On line supplement for “Antigen feast or famine”

Michael L. Dustin[1] and Michael Meyer-Hermann[2,3]
[1]Skirball Institute for Molecular Medicine, New York University School of Medicine, New York, NY 10016, USA.
[2]Department Systems Immunology, Helmholtz Centre for Infection Research, Braunschweig, Germany.
[3]Biocenter for Life Science, University of Technology, Braunschweig, Germany.
E-mail: michael.dustin@med.nyu.edu

We are convinced that mathematical modeling needs to become a standard tool in biology and that results from models should be introduced into our thinking about new findings. In our perspective on Thaunat et al we naturally sought a conceptual understanding of the relevance of asymmetric B cell division by modifying an existing model to incorporate this feature and then testing some different scenarios we could imagine. In order to make this process more transparent we describe the steps involved in modifying a recently published model to achieve this goal.

Starting from an advanced model for the GC (15), which is written in C++ programming language, we needed only three steps: 1) BCs that carry antigen had to be defined in the code. This was easy, as BCs were implemented in the published model to collect antigen from follicular dendritic cells. Thus, this quantity, being a variable in the BC C++-class needed just to be memorized beyond interaction with TFH. 2) We needed to introduce asymmetric division of BCs. The retained antigen memorized in the first step was saved in one daughter cell only while the other daughter reset its antigen variable to zero. 3) We programmed various fates of antigen carrying BCs (Figure 1SA). The antigen starved BCs were assumed to behave similarly to BC in the starting model, so no changes were needed. The antigen carrying BCs were programmed to have one of three possible fates: a) It searches for help by TFH and presents pMHC with a density corresponding to the amount of antigen retained from the previous round of selection (M1); b) It acquires further antigen from follicular dendritic cells (as the other BCs do) but adds the newly found antigen to the memorized antigen from the last round of selection (M2); c) It stops searching for antigen or TFH interaction but, instead, differentiates to a plasma cell without mutating its receptor (M3). Note that in cases a) and b) TFH cell selection determines differentiation to output cells in a probabilistic manner. Using a random number generator, selected BCs are primed to differentiate to output cells with a probability fixed in a parameter file. However, in case c) this probabilistic mechanism of output generation is switched off.

We introduced flags in the parameter files, which allowed us to switch between the three scenarios. The parameter files can be easily edited with any text editor and are, thus, accessible to any person with basic computer knowledge. Finally, we ran the simulations and evaluated the outputs in terms of affinity and number. For that purpose, 10 simulations were run in every of the three settings starting from random number generators initialized with the current time, and the results are

provided as mean and standard deviation over the 10 runs. The value tables can be plotted with any graph module. In our case we used the number and the mean affinity of output cells as read-out. These are presented as time course over the duration of the GC reaction (Figure S1B).

Note that in many cases it is necessary to investigate the robustness of the result with respect to altered settings in the simulation. For example, in the present case of asymmetric division we tested the impact of switching off and on somatic hypermutation in BCs carrying antigen. The weak effects seen on affinity maturation were inverted by this modification, which is a relevant but expected result.

While the programming steps were non-trivial, adjusting the parameter file, running and evaluating the simulations is accessible to any scientist with basic computer skills. Thus, it may be possible to think of asking specialized programmers to implement specific mechanisms and to run the simulations in the corresponding lab in order to evaluate the implications of a new experiment. This has allowed us to estimate that the dominant effect of asymmetric antigen retention is not on affinity maturation but on the number of plasma cells, which should be a testable prediction as more is learned about mechanisms of asymmetric division allowing its manipulation in vivo.

Figure S1 legend-
(A) Scheme of the three scenarios M1-3 for the fate of antigen retaining BCs: At the BC follicle boundary (lower left box) a TC activates a BC. The BC (blue) divides and mutates its antibody (box mutation). The daughters (blue) enter a phase of selection (box selection) and acquire antigen from follicular dendritic cells (FDC). The amount of collected and processed antigen is individual to every BC (green for low and red for high). The BC with highest amount of processed and presented antigen gets signals from TC (green and red BC competing for TC signals). A fraction of the selected BCs differentiates to output cells (PC, dashed line). All other BCs divide and mutate again (red cell returning to the mutation box). Asymmetric division resets one daughter to its initial state (blue) which restarts the whole process, and one daughter inherits antigen (red). The fate of this cell is the topic of this perspective and three possibilities are considered (M1-3): In M1 the antigen retaining BC (red) directly interacts with TCs again. There it might easily compete with a BC with higher affinity antibodies (magenta) and be out-selected. In M2 the antigen retaining BC (red) acquires further antigen from follicular dendritic cells. As bearing already pre-loaded antigen, these cells start from a more competitive starting point and will easily acquire more antigen in the sum (magenta). This cell is likely to out-compete other cells (like the red one competing for TC signals in the M2 path). In M3, the antigen retaining BC (red) directly differentiates to output cells (PC).
(B) In silico effect of M1-3 in (A) on the number of output cells (PC). Values are relative to the starting model (15) without asymmetric MIIC inheritance (BASE in the graph).