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The Inflammatory Twitch as a General Strategy for Controlling the Host Response

Joshua J. Pothen, Matthew E. Poynter, and Jason H. T. Bates

Allergic inflammation is a general host-defense mechanism for dealing with perceived foreign invaders. Although most effort has been directed toward understanding how this response gets turned on, how it gets turned off again when no longer needed is just as important to an organism’s survival. We postulate that the control of the allergic inflammatory response is achieved via frequency modulation whereby a sequence of self-resolving events is repetitively invoked only so long as Ag is present. This leads to the notion of a unitary inflammatory event that we argue has formal similarity to the skeletal muscle twitch, albeit manifest over a much longer time scale. To test the plausibility of this hypothesis, we created an agent-based computational model of the allergic inflammatory response in the lungs. Continual stimulation of the model results in cycles of tissue damage and repair interspersed with periods of nonresponsiveness indicative of a refractory period. These findings are consistent with the inflammatory twitch hypothesis and the notion that the allergic inflammatory response is controlled via frequency modulation. We speculate that chronic inflammatory diseases may represent a failure of the inflammatory twitch to resolve toward baseline. The Journal of Immunology, 2013, 190: 3510–3516.

The inflammatory response is a general biological defense mechanism for battling invading microbes or attending to injury. The symptomatic manifestations of inflammation, namely, tumor, rubor, calor, and dolor, reflect myriad molecular events that orchestrate a variety of resident and recruited cell types to operate in a specific manner within the affected tissue (1). Clearly, turning on an appropriate inflammatory response in time of need is critical to an organism’s survival. However, turning the response off again when it is no longer needed is equally important. Indeed, failure to resolve the inflammatory response is presumably behind the chronic inflammatory conditions that characterize many common diseases. This raises the general question as to what strategy the body uses to control both the upregulation and the downregulation of inflammation. Negative feedback has been proposed as a means for controlling the extent of allergic inflammation (2). However, recent work suggests this does not adequately explain the relationship between the stimulus and the allergic response (3). Another possibility is that these two events are subject to independent decision criteria; upregulation of inflammation is directed by a control mechanism that reacts to the appearance of a threat, whereas downregulation is controlled by a separate mechanism that detects the threat’s disappearance. This scenario is compelling because of its ready analogy to the fighting of military battles. However, it is not the only possibility.

An alternative control strategy for the inflammatory response is suggested by the formal similarity of its task structure to that of skeletal muscle. The inflammatory response is something that an organism must be ready to invoke, without warning, any time a threat arises, and yet it must dissipate when no longer needed. The same applies to muscle activation; muscles must be ready to generate force whenever the brain decides to undertake some task, but must cease to do so as soon as the task is completed. However, the force generation and cessation in muscle are not subject to separate decision processes, but rather are controlled jointly via frequency modulation. Specifically, a muscle continues to do the job asked of it so long as it receives a steady stream of periodic electrical impulses, the frequency of the impulses dictating the level of force. Once the need for the task has passed, however, the impulses stop and the muscle returns to quiescence. The functional unit of this control strategy is the muscle twitch, a transient manifestation of force driven by a sequence of events that includes not only those that cause force to escalate, but also those that bring about its subsequent resolution. In other words, the termination of a muscle twitch is an inevitable consequence of its initiation, so continuation and/or escalation of force is simply a consequence of how individual twitches summate when invoked in rapid succession. The singular advantage of this type of control strategy is that it obviates the need for additional decision resources beyond those involved in activation.

The above reasoning leads us to contemplate the possibility that inflammation might be controlled in a similar manner to skeletal muscle, that is, via the repetitive generation of self-limited, transient, unitary responses. This analogy implies the existence of an “inflammatory twitch,” an inevitably resolving sequence of cellular events having formal similarity to a muscle twitch, albeit over a greatly extended time scale. Further questions then arise as to the extent of this analogy. What is the duration of an inflammatory twitch? Can multiple inflammatory twitches summate in the same manner as muscle twitches? Do inflammatory twitches create a postinitiation refractory period? Answering these questions might elucidate important aspects of how the general host inflammatory response is controlled, and possibly even how its control might fail in disease.

Accordingly, the goal of this study was to investigate the plausibility of the inflammatory twitch hypothesis. We focused in...
particular on allergic inflammation in the lung because this condition has been well characterized in terms of the cell types involved (1). Also, we have previously observed that when allergically sensitized mice are continuously challenged with Ag over a period of weeks, their inflammatory response does not continue indefinitely, but instead eventually resolves toward baseline (4). Furthermore, if Ag challenge is interrupted for several weeks and then reinitiated, the animals again mount a vigorous inflammatory response (5). These observations appear to be consistent with our notion of the inflammatory twitch, but they do not demonstrate that it is feasible relative to the interactions of all the cells involved. Allergic inflammation in the lung is a complex event, localized around the lung and its associated mediastinal lymph nodes, yet involving a variety of cells recruited at different times from outside the organ (6, 7). It is not immediately obvious that a twitchlike, self-limited response to the appearance of an Ag in the lung could actually manifest from a system with these features.

Testing the plausibility of the inflammatory twitch hypothesis thus requires that the spatiotemporal dynamics of the various cellular players and chemical signals involved be taken into account. In this study, we undertook this task computationally, using a modeling technique that appears ideally suited to this purpose.

This technique, known as agent-based modeling, allowed us to simulate the dynamic environment comprising the pulmonary capillary and its associated alveolar compartment, and to determine whether something akin to an inflammatory twitch is indeed possible, and what its temporal and spatial morphology might look like.

Materials and Methods

Model structure

We used NetLogo 4.1.3 freeware (8) to design an agent-based model that simulates allergic inflammation in an alveolus of the lung in response to Ag stimulation. The model uses two types of variables known, respectively, as patches and agents. Patches represent fixed pieces of the local environment, and thus contain local variables representing information about that area. In our model of the allergic inflammatory response, the patches represent the capillary and alveolus, as well as the endothelial barrier between them. (The sizes of the capillary and alveolar spaces are arbitrary.) Each alveolar patch has a local parameter known as “tissue-life,” which indicates the amount of tissue damage that has occurred on that patch. It is set between 0 and 100, where 100 corresponds to full health and 0 indicates a fully destroyed patch. Thus, the average health of all alveolar patches represents the average health of the alveolus.

In contrast with patches, which represent the environment, agents represent individual entities capable of moving across patches and interacting with surrounding patches and with other agents. The agents in our model are the multiple cell types involved in the allergic inflammatory response in the lung. The behavior of the model is thus determined by the collection of rules that each agent obeys.

Our overall schema for the allergic response is shown in Fig. 1, and it includes what we believe to be the key mechanisms and cell types that are involved. To increase the manageability of the model, we have not included all known details of allergic inflammation in this schema. For example, following the approach of Brown et al. (8), we lumped dendritic cells, B cells, and macrophages together into a single APC type. Similarly, neutrophils, eosinophils, and other cell types that cause local tissue damage are merged into a single proinflammatory cell (PIC) type, whereas fibroblasts and other cells that are involved in tissue repair are combined into a single anti-inflammatory cell (AIC) type. This grouping of cell types is, of course, a gross oversimplification of reality, but we believe it represents the greatest degree of coarse graining that could reasonably be applied to the cellular community so that it still retains the ability to exhibit competition between inflammatory and reparative processes.

The inflammatory response is initiated by the sudden presence of particles at random locations in the alveolar space. Both mast cells and APCs are involved in this initiation. We focus on these two cell types because in vivo, mast cells release both preformed and synthesized chemical mediators such as PGs, leukotrienes, and vasoactive amines upon cross-linking of their receptors by bound Ag (1). This leads to many of the symptoms that are observed in the allergic inflammatory response, such as vasodilation and bronchoconstriction (1). In addition, APCs process Ag particles via pattern-recognition receptors, such as TLRs, and subsequently become activated. This affects cytokine production in such a way as to ultimately affect the T cell population, leading to amplification and perpetuation of the inflammatory phase of the allergic response (9).

The model was initialized with 5 mast cells, 10 APCs, and 10 PICs in the alveolus, and the same numbers in the capillary. The alveolus was also initialized with 20 AICs, 10 Th cells, and 10 regulatory T cells, whereas the capillary contained 5 Th and regulatory T cells. The capillary acts as a reservoir of cells, so if any of these cells dropped below these baseline values in the capillary, the appropriate number of additional cells was randomly added to the capillary space. The capillary effectively acts as a source and sink for cells in the alveolus. Thus, although the size of these spaces is arbitrary, changing the size of the capillary would not have a significant effect on the model.

The model includes an endothelial barrier between the capillary and the alveolus. Pores in the barrier allow restricted cell movement between the two spaces. If the sum of various PI chemical signals, namely, granules and PI cytokines in the lung space, is greater than a critical value (arbitrarily set at 200 for this model), the barrier is removed. This simulates the effects of vasodilation and endothelial leak by allowing uninhibited cell movement between the capillary and alveolar spaces.

Model dynamics

Inflammation in the model is initiated by random placement of a certain number of particles throughout the alveolus (8). Additional particles may be placed at any later time point to simulate continual stimulation of the inflammatory response.

Cell movement in the model is probabilistic. If there is no reason for a cell to move in any particular direction, the cell moves a distance of one patch either forward, back, right, or left with equal probability at each time step. However, if a patch contains a signal to which the cell is responsive, the probability of movement to that patch will be increased proportional to the strength of the signal. Thus, although, on average, a cell will move in the direction of the strongest signal, the movement at any particular time step may be in any direction.

Diffusion of chemical signals (i.e., granules, PI cytokines, and AI cytokines) is simulated by randomly distributing a specified fraction of each signal on a patch to its adjacent patches at each time step. Removal of these substances by enzymes, blood flow, and so on is simulated by having their strengths decrease by set proportions (specific for each substance) at each time step (8).

The life span of each cell type in the model follows an exponential distribution that is implemented as follows. At each time step, and for each cell in the model, we generate a random number on the uniform distribution between 0 and 1. If this number is greater than a critical value specific for the cell type in question, then the cell is eliminated. Mast cells and APCs are relatively long-lived compared with most of the other cell types (6, 10). (Although the most abundant CD4 T cell type, memory T cells, are also relatively long-lived, we do not consider them long-lived in our model because they may only be active for a shorter period after Ag exposure.) We thus chose the critical value for mast cells and APCs to be 0.9997, giving them an estimated mean life span of 2500 time steps, whereas the critical value for all the other cell types except the AICs was 0.9978, giving them an estimated mean life span of 200 time steps. The AICs were allowed to live indefinitely because fibroblasts are known to be very long-lived relative to the other cell types (11, 12).

Agent rules

The overall behavior of the model is a consequence of the way in which its agents (the cell types described earlier) behave. The behavior of each agent is governed by a set of rules designed to capture the essential elements of actual biological behavior. The various agents in our model are listed in Table I, together with the signals to which they respond and the rules that govern their behavior. The rule sets for each cell type are generally similar in that they cause the cells to move toward and become activated by certain chemical signals, and then release chemical signals of their own into the surrounding patches.

The initial cell types involved in the allergic response are mast cells and APCs, which both respond to particles and release chemical signals that initiate the subsequent events of the allergic response. Mast cells accomplish this task by binding to particles via the binding sites on the alveolar epithelial current (noncurrent) and then releasing a user-specified number of granules into the surrounding patches for 10 time steps (1). Mast cells initially exist in an immature state until a user-specified amount of time has passed, at which point they be-
come mature and functional. Mature mast cells move toward particles on adjacent patches, whereas immature mast cells move toward released attractants or else they move randomly (13, 14). In contrast, APCs eliminate particles on the patch they are currently on, releasing APC signals into the surrounding patches in the process (15). When either a PIC or a mast cell encounters a particle, it becomes sensitized. However, previous studies have shown that mast cells and APCs become desensitized after a period of continual stimulation (13). Accordingly, we allow mast cells and APCs in the model to be sensitized so long as they have encountered fewer than five particles, but they revert to a quiescent state otherwise.

Granules and APC signals serve as chemical signals for Th cells, that is, these cells preferentially move toward patches with high concentrations of these chemicals. Upon landing on these patches, Th cells are activated for 10 time steps during which they release PI cytokines (1). Afterward, they convert to PICs if they are still on patches with high PI cytokine levels.

PICs are signaled by both granules and PI cytokines, and become activated upon landing on a patch with high concentrations of these signals. They release PI cytokines and attractants for 10 activation steps and then die afterward. If activated PICs sense a strong signal on at least one of the nearby patches, they subtract 5 from the tissue-life parameter of the patch they are currently on; otherwise, they subtract 2.

The combination of both Th cell and PIC actions creates a positive feedback loop of PIC recruitment and PI cytokine release. This loop is ultimately hindered by T regulatory cells that respond to the PI cytokine chemical signal. Unlike PICs or Th cells, however, T regulatory cells remain permanently activated. Whenever they move toward PI cytokines, T regulatory cells release AI cytokines that subtract from the amount of PI cytokines on a patch and thus dampen the PI signal and its effect (1).

In contrast with the other cell types, AICs move preferentially toward damaged tissue, that is, any patch with a tissue-life parameter less than 100. Upon reaching a damaged tissue patch, an AIC will remain there and with each time step will add 1 to the tissue-life parameter of the patch until it reaches 100. At that point, the cells will either move toward another patch with a tissue-life parameter <100 or else it will move randomly. This behavior comes directly from the agent-based model developed by Brown et al. (8).

Fig. 2 shows an example output of the model. The baseline state of the model before application of any particles is shown in the left panel, where the light gray color corresponds to full tissue health. The middle and right panels show increasing levels of lung damage indicated by the progressively darkening alveolar patches.

### Results

All model simulations began with a run-in period of 250 time steps with no stimulation, which was found sufficient to have the model achieve steady-state. Fig. 3 shows the time course of tissue health over 15,000 time steps after the run-in period (average of 10 independent simulations) resulting from stimulating the model with 85 particles placed randomly within the alveolar space every 20 time steps. This caused oscillations in tissue health of progressively decreasing amplitude. Fig. 4 shows an expanded view of the initial portion of the simulation upon which we have superimposed data taken from a study by Tanaka et al. (3), who subjected OVA-sensitized mice to 3 wk of daily stimulation with OVA aerosol. The inflammatory status of the mice, including a variety of cell types in bronchoalveolar lavage fluid, were measured at four time points during this period to provide a time course for the inflammatory response. The data shown consist of the counts of PIC types in Fig. 4 (top panel; leukocytes plus lymphocytes) and macrophages (taken to represent AICs) in Fig. 4 (bottom panel). The two cell type counts from Tanaka et al. (3) shown in Fig. 4 have been scaled to be comparable with the simulated cell counts for ease of comparison of the shapes of these relationships with time. In addition, the time scales of the simulations have been adjusted so that 100 time steps equal 1 wk of real time, which leads to a good match between the simulated and experimental cell count profiles.

Fig. 5 shows the model behavior when it was subjected to the same stimulation regimen as used by Riesenfeld et al. (5), namely, three consecutive daily exposures to Ag followed by a single exposure 1 mo later. The dip in tissue health seen with the three early particle administrations is recapitulated, albeit to a somewhat reduced degree, when particles are administered again after the break. This shows that, given sufficient time, the model will recover sufficiently toward its naive state that it can mount a second response when restimulated.

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### Table 1. Summary of all agents and their respective rules included in the model

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Moves Toward</th>
<th>Rule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mast cell (immature)</td>
<td>Attractants</td>
<td>Moves preferentially to attractants, or randomly if there are no attractants</td>
</tr>
<tr>
<td>Mast cell (mature)</td>
<td>Particles, attractants</td>
<td>Upon binding particle, releases granules for 10 time steps; becomes inactive for user-set time if encounters user-set number of particles</td>
</tr>
<tr>
<td>APC</td>
<td>Particles</td>
<td>While digesting particle, releases APC signals; becomes inactive for user-set time if encounters user-set number of particles</td>
</tr>
<tr>
<td>Th cell</td>
<td>Granules, APC signals</td>
<td>If moving toward granules and/or APCs, releases PI cytokines for 10 time steps; afterward, if there is a strong chemical signal on the current patch, converts into a PIC</td>
</tr>
<tr>
<td>PIC</td>
<td>PI cytokines, granules</td>
<td>If moving toward PI cytokines and/or granules, become activated for 10 time steps; while activated, release PI cytokines and attractants; also, subtract 5 from the health of the patch currently on if cell has moved toward a chemical signal, or 2 if not; at the end of activation, the cell dies</td>
</tr>
<tr>
<td>T regulatory cell</td>
<td>PI cytokines</td>
<td>If moving toward PI cytokines, release AI cytokines</td>
</tr>
<tr>
<td>AIC</td>
<td>Patches with health &lt; 100</td>
<td>If on a patch with health &lt; 100, add 1 to that patch’s health parameter at each time step</td>
</tr>
</tbody>
</table>
Finally, Fig. 6 shows what happens to tissue health when the interval between application of particles is varied. Stimulation periods of 0.5, 1, and 2 wk yield rather similar results, characterized by an initial pronounced dip in tissue health followed by decreasing dips and more chaotic behavior as time progresses. By contrast, an application interval of 10 wk produces regular marked oscillations in tissue health that continue unabated.

Discussion
From the perspective of survival, turning off the body’s defense mechanisms when they are no longer needed is just as important as turning them on in response to a threat. Indeed, many chronic and debilitating diseases appear to be manifestations of a host response that fails to resolve when it should. Elucidating the pathophysiology of these diseases amounts, in large part, to finding out why control of the host response fails, and this begins with consideration of how it is controlled normally. Our thinking on this subject tends to be influenced by the common view of the host response as the waging of a military battle in which an army of defenders attempts to vanquish an invading foe. The danger with this analogy, however, is that it leads to the supposition of top-down command, yet there is no obvious analogue in living organisms of the general who surveys a battle scene and gives orders based on what is perceived to be happening.

Even more problematic, the military analogy suggests separate command and control systems for turning on the host response when it is needed, and then turning it off again when its job is done. Turning the response on presents no particular conceptual difficulty because it merely requires detection of a threat, and the various specialized cells of the immune system do just that. Turning the response off again via a separate controller is a problem, however,
FIGURE 5. Average of 10 simulations in which 3 particle challenges were placed in the alveolar space at roughly once per day followed by a fourth challenge 1 mo later (vertical arrows indicate the times of challenge).

because this would require detection of the absence of a threat, something that can only be done either by an intelligent entity capable of remembering all possible threats or by an innate sentinel poised to recognize molecular patterns indicative of “health” or threat absence, neither of which seems very likely. These considerations led us to postulate that the host response, and the allergic inflammatory response in particular, is controlled in a manner similar to that used by the nervous system to control the force exerted by skeletal muscles. This control is achieved by the repetitive invocation of a unitary event of short duration whose resolution is built into its initiation, namely, the muscle twitch. Force persists so long as twitches keep being initiated by neuronal action potentials, which themselves are instigated by the brain’s desire to move some part of the body. Control of muscle force thus requires only detection of the presence of something, but not detection of the absence of something.

This line of reasoning leads immediately to the notion of the inflammatory twitch as the unit of response of the immune system to an invader, but it brings with it some ancillary analogues. Most obvious is refractoriness, a period after twitch initiation during which a second twitch cannot be instigated. Refractoriness is a necessary requirement for twitch morphology because it ensures that the events involved in generating the twitch are properly turned off before they can be reinitiated. In the case of muscle force, the timing of refractoriness may allow for stacking (summation) of the forces from multiple twitches as occurs in skeletal muscle, or it may prevent stacking, as is the case for cardiac muscle. It is not obvious a priori which strategy the immune system would choose, but we have previously obtained evidence from sensitized mice treated with sequential daily exposures to a foreign protein (OVA) that the latter situation may pertain to allergic inflammation of the lung. Inflammation peaks after ∼3 d of exposure and then gradually abates as exposures are continued over days to weeks (4, 5). This is referred to as tolerization (16) and is thought to involve T regulatory cells. Resting the animals for several weeks, however, allows them to once again respond vigorously to a subsequent OVA challenge (5), suggesting that the inflammatory twitch in these animals lasts on the order of weeks and has a refractory character that prevents them from stacking.

These findings are recapitulated by the agent-based model we developed in this study, which exhibits clear oscillatory behavior after continual stimulation with particles (the analog of Ag exposure in mice). Of particular note is the fact that, for most stimulation regimens, the largest and most well-defined oscillations are observed early on, and these are followed by more behavior that becomes progressively more chaotic uniform with less well-defined peaks (Figs. 3, 6). In contrast, if the period between successive stimulations is long enough to allow resolution of the response to each challenge, the oscillations remain sharply defined with time (Fig. 6D), resembling a series of well-separated twitches that are unable to summate. The twitch hypothesis is further supported in the model by our finding that allowing the model to rest for a period of time results in a reiteration of the initial peaked response upon restimulation (Fig. 5), similar to our previous observations in mice (5).

Inferences drawn from the behavior of our agent-based model must be viewed in light of its numerous simplifying assumptions, which were made in the interests of conceptual and computational tractability. Many of these assumptions relate to the way in which individual biological entities behave. For example, we assume that cells have infinite stores of the chemical signals they release, and that the epithelium plays a purely passive role as a physical barrier to cell movement, which from our own work (17) and that of others (18) is clearly an oversimplification. Furthermore, the alveolar airspace in the model is inaccessible to any cell type, whereas in reality, cells do cross the epithelial barrier and some are cleared via the airways, which creates an additional sink for cells from the alveolar compartment. This might affect the magnitude and/or dynamics of predicted inflammatory oscillations, but would likely not affect their actual existence. Similar remarks can be made with respect to our model assumption that cells do not divide. Fibroblasts, for example, actively divide during the repair phase of the allergic response (19), which might not significantly affect the prediction of the early inflammatory oscillations but could result in greater suppression of the subsequent inflammatory activity (such as beyond 5000 time steps in Fig. 3).

FIGURE 6. Tissue health versus number of time steps when particles were placed in the alveolar space every (A) 0.5, (B) 1, (C) 2, and (D) 10 wk. All plots are an average of 10 simulations.
The most important assumptions in the model, however, relate to the way in which we coarse-grain the myriad details of reality into a much smaller number of independent components. Coarse graining is a hierarchical process, the success of which depends on appropriate binning of the underlying biological details into their various model groups. In our model, for example, we coarse-grain the dynamics of cell movement by lumping all the different movement velocities into a single average rate of random movement from location to location, regardless of whether the cells are activated. This presupposes that cell movement per se is the most important feature of the ability of cells to travel between different locations, and that different cells moving at different velocities is of secondary importance, following the approach taken by Brown et al. (8). In reality, for example, fibroblasts tend to remain localized to fixed locations within the lung, which could mean that nearby regions could be maintained, on average, in a more healthy state compared with regions far from a fibroblast, which could increase the topographical heterogeneity of predicted tissue damage in the model. We also coarse-grain cell size by assuming it is the same for all cell types. Similarly, by lumping multiple cell types into only two functional groups, the PICs and AICs, we assume that it is simply the existence of competing cell types that is paramount, whereas the existence of different phenotypes within each cell group is of secondary importance. For example, we ignore differences in life span and behavior between cells neutrophils and eosinophils, both of which are lumped together into the PIC category. The question thus remains whether such a crude level of coarse graining causes us to miss some crucial detail of overall system behavior that would have become apparent had we divided the PIC and AIC groups into subgroups with different properties. There are many known details of cell behavior that could be investigated in this regard. For example, the alveolar macrophage has a life span between that of other PICs and AICs, and can initially behave as a PIC, but then switch to a AIC depending on environmental stimuli (20), and indeed we invoked the macrophage data from Tanaka et al. (3) as representative AIC types in Fig. 4. Mast cells and APCs can signal to cells such as monocytes and macrophages, causing them to turn into PICs (21, 22). Some PI cytokines, such as TNF-α, inhibit their own synthesis, which self-limits their production (23). Thus, the number of ways in which we might delve into a finer level of model coarse graining is enormous. For the time being, however, we will let ourselves be guided by the notion that it is the competition between temporally offset PI and AI processes that gives rise to the inflammatory oscillations predicted by our model and that support the inflammatory twitch hypothesis. Accordingly, we take the position that the details alluded to earlier, although clearly important for refining the details of the model predictions, are not crucial to the actual existence of these predictions.

The behavior of our model can thus not be taken to constitute proof or otherwise of a biological theory. However, it does provide a test of plausibility to an extent that is impossible to achieve through any other approach. The allergic inflammatory response involves a large number of mutually interacting cell types, each playing different roles. Determining the details of the ensemble behavior of such a complex system defies human intuition. Agent-based computational modeling, in contrast, allows one to estimate how the system might possibly behave within its spatiotemporal constraints. This approach has been exploited convincingly by Brown and colleagues (8) in the exploration of a number of aspects of the inflammatory response. In the case of this model, we have demonstrated that the major cell types involved in the allergic inflammatory response could indeed conspire to produce collective behavior in the lung that is formally similar in many important respects to the muscle twitch.


