Computational models of human response to urban heat
*From physiology to behaviour*
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Chapter 6

Computational study of the performance of innate immune system response under exposure to heat stress

The previous chapters of this thesis focus on the three levels of human response to thermal environments to gain a comprehensive understanding of the process of OTC. However, the interaction of people with their thermal environment is not just a matter of comfort: exposure to stressful thermal regimes entails risks for the healthy functioning of the main biological mechanisms of the human body. The multi-level response considered in the previous chapters is the key way to regulate this exposure and to avoid the detrimental effects of heat on health. In this chapter we demonstrate the use of the thermophysiological model and the model of behavioural thermal regulation through modulation of activity intensity to predict the performance of the human innate immune system under heat stress. This allows us to identify the environment-activity regimes which are to be avoided to preserve the proper functioning of the human innate immune system. This chapter demonstrates how the models developed in this thesis can be coupled with other models to investigate phenomena beyond OTC, which are directly and critically affected.

This chapter is based on Presbitero A., Melnikov V. R. & Sloot P. M. A. (2021). Heat stress and the human innate immune system: balancing inflammation with physical activities, Submitted to BMC Environmental Health. First and second authors contributed equally.
by exposure of people to heat.

Abstract

Background

The human body has evolved to adapt to different heat conditions by regulating its core temperature. Fever, a paramount response to inflammation, has been passed over through millions of years of evolution. However, exposure to high temperatures poses risks to the survival of the organism. Currently, there is a critical knowledge gap between the inner workings of the innate immune system in response to heat and how this relates to the body’s reaction during heat-inducing physical activities. In this chapter we present the results of bridging these concepts through computational modelling.

Methods

We couple two experimentally validated computational models: the innate immune system and thermal regulation of the human body. We first simulate the dynamics of critical indicators of innate immunity as a function of human core temperature with the use of the human innate immune system model. Next, with a model of thermal regulation, we identify environmental and physical activity regimes that lead to core temperature levels that can potentially compromise the performance of the human innate immune system. Finally, to model the response of innate immunity to various intensities of physical activities, we utilise the dynamic core temperatures generated by the thermal regulation model in the innate immune system model. We compare the dynamics of all key players of the innate immunity for a variety of stresses like running a marathon, doing construction work, and walking, all in the setting of hot and humid tropical climate of Singapore.

Results

We find that exposure to moderate heat stress leading to core temperatures within the mild febrile range $(37, 38]^{°}$C, nudge the innate immune system
into activation and improves the efficiency of its response. Overheating corresponding to temperatures beyond 38°C, however, has detrimental effects on the performance of the innate immune system, as it further induces inflammation, which causes a series of reactions that may lead to the non-resolution of the ongoing inflammation. Among the three physical activities (marathon, construction work, and walking), marathon induces the highest level of inflammation that challenges the innate immune response with its resolution.

Conclusions

Our study advances the current state of research towards understanding the implications of heat exposure for such an essential physiological system as the innate immunity. Although we find that among considered activities, a marathon of 3 hours induces the highest level of inflammation, construction work that is done on a daily basis under the hot and humid tropical climate can produce a continuous level of inflammation triggering moieties stretched at a longer timeline beating the negative effects of running a marathon. We demonstrate that in order to preserve the normal function of the innate immune system and prevent elevation of core temperature beyond 38°C, people should employ behavioural thermal regulation and avoid prolonged strenuous activities in hot climates.

Introduction

The body’s tendency to generate heat in the form of fever is a paramount response to inflammation that has been conserved in 600 million years of evolution among warm and cold-blooded vertebrates. The fever response bestows the likely benefit of survival of the organism during inflammation [195]. Too much heat can also be detrimental. High ambient temperatures may lead to the failure of heat dissipating thermo-regulatory mechanisms after prolonged exposure or heavy exercise, where core temperatures reach 40°C, leading to severe heat stress, organ damage or heat stroke [196].

In this work, we take a closer look, down to the cellular level, on how heat affects the inner workings of the human innate immune system response,
trace this response and relate it to the body’s reaction during heat-inducing physical activities. While the effect of heat on cardiovascular [197], respiratory [198], endocrine [199] and reproductive [200] systems has been studied extensively, the interaction of the core temperature with the human innate immune system (HIIS) is not well studied in works on public and occupational heat-related health, safety and productivity [201]. In light of the global processes of climate change and urbanisation [32, 34], which put more and more people at risk against a threatening exposure to urban heat [202], this constitutes a critical knowledge gap. Thus, there is a need for comprehensive understanding of the interactions of climate, exposure, physiology and human innate immune system -to assess the associated benefits and risks and to suggest best mitigation strategies on an individual level and devise policies on a population level.

On a molecular level, heat stress increases the synthesis of HSP 70, intracellular proteins shown to possess the capacity of inducing lasting protective immune responses [203], up to a threshold temperature, which varies according to cell type. Beyond this threshold, their syntheses is constrained and exponential cell death follows [204, 205]. The threshold, at which thermal damage occurs in the immune system, was detected in individuals suffering from heat stress or heat stroke [206].

Fever-range temperatures heighten the respiratory burst that is often linked with neutrophil activation and increasing neutrophil’s bacteriolytic activity [207, 208]. An increase in granulocytes’ bactericidal capacity was observed at 40°C and 42°C relative to 37°C for majority of the bacteria population [209, 210]. Thermal stress increases the recruitment of neutrophils to the sites of infection and in distant tissues [211, 212]. It also increases the number of circulating neutrophils [213, 214, 215] in the body.

Heat is shown to improve the phagocytic capability of macrophages by heightening their responsiveness to inflammation triggering moieties (ITMs) [216, 217]. Koch et al. have shown that thermal treatment induces the release of cytokines, such as TNF [218]. Macrophages lining the synovial tissue of rheumatoid arthritis joints produce cytokines such as IL-1b, IL-6, and TNF-a in response to increase in body temperature [219, 220, 221, 222, 223, 224]. Humans and rats that are exposed to heat stress were found to have elevated
plasma concentrations of pro-inflammatory cytokines [225]. In the event of a heat stroke, both human- and animal models experience an increase in the levels of pro- and anti-inflammatory cytokines [226]. A loss of intestinal barrier integrity was observed in cows, which increased its permeability to ITMs, which implies gut leakiness activity attributed to alkaline phosphatase concentration changes [218].

For a healthy individual, where inflammatory processes are at a bare minimum, the core temperature is maintained by a complex physiological system of thermal regulation [227]. By employing mechanisms such as vasodilation and constriction, sweating and shivering, the system ensures that the body’s core temperature is maintained at the levels of approximately 36.8°C. The environmental conditions or the internal physiological processes can, however, undermine the functions of the thermoregulatory system. If the capacity of the mechanisms driving the thermal regulation is reached, hyperthermia and its associated heat illness occurs upon exposure to excessive heat, causing detrimental effects on health or even leading to mortality risks [197, 228, 79].

We trace the effect of heat starting from the inner workings of the innate immune response all the way to identifying its effects on the human physiology by coupling two validated computational models: a human innate immune system model and a model of thermo-regulatory response and core temperature dynamics. To do this, we first extend a previously developed model of HIIS [229] such that it can predict the dynamics of its key players as a factor of core temperature. This then allows us to identify the core temperature regimes, which either benefit or impede the efficient response of the innate immunity. We then couple this model of innate immunity with a model of thermal regulation of the human body [157] to investigate scenarios of heat exposure and human activity typical for the hot and humid tropical climate of Singapore. We show that even in such hot climate, the human physiology is capable of maintaining a healthy state by adapting to temperatures in the mild febrile range (37, 38)°C. However, prolonged strenuous activity, typical for runners or construction workers, in the outdoor environment of cities like Singapore can have detrimental effects on efficient functioning of immune system. To understand the influence of dynamically changing core temperatures on the innate immune response, we first simulate the core temperature...
dynamics by the thermo-regulatory response model for three physical activities, namely marathon running, construction work, and walking, all in the hot and humid climatic conditions typical of Singapore. We then feed these time-dependent core temperatures into the HIIS model to investigate how varying intensities of physical activities affect the dynamics of key players in HIIS within a 36-hour time frame. All these findings have direct implications for health and well-being of urban dwellers and may suggest preventive measures [230].

The chapter is structured as follows: Section 6.1 presents a model of HIIS in conjunction with the temperature changes and a system dynamics model of the human body thermal regulation. Section 6.2 presents the results of modelling scenarios of exposure and human activity and analysis of their effect on the innate immune system functions. We discuss the limitations and directions of our future work, and suggest recommendations to experimental validation of our findings in Section 6.3 and conclude the chapter with Section 6.4.

6.1 Methods

6.1.1 The human innate immune system model

The HIIS model [229] was previously developed and experimentally validated with careful consideration of the biological mechanisms of each of the key players in HIIS: ITMs, neutrophils, macrophages, pro- and anti-inflammatory cytokines, and alkaline phosphatase.

An overview of HIIS is shown in Figure 6.1. The inflammatory response is triggered when ITMs activate resting macrophages ($M_R$), which then differentiate into "activated" macrophages ($M_A$) in the tissue ($I$). $M_A$ secrete pro-inflammatory cytokines ($CH$), which via a series of intermediate steps trigger the increase of permeability of the endothelial barrier ($II$), the thin lining that separates the bloodstream from the tissue. Via a process called diapedesis, the resting neutrophils ($N_R$) -that are in circulation- enter the tissue via the endothelial barrier ($III$). $N_R$ become active ($N_A$) when they enter the tissue, where they phagocytose and/or release their granules to antagonise
6.1. Methods

the inflammation \((IV)\). If the inflammation is cleared, the neutrophils go into a programmed cell-death called apoptosis \((V)\). \(M_A\) remove the apoptotic neutrophils \((ND_A)\) through phagocytosis while simultaneously inducing anti-inflammatory effect as shown by the green arrows in Figure 6.1 \((VI)\). However, if the inflammation is too intense and not easily resolved, neutrophils go into a more chaotic death pathway called necrosis \((ND_N)\) as designated by the red arrows in Figure 6.1, which then releases \(ITMs\) in the tissue \((VII)\). The additional source of \(ITMs\) induces an inflammatory response that causes tissue damage, which then perpetuates the ongoing inflammation through macrophage activation and influx of neutrophils into the site of inflammation \((VIII)\). Additionally, endogenous Alkaline Phosphatase \((AP)\), which is naturally produced by the body, is also able to neutralise the ITMs at the site of inflammation.

The HIIS model is governed by 14 coupled ordinary differential equations, where each equation was devised to capture the biological mechanisms and the interactions of the components in the human innate immune response. A detailed description of the model, the parameters used, as well as an overview of the data sets used to validate and calibrate the model can be found in [229].

Modelling the influence of body core temperature on the dynamics of the human innate immune system

Assuming a normal core temperature of 36.8°C for healthy individuals, we identify 9 parameters of the HIIS model [229] that are particularly affected by high temperatures. Table 6.1 summarises the list of parameters, their behaviour with respect to increasing core temperature, and the corresponding references from literature.

We then proceed by devising a relationship between these parameters and core temperature. Although it has been shown that the Boltzmann–Arrhenius model, which is used in describing chemical reaction kinetics, can be utilised also to predict the rates of many biological metabolic processes [231], this would require the knowledge of activation energies for all the rates shown in Table 6.1. At the time of the writing of this article, these activation energies are yet unknown for the HIIS components.
### Table 6.1: Table of parameters adjusted in the human innate immune system model.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Parameter Description</th>
<th>Eq.</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\lambda_{ITM</td>
<td>ND_A}$</td>
<td>Phagocytosis rate of ITMs by activated neutrophils</td>
<td>6.2</td>
</tr>
<tr>
<td>$P_{NR}^{\text{max}}$</td>
<td>Maximum permeability of resting neutrophils</td>
<td>6.1</td>
<td>[211, 212]</td>
</tr>
<tr>
<td>$N_{R}^{\text{max}}$</td>
<td>Maximum concentration of resting neutrophils</td>
<td>6.1</td>
<td>[209, 213, 214, 215]</td>
</tr>
<tr>
<td>$\lambda_{ITM</td>
<td>M_A}$</td>
<td>Phagocytosis rate of ITMs by activated macrophages</td>
<td>6.1</td>
</tr>
<tr>
<td>$\beta_{N_{A}</td>
<td>ITM}$</td>
<td>Rate of pro-inflammatory cytokine production when activated macrophages/neutrophils phagocytose ITMs</td>
<td>6.1</td>
</tr>
<tr>
<td>$\alpha_{ACH</td>
<td>M_A}$</td>
<td>Rate at which anti-inflammatory cytokines are produced by activated macrophages</td>
<td>6.1</td>
</tr>
<tr>
<td>$P_{AP}^{\text{max}}$</td>
<td>Permeability of endothelial barrier to Alkaline Phosphatase</td>
<td>6.1</td>
<td>[218]</td>
</tr>
<tr>
<td>$\alpha_{ND_N}$</td>
<td>Rate of increase of ITMs due to necrosis</td>
<td>6.3</td>
<td>[195]</td>
</tr>
</tbody>
</table>
6.1. Methods

We tested two assumptions on the relationships between the parameters and core temperature, and found that a linear response for parameters $P_{N_R}^{max}$, $N_R^{max}$, $\lambda_{ITM|M_A}$, $\beta_{N_A|ITM}$, $\beta_{M_A|ITM}$, $\alpha_{ACH|M_A}$, $P_{AP}^{max}$, and $\lambda_{ITM|ND_A}$, while an exponential relationship for $\alpha_{ND_N}$ best models the desired shift in the effects on HIIS for core temperatures within and beyond the mild febrile range. We conjecture that other non-linear forms of equations may also be used, but in order to do this, we would need the data corresponding to these innate immune entities to calibrate our model with.

For a linear response, the change in parameters is directly proportional to the change in temperature with an arbitrary growth factor $\gamma$. For simplicity, we assume that $\gamma$ is the same for all parameters. The range of the parameter values we used still fall within or close to the accepted biological range specified in [229].
Equation 6.1 summarises this linear relationship:

\[ p(T_{\text{core}}) = p_0 + \gamma (T_{\text{core}} - T_{\text{core}_0}), \quad (6.1) \]

where \( p(T_{\text{core}}) \) is the value of the parameter at temperature \( T_{\text{core}} \), \( p_0 \) is the parameter value at normal core temperature 36.8°C, \( \gamma \) is the arbitrary factor that defines the rate at which parameter \( p \) grows with increasing core temperature.

Although we want to limit the number of parameters that we calibrate for this work, we found that the growth factor for \( \lambda_{ITM|ND_A} \) is different from the previously mentioned parameters in order to have the desired dynamics in HIIS with respect to change in temperature. We emphasise that we can explore more of these parameters once we get hold of necessary datasets to calibrate our model with. A parameter sensitivity analysis is also part of our future work. And thus, we model the linear behaviour of \( \lambda_{ITM|ND_A} \) with respect to temperature by Equation 6.2:

\[ \lambda_{ITM|ND_A}(T_{\text{core}}) = \lambda_{ITM|ND_A0} + \kappa (T_{\text{core}} - T_{\text{core}_0}), \quad (6.2) \]

where \( \lambda_{ITM|ND_A}(T_{\text{core}}) \) is the value of \( \lambda_{ITM|ND_A} \) at temperature \( T_{\text{core}} \), and \( \lambda_{ITM|ND_A0} \) is the parameter value at baseline temperature \( T_{\text{core}_0} = 36.8°C \) and \( \kappa \) is the arbitrary factor that defines the rate at which parameter \( \lambda_{ITM|ND_A} \) grows with increasing core temperature.

It has been shown that the rate at which cells are destroyed by hyperthermia exhibit an exponential behaviour with increasing temperature [232]. Since an induced cell death also induces ITMs [233], modeling the rate at which ITMs are induced due to necrosis (\( \alpha_{ND_N} \)) as exponential, is further justified.

To model the exponential behaviour for \( \alpha_{ND_N} \) with respect to temperature, we use Equation 6.3:

\[ \alpha_{ND_N}(T_{\text{core}}) = \alpha_{ND_N0} \exp[\epsilon (T_{\text{core}} - T_{\text{core}_0})], \quad (6.3) \]

where \( \alpha_{ND_N}(T_{\text{core}}) \) is the value of \( \alpha_{ND_N} \) at temperature \( T \), \( \alpha_{ND_N0} \) is the parameter value at baseline temperature \( T_{\text{core}_0} = 36.8°C \), and \( \epsilon \) is the growth rate of \( \alpha_{ND_N} \).
6.1. Methods

TABLE 6.2: Additional parameters used in the simulation of the HIIS response to increasing temperature, defined by equations 6.1, 6.2, and 6.3

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\gamma$</td>
<td>Slope or gradient of linear equation, defines the growth rate of parameters $P_{NR}^{\max}$, $N_{R}^{\max}$, $\lambda_{ITM</td>
<td>M_A}$, $\beta_{N_A</td>
</tr>
<tr>
<td>$\kappa$</td>
<td>Slope or gradient of linear equation, defines the growth rate of $\lambda_{ITM</td>
<td>ND_A}$.</td>
</tr>
<tr>
<td>$\epsilon$</td>
<td>Growth rate of $\alpha_{ND_A}$</td>
<td>4.75</td>
</tr>
<tr>
<td>$T_{core}$</td>
<td>Core temperature ($^\circ$C)</td>
<td>[36.8, 37, 38, 39, 40, 41, 42, 43]</td>
</tr>
</tbody>
</table>

We summarise the parameters used in our simulations in Table 6.2. Parameter values were chosen to reproduce the desired dynamics of the shift in behaviour of key components in HIIS as the temperature traverses from the mild febrile range to a nearly fatal core temperature of $T_{core0} = 43^\circ$C. To the best of our knowledge at the time of writing, data on temperature-dependence of the HIIS model parameters is not available, which renders further calibration of the model as part of future work.

6.1.2 Model of human thermo-regulatory response and core temperature dynamics

The human body consists of multiple tissue types, each having its own thermophysiological properties, resulting in different temperatures observed in, for example, muscles and fat. The most prominent difference, however, is between the outer shell of human body – skin – and tissues confined within the skin – core of the body [234]. While core temperature should be kept close to 36.8°C to ensure the proper functioning of vital organs, the skin serves as the main way of heat exchange between human body and surrounding thermal environment, leading to high variation of skin temperature tolerated by the human organism [227]. Rectal temperature, having the least observed variation, is usually considered a representative of the overall thermal state of the core of the body [235].

To model the human thermo-regulatory response and core temperature dynamics, we adopt the modified Gagge’s two-node model [100], which differentiates the temperatures in core and skin components of human body.
It was extensively applied in the studies of thermal sensation and perception and prediction of thermo-physiological state of human body in static indoor thermal environments. In previous work we re-calibrated the two-node model to better reproduce the dynamics of core and skin temperature in transient outdoor environments [157] and applied it to study the implications of the urban pace of life, expressed in observed walking speeds, on thermal stress [236].

In the body temperature model, core and skin components are considered as stocks of energy. The energy is exchanged between the stocks as well as with the environment through evaporation $E$, radiation $R$ and convection $C$ from and to the skin, respiration $Re$ and mechanical work $W$ from the core. The goal of the thermo-regulatory mechanisms (such as metabolic heat production $M$, core-skin blood flow, vaso- constriction and dilation, shivering $Sh$) is to maintain the body core temperature by eventually achieving the neutral heat storage ($S$) expressed by the following heat balance equation:

$$S = M + Sh - Re - W - C - E - R \left[ \frac{W}{m^2} \right]$$

The complete stocks-and-flow system dynamics representation of the model is provided in Figure 6.2. The reader is referred to [157] for a full mathematical specification of the model, its experimental validation, and a demonstration of its predictive performance in dynamic thermal conditions. The positive values of heat storage ($S > 0$) imply the accumulation of heat in the body, which is distributed between two components: skin and core. The core and skin temperatures change due to the source of the heat (internally produced or acquired from environment) and environmental parameters.
6.2 Results

6.2.1 Effect of varying core temperatures on the performance of the human innate immune system

Inflammation Triggering Moieties

Inflammation Triggering Moieties (ITMs) may refer to bacterial lipopolysaccharides and extracellular nucleotides serving as pro-inflammatory signals that trigger local and systemic inflammatory responses in HIIS. We look at two cases: one with very high initial ITM concentration patterned after patients experiencing severe inflammation like that of cardiac surgery (see [229], here we assumed that the core temperatures of the patients are normal at 36.8°C),
and one with low initial ITM concentration, which corresponds to healthy individuals (as low amount of ITMs are always circulating in the body in order keep the HIIS active).

In our simulations, we observe that ITM concentrations are lower for temperatures 37°C and 38°C (assumed mild febrile range) than at higher temperatures (see Figure 6.3), which can be interpreted as the beneficial effect of fever to the organism. Above the febrile range, ITM concentrations are at higher levels and may reach fatal concentrations, becoming a threat to the organism [237].

**A. High Initial ITMs**

**B. Low Initial ITMs**

![Figure 6.3: Dynamics of inflammation triggering moieties for a temperature-dependent human innate immune system.](image)

With a baseline normal temperature of 36.8°C, we observe that ITM concentrations are lower for temperatures 37°C and 38°C than at higher temperatures.

**Cytokines**

Cytokines are “messenger” proteins that orchestrate the complex mechanisms of the innate immune response. Cytokines can either be pro-inflammatory or anti-inflammatory. Pro-inflammatory cytokines are produced by immune cells called macrophages during the inflammation process and migrate to the endothelial barrier, opening it up, and thus allowing the entrance of neutrophils to the site of inflammation. Anti-inflammatory cytokines, also produced by macrophages, are immuno-regulatory molecules that control the production of pro-inflammatory cytokines.
The shift in dynamics of anti-inflammatory cytokines at temperatures in the mild febrile range is also seen in both high and low initial ITMs (Figure 6.4A and B, right panel). The heightened levels of anti-inflammatory cytokines help in the down-regulation of inflammation. Hence, the observed increase of anti-inflammatory effects for temperatures in the mild febrile range support the notion of mild temperatures pertaining to mild fever bestowing benefits to the body. Further increasing the temperature beyond the mild febrile range shows that the levels of anti-inflammatory cytokines are at much lower values than those in the mild febrile range. Pro-inflammatory cytokines, on the other hand, are generated in low concentrations for temperatures within the mild febrile range. This apparent divide is seen in Figure 6.4A and B, left panel), supporting again, the benefit of mild temperatures to the body. At higher temperatures, pro-inflammatory cytokines are produced in huge concentrations that aggravate the ongoing inflammation.

**Neutrophils**

Neutrophils are one of the key players in HIIS and one of the first responders rushing to the site of inflammation in the event of a so-called insult, where the organism is bombarded with ITMs. When the inflammation is taken care of, neutrophils go into a programmed cell death called apoptosis. However, in cases when the insult is too intense or persistent, they take on a violent death pathway called necrosis, spilling their cytoplasmic content into surrounding tissue, thus aggravating the inflammation. This delicate balance between apoptosis and necrosis has to be maintained in the body. In previous work, we studied this phenomenon using the concept of evolutionary game theory [238].

For temperatures within the mild febrile range (see Figure 6.5A), we observe higher concentrations of apoptotic neutrophils, but lower concentrations of necrotic neutrophils, again, supporting the beneficial effect of fever to HIIS. The presence of apoptotic neutrophils implies the production of anti-inflammatory cytokines, which are messenger proteins that down-regulate
Figure 6.4: Dynamics of cytokines for a temperature-dependent human innate immune system. The shift in dynamics of cytokines in the mild febrile range (37, 38)°C for anti-inflammatory cytokines is seen more prominently in high initial ITMs. Pro-inflammatory cytokines, on the other hand, are generated in low concentrations for temperatures within the mild febrile range.

The ongoing inflammation through the regulation of pro-inflammatory cytokines. Within the mild febrile range, it seems that apoptosis is mostly preferred, which may be attributed to its anti-inflammatory benefits as opposed to the harmful cost of necrosis. However, above the mild febrile core temperatures, the general trend of concentrations for the neutrophils begins to shift to the opposite direction, where apoptotic neutrophils are lower in concentrations, while necrotic neutrophils are higher in levels of concentration. We note that through necrosis, more ITMs are produced, which further aggravates the
ongoing inflammation. In the process, the body goes into overdrive, causing a cytokine storm, recruiting more and more neutrophils into the site of inflammation, which may eventually become detrimental or even fatal to the human body.

Figure 6.5: Dynamics of neutrophils for a temperature-dependent human innate immune system. For temperatures within the mild febrile range \((37, 38)\)°C, we observe higher concentrations of apoptotic neutrophils, but lower concentrations of necrotic neutrophils, supporting the beneficial effect of fever to the human innate immune system.

Alkaline phosphatase

Alkaline Phosphatase (AP) is an enzyme widely recognised as responsible for keeping the endothelial barrier intact. Apart from this, it has been established
that AP has the capability of neutralising ITMs. High initial ITMs (see Figure 6.6A) mimic the condition of patients undergoing cardiac surgery, where AP from the liver is flushed into the bloodstream, as explained in detail in our previous work [229]. Hence we see an initial high concentration of AP in the bloodstream. Since the body is already experiencing high initial levels of ITMs, all temperatures trigger the diffusion of AP from the bloodstream into the tissue (see snippet in Figure 6.6A). AP in the tissue is then readily used up especially at higher temperatures, or those temperatures beyond the mild febrile range.

For healthy individuals, the typical concentration of AP is 50 IU/L (see Figure 6.6B.) We observe that for temperatures within the mild febrile range, AP in the bloodstream is less used by the body, as is evident from the subtle dips in AP concentration, supporting again the benefits that fever bestows upon the body. However, at much higher temperatures, we observe a drop in concentration of AP in the bloodstream and tissue, which implies that the body is in need of the current available supply of AP to neutralise the ongoing inflammation.

**Figure 6.6:** Dynamics of alkaline phosphatase in blood (main) and tissue (inset) for a temperature-dependent human innate immune system. At high initial levels of ITMs, all temperatures trigger the diffusion of AP from the bloodstream into the tissue. For healthy individuals (low initial ITMs), we observe that for temperatures within the mild febrile range, AP in the bloodstream is less used by the body, as evident from the subtle dips in AP concentrations.
6.2. Results

6.2.2 Heat exposure and exertion risks for immune system

In the previous sections, we have identified that there are two different levels of elevated core temperature, which either have a beneficial or detrimental effect on HIIS. While the immune response is improved for core temperatures rising up to $38^\circ$C, higher temperatures have a detrimental effect on the performance of the innate immune system.

Here we provide the results of simulations of the core temperature dynamics over a period of 3 hours for a broad range of human activities varying from light to vigorous, while exposed to typical outdoor conditions of equatorial Singapore. In these scenarios we assume a constant level of metabolic rate production due to physical activity and initial state of the thermo-physiological system in steady state ($T_{\text{core}} = 36.84^\circ$C, $T_{\text{skin}} = 33.75^\circ$C) typical for sitting activity in thermally neutral indoor environment ($T_{\text{air}} = 22^\circ$C, mean radiant temperature $T_{\text{MRT}} = 22^\circ$C, relative humidity (RH) 50%, wind speed 0.05 m/s, clothing insulation $I_{\text{cl}} = 1.0$ clo, metabolic heat production $M = 80 \, W/m^2$).

The levels of metabolic rates for different occupational, sportive and leisure activities are taken from the Compendium of physical activities [239].

Figure 6.7A demonstrates the core temperatures, which will be reached in sunny conditions of a Singapore-like climate under specific intensities of activities and duration. We observe that in these environmental conditions the lower-than-moderate activities ($M < 6$ MET) do not lead to critical overheating even for a long duration. The time needed to reach the threshold value of core temperature ($38^\circ$C) decays exponentially as the activity intensity increases. For example, running at a speed of 9.7 km/hr (an activity of approximately 10 MET intensity) for longer than 7 minutes would result in crossing the threshold of $T_{\text{core}} = 38.0^\circ$C. We observe a similar behaviour in Figure 6.7B, which represents cloudy weather in Singapore-like climate (lower air and mean radiant temperatures, but higher humidity as compared to the previous scenario). The intensities of activities at the threshold level, however, are slightly higher. This is due to the absence of direct exposure to the sun. Its effect would be even higher if not for the increased relative humidity in this scenario, which reduces the evaporating capacity of the environment and consequently the opportunities of cooling through evaporation of sweat. This
complex interplay of a micro-climate and thermal regulation of the human body results in extreme levels of core temperature (i.e. $T_{core} = 42.0^\circ C$) that are reached earlier in the ‘cloudy’ (B) as compared to the ‘sunny’ (A) weather scenario.

In the last scenario, presented in Figure 6.7C, we reproduce the conditions of an early morning, no sun, suitable for a marathon. We set air velocity to a value of 3.9 m/s (14 km/hr), characteristic of the speed of an experienced medium- and long-distance runners, which significantly increases convective heat removal from the surface of the body. This level of activity would correspond to the extreme values of $M \geq 12$ MET. Thus, the 38°C threshold of core temperature would be reached after about 6 minutes into the run (or after about 1.5 km).

Considering the upper boundary of intensity of occupational construction work of 8 MET, the threshold level of core temperature would be reached after 9.5 and 11 minutes of continuous work in sunny and cloudy Singapore climate correspondingly. This implies that construction workers are subjected to the risk of compromising the functioning of immune system.

6.2.3 Innate immune response in three different activities

In the previous two sections, we have (1) identified the values of core temperatures that either induce benefits to the innate immune response or undermine its functions, and (2) pinpointed the regimes of physical activities and environmental conditions that these core temperature correspond to. In these simulations, core temperatures did not change over time. Those results provide a good understanding of 2 key points: how temperature affects the dynamics of the immune system and how HIIS battles the inflammation over a period of 36 hours. It however does not represent the dynamically changing core temperatures and their effects in real scenarios of physical activities and heat exposure.

In this section we investigate how HIIS responds to three physical activities: a marathon of three hours, construction work of 9 hours with an hour lunch break, and walking for 6 hours in Singapore setting. We then
6.2. Results

**Figure 6.7:** The dynamics of core temperature as a function of time and level of activity intensity. a) For sunny outdoor environment of Singapore, b) for cloudy outdoor conditions of Singapore, c) for cloudy morning conditions with air velocity $V_{air} = 3.9$ m/s $= 14$ km/hr equivalent to air velocity around running person (vigorous physical activity). Contour lines indicate the regimes of activity intensity and its duration resulting in the same value of core temperature $T_{core}$. $T_{core} > 38.0^\circ$C is predicted by our model to have detrimental effects on the performance of immune response. Thus, intensity and duration of activity in a given environment, for which $T_{core}$ exceeds 38.0 °C, should be avoided to minimise the risk of compromising the immune system.

Observe HIIS reaction over a period of 36 hours. This period covers the entire course of the activity and the recovery that follows. The activity schedule and conditions for each of the considered scenarios are provided in Table 6.3. Other parameters values are used as specified in the previous section on HIIS-temperature model. Further, modelling a healthy individual, we assume that the human body has a low initial level of ITMs.

**Inflammation Triggering Moieties**

The dynamics of ITM concentrations (Figure 6.8B) in construction work and walking scenarios follow the dynamics of core temperatures (Figure 6.8A). Construction work seems to induce lesser concentrations of ITMs compared to running a marathon. It is also evident from the peaks in ITM surges that there is indeed a rest period in between 4 hours of physical activity, representing a lunch break. Walking induces the lowest levels of ITMs among the three physical activities. The two activities then show an eventual decline in ITMs, signifying an efficient resolution of the ongoing inflammation. A marathon
Chapter 6. Heat stress and innate immune system response

Table 6.3: The schedule of three activity scenarios

<table>
<thead>
<tr>
<th>Activity</th>
<th>Intensity, MET</th>
<th>Duration, hours</th>
<th>$T_{air}$, °C</th>
<th>$T_{MRT}$, °C</th>
<th>RH, %</th>
<th>$v_r$, m/s</th>
<th>$I_{cl}$, clo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Marathon scenario</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Running</td>
<td>12</td>
<td>3</td>
<td>28</td>
<td>30</td>
<td>80</td>
<td>3.9</td>
<td>0.4</td>
</tr>
<tr>
<td>Cooling down</td>
<td>1.4</td>
<td>1</td>
<td>28</td>
<td>30</td>
<td>80</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>Resting</td>
<td>1</td>
<td>32</td>
<td>22</td>
<td>22</td>
<td>50</td>
<td>0.05</td>
<td>1</td>
</tr>
<tr>
<td><strong>Construction work scenario</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Work</td>
<td>6</td>
<td>4</td>
<td>30</td>
<td>30</td>
<td>80</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>Lunch break</td>
<td>1.4</td>
<td>1</td>
<td>30</td>
<td>30</td>
<td>80</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>Break</td>
<td>1.4</td>
<td>1</td>
<td>30</td>
<td>30</td>
<td>80</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>Resting</td>
<td>1</td>
<td>26</td>
<td>28</td>
<td>28</td>
<td>80</td>
<td>2</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>Urban walk scenario</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban hike</td>
<td>2.5</td>
<td>6</td>
<td>30</td>
<td>30</td>
<td>80</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>Resting</td>
<td>1</td>
<td>30</td>
<td>22</td>
<td>22</td>
<td>50</td>
<td>0.05</td>
<td>1</td>
</tr>
</tbody>
</table>

runner running for 3 hours in the hot and humid tropical climate of Singapore is shown to induce a high level of ITMs that initially follows the core temperature profile.

All activities have core temperatures that are slightly above the normal temperature of 36.8°C right after the physical activity. This is under the assumption that the marathon runner, construction workers, and the walkers enter an air-conditioned room after some time, where they eventually ease back to the normal core temperature. Since our model assumes that mild temperatures pose benefit to the innate immune response, we see a slight increase in ITMs after the activities, as the core temperature goes back to normal.

Finally, although a marathon induces the highest level of ITMs, the ITM concentration still decreases over time. Construction work, on the other hand, is done on a daily basis. Therefore, in the long run, construction work induces a greater impact on the innate immunity through the continuous production of ITMs at a longer period of time.
6.2. Results

Figure 6.8: Dynamics of core temperatures and inflammation triggering moieties during and after three physical activities. The profiles of ITMs for marathon and walking follows that of the core temperatures. Two peaks in the ITM concentrations of construction work signify a 9-hour work with an hour break in between. Marathon exhibits the highest induced ITMs, which remain at high level after 36 hours, signifying the inability of the innate immune system to resolve the ongoing inflammation.

Cytokines

Figure 6.9 summarises the concentrations of pro- and anti-inflammatory cytokines of marathon, construction work, and walking over a period of 36 hours. A marathon induces the highest level of pro-inflammatory cytokines among the three physical activities. We emphasise that pro-inflammatory cytokines are messenger proteins responsible for opening up the endothelial barrier, recruiting more of the circulating neutrophils into the site of inflammation, aggravating the ongoing inflammation. Anti-inflammatory cytokines are also produced, but exhausted at around 48 hours (see snippet in Figure 6.9B). The decay times for both pro- and anti-inflammatory cytokines for marathon runners were also observed in [240].

Pro-inflammatory cytokines are at low levels for construction work and walking, while anti-inflammatory cytokines remain high for both activities, signifying the efficient resolution of inflammation by HIIS. This is due to the remaining concentrations of apoptotic neutrophils in the system as we have shown in the previous section. Anti-inflammatory cytokones are produced by macrophages when neutrophils go into apoptosis as specified in our model.
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However, we emphasise that the combined model is not yet calibrated to real data and thus the rates at which anti-inflammatory cytokines as well as pro-inflammatory cytokines decrease have yet to be refined to realistically model HIIS in the context of a physical activity. We note that we have kept the calibrated parameters of the modified HIIS model to only three values. As such, this work is a proof of concept of how the core temperatures affect the performance of HIIS in different physical activities. Part of our future work is to collect data on concentrations of pro- and anti-inflammatory cytokines and to calibrate the combined model.

Figure 6.9: Dynamics of pro- and anti-inflammatory cytokines during and after three physical activities observed for 36 hours/1.5 days (main) and 120 hours/5 days (snippet). Marathon (3 hours) induced more pro-inflammatory cytokines than construction work (9 hours with a 1 hour break in between) and walking (6 hours), while all three physical activities induced similar concentrations of anti-inflammatory cytokines. Marathon’s anti-inflammatory cytokines decline after 10 hours, signifying the depletion of immune cells that produce them.

Neutrophils

Simulation results for the concentration of apoptotic and necrotic neutrophils for the three physical activities are summarised in Figure 6.10. Construction work triggers the highest concentration of apoptotic neutrophils, followed by walking and then marathon. On the other hand, higher concentrations of
ITMs trigger HIIS to go into the necrotic death pathway. Necrosis encourages the body to recruit more of the circulating neutrophils into the site of inflammation, aggravating the ongoing inflammation. This is why we see a higher level of induced necrotic neutrophils in Figure 6.10B for the marathon scenario.

**Figure 6.10:** Dynamics of apoptotic and necrotic neutrophils during and after three physical activities. Construction work induces the most apoptotic neutrophils followed by walking and marathon. Marathon, which induces the highest level of ITMs, induces the most necrotic neutrophils as the innate immune system picks the necrotic death pathway to further aggravate the ongoing inflammation.

**Alkaline Phosphatase**

Alkaline phosphatase helps neutralising inflammation. Hence, the stronger the stimulus is (that is, the more ITMs there are in the body) the more AP is induced to fight the ongoing inflammation. Alkaline phosphatase concentrations in blood as well as in tissue are shown in Figure 6.11. The snippets correspond to the same concentrations for a period of 120 hours or 5 days. Here we show that a marathon, the physical activity that contributes most of the ITMs, induces the strongest surge of AP from the bloodstream into the tissue (see Figure 6.11) and immediately uses it up to neutralise the ongoing inflammation. This is followed by construction work and walking. The behavior we see in marathon beyond 3 hours is again for two reasons: 1) the body has consumed much less of the AP at this point, therefore implying that
ITMs are being resolved and 2) pro-inflammatory cytokines, the messenger proteins that open up the endothelial barrier, are still at high concentrations, this allowing more of the AP from the bloodstream to enter the tissue. After about 36 hours, AP in the bloodstream begins to go back to normal levels. After some time, when the inflammation is nearly resolved for all activities, we see an increase in AP in blood as the the concentration goes back to normal.

**Figure 6.11:** Dynamics of alkaline phosphatase in blood(A) and tissue(B) during and after three physical activities. observed for 36 hours/1.5 days (main) and 120 hours/5 days (snippet). Marathon induces the highest level of alkaline phosphatase in tissue, followed by construction work and walking. Alkaline phosphatase is known to neutralise inflammation, hence, the more intense the inflammation is, the stronger it is induced.

### 6.3 Discussion

Although the human body has evolved to adapt to changes in ambient temperature, the imminent threat of climate change, which promises more heat-waves, will inevitably cause the rise of heat-related health problems. Despite the urgency of knowing the risks associated with a rising core temperature to the innate immune response, there is an apparent knowledge gap between understanding the underpinning cellular mechanisms and the associated processes of the innate immune system and its implications for the human body, and consequently the types of healthy physical activities humans are constrained to do in given thermal environment.
We bridged this gap by coupling two validated and established computational models: the human innate immune system model and a model of thermo-regulatory response and core temperature dynamics.

In order to do so, we first needed to modify the existing model of the human innate immune system in such a way that it takes temperature changes into consideration. We identified the parameters in a previously developed model of the innate immune response that are directly impacted by temperature. Since appropriate data to calibrate the modified HIIS model with respect to temperature is currently unavailable, we only chose those parameters that best describe the qualitative dynamics of HIIS based on known behaviours documented in literature. We found that a simple linear response for majority of the parameters coupled with an exponential increase in the rate for induced ITMs with respect to increasing core temperature, capture the shift of the dynamics of key components in HIIS from the beneficial regime of mild fever to a detrimental effect above 38.0°C. What we have shown is numerical evidence of the beneficial effect of mild febrile range of body core temperature (37, 38]°C to HIIS. Temperatures above the mild febrile range trigger a stronger and even detrimental effect on HIIS, which is more prominent at higher initial concentrations of ITMs. We conjecture that since the body has already been exposed to ITMs, and thus has already activated and charged up to resolve the ongoing inflammation, the effect of temperature only adds up on top of this resolving reaction of HIIS.

A total of nine parameters from the original HIIS model were identified to be affected by temperature. The next logical step is to trim down the parameters that truly contribute to the variance of results of the model. Model calibration and detailed validation is a next step, once the data become available.

Lastly, we looked into the dynamics of HIIS during and after three physical activities: a marathon, construction work, and walking, all in the hot and humid tropical climate of Singapore. We did so by modelling the dynamic core temperatures during the course of the activity, as well as the resting period that follows for a total period of 36 hours. We then fed these dynamic core temperatures into the HIIS-temperature model. Our simulations capture how a marathon of 3 hours induced the most ITMs, as compared to a 9-hour
construction work or a 6-hour walk. HIIS was able to resolve the inflammation induced by both construction work and walking. However, an extreme sport such as a marathon in hot humid conditions challenged the function of the innate immune system, inducing an inflammation that lasts long after the 3 hour physical activity. However, it is also important to note that although marathon induces the most intense level of inflammation, it eventually subsides at some point. Construction work, on the other hand, is a daily routine. And thus, the induced levels of ITMs due to construction work will even surpass that of a marathon once the body recovers. To the best of knowledge, this is the first time that the immune response due to running a marathon has been analysed using computational models. We hope to leverage our claims by collecting supporting data, specifically concentrations of immune cells for marathon runners, to calibrate our model and validate our results.

### 6.4 Conclusions

Combining the innate immunity model with a thermo-regulatory model, we identified climate-intensity-duration regimes which lead to body core temperature exceeding the threshold level of 38.0°C. In hot environmental conditions, prolonged strenuous activities, such as running or construction work, pose a risk of crossing the threshold of overheating, which results in compromising performance of the innate immune system response. As a proof of concept, we show how three physical activities affect the innate immune response by incorporating dynamic core temperatures into the HIIS-temperature model. We showed that a marathon for three hours in the hot and humid tropical climate of Singapore induces a high level of inflammation that challenges the function of the innate immune system. However, it is important to note that construction work is done on an almost daily basis as compared to a marathon of 3 hours, which then stretches construction work’s induced inflammation over a prolonged timeline. Thus, these activities should be limited in duration or other measures such as active cooling should be put in place to protect people from hazardous heat stress.

To the best of our knowledge this is the first time that core temperature is modeled in conjunction with the human innate immune response. This
allows for a better understanding of the underlying mechanisms of the human innate immune system in response to heat, and for us to be able to probe its consequent beneficial or detrimental effects on the human physiology.

In order to validate our claims, we recommend collecting data on concentrations of key players in HIIS, more specifically anti- and pro-inflammatory cytokines as well as neutrophil and alkaline phosphatase levels, for patients undergoing heat treatments. Often times, temperatures used during these procedures vary from 40-43°C, which raises the core temperature by 1-2°C from that of normal \[241\]. More so, a recommended good experiment is to collect swabs for samples of cytokines from people doing rigorous exercises as well as documenting their temperatures. All these can aid us in validating, and further enhancing our model. Finally, we aim to dig deeper into the devised HIIS-temperature model through sensitivity analyses to gain more insights on the model behaviour as well as its structure by probing its temperature-dependent parameters.

Our work aims to contribute to the existing knowledge on how changes in human thermoregulation affect innate immunity – not only on the cellular level, but more importantly, its implications on individuals and subsequently on society.

**List of abbreviations**

HIIS – Human Innate Immune System
ITM – Inflammation Triggering Moieties
AP – Alkaline Phosphatase
RH – Relative Humidity