How modelling can help understanding environmental triggers of disease

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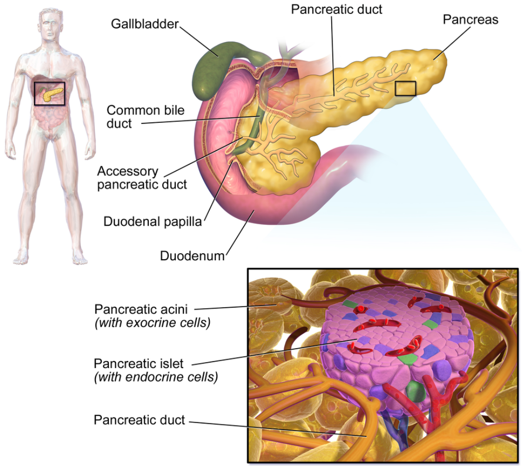
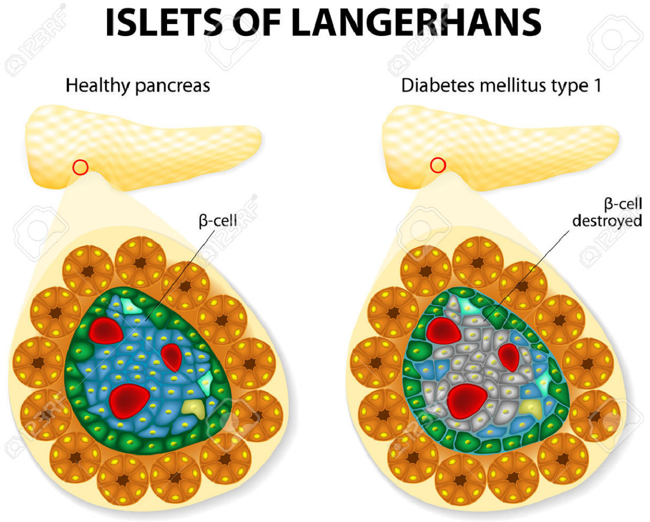
Type I diabetes

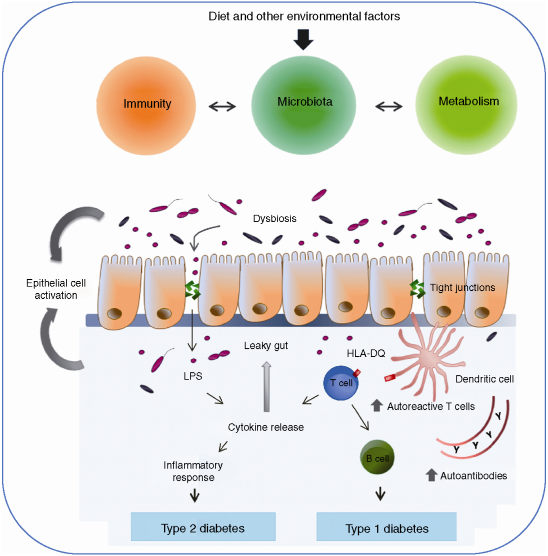


Pancreatic Tissue

Type I diabetes

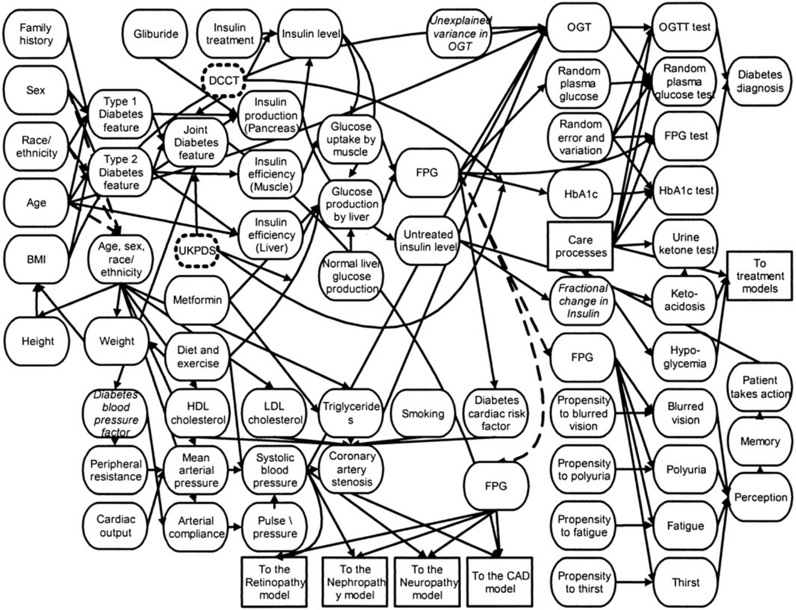


Innate immunity and intestinal microbiota in the development of Type 1 diabetes

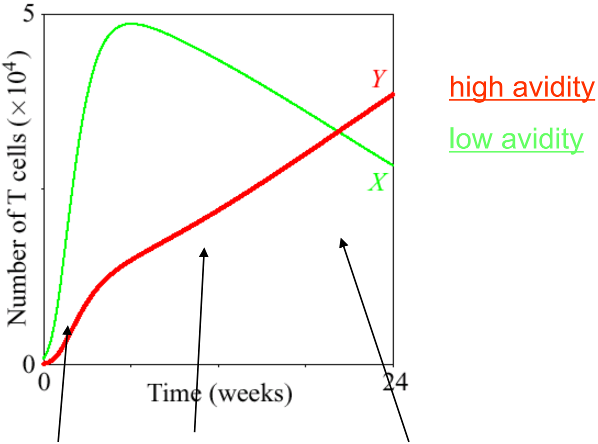


NOD mouse model

Trump modelling



Gaining insights



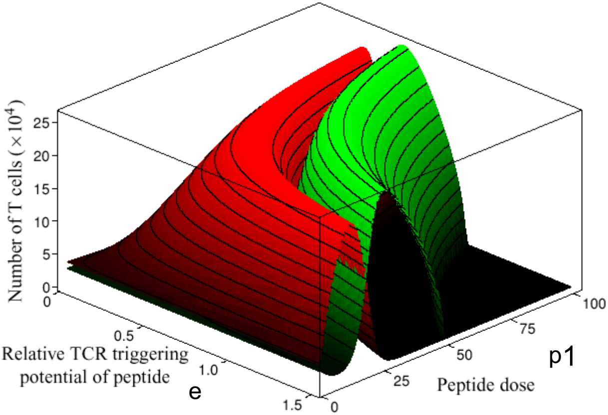
Weak competition

memory pool turnover

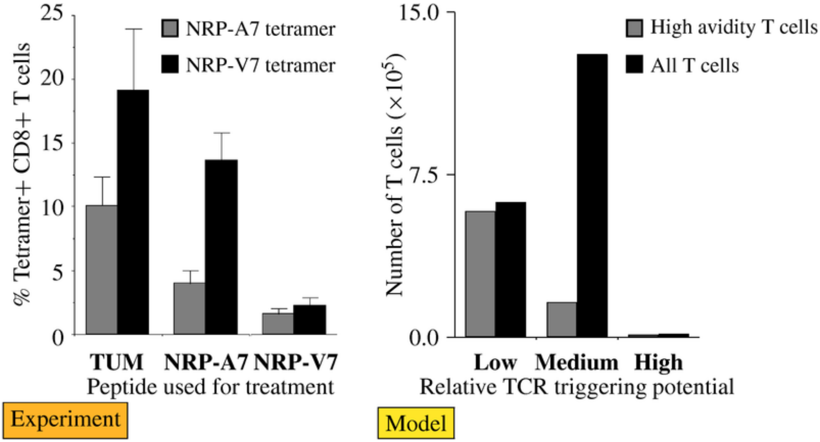
strong competition for sites on APC's;

Gaining insights

Relative size of high and low avidity populations depends on both peptide dose p and affinity (triggering potential), e. Small changes in either can be very damaging.



Gaining insights



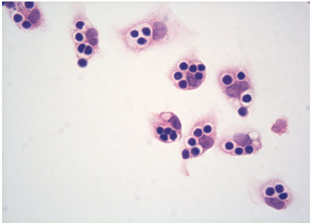
Macrophage issues

Isolate immune scavenger cells (macrophages)

How do macrophages from healthy animals compare to those prone to autoimmune diabetes?

Engulfment rate k_e

Digestion rate k_d

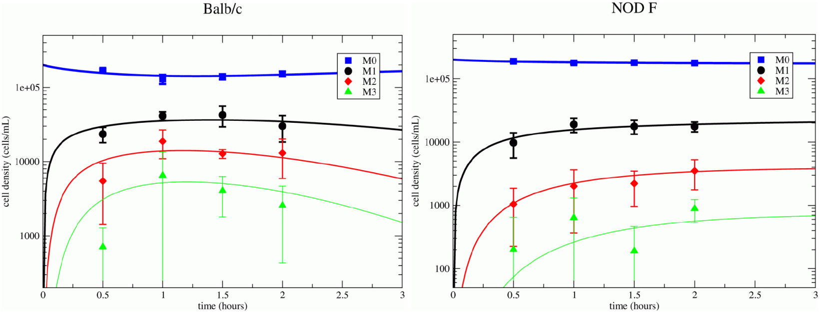


Expts:

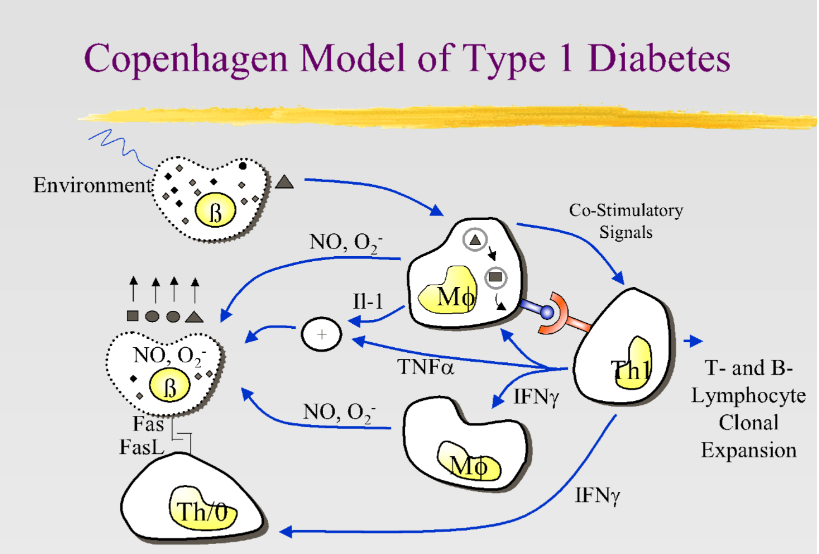
Count number of macrophages with 1, 2, 3, .. etc engulfed cells.

Quantifying the macrophage effect

We also use the full model differential equations and an optimization method (Marquard Levenberg) to fit parameter values to the model and its variants.

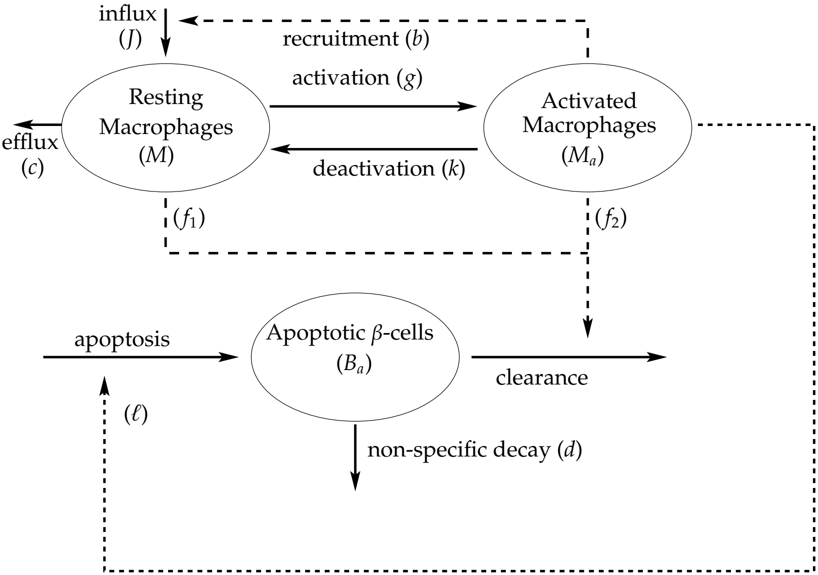


Copenhagen model



J. Nerup, original presentation

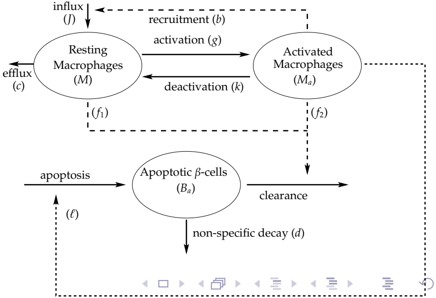
Basic model



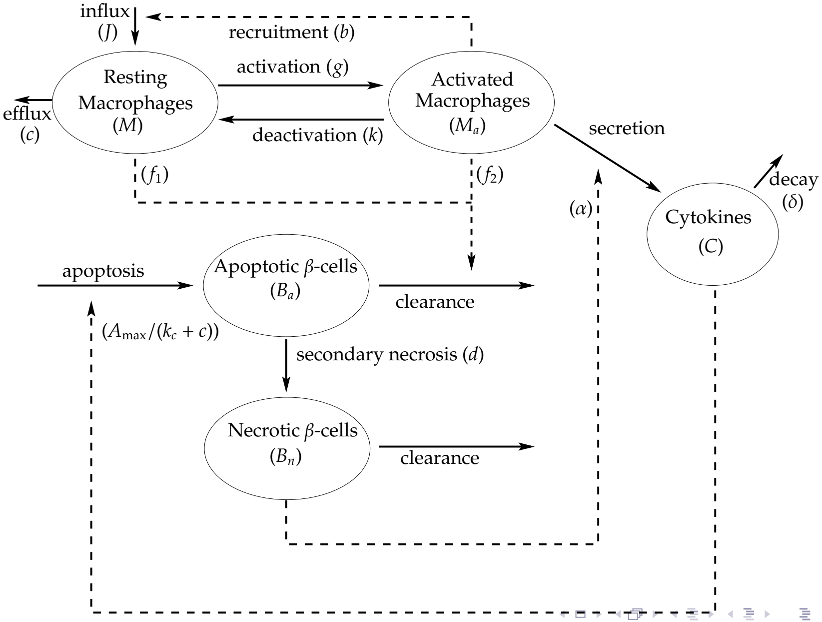
influx
(J)
recruitment (b)
activation (g)
Resting
Macrophages
(M)
Activated
Macrophages
(M_a)
efflux
(c)
deactivation (k)
(f_1)
(f_2)
apoptosis
Apoptotic β-cells
(B_a)
clearance
(ℓ)
non-specific decay (d)

Corresponding equations

$$\frac{dM}{dt} = J + (k+b)M_a - cM - gMB_a - e_1 M(M+M_a)$$
$$\frac{dM_a}{dt} = gMB_a - kM_a - e_2 M_a(M+M_a)$$
$$\frac{dB_a}{dt} = W(t) + \ell M_a - f_1 MB_a - f_2 M_a B_a - dB_a$$

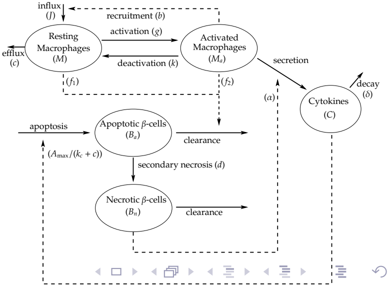


Extended model

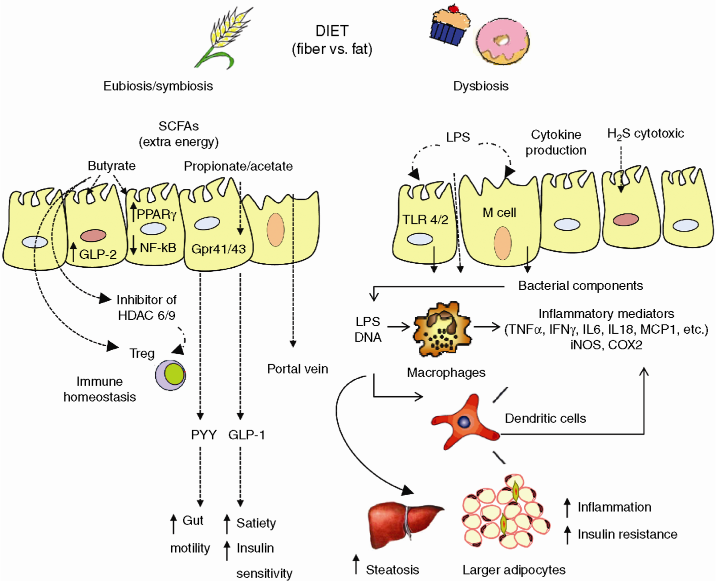


Corresponding equations

$$\frac{dM}{dt} = J + (k+b)M_a - cM - gMB_a - e_1 M(M+M_a)$$
$$\frac{dM_a}{dt} = gMB_a - kM_a - e_2 M_a(M+M_a)$$
$$\frac{dB_a}{dt} = \frac{A_{max}C}{k_c + C} - f_1 MB_a - f_2 M_a B_a - dB_a$$
$$\frac{dB_n}{dt} = dB_a - f_1 MB_n - f_2 M_a B_n$$
$$\frac{dC}{dt} = I + \alpha B_n M_a - \delta C$$



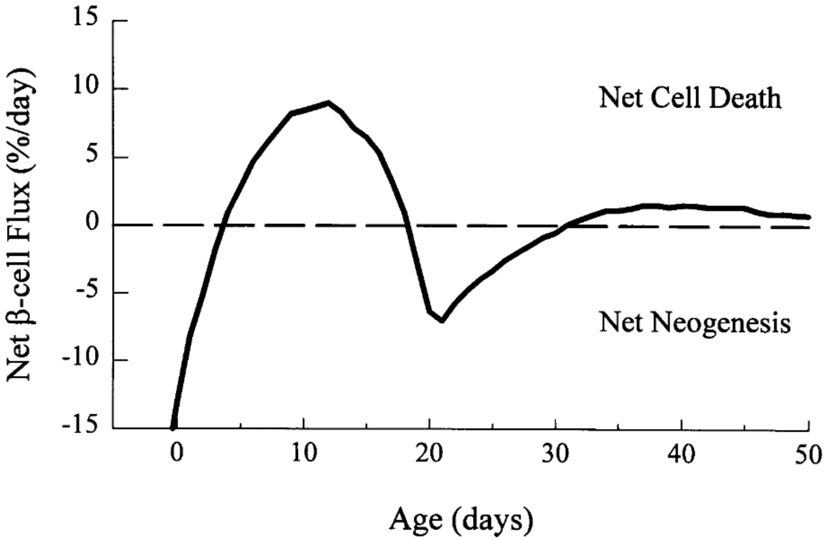
Cytokine level (e.g., IL1-β) and the gut

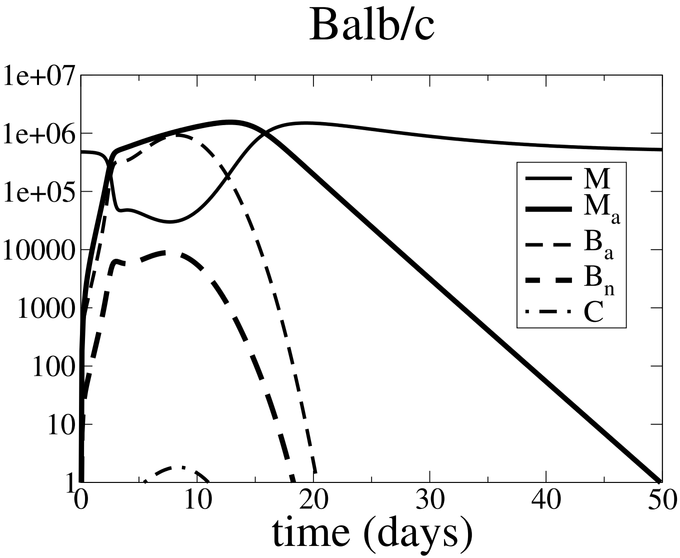


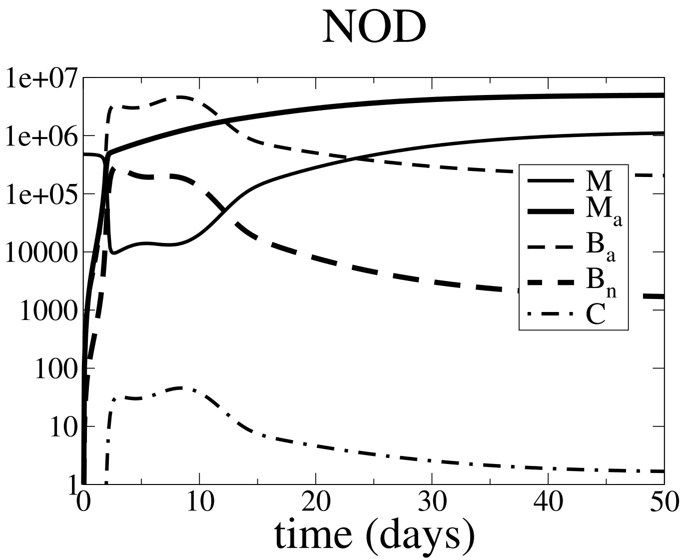
Realistic, carefully measured parameters

parameter	meaning	Balb/c	NOD	units
J	normal macrophage (M) influx	5		$\times 10^4$ cells ml^{-1} d^{-1}
c	macrophage egress rate	0.1		d^{-1}
b	recruitment rate of M by M_a	0.09		d^{-1}
ℓ	B_a apoptosis induced per M_a	0.41		d^{-1}
d	B_a non-specific decay rate	0.5		d^{-1}
k	M_a deactivation rate	0.4		d^{-1}
$g = f_1$	basal phagocytosis rate per M	2	1	$\times 10^{-5}$ ml cell^{-1} d^{-1}
f_2	activated phagocytosis rate per M_a	5	1	$\times 10^{-5}$ ml cell^{-1} d^{-1}
$e_1 = e_2$	anti-crowding terms	1		$\times 10^{-8}$ cell^{-1} d^{-1}

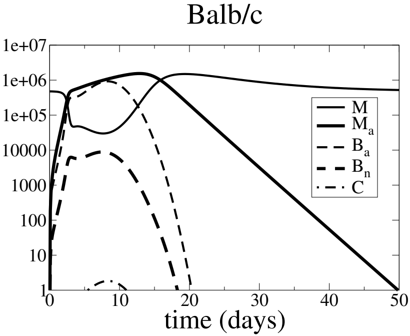
Apoptotic wave

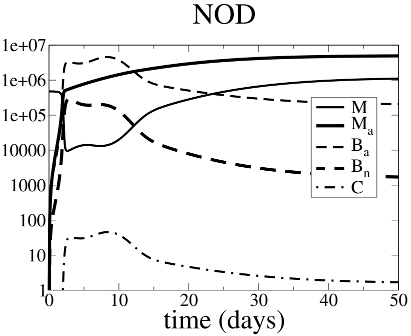



Balb/c
1e+07
1e+06
1e+05
10000
1000
100
10
1
0
10
20
30
40
50
time (days)
M
M_a
B_a
B_n
C


NOD
1e+07
1e+06
1e+05
10000
1000
100
10
1
0
10
20
30
40
50
time (days)
M
M_a
B_a
B_n
C

Running a model vs understanding





Simplifications:

- variables behave in the same manner: merge them
- variables change very slowly: treat them as a parameter
- variables change very fast: make a Quasi-Steady-State assumption

Acknowledgements

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