MiGHT, a multi-level Gillespie hybrid tracked modeling framework which allows for cellular and environmental adaptivity

Justin Melunis
Department of Biomedical Engineering and Science
Drexel University
Philadelphia, PA
jdm347@drexel.edu

Uri Hershberg
Department of Biomedical Engineering and Science
Drexel University
Philadelphia, PA
uh25@drexel.edu

Abstract— **Cells dynamically alter their behavior and adapt the profile of receptors and ligands they produce in response to their personal history. This is clear in development and, even more so, in our understanding of the differentiation and action of the cells of the immune system. To model the adaptive changes of leukocytes, we must incorporate the cell's internal state as it is shaped by the cell's history within an environment. To do so, we have developed a multi-level Gillespie hybrid tracked (MiGHT) modeling schema. MiGHT derives from our previous modeling framework TIPS, a tracked interacting particle system (IPS) modeling framework. TIPS expanded on the IPS modeling structure by tagging entities to allow for agent-based manipulations and the tracking of individual agents over the course of a simulation through complex binding via a hierarchical structure. In MiGHT we have incorporated the ability to model internal mechanisms as sub-level self-contained models, which can both respond to historical events and the microenvironment, as well as influence their agent's future behavior. MiGHT also includes the ability to utilize hybrid simulation methods, including tau-leaping estimations and differential equation time steps. This gives us the capability of efficiently simulating differing amounts of molecules, such as cytokines as well as the ability to efficiently model internal interactions. Lastly, MiGHT includes an environment restrictions method, which allows for the environment to directly affect the behavior of the simulation as well as the ability to alter the simulation techniques based on individual bin entity concentrations. This creates a multi-level simulation in which entities can actively adapt their behavior to both history and the environment. Using MiGHT we have simulated the macrophage response to lipopolysaccharide (LPS). We show that a single population of macrophages can transition through the stages of macrophage activation and inactivation via a simple set of dynamics. Furthermore, we show that the systemic response of macrophages is dependent on how individual macrophages are distributed within the environment.**

Keywords—MiGHT, TIPS, adaptation, stochastic, macrophage, agent-based

I. Introduction

Stochastic models allow investigators to simulate reactions in a discrete way that can account for fluctuations that are otherwise ignored within a deterministic approach. Chief among the list of stochastic simulation techniques is the Gillespie algorithm [1]. This approach assumes that all reactions occur between molecules which are homogeneously mixed. Reactions occur one at a time, chosen randomly, but weighted on the event's rate, and the time is updated based on the overall sum of event rates. By using a non-uniform timestep, the Gillespie algorithm introduces both time and event order fluctuations.

In certain cases, such as predator-prey models, both the distribution of agents in the simulation and the movement of these agents play a significant role in how the model behaves [2]. An interacting particle system (IPS) modeling framework is a multi-dimensional Gillespie algorithm in which the environment is binned. The IPS framework allows for a spatially stochastic model that can incorporate the heterogeneous mixing of agents in the model as well as environmental dependencies by allowing discrete agents in the model to interact locally and migrate between patches that are spatially connected. IPS models rely only on basic assumptions and thus, can retrace phenomena to basic components [3-5]. However, IPS models look exclusively at population dynamics and cannot detail the path or history of an individual agent within that model. Unlike IPS models, agent based models (ABMs) describe each agent separately. ABMs can therefore both track agents and apply individual differences in agent behavior. This, however, makes ABMs much more computationally intensive and the cause-effect connection of emergent events much more difficult to understand and quantify [6].

Here we present MiGHT, a multi-level Gillespie hybrid tracked modeling framework, which allows for agents to be tracked and adapt to the environment and the history of their events. This framework derives from our previously published, TIPS (tracked IPS), modeling framework [7]. TIPS expanded on the IPS modeling structure by tagging molecules to track the individual molecules over the course of a simulation while allowing the underlying dynamics of the simulation to behave as an IPS. In doing so, we allowed for agent tracking, agent-based manipulations, and the incorporation of history. However, TIPS was limited by the general restrictions of an IPS modeling framework, in which each event, movement and interaction, must happen one molecule or interaction at a time. TIPS can allow for agents within the simulation to adapt to their history in a very primitive way, but TIPS is not ideal for modeling biological phenomena where agents have complex adaptive behaviors to both their history and the environment.

978-1-5386-2726-6/17/$31.00 ©2017 IEEE
Authorized licensed use limited to: Drexel University. Downloaded on February 18,2025 at 19:29:54 UTC from IEEE Xplore. Restrictions apply.

To model the interactions of cells and their inter and intra-cellular signaling, it is more practical to model the internal workings of agents as internal models which can influence the behavior of the agent, directly interact with the environment, and respond to historical interactions.

MiGHT expands on TIPS by allowing for sub-level self-contained models of internal features within an individual agent, which can be influenced by historical events and the environment and can influence agent behavior. We implement this capability to utilize hybrid methods of simulation, improving on what can be simulated and reducing the computational time needed to simulate many biological phenomena. We further incorporate environmental restrictions which allow for the environment to directly affect the behavior of the simulation as well as the ability to alter the simulation techniques based on individual bin molecular counts. These methods allow us to create a time efficient multi-level simulation in which agents within our simulation can actively adapt their behavior to both history and the environment.

MiGHT is built on a long tradition of spatially resolved agent-based mathematical modeling techniques used to study cellular immune interactions [8-14]. Novel to MiGHT is the tracking of tagged agents with a hierarchical structure and the incorporation of environmental and agent intrinsic values which are updated either deterministically or discretely, through differential equations or binomial estimations. In doing so, we can implement both temporal and behavioral stochasticity in how entities are updated.

Looking at the macrophage inflammatory response, more specifically the macrophage response to lipopolysaccharide (LPS), we show the advantages of the MiGHT simulation system. Macrophages are white blood cells that are thought to be activated in a polarized way, either promoting inflammation or promoting healing and repair [15]. Current immunological models consider the switch from immune activation to be one of populations from naïve M0 macrophages to M1 activated macrophages, which switch to M2 when the immune system ends the immune response. These different macrophage populations are identified by associated expression of cytokines: tumor necrosis factor alpha (TNFα) for M1 and interleukin 10 (IL-10) for M2 macrophages. Previous macrophage simulations have relied on this concept of polarized macrophage populations to simulate a macrophage response to bacteria [34-36]. Macrophages were modeled as four distinct populations, resident (M0), infected (M1), classically (MA), and alternatively activated macrophages (M2) through compartmental ODE models. Within these models, TNF and IL10 were utilized to change the distribution of the macrophage populations. This paradigm, however, needs reassessment, as macrophage effector function appears to be more heterogeneous, acting on a gradient between two extremes, producing both TNFα and IL-10 in tandem. Moreover, it has been found that macrophage polarization can dynamically adapt to changes in cytokine microenvironments [28, 37]. We will use the MiGHT simulation system to model the macrophage LPS response and suggest an alternate view of macrophage inflammatory response that does not require polar opposite homogenous populations.

II. Methods

MiGHT is a simulation modeling framework which utilizes the exact Gillespie algorithm while considering the spatial dynamics and the internal regulation of interacting agents. The simulation environment of MiGHT is separated into a binned space in which each bin represents a volume in which we consider the entities to be well-mixed. Entities are able to move from bin to bin based on the bin size, the agent rate of motion, and environmental factors, allowing for heterogeneous mixing [38].

The entities of MiGHT are divided into TIPS based entities, environmental entities, and internal feature values. The TIPS based entities can be tracked and always have discrete counts. TIPS based entities that are tagged can be tracked, or undergo any type of agent based manipulation, or have a self-contained simulation within. In the case of our macrophage model, the macrophages are a tagged, TIPS based entity. Environmental entities cannot be tracked and unlike untagged TIPS based entities can have a discrete or non-discrete count. These entities can directly interact with TIPS based entities, other environmental entities, or with internal features. LPS, IL-10, and TNF are environmental entities in our macrophage model. Internal feature values correspond to an internal molecule count, historical value, or agent feature. The feature values can be altered by a historical event, can interact with the environment, or can be updated internally as a sub-level self-contained model. The internal feature values of the macrophage model correspond to P50, P65, STAT1, and STAT3 relative concentrations and are specific to each macrophage.

Our MATLAB coding of MiGHT and information on the underlying structures which we utilize to run MiGHT are here (https://github.com/DrexelSystemsImmunologyLab/MiGHT). We are constantly working on developing a more globally implemented MATLAB algorithm for MiGHT with an improved easy to use interface.

A. Hierarchical Structure of MiGHT

The ability in MiGHT to tag individual TIPS based entities is vital for agent tracking, agent-based manipulations, and the incorporation of history even throughout complex binding. The most basic entity structure is that of a single tagged agent. It is stored as the tag number in a cell, i.e. {1}. When this combines with another single agent, the two agents are removed from their individual cells and combined in a single cell representing a complex i.e. {1 2}. Each location within this cell is specific for a certain entity type in which the number represents the tag of an individual agent. If we were to combine this complex, {1 2}, with another agent, the behavior of the individual components would dictate the hierarchical structure that is formed. If the entity behavior of either agent of the complex behaved individually when combining, then the new combination remains on the same level as these entities, i.e. {1 2 3}. However, if entities behave as a single component within the new complex, then they move to a sub-level within the complex that is in a second cell, i.e. {{1 2} 3}. If this complex behaves as a single component within another complex, this would again be placed in its own cell, forming another level in the complex.

Authorized licensed use limited to: Drexel University. Downloaded on February 18,2025 at 19:29:54 UTC from IEEE Xplore. Restrictions apply.

As an example of the use of such complex binding let us consider the binding of T lymphocytes to an antigen presenting cell (APC). When these cells bind, an immune synapse is formed as an interface between the two cells [39]. Here, these cells may directly affect the internal state of each other [40]. Thus, it may be more beneficial to model these cells interacting over time instead of an instantaneous interaction. Our hierarchical structure gives the capability to track these cells through this interaction while adapting the future behavior of one or both cells while bound. For this example, consider T cells to be the 1st entity type, an APC to be the 2nd entity type, and the two cells bound by an immune synapse to be the 3rd entity type. Thus, if we consider their interaction to be in two dimensions, we would simulate the binding of the ith T cell with the tag, $T_{1,i}$, with the jth APC with the tag, $T_{2,j}$, in bin(x,y) as follows :

$$Ent(3).Bin(x,y).Tag(end+1) = \{T_{1,i}\, T_{2,j}\}$$
$$Ent(1).Bin(x,y).Tag(i) = [\,]$$
$$Ent(2).Bin(x,y).Tag(j) = [\,].$$

In this way MiGHT binds the two tags together within a hierarchical structure, adds this structure to the cell array which corresponds with the cells bound by an immune synapse, and removes the individual cell hierarchical structure tags from their individual cell arrays. If the ith T cell was instead chosen for a movement event from bin(x1,y) to bin(x2,y), then we would move the hierarchical structure to its new array based on the bin:

$$Ent(1).Bin(x_2,y).Tag(end+1) = \{T_{1,i}\}$$
$$Ent(1).Bin(x_1,y).Tag(i) = [\,]$$

Entities which are not being tracked do not need to be tagged; Instead, just the number of molecules within a bin can be recorded. i.e. if we were not tracking individual APCs, but just their overall unbound amount, the binding would look like:

$$Ent(3).Bin(x,y).Tag(end+1) = \{T_{1,i}\}$$
$$Ent(1).Bin(x,y).Tag(i) = [\,]$$
$$Ent(2).Bin(x,y).Count = Ent(2).Bin(x,y).Count - 1$$

There are a multitude of different binding event types which change how the hierarchical structures are manipulated. Many of these have been coded that can be found at our lab's repository: (https://github.com/DrexelSystemsImmunologyLab/MiGHT).

Parallel to the tagged hierarchical structure array of an entity is a feature value cell array in which each agent tag of the entity structure array has a corresponding vector of agent features, i.e. for the jth agent of entity i, we would have a feature vector corresponding to a tag, such that

$$\{T_{i,j}\} \Leftrightarrow \{F_{i,j,1}, F_{i,j,2}, \dots, F_{i,j,n}\}.$$

These features could be values for history, internal molecular counts, physical features, or a plethora of other aspects of an agent that impact the simulation by how the agent interacts with the environment or other entities. During any type of complex binding, these feature vectors follow the hierarchical structure parallel to their tags.

B. Environment Restrictions

Within MiGHT, the environment itself can be stochastic. Each bin represents an area in the environment with its own make up of entities, allowing us to simulate the spatial heterogeneity of entities. Furthermore, the dynamics of the simulation within a bin may differ from other bins. This allows us to simulate environmental heterogeneity in MiGHT simulation dynamics. To account for this, we have implemented in MiGHT the capability of environmental restrictions. These restrictions can be based on the bin location, the entity make-up of the bins, or a combination of the two. How this is implemented to control rates and interactions is better explained in section C.

C. MiGHT Initiation and Event Rates

To initialize MiGHT, the agents of the entities are placed throughout the environment. We calculate the rate of each agent in the case of an agent-based reaction, followed by the rate of each event within a given bin, the overall reaction rate of the bin, and then the total rate.

The rate of an event to occur in each bin can be dependent on multiple aspects of the model; these include entity counts, environmental restrictions, agent internal feature values, and rate constants. We store a function for each event's non-agent dependent rate and which entity counts and restrictions effect this rate. We then evaluate that function with the values of the restrictions. Consider event(i) to be a binding event of two entities with a rate, $R_{1,2}$, in which the rate was set as the multiplication of the rate constant, $C_{1,2}$, the count of the agents of that type of entity and the restriction, Res1,2, such that

$$R_{1,2} = Res_{1,2} * C_{1,2} * Num\big(Ent(1)\big) * Num(Ent(2)).$$

We would then evaluate the function for the rate, $R_{1,2}$, with the input of the entity counts of entity 1 and 2 and the value of the restriction, $Res_{1,2}$.

Event rates can be set to be agent-dependent, as opposed to being solely dependent on the entity counts. If this is the case, the rate of the event and the choice of which agent undergoes the event are based on the internal features of individual agents. In each simulated event in the Gillespie algorithm loop, we set the event's rate to be dependent on zero, one, or two agent's internal features. This is limited to two agents as the exact Gillespie algorithm never considers there to be an event in which three agents will bind simultaneously [1]. However, one of the agents may be a composite or complex of previously combined agents. In the case of the event's rate being dependent on zero agent's internal features, the rate is determined as above. If the rate is dependent on 1 or 2 agents, we consider the event's rate to be that of the multiplication of an agent dependent rate, *AR*, and an agent non-dependent rate, *R*. *R* is calculated as above and *AR* is calculated in an analogous way. The difference is that the inputs that go into an agent dependent rate are solely that of the internal value features of the agents. The individual rates are stored in a vector for a 1 agent based rate and as a matrix for a 2 agent based rate where each term corresponds to an agent or a set of agents rate. The

Authorized licensed use limited to: Drexel University. Downloaded on February 18,2025 at 19:29:54 UTC from IEEE Xplore. Restrictions apply.

overall event rate would be the sum of the agent dependent rates multiplied by the non-dependent rate, i.e., if the agent dependency equals zero, the rate is determined by:

$$\text{Event(i).Rate} = \text{Event(i).R}$$

Otherwise the event's rate is determined by:

$$\text{Event(i).Rate} = \text{Event(i).R} * \text{sum(Event(i).AR)}.$$

An example of two agent dependent binding is the T cell/APC binding example we discussed earlier. Here we cannot simply multiply a rate due to the T cell by the rate of the APC, but instead must consider the affinity between the T cell's receptor and the displayed antigen/MHC complex of the APC. This affinity of this binding would not change based on the environment. The rate of binding, however, could be altered by environmental features, such as cytokines. Due to this, if we wrote a simulation for T cell/APC binding, we would consider the agent-dependent rate as the factor that is the result of affinity and the non-agent dependent rate that is a result of cytokine concentrations and rate constants.

Monte Carlo Step and Updating

MiGHT utilizes a Monte Carlo step to determine the time interval for the next event to occur as well as randomly choose, in order, the bin in which an event occurs within, the event which occurs, and potentially which agent or set of agents undergoes the event. A random number, r, is utilized to determine the timestep, τ, for an event to occur based on the total sum of event rates by the formula:

$$\tau = \frac{1}{R_{tot}} ln\left(\frac{1}{r}\right).$$

The probability of Bin(x,y) being chosen as the bin for the next event to occur is set equal to the contribution of the rate of event occurrence from the bin, $R_{Bin(x,y)}$, to the total sum of event rates, R_{tot}, such that

$$P(Bin(x,y)) = \frac{R_{Bin(x,y)}}{R_{tot}}.$$

To choose a bin, we vectorize the probabilities of the bins, generate a random number, r, between 0 and 1, and choose the bin based on where this random number falls within the probabilities of bins, such that we choose bin(j) if

$$\sum_{i=1}^{j} P\big(Bin(i)\big) \geq r \quad \& \quad \sum_{i=1}^{j-1} P\big(Bin(i)\big) < r.$$

The event is chosen in an analogous way. Here, the probability that event i is chosen as the event to occur given that Bin(x,y) is chosen is the contribution of the rate of occurrence from the event, $R_{E(i)}$, to bin(x,y)'s total rate of occurrence, such that

$$P(E(i)|Bin(x,y)) = \frac{R_{E(i)|Bin(x,y)}}{R_{Bin(x,y)}}.$$

It is important to state that the order in which the event and bin is chosen theoretically should not at all effect how a simulation behaves. However, you would have to weigh the choice of bin conditionally on the chosen event.

When a TIPS based entity that is tagged is set to react, MiGHT randomly chooses which individual agent from that bin undergoes the interaction. This choice is weighted based on the agent dependent weight if the reaction is agent based. Here, an additional random number is utilized to determine the agent or set of agents that undergoes the event in a way analogous to the decision of which bin is chosen.

Once, these values are chosen, the system is updated to execute whichever event was chosen with the given agents as well as increase the time step and these steps are iterated until the simulation time has been exceeded. The internal state of an agent may be dependent on the event which has occurred. To update internal feature values due to an event occurring, we couple the event with a change of the internal feature values. To determine an internal feature's new value, we evaluate an equation which can consider the previous value of that internal feature, other internal features, the event that has occurred, and the environment. The event itself may also be to only update the internal state of an agent. This was designed to so that an agent's features can change independent of an interaction, as a self-contained sub-level simulation, in response to the environment, or in response to the internal features of a bound agent within the same hierarchical complex. For example, the internal state of the cell may change due to environmental factors, such as cytokines. This cell might also release signaling molecules, such as cytokines, into the environment over time.

To attempt to reduce the number of calculations for a given iteration, we choose to only update event rates which are dependent on the entity counts or internal feature values of an entity which may change due to the event chosen for the Monte Carlo Step in the bin or bins in which the event occurs. To do so, we attach a vector to each event corresponding to the entities which may change during the event. We also attach to each entity type a vector corresponding to the events whose rates are based on that entity. With this vector we can find the unique set of rates which need to be updated following the occurrence of each event. If any internal feature value is changed for an agent, we update all agent based rates of events in which the rate is dependent on that entity. However, we only update the components of the rate that are directly dependent on the specific agent which has undergone the event. If a new individual agent is added and we are calculating a 1 agent dependent rate, a new calculated value corresponding to that specific agent is added to the end of the agent dependent vector. If we are calculating a 2 agent dependent rate, we calculate and attach a new row or column to the end, depending on if the new agent is the first or second agent in the rate calculation. If the agent is removed during the event, we delete its corresponding value, row, or column. Lastly, if the agent is changed, we update its corresponding value, row, or column.

D. Hybrid Integration and Model Sampling

When an IPS model is not feasible, such as the diffusion of many molecules, MiGHT allows for the hybrid use of other modeling schemas in tandem to the stochastic simulation of TIPS. These modeling schemas include global events and tau-leaping approximation events that can be used to update the internal feature values and environmental entities of the simulation. Global events are events which occur in every bin.

Authorized licensed use limited to: Drexel University. Downloaded on February 18,2025 at 19:29:54 UTC from IEEE Xplore. Restrictions apply.

These events can be simulated via differential equations or binomial estimations and will generally be events which estimate the overall behavior of many agents, such as the simulation of cytokine diffusion.

Global events are not considered in the total rate within the main Gillespie algorithm loop of the MiGHT simulation. Instead, MiGHT updates global events at a given timestep parallel to the Gillespie loop [13]. Each global event's given timestep can be different for each global event type, i.e. the ith global event has a timestep, *Gtau(i)*. MiGHT first decides the timestep, τ, of the next event in the Gillespie algorithm loop. Next, the simulation loops through all global events which occur prior to that time step ordered by the time of their next occurrence, *Gtime*, and then by the order in which the events are in. Single global events can occur multiple times prior to the next stochastic event or vice versa, depending on their temporal scale:

```
while any(Gtime < T + τ)
        Idx = min(Gtime)
        Run_Global_Event(Idx)
        Gtime(Idx) = Gtime(Idx) + Gtau (Idx)
End
```

The second type of modeling schema that is incorporated into our modeling framework is a non-global approximation which resembles a tau-leaping methodology. In tau-leaping, at a given tau timestep in a simulation with N bins, an independent Monte Carlo method is used to choose a bin and update it and repeat this process for a total of N independent times, each time updating the chosen bin for an estimate of events within that bin for a timestep of tau [41]. The state of the bin can be updated in a non-discrete, deterministic way by using differential equations or in a discrete stochastic way by using a binomial estimation. We incorporate this modeling schema into the Gillespie simulation loop by giving each bin a rate of 1/tau of being updated by a tau-leaping methodology. When chosen, a bin is updated by the event's set of differential equations or binomial estimations for a timestep of tau.

E. Macrophage Model

MiGHT is applied to a model of macrophage activation and adaptation through the NF-kB pathway in response to LPS. LPS are endotoxins on the outer membrane of Gram negative bacteria that potently activates macrophages [16, 17]. When activated by LPS, macrophages produce pro-inflammatory cytokines such as TNFα [18]. IFNγ (interferon gamma) priming of macrophages prior to LPS stimulation enhances LPS-induced TNFα production [19] and the expression of NF-kB subunit P65 mRNA [20]. This is vital to a pro-inflammatory response, as P65 is required for induction of TNFα dependent genes [21], and TNFα further activates the cell through a positive feedback loop with NF-kB [22]. STAT1 and 3 are transcription factors that regulate NF-kB transactivation. IFNγ triggers prolonged STAT1 activation [23], while not activating STAT3 [24]. STAT3 downregulates the production of TNFα [25] and was found to bind and inhibit p65 transactivation [26]. STAT1, however, interacts with p65 without inhibiting transactivation [27]. Alternative activation of macrophages is characterized as an activation that downregulates inflammatory cytokines, promoting healing, and is characterized by an increase of the anti-inflammatory cytokine IL-10 [28]. IL-10 mediates an anti-inflammatory response through the activation of STAT3 [29] and selectively induces nuclear translocation and DNA-binding of p50 homodimers while blocking p65 translocation [30]. P50 homodimers lack transactivation domains and have been shown to be upregulated in LPS tolerance and to suppress TNFα gene expression and production [31, 32], and to selectively inhibit stimuli that transiently activate p65-p50 complexes [33].

To test the capabilities of a cell population level implementation of MiGHT, we created a simplified model of macrophage differentiation and inflammation. To do so, we limited the internal macrophage reactions to only contain P50, P65, STAT1, and STAT3 transcription factors with the external cytokines of IL-10 and TNF and the initiation of activation through LPS. We adjusted STAT1 within this simulation to allow us to simulate multiple levels of co-stimulation within cells.

We developed our macrophage model to show a potential set of macrophage dynamics based on physiologically realistic levels of TNF and IL10[42] expressed in a single diverse population of macrophages over time. Rates are given in table 1 and are relative to specific binding rates and TNF/IL10 concentrations. These parameters were calibrated to reduce the dimensionality of the parameter space and to make the model solvable, eliminating unknown parameters from the model. A value of 1 for STAT1 corresponds to the concentration which halves the production of STAT3, a value of 1 of STAT3 corresponds to the concentration which halves the production of P65, a value of 1 of P50 corresponds to the concentration of P50 for half maximal IL10 production, and a value of 1 of P65 corresponds to the concentration of P65 for half maximal TNF production when P50 is at a value of 1. A value of 1 of LPS corresponds to the concentration of LPS needed to produce P50 at a rate which is equal to 1 ng/ml of TNF. Our set of differential equations are below as follows:

$$d[IL10] = RIL\frac{[P50]^2}{1+[P50]^2} - DIL * [IL10]$$

$$d[TNF] = BTNF + RTNF\frac{([P50]*[P65])^2}{1+([P50]*[P65])^2} - DTNF * [TNF]$$

$$d[LPS] = DLPS * [LPS]$$

$$d[P50] = R1P50 * ([TNF]+[LPS]) + R2P50 * [IL10] - DP50 * [P50]$$

$$d[P65] = RP65 * \frac{([TNF]+[LPS])}{1+[STAT3]} - DP65 * [P65]$$

$$d[STAT3] = RS3 * \frac{[P50]^2}{(1+[STAT1])} - DS3 * [STAT3]$$

Authorized licensed use limited to: Drexel University. Downloaded on February 18,2025 at 19:29:54 UTC from IEEE Xplore. Restrictions apply.

Table 1. Model reaction rates and initial entity counts

Reaction Variable	Reaction Rate	Reaction Variable	Relative Rate
RIL	200 pg/(ml*hr)	R1P50	0.008/hr
DIL	1.2/hr	R2P50	0.06/hr
BTNF	720 pg/(ml*hr)	RP65	0.04/hr
RTNF	21.6 ng/(ml*hr)	RS3	10/hr
DTNF	24/hr	**Entity Relative Concentration**	**Initial Value**
DLPS	6/hr		
DP50	7/hr	[LPS]	600
DP65	3/hr	[P50]	0.04
DS3	1.2/hr	[P65]	0.2
Entity Concentration	**Initial Value**	[STAT3]	0
		[STAT1]	0
[IL10]	4 pg/ml		
[TNF]	30 pg/ml		

To implement MiGHT, we placed macrophages into an environment where cytokines can diffuse. The diffusion and degradation of TNF, IL10, and LPS were simulated through a global, differential equation, event. The internal workings which generate TNF and IL10, as well as the change in P50, P65, and STAT3 internal concentrations were simulated as a differential equation internal event which was updated using our tau-leaping methodology. We first modeled a single cell within a single bin environment with different amounts of STAT1 concentrations, allowing us to compare the implementation of this model with MiGHT to the differential equation implementation. Next, we placed 9 macrophages within a 9 by 9 binned environment, with each bin representing an area of 0.25 ml. We placed the macrophages in two configurations, a uniform spread distribution and a grouped distribution (**Fig. 1**). LPS was placed within the environment either locally, at the centermost bin, or globally among all bins. The generation rates of both IL10 and TNF were doubled in comparison to differential equation model to compensate for the loss of cytokines due to diffusion, and the diffusion rate of both cytokines was set to 20 bins per hour. We utilized a robust graphical estimate of confidence intervals (*CIs*) computed from upper (UQ) and lower (UL) quartiles for N data points by the equation $CI = 1.57 * (UQ - LQ)/\sqrt{N}$ [43].

III. Results

To frame our MiGHT results in a wider context, we first simulated the dynamics of the macrophage response to LPS through a set of ordinary differential equations (ODEs). We compared the ODE results to the MiGHT simulation of a single

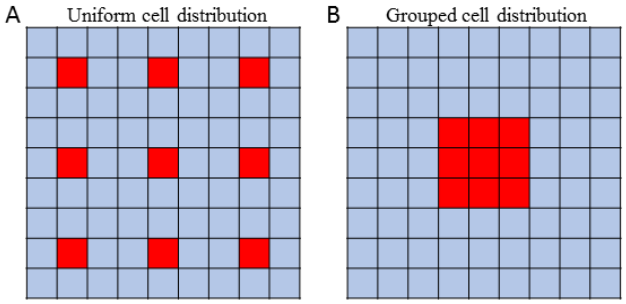


Fig 1: The distributions of cells within our simulation environment. **A**. A uniform distribution in which cells are equally dispersed. **B**. A grouped distribution of cells within the environment. This represents the cells being recruited to a local signal.

macrophage population within a single bin or homogeneous environment (**Fig. 2**). Both modeling techniques presented equivalent results for population dynamics, showing that global and internal events in MiGHT behave properly. The simulated macrophage population produced a TNF response followed by an IL10 response in the presence of only one cell type, showing that there is no need for multiple phenotypes for these cells to produce both pro and anti-inflammatory responses at the population level. The presence of co-stimulation, simulated by an increase in STAT1, showed a prolonged signal.

Next, we simulated multiple cells within an environment in either a uniform cell distribution or clustered in a group (**Fig. 1**). We simulated these cells without any concentration of STAT1, while introducing LPS either locally (at Bin(5,5), which is the central bin of the environment - **Fig. 1**) or globally (at every bin). We then measured cytokine expression locally and globally (**Fig. 3**). At the local level, TNF and IL10 cytokine concentrations changed much the same in response to global or local LPS administration. In both cases of LPS administration, local levels of TNF and Il-10 were higher when macrophages were in a grouped and not uniform distribution. The only different effect of local administration on local cytokine levels was a slight delay in cytokine dynamics (**Fig. 3a** and **b**). When we looked at the global response the effect of the distribution the activation signal and distribution of macrophages was more pronounced. While both distributions responded very similarly to a global LPS signal (**Fig3c**), the uniformly distributed macrophages did not globally respond to a local signal injected only at Bin(5,5), while grouped macrophages showed TNF and IL10 signals post local LPS activation that were comparable to those resulting from global LPS activation (**Fig. 3d**). This

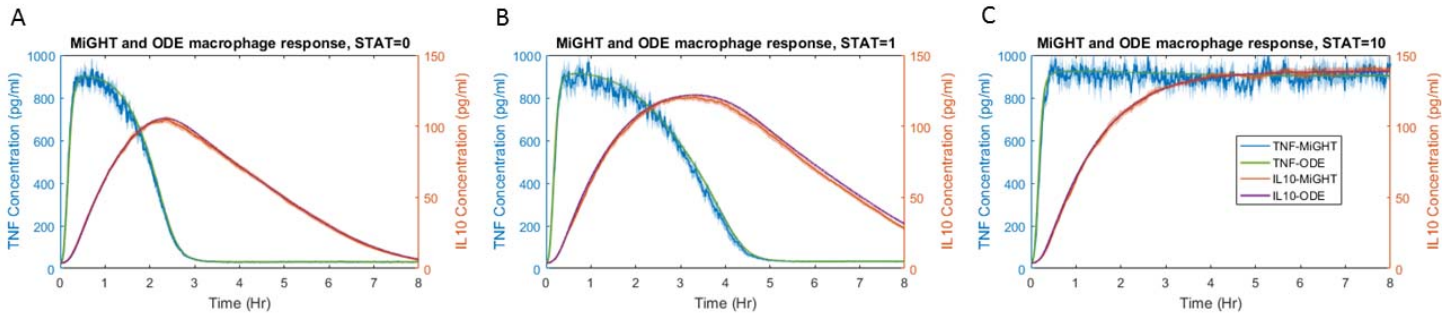


Fig 2. The macrophage response to LPS simulated with an ODE and a single-binned homogeneous implementation of MiGHT under various levels of STAT1. **A**. STAT1 concentration = 0 **B**. STAT1 concentration = 1 **C**. STAT1 concentration = 10. Shaded areas correspond to non-parametric 95% confidence intervals.

Authorized licensed use limited to: Drexel University. Downloaded on February 18,2025 at 19:29:54 UTC from IEEE Xplore. Restrictions apply.

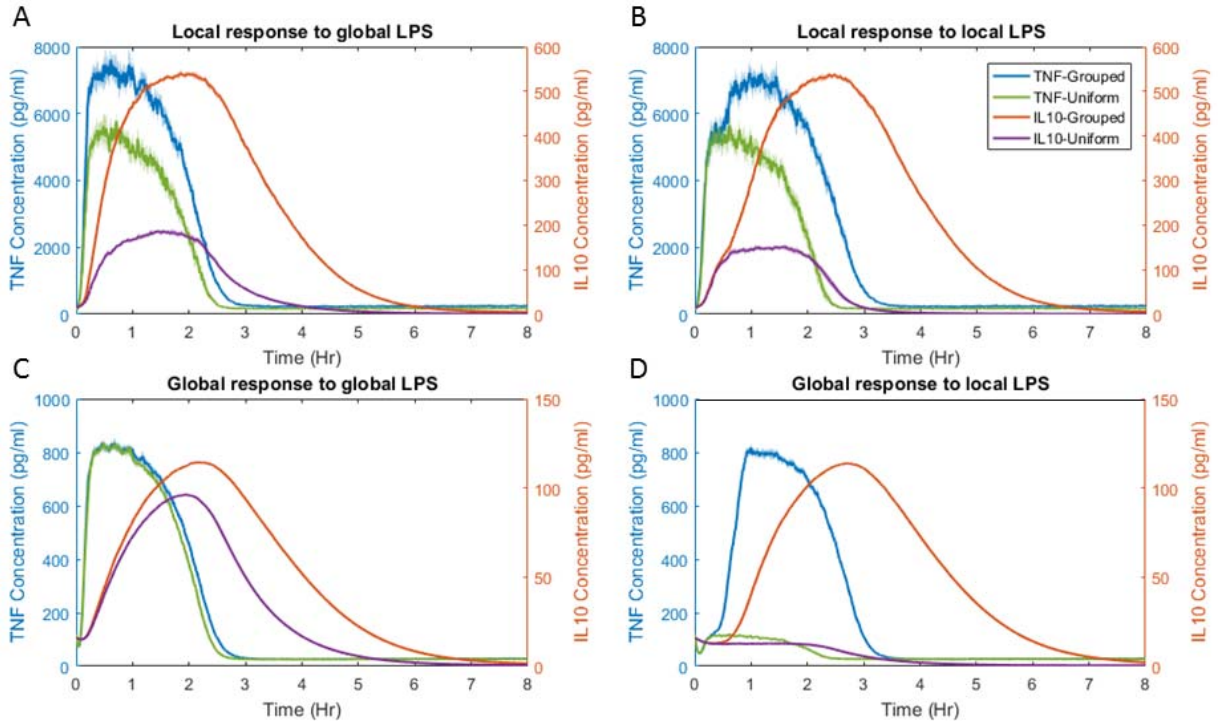


Fig 3. Local (Bin(5,5)) and global macrophage response to local and global LPS administration. Macrophages were distributed uniformly within the environment or grouped together, mimicking their recruitment to an infection. Shaded areas correspond to non-parametric 95% confidence intervals.

suggests that utilizing a population with the same parameters of action, we can shift from a state where local excitation elicits no response to one that does simply by changing the distribution of cells.

IV. Conclusions

We created a novel modeling framework which allows for cellular adaptation due to history and the environment. With this novel modeling schema, we can follow individual agents as they move and undergo complex binding within our simulation. We can model these agents' internal features as sub-level self-contained models which can directly impact the behavior of each given agent. By implementing multiple simulation techniques, we can efficiently model not only complex individual behaviors, but also the mass population dynamics which are needed to model biological phenomena such as cytokine diffusion. Taken together these components of MiGHT make it a powerful modeling technique, which can be implemented to fit a plethora of biological systems.

We applied MiGHT to model macrophage response to LPS. Macrophages were modeled to adapt their cytokine production based on the cell's internal state, which is dependent on the cell's history of cytokine interaction and co-stimulation. With this model we have shown that a heterogeneous population of macrophages can transition through the stages of macrophage activation through a simple set of dynamics. Furthermore, the systematic response of macrophages is dependent on how individual macrophages are distributed within the environment and not on mass action of homogenous polarized populations.

Acknowledgement

We would like to thank the SIM lab members and Louis J. Piscopo for their advice and conversations. Justin Melunis is recipient of the Department of Education Graduate Assistance in Areas of National Need (GAANN) Fellowship.

Refernces

[1] D. T. Gillespie, "Exact stochastic simulation of coupled chemical reactions," *The Journal of Physical Chemistry,* vol. 81, no. 25, pp. 2340-2361, 1977.

[2] Y. R. Zelnik, S. Solomon, and G. Yaari, "Species survival emerge from rare events of individual migration," *Scientific Reports,* vol. 5, p. 7877, Jan 19 2015.

[3] H. Behar, N. Brenner, and Y. Louzoun, "Coexistence of productive and non-productive populations by fluctuation-driven spatio-temporal patterns," (in eng), *Theor Popul Biol,* vol. 96, pp. 20-9, Sep 2014.

[4] N. M. Shnerb, Y. Louzoun, E. Bettelheim, and S. Solomon, "The importance of being discrete: Life always wins on the surface," *Proceedings of the National Academy of Sciences,* vol. 97, no. 19, pp. 10322-10324, Sept 12 2000.

[5] Y. B. Zion, G. Yaari, and N. M. Shnerb, "Optimizing Metapopulation Sustainability through a Checkerboard Strategy," *PLoS Computational Biology,* vol. 6, no. 1, p. e1000643, Jan 22 2010.

[6] A. J. Black and A. J. McKane, "Stochastic formulation of ecological models and their applications," *Trends in Ecology & Evolution,* vol. 27, no. 6, pp. 337-345, 2012.

[7] J. Melunis and U. Hershberg, "A spatially heterogeneous Gillespie algorithm modeling framework that enables individual molecule history and tracking," *Engineering Applications of Artificial Intelligence,* vol. 62, pp. 304-311, June 2017.

[8] M. Meier-Schellersheim, X. Xu, B. Angermann, E. J. Kunkel, T. Jin, and R. N. Germain, "Key Role of Local Regulation in Chemosensing Revealed by a New Molecular Interaction-Based

Authorized licensed use limited to: Drexel University. Downloaded on February 18,2025 at 19:29:54 UTC from IEEE Xplore. Restrictions apply.

Modeling Method," *PLoS Computational Biology,* vol. 2, no. 7, p. e82, July 2006.

[9] B. R. Angermann *et al.*, "Computational Modeling of Cellular Signaling Processes Embedded into Dynamic Spatial Contexts," *Nature methods,* vol. 9, no. 3, pp. 283-289, 01/29 2012.

[10] P. A. Robert, A. Rastogi, S. C. Binder, and M. Meyer-Hermann, "How to Simulate a Germinal Center," in *Germinal Centers: Methods and Protocols*, D. P. Calado, Ed. New York, NY: Springer New York, 2017, pp. 303-334.

[11] M. Meyer-Hermann, "A Mathematical Model for the Germinal Center Morphology and Affinity Maturation," *Journal of Theoretical Biology,* vol. 216, no. 3, pp. 273-300, 2002/06/07/ 2002.

[12] M. Meyer-Hermann, E. Mohr, N. Pelletier, Y. Zhang, Gabriel D. Victora, and K.-M. Toellner, "A Theory of Germinal Center B Cell Selection, Division, and Exit," *Cell Reports,* vol. 2, no. 1, pp. 162-174.

[13] Y. Shimoni, G. Nudelman, F. Hayot, and S. C. Sealfon, "Multi-Scale Stochastic Simulation of Diffusion-Coupled Agents and Its Application to Cell Culture Simulation," *PLOS ONE,* vol. 6, no. 12, p. e29298, 2011.

[14] U. Hershberg, Y. Louzoun, H. Atlan, and S. Solomon, "HIV time hierarchy: winning the war while, loosing all the battles," *Physica A: Statistical Mechanics and its Applications,* vol. 289, no. 1, pp. 178-190, 2001.

[15] C. D. Mills, K. Kincaid, J. M. Alt, M. J. Heilman, and A. M. Hill, "M-1/M-2 macrophages and the Th1/Th2 paradigm," (in eng), *J Immunol,* vol. 164, no. 12, pp. 6166-73, Jun 15 2000.

[16] F. O. Martinez and S. Gordon, "The M1 and M2 paradigm of macrophage activation: time for reassessment," *F1000Prime Reports,* vol. 6, p. 13, March 2014.

[17] M. J. Davis *et al.*, "Macrophage M1/M2 polarization dynamically adapts to changes in cytokine microenvironments in Cryptococcus neoformans infection," (in eng), *MBio,* vol. 4, no. 3, pp. e00264-13, Jun 18 2013.

[18] T. L. Kielian and F. Blecha, "CD14 and other recognition molecules for lipopolysaccharide: A review," *Immunopharmacology,* vol. 29, no. 3, pp. 187-205, 1995.

[19] F. Meng and C. A. Lowell, "Lipopolysaccharide (LPS)-induced macrophage activation and signal transduction in the absence of Src-family kinases Hck, Fgr, and Lyn," (in eng), *J Exp Med,* vol. 185, no. 9, pp. 1661-70, May 05 1997.

[20] J. Xaus *et al.*, "LPS induces apoptosis in macrophages mostly through the autocrine production of TNF-α," *Blood,* vol. 95, no. 12, pp. 3823-3831, 2000.

[21] S. Spinelle-Jaegle *et al.*, "Inflammatory cytokine production in interferon-gamma-primed mice, challenged with lipopolysaccharide. Inhibition by SK&F 86002 and interleukin-1 beta-converting enzyme inhibitor," (in eng), *Eur Cytokine Netw,* vol. 12, no. 2, pp. 280-9, Apr-Jun 2001.

[22] H. de Wit, D. Hoogstraten, R. M. Halie, and E. Vellenga, "Interferon-gamma modulates the lipopolysaccharide-induced expression of AP-1 and NF-kappa B at the mRNA and protein level in human monocytes," (in eng), *Exp Hematol,* vol. 24, no. 2, pp. 228-35, Feb 1996.

[23] A. A. Beg and D. Baltimore, "An essential role for NF-kappaB in preventing TNF-alpha-induced cell death," (in eng), *Science,* vol. 274, no. 5288, pp. 782-4, Nov 01 1996.

[24] Y. Kagoya *et al.*, "Positive feedback between NF-kappaB and TNF-alpha promotes leukemia-initiating cell capacity," (in eng), *J Clin Invest,* vol. 124, no. 2, pp. 528-42, Feb 2014.

[25] G. Regis, S. Pensa, D. Boselli, F. Novelli, and V. Poli, "Ups and downs: The STAT1:STAT3 seesaw of Interferon and gp130 receptor signalling," *Seminars in Cell & Developmental Biology,* vol. 19, no. 4, pp. 351-359, Aug 2008.

[26] Z. Zhong, Z. Wen, and J. E. Darnell, Jr., "Stat3: a STAT family member activated by tyrosine phosphorylation in response to epidermal growth factor and interleukin-6," (in eng), *Science,* vol. 264, no. 5155, pp. 95-8, Apr 01 1994.

[27] P. R. de Jong *et al.*, "STAT3 Regulates Monocyte TNF-Alpha Production in Systemic Inflammation Caused by Cardiac Surgery with Cardiopulmonary Bypass," *PLoS ONE,* vol. 7, no. 4, p. e35070, 2012.

[28] Z. Yu, W. Zhang, and B. C. Kone, "Signal transducers and activators of transcription 3 (STAT3) inhibits transcription of the inducible nitric oxide synthase gene by interacting with nuclear factor κB," *Biochemical Journal,* vol. 367, no. 1, pp. 97-105, 2002.

[29] O. H. Krämer *et al.*, "Acetylation of Stat1 modulates NF-κB activity," *Genes & Development,* vol. 20, no. 4, pp. 473-485, 2006.

[30] A. P. Hutchins, D. Diez, and D. Miranda-Saavedra, "The IL-10/STAT3-mediated anti-inflammatory response: recent developments and future challenges," (in eng), *Brief Funct Genomics,* vol. 12, no. 6, pp. 489-98, Nov 2013.

[31] F. Driessler, K. Venstrom, R. Sabat, K. Asadullah, and A. J. Schottelius, "Molecular mechanisms of interleukin-10-mediated inhibition of NF-κB activity: a role for p50," *Clinical and Experimental Immunology,* vol. 135, no. 1, pp. 64-73, 2004.

[32] J. Bohuslav *et al.*, "Regulation of an essential innate immune response by the p50 subunit of NF-kappaB," (in eng), *J Clin Invest,* vol. 102, no. 9, pp. 1645-52, Nov 01 1998.

[33] S. Kastenbauer and H. W. Ziegler-Heitbrock, "NF-kappaB1 (p50) is upregulated in lipopolysaccharide tolerance and can block tumor necrosis factor gene expression," (in eng), *Infect Immun,* vol. 67, no. 4, pp. 1553-9, Apr 1999.

[34] X. Tong, L. Yin, R. Washington, D. W. Rosenberg, and C. Giardina, "The p50-p50 NF-kappaB complex as a stimulus-specific repressor of gene activation," (in eng), *Mol Cell Biochem,* vol. 265, no. 1-2, pp. 171-83, Oct 2004.

[35] J. Day, A. Friedman, and L. S. Schlesinger, "Modeling the immune rheostat of macrophages in the lung in response to infection," *Proceedings of the National Academy of Sciences of the United States of America,* vol. 106, no. 27, pp. 11246-11251, June 2009.

[36] S. Marino, A. Myers, J. L. Flynn, and D. E. Kirschner, "TNF and IL-10 are major factors in modulation of the phagocytic cell environment in lung and lymph node in tuberculosis: a next generation two compartmental model," *Journal of theoretical biology,* vol. 265, no. 4, pp. 586-598, 05/25 2010.

[37] S. Marino and D. E. Kirschner, "The human immune response to Mycobacterium tuberculosis in lung and lymph node," *Journal of Theoretical Biology,* vol. 227, no. 4, pp. 463-486, 2004/04/21/ 2004.

[38] T. Kilch *et al.*, "Mutations of the Ca(2+)-sensing Stromal Interaction Molecule STIM1 Regulate Ca(2+) Influx by Altered Oligomerization of STIM1 and by Destabilization of the Ca(2+) Channel Orai1," *The Journal of Biological Chemistry,* vol. 288, no. 3, pp. 1653-1664, 2013.

[39] D. M. Davis and M. L. Dustin, "What is the importance of the immunological synapse?," *Trends in Immunology,* vol. 25, no. 6, pp. 323-327.

[40] A. Grakoui *et al.*, "The immunological synapse: a molecular machine controlling T cell activation," (in eng), *Science,* vol. 285, no. 5425, pp. 221-7, Jul 09 1999.

[41] D. T. Gillespie, "Approximate accelerated stochastic simulation of chemically reacting systems," *The Journal of Chemical Physics,* vol. 115, no. 4, pp. 1716-1733, 2001.

[42] E. Kemna, P. Pickkers, E. Nemeth, H. van der Hoeven, and D. Swinkels, "Time-course analysis of hepcidin, serum iron, and plasma cytokine levels in humans injected with LPS," *Blood,* vol. 106, no. 5, pp. 1864-1866, 2005.

[43] R. McGill, J. W. Tukey, and W. A. Larsen, "Variations of Box Plots," *The American Statistician,* vol. 32, no. 1, pp. 12-16, 1978.

Authorized licensed use limited to: Drexel University. Downloaded on February 18,2025 at 19:29:54 UTC from IEEE Xplore. Restrictions apply.