervention 6 - Using heated fixation to shorten fixation times
Intervention 7 - Changing the SLA to reflect the characteristics of specimens

To determine what organizational interventions are promising for LabPON, a Discrete-Event simulation model is built, the construction process is described in Chapter seven, the model in Appendix C. Two experimental designs are constructed, the first testing intervention individually using the One-Factor-At-a-Time (OFAT) approach, the second testing for interaction effects between a selection of interventions tested in the OFAT experiment, using a 2^k-factorial design.

The results of the OFAT simulation experiment encourage the implementation of embedding and sectioning on arrival order, that is switching from first-in-first-out processing on system level to first-in-first-out processing on process level, or the hourly delivery of specimens. The other simulated interventions showed no significant beneficial effects, this includes the shifted working hours for grossing with additional express tissue processing runs or extended staining and scanning shifts which were being considered for implementation by LabPON.

The results of the 2^k-factorial simulation experiment showed that combining embedding and sectioning on arrival order with hourly delivery of specimens resulted in negative interaction effects, suggesting that it is not beneficial to implement both interventions together. No other significant beneficial interaction effects were found, thus the largest improvement can be gained by implementing just embedding and sectioning on arrival order.

Implementation of this intervention will make the system less likely to accumulate excessive intermediate buffers, resulting in a better flow and lower throughput times for group 1, 2 and 3 specimens which account of 90% of the assessments. As a trade-off, the throughput times of group 4 specimens will increase slightly.

As the strict SLA norm for group 4 specimens was found to be the cause of the pressure on the system, and the proposed intervention will slightly increase group 4 processing times, it is suggested to relax the SLA standard for the group 4 specimens to four days. This will relax the system and improve the throughput time and throughput consistency of the other specimen groups.

In conclusion, the research question what organizational intervention are possible to reduce the throughput time and process variability of the histological process at LabPON can be answered with the implementation of embedding and sectioning on arrival order and the relaxation of the SLA for group 4 specimens.

In relation to literature, additional support is found for continuous throughput processing, as the batch resulting from overnight VIP processing creates the initial buffer which is propagated throughout the day by additional supply from the Express machines, causing waiting times at embedding and sectioning. Thus, eliminating the batch arrival using continuous throughput processing would make the buffers less likely to form.

Furthermore, the proposed intervention of embedding on arrival order is in line with lean thinking, as it will smooth the processing of different specimen groups over time in comparison to the current system, which is in line with the *Heijunka* (production levelling) principle which leads to decreasing the *Mura* (unevenness), ultimately resulting in less waste.

9.2. Discussion

In this discussion, the limitations of this research will be shortly discussed. For this purpose, first the scope and research design will be discussed, followed by limitations of Discrete-Event Simulation and finally the limitations of the actual model itself.

The scope of this research was, as requested, limited to the histology laboratory, as such not the entire histopathological production system has been taken into account. The performance of the pathologists and other connected departments have therefore only been analysed superficially and have not been included in this thesis. Although narrowing down a scope is necessary for research, it is important to include the entire process and be aware how different sub-processes are connected within an organization. Over the duration of this research, a feeling has grown and persists that significant improvements can be made in the coupling of the histology laboratory and the pathologists. This has been indicated but has been given no further attention as it was deemed out of scope.

The two methods used for structuring this thesis, the MPSM and the Sound Simulation Study Design method, complemented each other very well and together created a very diligent approach for the simulation study.

With regards to the data, the data available in the LIMS of LabPON was of great value and can be considered a precious source of information. The data in the database is very complete and required very little cleaning. This quality of the data facilitated analysis which is reflected in the data analysis.

With regards to simulation, and Discrete-Event Simulation in particular, there are some limitations to its use. Although simulation allows complete control over the experimental conditions, it is and always will be just an estimation of the true system. As such, it is a great tool for comparing complex systems with each other, but not a perfect tool for complete optimization, as it will always contain a slight deviation from reality. This should be kept in mind when looking at the results.

With regards of the scope and level of detail in the model, the histology laboratory is modelled from a medium to high level. This causes the model to be very suitable for investigation of assessment flow throughout the laboratory, but also means that some procedures are not included directly included in the simulation. This level of detail is always a consideration that must be made during the construction of a simulation model; in the current model, it feels very appropriate for the intended purpose.

A shortcoming of the current version of the model is that only the average throughput time for each specimen group is being tracked. Although this gives a good indication of the performance within a single simulation replication, but also provides limited information with regards to consistency throughput times within the simulation. A good addition to the model would therefore be a measure of the throughput time variability for each of the specimen groups within a single replication. By adding this output variable, an insight can be gained into the consistency of throughput times yielded by each of the interventions.

Furthermore, although the research succeeded in its goal of finding sources of variability in the histological process, these fluctuations tended to result in large outliers in the simulation. These outliers were cause because while in reality people intervene, the simulation will continue according to its given set of rules. With regards to these outliers, a choice had to be made on how to handle them. One approach could have been to model the intervention by coordinating analysts when buffers would get to high, however this would make the model difficult to validate and would

artificially improve performance of system configurations. As such the choice was made to allow the simulation to create outliers, proofing imbalances in the system. However, the prevalence of these outliers did make data such as the main- and interaction effects in the data analysis less reliable. As such it would be interesting to repeat the experiment while including only stable system configurations.

9.3. Recommendations for future research

In this study, LabPON is shown to be an efficient and capable organisation. The organisation shows a drive for self-improvement as exemplified by the implementation of digital pathology and the execution of improvement projects such as this study. As such a progressive organisation, few strong recommendations for future research remain.

However, for future research it is strongly recommended to research the transfer and distribution of slides from the laboratory to the pathologists. As discussed at the end of Paragraph 3.1.7. , the current method of distribution of slides to pathologists can be described as a system with multiple parallel single servers with a constant arrival rate. This creates inflexibility and can lead to unnecessary delays in the system, indications of which are seen in the data.

With regards to the simulation model, this research has been chiefly concerned with the identification of operational interventions and the construction of a valid simulation model to test intervention for the histological laboratory on the operational level. As the model has now been completed, it can be used to evaluate different interventions and it could be expanded upon to conduct simulations with more variation.

For further testing, recommendations include the influence of resource interventions, i.e. investigating what the influence would be of changing or adding machines in the process, or what kind of effect adding an extra employee would have to the system. In line with lean thinking, an effort should be made to reduce batched arrivals in the system. However, if the batched arrival and batched tissue processing cannot be eliminated, interventions should aim to reduce the impact of these batches by momentarily increasing process capacity upon entry of the batch at the process.

With regards to expanding the simulation model, the model could be expanded by introducing variable assessment generation, by finding and adding input distributions for assessment submission and including daily and weekly fluctuations in demand. If implemented this should be combined with flexible and potentially reactive scheduling of employees. Such a model could be used to test employee scheduling methods and capacity balancing procedures. However, care should be taken as such a model has the risk of quickly becoming overly complex, to the point where no valid information can be gained.

With regards to scientific contribution, the model is largely generalizable for use in different histological laboratories and as such could be applied to help improve the process. For this purpose, the model might be developed further to a general model, with the addition of frequently seen laboratory configurations which might not be present at LabPON and simplified parameter control. Such additions could make the simulation model accessible for people with less knowledge of

simulation programming, and can provide a good starting point to implement simulation to aid decision making.

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Appendix

Appendix A – MySQL queries for extraction of datasets

Grossing query

```
select distinct

analysis.an_number as onderzoek,
specimen.dissectiondate as uitsnijdatum,
materialkind.name as aard_materiaal,
materialkind.category,
terminal.name as werkstation_uitsnijden,
users.name as uitsnijder,
users.userjob

from container

inner join analysis on container.analysis = analysis.analysis
inner join specimen on container.analysis = specimen.analysis
left outer join MATERIALKIND on specimen.materialkind = materialkind.materialkind
inner join terminal on container.dissectedon = terminal.terminal
inner join users on specimen.user_out = users.users

where
container.dissectedon in (187,188,189,190,191,192) and          /* vul hier het database_id van de uitsnijtafel in */
container.date_in >= '1-1-2016' and     /* vul hier de startdatum in */
container.DATE_IN < '1-1-2017'          /* vul hier de einddatum in (meestal de volgende dag)*/

order by analysis.an_number
container.date_in as uitsnijdatum, l
```

Embedding query

```
select
analysis.an_number as onderzoek,
container.embeddate as uitsnijdatum,
/* materialkind.name as aard_materiaal, */
/* container.embeddate as inbeddatum, */
terminal.name as werkstation_inbedden,
users.name as inbedder

from container

inner join analysis on container.analysis = analysis.analysis
/* inner join specimen on container.analysis = specimen.analysis */
/* left outer join MATERIALKIND on specimen.materialkind = materialkind.materialkind */
inner join terminal on container.embedstation = terminal.terminal
inner join users on container.embeduser = users.users

where
container.embedstation in (145,146,147,148) and             /* zoek eerst het database-id in het LMS op
van het desbetreffende werkstation */
container.embeddate >= '1-1-2016' and     /* vul hier de startdatum in */
container.embeddate < '1-1-2017'  and          /* vul hier de einddatum in (meestal de volgende dag)*/
analysis.an_type in (1,27,29,30,31,39,52,54)

order by analysis.an_number
```

Microtome cutting query

```
select
  analysis.an_number as onderzoeken,
  staining.name as kleuringnaam,
  sample.cutterdate as datum_snijden,
  sample.container as cassette,
  terminal.name as werkstation,
  USERS.name as snijder

from sample

inner join analysis on sample.analysis = analysis.analysis
inner join users on sample.CUTTERUSER = users.users
inner join staining on sample.staining = staining.staining
inner join TERMINAL on sample.CUTTERTABLE = terminal.terminal

where
  sample.CUTTERDATE >= '01-01-2016' and    /* vul hier de startdatum in */
  sample.CUTTERDATE < '01-01-2017'      /* vul hier de einddatum in (meestal de volgende dag)*/


order by 3
```

Appendix B – Input simulation model

Cumulative chances used as input for the simulation model. Generation of specimens and cassettes is performed using a uniform distribution between 0 and 1. After sampling a number the corresponding number of specimens or cassettes is selected by selecting the lowest value which is higher than the sampled number. For example, generating the number of cassettes for group 1 with a random sampled value of 0,61 yields 6 cassettes.

Group \ Specimens	1	2	3
Group 1	0.912	0.985	1
Group 2	0.784	0.951	1
Group 3	0.906	0.975	1
Group 4	0.75	0.96	1

Cassettes	1	2	3	4	5	6	7	8	9	10
Group 1	0,24	0,33	0,41	0,54	0,60	0,65	0,69	0,73	0,75	0,78
Group 2	0,48	0,65	0,75	0,85	0,91	0,94	0,96	0,97	0,97	0,98
Group 3	0,45	0,64	0,75	0,83	0,88	0,91	0,93	0,95	0,96	0,97
Group 4	0,02	0,09	0,14	0,22	0,29	0,37	0,42	0,47	0,52	0,56
Cassettes	11	12	13	14	15	16	17	18	19	20
Group 1	0,81	0,85	0,88	0,89	0,90	0,92	0,93	0,94	0,94	1,00
Group 2	0,98	0,99	0,99	0,99	0,99	0,99	0,99	1,00	1,00	1,00
Group 3	0,98	0,98	0,98	0,99	0,99	0,99	0,99	0,99	0,99	1,00
Group 4	0,59	0,62	0,65	0,67	0,70	0,72	0,74	0,76	0,78	1,00

Appendix C – The simulation model

The first frame, shown in Figure 45, entails the generation, reception, administration of assessments and fixation of specimens. Assessments are generated in the form of *moveable units*, called MUs in short. The MUs are generated from three different sources: the two locations which currently have a front office, Enschede & Almelo, and the other locations. Using a chain of methods (objects which allow text based programming with the programming language SimTalk), the arrival of the MUs in the laboratory is modelled in a way that allows arrival times to be easily edited as a parameter in the ModelOverview frame. At the moment of arrival at the laboratory, attributes are randomly generated for each MU according to group specifications, these include the number of specimens, the number of cassettes, slides, and laboratory entry time. Next, specimens which originated from locations without a front office are first accessioned. Following accessioning, the specimens are distributed; group 4 specimens move to the wet room for preparation and fixation, and the rest of the material continue to grossing.

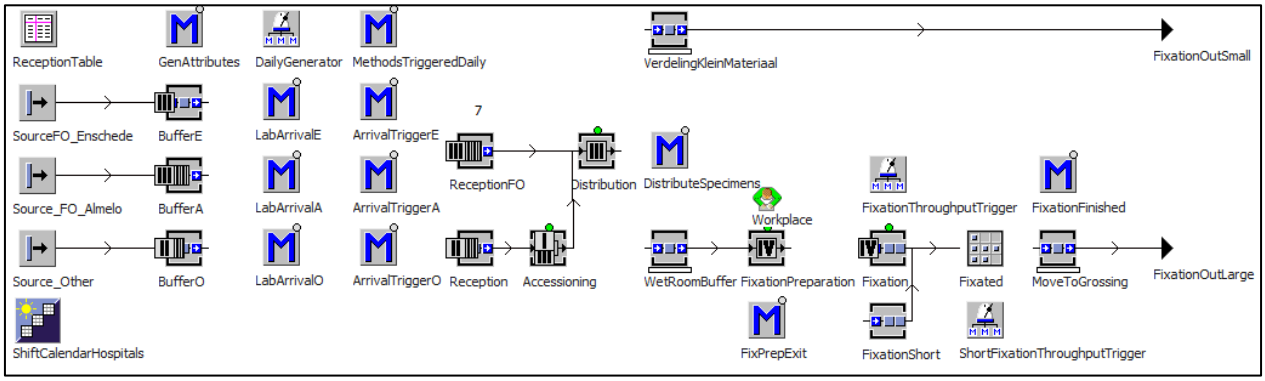

Figure 45 - Frame 1: Administration & fixation

The grossing frame is shown in Figure 46. It consists of six grossing stations, each preceded by a queue. The incoming specimens are automatically distributed by a method to the correct queue to await processing. The grossing times are generated using a continuous empirical distribution, the data of this distribution originates from the data analysis and is presented as PDF in Chapter 4. Grossing stations U4, U5 and U6 are dedicated to grossing only large specimens. Grossing stations U1, U2, and U3 initially gross their corresponding specimen group, however after completing grossing of these specimens the stations will assist neighbouring grossing stations. This assistance is prioritized with group 1 first, group 2 second and group 3 third. An analyst must be present for a grossing station to process specimens. In the scheduling, conducted via the ModelOverview, a distinction is made between large grossers and small grossers, the former is allowed to service all grossing stations while the latter may only service U1, U2, and U3. After a MU has finished processing, it continues to the post-fixation step. This takes 1 hour for group 1 specimens, 2 hours for group 3 and group 4 specimens, and is instantaneous for group 2 specimens.

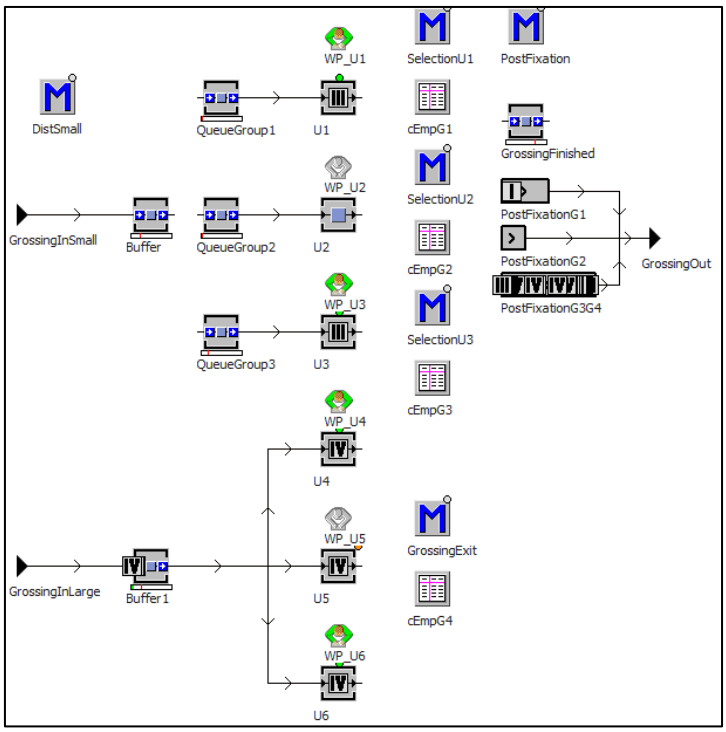

Figure 46 - Frame 2: Grossing

The third frame is concerned with the tissue processing process, as shown in Figure 47. To properly model the behaviour of the tissue processing process, ten methods are used. These ensure that assessments arrive in the correct machine, at the right time, without exceeding the capacity. The schedule of both the VIP and the Express machines can be altered by a parameter in the ModelOverview frame. The VIP is scheduled to start processing at 16:00 for overnight processing, the expresses start processing a batch every 20 and 35 minutes respectively taking 1h25 and 2h25.

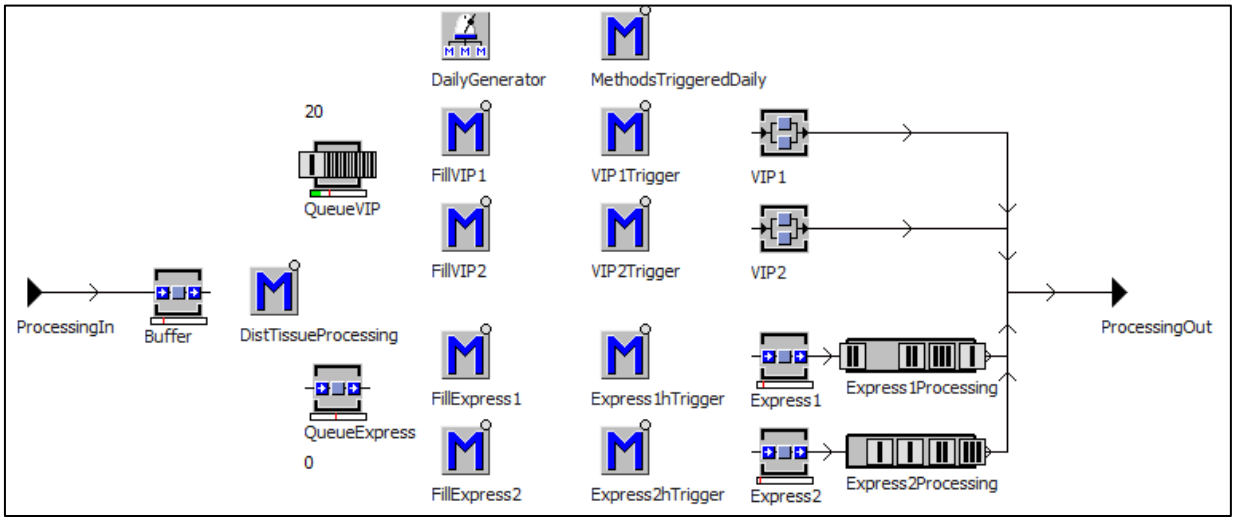

Figure 47 - Frame 3: Tissue fixation

In the fourth frame, the specimens are embedded as shown in Figure 48. The specimens are first sorted according on a setting in the ModelOverview, either being processed on order of assessment

number or on arrival order; group 1 specimens are always given priority. Four embedding stations are modelled which can be used for embedding, each requiring an analyst to continue production. Embedding times are generated using a continuous empirical distribution, and the process is repeated for the number of cassettes included in an assessment.

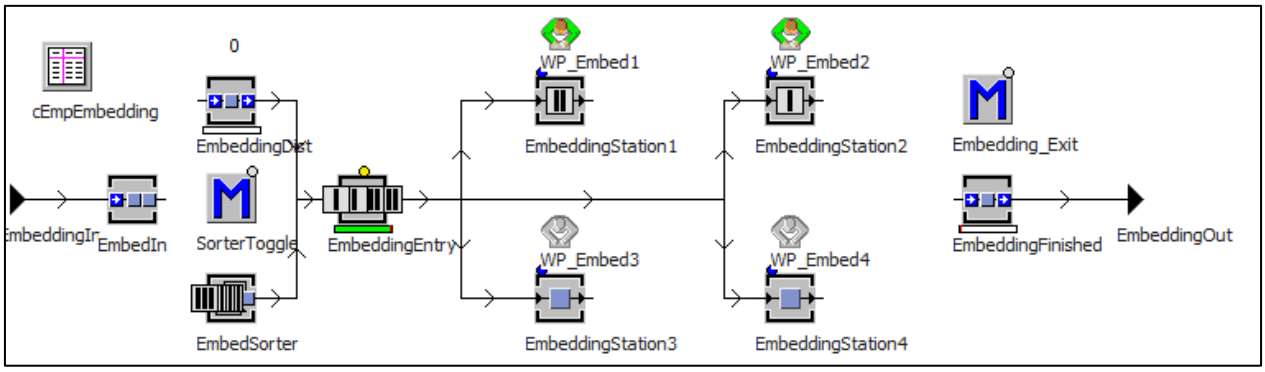

Figure 48 - Frame 4: Embedding

After embedding, MUs advance to sectioning, as shown in Figure 49. This process is similar to the embedding in programming, using a continuous empirical distribution for distribution times, repeating the process once for each slide in an assessment, and requiring an analyst.

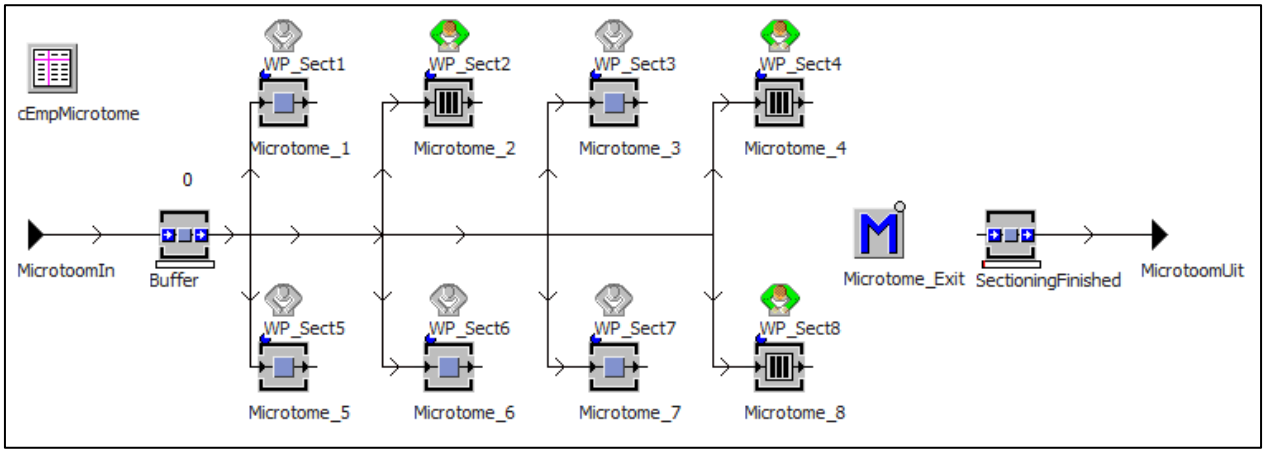

Figure 49 - Frame 5: Sectioning

After sectioning, the assessments are finally stained and scanned before exiting the system through the drain-object, as shown in Figure 50. When a MU exits the system, a data collection method is activated which writes relevant data of the MU to the performance statistics table on the model overview.

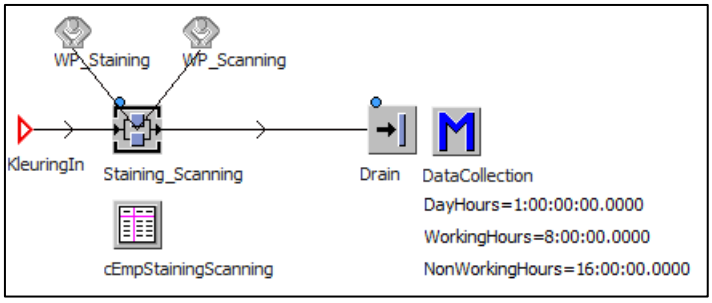

Figure 50 - Frame 6: Staining & Scanning