Hybridoma cell culture optimization using nonlinear model predictive control

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Abstract: This work addresses the application of control systems to the optimization of a monoclonal antibodies (MAb) production chain. The attention is focused on the maximization of hybridoma fed-batch culture productivity. The proposed model presents kinetics showing strong nonlinearities through min-max functions expressing overflow metabolism. A nonlinear model predictive control (NMPC) algorithm, choosing the best trajectory over a moving finite horizon among different sequences of inputs, is suggested in order to optimize productivity. Sensitivities of selected objective functions are considered in a minimax robust version of the NMPC in order to choose the best configuration with respect to practical operating conditions.

Keywords: hybridoma cultures, overflow metabolism, nonlinear model predictive control, bioprocess optimization

1. INTRODUCTION

Biopharmaceuticals spare today a lot of attention to any mean or device improving bioprocess yields. In a production chain of monoclonal antibodies (MAb), different key-operations are managed and optimized (i.e., cultivation, purification, filtration, capture, polishing steps, etc.). This work is focused on the productivity (compound production in a minimum of time) optimization of hybridomas expressing these MAb. In de Tremblay et al. (1992) and Dhir et al. (2000), optimization studies are conducted on the basis of simple macroscopic mass balance models established from experimental data. In Amribt et al. (2013), a kinetic model taking into account metabolic changes is suggested for the strain HB-58 that could be used for process optimization. Indeed, hybridoma, as cells like yeast or bacteria, presents metabolic changes in presence of feeding overflow. This metabolic phenomenon, induced when the rate of glycolysis exceeds the cell respiratory or oxidative capacity (i.e., the capacity to oxidize substrates), is called "Overflow metabolism" or "short-term Crabtree effect". The cell metabolism is consequently divided in two pathways: the oxidative or respiratory regime, and the respiro-fermentative regime when substrate is in excess, leading to the formation of by-products generally inhibiting the oxidative capacity. To avoid this undesirable effect, a closed-loop optimizing strategy is required, which could take various forms including nonlinear closed-loop strategies based on adaptive, probing, robust or predictive control respectively as in Pomerleau (1990), Akesson (1999), Dewasme et al. (2010) and Santos et al. (2012).

Nonlinear model predictive control (NMPC) is suitable especially for nonlinear fed-batch processes where a trajectory needs to be followed from the prediction of a nonlinear model. For these processes NMPC uses the nonlinear dynamic model to predict the effect of sequences of control steps on the controlled variables. There is a vast and rich literature with overviews on NMPC developments, research, and applications (e.g., Qin and Badgwell (2003), Lee (2011)). Some of these works address the problem of robust nonlinear model predictive control of fed-batch processes (e.g. Nagy and Braatz (2003), Nagy and Braatz (2004)). An overview of more recent developments on NMPC can be found in Magni et al. (2009) and references therein.

In this work, a NMPC algorithm comparable to Santos et al. (2012) is designed in order to optimize the HB-58 culture productivity taking model uncertainties and practical laboratory conditions into account.

In section 2, the mathematical model of HB-58 (Amribt et al. (2013) is briefly described and optimal closed-loop control objectives are suggested and discussed. The proposed NMPC algorithm is presented and performance is assessed in simulation comparing previously selected objective functions. The robustness facing parameter uncertainties is discussed in section 4. Conclusions and perspectives end this paper in section 5.
2. HYBRIDOMA CULTURE MODEL AND CONTROL OBJECTIVES

In the following subsection, the hybridoma HB-58 model of Amribt et al. (2013) is considered. Control objectives are derived from this model in the next subsection.

2.1 Bioreactor model

The following macroscopic reactions are extracted from the reduced metabolism network of HB-58 (Amribt et al. 2013):

\[ G \xrightarrow{\varphi_G} aX + bL \]  
\[ Gn \xrightarrow{\varphi_{Gn}} cX + dN \]

Glucose consumption : \[ G \xrightarrow{\varphi_{GOver-G}} 2L \]

Glutamine consumption : \[ Gn \xrightarrow{\varphi_{GnOver-Gn}} N + \frac{1}{2}L \]

where \( X, G, Gn, L \) and \( N \) are, respectively, the concentrations of biomass, glucose, glutamine, lactate and ammonia. \( a, b, c \) and \( d \) are the stoichiometric coefficients, and \( \varphi_i \) (\( i = G, Gn, Over - G, Over - Gn \)) the reaction rates given by the following discontinuous overflow kinetic model recalling the bottleneck of Sonnleitner and Kappeli (1986):

\[ \varphi_G = \min(\varphi_{G1}, \varphi_{G max}) \]  
\[ \varphi_{Gn} = \min(\varphi_{Gn1}, \varphi_{Gn max}) \]  
\[ \varphi_{GOver-G} = \max(0, \varphi_{G1} - \varphi_{G max}) \]  
\[ \varphi_{GnOver-Gn} = \max(0, \varphi_{Gn1} - \varphi_{Gn max}) \]

where each rate corresponds to the following Monod-type consumption rates \( r_i \) (\( i = G1, Gn1, G2, Gn2 \)) times the concentration of viable biomass \( X \) as in:

\[ \varphi_{G1} = r_{G1} X_v = \mu_{Gmax1} \frac{Gn}{K_G + Gn} X_v \]  
\[ \varphi_{Gn1} = r_{Gn1} X_v = \mu_{Gmax1} \frac{Gn}{K_{Gn} + Gn} X_v \]  
\[ \varphi_{G max} = r_{G max} X_v = \mu_{Gmax2} X_v \]  
\[ \varphi_{Gn max} = r_{Gn max} X_v = \mu_{Gmax2} X_v \]

where \( \mu_{Gmax} \) (\( i = G, Gn, j = 1, 2 \)) are the maximum values of the specific rates and \( K_G, K_{Gn} \) and \( K_Gn \) are the saturation coefficients. \( K_S \) is the ammonium inhibition constant over the oxidation of glutamine.

Sonnleitner’s kinetic model was first applied to the baker’s yeast strain called *Saccharomyces cerevisiae* and is based on the idea that the strain metabolism is ruled by its respiratory capacity. Indeed, during a culture, the cells are likely to change their metabolism because of their limited oxidative capacity. When the substrate is in excess (for instance, glucose concentration is above a critical level \( G > G_{crit} \) and the respective consumption rate \( r_{G1} > r_{Gmax} \)), the cells produce a byproduct (here, \( L \)) through the fermentative pathway, and the culture is said to be in (respiro-) fermentative (RF) regime. On the other hand, when substrate becomes limiting (for instance, glucose concentration is below a critical level \( G < G_{crit} \) and the substrate consumption rate \( r_{G1} < r_{Gmax} \)), the available substrate, and possibly the byproduct (as a substitute carbon source), if present in the culture medium, are oxidized (if the strain is able to oxidize it, which is not the case for HB-58). The culture is then said to be in respirative (R) regime. This metabolic mechanism is also applicable in parallel to glutamine and ammonia. However, it is important to note that oxygen is not represented as the system is assumed to be perfectly oxygenated and, consequently, metabolic switches are essentially due to substrate variations.

Mass balances on each component yield the following differential equations:

\[ \frac{dX}{dt} = a \varphi_G + c \varphi_{Gn} - \mu_G X_v - DX_v \]  
\[ \frac{dX_G}{dt} = \mu_G X_v - DX_G \]  
\[ \frac{dG}{dt} = -\varphi_{Gn} - \varphi_{GOver-G} + D(G_{in} - G) \]  
\[ \frac{dGn}{dt} = -\varphi_{Gn} - \varphi_{GnOver-Gn} + D(G_{in} - Gn) \]  
\[ \frac{dL}{dt} = b \varphi_{GOver-G} + 2 \varphi_{GnOver-Gn} - DL \]  
\[ \frac{dN}{dt} = d \varphi_{Gn} + \varphi_{GnOver-Gn} - DN \]  
\[ \frac{dV}{dt} = DN \]

where \( m_G \) is the maintenance coefficient of glucose (note that maintenance on glutamine is not considered as identification results obtained in Amribt et al. (2013) led to negligible values as compared to oxidation and overflow), \( V \) the reactor volume, \( D = \frac{F}{V} \) the dilution rate, \( F \) the inlet feed rate and \( G_{in} \) and \( Gn_{in} \) are the substrate concentrations in the feed medium. \( X_v \) represents the dead biomass concentration and \( \mu_d \) the corresponding rate given by:

\[ \mu_d = \mu_{max} \frac{K_{Gd}}{K_{Gd} + G} \frac{K_{Gnd}}{K_{Gnd} + Gn} \]  

The substrate inhibition terms of (5) simply mean that cell death is limited as long as there are enough glucose and glutamine in the bioreactor.

The parameter values listed in Table 1 were obtained following an identification procedure comparable to the one used by Amribt et al. (2013) using the same data sets and can be considered as extended results of Amribt et al. (2013). The only difference with previous results comes from the combination of sets used for simple and cross validations.

2.2 Control objectives

In Santos et al. (2010) and Santos et al. (2012), practical aspects behind the choice of the best optimizing criterion are discussed considering, of course first, the simple formulation of the current productivity optimization with respect to the product of interest (here, we speak about biomass productivity optimization represented by \( P = \frac{X}{t_f} \) where \( t_f \) represents the culture time) but then also the number of measurements, the existence
Table 1. Parameter values of Amribt et al. (2013)’s model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \mu_{G_{\text{max}1}} )</td>
<td>1.0006 h(^{-1} )</td>
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<tr>
<td>( \mu_{G_{\text{max}2}} )</td>
<td>0.0283 h(^{-1} )</td>
</tr>
<tr>
<td>( \mu_{G_{\text{max}3}} )</td>
<td>0.1992 h(^{-1} )</td>
</tr>
<tr>
<td>( \mu_{G_{\text{max}4}} )</td>
<td>0.0203 h(^{-1} )</td>
</tr>
<tr>
<td>( k_{G_1} )</td>
<td>0.0111 h(^{-1} )</td>
</tr>
<tr>
<td>( k_{G_2} )</td>
<td>23.235 mM</td>
</tr>
<tr>
<td>( k_{G_3} )</td>
<td>0.0004 mM</td>
</tr>
<tr>
<td>( k_{G_4} )</td>
<td>0.9911 mM</td>
</tr>
<tr>
<td>( K_{G_1} )</td>
<td>0.0005 mM</td>
</tr>
<tr>
<td>( K_{G_2} )</td>
<td>2.1862 mM</td>
</tr>
<tr>
<td>( K_{G_{\text{ind}}} )</td>
<td>0.0020 mM</td>
</tr>
</tbody>
</table>

of the corresponding probes, their price and, eventually, the possibility to express the optimizing criterion.

In this work, 4 optimizing criteria are considered:

\[
\Phi_1 = -\sum_{i=1}^{p} X_{k+i}
\]

(6a)

\[
\Phi_2 = \sum_{i=1}^{p} [r_{G} - r_{G_{\text{max}}}] + \sum_{i=1}^{p} [r_{G_{\text{max}}} - r_{G_{\text{max}}}] 
\]

(6b)

\[
\Phi_3 = \sum_{i=1}^{p} [r_{G_{\text{max}}} - r_{G_{\text{max}}}] 
\]

(6c)

\[
\Phi_4 = \sum_{i=1}^{p} [r_{G_{\text{max}}} - r_{G_{\text{max}}}] 
\]

(6d)

calculated over a time horizon of length \( p \) starting at \( k \).

- \( \Phi_1 \) considers live biomass concentration and not production \((X, V)\), assuming small changes in volume during the culture. In practice, a 1 liter bioreactor is indeed initiated at a level around 30 % of its maximum volume and the fed-batch culture ends around 70 to 80 % in order to avoid possible tank overflows. The final volume is then generally twice or three times the initial one while biomass concentration goes through different orders, starting, for instance, at order 0.1 and ending at order 1 or even 10, depending on the feeding density. In this work, predictive control horizons strictly smaller than the culture time are used, inducing very small volume variations and essentially biomass concentration variations, justifying the choice of \( \Phi_1 \).

- \( \Phi_2 \) represents the distance between any value of \( r_{G} \) and \( r_{G_{\text{max}}} \) and their optimal values \( r_{G_{\text{max}}} \) and \( r_{G_{\text{max}}} \), also limiting the production of inhibitory byproduct \( N \). \( \Phi_2 \) is then the expression of the productivity optimum, comparable to what was obtained in Santos et al. (2012) for \( E.\ coli \) but extended to two substrates saturating the respiratory capacity.

Even if this productivity optimum appears as evident as long as \( \mu_{d} \) remains relatively low (i.e., there are enough glucose

and glutamine in the bioreactor following (5)) in (4a), it is interesting to see how this optimum is evolving with the ammonium concentration following (3b). Indeed, this optimum is not unique as there exists an infinity of pairs \((N_{\text{crit}}, G_{\text{crit}})\) which guarantee that \((3b) = (3d)\) while \( G_{\text{crit}} \) depends on \( G_{\text{crit}} \) as shown in (3a). Following (4f), ammonium is a metabolic byproduct which is actively produced during glutamine over...
Fig. 1. Evolution of \( N_L \) with respect to the medium composition, i.e., \( G_{in} \) and \( G_{nin} \). The arrow indicates the increasing concentrations of \( G_{nin} \) while the circle indicates the \( N_L \) value of the current operating conditions (i.e., \( G_{in} = 15 \text{ mM} \) and \( G_{nin} = 4 \text{ mM} \)).

Figure 1 shows the solutions of (10) when coupled to (7b) in order to get the corresponding \( N_L \) values. This graph represents the evolution of \( N_L \) with respect to different values of \( G_{in} \) and \( G_{nin} \). It appears that the media composition plays an important role in the possibility to optimize the cell growth as there exist couples \( (G_{in}, G_{nin}) \) such that \( N_L = N_{UU} \), i.e., such that (11) is not respected.

An important conclusion on the way to design the experiments is drawn and the following theorem holds:

**Theorem 2.2.1** Provided that there is a significative but not excessive ammonium concentration in the bioreactor respecting (11), \( F_{Gn}(N_{crin}) \) as defined in (9b), is always an optimal feeding profile.

- \( \phi_1 \) (6c) and \( \phi_2 \) (6d) are therefore proposed in order to validate theorem 2.2.1. Indeed, if (11) is respected when finishing the batch phase, the profile tracking the minimization of \( \phi_1 \) should lead to the same solution as the profile minimizing \( \phi_2 \) while the one generated by the minimization of \( \phi_0 \) should be sub-optimal, following (10), in terms of biomass productivity over a fixed culture time.

3. NONLINEAR MODEL PREDICTIVE CONTROL

A nonlinear model predictive control (NMPC) strategy comparable to Santos et al. (2012) is applied to maximize the production of biomass within a defined time, using the minimization of one of the objective functions defined in (6), together with a penalization of the control moves in order to avoid too important feeding variations eventually leading to local minima as in:

\[
\psi_i = \phi_i + \sum_{j=1}^{m} (F_{in,k+j-1} - F_{in,k+j-1}^{ref}) \tag{12}
\]

where \( i = 1, 2, 3 \), \( p \) is the prediction horizon, and \( m \) is the control horizon, with \( m \leq p \). \( F_{in} \) is the manipulated variable, \( F_{in}^{ref} = F_{in,k+j-m}^{ref} \) is the feed rate of reference.

The NMPC problem is then stated as

\[
\min_{\mathbf{u}} \psi \tag{13a}
\]

s.t. \( \dot{\mathbf{x}} = f(x, u, \theta) \tag{13b} \)

where \( u(t) = u(t_{j-1+m}), \ t \in [t_{j+m}, t_{j+p}] \) \tag{13c}

\( x_L \leq \mathbf{x} \leq x_U \) \tag{13d}

\( u_L \leq u \leq u_U \) \tag{13e}

\( \Delta u_L \leq \Delta u_{j-1} \leq \Delta u_U \), \( j = 1, \ldots, m \) \tag{13f}

where (13b) is the process model, \( x \) and \( u \) are respectively the vector of state and control variables, and \( \theta \) is the vector of parameters. The subscripts \( L \) and \( U \) stand respectively for lower and upper. In this case study \( u = \{F_{in,k}, \ldots, F_{in,k+m-1}\} \) is the feed rate policy over a control horizon of \( m \) sampling time intervals, and \( x \) is the augmented vector of the state predictions \( \{x_{k+1}, \ldots, x_{k+p}\} \). Linear inequalities (13f) enforce control move rate constraints over the control horizon.

**Table 2. Productivities obtained for different objective functions**

<table>
<thead>
<tr>
<th>Objective function</th>
<th>Productivity [10^3 cells/h]</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \psi_1 )</td>
<td>3.50</td>
</tr>
<tr>
<td>( \psi_2 )</td>
<td>3.59</td>
</tr>
<tr>
<td>( \psi_3 )</td>
<td>3.59</td>
</tr>
<tr>
<td>( \psi_4 )</td>
<td>3.40</td>
</tr>
</tbody>
</table>

The results are shown in Figure 2 and biomass productivity values are listed in Table 2. Initial conditions force the controller to...
remain at zero until the glutamine is nearly depleted (around 50 h). At this moment, the batch phase ends and the first strictly positive inputs are calculated by the controller in order to catch an exponential trajectory, function of the criterion used among (6). The best values are obtained for $\psi_2$ and $\psi_3$ confirming theorem 2.2.1. However, performances of $\psi_1$ are less than 5% lower than the best case while less than 10% for $\psi_4$, which means that these criteria, failing to lead to the optimum, remain in a close neighborhood.

4. PRACTICAL CONDITIONS - MINIMAX ROBUST NMPC

The use of NMPC assumes a perfect knowledge of the model parameters and the availability of all the state measurements. Even if having all the probes is achievable in practice (or by means of observers as in Dewasme et al. (2013)), a perfect model parameter identification is impossible to achieve and a more robust version of the NMPC algorithm is then required. Taking into account results of section 3, only $\psi_1$ and $\psi_2$ are considered in the following ($\psi_4$ presents the lowest productivity and $\psi_2$ is comparable to $\psi_3$). Performances of the NMPC algorithm using $\psi_1$ and $\psi_2$ in the presence of parameter uncertainties are now assessed. This new study could be lead for all model parameters but following the structure of (6c), it is legitimate to think that sensitivity of the optimization with respect to model uncertainties is essentially due to $\mu_{G_{\text{max}1}}$, $\mu_{G_{\text{max}2}}$, $K_G$, and $K_N$. To justify this last sentence, note that even if the general model used to calculate state trajectories is not perfect, its influence on the states is attenuated by the reinitialization performed by the new measurements at each sampling period $t_s$ while the influence on the objective function is direct and never damped.

A robust formulation of the predictive controller is therefore proposed based on the solution at each sampling period of a minimax problem:

\[
\begin{align*}
\min_{\mu} & \quad \omega_1, \ldots, \omega_n \\
\text{s.t.} & \quad (13b - 13f) \quad (14b)
\end{align*}
\]

where each cost function, $\omega_j$, $j = 1, \ldots, n$, defined as in (12), is evaluated at one of the vertices of the uncertainty parameter polytope.

$\mu_{G_{\text{max}1}}$, $\mu_{G_{\text{max}2}}$, $K_G$, and $K_N$ nominal values are assumed to be influenced by uncertainties of maximum 15 percents (i.e., parameter identification is assumed to be well achieved but naturally tarnished by uncertainties). Table 3 shows the productivity means, maxima and standard deviations obtained for parameter variations applied first independently and then, in combination with others following a series of 14 times 50 runs.

Globally, the sensitivities of the algorithms using different objective functions reach the same order as the number of uncertain parameters increases ($O(10^6 \text{cells/h})$). Anyway, $\psi_3$ still presents higher productivities and also more robustness with respect to parameter sets in which $\mu_{G_{\text{max}2}}$ does not appear.

The algorithm is mainly sensitive to $\mu_{G_{\text{max}1}}$ and $\mu_{G_{\text{max}2}}$ (see Table 3) independently of the criterion. Reminding that these parameters define the metabolic threshold separating both pathways, it appears clearly that if $\mu_{G_{\text{max}2}}$ is underestimated, the productivity will decrease as the true critical level is never reached, while if $\mu_{G_{\text{max}1}}$ is overestimated, more ammonium will be produced generating an increase of $G_{\text{n crit}}$ (following (7b)) and a faster drift of the optimum which is, however, not so detrimental for the productivity as this optimum ($G_{\text{n crit}}, N_{\text{eq}}$) is never reached (as always moving) but correctly tracked. As all vertices of the polytope defined by the maximum parameter variations are considered before selecting the worst productivity level as in (14), Figure 3 shows consequently that the minimax algorithm using $\psi_1$ as objective function is likely to always reach a good productivity level if $\mu_{G_{\text{max}1}}$ is overestimated.

On the other hand, $K_G$ and $K_N$ do not severely alter the final productivity when using $\psi_3$ as standard deviations concerning these parameters alone never exceed 5 $10^4$ cells/h.

The algorithm using $\psi_1$ as objective function presents standard deviations of an order of $10^5$ cells/h (i.e., from 0.5 to 1 $10^6$ cells/h), regardless of the uncertain parameter set. This means that a good identification of $\mu_{G_{\text{max}2}}$ is a sufficient condition of robustness if $\psi_3$ is used as objective function while $\psi_1$ requires a more accurate identification of all the model parameters. Moreover, considering that $\psi_3$ basically reaches higher productivities than $\psi_1$, the choice of the user should be oriented towards $\psi_3$ in realistic experimental conditions.

5. CONCLUSION

In this work, optimization of hybridoma HB-58 fed-batch culture productivity using a mathematical model assuming overflow metabolism is performed. Nonlinearities and discontinuities of such biological kinetic models generally require the use of advanced controllers able to track unstable trajectories following exactly the boundary of two metabolic pathways. NMPC algorithms, optimizing sequences of trajectories over a finite horizon on the basis of objective cost functions minimization $\psi$, are able to solve this optimality problem as long as the minimum of $\psi$ corresponds to the productivity optimum. To illustrate this idea, four different mathematical criterions have been chosen and compared in terms of biomass productivity over a finite culture time. It appears clearly that, even if each of them leads to a satisfactory productivity level, only two of them represent the right cost functions to reach the productivity optimum: $\psi_2$, representing both metabolic overflows on glucose and glutamine and $\psi_3$, representing the overflow of glutamine.
only, based on an existence condition on ammonium. Considering those productivity levels but also practical conditions, two criteria are chosen: $\psi_1$ and $\psi_3$. Interestingly, the last criterion requires a minimum of parameter knowledge (i.e., four parameters) and leads to the productivity optimum. The main drawback of predictive control is the assumption of a perfect model and available state measurements which is, in practice, difficult to set up. Therefore, a minimax algorithm considering parameter uncertainties (often encountered following identification) allows to limit the loss of productivity especially thanks to the inherent robustness due to the choice of a particular cost function: $\psi_3$.

**ACKNOWLEDGEMENTS**

This paper presents research results of the Belgian Network DYSCO (Dynamical Systems, Control, and Optimization), funded by the Interuniversity Attraction Poles Programme, initiated by the Belgian State, Science Policy Office. Work has been supported by FEDER (European Union and Wallonia Region) in the Hainaut-Biomed program (OCPAM project).

**REFERENCES**


### Table 3. Productivity means, maxima and standard deviations for 14 series of 50 runs considering two objective functions $\psi_1$ and $\psi_3$ and possible parameter uncertainties (i.e., a total of 1400 runs)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Prod. mean [10^3/\text{cells/h}]</th>
<th>Prod. max [10^3/\text{cells/h}]</th>
<th>Prod. stand. dev. [10^3/\text{cells/h}]</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu_{\text{Gmax1}}$</td>
<td>3.42</td>
<td>3.56</td>
<td>3.49</td>
</tr>
<tr>
<td>$\mu_{\text{Gmax2}}$</td>
<td>3.31</td>
<td>3.53</td>
<td>3.43</td>
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<tr>
<td>$K_N$</td>
<td>3.41</td>
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<td>$K_S$</td>
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<td>$\mu_{\text{Gmax1}}$, $K_{\text{Gin}}$</td>
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<td>3.53</td>
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<td>$\mu_{\text{Gmax1}}$, $K_N$</td>
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<td>$\mu_{\text{Gmax1}}$, $K_S$</td>
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<td>$\mu_{\text{Gmax2}}$, $K_S$</td>
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<tr>
<td>$\mu_{\text{Gmax1}}$, $K_{\text{Gin}}$, $K_S$</td>
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<td>$\mu_{\text{Gmax2}}$, $K_{\text{Gin}}$, $K_N$</td>
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<td>$\mu_{\text{Gmax1}}$, $\mu_{\text{Gmax2}}$, $K_{\text{Gin}}$, $K_S$</td>
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<td>3.52</td>
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