

Optimal Control of the Intestinal Microbiome using Lotka-Volterra Model

BB-JR

Stein et al.
Jones et al.

1. Mathematical Model

$$\begin{aligned}\dot{x} = & \underbrace{(\text{diag } \gamma)}_{\text{Lotka-Volterra}} (Ax + b) \\ & + \underbrace{(\text{diag } \gamma)}_{\text{Probiotic, Antibiotic}} \sum w_i(t) E_i \\ & + \underbrace{\sum \lambda_i \delta(t - t_i)}_{\text{Transplantation, bactericide}} V_i\end{aligned}$$

- $x = (x_1, x_2, \dots, x_N)$ $N = 11$
- $x_1 = C\text{-difficile}$ (infected population)

Complexity $X(x) = (\text{diag } \gamma)(Ax + b)$
up to $2^{11} = 2048$ equilibria

Aim: Reduce x_1 -population

- Two types of controls

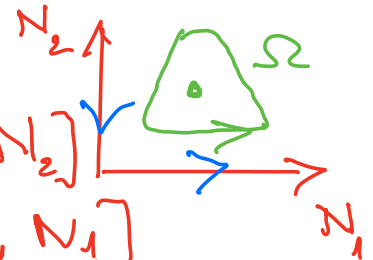
- Probiotics, antibiotics : permanent case but can be set in the sample-data control frame
- Transplantation, bactericides : invasive treatments : sampled-data control frame.

Volterra 1931

Origin of the Model : Lotka-Volterra

Historical d'Ancona : study the effect of the reduction of the fishing during the First World War on a prey-predator model :

$$\begin{aligned}\dot{N}_1 &= N_1 [r_1 - \alpha \lambda(t) - a_{12} N_2] \\ \dot{N}_2 &= N_2 [-r_2 - \beta \lambda(t) + a_{21} N_1]\end{aligned}$$



- $\lambda(t) = 0$: no fishing
- Every trajectory is periodic
- $\Omega = (K_1, K_2)$: interior equilibria

Theorem $\underbrace{\langle N_i \rangle}_{\text{Averaged population}} = \frac{1}{T} \int_0^T N_i(t) dt = K_i$

- $\lambda(t) = ct$: intensity of the fishing activity

Effect Shift the interior equilibria
and the averaged population

Objective of the talk

[Present the techniques from optimal
control to analyze the problem

- Step 1 $\left\{ \begin{array}{l} \text{One antibiotic or probiotic} \\ \text{only} : \dot{x} = X(x) + uY(x) \\ u \in [0, 1] \end{array} \right.$
- Step 2 2d-case
 - x_1 : C-difficile population
 - x_2 : reduced model: aggregation
of $(x_2, \dots, x_N)$

Formulation optimal problem terminal manifold N

- $\text{Min } x_1(t_f) \xLeftrightarrow{\text{dual}} \text{Reach} : x_1(t_f) = d$
in minimum time

- Indirect Method : Maximum Principle
(permanent case and sampled-data case)
- Direct Methods : MPC scheme

Sketch of the analysis

Maximum Principle

Open loop analysis :

$(x(\cdot), u(\cdot))$ optimal on $[0, t_f]$ solutions of :

$$\begin{cases} \dot{x} = \frac{\partial H}{\partial p} & , \quad \dot{p} = -\frac{\partial H}{\partial x} \\ H(x, p, u) = \max_{|v| \leq 1} H(x, p, v) \end{cases}$$

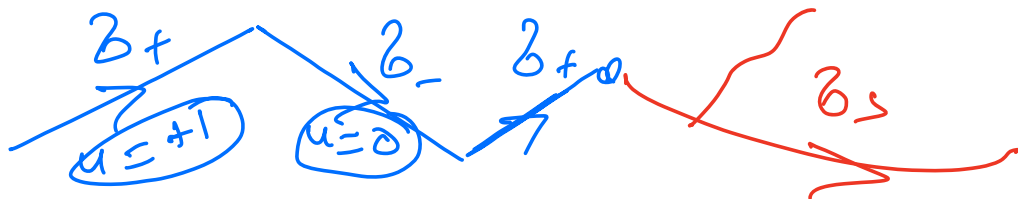
$$H = p \cdot (\dot{x} + u \gamma)$$

Classification

- Regular controls : $u(t) = 1$ if $p(t) \cdot \gamma(x(t)) > 0$ and $u(t) = 0$ if $p(t) \cdot \gamma(x(t)) < 0$

- Singular case $p(t) \cdot \gamma(x(t)) = 0$ identically.

Singular arc



Computations singul- arcs

Derive / t : $p(t) \cdot \gamma(hc(t)) = 0$
 $-p \cdot \frac{\partial x}{\partial x} + u \frac{\partial \gamma}{\partial x} + p \cdot \frac{\partial \gamma}{\partial x} (x + u \gamma) = 0$

Hence $p(t) [\gamma, x](hc(t)) = 0$ Lie bracket

Derive / t

$$p(t) \cdot [[\gamma, x], x](hc(t)) + u_s [[\gamma, x], \gamma](hc(t)) = 0$$

Theorem Singul- arcs are located on the determinantal set $\mathcal{S} : \det(\gamma, [\gamma, x]) = 0$ and the singular control is given by :

$$u_s(t) = u_s(hc) = - \frac{\det(\gamma, [[\gamma, x], x])}{\det(\gamma, [\gamma, x], x)}$$

Computations $\{x, \gamma\}$ $\begin{cases} x : (\text{diag } \epsilon)(Ax + e) \\ \gamma : (\text{diag } \epsilon) \in \end{cases}$

Singul- locus In the permanent domain : $x > 0, y > 0$: $\mathcal{S} =$ line passing through the origin

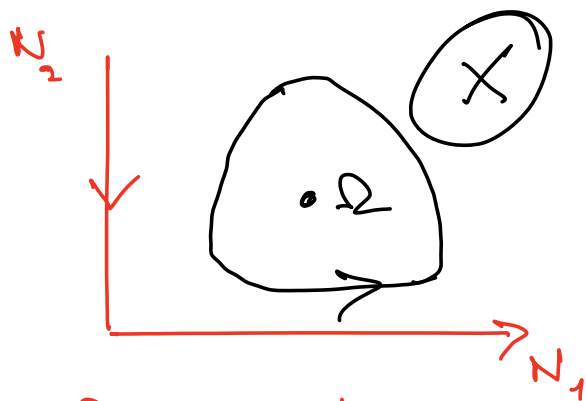
Collinear locus $\mathcal{C} : \det(x, \gamma) = 0$

Back to Lotka-Volterra model

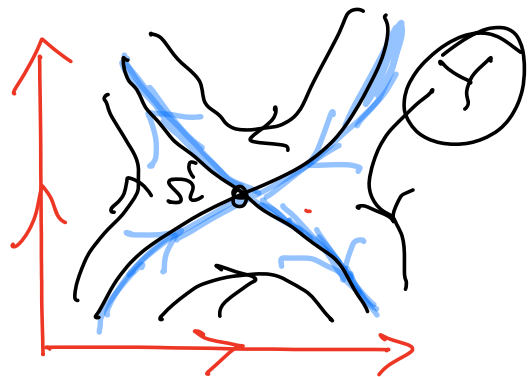
$$\dot{N}_1 = N_1 (r_1 - a_{12} N_2)$$

$$\dot{N}_2 = N_2 (r_2 - a_{21} N_1)$$

Two different cases



Prey-predator :
Equilibrium Ellipse



Equilibrium Hyperbola

Control system

$$\dot{x} = u X + (1-u) Y$$

$$u \in [0, 1]$$

$u = \lambda$ Bifurcation parameter

$X \rightarrow Y$

Interpretation

$\left\{ \begin{array}{l} u=0 : \text{no treatment} \\ u=1 : \text{maximal dosing} \end{array} \right.$

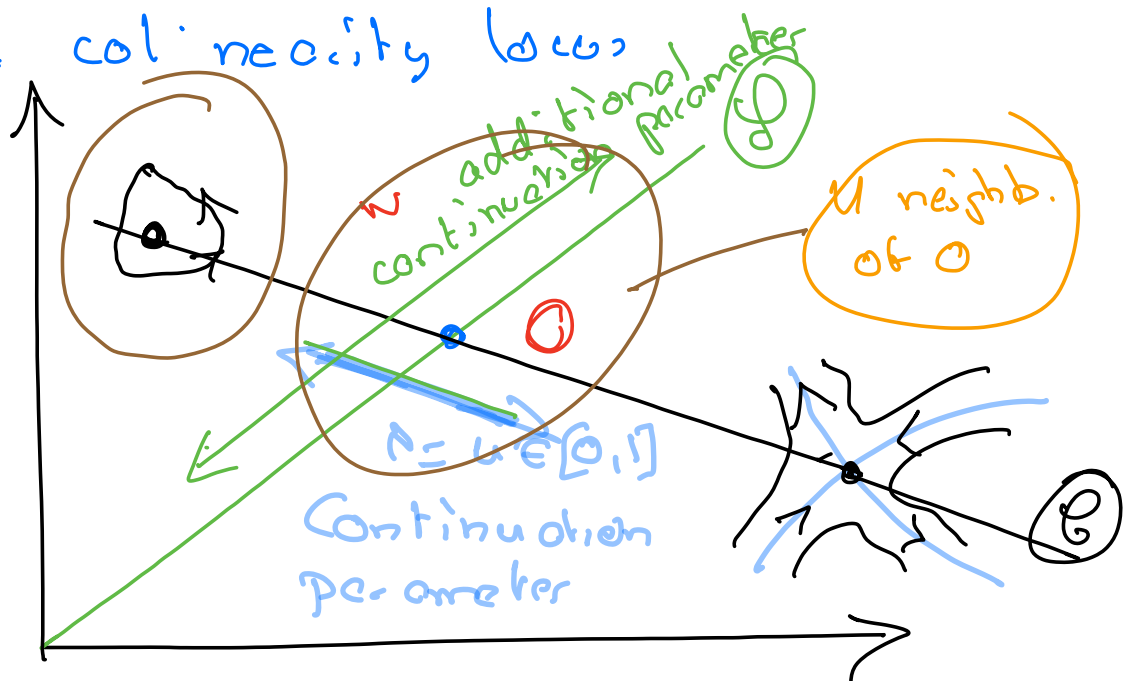
For every intermediate value $u = \lambda$ there exist a constant control u_c such that $(X + Y)(u_c)$ admits a persistent equilibrium

$$x_e = \Omega(\lambda)$$

Hence One has a general picture in the 2d-case to analyze the problem geometrically using :

$\mathcal{S}$: singular locus

$\mathcal{C}$: colinearity locus



Key point Understanding the time minimal synthesis (closed loop optimal control) at the point O .

Construction of a semi-normal form

$$\begin{cases} \dot{x} = -x + wy + \alpha^2 y^2 \\ \dot{y} = (u - u_e) \end{cases}$$

$$X \begin{cases} -x + wy + \alpha^2 y^2 \\ -u_e \end{cases} \quad Y \begin{cases} 0 \\ 1 \end{cases}$$

Singular line $\approx y=0$

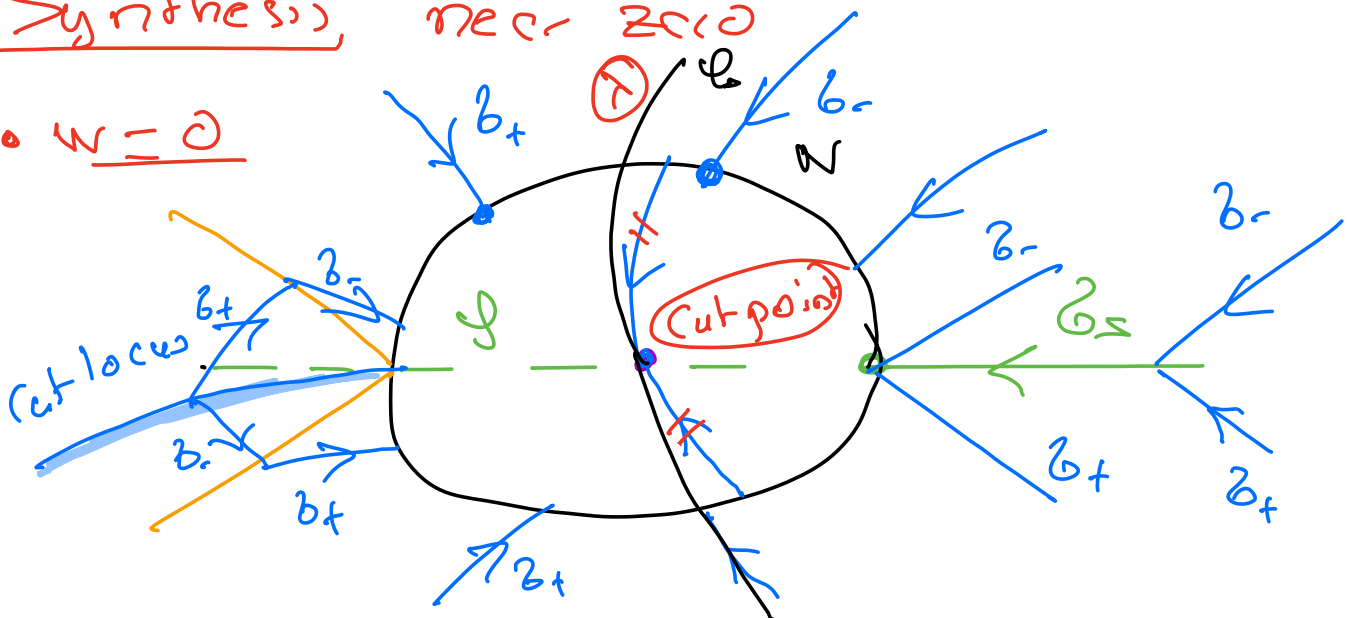
Singular dynamics $\dot{x} = -x$

$$\bullet [X, Y] = \begin{bmatrix} w + 2\alpha y \\ 0 \end{bmatrix} \quad [X, Y], Y \begin{bmatrix} 2\alpha \\ 0 \end{bmatrix}$$

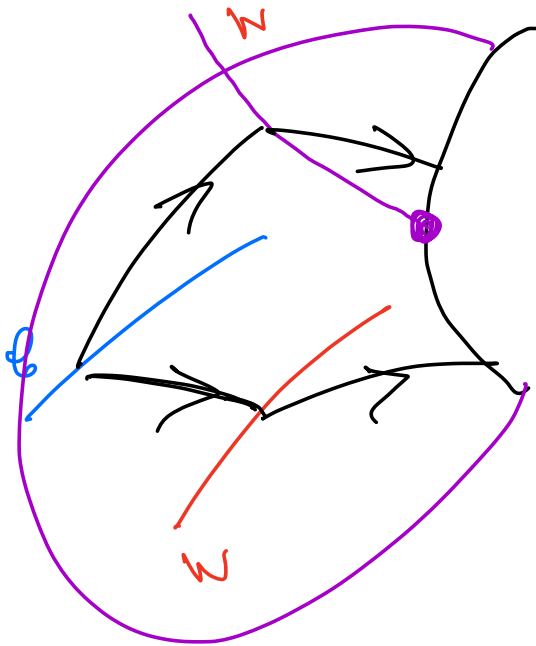
Target N : circle of radius 1 centered at 0

Synthesis, near zero

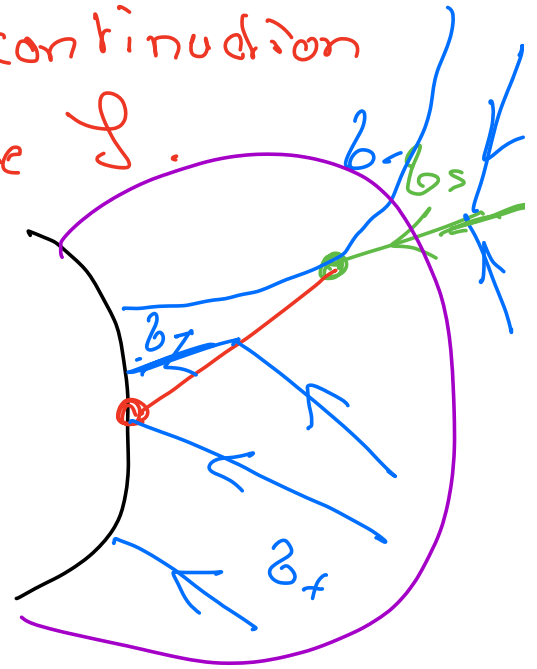
$$\bullet \underline{w=0}$$



- $w \neq 0$ paramètre de continuation
déploiement le long de $\mathcal{J}$.



- detachment of one branch of switching locus
- detachment of the cut locus



- birth of a switching locus
- detachment of the singular locus

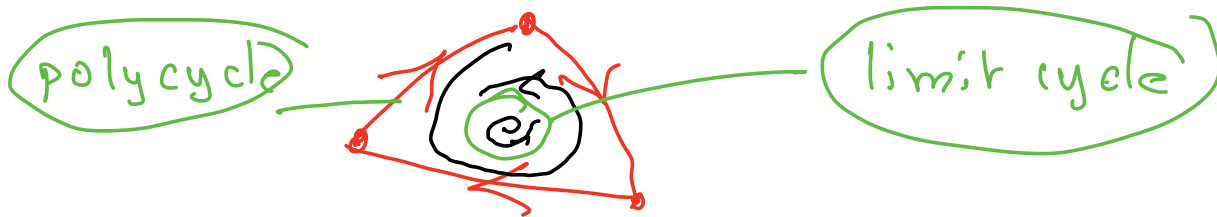
Conclusion

- Geometric study $\rightarrow$ automatic computation of the time minimal synthesis / Continuation method

- Singularity analysis : intersection of the collinearity locus and of the singular locus

generalization N-dimensional case

- More complicated 2d-models in relation with 16th Hilbert problem



Sampled-data control - Finite dimensional optimization - MPC

$$\dot{x} = X(x) + u \cdot f(x)$$

$$u \in [0, 1]$$

Digital constraints



- t_f : duration of the medical treatment
- N : fixed number of medical interventions

Inter-pulse: $T_k = t_k - t_{k-1} \geq \varepsilon > 0$

• $t_1, \dots, t_{N-1}$ are free $0 < t_1 < t_2 < \dots < t_{N-1} < t_f$

The LV-dynamics defines a finite dimensional input-output mapping:

$$\underbrace{(t_1, u_1, \dots, t_{N-1}, u_{N-1})}_{\lambda} \longrightarrow x(t, \lambda)$$

and a Mayer problem: $\min_{\lambda} P(t_f)$

Indirect scheme: Maximum Principle
sampled-data Forme

Origin: Back to the standard
calculus of variations

List of admissible perturbations

• L^∞ -type: u_i on $[t_i, t_{i+1}]$

Replace: $u_i \rightarrow u_i + \varepsilon \delta u_i$
on $[t_i, t_{i+1}]$

Maximum Principle: sampled case:

$$\int_{t_i}^{t_{i+1}} P(s) \gamma(x_s(t, u_i)) \delta u_i \leq 0 \quad (*)$$

$\forall \delta u_i$

"Averaged" Condition

- L^1 -type $u: u_i$ on $[t_i, t_{i+1}]$
 $\hookrightarrow u^* : u_i$ on $[t_i + \varepsilon, t_{i+1}]$

As before : Evaluate :

$$\lim_{\varepsilon \rightarrow 0} \frac{\varphi(x(t_F, u^*)) - \varphi(x(t_F, u))}{\varepsilon}$$

One can apply the different variations
to get a set of necessary optimality
conditions.

Difficult to implement numerically :

"Variational Inequalities"

see condition (*)

A more suitable optimization scheme

has to be applied

$$\min_{\Delta} \varphi(x(t_F, \Delta))$$

Practical application : MPC-scheme

Optimize over a finite horizon
of length k of sampling time:

- Step 1 t_0 : $\text{Min } P(t_0+k, \Delta)$
 $u = \Delta \leq k$
 $x(0) = x_0$
- Step 2 Apply $u_{\min}$ on $[t_0, t_0+1]$
 $x(0) \rightarrow x(t_0+1)$
- Iterate the construction up to
 t_F .

Short bibliography

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Nice, 14 Octobre 22
Gdr. MOA
