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Thymic Selection of T Cells as Diffusion with Intermittent Traps

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Abstract T cells orchestrate adaptive immune responses by recognizing short peptides derived from pathogens, and by distinguishing them from self-peptides. To ensure the latter, immature T cells (thymocytes) diffuse within the thymus gland, where they encounter an ensemble of self-peptides presented on (immobile) antigen presenting cells. Potentially autoimmune T cells are eliminated if the thymocyte binds sufficiently strongly with any such antigen presenting cell. We model thymic selection of T cells as a random walker diffusing in a field of immobile traps that intermittently turn "on" and "off". The escape probability of potentially autoimmune T cells is equivalent to the survival probability of such a random walker. In this paper we describe the survival probability of a random walker on a d-dimensional cubic lattice with randomly placed immobile intermittent traps, and relate it to the result of a well-studied problem where traps are always "on". Additionally, when switching between the trap states is slow, we find a peculiar caging effect for the survival probability.

Keywords Random walk · Immobile traps · Intermittent two-state traps · Immune system

1 Introduction

After bacterial or viral infection, the job of an organism's immune system is to recognize and eliminate pathogens from the host. T cells orchestrate adaptive immune responses by recognizing short peptides derived from pathogen proteins, and by distinguishing them from self-peptides derived from host proteins [14]. To ensure the latter, immature T cells (thymocytes) diffuse around the thymus gland, where they encounter an ensemble of self-peptides presented on (immobile) antigen presenting cells (APC) [13, 17]. If a thymocyte binds strongly to such an APC, it is eliminated; i.e. the APC acts as a trap for the diffusing thymocyte. Since the peptides presented by APCs are recycled, the traps are not permanent, but intermittently turn "on" and "off". Only a few percent of thymocytes survive thymic selection [4], but some

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of those might be autoimmune. We are interested in the escape probability of autoimmune T cells during thymic selection. To address this question we study the survival probability of a random walker on a d-dimensional cubic lattice with randomly placed immobile traps that intermittently switch between "on" and "off" states. First we review what is know about the survival probability in a well studied problem where traps are always "on". We then discuss the effect of intermittent two-state traps on the survival probability at short and long times and describe a peculiar caging effect at intermediate times when switching between trap states is slow.

2 Classical Trapping Problem

The problem of trapping in a random medium has been studied extensively, with applications including dynamical processes in disordered media, kinetics of reactions, electron-hole recombinations in random and amorphous solids, and exciton trapping and annihilation [3, 10]. Here we review what is known about the survival probability of a random walker in a field of randomly placed immobile traps on a d-dimensional cubic lattice, when averaged over all random trap configurations. At each step a walker hops from one site to a randomly chosen nearest neighbor site and if it lands on a trap, it dies. Suppose that a walker has survived the first n steps, during which it has visited S_n distinct lattice sites. If the trap concentration is c, then the probability that all S_n lattice sites were not traps is equal to $(1-c)^{S_n}$. The average survival probability of a walker after n steps is thus

$$\Phi_{\mathrm{ON}}(n,c) = \langle (1-c)^{S_n} \rangle = \langle e^{-\lambda S_n} \rangle, \tag{1}$$

where $\lambda = -\ln(1-c)$, and the averaging is over all realizations of random walks of length n. The exact analytical result of survival probability is only known in one dimension [3], while analytical approximations in higher dimensions are only known for small and large n.

At small and intermediate number of steps n the survival probability is accurately described by the Rosenstock approximation [18]

$$\Phi_{\mathrm{ON}}(n,c) \approx e^{-\lambda \langle S_n \rangle}. \tag{2}$$

Asymptotic values of $\langle S_n \rangle$ for large n are known in all dimensions d [16]:

$$\begin{array}{c|c} d & \langle S_n \rangle \\ \hline 1 & \sqrt{8n/\pi} \\ 2 & \pi n/\ln(8n) \\ \geq 3 & n/P(\mathbf{0};1), \end{array} \tag{3}$$

where $P(\mathbf{x};z) = \sum_{n=0}^{\infty} z^n P_n(\mathbf{x})$ is the generating function of the probability distribution $P_n(\mathbf{x})$ that a random walker is at location $\mathbf{x}$ after n steps. The Rosenstock approximation can be extended by rewriting the survival probability in terms of cumulants [20]:

$$\ln \Phi_{\mathrm{ON}} = \ln \langle e^{-\lambda S_n} \rangle = \sum_{j=1}^{\infty} (-1)^j \frac{\lambda^j}{j!} \kappa_j(n), \tag{4}$$

where the first two cumulants are $\kappa_1(n) = \langle S_n \rangle$ and $\kappa_2(n) = \langle S_n^2 \rangle_c = \langle (S_n - \langle S_n \rangle)^2 \rangle$. For fixed n the series converges rapidly when λ is small. This is because $1 \leq S_n \leq n+1$, which

implies that the jth cumulant, $\kappa_j(n)$ is at most of order n^j. The series is thus expected to converge rapidly when $n \ll \lambda^{-1}$. In practice only the first two terms can be used, because in $d \geq 2$ analytical expressions are known only for the first two cumulants [16, 19]. To estimate the range of validity of Rosenstock approximation, we check where $\lambda^2\kappa_2(n) \ll \lambda\kappa_1(n)$:

d	$\kappa_1(n)$	$\kappa_2(n)$	$\lambda^2\kappa_2(n) \ll \lambda\kappa_1(n)$
1	$a_1\sqrt{n}$	$b_1 n$	$n \ll (\frac{a_1}{b_1\lambda})^2$
2	$a_2 \frac{n}{\ln(8n)}$	$b_2 \frac{n^2}{\ln^4(8n)}$	$n \ll \frac{a_2}{b_2\lambda} \ln^3(\frac{1}{\lambda})$
3	$a_3 n$	$b_3 n \ln n$	$n \ll \exp(\frac{a_3}{b_3\lambda})$
≥ 4	$a_d n$	$b_d n$	all n.

(5)

Note that the estimate above appears to suggest that for $d \geq 4$ the Rosenstock approximation is valid for all n, but this is not correct as will be described next. Therefore it is only safe to assume that the Rosenstock approximation is valid for $n \ll \lambda^{-1}$.

In the limit of large n, Donsker and Varadhan [5, 6] proved that the survival probability falls asymptotically as a stretched exponential:

$$\Phi_{\mathrm{ON}}(n, c) = e^{-k_d \lambda^{2/(d+2)} n^{d/(d+2)}}, \tag{6}$$

where k_d is numerical constant which depends on dimension d and lattice properties. For a d-dimensional cubic lattice the value of k_d is:

$$k_d = \frac{(d+2)}{2} \left(\frac{2\gamma_d}{d} \right)^{d/(d+2)}, \tag{7}$$

where $\gamma_d = \frac{1}{2}\xi^2_{\frac{d}{2}-1}\omega_d^{2/d}$ is the lowest eigenvalue of the operator $-\frac{1}{2}\Delta$ for the sphere of unit volume in d dimensions with zero boundary values (absorbing boundary condition), with $\omega_d = \pi^{d/2}/\Gamma(1 + d/2)$ the volume of a d-dimensional sphere of unit radius, and ξ_p the smallest zero of the Bessel function of the first kind of order p. The stretched exponential at large times is a consequence of diffusion through large trap free regions which appear with exponentially small probability. The correct asymptotic result can be obtained also through a simple heuristic argument [9]. Since we are interested in long times and large trap free regions we can treat the problem in the continuum limit and replace a random walk with Brownian motion with diffusion constant $D = 1/(2d)$. The probability that there are no traps inside a sphere of radius R is $(1-c)^{\omega_d R^d} = \exp(-\lambda\omega_d R^d)$. The survival probability of a walker originally at the origin of the sphere satisfies the diffusion equation with absorbing boundary conditions. At long times the survival probability is dominated by the normal mode with the slowest decay $\exp(-nD\xi^2_{\frac{d}{2}-1}/R^2)$. The joint probability for there to be a trap-free sphere of radius R, and for the diffusing walker to stay inside the sphere for at least n steps is thus:

$$\Phi_{\mathrm{ON}}(R, n) = \exp\left[-\lambda\omega_d R^d - nD\xi^2_{\frac{d}{2}-1}/R^2 \right]. \tag{8}$$

The joint probability is maximized at the radius $R = (2nD\xi_{\frac{d}{2}-1}/d\lambda\omega_d)^{1/(d+2)}$, which results in

$$\Phi_{\mathrm{ON}}(n) \sim \exp\left[-\frac{(d+2)}{2} \left(\frac{2}{d} nD\xi^2_{\frac{d}{2}-1} \right)^{d/(d+2)} \left(\lambda\omega_d \right)^{2/(d+2)} \right]. \tag{9}$$

Note that this is identical to the Donsker-Varadhan result.

Interestingly, the survival probabilities for different concentrations are connected with scaling function [1, 8]. The scaling ansatz for a function F_d which connects small n (Rosenstock) and large n (Donsker-Vardahan) limit for all trap concentrations λ is:

$$\ln \Phi_{\mathrm{ON}} = -n^{\alpha_d} F_d\left(\lambda n^{\beta_d}\right), \tag{10}$$

with $F_d(x) = a_d x$ for small x and $F_d(x) = k_d x^{2/(d+2)}$ for large x. Exponents $\alpha_d = (d-2)/d$ and $\beta_d = 2/d$ for $d \geq 3$ ($\alpha_1 = 0$, $\beta_1 = 1/2$) are chosen such that the survival probability satisfies equations (2) and (6) for small and large n. In two dimensions logarithmic factors must be added to the scaling function to account for logarithmic factors in the Rosenstock regime, which result in

$$\ln \Phi_{\mathrm{ON}} = -\ln(8n) F_2\left(\frac{\lambda n}{\ln^2(8n)}\right). \tag{11}$$

The transition from Rosenstock to Donsker-Varadhan regime occurs at $a_d x_d^* \approx k_d x_d^{*2/(d+2)}$, where $x_d^* = \lambda n^{*\beta_d}$. The values x_c^* for the first three dimensions are $x_1^* = 27\pi^{7/2}/(128\sqrt{2}) \approx 8.2$, $x_2^* = \xi_0^2/\pi \approx 1.84$ and $x_3^* = (5^5\pi^8 P(\mathbf{0}; 1)^5/2^1 3^8)^{1/3} \approx 26.3$, which are slightly bigger then the ones reported by numerical simulations [1]. Note that for $d \geq 2$, the survival probability at the transition depends on the trap concentration, and except for the densely trapped cases of $c \approx 1$, the survival probability at the transition is too small for the Donsker-Varadhan limit to be observed by direct numerical simulations of random walks [3]. Several numerical techniques have been developed that allow exploration of the Donsker-Varadhan limit, e.g. exact enumeration method of clusters of non-trapping sites [11], using the complete distribution of S_n [7], mapping to a polymer model [1], and mapping to self-avoiding random walks [8].

Figure 1 summarizes all results for the survival probability from this section. We calculated survival probabilities at different trap concentrations ranging from $c = 10^{-5}$ to $c = 0.99$ by directly simulating random walks and averaging over different trap configurations. Survival probability curves for different concentrations collapse on a single curve confirming the scalings from (10) and (11). The Rosenstock approximation works very well for small values of x, except for very small n, where the asymptotic limit of $\langle S_n \rangle$ is not yet reached. The Donsker-Varadhan limit is only observed in one dimension, while in two and three dimensions only the early stages of the transition to the long time limit are seen.

3 Intermittent Traps

In the previous section we discussed a classical trapping problem in which traps are always in the absorbing ("on") state. In this section the second reflective ("off") state is added to the model (Fig. 2). If a random walker attempts to step on a trap in the "off" state it remains at the initial site, while it dies if it attempts to step on a trap in the "on" state. Switching times of trap states are exponentially distributed random variables, with traps staying in the "on" ("off") state for characteristic time n_{ON} (n_{OFF}). The probability that a trap is initially in the state x ("on", "off") is

$$p_x = \frac{n_x}{n_{\mathrm{ON}} + n_{\mathrm{OFF}}}. \tag{12}$$

To numerically obtain survival probabilities we directly simulate the process. We start with a large d-dimensional lattice grid (containing $\sim 10^{10}$ lattice points) that is divided

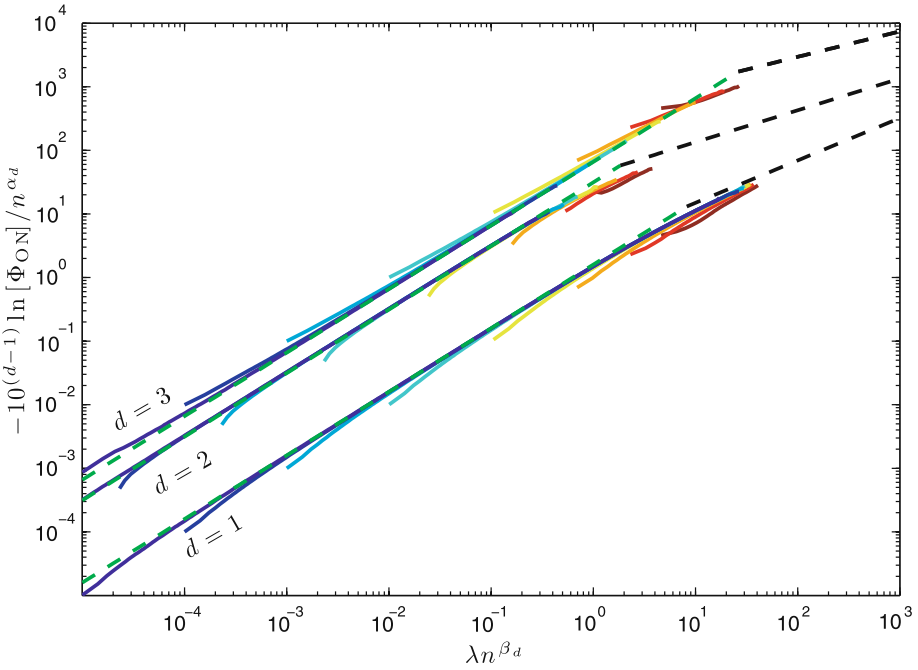

Fig. 1 Collapse of survival probabilities: Numerical simulations of the survival probability Φ_{ON} for different trap concentrations for $d = 1, 2, 3$ obey the scaling shown in equations (10) and (11). *Colored solid lines* from left to right correspond to $c = 10^{-5}$ (*dark blue*), $10^{-4}, 10^{-3}, 10^{-2}, 10^{-1}, 0.5, 0.9, 0.99$ (*dark red*). The Rosenstock approximation (*dotted green line*) works well at small λ and n, while the Donsker-Varadhan limit (*dotted black line*) is reached only in one dimension. In two and three dimensions only the early stages of the transition to the long time limit are seen. For clarity, results for different dimensions d are shifted as indicated by the vertical axis label

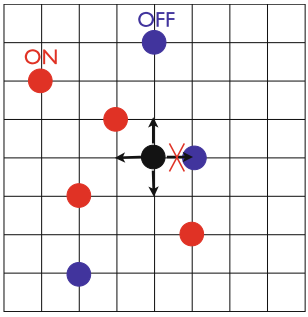

Fig. 2 Model. A random walker (*black circle*) steps on a lattice with randomly placed immobile traps. At each step a walker hops to a randomly chosen nearest neighbor site. If it steps on a trap in an absorbing "on" state (*red*), it dies, while if it attempts to step on a trap in a "reflective" state (*blue*) it remains at the initial site. Traps stay in the "on" ("off") state for typical time n_{ON} (n_{OFF}) before switching to the other state

into smaller hypercubes, each of which contains ~ 1000 lattice points. The grid is large enough that a random walker is always trapped before reaching the edges of the grid. To save computation time a random configuration of traps inside a hypercube is generated only after a random walker first enters that hypercube. The state of each trap is determined only after the random walker tries to jump on it and the state is chosen according to the probabilities in (12). After that the trap switches between the states with random exponentially distributed switching times. We simulate a random walk and measure how long the walker stays alive.

This process is repeated many times with different trap configurations to obtain the survival probability $\Phi(n, c, n_{\mathrm{ON}}, n_{\mathrm{OFF}})$ after n steps with trap concentration c.

What is the survival probability Φ of a random walker in this case, and how is it related to Φ_{ON} where traps are turned "on" all the time? The survival probability Φ is bounded from below by Φ_{ON}, because having all traps "on" increases the probability of trapping

$$\Phi \geq \Phi_{\mathrm{ON}}. \tag{13}$$

At large number of steps n in the Donsker-Varadhan limit the survival probability is dominated by large trap free regions. The slow step is diffusion through this region, while finding the trap in an "on" state outside this region is quicker. Therefore at large n

$$\Phi \simeq \Phi_{\mathrm{ON}}. \tag{14}$$

For small n and low trap concentrations c ($c\langle S_n\rangle \lesssim 1$), the probability of trapping $(1-\Phi)$ is dominated by the first collision with a trap, which must be turned on:

$$1-\Phi \simeq p_{\mathrm{ON}}\Big(1-\Phi_{\mathrm{ON}}\Big). \tag{15}$$

Figure 3 shows survival probabilities in $d = 1, 2, 3$ for different values of n_{ON} and n_{OFF}. The trapping relation (15) works well at short times n. Crossover to the long time Donsker-Varadhan limit (14) is seen only in one dimension and the transition is slower in higher dimensions. When switching times n_{ON} and n_{OFF} are slow we notice that the survival probability plateaus at some level, before it starts dropping again. The reason for this is a caging effect described below.

In $d = 1$ a random walker is always bounded by the nearest left and right traps. When switching between trap states is very slow, the trap configuration is "frozen" for $n \ll n_{\mathrm{ON}}, n_{\mathrm{OFF}}$. If at least one of the bounding traps is in "on" state, a random walker dies at that trap. With probability p_{OFF}^2 both bounding traps are in the "off" state, forming a cage. The walker diffuses inside this cage until one of the traps turns "on" and then it is quickly absorbed. The "survival" probability of the cage is:

$$\Phi_c(n) = p_{\mathrm{OFF}}^2 \exp[-2n/n_{\mathrm{OFF}}], \tag{16}$$

where exponential factors represent the probability that both bounding traps are still in the "off" state after n steps. After the survival probability Φ of a walker drops to the probability of caging, it is well approximated by the above equation (Fig. 4a). Φ_c decays faster than the stretched exponential in the Donsker-Varadhan limit, which comes from large trap free regions. Therefore at large n the survival probability is still dominated by the large trap free regions (Fig. 3).

In $d > 1$ traps always form a cage when the trap concentration c is above the percolation threshold. However, even at low trap concentration c, with low probability there are some trap configurations that form small cages around the origin. If at least one of the traps forming a cage is in the "on" state, then a random walker dies quickly. But if all cage forming traps are in the "off" state, and the typical switching time n_{OFF} is slow, then a random walker diffuses inside the cage until one of the traps switches to the "on" state. The average survival probability of a random walker that is caught in a cage is thus

$$\Phi_c = \sum_{k,\ell} \left(A_{\ell,k}(1-c)^k c^\ell\right) \times \left(p_{\mathrm{OFF}}^\ell \exp[-\ell n/n_{\mathrm{OFF}}]\right), \tag{17}$$

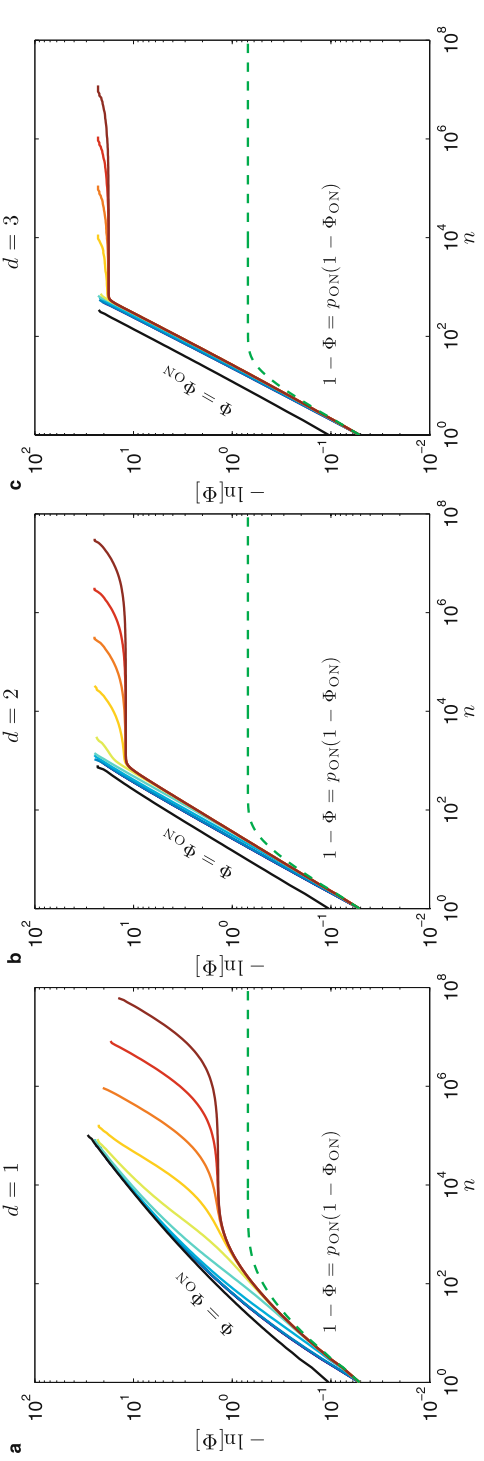

Fig. 3 Survival probability Φ in $d = 1, 2, 3$ ($c = 0.1, n_{OFF}/n_{ON} = 1$). *Colored solid lines* correspond to different values of n_{OFF}; the *darkest red color on the right* corresponds to the largest $n_{OFF} = 10^7$ and neighboring curves differ by factor 10 in n_{OFF}. For small n, the trapping relation (15, *dotted green line*) works well. Φ_{ON} (*solid black line*) represents a lower bound for Φ, which is reached in the Donsker-Varadhan limit of large n. Crossover to the Donsker-Varadhan limit is slower in higher dimensions. When switching times n_{ON} and n_{OFF} are slow (*yellow*, *orange*, *red*) the survival probability plateaus before it starts dropping again

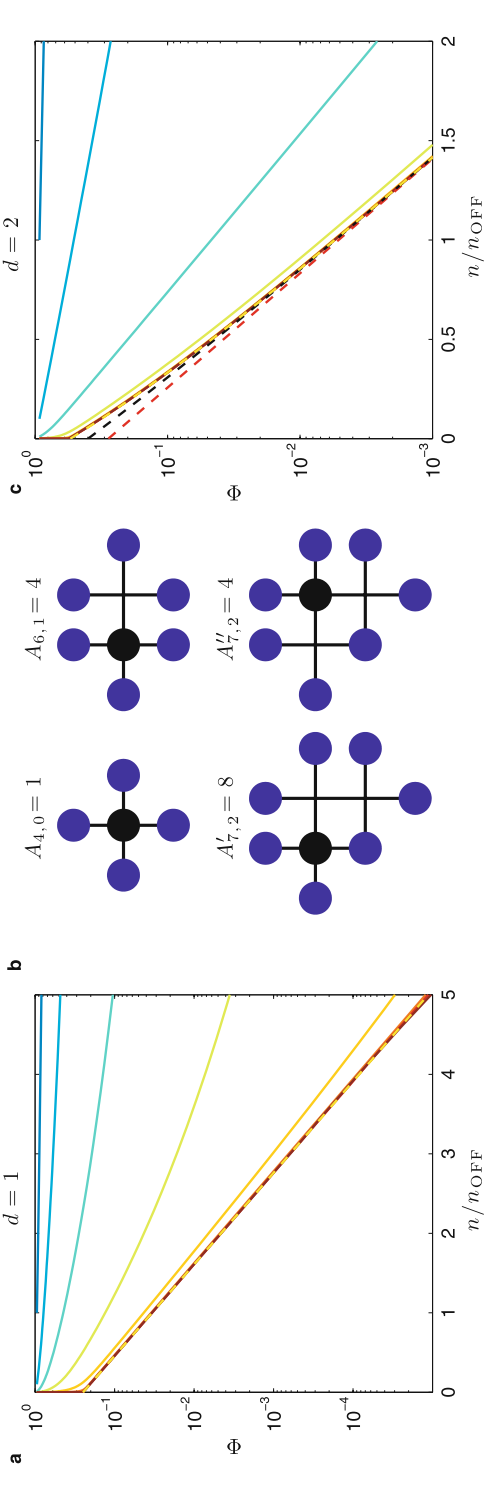

Fig. 4 Caging effect: **a** Survival probabilities in $d = 1$ ($c = 0.1$, $n_{\rm OFF}/n_{\rm ON} = 1$) agree well with the probability of caging ((16), *dotted yellow line*) when switching times are slow (*colored solid lines* in (**a**) and (**c**) are the same as in Fig. 3). The *solid yellow line* is initially close to the probability of caging, but at large n it starts deviating and approaches the stretched exponential of the Donsker-Varadhan limit. **b** Configuration of cages in $d = 2$ with the smallest number ℓ of cage forming traps. A random walker (*black*) sits at the origin and is surrounded by traps in the "off" state (*blue*). $A_{\ell,k}$ gives the number of equivalent cage configurations. **c** Survival probabilities in $d = 2$ ($c = 0.8$, $n_{\rm OFF}/n_{\rm ON} = 10$) agree well with the probability of caging (17) when switching times are slow. For large n it is sufficient to keep only one (*dotted red line*) or two (*dotted black line*) terms in (17). Because $c = 0.8$ and $p_{\rm OFF} = 10/11$ are close to 1, more terms need to be kept for accurate description of the caging probability at small n (*dotted yellow line*, up to $\ell = 11$)

where ℓ is the number of traps forming a cage, and k the number of empty sites inside the cage excepting the origin (because the origin—the initial location of the random walker—is always assumed to be empty). The first factor represents the probability of cage formation with $A_{\ell,k}$ being the combinatorial number of configurations with the same number of empty sites and cage forming traps. The second factor is the probability that all cage forming traps are initially in the "off" state and remain in the same state for n steps. In $d = 2$, the first few non-zero coefficients $A_{\ell,k}$ are $A_{4,0} = 1$, $A_{6,1} = 4$, $A_{7,2} = 12$ (Fig. 4b) and in general for $d > 1$ the first two non-zero coefficients are $A_{2d,0} = 1$ and $A_{4d-2,1} = 2d$. When c or p_{OFF} are small, or $n \gg n_{\mathrm{OFF}}$, it is enough to keep only the first few terms in (17), but if c and p_{OFF} are close to 1 and $n \lesssim n_{\mathrm{OFF}}$ then we must keep more terms (Fig. 4c). Like in one dimension, the survival probability Φ is well approximated for large n_{OFF} by (17) after Φ drops to the probability of caging Φ_c. Φ_c decays faster than the stretched exponential decay in the Donsker-Varadhan limit; therefore at large n the survival probability should still approach Φ_{ON} (Fig. 3).

4 Discussion

In conclusion, let us return to the question of escape probability of potentially autoimmune T cells from the thymus. First we estimate the relevant parameters in our model. The density of APCs in the thymus is 30,000–50,000 cells/mm^3 [2]. If we choose the lattice constant a_0 to be equal to the typical diameter of the antigen presenting cell $\sim$10 μm [2], the trap concentration is estimated at $c \sim 0.03$–0.05. From the T cell diffusion constant, $D \sim 100\ \mu\mathrm{m}^2\ \mathrm{min}^{-1}$ [2], we estimate the hopping time of a random walker as $t_1 = a_0^2/(6D) \sim 0.2$ min. T cells diffuse around the thymus for around 4–5 days [15], which is equivalent to $n \sim 30{,}000$–$40{,}000$ steps of a random walker. A typical lifetime of a self-peptide on the surface of APCs is on the order of hours [12], which corresponds to $n_{\mathrm{ON}} \sim 100$. Since many self-peptides are simultaneously presented on the surface of APCs, the effective n_{ON} could be even longer. Different T cells are represented with different n_{OFF}. A potentially autoimmune T cell is more likely to bind strongly to APCs and is thus associated with lower values of n_{OFF}. Let us first estimate the escape probability for an extremely autoimmune T cell, which reacts to every host cell. Such a T cell is characterized by $n_{\mathrm{OFF}} = 0$ and $\Phi = \Phi_{\mathrm{ON}}$. Since $x = \lambda n^{2/3} \sim 30$–$60$ is larger than the location $x_3^* = 26$ of the transition to the Donsker-Varadhan limit, we use the Donsker-Varadhan result to estimate $\Phi_{\mathrm{ON}} \sim 10^{-400}$–$10^{-300}$. This implies that an extremely autoimmune T cell cannot escape from the thymus.

In reality autoimmune T cells do not react to every host cell, but are directed toward particular tissues. Since tissue specific peptides are presented on 1–3% of APCs in the thymus [15], such autoimmune T cells are characterized by $n_{\mathrm{OFF}} \sim 3{,}000$–$10{,}000$ in our model ($p_{\mathrm{ON}} \sim 1$–3%). The model estimates that the escape probability of T cells specific for tissues that are represented with fewer peptides ($p_{\mathrm{ON}} \sim 1\%$) is $\sim 10^{-6}$–10^{-3} and the escape probability of T cells specific for tissues that are represented with more peptides ($p_{\mathrm{ON}} \sim 3\%$) is $\sim 10^{-20}$–10^{-10}. The estimates are very crude, because the survival probability depends exponentially on the parameters which are just approximately determined. However, we still see that the escape from the thymus is possible when tissue specific peptides are not presented in big amounts. This may be why the immune system contains specialized regulatory T cells, which try to shut down the response from autoimmune T cells.

Finally, we note that the caging effect is not relevant for thymic selection: since the trap concentration c is low, even small cages appear with very small probability and thus the

caging effect is not important on the relevant time scales. In any case, T cells can never be trapped inside cages, as they are delivered to the thymus via blood vessels and small cages around the entrance would completely block the flow of T cells through the thymus.

In this paper we introduce to study properties of a model initially motivated by T cell survival. While the main body of the text explores the full parameter range of this model, some of the results do not apply to the relevant parameters for the thymic selection. Furthermore for thymic selection the model parameters are only approximately known. Because the escape probability of autoimmune T cells depends exponentially on these parameters, we can only determine the order of magnitude for the escape probability, which could probably be estimated also with simpler models.

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