Geometric Optimal Control of the Generalized Lotka-Volterra Model with Applications Controlled Stability of Microbiota

Jérémy Rouot, Bernard Bonnard

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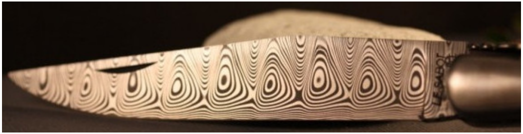


[1] joint work with B. Bonnard (INRIA) & C.J. Silva (CIDMA, Univ. Aveiro).

Controlled GLV-Model and Microbiota

$x = (x_1, \ldots, x_n)$ n–interacting species.

Species x_1: infected population

Dynamics.

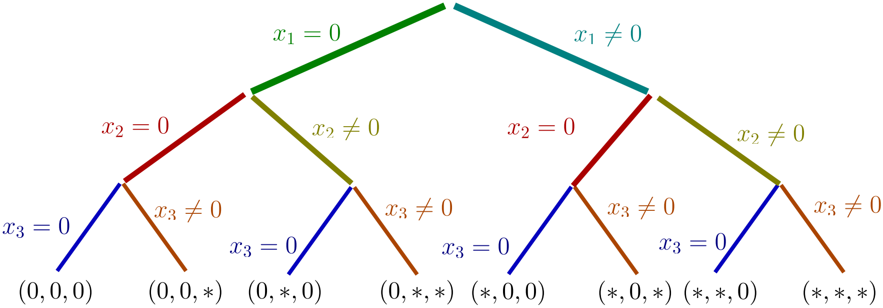
$$\dot{x} = (\mathrm{diag}\, x)\,(Ax + r)\,,$$

- $\mathrm{diag}\, x = \begin{pmatrix} x_1 & & & \\ & x_2 & & \mathbf{0} \\ & & \ddots & \\ \mathbf{0} & & & \ddots \\ & & & & x_n \end{pmatrix}$
- $A = (a_{ij})_{ij}$: interacting parameters matrix
- $r = (r_1, \ldots, r_n)^\intercal$: growth rates coefficients

Origin of the model. Lotka–Volterra prey-predator model (Volterra, 1931).

Interpretation: Describe the interaction of a population of n-species: x with linearly computable equilibria and stability.

Number of equilibria: **at most** $2^{\boldsymbol{n}}$.
Algorithm:



(to be compared with Models where the computations of equilibria are intricate).

Examples.

Chemical networks[2]**.** Dynamics depends upon the temperature using Arrhenius law.

$$A \to B \to C \text{ and } \begin{tikzcd} T + M \arrow[r, "k_1"] & A \arrow[r, "k_2"] \arrow[l, bend left, "k_3"] & B \arrow[ll, bend left=50, "k_4"] \end{tikzcd}$$

Feinberg, Horn & Jackson[3]: compute the equilibria and their stability with the concept of *deficiency*.

Biological network. Interaction with Michaelis-Menten functions generated using homographic functions.

Conclusion.

We bypass the problem of computing equilibria and their stability.

[2] E.D. Sontag, Global Stability of McKeithan's Kinetic Proofreading Model for T-Cell Receptor Signal Transduction, 1999.

[3] Feinberg and Horn-Jackson: articles in Archive Rational Mechanics, 1972.

Introduction of the control actions

- **Continuous controls:** $u(\cdot):[0,t_f]\to[0,1]$ corresponds to probiotics or antibiotics.
  Effect: Add to the dynamics : $u(t)\,(\mathrm{diag}\,x)\,\epsilon$,
  $\epsilon = (\varepsilon_1,\dots,\varepsilon_n)^\top$: sensitivity vector.

- **Impulsive controls:** $\delta(t-t')$ associated to transplantations or bactericids
  Effect: Jump at time t' in the current initial condition:
  $$x(0) \longrightarrow x(0) + \lambda v$$
  $v = (v_1,\dots,v_n)^\top$ constant $v=1$,
  λ: height of the jumps.

  Practically they correspond to the limit as $n\to\infty$ of $u_n = n$ on $[t', t'+1/n]$.

Controlled GLV–model.

$$\dot{x} = (\mathrm{diag}\,x)\,(Ax + r + u\,\epsilon) + \sum_i \lambda_i \delta(t-t_i')\,v$$

Constraints

Since impulsive controls are associated to invasive treatments only a finite number of medical interventions are allowed over $[0, t_f]$ and are defined by

$$(t'_1, \lambda_1, t'_2, \lambda_2, \ldots, t'_{p'}, \lambda_{p'}).$$

This leads to a mixture of permanent control actions and sampled-data control.

Aim: A general sampled-data control frame can be introduced since due to *medical constraints* continuous controls have to be replaced by $(u_0, \ldots, u_p)$, u_i constant in $[0, 1]$ on $0 = t_0 < t_1 < \cdots < t_p < t_f$.

$\Rightarrow$ **sampled-data control** problem with sampled defined by

$$\Xi = (t_1, \ldots, t_p, u_0, \ldots, u_p, t'_1, \ldots, t_{p'}, \lambda_1, \ldots, \lambda_{p'}).$$

Original Motivation

Reduce the *C. difficile* infection of the intestinal microbiota. [4]

$n = 11$ species. Controlled stability of the x_1 C. difficile bacteria using

- antibiotic treatments
- single fecal injection

Method. Reduce to a $2d$–model

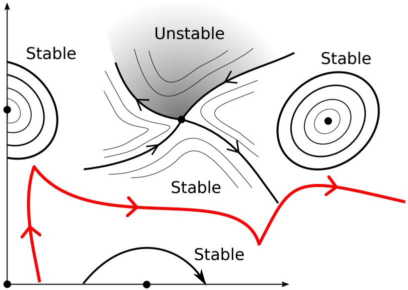


Figure: Schematic effect of Jones et al. protocol : antibiotic prior to infection & final fecal injection.

[4] Stein et al., PLOS Comp. Bio., 2013 · Jones et al., PLOS Comp. Bio, 2018

Geometric Control Theory

Mathematical difficulty : the Maximum Principle and the classification of geodesics

Back to controlled GLV-model written as

$$\dot{x} = F(x) + u\,G(x)$$

- $u = -1$: no treatment $X = F - G$.
- $u = +1$: maximal dosing treatment $Y = F + G$.

Introduce the **accessibility set** at time t_f:

$$A(x_0, t_f) = \bigcup_{u \in \mathcal{U}} x(t_f, x_0, u)$$

where $x(t_f, x_0, u)$ is the response to $u(\cdot)$.

Mathematical difficulty : the Maximum Principle and the classification of geodesics

Introduce the **accessibility set** at time t_f:

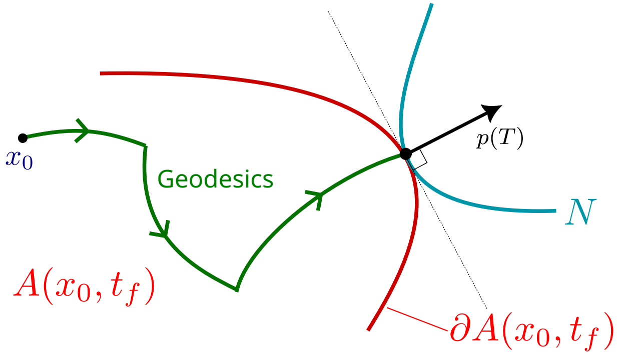
$$A(x_0, t_f) = \bigcup_{u \in \mathcal{U}} x(t_f, x_0, u)$$

where $x(t_f, x_0, u)$ is the response to $u(\cdot)$.

Basic fact: Under some mild assumptions one can restrict to **piecewise constant mappings** $u(\cdot)$ and the accessibility set $A(x_0, t_f)$ is the orbits for the action of the pseudogroup

$$S(\{X, Y\}) = \{\exp t_1 X \circ \exp t_2 Y \circ \cdots \circ \exp t_k Y,\ t_1 + \cdots + t_k = t_f,\ t_i > 0,\ k \in \mathbb{N}\}$$

(with $X = F - G$, $Y = F + G$) and geodesics belong to the boundary of the accessibility set.

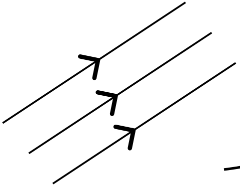


Hence it is sufficient to compute $A(x_0, t_f)$ and its boundary.

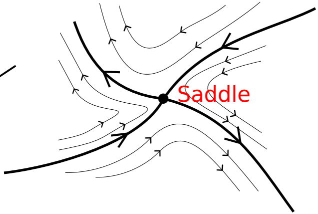
Bad news : This boundary has no real nice structure. Lipschitz ? Stratified manifold ?

Problem 1. Complexity of the dynamics of $\frac{\mathrm{d}x}{\mathrm{d}t} = Z(x)$.

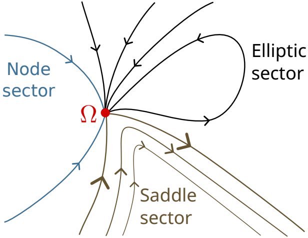
Local



regular point

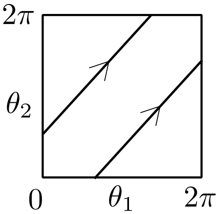


regular singular point

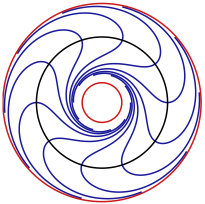


non regular singular point

Global



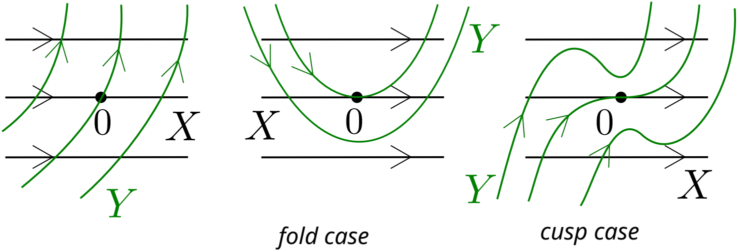
$\{\overline{\exp(tZ)}\} = \mathbb{T}^2$



$\mathbb{R}^2 \setminus \{\text{orbits not separated}\}$

- $G \sim \frac{\partial}{\partial x_n}$ in log–coordinates
- F:
  - at most 2^n computable equilibria with their linear stability
  - non regular singular point occurs at 0 related to confluence of the interactions.

Problem 2. Classification of pairs of vector fields $\{X, Y\}$ in relation with accessibility properties.



Transverse at 0 **Collinear at 0 (contact of order 2)**

Maximum Principle and Classification of Extremals up to fold points

Theorem (Pontryagin et al. 1958)

Parameterization of the boundary of the accessibility set.

Introduce $H(x,p,u) = H_F + u\,H_G$ with $H_F = p \cdot F(x)$, $H_G(x) = p \cdot G(x)$ the Hamiltonian lifts, $z = (x,p)$ and p is the adjoint vector.

The geodesics candidates to minimizers are projection of extremal curves: $t \to z(\cdot)$ solutions of

- $$\dot{x} = \frac{\partial H}{\partial p}, \quad \dot{p} = -\frac{\partial H}{\partial x},$$
  $$H(x,p,u) = \max_{|v|\leq 1} H(x,p,v).$$
- $H(x,p,u) = \max_{|v|\leq 1} H(x,p,v)$ is a **nonnegative constant** M.
- *Transversality condition.*

$$x(t_f) \in N \text{ and } p(t_f) \perp T_{x(t_f)}N.$$

Classification of extremals

First step. **Classification of singular extremals.**

- $u(t) = \text{sign}(H_G(z(t)))$ a.e. $\Rightarrow$ Regular extremals
- $H_G(z(t)) = 0$ identically $\Rightarrow$ Singular extremals
- Exceptional $M = 0 \Rightarrow$ Regular or Singular

Computing Singular Extremals

Poisson bracket: $\{H_F, H_G\} = p \cdot [F, G]$.

$$H_G = \{H_G, H_F\} = 0$$
$$\{\{H_G, H_F\}, H_F\} + u_s \{\{H_G, H_F\}, H_G\} = 0\,.$$

Once u_s is computed, define the singular extremal flow

$$\dot{z} = \vec{H}_s(z), \qquad H_s = H_F + u_s H_G.$$

One shall study this dynamics restricted to $H_G = \{H_G, H_F\} = 0$ (codim. 2).

Second step.
High Order Maximum Principle (Krener, SICON, 1977).

Discrimination of the extremals (assuming p unique up to a scalar):

- Small time minimizers Hyperbolic case

$$\frac{\partial}{\partial u}\frac{\mathrm{d}^2}{\mathrm{d}t^2}\frac{\partial H}{\partial u}(z) = \{\{H_G, H_F\}, H_G\}(z) > 0$$

- Small time maximizers Elliptic case

$$\frac{\partial}{\partial u}\frac{\mathrm{d}^2}{\mathrm{d}t^2}\frac{\partial H}{\partial u}(z) = \{\{H_G, H_F\}, H_G\}(z) < 0$$

- Exceptional $\boldsymbol{M} = 0$ (then can be both hyperbolic and elliptic).

Assuming u_s strictly admissible i.e. $u_s \in]-1, 1[$.
Saturating case: $|u_s| = 1$ at $t = t_f$.

Third step.

Classification of regular extremals near $\Sigma : H_G = 0$. (Ekeland – IHES – 1977, Kupka – TAMS – 1987)

Denote:

- σ_+: bang arc with $u = +1$
- σ_-: bang arc with $u = -1$
- σ_s: singular arc $u = u_s \in]-1, 1[$

$\sigma_1 \sigma_2$ is the arc σ_1 followed by σ_2.

Switching surface:

- $\Sigma : \{(x, p) \mid H_G(x) = 0\}$
- $\Sigma' : \{(x, p) \mid H_G(x) = H_{[G,F]}(x) = 0\} \subset \Sigma$

Switching function:

$$\Phi(t) = H_G(x(t), p(t))$$

Ordinary Switching time: $t \in]0, t_f[$ such that $\Phi(t) = 0$ and $\dot{\Phi}(t) \neq 0$.

Lemma

Near $z(t)$ every extremal solution projects onto $\sigma_+\sigma_-$ if $\dot{\Phi}(t) < 0$ and $\sigma_-\sigma_+$ if $\dot{\Phi}(t) > 0$

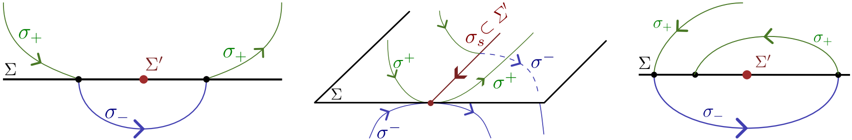
Fold case: $t \in]0, t_f[$ such that $\Phi(t) = \dot{\Phi}(t) = 0$ (then $z(t) \in \Sigma'$).

$$\ddot{\Phi}_\varepsilon = H_{[[G,F],F]+\varepsilon[[G,F],G]}, \qquad \varepsilon = \pm 1$$

Assumption: Σ' : surface of codimension two, $\ddot{\Phi}_\varepsilon(z(t)) \neq 0$ for $\varepsilon = \pm 1$.

- **parabolic case:** $\ddot{\Phi}_+(t)\ddot{\Phi}_-(t) > 0$
- **hyperbolic case:** $\ddot{\Phi}_+(t) > 0$ and $\ddot{\Phi}_-(t) < 0$
- **elliptic case:** $\ddot{\Phi}_+(t) < 0$ and $\ddot{\Phi}_-(t) > 0$

Fold case



Parabolic, Hyperbolic, Elliptic

In the parabolic case $|u_0| > 1$ and the singular arc is not admissible.

Theorem (I. Kupka, 1987 (TAMS))

In the neighborhood of $z(t) \in \Sigma'$ every extremals projects onto:

- *Parabolic case: $\sigma_+\sigma_-\sigma_+$ or $\sigma_-\sigma_+\sigma_-$*
- *Hyperbolic case: $\sigma_\pm\sigma_s\sigma_\pm$*
- *Elliptic case: every extremal is of the form $\sigma_+\sigma_-\sigma_+\sigma_-\dots$ (Bang-Bang) but the number of switches is not uniformly bounded.*

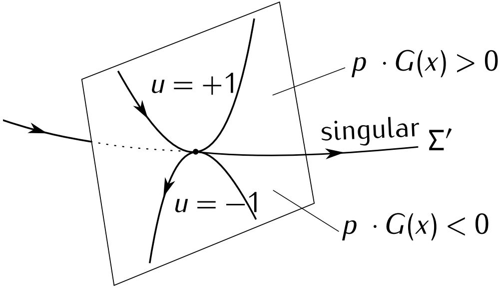


Figure: Fold case in the hyperbolic case and the turnpike phenomenon

Conclusion: Existence of the set $\Sigma' : H_G = H_{[F,G]} = 0$ leads to complicated extremal policies. This is coming from a pathology of the accessibility set in the singular directions.

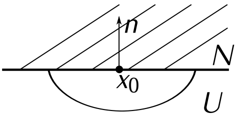
Time minimal synthesis of

$$\begin{cases} \min\ t_f \qquad |u| \le 1 \\ \dot{\mathbf{x}} = F(\mathbf{x}) + u\,G(\mathbf{x}) \\ \mathbf{x}_1(t_f) \in N = \{\mathbf{x}_1 = d\} \end{cases}$$

Methods: Two steps:

1. Calculation of the time minimal syntheses near the terminal manifold
2. Bounds on the number of switches

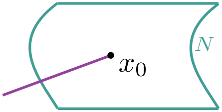
Step 1: Take $x_0 \in N$, $z_0 = (x_0, n(x_0))$ where $n(x_0)$ is the normal vector of N at x_0. Find, in a small neighborhood U of x_0, the time minimal closed loop control $u^*(x)$ to reach N starting from $\mathbf{x}$ in minimal time.



Whitney Charts and Unfolding.[5]

Construction. (U, φ, x_0) with $x_0 \in U$ an open set,
φ coordinate system $(x, y, y_1, \ldots, y_{n-3}, z)$
such that

- $G = \frac{\partial}{\partial z}$,
- $N : (1/2k\, s^2, w, w_1, \ldots, w_{n-3}, s)$ (k is the curvature),
- The (local) time minimal synthesis in U is C^0 and described with foliations by $2d$ or $3d$ synthesis.



Stratification of S.

- **Switching locus.** $W = W_+ \cup W_-$ of ordinary switching point.
- **Switching locus.** $W^s = W^s_+ \cup W^s_-$ associated to hyperbolic singular arcs.
- **Cut locus.** C where at least two minimizers with equal length are reaching the terminal manifold N.

[5](Bonnard–Kupka, Forum Math. 1991), (B.Bonnard–J.R., Annual Review Control, 2019)

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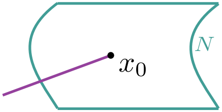

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[6] (Bonnard–Kupka, Forum Math. 1991), (B.Bonnard–J.R., Annual Review Control, 2019)

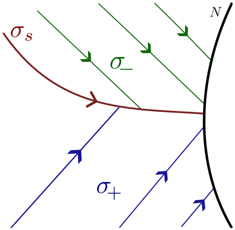
Classification and the concept of unfolding.

Example: 2 **dimensional hyperbolic case.**
Hyperbolic singular arc terminating at 0.

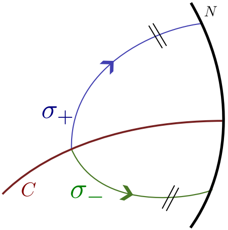
$$n \cdot G = n \cdot [G, F] = 0.$$

Normalize the singular extremal to: $\sigma_s : t \mapsto (t, 0)$.

Two generic cases :



σ_s optimal



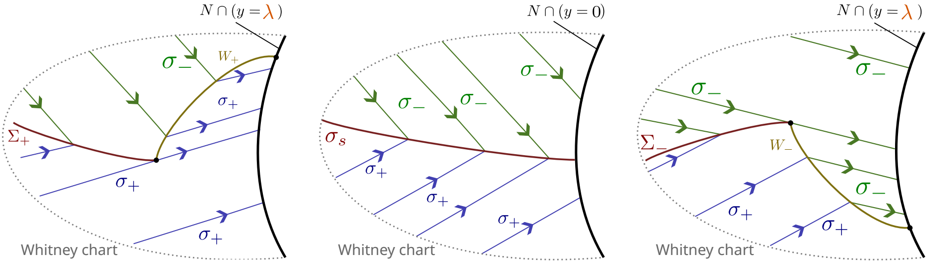
σ_s not optimal
(existence of a cut locus)

From $3d$-case to $2d$-case: Concept of Unfolding.

One can unfold the $2d$-case where σ_s is optimal as

$$N = \bigcup_{\lambda} N(\lambda)$$

where $N(\lambda)$ is one–dimensional so that the $3d$–synthesis are foliated:



$\lambda < 0$ $\qquad$ $\lambda = 0$ $\qquad$ $\lambda > 0$

This leads to compute Whitney neighborhood

$$n\text{–dimensional case} \longrightarrow 2d\text{–case}$$

where the switching locus is stratified into

$$W_+ \cup W_- \cup W_+^s \cup W_-^s$$

- W_+: $\sigma_-\sigma_+$
- W_-: $\sigma_+\sigma_-$
- W_+^s: singular locus terminating at N_+
- W_-^s: singular locus terminating at N_-

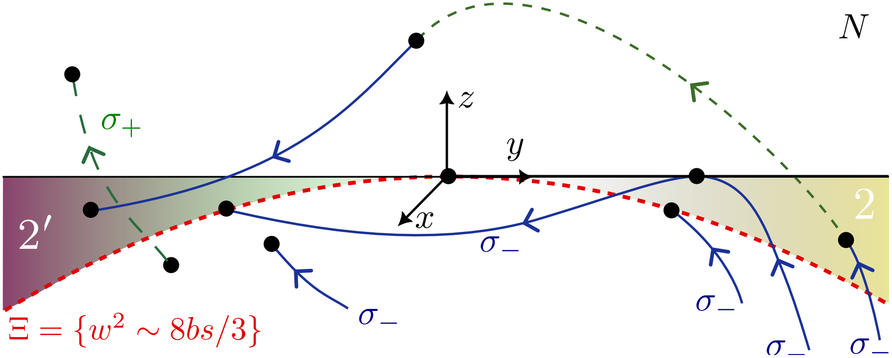
Other classifications are associated to elliptic, parabolic fold points.

Existence of a cut locus.

The limit of unfolding $3d$ to $2d$ case

- Non existence of $2d$–foliation
- Contact theory

Example: Regular Exceptional codimension 2 case.
$N = (0, w, s)$, $G = \frac{\partial}{\partial z}$.



Non-plane foliation with parameter : $w^2 - 8bs/3$.

- Every point of the target is accessible from the domain $x > 0$ by an arc σ_-.
- For $x < 0$ the optimal policy is σ_+.

In particular the dashed arc σ_- decomposes into two optimal subarcs in $x > 0$ and one subarc in $x < 0$ which is not optimal.

Such a case is not coming from an unfolding of $2d$–case.

Theorem

Every case up to codimension 2 Lie brackets relation can be unfolded as either a $2d$ or $3d$ cases.

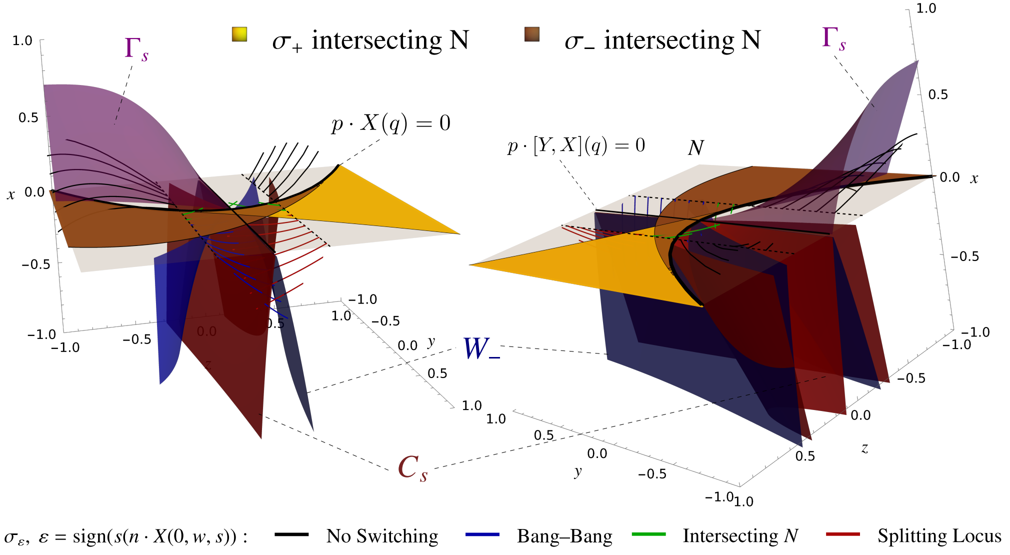
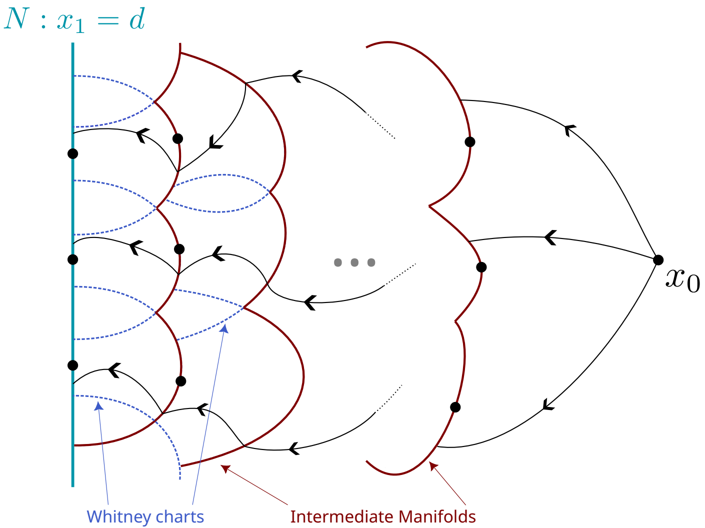


Figure: Strata of the surface S in the exceptional case.

Gluing charts

Construction of time minimal syntheses in the *n*–dimensional case by gluing together Whitney charts.



Conclusion

This allows to construct patchy time minimal regular synthesis based on the dictionary from B. Bonnard–J.R., Annual Review of Control, 2019.

The methods relies only on the Lie brackets computations and uses singular arcs.

Formal computations are used to construct seminormal forms and compute the time minimal synthesis.

Compare previous results with:

- Ancona–Bressan, "Patchy subotpimal synthesis, Annales IHP".
- Earliest works in $2d$–case : H. Sussmann–H. Schättler, Boscain–Piccoli.