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Mathematical Modeling of Energy Consumption in the Acute Inflammatory Response

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Abstract

When a pathogen invades the body, an acute inflammatory response is activated to eliminate the intruder. In some patients, runaway activation of the immune system may lead to collateral tissue damage and, in the extreme, organ failure and death. Experimental studies have found an association between severe infections and depletion in levels of adenosine triphosphate (ATP), increase in nitric oxide production, and accumulation of lactate, suggesting that tissue energetics is compromised. In this work we present a differential equations model that incorporates the dynamics of ATP, nitric oxide, and lactate accompanying an acute inflammatory response and employ this model to explore their roles in shaping this response. The bifurcation diagram of the model system with respect the pathogen growth rate reveals three equilibrium states characterizing the health, aseptic and septic conditions. We explore the domains of attraction of these states to inform the instantiation of heterogeneous virtual patient populations utilized in a survival analysis. We then apply the model to study alterations in the inflammatory response and survival outcomes in metabolically altered conditions such as hypoglycemia, hyperglycemia, and hypoxia.

Keywords

Immunology; Sepsis; Bioenergetics; Bifurcation analysis; Basins of attraction

Contributors

I.R.Z., J.E.R., D.S., and G.C. developed the model, analyzed the results and prepared the manuscript. I.R.Z. wrote the Matlab code and run the simulations. All authors have approved the final article.

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Declarations of interest

The authors declare that they have no competing interests.

1. Introduction

When pathogens enter the body, a complex chain of reactions occurs in which the immune system activates and attempts to eliminate the intruders and prevent persistent infection. For a short period of time, invading pathogens can reproduce rapidly. However, encounters with pathogens activate immune cells, such as macrophages and neutrophils, which release signaling molecules such as cytokines and eliminate pathogens through means such as phagocytosis and recruitment of additional immune cells. Under normal circumstances, as long as the initial insult is sufficiently limited, the immune response will satisfactorily eliminate the pathogen and the host will become healthy again. In some cases, however, the initial response may escalate into an overwhelming systemic inflammation. Such overreaction of the immune system can lead to tissue damage, organ failure, and possibly death. This state of uncontrolled inflammation is known as sepsis. Every year severe sepsis affects more than 1.7 million people in the U.S. alone and over 30 million people worldwide Alliance (2018).

Several studies have found associations between overproduction of nitric oxide (NO), mitochondrial dysfunction, and sepsis Brealey et al. (2002), Brealey et al. (2004), Brookes et al. (1999); moreover, it has been proposed that septic organ failure is caused by depression of mitochondrial function, Carré and Singer (2008). Because mitochondria are organelles responsible for the generation of most of the energy in a cell, mitochondrial dysfunction directly affects the production of ATP, which could contribute to this association. For instance, in a study performed on skeletal muscle of 28 patients with sepsis, Brealey et al. (2002) observed a relation between overproduction of NO, mitochondrial dysfunction and lowered adenosine triphosphate (ATP) levels. They reported a decrease in mitochondrial complex I activity, the magnitude of which was associated with the degree of NO production in skeletal muscles of patients admitted to intensive care with septic shock. In a subsequent study, similar results were found in muscle and liver in a long-term rodent model of fecal peritonitis Brealey et al. (2004). Furthermore, Brookes et al. (1999) found that adding NO to isolated rat brain mitochondria inhibits ATP synthesis. Since ATP provides energy for physiological processes including activation of immune cells, production and release of signaling molecules, protein synthesis, and tissue repair Buttgereit and Brand (1995), Buck and Hochachka (1993), lowered ATP levels are likely to compromise aspects of the inflammatory response; yet, since this response involves a complex balance of pro- and anti-inflammatory effects, the impact of these ATP-related alterations is not straightforward to predict.

In the present work, we develop a computational model to study the dynamics of acute inflammation that incorporates a reduced representation of relevant metabolic pathways and energy resources and demands. We use our model to investigate the role of energetics during infection and to explore the relation between overproduction of NO, altered ATP levels, and sepsis. Moreover, disorders in energy metabolism or other alterations in metabolic states, such as hypoglycemia, hyperglycemia and hypoxia, can trigger organ dysfunction as is characteristic in patients with sepsis Duran-Bedolla et al. (2014). These conditions can be associated with low levels of ATP and with lactate accumulation, and thus we apply our model to predict their impact on the acute inflammatory response as well.

Computational modeling provides an approach to deriving predictions about complex biological systems that can effectively complement experimental work and allow the exploration of manipulations that may not be experimentally feasible. In particular, a variety of previous works have drawn insights from reduced computational models of the inflammatory response. Often such models lump cytokine actions into a small number of classes exhibiting coarsely similar properties or simply combine together all pro-inflammatory components of the response, but they nonetheless can provide useful information. For instance, Kumar et al. (2004) proposed a simplified model for acute inflammation that includes pathogens, early pro-inflammatory effectors such as macrophages and neutrophils, and late pro-inflammatory feedback; despite its simplicity, the model yielded predictions about how changes in biologically interpretable parameters influenced inflammatory outcomes and was used to suggest therapeutic strategies. Soon afterwards, another reduced model was developed to describe the dynamics of the acute inflammatory response including pathogens, tissue damage and activated neutrophils along with an anti-inflammatory mediator, which was used to study how the dynamics of anti-inflammatory feedback contribute to patient outcomes, Reynolds et al. (2006). A related model was also used to suggest possible explanations for tolerance effects arising with repeated endotoxin exposure, Day et al. (2006). A somewhat more detailed model for the acute inflammatory response was shown to fit data from mice exposed to various inflammation-inducing insults and was used to predict mortality outcomes following endotoxin injection Chow et al. (2005), while another work used parameter optimization based on fits to data to demonstrate both that different balances of inflammatory processes could yield similar cytokine dynamics yet with different mortality expectancies, Daun et al. (2008). Such models have also been used to study control strategies for inflammation, Day et al. (2010), as well as to explore the impact of blood filtration on inflammation, R. S. Parker et al. (2016).

Unlike these earlier models, Cressler et al. (2014) derived several compartmental models describing the interaction between energy resources, a general pool of immune cells, and pathogens. These models were employed to study the scenario when the immune agents and pathogens have separate resources and the case when both depend on the same source. However, these models do not incorporate signaling components of the immune response, such as pro- and anti-inflammatory cytokines, and their level of abstraction poses an obstacle for model comparison with human and animal data.

In contrast to these works, other modeling frameworks offer alternatives that take into account spatiotemporal dynamics. For example, partial differential equations have been used to study the immune response to antigen including spatial effects such as immune cell recruitment and granuloma formation, Su et al. (2009). Similarly, agent-based models that treat pathogens as well as immune-related molecules and cells as discrete agents that move around in a spatial domain have been used in a variety of works (e.g., Dong et al. (2010) and the references therein). In these models, biological mechanisms can be encoded in rules used to perform discrete temporal updates of system states. We instead work with continuous ordinary differential equation models because we wish to apply dynamical systems methods such as bifurcation analysis and because our study is motivated by data sets that lack spatial information.

This paper is organized as follows. In Section 2, we provide a complete and detailed description of the mathematical model that we have developed. In Section 3, we present an analysis of the model starting with numerical simulations, bifurcation analysis and computation of basins of attraction of stable states across varying levels of pathogen growth rate. These results are followed by the application of the model to study the altered metabolic conditions of hypoglycemia, hyperglycemia, and hypoxia in comparison with baseline states. Finally, we perform a survival analysis for 300 virtual patients and compare their outcomes under each of the conditions mentioned above. In Section 4, we conclude with a discussion.

2. Mathematical Model

Here we present a reduced model of immune response to pathogen infection that includes several pro-inflammatory and anti-inflammatory drivers and that accounts for the energy consumption associated with the immune response and the effect of energy imbalance on the system. This model builds on the work of Reynolds et al. (2006) and consists of eight nonlinear ordinary differential equations that describe the interactions between the immune response to a pathogen and the associated energy production and demand. As in the Reynolds model, the state variable P denotes the number of pathogens present, N is the level of active phagocytes and also represents their pro-inflammatory effects, D is a marker of tissue damage, and C_A denotes the level of anti-inflammatory mediators. In addition, we introduce new state variables A_n , A_b , X , and L as follows: A_n measures the levels of ATP produced by phagocytes such as neutrophils and macrophages, A_b corresponds to the levels of ATP generated by all other cells in the body, and X and L are the levels of NO and lactate in the host, respectively. With this choice of new variables we seek to study the role of ATP in acute inflammation including the contributions of NO and the implications for lactate production. The inclusion of lactate is motivated by the fact that it is commonly measured as a risk factor for sepsis in the ICU; similarly, levels of ATP and of by-products of NO such as nitrate are available in animal data. Several terms in the model feature an ATP-dependent factor that scales the vigor of the process based on the availability of the relevant energy supply, while a collection of energy flux terms in the ATP equations effect energy consumption.

Our model is based on the interactions shown in Fig. (1). When pathogens enter the body, a complex chain of reactions occurs, starting with tissue damage and activation of phagocytes N . These activated effectors induce inflammation followed by a surge of anti-inflammatory cytokines that balance the recruitment of more phagocytes and down-regulate the production of harmful substances such as NO (X). Unlike previous work Reynolds et al. (2006), we do not include a direct reciprocal interaction between N and D ; that is, in our model N does not directly promote D . Instead, both N and D produce X , which in turn promotes D . These interactions clearly represent a positive feedback loop: NO causes tissue damage while tissue damage induces more inflammation that enhances NO release. Since every metabolic process requires energy in the form of ATP, the intensities of phagocyte activation, pathogen elimination, healing of tissue and production of anti-inflammatory mediators in the model are all modulated by ATP levels. Finally, as a byproduct of anaerobic ATP production, lactate L is produced.

The ATP energy source for the inflammatory response is produced in the cytosol and mitochondria through the sequential processes of glycolysis and oxidative phosphorylation, the latter of which requires oxygen (Fig. 2). Although in anaerobic respiration fewer molecules of ATP are produced, this process is about 100-times faster than oxidative phosphorylation and therefore is preferred for some immune cells as a quick source of energy, even if oxygen is abundant. Moreover, sites of inflammation are often hypoxic environments and although some oxydative phosphorylation takes place, neutrophils and macrophages depend mostly on glycolysis for energy production, Borregaard and Herlin (1982); Pfeiffer et al. (2001). Thus, we will introduce separate equations for a phagocyte ATP level, A_n , and an ATP level available to other cells in the body, A_b . Indeed, ATP is produced locally and has a very short half-life, justifying the use of two physically separated pools of ATP. Within each pool, both glycolysis and oxidative phosphorylation contribute to ATP production, although to different extents. Oxidative phosphorylation in both pools is compromised by X due to the known competitive inhibitory effect of NO on this pathway.

The following system of differential equations incorporates these many biological considerations. Values and meanings for all parameters are given in Table 1; note that the saturating function g modulates energy-intensive terms based on availability of relevant ATP supplies, while the Hill function f represents inhibitory effects:

$$\frac{dP}{dt} = k_{pg}P \left(1 - \frac{P}{P_\infty}\right) - (1 + k_{ns}g(A_b)) \frac{k_{pm}P}{\mu_m + k_{mp}P} - \frac{k_{pn}g(A_n)f\left(\frac{C_A}{C^*}\right)NP}{1 + k_{ps}P} \quad (1)$$

$$\frac{dN}{dt} = \frac{s_{nr}g(A_n)f\left(\frac{C_A}{C^*}\right)(k_{nn}N + k_{np}P + k_{nd}D)}{\mu_{nr} + f\left(\frac{C_A}{C^*}\right)(k_{nn}N + k_{np}P + k_{nd}D)} - \mu_n \left(1 + \frac{k_{de}g(A_n)f\left(\frac{C_A}{C^*}\right)P}{1 + k_{ps}P}\right)N \quad (2)$$

$$\frac{dD}{dt} = k_{dn}h(X + P) - g(A_b)\mu_d D \quad (3)$$

$$\frac{dC_A}{dt} = s_c + k_{cn} \left(\frac{g(A_n)f\left(\frac{C_A}{C^*}\right)N}{\mu_{cq} + f\left(\frac{C_A}{C^*}\right)N} + \frac{g(A_b)f\left(\frac{C_A}{C^*}\right)k_{cnd}D}{\mu_{cq} + f\left(\frac{C_A}{C^*}\right)k_{cnd}D} \right) - \mu_c C_A \quad (4)$$

$$\frac{dA_b}{dt} = c(A_b) \left(f\left(\frac{X}{X^*}\right) (1 - \lambda_{gb}) + \lambda_{gb} \right) - g(A_b) \sum_{i \in \{1, 4, 6\}} \Phi_i - \mu_A A_b \quad (5)$$

$$\frac{dA_n}{dt} = c(A_n) \left(f\left(\frac{X}{X^*}\right) (1 - \lambda_{gn}) + \lambda_{gn} \right) - g(A_n) \sum_{i \in \{2, 3, 5\}} \Phi_i - \mu_A A_n \quad (6)$$

$$\frac{dX}{dt} = f\left(\frac{C_A}{C^*}\right) (k_{non}N + k_{nod}D) - \mu_{no}X \quad (7)$$

$$\frac{dL}{dt} = \lambda L \left(1 - f\left(\frac{X}{X^*}\right) \right) \left((1 - \lambda_{gb})c(A_b) + (1 - \lambda_{gn})c(A_n) \right) - \mu_L L \quad (8)$$

$$\text{where } f(V) = \frac{1}{1 + V^2}; h(V) = \frac{V^6}{x_{dn}^6 + V^6}; c(A_x) = \frac{\mu_A(1 + k_2)}{k_2 + e^{k_1(A_x - 1)}}; g(A_x) = \frac{A_x^2}{c_g + A_x^2};$$

$$\Phi_1 = c_1 \frac{k_{pm}s_m k_{ns}P}{\mu_m + k_{mp}P}; \Phi_2 = c_2 \frac{k_{pm}f\left(\frac{C_A}{C^*}\right)NP}{1 + k_{ps}P}; \Phi_3 = c_3 \frac{s_{nr}f\left(\frac{C_A}{C^*}\right)(k_{nn}N + k_{np}P + k_{nd}D)}{\mu_{nr} + f\left(\frac{C_A}{C^*}\right)(k_{nn}N + k_{np}P + k_{nd}D)}; \Phi_4 = c_4 \mu_d D;$$

$$\Phi_5 = c_5 \frac{k_{cn}f\left(\frac{C_A}{C^*}\right)N}{\mu_{cq} + f\left(\frac{C_A}{C^*}\right)N}; \Phi_6 = c_6 \frac{k_{cn}f\left(\frac{C_A}{C^*}\right)k_{cnd}D}{\mu_{cq} + f\left(\frac{C_A}{C^*}\right)k_{cnd}D}$$

The first four equations in system (1)–(8) are based on the model given in Reynolds et al. (2006), where the reader can find a more detailed explanation of the derivation of these equations as well as a detailed description of the parameters used there. For consistency, we kept the same variable and parameter nomenclature. In Equation (1), the dynamics of P is driven by a logistic growth term where k_{pg} and P_∞ are the growth rate and carrying capacity of P , respectively. The second term of this equation describes the elimination of P by nonspecific immune responses, such as defensins and nonspecific antibodies Reynolds et al. (2006). We assume that this process includes two mechanisms: one that is local with negligible energy requirements and a second where the phagocytes spend energy either traveling to the infected area or activating. The third and last term of the P equation describes the removal of pathogens by activated neutrophils N through phagocytosis, the efficacy of which depends on A_n and is down-regulated by the anti-inflammatory mediators C_A .

In a positive feedback cycle, pro-inflammatory cytokines activate phagocytes, while activated phagocytes in turn release these cytokines. As in Reynolds et al. (2006), since our model includes a single combined pro-inflammatory variable N , we collapse this cycle into a positive feedback of N on itself, which appears in the first term of equation (2). This term also includes the recruitment of pro-inflammatory effects by tissue damage and by processes triggered by the presence of pathogen, all modulated by A_n and C_A . Equation (2) also includes a depletion term that encompasses an intrinsic decay rate μ_n as well as an energy-dependent collateral damage effect from phagocytosis.

The production of tissue damage D is controlled in equation (3) by the Hill function $h(X + P)$, based on the assumption that both NO and pathogens promote D ; indeed, NO is also associated with microvascular damage, organ dysfunction and induction of programmed cell death, or apoptosis. This term includes the same exponent used previously Reynolds et al. (2006), which provides a reasonable gradation of D levels across healthy, aseptic, and septic outcomes. Damage production increases in a saturating way with half-activation x_{dn} . We assume that healing occurs at a rate of μ_d and also requires energy. For simplicity we neglect any contributions of phagocytes to clearing damaged tissue and assume that only A_b fuels healing.

Equation (4) describes the dynamics of the anti-inflammatory mediators C_A as in Reynolds et al. (2006), with terms for a baseline anti-inflammatory level s_c , the promotion of anti-inflammatory release by N and D , and an intrinsic decay term. We make the modification, however, that C_A release related to activated phagocytes and tissue damage depend on A_n and A_b , respectively.

We define a rate function for production of A_x , where x stands for each of the subindices b and n , as a decreasing sigmoidal function $\alpha(A_x)$. This phenomenological term represents a ramping up of energy production when supplies diminish, J. M. Berg and Stryer (2002). It multiplies a sum of an aerobic respiration (pyruvic pathway) component $f(X/X^*) (1 - \lambda_{gx})$, downregulated by NO, Brown (2000); Moncada and Erusalimsky (2002), and an anaerobic respiration (glycolysis) term λ_{gx} . Because about 30 molecules of ATP are produced per molecule of glucose in the aerobic pathway, while only 2 molecules of ATP are produced in glycolysis, we estimated λ_{gb} in such way that $(1 - \lambda_{gb})/\lambda_{gb} = 15$. On the other hand, unlike the majority of cells in the body, phagocytes rely on ATP production from mostly the anaerobic pathway. For this reason, we estimated $\lambda_{gn} = 0.9$.

The A_x equations include sums of energy flux terms Φ_i that represent all of the processes in the model that consume energy and hence deplete the level of A_x . Specifically, phagocyte production/activation and migration of phagocytes to the infected area are all processes that require A_n and are represented in Φ_3 . Note that even though energy dependence arises in the final terms of both equations (1) and (2), these terms derive from the effects of the same process, phagocytosis. For this reason, the single flux term Φ_2 accounts for both of these terms. A_n is also consumed in the production of anti-inflammatory mediators by phagocytes in equation (4), represented by Φ_5 . Similarly, A_b is consumed by non-specific pathogen elimination and production of anti-inflammatory mediators as well as in healing and cellular regeneration. Corresponding terms appear in equations (1), (3), and (4) and these effects are

captured in the flux terms Φ_1 , Φ_4 , Φ_6 . We assume that both ATP supplies are naturally depleted at a constant rate of μ_A and in the absence of infection both reach an equilibrium level at 1.

The production of NO, denoted by X , is driven by tissue damage and by activated phagocytes via induction of iNOS through pro-inflammatory cytokines, such as IL-1 β , IL-2, IL-6, TNF and IF- γ , K. A. Kirkeboen (1999). The former process is included in the k_{nod} D term while the latter process motivates the k_{non} N term in the production of NO in xref (7). This production is modulated by anti-inflammatory mediators, such as IL-10 and IL-8, represented in equation (7) with the factor $f(C_A/C^*)$. Nitric oxide is assumed to be naturally depleted at a rate of μ_{no} .

Lactate, denoted by L , is generated in anaerobic glycolysis. In the absence of oxygen, glucose is metabolized into pyruvate generating lactate as a byproduct. Equation (8) was constructed such that the greater the inhibition of cellular respiration through NO, the more lactate is produced. Finally, lactate is assumed to be naturally depleted at a rate of μ_L . Lactate will play an important role in our model as there is available data of lactate for septic patients.

Some of the parameters in our model were extracted from existing literature as shown in Table 1. However, the remaining parameters were tuned to achieve biologically reasonable behavior. For instance, all the state variables must remain positive. Also, some processes are known to require more energy than others, and the parameters involved in the energy fluxes were estimated accordingly. Moreover, nitric oxide is known to have rapid dynamics Thomas et al. (2001) and ATP production depends on two different pathways with different production rates. All of these considerations were taken into account when tuning the model parameters. Most of these parameters are dimensionless since the variables represented by the model are assumed dimensionless as we are concerned here with qualitative behavior of the system rather than fitting specific data sets. The system of equations (1)–(8) was solved numerically using ode23s in Matlab R2018a. We choose this solver to avoid issues with stiffness and accuracy; results with ode45 were similar (data not shown).

3. Results

3.1. Fundamental asymptotic states and multi-stability

The system of equations (1)–(8) exhibits three biologically significant long term outcomes. The outcome that allows host survival, the healthy state, occurs when the immune system is able to completely eliminate the pathogen and there is resolution of inflammation. When the immune system satisfactorily eliminates the insult but in the process, a sustained immune activation occurs, leading to persistent inflammation and tissue damage, the patient is said to be in aseptic state. In this case, multiple organ dysfunction syndrome (MODS) may occur, followed eventually by death. The third and possible outcome, the septic state, occurs when a massive influx of pathogens attacks the host or when the pathogen growth rate is overwhelming. The immune response of the infected individual cannot wipe out the pathogen, leading to sustained presence of pathogen along with persistent inflammation, tissue damage, lactate accumulation, organ dysfunction and eventually death.

Representative time courses of these outcomes appear in Fig. 3, the pathogen growth rate k_{pg} was chosen to achieve the various states, while the initial conditions were identical and all other parameters are kept at the values reported in Table 1. In the *healthy case* (Fig. 3a), as a response to the initial insult, there is a surge in N as phagocytes become activated and travel to the infected area to eliminate pathogens. This process induces tissue damage, represented by a rise in D , and a release of anti-inflammatory mediators, given by an increase in C_A . Both NO and lactate levels also increase, while energy supplies drop below baseline due to enhanced energy consumption associated with all of these processes. The model suggests that the patient would eliminate the pathogen and that subsequently, the levels of ATP and all other inflammatory indicators would return to baseline.

In the *aseptic case* (Fig. 3b), a similar set of processes begins in response to the elevated pathogen level. In the example shown, despite the initial inflammatory response, the pathogen population size grows before subsequently decaying. The elimination of pathogen requires a greater surge in the components of the inflammatory response and a correspondingly more substantial reduction in energy levels. Interestingly, although phagocyte activity causes a decrease in A_n , the drop in A_b , associated with the baseline immune response and various tissue damage and healing effects including C_A production, is even more pronounced. Although the immune response eventually eliminates the infection and energy levels rise again, the associated elevation of phagocyte activation and pro-inflammatory effects cannot be fully countered by the anti-inflammatory mediators. In the long term, N tends to a non-zero value, D continues to grow, levels of both ATP pools remain below baseline, and sustained accumulation of both NO and lactate occurs. This sustained damage and other effects would be expected to cause organ dysfunction and death in patients.

The *septic case* also starts with a rise in levels of pathogen and immune agents (Fig. 3 c). As anti-inflammatory mediators accumulate, they cause mild reductions in N , X , and L , but P and D continue to rise. Energy levels fall and exhibit little (A_b) or no (A_n) recovery. Without elimination of pathogen, all immune components tend in the long term to elevated levels, with sustained energy depletion, which in patients would together result, as in the aseptic case, in severe tissue damage, organ dysfunction and death.

The example trajectories shown demonstrate clear relations between N , X , L , and both A_b and A_n . The presence of pathogens activates neutrophils, which leads to NO and lactate production. These three responses are clearly inversely proportional to ATP levels relative to baseline, or directly proportional to ATP consumption. High demand for neutrophil activation and other pro-inflammatory effects consumes large amounts of energy. In general we observe a strong relation between ATP levels and long term outcomes.

Each of the outcomes illustrated in Fig. 3 corresponds to an equilibrium point of system (1)–(8), as characterized in Table 2.

We performed a bifurcation analysis of the model using XPPAUT (Ermentrout (2002)) to explore more thoroughly the relations among these equilibrium points with respect to variations in the pathogen growth rate k_{pg} . Results are shown, projected onto the variables

P , N , A_b , and A_n in Fig 4, where stable equilibrium curves are presented as solid, unstable as dashed, and additional non-physiological bifurcation curves (e.g., with values for one or more variables negative) are not shown.

The healthy and aseptic equilibria, characterized by $P=0$, both exist for $k_{pg}=0$ and persist, with no change in equilibrium values of P , N , A_b , and A_n as k_{pg} increases. For sufficiently large k_{pg} , each of these equilibria loses stability by meeting an unstable equilibrium state in a transcritical bifurcation. These occur at $k_{pg}=1.125$ and $k_{pg}=1.143$, respectively; besides the destabilization of the healthy and aseptic states, these result in the previously unstable equilibria becoming stable but non-physiological (not shown). Well before these destabilizations, at $k_{pg}=0.048$, the stable septic equilibrium point arises, along with an unstable equilibrium state, through a fold bifurcation. In fact, this unstable equilibrium is the same one that eventually participates in the transcritical bifurcation that destabilizes the aseptic state. Unlike the other two equilibria, the coordinates of the septic equilibrium do depend on k_{pg} , although they do already approach asymptotic values at relatively low k_{pg} .

Putting these results together, we observe that while the healthy and aseptic are bistable for $0 < k_{pg} < 0.048$, the model exhibits tri-stability for $0.048 < k_{pg} < 1.125$. Once the healthy state loses stability, bi-stability between the septic and aseptic equilibria persists over the small range $1.125 < k_{pg} < 1.143$. Our model shows similar structure to the model presented in Reynolds et al. (2006) in the sense that they both have the same three biologically relevant equilibrium points. Although the bifurcations of health and sepsis for our model occur for slightly lower values of k_{pg} than in the earlier work, the values are fairly close. On the other hand, the fold bifurcation introducing the septic state in our model occurs at a much smaller k_{pg} value than in Reynolds et al. (2006).

This bifurcation analysis confirms that our model consistently exhibits a strong relation between low levels of ATP and sepsis. Similar results have been observed in human data, Brealey et al. (2002). In particular, in Fig. (10c) and (10d), we note that during sepsis, A_b attains an equilibrium at 0.62 while A_n drops to a new equilibrium at 0.73. The model analysis also verifies that accumulation of lactate and NO occurs during sepsis in general, although the projections of the bifurcation diagrams to these variables are not shown.

The bifurcation analysis shows that for our baseline parameter set, it is possible to choose the pathogen growth rate, k_{pg} , at a value for which either two or three physiologically relevant equilibrium points exist and are stable. For such a parameter set, different model trajectories will converge to different equilibria, selected by the choice of initial conditions for the model variables. In particular, by simulating model behavior over a long time period for each of a grid of values of k_{pg} and $P(0)$ (denoted by P_0), with all other parameters and initial conditions fixed, we can numerically explore how predicted outcome depends on the intensity of the pathogenic invasion. This simulation defines a basin of attractions for each type of equilibrium, defined as the set of (k_{pg}, P_0) for which the resulting trajectory converges to that equilibrium state. Fig. (5) displays the partitioning of the (k_{pg}, P_0) plane into basins of attraction resulting from this experiment. Note that the tristability observed in the bifurcation analysis here corresponds to the existence of a range of k_{pg} values at which a vertical line through the plot would intersect all three basins.

In the bifurcation diagram, sepsis loses stability at $k_{pg} = 1.143$, while in the basin of attraction, sepsis seems to disappear at about $k_{pg} = 0.2$. This apparent contradiction occurs because the basin of attraction and the bifurcation diagrams are obtained through different approaches. On the one hand, the basin of attraction is computed by solving the model on a grid of values of k_{pg} and P_0 and with the remaining initial conditions fixed at baseline levels. On the other hand, the bifurcation diagrams are found by studying the eigenvalues of the Jacobian of the system (1–8). More precisely, the initial conditions do not play a role in the classification of equilibrium points, but they do in the computation of the basins of attraction. What the bifurcation diagram suggests is that there must be some initial conditions where sepsis exists and is stable for $k_{pg} \in (0, 1.143)$.

The basin of attraction results are not as exact as the bifurcation analysis because they are based on simulations with finite time horizons, which may yield faulty conclusions in borderline cases in which pathogen are eliminated only after extremely long time periods, and because they are limited to a finite range of P_0 values. Nonetheless, they represent a valuable complement to the bifurcation analysis. They show, for example, that values of P_0 needed to produce septic outcomes for low k_{pg} (e.g., < 0.06) are relatively quite high (e.g., > 2), well above the level where healthy outcomes are no longer possible. This diagram is also useful in that it represents a prediction of the outcome of a standardized patient, characterized by our baseline parameter set and baseline initial conditions for all variables other than P , when exposed to a pathogen for which the growth rate and initial load are known.

3.2. Model application to altered metabolic states

Some altered metabolic states such as hypoglycemia, hyperglycemia, and hypoxia have been found to compromise the performance of the immune response against infection. With small variations our model can be used to study these three energetically dependent conditions. We compare the performance of our model with existent literature about the relation between these three conditions and sepsis.

Hypoglycemia is defined as low blood glucose or low blood sugar. Insufficient glucose in the blood will compromise the production of ATP and as a consequence it will reduce the effectiveness of the immune system in fighting the infection. Hyperglycemia, also known as high blood glucose, activates protein kinase C, which inhibits neutrophil activities such as migration, phagocytosis, apoptosis, and killing of microbes. Finally, hypoxia is characterized by the lack of the necessary oxygen to accomplish metabolic requirements. When an inadequate amount of oxygen reaches the tissues, cellular respiration (production of ATP) must rely more heavily on anaerobic glycolysis. Also, pro-inflammatory cytokine levels increase, causing inflammation and tissue damage during hypoxia.

3.2.1. Hypoglycemia—It seems natural to suggest that hypoglycemia in vivo involves a decrease in glucose production, an increase in glucose demand, or both. Possible factors contributing to hypoglycemia include depletion of glycogen stores, impaired gluconeogenesis and increased peripheral glucose utilization, Miller et al. (1980). In a study

performed in rats by Lang and Dobrescu (1991), it was found that during sepsis there is an increase in glucose utilization by macrophage-rich-tissues that could lead to hypoglycemia.

Several studies have been conducted to understand the relation between hypoglycemia and sepsis. In a study performed on nine human patients, Miller et al. (1980) observed that hypoglycemia was associated with overwhelming sepsis. In fact, in four of these patients, sepsis was the only cause of hypoglycemia. In five patients, another possible cause for hypoglycemia was present (alcoholism and chronic renal insufficiency). All patients exhibited metabolic and/or respiratory acidosis. Although serum lactate was not measured, their metabolic acidosis was presumably secondary to lactate accumulation.

Because our model does not contain an equation for glucose, but glucose is the fuel for ATP production, we indirectly represented the effects of hypoglycemia by a reduction in the rate of ATP production in equations (5)–(6). As we observed in our bifurcation analysis, the state variables A_n and A_b are always between 0.6 and 1. One can easily check that the behavior of the function $c(A_x)$ is mostly governed by the parameter k_1 in this range of A_x . Therefore, to lower the ATP production rate, we decreased the control parameter k_1 , which resulted in reduced A_n and A_b levels. Lowering A_b availability affects the healing process as well as the production of anti-inflammatory cytokines and the response of nonspecific immune cells. On the other hand, reducing A_n impacts the production and activation of neutrophils, undermines pro-inflammatory cytokine production, and slows phagocytosis.

Several studies have also found that hypoglycemia increases leukocytes and circulating pro-inflammatory cytokines, R. Nematollahi et al. (2009); Ratter et al. (2017). To include this effect, we also increased the parameter s_{nr} , which controls the rate of phagocyte production, by 25%. Combining this change with the alteration in k_1 , we found the same three physiological equilibria as in our baseline case and we recomputed the basins of attraction for these states.

As a result of the pro-inflammatory and energy effects of hypoglycemia, the lower boundaries of the basins for both the septic and aseptic equilibria shifted to smaller P_0 values, at the expense of healthy and aseptic territories, respectively (Fig. 6). The shift from health to an aseptic state was particularly pronounced for small k_{pg} . The shift from aseptic to septic, on the other hand, took the form of a translation of the boundary between the two outcomes to a lower k_{pg} level, fairly uniformly in P_0 . In general, our results agree with the findings of Miller et al. (1980) that hypoglycemia promotes sepsis, while providing a more detailed specification of how outcomes of pathogen invasion under hypoglycemia are predicted to depend on invasion characteristics.

3.2.2. Hyperglycemia—Septic patients may become hyperglycemic due to a combination of various factors. For instance, they may experience increases in insulin clearance, causing a reduction in insulin-mediated glucose uptake. Septic patients may also develop hyperglycemia due to adverse effects of certain therapies such as glucocorticoids or sympathicomimetic drugs. Additionally, insulin resistance, which is proportional to the severity of the stress response, also promotes hyperglycemia, A.Mathonnet and A.Cariou (2007).

Although hyperglycemia might naively be expected to benefit the inflammatory response by providing extra fuel to support pathogen elimination, it has in fact been found to have negative impacts on acute immune-related outcomes. In particular, in a study conducted on 62 patients with severe sepsis, Leonidou et al. (2007) found that stress hyperglycemia is related to high elevated cytokine levels (IL-6 and TNF- α) and the severity of the disease. Moreover, it is known that hyperglycemia increases vascular permeability as well as inflammatory cytokine levels, altering the balance between anti-inflammatory and inflammatory cytokines in a way that might promote run-away inflammation. It also increases neutrophil adherence, which inhibits cellular migration at sites of inflammation. Finally, hyperglycemia can actually suppress neutrophil activity including metabolism, phagocytosis and microbial killing. These effects could lead to an increase in infection intensity and cause tissue damage, Jafar et al. (2016).

To simulate a hyperglycemic state in a simple way with our model, we decreased the rate of phagocytosis and microbial killing by 25%, setting $k_{pn} = 0.5625$. Similarly, we reduced parameters associated with phagocyte recruitment and metabolism, decreasing their production and depletion rates by 15%, setting $s_{nr} = 0.136$ and $\mu_n = 0.085$; the choice of 15% rather than 25% here was made to represent compensation due to increased vascular permeability. Together, these changes not only slow down the immune system response but they also more generally affect the subsequent time course of inflammation. Interestingly, these changes lead to somewhat similar shifts in basins of attraction as occur with hypoglycemia, namely shrinking of the healthy region and a shift in the aseptic region to lower k_{pg} levels; see Fig (7). Our model predicts milder effects of hyperglycemia than hypoglycemia, however; specifically, the extent of the septic region does not change as significantly in hyperglycemia and the change in the aseptic basin at small k_{pg} is milder. Nonetheless, our model agrees with the literature suggesting that hyperglycemia promotes sepsis, again with detail about possible dependence on pathogen properties.

3.2.3. Hypoxia—Hypoxia-induced inflammation and inflammation during hypoxic conditions in the context of several human diseases have been studied in a variety of recent publications, Eltzschig and Carmeliet (2011). For instance, people with mountain sickness have exhibited increasing levels of pro-inflammatory cytokines as well as pulmonary or cerebral edema, Semenza (2007); Hackett and Roach (2001); Grocott et al. (2009). In another study, healthy volunteers experienced higher levels of IL-6 and other pro-inflammatory cytokines after spending 3 nights at an elevation above 3400 m, Hartmann et al. (2000). Also, studies in mice have found that after short-term exposure to low oxygen concentrations, vascular leakage, accumulation of inflammatory cells and high levels of cytokines occur Eltzschig and Carmeliet (2011). Further, ischemia and reperfusion injury have been associated with inflammatory responses that lead to subsequent organ dysfunction Eltzschig and Eckle (2011); Bartels et al. (2013).

We represented the pro-inflammatory effects of hypoxia in our model by increasing the parameter s_{nr} by 12.5%. Moreover, the reduced oxygen availability was addressed by introducing a new parameter $0 < \epsilon_H < 1$ and replacing $f(X/X^*)$ by $\epsilon_H f(X/X^*)$ in equations (5), (6) and $(1 - f(X/X^*))$ by $(1 - f(X/X^*))\epsilon_H$ in equation (8). Recall that equation (8) represents enhanced lactate production due to diminished function of the aerobic pathway

with rising X . The latter adjustment therefore implements a decrease in this additional lactate production, since for each X , the aerobic pathway is less active under hypoxic than control conditions.

As a result of these modifications, as seen in Fig. (8), the basin of attraction of the healthy state shrinks, making the aseptic outcome more likely. On the other hand, the septic region hardly changes in the presence of hypoxia, suggesting that hypoxia does not promote sepsis. This outcome is natural because the lack of oxygen does not affect A_n , which is the energy needed to produce inflammation. It does cause a reduction in the supply of A_b , however, which is the energy needed for healing and anti-inflammatory cytokine production, such that an over-exuberant pro-inflammatory response can result. These results are also consistent with the observations in a previous computational model that for low values of k_{pg} , such reduction in anti-inflammatory cytokines promotes aseptic outcomes (Reynolds et al. (2006)).

In general, our results suggest that maintaining patients blood sugar within an euglycemic range might be beneficial for recovery from sepsis as long as the pathogen load and pathogen growth rate are under moderate levels as well. Also, regulating oxygen delivery improves the chances of recovery as long as the patient is in aseptic state.

3.3. Survival analysis

So far, we have discussed results of a variety of simulations using our baseline parameter values given in Table 1 with variations in k_{pg} and P_0 , as well as some outcomes from modifications of a few specific parameters designed to represent effects of certain altered metabolic states. A more realistic situation would be to consider a heterogeneous collection of parameter sets, representing the variability inherent in actual patient populations.

We adopted this heterogeneity to generate predictions about survival rates among a population of 300 virtual patients. We introduced variability in those parameters on which we found that the model outcomes depended most sensitively. Specifically, we determined the set of most sensitive parameters in the model by computing the relative sensitivities $(\partial x(t)/\partial \theta)(\theta/x(t))$, where $x(t)$ corresponds to the vector of state variables and θ is the vector of parameters. The healthy state was taken as a baseline for generating $x(t)$, which included the variables P , N , and D . Choosing a sensitivity threshold of 0.09, we obtained the following subset of sensitive parameters:

$$k_{pg}, k_{pn}, k_{mp}, k_{pm}, s_{nr}, k_{np}, k_{nd}, \mu_n, k_{dn}, \mu_d, s_c, \mu_c, c_3, \mu_A, C^*, k_1.$$

In addition to these, we also included variability in the initial levels of anti-inflammatory mediators, C_{A_0} , and the pathogen load, P_0 . Therefore, to generate each virtual patient, a

total of 16 parameters and two initial conditions were perturbed randomly from their baseline value given in Table 1. We let k_{pg} and P_0 be uniformly distributed on the intervals $[0, 0.2]$ and $[0, 0.45]$, respectively, so that the outcomes of simulations of virtual patients were not driven primarily by pathogen-dependent parameters but by the parameter set as a whole. On the other hand, the remaining parameters, including the initial condition C_{A_0} ,

were taken to be normally distributed around their baseline values with a standard deviation of $\sigma = 0.2$ relative to the size of each parameter with the exception of k_1 , for which we used a smaller standard deviation of $\sigma = 0.03$ so that every patient would have relatively similar energy availability as the baseline level defined by the parameters in Table 1.

After producing our population of 300 virtual patients, we simulated the time courses of their inflammatory responses until they clearly approached one of the model equilibrium states, healthy, aseptic, or septic. Each virtual patient was assigned an outcome based on its asymptotic behavior. Fig. 9(a) depicts the outcomes, projected to the plane of the patients' P_0 and k_{pg} values. Note that, while lower (higher) k_{pg} and P_0 are naturally associated with more healthy (septic) outcomes, outcomes were certainly not dictated by this parameter pair but rather were intermingled in many regions of the plane. Of the model patients, 60.7% were classified as healthy, 19% as aseptic, and 20.3% as septic.

For those patients with aseptic and septic outcomes, we used our model to assign each a time of death. To do so, we considered levels of lactate and damage, which are associated with appraisals of patient status in clinical settings. Based on comparisons across long-time simulations, we determined that the maximum observed damage provided the most reliable separator between patients with healthy outcomes, or survivors ($n = 182$), and other patients, or non-survivors ($n = 118$). Specifically, we found that for all 300 virtual patients, $D(t) < 0.30635$ for the full simulation time if and only if the patient was in the survivor group. Thus, we defined the time of death of each non-survivor patient be the moment when the damage trajectory hits 0.30635 units. As one can notice from Fig. 9(b), the same separation would have also resulted from using any other value between 0.30635 and 0.5 as the designated damage threshold. Based on the damage threshold, we plotted the fraction of patients classified into each outcome group and of the total population that were still alive, with damage not yet exceeding threshold, as a function of time (Fig. 10(a)). The surviving fraction among septic patients dropped faster than among aseptic patients, with full loss of survival before 350 hours.

Finally, we explored how the conditions of altered metabolism discussed in subsection 3.2 affected survival trajectories among virtual patients. For each condition, we created a new group of virtual patients. To do so, we started from the baseline population we had already generated and we modified parameters in a way that was consistent with the desired condition. Specifically, to represent hypoglycemia in the population, we decreased k_1 by 66.67% for each patient and we increased each patient's s_{hr} value by 25%. As a result, the percentage of healthy patients dropped to 50.3%, the aseptic population size decreased to 23%, and the septic population fraction increased to 26.7%. As shown in Fig. 10(b), the aseptic hypoglycemic patients die at similar rate than in the normal (euglycemic) case, except that a tail of longest surviving patients is lost. Due to the enhanced pro-inflammatory effects and the lack of energy associated with hypoglycemia, the hypoglycemic septic patients die at a faster rate than the euglycemic ones. The overall acceleration of death by hypoglycemia can also be observed in Fig. 10(e), where combined survival curves are displayed.

Next, we induced hyperglycemia in the virtual patients by reducing their k_{pn} values by 25% and both s_{nr} and μ_n by 15%, just as we did to represent hyperglycemia from our baseline parameter set. As a result, the percentage of healthy patients was reduced to 56.3%, the aseptic population decreased slightly to 17%, and the septic population increased to 26.7%. The survival curves of the virtual hyperglycemia population are shown in Fig 10(c). When looking individually at the septic population, it is difficult to distinguish a significant difference between hyperglycemic and euglycemic death rates. The hyperglycemic aseptic population however dies at a faster rate compared to the euglycemic population and consequently the tail of longer survival patients dies out sooner again. The overall death rate in the population of hyperglycemic patients is indeed faster than in the euglycemic population, however (Fig 10(e)).

In general, our model suggests that hypoglycemic septic patients die at a faster rate than the hyperglycemic and euglycemic patients. In particular, in Fig. 10(e) we show the overall survival curves for the 4 populations (euglycemic or healthy, hypoglycemic, hyperglycemic, and hypoxic) for a period of 15 days. Here, we have shifted the x-axis so that day 0 starts at the 55 hour time point from the other panels, which is about the time the virtual patients start to die. For model validation, we compared the qualitatively behavior obtained in our simulations with a study performed in 418 Ugandan patients with severe sepsis, where 16.3% of the patients were diagnosed as hypoglycemic and 50.2% as hyperglycemic. Among these patients, the hypoglycemic cohort died at a faster rate than the hyperglycemic patients and both died faster than the euglycemic patients, Ssekitoleko et al. (2011). The survival curves of the euglycemic, hyperglycemic, and hypoglycemic patients in this study are reproduced in Fig. 10(f) and their results are consistent with our simulations shown in Fig. 10(e).

To finish, we represented hypoxia among the virtual patients by increasing the inflammatory parameter s_{nr} by 12.5% and set $\epsilon_H = 0.5$ to represent a 50% reduction of oxygenation. As a result, the percentage of healthy individuals dropped to 53%, the aseptic population size increased to 28%, and the septic component decreased slightly to 19% of the population. These results are consistent with what we observed in the basins of attraction in Fig. (8): hypoxia promotes the aseptic state and diminishes health, with relatively little impact on the likelihood of septic outcomes. The survival curves for the hypoxic population are depicted in Fig. 10(d). Here we observe that hypoxic patients with sepsis die at a faster rate than non-hypoxic septic patients and overall, hypoxic non-survivors die faster than non-survivors in the non-hypoxic group.

4. Discussion

The inflammatory response requires energy. As a result, a diminished energy supply compromises the body's ability to mount a response to the presence of pathogens or related insults. Interestingly, since a healthy inflammatory response requires an appropriate balance and temporal interplay of pro- and anti-inflammatory elements, the effects of this compromise are not obvious. With reduced energy, the activation and effectiveness of pro-inflammatory components are limited, suggesting that the inflammatory response could become inadequate to eliminate pathogens. Less energy could also prove detrimental by

limiting anti-inflammatory production and allowing inflammation to spiral out of control, or it could prove helpful by reducing damage-related effects of pro-inflammation. Clearly, the net result of reduced energy is difficult to predict. A computational model provides a helpful tool for evaluating the outcome of such tradeoffs in a variety of scenarios.

In this work, we present a reduced model system that describes the dynamics of the immune system in the presence of pathogens and incorporates energy production along with the energy requirements that arise in fighting such an infection. To the best of our knowledge, this is the first model that incorporates these features. This model builds on several previous models representing various aspects of the acute inflammatory response Reynolds et al. (2006), Kumar et al. (2004), Chow et al. (2005), Day et al. (2006), Daun et al. (2008), R. S. Parker et al. (2016). In addition to two ATP components, our model includes an equation for lactate, which can be measured experimentally in patients and thus will allow us to fit the model to data in future work.

From the point of view of dynamical systems, the model presents an interesting bifurcation structure with respect to variations in k_{pg} . In particular, tri-stability among healthy, aseptic, and septic states can be achieved for fixed values of k_{pg} , as in previous models Reynolds et al. (2006), which reflects a realistic tuning in that the same patient could end up in any one of these three states, depending on infection severity. While bifurcation analysis indicated which equilibrium states are present and over what ranges of k_{pg} they are stable, we also considered the basins of attraction of these states, which indicated the practical relevance of the available stable equilibria in terms of the levels of P_0 needed for them to emerge.

Our results show that both the energy supply to phagocytes and that to other cells in the body play fundamental roles in sepsis. As an infection progresses, the high level of ATP usage associated with the inflammatory response drives augmented energy production as well as a large accumulation of lactate, overproduction of NO, further inflammation, and tissue damage, which in patients could lead to organ dysfunction and death. In general, all of these findings are consistent with experimental data Brealey et al. (2002), Brealey et al. (2004), Brookes et al. (1999). The inclusion of energy dynamics in the model induced a reduction in the healing capacity of the inflammatory process due to limitations on pro-inflammation, pathogen elimination, and healing of damage imposed by energy consumption. Moreover, it allows us to simulate hyperglycemia, hypoglycemia, and hypoxia and to explore their effects on the inflammatory response. In particular, the immune consequences of hyperglycemia and hypoglycemia promote sepsis and make health and recovery less likely. We also observed that hypoxia favors an aseptic outcome and does not have a crucial effect on sepsis. This result arises because the non-phagocyte related energy demands in the model rely more on the aerobic ATP production pathway, whereas the energy supply associated with phagocytes and pro-inflammation is more biased towards the anaerobic route.

We created 300 virtual patients by introducing variability in a sensitive subset of model parameters. We included heterogeneity in k_{pg} among this virtual population to reflect the reality that in any infected patient population, infections of disparate severities would be represented. Based on outcomes arising in simulated infections, we subdivided our virtual

patient population into survivors and non-survivors. We predicted the times of death for the non-survivors via a threshold that we defined based on the damage level in each simulated patient.

The biological conclusions that can be drawn from our model are, however, limited by the fact that the model is simplified and does not consider many other interactions that occur in the immune system during infection. One of the weaknesses of the model is that it assumes that values of all parameter are kept fixed through the entire time course of infection, which is not entirely realistic. For example, with parameter variation over time, the model could account for metabolic reprogramming or the ability of tissue to survive by shutting down non-essential function and thus decreasing damage, Singer (2014). Another aspect of the model that could merit refinement in future work is the definition of death. We defined time of death as the moment when the D trajectory exceeded a certain threshold. However, the level of an appropriate “death threshold” could not be derived directly from biological principles and depends on the extent of variability that we included in the virtual population.

Future directions for extending this work include fitting the model to existing animal and human data that includes blood lactate levels, ATP/ADP levels, and measurements obtained at the cell, tissue and organ levels. Patient data will allow us to obtain values for the parameters that were estimated in this work so that the model can be used for more quantitative analyses. Further extensions of the model will account for adaptive mechanisms that cells have developed to accommodate shortages in energy supply, Singer (2014). We also intend to expand our model to consider the dynamics of different organs in the host and therefore use it to study multiple organ dysfunction syndrome (MODS). Moreover, optimal control techniques can be applied to determine optimal treatment strategies to fight infection and simultaneously reduce side effects Day et al. (2010), Tan and Zou (2015), Stengel et al. (2002). Finally, inclusion of certain treatments that address hyperglycemia, hypoglycemia or hypoxia might also be considered in future work. Hopefully, designing these treatment strategies using a computational model will allow for approaches that are tailored to individual patient characteristics, allowing for a much more extensive exploration of options, with a more refined capability to address specific patient needs, than can be achieved in clinical settings.

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Highlights

- A computational model accounts for the energy required by the immune system to fight an infection.
- The model exhibits three biologically significant equilibrium points: healthy, aseptic and septic.
- Bifurcation analysis yields bistability and tristability among equilibria with varying pathogen growth rate.
- Low levels of ATP, nitric oxide over-production and lactate accumulation are related to sepsis.
- Basins of attraction of equilibria and survival analysis reveal effects of hyperglycemia, hypoglycemia, and hypoxia.

Figure 1:

Interactions between the eight variables appearing in the system of equations (1)–(8). The system includes pathogens (P), a marker of tissue damage (D), active phagocytes (N), anti-inflammatory mediators (C_A), nitric oxide (X), and lactate (L), while A_n and A_b correspond to the levels of ATP produced by phagocytes and all other cells in the body, respectively. Arrows and bars indicate up and down regulation, respectively. The effects on model components influenced by levels of A_n are indicated by green arrows and bars while the effects dependent on A_b are denoted in purple.

Figure 2:

Schematic diagram of cellular respiration. One molecule of glucose is metabolized into two molecules of pyruvate. In the presence of oxygen, pyruvate enters mitochondria to be oxidized into acetyl-CoA by a process called pyruvate decarboxylation. Acetyl-CoA is then metabolized in the tricarboxylic acid cycle (TCA) or Krebs cycle. Here, acetyl-CoA undergoes a cycle of reactions where some ATP, as well as ETC substrates (such as NADH) are produced. These substrates, by virtue of electron exchange in the ETC, generate an electrochemical gradient at the internal mitochondrial inner membrane that is associated to the production of more ATP as protons move along this gradient. About 30 molecules of ATP are produced in this process. In contrast, in the absence of oxygen (anaerobic respiration or glycolysis respiration), the molecules of pyruvate are synthesized into two molecules of lactate in a process called fermentation. In this metabolic pathway only two molecules of ATP are produced. Anaerobic respiration, also called anaerobic glycolysis, is about 100-times faster than oxidative phosphorylation and therefore is preferred for some immune cells as a quick source of energy, even if oxygen is abundant.

Figure 3:

Transient behavior of model (1)–(8). Three outcomes are illustrated: (a) health, obtained by taking $k_{pg} = 0.01$, (b) aseptic, with $k_{pg} = 0.08$, and (c) septic, with $k_{pg} = 0.1$. The initial conditions in all three cases were identical: $P(0) = 1$, $N(0) = 0$, $D(0) = 0$, $C_A(0) = 0.0625$, $A_B(0) = 1$, $A_H(0) = 1$, $X(0) = 0$, $L(0) = 0$. Values for parameters other than k_{pg} are given in Table 1.

Figure 4:

Bifurcation diagrams for the system of equations (1)–(8). Equilibrium states are illustrated with solid red curves (stable), shown with dashed curves (unstable), or not shown at all if non-physiological. The three stable equilibrium points correspond to healthy, aseptic, and septic states. Health loses stability at a transcritical bifurcation at $k_{pg} = 1.125$. The aseptic state loses its stability at a transcritical bifurcation at $k_{pg} = 1.143$. At $k_{pg} = 0.048$, a fold bifurcation gives rise to the septic equilibrium point. (a) Bifurcation diagram for P versus k_{pg} . Here both healthy and aseptic equilibrium points coincide at $P = 0$. (b) Bifurcation diagram for N versus k_{pg} . (c) Bifurcation diagram for A_b versus k_{pg} . (d) Bifurcation diagram for A_n versus k_{pg} . All parameters other than k_{pg} are as in Table 1.

Figure 5:

Basins of attraction of healthy (H), aseptic (A), and septic (S) equilibria for equations (1)–(8). The healthy region is bounded by the coordinate axes and the solid blue curve, the aseptic region lies between the solid blue and red curves, and the septic region is above the red solid curve. All the parameters and initial conditions except k_{pg} and P_0 were taken as in Table 1 and Fig. 3.

Figure 6:

Basins of attraction for hypoglycemic versus normal states. The dashed blue and red lines correspond to the baseline boundaries distinguishing aseptic from healthy and septic outcomes, respectively, as shown in Fig. (5). The blue and red solid lines indicate the new boundaries in the presence of hypoglycemia. The arrows highlight the direction of the shift that occurs with hypoglycemia induction. To represent hypoglycemia, we took $k_1 = 1$, $s_{nr} = 0.2$, and all remaining parameter values are as in Table 1.

Figure 7:

Basin of attraction for hyperglycemic versus normal states. The dashed red and blue lines indicate the septic and healthy boundaries in the baseline scenario shown also in Fig (5). The solid red and blue lines indicate the boundaries with the introduction of hyperglycemia. The arrows indicate the direction of the transition. To represent hyperglycemia, we set $s_{nr} = 0.136$, $\mu_n = 0.085$, and $k_{pn} = 0.5625$. All the other parameters were taken as in Table 1.

Figure 8:

Basin of attraction for hypoxic versus normal states. The dashed blue and red curves indicate the healthy and septic boundaries for the baseline case as shown in Fig. (5). The solid blue and red curves indicate these boundaries in the presence of hypoxia. The arrow indicates the direction of the transition. To obtain hypoxia we take $s_{nr} = 0.18$ and set the new parameter $\epsilon_H = 0.5$ (see text), which diminishes the output of the aerobic pathway for energy production. All other parameter values were taken as in Table 1.

(a)

(b)

Figure 9:

Representation of outcomes for a population of 300 virtual patients. (a) Projection to the (P_0, k_{pg}) plane. (b) Projection with respect to P_0 and the maximum damage value attained over the course of patient simulation. The solid gray line indicates the threshold of 0.30635 units of damage used to separate survivors and non-survivors.

Figure 10:

Survival curves of the 300 virtual patients across metabolic conditions. (a) Baseline euglycemic or normal population. (b) Hypoglycemic population. (c) Hyperglycemic population. (d) Hypoxic population. The red solid lines show fraction surviving from the septic group, the green correspond to the aseptic group, and the black combines both. (e) Survival curves of the total euglycemic, hypoglycemic, and hyperglycemic virtual patient populations. The 15 day time courses shown correspond to the range from 55–415 hours of the virtual population simulation shown on Figures 10(a)–(d) (f) Data from three Ugandan hospitals in 2011; figure adapted from Ssekitoileko et al. (2011).

Table 1:

Parameters Values

Parameter	Range	Value	Description	Sources
k_{pg}	0.021–2.44/h	Varies	Pathogen growth rate	(Ed.), Todar (2012),
P_{co}	Estimated	$20 \times 10^6/\text{cc}$	Carrying capacity for pathogen	Vodovotz, Y. pers. comm.
k_{pm}	Estimated	0.002	Rate parameter for the elimination of pathogens by the non-specific local response	
k_{ns}	Estimated	0.25	Weighting of the energy-dependent component of non-specific pathogen elimination	
μ_m	0.0013–0.0048/h	0.002/h	Half-activation parameter for the non-specific local response	Janeway et al. (2001)
k_{mp}	Estimated	0.1	Saturation rate parameter for the non-specific local response	
k_{pn}	Maximum 2.5/N-units/h	0.75	Phagocytosis rate	Branwood et al. (1992)
c^*	Estimated	0.17	Saturation parameter for effects of anti-inflammatory mediators	Isler et al. (1999)
k_{ps}	Estimated	0.3	Phagocytosis saturation constant	
s_{nr}	Estimated	0.16	Production rate for activated phagocytes (based on resting phagocyte level Reynolds et al. (2006))	
k_{nn}	Estimated	0.007	Weighting of contribution to activation of resting phagocytes by previously activated phagocytes and their cytokines	
k_{np}	Estimated	0.5	Weight of contribution to activation of resting phagocytes by pathogen	
k_{nd}	Less than k_{np}	0.03/h	Weight of contribution to activation of resting phagocytes by tissue damage	Andersson et al. (2000)
μ_{nr}	0.069–0.12/h	0.1/h	Decay rate of resting phagocytes Reynolds et al. (2006)	Coxon et al. (1999)
μ_n	Less or equal than μ_{nr}	0.1/h	Decay rate of activated phagocytes	Coxon et al. (1999)
k_{de}	Estimated	0.75	Pathogen degradation enhancement constant	
k_{dn}	Estimated	0.0037	Maximum rate of damage produced by activated phagocytes	
x_{dn}	Estimated	0.14	Determines levels of pathogens and nitric oxide needed to bring damage production up to half its maximum	
μ_d	Estimated	0.01/h	Decay rate of damage	
s_c	Estimated	0.0625	Source of anti-inflammatory mediators	Tsukaguchi and B. de Lange (1999)
k_{cn}	Estimated	0.02	Maximum production rate of anti-inflammatory mediators	
k_{cnd}	Estimated	48	Effectiveness of damaged tissue relative to activated phagocytes in inducing production of anti-inflammatory mediators	
μ_{cq}	Estimated	1	Determines the levels of activated phagocytes and damage that are needed to bring rate of anti-inflammatory mediator production to half its maximum	
μ_c	0.15–2.19/h	1/h	Decay rate of anti-inflammatory mediators	Bacon et al. (1973), Bocci (1921) Fuchs et al. (1996), Huhn et al. (1997)
μ_A	Estimated	0.1	Baseline depletion rate of both ATP supplies	
c_g	Estimated	1	Half-saturation energy level for the driving of various processes	

Parameter	Range	Value	Description	Sources
k_1	Estimated	3	Phenomenological energy production parameter	
k_2	Estimated	0.01	Phenomenological energy production parameter	
c_1	Estimated	0.03	Energy consumption rate of Φ_1	
c_2	Estimated	0.015	Energy consumption rate of Φ_2	
c_3	Estimated	2.25	Energy consumption rate of Φ_3	
c_4	Estimated	4	Energy consumption rate of Φ_4	
c_5	Estimated	0.05	Energy consumption rate of Φ_5	
c_6	Estimated	0.05	Energy consumption rate of Φ_6	
k_{non}	Estimated	3	Rate of NO release due to presence of pro-inflammatory cytokines	
k_{nod}	Estimated	0.1	Rate of NO release due to tissue damage	
μ_{no}	Estimated	1	Natural depletion rate of NO	
X^*	Estimated	0.5	Half saturation level of NO	
λ_L	Estimated	0.5	Production rate of lactate	
μ_L	Estimated	0.05	Decay rate of lactate	
λ_{gb}	Estimated	0.0625	Fraction of A_b produced via the anaerobic pathway in the absence of NO	
λ_{gn}	Estimated	0.9	Fraction of A_n produced via the anaerobic pathway in the absence of NO	

Table 2:

Biologically significant equilibrium points

Name	Equilibrium Point
Health	$(P=0, N=0, D=0, C_A>0, A_b=1, A_n=1, X=0, L=0)$
Aseptic	$(P=0, N>0, D>0, C_A>0, 0<A_b<1, 0<A_n<1, X>0, L>0)$
Septic	$(P>0, N>0, D>0, C_A>0, 0<A_b<1, 0<A_n<1, X>0, L>0)$