Lymph node swelling combined with temporary effector T cell retention aids T cell response in a model of adaptive immunity

Supplementary File 1 : Supplementary Methods A

1.1 LN geometry and swelling

Paracortical areas are defined using a percentage of the outer radius (Fig A i). Entry areas are defined as grid compartments within 50% of the outer radius in accordance with HEV positioning [1]. Grid compartments are designated exit compartments in an area with thickness 7% of the outer radius. A cap shaped area void of exit points is defined using 70% of the radius. The boundary region is one grid compartment thick and all grid compartments outside this region are defined as 'outside'.

In repastSimphony a 'valueLayer' is a parallel grid that stores a value for each grid-compartment that agents can access. For example, an entry area is designated a value of 24, and a region that is neither entry, exit, boundary or outside is designated a value of 20. Definition occurs during initialisation (line 70 lymph_nodeBuilder) and every 10 time-steps (line 446 lymph_node3DContext). A cylindrical entry region, with radius 30% of the outer radius, representing T cell (TC) entry from afferent lymphatics is defined in function addAfferent (line 941 lymph_node3DContext).

A sigmoidal relationship was estimated between paracortical volume and number of TCs present, based on patterns of behaviour recorded in Table A. To implement these changes, area represented by each grid compartment could be redefined using the new desired outer radius.

Fig A Modelling Methods. (i). Definitions of different areas of the paracortex are based on the overall paracortical radius, and therefore alter in volume during expansion. (ii). During interactions, TCs gain stimulation at a rate proportional to the presented antigenic signal, which is itself decaying. Accumulated TC simulation also undergoes constant decay. (iii). Accumulated stimulation is to determine probability of TC activation or differentiation, dependent on the satisfaction of other criteria.(iv) The progression of TC proliferation and differentiation into effector and long-lived memory TCs with sufficient stimulation.

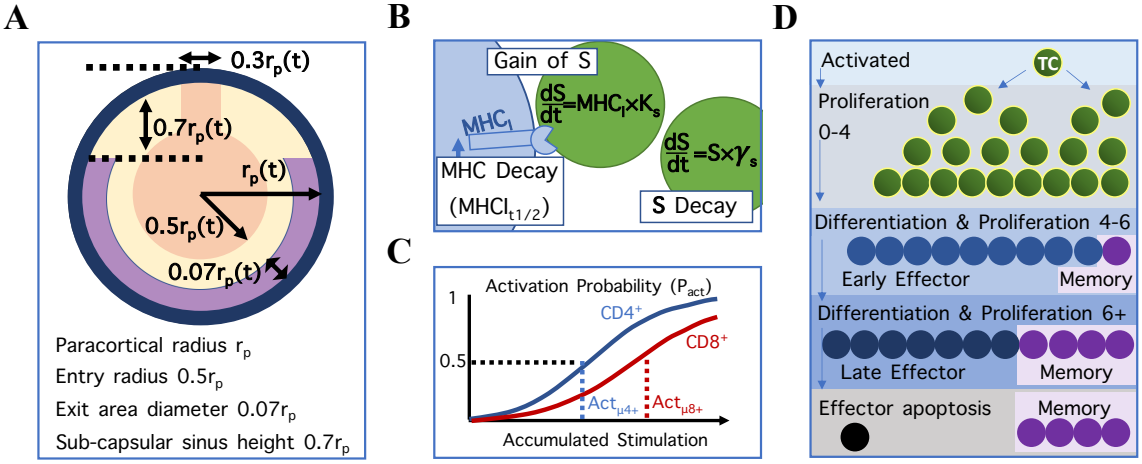


Table A Data regarding changes in lymphocyte counts and proliferation, LN mass, LN volume, blood flow and stromal cell counts and proliferation were collected from a range of sources and analysed to identify common relationships between T cells and LN volume.

Description	Stimuli	Model	Reference
LN mass, T cells, B cells, lymphocytes, total cellularity, Blood Endothelial Cells, migratory DCs, FRCs	Hindpad CFA/OVA injection	murine	[2]
LN volume, HEV length, LN images	Hindpad CFA/OVA injection	murine	[3]
LN volume, HEV length, B cell volume,	Hindpad LCMV injection	murine	[4]
LN images, Dendritic cells, endothelial cell proliferation, total LN cellularity, HEV proliferation	LPS-matured BMDC injection	murine	[5]
LN mass, peripheral blood T cells ($CD4^+$ /$CD8^+$), lymphocytes, T cell $CD4^+$, T cell $CD8^+$	skin-application of dinitrofluorobenzene	murine	[6]
LN blood flow, LN weight, lymphocyte influx, HEV proliferation, cell proliferation	sheep erythrocytes	rat	[7]
LN total cell count, blood flow T cells (CD4+/CD8+), B cells, T cell proliferation, B cell proliferation	HCpG/LPS +/- OVA also HSV	murine	[8]
LN cellularity, FRCs, LECs, BECs, T cells (CD4+/CD8+), FRC/LEC/BEC proliferation	OVA/Mont-immunized	murine	[9]

1.2 TC recruitment

Under non-inflammatory conditions, it was assumed that TC entry and exit remain constant and TCs occupy a constant percentage (55%) of total paracortical volume.Our hemispheric model has a radius of 200μm and average TC volume is assumed to be 150μm^2, resulting in approximately 50000 TCs at initiation. Scaling paracortical radius to paracortical radius in LN images, we estimate that the model represents a LN of 0.113-0.268 mm^3, implying a LN mass of 0.18-0.44mg (based on collaborative unpublished measurements of murine popliteal LN mass versus volume). Reported lymphocyte recruitment for a popliteal LN of 1.15g is $4x10^7$ lymphocytes/hour and up to 40% of lymphocytes are B cells [10–12]. The model represents half a paracortex, therefore TC recruitment rate was estimated as 1950-9000 TCs/hour under non-antigenic conditions. Naive TC transit time through the LN (T_{res}) was estimated as 6-24 hours [13].

1.3 Agents and agent migration

The agents were designated as members of the TC or DC class each containing individual properties (eg. age) that are updated each timestep (Fig C). Agent properties such as life-span and size are fixed parameters displayed in Table B.

The starting TC population is composed of 70% helper TCs ($CD4^+$) and 30% cytotoxic TCs ($CD8^+$) [14]. Each timestep (δt=20s), TCs can move one grid length to an available neighbouring

grid compartment, moving with probability, β, and where availability is governed by crowding parameter γ. TC migration was assumed to follow a random walk with pauses. Previous models have described TC migration with Brownian motion, a random-walk with persistence,run and tumble, and Lévy walks amongst other methods, partly due to differing reports of *in-vivo* migration. [15–18].

DC entry rate and total number was scaled from counts of migrating DCs and initial TCs in a murine LN post-immunisation [2]. Total number of DCs to enter at default was estimated as 4% of T cells present (ϕ_{DC}=0.05), therefore approximately 2500 DCs. Simulated DCs appear at points throughout the initial paracortex, at a constant entry rate for 2 days, with entry rate subsiding over the following 12 hours. Each DC has an average life span of 60 hours (+/-2.7h), after which the DC undergoes apoptosis and is removed from the model.

1.4 Agent interaction and signal integration

Interaction times with agDCs are drawn from uniform probability distributions with a mean of 3 minutes for non-cognate TCs (T_{NC}). Cognate TCs progress from 10-15 minute short interactions (T_{short}) to longer 50-70 minute interactions (T_{long}). During interactions TCs remain stationary. Antigenic signal is presented by the DCs in the form of representative values of MHCI or MHCII (), and decays with time (t) with the form :

$$MHCI(t) = MHCI_i(0.5)^{\frac{t}{MHCI_{\frac{1}{2}}}} \tag{1}$$

$MHCII_i$ is the initial MHCI or initial MHCII presented with respective MHC half-lives $MHCI_{1/2}$ and $MHCII_{1/2}$ estimated from *in-vitro* labelling of MHC molecules [19–22]. During cognate TC-DC interaction, $CD4^+$/$CD8^+$ TCs gain (S) at rate κs while losing stimulation at rate λS (Fig B.iii).Total change in TC stimulation is therefore given according to the first order rate equation:

$$\frac{dS}{dt} = K_s\, MHCII(t) - \lambda_S\, S(t) \tag{2}$$

Accumulated simulation decays to a minimal value of S=1 to allow differentiation between cognate TCs that gain and lose simulation (S=1) and those that never gain simulation (S=0). Probability of cognate CD_{4^+}activation (P_{a4^+}) or cognate CD_{8^+}activation (P_{a8^+}) is calculated with a sigmoidal function given by:

$$P_{a4^+} = \frac{1}{1 + e^{\frac{-S - Act\mu_4}{Actl_4}}} \tag{3}$$

Parameter Actμ_4 determines the value of S required for 50% probability of activation and Actl_4 determines steepness of sigmoid inflection (Fig A.iv). Activation probability for $CD8^+$ TCs (P_{a8^+}) is determined with a sigmoid curve using a lower inflection point, (Actμ_8), than for $CD4^+$ TCs. However, if the DC is 'licenced', which occurs post-interaction with an activated $CD4^+$ TC, $CD8^+$ TC and $CD4^+$ TC stimulation requirements are equal. This is to reflect facilitated $CD8^+$ activation as a result of activated $CD4^+$ induced production of cytokines [23]. Model parameters were estimated such that TC activation became apparent 8-15 hours post DC-arrival [24–26]. This method of signal integration and the subsequent progressive patterns of TC proliferation and differentiation is supported by *in-vivo* observations and modelling descriptions [26–29]. It is assumed that co-stimulatory requirements are met as agDCs are highly efficient antigen-presenting cells.

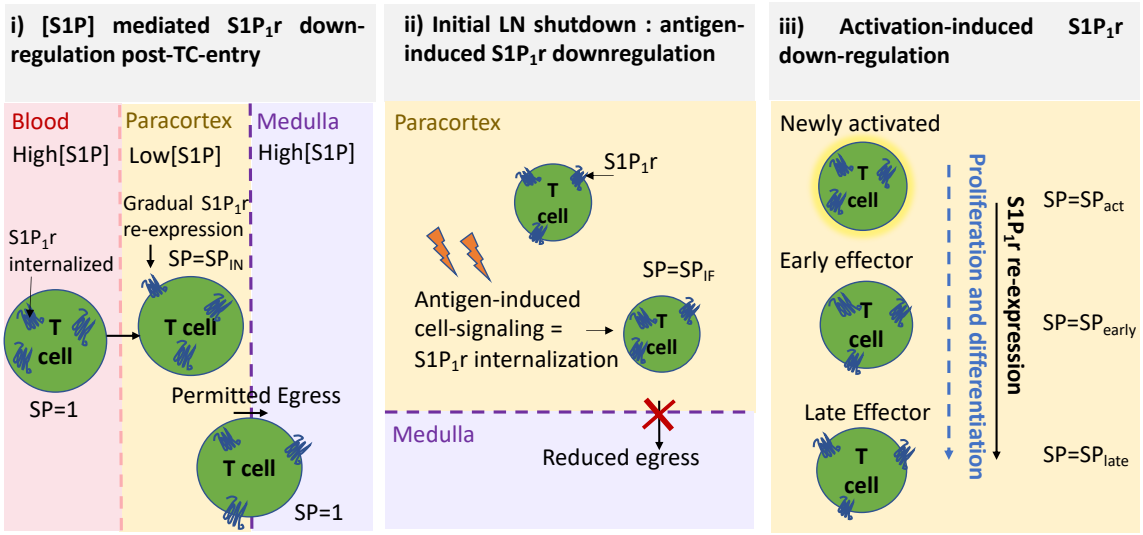
Post-activation, proliferation is possible every 11 ($CD4^+$) or 9 ($CD8^+$) $\pm$1hr [30–33]. Differentiation to effector or memory TCs is possible after >=4 divisions, with differentiation probability determined with a second set of sigmoidal probability curves with midpoint Difμ_{4+} and Difμ_{8+} respectively [34,35]. Greater $CD4^+$ TCs dependence on continued stimulation for differentiation than $CD8^+$ TCs was implemented by using a higher minimum threshold of accumulated stimulation for $CD4^+$ differentiation than for $CD8^+$ TCs [36–40]. The fraction of effector TCs that differentiate into memory TCs increases from 0.01 to 0.04 as TCs progress from 'early effectors' (< 8 proliferations) to 'late effectors' [41]. This was implemented by assigning differentiation ratios of dif_{early} and dif_{late} to the two subsets.

1.5 T cell egress

When a T cell enters an exit area, the probability that it may egress (P_e) is calculated by multiplying a factor representing each T cell's $S1P_1r$ expression (SP) by a exit probability (E). Naive T cells have default SP value of 1, and E was experimentally determined under non-inflammatory conditions to produce T cell influx and egress equilibrium.

Change in relative $S1P_1r$, from a default of SP=1 expressed by naive TCs, was considered and estimated in three scenarios, using *in-vivo* and *in-vitro* observations [42–44]. Firstly, $S1P_1r$ is temporarily down-regulated (4 hours) following TC migration into the paracortex from the blood, due to the change from a high SP to low SP concentration environment. This is applied by tracking the time since each T cell entered (in an internal property), and setting SP equal to SP_{in}. Secondly, LN shutdown is triggered with sufficient increase in paracortical inflammatory state, determined by summation of MHC signal present, and a non-specific decrease in $S1P_1r$ expression occurs (SP=SP_{inflam}) until the inflammatory signal subsides. Thirdly $S1P_1r$ is down-regulated on activated TCs (SP_{act}) and gradually re-expressed on effector TCs (SP_{early}, SP_{late}) (Fig B) .

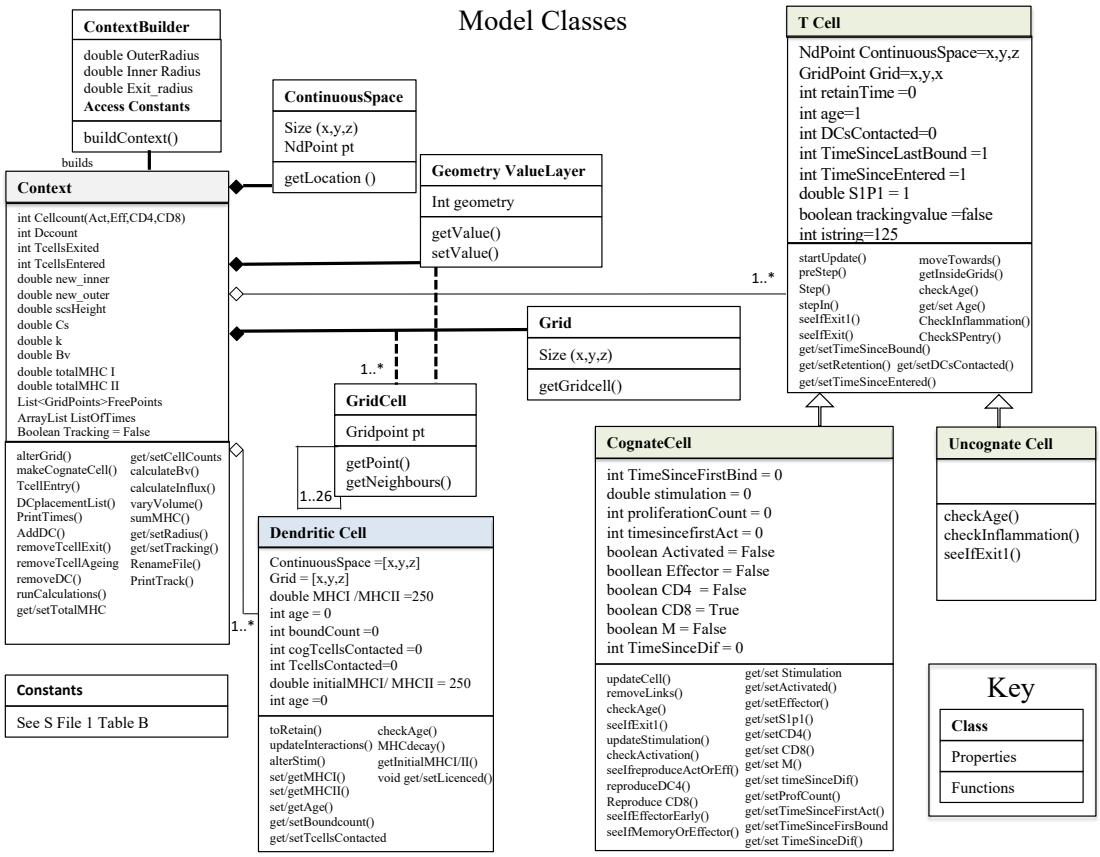
Fig B Modelling Sphingosine-1-phospate-1 receptor ($S1P_1r$)-mediated retention. Regulation of $S1P_1r$ on (i) naïve TCs post-transmigration from the blood, (ii) naïve TCs during LN shutdown due to detection of inflammatory signals and (iii) activated and early effector TCs.



Model Structure

The model was built using a class based structure, depicted in Fig C. The 'Constants' class stores initialisation values and constant properties. The 'ContextBuilder' starts by creating a single copy of the Grid and/or Continuous Space. A GridCell class allows definition of grid compartments at each gridpoint. A 'valueLayer' is also created, which is a parallel grid that we used to store properties of each grid compartment (see 1.1). Agents are also created using the classes as templates and positioned by assigning grid point coordinates.

Fig C A class diagram displaying the underlying ABM structure.



The are two agent classes - T cells and DCs. Two sub-classes - CognateCell and UncognatCell inherit properties and functions from the T cell class, alongside additional properties and/or functions. It is unneccesary for activation properties, and information about the type of cell (eg. CD4+/CD8+) to be stored in unCognate cells as only cognate TCs will respond to antigenic stimuli.

T cell properties include counters updated each timestep, such as 'timeSinceEntered', set at 1 when TCs enter, to implement S1P1r down-regulation on newly entered T cells. However, T cells that are present on initialisation have timeSinceEntered set at 0 and are never updated. An equilibrium period allows the majority of these initial TCs to transit the LN prior to application of the antigenic stimuli. Properties such as 'DC contacted' can store T cell interaction history, and 'retainTime' and

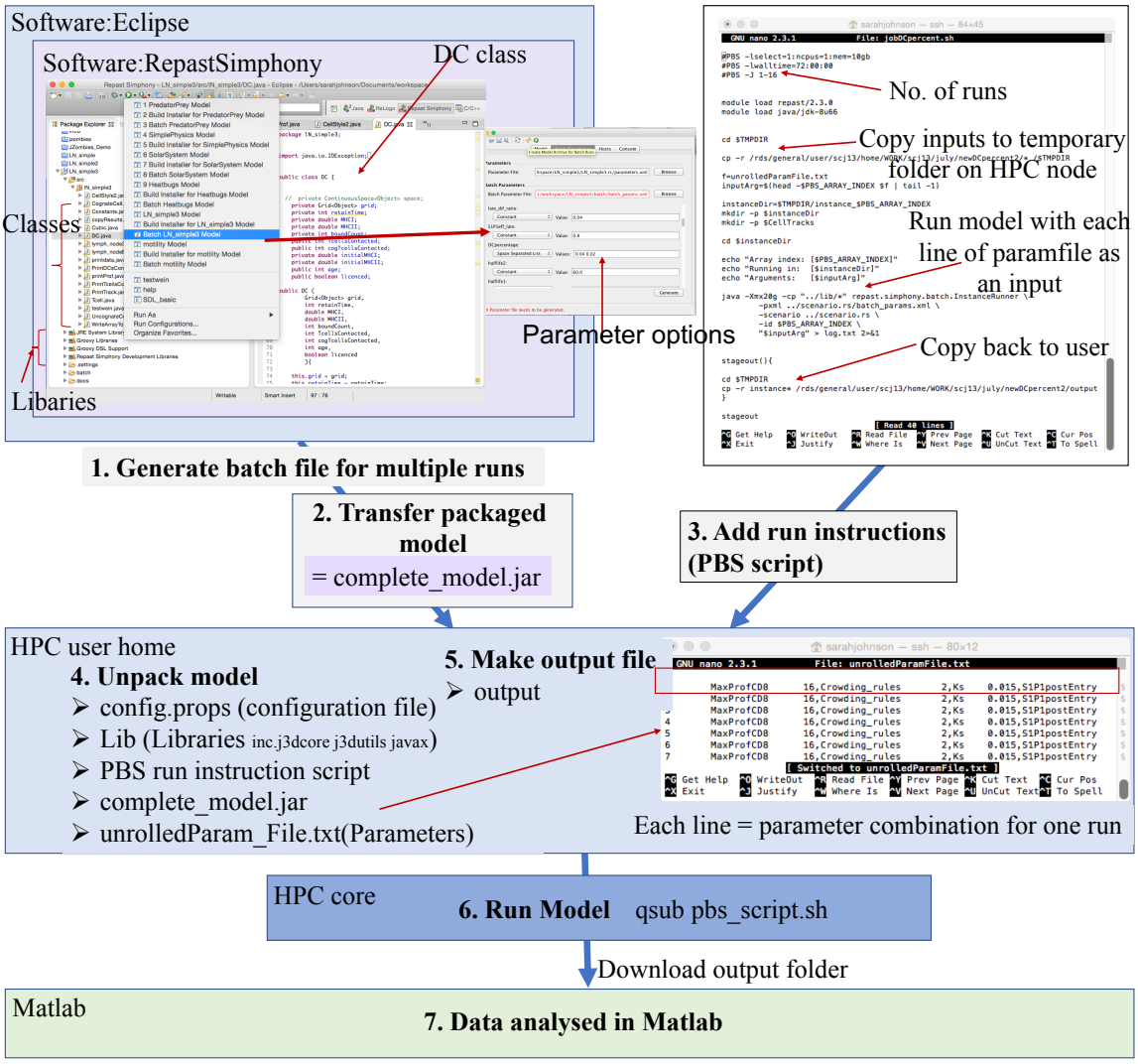
'timeSinceLastBound' are adjusted during interactions with DCs. Cognate T cells store additional properties related to activation state and stimulation level. DC properties include age, licensing state, history of interactions, current MHC level and current number of TCs bound. Interaction between TCs and DCs is applied by creating projections (links). Both ends of the link (eg. DC and TC) can be accessed via functions in either agent class and agent properties are used to record interaction duration, interaction history and T cell type, to determine remaining interaction duration.

The 'context' class initiates the main functions, described in Figure 2B, that are called each time. The rules and cell behaviour described in the methods above are integrated within these functions and sub-functions explained in S2 File. The class files have also been annotated.

Running the model in RepastSimphony

RepastSimphony is available at repast.github.io/.Our code can be downloaded from github.com/johnsara04/paracortex_model_johnson19 and the LN_simple5 package imported into repast symphony. The individual class files are located under '/LN_simple5/src/lN_simple5'. To run the model, once imported, the model with a visual interface can be initiated by clicking the down arrow next to the the green play button and selecting LN5_simple model. However, we recommend using the batch lnSimple5 option without a visual interface for speed. The default batch method uses the capacity of the local machine but we used an external high performance computing (HPC) system. This involved generating a jar file containing the necessary model classes and transferring to a HPC system (see Fig D) pre-installed with repastSimphony and a java development kit. We also edited the configuration file and manually added a Jobscript file containing instructions to run simulations on a PBS batch system. The repast documentation has since been updated to accurately explain how to run a batch simulation using an EC2 instance on Amazon Web Services, in a manner that avoids file transfer and manual JobScript editing, which we would recommend as an effective batch simulation method-
see repast.github.io/docs/RepastBatchRunsGettingStarted.pdf.

Fig D The process of generating the model for batch simulations. We used an external HPC system with RepastSimphony and a Java-development-kit installed. We generated locally a jar-file containing the model classes, required libraries and parameters and transferred this along with a configuration file and a PBS jobscript file containing run and output instructions to our HPC instance. Output was transferred back to our local computer and data analysis performed in Matlab.



S1 File Supplementary Parameter Tables

Table B Parameters and properties that were not varied in the global sensitivity analysis

Symbol	Parameter	Value	Reference
	Model Geometry		
r_p	Initial paracortex radius	200μm	[45,46]
-	Entry radius	0.5 r_p	[1]
-	Afferent entry radius	0.3 r_p	[1]
-	Exit radius	0.07r_p	[45,46]
-	Sub Capsular Sinus height	0.7r_p	[45,46]
GS	Grid Size	6μm	-
	TC Properties		
-	Initial occupation	55%	[47]
-	Radius	3.3μm	[48]
-	Ratio CD4:CD8	0.7:0.3	[45,46]
-	Lifespan naive	365 days	[49,50]
-	Lifespan activated	41 hours	[49,50]
-	Lifespan effectors	3.5 days	[49,50]
-	TC entry Afferent:HEV ratio	0.1:0.9	[51,52]
Actl_{4+}	Slope of CD4$^+$ activation curve	-69.81	-
Actl_{8+}	Slope of CD4$^+$ activation curve	-80.71	-
Difl_{4+}	Slope of CD4$^+$ differentiation curve	-17.26	-
Difl_{8+}	Slope of CD8$^+$ differentiation curve	-13.58	-
	T cell movement		
β	Probability of movement	0.6	[1,34,53–55]
P_e	Probability of egress constant	0.0126	-
γ	Max cells per grid	2	-
T_{res}	TC residence time	24hrs	[13,56]
	DC properties		
-	DC span	2 grids	[48,57,58]
-	DC Lifespan	60 hours	[2,59,60]

Table C Parameters varied in the global sensitivity analysis. Continued overleaf.

Symbol	Parameter Description	Default	Min	Max	Mean	SD	Distrib.	Ref
	TC response parameters							
$Act\mu_4$	$CD4^+$ activation curve mean	120	70	230	-	-	Unif	[61–66]
$Act\mu_8$	$CD8^+$ activation curve mean	140	90	250	-	-	Unif	[61–66]
$Dif\mu_4$	$CD4^+$ differentiation curve mean	60	30	90	-	-	Unif	[61–66]
$Dif\mu_8$	$CD8^+$ differentiation curve mean	40	20	60	-	-	Unif	[61–66]
TP_4	Min time between $CD4^+$ proliferations (hrs)	11	-	-	11	1.16	Norm	[30–33]
TP_8	Min time between $CD8^+$ proliferations (hrs)	7	-	-	7	0.88	Norm	[30,31]
Max_{P8}	Max proliferations $CD8^+$	16	-	-	16	1.2	Norm	[39,67–69]
Max_{P4}	Max proliferations $CD4^+$	10	-	-	10	1.2	Norm	[31–33]
Dif_{early}	Early Memory:Effector cell differentiation	0.01	0.001	0.02	0.01	-	Exp	[70]
Dif_{late}	Late Memory:Effector cell differentiation	0.04	0.01	0.08	-	-	Unif	[70]
	TC interaction dynamics							
T_{NC}	Mean non-cognate T-DC interaction (min)	3.5	-	-	3.5	1	Norm	[60,71]
T_{short}	Short cognate TC-DC interaction (min)	10-15	-	-	10	3	Norm	[25,60,71]
T_{long}	Long cognate TC-DC interaction (min)	50-70	-	-	50	12	Norm	[24–26,72]
T_{change}	Time TCs switch to long interactions (hr)	8	-	-	8	1	Norm	[24–26,72]
B_{max}	Max TCs a DC can bind per-step	3	1	5	-	-	Unif	-
B_{step}	Max TCs a DC can bind	15	4	20	-	-	Unif	[73]
	TC Stimulation							
K_s	Stim. gain coefficient	0.015	0.005	0.02	-	-	Unif	-
λ	TC stim. decay factor	0.99	0.99545	0.9999	-	-	Unif	-
MHC_i	Initial MHCI/II	250	150	350	-	-	Unif	[19–22]
$MHCI_{1/2}$	MHCI half life (hrs)	19.7	-	-	19.7	6	Norm	[19,20]
$MHCII_{1/2}$	MHCII half life (hrs)	60	-	-	60	6	Norm	[21,22]
F_{cog}	Frequency of cognate TCs that enter	1e-4	5e-5	1.5e-4	-	-	Unif	[32,74–76]
Φ_{DC}	Total DCs entering as % of initial TCs	0.04	0.02	0.06	-	-	Unif	[2]
T_{DCin}	DC entry duration (days)	2.5	0.5	4.5	-	-	Unif	[2]

Symbol	Parameter Description	Default	Min	Max	Mean	SD	Distrib.	Ref
	Sphingosine-1-phosphate receptor regulation							
SP_{entry}	$S1P_1r$ expression post entry	0.1	0.01	1	-	-	Unif	[42,43,77]
SP_{act}	$S1P_1r$ expression when activated	0.01	0.001	0.02	-	-	Unif	[42–44,77]
$S1_{early}$	Effector $S1P_1r$ (Proliferation<=6)	0.4	0.01	1	-	-	Unif	[42,44]
SP_{late}	Effector $S1P_1r$ (Proliferation>6)	0.8	0.3	1.3	-	-	Unif	[42,44]
SP_{mem}	Memory $S1P_1rr$	1	-	-	1	0.1	Norm	[42,44]
SP_{IF}	$S1P_1r$ on all TCs during inflam.	0.4	0.2	0.8	-	-	Unif	-
T_{Entry}	Time $S1P_1rr$ is low post-entry (min)	60	13	120	-	-	Unif	-
T_{Inflam}	Time to alter $S1P_1r$ during inflam.(hr)	4	1	7.5	-	-	Unif	-
	T cell recruitment							
RT1	recruitment increase stim. threshold	2e4	2e4	1e5	-	-	Unif	[5,7,78,79]
RT2	Stim. threshold for max. recruitment	4e5	2e5	2e6	-	-	Unif	[5,7,78,79]
R_F	Recruitment Factor	3e-6	1e-6	4e-6	-	-	Unif	[5,7,78,79]
	Paracortex expansion							
V_{Max}	Max fold-volume increase	1.00	2.00	2.50	-	-	Unif	-
l	Rate of volume change around m	7e-05	3e-05	1e-04	-	-	Unif	-
T_{mid}	No. of TCs for 50% max-volume	120000	90000	150000	-	-	Unif	-

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