BioSim NETWORK OF EXCELLENCE

LUNDBECKFONDEN

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UNIVERSITY OF PADOVA

Spanning time scales and levels of organization of insulin secretion with mathematical modeling:

From seconds to hours, from molecules to organ

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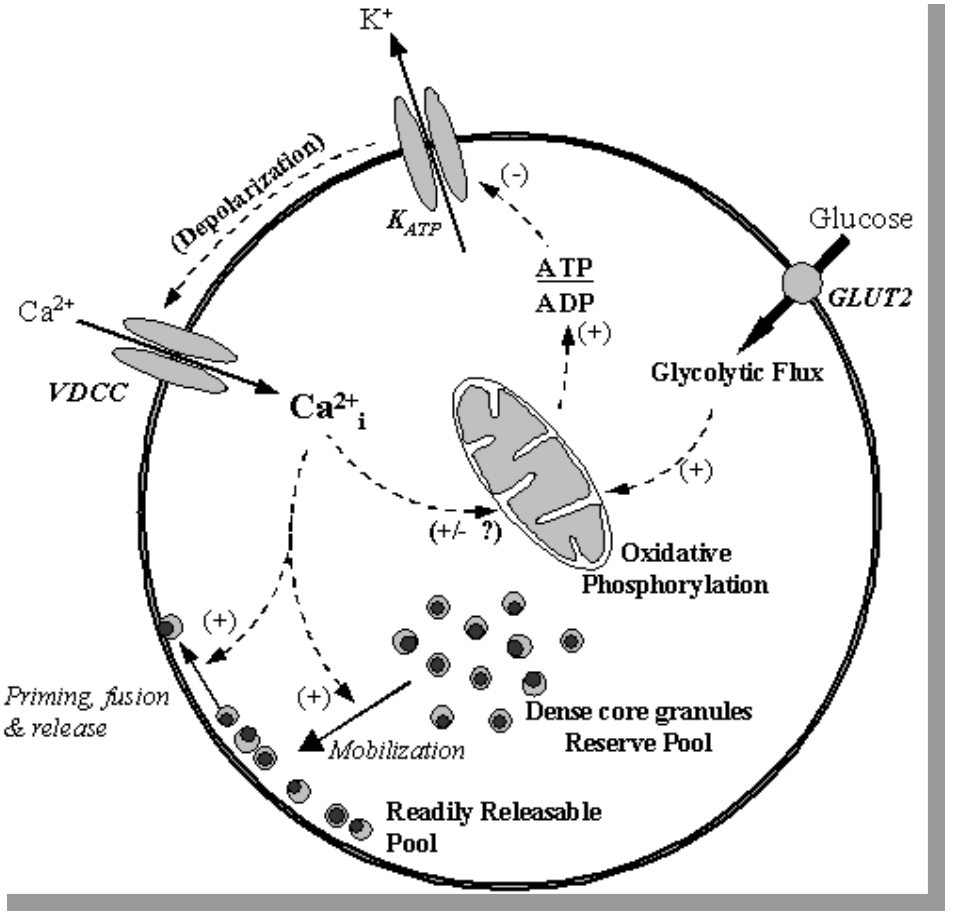
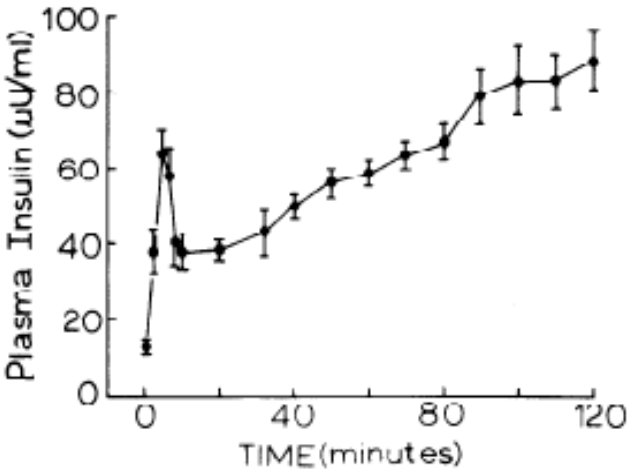
Glucose stimulated insulin secretion

- Insulin is secreted from the pancreatic beta-cells in response to (mainly) glucose
- Insulin is stored in *secretory granules*
- Released by Ca^{2+} *triggered exocytosis*

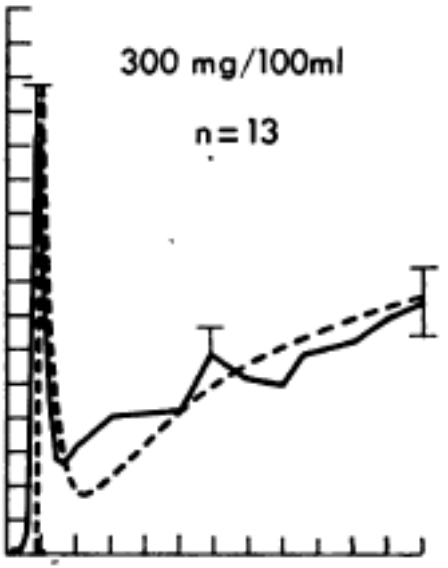


Phasic insulin secretion

- Insulin is secreted in typical biphasic pattern in response to glucose-step
- Seen *in vivo*, from pancreases and from islets
- Pools of granules?



In vivo glucose clamp (De Fronzo et al., 1979)

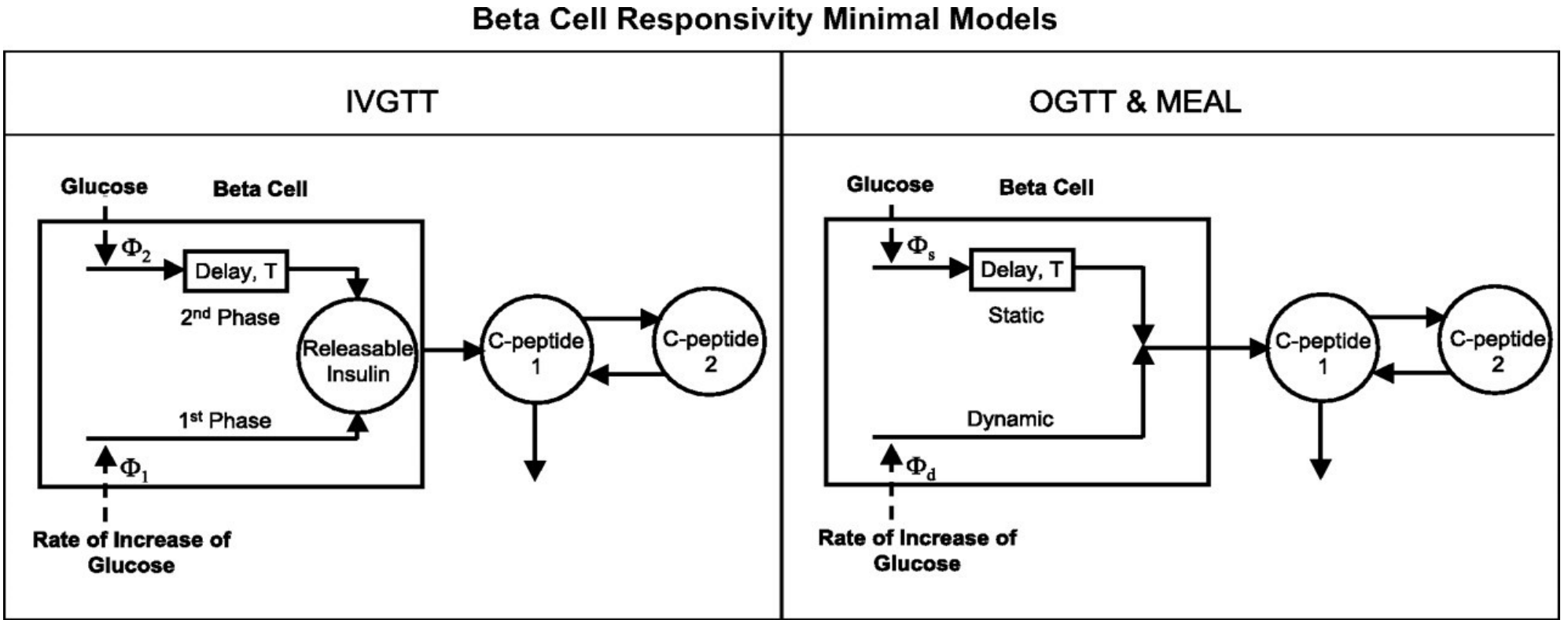


Perfused rat pancreas (Grodsky, 1972)

Minimal models of insulin secretion – estimated from in vivo data

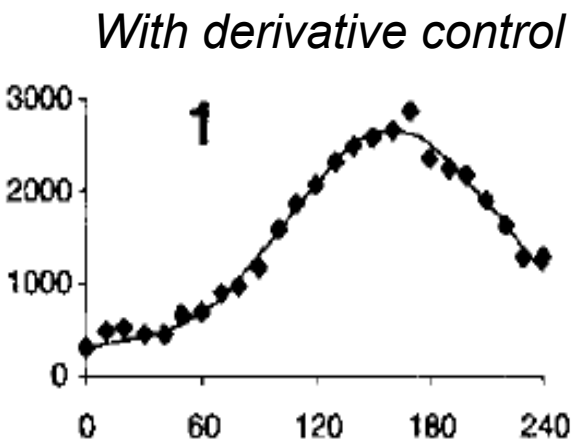
- C-peptide minimal model allows estimation of dynamic and static beta-cell responsitivity

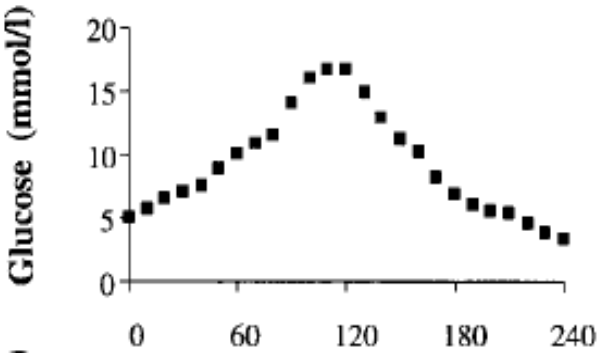
  (Toffolo et al., Diabetes 1995, AJP 2001; Cobelli et al., AJP 2007)

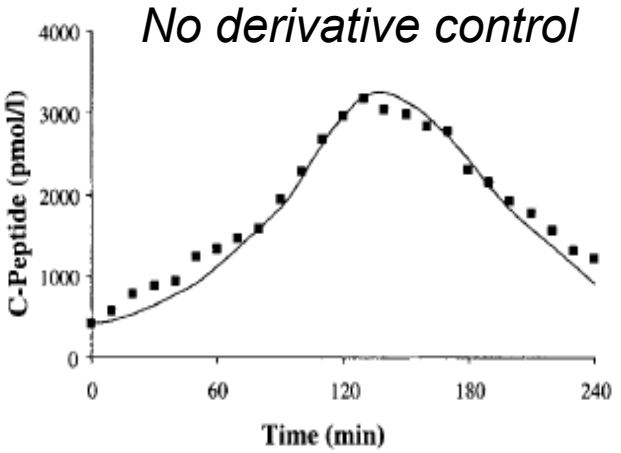


Dynamic secretion term

- Derivative control: The pancreas responds not only to glucose concentration *G* (“static”, with delay), but also to rate-of-change *dG/dt*
- Necessary to fit in vivo data
  (Graded up-down: Toffolo et al., AJP 2001; OGTT: Breda et al., Diabetes 2001)



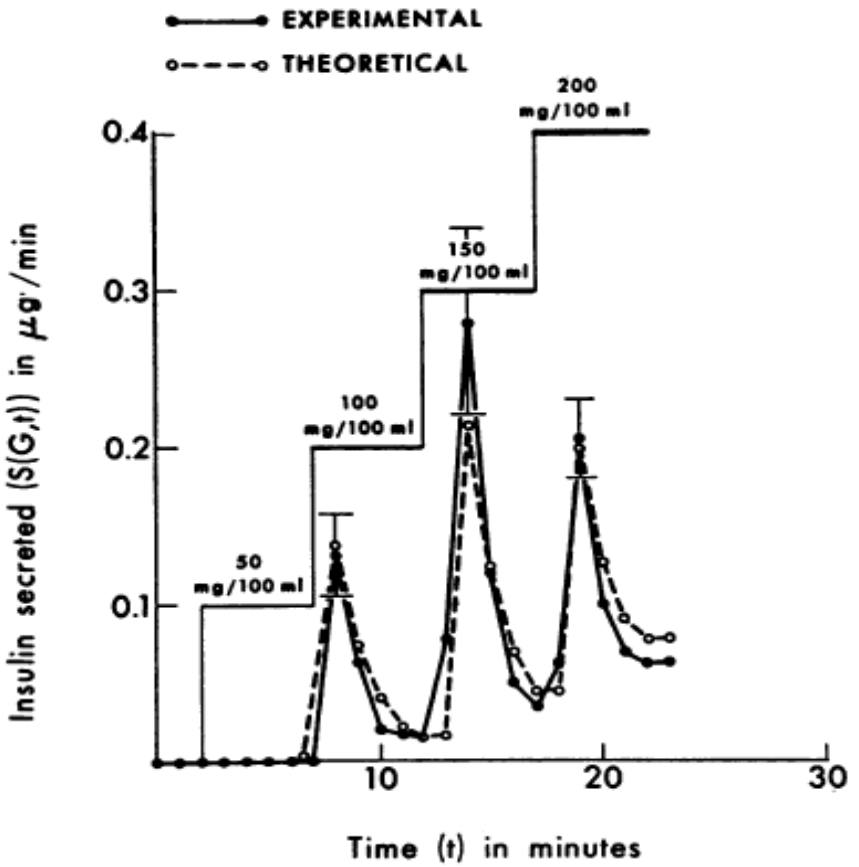




- Where does it come from?

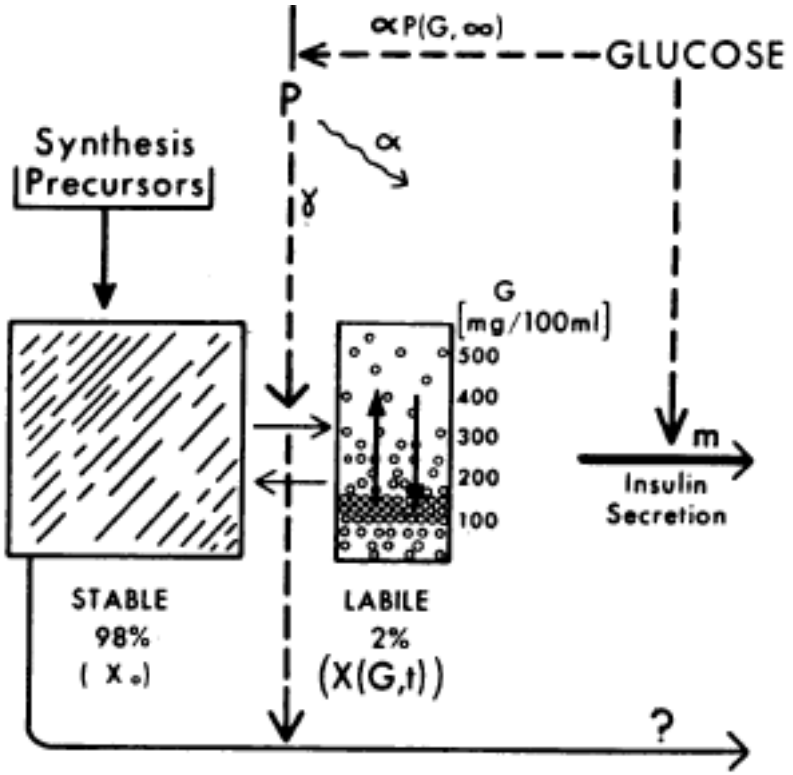
Staircase experiment

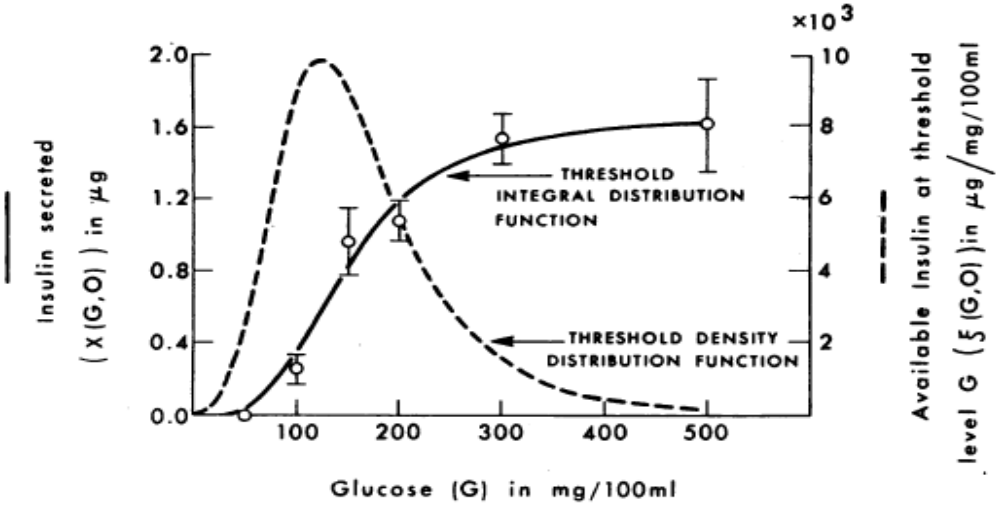
- Rat pancreas
  (Grodsky, JCI 1972)
- Sum of peaks = peak at max concentration → *threshold hypothesis*
  (Grodsky, JCI 1972)



Grodsky's threshold hypothesis

- Two pools of "packages"
- "Labile packages" are heterogeneous, different glucose thresholds for release

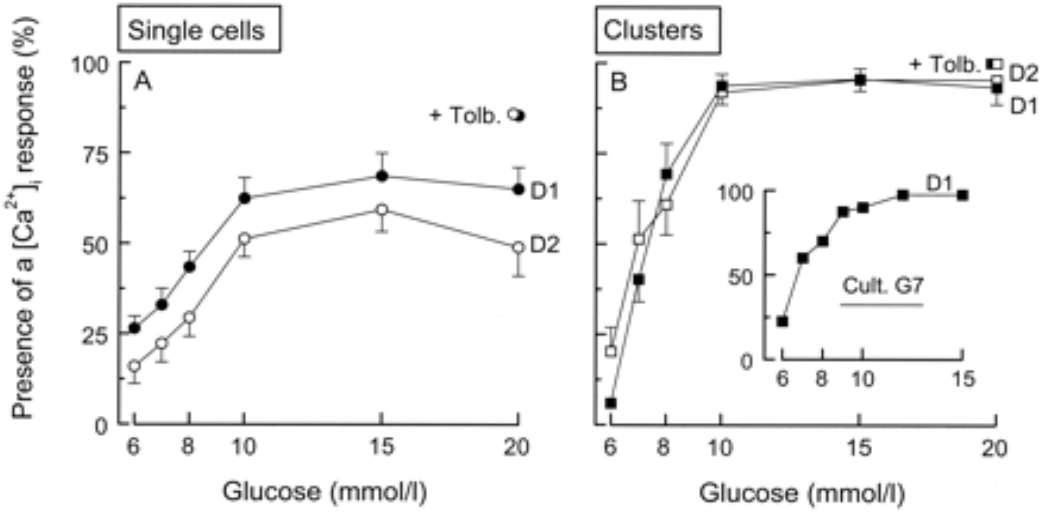




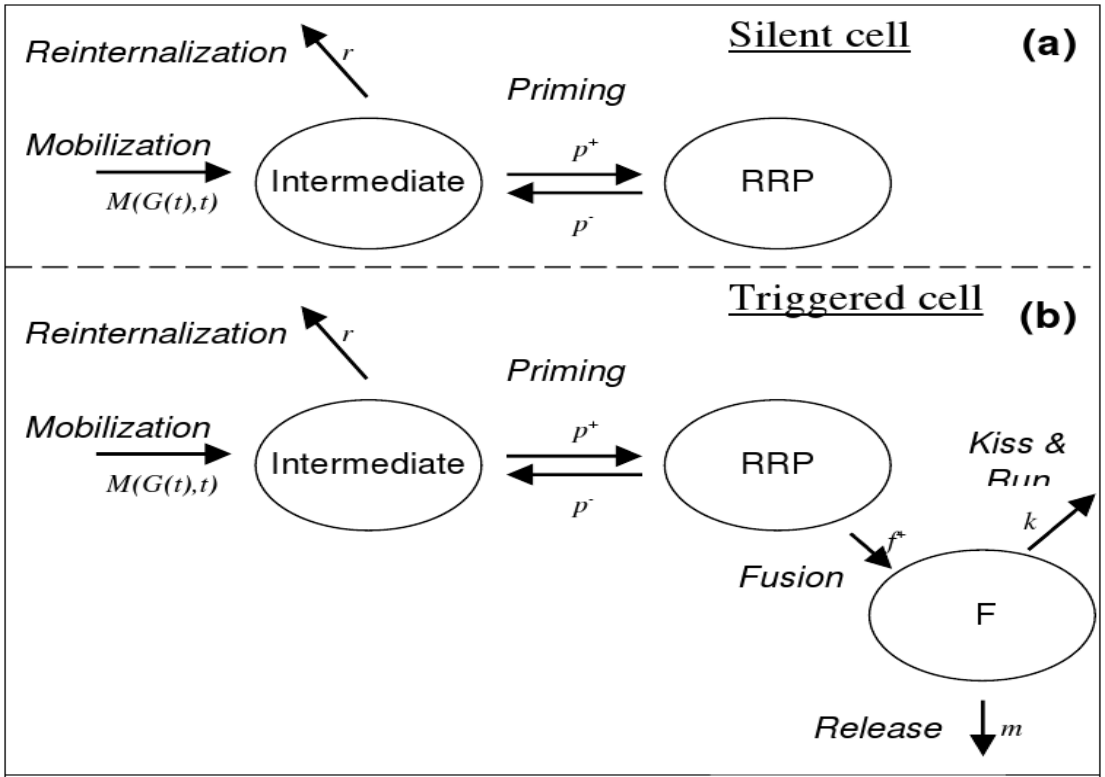
Model development

- Previous attempts:
  Grodsky (JCI '72),
  Landahl & Grodsky (BMB '82)
- Recent granule models:
  Bertuzzi et al. (AJP '07),
  Chen et al. (BJ '08),
  Pedersen & Sherman
  (PNAS '09)
- Cells (not granules!) activate at different glucose concentrations → *heterogeneous RRP*

(Pedersen et al.,
Phil Trans Roy Soc A 2008)

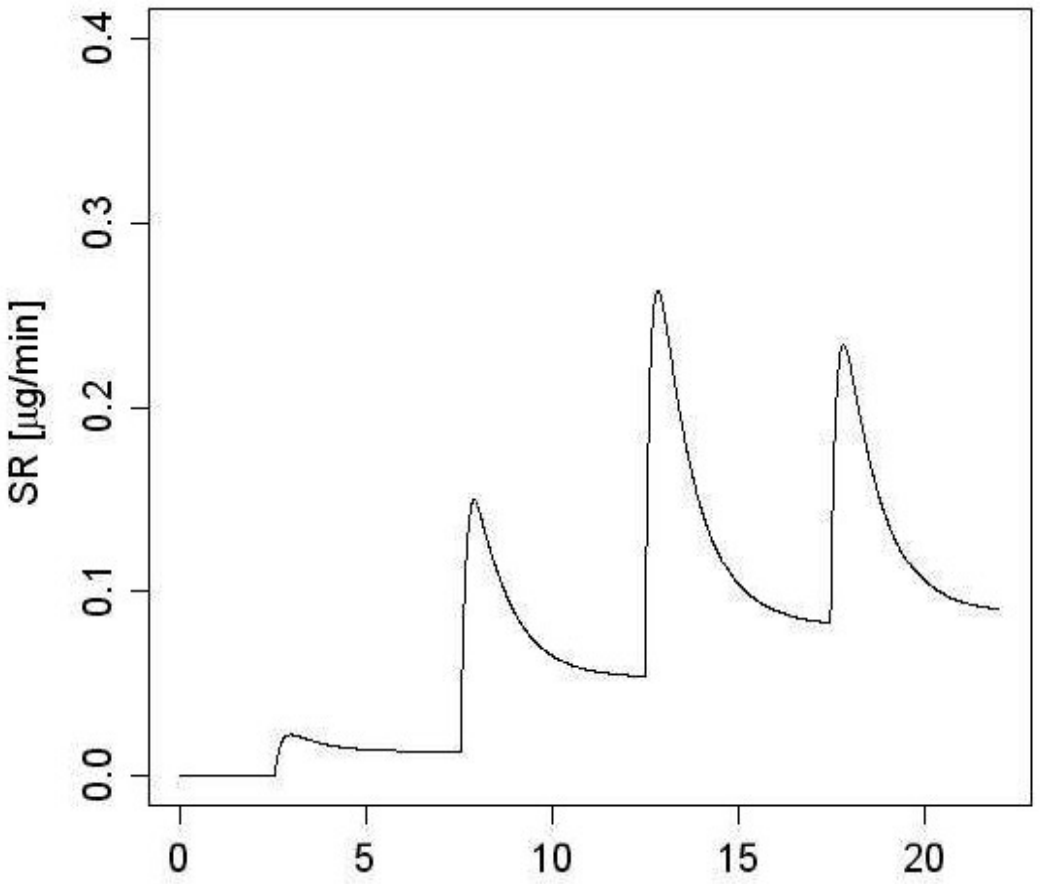


(Jonkers & Henquin, Diabetes 2001)



It does the job...

Staircase



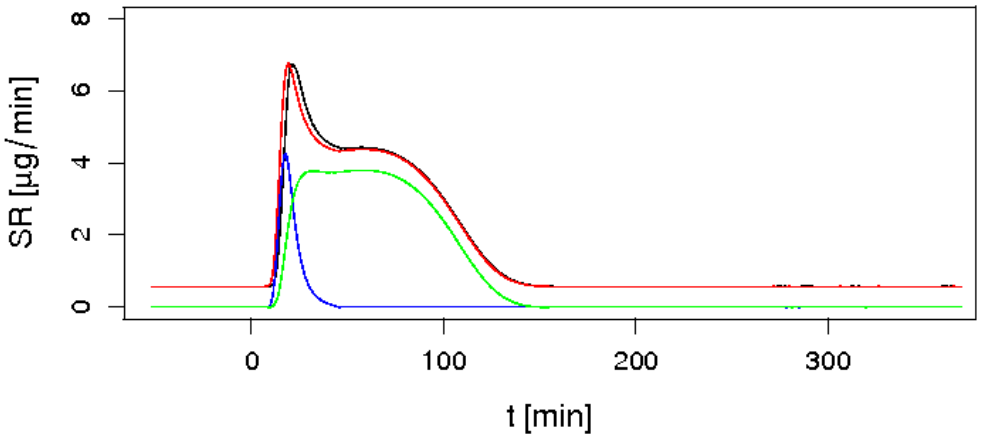
- Other recent models do not reproduce staircase
- Heterogeneous RRP allows reproduction of staircase experiment
- In contrast to Grodsky, due not to threshold on *granules* but on *cells* (or islets?) as seen in experiments

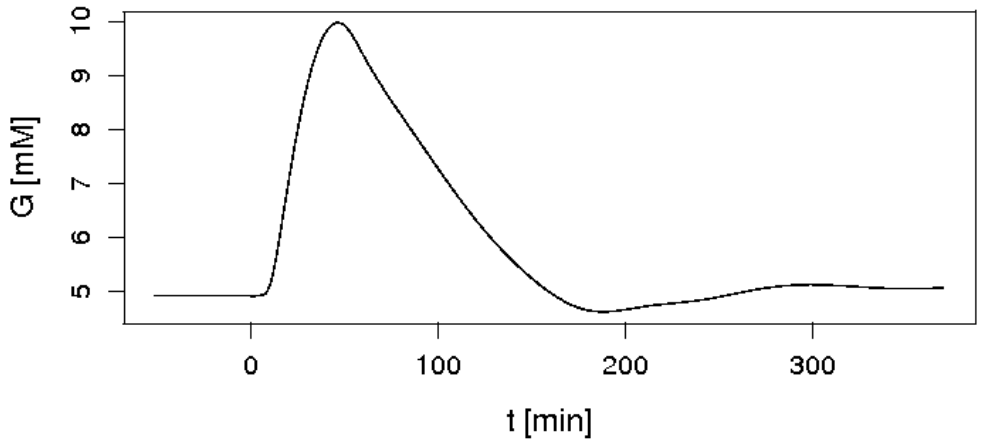
Where does derivative control come from?
(Pedersen et al., AJP 2010)

- Threshold distribution underlies derivative control (Grodsky, JCI 1972; Licko, Bull Math Biol 1973)
- Here:
  - $SR = mF$
  - $dF/dt = -(m+k)F + f\,H(G), \quad H(G) = \int_0^G h(g)dg$
  - $dH/dt = \int_0^G dh(g)/dt\, dg + h(G)\, dG/dt$
    $= -(f+p^-)H(G) + p^+ I\, \Phi(G) + h(G)\, dG/dt$
  - Assume quasi steady-state
    - $SR(t) = \text{const}\,[\, p^+ I(t,\tau)\, \Phi(G(t)) + h(G(t))\, dG/dt(t)\,]$

Static responsitivity Dynamic responsitivity

Relative contributions of dynamic vs. static secretion





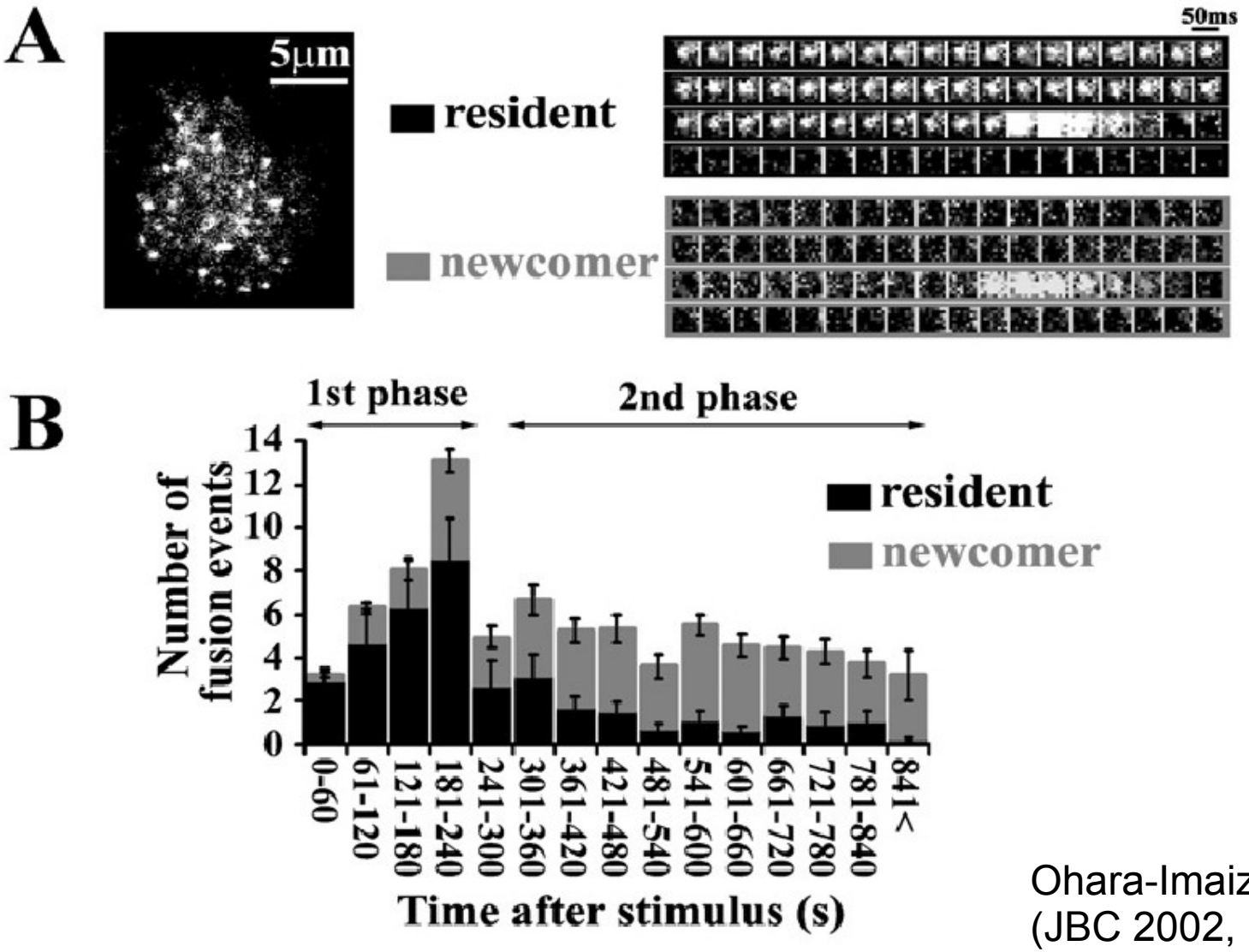
- Glucose profile following a meal
- Model parameters adjusted to give reasonable C-peptide data
- Legend:
  - Full model
  - Approximation
  - Dynamic
  - Static

Conclusions (part 1)

- Relatively simple model, but founded on biologically established principles (non-phenomenological)
- Can explain static and dynamic secretion terms
  - *Dynamic* due to recruitment of cells (or islets?)
  - *Static* due to refilling of RRP (introduces delay)
- The model could (should!?) be coupled to models of calcium dynamics
- Such models provide mechanistic underpinning of the assumptions of the minimal models

  Granules → cells → pancreas
- … and could help in interpreting in vivo data (disturbances in diabetics?)

Distinct mechanisms account for 1st and 2nd phase secretion



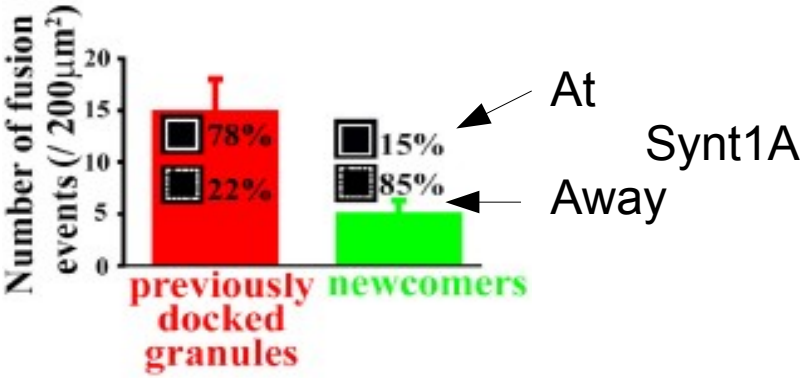
Ohara-Imaizumi et al.
(JBC 2002, Biochem J 2004)

1st (resp. 2nd) phase secretion occurs mainly near (resp. away from) Ca^{2+} channels

Docked granules fuse *at* Synt1A clusters (~80%), newcomers fuse *away from* Synt1A clusters (~85%)

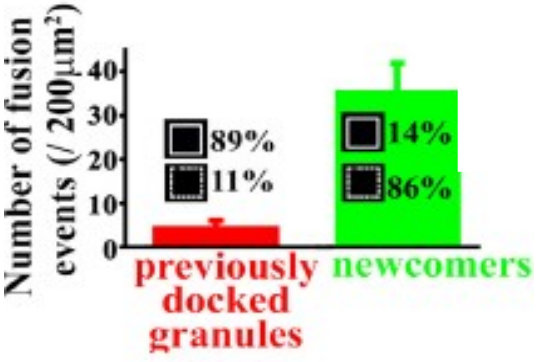
Synt1A cluster are co-located with L-type Ca^{2+} channels (Yang et al., PNAS 1999)

1st



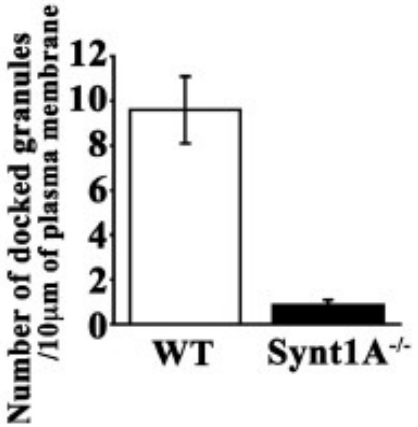
Ohara-Imaizumi et al. (J Cell Biol 2007)

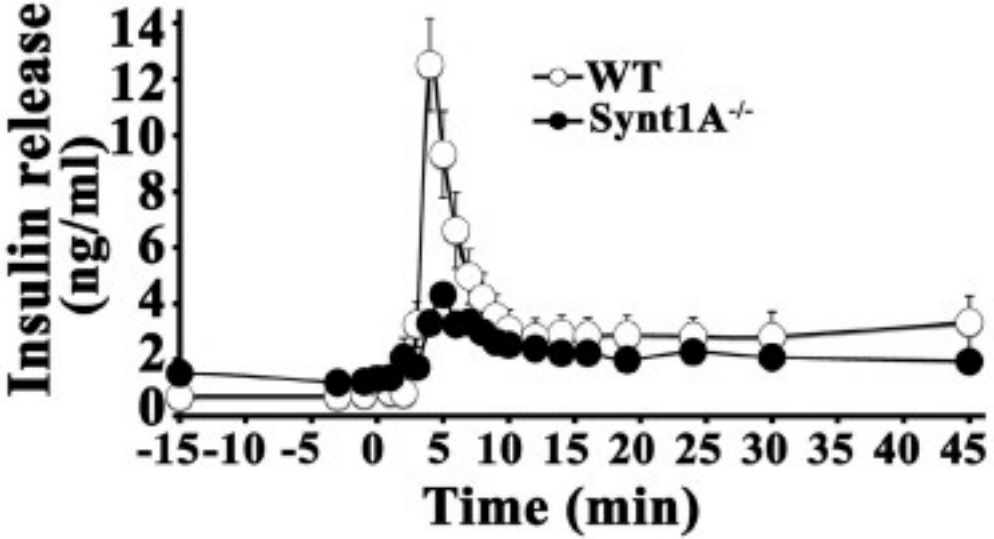
2nd



... and docking is not a prerequisite for the 2nd phase

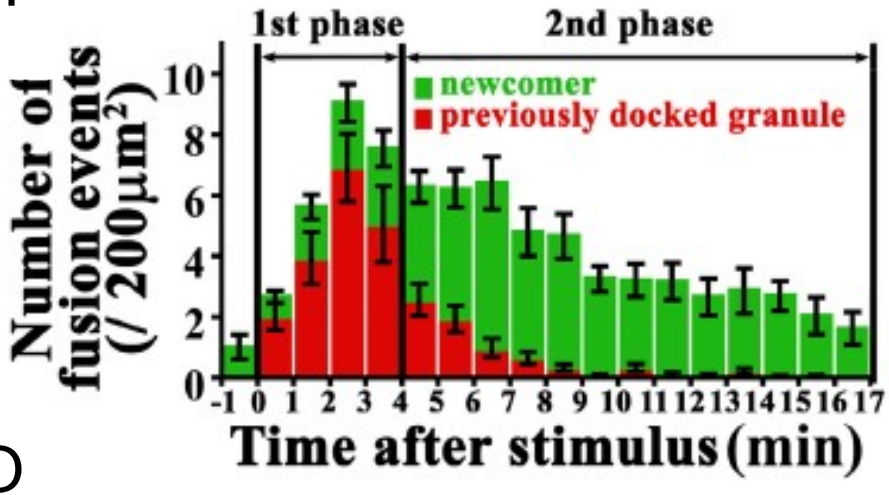
Syntaxin (Synt)-1A knock-out cells show impaired docking and 1st phase, but not 2nd phase, secretion (Ohara-Imaizumi et al., J Cell Biol 2007)



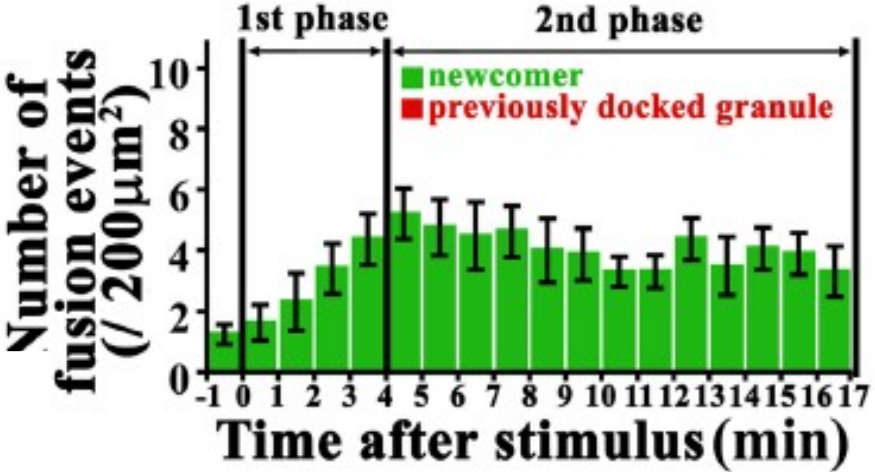


Due to fusion of newcomer granules

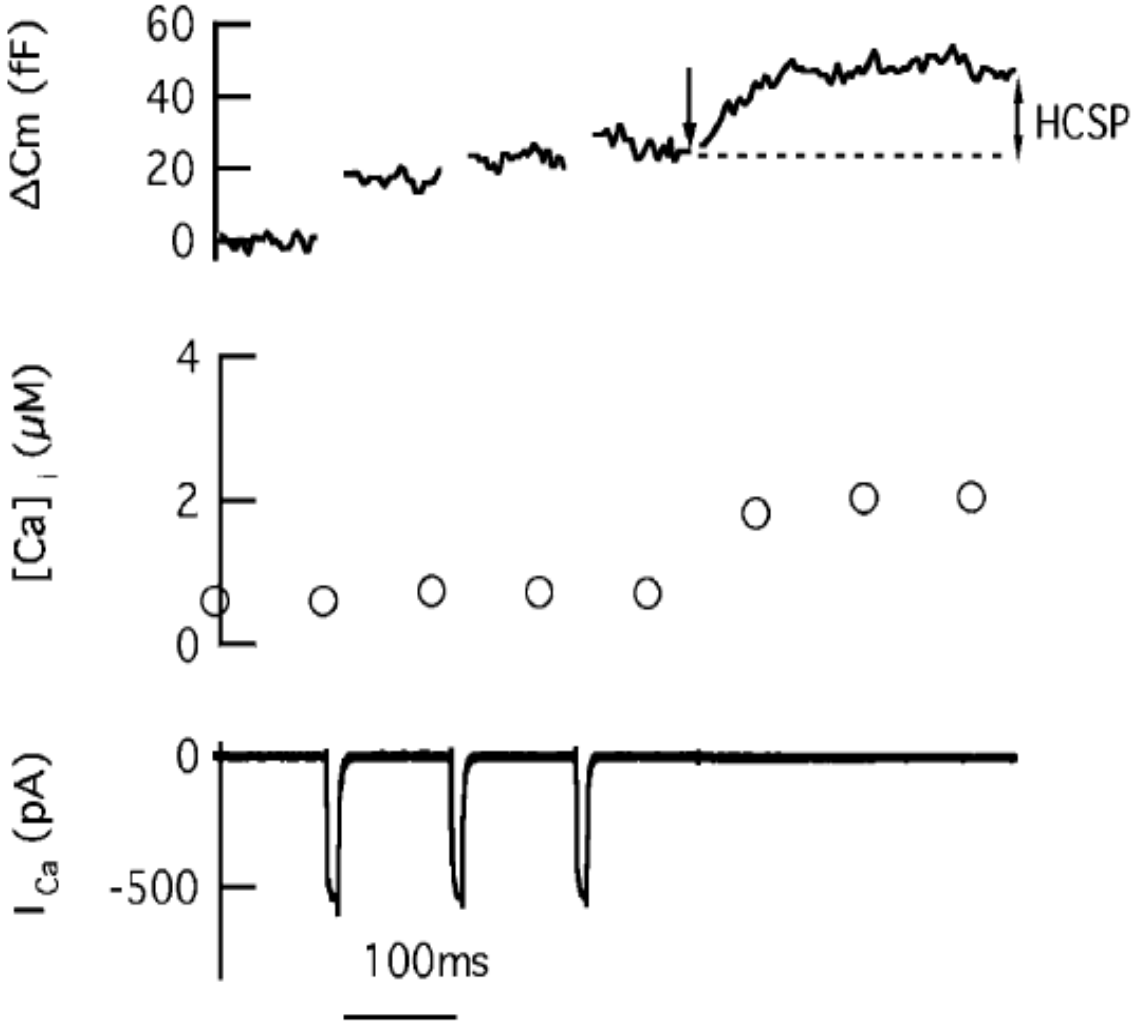
WT



KO



Highly calcium sensitive pool (HCSP) of granules

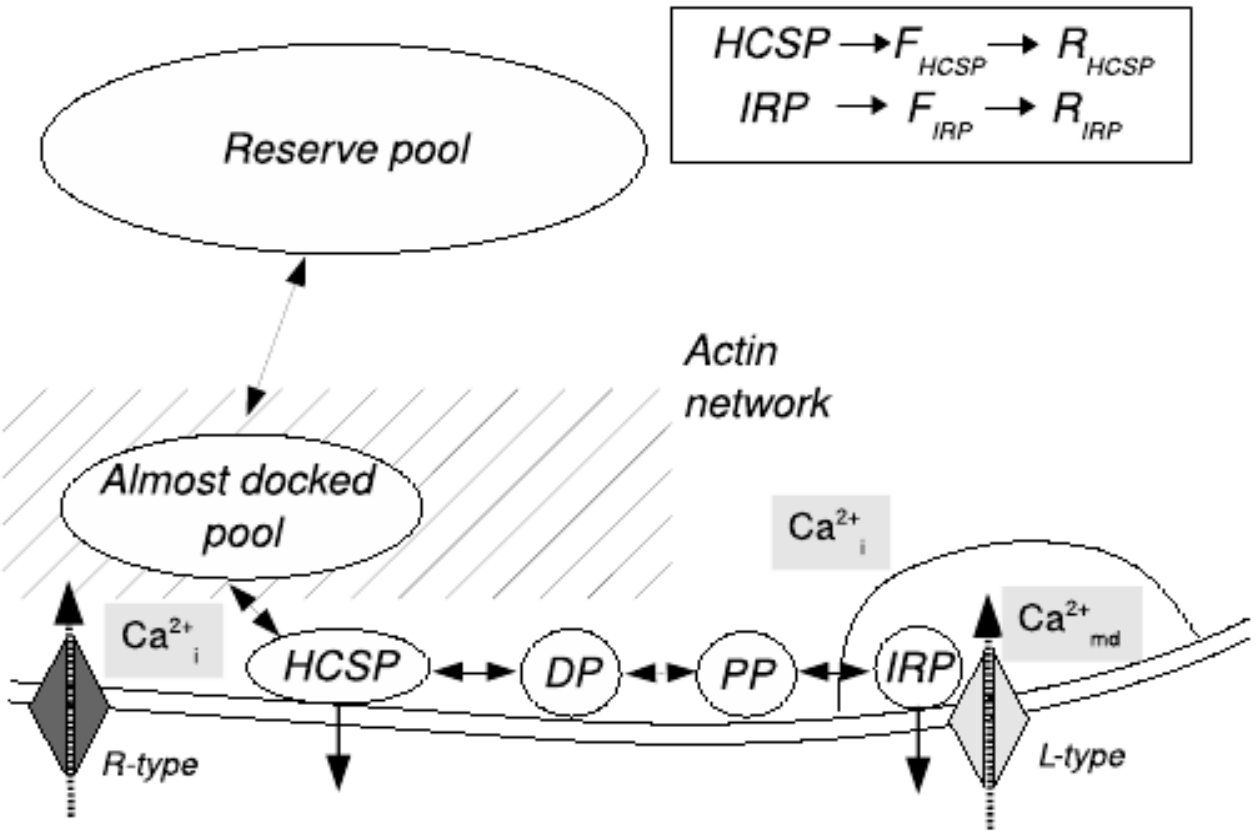


- Wan et al. + Yang & Gillis (JGP 2004)
- Affinity ~ 2 μM (~ 20 μM for RRP)
- The HCSP resides away from calcium channels since depolarizations do not empty it
- Newcomers also fuse away from calcium channels

Including the HCSP

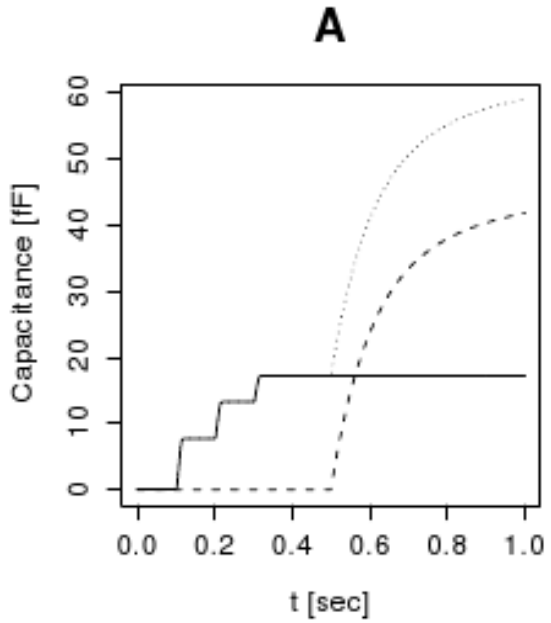
... in the model by Chen et al. (Biophys J 2008)

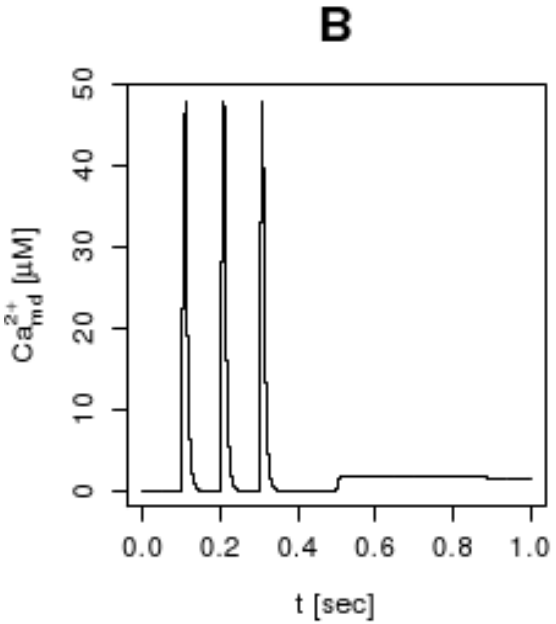
- Distinction between global, cytosolic and local, microdomain calcium, and between L- and R-type calcium channels
- HCSP assumed to reside away from Ca^{2+} channels
- HCSP assumed to be independent of syntaxin-1A, and to consist of granules that are tethered, but still not completely docked

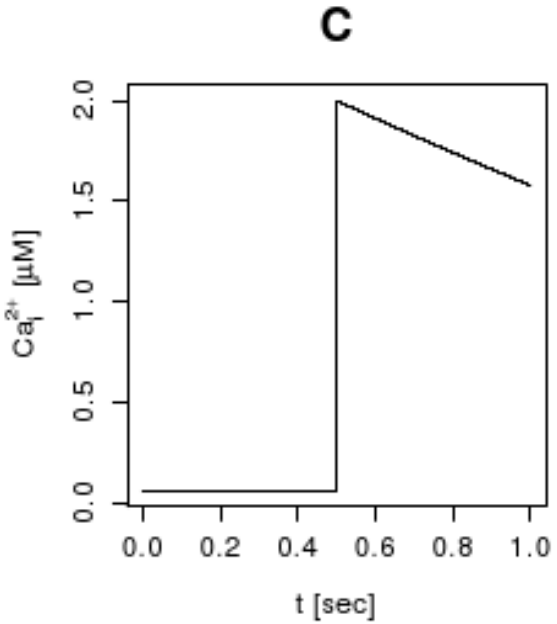


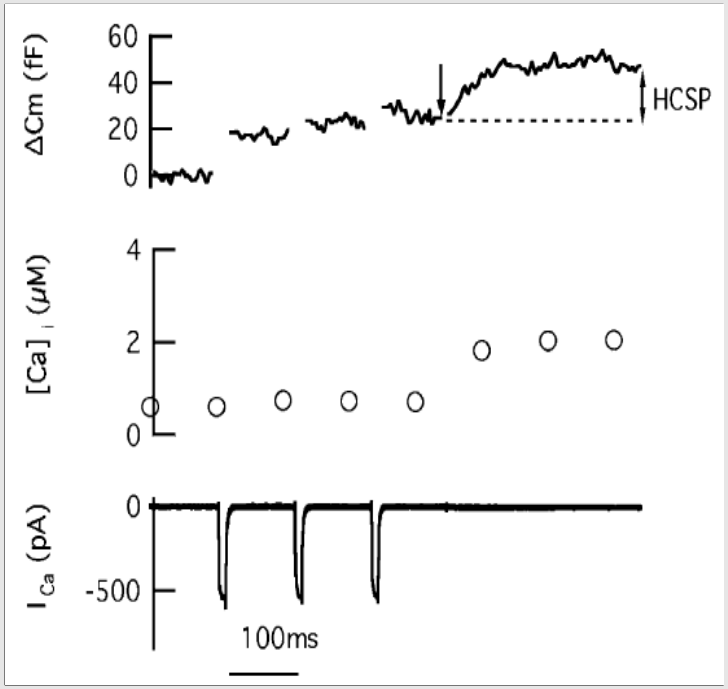
Pedersen & Sherman (PNAS 2009)

Simulations: Yang & Gillis protocol

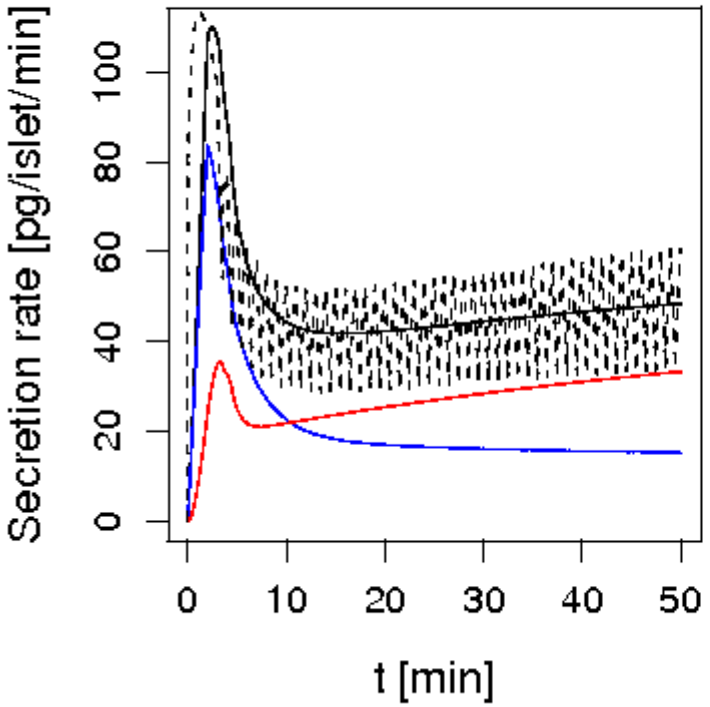


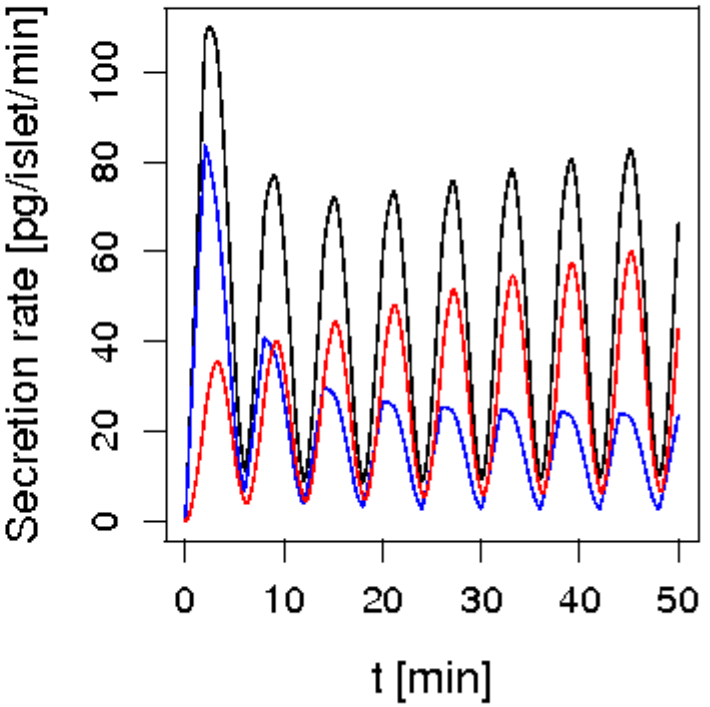




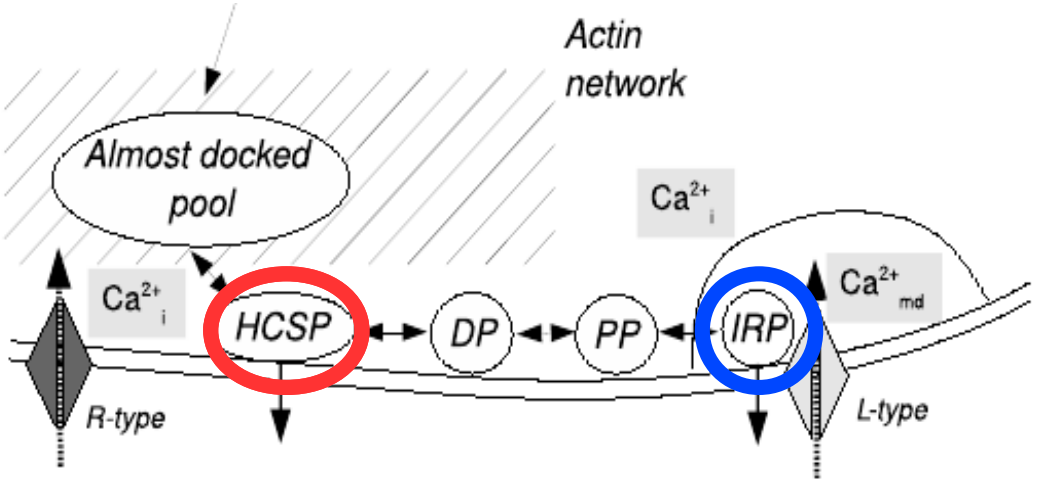


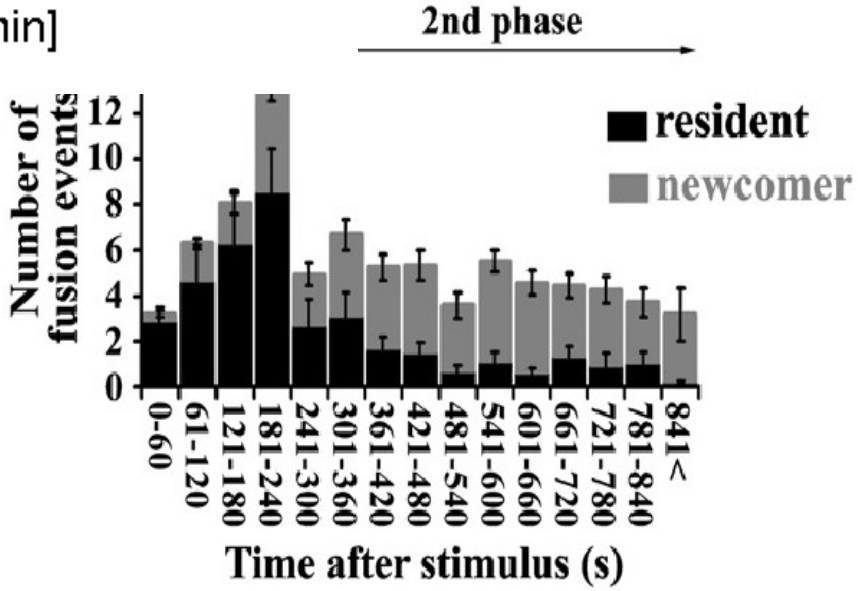
Simulations:
Newcomer granules fuse from the HCSP





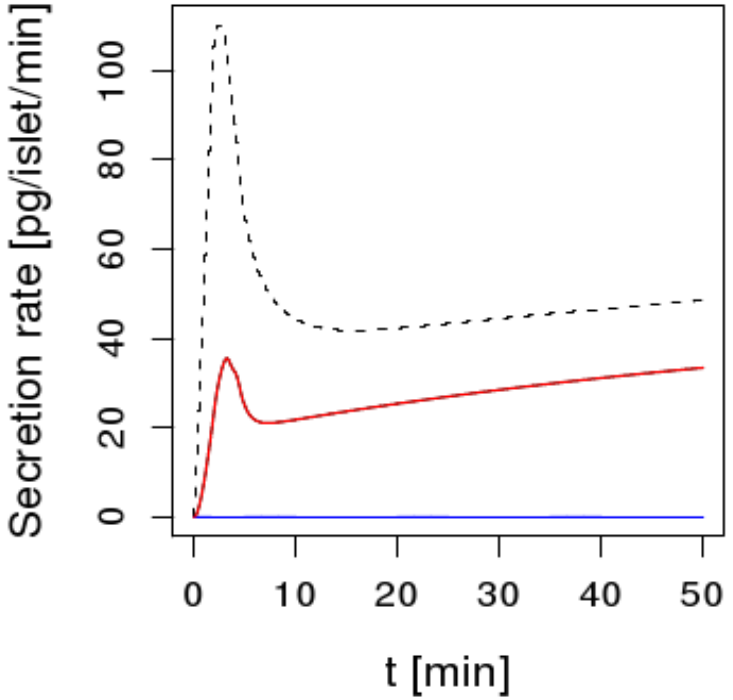
IRP secretion
HCSP secretion
Total secretion



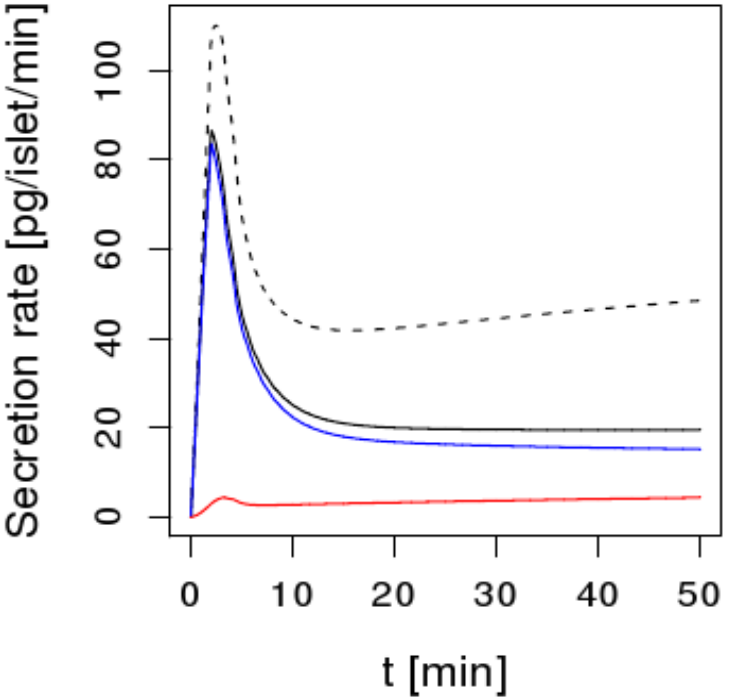


Simulations: Calcium channel KO

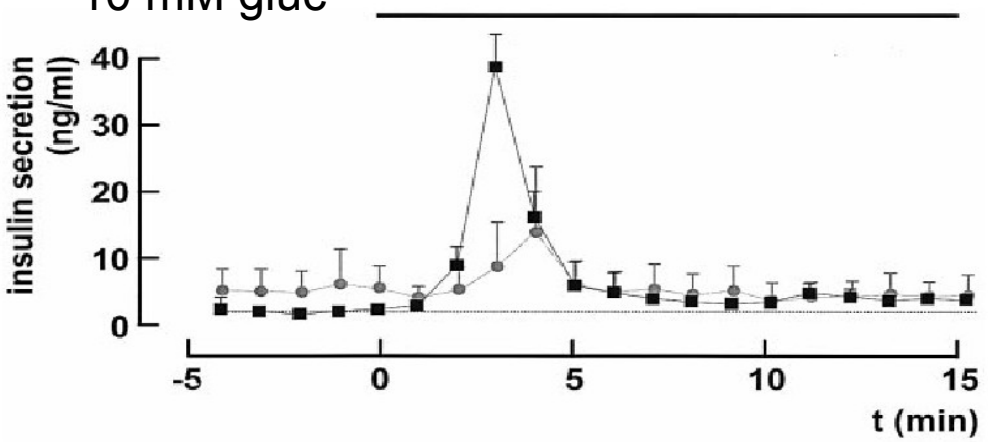
L-type KO/block
(Schulla et al., EMBO J 2003)

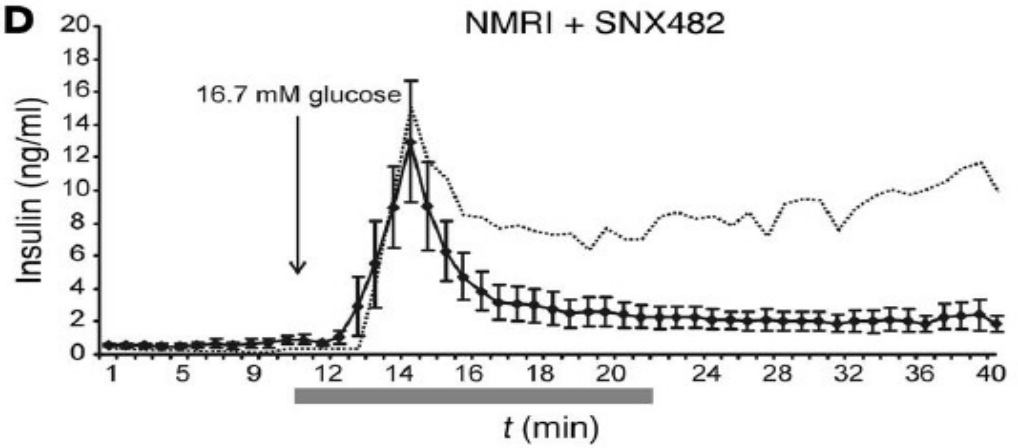


R-type KO/block
(Jing et al., JCI 2005)

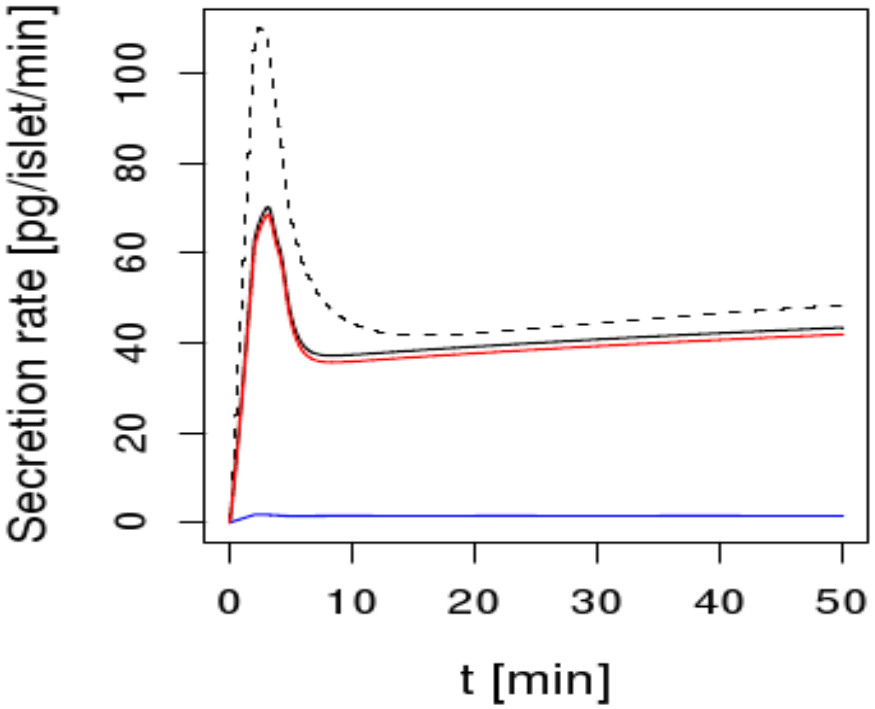


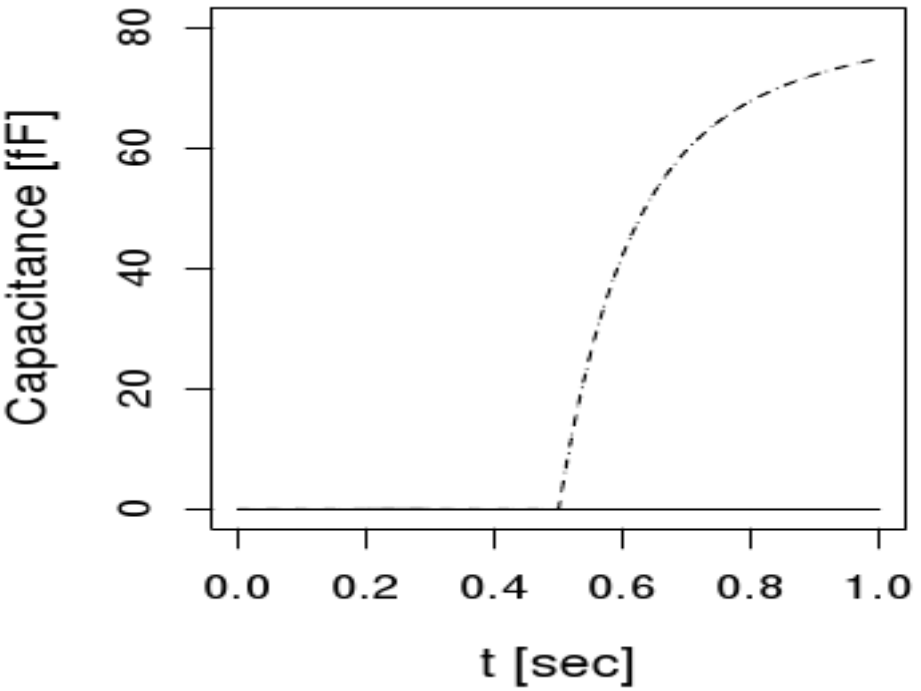
10 mM gluc

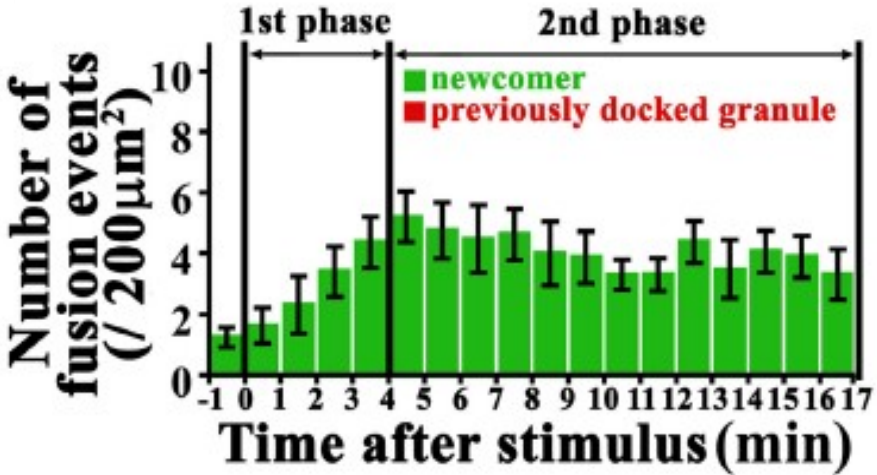




Simulations: Synt1A KO cells by assuming reduced docking rate





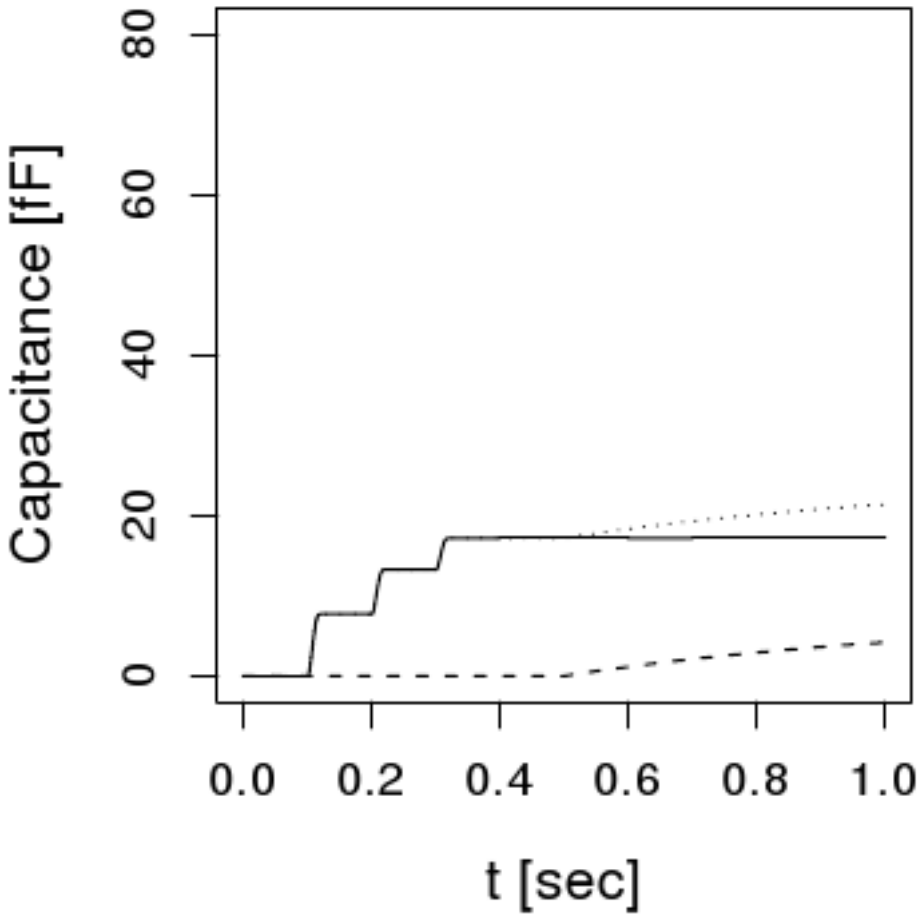


Prediction and crucial test of the model:
The HCSP is intact and possibly increased in Synt1A cells

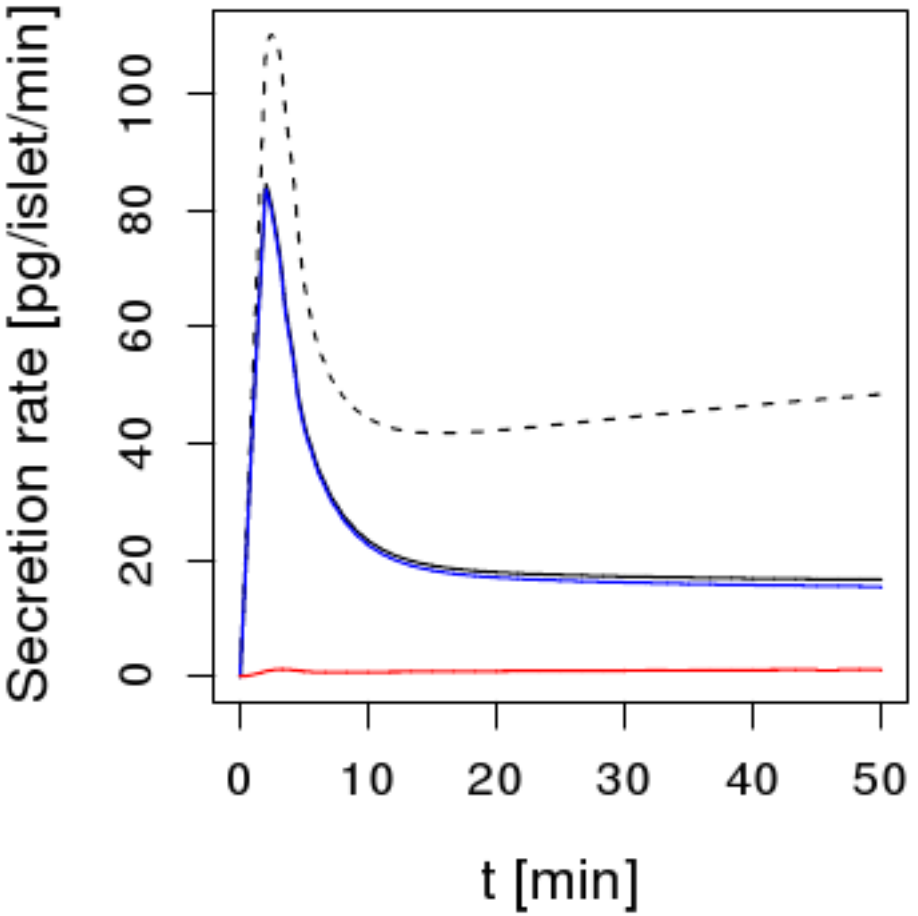
Different calcium sensors?

- Synaptotagmins (Syt's) are believed to be the sensors of calcium
  - Syt-9 is a low affinity (tens of μM) sensor present in beta-cells, and is likely the IRP sensor
  - Syt-7 and Syt-3 are high affinity (few μM) sensors, and have been suggested to be involved in insulin secretion (Syt-3 controversial). Could be the HCSP sensors

Simulations: KO of the HCSP sensor

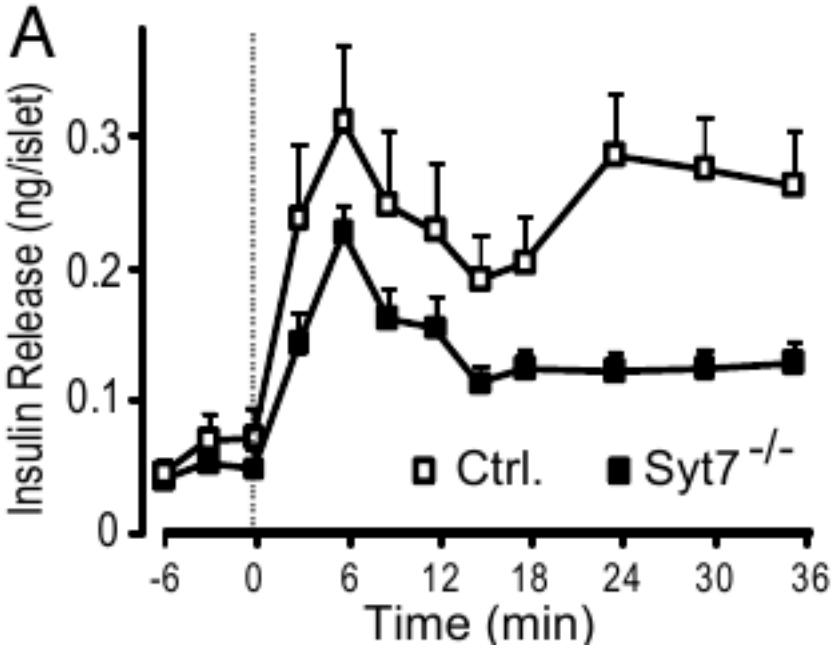


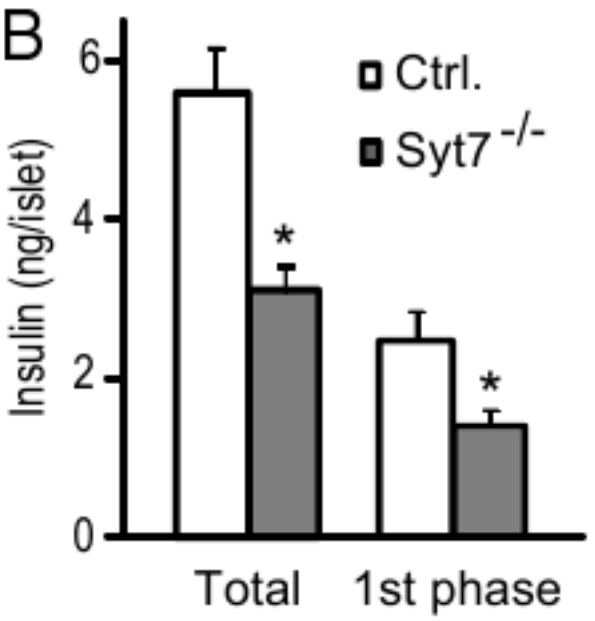
... as expected



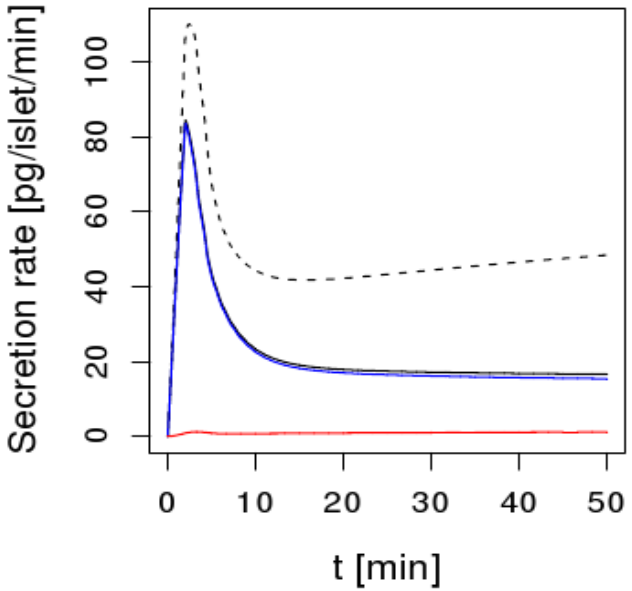
Prediction: Second phase secretion is impaired

Is Syt-7 the HCSP sensor?





Gustavsson et al. (PNAS 2008)



Both reduced 1st and 2nd phase – but there might be Syt-7/Syt-9 interactions changing the properties of IRP release (Schonn et al., PNAS 2008)

Summary (part 2)

- Part 1 bridges levels of organization (*granules* → *organ*)
- Part 2 spans timescales by coupling secretion (*minutes*) to capacitance measurements (*milliseconds*) for various perturbed situations
  - Ca^{2+} channels KO/blocking
  - Syntaxin-1A KO
  - Ca^{2+} sensor/synaptotagmin KO
- Including a HCSP as a transient state away from L-type calcium channels, naturally identified the HCSP with newcomer granules.
- Mathematical modeling was used to test the plausibility of the biological hypothesis

Conclusions

- Mathematical models are used to integrate separate experiments in a structured, coherent way
- Can be used to span timescales and levels of organization
- Two classes:
  - "Models to simulate"
    (test hypotheses, predict outcome of experiments; can include different levels of detail depending on the scope of the model)
  - "Models to measure"
    (extract information from data; must be simple/minimal to allow parameter estimation)

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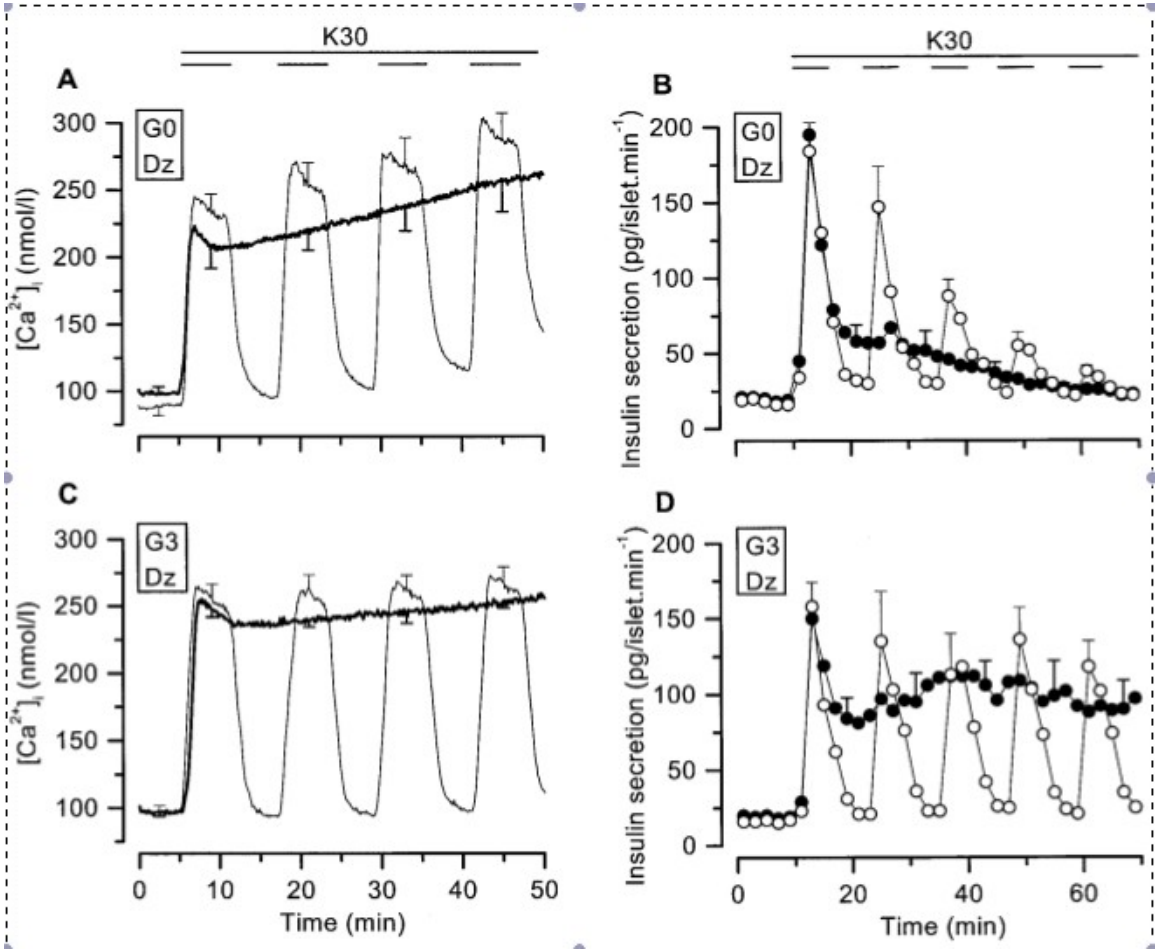
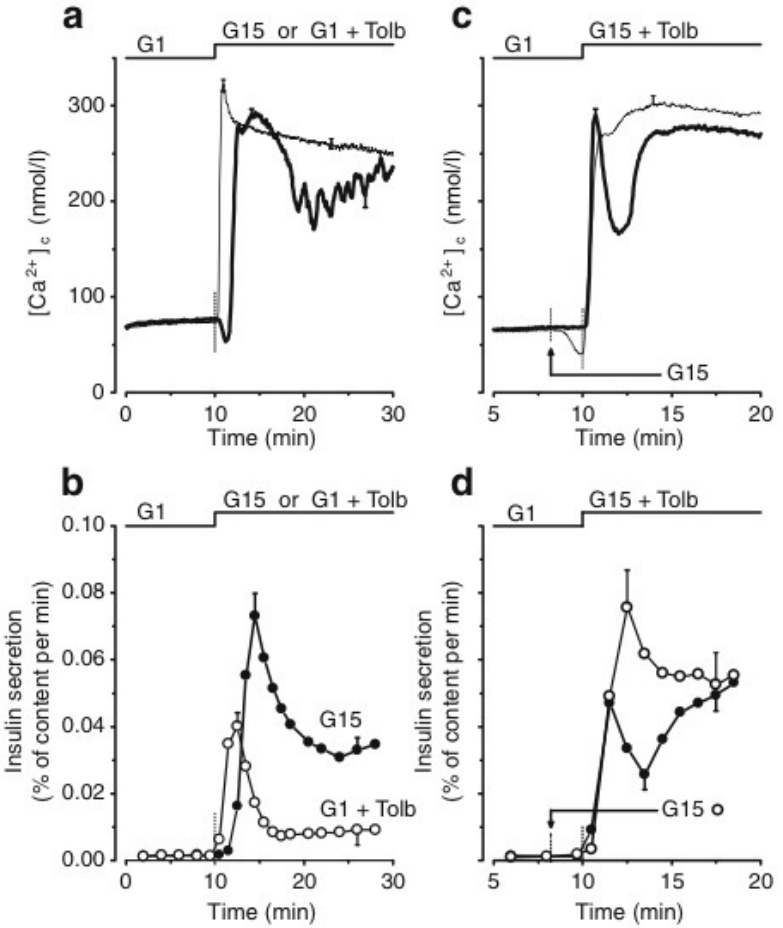
Thank you!

Pools?



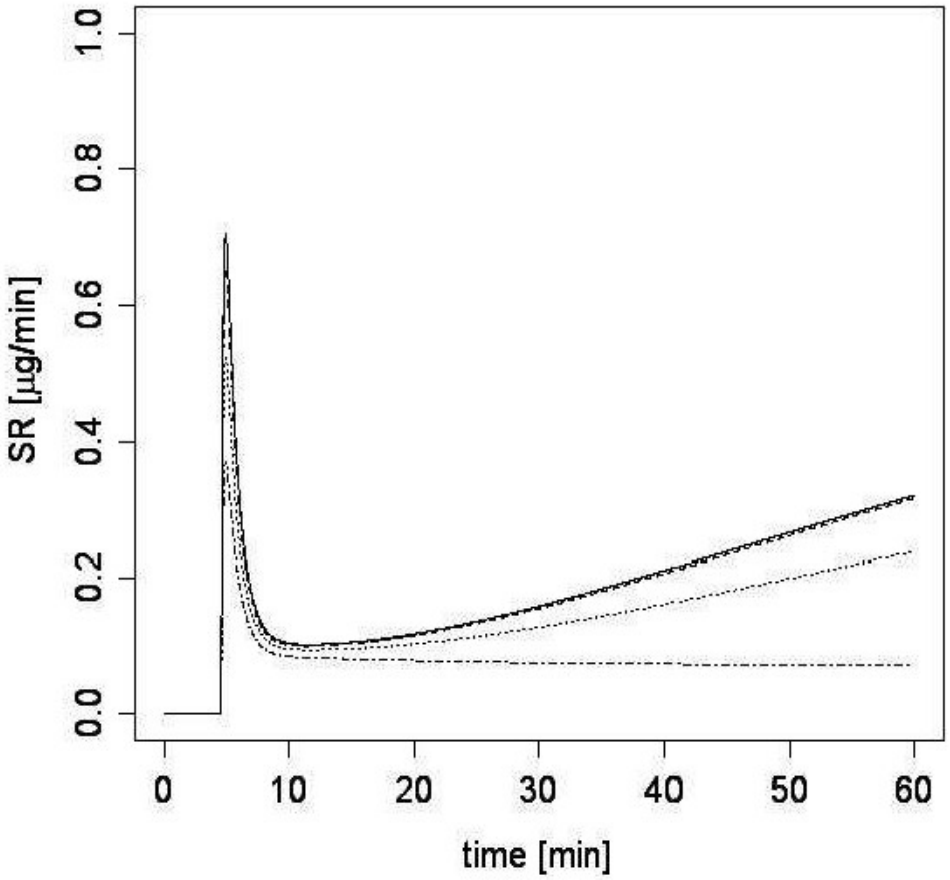
Henquin, 2002



Henquin, 2009

Results

Biphasic



Potentiation