Periodica Mathematica Hungarica Vol. 63 (2), 2011, pp. 215–225
DOI: 10.1007/s10998-011-8215-9

TIME-DELAYED MODEL OF THE UNBIASED MOVEMENT OF TETRAHYMENA PYRIFORMIS

Orsolya Sáfár[1], László Kőhidai[2] and Andrea Hegedűs[3]

[1]Department of Analysis, Budapest University of Technology and Economics
E-mail: safaro@math.bme.hu

[2]Department of Genetics, Cell- and Immunology, Semmelweis University

[3]Department of Genetics, Cell- and Immunology, Semmelweis University

(*Received August 31, 2010; Accepted July 10, 2011*)

Abstract

In our paper we investigate the unbiased movement of the unicellular eukaryotic ciliate Tetrahymena Pyriformis. We use a time-delayed version of the previously known model to describe the specific movement of this species. With the help of semi-discretization, we state analytic results for the model.

1. Introduction

The most common principle for modeling self-organizing systems in developmental biology is the law of conservation. With an arbitrary surface $\partial\Omega$ enclosing the volume Ω, the rate of change of the amount of the substance inside Ω is equal to the flux across the surface $\partial\Omega$ plus the production of material inside Ω. Thus

$$\frac{\partial}{\partial t}\int_\Omega u(t,x)\mathrm{d}V = -\int_{\partial\Omega}\mathbf{J}\mathrm{d}s + \int_\Omega f(u,t,x)\mathrm{d}V,$$

where $u(t,x)$ is the amount of material at point x at time t, $\mathbf{J}$ is the flux of material and $f(u,t,x)$ is the rate of production of $u(t,x)$. Applying the divergence theorem and taking into account that the volume Ω is arbitrary yields

$$\frac{\partial}{\partial t}u(t,x) = -\nabla\mathbf{J} + f(u,t,x)$$

Assuming there is no cell proliferation, the unbiased motion of the cells is described by Fick's equation (see [5]):

Mathematics subject classification number: 92C17, 34K60.
Key words and phrases: eukaryotic ciliate, time-delay, semi-discretization.

0031-5303/2011/$20.00 *Akadémiai Kiadó, Budapest*

$$\frac{\partial u(t,x)}{\partial t} = D\frac{\partial^2}{\partial x^2}u(t,x) \tag{1.1}$$

where $u(t,x)$ is the concentration of cells at time t at point x. $D > 0$ is the Fick constant, which is proportional to the typical displacement of the cells in a given time. To have a unique solution, we have to specify the initial conditions $u(0,x) = u_0(x)$, and boundary conditions (for a closed system, $\frac{\partial u(t,x)}{\partial \nu}$=0).

The idea that the unbiased movement of the unicellulars can be approximated with the same equation as molecular diffusion is based on the observation that if a system of bacteria is left alone, the cells move fast and randomly. This random bacterial movement can be approximated with the diffusion (in fact, very accurately).

2. The delay

Due to the fact that in an average Tetrahymena Pyriformis population, a considerable amount of cells (even up to one third of them, see [2]) is in "rest state" (they do not move or react to chemical compounds), there is a delay in their reaction to the changes of the environment (like the changes of cell density or gradient of a chemotactical compound), while equation (1.1) assumes immediate response. The delay we have to deal with is, however, not constant, since at any given time just a portion of the cells is unresponsive. So the change of the system is based on the present and on the past. To describe this type of delay, we have to use a convolution of the present and past state of the system with an appropriate density function $s(t)$ to express the influence of the past. For the derivation of the delayed diffusion equation see [6]. The delayed form of (1.1) is the following:

$$\frac{\partial u(t,x)}{\partial t} = \int_{-\infty}^{t} D\frac{\partial^2}{\partial x^2}u(\tau,x)s(t-\tau)\mathrm{d}\tau \tag{2.1}$$

To have a unique solution, we need an initial function instead of an initial condition which is defined on the support of $s(t)$.

In what follows, we consider the system in one dimension, on the finite interval $[0,L]$. To be able to state analytical results, we approximate this system with the help of semi-discretization. Time is still considered to be continuous, but the discretized version of (2.1) in space is taken instead. We divide the interval on which our equation holds to $n+1$ uniform sections (their diameter is denoted by h), and we consider the approximation of the partial space derivatives. All of our analytic results are valid for this semi-discretized version, which is a good approximation for the original equation if h is small. At point $x_i = i \cdot h$ $(i = 0, 1, \ldots, n+1)$, let us denote $u(t,x_i)$ by $u_i(t)$. We use the following approximation for the derivatives:

$$\frac{\partial^2}{\partial x^2}u(t,x)\bigg|_{x=x_i} \sim \frac{u_{i+1}(t) - 2u_i(t) + u_{i-1}(t)}{h^2}.$$

From Neumann boundary conditions it follows that $u_0(t) = u_1(t)$ and $u_{n+1}(t) = u_n(t)$. We have the following differential equations for each $u_i(t)$, $i = 1, 2, \ldots, n$:

$$\begin{aligned}
\frac{\mathrm{d}u_1(t)}{\mathrm{d}t} &= d\int_{-\infty}^{t}(u_2(\tau) - u_1(\tau))s(t-\tau)\mathrm{d}\tau,\\
\frac{\mathrm{d}u_i(t)}{\mathrm{d}t} &= d\int_{-\infty}^{t}(u_{i+1}(\tau) - u_i(\tau))s(t-\tau)\mathrm{d}\tau +\\
&\qquad + \int_{-\infty}^{t}(u_{i-1}(\tau) - u_i(\tau))s(t-\tau)\mathrm{d}\tau \quad i = 2, \ldots, n-1,\\
\frac{\mathrm{d}u_n(t)}{\mathrm{d}t} &= d\int_{-\infty}^{t}(u_n(\tau) - u_{n-1}(\tau))s(t-\tau)\mathrm{d}\tau.
\end{aligned}$$

The constant $d > 0$ is the Fick coefficient multiplied by h^2.

REMARK. This kind of approximation actually leads to the patchy environment method.

There is no analytical solution for this system for arbitrary $s(t)$, so we investigate a special type of delay function, namely the exponential and gamma function.

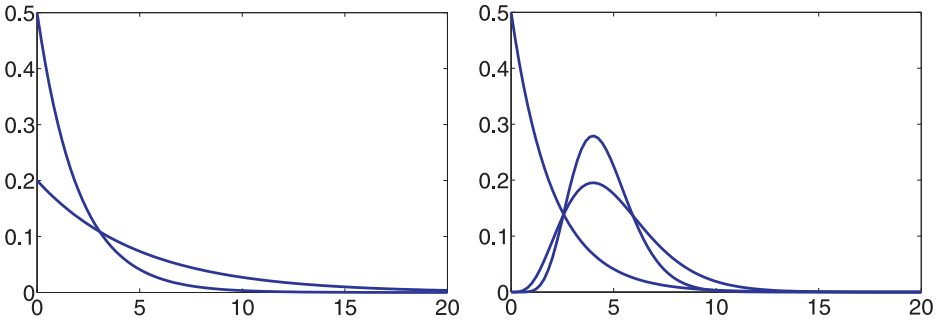

FIGURE 1. The exponential (left) and gamma (right) density functions for different parameters

On the left side of Figure 1 we can see the single parameter exponential density function (ae^{-at}) for different parameter values. If a is relatively large, then the function is mainly concentrated on the neighborhood of 0. In terms of the delayed equation, this means that the influence of the past state for the present dynamics is quite little.

REMARK. The substitution method we apply later also works for gamma density function. This type of distribution (see the right side of Figure 1) can be concentrated on the neighborhood of any positive number $r > 0$ for appropriate parameters. If this kind of density function was used for $s(t)$, then the present dynamics would mainly depend on the state r seconds before.

In our article we investigate the case $s(t)$ to be the exponential density function, since in the investigated population, most of the cells are able to respond immediately at any given point in time.

The following substitution is useful for this type of density functions (see [1]):

$$K_i(t) := \int_{-\infty}^{t} (u_{i+1}(\tau) - u_i(\tau)) a e^{-a(t-\tau)} \mathrm{d}\tau;$$

from this we get

$$\begin{aligned} \frac{\mathrm{d}K_i(t)}{\mathrm{d}t} &= -aK_i(t) + a(u_{i+1}(t) - u_i(t)), \\ \frac{\mathrm{d}u_i(t)}{\mathrm{d}t} &= dK_{i+1} - dK_i. \end{aligned}$$

Due to the Neumann boundary conditions $K_0(t) = 0 = K_n(t)$ and

$$\frac{\mathrm{d}u_1(t)}{\mathrm{d}t} = dK_1(t), \tag{2.2}$$

$$\frac{\mathrm{d}u_i(t)}{\mathrm{d}t} = -dK_{i-1}(t) + dK_i(t), \quad i = 2, \ldots, n-1, \tag{2.3}$$

$$\frac{\mathrm{d}K_i(t)}{\mathrm{d}t} = -aK_i(t) + a(u_{i+1}(t) - u_i(t)), \quad i = 1, \ldots, n-1, \tag{2.4}$$

$$\frac{\mathrm{d}u_n(t)}{\mathrm{d}t} = -dK_{n-1}(t). \tag{2.5}$$

With this substitution, the initial functions transform into initial conditions, since

$$\begin{aligned} u_i(0) &= \int_{-\infty}^{0} u_i(\tau) a e^{-a(t-\tau)} \mathrm{d}\tau, \\ K_i(0) &= \int_{-\infty}^{0} (u_{i+1}(\tau) - u_i(\tau)) a e^{-a(t-\tau)} \mathrm{d}\tau. \end{aligned}$$

3. Main results

THEOREM 3.1. *Let $n \in \mathbb{N}$ arbitrary. The system (2.2)–(2.5) has a unique solution on $(0,\infty)$. Each solution converges to one of the elements of the subspace $(c,0,c,\ldots,0,c)$, which is a continuum of equilibria. The value of c is determined by the initial condition:*

$$c = \frac{\sum_{i=1}^{n} u_i(0)}{n}.$$

REMARK. Let us notice that $\sum_{i=1}^{n} u_i(t) = c \cdot n$ is an invariant quantity, since $\sum_{i=1}^{n} \frac{\mathrm{d}u_i(t)}{\mathrm{d}t} = 0$, so Theorem 3.1 states that the system converges to the uniform concentration distribution, since the zeros in the equilibrium vector correspond to the auxiliary variable $K_i(t)$.

PROOF. First let us apply the substitution $t = a \cdot \tau$. This transforms the system (2.2)–(2.5) to the simpler form

$$\frac{\mathrm{d}u_1(t)}{\mathrm{d}t} = \frac{d}{a}K_1(t), \tag{3.1}$$

$$\frac{\mathrm{d}u_i(t)}{\mathrm{d}t} = -\frac{d}{a}K_{i-1}(t) + \frac{d}{a}K_i(t), \quad i = 2,\ldots,n-1, \tag{3.2}$$

$$\frac{\mathrm{d}K_i(t)}{\mathrm{d}t} = -K_i(t) + u_{i+1}(t) - u_i(t), \quad i = 1,\ldots,n-1, \tag{3.3}$$

$$\frac{\mathrm{d}u_n(t)}{\mathrm{d}t} = -\frac{d}{a}K_{n-1}(t). \tag{3.4}$$

Let us denote d/a by $\tilde{d}$ from now on. We take the equations in the following order: $u_1, K_1, u_2, K_2, \ldots, u_{n-1}, K_{n-1}, u_n$. The corresponding matrix of the system is tridiagonal; the main diagonal is $(0,-1,0,-1,\ldots,-1,0)$, the upper subdiagonal is $(\tilde{d},1,\tilde{d},1\ldots,\tilde{d},1)$, the lower subdiagonal is $(-1,-\tilde{d},-1,\ldots,-1,-\tilde{d})$.

We can give a recursive formula for the characteristic polynomial:

$$p_n(\lambda) = \begin{cases} -\lambda p_{n-1}(\lambda) + \tilde{d}p_{n-2}(\lambda), & \text{if } n = 2k+1, \\ (-1-\lambda)p_{n-1}(\lambda) + \tilde{d}p_{n-2}(\lambda), & \text{if } n = 2k. \end{cases}$$

We have $p_1(\lambda) = -\lambda$, $p_2(\lambda) = \lambda^2 + \lambda + \tilde{d}$.

REMARK. The value of $\tilde{d}$ actually depends on n. To get the proper $p_n(\lambda)$ we have to fix n and substitute the corresponding $\tilde{d}$ in the recursion for every n.

LEMMA 3.2. *Let us denote $p_n(\lambda) = a_0^n + a_1^n\lambda + \cdots + a_n^n\lambda^n$ if n is odd and $p_n(\lambda) = b_0^n + b_1^n\lambda + \cdots + b_n^n\lambda^n$ if n is even. Then*

(a) $a_0^{2n+1} = 0$,
(b) $b_0^{2n} = \tilde{d}^n$,
(c) $a_1^{2n+1} = -\tilde{d}^n(n+1)$,
(d) $b_1^{2n} = -\tilde{d}^{n-1}\frac{n(n+1)}{2}$.

PROOF OF LEMMA 3.2. Since $a_0^{2n+3} = da_0^{2n+1}$ and $a_1 = 0$, part (a) follows.

We have $b_0^{2n+2} = \tilde{d}b_0^{2n} - a_0^{2n+1}$ and $b_2 = \tilde{d}$, so (b) follows by induction.

We handle the last two statements together. From the recursion and (a)–(b), we have

$$a_1^{2n+1} = -\tilde{d}^n + \tilde{d}a_1^{2n-1}, \tag{3.5}$$

$$b_1^{2n+2} = \tilde{d}^n(n+1) + \tilde{d}b_1^{2n}. \tag{3.6}$$

By induction the lemma follows.

□

REMARK. From this lemma it follows that 0 is an eigenvalue of (3.1)–(3.4) with multiplicity 1. Straightforward calculations show that the corresponding eigenvector is $(1, 0, 1, 0, \ldots, 0, 1)$.

From [3] we use the following theorem:

THEOREM. *If λ is an eigenvalue of a (possibly) complex tridiagonal matrix whose diagonals are $(a_1, a_2, \ldots, a_{n-1})$, $(b_1, b_2, \ldots, b_n)$, $(c_1, c_2, \ldots, c_{n-1})$, where $a_k c_k$ is real and moreover $a_k c_k \le 0$ for $k = 1, \ldots, n-1$, then*

$$\min\{\Re b_j | j = 1, \ldots, n\} \le \Re\lambda \le \max\{\Re b_j | i = 1, \ldots, n\}.$$

PROOF. In our case, this means that the real parts of the eigenvalues are non-positive (and greater than -1), thus the solutions converge to the equilibrium $(c, 0, c, \ldots, 0, c)$. This completes the proof of Theorem 3.1.

□

However, this model can not be applied for any choice of a and d. For certain values of the parameters, due to the very strong oscillation, the solution may became negative in the beginning, which of course does not have a biological meaning. In a special case, which has an important application (see Section 4), we can guarantee the positivity of the solution for all $t \in \mathbb{R}$.

THEOREM 3.3. *We consider the system* (2.2)–(2.5) *for $n = 2$, with the initial conditions $u_1(0) = 0$, $u_2(0) = 1$. This system has a unique solution on $(0, \infty)$ with the following properties:*

(a) *The equilibrium $(1/2, 0, 1/2)$ is asymptotically stable.*

(b) *The system undergoes a node-focus bifurcation at $d/a = 1/8$, that is, the monotone convergence becomes oscillatory at this parameter value.*

(c) *If*

$$\frac{1}{2}\ln 2 < -\frac{1}{2}\ln\frac{d}{a} + \frac{-\arctan\left(\sqrt{-1+8d/a}\right) + \pi}{\sqrt{-1+8d/a}},$$

(that is, $d/a < 1.52\ldots$) then $u_1(t)$ and $u_2(t)$ are positive on $(0, \infty)$.

PROOF. If $n = 2$, the corresponding equations are

$$\begin{aligned}\frac{\mathrm{d}K(t)}{\mathrm{d}t} &= a(u_2(t) - u_1(t)) - aK(t)),\\ \frac{\mathrm{d}u_1(t)}{\mathrm{d}t} &= dK(t),\\ \frac{\mathrm{d}u_2(t)}{\mathrm{d}t} &= -dK(t).\end{aligned}$$

The initial conditions are

$$u_1(0) = 0, \qquad u_2(0) = 1, \qquad K(0) = 1.$$

Now let $t = a \cdot \tau$ again. With the new time variable τ, the equations have the following form:

$$\begin{aligned}K'(\tau) &= u_2(\tau) - u_1(\tau) - K(\tau),\\ u_1'(\tau) &= \frac{d}{a}K(\tau),\\ u_2'(\tau) &= -\frac{d}{a}K(\tau).\end{aligned}$$

As in the previous proof, let us denote $0 < \tilde{d} = d/a$. Since

$$u_1'(t) = -u_2'(t) \tag{3.7}$$

and $u_1(0) + u_2(0) = 1$, we have

$$u_2(t) = 1 - u_1(t). \tag{3.8}$$

We compute only the solution $u_1(t)$.

The characteristic polynomial is $\lambda(\lambda^2 + \lambda + 2\tilde{d})$, so $\lambda_1 = 0$ is a root. The other two roots are

$$\lambda_2(\tilde{d}) = -\frac{1}{2} - \frac{\sqrt{1 - 8\tilde{d}}}{2}, \qquad \lambda_3(\tilde{d}) = -\frac{1}{2} + \frac{\sqrt{1 - 8\tilde{d}}}{2}.$$

Their real part is negative if and only if $\tilde{d} > 0$, thus the solutions are asymptotically stable, which proves (a).

The eigenvalues are real if $\tilde{d} \le 1/8$ and complex if $\tilde{d} > 1/8$, and for every parameter value the real part is negative, which proves (b).

LEMMA 3.4. *The solution of the system* (2.2)–(2.5) *for* $n = 2$ *with the initial conditions* $u_1(0) = 0$, $u_2(0) = 1$ *is strictly monotone if* $\tilde{d} \le 1/8$ *and oscillates* (*with an amplitude that tends to* 0) *if* $\tilde{d} > 1/8$.

PROOF OF LEMMA 3.4. If $\tilde{d} < 1/8$, the solution has the form

$$u_1(t) = \frac{1}{2} + c_2(\tilde{d})e^{\lambda_2(\tilde{d})t} + c_3(\tilde{d})e^{\lambda_3(\tilde{d})t}, \tag{3.9}$$

where

$$\lambda_2(\tilde{d}) = -\frac{1}{2} + \frac{\sqrt{1-8\tilde{d}}}{2}, \qquad \lambda_3(\tilde{d}) = -\frac{1}{2} - \frac{\sqrt{1-8\tilde{d}}}{2},$$
$$c_2(\tilde{d}) = -\frac{1}{4} + \frac{4\tilde{d}-1}{4\sqrt{1-8\tilde{d}}}, \qquad c_3(\tilde{d}) = -\frac{1}{4} + \frac{1-4\tilde{d}}{4\sqrt{1-8\tilde{d}}}.$$

By differentiating (3.9), we get $u_1'(t) > 0$ for all $t > 0$, $\tilde{d} \in (0, 1/8)$, so $u_1(t)$ is strictly increasing and from (3.8) it follows that $u_2(t)$ is strictly decreasing.

If $\tilde{d} = 1/8$, then the solution is

$$u_1(t) = -\frac{1}{2}e^{-\frac{1}{2}t} - \frac{1}{8}te^{-\frac{1}{2}t} + \frac{1}{2}$$

which is also strictly decreasing.

If $1/8 < \tilde{d}$, then the solution has the form

$$u_1(t) = \frac{1}{2} + c_2(\tilde{d})e^{\Re\lambda(\tilde{d})t}\sin(\Im\lambda\tilde{d}t) + c_3(\tilde{d})e^{\Re\lambda(\tilde{d})t}\cos(\Im\lambda\tilde{d}t)$$

where

$$\lambda(\tilde{d}) = -\frac{1}{2} + i\frac{\sqrt{8d-1}}{2}, \quad c_2(\tilde{d}) = \frac{1}{4}\sqrt{8d-1} - \frac{1}{4\sqrt{8d-1}}, \quad c_3(\tilde{d}) = -\frac{1}{2}.$$

Since

$$A\sin(\alpha) + B\cos(\alpha) = \sqrt{A^2+B^2}\sin\Big(\alpha + \arccos\Big(\frac{A}{\sqrt{A^2+B^2}}\Big)\Big),$$

$u_1(t)$ can be transformed to the form

$$\frac{1}{2} + \hat{c_1}e^{-\frac{1}{2}t}\sin((\Im\lambda\tilde{d} + \hat{c_2})\,t) \tag{3.10}$$

The amplitude of the oscillation is $\hat{c_1}e^{-\frac{1}{2}t_n}$, for some $t_n \in \mathbb{R}$ which goes to 0 if $t_n \to \infty$. This finishes the proof of Lemma 3.4.

□

If $\tilde{d} \leq 1/8$, then the solutions are positive, since $u_1(0) = 0$, and $u_1(t)$ is increasing. $u_2(0) = 1$ and $u_2(t) \to 1/2$ decreasing, so $u_2(t)$ is also positive.

If $1/8 < \tilde{d}$, then $u_1'(t) = 0$, $u_2'(t) = 0$ infinitely many times. From the form (3.10) it follows that it is enough to examine the sign of $u_2(t)$ in the first minimum

(let us denote it by t_1), since the function sin(.) is multiplied by a strictly decreasing positive function. From (3.7) and (3.8), we get that if $u_2(t_1) > 0$, then $u_1(t)$ and $u_2(t)$ are positive on $(0, \infty)$.

By differentiating $u_2(t) = 1 - u_1(t)$ we get that the first zero is

$$t_1 = \frac{2\arctan(-\sqrt{8\tilde{d} - 1}) + 2\pi}{\sqrt{8\tilde{d} - 1}}. \tag{3.11}$$

Substituting into $u_2(t)$ and using $\sin(\arctan(x)) = 1/\sqrt{1 + x^2}$, we get the following inequality:

$$-\sqrt{\frac{\tilde{d}}{2}} e^{-\frac{1}{2}t_1} + \frac{1}{2} > 0. \tag{3.12}$$

Substituting (3.11) into (3.12) we obtain

$$\frac{1}{2}\ln 2 < -\frac{1}{2}\ln\frac{d}{a} + \frac{-\arctan(\sqrt{-1 + 8d/a}) + \pi}{\sqrt{-1 + 8d/a}}. \tag{3.13}$$

Solving (3.13) numerically we get (c).

□

4. The capillary assay

In this section we apply the system (2.2)–(2.5) to model the capillary assay (for a more detailed description see [4]). The sketch of the assay is on Figure 2.

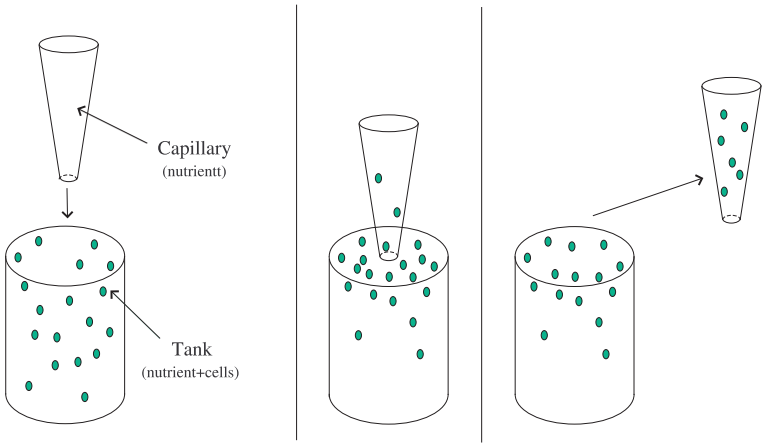

FIGURE 2. Capillary assay

At the beginning of the measurement the cells are placed in the lower tank, then the free surfaces are joined. The cells can move through the common fluid surface. After a period of time, the upper tank is removed, and the cell density in the upper tank is determined. The result refers to the general state of the cells, and can be used as a control value for further measurements (where chemical compounds are placed in the capillary).

We apply the slightly modified system (2.2)–(2.5) to describe this assay, with $n = 2$. The value of $u_1(t)$ corresponds to the density in the upper tank, $u_2(t)$ in the lower tank. Since the volume of the two tanks differ, we have to use a non-equidistant division of the original interval (the length of the steps corresponds to the volume of the tanks). We have

$$\begin{aligned}
\frac{\mathrm{d}K(t)}{\mathrm{d}t} &= a(\alpha u_2(t) - u_1(t)) - aK(t),\\
\frac{\mathrm{d}u_1(t)}{\mathrm{d}t} &= dK(t),\\
\frac{\mathrm{d}u_2(t)}{\mathrm{d}t} &= -dK(t),
\end{aligned}$$

where the parameter $\alpha > 0$ refers to the ratio of the two tanks' volume.

The initial conditions are

$$u_1(0) = 0, \qquad u_2(0) = 1, \qquad K(0) = 1.$$

Similarly to Theorem 3.3, straightforward calculation shows that the solutions are asymptotically stable for all $\tilde{d} > 0$, monotone if $\tilde{d} < \frac{1}{4(1+\alpha)}$. However the condition for the positivity of the solution can be no longer described by a simple inequality, since the equations for the zeros of the solution derivative have no analytical solution.

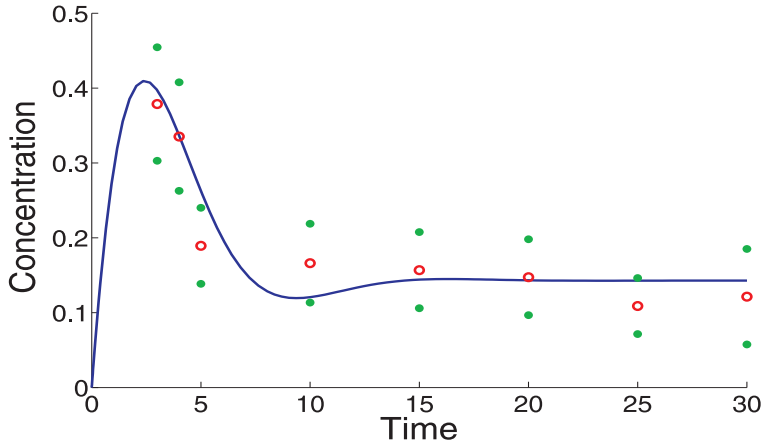

FIGURE 3. The cell density in the capillary

On Figure 3, the curve shows the solution $u_1(t)$ for the parameter values $a = 0.7$, $d = 0.4$, $\alpha = 1/6$ while the circles show the corresponding densities in the upper tank and the dots show their variances corresponding to the measurement. Note that for this special choice of parameters, the solution is positive.

If $\frac{d}{a} < \frac{1}{4\alpha}$ holds for the parameters, then the solutions are monotonous. This means that, compared to the diffusivity and the memory of the cells, the surface area over which diffusion is taking place has to be large enough to avoid oscillation. If oscillation occurs, one has to wait until the cell densities stabilize to get precise results on the steady state, like in our current case.

5. Conclusions

In our present article our interest is to study the movement of the eukaryotic ciliate Tetrahymena Pyriformis. We modeled the movement of the cells with regard to the fact that at any specific time a considerable amount of cells is not active. This observation led us to the delayed equation, which gives a good qualitative description of the capillary assay for a feasible set of parameters. Our goal in the future is to model the chemical compound biased movement of the cells.

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