11 M11 – Chen et al 2008 – Insulin secretion, model of the β-cell

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Model Name

Short name: Chen2008

Long name: Chen-Wang-Sherman's model of Insulin Secretion by Kinetic Modeling of Granule Exocytosis

General information

References:

1. Chen Y, Wang S, Sherman A. Identifying the Targets of the Amplifying Pathway for Insulin Secretion in Pancreatic β-Cells by Kinetic Modeling of Granule Exocytosis. *Biophysical Journal*. 2008 Set 1;95(5):2226–41. 10.1529/biophysj.107.124990 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2517041/
2. Supplementary material for the above (online) "Beta Cell Exocytosis Model", http://mrb.niddk.nih.gov/sherman/gallery/beta/Vesicle/henquin-pools.ode

Abstract (from Ref 1)

A kinetic model for insulin secretion in pancreatic β-cells is adapted from a model for fast exocytosis in chromaffin cells. The fusion of primed granules with the plasma membrane is assumed to occur only in the "microdomain" near voltage-sensitive L-type Ca2+-channels, where [Ca2+] can reach micromolar levels. In contrast, resupply and priming of granules are assumed to depend on the cytosolic [Ca2+]. Adding a two-compartment model to handle the temporal distribution of Ca2+ between the microdomain and the cytosol, we obtain a unified model that can generate both the fast granule fusion and the slow insulin secretion found experimentally in response to a step of membrane potential. The model can simulate the potentiation induced in islets by preincubation with glucose and the reduction in second-phase insulin secretion induced by blocking R-type Ca2+-channels (CaV2.3). The model indicates that increased second-phase insulin secretion induced by the amplifying signal is controlled by the "resupply" step of the exocytosis cascade. In contrast, enhancement of priming is a good candidate for amplification of first-phase secretion by glucose, cyclic adenosine 3′:5′-cyclic monophosphate, and protein kinase C. Finally, insulin secretion is enhanced when the amplifying signal oscillates in phase with the triggering Ca2+-signal.

Short summary:

The model includes: a membrane; two types of inward Ca^{++} voltage-gated channels (L- and R-type); two corresponding compartments for calcium (microdomain and cytosol, respectively, Figure a below); insulin-carrying vesicles, arranged as a chain of states (from resupply to releasing, Figure b).

- Membrane depolarization is modeled as an input function *V(t);*
- *V* influences the fraction of open L- and R- channels through the sigmoid function minf(*V*);
- Ions flow through L-type channels into C_{md} and through R-type channels into C_i (Ref. 1, Figure 1 and Figure a, left);
- C_i leaks through the currents SERCA, PMCA, NCX and leak (eq. (6) and Figure a, right);
- C_i gates priming (r_2) and resupply (r_3) rates for pre-docked granules;
- C_{md} gates binding and fusion.

The equations for C_{md}, C_i are a nonlinear 2-ODE system coupled to the membrane depolarization (glucose) input. Granule compartments $N_{<...>}$ are a linear 10-ODE system with time-varying coefficients. Secretion is a simple integral; ISR is the secretion in the

last 2 min (per min). The original paper used a least-squares approach to fit the following parameters: $g_L, B, k_1, k_{-1}, r_1, r_{-1}, r_2^0, r_{-2}, r_3^0, r_{-3}, u_1, u_2, u_3, K_p,$ plus the steady state (used as initial values).

Model and data source

The model and data have been derived from publications and the XPP implementation provided as supplementary material (Refs. 1-2).

Curators

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Structural model

Variables [symbol: description (units, ref values)]:

Symbol (eqns.)	Variable (code)	Description	Ref. v.	Units
t	`t`	time	0 – 60	min
r_2	`r2`	calcium-gated resupply rate	0 – r_2^0	s^{-1}
r_3	`r3`	calcium-gated priming rate	0 – r_3^0	s^{-1}
N_1	`N1`	no. of granules in primed microdomain pool	14.71 (*)	granules
N_2	`N2`	no. of granules in bound microdomain pool	0.612 (*)	granules
N_3	`N3`	no. of granules in triggered microdomain pool	0.008 (*)	granules
N_4	`N4`	no. of granules in fused microdomain pool	0 (*)	granules
N_5	`N5`	no. of granules in primed cytosol pool	24.54 (*)	granules
N_6	`N6`	no. of granules in docked cytosol pool	218.02 (*)	granules
N_F	`NF`	number of granules in fused pool	0.003 (*)	granules
N_R	`NR`	number of granules in releasing pool	0.51 (*)	granules
SE	`SE`	total secretion	0 – 250	granules
ISR	`ISR`	average secretion over the last 2 min	0 – 200	pg/islet/min
V	`V`	Current membrane depolarization	-70 – -20	mV
J_{SERCA}	`Jserca`	Leak through SERCA	0 – J_{SERCA}^{max}	µM/s
J_{PMCA}	`Jpmca`	Leak through PMCA	0 – J_{PMCA}^{max}	µM/s
J_{NCX}	`Jncx`	Leak through NCX	-4 – 2	µM/s
L	`L`	Instantaneous total leak		µM/s
I_L	`IL`	Current through L-type channel	~ -1	fA
I_R	`IR`	Current through L-type channel	~ -0.3	fA
J_L	`JL`	Molar flux through L-type channel	~ -1.3	µM/ms
J_R	`JR`	Molar flux through R-type channel	~ -0.001	µM/ms
C_{md}	`Cmd`	Microdomain calcium concentration	0 – 40	µM
C_i	`Ci`	Cytosol calcium concentration	0 – 0.3	µM

(*) Steady-state value

Parameters [symbol: description (units, ref values)]:

Symbol (eqns.)	Variable (code)	Description	Values	Units
– (*)	GlucFact	factor amplifying resupply in presence of glucose (1.2 at 3 mM glucose)	0 or 1.2	–
k_1	k1	Binding rate in microdomain (maximum)	20	$\mu M^{-1}\ s^{-1}$
k_{-1}	km1	Unbinding rate in microdomain	100	s^{-1}
r_1	r1	Cytosol to microdomain migration rate	0.6	s^{-1}
r_{-1}	rm1	Microdomain to cytosol migration rate	1	s^{-1}
r_2^0	r20	Priming rate in cytosol (maximum)	0.006	s^{-1}
r_{-2}	rm2	Cytosol un-priming rate	0.001	s^{-1}
r_3^0	r30	Resupply rate (maximum)	1.205	s^{-1}
r_{-3}	rm3	Un-resupply rate	0.0001	s^{-1}
u_1	u1	Fusion rate	2000	s^{-1}
u_2	u2	Fused-to-relasing rate	3	s^{-1}
u_3	u3	Release rate	0.02	s^{-1}
K_p	Kp	[Ca++] for half-maximal effect on priming	2.3	µM
K_p (*)	Kp2	[Ca++] for half-maximal effect on resupply	2.3	µM
g_L	gL	L-type channel conductivity	250	pS
B	B	Transport rate from microdomain to cytosol	200	s^{-1}
V_m	Vm	L-type channel switching voltage	-20	mV
s_m	sm	L-type channel switching range	5	mV
V_{Ca}	Vca	Calcium membrane reversal potential (?)	25	mV
v_{cell}	vcell	Volume of cell	1.15e-12	L
v_{md}	vmd	Volume of microdomain	4.2e-15	L
f_V	fv	$v_{md}/\ v_{cell}$	0.00365	-
f_i	fi	Free to bound Ca++ ratio in cytosol	0.01	-
f_{md}	fmd	Free to bound Ca++ ratio in microdomain	0.01	-
J_{SERCA}^{max}	Jsercamax	SERCA maximum leak flux	41	µM/s
K_{SERCA}	Kserca	SERCA Ca++ half-switching concentration	0.27	µM
J_{PMCA}^{max}	Jpmcamax	PMCA maximum leak flux	21	µM/s
K_{PMCA}	Kpmca	PMCA Ca++ half-switching concentration	0.5	µM
J_{NCX}^0	Jncx0	NCX leak rate constant	18.67	µM/s
J_{leak}	Jleak	Time-independent Ca++ leak	-0.94	µM/s

(*) notation used in the paper's equations is slightly different from the code. See "implementation notes"

Constants [symbol: description (units, values)]:

Symbol (eqns.)	Variable (code)	Description	Values	Units
α	alpha	(1/2) $Faraday^{-1}$	5.18e-16	µM/ms/fA

Equations

Chain of granules (see Figure b for interpretation of the subscripts to N):

$$dN_1/dt = -[3k_1C_{md}(t) + r_{-1}]N_1 + k_{-1}N_2 + r_1N_5$$
$$dN_2/dt = 3k_1C_{md}(t)N_1 - [2k_1C_{md}(t) + k_{-1}]N_2 + 2k_{-1}N_3$$
$$dN_3/dt = 2k_1C_{md}N_2 - [k_1C_{md}(t) + 2k_{-1}]N_3 + 3k_{-1}N_4$$
$$dN_4/dt = k_1C_{md}(t)N_3 - [3k_{-1} + u_1]N_4$$
$$dN_5/dt = r_{-1}N_1 - [r_1 + r_{-2}]N_5 + r_2N_6$$
$$dN_6/dt = r_3 + r_{-2}N_5 - [r_{-3} + r_2]N_6$$
$$dN_F/dt = u_1N_4 - u_2N_F$$
$$dN_R/dt = u_2N_F - u_3N_R,$$

Calcium dynamics:

$$dC_{md}(t)/dt = f_{md}J_L(t) - f_{md}B[C_{md}(t) - C_i(t)],$$
$$dC_i(t)/dt = f_iJ_R(t) + f_Vf_iB[C_{md}(t) - C_i(t)] - f_iL(C_i(t)),$$

Ca++ inward currents:

$$J_L(t) = -\alpha I_L(t)/v_{md},$$
$$J_R(t) = -\alpha I_R(t)/v_{cell},$$
$$I_L(t) = g_Lm_\infty(V(t))[V(t) - V_{Ca}],$$
$$I_R(t) = 0.25g_Lm_\infty(V(t))[V(t) - V_{Ca}],$$

Ca++ leak currents:

$$L(C_i) = J_{SERCA} + J_{PMCA} + J_{NCX} + J_{leak},$$
$$J_{SERCA} = J_{SERCA}^{max}/[1 + (K_{SERCA}/C_i)^2],$$
$$J_{PMCA} = J_{PMCA}^{max}/[1 + K_{PMCA}/C_i],$$
$$J_{NCX} = J_{NCX}^0[C_i - 0.25],$$
$$J_{leak} = -0.94\mu M/s.$$

Effect of Ca++ on granule dynamics:

$$r_2 = r_2^0C_i(t)/[C_i(t) + K_p]$$
$$r_3 = r_3^0C_i(t)/[C_i(t) + K_p],$$

Input data

V(t): membrane depolarization. Square wave between -70 and -20 mV with 6 min down and 6 min up to reproduce Figure 4, left; steady high for Figure 4, right. Other protocols are also used.

Predicted values

ISR: "instantaneous" insulin secretion in the last 2 min (per minute). The model predicts (and parameters were fitted to reproduce) this quantity.

Graphical representation

The graphical representations below are adapted from Ref. 1.

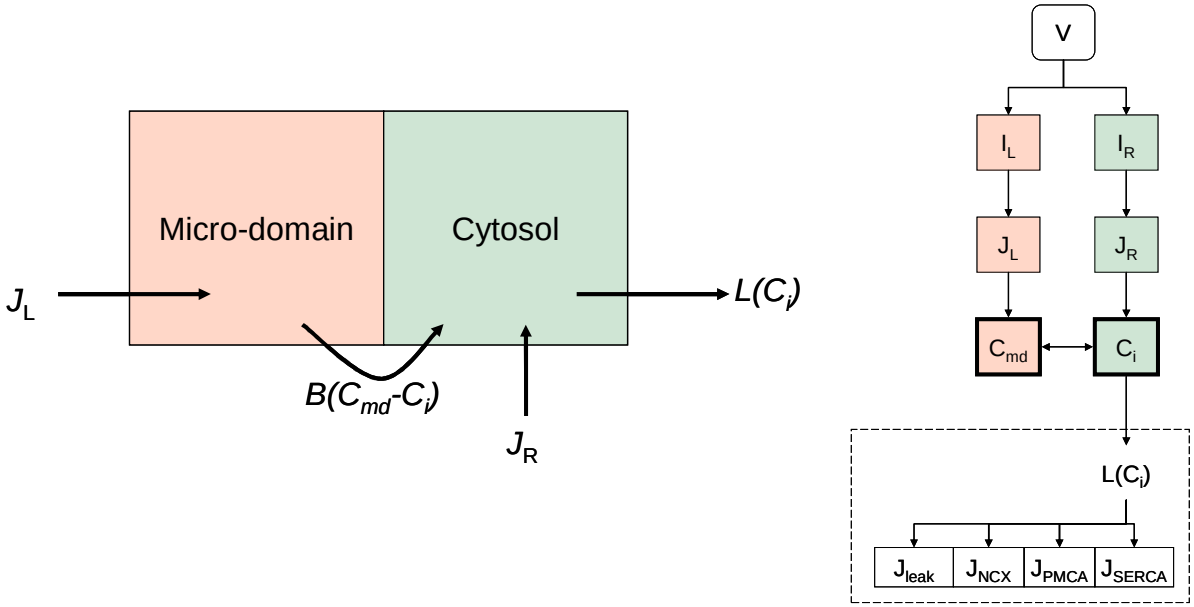

Figure a: Calcium compartments (left) and block diagram of the effect of V on calcium concentrations C through the currents I and ion fluxes J (right). Cytosol calcium leaks through the currents shown in the dashed box.

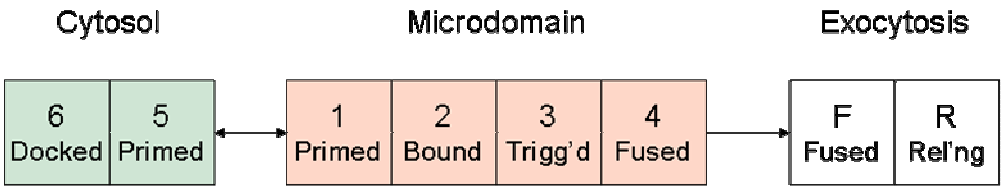

Figure b: Chain of granules. One-character labels refer to the subscripts in the ODEs.

Statistical model

This model has no stochastic components.

Simulation/Estimation

Equation solver

Used ode15s in Matlab/Simulink; other solvers may work. Where allowed by the language, discontinuities in the square-wave *V* input are implemented as events. Otherwise, the integration timestep becomes important.

Estimated parameters

No parameters are estimated.

Implementation remarks

Each of the implementations is a refactoring of the original XPP code (found in Ref. 2 above). Modular language constructs have been used where possible to split the model into separate calcium and vesicle components for readability.

Variables, parameters and units have been kept the same as the original code. Resupply rates r_1 and r_2 are affected by two different parameters, called `Kp` and `Kp2` in the code, with the same value; the equations use a single symbol K_p. Intervals given for variables and parameters reflect the ones used to reproduce paper's Figure 4.

Data description

The model in the original paper fits data provided in Henquin J-C, Ishiyama N, Nenquin M, Ravier MA, Jonas J-C. Signals and Pools Underlying Biphasic Insulin Secretion. Diabetes. 2002 Feb 1;51(90001):60S–67.

Model encoding

Languages

The model has been implemented in several languages in order to benchmark the expressivity of the different approaches to modularity and language features.

Code

File "Readme_Chen2008.txt" provides a technical description of the different implementations. The code for each can be found in its own directory, as follows:

- XPP (original code available at http://lbm.niddk.nih.gov/sherman/gallery/beta/Vesicle/)
- Matlab (tested in R2012a) and Octave (tested in 3.6.2)
- Simulink (tested in R2012a)
- Modelica (tested in OpenModelica)
- Berkeley Madonna (tested with Madonna v. 9.0.74, JEngine 1.8, JRE 1.6.0)
- Antimony, from which these are automatically generated (tested with QTAntimony 2.3 beta):
    - Flat SBML (tested in COPASI 4.8, www.copasi.org, and RoadRunner/SBW Simulation Tool v1.4.4424.32048, sbw.sourceforge.net). See enclosed *NOTES.txt* file for details.
    - Modular SBML, according to the *sbml-comp* extension.

Consistency with published results

Reproduction of artworks

The model correctly reproduces the simulated [Ca^{++}] in the microdomain and cytosol when a square wave of 16 sec period is applied as the membrane potential. Figure c below closely corresponds to Figure 2 of the original paper, Ref. [1]; it was obtained using the Matlab implementation with the ode15s solver.

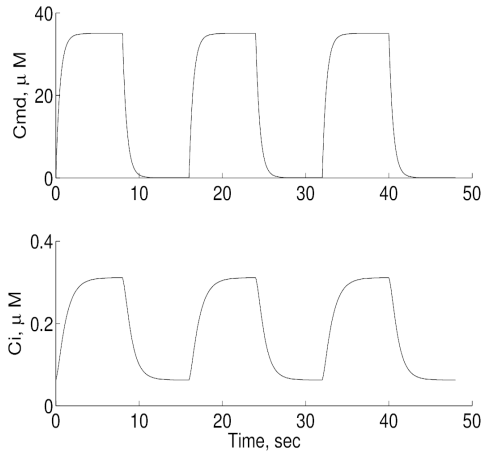

Figure c: C_i and C_{md} as output by the Matlab implementation. Compare with Figure 2 of Ref. [1].

The model also correctly reproduces the simulated ISR, provided as in Chen's paper (compare with open squares of Figure 4 in [1]). Outputs from Octave/lsode (Figure d1) and Simulink/ode15s solvers (Figure d2) are shown below.

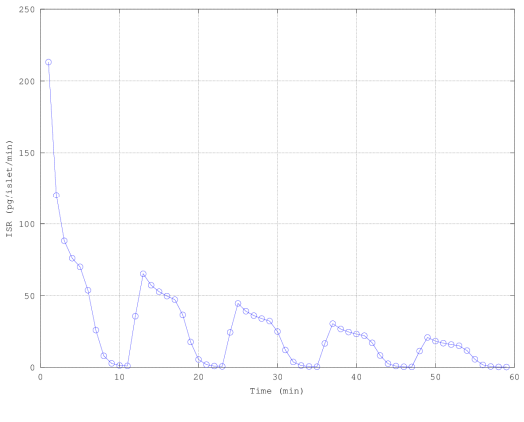

Figure d1: ISR output of the provided Octave implementation

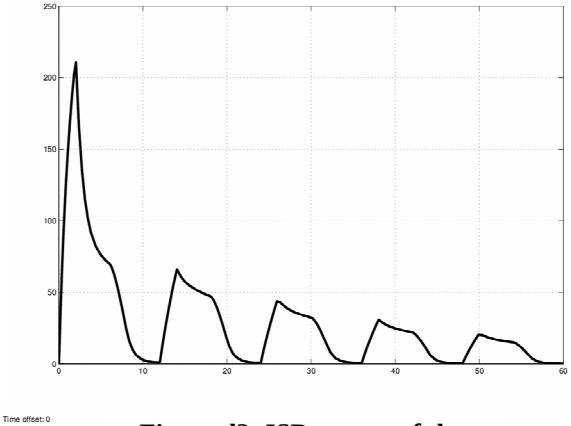

Figure d2: ISR output of the provided Simulink implementation

Inconsistent results

No inconsistent results found.

Suggested additional outputs

No relevant additional outputs.