A VERY SHORT PRIMER ON
MULTISCALE MODEL REDUCTION

Antonios Zagaris

APPLIED ANALYSIS AND COMPUTATIONAL SCIENCE
DEPARTMENT OF APPLIED MATHEMATICS
UNIVERSITY OF TWENTE
ENSCHEDE, THE NETHERLANDS

WINTER SCHOOL AND PH.D. COURSE
"MULTI-SCALE ANALYSIS IN DYNAMICAL SYSTEMS"
APPLIED MATHEMATICS AND COMPUTER SCIENCE | DTU
DECEMBER 09–13, 2013

A Glass Half ~~Empty~~ Full

- Mathematical modeling expands like never before in recent times.
- Strong drive towards more detailed and/or fine-grained models.
- Progress and impact create novel opportunities...

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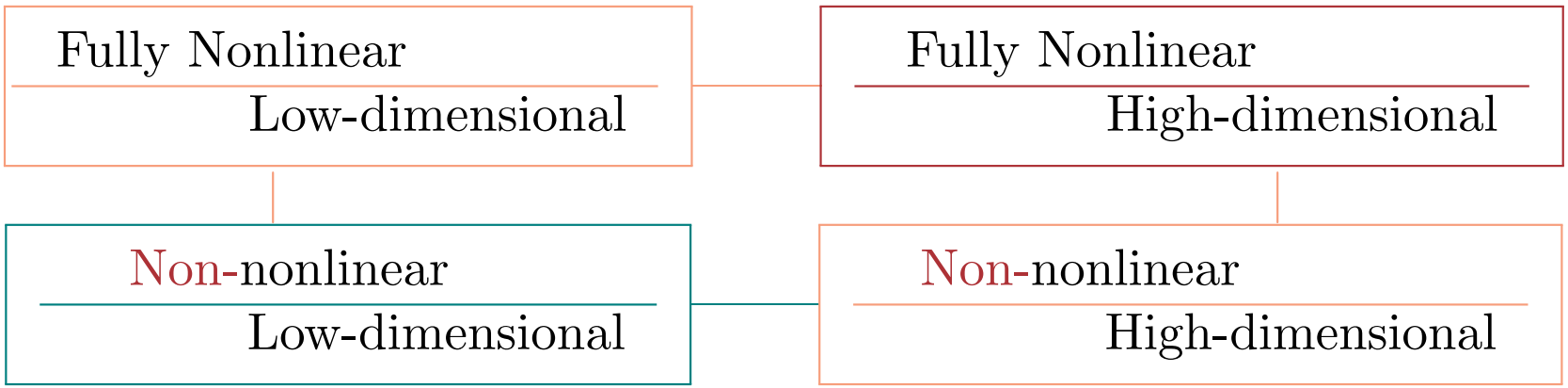
...but come at a cost.



The Enzymatic Paradigm

Reaction	$\text{sucrose} \underset{\text{invertase}}{\overset{\text{invertase}}{\rightleftharpoons}} \text{fructose} + \text{glucose}$

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Model	$S + E \rightleftharpoons C \to P + E$

$$\begin{aligned} \dot{s} &= -k_1(e_T - c)s + k_{-1}c \\ \dot{c} &= k_1(e_T - c)s - (k_{-1} + k_2)c \\ s_T &= s + c + p \\ e_T &= e + c \end{aligned}$$

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Slaving $\dot{c} = 0$	$c = e_T \dfrac{s}{s + K}$
Reduced Model	$\dot{s} = -V_{max} \dfrac{s}{s + K}$ $\Rightarrow \dot{p} = -g(p)$
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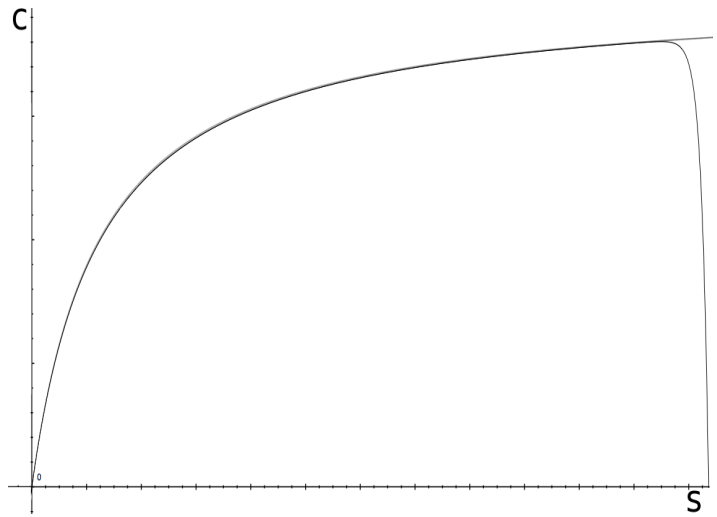

The Prehistory of Multiscale Reduction

Jean-Baptiste Biot

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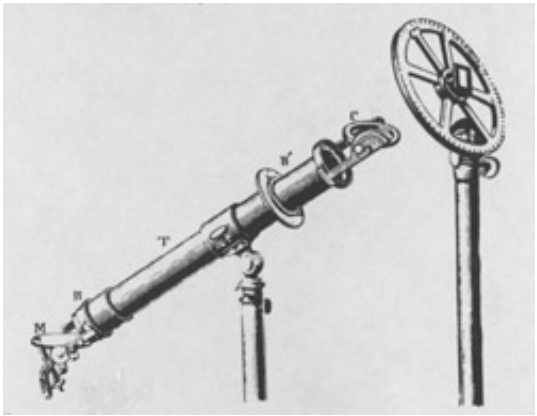

Polarimetric Saccharimeter (1833)

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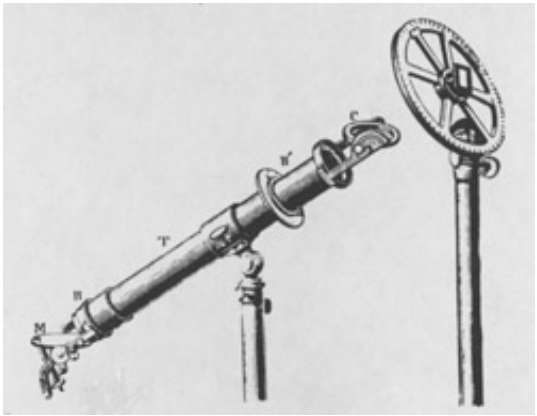

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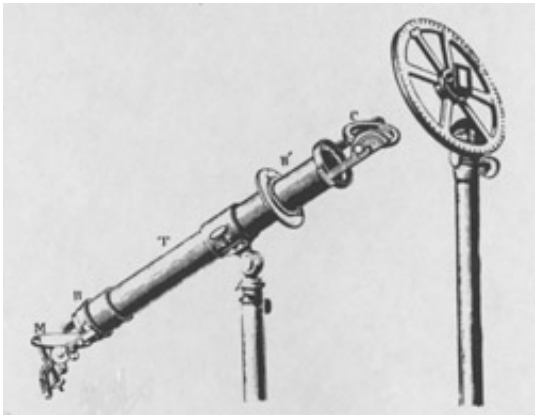

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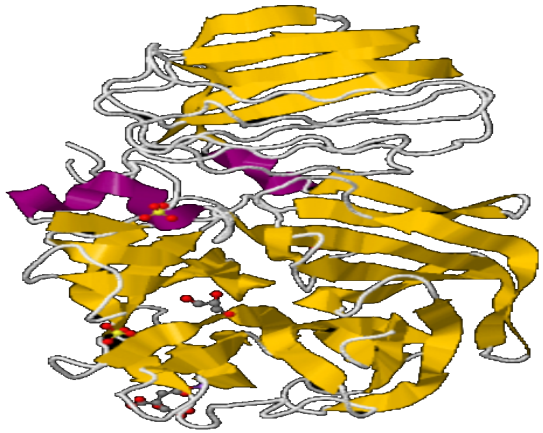
Anselme Payen



Diastase/Invertase (1^{st} Enzyme) (1833)

Ensuing Uncertainty

- Different researchers reported different polarimetric data...
- ...some insisted that the reaction did follow the law of mass action...
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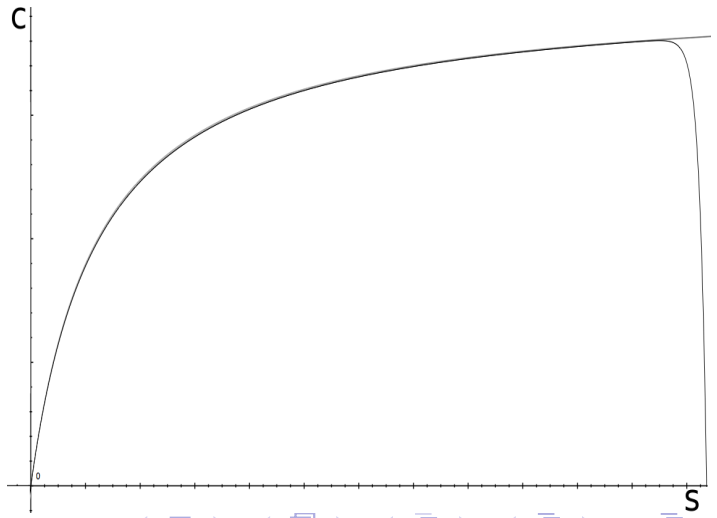

Ensuing Uncertainty

- Different researchers reported different polarimetric data...
- ...some insisted that the reaction did follow the law of mass action...
- ...while others maintained that it was of zeroth order.
- Progress was unduly hindered by the ongoing battle on vitalism.
- Finally, researchers thought of a rate-limiting intermediate complex.

Partial Chronology

[1902] Qualitative description by A.J. Brown

Trans J Chem Soc 81

XXXVI.—*Enzyme Action.*

By Adrian J. Brown.

It follows, therefore, that if, in a series of changes like the imaginary ones described, a constant amount of enzyme is in the presence of varying quantities of a reacting substance, and in all cases the quantity of reacting substance present ensures a greater number of molecular collisions in unit time than the possible number of molecular changes, then a *constant weight* of substance may be changed in unit time in all the actions.

Partial Chronology

[1902] Qualitative description by A.J. Brown

Trans J Chem Soc 81

[1903] Quantification by V. Henri

PhD Thesis, Université de Paris

SÉRIE A. n° 433
N° D'ORDRE
1114

THÈSES

PRÉSENTÉES

A LA FACULTÉ DES SCIENCES

POUR OBTENIR

LE GRADE DE DOCTEUR ÈS-SCIENCES NATURELLES

PAR

VICTOR HENRI

DOCTEUR EN PHILOSOPHIE
PRÉPARATEUR DE PHYSIOLOGIE A LA SORBONNE

Ecrivons donc les équations qui expriment les conditions d'équilibre. Nous avons pour l'équilibre entre le ferment et le saccharose dont la quantité est $a - x$:

$$X.(a - x) = \frac{1}{m} z. , \qquad (1)$$

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[1913] Experimental validation by L. Michaelis & M. Menten

Biochem Zeitsch 49

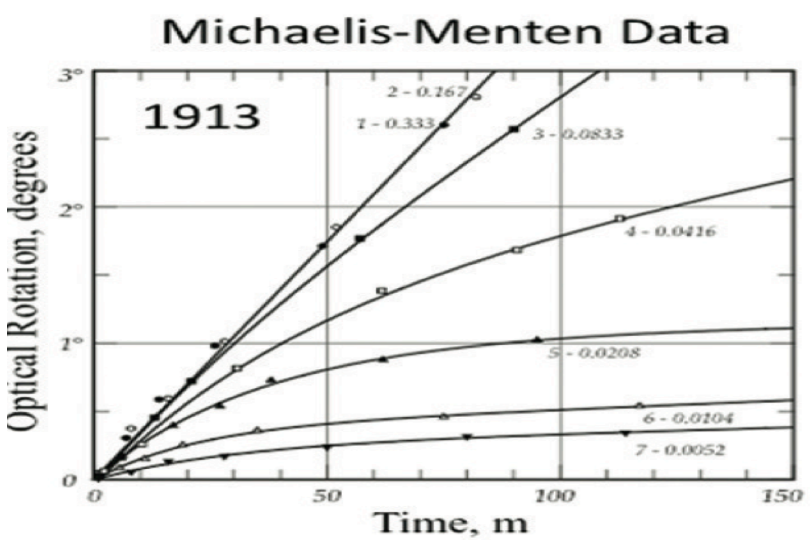
Die Kinetik der Invertinwirkung.

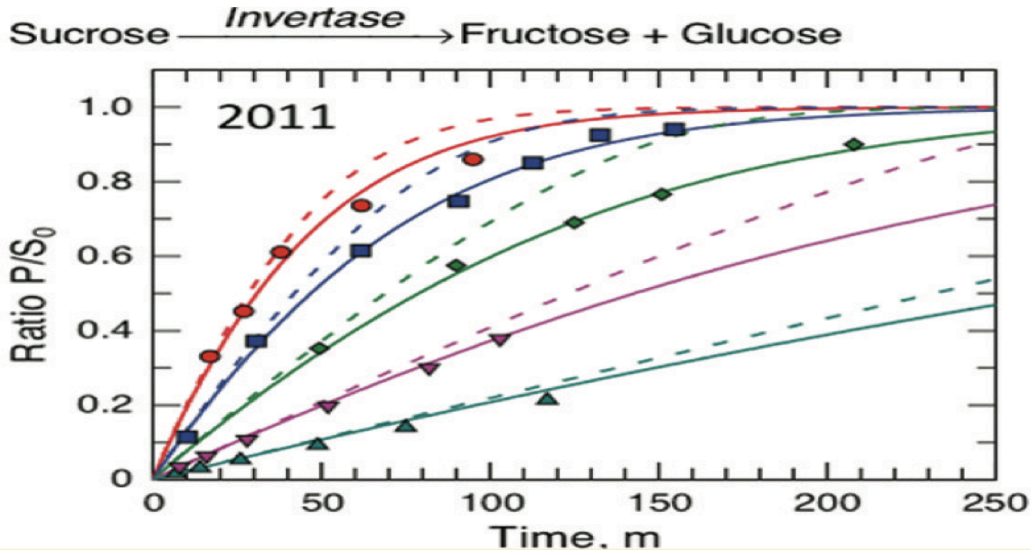
Von

L. Michaelis und Miß Maud L. Menten.

(Eingegangen am 4. Februar 1913.)

Mit 19 Figuren im Text.





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[1925] QSSA formulation by G.E. Briggs & J.B.S. Haldane

Biochem J 19

L. A NOTE ON THE KINETICS OF ENZYME ACTION.

By GEORGE EDWARD BRIGGS and JOHN BURDON SANDERSON HALDANE.

(From the Botanical and Biochemical Laboratories, Cambridge.)

(Received March 9th, 1925.)

Hence
$$k_1(a-x)(e-p) - k_2 p - k_3 p = 0.$$
$$\therefore\ p = \frac{k_1 e(a-x)}{k_2 + k_3 + k_1(a-x)}$$
$$= \frac{e(a-x)}{a - x + \frac{k_2 + k_3}{k_1}}$$
$$\therefore\ \frac{dx}{dt} = k_3 p = \frac{k_3 e(a-x)}{a - x + \frac{k_2 + k_3}{k_1}}.$$

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[1963] Analysis by J.R. Bowen, A. Acrivos & A.K. Oppenheim — Chem Eng Sci 18

Singular perturbation refinement to quasi-steady state approximation in chemical kinetics†

J. R. Bowen,‡ A. Acrivos§ and A. K. Oppenheim‖

(*Received* 31 *July* 1962)

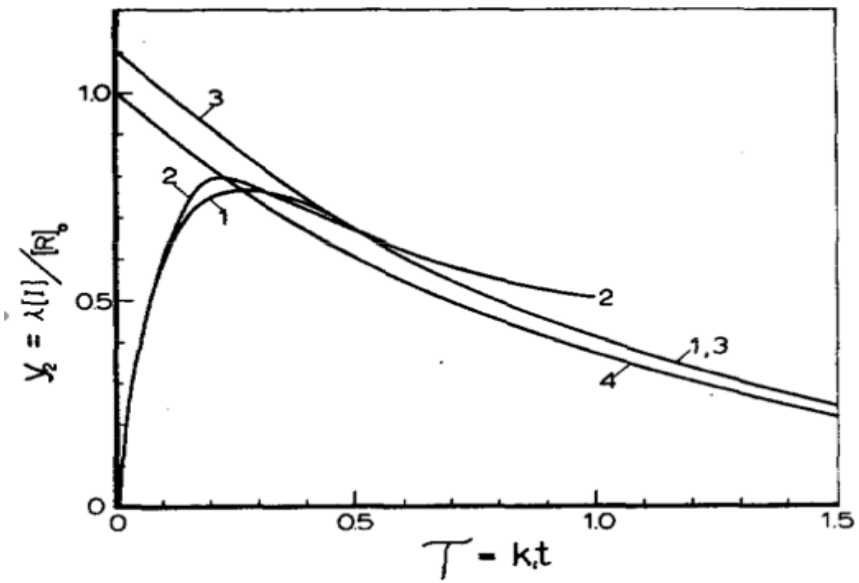

FIG. 1. History of concentration of intermediate species for the case of

The examples which follow will, it is hoped, illustrate the steps of the singular perturbation technique more fully and show why it is ideally suited as an analytical tool for those problems in chemical kinetics for which the Q.S.S.A. ceases to be adequate and must therefore be refined.

THE USEFULNESS OF THE MATCHING REQUIREMENT

Let us next consider a system with two simultaneous reversible first-order reactions

$$R \underset{k_1}{\overset{k_0}{\rightleftarrows}} I$$

$$I \underset{k_3}{\overset{k_2}{\rightleftarrows}} P$$

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[1967] Analysis by F.G. Heineken, H.M. Tsuchiya & P. Aris — Math Biosci 1

On the Mathematical Status of the Pseudo-steady State Hypothesis of Biochemical Kinetics*

F. G. HEINEKEN,** H. M. TSUCHIYA, AND R. ARIS
Department of Chemical Engineering, University of Minnesota, Minneapolis, Minnesota

Communicated by Richard Bellman

Let us make Eqs. 6 and 7 dimensionless by taking

$$y = \frac{s}{s_0}, \qquad z = \frac{c}{e_0}, \qquad \mu = \frac{e_0}{s_0}, \tag{10}$$

$$\tau = k_1 e_0 t, \qquad \varkappa = \frac{(k_{-1} + k_2)}{k_1 s_0}, \qquad \lambda = \frac{k_2}{k_1 s_0}. \tag{11}$$

Then, if a dot is used to denote $d/d\tau$, we have

$$\dot{y} = -y + (y + \varkappa - \lambda)z, \tag{12}$$

$$\mu \dot{z} = y - (y + \varkappa)z, \tag{13}$$

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SIAM REVIEW
Vol. 31, No. 3, pp. 446–477, September 1989

THE QUASI-STEADY-STATE ASSUMPTION: A CASE STUDY IN PERTURBATION *

LEE A. SEGEL† and MARSHALL SLEMROD‡

with which the governing equations (3) become

$$\frac{ds}{d\tau} = \epsilon\left[-s + \frac{\sigma}{\sigma+1}cs + \frac{\kappa(\kappa+1)^{-1}}{\sigma+1}c\right], \tag{21a}$$

$$\frac{dc}{d\tau} = s - \frac{\sigma}{\sigma+1}cs - \frac{1}{\sigma+1}c, \tag{21b}$$

$$s(0) = 1, \tag{21c}$$

$$c(0) = 0. \tag{21d}$$

Here, as suggested by (18b) and (19), the small parameter ϵ is defined by

$$\epsilon \equiv \frac{\eta}{1+\sigma} \equiv \frac{E_0}{K_m + S_0}. \tag{22}$$

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[1989] Definitive analysis by L.A. Segel & M. Slemrod — SIREV 31

[1996] Extension by J.A.M. Borghans, R.J. de Boer & L.A. Segel

Bull Math Biol 58

EXTENDING THE QUASI-STEADY STATE APPROXIMATION BY CHANGING VARIABLES

JOSÉ A. M. BORGHANS* and ROB J. DE BOER
Theoretical Biology,
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The Netherlands

LEE A. SEGEL
Dept. of Applied Mathematics and Computer Science,
The Weizmann Institute of Science,
Rehovot 76100,
Israel

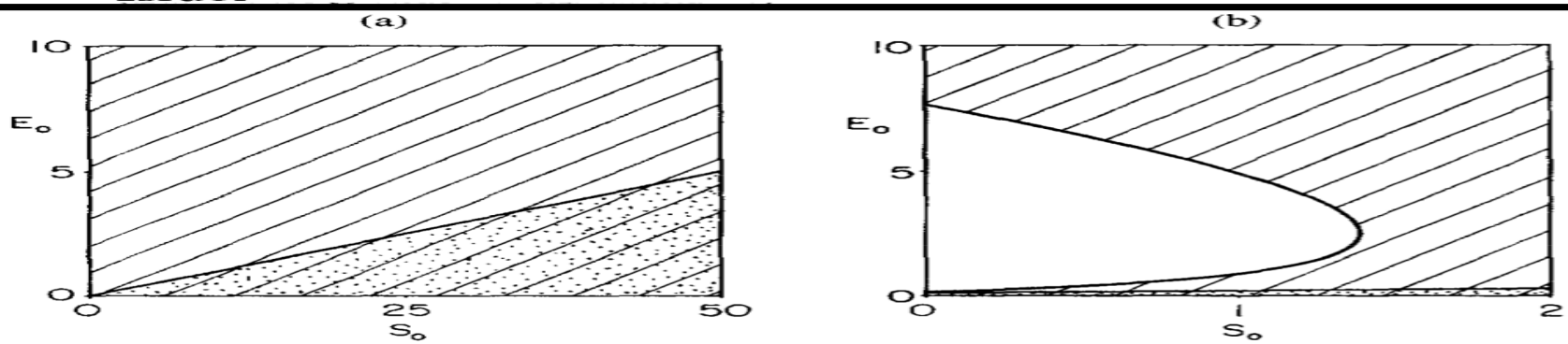
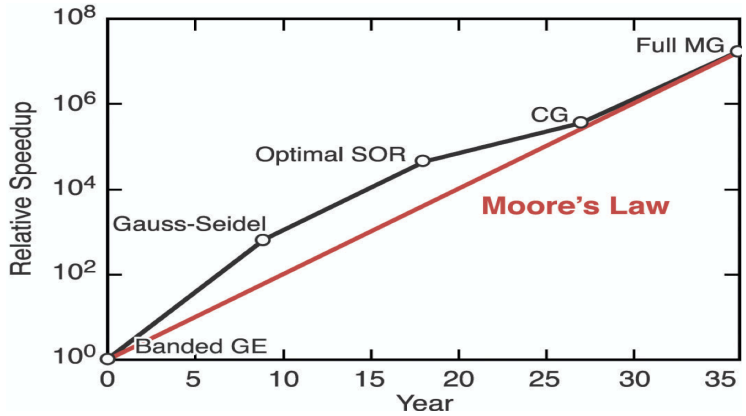


Figure 1. Validity of the QSS and the tQSS assumptions for the standard enzyme–substrate–complex scheme (1a), in the E_0–S_0 plane. Parameters: $k_1 = 10$ and $k_{-1} = 1$, (a) $k_2 = 0.1$ ($K_m = 0.11$); (b) $k_2 = 10$ ($K_m = 1.1$). Dotted domain: QSSA valid; shaded domain: tQSSA valid.

The Era of Large-Scale Models

‘ Over a four-decade period [...], **algorithms** alone have brought a **speed increase** [...] to computing the electrostatic potential induced by a charge distribution [...] **comparable** to that resulting from the hardware speedup due to **Moore’s Law** over the same length of time. ’



‘ **New** methodologies for **closure** should be developed and used to derive **multiscale** models for some of the “difficult” cases in multiscale science, for example, problems without strong scale separation, rare event problems, or **reduction of high-dimensional state spaces** to a small number of degrees of freedom. ’

‘A Science-Based Case For Large-Scale Simulation’ (U.S. DOE 2003-04)

A Partial List of Multiscale Reduction Methods

- Quasi-Steady State Approximation [QSSA] — Briggs & Haldane 1925
- Functional Iteration Method — Fraser & Rousel 1988
- Computational Singular Perturbation [CSP] — Lam & Goussis 1988
- Method of Invariant Manifold [MIM] — Gorban & Karlin 1992
- Intrinsic Low-Dimensional Manifold [ILDM] — Maas & Pope 1992
- Predictor–Corrector — Davis & Skodje 1999
- Approximate Slow Invariant Manifold [ASIM] — Singh, Powers & Paolucci 2002
- Transformation into Explicit Slow–Fast Form — Gerdtzen, Daoutidis & Hu 2004
- Variational Approaches — Lebiedz 2004
- Straightening Out Method — MacKay, Uldall Kristiansen, Brøns & Starke 2004
- Reduction in Metabolic Networks — Gerdtzen, Daoutidis & Hu 2004
- Zero-derivative Principle [ZDP] — Gear, Kevrekidis, Kaper & Zagaris 2005
- Finite-Time Lyapunov Vectors — Mease & Topcu 2005
- ICE-PIC — Ren, Pope, Vladimirsky & Guckenheimer 2006
- Local Embedding Algorithm — Adrover, Creta, Giona & Valorani 2007

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Geometric Singular Perturbation Theory

Fast System

$$
\begin{aligned}
\dot{x}_1 &= \varepsilon\, g_1(x;\varepsilon) \\
\dot{x}_2 &= g_2(x;\varepsilon)
\end{aligned}
$$

Geometric Singular Perturbation Theory

Fast System			$\xrightarrow{t=\varepsilon T}$ / $\xleftarrow{T=t/\varepsilon}$	Slow System		
$\dot{x}_1$	$=$	$\varepsilon\, g_1(x;\varepsilon)$		x_1'	$=$	$g_1(x;\varepsilon)$
$\dot{x}_2$	$=$	$g_2(x;\varepsilon)$		$\varepsilon\, x_2'$	$=$	$g_2(x;\varepsilon)$

Geometric Singular Perturbation Theory

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$$\mathcal{S}_0 = \{x \mid g_2(x;0) = 0\} = \{x \mid x_2 = S_0(x_1)\}$$ critical manifold

$$\mathcal{F}_0(x_1) = \{x \mid x_1 = \text{const.}\}$$ attracting fiber

Geometric Singular Perturbation Theory

Fast System			$t=\varepsilon T$	Slow System		
$\dot{x}_1$	$=$	$\varepsilon\, g_1(x;\varepsilon)$	$\longrightarrow$	x_1'	$=$	$g_1(x;\varepsilon)$
$\dot{x}_2$	$=$	$g_2(x;\varepsilon)$	$\longleftarrow$	$\varepsilon\, x_2'$	$=$	$g_2(x;\varepsilon)$
			$T=t/\varepsilon$			

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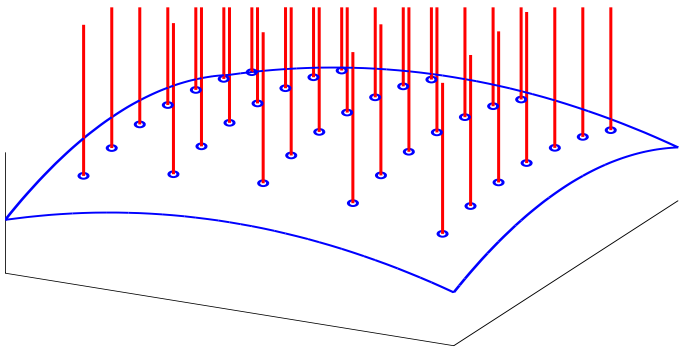
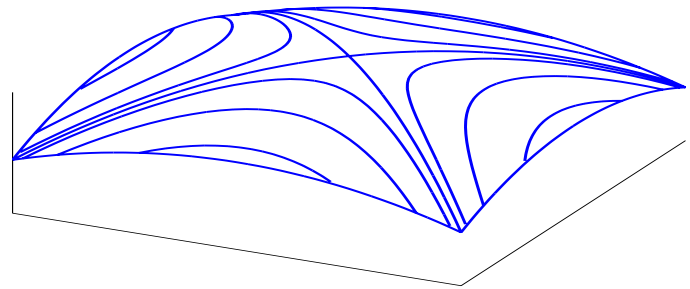
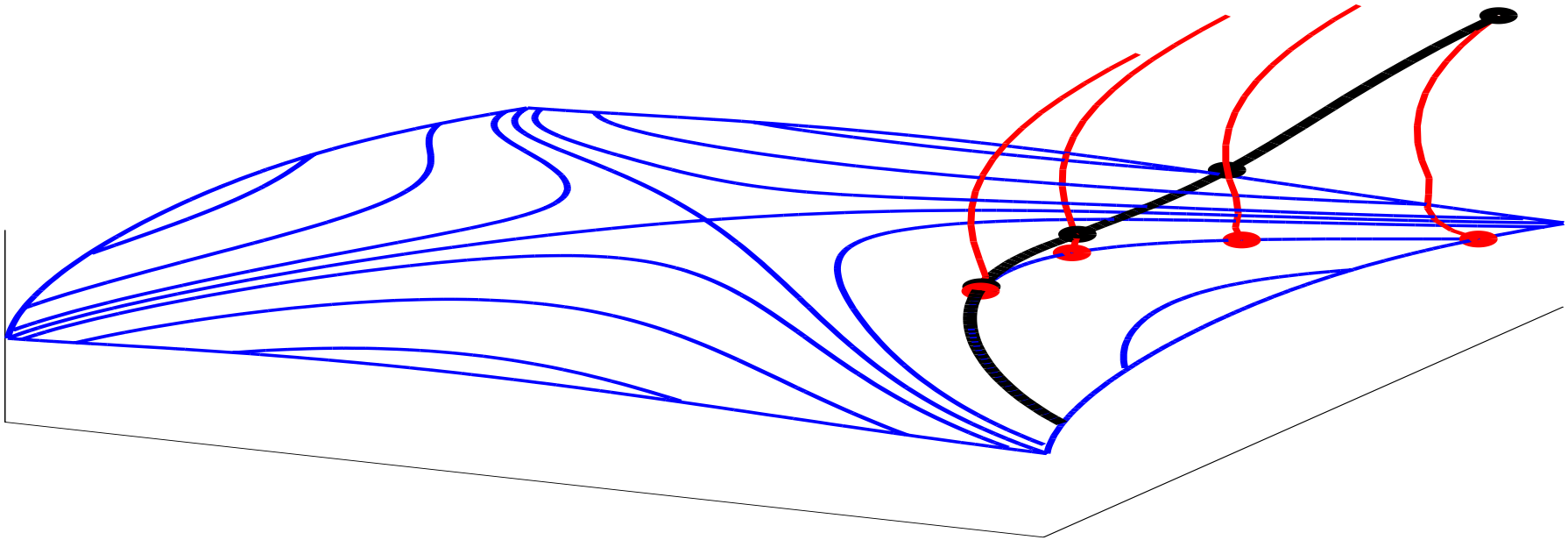


$\mathcal{S}_0$ is fixed



Dynamics only on $\mathcal{S}_0$

Finite Timescale Separation



$\mathcal{S}_0$ perturbs to invariant manifold $\mathcal{S}_\varepsilon = \{ \mathrm{x} \,|\, \mathrm{x}_2 = \mathrm{S}_\varepsilon(\mathrm{x}_1) \}$ slow manifold

$\{\mathcal{F}_0(\mathrm{p}) \,|\, \mathrm{p} \in \mathcal{S}_0\}$ perturbs to invariant family $\{\mathcal{F}_\varepsilon(\mathrm{p}) \,|\, \mathrm{p} \in \mathcal{S}_\varepsilon\}$ fast fibers

Evolution = fast fiber dynamics + slow basepoint dynamics reduction

Example: Enzyme Kinetics

Substrate	$\dot{\mathrm{s}}$	$=$	$\varepsilon\left(-\mathrm{s}+(\kappa-\lambda)\,\mathrm{c}+\mathrm{c}\,\mathrm{s}\right)$	$s+\varepsilon\,c+p$	$=$	1
Complex	$\dot{\mathrm{c}}$	$=$	$\mathrm{s}-(\kappa+\mathrm{s})\,\mathrm{c}$	$c+e$	$=$	1

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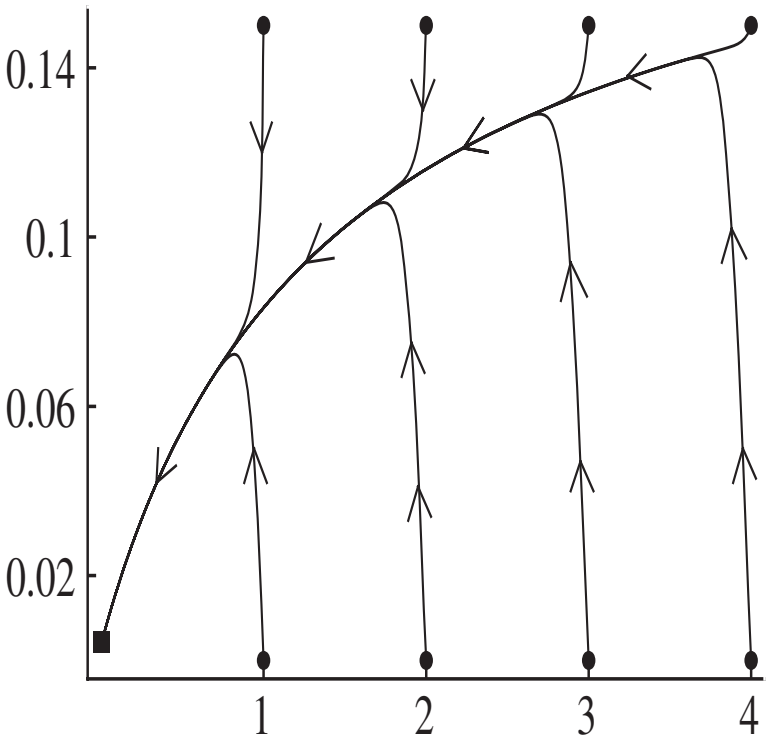

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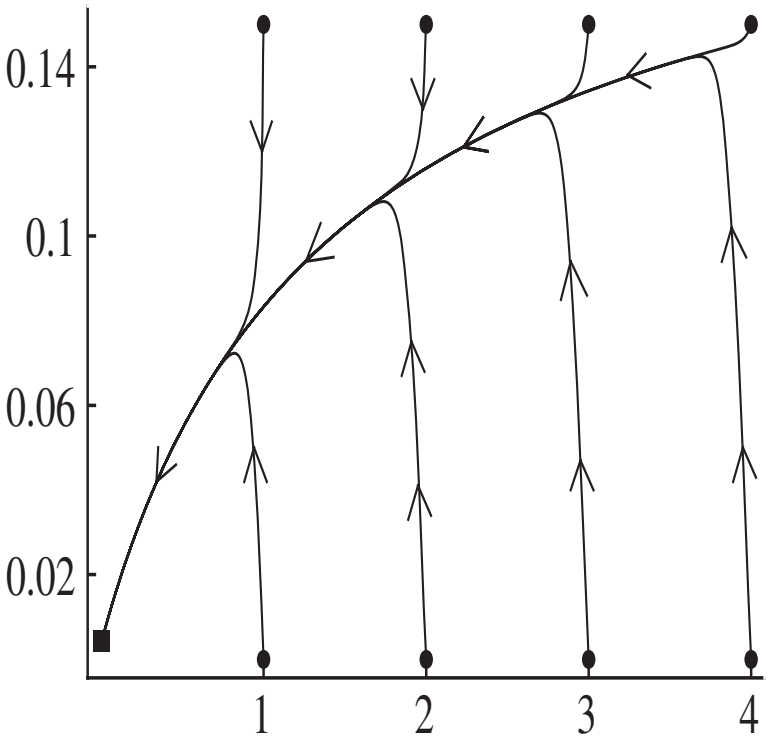
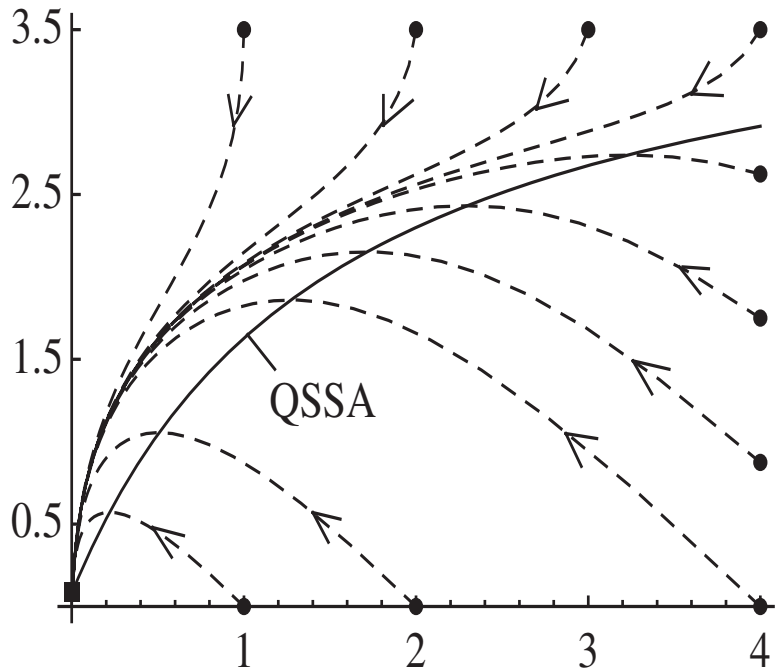
Substrate	$\dot{\mathrm{s}}$	$=$	$\varepsilon\left(-\mathrm{s}+(\kappa-\lambda)\,\mathrm{c}+\mathrm{c}\,\mathrm{s}\right)$	$s+\varepsilon\,c+p$	$=$	1
Complex	$\dot{\mathrm{c}}$	$=$	$\mathrm{s}-(\kappa+\mathrm{s})\,\mathrm{c}$	$c+e$	$=$	1





Example: Catastrophic Predation

Predator	$\dot{x}_1 = \varepsilon\, x_1 \left(\frac{a\, x_2}{x_2 + d} - 1 \right)$		exponential growth single food source
Prey	$\dot{x}_2 = x_2 \left(1 - x_2 - \frac{a\, x_1}{x_2 + d} \right)$		logistic growth fast adjustment to predators

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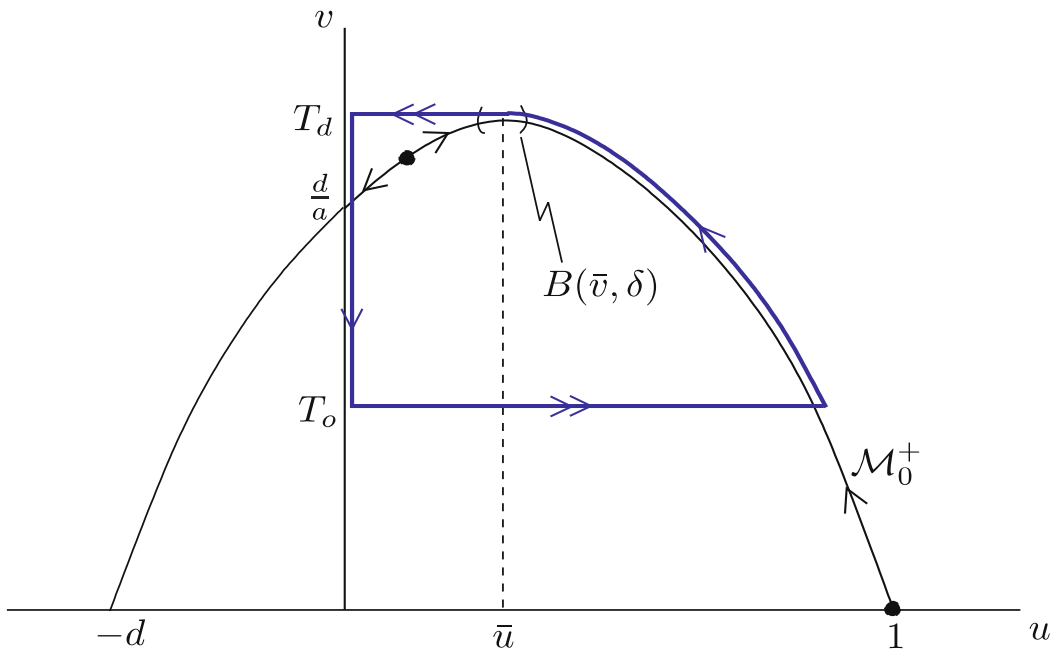
Catastrophic collapse of the prey population with hardly any warning signal. No build-up of the prey colony as predator numbers fall below criticality. Instead, sudden build-up at lower predator population. [Similar to 1992 collapse of Canadian cod fisheries.]



[1992] Rinaldo & Muratori, Ecol Model 61

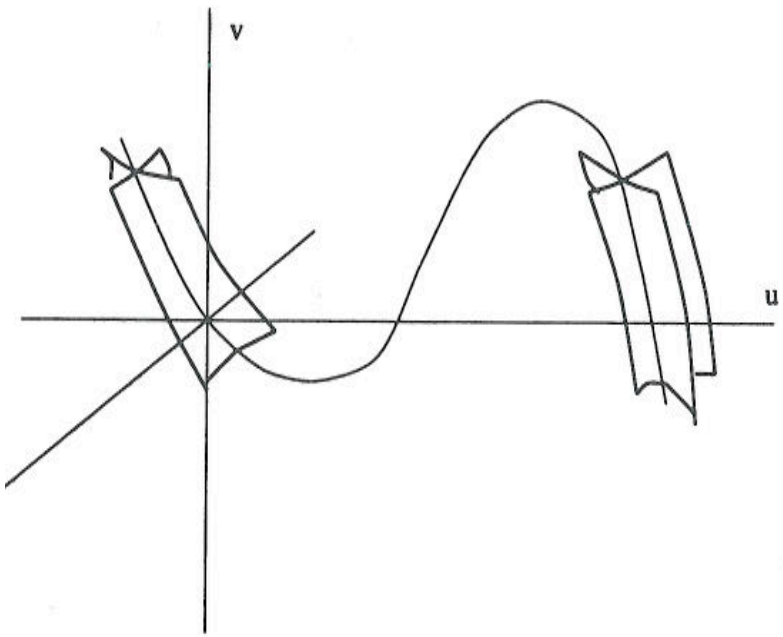
Example: Travelling Pulses

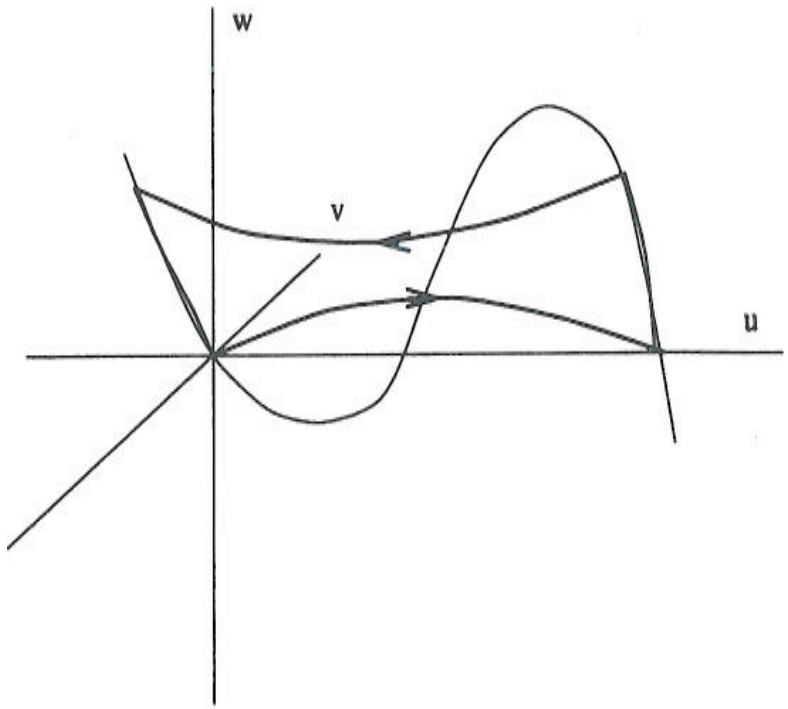
FitzHugh–Nagumo	w_t	$=$	$\varepsilon\,(u - \gamma\, w)$	recovery variable
Neuron Model	u_t	$=$	$u_{xx} + f(u) - w$	excitation variable

Example: Travelling Pulses

Existence of Travelling Waves

$$
\begin{aligned}
\dot{c} &= \varepsilon\, 0 \\
\dot{w} &= -\frac{\varepsilon}{c}(u - \gamma\, w) \\
\dot{u} &= v \\
\dot{v} &= -c\, u - f(u) + w
\end{aligned}
$$

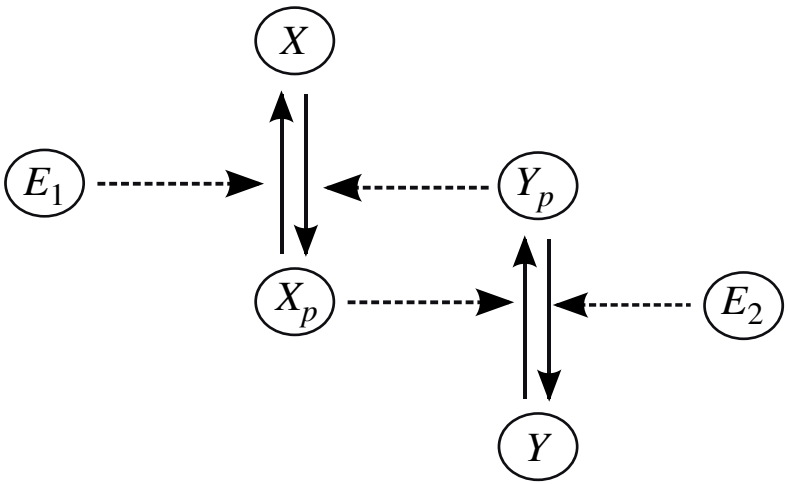




[1996] Jones, Kaper & Kopell, SIMA 27

Example: Coupled Enzymatic Reactions

$$
\begin{aligned}
\dot{x}_p &= -k_1\, x_p\,(y^T - y_p - c_x - c_y - c_y^e) - k_1\, x_p\,(E_1^T - c_x^e) \\
&\quad + k_{-1}\, c_x^e + (k_{-1} + k_2)\, c_y + k_2\, c_x \\
\dot{y}_p &= -k_1\, y_p\,(x^T - x_p - c_x - c_y - c_x^e) - k_1\, y_p\,(E_2^T - c_y^e) \\
&\quad + k_{-1}\, c_y^e + (k_{-1} + k_2)\, c_x + k_2\, c_y \\
\dot{c}_x &= k_1\, y_p\,(x^T - x_p - c_x - c_y - c_x^e) - (k_{-1} + k_2)\, c_x \\
\dot{c}_y &= k_1\, x_p\,(y^T - y_p - c_x - c_y - c_y^e) - (k_{-1} + k_2)\, c_y \\
\dot{c}_x^e &= k_1\, x_p\,(E_1^T - c_x^e) - (k_{-1} + k_2)\, c_x^e \\
\dot{c}_y^e &= k_1\, y_p\,(E_2^T - c_y^e) - (k_{-1} + k_2)\, c_y^e
\end{aligned}
$$



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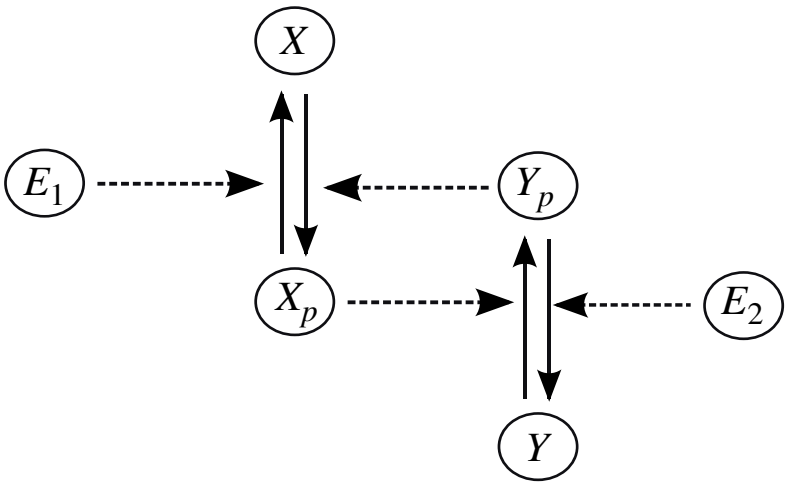
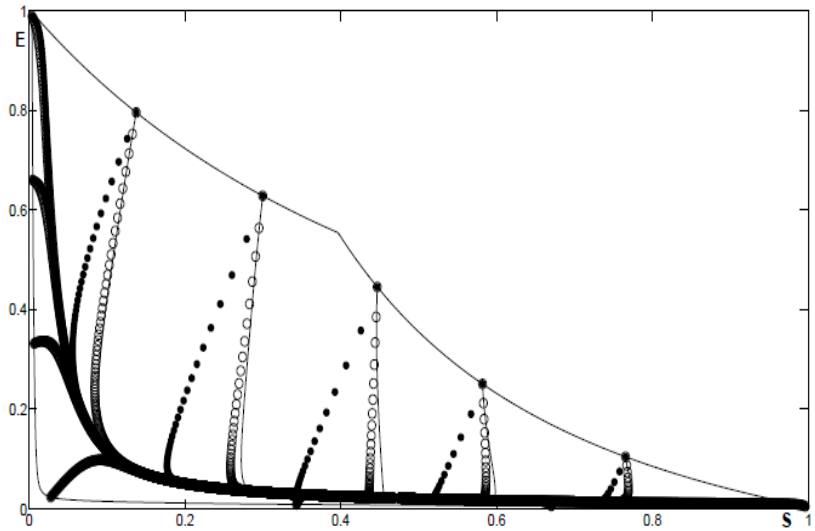
\dot{c}_y^e &= k_1\, y_p\,(E_2^T - c_y^e) - (k_{-1} + k_2)\, c_y^e
\end{aligned}
$$



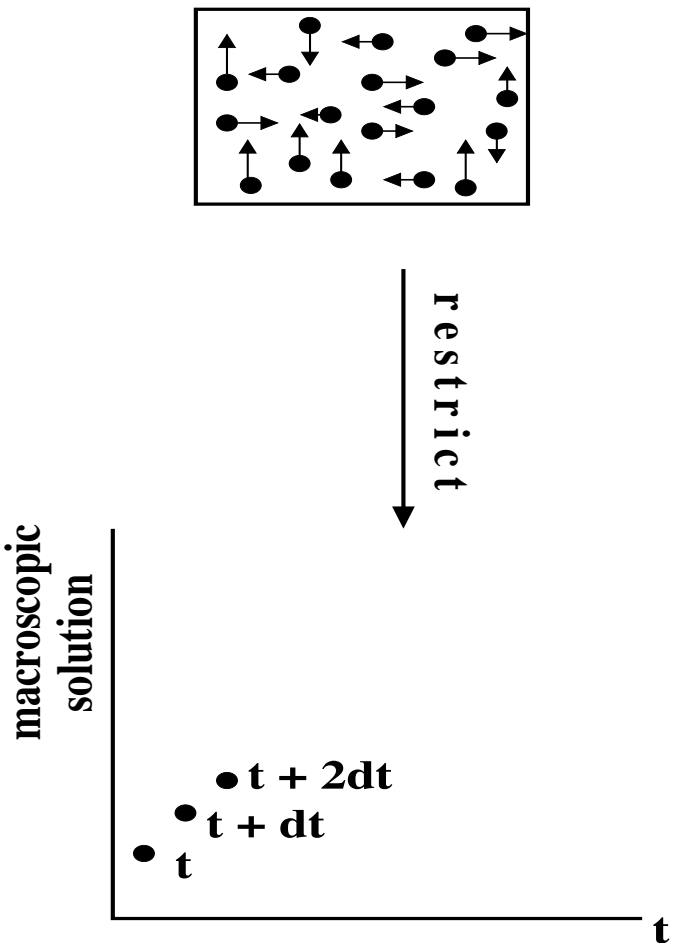


[2011] Kumar & Josić, J Theor Biol 278

[2012] Zagaris, Vandekerckhove, Gear, Kaper & Keverekidis, DCDS-A 32

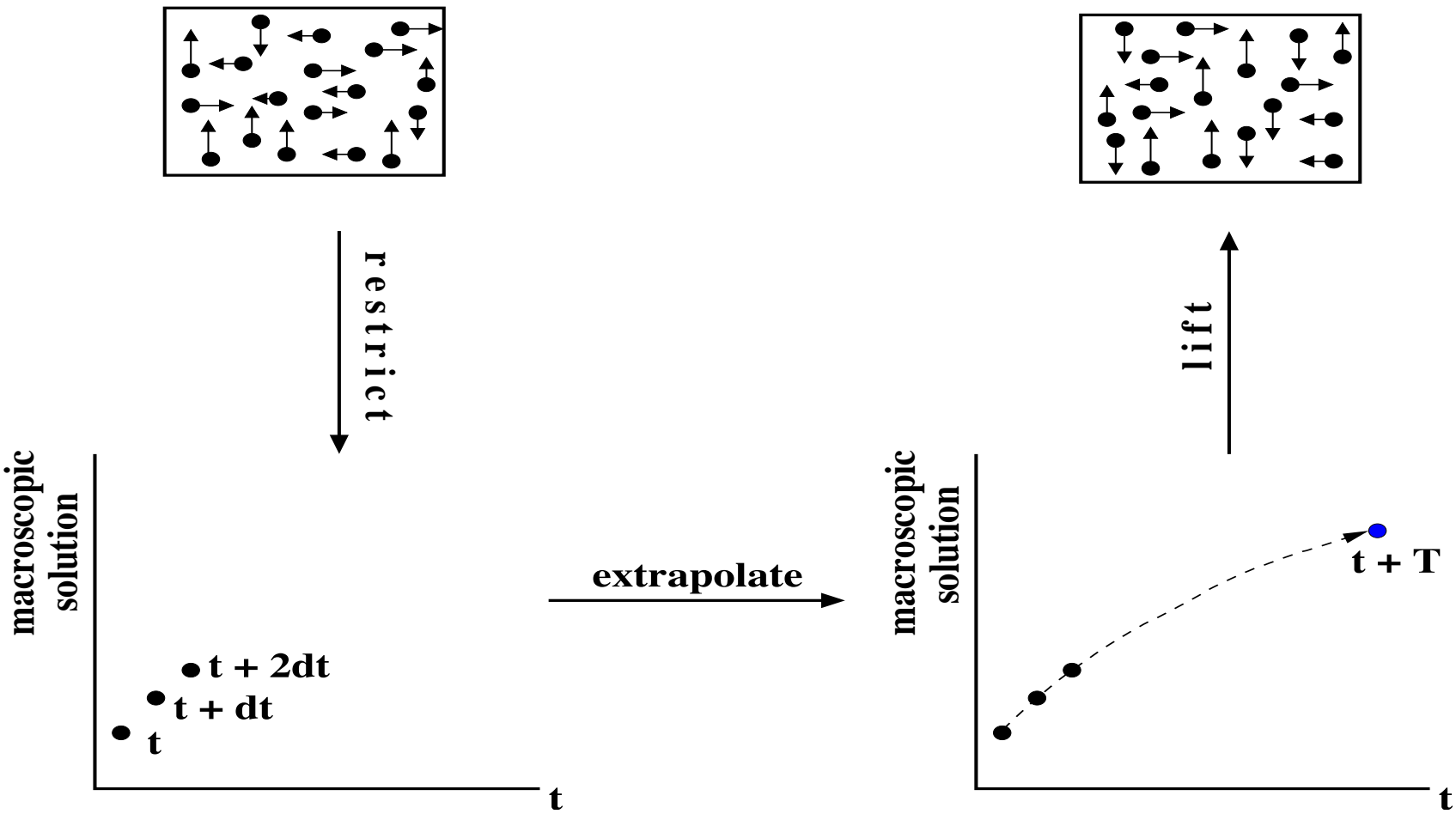
Example: Computational Coarse-graining

Mesoscopic simulations



Example: Computational Coarse-graining

Mesoscopic simulations $\longrightarrow$ Macroscopic information



Example: Computational Coarse-graining

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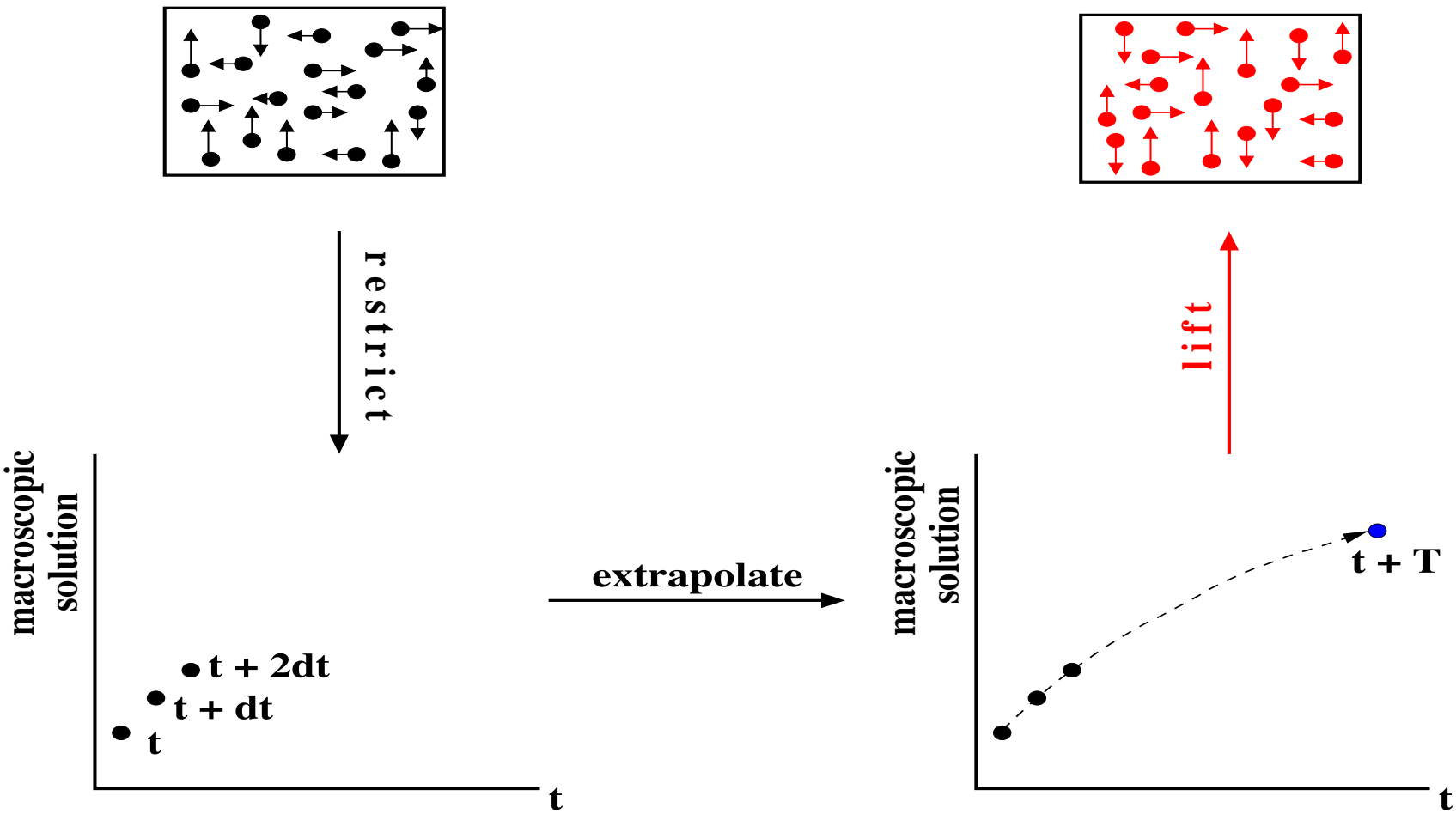
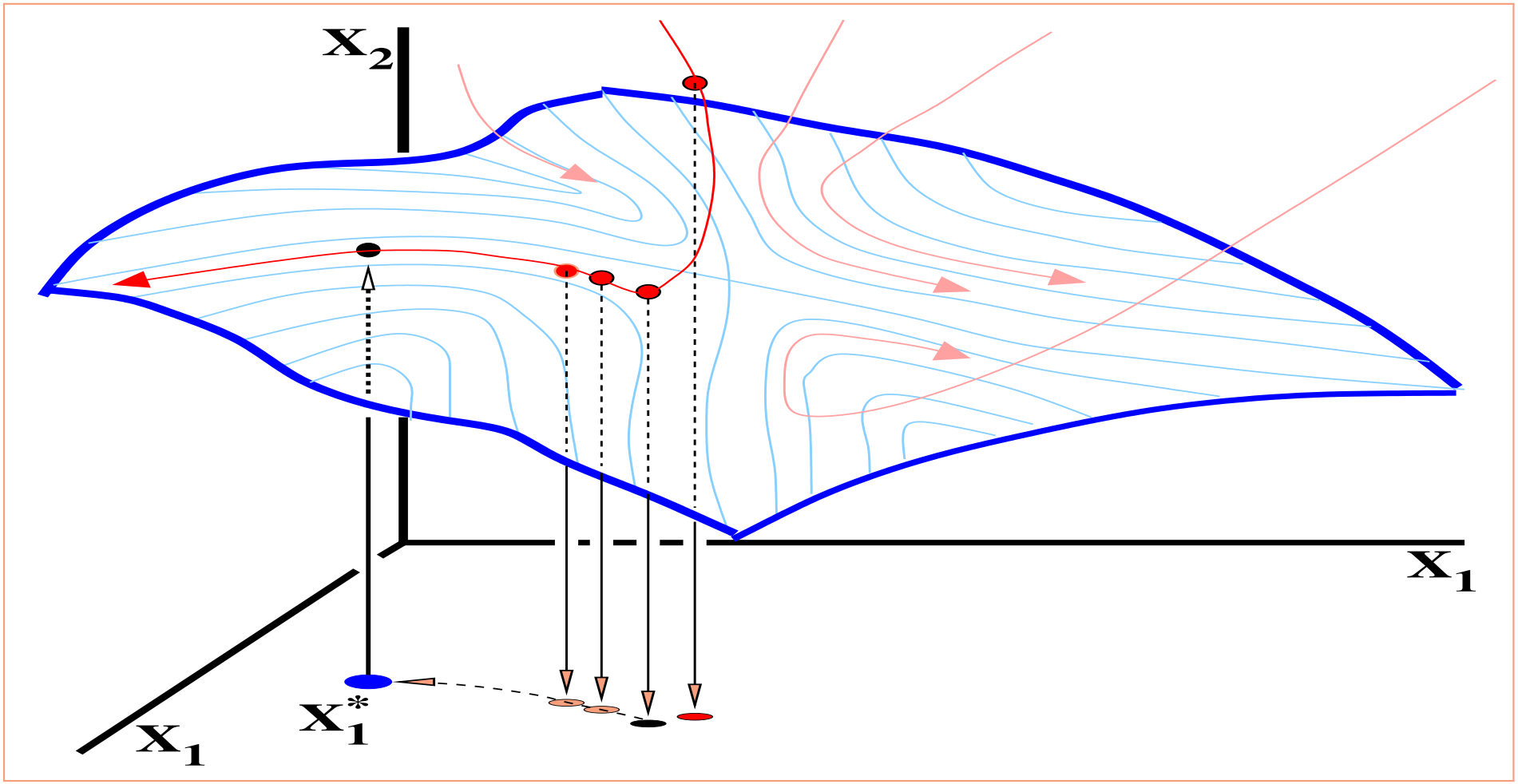


Lifting Scheme

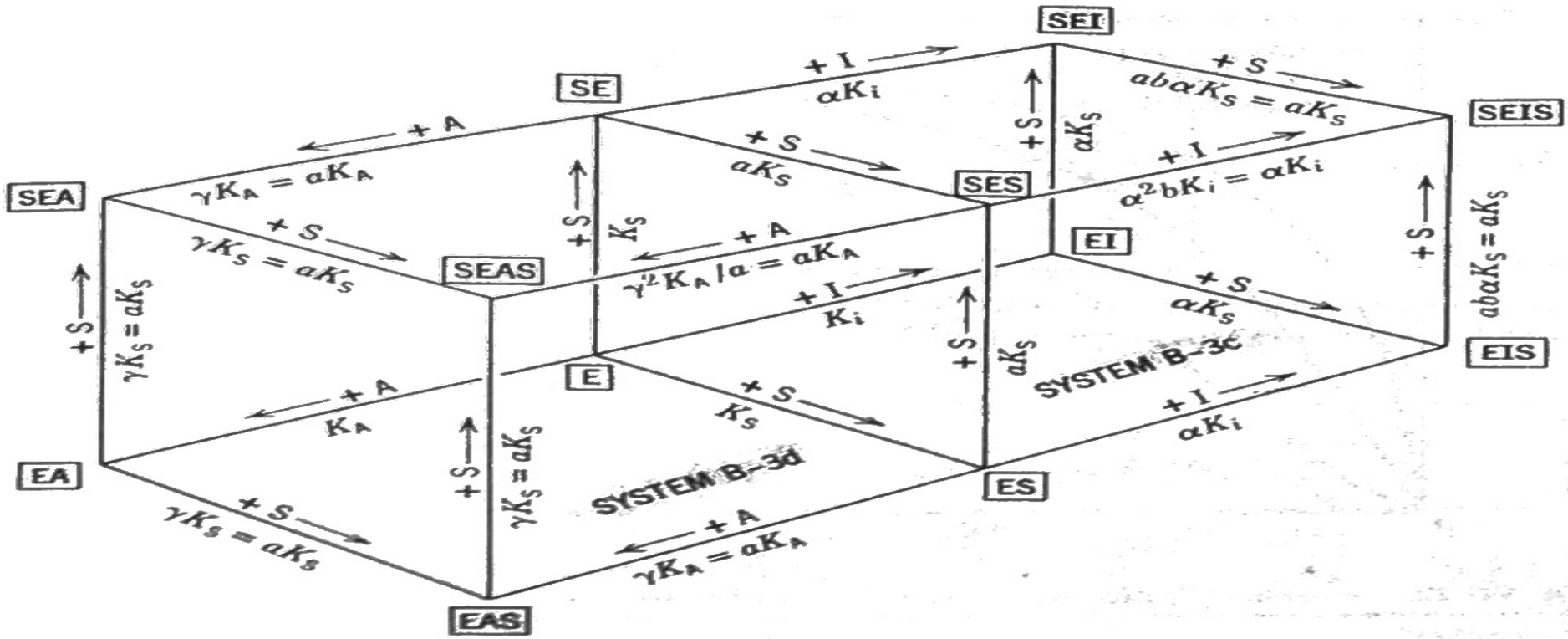
Lift to a slow, normally attracting, invariant manifold



[2003] Gear, Kevrekidis et al, Commun Math Sci 1

Quasi-Steady State Assumption (QSSA)

- Widely used in enzyme kinetics
- Well-diffused in other application areas
- Chemical intuition needed to identify QSSA variables



[1993] Segel, Enzyme Kinetics

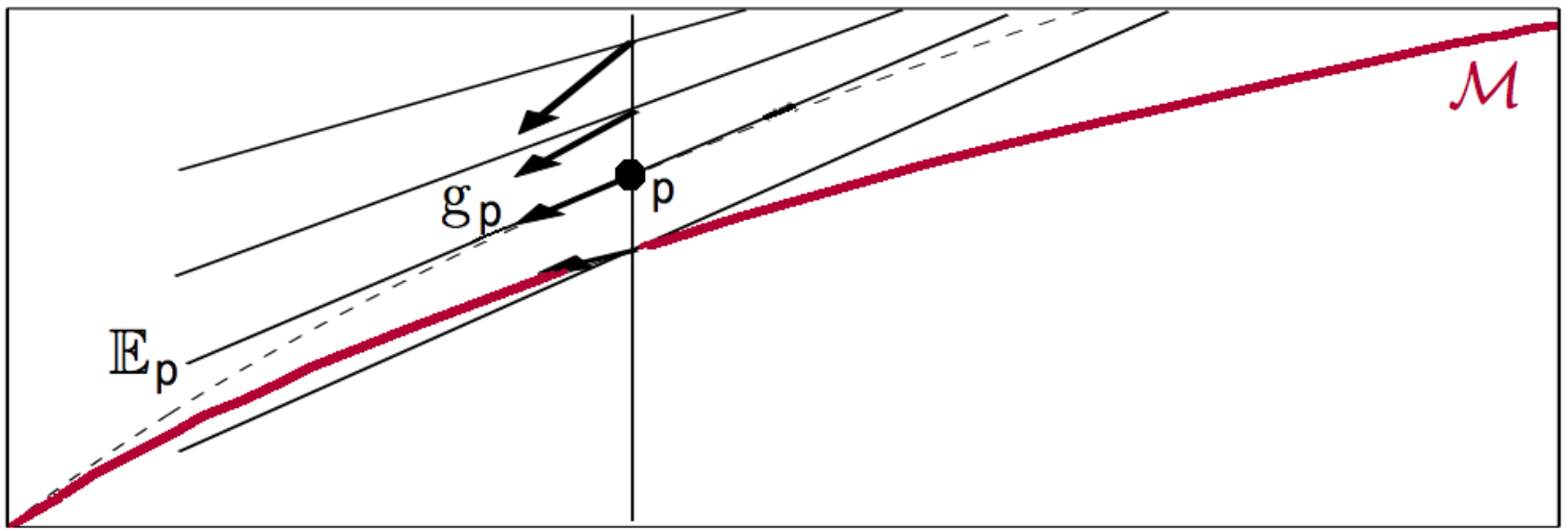
Intrinsic Low-dimensional Manifold (ILDM)

Observation $\forall_{p \in \mathcal{M}} \left[g_p \in T_p \mathcal{M} \right]$ invariance of $\mathcal{M}$

$\Downarrow$

Idea

- $\forall_p$ [locate some "*slow*" subspace $\mathbb{E}_p$]
- approximate $\mathcal{M} \approx \{p \mid g_p \in \mathbb{E}_p\}$



Space? $\mathbb{E}_p =$ slow eigenspace of Dg_p be wise: linearize!

ILDM

- Developed by combustion engineers
- Mostly used in combustion problems
- Suffers from the existence of ghost manifolds

1	$C_3H_8 \rightarrow C_2H_5 + CH_3$	21	$H + C_3H_6 \rightarrow C_2H_4 + CH_3$	42	$HO_2 + C_2H_6 \rightarrow C_2H_5 + H_2O_2$	63	$HCO + O_2 \rightarrow CO + HO_2$
2[a]	$C_3H_8 + O_2 \rightarrow C_3H_7 + HO_2$	22	$H + C_3H_6 \rightarrow C_3H_5 + H_2$	43	$C_2H_5 + O_2 \rightarrow C_2H_4 + HO_2$	64	$OH + CO \rightarrow CO_2 + H$
3[a]	$C_3H_8 + O_2 \rightarrow H_7C_3 + HO_2$	23	$OH + C_3H_5 \rightarrow C_2H_4 + CH_2O$	44	$H + C_2H_5 \rightarrow 2\ CH_3$	65	$HO_2 + CO \rightarrow CO_2 + OH$
4	$CH_3 + C_3H_8 \rightarrow C_3H_7 + CH_4$	24	$O + C_3H_6 \rightarrow C_2H_5 + HCO$	45	$H + C_2H_5 \rightarrow H_2 + C_2H_4$	66	$CO + O + M \rightarrow CO_2 + M$
5	$CH_3 + C_3H_8 \rightarrow H_7C_3 + CH_4$	25	$OH + C_3H_6 \rightarrow C_2H_5 + CH_2O$	46	$H + C_2H_4 \rightarrow C_2H_3 + H_2$	67	$H + O_2 \rightarrow OH + O$
6	$H + C_3H_8 \rightarrow C_3H_7 + H_2$	26	$C_2H_5 \rightarrow C_2H_4 + H$	47	$O + C_2H_4 \rightarrow CH_3 + HCO$	68	$OH + H_2 \rightarrow H_2O + H$
7	$H + C_3H_8 \rightarrow H_7C_3 + H_2$	27	$M + CH_4 \rightarrow CH_3 + H + M$	48	$OH + C_2H_4 \rightarrow C_2H_3 + H_2O$	69	$O + H_2 \rightarrow OH + H$
8	$O + C_3H_8 \rightarrow C_3H_7 + OH$	28	$H + CH_4 \rightarrow CH_3 + H_2$	49	$M + C_2H_3 \rightarrow C_2H_2 + H + M$	70	$OH + OH \rightarrow H_2O + O$
9	$O + C_3H_8 \rightarrow H_7C_3 + OH$	29	$O + CH_4 \rightarrow CH_3 + OH$	50	$H + C_2H_2 \rightarrow C_2H + H_2$	71	$H + OH + M \rightarrow H_2O + M$
10	$OH + C_3H_8 \rightarrow C_3H_7 + H_2O$	30	$OH + CH_4 \rightarrow CH_3 + H_2O$	51	$O + C_2H_2 \rightarrow CH_2 + CO$	72	$H + H + M \rightarrow H_2 + M$
11	$OH + C_3H_8 \rightarrow H_7C_3 + H_2O$	31	$CH_3 + O \rightarrow CH_2O + H$	52	$OH + C_2H_2 \rightarrow C_2H + H_2O$	73	$H + O_2 + M \rightarrow HO_2 + M$
12	$HO_2 + C_3H_8 \rightarrow C_3H_7 + H_2O_2$	32	$CH_3 + O_2 \rightarrow CH_3O + O$	53	$C_2H + O_2 \rightarrow HCO + CO$	74	$OH + HO_2 \rightarrow H_2O + O_2$
13	$HO_2 + C_3H_8 \rightarrow H_7C_3 + H_2O_2$	33	$CH_3 + HO_2 \rightarrow CH_3O + OH$	54	$CH_2 + O_2 \rightarrow HCO + OH$	75	$H + HO_2 \rightarrow H_2 + O_2$
14	$C_3H_7 \rightarrow C_2H_4 + CH_3$	34	$CH_3 + OH \rightarrow CH_2O + H_2$	55	$H + CH_2O \rightarrow HCO + H_2$	76	$H + HO_2 \rightarrow 2\ OH$
15	$H_7C_3 \rightarrow C_2H_4 + CH_3$	35	$M + CH_3O \rightarrow CH_2O + H$	56	$O + CH_2O \rightarrow HCO + OH$	77	$O + HO_2 \rightarrow OH + O_2$
16	$C_3H_7 \rightarrow C_3H_6 + H$	36	$CH_3O + O_2 \rightarrow CH_2O + HO_2$	57	$OH + CH_2O \rightarrow HCO + H_2O$	78	$HO_2 + HO_2 \rightarrow H_2O_2 + O_2$
17	$H_7C_3 \rightarrow C_3H_6 + H$	37	$CH_3 + CH_3 \rightarrow C_2H_6$	58	$HO_2 + CH_2O \rightarrow HCO + H_2O_2$	79	$HO_2 + H_2 \rightarrow H_2O_2 + H$
18	$C_3H_7 + O_2 \rightarrow C_3H_6 + HO_2$	38	$CH_3 + C_2H_6 \rightarrow C_2H_5 + CH_4$	59	$M + HCO \rightarrow CO + H + M$	80	$OH + H_2O_2 \rightarrow HO_2 + H_2O$
19	$H_7C_3 + O_2 \rightarrow C_3H_6 + HO_2$	39	$H + C_2H_6 \rightarrow C_2H_5 + H_2$	60	$H + HCO \rightarrow CO + H_2$	81	$M + H_2O_2 \rightarrow 2\ OH + M$
20	$CH_3 + C_3H_6 \rightarrow C_3H_5 + CH_4$	40	$O + C_2H_6 \rightarrow C_2H_5 + OH$	61	$O + HCO \rightarrow CO + OH$	82	$H + H_2O_2 \rightarrow H_2O + OH$
		41	$OH + C_2H_6 \rightarrow C_2H_5 + H_2O$	62	$OH + HCO \rightarrow CO + H_2O$	83	$O + H_2O_2 \rightarrow HO_2 + OH$

[1997] Norris, NASA report

Computational Singular Perturbation (CSP)

Same as ILDM but works with the Lie bracket $[\cdot, g]$ instead of with Dg

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CSP: Compute basis A_p s.t. $A_p^{-1}\, [A_p, g_p]$ in canonical form

- $[v, g] = (Dg)v - (Dv)g \longrightarrow A^{-1}[A, g] = A^{-1}(Dg)A - A^{-1}(DA)g$

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- Canonization of $A^{-1}[A, g]$ is a PDE problem
- Proceed iteratively

CSP

- Developed by combustion engineers
- Diffused into biology & biochemistry
- Enables a full timescale analysis

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1	$\leftrightarrow Glc_x$	13	$EtOH \leftrightarrow EtOH_x$
2	$Glc_x \leftrightarrow Glc$	14	$EtOH_x \rightarrow$
3	$Glc + ATP \rightarrow G6P + ADP$	15	$DHAP + NADH \rightarrow Glyc + NAD^+$
4	$G6P \leftrightarrow F6P$	16	$Glyc \leftrightarrow Glyc_x$
5	$F6P + ATP \rightarrow FBP + ADP$	17	$Glyc_x \rightarrow$
6	$FBP \leftrightarrow GAP + DHAP$	18	$ACA \leftrightarrow ACA_x$
7	$DHAP \leftrightarrow GAP$	19	$ACA_x \rightarrow$
8	$GAP + NAD^+ \leftrightarrow BPG + NADH$	20	$ACA_x + CN_x^- \rightarrow$
9	$BPG + ADP \leftrightarrow PEP + ATP$	21	$\leftrightarrow CN_x^-$
10	$PEP + ADP \rightarrow Pyr + ATP$	22	$G6P + ATP \rightarrow ADP$
11	$Pyr \rightarrow ACA$	23	$ATP \rightarrow ADP$
12	$ACA + NADH \rightarrow EtOH + NAD^+$	24	$ATP + AMP \leftrightarrow 2\,ADP$

[2016] Kourdis, Goussis & Steuer, Phys D 239

Zero-derivative Principle (ZDP)

$$\left.\begin{aligned}\dot{\mathrm{X}}_1 &= \mathrm{G}_1(\mathrm{X}) \\ \dot{\mathrm{X}}_2 &= \mathrm{G}_2(\mathrm{X})\end{aligned}\right| \; \mathrm{X}_1 \text{ parametrize } \mathcal{S}_\varepsilon$$

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- Approximate $S_\varepsilon(X_1^*)$ by X_2^* solving

$$\left.\frac{d^m X_2}{dt^m}\right|_{(X_1^*, X_2^*)} = 0 \qquad \text{ZDP}$$

$$\frac{d\cdot}{dt} = \left(D_{X_1}\cdot\right) G_1 + \left(D_{X_2}\cdot\right) G_2$$

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$$\frac{d\cdot}{dt} = \left(D_{X_1}\cdot\right) G_1 + \left(D_{X_2}\cdot\right) G_2$$

$$||X_2^* - S_\varepsilon(X_1^*)|| = \mathcal{O}(\varepsilon^m)$$

Gravity waves and quasi-geostrophic oscillations in this model are distinguished by their frequencies, which differ by about an order of magnitude. It follows that, in a particular solution, if the value of one variable, say x_1, can be resolved into gravity-wave and quasi-geostrophic components, the ratio of these components will be exceeded by about n orders of magnitude by the ratio of the same components of $d^n x_1/d\tau^n$. Hence, relative to its value in an arbitrary solution, the value of $d^n x_1/d\tau^n$ in a solution without gravity waves should be close to zero for large n. This property leads to an algorithm for finding points on the manifold.

We choose fixed values of y_1, y_2, y_3, and seek the remaining variables. For notational convenience we let $z_i - y_i = x_{i+3}$ for $i = 1, 2, 3$, and let $\mathbf{Y}$ and $\mathbf{X}$ be three- and six-dimensional vectors with components (y_1, y_2, y_3) and $(x_1, \ldots, x_6)$. For a starting approximation we choose $\mathbf{X} = 0$, and in successive approximations we determine $\mathbf{X}$ so that $d\mathbf{X}/d\tau = 0$, $d^2\mathbf{X}/d\tau^2 = 0$, etc.

To find these values of $\mathbf{X}$ numerically we use a double approximation procedure. We let $\mathbf{X}_{n,k}$ be the kth approximation to the value of $\mathbf{X}$ which makes $d^n\mathbf{X}/d\tau^n$ vanish. We set $\mathbf{X}_{1,0} = 0$, i.e., we begin with the geostrophic approximation, and in general we let

$$\mathbf{X}_{n,k+1} = \mathbf{X}_{n,k} - (d^n\mathbf{X}_{n,k}/d\tau^n)[\partial(d^n\mathbf{X}_{n,k}/d\tau^n)/\partial\mathbf{X}_{n,k}]^{-1},$$

where the quantity in brackets is a sixth-order square matrix, which may be estimated by perturbing the components of $\mathbf{X}$ one at a time, and reevaluating the components of $d^n\mathbf{X}/d\tau^n$. When the procedure has converged for a particular value of n, say, when $k = K(n)$, we let

$$\mathbf{X}_{n+1,0} = \mathbf{X}_{n,K(n)} \qquad (57)$$

[1980] Lorenz, J Atmos Sci 37

ZDP

- Component of equation–free computing
- Applications in biochemistry, genetics, pattern formation ...
- One-trick pony

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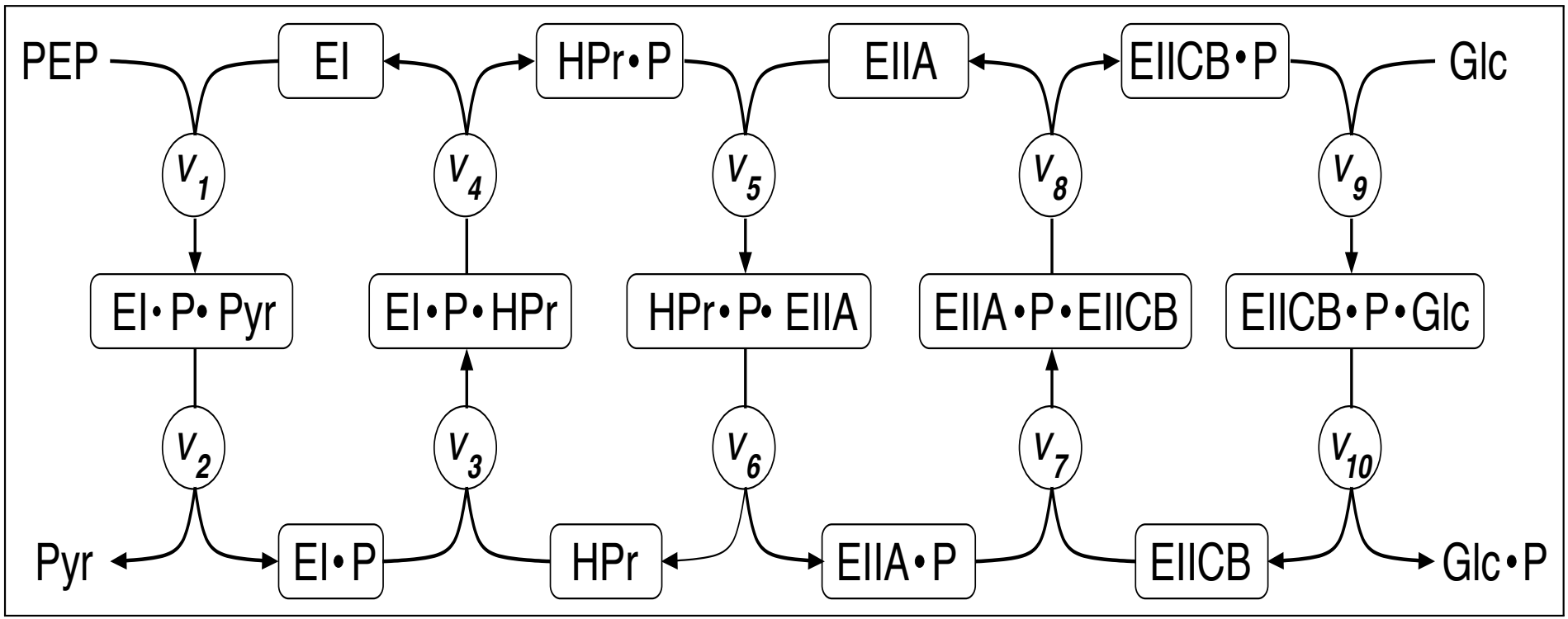

[2009] Härdin, Zagaris, Krab & Westerhoff, FEBS J 276

A Common Geometric Framework

All slaving relations can read $B(x)g(x) = 0$ for a matrix $B(x)$

QSSA	ILDM	CSP & ZDP
$B(x) = \begin{bmatrix} 0\,0\ldots 1\ldots 0 \\ 0\,1\ldots 0\ldots 0 \\ \vdots\,\vdots \quad \vdots \quad \vdots \\ 0\,0\ldots 0\ldots 1 \end{bmatrix}$	$B(x) \perp$ slow eigenspace of $Dg(x)$	$B(x) \perp$ slow eigenspace of $[\cdot, g(x)]$

A Common Geometric Framework

All slaving relations can read $B(x)g(x) = 0$ for a matrix $B(x)$

QSSA	ILDM	CSP & ZDP
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$$\Downarrow$$

$$\mathcal{S}_\varepsilon \text{ invariant} \Leftrightarrow g(x) \in T_x\mathcal{S}_\varepsilon \Leftrightarrow B(x)g(x) = 0 \wedge \operatorname{span}(B(x)) = N_x\mathcal{S}_\varepsilon$$

$$\operatorname{span}\big(B(x)\big) \approx N_x\mathcal{S}_\varepsilon \qquad \operatorname{span}\big(B(x)\big) \approx N_x\mathcal{S}_\varepsilon \;\Rightarrow\; \mathcal{S}_{\text{approx}} \approx \mathcal{S}_\varepsilon$$

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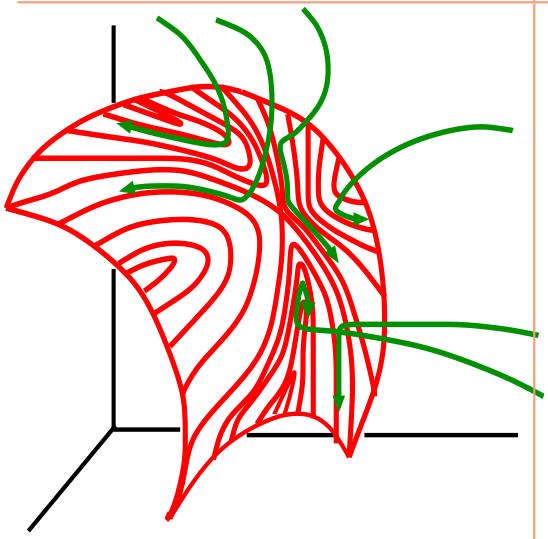
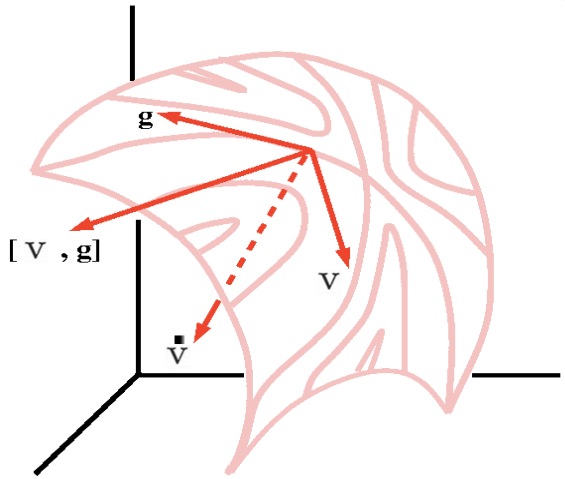
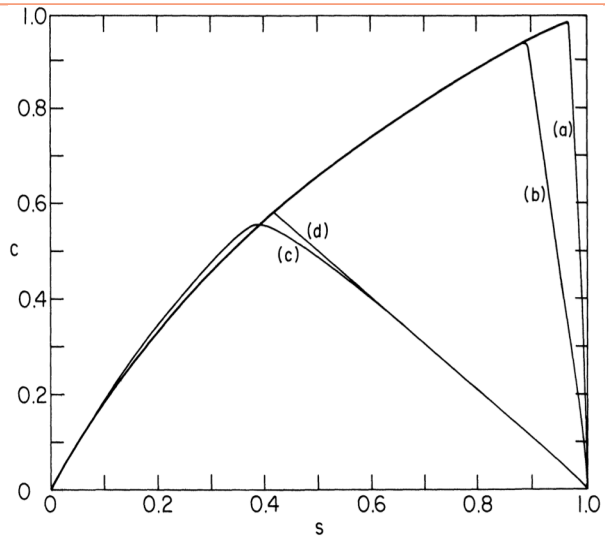
$$\Downarrow$$

Approximation properties of $\mathcal{S}_{\text{approx}}$ relative to $\mathcal{S}_\varepsilon$

Analytic Results

CSP & ZDP	ILDM	QSSA
B(x) $\perp$ slow e−space of $[\cdot, g(x)]$	B(x) $\perp$ slow e−space of Dg(x)	$B = \begin{bmatrix} 0\,0\ldots1\ldots0 \\ 0\,1\ldots0\ldots0 \\ \vdots\ \vdots\quad\ \vdots\quad\ \vdots \\ 0\,0\ldots0\ldots1 \end{bmatrix}$
• B ✓ • $\mathcal{S}_{\text{approx}}$ ✓	• B leading order ✓ • $\mathcal{S}_{\text{approx}}$ second order ✓	• B chosen haphazardly • $\mathcal{S}_{\text{approx}}$ leading order ✓
	$(Dg)v - [v,g] = (Dv)g = \dot{v}$ 	

The Plan

- Introduction to GSPT — today
- Qualitative introduction to multiscale reduction — today
- Quantitative introduction to multiscale reduction — tomorrow
- Theoretical and computational exercises — tomorrow
- Final project — near future