Lecture 19 summary

3.4.4. Coherence resonance in Duffing – van der Pol oscillator

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

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

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

averaged equations for amplitude and phase

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

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

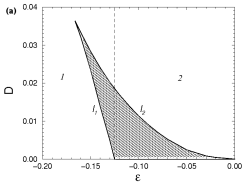
Consider equation for a separately →

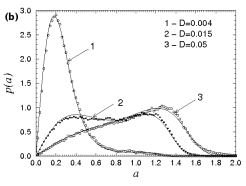
→ 1D stochastic process with drift and diffusion

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

Stationary solution of FPE

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





$\varepsilon = -0.13$

($D = 0$, stable focus)

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

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

- Power spectral density demonstrates minimal width for interm./optimal noise ➡ CR

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

Example of synthetic gene oscillator

- subcritical HB → bistability ($D = 0$)
- $D \neq 0$: stochastic bifurcations (P-bifurcations) and bimodality.

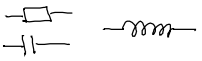
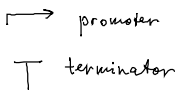
3.5 Stochastic bifurcations in genetic oscillators (cellular networks).

Oscillating gene 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

Synthetic biology – 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.

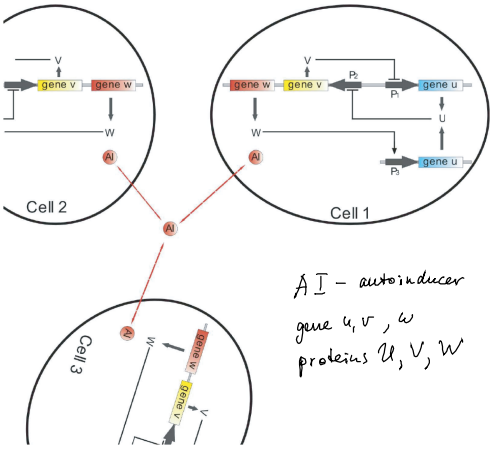
electronic circuits	genetic circuits
	 promoter, terminator

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

Steps in gene expression : transcription, RNA splicing, translation

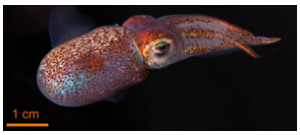
gene regulation
- ↙ gives a cell control over structure and function
- ↘ the basis of cellular differentiation, morphogenesis.

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.

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

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

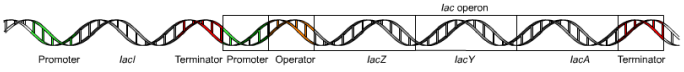
$$\frac{d\omega_i}{dt} = \varepsilon\left(\alpha_4 g(u_i) - \omega_i\right) + 2d\left(\omega_e - \omega_i\right) + \sqrt{2D}\,\xi(t)$$

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

synthetic gene relaxation oscillator

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 $f(v)$, $g(u)$, $h(\omega)$:

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

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.

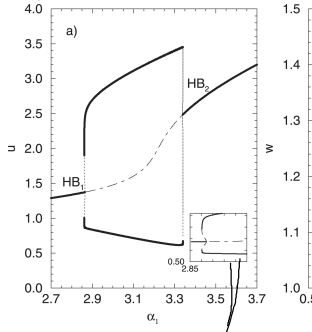
[Kuznetsov A. et al. (2004) SIAM Journal on Applied Math 65: 392–425]

Single cell

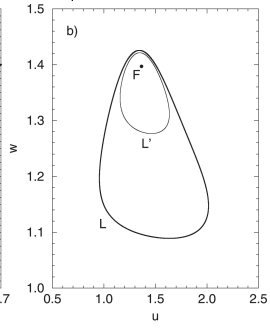
α_1 – bifurcation parameter → strength of the expression for gene u.

$D = 0$ (no noise)

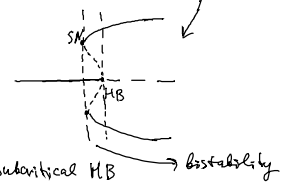
bifurcation diagram



phase space (u, w)



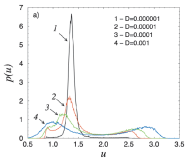
bistability: stable focus F, unstable LC L' and stable LC L

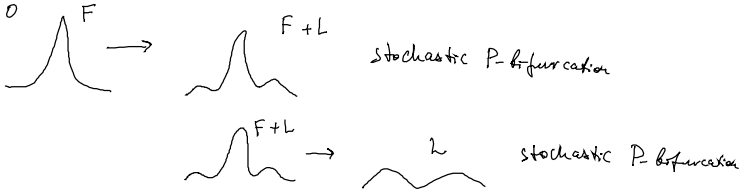


subcritical HB → bistability

p(u) – probability distribution

Stochastic bifurcations $\mathcal{D} \neq 0$





bifurcation diagram