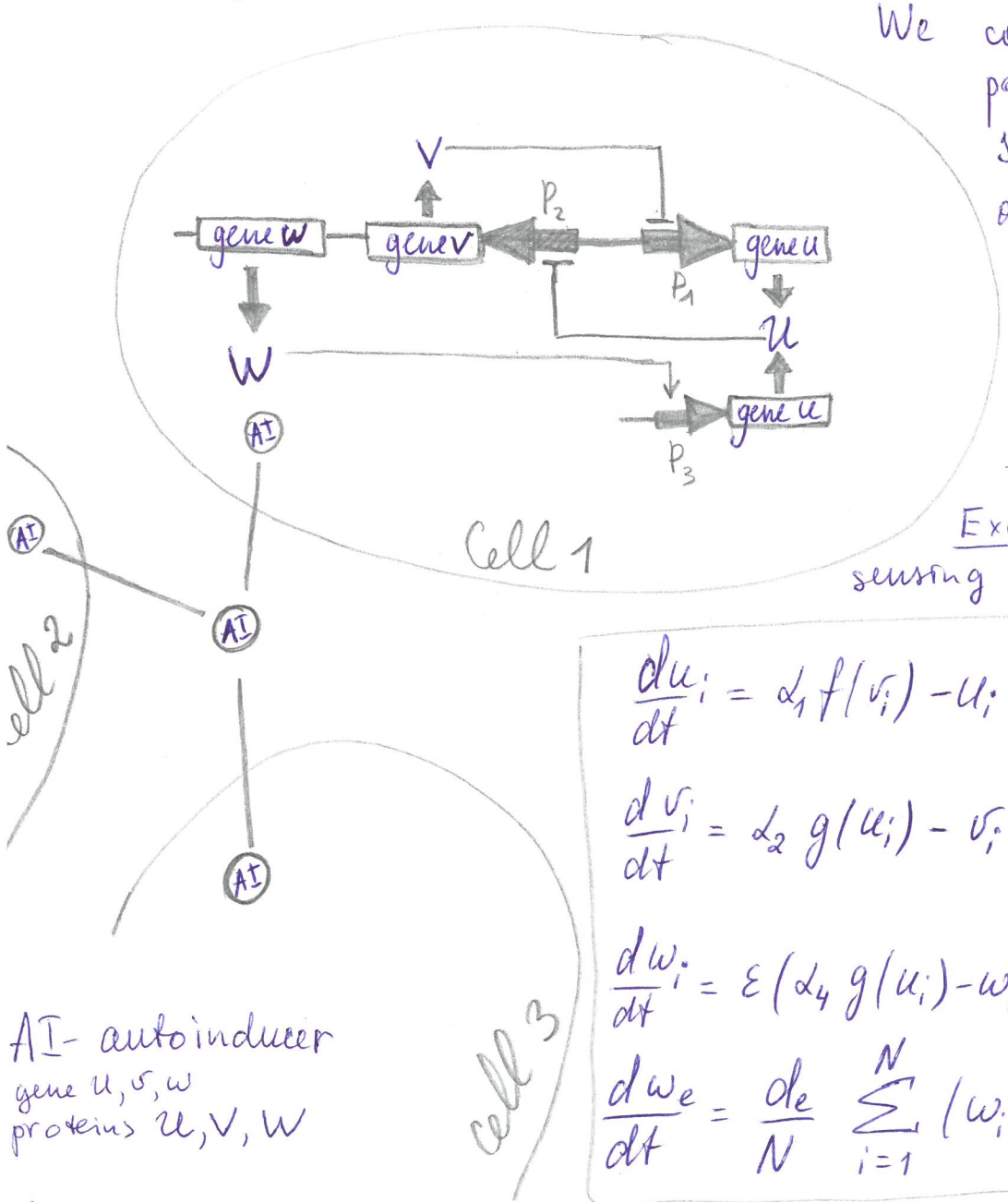
Lecture 12
18.01.2017

7. Coherence resonance

- 7.1 in excitable systems
  - Fitz Hugh-Nagumo system
  - SNIPER-model
- 7.3 in non-excitable systems
  - Stuart-Landau oscillator 7.3.1
  - Duffing-van der Pol oscillator
  - ...
- 7.2 - measures of coherence

7.4 Synthetic gene oscillator



AI - autoinducer
gene U, V, W
proteins U, V, W

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

Example for quorum sensing mechanism → Hawaiian

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

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

$$\frac{dw_i}{dt} = \varepsilon(\alpha_4 g(u_i) - w_i) + 2d(w_e - w_i) + \sqrt{2D}\,\xi_i(t)$$

$$\frac{dw_e}{dt} = \frac{d_e}{N}\sum_{i=1}^{N}(w_i - w_e)$$

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 biology - biology + engineering

- designing and constructing biological modules, biological systems, biological machines for various purposes.

- artificial design and engineering of biological systems and living organisms for purposes of improving applications for industry or biological research.

- genetic switch
- genetic oscillator

genetic circuits

- ⌐→ promoter
- T terminator

gene expression ← genetic code stored in DNA

information from a gene is transformed into (used in the synthesis) a functional gene product (proteins or non-protein coding genes - RNA)

steps in the gene expression: transcription, RNA splicing, translation.

gene regulation

- ↓ gives the cell control over structure and function
- ↘ the basis for cellular differentiation, morphogenesis and versatility and adaptivity of any organism.

Genes are expressed by being transcribed into RNA and this transcript may then be translated into protein.

The genetic circuit we consider 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 is the total number of cells, i is the cell index; the activity of the promoters P_1, P_2 and P_3 are described by the Hill functions $f(v)$, $g(u)$ and $h(w)$:

$$f(v) = \frac{1}{1+v^\beta}, \quad g(u) = \frac{1}{1+u^\beta}, \quad h(w) = \frac{w^2}{1+w^2}.$$

The parameters α_1 and α_2 define the expression strength of the toggle switch genes and α_3 represents the activation of u from promoter P_3. The expression of the 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 autoinducer molecule which is able to diffuse in and out of the cell. The AI activates transcription of the promoter P_3. Placing a second copy of the 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.

The autoinducer molecules can be, therefore, inside and outside the cell.

- w_e → extracellular concentration of AI
- w_i → intracellular concentration of AI

Parameter ε of the model is a time scale separation parameter: the dynamics of the cells is separated into two different time scales: fast dynamics of u, v and w_e and slow dynamics of w_i. We fix $\varepsilon = 0.01$.

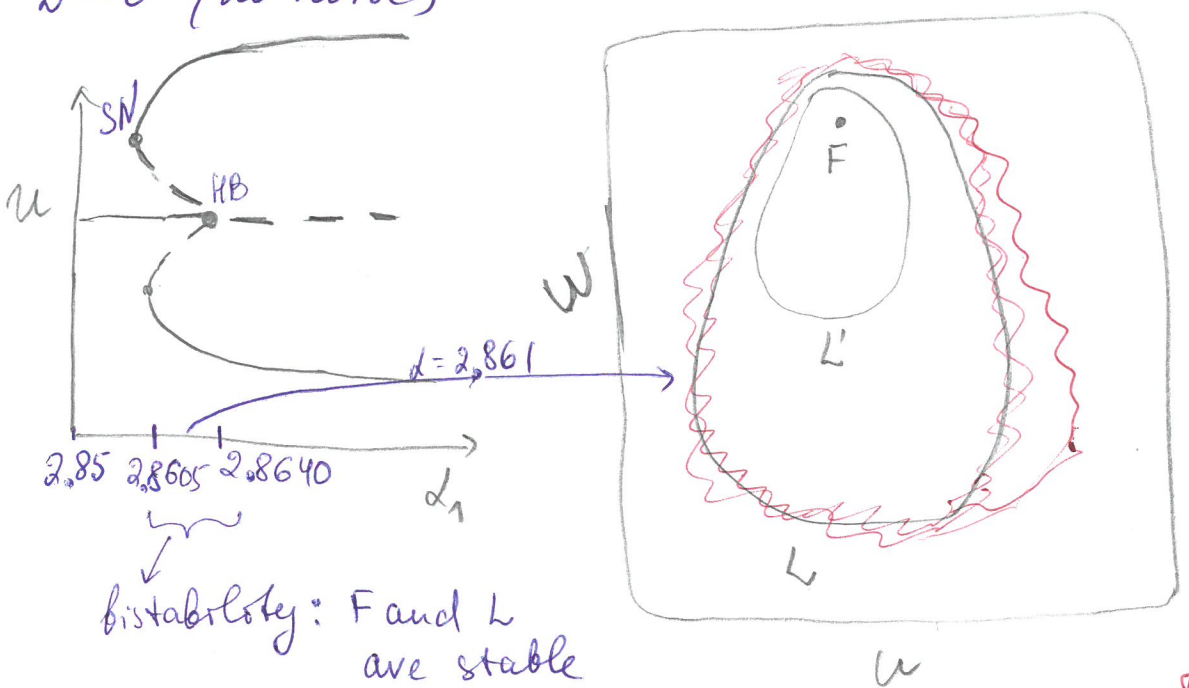
The dynamics of AI introduces an additional feedback loop into the switch and can lead to oscillatory behaviour even in isolated cells. The coupling coefficients d and d_e depend on the diffusion of the AI through the cell membrane.

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

Single cell

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

$D = 0$ (no noise)



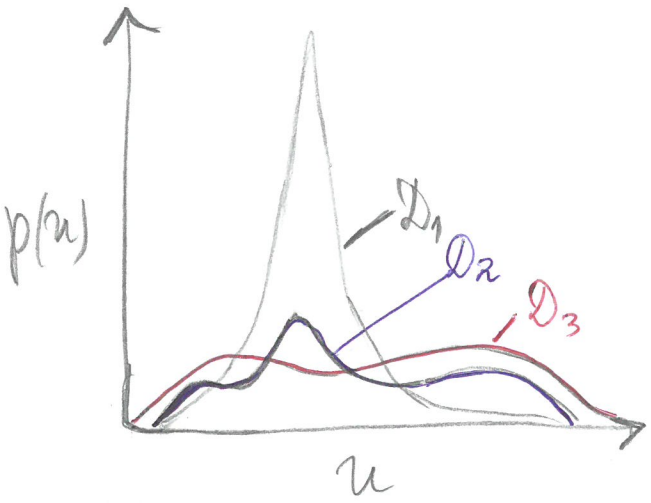
bistability: F and L are stable

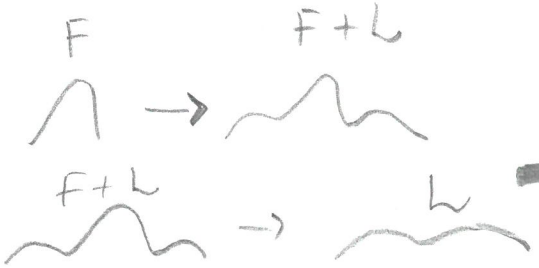
L' is unstable

$D \neq 0$

$\alpha = 2.85$

even for $\alpha_1 = 2.85$ for which in the deterministic case there exist only one attractor, the stable focus F, the system performs an oscillatory behaviour → similar to the motions on the limit cycle.





Here we consider the distributions of the phase variables (not the amplitude).

Coherence resonance is observed → for an intermediate noise intensity the width of the spectrum becomes minimal.

What does CR mean for the cell?

There is an optimal value of noise (stochastic influence) for which the genetic unit displays most ordered dynamical behaviour → noise is profitable for the cell.

Genetic networks in the presence of noise
($N=2$; $N=500$)

For coupled cells one can also detect stochastic P-bifurcations.

Due to the stochastic influence the expression of proteins can be confined in several different concentration intervals, some of which are more probable than the others depending on how strong is the noise in the system.

The cells are initially identical and produce protein with one concentration (one main peak → (stable focus) for $\delta = 0$).

The occurrence of new intervals of protein production means that cells function differently →

different protein concentrations in identical cells mean different cellular functionality.

Under stochastic influence the protein production is defined by the probability distribution of the phase variable which represents one of the genes.

changing stochastic conditions → different prob. distributions

↙

the probability of expressing certain protein concentration is different

↙

different cell functionality

↙

differentiation of the cells into various types.