Analytical distribution of released synaptic vesicles: Binomial or not ?

Dibyendu Das

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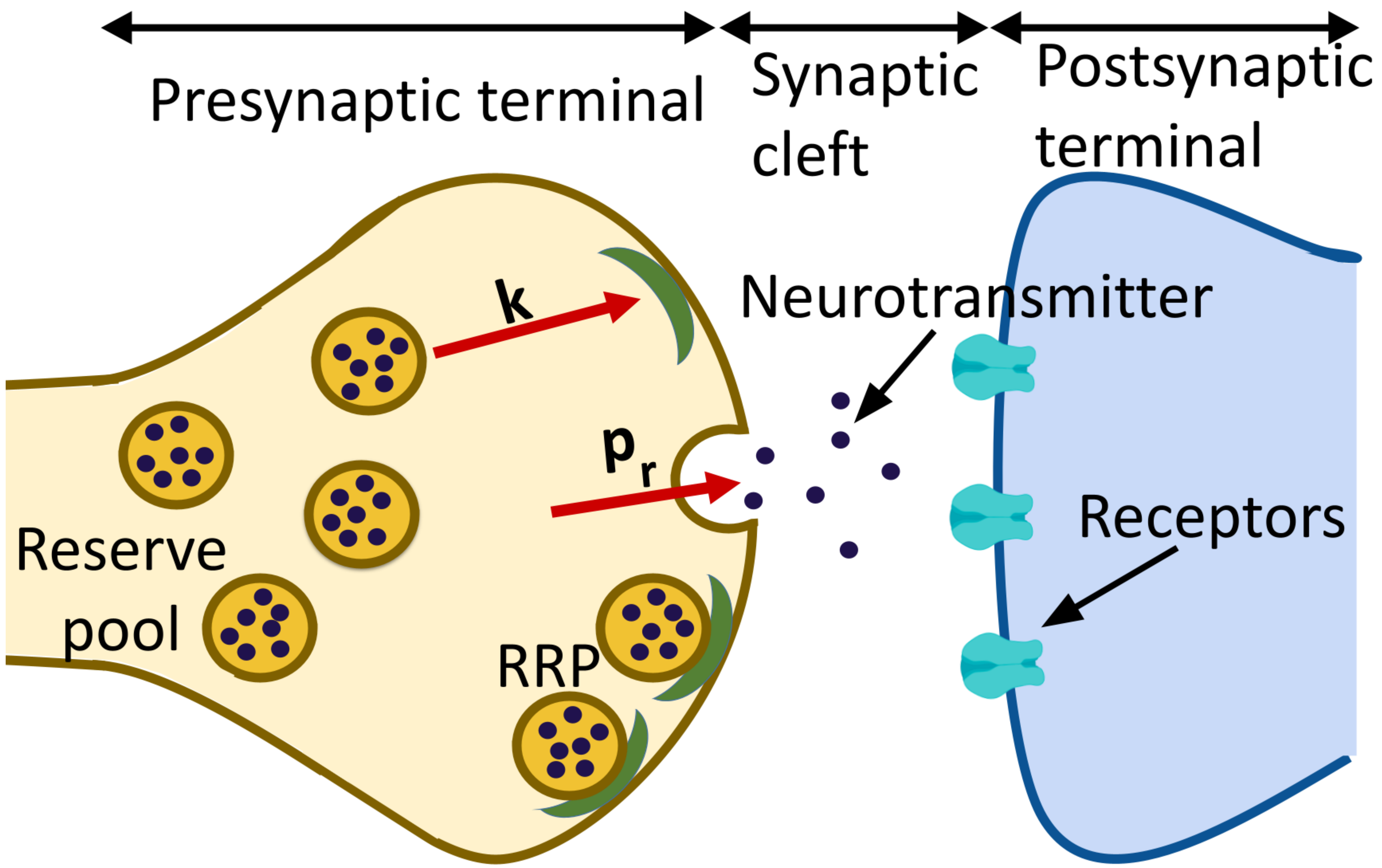

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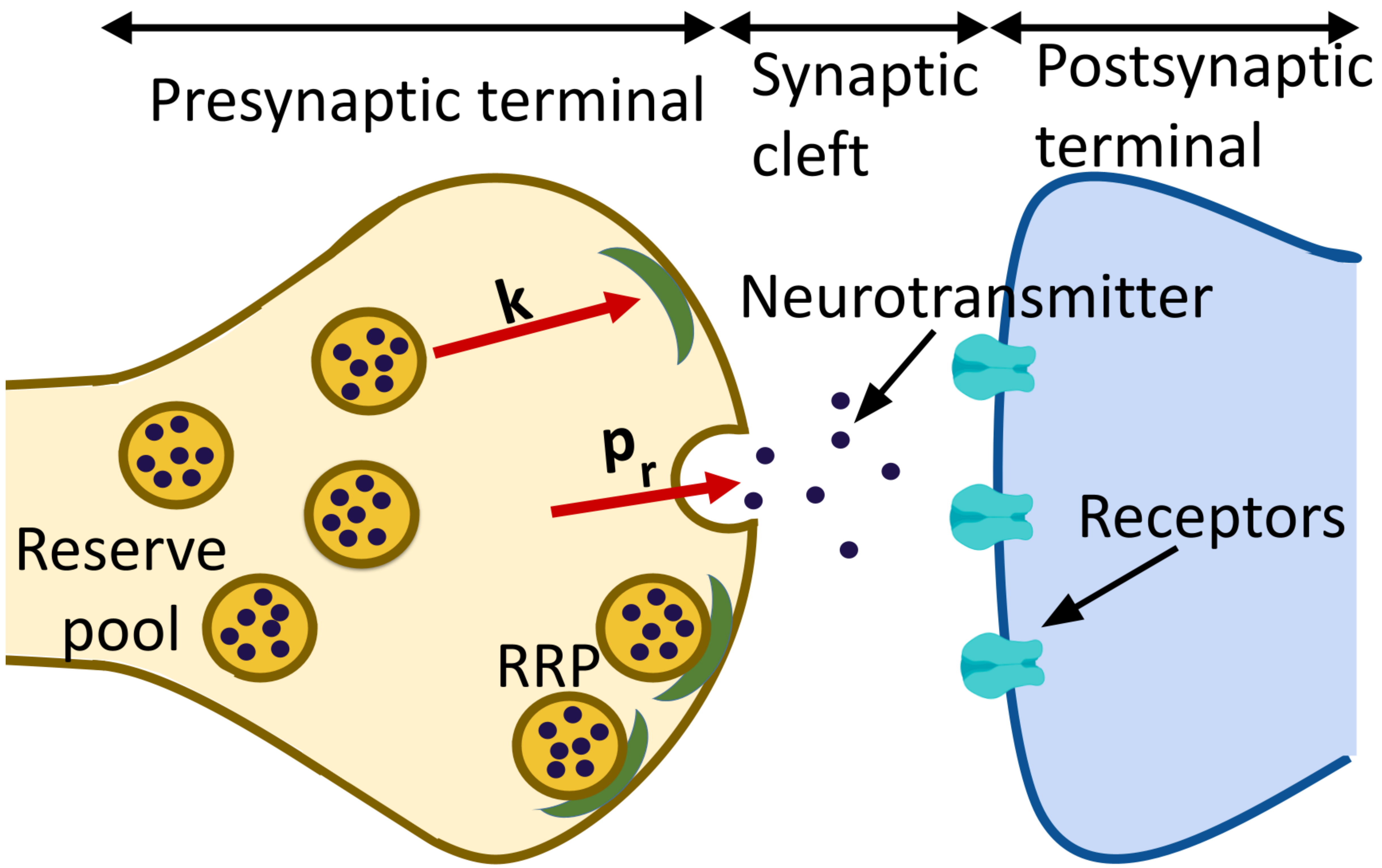

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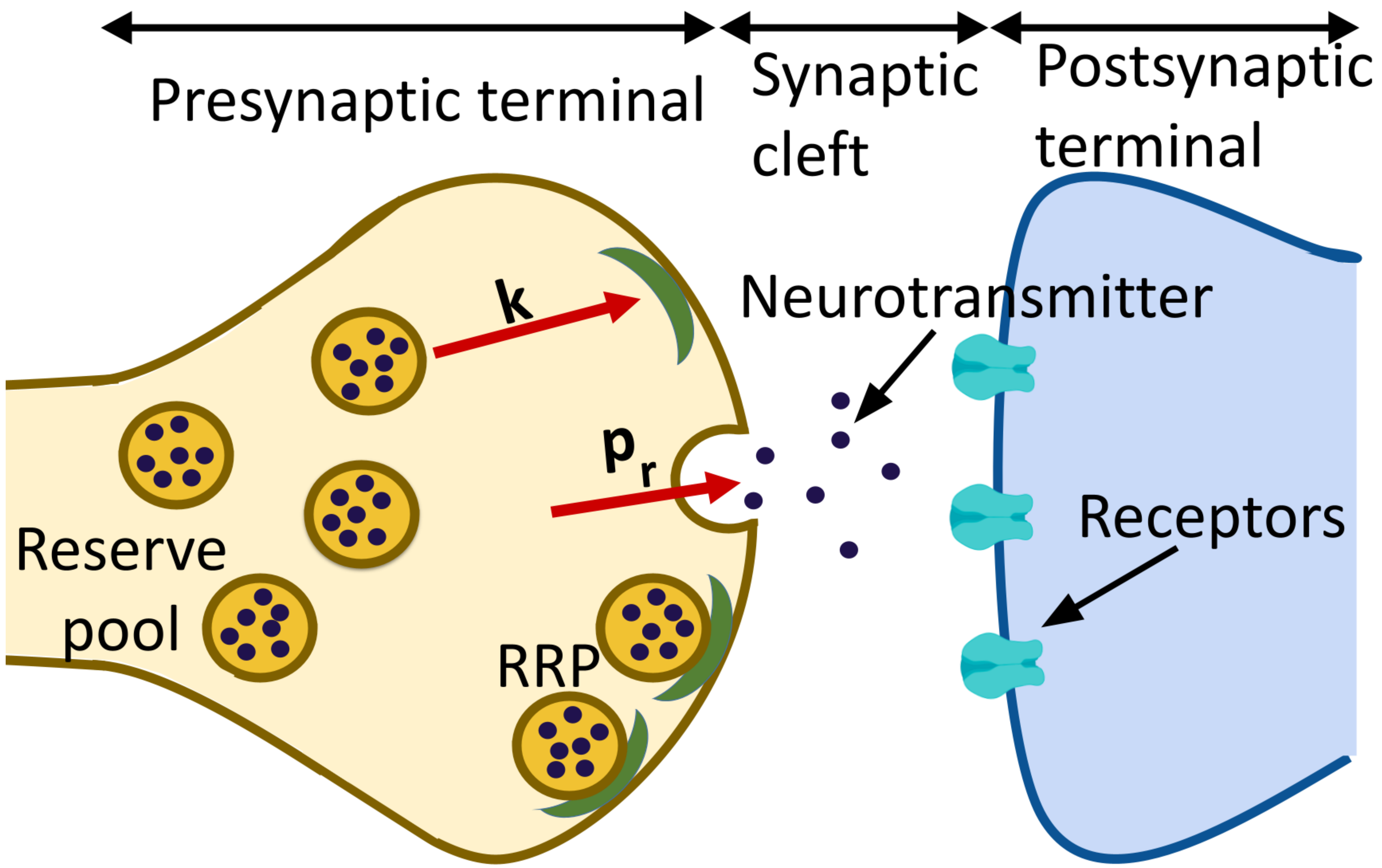

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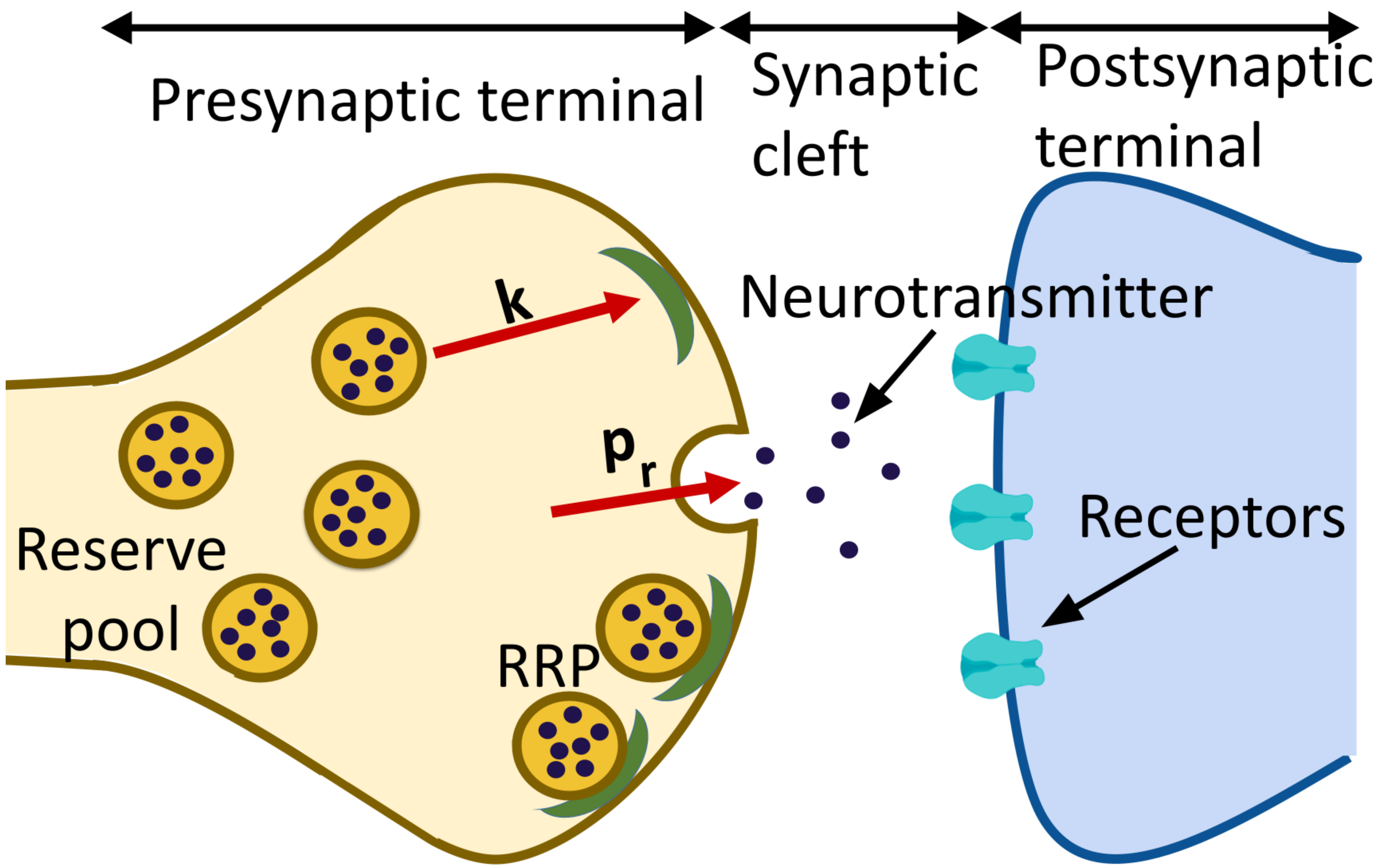

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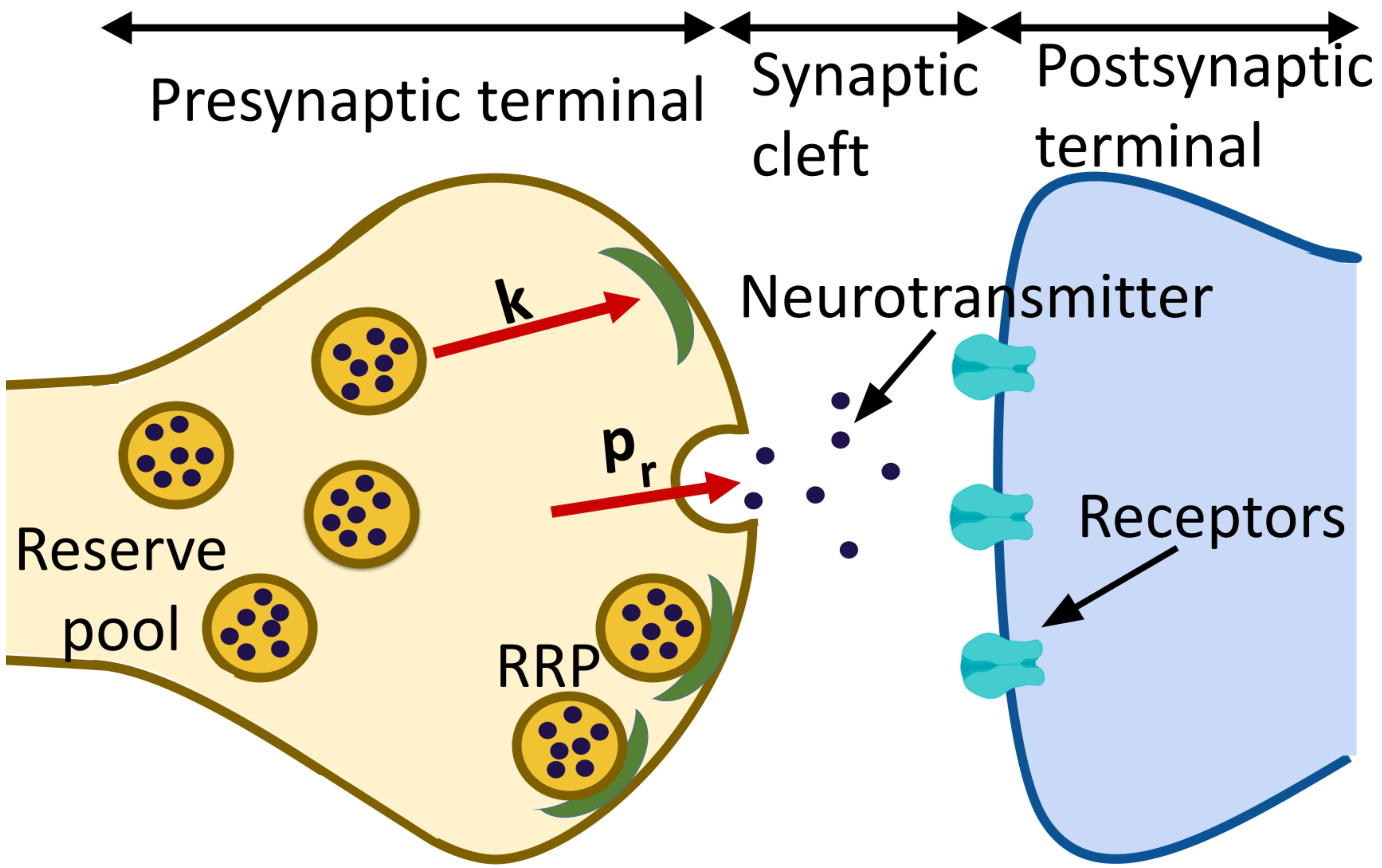

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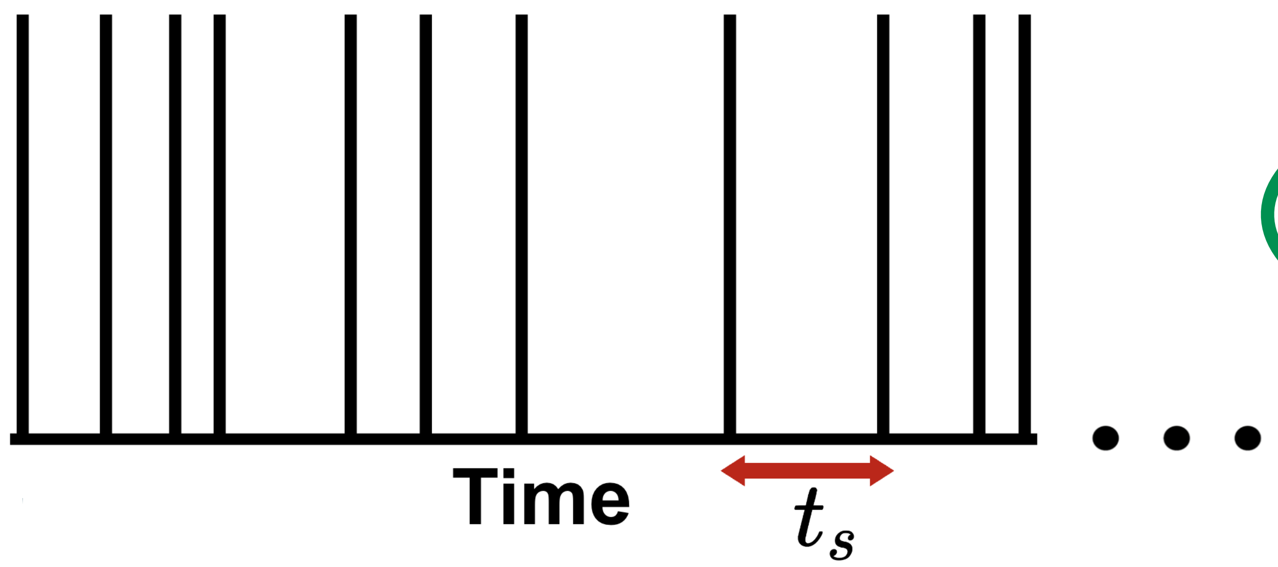
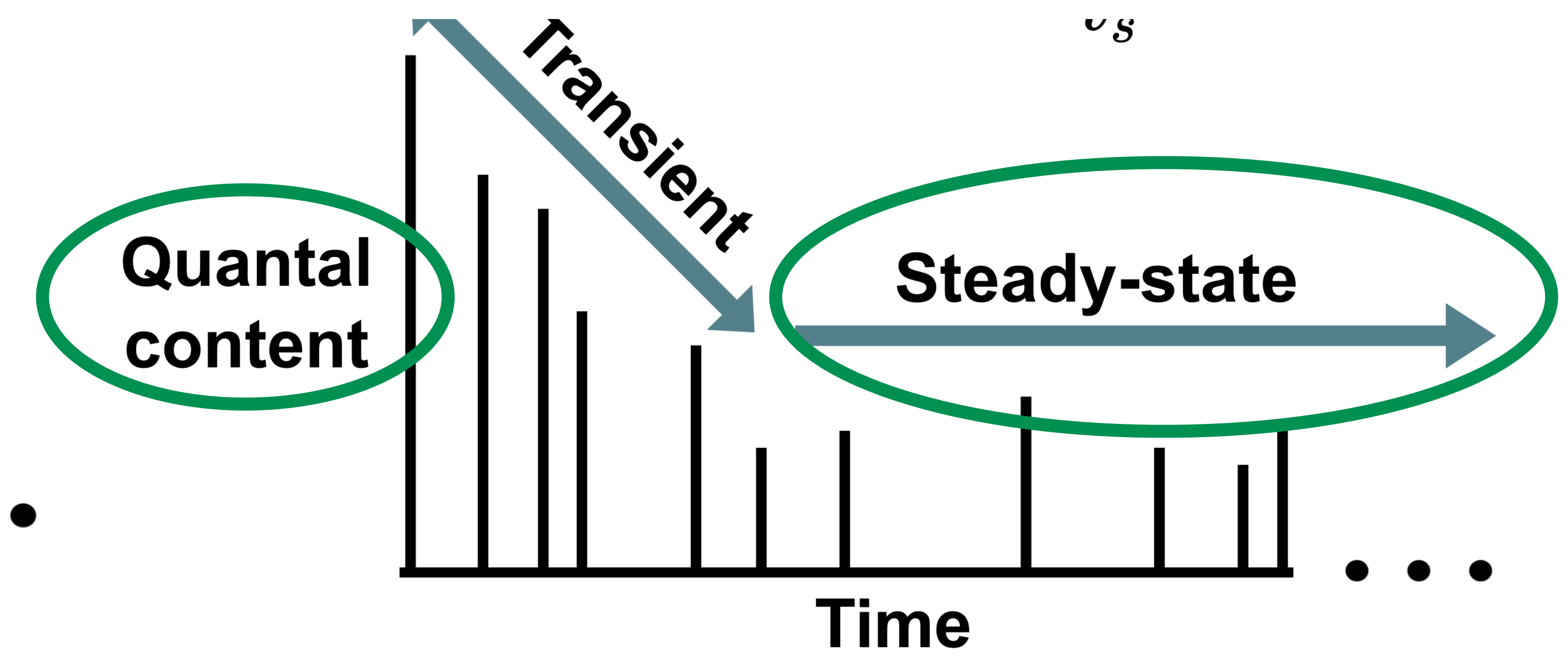
Input AP spikes





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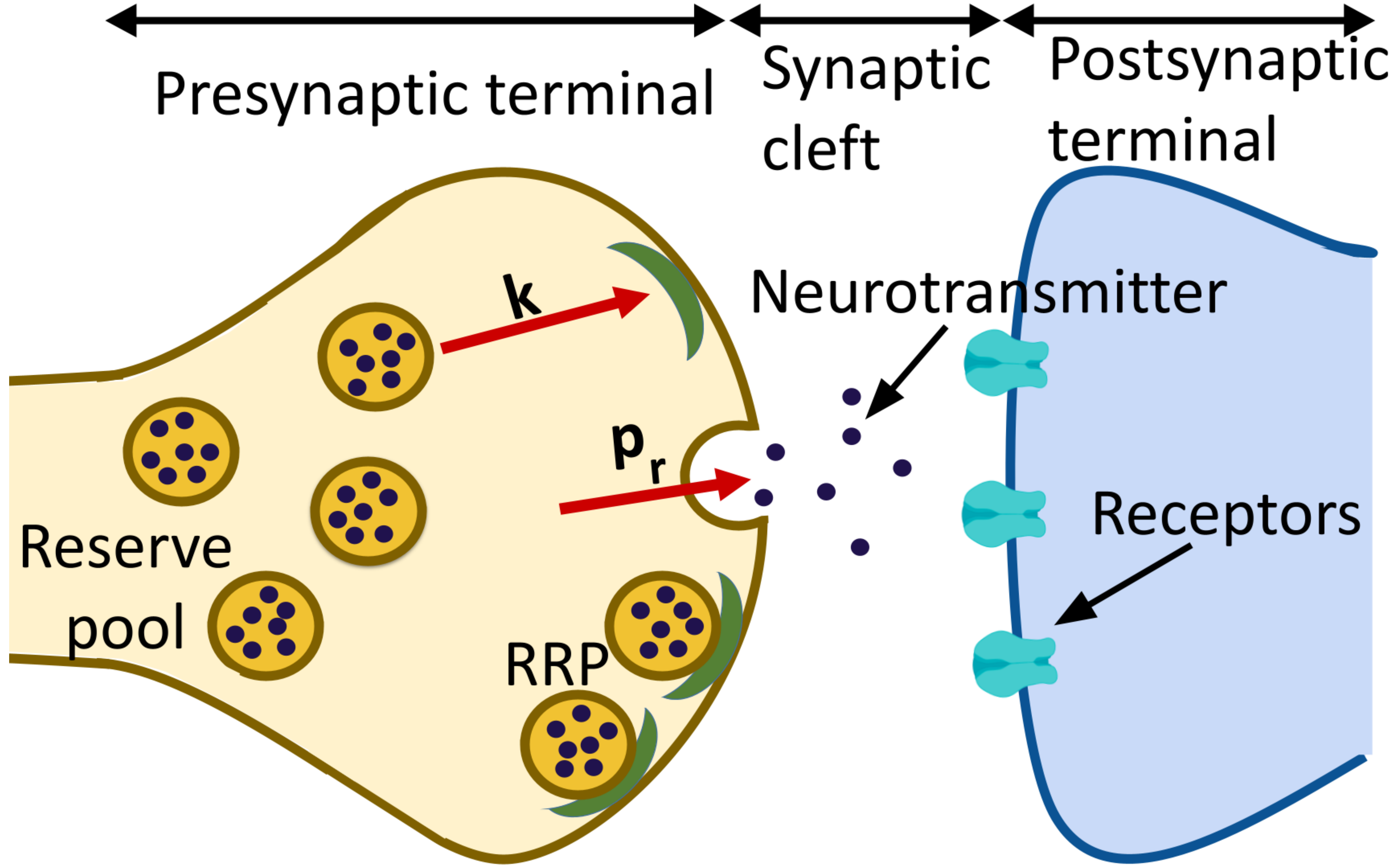

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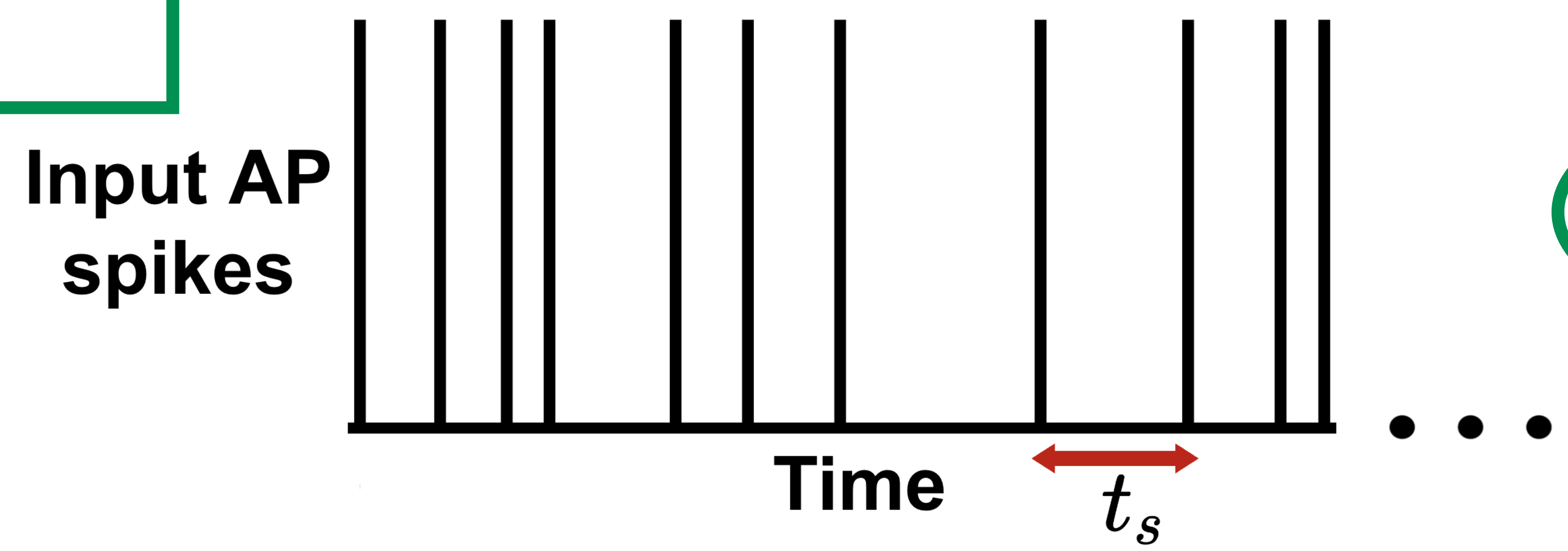

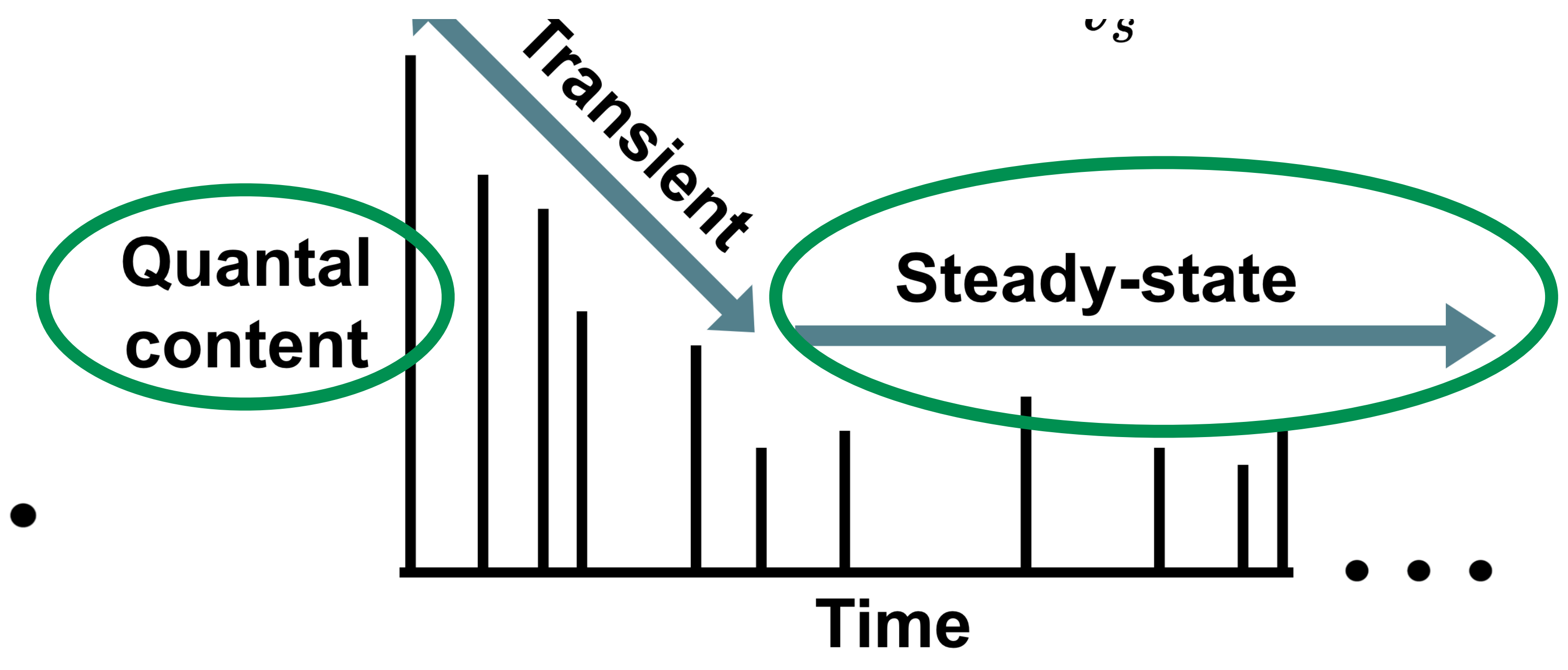

- **A train** of Action potentials (AP) **—> train of released "quantal contents" : What is its statistics?**

Motivation :- Correct averaged distribution of quantal content ? Why even bother?

In the literature, often **ad-hoc Binomial distributions have been used** — *IEEE, New York*, 2019, p 4729; *J. Neurosci.* 36, 4010 (2016); *Neuron* 85, 159 (2015); *J. Neurosci.* 21, 8362 (2001); *Physiol. Rev.* 97, 1403 (2017); *PNAS* 104, 14134 (2007), *PNAS* 113, E378 (2016)

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From Stochastic process perspective —

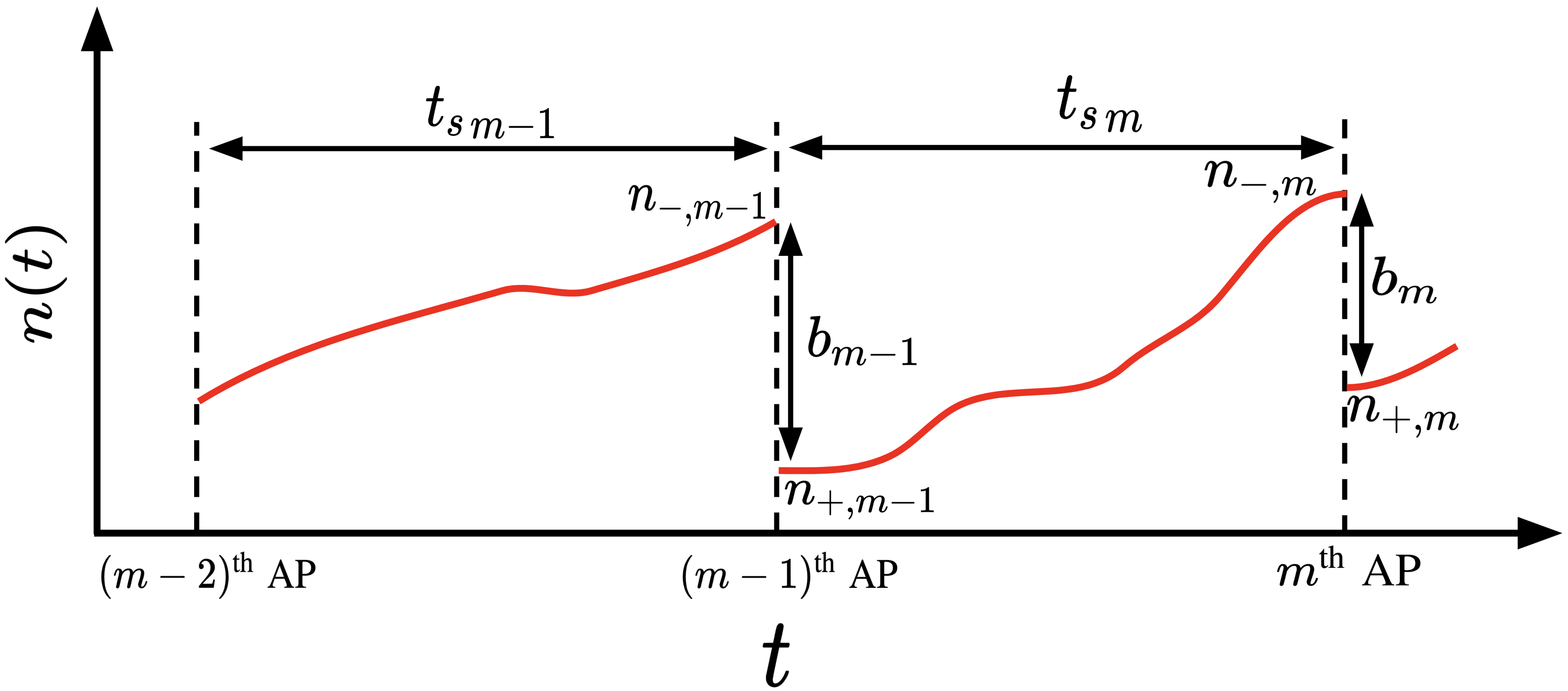
- Is it Binomial or not ?

(Biological) Neuroscience interest:

- Parameters ***p_r* (release probability), *k* (replenishment rate), *M* (maximum docking sites)** **characterize a neuron**. Under conditions of disease these change.

—> These parameters may be inferred from the statistics of quantal content.

History dependence, and the nested nature of the distributions



$$P_-^m(n_{-,m}, t_{sm}) = \sum_{n_{+,m-1}} p(n_{-,m}, t_{sm} | n_{+,m-1}) \times P_+^{m-1}(n_{+,m-1}, t_{sm-1})$$

$$P_+^m(n_{+,m}, t_{sm}) = \sum_{n_{+,m-1}, b_m} B(n_{+,m} + b_m, p_{rt}, b_m) \times p(n_{+,m} + b_m, t_{sm} | n_{+,m-1}) \times P_+^{m-1}(n_{+,m-1}, t_{sm-1})$$

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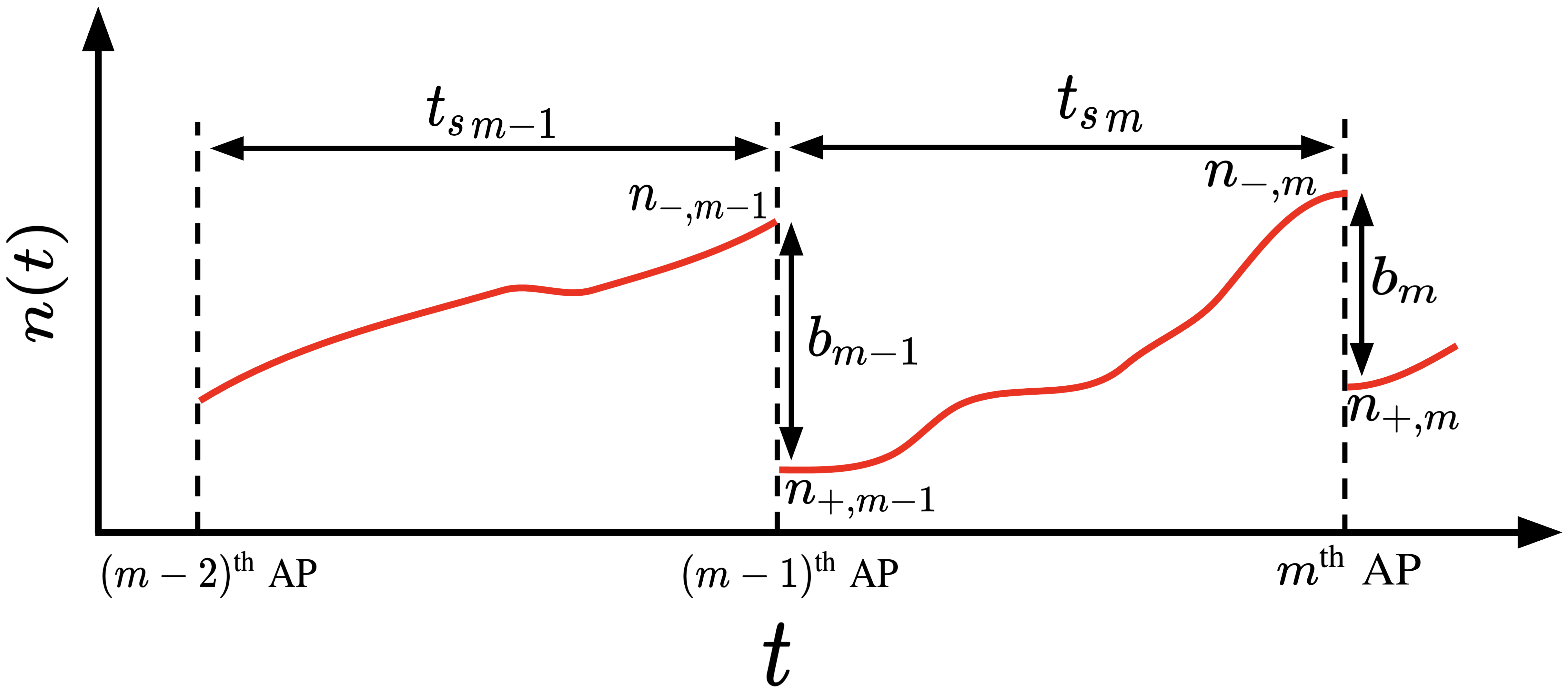

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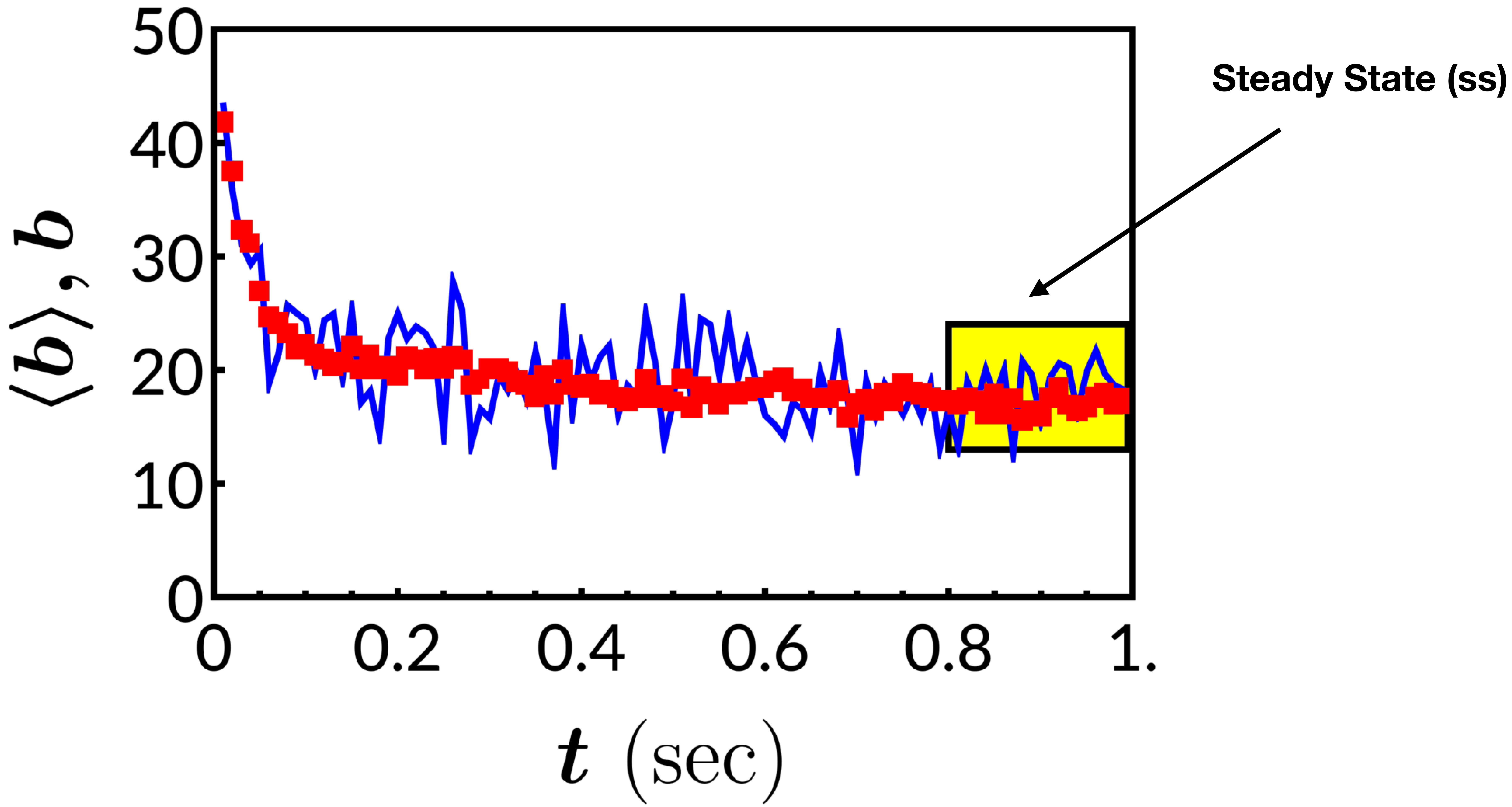
- (Bayesian inference, & left as computational protocols) — *Frontiers in Computational Neuroscience* 10, 116 (2016)

(a) Initial condition? (Memory)   (b) Model? Parameter estimation?   (c) Correlations in { t_{sm} }

Does the Steady State really exist? [Experimental data from our work]



MNTB-LSO synapses from juvenile mice brain:
between 0.8s -1s, steady state may be assumed. [100 Hz AP train.]
We need statistics of the **blue curve** in the boxed region.
Red curve — Average over 20 histories each 1 sec, separated by sufficient rest period.

Steady State and Uncorrelated interspike intervals (ISIs)

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$$\int_0^\infty \int_0^\infty dt_{sm} dt_{sm-1} g_2(t_{sm}, t_{sm-1}) \times P_+^m(n_{+,m}, t_{sm})$$

$$= \int_0^\infty \int_0^\infty dt_{sm} dt_{sm-1} g_2(t_{sm}, t_{sm-1}) \sum_{n_{+,m-1}, b} p(n_{+,m} + b, t_{sm} | n_{+,m-1}) B(n_{+,m} + b, p_r, b) P_+^{m-1}(n_{+,m-1}, t_{sm-1})$$

$$P_+^{ss}(n_+) = \int_0^\infty dt_{sm} g(t_{sm}) P_+^m(n_{+,m}, t_{sm})$$

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(Uncorrelated ISIs)

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(Uncorrelated ISIs)

$$P_+^{ss}(n_+) = \sum_{n'_+,b} \int_0^\infty dt_s g(t_s) B(n_+ + b, p_r, b) \times p(n_+ + b, t_s | n'_+) P_+^{ss}(n'_+)$$

Similarly, $P_-^{ss}(n_-) = \sum_{n'_+} \int_0^\infty dt_s g(t_s) p\left(n_-, t_s | n'_+\right) P_+^{ss}(n'_+)$

$$Q^{ss}(b) = \sum_{n_-=0}^{M} B(n_-, p_r, b) P_-^{ss}(n_-)$$

Thus in the steady state (ss), what are: $P_+^{ss}(n_+), P_-^{ss}(n_-), Q^{ss}(b)?$

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$$P_{-}^{ss}(n_{-}) = \sum_{n'_{+}} \int_{0}^{\infty} dt_s g(t_s) p\left(n_{-}, t_s | n'_{+}\right) P_{+}^{ss}(n'_{+})$$

Binomial

$$P_{+}^{ss}(n_{+}) = \sum_{n'_{+}, b\, M} \int_{0}^{\infty} dt_s g(t_s) B(n_{+} + b, p_r, b) \times p(n_{+} + b, t_s | n'_{+}) P_{+}^{ss}(n'_{+})$$

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Binomial ?

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Binomial ?

Next: How to get $p(n_-, t_s | n'_+)$?

M —> Maximum number of docking sites
n(t) —> Number of docked sites
M - n(t) —> Number of empty sites

$$\frac{\partial p(n, t | n'_+)}{\partial t} = k\left(M - (n-1)\right) p(n-1, t | n'_+) - k(M-n) p(n, t | n'_+)$$

$$p(n, t \mid n'_+) = \binom{M - n'_+}{n - n'_+} \left(1 - e^{-kt}\right)^{n - n'_+} e^{-[k(M-n)]t}$$

Generating functions of the 3 distributions

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$$F_-(q) = \sum_{n_-=0}^{\infty} q^{n_-} P_-^{ss}(n_-) = F_+\left(\frac{q-p_r}{1-p_r}\right) \quad \& \quad F_b(q) = \sum_{b=0}^{\infty} q^b Q^{ss}(b) = F_+\left(\frac{p_r(q-1)}{1-p_r}+1\right)$$

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$$F_+(q) = \sum_{n=0}^{\infty} \frac{(q-1)^n}{n!} F_+^{(n)}(1)$$

$$F_+^{(n)}(1) = \binom{M}{n} n! \frac{(1-p_r)^n}{1-(1-p_r)^n L_n}\left[\phi_{n,0} + \sum_{\{S_{(n-1)}\}} \frac{(1-p_r)^{\sum_i m_i}\phi_{n,m_z}\phi_{m_z,m_{z-1}}\cdots\phi_{m_1,0}}{\prod_i (1-(1-p_r)^{m_i}L_{m_i})}\right]$$

$$\phi_{n,m} = \binom{n}{m}\int_0^{\infty} dt_s g(t_s) e^{-nkt_s}(e^{kt_s}-1)^{n-m} \qquad L_n = \int_0^{\infty} dt_s g(t_s) e^{-nkt_s}$$

$$S_{(n-1)} = (m_z, m_{z-1}, \cdots, m_1); \quad 1 \le z \le (n-1); \quad m_i \in \{1, 2, \cdots, n-1\}$$

Exact distribution of “quantal content” (b) & cumulants

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- In general the distribution need NOT be Binomial !
- Is it useful in practice ? Can this clumsy looking expression be simplified ?

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- In general the distribution need NOT be Binomial !
- Is it useful in practice ? Can this clumsy looking expression be simplified ?
- Moments are useful to estimate the (ii) synaptic parameters M, p_r, and k

Mean:

$$\langle b \rangle = \frac{M p_r \phi_{1,0}}{1-(1-p_r)L_1}$$

Coefficient of variation:

$$CV^2 = \frac{\langle b^2 \rangle - \langle b \rangle^2}{\langle b \rangle^2} = \frac{\phi_{1,0} + p_r L_1}{M \phi_{1,0}} \left[\frac{(M-1)}{1-(1-p_r)^2 L_2} \left[\phi_{2,0} \left(1 + \frac{p_r L_1}{\phi_{1,0}} \right) + (1-p_r)\phi_{2,1} \right] + \frac{1}{p_r} \right] - 1$$

Special case 1: Constant ISI “T” — most often used by experimentalists

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$$g(t_s) = \delta(t_s - T)$$

$$\phi_{n,m} = \binom{n}{m} e^{-nkT}(e^{kT} - 1)^{n-m}, \qquad L_n = e^{-nkT}$$

We prove an identity by induction:

$$1 + \sum_{\{S_{(n-1)}\}} \binom{n}{m_z}\binom{m_z}{m_{z-1}} \cdots \binom{m_2}{m_1} \prod_i \frac{x^{m_i}}{(1 - x^{m_i})} = \frac{1 - x^n}{(1 - x)^n}$$

$$Q^{ss}(b) = \binom{M}{b} (p_{rb})^b (1 - p_{rb})^{M-b} = B(M, p_{rb}, b)$$

- **Surprise: A Binomial indeed, but with** $p_{rb} = \dfrac{(1 - e^{-kT})p_r}{1 - (1 - p_r)e^{-kT}}$

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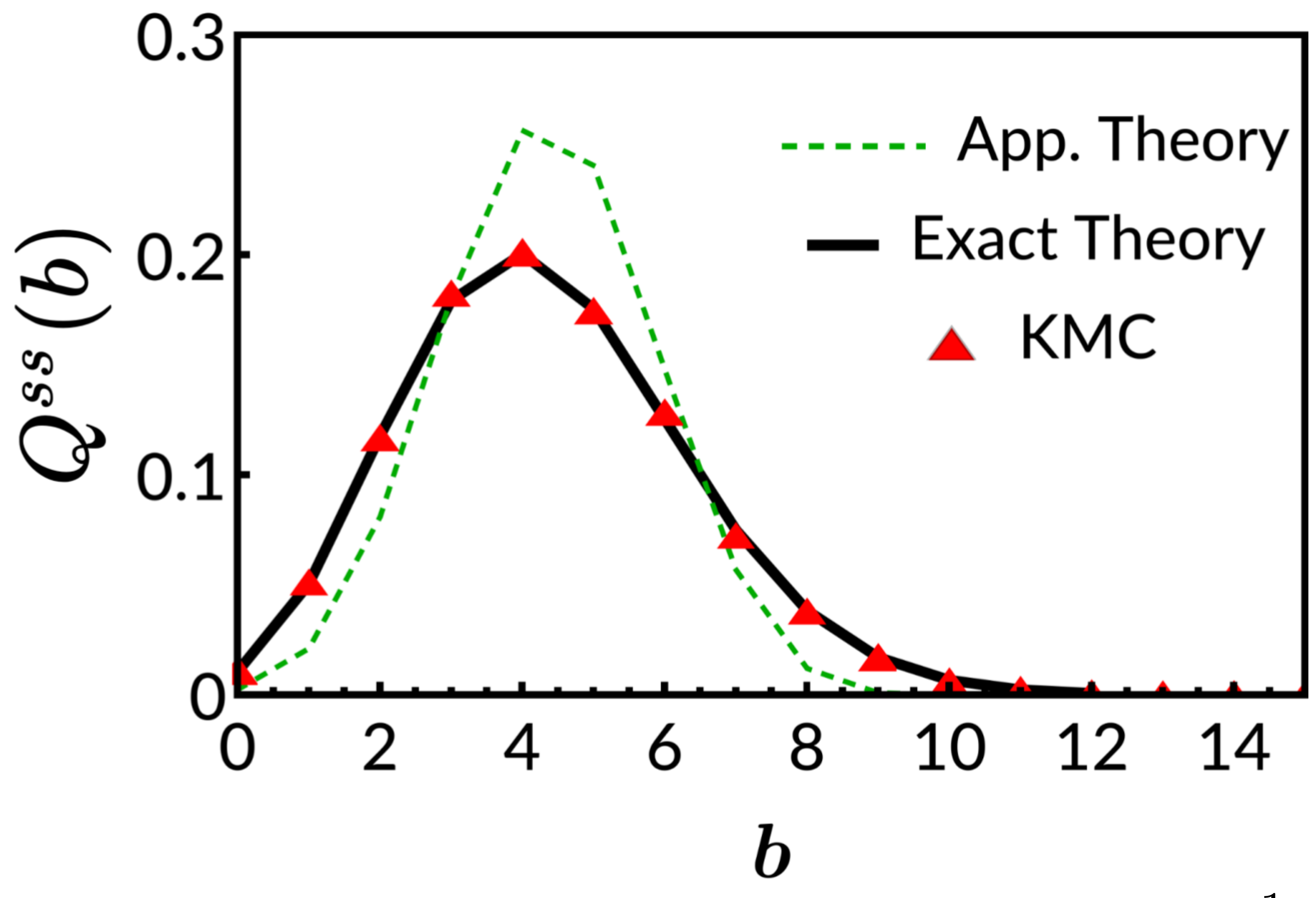

$T = 0.05s, M = 50, p_r = 0.5, k = 2s^{-1}$

- **Surprise: A Binomial indeed, but with** $p_{rb} = \dfrac{(1-e^{-kT})p_r}{1-(1-p_r)e^{-kT}}$

Earlier papers often used an ad-hoc Binomial: $B(\langle n_- \rangle, p_r, b)$

Exact mean: $M p_{rb} = \langle n_- \rangle p_r$

Exact variance: $M p_{rb}(1-p_{rb}) \neq \langle n_- \rangle p_r (1-p_r)$

- ***k* and *p_r* don’t appear separately but jointly in *p_{rb}* (Hence parameter estimation is challenging)**

Constant ISI “T” : Comparison with experiments

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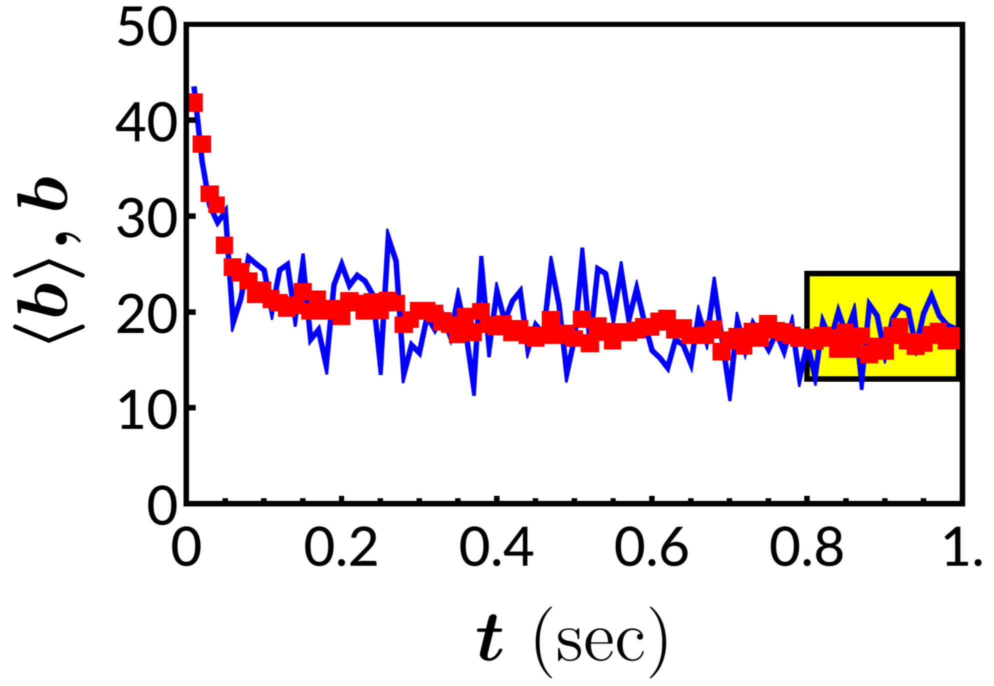
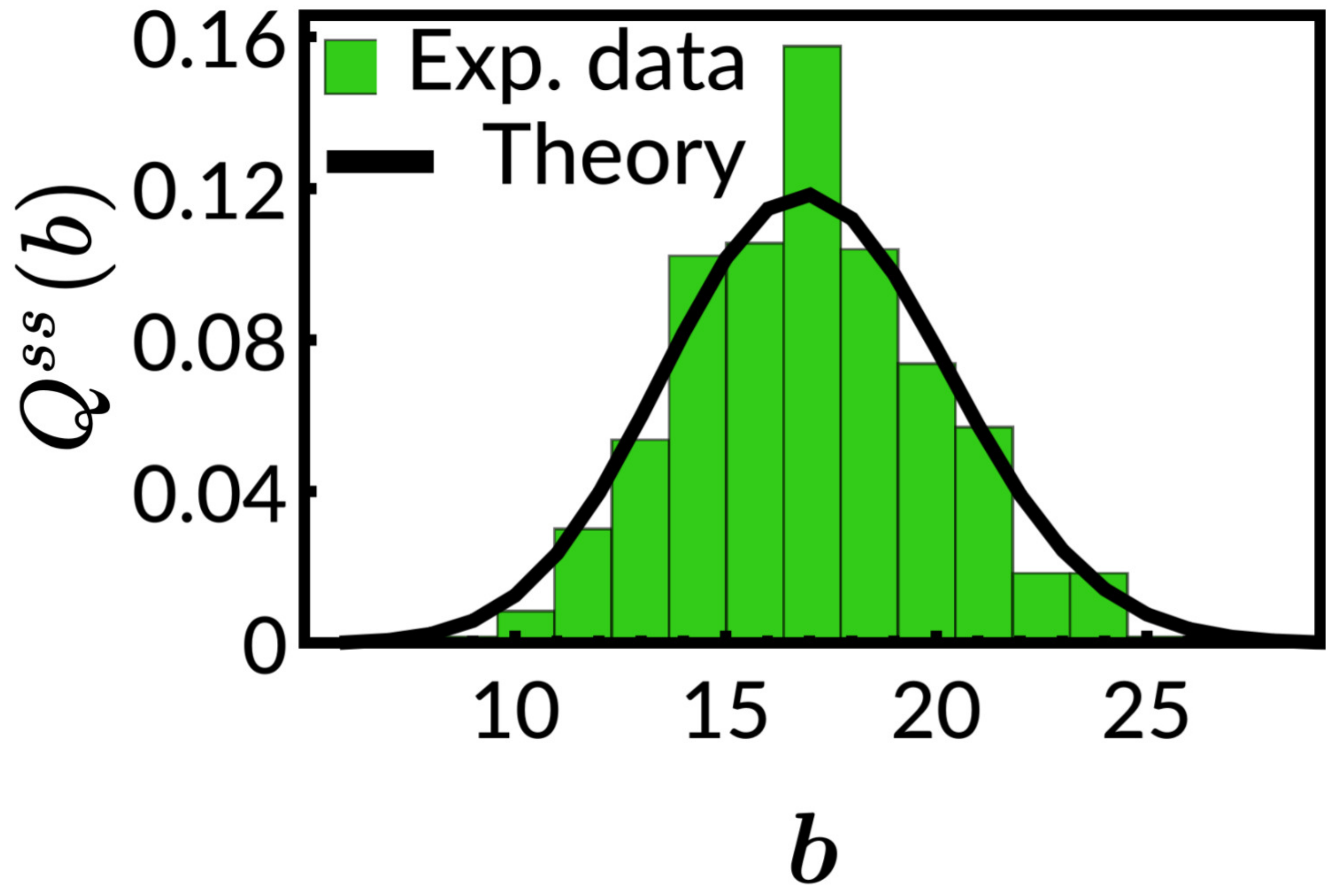
MNTB-LSO synapses from juvenile mice brain:
between 0.8s -1s, over 20 histories (400 sample points)





– First AP (b_0) distribution: $B(M, p_{r0}, b_0)$,
match experiment mean & variance of b_0 and get M

– Match experimental $\langle b \rangle = M p_{rb}$ (Analytical mean), get p_{rb}

Kullback-Leibler divergence $= \sum_b Q^{ss}(b) \ln(Q^{ss}(b)/Q^{ex}(b)) = \mathbf{0.034}$

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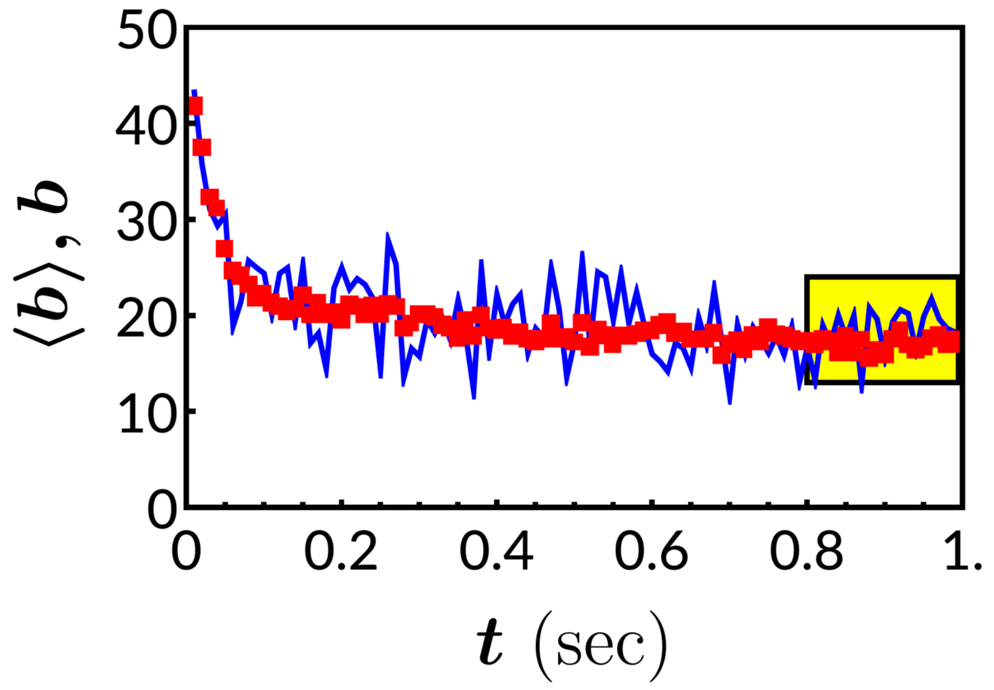

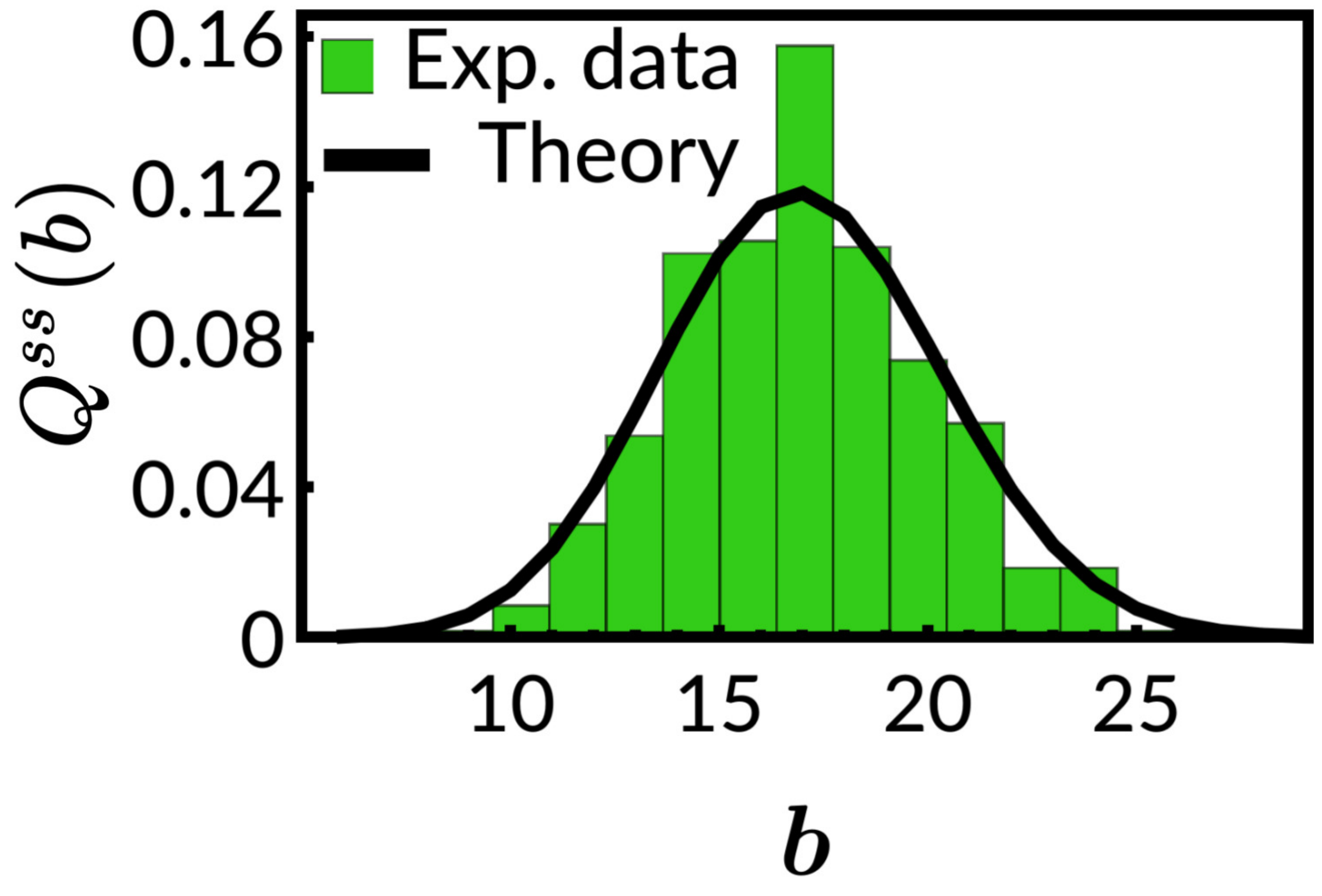

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Published data to parameter estimation:

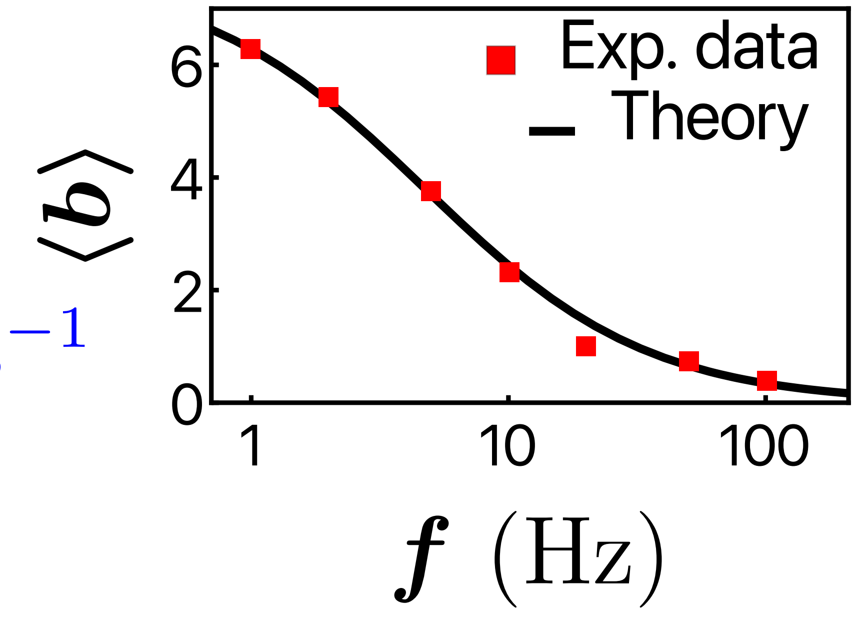
The Journal of Physiology 595, 839 (2017)

$$\langle b \rangle = M p_{rb} = M \frac{(1 - e^{-k/f}) p_r}{1 - (1 - p_r) e^{-k/f}}$$

kM and p_r were reported experimentally.

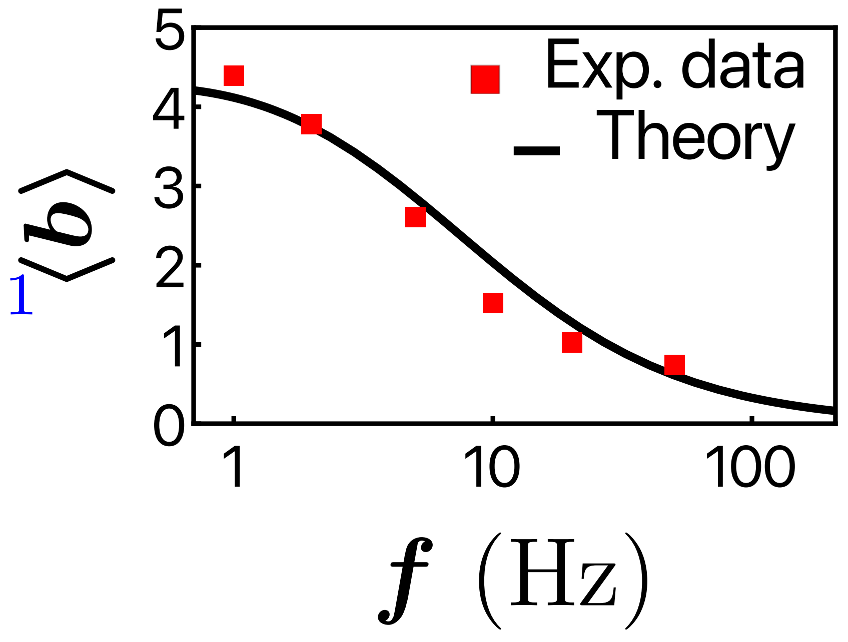
Hippocampal CA3 - CA1

Fitted: $M = 688,\ k = 0.0523\ \mathrm{s}^{-1}$



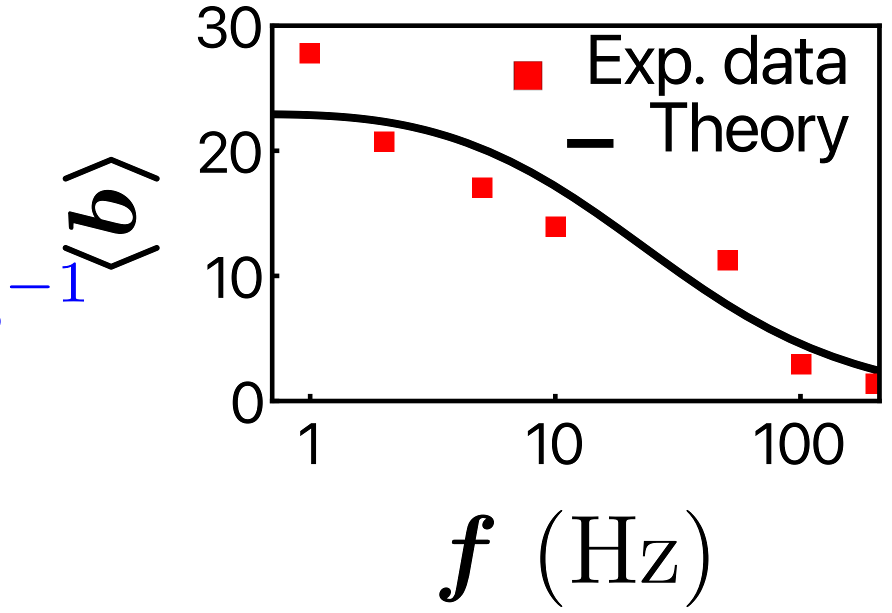
Hippocampal EC - DG

Fitted: $M = 17,\ k = 2.058\ \mathrm{s}^{-1}$



Auditory MNTB - LSO

Fitted: $M = 147,\ k = 3.816\ \mathrm{s}^{-1}$



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Special case 2: Exponentially distributed ISIs

Relevant for visual neurons:

— Journal of Neuroscience 18, 3870 (1998)
— Neuron 62, 426 (2009)

Special case 2: Exponentially distributed ISIs

Relevant for visual neurons:

— Journal of Neuroscience 18, 3870 (1998)
— Neuron 62, 426 (2009)

$$g(t_s) = f_0 e^{-f_0 t_s}$$

$$\phi_{n,m} = \binom{n}{m} \frac{f_0}{k} \frac{\Gamma(-m+n+1)\Gamma\left(\frac{f_0}{k}+m\right)}{\Gamma\left(\frac{f_0}{k}+n+1\right)}, \quad L_n = \frac{f_0}{f_0+nk}$$

We prove an identity by induction:

$$1 + \sum_{\{S_{(n-1)}\}} \prod_i \frac{f(m_i)}{1-f(m_i)} = \frac{1}{\prod_{i=1}^{n-1}(1-f(i))}$$

$$Q^{ss}(b) = \sum_{n=0}^{\infty} (-1)^{n-b} \binom{n}{b} \binom{M}{n} \frac{n!(kp_r)^n}{\prod_{i=1}^{n}(f_0 + ki - (1-p_r)^i f_0)}$$

- **Not a Binomial !**

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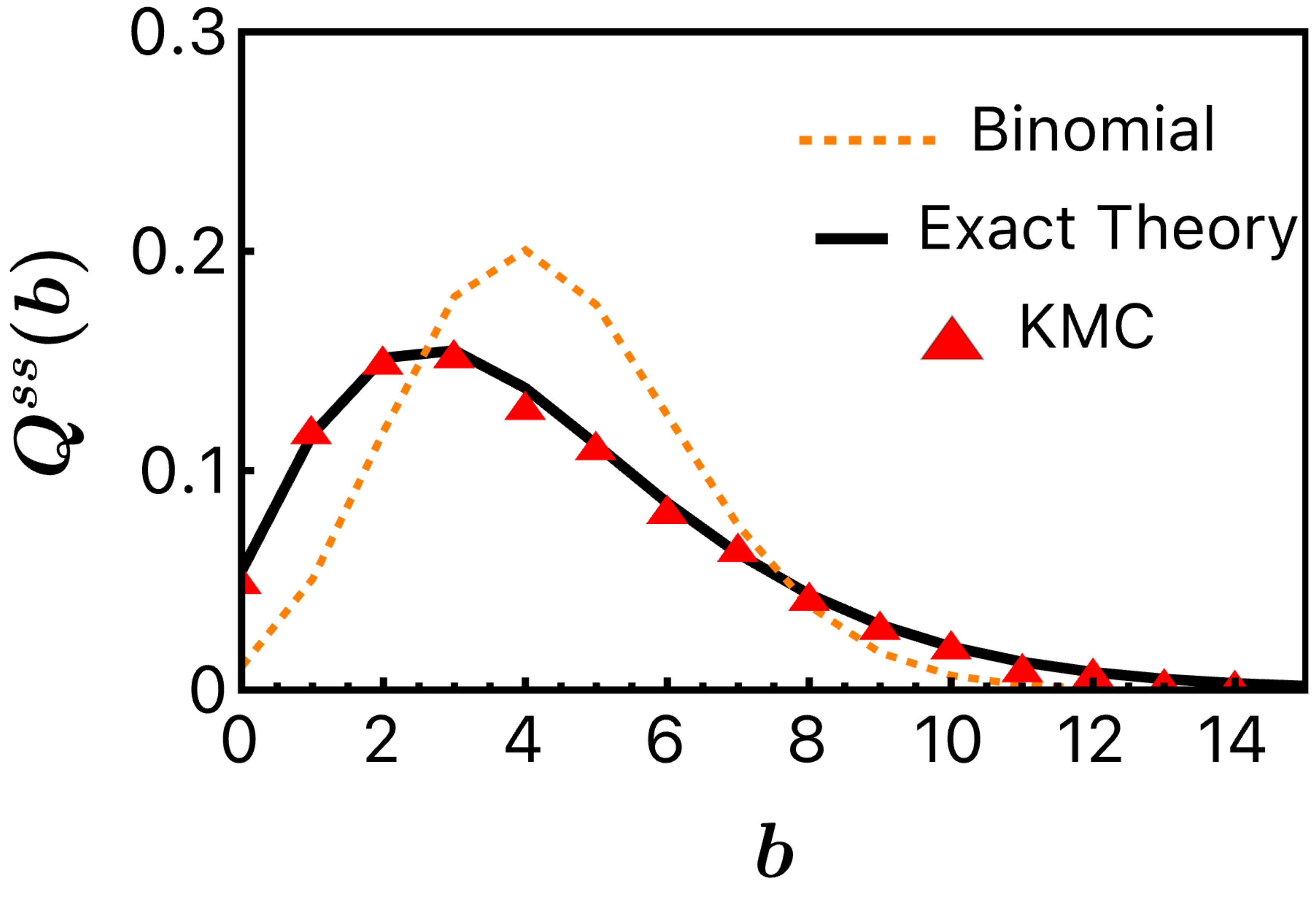
Exact mean: $\langle b \rangle = \frac{Mkp_r}{k+f_0 p_r}$

Exact CV²: $\frac{\sigma^2}{\langle b \rangle^2} = \frac{1}{M}\left(\frac{2(M-1)(k+f_0 p_r)}{2k+f_0 p_r(2-p_r)} + \frac{f_0}{k} - M + \frac{1}{p_r}\right)$

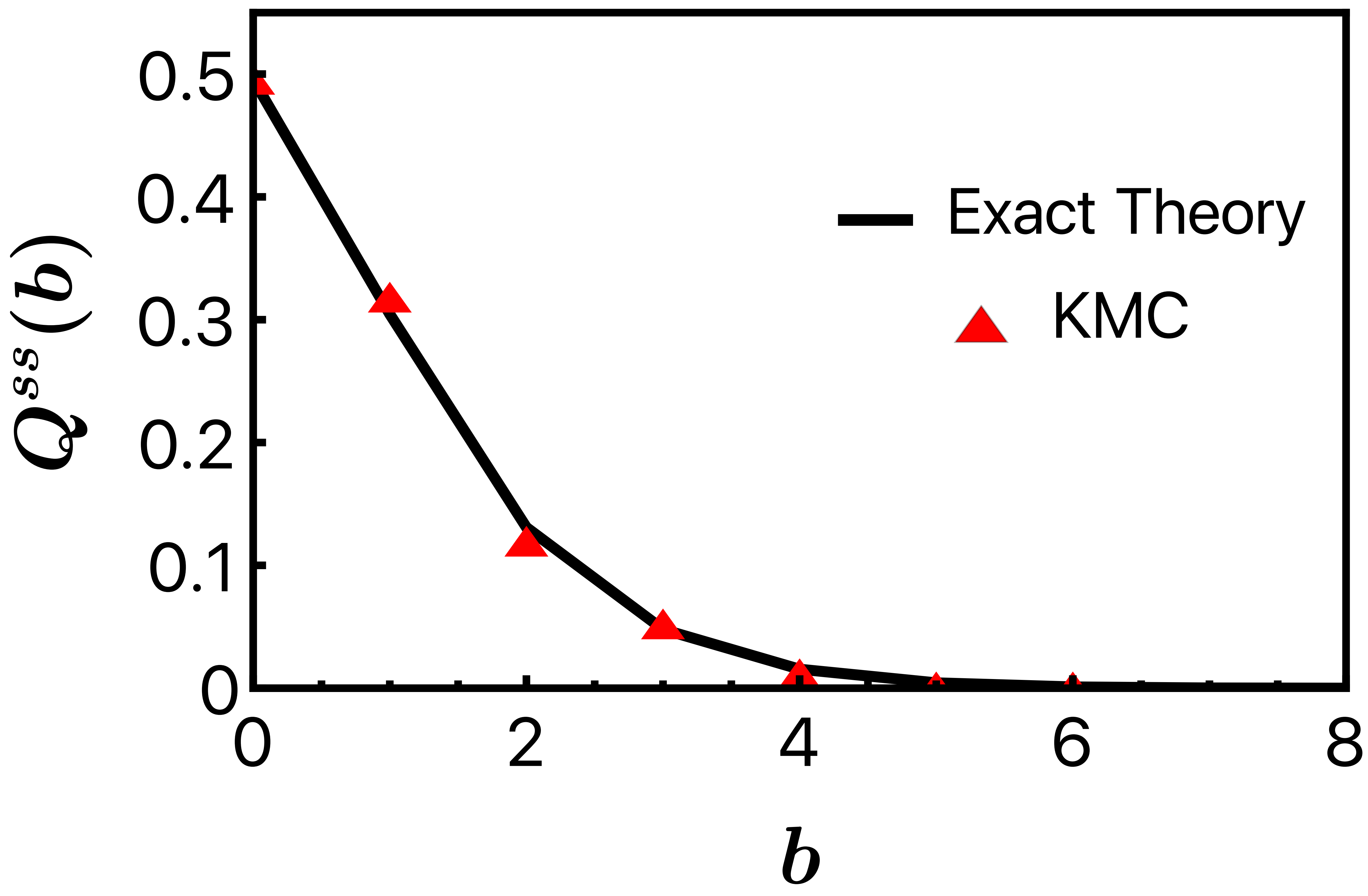


$f_0 = 20Hz, M = 50, p_r = 0.5, k = 2s^{-1}$

- ***k* and *p_r* appear separately in the two moments (Hence parameter estimation is possible using moments)**

Another special case: A Gamma distribution

$$g(t_s) = \frac{\sqrt{f}}{\sqrt{2\pi}} {t_s}^{-\frac{1}{2}} e^{-\frac{f t_s}{2}}$$



$M = 10,\ p_r = 0.5,\ k = 2,\ \text{and}\ f = 20\ Hz.$

Correlated ISIs — Monte Carlo

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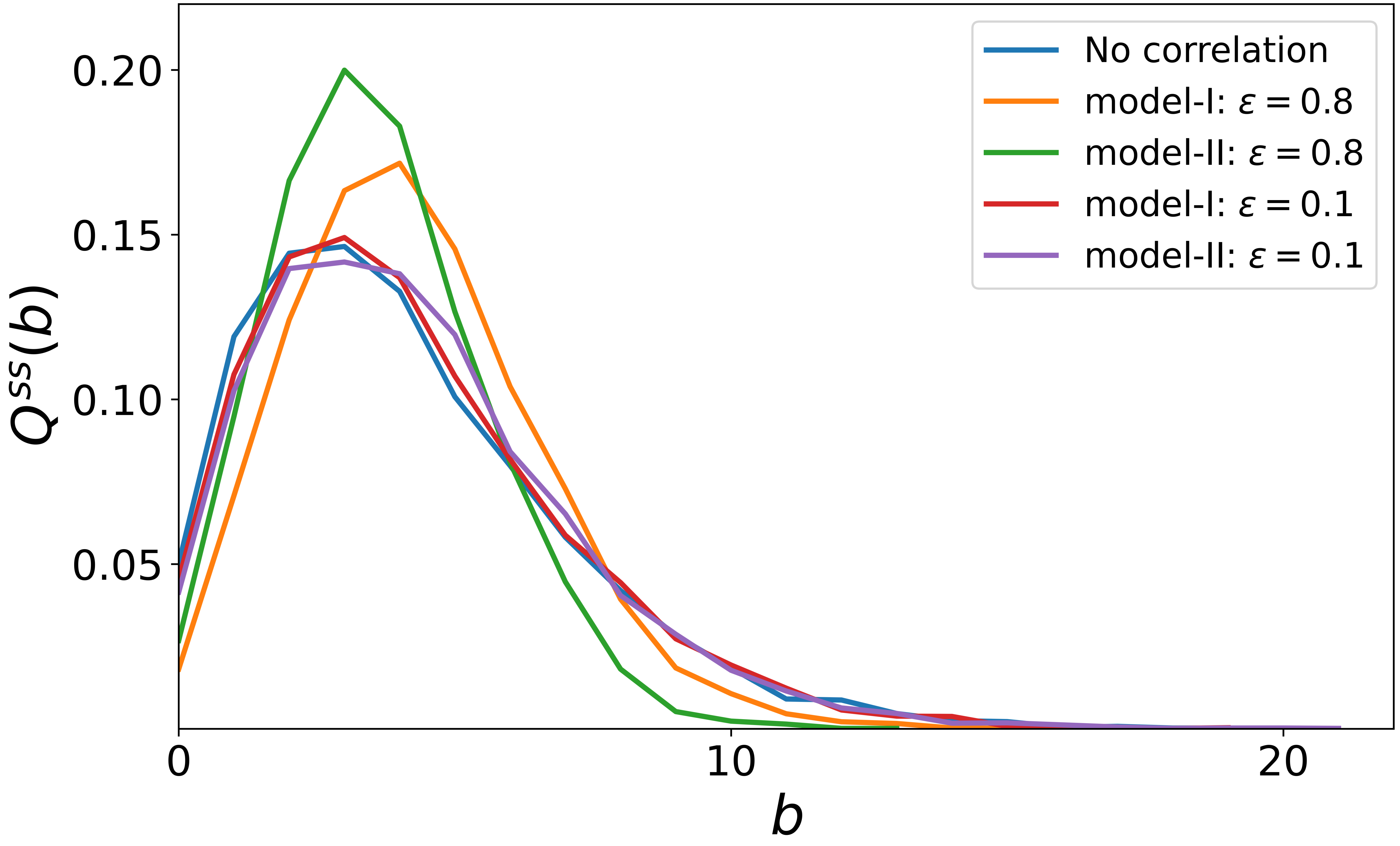
How correlations cause deviations from the pedicted $Q^{ss}(b)$



Model-I: $t_{sm} = (1-\epsilon)(ran)_m + \epsilon t_{sm-1}$;

Model-II: $t_{s,m} = (1-\epsilon)(ran)_m + \epsilon \frac{1}{(m-1)} \sum_{i=1}^{m-1} t_{si}$

. $(ran)_m$ Poisson train

To relate more closely to Biology — it is complicated:

(based on years of electrophysiological and micro-structural studies)— *Annu Rev Neurosci* 26, 701 (2003); *Nat Rev Neurosci* 6, 57 (2005); *Cold Spring Harb Pers Biol* 4, a013680 (2012); *Neuron* 87, 1131 (2015).

— There are multiple pools. Recycling, Priming before fusion — complicated.

[We assumed a simple docking process

— Sometimes, re-fusion happens back of released vesicles to the presynaptic neuron

[These feedbacks remain a challenge]

— There is stochasticity between quantal content release and Post-synaptic current

[We assumed proportionality — may try to go beyond]

Exact Distribution of the Quantal Content in Synaptic Transmission

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Concluding Remarks

- For the **simplest model** of synaptic transmission, on sustained stimulation by **any random uncorrelated** train of Action Potentials, in the **steady state,**

we derived **the general exact distribution (and moments)** of the **Quantal content**.

Generically it seems -> **Non-Binomial.**

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Looking forward to experiments on electrophysiology of synaptic transmissions …

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Thank you