Table 1 Table showing common parameters in tables from the three sources by DeGaetano. Please note that 1mM $\equiv 1mmol/litre$.

Parameter name	Notation	Value1	Source1	Value2	Source2	Units
initial β-cell mass	B_0, $Bcell0$	1,000	Table 2 in [1]			Mc in [2], nothing in [1], 1 in the table of [3]
insulinemia at age t_0	I_0	30	Table 2 in [1]	50	E1468 [3]	pM
glycemia at age t_0	G_0	4.2	Table 2 in [1]	might be 5 or even 10	E1463,E1467/ initial value of T_η E1471 [3]	mM
glycemia of maximal sensitivity of regulation of β cells	G_λ	G_0	[3]			mM
liver glucose output	T_{gl}					mM/min
1^{st} order insulin independent glucose tissue uptake rate	K_{xg}	0	Table 2 in [1]			min^{-1}
1^{st} order elimination rate for insulin at baseline (e.g. at 18 yr)	$K_{xiStart}$	0.05	Table 2 in [1]			min^{-1}
1^{st} order elimination rate for insulin at the end of life (e.g. at 90 yr)	K_{xiEnd}	0.035	Table 2 in [1]			min^{-1}
value of K_{xgI} at t_0	K_{xgI0}	0.0001 $(4.3month^{-1}/pM)$	Table 2 in [1]			min^{-1}/pM
Elapsed time after adulthood (t0) of midpoint K_{xgI} $(0.5 \times K_{xgI})$ decrease	t_I	125 (double check, as phrased as -125)	Table 2 in [1]			mo in [2, 3], nothing in [1]
steepness of hill-function decrement in insulin sensitivity	ν_I	18 (double check- seems extremely high) (checked- on page E1466, 2^{nd} column [3] it is mentioned that the steepness and time at 50% decrease is arbitrarily made to vary wildly depending on the simulated pathological condition)	Table 2 in [1]			1
minimum value of λ (β cell replication rate), i.e. the maximum net apoptosis rate	λ_{min}	-0.02	Table 2 in [1]	-0.06	E1466 [3]	mo^{-1}
value of η(baseline pancreatic reserve at t_0 (determined)	η_0	0.04 ?	Table 2 in [1]	maybe 0.08	based on figure 1	mo^{-1}
pancreatic glucose toxicity coefficient	$K_{\eta g}$	0.02	Table 2 in [1]			$mo^{-1}(mM)^{-1}$
centering glucose concentration for Hill-shaped glycemia effect on pancreatic insulin release	G_h	9	Table 2 in [1]			mM
power coefficient for Hill-shaped glycemia effect on pancreatic insulin release	ν_h	4	Table 2 in [1]			1
initial condition on glycosylated Haemoglobin(HbA1c)	A_0	5 (? Double Check)(checked! should be 5 not 5%=0.05)	Table 2 in [1]			%
the spontaneous elimination rate of (glycosylated) Haemoglobin	K_{xa}	0.1	Table 2 in [1]	0.238	E1467 [3]	mo^{-1}
Maximum age for aging in insulin first-order eliminate rate in a person	t_{max}	90	E1467[3]			mo
Initial value of x	x_0					1

Table 2 Table showing parameters not mentioned in all the articles

Parameter name	Notation	Value	Source	Units
maximal $\beta - cell$ population	B_{max}	4,000	Table 2 in [1], [2]	Mc
fractional minimal reachable insulin sensitivity	$K_{xgI}min$	0.025	Table 2 in [1]	1
End-of-life pancreatic reserve restoration rate as a fraction of baseline(normal) value	$T_\eta End$	0.94	[1]. (Double check use)	1
The value of the h(G) function at t_0 (determined)	h_0		[2, 3]	1
the scaling factor for the X support variable, computed so as to center the X sigmoid curve on the value $\lambda = 0$	ξ	$\frac{G_\lambda}{G_0}\sqrt[3]{-\frac{\lambda_{min}}{\eta_0}/(1+\frac{\lambda_{min}}{\eta_0})}$ [3]	[2, 3]	1
value of I_{maxB} at t_0	I_{maxB0}	$\frac{I_0}{h_0 B_0}$	[2, 3]	pM/Mc
Starting age, with system at equilibrium, in month	t_0	18 yr	p E1465 in [3] [2]	mo
Half-life of pancreatic reserve at 10 mM glucose	$t_{\eta 10}$	$\frac{log(2)}{10K_{\eta g}}$[3]	[2, 3]	mo

Table 3 Table showing model states and dynamic variables

Equation	Source	Unit of state/variable
$\frac{dB(t)}{dt} = \lambda(G)B(1-\frac{B}{B_{max}}),\ B(t_0)=B_0$	[1, 2]	Mc
$\frac{dB(t)}{dt} = \lambda B,\ B(t_0)=B_0$	[3]	Mc
$\frac{d\eta(t)}{dt} = -K_{\eta g}G\eta + T_\eta,\ \eta(t_0)=\eta_0$	[2, 1, 3]	mo^{-1}
$G = \frac{\gamma}{\rho+I}$	[2, 1, 3]	mM
$I = h(G)I_{maxB}B$	[2, 1, 3]	pM
$h(G) = \frac{(G/G_h)^{\nu_h}}{1+(G/G_h)^{\nu_h}} = \frac{G^{\nu_h}}{\alpha_h+G^{\nu_h}},\ \alpha_h = G_h^{\nu_h}$	[2, 1, 3]	1
$\lambda(G) = \lambda_{min} + \eta\frac{x^3}{1+x^3},\ x(G) = x_0\frac{G}{G_\lambda}$	[2, 1, 3]	mo^{-1}
$K_{xi}(t) = K_{xiStart} + \frac{t-t_0}{t_{max}-t_0}(K_{xiEnd} - K_{xiStart})$	[2, 1, 3]	min^{-1}
$K_{xgI}(t) = \begin{cases} K_{xgI0}(1-\frac{(\frac{t-t_0}{t_I-t_0})^{\nu_I}}{1+(\frac{t-t_0}{t_I-t_0})^{\nu_I}}) & ,t \geq t_0 \\ K_{xgI0} & ,t \leq t_0 \end{cases}$	[3]	min^{-1}/pM
$K_{xgI}(t) = \begin{cases} K_{xgI0}(1-(1-K_{xgImin})\frac{(t-t_0)^{\nu_I}}{(t_I-t_0)^{\nu_I}+(t-t_0)^{\nu_I}} & ,t \geq t_0 \\ K_{xgI0} & ,t \leq t_0 \end{cases}$	[1]	min^{-1}/pM
$\frac{dA}{dt} = -K_{xa}A + K_{ag}G\frac{(100-A)}{100},\ A(t_0)=A_0$	[2, 1, 3]	%
$\gamma = \frac{T_{gl}}{K_{xgI}}$	[2, 1, 3]	$mM \times pM$
$\rho = \frac{K_{xg}}{K_{xgI}}$	[2, 1, 3]	pM
$I_{maxB} = \frac{T_{igB}}{K_{xi}}$	[2, 1, 3]	pM/Mc
$T_{igB} = \frac{K_{xiStart}I_0}{h(G_0)B_0}$	[2, 1, 3]	$pM/min/Mc$
$K_{ag} = \frac{K_{xa}A_0}{G_0\frac{(100-A_0)}{100}}$	[2, 1, 3]	$\%/mo/mM$
$\lambda_{max} = \lambda_{min} + \eta$	[2, 1, 3]	mo^{-1}
$T_{gl} = (K_{xg} + K_{xgI}I_0)G_0$	[3]	mM/min
$T_\eta = K_{\eta g}G_0\eta_0$ static parameter or from figure 1	[3]	mo^{-2}

1 Mistakes

1. Table 1 , page E1464 [3] : the unit of $K_{\eta g}$ is mo^{-1}/mM^{-1} while it should be $mo^{-1}mM^{-1}$
2. Page E1465 [3]: "we considered reasonable a range of β-cell number from 0.1×10^9 to 8×10^9", while the initial value hs been considered as 1000 Mc
3. Fig1, Page E1467 : The unit of K_xgI is mo^{-1}/pM while in the tables as well as in the text on page E1466 the unit is mentioned as min^{-1}/pM [3]. In table2 of [1] K_{xgI_0} has been written as $K_{xgI}I_0$, but the unit and description is consistent with K_{xgI_0}
4. T_{igB} on page E1467 [1] is 0.0287 and not 0.00287

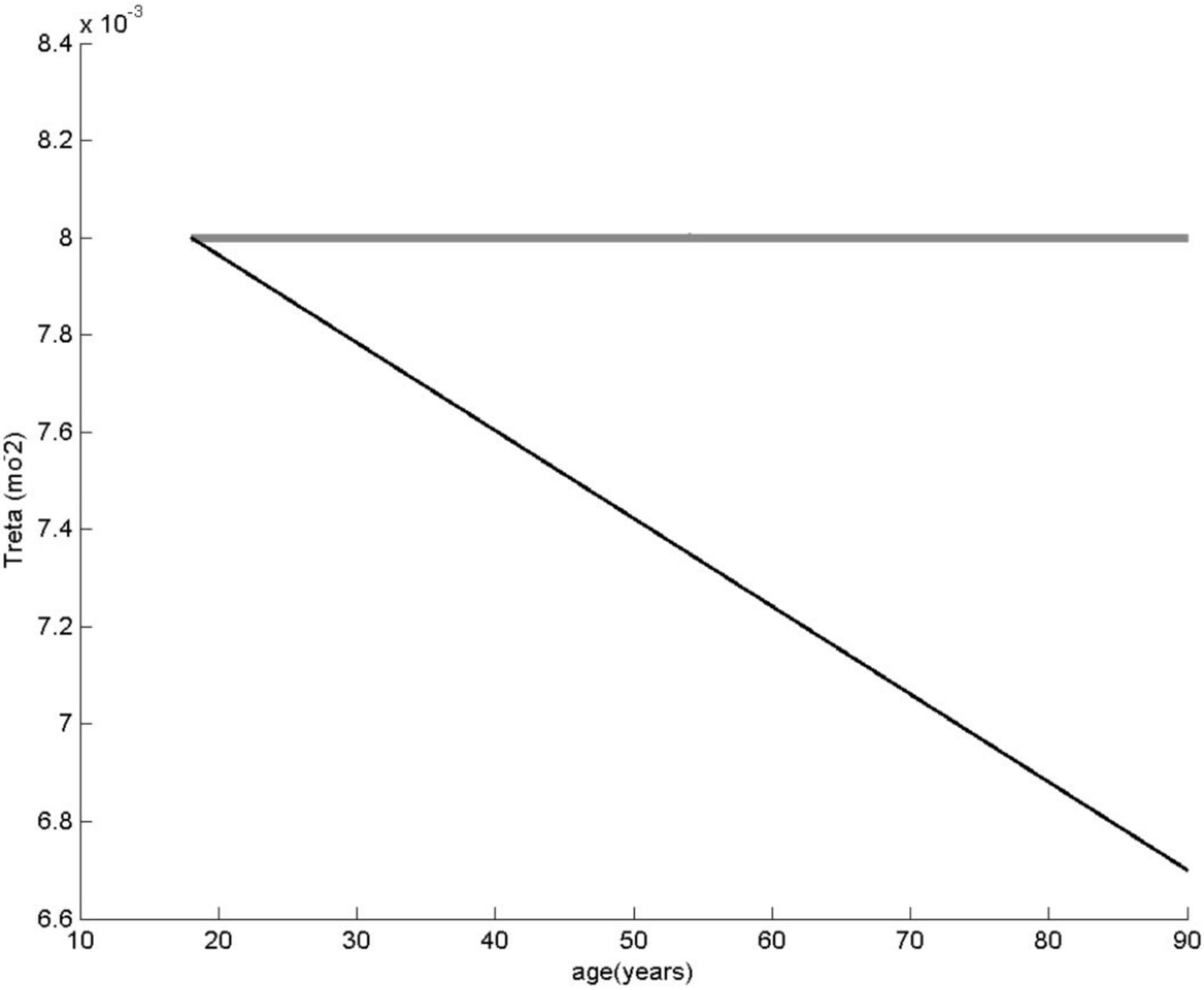

Fig. 8. Predicted time course of spontaneous pancreatic replication recovery (T_η) when kept at normal levels throughout life (gray line) and when made to decrease slowly but constantly (black line). Solid and dashed lines (corresponding to normal or impaired insuliln sensitivity) are superimposed and indistinguishable.

Figure 1 T_η

2 Double Values

1. Fig8, Page E1471 : The initial value of $T-$ is 8×10^{-3}, but 4×10^{-3} in the table. The correct value based on reconstructing the graphs should be 4×10^{-3}.
2. value of K_{xa} has been found to be 0.238 based on reconstructing the graphs in [1].
3. $\lambda_{min} = 0.02$ based on reconstructing the graphs in [1].
4. T_{igB} on page E1467 [1] is 0.0287 and not 0.00287
5. K_{xgI} on Fig 9 page E1471 [1] has in fact a unit of min^{-1}/pM and the initial value has been considered as $1 \times 10^{-4} min^{-1}/pM$ which is about $4.3 month^{-1}/pM$

3 Final Report

3.1 DeGaetano's compartmental model

All equations used in the final version of the model are extracted from [3], except for the equation describing Beta cells(B), which is extracted from latest version of Degaetano's work as $\frac{dB(t)}{dt} = \lambda(G)B(1 - \frac{B}{B_{max}}), \quad B(t_0) = B_0$

To speed up the model all stocks, flows, dynamic variables and links are ignored. The compartmental equations are instead solved in a the "equationSolverFunction". This function gets updated at each "dt" the value of which is currently set to 10^{-1} years.

The original system dynamics model before being used in the Hybrid model has been put in the folder as "DeGaetano-v12-2008".

3.2 Important functions in SD

3.2.1 updateGfastingGlucoseAndIFastinInsulin

This function finds and updates the values for Glucose and Insulin based on Newton–Raphson method. The other import functionality of this function is updating all the components of System-Dynamics including "States" and "Dynamic variables".

3.2.2 equationSolverFunction

This function finds the integration of all flows using Euler method, replacing the integration process in Anylogic.

3.2.3 calculateInsulinSensitivityFunction

In this function, Insulin Sensitivity is being calculated considering different trimesters of pregnancy, postpartum, different treatment strategy such as life-style session, metformin and even insulin. One very important issue that should be reconsidered is the dose of metformin and insulin. Currently the dose of Insulin is set to a value of 0. The impact of metformin and lifestyle treatment is based on the third paper of DeGaetano. The impact of treatment with Insulin on Insulin sensitivity has been considered by adding an additional term to the equation describing I in the slow model of Degaetano and find G and I based on this extra term. So the impact of treatment with insulinn has been calculated in the body of the function "updateGfastingGlucoseAndIFastinInsulin".

3.3 Birth Outcomes

NICU or SCN Admissions, Shoulder injury, Macrosomia and C-section occurrences have been found based on the average of fasting blood glucose level during pregnancy. The Odds ratios associated with each outcome for each increase of 0.4 mmol/litres (i.e., 0.4 mM) are extracted from [4] and [5].

The probability of each birth-outcome occurrence is calculated as follows:

$$p = \frac{1}{1 + (\frac{1-P_N}{P_N})(e^{\beta_1 * (\frac{(G_N - G)}{0.4mM}})} \tag{1}$$

, where e_1^{β} is the odds–ratio extracted from Table 3 of [4], G is the glucose level extracted from the model, G_N is the level of normal glucose and P_N is the probability of each birth-outcome occurrence given that mother had a normal glucose level [5]. My personal interest made me include the photo of one my favourite pieces of papers –which describes equation 1– to this report 3.3. Please note, however, that this derivation did not account for the fact that the odds ratio was defined as applying for each increase of 0.4mM; the formula given above for p takes this properly into account, unlike the original hand-written derivation.

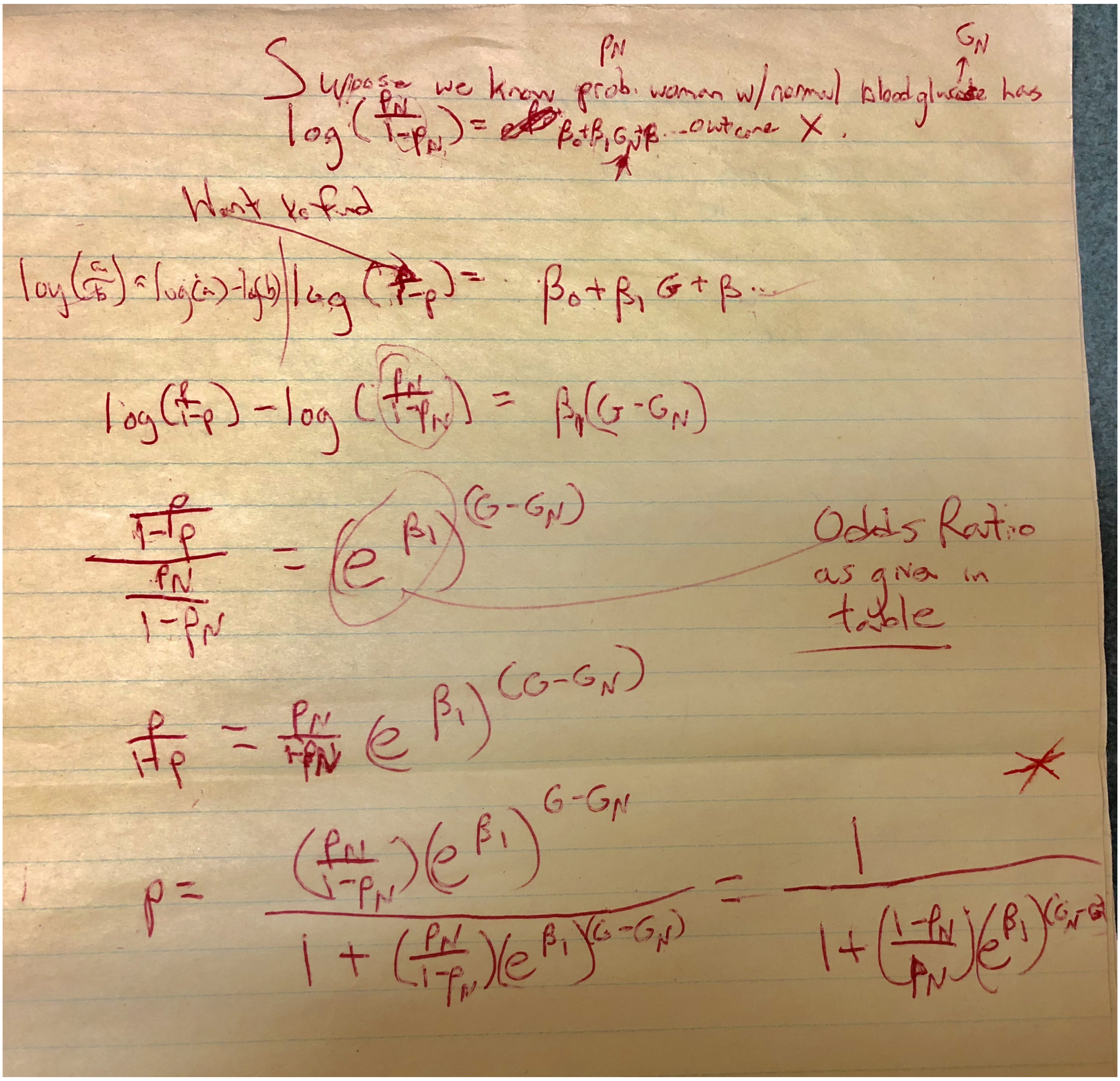

Figure 2 Extraction of probability of birth out comes

Appendix A:
Original equations

$$\frac{dB(t)}{dt} = \varepsilon\lambda B, \quad B(t_0) = B_0 \tag{2}$$

$$\frac{d\eta(t)}{dt} = \varepsilon(-K_{\eta g}G\eta + T_\eta), \quad \eta(t_0) = \eta_0 \tag{3}$$

$$\frac{dG(t)}{dt} = T_{gl} - K_{xg}G - K_{xgI}IG, \quad G(t_0) = G_0 \tag{4}$$

$$\frac{dI(t)}{dt} = h(G)T_{igB}B - K_{xi}I, \quad I(t_0) = I_0 \tag{5}$$

$$h(G) = \frac{(G/G_h)^{\nu_h}}{1 + (G/G_h)^{\nu_h}} = \frac{G^{\nu_h}}{\alpha_h + G^{\nu_h}}, \quad \alpha_h = (G_h)^{\nu_h} \tag{6}$$

$$\lambda(G) = \lambda_{min} + \eta\frac{x^3}{1 + x^3}, \quad x(G) = x_0\frac{G}{G_\lambda} \tag{7}$$

$$\frac{dA}{dt} = -K_{xa}A + K_{ag}G\frac{(100 - A)}{100}, \quad A(t_0) = A_0 \tag{8}$$

Appendix B:

Fast equations

$$\frac{dB(t)}{dt} = 0, \quad B(t_0) = B_0, \quad \Rightarrow \quad B \equiv B_0 \tag{9}$$

$$\frac{d\eta(t)}{dt} = 0, \quad \eta(t_0) = \eta_0 \quad \Rightarrow \quad \eta \equiv \eta_0 \tag{10}$$

$$\frac{dG(t)}{dt} = T_{gl} - K_{xg}G - K_{xgI}IG, \quad G(t_0) = G_0 \tag{11}$$

$$\frac{dI(t)}{dt} = h(G)T_{igB}B - K_{xi}I, \quad I(t_0) = I_0 \tag{12}$$

Appendix C: Slow equations

$$\frac{dB(t)}{dt} = \lambda B, \quad B(t_0) = B_0 \tag{13}$$

$$\frac{d\eta(t)}{dt} = \varepsilon(-K_{\eta g} G\eta + T_\eta), \quad \eta(t_0) = \eta_0 \tag{14}$$

$$0 = T_{gl} - K_{xg}G - K_{xgI}IG, \quad \Rightarrow \quad G = \frac{T_{gl}}{K_{xg} + K_{xgI}I} \tag{15}$$

$$0 = h(G)T_{igB}B - K_{xi}I, \quad \Rightarrow \quad I = h(G)\frac{T_{igB}}{K_{xi}}B \tag{16}$$

$$\frac{dA}{dt} = -K_{xa}A + K_{ag}G\frac{(100 - A)}{100}, \quad A(t_0) = A_0 \tag{17}$$

Author details

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