Slow Manifolds for CRNs

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Unique Slow Manifold in a Trapping Region

For a two-dimensional system with a globally stable equilibrium point, we seek a trapping region which contains a unique invariant manifold approaching the equilibrium point in the slow direction. This idea is originally due to the chemists Simon Fraser and Marc Roussel.

Michaelis-Menten-Henri Enzyme Model

$$S + E \underset{}{\overset{}{\rightleftarrows}} C \longrightarrow P + E$$

$$\begin{cases} \dot{s} = -k_1 se + k_{-1}c \\ \dot{e} = -k_1 se + (k_{-1} + k_2)c \\ \dot{c} = k_1 se - (k_{-1} + k_2)c \\ \dot{p} = k_2 c \end{cases}$$

$$s(0) = s_0,\ e(0) = e_0,\ c(0) = 0,\ p(0) = 0$$
$$e + c = e_0 \ \Rightarrow \ e = e_0 - c$$

$$\begin{cases} \dot{s} = -k_1 s(e_0 - c) + k_{-1}c \\ \dot{c} = k_1(e_0 - c) - (k_{-1} + k_2)c \end{cases}$$

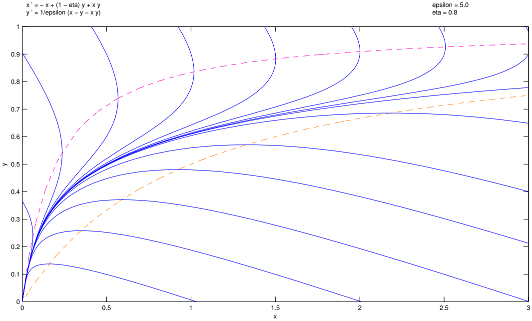

Figure 1: c vs. s

The origin $(0, 0)$ is a node with eigenvalues $\lambda_2 < \lambda_1 < 0$ and slow eigenvector $(1, \sigma)^T$, $\sigma > 0$. Let $\tilde{k} = k_{-1} + \frac{k_2}{1+\sigma}$. Then $k_{-1} < \tilde{k} < k_{-1} + k_2$.

Horizontal Isocline [Quasi-Steady-State Approximation]:
$c = h(s) = \frac{k_1 e_0 s}{k_1 s + k_{-1} + k_2}$

Vertical Isocline [Rapid Equilibrium Approximation]:
$c = v(s) = \frac{k_1 e_0 s}{k_1 s + k_{-1}}$

σ-Isocline: $c = w(s) = \frac{k_1 e_0 s}{k_1 s + \tilde{k}}$

For trajectories below the vertical isocline, consider c as a function of s, with $\frac{dc}{ds} = f(s, c) = \frac{k_1 s(e_0 - c) - (k_{-1} + k_2)c}{-k_1 s(e_0 - c) + k_{-1} c}$.

We have $w'(0) = \sigma$ and $w'(s) < \sigma = f(s, w(s))$ for $s > 0$. Also, $\lim_{s\to\infty}(w(s) - h(s)) = 0$. Thus the region between the horizontal isocline and the σ-isocline is a narrowing anti-funnel [terminology of Hubbard & West]. Therefore, it contains a unique trajectory, $c = M(s)$. It is a unique globally defined slow manifold.

Asymptotics of M near 0: Let $\kappa = \frac{\lambda_2}{\lambda_1}$ and $\sigma_1 = \sigma$.

For $\kappa \notin \mathbb{N}$: $c = \sum_{n=1}^{\lfloor\kappa\rfloor} \sigma_n s^n + Cs^\kappa + \text{o} + (s^\kappa)$ as $s \to 0$.

For $\kappa = 2$; $c = \sigma_1 s + \sigma_2 s^2 \ln s + Cs^2 + \text{o}(s^2)$ as $s \to 0$.

For $\kappa \in \{3, 4, \dots\}$: $c = \sum_{n=1}^{\kappa-1} \sigma_n s^n + Cs^\kappa + \text{o}(s^\kappa)$ as $s \to 0$.

The proof involes an iteration procedure, based on integral equations, which is insensitive to resonance.

Lindemann Model

$$2A \underset{\longleftarrow}{\overset{\longrightarrow}{}} A + B, \quad B \longrightarrow P$$

$$\begin{cases} \dot{a} = -k_1 a^2 + k_{-1} ab \\ \dot{b} = k_1 a^2 - K_{-1} ab - k_2 b \\ \dot{p} = k_2 e \end{cases}$$

$$a(0) = a_0, \; b(0) = 0, \; p(0) = 0$$

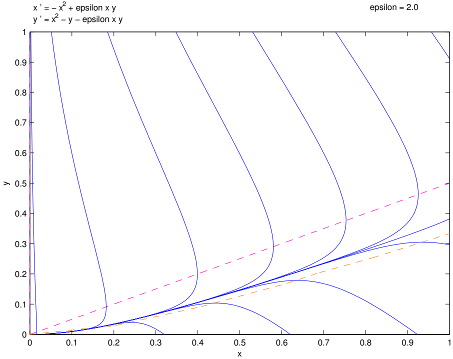

Figure 2: b vs. a

The origin is a globally attracting degenerate equilibrium point. It has eigenvalues $-k_2$ and 0. The centre direction is along the a-axis. For trajectories below the vertical isocline, we consider b as a function of a, satisfying $\frac{db}{da} = f(a,b) = \frac{k_1 a^2 - k_{-1}ab - k_2 b}{-k_1 a^2 + k_{-1}ab}$

Vertical Isocline: $b = v(a) = \frac{k_1}{k_{-1}} a$

Horizontal Isocline: $b = h(a) = \frac{k_1 a^2}{k_2 + k_{-1}a}$.

Intermediate Isoclne: $b = w(a) = \frac{k_1 a^2}{\tilde{k} + k_{-1}a}$, $0 < \tilde{k} < k_2$, $\tilde{k}$ chosen as large as possible so that $w'(a) < f(a, w(a))$ for $a > 0$. This gives the smallest anti-funnel. Therefore, there exists a unique invariant curve, $b = M(a)$ between h and w. Note: the anti-funnel is not narrowing as $a \to \infty$.

Near the origin, we have $M(a) = h(a) + O(a^3)$ as $a \to 0$.

Perturbative Approaches

Consider the Michaelis-Menten-Henri (MMH) Model.
Introduce nondimensional variables:
$\bar{t} = k_1 e_0 t, \ \lambda = \frac{k_2}{k_1 s_0}, \ \kappa = \frac{k_{-1}+k_2}{k_1 s_0}$
$x(\bar{t}) = \frac{s(t)}{s_0}, \ y(\bar{t}) = \frac{c(t)}{e_0}, \ \epsilon = \frac{e_0}{s_0}$
Dropping the bar on t, we have:

$$\text{Slow System } S_\epsilon \ \left\{ \begin{array}{l} \dot{x} = f(x,y) = -x + (x+\kappa-\lambda)y \\ \epsilon\dot{y} = g(x,y) = x - (x+\kappa)y \end{array} \right.$$

$x(0) = 1, \ y(0) = 0.$ This is a singularly perturbed initial value problem.
Let $\tau = \frac{t}{\epsilon}$ and denote a derivative with respect to τ by a prime.
We have: Fast System F_ϵ $\left\{ \begin{array}{l} x' = \epsilon f(x,y) \\ y' = g(x,y) \end{array} \right.$

Tikhonov–Levinson Theory

Consider general f, g, $x(0)$ and $y(0)$. Motivated by S_0, assume $g(x,y)=0$ has a solution $y=\phi_0(x)$ and the reduced problem $\dot{X}_0 = f(X_0, \phi_0(X_0)),\ X_0(0)=x(0)$ has a solution for $0 \le t \le T$. Let $Y_0 = \phi_0(X_0)$.

Seek a solution in the form $\left\{ \begin{array}{l} x(t,\epsilon) = X(t,\epsilon) + \epsilon\xi(\tau,\epsilon) \\ y(t,\epsilon) = Y(t,\epsilon) + \eta(\tau,\epsilon) \end{array} \right.$

$$\begin{pmatrix} X(t,\epsilon) \\ Y(t,\epsilon) \end{pmatrix} \sim \sum_{j=0}^{\infty} \begin{pmatrix} X_j(t) \\ Y_j(t) \end{pmatrix} \epsilon^j, \ \begin{pmatrix} \xi(\tau,\epsilon) \\ \eta(\tau,\epsilon) \end{pmatrix} \sim \sum_{j=0}^{\infty} \begin{pmatrix} \xi_j(\tau) \\ \eta_j(\tau) \end{pmatrix} \epsilon^j$$

$\xi_j(\tau),\ \eta_j(\tau) \to 0$ as $\tau \to \infty$.

Assume that $g_y(X_0(t), Y_0(t)) < 0$ for $0 \leq t \leq T$. We have: $\eta_0' = g(x(0), \phi_0(x(0)) + \eta_0),\ \eta_0(0) = y(0) - \phi_0(x(0))$. Assume that $\eta_0(0)$ lies in the domain of attraction of $\eta_0 = 0$. Under these assumptions, there is a unique asymptotic series as $\epsilon \to 0$.
Note: there are formulations where f and g depend on x, y, t, ϵ. As well, under some conditions, we may take $T = \infty$ [Hoppensteadt].

Normally Hyperbolic Invariant Manifolds

Consider F_0 and the manifold $\mathcal{M}_0$ given by $y = \phi_0(x)$. Assume that $g_y(x, \phi_0(x)) \leq r < 0$. $\mathcal{M}_0$ consists of equilibrium points and the trajectories are on vertical lines and approach $\mathcal{M}_0$ in a neighbourhood of $\mathcal{M}_0$. $\mathcal{M}_0$ is a NHIM. The vertical lines are fibers. For MMH, $g_y = -(x + \kappa) \leq -\kappa$.

NHIMs are persistent under perturbations of a system [Fenichel]. This implies that there is an NHIM $\mathcal{M}_\epsilon$ close to $\mathcal{M}_0$ for ϵ sufficiently small.

Invariance of $\mathcal{M}_\epsilon$ can be used to give an asmyptotic series for it: $y = \phi(x, \epsilon) = \phi_0(x) + \phi_1(x)\epsilon + \cdots$. For MMH, $\phi_0(x) = \frac{x}{x+\kappa}$, $\phi_1(x) = \frac{\lambda\kappa x}{(x+\kappa)^4}$.

Directions

(1) Look for higher dimensional examples of a trapping region containing a unique slow manifold. Ważewski's principle could be useful.
(2) Use persistence of NHIMs to generate slow manifolds, perhaps by continuation.

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