

Analytical Approach to Cell Geometry Description

P. Dabnichki¹ and A. Zhivkov²

Abstract: A novel method for geometric reconstruction of smooth pseudo-rotational objects based on elliptic functions is developed. Based on the apparatus of theta functions analytical expressions for the main geometric invariants are derived. Reconstruction of asymmetric and irregular objects is illustrated. The advantages of the proposed technique lay in the following: i) reconstruction is computationally very fast and would allow a qualitative change in the current research practices, i. e. real-time monitoring and analysis of the responses of large cell samples ii) the accuracy of the method is very high and can be flexibly varied iii) the method allows quantitative analysis as demonstrated by the derived analytical representation for the main geometric invariants. Potential applications to existing experimental techniques and fundamental theoretical issues in mathematical models in cell physiology are briefly discussed.

keyword: Elliptic functions, theta functions, cells, geometric reconstruction.

1 Introduction

Understanding the mechanical properties of cells is a very significant step to the understanding of blood circulation, tissue response to external loads and signals, remodelling processes to name but few. Certain types of cells in the living organisms are not physically connected within the tissue structure. So to a certain extent they function independently without a visible direct contact or detectable exchanges with other cells.

The most obvious examples are cartilage cells called chondrocytes, red blood cells – erythrocytes, white blood cells – leukocytes and trombocytes. Changes in the shape of these cells are induced by their status, functions or interaction with the surrounding media and hence could be used as an indicator for a variety of underlying processes and study of different pathways [Guilack, Sato, Stanford

and Brand (2000); Erickson, Alexopoulos and Guilack (2001)]. For example, study of the deformation of the white blood cells caused by external forces is expected to provide insight on how these cells flow through capillaries and reach different tissues [Hochmuth (2000)]. Cell response to external forces and internal stress distribution is an indicator for the integrity and viability of cartilage [Guilack (1995)]. A study of chondrocytes' response to loading [Jones, Ting-Beall, Lee, Kelley, Hochmuth and Guilak (1999)] found that the volumetric properties of osteoarthritic cartilage differ significantly in statistical from normal sample. However the selected measure is too simplistic – cells' height that provide very little further information on the nature of pathological changes in this particular condition. There is still a complete lack of quantitative measure to identify pathological against normal responses to external loading although a good study of [Kaspar, Seidl, Neidlinger-Wilke, Ignatius and Claes (2000)] presents some very interesting findings.

The relationship between cell deformation and the corresponding tissue changes has not been fully understood and one of the main reasons behind is the lack of accurate and reliable experimental data. Such data can only be obtained by non-direct, usually image based measuring techniques. That is why a powerful analytical apparatus is needed to allow a very fast quantitative assessment in the changes in the global geometrical characteristics of cells in real time. Such apparatus should be highly accurate and computationally fast in order to maximize the benefits of real time analysis.

One of the outstanding issues in describing cellular responses is the rate of exchange between cells and the surrounding environment and how this exchange affects their functions and viability. A necessary first step in successful analysis of cellular exchange is an accurate description of global geometric invariants including volume area, global curvatures. The aim of this work is to assess the potential for the introduction of methods for global analysis in cell mechanics research - in particular the use of elliptic functions. The novel method developed

¹ Department of Engineering, Queen Mary, University of London

² Department of Mathematics, Sofia University, Bulgaria.

is presented below.

2 Theta functions

It turns out that the solutions of some of the fundamental integrable differential equations arising in the classical mechanics can be usually expressed in terms of theta functions [Whittaker and Watson (1935)]. For example the classic equation of the harmonic oscillator $\ddot{x} = -\omega^2 x$ possess a general solution $x = A \cos(\omega t - \phi)$ with two arbitrary constants A and ϕ representing the amplitude and the phase shift of the oscillation respectively. So $\cos u$ is defined as a genus 0 theta function that is obviously periodic with a period 2π . There is a multitude of other very important applications of genus 0 theta functions an notable example being the heat diffusion equation.

The higher order theta functions, i.e. genus one or better known as elliptic functions, were introduced in the 19th century following the milestone works of some of the most distinguished mathematicians of the time – Bernoulli, Gauss, Abel, Jacobi and Legendre amongst them. Their introduction was needed in order to derive effective solutions of some more complex problems in classical mechanics such as the simple pendulum equation $\ddot{x} = -\sin x$, the rotation of a planet about its centre of gravity [Jacobi (1849)] or more recently the Lagrange's top equation [Gavrilov and Zhivkov (1998)]. In the following centuries the elliptic functions facilitated great advances in pure and applied mathematics [Lawden (1989)]. The most celebrated application of theta functions in modern mathematics is undoubtedly their use in the proof of the great Fermat theorem [Wiles (1995)].

Despite all these remarkable successes this powerful apparatus is far from being utilised to its full potential. A very promising area for applications of theta/elliptic functions – accurate geometric representation of rotational and pseudo-rotational bodies has not been explored. This is an area of a great significance in biological and medical research as biological objects such as human organs, micro-organisms or aquatic animals such as fish and sepia are more complicated for description and reconstruction compared to manmade objects such as machine parts. However, an important common feature of biological objects is that a large proportion of them represent smooth pseudo-rotational bodies that cannot be presented in closed analytical form. Accurate representation of biological objects is very rear as simplified reconstruction are the norm [Aritan, Dabnichki and

Bartlett (1997)]. A thorough review of papers devoted to theoretical and computational analysis of cells [Guilack and Mao (2000); Iglic, Vranic, Batista and Kralj-Iglic (2001)] show that as a rule cells are replaced with prime geometrical curves such as ellipses or spheroids and ellipsoids in three dimensional studies. Similar status is evident in studies of blood flow [Moore, Steinman and Ethier (2000)]. As it is claimed that cell membranes can undergo only relatively small strains of no more than four [Fung (1993)], most of the current approaches achieve similar order of reconstruction accuracy rendering them inappropriate. Furthermore closer analysis is needed in sub-cellular structure such as cell nucleus that sets even more stringent requirements towards the accuracy of the cell reconstruction [Caille, Thoumine, Tardy and Meister (2002)].

A natural resolution of the above issue can be achieved by the introduction of the theta functions in their more elaborate form known as Jacobi's functions. The importance of the Jacobi's functions defined below stems from the fact that they are closely related to circular and hyperbolic functions that have been proven extremely useful for the solution of fundamental problems in celestial mechanics, geometry, electrodynamics and many other fields [Lawden (1989)].

The four Jacobi's theta function defined below by their Fourier series are used in this work to describe the geometry of different cells:

$$\theta_0(z, q) := 1 + 2q \cos 2z + 2q^4 \cos 4z + 2q^9 \cos 6z + \dots,$$

$$\theta_1(z, q) := 1 - 2q \cos 2z + 2q^4 \cos 4z - 2q^9 \cos 6z + \dots,$$

$$\theta_2(z, q) := 2q^{\frac{1}{4}} \cos z + 2q^{\frac{9}{4}} \cos 3z + 2q^{\frac{25}{4}} \cos 5z + \dots,$$

$$\theta_3(z, q) := 2q^{\frac{1}{4}} \sin z - 2q^{\frac{9}{4}} \sin 3z + 2q^{\frac{25}{4}} \sin 5z + \dots.$$

Each function θ_n depends on the complex arguments u and q , $|q| < 1$. In order to ensure that the series represent real-valued theta functions, the following constrains are additionally imposed:

$$q \in \mathbb{R}, \quad 0 \leq q < e^{-\frac{\pi}{4}},$$

$$z = u \in \mathbb{R} \quad \text{or} \quad z = iv \in i\mathbb{R}, \quad i := \sqrt{-1}.$$

It is important to point out that the condition $|q| < 0.46$ assures exponentially fast convergence of all theta series and their derivatives of any order $\frac{d^n}{dz^n} \theta_n(z, q)$.

Particularly, we shall use the following ratios of thetas:

$$\Theta_1(u, v, q) := \frac{\theta_1(u, q) \theta_1(iv, q)}{\theta_0(u, q) \theta_0(iv, q)},$$

$$\Theta_2(u, v, q) := \frac{\theta_2(u, q) \theta_2(iv, q)}{\theta_0(u, q) \theta_0(iv, q)},$$

$$\Theta_3(u, v, q) := \frac{\theta_3(u, q) \theta_3(iv, q)}{i \theta_0(u, q) \theta_0(iv, q)}.$$

These functions are real-valued if u, v and q are real. In effect they represent a set of analytical coordinates for any point on the sphere:

$$\Theta_1(u, v, q)^2 + \Theta_2(u, v, q)^2 + \Theta_3(u, v, q)^2 \equiv 1 \quad (1)$$

and this statement also applies to ellipsoids.

Θ_1 , Θ_2 and Θ_3 have two independent semi-periods: π with respect to u and $\ln q$ with respect to v :

$$\Theta_1(u + \pi, v, q) = \Theta_1(u, v, q),$$

$$\Theta_2(u + \pi, v, q) = -\Theta_2(u, v, q),$$

$$\Theta_3(u + \pi, v, q) = -\Theta_3(u, v, q),$$

$$\Theta_1(u, v + \ln q, q) = -\Theta_1(u, v, q),$$

$$\Theta_2(u, v + \ln q, q) = \Theta_2(u, v, q),$$

$$\Theta_3(u, v + \ln q, q) = -\Theta_3(u, v, q).$$

Up to some non-significant constants, $\Theta_{1,2,3}(u, v, q)$ are equal to

$$\operatorname{sn}(u, q) \operatorname{sn}(iv, q), \quad \operatorname{cn}(u, q) \operatorname{cn}(iv, q), \quad \operatorname{dn}(u, q) \operatorname{dn}(iv, q)$$

respectively; sn , cn and dn stand for the classical Jacobi's elliptic functions.

The first derivatives of Θ_1 , Θ_2 and Θ_3 can be computed with the help of the following identities:

$$\begin{aligned} \frac{d}{dz} \frac{\theta_1(z, q)}{\theta_0(z, q)} &= \theta_2(0, q)^2 \frac{\theta_2(z, q)}{\theta_0(z, q)} \frac{\theta_3(z, q)}{\theta_0(z, q)}, \\ \frac{d}{dz} \frac{\theta_2(z, q)}{\theta_0(z, q)} &= -\theta_1(0, q)^2 \frac{\theta_3(z, q)}{\theta_0(z, q)} \frac{\theta_1(z, q)}{\theta_0(z, q)}, \\ \frac{d}{dz} \frac{\theta_3(z, q)}{\theta_0(z, q)} &= \theta_0(0, q)^2 \frac{\theta_1(z, q)}{\theta_0(z, q)} \frac{\theta_2(z, q)}{\theta_0(z, q)}. \end{aligned} \quad (2)$$

Using again these formulas, we compute the second, third, etc. derivatives of the thetas.

3 The smooth ellipsoid as a model of the cell

A natural first step of the geometrical reconstruction of a stand alone cell is its approximation with a smooth three-axial ellipsoid E . This of course places that assumption that the cell is an ellipsoid or an equivalent geometric shape – this holds for biological cells. Suppose that some coordinates

$$(x_{1,1}, x_{2,1}, x_{3,1}), (x_{1,2}, x_{2,2}, x_{3,2}), \dots, (x_{1,N}, x_{2,N}, x_{3,N})$$

of N points $(x_{1,k}, x_{2,k}, x_{3,k})$ lying on the cell surface are experimentally derived. Then the analytical equation of the ellipsoid E in the same reference system can be presented in the form

$$E : A_1 x_1^2 + A_2 x_2^2 + A_3 x_3^2 + A_4 x_1 x_2 + A_5 x_1 x_3 + A_6 x_2 x_3 + A_7 x_1 + A_8 x_2 + A_9 x_3 + A_{10} = 0.$$

The coefficients A_s in the above equation can be explicitly computed from the quadratic form

$$\begin{aligned} &\sum_{k=1}^N \left(A_1 x_{1,k}^2 + A_2 x_{2,k}^2 + A_3 x_{3,k}^2 + A_4 x_{1,k} x_{2,k} + \dots + A_{10,k} \right)^2 \\ &= \sum_{i,j=1}^{10} c_{ij} A_i A_j, \end{aligned}$$

which is positively defined as a sum of N squares. Let λ_{\min} be the smallest eigenvalue of the matrix $C := (c_{ij})_{i,j=1}^{10}$. Then we define $A := (A_1, A_2, \dots, A_{10})$ to be the eigenvector of the matrix C , corresponding to the eigenvalue λ_{\min} : $CA = \lambda_{\min} A$.

Let us denote by μ_1 , μ_2 and μ_3 the eigenvalues of the matrix

$$A = \begin{pmatrix} A_1 & A_4/2 & A_5/2 \\ A_4/2 & A_2 & A_6/2 \\ A_5/2 & A_6/2 & A_3 \end{pmatrix}$$

and let $\xi_s = (\xi_{s1}, \xi_{s2}, \xi_{s3})^t$ are the correspondent eigenvectors. Hence $A \xi_s = \mu_s \xi_s$, where all the eigenvectors are of unit length: $\|\xi_s\| = 1$, $s = 1, 2, 3$. Then the equation of the ellipsoid takes the form

$$\begin{aligned} 0 &= A_1 x_1^2 + A_2 x_2^2 + A_3 x_3^2 + A_4 x_1 x_2 + A_5 x_1 x_3 \\ &\quad + A_6 x_2 x_3 + A_7 x_1 + A_8 x_2 + A_9 x_3 + A_{10} \\ &= \sum_{j=1}^3 \mu_j \left(\sum_{s=1}^3 \xi_{js} x_s + \eta_j \right)^2 - \eta_0 \\ &= \text{constant} \cdot \left(\frac{y_1^2}{I_1} + \frac{y_2^2}{I_2} + \frac{y_3^2}{I_3} - 1 \right), \end{aligned}$$

i. e.

$$E : \frac{y_1^2}{I_1} + \frac{y_2^2}{I_2} + \frac{y_3^2}{I_3} = 1, \tag{3}$$

$$I_1 = \frac{\eta_0}{\mu_1}, \quad I_2 = \frac{\eta_0}{\mu_2}, \quad I_3 = \frac{\eta_0}{\mu_3}.$$

This is a classical procedure which transforms the moment of inertia tensor to its principal axes. Without loss of generality we may consider that the main inertia moments $I_{1,2,3}$ satisfy the condition

$$0 < I_1 \leq I_2 \leq I_3.$$

This can always be met by a re-ordering of the coordinates y_1, y_2 and y_3 .

Therefore the coordinate solution of equation (3) can be derived in terms of elliptic theta functions as

$$\begin{aligned} y_1 &= \sqrt{I_1} \Theta_1(u, v, q), & I_1 &= R^2 (\theta_2(0, q)^4 - \lambda), \\ y_2 &= \sqrt{I_2} \Theta_2(u, v, q), & I_2 &= R^2 (\theta_1(0, q)^4 - \lambda), \\ y_3 &= \sqrt{I_3} \Theta_3(u, v, q), & I_3 &= R^2 (\theta_0(0, q)^4 - \lambda), \end{aligned} \tag{4}$$

where the constants R, q and λ define the form of the ellipsoid E ; $u \in [0, 2\pi)$ and $v \in [0, -\ln q)$ are the surface coordinates defining uniquely any point on the ellipsoid E . Explicitly,

$$R^2 \lambda = I_3 - I_1 - I_2 \quad (\text{defines } R^2 \lambda),$$

$$\frac{I_1 + R^2 \lambda}{I_2 + R^2 \lambda} = \frac{\theta_2(0, q)^4}{\theta_1(0, q)^4} \quad (\text{defines } q),$$

$$I_3 = R^2 (\theta_0(0, q)^4 - \lambda) \quad (\text{defines } R > 0 \text{ and } \lambda).$$

According to the signs of $y_1(u, v), y_2(u, v)$ and $y_3(u, v)$, the ellipsoid E can be divided into 8 parts

$$(+++), (++)-, \dots, (---) :$$

Recall that correspondingly

$$\begin{aligned} \Theta_1(u, v, q) &= 0 \text{ if } v = \frac{n}{2} \ln q, \\ \Theta_2(u, v, q) &= 0 \text{ if } u = \frac{2n+1}{2} \pi, \\ \Theta_3(u, v, q) &= 0 \text{ if } u = n\pi \end{aligned}$$

for $n = 0, \pm 1, \pm 2, \dots$, and this defines the zeroes of $y_{1,2,3}$.

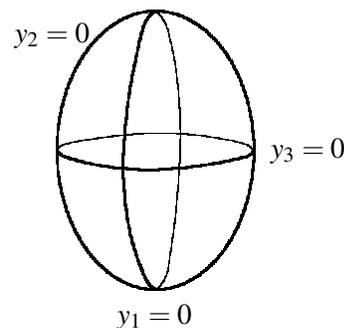


Figure 1 : The 8 parts of the ellipsoid.

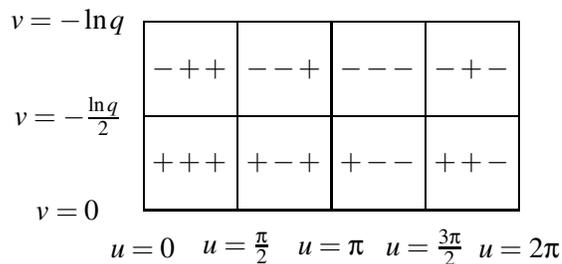


Figure 2 : The (u, v) -parameterization of the ellipsoid.

4 Asymmetric cells

Varying the coefficients R_0, R_1, R_2, \dots in the form

$$\begin{aligned} R &= R_0 + R_1 \cos u + R_2 \sin u + R_3 \cos w + R_4 \sin w \\ &+ R_5 \cos u \cos w + R_6 \cos u \sin w + R_7 \sin u \cos w \\ &+ R_8 \sin u \sin w + \dots \\ &+ R_j \cos nu \cos kw + R_{j+1} \cos nu \sin kw \\ &+ R_{j+2} \sin nu \cos kw + R_{j+3} \sin nu \sin kw + \dots, \end{aligned}$$

$$w := -\frac{\pi v}{\ln q},$$

we can obtain all possible asymmetric cells.

Next examples illustrate correspondingly (i) a concave blood cell, (ii) a rough cell, (iii) and (iv) are two different asymmetric cells: Combinations of the above shape could represent every possible type of cells. The more important issue is whether essential quantitative assessment could be undertaken by applying theta functions.

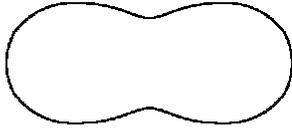


Figure 3 : A concave blood cell: $q = 0.02, \lambda = 0, R = 2 - \cos 2u$.

All the important geometric invariants can be explicitly formulated. It should also be added that these presentations allow direct high-speed computation of those invariants. Some of the most important ones are described below.

The surface area of any type of cell can be obtained from

$$S = \iint_{\substack{0 \leq u < 2\pi \\ 0 \leq v < -\ln q}} dS = \iint_{\substack{0 \leq u < 2\pi \\ 0 \leq v < -\ln q}} \sqrt{A^2 + B^2 + C^2} du dv, \quad (5)$$

where

$$A = \frac{\partial y_2}{\partial u} \frac{\partial y_3}{\partial v} - \frac{\partial y_3}{\partial u} \frac{\partial y_2}{\partial v}, \quad B = \frac{\partial y_3}{\partial u} \frac{\partial y_1}{\partial v} - \frac{\partial y_1}{\partial u} \frac{\partial y_3}{\partial v},$$

$$C = \frac{\partial y_1}{\partial u} \frac{\partial y_2}{\partial v} - \frac{\partial y_2}{\partial u} \frac{\partial y_1}{\partial v},$$

and (2) has to be used in order to calculate $\frac{\partial y_i}{\partial u}$ and $\frac{\partial y_i}{\partial v}$.

The volume of a cell can be expressed as

$$V = \iiint_{\substack{0 \leq u < 2\pi \\ 0 \leq v < -\ln q}} \frac{1}{3} (y_1 A + y_2 B + y_3 C) dudv.$$

Recall that the local geometry of the cell is defined by the first and second quadratic forms $g_{11} du^2 + 2g_{12} dudv +$

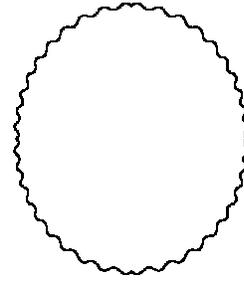


Figure 4 : A rough cell: $q = 0.03, \lambda = -2, R = 4 + \frac{1}{10} \sin 40u$.

$g_{22} dv^2$ and $b_{11} du^2 + 2b_{12} dudv + b_{22} dv^2$,

$$g_{11} = \sum_{s=1}^3 \left(\frac{\partial y_s}{\partial u} \right)^2, \quad g_{12} = \sum_{s=1}^3 \frac{\partial y_s}{\partial u} \frac{\partial y_s}{\partial v}, \quad g_{22} = \sum_{s=1}^3 \left(\frac{\partial y_s}{\partial v} \right)^2,$$

$$b_{11} = \frac{1}{\sqrt{A^2 + B^2 + C^2}} \left(A \frac{\partial^2 y_1}{\partial u^2} + B \frac{\partial^2 y_2}{\partial u^2} + C \frac{\partial^2 y_3}{\partial u^2} \right),$$

$$b_{12} = \frac{1}{\sqrt{A^2 + B^2 + C^2}} \left(A \frac{\partial^2 y_1}{\partial u \partial v} + B \frac{\partial^2 y_2}{\partial u \partial v} + C \frac{\partial^2 y_3}{\partial u \partial v} \right),$$

$$b_{22} = \frac{1}{\sqrt{A^2 + B^2 + C^2}} \left(A \frac{\partial^2 y_1}{\partial v^2} + B \frac{\partial^2 y_2}{\partial v^2} + C \frac{\partial^2 y_3}{\partial v^2} \right).$$

Finally, the solutions $\mu = \mu_1$ and $\mu = \mu_2$ of the quadratic equation

$$(b_{11} - \mu g_{11})(b_{22} - \mu g_{22}) = (b_{12} - \mu g_{12})^2$$

are the main curvatures, $\mu_1 \mu_2$ is the scalar curvature and $\mu_1 + \mu_2$ is the mean curvature.

5 Discussion

An advanced technique for geometric reconstruction and analysis of cell interactions is proposed. The advantages of the proposed technique lay in the following:

- geometric reconstruction is computationally very fast, highly accurate and it is applicable to non-symmetric objects. This would allow a qualitative change in the current research – namely to monitor and analyse the response of large cell samples allowing more representative and accurate conclusions
- the accuracy of the method is very high and can be flexibly adjust according to the requirements of a particular task without significantly affecting the computational speed

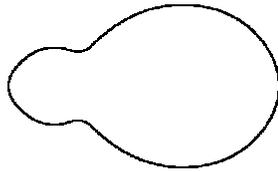


Figure 5 : An asymmetric cell: $q = 0.02, \lambda = 0, R = 2 - \sin u - \cos 2u$.

- the method allows real-time quantitative analysis as demonstrated by the derived expressions for the main geometric invariants.

The three most important characteristics described above allow the introduction of quantitative global analysis in cells' response to external signals and loads. One extremely important application is the accurate estimate of matter exchanged by chondrocytes during mechanical loading and the associated change in the surface area that will be accomplished in a very near future.

The reader can notice in the previous sections that the experimental data input are considered error-free. It is obviously not the case in real situations. However, this issue is beyond the scope of the current work as it is not specific to the proposed apparatus. Existing current techniques for reduction in the error of data measurement or conditioning of the signal input can be utilised similarly to other signal processing applications. There are also a number of theoretical methods for approximation of the input data coordinates.

Below we outline a number of problems that the proposed apparatus is to be applied. They can be divided into two categories – practical improvements in existing experimental techniques and application to fundamental theoretical issues.

We would like to point out that the developed apparatus could be immediately applied in existing observational techniques such as confocal or electronic microscopy as these techniques already utilise computers for data processing and their reconstruction algorithms can be easily modified. Similarly the apparatus can be applied for improved image reconstruction of blood vessels of MRI scans [Moore, Steinman and Ethier (1998)] or CT-scans

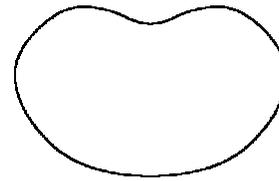


Figure 6 : Second asymmetric cell: $q = 0.04, \lambda = 0, R = 2 - 1.5 \cos u$.

of bones. Even the accuracy of the computation the material parameters of well-established techniques such as micro-pipette aspiration [Cheng, Hartemink, Hartwig and Forbes Dewey Jr (2000)] can be further improved and fine-tuned.

The theoretical issues that the authors intend to tackle are: i) mass exchange between red blood cells and endothelial cells [Dong (2000)] ii) analytical method for establishment the homeostatic shape of chondrocytes iii) non-isochoric interactions of the blood cell and capillaries. The technique allows the development of sophisticated models for dynamic interactions between the cells and the surrounding environment.

The technique allows the development of sophisticated models for dynamic interactions between the cells and the surrounding environment. It is obvious that a perceived shortcoming is that this apparatus cannot deal with edges or similar irregularities. This is not really the case as such irregularities may be approximated with an any desirable accuracy as only the number of the curves will increase. Similar approach has already been applied in signal processing where Fourier transformation is applied to irregular signals – this in effect is the built-in capability of the apparatus to act as simultaneously as a filter.

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