ANALYSIS AND CONTROL OF A DELAYED DIFFERENTIAL EQUATION MODEL FOR CIRCADIAN RHYTHMS

Lakshmi N Sridhar

Chemical Engineering Department University of Puerto Rico Mayaguez, PR 00681

ABSTRACT

Understanding the dynamics of Circadian rhythms that regulate several physiological processes in human beings is important. Many Circadian rhythm models involve time delay functions as the rhythmic processes are initiated at different times. The main objectives of this paper are to perform bifurcation analysis and multi objective nonlinear model predictive control (MNLMPC) of the delayed differential equations (DDE) of a three-dimensional Circadian rhythm model. The bifurcation analysis reveals several intermediate oscillations causing Hopf bifurcations which are eliminated using an activation factor. The multi objective nonlinear model predictive control reveals a control profile with a lot of noise that is eliminated using the Savitsky Golay filter. Bifurcation analysis was performed using the MATLAB software DDEB if tool. Multi-objective nonlinear model predictive control was performed with the optimization language PYOMO.

KEYWORDS

Optimal control, Circadian Models, Bifurcation, Hopf

1. INTRODUCTION

Decoursey [1] discussed an ecologist's viewpoint of photoentrainment of circadian rhythms, while Aronson et al [2] discussed the negative feedback defining a circadian clock focusing on the autoregulation of the clock gene frequency. Edery, et al [3] researched the temporal phosphorylation of the Drosophila period protein. Crosthwaite, and co-workers [4,5] researched resetting of circadian clocks and the origins of circadian rhythmicity. Hunter-Ensor [6] concluded that the regulation of the Drosophila protein timeless suggests a mechanism for resetting the circadian clock by light. Shigeyoshi et al [7] showed that a Light-induced resetting of a mammalian circadian clock is associated with rapid induction of the mPer transcript. Mackey [8] discussed the various mathematical models of hematopoietic cell replication and control. Merrow, et al [9] dissected circadian oscillation into several discrete domains. Albrecht et al [10] studied the differential response of two putative mammalian circadian regulators, mPer1 and mPer2, to light. Details of the cyanobacterial circadian system were presented by Golden et al [11]. Ishiura et al [12] developed an expression of a gene cluster kai ABC as a circadian feedback process in cyanobacteria. Jewett, and Kronauer [13] modeled effects of light on the human circadian pacemaker. Gekakis et al [14] discussed the role of the clock protein in the mammalian circadian mechanism. Nunes [15] developed a double circadian oscillator model for quantitative photoperiodic time measurement in insects and mites. Sangoram et al [16] showed how a timeless ortholog and mPer1 interact and negatively regulate clock-bmal1-- induced transcription. Leloup and Goldbeter [17] developed a model for circadian rhythms in Drosophila incorporating the formation of a complex between per and tim proteins. Darlington and co-workers [18] discussed the closing of the circadian loop and the clock-induced transcription of its own inhibitors per and Tim. Jin et al [19] developed a molecular mechanism regulating output from the suprachiasmatic circadian clock. Lee et al [20] developed a strategy to reset the Drosophila clock by photic regulation of PER and a PER-TIM complex. Scheper and co-workers (21, 22) performed interesting modeling work involving Circadian rhythms. Blasius et al [23] developed an oscillatory model of crassulacean acid metabolism with a dynamic hysteresis switch. Dunlap [24] investigated the molecular bases for circadian clocks. Lema et al [25] developed a delayed model of the circadian pacemaker. Van Soest et al [26] developed a three-dimensional model involving three delay differential equations of the circadian clock.

2. OBJECTIVES

The main objectives of this paper are to perform bifurcation analysis and multiobjective nonlinear model predictive control (MNLMPC) of the delayed differential equations (DDE) of the three-dimensional model developed by Van Soest et al [26]. The bifurcation analysis reveals several intermediate oscillations causing Hopf bifurcations which are eliminated using an activation factor. The multiobjective nonlinear model predictive control reveals a control profile with a lot of noise that is eliminated using the Savitsky Golay filter. This paper is organized as follows. First, the three DDE model involving Circadian rhythms are presented. The bifurcation analysis and the MNLMPC procedures are then described followed by the discussion of the results obtained and the conclusions.

3. THE THREE DDE CIRCADIAN MODEL

This model is transcription-based, displaying two negative feedback loops described in three delay differential equations (DDEs). B, P, and R represent the core clock genes BMAL1, PER, and REVERB. BMAL1 (B) drives the expression of clock genes and should be maximized. REVERB activates BMAL1 but also produces PER which inhibits BMAL1. PER the inhibitor of BMAL1 should be minimized.

The equations representing this model are

$$\begin{aligned}
\frac{dP}{dt} &= \left(\frac{vp}{(kp+P(t-\tau)}\right)^2 \left(\frac{cp+bpB(t-\tau)}{(cp+B(t-\tau))}\right)^2 - dpP(t) \\
\frac{dB}{dt} &= \left(\frac{vb}{(kb+R(t-\tau)}\right)^2 - dbB(t) \\
\frac{dB}{dt} &= \left(\frac{vr+brB((t-\tau)}{(kr+B(t-\tau)}\right)^3 \left(\frac{cr}{(cr+P(t-\tau))}\right)^2 - drR(t)
\end{aligned} \tag{1}$$

The parameter values are

$db = 0.0014$, $dr = 0.29$, $vp = 1$, $vb = 0.9$, $vr = 0.6$,
$kp = 0.1$, $kb = 0.05$, $kr = 0.9$, $cp = 0.1$, $cr = 35$, $bp = 1$, $br = 8$

dp is the bifurcation parameter and the control value.

The time delay τ is equal to 3.

4. BIFURCATION ANALYSIS OF DELAY DIFFERENTIAL EQUATIONS

DDE-BIFTOOL is a MATLAB package that performs a bifurcation analysis of delay differential equations with several delays where the continuation of steady-state solutions is implemented. Fold points and Hopf bifurcation points that result in periodic solutions are determined. The periodic solutions are computed using orthogonal collocation with adaptive mesh selection. The DDE-BIFTOOL package encourages the use of time delays in modeling. More details can be found in Engelborghs et al [27].

5. MULTIOBJECTIVE NONLINEAR MODEL PREDICTIVE CONTROL ALGORITHM

The Multiobjective Nonlinear Model Predictive Control method used is similar to the one used by Flores Tlacuahuaz [28] For a a set of delay differential equations

$$\frac{dx}{dt} = F(x(t-\tau), u) \qquad (2)$$

For a final time of t_f let $p_j(t_f)\ j = 1, 2, ..n$ be the variables that need to be optimized (maximized or minimized). Simultaneously. n the total number of variables that need to be optimized simultaneously. In this MNLMPC method dynamic optimization problems that independently minimize/maximize each variable $p_j(t_f)\ j = 1, 2, ..n$ are solved individually. The individual minimization/maximization of each $p_j(t_f)\ j = 1, 2, ..n$ will lead to the values p_j^* . Then the multiobjective optimal control problem that will be solved is

$$\min\left(\sum_{j=1}^{n} (p_j(t_f) - p_j^*)\right)^2 \qquad (3)$$
$$subject\ to\ \ \frac{dx}{dt} = F(x(t-\tau), u);$$

This will provide the control values for various times. The first obtained control value is implemented and the rest are ignored. The procedure is repeated until the implemented and the first obtained control values are the same or if the Utopia point ($p_j(t_f) = p_j^*$; for all j from 1 to n is achieved. The optimization package in Python, Pyomo (Hart et al [29]), where the differential equations are automatically converted to algebraic equations will be used. The resulting optimization problem was solved using IPOPT (Wächter And Biegler [30]). The obtained solution is confirmed as a global solution with BARON (Tawarmalani, M. and N. V. Sahinidis[31]). Pyomo can handle functions with time. For example, if xdelay is the value of x at the time tau (where tau is the delay) the corresponding code would read:

```
def _msa1(m,t):
if ( t  - m.tau).in m.t:
return m.xdelayed[t] == m.x[t - m.delayp]
else:
return  Constraint.Skip
m.msa1con= Constraint(m.t,rule=_msa1)
def _msb1(m,t):
if t < m.tau:
return m xdelay[t]==0
else:
```

```
return Constraint.Skip
m.msb1con= Constraint(m.t,rule=_msb1)
```

The value of xdelay is 0 when the time is less than tau and is equal to x(t-tau) when t is greater than or equal to tau.

6. RESULTS AND DISCUSSION

The DDEbiftool package has revealed three bifurcation points at [P,B,R] values of (1,2307,0, 0.9219); (0.73581, 0, 0.95989) and (0.59088, 0 0.91766). The values of dp at these Hopf bifurcation points are 0.45884, 1.9455, and 3.5457. These Hopf bifurcation points are indicated in Fig. 1 The limit cycles caused by the three Hopf bifurcation points are shown in Figures 2 3 and 4. The limit cycles caused by the Hopf bifurcations disrupt the Circadian rhythm and should be eliminated. Sridhar (2024) explained with several examples how the activation factor involving the tanh function successfully eliminates the limit cycle causing Hopf bifurcation points. This is found to be true in the three DDE circadian model. When dp was replaced by dptanh(dp)/20 the three Hopf bifurcation points disappeared. This is demonstrated in Fig. 5.

For the MNLMPC $P(t_f)$ was minimized and $B(t_f)$ was maximized. The minimization of $P(t_f)$ resulted in a value of 0.591 and the maximization of $B(t_f)$ yielded a value of 105.233. The function that was then minimized was $[(\frac{P(t_f)-0.591}{0.591})^2+(\frac{B(t_f)-105.233}{105.233})^2]$. The first obtained control values of dp was implemented and the remaining values were discarded. This procedure was repeated until there was no difference between the implemented and the first obtained dp values. This MNLMPC value of dp that was obtained was 0.2509. The B, P R profiles are shown in Fig. 6. This figure demonstrates the haphazard nature of the REVERB(R). This is because REVERB(R) activates BMAL1 but also produces PER which inhibits BMAL1. The obtained control profile of dp exhibited a lot of noise (fig.7). This was remedied using the Savitzky-Golay Filter. The Savitzky-Golay filter, is a digital filter widely used for data smoothing and differentiation. The Savitzky-Golay filter maintains the integrity of the original signal preserving the shape and features of the signal. The smoothed-out version of this profile is shown in Fig. 8.

CONCLUSIONS

Bifurcation analysis and Multiobjective nonlinear model control were performed on the mammalian circadian clock that involves three delay differential equations. The bifurcation analysis revealed the existence of intermediate Hopf bifurcations which were eliminated using the hyperbolic tangent activation function. The multiobjective nonlinear model caculation revealed a control profile with a lot of noise that was eliminated using the Savitzky Golay filter.

ACKNOWLEDGMENT

Dr. Sridhar thanks Dr. Jan Sieber for his help with the DDEbiftool .

REFERENCES

[1] Decoursey, P. J. (1989). Photoentrainment of circadian rhythms: an ecologist's viewpoint. In: *Circadian Clocks and Ecology* (Hiroshige, T. & Honma, K., eds), pp. 187}206.Sapporo: Hokkaido University Press.

[2] Aronson, B. D., Johnson, K. A., Loros, J. J. & Dunlap,J. C. (1994). Negative feedback defining a circadian clock: autoregulation of the clock gene frequency. *Science* 263,1578-1584.

[3] Edery, I., Zwiebel, L. J., Dembiska, M. E.&Rosbash, M. (1994). Temporal phosphorylation of the Drosophila period protein. *Proc. Nat. Acad. Sci.* ;*.S.A.* 91, 2260}2264.

[4] Crosthwaite, S. K., Dunlap, J. C. & Loros, J. J. (1997). Neurospora wc-1 and wc-2: transcription, photo responses, and the origins of circadian rhythmicity. *Science* 276, 763-769.

[5] Crosthwaite, S. K., Loros, J. J. & Dunlap, J. C. (1995). Light-induced resetting of a circadian clock is mediated by a rapid increase in frequency transcript. *Cell* 81, 1003-1012.

[6] Hunter-Ensor, M., Ousley, A. & Sehgal, A. (1996). Regulation of the Drosophila protein timeless suggests a mechanism for resetting the circadian clock by light. *Cell* 84, 677 -685.

[7] Shigeyoshi, Y., Taguchi, K., Yamamoto, S., Takeida, S., Yan, L., Tei, H., Moriya, T., Shibata, S., Loros, J. J., Dunlap, J. C. & Okamura, H. (1997). Light-induced resetting of a mammalian circadian clock is associated with rapid induction of the mPer transcript. *Cell* 91, 1043-1053.

[8] Mackey, M. C. (1997). Mathematical models of hematopoietic cell replication and control. In: *Case studies in mathematical modeling* (Othmer, H. G., Adler, F., Lewis, M. & Dallon, J., eds), pp. 149}178. Englewood Cli!s, NJ: Prentice Hall.

[9] Merrow, M. W., Garceau, N. Y. & Dunlap, J. C. (1997). Dissection of a circadian oscillation into discrete domains. *Proc. Nat. Acad. Sci.* ;*.S.A.* 94, 3877}3882.

[10] Albrecht, u., Sun, z. S., Eichele, g. & Lee, C. C. (1997). A differential response of two putative mammalian circadian regulators, mPer1 and mPer2, to light. *Cell* 91, 1055-1064.

[11] Golden, S. S., Johnson, C. H. & Kondo, T. (1998). The cyanobacterial circadian system: a clock apart. *Curr. Opin. Microbiol.* 1, 669-673.

[12] Ishiura, M., Kutsuna, S., Aoki, S., Iwasaki, H., Andersson, C. R., Tanabe, A., Golden, S. S., Johnson, C. H. &Kondo, T. (1998). Expression of a gene cluster kai ABC as a circadian feedback process in cyanobacteria. *Science* 281, 1519-1523.

[13] Jewett, M. E. & Kronauer, R. E. (1998). Refinement of a limit cycle oscillator model of the e!ects of light on the human circadian pacemaker. *J. theor. Biol.* 192, 455}465.

[14] Gekakis, N., Staknis, D., Nguyen, H. B., Davis, F. C., Wilsbacher, L. D., King, D. P., Takahashi, J. S. & Weitz, C. J. (1998). Role of the clock protein in the mammalian circadian mechanism. *Science* 280, 1564}1569.

[15] Nunes, M. V. (1998). A double circadian oscillator model for quantitative photoperiodic time measurement in insect and mites. *J. theor. Biol.* 194, 299}311.

[16] Sangoram, A. M., Saez, L., Antoch, M. P., Gekakis, N., Staknis, D., Whiteley, A., Fruechte, E. M., Vitaterna, M. H., Shimomura, K., King, D. P., Young, M. W., Weitz, C. J. & Takahashi, J. S. (1998). Mammalian circadian autoregulatory loop: a timeless ortholog and mPer1 interact and negatively regulate clock-bmal1- induced transcription. *Neuron* 21, 1101-1113.

[17] Leloup, J. C. & Goldbeter, A. (1998). A model for circadian rhythms in Drosophila incorporating the formation of a complex between per and tim proteins. *J. Biol. Rhythms* 13, 70-87.

[18] Darlington, T. K., Wager-Smith, K., Ceriani, M. F., Staknis, D., Gekakis, N., Steeves, T. D. L.,Weitz, C. J., Takahashi, J. S.&Kay, S. A. (1998). Closing the circadian loop: clock-induced transcription of its own inhibitors per and tim. *Science* 280, 1599-1603.

[19] Jin, X., Shearman, L., Weaver, D., Zylka, M., Devries, G. & Reppert, S. (1999). A molecular mechanism regulating output from the suprachiasmatic circadian clock. *Cell* 96, 57-68.

[20] Lee, C., Parikh, V., Itsukachi, T., Bae, K. & Edery, I. (1996). Resetting the Drosophila clock by photic regulation of PER and a PER-TIM complex. Neuron 21, 857-867.

[21] Scheper, T. O., Klinkenberg, D., Pennartz, C. & Pelt, J. V. (1999a). A mathematical model for the intracellular circadian rhythm generator. *J. Neurosci.* 19, 40-47.

[22] Scheper, T. O., Klinkenberg, D., Pelt, J. V. & Pennartz, C. (1999b). A model of molecular circadian clocks: multiple mechanisms for phase shifting and a requirement for strong nonlinear interactions. *J. Biol. Rhythms* 14, 213-220.

[23] Blasius, B., Neff, R., Beck, F. & Lug Ttge, U. (1999).Oscillatory model of crassulacean acid metabolism with a dynamic hysteresis switch. *Proc. R. Socond.* 266, 93-101.

[24] Dunlap, J. C. (1999). Molecular bases for circadian clocks. *Cell* 96, 271, 290.

[25] Lema, Martín A.; Golombek, Diego Andrés; Echave, Julián (2000); Delay model of the circadian pacemaker; Academic Press Ltd - Elsevier Science Ltd; Journal of Theoretical Biology; 204; 4; 6-565-573

[26] Van Soest I, del Olmo M, Schmal C, Herzel H. (2020) Nonlinear phenomena in models of the circadian clock. J. R. Soc. Interface 17: 20200556.

[27] Engelborghs, K., Luzyanin, T. Roose D. (2002) , Numerical bifurcation analysis of delay differential equations using DDE-BIFTOOL, ACM Transactions on Mathematical Software, Vol. 28, Number 1, p. 1-21,

[28] Flores-Tlacuahuac, A. Morales Pilar ; Rivera Toledo Martin (2012); "Multiobjective Nonlinear model predictive control of a class of chemical reactors" . *I & EC research*; 5891-5899 .

[29] Hart, William E., Laird, Carl D., Watson, Jean-Paul Woodruff, David L., Hackebeil, Gabriel A., Nicholson, Bethany L. and Siirola, John D., (2017) "Pyomo – Optimization Modeling in Python" Second Edition. Vol. 67.

[30] Wächter, A., Biegler, Lorenz (2006) "On the implementation of an interior-point filter line-search algorithm for large-scale nonlinear programming". *Math. Program.* **106**, 25–57 .

[31] Tawarmalani, M. and Sahinidis, N. V. (2005) "A polyhedral branch-and-cut approach to global optimization", *Mathematical Programming*, 103(2), 225-249.

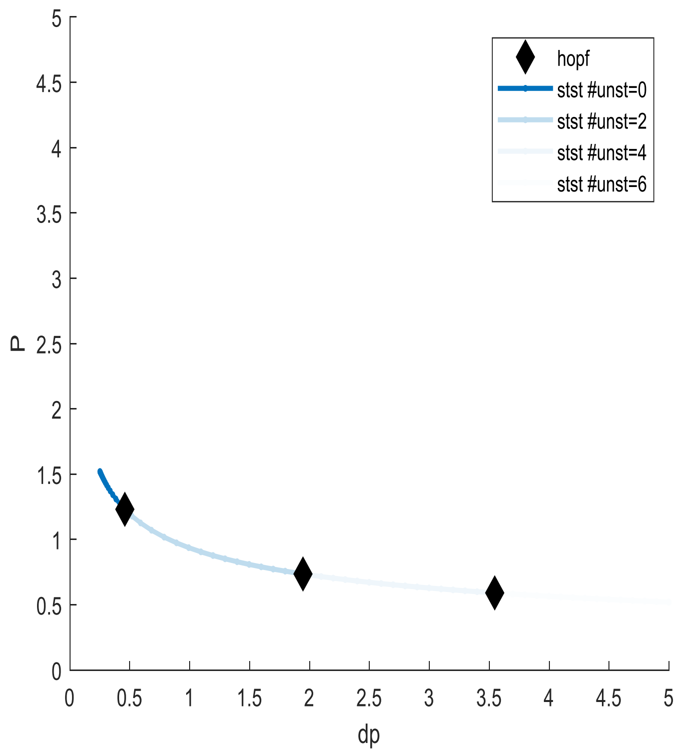

Fig. 1 Bifurcation diagram dp versus P showing three Hopf bifurcation points

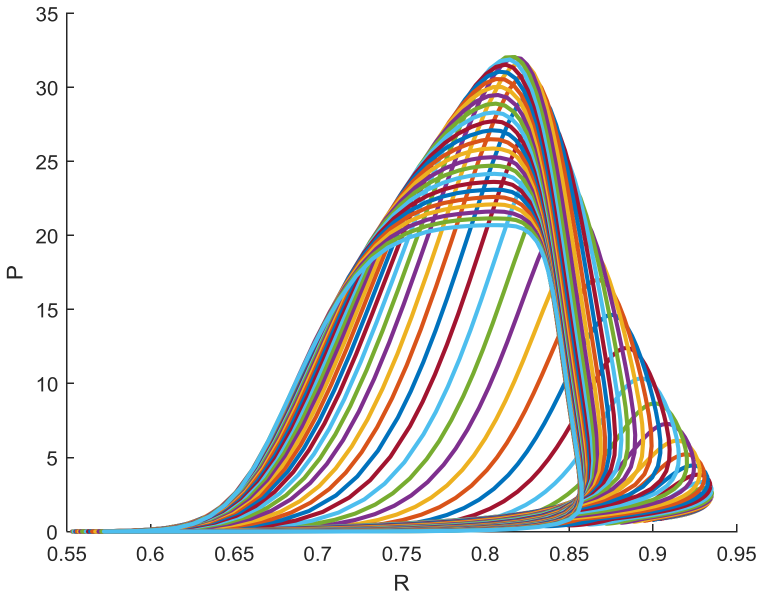

Fig. 2 Limit Cycle for the first Hopf bifurcation Point

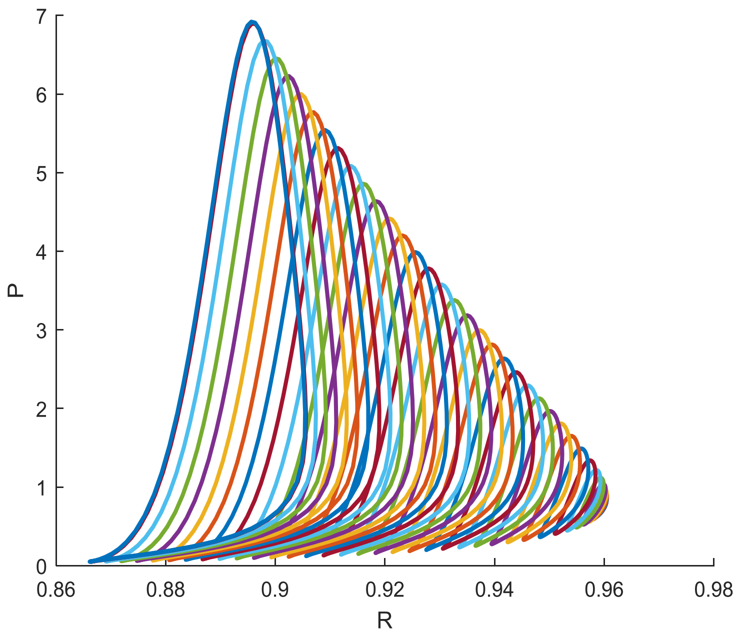

Fig. 3 Limit Cycle for the second Hopf bifurcation Point

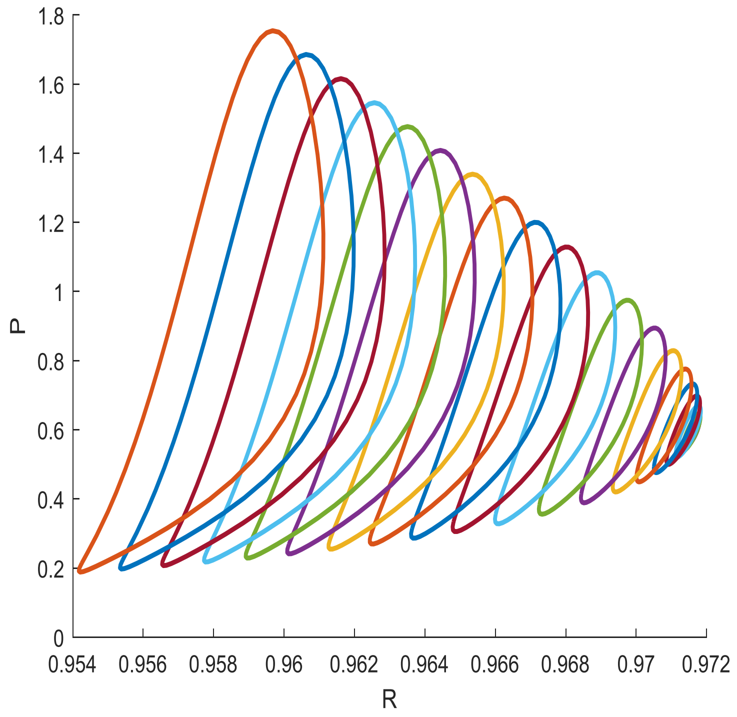

Fig.4 Limit Cycle for the third Hopf bifurcation Point

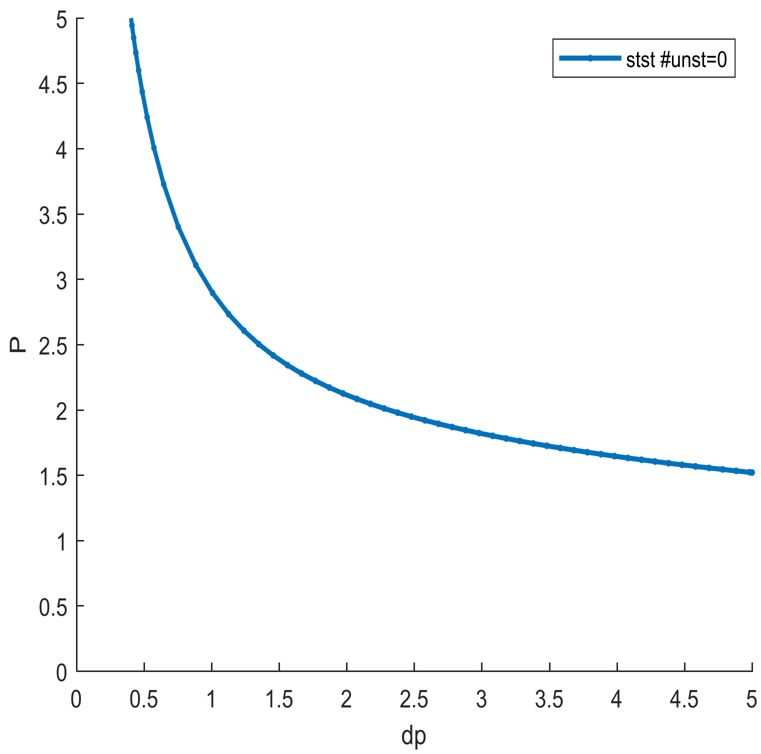

Fig. 5 Hopf Bifurcation points disappear when dp is modified to dpTanh(p)/20

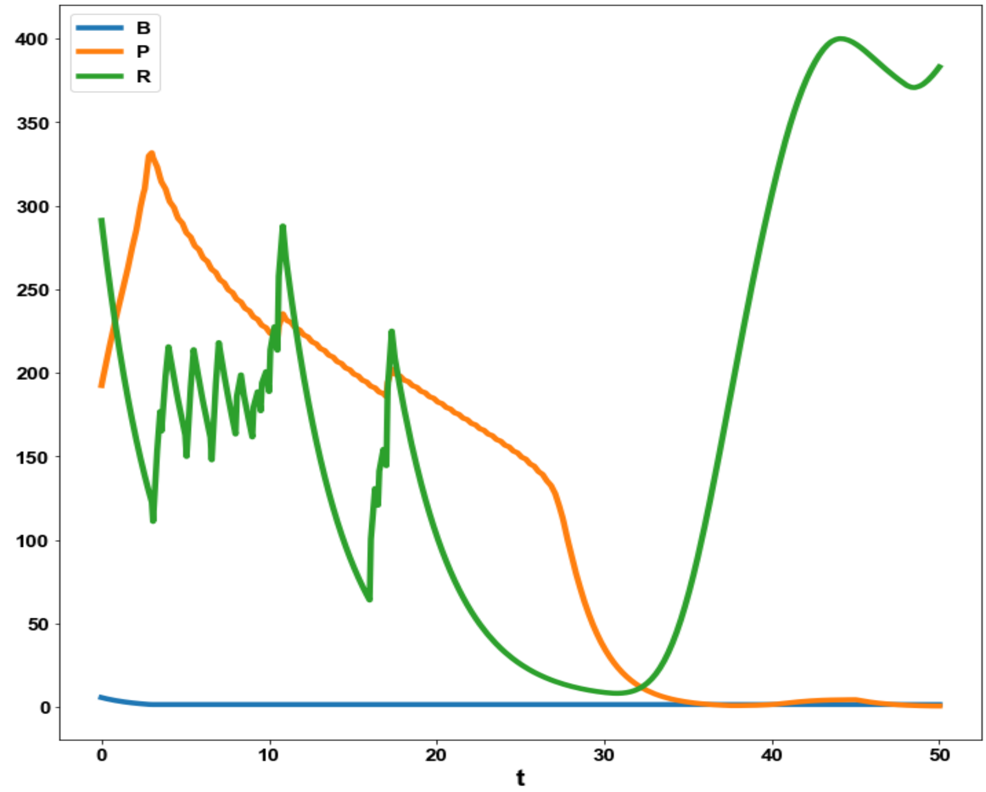

Fig. 6 The MNLMPC profiles of B P and R

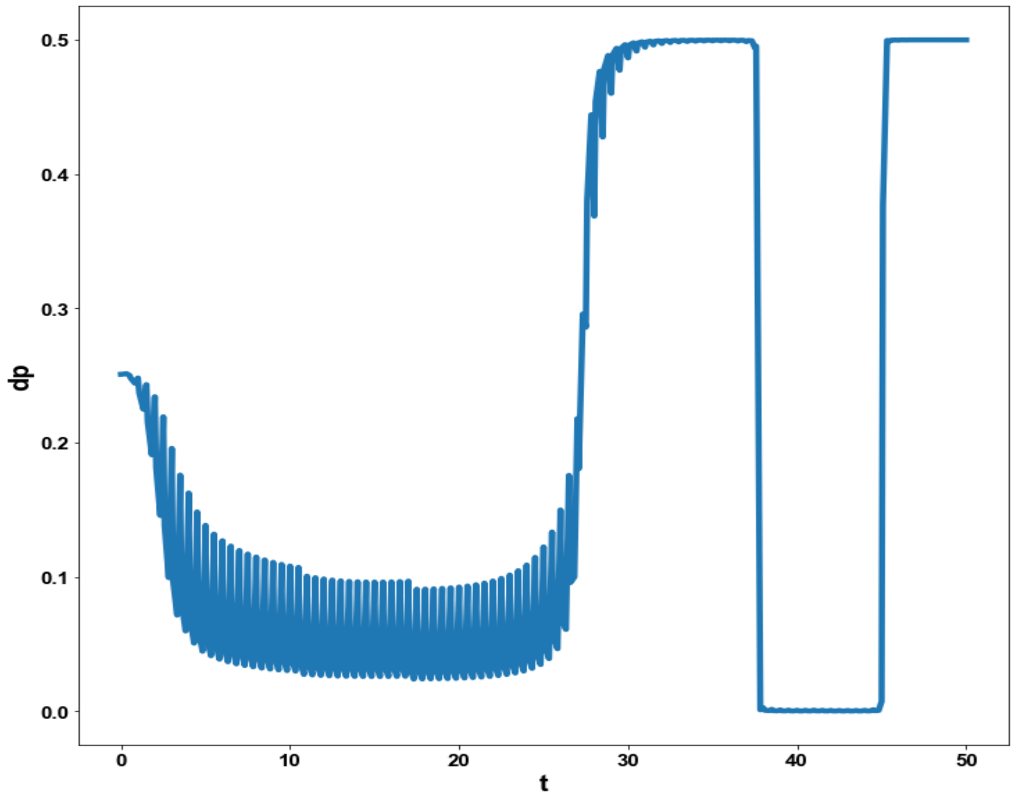

Fig. 7 dp versus R for MNLMPC calculations indicating “noise”

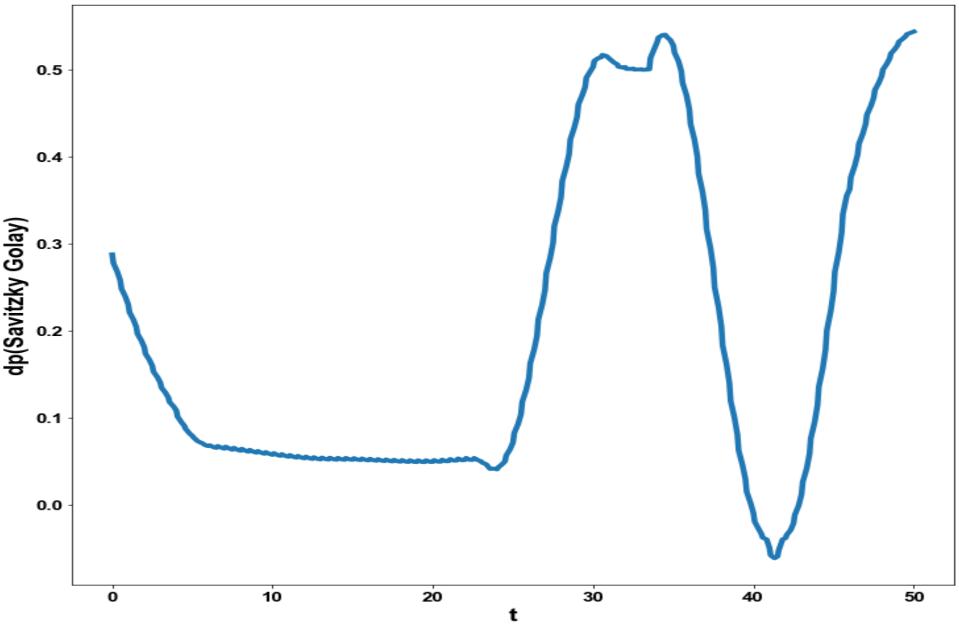

Fig. 8 dp versus R for MNLMPC calculations noise removed with Savitsky Golay Filter