

OPTIMAL NONLINEAR STABILITY IN PDES AND APPLICATIONS

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- **New idea: introduce “optimal Lyapunov function” in the PDEs models to study nonlinear stability - up to linear criticality - (applications to diffusion models in biology)**
- Epidemic model with diffusion and cross diffusion
- Finding a (nonlinear) threshold such that glia will not aggregate in the brain (connected with the Alzheimer's disease)
- Some open problems

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OUTLINE

We address the question of relating the stability properties of a linear operator with the stability properties of its associate symmetric operator. The linear-algebra results of Bendixson and Hirsch give a *precise result* in the ODEs case.

We show that in a variety of cases, including infinite dimensional cases associated to systems of PDEs, the *same result is valid*.

We give a method to build an **optimal Lyapunov function** for the **coincidence of critical linear and nonlinear** stability thresholds for PDEs systems with biological applications.

- ODEs - Bendixon-Hirsch theorem
- PDEs - Reaction-diffusion systems
- Biomedical applications
- Conclusion and open problems

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AUTONOMOUS ODES

Consider the linear ODE system

$$\dot{\mathbf{x}} = A\mathbf{x}, \quad (1)$$

where $\mathbf{x} = (x_1, x_2, \dots, x_n)^T \in \mathbb{R}^n$, A is a constant $n \times n$ matrix with real entries. Let us denote with A^H its **symmetric** part and by A^A its **skew-symmetric** part.

We want to study the stability of the **zero solution** $(0, 0, \dots, 0)$ for the systems $\dot{\mathbf{x}} = A\mathbf{x}$, $\dot{\mathbf{x}} = A^H\mathbf{x}$, $\dot{\mathbf{x}} = A^A\mathbf{x}$ (Routh-Hurwitz conditions).

Let us begin with an easy example (a is a real number):

$$\begin{cases} \dot{x} = -2x + ay \\ \dot{y} = -x - 3y, \end{cases} \quad (2)$$

$$A = \begin{pmatrix} -2 & a \\ -1 & -3 \end{pmatrix}, \quad A^H = \begin{pmatrix} -2 & \frac{a-1}{2} \\ \frac{a-1}{2} & -3 \end{pmatrix}$$

$$A^A = \begin{pmatrix} 0 & \frac{a+1}{2} \\ -\frac{a+1}{2} & 0 \end{pmatrix}$$

The (complex) eigenvalues σ_1, σ_2 of the matrix A are

$$\sigma_{1,2} = \frac{-5 \pm \sqrt{1 - 4a}}{2}.$$

They are real numbers if $a \leq \frac{1}{4}$ and complex conjugate if $a > \frac{1}{4}$.

The zero solution of system $\dot{\mathbf{x}} = A^H \mathbf{x}$, is **asymptotically stable** if $a \in (1 - 2\sqrt{6}, 1 + 2\sqrt{6})$.

The zero solution of (2) is **asymptotically stable** if $a \in (-6, +\infty)$.

The zero solution of system $\dot{\mathbf{x}} = A^A \mathbf{x}$, is **stable** if $a \in \mathbb{R}$.

If S_1 , S_2 and S_3 are the “stability domains” (the subsets of \mathbb{R} where the corresponding system is stable) of $A^H(a)$, $A(a)$ and $A^A(a)$, respectively, we have

$$S_1 \subset S_2 \subset S_3$$

in the particular case:

$$(1 - 2\sqrt{6}, 1 + 2\sqrt{6}) \subset (-6, +\infty) \subset \mathbb{R}$$

Now we use the Lyapunov method with the "Euclidean norm"

$$E_0 := \frac{1}{2} \|\mathbf{x}\|^2,$$

we have:

$$\dot{E}_0 = \mathbf{x}^T A^H \mathbf{x}.$$

In the case of the previous example we have:

$\dot{E}_0 < 0$ when $a \in (1 - 2\sqrt{6}, 1 + 2\sqrt{6})$ for **both** systems

$$\dot{\mathbf{x}} = A\mathbf{x}, \quad \dot{\mathbf{x}} = A^H\mathbf{x}$$

$$\dot{E}_0 = 0 \text{ for system } \dot{\mathbf{x}} = A^A\mathbf{x}.$$

From this example it appears that:

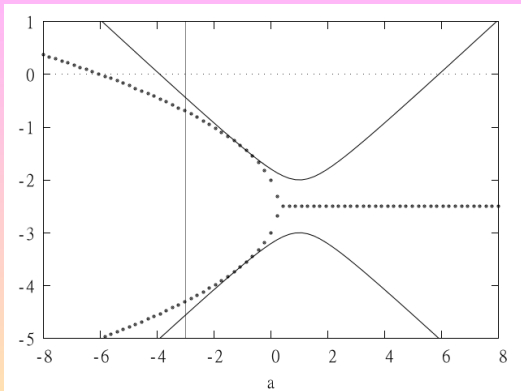
the symmetric part of a matrix **does not “help”** stability, in the sense that it *shrinks* the stability domain.

Moreover, the stability boundaries obtained with the eigenvalues method and with the “Euclidean norm” - in the case of a symmetric matrix - coincide.

A Lyapunov function is said to be *optimal* if it ensures stability when the system is (spectrally) stable.

In the symmetric case, the Euclidean norm is an **optimal** Lyapunov function

Is this a *particular* or a *general* result? What happens for PDEs?



Eigenvalues of A^H (continuous line) and real part of eigenvalues of A (dotted line) for the sample system (2), as functions of parameter a . Note that for every choice of a (e.g. vertical line at $a = -3$ in the figure) the eigenvalues of A^H bound the eigenvalues of A both from below and above; for $a > 1/4$, the eigenvalues of A^H bound the real part of eigenvalues of A .

BENDIXSON-HIRSCH THEOREM (1900)

Let A be a matrix $n \times n$ with real entries.

Let us denote with $A^H = \frac{A + A^T}{2}$ its symmetric part.

Denote by $\sigma_1, \sigma_2, \dots, \sigma_n$, the eigenvalues (in general complex numbers, $\sigma_k = \text{Re}(\sigma_k) + i \text{Im}(\sigma_k)$) of A and by $\lambda_1, \lambda_2, \dots, \lambda_n$, the eigenvalues of A^H .

In 1900 **Bendixson** [1] proved:

THEOREM

$$\min(\lambda_1, \lambda_2, \dots, \lambda_n) \leq \text{Re}(\sigma_k) \leq \max(\lambda_1, \lambda_2, \dots, \lambda_n), \quad k = 1, \dots, n$$

This result has been improved and generalized by Hirsch 1902, [2] and others (Bromwich 1906, [3], Browne 1928, [4], Bellman 1960, [5], ... Adam and Tsatsomero 2006, [6]).

From this result it follows that for the linear autonomous ODE system

$$\dot{\mathbf{x}} = A\mathbf{x}, \quad (3)$$

the **smallest stability domain** of the equilibrium point $(0, 0)$ is obtained by the system

$$\dot{\mathbf{x}} = A^H\mathbf{x}. \quad (4)$$

Then

- the symmetry of a matrix **does not “help”** stability (one has the smallest stability region)
- If we have a symmetric matrix A^H we can enlarge its stability region by adding a skewsymmetric matrix to it

In the case of a **nonlinear** ODE system

$$\dot{\mathbf{x}} = A\mathbf{x} + f(\mathbf{x}) \quad (5)$$

where $f(\mathbf{x}, \cdot)$ is a C^1 function with $f(\mathbf{0}) = f'(\mathbf{0}) = \mathbf{0}$ and if $\mathbf{0}$ is a hyperbolic point, then **the linearization principle** (Th. of Hartman and Grobman) holds. In this case a local stability result is valid.

In the general case, the Lyapunov direct method can be applied.

- The "Euclidean norm" $E_0 := \frac{1}{2}\mathbf{x}^T A\mathbf{x}$, if $A = A^H$ (symmetric case), is an **optimal Lyapunov function**.
- In general, with this norm, the linear and nonlinear critical stability thresholds are not equal.

In order to have the same linear and nonlinear thresholds, a new Lyapunov function must be introduced. For this, the **classical reduction method** has been introduced.

Given the system

$$S_{old} : \quad \dot{\mathbf{x}} = A\mathbf{x} + f(\mathbf{x}),$$

the *canonical reduction method* is based on the classical eigenvalues-eigenvectors method:

we introduce the change of variables, the *new canonical field variables* \mathbf{y}

$$\mathbf{x} = Q\mathbf{y},$$

and obtain the new (topologically equivalent) system

$$S_{new} : \quad \dot{\mathbf{y}} = B\mathbf{y} + Q^{-1}f(Q\mathbf{y}),$$

where $B = Q^{-1}AQ$ is a *similar matrix* to A and Q is a *transformation matrix*. It is a non singular matrix of eigenvectors (or generalized eigenvectors).

As it is well known “similar operators define differential equations that have the same dynamical properties”, [7], pag 39.

Now if we define the new *optimal Lyapunov function* (equivalent to energy E_0)

$$E := \frac{1}{2} \|\mathbf{y}\|^2 = \frac{1}{2} [y_1^2 + y_2^2 + \cdots + y_n^2],$$

we *reach* the critical linear and (at least local) nonlinear stability thresholds and we obtain a known basin of attraction of initial data. We observe that the *linear part* of system \mathcal{S}_{new} is in a canonical form (diagonal or a general Jordan form) and the Euclidean norm is an optimal Lyapunov function for the coincidence of the critical linear and nonlinear stability thresholds.

In the case of the previous example (linear system (2)), we have:

$$\dot{E} = -\frac{1}{2} [(5 + \sqrt{1 - 4a})y_1^2 + (5 - \sqrt{1 - 4a})y_2^2] \quad \text{if } a < \frac{1}{4},$$

$$\dot{E} = -\frac{5}{2} [y_1^2 + \frac{1}{5}y_1y_2 + y_2^2] \quad \text{if } a = \frac{1}{4},$$

$$\dot{E} = -\frac{5}{2} [y_1^2 + y_2^2] \quad \text{if } a > \frac{1}{4}.$$

REACTION-DIFFUSION SYSTEMS

Let us consider the linearized perturbation equations of a given constant solution \tilde{U} to a reaction-diffusion system

$$U_t = D\Delta U + LU \quad (6)$$

where U is a vector with n components, D and L are constant $n \times n$ matrices, with D symmetric and positive definite. Assuming Dirichlet boundary conditions, a [Bendixson-Hirsch theorem](#) holds.

- If L is a linear symmetric operator, then the $L_2(\Omega)$ energy $E_0 = \frac{1}{2} \int_{\Omega} |U|^2 d\Omega$ is an optimal Lyapunov function (and also here we have the "smallest stability region").
- If L is **not a linear symmetric operator**, then optimal Lyapunov functions for the coincidence of linear and nonlinear critical thresholds can be defined.

An operative method (REDUCTION METHOD) to build an optimal Lyapunov function is presented here.

An alternative method (*auxiliary system method*) for a nonlinear reaction-diffusion system is given by Rionero in several papers in the last decade.

Given the system (perturbation to a steady solution)

$$U_{i,t} = D_{ik} \Delta U_k + L_{ik} U_k + N_i(U_1, \dots, U_n) \quad (7)$$

with initial condition $U(x, 0) = U_0(x)$ and

$$U_i(x, t) = 0, \quad \forall (x, t) \in \partial\Omega \times (0, +\infty) \quad (8)$$

(Dirichlet boundary conditions) or (Neumann b. c., with given average in Ω):

$$\frac{\partial U_i(x, t)}{\partial n} = 0, \quad \forall (x, t) \in \partial\Omega \times (0, +\infty), \quad \langle U_i \rangle = \int_{\Omega} U_i(x, t) d\Omega = 0 \quad (9)$$

- ① First we **linearize**:

$$U_{i,t} = D_{ik}\Delta U_k + L_{ik}U_k, \quad (10)$$

and denote by ξ_p (p positive integer) the generic *eigenvalue* of the Laplacian with boundary conditions with boundary

conditions (8) or (9), $\xi_p = \frac{p^2\pi^2}{l^2}$, with

$l^{-2} = l_1^{-2} + l_2^{-2} + \dots + l_m^{-2}$ (the *box case*)

We define

$$A_\xi = -\xi D + L$$

where ξ is the **principal eigenvalue** of the operator

$A_\xi = -\xi D + L$ (i.e., the eigenvalue corresponding to the critical linearized instability parameter), and compute the eigenvalues of A_ξ .

- ② We introduce a **transformation matrix** Q of eigenvectors (and/or generalized eigenvectors) of the matrix A_ξ , and its inverse Q^{-1} .

- ③ We define the new field variables $V = Q^{-1}U$ and write the new (nonlinear) *reaction-diffusion system* equivalent to (7),

$$V_{i,t} = F_{ik}\Delta V_k + G_{ik}V_k + \bar{N}_i(V), \quad V(0) = V_0, \quad (11)$$

where

$$F = Q^{-1}DQ, \quad G = Q^{-1}LQ, \quad (12)$$

and

$$\bar{N}(V) = Q^{-1}N(QV). \quad (13)$$

- ④ We introduce the Lyapunov function

$$E_1(t) = \frac{1}{2}\|V(t)\|^2$$

for the new linearized system and study the (linear) stability of the zero solution.

- ⑤ We write the balance equation for the Lyapunov function $E_1(t)$:

$$\dot{E}_1(t) = (GV, V) - (F\nabla V, \nabla V),$$

we assume that the quadratic form $(F\nabla V, \nabla V)$ is positive definite and study the **maximum problem**

$$M = \max_{\mathcal{S}} \frac{(GV, V)}{(F\nabla V, \nabla V)}, \quad (14)$$

where \mathcal{S} is the space of the *admissible* functions (for example, in the case of zero Dirichlet b.c., it is the Sobolev space $W_0^{1,2}(\Omega)$).

M is obtained by solving the equation

$$\det(T_{ij}) = 0, \quad (15)$$

where

$$T_{ij} = \begin{cases} 2(G_{ij} - M(p)\xi_p F_{ij}) & \text{if } i = j, \\ G_{ij} + G_{ji} - M(p)\xi_p(F_{ij} + F_{ji}) & \text{if } i \neq j, \end{cases} \quad (16)$$

and maximizing the generic eigenvalue $M(p)$ with respect to the integer p .

- ⑥ We consider the *nonlinear system* (33) and define the new Lyapunov function

$$E(t) = E_1(t) + \tilde{b}E_2(t), \quad \tilde{b} \geq 0,$$

with a *suitable* E_2 which controls the nonlinearities, and write the energy equation of $E(t)$ (in some problems, and for particular space dimensions, we can choose $\tilde{b} = 0$ and the optimal Lyapunov function $E(t)$ coincides with $E_1(t)$).

- ⑦ Finally, we show that the condition

$$M < 1$$

is the *nonlinear stability condition*, and

$$M = 1$$

gives the **critical Lyapunov number** R_E which coincides with R_c .

If we are able to control the nonlinearities (this holds e.g. in the case the nonlinear term N satisfies the condition

$$|(NU, U)| \leq K_0 \|U\|^{\alpha_0} \|\nabla U\|^2$$

with K_0 and α_0 positive numbers) we obtain the **coincidence** of the linear and nonlinear stability boundaries with a **computable value for the basin of attraction** of the initial data.

AN EPIDEMIC MODEL WITH DIFFUSION

For the epidemic models described by reaction-diffusion systems, it is generally assumed that **susceptible individuals and infected individuals move randomly**.

- Spatial diffusions of susceptible individuals: $d\Delta S$
- Spatial diffusions of infected individuals $d\Delta I$,

where S and I are the densities of susceptible individuals and infectious individuals in space, and d is the diffusion coefficient.

However, from biological perspective, the diffusion of individuals may be connected with searching foods, escaping high infection risks. In the first case, individuals tend to diffuse in the direction of lower density of a population, where there are richer resources. In the second case, individuals may move along the gradient of infectious individuals to avoid higher infection.

Motivated by these observations, we consider an epidemic model that incorporates these ingredients, [M., Straughan, Wang 2007] .

We begin from a *kinetic* model and choose a fundamental epidemic model of SI type as a framework to develop:

$$\begin{aligned}\frac{dS}{dt} &= \mu - \mu S - \beta SI, \\ \frac{dI}{dt} &= \beta SI - (\mu + \epsilon)I,\end{aligned}\tag{17}$$

where μ is the recruitment rate of the population and the per capita death rate of the population, β is the disease transmission coefficient and ϵ is the disease-induced death rate.

To include the spatial heterogeneity, *as a first approach*, we assume that the population is distributed *on the interval* $[0, L]$ of one dimensional space. Let $S(t, x)$ and $I(t, x)$ be the densities of susceptible individuals and infectious individuals at the spatial position x and the time t , respectively. Let $N = S + I$ be the population density.

AN EPIDEMIC MODEL WITH DIFFUSION

The epidemic model with diffusion and cross-diffusion is given by:

$$\begin{aligned} S_t &= a\Delta S + c\Delta I + \mu - \mu S - \beta SI \\ I_t &= c\Delta S + a\Delta I - (\mu + \epsilon)I + \beta SI \end{aligned} \quad (18)$$

in $\Omega \times (0, \infty)$, where $S(t, \mathbf{x})$ and $I(t, \mathbf{x})$ are the densities of susceptible individuals and infectious individuals of a biological population at the spatial position \mathbf{x} and the time t , respectively, μ is the recruitment rate of the population and the per capita death rate of the population ($1/\mu$ is the mean lifetime), β is the disease transmission coefficient (contact rate) and ϵ is the disease-induced death rate ($1/\epsilon$ is the average infectious period), a is a diffusion term and c is a cross-diffusion term, $0 \leq c < a$.

Rescaling the variables by introducing $t^* = t(\mu + \epsilon)$,

$\mathbf{x}^* = \sqrt{\frac{\mu + \epsilon}{a}} \mathbf{x}$, $R_0 = \frac{\beta}{\mu + \epsilon}$, $p = \frac{c}{a}$, $\lambda = \frac{\mu}{\mu + \epsilon}$, we obtain
(omitting the asterisks)

$$\begin{aligned} S_t &= \Delta S + p\Delta I + \lambda(1 - S) - R_0 SI \\ I_t &= p\Delta S + \Delta I - I + R_0 SI. \end{aligned} \tag{19}$$

We note that $0 \leq p < 1$ and $0 < \lambda < 1$, and **the basic reproduction number R_0** is used as the threshold quantity that determines *whether a disease can invade* a population.

The equilibria are the **disease-free** $H_0 = (1, 0)$, for any R_0 , and, for $R_0 > 1$, the **endemic**

$$H_1 = (S_e, I_e) = \left(\frac{1}{R_0}, \lambda \left(1 - \frac{1}{R_0} \right) \right).$$

M., Straughan and Wang (2007) have proved that, by choosing the *classical energy* of perturbation (s, i) to H_0 , the *critical energy reproduction number* R_{0E_0} is below the linearized instability reproduction number R_{0c} .

By using the reduction method, as introduced above, the coincidence of the critical linear and nonlinear reproduction numbers has been proved and a known radius of attraction for the initial data has been given.

THEOREM

If $\epsilon < \beta$ and

$$R_0 < R_{0c} := 1 + \frac{(a - c)\xi}{\mu + \epsilon} - \frac{c\xi\epsilon}{(\mu + \epsilon)(c\xi + a\xi + \mu)}, \quad (20)$$

the disease free equilibrium $(1, 0)$ is nonlinearly stable.

$$\xi_n = n^2\pi^2/L^2, \quad \xi_1 = \xi.$$

According to their eigenvectors, we obtain the transformation matrix:

$$Q = \begin{bmatrix} \frac{-2(c\xi + \beta)}{\beta - \epsilon + h} & 1 \\ 1 & -\frac{(\beta - \epsilon - h)}{2(c\xi + \beta)} \end{bmatrix},$$

where h is a known function of β , c , and ϵ . Defining:

$$\mathcal{A} = \sqrt{2}\beta \left[\frac{1}{a-c} \left(1 + \frac{\beta}{c\xi + \beta} \right) + \frac{c\xi}{(a+c)(c\xi + \beta)} \right]. \quad (21)$$

The condition

$$E(0) < \left(\frac{\mu \left[1 + \frac{a-c}{\mu} - R_0 \right]}{\mathcal{A}} \right)^2, \quad (22)$$

assures that the new energy $E(t)$ decays exponentially.

The method can be applied also to study the stability of H_1 [MSW 2007].

APPLICATION TO BIOLOGY: GLIA AGGREGATION

M. Helal, E. Hingant, L. Pujo-Menjouet, G. F. Webb, (2014),
Alzheimers disease: analysis of a mathematical model incorporating
the role of prions *J. Math. Biol.* **69**, Issue 5, 1207–1235

“Alzheimers disease (AD) is acknowledged as one of the most widespread diseases of age-related dementia with $\cong 35.6$ million people infected worldwide according to Wimo and Prince (2010). By the 2050s, this same report has predicted three or four times more people living with AD. AD affects memory, cognizance, behavior, and eventually leads to death. Apart from the social dysfunction of patients, another notable societal consequence of AD is its economic cost (\approx \$422 billion in 2009, e.g. Wimo and Prince 2010)”.

We now address the problem of **finding a threshold such that glia cells, which are the support structure for the central nervous system, will not aggregate in the brain**. Mathematically this is an example where we have three PDE equations, strong nonlinearities, cross diffusion effects, and Neumann boundary conditions.

Luca et al. [9] explain the biological background of Alzheimer's disease and the possible connection with the aggregation of cells found in the brain, glia, into the formation of senile plaques. These writers develop a simplified model for glia aggregation which is based on the glia cell density $m(\mathbf{x}, t)$ and two chemicals secreted by the glia, or produced in the aggregation process, interleukin 1- β , IL1- β , and tumor necrosis factor, TNF- α . The concentrations of the latter in the brain are denoted by $c_1(\mathbf{x}, t)$, $c_2(\mathbf{x}, t)$.

In the model of Luca et al. [9], IL1- β acts as a chemoattractant while TNF- α plays the role of a chemorepellant.

Luca et al. [9] write their equations in one space dimension, but in 3-D they are

$$\begin{aligned}\frac{\partial m}{\partial t} &= \mu \Delta m - \nabla \cdot (\chi_1 m \nabla c_1 - \chi_2 m \nabla c_2) \\ \frac{\partial c_\alpha}{\partial t} &= D_\alpha \Delta c_\alpha + a_\alpha m - b_\alpha c_\alpha, \quad \alpha = 1, 2.\end{aligned}\tag{23}$$

The coefficients μ (motility), χ_1 (attractant chemotactic), χ_2 (repellent chemotactic), D_α (diffusion), a_α (rates of production of the chemicals), b_α (rates of decay of the chemicals), are taken to be positive constants. Let Ω be the domain (of the brain) with boundary Γ . The boundary conditions are of zero flux type and so on Γ

$$\frac{\partial m}{\partial n} = \frac{\partial c_1}{\partial n} = \frac{\partial c_2}{\partial n} = 0. \quad (24)$$

Initial conditions are given so that at time $t = 0$

$$m(\mathbf{x}, 0) = m_0(\mathbf{x}), \quad c_1(\mathbf{x}, 0) = g_1(\mathbf{x}), \quad c_2(\mathbf{x}, 0) = g_2(\mathbf{x}). \quad (25)$$

Consider a **constant steady state** \bar{m} , \bar{c}_1 , \bar{c}_2 , and the perturbation equations.

Now let m' , ϕ and ψ be perturbations to \bar{m} , \bar{c}_1 , \bar{c}_2 , it can be proved (see M. and Straughan, *SIAM J. Appl. Math.* 2009, [8]) that the perturbations have zero mean, provided they have zero mean initially, i.e.

$$\int_{\Omega} m'(\mathbf{x}, t) dx = 0, \quad \int_{\Omega} \phi(\mathbf{x}, t) dx = 0, \quad \int_{\Omega} \psi(\mathbf{x}, t) dx = 0. \quad (26)$$

Equations (26) are important in the analysis which follows to ensure the validity of Poincaré and Sobolev inequalities.

Luca et al. [9] develop a complete linearized instability analysis about the constant steady state $\bar{m}, \bar{c}_1, \bar{c}_2$.

Biologically this is relevant because it corresponds to the (normal) situation in the brain before any glia aggregation commences.

Their analysis derives a threshold between the parameter $a = L_2/L_1$ and $A = \chi_1 a_1 D_1 / \chi_2 a_2 D_2$ which represent the ratio of length scales of attraction and repulsion and the ratio of strengths of attraction and repulsion. When the chemorepulsion is strong and short-ranged ($A < 1, a > A^{1/2}$), the homogeneous steady state is stable.

($L_\alpha = D_\alpha / b_\alpha$ are the distance over which chemicals spread during the characteristic time of decay).

In terms of a non-dimensionalized steady state $\bar{m} = 1, \bar{c}_1 = 1, \bar{c}_2 = 1$, we introduce non-dimensional perturbations m', ϕ, ψ , and then the non-dimensional, nonlinear equations and boundary conditions may be written

$$\begin{aligned}
\frac{\partial m'}{\partial t} &= \Delta m' - A_1 \Delta \phi + A_2 \Delta \psi - A_1 \nabla \cdot (m' \nabla \phi) + A_2 \nabla \cdot (m' \nabla \psi) \\
\epsilon_1 \frac{\partial \phi}{\partial t} &= \Delta \phi + a^2(m' - \phi) \\
\epsilon_2 \frac{\partial \psi}{\partial t} &= \Delta \psi + m' - \psi
\end{aligned} \tag{27}$$

in $\Omega \times (0, T)$, for some time $T > 0$,

$$\frac{\partial m'}{\partial n} = \frac{\partial \phi}{\partial n} = \frac{\partial \psi}{\partial n} = 0 \quad \text{on } \Gamma. \tag{28}$$

We should mention that [Quinlan & Straughan](#) [11] have performed a nonlinear stability analysis for (27), (28). They used a Lyapunov function of form

$$E(t) = \|m'\|^2 + \lambda_1 \|\nabla \phi\|^2 + \lambda_2 \|\nabla \psi\|^2 \tag{29}$$

however, measure (29) **does not lead to an optimal result** and their nonlinear stability thresholds lie below the linear instability ones.

By using **the reduction method**, we show **how to recover the instability boundary** and derive a fully nonlinear stability result.

We begin with the linearized version of (27), namely

$$\begin{aligned}m'_t &= \Delta m' - A_1 \Delta \phi + A_2 \Delta \psi \\ \phi_t &= \epsilon_1^{-1} [\Delta \phi + a^2 (m' - \phi)], \\ \psi_t &= \epsilon_2^{-1} [\Delta \psi + m' - \psi].\end{aligned}\tag{30}$$

Define the vector U by

$$U = (U_1, U_2, U_3)^T = (m', \phi, \psi)^T.\tag{31}$$

Let $-\xi_{\bar{n}}$ be the eigenvalue of the Laplacian which yields the linear instability boundary of [Luca et al. \[9\]](#) (usually $\bar{n} = 1$, but this is not always the case), so

$$\Delta\zeta = -\xi_{\bar{n}}\zeta.$$

Let us define $\xi = \xi_{\bar{n}}$, then replace Δ by $-\xi$. The matrix A_{ξ} is given by

$$A_{\xi} = \begin{pmatrix} -\xi & A_1\xi & -A_2\xi \\ a^2\epsilon_1^{-1} & -\epsilon_1^{-1}(\xi + a^2) & 0 \\ \epsilon_2^{-1} & 0 & -\epsilon_2^{-1}(\xi + 1) \end{pmatrix}$$

from the right hand side of (30).

Let A_ξ have eigenvalues $\lambda_1, \lambda_2, \lambda_3$ (not necessarily real and distinct). Let $\mathbf{a}_1, \mathbf{a}_2, \mathbf{a}_3$, be the generalized eigenvectors (or vectors) corresponding to $\lambda_1, \lambda_2, \lambda_3$ and then define the transformation matrix

$$Q = \left(\mathbf{a}_1^T, \mathbf{a}_2^T, \mathbf{a}_3^T \right).$$

We transform from U to $V = (V_1, V_2, V_3)^T$ by

$$V = Q^{-1}U. \quad (32)$$

And then rewrite the fully nonlinear version of (27) as

$$V_{i,t} = F_{ik} \Delta V_k + G_{ik} V_k + \tilde{N}_i(V), \quad V(0) = V_0, \quad (33)$$

$$F = Q^{-1}DQ, \quad G = Q^{-1}LQ, \quad \tilde{N}(V) = Q^{-1}N(QV). \quad (34)$$

The matrices D and L are given by

$$D = \begin{pmatrix} 1 & -A_1 & A_2 \\ 0 & -\epsilon_1^{-1} & 0 \\ 0 & 0 & -\epsilon_2^{-1} \end{pmatrix}$$

$$L = \begin{pmatrix} 0 & 0 & 0 \\ a^2 \epsilon_1^{-1} & -a^2 \epsilon_1^{-1} & 0 \\ \epsilon_2^{-1} & 0 & -\epsilon_2^{-1} \end{pmatrix}$$

(We have implemented a *Maple* program to give Q , F , and G once we give explicit values of the coefficients. This rapidly yields the required matrices in any situation).

The key is now to multiply (33) by V_i and integrate over Ω to find

$$\dot{E}(t) = -(F \nabla V, \nabla V) + (GV, V) + (\tilde{N}, V), \quad (35)$$

where $E = \frac{1}{2} \|V\|^2$ and F and G give rise to bilinear forms as indicated, (\cdot, \cdot) being the inner product on $L^2(\Omega)$. Note that due to (32) V_i also satisfy Neumann boundary conditions on Ω . We need to restrict the coefficients of F such that $(F \nabla V, \nabla V)$ is a positive-definite form, indeed, these are also conditions required in a linear stability analysis.

Then define

$$M = \max_H \frac{(GV, V)}{(F\nabla V, \nabla V)}, \quad (36)$$

H being the space of admissible solutions V_1, V_2, V_3 . From (35) we may derive

$$\dot{E}(t) \leq -(F\nabla V, \nabla V)(1 - M) + (\tilde{N}, V). \quad (37)$$

The condition that $M = 1$ yields exactly the linear stability - instability threshold of [Luca et al. \[9\]](#).

Of course, it remains to handle the nonlinear term (\tilde{N}, V) .

For this, we use a Lyapunov function of form

$$\mathcal{E}(t) = E(t) + \beta_1 \|\nabla V\|^2 + \beta_2 \|\Delta V\|^2, \quad (38)$$

where $\beta_1 > 0$ and $\beta_2 > 0$ are positive constants to be chosen.

If we are inside the linear stability boundary of Luca et al. [9] then we have shown $\mathcal{E} \rightarrow 0$ exponentially provided $\mathcal{E}^{1/2}(0) < \frac{k}{\tilde{h}}$, for explicit positive values of k, \tilde{h} .

A NOTE ON HEROIN EPIDEMICS

Treatment of heroin users or users of other drugs such as crack cocaine is a costly procedure and is a major burden on the health system of any country. Two very interesting models have recently been proposed. One for treating heroin users, proposed by White and Comiskey, E. White, C. Comiskey, *Heroin epidemics, treatment and ODE modelling*, *Math. Biosci.* 208 (2007) 312, and a similar one for those with alcohol problems, see Sánchez et al., F. Sánchez, X. Wang, C. Castillo-Cáñez, D.M. Gorman, P.J. Gruenwald, *Drinking as an epidemic: a simple mathematical model with recovery and relapse*, in: K. Witkiewitz, G. Alan Marlett (Eds.), *Therapists Guide to Evidence-Based Relapse Prevention*, Academic Press, New York, 2007, p. 353.

Both models divide the mathematical problem into three classes, namely **susceptibles**, **heroin users or alcoholics**, and **heroin users or alcoholics undergoing treatment**. In fact, the two types of model are very similar. The one of Sánchez et al. differs from that of White and Comiskey only in that Sánchez et al. assume the same death/removal rate for each of the three classes, whereas White and Comiskey allow the drug users and those in treatment to have enhanced death rates.

Two key terms are the probability of becoming a drug user per unit time, and the probability of a drug user in treatment relapsing to untreated use per unit time. White & Comiskey denote these, respectively, by β_1 and β_3 . The value for β_1 is usually relatively small.

- $\beta_1 = O(0.02)$ and $\beta_3 = O(0.8)$ seem reasonable.

THE WHITE-COMISKEY MODEL

$$\begin{cases} \dot{S} = \Lambda - \frac{\beta_1 U_1 S}{N} - \mu S \\ \dot{U}_1 = \frac{\beta_1 U_1 S}{N} - p U_1 + \frac{\beta_3 U_1 U_2}{N} - (\mu + \delta_1) U_1 \\ \dot{U}_2 = p U_1 - \frac{\beta_3 U_1 U_2}{N} - (\mu + \delta_2) U_2. \end{cases} \quad (39)$$

Here S , U_1 , U_2 , $N (= S + U_1 + U_2)$ are the number of susceptibles in the population, the number of drug users not in treatment, the number of drug users in treatment, and the total population size, respectively.

The quantities Λ , μ , δ_1 , δ_2 , β_1 , β_3 , p are

Λ : the number of individuals entering the susceptible population,

μ : the natural death rate of the general population,

δ_1 : an enhanced removal/death rate for drug users,

δ_2 : an enhanced removal/death rate for drug users undergoing treatment,

β_1 : the probability of becoming a drug user, per unit time,

β_3 : the probability of a drug user in treatment relapsing to untreated use, per unit time,

p : the portion of drug users who enter treatment, per unit time.

White and Comiskey assume

$$\Lambda = \mu S + (\mu + \delta_1)U_1 + (\mu + \delta_2)U_2. \quad (40)$$

However, when they analyze equilibrium solutions and their stability they take Λ to be constant.

In [M. and Straughan (2009)], we revisit the heroin addiction problem with the model of White and Comiskey but when Λ is given by (40).

In this case the ODE system is the following

$$\begin{cases} \dot{S} = (\mu + \delta_1)U_1 + (\mu + \delta_2)U_2 - \frac{\beta_1 U_1 S}{N} \\ \dot{U}_1 = \frac{\beta_1 U_1 S}{N} - pU_1 + \frac{\beta_3 U_1 U_2}{N} - (\mu + \delta_1)U_1 \\ \dot{U}_2 = pU_1 - \frac{\beta_3 U_1 U_2}{N} - (\mu + \delta_2)U_2 \end{cases} \quad (41)$$

Since $N = S + U_1 + U_2$ is constant, we introduce the fractions of S , U_1 and U_2 :

$$s = \frac{S}{N}, \quad u_1 = \frac{U_1}{N}, \quad u_2 = \frac{U_2}{N},$$

with $s + u_1 + u_2 = 1$.

This results in the equations:

$$\begin{cases} \dot{s} = (\mu + \delta_1)u_1 + (\mu + \delta_2)u_2 - \beta_1 u_1 s \\ \dot{u}_1 = \beta_1 u_1 s - \rho u_1 + \beta_3 u_1 u_2 - (\mu + \delta_1)u_1 \\ \dot{u}_2 = \rho u_1 - \beta_3 u_1 u_2 - (\mu + \delta_2)u_2. \end{cases} \quad (42)$$

Since $u_2 = 1 - s - u_1$, we may consider the system for s and u_1 (which is the *analogue* of the s, i system in the epidemic model with vital dynamics, Hethcote [26]):

$$\begin{cases} \dot{s} = (\mu + \delta_1)u_1 + (\mu + \delta_2)(1 - s - u_1) - \beta_1 u_1 s \\ \dot{u}_1 = \beta_1 u_1 s - \rho u_1 + \beta_3 u_1(1 - s - u_1) - (\mu + \delta_1)u_1. \end{cases} \quad (43)$$

Simplifying, we obtain

$$\begin{cases} \dot{s} = \mu + \delta_2 + (\delta_1 - \delta_2)u_1 - (\mu + \delta_2)s - \beta_1 u_1 s \\ \dot{u}_1 = (\beta_3 - \rho - \mu - \delta_1)u_1 + (\beta_1 - \beta_3)u_1 s - \beta_3 u_1^2. \end{cases} \quad (44)$$

From system (44) we see that $(s = 1, u_1 = 0, u_2 = 0)$ is a **disease-free** equilibrium.

If $R_0 := \frac{\beta_1}{\rho + \mu + \delta_1} < 1$, we have stability, if $R_0 > 1$ the disease-free state is unstable.

- **Endemic equilibrium** ($R_0 > 1$)

We may assume that $0 < \beta_1 < \beta_3$, which is reasonable in real life.

$$\bar{s} = \frac{\beta_3}{\beta_1 - \beta_3} \bar{u}_1 + \frac{\rho + \mu + \delta_1 - \beta_3}{\beta_1 - \beta_3} = -\frac{\beta_3 \bar{u}_1}{\beta_3 - \beta_1} + \frac{(\beta_3 - \rho - \mu - \delta_1)}{\beta_3 - \beta_1}, \quad (45)$$

$$\bar{u}_1 = \frac{-h + \sqrt{h^2 + 4\beta_1\beta_3(\mu + \delta_2)(\beta_1 - \rho - \mu - \delta_1)}}{2\beta_1\beta_3}, \quad (46)$$

where

$$h = \beta_1(\rho + \mu + \delta_2 - \beta_3) + \beta_3(\delta_1 + \mu).$$

The sign of h depends on the size of β_3 .

The nonlinear system of perturbation equations for studying the stability of the endemic equilibrium is

$$\begin{cases} \dot{s} = -(\beta_1 \bar{u}_1 + \mu + \delta_2)s + \frac{(\mu + \delta_2)(\bar{s} - 1)}{\bar{u}_1} u_1 - \beta_1 u_1 s \\ \dot{u}_1 = (\beta_1 - \beta_3) \bar{u}_1 s - \beta_3 \bar{u}_1 u_1 + (\beta_1 - \beta_3) u_1 s - \beta_3 u_1^2. \end{cases} \quad (47)$$


We put

$$H = \frac{(\mu + \delta_2)(1 - \bar{s})}{\bar{u}_1}, \quad K_1 = (\beta_3 - \beta_1) \bar{u}_1, \quad \beta_3 > \beta_1.$$

By studying the eigenvalues of the Jacobian matrix, we prove that the **endemic equilibrium is stable**.

The nonlinear system of perturbation equations for studying the stability of the endemic equilibrium is given by (47), observing $\beta_3 > \beta_1$. In terms of H and K_1 this system is

$$\begin{cases} \dot{s} = -(\beta_1 \bar{u}_1 + \mu + \delta_2)s - H u_1 - \beta_1 u_1 s \\ \dot{u}_1 = -K_1 s - \beta_3 \bar{u}_1 u_1 + (\beta_1 - \beta_3) u_1 s - \beta_3 u_1^2. \end{cases} \quad (48)$$

For this case the linear operator attached to (48) is trivially **symmetrizable** (multiply (48)₂ by H/K_1). Hence, since **the linear** 

operator becomes symmetric nonlinear stability follows, at least in a neighborhood of (\bar{s}, \bar{u}_1) , cf. Straughan [17], pp. 77-87.

It is also possible (Poincaré-Bendixson) to prove that the equilibrium (\bar{s}, \bar{u}_1) is globally asymptotically stable for positive initial conditions when $R_0 > 1$.

We believe the analysis given here places the White & Comiskey [29] model for heroin users/treatment on a very firm footing. There are further aspects / generalizations we should like to consider in the future. Among these we mention the possibility of considering the male/female distribution of drug users. For example, see Hay [24], in the 2004/5 assessment, the prevalence rate of opiate users in the North East of England shows a big variation between male and female rates. In Middlesbrough the prevalence rates were, female 7.73, male 34.91, in Northumberland, female 2.80, male 5.97, in Newcastle, female 6.56, male 19.25. Such a large variation probably deserves investigation.

We also believe **effects of movement between places could be very important**. This would lead to a system of coupled nonlinear partial differential equations, although this would be of parabolic-hyperbolic type since the diffusion coefficient of those in treatment is presumably zero or very small since they should stay close to their place of treatment. Such degenerate parabolic-hyperbolic systems represent a difficult class of partial equations to analyze, cf. M. & Solonnikov [28].

CONCLUSION

- Symmetry of a constant linear operator does not “help” stability
- The previous result does not hold for non-autonomous system (both in ODEs and PDEs), for example in the presence of delay effects
- Optimal Lyapunov functions in PDEs of biological systems with diffusion
- Global stability results or local stability with a known attracting radius

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