Supplementary Material for *An In Silico Model of Cytotoxic T-Lymphocyte Activation in the Lymph Node Following Short Peptide Vaccination*, Journal of the Royal Society Interface

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A Comparison to previous work

Parameter	**Our model**	**Celli *et al*'s model**
T cell motion	Run-and-tumble	Diffusion
Velocity distribution	Gamma	Gaussian
Mean 3D speed	10μm/min	22.6μm/min
Variance of 3D speed	44.3μm/min^2	90.4μm/min^2
Mean free path	25μm	0 or $v\Delta t$
Antigen off-rate	k_{off}	N/A (0)
DC contact radius	20μm	12μm
LN radius	500μm	400μm
Modelled animal	Human	Mouse
Modelled cells	CD8$^+$	CD4$^+$

Table A1. A summary of the changes that must be made to the model in order to reproduce the results of Celli *et al*.

A component of our model is related to the *in-silico* mouse model reported by Celli *et al*: namely, that dendritic cells (DCs) and T cells interact in an off-lattice sphere. It is possible to reproduce their results for a consistency check by changing suitable elements of our model, as summarised in Tab. A1. In particular, the T cell velocity is made to imitate diffusion instead of drawing velocities and free paths from defined distributions, the antigen off-rate is set to zero and the initial cognate to total antigen ratio to unity, so that interactions are always successful. Celli *et al* model CD4$^+$ T lymphocytes, whereas we model CD8$^+$ cells. We could not find a reason to suggest that the naïve dynamics of

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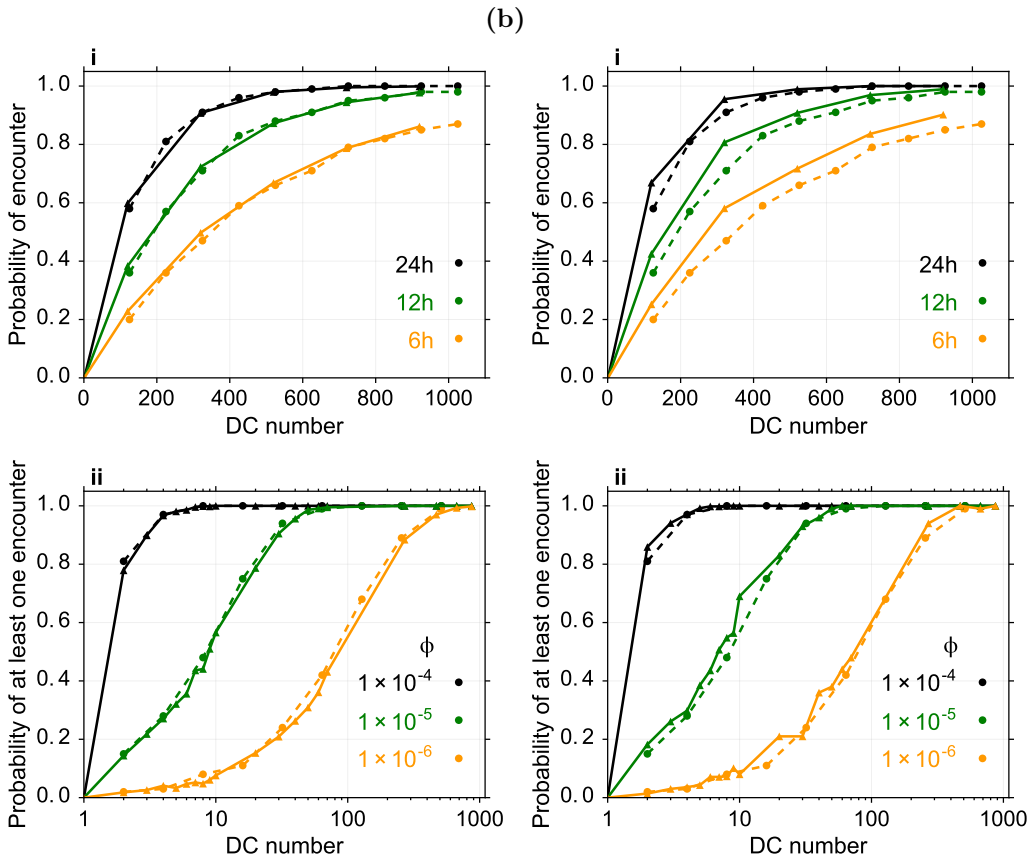

Figure A1. Comparison with figure 2 of Celli *et al*'s report. Dotted lines with circles show their results, solid lines with triangles are the results of the model presented here, with parameter values as discussed in the text. Time 0 is defined as the time that the first dendritic cell enters the lymph node. Simulated cell dynamics in **a)** match those of Celli *et al*'s model, whilst the plots in **b)** use our own choice of dynamics and thus results differ slightly. In particular, the velocity is sampled from a gamma distribution with mean 10.1µm/min and cells move unimpeded in one direction for a duration drawn from a Gaussian distribution, to match observations of cell motility [1].

these cells differ, so we assume that comparison of our results is valid. Similarly, Celli *et al* parameterised their model for mice rather than humans, but after scaling parameters and assuming that cell velocities are unchanged between the species, the models are equally applicable to both species.

A comparison between Celli *et al*'s results and our own is shown in Figure. A1, in the case that simulated dynamics (velocity and free path distributions) are made to match Celli *et al*'s and in the case that they are unchanged from our definitions. For the former, there is good agreement except at very early times (data not shown), for which we could not find a reason. When cell dynamics are the same as used in the main text, the reduction in mean velocity and choice of gamma distribution lowers overall cell displacement. However, the increase to the mean free path F increases the displacement. This can be seen by relating the mean free path to motility through the time-step: assuming a constant mean free path F and velocity v, we can define a timestep of motion $\Delta t = \frac{F}{v}$, as in a random walk. The motility is given by $M \approx \frac{F^2}{2\Delta t} = \frac{Fv}{2}$, and the expected 3D displacement after a time $t \gg \Delta t$ is $\sqrt{6Mt} \approx \sqrt{3Fvt}$. The changes to the velocity and mean free path together

slightly reduce the volume that T cells can search in finite time and thus the probability that they become activated by a DC.

B T cell velocity distribution

We used previously published (mouse) data [1] to fit and select velocity distributions to T cells and DCs, as shown in Figure. A2. We expect the velocities of T cells and DCs to be similar between mice and human and so use this data to parameterise our human model. For each distribution and each data set, the distribution parameters were selected from the best least-squares-fit predicted by SciPy [2]. The gamma distribution provides the best fit to both T cells and DCs, so although we cannot justify a mechanistic basis for it, we chose this distribution for both cell types in our model.
No theoretical distribution that we considered provides a good fit to velocities of T cells in the absence of DCs. The authors [1] suggest that the T cell velocity distribution changes in the presence of DCs due either to factors released by DCs or to cell-cell contacts, though it occurs regardless of whether the DCs carry cognate antigen. Since they note that the change in T cell motility occurs only after first contact and because the first contact is the limit of our model, the correct distribution to use is in the absence of DCs. For the reasons above, we chose to fit the gamma distribution to this distribution. This ensures that the shape of the velocity distribution is similar to other data and that the observed mean velocity is correctly reproduced.

C Probability of T cell – DC interaction success

We assume in the main text that the binomial distribution can be used to describe the probability that a T cell contacts at least T cognate antigen when it interacts with a dendritic cell (DC). As the binomial distribution represents sampling with replacement, it is not strictly correct; the hypergeometric distribution should instead be used. In this section, we show that the two distributions are equivalent in our parameter regime. Suppose that there are c MHC-I on a DC bound to cognate antigen and r that are not, so that the proportion of bound antigen for the cell is given by $A = \frac{c}{r+c}$. Further, suppose that N MHC-I are sampled from the population of the DC *without replacement*, representing the sampling of the DC's receptors by a nearby T cell. Then the probability that x from this sample are cognate is given by the hypergeometric distribution,

$$\frac{\binom{c}{x}\binom{r}{N-x}}{\binom{r+c}{N}}.$$

In the limit $r, c \to \infty$, this reduces to the binomial distribution, which is equivalent to the result for sampling with replacement. In this case, the probability that x of the sampled N receptors are cognate is given by,

$$\frac{N!}{x!(N-x)!}A^x(1-A)^{N-x}.$$

Then, the probability that the number of cognate receptors x within the sampled population N surpasses some threshold $T \leq N$ is given by:

$$p_*(A) = 1 - \sum_{x=0}^{T-1} \frac{N!}{x!(N-x)!} A^x (1-A)^{N-x}.$$

We assume that $r + c = 10^5$ [3–7] and so for all values $\frac{T}{N} < A < 1$, the fractional difference between the hypergeometric and binomial distributions is less than one part in a thousand regardless of the values of T and $N \leq 1000$ (data not shown) and hence we work with the simpler and more intuitive binomial distribution.

D Data tables for sensitivity analysis

The values for the sensitivity analyses presented in the text are shown in Table A2.

Parameter	Sensitivity index	Total sensitivity index	Random forest importance
Within transition			
LN radius cubed	0.01	0.05	0.01
Contact radius cubed	0.00	0.03	0.00
Num T cells	0.00	0.03	0.00
Num DCs	0.00	0.02	0.01
Antigen in contact area	0.09	0.15	0.12
T cell act. threshold	0.10	0.18	0.16
Dermis cog. ag ratio	0.09	0.16	0.00
First DC arrival	0.16	0.27	0.65
DC arrival duration	0.00	0.08	0.00
Antigen off-rate	0.37	0.50	0.00
T cell velocity	0.01	0.08	0.02
T cell free path mean	0.00	0.05	0.01
T cell free path std. dev.	0.00	0.05	0.00
Sum	0.83	1.64	1.00
Above transition			
LN radius cubed	0.03	0.78	0.23
Contact radius cubed	0.01	0.70	0.07
Num T cells	0.00	0.33	0.01
Num DCs	0.05	0.53	0.25
Antigen in contact area	0.00	0.27	0.03
T cell act. threshold	0.01	0.79	0.01
Dermis cog. ag ratio	0.01	0.37	0.01
First DC arrival	0.01	0.70	0.02
DC arrival duration	0.01	0.82	0.01
Antigen off-rate	0.00	0.26	0.04
T cell velocity	0.06	0.78	0.01
T cell free path mean	0.03	0.54	0.24
T cell free path std. dev.	0.01	0.85	0.07
Sum	0.22	7.73	1.00

Table A2. A sensitivity analysis of the model in different ranges of k_{off}, with the other parameters varied as described in the main text.

References

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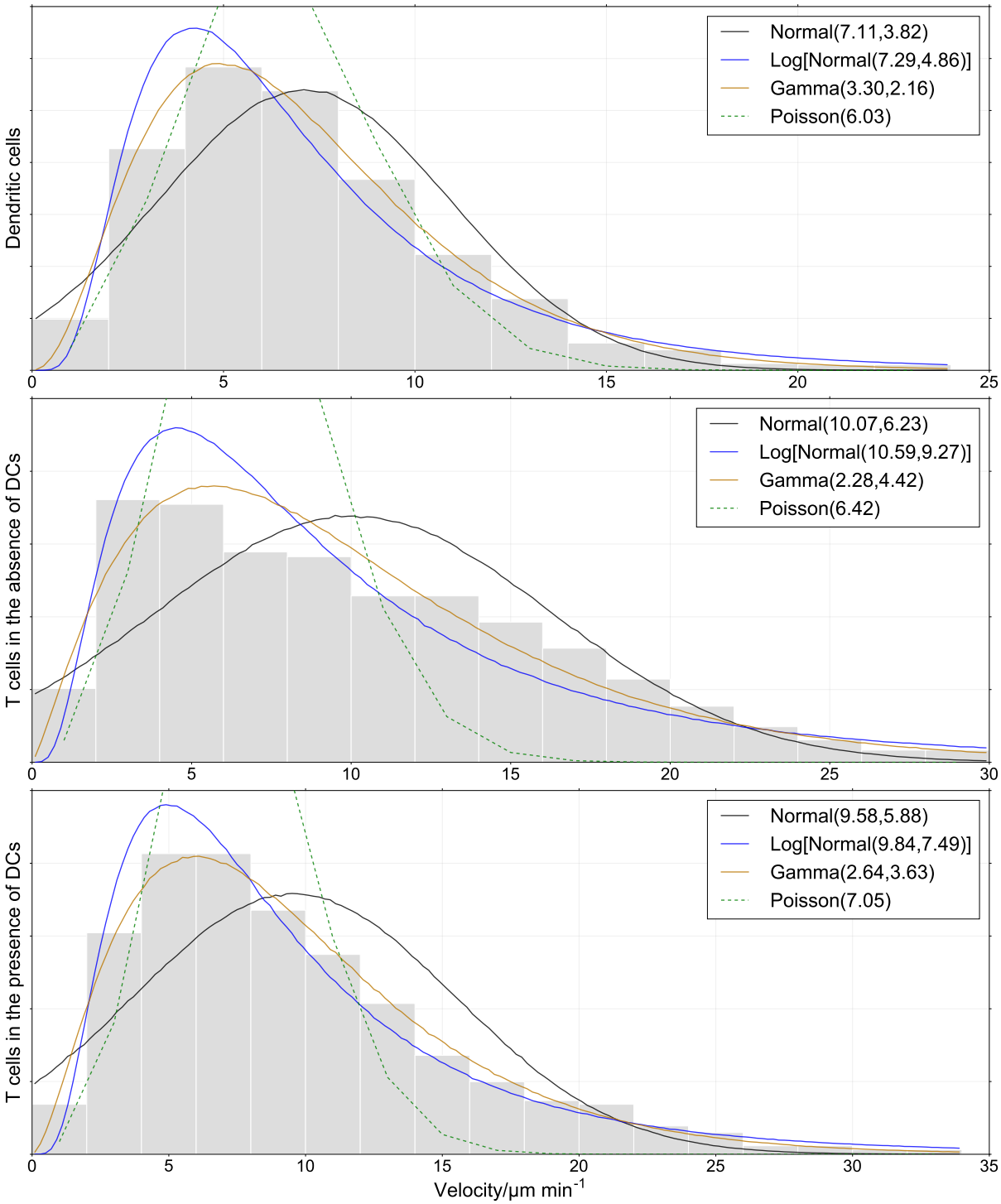

Figure A2. Histogram of velocity measurements of T cells and dendritic cells in mice as in figures 1–2 of Mempel *et al*'s letter [1], with various velocity distributions fit to them. The parameters used for each distribution are indicated in the figure legends.