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Model Predictive Control for Designing Proactive Therapy of Atopic Dermatitis

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Abstract— **Atopic dermatitis (AD) is a chronic inflammatory skin disease, affecting up to 25% of children worldwide. While the current mainstay of AD treatment is topical application of corticosteroids and emollients, clear guidance for effective use of these treatments, such as the frequency, duration and potency, are not fully established. This paper proposes a computational method to design personalized treatment strategies for AD by applying model predictive control (MPC) to a hybrid nonlinear mathematical model of AD pathogenesis. We demonstrate that our method can suggest effective schedules for corticosteroid treatments that can achieve long-term management of moderate to severe AD symptoms. The proposed MPC uses a single linearized model of AD for prediction of disease progression based on daily measurement of the disease state, and provides a computational framework to suggest personalized treatment strategies with a small computational burden.**

I. Introduction

Atopic dermatitis (AD) is a common skin disease, characterised by chronic or recurrent inflammation (AD flares) accompanied with itch and a damaged skin barrier [1]. It affects up to 25% of children and 10% of adults worldwide, with associated socioeconomic burdens [2]. While a new biologic treatment for severe adult AD patients has been approved recently [3], the current mainstay of AD treatment is still topical application of corticosteroids and emollients [4]. However, clear guidance for effective use of these treatments, such as the frequency, duration and potency, are not fully established [5]. Personalized treatment is considered to be greatly beneficial for AD patients due to a large variety of interpersonal differences in clinical phenotypes, as well as genetic, epidermal and environmental factors [6].

We previously proposed a computational method to suggest personalised treatment strategies for individual virtual AD patient cohorts, by recursively solving optimal control problems using a differential evolution algorithm [7]. However, the proposed method was computationally expensive due to the hybrid nonlinear nature of the mathematical model of AD pathogenesis [8] that reflects the complex dynamic interplay between environmental stressors, immune responses and skin barrier integrity.

In this paper, we apply model predictive control (MPC) to this problem. MPC has been successfully applied to design treatment schedules for numerous diseases, e.g. for insulin treatment for diabetes management [9], [10], anti-HIV drugs administration [11] and androgen suppression of prostate cancer [12]. MPC calculates the optimal treatment schedules using constantly updated information on the current disease state, and thus can be robustly applied even with model uncertainties and disturbances in environments or measurements [13].

We specifically consider designing treatment schedules for a 'proactive therapy' [14] for long-term management of moderate to severe AD symptoms. Proactive therapy aims to first achieve remission (stop inflammation) to 'get control', and then 'keep control' by preventing AD flares (inflammation) and achieving skin barrier stabilisation by intermittent and scheduled use of low-dose topical corticosteroids, even in the absence of the clinical symptoms [15]. Due to a fear of skin thinning by the long-term use of corticosteroids [16], patients are often advised to minimise the use of the corticosteroids. Ideally, effective treatment schedules for proactive therapy can be personalized, based on the patient's information, such as genetic risk factors and the responses to the treatments.

Here we demonstrate a proof-of-concept for the use of MPC to inform the design of such personalized effective treatment schedules for proactive therapy, with much reduced computational costs compared to our previous methods. We use the mathematical model of AD pathogenesis and treatment proposed in [7] as 'virtual patients', and assume the ideal situations where the virtual patients' disease states are measurable and the patients' model parameters are known.

This paper is organised as follows: Section II introduces the AD treatment model that we consider as virtual patients and formulate the goals of the proactive therapy. Section III explains the design of MPC that suggests the amount of corticosteroids to be applied based on daily measurement of disease states. Section IV demonstrates simulation results of the MPC applied to different virtual patients, and discuss potentials for using the proposed method to suggest personalized treatment strategies. Finally, we summarise the results and discuss future plans in Section V.

II. Model Description

This section presents the *AD treatment model* considered in this paper, and discusses the treatment goals of the proactive therapy, for which we design an MPC controller.

A. Atopic Dermatitis Treatment Model

The AD treatment model considered in this paper is based on that proposed in [7]. The model describes the

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effects of treatments using corticosteroids and emollients on AD pathogenesis, which is determined by the dynamic interplay between skin barrier integrity, immune reactions and environmental stressors. The model (Fig. 1a) is given by

$$\dot{P}(t)=P_{\mathrm{env}}\frac{\kappa_{\mathrm{P}}}{1+\gamma_{\mathrm{B}}B(t)}-\left(\alpha_{\mathrm{I}}\frac{R(t)}{1+\beta_1 C(t)}+\delta_{\mathrm{P}}\right)P(t),$$
$$\dot{B}(t)=\frac{\kappa_{\mathrm{B}}(1-B(t))}{\left(1+\gamma_{\mathrm{R}}\frac{R(t)}{1+\beta_2 C(t)}\right)\left(1+\gamma_{\mathrm{G}}\frac{G(t)}{1+\beta_3 C(t)}\right)}+E(t)-\delta_{\mathrm{B}}K(t)B(t), \tag{1}$$

where infiltrated pathogen load, $P(t)$, and skin barrier integrity level, $B(t)$, are the two state variables representing the disease state of an AD patient, and $E(t)$ and $C(t)$ represent the amounts of topically applied emollients and corticosteroids, respectively. Description of the parameters and their nominal values are summarised in Table I, taken from [7].

Environmental pathogens (P_{env}) infiltrate through the skin with barrier integrity $B(t)$. The infiltrated pathogens ($P(t)$) activate innate immune receptors ($R(t)$), leading to AD flares (inflammation). Activation of the immune receptors also activates kallikreins ($K(t)$) that degrade the skin barrier components resulting in a weakened barrier, and triggers innate immune responses that lead to eradication of infiltrated pathogens.

Our model assumes that AD flares occur due to activation of innate immune receptors ($R(t)$), which is described by a reversible switch (Fig. 1b),

$$R(t)=\begin{cases}R_{\mathrm{off}}\to R_{\mathrm{on}}, & \text{if } \dot{P}(t)>0 \text{ and } P(t)=P^{+},\\ R_{\mathrm{on}}\to R_{\mathrm{off}}, & \text{if } \dot{P}(t)<0 \text{ and } P(t)=P^{-},\end{cases}$$

where R_{on} and R_{off} are constant values. When an increasing $P(t)$ exceeds an activation threshold value, P^{+}, the switch is activated resulting in AD flares. When a decreasing $P(t)$ falls below an inactivation threshold value, P^{-}, the switch is inactivated and AD flares cease. Accordingly, AD flares stop when $P(t)$ goes below P^{-}, and only reoccur when $P(t)$ surpasses P^{+}. The kallikrein level, $K(t)$, is also determined by a reversible switch with the same activation threshold (P^{+}) and inactivation threshold (P^{-}) as for $R(t)$, and switches between a constant K_{off} and $K_{\mathrm{on}}(t)=m_{\mathrm{on}}P(t)-\beta_{\mathrm{on}}$.

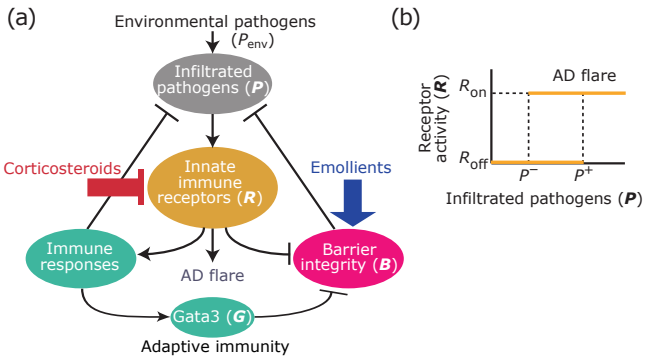

Fig. 1. AD treatment model considered in this paper. (a) Model overview. (b) A perfect switch of $R(t)$ leading to AD flares. Adapted from [7].

In our model, patient cohorts with different AD characteristics are represented by varying the values of two parameters, α_{I} and κ_{P}, that correspond to two known genetic AD risk factors: dysregulated expression of innate immune system components (α_{I}) and filaggrin gene mutations (κ_{P}) [8]. A smaller α_{I} corresponds to weaker immune responses to eradicate pathogens and a larger κ_{P} corresponds to a weaker barrier integrity leading to higher infiltration of environmental pathogens into the skin.

Here we choose the nominal value of (α_{I}, κ_{P}), for which the system has a unique stable equilibrium corresponding to the diseased state with AD flares ($R(t)=R_{\mathrm{on}}$), barrier damage ($B=0$) and systemic TH2 sensitization is established ($G(t)=G_{\mathrm{on}}$) [8]. The nominal (α_{I}, κ_{P}) represents moderate to severe AD patient cohorts who require long-term treatments using corticosteroids and emollients to control symptoms and who will benefit from optimally designed treatment schedules.

B. Treatment Goals of Proactive Therapy

The proactive therapy consists of two phases (Fig. 2a), an 'induction of remission' phase where we aim to suppress the clinical inflammation, followed by a 'maintenance of remission' phase where we apply intermittent but scheduled treatment to prevent the recurrence of AD flare [14]. We refer the two phases as 'induction phase' and 'maintenance phase' hereafter.

To comply with the current clinical recommendations [5], we assume that emollients are applied constantly throughout both phases at a low level, E_0, which cannot achieve remission by itself for moderate to severe AD patients [17]. We therefore design the optimal schedules for $C(t)$ that can induce and maintain the remission (Fig. 2b).

During the induction phase, corticosteroids are applied daily to induce remission, by decreasing $P(t)$ below P^{-} and thereby deactivating the innate immune receptors (Fig. 1b). We design an MPC controller for the induction phase to derive the amount of corticosteroids, $C(t)$, to be applied every

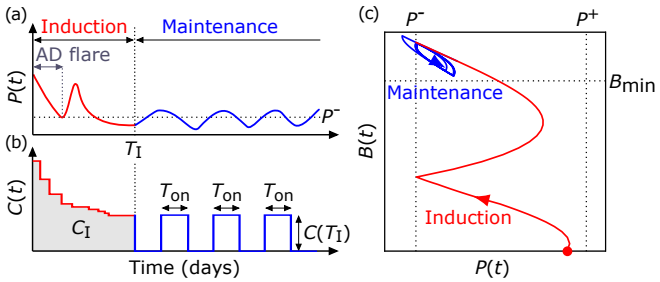

Fig. 2. Problem formulation for designing proactive therapy of AD. Example dynamics of (a) $P(t)$ and (b) $C(t)$, and (c) the trajectory in the $(P(t), B(t))$-plane, during the induction (red) and maintenance (blue) phases. AD flare ceases when $P(t)$ reaches P^{-}. When the optimal control input, $C(t)$, reaches the steady state and $B(t)$ goes above B_{min}, we terminate the induction phase and start the maintenance phase. During the maintenance phase, $P(t)$ should be kept below P^{+} to avoid AD flares and $B(t)$ above B_{min} to ensure skin barrier stabilisation, respectively, by an intermittent and weekly periodic application of corticosteroids.

day based on the daily measurement of the updated disease state. Once the disease state is stabilized, corresponding to a 'controlled' AD state which can be maintained only with intermittent treatments without causing AD flares, we move to the maintenance phase at time T_I.

During the maintenance phase, we continue to use the same amount of corticosteroids, $C(T_I)$, as applied at the end of the induction phase when $t=T_I$ but with recurrent weekly schedule. We minimize the number of days (T_{on} days) per week when the corticosteroids are applied to maintain the controlled state, by keeping $P(t)$ away from P^+ to prevent AD flares and $B(t)$ above a minimum barrier integrity level, B_{min} (Fig. 2c). Derivation of the optimal value of T_{on} does not require daily measurement of the disease state.

III. Model Predictive Control to Design Therapy

Nonlinear and hybrid characteristics of our AD treatment model in (1) make it computationally expensive to obtain an optimal solution for the MPC, whereas an analytical solution can be found for a linear system [13]. Accordingly, we linearize and discretize the model and use it to design an MPC that will determine the optimal schedule for daily application of corticosteroids, $C(t)$, during the induction phase (Fig. 3). The MPC obtains the daily measurement of the disease state from the AD treatment model, predicts the disease progression using the linear discrete model, and calculates the optimal amount of corticosteroids to be applied that minimizes the cost function. The calculated amount of corticosteroids is then applied to the AD treatment model, whose disease state is updated. There are no stability issues with applying the MPC controller, as the nonlinear system is stable for all considered treatment inputs.

In this section, we first derive a linearized and discretized AD treatment model, define the cost function for the MPC to design the therapy during the induction phase, define the conditions we use to move from the induction phase to the maintenance phase, and formulate the optimal control problem to be solved to design the therapy during the maintenance phase.

A. Linearized and Discretized model

We rewrite our AD treatment model in (1) in a simplified way as

$$\dot{\boldsymbol{x}}(t)=\boldsymbol{f}(\boldsymbol{x}(t),\,\boldsymbol{u}(t),\,\boldsymbol{s}(t)), \tag{2}$$

where $\boldsymbol{x}(t)=[P(t)\ B(t)]^T$, $\boldsymbol{u}(t)=[E(t)\ C(t)]^T$ and $\boldsymbol{s}(t)=[R(t)\ K(t)]^T$ are the state vector, the input vector and the switch vector, respectively, and $\boldsymbol{f}=[f_P\ f_B]^T$ with f_P and f_B denoting the dynamics of $\dot{P}$ and $\dot{B}$ in (1), respectively. We assume that the initial state, $\boldsymbol{x}(0)$, is the steady state, $\bar{\boldsymbol{x}}=[\bar{P}\ \bar{B}]^T$, for moderate to severe AD patients with $\bar{\boldsymbol{s}}(t)=[\bar{R}\ \bar{K}]^T=[R_{on}\ K_{on}(0)]^T$ without any treatment, i.e. $\bar{\boldsymbol{u}}=[\bar{E}\ \bar{C}]^T=[0\ 0]^T$. Note that the steady state, $\bar{\boldsymbol{x}}$, corresponds to the unique unhealthy disease state of moderate to severe AD patients with AD flares described by the activated state of the switch.

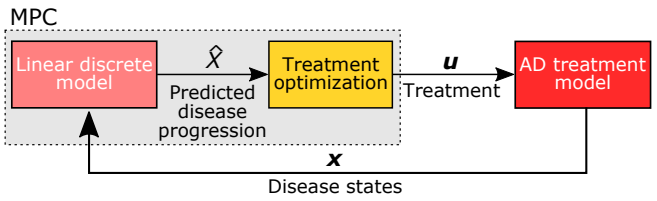

Fig. 3. A block diagram for MPC to design the therapy during the induction phase. MPC uses the current disease state and the linearized and discretized model to predict disease progression, and obtains the optimal treatment to minimize the defined cost function.

We first linearize the model (2) around the initial unhealthy steady state, $\bar{\boldsymbol{x}}$, and obtain

$$\boldsymbol{\delta}_x(t)=A\boldsymbol{\delta}_x(t)+B\boldsymbol{\delta}_u(t), \tag{3}$$

where $\boldsymbol{\delta}_x=\boldsymbol{x}-\bar{\boldsymbol{x}}$ and $\boldsymbol{\delta}_u=\boldsymbol{u}-\bar{\boldsymbol{u}}$ are the deviations of $\boldsymbol{x}$ and $\boldsymbol{u}$ from $\bar{\boldsymbol{x}}$ and $\bar{\boldsymbol{u}}$, respectively. The matrices A and B are the Jacobians evaluated at $(\bar{\boldsymbol{x}},\,\bar{\boldsymbol{u}},\,\bar{\boldsymbol{s}})$ and described by

$$A=\left[\begin{matrix}\frac{\partial f_P}{\partial P} & \frac{\partial f_P}{\partial B}\\ \frac{\partial f_B}{\partial P} & \frac{\partial f_B}{\partial B}\end{matrix}\right]\Bigg|_{\substack{\bar{\boldsymbol{x}}\\ \bar{\boldsymbol{u}}\\ \bar{\boldsymbol{s}}}}$$

$$=\left[\begin{matrix}-\left(\alpha_I\frac{\bar{R}}{1+\beta_1\bar{C}}+\delta_P\right) & -P_{env}\frac{\kappa_P\gamma_B}{(1+\gamma_B\bar{B})^2}\\ -\delta_B K'\bar{B} & -\delta_B\bar{K}-\frac{\kappa_B}{\left(1+\gamma_R\frac{\bar{R}}{1+\beta_2\bar{C}}\right)\left(1+\gamma_G\frac{1}{1+\beta_3\bar{C}}\right)}\end{matrix}\right],$$

$$B=\left[\begin{matrix}\frac{\partial f_P}{\partial E} & \frac{\partial f_P}{\partial C}\\ \frac{\partial f_B}{\partial E} & \frac{\partial f_B}{\partial C}\end{matrix}\right]\Bigg|_{\substack{\bar{\boldsymbol{x}}\\ \bar{\boldsymbol{u}}\\ \bar{\boldsymbol{s}}}}=\left[\begin{matrix}0 & \frac{\alpha_1\beta_1\bar{P}\bar{R}}{(\beta_1\bar{C}+1)^2}\\ 1 & -\frac{\beta_3 G_{on}\gamma_G\kappa_B(\bar{B}-1)}{\sigma_1\sigma_2^2(\beta_3\bar{C}+1)^2}-\frac{\beta_2\bar{R}\gamma_R\kappa_B(\bar{B}-1)}{\sigma_1^2\sigma_2(\beta_2\bar{C}+1)^2}\end{matrix}\right],$$

where $\sigma_1=\frac{\bar{R}\gamma_R}{\beta_2\bar{C}+1}+1$, $\sigma_2=\frac{G_{on}\gamma_G}{\beta_3\bar{C}+1}+1$, and $K'=0$ or m_{on} when the switch is off or on, respectively.

We further discretize the model in (3) via exact discretization, with the sampling period, Δ. The discretized linearized model is then described by

$$\boldsymbol{\delta}_x(k+1)=A'\boldsymbol{\delta}_x(k)+B'\boldsymbol{\delta}_u(k), \tag{4}$$

with $A'=e^{A\Delta}$ and $B'=\left(\int_0^\Delta e^{A\tau}d\tau\right)B=A^{-1}\left(e^{A\Delta}-I\right)B$. We assume $\Delta=1$ day to reflect daily measurements of the disease state and changes of the amount of corticosteroids applied.

The obtained linear and discrete model (4) is used at each discrete time, k, to predict the disease progression, $\{\hat{\boldsymbol{x}}(k+1),\,\hat{\boldsymbol{x}}(k+2),\,...,\,\hat{\boldsymbol{x}}(k+N_P)\}$, for the prediction horizon of N_P, given the current state, $\boldsymbol{x}(k)$, and the predicted input, $\{\hat{\boldsymbol{u}}(k),\,\hat{\boldsymbol{u}}(k+1),\,...,\,\hat{\boldsymbol{u}}(k+N_c-1)\}$, for the control horizon of N_C.

B. MPC cost function

The cost function, $J(k)$, to be minimized at each k is defined by

$$J(k)=\left[S_{\boldsymbol{x}}^{-1}\left(\hat{X}-X_r\right)\right]^T W_{\boldsymbol{x}}\left[S_{\boldsymbol{x}}^{-1}\left(\hat{X}-X_r\right)\right]+\left(S_{\boldsymbol{u}}^{-1}\hat{U}\right)^T W_{\boldsymbol{u}}\left(S_{\boldsymbol{u}}^{-1}\hat{U}\right).$$

The first term corresponds to the cost for the predicted state trajectories described by $\hat{X}(k)=\left[\ \hat{\boldsymbol{x}}(k+1)^T\ \ \hat{\boldsymbol{x}}(k+2)^T\ \ ...\ \ \hat{\boldsymbol{x}}(k+N_P)^T\ \right]^T$ being deviated from the target state, $[P_r\ \ B_r]^T$, and thus $X_r=\mathbf{1}_{N_P}\otimes[P_r\ \ B_r]^T$, where $\mathbf{1}_{N_P}$ is a vector of ones of length N_P. The second term corresponds to the cost of applying treatment for the predicted input, $\hat{U}(k)=\left[\ \hat{\boldsymbol{u}}(k)^T\ \ \hat{\boldsymbol{u}}(k+1)^T\ \ ...\ \ \hat{\boldsymbol{u}}(k+N_c-1)^T\ \right]^T$.

Note that $S_{\boldsymbol{x}}=I_{N_p}\otimes\mathrm{diag}(s_P,\,s_B)$ and $S_{\boldsymbol{u}}=I_{N_c}\otimes\mathrm{diag}(s_E,\,s_C)$ are the scaling matrices to normalize P, B, E and C, with the

corresponding elements being determined by their respective maximum values. Accordingly, the trade-off between the two terms in $J(k)$ is described by the weight matrices, $W_{\boldsymbol{x}}=I_{N_\mathrm{p}}\otimes\mathrm{diag}(w_P, w_B)$ and $W_{\boldsymbol{u}}=I_{N_\mathrm{c}}\otimes\mathrm{diag}(w_E, w_C)$, with w_P and w_B being the weights for the cost on the distance from the target values for P and B, respectively, and w_E and w_C being those for the amount of E and C, respectively. Larger values of w_P and w_B, compared to w_C, result in a faster approach of the state to the target state leading to a faster induction of remission, but with a larger amount of corticosteroids applied. Smaller values of w_P and w_B, compared to w_C, result in application of a smaller amount of corticosteroids for a longer duration to achieve remission. Here we set $w_E=0$, as we assume a constant application of $E(t)=E_0$.

C. MPC to Design Therapy for Induction Phase

At each k, we obtain $\widehat{U}(k)$ that minimizes $J(k)$ subject to $E(t)=E_0$ and $0\leq C(t)\leq C_{\max}$. We then take the first element, $\hat{\boldsymbol{u}}(k)$ of $\widehat{U}(k)$ and apply the optimal input $\boldsymbol{u}(t)=\hat{\boldsymbol{u}}(k)$ for $k\Delta\leq t<(k+1)\Delta$ to the AD treatment model (1) to update the disease state.

This process is repeated until remission is achieved and the disease state is stabilized at a 'controlled' AD state without AD flares. We define the controlled AD state by the constant level of the optimal input (reflecting the steady level of the disease state) at least for 3Δ days and a sufficiently high $B(t)>B_{\min}$ to avoid the risk of AD flares by P going above P^+. Accordingly, the conditions to terminate the induction phase and move to the maintenance phase at time T_I are summarised by

$$\begin{aligned} P(t^-)&=P^-, && 0<{}^{\exists}t^-<T_\mathrm{I},\\ P(t)&<P^+, && t^-<t<T_\mathrm{I},\\ \left|1-\frac{C(T_\mathrm{I}-i\Delta)}{C(T_\mathrm{I})}\right|&<0.005, && i=1,\ 2,\ 3,\\ B(T_\mathrm{I})&>B_{\min}. \end{aligned}$$

D. Optimization of Therapy for Maintenance Phase

The weekly corticosteroid treatment schedule, $C(t)$, during the maintenance phase ($t>T_\mathrm{I}$) is described by a pulse-width modulation function,

$$C(t)=\begin{cases} 0, & \text{if } 0\leq(t-T_\mathrm{I})\ (\mathrm{mod}\ 7)<T_{\mathrm{on}},\\ C(T_\mathrm{I}), & \text{if } T_{\mathrm{on}}\leq(t-T_\mathrm{I})\ (\mathrm{mod}\ 7)<7. \end{cases}$$

No corticosteroids are applied for the first $7-T_{\mathrm{on}}$ consecutive days per week, and corticosteroids of a fixed amount of $C(T_\mathrm{I})$ are applied for the rest of T_{on} days. The duration of the on-treatment days per week is obtained by the minimum value of T_{on}, with which $C(t)$ can still maintain the controlled AD state defined by $B(t)>B_{\min}$ and $P(t)<P^+$ for $t>T_\mathrm{I}$ without occurrence of AD flares.

IV. Results

In this section, we show the simulation results obtained by the method proposed above to design proactive therapy for different cases. The performance of the designed therapy is evaluated by (i) the duration of the induction phase (T_I), (ii) the total amount of corticosteroids applied during the induction phase (C_I), (iii) the value of $B(t)$ at the end of the induction phase when $t=T_\mathrm{I}$, ($B(T_\mathrm{I})$), and (iv) the constant amount of corticosteroids applied at $t=T_\mathrm{I}$ and intermittently during the maintenance phase ($C(T_\mathrm{I})$). The therapy is generally considered to be better with a shorter T_I, a smaller C_I, a larger $B(T_\mathrm{I})$, and a smaller $C(T_\mathrm{I})$. Nominal values of the parameters used for our simulations are listed in Table II.

For all our simulations, we set the control horizon, N_C, to be 4 days and the prediction horizon, N_P, to be 20 days, to keep computational costs low. We confirmed that increasing N_C and N_P does not affect the results shown here, although it is known that N_C and N_P affect the stability and convergence properties of the controller [18]. The choice of $N_\mathrm{C}=4$ days ensures that we consider the total amount of corticosteroids applied over the next 4 days in the cost function. Decreasing N_C to 1 or 2 days is not appropriate as the cost will consider only the amount of the corticosteroids applied currently (and next day), which allows the total amount of corticosteroids applied to be large. We set the target state to be $B_\mathrm{r}=1$ and $P_\mathrm{r}=26<P^-$ to ensure the switch is deactivated during the induction phase.

All simulations were conducted using Matlab v. R2016b (The MathWorks, Inc., Natick, MA, USA). We used `ode45` for the numerical integration of the system and `events location` functionality of Matlab to identify the switching boundaries.

A. Nominal Case

The optimization using the nominal parameters suggests a schedule for the proactive therapy that achieves induction and maintenance of remission (Fig. 4a). The calculated therapy requires a smaller amount of corticosteroids applied ($C_\mathrm{I}=$ 132.8 vs 241.9 arbitrary units) during a shorter induction phase ($T_\mathrm{I}=16$ days vs 19 days), compared to the optimal therapy obtained by our previous method shown in [7].

During the maintenance phase, $C(T_\mathrm{I})=5$ is applied $T_{\mathrm{on}}=3$ days per week to ensure that $B(t)$ stays above $B_{\min}$. Our simulation results demonstrate that $B(t)$ oscillates between $B_{\min}$ and $B(T_\mathrm{I})=0.88$, which is the steady state of B when $C(T_\mathrm{I})$ is constantly applied. The oscillation occurs as $B(t)$ decreases towards the steady state of $B_0=0.51<B_{\min}$ when no corticosteroids are applied.

B. Choice of Weights in Cost Function

The choice of the weights for the cost function affects the suggested therapy obtained by our method.

For example, increasing w_C to five times the nominal value and thus putting a stronger penalty in the total amount of corticosteroids applied, while keeping all the other parameter values, results in a 27% reduction in C_I and a 42% reduction in $C(T_\mathrm{I})$ (Fig. 4b). However, a further increase in w_C, thereby putting a much stronger penalty in the total amount of corticosteroids applied, results in a failure to induce remission due to the insufficient amount of corticosteroids applied (Fig. 4c with w_C being six times the nominal value).

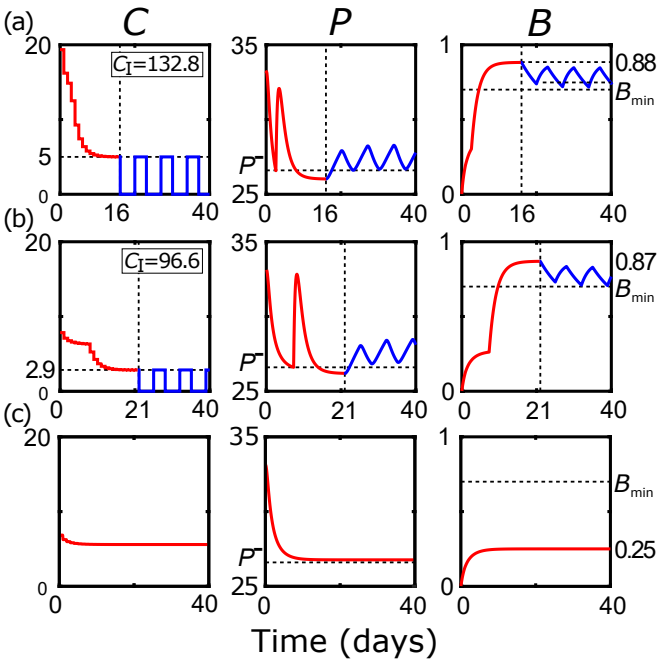

Fig. 4. Computationally suggested strategies for the proactive therapy for (a) nominal case with nominal parameter values, (b) a high weight (w_C= 400) in the cost function to penalize more the total amount of corticosteroids applied, (c) a higher weight (w_C=480) for which induction is not induced due to a smaller amount of corticosteroids applied. For all simulation results shown, the maintenance phase requires application of $C(T_\mathrm{I})$ for T_on=3 days per week to maintain $B(t)>B_\mathrm{min}$. The dynamics during the induction phase and maintenance phase is shown by red and blue lines, respectively. The vertical dotted lines represent T_I, and the horizontal dotted lines represent $C(T_\mathrm{I})$, P^-, B_min and $B(T_\mathrm{I})$.

These results imply that the trade-off between the weights for different terms in the cost function need to be appropriately chosen for the MPC controller to suggest the optimal therapy successfully.

C. Personalized Treatments

Designing personalized treatments for AD is considered to be beneficial for AD patients due to a wide individual variance in, for example, AD phenotypes, genetics and reactiveness to treatments. Our numerical simulations confirmed that our proposed method could find appropriate treatment strategies for the proactive therapy for other patient cohorts with varied parameters of (α_I, κ_P) than the nominal values.

However, the patient cohorts with more severe AD phenotypes with a smaller α_I or a larger κ_P may require adjustment in some optimisation parameters so that our method can find the therapy that achieves the treatment goals. For example, lowering the target state (P_r) results in a much lower $P(t)$ during the induction phase, making P^- more easily reachable and remission more easily induced (Fig. 5a). Lowering the weight w_C allows us to put less penalty on applying a larger amount of corticosteroids to achieve the remission (Fig. 5b). By changing these optimization parameters or constraints, a variety of patient cohorts could benefit from personalized controllers.

Information on different needs for adjustment in the setting for optimization can be used for stratification of patients for whom systemic therapy, including oral administration of potent corticosteroids, is required. If our method does not achieve remission even after lowering w_C and P_r, it may suggest that these patients will require systemic therapy.

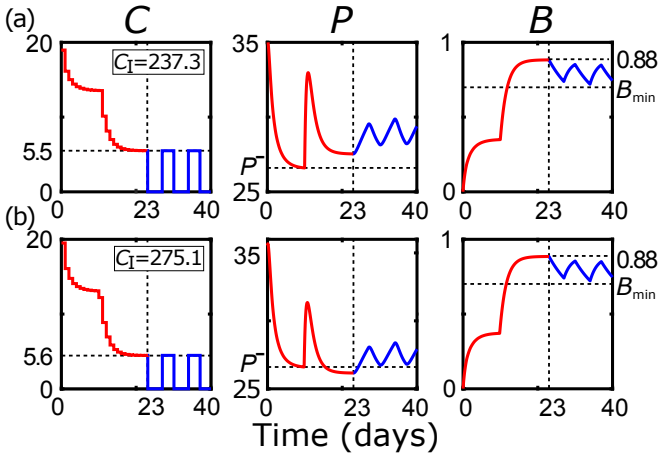

Fig. 5. Computationally suggested strategies for the proactive therapy for different patient cohorts described by (a) (α_I, κ_P)=(0.05,0.9), with P_r=25 and nominal w_C=80, (b) (α_I, κ_P)=(0.04,0.85), with nominal P_r=26 and w_C=35. For all simulation results shown, the maintenance phase requires application of $C(T_\mathrm{I})$ for T_on=3 days per week to maintain $B(t)>B_\mathrm{min}$.

V. Discussion and Conclusions

In this paper, we proposed a method to design an MPC controller that optimizes the treatment schedules for the proactive therapy for moderate to severe AD patients. Proactive therapy aims to first induce remission by continuous application of topical corticosteroids that help to deactivate the innate immune receptors, while restoring the barrier integrity. Once the 'controlled AD state' is achieved, the proactive therapy uses intermittent corticosteroid treatment to maintain a low level of infiltrated pathogens and a barrier integrity that is strong enough to prevent reoccurrence of inflammation and AD flares.

The proposed MPC controller uses progression of the disease state predicted by a linearized and discretized model (4) of the AD treatment model (1). The use of the linearized and discretized model allows us to obtain the optimal treatment schedules by analytical calculations and thus significantly reduces the computational cost (about 30 times faster), compared to our previous method by recursively solving the optimal control problem [7].

While the nonlinear hybrid AD treatment model (1) has two hybrid regions defined by the switch for both $R(t)$ and $K(t)$ being either on or off (the 'on-region' and the 'off-region'), we used only the model obtained by linearization around the initial steady state in the on-region, which corresponds to the chronic unhealthy state characterizing moderate to severe AD patients. Our simulation results suggest that the same linearized model can be used for the MPC to achieve the treatment goals, even after the state moves to the off-region. Indeed, MPC based on two linearized models, one

for the on-region and another for the off-region (around the new equilibrium point in the off-region) did not outperform MPC using the single linearized model as shown here.

The proposed MPC with the linearized model provides a computational framework suitable for an extensive search to design different treatment strategies with a very small computational burden. As a next step, we will study the robustness of the MPC to perturbations such as external disturbance of P_{env} or non-adherence to scheduled treatment, identify the appropriate weights and conditions for a specific patient cohort of (α_{I}, κ_{P}), and evaluate the performance of the proposed method through comparison with clinical data. Comparison between the simulation results and the clinical data could inform the model and optimization parameters, and confirm the accuracy and effects of the predicted disease progression and treatment.

TABLE I

MODEL PARAMETERS AND THEIR NOMINAL VALUES.

Symbol	Description	Nominal value
P_{env}	Environmental stress load	95 [mg/ml]
γ_{B}	Barrier-mediated inhibition of pathogen infiltration	1
κ_{P}	Nominal skin permeability	0.85 [1/day]
α_{I}	Rate of pathogen eradication by innate immune responses	0.05 [1/day]
δ_{P}	Basal pathogen death rate	1.6 [1/day]
κ_{B}	Barrier production rate	0.5 [1/day]
γ_{R}	Innate immunity-mediated inhibition of barrier production	10
δ_{B}	Rate of Kallikrein-dependent barrier degradation	0.1
γ_{G}	Adaptive immunity-mediated inhibition of barrier production	1
P^{-}	Receptor inactivation threshold	26.6 [mg/ml]
P^{+}	Receptor activation threshold	40 [mg/ml]
R_{off}	Receptor-off level	1
R_{on}	Receptor-on level	16.7
G_{on}	Gata3-on level	1
K_{off}	Kallikrein-off level	1
m_{on}	Slope of the linear relation between $P(t)$ and K_{on}	0.45
β_{on}	Y-intercept of the linear relation between $P(t)$ and K_{on}	6.71
β_1	Corticosteroid-mediated rate of reduction of AMP expression	0.005
β_2	Corticosteroid-mediated rate of reduction in barrier damage	10
β_3	Corticosteroid-mediated rate of reduction of Th2 cytokine production	10

TABLE II

SIMULATION PARAMETERS AND THEIR NOMINAL VALUES.

Symbol	Description	Nominal value
$C_{\max}$	Maximum corticosteroid potency	50
E_0	Amount of emollients applied	0.04
N_{P}	Prediction horizon	20 [days]
N_{C}	Control horizon	4 [days]
P_{r}	Target of $P(t)$	26
B_{r}	Target of $B(t)$	1
w_C	Weight for cost of $C(t)^2$	80
w_P	Weight for cost of $(P(t)-P_{\text{r}})^2$	100
w_B	Weight for cost of $(B(t)-B_{\text{r}})^2$	100
s_B	Scaling factor for $B(t)$	1
s_P	Scaling factor for $P(t)$	50
s_E	Scaling factor for $E(t)$	0.04
s_C	Scaling factor for $C(t)$	50
$B_{\min}$	Minimum level of barrier integrity	0.7
Δ	Discretization time step	1 [day]

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