Mathematical strategies in the study of epidemiological models based on nonlinear differential equations

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1 Background

2 Find Lyapunov functions using Picard iterations

3 Control Simulations

4 Uncertainty

5 Results
Performance a simple analysis of model parameters which could be influenced by control strategies. Also we want to establish a framework to formulate the inverse problem associated to estimate interval-valued parameters by considering the uncertainty to obtain robust solutions for epidemiological models.
Method of sum of squares

Nonlinear System
\[ \dot{x} = f(x) \]

Equilibrium Points

Define the degree of Lyapunov function (even)

Define the vector of monomials \( z \)

Express the Lyapunov function and its orbital derivative as a quadratic form

Solve the SDP
**Theorem (Parrilo, 2000, 2003)**

A multivariate polynomial $p(x)$ in $n$ variables and of degree $2d$ is a sum of squares if and only if there exists a positive semidefinite matrix $Q$ such that

$$p(x) = z^T Q z,$$

where $z$ is the vector of monomials of degree up to $d$

$$z^T = [1, x_1, x_2, \ldots, x_n, x_1 x_2, \ldots, x_n^d]$$
\[ \frac{ds}{dt} = \mu - \beta si - \mu s \]
\[ \frac{di}{dt} = \beta si - (\gamma + \mu)i \]
\[ \frac{dr}{dt} = \gamma i - \mu r \]

\[ \frac{ds}{dt} = \mu - \beta si - \mu s \]
\[ \frac{di}{dt} = \beta si - (\gamma + \mu)i \]  \hspace{1cm} (1)

**Basic Reproductive Number**

\[ R_0 = \frac{\beta}{\gamma + \mu} \]

**Equilibrium Points**

- Disease-free point, 
  \[ E_0 = (1, 0) \]
- Endemic equilibrium point, 
  \[ E_1 = (s^*, i^*), \text{ where} \]
  \[ s^* = \frac{1}{R_0}, \text{ and } i^* = \frac{\mu}{\beta}(R_0 - 1) \]
In general, for sir model we found \( V(s, i) = q_{11}(s - 1)^2 + q_{22}i^2 \)
where \( q_{11} = \epsilon \) and \( q_{22} = \frac{\epsilon(\mu+\gamma)}{(\gamma+1)} \)

\[ \mu = 0.2, \beta = 0.5, \gamma = 0.8, R_0 = 0.5, q_{11} = 1.201 \times 10^{-4}, \text{ and } q_{22} = 5.666 \times 10^{-5} \]
Dengue transmission model

\[
\frac{dm_e}{dt} = b\beta_m h_i (1 - m_e - m_i) - (\theta_m + \mu_m) m_e
\]

\[
\frac{dm_i}{dt} = \theta_m m_e - \mu_m m_i
\]

\[
\frac{dh_s}{dt} = \mu_h - b\beta_h m_i h_s - \mu_h h_s
\]

\[
\frac{dh_e}{dt} = b\beta_h m_i h_s - (\theta_h + \mu_h) h_e
\]

\[
\frac{dh_i}{dt} = \theta_h h_e - (\gamma_h + \mu_h) h_i
\]

The disease-free point, \( P_0 = (0, 0, 1, 0, 0) \).
In general, we found
\[ V(m_e, m_i, h_s, h_e, h_i) = q_{11} m_e^2 + q_{22} m_i^2 + q_{33} (h_s - 1)^2 + q_{44} h_e^2 + q_{55} h_i^2 \]
where

\[ q_{11} = \epsilon \]

\[ q_{22} = \frac{\lambda}{\sqrt{(\theta_m + \mu_m)}} + \epsilon \]

\[ q_{33} \leq \frac{4\mu_h \mu_m}{b^2 \beta_h^2} (q_{22} - \epsilon) + \epsilon \]

\[ q_{44} \leq \frac{4\mu_m (\theta_h + \mu_h)}{b^2 \beta_h^2} (q_{22} - \epsilon) + \epsilon \]

\[ q_{55} \leq \frac{4(\theta_h + \mu_h)(\gamma_h + \mu_h)}{\theta_h^2} (q_{44} - \epsilon) + \epsilon \]

with \( \epsilon > 0 \)
Theorem
(Peet and Papachristodoulou, 2012) Suppose that $f$ is a polynomial of degree $q$ and that system

$$\dot{x}(t) = f(x(t)), \ x(0) = x_0$$

(2)

is exponentially stable on $M$ with

$$\|x(t)\| \leq K \|x_0\| e^{-\lambda t}$$

where $M$ is a bounded nonempty region of radius $r$. Then, there exist a $\alpha, \beta, \gamma > 0$ and a sum of squares polynomial $V(x)$ such that for any $x \in M$,

$$\alpha \|x\|^2 \leq V(x) \leq \beta \|x\|^2$$

(3)

$$\nabla V(x)^T f(x) \leq -\gamma \|x\|^2$$
Further, the degree of $V$ will be less than $2q^{(Nk-1)}$, where $k(L, \lambda, K)$ is any integer such that $c(k) < K$ and

$$c(k)^2 + \frac{\log 2K^2}{2\lambda} K \frac{(TL)^k}{T} (1 + c(k))(K + c(k)) < \frac{1}{2}. \quad (4)$$

$$c(k)^2 > \frac{\lambda}{KL \log 2K^2} (1 - (2K^2)^{-\frac{L}{\lambda}}) \quad (5)$$

where $c(k)$ is defined as

$$c(k) = \sum_{i=0}^{N-1} (e^{TL} + K(TL)^k)^i K^2(TL)^k \quad (6)$$

and $N(L, \lambda, K)$ is any integer such that $NT > (\log 2K^2/2\lambda)$ and $T < (1/2L)$ for some $T$ and where $L$ is a Lipschitz bound on $f$ on $B_{4Kr}$. 
Moving the disease-free point $E_0 = (1, 0)$ to the origin, the system (1) becomes:

\[
\begin{align*}
\dot{x}_1 &= \mu - \beta (1 + x_1)x_2 - \mu (1 + x_1) \\
\dot{x}_2 &= \beta (1 + x_1)x_2 - (\mu + \gamma)x_2
\end{align*}
\] (7)

where $x_1 = s - 1$, and $x_2 = i$.

The Lipschitz bound for this system is given by:

\[
L = \sup_{x \in B_r} \{\beta + \mu, \beta + 1, \beta, \beta + (\mu + \gamma)(1 - R0)\}
\]
To find the converse Lyapunov function we construct the Picard iteration:

\[
(Pz)(t, x) = x + \int_0^t f(0)ds = x
\]

\[
(P^2z)(t, x) = x + \int_0^t f((Pz)(s, x))ds = x
\]

\[
= x + \int_0^t f(x)ds = x + f(x)t
\]
The converse Lyapunov function is

\[
V(x) = \int_0^\delta (P^2 z(s, x))^T (P^2 z(s, x)) ds \\
= \int_0^\delta (x + f(x)s)^T (x + f(x)s) ds \\
= \int_0^\delta \begin{bmatrix} x \\ f(x) \end{bmatrix}^T \begin{bmatrix} I \\ sI \end{bmatrix} \begin{bmatrix} I & sI \end{bmatrix} \begin{bmatrix} x \\ f(x) \end{bmatrix} ds \\
= \begin{bmatrix} x \\ f(x) \end{bmatrix}^T \begin{bmatrix} \delta I & \delta^2/2I & \delta^3/3I \\ \delta^2/2I & \delta^3/3I & \delta^4/4I \\ \delta^3/3I & \delta^4/4I & \delta^5/5I \end{bmatrix} \begin{bmatrix} x \\ f(x) \end{bmatrix}
\]
If $\delta = \frac{1}{2L}$, for the sir model, we get the SOS Lyapunov function

$$24L^3 V(x) = \begin{bmatrix} x_1 \\ x_2 \\ f_1(x_1, x_2) \\ f_2(x_1, x_2) \end{bmatrix}^T \begin{bmatrix} 12L^2 & 0 & 3L & 0 \\ 0 & 12L^2 & 0 & 3L \\ 3L & 0 & 1 & 0 \\ 0 & 3L & 0 & 1 \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \\ f_1(x_1, x_2) \\ f_2(x_1, x_2) \end{bmatrix} = Z^T Q Z$$

In this case,

$$Q = L^T L, \text{ where } L = \begin{bmatrix} 2\sqrt{3}L & 0 & \frac{3}{2\sqrt{3}} & 0 \\ 0 & 2\sqrt{3}L & 0 & \frac{3}{2\sqrt{3}} \\ 0 & 0 & \frac{1}{2} & 0 \\ 0 & 0 & 0 & \frac{1}{2} \end{bmatrix}$$
And therefore we have the sum of squares decomposition:

\[ 24L^3 V(x_1, x_2) = \left( \left( 2\sqrt{3}L - \frac{3}{2\sqrt{3}} \mu \right) x_1 - \frac{3}{2\sqrt{3}} \beta x_2 - \frac{3}{2\sqrt{3}} \beta x_1 x_2 \right)^2 \]

\[ + \left( \left( 2\sqrt{3}L - \frac{3}{2\sqrt{3}} (\mu + \gamma)(1 - R_0) \right) x_2 + \frac{3}{2\sqrt{3}} \beta x_1 x_2 \right)^2 \]

\[ + \frac{1}{4} \left( -\mu x_1 - \beta x_2 - \beta x_1 x_2 \right)^2 \]

\[ + \frac{1}{4} \left( \beta x_1 x_2 - (\mu + \gamma)(1 - R_0) x_2 \right)^2 \]
Figure: $\mu = 0.2, \beta = 0.5, \gamma = 0.8, R_0 = 0.5, L = \beta + 1 = 1.5$
Threshold theorem (basic reproductive number, $R_0$)

If the average number of secondary infections caused by an average infective is less than one, a disease will die out, while if it exceeds one there will be an epidemic (Brauer and Castillo-Chavez, 2001).

**Figure:** Basic reproductive number for some infectious disease. Image taken from https://goo.gl/vDc70u
In (a) $R_0 \leq 1$

(b) $R_0 > 1$

Figure: In (a) $\mu = 0.2, \beta = 0.5, \gamma = 0.8, R_0 = 0.5$, in (b) $\mu = 0.08, \beta = 0.9, \gamma = 0.5, R_0 = 1.55$
Figure: \( \mu = 0.06, \beta = 1, \gamma = 0.5, R_0 = 1.8, s^* = 0.42, \) and \( i^* = 0.028 \)
For *sir* model (1), the control parameters are: $\mu$, mortality rate.

Figure: $\mu = 0.06$, $\beta = 1$, $\gamma = 0.3$, $\mu_c = 0$, 0.15, 0.25 respectively
For *sir* model (1), the control parameters are: $\beta$, transmission probability:

\[ \mu = 0.06, \quad \beta = 1, \quad \gamma = 0.3, \quad \beta_c = 1, 0.55, 0.36, \]
\[ R_0 = 2.78, 1.54, 0.9 \text{ respectively} \]
\[
\frac{dA}{dt} = \delta \left(1 - \frac{A}{C}\right) M - (\gamma_m + \mu_a)A
\]

\[
\frac{dM_s}{dt} = f\gamma_m A - b\beta_m \frac{H_i}{H} M_s - (\mu_m + \mu_c)M_s
\]

\[
\frac{dM_e}{dt} = b\beta_m \frac{H_i}{H} M_s - (\theta_m + \mu_m + \mu_c)M_e
\]

\[
\frac{dM_i}{dt} = \theta_m M_e - (\mu_m + \mu_c)M_i
\]

\[
\frac{dH_s}{dt} = \mu_h H - b\beta_h \frac{M_i}{M} H_s - \mu_h H_s
\]

\[
\frac{dH_e}{dt} = b\beta_h \frac{M_i}{M} H_s - (\theta_h + \mu_h)H_e
\]

\[
\frac{dH_i}{dt} = \theta_h H_e - (\gamma_h + \mu_h)H_i
\]

\[
\frac{dH_r}{dt} = \gamma_h H_i - \mu_h H_r
\]
\[
R_0 = \frac{b^2 \beta_m \beta_h \theta_h \theta_m}{(\theta_m + \mu_m)(\gamma_h + \mu_h)(\theta_h + \mu_h)\mu_m M} \cdot \frac{f\gamma_m}{\mu_m} \frac{\delta MC}{\delta M + C(\gamma_m + \mu_a)}
\]

\[
= \frac{b^2 \beta_m \beta_h \theta_h \theta_m}{(\theta_m + \mu_m)(\gamma_h + \mu_h)(\theta_h + \mu_h)\mu_m} \cdot \frac{M^*}{M}
\]

**Control Parameters**

<table>
<thead>
<tr>
<th>Param.</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>(b)</td>
<td>Biting rate</td>
</tr>
<tr>
<td>(\mu_a)</td>
<td>Mortality rate in the aquatic phase</td>
</tr>
<tr>
<td>(\mu_m)</td>
<td>Mortality rate in the adult phase</td>
</tr>
<tr>
<td>(C)</td>
<td>Carrying capacity of the environment</td>
</tr>
</tbody>
</table>
Figure: $\mu_c = 0, 0.05, 0.1$, $\delta = 65$, $\gamma_m = 1.4$, $\mu_a = 0.12$, $b = 4$, $\mu_m = 0.12$, $\theta_m = 0.58$, $f = 0.5$, $\theta_h = 0.7$, $C = 10000$, $\gamma_h = 1.2$, $\beta_m = 0.75$, $\beta_h = 0.15$, and $\mu_h = 0.0004$, and the initial conditions $A(0) = 9000$, $M_s(0) = 1199976$, $M_e(0) = 18$, $M_i(0) = 6$, $H_s(0) = 321710$, $H_e(0) = 18$, $H_i(0) = 6$, and $H_r(0) = 81501$. 
Estimates of model parameters

\[ \mu = c_1 \]
\[ \beta = c_2 \]
\[ \gamma = c_3 \]

Quantitative model

\[ \frac{dS}{dt} = \mu N - \beta SI - \mu S \]
\[ \frac{dI}{dt} = \beta SI - (\gamma + \mu)I \]
\[ \frac{dR}{dt} = \gamma I - \mu R \]

Predictions of data
Inverse Problem

Estimates of model parameters

Quantitative model

\[
\frac{dS}{dt} = \mu N - \beta SI - \mu S \\
\frac{dI}{dt} = \beta SI - (\gamma + \mu)I \\
\frac{dR}{dt} = \gamma I - \mu R
\]

Observations of data

\[\mu = ? \quad \beta = ? \quad \gamma = ?\]
Strategies to Solve Inverse Problem

Strategies

- Least squares
- Heuristic and Metaheuristic algorithms
- Monte Carlo
- Least-Squares Gradient and Hessian

Assumptions

- Independence in database
- Normal distribution
- All initial uncertainties in the problem can be modeled using Gaussian distributions (Tarantola, 2005)
Uncertainty in the dengue cases reported

- Reported Cases 2009 – 2010
- Reported Cases 2009 – 2010 considering a subreport of 75%
Uncertainty in experimental data
Probability approximation

- Has been widely studied and applied to practical engineering problems.
- This method is based on probability distributions of the parameters with uncertainty.
- Sufficient information on the uncertainty is not always available or sometimes expensive for many practical problems.
- There are researches indicating that even a small deviation of the probability distribution is likely to cause a large error of the reliability analysis (Ben-Haim and Elishakoff, 2013).
Interval-valued approximation

- In the last two decades, the interval method in which *interval* is employed to model the uncertainty has been attracting more and more attentions (Moore, 1979; Braems et al., 2005).
- We only have to establish a bounds of the uncertainty of a parameter
- This approximation can make the uncertainty analysis more convenient and economical
- Interval method has been successfully applied to uncertainty optimization problems (Jiang et al., 2008; Gallego-Posada and Puerta-Yepes, 2017)
Figure: Inverse analysis process for uncertainty inverse problems. Image taken from (Jiang et al., 2008)
Without Uncertainty
\[
\begin{align*}
\frac{dS}{dt} &= -\beta SI \\
\frac{dI}{dt} &= \beta SI - \gamma I \\
\frac{dR}{dt} &= \gamma I
\end{align*}
\]
where,
\[
\begin{align*}
S(0) &= S_0 \\
I(0) &= I_0 \\
R(0) &= R_0
\end{align*}
\]

With Uncertainty
\[
\begin{align*}
\frac{dS}{dt} &= -[\beta_1, \beta_2] SI \\
\frac{dI}{dt} &= [\beta_1, \beta_2] SI - [\gamma_1, \gamma_2] I \\
\frac{dR}{dt} &= [\gamma_1, \gamma_2] I
\end{align*}
\]
where,
\[
\begin{align*}
S(0) &= [S_{01}, S_{02}] \\
I(0) &= [I_{01}, I_{02}] \\
R(0) &= [R_{01}, R_{02}]
\end{align*}
\]
\[
\begin{align*}
\frac{dA}{dt} &= [\delta_1, \delta_2] \left(1 - \frac{A}{[C_1, C_2]}\right)M - ([\gamma_{m1}, \gamma_{m2}] + [\mu_{a1}, \mu_{a2}])A \\
\frac{dM_s}{dt} &= [f_1, f_2][\gamma_{m1}, \gamma_{m2}] A - [b_1, b_2][\beta_{m1}, \beta_{m2}] \frac{H_i}{H} M_s - [\mu_{m1}, \mu_{m2}] M_s \\
\frac{dM_e}{dt} &= [b_1, b_2][\beta_{m1}, \beta_{m2}] \frac{H_i}{H} M_s - ([\theta_{m1}, \theta_{m2}] + [\mu_{m1}, \mu_{m2}]) M_e \\
\frac{dM_i}{dt} &= [\theta_{m1}, \theta_{m2}] M_e - [\mu_{m1}, \mu_{m2}] M_i \\
\frac{dH_s}{dt} &= [\mu_{h1}, \mu_{h2}] H - [b_1, b_2][\beta_{h1}, \beta_{h2}] \frac{M_i}{M} H_s - [\mu_{h1}, \mu_{h2}] H_s \\
\frac{dH_e}{dt} &= [b_1, b_2][\beta_{h1}, \beta_{h2}] \frac{M_i}{M} H_s - ([\theta_{h1}, \theta_{h2}] + [\mu_{h1}, \mu_{h2}]) H_e \\
\frac{dH_i}{dt} &= [\theta_{h1}, \theta_{h2}] H_e - ([\gamma_{h1}, \gamma_{h2}] + [\mu_{h1}, \mu_{h2}]) H_i \\
\frac{dH_r}{dt} &= [\gamma_{h1}, \gamma_{h2}] H_i - [\mu_{h1}, \mu_{h2}] H_r
\end{align*}
\]
Initial Conditions

\[ A(0) = [A_0, A'_0] \]
\[ M_s(0) = [M_{s0}, M'_{s0}] \]
\[ M_e(0) = [M_{e0}, M'_{e0}] \]
\[ M_i(0) = [M_{i0}, M'_{i0}] \]
\[ H_s(0) = [H_{s0}, H'_{s0}] \]
\[ H_e(0) = [H_{e0}, H'_{e0}] \]
\[ H_i(0) = [H_{i0}, H'_{i0}] \]
\[ H_r(0) = [H_{r0}, H'_{r0}] \]
Figure: On the right, interval-valued plot of the estimated Fourier series model, and on the left, Real data vs Model output. Images taken from (Gallego-Posada and Puerta-Yepes, 2017)
We found robust Lyapunov functions to test the asymptotic stability of disease-free equilibrium points in some models simulating the transmission of mosquito-borne infectious diseases.

From the basic reproductive number $R_0$ it is possible determined how much should change the parameters of the model to satisfy the condition $R_0 \leq 1$.


