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Simulating T cell motility in the lymph node paracortex with a packed lattice geometry

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Abstract

Agent-based simulation modeling of T cell trafficking, activation and proliferation in the lymph node paracortex requires a model for cell motility. Such a model must be able to reproduce the observed random-walk behaviour of T cells, while accommodating large numbers of tightly packed cells, and must be computationally efficient. We report the development of a motility model, based on a 3-D lattice geometry, that meets these objectives. Cells make discrete jumps between neighbouring lattice sites in directions that are randomly determined from specified discrete probability distributions, which are defined by a small number of parameters. It is shown that the main characteristics of the random motion of T cells as typically observed in vivo can be reproduced by suitable specification of model parameters. The model is computationally highly efficient, and provides a suitable engine for a model capable of simulating the full T cell population of the paracortex.

Keywords

lattice; motility; random walk; simulation; T cell

Introduction

Understanding how T cell responses begin requires an understanding of the interactions between T cells and antigen-presenting cells in lymphoid tissues such as lymph nodes. Two-photon microscopy has revealed that T cells roam in the paracortex of a lymph node in a way that appears largely random.¹⁻¹⁰ Interactions with APC such as dendritic cells often occur in a number of stages that can include sequential binding to many different DC before T cell activation is initiated. Conceptualising the initiation of T cells responses now requires T cell motility to be taken into account along with other well-established parameters, such as the frequency of antigen-specific T cells, the signals necessary for T cell activation, and the factors necessary to support T cell proliferation. Integrating all this information into a satisfactory model of T cell behaviour in lymphoid tissue will require sophisticated computer models capable of incorporating spatial factors and cell motility with factors governing T cell activation.

Two reasons have been proposed for the apparently random motion of T cells: the structure of stromal cell networks in the paracortex, and interactions between the densely packed cells. Electron microscopy has revealed the complex architecture of lymph nodes.¹¹⁻¹³ The paracortex is occupied by an open random three-dimensional network of reticular fibers made up of fibroblastic reticular cells (FRC), as has been graphically illustrated.¹² Fluorescence immunohistochemistry with confocal imaging supports the idea that lymphocytes use the reticular fiber network as a foothold,^{14, 15} and through a painstaking combination of confocal, electron and intravital microscopy it has been verified that T cells move by crawling along the randomly branching network of reticular fibers.¹⁶ The implication is that the random walk behavior exhibited by T cells is a manifestation of the structure of the underlying fiber network.

On the other hand, some physics-based simulations show that interactions between T cells and with DC can generate the kind of random motion that has been observed.^{17, 18} A complete understanding of the issue remains in the future, but it seems likely that the random walk trajectories that T cells follow are influenced both by the architecture of the reticular network and by interactions between cells. Probably both FRCs and the surfaces of other lymphocytes provide a substrate for cellular locomotion. We are agnostic on the question of what underlying mechanisms determine cell motility. A motility model is considered sufficiently realistic for our purposes if it captures, in a statistical sense, the main features of the cell motion, *i.e.* mean cell speed, and the motility coefficient, as defined in the Methods.

Modeling T cell motility is in its infancy, and although a few approaches have been published, none to date is really suitable for simulating T cell aggregations at the level of a whole lymph node. The range of available approaches can be broadly classified as either spatially-continuous, or spatially-discrete. As discussed below, while spatially-continuous models can simulate cell paths that are realistic-looking and reproduce motility parameters, they are not computationally efficient when simulating large numbers of cells if interactions between cells are to be taken into account, in particular volume exclusion. We were interested in the possibilities presented by spatially-discrete approaches that are free from the drawbacks of spatially-continuous models, making them more suitable for large-scale modeling T cell interactions in the lymph node paracortex.

Our goal was to develop a three-dimensional model of T cell motility that (1) is consistent with T cell motility measured in intravital microscopy experiments (2) can handle densely packed cells (3) is capable of simulating biologically realistic numbers of cells (> 1 million) to allow an entire lymph node paracortex to be modeled (4) is efficient enough to enable modeling over several days of simulated time.

We decided to base our approach on cell motion on a three-dimensional lattice. It was anticipated that the gains in computational efficiency would justify sacrificing some physical realism in the detail of cell trajectories. Lattice methods have been used for T cell modeling, but unlike existing models, our approach allows simulation of random motion in a paracortex densely packed with a large number of T cells. In this paper we describe the mathematical algorithm that has been developed, and show that the model's computational efficiency permits it to be scaled up to account for all the T cells present in a typical lymph node.

Once the model had been developed, we sought to validate it by tuning the model parameters under our control to deliver T cell behaviour consistent with measured values. The apparently random motility measured by intra-vital microscopy can be conveniently characterised by a small number of parameters. Many of the papers in the field have

produced estimates of the range of values of two key parameters – T cell speed, and motility coefficient, which is a statistical measure of how rapidly cells move away from their starting positions, analogous to a diffusion coefficient. In this paper our aim has been to determine whether our model can be tuned to reproduce these measured values.

One potential disadvantage to our lattice-based approach is that the T cell movement patterns can look “jerky” because of the constrained possibilities for step directions in each time step. Modifying the rules to allow more step directions improved the smoothness of the motility patterns without excessive computational cost.

We conclude that this kind of model is feasible for large-scale simulation of T cell motility in lymph nodes. It also has the additional advantages of allowing other spatial elements, such as cytokine and chemokine gradients, to be readily grafted over the lattice, and of readily accommodating the changes in T cell numbers and paracortical volume that occur during an immune response.

Results

Characteristics of the models

Scanning electron and confocal microscopy studies have shown that T cells are tightly crowded together in the paracortex.¹⁹ It is difficult to find firm estimates of the fractions of the paracortical volume occupied by the various constituents, but on the basis of the information available we have estimated that T cells occupy about 60% of the paracortical volume, with extra-cellular fluid accounting for about 10% and the remaining space mostly being taken up by reticular structures, HEV (high endothelial venules), DC and other cell types. The value we use for the T cell fraction of paracortical volume is higher than the figure of 53% used in another model study¹⁸, partly because of impressions gleaned from unpublished confocal images of a rat LN. The parameter will be adjusted as better data become available concerning the volume fraction. The lattice grid in our model was sized to approximate the way T cells are packed in the paracortex. Accordingly, the lattice spacing was chosen such that the volume of a T cell is 60% of the lattice site volume. Setting the number of cells in the modeled region equal to the number of available lattice sites then ensured that the correct fraction of the volume is taken up by T cells. The close packing of cells - one per lattice site - complicates the generation of random cell motion. The previous models of T cells moving on a lattice allowed jumps only into vacant sites,^{20, 21} but this approach is not valid when almost every site is occupied by a T cell. When sites are fully occupied the motion of all cells becomes interdependent, since the cell in a target site must move to make way for the incoming cell.

Thus the “one cell per site” condition, in combination with a fully occupied lattice makes it difficult to design a model for cell motion. The observation that in reality T cells are capable of radical shape changes, and able to slide around each other, suggested the idea of some relaxation the “one cell per site” condition, allowing two cells to occupy the same site temporarily. This change would reduce the dependence of each cell’s motion on that of the other cells. Although this amounted to “bending the rules” we considered that it would be acceptable provided the resulting rate of occurrence of lattice site overcrowding (two cells per site) was limited.

The volume of a T cell is about $150 \mu\text{m}^3$, equivalent to a sphere of radius $3.3 \mu\text{m}$. The assumption that T cells occupy 60% of the volume of the paracortex implies that the lattice site volume must be $250 \mu\text{m}^3$, *i.e.* that the grid spacing must be $6.3 \mu\text{m}$. We have developed three models for cell motion on this lattice, based on the same idea, but with different levels of complexity. The first model, much simpler than the other two, is based on the so-called

von Neumann neighborhood; cells are allowed to move in the six principal directions ($\pm x$, $\pm y$, $\pm z$). We refer to this as Model N (for Neumann). As discussed below, this simple model is capable of generating the required values of the motility parameters. Model N is not totally satisfactory, however, because the cell paths that it generates have a distinctly jerky appearance, a result of the fact that changes of direction are always through 90 deg. Although it isn't clear what practical significance this jerkiness has in a model of aggregations of cells, we decided to seek an approach that would generate smoother cell paths. The result is two rather more complex models, based on the so-called Moore neighborhood (for which, in 3-D, each site has 26 neighboring sites), allowing cells to move diagonally. These are labelled M18 and M26, where the number refers to the number of allowed step directions.

In all three models a sweep in random order is made through the cells in each time step, and a decision is made regarding how to move each cell. Each cell "jumps" to one of the adjacent positions in the grid (though in many instances the cell may stay in the same site during a particular time step without jumping, for reasons described below). The direction of any jump is chosen randomly from the possible moves allowed by the grid, but each potential direction is first weighted according to a pre-calculated set of probabilities, so that all directions are not equally likely. Over a large number of jumps, these probabilities influence the overall path taken by the cell. For example, if cells were assigned a probability of 1 of jumping upwards, each cell would move in a straight line upwards over time. If that probability is less than 1, then the cells will deviate from a straight line over time. A series of equations describes how the probabilities of moving in a particular direction are determined, and these equations are in turn dependent on the user-defined values described below, so that the user can control the cells' broad motility parameters. These equations are relatively simple for Model N, where only 6 adjacent grid positions are made available for a jump, but they become far more complex for Model M18, which makes available 18 adjacent positions (including 12 diagonals), and Model M26, which allows all 26 adjacent positions.

Persistence of the direction of motion is a fundamental property of a persistent random walk, the form of motion that best describes how T cells move in the paracortex. In order to allow persistence of direction, and to control the degree of this persistence, the probabilities associated with each jump direction are defined relative to the direction of the cell's previous jump. Specification of two parameters, β and ρ , determines the general characteristics of cell motion, through the calculation of the directional probabilities at each time step (as detailed in the Methods). The first parameter β is effectively used to control cell speed. β is defined as the probability that the cell makes a move, *i.e.* if β is set at 0 at the beginning of the simulation, all the cells will remain static, while if β is set at 1, all the cells will move in every time step. Given that each cell can move only a defined distance (determined by the lattice grid spacing) in a particular time step, the probability of moving effectively controls its speed. The second parameter ρ is designed to influence the directional persistence of the cell's motion. The formulae controlling cell movement are structured such that as ρ increases, the probability increases that a cell will jump in the same direction as its previous jump; the probability that a cell will jump in any other direction decreases correspondingly, with the lowest probability reserved for a reversal of direction from the previous jump. (A pertinent analogy might be that ρ controls the degree to which the direction of the cell's next move is affected by its previous momentum, as illustrated in Figures 7-9.)

As each cell is processed during the sweeps through the lattice, the occupancy of the lattice sites changes, with some sites gaining a second cell, and other sites becoming vacant. The possibility that too many sites might become "crowded" with more than one cell can be

conveniently controlled by increasing the probability of movement out of grid sites that contain two cells, and preventing movement of a third cell into a site already occupied by two cells (by reducing its probability to zero). In addition, cells are “encouraged” to move into lattice sites that are vacant rather than those that are already occupied with a single cell. This is achieved by scaling back the probabilities of moving into occupied sites by a factor determined by the user; this third user-controlled parameter is a “crowding” parameter γ , and its effects on probabilities of moving into occupied sites are detailed in the Methods.

Hence at the beginning of each simulation, the user selects three parameters, which influence the calculation of the probabilities of cells moving in a particular direction at each time step. The β parameter is the main influence on cell speed, the ρ parameter affects the degree to which each cells’ motion persists in a particular direction, and the γ parameter can be used to fine-tune the extent to which the lattice sites become crowded with two cells.

Calibration of the models to experimental observations

The two parameters of cell motility our models were required to reproduce were mean speed S (averaged over one time step) and motility coefficient C_m . There is some uncertainty about the “true” values of the quantities, since various numbers have been obtained experimentally. Based on published evidence (reviewed in the Methods) we calculate that the mean speed of T cells in the paracortex is in the range 10-17 $\mu\text{m}\cdot\text{min}^{-1}$, and that the motility coefficient of naïve T cells in the paracortex is typically somewhere in the range 40 - 100 $\mu\text{m}^2\text{min}^{-1}$. The time interval over which speed measurements are made must also be taken into account (as described in Methods). For our model, a time step of 15 sec was chosen for consistency with most experimental data.

We explored the sensitivity of the two motility models to the model parameters through numerical simulation, with a rather arbitrary “typical” motility target of mean speed = 15 and $C_m = 65$. A lattice $100 \times 100 \times 100$ was fully populated with cells, and approximately 4300 cells occupying a spherical zone in the centre of the lattice (with a radius of 10 sites) were tagged. Motion of all 10^6 cells was then simulated for 60 time steps of 0.25 min. The displacement of the tagged cells from their starting positions was computed at each time step, and C_m was computed as 1/6 of the rate of change of mean squared displacement with time. For any specified parameter values the slope of the mean squared displacement plot increased initially, then approached a constant value, consistent with Eq. (3) in Methods. The linear growth of the mean squared displacement continued until cells started to reach the boundary of the modeled region – after about 80 min. As Figure 1 illustrates, the influence of the boundary led to a steady reduction in the slope of the curve after this point. Since the linear part of the curve was always reached within 5 min, the C_m value was estimated from the slope of the line of best fit over the range 5 to 15 min. In all cases the fit to a straight line was very good, with R^2 always greater than 0.999.

The parameter γ , which determines the relative “attractiveness” of vacant and occupied sites, influences how many sites are “crowded”, i.e. occupied by two cells, at any time. The number of crowded sites is of course the same as the number of vacant sites. Crowding is a necessary evil in this model, and it was arbitrarily decided that it should be limited to less than 20% of the sites. With $\gamma = 0.2$, and typical values of the motility parameters, the fraction of crowded sites is about 17% with all model versions. Detailed calibration results are now presented for each version of the model.

Model N—Numerical experiments established that values of β and ρ of 0.51 and 0.71 respectively generated the target motility measures of mean speed = 15 $\mu\text{m}\cdot\text{min}^{-1}$ and $C_m = 65 \mu\text{m}^2\text{min}^{-1}$, computed as averages over 4272 cell trajectories. Figure 2 shows the mean squared displacement for a typical run plotted as a function of time, together with the best-fit

line. (Fitting a straight line to the plot of mean displacement vs. $t^{1/2}$ yields an estimate of 59.3 for C_m in this case, i.e. a reduction of about 8%.) By varying β over 30 values in the range 0.25 - 0.9, and ρ over 50 values in the range 0.2 - 0.85, running the simulation with each pair of parameter values, and analyzing the results, tables of mean speed and C_m were constructed for the 1500 (β, ρ) pairs. From these tables contour plots were prepared (using Matlab's `contourc` function). Figure 3(a) shows how the mean speed depends mainly on β , and only slightly on ρ , while from Figure 4(a) it can be seen that both β and ρ influence the motility coefficient. The output from these simulations has been used to derive approximate values of β and ρ needed to generate specified motility behavior, as presented in Table 1. These values were estimated by computing contour lines for specified mean speed and C_m then determining their intersection. The values are only approximate because the underlying 1500 data points were each obtained from a single trial (4272 cells for 60 time steps), then contour lines were estimated from these noisy data. Figure 5(a) shows the 2-D projections of 20 T cell trajectories of 75 minutes duration generated by the model, with their starting positions shifted to a common origin. While most changes in direction are through 90 deg, some diagonal jumps can be seen, a consequence of the random sweep through sites, which occasionally moves a cell more than once within the same time step.

Model M18—The target mean speed of $15 \mu\text{m}\cdot\text{min}^{-1}$ and motility coefficient of $65 \mu\text{m}^2\text{min}^{-1}$ were reproduced by this model with $\beta = 0.41$ and $\rho = 0.76$. Simulations were carried out to estimate the motility behavior generated with a wide range of combinations of the two parameters β and ρ . In this case the variation of β was in the range 0.15 - 0.8. Contour plots were produced (Figures 3(b) and 4(b)) showing again that β determines the mean speed, but both β and ρ influence C_m . Table 2 lists more examples of the (β, ρ) parameter combinations that generate specified motility behavior. Typical T cell paths are displayed in Figure 5(b).

Model M26—The target mean speed of $15 \mu\text{m}\cdot\text{min}^{-1}$ and motility coefficient of $65 \mu\text{m}^2\text{min}^{-1}$ were reproduced by this model with $\beta = 0.38$ and $\rho = 0.76$. The contour plots in Figures 3(c) and 4(c) show how motility behaviour depends on β and ρ . Table 3 lists more examples of the (β, ρ) parameter combinations that generate specified motility behavior. Typical T cell paths are displayed in Figure 5(c).

Model checking

The turning angle distributions generated by the two Moore models have been estimated and compared with an experimentally determined distribution⁴ in which the frequencies were reported for T cell turning angles in 10° intervals. The lattice model permits only a limited number of discrete turning angles - $0^\circ, 45^\circ, 90^\circ, 135^\circ, 180^\circ$ in the case of M18, and $0^\circ, 45^\circ, 54.7^\circ, 90^\circ, 135^\circ, 144.7^\circ, 180^\circ$ in the case of M26 - therefore for the purposes of comparison the experimental distribution was reworked to derive a distribution with angle ranges $0^\circ-22.5^\circ, 22.5^\circ-67.5^\circ, 67.5^\circ-112.5^\circ, 112.5^\circ-157.5^\circ, 157.5^\circ-180^\circ$, and the modeled distributions were computed using these ranges (note that negative and positive turning angles have been combined). The computer simulations were carried out with parameter values that generated motility measures similar to those that were experimentally observed, i.e. mean speed = $12 \mu\text{m}\cdot\text{min}^{-1}$ and $C_m = 52 \mu\text{m}^2\text{min}^{-1}$. The model and experimental distributions are compared in Figure 6. Model M18 clearly underestimates the turning angle in the range $22.5^\circ-67.5^\circ$, and overestimates the numbers for the bins on each side. This is not surprising, since four of the eight possible diagonal step directions (with angles of 54.7°) are not permitted in this model. When all directions are allowed the agreement between model and experiment is much improved.

The limited set of directions of cell motion raises the possibility that cells tend to move further, over time, in the allowed directions. We carried out tests to explore this issue, in the following way. The full Moore neighbourhood (26 neighbours) defines 13 axes, made up of the 9 axes of the M18 model plus the 4 intermediate diagonal axes added in M26. To assess the degree to which cells have moved along these 13 axes, at any point in the simulation, we first evaluated the displacement vector of each cell from its start location (at time 0). We then computed, for each of the 13 axes, the mean of the absolute value of the projection of the displacement vectors onto the axis. In other words, if $a(k)$ is the normalized vector representing axis k , $k=1, \dots, 13$, and the displacement of cell j (of N) from its initial position is the vector $r(j)$, the mean projection is

$$Q(k) = \frac{1}{N} \sum_{j=1}^N |r(j) \cdot a(k)|$$

The 13 axis directions can be classified into three groups. The first group contains the three directions corresponding to the x, y and z axes. The second group contains the six directions that are diagonal and lie in one of the xy, yz and zx planes, while the third group contains the other four directions (the intermediate diagonals). If the direction of cell movement over time is random, we would expect the average value of Q in each of these groups to be equal. We adopted the same procedure as in the calibration runs, focussing attention on the cells that are initially within 10 grids of the centre of the lattice, giving in this case $N = 4272$. After 60 min the variation of the average value of Q in each group from the overall average is consistently less than 0.3% for all three models. This shows that none of the models generates preferred directions of motion.

The models have been coded in Fortran95 (Intel Fortran 10.1) and run on a PC with an Intel 2.4 GHz Quad Q6600 and 3 GB of RAM (Windows XP). Parts of the code have been structured to take advantage of multiple processors, when they are available, using OpenMP. The speed performance of the models has been measured with $50 \times 50 \times 50 = 125k$ cells, and with $100 \times 100 \times 100 = 1m$ cells - this latter number is of the order of the entire T cell population of a lymph node paracortex. The speed results for Model M18 (with $\beta = 0.41$, $\rho = 0.76$, $\gamma = 0.2$) are expressed in terms of a speed-up factor, the number of hours of biological time simulated per hour of computer time. The tests showed that for simulations with a million cells Model N is consistently about 40-45% faster than Model M18, while Model M26 is about 16% slower than Model M18. Table 4 shows Model M18 speed on the PC using 1, 2, 3 and 4 threads. The speed results show that the scaling of performance with the number of cells is slightly worse than linear. With one CPU, 1m cells take 9 times as long as to process as 125k cells, rather than 8 times, presumably as a consequence of an increase in memory access times with larger arrays.

As supplementary material we have provided three videos showing T cell motion simulated by the models. In each case the model was run with about 113000 cells constrained to move within a spherical region, with a radius of 30 lattice sites. Motion of all the cells was simulated for 480 15 sec time steps, i.e. for two hours, and a video was made showing the motion of 0.1% (113) randomly-selected cells.

Discussion

Advantages of a lattice approach to modeling T cell motility

Spatially-discrete lattice methods have been widely applied in mathematics, physics and chemistry, and more recently in ecology and biology. Depending on the details of the

assumptions and implementation, they go by a variety of names: *e.g.* lattice-Boltzmann, lattice gas, cellular automata (CA), cellular Potts model (CPM). In some models (*e.g.* CA and CPM) the focus is on states associated with lattice sites – the evolution of the state of a lattice site depends, deterministically and/or probabilistically, on the states of neighbouring lattice sites. In the lattice gas approach, by contrast, particles are free to move around on the lattice, and it is the distributions or patterns of particles that are of interest. For example, diffusion has been modeled by a random walk on a lattice. At small spatial or temporal scales the motion of particles appears unrealistic, since the path is constructed (in general) from successive steps of equal length either in the same direction or at right angles. At longer scales this motion “graininess” diminishes in importance.

Previous studies have applied the lattice approach to T cell motion. A 2-D lattice was employed to investigate T cell trafficking through the lymph node paracortex.²¹ In this agent-based model the motion of 1375 T cells was simulated on a lattice of $100 \times 100 = 10,000$ sites, where each $5\mu\text{m} \times 5\mu\text{m}$ site could hold one T cell. Although it isn't clear how the 2-D numbers should be extrapolated to 3-D, it seems that only 14% of the space was occupied by T cells in this model. A 3-D agent-based model with lattice geometry was created to investigate the influence of cytokine secretion on Th1-Th2 development.²⁰ A lattice of $100 \times 100 \times 100 = 10^6$ sites was used, each $10\mu\text{m} \times 10\mu\text{m} \times 10\mu\text{m}$ site permitted to hold at most one T cell (although the average volume of a T cell is approximately $150\mu\text{m}^3$). In other words, the fraction of the paracortex volume occupied by T cells in this model is less than 15%. A recent study, addressing the first phase of activation of T cells in a lymph node, the phase of rapid movement, used a $30 \times 30 \times 30$ lattice with a grid spacing of $10\mu\text{m}$ and periodic boundary conditions²². Each site in this model was allowed to hold at most a single cell, and the maximum site occupancy simulated was 50%. In other words, the fraction of the paracortex volume occupied by T cells was at most 7.5%, and it appears that most runs were carried out with much lower occupancy levels - the authors specifically mentioned the problem of “jamming” in the lattice when higher cell numbers were used. The unrealistically low T cell densities used in all of these models enabled their authors to avoid the difficulties created by dense cell packing.

Our goal was to develop a model for 3-D cell motility that could handle realistic cell densities, while reproducing the main statistical measures of motility with high computational efficiency. These requirements have been achieved, with three versions of the model. Assigning one cell per lattice site and sizing the lattice grid appropriately ensures that T cells are packed together as closely in the model as they are in the paracortex. Allowing two cells to briefly occupy the same site makes it possible to generate cell motion with the observed speed and motility coefficient – these occurrences of crowding are restricted to fewer than 20% of cells. The lattice grid size can be adjusted to reproduce the desired density of cells, and the three model parameters β , ρ and γ can be tuned to match desired cell motility characteristics over a wide range. Finally, the method is very fast. Multi-day simulations with 10^5 cells are feasible on a desktop machine, and the code is readily scalable to much larger problems. The chosen approach largely overcomes the drawback of simple spatially-continuous methods (*e.g.* Eq. (1) below, or a model that makes jumps in randomly chosen directions²³) - that there is no mechanism to prevent cells from occupying the same space.

There is a degree of arbitrariness in the way the step direction probabilities were defined and parameterized. The composite spheroid shape for the probability surface is a reasonable choice, but no doubt other shapes could be defined that are equally effective. Provided the shape conveys the same kind of polarization of direction, we do not believe that the details will have much influence on the cell motion that results.

Comparison of the lattice approach with other models

The lattice approach is inherently less realistic than methods (*e.g.* the CPM17 or FLAME24 models) that account for cell interactions explicitly, or possible methods that explicitly account for the influence of reticular fibers. But apart from the uncertainty regarding which physical description is the correct one, there are disincentives to using both the CPM and the fiber network approach. In the case of the CPM, although it generates realistic-looking cell paths, the computational expense would be considerable when many long simulations are required. The idea of building a cell motion model based on a random reticular network is intriguing, but as far as we know this has not yet been attempted. At first sight it looks like a very challenging task, and it seems likely that this approach would also be computationally very demanding. Judging by progress in this field, one day we will have a model that combines realistic cell crawling behaviour with an accurate representation of the reticular architecture of the cortex, but that day is still some way off.

In an unpublished model we have used a discrete-time continuous-space formulation to generate T cell paths. In this model T cell motion is represented by the discrete-time version of the OU persistent random walk. Cell displacement in the n^{th} time step is $\Delta t \mathbf{v}_n$, where the velocity vector $\mathbf{v}_n$ is generated by an auto-regressive lag-1 sequence:

$$\mathbf{v}_n = \kappa \mathbf{v}_{n-1} + (1 - \kappa^2)^{1/2} \mathbf{z}_n \quad (1)$$

In Eq. (1) the velocity at an instant, $\mathbf{v}_n$, is related to the velocity $\mathbf{v}_{n-1}$ at the previous instant (separated by Δt) and to a zero-mean Gaussian random vector $\mathbf{z}_n$. The two parameters of the model are the persistence parameter κ and the variance of each component of $\mathbf{z}_n$, which is directly related to the mean speed. With a suitable choice of the parameters, this simple approach gives rise to realistic-looking cell trajectories and reasonable values of C_m and mean speed. Although the generating procedure is different, this approach is similar to a model in which cells are alternately stationary and moving with a fixed speed in a randomly chosen direction.²³ These two approaches share the serious drawback that because T cells move independently of each other, there is nothing to prevent cells from occupying the same space at the same time. This is the volume exclusion issue. In our previous model we introduced an extra velocity term that moves cells away from crowded regions toward less populated regions, but although this mitigates the problem to some degree it is not a wholly satisfactory solution. A rigorous implementation of a continuous-space model would require a full treatment of interactions between cells, along the lines of the CPM17,18 or FLAME26 models, for example. However, the computational demands of these approaches are daunting when cell counts of millions and immune response durations of many days are envisaged. Personal communications with the authors of these models gave the following approximate speed information. CPM model: on a 3 GHz PC, simulating 3500 cells for 24 hours would take 12-24 hours. FLAME model: on a PC, simulating 1000 cells for 24 hours would take about 2 hours, implying that, with linear scaling, 3500 cells would take 7 hours. The M18 version of the lattice model takes 10.8 sec to simulate the motion of 3500 cells for 24 hours, running on one CPU of a quad-core PC. This is at least 1600 times the speed of CPM, and about 900 times the speed of FLAME.

Another drawback of the spatially-continuous approach, in the context of the current T cell activation modeling project, relates to our interest in cell-cell interactions that occur when cells are close together. When cell motion is spatially continuous a considerable computational effort must be expended in keeping a record of the neighbours of each cell.

Future developments

The importance of chemical signaling on T cell motility is not yet fully resolved, but it appears likely that both chemokinesis and chemotaxis are involved to some degree. It has been shown that CCR7 ligands provide chemokinetic stimulus to CD4⁺ T cells, increasing their motility inside lymph nodes.²⁵ As these authors pointed out, the observation that T cells travel along the FRC network¹⁶ suggests that the stimulation may be provided by ligands immobilized on the reticular fibers rather than by soluble chemokines. This raises the possibility that spatial gradients of CCR7 stimulation within the paracortex (determined perhaps by the varying density of FRC) could lead to a spatial variation in T cell motility. Although dynamic imaging studies reveal T cell motion that resembles a random walk, this does not preclude the possibility that chemokines are causing a directional bias to T cell motion, for example in the local neighborhood of DC,²⁶ and it has been shown that in immunogen-draining lymph nodes CD8⁺ T cells are attracted to the sites of interacting antigen-specific CD4⁺ T cells and DC by the chemokines that these cells secrete.²⁷ The possibility that such chemotaxis could increase DC scanning rates has been investigated using a 2-D agent-based model.²¹ According to this model, when DC exert attraction on T cells the result is an increase in the number of times T cells encounter DC, but the increase is caused by a higher rate of visits to a smaller set of DC, and in fact the number of distinct DC visited by each T cell is reduced. The authors concluded that chemotaxis would produce fewer activated T cells than random motion alone. Until the role of chemical signalling is better understood it will not be feasible to include it in T cell motility models. When chemotaxis and/or chemokinesis in the paracortex have been well characterized it will be possible to add these effects into the lattice model, as dynamically varying adjustments to the step probabilities $P(k)$.

The motility model is being used as the “engine” of a spatially-based model of T cell activation and proliferation. The lattice approach is particularly convenient because it also serves as the computational grid for the simulation of fields of cytokine concentration, the result of the combined effects of cytokine secretion, uptake and diffusion. In this model cell division and cell death are accommodated in the lattice by a procedure that makes the extent of the lattice depend on the number of live cells. The method allows specification of the shape of the region within which the cells move. The current version been parallelized to perform simulations with cell counts of the order of one million on a shared-memory multi-processor computer using OpenMP. The model is being modified to enable it to run on a distributed-processor system using MPI. We anticipate that these capabilities together will make it feasible to simulate all the cells in the paracortex of a lymph node, using an approximately realistic geometry.

Methods

Definition of motility parameters

The standard mathematical model for cell migration is a variation of Brownian motion, the Ornstein-Uhlenbeck (OU) process,²⁸ and the standard way to analyze experimental data is to assume Fürth's formula

$$\langle d(t)^2 \rangle = 2nD \left(t - P \left(1 - e^{-t/P} \right) \right) \quad (2)$$

for the mean of the square of displacement $d(t) = |\mathbf{r}(t) - \mathbf{r}(0)|$.²⁹ Here t is time, the vector $\mathbf{r}(t)$ is the cell trajectory, n is the dimension of the space and $\langle \dots \rangle$ denotes expectation value. D is the diffusion coefficient of the OU process, which in the case of cell motion we refer to as the motility coefficient and denote by C_m . P is the persistence time of the motion, which is zero in the case of pure random walk. The OU process is an idealization, and does not

necessarily provide an accurate representation of cell motion for small t ,³⁰ but in the case of T cells Eq. (2) is found to be valid for large t ($t \gg P$). In 3-D, when C_m is estimated, following the mathematical convention for the diffusion coefficient, as

$$C_m = \frac{1}{6} \frac{d}{dt} \langle |\mathbf{r}(t) - \mathbf{r}(0)|^2 \rangle \quad (3)$$

it is found that C_m approaches a constant value as t increases. The mean squared distance that cells have moved is plotted vs. time, and C_m is 1/6 of the slope of this curve (usual units $\mu\text{m}^2\text{min}^{-1}$). In fact some T cell researchers have plotted the mean distance that cells have moved vs. the square root of time, and estimated C_m from M , the slope of this curve, as $M^2/6$.^{25, 31} This is not consistent with Eq. (3), since the expected value of the square of a random variable is not in general equal to the square of the expected value.

The “mean” speed is a slightly more elusive quantity. In a continuous-time random walk model the speed of a cell depends on the time interval over which speed is averaged – as the averaging interval is decreased, the speed increases. What is usually reported as cell speed by experimenters is in fact the speed averaged over some time interval. The convention in cell motility research is to derive cell speed from the change in position over successive microscope image frames, therefore it is effectively averaged over the time interval between frames, which is usually 20-30 sec.

It is desirable that a model generate the correct value of mean T cell speed (averaged over the appropriate interval) in addition to generating the correct motility coefficient, in order to ensure that the simulated cell motion at least meets the minimum requirements of physical reasonability. This is because the random motion is the result of the combined effect of cell speed and persistence, that is, the tendency for motion to continue in the same direction. Some researchers have quantified persistence through the “meandering index”, defined as the ratio of total displacement D to path length L .^{25, 32} In the limit of maximum persistence, i.e. motion in a straight line, $D/L = 1$. Unfortunately D/L , also referred to as the “straightness index”, and related to the “sinuosity index” (or “tortuosity index”) which is $1 - D/L$, is not an appropriate measure to characterize random walk paths because its value depends on L and tends to 0 as L increases.³³ In terms of the measurement period T , as T is increased the numerator grows (in the expected value sense) roughly as $T^{1/2}$, while the denominator grows as T , therefore comparisons can only be made between experiments of the same duration.

Calculation of target values for motility parameters

The model aimed to reproduce the T cell motility patterns observed experimentally in the lymph node paracortex. Key values that the model sought to replicate were mean speed S and motility coefficient C_m . We re-calculated the appropriate targets for these values based on published evidence.

Experimental estimates of cell speed are made by comparing cell positions extracted from microscope images taken at discrete time intervals. The estimated speed is the 3-D distance that a cell has moved divided by the time interval Δt . The quasi-random walk behaviour of T cells makes the speed measured in this way a function of the selected time interval. Experimenters usually choose a time interval in the range 15-30 seconds, and they usually publish the value. Unfortunately, without knowing how T cells move it isn't possible to characterize the dependence of S on Δt precisely. The issue is important for modelling because the mean speed generated by a model with one time step size often must be compared with values determined experimentally with different time step sizes. Another issue concerns the use of 2-D projections of T cell trajectories.²⁵ As these authors showed, a

speed value obtained from 2-D projections must be scaled to get the true speed in 3-D. It appears that the scaling factor given,²⁵ $(3/2)^{1/2} = 1.225$, is not correct, although it is close to the correct value of $4/\pi = 1.273$.²⁵ Experimenters often report the 2-D projection value, but in the current work the mean speed generated by the model is always the 3-D value.

Once the correction for 2-D projection is made, T cell mean speed measurements by several groups are in reasonably good agreement. In vivo studies by a group at the University of California at Irvine (UCI) provided speed estimates of 10-12 (in the following the units of speed are $\mu\text{m} \cdot \text{min}^{-1}$), which after scaling by 1.273 gives the range 13-15.6, 7 Measurements on CD4+ T cells in explanted lymph nodes gave a value of 15.32 while experiments with helper T cells gave a value of 14.34 Intravital microscopy using CD4+ T cells gave speed values of about 15.25 while another group estimated T cell speed at about 9.17 Reanalysis of data from four previous experiments^{4, 6-8} led to a best estimate of mean T cell speed of 16.6.²³ It appears that the mean speed of T cells in the paracortex is in the range 10-17 $\mu\text{m} \cdot \text{min}^{-1}$. The situation with the motility coefficient C_m is somewhat clouded because of the 2-D vs. 3-D issue, and also because many researchers have been estimating C_m from the variation of mean distance with $t^{1/2}$, while we use the definition that follows from analogy with the diffusion coefficient. Luckily it appears that in practice the two methods yield values that differ by less than 5% (Miller, personal communication).

From their plotted data for mean displacement vs. $t^{1/2}$, it appears that the UCI group measured a C_m value of about 43 (in the following the units of C_m are $\mu\text{m}^2 \cdot \text{min}^{-1}$).⁸ Subsequent work by this team gave values for C_m in the range 60 - 90.5, 6 Results have been presented showing C_m values in the range 100 - 130 for mesenteric LNs and 40 - 110 for cervical LNs,³² and C_m estimates in the range 61 ± 6 and 72 ± 11 (for low CD44-expressing cells) have been obtained.²⁵ The previously mentioned study reanalysing data from earlier experiments did not report C_m values, but the best-fit plots of mean displacement imply a value of about 53.²³ All these estimates were for naïve T cells.

Sweeping through the lattice sites at each time step

At each time step, the sites in the lattice are swept through in a randomized order, and the cell at that lattice site is moved to an adjacent site within the lattice. The rules governing this “jump” are influenced by its previous jump, as described below, to enable cells to move with a degree of persistent motion. In many cases the cell may not move at all in a particular time step. Using a random sweep enables the code to be parallelized, but it does imply that some cells may be visited more than once in a time step, when a cell is moved to a site that is reached later in the sweep, while other cells may not be visited at all during that time step. When there are two cells at a site, due to the crowding described below, one of the cells is chosen randomly to jump during that time step.

Determining the direction of cell jumps

When a cell is identified during the sweep of the lattice sites at each time step, it can jump to an adjacent site in the lattice. The direction it moves is chosen according to a series of probabilities: effectively each of the adjacent sites is assigned a probability which makes it more or less likely that the cell will move to that site. In Model N, only 6 adjacent sites are made available, so there are 7 probabilities including not moving at all; in Model M, 18 or 26 adjacent sites are made available because diagonal jumps are allowed. Formally, the probabilities of steps in the possible directions, conditional on the direction of the last step, are given by $P(k)$, $k=0, \dots, N_d$, which are pre-computed from the speed parameter β and the persistence parameter ρ . The case $k=0$ corresponds to no movement, and $N_d=6$ for Model N, 18 for Model M18 and 26 for Model M26. As each cell is processed the occupancy of the candidate destination sites is taken into account to adjust these probabilities, subject to a

third “crowding” parameter γ . A step is then chosen in the usual way by generating a uniformly distributed pseudo-random variate.

Model N—In general there are six step directions, giving a total of seven possibilities. It is convenient to denote the relative directions by the index k in the following way:

k	Direction
0	No motion
1	Last step direction
2,3,4,5	Perpendicular to last step direction
6	Opposite to last step direction

If the previous step was parallel to the x axis, the six steps are: $k=1$, (1,0,0); $k=2$, (0,1,0), $k=3$, (0,-1,0); $k=4$, (0,0,1); $k=5$, (0,0,-1); $k=6$, (-1,0,0). A probability $P(k)$ is associated with each possible step direction. In the case of a pure random walk all directions would be equally likely, i.e. $P(1) = P(2) = \dots = P(6)$. When the motion exhibits persistence of direction the probability of a step in the same direction as the previous step, i.e. $P(1)$, must be increased and the other step probabilities must be reduced. The probability of reversal of direction must be reduced more than the probabilities of the perpendicular steps. These requirements have been met through the use of two parameters: β = speed parameter ($0 < \beta < 1$); ρ = persistence parameter ($0 < \rho < 1$). The parameter β is the probability that the cell makes a move, i.e. $1 - \beta$ is the probability that it stays still. A step perpendicular to the last direction is given a probability that is a fraction $(1 - \rho)^2$ of the probability of a step with no change of direction, and for direction reversal the factor is $(1 - \rho)^4$. This parameterization provides an arbitrary but convenient way to control the motion characteristics.

$$P(0) = 1 - \beta \quad (4)$$

$$P(1) = \beta / (1 + 4(1 - \rho)^2 + (1 - \rho)^4) \quad (5)$$

$$P(k) = (1 - \rho)^2 P(1), \quad \text{for } k=2, 3, 4, 5 \quad (6)$$

$$P(6) = (1 - \rho)^4 P(1) \quad (7)$$

With $\rho = 0$ all directions would be equally likely, while with $\rho = 1$ movement could occur only in the same direction as the last step. Clearly this is just one of many possible parameterizations, but it has the virtue of simplicity. Probability-weighted jump vectors are shown in Figure 7 for the case with $\beta = 1.0$ and $\rho = 0.0, 0.2, 0.4$, and 0.6 . The grey arrow shows the direction of the previous step, also serves as a scale bar with length 0.1.

The probabilities computed as above would be used to determine the step taken by a cell if each of the possible target sites were vacant - clearly a highly improbable case. If a target site is unavailable (i.e. either it is already occupied by two cells or it lies outside the modeled region) the associated probability is set to zero. If the target site currently holds one cell, the associated probability is reduced by multiplying it by a third parameter, γ , called the crowding parameter. When the starting site currently holds two cells, the probability of no movement, $P(0)$, is set to zero, ensuring that a cell always moves off a crowded site. When any of the probabilities has been modified in one of these three ways (as in fact occurs

almost always), the six jump probabilities are rescaled to sum to $1 - P(0)$. The actual step taken by a cell is then determined in the usual way by generating a uniformly distributed random variate.

Model M—If all possible diagonal steps are included a lattice site has 26 neighbour sites, implying 27 possibilities for cell motion (including staying still) and making the model considerably more complex. In our approach the complexity is reduced somewhat by a convenient simplification. For the purposes of determining possible jump directions and their associated probabilities on the basis of the direction of the previous jump, previous directions are restricted to the six principal directions (without this limitation computing jump probabilities conditional on the previous step direction would be very difficult). When the previous direction was parallel to an axis no special treatment is required. When the last step was on a diagonal, the modified previous direction is chosen randomly from the two or three axis directions that bracket the step. For example, if the previous step was really $(1,0,-1)$, the modified previous direction is chosen randomly from $(1,0,0)$ and $(0,0,-1)$, each with a probability of 0.5. This approach means that in an average sense the previous step direction is correctly accounted for.

Two versions of Model M have been developed. In the restricted version, labeled M18 because there are 18 possible step directions, the 8 diagonal directions that do not lie in one of the three principal planes are excluded. In the M26 version all possible steps to neighbour sites are allowed.

M18: Of the 18 possible steps, one is in the same direction as the previous step, four are at an angle of 45° to the previous step (these are all diagonal), eight are at right angles to the previous step (four of these are diagonal), four are at an angle of 135° to the previous step (these are all diagonal), one is in the reverse direction. The possible step directions are indexed as follows:

k	Direction
0	No motion
1	Last step direction (group 1)
2,3,4,5	Diagonals at 45° to last step (group 2)
6,7,8,9	On axes at 90° to last step (group 3)
10,11,12,13	Diagonals at 90° to last step (group 4)
14,15,16,17	Diagonals at 135° to last step (group 5)
18	Opposite to last step (group 6)

Step probabilities $P(k)$, $k=1,\dots,18$ are assigned in six groups. Within each group all probabilities are equal, e.g. $P(2) = P(3) = P(4) = P(5)$. Denoting by $d(k)$ the step lengths relative to the lattice spacing, $d(1) = d(6) = d(7) = d(8) = d(9) = d(18) = 1$, while the remaining 12 diagonal steps in groups 2, 4 and 5 have $d(k) = 2$. In order to mitigate to some extent the asymmetry introduced by the two different step lengths, a procedure has been developed for scaling the step probability to account for the step length. As in Model N, β is defined as the speed parameter, with $P(0) = 1 - \beta$, and the persistence parameter ρ ($0 < \rho < 1$) is defined such that when $\rho = 0$, all 18 probabilities weighted by the step lengths are the same, i.e. $P(k)d(k) = E$, say, for $k=1,\dots,18$. Since these probabilities sum to β ,

$$\sum_{k=1}^{k=18} P(k) = E \sum_{k=1}^{k=18} \frac{1}{d(k)} = \beta \quad (8)$$

$$E = \beta / \left(6 + \frac{12}{\sqrt{2}} \right) = \frac{\beta}{14.48} \quad (9)$$

$$P(k) = \frac{\beta}{14.48 d(k)}, \quad \text{for } k=1, \dots, 18. \quad (10)$$

When $\rho = 1$ the only non-zero step probability is $P(1) = \beta$. Specifying the step probabilities for intermediate values of ρ is less straightforward than in Model N. In the case $\rho = 0$ the steps scaled by their probabilities fall on the surface of a sphere of radius E . This suggested the idea that when $\rho > 0$ it should be possible to define a quadric surface with appropriate shape and use it to derive step probabilities by making the probability-weighted step lengths proportional to the distances to the surface. Consider a local coordinate system with the origin at the current location of the cell, and the x axis aligned with the previous step direction. On the positive x side of the yz plane through the origin a prolate (blimp-shaped) spheroid with its long axis parallel to the x axis looked like a good candidate surface. A matching oblate spheroid on the negative x side of the yz plane completed a surface with the required polarized shape, as illustrated in Figure 8. A prolate spheroid is given by the equation

$$\frac{x^2}{a^2} + \frac{y^2}{b^2} + \frac{z^2}{b^2} = 1 \quad (11)$$

with $b < a$, and is parameterized thus:

$$x = a \sin \theta \quad (12)$$

$$y = b \cos \theta \cos \lambda \quad (13)$$

$$z = b \cos \theta \sin \lambda \quad (14)$$

where $-\frac{\pi}{2} \leq \theta \leq \frac{\pi}{2}$ and $-\pi \leq \lambda \leq \pi$.

Setting $a = 1$ and $b = (1 - \rho)^2$ gives a family of prolate spheroids with the properties required when $x > 0$: when $\rho = 0$ the spheroid is a sphere, and in the limit as ρ approaches 1 it approaches a straight line. Similarly on the negative x side a matching oblate spheroid is obtained by setting $b = (1 - \rho)^2$ and $a = c < b$. It is easy to show that for lines drawn in the step directions in each of the groups the distances $R(k)$ from the origin to the surface of the composite shape are as follows:

$$\begin{array}{lll} \text{group 1: } R(1) = 1; & \text{group 2: } R(2) = \sqrt{2} \frac{b}{\sqrt{b^2+1}}; & \text{group 3: } R(6) = b; \\ \text{group 4: } R(10) = b; & \text{group 5: } R(14) = \sqrt{2} \frac{bc}{\sqrt{b^2+c^2}}; & \text{group 6: } R(18) = c. \end{array}$$

The probability-weighted step lengths must be proportional to these distances, and using the fact that the $P(k)$ must sum to β , and following the same procedure as before we can set $P(k)d(k) = E(b)R(k)$, for $k=1,...,18$ and derive the general result:

$$E(b) = \frac{\beta}{1 + 4\frac{b}{\sqrt{b^2+1}} + 4b + 4\frac{b}{\sqrt{2}} + 4\frac{bc}{\sqrt{b^2+c^2}} + c} \quad (15)$$

A convenient choice for c is $b^2 = (1-\rho)^4$. The step probabilities are then given by

$$P(k) = \frac{E(b)R(k)}{d(k)} \quad \text{for } k=1,...,18. \quad (16)$$

The limit when $\rho = 0$ yields $b = c = 1$, and $E(b)$ and $P(k)$ reduce to the values previously determined in Eqs.(9) and (10). In the limit when $\rho = 1$, $b = c = 0$ and the only non-zero probability value is $P(1) = \beta$.

Figure 9 shows the probability-weighted jump vectors, that is, vectors in the direction of the jumps with length $P(k)d(k)$, for $\beta = 1.0$ and $\rho = 0.0, 0.2, 0.4$, and 0.6 . With $\rho = 0$ all step directions are equally likely. The grey arrow indicates the direction of the previous step, and also provides a scale bar of length 0.1. The process of randomly determining which direction a cell jumps in is carried out just as for Model N, except that there are now 18 possibilities instead of six. The crowding parameter γ functions as before.

M26: The development of the model with all 26 step directions follows the same course as for the M18 model. There are now 8 groups of step directions:

k	Direction
0	No motion
1	Last step direction (group 1)
2,3,4,5	Diagonals at 45° to last step (group 2)
6,7,8,9	Diagonals at 54.7° ($\arctan(2)$) to last step (group 3)
10,11,12,13	On axes at 90° to last step (group 4)
14,15,16,17	Diagonals at 90° to last step (group 5)
18,19,20,21	Diagonals at 144.7° to last step (group 6)
22,23,24,25	Diagonals at 135° to last step (group 7)
26	Opposite to last step (group 8)

Step probabilities are $P(k)$, $k=1,...,26$. Denoting by $d(k)$ the step lengths relative to the lattice spacing, $d(1) = d(6) = d(7) = d(8) = d(9) = d(18) = 1$, the 12 diagonal steps in groups 2, 5 and 7 have $d(k) = 2$, while the remaining 8 diagonal steps in groups 3 and 6 (these are the diagonals that do not lie in a principal plane) have $d(k) = 3$. As before, β is defined as the speed parameter, with $P(0) = 1-\beta$, and the persistence parameter ρ ($0 < \rho < 1$) is defined such that when $\rho = 0$, all 26 probabilities weighted by the step lengths are the same, i.e. $P(k)d(k) = E$, say, for $k=1,...,26$. Since these probabilities sum to β ,

$$\sum_{k=1}^{k=26} P(k) = E \sum_{k=1}^{k=26} \frac{1}{d(k)} = \beta \quad (17)$$

$$E = \beta / \left(6 + \frac{12}{\sqrt{2}} + \frac{8}{\sqrt{3}} \right) = \frac{\beta}{19.10} \quad (18)$$

$$P(k) = \frac{\beta}{19.10 d(k)}, \quad \text{for } k=1, \dots, 26. \quad (19)$$

When $\rho = 1$ the only non-zero step probability is $P(1) = \beta$. Specification of the step probabilities for intermediate values of ρ is carried out as for Model M18, using the surface made of half of a prolate spheroid joined to half of an oblate spheroid. The distances $R(k)$ from the origin to the surface of the composite shape are as follows:

$$\begin{array}{ll} \text{group 1: } R(1) = 1; & \text{group 2: } R(2) = \sqrt{2} \frac{b}{\sqrt{b^2+1}}; \\ \text{group 3: } R(6) = \sqrt{2} \frac{b}{\sqrt{b^2+1}}; & \text{group 4: } R(10) = b; \\ \text{group 5: } R(14) = b; & \text{group 6: } R(18) = \sqrt{2} \frac{bc}{\sqrt{b^2+c^2}}; \\ \text{group 7: } R(22) = \sqrt{2} \frac{bc}{\sqrt{b^2+c^2}}; & \text{group 8: } R(26) = c. \end{array}$$

The probability-weighted step lengths must be proportional to these distances, and using the fact that the $P(k)$ must sum to β , and following the same procedure as before we can set $P(k)d(k) = E(b)R(k)$, for $k=1, \dots, 26$ and derive the result:

$$E(b) = \frac{\beta}{1 + 4 \left(1 + \frac{\sqrt{2}}{\sqrt{3}} \right) \frac{b}{\sqrt{b^2+1}} + 4b + 4 \frac{b}{\sqrt{2}} + 4 \left(1 + \frac{\sqrt{2}}{\sqrt{3}} \right) \frac{bc}{\sqrt{b^2+c^2}} + c} \quad (20)$$

As before we choose $c = b^2 = (1 - \rho)^4$. The step probabilities are then given by

$$P(k) = \frac{E(b)R(k)}{d(k)} \quad \text{for } k=1, \dots, 26. \quad (21)$$

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Mean squared displacement of 4272 cell paths generated with Model N, plotted as a function of time, over 6 hours. After a linear section spanning about 80 minutes the plot begins to flatten as the cell trajectories are limited by the boundary of the modeled region.

Figure 2. Mean squared displacement of 4272 cell paths generated with Model N, plotted as a function of time, together with the line of best fit for $t > 5$ min. These results were obtained with $\beta = 0.51$, $\rho = 0.71$.

Figure 3. Mean speed contour lines computed from model results generated with 1500 (β, ρ) parameter pairs, showing how the mean speed depends mainly on β . (a) Model N, (b) Model M18, (c) Model M26.

Figure 4. Motility coefficient contour lines computed from model results generated with 1500 (β, ρ) parameter pairs, showing how C_m depends on both β and ρ . (a) Model N, (b) Model M18, (c) Model M26.

Figure 5. 2-D projections of 20 T cell trajectories of 75 minutes duration generated with Model N, with $\beta = 0.51$, $\rho = 0.71$. (a) Model N, with $\beta = 0.51$, $\rho = 0.71$, (b) Model M18, with $\beta = 0.41$, $\rho = 0.76$, (c) Model M26, with $\beta = 0.38$, $\rho = 0.76$.

Figure 6. Comparison of turning angle distributions from experimental data (blue) and the model (green). (The experimental data are replotted from Mempel et al.,⁴ combining data for positive and negative angles.) (a) Model M18. (b) Model M26.

Figure 7. Model N probability-weighted jump vectors for the cases with $\beta = 1.0$ and $\rho = 0.0, 0.2, 0.4,$ and 0.6 . Since the step lengths are independent of direction, the vector lengths are simply proportional to the probabilities. The dark grey vector in the direction of the previous step has length = 0.1.

Figure 8.

A composite ellipsoidal surface, half prolate and half oblate. The probabilities associated with cell jumps are specified such that the probability-weighted step distances are proportional to the distances from the origin to the surface.

Figure 9.

Model M18 probability-weighted jump vectors for the cases with $\beta = 1.0$ and $\rho = 0.0, 0.2, 0.4$, and 0.6 . The six directions parallel to the axes correspond to a step length of one unit, the other 12 to a step length of $\sqrt{2}$ units (unit = grid spacing). The dark grey vector in the direction of the previous step has length = 0.1.

Table 1

Model N parameters (β, ρ) that generate specified mean speed S (units of $\mu\text{m} \cdot \text{min}^{-1}$) and motility coefficient C_m (units of $\mu\text{m}^2 \cdot \text{min}^{-1}$)

	$C_m = 50$	$C_m = 60$	$C_m = 70$	$C_m = 80$
$S = 10$	0.28, 0.71	0.28, 0.75	0.27, 0.80	0.27, 0.82
$S = 12$	0.33, 0.69	0.32, 0.74	0.31, 0.79	0.30, 0.81
$S = 14$	0.45, 0.62	0.44, 0.70	0.43, 0.78	0.43, 0.76
$S = 16$	0.61, 0.54	0.59, 0.65	0.57, 0.76	0.58, 0.69
$S = 18$	0.60, 0.55	0.63, 0.64	0.67, 0.75	0.64, 0.67

Table 2

Model M18 parameters (β, ρ) that generate specified mean speed S (units of $\mu\text{m} \cdot \text{min}^{-1}$) and motility coefficient C_m (units of $\mu\text{m}^2 \text{min}^{-1}$)

	$C_m = 50$	$C_m = 60$	$C_m = 70$	$C_m = 80$
$S = 10$	0.19, 0.78	0.19, 0.82	0.19, 0.85	0.18, 0.87
$S = 12$	0.26, 0.74	0.26, 0.78	0.27, 0.83	0.27, 0.85
$S = 14$	0.35, 0.68	0.36, 0.74	0.36, 0.80	0.36, 0.82
$S = 16$	0.49, 0.59	0.50, 0.67	0.50, 0.76	0.51, 0.79
$S = 18$	0.56, 0.54	0.56, 0.64	0.56, 0.74	0.56, 0.77

Table 3

Model M26 parameters (β , ρ) that generate specified mean speed S (units of $\mu\text{m}\cdot\text{min}^{-1}$) and motility coefficient C_m (units of $\mu\text{m}^2\text{min}^{-1}$)

	$C_m = 50$	$C_m = 60$	$C_m = 70$	$C_m = 80$
$S = 10$	0.18, 0.79	0.18, 0.83	0.18, 0.86	0.18, 0.88
$S = 12$	0.25, 0.75	0.25, 0.79	0.25, 0.83	0.25, 0.85
$S = 14$	0.33, 0.69	0.33, 0.76	0.33, 0.80	0.33, 0.83
$S = 16$	0.41, 0.61	0.41, 0.73	0.42, 0.79	0.43, 0.80
$S = 18$	0.50, 0.56	0.50, 0.67	0.50, 0.73	0.51, 0.78

Table 4

Model M18 performance on a Quad Core PC expressed as biological hours simulated per computing hour

	1 thread	2 threads	3 threads	4 threads
125k cells	224	327	407	431
1m cells	25	35	42	45