Detecting Critical Transitions in the Human Innate Immune System Post-cardiac Surgery

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Abstract. Coronary artery bypass grafting with cardiopulmonary bypass activates the human innate immune system (HIIS) and invokes a vigorous inflammatory response that is systemic. This massive inflammatory reaction can contribute to the development of postoperative complications that could topple the state of the system from health to disease, or even to some extent, death. The body, after all, is in a state where majority of its immune cell populations have been depleted, and sometimes needs days or even longer to recuperate. To obtain a deeper understanding on how HIIS responds to complications after cardiac surgery, we perturb the immune system model that we have developed in an earlier work *in-silico* by adding another source of inflammation triggering moieties (ITMs) hours after surgery in various regimes. A critical transition occurs upon the addition of a critical concentration of ITMs when the insult is sustained for approximately 3 h – a total concentration that corresponds to the fatal concentration of ITMs documented in literature. By perturbing HIIS *in-silico* with additional sources of ITMs to mimic persistent and recurring episodes of post-surgery complications, we are able to specify under which conditions critical transitions occur in HIIS, as well as pinpoint important blood parameters that exhibit critical transitions in our model. More importantly, by applying early warning signals on the clinical trial data used to calibrate and validate HIIS model, we are able to detect blood parameters that exhibit critical transitions in patients who died post-surgery, where pro-inflammatory cytokines are deemed potential markers for critical transitions.

Keywords: Human innate immune response · Post-surgery complications · Critical transitions · Early warning signals

1 Introduction

Coronary artery bypass grafting (CABG) with cardiopulmonary bypass (CPB) invokes a systemic inflammatory response that activates HIIS. Contact of blood components with the artificial surface of the bypass circuit induces sheer stress on blood cells. Ischemia-reperfusion injury due to accumulated ITMs that have crossed the gut-barrier during hypo-perfusion [1], endotoxemia or the presence of endotoxins such as ITMs in

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the blood, as well as tissue damage caused by the surgical wound are all possible causes of systemic inflammatory response syndrome (SIRS). This massive inflammatory reaction may contribute to the development of postoperative complications such as myocardial dysfunction, respiratory failure, renal and neurologic dysfunction, bleeding disorders, altered liver function, and sequentially, multiple organ failure [2]. Taking into account that more than 800,000 patients per year undergo coronary artery bypass grafting (CABG) surgery worldwide while approximately 150,000 patients undergo valve surgery [3, 4], postoperative respiratory failure has a mortality rate of 80% in patients undergoing cardiac surgery [5, 6]. Myocardial dysfunction that escalates to symptomatic heart failure accounts for 50% of medical admissions to hospitals, and is associated with in-hospital mortality of 12% and a 1-year mortality of 20–35% [7, 8]. The Society of Thoracic Surgeons National Database reported that 20% (22,000 patients) of "low-risk" patients developed postoperative complications.

Using the HIIS model that we have developed in an earlier work [9], we show how HIIS reacts to complications after surgery by adding a source of ITMs *in-silico* hours post-surgery. The developed model is an ordinary differential equations model of that of HIIS in response to systemic inflammation. The model has been calibrated and validated against clinical trials data of patients undergoing cardiac surgery. ITMs may refer to any cell or enzyme that triggers the innate immune response, such as bacterial lipopolysaccharides (LPS) and extracellular nucleotides [10, 11]. In case of a massive insult, HIIS' response becomes amplified and dysregulated [12], which leads to the imbalance between pro-inflammatory and anti-inflammatory cytokines [13]. By perturbing the *in-silico* system with different intensities of ITMs, we aim to test the resilience of HIIS and assess at which point the system shifts between alternative regimes: from state of health to disease.

Various and diverse complex dynamical systems have been shown to exhibit transitions or so-called tipping points, where there occurs an abrupt shift in stable states. In biological systems, such as the human body, this tipping point can occur as a rapid shift from state of health to disease in various manners [14, 15]. In depression, fluctuations of emotions serve as indicators for tipping points from normal to the onset of a depressive state [16]. Other examples also include systemic market crashes observed in financial systems [17, 18], the slowing down of fluctuations before a climate shift [19, 20], trends of a declining population prior to extinction [21, 22], blood parameters as indicators of tipping points in patients undergoing cardiac surgery [23], and early warning systems in floods [24] and dams.

Early warning signals (EWS) are hypothesized to serve as indicators of loss of system resilience prior to transitions between regimes. Subtle statistical properties of measurements in the system are assessed to indicate presence of critical transitions [25]. Sometimes, these transitions are observed in changes in correlations, standard deviation, and skewness of system measurements through time [26].

We define critical transition occurring in the *in-silico* model when blood parameter concentrations exhibit either a saturation to a maximum value, as in the case of increasing concentrations of ITMs, accompanied by the depletion of other immune cell populations. These serve as strong indicators that the body is no longer able to neutralize the ongoing inflammation. We show that the system shifts abruptly and irreversibly from the state of health to disease given a critical threshold of ITMs in our model.

This startling transition in HIIS poses an urgent and crucial concern as it might be difficult, or even impossible for medical practitioners to act upon beforehand due to the abrupt nature of the transition. Due to the urgency of the situation, it calls for a deeper understanding on the nature of the instances that contribute to the occurrence of these transitions. More importantly, there is a need to investigate the possibility of detecting these transitions at a considerable time before the event happens. We define a *healthy* state when HIIS can resolve or neutralize all ITMs, while *disease* when ITMs are not resolved within incubation time. Consequently, critical transition is the point when the state of the system shifts from health to disease. Finally, we assess the capability of EWS in detecting critical transitions in clinical trials data of patients undergoing cardiac surgery that was used to calibrate and validate HIIS model in [9]. In the clinical trials data, 3 out of 52 patients died post-surgery. In the context of our model, we define the 3 patients who died as *critical* patients who exhibited critical transitions in their blood parameters, while the remaining patients we refer to as *non-critical.*

2 Methods

2.1 Metric and Model-Based Indicators

EWS for detecting critical transitions in systems can be divided into two categories: metric and model-based. Both methods aim to quantify the variations in correlation structure, and changes in variability in measurements prior to the system's transition between alternate regimes [27]. Metric-based indicators aim to quantify changes in statistical properties of measurements without attempting to fit the measurements onto a model. We use *variance*, *skewness*, and *kurtosis* as metric-based indicators for transition from state of health to disease, which are explained each in turn next.

The most important hints of whether a system is close to a critical transition is referred to in dynamical systems theory as "critical slowing down" [28]. It's most straightforward implication is when the rate of recovery after tiny perturbations can be used as an indicator on whether a system is close to a bifurcation point [29]. That is, the time it takes to return to equilibrium even after tiny perturbations strongly increases as the system approaches the threshold of bifurcation. Hence, referring to how the system "slows down" going back to equilibrium [30, 31].

Variance. An increase in variance in fluctuation patterns could be another consequence of critical slowing down. As a system approaches a tipping point it could exhibit increasingly strong variations at measurements around the equilibrium as the impacts of perturbations do not decay, and only accumulates. *Skewness.* Perturbations drive the state of the system to shift between alternate regimes. Critical slowing down, which refers to a decreasing return rate of the system towards equilibrium results in distribution asymmetry [32]. Hence skewness either increases or decreases depending on the direction of transition. *Kurtosis.* Strong perturbations provokes the system to take on extreme values close to transition, increasing the occurrence of rare values in the measurements [33]. Therefore, an increase in *kurtosis*, or "bulging" is observed in the measurements leading to a tipping point.

Model-based indicators quantify variations in measurements by fitting the data to a model. Autocorrelation is a simple method used to quantitatively describe slowing down in a system nearing tipping point. *Autocorrelation* is one of the simplest ways in measuring slowing down. Increasing autocorrelation implies that consecutive points in the time series have become increasingly similar [34]. *Time-varying Autoregressive models (AR)* at time lag p is also one of the numerous methods used to estimate the local dynamics in measurements of a system [35]. The first step is calculating the inverse of the characteristic root (λ), by estimating the autoregressive function. Values for λ that approaches 0 imply that the system quickly returns or stabilizes towards the mean. This is because we used a time lag equal to one, which indicates that the current value is based on the value immediately preceding it. Hence, λ would simply be the slope of change between two time points, $y(t)$ and $y(t-1)$. See equation for time-varying AR(1) model in Eq. (1). The smaller this slope is, the more similar the measurements are at time $t-1$ with t. Hence, it would be quicker for the system to go back to equilibrium. On the other hand, when values for λ approach 1, measurements become increasingly varied hence implying instability.

$$y(t) = a(t)y(t-1) + \varepsilon(t), \tag{1}$$

where $a(t)$ corresponds to the autoregressive coefficient, and $\varepsilon(t)$ corresponds to the environmental variability [27].

2.2 Trend Detection

Any presence of statistically significant increasing trends captured by early warning indicators are evaluated using the Mann-Kendall trend test. The Mann-Kendall trend test is a non-parametric test that analyzes consistent increasing or decreasing patterns in data series. The null hypothesis being a monotonic trend does not exist, while the alternate hypothesis assumes the existence of a trend. These trends are tested to a significance level of 5%. We used a one-tailed test. This means that we only look at positive trends in values of EWS to be able to fully understand the system.

3 Results and Discussion

3.1 Effects of Adding Inflammation Triggering Moieties *In-Silico* to the Human Innate Immune System 2 Days After Surgery

Cardiac surgery with CABG activates HIIS, which invokes a vigorous response that most likely depletes the body's reservoir of immune cells, proteins, and enzymes, such as macrophages, neutrophils. Depending on the patient's conditions, it may take days, weeks or even months for immune cell levels to fully recuperate to normal levels. Nguyen et al. have shown that the activity of immune cells in cardiac surgery patients was impaired on the 3rd day post-surgery. These levels, however, returned to normal after a week after surgery [36]. The occurrence of complications post-operation becomes a serious threat as the body has not yet fully recovered. Complications sometimes happen from 2 to 9 days after surgery [37]. In a study conducted by

Hashemzadeh et al., the majority of the complications, more specifically postoperative atrial fibrillation, develop within the first 2 days after surgery [38]. Hence, in all our experiments, we add a source of ITMs that starts at 48 h after cardiac surgery.

Below we explore the effects of adding various concentrations of ITMs *in-silico* 48 h after surgery for a duration of 3 h. These ITMs may come from complications from inflicted wound due to surgery, oxidative stress coming from various sources in the body, or external factors that invoke further production of ITMs. 3 h is the duration of insult that is typically observed in patients undergoing cardiac surgery before they stabilize back to normal values, often 7 days after surgery [36, 39]. We show that this duration of adding ITMs is able to tip the balance, pushing the state of the system from health to disease, which we will later show numerically in Sect. 3.2. We summarize our results in Fig. 1.

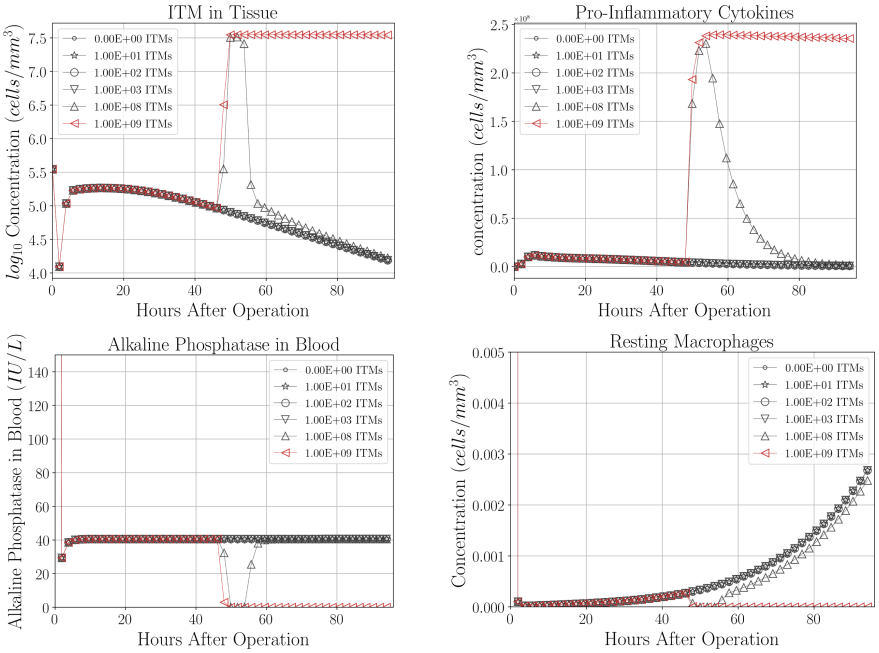

Fig. 1. Human Innate Immune Response to Post-Operative complications. Excess ITMs are continuously added for 3 h in-silico at exactly 48 h (2 days) after surgery. Our results show that at an ITM concentration of $1 \times 10^9 \frac{\text{cells}}{\text{mm}^3}$, the concentration of ITMs in the tissue remains unneutralized even after 96 h of surgery. Compared to $1 \times 10^9 \frac{\text{cells}}{\text{mm}^3}$, this concentration HIIS can completely neutralize the inflammation at 60 h post-surgery. Pro-inflammatory cytokines, proteins responsible for opening the endothelial barrier to allow recruitment of more neutrophils from the bloodstream into the tissue, exhibit a saturation of concentration at added ITMs of $1 \times 10^9 \frac{\text{cells}}{\text{mm}^3}$. AP, enzymes known to neutralize ITMs, are depleted both in blood and tissue at added ITM concentration of $1 \times 10^9 \frac{\text{cells}}{\text{mm}^3}$. Resting macrophages show slight differences for various ITM concentration regimes due to the slow replenishment rate from the bone marrow. Nonetheless, we still see a depletion of concentration of resting macrophages at a critical ITM concentration of $1 \times 10^9 \frac{\text{cells}}{\text{mm}^3}$. Cells, in the context of our work, also refer to proteins, enzymes, and molecules as a unifying unit in our system. (Color figure online)

The abrupt change in blood parameter concentrations shown in our results imply that there seems to be a critical concentration of ITMs where HIIS is no longer able to neutralize the inflammation. We highlight this in red as shown in Fig. 1. With overwhelming concentration of ITMs, activated neutrophils that are at the site of inflammation go into necrosis, as an attempt, paradoxically, to aggravate the inflammation, which results in the recruitment of more neutrophils into the site of inflammation. This peculiar choice in death pathway (apoptosis or necrosis) is explained and modeled in [40, 41]. Necrosis, a violent death pathway that involves the rupture of the neutrophil's cytoplasmic content into its surroundings, releases an additional source of ITMs that invokes a series of immune cell responses, which fuels, and further aggravates the ongoing inflammatory response. One could imagine the effect of a considerable amount of ITMs on HIIS. More specifically, how it induces a magnified and continuous production of concentrations of pro-inflammatory cytokines.

With additional ITM concentrations of $1 \times 10^8 \frac{\text{cells}}{\text{mm}^3}$, ITMs in tissue decrease 60 h after surgery, implying that the body is still capable of neutralizing the additional amount of insult. On the other hand, this ITM concentration saturates when the added concentration of ITMs is $1 \times 10^9 \frac{\text{cells}}{\text{mm}^3}$. One of the key functions of pro-inflammatory cytokines is to open up the endothelial barrier, which consequently recruits a fresh fleet of neutrophils into the site of inflammation. We show in our results that the concentration of pro-inflammatory cytokines increases and saturates to a steady level when the added concentration of ITMs $1 \times 10^9 \frac{\text{cells}}{\text{mm}^3}$ while AP in blood and in tissue becomes depleted. In contrast, for added ITMs of $1 \times 10^8 \frac{\text{cells}}{\text{mm}^3}$, pro-inflammatory cytokines level slides back to zero and AP stabilizes back to normal roughly 60 h after surgery.

Added ITMs do not seem to affect activated macrophages and neutrophils as shown in Fig. 2.

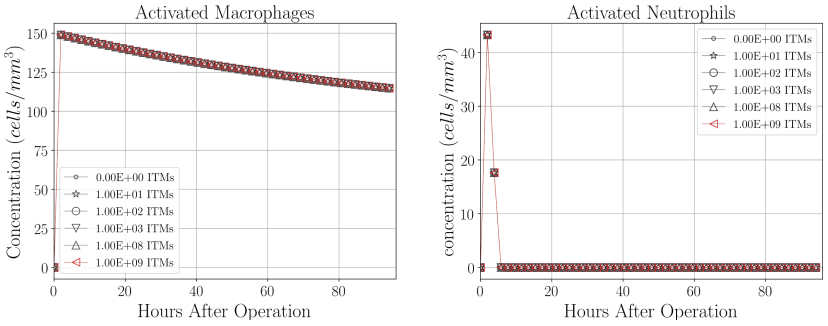

Fig. 2. Resting and Activated Macrophages and Neutrophils' Response to Added ITMs. Even without additional ITMs, our model predicts the activation of all resting macrophages and neutrophils due to the scale of insult cardiac surgery with CABG invokes on HIIS. Therefore, additional source of ITMs, especially when the immune cells, proteins, and enzymes are already depleted, will still invoke the maximum effect on macrophages and neutrophils. Cells, in the context of our work, also refer to proteins, enzymes, and molecules as a unifying unit in our system.

This is because even without a new source of ITMs, resting macrophages and neutrophils have already been fully activated. Hence, *additional* source of ITMs will not significantly change the profiles of these immune cells, proteins, and enzymes. During systemic insult, the bone marrow releases both mature and immature neutrophils into the bloodstream. This is the so-called "left shift," which refers to the increase in the number of immature neutrophils in the bloodstream [42]. After which, it takes roughly a week for the bone marrow to release a new set of *mature* neutrophils into the bloodstream [43, 44].

3.2 How Does the Human Innate Immune System Respond to Persistent and Recurrent Episodes of Post-surgery Complications?

In this section, we further explore how HIIS responds to complications that are either recurring or persistent by adding ITMs in various regimes: 1) changing intervals and 2) changing durations.

Effects of Adding Inflammation Triggering Moieties In-Silico at Different Time Intervals?

Here we introduce an additional source of ITMs at various intervals: 8 h, 16 h, and 24 h intervals. The concentration of ITMs is continuously added for 30 min to mimic those complications that are persistent. Our results are summarized in Fig. 3.

Our results show that recurrent episodes of post-surgery complications that are sustained for 30 min only exhibit critical transitions when the intervals between episodes are 8 h. Our initial results show a proof-of-concept that there exists a critical interval between episodes that drives the state of the system to shift from one regime to another, which could possibly make interventions by medical practitioners feasible.

Effects of Adding Inflammation Triggering Moieties In-Silico at Different Time Range?

In order to mimic post-surgery complications that are persistent, we added ITMs in various durations starting from 30 min of continuous infusion, to 1 h, 2 h and 3 h. Our results are summarized in Fig. 4.

Our results show that the system can no longer neutralize the inflammation when the added insult is sustained for 3 h. This can be deduced based on the profiles of ITMs in the tissue as well as pro-inflammatory cytokines, which portray high values. AP in blood and tissue, however, are depleted.

Intuitively, we are able to show numerically that the duration of added ITMs in the system has prominent effects on ITMs in tissue, pro-inflammatory cytokines, and AP concentrations in blood and in tissue. As the body recuperates after cardiac surgery, there comes a point when the system can no longer neutralize the inflammation. We have shown in the previous section that recurrent episodes of post-surgery complications could tip the balance between health and disease when the time interval reaches 8 h apart. In this section, we show that this critical transition happens when the post-surgery complication is persistent and lasts for 3 h. This is in fact consistent with the findings of Damas et al., where the overall concentration of ITMs within this 3-h duration corresponds to the fatal concentration of ITMs in humans [45].

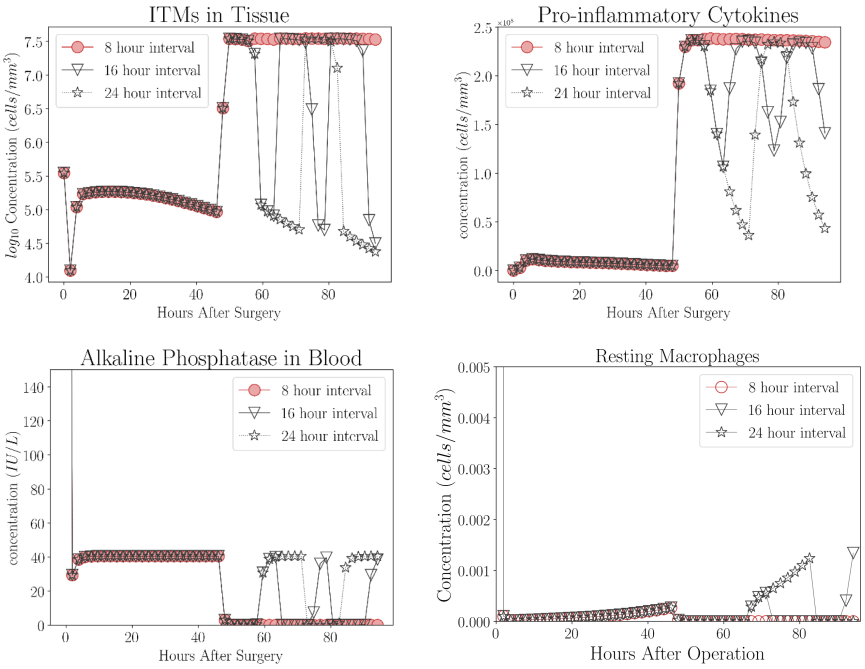

Fig. 3. Human Innate Immune Response to Additional Sources of ITMs at Varying Time Intervals. A non-fatal concentration of $1 \times 10^9 \frac{\text{cells}}{\text{mm}^3}$ ITMs [45] was added at different time intervals starting at 2 days (48 h) after surgery continuously for 30 min to mimic a persistent and recurring post-surgery complication. Our results show that when the interval between each episode decreases to 8 h, the system undergoes a transition where it is no longer able to neutralize the ITMs effectively. Hence, we see that the ITMs in the tissue remain at a stable concentration because the remaining population of immune cells, proteins and enzymes are no longer able to neutralize the ITMs. Moreover, more pro-inflammatory cytokines are induced due to the intense scale of insult. Cells, in the context of our work, also refer to proteins, enzymes, and molecules as a unifying unit in our system.

Critical Transitions in Blood Parameter Timeseries of Patients Undergoing Cardiac Surgery?

The clinical trials data is composed of concentrations of 43 various blood parameters sampled from 52 patients who have undergone cardiac surgery with bypass filter. Time stamps at which the samples were taken were also recorded and indicated in the data. The data was collected from two separate hospitals: Catharina Hospital Eindhoven (The Netherlands), and Zuid Oost-Limburg Hospital (Belgium). The conditions at which the patients have undergone, methods used to obtain the blood parameter samples, as well as time intervals for the data collection were standardized between the hospitals. A more detailed description of the population of patients can be found in [9].

The raw data contains a huge amount of missing data points (58.7%) because not all blood parameters are sampled. Missing values are inevitable in clinical trial data, so it is necessary that the methods are able to deal with this type of data. Numerous

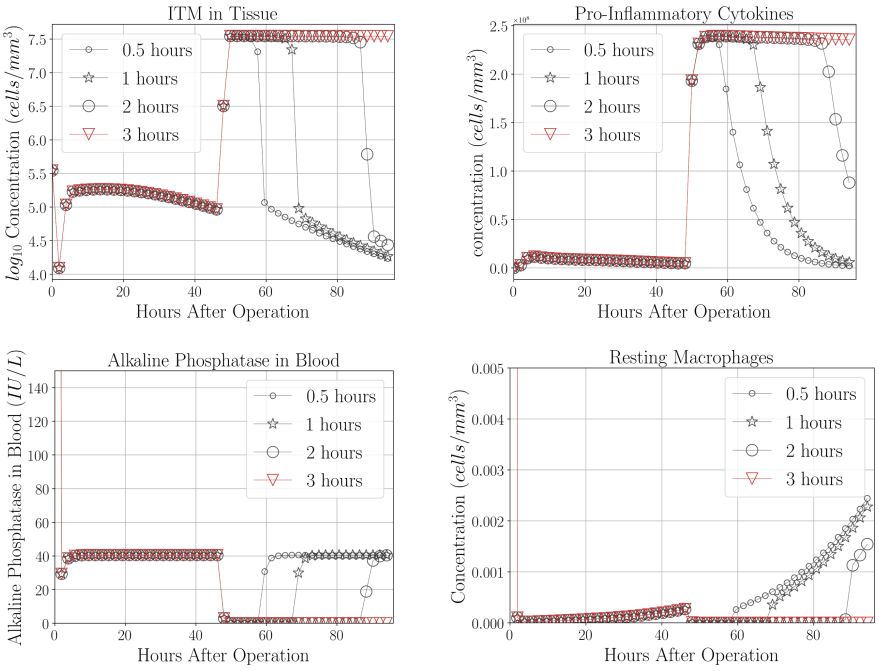

Fig. 4. Human Innate Immune Response to Added ITMs at Different Time Durations. A non-fatal concentration of $1 \times 10^9 \frac{\text{cells}}{\text{mm}^3}$ ITMs [45] was added at increasing durations starting at 2 days (48 h) after surgery continuously for 30 min, 1, 2, and 3 h to model persistent post-surgery complications. Our results show that when the infusion of ITMs is 3 h, the system undergoes a transition where it is no longer able to neutralize the ITMs effectively

techniques are able to handle missing values. But what is important is that, these techniques should not significantly increase the rate at which *false positives* are being detected or labeling critical patients as non-critical; labeling critical patients as healthy. Otherwise, it makes the signal noisy as well as impractical for medical practitioners to act upon.

Missing values are dealt with by using a simple technique called *bootstrapping*. The basic idea behind bootstrapping involves a repeated random sampling with replacement from the original data to come up with random samples (or bootstrap samples) that have the same size as the original data. Each measurement can be sampled more than once and only within the distribution of the type of patients involved. That is, bootstrapping of non-critical patient is only resampled within the distribution of non-critical patients. The same goes with critical patients, where missing data points are resampled within the distribution of critical patients. In this way we limit the possibility of increasing false negatives in our bootstrapped data. We resampled 100 times to ensure variability in the bootstrap samples.

Since we are dealing with an imbalanced data set – 6% of the data are critical patients and the rest are non-critical, we assess the performance of EWS in detecting critical and non-critical patients by calculating the F1 score based on outcomes of the detection based on the definitions summarized in Table 1.

Table 1. Definition of terms used for assigning critical and non-critical patients.

Symbol	Interpretation	Definition
T_P	True positive	Assigning critical patients as critical
F_P	False positive	Assigning non-critical patients as critical
F_N	False negative	Assigning critical patients as non-critical
T_N	True negative	Assigning non-critical patients as non-critical

The F1 score is calculated based on Eq. (2):

$$F_1 = 2\frac{P \cdot R}{P + R}, \tag{2}$$

where P corresponds to precision, which provides a measure or percentage of the results that are relevant as it measures the percentage of *true positive* with respect to the total predicted positive (*true positive* + *false positive*). R is Recall, which measures the fraction of relevant instances retrieved or what percentage of the actual number of critical patients are correctly identified by the methods. Precision provides a good measure when the cost of *false positive* is high. On the other hand, Recall is a good measure when the cost of *false negative* is high. F1 score provides a good measure that seeks the balance between precision and recall especially when the dataset exhibits an imbalanced class distribution. We correct this from a previously published work, where we used Recall and Precision as measures of our model [23].

Using Early Warning Signals to Pinpoint Blood Parameter Markers of Death
Each time series corresponding to a timely record of a patient's concentrations of blood parameter is assessed on whether a critical transition is detected or not using EWS. This is done by using a rolling window of half the size of the time series data for each methodology for EWS. The Mann Kendall trend test is then used to test the presence of a significant increasing trend. The results are evaluated by calculating for the F1 scores per blood parameter. The motivation here is to pinpoint blood parameters that may be the best option for medical practitioners to focus on, as opposed to doing an extensive scan on all blood parameters that in fact do not reveal signs of critical transitions in patients at all. In this way, resources as well as time are wisely conserved and patients, who are prone to criticalities, can readily be given the immediate treatment they need. We processed both bootstrapped and original data, but the results of our simulations are similar for both data sets. These results are summarized in Fig. 5.

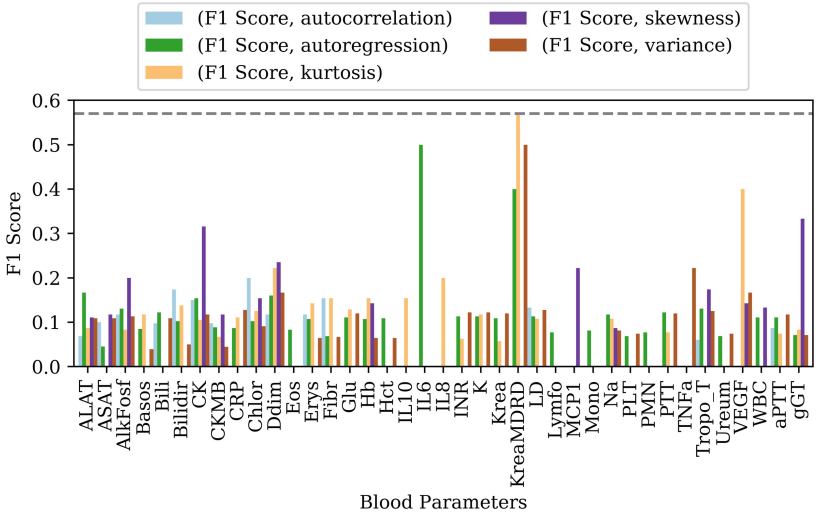

Fig. 5. F1 Score of model output after using early warning signals in detecting critical and non-critical patients. The highest F1 score corresponds to KreaMDRD, which corresponds to the level of creatinine in blood calculated using the MDRD (Modification of Diet in Renal Disease Study) equation with Kurtosis as EWS. This is followed by IL6 (pro-inflammatory cytokine) and LD (Lactate Dehydrogenase) with autoregression and variance as EWS respectively.

4 Summary and Conclusion

Using our model of the human innate immune response for patients undergoing cardiac surgery, we show how HIIS reacts to complications that occur post-surgery. We did this by adding *in-silico ITMs* at 48 h (2 days) after surgery. We showed that an additional concentration of $1 \times 10^9 \frac{\text{cells}}{\text{mm}^3}$ ITMs continuously added for 3 h lead to a rapid and irreversible critical transition from health to disease. In fact, this concentration of ITMs corresponds to the fatal concentration of ITMs documented in literature. We used EWS to detect the presence or absence of critical transitions in clinical trials data of patients undergoing cardiac surgery. Our initial findings show that by using EWS, blood parameter markers such as Creatinine, IL6 and Lactate Dehydrogenase reveal significant presence of critical transitions. IL6, a pro-inflammatory cytokine, was also pinpointed in the *in-silico* model as one of the blood parameters that exhibit critical transitions. However, more experiments need to be done to carefully assess the strength of positive trends that we have detected using EWS.

We have provided a proof-of-concept on the existence of critical transitions in HIIS model, with ITMs as the driving force for this bifurcation. Our initial findings call for a thorough investigation on the conditions at which critical transitions occur in HIIS. More importantly, to explore if the onset of this bifurcation can be detected using known methods in EWS, which we perceive as potentially interesting and helpful to medical practitioners as these might serve as indicators to warn, or better yet prevent the onset of disease leading to fatalities.

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