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Comprehensive Guidelines and Templates for Thesis Writing

Master's Thesis

of

Author

Date of issue:
Date of submission:
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Supervisor:

Statutory Declaration

I, Author, hereby affirm that the following Master's thesis has been elaborated solely by myself. No other means and sources except those stated, referenced and acknowledged have been used.

(Author)

Abstract

Contents

Acronyms Index

TUHH:	Hamburg University of Technology
SOFA:	Sequential Organ Failure Assessment
qSOFA:	Quick Sequential Organ Failure Assessment
ICU:	Intensive Care Unit
EHR:	Electronic Health Record
YAIB:	Yet Another ICU Benchmark
FSQ:	Finite Scalar Quantization
SI:	Suspected Infection
ABX:	Antibiotics
DNM:	Dynamic Network Model
LDM:	Latent Dynamics Model
ML:	Machine Learning
DL:	Deep Learning

1 List of Notes

2 Notes

actual functional model what is learned connecting parts

2.0.1 Kuramoto Parameter

Kuramoto Order Parameter

$$R_2^\mu = \frac{1}{N}\left|\sum_j^N e^{i\cdot\varphi_j(t)}\right| \quad \text{with} \quad 0 \leq R_2^\mu \leq 1 \tag{1}$$

cite

$R_2^\mu = 0$ splay-state and $R_2^\mu = 1$ is fully synchronized.

Entropy, Splay Ratio, MPV Std, Cluster Ratio

3 Introduction

4 Medical Background (Sepsis)

As the most extreme course of an infectious disease, sepsis poses a serious health threat, with a high mortality rate and frequent long-term consequences for survivors. In 2017, an estimated 48.9 million people worldwide suffered from sepsis and the same year, 11.0 million deaths were associated with sepsis [1], which makes up 19.7% of yearly deaths. Sepsis is also the most common cause of in-hospital deaths. Untreated, the disease is always fatal and even with successful treatment, around 40% of those affected suffer long-term consequences, such as cognitive, physical or physiological problems, the so called *post-sepsis syndrome* [2]. Overall, treated and untreated septic diseases in particular represent an enormous burden on the global healthcare system.

The triggers for sepsis are varied, but almost half of all sepsis-related deaths occur as a secondary complication of an underlying injury or a non-communicable, also known as chronic disease [3]. A recent study [4] highlights the importance of early recognition and subsequent treatment of infections in patients, reducing the mortality risk caused from sepsis. Each hour of earlier detection can significantly increase the chance of survival [4], it urges to develop accurate and robust detection and prediction methods, i.e. reducing the time to receive the appropriate medical attention.

Per definition, sepsis is a "life-threatening organ dysfunction caused by a dysregulated host response to infection" [5]. There are multiple (now historic) more specific definitions available and sometimes blurry terminology used when dealing with the sepsis and septic shocks. The following Section 4.1 gives a more detailed introduction to the most commonly used sepsis definition, which is referred to as Sepsis-3. Additionally, Section 4.2 provides a short introduction of both the pathology and biology of sepsis and Section 4.3 talks about the need for reliable sepsis prediction systems.

4.1 Sepsis-3 definition

Out of the need for an update of an outdated and partly misleading sepsis model a task force led by the "Society of Critical Care Medicine and the European Society of Intensive Care Medicine", was formed in 2016. Their resolution, named "Third International Consensus Definitions for Sepsis and Septic Shock" [5], provides until today the most widely used sepsis definition and guidance on sepsis identification.

In general, sepsis does not classify as a specific illness, rather a multifaceted condition of "physiologic, pathologic, and biochemical abnormalities" [5], where the original causes are mostly uncertain. Most commonly the underlying cause of sepsis is diarrhoeal disease, road

traffic injury the most common underlying injury and maternal disorders the most common non-communicable disease causing sepsis [1].

According to the Sepsis-3 definition, a patient is in a septic condition if the following two criteria are fulfilled:

- a documented or Suspected Infection (SI) and
- the presence of a dysregulated host response

The combination of the two criteria represents an exaggerated immune reaction that results in organ dysfunction, when infection is first suspected, even modest organ dysfunction is linked to a 10% increase of in-hospital mortality. A more pathobiological explanation of what a "dysregulated host response" means is given in the next Section 4.2.

Confirmed or Suspected Infection is suggested to characterize any patient prescribed with Antibiotics (ABX) followed by the cultivation of body fluids, or the other way around, with a suspected infection. The timings of prescription and fluid samplings play a crucial role. If the antibiotics were administered first, then the cultivation has to be done in the first 24h after first prescription, if the cultivation happened first, the ABX have to be prescribed in the following 72h [5]. This can be seen in the lower part of figure Figure 1, with the abbreviated ABX. Regardless which happened first, the earlier of the two times is treated as the time of suspected infection onset time.

Dysregulated Host Response is characterized by the worsening of organ functionality over time. Since there is no gold standard for measuring the amount of "dysregulation" the Sepsis-3 consensus relies on the Sequential Organ Failure Assessment (SOFA)-score introduced in ([5], [6]). The score is now regularly used to evaluate the functionality of organ systems and helps to predict the risk of mortality, also outside of a sepsis context. The SOFA score is calculated at least every 24 hours and assess six different organ systems by assigning a score from 0 (normal function) to 4 (high degree of dysfunction) to each. The overall score is calculated as sum of each individual system. It includes the respiratory system, the coagulation/clotting of blood, i.e. changing from liquid to gel, the liver system, the cardiovascular system, the central nervous system and the renal system/kidney function. A more detailed listing of corresponding markers for each organ assessment can be found in table Table 1 in the Section 13. The magnitude of a patients initial SOFA-score captures preexisting organ dysfunction. An increase in SOFA score ≥ 2 corresponds to an acute worsening of organ functionalities and a drastic worsening in the patients condition, the indicator for a dysregulated response.

can
we fix pleas

4.1.1 Sepsis Classification

The Sepsis-3 definition not only provides the clinical critera of septic conditions, but also introduces the necessary time windows for sepsis classification. An increase of SOFA ≥ 2 in the 48h before or 24h after the SI time, the so called SI-window, is per Sepsis-3 definition the "sepsis onset time". A schematic of the timings is shown in figure Figure 1.

With respect to which value the increase in SOFA is measured, i.e. the baseline score, is not clearly stated in the consensus and leaves room for interpretation, commonly used approaches include:

- the minimal value inside the SI-window before the SOFA increase,

- the first value of the SI-window,
- or the lowest value of the 24h previous to the increase.

Differences in definitions greatly influence the detection of sepsis, which are used for prevalence estimates for example [7]. Using the lowest SOFA score as baseline, the increase ≥ 2 for patients with inspected infection was associated with an 18% higher mortality rate according to [6] a retrospective Intensive Care Unit (ICU)-data analysis.

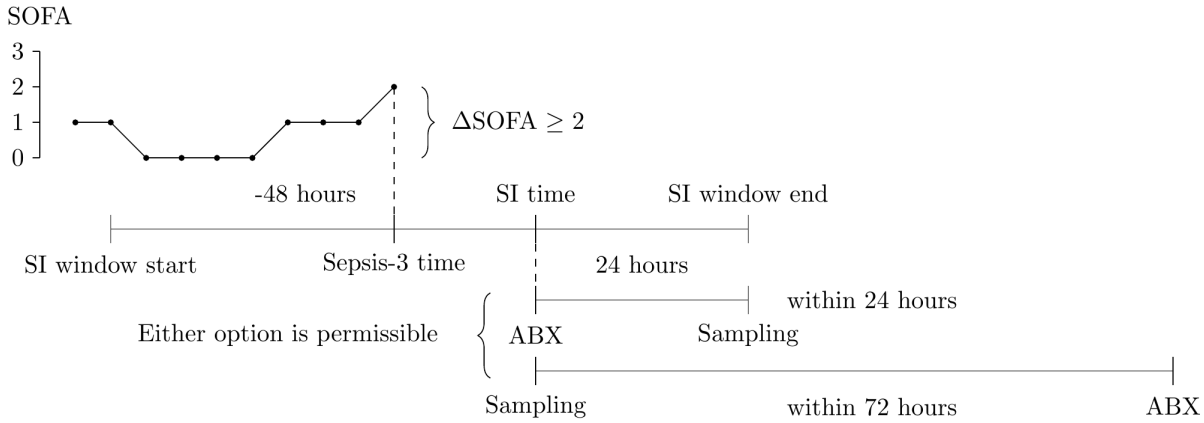


Figure 1: Graphical representation of the timings in the Sepsis-3 definition, taken from [8]

Up until today, even though SOFA was created as a clinical bedside score, some of the markers used in it are not always available to measure or at least not at every 24h [9]. For a faster bedside assessment [6] also introduced a clinical score termed Quick Sequential Organ Failure Assessment (qSOFA), with highly reduced marker number and complexity, it includes:

- Respiratory rate ≥ 22/min
- Altered mentation
- Systolic blood pressure ≤ 100 mm Hg

Patients fulfilling at least two of these criteria have an increased risk of organ failure. While the qSOFA has a significantly reduced complexity and is faster to assess it is not as accurate as the SOFA score, meaning it has less predictive validity for in-house mortality [6].

center

4.2 Biology of Sepsis and Cytokine Storms

The hosts dysregulated response to an infection connected to the septic condition is driven by the release of an unreasonable amount of certain signaling proteins, so called *cytokines* [10]. Cytokines are a broad family of different cells which play a special role in the communication between other, both neighboring and distant, cells [11], this includes immune-cell to immune-cell or immune-cell to other cell types. In the innate immune system, i.e. the body's first line of non-specific defense [12] they regulate the production of anti- and pro-inflammatory immune cells which help with the elimination of pathogens and trigger the healing process right after. They are also involved in the growing process of red and white blood cells.

One specialty of these relatively simple cells is that they can be produced by immune cells or non-immune cells, with different cells being able to produce the same cytokine. Further, cytokines are redundant, meaning targeted cells can show identical responses to different cytokines [13], these features seems to fulfill some kind of safety mechanism to guarantee vital communication flow. After coming to life cytokines have relatively a short half-life (only a

few minutes) but through cascading-effects the cytokines can have substantial impact on their micro-environment.

Normally, the release of inflammatory cytokines automatically fades out once the initial pathogen is controlled. In certain scenarios a disturbance to the regulatory mechanisms triggers a chain reaction, followed by a massive release of cytokines, coupled with self-reinforcement of other regulatory mechanisms [10], leading to a continuous and uncontrolled release of cytokines that fails to shut down. This overreaction, called *cytokine storm*, is often harmful to the hosts body and can lead to multi organ failure, like in sepsis, and subsequently death. In these cases, the damage done by the immune system's reaction is magnitudes greater than the triggering infection itself.

Even though the quantity of cytokines roughly correlates with disease severity, concentrations of cytokines vary between patients and even different body-parts making a distinction between an appropriate reaction and a harmful one almost impossible [10]. Out of all cytokines, only a very small subset or secondary markers can be measured blood samples to evaluate increased cytokine activity. This makes them hard to study and little useful as direct indicators of pathogenesis or prediction purposes. Since the 90s there has been a lot of research focused on cytokines and their role in the innit immune system and overall activation behavior. But to this day no breakthrough has been done and underlying principles have not been uncovered.

4.3 The need for sepsis prediction

4.4 Maybe Treatment

what happens with the organs in the storm

5 Problem definition

This section provides some background on the specific research questions which are investigated in Section 11 using the methods introduced in Section 8 and Section 9 respectively. As discussed in Section 4.3, there is a substantial need for robust methods to identify patients sepsis onset and overall progression. This work provides a proof of concept for such a prediction system.

The increasing availability of high-quality medical data, i.e. multiple physiological markers with high temporal resolution, enables both classical statistical and Machine Learning (ML) (including Deep Learning (DL)) methods (see Section 7). While these purely data-driven approaches often achieve acceptable performance but the explainability of the prediction suffers and limits their adoption in clinical practice .

cite

In parallel, recent advances in the field of network physiology have introduced new ways to model physiological systems as interacting subsystems rather than isolated organs [14]. The Dynamic Network Model (DNM) introduced in [15], allows for a functional description of organ failure in sepsis and shows realistic system behavior in preliminary analysis. An in-depth introduction to the DNM is provided in Section 8. But up until now the dynamic model has not yet been verified on real data, in this work we want to change that. However, this model has not yet been validated against real-world observations, which will be addressed in this work .

eher project???

To summarize, the specific research questions include:

- **Usability of the DNM**: How and to what extent can the ML-determined trajectories of the DNM be used for detection and prediction, especially of critical infection states and mortality.
- **Comparison with data-based approaches**: How can the model-based predictions be compared with those of purely data-based approaches in terms of predictive power and interpretability.

6 The Data and Task problems

In [16], a survey among clinicians regarding AI-assistance in healthcare, one participant emphasizes that specific vitals signs might not be to be of less importance, rather the change/ trend of a patients trajectory. Another piece of finding of the same study was the preference of trajectories over plain event predictions.

Figure 2: Sets of [17]

RICU and YAIB use delta_cummin function, i.e. the delta SOFA increase is calculated with respect to the lowest observed SOFA to this point.

7 State of the Art

7.1 Model Based Methods

7.2 Data Based Methods

7.2.1 Selected Works

8 Dynamic Network Model (DNM)

The Parenchymal (Equation 2.1° and Equation 2.2°) and Immune (Equation 2.3° and Equation 2.4°) layer and their respective states of the dynamical system naturally are consistent with the two cornerstones of the Sepsis-3 definition [5], i.e. SOFA score and suspicion of an infection.

Healthy → sync $\langle\dot{\varphi}_j^1\rangle$ and $\langle\dot{\varphi}_j^1\rangle$

SOFA → desync $\langle\dot{\varphi}_j^1\rangle$

Suspected infection → splay/desync $\langle\dot{\varphi}_j^2\rangle$

septic → desync $\langle\dot{\varphi}_j^1\rangle$ and $\langle\dot{\varphi}_j^1\rangle$

8.1 Description

$$\dot{\varphi}_i^1 = \omega^1 - \frac{1}{N}\sum_{j=1}^{N}\{(a_{ij}^1 + \kappa_{ij}^1)\sin(\varphi_i^1 - \varphi_j^1 + \alpha^{11})\} - \sigma\sin(\varphi_i^1 - \varphi_i^2 + \alpha^{12}) \tag{2.1}$$

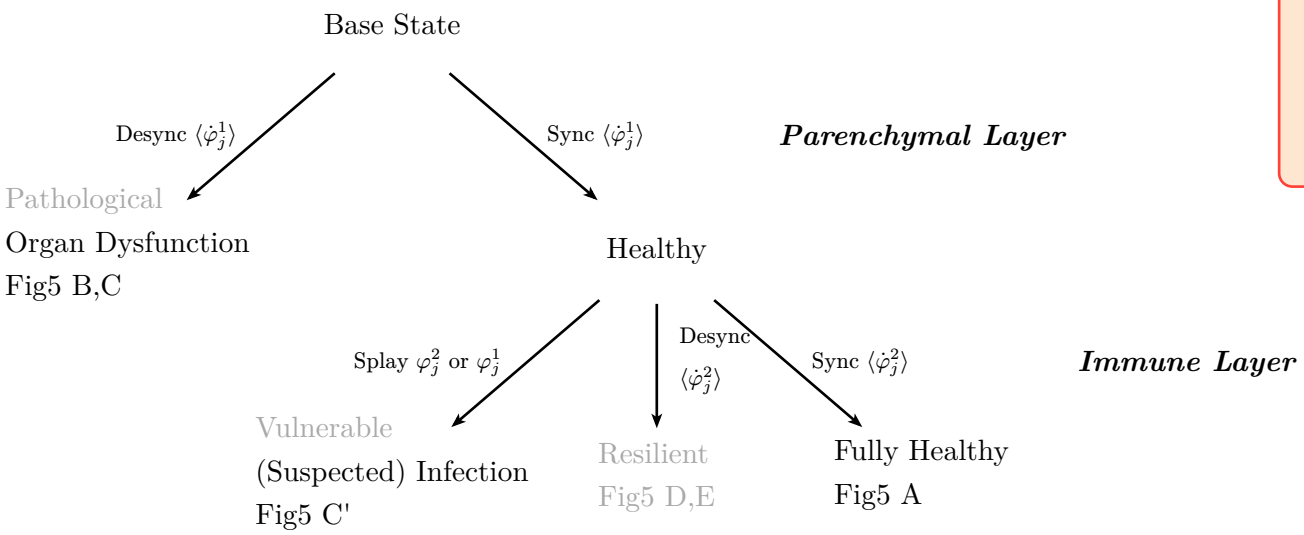
$$\dot{\kappa}_{ij}^1 = -\varepsilon^1(\kappa_{ij}^1 + \sin(\varphi_i^1 - \varphi_j^1 - \beta)) \tag{2.2}$$

$$\dot{\varphi}_i^2 = \omega^2 - \frac{1}{N}\sum_{j=1}^{N}\kappa_{ij}^2\sin(\varphi_i^2 - \varphi_j^2 + \alpha^{22}) - \sigma\sin(\varphi_i^2 - \varphi_i^1 + \alpha^{21}) \tag{2.3}$$

$$\dot{\kappa}_{ij}^2 = -\varepsilon^2(\kappa_{ij}^2 + \sin(\varphi_i^2 - \varphi_j^2 - \beta)) \tag{2.4}$$

Introduced in [15] and slightly adapted in [18].

table for parameters



Mean Phase Velocities are calculated as followed:

$$\langle \varphi^{\mu} \rangle = \frac{1}{N} \sum_{j}^{N} \varphi_j^{\mu} \tag{3}$$

8.1.1 Functional Models

8.1.2 Parenchymal

8.1.3 Immune System

8.1.4 Kuramoto

8.2 Implementation

For parts in the form of $\sin(\theta_l - \theta_m)$ following [19] one can calculate and cache the terms $\sin(\theta_l), \sin(\theta_m), \cos(\theta_l), \cos(\theta_m)$ in advance:

$$\sin(\theta_l - \theta_m) = \sin(\theta_l)\cos(\theta_m) - \cos(\theta_l)\sin(\theta_m) \qquad \forall l, m \in \{1, ..., N\} \tag{4}$$

so the computational cost for the left-hand side for N oscillators can be reduced from $N(N-1)$ to $4N$ trigonometric function evaluations, positively impacting the computational efficiency of the whole ODE-system significantly.

8.2.1 Standard

- Actual Mean Phase Velocity instead of averaged difference over time.
- +They Calculate the difference wrong since the phase difference should be mod$[2\pi]$
- Different solver accuracy, but very similar
- They are not batching the computation

8.2.2 Lie

9 Latent Dynamics Model

9.1 Task - Definition of Ins and Outs

9.2 Data

9.2.1 MIMIC-III/IV

9.2.2 YAIB + (Further) Preprocessing

9.2.2.1 ricu-Concepts

9.3 Latent Dynamics Model (LDM)

9.3.1 The high level ideas

9.3.1.1 Representation Learning and Latent Spaces

9.3.1.2 Semantics

9.3.1.3 Autoregressive Prediction

9.3.2 The Lookup (FSQ)

9.3.3 Encoder

9.3.4 Decoder

9.3.5 Introducing time

9.3.6 Combining the building blocks

For a general model setup, the latent space $z = \left(a^1, \sigma, \alpha, \beta, \omega^1, \omega^2, \frac{C}{N}, \varepsilon^1, \varepsilon^2\right)$ represents the parameter of the dynamic network model, so we have

$$z \in \mathbb{R}^d \quad \text{with} \quad d = 9 \tag{5}$$

As shown in the supplemental material of [18], for example, the parameter α exhibits a π-periodicity, allowing to reduce the effective parameter space by constraining certain parameters with upper and lower bounds. These bounds are omitted here for simplicity but are included in

. To further reduce the latent space z, the we keep $a^1, \omega^1, \omega^2, \frac{C}{N}, \varepsilon^1$ and ε^2 fixed. The reduced latent space $z' = (\sigma, \alpha, \beta)$:

table

$$z' \in \mathbb{R}^{d'} \quad \text{with} \quad d' = 3 \tag{6}$$

where both alpha and beta exhibit a periodic behavior Each point in the latent space z_j can be categorized as either of *healthy*, *vulnerable* or *pathological*.

We relate high-dimensional physiological observations (e.g. samples from the MIMIC-III database) to the latent space via:

$$x_j = f(z_j) + \varepsilon \tag{7}$$

where f is unknown an unknown function and ε the measurement noise. Note that different observations x_j can be mapped to the same classification, as for the latent space. We define two the two class mappings Q and R:

$$Q(x_j) = c_j = R(z_j) \quad \text{where} \quad x_j = f(z_j) + \varepsilon \tag{8}$$

mapping observations and the latent representation to a shared class label c. To make things more complicated, R does not directly act on z, but rather the metrics derived from the solution to a dynamical system (initial value problem) (Equation 2) parameterized by z. The metrics are detailed in.

In the setting of structured latent variational learning we want to approximate an encoder $q(z|x)$ to infer the latent variables from observed data X and the class.

How to structure the latent space? Binary classification (sepsis, no sepsis) may not provide enough information to accurately structure the latent space. The options:

- Add more classes like resilient/vulnerable… maybe even the full spectrum?
  - need to be modeled by R

For the cohort extraction and SOFA calculation I use [20] and [17]. The nice thing is we could interpret larger SOFA scores (> 3) as the vulnerable state introduced by [18]. Increases in SOFA score ≥ 2 could then be used as definition for sepsis.

mapping not really clear, which metrics correspond to sofa/infection

YAIB [17] and other resources care about the "onset" of infection and sepsis [21]. For sepsis this isn't really problematic since we could use the "state transitions" as indicators. But for the suspected infection it is problematic, maybe use si_upr and si_lwr provided by [20] (https://eth-mds.github.io/ricu/reference/label_si.html°). These would be 48h - SI - 24h adapted from [22], maybe a bit too much.

10 Metrics (How to validate performance?)

11 Experimental Results placeholder

11.1 Metrics

11.2 Further Experiments

11.2.1 Custom Latent Space

11.2.2 SOFA vs Infection

12 Conclusion

13 Appendix

Category	Indicator	1	2	3	4
Respiration	PaO_2/FiO_2 [mmHg]	< 400	< 300	< 200	< 100
	Mechanical Ventilation			yes	yes
Coagulation	Platelets $[\times \frac{10^3}{mm^3}]$	< 150	< 100	< 50	< 20
Liver	Bilirubin $[\frac{mg}{dl}]$	1.2-1.9	2.0-5.9	6.0-11.9	> 12.0
Cardiovascular[1]	MAP [mmHg]	< 70			
	or Dopamine		≤ 5	> 5	> 15
	or Dobutamine		any dose		
	or Epinephrine			≤ 0.1	> 0.1
	or Noepinephrine			≤ 0.1	> 0.1
Central Nervous System	Glasgow Coma Score	13-14	10-12	6-9	< 6
Renal	Creatinine $[\frac{mg}{dl}]$	1.2-1.9	2.0-3.4	3.5-4.9	> 5.0
	or Urine Output $[\frac{ml}{day}]$			< 500	< 200

caption

[1] Adrenergica agents administered for at least 1h (doses given are in [µg/kg · min]

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