

5/19/04

lecture 3

biochemical oscillations

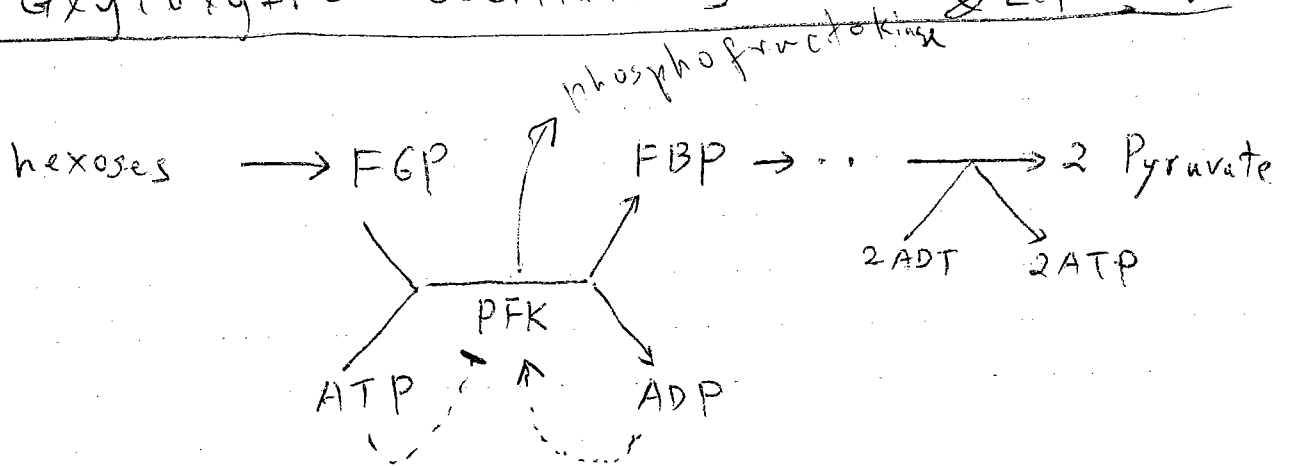
Introduction

- △ steady state vs. oscillatory behavior
- △ prevalence of biological oscillations
 - cell cycle
 - heart beat
 - circadian rhythms
 - calcium oscillation
 - glycolytic oscillations
- △ common underlying mathematics
 - nonlinear system
 - more than two variables
 - limit cycle
 - Hopf bifurcation
- ① some observation connection to geophysical oscillations
- ② the example of glycolytic oscillation (analyze in detail)

example

Selkov 68
Goldbeter
& Lefever 72

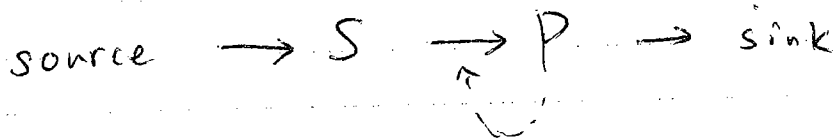
Glycolytic Oscillations



simplify

substrate

product

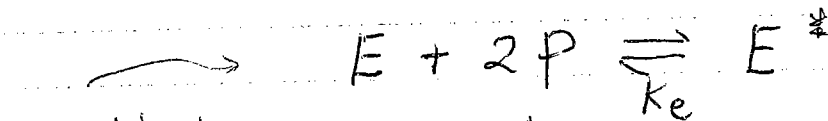
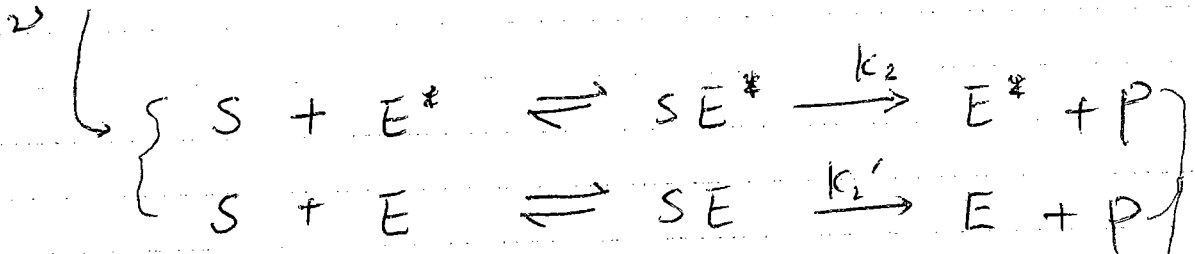


kinetic equations

Allosteric enzyme in two forms

E and E* more active

input rate



cooperativity

removal of P

quasi-steady state for enzyme kinetics

Michaelis-Menten

fast dynamics for $E + 2P \xrightleftharpoons{k_e} E^*$

the rate of $S \rightarrow P$ conversion

$$R = \frac{S}{S + k_m} V_{\max}(E^*) + \frac{S}{S + k'_m} V_{\max}(E)$$

$$V_{\max}(E^*) = E_{\text{tot}}^* \cdot k_2$$

$$V_{\max}(E) = E_{\text{tot}} \cdot k'_2$$

Assuming $S \ll k_m$, $S \ll k'_m$

$$R = \frac{S k_2}{k_m} E_{\text{tot}}^* + \frac{S k'_2}{k'_m} E_{\text{tot}}$$

fast binding dynamics \rightarrow binding equilibrium

$$E_{\text{tot}}^* = E_0 \cdot \frac{P^2 k_e}{1 + P^2 k_e}$$

$$E_{\text{tot}} = E_0 \cdot \frac{1}{1 + P^2 k_e}$$

again assume $P^2 k_e \ll 1$

$$E_{\text{tot}}^* \approx E_0 P^2 k_e$$

$$E_{\text{tot}} \approx E_0$$

E_0 :
total
enzyme

reaction rate

$$R = \frac{k_2 E_0 k_e}{k_m} S P^2 + \frac{k_2' E_0}{k_m} S$$

$$\equiv \alpha S P^2 + \beta S$$

$$\alpha = \frac{k_2}{k_m} E_0 k_e, \quad \beta = \frac{k_2' E_0}{k_m}$$

knowing reaction rate, we can write down the kinetic equations for S & P

$$\frac{ds}{dt} = \overset{\rightarrow \text{input}}{\nu} - \alpha S P^2 - \beta S$$

$$\frac{dp}{dt} = -\underset{\downarrow \text{removal}}{\gamma} p + \alpha S P^2 + \beta S$$

now we wish to de-dimensionalize the equation by rescaling P, S, and t and we want to remove as many as possible parameters

* rescale t can using γ can remove γ

* rescale S & P the same way so we still say the conservation due to reaction

* can rescale p and s
to get rid of α

↓ motivate us to do

$$\left\{ \begin{array}{l} x = \lambda \frac{p}{k_m} \quad p = \frac{k_m x}{\lambda} \\ y = \lambda \frac{s}{k_m} \quad s = \frac{k_m y}{\lambda} \\ \tau = \gamma t \quad t = \frac{\tau}{\gamma} \end{array} \right.$$

substitute into the equations

$$\gamma \frac{k_m}{\lambda} \frac{dy}{d\tau} = \nu - \alpha \left(\frac{k_m}{\lambda} \right)^3 x^2 y - \beta \frac{k_m}{\lambda} y$$

$$\gamma \frac{k_m}{\lambda} \frac{dx}{d\tau} = -\gamma \frac{k_m}{\lambda} x + \alpha \left(\frac{k_m}{\lambda} \right)^3 x^2 y + \beta \frac{k_m}{\lambda} y$$

$$\text{or } \frac{dy}{d\tau} = \frac{\nu \lambda}{\gamma k_m} - \frac{\alpha}{\gamma} \left(\frac{k_m}{\lambda} \right)^2 x^2 y - \frac{\beta}{\gamma} y$$

$$\frac{dx}{d\tau} = -x + \frac{\alpha}{\gamma} \left(\frac{k_m}{\lambda} \right)^2 x^2 y + \frac{\beta}{\gamma} y$$

choose λ such that $\frac{\alpha}{\gamma} \left(\frac{k_m}{\lambda} \right)^2 = 1$

$$\triangle \lambda = k_m \sqrt{\frac{\alpha}{\gamma}}$$

then

$$\frac{dx}{dt} = -x + x^2 y + ay$$

$$\frac{dy}{dt} = b - x^2 y - ay$$

$$b = \frac{v \lambda}{\gamma k_m} = \frac{v}{\gamma} \sqrt{\frac{\alpha}{\gamma}} = \frac{v}{\gamma} \sqrt{\frac{k_2 E_0 k_e}{k_m \gamma}}$$

$$a = \frac{\beta}{\gamma} = \frac{E_0 k_2'}{\gamma k_m'}$$

the behavior of the equations

first consider a simple case

with no product-activation

→ the simple enzyme kinetics

$$\frac{dx}{dt} = -x + ay$$

$$\frac{dy}{dt} = b - ay \rightarrow \text{exponential decay}$$

system is stable

$$J = \begin{bmatrix} \frac{\partial \dot{x}}{\partial x} & \frac{\partial \dot{x}}{\partial y} \\ \frac{\partial \dot{y}}{\partial x} & \frac{\partial \dot{y}}{\partial y} \end{bmatrix}$$

$$= \begin{bmatrix} -1 & a \\ 0 & -a \end{bmatrix}$$

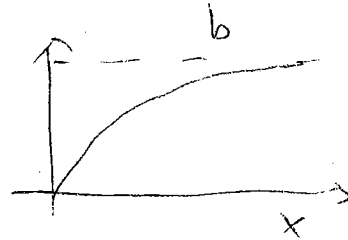
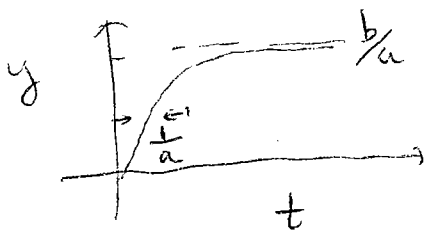
$$\text{Tr} = -(1+a)$$

$$\Delta = a$$

$$\lambda_{1,2} = \frac{\text{Tr} \pm \sqrt{\text{Tr}^2 - 4\Delta}}{2} = \frac{-(1+a) \pm \sqrt{(1+a)^2 - 4a}}{2}$$

$$= \begin{cases} -1 \\ -a \end{cases}$$

initially substrate $y=0$



no oscillation

now consider

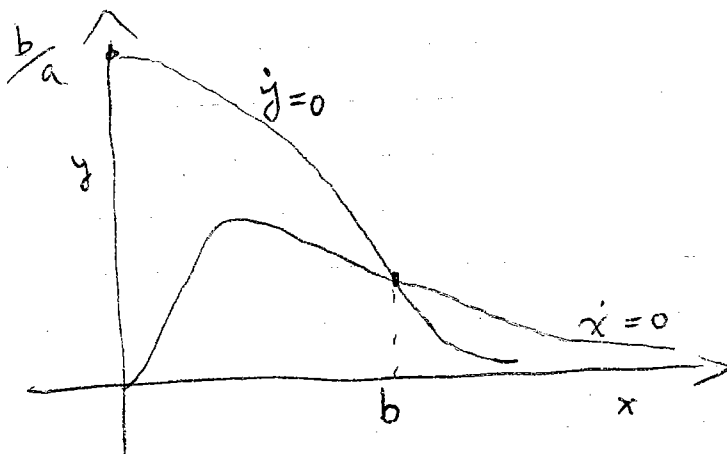
$$\dot{x} = -x + x^2 y + a y$$

$$\dot{y} = b - x^2 y - a y$$

sketch null-cline

$$\dot{x} = 0 \quad y = \frac{x}{x^2 + a}$$

$$\dot{y} = 0 \quad y = \frac{b}{x^2 + a}$$



only one fixed point

where $\dot{x} = 0$ and $\dot{y} = 0$ intersect

$$\Rightarrow \begin{cases} x_0 = b \\ y_0 = \frac{b}{b^2 + a} \end{cases}$$

let's examine the stability of the fixed point

$$J = \begin{bmatrix} \frac{\partial \dot{x}}{\partial x} & \frac{\partial \dot{x}}{\partial y} \\ \frac{\partial \dot{y}}{\partial x} & \frac{\partial \dot{y}}{\partial y} \end{bmatrix} = \begin{bmatrix} -1 + 2xy & a + x^2 \\ -2xy & -a - x^2 \end{bmatrix}$$

evaluate J at x_0, y_0

$$J = \begin{bmatrix} -1 + \frac{2b^2}{b^2 + a} & a + b^2 \\ \frac{-2b^2}{b^2 + a} & -a - b^2 \end{bmatrix}$$

$$\text{Tr} = -(a + b^2 + 1) + \frac{2b^2}{b^2 + a}$$

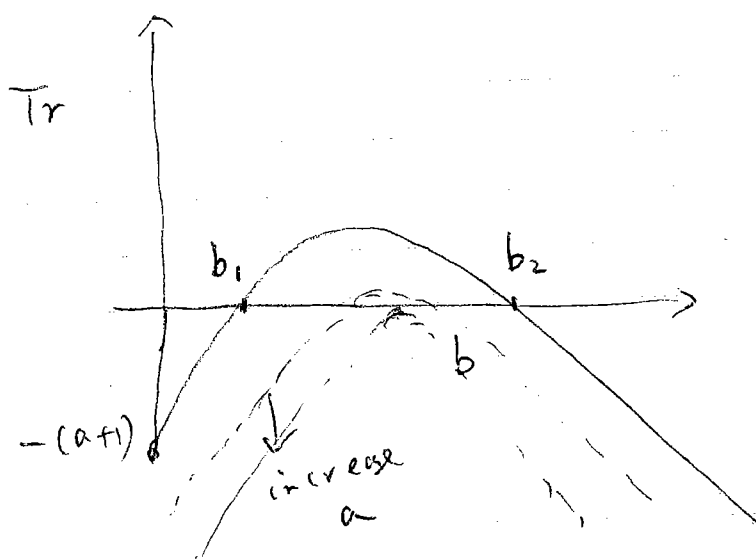
$$\Delta = (a + b^2 - 2b^2) + 2b^2 = a + b^2$$

behavior of the Tr as a function of b

$$\text{Tr}(b=0) = -(a+1) < 0$$

$$\text{Tr}(b=\infty) = -(b^2 + a + 1) + 2 < 0$$

therefore for sufficiently large
and small b , $\text{Tr} < 0$, fixed
point stable



for
 $b_1 < b < b_2$

$$\text{Tr} > 0$$

the fixed
point
unstable

b_1, b_2 found by

$$\text{Tr} = 0 \quad \frac{2b^2}{b^2 + a} = a + b^2 + 1$$

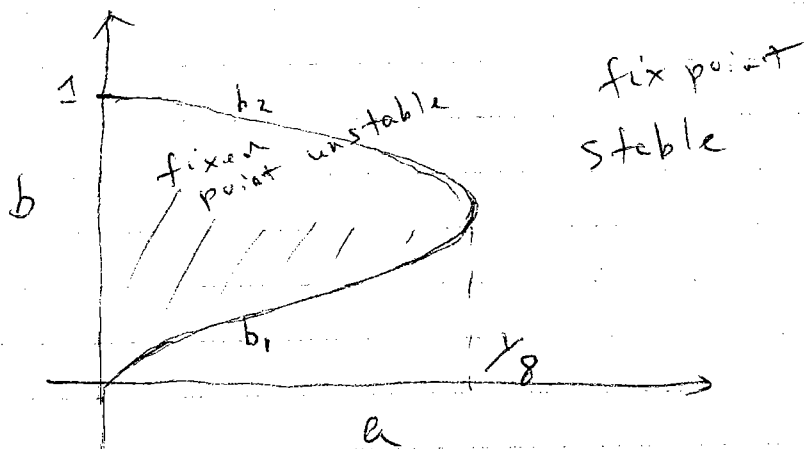
solve this equation for critical b

$$b_2^2 = \frac{1}{2} (1 - 2a + \sqrt{1 - 8a})$$

$$b_1^2 = \frac{1}{2} (1 - 2a - \sqrt{1 - 8a})$$

as long as $a < \frac{1}{8}$

$0 < b_1 < b_2$ positive



What happened when the fixed point become unstable?

* only one fixed point

* trajectory can not cross itself

$(\dot{x}, \dot{y}) = [f(x,y), g(x,y)]$ unique

either spiral to infinity

or reach a stable limit

cycle

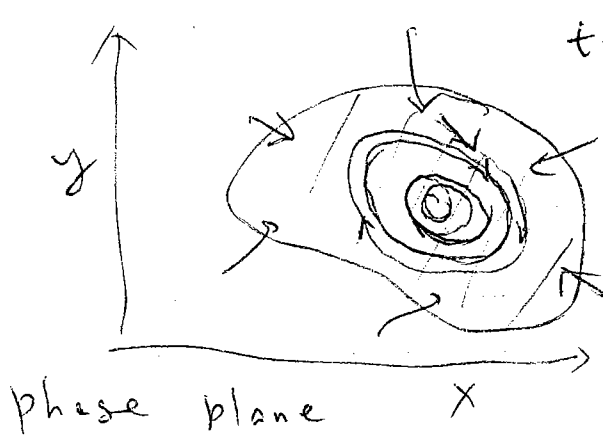
in fact limit cycle is

what happens

Ⓐ limit cycle : isolated closed trajectory

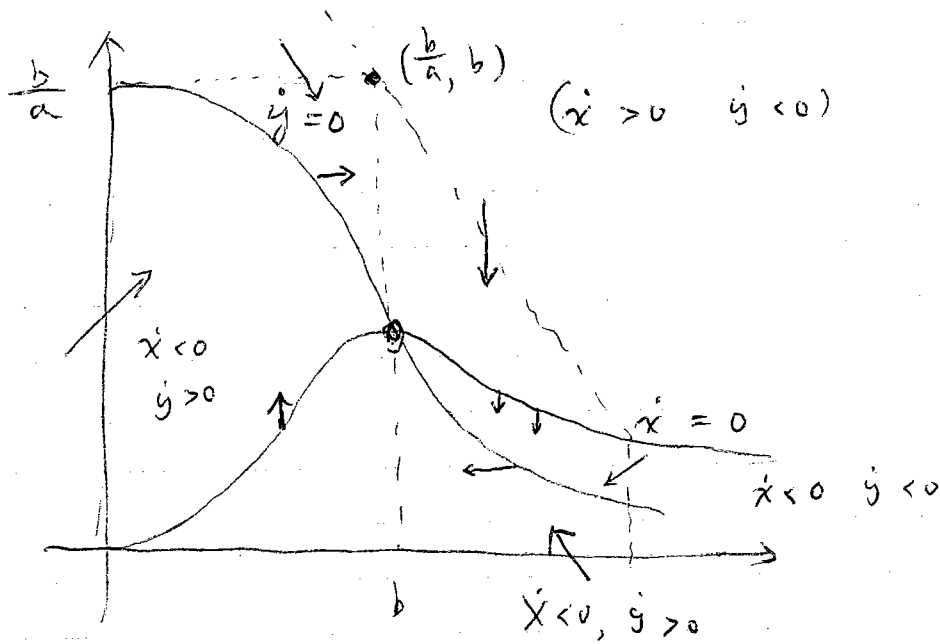
The existence of limit cycle

Poincaré - Bendixson Theorem (2 dim flow)



no fixed point inside
(only unstable fixed point)

Phase plane analysis of our system



only need to show that at
the diagonal line $|y| > x$

$$\text{or } -\dot{y} > \dot{x} \quad \dot{x} + \dot{y} < 0$$

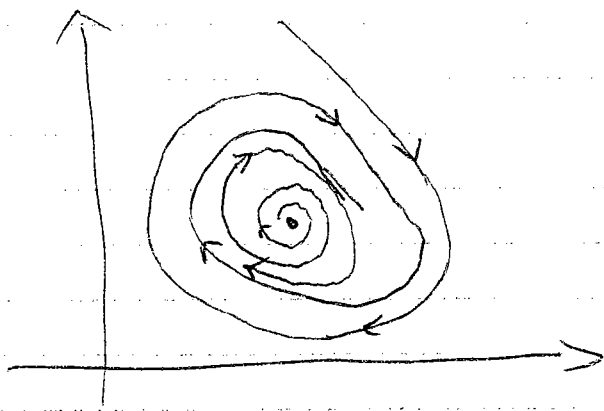
the line is given by

$$\left(y - \frac{b}{a}\right) = -(x - b)$$

from the equation of motion

$$\dot{x} + \dot{y} = b - x \quad \text{for } x > b \\ < 0$$

Ok, proved that when the only fixed point become unstable, we get stable limit cycle



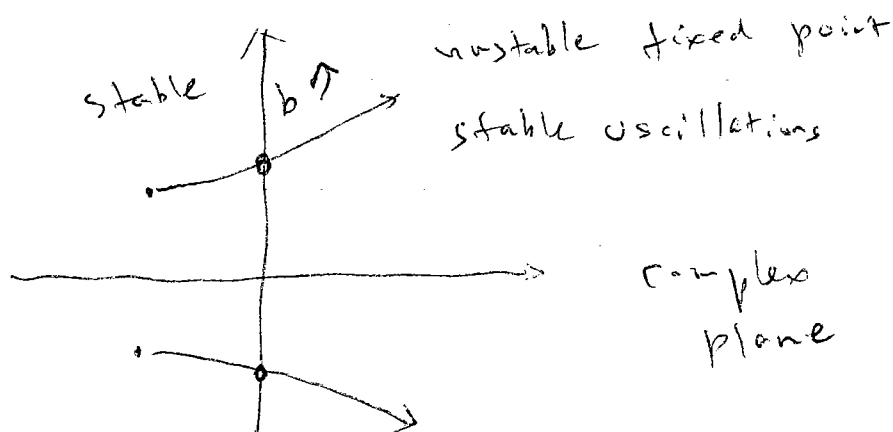
as b increase from $0 \rightarrow b_1$

stable fixed point \rightarrow stable limit cycle

△ independent of initial condition stable oscillating

△ Harmonic oscillator not limit cycle

in terms of the eigen values of
the Jacobian matrix



$$\lambda_{1,2} = \frac{\text{Tr} \pm \sqrt{\text{Tr}^2 - \Delta}}{2}$$

Hopf bifurcation

right at the bifurcation point

$$\lambda_{1,2} = \pm i\omega$$

$$\omega = \frac{\sqrt{\Delta}}{2} = \frac{\sqrt{a+b^2}}{2}$$

small amplitude oscillations
(much harder to establish, in general
as $b = b_c + \epsilon$, ϵ small
amplitude can be either small
or have a discontinuous jump
corresponding to super-critical
or sub-critical Hopf bifurcation
a fast way is to do numerical

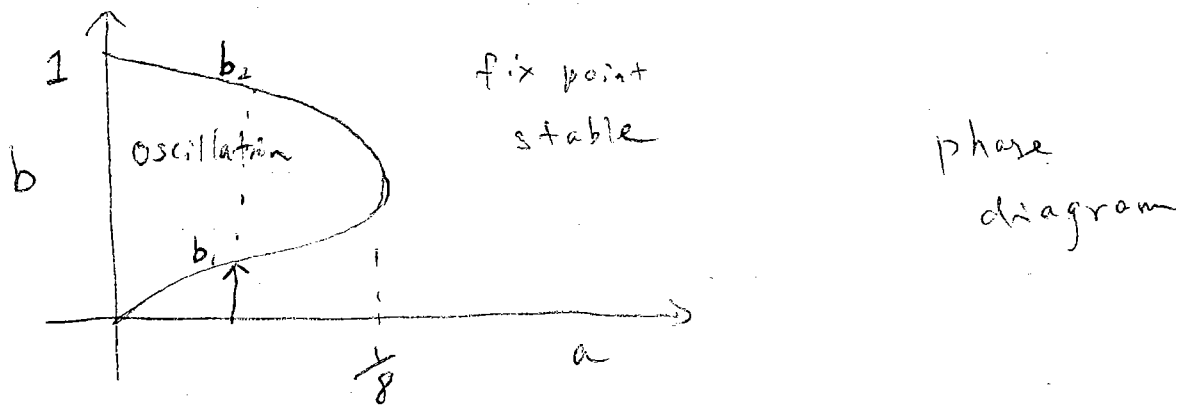
integration)

↳ Hopf bifurcation \rightarrow limit cycle
is a general scheme to get
sustained oscillation

↳ models for other oscillatory
behavior such as
Ca oscillation
mitotic oscillators
employ similar mechanism

↳ only non-linear, multi-component
system give rise to limit cycle
behavior

predictions of Selkov / Goldbeter-Lefever model.



recall $b = \frac{2}{\gamma^{3/2}} \sqrt{\frac{k_2 E_0 k_e}{k_m}}$

$$a = \frac{E_0 k_2'}{\gamma k_m}$$

ν : injection rate

1) for given a , use ν as control parameter.

there exists a window of injection rate where oscillation possible

ν too low or too high, no

oscillation experiment: [20, 60] mM/h

2) period of oscillation at onset of oscillation

$$\omega = \sqrt{a + b^2}$$

as injection rate increase

for $b_1 \rightarrow b_2$

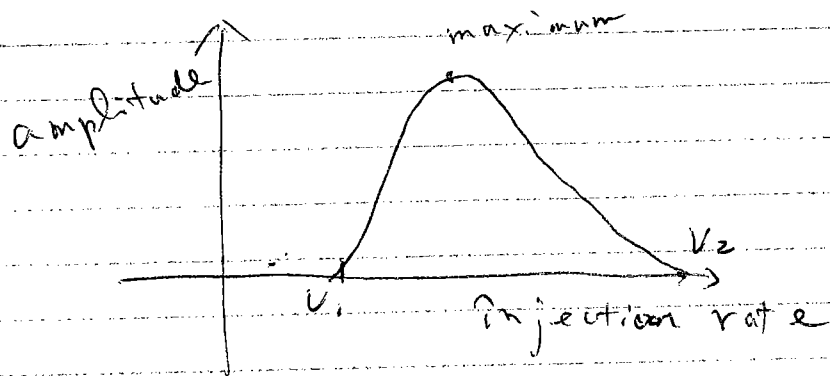
$$\omega : \sqrt{a+b_1^2} \rightarrow \sqrt{a+b_2^2}$$

ω increase with increasing injection rate

T : period decrease with increasing \downarrow
[10, 2] min

3) amplitude

both at b_1 and b_2 , amplitude are small



4) similar dependence of period and amplitude on enzyme activity

these all confirmed by experiments

biological intuition for oscillation

beginning \rightarrow low product P

gradual accumulation of P by E

enough P triggers $E \rightarrow E^*$

accelerated production of $P \rightarrow$ peak of P

[higher degradation of P
+ depleted $S \rightarrow$ decreasing P

lower $P \quad E^* \rightarrow E$

further decrease of $P \rightarrow$ beginning

Why a window of injection rate

1) \approx too low
 P never build up enough to
trigger $E \rightarrow E^*$

steady low product fixed point
catalyzed by E

2) \approx too high
never enough depletion of S
to cause P fall back

high P catalyzed by E^*
steady