In silico stochastic simulation of Ca^{2+} triggered synaptic release

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Models of the neural function

- The functional capabilities of the nervous system arise from the complex organization of the neural network
- Models are needed to understand
  - the ways in which neural circuits generate behavior,
  - the ways in which experience alters the functional properties of circuits and therefore their behaviour (plasticity/memory),
  - ... (and many other issues).
- (some) Key elements are
  - the intrinsic biophysical/biochemical properties of the individual neurons
  - the pattern of the synaptic connections amongst neurons
  - the physiological properties of synaptic connections

Models of the neural function

Focus:

1. A model of a pre-synaptic calcium triggered release
   - Synapses: points of functional contact between neurons
   - Chemical synapses: presynaptic action potentials cause chemical intermediary (neurotransmitters) to influence postsynaptic terminal
   - Chemical synapses are plastic: modified by prior activity

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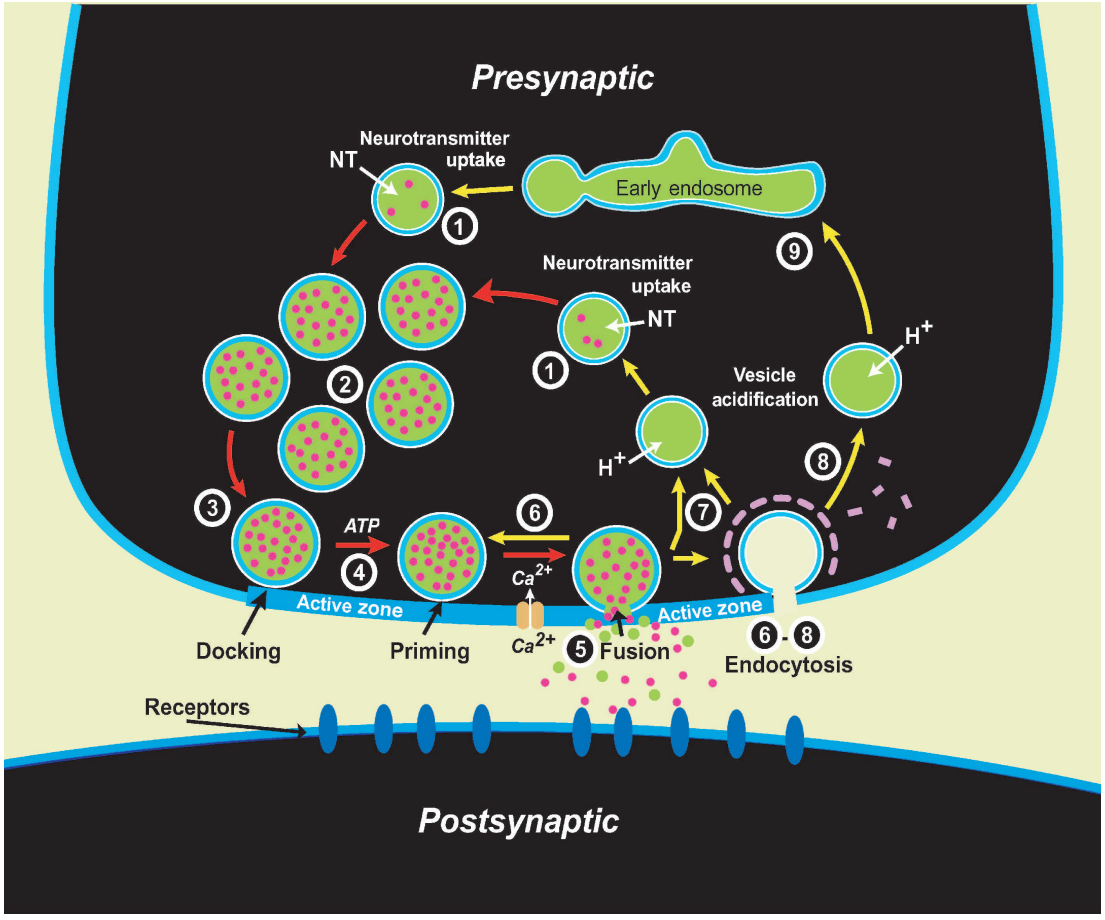
   - Chemical synapses are plastic: modified by prior activity
2. A (first) stochastic model
3. A computational (process-algebra based) approach
   - formal
   - executable
   - compositional

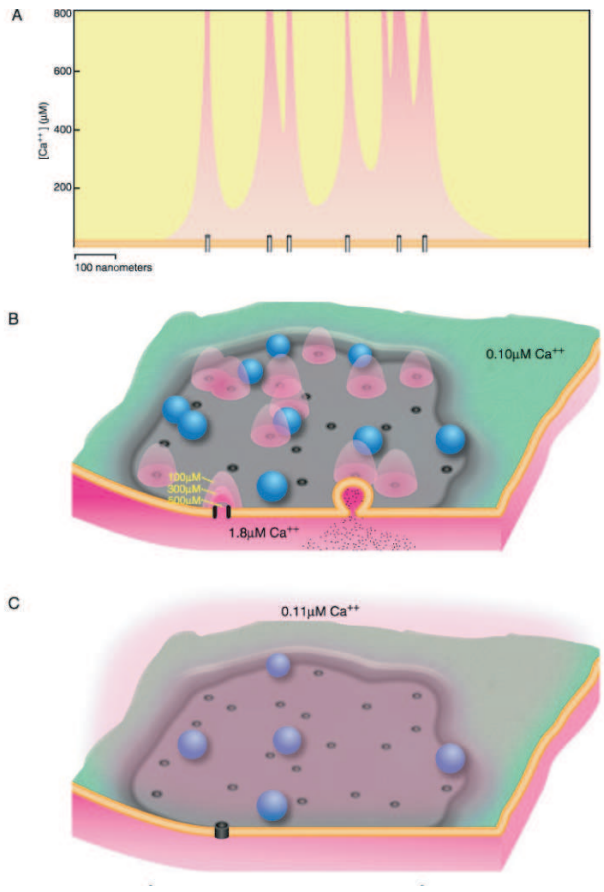
Presynaptic calcium triggered release



From: Sudhof TC. The synaptic vesicle cycle. Annu Rev Neurosci. 27:509-47, 2004.

1. Calcium gradient
2. Vescicle activation (exocitosis)
3. Neuro-transimitter release
4. Calcium extrusion
5. Vescicle recharging
6. . . .
7. Neuro-transmitter reception
8. . . .

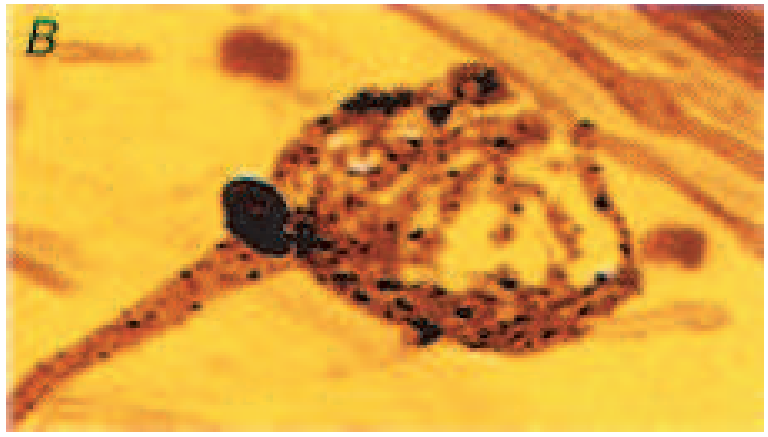
Presynaptic calcium concentration profile

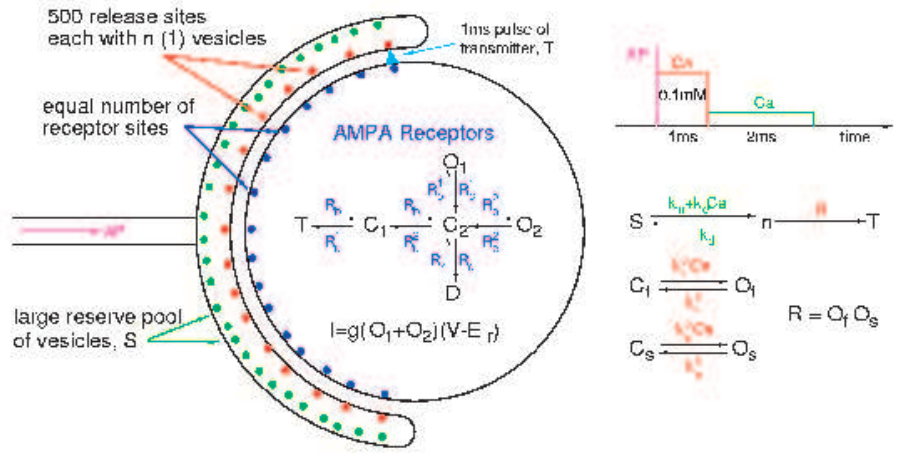


From: Zucker RS, Kullmann DM, Schwartz TL. Release of Neurotransmitters. In: From molecules to networks - An introduction to cellular and molecular neuroscience. Elsevier pp 197-244 2004.

- Microdomains of Calcium concentrations near open channels
- trigger the exocytosis of synaptic vescicles.
- Calcium concentration during release is *not homogeneous*
- unless subsequently in not effective concentrations.
- *Uncaging:* An experimental method capable to induce spatially homogeneous Calcium elevation in the presynaptic terminal. Applied to the synapse *Calyx of Held*.

Calyx of Held: deterministic model





From: www.cs.stir.ac.uk/ bpg/research/syntran.html

By means of the uncaging method, a 5-step model of release has been defi ned based on *concentrations,* [SN00N]:

$$Ca_i^{2+} + V \underset{k_{off} b^0}{\overset{5k_{on}}{\rightleftharpoons}} V_{Ca_i^{2+}} + Ca_i^{2+} \quad \dots \quad V_{4Ca_i^{2+}} + Ca_i^{2+} \underset{5k_{off} b^4}{\overset{k_{on}}{\rightleftharpoons}} V_{5Ca_i^{2+}} \xrightarrow{\gamma} T$$

where $k_{on} = 9 \times 10^7\ M^{-1}s^{-1}$, $k_{off} = 9500\ s^{-1}$, $\gamma = 6000\ s^{-1}$ and $b = 0.25$

have been defi ned by experimental fitting (complex).

Calyx of Held: stochastic model of calcium uncaging

Deterministic model: unsuitable for small concentrations and volumes, e.g.

- if [Ca^{2+}] = 10 μM, in a volume of 60 nm^3 there is a single free ion;
- the assumption that binding of Ca^{2+} to vescicle does not affect the [Ca^{2+}] concentration not adequate
  (with vescicle diameter $\sim 17 - 22\ nm$, $V = 60\ nm^3$ few Ca^{2+} ions).

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Stochastic model: actual quantities and stochastic rate constants:

$c = k$ 1st order $\qquad\qquad$ $c = k/(NA \times \mathbf{V})$ 2nd order

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Calyx [SF06CTR]:

- a vast “parallel” arrangement of active zones (3-700)
- each one with up to 10 vescicles
- clustered in groups of about 10 in a volume with a diameter of almost 1 μm.
- action potential activates all the active zones.

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A cluster of 10 active zone each one with 10 vescicles in $V = 0.5\ 10^{-15}\ liter$

Calyx of Held: stochastic model of calcium uncaging

The obtained stochastic model:

$$c_{on} = 9 \times 10^7 \ / \ (6.02 \times 10^{23} \times 0.5 \times 10^{-15}) \ s^{-1} = 0.3 \ s^{-1},$$

$$c_{off} = 9500 \ s^{-1},$$

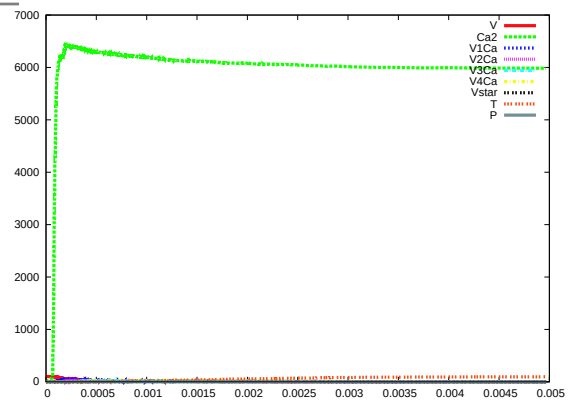
$$\gamma = 6000 \ s^{-1}$$

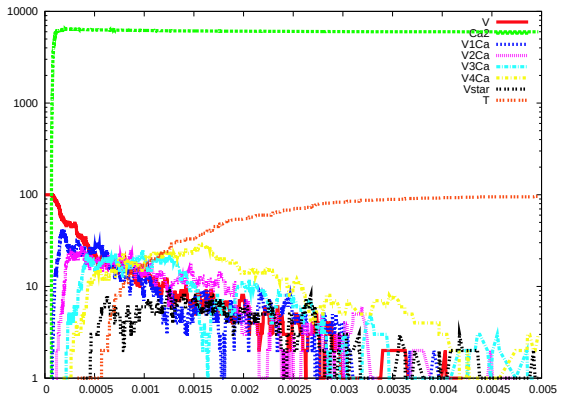
$$b = 0.25.$$

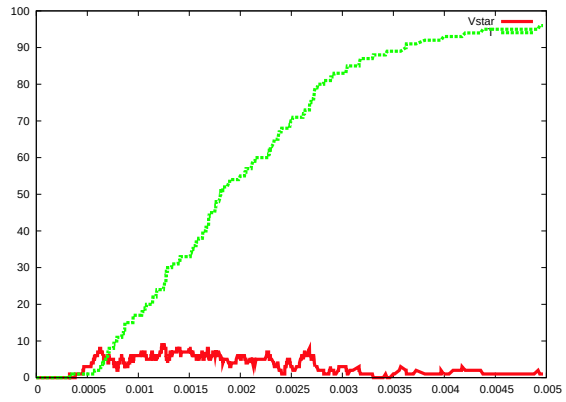
Ca^{2+} ions: 300, 3000 and 6000, corresponding to molar concentrations [Ca^{2+}] of 1, 10 and 20 μM.

$$Ca_i^{2+} + V \underset{c_{off} b^0}{\overset{5c_{on}}{\rightleftharpoons}} V_{Ca_i^{2+}} + Ca_i^{2+} \quad \dots \quad V_{4Ca_i^{2+}} + Ca_i^{2+} \underset{5c_{off} b^4}{\overset{c_{on}}{\rightleftharpoons}} V_{5Ca_i^{2+}} \xrightarrow{\gamma} T$$

Results



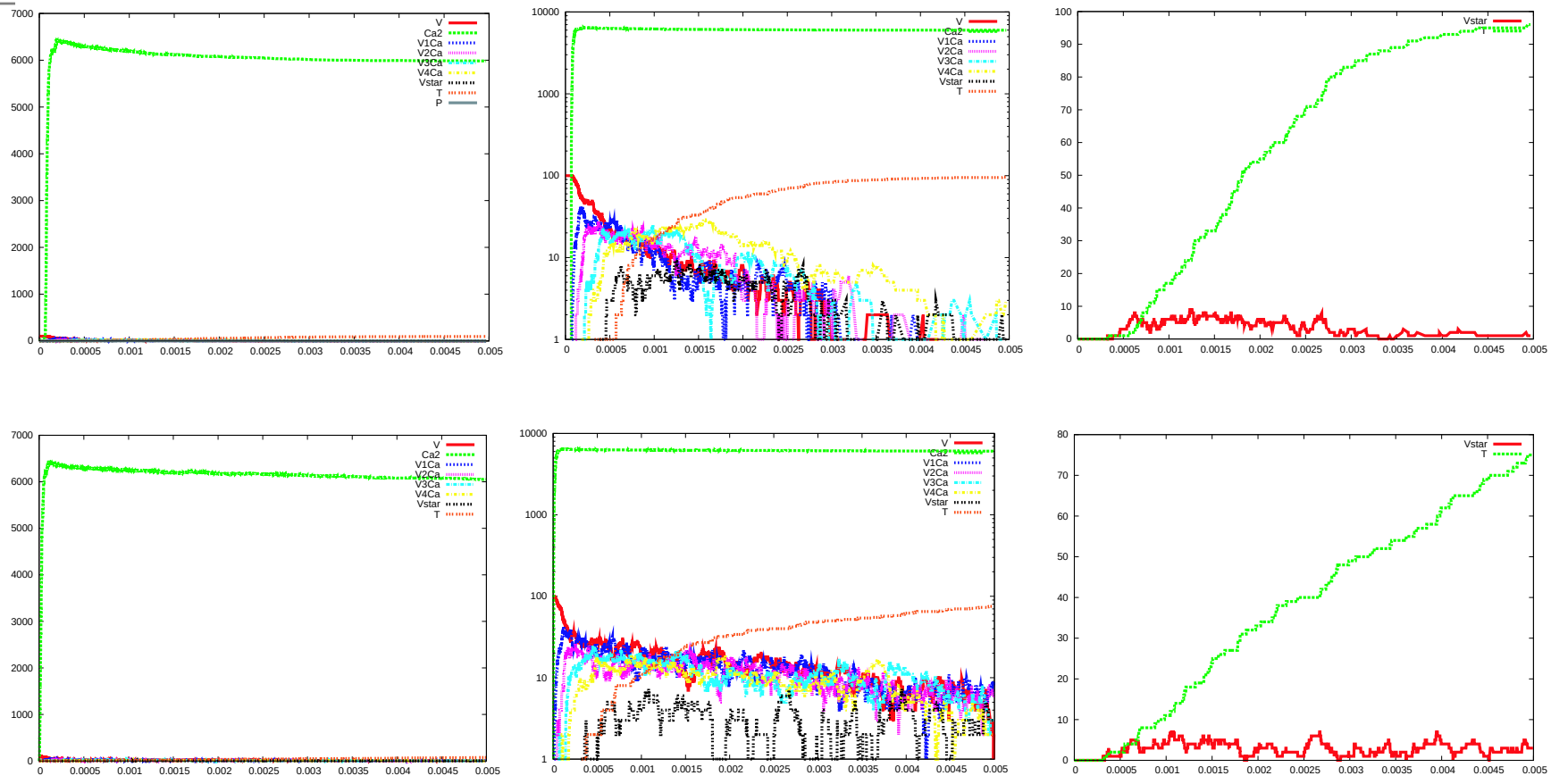




Step-like calcium uncaging, $V = 100, Ca^{2+} = 6000$.
Results are coherent with literature, [SN00N], e.g.

- High sensitivity of vescicles to Ca^{2+} concentration
- Calyx of Held triggers vescicle release with concentrations lower than $100\ \mu M$ (usual values for other synapses are $100 - 300 \mu M$). In the fi gure $6000\ Ca^{2+}$ correspond to $20 \mu M$.

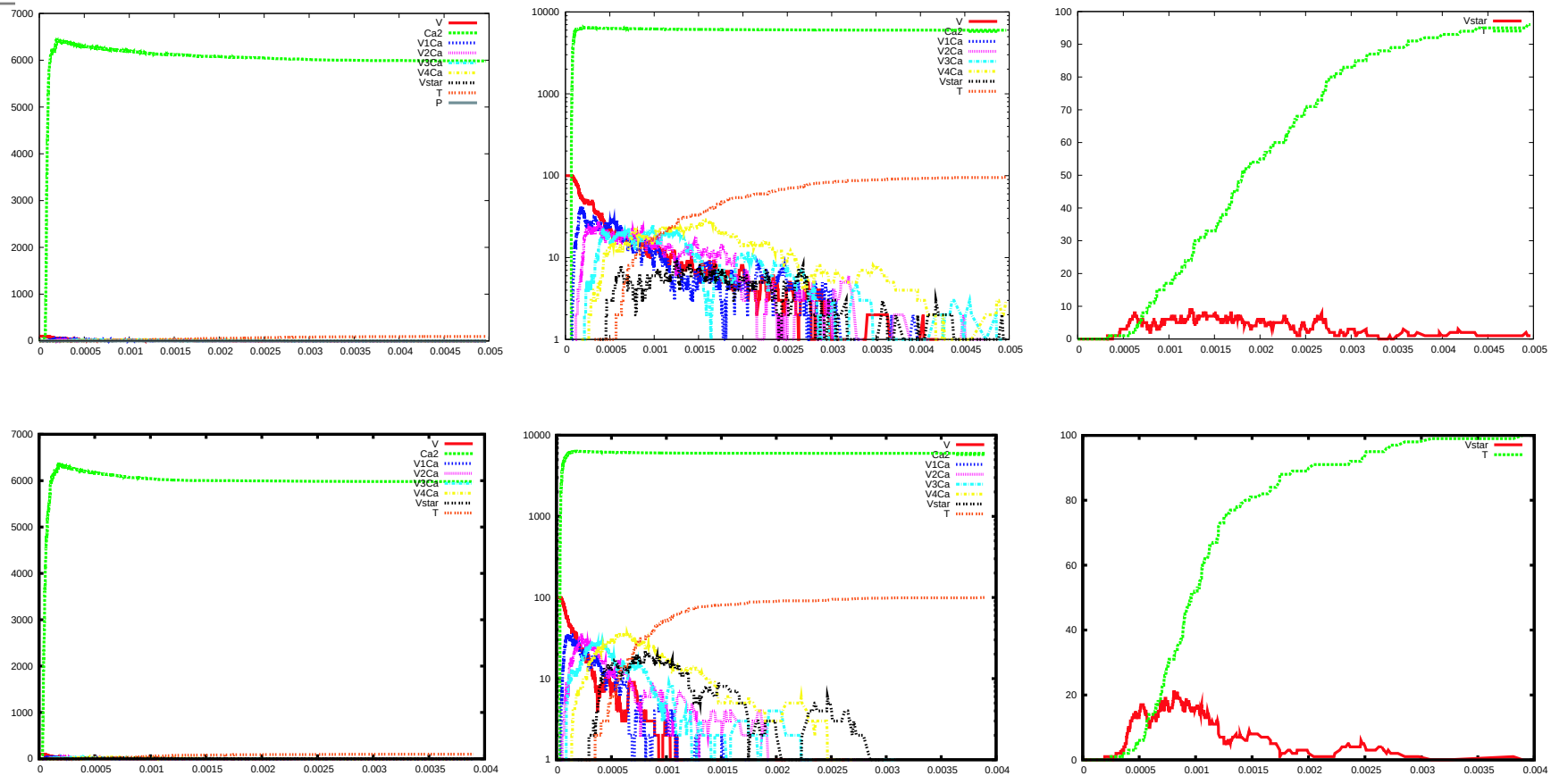
Results



Variation of $b = 0.4$ (was $b = 0.25$): lower and more uniform release rate

$$Ca_i^{2+} + V \underset{c_{off}\, b^0}{\overset{5 c_{on}}{\rightleftharpoons}} V_{Ca_i^{2+}} + Ca_i^{2+} \quad \dots \quad V_{4Ca_i^{2+}} + Ca_i^{2+} \underset{5 c_{off}\, b^4}{\overset{c_{on}}{\rightleftharpoons}} \quad \dots$$

Results



Variation of $c_o n = 0.5$ (was $c_o n = 0.3$): increase of the release rate

$$Ca_i^{2+} + V \underset{c_{off} b^0}{\overset{5c_{on}}{\rightleftharpoons}} V_{Ca_i^{2+}} + Ca_i^{2+} \quad \dots \quad V_{4Ca_i^{2+}} + Ca_i^{2+} \underset{5c_{off} b^4}{\overset{c_{on}}{\rightleftharpoons}} \quad \dots$$

Cell as computation [RS02N]

A process-algebra approach [recall previous Degano's talk]

- interaction as communication
- processes [molecules, ions, proteins, vescicles, ...] defi ned as sequential, parallel, choice composition of communications
- stochastic reaction rates - associated to each communication - determine the next most probable interaction ...
- – Gillespie algorithm: rate $\times$ # Processes ready to interact –
- ... and the system evolves.

A dialect of Pi-calculus as modeling language

the SPiM interpreter [PC2004BC] as programming language/execution environment

Model implementation — overview

```
directive sample 0.005 1

val con5 = 1.5
val b = 0.25
val coff5 = 47500.0 * b * b * b * b

new vca@con5:chan

ca() = do ?vca;()
     or ?v2ca;()
     ...

v() = !vca; v_ca()

v_ca() = do !bvca; v()
     or !v2ca; v_2ca()

Dv_ca() = ?bvca; ( ca() | Dv_ca() )

run 6000 of ca()
run 100 of v()
run 1 of (Dv_ca() | Dv_2ca()| ... )
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Initial set-up (creation of communication channels)

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Second order reaction

Model implementation — overview

```
directive sample 0.005 1

val con5 = 1.5
val b = 0.25
val coff5 = 47500.0 * b * b * b * b

new vca@con5:chan

ca() = do ?vca;()
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run 6000 of ca()
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```

First order reaction (via single, dummy processes)

Model implementation — overview

```
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new vca@con5:chan

ca() = do ?vca;()
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v() = !vca; v_ca()
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run 6000 of ca()
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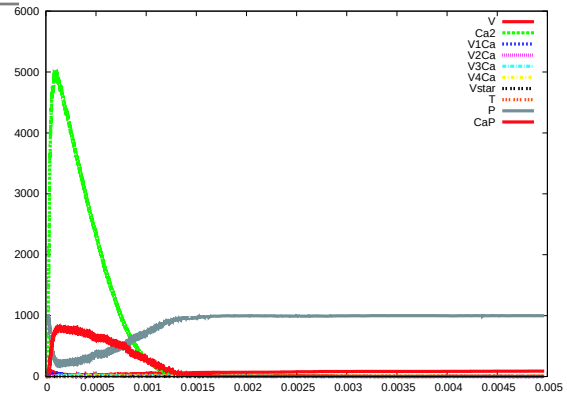
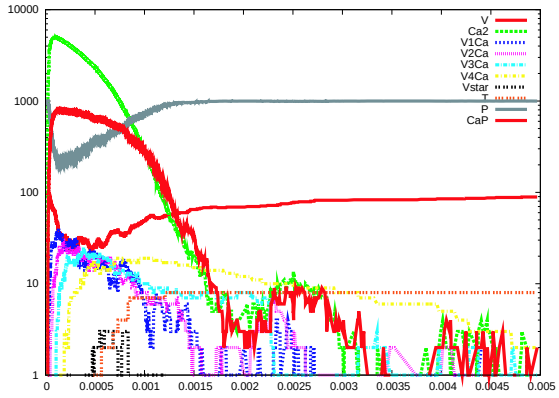
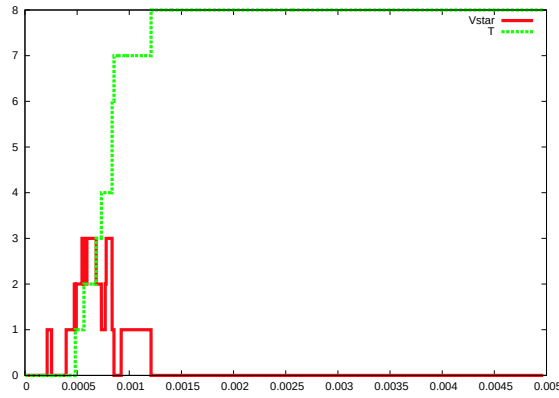
```

Setting initial conditions (quantities)

A (modular) extension: Wave-like uncaging







$$Ca_i^{2+} + P \underset{c_2}{\overset{c_1}{\rightleftarrows}} CaP \xrightarrow{c_3} Ca_o^{2+}$$

```
...
val c1 = 8.00

new cp@c1:chan

ca() = do ?vca;()
     or ?v2ca;()
     ...
     or ?cp;()

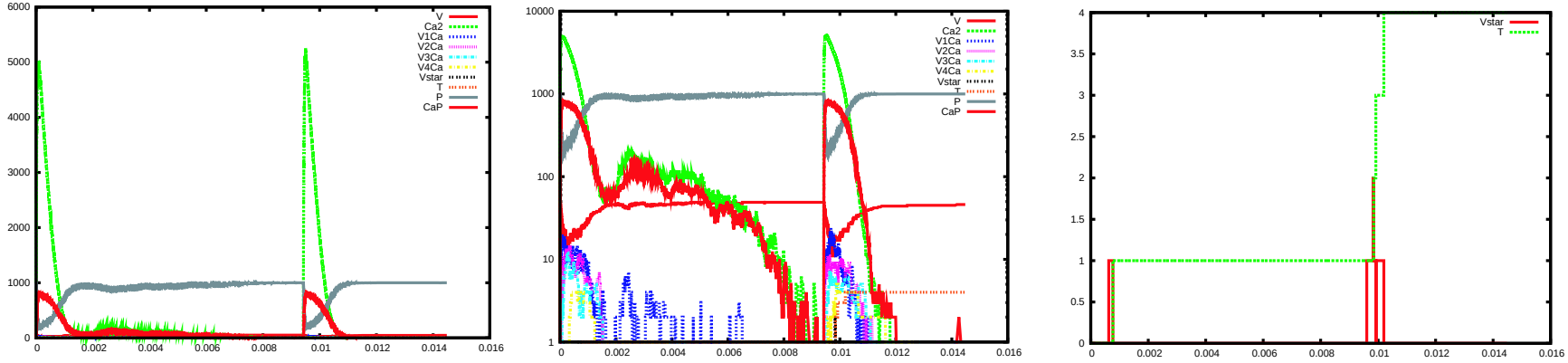
p() = !cp; ca_p()

ca_p() = do !cpout; p()
     or !cpback; ( p() | ca() )
```

```
...
w( cnt : int) =
     do delay@40000.0;
     if 0 <= cnt
       then ( 80 of ca() | 80 of w(cnt - 1))
       else ()
     or !void; ()

run 1 of w(1)
run 1000 of p()
 run 100 of v()
run 1 of (Dv_ca() | Dv_2ca()| ... )
```

Further ongoing developments [CMBS07]



- addressing plasticity: 2nd wave sensitive to residual calcium
- Moreover, compartimentalisation of the pre-synaptic terminal,
- ...

Conclusions

- A fi rst stochastic model for (pre-)synaptic terminal
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- further pursuing the modular construction of one (more) synapses - post-synaptic terminal, ...

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- studying linguistic and semantic suitable constructs, e.g. expressing locality, dynamically varying rates, ...
- devising qualitative/predictive analysis techniques
- making available results in an accessible (graphical) form.

End of the talk

References

[SN00N] Schneggenburger N. and Neher E. “Intracellular calcium dependence of transmitter release rates at fast central synapse”, Nature 46:889-893, 2000.

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