Anemia mediterranea

(o legge di Hardy-Weinberg)

2 geni con due alleli : A dominante (o sano)
a recessivo (o malato)

3 possibili genotipi (o individui) : AA sano (1)
Aa portatore sano (2)
aa malato (3)

$N_1(t), N_2(t), N_3(t)$: numero di genotipi 1, 2, 3 rispettivamente presenti alla generazione t

$N(t) = N_1(t) + N_2(t) + N_3(t)$: numero totale di genotipi

$p(t)$: probabilità di trovare un allele A nella generazione t

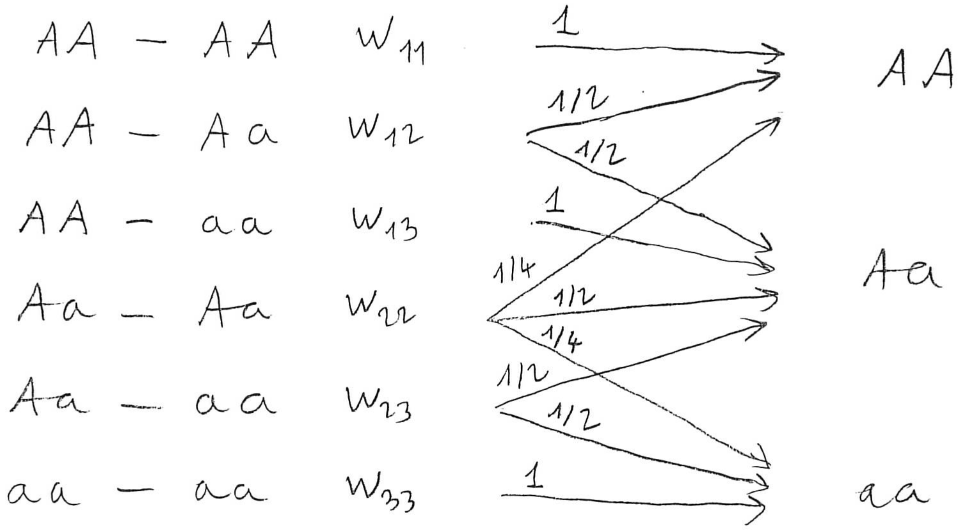
Ipotesi 1 : $N(t)$ è grande, quindi

$$N_1(t) = p^2(t)\, N(t)$$
$$N_2(t) = 2p(t)(1-p(t))\, N(t)$$
$$N_3(t) = (1-p(t))^2\, N(t)$$

Ipotesi 2 : la popolazione è ben mescolata, quindi la probabilità di incontro (e riproduzione) fra due genotipi è pari alla probabilità di estrarre a caso i due genotipi dalla popolazione. In altre parole, la frequenza degli incontri tra due genotipi è pari alla frequenza con cui una coppia di tali genotipi è estratta a caso dalla popolazione.

Ipotesi 3 : una coppia di genotipi i-j che si incontrano, genera w_{ij} genotipi nella generazione successiva ($w_{ij} = w_{ji}$).

Ipotesi 4: ogni individuo eredita in modo equiprobabile uno dei due alleli da ognuno dei genitori. L'accoppiamento tra genotipi ha pertanto il seguente contributo alla generazione successiva



Dinamica di popolazione

$$N_1(t+1) = w_{11} N_1^2(t) + w_{12}\, 2N_1(t)N_2(t)\,\frac{1}{2} + w_{22} N_2^2(t)\,\frac{1}{4}$$

$$= \left(w_{11} p^4(t) + 2w_{12} p^3(t)(1-p(t)) + w_{22} p^2(t)(1-p(t))^2 \right) N(t)$$

$$N_2(t+1) = w_{12}\, 2N_1(t)N_2(t)\,\frac{1}{2} + w_{13}\, 2N_1(t)N_3(t) + w_{22} N_2^2(t)\,\frac{1}{2} +$$

$$+ w_{23}\, 2N_2(t)N_3(t)\,\frac{1}{2} =$$

$$= \left(2w_{12} p^3(t)(1-p(t)) + 2(w_{13}+w_{22}) p^2(t)(1-p(t))^2 + 2w_{23} p(t)(1-p(t))^3 \right) N(t)$$

$$N_3(t+1) = w_{22} N_2^2(t)\,\frac{1}{4} + w_{23}\, 2N_2(t)N_3(t)\,\frac{1}{2} + w_{33} N_3^2(t) =$$

$$= \left(w_{22} p^2(t)(1-p(t))^2 + 2w_{23} p(t)(1-p(t))^3 + w_{33}(1-p(t))^4 \right) N(t)$$

$$p(t+1) = \frac{\text{num. alleli } A \text{ nella generazione } t+1}{\text{num totale di alleli nella generazione } t+1} =$$

$$= \frac{2N_1(t+1) + N_2(t+1)}{2N(t+1)} =$$

$$= \frac{w_{11}p^4(t) + 3w_{12}p^3(t)(1-p(t)) + (w_{13}+2w_{22})p^2(t)(1-p(t))^2 + w_{23}p(t)(1-p(t))^3}{w_{11}p^4(t) + 4w_{12}p^3(t)(1-p(t)) + 2(w_{13}+2w_{22})p^2(t)(1-p(t))^2 + 4w_{23}p(t)(1-p(t))^3 + w_{33}(1-p(t))^4}$$

$$\triangleq p(t)\,\frac{w_1(p(t))}{r(p(t))}$$

$$w_1(p) = w_{11}p^3 + 3w_{12}p^2(1-p) + (w_{13}+2w_{22})p(1-p)^2 + w_{23}(1-p)^3$$

$$w_2(p) = w_{12}p^3 + (w_{13}+2w_{22})p^2(1-p) + 3w_{23}p(1-p)^2 + w_{33}(1-p)^3$$

$$r(p) = p\,w_1(p) + (1-p)\,w_2(p)$$

Equilibri:

$p=0$, $p=1$ sempre (nota $p=0 \rightarrow r(p)=w_{33} \rightarrow p=0$ equilibrio se $w_{33} \neq 0$ altrimenti $\nexists$ la generazione successiva a $p=0$)

$$pr = pw_1,\ p \neq 0 \rightarrow r = w_1 \rightarrow w_1 = w_2$$

$$(w_{11}-w_{12})p^3 + (3w_{12}-w_{13}-2w_{22})p(1-p) + (w_{13}+2w_{22}-w_{23})p(1-p) + (w_{23}-w_{33})(1-p)^3 = 0$$

ci interessano le radici reali $\bar{p} \in (0,1)$

Il caso particolare dell'anemia mediterranea:

$$W_{11} = W_{12} = W_{22} = W \quad , \quad W_{13} = W_{23} = W_{33} = 0$$

perchè i malati (aa) non riproducono e i sani e i portatori sani hanno lo stesso tasso di riproduzione W.

$$p(t+1) = \dots = \frac{1}{2-p(t)} \quad , \quad p(t) \neq 0$$

$$\left(p \quad \frac{p(2-p)}{p^2(2-p)^2} \right)$$

Equilibri:

$p = 1$

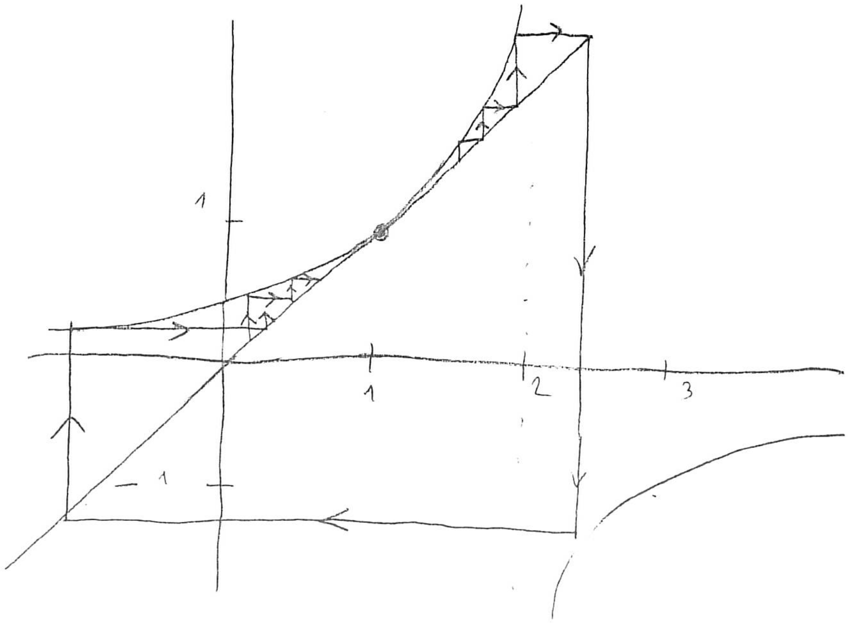
$p = 0$ non è più un equilibrio, ma la dinamica è valida per $p \neq 0$.

Linearizzazione:

$$\delta p(t+1) = \frac{d}{dp}\left(\frac{1}{2-p}\right)\Bigg|_{p=1} \delta p(t) = \frac{1}{(2-p)^2}\Bigg|_{p=1} = \delta p(t)$$

$\lambda = 1$ la linearizzazione non ci dice nulla sulla stabilità dell'equilibrio $p=1$

Costruzione grafica

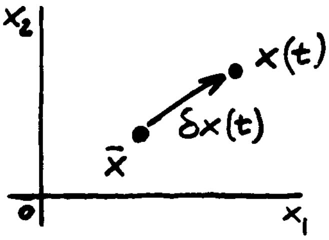


$p = 1$ è instabile ma è un **attrattore** con convergenza lenta (più lenta di un qualsiasi esponenziale λ^t con $|\lambda| < 1$!)

IL SISTEMA LINEARIZZATO E LA MATRICE JACOBIANA

Consideriamo $\dot{x}(t) = f(x(t))$ e un suo equilibrio $\overline{x}$ ($f(\overline{x}) = 0$).

$$\partial x(t) = x(t) - \overline{x}$$



$\partial x(t)$ è governato dall'equazione di stato

$$\partial \dot{x}(t) = \dot{x}(t) = f(x(t)) = f(\overline{x} + \partial x(t)) = f(\overline{x}) + \left[\frac{\partial f}{\partial x}\right]_{\overline{x}} \partial x(t) + O(\partial x(t)^2)$$

$$= \left[\frac{\partial f}{\partial x}\right]_{\overline{x}} \partial x(t) + O(\partial x(t)^2)$$

Definiamo sistema linearizzato nell'intorno di $\overline{x}$ il sistema lineare che si ottiene troncando lo sviluppo di Taylor al primo ordine:

$$\partial \dot{x}(t) = J(\overline{x}) \partial x(t)$$

dove J(x) è la matrice Jacobiana ($n \times n$)

$$J(x) = \left[\frac{\partial f}{\partial x}\right] = \begin{bmatrix} \frac{\partial f_1}{\partial x_1} & \frac{\partial f_1}{\partial x_2} & \cdots & \frac{\partial f_1}{\partial x_n} \\ \frac{\partial f_2}{\partial x_1} & \frac{\partial f_2}{\partial x_2} & \cdots & \frac{\partial f_2}{\partial x_n} \\ \vdots & \vdots & & \vdots \\ \frac{\partial f_n}{\partial x_1} & \frac{\partial f_n}{\partial x_2} & \cdots & \frac{\partial f_n}{\partial x_n} \end{bmatrix}$$

VARIETÀ STABILE, INSTABILE, CENTRO

Se $J(\bar{x})$ possiede

$$\begin{aligned} &n^- \text{ autovalori con } Re(\lambda) < 0 \\ &n^+ \text{ autovalori con } Re(\lambda) > 0 \\ &n^0 \text{ autovalori con } Re(\lambda) = 0 \end{aligned}$$

allora nell'intorno di $\bar{x}$ esistono

$$\begin{aligned} W^s &= \text{varietà stabile } (\dim W^s = n^-) \\ W^u &= \text{varietà instabile } (\dim W^u = n^+) \\ W^0 &= \text{varietà centro } (\dim W^0 = n^0) \end{aligned}$$

tali che

- sono invarianti ($x(0) \in W^{s,u,0}$ implica $x(t) \in W^{s,u,0}$ $\forall t \geq 0$)

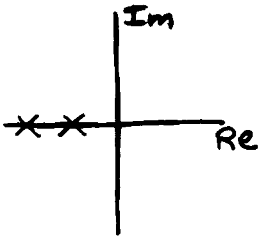
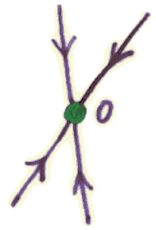
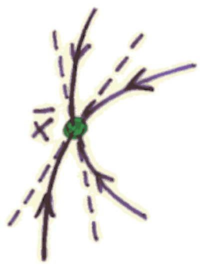
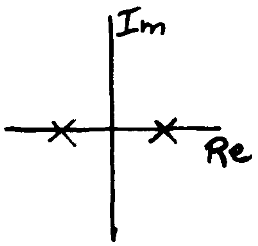
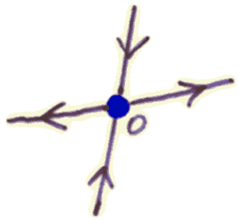
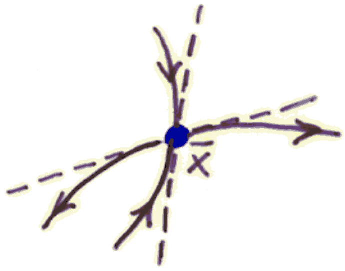
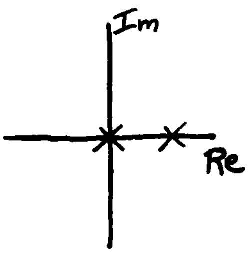
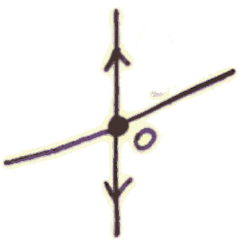
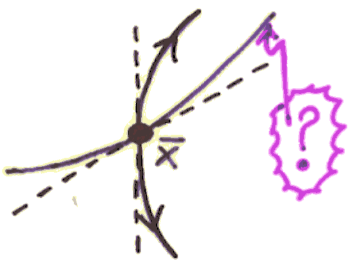
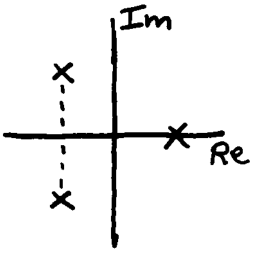
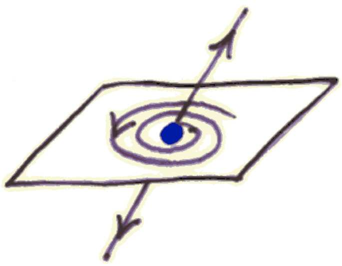
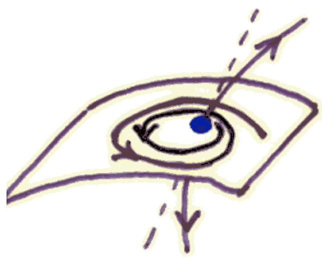
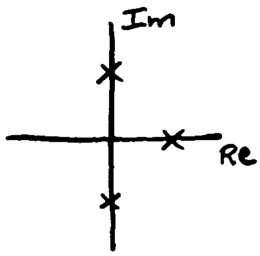
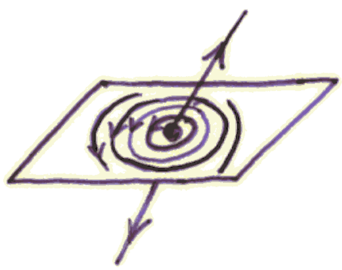
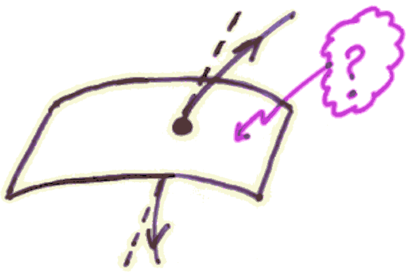
- sono tangenti in $\bar{x}$ alle corrispondenti varietà del sistema linearizzato

- la dinamica su W^s e su W^u è equivalente a quella del sistema linearizzato

- la dinamica su W^0 dipende invece dai termini di ordine superiore al primo dello sviluppo di Taylor ($O(\partial x(t)^2)$) $\Rightarrow$ non può essere studiata per mezzo del sistema linearizzato

Nota Bene: nel caso di sistema a tempo discreto $x(t+1)=f(x(t))$, il sistema linearizzato nell'intorno di un equilibrio $\bar{x}$ si definisce in modo del tutto analogo. Le varietà stabile, instabile, centro, sono associate rispettivamente agli autovalori con $|\lambda| < 1$, $|\lambda| > 1$, $|\lambda| = 1$.

ESEMPI

autovalori di J	$\partial\dot{x} = J(\bar{x})\partial x$	$\dot{x} = f(x)$
		
		
		
		
		

Le proprietà relative a W^s, W^u, W^0 implicano i risultati seguenti.

Teorema

$$J(\overline{x}) \text{ asintoticamente stabile} \Rightarrow \overline{x} \text{ asintoticamente stabile}$$

$J(\overline{x})$ asintoticamente stabile significa che $J(\overline{x})$ ha tutti gli autovalori strettamente stabili ($\mathrm{Re}(\lambda_i) < 0$ o $|\lambda_i| < 1 \ \forall i$).

Teorema

$$J(\overline{x}) \text{ esponenzialmente instabile} \Rightarrow \overline{x} \text{ instabile}$$

$J(\overline{x})$ esponenzialmente instabile significa che $J(\overline{x})$ ha almeno un autovalore strettamente instabile ($\exists i$ tale che $\mathrm{Re}(\lambda_i) > 0$ o $|\lambda_i| > 1$).

Esempio: crescita logistica:

$$\dot{x} = rx\left(1 - \frac{x}{k}\right) \quad \Rightarrow \quad J(x) = r\left(1 - 2\frac{x}{k}\right)$$

$$\text{2 equilibri: } \begin{cases} \overline{x} = 0, & J(0) = r, \quad \text{instabile} \\ \overline{x} = k, & J(k) = -r, \quad \text{asintoticamente stabile} \end{cases}$$

Nota Bene: se $J(\overline{x})$ è semplicemente stabile o debolmente (non esponenzialmente) instabile non si può dedurre nulla a proposito della stabilità di $\overline{x}$.

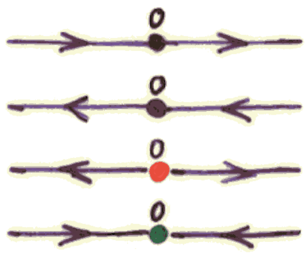
Esempio: sistemi quadratici e cubici:

$\dot{x} = x^2$, $\quad \overline{x} = 0$, $\quad J(x) = 2x$, $\quad J(\overline{x})=0 \Rightarrow ???$

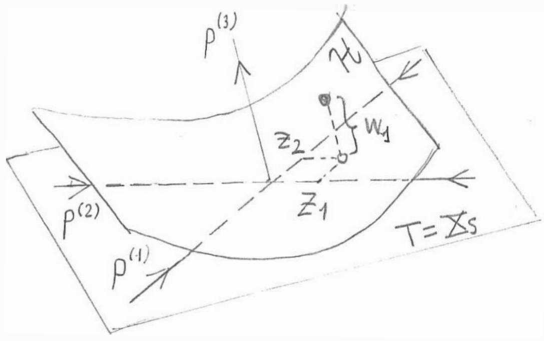
$\dot{x} = -x^2$, $\quad \overline{x} = 0$, $\quad J(x) = -2x$, $\quad J(\overline{x})=0 \Rightarrow ???$

$\dot{x} = x^3$, $\quad \overline{x} = 0$, $\quad J(x) = 3x^2$, $\quad J(\overline{x})=0 \Rightarrow ???$

$\dot{x} = -x^3$, $\quad \overline{x} = 0$, $\quad J(x) = -3x^2$, $\quad J(\overline{x})=0 \Rightarrow ???$



Computation of invariant manifolds, locally to an equilibrium $\bar{x}$



Full dynamics : $\dot{x} = f(x)$, $x \in \mathbb{R}^n$

Equilibrium : $f(\bar{x}) = 0$

Linearized dyn. : $\dot{\delta x} = \bar{J}\,\delta x$, $\delta x = x - \bar{x}$

$$\bar{J} = \left.\frac{\partial f}{\partial x}\right|_{x=\bar{x}}$$

<u>Invariant manifold</u> $\mathcal{H} : x = H(z)$, $\bar{x} = H(0)$, $z \in \mathbb{R}^d$, $d < n$

$\{z_1, \dots, z_d\}$ are the (local) coordinates on $\mathcal{H}$

The subspace T tangent to $\mathcal{H}$ at $\bar{x}$ is spanned by the eigenspace of d eigenvalues of $\bar{J}$, say $\{\lambda_1, \dots, \lambda_d\}$ and $T = \mathrm{span}\{p^{(1)}, \dots, p^{(d)}\}$.

T is invariant for the linearized dynamics, but not for the full ones.

Let $\{\lambda_{d+1}, \dots, \lambda_n\}$ and $\{p^{(d+1)}, \dots, p^{(n)}\}$ be the remaining eigenvalues and corresponding (possibly generalized) eigenvectors of $\bar{J}$, so that $\{p^{(i)}\}_{i=1,\dots,n}$ is a base of $\mathbb{R}^n$.

One good choice (certainly well-defined locally to $\bar{x}$) for the coordinates z_i is the eigencoordinates along $\{p^{(1)}, \dots, p^{(d)}\}$, so that

$$x = H(z) = \sum_{i=1}^{d} z_i\, p^{(i)} + \sum_{i=1}^{n-d} w_i(z)\, p^{(d+i)} , \quad w_i(0) = 0 ,\ w_i(z) = O(\|z\|^2) ,$$

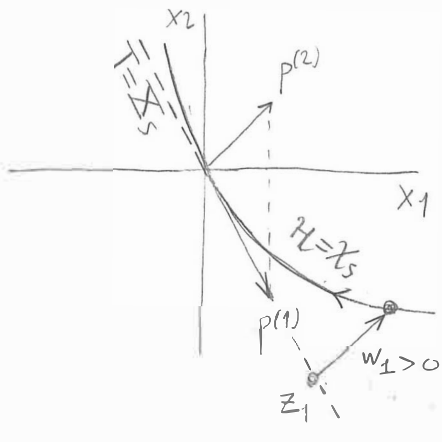
where $w_i : \mathbb{R}^d \to \mathbb{R}$, $i = 1, \dots, n-d$, are nonlinear functions of z with at least quadratic leading terms locally to $z = 0$.

Example: stable manifold $\mathcal{H}$ of a 2-dim saddle ($d = 1$, $n = 2$)

$$\bar{J} = \begin{vmatrix} 0 & 1 \\ 2 & -1 \end{vmatrix} \quad \lambda_1 = -2 ,\ \lambda_2 = 1$$

$$p^{(1)} : \bar{J}\begin{vmatrix} p_1 \\ p_2 \end{vmatrix} = -2\begin{vmatrix} p_1 \\ p_2 \end{vmatrix} , \ \left\{ \underline{p_2 = -2p_1} \right. \to p^{(1)} = \begin{vmatrix} 1 \\ -2 \end{vmatrix}$$

$$p^{(2)} : \bar{J}\begin{vmatrix} p_1 \\ p_2 \end{vmatrix} = \begin{vmatrix} p_1 \\ p_2 \end{vmatrix} , \ \left\{ \underline{p_2 = p_1} \right. \to p^{(2)} = \begin{vmatrix} 1 \\ 1 \end{vmatrix}$$



<u>Restricted dynamics</u> : $\dot{z} = G(z)$, $G(0) = 0$

<u>Unknown functions</u> (of z) : w_i , $i = 1, \dots, n-d$ and G

Invariance of $\mathcal{H}$: $x(0) = H(z(0)) \longrightarrow x(t) = H(z(t))$, $t>0$
(locally to $z=0$)

d/dt

Homological eq.: $f(H(z)) = H_z(z)\,G(z) \quad \forall z \quad (\|z\| \text{ small})$

Expansions (locally to $x = \bar{x}$ and $z = 0$)

$$f(x) = \underset{\substack{\| \\ 0}}{f(\bar{x})} + \bar{J}\,\delta x + \frac{1}{2}\bar{f}_{x^2}[\delta x, \delta x] + \frac{1}{6}\bar{f}_{x^3}[\delta x, \delta x, \delta x] + \dots$$

with $\bar{f}_{x^2 i}[e^{(k_1)}, e^{(k_2)}] = \left.\dfrac{\partial^2 f_i}{\partial x_{k_1}\partial x_{k_2}}\right|_{x=\bar{x}}$, $\bar{f}_{x^3 i}[e^{(k_1)}, e^{(k_2)}, e^{(k_3)}] = \left.\dfrac{\partial^3 f_i}{\partial x_{k_1}\partial x_{k_2}\partial x_{k_3}}\right|_{x=\bar{x}}$

$$H(z) = \underset{\substack{\| \\ \bar{x}}}{H(0)} + H_z^0\, z + \frac{1}{2}H_{z^2}^0[z,z] + \frac{1}{6}H_{z^3}^0[z,z,z] + \dots$$

$i, k_1, k_2, k_3 = 1, \dots, n$
$e_k^{(k)} = 1$; $e_j^{(k)} = 0$ for $j \neq k$
$e^{(k)} \in \mathbb{R}^n \quad j = 1, \dots, n$

where $H_z^0 = \left.\dfrac{\partial H}{\partial z}\right|_{z=0} = [p^{(1)}, \dots, p^{(d)}]$ is the $n \times d$ Jacobian of H at $z=0$,

$$H_{z^2 i}^0[e^{(k_1)}, e^{(k_2)}] = \left.\frac{\partial^2 H_i}{\partial z_{k_1}\partial z_{k_2}}\right|_{z=0}, \quad H_{z^3}^0[e^{(k_1)}, e^{(k_2)}, e^{(k_3)}] = \left.\frac{\partial^3 H_i}{\partial z_{k_1}\partial z_{k_2}\partial z_{k_3}}\right|_{z=0}$$

$e^{(k)} \in \mathbb{R}^d$, $i = 1, \dots, n$, $k_j = 1, \dots, d$

and, in terms of the functions w_i

$$H_{z^2}^0[e^{(k_1)}, e^{(k_2)}] = \sum_{i=1}^{n-d} w_{i\,z^2}^0[e^{(k_1)}, e^{(k_2)}]\,p^{(d+i)}, \quad H_{z^3}^0[e^{(k_1)}, e^{(k_2)}, e^{(k_3)}] = \sum_{i=1}^{n-d} w_{i\,z^3}^0[e^{(k_1)}, e^{(k_2)}, e^{(k_3)}]\,p^{(d+i)}$$

$$G(z) = \underset{\substack{\| \\ 0}}{G(0)} + \underbrace{G_z^0}_{d \times d \text{ matrix}} z + \frac{1}{2}G_{z^2}^0[z,z] + \frac{1}{6}G_{z^3}^0[z,z,z] + \dots$$

with $G_{z^2 i}^0[e^{(k_1)}, e^{(k_2)}] = \left.\dfrac{\partial^2 G_i}{\partial z_{k_1}\partial z_{k_2}}\right|_{z=0}$, $G_{z^3 i}^0[z,z,z] = \left.\dfrac{\partial^3 G_i}{\partial z_{k_1}\partial z_{k_2}\partial z_{k_3}}\right|_{z=0}$, $e^{(k)} \in \mathbb{R}^d$, $i, k_j = 1, \dots, d$

Note that matrix $H_z(z)$ in the homological eq. can be expanded as

$$H_z(z)_{i,j} = H_{z\,ij}^0 + H_{z^2 i}^0[e^{(j)}, z] + \frac{1}{2}H_{z^3 i}^0[e^{(j)}, z, z] + \frac{1}{6}H_{z^4 i}^0[e^{(j)}, z, z, z] + \dots$$

moreover

$$\delta x = x - \bar{x} = H(z) - H(0) = H_z^0\, z + \frac{1}{2}H_{z^2}^0[z,z] + \frac{1}{6}H_{z^3}^0[z,z,z] + \dots$$

Solving the homological eq.

Substitute the expansions in the eq. and iteratively solve for the unknowns by balancing the coefficients of each monomial in the components of z.

order 0 : $\underset{0}{\underset{\parallel}{f(\bar{x})}} = H^0_z \underset{0}{\underset{\parallel}{G(0)}} \rightarrow$ identity

order 1 : $\bar{J} H^0_z z = H^0_{z^2}[\underset{0}{\underset{\parallel}{G(0)}}, z] + H^0_z G^0_z z \rightarrow \underbrace{\bar{J} H^0_z}_{n\times d} = \underbrace{H^0_z G^0_z}_{n\times d}$ (1)

$n\times d$ eqs. in the $d\times d$ unknown G^0_z

there is a unique solutions because we know that the subspace T (spanned by H^0_z) is invariant for the 1-st-order dynamics

order 2 : $\frac{1}{2}\bar{J} H^0_{z^2}[z,z] + \frac{1}{2}\bar{f}_{x^2}[H^0_z z, H^0_z z] = \frac{1}{2} H^0_{z^3}[\underset{0}{\underset{\parallel}{G(0)}}, z, z] + H^0_{z^2}[G^0_z z, z] + \frac{1}{2} H^0_z G_{z^2}[z,z]$

$\bar{J} H^0_{z^2}[e^{(k_1)}, e^{(k_2)}] + \bar{f}_{x^2}[H^0_z e^{(k_1)}, H^0_z e^{(k_2)}] = 2 H^0_{z^2}[G^0_z e^{(k_1)}, e^{(k_2)}] + H^0_z G^0_{z^2}[e^{(k_1)}, e^{(k_2)}]$

$n\times d^2$ eqs. in the unknowns $G^0_{z^2}[e^{(k_1)}, e^{(k_2)}]$ (d^3) (2)

and $W^0_{iz^2}[e^{(k_1)}, e^{(k_2)}]$, $i = 1,\dots,n-d$ ($n-d\times d^2$)

order 3 : $\frac{1}{6}\bar{J} H^0_{z^3}[z,z,z] + \frac{1}{2}\bar{f}_{x^2}[H^0_z z, H^0_{z^2}[z,z]] + \frac{1}{6}\bar{f}_{x^3}[H^0_z z, H^0_z z, H^0_z z] =$

$\frac{1}{6} H^0_{z^4}[\underset{0}{\underset{\parallel}{G(0)}}, z, z, z] + \frac{1}{2} H^0_{z^3}[G^0_z z, z, z] + \frac{1}{2} H^0_{z^2}[G^0_{z^2}[z,z], z] + \frac{1}{6} H^0_z G^0_{z^3}[z,z,z]$

$\bar{J} H^0_{z^3}[e^{(k_1)}, e^{(k_2)}, e^{(k_3)}] + 3\bar{f}_{x^2}[H^0_z e^{(k_1)}, H^0_{z^2}[e^{(k_2)}, e^{(k_3)}]] + \bar{f}_{x^3}[H^0_z e^{(k_1)}, H^0_z e^{(k_2)}, H^0_z e^{(k_3)}] =$

$+ 3 H^0_{z^3}[G^0_z e^{(k_1)}, e^{(k_2)}, e^{(k_3)}] + 3 H^0_{z^2}[G^0_{z^2}[e^{(k_1)}, e^{(k_2)}], e^{(k_3)}] + H^0_z G^0_{z^3}[e^{(k_1)}, e^{(k_2)}, e^{(k_3)}]$

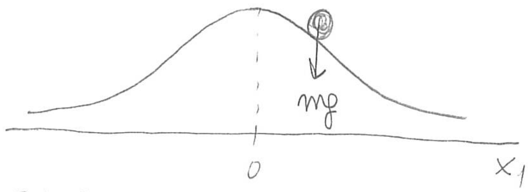
$n\times d^3$ eqs in the unknowns $G^0_{z^3}[e^{(k_1)}, e^{(k_2)}, e^{(k_3)}]$ (d^4) (3)

and $W^0_{iz^3}[e^{(k_1)}, e^{(k_2)}, e^{(k_3)}]$, $i = 1,\dots,n-d$ ($n-d\times d^3$)

Example:

$$\dot{x}_1 = x_2$$

$$\dot{x}_2 = \underset{\substack{\uparrow \\ \text{slope}}}{-P'(x_1)} - \underset{\substack{\uparrow \\ \text{friction}}}{x_2} = 2x_1\exp(-x_1^2) - x_2$$



$P(x_1) = \exp(-x_1^2)$ (profile)

$$\bar{x} = \begin{vmatrix} 0 \\ 0 \end{vmatrix}, \quad \bar{J} = \begin{vmatrix} 0 & 1 \\ 2 & -1 \end{vmatrix}, \quad \lambda_1 = -2, \ \lambda_2 = 1, \quad p^{(1)} = \underset{\substack{\shortparallel \\ H^{\circ}_z}}{\begin{vmatrix} 1 \\ -2 \end{vmatrix}}, \quad p^{(2)} = \begin{vmatrix} 1 \\ 1 \end{vmatrix}$$

$$J(x) = \begin{bmatrix} 0 & 1 \\ \exp(-x_1^2)(2-4x_1^2) & -1 \end{bmatrix}$$

$$f_{x^2}[\cdot,\cdot] = \begin{bmatrix} [0,0] & [0,0] \\ [\exp(-x_1^2)(-12x_1+8x_1^3),\ 0] & [0,0] \end{bmatrix} \rightarrow \bar{f}_{x^2}[e^{(k_1)}, e^{(k_2)}] = 0 \quad \forall (k_1 k_2)$$

$$f_{x^3}[\cdot,\cdot,\cdot] = \begin{bmatrix} [[0,0],[0,0]] & [[0,0],[0,0]] \\ [[\exp(-x_1^2)(-12+48x_1^2-16x_1^4),\ 0],[0,0]] & [[0,0],[0,0]] \end{bmatrix}$$

$$\rightarrow \bar{f}_{x^3}[e^{(1)}, e^{(1)}, e^{(1)}] = \begin{bmatrix} 0 \\ -12 \end{bmatrix}, \quad \bar{f}_{x^3}[e^{(k_1)}, e^{(k_2)}, e^{(k_3)}] = \begin{bmatrix} 0 \\ 0 \end{bmatrix} \text{ for } (k_1,k_2,k_3) \neq (1,1,1)$$

order 1: $\begin{vmatrix} 0 & 1 \\ 2 & -1 \end{vmatrix} \begin{vmatrix} 1 \\ -2 \end{vmatrix} = \begin{vmatrix} 1 \\ -2 \end{vmatrix} G^{\circ}_z, \quad \begin{cases} -2 = G^{\circ}_z \\ 4 = -2G^{\circ}_z \end{cases} \rightarrow \boxed{G^{\circ}_z = -2}$ i.e. λ_1!

order 2: $\begin{vmatrix} 0 & 1 \\ 2 & -1 \end{vmatrix} w^{\circ}_{1z^2} \begin{vmatrix} 1 \\ 1 \end{vmatrix} + \overset{0}{\overset{\shortparallel}{\bar{f}_{x^2}}} \left[\begin{vmatrix} 1 \\ -2 \end{vmatrix}, \begin{vmatrix} 1 \\ -2 \end{vmatrix} \right] = 2 w^{\circ}_{1z^2} \begin{vmatrix} 1 \\ 1 \end{vmatrix} \underset{\substack{\shortparallel \\ -2}}{G^{\circ}_z} + \begin{vmatrix} 1 \\ -2 \end{vmatrix} G^{\circ}_{z^2}$

$$\begin{cases} w^{\circ}_{1z^2} = -4w^{\circ}_{1z^2} + G^{\circ}_{z^2} \\ w^{\circ}_{1z^2} = -4w^{\circ}_{1z^2} - 2G^{\circ}_{z^2} \end{cases} \rightarrow \boxed{w^{\circ}_{1z^2} = 0} \quad \boxed{G^{\circ}_{z^2} = 0}$$

order 3: $\begin{vmatrix} 0 & 1 \\ 2 & -1 \end{vmatrix} w^{\circ}_{1z^3} \begin{vmatrix} 1 \\ 1 \end{vmatrix} + \underset{\substack{\shortparallel \\ 0}}{3\bar{f}_{x^2}} \left[\begin{vmatrix} 1 \\ -2 \end{vmatrix}, \overset{0}{\overset{\shortparallel}{w^{\circ}_{1z^2}}} \begin{vmatrix} 1 \\ 1 \end{vmatrix} \right] + \bar{f}_{x^3} \left[\begin{vmatrix} 1 \\ -2 \end{vmatrix}, \begin{vmatrix} 1 \\ -2 \end{vmatrix}, \begin{vmatrix} 1 \\ -2 \end{vmatrix} \right] = 3w^{\circ}_{1z^3} \begin{vmatrix} 1 \\ 1 \end{vmatrix} \overset{-2}{\overset{\shortparallel}{G^{\circ}_z}} + 3\overset{0}{\overset{\shortparallel}{w^{\circ}_{1z^2}}} \begin{vmatrix} 1 \\ 1 \end{vmatrix} \overset{0}{\overset{\shortparallel}{G^{\circ}_{z^2}}} + \begin{vmatrix} 1 \\ -2 \end{vmatrix} G^{\circ}_{z^3}$

$$\begin{cases} w^{\circ}_{1z^3} = -6w^{\circ}_{1z^3} + G^{\circ}_{z^3} \\ w^{\circ}_{1z^3} - 12 = -6w^{\circ}_{1z^3} - 2G^{\circ}_{z^3} \end{cases}, \quad \begin{vmatrix} 7 & -1 \\ 7 & 2 \end{vmatrix} \begin{vmatrix} w^{\circ}_{1z^3} \\ G^{\circ}_{z^3} \end{vmatrix} = \begin{vmatrix} 0 \\ 12 \end{vmatrix} \rightarrow \boxed{w^{\circ}_{1z^3} = 0{,}5714} > 0, \quad \boxed{G^{\circ}_{z^3} = 4}$$