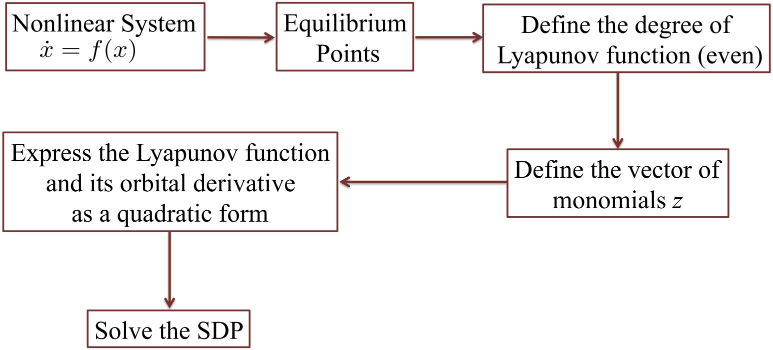
Mathematical strategies in the study of epidemiological models based on nonlinear differential equations

Paola Lizarralde-Bejarano
PhD Student in Mathematical Engineering

Supervisor: María Eugenia Puerta
Co-supervisor: Sair Arboleda-Sánchez

Doctoral Seminar 3
Universidad EAFIT
Medellín, Colombia
22 September, 2017

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.


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

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

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

$$z^T = [1, x_1, x_2, \cdots, x_n, x_1x_2, \cdots, x_n^d]$$

$$\frac{ds}{dt} = \mu - \beta si - \mu s$$
$$\frac{di}{dt} = \beta si - (\gamma + \mu)i$$
$$\frac{dr}{dt} = \gamma i - \mu r$$

$$\begin{aligned}\frac{ds}{dt} &= \mu - \beta si - \mu s \\ \frac{di}{dt} &= \beta si - (\gamma + \mu)i\end{aligned} \tag{1}$$

Basic Reproductive Number R_0

$$R_0 = \frac{\beta}{\gamma + \mu}$$

Equilibrium Points

- Disease-free point, $E_0 = (1, 0)$
- Endemic equilibrium point, $E_1 = (s^*, i^*)$, where $s^* = \frac{1}{R_0}$, 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 $q_{22} = \frac{\epsilon(\mu+\gamma)}{(\gamma+1)}$

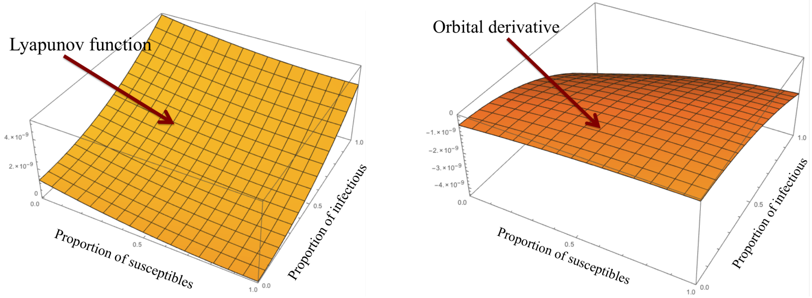


Figure: $\mu = 0.2$, $\beta = 0.5$, $\gamma = 0.8$, $R_0 = 0.5$, $q_{11} = 1.201 \times 10^{-4}$, and $q_{22} = 5.666 \times 10^{-5}$

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

$$\begin{aligned}
q_{11} &= \epsilon \\
q_{22} &= \frac{\lambda}{\sqrt{(\theta_m + \mu_m)}} + \epsilon \\
q_{33} &\leq \frac{4\mu_h \mu_m}{b^2 \beta_h^2}(q_{22} - \epsilon) + \epsilon \\
q_{44} &\leq \frac{4\mu_m(\theta_h + \mu_h)}{b^2 \beta_h^2}(q_{22} - \epsilon) + \epsilon \\
q_{55} &\leq \frac{4(\theta_h + \mu_h)(\gamma_h + \mu_h)}{\theta_h^2}(q_{44} - \epsilon) + \epsilon
\end{aligned}$$

with $\epsilon > 0$

Theorem

(Peet and Papachristodoulou, 2012) Suppose that f is a polynomial of degree q and that system

$$\dot{x}(t) = f(x(t)),\ x(0) = x_0 \tag{2}$$

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 $x \in M$,

$$\begin{gathered} \alpha||x||^2 \leq V(x) \leq \beta||x||^2 \\ \nabla V(x)^T f(x) \leq -\gamma||x||^2 \end{gathered} \tag{3}$$

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

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

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

where $c(k)$ is defined as

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

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:

$$\begin{aligned} \dot{x_1} &= \mu - \beta(1 + x_1)x_2 - \mu(1 + x_1) \\ \dot{x_2} &= \beta(1 + x_1)x_2 - (\mu + \gamma)x_2 \end{aligned} \tag{7}$$

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

$$\begin{aligned}
V(x) &= \int_0^{\delta} (P^2 z(s,x))^T (P^2 z(s,x)) ds \\
&= \int_0^{\delta} (x + f(x)s)^T (x + f(x)s) ds \\
&= \int_0^{\delta} \begin{bmatrix} x \\ f(x) \end{bmatrix}^T \begin{bmatrix} I \\ sI \end{bmatrix} \begin{bmatrix} I & sI \end{bmatrix} \begin{bmatrix} x \\ f(x) \end{bmatrix} ds \\
&= \begin{bmatrix} x \\ f(x) \end{bmatrix}^T \begin{bmatrix} \delta I & \delta^2/2I \\ \delta^2/2I & \delta^3/3I \end{bmatrix} \begin{bmatrix} x \\ f(x) \end{bmatrix}
\end{aligned}$$

If $\delta = \frac{1}{2L}$, for the *sir* model, we get the SOS Lyapunov function

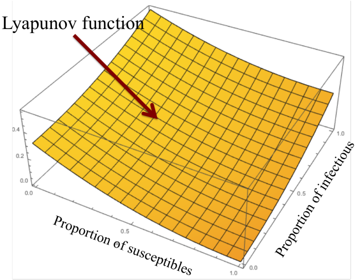
$$\begin{aligned} 24L^3 V(x) &= \begin{bmatrix} x_1 \\ x_2 \\ f_1(x_1, x_2) \\ f_2(x_1, x_2) \end{bmatrix}^T \begin{bmatrix} 12L^2 & 0 & 3L & 0 \\ 0 & 12L^2 & 0 & 3L \\ 3L & 0 & 1 & 0 \\ 0 & 3L & 0 & 1 \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \\ f_1(x_1, x_2) \\ f_2(x_1, x_2) \end{bmatrix} \\ &= Z^T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

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:

$$\begin{aligned} 24L^3 V(x_1, x_2) = & \left(\left(2\sqrt{3}L - \frac{3}{2\sqrt{3}}\mu \right) x_1 - \frac{3}{2\sqrt{3}}\beta x_2 - \frac{3}{2\sqrt{3}}\beta x_1 x_2 \right)^2 \\ & + \left(\left(2\sqrt{3}L - \frac{3}{2\sqrt{3}}(\mu + \gamma)(1 - R_0) \right) x_2 + \frac{3}{2\sqrt{3}}\beta x_1 x_2 \right)^2 \\ & + \frac{1}{4} \left(-\mu x_1 - \beta x_2 - \beta x_1 x_2 \right)^2 \\ & + \frac{1}{4} \left(\beta x_1 x_2 - (\mu + \gamma)(1 - R_0) x_2 \right)^2 \end{aligned}$$



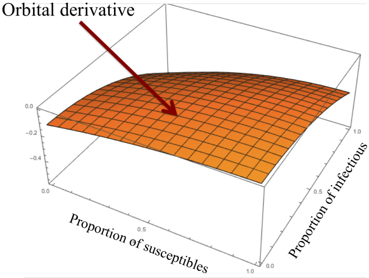


Figure: $\mu = 0.2,\ \beta = 0.5,\ \gamma = 0.8,\ R_0 = 0.5,\ L = \beta + 1 = 1.5$

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).

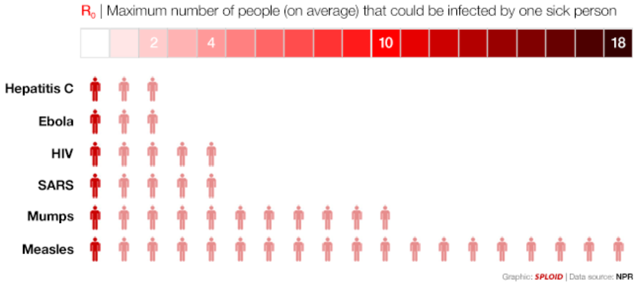


Figure: Basic reproductive number for some infectious disease. Image taken from `https://goo.gl/vDc70u`

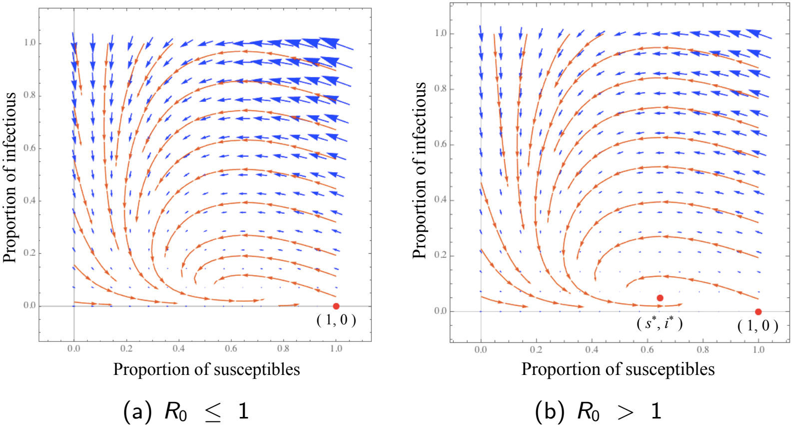


Figure: In (a) $\mu = 0.2$, $\beta = 0.5$, $\gamma = 0.8$, $R_0 = 0.5$, in (b) $\mu = 0.08$, $\beta = 0.9$, $\gamma = 0.5$, $R_0 = 1.55$

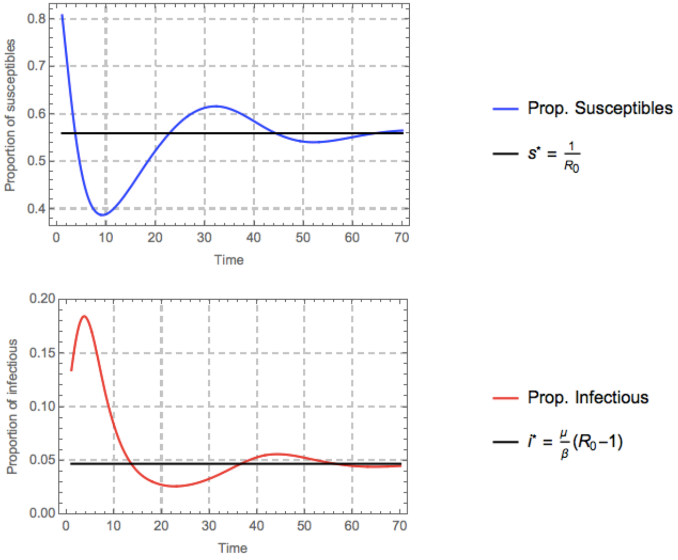


Figure: $\mu = 0.06$, $\beta = 1$, $\gamma = 0.5$, $R_0 = 1.8$, $s^* = 0.42$, and $i^* = 0.028$

For *sir* model (1), the control parameters are: μ, mortality rate.

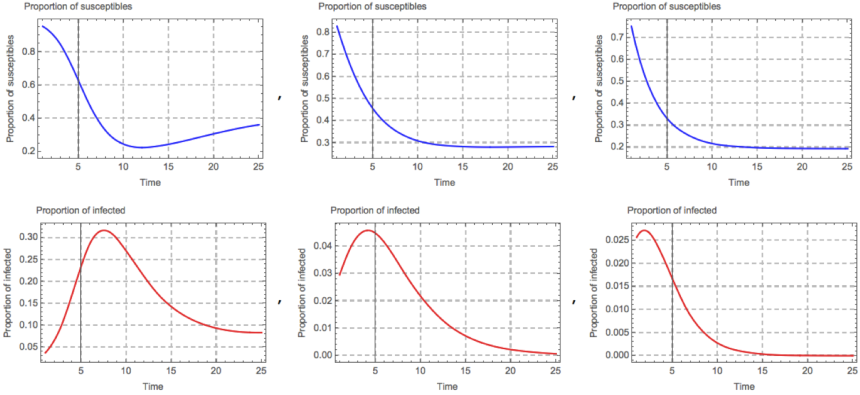


Figure: $\mu = 0.06$, $\beta = 1$, $\gamma = 0.3$, $\mu_c = 0$, 0.15, 0.25 respectively

For *sir* model (1), the control parameters are: β, transmission probability:

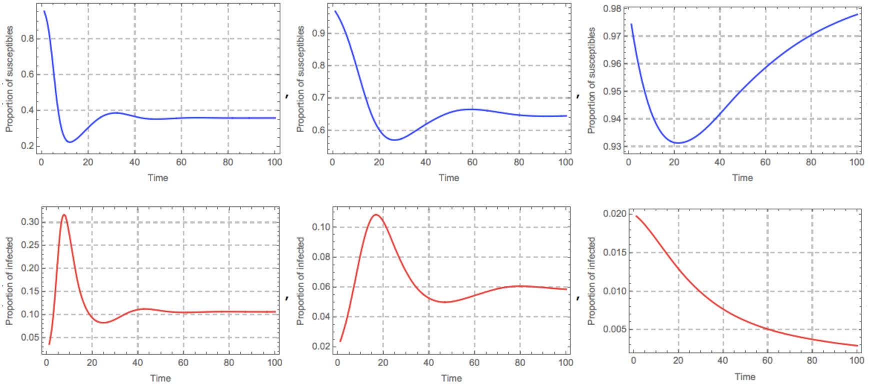


Figure: $\mu = 0.06$, $\beta = 1$, $\gamma = 0.3$, $\beta_c = 1, 0.55, 0.36$, $R0 = 2.78, 1.54, 0.9$ respectively

Example: Dengue model, Bello's case

$$
\begin{aligned}
\frac{dA}{dt} &= \delta\left(1-\frac{A}{C}\right)M-(\gamma_m+\mu_a)A\\
\frac{dM_s}{dt} &= f\gamma_m A-b\beta_m\frac{H_i}{H}M_s-(\mu_m+\mu_c)M_s\\
\frac{dM_e}{dt} &= b\beta_m\frac{H_i}{H}M_s-(\theta_m+\mu_m+\mu_c)M_e\\
\frac{dM_i}{dt} &= \theta_m M_e-(\mu_m+\mu_c)M_i\\
\frac{dH_s}{dt} &= \mu_h H-b\beta_h\frac{M_i}{M}H_s-\mu_h H_s\\
\frac{dH_e}{dt} &= b\beta_h\frac{M_i}{M}H_s-(\theta_h+\mu_h)H_e\\
\frac{dH_i}{dt} &= \theta_h H_e-(\gamma_h+\mu_h)H_i\\
\frac{dH_r}{dt} &= \gamma_h H_i-\mu_h H_r
\end{aligned}
$$

$$
\begin{aligned}
R_0 &= \frac{b^2\beta_m\beta_h\theta_h\theta_m}{(\theta_m+\mu_m)(\gamma_h+\mu_h)(\theta_h+\mu_h)\mu_m M}\cdot\frac{f\gamma_m}{\mu_m}\frac{\delta MC}{(\delta M + C(\gamma_m+\mu_a))} \\
&= \frac{b^2\beta_m\beta_h\theta_h\theta_m}{(\theta_m+\mu_m)(\gamma_h+\mu_h)(\theta_h+\mu_h)\mu_m}\cdot\frac{M_s^*}{M}
\end{aligned}
$$

Control Parameters

Param.	**Meaning**
b	Biting rate
μ_a	Mortality rate in the aquatic phase
μ_m	Mortality rate in the adult phase
C	Carrying capacity of the environment

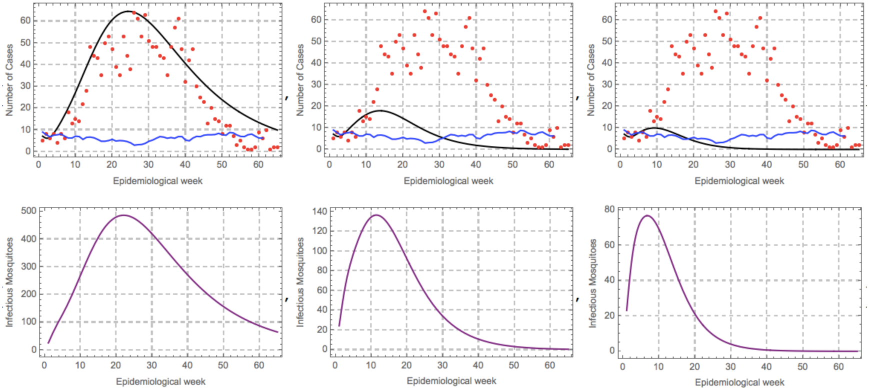


Figure: $\mu_c = 0, 0.05, 0.1$, $\delta = 65$, $\gamma_m = 1.4$, $\mu_a = 0.12$, $b = 4$, $\mu_m = 0.12$, $\theta_m = 0.58$, $f = 0.5$, $\theta_h = 0.7$, $C = 10000$, $\gamma_h = 1.2$, $\beta_m = 0.75$, $\beta_h = 0.15$, and $\mu_h = 0.0004$, and the initial conditions $A(0) = 9000$, $M_s(0) = 1199976$, $M_e(0) = 18$, $M_i(0) = 6$, $H_s(0) = 321710$, $H_e(0) = 18$, $H_i(0) = 6$, and $H_r(0) = 81501$.

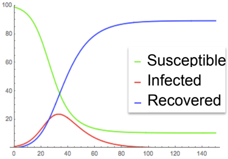
Estimates of model parameters

$$\mu = c_1$$
$$\beta = c_2$$
$$\gamma = c_3$$

Quantitative model

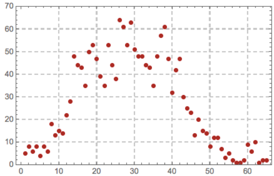
$$\frac{dS}{dt} = \mu N - \beta S I - \mu S$$
$$\frac{dI}{dt} = \beta S I - (\gamma + \mu) I$$
$$\frac{dR}{dt} = \gamma I - \mu R$$

Predictions of data



Inverse Problem

Observations of data



Quantitative model

$$\frac{dS}{dt} = \mu N - \beta SI - \mu S$$

$$\frac{dI}{dt} = \beta SI - (\gamma + \mu) I$$

$$\frac{dR}{dt} = \gamma I - \mu R$$

Estimates of model parameters

$$\mu = ?$$

$$\beta = ?$$

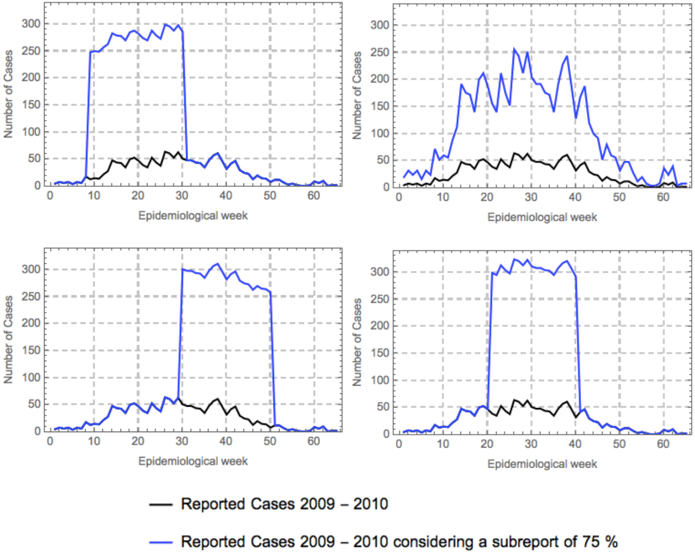
$$\gamma = ?$$

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)


Number of Cases
Epidemiological week
0
10
20
30
40
50
60
50
100
150
200
250
300
Reported Cases 2009 – 2010
Reported Cases 2009 – 2010 considering a subreport of 75 %


Bello (21 egg) Niquia
13-09-13
F2

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)

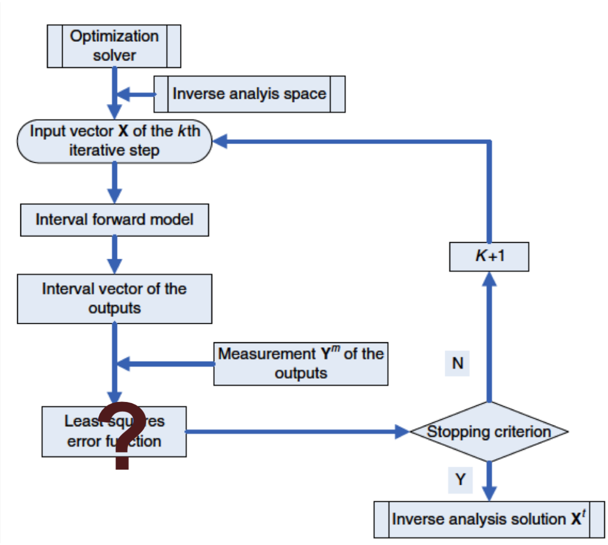


Figure: Inverse analysis process for uncertainty inverse problems. Image taken from (Jiang et al., 2008)

Without Uncertainty

$$\frac{dS}{dt} = -\beta SI$$
$$\frac{dI}{dt} = \beta SI - \gamma I$$
$$\frac{dR}{dt} = \gamma I$$

where,

$$S(0) = S_0$$
$$I(0) = I_0$$
$$R(0) = R_0$$

With Uncertainty

$$\frac{dS}{dt} = -[\beta_1, \beta_2]\, SI$$
$$\frac{dI}{dt} = [\beta_1, \beta_2]\, SI - [\gamma_1, \gamma_2]\, I$$
$$\frac{dR}{dt} = [\gamma_1, \gamma_2]\, I$$

where,

$$S(0) = [S_{0_1}, S_{0_2}]$$
$$I(0) = [I_{0_1}, I_{0_2}]$$
$$R(0) = [R_{0_1}, R_{0_2}]$$

$$
\begin{aligned}
\frac{dA}{dt} &= [\delta_1, \delta_2] \left(1 - \frac{A}{[C_1, C_2]}\right) M - ([\gamma_{m_1}, \gamma_{m_2}] + [\mu_{a_1}, \mu_{a_2}])\, A \\
\frac{dM_s}{dt} &= [f_1, f_2][\gamma_{m_1}, \gamma_{m_2}]\, A - [b_1, b_2][\beta_{m_1}, \beta_{m_2}]\, \frac{H_i}{H} M_s - [\mu_{m_1}, \mu_{m_2}]\, M_s \\
\frac{dM_e}{dt} &= [b_1, b_2][\beta_{m_1}, \beta_{m_2}]\, \frac{H_i}{H} M_s - ([\theta_{m_1}, \theta_{m_2}] + [\mu_{m_1}, \mu_{m_2}])\, M_e \\
\frac{dM_i}{dt} &= [\theta_{m_1}, \theta_{m_2}]\, M_e - [\mu_{m_1}, \mu_{m_2}]\, M_i \\
\frac{dH_s}{dt} &= [\mu_{h_1}, \mu_{h_2}]\, H - [b_1, b_2][\beta_{h_1}, \beta_{h_2}]\, \frac{M_i}{M} H_s - [\mu_{h_1}, \mu_{h_2}] H_s \\
\frac{dH_e}{dt} &= [b_1, b_2][\beta_{h_1}, \beta_{h_2}]\, \frac{M_i}{M} H_s - ([\theta_{h_1}, \theta_{h_2}] + [\mu_{h_1}, \mu_{h_2}])\, H_e \\
\frac{dH_i}{dt} &= [\theta_{h_1}, \theta_{h_2}]\, H_e - ([\gamma_{h_1}, \gamma_{h_2}] + [\mu_{h_1}, \mu_{h_2}])\, H_i \\
\frac{dH_r}{dt} &= [\gamma_{h_1}, \gamma_{h_2}] H_i - [\mu_{h_1}, \mu_{h_2}] H_r
\end{aligned}
$$

Initial Conditions

$$
\begin{aligned}
A(0) &= [A_0, A_0'] \\
M_s(0) &= [M_{s_0}, M_{s_0}'] \\
M_e(0) &= [M_{e_0}, M_{e_0}'] \\
M_i(0) &= [M_{i_0}, M_{i_0}'] \\
H_s(0) &= [H_{s_0}, H_{s_0}'] \\
H_e(0) &= [H_{e_0}, H_{e_0}'] \\
H_i(0) &= [H_{i_0}, H_{i_0}'] \\
H_r(0) &= [H_{r_0}, H_{r_0}']
\end{aligned}
$$

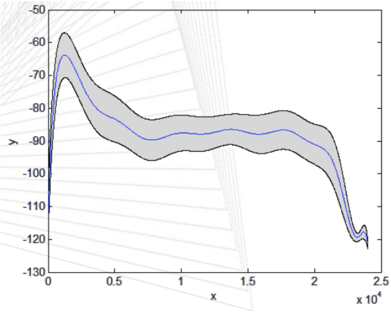


Figure: On the right, interval-valued plot of the estimated Fourier series model, and on the left, Real data vs Model output. Images taken from (Gallego-Posada and Puerta-Yepes, 2017)

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 $R_0 \leq 1$

Brauer, F., Castillo-Chavez, C. (2001). *Mathematical models in population biology and epidemiology*. Springer.

Ben-Haim, Y., Elishakoff, I. (2013). Convex models of uncertainty in applied mechanics (Vol. 25). Elsevier.

Parrilo, P. A. (2000). *Structured semidefinite programs and semialgebraic geometry methods in robustness and optimization*. PhD thesis, California Institute of Technology.

Parrilo, P. A. (2003). *Semidefinite programming relaxations for semialgebraic problems*. Mathematical programming, 96(2), 293-320.

Peet, M. M., Papachristodoulou (2012). *A Converse Sum of Squares Lyapunov Result With a Degree Bound*. IEEE Transactions on Automatic Control, 57(9), pp. 2281-2293.

Moore, R. E. (1979). Methods and applications of interval analysis. Prentice-Hall, London.

Tarantola, A. (2005). Inverse problem theory and methods for model parameter estimation. Society for Industrial and Applied Mathematics.

Braems, I., Ramdani, N., Boudenne, A., Kieffer, M., Jaulin, L., Ibos, L., Candau, Y. (2005). New set-membership techniques for parameter estimation in presence of model uncertainty. In Proceedings of the 5th International Conference on Inverse Problems in Engineering: Theory and Practice, Cambridge.

Jiang, C., Liu, G. R., Han, X. (2008). A novel method for uncertainty inverse problems and application to material characterization of composites. Experimental Mechanics, 48(4), 539-548.

Gallego-Posada, J. D., Puerta-Yepes, M. E. (2017). Interval analysis and optimization applied to parameter estimation under uncertainty. Boletim da Sociedade Paranaense de Matemática, 36(2), 107-124.