On Muldowney's Criteria for Polynomial Vector Fields with Constraints

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Abstract. We study Muldowney's extension of the classical Bendixson-Dulac criterion for excluding periodic orbits to higher dimensions for polynomial vector fields. Using the formulation of Muldowney's sufficient criteria for excluding periodic orbits of the parameterized vector field on a convex set as a quantifier elimination problem over the ordered field of the reals we provide case studies of some systems arising in the life sciences. We discuss the use of simple conservation constraints and the use of parametric constraints for describing simple convex polytopes on which periodic orbits can be excluded by Muldowney's criteria.

1 Introduction and Preliminaries

In the study of ordinary differential equations the analysis of periodic trajectories is seen as an important goal in addition to describing the dynamics around fixed points. However, already for two-dimensional polynomial systems this question is related to Hilbert's 16th problem, which is still unsolved [1].

For the two-dimensional case the Bendixson-Dulac criterion gives a sufficient condition for the non-existence of periodic orbits. This criterion is parameterized by a Dulac function, and various techniques have been proposed to construct Dulac functions, which range form algebraic constructions for special systems to techniques involving the solution of certain partial differential equations [2–6].

For the higher-dimensional case there are extensions of the criterion of Bendixson-Dulac that also allow the use of Dulac functions [7]. However, little work seems to have been done to construct Dulac functions in the higher dimensional cases—except for addressing it as a problem [8, 9].

Moreover, the common case of algebraic constraints in the simple form of conservation constraints have been used in ad hoc form by many authors—mainly to reduce 3D systems to 2D systems to be able to use the classical Bendixson-Dulac criterion—but have not been discussed in a more general setting.

In case studies of some systems arising in the life sciences we discuss the use of simple conservation constraints in a first line of investigation.

On the example of classical SIRS epidemiological model we show that even in this rather simple case different algorithmic strategies to use conservation constraints might lead to non-conclusive results for some, whereas others lead to conclusive results. Thus the fact that Muldowney's criteria are not coordinate independent pose an algorithmic problem.

In a second line of investigation we discuss the use of parametric constraints for describing simple convex polytopes on which periodic orbits can be excluded by Muldowney's criteria. We will show that for a 3-dimensional model of viral dynamics [10], for which Muldwowney's criteria cannot exclude the existence of periodic orbits on the entire positive real octant, there is a cuboid on which periodic orbits can be excluded.

1.1 The Bendixson-Dulac criterion for 2-dimensional vector fields

Consider an autonomous planar vector field

$$\frac{dx}{dt} = F(x,y), \qquad \frac{dy}{dt} = G(x,y), \qquad (x,y) \in \mathbb{R}^2.$$

Bendixson in 1901 [11] was the first to give a criterion yielding sufficient conditions for excluding oscillations. Dulac in 1937 [12] was able to generalize the result of Bendixson as follows:

Theorem 1 (Bendixson-Dulac criterion). *Let $B(x,y)$ be a scalar continuously differentiable function defined on a simply connected region $D \subset \mathbb{R}^2$ with no holes in it. If $\frac{\partial(BF)}{\partial x} + \frac{\partial(BG)}{\partial y}$ is not identically zero and does not change sign in D, then there are no periodic orbits lying entirely in D.*

For a modern proof we refer to [13, Theorem 1.8.2].

A common class of Dulac functions uses $B(x,y) = \mathrm{e}^{(U(x,y))}$, see e.g. [3]. By the chain rule the exponential function can be factored out yielding $\mathrm{e}^U \left(\frac{\partial U}{\partial x} F + \frac{\partial U}{\partial y} G + \frac{\partial F}{\partial x} + \frac{\partial G}{\partial y} \right)$. Hence, if F, G, $\frac{\partial U}{\partial x}$, and $\frac{\partial U}{\partial y}$ are rational functions, the Bendixson-Dulac criterion remains in the realm of the ordered field of the reals.

1.2 Muldowney's Extensions of the Bendixson-Dulac Criterion to Higher Dimensions

The algorithmic criteria discussed in the following can be seen as generalizations of the Bendixson-Dulac criterion for 2-dimensional vector fields to arbitrary dimensions.

The following theorem was proved by Muldowney [7, Theorem 4.1]: Suppose that one of the inequalities

$$\mu\left(\frac{\partial f^{[2]}}{\partial x}\right) < 0, \qquad \mu\left(-\frac{\partial f^{[2]}}{\partial x}\right) < 0 \tag{1}$$

holds for all $x \in \mathbb{R}^n$. Then the autonomous system with vector field $f : \mathbb{R}^n \longrightarrow \mathbb{R}^n$ has no nonconstant periodic solutions. Here μ is some Lozinskiĭ norm and $f^{[2]}$ is one of the "compound matrices" of the Jacobian of the vector field f defined in [7]. As is also shown in [7] the criterion given in [7, Theorem 4.1] also holds when $x \in C$, where $C \subseteq \mathbb{R}^n$ is open and convex.

Remark. When $n = 2, \partial f^{[2]}/\partial x = \operatorname{Trace} \partial f/\partial x = \operatorname{div} f$, so that [7, Theorem 4.1] basically yield the results of Bendixson, i.e. the criterion of Muldowney can be seen as a generalization of the criterion of Bendixson from the planar case to arbitrary dimensions.

According to [7, (2.2)], the following expressions may be used as $\mu\left(\partial f^{[2]}/\partial x\right)$ in [7, Theorem 4.1], if the underlying norms for μ are the 1-norm, ∞-norm, and 2-norm respectively:

$$\max\left\{ \frac{\partial f_r}{\partial x_r} + \frac{\partial f_s}{\partial x_s} + \sum_{q \neq r,s} \left|\frac{\partial f_q}{\partial x_r}\right| + \left|\frac{\partial f_q}{\partial x_s}\right| \;:\; r,s = 1,\dots,n,\; r \neq s \right\}, \tag{2}$$

$$\max\left\{ \frac{\partial f_r}{\partial x_r} + \frac{\partial f_s}{\partial x_s} + \sum_{q \neq r,s} \left|\frac{\partial f_r}{\partial x_q}\right| + \left|\frac{\partial f_s}{\partial x_q}\right| \;:\; r,s = 1,\dots,n,\; r \neq s \right\}. \tag{3}$$

$$\lambda_1 + \lambda_2, \tag{4}$$

where λ_1, λ_2 are the two largest eigenvalues of $\left(\partial f^*/\partial x + \partial f/\partial x\right)/2$.

Thus for a formula Γ over the reals defining an open convex subset C of $\mathbb{R}^n$ and an autonomous polynomial vector field $f : \mathbb{R}^n \to \mathbb{R}^n$ a first-order formula φ over the ordered field of the reals defines a sufficient condition such that the vector field defined by f has no non-constant periodic solution on C. As usual with real quantifier elimination we use the language of ordered rings. In addition, we admit function symbols for the maximum and for the absolute values, which are both definable.

Specifically, for the criterion involving the 1-norm we obtain

$$\varphi_1 \equiv \forall x_1 \forall x_2 \cdots \forall x_n \Bigg(\Gamma \Longrightarrow \max\left\{ \frac{\partial f_r}{\partial x_r} + \frac{\partial f_s}{\partial x_s} + \sum_{q \neq r,s} \left|\frac{\partial f_q}{\partial x_r}\right| + \left|\frac{\partial f_q}{\partial x_s}\right| \;:\; r,s = 1,\dots,n,\; r \neq s \right\} < 0 \Bigg), \tag{5}$$

and for the criterion involving the ∞-norm we obtain

$$\varphi_\infty \equiv \forall x_1 \forall x_2 \cdots \forall x_n \Bigg(\Gamma \Longrightarrow \max\left\{ \frac{\partial f_r}{\partial x_r} + \frac{\partial f_s}{\partial x_s} + \sum_{q \neq r,s} \left|\frac{\partial f_r}{\partial x_q}\right| + \left|\frac{\partial f_s}{\partial x_q}\right| \;:\; r,s = 1,\dots,n,\; r \neq s \right\} < 0 \Bigg). \tag{6}$$

In [8] the problem of efficient automatic resolution of maxima and absolute values is addressed and computation examples are given. If all variables and parameters are known to be positive, the technique of *positive quantifier elimination* [14, 15] can be used, which was first used to solve semi-algebraic criteria for the existence of Hopf bifurcation fixed points [16, 17] arising in the context of chemistry and algebraic biology [18–21].

Extending Muldowney's criteria with Dulac functions. Although a simple generalization of the Dulac criterion to higher dimensions does not seem to hold in the general setting [7], for *positive* functions $0 < r \in C^1(\mathbb{R}^n \longrightarrow \mathbb{R})$ one can replace f by rf in [7, Theorem 4.1], cf. (1). The rather simple proof is given in [7, Remark (d)].

If $B = \mathrm{e}^U$ is used as a Dulac test function then by the chain rule the exponential function can be factored out also for Muldowney's criteria and the criterion remains in the realm of the ordered field of the reals, if all partial derivatives of U are rational functions.

Using conservation constraints. Any algebraic constraints on the vector field can be transferred into the first-order formula over the ordered field of the reals expressing Muldowney's criteria. Simple conservation constraints stating that the sum of certain state variables is constant—conditions that are commonly found in chemical reaction systems or in epidemiological models—will not induce a failure of the degree limited virtual substitution methods [22] for quantifier elimination, if these were successful on the unconstrained system.

Nevertheless, an elimination of a variable by the others in a conservation constrained will reduce the dimension of the system and thus change Muldowney's criteria instead of adding another equality to Muldowney's criteria on the original system. We will report on the results of some systematic tests on the simple SIRS system in Sect. 2.1.

Parametric specification of a convex subset. The first-order formula γ specifying the convex subset on which a proof for the non-existence of periodic orbits is sought by Muldowney's criteria can very well contain parameters, too. The quantifier elimination procedure automatically yields conditions on the parameters that are exact with respect to Muldowney's criteria—potentially not mentioning input parameters if no constraint on any of them is necessary.

In Sect. 2.3 we will use this technique using simple parametric cuboids in a case, for which the Muldowney criteria do not give a conclusive answer on the entire positive real octant, but the specification of a 3-dimensional parametric cuboid shows that only a parametric restriction on one variable is necessary.

2 Case Studies

2.1 The SIRS epidemiological model

We consider the widely used SIRS epidemiological model, a parameterized formally 3-dimensional system of ordinary differential equations, cf. (7–9). The systems is widely used and well studied [23–27]. So we will not provide new insights into the structure of the system, but it is well suited as a test object for our algorithmic methods.

To account for the lost of immunity, the classical susceptible (S), infected (I) and recovered (R) model is adjusted by allowing a fraction of the recovered individuals R to move back into the susceptible pool S at a rate γ. This susceptible, infected, recovered and susceptible (SIRS) model is expressed as

$$\frac{d}{dt}S(t) = \mu\,(S(t) + I(t) + R(t)) - \mu\,S(t) - \beta\,S(t)\,I(t) + \gamma\,R(t) \tag{7}$$

$$\frac{d}{dt}I(t) = \beta\,S(t)\,I(t) - (\mu + \nu)\,I(t) \tag{8}$$

$$\frac{d}{dt}R(t) = \nu\,I(t) - (\mu + \gamma)\,R(t) \tag{9}$$

where ν is the rate of loss of infectiousness and the total population size N remains constant (i.e. $S + I + R = N$ is constant). The parameter μ represents both, the birth and mortality rates. Assuming that birth and mortality rates are equal is justified on the grounds that the annual infection rate is considerably higher than the population growth. The parameter β is the transmission rate of the infection.

Using ad-hoc reductions to 2D-models In the literature, reductions to 2D models using $S + I + R = N$ and replacing a suitable variable are commonly used. However, the question, which variable to choose is never addressed. In the following we give results for all possibilities showing that even for this simple example the results strongly differ. In all cases we use the scaling $N = 1$.

Eliminating R by $R = 1-(I+S)$. In this case the criterion using the Dulac test function 1 returned the non-conclusive *true* as answer for $\neg\varphi$. However, using the Dulac function $\frac{1}{I(t)}$ the conclusive *false* as answer for $\neg\varphi$ was found within some milliseconds of computation time by REDLOG.

Eliminating I by $I = 1 - (S + R)$. Also in this case the criterion using the Dulac test function 1 returned the non-conclusive *true* as answer for $\neg\varphi$. We also obtained the the non-conclusive *true* as answer for $\neg\varphi$ when using the following Dulac test functions:

$$\frac{1}{R(t)S(t)}$$
$$\frac{1}{S(t)}$$
$$\frac{1}{R(t)}$$
$$R(t)$$
$$S(t)$$

Moreover, the computations using REDLOG did not come up with answers within 60 sec of computation time for several other Dulac test functions.

So using this elimination we did not come up with a conclusive answer by the Muldowney criteria.

Eliminating S by $S = 1 - (I + R)$. In this case the criterion using the Dulac function 1 returned $\beta - \gamma - 2\mu - \nu > 0$ as answer for $\neg\varphi$. Using the Dulac function $\frac{1}{I(t)}$ returned the conclusive *false*, as was the case for the Dulac function $\frac{1}{I(t)R(t)}$; for the Dulac function $\frac{1}{R(t)}$ the criterion returned $\beta - \mu - \nu > 0$. As the conclusive *false* was found for some Dulac function, we thus have proved that the SIRS system does not have periodic orbits on the positive real octant.

2.2 Computations on the 3D model

Unconstrained model. For the 3D-SIRS model *not* using any conservation constraint the criterion using the Dulac test function 1 returned the non-conclusive *true* as answer for $\neg\varphi$. For all other Dulac tests functions we used we either obtained the non-conclusive *true* as answer for $\neg\varphi$, or REDLOG could not come up with a result within 60 sec of computation time.

Using the constraint $S + I + R = 1$. When adding the equation $S + I + R = 1$ to the input formula for the Muldowney criterion, we obtained for the Dulac test function the following formula as result for $\neg\varphi$:

2.3 A model of viral dynamics

The following example is discussed in more depth in [8]. It consists of a simple mathematical model for the population dynamics of the human immunodefficiency type 1 virus (HIV-1) investigated in [10]. There a three-component model is described involving uninfected CD4 + T-cells, infected such cells and free viruses, whose densities at time t are denoted by $x(t), y(t), v(t)$, respectively.

$$\frac{d}{dt}x(t) = s - \mu\, x(t) - kx(t)\, y(t)$$
$$\frac{d}{dt}y(t) = kx(t)\, y(t) - \alpha\, y(t)$$

$$\frac{d}{dt}x(t) = s - \mu\, x(t) - \beta\, x(t)\, v(t)$$
$$\frac{d}{dt}y(t) = \beta\, x(t)\, v(t) - \alpha\, y(t)$$
$$\frac{d}{dt}v(t) = cy(t) - \gamma\, v(t)$$

Fig. 1. The 2D- and 3D-Tuckwell-Wan examples

In [10] a simplified two-component model employed by Bonhoeffer et al. [28] is investigated analytically. In [10] using the general Bendixson-Dulac criteria for 2D-vector fields with an ad hoc Dulac function $B(x, y) = 1/y$ it is shown that there are no periodic solutions for the system for positive parameter values and positive values of the state variables, i.e. the biologically relevant ones.

Remark. By "ad hoc" Dulac function we mean that the authors provide this function only and show that it is a Dulac function, but no other functions. No explanations or hints are given to the reader how this function was obtained.

In Table 1 the results for various low-degree rational and polynomial Dulac test functions are summarized. Notice that computation times for generating the formulas are negligible for these examples. Note that for $\neg\varphi$ the answer **false** gives the conclusive proof on the non-existence of periodic orbits on the positive cone.

As can be seen from the computation times given in Table 1 the quantifier elimination problems are not too hard. When performing tests with QEPCAD B [29] we could also solve all of these quantifier elimination problems in less than one second of computation time.

Table 1. Computation Results for the 2D-Tuckwall-Wan example (cf. Fig. 1) on the full positive octant

The computation times are the ones for the positive quantifier elimination in REDLOG.

Tuckwell-Wan 2D model	Used Dulac test function 1	$\frac{1}{x}$	$\frac{1}{y}$	$\frac{1}{xy}$	$\frac{1}{x+y}$	x	y	xy
Comp. Time [sec]	0.07	0.07	0.02	0.02	0.07	0.09	0.07	0.07
Result ($\neg\varphi$)	pc	pc	**false**	**false**	pc	pc	pc	pc

Here pc is the positivity condition on the parameters.

For the 3D-Tuckwell-Wan Model we tried several Dulac test functions but could not exclude the existence of a periodic orbit on $\mathbb{R}^{+3}$ for any of them. When specifying the parametric cube $(0, u_x) \times (0, u_y) \times (0, u_v)$ by adding the conditions $x(t) < u_x$, $y(t) < u_y$, and $v(t) < u_v$ for new parameters $u_x > 0$, $u_y > 0$, and $u_v > 0$—cf. Sect. 1.2—and using the trivial Dulac function 1—we obtain the following first-order formula for $\neg\varphi$ using Muldowney's criterion for the 1-norm (displayed in slightly hand edited form for better readability):

$$\begin{aligned}
&\exists v_1 \exists v_2 \exists v_3 : 0 < v_1 \wedge 0 < v_2 \wedge 0 < v_3 \wedge 0 < u_v \wedge 0 < u_x \wedge 0 < u_y \wedge \\
&\quad 0 < c \wedge 0 < \mu \wedge 0 < s \wedge 0 < \alpha \wedge 0 < \beta \wedge 0 < \gamma \wedge \\
&\quad v_1 < u_v \wedge v_2 < u_x \wedge v_3 < u_y \wedge \\
&\quad 0 \le \max(-\gamma - \alpha + |\beta v_2|, -\mu - \beta v_1 - \alpha + |c|, -\gamma - \mu - \beta v_1 + |\beta v_2| + |\beta v_1|)
\end{aligned}$$

This quantifier elimination problem can also be solved "by hand" rather easily, and accordingly in less than 0.1 sec of computation time we obtain by the positive quantifier elimination procedure of REDLOG the following quantifier-free equivalent for φ:

$$\min\left(\frac{\alpha+\gamma}{\beta}, \frac{\mu+\gamma}{\beta}\right) \ge u_x \wedge \alpha + \mu \ge c \tag{10}$$

For better readability we have provided in (10) a slightly hand-edited version of the result formula.

Notice that there is no dependency on u_y and u_v, i. e. we have given a proof that the parametric 3D-Tuckwall-Wan does not have periodic orbits on

$$(0, u_x) \times (0, \infty) \times (0, \infty)$$

provided u_x (and $\alpha, \mu, \gamma, \beta$) fulfills the condition given in (10).

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References

1. Ilyashenko, Y.: Centennial history of Hilbert's 16th Problem. Bull. Am. Math. Soc., New Ser. **39**(3) (2002) 301–354
2. Osuna, O., Villaseñor, G.: On the Dulac functions. Qualitative Theory of Dynamical Systems (2011) 1–7
3. Cherkas, L., Grin, A.: On a Dulac function for the Kukles system. Differential Equations **46** (2010) 818–826
4. Cherkas, L.: Quadratic systems with maximum number of limit cycles. Differential Equations **45** (2009) 1440–1450 10.1134/S0012266109100061.
5. Cherkas, L.A., Grin, A.: Algebraic aspects of finding a Dulac function for polynomial autonomous systems on the plane. Differential Equations **37** (2001) 411–417
6. Cherkas, L.A.: Dulac function for polynomial autonomous systems on a plane. Differential Equations **33** (1997) 692–701
7. Muldowney, J.S.: Compound matrices and ordinary differential equations. Rocky Mt. J. Math. **20**(4) (1990) 857–872
8. Weber, A., Sturm, T., Abdel-Rahman, E.O.: Algorithmic global criteria for excluding oscillations. Bulletin of Mathematical Biology **73**(4) (2011) 899–917
9. Weber, A., Sturm, T., Seiler, W.M., Abdel-Rahman, E.O.: Parametric qualitative analysis of ordinary differential equations: Computer algebra methods for excluding oscillations (extended abstract) (invited talk). In Gerdt, V.P., Koepf, W., Mayr, E.W., Vorozhtsov, E.V., eds.: Computer Algebra in Scientific Computing – 12th International Workshop (CASC 2010). Volume 6244 of Lecture Notes in Computer Science., Springer-Verlag (September 2010) 267–279
10. Tuckwell, H.C., Wan, F.Y.M.: On the behavior of solutions in viral dynamical models. BioSystems **73**(3) (2004) 157–161
11. Bendixson, I.: Sur les curbes définiés par des équations différentielles. Acta Math. **24** (1901) 1–88
12. Dulac, H.: Recherche des cycles limites. CR Acad. Sci. Paris **204** (1937) 1703–1706
13. Guckenheimer, J., Holmes, P.: Nonlinear Oscillations, Dynamical Systems, and Bifurcations of Vector Fields. Volume 42 of Applied Mathematical Sciences. Springer-Verlag (1983)
14. Sturm, T., Weber, A.: Investigating generic methods to solve Hopf bifurcation problems in algebraic biology. In Horimoto, K., Regensburger, G., Rosenkranz, M., Yoshida, H., eds.: Algebraic Biology – Third International Conference (AB 2008). Volume 5147 of Lecture Notes in Computer Science., Castle of Hagenberg, Austria, Springer-Verlag (2008)

15. Sturm, T., Weber, A., Abdel-Rahman, E.O., El Kahoui, M.: Investigating algebraic and logical algorithms to solve Hopf bifurcation problems in algebraic biology. Mathematics in Computer Science **2**(3) (March 2009) 493–515 Special issue on 'Symbolic Computation in Biology'.
16. El Kahoui, M., Weber, A.: Deciding Hopf bifurcations by quantifier elimination in a software-component architecture. Journal of Symbolic Computation **30**(2) (August 2000) 161–179
17. Weber, A.: Quantifier elimination on real closed fields and differential equations. In Löwe, B., ed.: Algebra, Logic, Set Theory – Festschrift für Ulrich Felgner zum 65. Geburtstag. Volume 4 of Studies in Logic. College Publications (2007) 291–315
18. Boulier, F., Lefranc, M., Lemaire, F., Morant, P.E.: Applying a rigorous quasi-steady state approximation method for proving the absence of oscillations in models of genetic circuits. In Horimoto, K., Regensburger, G., Rosenkranz, M., Yoshida, H., eds.: Algebraic Biology (AB 2008) – Third International Conference. Volume 5147 of Lecture Notes in Computer Science., Castle of Hagenberg, Austria, Springer-Verlag (August 2008) 56–64
19. Boulier, F., Lefranc, M., Lemaire, F., Morant, P., Ürgüplü, A.: On proving the absence of oscillations in models of genetic circuits. In Anai, H., Horimoto, H., Kutsia, T., eds.: Algebraic Biology (AB 2007). Volume 4545 of Lecture Notes in Computer Science., Castle of Hagenberg, Austria, Springer-Verlag (2007) 66–80
20. Gatermann, K., Eiswirth, M., Sensse, A.: Toric ideals and graph theory to analyze Hopf bifurcations in mass action systems. Journal of Symbolic Computation **40**(6) (2005) 1361–1382
21. Niu, W., Wang, D.: Algebraic approaches to stability analysis of biological systems. Mathematics in Computer Science **1**(3) (2008) 507–539
22. Weispfenning, V.: Quantifier elimination for real algebra—the quadratic case and beyond. Applicable Algebra in Engineering Communication and Computing **8**(2) (February 1997) 85–101
23. Lin, X.D., van den Driessche, P.: A threshold result for an epidemiological model. Journal of Mathematical Biology **30**(6) (1992) 647–654
24. Hadeler, K.P., van den Driessche, P.: Backward bifurcation in epidemic control. Mathematical Biosciences **146**(1) (1997) 15–35
25. Weber, A., Weber, M., Milligan, P.: Modeling epidemics caused by respiratory syncytial virus (RSV). Mathematical Biosciences **172**(2) (September 2001) 95–113
26. Brown, C.W., El Kahoui, M., Novotni, D., Weber, A.: Algorithmic methods for investigating equilibria in epidemic modeling. Journal of Symbolic Computation **41**(11) (2006) 1157–1173 Special Issue on the Occasion of Volker Weispfenning's 60th Birthday.
27. Ponciano, J.M., Capistrán, M.A.: First principles modeling of nonlinear incidence rates in seasonal epidemics. PLoS Computational Biology **7**(2) (2011) e1001079
28. Bonhoeffer, S., Coffin, J.M., Nowak, M.A.: Human immunodeficiency virus drug therapy and virus load. The Journal of Virology **71**(4) (1997) 3275
29. Brown, C.W.: QEPCAD B: A system for computing with semi-algebraic sets via cylindrical algebraic decomposition. ACM SIGSAM Bulletin **38**(1) (2004) 23–24