

Lecture 20 summary

3.5 Stochastic bifurcations in genetic oscillators

Synthetic Biology - artificial design and engineering of biological systems and living organisms

genetic circuits

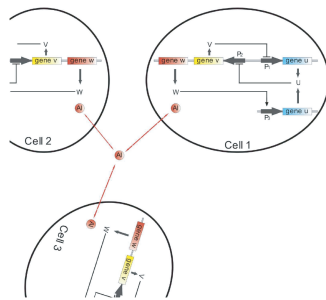
→ promoter
T terminator

gene expression

information from a gene →
functional gene product (e.g. protein)

quorum sensing mechanism: coupling via intercellular signaling mechanism

Population of synthetic gene relaxation oscillators



N cells; genes: u, v, w

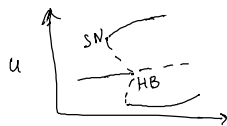
α_1 - expression strength for gene u

AI - autoinducer

↓ ↓
 w_i w_e

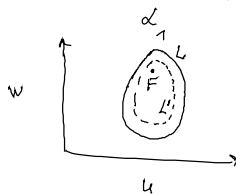
Dynamics of AI introduces additional feedback loop into the switch $\Rightarrow$
oscillatory beh. even in isolated cells.

$N=1, D=0$: one cell and no noise



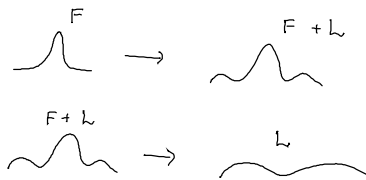
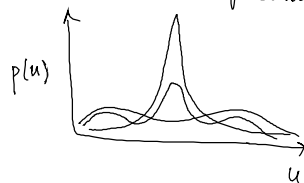
subcritical HB:

between HB and SN there is bistability (stable focus and stable LC)



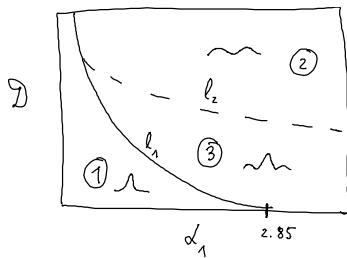
$N=1, D \neq 0$: one cell + noise

Stochastic P-bifurcations



Here we consider distributions of phase variable (not the amplitude) $\Rightarrow$
 $\Rightarrow$ instead of bimodal distribution we obtain a 3-peak distribution.

Stochastic bifurcation diagram

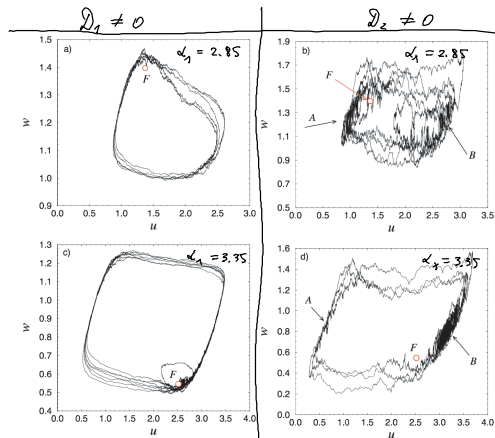


for $\alpha_1 = 2.85$

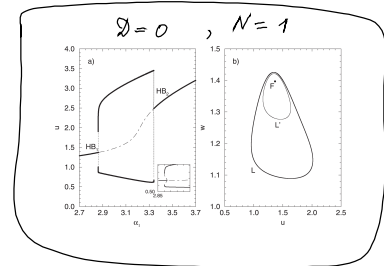
$\mathcal{D}=0$ only stable focus is present (below SN)

What happens in the phase space?

$\alpha_1 = 2.85, \mathcal{D} \neq 0$; $\alpha_1 = 3.35, \mathcal{D} \neq 0$



$\mathcal{D}_2 > \mathcal{D}_1$



Even for parameter values corresp. to stable deterministic focus F we observe oscillatory dynamics induced by noise $\rightarrow$ dynamic is similar to excitable system
Large noise intensity $\mathcal{D}_2$: two regions A and B where the stochastic trajectory spends dominant part of the time.

Why? Slow w ; (we have no w_2 for a single cell) and fast u .

What are these two regions A and B ?

They corr. to minimal (A) and maximal (B) concentration of protein u .

Synthetic gene oscillator demonstrates CR!

For interm./optimal noise intensity the width of the spectrum becomes min.

What does this mean for a cell?

There is optimal value of noise (stochastic influence)
for which a genetic unit displays most ordered dynamics.

$\Downarrow$

Noise that is inherently present in biol. systems
is profitable for the cell.

Cellular fate controlled by external signal

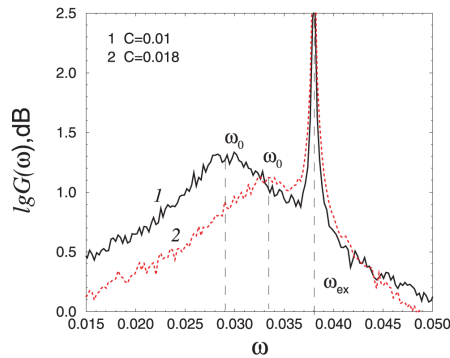
$N = 1, \mathcal{D} \neq 0$

$$\frac{du_i}{dt} = d_1 f(v_i) - u_i + d_3 h(w_i) + C \cos(\omega_{ex} t)$$

C - amplitude of the external periodic force

ω_{ex} - frequency —//—

The expression of a particular protein of interest is in general determined by environmental signals or (co)regulating networks in the cellular organism.



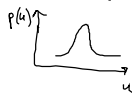
Weak noise, $d_1 = 2.85$

1: small amplitude of external force
 $\Rightarrow$ 2 frequencies (ω_0 and ω_{ex})

2: larger amplitude of external force $\rightarrow \omega_0$ shifts towards the frequency of external force

Conclusions: external factors influence strongly the expression of a particular gene

noise: the intervals of expression are modified by noise



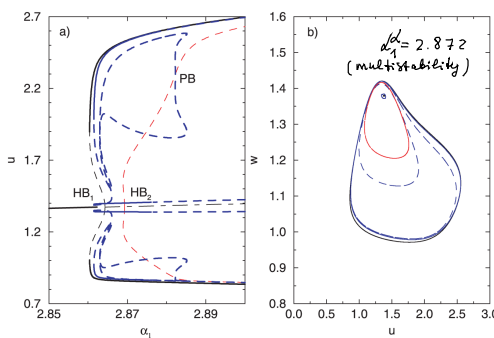
periodic signal: the frequency of protein expression can be regulated by deterministic periodic signal.

Genetic networks in the presence of noise

$N=2$, $N=500$

$\delta=0$, $N=2$: two coupled genetic oscillators

Bifurcation diagram

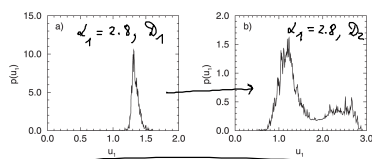


high multistability,
 two HB close to each other, pitchfork bifurcation (PB).

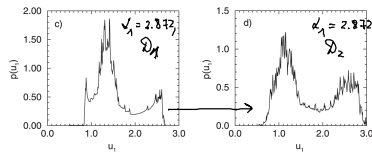
$d_1 = 2.872$: two stable attractors

$\downarrow$
 - in-phase oscillations
 - asymmetric oscillations (small and large amplitude oscillations)

Stochastic bifurcations for two coupled genetic oscillators



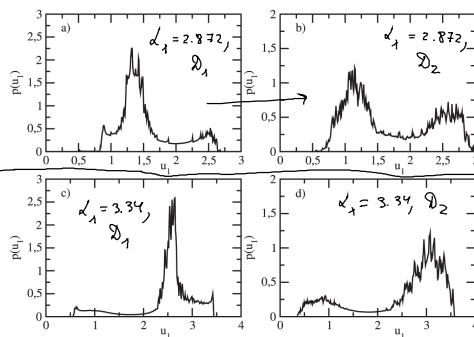
$D_2 > D_1$
for $D=0$ only focus is stable



for $D=0$ multistability

Conclusion for $N=2$: more complex deterministic bif. diagram;
in the presence of noise $\rightarrow$ stochastic P-bifurcations

Stoch. bifurcations for $N=500$ coupled units



$D_2 > D_1$

$D_2 > D_1$

Conclusion for $N=500$ coupled genetic units: the same type of
stochastic P-bifurcations as for $N=1$ $N=2$.

Zakharova, Kurths, Vadivasova, Koseska "Analysing dynamical
behav. of cellular networks via stoch. bifurcations"
PLOS ONE 6(5) 2011.