

# Prediction of Patient’s Response to an Acute Inflammation Treatment by Mixture of Experts

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**Abstract.** Acute inflammation is a progressive medical condition characterized as systemic inflammatory response to an infection. If inadequately diagnosed and treated, acute inflammation culminates in sepsis, which is the leading cause of death in non-coronary intensive care units in the United States. In practice, clinicians make diagnostic and therapeutic decisions based on their experience and understanding of the relationships between treatments and expected outcomes of such treatments, which is often suboptimal due to limited knowledge about patient response to therapy. To develop adequate sepsis treatment strategies, accurate prediction of patient response to therapy is essential. However, complex multi-stage nature of acute inflammation makes patient response to treatment difficult to predict. The complexity and heterogeneity of inflammatory response that consists of different stages with significantly different properties is one of the main reasons of unsuccessful treatments. Therefore, there is a critical need for tools for predicting patient’s response to therapy, which can help clinicians to design more effective therapies for this potentially fatal condition. Towards this objective we developed a data-driven prediction model based on mixture of experts. The proposed model identifies stages (regimes) of patient state and builds specialized predictors for each stage. In experiments conducted on 500 virtual patients generated by a mathematical model for acute inflammation, our method not only outperformed all baselines accuracy wise but also identified three stage-specific experts that can play an important role in improving perception of complex systems such as response to acute inflammation treatment.

## 1 Introduction

An inflammatory response is a complex defending mechanism of the patient’s body against an infection. In the event of an infection, inflammatory system clears the pathogen, begins a repair process, and leads a patient to healthy state. At the same time inflammation itself damages tissue, which is negligible in controlled inflammatory response. On the other hand, uncontrolled inflammatory response can lead to organ failure and death. When accompanied by an infection, the uncontrolled inflammation is defined as sepsis, which is a common and frequently fatal condition, with 750,000 cases annually in the

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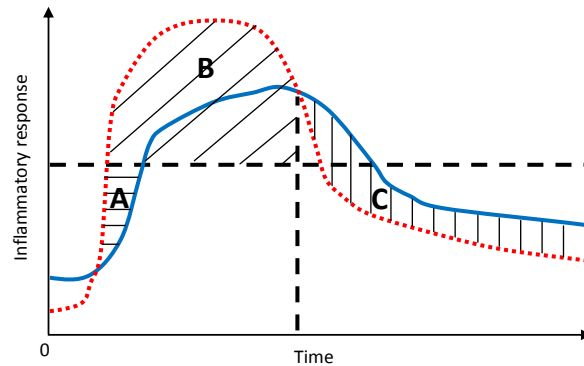


Fig. 1: Theoretical considerations of the sepsis stages and treatment effects.  $Time = 0$  - occurrence of an infection; red dotted line - pro-inflammatory response; blue solid line - anti-inflammatory response; black dashed horizontal line - response beyond which the process becomes adversary; black dashed vertical line - a tip-over point beyond which any therapy might be counterproductive; horizontal pattern (area A) - anti-inflammatory therapy likely harmful, pro-inflammatory therapy beneficial; diagonal pattern (area B) - likely maximal benefit from anti-inflammatory therapy; vertical pattern (area C) - anti-inflammatory response restoring patient state, any therapy likely harmful.

United States alone [1]. Due to its complex nature, sepsis is often diagnosed too late and the patient is then treated with broad-spectrum antibiotics and/or intravenous fluids with dosages adjusted manually, even though more specific therapy would be far more effective. Inadequate treatment results in a mortality rate of 30-35%, and for every hour that the administration of appropriate therapy is delayed, the mortality rate increases by about 7% [2].

Limited understanding and knowledge about the complex acute inflammatory response has led to only a few effective therapies against sepsis. The single approved anti-sepsis drug therapy was withdrawn from global markets in fall 2011 following the failure of its worldwide trial to demonstrate improved patient outcome [3]. The complexity and heterogeneity of inflammatory response that consists of different stages, having significantly different properties, is one of the main reasons behind unsuccessful treatments. Sepsis treatment requires both a strong pro-inflammatory phase for the clearance of pathogen (Figure 1, area A) and an anti-inflammatory phase for recovery (Figure 1, area C). A stage of an adversary influence of the pro-inflammatory response, which is disproportionate and counterproductive, is presented in Figure 1, area B. An inadequate treatment in either the pro-inflammatory (area A) or the immune-recovering anti-inflammatory phase (area C) might do more harm than good, while delayed treatment when immune response is counterproductive (area B) may significantly reduce the chance of survival.

In practice, clinicians make diagnostic and therapeutic decisions based on the clinician's understanding of the relationships between treatments and expected outcomes of such treatments, which is often suboptimal because of limited knowledge of the patient

stage and patient response to therapy. Therefore, there is a critical need for tools that can simultaneously identify different acute inflammation stages and build specialized patient response predictors for each of the stages. These tools can be of significant help to clinicians in designing the most effective optimal strategies for any stage of acute inflammation. Appropriate predictive tools can be data-driven machine learning models that use historical data to learn associations between observed and future measurements. A key feature of machine learning models is that predictions are not based on domain assumptions, but on historical data only.

Learning a single predictor on historical data with different stages (regimes) could result in an overly complicated model suffering from overfitting [4]. As an alternative, it may be more effective to learn predictors on each stage (regime) separately. Since the regimes are not known beforehand, this idea can be implemented through the mixture of experts method [4]. In this paper we propose a mixture of experts model for patient response prediction on acute inflammation therapy, which simultaneously detects regimes (stages) by gating function and learns specified predictors on identified regimes. In our proposed design, experts and gating function are composed of feed forward neural networks. Such design alleviates the overfitting problem and retains modeling flexibility.

The rest of the paper is organized as follows. In Section 2 we introduce a virtual patient model that emulates therapy response. In Section 3 we propose a predictive model composed of mixture of experts. We evaluate the proposed model in Section 4. Finally, conclusions are stated in Section 5.

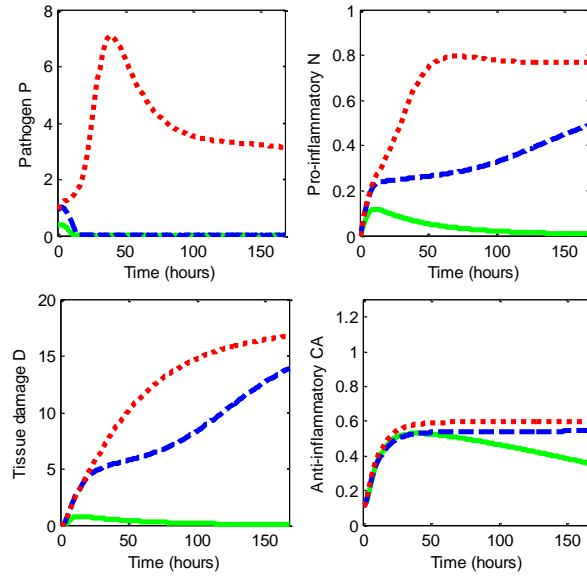


Fig. 2: Evolution of pathogen population ( $P$ ), pro-inflammatory mediators ( $N$ ), tissue damage ( $D$ ), and anti-inflammatory mediators ( $CA$ ) of three virtual patients with healthy (green/solid), aseptic (blue/dashed), and septic (red/dotted) outcomes in the absence of therapy.

## 2 Virtual Patient Model

To significantly reduce the chance of a clinical failure and to save on the costs of clinical trials, biomedical researchers use computer simulations of body processes (often called virtual patients) to perform preliminary tests of hypotheses before they prove them in real patient studies. Virtual patients are generated using a carefully determined mathematical model to simulate the process of interest. A significant advantage of having a virtual patient model for experiments is the possibility of testing different approaches for finding adequate therapies on the same virtual patient and comparing the outcomes. In order to follow a real-life scenario, virtual patient models are accompanied with well-defined constraints in therapy that are in accordance with clinical practice [5].

### 2.1 Patient model

The mathematical model for inflammatory response to severe infection is derived in [6]. This model has not incorporated drug effect on inflammatory response and it was not applicable for predicting the response of acute inflammation treatment. We will use a slightly modified mathematical model recently proposed in [5] that is capable of simulating:

- an evolution of a pathogen ( $P$ ) that initiates the cascade of inflammation,
- dynamics of early pro-inflammatory mediators ( $N$ ),
- markers of tissue damage/dysfunction ( $D$ ),
- the evolution of anti-inflammatory mediators ( $CA$ ),

which are controlled by doses of pro-inflammatory ( $PIDOSE$ ) and anti-inflammatory ( $AIDOSE$ ) therapies. This mathematical model is based on the system of ordinary differential equations (ODE)

$$\frac{dP}{dt} = k_{pg} \left( 1 - \frac{P}{P_\infty} \right) - \frac{k_{pm}s_m P}{\mu_m + k_{mp}P} - k_{pn}f(N)P, \quad (1)$$

$$\frac{dN}{dt} = \frac{s_{nr}R}{\mu_{nr} + R} - \mu N + PIDOSE(t), \quad (2)$$

$$\frac{dD}{dt} = \frac{k_{dn}f(N)^6}{x_{dn}^6 + f(N)^6} - \mu_d D, \quad (3)$$

$$\frac{dCA}{dt} = s_c + \frac{k_{cn}f(N + k_{cnd}D)}{1 + f(N + k_{cnd}D)} - \mu_c CA + AIDOSE(t), \quad (4)$$

where

$$R = f(k_{np}P + k_{nn}N + k_{nd}D), f(x) = \frac{x}{1 + \left( \frac{CA}{c_\infty} \right)^2}. \quad (5)$$

Although conceptual, ODE is capable of modeling the complex effect of pathogen ( $P$ ) on the patient. An increase of pathogen level  $P$  leads to the series of positive and negative feedback reactions that are all successfully modeled by ODE. In particular, an

increase of  $P$  leads to the development of a pro-inflammatory response, which causes an increase of  $N$  in (2) and to the development of tissue damage, which causes an increase of  $D$  in (3). Equation (1) simulates a positive effect of inflammation where an increase of  $N$  reduces level of pathogen  $P$ . However, (3) simulates a negative effect of inflammation where an increase of  $N$  further damages tissue causing rapid increase of  $D$ . An increase of  $D$  mobilizes a negative feedback in (4), or anti-inflammatory response ( $CA$ ), which lowers level of  $N$  and inhibits damage to tissue (decrease of  $D$ ) [5]. The strength of positive and negative feedbacks depends on the parameter values in ODE. By varying parameter values we can simulate variability among patients.

Variability in the population of virtual patients is obtained by random initialization of three parameters in ODE  $k_{pg}$ ,  $k_{cn}$ , and  $k_{nd}$  and by random initialization of the initial conditions  $P_0$  and  $CA_0$  from uniform distribution on valid ranges ( $k_{pg} \in [0.3, 0.6]$ ,  $k_{cn} \in [0.03, 0.05]$ ,  $k_{nd} \in [0.015, 0.025]$ ,  $P_0 \in [0, 1]$ ,  $CA_0 \in [0.0938, 0.1563]$ ). All other parameters were fixed to referent values as in [5] except ( $k_{cnd}$  that covaries with  $k_{cn}$  and  $k_{np}$  that covaries with  $k_{nd}$  [5]). In all of the simulations,  $t$  is an hourly step that starts from  $t = 0$  when patient state and parameters are initialized. Then, patient state evolves according to ODE through the simulation time of 168 hours (one week). According to [5] there are three possible outcomes at the end of simulation time, which are shown in Figure 2. A patient is in healthy state if  $P = 0$ ,  $N = 0$ ,  $D = 0$ , and  $CA > 0$  at the end of simulation. The aseptic death state of the patient is defined as  $P = 0$ ,  $N > 0$ ,  $D > 0$ , and  $CA > 0$ . The third possible outcome is septic death, where these four variables are non-zero.

### 3 Predictive model

Virtual patient state is represented by four outputs  $P$ ,  $N$ ,  $D$ , and  $CA$ . The goal of the predictive model is to accurately predict future states using past states along with past drugs' doses as inputs. To predict four-dimensional state with a single model we propose as in [7] splitting the predictive model into four sub-models, each of which is responsible for prediction of one of the outputs  $P$ ,  $N$ ,  $D$ , and  $CA$ , keeping the same set of inputs for each of the sub-models. If we denote  $\mathbf{y}_j$  and  $\mathbf{u}_j$  to represent patient's state and drugs' doses at time point  $j$  respectively, it can be written

$$\mathbf{y}_j = (P_j, N_j, D_j, CA_j)^T, \quad (6)$$

$$\mathbf{u}_j = (AIDOSE_j, PIDOSE_j)^T. \quad (7)$$

Having observed patients' states and control signals up to time point  $j$ , the sub-model responsible for predicting  $\hat{P}_{j+1}$  can be represented by

$$\hat{P}_{j+1} = F_P(\mathbf{x}, \Theta_P), \quad \mathbf{x} = (\mathbf{y}_j, \dots, \mathbf{y}_{j-n_{py}+1}, \mathbf{u}_j, \dots, \mathbf{u}_{j-n_{pu}+1}), \quad (8)$$

where  $F_P$  is a function with unknown parameters  $\Theta_P$  that models the input-output relation;  $n_{py}$  and  $n_{pu}$  are time lags for state and control signals respectively. Sub-models responsible for prediction of  $\hat{N}_{j+1}$ ,  $\hat{D}_{j+1}$ , and  $\hat{CA}_{j+1}$  have similar functional form but each of them has its own function  $F_N$ ,  $F_D$ ,  $F_{CA}$  with parameters  $\Theta_N$ ,  $\Theta_D$ ,

$\Theta_{CA}$  respectively. Learning parameters  $\Theta_N, \Theta_D, \Theta_{CA}$  depends on the design of sub-models. We propose mixture of experts model for each sub-model. As each sub-model has identical functional form in following sections we denote output variables a target  $t \in \{P, N, D, CA\}$ .

### 3.1 Mixture of experts

Proposed mixture of models that is composed of gated experts (described in [4]) will address the problem of different regimes in acute inflammation progress during the therapy. The basic idea of gated experts is to learn several local models (experts) on different splits of the input space (input data) instead of using a single global model. Mixture of models assumes that splitting of input space is unknown (hidden) but it would be discovered during the learning procedure. It allows each input to be assigned softly to several regimes (experts). Responsibilities of each regime for different inputs are different and determined as the outputs of the gating function. This allows the experts to specialize (learn) only on the partitions of input space for which they are responsible. Figure 3 shows the architecture of gated experts. As we can see, both the experts and the gating network have access to all the inputs, but they do not have to share the same sets of inputs.

**Gated experts.** When the data generating process changes over time (for example different stages in inflammatory response), prediction accuracy can be significantly improved by learning a number of regression models specialized for certain temporal partition (stage) as compared to a single (global) model learned on whole dataset. Let us assume that a temporal dataset is a union of  $K$  disjoint partitions  $T_k, k = 1, \dots, K$ , where the number of partitions  $K$  and their temporal locations are not known in advance. Under the Gaussian noise assumption, the data generating process for  $T_k$  can be represented as

$$t^{(i)} = o_k(\mathbf{x}_e^{(i)}, \boldsymbol{\theta}_k) + e^{(i)}, e^{(i)} \sim N(0, \sigma_k^2), \text{ for } i \in T_k, \quad (9)$$

where  $o_k$  is the regression function (expert) of partition  $T_j$ ,  $\mathbf{x}_e^{(i)}$  and  $e^{(i)}$  are the expert attribute vector and the error term of data point  $i$  ( $\mathbf{x}_e^{(i)} \subseteq \mathbf{x}^{(i)}$ ) respectively. Then, the probability of generating target  $t^{(i)}$  by expert  $k$  is

$$P(t^{(i)}|\mathbf{x}^{(i)}, \boldsymbol{\theta}_k) = \frac{1}{\sqrt{2\pi}\sigma_k} \exp\left(-\frac{(t^{(i)} - o_k(\mathbf{x}_e^{(i)}, \boldsymbol{\theta}_k))^2}{2\sigma_k^2}\right) \quad (10)$$

where parameters  $\boldsymbol{\theta}_k$  and variance  $\sigma_k^2$  characterize expert  $k$ .

**Gating function.** Since we have  $K$  experts, the probability of generating target  $t^{(i)}$  by all experts is

$$P(t^{(i)}|\mathbf{x}) = \sum_{k=1}^K P(\text{expert}_k|\mathbf{x}^{(i)}) \frac{1}{\sqrt{2\pi}\sigma_k} \exp\left(-\frac{(t^{(i)} - o_k(\mathbf{x}_e^{(i)}, \boldsymbol{\theta}_k))^2}{2\sigma_k^2}\right), \quad (11)$$

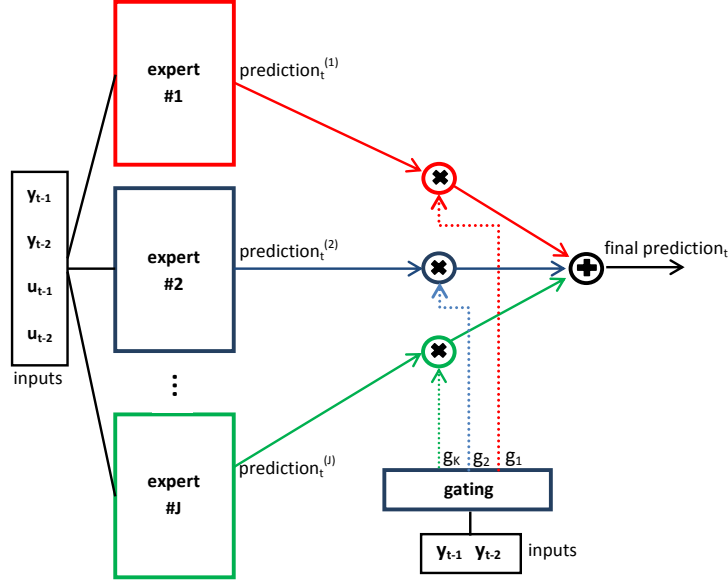


Fig. 3: Mixture of gated experts architecture for modeling patient's inflammation response.

where  $P(\text{expert}_k | \mathbf{x}^{(i)})$  is the probability that expert  $k$  is responsible for point  $\mathbf{x}^{(i)}$ .

Probabilities  $P(\text{expert}_k | \mathbf{x}^{(i)})$  are determined as outputs of gating network. The gating network contains a standard neural network (*tanh* activation function in hidden unit and *linear* in output unit) with parameters  $\theta_g$  and multiple outputs such that each output is assigned to exactly one expert denoted by  $s_k, k = 1 \dots K$ . The outputs of the gating network are normalized exponentials

$$g_k^{(i)} = \frac{\exp(s_k^{(i)})}{\sum_{k=1}^K \exp(s_k^{(i)})}, \quad (12)$$

which constrains gating outputs to sum to 1 providing competition among experts. The gating outputs  $g_k(\mathbf{x}_g^{(i)}, \theta_g)$  weight expert outputs  $o_k(\mathbf{x}_e^{(i)})$  such that overall expected output value  $o(\mathbf{x}^{(i)})$  (final prediction) of the model is

$$E[o(\mathbf{x}^{(i)})] = \sum_{k=1}^K g_k(\mathbf{x}_g^{(i)}) o_k(\mathbf{x}_e^{(i)}, \theta_k), \quad (13)$$

where  $\mathbf{x}_g^{(i)}$  is input to the gating network ( $\mathbf{x}_g^{(i)} \subseteq \mathbf{x}^{(i)}$ ).

**Maximum likelihood learning.** In order to learn both gating network and expert parameters, we need to evaluate the likelihood of the data given the model. The assumption of statistical independence of measurement errors of each data point  $i, i = 1 \dots N$ ,

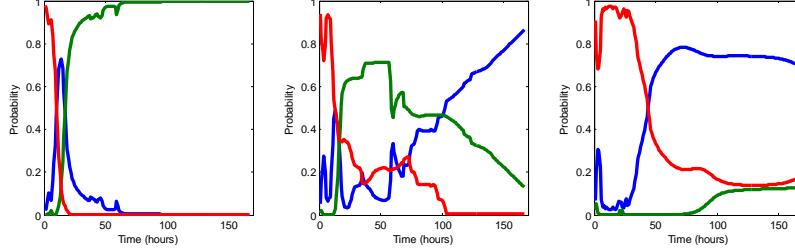


Fig. 4: Evolution over time of gating outputs (probabilities) for three specialized predictors (red, green and blue) of pathogen P. Probabilities are averaged over healthy, aseptic, and septic patients and shown respectively.

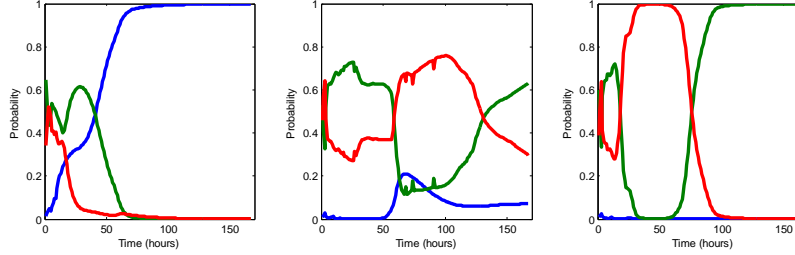


Fig. 5: Evolution over time of gating outputs (probabilities) for three specialized predictors (red, green and blue) of tissue damage D. Probabilities are averaged over healthy, aseptic, and septic patients and shown respectively.

allows us to obtain the full likelihood by taking products of individual likelihoods in the form

$$\begin{aligned}
 L &= \prod_{i=1}^N P(t^{(i)} | \mathbf{x}^{(i)}) = \prod_{i=1}^N \sum_{k=1}^K g_k(\mathbf{x}_g^{(i)}, \boldsymbol{\theta}_g) P(t^{(i)} | \mathbf{x}^{(i)}, \boldsymbol{\theta}_k) \\
 &= \prod_{i=1}^N \sum_{k=1}^K g_k(\mathbf{x}_g^{(i)}, \boldsymbol{\theta}_g) \frac{1}{\sqrt{2\pi}\sigma_k} \exp\left(-\frac{(t - o_k(\mathbf{x}_e^{(i)}, \boldsymbol{\theta}_k))^2}{2\sigma_k^2}\right) \quad (14)
 \end{aligned}$$

To estimate parameters  $\boldsymbol{\theta}_g, \boldsymbol{\theta}_1, \dots, \boldsymbol{\theta}_K, \sigma_1, \dots, \sigma_K$  we need to minimize the negative logarithm of likelihood function  $L$ , which is not achievable by using a gradient descent algorithm. In order to make optimization feasible, the problem needs to be slightly modified such that it allows us to apply the *Expectation-Maximization* (EM) algorithm [8].



**Expectation Maximization (EM) algorithm.** To map the problem to an EM algorithm we construct a set of indicator (hidden) variables  $z_k^{(i)}$ ,  $i = 1 \dots N, k = 1, \dots, K$  to indicate that given data point  $i$  is generated by expert  $k$ . Indicator variables allow us to replace sum over experts in the likelihood expression with product

$$L_C = \prod_{i=1}^N \prod_{k=1}^K \left[ g_k(\mathbf{x}_g^{(i)}, \boldsymbol{\theta}_g) P(t^{(i)} | \mathbf{x}^{(i)}, \boldsymbol{\theta}_k) \right]^{z_k^{(i)}} \quad (15)$$

The problem is that we do not know the values of  $z_k^{(i)}$  but we can compute their expected values in the E-step and then update model parameters in the M-step. We will iterate between the E and M steps until guaranteed convergence [8]. In the E-step of the algorithm we compute expected values of  $z_k^{(i)}$  using Bayesian rule

$$\begin{aligned} E[z_k^{(i)}] &= P(z_k^{(i)} = 1 | \mathbf{x}, \mathbf{t}, \boldsymbol{\theta}) = \frac{P(z_k^{(i)} = 1 | \mathbf{x}^{(i)}) P(t^{(i)} | \mathbf{x}^{(i)}, z_k^{(i)} = 1)}{P(t^{(i)} | \mathbf{x}^{(i)})} \\ &= \frac{g_k(\mathbf{x}^{(i)}, \boldsymbol{\theta}_g) \frac{1}{\sqrt{2\pi\sigma_k}} \exp\left(-\frac{(t - o_k(\mathbf{x}_e^{(i)}, \boldsymbol{\theta}_k))^2}{2\sigma_k^2}\right)}{\sum_{k=1}^K g_k(\mathbf{x}_g^{(i)}, \boldsymbol{\theta}_g) \frac{1}{\sqrt{2\pi\sigma_k}} \exp\left(-\frac{(t - o_k(\mathbf{x}_e^{(i)}, \boldsymbol{\theta}_k))^2}{2\sigma_k^2}\right)} \end{aligned} \quad (16)$$

In the M-step we minimize the expected value of the negative logarithm of (15)

$$\begin{aligned} -\ln(L_C^{(M)}) &= \sum_{i=1}^N \sum_{k=1}^K -E[z_k^{(i)}] \ln(g_k(\mathbf{x}_g^{(i)}, \boldsymbol{\theta}_g)) + \\ &+ \frac{1}{2} \sum_{i=1}^N \sum_{k=1}^K E[z_k^{(i)}] \left[ \frac{(t - o_k(\mathbf{x}_e^{(i)}, \boldsymbol{\theta}_k))^2}{\sigma_k^2} + \ln(\sigma_k^2) + \ln(2\pi) \right] \end{aligned} \quad (17)$$

Minimization of (17) is done by using a gradient descent approach on the following update equations

$$\sigma_k^2 = \frac{\sum_{i=1}^N E[z_k^{(i)}] (t^{(i)} - o_k(\mathbf{x}_e^{(i)}, \boldsymbol{\theta}_k))^2}{\sum_{i=1}^N E[z_k^{(i)}]} \quad (18)$$

$$\frac{\partial L_C^{(M)}}{\partial \boldsymbol{\theta}_k} = \frac{\partial L_C^{(M)}}{\partial o_k} \frac{\partial o_k}{\partial \boldsymbol{\theta}_k} = - \sum_{i=1}^N E[z_k^{(i)}] \frac{1}{\sigma_k^2} (t^{(i)} - o_k(\mathbf{x}_e^{(i)}, \boldsymbol{\theta}_k)) \frac{\partial o_k}{\partial \boldsymbol{\theta}_k} \quad (19)$$

$$\frac{\partial L_C^{(M)}}{\partial \boldsymbol{\theta}_g} = \frac{\partial L_C^{(M)}}{\partial s_k} \frac{\partial s_k}{\partial \boldsymbol{\theta}_g} = - \sum_{i=1}^N \left( E[z_k^{(i)}] - g_k(\mathbf{x}_g^{(i)}, \boldsymbol{\theta}_g) \right) \frac{\partial s_k}{\partial \boldsymbol{\theta}_g} \quad (20)$$

where variance of the  $k$ th expert has a closed form solution. Learning procedure is summarized in Algorithm 1.

## 4 Experiments

In the experiments we want to validate our hypothesis that patients response to an infection and medications switches between regimes. If the hypothesis holds at least  $K$

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**Algorithm 1** Learning a sub-model

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**Input:**  $X, T, K$ , maximum number of iterations

**Initialization:** split input data randomly into  $K$  subsets(regimes), learn experts on the splits, set corresponding expectations to 1.

**repeat**

  compute expectations (16)

  update variance (18)

  adjust experts (19)

  update gating network using (20)

**until** convergence or maximum number of iterations exceeded

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experts ( $K > 1$ ) have to survive the learning process. As we have competition of experts, initialization to a certain number of experts does not mean that this would be their final number in our sub-model. Actually, some of them can disappear by finding corresponding outputs of the gated network close to zero for all inputs. To train and validate our sub-models, we have generated two independent sets of virtual patients.

#### 4.1 Data sets

The critical aspect of the predictive model design is the availability of representative training data to learn unknown model parameters. Our objective was to address a real-life scenario in which data available for training of the predictive model come from clinical trials done on a group of diverse patients observed in time. Accordingly, a set of 100 virtual patients with hourly observations for one week (168 hours) was generated from ODE equations. To generate a sequence of observations for a virtual patient we need to know model parameters, initial conditions and a drugs dosage. Initial conditions and parameters are randomly generated following allowable ranges, while a drugs dosage was carefully chosen to simulate a real-life scenario (for more details see [7]). We validated results of gated experts on 500 hundred patients generated in the same manner but with different initial conditions and parameters applied in ODE.

Table 1: Prediction error ( $RMSE$ ) of gated experts and baselines on validation set of 500 virtual patients generated by a mathematical model. Gated experts model is compared to two alternatives with respect to pathogen level ( $\text{mean}(P) = 0.37$ ) and tissue damage ( $\text{mean}(D) = 1.58$ ).

<i>Algorithm</i>	$P < 0.37$	$P \geq 0.37$	$D < 1.58$	$D \geq 1.58$
Gated experts	<b>0.003</b>	<b>0.025</b>	<b>0.009</b>	<b>0.005</b>
Neural network	0.033	0.222	0.080	0.181
Linear regression	0.024	0.161	0.033	0.074

## 4.2 Structure of gated experts

To create gated experts, we firstly need to determine the number of past patient states and drug doses (model order) used as inputs to the predictive model. As discussed in [7], the predictive model which uses time lag set to 1 cannot provide satisfactory results in terms of predictive accuracies. We will follow [7] and build the predictive model using time lag set to  $n_{py} = n_{pu} = 2$ . We used two-layer feed forward neural networks to model both specialized predictors and the gating function. Moreover, in order to achieve stability in predictions of both gating function and specialized predictors, we constructed ensembles composed of 5 neural networks for each of them. We used a hyperbolic tangent sigmoid transfer function for hidden neurons and a linear function for output neurons in all two-layer feed forward neural networks deployed in our model. Each neural network in a particular ensemble is trained using the same training set but different initialization of weights. Neural networks in the ensemble for the gating function had 5 hidden neurons, while neural networks in specialized predictor ensembles contained 3 hidden neurons. The gating function uses only past patient state variables and does not depend on control, while specialized predictors use both patient state variables and past dosages.

## 4.3 Results

We found in the training set that ideal number of regimes is 3 by looking at survival experts while changing  $K$ . We validated our model on 500 patients. In order to confirm our hypothesis of the existence of different regimes, we expect to obtain better accuracies of gated experts than single-regime models. We consider a neural network and linear regression trained on the entire training set as single models for baselines. Model accuracies are compared using root mean squared error (RMSE) defined as

$$RMSE = \sqrt{\frac{\sum_{i=1}^N (t^{(i)} - o^{(i)}(x))^2}{N}} \quad (21)$$

The lower RMSE is, the better the predictor is. Accuracies for pathogen level ( $P$ ) and tissue damage ( $D$ ) are reported in Table 1, as they are considered more important for application purposes than pro-inflammatory mediator ( $N$ ) and anti-inflammatory mediator ( $CA$ ). We decided to show predictor performances above and below mean of the target variables ( $\text{mean}(P) = 0.37$ ,  $\text{mean}(D) = 1.58$ ). We have seen the same trend in accuracies for  $N$  and  $CA$ . It is noticeable that gated experts outperform the baseline by one order of magnitude. We can notice that neural network performance is worse than linear regression because linear regression is more robust to regime-switchings. We also analyzed the evolution of probabilities (gating outputs) over time for three specialized predictors (red, green and blue) of pathogen  $P$  and presented them in Figure 4. Regime #1 (red line in Figure 4) is dominant at the beginning of therapy and represents the increasing of pathogen level  $P$  (Figure 2). In healthy patients (Figure 4) pathogen level  $P$  declines soon after the beginning of therapy and regime #2 (blue line) becomes dominant. As soon as tissue damage starts to decline, regime #3 becomes dominant and stays elevated until the end of therapy. In aseptic (Figure 4) and septic (Figure 4)

patients tissue damage stays elevated, which is reflected through dominance of regime #2 at the end of therapy. Slow increase of tissue damage in aseptic patients is reflected through dominance of regime #3 (green in Figure 4). Similar analysis can be performed for evolution of gating outputs over time for three specialized predictors (red, green, and blue) of tissue damage  $D$  (Figure 5).

## 5 Conclusion and Future Work

We have developed a new approach for prediction of patient response to acute inflammation treatment based on the use of the mixture of experts. Each patient outcome variable was modeled by separate mixture (sub-model). We discovered three regimes in each sub-model, meaning that three experts were necessary to model each outcome variable in patient response. Results obtained from experiments conducted on virtual patients have undoubtedly shown that our method outperformed baselines (single models) regarding the accuracy. This result confirms our hypothesis of the existence of several regimes in patient response. Also it provides evidence that potential solutions for acute inflammation treatment can be based on the joint work of domain scientists and the data mining community.

## 6 Acknowledgement

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## References

1. S. M. Zuev, S. F. Kingsmore, and D. D. Gessler, "Sepsis progression and outcome: A dynamical model," *Theoretical Biology and Medical Modelling*, 2006.
2. S. W. Thiel, J. M. Rosini, W. Shannon, J. A. Doherty, S. T. Micek, and M. H. Kollef, "Early prediction of septic shock in hospitalized patients." *Journal of hospital medicine : an official publication of the Society of Hospital Medicine*, vol. 5, no. 1, pp. 19–25, 2010.
3. D. Angus, "The search for effective therapy for sepsis: Back to the drawing board?" *JAMA*, vol. 306, no. 23, pp. 2614–2615, 2011.
4. A. S. Weigend, M. Mangeas, and A. N. Srivastava, "Nonlinear gated experts for time series: Discovering regimes and avoiding overfitting," 1995.
5. G. Clermont, J. Rubin, and J. Day, "Using nonlinear model predictive control to find optimal therapeutic strategies to modulate inflammation," *Mathematical Biosciences and Engineering*, vol. 7, no. 4, pp. 739–763, 2010.
6. A. Reynolds, J. Rubin, G. Clermont, J. Day, Y. Vodovotz, and G. Bard Ermentrout, "A reduced mathematical model of the acute inflammatory response: I. Derivation of model and analysis of anti-inflammation." *Journal of theoretical biology*, vol. 242, no. 1, pp. 220–36, 2006.
7. K. Ristovski, V. Radosavljevic, and Z. Obradovic, "A data mining approach for optimization of acute inflammation therapy," in *IEEE International Conference on Bioinformatics and Biomedicine*, 2012.
8. C. M. Bishop, *Pattern Recognition and Machine Learning*. Springer, 2006.