Research Article

Mathematical modeling of septic shock: an innovative tool for assessing therapeutic hypotheses

Gang Zhao[1] · François Gueyffier[1] · Guillaume Monneret[2] · Feng Chen[3] · Feng Li[4]

Abstract
Septic shock is provoked by hyper-activation of the pro-inflammatory response after infection and the patient requires anti-inflammatory treatment. However, the immune system develops a compensatory mechanism where the resulting feedback leads to an anti-inflammatory response after the initial state, which is referred to as immunodeficiency. Therefore, the initial therapeutic treatment with anti-inflammatory intervention has failed for almost 20 years and it has been changed in the last 10 years based on modulation of the inflammatory response. Using in silico methods, it is possible to develop a new approach based on physiopathology for treating septic shock. According to our new mathematical model, we can consider the dysfunctional immune system in a patient with septic shock and modify two parameters at different times to determine a possible treatment, and bearing out the single nucleoid polymorphism (SNP) may predominate the further deterioration of sepsis. The result represents the initial anti-inflammatory treatment with interleukin-10 activation and an increased risk of mortality over time for the septic shock patient, excluding the early stages. However, a hypothetical treatment based on interleukin-10 inhibition can change the patient's immune stage and provide a new therapy according to our results, and show that the frequency of pro-inflammatory related gene SNP can be the possibility of increase sepsis risk. In conclusion, our proposed in silico method can explore therapeutic strategies and predict their associated efficacy and important factors, with the ultimate objective of improving treatments to reduce mortality.

Keywords Mathematical modeling · Septic shock · Sepsis · Pro-inflammatory · Infection · Interleukin-10 · Anti-inflammatory · Dysfunctional immune system · Immunosuppression

1 Introduction

Septic syndromes represent a major problem worldwide and account for thousands of deaths each year [1–13]. In particular, septic shock is characterized by multiple organ dysfunctions and hypotension, with a mortality rate of 30–40% [6–14]. Sepsis remains the main cause of mortality in intensive care units (ICUs) and no new therapies have improved the prognosis despite many clinical trials of adjunctive therapies [11–15]. In addition, septic shock patients are characterized by high heterogeneity, and the main reasons for the failure to improve the prognosis are probably the rapid and sometimes antagonistic modifications of inflammation and immunity during this process [12–14, 16, 17].

In the early stage of the disease, monocytes, macrophages and neutrophils activate the innate immune system, which correspond to increases in pro-inflammatory cytokines and chemokines, to help the fight against infection [11–13, 17, 18]. However, when extreme reactions occur, they can also lead to harmful failures of various organs [6, 8, 9, 11–13, 17–20]. This response is balanced by

✉ Gang Zhao, gang.zhao19@outlook.com | [1]Laboratoire de Biologie et Biometrie Evolutive–Service de Pharmacologie Clinique, Equipe Modelisation des Effets Therapeutiques (EMET), UMR5558, Universite Claude Bernard Lyon 1, Lyon, France. [2]EA 7426, Pathophysiology of Injury-Induced Immunosuppression (Université Claude Bernard Lyon 1/HCL/BioMérieux), Lyon, France. [3]Department of Thoracic Surgery, Shandong Cancer Hospital Affiliated to Shandong University, Shandong Academy of Medical Sciences, Jinan, China. [4]Changchun Wancheng Bio Electron, Co., Ltd, Changchun, China.

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negative feedback leading to the release of anti-inflammatory mediators, which protect against extreme inflammation. In severe sepsis and septic shock, this activation can have defensive effects during the first few hours, but it may become deleterious if it persists over time by leading to drastic reductions in the usual immune system functions [6–9, 11–13, 18, 21–24]. This phenomenon is called sepsis-induced immunosuppression and it is illustrated by the difficulties fighting primary bacterial infections and the decreased resistance to secondary nosocomial infections in a prolonged hypo-immune state [6, 8, 9, 21–24].

Interestingly, if early and aggressive treatments (appropriate antibiotherapy, fluid resuscitation) are applied, the prognosis is improved in the first hours of shock and many patients now survive after this critical step [6, 14, 17, 18, 21–26]. However, a significant proportion of these patients enter an immunosuppressed stage and die after a delayed phase of the disease. According to recent estimates, this process accounts for 50% of septic shock patients and represents > 65% of the total mortalities [21–24, 27]. Thus, a key issue is providing targeted therapy at the appropriate time to patients because the same drug may be beneficial or deleterious depending on the time-course of the disease.

Numerical modeling has been applied to studies of the immune system and models may help to understand the relationships between various immune system components and the physiopathology of sepsis, thereby explaining phenomena that cannot be predicted intuitively [28, 29]. Models could also help a physician to analyze a disease and make an optimal decision regarding the patient's treatment [29]. Furthermore, models can be used to simulate and test new therapeutic interventions. Thus, numerical modeling appears to be suitable for analyzing a complex syndrome such as septic shock. In the present study, we based our approach on the model developed by Calvano et al. [28], who considered an example of infection by a Gram-negative bacterium, where two complex behaviors observed in patients were stimulated: (1) the explosion of inflammatory phenomena following a sufficient level of stimulus, as seen in septic shock; and (2) the occurrence of endotoxin tolerance [30–33].

In order to consider the increasing importance of epigenetic regulation (including microRNA; miRNA) in sepsis [34–38], the objective of the present study was to improve the model proposed by Calvano et al. [28] by adding epigenetic regulatory loops. Moreover, we aimed to obtain further insights into the therapeutic options for modifying the pro-/anti-inflammatory balance by including a pharmacology modeling stratum. This enhanced model appears to exhibit more realistic behavior when simulating septic shock. We illustrated our aim by considering two opposing strategies ("interleukin [IL]-10-like" or "anti-IL-10-like") at different time points in the disease time course, and we compared our results with those obtained in clinical trials and experimental data from animal models. Recently, different researcher groups find the minor frequency of gene SNP of different pro-inflammatory cytokines associated with increased sepsis risk [39–43]. By introduce the new parameter value in the model, we simulate the SNP phenomena in different gene regulation, and identify which have strong influence in the impact of sepsis.

2 Materials and methods

2.1 Numerical model

In the model proposed by Calvano et al. [28], the inflammatory response is activated when endotoxin (lipopolysaccharide; LPS) is recognized by the Toll-like receptor 4 (TLR4), which stimulates complex signaling cascades and activates transcriptional factors (e.g. nuclear factor kappa-B (NF-κB) and activator protein 1 (AP-1)) [17, 18, 20, 34, 44]. This amplified signal activates the transcription of inflammatory genes. In this cascade of events, there is a delay in the counter-regulation of the anti-inflammatory response, which is considered to be negative feedback that inhibits its activation of the pro-inflammatory response. This mechanism protects the immune system and ultimately decreases the expression of genes used in cellular bioenergetic processes (Fig. 1). These transcriptional events can be captured using indirect response models, which are employed widely in pharmacodynamics and pharmacogenomics modeling [45, 46]. The indirect response model includes eight variables: LPS, R (LPS binding receptor TLR4), mRNA-R, LPSR (LPS-R complex), SI* (signaling pathway of TLR4 following its activation by LPS), P (pro-inflammatory response), A (anti-inflammatory response), and E (energy production) [28]. These numerical model parameters were estimated based on the expression levels

Mathematical representation of an indirect response model of endotoxin-induced human inflammation

(a) $\frac{dLPS}{dt} = K_{lps1} \times LPS \times (1 - LPS) - K_{lps2} \times LPS$

(b) $\frac{dR}{dt} = K_{syn} \times mRNA, R + K_2 \times (LPSR) - K_1 \times LPS \times R - K_{syn} \times R$

(c) $\frac{dmRNA,R}{dt} = K_{in,mRNA,R} \times \left(1 + H_{mSI}\right) - K_{out,mRNA,R} \times mRNA, R$

(d) $\frac{d(LPSR)}{dt} = K_1 \times LPS \times R - K_3 \times (LPSR) - K_2 \times (LPSR)$

(e) $\frac{d[SI^*]}{dt} = K_3 \times \frac{LPSR}{A} + K_c \times \left(\frac{[SI^*]^5}{1+[SI^*]^5}\right) - K_4 \times [SI^*]$

(f) $\frac{dP}{dt} = \frac{K_{inP}}{A} \times \left(1 + H_{PSI}\right) \times \left(1 + H_{PE}\right) - K_{outP} \times P$

(g) $\frac{dA}{dt} = K_{inA} \times \left(1 + H_{AP}\right) \times \left(1 + H_{AE}\right) - K_{outA} \times A$

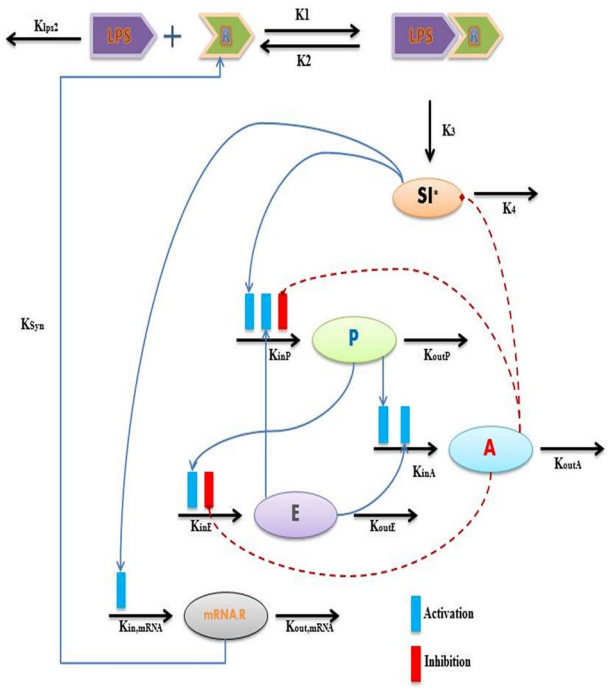


Fig. 1 Calvano et al. [28]. Qualitative structure of the indirect response model. LPS binds to the receptor (R) and forms the complex (LPSR), which activates the signaling complex (SI*) and indirectly stimulates the production rate K_{inP} of the pro-inflammatory (P) response. The pro-inflammatory response then indirectly stimulates the production rate of the energetic (E) response (K_{inE}) and the production rate of the anti-inflammatory (A) response (K_{inA}). The energetic response stimulates both pro-inflammation and anti-inflammation, while anti-inflammation serves as the immuno-regulatory component of the system by restoring intracellular homeostasis

(h) $\frac{dE}{dt} = \frac{K_{inE}}{A} \times \left(1 + H_{EP}\right) - K_{outE} \times E$

(i) $H_{mSI} = K_{mSI} \times SI^*$

(j) $H_{PSI} = K_{PSI} \times SI^*$

(k) $H_{PE} = K_{PE} \times E$

(l) $H_{AP} = K_{AP} \times A$

(m) $H_{AE} = K_{AE} \times E$

(n) $H_{EP} = K_{EP} \times P$

of leukocyte genes in the blood of eight human subjects at 0 (before endotoxin infusion), 2, 4, 6, 9 and 24 h after receiving an intravenous injection of either endotoxin at a dose of 2 ng/kg body weight or 0.9% sodium chloride (placebo treated subjects) [47] (Table 1). The fifth variable represents SI*, which activates the immune system. This equation includes a positive feedback loop responsible for maintaining self-activation and provoking the irreversible hyper-activation response regardless of the stimulus level. The inflammatory response exhibits hyper-activation when the concentration of LPS exceeds a critical threshold (LPS = 4), because the host responds to the endotoxin rather than the stimulus itself. These responses progress toward a systemic inflammatory response, which fails to improve as if the immune regulation system has been perturbed.

The model was then modified under the hypothesis that another regulatory level is involved with the degradation of the pro- and anti-inflammatory responses according to the two equations for A and P, which should be considered. SI* acts as the regulatory center, which activates the production of P. P corresponds to the early upregulation response of the immune system function and it induces negative feedback via the production of A, which inhibits the immune system function. These mechanisms can be characterized by the three balances represented in Fig. 2a for P regulation, A regulation, and equilibration of these two processes.

In general, gene expression involves two states: the dynamic gene transcription state produces pre-mRNA, where a transcription factor can activate or inhibit the transcription level; and the post-transcriptional state comprises splicing, translation, translocation, etc., which modify the pre-mRNA to yield mature mRNA. The equations for P and A (f, g) describe the dynamics of gene transcription, which are controlled by the transcription rate and decay rate, where these are represented by K_{inA} and K_{outA} for anti-inflammation, respectively (K_{inP} and K_{outP} for pro-inflammation, respectively). These two equations represent how indirect regulation stimulates the transcription rate. However, we assume that the post-transcription state controls the decay rate. We also assume that miRNA comprise an important

Table 1 The values of the parameters based on self-limited response data

Parameter	Value	Parameter	Value	Parameter	Value	Parameter	Value
Klps1	4.500	Klps2	6.790	Ksyn	0.020	K1	3.000
K2	0.040	Kin,mRNA,R	0.2114	Kout,mRNA,R	0.2114	K3	2.000
Kc	3.000	K4	0.330	KinP	0.093	KoutP	2.428
KinA	0.256	KoutA	0.860	KinE	0.05	KoutE	0.234
KmSI	13.467	KPSI	15.717	KPE	25.191	KAP	0.022
KAE	2.291	KEP	3.644				

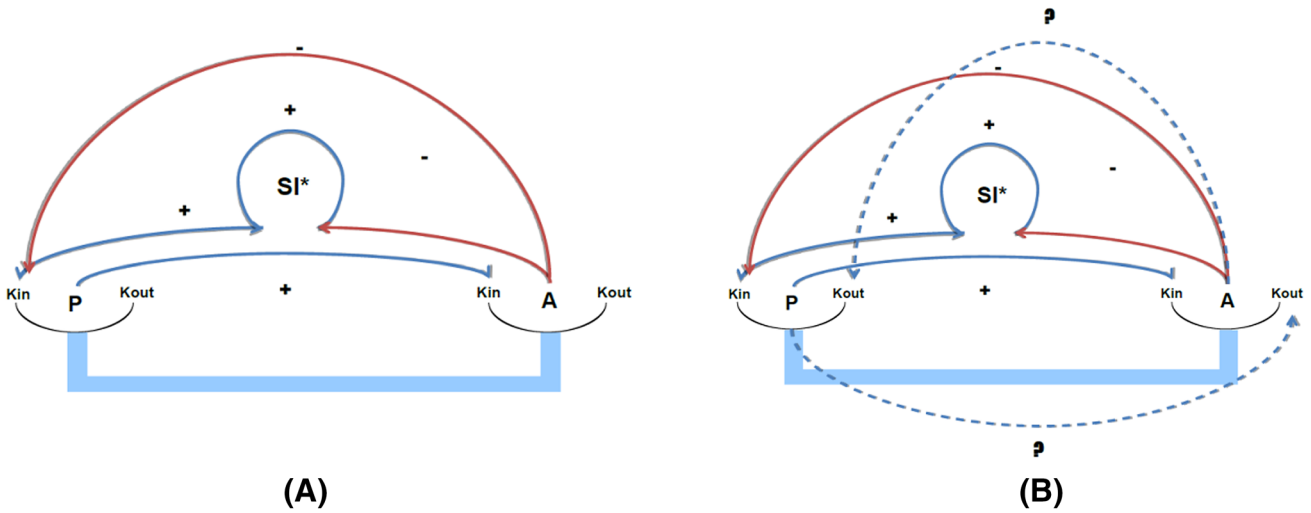


Fig. 2 Mechanism of the model representing the interactions between the three variables: SI*, P, and A. **a** Red and blue arrows represent activation and inhibition, respectively. There are three balances: K_{in}–K_{out} (P), K_{in}–K_{out} (A) and A–P. **b** The dotted arrow represent the new regulatory unknown introduced in the two parts of K_{out}

post-transcriptional regulatory mechanism for gene expression in many cellular processes, including the immune response, as well as playing a crucial role in the endotoxin tolerance system [34–38, 48–50]. For example, when miR146, miR155 and miR125b are stimulated by LPS in human monocytic cells [51–53], they can inhibit TLR4/IL-1R signaling via the post-transcriptional regulation of signaling proteins such as IL-1 receptor-associated kinase 1 (IRAK-1) and TNF receptor-associated factor 6 (TRAF6) [49, 53]. Thus, miRNA may act by inhibiting the SI* and P responses in the post-transcriptional state [30, 50, 53, 54]. However, the miRNA (miR98) can control the production of IL-10 in the post-transcriptional state [55, 56].

In addition, Cytochrome P450s (CYPs) are superfamily proteins including a variety of enzymes and can convert the proinflammatory 20-hydroxyeicosatetraenoic acid (20-HETE) and anti-inflammatory epoxyeicosatrienoic acids (EETs) [57]. The CYP450 gene can motive during the inflammation progression and lead to the activation, suppression and resolution of the inflammation [57–59]. In general, CYP gene expression is reduced by high concentration of pro-inflammatory cytokine, such as IL-6, TNF-α and interferon-β [57, 60–63]. CYP450 can play an important role in maintaining the correction of pro/anti-inflammatroy balance [57–59]. Finally, we consider that miRNAs as components of P and A can regulate P and A in the post-transcription state, and CYP450 may activate or inhibit the P and A to form the cycle regulation.

In order to introduce this new regulatory level, we suggest that at the levels of K_{outA} and K_{outP}, this new regulatory loop can be activated by the opposing factor but in two different directions, where the production level of A will stimulate the post-transcriptional degradation of P, whereas the production of P will inhibit the post-transcriptional degradation of A. This can be viewed as changing the fundamental point of the balance support (f1, g1; Fig. 2b).

$$\text{(f)}\quad \frac{dP}{dt} = \frac{K_{inP}}{A} * \left(1 + H_{P.SI*}\right) * \left(1 + H_{P.E}\right) - K_{outP} * P$$

$$\text{(g)}\quad \frac{dA}{dt} = K_{inA} * \left(1 + H_{A.P}\right) * \left(1 + H_{A.E}\right) - K_{outA} * A$$

$$\text{(f1)}\quad \frac{dP}{dt} = \frac{K_{inP}}{A} * \left(1 + H_{P.SI*}\right) * \left(1 + H_{P.E}\right) - K_{outP} * P * A$$

$$\text{(g1)}\quad \frac{dA}{dt} = K_{inA} * \left(1 + H_{A.P}\right) * \left(1 + H_{A.E}\right) - K_{outA} * \frac{A}{P}$$

2.2 Virtual treatment

In this study, we aimed to simulate immune system treatments for sepsis. We tested two possible logical treatments for sepsis shock: activating A by increasing the rate of production for the A response (by changing the A production rate parameter, where an increase in K_{inA}, replicates activation by IL-10 treatment); or limiting A by increasing clearance of the A response (by changing the A decay rate parameter, where an increase in K_{outA} replicates an anti-IL-10 treatment). We simulated these two possibilities as virtual treatments, Thus, the activation of IL-10 and inhibition of IL-10 were tested using our in silico model and with the initial model proposed by Calvano et al. [28] at different times in the initial phase of septic shock, i.e., 0.2 h following the infectious stimulus, and in later phases at 30, 72 and 120 h after the infectious stimulus.

2.3 SNP simulation

We considered the SNP of gene could play the regulated role during the sepsis and may increase the expression of the TLR and pro-inflammation cytokines [39–43]. Through our new numeric model, we suppose the ratio of the parameter of Kin,mRNA,R for simulating the activation of SNP to TLR4 receptor during the LPS activation. However, the parameter Kc is control factor of SI to P for identification of the gene SNP which regulate the expression of pro-inflammatory cytokine. Thus, the modification of two parameter value was introduced in the new mathematic model and try different initial LPS value to test the SNP regulation consequence.

3 Results

3.1 In silico simulation of septic shock

When the infectious stimulus exceeded a critical threshold (LPS = 4), the system exhibited an irreversible hyper-stimulated status, which we considered similar to the loss of control seen during septic shock. At this time, the host immune system lost control of the ability to stabilize the system by self-hyper-activation of complex signaling, which can be viewed as an accurate representation of immunodysfunction.

When the same stimulus was applied with LPS = 4, the new model exhibited an irreversible response in terms of SI*, which was similar to the original. However, A became sufficiently strong to not return to a normal state following explosive deregulation. A had a higher value when LPS = 4 in the dysfunctional system compared with the maximum value when LPS = 1, 2, or 3. However P decreased to a lower value, which corresponded to the maximum value when LPS = 2. A reached a higher activity level compared with that of P, thereby leading to an imbalance in the immune system that favored the production of anti-inflammatory mediators, such as IL-10, and overall strong inhibition of the immune function (Fig. 3a). E was at lower level following explosive deregulation, which could have important health consequences. It is important to note that the immune system downregulated P and E, but upregulated A after stimulation with LPS. Monneret et al. [8] represented the immunoparalysis by initial system inflammatory response that is reduced by the anti-inflammatory process as the negative feedback during the sepsis. The clinical data showed that the anti-inflammatory response can dominate the septic patient for the long term [8, 21–24]. The new model simulated result showed that the anti-inflammatory response resists the high level, can compensated pro-inflammatory response which is hyper-active at the beginning stage after 24 h injection of LPS = 4 (Fig. 3a). In addition, when LPS = 4 the new model showed that energy response was at lower level which correspond the mitochondrial dysfunction and a consequence of a progressive decrease in energy availability during the septic process proposed by Singer et al. [64–72]. Finally, we considered the result is similar to the immunosuppression mechanism associated with septic shock.

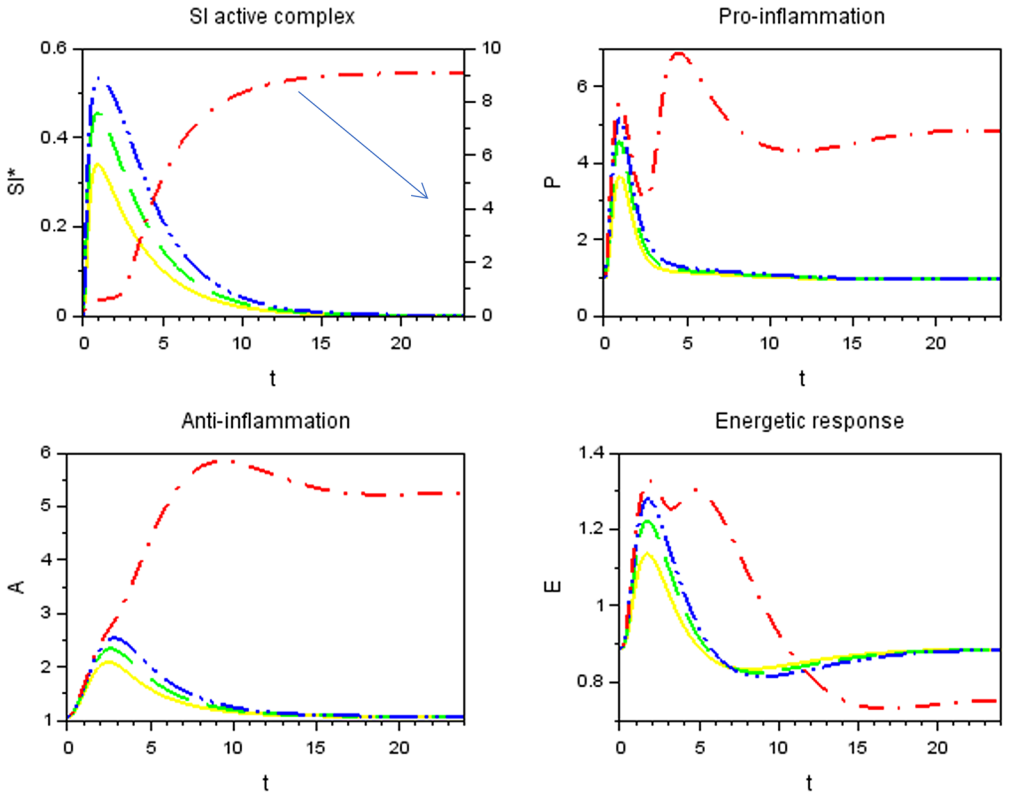
3.2 Comparison of the two models

After the injection of LPS < 4 at t = 0 h, there was a large difference between the two models. The result obtained by the new model indicated an earlier response compared with the original model and the maximum value was low. The two models had the same critical threshold for the injection of LPS (= 4), which led to the hyper-activation of SI* and malfunction of the host immune system function. However, after the injection of LPS = 4 at t = 0 h, hyper-activation of P and A were exhibited by the original model, whereas our model indicated an imbalance that favored the hyper-activation of A (Fig. 3), and E was abnormal when the system lost control of intracellular signaling. By contrast, Calvano et al. [28] used the reciprocal energy response to determine the energy failure and negative regulation of the energetic process, but we consider that this result explains the metabolic flux event (Fig. 1). In the model, the energy response activates the entire system, and thus we consider it as an action due to energy consumption (or demand). The result obtained by the new model differed from those produced by the initial model after the modification, although the overall model was not changed, and we did not obtain exact measurements.

We compared the three terms for endotoxin tolerance in the two models where after a double stimulus, the new model had a second peak in the anti-inflammatory response corresponding to the second injection of LPS, which was not present in the initial model (data not show) [28]. In general, the immune system and cellular bio-energetic processes reacted faster than those in the initial model [28], which was also the case after the re-stimulation by LPS. Finally, the new model did not change the compartments in the initial model and can simulate mechanism of septic shock, so we can consider it as a version of the sepsis model.

3.3 Virtual treatments

The activation of A (as IL-10) as a treatment was applied during the initial stage at t = 0.2 h, which resulted in the reduced activation of P and the severity of sepsis in the earlier shock stage (Fig. 4). The application of this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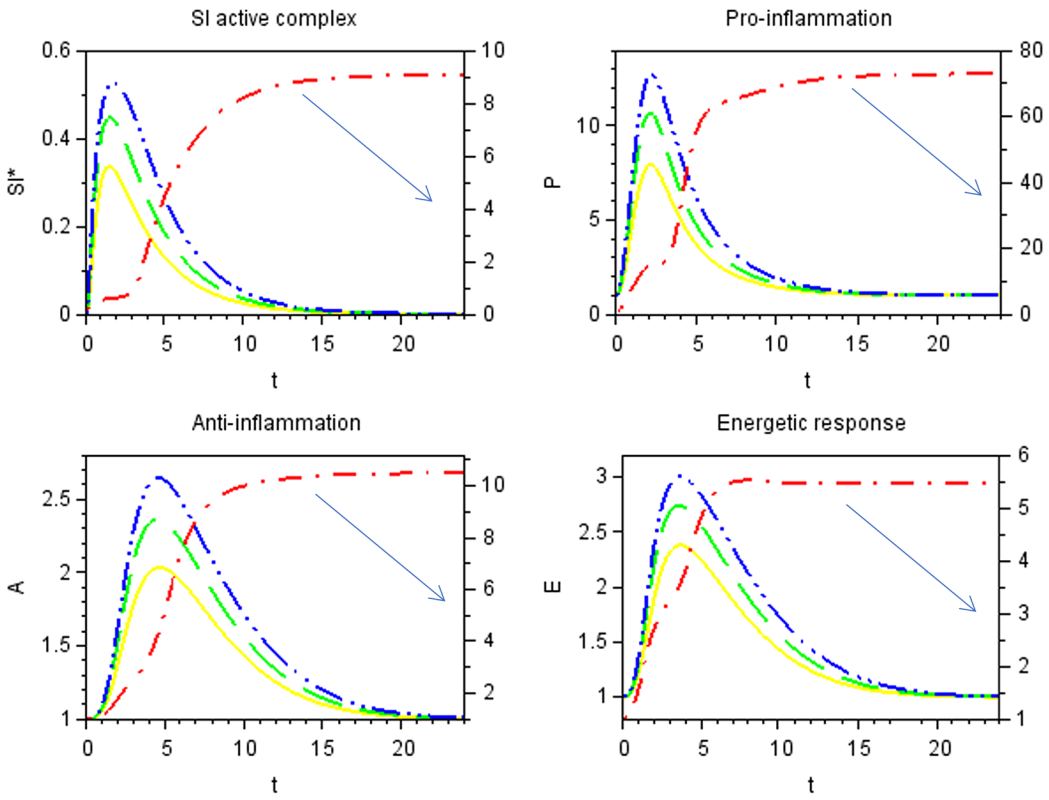
(A)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(B)

◂**Fig. 3** Temporal responses of the critical inflammatory components to various initial conditions for the inflammatory stimulus. A high concentration of LPS could lead to a malfunction in terms of the dynamics of the host response to infection, which is represented by an exacerbated inflammatory response (red line). (A) New model: yellow solid line: LPS (0) = 1, green dashed line: LPS (0) = 2; blue dotted line: LPS (0) = 3; red dash-dotted line: LPS (0) = 4. (B) Initial model: yellow solid line: LPS (0) = 1, green dashed line: LPS (0) = 2; blue dotted line: LPS (0) = 3; red dash-dotted line: LPS (0) = 4

treatment at a later stage, e.g., 30, 72 and 120 h, also led to an increase in immunoparalysis, which increased A, but decreased P and E to lower values than those obtained without treatment (Fig. 4). In particular, the treatment at 0.2 h suppressed the irreversible SI* response and returned the immune system to a normal state (Fig. 4).

The virtual treatment comprising the inhibition of A (as IL-10) at t = 0.2 h led to increases in P and the severity of sepsis (Fig. 5) during the earlier shock state. However, after continuing these treatments, P and E increased, whereas A remained unchanged (the result was the same at 30, 72, and 120 h) (Fig. 5) compared with the results of without treatment. Thus, the inhibition of A shifted the pro-inflammatory and anti-inflammatory balance toward the activation of P in the post shock state.

After introducing these virtual treatments into the initial model (data not shown), the activation of A at 0.2 h interrupted the formation of the irreversible SI* response and hyper-activated E. The results obtained after treatment in the later states (30, 72, and 120 h) showed that the activation of anti-inflammation could reduce the hyper-activation of P, activate E, and possibly balance the immune system. By contrast, the inhibition of A in the long term led to the hyper-activation of P and E decreased. Finally, the results obtained with the virtual treatments in the initial model showed that the activation of anti-inflammation is the best solution for re-establishing the immune system after hyper-stimulation by endotoxin.

3.4 SNP simulation

The parameter Kin,mRNA is considered the gene SNP frequency of the LPS receptor TLR4 regulation and Kc is as the gene SNP frequency of the pro-inflammatory cytokine. Therefore, we increase the value simulate fort sensibility of SNP with initial LPS value 1, 2, 3, 4 at t = 0 (Figs. 6, 7). Normal the model show the LPS = 4 can produce the sepsis shock phenomena, but when we changing the Kin,mRNA,R = 10 (minimal) via 0.2114 or Kc = 4 (minimal) via 3, at t = 0 LP = 3 might destroy the balance of immune system and increase the sepsis possible (Figs. 6, 7). So that the Kc increased 1.3 fold may cause the septic shock, in contrast Kin,mRNA,R need 46.7 fold change may cause the septic shock by the in silico simulation. We hypotheses that the gene SNP of the pro-inflammatory cytokine could play important role for the sepsis risk.

4 Discussion

The pathogenesis of sepsis is not clearly understood, but in the last few decades, new observations have suggested that the course of septic shock can be divided into two contrasting stages. In the early stage, the massive release of inflammatory mediators is responsible for organ dysfunctions and hypo-perfusion. In the late stage, the anti-inflammatory response persists and leads to immune paralysis. The capacity to treat patients during the early hours of shock has improved (early and intensive initial supportive therapy) and many patients now survive this critical stage, but they eventually die later in an immunosuppressed state due to difficulties fighting the primary bacterial infection and decreased resistance to secondary nosocomial infections [6, 8, 9, 11, 18, 21–26].

LPS is a component of the Gram-negative bacterial cell wall and its effects represents an appropriate model for studying endotoxin tolerance [32–34, 44, 73] as well the immuno-inflammatory response during infection [11–13, 17–20, 73–75]. In this model, the host inflammatory response is a consequence of multiple and complex cascades of mediators, where the endotoxin binds to a pattern recognition receptor, i.e., TLR4. The binding of endotoxin to this receptor activates signaling of the intracellular transcriptional factor NF-κB, which seems to play a central role [18–20, 76–80] in driving the immune response and changing the inflammatory state. This model comprises eight variables that are considered to play parts in the indirect response [45, 46] to simulate the effects of LPS.

In this study, we explored a simulation using a numerical model after modifying an initial model by introducing a novel regulatory mechanism. Figure 2 (K_{in} corresponds to the transcription rate and K_{out} corresponds to the post-transcription rate) shows the new regulatory mechanism added to K_{out}. This regulatory factor appeared to modify the fundamental point of the balance between the K_{in} and K_{out}, where the results of the simulation were closer to reality after its introduction. By injecting a high concentration of LPS (LPS ≥ 4) at t = 0, the host immune system was blocked by a strong positive feedback loop and P remained at a low level, whereas the value of A stayed at a high level, which differed from the maximum

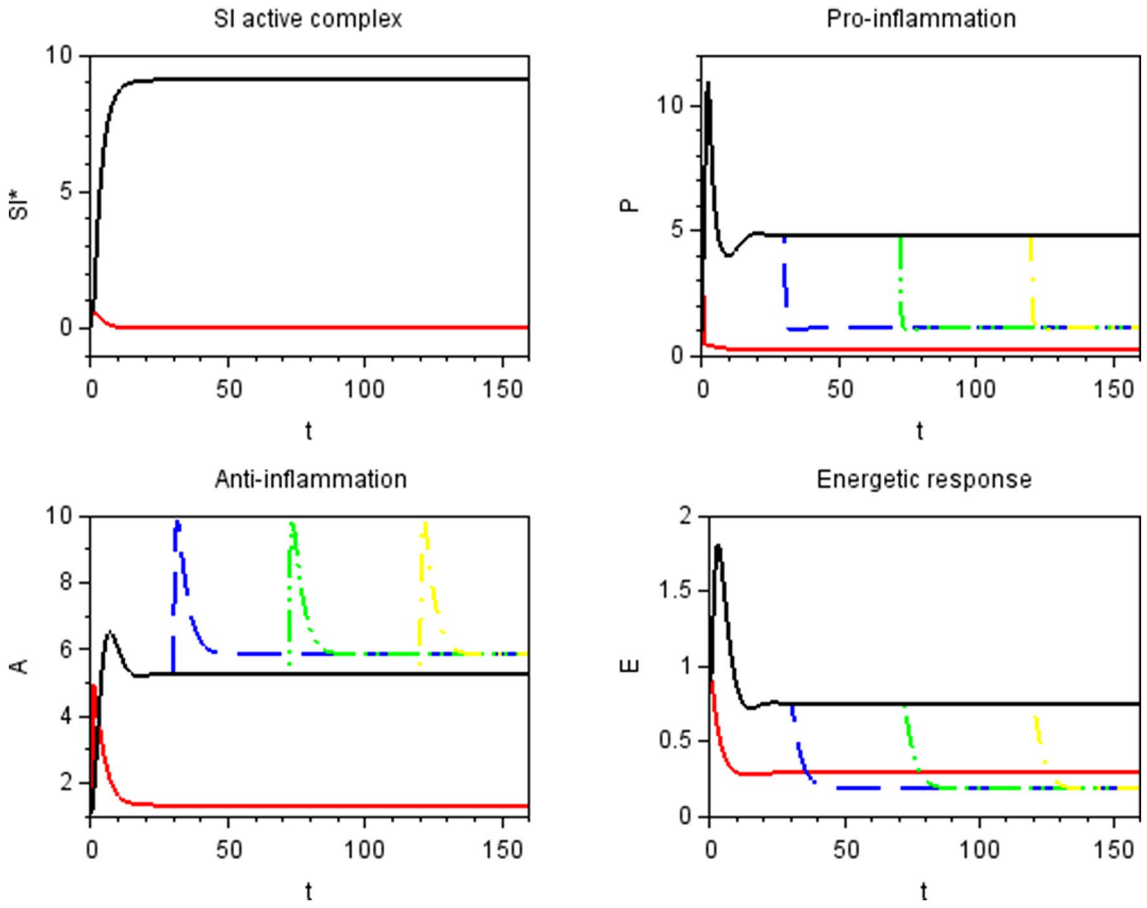

Fig. 4 Virtual treatment to simulate the activation of anti-inflammation at four times: 0.2, 30, 72, and 120 h. Red solid line: LPS = 10, K_{inA} = 0.256 (t = 0 h), K_{inA} = 2.56 (t = 0.2 h). Blue dashed line: LPS = 10, K_{inA} = 0.256 (t = 0 h), K_{inA} = 2.56 (t = 30 h). Green dotted line: LPS = 10, K_{inA} = 0.256 (t = 0 h), K_{inA} = 2.56 (t = 72 h). Yellow dash-dotted line: LPS = 10, K_{inA} = 0.256 (t = 0 h), K_{inA} = 2.56 (t = 120 h). Black solid line: LPS = 10, K_{inA} = 0.256 (t = 0 h)

value when LPS < 4 at t = 0. Thus, we consider that A plays an important role in the sequence of dysfunctions in the immune system, where it inhibits the function of the immune system and provokes immunoparalysis. We also note that the energy response declined below the normal level during immunoparalysis and this poor energy response might impair the functions of organs. After applying a virtual treatment, the first injection of LPS = 10 may simulated the septic shock syndrome and immunoparalysis in the post-shock state. We conclude that treatment via the inhibition of A (as IL-10) produced better results in the post-shock state (at 30, 72 and 120 h) because it reactivated the immune system so P and E were at high levels. However, when we began the treatment in a premature shock stage at t = 0.2 h, P increased during the earlier stage of septic shock and the severity of sepsis increased. By contrast, treatment by activating A (as IL-10) at t = 0.2 h reduced the shock and removed the blockage of SI*. However, when we continued this treatment or began it at a later time (30, 72, and 120 h) the immune system entered more severe immunoparalysis. These results demonstrate that the application of different septic shock therapies will have diverse outcomes in each stage of the syndrome. The results obtained by the treatment according to the initial model showed that activation by anti-inflammatory therapeutics would be efficient at helping a patient to survive sepsis throughout the whole process. However, in septic patients, the immunosuppressed state cannot follow activation by the anti-inflammatory treatment, which can increase the severity of immunoparalysis. Finally, the new version of the model simulated the immunosuppressed state of

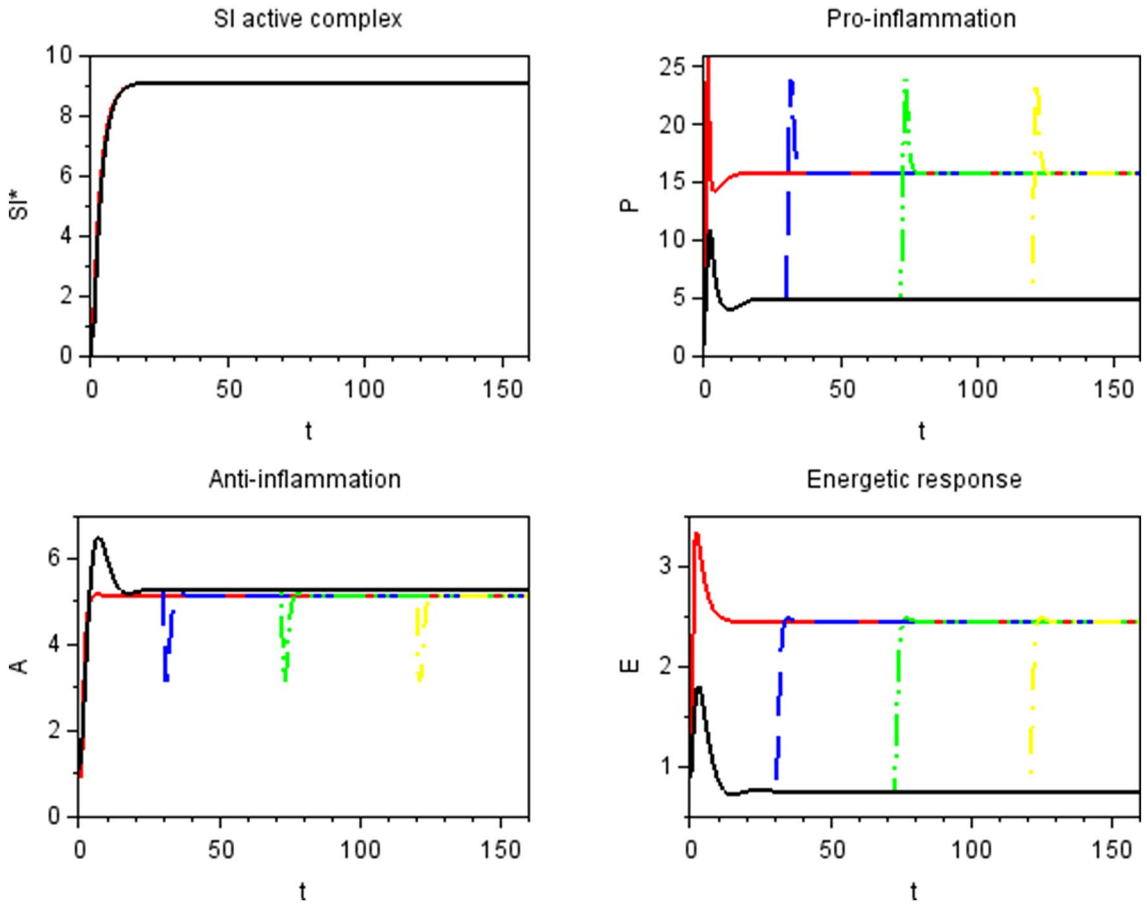

Fig. 5 Virtual treatment to simulate the inhibition of anti-inflammation at four times: 0.2, 30, 72, and 120 h. Red solid line: LPS = 10, K_{outA} = 0.7 (t = 0 h), K_{outA} = 7 (t = 0.2 h). Blue dashed line: LPS = 10, K_{outA} = 0.7 (t = 0 h), K_{outA} = 7 (t = 30 h). Green dotted line: LPS = 10, K_{outA} = 0.7 (t = 0 h), K_{outA} = 7 (t = 72 h). Yellow dash-dotted line: LPS = 10, K_{outA} = 0.7 (t = 0 h), K_{outA} = 7 (t = 120 h). Black solid line: LPS = 10, K_{outA} = 0.7 (t = 0 h)

sepsis patients better and allowed us to explore possible treatments.

Importantly, our results agree with the outcomes observed in clinics as well as in animal models where various approaches related to IL-10 have been tested [17, 24, 81–88]. Especially our activation of IL-10 result showed the increasing of anti-inflammatory response and inhibition of pro-inflammatory response cause aggravation of immunoparalysis as animal model testing result [89–92]. In addition, AS101 with capacity to inhibit the IL-10, have been shown the increasing survival and restore the pro-inflammatory cytokines: IFN-gamma, TNF-alpha and IL-1 beta in the septic animal model as demonstrated in our result of anti-IL-10 virtual treatment [86, 93]. Considering the schematic representation of the pro-/anti-inflammatory balance in the pathophysiology of sepsis, we suggest that if possible, a very early anti-inflammatory therapy would be helpful, whereas a pro-inflammatory strategy would be more appropriate in the delayed stage of this disease. We showed that IL-10 treatment had beneficial effects only when it was applied at 20 min, after which it had no effects or deleterious outcomes. This very narrow therapeutic window may explain the failure of many clinical assessments of various anti-inflammatory drugs [94]. Indeed, this window is already closed when most patients are admitted to ICUs. By contrast, the pro-inflammatory strategy appears to be beneficial after 30 h, as suggested recently by experts [27, 31, 95]. In addition to the convincing "IL-10/anti-IL-10" results, this model may facilitate further investigation of new therapeutic strategies.

The SNP simulation result showed that pro-inflammatory cytokine gene regulation can influence the immune system and increase the sepsis risk after infection [43].

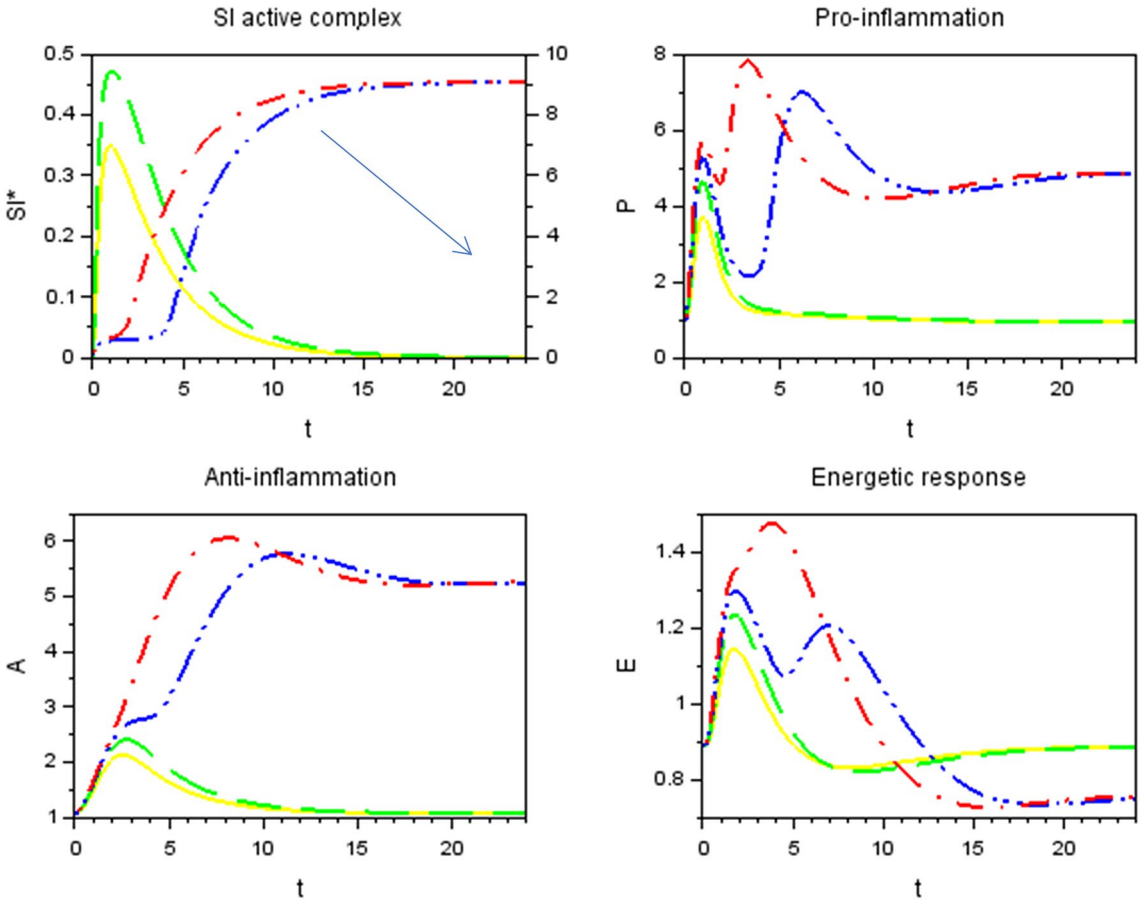

Fig. 6 Gene SNP of TLR4 simulation by modifier the parameter Kin,mRNA,R at t = 0 with different initial LPS introduce value. A high concentration of LPS could lead to a malfunction in terms of the dynamics of the host response to infection, which is represented by an exacerbated inflammatory response (blue dotted and red dash-dotted line). Yellow solid line: LPS (0) = 1, green dashed line: LPS (0) = 2; blue dotted line: LPS (0) = 3; red dash-dotted line: LPS (0) = 4

However, the TLR4 gene regulation of SNP can be negligent. By our numeric model, we can analyze the different possibilities of gene SNP regulation, which may play an important role in the sepsis. In addition, the sensibility of the SNP may be depending on the patient condition, age, gender, etc. [41, 42]. Furthermore, for SNP regulation, new equation may be added to the mathematical model to better simulate the mechanism and better understand genetic regulation pathway in sepsis.

In conclusion, our improvements allowed the initial mathematical model to simulate sepsis. Our changes are based on new research results obtained in recent years. Sepsis may cause a series of physiological changes, particularly in terms of gene expression, including gene reprogramming and post-transcriptional regulation. However, we introduced the novel regulatory mechanism into the part responsible for the degradation of P and A. This type of regulation is a post-transcription mechanism and it establishes the balance of the immune system. Thus, this new model can reflect septic shock better. Finally, new therapies for immunoparalysis may be explored in two new areas based on cellular energy and signal transduction pathways, and a numerical model can be used to simulate these two areas in a more complex model in order to understand the function of inflammation .

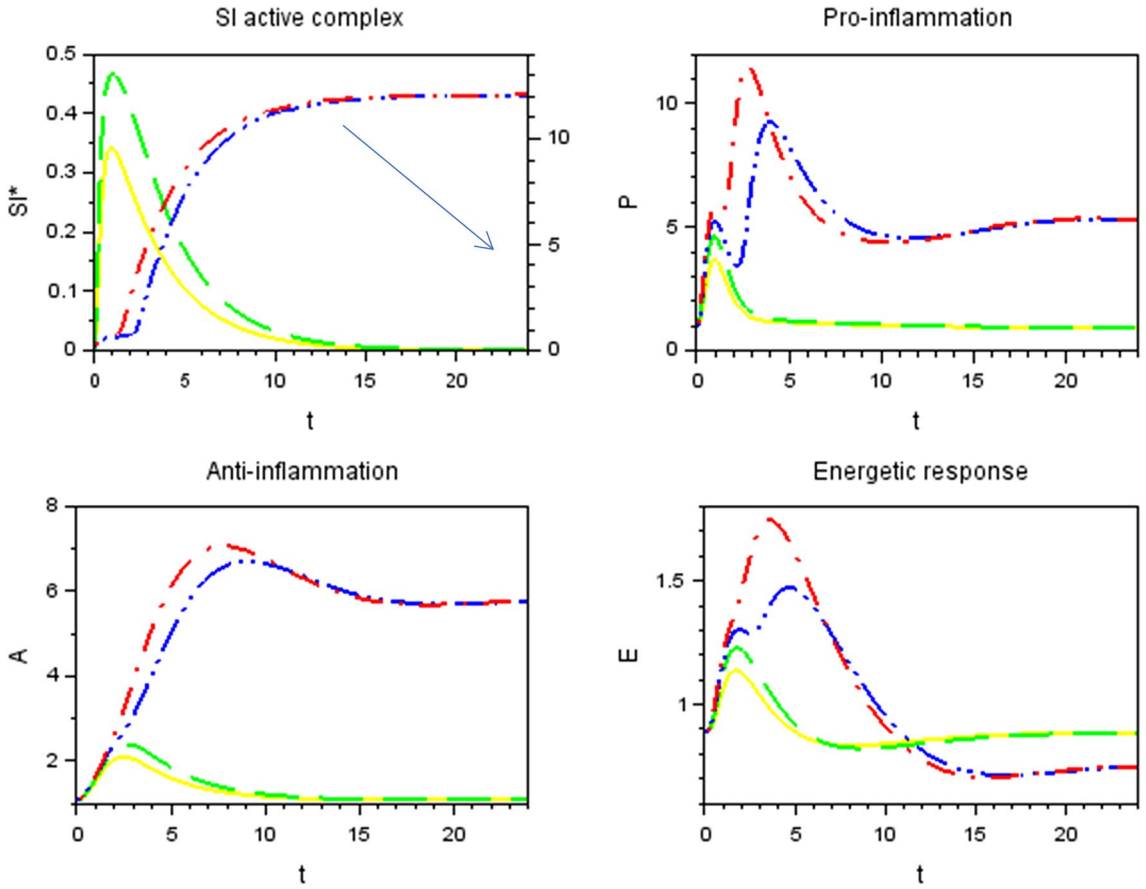

Fig. 7 Gene SNP of pro-inflammatory cytokine simulation by modifier Kc the parameter at t = 0 with different initial LPS introduce value. A high concentration of LPS could lead to a malfunction in terms of the dynamics of the host response to infection, which is represented by an exacerbated inflammatory response (blue dotted and red dash-dotted line). Yellow solid line: LPS (0) = 1, green dashed line: LPS (0) = 2; blue dotted line: LPS (0) = 3; red dash-dotted line: LPS (0) = 4

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.w

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