

# ENGSCI 711

## QUALITATIVE ANALYSIS OF DIFFERENTIAL EQUATIONS

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### LECTURE 13

- Extension to systems with parameters
  - Application to bifurcation theory
  - Application to fast/slow systems: enzyme-mediated reactions

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## MODULE OVERVIEW

Qualitative analysis of differential equations (Oliver Maclaren) [~16-17 lectures/tutorials]

4. Centre manifold theory and putting it all together  
[4 lectures/tutorials]

Putting everything together - asymptotic stability, structural stability and bifurcation using the geometric perspective. In particular: centre manifold theorem and reduction/emergence principle.

### EXTENDED CENTRE MANIFOLD - EXTENSION TO PARAMETERS

Note: the material on *extended* centre manifolds that *follows next is not on the exam*, but may be relevant to the assignment/tutorial to some extent.

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## EXTENDED CENTRE MANIFOLD - EXTENSION TO PARAMETERS

We surely want to consider systems where *some eigenvalues are much smaller* than the others but *not exactly zero*.

We also want to analyse the *dynamics in systems with parameter-dependent bifurcations*.

Both of these cases can handled by constructing an *extended* centre manifold which *includes the parameter(s)* of interest.

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## EXTENDED CENTRE MANIFOLD - EXTENSION TO PARAMETERS

The key trick is simple: treat the *parameter* of interest as a (*super slow!*) *centre state variable*. i.e. rewrite a system like

$$\dot{x} = f(x; \mu)$$

as

$$\begin{aligned}\dot{x} &= f(x, \mu) \\ \dot{\mu} &= 0\end{aligned}$$

where  $\mu$  is *now a state variable*. Note: this means that in the second system terms like e.g.  $\mu x$  in  $f$  are now considered *nonlinear!*

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## EXTENDED CENTRE MANIFOLD - APPLICATION TO BIFURCATION THEORY

How is this relevant to *bifurcation* theory? Suppose we have a *non-hyperbolic fixed point*  $x = 0$  when  $\mu = 0$ . From Wiggins (2003):

...the center manifold exists for all  $\mu$  in a sufficiently small neighborhood of  $\mu = 0$ ... [but as we know] it is *possible for solutions to be created or destroyed* by perturbing nonhyperbolic fixed points...

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## EXTENDED CENTRE MANIFOLD - APPLICATION TO BIFURCATION THEORY

...Thus, since the invariant center manifold exists in a sufficiently small neighborhood in both  $x$  and  $\mu$  of  $(x, \mu) = (0, 0)$ , *all bifurcating solutions will be contained in the lower dimensional [extended] center manifold.*

i.e.

...all the action is on the centre manifold...!

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## EXTENDED CENTRE MANIFOLD - APPLICATION TO BIFURCATION THEORY

The easiest way to understand this is via an example.

Transcritical bifurcation example: *bifurcation analysis the long way* (using centre manifold theory).

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## CENTRE MANIFOLD THEOREM - APPLICATION ENZYME REACTIONS

Usually approached via 'quasi-steady' or 'quasi-equilibrium' assumptions

*We can justify and improve via centre manifold theory!*

Also: comparison with more common 'singular perturbation' approach

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## THE MICHAELIS-MENTEN MODEL

Michaelis-Menten (1913) introduced one of the first, and simplest, mathematical models of enzyme activity

*Each step of full system obeys 'mass action' kinetics*

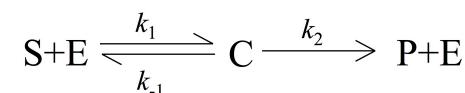
But result is

*The overall, effective  $S \rightarrow P$  reaction does not obey mass action*

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## THE MICHAELIS-MENTEN MODEL: DERVIATION

Assumed reaction mechanism:



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## THE MICHAELIS-MENTEN MODEL: FULL MODEL

Full system of equations:

$$\begin{aligned}\frac{d[S]}{dt} &= -k_1[E][S] + k_{-1}[C] \\ \frac{d[E]}{dt} &= -k_1[E][S] + (k_{-1} + k_2)[C] \\ \frac{d[C]}{dt} &= k_1[E][S] - (k_{-1} + k_2)[C] \\ \frac{d[P]}{dt} &= k_2[C]\end{aligned}$$

*Let's see what centre manifold theory has to say about this!*

Initial conditions:

$$[S](0) = S_0, \quad [E](0) = E_0, \quad [C](0) = 0, \quad [P](0) = 0$$

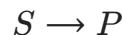
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## THE MICHAELIS-MENTEN MODEL: REDUCED MODEL

Goal: reduction to 'effective' constitutive equation for

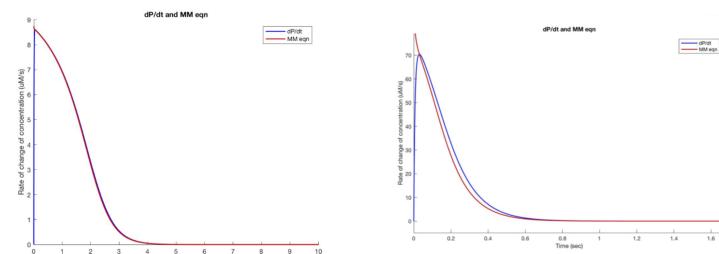


i.e.

$$J_P = \frac{d[P]}{dt} = f([S])$$

Note: people often use  $v$  instead of  $J$  in this context.

## NAIVE MM APPROXIMATION



Dependence on  $\epsilon$ . *Challenge: improve with CMT!*

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## EngSci 711 L13 Centre manifold theory cont'd... cont'd

Extended centre manifolds:

dealing with/making use of  
parameters in centre manifold theory

- Application to bifurcation theory
- Application to slow-fast enzyme kinetics  
↳ + comparison to singular perturbation theory.

**Key:** parameters as 'super slow' variables

### Example Questions

- Not examinable
- See this lecture & tutorial for examples.
- See eg laser physics papers I posted to canvas:

'quasi-steady state'

The adiabatic-elimination (AE) procedure is used [1] to simplify the equations of motion close to bifurcation points, where the slowing-down of a few variables let the fast ones relax to their instantaneous equilibrium positions. This procedure is particularly successful in those physical systems where some variables undergo fast-relaxation processes. A particular care has to be taken, however, in these cases, first suitably rescaling the variables, and then examining their effective fastness. LUGIATO and co-workers have recently suggested [2] a series of conditions to be fulfilled in order to guarantee the correctness of AE, and showed some examples where it cannot be applied.

In this letter, following the guideline of the centre manifold theory [3], we develop a more general approach, and apply it to the homogeneously broadened resonant laser. The main idea is to look for a global expression of the invariant surface where the slow motion develops, thus overcoming the explicit dependence on the co-ordinates of the standard method. In this way we will be able to handle general cases where no component of the vector field vanishes on the manifold.

(Oppo & Politi 1986)

### Systems depending on parameters

Now we look at how to apply centre manifold theory to systems depending on parameters, ie

$$\dot{x} = f(x; u)$$

↑                    ↓  
state vector      vector of  
'external' or 'control'  
parameters

Why? This is useful for at least two reasons:

1. To connect centre manifold theory & bifurcation theory

↳ we will derive the simple, low-dimensional systems in which bifurcations occur by reducing larger systems to just the 'critical' (slow/centre) variables

→ near a bifurcation, 'all the action' occurs on the centre manifold

} low dimensional bifurcations are 'contained' in larger systems

2. Parameters allow us to 'widen' the scope of application of centre manifold theory

'close to zero'  
e.g.  
ex (x) x

↳ exactly zero eigenvalues are rare, but widely separated eigenvalues, with some  $\approx 0$  are much more common

$\leftrightarrow$

→ can use small parameters to represent this  
→ creates a centre manifold in  $\epsilon$  that we can use

$\leftrightarrow$

→ alternative/complement to 'singular perturbation theory'

## Motivating example 1.

Recall the example from lecture 12 (Based on Glendinning exercise 8-3)

$$\begin{aligned}\dot{x} &= y - x - x^2 \\ \dot{y} &= x - y - y^2\end{aligned}$$

We saw that this has one zero eigenvalue, } is nonhyperbolic  
& hence a one-dimensional centre manifold

(we had to change coord. to identify/separate  
the fast/slow dynamics though!)

Consider next the parameter dependent system:

$$\begin{aligned}\dot{x} &= y - x - x^2 \\ \dot{y} &= (1+u)x - y - y^2\end{aligned}$$

For  $u=0$  this reduces to our previous system.

for  $u \neq 0$  this will no longer be nonhyperbolic

→ thus we expect to pass through a  
bifurcation point as we vary  $u$  through  
zero.

→ we also hope/expect that we only need to  
consider the 'slow' variable equation.

↪ we need to justify for  $u \neq 0$ !

### Steps.

1. Fp. → just look at  $(0,0)$  here

$$\rightarrow \dot{x}(0) = \dot{y}(0) = 0 \quad \checkmark$$

$$2. Df(0,0) = \begin{pmatrix} -1 & 1 \\ 1+u & -1 \end{pmatrix}$$

$$\text{tr} = -2$$

$$\det = 1 - (1+u) = -u$$

Note:  $\det \neq 0$  if  $u \neq 0$

$$\begin{aligned}\lambda_1 &= -1 - \sqrt{1+u} \\ \lambda_2 &= -1 + \sqrt{1+u}\end{aligned}\quad \left. \begin{array}{l} \lambda_1 \neq 0 \text{ if } u \neq 0 \\ \lambda_2 \neq 0 \text{ if } u \neq 0 \end{array} \right\}$$

Problem: no centre manifold for  $u \neq 0$

→ no reduction!

Q: does a centre manifold still exist for  $u \neq 0$ ?

can we still reduce to it for  $u \neq 0$

A: yes!

### Key trick

Treat  $m$  as a state var

→ consider extended system:

$$\begin{aligned}\dot{x} &= y - x - x^2 \\ \dot{y} &= (1+m)x - y - y^2 \\ \dot{m} &= 0\end{aligned}$$

? note: 'super slow'  
(frozen to all orders)

How is this useful?

→ terms like  $m x$  are non-linear

→ we can consider neighbourhood of  $m=0$

1. Fixed point?

$$(x, y, m) = (0, 0, 0) \checkmark$$

(actually  $m$  can be anything ...)

$$2. Df(0,0,0) = \begin{pmatrix} [-1 & 1] & 0 \\ [1 & -1] & 0 \\ 0 & 0 & [0] \end{pmatrix}$$

eigenvalues = eigenvalues of diagonal blocks

→  $\text{tr}(\text{upper}) = -2$ ,  $\det(\text{upper}) = 0$

$$\Rightarrow \lambda_1 = 0, \lambda_2 = -2$$

$$\text{lower} \Rightarrow \lambda_3 = 0$$

### Recap so far:

2D  $x, y$  system → no reduction

3D  $x, y, m$  system → reduction to 2D

is this useful?

→ yes! one of remaining 2D will just be  $m = 0 \Rightarrow$  trivial

→ other will be slow var

→ fast var can be eliminated.

really  
2D → 1D  
via  
3D → 2D.

Let's see

First we transform coordinates so that our system is 'linearly separated' into 'fast/slow' subsystems

$$\left. \begin{array}{l} u = \frac{1}{2}(x+y) \\ v = \frac{1}{2}(x-y) \end{array} \right\} \text{see lecture 12 for details.} \rightarrow u = \frac{1}{2}(x+y)$$

Get:

$$\begin{aligned} \dot{u} &= -(u^2 + v^2) + \frac{1}{2}m(u+v) \\ \dot{v} &= -2v - 2uv - \frac{1}{2}m(u+v) \\ \dot{m} &= 0 \end{aligned}$$

Note:  $m=0$

gives same as

L12.

Form:

$$\begin{pmatrix} \dot{u} \\ \dot{v} \\ \dot{w} \end{pmatrix} = \begin{pmatrix} C & & \\ & F & \\ & & F \end{pmatrix} \begin{pmatrix} u \\ v \\ w \end{pmatrix} + \begin{pmatrix} -(u^2+v^2) + \frac{1}{2}w(u+v) \\ 0 \\ -2uv - \frac{1}{2}w(u+v) \end{pmatrix}$$

C : 'centre/slow' block: zero eigenvalues

F : 'fast' block: non-zero.

(note: here stable).

→ in appropriate form for centre manifold reduction

slow vars are $u, v$
fast var is $w$ .

→ use same approach:

$$\text{fast} = f(\text{slow})$$

$$\text{let } \boxed{w = f(u, v)} \quad \text{"slaving principle"}$$

→ fast become  
'slaved' by  
slow.



Reduction

consider the linear part

$$A = \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & -2 \end{pmatrix}$$

E.C.

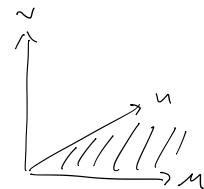
Diagonal → axes are eigenvectors

or explicitly  $Au = \lambda u$

$$\lambda = 0 \Rightarrow \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & -2 \end{pmatrix} \begin{pmatrix} u_1 \\ u_2 \\ u_3 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix}$$

$\Rightarrow u_3 = 0$ ,  $u_1, u_2$  free.

$$\text{choose } u_{(1)} = \begin{pmatrix} 1 \\ 0 \\ 0 \end{pmatrix}, u_{(2)} = \underbrace{\begin{pmatrix} 0 \\ 1 \\ 0 \end{pmatrix}}_{u, v \text{ plane.}}$$



$$w = V(u, v) = a + bu + cv + du^2 + evu + fv^2$$

CMT:  $V(u, v)$  tangent to  $u, v$  plane & goes through  $(0, 0)$ .

$$\Rightarrow V(0, 0) = 0, \underbrace{\frac{\partial V}{\partial u}(0, 0) = 0, \frac{\partial V}{\partial v}(0, 0) = 0}_{a=0, b=0, c=0}$$

→

Reduction cont'd.

$$v = V(u, m) = du^2 + emu + fm^2$$

1. chain rule

$$\begin{aligned} \dot{v} &= \frac{\partial V}{\partial u} \dot{u} + \frac{\partial V}{\partial m} \dot{m} \\ &\stackrel{i=0}{=} (2du + 2mu) (O(\| \cdot \| ^2)) \\ &= 0 + O(\| \cdot \| ^3) \end{aligned}$$

Interlude:  $O(\| \cdot \| ^3)$  ? , where  $\| \cdot \| \rightarrow$  'size' ie  
 whatever /  $\sqrt[3]{(\text{norm of vector/object})}$   
 "order size cubed"

e.g.  $x = (x_1, x_2) \leftarrow$  vector/multivariate

$$O(\| x \| ^3) \text{ includes } \left\{ \begin{array}{l} x_1^3 \\ x_1 x_2 \\ x_1^2 x_2 \\ x_2^3 \end{array} \right.$$

Reduction

2. subst.

$$\begin{aligned} \dot{v}(u, m, V(u, m)) &= O(\| \cdot \| ^3) \\ -2(du^2 + emu + fm^2) - 2u \cancel{(}) \\ -\frac{1}{2}mu + O(\| \cdot \| ^3) \end{aligned}$$

$$\textcircled{1} = \textcircled{2}$$

$$\Rightarrow 0 = -2du^2 - (2e - \frac{1}{2})mu + fm^2$$

$$\Rightarrow e = \frac{1}{4}, d = 0, f = 0$$

$$v = \frac{1}{4}mu + \text{h.o.t.}$$

$$\& W^c = \{ (u, m, v) \mid v = \frac{1}{4}mu \}$$

$$\text{Dynamics: } \dot{u} = -(u^2 + O(\| \cdot \| ^4)) + \frac{1}{2}mu + O(\| \cdot \| ^3)$$

$$= -u^2 + \frac{1}{2}mu = \frac{u}{2}(u - 2u)$$

$\rightarrow$ .

$$\& \dot{m} = 0. \quad \text{"super slow"}$$

$\nearrow$   
 don't  
 forget!

$\rightarrow$

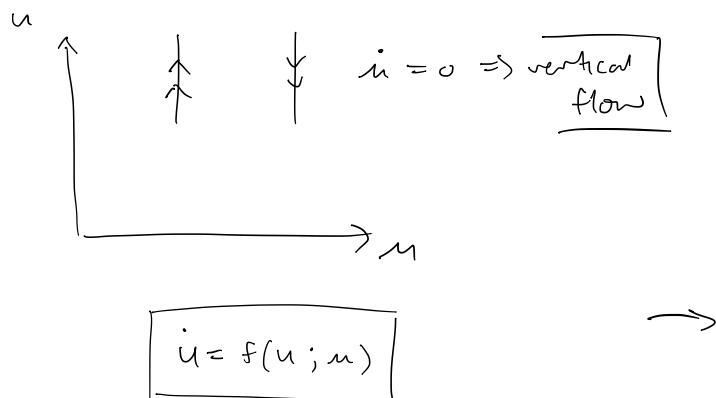
## Bifurcation theory

$$\begin{cases} \dot{u} = \frac{u}{2}(u - 2u) \\ \dot{m} = 0 \end{cases} \quad \left. \begin{array}{l} \text{centre manifold} \\ \text{dynamics} \end{array} \right\}$$

Either  
 - downgrade  $m$  back to 'parameter'  
 $\hookrightarrow$  plot FP of  $u$  as function of  $m$

- think of  $m$  as 'super slow' & carry out another 'reduction' based on time-scale separation.

regardless: effectively a one-dimensional (states) system, depending on one parameter

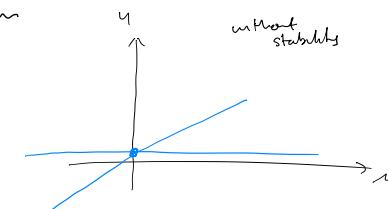


## Bifurcation diagram?

FP:  $\dot{u} = 0 \Rightarrow u = 0 \text{ or } u = \frac{m}{2}$ .

always exist  $\rightarrow$  expect non-hyperbolic  
 $\Rightarrow$  expect swallow stability  
 $\Rightarrow$  Transcritical

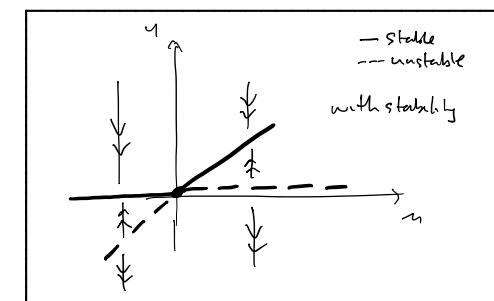
### Diagram



### Stability

$$\begin{aligned} Df &= \frac{u}{2} - 2u & Df(u=0) &= Df = \frac{m}{2} & \left\{ \begin{array}{l} < 0 \text{ if } m < 0 \\ > 0 \text{ if } m > 0 \end{array} \right. \\ &= 2\left(\frac{m}{4} - u\right) & Df(u=\frac{m}{2}) &= -\frac{m}{2} & \text{opposite.} \end{aligned}$$

### Final diagram



Bifurcation diagram = extended centre manifold phase portrait!

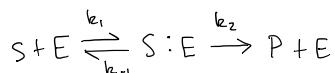
## Motivating example 2 : Fast/slow systems with small parameters

Here we will look at a problem with widely separated time scales, where the 'size' of the separation is indicated by a 'small parameter'

→ This is usually treated by quasi-steady state approximations or singular perturbation theory

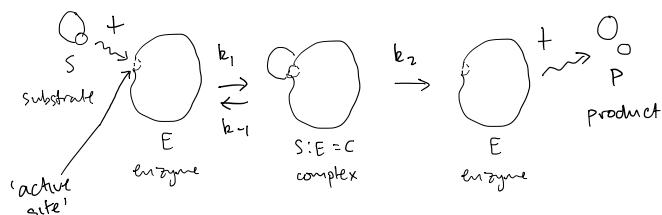
→ Instead we will use --- you guessed it --- centre manifold theory.

### Model: Enzyme kinetics

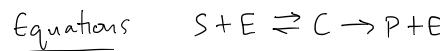


Enzyme: - biological 'catalyst'

- 'helps' reaction along (speeds up)
- not used up in process



Note:  $S + E \rightleftharpoons C \rightarrow P + E$  } :  $S \rightarrow P$   
 detailed model      overall: can we derive?



See eg Biomeng 261 notes (eg my github).

Idea :  $\begin{cases} \text{conservation of mass} \\ + \\ \text{constitutive equations} \end{cases} \quad \left\{ \begin{array}{l} \frac{dS}{dt} = -J_1 + J_2 \\ J_1 = k_1 S \cdot E \\ (\text{'law of mass action'}) \end{array} \right. \quad \begin{array}{l} \text{etc} \\ \text{etc} \end{array}$

Get ( $S$ : substrate,  $C$ : complex,  $P$ : product,  $E$ : enzyme)

$\frac{dS}{dt} = k_1 C - k_2 S \cdot E$	$S(0) = S_0$
$\frac{dE}{dt} = (k_1 + k_2) C - k_1 S \cdot E$	$E(0) = E_0$
$\frac{dC}{dt} = -\frac{dE}{dt} \Rightarrow C + E = E(0) = E_0$ $\Rightarrow E = E_0 - C$	$C(0) = 0$
$\frac{dP}{dt} = k_2 C$ <u>(elim. E)</u>	$P(0) = 0$



System in S, C, P (no approximation so far).

$$\frac{ds}{dt} = k_{-1}c - k_1 s \cdot [E_0 - c]$$

$$\frac{dc}{dt} = -(k_{-1} + k_2) c + k_1 s [E_0 - c]$$

$$\frac{dp}{dt} = k_2 c$$

$$S(0) = S_0$$

$$C(0) = 0$$

$$P(0) = 0.$$

Q: Can we 'coarse-grain' c out & get an 'effective'  $S \rightarrow P$  equation just in terms of known quantities?

→ yes! But we need to assume some separation of scales, i.e. we need to find when c is much faster than S & P

→ to help us identify the minimal 'governing parameters' we can non-dimensionalise the system

↳ easier to find key parameters.



### Non-dimensionnalisation & Scaling

(see Richard's material for more)

For concentrations we will choose to measure relative to 'max' or close to max scales:  
→ we will base these on our ICs.

For time we will choose based on balancing/ simplifying equations

Let  $s = S_0 s'$  ← non-dimensional var.  
 ↑ dimensional var      ↑ dimensional constant  
 (subtract  $S_0$ )

$$c = E_0 c' \quad (\text{complex } \sqrt{E_0})$$

$$p = S_0 p' \quad (\text{product } \leq S_0?)$$

$$t = T \tilde{t}$$



Goal: identify 'small' parameters

→ scale separation

$$\text{use: } \frac{ds}{dt} = \frac{d(S_0 s)}{dT \tau} = \frac{S_0}{T} \frac{ds}{d\tau} \quad \text{etc}$$

get

$$\left. \begin{aligned} \frac{S_0}{T} \frac{ds}{d\tau} &= k_{-1} E_0 c - k_1 S_0 E_0 [1-c] s \\ \frac{E_0}{T} \frac{dc}{d\tau} &= -(k_{-1} + k_2) E_0 c + k_1 S_0 E_0 [1-c] s \\ \frac{S_0}{T} \frac{dp}{d\tau} &= k_2 E_0 c \end{aligned} \right\}$$

Choosing T?

common to choose based on long time  
scale e.g. by 'balancing' a  
(suspected) 'slow' equation like  $\dot{p}$ .

$$\text{e.g. } \underbrace{\left( \frac{S_0}{T} \frac{1}{k_2 E_0} \right) \frac{dp}{d\tau}}_{\text{set } = 1} = c$$

set = 1

$$\Rightarrow T = \frac{S_0}{k_2 E_0} \rightarrow$$

This gives:

$$\frac{ds}{d\tau} = \left( \frac{k_{-1}}{k_2} \right) c - \left( \frac{k_1 S_0}{k_2} \right) [1-c] s$$

$$\left( \frac{E_0}{S_0} \right) \frac{dc}{d\tau} = - \left( 1 + \frac{k_{-1}}{k_2} \right) c + \left( \frac{k_1 S_0}{k_2} \right) [1-c] s$$

$$\frac{dp}{d\tau} = c$$

ie

$$\begin{array}{l} \dot{s} = K_{-1} c - K_1 [1-c] s \\ \dot{c} = - (1 + K_{-1}) c + K_1 [1-c] s \\ \dot{p} = c \end{array}$$

only three param.

$\epsilon = E_0 / S_0 \ll 1$ $K_{-1} = k_{-1} / k_2$ $K_1 = k_1 S_0 / k_2$	typically: much less enzyme than substrate
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$$\& \quad s(0) = 1$$

$$c(0) = 0$$

$$p(0) = 0$$



## Singular perturbation theory (see Richard material?)

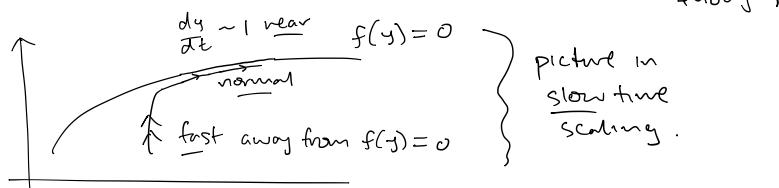
- This form, where a small parameter multiplies a key term like a derivative }  
 is called 'singular' }  
 }  $\epsilon y' = \dots$   
 or  $\epsilon y'' + y' = \dots$   
 etc.

Idea: setting  $\epsilon = 0$  gives a qualitative change in problem structure }  
 hint of bifurcation/centre manifold.  
 → e.g. lose an ODE, can't satisfy an IC etc

Note:  $\epsilon \frac{dy}{dt} = f(y)$  } meaning?

⇒

If }  $\epsilon$  small &  $f(y) \sim 1 \Rightarrow \frac{dy}{dt} \sim \frac{1}{\epsilon}$  → large! 'fast'  
 }  $\epsilon$  small &  $f(y) \sim \epsilon \Rightarrow \frac{dy}{dt} \sim \frac{1 \cdot \epsilon}{\epsilon} \sim 1$  'normal'  
 (or slow time scale though)



→ fast motion to  $f(y)=0$

→ normal motion ( $\sim 1$  on 'slow time')  
 near  $f(y)=0$       ↴ note!

## Singular perturbation theory & quasi-steady states:

To the mathematician this hypothesis, known as the pseudo-steady state hypothesis (pssh), is somewhat scandalous. For clearly  $dc/dt = 0$  in the strict sense at only one instant, and it is notorious that to say that  $c$  is small does not of itself assert anything about the smallness of  $dc/dt$ . To the biochemist the pssh is a valued method of simplifying equations, justified by the excellent agreement with experiment that it gives. In fact, it is related to the smallness of the initial ratio of enzyme to substrate concentration through the singular perturbation theory of differential equations. Although this observation is not new (see the

Hemelken et al 1967

→ yet another approach ↴

## Centre manifold approach

Instead of scaling so that

'slower' ~ 'normal scale', regular

'faster' ~ 'fast scale', singular ( $\frac{1}{\epsilon} \rightarrow \infty$ )

we use:

'slower' ~ 'nonlinear terms', frozen ( $\epsilon \rightarrow 0$ )

'faster' ~ 'linear terms', regular

i.e. our standard centre manifold form

Basically: rather than deal with  
 'singular' fast dynamics  
 we choose 'frozen' slow  
 dynamics

→ equivalent but easier for  
 us here.

} we can  
 use  
regular  
 perturbation  
 theory  
 when in  
 this  
 form!

(similar ideas are used in  
 singular perturbation theory)

- time rescaling
- dominant balances )

So, we balance the c equation to }  
 choose T in:

balance the fast scale.  
 → make this 'normal'  
 & slow 'frozen'  
 on linear scale

$$\frac{s_0 ds}{T d\tau} = k_{-1} E_0 c - k_1 s_0 E_0 [1-c] s$$

$$\frac{E_0}{T} \frac{dc}{d\tau} = -(k_{-1} + k_1) E_0 c - k_1 s_0 E_0 [1-c] s$$

$$\frac{s_0 dp}{T d\tau} = k_2 E_0 c$$

$$\rightarrow T \sim \frac{1}{k_2}$$

$T = 1/k_2$  (thinking: want fast to be simple linear dyn):

$$\dot{s} = \frac{E_0}{S_0} \left[ \frac{k_{-1}}{k_2} c - \frac{k_1 S_0}{k_2} (1-c) s \right]$$

$$\dot{c} = -\frac{(k_{-1} + k_1)}{k_2} c - \frac{k_1 S_0}{k_2} (1-c) s$$

$$\dot{p} = \frac{E_0}{S_0} c$$

ie

$\dot{s} = \epsilon [K_{-1} c - K_1 (1-c) s]$		slow
$\dot{p} = \epsilon c$		
$\dot{\epsilon} = 0$		
$\dot{c} = -(1+K_{-1}) c - K_1 (1-c) s$		fast

where:  
 (three  
 param  
 again).

$E = E_0 / S_0$	
$K_1 = k_1 S_0 / k_2$	
$K_{-1} = k_{-1} / k_2$	

→ extended system  
 ready for CML!

Reduction ready

$$\begin{aligned} \dot{s} &= E [K_{-1}c - K_1(1-c)s] \\ \dot{p} &= E c \\ \dot{e} &= 0 \\ \dot{c} &= -(1+K_{-1})c + K_1(1-c)s \end{aligned} \quad \left. \begin{array}{l} \text{slow} \\ \text{fast} \end{array} \right\}$$

Fast =  $f(\text{slow})$ . i.e.  $c = f(s, p, E)$

$$\frac{dp}{dt} = \left( \frac{1}{k_2 s_0} \right) \frac{dp}{dt} = \frac{E_0}{s_0} \frac{k_1 s_0}{k_2} \frac{s}{s_0} \frac{1}{\left( \frac{k_1 s_0}{k_2 s_0} \frac{s}{s_0} + 1 + \frac{k_{-1}}{k_2} \right)}$$

$$\Rightarrow \frac{dp}{dt} = \frac{\frac{k_1 E_0}{k_2} S}{S + \frac{k_2 + k_{-1}}{k_1}}$$

$$\frac{dp}{dt} = \frac{V_{\max} \cdot S}{S + K_M} \quad \left. \begin{array}{l} \\ \text{Key result} \end{array} \right\}$$

$$\begin{aligned} V_{\max} &= k_2 E_0 \\ K_M &= \frac{k_2 + k_{-1}}{k_1} \end{aligned} \quad \left. \begin{array}{l} \\ \end{array} \right\}$$

"famous" Michaelis-Menten equation

i.e. "effective"  $P \rightarrow S$  law  
 $\rightarrow$  coarse-grained constitutive eqn for  
 an enzyme mediated reaction.

put back in original dimensional form

$$p = \frac{P}{s_0}, \quad s = \frac{S}{s_0} \quad \rightarrow$$

$$\tau = k_2 t$$

Exercise: do the full centre manifold reduction  
 $\rightarrow$  find the 'corrections'

} valid for  
 larger  $E$   
 ranges

(also: try simulating full vs reduced).