Abstract—The inflammatory response is a complex, highly nonlinear biological process, for which complete measurements of all variables are not usually available. Since it is desirable to find therapeutic inputs that enable the response to be controlled toward a favorable outcome, it is crucial to estimate the states that are impossible to measure, and use them for the appropriate control strategy. This article begins with a study of nonlinear observability of a reduced mathematical model of the acute inflammatory response. This will provide theoretical support for employing various state estimation approaches, including the extended Kalman filter (EKF), the unscented Kalman filter (UKF), and the particle filter (PF). A comparison of these techniques is presented with respect to the reduced model of inflammation and the performance of each filter is evaluated in terms of accuracy and consistency.

Index Terms—Particle Filter, EKF, UKF, state estimation, inflammation modeling

I. INTRODUCTION

In this paper, we present a clear study of the nonlinear observability of the inflammation model used in Day et al.[3] and compare the performance of several state estimation techniques applied to the model. A (virtual) patient’s inflammatory response is simulated using the model developed in [1]. In the latter, the biological relevance of the model was discussed. The model reproduces several important observations related to severe systemic inflammation in biological organism.

The natural behavior of the body to respond to a (bacterial) infection is known as inflammation. Control of the inflammatory response is crucial for maintaining a healthy state in critically ill patients. One way to achieve this is through manipulating inflammatory mediators [1], [3]. Many mediators can be present during the course of an inflammatory response. Therefore, initial theoretical work focused on how these mediators interact and what gives rise to severe and persistent inflammation [10], [11], [1], [2]. Experimental work showed that finding appropriate intervention targets and strategies was not a simple endeavor [6], [8], [9]. Thus, the use of control algorithms such as MPC was suggested as a way to help determine this.

A reduced mathematical model of the inflammatory response was first introduced by [15]. While that model captured a variety of clinically relevant scenarios associated with the inflammatory response to infection, further work provided in [1] came to give insight into the advantage of including a dynamic anti-inflammatory response.

It is hard to obtain information of the amount of tissue damage in the body after an inflammatory response has been initiated or count the total number of bacteria. Therefore, a method for estimating these states given a set of observations is required. We adopt the state-space approach to modeling dynamic systems and focus on the discrete time formulation of the problem. Optimal estimation problems for non-linear, non-Gaussian state-space models do not generally accept analytic solutions. Nonlinear estimation problems are often addressed by using linearized filters, such as the extended Kalman filter (EKF). The latter is the most widely applied state estimation algorithm for nonlinear systems. The idea is to linearize the system around the Kalman filter estimate, where the Kalman filter estimate is based on the linearized system. Since these filters suffer from linearization errors, especially when dealing with severe nonlinearities, an attempt to reduce these errors was to introduce the iterated EKF (IEKF)[7], which iterates the filter update until convergence by relinearizing the measurement function at each iteration. Alternatively, another solution has been proposed and is know as the unscented Kalman filter (UKF)[13]. The UKF deterministically samples the nonlinear function around the state estimate, thus improving the nonlinear approximation. Lastly, particle filtering methods have become an appealing class of algorithms to solve these estimation problems in an online and recursive way as observations become available. They were first applied in the area of signal processing [12] and belong to the class of sequential Monte Carlo methods [14]. They are based on the idea of approximating the target distributions sequentially by sets of weighted samples \( \{x_i, w_i\}_{i=1}^N \), known as (weighted) particles.

In the work of [3], MPC was used as a tool to explore appropriate intervention strategies to control the inflammatory response, a complex cascade of immune events that occur in response to an infection. A four dimensional ordinary differential equations model of the inflammatory response was used in that study (see [1] for model development); however, the observability of the model was not explored and no state estimation techniques were employed even though only two of the four states were assumed to be measurable. This paper comes to give some insight on the different applicable state estimation techniques with respect to the given model.

The simulation results show that particle filter provides better estimates for the states when compared to the EKF and UKF.
and deals better with high process and measurement noise.

The remainder of the paper is structured as follows:

We start by introducing the observability of nonlinear system in Section II, we follow by defining the immune system response model in Section III. Nonlinear observability analysis is presented in Section IV. A brief introduction to particle filter is found in Section V. And lastly, a comparative simulation result of EKF, UKF, and PF is provided in Section VI. Finally, Section VII concludes this work and outlines possible directions of future research.

II. Nonlinear System Observability

In this section we introduce an important concept related to the observability of nonlinear system that will serve as a support for using nonlinear state estimation algorithms.

Herman and Krener [17] associated observability to the idea of distinguishability of states with respect to the inputs. (Two states are called U-distinguishable if there exist a bounded measurable input u(t), t ∈ [0 T] such that both state trajectory remain in U and each one resulting in different output). Specifically they emphasise the dependence of observability of nonlinear system on the control inputs unlike linear system. For further explanation consider the following system:

\[ \Sigma \begin{cases} \dot{x} = f(x) + \sum_{i=1}^{m} g_i u_i \\ z = h(x) \end{cases} \]  

(1)

Where \( f(x) \) is a \( n \times 1 \) nonlinear vector function, and \( x \) is the \( n \times 1 \) state vector. \( z \) is a \( p \times 1 \) measurement vector and the number of input is \( m \). The system \( \Sigma \) is said to be observable at \( x_0 \) if the state vector \( x(t_0) \) can be determined from the observation \( z(t) \) over a finite time. The Nonlinear observability analysis is based on the observability rank condition introduced by Herman and Krener [17], noting that if the system \( \Sigma \) is weakly observable, then "one can distinguish each point from its neighbors." Now, since the system may travel a considerable distance to distinguish between states, the property of local distinguishability or local weak observability has been introduced. A necessary condition for local weak observability is stated in [17] as follows: if \( \Sigma \) is locally weakly observable, then the observability rank condition is satisfied generically. In other words if the system fails to satisfy the proposed rank condition, then it will not be locally weakly observable, neither locally observable. The system \( \Sigma \) satisfies the the observability rank condition if any of the observability matrices are of rank \( n \). The observability matrices are given by:

\[ d\zeta = \text{span}(dL_1 h_j, dL_{g_1} h_j, dL_{g_2} h_j, ..., dL_{g_1} h_j) \]

where \( i = 1, ..., n-1 \) and \( j = \{1, ..., p\} \). Further details about how to calculate this matrix are given in section III.

To establish the above test, the exact nonlinear system must be specified. In the next section we define the nonlinear immune response model used in the estimation approach.

III. System Model

A model for the acute inflammatory response to pathogenic infection has been described in [1] together with the definition of each constant parameter. The system can be expressed in the following ODE:

\[ \frac{dP}{dt} = k_{pn}P(1 - \frac{P}{P_\infty}) - k_{pn}g_m P - k_{pn}f(N)P \]  

(2)

\[ \frac{dN}{dt} = \frac{s_{nr} R}{\mu_{nr} + R} - \mu_P N + u_p(t) \]  

(3)

\[ \frac{dD}{dt} = k_{dn} x_{dn} + f(N)^\mu - \mu_d D \]  

(4)

\[ \frac{dC_a}{dt} = s_c + k_{cn} f(N + k_{cd} D) - (1 + f(N + k_{cd} D)) - \mu_c C_a + u_c(t) \]  

(5)

The functions \( R \) and \( f \) are given by:

\[ R = f(k_{np} P + k_{nn} N + k_{nd} D) \]

\[ f(x) = \frac{x}{1 + (\frac{x}{x_{\infty}})} \]

The two inputs \( u_p \) and \( u_c \) represent respectively the pro-inflammatory and the anti-inflammatory therapy of the system. They both promote either a pro or anti-inflammation effect. Clearly, these inputs are always positive. Equation (2) represents the evolution of the bacterial pathogen population \( P \) that causes the inflammation. Equation (3) governs the dynamics of the concentration of a collection of early pro-inflammatory mediators such as activated phagocytes and the pro-inflammatory cytokines they produce \( N \). Equation (4) corresponds to tissue damage \( D \), which helps to verify response outcomes. Finally, equation (5) describes the evolution of the concentration of a collection of anti-inflammatory mediators \( C_a \).

The system admits the following three stable equilibrium points under certain parameter choices (see [1] for details):  

1. Healthy: \( (P, N, D, C_a) = (0, 0, 0, 0, 125) \)
2. Aseptic: \( (P, N, D, C_a) = (0, N, D, C_a) \) for \( N, D, C_a > 0 \)
3. Septic: \( (P, N, D, C_a) = (P, N, D, C_a) \) for \( P, N, D, C_a > 0 \) with all component positive

After defining the model and setting the framework of knowing if a nonlinear system is observable, the next section applies this approach to the model defined above.

IV. Observability Analysis of Immune Model

The observability matrix is found by calculating the Lie derivative of the nonlinear system. Following after [17], we define the Lie derivative of a \( C^\infty \) scalar function \( h \) on an open subset \( S \subset \mathbb{R}^{\dim(x)} \) along an analytic vector field \( f \) on \( S \), as the scalar function given by:

\[ L_f h = dh f \]

where \( dh \) is the gradient of \( h \). Repeated Lie derivatives can be defined recursively as

\[ L_f^0 h = h \]

\[ L_f^i h = L_f(L_f^{i-1} h) \text{ for } i = 1, 2, ... \]

Given the measurements \( N \) and \( C_a \), we define the vector \( z \) as follow:

\[ z = [h_1 \ h_2]^T = [N \ C_a]^T \]

The following represent the span of all Lie derivatives of \( h_1 \) and \( h_2 \) both with respect to \( f, g_1 \) and \( g_2 \) up to order \( n - 1 \):

\[ \zeta = \text{span}(L_f h_1, L_f h_2, L_{g_1} h_1, L_{g_1} h_2, L_{g_2} h_1, L_{g_2} h_2, ..., L_{g_2} h_2) \]
A simple comparison with equation 1 gives:
\[ f(x) = [f_1, f_2, f_3, f_4]^T \]
with
\[ f_1 = \dot{P}, f_2 = \dot{N}, f_3 = \dot{D}, f_4 = \dot{Ca} \]
and
\[ g_1 = \ldots \text{noise are chosen.} \]
The increase of the number of particles for the PF did not give a considerable improvement.

It is easy to proceed with higher order derivatives. Since the gradient of the constants will give 0, we follow with the second order Lie derivative. That is, we continue the derivatives using \( L_T h_1 \) and \( L_T h_2 \). The Observability matrix is defined below as the space \( d\zeta \) spanned by the gradients of \( \zeta \):
\[ d\zeta = \text{span}\{dL_f h_1, dL_f h_2, dL_g h_1, dL_g h_2, dL_{g_1} h_1, dL_{g_1} h_2, \ldots, dL_{g_3} h_2\} \]
Using Maple, it has been sufficient to calculate the Lie derivative up to order 2 to show that the matrix \( d\zeta \) has full rank: i.e rank 4. Note that this was computed on the model using a reference set of parameter values given in [1], and at the healthy state, i.e., \([P, N, D, Ca] = [0, 0, 0, 0.125]\)

V. NONLINEAR ESTIMATION
The EKF and UKF algorithms are not going to be presented. One can refer to [16] for an elegant explanation. PF is briefly described in the following section.

A. Particle Filter
The Particle Filter (PF) is a Bayesian state estimation technique widely used for its capability of solving the nonlinear non-Gaussian state space estimation problem. The goal of PF is to approximate the posterior distribution of the entire state vector, \( p(x_{0:T}|z_{0:T}) \), sequentially, using a set of \( N \) weighted samples or particles, \( \{x_{0:T}^i\}_{i=1}^{N} \), where \( x_{0:t} = [x_0, \ldots, x_t] \) denotes all the states up to time \( t \), and \( z_{0:t} \) denotes all the measurements from 0 to \( t \). The state estimate, \( \hat{x}_t \), is usually obtained as \( E[x_t|y_{1:t}] = \int x_t p(x_t|y_{1:t}) dx_t \). The Particle filter recursion with resampling can be summarized in the following simple steps:

Given particle \( \{x_{i-1}, 1/N\}_{i=1}^{N} \) which approximate \( p(x_{t-1}|z_{1:t-1}) \):

1) **Prediction:** Sample \( x_t^i \sim p(x_t|x_{t-1}^i), \quad i = 1, \ldots, N \).

2) **Updating:**
   - Compute weight: \( \tilde{w}_t^i \propto p(z_t|x_t^i)^{-1}, \quad i = 1, \ldots, N \).
   - Normalize weight: \( w_t^i = \tilde{w}_t^i / \sum_{j=1}^{N} \tilde{w}_t^j, \quad i = 1, \ldots, N \).

3) **Resampling:** \( \{x_t^i, w_t^i\}_{i=1}^{N} \rightarrow \{\tilde{x}_t^i, 1/N\}_{i=1}^{N} \).

The Result is particles \( \{\tilde{x}_t^i, 1/N\}_{i=1}^{N} \) that approximate \( p(x_t|z_{1:t}) \). The mean of the distribution is used to obtain the corresponding estimate. For more details on the algorithm, the reader may refer to [16]. The main challenge in PF is to design the right optimal proposal distribution (which is used to draw particle) to fit the given estimation problem. In this work, we choose the most widely used distribution: \( p(x_t|z_{t-1}) \).

The metrics used to evaluate the estimator performance are the root mean squared error (RMSE) and the normalized estimation error squared (NEES) [7]. The consistency being satisfied if the actual mean square error (MSE) matches the filter-calculated covariance, i.e., the following equality is satisfied: \( E[(x(k) - \hat{x}(k|k))' (x(k) - \hat{x}(k|k))] = P(k|k) \).

VI. SIMULATION RESULTS

The EKF, UKF and particle filter were simulated with respect to the inflammation model given by Equations (2)-(5). The various filters are also compared across four different sets of initial conditions and parameter sets, representing the immune response of four different (virtual) patients (see [3]).

The test is performed over 1000 Monte Carlo simulation for the particle filter and the prior is used as the proposal distribution to draw particles. The measurements corresponding to \( N \) and \( Ca \) are generated from a reference (virtual) patient model. These values are used in all cases. For the results presented in this section, the inputs \( u_p \) (See Eq 3) and \( u_i \) (See Eq 5) were calculated by a nonlinear MPC strategy presented in [3] (in the absence of process noise). The inputs are used in different nonlinear state estimation algorithms explored here. In our implementation, the continuous system model (Eq2-Eq5) is discretized with time step \( T = 1 \) hour.

For the results shown in Figure 1, the measurements were corrupted by zero mean white Gaussian noise, with standard deviation \( \sigma = 0.01 \), and the process noise is chosen to be \( \sigma = 0.001 \). Figure 1 represents a simulation of the first (virtual) patient model. It shows a comparison of different state estimation algorithms. It is important to notice that a value as high as \( Q = 0.01 \) will cause both EKF and UKF covariance matrix to lose rank for most considered (virtual) patients. In other words, the covariance matrix for both filters becomes ill conditioned. Figure 2 shows the squared error corresponding to Fig 1. Notice that the EKF failed to give a good estimation. Figure 3 is another simulation corresponding to patient 3. The behavior of the estimates are different from Figure 1. This is essentially due to the high level of pathogen (1.0017) at the initial condition. UKF and PF were still able to track the states reasonably well. Tables I to IV show a summary of the state estimation simulation corresponding to the four (virtual) patients. It is clear that the EKF estimates are inaccurate, specifically for patients 3 and 4, where the empty case shows the failure of both filters to provide an estimate. As expected, the PF and UKF attain better estimation accuracy (RMSE) than the EKF. The NEES values for PF are significantly better than the remaining filters. Interestingly, the UKF performs quite accurately, sometimes as accurately as PF, though this is not always guaranteed when high values of measurement and process noise are chosen. The increase of the number of particles for the PF did not give a considerable improvement.
for this kind of problem. However, for higher values of noise, the PF showed more stability and resulted in better estimations.

VII. CONCLUSIONS AND FUTURE WORK

In this paper, the nonlinear observability of the patient model has been studied using the theory developed by [17]. The system was found to be observable, which initially encouraged the use of some well known nonlinear filters, namely EKF, UKF and PF. A comparative study was then carried out to determine the accuracy and consistency of each filter at estimating the states of a highly nonlinear system describing the inflammatory response in four different cases involving different initial conditions and parameter sets. Our results show that good estimations of the states were obtained for the UKF, although this was not the case, when high

![Fig. 1. Estimation for Patient 1](image-url)
process noise plus measurement noise were chosen. The EKF was more sensitive to noise and failed in some simulations to converge. The PF indeed showed better estimates for most simulations and better stability with respect to different process and measurement noise levels. Although PF requires more time to run all the Monte Carlo simulations, it remains the more interesting choice, especially since the sampling time considered is one hour and the fact that it deals better
with different kinds of noise.

Future work includes the use of PF together with nonlinear model predictive control (NMPC) to compare to previous work in [3] which used NMPC to find optimal therapeutic strategies to modulate inflammation. Also, we plan to focus on the PF methodology, with this time, letting the noise follow a log-normal distribution, to prevent the states from taking negative values and therefore, be more realistic about the meaning of the state variables of the system.

ACKNOWLEDGMENT

This work has been supported in part by the National Science Foundation under Contract NSF-DMS 1122462.

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