Lecture 19 summary

3.4.4. Coherence resonance in Duffing – van der Pol oscillator

$$\ddot{x} - (\varepsilon + x^2 - x^4)\dot{x} + \omega_0^2 x + \beta x^3 = \sqrt{2\mathcal{D}}\, n(t), \quad \beta \geq 0$$

$\downarrow$ new variables $a(t)$ and $\varphi(t)$

assumption: slow variables – change slowly compared to the period of oscillation

averaged equations for amplitude and phase

$$\dot{a} = \left(\frac{\varepsilon}{2} + \frac{a^2}{8} - \frac{a^4}{16}\right) a + \frac{\mathcal{D}}{2a} + \sqrt{\mathcal{D}}\, n_1(t) \qquad \text{Langevin}$$

$$\dot{\varphi} = \frac{3\beta}{8} a^2 + \frac{\sqrt{\mathcal{D}}}{a} n_2(t)$$

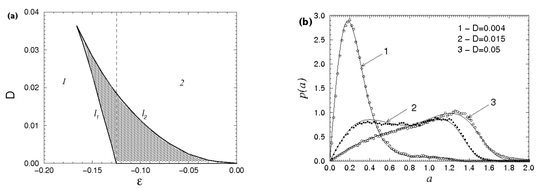
Consider equation for a separately $\to$

$\to$ 1D stochastic process with drift and diffusion

$$\frac{\partial}{\partial t} p(a,t) = -\frac{\partial}{\partial a}\left[\left(\frac{\varepsilon a}{2} + \frac{a^3}{8} - \frac{a^5}{16} + \frac{\mathcal{D}}{2a}\right) p(a,t)\right] + \frac{\mathcal{D}}{2}\frac{\partial^2 p(a,t)}{\partial a^2} \qquad \text{FPE}$$

Stationary solution of FPE

$$p(a) = N a \exp\left\{-\frac{1}{48\mathcal{D}} a^2 (a^4 - 3a^2 - 24\varepsilon)\right\}$$



$\varepsilon = -0.13$
($\mathcal{D} = 0$, stable focus)

– Stochastic bifurcations: qualitative change of stationary amplitude distribution for varying noise intensity
can be analyzed analytically

– For $\varepsilon = -0.13$ deterministic ($\mathcal{D} = 0$) system has only one attractor: stable focus. By adding noise we have stochastic P-bifurcations for varying noise intensity $\mathcal{D}$. The regime of bimodality occurs $\to$ analog of deterministic bistability.

- Power spectral density demonstrates minimal width for interm./optimal noise $\Rightarrow$ CR

- CR occurs after stochastic P-bifurcation (see line ℓ_1).

<u>Example of synthetic gene oscillator</u>

- subcritical HB $\rightarrow$ bistability ($\mathcal{D}=0$)
- $\mathcal{D} \neq 0$: stochastic bifurcations (P-bifurcations) and bimodality.

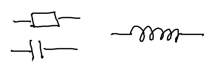
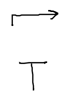
3.5 Stochastic bifurcations in genetic oscillators (cellular networks).

<u>Oscillating gene</u> is a gene that is expressed in periodic cycles (24 hours)

- plant leaves opening and closing at different times of the day
- sleep-wake schedule of animals

<u>Synthetic biology</u> – biology & eng.

- design & construct biol. systems, machines for various purposes
- artificial design and engineering of biol. systems and living organisms for purposes of improving appl. for industry or biol. research.

<u>electronic circuits</u>	<u>genetic circuits</u>
	promoter
	 terminator

Gene expression – inform. from a gene (genetic code stored in DNA) is transformed into functional gene product (protein or non-protein coding genes – RNA).

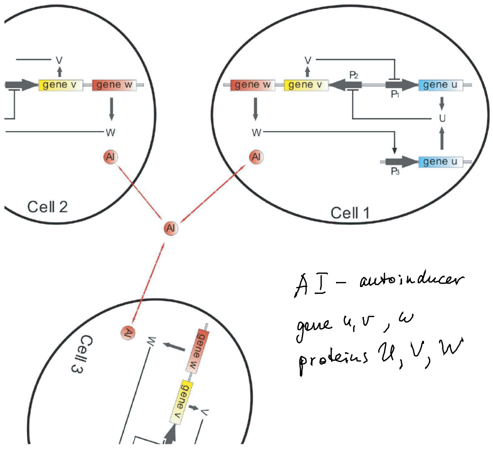
<u>Steps in gene expression</u> : transcription, RNA splicing, translation

<u>gene regulation</u>

$\swarrow$ gives a cell control over structure and function

$\searrow$ the basis of cellular differentiation, morphogenesis.

We consider a populations of (cells) synthetic gene relaxation oscillators coupled via intercellular signaling mechanism (quorum sensing mechanism).

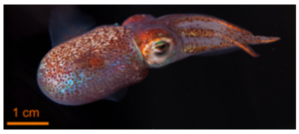


AI – autoinducer

gene u, v, w

proteins U, V, W

Example for quorum sensing mechanism



Hawaiian bobtail squid → (A. fischeri) a bioluminescent bacterium in the light producing organ: free living cells do not luminesce → only when they are highly concentrated and the AI (signaling molecules) is at high concentration.

synthetic gene relaxation oscillator

$$\frac{du_i}{dt} = \alpha_1 f(v_i) - u_i + \alpha_3 h(\omega_i)$$

$$\frac{dv_i}{dt} = \alpha_2 g(u_i) - v_i$$

$$\frac{d\omega_i}{dt} = \varepsilon(\alpha_4 g(u_i) - \omega_i) + 2d(\omega_e - \omega_i) + \sqrt{2\vartheta}\,\xi(t)$$

$$\frac{d\omega_e}{dt} = \frac{d_e}{N}\sum_{i=1}^{N}(\omega_i - \omega_e)$$

The genetic circuit contains a switch composed of two genes: u (lacI) and v (cI857), that inhibit each other by repressing transcription from their promoters P_1 and P_2.

(Promoter is a region of DNA that initiates transcription)

N – number of cells, i is the cell index;

Activity of promoters: P_1, P_2, P_3 is described by the Hill functions $f(v)$, $g(u)$, $h(\omega)$:

$$f(v) = \frac{1}{1+v^{\beta}}, \quad g(u) = \frac{1}{1+u^{\gamma}}, \quad h(\omega) = \frac{\omega^{\eta}}{1+\omega^{\eta}}$$

α_1 and α_2 define expression strength of the switch and α_3 represents the activation of u from promoter P_3. The expression of gene w is measured by the parameter α_4.

This circuit is known to demonstrate bistable behaviour.
The promoter P_2 also drives the expression of a third gene w (lux I) that produces AI → small molecule which is able to diffuse in and out the cell. The AI activates transcription of the promoter P_3. Placing a second copy of gene u under the control of this promoter provides both

an additional feedback loop to the switch

a mechanism that couples the switch to all cells in the population via quorum sensing.

AI

w_e extracellular concentration of AI

w_i intracellular concentration of AI

ε – time scale separation. Two time scales:
fast u, v and w_e and slow dynamics of w_i.
We fix $\varepsilon = 0.01$.

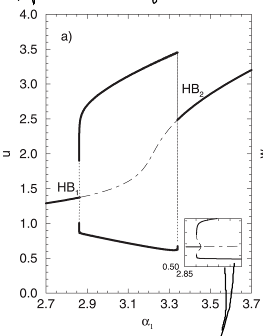
The dynamics of AI introduces additional feedback loop into the switch ⇒ oscillatory beh. even in isolated cells.
The coupling coefficients d and d_e depend on the diffusion of the AI through the cell membrane.

[Kuznetsov A. et al. (2004) SIAM Journal on Applied Math 65: 392–425]

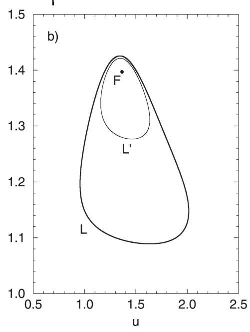
Single cell

α_1 – bifurcation parameter → strength of the expression for gene u.
$D = 0$ (no noise)

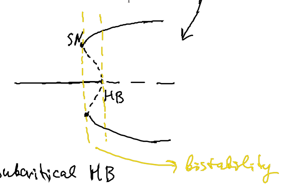
bifurcation diagram



phase space (u, w)



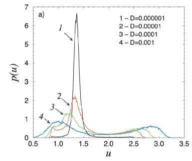
bistability:
stable focus F, unstable LC L' and stable LC L

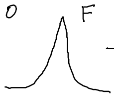


subcritical HB

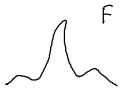
$p(u)$ – probability distribution

stochastic bifurcations $D \neq 0$



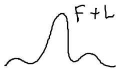


F $\longrightarrow$



F + L

Stochastic P-bifurcation



F + L $\longrightarrow$

L

stochastic P-bifurcation

bifurcation diagram