Time-delayed model of the unbiased movement of Tetrahymena Pyriformis

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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 describe the specific movement of this species. With the help of semi-discretization, we state analytic results for the model.

Keywords: eukaryotic ciliate, time-delay, semi-discretization

1 Introduction

The most common principle for modeling self-organizing systems in developmental biology is the law of conservation. With a $\partial\Omega$ arbitrary surface 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

$$\frac{\partial}{\partial t}\int_{\Omega} u(t,x)dV = -\int_{\partial\Omega} \mathbf{J}\mathrm{d}s + \int_{\Omega} f(u,t,x)\mathrm{d}V, \tag{1.1}$$

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

$$\frac{\partial}{\partial t}u(t,x) = -\nabla\mathbf{J} + f(u,t,x) \tag{1.2}$$

Assuming there is no cell proliferation, the unbiased motion of the cells is described by Fick's equation (see [6]):

$$\frac{\partial u(t,x)}{\partial t} = D\frac{\partial^2}{\partial x^2}u(t,x) \tag{1.3}$$

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 speed of the diffusion. The system is closed by proper initial conditions and Neumann boundary conditions (for a closed system).

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

2 The delay

Due to the fact that in an average Tetrahymena Pyriformis population, the 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 (1.3) 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 the past. The delayed form of (1.3) is the following:

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

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. To be able to state analytical results, we approximate this system with the help of semi-discretization. The 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 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 ($i = 0, 1 \dots n+1$), $u_i(t)$ denotes the value of the solution at time t, and we use the following approximation for the derivatives:

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

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 $u_i(t)$, $i = 1, 2, \ldots n$:

$$\frac{\mathrm{d}u_1(t)}{\mathrm{d}t} = d\int_{-\infty}^{t}(u_2(\tau) - u_1(\tau))s(t-\tau)\mathrm{d}\tau \tag{2.2}$$

$$\frac{\mathrm{d}u_2(t)}{\mathrm{d}t} = d\int_{-\infty}^{t}(u_3(\tau) - u_2(\tau))s(t-\tau)\mathrm{d}\tau + \int_{-\infty}^{t}(u_1(\tau) - u_2(\tau))s(t-\tau)\mathrm{d}\tau \tag{2.3}$$

$$\vdots$$

$$\frac{\mathrm{d}u_{n-1}(t)}{\mathrm{d}t} = d\int_{-\infty}^{t}(u_n(\tau) - u_{n-1}(\tau))s(t-\tau)\mathrm{d}\tau + \int_{-\infty}^{t}(u_{n-2}(\tau) - u_{n-1}(\tau))s(t-\tau)\mathrm{d}\tau$$

$$\frac{\mathrm{d}u_n(t)}{\mathrm{d}t} = d\int_{-\infty}^{t}(u_n(\tau) - u_{n-1}(\tau))s(t-\tau)\mathrm{d}\tau \tag{2.4}$$

$$\tag{2.5}$$

The constant $d > 0$ is the Fick coefficient multiplied by h^2.
Remark. This kind of approximation is actually leads to the patchy environment method.

Let us choose $s(t)$ to be the exponential density function, i.e. $s(t) = ae^{-at}$. In this case, the parameter $a > 0$ describes the rate of the delay. The greater a is, the weaker impact the past (has for more details see [5]).

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

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

we get

$$\frac{\mathrm{d}K_i(t)}{\mathrm{d}t} = -aK_i(t) + a(u_{i+1}(t) - u_i(t)) \tag{2.6}$$

$$\frac{\mathrm{d}u_i(t)}{\mathrm{d}t} = dK_{i+1} - dK_i \tag{2.7}$$

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

$$\frac{\mathrm{d}u_1(t)}{\mathrm{d}t} = dK_1(t) \tag{2.8}$$

$$\frac{\mathrm{d}K_1(t)}{\mathrm{d}t} = -aK_1(t) + a(u_2(t) - u_1(t)) \tag{2.9}$$

$$\frac{\mathrm{d}u_2(t)}{\mathrm{d}t} = -dK_1(t) + dK_2(t) \tag{2.10}$$

$$\frac{\mathrm{d}K_2(t)}{\mathrm{d}t} = -aK_2(t) + a(u_3(t) - u_2(t)) \tag{2.11}$$

$$\vdots$$

$$\frac{\mathrm{d}u_{n-1}(t)}{\mathrm{d}t} = -dK_{n-1}(t) + dK_{n-2} \tag{2.12}$$

$$\frac{\mathrm{d}K_{n-1}(t)}{\mathrm{d}t} = -aK_{n-1}(t) + a(u_n(t) - u_{n-1}(t)) \tag{2.13}$$

$$\frac{\mathrm{d}u_2(t)}{\mathrm{d}t} = -dK_{n-1}(t) \tag{2.14}$$

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

$$u_i(0) = \int_{-\infty}^{0} u_i(\tau) a e^{-a(t-\tau)} \mathrm{d}\tau \tag{2.15}$$

$$K_i(0) = \int_{-\infty}^{0} (u_{i+1}(\tau) - u_i(\tau)) a e^{-a(t-\tau)} \mathrm{d}\tau. \tag{2.16}$$

3 Main results

Theorem 3.1. *Let $n \in \mathbb{N}$ arbitrary. The system (2.8)-(2.14) has a unique solution on $(0, \infty)$. The equilibrium $(c, 0, c, \dots, 0, c)$ is asymptotically stable, where $c \in \mathbb{R}$ depends on the initial conditions.*

Remark. Theorem 3.1 states that the system converges to uniform concentration distribution, since the zeros in the equilibrium vector correspond to the auxiliary variable $K_i(t)$.

In a special case, which has an important application, we can state more about the positivity and monotonicity of the solution.

Theorem 3.2. *We consider the system (2.8)-(2.14) 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 $\left(\frac{1}{2}, 0, \frac{1}{2}\right)$ is asymptotically stable,

b, The system undergoes a node-focus bifurcation at $\frac{d}{a} = \frac{1}{8}$.

c, If

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

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

Proof. First let us apply the substitution $t = a\cdot\tau$. This transforms the system (2.8)-(2.14) to the simpler form

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

$$\frac{\mathrm{d}K_1(t)}{\mathrm{d}t} = -K_1(t) + u_2(t) - u_1(t) \tag{3.2}$$

$$\frac{\mathrm{d}u_2(t)}{\mathrm{d}t} = -\frac{d}{a}K_1(t) + \frac{d}{a}K_2(t) \tag{3.3}$$

$$\frac{\mathrm{d}K_2(t)}{\mathrm{d}t} = -K_2(t) + u_3(t) - u_2(t) \tag{3.4}$$

$$\vdots$$

$$\frac{\mathrm{d}u_{n-1}(t)}{\mathrm{d}t} = -\frac{d}{a}K_{n-1}(t) + \frac{d}{a}K_{n-2} \tag{3.5}$$

$$\frac{\mathrm{d}K_{n-1}(t)}{\mathrm{d}t} = -K_{n-1}(t) + u_n(t) - u_{n-1}(t) \tag{3.6}$$

$$\frac{\mathrm{d}u_2(t)}{\mathrm{d}t} = -\frac{d}{a}K_{n-1}(t) \tag{3.7}$$

Let us denote $\frac{d}{a}$ with $\tilde{d}$ from now on. The corresponding matrix of the system is tridiagonal; the main diagonal is $(0,-1,0,-1,\ldots,-1,0)$, the upper sub diagonal is $(\tilde{d},1,\tilde{d},1\ldots,\tilde{d},1)$, the lower sub diagonal is $(-1,-\tilde{d},-1,\ldots,-1,-\tilde{d})$.

We can give a recursive formula to the characteristic polynomial:

$$p_n(\lambda) = \begin{cases} -\lambda p_{n-1}(\lambda) + \tilde{d}p_{n-2}(\lambda) & \text{if } n = 2k+1 \\ (-1-\lambda)p_{n-1}(\lambda) + \tilde{d}p_{n-2}(\lambda) & \text{if } n = 2k \end{cases} \tag{3.8}$$

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

Lemma 3.3. *Let us denote $p_n(\lambda) = a_0^n + a_1^n\lambda + \ldots a_n^n\lambda^n$ if n is odd and $p_n(\lambda) = b_0^n + b_1^n\lambda + \ldots b_n^n\lambda^n$ 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 3.3

Since $a_0^{2n+3} = da_0^{2n+1}$ and $a_1 = 0$, 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, and b, we have:

$$a_1^{2n+1} = -\tilde{d}^n + \tilde{d}a_1^{2n-1} \tag{3.9}$$

$$b_1^{2n+2} = \tilde{d}^n(n+1) + \tilde{d}b_1^{2n}. \tag{3.10}$$

By induction the Lemma follows.

Remark. From the Lemma it follows that 0 is an eigenvalue of (3.1)-(3.7) 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 tridiagonal matrix whose diagonals are $(a_1, a_2, \ldots, a_{n-1})$, $(b_1, b_2, \ldots, b_n)$, $(c_1, c_2, \ldots, c_{n-1})$ and moreover $a_k c_k \leq 0$ for $k = 1, \ldots, n-1$, then*

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

In our case this means that the real parts of the eigenvalues are non-positive (and greater then -1), thus the equilibrium $(c, 0, c, \ldots, 0, c)$ is asymptotically stable. The proof of the first Theorem 3.1 complete. □

Now we turn to Theorem 3.2.

Proof. If $n = 2$, the corresponding equations are:

$$\frac{\mathrm{d}K(t)}{\mathrm{d}t} = a(u_2(t) - u_1(t)) - aK(t) \tag{3.11}$$

$$\frac{\mathrm{d}u_1(t)}{\mathrm{d}t} = dK(t) \tag{3.12}$$

$$\frac{\mathrm{d}u_2(t)}{\mathrm{d}t} = -dK(t) \tag{3.13}$$

The initial conditions are:

$$u_1(0) = 0,$$

$$u_2(0) = 1,$$

$$K(0) = 1$$

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

$$K^{'}(\tau) = u_2(\tau) - u_1(\tau) - K(\tau) \tag{3.14}$$

$$u_1^{'}(\tau) = \frac{d}{a}K(\tau) \tag{3.15}$$

$$u_2^{'}(\tau) = -\frac{d}{a}K(\tau) \tag{3.16}$$

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

$$u_1^{'}(t) = -u_2^{'}(t) \tag{3.17}$$

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

$$u_2(t) = 1 - u_1(t). \tag{3.18}$$

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:

$$\lambda_2(\tilde{d}) = -\frac{1}{2} - \frac{\sqrt{1-8\tilde{d}}}{2}$$

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

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

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

Lemma 3.4. *The solution of the system is strictly monotone if $\tilde{d} \leq \frac{1}{8}$ and oscillates (with an amplitude that tends to 0) if $\tilde{d} > \frac{1}{8}$.*

Proof of Lemma 3.4

If $\tilde{d} < \frac{1}{8}$, the solution has the form:

$$u_1(t) = \frac{1}{2} + c_2(\tilde{d})e^{\lambda_2(\tilde{d})t} + c_3(\tilde{d})e^{\lambda_3(\tilde{d})t}, \tag{3.19}$$

where

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

$$\lambda_3(\tilde{d}) = -\frac{1}{2} - \frac{\sqrt{1-8\tilde{d}}}{2}$$

$$c_2(\tilde{d}) = -\frac{1}{4} + \frac{4\tilde{d}-1}{4\sqrt{1-8\tilde{d}}}$$

$$c_3(\tilde{d}) = -\frac{1}{4} + \frac{1-4\tilde{d}}{4\sqrt{1-8\tilde{d}}}$$

By differentiating (3.19), we get $u_1^{'}(t) > 0 \,\forall t > 0, \tilde{d} \in (0, \frac{1}{8})$, so $u_1(t)$ is strictly increasing and from (3.18) it follows that $u_2(t)$ is strictly decreasing.

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

$$u_1(t) = \frac{1}{2} + c_2(\tilde{d})e^{\Re\lambda(\tilde{d})t}\sin(\Im\lambda\tilde{d}t) + c_3(\tilde{d})e^{\Re\lambda(\tilde{d})t}\cos(\Im\lambda\tilde{d}t) \tag{3.20}$$

where

$$\lambda(\tilde{d}) = -\frac{1}{2} + i\frac{\sqrt{8d-1}}{2}$$

$$c_2(\tilde{d}) = \frac{1}{4}\sqrt{8d-1} - \frac{1}{4\sqrt{8d-1}}$$

$$c_3(\tilde{d}) = -\frac{1}{2}$$

Since

$$A\sin(\alpha) + B\cos(\alpha) = \sqrt{A^2+B^2}\sin\left(\alpha + \operatorname{sign}\left(\arccos\left(\frac{A}{\sqrt{A^2+B^2}}\right)\right)\right),$$

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

$$\frac{1}{2} + \hat{c_1}e^{-\frac{1}{2}t}\sin\left(\left(\Im\lambda\tilde{d} + \hat{c_2}\right)t\right) \tag{3.21}$$

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

If $\frac{1}{8} < \tilde{d}$, then $u_1^{'}(t) = 0$, $u_2^{'}(t) = 0$ infinitely many times. From the form (3.21) 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 (3.17) and (3.18), 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 positive root is:

$$t_1 = \frac{2\arctan(-\sqrt{8\tilde{d}-1}) + 2\pi}{\sqrt{8\tilde{d}-1}}. \tag{3.22}$$

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

$$-\sqrt{\frac{\tilde{d}}{2}}e^{-\frac{1}{2}t_1} + \frac{1}{2} > 0 \tag{3.23}$$

Substituting (3.22) into (3.23) we obtain:

$$\frac{1}{2}\ln 2 < -\frac{1}{2}\ln\frac{d}{a} + \frac{-\arctan\left(\sqrt{-1+8\frac{d}{a}}\right)+\pi}{\sqrt{8\frac{d}{a}-1}} \tag{3.24}$$

Solving (3.24) numerically we get c,.

□

4 The capillary assay

In this section we apply the system (2.8)–(2.14) to model the capillary assay (for more detailed description see [4]). The sketch of the assay is on Figure 1.

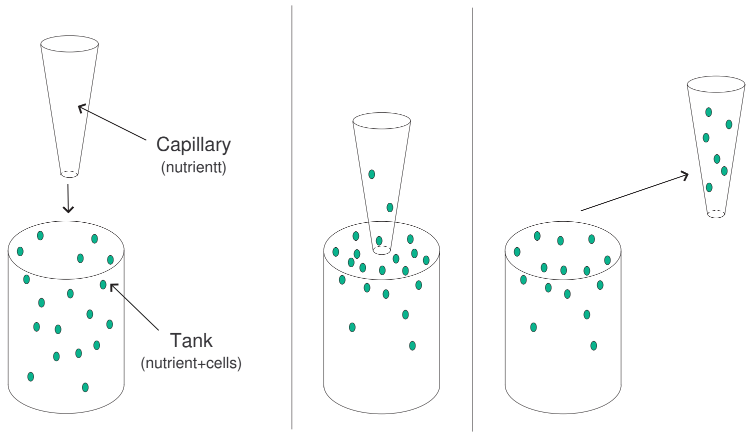

Figure 1: Capillary assay

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 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 applied the system (2.8)-(2.14) 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. On Figure 2, the blue line shows the solution $u_1(t)$ multiplied by the volume of the upper tank, while the red dots show the corresponding densities in the upper tank and the green dots show their variances corresponding to the measurement.

From Theorem 3.2 it follows that if $\frac{d}{a} < \frac{1}{8}$ holds for the parameter, then the solutions are monotonous. This means that, compared to the diffusivity and the

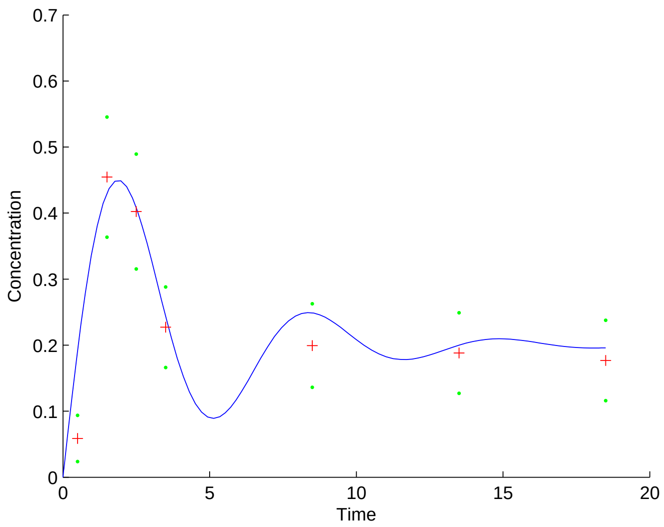

Figure 2: The cell density in the capillary

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 on our current figure.

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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