Model-free immune therapy: A control approach to acute inflammation
Ouassim Bara, Michel Fliess, Cédric Join, Judy Day, Seddik Djouadi

To cite this version:
Ouassim Bara, Michel Fliess, Cédric Join, Judy Day, Seddik Djouadi. Model-free immune therapy: A control approach to acute inflammation. 15th European Control Conference, ECC’16, Jun 2016, Aalborg, Denmark. hal-01341060

HAL Id: hal-01341060
https://hal-polytechnique.archives-ouvertes.fr/hal-01341060
Submitted on 3 Jul 2016

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L’archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.
Model-free immune therapy: A control approach to acute inflammation

Ouassim Bara¹, Michel Fliess²,³, Cédric Join³,⁵,⁶, Judy Day⁴, Seddik M. Djouadi¹

Abstract—Control of an inflammatory immune response is still an ongoing research. Here, a strategy consisting of manipulating a pro and anti-inflammatory mediator is considered. Already existing and promising model-based techniques suffer unfortunately from a most difficult calibration. This is due to the different types of inflammations and to the strong parameter variation between patients. This communication explores another route via the new model-free control and its corresponding “intelligent” controllers. A “virtual” patient, i.e., a mathematical model, is only employed for digital simulations. A most interesting feature of our control strategy is the fact that the two outputs which must be driven are sensorless. This difficulty is overcome by assigning suitable reference trajectories to two other outputs with sensors. Several most encouraging computer simulations, corresponding to different drug treatment strategies, are displayed and discussed.

Index Terms—Immun system; inflammatory response; model-free control, intelligent proportional controller.

I. INTRODUCTION

The importance, complexity and ubiquity of the notions of infection and inflammation are well explained by the following quotation [40]: The ‘inflammatory process’ includes a tissue-based startle reaction to trauma; go/no-go decisions based on integration of molecular clues for tissue penetration by microbes; the beckoning, instruction and dispatch of cells; the killing of microbes and host cells they infect; liquefaction of surrounding tissue to prevent microbial metastasis; and the healing of tissues damaged by trauma or by the host’s response. If at any step an order to proceed is issued but progress to the next step is blocked, the inflammatory process may detour into a holding pattern, such as infiltration of a tissue with aggregates of lymphocytes and leukocytes (granulomas) that are sometimes embedded in proliferating synovial fibroblasts (pannus), or distortion of a tissue with collagen bundles (fibrosis). Persistent inflammation can oxidize DNA badly enough to promote neoplastic transformation. According to [12], the overall mortality is approximately 30%, rising to 40% in the elderly and is 50%

or greater in patients with the more severe syndrome. The corresponding literature is of course huge. See, e.g.,

• [48] on the cause,
• [19], [43], [44], [47], [56], [57] for the connections with cancer,
• [11], [17], [27], [31] for the interactions with the human immunodeficiency virus (HIV),
• [13], [36] for the possible relationship with depression.

Although applying automatic control to immune therapy has attracted some interest, as depicted in [42], it is much less developed than in other domains, like, e.g., for insulin-dependent diabetes (see, e.g., [9], [19], and the references therein). Let us nevertheless mention promising papers using respectively optimal control ([6], [8], [30], [52], [53], [54]) and predictive control ([15], [26], [60]). Those approaches are model-based. Among those papers, the most recent ones ([6], [8], [15], [60]) use the same set of phenomenological ordinary differential equations from [45] (see also [44] and [16]):

• The corresponding model is based on the non-specific protective mechanism, namely, the innate immune response, in contrast to the adaptive immune system. The latter provides a more advanced and strategic response producing B and T cells together with specific antibodies.

• Anti-inflammatory mediators are included. They play an important rôle to mitigate a severe inflammation and, therefore, avoid tissue damage and high pathogen proliferation.

• Its biological relevance has been confirmed via a good qualitative reproduction of severe systemic inflammation in a biological organism.

Other mathematical modelings have been proposed (see, e.g., [11], [13], [23], [31], [43], [45], [51], [58]). In spite of interesting preliminary results in [8], [7], [60], state observation and parameter identification are not yet fully mastered. Its calibration, which depends heavily on the type of inflammatory response and on patient differences (genetics, age, gender, . . . ), is therefore most intricate.

This paper suggests another route, namely the recent model-free setting and the corresponding “intelligent” controllers [20]. It is worthwhile to recall that model-free control has already been successfully applied in quite diverse case-studies (see, e.g., [32], [37], [38], [55] in the field of “life engineering”). The modeling remains nevertheless

¹Work partially supported by the NSF-DMS Award 1122462 and a Fulbright Scholarship.
²Department of Electrical Engineering and Computer Science, University of Tennessee, Knoxville, TN 37996, USA.
³obara, mdjouadi@utk.edu
⁴LIX (CNRS, UMR 7161), École polytechnique, 91128 Palaiseau, France. Michel.Fliess@polytechnique.edu
⁵CRAN (CNRS, UMR 7059), Université de Lorraine, BP 239, 54506 Vandoeuvre-lès-Nancy, France.
⁶cedric.join@univ-lorraine.fr
⁷Department of Mathematics, University of Tennessee, Knoxville, TN 37996, USA. judyday@utk.edu
⁸AL.I.E.N. (ALgèbre pour Identification & Estimation Numériques), 24-30 rue Lionnois, BP 60120, 54003 Nancy, France.
⁹michel.fliess, cedric.join@allen-sas.com
¹⁰Projet NON-A, INRIA Lille – Nord-Europe, France.

See also [5], [20], [33].
irreplaceable at this stage for \textit{in silico} testing, \textit{i.e.}, for computer simulations. We will also be employing \cite{45}. Let us emphasize the following key point: there is no need for the proposed control technique to use any state observer and any parameter identification technique.

From a purely control-theoretic standpoint, a major novelty of this study lies in the necessity to drive sensorless states. The poor knowledge of the system makes the derivation of an observer quite intractable. The solution lies in a “good understanding” of the system, \textit{i.e.}, in the design of an “efficient” reference trajectories tracking with respect to the states with sensors. Such a feedforward “philosophy” is of course inspired by flatness-based control (see \cite{21} and \cite{4, 34, 49}).

Our paper is organized as follows. Sections \textbf{II} and \textbf{III} review respectively the mathematical modeling and model-free control. Several computer simulations are displayed and discussed in Section \textbf{IV}. Suggestions for future research may be found in Section \textbf{V}.

\section{II. A Virtual Patient}

A mathematical model, \textit{i.e.}, a virtual patient, via four ordinary differential equations, for an acute inflammatory response to pathogenic infection has been proposed \cite{45}:

\begin{align}
\frac{dP}{dt} & = k_{pp}P(1 - \frac{P}{P_{\infty}}) - \frac{k_{pm}n_{m}P}{\mu_{n} + k_{mp}P} - k_{pn}f(N)P \\
\frac{dN}{dt} & = \frac{s_{n}R}{\mu_{n} + R} - \mu_{n}N + u_{p}(t) \\
\frac{dD}{dt} & = k_{dn}f(N)^{6} - \mu_{d}D \\
\frac{dC_{a}}{dt} & = s_{c} + k_{cn}f(N + k_{cd}D) - \mu_{c}C_{a} + u_{a}(t)
\end{align}

Set

\[ R = f(k_{np}P + k_{nn}N + k_{nd}D), \quad f(x) = \frac{x}{1 + \left(\frac{x}{C_{a}}\right)^{2}} \]

Table I gives the reference parameter values. Note that the state variables \(P(t), N(t), D(t), C_{a}(t)\) and the control variables \(u_{p}(t), u_{a}(t)\) take nonnegative values \(\forall t\).

- Equation (1) represents the evolution of the bacterial pathogen population \(P\) that causes the inflammation.
- Equation (2) 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 (3) corresponds to tissue damage (D), which helps to verify the response outcomes.
- Equation (4) describes the evolution of the concentration of a collection of anti-inflammatory mediators \(C_{a}\).
- See Tables I and II for the numerical values of the parameters and of the initial conditions.

The above model possesses three steady states:
- one which corresponds to the healthy equilibrium,
- two which are associated respectively with a septic state and an aseptic one.

Those properties agree with clinical observations:

- The healthy equilibrium corresponds to \(P = N = D = 0\) and \(C_{a}\) at a background level.
- A septic equilibrium is related to the situation where all mediators, \(N, C_{a}, D\) together with the pathogen \(P\) are rather high.
- The patient is in an aseptic equilibrium when the values of \(N, C_{a}, D\) are important, while the pathogen has been eliminated, \textit{i.e.}, \(P = 0\).

See in Figure 1 the results of two virtual patients with different initial conditions. The presence of pathogen in the body stimulates inherently the activation of phagocytes (pro-inflammatory mediator). The resulting damage is affected by the degree of inflammation which tries to eliminate the actual pathogen as quickly as possible. Note that the actual anti-inflammatory mediator (cortisol and interleukin-10) can mitigate the inflammation and its harmful effect. The resting value \(C_{a}\) is 0.125 for the reference virtual patient. The patient is healthy when \(D = 0\) and \(P = 0\). He/she is considered to be dead when \(D \geq 17\). When starting, \textit{e.g.}, from \([0.3 \ 0.0 \ 0.0 \ 0.0125]\), and allowing the pathogen to rise from a level of \(P = 0.3\) to \(P = 0.6\), at some point the immune system is not strong enough to cope with the pathogen attack which will inevitably attract the virtual patient to a septic or aseptic state (see Figure 1). Some intervention to stabilize the patient to its healthy equilibrium, \textit{i.e.}, to homeostasis, becomes mandatory.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reference Value</th>
<th>Parameter</th>
<th>Reference Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(k_{pp})</td>
<td>0.06/M units hr</td>
<td>(\mu_{n})</td>
<td>0.05/hr</td>
</tr>
<tr>
<td>(k_{np})</td>
<td>0.01/P units hr</td>
<td>(k_{na})</td>
<td>0.02/D units hr</td>
</tr>
<tr>
<td>(s_{n})</td>
<td>0.005 M units/hr</td>
<td>(k_{np})</td>
<td>0.35 units of D/hr</td>
</tr>
<tr>
<td>(\mu_{n})</td>
<td>0.002/hr</td>
<td>(k_{nm})</td>
<td>0.06 N*/units</td>
</tr>
<tr>
<td>(k_{pp})</td>
<td>Various in range: (0.021-2.44)/hr</td>
<td>(\mu_{n})</td>
<td>0.02/hr</td>
</tr>
<tr>
<td>(\mu_{n})</td>
<td>20x10^{6}/cc</td>
<td>(c_{n})</td>
<td>0.28 C0 units</td>
</tr>
<tr>
<td>(k_{pp})</td>
<td>1.9<em>N</em>/units hr</td>
<td>(s_{n})</td>
<td>0.0125 C0 units/hr</td>
</tr>
<tr>
<td>(k_{np})</td>
<td>0.1/P units hr</td>
<td>(k_{na})</td>
<td>0.04 C0 units/hr</td>
</tr>
<tr>
<td>(k_{np})</td>
<td>0.01/N* units hr</td>
<td>(k_{nm})</td>
<td>48 N*/units/D units</td>
</tr>
<tr>
<td>(s_{n})</td>
<td>0.08 N0 units/hr</td>
<td>(\mu_{c})</td>
<td>0.1/hr</td>
</tr>
<tr>
<td>(\mu_{c})</td>
<td>0.12/hr</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\section{III. A Virtual Patient}

\begin{table}[h]
\begin{tabular}{|c|c|c|}
\hline
Parameter & Reference Value & Parameter Ranges \tabularnewline \hline
\(P_{0}\) & 0.0 – 1.0 & \tabularnewline \(C_{A0}\) & 0.0938 – 0.1563 & \tabularnewline \(k_{pp}\) & 0.3 – 0.6 & \tabularnewline \(k_{np}\) & 0.03 – 0.05 & \tabularnewline \(k_{na}\) & 0.015 – 0.025 & \tabularnewline \(k_{nm}\) & 0.075 – 0.125 & \tabularnewline \(k_{nn}\) & 36.0 – 60.0 & \tabularnewline \(k_{nn}\) & 0.0075 – 0.0125 & \tabularnewline \hline
\end{tabular}
\caption{Variability of the model parameters}
\end{table}
III. MODEL-FREE CONTROL

A. The ultra-local model

Replace the unknown global description by the ultra-local model:

\[ \dot{y} = F + \alpha u \]  

(5)

where

- the control and output variables are \( u \) and \( y \),
- the derivation order of \( y \) is 1 like in most concrete situations,
- \( \alpha \in \mathbb{R} \) is chosen by the practitioner such that \( \alpha u \) and \( \dot{y} \) are of the same magnitude.

The following explanations on \( F \) might be useful:

- \( F \) is estimated via the measure of \( u \) and \( y \),
- \( F \) subsumes not only the unknown system structure but also any perturbation.

Remark 3.1: In Equation (5) \( \dot{y} \) is seldom replaced by \( \ddot{y} \) (see, e.g., [20], [35], and the references therein). Higher order derivatives were never utilized until today.

B. Intelligent controllers

The loop is closed by an intelligent proportional controller, or iP,

\[ u = -\frac{F - \dot{y}^* + K_P e}{\alpha} \]  

(6)

where

- \( \dot{y}^* \) is the reference trajectory,
- \( e = y - \dot{y}^* \) is the tracking error,
- \( K_P \) is the usual tuning gain.

Combining Equations (5) and (6) yields:

\[ \dot{e} + K_P e = 0 \]

where \( F \) does not appear anymore. The tuning of \( K_P \), in order to insure local stability, becomes therefore quite straightforward. This is a major benefit when compared to the tuning of “classic” PIDs (see, e.g., [2], [4], and the references therein), which

- necessitate a “fine” tuning in order to deal with the poorly known parts of the plant,
- exhibit a poor robustness with respect to “strong” perturbations and/or system alterations.

C. Estimation of \( F \)

The calculations below stem from new estimation techniques (see [22], [23], and [50]).

1) First approach: The term \( F \) in Equation (5) may be assumed to be “well” approximated by a piecewise constant function \( F_{\text{est}} \). Rewrite then Equation (5) in the operational domain (see, e.g., [59]):

\[ sY = \frac{\Phi}{s} + \alpha U + y(0) \]

where \( \Phi \) is a constant. We get rid of the initial condition \( y(0) \) by multiplying both sides on the left by \( \frac{d}{ds} \):

\[ Y + s\frac{dY}{ds} = \frac{\Phi}{s^2} + \alpha \frac{dU}{ds} \]

Noise attenuation is achieved by multiplying both sides on the left by \( s^{-2} \). It yields in the time domain the realtime estimate, thanks to the equivalence between \( \frac{d}{ds} \) and the multiplication by \( -t \),

\[ F_{\text{est}}(t) = -\frac{6}{\tau^3} \int_{t-\tau}^{t} [(\tau - 2\sigma)y(\sigma) + \alpha \sigma (\tau - \sigma)u(\sigma)] d\sigma \]

(7)

2) Second approach: Close the loop with the iP (6):

\[ F_{\text{est}}(t) = \frac{1}{\tau} \int_{t-\tau}^{t} (\dot{y}^* - \alpha u - K_P e) d\sigma \]

(8)

Remark 3.2: Note the following facts:

- integrals (7) and (8) are low pass filters,
- \( \tau > 0 \) might be quite small,
- the integrals may of course be replaced in practice by classic digital filters.

Remark 3.3: A hardware implementation of the above computations is easy [29].

IV. COMPUTER SIMULATIONS

A. Control design

The state component \( N \) (resp. \( C_a \)) in Equation (2) (resp. (4)) is

- easily measured, whereas it is difficult today to do it with \( P \) and \( D \) in Equations (1) and (4),
- mostly influenced by the control variable \( u_p \) (resp. \( u_a \)).

Introduce therefore the two Equations of type (5):

\[ \dot{N} = F_1 + \alpha_p u_p(t) \]

(9)

\[ \dot{C}_a = F_2 + \alpha_a u_a(t) \]

(10)

\[ \dot{\Phi} = F_3 + \alpha_p u_p(t) \]

See [20] for more details.
The evolution of $Ca$ and its reference trajectory

Let us emphasize that, like in [32], those two ultra-local systems may be “decoupled”: they are considered as monovariable systems. The two corresponding iPs read

\begin{align}
\nu_p &= - \frac{F_1 - \dot{N}^* + K_{P1}e_p}{\alpha_p} \\
\nu_a &= - \frac{F_2 - \dot{C}_a^* + K_{P2}e_a}{\alpha_a}
\end{align}

where the tracking errors are defined by

\[ e_p = N - \dot{N}^* \quad \text{and} \quad e_a = C_a - \dot{C}_a^* \]

$F_1, F_2$ are estimated according to Section III-C. See Figure 3 for the corresponding block diagram.

B. Reference trajectories and results

Two virtual patients are considered, the first (resp. second) one with a septic (resp. aseptic) outcome. The fact that a virtual patient may, or may not, return to an healthy state depends on the parameters and initial conditions. Their numerical characteristics are given below:

1) Patient 1 (septic).

- Initial conditions $P(0) = 0.47360, N(0) = 0.0660, D(0) = 0.0477, C_a(0) = 0.1635$.
- Model coefficients $k_{pg} = 0.47846, k_{cn} = 0.0409, k_{nd} = 0.0242, k_{np} = 0.1211, k_{cnd} = 49.1243, k_{mn} = 0.012$.

2) Patient 2 (aseptic).

- Initial conditions $P(0) = 1.0017, N(0) = 0.0711, D(0) = 0.0732, C_a(0) = 0.1314$.
- Model coefficients $k_{pg} = 0.4746, k_{cn} = 0.0386, k_{nd} = 0.0223, k_{np} = 0.1116, k_{cnd} = 46.3367, k_{mn} = 0.0112$.

The reference trajectories of $N$ and $Ca$ are adjusted from Table I:

\[ N^* = N_{\text{free}}, C_a^* = (C_a^{\text{free}} - 0.125).C_2 + 0.125 \]

where

- $N_{\text{free}}$ and $C_a^{\text{free}}$ correspond to the free trajectories of $N$ and $Ca$ for a healthy virtual patient,
- $C_1$ and $C_2$ are suitable constants.

We decided in our scenario to amplify the trajectory corresponding to the concentration of the pro-inflammatory mediator. Therefore

\[ C_1 = 4, \quad C_2 = 1 \]

There are of course other possibilities for the reference trajectories. We could select higher amplitudes in order to heal most patients. The price to pay would be more drug injection and, therefore, more tissue damage. The simulation were performed

- with a sampling time of 1 minute,
- with $\alpha_p = \alpha_a = 2$ in Equations (9)-(10),
- with $K_{P1} = K_{P2} = 0.47$ in Equations (11)-(12),
- during 500 hours.\(^4\)

Figure 4(a) shows clearly that we have been able to eliminate the pathogen and reduce the damage to zero using the generated doses displayed on the right hand side. Many simulations show a quick rise in the pro-inflammatory mediator $N$. According to Figure 2(b), its maximum is reached after about 10 to 15 hours and is followed by an exponential decrease to zero. As shown by Figure 4(a), the analogous behavior of the anti-inflammatory mediator $C_a$ is much slower. Similar facts are observed with all patients who do not necessitate any treatment. The motivation for the choice of the reference trajectories should now become clear.\(^5\)

\(^4\)It should be nevertheless clear from a purely mathematical standpoint that $F_1$ (resp. $F_2$) is not necessarily independent of $\nu_a$ (resp. $\nu_p$).

\(^5\)Let us stress that our control objective was reached in less than 250 hours.
The similarities of the generated doses can be partly explained by the same choice of the reference trajectory. In this case, it was enough to stabilize both patients. Observe that for each dose associated with an increase of the pro-inflammatory mediator a lower dose of anti-inflammation follows (see also [6], [15]). It may be explained by the fact the immune system needs an initial boost of activated phagocytes in order to eliminate the pathogen threat. The resulting inflammation causes an increase of tissue damage, observed in Figure 4(a), which decreases after to zero thanks in part to the anti-inflammatory dose that is applied with a longer duration. Notice that injecting a larger dose of $U_a$ at the wrong time and with an inappropriate amplitude may foster the development of pathogen $P$ at rates that can drive the patient to a no-return point.

V. CONCLUSION

Our results should of course be further tested and developed. Future publications will emphasize

- the robustness of our setting with respect to parameter variation and different initial conditions,
- a deeper understanding of the choice of "good" reference trajectories,
- the applicability of our approach to most types of inflammations and virtual patients.

The past success of model-free control in so many concrete situations should certainly be viewed as encouraging.

REFERENCES
