Abstract

Neutrophils are one of the key players in the human innate immune system. Depending on the level of insult, neutrophils are activated and could either go into apoptosis or necrosis. Apoptosis or programmed death of neutrophils poses benefits to the human body through anti-inflammatory effects. Necrosis, on the other hand, triggers the rupture of the cell, spilling all of its contents in the surrounding tissue thus aggravating the level of inflammation as it already is. This, however indirectly triggers the recruitment of more activated neutrophils into the site of inflammation. Despite the risk on the body, the human innate immune system still chooses to do so. We model this delicate balance between apoptosis and necrosis as the innate immune system in order to resolve inflammation through game theory coupled with cellular automata motivated by the idea that one part of the body centered at a neutrophil is playing a game, much like a rational individual, with another part of the body, based on payoffs proportional to the initial concentration of inflammation triggering moieties. We show that the body prefers apoptosis with decreasing inflammation triggering moieties (ITMs) concentration. However, as the concentration of ITMs increases, the body shifts its equilibrium to necrosis.

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1. Introduction

The human innate immune system (HIIS) is the first line of defence against insults [1]. HIIS’ defining feature is a fast reaction to pathogen exposure: it normally responds within minutes. The resolution of this invasion is normally manifested in the form of inflammation – an essential mechanism of HIIS [2]. Inflammation triggers the activation of key players in HIIS, where neutrophils play an important role. Neutrophils have always been known as short-lived “effector cells” defending us against extracellular pathogens [3]. This defence process involves complex interactions with other immune cells [4].

In case of an insult, the immune system resolves inflammation through a well-orchestrated series of activation and regulation of immune cells. Neutrophils could go into either apoptosis or necrosis. Apoptosis is a programmed death, which indirectly triggers the release of anti-inflammatory entities (see a detailed review in [5]). Necrosis results in a cell rupture, where the cell bursts and spills out all of its contents into the surrounding tissue, which further aggravates inflammation [6–10]. As a consequence, adding more inflammation-triggering moietyts (ITMs) into the system indirectly triggers the recruitment of resting neutrophils in the bloodstream to enter the tissue. Necrosis clearly has detrimental effects on the body, because the release of the cell’s toxic contents into surrounding tissue increases the amount of ITMs that are already being handled by the system. However, necrosis at the same time, offers a potential benefit by indirectly opening up the endothelial barrier, thus allowing the recruitment of more neutrophils into the tissue. Maintaining this delicate balance between apoptosis and necrosis – coupled with the latter’s pros and cons of intentionally inducing the levels of ITM concentrations through cellular “suicide”– is indeed a challenging problem. Despite this, it seems that the body could, in one way or another, weigh the advantages and disadvantages of choosing a certain pathway (apoptosis or necrosis) depending on the impeding threat. It was discovered that the greater the insult, the higher the occurrence of necrosis [11].

In this paper, we propose a game-theoretic approach motivated by the idea that in the case of an insult, one part of the body (the tissue centered at a neutrophil) “plays” with another part of the body to eventually come up with a favourable strategy in choosing which pathway to take: apoptosis or necrosis, under varying levels of insult. In other words, we model how the body go into apoptosis and necrosis of neutrophils by a two-player game, where we assume that each player (a part of the body) acts as a rational individual playing with another part of the body, by choosing a strategy that would benefit this player the most. A player could choose to:

1. go into apoptosis, which we label as cooperate in the context of game theory [12], because of its beneficial effect on the body;
2. go into necrosis, which is labelled defect in the game theoretical context.

We also use cellular automata (CA) to model spatial dynamics, where each lattice site could be populated by a neutrophil. Using CA coupled with game theory, we model the body’s reaction to varying concentrations of ITMs. Our model allows to predict the critical ITM concentrations, when the body shifts from cooperation (apoptosis) to defection (necrosis). We then add three mechanisms: (1) death, (2) neutrophil recruitment, and (3) positive feedback of inflammation. These mechanisms model (1) immune cell death, (2) indirect recruitment of activated neutrophils by necrotic neutrophils, and (3) the positive feedback mechanism that aggravates inflammation due to the presence of necrotic neutrophils in the system when the insult is large.

The paper is structured as follows: First, we present the methods we used in the Methodology section. Then we summarize our results and discuss them. Finally, we give our conclusions and future directions of our research.

2. Methodology

The payoff matrix for the game of neutrophils is summarized in Table 1. Here $\alpha$ refers to the payoff that both players 1 and 2 receive if both choose to go into apoptosis (mutual cooperation), $\beta$ is given to the player that goes into apoptosis, while the other that goes into necrosis receives $\gamma$. If both players go into necrosis (mutual defection), both receive a payoff of $\zeta$.

We assume that the body’s first choice of pathway is apoptosis due to its anti-inflammatory effects, which is indeed a straightforward benefit to the human body, especially in the case of an insult. In this case, we are left with
the inequality $\beta > a > \gamma > \zeta$, which describes the natural affinity of the body to go into apoptosis. Therefore, the game is reduced to a reverse dead-lock game having only a single equilibrium. This means that both players would choose to cooperate, no matter what the other player chooses.

**Table 1.** Game of Neutrophils Payoff Matrix. Player 1 (one part of the body) is playing with Player 2 (another part of the body). Each player has the option to do apoptosis (cooperate) or do necrosis (defect). The value in each cell represents the payoff of Player 1 for four combinations of the strategies of both players.

<table>
<thead>
<tr>
<th>Player 1</th>
<th>Player 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apoptosis (cooperate)</td>
<td>$\alpha(1 - x_{ITM})$</td>
</tr>
<tr>
<td>Necrosis (defect)</td>
<td>$\gamma x_{ITM}$</td>
</tr>
</tbody>
</table>

Although apoptosis clearly has a straightforward benefit to the system, sometimes the body still chooses for neutrophils to go into necrosis, despite the risks it poses. Furthermore, it was observed that the greater the insult, the higher the occurrence of necrosis [11]. That is, the higher the concentration of ITMs, the more likely the equilibrium is shifted from cooperation (apoptosis) to defection (necrosis).

In order to shift the equilibrium of the system depending on the concentration of ITMs ($x_{ITM}$), we model the payoffs for apoptosis and necrosis dependent on $(1 - x_{ITM})$ and $x_{ITM}$ respectively. We assign $x_{ITM} \in [0, 1]$ pertaining to the normalized concentration of ITMs, where 0 corresponds to no insult (healthy state) and 1 to the highest possible insult. At $x_{ITM} = 0$ the equilibrium of the system is apoptosis, and at $x_{ITM} = 1$ the equilibrium is necrosis.

Spatial dynamics is modelled by the cellular automaton. A rectangular empty lattice of size $n \times m$ cells is partially populated randomly with activated neutrophils. The remaining cells of the lattice are left empty. The lattice uses periodic boundary conditions to approximate a large system corresponding to the entirety of the human body. The game starts by randomly selecting a non-empty lattice cell containing an activated neutrophil, which in the context of our game is Player 1. Player 1 then makes a fictitious play with all of its neighbours by first choosing a strategy with a probability of $(1 - x_{ITM})$ to go into apoptosis and $x_{ITM}$ to go into necrosis. This means that the larger the insult is, the greater the probability of necrosis would be.

We consider a Moore neighbourhood with 8 neighbours around each lattice cell on a lattice size of $100 \times 100$. The player then calculates its payoff based on the payoff matrix summarized in Table 1. We set $\beta = 3$, $\alpha = 2$, $\gamma = 1$ and $\zeta = 0.5$ as the base-line values. The player chooses the best strategy, which could be either to cooperate (apoptosis) or defect (necrosis). This is repeated to all of the non-empty sites in the lattice, strategizing in a random sequential manner. This corresponds to a single time step in the simulation. The algorithm is summarized in Figure 1.

We then look at the temporal dynamics of the apoptotic and necrotic neutrophil population with varying initial ITM concentrations. After that, we introduce neutrophil cell death and recruitment mechanism. Death is modelled by deleting 75 apoptotic and 75 necrotic neutrophil per time step. This value is chosen under the assumption that neutrophils die in approximately 5 days [13]. We note that 10 time steps in our simulations correspond to 1 day. Recruitment is modelled by adding up to 150 activated neutrophils (depending on ITM concentration) per time step to mimic the ability of neutrophils to recruit activated neutrophils from the bloodstream into the tissue by indirectly making the endothelial barrier permeable. In other words, the more necrotic neutrophils there are in the system, the more activated neutrophils are being recruited from the bloodstream into the tissue. The concentration of ITMs per time step then changes relative to the concentration of necrotic neutrophils through a positive feedback by further aggravating inflammation, and activated neutrophils that neutralizes the inflammation.
3. Results and Discussion

3.1. Neutrophil Dynamics with Varying Initial Concentration of Inflammatory Triggering Moeties

It was observed that the larger the insult, the more necrotic neutrophils there are in the system [11]. And this is exactly what we see in Figure 2. Here we show that the proportion of neutrophils going into apoptosis grows, while the number of neutrophils going into necrosis declines, as the concentration of ITMs increases. This is because at high ITM concentrations the neutrophils favour the second pathway: necrosis. Notice that at $x_{ITM} = 0.2$ (inset in Figure 2), majority of the activated neutrophils in the system have gone into apoptosis, rendering the lattice filled mainly by blue cells.

We find it interesting that the concentration of apoptotic (necrotic) neutrophils gradually decreases (increases) up until $x_{ITM} = 0.6$. After this critical point, the transition happens much faster. More interestingly still, there seems to be a saddle point at $x_{ITM} = 0.8$, where both populations of apoptotic and necrotic neutrophils are equal.
So far, we have used the following inequality to define the neutrophil game: $\beta > \alpha > \gamma > \zeta$. Now we vary the values of $\alpha$ with respect to $\beta$, and vary $\gamma$ with respect to $\zeta$ between 0 to 6 and look at how these variations affect the Nash equilibrium of the system, where Nash equilibrium refers to the most stable strategy in the system. We pick $x_{ITM} = 0.8$, since this is where we observed a transition from majority of neutrophils being apoptotic to necrotic. We do this by measuring the fraction of neutrophils that go into apoptosis after 50 time steps. We summarize our results in Figure 3.

![Figure 2](image1.png)

**Fig 2.** Final fractions of apoptotic and necrotic neutrophil populations with varying initial ITM concentrations. Necrotic neutrophil population grows as initial concentration of ITMs increases.

![Figure 3](image2.png)

**Fig 3.** Apoptotic neutrophil population fractions for $x_{ITM} = 0.8$. (A): Values of $\alpha$ and $\beta$ vary from 0 to 6 at fixed $\zeta = 0.5$ and $\gamma = 1$. (B): Values of $\gamma$ and $\zeta$ vary from 0 to 6 at fixed $\alpha = 2$ and $\beta = 3$. Yellow colour signifies the final set entirely populated by apoptotic neutrophils, while black signifies the absence of apoptotic neutrophils in the system.

Yellow represents the entire system going into apoptosis, and black to necrosis. What is interesting here is the apoptotic population of neutrophils near 50% (red colour in Figure 3). These are the instances when the system has no Nash equilibrium and could flip from one strategy to another.
The body tends to prefer total defection (all activated neutrophils going into necrosis) when $\beta < 4$ and $\alpha < 0.1$ at fixed $\zeta = 0.5$ and $\gamma = 1$ as attributed to a very large insult (see Figure 3A). However, beyond these values, the equilibrium then shifts to apoptosis, to which the peak percentage is when $\beta > 4$ and $\alpha > 0.1$.

Interestingly, the reverse could be observed when $\gamma$ and $\zeta$ are varied from 0 to 6 at fixed $\alpha = 2$ and $\beta = 3$ (see Figure 3B). Total defection is observed when $\gamma > 1.6$ and $\zeta > 1.6$. The system then shifts to apoptosis below these values. Looking back at the inequality $\beta > \alpha > \gamma > \zeta$, it is easy to see that the contribution of such a large insult to the system shifts the equilibrium to necrosis most of the time.

### 3.2. Neutrophil Dynamics with Death, Recruitment and Positive Feedback Mechanisms

Neutrophils die within 5 days. In our simulation, we model death by deleting 75 apoptotic neutrophils and 75 necrotic neutrophils per time step. We note that 10 time steps in our simulation correspond to 1 day. Hence, we expect that all neutrophils would have died by the end of the 50 time steps. Presence of necrotic neutrophils, through a series of processes, leads to the opening up the endothelial barrier, which recruits neutrophils circulating in the bloodstream to enter the tissue [14]. In our simulation, a maximum number of 150 activated neutrophils could then appear in the system at each time step. Finally, the more necrotic neutrophils there are, the more inflammation is aggravated. As necrotic cells are ruptured, spilling out all of their contents in the surrounding tissue, the higher the concentration of ITMs becomes. Hence, it is referred to as a positive feedback mechanism for inflammation. We model this in our simulation as an additional source of ITMs. Our results are summarized in Figure 4.

![Fig 4](image-url)

Fig 4. Dynamics of apoptotic and necrotic populations at varying initial ITM concentrations with death and recruitment mechanisms. Dynamics of (A) Inflammation Triggering Moeties, (B) Activated Neutrophils, (C) Apoptotic Neutrophils, and (D) Necrotic Neutrophils.
The concentration of ITMs gradually decreases for initial concentrations less than or equal to \( x_{ITM} = 0.6 \), as seen in Figure 4A. That is, the system is able to slowly resolve the inflammation over time. However, this concentration of ITMs for initial concentration greater than or equal to \( x_{ITM} = 0.8 \) remains high over time. This dynamics corresponds to the saddle point we saw earlier even without the added mechanisms of death, recruitment, and positive feedback.

At \( x_{ITM} = 0.8 \), concentration of necrotic neutrophils gradually decreases (see green line in Figure 4D), approaching the values attained at the lower initial concentrations of ITMs. Due to the presence of these necrotic neutrophils, more activated neutrophils are indirectly being recruited into the site of inflammation (Figure 4B). Notice that there is no longer recruitment of activated neutrophils for ITM concentration lower than \( x_{ITM} = 0.8 \) at time step 40.

Apoptosis on the other hand initially dominates the system for concentrations lower than \( x_{ITM} = 0.8 \) (see Figure 4C). As inflammation is resolved, the system shifts its equilibrium to apoptosis. Hence, neutrophils then eventually die through natural death. It is not surprising, however, that the system seems to be locked to necrosis when the concentration of ITMs is set to a maximum.

4. Conclusions

We introduce a game-theory approach coupled with the cellular automaton for modelling human immune system response to infectious insult. Activated, apoptotic and necrotic neutrophils were considered. The parameters of the payoff matrix have been varied in order to find the ranges of values that shift the equilibrium of the system from cooperation (apoptosis) to defection (necrosis) depending on the scale of insult or presence of inflammation triggering moieties (ITMs) in the system. By assuming a two-player game, where one body part is assumed to be playing with another body part, we were able to show how the body reacts to different concentrations of ITMs. Simulation results show that with lower concentrations of ITMs, majority of the neutrophils go into apoptosis, while with higher concentrations of ITMs, the system goes into necrosis. A critical value of ITM concentration where the system undergoes a transition into necrotic state is \( x_{ITM} = 0.8 \) for a system without death and recruitment mechanisms and even in a system with added death, recruitment and positive feedback mechanisms. Our findings would pave the way to better understand the behaviour of neutrophils using a novel approach such as game theory. Our future work will include validation of our model with actual data from clinical trials.

Acknowledgements


References

4. Conclusions

As inflammation is resolved, the system shifts its equilibrium to apoptosis. Hence, neutrophils then eventually die through natural death. It is not surprising, however, that the system seems to be locked into necrosis when the concentration of ITMs is set to a maximum.

Notice that there is no longer recruitment of activated neutrophils for ITM concentration lower than $x_{ITM} = 0.8$ (see Figure 4D), as seen at $x_{ITM} = 0.6$ for a system without death and recruitment positive feedback.

Simulation results show that with lower concentrations of ITMs, majority of the neutrophils go into apoptosis, while at $x_{ITM} = 0.8$ (see Figure 4A), the system is able to slowly resolve the inflammation over time. However, this concentration corresponds to the saddle point we saw earlier even without the added mechanisms of death, recruitment, and positive feedback.

Our future work will include validation of our model with actual data from clinical trials. This would pave the way to better understand the behaviour of neutrophils using a novel approach such as game theory.

Acknowledgements


References


