Information transfer in Ca^{2+} signal transduction

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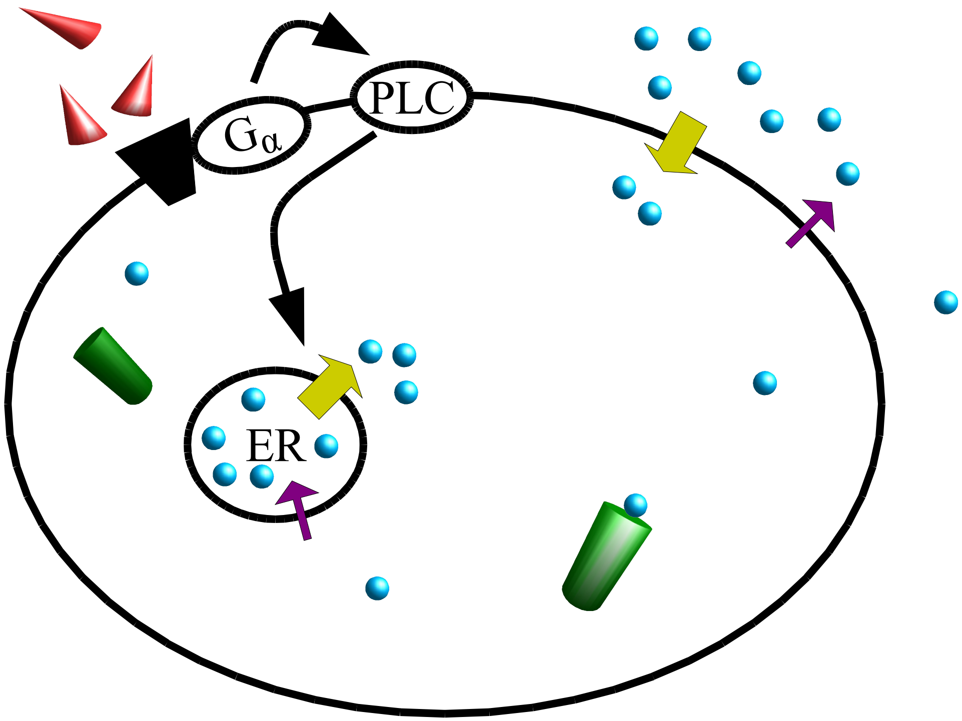
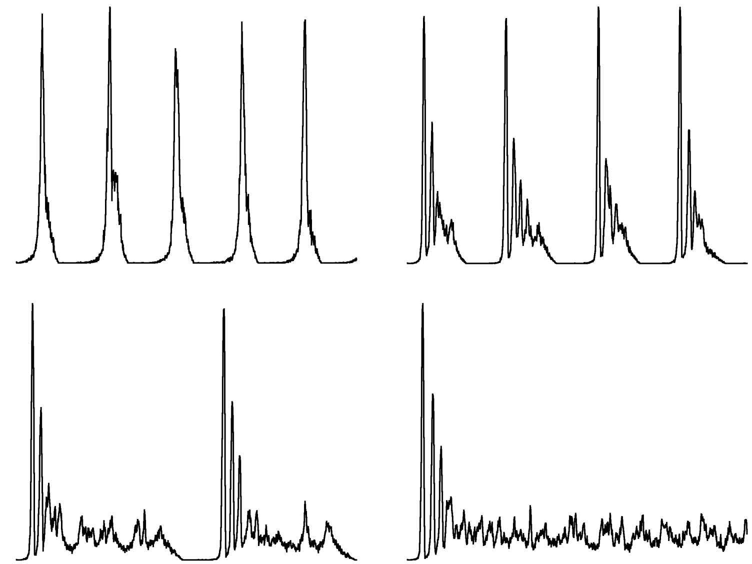
Signal transduction via Ca^{2+}-ions



different Ca^{2+}-dynamics:



data:

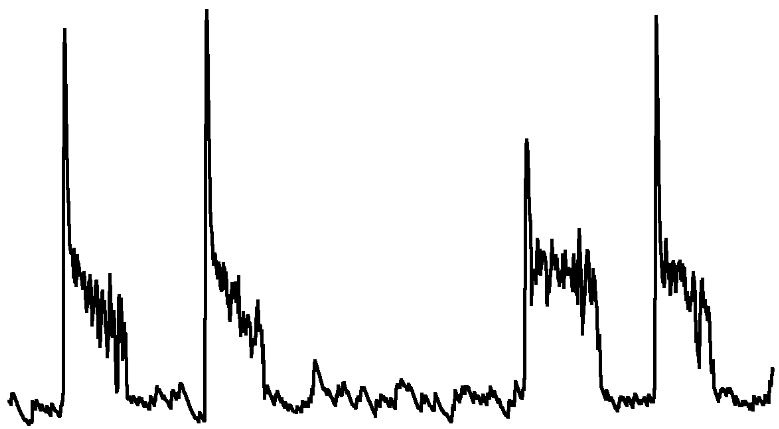
- single-cell measurements using Ca^{2+}-markers (aequorin, etc.) or
- computer simulations using stochastic simulation techniques
  - Ca^{2+}-model *(U. Kummer et al. (2000) Biophys. J., **79**:1188-1195)*
  - Stochastic Simulation *(D.T. Gillespie (1976) J. Comp. Phys, **22**:403-434)*

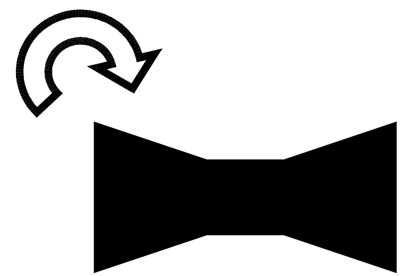
Signal transduction via Calcium

Hormones (Angiotensin II, Vasopressin etc.)

Nucleotides (ATP, UTP)

Ca^{2+}-signal





bow tie structure

calcium code?

Target proteins (Calmodulin, Phosphorylase b kinase, etc.)

Transcription factors (NF-κB, etc.)

Transfer Entropy

- Enzyme dynamics is influenced by calcium
  How much of the uncertainty about the enzyme dynamics is taken away, if we know the calcium signal?

  → Information transferred from calcium to target enzyme

Kullback-Leibler form *(T. Schreiber (2000) Phys. Rev.,* ***85****(2):461-4)*

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

Kernel density estimation (rectangular/gaussian kernel) or
Histogram-based techniques

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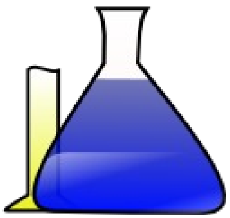
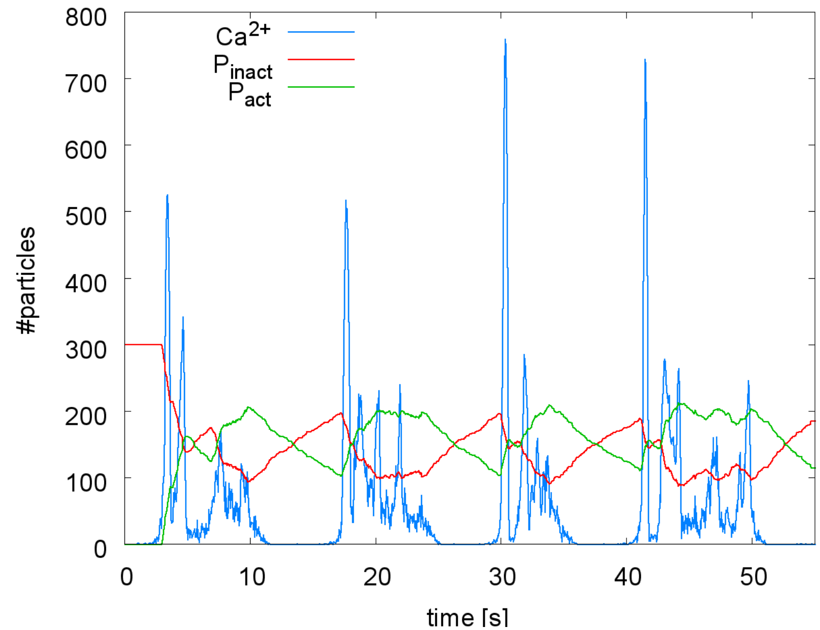
Coupled enzyme activation



stoch. coupling
with simulated
enzyme

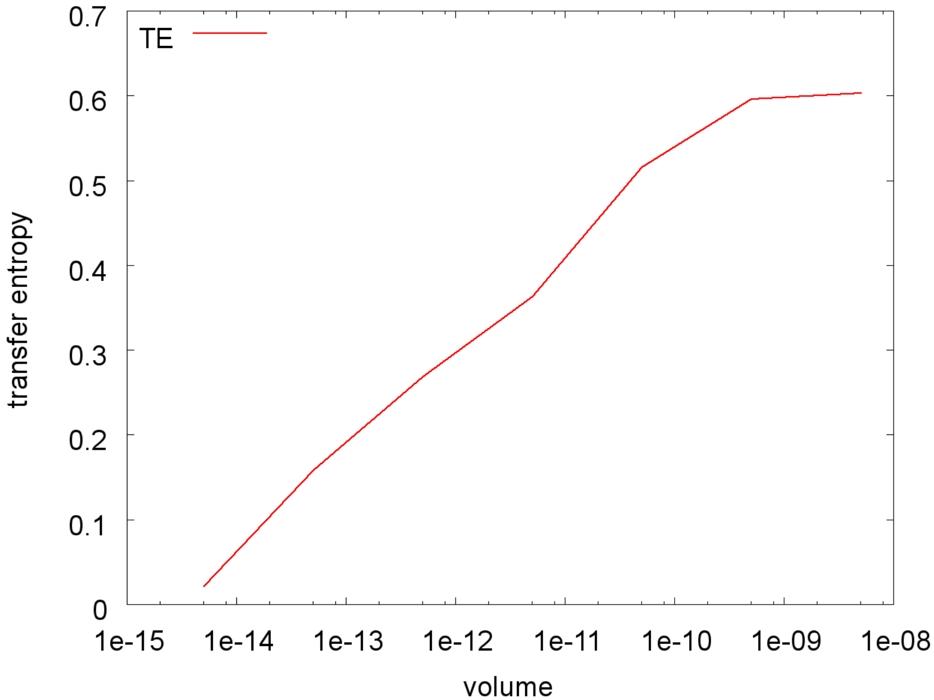


estimation of the transfer entropy

- (box-assisted) kernel density estimation (rectangular or gaussian kernel)
- rank-based adaptive histogram method

`implemented in` **`octave`** `with dynamically-linked C++-functions`

Results



- The rate of information transfer increases with increasing volume (and number of particles) until it reaches a maximum.
  Bursting: max. rate ~ 0.6 bit/sample
- There is a slight increase in transfer entropy from spiking to increasingly complex bursting oscillations. In the case of an (elevated) steady state the TE drops to a very low value.

Stimulus strength (k2)	Dynamic behavior	TE
2	Spiking	0.52
2.5	Bursting	0.59
2.85	Bursting	0.60
3.2	Steady state (overstim.)	0.15

Take-home message

- Ca^{2+} in cells carries information from hormones, etc., to different intracellular targets (enzymes)
- Specific information is encoded in this calcium signal → calcium code
- Important step to decrypt this code is to quantify the information, which is actually carried under different cellular conditions
- Information theory (together with stochastic simulation methods) offers the tools → Transfer Entropy

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