# Numerical Simulation of sea urchin's morphogenesis during its structural development at early stage by using PDE Methods

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***Abstract*— In this paper, we study a methodology for numerical simulation of sea urchin shapes in biological organism's development particularly at the blastula phase, consisting of a hollow, two-layered sac of ectoderm and endoderm surrounding an archenteron that communicates with the exterior through the blastopore with the help of newly developed "PDE Methods". The geometric modeling of the sea urchin shapes are under taken by means of surfaces generated as Partial Differential Equations (PDEs). We merge PDE based geometric modeling technique with numerical optimization in order to study the stable shapes adopted by the sea urchin during its blastula phase. Thus, by using the PDE method we produce a generic model which is then capably parameterized. Using this parameterization to set up a numerical optimization process which enables us to predict a series of sea urchin shapes at the early stage subject to given surface area and volume at that time.**

***Key Words:- Tissues, Sea urchins, Morphogenetic, Optimization, Partial Differential Equations, Surface Modeling.***

## 1. INTRODUCTION

### 1.1 MORPHOLOGYCAL CHANGES OF A SEA URCHIN SHAPES

Today, morphogenesis becomes commonly used term not only in biology but in the field of evolutionary computations also. Morphogenesis is one of the major outstanding problems in the biological sciences. It concerns the fundamental question of how organic form and structure are generated. Morphogenesis encompasses a broad scope of biological processes. It concerns adult as well as embryonic tissues, and includes an understanding of the maintenance, degeneration, and regeneration of tissues and organs as well as their formation. Morphogenesis also addresses the problem of biological form at many levels, from the structure of individual cells, through the formation of multi cellular arrays and tissues, to the higher order assembly of tissues into organs and whole organisms. While related to the field of developmental biology with its traditional emphasis on the control of gene expression and the acquisition of cell fates, morphogenesis investigates how this regulation of cell fates contributes to the form and structure of the organism and its component parts.

When an egg fertilizes, it divides rapidly into a mass of undifferentiated cells that eventually, in vertebrates, form a hollow, one cell thick, fluid-filled ball of cells called a blastula. There's a kind of hole or opening in the blastula called a blastopore, and the cells of the blastula begin to expand and burrow in through the blastopore, giving rise to a ball that is two cells thick. This movement (of cells) is known as gastrulating, and the resulting thickened embryo is called a gastrula. The two layers of the gastrula are called the ectoderm and the endoderm ("outside skin and inside skin"), and eventually a third layer forms between them, called a mesoderm ("middle skin"). This is the first stage of the sea urchin when the cells have become recognisable, and these three layers are destined to give rise to different parts of the mature animal. The ectoderm will eventually give rise to the skin and nervous system. The mesoderm gives rise to muscle, blood, and bone and the endoderm gives rise to the gut and internal organs of the animal [13].

As we know Genes regulating complex integrated functions, such as the programming of early development, often encode proteins with multiple conserved domains (such as HOX genes, Zinc-Finger and leucine-Zipper genes) [9]. The expression of genetic information in terms of pattern and form is a central problem, not only for Biology, but for Artificial Life also. The translation of genetic information into shapes and patterns is what links genetics to morphology - genotype to phenotype and must have crucial consequences for a variety of central issues from evolution to learning.

Although a large literature exists for equations which specify fields of values in the plane with specified boundary values, or sphere, very little literature exists for the case where the "morphogen field" interacts with the surface to change its shape, and the field in turn is itself changed because of the changed surface [15, 16]. Change of shape could of course involve aspects of mechanical forces which are important as the chemical-kinetics aspects, and equally deserving of inclusion in the differential equations. However, in the pattern-form interplay models we explore the possibility that the secondary role of mechanics could be represented algorithmically [15, 16]. Certainly, the model present in this paper of morphogenesis is capable at best of providing only an insight into such a complex process, and only on the highest scale, that of the cell collective.

As we know all Turing-like models require two diffusing substances as a minimum, one “X” comparatively slow-diffusing one and a second “Y” that is much faster [17]. All 2-morphogen models require X-autocatalysis and cross-inhibition via a second species, Y. The Y can be inhibited or depleted by X formation but activates the latter, as in the Brusselator. While symmetry in 4-morphogen systems (one pair of Xs and Ys each, as in the case of dual Brusselator) belong to models with general attributes of mutually exclusive states for production of each of two self-activating morphogenesis that are cross-activating via two further, faster diffusing morphogenesis [10].

According to “Harrison, Kolar” [15, 16] the Brusselator as a system that has been extensively studied in relation to chemical pattern formation as well as dual Brusselator as system with perfect interpretation in molecular biology terms [19]. Assuming the morphogens involved in gradient formation are primary gene products and not metabolites, the main steps in the reaction scheme leading to X and Y formation must represent some combination of gene transcription processes. This, in itself, implies considerable complexity and regulatory control. The model specifically requires there be multiple inputs, including some type of the gene self-activation by products [19].

In this study we consider the application of above ideas on the modelling of specific morphogenetic processes such as gastrulation of an object. Initially the model describes geometry of a spherical layer. The program considers each of about 51 Xs cells and 51 Ys cells as CELL-object with known space co-ordinates of Xs and Ys. LIST of all CELL-objects is used for generation of new object "GASTRULA". Each cell produces and exchanges the morphogens Xs and Ys in conformity with dual Brusselator model.

### 1.2 The Partial differential equation (PDE) based modeling

Computer Aided Design and Manufacturing area is one of the fastest growing areas in every field today. CAD/CAM systems have become basic systems that can help the designer to design a product by using the speed and efficiency of a computer. At the same time significant technological advances have been occurring in the areas of computer-aided design and in computer aided manufacturing.

In this research we applied a method for modeling which was first time used by Bloor and Wilson [20] is called the partial differential equation (PDE) based modeling approach. The PDE method is especially suitable for satisfying surface boundary constraints. Is is also effective for the generation of families of free-form surfaces, which share a common base and differ in their secondary features. We used the PDE modeling approach to simulate the sea urchin’s morphogenesis because it has the following advantages on other methods.

1) PDE surfaces are controlled by physical laws, so it is natural and close to the real world. They can potentially integrate geometric attributes with functional constraints for surface modeling, designing, and analysis.

2) The formulation of differential equations is well conditioned and technically sounds. Therefore, Smooth surfaces (with high-order continuity requirements) easily define through PDEs.

3) Users can easily understand the underlying physical process associated with PDE’s; therefore, high-level intuitive and natural control is possible through the modification of physical parameters.

4) PDE surfaces may potentially unify both geometric and physical aspects [18]. They are invaluable throughout the entire modeling, design, analysis, and manufacturing tasks. Various heterogeneous requirements can be enforced and satisfied simultaneously.

5) PDE-based techniques are able to create free-form surfaces as fast and almost as accurately as the closed-form (analytical) solutions. Because it has sufficient degrees of freedom to accommodate the

continuity of 3-sided and 4-sided surface patches at their boundaries, hence this method is able to generate the model of complex surfaces (consisting of multiple patches).

Our aim in this paper is to show how Partial Differential Equation (PDE) based geometric modeling combined with numerical optimization can be utilized to study the numerical simulation of sea urchin shapes in biological organism's development.

## 2. FORTH ORDER ELLIPTIC PDE METHOD

In the 4rth order "PDE Method" [1, 2, 3, 4] we have parametric surface $\underline{X}(u,v)$, defined as a function of two parameters $u$ and $v$ on a finite domain $X \subset \Omega$.

To illustrate the method we used biharmonic equation $\Delta^4 \Psi = 0$ in the following fourth order elliptic PDE form,

$$\left(\frac{\partial^2}{\partial u^2} + a^2 \frac{\partial^2}{\partial v^2}\right)^2 \underline{X}(u,v) = 0, \qquad (1)$$

Where " $a$ " is known as the smoothing parameter. [1, 6]

The solution of equation (1) over the finite domain { $\Omega:\ 0 \le u \le 1 \quad 0 \le v \le 2\pi$ } is written as

$$\underline{X}(u,v) = \underline{A}_0(u) + \sum_{n=1}^{\infty} \{\underline{A}_n(u)\cos(nv) + \underline{B}_n(u)\sin(nv)\} \qquad (2)$$

Where:

$$\underline{A}_0 = \underline{a}_{00} + \underline{a}_{01}u + \underline{a}_{02}u^2 + \underline{a}_{03}u^3, \qquad (2.1)$$

$$\underline{A}_n(u) = \underline{a}_{n1}e^{anu} + \underline{a}_{n2}ue^{anu} + \underline{a}_{n3}e^{-anu} + \underline{a}_{n4}ue^{-anu} \qquad (2.2)$$

$$\underline{B}_n(u) = \underline{b}_{n1}e^{anu} + \underline{b}_{n2}ue^{anu} + \underline{b}_{n3}e^{-anu} + \underline{b}_{n4}ue^{-anu} \qquad (2.3)$$

Where $\underline{a}_{00}, \underline{a}_{01}, \underline{a}_{02}, \underline{a}_{03}, \underline{a}_{n1}, \underline{a}_{n2}, \underline{a}_{n3}, \underline{a}_{n4}, \underline{b}_{n1}, \underline{b}_{n2}, \underline{b}_{n3}$ and $\underline{b}_{n4}$ are vector valued constants, determine boundary imposed on the isoperimetric lines $u = 0$ and $u = 1$. These conditions are described as follows,

$$\underline{X}(0,v) = \underline{c}_1(v), \qquad (2.4)$$

$$\underline{X}(1,v) = \underline{c}_2(v), \qquad (2.5)$$

$$\underline{X}_u(0,v) = \underline{d}_1(v), \qquad (2.6)$$

$$\underline{X}_u(1,v) = \underline{d}_2(v), \qquad (2.7)$$

Figure 1 shows sample PDE surfaces generated by varying the Fourier modes associated with the boundary conditions.

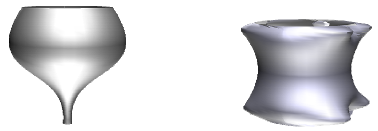


FIGURE 1 SOME SURFACES CONSTRUCTED BY 4RTH ORDER PDE METHOD

## 3. SIXTH- ORDER PDE METHOD

In this paper, we used elliptic partial differential equations, in particular equations based on the Laplace equation. This PDE Method provides enough degrees of freedom not only to handle easily spontaneous tangent, but also curvature boundary conditions and offers more shape control parameters to serve as user controls for the manipulation of surface shapes. In order to achieve real-time performance, we have constructed a surface function and developed a high-precision approximate solution to the sixth order PDE.

Mathematically, the surface is given by a function $X(u,v)$ such that,

$$X(u,v) = (x(u,v), y(u,v), z(u,v)), \qquad (3)$$

Where $u$ and $v$ are parameters for a finite two-dimensional region $\Omega$, which map onto a point in physical space. The sixth order PDE is

$$\left(\frac{\partial^2}{\partial u^2} + a^2 \frac{\partial^2}{\partial v^2}\right)^3 X(u,v) = 0, \qquad (4)$$

For each of the Cartesian coordinates $x, y$ and $z$ [5, 11, 14]. The “smoothing parameter” $a$ controls the relative smoothing of the dependent variables between $u$ and $v$ direction Altering $a$ changes the length scale over which the boundary conditions influence the interior of the surface.

Taking parameter space $\Omega$ to be the region $\{u, v : 0 \le u \le 1; 0 \le v \le 2\pi\}$ and a solution that is periodic in $v$ (The solution can be obtained analytically). Equation (4) is elliptic and is solved subject to the following boundary conditions,

$$X(0,v) = f_0(v), \qquad (4.1)$$
$$X(1,v) = f_1(v), \qquad (4.2)$$
$$X_u(0,v) = g_0(v), \qquad (4.3)$$
$$X_u(1,v) = g_1(v), \qquad (4.4)$$
$$X_{uu}(0,v) = h_0(v), \qquad (4.5)$$
$$X_{uu}(1,v) = h_1(v), \qquad (4.6)$$

For the following solution, all the given boundary conditions required to be continuous, and closed in the sense that $f_0(0) = f_0(2\pi)$.

Assuming the solution of Eq. (4) we are looking for is subject to periodic boundary conditions, the method of separation of variables can be utilized to write the down the solution as,`

$$X(u,v) = A_0(u) + \sum_{n=1}^{N}\left[A_n(u)\cos(nu) + B_n(u)\sin(uv)\right],$$
(5)

Where the coefficient functions $A_n(u)$ and $B_n(u)$ are of the form,

$$A_0(u) = a_{00} + a_{01}u + a_{02}u^2 + a_{03}u^3 + a_{04}u^4 + a_{05}u^5$$
(5.1)

$$A_n(u) = a_{n0}e^{anu} + a_{n1}e^{-anu} + a_{n2}u\ e^{anu} + a_{n3}ue^{-anu} + a_{n4}u^2e^{anu} + a_{n5}u^2e^{-anu}$$
(5.2)

$$B_n(u) = b_{n0}e^{anu} + b_{n1}e^{-anu} + b_{n2}u\ e^{anu} + b_{n3}ue^{-anu} + b_{n4}u^2e^{anu} + b_{n5}u^2e^{-anu}$$
(5.3)

Using Fourier analysis, the boundary condition $f_0(v), f_1(v), g_0(v), g_1(v), h_0(v)$ and $h_1(v)$ can be written in the form,

$$f_0(v) = c_{00}(u) + \sum_{n=1}^{N}[c_{n0}(u)\cos(nv) + d_{n0}(u)\sin(nv)]$$
(5.4)

$$f_1(v) = c_{01}(u) + \sum_{n=1}^{N}[c_{n1}(u)\cos(nv) + d_{n1}(u)\sin(nv)]$$
(5.5)

$$g_0(v) = c_{02}(u) + \sum_{n=1}^{N}[c_{n2}(u)\cos(nv) + d_{n2}(u)\sin(nv)]$$
(5.6)

$$g_1(v) = c_{03}(u) + \sum_{n=1}^{N}[c_{n3}(u)\cos(nv) + d_{n3}(u)\sin(nv)]$$
(5.7)

$$h_0(v) = c_{04}(u) + \sum_{n=1}^{N}[c_{n4}(u)\cos(nv) + d_{n4}(u)\sin(nv)]$$
(5.8)

$$h_0(v) = c_{05}(u) + \sum_{n=1}^{N}[c_{n5}(u)\cos(nv) + d_{n5}(u)\sin(nv)]$$
(5.9)

The vector constant of the general solution $a_{ni}$ and $b_{ni}$ are calculated from the vector constant $c_{ni}$ and $d_{ni}$ of the Fourier terms in the boundary conditions, where $i = 0,1,2,3,4,5$.

Figure 2 shows sample PDE surfaces generated by varying the Fourier modes associated with the boundary conditions. It is notice that a wide variety of surface shapes can be generated by varying the Fourier modes associated with the boundary conditions. Thus, in this work we use the Fourier modes associated with boundary conditions as a basis of parameterzing the shape of the surface.

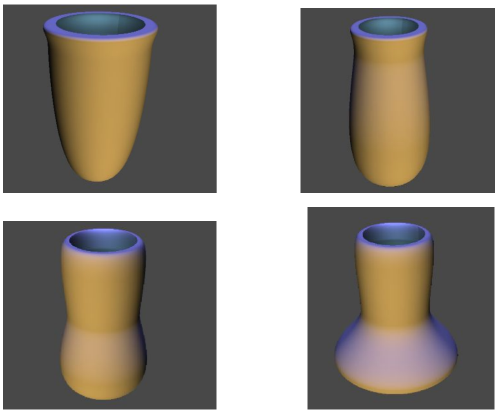


FIGURE 2 SAMPLE PDE SURFACES GENERATED BY VARYING THE FOURIER MODES ASSOCIATED WITH THE BOUNDARY CONDITIONS

## 4. SIMULATION OF *BLASTULA PHASE OF A SEA URCHIN*

Computer model of tissue's morphogenesis during structural development, presented in this paper is simulating an organism in early stages of development. The characteristic feature of the model is feedback loops between the processes in regulatory gene network, biochemical pattern formation and tissue's morphogenesis changes. In the model, formation of biochemical/physiological gradient causes subsequent morphogenetic movements. Therefore, the geometrical transformation of the model disturbs its biochemical patterns and a new pattern appears. In addition, continue this procedure a new pattern cause further morphogenetic movements. Lastly, it achieves the equilibrium between the geometry of the model and the distribution of morphogenesis. Moreover, we examine the different stages of elastic bending energy, with prescribed volume and surface area. To minimize the elastic bending energy we use (Broydon-Fletcher-Goldfarb-Shanno) in brief BFGS [23]

"Optimization Algorithm" BFGS is more efficient because BFGS algorithm calculates a gradient-based search direction followed by a line search along that direction through function evaluations. The function evaluations for gradient calculations are inherently parallelizable, since no data dependencies are involved [12].

In this paper, we discuss the different stages of morphogenesis during structural development of a tissue, under the elastic bending energy with prescribed volume and surface area. For this, we use the following bending energy [7, 8]

$$E_{elastic} = \int_{\Gamma} \frac{k}{2} H^2 ds, \qquad (6)$$

Where $H = \frac{(k_1+k_2)}{2}$ a mean curvature of the membrane while $k_1$ and $k_2$ are the principle curvatures which are the Weingarten matrix of the surface [7, 8]. The parameter $k$ is the bending rigidity ($k$ can depend on the local heterogeneous concentration of the species). The bending energy in (6) is a special case of a general form obtain the Hooke's Law [16]

$$E = \int_{\Gamma} (l + m(H - k_0)^2 + nG) ds, \qquad (7)$$

Where $l$, $m$, $n$ and $k_0$ is the surface tension, bending rigidity, stretching rigidity and spontaneous curvature respectively that describe the asymmetry effect of the sea urchin shape . $G$ is the Gaussian curvature. Because in our model the first term $l$ can be neglected as it remains constant in morphogenesis during structural development with a given surface area for a smooth compact surface with a constant $n$, the last term is related to the Euler index that represents the topological structure of the tissue [7, 21]. For simplicity, here we choose to consider only the energy given in (6) and the case where the bending rigidity k is a constant. If $l = 0 = n$ and $m = 1$ in (7) the bending energy can be simplified as

$$E = \int_\Gamma (H - k_0)^2 ds, \quad (8)$$

In equation (8), the only effect of the spontaneous curvature retained and the bending rigidity assumed to become a constant. The problem considered in this paper is to study tissue's morphogenesis during structural development phases to minimizing the bending energy (8) with constraints on the cell volume and surface area. Hence assume a domain $\Psi$ in $\Re^3$, and a smooth compact surface $\Gamma \subset \Psi$ which is the candidate surface for minimizes the bending energy (6). So from [7] bending energy define as

$$E(\phi) = \int_\Psi \frac{1}{\varepsilon}\left(\varepsilon\Delta\phi + \left(\frac{1}{\varepsilon}\phi + K\right)(1-\phi^2)\right)^2 dx \quad (9)$$

Where, $\varepsilon$ is a transition parameter, $\phi(x) = \tanh(\frac{d(x)}{\sqrt{2}\varepsilon})$ where $d(x)$ is the signed distance between point $x$ and $\Gamma$ (if $x$ is inside the surface then $d(x)$ is positive otherwise is negative) and $K = \sqrt{2}k_0$.

To solve for the minimization of energy we use the "BFGS Method" in the objective function

$$F(\phi) = E(\phi) + V^2 + A^2 \quad (10)$$

Where $V$ and $A$ are the difference of cell volume and area with their target cell volume and surface area respectively.

*5. Results*

The approach to predicting the stable shapes of sea urchins is to utilize the 6th order PDE method for surface parameterization which is coupled with a design optimization algorithm. The parameterization is achieved through the Fourier series representing the boundary conditions of the chosen PDE. The optimization is performed by solving a constrained optimization problem using an augmented Lagrange multiplier method [22] along with the Broyden-Fletcher-Goldfarb-Shanno (BFGS) method [23] whereby the objective function is taken to be that given in Equation (10).

With the above formulation, the optimization is started at some initially chosen point in the parameter space within the Fourier domain. The routine allows detecting the local minimum of the surface energy for a given value of the spontaneous curvature, sea urchin volume and surface area. To achieve this a starting value of spontaneous curvature, sea urchin volume, surfaces area and a starting set of values of Fourier modes for the design parameters of the PDE are chosen. The optimisation procedure then enables to locate a stationary state for the energy of the sea urchin. Hence for a given value of spontaneous curvature, once this initial stationary state is found the optimization is repeated by incrementing the volume until further stationary states are found.

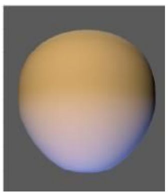


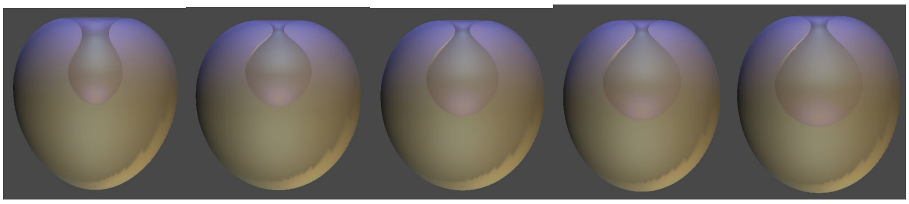
FIGURE 3 SAMPLE STATIONARY SEA URCHIN'S MODEL USING FOR NUMERICAL SIMULATIONS OF MORPHOGENESIS

| Figure | K | v | a |
|---|---|---|---|
| 3 | 0.01 | 0.55 | 11.39 |

TABLE 1. VALUES OF SPONTANEOUS CURVATURE, SEA URCHIN VOLUME AND SURFACE AREA FOR THE STATIONARY SHAPES SHOWN IN FIGURE 3.

Figure 3 shows sample stationary sea urchin's model obtained for a given value of spontaneous curvature, sea urchin volume and surface area. The parameter values taken for this simulation is shown in Table 1.

Note all the sea urchin shapes obtained in the simulations we have agreed to be verifiable. Interested reader is for example referred to [23]. For some basic knowledge reader can concern http://worms.zoology.wisc.edu/dd2



A B C D E

FIGURE 4 DIFFERENT STAGES DURING DEVELOPMENT OF BLASTULA PHASE OF A SEA URCHIN SHAPES FOR SPONTANEOUS CURVATURE OF 5.5

| Figure | E | v | a |
|---|---|---|---|
| 4(A) | 1.98 | 0.55 | 12.07 |
| 4(B) | 2.07 | 0.69 | 12.39 |
| 4(C) | 2.43 | 0.89 | 12.89 |
| 4(D) | 2.91 | 0.97 | 13.08 |
| 4(E) | 3.67 | 1.09 | 13.73 |

TABLE 2. VALUES OF SEA URCHIN VOLUME, SURFACE AREA AND BENDING ENERGY DURING BLASTULA PHASE SHOWN IN FIGURE 4.

Figure 4 shows some sample models obtained during development of blastula phase of a sea urchin with a given spontaneous curvature value. Here the spontaneous curvature value is taken to be 5.5.

Table 2 shows the various parameter values arrived during this simulation.

## 5. CONCLUSION

This paper has been concerned with the efficient shape parameterization of Blastulosphere in order to simulate their stable structures. This paper also investigates the possible use of "Partial Differential Equation Method" for representation geometry of biological shapes, morphological process and analysis and optimization. Surface design using PDE is a boundary value problem therefore these boundaries determine the shape of the surface. One attractive advantage of this method is its capability to generate smooth surfaces, to keep up continuity between the adjacent surface patches and the ability to control the shape globally with the design parameters besides being highly intuitive for the user in the design process. Our future work will include extending the shape parameterization methodology in order to furnish for complex geometry involving arbitrary topology changes.

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## 7. References:-

[1] M. I. G. Bloor and M J., Wilson, '"Generating blend surfaces using partial differential equation" Compute. Aided Des. Vol 21 No 3 pp 165-171, (1989)

[2] M. I. G. Bloor and M J., Wilson. "Using partial differential equations to generate free form surfaces." 'Compute. Aided Des. Vol 22,202-212 (1990)

[3] H. Ugail, M. I. G. Bloor and M J. Wilson. "Techniques for interactive design using the PDE method." ACM Transactions on graphics 18, 195-212 (1999)

[4] H. Ugail and M J. Wilson. "Efficient shape parameterization for automatics design optimization using a partial differential equation formulation." Elsevier Ltd. Doi:10.1016/S0045-7949(03)00321-3 (2003)

[5] S. Kubiesa and H. Ugail, M. J. Wilson: "Interative design using higher order PDEs." The visual Computer (2004) 20:68-693

[6] Hassan Ugail, Raja Noshad Jamil, Razvan Satnoianu; "Method of Numerical Simulation of Stable Structures of Fluid Membranes and Vesicles" WSEAS TRANSACTIONS on MATHEMATICS Issue 9, Volume 5, September 2006 ,1109-1114

[7] Q. Du, Chun and L. X. Wang: "A phase field approach in the numerical study of the elastic bending energy for vesicle membranes." Journal of computational physics 19 (2004), 450- — 4468

[8] Q. DU, C.LIU, R. Ryham, X. Wang: "Modeling the Spontaneous curvature effects in static cell membrane deformations by a phase field formulation." Communications on pure and applied analysis volume 1, Number 4, October 2002

[9]Alexander, V. Spirove: "Computer modeling of genes Expression and Morphogenetic movement in embryo development". In: Proceedings of the 1993 Summer Society of Computer Simulation Conference, Joel .Schoen (ed.). Boston, Massachusetts, 1993. P.185-191.

[10] A.V., Spirov , "Game of Morphogenesis: What Can We Learn from the Pattern-Form Interplay Models?" INTERNATIONAL JOURNAL OF BIFURCATIONS AND CHAOS, [Berkeley], 1998, 8, (5), 991-1001.

[11] Jian. J. Zhang and L. H. You;- "Fast Surface Modeling using 6th order PDE." Eurographics 2004 Volume 23 (2004) Number 3

[12] Byung , Jeffrey A. Reinbolt, Benjamin J. Fregly, Alan D. George:- "Parallel Decomposition Methods for Biomedical Optimization" G. Reiness's:- Lewis & Clark College Portland , Oregon USA http://www.lclark.edu/~reiness/neurobiology/Lectures

[13] F. W., Cummings :- "Apttern-surface interactive model of morphgenesis" J. theor. Biol. (1985) 137, 215-220

[14] F. W., Cummings "Aspects of growth and form" - Physica D, 79 (1994), 146-163.

[15] T. C. Lacalli and L.G.Harrison, :- "From gradient to segments: models for pattern formation in early Drosophila embryogenesis," Series in Devl. Biology, 2, (1991) 107-117.

[16] L.G. Harrison and M. Kolar:- "Coupling between reaction-diffusion prepattern and expressed morphogenesis, applied to desmids and dasyclads", - J. theor. Biol.v . (1988),, 130, 493-515.

[17] T. Lacalli.,- "Modeling the Drosophila pair-rule pattern by reaction-diffusion: gap input and pattern control in a 4-morphogen system," - J. theor. Biol., 144 (1990), 171-194.

[18] H. Du and H. Qin :- " Dynamic PDE-based surface design using geometric and physical constraints" Elsevier June 2004)

[19] R. Allena, A.-S. Mouronval, E. Farge and D. Aubry:- “Concurrent Simulation of Morphogenetic Movements in Drosophila Embryo”. 13th International Conference on Biomedical Engineering ICBME 2008 3–6 December 2008 Singapore

[20 ]Malcolm I. G. Bloor, Michael J. Wilson:- Local control of surfaces generated using partial differential equations. Computers & Graphics 18(2): 161-169 (1994)

[21] Sahlin P, Jo¨nsson H:- A Modeling Study on How Cell Division Affects Properties of Epithelial Tissues Under Isotropic Growth. PLoS ONE 5(7):e11750. doi:10.1371/journal.pone.0011750 (2010)

[22] D. M. Greig, Optimisation, Longman, London, 1980.

[23] W.H. Press, S.A. Teukolsky, W.T. Vetterling, and B.P. Flannery, Numerical Recipes in C, Cambridge University Press, UK, 1992.

[24] L.M. Angerer, R. C.Angerer Patterning the sea urchin embryo: gene regulatory networks, signaling pathways,and cellular interactions. Curr Top Dev Biol, 53:159–198 2003.