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Evaluation of Paramita Chatterjee
doctor's thesis:
Mathematical analysis of a new model of bone pattern formation

The PhD thesis of Paramita Chatterjee is devoted to mathematical analysis of systems of partial differential equations modeling bone pattern formation. Bone formation is a very complex process and it is difficult to imagine that a system consisting of a few partial differential equations with some boundary conditions could fully describe limbs development. I suppose that an advanced gene regulatory network and transcriptional mechanisms additionally control these processes, but even simple mathematical models should be useful to understand basic interactions. The discussed dissertation is devoted only to mathematical analysis of a model given by Glimm, Bhat and Newman [16] published in J. Theor. Biol. and I will also concentrate on mathematical aspects of the PhD thesis.

The initial model is a system of parabolic equations of degenerate type with boundary conditions of Dirichlet type and with an initial condition. This system describe the density of space distribution of five different types of cells and it is rather difficult to direct analysis. The main aim of the PhD thesis is to prove the existence of solutions of some simplified forms of this system. The proofs of these results are long, technical and need a lot of attention. The thesis begins with equation (3.1), which describes a density of the distribution of a degenerate diffusion in five dimensional space. I my opinion it will be easier to investigate this equation using stochastic interpretations and most of results in Sections 5-8 follow from this interpretation. I give detailed remarks on this subject at the end of my review. P. Chatterjee also studies an inhomogeneous version of (3.1) and she finds its solutions. Much more orginal are Sections 9-12. In Section 9 she consider inhomogeneous version of (3.1) with a diffusion term with respect to (T_1, T_8). On one side a diffusion term helps a little bit because the new equation has a classical parabolic form but now the boundary conditions are really needed if we want to give a probabilistic interpretation of the problem. The part of the process corresponding to variables (T_1, T_8) is absorbed at the boundaries $T_1 = 0$ and $T_2 = 0$, but we do not need the assumptions $B(0) \geqslant 0$ and $\Gamma(0) \geqslant 0$. Equations in bounded domains with respect $\mathbf{x}$ are studied in Sections 11-12.

In my opinion Part III contains the most interesting fragments of the thesis. The

Rothe numerical scheme allows us not only to find an approximate solution but also to prove the existence and uniqueness of solutions of the initial-boundary value problem. Moreover, using this method we can study much more general equations than that considered in Part II. This part is very technical and certainly, using more subtle mathematical tools, we could omit some number of exhausting calculations, but the aim of the thesis was reached.

It should be mentioned that P. Chatterjee is also a cooauthor of an interesting review paper with T. Glimm and B. Kazmierczak, *Mathematical modeling of chondrogenic pattern formation during limb development: Recent advances in continuous models*, submitted to the journal of Mathematical Biosciences. Frankly speaking, it will be very difficult to understand the background and motivations of the thesis without this article.

Remarks concerning Part II.

It would be a good idea to present assumptions concerning functions Γ and B before the analysis of the properties of solutions of equation (3.1). One reason is that in many results in Part II the assumptions are introduced *ad hoc* and it is not easy to check when they are fulfilled, e.g. the assumption in Lemma 3.1 concerning properties of the function R as $\|\mathbf{x}\| \to \infty$. The second reason is that the problem (3.1) with the boundary conditions

$$R(t, \mathbf{x}, T_1, T_8) = 0 \text{ for } T_1 = 0 \vee T_2 = 0$$

and the initial condition $R(0, \mathbf{x}, T_1, T_8) = R_0(\mathbf{x}, T_1, T_8)$ is not well-posed if $\Gamma(0) < 0$ or $B(0) < 0$. In order to explain this statement consider a simpler equation:

$$\frac{\partial u}{\partial t} = \frac{\partial u}{\partial x}, \quad t, x \geqslant 0.$$

It is clear that each solution of this equation is of the form $u(t,x) = f(t+x)$, where f is a differentiable function. If we assume that u satisfies the boundary condition $u(t,0) = 0$, then $f(t) = 0$ for all $t \geqslant 0$. Hence $u \equiv 0$ and therefore the initial-boundary problem is not well-posed. A similar problem appears if we consider equation (3.1), so we should assume that

$$\Gamma(0) \geqslant 0, \quad B(0) \geqslant 0. \tag{1}$$

It should be also assumed that Γ and B are C^1-functions and there exists C such that $\Gamma(x) \leqslant Cx$ and $B(x) \leqslant Cx$ for sufficiently large x. This assumption guarantees the existence and uniqueness of solutions of the initial value problems $x' = \Gamma(x)$ and $x' = B(x)$ for $t \geqslant 0$. It is all what is needed to prove all properties of solutions of (3.1). Indeed equation (3.1) describe the evolution of a stochastic process $(\xi_t)_{t \geqslant 0}$ with values in the space $\mathbb{R}^3 \times \mathbb{R}^2_+$. First three coordinates of this process form a Wiener process in

$\mathbb{R}^3$ and the next two coordinates are independent deterministic processes with values in $[0,\infty)$ which are solutions of ordinary differential equations (3.5). In order to find solutions of (3.1), we consider a simpler initial problem: $x' = g(x)$, $x(0) = x_0$, and we denote by $\pi_t x_0$ its solution. Denote by $(\eta_t)_{t\geqslant 0}$ the process with values in $[0,\infty)$ given by $\eta_t = \pi_t \eta_0$. If the random variable η_0 has density $u_0(x)$ then η_t has density $u(t,x)$, which is a solution of the boundary-initial problem

$$\frac{\partial u}{\partial t} = -\frac{\partial(g(x)u(t,x))}{\partial t}, \quad u(0,x) = u_0(x), \quad u(t,0) = 0,$$

and $u(t,x)$ is given by the formula:

$$u(t,x) = u_0(\pi_{-t}x)\frac{\partial}{\partial x}\pi_{-t}x = u_0(\pi_{-t}x)\frac{g(\pi_{-t}x)}{g(x)} \tag{2}$$

if $\pi_{-t}x > 0$ and $u(t,x) = 0$ if $\pi_{-t}x \leqslant 0$. From (2) and from the well known formula for the distribution of the Wiener process we will finally find the solution of (3.1):

$$R(t,\mathbf{x},T_1,T_8) = \frac{1}{(4\pi d_R t)^{3/2}} \int_{\mathbb{R}^3} e^{-\|\mathbf{x}-\mathbf{y}\|^2/(4d_R t)} R_0(\mathbf{y}, \pi^1_{-t}T_1, \pi^3_{-t}T_8) \frac{B(\pi^1_{-t}T_1)}{B(T_1)} \frac{\Gamma(\pi^8_{-t}T_8)}{\Gamma(T_8)}\, d\mathbf{y},$$

if $\pi^1_{-t}T_1 > 0$ and $\pi^8_{-t}T_8 > 0$, where $\pi^i_t T_i$, $i = 1, 8$, are the solutions of (3.5). If $\pi^1_{-t}T_1 \leqslant 0$ or $\pi^8_{-t}T_8 \leqslant 0$ then $R(t,\mathbf{x},T_1,T_8) = 0$ (compare with Lemma 5.2). Most properties of solutions of (3.1) given in Sections 5-7 are direct consequences of probabilistic interpretation.

Detailed remarks:

1. I found some awkward phrases, e.g. in Abstract: "there are no theorems guaranteeing the existence of such equations".

2. Some notations are not introduced or they are no clear. For example what does mean that we integrate with respect to dP or $d\tilde{P}$. What is $D_{\rho_0}(\mathbf{x}_0)$?. The usual notation for a ball is $B_{\rho_0}(\mathbf{x}_0)$. There is not clear what are the regions of integration in formulas (1.2)-(1.3), (1.7) ?

3. The author use sometimes different notations for the same object, e.g. $\mathbf{x}$ and x.

In recapitulation, the PhD thesis of Paramita Chatterjee contains original and interesting mathematical and numerical results. She has very good knowledge of the theory of differential equations and numerical methods. She is able to study difficult problems and solve them. She has chosen a field of interest with large perspective of development. This is a good thesis, and I **highly recommend** its acceptance.

This thesis is ready to be defended orally and certainly meets the requirements laid down for the degree of Ph.D. in mechanical engineering (inżynieria mechaniczna) by the statutes in the Journal of Laws of the Republic of Poland (Dziennik Ustaw, art.13

ust. 1 ustawy o stopniach i tytule naukowym, w związku z art. 179 Ustawy z dnia 3 lipca 2018 roku).

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