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

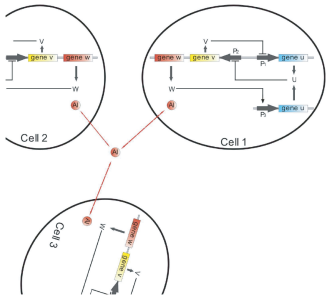
⊤ terminator

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

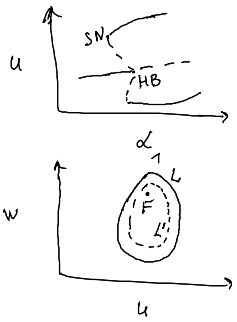
α_1 – expression strength for gene u

AI – autoinducer

w_i w_e

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

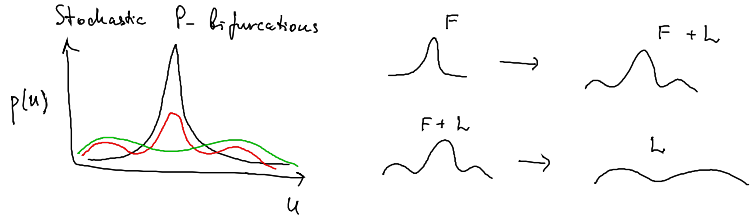
$N=1$, $D=0$: one cell and no noise



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

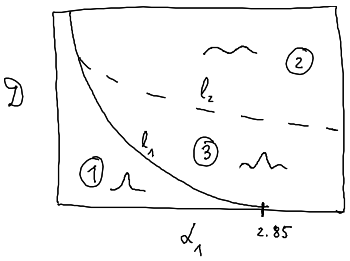
$N=1$, $D\neq 0$: one cell + noise

Stochastic P- bifurcations



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

Stochastic Bifurcation diagram

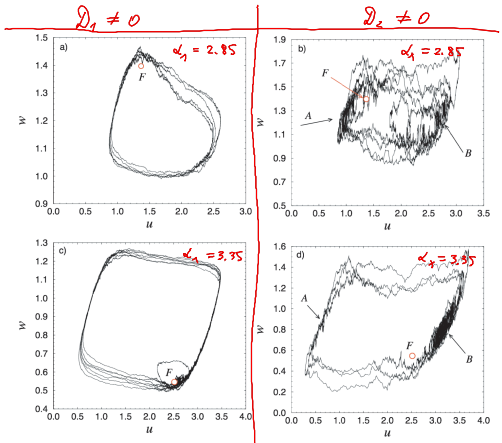


for $\alpha_1 = 2.85$

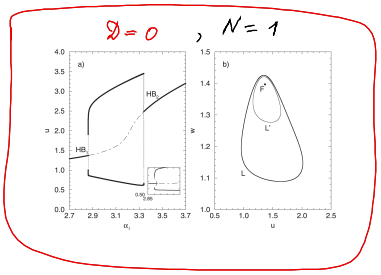
$D = 0$ only stable focus is present (below SN)

What happens in the phase space ?

$\alpha_1 = 2.85$, $D \neq 0$; $\alpha_1 = 3.35$, $D \neq 0$



$D_2 > D_1$



Even for parameter values corresp. to stable deterministic focus F we observe oscillatory dynamics induced by noise → dynamic is similar to excitable system

Large noise intensity D_2: two regions A and B where the stochastic trajectory spends dominant part of the time.

Why? Slow W_i (we have no W_e 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.

⇓

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

Cellular fate controlled by external signal

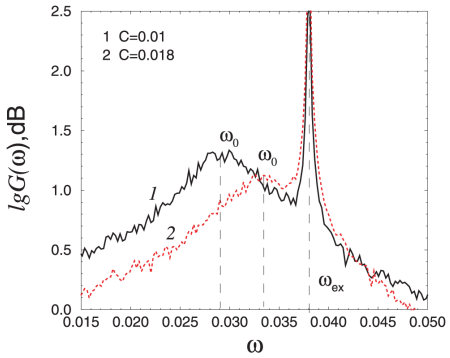
$N = 1$, $D \neq 0$

$$\frac{du_i}{dt} = \alpha_1 f(v_i) - u_i + \alpha_3 h(w_i) + C\cos(\omega_{ex} t)$$

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, $\alpha_1 = 2.85$

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

2: larger amplitude of external force → ω_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

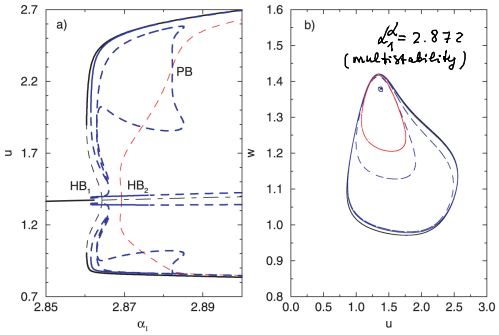
periodic signal: the frequency of protein expression can be regulated by deterministic periodic signal.

Genetic networks in the presence of noise

$N = 2$, $N = 500$

$D = 0$, $N = 2$: two coupled genetic oscillators

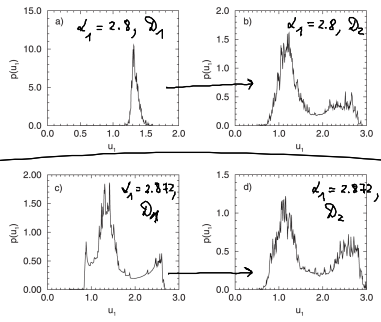
Bifurcation diagram



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

$\alpha_1 = 2.872$: two stable attractors
↓
- in-phase oscillations
- asymmetric oscillations (small and large amplitude oscillations)

Stochastic bifurcations for two coupled genetic oscillators



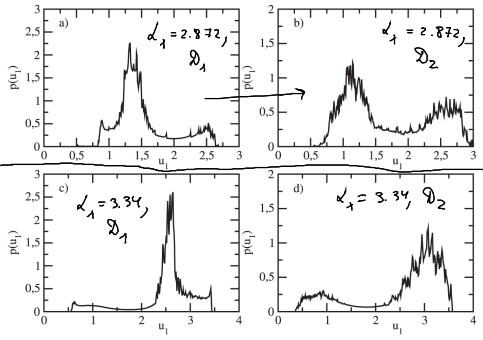
$D_2 > D_1$

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 → 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.