Granule membranes play dice. The quantal nature of secretion

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To the memory of Bruno Bassan

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E. NITZANY, I. HAMMEL, I. MEILIJSON, *JTB* 2010

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I. HAMMEL, M. KREPELOVA, I. MEILIJSON, *MRT* 2014

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D. AMIHAI, I. HAMMEL, I. MEILIJSON, J. TERKEL, *TO BE SUBMITTED*
Pancreatic Acinar Cell
Two fundamental reasons for keeping granule inventory:

1. **Uncertainty of demand:** Granule stock is maintained as a buffer to meet uncertainty in demand by the extracellular environment.

2. **Lead time for production:** A source of supply during the lead time to produce granules of adaptive content.
Quantal nature of granular volume
Most researchers hypothesize that granules stay as created and exit many-at-a-time.

Bernard Katz (Nobel Prize 1970) group in England

Cope & Williams 1992 review
Is *Quantal size* the synaptic content of a single vesicle out of a heterogeneous pool?

\[ G_n = nG_1 \]

Is *Quantal content* the number of homogeneous vesicles released in a single response of cell activation?
Granule Quantal Growth
addition of unit granule

All agree on Granule-Membrane fusion

But not on Granule - Granule fusion
Baumeister et al 2010 diameter data
Histogram of volume data

Baumeister et al. (2010) diameter data, converted to volume

Empirical density of volume, converted from diameter

(1/1000)th of granule volume in mm³: mean granule size is 3.94 unit granules
Markov Stationary Model

Markov process: The distribution of Future given History is summarized by Present state. 

Granule Growth & Elimination : “state” is granule size

\[
\text{Probability of advancing from size } n \text{ to size } n+1 = \frac{\lambda_n}{(\lambda_n + \mu_n)}
\]

\[
\lambda_n = \lambda n^\beta = \lambda n^{(2/3)(K^\beta - 1)} \quad \mu_n = \mu n^\gamma = \mu n^{(2/3)(K^\gamma - 1)}
\]

\[
\begin{align*}
G_1 & \quad \lambda_1 \quad \mathcal{G}_1 \\
G_2 & \quad \lambda_2 \quad G_2 \\
G_3 & \quad \lambda_3 \quad G_3 \\
& \vdots \\
G_n & \quad \lambda_{n-1} \quad G_{n-1} \\
& \quad \lambda_n \quad G_n
\end{align*}
\]

\[
\lambda = \text{addition} \quad \mu = \text{elimination}
\]
Granule steady-state model

Stationary distribution ≠ Exit distribution

Ryan et al. (1997) used optical microscopy and fluorescent dyes to track the spontaneous and evoked vesicle release.
Three-parameter model \( \mu/\lambda, \gamma, \beta \)

- Exit rate from \( n \): \( \mu n^\gamma \)
- Transition rate from \( n \) to \( n+1 \): \( \lambda n^\beta \)
- Markov: independent exponentials, earliest wins
- Mean sojourn in \( n \): \( 1/(\mu n^\gamma + \lambda n^\beta) \)
- Probability of exit \( \mu n^\gamma / (\mu n^\gamma + \lambda n^\beta) \)
SNARE, ROSETTE, POROSOME

Atomic force microscopy

Porosome - Jena BP, 1997
The rudder: The SNARE SYSTEM

Human subtlety will never devise an invention more beautiful, more simple or more direct than does nature because in her inventions nothing is lacking, and nothing is superfluous.

—Leonardo da Vinci

(http://www.brainyquote.com/quotes/authors/l/leonardo_da_vinci.html)
Rationale for rate shape
SNARE: $\mu n^\gamma$ and $\lambda n^\beta$

$N$ “rings” diffuse randomly on surface (area $n^{2/3}$) of granule, of which $K$ must be close to each other and to $K$ “hooks” in unit granule or membrane. Probability is of order

$\left(\frac{\text{const}}{\text{area}}\right)^{K-1} = \text{const}n^{-(2/3)(K-1)} = \mu n^\gamma$ or $\lambda n^\beta$

Similar to Hua & Scheller PNAS 2001
Steady-state condition: flow into $n+1$ equals flow out of $n+1$

$$\text{STAT}(n) \lambda n^\beta = \text{STAT}(n+1) \left( \mu (n+1)^\gamma + \lambda (n+1)^\beta \right)$$
EXIT distribution

EXIT(n+) = GROW(1)*GROW(2)*...*GROW(n-1) and

GROW(m) = \( \frac{\lambda \cdot m^\beta}{(\mu \cdot m^\gamma + \lambda \cdot m^\beta)} \)

EXIT(n) = EXIT(n+) - EXIT((n+1)+)
The role of $\gamma$

- $\text{STAT}(n)/\text{EXIT}(n) = \exp\{-\gamma \log(n) - b(\gamma)\}$
- STAT is exponential-type family with EXIT as case $\gamma=0$

- Perhaps evoked case needs one hook-ring pair!
- Reminder: $\gamma = -(2/3)(K-1)$
Statistical tools

- EM algorithm for Gaussian mixture with equally spaced means and variance
- MLE of $\mu/\lambda$, $\gamma$, $\beta$ based on evoked and spontaneous data
- Omnibus program for five parameters
- CUSUM detection of change-point
- Simulation study of transient behavior
- Euclidean Geometry considerations
$K_\beta = 20 = K_\gamma + 1$

$K_\beta = 20 = K_\gamma$
Detecting that spontaneous secretion turned evoked secretion

- CUSUM - Statistical tool for detecting change-point in distribution
- Performance measured by Kullback-Leibler divergence KLD
- CUSUM calculations may use common action potential monitoring.
CUSUM of Page (1953)

- Declare change when log likelihood
- $S_n = \sum \log g(X_i)/f(X_i)$ exhibits draw-up
- $S_n - \min_{m \leq n} S_m$
- of at least a pre-assigned size.

- $E_g[\log g(X)/f(X)] > 0$ is $KLD(g,f)$
- $E_f[\log g(X)/f(X)] < 0$ is $KLD(f,g)$
SUMMARY, FORMULA

- For log likelihoods $\rho = 1$.
- Putting all together, Mean Granules to Detection is

$$\ln[MGFA] + \ln[KLD(E,S) + \eta_2/\eta_1 - 1 - \ln(\eta_2/\eta_1)]$$

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$$KLD(S,E) + \eta_1/\eta_2 - 1 - \ln(\eta_1/\eta_2)$$
One word = 1 bit = 8-10 vesicles

If spontaneous secretion is steady at (the common rate of neurons) 1Hz, a false recognition alarm will be declared once every 15 minutes (10^3), once a day (10^5) or every four months (10^7).
If the rate of secretion is increased

- by a small factor ($\approx 2$), granule size distribution plays a critical role
- by significant bursts (rate of increase = $\eta_2 / \eta_1 > 10$) the role of granule size distribution is minor.

The G&E model suggests that granule polymerization has an advantage for the information gain it achieves under limited exocytosis of a small number of granules.