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3-Dimensional Model and Simulations of Sperm Movement

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Worcester Polytechnic Institute

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3-Dimensional Model and Simulations of Sperm Movement

by

Yunyun Zhang

A Project Report

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of the

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APPROVED:

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Professor Sarah D. Olson, Project Advisor

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Professor Bogdan M. Vernescu, Head of Department

Abstract

In this project we are building a mathematical model to track the movement of spermatozoa during the process of chemotaxis. Our model is built on an off-lattice spherical biased random walk in 3-dimensional space, an extension of previous conventional deterministic 2-dimensional models. The sperm's type of movement is decided based on a comparison of the current and previous chemoattractant concentration which can be used to see whether it is approaching the egg. From the statistical analysis of the simulation results, we find that chemotaxis is an effective mechanism to increase the number of sperm reaching the egg.

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1   Introduction

1.1   What is chemotaxis?

When a wolf is on the hunt, he can locate prey from their scent and then approach the prey on an optimal path using other senses such as sight and sound [21]. Mosquitoes are able to find hosts such as birds via olfactory cues, e.g. carbon dioxide concentration [8]. In both of these examples, chemical cues or odorants, are the main attractant for the predator to find the prey or host. The ability of these organisms to find their target will depend on factors such as the wind direction, but overall, the organisms are able to reorient and move in the direction of a higher concentration of the cue in order to find their targets. The process by which organisms find a given target in a varying concentration field by going up the gradient is called chemotaxis and the attracting chemical is called the chemoattractant. But how can microorganisms such as *Escherichia coli* (*E. coli*) and ciliates who have no eyes, ears or nose find their food in a fluid environment?

In the case of this project, how does a spermatozoon find the oocyte (egg)? Sperm can also "smell"; however, instead of perceiving or tasting an odorant in the surrounding fluid, these organisms can feel the concentration of certain chemicals via chemoreception [11, 25, 26]. Chemicals that are present in the fluid are able to bind to specific receptors on the membrane of the sperm flagellum (tail), transmitting the signal that the chemical is present. In the case of sperm, proteins in the jelly layer of the egg coat are released into the surrounding fluid. Egg proteins that bind to receptors on the sperm act as a chemical communication system between the egg and the sperm, causing the sperm to alter its swimming direction in order to reach the egg. The sperm are then able to sense whether they are approaching or moving away from their target, the egg, by sensing the egg protein

concentration. Fig. 1 is an illustrative example of how a marine spermatozoon makes a turn by changing the symmetrical tail beating to asymmetrical beatings when it feels a decrease chemoattractant concentration and finally reaches the egg.
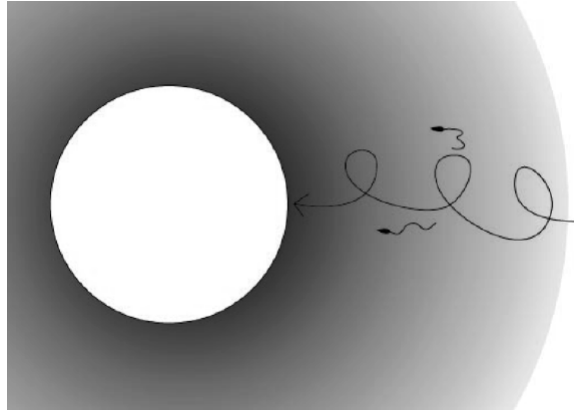
Figure 1: Turn-and-run model in marine sperm chemotaxis. A marine spermatozoon goes relatively straight towards the egg before it feels a decreasing in chemoattractant concentration. Then it will make a turn by asymmetrical tail beating to find the right direction again. Figure reproduced from [4].

1.2 How does chemotaxis guide the sperm?

The ability for a sperm to swim and reorient itself in a fluid environment is vital in the process of fertilization. To propel a spermatozoon, the tail (flagellum) whips back and forth using energy produced by the mitochondria through the metabolism of sugar. Based on the surrounding chemical environment, i.e. the concentration of the egg protein in the fluid, a spermatozoon is able to change its swimming pattern by altering the motion (flagellar bending) of its tail [3, 13, 29, 31].

Constant amplitude, symmetrical, tail bending would lead to a highly linear trajectory. Asymmetric, larger and varying amplitude tail bending causes the

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sperm to swim in tight circles rather than a straight line. This circular swimming is called hyperactivation. Hyperactivative motility has been determined to play a major role in the sperm's ability to penetrate the cumulus matrix and zona pellucida of the oocyte (egg), escaping from the sperm reservoir in mammalian fertilization, and enabling sperm to swim effectively through the fluid [13, 23, 27, 32]. Fig. 2 shows the tracks of spermatozoa in a controlled experiment. All the sperm swim straight in fluid with no chemoattractant before a photorelease of progesterone which is a type of chemoattractant. In response to the sudden increase in chemoattractant, most sperm in the experiment turn hyperactivated with a delay.
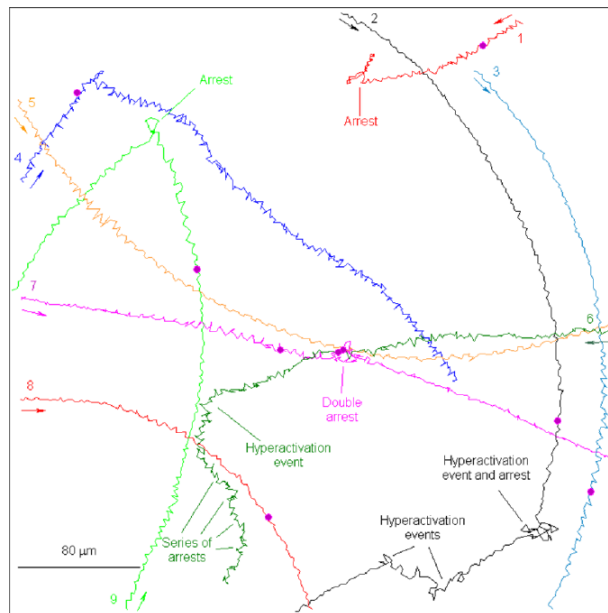
Figure 2: Tracks of spermatozoa in a controlled experiment. In the fluid with zero chemoattractant concentration, sperm swim relatively straight. When a photorelease of progesterone is introduced (the purple dot), most sperm switch to a hyperactivated motility pattern. Figure reproduced from [2].

In the presence of a zero chemoattractant concentration fluid environment, sperm have been observed to randomly alternate between periods of straight swimming and random tumbles (re-orienting in a new, random direction). For example, in Fig. 2 all the spermatozoa swim in a straight way before a photore-
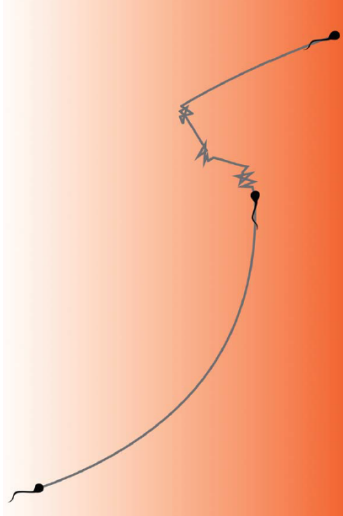
Figure 3: Sperm track in a gradient of chemoattractant. The darker color here represents a higher chemoattractant concentration. The spermatozoon will keep swimming roughly straight when it feels an increasing chemoattractant concentration. When it feels a decreasing concentration, it will turn hyperactivated to adjust the direction. And it may do several turns before it feels an increasing concentration again. Figure reproduced from [2].

lease of progesterone [2]. While in the presence of a chemoattractant gradient, sperm are able to bias their random walk. This is done by deciding which movement it will take based on the concentration change it feels. Fig. 3 is an illustration of this. If the sperm senses that it's swimming in the correct direction as the surrounding concentration is increasing, it will keep going in a straight line for a longer time before it turns hyperactivated. If it's moving in a wrong direction (surrounding concentration is decreasing), it will try to do hyperactivation sooner to pick a random direction trying to replace the current one. In this way, the sperm could switch between the two types of motility based on this condition. This strategy would highly improve their chance to reach the oocyte as we will show later.

2 Modeling Sperm Chemotaxis

2.1 Previous Models

Chemotaxis models have been developed for many organisms, including very detailed models using systems of partial differential equations, differential equations describing movement and curvature of paths, as well as random biased walks [5, 9, 30]. Most existing mathematical models describing sperm swimming in a gradient of chemoattractant are built based on the curvature of trajectories. And the majority of them are in 2 dimensional space. Friedrich and Julicher built a theoretical description of sperm chemotaxis by regulating the curvature and torsion of the swimming path [10]. In the presence of a chemoattractant, swimming paths are drifting circles in two dimensional space and the swimming path $\mathbf{r}(t)$ is guided by:

$$\dot{\mathbf{r}} = \nu\mathbf{t}, \quad \dot{\mathbf{t}} = \nu\kappa\mathbf{n}, \quad \dot{\mathbf{n}} = -\nu\kappa\mathbf{t},$$

where the dot denotes derivative with regard to time, velocity $\nu = |\dot{\mathbf{r}}|$, the tangent vector $\mathbf{t} = \dot{\mathbf{r}}/\nu$, the normal $\mathbf{n}$ is orthogonal to t, and κ is the local curvature of the swimming path. It is also directed by the stimulus $s(t) = c(\mathbf{r}(t))$ via a temporal concentration perceived. This model would draw smooth circles as the sperm approaches the egg, which is beautiful but lacks some authenticity. For example, hyperactivated motility could not be characterized and the trajectories are always determined once the background concentration is specified.

Alvarez et al. raised another deterministic model [1] by suggesting that the path curvature $k(t)$ after stimulation can be described by the linear relationship

$$k(t) = k_1 + \beta\frac{dF_r}{dt},$$

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where β is a proportionality factor, k_1 is a parameter that characterizes the basal curvature, and F_r is the normalized relative change in fluorescence. The changing rate of fluorescence $\left(\frac{dF_r}{dt}\right)$ is a result of the Ca^{2+} concentration change. When the chemoattractant binds to receptors on the sperm tail, Ca^{2+} channels open, increasing the Ca^{2+} inside the sperm flagellum. These parameters are approximated using experimental data.

In Ishikawa et al. [15], a two dimensional model was developed where the sperm were described as points whose locations were updated at regular time intervals ($\Delta t = 1.0$ ms) to determine the sperm's trajectory. The radius of curvature of the trajectory was dependent on the chemoattractant concentration. At each time step, the position was updated as

$$\mathbf{p}(t + \Delta t) = \mathbf{p}(t) + \Delta t \mathbf{v}(t)$$

$$\phi(t + \Delta t) = \phi(t) + \Delta t \mathbf{v}/r(t)$$

$$r(t) = 400(1 - c(\mathbf{p}))$$

where position of the sperm at time t is $\mathbf{p}(t)$, the velocity vector is $\mathbf{v}(t) = \mathbf{v}\{cos(\phi(t)), sin(\phi(t))\}$, $r(t)$ is curvature and $c(\mathbf{p})$ is concentration of chemoattractant at point $\mathbf{p}$. Note that this model is 2-dimensional. The trajectory is controlled by curvature, which is determined by the chemoattractant concentration. Thus, the trajectory is fixed once we know the concentration distribution and the starting position of the sperm.

2.2 Our Model

Instead of calculating the trajectory from the curvature, we build a model based on Brownian motion. Also, our model is developed in 3-d instead of 2-d. For each time step, there are two types of motions to choose from, the activated motility, and the hyperactivated motility. The decision for the type of movement is made based on the change of concentration the sperm senses. We will use a 3-d off-lattice approach where the sperm movement in each step will be uniformly or biased randomly chosen to be a point on the sphere of a given radius surrounding the current position.

2.2.1 Hyperactivation

The first type of movement, hyperactivation, is represented by a non-biased Brownian motion [14]. Before introducing our model, let's first take a look at the properties of a continuous Brownian motion $\{B(t) : t \geq 0\}$

1. for all time $0 \leq t_1 \leq t_2 \leq ... \leq t_n$ the random variables

$$B(t_n) - B(t_{n-1}), B(t_{n-1}) - B(t_{n-2}), ..., B(t_2) - B(t_1)$$

   are independent and we say that the process has independent increments.

2. the distribution of the increment $B(t+h) - B(t)$ does not depend on t, where h is an increment in time. We say that the process has stationary increments.

3. the process $\{B(t) : t \geq 0\}$ has almost surely continuous paths.

4. for every $t \geq 0$ and $h \geq 0$ the increment $B(t + h) - B(t)$ is multivariate normally distributed with mean zero and covariance matrix $h \sum \sum^T$, where $\sum$ is identity for a Brownian motion.

Guided by the properties above, we can build our 3-d discrete Brownian motion by the following rules: the movement at each time step is independent of other movements and the length of the movement is always the same since the time step is fixed. The position of sperm at time $t + \Delta t$ is given by

$$\mathbf{p}(t + \Delta t) = \mathbf{p}(t) + \Delta t v_h \mathbf{d}_i, \tag{1}$$

where v_h is the velocity of hyperactivated motility and $\mathbf{d}_i = (x_i, y_i, z_i)$ is a 3d vector which is the direction of movement at step i. Here $x_i^2 + y_i^2 + z_i^2 = 1$ means all $\mathbf{d}_i's$ lie on the unit sphere. We use eq. (1) for all time if a spermatozoon is always doing hyperactivated motility. Since this is an off-lattice approach, we next describe how to randomly choose a direction such that the next position lies on the sphere surrounding the current position.

We pick a direction for step i, $\mathbf{d}_i = (x_i, y_i, z_i)$ by the following algorithm to make $\mathbf{d}_i$ uniformly random on a unit sphere:

1. Pick u uniformly from $[-1, 1]$

2. Pick θ uniformly from $[0, 2\pi)$

3. Determine $\mathbf{d}_i$: $x_i = \sqrt{1 - u^2}cos\theta$, $y_i = \sqrt{1 - u^2}sin\theta$, $z_i = u$

Note that if $u \in [-1, 1]$, this implies that $\sqrt{1 - u^2} \in [0, 1]$ and the cosine and sine terms are in the interval $[-1, 1]$ for $\theta \in [0, 2\pi)$. This algorithm has been previously derived [6, 20] and the randomness of the points can be verified using a procedure detailed in [28].

These rules comply with all the properties of Brownian motion since movement at each step is independent of any other movement and the distance traveled at each time step is the same since the length of each time step is fixed. In
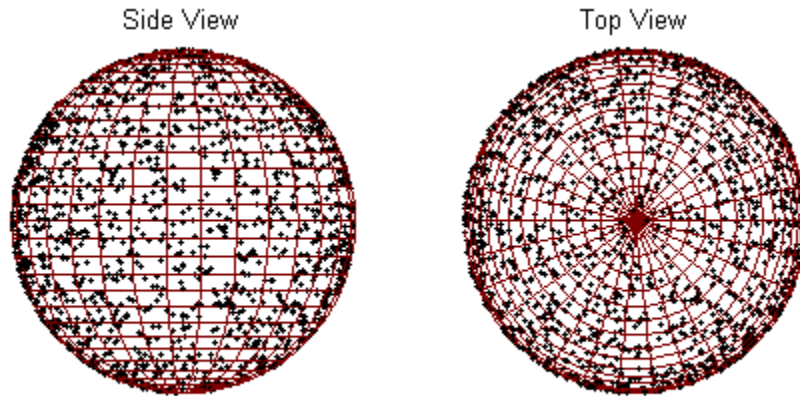
Figure 4: Random points generated on the surface of a unit sphere viewed from the side and from above. The code used to generate these random points is given in §5.1

Fig. 4, this algorithm is used to create 1500 $\mathbf{d}_i$ vectors or points on the unit sphere. As can be seen in the figure from both the top and side view, the points are randomly distributed. The code for this algorithm is given in §5.1.

2.2.2 Straight Swimming

Comparing with the hyperactivated motility, activated spermatozoon moves in a more straight or linear trajectory. So we can model this process with a biased random walk. It is built in a similar way with the first type of movement. The only difference is that we now give a heavier weight to the direction which the sperm has been moving in the past several steps, so that the sperm is more likely to move straight. Thus, when feeling itself going towards the egg, the sperm could continue to go in this direction without taking an unnecessary turn.

In terms of the model, the difference is in the algorithm when we pick the direction. In §2.2.1, the direction vector $\mathbf{d}$ was random. Now, the biased direction

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vector $\mathbf{b}$ is chosen with different weights in each direction. The position of sperm at time $t + \Delta t$ is given by

$$\mathbf{p}(t + \Delta t) = \mathbf{p}(t) + \Delta t v_a \mathbf{b}_i, \tag{2}$$

where v_a is the velocity of activated motility and $\mathbf{b}_i = (x_i, y_i, z_i)$ is a weighted random point on the unit sphere, and i is the time step. Eq. (2) is used if using activated motility on biased motion. Once again, we are using an off-lattice model, so we need to describe how to choose a biased point on a sphere surrounding $\mathbf{p}(t)$.

We pick a random direction $\mathbf{b}_i$ in two steps. First, we tilt the average direction by an angle θ. In Fig. 5, the positive z-axis corresponds to the average direction of the sperm's last several steps. Then we rotate the tilted direction by an angle γ with the average direction as the axis to obtain $\mathbf{b}_i$. When we draw a random θ, the weight is calculated from the exponential distribution $w(\theta) = \lambda e^{-\lambda \theta}$ where $\theta \in [0, \pi]$. So the points are denser in the top region because smaller θ have heavier weights. If we choose the parameter λ to be larger, the points would be even more concentrated. The code for this algorithm is detailed in §5.2. The angle γ is drawn uniformly from $\gamma \in [0, 2\pi]$.

2.2.3   Full Model

We can obtain the formula for the position of sperm by putting the two types of movements together:

$$\mathbf{p}(t) = \mathbf{p}(0) + \Delta t \left[v_a \sum_i \mathbf{b}_i s_i + v_h \sum_i \mathbf{d}_i (1 - s_i) \right]$$
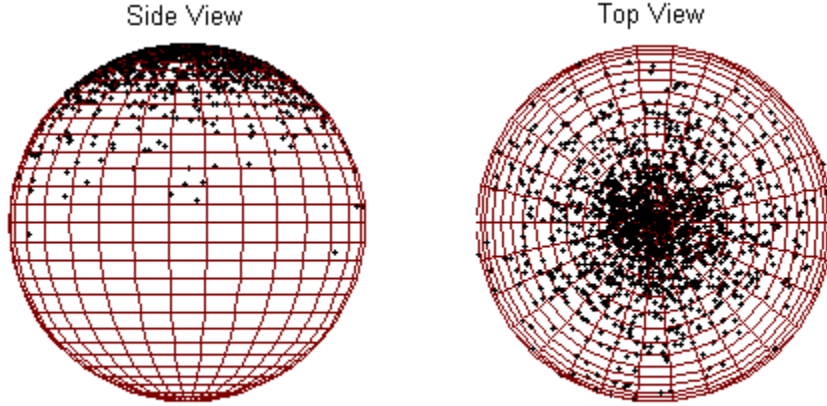
Figure 5: Weighted random points on unit sphere viewed from side and above. The z axis runs from the bottom of the sphere to the top and the previous direction was $\mathbf{d}_{i-1} = (0, 0, 1)$. Thus, the points generated on the sphere are clustered in this direction. The code for this algorithm is detailed in §5.2

where $s_i = \begin{cases} 1 & \text{when step } i \text{ is activated} \\ 0 & \text{when step } i \text{ is hyperactivated} \end{cases}$

Now we have the model of the two types of movements, and the question becomes how to choose between these two. Here are some observed strategies by sperm:

1. When the spermatozoon swims down the gradient or senses no change in the chemoattractant concentration, it exhibits turns and hyperactivation episodes to modify its direction of swimming. In the case of sensing no change, the cell adapts to the constant chemoattractant and restores its non-stimulated swimming mode, consisting of rather straight swimming with occasional hyperactivation events and turns [17, 18, 19].

2. In responsive sperm cells, there was a delayed turn. On average, the change

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in movement was $2.2 \pm 0.3s$ after introduction of a chemoattractant [2].

3. In *E. coli*, movement has shown to be related to concentrations in the previous 4 seconds. The past second is given a positive weighting, the previous 3 seconds are given a negative weighting, and the cells respond to the difference [24].

Given this information, we are able to build the strategies into our model. Assuming that the chemoattractant concentration is higher at a point closer to the egg, the sperm compare the concentration ML1 $= 3$ seconds ago with the concentration ML2 $= 1$ second ago. If the concentration 1 second ago is higher, the sperm knows it is probably going in the right way, so it will tend to move on by choosing the straight swimming ($s_i = 1$). Otherwise, it will do hyperactivation ($s_i = 0$).

The sperm is not comparing the concentrations at a more recent and smaller time interval basically for two reasons: there's some biological constrains preventing the sperms to sense the concentration change quicker. It is not always better to make rapid decisions because in the real world, a concentration rise does not necessarily mean the sperm is approaching the egg since the fluid flow is also a factor for the background concentration [33]. Also, it is a better strategy to wait some time before switching the movement pattern.

Also, we set two biological restrictions to the sperm: the sperm cannot do hyperactivation consecutively for too long, since it requires greater energy than activated (linear) swimming. The spermatozoon requires a certain amount of time to rest before it can do hyperactivation again [16, 22, 7]. The values of these two parameters ML1 and ML2 are not set at this moment because we hope to find an optimized combination of them. We'll talk about that in the next chapter.

3   Model Testing and Results

3.1   Parameters, Initialization, and Setup

For simplicity of the model at the moment, we make the following assumptions.

1. Egg has been there long enough to have the prescribed concentration profile.

2. Chemoattractant concentration is fixed for the period of our simulation.

3. There is no background flow.

Since the chemoattractant concentration is higher where it's closer to the egg in the ideal situation, it's reasonable to set up the concentration profile $C(t)$ as

$$C(t) = \frac{1}{||\mathbf{p(t)} - \mathbf{E_c}||} \tag{3}$$

where $\mathbf{p(t)}$ is the position of the sperm at time t and $\mathbf{E_c}$ is the location of the center of the egg, and $|| \cdot ||$ denotes the Euclidean norm.

Parameters in the model are given in Table 3.1. Here we are simulating the sperm in a cubic box of size $[0,\text{xmax}] \times [0,\text{xmax}] \times [0,\text{xmax}]$ and placing the egg at the center $(\frac{xmax}{2}, \frac{xmax}{2}, \frac{xmax}{2})$. By setting the periodic boundary condition, we are assuming the space consists of repeats of the same box, each with an egg in the center. So once the egg goes out of the boundary of one box, it will enter another.

All sperm are initialized at the same point $\mathbf{p}(0) = (\frac{xmax}{2}, \frac{xmax}{2}, 0)$. The first step is always hyperactivated since there is no previous path to follow. The length of the time step in our model is set to be $\Delta t = 1/35$ sec. Since the tail of a sperm

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Table 1: Parameter Values used in the simulation

Parameters		Value
eggR	Diameter of sea urchin egg	$100\ \mu m$
v_a	Average spermatozoa speed when swim straight	$50\ \mu m/s$
v_h	Average spermatozoa speed when hyperactivated	$150\ \mu m/s$
Δt	length for each step	$1/35$ sec
T	Total time for simulation	200 sec
xmax	side length of the box for periodic BC	$2000\ \mu m$
$\mathbf{E_c}$	Location of center of egg	$(0, 0, 0)$
λ	parameter of the exponential distribution	60
tHyper	max. length of time for a sperm to stay hyperactivated	0.4 sec
tRestore	min. length of time between two hyperactivation	1.5 sec
ML1	decide motility type by comparing conc. at ML1 and ML2	3 sec ago
ML2	used together with ML1	1 sec ago

is beating at 35 times per second, we set the time step at the same rate of tail beating.

3.2   Results: Hyperactive, Active, and "Smart" Sperm

Before testing a "smart" sperm, let's take a look at the sperms' behavior when they are not able to change their state of motility. Fig. 6(a) and (b) are trajectories of two spermatozoa, both simulated for 100 seconds. We can see that when a sperm is only allowed to do activated motility, shown in Fig. 6(a), it covers a fairly long distance in the given time. However, it couldn't do any immediate adjustment to its direction when it is going away from the egg because the position is only being updated via Eq. (2). Note that in (a), the sperm trajectory starts to move outside of the box and using our periodic boundary conditions, reenters on the bottom. As for the sperm on the right in Figure 6(b), which is always hyperactivated, it is obviously not a good strategy since the space it searched is quite limited and its trajectory seems to be circling around in the same area for quite a long time. Position is only being updated via Eq. (1).
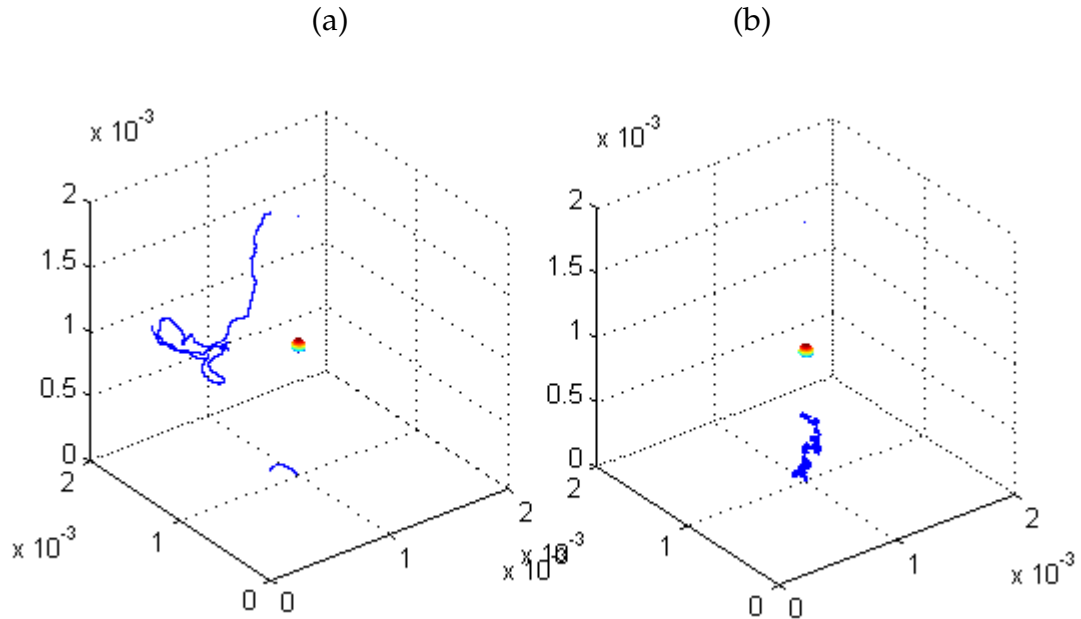
(a)   (b)

Figure 6: Trajectory of activated/hyperactivated only movement. In (a), the sperm is activated only. The position is updated using Eq. (2); In (b), the sperm is hyperactivated only, position vector updated using Eq. (1).

Now we present our "smart" sperm. Comparing with the previous two "unsmart" sperm, this sperm is smart in two ways: it knows whether or not it is approaching the egg by comparing two concentrations with a time lag and it can change its type of movement based on the concentration.

The trajectory in Fig. 7 is of a smart sperm who successfully reached the egg. We see that for most of the time the sperm swims straight which it is marked by blue lines. The separate blue line segments are connected by short red lines which indicates hyperactivation. It is noticeable that every time the blue trajectory bends to a level that the sperm is no longer going towards the egg, the sperm would switch to hyperactivation which resets the direction. This mechanism enables the sperm not only to cover enough space by swimming straight, but also to adjust its direction by hyperactivation.
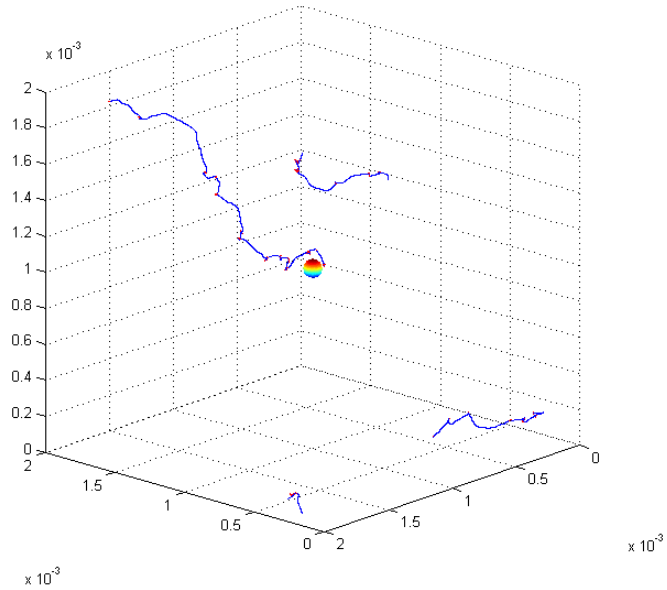
Figure 7: Trajectory of a sperm: the blue lines indicate straight swimming while red lines indicate hyperactivation.

Table 2: Number of sperm reaching the egg for each type

	Activated	Hyperactivated	"Smart"
Reached the egg	1	0	6

Although this strategy seems to be more efficient than the previous two judging from its trajectory, to confirm that, we still need a simple statistical test. We simulate 1000 sperms for 300 seconds in each of the three conditions and count the number of sperm that reached the egg.

Now let us carry out a t-test with the data. The t statistic is $t = \frac{p_1 - p_2}{s_{p_1 - p_2}}$, where $s_{p_1 - p_2} = \sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}}$. In our case, $n_1 = n_2 = 1000$, so $s_{p_1 - p_2} = \sqrt{\frac{p_1(1-p_1) + p_2(1-p_2))}{n}}$ where $p_i = \frac{\# \text{ of sperm at egg}}{\text{total } \#}$ The "smart" sperm has the largest number of sperm reaching the egg. When we carry out t-tests between the "smart" sperm and the

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other two, the p-value for the tests are 0.0584 and 0.0141.This indicates that if we set the significant level to be 0.9, we are able to claim the "smart" sperm with combination of movements has a higher chance to reach the egg than the other two types of "less smart" sperm.
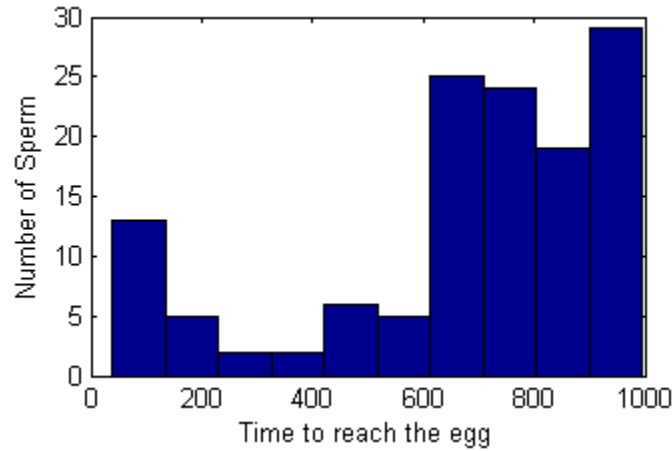
Figure 8: Histogram of arrival times of sperm whichhave reached the egg.

Fig. 8 shows the distribution of arrival times for sperm reaching the egg. The first several sperm arrived at the egg quite quickly because they were at the right direction from the beginning. There is a peak after 600 seconds since these sperm had picked wrong directions at first, but reoriented their movements by hyperactivation. The shape of the distribution of arrival times may vary according to different parameter values.

3.3 Positive vs. Zero Concentration Gradient

Still, we may wonder if the concentration part in our model is necessary since the sperm may switch between activated and hyperactivated motilities even with zero background concentration. To verify this, we need to run simulations with spermatozoa in two different backgrounds, positive concentration gradient and

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zero gradient.

According to Armon's study [2], capacitated cells repress their hyperactivation events and maintain their course of swimming toward the chemoattractant upon sensing an increase in chemoattractant. As observed in the controlled experiments, the fraction of hyperactivated spermatozoa in positive gradient background (4%) is significantly lower than the fraction in zero gradient background (6.5%).

In light of this result, we imitate the behavior of spermatozoa in zero gradient by setting its fraction of hyperactivation to be 6.5% which occurs randomly. Then we run the two groups of simulations each with 1000 sperms for 150 seconds and count how many of them could reach the egg. In Fig. 9 we show how the two types of movement are distributed over time. And Fig. 10 is a comparison of the two ratios of sperm reaching the egg in positive and zero gradient concentrations.

Table 3: Number of smart sperm reaching the egg for positive and zero gradient

	Positive Gradient	Zero Gradient
Reach the egg	6	1

In Table 3, we can see that more sperm reached the egg in the positive gradient of chemoattractant. Based on this result, we calculate the p-value for the t-test, 0.0584, which means that the chance of the spermatozoa reaching the egg in positive gradient is significantly higher than in zero gradient when the significance level is set to be 0.9.

The results of the two simulations above tell us that the strategy which the spermatozoa uses is very effective in increasing the chance to reach the target. These results verify that our 3-d model is applicable in characterizing some important features of spermatozoa's motility behavior.
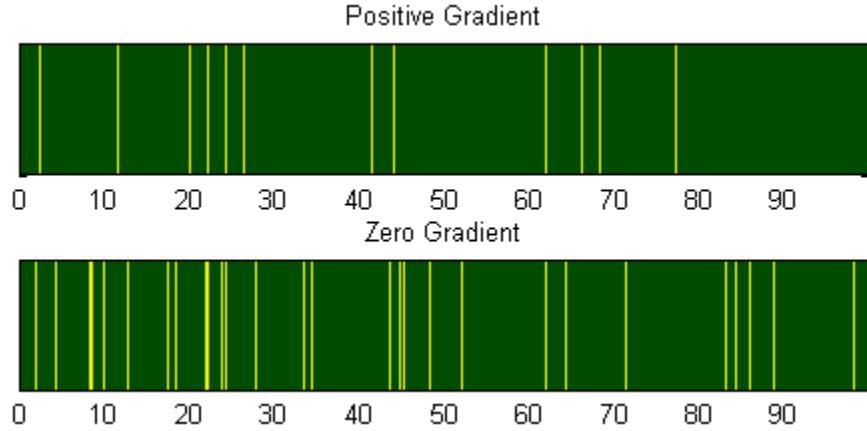
Figure 9: Types of movement along time: green sections represent straight swimming and yellow sections represent hyperactivation.
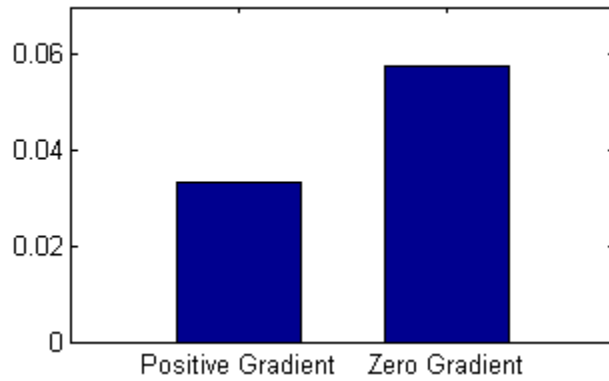
Figure 10: Fractions of hyperactivation in the two groups of simulations

3.4 Sensitivity Analysis of Smart Sperm

To explore the effects of varying parameter values on the chance of a sperm reaching the egg, we ran a simulation varying the three parameters λ, ML1 and ML2. ML1 and ML2 are changing in proportion to each other such that ML1 $= 3\times$ ML2 , so in the following contest we use only ML1 to represent the two parameters. This simulation is ran for 10×10 combinations with ML1 $\in [3/35, 112/35]$ sec and $\lambda \in [40, 130]$.
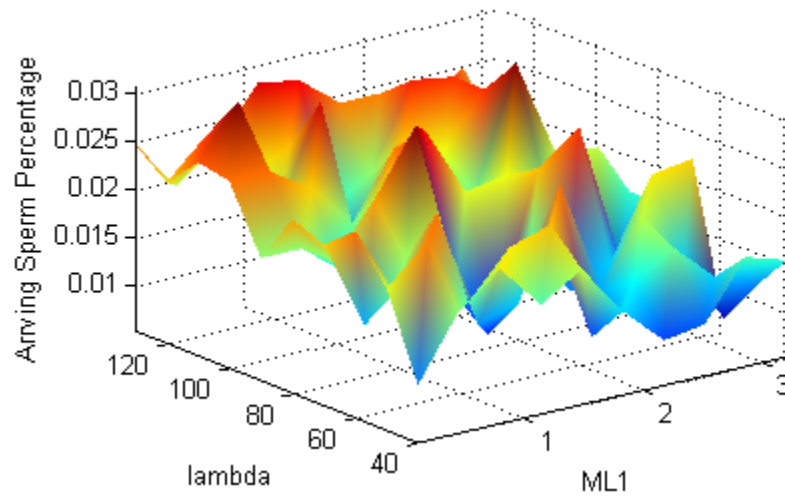
Figure 11: Percentage of sperm that have reached the egg with different combinations of λ and ML1 values. The x and y axes correspond to varying the parameters and the z axis corresponds to the percentage of sperm that have arrived at the egg.
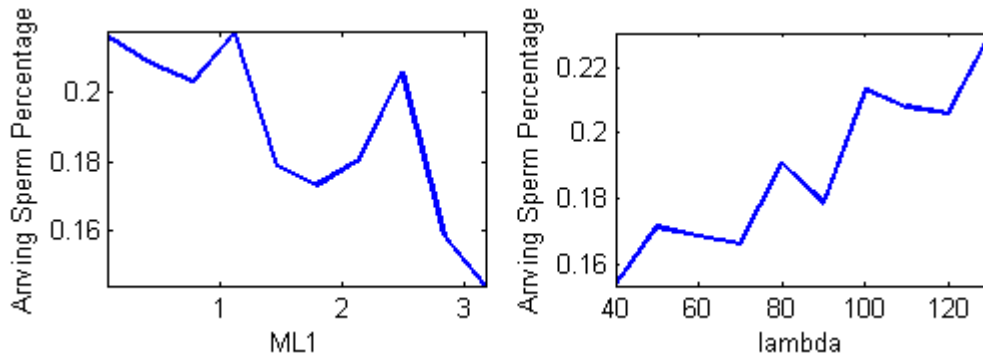
Figure 12: Percentage of sperm that have arrived at the egg shown for varying ML1 (left) and λ (right).

The result is shown in Fig. 11. There seems to be a trend that as λ increases, the percentage becomes larger. But the trend with varying ML1 is hard to tell. To investigate this further, we sum up the percentages by fixing one parameter to take a look at the trends with only one varying parameter as shown in Fig. 12. It is clear that the percentage becomes smaller when ML1 and ML2 increase. It

implies that if the sperm decide the motility type by comparing chemoattractant concentrations at two moments closer to the current time, the sperm may have a better chance of reaching the egg. Also, with λ increasing, the percentage also increases. Recall that λ is the parameter to control the straightness of the activated motility. This result tells us that if the sperm could swim more straight or linearly when doing activated motility, a greater percentage of the sperm would arrive at the egg in a shorter period of time.

4   Discussion

4.1   Parrondo's paradox

Parrondo's paradox is used extensively in game theory, and its application in engineering, population dynamics, financial risk, etc., are also being looked into [12]. However, not too much attention has been put to its application in biology. The model in this project might build a link between Parrondo's paradox and spermatozoa's movement.

Parrondo's paradox is a combination of losing strategies that becomes a winning strategy. That is, there exists two strategies for a game, each with a higher probability of losing than winning, for which it is possible to construct a winning strategy by playing these strategies alternately. The key to how two losing strategies becoming winning is in how they are combined since only some carefully picked sequences can make a winning strategy. This is surprisingly a proper analogy to the motility of spermatozoa which is intelligently choosing its movement between the two types: activated and hyperactivated. The results in our first simulation indicate that the chance of winning is significantly increased when alternating between these two strategies based on the local concentration of chemoattractant.

4.2   Background Concentration

There is a big assumption for the model in this project that the background concentration is always fixed and the concentration of a point closer to the egg is always higher. This is obviously not always true in the real world since the flow of fluid could have a larger influence on the chemoattractant concentration relative to diffusion of the chemoattractant.
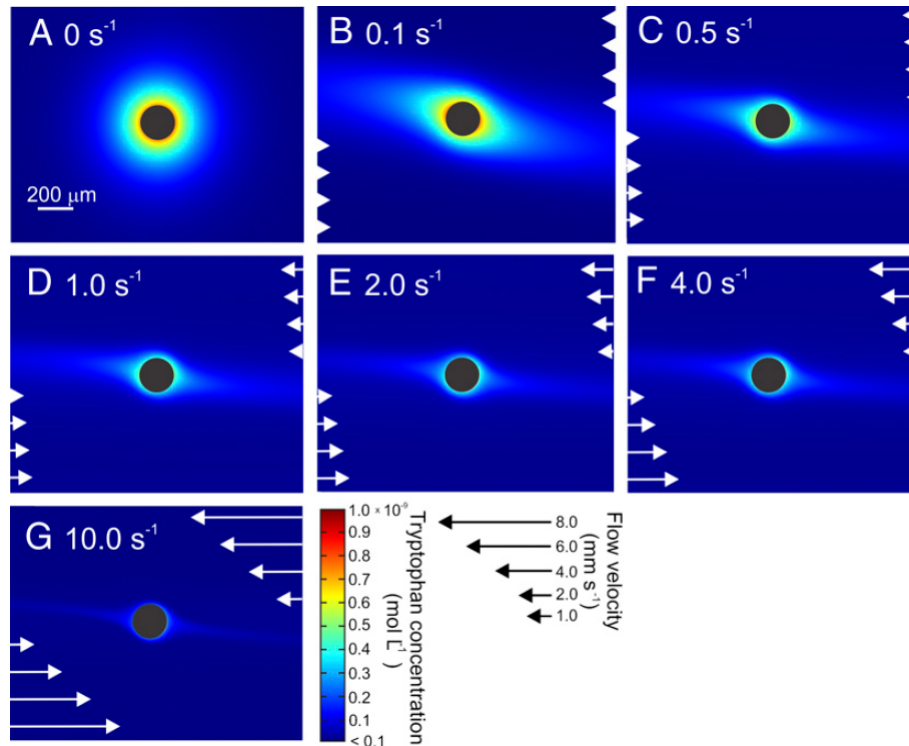
Figure 13: Concentration of chemoattractant under different shear flows. Reproduced from [33].

Fig. 13 shows that shear flows could make the chemoattractant concentration at a further place from the egg higher than the that of a closer point [33]. This would make it harder for the spermatozoa to recognize whether it's in the right course at the current moment. Also, the turbulent flow in the ocean could make the situation even more complicated. It is really amazing that the spermatozoa can overcome all these difficulties to find the egg.

4.3   Conclusions

In this project we have built a 3-dimensional model of sperm movement. The activated and hyperactived movements are combined based on the surrounding concentration to imitate the process of chemotaxis. This approach uses a spherical

off-lattice biased random walk. It proves to be an effective way to increase the chance for sperm to find the egg.

In future models, we could take more complicated background fluids into consideration. Also, we can introduce the interaction of sperm. If more sperm could reach the egg when they swim together, maybe we can say that there is a "wisdom of crowds".

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5   Appendix

5.1   Code to generate Random points on unit sphere

This is called by main file if sperm is hyperactivated in step i to calculate the direction vector $\mathbf{d_i}$.

```
figure
subplot(1,2,1)
title('Side View')
[x,y,z]=sphere(30);
DarkRed = [0.5 0 0];
surface(x,y,z,'FaceColor', 'none','EdgeColor',DarkRed )
hold on
axis square
axis off


for ii=1:1500
    theta=2*pi*rand(1);
    u=2*rand(1)-1;
    xnew=sqrt(1-u^2)*cos(theta);
    ynew=sqrt(1-u^2)*sin(theta);
    znew=u;
    scatter3(xnew,ynew,znew,5,'filled','k');
end


view([0,0])
```

```matlab
subplot(1,2,2)

title('Top View')

[x,y,z]=sphere(30);

DarkRed = [0.5 0 0];

surface(x,y,z,'FaceColor', 'none','EdgeColor',DarkRed )

hold on

axis square;

axis off


for ii=1:1500

    theta=2*pi*rand(1);

    u=2*rand(1)-1;

    xnew=sqrt(1-u^2)*cos(theta);

    ynew=sqrt(1-u^2)*sin(theta);

    znew=u;

    scatter3(xnew,ynew,znew,5,'filled','k');

end


view([0,90])
```

5.2 Code to generate weighted random points on unit sphere with $\lambda = 15$

This is called by main file if sperm is activated in step i to calculate the direction vector $\mathbf{b_i}$.

```
lambda = 15;
prob = zeros(1,100);
for ii = 1:100
    prob(ii) = (exp(-lambda*(ii-1)*.01)-exp(-lambda*ii*.01));
    bandS = cos((ii-1)*.01*pi)-cos(ii*.01*pi);
    prob(ii) = prob(ii)*bandS;
end
prob = prob/sum(prob);


figure
subplot(1,2,1)
title('Side View')
[x,y,z]=sphere(30);
DarkRed = [0.5 0 0];
surface(x,y,z,'FaceColor', 'none','EdgeColor',DarkRed )
hold on
axis square
axis off


for ii = 1:1500
    alpha = wtrand(prob);
```

```matlab
    P1 = [sin(alpha), 0, cos(alpha)];

    beta = 2*pi*rand;

    P2 = [sin(beta)*P1(1), cos(beta)*P1(1), cos(alpha)];

    scatter3(P2(1),P2(2),P2(3),5,'filled','k');

end


view([0,0])


subplot(1,2,2)
title('Top View')
[x,y,z]=sphere(30);
DarkRed = [0.5 0 0];
surface(x,y,z,'FaceColor', 'none','EdgeColor',DarkRed )
hold on
axis square
axis off


for ii = 1:1500
    alpha = wtrand(prob);

    P1 = [sin(alpha), 0, cos(alpha)];

    beta = 2*pi*rand;

    P2 = [sin(beta)*P1(1), cos(beta)*P1(1), cos(alpha)];

    scatter3(P2(1),P2(2),P2(3),5,'filled','k');
end
view([0,90])
```

5.3 Main File

The main file of codes.

```matlab
matlabpool(2);
clear all;
%% Parameters Initialization
T          =      300;           % Total time for simulation
frm        =      35;            % Frames per second
Tsteps     =      T*frm;         % Number of steps
vlinear    =      5e-5;          % Velocity of linear motion
vhyper     =      15e-5;         % Velocity of hyperactivation
rlinear    =      vlinear/frm;   % Length of each step of activation
rhyper     =      vhyper/frm;    % Length of each step of hyperactivation
xmax       =      0.002;         % Size of the box
ymax = xmax; zmax = xmax;
eggR       =      5e-5;          % Radius of egg
minR       =      1e-5;


Nloop = 5;
nsperm = 10;


redo = 0;
TimePool=0;


% Distribution of time spent on each region.
nReg = 3;
Region = zeros(Nloop,Nloop,nReg);
% Radius of regions. Each region has the same volume.
```

```matlab
rad = zeros(1,nReg);
for ii = 1:nReg
    rad(ii) = (ii/nReg)^(1/3)*xmax/2;
end


% Random trajectory for linear movement.
% prob stores the weights for sampling alpha;
% Lambda is the parameter in exponential distribution, higher value of
% lambda means a straighter moving direction.


lambda = 60;
prob = zeros(1,100);
for ii = 1:100
    prob(ii) = (exp(-lambda*(ii-1)*.01)-exp(-lambda*ii*.01));
    bandS = cos((ii-1)*.01*pi)-cos(ii*.01*pi);
    prob(ii) = prob(ii)*bandS;
end
prob = prob/sum(prob);



%% Update 1
dd=0;
% lengths of memory, compare the concentration 3 seconds ago with 1
% second ago.
memoryL1 = 3;
memoryL2 = 1;


%% Loops
```

```matlab
parfor mm = 1:Nloop

    for kk = 1:Nloop

        tic

        ConcMemory = zeros(nsperm,memoryL1*frm);

        ReachFlag = zeros(1,nsperm);

        Reach = 0;

        HyperCount = zeros(1,nsperm);

        % Biological Constrains

        % the max time a sperm can keep hyper

        tHyper = .1*mm;

        % the minimal time to go hyper again.

        tRestore = kk/5;

        % Count the number of consecutive hyper movements

        ConsecHyper = zeros(1,nsperm);

        % Count the number of consecutive linear movemnets

        ConsecLinear = zeros(1,nsperm);

        % A "smart" sperm

        % Initialize the starting positions randomly on the plane

        % z=0, x@[0,xmax], y@[0,ymax].

        x = rand(1, nsperm)*xmax;

        y = rand(1, nsperm)*ymax;

        z = zeros(1, nsperm);

        xold1 = x; yold1 = y; zold1 = z;

        xold2 = x; yold2 = y; zold2 = z;

        xbackup = x; ybackup = y; zbackup = z;

        % Set the movement of first step to be always Hyper

        for jj = 1:nsperm

            Move = MoveHyper(x(jj),y(jj),z(jj),xmax,ymax,zmax,rhyper);
```

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```matlab
        xold1(jj) = x(jj); yold1(jj) = y(jj); zold1(jj) = z(jj);

        x(jj) = Move(1); y(jj) = Move(2); z(jj) = Move(3);

end


ConcMemory(:,1) = 1./sqrt((mod(x,xmax)-xmax/2).^2+...

(mod(y,ymax)-ymax/2).^2+(mod(z,zmax)-zmax/2).^2);

ConcIncrease = ones(1,nsperm);


for ii = 2:Tsteps

    ConcMemory(:,end) = [];

    ConcMemory = [zeros(nsperm, 1) ConcMemory];

    jj = 1;

    while jj <= nsperm

        if ReachFlag(jj) == 1

            jj = jj+1;

            % Ignore sperms already reached the egg.

            continue;

        end


        % set minimal distance between the new current point and other new points.

        mindis = 1;


        if ConcIncrease(jj) == -1   && ConsecHyper(jj) < tHyper*frm &&...

        ConsecLinear(jj) > tRestore*frm

            Move = MoveHyper(x(jj),y(jj),z(jj),xmax,ymax,zmax,rhyper);

            xbackup(jj) = xold2(jj); ybackup(jj) = yold2(jj); zbackup(jj) = zold2(jj);

            xold2(jj) = xold1(jj); yold2(jj) = yold1(jj); zold2(jj) = zold1(jj);

            xold1(jj) = x(jj); yold1(jj) = y(jj); zold1(jj) = z(jj);
```

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```matlab
x(jj) = Move(1); y(jj) = Move(2); z(jj) = Move(3);


D = sqrt((mod(x(jj),xmax)-xmax/2)^2 + (mod(y(jj),ymax)-ymax/2)^2 +...
(mod(z(jj),zmax)-zmax/2)^2);


% test the position (in which region)
for rr = 1:nReg
    if D < rad(rr)
        Region(kk,mm,rr) = Region(kk,mm,rr)+1;
        break
    end
end
if D <= eggR
    ReachFlag(jj) = 1;
    TimePool = [TimePool, ii/frm];
    continue;
end


redo = 0;


ConcMemory(jj,1) = 1/sqrt((mod(xold2(jj),xmax)-xmax/2)^2 +..
 (mod(yold2(jj),ymax)-ymax/2)^2 + (mod(zold2(jj),zmax)-zmax/2)^2);
ConcIncrease(jj) = sign(ConcMemory(jj,memoryL2*frm) - ConcMemory(end-1));


HyperCount(jj) = HyperCount(jj) + 1;
ConsecLinear(jj) = 0;
ConsecHyper(jj) = ConsecHyper(jj) + 1;
```

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```
        else
            Move = MoveLinear(x(jj),y(jj),z(jj),xold1(jj),yold1(jj),zold1(jj),...
             xmax,ymax,zmax,rlinear,prob);
            xbackup(jj) = xold2(jj); ybackup(jj) = yold2(jj); zbackup(jj) = zold2(jj);
            xold2(jj) = xold1(jj); yold2(jj) = yold1(jj); zold2(jj) = zold1(jj);
            xold1(jj) = x(jj); yold1(jj) = y(jj); zold1(jj) = z(jj);
            x(jj) = Move(1); y(jj) = Move(2); z(jj) = Move(3);


            if sqrt((mod(x(jj),xmax)-xmax/2)^2 + (mod(y(jj),ymax)-ymax/2)^2 +...
              (mod(z(jj),zmax)-zmax/2)^2) <= eggR
                ReachFlag(jj) = 1;
                TimePool = [TimePool, ii/frm];
                continue;
            end


            redo = 0;


            ConcMemory(jj,1) = 1/sqrt((mod(xold2(jj),xmax)-xmax/2)^2 +...
              (mod(yold2(jj),ymax)-ymax/2)^2 + (mod(zold2(jj),zmax)-zmax/2)^2);
            ConcIncrease(jj) = sign(ConcMemory(jj,memoryL2*frm) - ConcMemory(end-1));
            ConsecHyper(jj) = 0;
            ConsecLinear(jj) = ConsecLinear(jj) + 1;
        end
        jj = jj+1;
    end
end
ReachCount(kk,mm) = sum(ReachFlag);
[mm,kk]
```

```
        toc
    end
end


aa = [1:Nloop]*.1;
bb = [1:Nloop];
figure
surf(aa,bb,ReachCount/nsperm);
shading interp
xlabel('tHyper');
ylabel('tRestore');
zlabel('Percentage of Sperm Arrived');


TimePool(1) =[];
figure;
hist(TimePool);
xlabel('Time to Reach Eggs');
ylabel('Number of Sperm');



for ii = 1:Nloop
    for jj = 1:Nloop
        for kk = 1:nReg
            RegionRatio(ii,jj,kk) = Region(ii,jj,kk)/sum(Region(ii,jj,:));
        end
    end
end
```

```matlab
figure
surf(RegionRatio(:,:,1))
set(gca,'zlim',[0 1]);
shading interp;
xlabel('tHyper');
ylabel('tRestore');
title('Region 1')

figure
surf(RegionRatio(:,:,2))
set(gca,'zlim',[0 1]);
shading interp;
xlabel('tHyper');
ylabel('tRestore');
title('Region 2')

figure
surf(RegionRatio(:,:,3))
set(gca,'zlim',[0 1]);
shading interp;
xlabel('tHyper');
ylabel('tRestore');
title('Region 3')

ReachCount

matlabpool close;
```