

Comprehensive Guidelines and Templates for Thesis Writing

Master's Thesis

of
Author

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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

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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
ODE:	Ordinary Differential Equation

1 List of Notes

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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			38
mapping not really clear, which metrics correspond to sofa/infection					39
YAIB	and other resources care about the onset of infection and sepsis	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 (https://eth-mds.github.io/ricu/reference/label_si.html). These would be 48h - SI - 24h adapted from , maybe a bit too much.			39
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- Sections to Chapters
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2 Notes

actual functional model what is learned connecting parts

2.0.1 Kuramoto Parameter

Kuramoto Order Parameter

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

cite

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

En-
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Splay
Ratio,
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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 overview 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. Lastly, in Section 4.3 the necessity for reliable sepsis prediction systems is discussed.

4.1 The 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], and septic patients are largely heterogeneous. 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.

can
we fix please

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.

4.1.1 Sepsis Classification

The Sepsis-3 definition not only provides the clinical criteria 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.

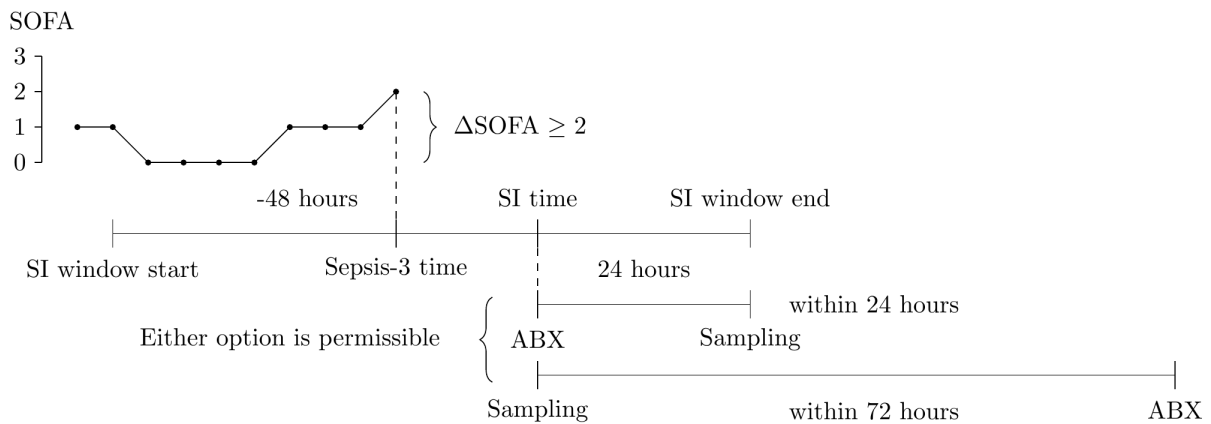


Figure 1: Graphical representation of the timings in the Sepsis-3 definition, taken from [8]

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 $\geq 22/\text{min}$
- Altered mentation
- Systolic blood pressure $\leq 100 \text{ mm Hg}$

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].

4.2 Biology of Sepsis

This part tries to give an introduction into the biological phenomena that underlie sepsis. First we take a look on the way tissue is reacting to local infections or injuries on a cellular level in Section 4.2.1 and how this escalates to *cytokine storms* in Section 4.2.2 and this ends with systemic organ failure in Section 4.2.3.

Certain details and specificities are left out when not essential for the understanding of this project. The interested reader should refer to the primary resources provided throughout this section.

4.2.1 Cellular Description

Human organ tissue can be differentiated into two broad cell-families called *parenchymal* and *stroma* which are separated by a boundary consisting of *basal lamina*. The parenchymal cells conduct the specific function of the organ, with every organ hosting distinct parenchymal cells, everything else is part of the stroma, including the structural or connective tissue, blood vessels and nerves. When a pathogen enters the body the first line of non-specific defense, the innate immune system [10], gets activated. Besides the so called resident-immune-cells (most prominently macrophages) also the stroma cells are able to detect the pathogen via pattern-recognition-receptors and will start releasing signaling proteins, so called *cytokines* [11].

Cytokines are a diverse group of signaling proteins which play a special role in the communication between other, both neighboring and distant cells, and will attract circulating immune cells [11]. Generally cytokines, besides being involved in the growing process of blood cells, regulate the production of anti- and pro-inflammatory immune cells which help with the elimination of pathogens and trigger the healing process right after. One specialty of these relatively simple proteins is that they can be produced by almost every other cell, with different cells being able to produce the same cytokine. Further, cytokines are redundant, meaning targeted cells can show identical responses to different cytokines [12], these features seems to fulfill some kind of safety mechanism to guarantee vital communication flow. After release 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.

4.2.2 Cytokine Storms

The hosts dysregulated response to an infection connected to the septic condition is driven by the release of an unreasonable amount of cytokines. Normally, the release of inflammatory cytokines automatically fades out once the initial pathogen is controlled and the host returns to a healthy and balanced state, the *homeostasis*. In certain scenarios a disturbance to the regulatory mechanisms triggers a chain reaction, followed by a massive release of cytokines. It is further coupled with self-reinforcement of other regulatory mechanisms [13], leading to a continuous and uncontrolled release of cytokines that fails to shut down. With this overreaction, called *cytokine storm*, the immune system's reaction damages the body while being 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 [13]. Out of all cytokines, only a very small subset or secondary markers can be measured through blood samples to detect increased cytokine activity. This makes them hard to study in general 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 innate immune system and overall activation behavior. But to this day no breakthrough has been done and underlying principles have not been uncovered.

4.2.3 Systemic Consequences and Organ Failure

While more and more cytokines flood not only the infected areas, surrounding parts of the tissue and circulation are also affected. This disrupts the metabolism of parenchymal cells due to a

deficiency in oxygen and nutrients. The cells switch from an oxygen-based metabolism to an anaerobic glycolysis [14], generating energy less efficiently from glucose. As a result, metabolic by-products such as lactate accumulate, leading to cellular dysfunction. At the same time, the cells' mitochondria start to fail, blood vessels become leaky and tiny blood clots form, further reduce cell functionality. These processes cause progressive cell death and ultimately organ failure. When multiple organs fail simultaneously, the condition becomes irreversible [5]. Multi-organ-failure is the final and most lethal stage of sepsis, with each additional affected organ the mortality increases drastically.

4.3 The need for sepsis prediction

Important to finish

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 .

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 [15]. The Dynamic Network Model (DNM) introduced in [16] and adapted in [17], 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 .

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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.

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End this

6 The Data and Task problems

In [18], 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 [19]

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)

As outlined in Section 4, the macroscopic multi-organ failure associated with sepsis is driven by a dysregulated cascade of signaling processes on a microscopic level (see Section 4.2). This cascade involves a massive amount of interconnected components, where the connections mechanics and strengths vary over time and space. For example, these interactions differ across tissues and evolve as sepsis progresses, with crossing biochemical thresholds the behavior of cells can be changed [20].

In essence, cell-to-cell and cell-to-organ interaction in septic conditions form a highly dynamic, nonlinear and spatio-temporal network of relationships [21], which cannot be fully understood by a reduction to single time-point analyzes. Even though many individual elements of the inflammatory response are well characterized, we still fail to integrate them into a coherent system-level picture.

To address this complexity, the emerging field of *Network Physiology* provides a promising conceptual framework. Rather than studying components in isolation, network physiology focuses on the coordination and interconnection among the diverse organ systems and subsystems [15]. It enables the study of human physiology as a complex, integrated system, where emergent macroscopic dynamics arise from interacting subsystems that cannot be explained by their individual behavior. This perspective translates to the mesoscopic level, i.e. the in-between of things, where the coupling mechanisms collectively determine the overall physiological function.

In network physiology, the analytical basis of the bodies interacting systems is often graph based. Nodes represent subsystem such as organs or cell populations and links represent functional couplings or communication pathways [15]. Unlike classical graph theory, where dynamics are introduced by changing the graph topology (e.g. adding or removing links or nodes), in *Complex Networks* the links themselves can evolve dynamically in response to other system variables. These adaptive connectivities allow for information to propagate through the whole network, giving rise to emerging phenomena on global scales for otherwise identical network topologies.

Complex networks are well studied in physics and biology and have been applied to various physiological domains. Early works, such as [22] that have studied the cardiovascular system, while more recent studies have focused on the cardio-respiratory coupling [23] and large-scale brain network dynamics [24]. Network approaches have also provided mechanistic insights into disease dynamics, for example Parkinson [25] and Epilepsy [26], just to name a few.

Building on these interaction centric principles has opened up new opportunities to study how the inflammatory processes, such as those underlying sepsis, emerge from the complex inter-

and intra-organ communication. In particular [16] and [17] have introduced a dynamical system that models the cytokine behavior in patients with sepsis and cancer. This functional model will be referred to as Dynamic Network Model and forms the conceptual foundation for this whole project.

The remainder of this chapter is structured as follows: In Section 8.1 introduces the theoretical backbone of the DNM, the Kuramoto oscillator model, which provides a minimal description of synchronization phenomena in complex systems. Section 8.2 presents the formal mathematical definition of the DNM and its medical interpretation, followed by implementation details in Section 8.3 and a presentation of selected simulation results in Section 8.3.3.

8.1 Theoretical Background: The Kuramoto Oscillator Model

To mathematically describe natural or technological phenomena, *coupled oscillators* have proven to be a useful framework [27], for example, to model the relative timing of neural spiking, reaction rates of chemical systems or dynamics of epidemics [27]. In these cases complex networks of coupled oscillators are often capable of bridging microscopic dynamics and macroscopic synchronization phenomena observed in biological systems.

One of the most influential system of coupled oscillators is the *Kuramoto Phase Oscillator Model* which is often used to study how synchronization emerges from simple coupling rules. In the simplest form it consists of N identical, fully connected and coupled oscillators with phase $\varphi_i \in [0, 2\pi)$, for $i \in 1 \dots N$ and an intrinsic frequency ω_i [27]. The dynamics are given by:

$$\dot{\varphi}_i = \omega_i - \frac{K}{N} \sum_{j=1}^N \sin(\varphi_i - \varphi_j) \quad (2)$$

Here the $\dot{\varphi}$ is used as shorthand notation for the time derivative of the phase $\frac{d\varphi}{dt}$, the instantaneous phase velocity. An additional parameter is the global coupling strength K between oscillators i and j .

The model captures the essential mechanism of self-synchronization, and a fundamental collective transition from disorder to order, that underlie many real world processes, which is the reason the model has attracted so much research. When evolving this system with time, oscillator i 's phase velocity depends on each other oscillator j . If $\varphi_j > \varphi_i$ the phase oscillator i accelerates $\dot{\varphi}_i > 0$, if $\varphi_j < \varphi_i$ decelerates. For sufficiently large N the oscillator population can converge towards system-scale states of coherence or incoherence based on the choice of K . Coherent in this case means oscillators synchronize with each other, so they share the same phase and phase velocity, incoherence on the other hand is the absence of synchronization (desynchronized), see Figure 3. Synchronous states can be reached if the coupling is stronger than a certain threshold $K > K_c$, the critical coupling strength. In between these two regimes there is a transition-phase of partial synchronization, where some oscillators phase- and frequency-lock and others do not.

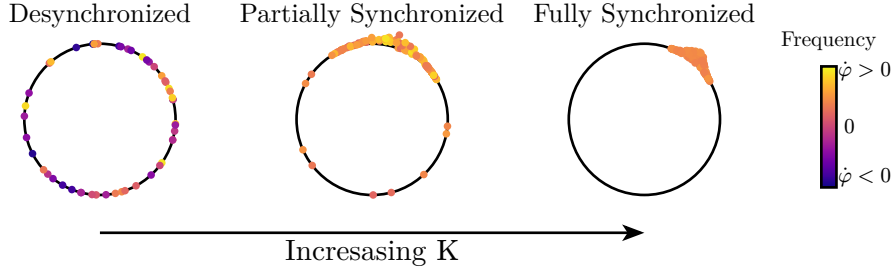


Figure 3: The two stable regimes for the basic Kuramoto model. From an incoherent system state with desynchronized oscillators (heterogeneous phases and frequencies), to a synchronized system state with phase- and frequency-locked oscillators with increasing coupling strength K)

8.1.1 Extensions to the Kuramoto Model

To more accurately describe real world systems, various extensions of the basic Kuramoto model have been proposed and studied numerically and analytically. Several extensions are directly relevant to the DNM and their definitions and effects on synchronization will be shortly introduced:

Phase Lag α introduced in [27] (Kuramoto Sakaguchi 86) , brings a frustration into the synchronization process:

$$\dot{\varphi}_i = \omega_i - \frac{K}{N} \sum_{j=1}^N \sin(\varphi_i - \varphi_j + \alpha) \quad (3)$$

cite

Positive values of α act as an inhibitor of synchronization by shifting the coupling function, so the coupling does not vanish even when the phases align. As a result the critical coupling strength K_c increases with α .

Adaptive coupling $\mathbf{K} \in \mathbb{R}^{N \times N}$ moves from a global coupling strength K for all oscillator pairs to an adaptive coupling strength for each individual pair κ_{ij} :

$$\dot{\varphi}_i = \omega_i - \frac{1}{N} \sum_{j=1}^N \kappa_{ij} \sin(\varphi_i - \varphi_j) \quad (4.1)$$

$$\dot{\kappa}_{ij} = -\varepsilon(\kappa_{ij} + \sin(\varphi_i - \varphi_j + \beta^\mu)) \quad (4.2)$$

Here adaption rate $0 < \varepsilon \ll 1$ separates the fast moving oscillator dynamics from slower moving coupling adaptivity [27] (Birth). Such adaptive couplings have been used to model neural plasticity and learning-like processes in physiological systems [27]. The so called new phase lag parameter β of the adaptation function (also called plasticity rule) plays an essential role. At a value of $\beta^\mu = \frac{\pi}{2}$ the coupling, and therefore the adaptivity, is at a maximum positive feedback, strengthening the link κ_{ij} (Hebbian Rule: fire together, wire together [27]) and encouraging synchronization between oscillators i and j . For other values $\beta^\mu \neq \frac{\pi}{2}$ the feedback is delayed $\varphi_i^\mu - \varphi_j^\mu = \beta^\mu - \frac{\pi}{2}$ by a phase lag, a value of $\beta^\mu = -\frac{\pi}{2}$ we get an anti-Hebbian rule which inhibits synchronization.

Multiplex Networks represent systems with multiple interacting layers. Multiplexing introduces a way how several Kuramoto networks can be coupled via interlayer links:

$$\dot{\varphi}_i^\mu = \omega_i - \frac{K}{N} \sum_{j=1}^N \sin(\varphi_i - \varphi_j + \alpha^{\mu\mu}) - \sigma^{\mu\nu} \sum_{\nu=1, \nu \neq \mu}^L \sin(\varphi_i^\mu - \varphi_i^\nu + \alpha^{\mu\nu}) \quad (5)$$

Here μ and ν represent distinct subsystems, and are connected via interlayer coupling weights $\sigma^{\mu\nu}$, acting one-to-one.

These extensions combined serve as the source of dynamics for the DNM and give rise to more intricate system states than the straightforward synchronization in the base model. Even for single layers, non-multiplexed but phase-lagged and adaptively coupled oscillators, one can observe three stable system states: (multi-)clustered, chimera and splay states. Emergence of these states depends on the choice of the phase-lag parameters α and β . In the multi-clustered state, oscillators synchronize their frequencies but two or more phase clusters form. For chimera states, a special type of partial synchronization, only a subset of oscillators synchronizes and leaves others desynchronized, in contrast to “normal” partial synchronization they occur when the coupling symmetry breaks. For splay states, oscillators fully synchronize their frequencies but do not align their phases, instead they uniformly spread around the unit circle [28].

The introduction changes the system behavior once more, for example single layers of a multiplexed system can result in the multi-clustered regime for parameters they wouldn't in the monoplex case. In multiplexed systems it is also possible connected layers end up in different stable state, one in a clustered the other in a splay state for example.

Wo sind die freq cluster?

8.2 Description

The DNM is a **functional** model, that means it **does not try to model things accurately on any cellular, biochemical, or organ level**, it instead tries to model dynamic interactions. At the core, the model does differentiate between two broad classes of cells, introduced in Section 4.2.1, the stroma and the parenchymal cells. It also includes the cell interaction through cytokine proteins and an information flow through the basal membrane.

Cells of one type are aggregated into layers, everything associated with parenchymal cells is indicated with an ¹ superscript and is called the *organ layer*, stroma cells are indicated with ² and is referred to as non specific *immune layer*. Each layer consists of N phase oscillators $\varphi_i^{1/2} \in [0, 2\pi)$. To emphasise again the function aspect of the model: individual oscillators do not correspond to single cells, rather the layer as a whole is associated with the overall state of all organs or immune system functionality respectively.

The metabolic cell activity is modeled by rotational velocity $\dot{\varphi}$ of the oscillators, the faster the rotation, the faster the metabolism. Each layer is fully coupled via an adaptive possibly asymmetric matrix $\mathbf{K}^{1/2} \in [-1, 1]^{N \times N}$ with elements $\kappa_{ij}^{1/2}$, these couplings represent the activity of cytokine mediation. Small absolute coupling values indicate a low communication via cytokines and grows with larger coupling strength. For the organ layer there is an additional non-adaptive coupling part $\mathbf{A}^1 \in [0, 1]^{N \times N}$ with elements a_{ij}^1 , representing a fixed connectivity within an organ.

The dimensionless system dynamics are described with the following coupled Ordinary Differential Equation (ODE) terms, build on the classical Kuramoto model described in Section 8.1 and its extensions from Section 8.1.1:

$$\dot{\varphi}_i^1 = \omega^1 - \frac{1}{N} \sum_{j=1}^N \{(a_{ij}^1 + \kappa_{ij}^1) \sin(\varphi_i^1 - \varphi_j^1 + \alpha^{11})\} - \sigma \sin(\varphi_i^1 - \varphi_i^2 + \alpha^{12}) \quad (6.1)$$

$$\dot{\kappa}_{ij}^1 = -\varepsilon^1 (\kappa_{ij}^1 + \sin(\varphi_i^1 - \varphi_j^1 - \beta)) \quad (6.2)$$

$$\dot{\varphi}_i^2 = \omega^2 - \frac{1}{N} \sum_{j=1}^N \kappa_{ij}^2 \sin(\varphi_i^2 - \varphi_j^2 + \alpha^{22}) - \sigma \sin(\varphi_i^2 - \varphi_i^1 + \alpha^{21}) \quad (6.3)$$

$$\dot{\kappa}_{ij}^2 = -\varepsilon^2 (\kappa_{ij}^2 + \sin(\varphi_i^2 - \varphi_j^2 - \beta)) \quad (6.4)$$

Where the interlayer coupling, i.e. a symmetric information through the basal lamina, is modeled by the parameter $\sigma \in \mathbb{R}_{\geq 0}$. The internal oscillator frequencies are modeled by the parameters $\omega^{1/2}$ and correspond to a natural metabolic activity.

Besides the coupling weights in $\mathbf{K}^{1/2}$ the intralayer interactions also depend on the phase lag parameters α^{11} and α^{22} modeling cellular reaction delay. To separate the fast moving oscillator dynamics from the slower moving coupling weights adaption rates $0 < \varepsilon \ll 1$ are introduced. Since the adaption of parenchymal cytokine communication is assumed to be slower than the immune counterpart [16], it is chosen $\varepsilon^1 \ll \varepsilon^2 \ll 1$, which introduces dynamics on multiple timescales.

Lastly, the most influential parameter is β which controls the adaptivity of the cytokines. Because β has such a big influence on the model dynamics it is called the *(biological) age parameter* and summarizes multiple physiological concepts such as age, inflammatory baselines, adiposity, pre-existing illness, physical inactivity, nutritional influences and other common risk factors [17].

8.2.1 Pathology in the DNM

A biological organism, such as the human body, can be regarded as a self-regulating system that, under healthy conditions, maintains a homeostatic state [27]. Homeostasis refers to a dynamic but balanced equilibrium in which the physiological subsystems continuously interact to sustain stability despite external perturbations. In the context of the DNM, this equilibrium is represented by a synchronous regime of both layers in the duplex oscillator system. In synchronous states, the organ layer and immune layer exhibit coordinated phase and frequency dynamics, reflecting balanced communication, collective frequency of cellular metabolism and stable systemic function.

Pathology, in contrast, is modeled by the breakdown of the synchronicity and the formation of frequency clusters in the parenchymal layer, i.e. loss of homeostatic balance. In the DNM least one cluster will exhibit increased frequency and one with lower or unchanged frequency. This aligns with medical observation, where unhealthy parenchymal cells change to an less efficient anaerobic glycolysis based metabolism, forcing them to increase their metabolic activity to keep up with the energy demand. Remaining healthy cells are expected to stay frequency synchronized to a lower and “healthy” frequency.

SYMBOL	NAME	PHYSIOLOGICAL MEANING
Variables		
φ_i	Phase	Group of cells
$\dot{\varphi}_i$	Phase Velocity	Metabolic activity
κ_{ij}	Coupling Weight	Cytokine activity
Parameters		
α	Phase lag	Metabolic interaction delay
β	Plasticity rule	Combined of risk factors
$\omega^{1/2}$	Natural frequency	Natural cellular metabolism
ε	Time scale ratios	Temporal scale of cytokine activity
a_{ij}	Connectivity	Interaction between Parenchymal and Immune cells through basal lamina
σ	Interlayer coupling	Fixed intra-organ cell-to-cell interaction
Measure		
s	Standard deviation of frequency (see Equation 7)	Pathogenicity (Parenchymal Layer)

Mean Phase Velocities are calculated as followed:

$$\langle \varphi^\mu \rangle = \frac{1}{N} \sum_j^N \varphi_j^\mu \quad (7)$$

8.3 Implementation

- Savings
- Eqx + diffrax
- Lie

For parts in the form of $\sin(\theta_l - \theta_m)$ following [29] one can calculate and cache the terms $\sin(\theta_l), \sin(\theta_m), \cos(\theta_l), \cos(\theta_m)$ in advance:

$$\sin(\theta_l - \theta_m) = \sin(\theta_l) \cos(\theta_m) - \cos(\theta_l) \sin(\theta_m) \quad \forall l, m \in \{1, \dots, N\} \quad (8)$$

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.

8.3.1 Standard

- Actual Mean Phase Velocity instead of averaged difference over time.

- +They Calculate the difference wrong since the phase difference should be mod[2π]
- Different solver accuracy, but very similar
- They are not batching the computation

8.3.2 Lie

8.3.3 Simulation Results

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

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

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

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

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

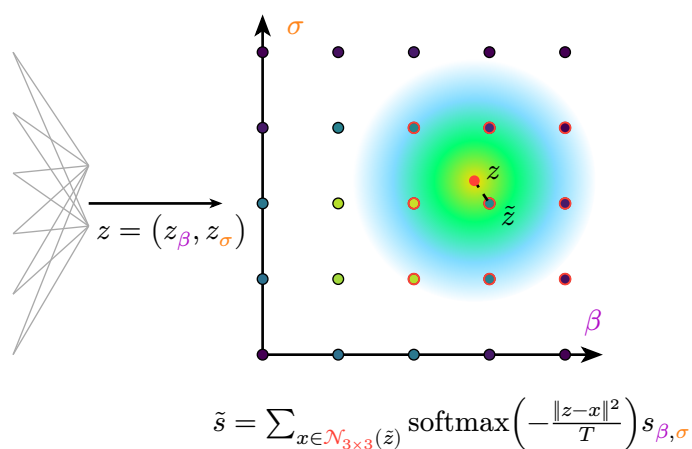
9.3.1.1 Representation Learning and Latent Spaces

9.3.1.2 Semantics

9.3.1.3 Autoregressive Prediction

9.3.2 The Lookup (FSQ)

Quantized Latent-Lookup
with Gaussian Kernel Smoothing



Fix
the
edges

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

$$z \in \mathbb{R}^d \quad \text{with } d = 9 \quad (9)$$

As shown in the supplemental material of [17], 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 [17]. To further reduce the latent space z , we keep $a^1, \omega^1, \omega^2, \frac{C}{N}, \varepsilon^1$ and ε^2 fixed. The reduced latent space $z' = (\sigma, \alpha, \beta)$:

$$z' \in \mathbb{R}^{d'} \quad \text{with } d' = 3 \quad (10)$$

table

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:

$$x_j = f(z_j) + \varepsilon \quad (11)$$

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 :

$$Q(x_j) = c_j = R(z_j) \quad \text{where } x_j = f(z_j) + \varepsilon \quad (12)$$

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 6) 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 [30] and [19]. The nice thing is we could interpret larger SOFA scores (> 3) as the vulnerable state introduced by [17]. Increases in SOFA score ≥ 2 could then be used as definition for sepsis.

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

YAIB [19] and other resources care about the “onset” of infection and sepsis [31]. 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 [30] (https://eth-mds.github.io/ricu/reference/label_si.html). These would be 48h - SI - 24h adapted from [32], maybe a bit too much.

10 Metrics (How to validate performance?)

11 Experimental Results

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 [$\times \frac{10^3}{\text{mm}^3}$]	< 150	< 100	< 50	< 20
Liver	Bilirubin [$\frac{\text{mg}}{\text{dl}}$]	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 [$\frac{\text{mg}}{\text{dl}}$]	1.2-1.9	2.0-3.4	3.5-4.9	> 5.0
	or Urine Output [$\frac{\text{ml}}{\text{day}}$]			< 500	< 200

caption

¹Adrenergica agents administered for at least 1h (doses given are in [$\mu\text{g}/\text{kg} \cdot \text{min}$])

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