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The dynamics of acute inflammation

Rukmini Kumar[a], Gilles Clermont[b], Yoram Vodovotz[c], Carson C. Chow[d,*]

[a]Departments of Physics and Astronomy, University of Pittsburgh, Pittsburgh, PA 15260, USA
[b]Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA 15260, USA
[c]Department of Surgery, University of Pittsburgh, Pittsburgh, PA 15260, USA
[d]Department of Mathematics, University of Pittsburgh, Pittsburgh, PA 15260, USA

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Abstract

When the body is infected, it mounts an *acute inflammatory response* to rid itself of the pathogens and restore health. Uncontrolled acute inflammation due to infection is defined clinically as *sepsis* and can culminate in organ failure and death. We consider a three-dimensional ordinary differential equation model of inflammation consisting of a pathogen, and two inflammatory mediators. The model reproduces the healthy outcome and diverse negative outcomes, depending on initial conditions and parameters. We analyze the various bifurcations between the different outcomes when key parameters are changed and suggest various therapeutic strategies. We suggest that the clinical condition of sepsis can arise from several distinct physiological states, each of which requires a different treatment approach.
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Keywords: Systemic inflammation; Sepsis; Ordinary differential equation (ODE) models; Phase-space and bifurcation analysis

1. Introduction

The initial response of the body to an infection or trauma is called the acute inflammatory response. This response is non-specific and is the first line of defense of the body against danger (Janeway and Travers, 1997). It consists of a coordinated local and systemic mobilization of immune, endocrine and neurological mediators. In a healthy response, the inflammatory response becomes activated, clears the pathogen (in the event of infection), begins a repair process and abates. However, inflammation itself can damage otherwise healthy cells which could then further stimulate inflammation. This runaway inflammation can lead to organ failure and death. Systemic inflammation accompanied by infection, based on its clinical manifestations, is defined as sepsis (Bone et al., 1992). Sepsis is a common and frequently fatal condition, with 750,000 cases annually in the United States alone in 1995 (Angus et al., 2001).

Though much has been learned about the molecular and physiological pathways of the acute inflammatory response, this knowledge has not led to many effective therapies against sepsis. The sole approved drug therapy for severe sepsis is activated Protein-C, which only reduced mortality by 6% compared with controls in clinical trials (Bernard et al., 2001; Cross and Opal, 2003). One reason for the lack of effective treatments may be that the complex nature of the inflammatory response renders the effect of targeting isolated components of inflammation difficult to predict. Thus, mathematical modeling may provide insights into the global dynamics of the inflammatory process from which therapies may be developed. We propose that simple models of the acute inflammatory response can exhibit various outcomes and facilitate an understanding of the complex interactions between the various components of the response.

*Corresponding author. Present address: Laboratory for Biological Modeling, NIDDK, NIH, Bethesda, MD 20892, USA.
E-mail address: ccchow@pitt.edu (C.C. Chow).

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We present a simple three-dimensional model of the inflammatory response to infection that captures the following clinically relevant scenarios: a *healthy* response where pathogen is cleared and the body returns to homeostasis, *recurrent infection* where inflammation is inadequate and the pathogen cannot be completely eliminated, *persistent infectious inflammation* where the pathogen levels and inflammation are high, *persistent non-infectious inflammation* where pathogen is cleared but inflammation persists and *severe immuno-deficiency* where pathogen has grown to saturation but the inflammatory response is very low. The model suggests that sepsis is a multi-faceted disease and narrowly targeted interventions are unlikely to succeed.

2. Reduced model of acute inflammation

Invading pathogens such as bacteria are rapidly detected by the body and an acute inflammatory response ensues. Among the first responders are phagocytic immune cells such as neutrophils and macrophages. These immune cells detect the bacterial cell components, become "activated" and begin to release pro-inflammatory cytokines such as Tumor Necrosis Factor-α (TNF-α), Interleukins (IL)-1, IL-6, IL-8 and High Motility Group Box-1 (HMGB-1) that activate more immune cells and recruit them to the sites of the infection (Cross and Opal, 2003). In addition, anti-inflammatory mediators such as IL-10 and Transforming Growth Factor-β (TGF-β) are also released which inhibit the production of the pro-inflammatory mediators. The activated phagocytic cells kill bacteria directly by engulfment and secretion of toxic chemicals such as oxygen free radicals (Janeway and Travers, 1997). These substances can damage otherwise healthy cells. These damaged or dysfunctional cells can then induce more inflammation (Jaeschke and Smith, 1997).

Ideally, the inflammatory response eliminates the pathogen and then subsides. In some cases, the response might not be strong enough to clear the pathogen. In other cases, a positive feedback loop could arise between the early and late pro-inflammatory waves leading to a non-abating inflammatory response. Clinically, a sustained acute inflammatory response is manifested as septic shock and could culminate in organ failure and death. Though this is a simplification of the pathogenesis of sepsis, the idea is supported by the persistence of high levels of pro-inflammatory cytokines in non-survivors of sepsis (Pinsky et al., 1993; Abraham, 1997).

A simplified picture of the acute inflammatory response is that an infectious pathogen triggers early pro-inflammatory responders which attempt to kill the pathogen. The early inflammatory mediators then activate later inflammatory mediators which can further excite the early mediators. This is the basis of our model which consists of three variables: (1) a pathogen p, which is an instigator of the innate immune response; (2) an early pro-inflammatory mediator m, which can be thought of as representing the combined effects of immune cells such as macrophages and neutrophils together with early pro-inflammatory mediators such as TNF-α and IL-1; (3) a late pro-inflammatory mediator l which represents a late pro-inflammatory feedback. This is a combined effect of cytokines such as IL-6, HMGB-1 and stimulatory effects of tissue damage and dysfunction. Although our model is extremely simple, it captures qualitatively all the salient features of a more complicated and biologically faithful model that is currently being developed (Clermont et al., 2004).

We consider mass-action type kinetics in a well-mixed volume. The dynamics obey:

$$\frac{\mathrm{d}p}{\mathrm{d}t} = k_p p(1-p) - k_{pm} mp, \tag{1}$$

$$\frac{\mathrm{d}m}{\mathrm{d}t} = (k_{mp} p + l)m(1-m) - m, \tag{2}$$

$$\frac{\mathrm{d}l}{\mathrm{d}t} = k_{lm} f(m) - k_l l, \tag{3}$$

where

$$f(m) = 1 + \tanh\left(\frac{m-\theta}{w}\right), \tag{4}$$

θ is an activation threshold and w is an activation width. All the variables and parameters are non-negative. The pathogen p obeys logistic growth and is killed when it interacts with m. The presence of p or l and m will stimulate the growth of m which also has an intrinsic death rate. This growth saturates as m increases towards unity mimicking the effects of cell depletion and anti-inflammatory cytokines. The late mediator l is recruited by m through a sigmoidal coupling function (4) and is cleared with the rate of k_l. In summary, the dynamics obey predator–prey dynamics with a delayed response.

We note that the specific nature of the interactions of our model are not essential for the qualitative dynamics we find. As an example, the factor $1-m$ in Eq. (2) may be replaced by $1/(1+m)$ or the form of the coupling function (4) can be changed without affecting our conclusions. The important element is that there be an early and late inflammatory mediator with saturating kinetics.

3. Dynamics of the model

3.1. Numerical examples

Model (1)–(3) exhibits behavior reminiscent of what is observed in clinical settings. Given an initial condition of $p>0$, $m>0$ and $l>0$, p grows, inducing m and l to

grow and attempt to eliminate p. Depending on initial conditions and parameters, the ensuing orbits either approach stable fixed points or undergo oscillations, each having a physiological interpretation. We note from Eq. (2) that a non-zero positive initial value for m is necessary to generate an inflammatory response. The background level of late mediators is given by $l^0 = (k_{lm}/k_l)f(0)$ and is non-zero for our choice of parameters. Both these properties are consequences of our particular choice for the form of the model and not essential for the qualitative results we find.

We must adopt one crucial element before we can interpret our results. In a healthy response to infection, the inflammatory response should become activated, eliminate the bacteria and return to rest. However, in models (1)–(3), while p can diminish exponentially fast, it can never become completely eliminated in a finite time. Thus a consequence is that if m returns to rest after an inflammatory episode, p can re-grow from an infinitesimal quantity. This is an artifact of the model that arises because the approximation of p as a continuous variable breaks down when the population becomes small and the discreteness of the pathogen number becomes important. In this regime, a stochastic or agent-based model where the pathogen can be completely eliminated is more appropriate. We finesse the discreteness problem by introducing a threshold for pathogen level. When p falls below this threshold, we consider it to be completely cleared. We propose that there is an effective threshold representing a single pathogen particle below which, on average, the pathogen population is eliminated. We will show how to calculate this threshold explicitly for various models in a future publication.

We consider numerical examples for various values of k_{pm}, k_{mp}, and k_{lm}. In Section 3.2, we show that these are natural bifurcation parameters of the system. The other parameters are fixed at $k_{pg} = 3$, $k_l = 1$, $\theta = 1$ and $w = 0.5$. We show the effects of varying θ and w in Appendix A.2.1. Numerical simulations and bifurcation plots were generated with XPPAUT (Ermentrout, 2002).

A *healthy response* to infection as seen in Fig. 1 corresponds to an orbit that spirals outwards so that p falls below threshold during the oscillation. The pathogen is then completely cleared which allows the inflammatory response to relax back to rest.

In Fig. 2, the same parameters are used but the initial pathogen load is higher so that instead of returning to background levels, the inflammatory mediators are over-excited and remain elevated. We relate this situation to a state of *persistent non-infectious inflammation* where even though the pathogen is cleared, the inflammatory response does not abate. In our model, this state is a fixed point but in a real organism we expect that if this condition continued, it would eventually lead to multiple organ failure and death (Reyes et al., 1999).

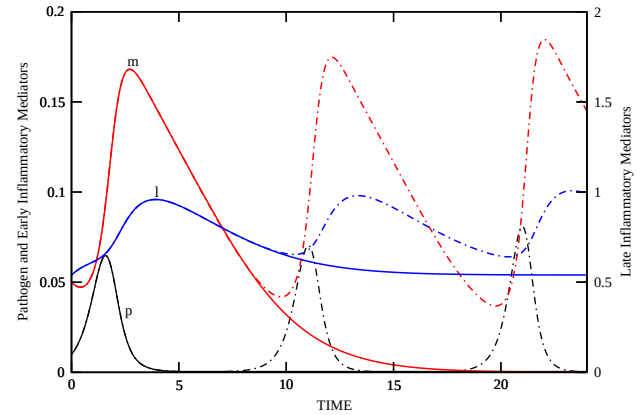

Fig. 1. Time courses of p (black), m (red) and l (blue) for the *healthy* response. We show orbits with the p elimination threshold (solid line) and without (dotted line). With the threshold (set at $p_0 = 0.0005$), when p drops below p_0, p is set to zero and m and l return to background values. Without the threshold, the orbits spiral outwards. Parameters used are $k_{pm} = 30$, $k_p = 3$, $k_{mp} = 25$, $k_{lm} = 15$, $k_l = 1$. Initial conditions are $p(0) = 0.01$, $m(0) = 0.05$, $l(0) = 0.539$.

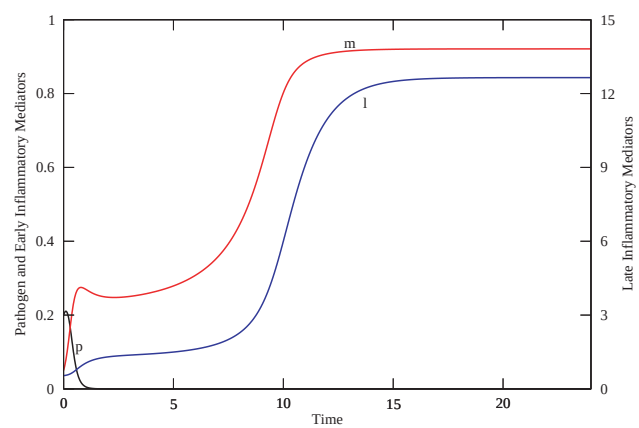

Fig. 2. In *persistent non-infectious inflammation*, p (black) is eliminated but m (red) and l (blue) remain elevated. Parameters used are $k_{pm} = 30$, $k_p = 3$, $k_{mp} = 25$, $k_{lm} = 15$, $k_l = 1$. Initial conditions are $p(0) = 0.2$, $m(0) = 0.05$, $l(0) = 0.539$.

Starting again from a healthy situation, if the pathogen susceptibility to the host's defenses ($k_p m$) is decreased, we can enter a domain of *persistent infectious inflammation* where the inflammatory response is high but the pathogen still cannot be cleared as seen in Fig. 3. We would equate this condition with a severe septic state where both infection and inflammation are uncontrolled. In this case, the damage caused by both the pathogen and inflammation are disrupting body function and if unabated death will result. Patients with systemic inflammation, with and without documented infection, are observed in clinical settings (Alberti et al., 2002).

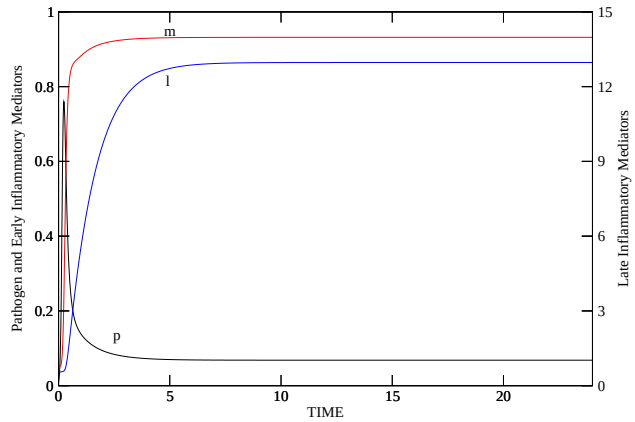

Fig. 3. In *persistent infectious inflammation*, p (black) cannot be eliminated and m (red) and l (blue) remain elevated (as in severe sepsis). Parameters used are $k_{pm} = 3$, $k_p = 3$, $k_{mp} = 25$, $k_{lm} = 15$, $k_l = 1$. Initial conditions are $p(0) = 0.01$, $m(0) = 0.05$, $l(0) = 0.539$.

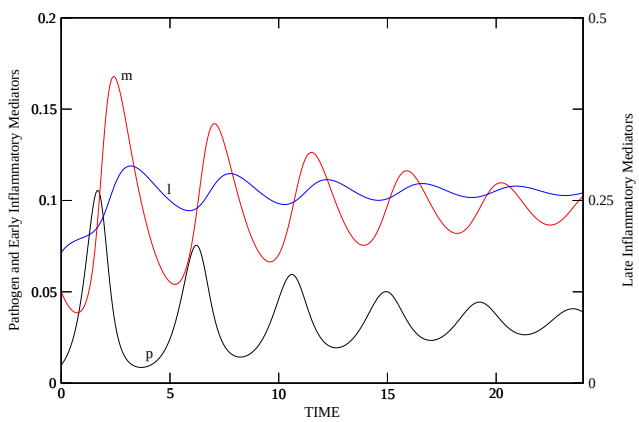

Fig. 4. In *recurrent infection*, p (black) is low and m (red) and l (blue) remain above background values but not very high (as in a low-grade infection). Parameters used are $k_{pm} = 30$, $k_p = 3$, $k_{mp} = 25$, $k_{lm} = 5$, $k_l = 1$. Initial conditions are $p(0) = 0.01$, $m(0) = 0.05$, $l(0) = 0.179$.

If we reduce the recruitment rate of l (k_{lm}), the healthy response can be turned into one of recurrent infection as seen in Fig. 4. (Changes in other parameters could also lead to recurrent infection as we see in the next section). In this case, low levels of infection persist indefinitely. This could be likened to infection with tuberculosis, yeast infections or low-grade bacterial infections that persist for long periods of time (Beatty et al., 1994). Although, an organism could survive this state for a long duration it may eventually succumb.

Finally, in Fig. 5, the activation rate of m due to p (k_{mp}) is very weak, and we have a state of *immuno-suppression* or *immuno-deficiency* where the pathogen grows to saturation and does not elicit any response from the body. This could happen if the immune-system had already been compromised by previous infection or trauma and then the organism is reinfected. Opportunistic bacterial and fungal infections have been observed in immuno-suppressed patient populations such as HIV infected patients, the elderly and those with organ transplants (Schultz et al., 2001). These five scenarios are the only possible outcomes in the model.

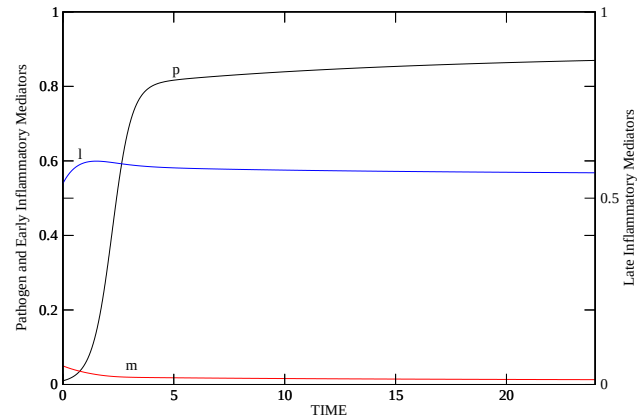

Fig. 5. In *severe immuno-deficiency*, p (black) grows to saturation and m (red) and l (blue) remain low or absent. Parameters are $k_{pm} = 30$, $k_p = 3$, $k_{mp} = 0.4$, $k_{lm} = 15$, $k_l = 1$, $p(0) = 0.01$, $m(0) = 0.05$, $l(0) = 0.539$.

3.2. Fixed points and bifurcations

These various regimes and transitions are best understood by examining the fixed points and associated bifurcations of model (1)–(3). The fixed points satisfy the following conditions:

$$0 = p\left[p - 1 + \left(\frac{k_{pm}}{k_p}\right)m\right], \tag{5}$$

$$0 = m\left[m - 1 + \left(\frac{1}{k_{mp}p + l}\right)\right], \tag{6}$$

$$l = \frac{k_{lm}}{k_l} f(m). \tag{7}$$

Substituting Eq. (7) into Eq. (6) and rearranging gives

$$0 = m\left[p - \frac{1}{k_{mp}}\left(\frac{1}{1-m} - \frac{k_{lm}}{k_l} f(m)\right)\right]. \tag{8}$$

We consider three natural parameters $a \equiv k_{pm}/k_p$, k_{mp}, and $b \equiv k_{lm}/k_l$, that appear in the fixed point conditions (5) and (8). These three parameter combinations represent the pathogen susceptibility to m compared to its growth rate (i.e. inverse of the pathogen virulence), the activation rate of early responders m due to p, and the effective recruitment rate of l due to m, respectively.

The intersections of conditions (5) and (8) give the fixed points of the system. The dependence of the fixed points with the parameters is best observed as a projection in the p–m plane as shown in Fig. 6 where the fixed point conditions (5) and (8) are plotted. Lines

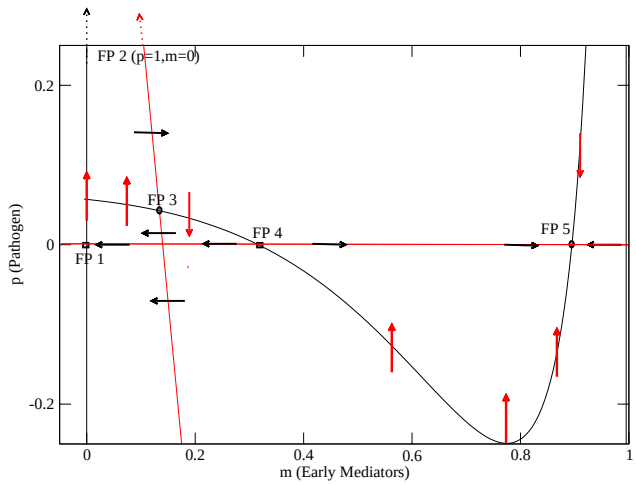

Fig. 6. Projection of fixed-point conditions onto the p–m plane. Projected directions of field-flow are also marked. The red curves correspond to conditions $p = 0$ and (9) and the black curves correspond to conditions $m = 0$ and (10). The fixed points are at the intersections of black and red curves and the direction of flow along a curve reverses at fixed points. The projection of the phase-space for a typical set of parameters is shown. FP 1 and FP 4 are saddles. FP 3 is a spiral which is stable or unstable based on the actual values of the parameters. FP 5 is a stable fixed point. FP 2 (not shown) is also a saddle in this case.

$p = 0$ and $m = 0$ are unaffected by changes in parameters. The line

$$p = 1 - am \tag{9}$$

is affected only by a and sweeps across the p–m plane as a is decreased. The curve

$$p = \frac{1}{k_{mp}}\left(\frac{1}{1-m} - bf(m)\right) \tag{10}$$

is affected only by the immune parameters b and k_{mp}. It drops below $p = 0$ as b is increased. Changing k_{mp} affects the height and angle at which Eq. (10) intersects Eq. (9).

There are five fixed points which we have labeled from FP 1 to FP 5. FP 1 is given by $p = 0$, $m = 0$, and $l = (k_{lm}/k_l)f(0)$. This fixed point is always unstable because the pathogen is growing. FP 2 is given by $p = 1$, $m = 0$, $l = (k_{lm}/k_l)f(0)$ and may be interpreted as a severely *immuno-deficient* state. Here the pathogen has grown to saturation, but there is no early immune response and the late response remains at the background level. This point is stable when the early immune response is very weak as shown in Appendix A.1.2.

FP 4 and FP 5 arise from a saddle node bifurcation when $p = 0$ in (10). This can be achieved by increasing b from zero as seen in the bifurcation plot in Fig. 9. FP 4 is always unstable and never represents any physiologically relevant scenario. When stable, FP 5 represents the *persistent non-infectious inflammation* fixed point. FP 3 is given by the intersection of the line (9) with the curve (10). FP 3 could represent *healthy*, *recurrent infection* or *persistent infectious inflammation* states, depending on parameter values. Below, we vary the three parameter combinations a, k_{mp} and b and examine the bifurcation plots.

In the healthy scenario, a is large enough so that FP 3 is an unstable spiral and FP 5 is the only stable node ($k_{pm} = 20$ in Fig. 7). In this case, initial conditions close to FP 3 undergo oscillations that take the pathogen below the elimination threshold and are interpreted as healthy trajectories. A higher pathogen initial condition for the same set of parameters takes the trajectories directly to FP 5 and this behavior is interpreted as persistent non-infectious inflammation. When a is decreased, the slope of line (9) decreases and it sweeps through FP 4 rendering it unstable through a transcritical bifurcation. However, p is negative and thus FP 3 becomes unphysical ($k_{pm} = 10$ in Fig. 7). Hence FP 5 is the only stable fixed point for all initial conditions in this regime. As a is decreased further FP 3 crosses FP 5 and they exchange stability through another transcritical bifurcation. FP 3 then becomes the only stable fixed point and is the global attractor for all initial conditions.

As expected, starting from a healthy scenario, the outcome of the system becomes more and more severe

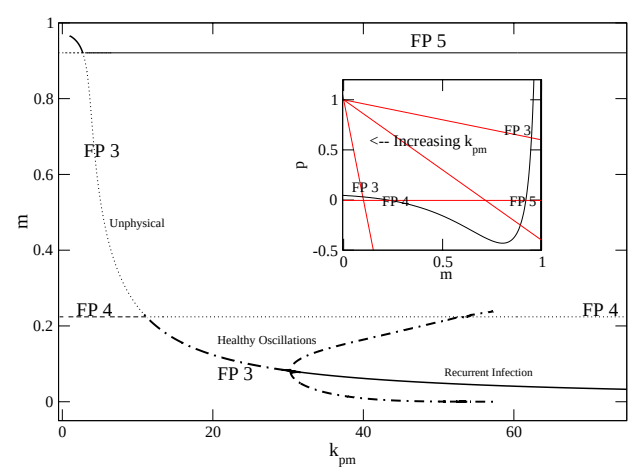

Fig. 7. Bifurcation plot showing outcome as k_{pm} and hence $a = k_{pm}/k_p$ is increased. For low k_{pm}, FP 3 interpreted as *persistent infectious inflammation* is the only fixed point of the system. As k_{pm} is increased to ≈ 2.7, FP 5 (*persistent infectious inflammation*) becomes the attractor of the system. FP 3 becomes unphysical and moves leftward in the p–m plane (see inset). At $k_{pm} \approx 11$, FP 3 undergoes a transcritical bifurcation with FP 4, becoming physical again. It is an unstable spiral, oscillations around which are interpreted as *healthy*. On further increasing k_{pm}, FP 3 undergoes a subcritical Hopf bifurcation and is surrounded by an unstable limit-cycle, oscillations around which are interpreted as *healthy*. Trajectories within the limit-cycle, which spiral into FP 3, are interpreted as *recurrent infection*. *Healthy* behavior is lost to a homoclinic bifurcation at $k_{pm} \approx 57$. For large k_{pm}, FP 3 and FP 5 are bistable (i.e. *recurrent infection* and *persistent non-infectious inflammation* are possible outcomes of the system). (Inset: In the p–m plane, line (9) sweeps across the plane causing the above bifurcations.)

with decreasing pathogen susceptibility (i.e. increasing effective pathogen virulence). If we were to increase susceptibility a starting from the healthy scenario, FP 3 changes into a stable spiral surrounded by an unstable limit cycle through a subcritical Hopf bifurcation. Now, trajectories within the unstable limit cycle spiral into the stable fixed point FP 3 resulting in *recurrent infection* and unstable spiral trajectories outside the unstable limit cycle will eventually dip below threshold and be interpreted as healthy. As FP 5 is still the attractor when the initial p or m is very high, this set of parameters could lead to three different outcomes based on the initial conditions ($k_{pm} = 40$ in Fig. 7). Increasing a further, increases the radius of the unstable limit cycle until it undergoes a homoclinic bifurcation when it collides with FP 1. Here FP 3 is a stable spiral and only recurrent infection is supported. The model therefore predicts that pathogen clearance is not possible for a range of high pathogen susceptibility. However, as we increase susceptibility much further, FP 3 gets closer to the origin so that oscillations around it take p below threshold and may be interpreted as healthy.

Varying k_{mp}, the strength of the early response, does not affect the stability or position of FP 5, the persistent non-infectious inflammation point. Decreasing k_{mp} takes a healthy state to a state where healthy and recurrent infection co-exist and finally to one of recurrent infection only as shown in Fig. 8. Decreasing k_{mp} below $1-(k_{lm}/k_l)f(0)$ makes FP 3 collide with FP 2 (the severely immuno-deficient state where p grows to saturation and m and l remain at background values). In a transcritical bifurcation, FP 2 becomes the stable fixed point of the system and FP 3 becomes unphysical since $m<0$. Increasing k_{mp} from the healthy value reduces the value of p in FP 3—this reduces the range of initial conditions for healthy behavior. However, for even very large values of k_{mp}, FP 3 is an unstable spiral with complex eigenvalues supporting healthy behavior for initial conditions starting close to FP 3.

Varying the strength of the late response, b affects both FP 3 and FP 5. As we decrease b, FP 3 undergoes a sub-critical Hopf followed by the homoclinic bifurcation of the unstable limit cycle similar to the above cases (Fig. 9). FP 4 and FP 5 are created in a saddle-node bifurcation when Eq. (10) intersects $p = 0$ by increasing b. However, there is also an upper limit to b beyond which healthy behavior is not supported. Curve (10) is below zero when it intersects Eq. (9) and FP 3 is unphysical. Thus when the late response is too high, persistent non-infectious inflammation is the only possible outcome.

In the preceding, although we have examined the behavior of the system by varying one parameter at a time, it gives us a picture of the global dynamics of the system. Given the strong nonlinear saturation in the

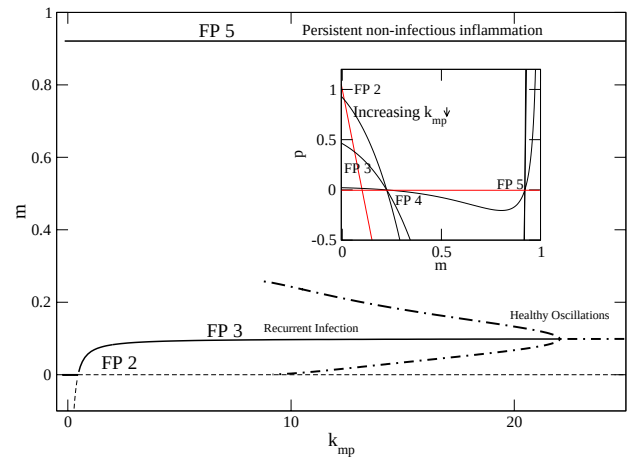

Fig. 8. Bifurcation plot showing outcome as k_{mp} is increased. For very low $k_{mp}(<0.5)$, FP 2 is stable and is interpreted as the *severely immuno-deficient* state. As k_{mp} is increased, FP 3 becomes stable through a transcritical bifurcation and *recurrent infection* is a possible outcome of the system. As k_{mp} is increased further FP 3 undergoes a subcritical Hopf bifurcation ($k_{mp} \approx 22$). Oscillations around the unstable limit cycle surrounding FP 3 are interpreted as *healthy* and are lost through a homoclinic bifurcation ($k_{mp} \approx 9$). Trajectories within the limit-cycle spiral into FP 3 and are interpreted as *recurrent infection*. Beyond the Hopf bifurcation ($k_{mp} > 22$), FP 3 remains an unstable spiral, up to very large k_{mp} ($k_{mp} \approx 2000$) and oscillations around FP 3 are interpreted as *healthy*. On varying k_{mp}, only the position and eigenvalues of FP 3 are changed. FP 5 remains unaffected which is interpreted as *persistent infectious inflammation* and remains a possible outcome of the system. If curve (10) is shallow enough (b is small enough) so that FP 5 is not yet created, then FP 3 remains the stable global attractor through changes in k_{mp}. (Inset: In the p–m plane, FP 3 varies in position and stability as (10) varies, causing the above bifurcations. FP 5 remains unaffected.)

dynamics, orbits can either approach a fixed point, a limit cycle, or a strange attractor. Given that FP 1 and FP 4 are always unstable and FP 2 is stable only when k_{mp} is very low, this leaves FP 3 (or stable limit cycles around it) and FP 5 as the only candidates for global attractors. Ideally however, we would like FP 3 to be an unstable spiral or be surrounded by an unstable limit cycle, so that oscillations around it can be interpreted as healthy behavior.

This gives an explanation for why healthy behavior always entails the risk of uncontrolled inflammation. In order for the pathogen to be cleared, we require an unstable spiral that can take p below threshold. However, if it were not for the (externally imposed) elimination threshold the orbit would eventually end up at some attractor and persistent non-infectious inflammation is the global attractor. Conversely, if curve (10) has not yet intersected $p = 0$ to form FP 4 and FP 5 (no persistent inflammation fixed point), FP 3 or a stable limit cycle around it (recurrent infection) is the global attractor.

There is a possibility that FP 3 could undergo a supercritical Hopf bifurcation (discussed in Appendix

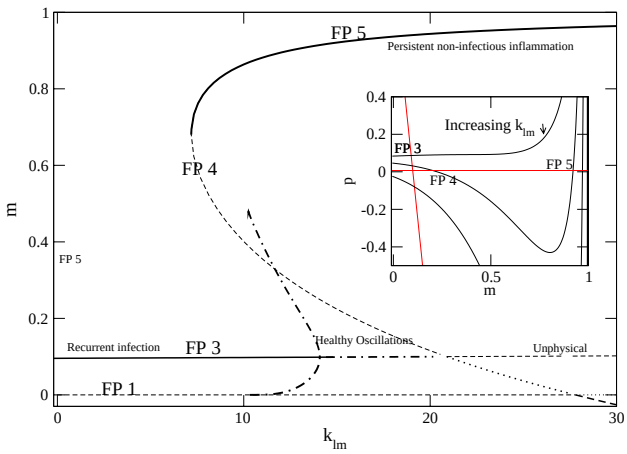

Fig. 9. Bifurcation plot showing outcome as k_{lm} or $b = k_{lm}/k_l$ is increased. For low k_{lm}, FP 3 is a stable spiral representing *recurrent infection*. As k_{lm} is increased, FP 4 and 5 are created through a saddle-node bifurcation at $k_{lm} \approx 7$ and the *persistent non-infectious inflammation* is now a possible outcome. At $k_{lm} \approx 14$, FP 3 undergoes a subcritical Hopf bifurcation and is surrounded by an unstable limit cycle. The oscillations around the unstable limit cycle are interpreted as *healthy* behavior and trajectories inside the limit cycle spiral into FP 3 and are interpreted as *recurrent infection*. *Healthy* behavior is lost at $k_{lm} \approx 10$ due to a homoclinic bifurcation. Beyond the Hopf bifurcation, *healthy* oscillations are still supported by FP 3 which is now an unstable spiral. At $k_{lm} \approx 21$, FP 3 meets FP 4 and becomes unphysical through a transcritical bifurcation (as its $p<0$). Beyond this point, FP 5 is the only stable attractor and *persistent non-infectious inflammation* is the only possible outcome of the system. (Inset: In p–m plane, (10) descends as k_{lm} is increased causing the above bifurcations.)

A.1.3) which leads to a stable limit cycle around it. However, this is generically interpreted as recurrent infection because fine tuning would be required to ensure that the limit cycle takes p below threshold. Although, not possible in our model, a strange attractor might occur in higher-dimensional models. We believe that this is unlikely given the large amounts of negative feedback and dissipation in the system. However, even if it were to exist, it may still not lead to a healthy situation as p may never be eliminated or the early and late inflammatory mediators could stay elevated albeit in a chaotic manner.

Physiologically, this implies that in order to completely rid the body of a pathogen, the inflammatory response must respond strongly and remain elevated for a long enough time. If it responds too weakly, then the pathogen persists. If it abates too quickly, then there will be recurrent oscillatory infection. However, if it responds too strongly and too persistently then there is a risk that it will be self-sustaining even after the pathogen is cleared. Thus, there is a trade-off between being able to eliminate pathogens completely and risking non-abating inflammation. In Appendix A.2, we calculate the parameter ranges where a healthy response is possible.

4. Discussion

Systemic inflammation and the ensuing organ damage is a major cause of mortality today (Tilney et al., 1973; Eiseman et al., 1977). This is also a disease created by modern medicine. Before the discovery of advanced resuscitation techniques, patients could not be kept alive long enough for the condition to fully unfold. Patients often died from blood loss and severe infections before uncontrolled inflammation arose. With the advent and improvement of antibiotics and organ support therapy, the condition has become increasingly relevant (Bone, 1996). The incidence of systemic inflammation is also expected to increase with further advancement of medical technology and the aging of the population which are more susceptible (Angus et al., 2001).

It is now recognized that the dysregulation of the underlying processes of acute inflammation can lead to multiple organ failure and death and that this is a common pathway for diverse instigators such as trauma, hemorrhage and infection. Our simple model of acute inflammatory response to infection shows the various negative outcomes that arise from improper inflammatory response. These scenarios of persistent inflammation (with and without infection), immuno-suppression and recurrent infection have all been observed in critically ill patients (Alberti et al., 2002; Bone, 1996). Although strict correspondence with clinical reality is difficult to establish because of the simplicity of our model, we are able to classify our model behavior into the same broad categories. The model has a rich bifurcation structure and exploring it allows us to understand how changing parameters can take the system from one outcome to another. The model shows that in order to have a healthy response to infection the virulence of the pathogen cannot be too strong or too weak, the early pro-inflammatory response cannot be too weak, and the late response cannot be too strong or too weak. Analysis of this model gives clues to approach the problem of treating severe sepsis. Vastly different therapeutic strategies are called for to deal with the diverse negative outcomes.

The strength of the acute inflammatory response varies in different individuals and may vary depending on age and environmental factors in the same individual. Studies suggest a strong genetic influence on the outcome of sepsis, and genetics may explain the wide variation in the individual response to infection (Holmes et al., 2003). We examined the effect of the strength of early and late pro-inflammatory responses. The model suggests that only the strength of the late pro-inflammatory wave governs predisposition towards a state of persistent inflammation. No matter how exuberant the early wave may be, only controlling the feedback from the late wave can determine whether the outcome is healthy recovery or uncontrolled

inflammation. Thus any therapy for persistent non-infectious inflammation must target the slow pro-inflammatory mediators.

Experiments have found that survival was improved in infected mice when the moderately slow cytokine IL-6 was reduced (Riedemann et al., 2003). However, if too much IL-6 was removed then there was a detrimental effect. This result is consistent with our model in that a small reduction lowered the possibility of a sustained inflammatory response but lowering it too much precluded the possibility of eliminating the bacteria. Evidence also has suggested that down-regulating HMGB-1, a late acting pro-inflammatory mediator might be a potential target for anti-sepsis therapies (Wang et al., 2001). Activated Protein-C which has been recently approved for treatment, is also partially a late anti-inflammatory agent (Bernard et al., 2001). Previous therapeutic attempts have mostly focused on down-regulating the early pro-inflammatory mediators and as predicted by the model have not shown great effectiveness (Abraham et al., 1998; McCloskey et al., 1994).

On the other hand, if the patient is suffering from persistent infectious inflammation, then therapies must be aimed at both reducing the pathogen load and the late pro-inflammatory response. In this case, timing of the therapies may be important. It would be necessary to reduce the bacterial load first before reducing the inflammation.

Conversely, low pathogen virulence or a weak immune response can lead to low level persistent or recurrent infection. Other theoretical models of infection have similar predictions. Persistence of the tuberculosis bacterium *Mycobacterium tuberculosis* at low densities for extended periods has been suggested to be the result of slow growth rates (Antia et al., 1996). Similarly, a down-regulated immune response to *Helicobacter pylori* bacteria has been suggested to result in its persistent colonization of the human stomach (Kirschner and Blaser, 1995). In the clinical setting, patients in the ICU with decreased host defenses are susceptible to hospital-acquired infections (Schultz et al., 2001). These infections which may be easily resolved in a healthy individual might result in unresolved inflammation and prove fatal to a compromised individual. Immuno-stimulatory therapy might be effective in such a situation.

The model suggests that a healthy outcome is possible only when the risk of persistent inflammation is also present. A strong late immune response that increases the risk of unabated inflammation also ensures complete elimination of pathogen. This could explain why this risk has been retained by the evolution.

In the clinical setting, inflammatory states are defined by symptoms and a few biological markers (Bone et al., 1992). For example, Systemic Inflammatory Response Syndrome (SIRS) is a condition characterized by elevated respiratory and heart rates, fever, and an abnormal white blood cell count. The severity of sepsis is based on the presence of circulatory shock (low blood perfusion) and organ failure (ACCP/SCC, 1992; Muckart and Bhagwanjee, 1997). Similarly, treatment and support of these critically ill patients is largely based on clinical signs and a few biochemical and hematological parameters. However, the various outcomes of our model are based on the levels of the immune responders and the pathogen. Diverse physiological states as exemplified in the model could be manifested by the same clinical symptoms. Hence, one major problem for finding an effective treatment of sepsis is a diagnostic one. The model shows that sepsis should be considered as a set of distinct physiological disorders that require separate therapies even though they may have overlapping symptoms. Categorizing septic states based on levels of bio-markers rather than clinical symptoms would be the first step in addressing this problem and effort is ongoing in that direction (Levy et al., 2003; Marshall et al., 2003).

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Appendix A

A.1. Eigenvalues of fixed points

The Jacobian matrix of models (1)–(3) is

$$\begin{pmatrix} k_p(1-2p)-k_{pm}m & -k_{pm}p & 0 \\ k_{mp}m(1-m) & (k_{mp}p+l)(1-2m)-1 & m(1-m) \\ 0 & \frac{k_{lm}}{w}\operatorname{sech}^2\left(\frac{m-\theta}{w}\right) & -k_l \end{pmatrix}. \tag{A.1}$$

A.1.1. FP 1

For FP1: $p=0,\ m=0,\ l=k_{lm}/k_l(1+\tanh(\theta/w))$ $(\equiv l^0)$, the Jacobian is

$$\begin{pmatrix} k_p & 0 & 0 \\ 0 & l^0-1 & 0 \\ 0 & \frac{k_{lm}}{w}\operatorname{sech}^2\frac{\theta}{w} & -k_l \end{pmatrix}. \tag{A.2}$$

This matrix is lower-triangular and the eigenvalues are $k_p, l^0-1, -k_l$. The fixed point is never stable as one of the eigenvalues k_p is always positive.

A.1.2. FP 2

For FP2: $p = 1,\ m = 0,\ l = l^0$, the Jacobian is

$$\begin{pmatrix} -k_p & -k_{pm} & 0 \\ 0 & (k_{mp} + l^0) - 1 & 0 \\ 0 & \frac{k_{lm}}{w}\operatorname{sech}^2\frac{\theta}{w} & -k_l \end{pmatrix}. \tag{A.3}$$

The characteristic polynomial for the eigenvalue λ is

$$(-k_p - \lambda)(-k_l - \lambda)(k_{mp} + l^0 - 1 - \lambda) = 0$$

with roots: $\lambda = -k_p$, $\lambda = -k_l$ and $\lambda = k_{mp} + l^0 - 1$. Thus the condition for stability of FP2 is $k_{mp} < 1 - l^0$ or $k_{mp} < 1 - k_{lm}/k_l(1 - \tanh(\theta/w))$. The other two eigenvalues are always negative.

A.1.3. FP 3

FP3 is the solution of the following equations,

$$p = 1 - am, \tag{A.4}$$

$$m = 1 - \frac{1}{k_{mp}p + l}, \tag{A.5}$$

$$l = bf(m). \tag{A.6}$$

This may be reduced to a single transcendental equation for m:

$$m = 1 - \left(\frac{1}{k_{mp}}\left(\frac{1}{1 - am}\right) + bf(m)\right). \tag{A.7}$$

All the parameter combinations affect the position and eigenvalues of FP 3. Parameter choices for which p or m of FP 3 is negative are unphysical. FP 3 could also have real or complex eigenvalues. FP 3 has complex eigenvalues and can support oscillatory behavior when Eq. (9) intersects Eq. (10) such that m of FP 3 is less than m of FP 4 (Fig. 6). FP 3 can undergo Hopf bifurcations in this part of the phase-space—the subcritical Hopf bifurcations on varying the three parameter combinations are shown in Figs. 7–9.

A supercritical Hopf bifurcation occurs when we change the coupling curve (4) so that θ is small (low threshold for activation) and w is large (shallow coupling curve). In this case, for increasing b while keeping a and k_{mp} fixed at moderate values, a state of persistent non-infectious inflammation will follow recurrent infection and a small zone of stable limit cycles. (Varying the other parameters, for small θ and large w, does not result in Hopf bifurcations). In the case of small w (sharp coupling curve) and small θ (low threshold of activation), it is possible that more than one fixed point satisfies the conditions for FP 3. In this case, curve (10) intersects line (9) twice before dipping below zero. On varying the parameter combinations, recurrent infection is bistable with persistent inflammation and healthy behavior is never supported. These cases are discussed in greater detail in Appendix A.2.1. In our numerical examples, we have considered moderate w and large θ, which result in subcritical Hopf bifurcations.

A.1.4. FP 4 and FP 5

These fixed points are the solutions of the following equations:

$$p = 0, \tag{A.8}$$

$$m = 1 - \left(\frac{1}{k_{mp}k_{pm}p + l}\right), \tag{A.9}$$

$$l = \frac{k_{lm}}{k_l} f(m). \tag{A.10}$$

This may be reduced to one transcendental equation

$$bf(m) = \frac{1}{1 - m}. \tag{A.11}$$

Eq. (A.11) may have 0, 1 or 2 solutions depending on the parameters. Approximate solutions can be found for Eq. (A.11) by substituting a piece-wise linear function such as $f(m) = 0,\ m < \theta - w$; $f(m) = 1 + (m - \theta)/w,\ \theta - w < m < \theta + w$; $f(m) = 2,\ m > \theta + w$. Using the above approximate function and assuming that FP 4 and 5 occur in region $\theta - w < m < \theta + w$, we arrive at the following expressions for FP 4 and 5.

$$p = 0, \tag{A.12}$$

$$m = \frac{q \mp \sqrt{q^2 - \frac{4w}{b}}}{2}, \tag{A.13}$$

$$l = bf(m), \tag{A.14}$$

where $q \equiv 1 - \theta + w$.

This gives $b > 4w/q^2$ as a lower limit on b for the existence of FP 4 and 5. When there are two solutions, they are formed through a saddle-node bifurcation as shown in Fig. 9. FP 4 is a saddle point and FP 5 is a stable node.

The eigenvalues of FP 4 and 5 can be found by substituting the solutions $m = m^0$ of Eq. (A.11) into Jacobian (A.1). One of the eigenvalues is $\lambda_1 = k_p - k_{pm}m^0$ and the other two are functions of the parameters k_l, k_{lm}, θ and w. We note that k_{mp} does not appear in the expressions for the position or eigenvalues of FP 4 and 5.

A.2. Regimes for healthy response

Trajectories can be interpreted as healthy when FP 3 supports unstable oscillations as an unstable spiral or as a stable spiral surrounded by an unstable limit cycle. The unstable limit cycle is lost when it undergoes a non-generic homoclinic bifurcation when it collides with FP 1. The regimes of the various parameters (for fixed θ and w) which maintain healthy behavior are discussed below.

For healthy behavior, a should be large enough so that FP 3 is to the left of FP 5 in Fig. 6 or $(1/a)<(q-\sqrt{q^2-4w/b})/2$. Increasing k_{mp} even over a large range, does not make FP 3 unphysical, nor does FP 3 lose its complex eigenvalues—thus even for very large k_{mp}, healthy oscillations are supported. The upper limit for a and the lower limit for k_{mp} to maintain healthy oscillations are difficult to find in closed form as these variations result in the radius of the limit cycle increasing and oscillations being lost through a non-generic homoclinic bifurcation.

The strength of the late immune response b should not be too high or too low. If b is too high, then FP 3 has $p<0$ and hence healthy behavior cannot be supported. In order for the late immune response to not be too high, we require that p of condition (10) be positive so that FP 3 is not unphysical. Applying this to Eq. (10) gives the condition

$$b<\frac{1}{1-\tanh(\theta/w)}. \tag{A.15}$$

If b is too low, FP 4 and 5 are not yet formed and Eq. (10) is well above $p=0$ so FP 3 remains the global attractor and is a stable spiral. To avoid too low of a response, we would like FP 4 and 5 to exist so that unstable oscillations from FP 3 are eventually attracted to FP 5. Thus the condition for existence for FP 4 and 5, as calculated above in A.1.4, is

$$b>\frac{4w}{(1-\theta+w)^2}. \tag{A.16}$$

A.2.1. Effect of varying the coupling curve

The shape of the coupling curve (4) (i.e. parameters θ and w) can alter the results. We used $\theta=1$ and $w=0.5$ in our analysis. Parameter θ sets the threshold where l is activated by m and parameter w gives the steepness of recruitment.

From numerical simulations, we find that when w is too small, FP 3 never undergoes a Hopf bifurcation, and as k_{lm}/k_l is increased, recurrent infection and persistent inflammation are bistable (For example, $w=0.005$ with "healthy" parameter set in Fig. 1). As discussed in Appendix A.1.3, small w could result in a shallow enough curve (10) that intersects line (9) more than once. The two fixed points replacing FP 3 arise in a saddle-node bifurcation. The stable node is bistable with FP 5 implying that recurrent infection is bistable with persistent non-infectious inflammation. When w is too large ($w=1$), FP 3 is a stable spiral that becomes unphysical as k_{lm}/k_l increases. Thus the system supports recurrent infection followed by persistent inflammation and healthy behavior does not exist. In summary, for w too small or large the subcritical Hopf bifurcation of FP 3 (and hence healthy behavior) does not occur for any of the parameter combinations.

When θ is small ($\theta=0.1$), FP 3 undergoes a supercritical Hopf bifurcation as b is varied but this cannot be generically interpreted as healthy behavior as oscillations about a stable limit cycle may not always take p below threshold. As θ is increased, subcritical Hopf bifurcations are possible. The range of parameter b, given by Eqs. (A.15) and (A.16), where oscillatory behavior is observed also increases as θ is increased. Thus, large θ and moderate w would maximize the region for healthy response.

In the above analysis, we have looked at varying parameter combinations rather than individual parameters for conciseness of the discussion. Varying the parameters such as k_p and k_{pm} individually does not change the bifurcation diagrams qualitatively and our interpretations of the effect of pathogen susceptibility remain unchanged. Similarly, varying k_{lm} and k_l individually does not change our conclusions about the strength of late response. The phase-space analyzed is restricted between $0<m<1$ since condition (10) prevents m from increasing beyond one. Using any other function such as $1/(1+m)$ to saturate m can change the upper bound of m but the same behavior is retained.

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