Volume 6 • Issue 1 • 2024

Research Article

Journal of Pharmacy and Drug Development

Multiobjective Nonlinear Model Predictive Control of Complex Metabolic Pathways

Lakshmi N Sridhar*

Chemical Engineering department, University of Puerto Rico, Mayaguez PR

***Corresponding Author:** Lakshmi N Sridhar. Chemical Engineering department, University of Puerto Rico, Mayaguez PR.

Received: January 20, 2024; **Published:** February 28, 2024

Abstract

Most of the dynamic optimization work regarding complex metabolic pathways involves single objectives without any control. This just predicts values of beneficial parameters without any control tasks to obtain the best possible product. This work involves the use of a rigorous multiobjective nonlinear model predictive control to regulate complex metabolic pathways in biochemical processes. The problems involve the maximization of the required products the minimization of the time required and the chemicals that inhibit the product formation. Seven problems involving different biochemical pathways of different sizes and structures have been considered achieving a tradeoff between the benefit and costs. Product and control profiles are generated. The strategy is shown to be effective in maximizing the required product and meeting all the other required objectives. The optimization language PYOMO was used in conjunction with the state- of-the-art optimization solvers, IPOPT and BARON. The key result is that multiobjective nonlinear model predictive control is very effective in being able to control metabolic pathways. The main conclusion is that this strategy should be used to maximize the required product while minimizing the time required and the chemicals that inhibit the product formation.

Key Words: *Optimal control; Metabolic pathways; Multiobjective Abbreviations MNLMPC multiobjective nonlinear model predictive control*

Introduction

The use of Mathematical modelling involving complex biological systems has been studied by several workers such as Doyle et al (2006) who focused on interface biology, DiStefano (2015), Wolkenhauer (2014) who discussed systems biology and Wolkenhauer and Mesarovic (2005). Who investigated cell dynamics? Dynamic modeling of biological and physiological systems using ordinary differential equations was I nvestigated by Aldridgeet al (2006) and Chen et al (2010). The use of applied mathematics to understand the dynamics of molecular biological systems has led to a lot of computational research. The role of dynamical systems theory in physiology.was discussed by Sherman et al (2011) and Crampin et al (2004) The use of kinetic models in genetics was investigated by (Almquist et al, 2014; LeNovere 2015; and Srinivasan et al, 2015). Heinemann et al (2016) have discussed model calibration while Saa et (2017) have reviewed modeling frameworks involving metabolism. Computational work involving metabolic models was by several workers (Widmer et al; (2018) who looked at. Bridging intracellular scales by mechanistic computational models.

Tummier et al (2018) who investigated the discrepancy between data for and expectations on metabolic models, Frohlich et al (2019) who studied the scalable inference of ordinary differential equation models of biochemical processes; Strutz al (2019),

who did metabolic kinetic modeling of complex biological systems Wolkenhauer et al (2005) who researched the dynamic systems approach to control and regulation of intracellular networks.and Kremling et al (2007). Who provided an engineering? Perspective on systems biology. The use of control techniques in systems involving metabolism and metabolic activities was investigated by Wellstead et al (2008) who studied the role of control and system theory in systems biology., Iglesias et al (2010) who used control theory in systems biology, Blanchini et al (2018), who extended this work to biological networks, Thomas et al 2019) used control theory in biology and medicine, Arcak et al (2019). Menolascina et al (2012) and He et al (2016), who introduce control engineering in biological systems Prescott et al (2016). Del Vechio et al (2016), Hsiao et al (2018) who incorporated design and control in biological systems. Dynamic optimization studies involving metabolic pathways were performed by several workers (Otero- Muras and Banga, (2017); who developed. An automated design framework for synthetic biology exploiting pareto optimality, Li et al., (2018), who worked on enabling controlling complex networks with local topological information; Lo- Thong et al.,(2020), who identify flux checkpoints in metabolic pathways.Tsiantis and Banga, (2020) who use optimal control to understand complex metabolic networks, Hijas-Liste et al (2014) who use global dynamic optimization in metabolic pathways problems and Baoda et al (2022)) who optimize molecular biocontrollers. Most of the work so far involves single-objective optimization. What is needed is to perform multiobjective optimal control where one is able to maximize the product while keeping the substances that inhibit product formation and the time required at a minimum value and this is the research gap.

The main objective of this work is to perform a rigorous multiobjective nonlinear model predictive control strategy (MNLMPC) method on problems involving complex metabolic pathways. The paper is organized as follows. First, the algorithm for the MNLMPC is described. Seven different case studies involving metabolic pathways where the MNLMPC method is applied are then presented followed by the conclusions.

Materials and Methods

MNLMPC (Multiobjective Nonlinear Model prediotive control) method

The multi objective nonlinear model predictive control strategy (MNLMPC) method was first proposed by Flores Tlacuahuaz (2012) and used by Sridhar [2019]. This method does not involve the use of weighting functions, nor does it impose additional constraints on the problem unlike the weighted function or the epsilon correction method (Miettinen, 1999). For a problem that is posed as

$$\begin{aligned} &\min J(x,u) = (x_1, x_2 \ldots . x_k) \\ &subject\ to\ \frac{dx}{dt} = F(x,u) \\ &h(x,u) \le 0 \\ &x^L \le x \le x^U \\ &u^L \le u \le u^U \end{aligned} \qquad (1)$$

The MNLMPC method first solves dynamic optimization problems independently minimizing/maximizing each χ_i individually. The minimization/maximization of χ_i will lead to the values χ_i^* . Then the optimization problem that will be solved is

$$\begin{aligned} &\min \sqrt{\{x_i - x_i^*\}^2} \\ &subject\ to\ \frac{dx}{dt} = F(x,u) \\ &h(x,u) \le 0 \\ &x^L \le x \le x^U \\ &u^L \le u \le u^U \end{aligned} \qquad (2)$$

This will provide the control values for various times. The first obtained control value is implemented and the remaining discarded. This procedure is repeated until the implemented and the first obtained control value are the same.

The optimization package in Python, Pyomo [Hart et al, 2017], where the differential equations are automatically converted to a Nonlinear Program (NLP) using the orthogonal collocation method (Biegler, 2007) The Lagrange-Radau quadrature with three collocation points is used and 10 finite elements are chosen to solve the optimal control problems. The resulting nonlinear optimization problem was solved using the solvers IPOPT (Wachter et al 2006) and confirmed with Baron (Tawarmalani, 2005) to summarize the steps of the algorithm are as follows.

1. Minimize/maximize χ_i subject to the differential and algebraic equations that govern the process using Pyomo with IPOPT and Baron. This will lead to the value χ_i^* at various time intervals ti. The subscript i is the index for each time step.
2. Minimize $\sqrt{\{x_i - x_i^*\}^2}$ subject to the differential and algebraic equations that govern the process using Pyomo with

IPOPT and Baron. This will provide the control values for various times.

3. Implement the first obtained control values and discard the remaining. Repeat steps 1 to 4 until there is an insignificant difference between the implemented and the first obtained value of the control variables.

Results

Case studies

Seven case studies where the MNLPMC method to problems involving metabolic pathways are now discussed.

Problem 1

In this problem (Bartl et al; 2010) Hijas-Liste et al 2014) the metabolic pathway consists of three enzymatic reactions with mass action kinetics (figure 1) Each reaction is catalyzed by a specific enzyme (e_i i= 2,3,4). (S_1, S_2, S_3, S_4) Represent the substrate, the two intermediate metabolites and the product. The equations governing the process are as follows. For a matrix

$$N = \begin{bmatrix} 0 & 0 & 0 \\ 1 & -1 & 0 \\ 0 & 1 & -1 \\ 0 & 0 & 1 \end{bmatrix} \quad (3)$$

The variation of S_i with t is given by

$$\frac{dS}{dt} = Nv \quad (4)$$

Where

$$v_i = k_i s_i e_i \quad i = 2,3,4 \quad k_i = 1 \quad (5)$$

The multi objective optimal control involves the maximization of the $e \sum_0^{t_f} S_4(t)$ The minimization of t_f (the final time) and the minimization of $\sum_0^{t_f} e_2(t) + e_3(t) + e_4(t)$ the control variables are $[e_2(t), e_3(t), e_4(t)]$ All concentration units are in mM/litre the minimization of t_f is achieved by defining a time interval of [0, 1] and modifying the differential equations as

$$\frac{dS}{dt} = t_f(Nv) \quad (6)$$

Unfortunately, the multi objective optimal control results in the control profiles exhibiting spikes (Figure 1a). This issue was remedied by replacing the control values e_i by $\frac{e_i \tanh e_i}{\varepsilon}$ for I =2, 3, 4. This eliminates the spikes (figure 1b) However the product profiles with time do not change significantly demonstrating the effectiveness of the activation factor (figuress 1c and 1d) Using this factor, the NLMPC control values obtained were $[e_2, e_3, e_4]$ =[0.81,0.81,1.0]. The units of e and S are mM while the units of rare mM/cm^3 and time is in seconds. Fig. 1e shows the Pareto surface S_4, e_1, t Pareto profile.

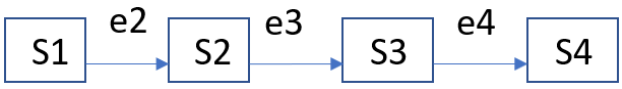

Figure 1: *(Pathway for problem 1).*

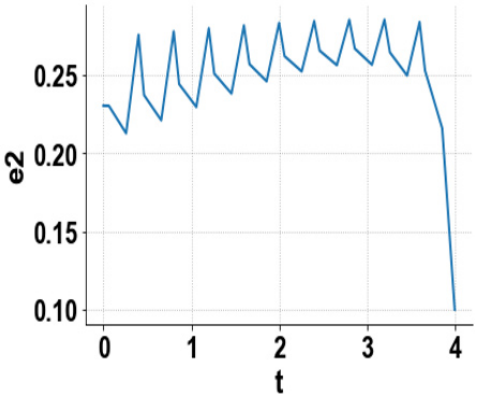

Figure 1a: *Problem 1e2 vs t without tanh activation factor.*

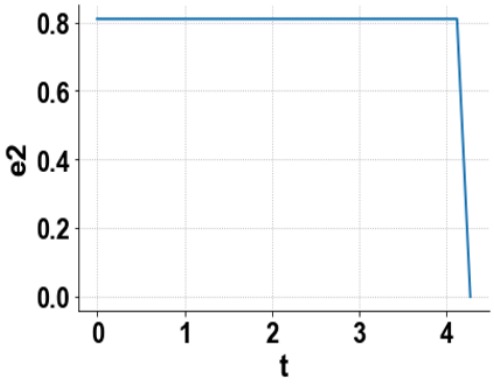

Figure 1b: *Problem 1e2 vs t with tanh activation factor.*

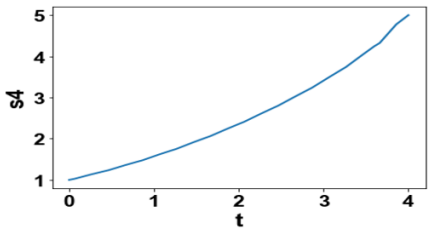

Figure 1c: *Problem 1 S4 vs t without tanh activation factor.*

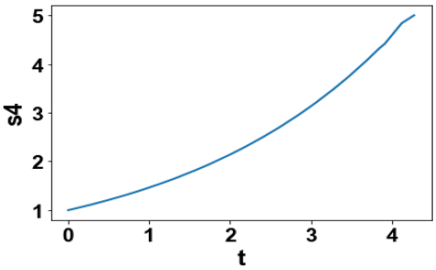

Figure 1d: *Problem 1 S4 vs t with tanh activation factor.*

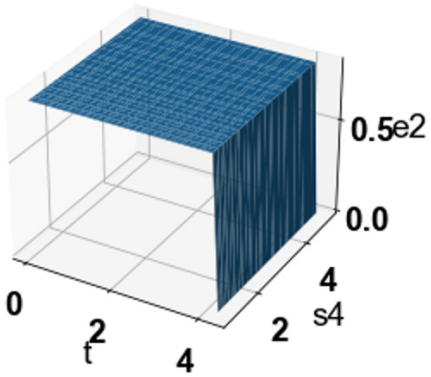

Figure 1e: *Problem 1 S4 e1, t pareto surface.*

Problem 2

This example considers a four-step linear pathway y (Oyarzún et al 2009, Hijas-Liste et al 2014) (figure 2). the equations involved are as follows. For a matrix

Figure 2: *Pathway for problem 2.*

$$N = \begin{bmatrix} -1 & 0 & 0 & 0 \\ 1 & -1 & 0 & 0 \\ 0 & 1 & -1 & 0 \\ 0 & 0 & 1 & -1 \end{bmatrix} \quad (7)$$

$$\frac{dS}{dt} = Nv \quad (8)$$

$$\frac{de}{dt} = r - \lambda e \quad (9)$$

$K_M(\sec^{-1}) = 1$,

$K_{cati}(\sec^{-1}) = [1, 2, 4, 3]$ For i = 1,2,3,4.

$e = [e_1, e_2, e_3, e_4]; r = [r_1, r_2, r_3, r_4]; v = [v_1, v_2, v_3, v_4]; S = [S_1, S_2, S_3, S_4]$ are variable vectors. λ = 0.5. The units of e and S are mM while the units of rare mM/cm^3 and time is in seconds.

The multiobjective optimal control involves the maximization of $\sum_0^{t_f} S_4(t)$ the minimization of t_f and the minimization of $\sum_0^{t_f} e_1(t) + e_2(t) + e_3(t) + e_4(t)$

The control variables are [$e_1(t)$, $e_2(t)$, $e_3(t)$, $e_4(t)$]. The minimization of t_f is achieved by defining a time interval of [0, 1] and modifying the differential equations as and

$$\frac{dS}{dt} = t_f(Nv) \quad (10)$$

$$\frac{de}{dt} = t_f(r - \lambda e) \quad (11)$$

The minimization of t_f $\sum_0^{t_f} S_4(t)$ results in a value of 4 while involves the maximization of $\sum_0^{t_f} e_1(t) + e_2(t) + e_3(t) + e_4(t)$ results in a value of 10. The minimization of the minimization of results in a value of 0.6. The multi objective nonlinear model predictive control problem will result in the minimization of $[\{\sum_0^{t_f} e_1(t) + e_2(t) + e_3(t) + e_4(t) - 0.6\}^2 + \{t_f - 4\}^2 + \{\sum_0^{t_f} S_4(t) - 10\}^2]^{1/2}$. Subject to the ordinary differential The NLMPC control variables of [e_1, e_2, e_3, e_4] are (0.1, 0.1, 0.7, 0.1). Figure 2a shows the variation of S_4 versus time, while Figure 2b shows the Pareto surface of S_4 and e_1 versus time. There is a constant increase in S_4 demonstrating the effective working of the MNLMPC strategy.

Problem 3

This example involves a metabolic pathway that is a Glycolysis inspired network (GBD) Bartl et al; 2010) Hijas-Liste et al 2014). (Figure 3) The equations involved are as follows for a matrix

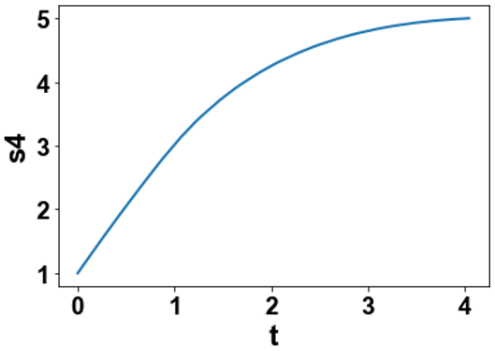

Figure 2a: *Problem 2 (S_4, t plot).*

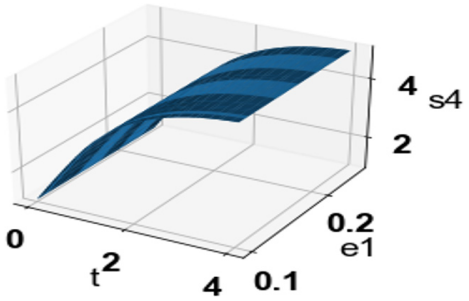

Figure 2b: *Problem 2 S_4, e_1, t surface.*

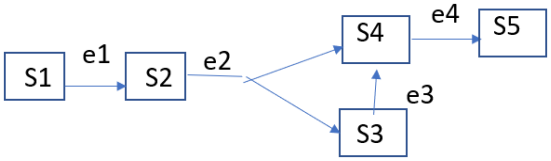

Figure 3: *Pathway for problem 3.*

$$N = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 1 & -1 & 0 & 0 \\ 0 & 1 & -1 & 0 \\ 0 & 1 & 1 & -1 \\ 0 & 0 & 0 & 1 \end{bmatrix} \quad (12)$$

$$\frac{dS}{dt} = Nv \quad (13)$$

$$\frac{de}{dt} = r - \lambda e \quad (14)$$

$$v_i = \frac{k_{cati} S_i e_i}{K_m + S_i} \quad (15)$$

$K_M(\sec^{-1}) = 1$ $K_{cati}(\sec^{-1}) = [1,1,1,1]$ i= 1,2,3,4.

$e = [e_1, e_2, e_3, e_4]$; $r = [r_1, r_2, r_3, r_4]$; $v = [v_1, v_2, v_3, v_4]$; $S = [S_1, S_2, S_3, S_4, S_5]$ are variable vectors. λ = 0.5. The units of e and S are mM while the units of rare mM/sec. The multi objective optimal control involves the maximization of $\sum_0^{t_f} S_5(t)$, the minimization of t_f and the minimization of $\sum_0^{t_f} e_1(t) + e_2(t) + e_3(t) + e_4(t)$ The control variables are $[e_1(t), e_2(t), e_3(t), e_4(t)]$

The minimization of t_f is achieved by defining a time interval of [0, 1] and modifying the differential equations as and

$$\frac{dS}{dt} = t_f(Nv) \quad (16)$$

$$\frac{de}{dt} = t_f(r - \lambda e) \quad (17)$$

The minimization of t_f results in a value of 4 while involves the maximization of $\sum_0^{t_f} S_5(t)$ is in a value of 9.0185. The minimization of the minimization of $\sum_0^{t_f} e_1(t) + e_2(t) + e_3(t) + e_4(t)$ results in a value of 0.8. The multi objective nonlinear model predictive control problem will result in the minimization of

$$[\{\sum_0^{t_f} e_1(t) + e_2(t) + e_3(t) + e_4(t) - 0.8\}^2 + \{t_f - 4\}^2 + \{\sum_0^{t_f} S_5(t) - 9.0185\}^2]^{1/2}$$

Subject to the equations governing this problem The NLMPC control variables of $[e_1, e_2, e_3, e_4]$ are (0.27, 0.27, 0.29, 0.15). Figure 3a shows the variation of S_4 versus time, while figure 3b shows the Pareto surface of S_5 and e_1 versus time. There is a constant increase in S_5 demonstrating the effective Working of the MNLMPC strategy.

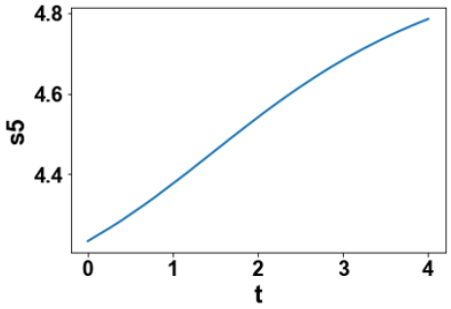

Figure 3a: *Problem 3 S5 vs t.*

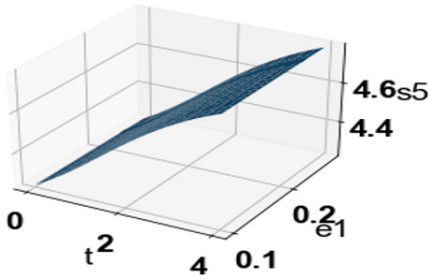

Figure 3b: *Problem 3 S5, e1, t Pareto Surface.*

Problem 4

A variation of problem 3 involves a situation in branched pathways is that the system could have two different outputs. This pathway is presented in figure 4. For the problem involved in such a situation, the equations would be as follows.

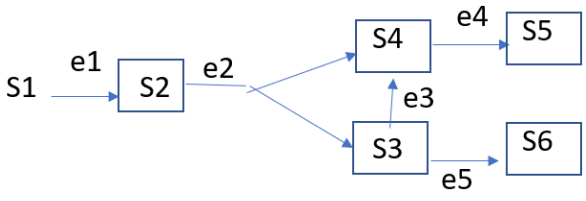

Figure: 4 *Pathway for problem 4.*

$$N = \begin{Bmatrix} 0 & 0 & 0 & 0 \\ 1 & -1 & 0 & 0 \\ 0 & 1 & -1 & 0 \\ 0 & 1 & 1 & -1 \\ 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 1 \end{Bmatrix} \quad (18)$$

$$\frac{dS}{dt} = Nv \quad (19)$$

$$\frac{de}{dt} = r - \lambda e \quad (20)$$

$KM\ (sec^{-1}) = 1$ $K_{cati}\ (sec^{-1}) = [1, 1, 1, 1]$ for I = 1,2,3,4

$e = [e_1, e_2, e_3, e_4]$; $r = [r_1, r_2, r_3, r_4]$; $v = [v_1, v_2, v_3, v_4]$; $S = [S_1, S_2, S_3, S_4, S_5]$ are variable vectors. λ =0.5. The units of e and S are mM while the units of rare mM/sec. The multi objective optimal control involves the maximization of $\sum_0^{t_f} S_5(t)$ and $\sum_0^{t_f} S_6(t)$ the minimization of t_f and the minimization of $\sum_0^{t_f} e_1(t) + e_2(t) + e_3(t) + e_4(t)$ the control variables are $[e_1(t), e_2(t), e_3(t), e_4(t)]$ the minimization of is achieved by defining a time interval of [0, 1] and modifying the differential equations as and

$$\frac{dS}{dt} = t_f(Nv) \quad (21)$$

$$\frac{de}{dt} = t_f(r - \lambda e) \quad (22)$$

The minimization of t_f results in a value of 4 while involves the maximization of $\sum_0^{t_f} S_5(t)$ results in a value of 9.0185 and the maximization of $\sum_0^{t_f} S_6(t)$ results in the value of 10. The minimization of $\sum_0^{t_f} e_1(t) + e_2(t) + e_3(t) + e_4(t)$ results in a value of 0.8. The multi objective nonlinear model predictive control problem will result in the minimization of

$$[\{\sum_0^{t_f} e_1(t) + e_2(t) + e_3(t) + e_4(t) - 0.8\}^2 + \{t_f - 4\}^2 + \{\sum_0^{t_f} S_5(t) - 9.668\}^2 + \{\sum_0^{t_f} S_6(t) - 10\}^2]^{1/2}$$

Subject to the equations 16-20.

The NLMPC control variables of $[e_1, e_2, e_3, e_4]$ are (0.26, 0.26, 0.26, 0.1). Figure 4a shows the variation of e_1 versus time, while figure 4b and 4c show the variation of S_5, S_6 with time. The constant increase of S_5, S_6 with time demonstrates the effective working of the NLMPC strategy. Figures 4d and 4e show the $[S_5, e_1, t]$; $[S_6, e_1, t]$ Pareto surfaces.

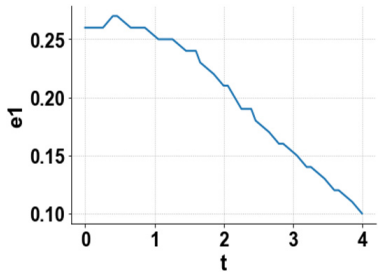

Figure 4a: *Problem 4 e1 verssus t.*

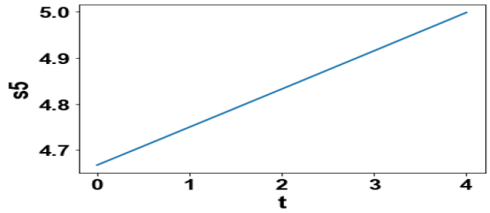

Figure 4b: *Problem 4 S5 verssus t.*

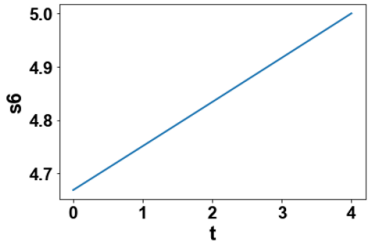

Figure 4c: *Problem 4 S5 verssus t.*

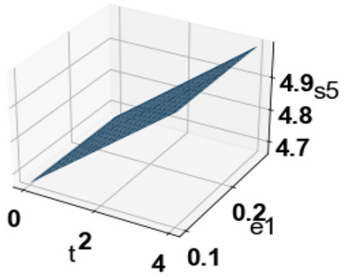

Figure 4d: *Problem 4 S5 e1 t surrface.*

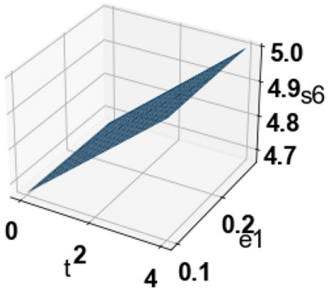

Figure 4e: *Problem 4 S6 e1 t surrface.*

Problem 5

The next problem involves the diauxic shift characterized by decreased growth rate and by switching metabolism from glycolysis to aerobic utilization of ethanol under conditions of glucose depletion. The aim is to maximize NADH and ATP levels. This problem was discussed by Klipp et al (2000, 2002) and Hijas-Liste et al 2014. The equations involved are as follows. For a matrix given by and

$$N = \begin{bmatrix} -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 2 & -1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & -1 & 1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 \\ 0 & 1 & -1 & 1 & -4 & -1 & -1 & 0 \\ -1 & 0 & -2 & 0 & 0 & 3 & 0 & -1 \\ 0 & -1 & 1 & -1 & 4 & 1 & 1 & 0 \\ 1 & 2 & 0 & 0 & 0 & -3 & 0 & 1 \end{bmatrix} \quad (23)$$

$$\begin{aligned} v_1 &= e_1 S_1 S_6 \\ v_2 &= e_2 S_2 S_7 S_8 \\ v_3 &= e_3 S_3 S_5 \\ v_4 &= e_4 S_4 S_7 \\ v_5 &= e_5 S_3 S_7 \\ v_6 &= e_6 S_5 S_8 \\ v_7 &= k_7 S_6 \\ v_8 &= k_8 S_7 \end{aligned} \quad (24)$$

$$\frac{dS}{dt} = (Nv) \quad (25)$$

Where $[\{\sum_0^{t_f} e_1(t)+e_2(t)+e_3(t)+e_4(t)-0.8\}^2+\{t_f-4\}^2+\{\sum_0^{t_f} S_5(t)-9.668\}^2+\{\sum_0^{t_f} S_6(t)-10\}^2]^{1/2}$

The minimization of t_f is achieved by defining a time interval of [0,1] and modifying the differential equations as

$$\frac{dS}{dt} = t_f (Nv) \quad (26)$$

The MNLMPC control values of [e_1, e_2, e_3, e_4,e_5, e_6] are [0.037, 0.004, 0.007, 99.99, 7.017e-06, 0.011]. The minimization of t_f results in a value of 4.786, the maximization of $\sum_0^{t_f} S_5(t)$ results in a value of 1.7. The maximization of $\sum_0^{t_f} S_6(t)$ results in a value of 1.8 and the minimization of $\sum_0^{t_f} e_1(t) + e_2(t) + e_3(t) + e_4(t) + e_5(t) + e_6(t)$ results in a value of .6. The multi objective nonlinear model predictive control problem will result in the minimization of the function

$$[(\sum_0^{t_f} e_1(t)+e_2(t)+e_3(t)+e_4(t)+e_5(t)+e_6(t)-202.6)^2+(\sum_0^{t_f} S_6(t)-1.7)^2 +(\sum_0^{t_f} S_5(t)-1.8)^2+(t_f-4.786)^2]^{-1/2}$$

Subject to the equations 23-246. Figure 5a shows the variation of s5 versus t the imposed constraint that S5 and S6 always be greater than equal to 0.5 and 0.7 results in the profile shown in figure 5a and 5b while 5c and 5d show the Pareto surfaces for S5 and S6 with e1 and t.

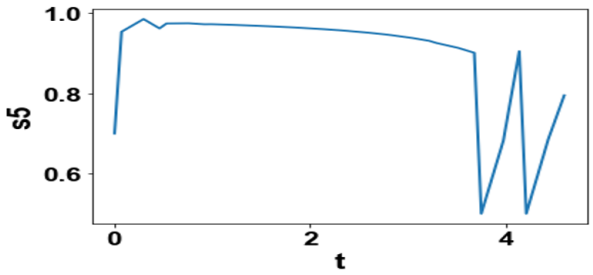

Figure 5a: *Problem 5 S5(NADH) versus t.*

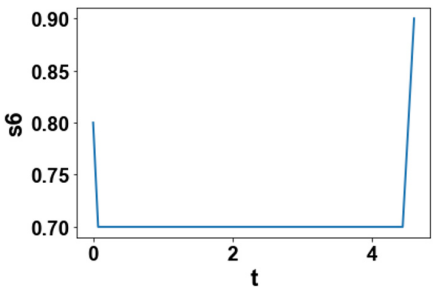

Figure 5b: *Problem 5 S6(ATP) versus t.*

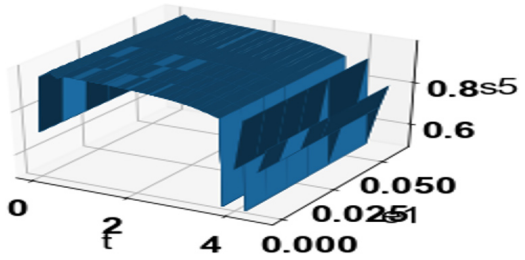

Figure 5c: *S5(NADH) e1 t surface.*

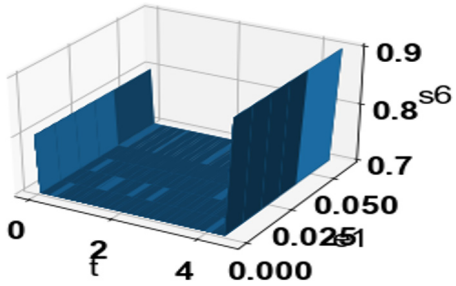

Figure 5d: *S6 (ATP) e1 t surface.*

Problem 6

This problem (Tsiantis and Banga, 2020), involves a simplified kinetic model of the central carbon metabolismof *B. subtilis*. The model considers important pathways such as upper and lower glycolysis, TCA cycle, glyconeogenesis, overflow metabolism and biomass production. The equations in this problem are

$$\frac{dx}{dt} = f(x, a, t) \quad (27)$$

$$0.0025 \le a(t) \le 0.125 \quad (28)$$

X = [FBP, PEP, PYR, CIT, MAL, ATP, ADP, $E_{1\text{-}13}$, G, M] (29)

$f_1 = x_{21}\, x_8\, x_2\, x_6 - x_9\, x_1 - x_{10}\, x_1\, x_7 + x_{11}\, x_2$

$f_2 = -x_{21}\, x_8\, x_2\, x_6 + 2x_{10}\, x_1\, x_7 - 2x_{11}\, x_2 - x_{12}\, x_2\, x_7 + x_{19}\, x_6\, v_5$

$f_3 = x_{21}\, x_8\, x_2\, x_6 + x_{12}\, x_2\, x_7 - x_{13}\, x_3 - x_{14}\, x_3 - x_{15}\, x_3\, x_5 - x_{18}\, x_3$

$f_4 = x_{15}\, x_3\, x_5 - x_{16}\, x_4 - x_{17}\, x_4\, x_7$

$f_5 = 3x_{22}\, x_{20} + x_{17}\, x_4\, x_7 - x_{15}\, x_3\, x_5 + x_{18}\, x_3 - x_{19}\, x_6\, x_5$

$f_6 = -x_{21}\, x_8\, x_2\, x_6 + 2x_{10}\, x_1\, x_7 + x_{12}\, x_2\, x_7 + 5x_{17}\, x_4\, x_7 - x_{19}\, x_6\, x_5 - 8x_6$

$f_7 = -f_6$

$f_8 = a_1 - \beta x_8$

$f_9 = a_2 - \beta x_9$

$f_{10} = a_3 - \beta x_{10}$

$f_{11} = a_4 - \beta x_{11}$

$f_{12} = a_5 - \beta x_{12}$

$f_{13} = a_6 - \beta x_{13}$

$f_{14} = a_7 - \beta x_{14}$

$f_{15} = a_8 - \beta x_{15}$

$f_{16} = a_9 - \beta x_{16}$

$f_{17} = a_{10} - \beta x_{17}$

$f_{18} = a_{11} - \beta x_{18}$ (30)

$f_{19} = a_{12} - \beta x_{19}$

$f_{20} = a_{13} - \beta x_{20}$

$f_{21} = -0.01 x_{21}\, x_8\, x_2\, x_6$

$f_{22} = -0.03 x_{22}\, x_{20}$

$\beta = 0.25$, $E_{total} = \sum_{1}^{13} E_i$. The objective is to maximize, ATP $(\sum_{0}^{t_f} X_6)$ and minimize $(\sum_{0}^{t_f} E_{total})$ which is the total enzyme concentration. The maximization of ATP $(\sum_{0}^{t_f} X_6)$ resulted in a value of 600 while the minimization of $(\sum_{0}^{t_f} E_{total})$ resulted in a value of 0.13. The resulting optimal control problem involved the minimization of the function

$$((\sum_{0}^{t_f} X_6) - 600) / 600)^2 + (\sum_{0}^{t_f} E_{total} - 0.13) / 0.13)^2)^{-1/2}$$

subject to the equations governing the problem the value of E_{total} was updated until there was no difference between the first and second values. The obtained MNLMPC value of E_{total} was 3.61, Figures 6a and 6b show the variation of E_{total} and ATP with respect to time. The figures indicate that the value of E_{total} stays approximately constant with time and then decreases and this causes an increase in the value of the ATP before marginally decreasing because of the reduction in value of E_{total}. Figures 6c shows the Pareto surface of the ATP, E_{total} and time.

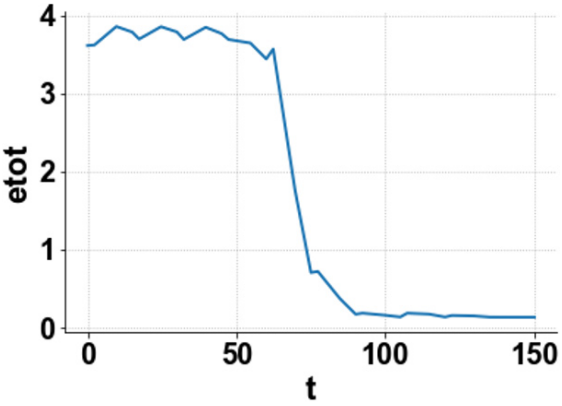

Figure 6a: *Problème 6 E total versus t.*

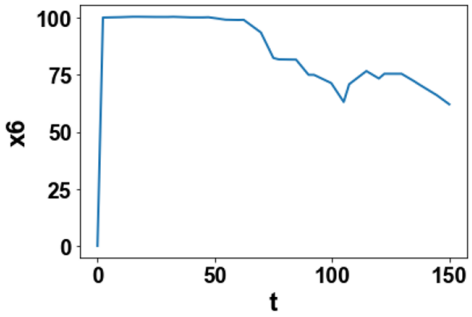

Figure 6b: *Problème 6 x6(ATP) versus t.*

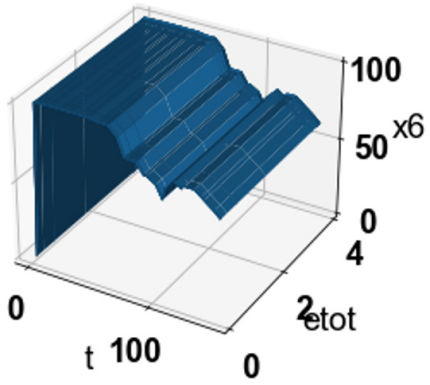

Figure 6c: *Problem 6 x 6, E total t surface.*

Problem 7

This problem deals with the model of the Dynamic Regulation of the Naringenin Metabolic Pathway (Baoda et al, 2022). The model of the naringenin pathway involves the mass balance equations of the enzyme-catalyzed reactions of the metabolic pathway from L-tyrosine to naringenin.

For each reaction, the corresponding flux is V (moleculesmmin−1). Lt is the number of molecules of L-tyrosine, pC is p-coumaric acid, pA is p-coumaroyl-CoA, Nc is naringenin chalcone, and N is the target metabolite naringenin. Ma is the Malonyl-CoA, and μ is the dilution rate. The equations involved are (Baoda et al, 2022)

$$\frac{dLT}{dt} = V_0 - V_{LT} - \mu LT \quad (31)$$

$$\frac{dPC}{dt} = V_{LT} - V_{PC} - \mu PC \quad (32)$$

$$\frac{dPA}{dt} = V_{PC} - V_{PAMA} - \mu PA \quad (33)$$

$$\frac{dNC}{dt} = V_{NC} - V_{PAMA} - \mu NC \quad (34)$$

$$\frac{dNC}{dt} = V_{NC} - V_N - \mu N \quad (35)$$

$$V_0 = K_{LT} \quad (36)$$

$$V_{LT} = K_{CatTAL} TAL \frac{LT}{K_{mLT} + LT} \quad (37)$$

$$V_{PC} = K_{Cat4CL} 4CL \frac{PC}{K_{mPC} + PC} \quad (38)$$

$$V_{PA} = K_{CatCHS} CHS \frac{PAMA}{K_{MPA} K_{MMA} + K_{MMA} PA + K_{MPA} MA + PAMA} \quad (39)$$

$$V_{NC} = K_{CatCHI} CHI \frac{NC}{K_{mNC} + NC} \quad (40)$$

$$V_N = K_{CatF3H} F3H \frac{N}{K_{mN} + N} \quad (41)$$

The parameter values are

K_{LT} = 2.0X10^6, K_{CatTAL} = 1.2, K = 174$_{Cat4CL}$ = 0.492, K_{CatCHS} = 1.68, K_{CatCHI} = 4.2, K_{CatF3H} = 174

K_{mLT} = 1.9X10$_4$, K_{mPC} = 1.4X10^4, K_{mMA} = 1X10$^{(-3)}$, K_{mPA} = 1X10$^{(-3)}$, K_{mNC} = 2.8X10^4, K_{mN} = 5X10^8

The objective is to maximize, the naringenin $(\sum_0^{t_f} n(t)$ and minimize the malonyl-CoA $(\sum_0^{t_f} MA(t)$. The maximization of naringenin $(\sum_0^{t_f} n(t)$ resulted in a value of 52031.66 While the minimization of the malonyl-CoA $(\sum_0^{t_f} MA(t)$. Resulted in a value of 8. The Resulting optimal control problem involved the minimization of the function $((\sum_0^{t_f} n) - 52031.6) * 10^{-4})^2 + (\sum_0^{t_f} MA - 8))^2)^{-1/2}$

Subject to the equations governing the Problem. A scaling factor of 10^{-4} was used. The MNLMPC value of μ is 0.339, Figure 7a Shows the variation of narigenin with time. This figure demonstrates am eventual Increase of the naringenin indicating the effectiveness of the MNLMPC strategy. While Figure 7b shows the variation of malonyl-CoA with time. Figure 7c shows the Pareto surface of the naringenin, versus the dilution rate μ and time.

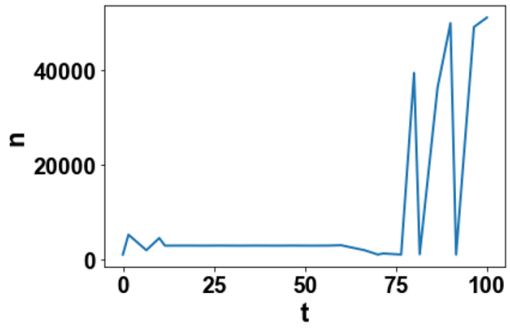

Figure 7a: *Problem 7 naringenin versus t.*

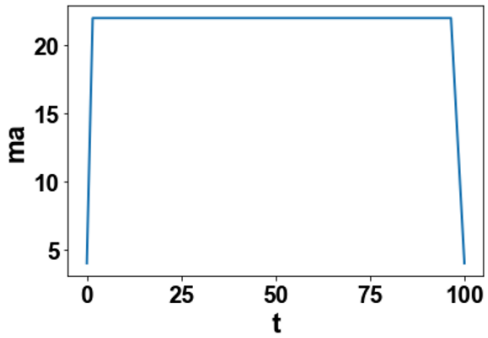

Figure 7b: *Problème 7 ma (malonyl-CoA) versus t.*

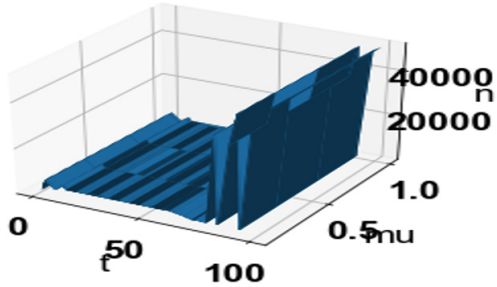

Figure 7c: *Problem 7 t mu n pareto surface.*

Discussion

The main result is that it is possible control the metabolic pathways so as to maximize the product and minimize both the time required and the quantity of unwanted substances that inhibit the product formation. The multi objective nonlinear model predictive control strategy used to control the pathways is very effective and rigorous and will enable to the metabolic processes to take place in the most beneficial manner possible.

Conclusions

A rigorous multi objective nonlinear model predictive control strategy is used on seven problems involving metabolic pathways. In all of these cases it is demonstrated that this technique maximizes the required product while minimizing the time required and the chemicals that inhibit the product formation. The key result is that multi objective nonlinear model predictive control is very effective in being able to control metabolic Pathways. The optimization language Pyomo and the state of the art optimization solvers IPOPT and BARON are used to solve the problems and confirm the globality of the solutions The strategy is effective in maximizing the required product and meeting all the other objectives and hence achieve an effective tradeoff between the benefit and costs.

Acknowledgements

Dr. Sridhar thanks Dr. Bielger for teaching him about the tanh activation function and Dr. Carlos Ramirez for encouraging him to write single author papers

Data Availability Statement

All data used is presented in the paper

Conflict of interest

The author, Dr. Lakshmi N Sridhar has no conflict of interest.

Nomenclature

S: Substrate, metabolite product
e: Control variable, enzyme
t: Time
v: Reaction rate
X: Chemicals involved in the reaction
μ: Dilution rate
Lt: Number of molecules of L-tyrosine,
pC: p-coumaric acid
pA: p-coumaroyl-CoA
Nc: Naringenin chalcone,
Ma: Malonyl-CoA,
MNLMPC multi objective nonlinear model predictive control

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