Exercises EI Workshop Connecting Nutrition and Health: No way back? Modelling case-study how the environment and nutritional choices can trigger a chronic disease.

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Model of the initial damage to the pancreas

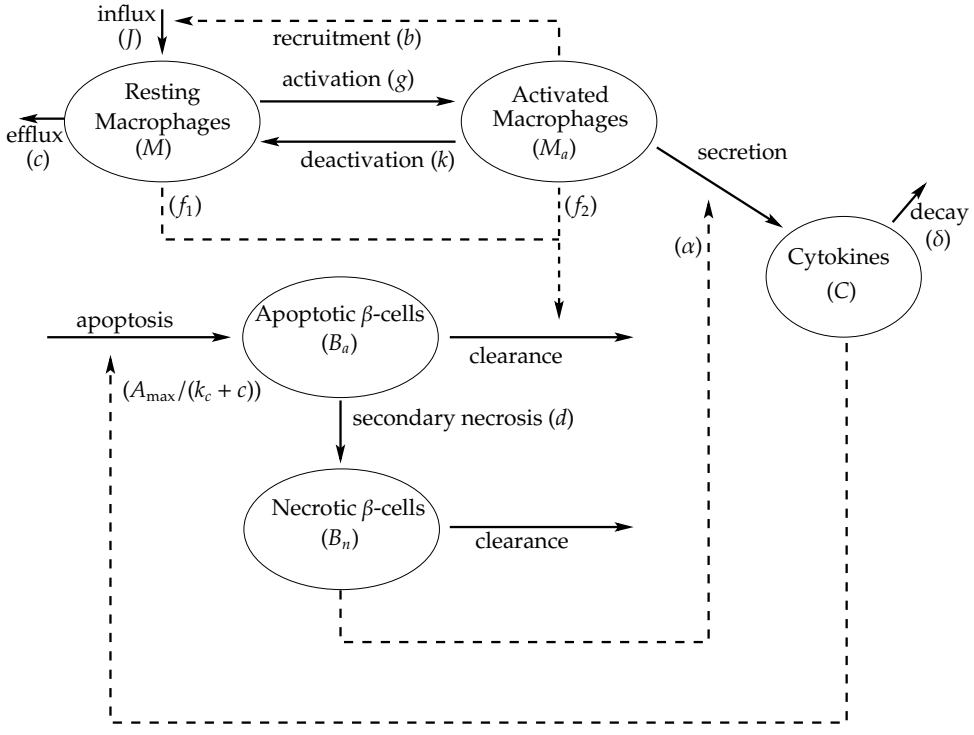

Figure 1: Schematic of the interactions taken into account.

These interactions underlying the triggering of type I diabetes can be captured by the following model:

$$\frac{dM}{dt} = J + (k+b)M_a - cM - gMB_a - e_1M(M+M_a)$$
$$\frac{dM_a}{dt} = gMB_a - kM_a - e_2M_a(M+M_a)$$
$$\frac{dB_a}{dt} = \frac{A_{max}C}{k_c+C} - f_1MB_a - f_2M_aB_a - dB_a$$
$$\frac{dB_n}{dt} = dB_a - f_1MB_n - f_2M_aB_n$$
$$\frac{dC}{dt} = I + \alpha B_nM_a - \delta C$$

1. Make sure you understand all the variables, terms and parameters in the model.

2. To be able to analyse this set of coupled ODEs, we will use a program called GRIND[1]. GRIND has been developed by Rob de Boer, Theoretical Biology/Bioinformatics, Utrecht University, the Netherlands. The program is specifically developed for simulating and analysing ODEs. (GRIND is open-source software, and can be obtained at `http://bioinformatics.bio.uu.nl/rdb/grind.html`.) The file `full_model.grd` contains the model. You can start it up by typing `grind full_model.grd`. A prompt will appear which you have to use to type in commands. All commands can be shortcut to the first two letters. (So, when the text below states `di(splay)`, it means that you can either type `di` or `display`.) To start, to look at the model itself, type `di(splay) full_model.grd`. The notation `M'` = is a shortcut of writing `dM/dt=`. If you want to modify the file itself, or create another model, you cannot do this directly, but you have to open the file in a basic editor, such as `notepad`. We also use two parameter files, `balbc.par` and `nod.par`. Look at this file with `di(splay) balbc.par`. Type `re(ad) balbc.par` to read in the parameters. The file `model.run` defines what should be plotted along the axes (`ax v` is the vertical axis of a timeplot), and how long simulations should run (`finish 50 500` means run for 50 days, and generate 500 output values). Now `re(ad) model.run` to set this all up and generate a first timeplot. What do you observe?

3. Now read in `nod.par` and generate again a timeplot. To do so, a useful combination is `ert`, which stands for `erase;run;timeplot`. Describe what you observe. Are the dynamics different?

4. We had started with a small gut-triggered inflammatory response (i.e., the value of I is non-zero). Now put I to zero (by typing `I=0.`). What do you observe, and what does this imply?

5. Run again, each time for slightly higher initial values of I (for example, by typing `I=0.001`; `I=0.0012`; etc.). Describe what you observe. Do you notice something peculiar?

   To understand this behaviour we wish to further simplify the model using the QSS assumption.

6. Use two other windows to type `grind reduced_model.grd`. and `grind further_reduce`
   Does the QSS assumption have a strong effect on the dynamics?

[1] **GR**eat **IN**tegrator **D**ifferential equations

7. The further reduced model has only two variables and therefore allows for a phase plane analysis. Use this model, read in the parameters, and type `re(ad) nullclines.run`, for both the parameter settings. In this plot the variables are plotted against one another instead of against time.

8. Start at different initial conditions. This can be done using the command `cu(rsor)`, after which with the mouse a point can be selected, followed by the command `ru(n)`. What do you observe? Do you understand what you are doing?

9. Point out within a timeplot (as generated in the previous questions) the moments at which one of the variables does not change. How do you observe for example dM/dt within a timeplot? What is dM/dt when the variable does not change?

10. The nullclines of M_a and of B_a are the combinations of all values of (M_a, B_a) for which either $dM_a/dt = 0$ or $dB_a/dt = 0$. Draw them again in GRIND, using the command `nu` (`nu Ma` draws the nullcline of M_a; `nu Ba` of Ba; and `nu Ma Ba` both nullclines). Make sure you understand what the nullclines represent.

11. Is it possible to change in time from $dMa/dt < 0$ to $dMa/dt > 0$ without passing through $dMa/dt = 0$? Why (not)? What does this imply for the direction of the trajectories in the phase-plane?

12. Are there points in the phase-plane where none of the variables change? What does this imply?

13. Using GRIND, start close to each of the equilibria (with `cu(rsor)`) and `ru(n)`. Do you move towards the equilibrium? Can you determine the stability of each equilibrium?

14. We can plot the values and stability of the equilibria as a function of the gut-triggered level of inflammation. To do so type `re(ad) bifurcation_balbc.run` or `re(ad) bifurcation_nod.run`, for each parameter setting. A blue line indicates a stable equilibrium, a white one an unstable one. What do you observe? What does this imply? Make sure you understand this graph.

15. Make timeplots for each qualitatively different setting.

16. Can you now understand what caused in model the sudden onset of Type I diabetes, and why, once diabetes is acquired, it basically never goes away?

17. Do you think that these results are just mathematical artefacts?