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Algorithmic methods for investigating equilibria in epidemic modeling

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Abstract

The calculation of threshold conditions for models of infectious diseases is of central importance for developing vaccination policies. These models are often coupled systems of ordinary differential equations, in which case the computation of threshold conditions can be reduced to the question of stability of the disease-free equilibrium. This paper shows how computing threshold conditions for such models can be done fully algorithmically using quantifier elimination for real closed fields and related simplification methods for quantifier-free formulas. Using efficient quantifier elimination techniques for special cases that have been developed by Weispfenning and others, we can also compute whether there are ranges of parameters for which sub-threshold endemic equilibria exist.

Keywords: Quantifier elimination; Ordinary differential equations thresholds

1. Introduction

Here at the beginning of the 21st century, infectious diseases are still major mortality factors in developing countries. In the past few decades several previously unknown infectious diseases like AIDS, Hepatitis C and E, Lyme disease, Legionnaires' disease, Ebola hemorrhagic fever

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etc. have emerged, and known diseases have re-emerged, e.g. Yellow Fever, rabies, tuberculosis etc. Some of these diseases play an important role as mortality and morbidity factors even in developed countries. Therefore modeling epidemics of infectious diseases is important for public health programs, especially for planning vaccinations.

One important problem regarding these models is the computation of *threshold conditions*, conditions on the parameters defining the models that tell us when certain kinds of qualitative behavior are present. In the epidemiological community, these calculations, which are inherently symbolic, have been done by hand—often quite laboriously. In this paper we show how sophisticated tools from computer algebra, notably quantifier elimination and simplification for formulas over the real numbers, can be used to compute threshold conditions completely algorithmically. This presents the possibility of allowing epidemiologists to easily experiment with new models or with modifications of existing models by freeing them from difficult and error-prone calculations. We apply these methods to successfully compute threshold conditions for several models from the epidemiological literature. We also present a few examples showing the shortcomings of current quantifier elimination and simplification tools, and examine improvements in these methods that would allow such examples to be solved.

1.1. Epidemiological background

Epidemics are typically modeled by systems of ordinary differential equations. Examples are SEIR models (Earn et al., 2000; Olsen and Schaffer, 1990), which are frequently used to model measles epidemics, models considering reinfections such as SIS models (Kribs-Zaleta and Velasco-Hernandez, 2000), SIRS models (Lin and van den Driessche, 1992; Hadeler and van den Driessche, 1997; Weber et al., 2001), SEIRS models (Liu and van den Driessche, 1995), MSEIRS4 models (Weber et al., 2001), or models taking into account the effects of treatments (van den Driessche and Watmough, 2002; Blower et al., 1996) such as SEIT models (van den Driessche and Watmough, 2002). These models incorporate disease specific characteristics into the model while staying in the realm of ordinary differential equations by dividing the population into different groups in their relation to various stages of infectiousness, immunity, susceptibility, behavior, etc. (Anderson and May, 1992; Diekmann and Heesterbeek, 2000; Hethcote, 2000; van den Driessche and Watmough, 2002). Several of these models are examined in this paper, and descriptions of them can be found in Appendix A.

While the above models incorporate a priori medical knowledge on the specific disease, they are strong simplifications. Justification for them is then obtained a posteriori: the simple models – often involving only 3 or 4 variables – are good if they can reproduce the complex dynamics of epidemic outbreaks. As non-linear dynamical systems can be complex, such a justification has been found in several cases (Earn et al., 2000; May, 2000).

Epidemiological models involve many parameters, such as the rate of loss of immunity or parameters describing how infections are transmitted, that differ for specific diseases, locations or populations. Estimating these model parameters falls in the realm of numeric techniques (Kalivianakis et al., 1994; Novotni and Weber, 2003). However, there is also a very important kind of calculation involving these parameters that is best formulated as a symbolic problem, namely the computation of *threshold conditions*. Threshold conditions are conditions that the parameters must satisfy in order for the model to exhibit certain kinds of qualitative behaviors. The most important qualitative question is whether a disease present in a population will die out eventually or reach an endemic stage in which it is always remain present in the population. The latter will be the case if the number of secondary infections from each infected individual

exceeds one. This concept, formalized by the *basic reproduction ratio* R_0, is the key concept in the literature behind modeling threshold conditions—see e.g. Diekmann and Heesterbeek (2000), Hethcote (2000) and van den Driessche and Watmough (2002). Since the value of R_0 for a given model is a function of the parameters, R_0 provides a threshold condition on the parameters. As some parameters can be changed by vaccinations or behavior, knowledge of threshold conditions can be very important for public health policy.

1.2. This paper's contribution

Experts in the field have calculated threshold conditions "by hand", either solely by paper and pencil, or in part using computer algebra systems such as Maple or Mathematica as "symbolic calculators". In this paper we will show that by using more advanced techniques of computer algebra – especially quantifier elimination for real closed fields and related techniques of simplifying large quantifier-free formulas over the field of the real numbers – threshold conditions can be computed completely algorithmically from the ODE models of the infectious diseases.

We present two approaches. One is along the lines of previous hand calculations and is basically a local analysis of the disease-free state. In this approach, we ask whether the equilibrium at which the disease is not present is stable. The approach does not involve general purpose quantifier elimination algorithms, but does require the simplification of large formulas over the reals. It is possible that there are multiple equilibria at which the disease is absent. We leave the question of dealing with this situation efficiently for future work.

Our second approach works globally by asking whether there is an *endemic equilibrium*, i.e. an equilibrium at which the disease is present in the population. This approach requires quantifier elimination as well as simplification, but as many of the models used in epidemic modelling are of a quite special form – mostly linear with only some quadratic or higher-order terms – we can use the efficient methods for linear, quadratic and cubic quantifier elimination Weispfenning (1988), Hong (1993) and Weispfenning (1994) as they are implemented in the quantifier elimination package Redlog (Dolzmann and Sturm, 1999).

Comparing the answers to these two problems allows us to decide whether there are *sub-threshold endemic equilibria*, in other words whether the same parameter values produce models in which the disease-free equilibrium is stable and endemic equilibria exist. The analysis of sub-threshold endemic equilibria in the epidemiology community has required a conceptually much more complicated bifurcation analysis at $R_0 = 1$. Moreover, their analysis only involves a neighborhood of the disease-free equilibrium, whereas the approach given here produces global results.

2. Models considered and problems solved

The models of diseases considered in this paper all have a common form. They break the population up into several groups whose characteristics with respect to the disease are different. For each group, there is a variable in the model representing the proportion of the population that falls into that group. The birth and death rates are supposed to be equal, and to be the same for each group. The actual model is an autonomous, generally non-linear, system of ordinary differential equations. We will first consider the simplest possible model of the same form as the examples from the epidemiology literature which we later consider, the SI model given in Fig. 1. The variable S represents the proportion of the population without the disease (the

$$\begin{aligned} \dot{S} &= \mu - \mu S - \beta SI + rI \\ \dot{I} &= \beta SI - rI - \mu I \end{aligned}$$

S	susceptibles
I	infected
β	transmission parameter
μ	birth rate = mortality rate
r	recovery rate

Fig. 1. The SI model, the simplest possible model.

"susceptibles"), and I represents the proportion of the population that is infected with the disease. Notice that if $S + I = 1$ initially, $S + I = 1$ will hold for all time, because the sum of the two equations yields $\dot{S} + \dot{I} = \mu(1 - S - I)$. This property holds for all the models considered.

Terms in this system of differential equations model the transitions from one group to another. Transmission of the disease is modelled with a simple linear mass-action law, βIS, which is the source of the model's non-linearity. The "transmission parameter" β controls the infectiousness of the disease in the model. All parameters in the model are assumed to be positive.

Equilibria of physical significance for models of this type fall into two categories: *disease-free* and *endemic*. To be physically significant, of course, the dependent variables must be non-negative. A disease-free equilibrium is one in which all dependent variables corresponding to the presence of the disease in the population are zero. An endemic equilibrium is one in which there are variables corresponding to the presence of the disease in the population that are non-zero. In the models we consider there is a disease-free equilibrium for every assignment of positive values to parameters, but not necessarily an endemic equilibrium. Our problem is to compute necessary and sufficient conditions on the parameters for (1) the local asymptotic stability of the disease-free equilibrium, and (2) the existence of an endemic equilibrium. We only require conditions that are "generically" correct, meaning that they are allowed to misclassify some points as long as these points comprise a measure-zero subset of the space of positive parameter values, since physical parameters cannot be constrained to a measure-zero set. In the following sections we will propose algorithms solving these two problems, and we will describe their application to four models from the epidemiology literature, which are given in Appendix A.

3. Quantifier elimination and formula simplification

The algorithms presented in this paper make fundamental use of real quantifier elimination and formula simplification. In this section we briefly survey the methods and implementations considered for these problems.

Real quantifier elimination and formula simplification are both concerned with boolean combination of polynomial equalities and inequalities, where variables are assumed to range over the real numbers. Given such a formula, the simplification problem is, of course, to find an equivalent formula that is simpler. When formulas are extended by allowing quantification of variables, we may ask for a particular kind of simplification: quantifier elimination. In the 1930s, Tarski proved that any formula containing quantifiers equivalent to a formula without quantifiers by giving an algorithm to construct a quantifier-free equivalent formula. Many quantifier elimination algorithms have been proposed since.

Redlog and Qepcad (and SLFQ, which is built on top of QepcadB) are the systems providing quantifier elimination and formula simplification[1] that we use in this paper.

[1] Mathematica also provides simplification and quantifier elimination.

Redlog provides quantifier elimination based on virtual term substitution, hermitian quantifier elimination, and quantifier elimination by cylindrical algebraic decomposition. Its simplification facilities employ a variety of techniques, which are described in Dolzmann and Sturm (1997). QepcadB and SLFQ are based on cylindrical algebraic decomposition.

When its degree restrictions allow it to be used, virtual term substitution is generally much faster than CAD-based methods—especially when there are many parameters, as is the case with epidemiological models. However, the quantifier-free formulas it produces are often quite large. In one example described later, Redlog's virtual term substitution produces a quantifier-free equivalent formula comprised of 54 atomic formulas. Simplification of such a result (the formula simplifies to a single inequality, excluding the assumed positivity conditions on parameters) is necessary if it is to be useful. In fact without simplification it is quite difficult to even determine whether the quantifier elimination result agrees with the result in the literature.

CAD-based quantifier elimination is able to produce simple quantifier-free equivalent formulas. However, its time and space complexities are heavily dependent on the number of variables and parameters. In the SEIRS model, the simplest we consider, there are 9 parameters/variables, and straightforward quantifier elimination by CAD turns out to be infeasible. Typically, for these models, it is better to eliminate quantified variables by virtual term substitution rather than CAD.

Simplification of quantifier-free formulas plays a major role both in computing conditions for the stability of the disease-free equilibrium and for computing conditions for the existence of endemic equilibria. However, simplification is a very difficult problem. Indeed, in as much as an unsatisfiable formula should be simplified to false, simplification is at least as hard as deciding fully existentially quantified formulas.

There are two algorithmic techniques that we are aware of for simplification of large quantifier-free formulas, that described in Dolzmann and Sturm (1997) and implemented in Redlog, and that described in Brown (2001) and implemented in the SLFQ system Brown (2002). The goals of the two methods are very different. The former is intended primarily to combat intermediate expression swell during virtual term substitution. As such it needs to be fast. The latter is intended to reduce the size of the formula, in terms of number of irreducible polynomials appearing, as much as possible, regardless of time required to do so. In our application, the results of quantifier elimination or the application of the Routh–Hurwitz condition are simplified for human comprehension, so that it is worth allowing the simplification program to take a long time if the result is a formula that is easier for people to understand. Thus, the approach taken in Brown (2001) and implemented in SLFQ is more appropriate.

4. The disease-free equilibrium stability algorithm

In compartmental ODE models for infectious diseases there is generally an equilibrium for the disease-free state (or states). If this equilibrium is asymptotically stable then a state involving a small number of infected will converge back to this disease-free equilibrium. Investigation of the stability of this disease-free equilibrium was done by the above mentioned "hand calculations", see e.g. Hethcote (2000) and van den Driessche and Watmough (2002) for some recent examples.

As has been previously seen in other contexts the question of stability of an equilibrium point can be reduced to a first-order formula over the ordered field of the real numbers, see e.g. Hong et al. (1997) and El Kahoui and Weber (2000). We refer to these articles for a more precise description of the reduction and the techniques it uses, such as the Routh–Hurwitz criterion.

For studies of equilibria for non-linear control models using quantifier elimination we refer to Jirstrand (1996, 1997).

In this section we describe an algorithm that computes generic necessary and sufficient conditions for the local stability of the disease-free equilibrium.

If we were considering a model with constant coefficients – for example if we fixed values for each parameter in one of our models – we would likely attempt to answer the stability question by applying the Hurwitz test to the characteristic polynomial of the linearized system evaluated at the disease-free equilibrium. This answers the stability question for us as long as the disease-free equilibrium is isolated and the characteristic polynomial has no roots on the imaginary axis, but otherwise we cannot necessarily trust the result. In other words, we cannot just follow the above procedure, we also need a test to validate the procedure's result.

We can try the same approach when coefficients are polynomial functions in the parameters, but we run into some problems. First of all, how do we "evaluate at the disease-free equilibrium"? With parametric coefficients there may not be a disease-free equilibrium, or there may be many, or there may be a unique disease-free equilibrium that can only be expressed using algebraic functions of the parameters. We address this by narrowing our focus to only consider the case in which the disease-free equilibrium is defined by a non-singular linear system. Presently all the models we have considered have this property, though addressing the non-linear case as efficiently is a possible direction for future work if we find interesting models in which it arises. The second problem we run into is more subtle and that is how to deal with the validity test when coefficients are defined parametrically. The algorithm we propose, Algorithm 1, incorporates a validity test that is sufficient, though not necessary, for the generic correctness of the approach described above.

One should note that the result of the Hurwitz test will be a conjunction of polynomial inequalities in the parameters. We expect for these models that it will be a more complicated formula than necessary, especially when assumptions on the parameters (positivity, for example) are taken into account. Therefore, formula simplification is required in order to get a result suitable for human consumption.

Theorem 1. *Suppose Algorithm* 1 *does not return* FAIL. *For all but a measure-zero subset of parameter space, if a point satisfies* $\mathcal{C}$ *then it satisfies the condition returned by Algorithm* 1 *if and only if the system* $\mathcal{S}$ *is stable at the disease-free equilibrium.*

Proof. First, we show that for all parameter values satisfying $\mathcal{C}$ (except for some measure-zero subset of parameter space) the disease-free equilibrium exists and is unique. Step 4 ensures that there is a unique equilibrium in which the variables corresponding to groups in which the disease is present are zero, and Step 5 determines that no variable is negative at this equilibrium point, so that in fact the point is a true disease-free equilibrium. The equilibrium coordinates are expressed as rational functions of the parameters. As long as none of the denominators vanish we have a unique disease-free equilibrium and, of course, the set of points at which some denominator vanishes has measure zero in the space of all parameters.

Second, notice that since FAIL is not returned at Step 3, we are guaranteed that for all but a measure-zero subset of parameter space the equilibria of the system $\mathcal{S}$ are isolated points. Why? Because as long as an assignment of values to parameters doesn't produce a zero denominator in any of the coefficients of elements of G or cause a leading coefficient of an element of G to vanish, G after the substitution is a Gröbner basis for A after the substitution, and the ideal it defines is still 0-dimensional.

Algorithm 1 Conditions for the stability of the disease-free equilibrium.

Input: $\mathcal{S}$ an autonomous system of ordinary differential equations whose coefficients are polynomial in the set of parameters; $\mathcal{C}$ a formula defining the assumed constraints on parameters; V_p, V_a a decomposition of the set of independent variables into those representing groups in which the disease is present and absent, respectively.

Output: A condition on the parameters which is, except for a measure-zero subset of the parameter space, necessary and sufficient for the local stability of the disease-free equilibrium; or FAIL.

1: set A to the algebraic system defined from S by setting all derivatives to zero
2: set G to a Gröbner basis for A in the dependent variables $V_p \cup V_a$
3: if for some $v \in V_p \cup V_a$ no element of G has a pure power of v as its leading power product, return FAIL
4: if the system obtained from S by setting the variables V_p to zero is non-linear or does not have a unique solution return FAIL, otherwise let T be the solution. (This simply involves linear algebra over the field of rational functions in the parameters.)
5: for each $v \in V_a$, using quantifier elimination determine whether the rational function for v in T is positive semi-definite under the assumptions $\mathcal{C}$ (and assuming the non-vanishing of the denominator). If not, return FAIL.
6: set J to the Jacobian of the vector field $\mathcal{S}$
7: in J make assignment T for elements of V_q and assign zero to the elements of V_p, call the result J_b [i.e. evaluate J at the disease-free equilibrium]
8: let $f_1, \ldots, f_k$ be the irreducible factors of the characteristic polynomial of J_b
9: if $\mathrm{res}_y(\mathrm{Re}(f_j(iy)), \mathrm{Im}(f_j(iy))) = 0$ for any $j \in \{1, \ldots, k\}$ return FAIL
10: for $j \in \{1, \ldots, k\}$ set H_i to the Hurwitz condition for f_j
11: Simplify $\bigwedge_{j=1}^{k} H_j$ under the assumption $\mathcal{C}$ and return result

Finally, we notice that if one of the f_j has a root on the imaginary axis for some point α in parameter space, $\mathrm{res}_y(\mathrm{Re}(f_j(iy)), \mathrm{Im}(f_j(iy)))$ is zero at α.[2] The set of such points at which there is a f_j with a root on the imaginary axis has measure zero if none of the resultants computed in Step 9 are zero, which is indeed the case if the algorithm doesn't return FAIL.

Thus, if Algorithm 1 does not return FAIL, on all but a measure-zero subset of parameter space the returned condition evaluated at a point satisfying $\mathcal{C}$ gives the same result one would get from the validated linear analysis of the system $\mathcal{S}$ specialized to that point. □

Of course, if Algorithm 1 simply returned FAIL every time it was called, it would still satisfy Theorem 1. In fact, however, if Algorithm 1 returns FAIL it indicates something either very interesting or very wrong with the epidemiological model being studied. In particular, Algorithm 1 does not return FAIL for any of the examples we have examined.

5. Examples applying Algorithm 1

In this section we follow Algorithm 1 in detail on one example model, and report on its results for the remaining models described in Appendix A. Each step of this algorithm more

[2] We cannot make this "if and only if" because it might be possible that while the resultant is zero, the common solution is a complex number or is a "root at infinity".

or less corresponds to a Maple command or a call to SLFQ or Redlog for simplification. The only exception is the computation of the Hurwitz condition. For this we use existing code from Chauvin, El Kahoui and Weber (http://cg.cs.uni-bonn.de/project-pages/symbolicanalysis/).

The model we follow in detail is the SIS model described in Appendix A. It is the most general of these examples in that the disease-free equilibrium depends on the parameters, which is not the case for the other models. Step 1 of the algorithm constructs A:

$$A = \{\mu - \beta SI - (\mu+\phi)S + cI + \theta V, \beta SI + \sigma\beta VI - (\mu+c)I, \phi S - \sigma\beta VI - (\mu+\theta)V\}.$$

Step 2 produces a Gröbner basis (using total degree order in this case) of four polynomials with leading terms S, $\sigma\beta(\sigma\theta - \mu - \theta + \sigma\mu + \sigma\phi - \phi)V^2$, $\sigma\beta VI$ and $\sigma\beta I^2$, which means the requirements of Step 3 are satisfied and FAIL is not returned. Setting $I = 0$ leaves us with the system $\mu - (\mu+\phi)S + \theta V = \phi S - (\mu+\theta)V = 0$, which is a non-singular linear system. Solving for S and V gives

$$T = \left\{ S = \frac{\mu+\theta}{\phi+\mu+\theta}, V = \frac{\phi}{\phi+\mu+\theta} \right\}.$$

Quantifier elimination shows that the expressions for both S and V are positive definite given the assumptions on the parameters, i.e. that they are all positive. The Jacobian of the system $\mathcal{S}$ is

$$\begin{bmatrix} -\beta I - \mu - \phi & -\beta S + c & \theta \\ \beta I & \beta(S + \sigma V) - \mu - c & \sigma\beta I \\ \phi & -\sigma\beta V & -\sigma\beta I - \mu - \theta \end{bmatrix}$$

which after setting $I = 0$ and applying substitution T yields

$$\begin{bmatrix} -\mu - \phi & -\frac{\beta(\mu+\theta)}{\theta+\mu+\phi} + c & \theta \\ 0 & \beta\left(\frac{\mu+\theta}{\theta+\mu+\phi} + \frac{\sigma\phi}{\theta+\mu+\phi}\right) - \mu - c & 0 \\ \phi & -\frac{\sigma\beta\phi}{\theta+\mu+\phi} & -\mu - \theta \end{bmatrix}.$$

The three irreducible factors of the characteristic polynomial for Jb are $\lambda + \mu$, $\mu + \lambda + \theta + \phi$ and $-\mu\theta - \lambda\theta + \theta\beta - c\theta - \mu^2 + \mu\beta - \phi\mu - \lambda\mu - c\mu - \phi c - \phi\lambda + \sigma\beta\phi$. From the three factors we get stability conditions $\mu > 0$, $\mu + \theta + \phi > 0$ and $(-\mu - \theta - \phi)(-\mu\theta + \mu\beta + \theta\beta - c\theta - \mu^2 - \phi c - \phi\mu + \sigma\beta\phi - c\mu) > 0$, whose conjunction given our positivity conditions simplifies to $-\mu\theta + \mu\beta + \theta\beta - c\theta - \mu^2 - \phi c - \phi\mu + \sigma\beta\phi - c\mu < 0$. As one would hope, this agrees with the result obtained by hand computation in Kribs-Zaleta and Velasco-Hernandez (2000). This example is simple — the CPU time to compute this on a Sun Blade 1500 is less than one second. Simplifying the Hurwitz condition is much easier than expected, because the characteristic polynomial factors into linear factors. In the other models considered this does not happen, so the simplification problem is more substantial.

For the SEIRS model, Algorithm 1 returned $\sigma\beta - \sigma\nu - \mu\nu - \mu\sigma - \mu^2 < 0$ after 0.3 s in Maple and 0.15 s in SLFQ. For the SEIT model, Algorithm 1 returned $\nu\beta_1 - r_2r_1 - dr_1 - r_2\nu q - d\nu - dr_2 - d^2 < 0$ after 0.2 s in Maple and 0.15 s in SLFQ. For the MSEIRS model, Algorithm 1 returned $\sigma\beta - \sigma\nu - \mu\nu - \mu\sigma - \mu^2 < 0$ after 0.35 s in Maple and 0.15 s in SLFQ. These results

agree with those computed by hand in the epidemiological literature. It should be noticed that the SEIRS and MSEIRS models have the same threshold condition. While the MSEIRS model is an extension of the SEIRS model, it is not obvious that they would have the same conditions for the stability of the disease-free equilibrium. Also notice that parameters γ and ξ do not appear in the threshold condition, despite the fact that they do appear in the characteristic polynomial computed in Step 8 of the algorithm.

These threshold conditions are computed quickly primarily because the characteristic polynomial computed in Step 8 factors for all our examples. This is, to some extent, a general property of these models. Because there is a progression from one stage of the disease to the next, as opposed to jumping from one group to another arbitrarily, the Jacobian is close to triangular and the characteristic polynomial factors.

6. Endemic equilibria existence algorithm

For communicable disease models, we expect that disease-free states cannot lead to states in which the disease is present, i.e. someone needs to have the disease in order for it to spread. We expect in these models that the dynamics between the various disease-free states will include equilibria, so that there will always be disease-free equilibria for the models. The situation for endemic equilibria is different — whether or not disease-free equilibria exist depends on the model's parameters. Epidemiologists are interested in knowing for which parameter values they exist and, in particular, whether there are parameter values for which disease-free equilibria are stable and endemic equilibria exist. In this latter case epidemiologists speak of "sub-threshold endemic equilibria" (Hadeler and van den Driessche, 1997; van den Driessche and Watmough, 2002; Kribs-Zaleta and Velasco-Hernandez, 2000). Parameter values for which sub-threshold endemic equilibria exist are particularly relevant for epidemic control.

In this section we will consider the problem of computing necessary and sufficient conditions for the existence of endemic equilibria. Using SLFQ's strong simplification on the conjunction of such a condition with the condition for the stability of the disease-free equilibrium tells us if a model has sub-threshold endemic equilibria and, if so, gives a simple description of the parameter values for which there are sub-threshold endemic equilibria.

Basically, a model given by the system $\mathcal{S}$ has an endemic equilibrium if the algebraic system derived from $\mathcal{S}$ by setting all derivatives to zero has a solution in which each variable is positive. That none of the variables can be zero at an equilibrium corresponding to a state in which the disease is present follows from the form of these models. Thus, the problem of the existence of endemic equilibria becomes a problem about the existence of real solutions to a system of polynomial equations with inequality side constraints. This can be solved by quantifier elimination. Hence, the algorithm for computing conditions on the parameters for the existence of endemic equilibria is essentially an application of quantifier elimination.

The correctness of the above approach, formalized in Algorithm 2, is clear. However, it is not a trivial application of quantifier elimination and simplification because the size of the problems considered is substantial. The SEIT model, for instance, gives rise to a non-linear system in 7 parameters and 4 variables. This is a large problem for current quantifier elimination and simplification algorithms. The performance of Redlog,QepcadB and SLFQ on these problems offers interesting insights into real quantifier elimination and simplification as well as showing the potential of these tools to the subject of epidemiological modelling.

Algorithm 2 Conditions for the existence of endemic equilibria.

Input: $\mathcal{S}$ an autonomous system of ordinary differential equations whose coefficients are polynomial in the set of parameters; $\mathcal{C}$ a formula defining the assumed constraints on parameters; $V = \{v_1, \ldots, v_n\}$ the set of independent variables

Output: A condition on the parameters which is necessary and sufficient for the existence of endemic equilibria.

1: set A to the algebraic system defined from S by setting all derivatives to zero
2: set F to the formula $\exists v_1, \ldots, v_n[A \ \wedge \ v_1 > 0 \wedge \cdots \wedge v_n > 0]$
3: perform quantifier elimination on F under assumption $\mathcal{C}$ and set G to the result
4: simplify G and return result

7. Examples applying Algorithm 2

In this section we apply Algorithm 2 to the four models described in Appendix A. Step 3 of the algorithm states that quantifier elimination is to be performed, but it is important to note that, as there are several different specialized and general quantifier elimination methods available, it is by no means clear cut as to how this is best done. In situations in which it applies, the method of virtual term substitution is generally much faster than CAD-based quantifier elimination. On the other hand, its output formulas are often extremely large. In all four of our examples virtual term substitution does apply, so our first approach is to perform quantifier elimination by virtual term substitution and simplify the result using SLFQ.

For the SEIRS model the input to Redlog is the following:

```
A := mu+gamma*R - mu*S - beta*J*S = 0
     and beta*J*S - (mu+sigma)*F = 0
     and sigma*F - (nu+mu)*J = 0
     and nu*J - (mu+gamma)*R = 0;

F := ex({S,F,J,R}, A and F > 0 and J > 0 and R > 0 and S > 0);

C :={beta > 0, nu > 0, sigma > 0 , gamma > 0, mu > 0};

G := rlqe(F,C);
```

Note that variables E and I, which have special meaning in Reduce, have been replaced with F and J respectively. Redlog computes a quantifier-free equivalent formula G consisting of 25 atomic formulas. Given the assumptions on the parameters, SLFQ simplifies this to $\sigma\beta - \sigma\nu - \mu\nu - \mu\sigma - \mu^2 > 0$ with the following input:

```
slfq -a "beta > 0 /\ nu > 0 /\ sigma > 0 /\ gamma > 0 /\ mu > 0" G
```

The whole process takes less than one second. For the MSEIRS model the situation is more or less the same. Redlog produces a quantifier-free equivalent formula containing 54 atomic formulas. SLFQ simplifies this to $\sigma\beta - \sigma\nu - \mu\nu - \mu\sigma - \mu^2 > 0$, which is in fact the same condition as for the SEIRS model, and the whole process takes less than one second. The fact that, in both cases, the condition for the local stability of the disease-free equilibrium and the existence of an endemic equilibrium partition the space of valid parameters tells us that there are no parameter values that produce sub-threshold endemic equilibrium for these models.

Using Redlog for quantifier elimination and SLFQ for simplification, Algorithm 1 fails on the SEIT model and the SIS model. For the SEIT model, Redlog is unable to produce a

quantifier-free formula in a reasonable amount of time. For the SIS model Redlog produces a quantifier-free formula containing 82 atomic formulas, which SLFQ is unable to simplify in a reasonable amount of time.

8. Learning from failure

It is instructive to look at the problems for which Algorithm 2 failed a bit more deeply in order to gain some insights about possible improvements in quantifier elimination or simplification that might make these calculations feasible.

8.1. The SEIT model

The SEIT model includes seven parameters, cf. Appendix A. It is, in that sense, the largest of the models considered. While Redlog's quantifier elimination failed to eliminate all four variables, the variables E, I and T are easily eliminated by hand, leaving the quantifier elimination problem $\exists S\,[P(S) = 0 \ \wedge \ 0 < S < 1]$ where

$$\begin{aligned} P \ = \ & -\nu S^2\beta_1^2 + \beta_1\nu S^2\beta_2 + d\beta_1 S r_2 - d^2\beta_2 S + d^2\beta_1 S + \beta_1 S r_1 r_2 - d\nu S\beta_2 \\ & + \nu\beta_1 S q r_2 - d\beta_2 r_2 S + d\nu S\beta_1 - \beta_1 S\nu\beta_2 + \beta_1 S r_1 d + \beta_2 d^2 + \nu\beta_2 d + \beta_2 d r_2. \end{aligned}$$

This problem can be solved directly by CAD-based quantifier elimination to produce the simple solution expected. The question is why can one do this easily by hand, and can this kind of preprocessing of input before quantifier elimination algorithms are applied be automated?

The reason that E and I and T can be eliminated by hand is that they appear linearly, so one may solve for I in one equation, for instance, and substitute the solution into the other equations and inequalities, and so on. Denominators do appear in the process, but the positivity conditions on the dependent variables and the assumptions on the parameters guarantee that they are always positive, so no case distinctions are introduced. This "by hand" elimination is, of course, ad hoc. We try solving for one variable in a particular equation, then perhaps try a different equation or a different variable. Furthermore, in doing this by hand, we use the simple conditions, like $T > 0$ to deduce that denominators never vanish, and thus avoid case distinctions.

Situations like this, in which we have a system of equations with side conditions, are not uncommon and, of course, are intrinsic to this application of quantifier elimination. Preprocessing the input by searching for equations that can be solved for one variable, using quantifier elimination on the simple side conditions and parameter restrictions to try and prove that denominators introduced in the process do not vanish, and substituting these solutions into the remaining equations and inequalities is likely to be of benefit in applications like ours regardless of the method of quantifier elimination that is to be used subsequently. What is suggested here differs from what Redlog does with virtual term substitution (according to our understanding), in that we are suggesting a backtracking search approach that tries many different orders of equations and variables, and which aggressively attempts to use quantifier elimination to determine that denominators do not vanish so that multiple branches or cases are not generated. This is in contrast to generating different branches or cases and checking subsequently to see if formulas describing some cases are unsatisfiable. The fundamental idea is that quantifier elimination algorithms do not make good black boxes. Problems must be formulated in intelligent ways in order for the algorithms to be successful in practice. A preprocessor that tries to do some of this automatically would be very useful, and indeed Redlog's powerful formula manipulation and simplification does some of this already. Here we suggest a preprocessing approach that

seems to be particularly well suited to our application, and which may apply more widely as well.

8.2. The SIS model

The result of Redlog's quantifier elimination for the SIS model is the following formula:

```
beta**2*sigma**2 - 2*beta*c*sigma**2 - 2*beta*mu*sigma**2 +
2*beta*mu*sigma + 2* beta*phi*sigma**2 + 2*beta*sigma*theta +
c**2*sigma**2 + 2*c*mu*sigma**2 - 2*c* mu*sigma + 2*c*phi*sigma**2 -
4*c*phi*sigma - 2*c*sigma*theta + mu**2*sigma**2 -
 2*mu**2*sigma + mu**2 + 2*mu*phi*sigma**2 - 2*mu*phi*sigma
 - 2*mu*sigma*theta + 2*mu*theta + phi**2*sigma**2
 + 2*phi*sigma*theta + theta**2 >= 0
and (beta**2* sigma**2 - beta*c*sigma**2 - beta*mu*sigma**2 -
beta*mu*sigma - beta*phi*sigma** 2 - beta*sigma*theta > 0 and
beta*mu*sigma + beta*phi*sigma**2 + beta*sigma* theta - c*mu*sigma -
c*phi*sigma - c*sigma*theta - mu**2*sigma - mu*phi*sigma -
mu*sigma*theta < 0 and (beta**2*sigma**3 - beta**2*sigma**2 -
beta*c*sigma**3 + beta*c*sigma**2 - beta*mu*sigma**3 +
2*beta*mu*sigma**2 - beta*mu*sigma + beta* phi*sigma**3 -
beta*phi*sigma**2 + beta*sigma**2*theta - beta*sigma*theta < 0 or
 c*phi*sigma**2 - c*phi*sigma + mu*phi*sigma**2 - mu*phi*sigma > 0)
and (c*phi* sigma**2 - c*phi*sigma + mu*phi*sigma**2 - mu*phi*sigma
< 0 or sigma**2 - sigma < 0) or (beta**2*sigma**3 - beta**2*sigma**2
- beta*c*sigma**3 + beta*c*sigma**2
 - beta*mu*sigma**3 + 2*beta*mu*sigma**2 - beta*mu*sigma
 + beta*phi*sigma**3 - beta*phi*sigma**2 + beta*sigma**2*theta
 - beta*sigma*theta < 0 or
c*phi*sigma**2 - c*phi*sigma + mu*phi*sigma**2 - mu*phi*sigma > 0)
and (c*phi*sigma**2 - c*phi *sigma + mu*phi*sigma**2 - mu*phi*sigma
< 0 or sigma**2 - sigma > 0) and (beta** 2*sigma**2 -
beta*c*sigma**2 - beta*mu*sigma**2 - beta*mu*sigma - beta*phi*sigma
**2 - beta*sigma*theta > 0 or beta*mu*sigma + beta*phi*sigma**2 +
beta*sigma* theta - c*mu*sigma - c*phi*sigma - c*sigma*theta -
mu**2*sigma - mu*phi*sigma - mu*sigma*theta > 0))
```

While this formula is not terribly large, it is considerably larger and more complex than the result reported in Lemma 2 of Kribs-Zaleta and Velasco-Hernandez (2000), and it is not at all clear that the two are even equivalent. Unfortunately, SLFQ cannot simplify this formula in a reasonable amount of time. The 6 parameters and several extraneous polynomials result in CAD computations that are just prohibitive. However, replacing the expressions $\mu + c$ and $\mu + \theta$ in Redlog's output with two new variables actually eliminates μ, c and θ. With this substitution, SLFQ simplifies Redlog's output to

```
[ muc - beta < 0 /\ mutheta^2 + 2 sigma phi mutheta - 2 sigma muc
mutheta + 2 sigma beta mutheta + sigma^2 phi^2 + 2 sigma^2 muc phi -
4 sigma muc phi + 2 sigma^2 beta phi + sigma^2 muc^2 - 2 sigma^2
beta muc + sigma^2 beta^2 >= 0 /\ [ sigma muc phi - muc phi + sigma
muc^2 - 2 sigma beta muc + sigma beta^2 > 0 \/ muc mutheta - beta
mutheta + muc phi - sigma beta phi < 0 ] ]
```

which is the same size as the formula reported in Kribs-Zaleta and Velasco-Hernandez (2000). Checking with QepcadB, we find that the two are not equivalent because of a small error in Kribs-Zaleta and Velasco-Hernandez (2000)—one of their strict inequalities should be non-strict! We can also compare this result with the condition Algorithm 1 produced, i.e. $\beta(\mu + \theta) - (\mu + c)(\mu + \theta) - \phi(\mu + c) + \sigma\beta\phi$, and use quantifier elimination to show that there are indeed sub-threshold endemic equilibria for this model.

This example in which the automated approach failed is instructive. The parameters in this problem were chosen for their physical interpretations, not with quantifier elimination in mind, and in this case that leads to a problem formulation containing more parameters than necessary. In fact, inspecting the SEIRS model one sees that dividing all equations by the parameter μ leaves an equation in parameters γ/μ, β/μ, σ/μ, and ν/μ. Once again the number of parameters can be reduced. The situation is the same for the SEIT and MSEIRS models. In light of this, an automated search for substitutions that reduce the number of parameters in the problem is worth investigating.

9. Further remarks concerning epidemiology

In this section we offer some remarks considering applications and extensions of this work in epidemiological modeling.

9.1. Other models

In the models considered in this paper a linear mass-action law of the form βIS is used to model the rate of infection. If we want to exclude "spontaneous infection" without the presence of infectious individuals, this linear mass-action law is the first-order Taylor approximation of a general function of the form $Sf(I)$, where $f(I) = \sum_{n=1}^{\infty} \beta_n I^n$.

When we replace the linear mass-action law with this more general law in our example models we nevertheless obtain the same threshold conditions: At the disease-free equilibrium the Jacobian remains the same, as all new terms, which arise by considering the entire Taylor expansion instead of the linear approximation, in the partial derivatives contain at least one factor of I and are thus 0.

Although the general proof has to be done by such an argument, we nevertheless found it useful to have our algorithmic method at hand, which easily allowed to experiment with higher-order laws.

9.2. Vaccination policies

One of the parameters that can be influenced by social factors and policy is the transmission parameter β (or its variants). By estimating the transmission parameter from empirical data and using estimates for the other parameters out of the medical literature, one can see how far away from the threshold one is. Our symbolic computation of the threshold condition has the major advantage that the influences of changes on the parameters can be estimated much better than would be the case by numerical estimates. This might be one of the reasons why a lot of effort involving tedious "hand calculations" has been expended to obtain symbolic threshold conditions.

One way to bring a population below the threshold is to reduce the number of susceptibles by vaccinations. If a proportion p of newborns is vaccinated it can be easily shown by a simple change of variables for most of the models we are considering that the effect on the dynamics is the same as if in the original model the transmission parameter β is replaced by $\beta(1-p)$. We refer to Earn et al. (2000) for the details in the case of the SEIR model. Thus by vaccinating a sufficiently high fraction of susceptibles it is possible to avoid infections also in the group of remaining susceptibles.

Example 9.1. In the case of measles epidemics the numerical value of the threshold for β in the SEIR model is about 40, when using the disease specific values for average latency period, average duration of infectiousness and the birth rates for developed countries. The estimate of β for pre-vaccination epidemics is about 800. Thus the critical percentage of vaccinations is 95% for this example.

9.3. Bifurcation analysis

In the literature a conceptually much more complicated (and more restricted approach) for investigating possible sub-threshold equilibria has been used: a *bifurcation analysis* at the disease-free equilibrium at $R_0 = 1$ (see Hadeler and van den Driessche (1997) and van den Driessche and Watmough (2002)). If a so called "backward bifurcation" occurs then sub-threshold endemic equilibria exist.

While the existence of a backward bifurcation implies the existence of a sub-threshold equilibrium, the opposite case does not globally exclude the existence of sub-threshold equilibria, it only excludes them in a neighborhood of the disease-free equilibrium. Nevertheless, this bifurcation analysis in its various refinements, done by hand, is the standard technique in the literature. However, even these hand calculations can be transformed into algorithmic methods. The Jacobian matrix of the disease-free equilibrium will be singular at $R_0 = 1$, i.e. will have 0 as eigenvalue. It is possible, using center manifold techniques, to analyze the singular cases and come up with a first-order formula which involves higher-order partial derivatives. This leads in principle to a first-order formula for every multiplicity of 0 as eigenvalue. The case where 0 is a simple eigenvalue of the Jacobian matrix is analyzed in van den Driessche and Watmough (2002), and one can easily extract from their analysis a first-order formula involving partial derivatives up to degree 2 stating the existence of a "backward bifurcation". Using quantifier elimination this formula can be reduced to an equivalent quantifier-free condition on the parameters stating the existence of a "backward bifurcation" and thus of sub-threshold endemic equilibria.

10. Conclusion and future work

We have shown that the computation of threshold conditions for epidemic models can be done fully algorithmically using the techniques of quantifier elimination for real closed fields and related simplification methods for quantifier-free formulas. In this work we have reproduced known results – previously obtained by some more or less tedious hand computations – by fully algorithmic methods.

A major advantage of our novel technique is the relative ease with which we can now explore the properties of variations of the models. It is not only possible to explore the threshold properties of several "meaningful" variations of the models but also variations of many other epidemic models.

While the algorithmic methods for computing *threshold conditions* have been successful on all the examples that we have considered, the algorithmic methods for computing conditions on the existence of *sub-threshold equilibria* have been successful on some but not all. It has been instructive to look at these problems a bit more deeply in order to gain some insights about possible improvements in quantifier elimination or simplification that might make these calculations feasible.

We hope that our algorithmic methods are useful tools for the task of modeling disease transmission and other processes in the life sciences, because potentially the "threshold condition

properties" of many more models can be explored in a parametric way by our algorithmic methods than could be done by hand calculations.

Threshold conditions are relevant to many ecological models, not just those for disease transmission. The species to be considered can be macroscopic as in the examples considered above, but also microscopic – see e.g. the models for competition of microorganisms in the "gradostat" (Jäger et al., 1987; Smith et al., 1991) – or are entities on the cellular, sub-cellular or even molecular level (Ruan et al., 2003; Beuter et al., 2003; Voit, 2000).

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Appendix A. The SEIRS, MSEIRS, SEIT, and SIS Models

See Figs. A.1–A.4.

$$\begin{aligned}\dot{S} &= \mu + \gamma R - \mu S - \beta IS\\ \dot{E} &= \beta IS - (\mu+\sigma)E\\ \dot{I} &= \sigma E - (\nu+\mu)I\\ \dot{R} &= \nu I - (\mu+\gamma)R\end{aligned}$$

S	susceptibles
E	exposed (not yet infectious)
I	infectious
R	recovered (currently immune)
β	transmission parameter
μ	birth rate = mortality rate
σ	rate of change from exposed to infectious
γ	rate of loss of immunity
ν	rate of loss of infectiousness

Fig. A.1. The SEIRS model of Liu and van den Driessche (1995). This model includes temporary immunity following recovery, and a delay between the infected and infectious stages.

$$\begin{aligned}\dot{S} &= d - dS - \beta_1 IS\\ \dot{E} &= \beta_1 IS + \beta_2 IT\\ &\quad + (1-q)r_2 I\\ &\quad - (d+v+r_1)E\\ \dot{I} &= vE - (d+r_2)I\\ \dot{T} &= -dT + r_1 E\\ &\quad + qr_2 I - \beta_2 TI\end{aligned}$$

S	susceptibles
E	exposed (not yet infectious)
I	infectious
T	under treatment
β_1	transmission parameter for S
β_2	transmission parameter for T, $\beta_1 > \beta_2$
d	birth rate = mortality rate
v	rate of change from exposed to infectious
r_1	treatment rate for exposed
r_2	treatment rate for infectious
q	fraction of infectious successfully treated

Fig. A.2. The SEIT model of van den Driessche and Watmough (2002). The effects of treatment are modelled by adding a group T of individuals under treatment for the disease. It was used to model tuberculosis in van den Driessche and Watmough (2002).

$$
\begin{aligned}
\dot{M} &= \mu(1-S) - (\xi+\mu)M \\
\dot{S} &= \mu S + \xi M + \gamma R - \mu S - \beta I S \\
\dot{E} &= \beta I S - (\mu+\sigma)E \\
\dot{I} &= \sigma E - (\nu+\mu)I \\
\dot{R} &= \nu I - (\mu+\gamma)R
\end{aligned}
$$

M	newborns protected by maternal antibodies
S	susceptibles
E	exposed (not yet infectious)
I	infectious
R	recovered (currently immune)
β	transmission parameter
μ	birth rate = mortality rate
ξ	rate of loss of protection by maternal antibodies
σ	rate of transition from E to I
γ	rate of loss of immunity
ν	rate of loss of infectiousness

Fig. A.3. The MSEIRS model. Newborn children of mothers who are immune to a specific disease are passively protected by maternal antibodies for a certain time. Generalizations of the SEIR model and SEIRS model that incorporate a group of children being protected by maternal antibodies are the MSEIR model described by Hethcote (2000) and the MSEIRS model.

$$
\begin{aligned}
\dot{S} &= \mu - \beta S I - (\mu+\phi)S + cI + \theta V \\
\dot{I} &= \beta S I + \sigma\beta V I - (\mu+c)I \\
\dot{V} &= \phi S - \sigma\beta V I - (\mu+\theta)V
\end{aligned}
$$

S	susceptibles
I	infected
V	vaccinated
β	transmission parameter
μ	birth rate = mortality rate
c	cure rate
ϕ	vaccination rate
θ	rate vaccine wears off
σ	vaccine efficacy, $0 < \sigma < 1$

Fig. A.4. The SIS model of Kribs-Zaleta and Velasco-Hernandez (2000) (rewritten to explicitly match the form of the other models). The model is appropriate for diseases like pertussis and tuberculosis in the presence of a vaccination program.

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