Expressive Models for Synaptic Plasticity

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Aims of the talk

Two views of a multidisciplinary research

- A model of the (Calyx of Held) synapse
  - Motivations and long-term goals
  - Issues
- Methodology: A (first) stochastic model based on a computational (process-algebra based) approach
  - Adequacy
  - Expressiveness
  - Compositionality
  - Scalability
- Further developments

Models of the neural function

- The functional capabilities of the nervous system arise from the complex organization of the neural network, e.g.
  - the intrinsic biophysical/biochemical properties of the individual neurons
  - the physiological properties of synaptic connections
  - the pattern of the synaptic connections amongst neurons
- Long term goals: Models for understanding
  - 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).

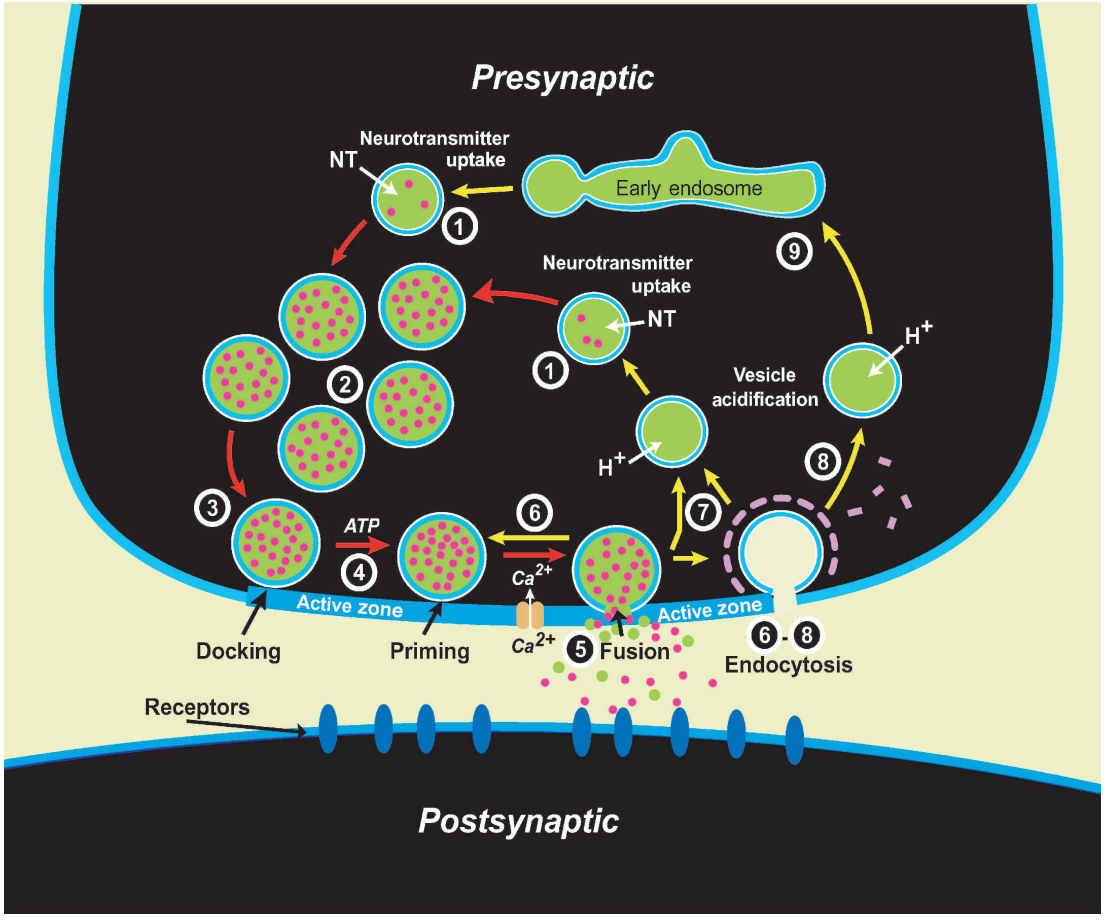
Pre-synaptic calcium triggered release

- 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

Calyx of Held:

- large synapse of the auditory tract in CNS
- chemically activated
- high-sensitivity to calcium

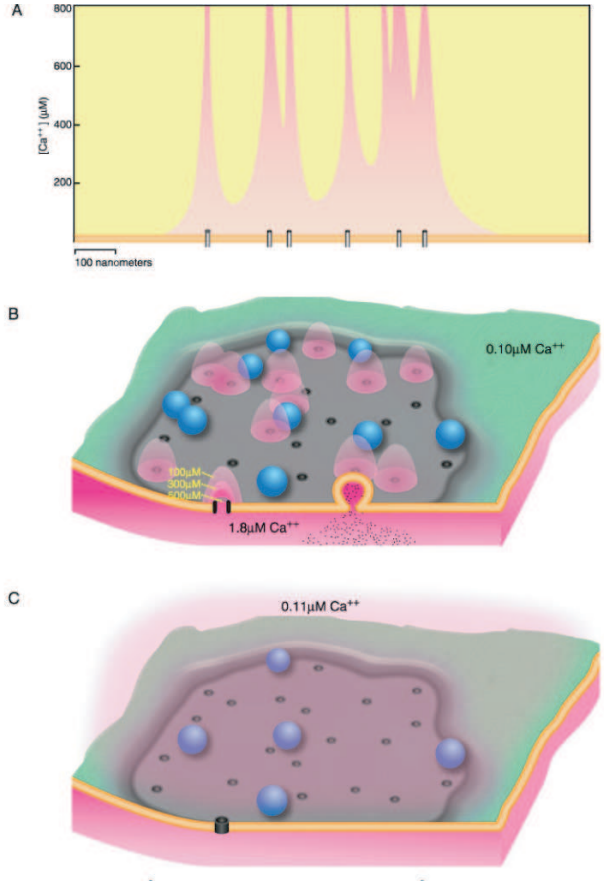
Presynaptic calcium triggered release



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. . . .

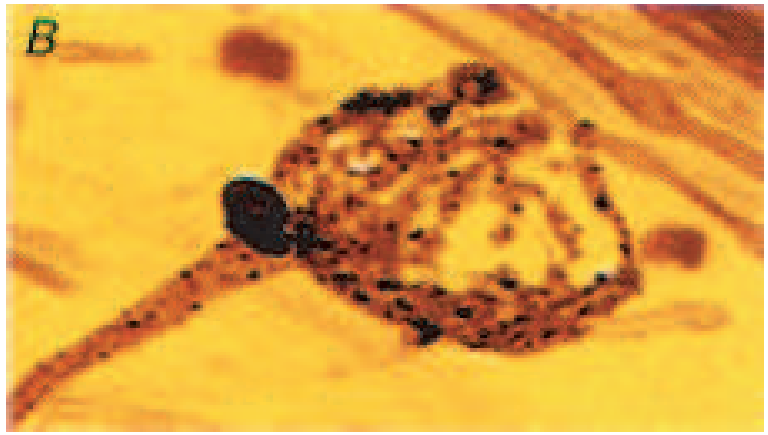
Presynaptic calcium concentration profile

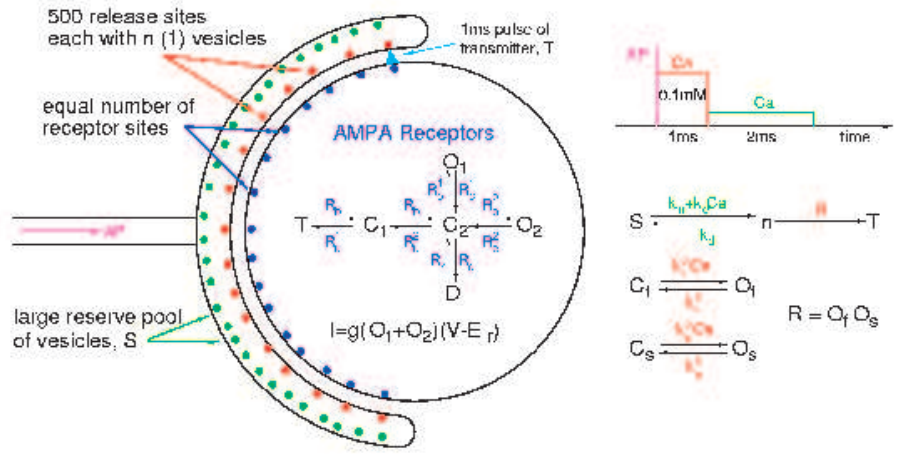


From: Zucker RS, Kullmann DM, Schwartz TL. Release of Neurotransmitters. In: From molecules to networks - An introduction to cellular and molecular neuroscience. Elsevier pp 197-244 2004.

- 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.
- Calcium dynamics in time and space: unclear until a few years ago [no suitable imaging techniques]
- *Uncaging:* An experimental method capable to induce spatially homogeneous Calcium elevation in the presynaptic terminal *plus* fitting of kinetic model.

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 defined 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 defined by experimental fitting (complex).

Calyx of Held: deterministic model

Traditional models based on concentration variations (ODEs) are not always fully satisfactory:

- *Continuity-homogeneity of concentrations* But at low concentrations stochastic and discrete [W06], if $[Ca^{2+}]$ = 10 μM, in a volume of 60 nm^3 there is a single free ion;
- *Binding Ca^{2+} to vescicle does not affect the $[Ca^{2+}]$ concentration*, but with vescicle diameter $\sim 17 - 22\ nm$, the volume is again about 60 nm^3, with few Ca^{2+} ions.
- Analytical, computational, scalability, compositionality difficulties.

Calyx of Held: stochastic model of calcium uncaging

Stochastic model: actual quantities and stochastic rate constants:

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

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.

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:

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

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

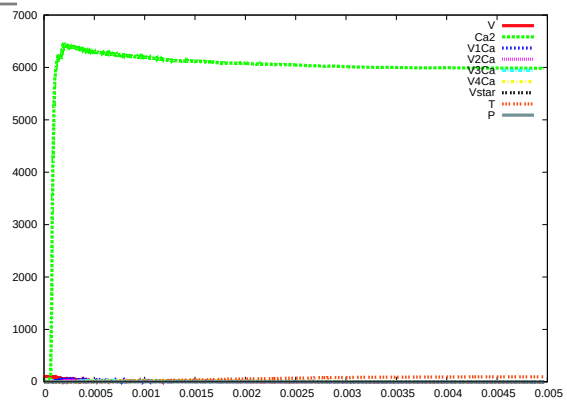
$$\gamma = 6000 \ s^{-1}$$

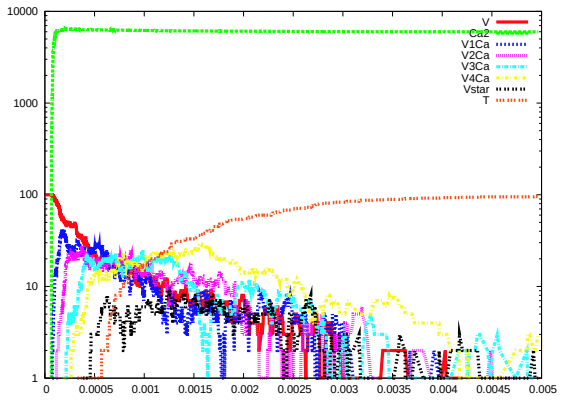
$$b = 0.25.$$

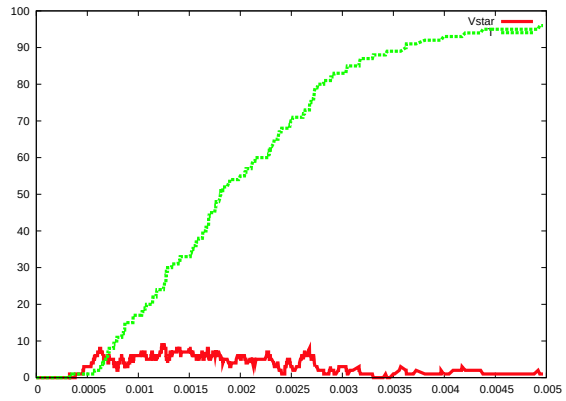
Ca^{2+} ions: 300, 3000 and 6000, corresponding to molar concentrations [Ca^{2+}] of 1, 10 and 20 μM.

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

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* $20 \mu M$.
- Sensitivity analysis: parameter variations

Cells as computation [RS02N]

A process-algebra approach, basic ingredients:

A process-algebra approach

- interaction as communication
- processes [molecules, ions, proteins, vescicles, ...] defined 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

Recent coherence results [From Processes to ODEs by Chemistry, Cardelli]

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)

Model implementation — overview

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

run 6000 of ca()
run 100 of v()
run 1 of (Dv_ca() | Dv_2ca()| ... )
```

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;()
     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()| ... )
```

First order reaction (via single, dummy processes)

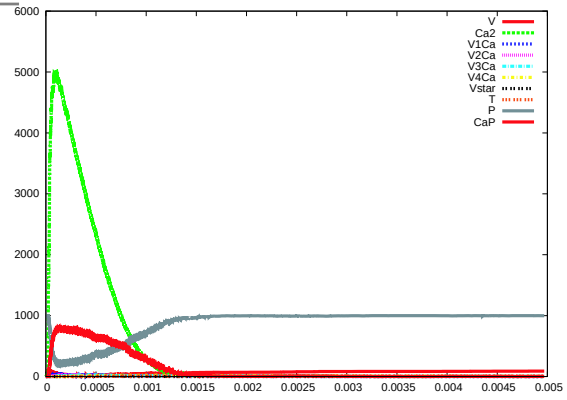
Model implementation — overview

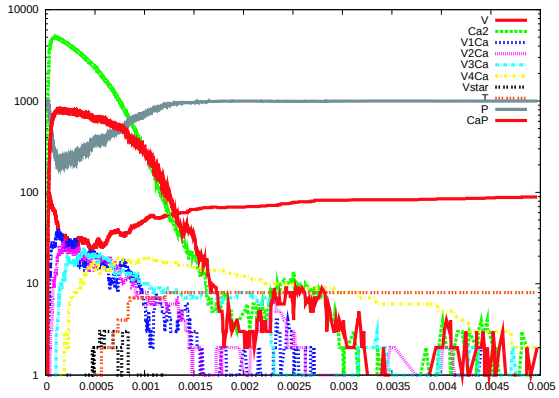
```
directive sample 0.005 1

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()
```

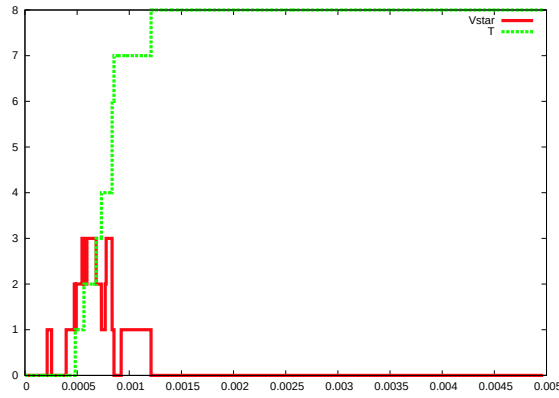
```
v_ca() = do !bvca; v()
     or !v2ca; v_2ca()

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

run 6000 of ca()
run 100 of v()
run 1 of (Dv_ca() | Dv_2ca()| ... )
```

Setting initial conditions (quantities)

A (modular) extension: Wave-like uncaging





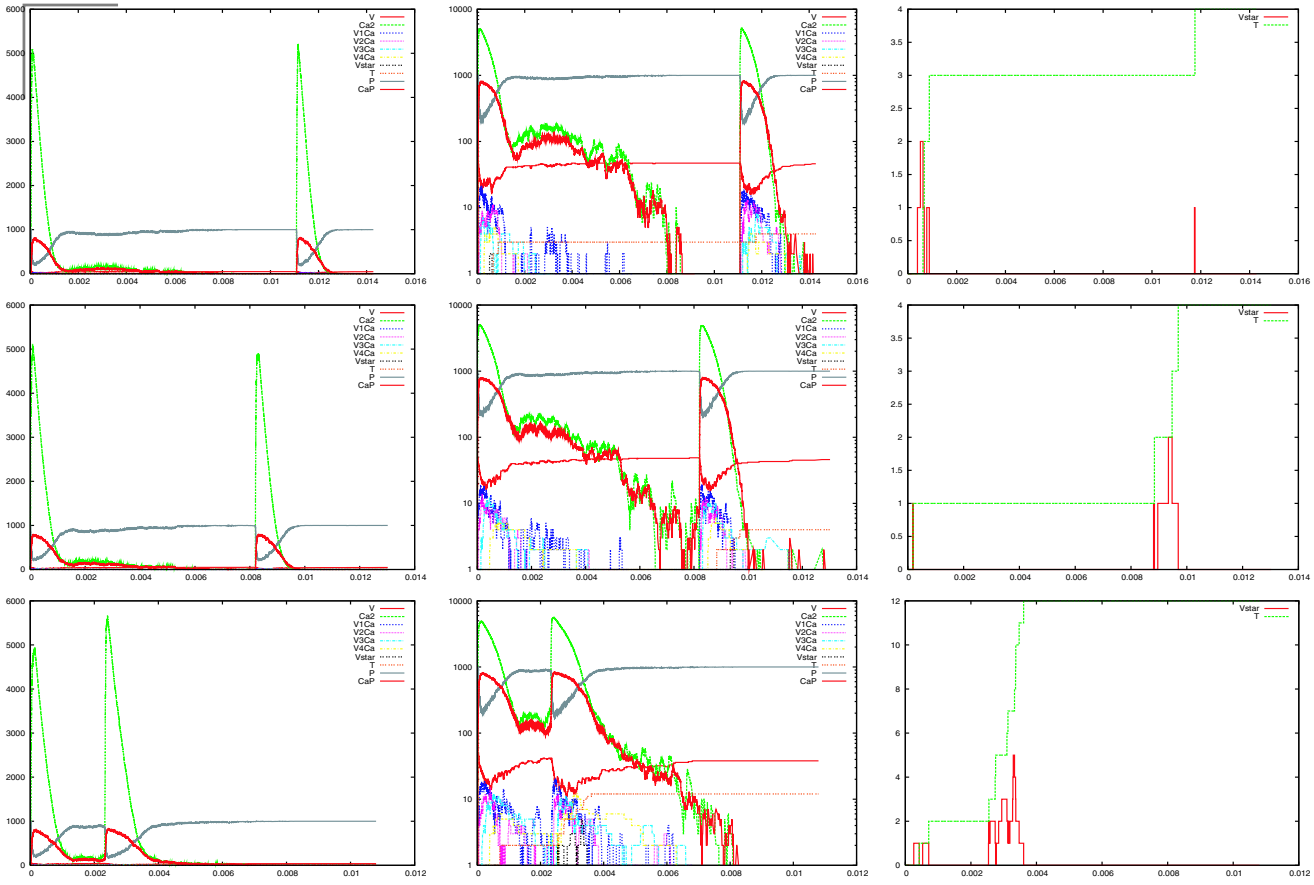


$$Ca_i^{2+} + P \underset{c_2}{\overset{c_1}{\rightleftarrows}} CaP \xrightarrow{c_3} Ca_o^{2+}$$

```
...
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()| ... )
```

Results

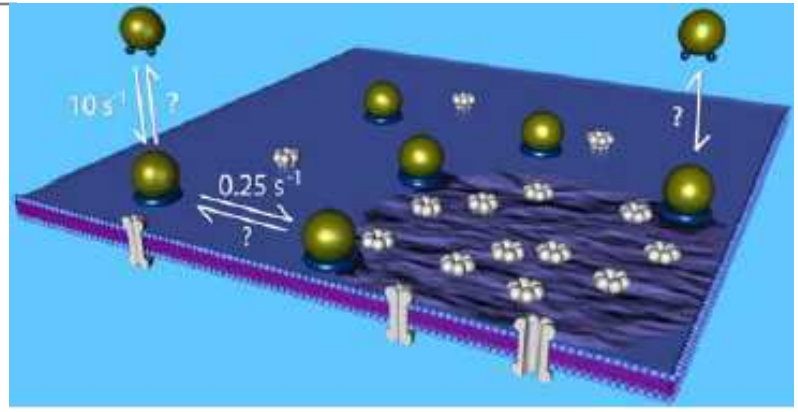


snd_w() =

delay@125.0; w2(1)

- Addressing plasticity: synaptic facilitation by repeated activations
- Shorter intervals, noticeable increase of release,
- low residual Ca^{2+}(ca. 300 == 1μM — 2nd column) [!],
  P occupancy [?]

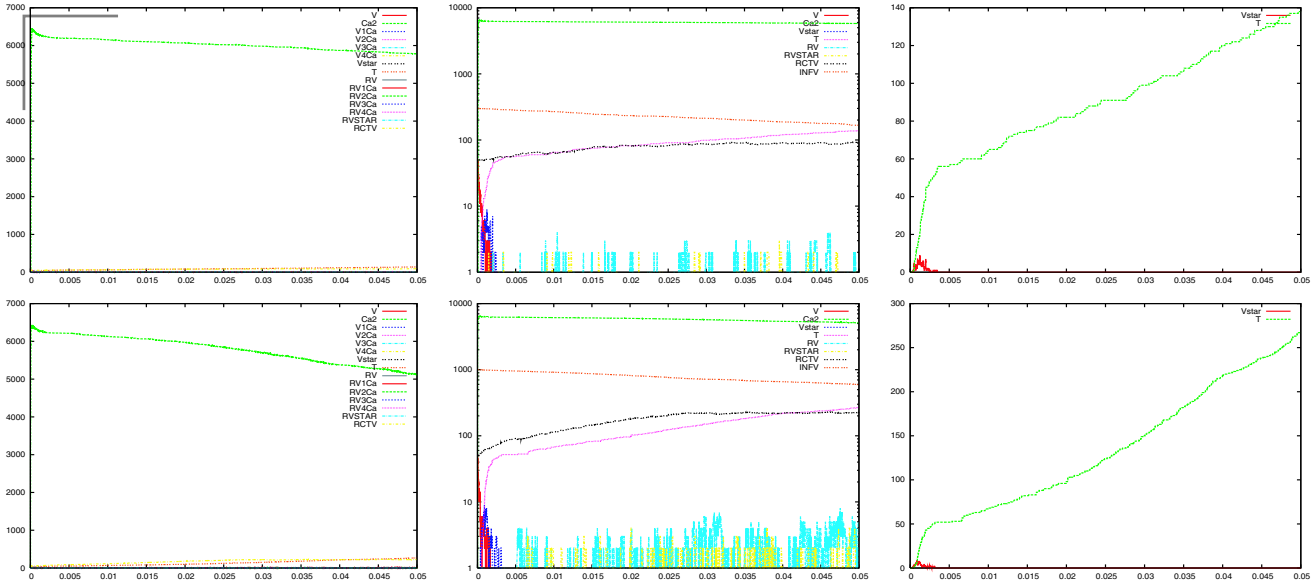
Results



- Short-term synaptic depression:
  Readily vs. reluctantly releasable vescicles
- Synapse depolarisation [maximal Ca^{2+}]: all vescicles released
- 3 vs. 30 ms [!] – reluctant (more rapidly replaced) precursor of rapidly [?]
- Stochastic multi-pool model [coefficients both from literature and fitting]
- 50 “standard”, 50 reluctant, 300/1000 infinity vescicles

$$Inf\_V \underset{1s^{-1}}{\overset{10s^{-1}}{\rightleftarrows}} Rct\_V \underset{0.1s^{-1}}{\overset{2.5s^{-1}}{\rightleftarrows}} R\_V + Ca_i^{2+} \underset{c_{off}b^0}{\overset{5c_{on}}{\rightleftarrows}} \dots \underset{c_{off}b^4}{\overset{c_{on}}{\rightleftarrows}} R\_V_{5Ca_i^{2+}} \xrightarrow{\gamma} \mathbf{T}$$

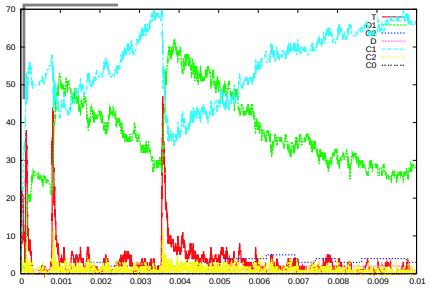
Results

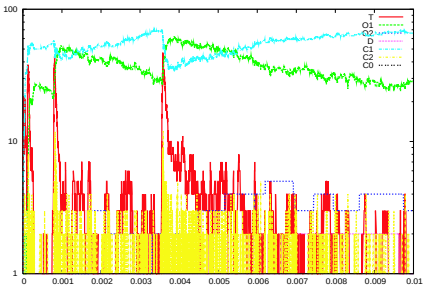


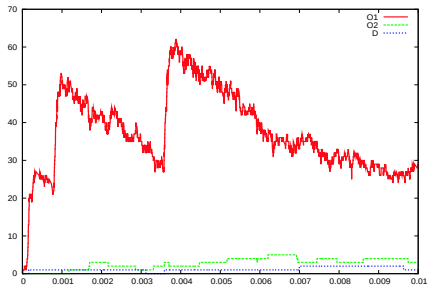
```
ca() =
   do ?vca;() or ...
...
rct_v() =
   do !rvgo; rv()
   or !bvinfgo; inf_v()
rv() =
   do !vca; rv_ca()
   or !brvgo; rct_v()
...
rvstar() =
   do !bv5ca; rv_4ca()
   or !vt; t()
```

- Step-like uncaging (synapse depletion),
- “fast” 50 v release (3 ms, red in 2nd and 3rd column)
- “slow” 50-150 rv release (30 ms, green)
- 50 rv more adherent to experimental findings (inf_v = 300)
- definition of parameters (v, rv, inf_v, rates),
- rates might need to be variables for equilibrium [?].

Results [ongoing - I]: post-synaptic terminal





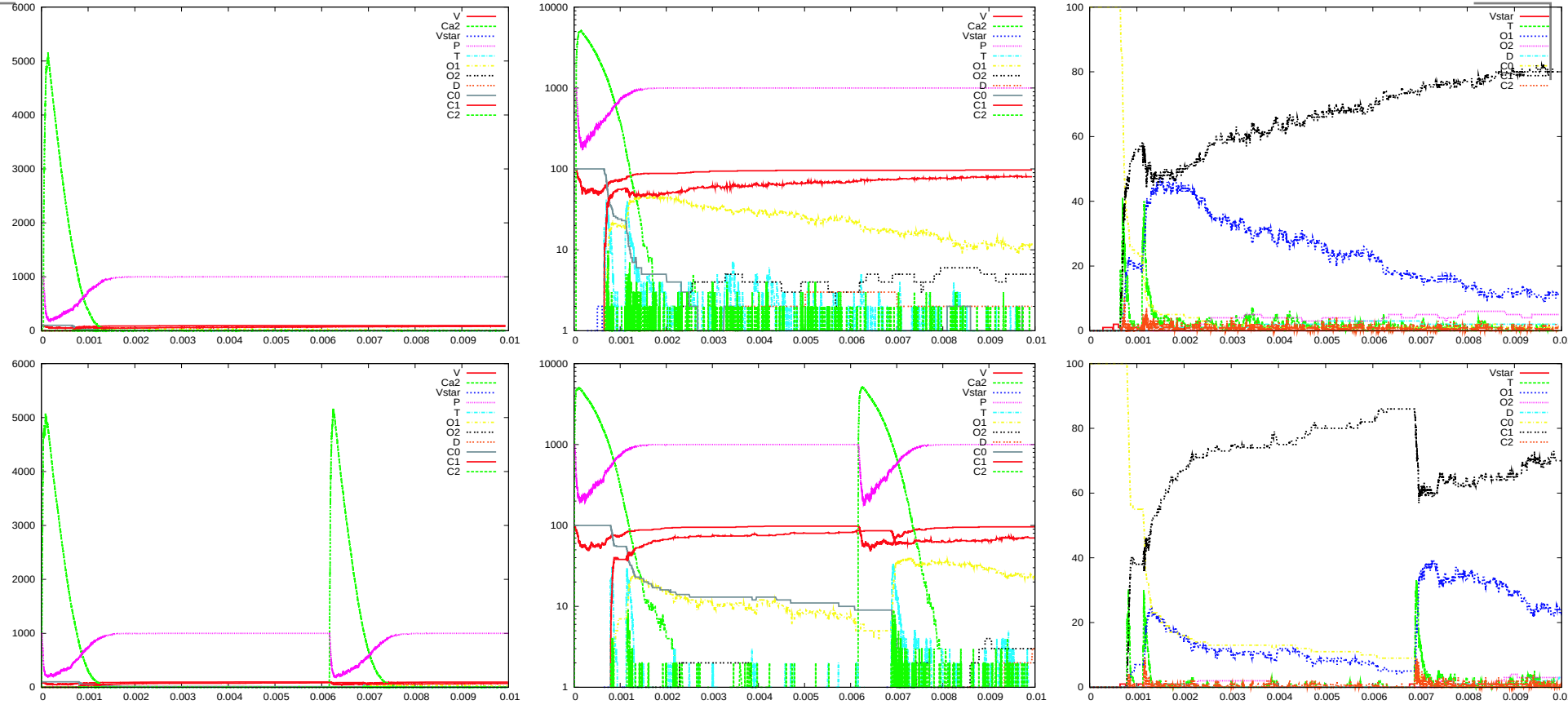


- Post-synaptic stochastic model
- $\ldots \xrightarrow{\gamma} \mathbf{T}$ becomes a wave.

$$C_0 + \bar{\mathbf{T}} \underset{r_u^1}{\overset{r_b}{\rightleftarrows}} C_1 + \bar{\mathbf{T}} \underset{r_u^2}{\overset{rb}{\rightleftarrows}} C_2 \qquad C_2 \underset{r_c^2}{\overset{r_o^2}{\rightleftarrows}} O_2 \qquad C_2 \underset{r_c^1}{\overset{r_o^1}{\rightleftarrows}} O_1 \qquad C_2 \underset{r_r}{\overset{r_d}{\rightleftarrows}} D$$

- interaction volume of $\bar{\mathbf{T}}$ is a surface – diffi cult to estimate.

Results [ongoing - II]: composing all together



vstar() = ... ; tt(1) tt(n:int) = « Wave of t() » t() = « Same defi nition of $\bar{\mathbf{T}}$ »

$$\ldots \xrightarrow{\gamma} \mathbf{T} \qquad \mathbf{T} \to \bar{\mathbf{T}} \qquad C_0 + \bar{\mathbf{T}} \underset{r_u^1}{\overset{r_b}{\rightleftarrows}} C_1 + \bar{\mathbf{T}} \underset{r_u^2}{\overset{rb}{\rightleftarrows}} C_2 \ldots$$

Summing up

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- reconciling qualitative/predictive analysis techniques with quantitative approaches [?]

End of the talk

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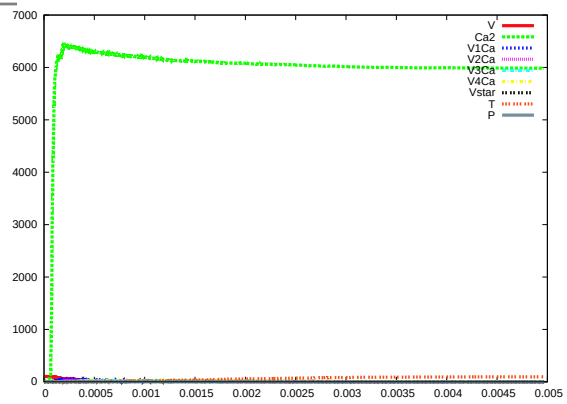
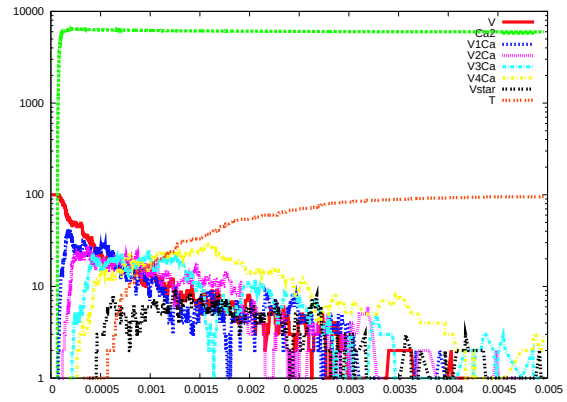
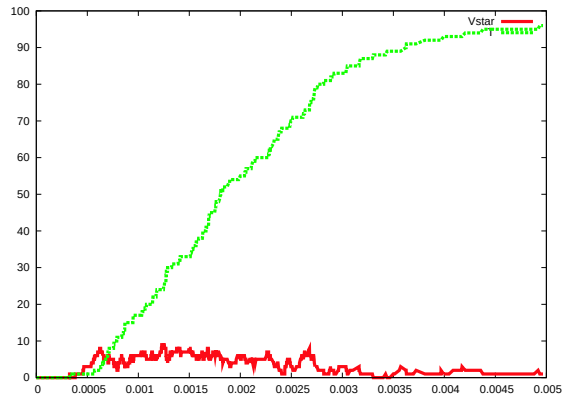
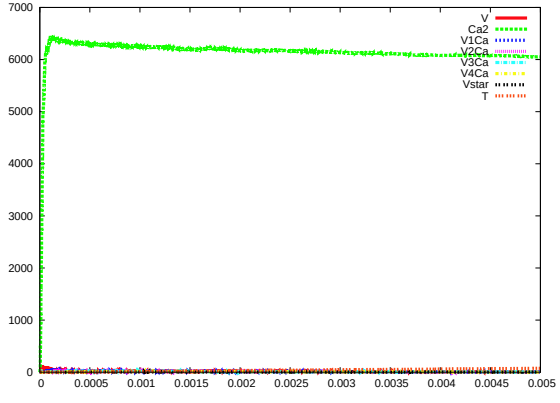
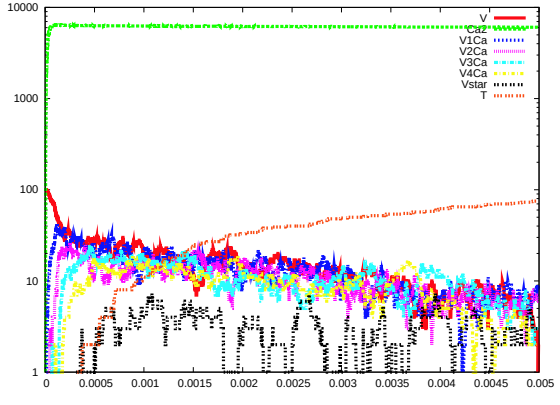
Results

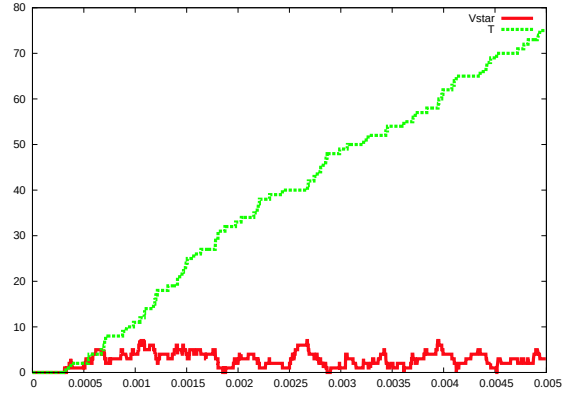








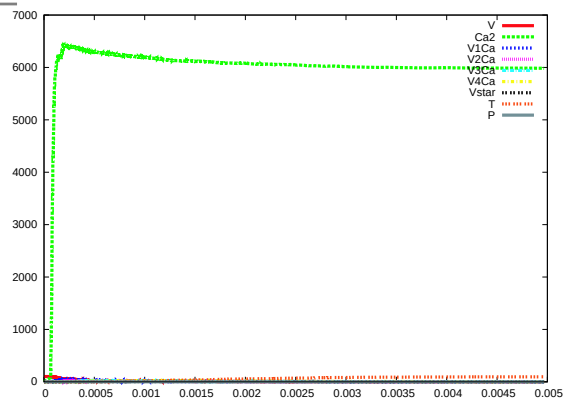


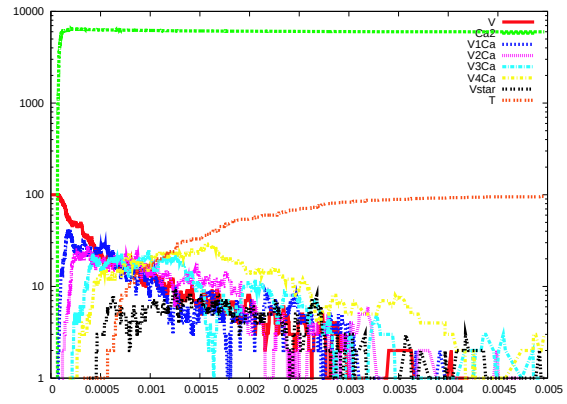


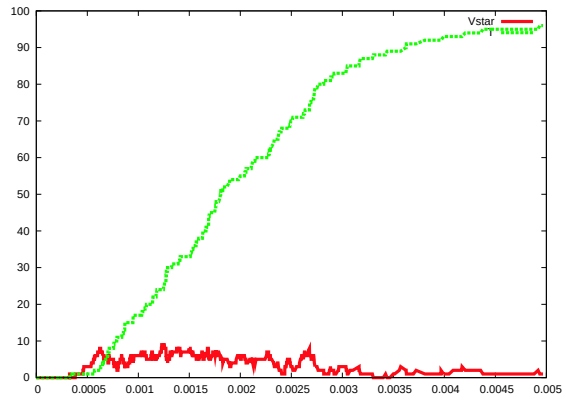
Variation of $b = 0.4$ (was $b = 0.25$): lower and more uniform release rate

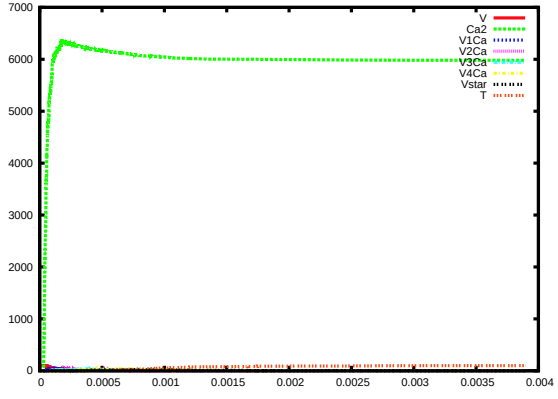
$$Ca_i^{2+} + V \underset{c_{off}\, b^0}{\overset{5c_{on}}{\longleftrightarrow}} V_{Ca_i^{2+}} + Ca_i^{2+} \quad \dots \quad V_{4Ca_i^{2+}} + Ca_i^{2+} \underset{5c_{off}\, b^4}{\overset{c_{on}}{\longleftrightarrow}} \quad \dots$$

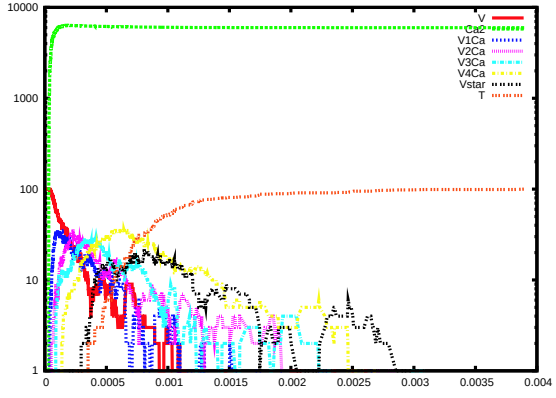
Results

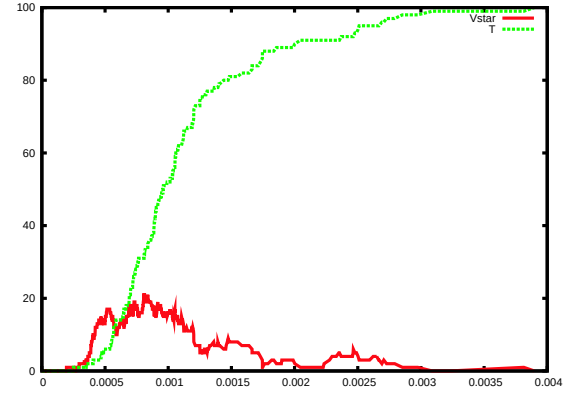












Variation of $c_on = 0.5$ (was $c_on = 0.3$): increase of the release rate

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