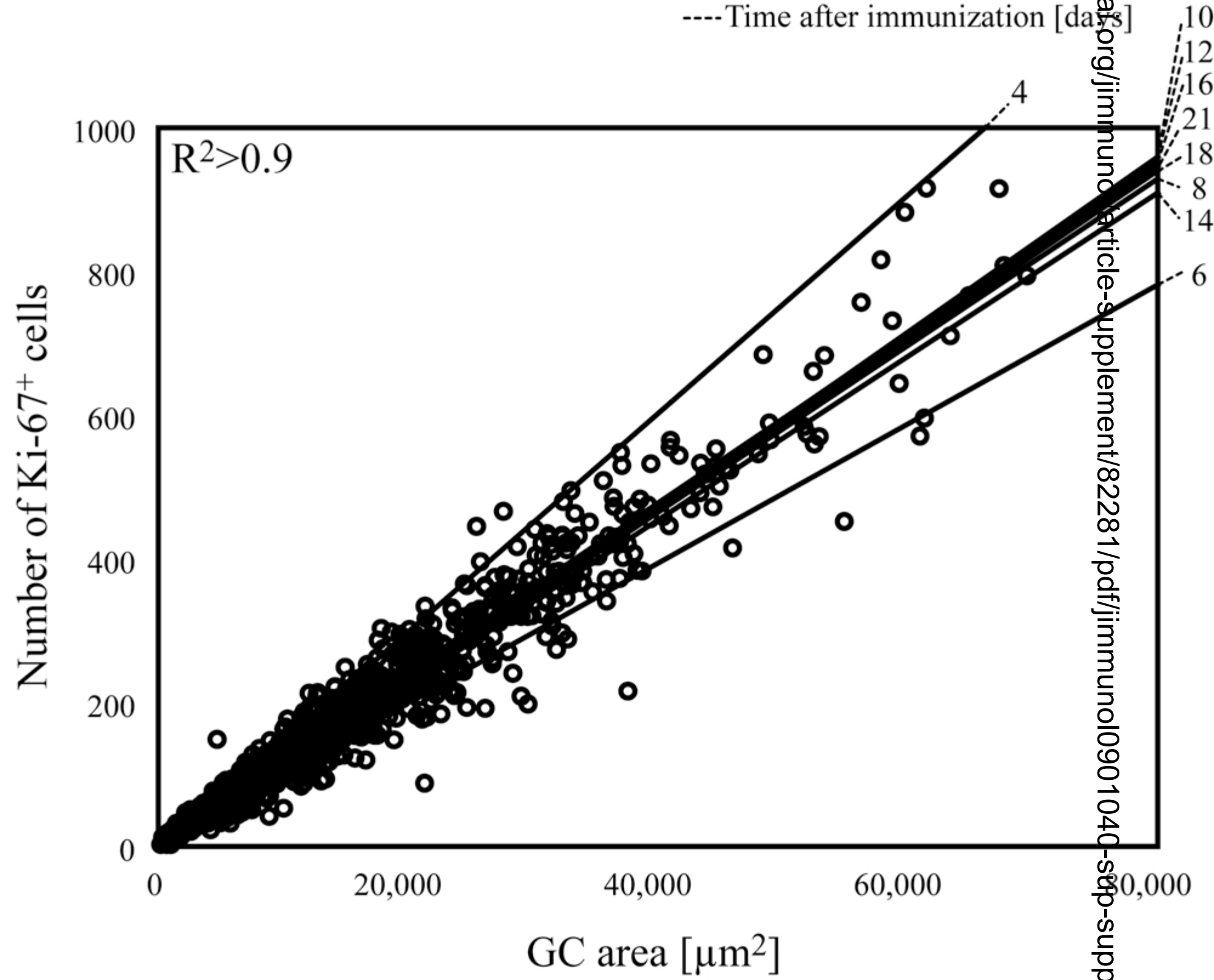
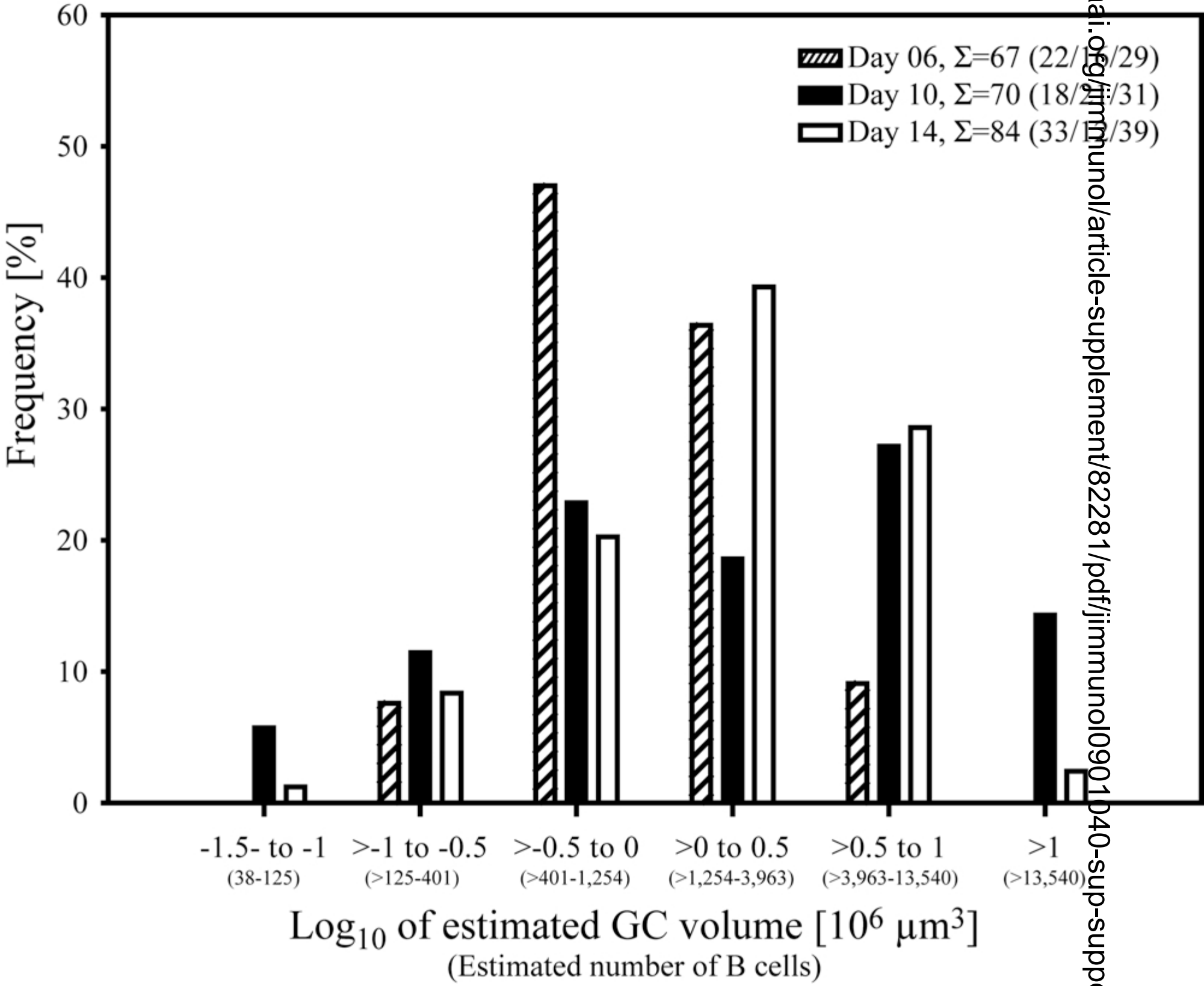
SUPPLEMENTAL FIGURE 1. The number of Ki-67$^+$ proliferating cells correlates with the underlying cross-sectional area of GCs. GCs were identified as Ki-67$^+$ cell clusters and by anatomical location in triple immunofluorescence stainings of proliferating cells (mAb Ki-67), T cells (mAb CD3) and FDC networks (mAb FDC-M2) as illustrated in Fig. 1. The cross-sectional areas and numbers of Ki-67$^+$ cells of GCs were measured after manual assignment of GC boundaries using the ImageJ software (17). Open circles refer to one recorded GC, solid lines indicate the linear regression relationships for the respective time points [d] after primary immunization with phOx-CSA, as denoted on the right of the graph. Squared correlation coefficients (R^2) exceeded 0.9 at all time points analyzed. Due to the correlation between the numbers of Ki-67$^+$ cells and cross-sectional GC areas, the density of Ki-67$^+$ cells within GCs can be calculated as 0.0116±0.0008 cells per μm^2.

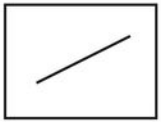
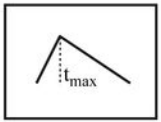
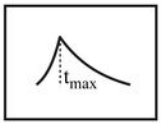
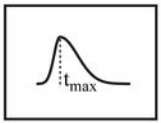
SUPPLEMENTAL FIGURE 2. Semi-logarithmic presentation of the volume distribution of GCs as revealed by 3-D evaluation. Illustrated are the semi-logarithmic histograms of the volume distributions of three-dimensionally reconstructed splenic GCs at days 6, 10 and 14 postimmunization (for details see Fig. 2 and Fig. 4). The quoted frequencies of GC volumes refer to merged data sets of three mice at each time point and include all GCs that crossed the central section (s04) and were either wholly contained within or spanned the overall analyzed splenic volumes. GC sizes are presented as Log_{10} volumes and estimated numbers of B cells contained in these volumes. The total numbers of GCs are indicated (Σ), with values of individual mice given in parentheses.

SUPPLEMENTAL FIGURE 3. The extended Ricker map best reproduces the experimental data on GC growth kinetics. In order to select the optimal mathematical model, 5 simple deterministic growth models (linear, piece-wise linear, exponential, piece-wise exponential,

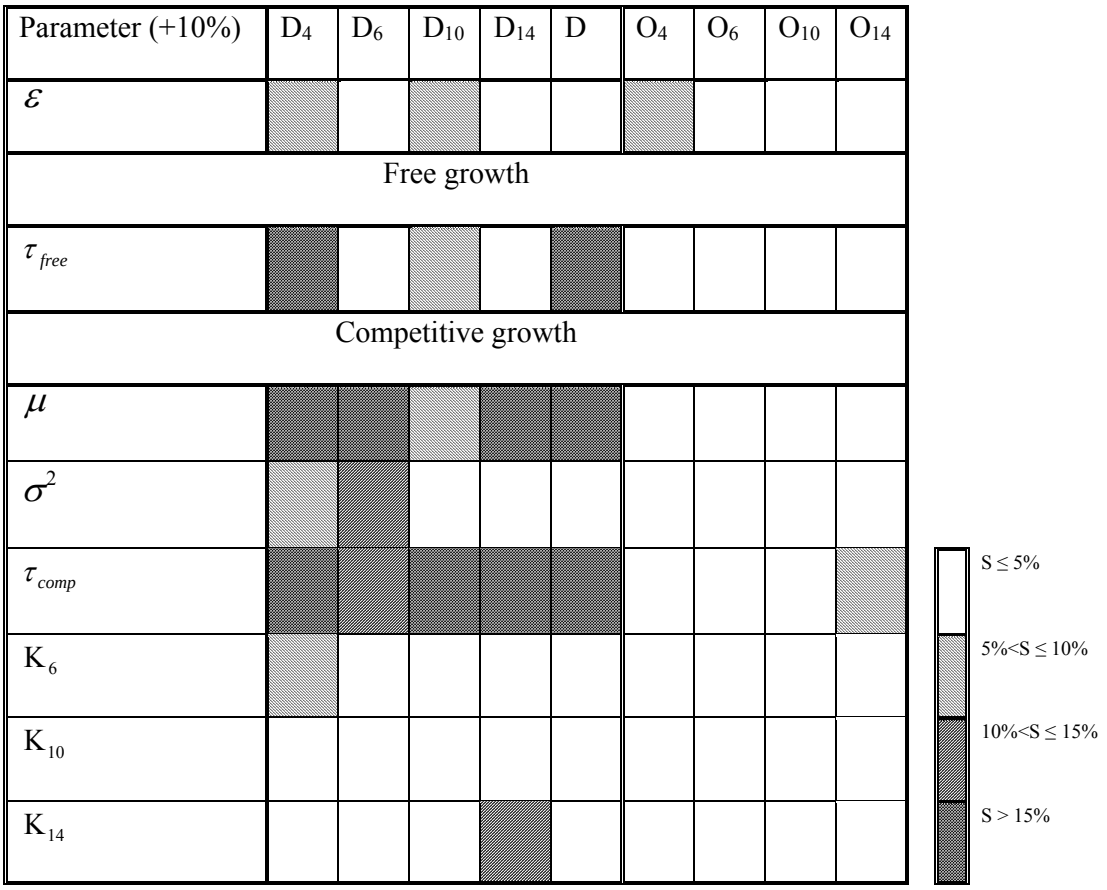
piece-wise gaussian) and the extended Ricker map were evaluated with respect to their capability to reproduce the experimentally recorded GC growth kinetics. Using the experimentally recorded GC size distribution at day 6 as the initial condition, rank plots of the size distributions at day 10 and 14 were simulated and subsequently the capability of a given model to reproduce the experimental data was quantified by calculating the sum of the mean distances ($D = \Sigma_{day} \sqrt{\frac{1}{index_{\max}} \Sigma_{index} (simulated - measured)^2}$) between the simulated rank plots and the experimental data. A systematic parameter sweep showed that none of the deterministic models reproduced the experimental data as closely as the extended Ricker map, not even those with equal numbers of free parameters (#P). To keep the analysis assessable as well as simple, i.e. to minimize the number of model parameters, the following simplifications and assumptions were made: The two-phased model as described in Materials and Methods was reduced to its most characteristic part, i.e. the extended Ricker map of the competitive growth phase. The carrying capacity (K) of follicular niches is held constant between day 6 and 10, and day 10 and 14. In the deterministic models, at day 6, all follicular niches have been seeded and GCs have not yet reached their maximum size.





Model	Functional form	Graph	#P	D_{min}
linear	$y = \alpha t$		1	0.37
piece-wise linear	$if\ t < t_{max}$ $\quad y = y_{max} - \alpha\ \lvert t-t_{max}\rvert$ $if\ t > t_{max}$ $\quad y = y_{max} - \beta\ \lvert t-t_{max}\rvert$		3	0.32
exponential	$y = e^{\alpha t}$		1	0.35
piece-wise exponential	$if\ t < t_{max}$ $\quad y = y_{max}\ e^{-\alpha\lvert t-t_{max}\rvert}$ $if\ t > t_{max}$ $\quad y = y_{max}\ e^{-\beta\lvert t-t_{max}\rvert}$		3	0.77
piece-wise gaussian	$if\ t < t_{max}$ $\quad y = y_{max}\ e^{-\alpha(t-t_{max})^2}$ $if\ t > t_{max}$ $\quad y = y_{max}\ e^{-\beta(t-t_{max})^2}$		3	0.04
extended Ricker map	$y_{t+1} = y_t\ e^{r(1-y_t/K)}\ \chi$		3	0.32

Supplemental Table I. *Sensitivity analysis of the two-phased extended Ricker model*[a]



[a]The extended Ricker model involves two different phases of GC growth, i.e. free growth and competitive growth (see Materials and Methods). Whereas the free growth phase depends on the parameters for the seeding rate (ε) and division time (τ_{free}), the competitive growth phase depends on the parameters defining the intial B cell population size of iGCs entering the competitive phase (μ and σ^2), as well as on the parameters for B cell division time τ_{comp} and the carrying capacities of follicular niches (K_6, K_{10} and K_{14}). Since the model is complex, a sensitivity analysis was carried out to assess the impact of the model's various input parameters on the model output, that is the capability to reproduce the experimental data at the indicated time points by means of i) the sum of the mean distances between the

Non-synchronized GC growth

simulated rank plots and the experimental data ($D = \Sigma_{day} \sqrt{\frac{1}{index_{\max}} \Sigma_{index} (simulated - measured)^2}$) and ii) the comparison of the simulated and experimental occupation index (O) of follicular niches at the respective time points. The sensitivity (S) of the modified Ricker model to a given parameter is the rate of change [%] in the output of the model with respect to a +10% increase in the value of the parameter while the other parameters are kept constant. The sensitivity analysis shows that the two-phased extended Ricker model is sensitive to parameters related to the exponential growth of the B cell population (τ_{free}, μ and τ_{comp}). The performance of the model is hardly affected by a 10% increase in other parameter values.