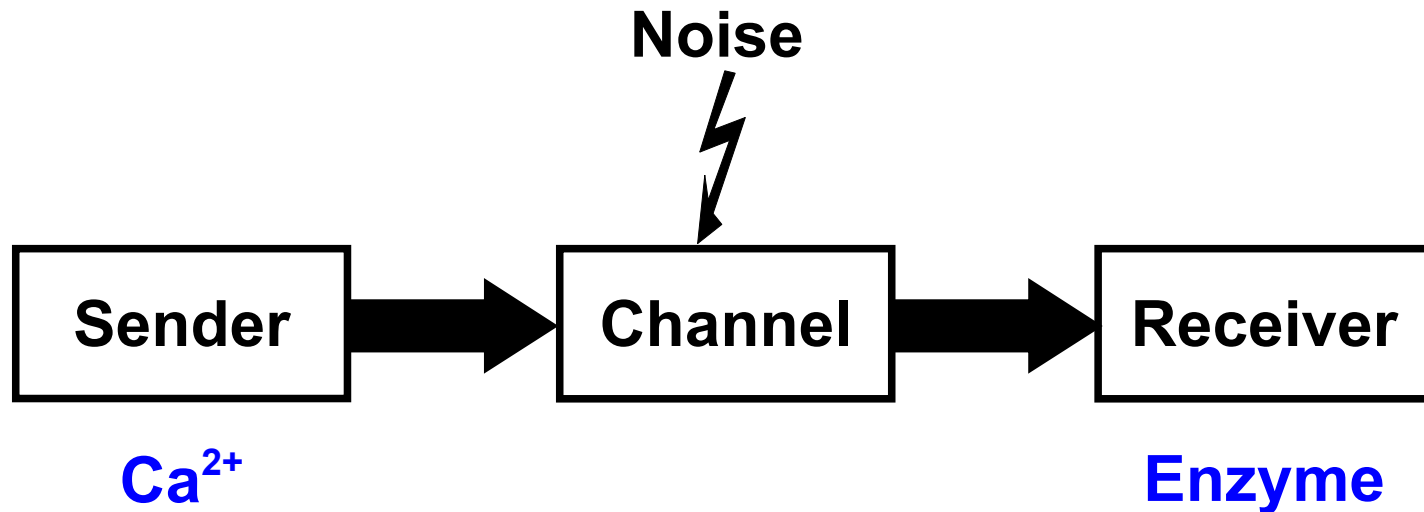


Seminar
Information processing
in living systems

Dr. Jürgen Pahle
UdS, Saarbrücken
27.4.2012

Information theory

- Claude E. Shannon (1916-2001)
“Mathematical Theory of Communication” (1948)
- Information theory can answer questions about limits of faithful information transfer over a given (noisy) channel etc.

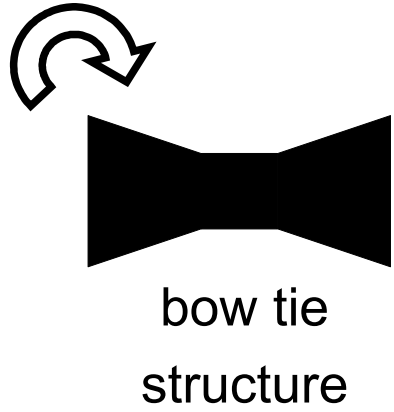
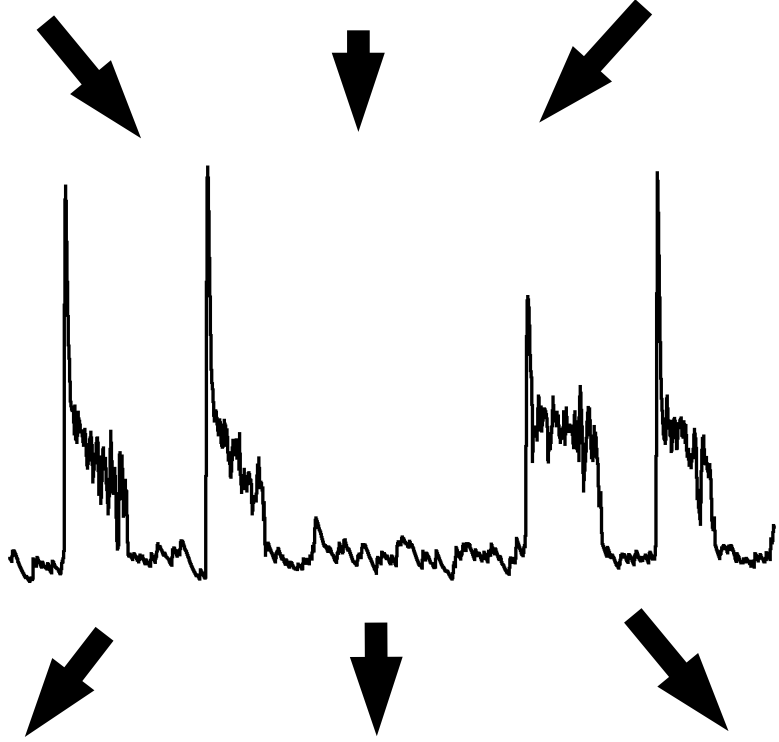


Signal transduction via Calcium

Hormones (angiotensin II, vasopressin etc.)

Nucleotides (ATP, UTP)

Ca²⁺-signal



calcium code?

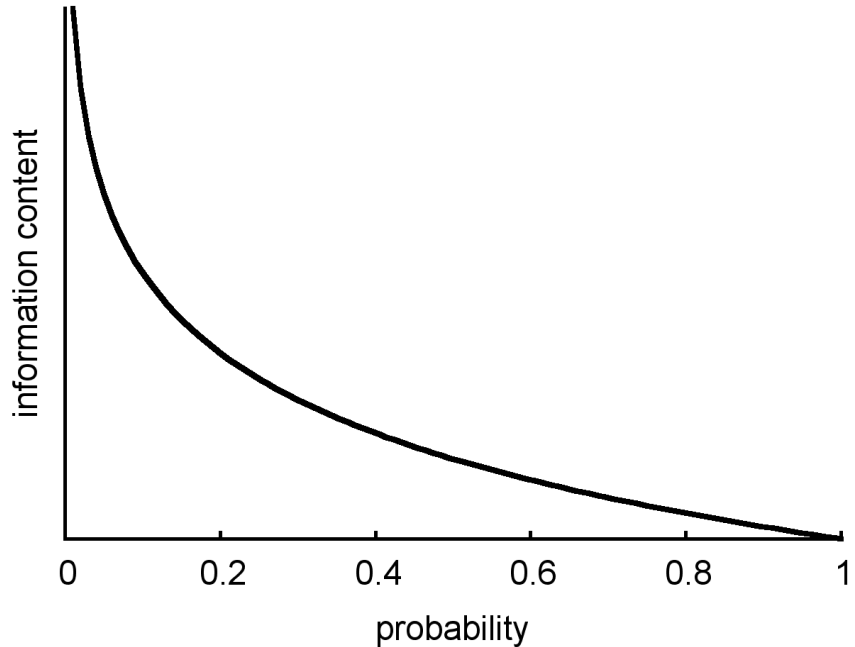
Target proteins (calmodulin, phosphorylase b kinase, etc.)

Transcription factors (NF-κB, etc.)

How to quantify information?

Information content of
an event

→ **uncertainty**
(negative log of probability)

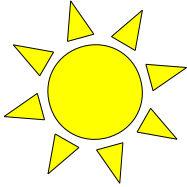


Average uncertainty of all possible events

→ so-called **entropy**

Information = decrease in uncertainty

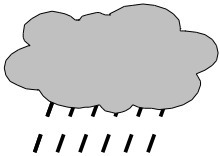
Weather example



50%

Probability(sunny) = $\frac{1}{2}$

→ Uncertainty(sunny) = 1.0



50%

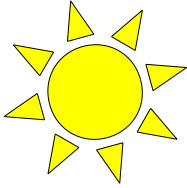
Probability(rainy) = $\frac{1}{2}$

→ Uncertainty(rainy) = 1.0

On average (entropy of the weather)

→ 1.0 [bit/day]

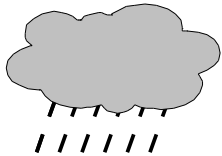
Weather example



100%

Probability(sunny) = 1.0

→ Uncertainty(sunny) = 0.0



0%

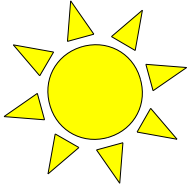
Probability(rainy) = 0

→ Uncertainty(rainy) = 0.0 per convention

On average (entropy of the weather)

→ 0.0 [bit/day]

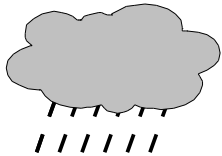
Weather example



80%

Probability(sunny) = 0.8

→ Uncertainty(sunny) = 0.32



20%

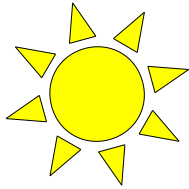
Probability(rainy) = 0.2

→ Uncertainty(rainy) = 2.32

On average (entropy of the weather)

→ 0.64 [bit/day]

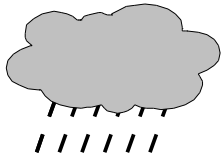
Weather example (London)



220/365

Probability(sunny) = 0.603

→ Uncertainty(sunny) = 0.73



145/365

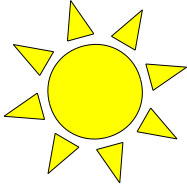
Probability(rainy) = 0.397

→ Uncertainty(rainy) = 1.33

On average (entropy of the weather in London)

→ 0.97 [bit/day]

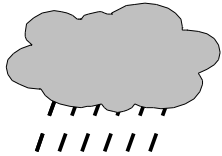
Weather example



$p\%$

Probability(sunny) = p

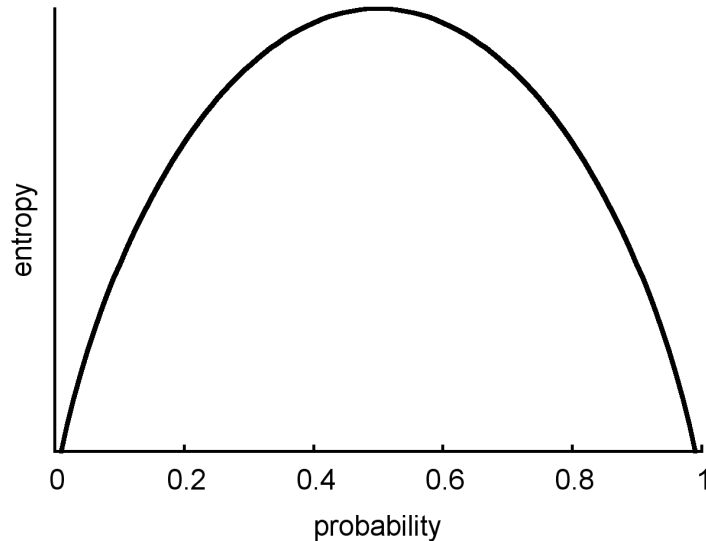
→ **Uncertainty(sunny) = $-\log_2(p)$**



$(1-p)\%$

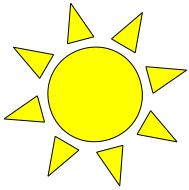
Probability(rainy) = $1-p$

→ **Uncertainty(rainy) = $-\log_2(1-p)$**



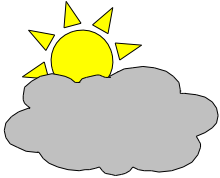
On average (entropy of the weather) [bit/day]

Weather example



Probability(sunny) = 0.25

→ **Uncertainty(sunny) = 2.0**



Probability(cloudy) = 0.25

→ **Uncertainty(cloudy) = 2.0**



Probability(rainy) = 0.25

→ **Uncertainty(rainy) = 2.0**



Probability(thunderstorm) = 0.25

→ **Uncertainty(thunderstorm) = 2.0**

On average (entropy of the weather)

→ **2.0** [bit/day]

Entropy and Mutual information

$$H(X) = - \sum_x p(x) \log p(x)$$

Entropy

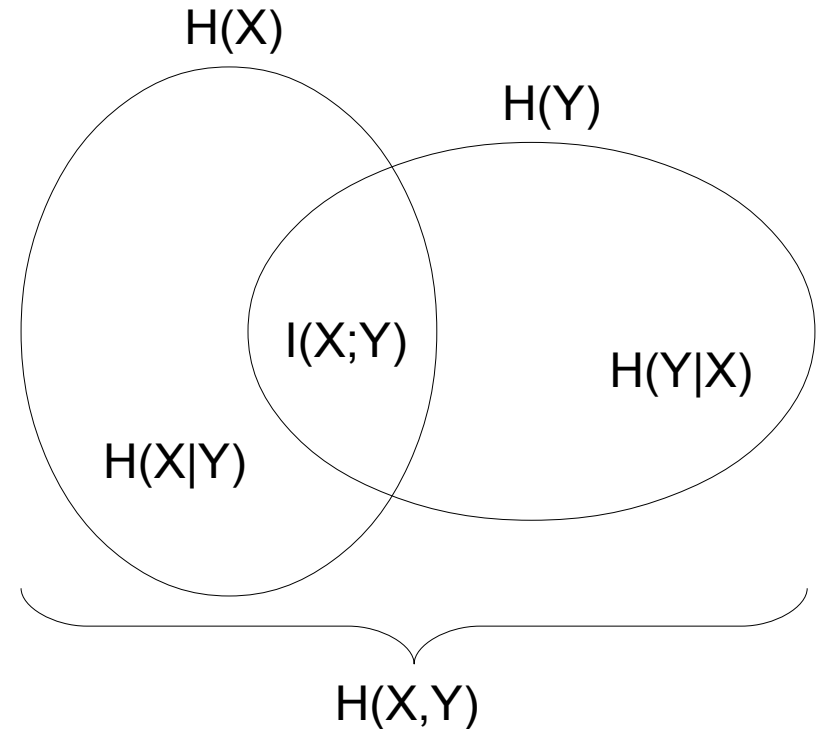
$$D(p||q) = \sum_x p(x) \log \frac{p(x)}{q(x)}$$

Relative Entropy /
Kullback-Leibler Divergence

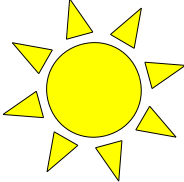

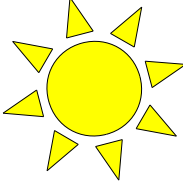
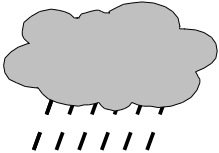
$$I(X; Y) = \sum_{x,y} p(x,y) \log \frac{p(x,y)}{p(x)p(y)}$$

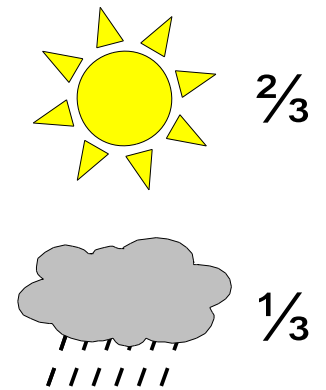
Mutual
Information

"Reduction of uncertainty about X
due to the knowledge of Y"



Weather dynamics

		
	0.75	0.25
	0.5	0.5



Markov process

- **Markov process** can not remember former states, only current state determines future
- *Markovian* modeling is used in a variety of fields:
 - Communication:
Telephone system (Hidden Markov models)
 - Hard disks
 - Language recognition
 - PageRank algorithm of Google
 - Biological modeling: Population dynamics, etc.
 - Games of chance (chutes and ladders)



Information/Entropy-rate

The information gained by observing tomorrow's weather, when the today's weather is known:

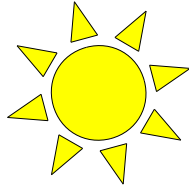
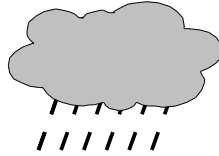
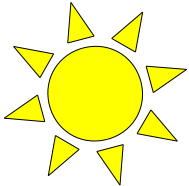
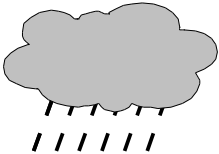
Entropy(tomorrow's weather | today's weather)
→ conditional probabilities

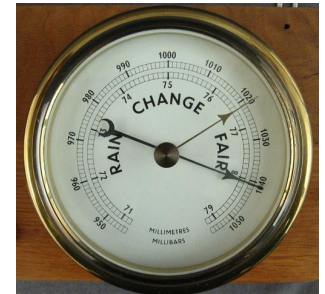
In our example:

Entropy(tomorrow's weather) = 0.92 [bit/day]

Entropy(tomorrow's weather | today's weather) = 0.87
[bit/day]

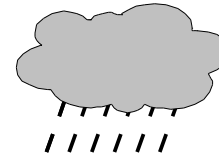
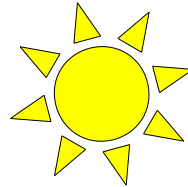
Weather dynamics

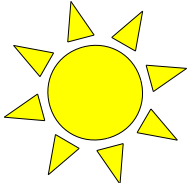
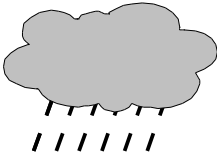
			
	high	0.9	0.1
	low	0.6	0.4
	high	1	0
	low	0	1

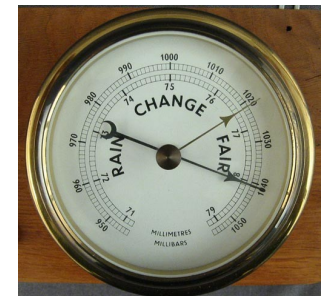


Weather dynamics (London)

1.3.2010, 12:00:
1012 hPa → slightly low



	high	0.9	0.1
	low	0.6	0.4
	high	1	0
	low	0	1



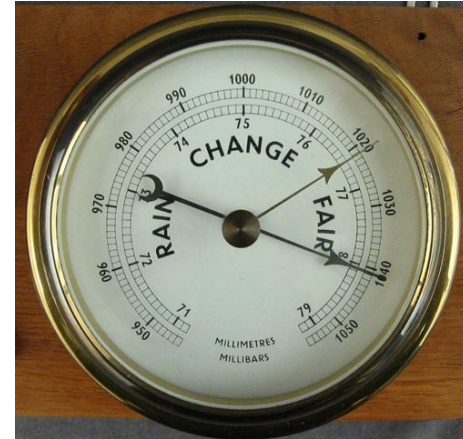
Information provided by the barometer

Information =

Uncertainty (without barometer)

minus

Uncertainty (with barometer)



Assumption Probability(high) = Probability(low) = 0.5

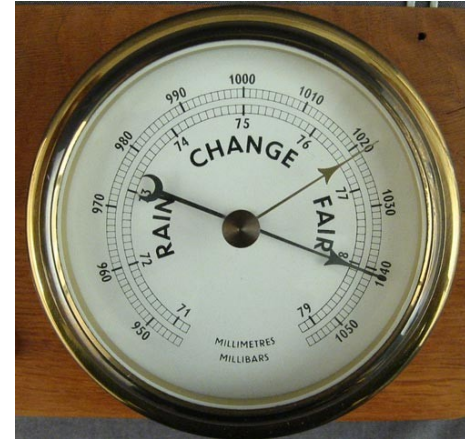
Information provided by the barometer

Information =

Uncertainty (without barometer)

minus

Uncertainty (with barometer)



Assumption Probability(high) = Probability(low) = 0.5

Information = 0.39 [bit/day]

Transfer Entropy

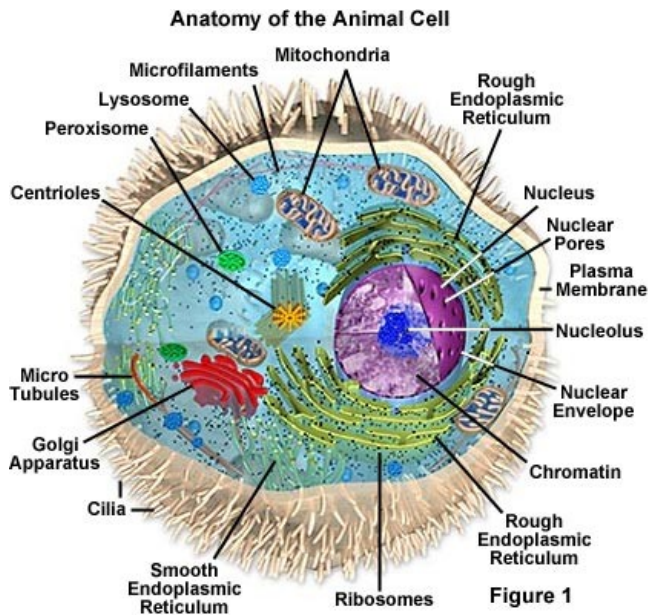
Quantifies the information transferred by calculating how much uncertainty is lost (or information gained) about a dynamic stochastic process, when the value of the driving signal is known

Kullback-Leibler-form

T. Schreiber (2000), Phys. Rev., 85(2), 461-4

$$T_{J \rightarrow I} = \sum p(i_{n+1}, i_n^{(k)}, j_n^{(l)}) \log \left(\frac{p(i_{n+1} | i_n^{(k)}, j_n^{(l)})}{p(i_{n+1} | i_n^{(k)})} \right)$$

How-To (Biochemical modeling)



- Compartments (nucleus, cytosol, ...)
- Species (proteins, small molec., ions,...)
- Reactions (decay, ...)
- Kinetics (velocity of reactions)

$$\begin{aligned} \frac{dG_\alpha}{dt} &= k_1 + k_2 \cdot G_\alpha - \frac{k_3 \cdot PLC \cdot G_\alpha}{(K_4 + G_\alpha)} - \frac{k_5 \cdot [Ca^{2+}] \cdot G_\alpha}{(K_6 + G_\alpha)} & G_\alpha(t_0) &= 0.01 \text{ nmol} \\ \frac{dPLC}{dt} &= k_7 \cdot G_\alpha - \frac{k_8 \cdot PLC}{(K_9 + PLC)} & PLC(t_0) &= 0.01 \text{ nmol} \\ \frac{d[Ca^{2+}]}{dt} &= k_{10} \cdot G_\alpha - \frac{k_{11} \cdot [Ca^{2+}]}{(K_{12} + [Ca^{2+}])} & [Ca^{2+}](t_0) &= 0.01 \text{ nmol} \end{aligned}$$

Simulation:

- How does the system change over time?

Analysis of the model:

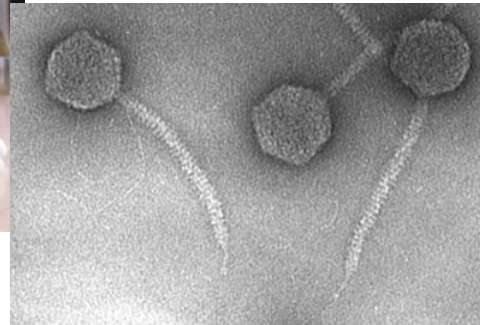
- Which parts influence the behavior most?
- Which states are stable (steady state, oscillations)?

Reasons for stochastic modeling

- Small particle numbers on single cell level (e.g. signal transduction, gene expression)
→ discreteness of the system, random fluctuations
- Bi-stable systems:



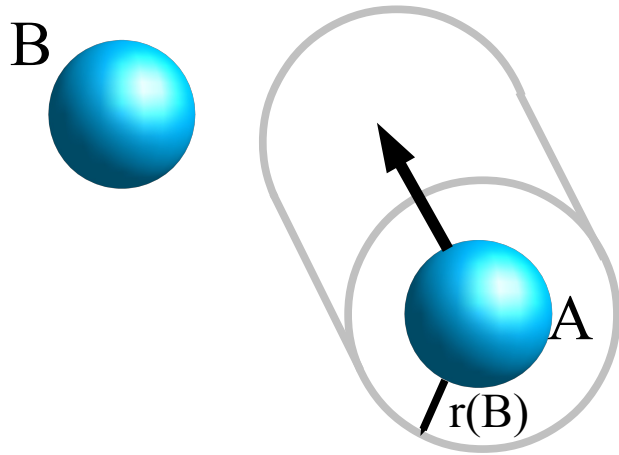
Calico cat



λ phage

- Stochasticity as an important property of the system:
noise-sustained oscillations, stochastic resonance, etc.
- Extinction of species
- Rare events

Basis of the Stochastic Approaches



$$a_{\mu}(x) \cdot dt = c_{\mu} \cdot h_{\mu}(x) \cdot dt$$

specific probabilistic **reaction rate**
product of

probability of collision
(~ average relative speed * collision
cross-section area / volume) and

probability of reaction after collision
(collision energy larger than threshold)

number of different
combinations of
substrate particles

Chemical Master Equation (CME)

$$\frac{\partial P(x, t | x_0, t_0)}{\partial t} = \sum_{j=1}^M [a_j(x - v_j) * P(x - v_j, t | x_0, t_0) - a_j(x) * P(x, t | x_0, t_0)]$$

“probability flux”
to x from other states

“probability flux”
from x to other states

- v_j is stoichiometric vector of reaction j
- More important for the simulation methods is the so-called **Reaction Probability Density Function**
 - When will the next reaction take place?
 - Which reaction will it be?

$$P(\tau, \mu) = \begin{cases} a_\mu \exp(-a_0 \tau) & \text{if } 0 \leq \tau < \infty \wedge \mu = 1, \dots, M \\ 0 & \text{otherwise} \end{cases}$$

Stochastic Simulation (Gillespie 1976)

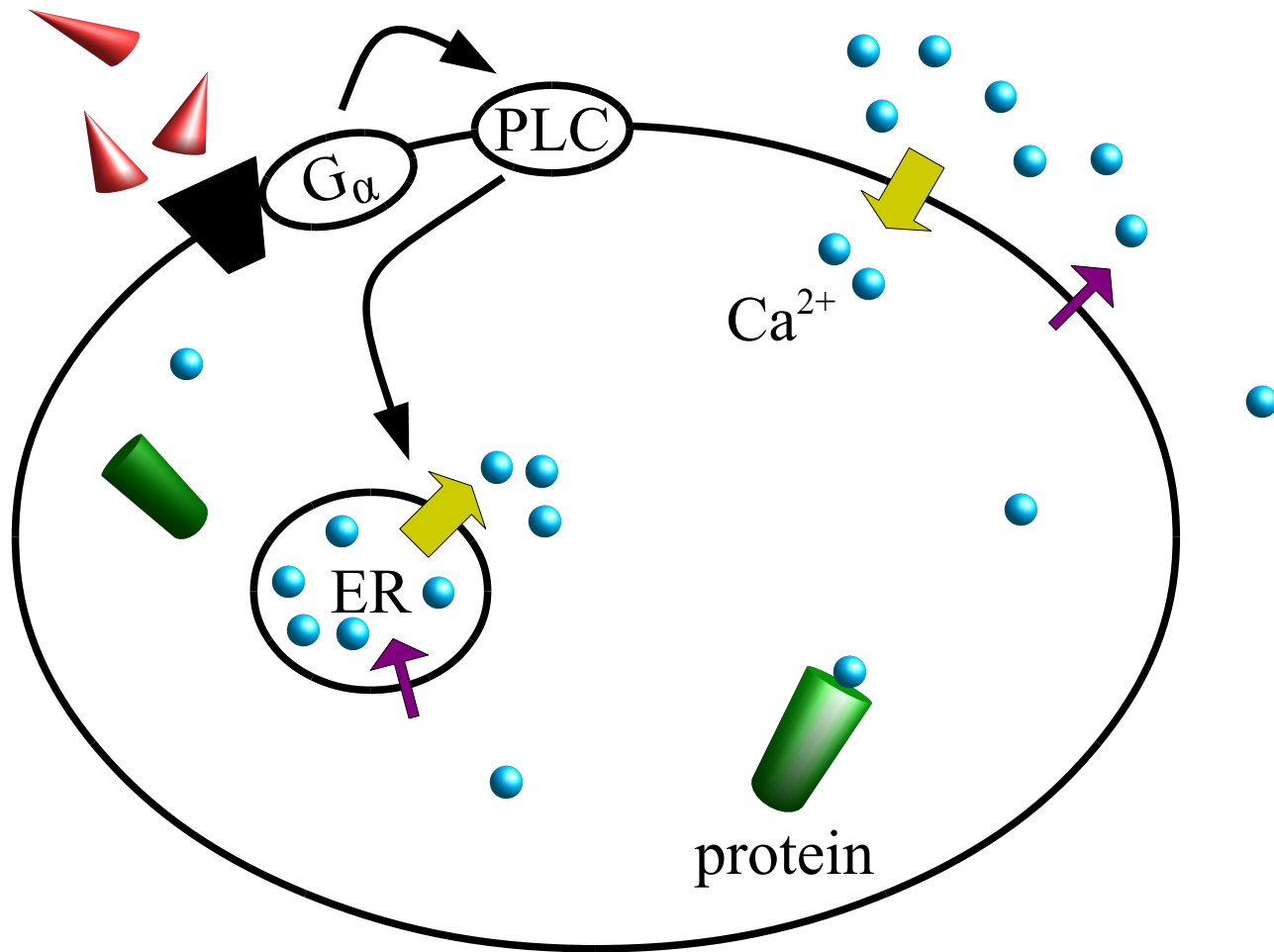
- 1) Calculate probabilities for all reactions
- 2) Calculate stochastic time step t (exponentially distributed, sum of all reaction prob.) $t = \frac{1}{a_0} \ln(r_1)$
- 3) Monte Carlo Simulation: The reaction to be realized is chosen by “playing roulette”, discrete distribution

$$\sum_{\alpha=1}^{\mu-1} \frac{a_{\alpha}}{a_0} \leq r_2 \leq \sum_{\alpha=1}^{\mu} \frac{a_{\alpha}}{a_0}$$



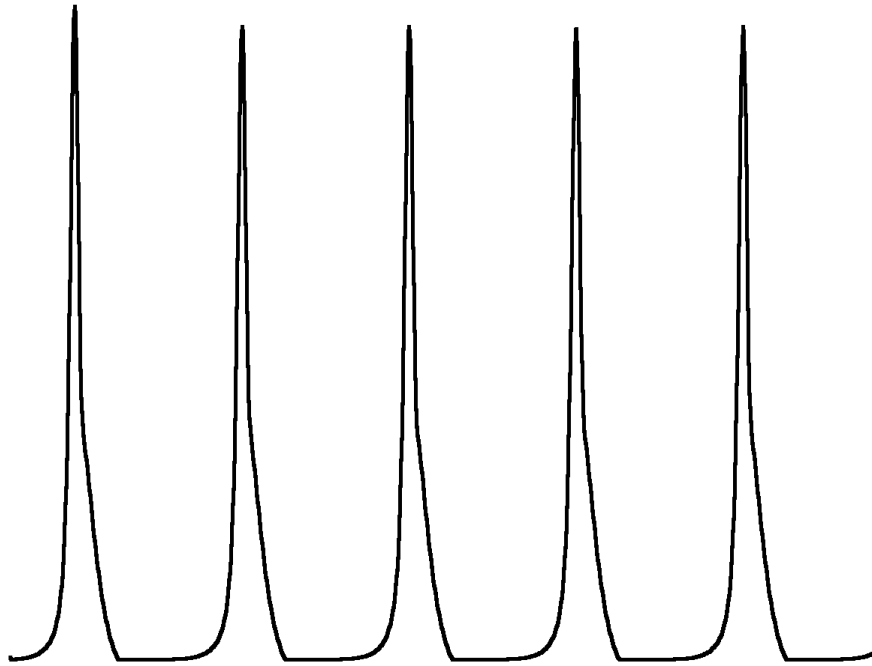
- 4) Instantiate the reaction: Change particle numbers according to stoichiometry

Signal transduction via Ca^{2+} -ions



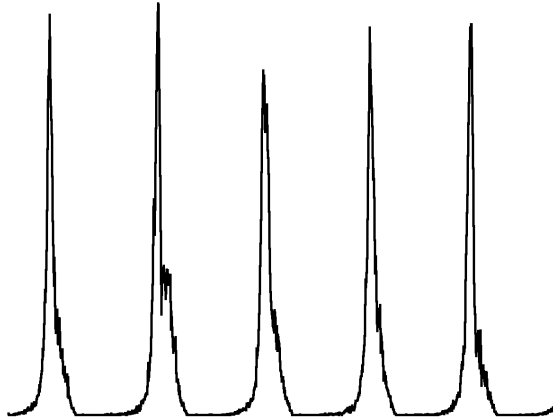
Calcium dynamics (simulated deterministically)

spiking

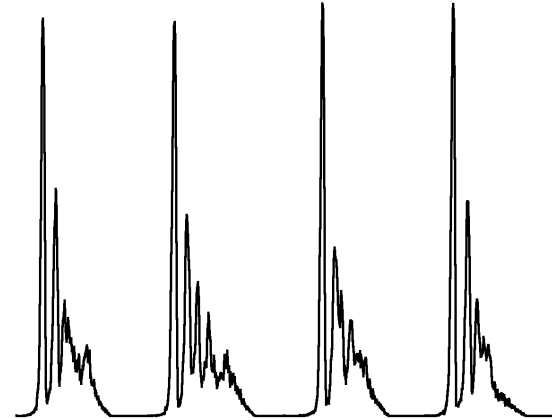


Calcium dynamics (simulated)

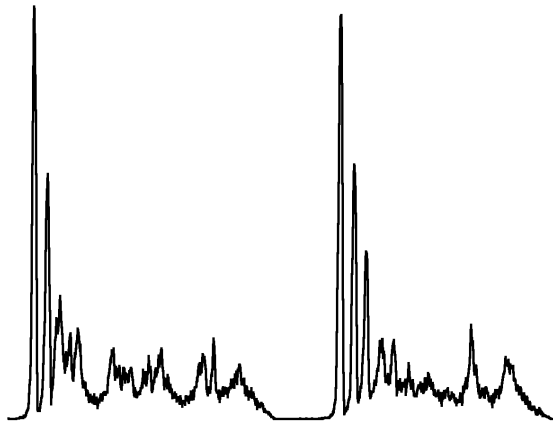
spiking



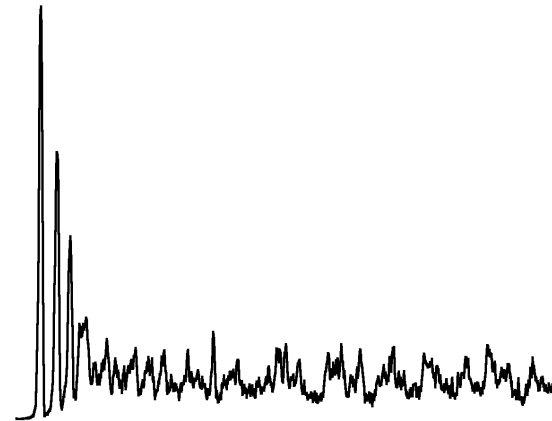
bursting



irregular/chaotic



overstimulation



Presentations & Write-ups

- What is/are the main question/s of the article?
- Have these questions been adequately answered?
- Summarize and **explain** the most important steps taken in the approach.
- Are there errors, inconsistencies, omissions?

- Would there be alternative approaches? Which ones? Why did the authors choose theirs?
- If approximations are involved, under which circumstances are they valid? When do they break?
- How does this work fit into the bigger field of research? Do the authors refer to closely related work?
- ...

Literature

Information Theory

- Cover and Thomas (1991) *Elements of Information Theory*. John Wiley & Sons, Inc., ISBN 0-471-06259-6
- Shannon (1948) A Mathematical Theory of Communication. *Bell System Technical Journal* **27**:379-423, 623-656

(Computational) Systems Biology

- Klipp et al. (2009) *Systems Biology - A Textbook*. WILEY-VCH, ISBN 978-3-527-31874-2

To agree on...

- Presentation days (14th and 15th June 2012, from 14:30)
- Opponents assignments
 - Pahle 2008 (Thorsten Klingen): Ugur Kira, Abirami Veluchamy
 - Gourevitch 2007 (Zeinab M.P.Aghdam): Thorsten Klingen, Pramod Kaushik Mudrakarta
 - Niven 2007 (Azim Dehghani Amirabad): Thorsten Klingen, Zeinab M.P.Aghdam
 - Staniek 2008 (Ugur Kira): Zeinab M.P.Aghdam, Azim Dehghani Amirabad
 - Ziv 2007 (Pramod Kaushik Mudrakarta): Daria Gaidar, Ugur Kira
 - Tkacik 2008 (Abirami Veluchamy): Azim Dehghani Amirabad, Daria Gaidar
 - Waltermann 2011 (Daria Gaidar): Abirami Veluchamy, Pramod Kaushik Mudrakarta