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### Understanding the human innate immune system

*In-silico studies*

Presbitero, L.A.

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# 2

## Evolutionary Game Theory and Modeling the Human Innate Immune Response

The human innate immune system (HIIS) is composed of a manifold of enzymes and cells that work together to protect the body from harmful stimuli. This adverse reaction comprises the interplay of a myriad of complex processes by HIIS' subcomponents. These immune cells interact among each other to set forth a well-orchestrated and targeted response designed to neutralize the insult. In fact, so well-orchestrated, that despite its complexity, it appears the processes are controlled by a central factor that limits the choices of sub-components to act in a way that is *not* necessarily beneficial to the subcomponents (cells or the surrounding local tissue), but nevertheless importantly beneficial to the organism.

In the first part of **Chapter 2**, I look at how two death pathways of neutrophils (apoptosis and necrosis), that have interestingly contradictory immediate effects on the body during inflammation, have been optimized by nature over the course of evolutionary time. Here I utilized a mathematical framework

called *evolutionary game theory* (EGT), that is suitable for optimizing competing goals or maximizing the fitness of a disparate number of interacting individuals or, in the context of EGT, the so-called *players* of the game.

Assuming that the percentage of apoptosis and necrosis that we observe in neutrophils is the result of optimization done by nature (presumably to maximize the chance of the organism's survival), I show as a validation that the driving mechanism that results in the optimized percentages of necrosis and apoptosis observed in the data is evidently the work of a central factor that is none other than the concentration of remaining inflammation triggering moieties (ITMs) in the system. On top of this, I incorporate concepts of cellular automata (CA) to incorporate spatial interactions that are observed in biological entities on a cellular level. Using CA coupled with the EGT framework, I investigate whether the choice of strategy (apoptosis or necrosis) is based on local interactions that occur among immediate neighbors of necrotic entities, or whether the optimized percentage of apoptosis or necrosis observed in data is driven by a much larger cause. It turns out indeed that the subcomponents of the innate immune response strategize for the greater good, hence providing numerical evidence that neutrophils need sufficient information, by virtue of cytoplasmic spill and release of cytokines, of the overall magnitude of inflammation to elicit an effective response to insult.

In the second part of **Chapter 2**, I look at various conditions when and how this sense of global cooperation crumbles<sup>12</sup>. Cooperation exists in various levels of biological systems. HHS is no exception. In this part of my thesis, I explore how cooperation propagates and eventually ceases to do so in a system when bombarded with stochasticity, despite having its subcomponents strategizing for the greater good. In HHS, this stochasticity may be the result of the body's inability to function effectively in times of disease. In this line of work, I show that a system that survives and works much like having a central control, cooperation can eventually crumble despite having a strong sense of homeostasis.

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# 2.1

## Game of neutrophils: modeling the balance between apoptosis and necrosis

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Presbitero, A., Mancini, E., Castiglione, F., Krzhizhanovskaya, V. V.,  
Quax, R.

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# 2.1

## Modeling the Balance Between Apoptosis and Necrosis Using Evolutionary Game Theory

### Abstract

**Background:** Neutrophils are one of the key players in the human innate immune system (HIS). In the event of an insult where the body is exposed to inflammation triggering moieties (ITMs), neutrophils are mobilized towards the site of insult and antagonize the inflammation. If the inflammation is cleared, neutrophils go into a programmed death called *apoptosis*. However, if the insult is intense or persistent, neutrophils take on a violent death pathway called *necrosis*, which involves the rupture of their cytoplasmic content into the surrounding tissue that causes local tissue damage, thus further aggravating inflammation. This seemingly paradoxical

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*Chapter 2.1 Modeling the Balance Between Apoptosis and Necrosis Using Evolutionary Game Theory*

phenomenon fuels the inflammatory process by triggering the recruitment of additional neutrophils to the site of inflammation, aimed to contribute to the complete neutralization of severe inflammation. This delicate balance between the cost and benefit of the neutrophils' choice of death pathway has been optimized during the evolution of the innate immune system. The goal of our work is to understand how the tradeoff between the cost and benefit of the different death pathways of neutrophils, in response to various levels of insults, has been optimized over evolutionary time by using the concepts of evolutionary game theory.

**Results:** We show that by using evolutionary game theory, we are able to formulate a game that predicts the percentage of necrosis and apoptosis when exposed to various levels of insults.

**Conclusion:** By adopting an evolutionary perspective, we identify the driving mechanisms leading to the delicate balance between apoptosis and necrosis in neutrophils' cell death in response to different insults. Using our simple model, we verify that indeed, the global cost of remaining ITMs is the driving mechanism that reproduces the percentage of necrosis and apoptosis observed in data and neutrophils need sufficient information of the overall inflammation to be able to pick a death pathway that presumably increases the survival of the organism.

**Keywords:** neutrophils, evolutionary game theory, apoptosis, necrosis

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### 2.1.1. Introduction

Neutrophils play a crucial role in the human innate immune response. These human immune cells are not only the most abundant among immune cells, but also are the first to arrive at the sites of insult, where they execute their anti-inflammatory functions<sup>77-79</sup>. Approximately  $10^{11}$  neutrophils circulating in the bloodstream undergo programmed cell death, also known as *apoptosis*, per day. Neutrophils still undergo this natural death process even under healthy conditions in order to maintain homeostasis<sup>80,81</sup>. In case of an insult, inflammation triggering moieties (ITMs) like bacterial lipopolysaccharides (LPS) and extracellular nucleotides induce inflammation, an essential mechanism of the innate immune response<sup>82</sup>. These ITMs are phagocytosed by active neutrophils or neutralized through the release of granules, depending on the nature of the ITMs. When inflammation is easily resolvable by the available population of immune cells at the site of inflammation, previously active neutrophils proceed to apoptosis<sup>83</sup>. However, if the inflammation is too intense or persistent, such as in systemic inflammation where ITMs are simultaneously originating from various sources in the body, neutrophils take on a dangerous death pathway called *necrosis*. Necrosis is a violent cell death that involves the rupture of the cell membrane, spilling out its cytoplasmic contents into the site of inflammation, thus further aggravating the inflammation. Necrosis is one of the major causes of tissue damage during inflammation, contributing to sepsis and potentially leading to lethal complications during the inflammation. It has been observed that the proportion of neutrophils going into either death pathway depends on the scale of the insult<sup>84,85</sup>. The intricate details and the underlying mechanisms regarding the resolution of inflammation by neutrophils is still an active evolving field. For a comprehensive review, see<sup>86</sup>.

It is reasonable to assume that the tradeoff between the evolutionary cost and benefit of inflammation, more specifically the choice of death pathway

for neutrophils in response to various levels of insults, is the result of an optimization performed by evolution during the development of the human immune system. We refer to the cost and benefit as the overall factors that affect the reproduction rate and the energetic cost of the organism.

In the modern era where availability of medical treatment has paralleled the surge of technology, and novel breakthroughs in modern medical research and development has redefined state-of-the-art medical care <sup>87</sup>, the human physiology, however, is not optimized with respect to the modern environment because evolution happens on a much larger timescale than a few centuries. Consequently, the body's tendency to "overreact" to pathogens in the form of inflammation might be unnecessarily large in terms of intensity when faced with the present environment as compared to the environment millennia ago, when healthcare was not yet developed. It has been hypothesized in a seminal work by Okin et al. that given the high-cost feature of the human inflammatory response, a suboptimal tradeoff between the cost and benefit of inflammation has a high probability to adversely affect the fitness thus causing disease <sup>88</sup>.

In the present article we extend the concepts presented in <sup>89</sup> by introducing the use of evolutionary game theory to model the choice of death pathways in neutrophils given an initial concentration of inflammation triggering moieties (ITMs). To the best of our knowledge, this is the first time that a subsystem of the innate immune response is modeled in the context of evolutionary game theory. Existing models found in literature use ordinary and partial differential equations <sup>7,48,50</sup>, as well as agent-based and cellular automata models <sup>90-92</sup>. In the previous article <sup>89</sup>, we limited our study to the use of mean-fields as scheme of interactions between neutrophils. Here, we introduce the use of cellular automata to better detail these interactions and to conform to the realistic limitation of the propagation of stimuli due to the physical constraints of biological tissues.

For the sake of simplicity, we will assume the human body to be an

ensemble of biological (cellular) components somehow (i.e., directly or indirectly) interacting with and influencing each other. These cellular components are neutrophils that could either go into *apoptosis* or *necrosis* when responding to an insult in a specific body tissue. Since the choice of pathway of one neutrophil could influence that of another, we utilize the concept of game theory in which components of the system can “play” among them and where their interactions determine the fate (the dynamics) of the system. Game theory is a branch of mathematics dealing with interactions between “rational decision makers”, called *players* (e.g., neutrophils in tissue in our case), where each player can perform one of several actions called *strategies* (e.g., here apoptosis or necrosis), based on well-defined preferences among various outcomes represented by numerical *payoffs*.

The classic interpretation of game theory is that the analyzed *game* (i.e., the game of neutrophils) can be played exactly once by fully rational individuals who know the details of the game, which include the outcomes of each other’s strategies. *Evolutionary game theory*, on the other hand, considers the game that is played repeatedly over a long period of time by living entities that are “pre-programmed” to choose a certain strategy<sup>93</sup>. In the context of this study, a living entity can therefore only choose a single strategy in a single lifetime and the game is played by different generations of population of players for long periods of time. In essence, evolutionary game theory combines evolutionary ecology with game theory.

The benefit of apoptosis is apparent, since apart from getting rid of a small amount of ITMs, it also triggers macrophages to secrete anti-inflammatory mediators like anti-inflammatory cytokines, which lead to the resolution of inflammation<sup>83</sup>. In contrast, necrosis carries a risk to the body as it triggers death of a cell that damages the surrounding tissue, further aggravating inflammation. Yet on the other hand, necrosis indirectly triggers potentially life-saving actions such as the recruitment of more neutrophils into the site

of inflammation by releasing pro-inflammatory mediators called pro-inflammatory cytokines. In other words, necrosis sacrifices a “local” cost to the tissue while simultaneously leading eventually to a “global” benefit to the organism (surviving and reproducing).

We define necrotic neutrophils in tissue (*necrotic entities*), in the context of game theory, as *cooperators* or *altruists* because these players are willing to undergo a violent death as well as inflict local tissue damage for the greater good. To conform with the EGT common terminology, we further define apoptotic neutrophils in the tissue (*apoptotic entities*) as *defectors* or *cheaters* for the reason that these *cheaters entities* in fact acquire a number of benefits due to the “sacrifice” made by the altruist *necrotic entities*. Given the inherently stochastic nature of biological processes, we formulate the “game of neutrophils” as a mixed strategy game: players could choose a strategy with a certain probability, which is interpreted as the fraction of the population choosing a set of strategies. The payoffs correspond to the evolutionary fitness, and the game dynamics acquired correspond to the stable evolutionary population dynamics observed in biological systems and as the outcome of the evolutionary game<sup>94,95</sup>. We hypothesize that the scale of insult pertaining to the concentration of ITMs that remain in the system is the main force that dictates the optimized balance of apoptosis and necrosis that most likely ensures the survival of the system. By using evolutionary game theory, we are able to verify that the global cost of remaining ITMs is the driving mechanism that describes the balance between the two death pathways for neutrophils given the level of insult as well as interpret on a molecular level how this balance is achieved by coupling evolutionary game theory with cellular automata.

### 2.1.2. The Neutrophil Game

The neutrophil game is a two-player game that utilizes either of two strategies namely: *necrosis* and *apoptosis*. The payoffs for each pair of strategies are summarized in **Table 3**. A row corresponds to the strategy

played by player 1 and a column corresponds to the strategy played by player 2. The neutrophil game follows a mixed strategy game, meaning, we assign a probability for each strategy. This allows a player to probabilistically choose between apoptosis and necrosis. The rationale behind this choice is that the pathways leading to apoptosis or necrosis depend on a series of biochemical reactions in response to external stimuli and internal processes of the cell. All these processes are stochastic, so that a cell exposed to a given environment might take one pathway or the other with a certain probability. In our model, player 1 chooses to go into necrosis with a probability  $q$  and apoptosis with a probability  $(1 - q)$ . Player 2, on the other hand, chooses to go into necrosis with a probability  $p$  and apoptosis with a probability  $1 - p$ .

The neutrophil game is a symmetric game where all players are of the same type, leading to a symmetric payoff matrix. For instance, both players 1 and 2 will receive a payoff of C if *playing Apoptosis* while the other player is *playing Necrosis*.

**Table 3.** Payoff Matrix of the Neutrophil Game.

		Player 2	
		Necrosis ( $p$ )	Apoptosis ( $1 - p$ )
Player 1	Necrosis ( $q$ ) <i>m</i> : ITMs neutralized by granules per necrotic neutrophil	$A, A$	$B, C$
	Apoptosis ( $1 - q$ ) <i>n</i> : ITMs neutralized by granules per apoptotic neutrophil	$C, B$	$D, D$

We specify the payoffs of the neutrophil game as follows:

$$A = -c_{Necrosis} \quad (34)$$

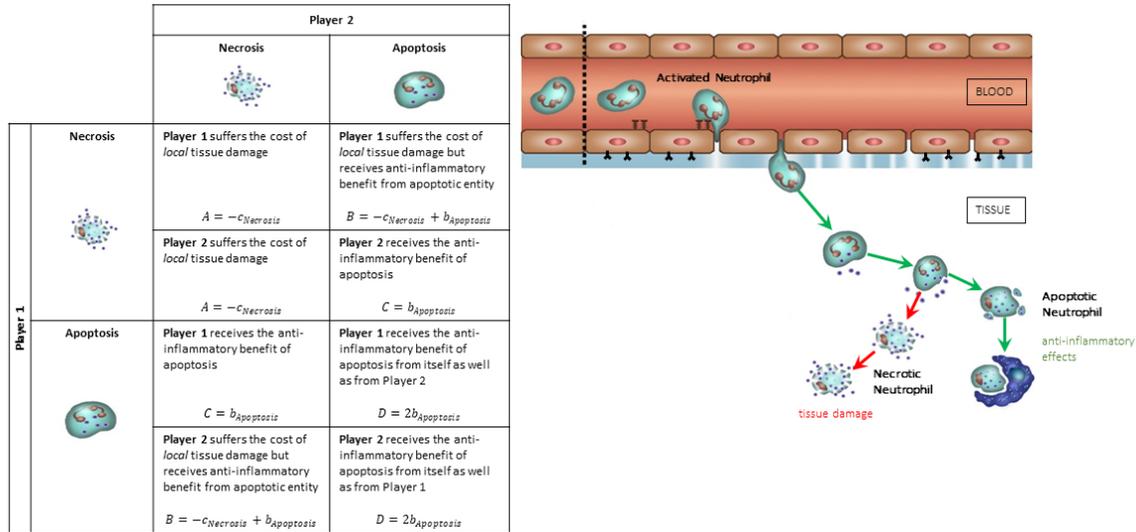
$$B = -c_{Necrosis} + b_{Apoptosis} \quad (35)$$

$$C = b_{Apoptosis} \quad (36)$$

$$D = 2b_{Apoptosis} \quad (37)$$

When a necrotic entity plays the game with another necrotic entity, they both receive the cost  $c_{Necrosis}$ , which biologically corresponds to the local tissue damage caused by the spilling out of the neutrophil's cytoplasm contents into the surrounding tissue. A necrotic entity playing with an apoptotic entity receives a cost  $c_{Necrosis}$  corresponding to the tissue damage, and the benefit of apoptosis  $b_{Apoptosis}$  corresponding to the anti-inflammatory effects of apoptosis during inflammation. It also follows that an apoptotic entity playing with another apoptotic entity receives  $2b_{Apoptosis}$ .

An overview of the biological mechanism and its mapping to evolutionary game theory is summarized in Figure 12.



**Figure 12. Biological Mechanism to Evolutionary Game Theory Mapping.** In the case of an insult or presence of inflammation triggering moieties in the tissue, neutrophils circulating the bloodstream enters the tissue through the endothelial barrier. After the inflammation is fully neutralized by the neutrophils, they go into a programmed death called apoptosis, which has anti-inflammatory effects on the system. However, if the insult is too intense or persistent, the neutrophils take on a violent death pathway called necrosis that involves spilling out all of its cytoplasmic contents into the surrounding tissue, causing local tissue damage and further aggravating inflammation. The table on the left summarizes the payoff matrix of the game that the neutrophils play. In the event that both players play necrosis, each of them suffers a cost of  $c_{Necrosis}$ , pertaining to the local tissue damage each one endures. However, in the case when both players play apoptosis, each one of them receives the benefit of apoptosis from itself as well as from the neutrophil it is playing with, garnering a payoff to a total of  $2b_{Apoptosis}$ .

### 2.1.3. Mean-field Scheme

Let  $F(q, p)$  be the average payoff to an individual playing necrotic “ $q$ ” of the time in a population which overall plays Necrotic “ $p$ ” of the time.

$$F(q, p) = qpA + q(1 - p)B + (1 - q)pC + (1 - q)(1 - p)D - e^{\alpha ITMs_{remaining}} \quad (38)$$

The last term in (38) models the cost of the remaining ITMs in the system. An exponential is chosen to ensure that the last term in (38) does not become negative. In addition, by using this exponential term, we were able to match our model against the data as shown in the Results and Discussion (Data Parameter Space), as well as being amenable to analytical simplification. However, we do suspect that sub-linear forms such as logarithms would not work since it would not necessarily outweigh the linearly increasing positive pay-off contributions. We assume that the term  $\alpha ITMs_{remaining}$  in Equation (38) corresponds to the global cost of the individual playing necrotic with probability  $q$  due to the “threat” of remaining ITMs in the system, where  $\alpha$  is the “strength” of this global cost that we have calibrated against the data presented in Results and Discussion.  $ITMs_{remaining}$  is defined as follows:

$$ITMs_{remaining} = ITMs_{initial}^k - pm(N_T - 1) - qm - (1 - p)n(N_T - 1) - (1 - q)n \quad (39)$$

where  $ITMs_{initial}$  corresponds to the initial concentration of ITMs,  $N_T$  is the total number of neutrophils,  $n$  corresponds to the amount of ITMs a single apoptotic neutrophil could neutralize while  $m$  is the amount of ITMs a single necrotic neutrophil eventually neutralizes through the recruitment of additional neutrophils, and  $k$  models the observed power law behavior in the data <sup>84</sup> of necrotic neutrophil population with respect to the initial concentration of ITMs. See Section 2.1.7 for a more detailed explanation of how  $k$  was obtained.

John Forbes Nash demonstrated that there is always at least one mixed strategy equilibrium in a finite (i.e., having a finite number of strategies, in our case two) game <sup>96</sup>. In order to find this equilibrium, we calculate the optimal strategy of a player choosing necrosis with probability  $q$  by taking the partial derivative of Equation (38) with respect to  $q$  and equating it to zero as shown in Equation (40).

$$\begin{aligned} & \frac{dF(q, p)}{\delta q} \\ &= pA + (1 - p)B - pC - (1 - p)D \\ & - \alpha(n - m)e^{\alpha[ITMs_{initial}^k - pm(N_T - 1) - qm - (1 - p)n(N_T - 1) - (1 - q)n]} = 0 \end{aligned} \quad (40)$$

Because  $F(q, p) = F(p, p)$  when the optimal  $q^* = p$ , it is clear to see that  $F(q, p)$  reaches a *maximum* at  $q^* = p$ , provided that  $0 < p < 1$ . Hence, the optimal  $q^*$  must be equal to  $p$  in the stationary state. In fact, it would be internally inconsistent if each neutrophil decides with probability  $q$  while at the same time the population average remains probability  $p \neq q$ .

The optimal value  $p = q^*$  represents the optimal population of necrotic neutrophils given the values of payoff  $b_{Apoptosis}$ ,  $c_{Necrosis}$ , global cost factor  $\alpha$ , neutralizing factors  $m$  and  $n$ , total neutrophils  $N_T$ , and  $ITMs_{initial}$ .

$$p = q^* = - \frac{\ln\left(\frac{b_{Apoptosis} + c_{Necrosis}}{\alpha(m - n)}\right) + \alpha n N_T - \alpha ITMs_{initial}^k}{\alpha m N_T - \alpha n N_T} \quad (41)$$

with the following technical constraints:

$$\begin{aligned} & b_{Apoptosis} + c_{Necrosis} \neq 0 \\ & m \neq n \\ & \alpha \neq 0 \end{aligned} \quad (42)$$

In conclusion, we can define the average fitness  $F(q, p)$  of necrosis by using the payoffs specified in **Table 3** together with the global cost of the

remaining ITMs. In our model we optimize this average fitness during evolutionary time. The game is played via mean-field interactions between players represented by the average evolutionary fitness in Equation (38). The game ends when an evolutionary stable point is achieved as specified in Equation (40). This means that the percentage of necrotic population does not change anymore through evolutionary time and is calculated in Equation (41). The outcome of this evolutionary game corresponds to the stable population dynamics, which we can then compare to that of biological systems.

#### 2.1.4. Cellular Automata

What we have described so far is a mean-field type of interaction where neutrophils interact with equal probability with *all* the other neutrophils in the system. In other words, each neutrophil "*plays*" the game with *the ensemble of all* other neutrophils. However, in biological systems these interactions among neutrophils (either direct or indirect through the release of cytokines and other stimuli) are spatially limited by the characteristic lengths of biological signals (such as diffusion lengths) that characterize the extent at which these stimuli are released and propagated in the body. Hence, a mean-field assumption may neglect the role of spatial interactions observed in biological systems<sup>91</sup>, and may not in fact represent faithfully what we observe biologically in real systems.

By utilizing cellular automata, we aim to gain deeper insights into the microscopic interactions that occur among neutrophils when spatial proximity is taken into account<sup>91</sup>. We model this type of interaction by utilizing cellular automata as follows.

First, we create an empty lattice of size  $50 \times 50$ . In our model, the entire lattice space is interpreted to correspond to a small portion of tissue. In order to model a bigger tissue that represents the entire body, we use periodic boundary conditions in our simulations. Additionally, since we assume a systemic inflammation, where ITMs are simultaneously originating from various sources in the body, we assume that the

concentration of ITMs are equally distributed all over the simulated lattice. This follows that the distribution of the neutrophils in the tissue should also be homogenous. Hence, a single lattice site is occupied by a *neutrophil entity*, which, in the context of our model, refers to the neutrophil cell and the tissue the neutrophil occupies. The  $50 \times 50$  lattice site, therefore, contains a total of 2500 neutrophils. Because we do not have spatial information of choice of death pathway, we picked the simplest topological feature, which is a square lattice site. We assume that the exact local spatial structure is not important, as long as the locality of the interactions between neighboring neutrophils in the tissue is reproduced in order to allow for local fluctuations.

Biologically, 2500 neutrophils occupy a volume of  $1 \text{ mm}^3$  in the blood <sup>62</sup>. However, this volume is increased by a factor of 15 as the neutrophils diffuse from the bloodstream, a smaller “chamber” with volume approximately equal to 5 Liters, into the tissue, which is a much larger “chamber” of 75 Liters, assuming an 80 kg person. One could then imagine that these 2500 neutrophils will be occupying a volume of  $15 \text{ mm}^3$  in the tissue, where a single neutrophil occupies a  $6 \mu\text{m}^3$  and the distance from one neutrophil to the other is  $6 \mu\text{m}$ . Our model is a simplification of the dynamics of neutrophils in two dimensions, due in part to the limitation of spatial information in the data. Hence, our lattice site that contains 2500 neutrophils corresponds to a  $0.3 \text{ mm}^2$  patch of tissue. Neutrophils are able to “communicate” with each other via the spillage of cytoplasmic content or the release of chemical signals such as cytokines. The distance of one lattice site to the adjacent site corresponds to  $6 \mu\text{m}$ , which is a value that is in fact well within the communication range of neutrophils via messenger proteins called cytokines <sup>97</sup>. Hence, a neutrophil entity is well able to communicate with its nearest neighbors. We simplify this scenario in our model by putting the neutrophil entities next to each other in the lattice. Additionally, this reduced the processing time as the range of the Moore neighborhood is simply a lattice site away.

ITMs are introduced homogenously by distributing the total ITM concentration equally in the lattice. In the simulation, this is simply

calculated by assigning the concentration of ITMs to a global value that is neutralized at every iteration step, which corresponds to when an activated neutrophil picks a strategy.

The algorithm commences by choosing an activated neutrophil randomly inside the 50x50 lattice that is initially filled with 2500 activated neutrophils. The chosen activated neutrophil plays the game based on the payoffs summarized in **Table 3** with all of its immediate neighbors in a Moore neighborhood of range equal to 1<sup>98</sup>.

The choice of strategy of an activated neutrophil is decided based on a fitness comparison made by choosing either strategy. The payoff the activated neutrophil gets from playing with *all* its immediate neighbors is subtracted by the cost of the remaining ITMs in the system. We emphasize that the fitness calculated in cellular automata is similar to the fitness we calculated in the mean-field scheme: the fitness for picking a strategy is subtracted by the cost or “threat” of the presence of ITMs that remain in the system. This total payoff is compared for either apoptosis or necrosis. The strategy with the greater payoff is chosen as the winning strategy for the current iteration.

When the payoffs for going into apoptosis is exactly the same as deciding on necrosis, the activated neutrophil takes the apoptotic pathway. We model it this way because we assume that apoptosis is the default pathway that neutrophils take with or without inflammation. It is after all a type of programmed death that take place regardless of the intensity of inflammation.

The process for a single activated neutrophil choosing a strategy corresponds to a single iteration in the algorithm. The same steps are done to all the activated neutrophils in the lattice. Hence, the algorithm stops when all activated neutrophils have picked a strategy. The outcome is a percentage of necrosis as well as apoptosis given the initial concentration of ITMs.

What is known so far is that the more intense the inflammation is, the greater

the percentage of necrosis. This means that in one way or another, neutrophils have a way of “sensing” any presence of threat in the system either directly from the concentration of ITMs nearby or indirectly via release of chemicals from other neutrophils and immune cells. Mechanisms regarding the recruitment of neutrophils into the site of inflammation have been well-documented and is still largely an active field<sup>99–101</sup>. However, the extent to which an activated neutrophil “senses” this threat, remains relatively unknown. What is known is that neutrophils are directed towards an inflammation via the release of pro-inflammatory cytokines. Pro-inflammatory cytokines are produced by macrophages upon engulfment of ITMs at the site of inflammation. Pro-inflammatory cytokines are also produced when necrotic neutrophils neutralize ITMs. On the other hand, anti-inflammatory cytokines, which controls the response of pro-inflammatory cytokines, are secreted by macrophages upon phagocytosis of apoptotic neutrophils. Hence, we introduce two hypothetical mechanisms for calculating fitness, which will hopefully shed light to the biological mechanisms: *Local ITMs Scheme* and *Global ITMs Scheme*.

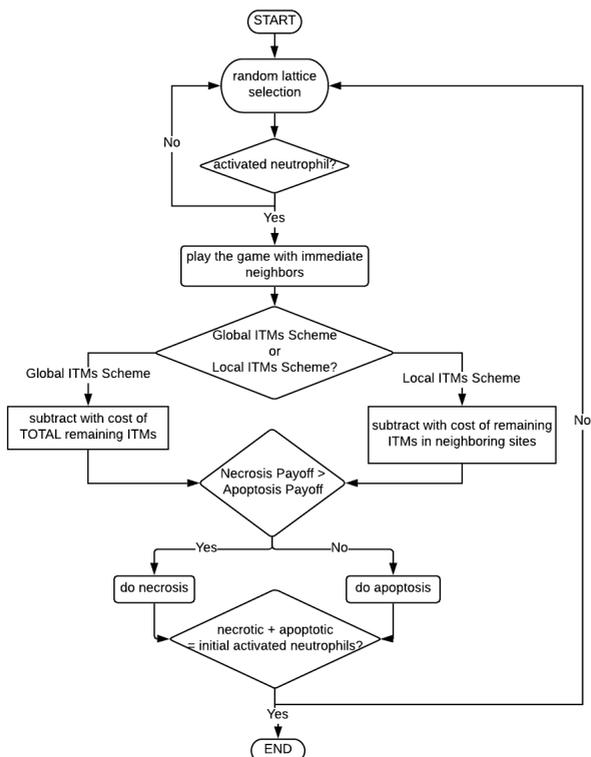
***Local ITMs Scheme*** explores the assumption that activated neutrophils choose to go into apoptosis or necrosis based on two conditions: 1) intensity of *local* inflammation – pertaining to the concentration of ITMs that are in its proximity and 2) strategies of its immediate neighbors, which considers the summation of strategies within the neighborhood much like a majority rule. This condition is based on the cumulative effect of the release of stimulators, such as pro- and anti-inflammatory cytokines by apoptotic and necrotic neutrophils that are located within the immediate neighborhood of the activated neutrophil.

***Global ITMs Scheme***, is motivated by the assumption, alternative to the one used in the local ITMs Scheme, that activated neutrophils “sense” the overall intensity of the ITMs as a result of faster diffusion of cytokines that would provide information about the overall state of inflammation in the tissue. In this scheme, activated neutrophils pick a strategy based on two conditions: 1) the cost of remaining ITMs is calculated for the entire lattice space and

2) the cumulative strategies of its immediate neighbors. This is under the assumption that the release of neutrophil by either apoptotic or necrotic neutrophils are limited only within the immediate neighborhood where the activated neutrophil is located.

We emphasize that condition 2 is the same for both local and global schemes. We claim that sensing ITMs at a long distance is mediated by the diffusion of cytokines. On the other hand, sensing the strategy of another neutrophil in the system is related to the spill of cytoplasmic content which we assume to diffuse at a slower speed. Hence, we only look into immediate neighbors surrounding the activated neutrophil and assume that cytokines diffuse faster than the cytoplasmic spill.

The summary of the cellular automata algorithm used is summarized in Figure 13. The algorithm starts with a random lattice selection that is done on a lattice initially occupied by activated neutrophils. If the selected neutrophil is an activated neutrophil (and not an apoptotic or necrotic neutrophil, which shall be present in the succeeding runs) the chosen activated neutrophil plays the game with its immediate neighbours. Depending on whether the ITMs scheme is global or local, the cost of remaining ITMs is consequently calculated. If the payoff for necrosis is greater than the payoff for apoptosis, the activated neutrophil goes into necrosis. Otherwise, it goes into apoptosis. The choice for apoptosis or necrosis corresponds to a single iteration in the cellular automata algorithm. A checkpoint is then established (see diamond with text "necrotic + apoptotic = initial activated neutrophils?"), which counts the total number of apoptotic and necrotic neutrophils. If this value is equal to the initial number of activated neutrophils, implying that all activated neutrophils have gone into either apoptosis or necrosis, the algorithm ends. Otherwise, a random lattice selection is made again until the checkpoint condition is satisfied.



**Figure 13. Summary of the Cellular Automata Algorithm.** The iteration starts by randomly choosing a single activated neutrophil in the lattice. The chosen activated neutrophil then plays the game with all its immediate neighbors by calculating a payoff that is based on the payoff matrix specified in **Table 3**. The cost of remaining ITMs, on the other hand is calculated depending on the ITMs scheme (local or global) selected. The strategy with the higher payoff wins the game and is therefore chosen for this iteration. The absence of an activated neutrophil in the lattice means the end of the algorithm. The final number of apoptotic and necrotic neutrophils are counted.

### 2.1.5. Code Implementation and Repository

We used Python 3.7 on a 3.30 GHz Intel® Core™ i7-5820K CPU with 16.0 GB RAM in all our simulations. The code has been uploaded to <https://github.com/avpresbitero/GON>.

### 2.1.6. Model Results for a Changing Environment

In this section, we take a closer look into how the mechanisms we have

identified ( $\alpha$ ,  $b_{Apoptosis}$ ,  $c_{Necrosis}$ ,  $m$  and  $n$ ) contribute to the final distribution of necrotic and apoptotic strategies in the system. In order to do this, we explore how nature plays the evolutionary game to arrive at optimal fractions of neutrophil population when certain parameters are varied. The motivation for this is that certain factors that affect the cost and benefit of choosing either strategy is assumed dependent on the type of environment the human body is exposed to. We have identified the following parameters  $\alpha$ ,  $b_{Apoptosis}$ ,  $c_{Necrosis}$ ,  $m$  and  $n$  as determining factors to the fitness of neutrophils. However, due to a high degree of freedom that our model exhibits, a global sensitivity analysis would not deliver meaningful results. Hence, we vary the parameters one at a time for different values of  $m$  and look at the effect it has on the stable distribution of strategies in the system.

We start by looking at the optimal fractions of necrotic populations ( $p$ ) by simultaneously varying the cost of necrosis ( $c_{Necrosis}$ ) and the amount of ITMs a single apoptotic neutrophil can neutralize ( $n$ ) in Figure 14 (*left column*) while fixing parameters  $\alpha$ ,  $b_{Apoptosis}$ , and  $m$ . Using our model, we show that the system evolves to an optimal fraction of necrotic and apoptotic neutrophils that corresponds to an increasing cost of necrosis as well as increasing capacity of ITM neutralization by apoptotic neutrophils as the insult intensifies. For the system to survive increasing threat due to ITMs, the system to increase its ITM resolution capacity by increasing  $n$  while also making it costly to go into necrosis. Necrosis, in the biological point of view, has detrimental effects to the system brought about by aggravating the initial level of inflammation by generating more ITMs.

Next we vary the global cost ( $\alpha$ ) and benefit of apoptosis ( $b_{Apoptosis}$ ) while fixing  $c_{Necrosis}$ ,  $n$ , and  $m$  as shown in Figure 14 (*middle column*). Here we show that the system copes with increasing levels of insult by shifting the optimized fractions of neutrophils towards decreasing global cost and increasing the benefit of apoptosis. With all other parameters held constant, that is with a fixed ITM neutralizing capacity of both apoptotic and necrotic neutrophils coupled with also a fixed cost of necrosis, nature plays an evolutionary game where the system copes with an increasing level of insult

by lowering the cost imposed by the remaining ITMs and also by increasing the benefit that can be reaped from the act of apoptosis via anti-inflammatory factors.

Finally, in Figure 14 (*right column*), we vary  $b_{Apoptosis}$  and  $c_{Necrosis}$  while fixing the values for  $n$ ,  $m$  and  $\alpha$ . Here we show that with increasing intensity of insult, the optimized fractions of neutrophils are achieved after playing the game only with increasing contributions from the cost of necrosis and benefit of apoptosis. Hence, by increasing the cost to go into necrosis coupled with increasing the anti-inflammatory effects of apoptosis, the game finds stable concentrations of neutrophil populations.

There is an apparent transition of strategy from largely necrosis to apoptosis (that is, from dominantly red to blue from left to right) as  $n$  (left column),  $b_{Apoptosis}$  (middle column) and  $c_{Necrosis}$  (right column) increases, thus favoring apoptosis. Hence, we interpret that increasing the cost of necrosis lowers the fitness for the necrotic strategy. Therefore, the system stabilizes into apoptosis (apparent in left and right columns). Conversely, increasing the cost of remaining ITMs ( $\alpha$ ) in the system shifts the equilibrium to necrosis. Note that we also see the same trends when  $\alpha$  is plotted with respect to  $c_{Necrosis}$ , the same as what we see in the middle column. Hence, with increasing initial concentrations of ITMs, the stable evolutionary strategies are shifted towards increasing  $c_{Necrosis}$ .

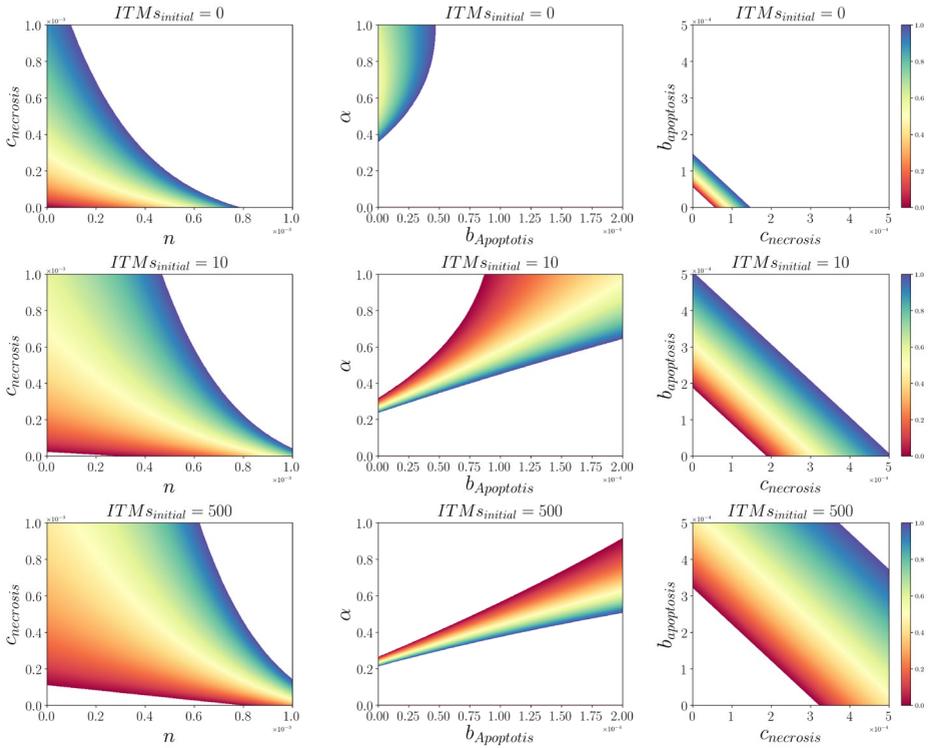


Figure 14. Exploring the payoff matrix for (left column)  $c_{Necrosis}$  and  $n$ , (middle column)  $\alpha$  and  $b_{Apoptosis}$  and (right column)  $b_{Apoptosis}$  and  $c_{Necrosis}$  with varying  $ITMs_{initial}$ . The colors correspond to the evolutionary stable fraction of necrotic neutrophils after the game is played for varying concentrations of initial insult. A system that stabilizes at necrosis is shown dominantly red. Conversely, a system that stabilizes at apoptosis is shown in blue. Note that black area denotes solutions that are invalid. This includes  $p$  (fraction of necrotic neutrophils) that do not lie within the interval  $[0,1]$ , and those that do not obey the constraints set in Equation (42).  $N_T = 2500$  was held constant for all simulations. On the left column, we set the value  $\alpha = 1.0$ ,  $b_{Apoptosis} = 0.0001$ , and  $m = 0.0015$ . In the middle column,  $n = 0.0004$ ,  $m = 0.0008$ ,  $c_{Necrosis} = 0.0001$  were held constant. In the right column,  $\alpha = 1.0$ ,  $n = 0.0004$ , and  $m = 0.0008$  were fixed. The black area corresponds to invalid solutions.

### 2.1.7. Data Parameter Space

Following the observation in <sup>84</sup>, it was shown *in-vitro* that the proportion of neutrophils going into apoptosis or necrosis actually depends on the scale of insult. We utilize data on the peak values of necrotic population at time point 24 hours. We also used an additional finding by Damas et al where they

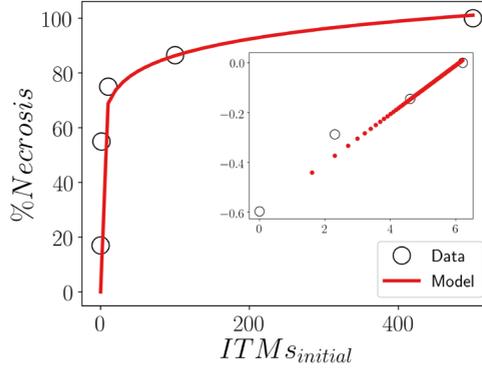
show that 500 ng/ml LPS corresponds to the fatal concentration of LPS in humans, <sup>53</sup>. This corresponds to 100% necrosis, where the level of inflammation becomes uncontrollable due to the growing detrimental effects of local tissue damage generated from necrosis and the lack of anti-inflammatory functions from apoptosis. We are well aware that the assumptions we make using our model is limited by the data that we have at the moment. In particular, the power-law relation may turn out to actually be a different functional relationship when more data would be collected. However, the current work aims to provide baseline research to show what the concepts behind the model can do. Although the analytical derivations would change, we believe that the main methodology and qualitative conclusions would remain unchanged. Hopefully, our work motivates other researchers to take a deeper look into these concepts as well as invites stakeholders to generate additional data.

The data in <sup>84</sup> reports a 17% baseline level of necrosis even in absence of ITMs. This might be due to experimental setup and other laboratory procedures of the in-vitro experiment. However, it is reasonable to assume that no necrosis occurs in-vivo in absence of ITMs). Additionally, the data is not normalized since in the experiments not all neutrophils measured were in apoptosis or necrosis. For this reason, we correct the population of necrotic neutrophils in the data by normalizing it with respect to the total percentage of apoptotic and necrotic neutrophils used in the *in-vitro* study. This normalization is necessary since our model does not take into account the population of activated neutrophils that have not yet gone into apoptosis or necrosis. We show that, after such normalization, the percentage of necrotic neutrophils seem to exhibit a power-law behavior with respect to the initial concentration of ITMs that trigger an inflammatory response.

We model this power-law behavior in Equation (43):

$$p - \gamma = \beta \cdot ITMs_{initial}^k \quad (43)$$

where  $ITMs_{initial}$  corresponds to the initial concentration of ITMs,  $k = 0.0929$ ,  $\beta = e^{-0.6}$  and a constant term  $\gamma$ , which we will explain shortly. In the log-log plot we observe a linear relation between percentage of necrosis with respect to the initial concentration of ITMs. This relation has an intercept on the y axis of  $-0.6$  and a slope  $k$  equal to  $0.0929$ .



**Figure 15. Data Distribution and Model Output in Terms of Percent Necrosis (*main*) and Corresponding Log-Log Plot (*inset*).** Based on the log-log plot, the percentage of necrotic neutrophil population follows a power-law behavior with power  $k = 0.0929$ . However, at initial concentration of 10 ITMs, the data point seems to deviate from this power law behavior (*inset*), which is also seen slightly higher than the predicted percent necrosis (*main*).

However, the data report 17% necrosis even without the presence of LPS. In order to remove this baseline amount of necrosis from the experimental dataset, we subtract a constant term  $\gamma = 0.17$  in the power-law equation. We consider this baseline necrosis as originating from sources other than a systemic inflammation, which we do not take into account in our model.

In order to determine the parameter space of the EGT model which reproduces this experimental relation, we compare Equation (43) with Equation (41). It is easy to see that  $\gamma$  and  $\beta$  are as follows:

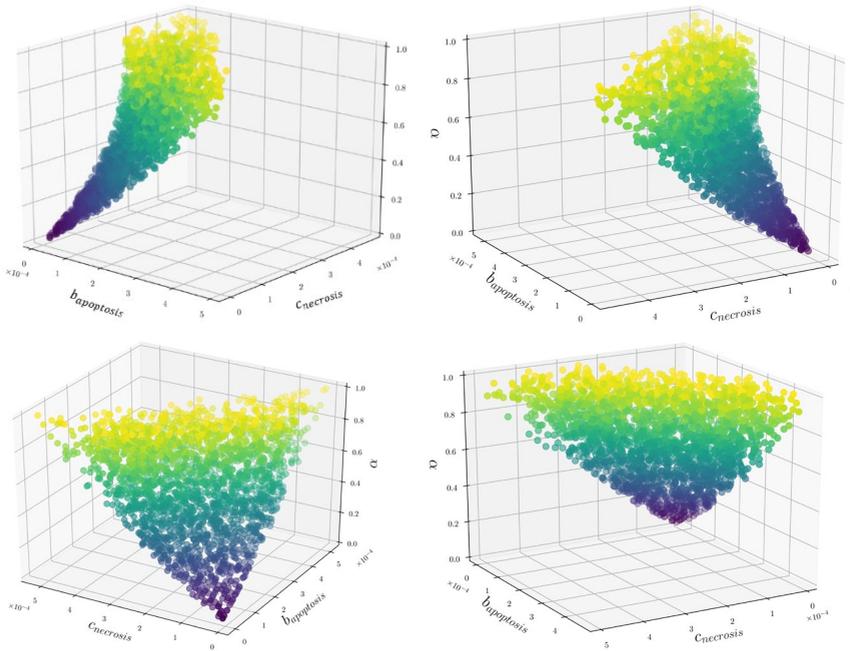
$$\gamma = - \frac{\log\left(\frac{b_{Apoptosis} + c_{Necrosis}}{\alpha(m-n)}\right) + \alpha n N_T}{\alpha m N_T - \alpha n N_T} \quad (44)$$

$$\beta = \frac{1}{N_T(m - n)} \quad (45)$$

We can reduce this 5-dimensional parameter space  $(b_{Apoptosis}, c_{Necrosis}, m, n, \alpha)$  to 4 dimensions by extracting  $n$  from (45), which is the equation shown in (46).

$$n = m - \frac{1}{N_T\beta} \quad (46)$$

Based on Equations (44) to (46), we are able to identify the parameter space for which the relation between necrosis and ITMs reported in the dataset is fulfilled. In order to visualize the parameter space that satisfies all our conditions we plot the solutions in Figure 16 to Figure 18.

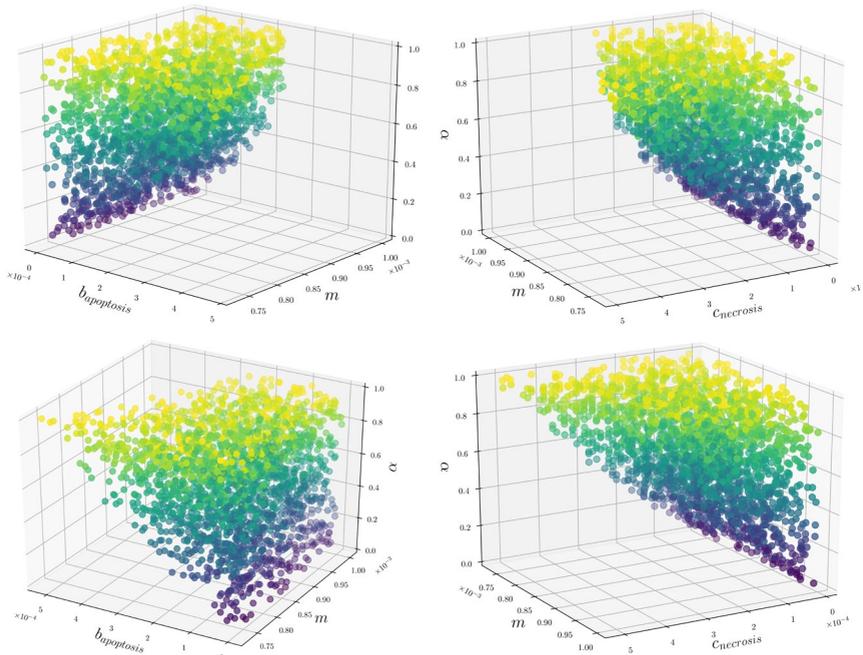


**Figure 16. Data Parameter Space ( $\alpha$ ,  $b_{Apoptosis}$ ,  $c_{Necrosis}$ ).** Each point in the plot corresponds to the combination of parameters that satisfies the data. This 3-dimensional parameter data space can be better visualized via an interactive plot, which we have uploaded to the following link: <https://github.com/avpresbitero/EGTN> (1). The colors are chosen only to add visual depth to the plot, where purple to yellow corresponds to increasing values of  $\alpha$ . Nature has evolved into stable percentage of necrotic and apoptotic neutrophils that correspond to a set of parameters ( $\alpha$ ,  $b_{Apoptosis}$ ,  $c_{Necrosis}$ ) that exhibit direct proportionality towards each other. That is, with higher cost of necrosis, higher values for global cost of remaining ITMs is preferred. This shows that nature made necrosis to be damaging on purpose for the organism to make sure that this event only happens a few times, that is, only when necessary.

Nature, through a course of evolutionary time, has driven neutrophils to adopt these specific set of parameter values shown in Figure 16. We show that the system evolved into stable percentages of neutrophil population that correspond to a combination of values of  $\alpha$ ,  $b_{Apoptosis}$ ,  $c_{Necrosis}$ , where these three parameters have direct proportionality towards each other. That is, nature plays the evolutionary game and achieves stable percentages of neutrophil population by simultaneously opting for lower cost of going into necrosis while the global cost of remaining ITMs is also low. With higher cost of necrosis, higher values for the global cost of remaining ITMs is

preferred. A higher cost for necrosis means further aggravating the current level of inflammation by inducing local tissue damage that increases the ITM levels in the system. The system, in response, imposes higher global cost of remaining ITMs in the system. This goes to show that nature might have made the necrosis death pathway purposely damaging to the organism so that the fitness will make sure that the events of necrosis are done only as few times as possible.

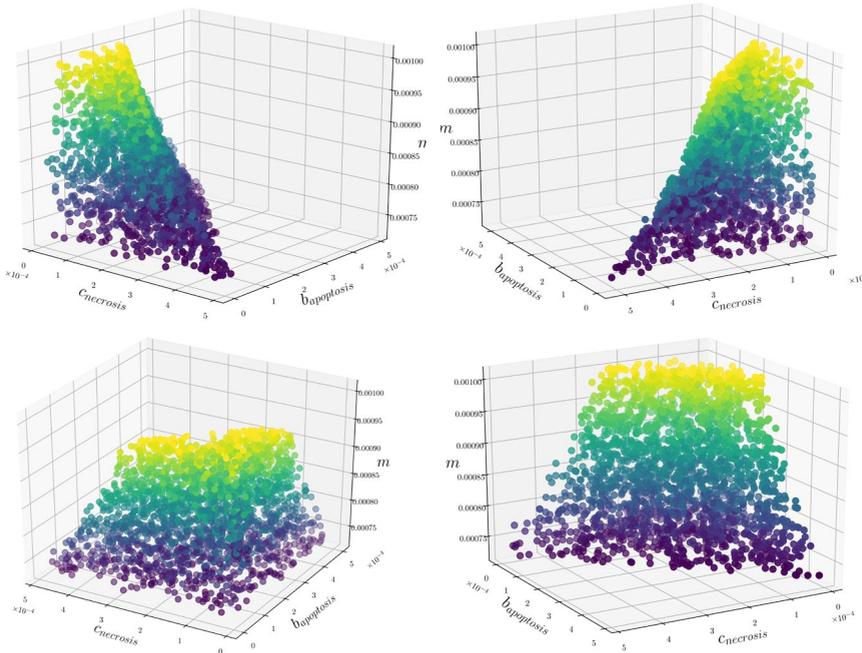
We visualize the same data parameter space in terms of parameters  $m$ ,  $b_{Apoptosis}$ ,  $\alpha$  on the left panel (A) and  $m$ ,  $c_{Necrosis}$ ,  $\alpha$  on the right panel (B) of Figure 17. We show that when the threat of remaining ITMs is high, the evolutionary stable percentages of neutrophil population for high, or effective resolving capacity of neutrophils, correspond to a low range of values for benefits of apoptosis (A), and by Equation (46), low range of values for costs of necrosis (B). This range of values for benefits of apoptosis and costs of necrosis become narrower and spans lower values when the threat of remaining ITMs is low. This is shown by the narrow wedge shape located at the bottom of the plot of panel A (shown in purple). This shows that nature could not have only made necrosis deliberately detrimental to the organism, it also could have made the anti-inflammatory benefits of apoptosis more effective especially when the presence of remaining ITMs in the system becomes increasingly threatening.



**Figure 17. Data Parameter Space ( $m$ ,  $b_{Apoptosis}$ ,  $\alpha$ ).** Each point in the plot corresponds to the combination of parameters that satisfies the data. This 3-dimensional parameter data space can be better visualized via an interactive plot, which we have uploaded to the following link for (A) and (B) respectively: <https://github.com/avpresbitero/EGTN> (2) and (3). The colors are chosen only to add visual depth to the plot, where purple to yellow corresponds to increasing values of  $\alpha$ . The evolutionary stable percentages of neutrophils correspond to lower benefits of apoptosis and costs of necrosis when the costs of remaining ITMs become threatening to the system. Stronger resolving power of ITMs, or higher values of  $m$ , correspond to narrower range and lower benefits of apoptosis and costs of necrosis in the data parameter space. Despite making necrosis detrimental to the system, nature balances the collective effect of the intrinsic property of neutrophils, cost of necrosis and benefit of apoptosis. Nature could have also made the anti-inflammatory benefits of apoptosis more effective especially when the presence of remaining ITMs becomes increasingly threatening to the organism.

Furthermore, with stronger resolving power of ITMs, or the higher  $m$  is, the narrower the range of values for benefits of apoptosis and costs of necrosis, which spans lower values in the data parameter space. This goes to show how well the system compensates by choosing combinations of parameters that balance the intrinsic property of neutrophils to neutralize ITMs, the damaging effects of necrosis, and the anti-inflammatory benefit of apoptosis.

The preference for range of costs of necrosis and benefits of apoptosis at lower values with increasing ITM-resolving capacity  $m$  is also apparent in the data parameter space shown in Figure 18. Nature could have made necrosis intentionally detrimental to the system, but when the intrinsic property of neutrophils to neutralize ITMs is favorable, costs for necrosis and the benefits of apoptosis adjust accordingly by having lower values. Nature could have chosen to maximize the organism's fitness by limiting the number of neutrophils that go into apoptosis or necrosis when even a small amount of neutrophils can completely resolve the inflammation. By doing so, the organism has conserved a considerable amount of energy, which is favorable for its survival.



**Figure 18. Data Parameter Space ( $m$ ,  $b_{Apoptosis}$ ,  $c_{Necrosis}$ ).** Each point in the plot corresponds to the combination of parameters that satisfies the data. This 3-dimensional parameter data space can be better visualized via an interactive plot, which we have uploaded to the following link: <https://github.com/avpresbitero/EGTN> (4). The colors are chosen only to add visual depth to the plot, where purple to yellow corresponds to increasing values of  $m$ . With increasing ITM resolving strength of neutrophils, low range of values for costs of necrosis and benefits of apoptosis correspond to evolutionary

stable percentages of neutrophil population. That is, with favorable intrinsic ITM resolving properties of neutrophils is compensated by lowering both costs of necrosis and benefits of apoptosis to maximize the overall fitness of the system.

### 2.1.8. Emergence of Necrosis Among Neutrophils with Limited Interactions in Cellular Automata Scheme

We use all the combinations of parameters derived in the mean-field scheme that corresponds to the experimental relation as input parameters for game played in the cellular automata algorithm. We do this under the assumption that these combinations of parameter values correspond to those that have been optimized during evolution by nature. The Global ITMs scheme assumes that an activated neutrophil bases its strategy on the strategy of its immediate neighbors and the total concentration of ITMs in the system.

Here we explore a lattice size of  $50 \times 50$ , so that the entire lattice is occupied by all 2500 neutrophils. In order to model systemic inflammation where ITMs are everywhere in the body, we 1) distribute the initial concentration of ITMs uniformly over the lattice and 2) assume periodic boundary conditions to assume a larger area of the tissue that corresponds to the entire body. Our results are summarized in Figure 19.

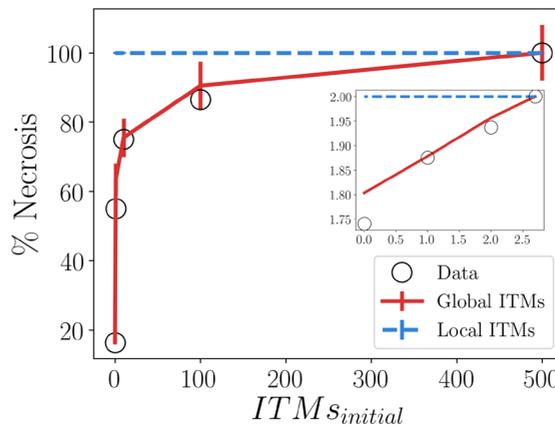


Figure 19. Emergence of Cooperation in Restricted Interactions via Cellular Automata (main) and Corresponding Log-Log Plot (inset). Global ITMs scheme refers to when neutrophils are able to detect the concentration of ITMs in a global scale. Local ITMs scheme, on the other hand, refers to when the neutrophils could detect the concentration of ITMs only within a certain range that is immediate to the activated

neutrophil. Each point in the plot corresponds to the mean percentage of necrosis calculated from the cellular automata algorithm for all combinations of parameter values in the data parameter space given the initial concentration of ITMs. Error bars correspond to the standard deviation from the mean of percentage of necrosis calculated for all combinations of parameters in the data parameter space.

The results using the Global ITMs scheme fits well with the data. On other hand, the percentage of necrosis in the Local ITMs scheme shows that regardless of initial ITM concentration, necrosis is always the dominant strategy and that this percentage of necrosis is maintained at about 100%.

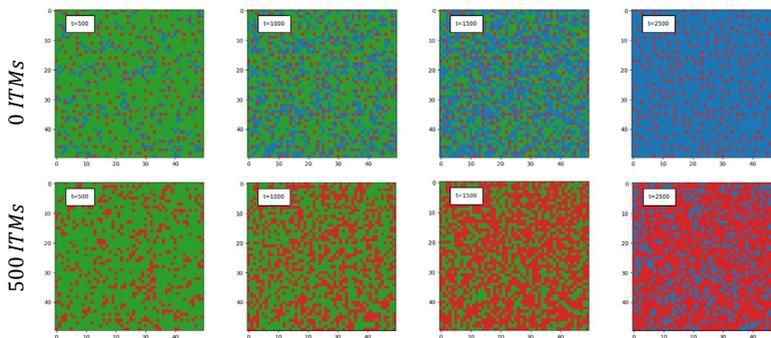
The results of our simulations provide numerical evidence that indeed, neutrophils need sufficient information regarding the intensity of inflammation, which may biologically pertain to stimuli that originates directly or indirectly (via pro-inflammatory cytokines and other substances released by cells in the innate immune system) from the source of ITMs. On the other hand, relying solely on local stimuli that originate from surrounding cells would be an insufficient deciding measure for neutrophils to pick a death pathway.

Snapshots of what the Global ITMs lattice looks like for various initial concentrations of ITMs evolving through time are summarized in Figure 20. Note that a single time step in our simulation corresponds to a single iteration in the algorithm where an activated neutrophil chooses a strategy based on a computed fitness. It is apparent that in a system with lower concentration of ITMs, necrotic neutrophils are better off isolated. This implies that their payoffs are maximized if they are situated away from the other necrotic entities, most likely to avoid aggravating the cost of necrosis which we interpret biologically as local tissue damage. On the other hand, apoptotic neutrophils tend to form clusters and position themselves in between necrotic neutrophils to maximize their payoffs. However, the tendency of necrotic neutrophils to isolate themselves is not evident in a system with higher concentration of ITMs. At 500 ITMs, we observe that necrotic neutrophils tend to cluster together, which can be biologically interpreted as the process when necrotic neutrophils intentionally aggravate inflammation by inducing local tissue damage.

We emphasize that the simulations shown in Figure 20 aim to show how

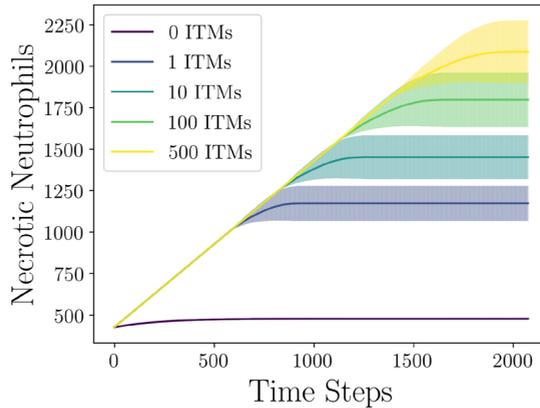
certain strategies dominate and propagate in the system through the course of time. Showing these dynamics provide a snapshot of how the system behaves at a particular point in time based on rules we specified in the payoff matrix. With minimal insult (0 ITMs), the system opts to take apoptosis as the optimal choice of strategy. However, when faced with an intense magnitude of insult (500 ITMs), activated neutrophils prefer to go into necrosis *early on* in the iteration, assumedly as an attempt to purposely aggravate the inflammation, which, biologically speaking, enhances the innate immune system's response by recruiting more immune cells into the tissue. Apoptosis comes on later in the iteration as an attempt to exercise their anti-inflammatory benefits. Indeed, the higher the magnitude of insult is, the higher the *overall* benefit necrosis contributes to the survival of the system, which is not only prominent at the end point of the iteration, but also is observed at the beginning of the iteration process. In fact, this corresponds well to what is observed in data<sup>84</sup>. The authors were able to show that through the course of 36 hours, apoptosis slowly increases and dominates when the insult is minimal. However, with higher magnitude of ITMs, apoptosis remains minimal, and only shows a slight increase at the end of the experiment (see Figure 2 in<sup>84</sup>).

Legend: Activated | Necrotic | Apoptotic



**Figure 20. Global ITMs Scheme. Snapshots of the  $50 \times 50$  lattice for 0 and 500 ITMs through iteration time (left to right).** Green in the lattice corresponds to activated neutrophils, red to necrotic neutrophils, and blue to apoptotic neutrophils. Apoptosis (blue) remains dominant with less concentration of ITMs (top right). Conversely, necrosis (red) dominates with intensifying level of inflammation (bottom right). At 0 ITMs, necrotic neutrophils are better off isolated, which could be interpreted biologically as the system's way to minimize local damage by allowing apoptotic neutrophils to settle in the space that separates them.

Increasing the concentration of ITMs to 500, however reveals clustering of necrotic neutrophils together, which intensifies local tissue damage thus further aggravating the level of inflammation in the system. Using cellular automata to model the choice of death pathway reveals behaviors that emerge from microscopic interactions. We investigate these microscopic behaviors by looking at the cumulative number of activated neutrophils that go into necrosis per unit timestep. Our results are summarized in Figure 21.



**Figure 21. Cumulative number of necrotic neutrophils per time step in cellular automata.** A single iteration corresponds to a single time step, where an activated neutrophil is made to choose a strategy. The plots correspond to the average number of necrotic neutrophils from 20 randomly chosen parameters in the data parameter space and the error bars correspond to the standard deviation.

The bold lines in the plots correspond to the average number of necrotic neutrophils obtained per timestep by setting 20 combinations of parameters which we have randomly chosen from the data parameter space. Here we show that the cumulative number of activated neutrophils going into necrosis stabilizes at points that follow a linear trend with respect to the iteration time step. Note that a single time step corresponds to a single iteration where an activated neutrophil chooses to go into apoptosis or necrosis. This is simply because a single iteration limits a single activated neutrophil to go into apoptosis or necrosis. In our simulation, the preferred strategy in the early part of the iteration is necrosis, which means that pro-inflammatory functions due to local tissue damage comes first, followed by apoptosis, which induces anti-inflammatory signals. Note that each iteration step here does not directly correspond to the biological time frame. That is, we only look at the end point where stable strategies are achieved.

### 2.1.9. What Kind of Game Are the Neutrophils Playing?

In this section we identify where the neutrophil game lies among existing games known in game theory. Based on the payoff values specified in **Table**

3, it is easy to see that what we have is a symmetric game, where the payoffs are only dependent on the strategies employed, but not on the players. More so, the payoff inequality of  $D > C > B > A$  perfectly describes a so-called deadlock game, where the strategy that is mutually beneficial is also the most dominant – apoptosis. However, due to the added effect of global cost to the average payoff as in (38), instead of having a pure strategy dominating as the Nash equilibrium (apoptosis, in this case), a mixed Nash equilibrium is observed as stable equilibrium.

It is easy to show that a mixed Nash equilibrium does not exist when the global cost term is not taken into account. The average payoff  $F(q, p)$  of an individual playing necrotic with probability “ $q$ ” in a population, which overall plays necrotic with probability “ $p$ ” would then be given by:

$$F(q, p) = qpA + q(1 - p)B + (1 - q)pC + (1 - q)(1 - p)D \quad (47)$$

We can calculate the optimal  $q$  by taking the derivative of the average fitness cost as shown below:

$$\frac{dF(q, p)}{\delta q} = pA + (1 - p)B - pC - (1 - p)D = 0 \quad (48)$$

Substituting the exact values from the payoff matrix in **Table 3** leads us to the following inequality:

$$\begin{aligned} -pC_{Necrosis} + (1 - p)(-c_{Necrosis} + b_{Apoptosis}) - pb_{Apoptosis} \\ - (1 - p)2b_{Apoptosis} = 0 \\ -c_{Necrosis} - b_{Apoptosis} \neq 0 \end{aligned} \quad (49)$$

The value  $p$  is undefined when searching for a mixed equilibrium where the fitness of going into apoptosis and that of necrosis is equal. This shows that indeed, a mixed Nash equilibrium does not exist for the game of neutrophils when the global cost term is omitted from the average fitness equation. This also implies that the global cost is necessary to replicate the percentage of

neutrophils observed in data. This exact mechanism also matches with the cellular automata scheme, where we show that information on the *global* concentration of remaining ITMs in the body via direct or indirect stimuli is necessary in order for the neutrophils to function as they do to resolve inflammation in the body. This global rule that appears to be the driving force for cooperation, which we refer to as *necrosis*, has been explored in a previous study<sup>102</sup>. Indeed, having global information of the system is sufficient to drive the percentages of necrotic and apoptotic population that are needed to resolve the inflammation in the body.

### **2.1.10. Summary and Conclusion**

Inspired by evolutionary game theory we construct a game that describes the choice between two death pathways for neutrophils exposed to various levels of insult. Although the game of neutrophils resembles a dead lock game, the characteristics of this evolutionary game are those of a mixed strategy game where the evolutionary stable strategies are a combination of apoptotic and necrotic strategies. We demonstrate that using the payoff matrix alone cannot describe the stable evolutionary states that lead to the delicate balance between the two death pathways. Instead, the global cost of remaining ITMs is necessary to replicate the percentage of neutrophils observed in data. Using our model, we reproduce the power-law behavior exhibited by the percentage of necrotic neutrophils with respect to different levels of ITMs in data. We also use data to reconstruct the space of possible evolutionary games which nature could have played to optimize the balance between apoptosis and necrosis depending on the level of insult. Using evolutionary game theory, we are able to identify and relate the mechanisms such as the benefit of apoptosis, cost of necrosis, strength of ITM resolution by apoptotic and necrotic neutrophils, and the global cost factor of remaining ITMs in the system that altogether contribute to the overall cost and benefit that establishes the optimal balance between necrosis.

Hence, using our simple model, we are able to pinpoint the driving mechanism that leads to the percentage of necrosis and apoptosis that

reproduces the data – *global cost of remaining ITMs*. More importantly, we provide numerical evidence that neutrophils need sufficient information of the scale of inflammation in its entirety in order to choose a death pathway effectively by utilizing cellular automata.

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# 2.2

## Challenging the evolution of cooperation in a community governed by central control

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Presbitero, A., Monterola, C.

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# 2.2

## Challenging the Evolution of Cooperation Governed by Central Control

### Abstract

Self-organization of cooperative behavior has been particularly interesting especially in communities where selfishness dominates more than social cooperativeness. These situations have often been described by the spatial prisoner's dilemma game. In reality, however, a centralized control is often necessary to establish social order. But the robustness of this established social cooperation remains unclear. Using the spatial prisoner's dilemma, we explore the evolution of cooperation not only in a community governed by central control, but also in selfish and realistic (law-abiding but selfish individuals) communities, by introducing two sources of stochasticities: defection-driven noise and stochastic payoff mutations. Individuals could imitate their best-performing neighbors, migrate to better locations, or do both. We show that although the presence of a central control is able to drive and maintain cooperation that is robust even in the presence of noise, social cooperation instantly collapses in the presence of defection-driven noise when migration alone is the only viable option. We also show that stochastic

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payoff variations enhance cooperation in realistic communities, while selfish communities are highly susceptible to defection-driven noise and stochastic payoff mutations.

**Keywords:** game theory, emergence of cooperation, prisoner's dilemma

### 2.2.1. Introduction

Cooperation comes in many forms and exists in various levels of biological and social hierarchies. Despite being common in nature, cooperation remains vulnerable from exploitation through acts of selfishness<sup>103,104</sup>. In order to understand the emergence and prevalence of cooperative behavior among selfish individuals, scientists turn to concepts in evolutionary game theory<sup>11,105-110</sup>. The most established paradigm among which is the evolutionary prisoner's dilemma game (PD). PD is a two-person game that makes use of two strategies: cooperation and defection. Mutual cooperation pays each player a reward  $R$ , while mutual defection costs them each punishment  $P$ . When the players choose different strategies, the defector receives the temptation to unilaterally defect  $T$  and the cooperator acquires the "sucker's pay-off"  $S$ . Classical PD is formally described by the following inequalities:  $T > R > P > S$  and  $2R > (S + T)$ . The stable state, or so-called Nash equilibrium, is mutual defection. This means that although mutual cooperation yields the highest collective payoff, rational individuals are naturally inclined to defect at all times. PD creates a social dilemma where there is conflict of interest between what is best for the individual, and what is best for the community.

For the past couple of decades, a vast amount of work has been devoted into understanding the emergence of cooperation. Pioneers in the field are Nowak and May with their seminal work on the evolution of cooperation in the spatial PD<sup>111</sup>. This triggered the development of various mechanisms in promoting cooperation such as reward<sup>112,113</sup>, punishment<sup>114-119</sup>, mobility<sup>120-123</sup>, and even noise<sup>124-127</sup>. A comprehensive review of understanding human cooperation in the context of co-evolutionary games can be found in<sup>128</sup> and<sup>129</sup>. Most of these works deal with selfish individuals that constantly strive at improving their current situation with little to no regard for others, nor the community they are part of. We argue that social cooperation is achieved more efficiently in the presence of a centralized control, such as a governing body that establishes social order. Individuals, therefore, choose

strategies that benefit the entire community, hence, in a sense, altruistic. Altruism, apart from selfishness, is prevalent in nature, and is in fact an innate strategy for reinforcing survival<sup>130</sup>. This behavior is seen in slime molds<sup>130</sup>, honeybees<sup>131</sup>, and rats<sup>132</sup>. Two experiments conducted separately by Capraro et al.<sup>133</sup> and Crockett et al.<sup>134</sup> demonstrates that altruism is preferred over selfish acts among rational individuals. Helbing and Yu studied the emergence of cooperation among selfish individuals through success-driven migration where players assess a potential destination through fictitious play<sup>11</sup>. We extend Helbing and Yu's model by analyzing the evolution of cooperation in a community controlled by a governing body. This centralized control implements laws so that individuals could only choose strategies that could either improve or preserve the collective payoff of the community. In our paper, we call this type of interaction among individuals as "global interactions" in a sense that the individuals are well aware of how their choice in strategies would affect the collective payoff of the community. Whereas we refer to the interactions among individuals in Helbing and Yu's model as "local interactions" since individuals only "play" with their immediate neighbors. Local and global interactions provide ways to understand how cooperation evolves in a community composed of completely selfish, and completely altruistic individuals respectively. In real-world negotiations, however, "realistic" individuals do not blindly oblige to central control. Instead, initially, they assess the benefit they would receive if they were to choose a particular strategy (much like in local interactions), and finally, if the strategy is in accordance with the rules of the governing body. We call these interactions among individuals as "local-global interactions" in the sense that individuals take into account what is best for themselves as well as the community. Finally, in order to test the sensitivity of the evolved social cooperation in local (selfish), global (altruistic) and combined interactions (realistic), we introduce two sources of stochasticities into the community namely: defection-driven noise (Noise 1), and stochastic payoff variations (Noise 2). We show that the mere existence of an imitation regime in a global

community structure suffices to drive the emergence of cooperation among majority, if not all of the individuals in the community. The resulting cooperation is in fact more robust and evolves faster than cooperation due to local and combined interactions. Interestingly, increasing stochastic payoff variations (Noise 2) in combined local–global interactions found in realistic communities, enhanced the formation of cooperation that is robust – a behavior that is counter-intuitive but also has a striking similarity with the pioneering work of Lotem *et al.* which demonstrated that the presence of defectors, to some extent, paradoxically allows the persistence of cooperation<sup>135</sup>. Lotem *et al.*'s idea has been extended to concepts such as the punishment system<sup>136</sup>, and social vaccine<sup>137</sup>. Additionally, works by Perc *et al.* were one of the significant works that showed variations in payoffs, either quenched or dynamic, promote cooperation<sup>138,139</sup>.

### **2.2.2. Imitation and migration in spatial prisoner's dilemma**

It has been shown that social cooperation can emerge from a community that is dominated by selfish individuals through repeated interactions among neighboring entities<sup>103</sup>. Rational individuals always try to improve their current situation. In order to do so, individuals normally adapt to their environment by copying the strategy of their best-performing neighbor ("imitation"). Individuals can also relocate to a better neighborhood if the current neighborhood does not suit their needs ("migration")<sup>11</sup>. However, random relocations, strategy alterations, and other sources of stochasticities ("noise") could significantly challenge the formation of cooperation in a community. In order to look into the sensitivity of this evolved cooperation with respect to noise, we compare two sources of stochasticities: 1) Noise 1, which allows strategy mutations that favor defection 95% each time the prisoner's dilemma game is played, and 2) Noise 2, an additive white Gaussian noise that stochastically mutates the individuals' payoffs.

**Table 4.** Values on the left of each column correspond to payoffs of Individual *i* while values on the right are for Individual *j*. The Prisoner’s Dilemma payoff matrix highly favors defection for both individuals, a phenomenon known as Nash Equilibrium. Say for instance, if Individual *i* chooses either to cooperate (payoff equal to 1) or defect (payoff of 1.3), Individual *j* will choose to defect at all times since defection gives more favorable payoffs equal to 1.3 and 0.1 respectively. Whereas cooperation, on the other hand, gives lesser payoff values equal to 1 and 0 respectively. The same circumstances apply if Prisoner 2 was made to strategize first.

		Player <i>i</i>	
		Cooperate	Defect
Player <i>j</i>	Cooperate	$1 + \xi_i, 1 + \xi_j$	$0 + \xi_i, 1.3 + \xi_j$
	Defect	$1.3 + \xi_i, 0 + \xi_j$	$0.1 + \xi_i, 0.1 + \xi_j$

We begin our simulation by randomly placing *N* individuals inside a square lattice, where 50% of which are cooperators and the other 50% are defectors. The square lattice has  $L \times L$  sites that could either be empty or occupied and is set to follow periodic boundary conditions. Each individual in the lattice is updated, either strategy-wise (i.e. switches strategy) or location-wise (i.e. individual transfers to another lattice site), asynchronously in a random sequential manner.

We look into the evolution of social cooperation in three schemes: imitation, migration, and combined imitation and migration for three types of interactions: local, global and local–global interactions. Note that for the imitation scheme, an individual is only allowed to imitate and not migrate or relocate to another lattice site all throughout the simulation. The same goes for migration scheme, where individuals only migrate or relocate but not imitate. In the combined imitation– migration scheme, however, individuals do migration first, followed by imitation to model how individuals who are moving from one neighborhood to another adapt to their new environment through imitating their best-performing neighbors. We further describe them in detail below.

Local interactions assume that individuals are completely selfish, and only choose strategies that would benefit them the most. We refer to a

community interacting mostly through local interactions as a selfish community. Global interactions assume altruistic behavior, where individuals only choose strategies that either increases or maintains the overall payoff of the community. This scenario is comparable to a central control that establishes social order in a community. We refer to a community interacting mostly through global interactions as an altruistic community. Local–global interactions assume that individuals choose a strategy that benefits both self and community. We refer to a community interacting through local–global interactions as a realistic community.

In the imitation scheme, a randomly selected individual simultaneously compares payoff with  $m$  8 immediate neighbors and copies the strategy of the best-performing neighbor: No Noise.

**Noise 1** (defection-driven noise) assumes that the strategy of the best-performing neighbor is copied with probability  $1 - r$ . But with probability  $r$ , the individual’s strategy “resets”. Reset means that the individual either cooperates with probability  $q$  or defects with probability  $1 - q$ .

**Noise 2** (stochastic payoff variations) is implemented as follows. The PD payoff matrix in Table 1 is subjected to temporal and spatial white additive Gaussian noise (AWGN) satisfying the correlation function given below <sup>140</sup>:

$$\xi_i(k)\xi_j(l) = \sigma^2 \delta_{ij} \delta_{kl} \quad (50)$$

Indices  $i, j$  correspond to two neighboring players, while  $k, l$  refer to two consecutive pair interactions. An individual  $i$  can adopt the strategy of nearest neighbor  $j$  with the following probability:

$$\omega(i \leftarrow j) = \frac{1}{1 + e^{\frac{S_i - S_j}{K}}} \quad (51)$$

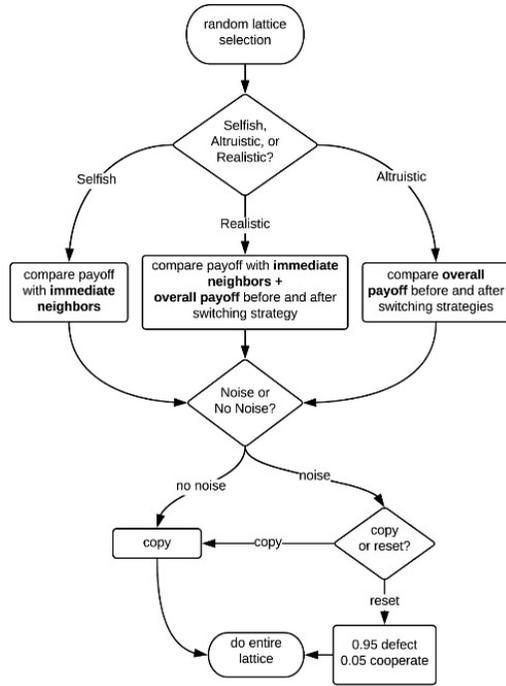
where  $S_i$  and  $S_j$  are the cumulative payoffs of individuals  $i$  and  $j$  respectively and  $K$  is the uncertainty to which a strategy is adopted satisfying the

inequality  $0 < K < 1$ . Without loss of generality, we set  $K$  to 0.1 as adapted from <sup>141</sup> where it has been shown that the qualitative results would still be the same even with a deterministic adoption rules where better (worse) performing individuals are always (never) adopted.

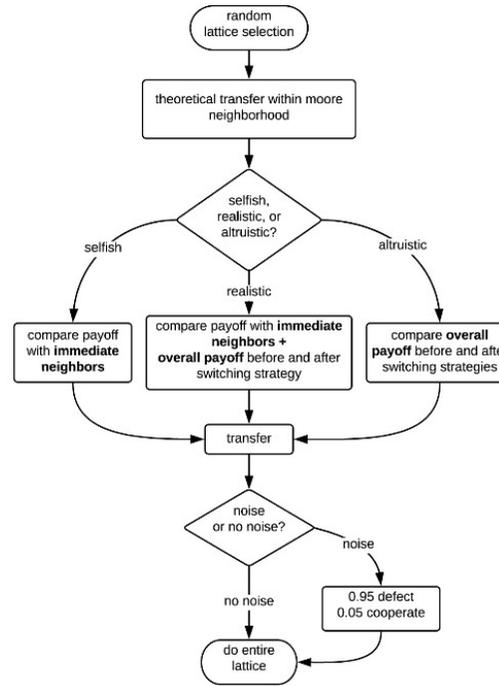
“Migration” is described as follows. A randomly selected individual plays fictitiously by checking prospective payoffs at sites that are available within the migration neighborhood of size  $(2M + 1) \times (2M + 1)$  ( $M$  is the range of the Moore neighborhood). If the fictitious payoff at the new location is greater than in the current location, the individual relocates to the new location. In cases when several sites have the same payoff, the individual moves with equal probability to any of these sites; otherwise, it stays put: **No Noise**. After implementing the migration scheme, **Noise 1** resets the selected individual’s strategy to either cooperate, with probability  $q$ , or defect, with probability  $1 - q$ . **Noise 2** integrates stochastic variations in payoffs, while following the No Noise migration scheme. A combined imitation and migration scheme implements the imitation scheme first followed by migration scheme. See Figure 22.

### **2.2.3. Entropy and index of dissimilarity as tools for measuring segregation and clustering**

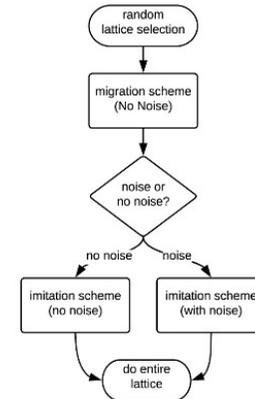
Segregation and clustering among individuals are analyzed through index of dissimilarity (ID) and entropy (S) <sup>142,143</sup>. These measures are used to quantitatively assess the spatial distribution of cooperating and defecting individuals in the virtual community.



(a) Imitation Scheme



(b) Migration Scheme



(c) Migration and Imitation Scheme

Figure 22. Community behavior for imitation, migration, and combined imitation and migration schemes for Noise 1 (defection-driven noise).

Demographers have first developed the concept of index of dissimilarity as means to calculate degree of segregation in residence patterns among ethnic groups. For example, in a country with individuals either belonging to one of two types of nationalities, an index of dissimilarity equal to one means nationalities 1 and 2 are fully segregated in the country. An index of dissimilarity equal to zero, on the other hand, implies an even distribution of both nationalities in the country<sup>144</sup>. For a geographic area partitioned by  $M$  number of boxes, the index of dissimilarity is calculated through the following formula:

$$ID = \frac{1}{2} \sum_{i=1}^M |p_{1_i} - p_{2_i}| \quad (52)$$

where  $p_{1_i}$  and  $p_{2_i}$  are the fractions of individual 1 and 2 respectively in box  $i$ . Entropy ( $S$ ), on the other hand, is used to measure aggregation or clustering of individuals in a geographic area. Lower levels of entropy imply greater levels of order and/or clustering. Entropy is represented by the following formula:

$$S = - \sum_{i=1}^M p_{\alpha_i} \ln p_{\alpha_i} \quad (53)$$

where  $p_{\alpha_i}$  is the fraction of individual  $\alpha$  (either cooperating or defecting individual) in the  $i$ th box<sup>142</sup>.

#### **2.2.4. Impact of defection-driven noise and random payoff stochasticities on selfish, altruistic, and realistic communities**

Helbing and Yu<sup>11</sup> showed that cooperation in a prominently defection-infested community can only evolve by combining two different schemes:

(1) imitation, where individuals copy their best-performing neighbors, and (2) migration, where individuals migrate to potential locations that offer more benefits than in the current location (Figure 23C). We show that a selfish community is susceptible to defection-driven noise (Noise 1), where strategies are flipped to defection 95% of the time, when imitation alone is the only viable option. Although combining imitation with success-driven migration somehow managed to increase the percentage of cooperators, migration is not able to maximize the population of cooperators in the community (Figure 23F). Interestingly, this result is in stark contrast when stochastic payoff variations (Noise 2) are introduced (Figure 23I). Adding Gaussian noise into the payoff matrix is able to drive majority of the community to cooperation, albeit slower than without noise, especially when imitation is combined with success-driven migration.

A community composed of altruistic individuals is able to drive majority of the community to cooperation almost instantly, while constantly maintaining this percentage of cooperators over time (Figure 23A). This percentage is increased to a maximum especially when imitation is combined with success-driven migration (Figure 23C). One could argue that indeed, this is as expected since the collective payoff of the community is maintained to a maximum at each iteration step. However, the number of cooperators in an altruistic community is still maintained at a relatively high percentage even in the presence of noise, making global interactions robust to attacks via defection (Figure 23D, F, G, and I). An altruistic community with only migration as choice of strategy, however, is shown to be highly susceptible to defection-driven noise as in Figure 23E. Migration gives individuals the opportunity to scout for better neighborhoods. But as soon as individuals are relocated, defection-driven noise takes over and flips strategies to defection, that even an “all-seeing” centralized government is not able to overcome such “unforeseen” circumstances. Every time an individual migrates and mutates to defection, there lacks a balancing mechanism that would be able to pull defection back into cooperation.

Imitation provides exactly this mechanism by copying strategies that best benefit the community. Perhaps, one could imagine a real-world scenario where a governing body, such as a group of law enforcers, implements taxes in a community aimed for the betterment of human lives. Taxes are used to raise funds for the construction of better infrastructures, research and development for medical care, and the manufacture of cheaper and readily accessible commodities. Individuals have the option to be honest (“cooperate”) or lie (“defect”) about their income statements, from which, of course, taxes are calculated from. This creates a social dilemma between what is best for the individual, and what is best for the community in the long run.

In a “realistic” scenario, where individuals choose strategies beneficial for themselves as well as for the community, we observe certain behaviors that are shared between selfish and altruistic communities. Although central control is able to drive individuals’ strategies to cooperation, local rules limit the players’ interactions with neighboring entities only. As a consequence, realistic communities are also susceptible to defection-driven noise (Noise 1), much like selfish communities as seen in Figure 23D. Imitation combined with migration allows individuals to initially relocate to better neighborhoods then copy their best-performing neighbor. Adding defection-driven noise mutates strategies to defection right before imitation. Realistic individuals escape defection through relocation and imitation. This initially promotes cooperative behavior. However, constant bombardment of defection from defection-driven noise inhibits the full emergence of cooperation. Combined selfish and altruistic behaviors seems to slow down the collapse of cooperation in the community (Figure 23F).

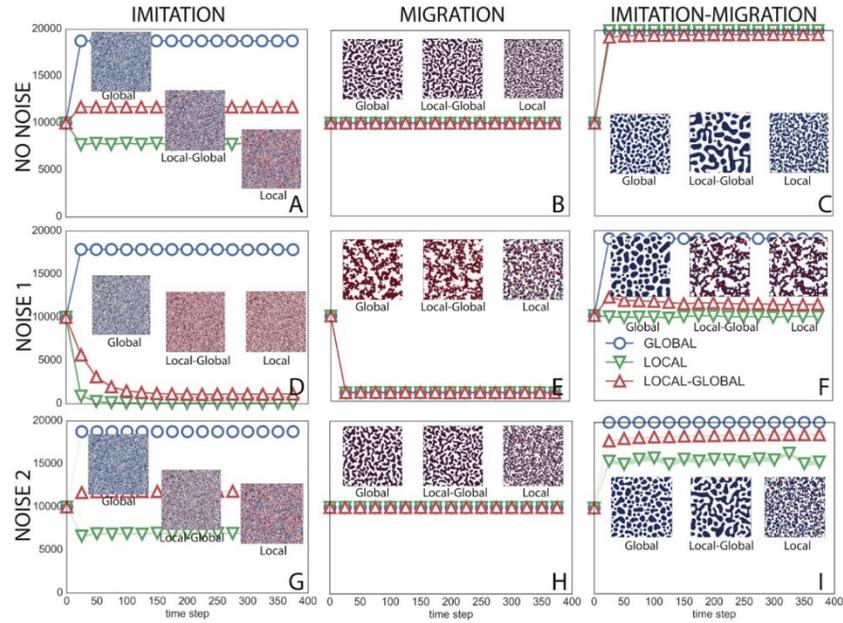


Figure 23. Simulation results after 400 iterations of one out of ten realizations in selfish (“local”), altruistic (“global”), and realistic (“local–global”) individuals. In an altruistic community (global), imitation alone is able to drive cooperation even in the presence of noise. However, it is susceptible to defection-driven noise (Noise 1) when migration is the only viable option. In a selfish community, cooperation only evolves when imitation is combined with migration, but susceptible to Noise 1. A realistic community (local–global) shows shared attributes from altruistic and selfish communities. The same sets of random numbers were used in our simulations with Prisoner’s Dilemma payoff values  $T = 1.3$ ,  $R = 1$ ,  $P = 0.1$ , and  $S = 0$ ,  $r = q = 0.05$ , and mobility  $M = 5$ . Cooperators are rendered blue while defectors are red. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

In order to further explore the effects of global rules on either imitation or combined imitation and migration schemes in noisy conditions, we reverse the concept of “defector’s paradise” as introduced by Helbing and Yu. That is, instead of having a single defector in the middle of a massive circle of cooperators, as in defector’s paradise, we now have a lone cooperator surrounded by defectors with diameter 25. Despite the constant bombardment of defection-driven noise at every time step in the reverse defector’s paradise (Figure 24), cooperation remains robust. It even maintains the central cooperative island intact. Global rules combined with imitation and migration schemes result in the immediate propagation of cooperation throughout the virtual community in as early as  $t = 10$ .

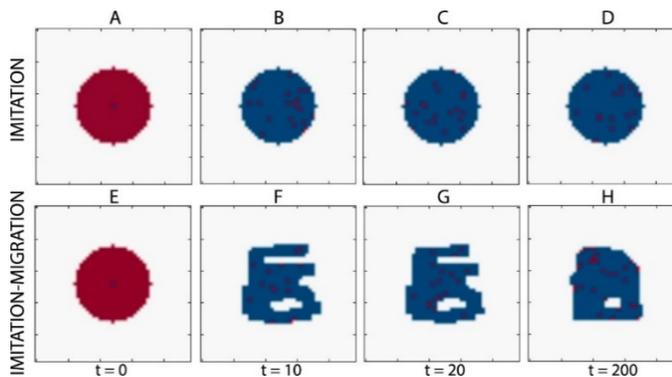


Figure 24. Reverse defector’s paradise is represented by a circle composed mainly of defectors with diameter equal to 25 and a lone cooperator at the center. The reverse defector’s paradise is observed in both imitation and combined imitation and migration schemes subjected to global rules. Cooperators are rendered blue while defectors are red. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

The community behavior can be summarized by the following points:

- 1) In a selfish community, imitation combined with migration triggers cooperation.
- 2) In an altruistic community, imitation alone can trigger cooperation.
- 3) Realistic communities share the characteristics of selfish and

altruistic communities.

### **2.2.5. Varying stochastic payoff variations**

We have shown that stochastic payoff variations using additive white Gaussian noise (AWG) reduces cooperative behavior for selfish and realistic communities as compared to similar schemes without noise. Altruistic communities, on the other hand, are robust to noise and maintains universal cooperation even in the presence of Noise 2. Sigma in Equation (50) aims to vary the standard deviation of AWG. Hence, the bigger  $\sigma$  is, the wider the Gaussian distribution becomes, therefore, payoff variations are done in a wider range of values. In order to investigate the effect of increasing stochastic payoff variations in altruistic, selfish, and realistic communities, we assign  $\delta$ s to 0.1, 0.4, and 0.8. We summarize our results in Figure 25.

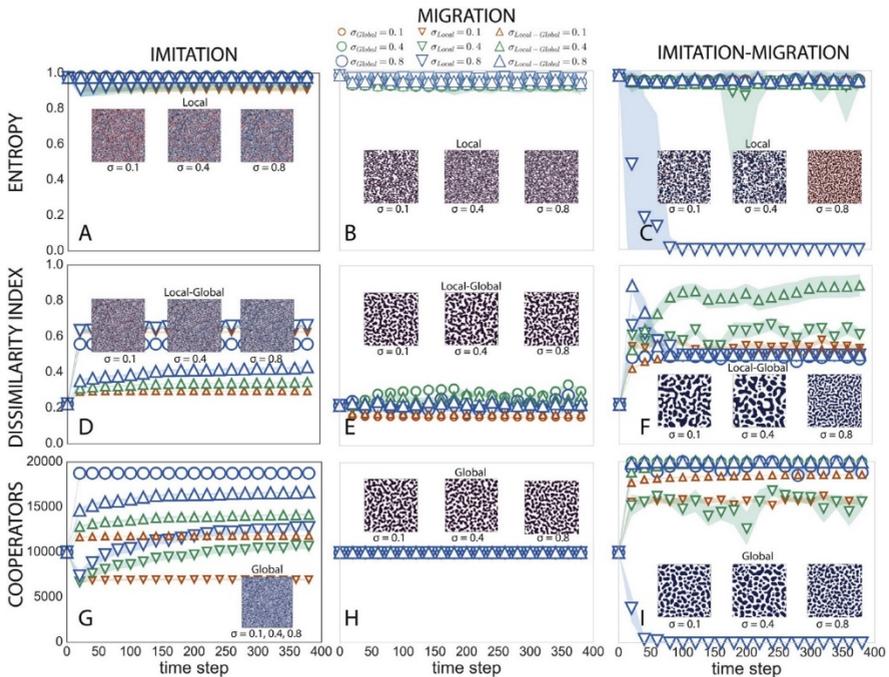


Figure 25. Simulation results after 400 iterations of one out of ten realizations for varying stochastic variations of  $\sigma$  0.1, 0.4, and 0.8 (Noise 2) in selfish ("local"), altruistic ("global"), and realistic ("local-global") communities. The same sets of random numbers were used in order to assume comparison among cases. Cooperators are rendered blue while defectors are red. Imitation alone is able to drive cooperation in altruistic communities. Altruistic communities are robust to increasing stochastic payoff variations. Stochastic payoff variations enhance cooperation in realistic communities. Selfish communities are highly susceptible to increasing stochastic payoff variations. But with imitation scheme alone, higher stochastic variations push the selfish community to a majorly cooperative regime. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Altruistic communities are generally robust to increasing stochastic payoff variations (see Figure 25G–I). In as early as 10 time steps, the number of cooperators shoot up to maximum especially when imitation is combined with migration, which is exactly why the index of dissimilarity is equal to 0.5 (see Figure 25F). That is, only a single type of individual (cooperators only) exists in the community. Entropy, on the other hand is a little bit higher in the imitation scheme, implying that there is a lower level of order in the community (see Figure 25G). Entropy decreases with migration and

combined schemes. This is because migration triggers cooperators to “stick” together (see Figure 25H and I). Moreover, we observe that the larger  $\sigma$  is, the smaller the clusters become. As the level of noise increases, therefore, the more unstable the system becomes. Hence, cooperators benefit more by sticking together and maintaining a cooperative cluster that is as tiny as possible in attempt to minimize defection invasion.

Increasing  $\sigma$  for payoff stochastic variations (Noise 2) tends to be highly detrimental to the formation of cooperation in selfish communities especially when imitation is combined with migration. This observation is in stark contrast with the observation of Helbing and Yu, who observed that success-driven migration, when combined with imitation can be the driving force for cooperation to emerge in a selfish community. Selfish communities, however, have the tendency to form cooperative clusters (see Figure 25B, and C), thus portraying low entropy, that is, showing a greater sense of order. This is as expected because individuals are only limited to playing the PD game within their Moore neighborhood, and thus can only influence their direct neighbors. Visually, defectors tend to be more scattered in areas between cooperative islands the greater  $\sigma$  becomes (note that we only plot index of dissimilarities of cooperators, therefore with very high  $\sigma$  where defection takes over, cooperative entropy disappears as seen in Figure 25C). Due to the increase in payoff variations, defectors are able to survive by preferring locations with no neighbors at all (see Figure 25B). If this configuration is directly followed by imitation (which is essentially the combined imitation–migration scheme), it would be difficult to maintain a cooperative regime mainly because defectors are scattered all over a greater surface area and this potentially increases the spread of defection throughout the community. Then, it is not surprising that defection is able to invade the community entirely. However, if we look closely at imitation only scheme (see Figure 25G), interestingly, the stronger the stochastic variation is, the faster the community bounces back to a majorly (more than the initial cooperative population) cooperative regime.

Interestingly, increasing the level of noise by increasing  $\sigma$  enhances the level of cooperation in realistic communities as compared to the case when there is no noise (see Figure 25I and compare with Figure 23C). Although this phenomenon seems counter-intuitive at first, it is in fact a known occurrence. Perc et al. are among the first to show that variations in payoff could in fact promote cooperation<sup>145,146</sup>. Additionally, this finding is also consistent with that of Yamamoto and Okada's, where they showed that introducing few specific non-cooperative behaviors, such as social vaccine, can robustly maintain a cooperative regime<sup>147</sup>.

We note that Noise 2, as opposed to Noise 1, does not alter the number of original cooperators nor defectors in the migration scheme. Individuals, however, migrate to newer locations based on payoff values that have been modified through stochastic variations. Altruistic and realistic communities show generally low segregation (low index of dissimilarity) (see Figure 25E) and medium to low levels of clustering (high entropy). That is, cooperators and defectors are generally found mixed together.

The community behavior for increasing stochastic payoff variations is summarized below:

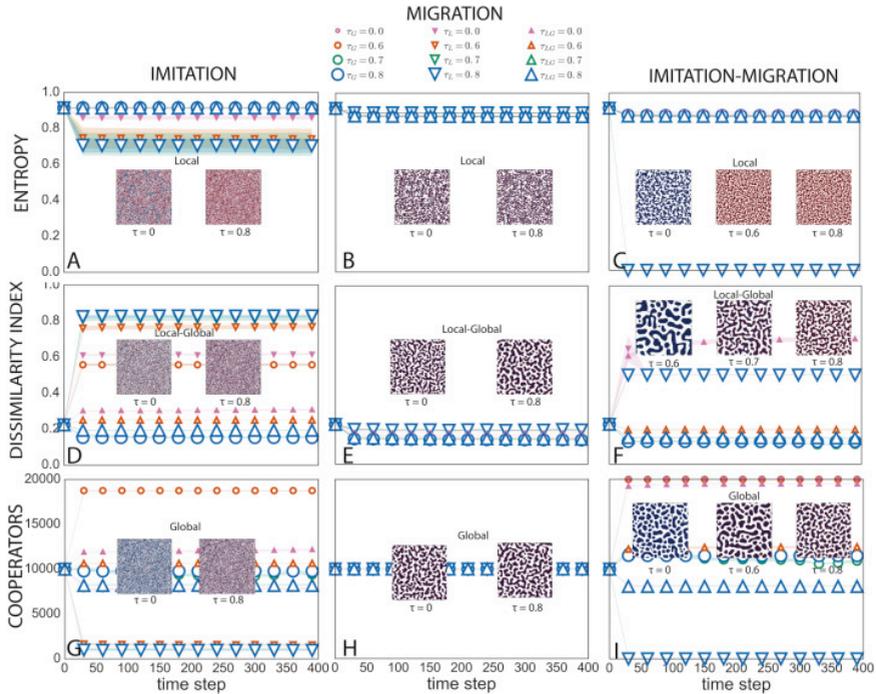
- 1) Altruistic communities are robust to increasing stochastic payoff variations.
- 2) In realistic communities, increasing  $\sigma$  in enhances cooperation.
- 3) Selfish communities are highly susceptible to stochastic payoff variations. However, with imitation scheme alone, increasing stochastic variations is able to push back the system to a majorly cooperative regime.

### **2.2.6. Varying the temptation to unilaterally defect**

Classical PD follows these rules  $T > R > P > S$  and  $2R > (S + T)$ .. The inequality  $2R > (S + T)$  assures that the collective payoff for cooperators is always greater than the collective payoffs for defectors. In this section, we

challenge the formation of cooperators by adding a variable  $\tau$  to  $T$ , so that  $2R > (S + T + \tau)$ , and then explore how this new value will affect the evolution of cooperation in altruistic, selfish, and realistic communities. We choose  $\tau$  with values 0.6, 0.7, and 0.8, where 0.7 and 0.8 are intentionally assigned to violate the PD rule. We summarize our results in Figure 26. We also include  $\tau = 0$ , therefore maintaining the original value  $T = 1.3$ , as base scenario for comparison.

Our results show that in altruistic communities, increasing the temptation to unilaterally defect by  $\tau = 0.6$  has no significant effect on the formation of cooperation compared to the case when noise is not present at all. That is, emergence of cooperation is still immediate and maintained up until 400 iteration steps (see Figure 26G and I). Therefore, index of dissimilarity is 0.5 for imitation and combined schemes because only cooperators at this point exist in the community (see Figure 26D). Interestingly, even when the prisoner's dilemma is validated, that is by setting high values for temptation to unilaterally defect ( $\tau = 0.7$  and  $0.8$ ), cooperation still manages to maintain a percentage either equal to (see Figure 26G) or greater than the initial number of cooperators (see Figure 26I) in the system.



**Figure 26. Community behavior with varying temptation to unilaterally defect.** Simulation results after 400 iterations of one out of ten realizations for varying temptation to unilaterally defect with  $\tau$  set to 0.0, 0.6, 0.7, and 0.8 in selfish (“local”), altruistic (“global”), and realistic (“local–global”) communities. The same sets of random numbers were used in order to assume comparison among cases. Cooperators are rendered blue while defectors are red. The evolved social cooperation in altruistic communities is maintained to either the initial percentage of cooperators, or a percentage above it with increasing  $\tau$  or temptation to unilaterally defect. Selfish communities, on the other hand, portray cooperation that is highly susceptible to increasing values for  $\tau$ , as increasing payoffs do defect becomes more beneficial. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Selfish communities are highly susceptible to defection for  $\tau$  values 0.6, 0.7, and 0.8. That is, individuals tend to favor defection as temptation to unilaterally defect becomes a more beneficial strategy (see Figure 26C). Upon close scrutiny, it is apparent that individuals tend to form cooperative clusters (see Figure 26A and B) as means to evade defectors (low entropy). Defectors, on the other hand, benefit more by surrounding these small cooperative clusters. Combining migration with imitation worsened the

condition as defection becomes a predominant choice of strategy. As opposed to imitation scheme, where cooperative individuals are in a sense “kept safe” from defectors due in part to the “frozen” configuration of the community, incorporating migration allows defectors to invade cooperative individuals. Defection then spreads throughout the community with individuals preferably clustering together. It is important to note that we only take cooperators into account when computing for entropy. Increasing the temptation to defect drives the community to universal defection. Hence cooperators disappear from the community and entropy values, as shown in Figure 26C, approach zero.

Realistic communities seem to share characteristics exhibited by altruistic and selfish communities. For instance, in combined imitation and migration schemes, the community seems to be more susceptible to defection than in altruistic communities as  $\tau$  is increased – a characteristic evident of selfish communities (see Figure 26). However, the number of surviving cooperators remain greater than the fraction of cooperators in selfish communities. Much like in altruistic communities, realistic communities exhibit low segregation between cooperators and defectors regardless of  $\tau$  (low index of dissimilarity) as seen in Figure 26F. A close inspection would reveal that cooperators and defectors coexist within each cluster, which is why this type of community exhibits high entropy as well as seen in Figure 26C. The community behavior upon stochastic payoff variations can be summarized by the following points:

- 1) A cooperative regime evolved from altruistic communities is maintained or increased to more than the initial cooperative percentage even with high temptation to unilaterally defect.
- 2) Cooperation collapses in selfish communities with increasing temptation to unilaterally defect.
- 3) Cooperation in realistic communities exhibit shared characteristics between altruistic and selfish communities and are moderately susceptible to increasing temptation to unilaterally defect.

### 2.2.7. Summary and Conclusion

This article analyzed the emergence of cooperation in altruistic (community governed by central control, where individuals choose strategies that benefit the community), selfish ( individuals choose strategies that only benefit themselves), and realistic (individuals choose strategies that are beneficial to themselves as well as the community) communities even in the presence *defection-driven noise* (Noise 1) and *stochastic payoff variations* (Noise 2). We also looked into the emergence of cooperation when the temptation to unilaterally defect increases to a point where the classical prisoner's dilemma inequality is violated.

We first showed that in selfish communities, cooperation is greatly enhanced when imitation is combined with migration. However, selfish communities remain susceptible to *defection-driven noise* (Noise 1). In altruistic communities, imitation alone triggers and maintains a majorly cooperative regime among individuals in the community. This evolved cooperation is robust to either Noise 1 or 2. However, the established cooperation collapsed immediately in altruistic communities when migration is coupled with Noise 1. Realistic communities seem to share some characteristics exhibited by altruistic and selfish communities. That is, cooperation in realistic communities are only enhanced when imitation is combined with migration – a characteristic of selfish communities, but robust to Noise 1 and Noise 2 – a characteristic of altruistic communities.

Secondly, we showed that even with increasing  $\sigma_s$ , and therefore increasing stochastic payoff variations, the emergence of cooperation in altruistic communities remains robust. Remarkably, increasing  $\sigma_s$  in Noise 2 is able to enhance cooperation in realistic communities, while selfish communities, on the other hand, are highly susceptible to increasing noise.

Finally, adding a variable  $\tau$  that aims to incrementally increase the

temptation to unilaterally defect seems to have no effect on altruistic communities. In fact, cooperation remains robust and is maintained for the entire 400 iteration steps. In selfish communities, however, cooperation became increasingly susceptible to defection with increasing  $\tau$ . The same goes with realistic communities, only that it is only moderately affected by the increase in temptation to unilaterally defect.

Although our results reveal that altruistic behaviors are capable of driving majority, if not all, of the individuals in the community to cooperation that is seemingly robust, an altruistic community, or a community governed by central control, still remains susceptible to defection-driven noise when migration is the only viable option. Our findings suggest that, indeed, imitation, or the copying mechanism of better-performing individuals is the sole driving-force for the emergence of robust cooperation in a community governed by central control.