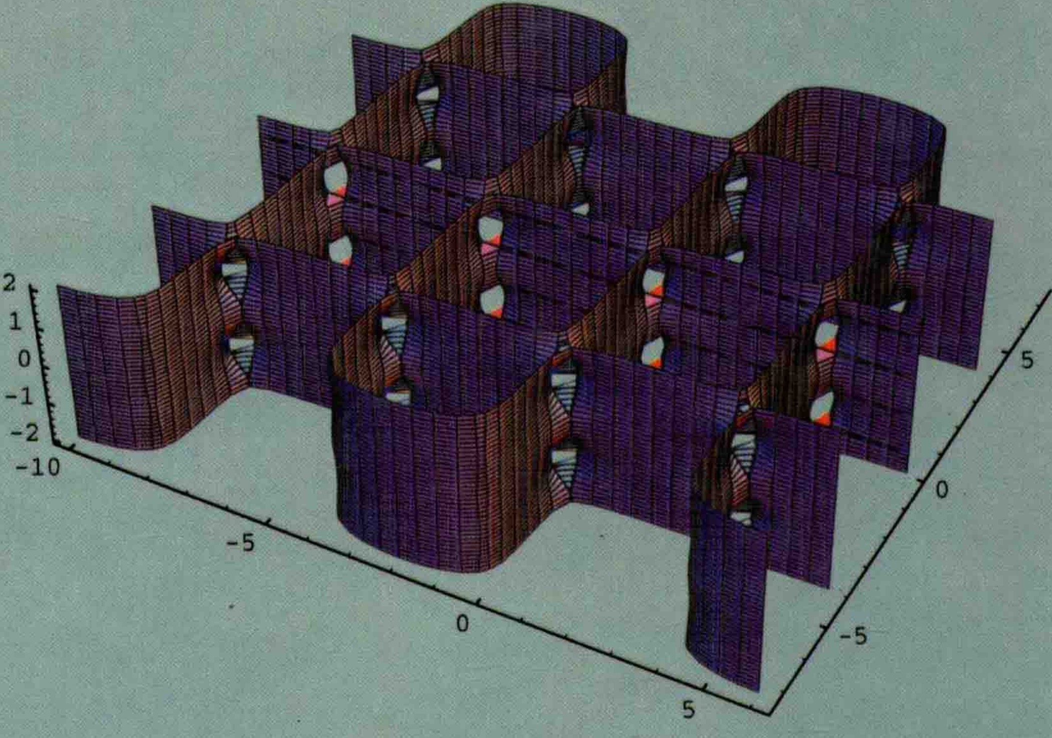
BIOMATHEMATICS

Mathematics of Biostructures and Biodynamics



Sten Andersson
Kåre Larsson
Marcus Larsson
Michael Jacob

Elsevier

BIOMATHEMATICS

Mathematics of Biostructures and Biodynamics

Sten Andersson
Sandviks Forskningsinstitut, S-380 74 Löttorp, Sweden

Kåre Larsson
KL Chem AB, S-237 34 Bjärred and Camurus Lipid Research, S-223 70 Lund, Sweden

Marcus Larsson
Lund University, Department of Clinical Physiology, S-214 01 Malmö, Sweden

Michael Jacob
Department of Inorganic Chemistry, Arrhenius Labatory, University of Stockholm, S-106 91 Stockholm, Sweden

1999
Elsevier
Amsterdam – Lausanne – New York – Oxford – Shannon – Singapore – Tokyo

ELSEVIER SCIENCE B.V.
Sara Burgerhartstraat 25
P.O. Box 211, 1000 AE Amsterdam, The Netherlands

© 1999 Elsevier Science B.V. All rights reserved.

This work and the individual contributions contained in it are protected under copyright by Elsevier Science, and the following terms and conditions apply to its use:

Photocopying
Single photocopies of single chapters may be made for personal use as allowed by national copyright laws. Permission of the Publisher and payment of a fee is required for all other photocopying, including multiple or systematic copying, copying for advertising or promotional purposes, resale, and all forms of document delivery. Special rates are available for educational institutions that wish to make photocopies for non-profit educational classroom use.

Permissions may be sought directly from Elsevier Science Rights & Permissions Department, PO Box 800, Oxford OX5 1DX, UK; phone: (+44) 1865 843830, fax: (+44) 1865 853333, e-mail: permissions@elsevier.co.uk. You may also contact Rights & Permissions directly through Elsevier's home page (http://www.elsevier.nl), selecting first 'Customer Support', then 'General Information', then 'Permissions Query Form'.

In the USA, users may clear permissions and make payments through the Copyright Clearance Center, Inc., 222 Rosewood Drive, Danvers, MA 01923, USA; phone: (978) 7508400, fax: (978) 7504744, and in the UK through the Copyright Licensing Agency Rapid Clearance Service (CLARCS), 90 Tottenham Court Road, London W1P 0LP, UK; phone: (+44) 171 631 5555; fax: (+44) 171 631 5500. Other countries may have a local reprographic rights agency for payments.

Derivative Works
Tables of contents may be reproduced for internal circulation, but permission of Elsevier Science is required for external resale or distribution of such material. Permission of the Publisher is required for all other derivative works, including compilations and translations.

Electronic Storage or Usage
Permission of the Publisher is required to store or use electronically any material contained in this work, including any chapter or part of a chapter.

Except as outlined above, no part of this work may be reproduced, stored in a retrieval system or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without prior written permission of the Publisher.
Address permissions requests to: Elsevier Science Rights & Permissions Department, at the mail, fax and e-mail addresses noted above.

Notice
No responsibility is assumed by the Publisher for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions or ideas contained in the material herein. Because of rapid advances in the medical sciences, in particular, independent verification of diagnoses and drug dosages should be made.

First edition 1999

Library of Congress Cataloging in Publication Data
A catalog record from the Library of Congres has been applied for.

ISBN: 0 444 50273 4

Transferred to digital printing 2005

Printed and bound by Antony Rowe Ltd, Eastbourne

BIOMATHEMATICS

Mathematics of Biostructures and Biodynamics

Contents

Chapter 1

Chapter 2

Chapter 3

Chapter 4

Chapter 5

Chapter 6

Chapter 7

Chapter 8

Chapter 9

Chapter 10

Chapter 11

Chapter 12

Chapter 13

Chapter 14

Chapter 15

Appendix 1

Appendix 2

Appendix 3

Appendix 4

Appendix 5

Appendix 6

Appendix 7

Appendix 8

Appendix 9

1 Introduction

There is no permanent place in the world for ugly mathematics [Hardy,1].

This book deals with the shape of cells and cell organelles in plants and animals, and changes of shape associated with various life processes. The cell membranes and cytoskeleton proteins build these shapes based on physical forces. A mathematical/geometrical description of cellular and molecular shapes is presented in this book, and the biological relevance is discussed in the epilogue. We demonstrate here new mathematics for cellular and molecular structures and dynamic processes.

Life began in water, and every single function of life takes place in an aqueous environment. A profound way of classification in chemistry is the relation and interaction between molecules, or groups within molecules, and water. Molecules (or parts of molecules) can attract water in which case they are called *hydrophilic*. As the opposite extreme they can strive to avoid water; these molecules or molecular parts are termed *hydrophobic*. Most biomolecules possess both these properties; they are *amphiphilic*. This is a fundamental principle which determines the organisation of biomolecules - from the folding of peptide chains into native structures of proteins, to self-assembly of lipid and protein molecules into membranes. One consequence of the existence of these two media is that the interface between them define surfaces that tend to be closed. The lipid bilayer of membranes, for example, always form closed surfaces; the hydrocarbon chain core is never exposed to water. The curvature of these surfaces is an important concept in order to understand structural features above the molecular level. Surface and colloid science deals with forces involved in formation of such organisations. The behaviour of the colloidal state of matter involves van der Waals interaction, electrostatic forces, so-called hydration forces and hydrophobic forces. The colloidal level of structure extended towards curvature of surfaces and finite periodicity is a main theme in our book. These concepts are seldom considered in molecular biology.

Our present understanding of the cell membrane dates back to Luzzati's classical work from 1960 [2], where the liquid character of the hydrocarbon chains in liquid-crystalline lipid-water phases with the combination of long-range order with short-range disorder first were revealed. Another important aspect was introduced by Helfrich [3]; the curvature elastic energy. Long time ago, two of us [4] proposed the idea that a bilayer conformation analogous to that of cubic phases might occur in cell membranes. Phase transitions in three dimensions, obtained by exposure of membrane lipids to general anaesthetic agents, for example, were interpreted as experimental evidence [5]. These aspects were summarised in a monograph - The Language of Shape [6] - focusing on the role of curvature in membranes. Cubic lipid-water phases and cubic cell membrane assemblies were described as infinite periodic minimal surfaces (IPMS). Some thousand examples where the membrane is folded into a three-dimensional aggregate were shown to be cubic structures consistent with the three fundamental IPMS (the P-, D- and G-surface). Here we propose that the occurrence of perfect cubic symmetry of membrane assemblies reflects a vegetative state with lack of concentration gradients, resulting in an equilibrium-like situation. We conclude that active states of membrane systems, such as the endoplasmatic reticulum, are far from a compositional equilibrium, and therefore exhibit systematic variations of curvature. Such active states of membrane organisations are characterised based on the new mathematics introduced here.

The IPMS description reflects a static structure and might be regarded as a time-averaged conformation of the bilayer. Recently we introduced a description of the lipid bilayer of membranes based on nodal surfaces of standing wave conformations [7,8]. We consider this description to be significant to cellular phenomena, providing a true description of the dynamic character of cell membranes. The mathematical basis of the wave dynamics is extended in this book. We consider this feature to be of utmost importance in cell membrane physiology, providing space-time relations.

Cell membranes exhibit lipid bilayer states on the border towards a transition into a reverse type of structure (in three dimensions corresponding to phase transitions from lamellar to cubic or reverse hexagonal lipid-water phases). This tendency results in a high inner packing pressure of the bilayer, and therefore increases the elastic rigidity of the lipid bilayer. The wave motions of the bilayer are related to this elastic rigidity. Membrane-embedded enzymes responsible for lipid synthesis/modification can utilise the inner packing pressure as an on/off switch to control membrane lipid composition. This is an example of shape control *via* physical properties. The mathematical wave description reflects the dynamics of shape.

Another important feature of the cell membranes is their control of topology in the cell - separation of the inside and the outside. Considering any cell in our body and moving backwards in time via the embryo and through earlier generations down the evolution, the DNA has never been exposed to the outside world. There is always a membrane enveloping DNA in all forms of life, as we know them. A closed membrane providing shape and topology is thus a necessity for life. Its implicit expression in DNA is a challenging question, which we will consider in the epilogue.

There are hundreds of journals in molecular biology today dealing with structure and function. In our interdisciplinary approach we can only deal with some basic principles behind shape and shape changes. In our description of vesicle traffic between cellular compartments, for example, we apply only mathematics of lipid bilayers with varying curvature. We are aware of the numerous studies which have demonstrated involvement of for example kinesin in the endoplasmatic reticulum and of dynein in the Golgi structure. Our model of cell membrane dynamics and morphology, although ignoring the role of microtubuli, still gives a description consistent with reality. This might be due to the redundancy in biology; systems working in parallel to guarantee functional safety. Evidence is also given for the occurrence of mechanical waves at the axon membrane, with a conformational transition accompanying the electrical pulse. Finally by applying these new mathematics it has been possible to derive the structure of the surface film lining the lung alveoli.

We describe the lipid bilayer of cell membranes by surfaces located at the middle of the bilayer. The liquid-like hydrocarbon chains extend about 15 - 20 Å from this surface, and they might be compared with the delocalised electrons forming molecular surfaces. It is in this context tempting to go further in this analogy, perhaps to speculate on the possibility of quantum phenomena with phonons involved in the lipid bilayer motions.

In order to derive the various cell structures discussed in this book the following new tools/concepts have been used:

The *exponential scale* [9], which was developed to describe shapes of bodies like polyhedra, crystals, or anything that may be described with faces. Structures, crystal structures, symmetries, rod structures and molecules are also conveniently described.

The symmetry and structure of lipid membranes in confined space, like a cubosome, follow the electron densities of smaller molecules, like B_4H_4 and $B_{12}H_{12}$. We propose such lipid structures also have a standing wave behaviour - quantized or not. We describe this analogy of the quantized space and the lipid space with the exponential scale. We find great parts of these mathematics to be closely related to shapes in biology.

The *Gaussian distribution function* (GD) - a special case of the exponential scale - which is also known as the error function. It is used to describe diffusion, and it is also the ground state solution for the Schrödinger harmonic oscillator. We use the GD function to generate finite periodicity to describe structures like the cubosomes. We use the GD function to describe *biological motion* and we use the related Hermite operator to describe periodic biological motion. Examples are the flagella motion, the motor proteins and cell division. The fractal growth of a tree and the formation of icosahedral symmetry of virus are other examples.

We describe transportation with exponential functions. We describe budding and docking of vesicles, the endoplasmatic reticulum and the Golgi machine, holes in double membranes, the nuclear pore complex, and much more.

The GD-function is used here to define surfaces of the condensed state of cellular biomolecules. To illustrate this approach let us again consider a lipid bilayer with water on each side. Most of the lipid constituents have very low solubility (down to 10^{-12} M), which varies with environmental factors, such as pH and present ions. We are dealing with non-equilibrium conditions, with lipid molecules either moving inwards to condensate at the surface, or moving out into the water phase from the surface. The molecular distribution at the surface follows the GD function. Such concentration changes may even result in transient shape changes of cell membranes.

The *standing wave dynamic conformation of membranes* is a third new concept we apply in order to describe membrane shape. As mentioned earlier the membrane assemblies exhibiting cubic symmetry can be described as IPMS when the conformation is averaged over time but the wave character provides information on dynamic membrane processes.

Readers who directly want to see the biological relevance of this approach can start with chapters 8, 13 and 14 and later read the earlier chapters focusing on the mathematics. For readers who lack a mathematical background, the basic concepts we are using are introduced in the appendices. The use of Mathematica in the calculations is shown with examples in appendix 9.

References 1

1. G.H. Hardy; *A MATHEMATICIAN'S APOLOGY,* Cambridge University press, 1976, page 85.

2. V. Luzzati, H. Mustacchi, A. Skoulios, and F. Husson, Acta Cryst. **13** (1960) 660.

3. W. Helfrich, Z. Naturforsch. **A28** (1973) 693.

4. K. Larsson and S. Andersson, Acta Chem Scand. **B40** (1986) 1.

5. K. Larsson, Langmuir **4** (1988) 215.

6. S. Hyde, S. Andersson, K. Larsson, Z. Blum, T. Landh, S. Lidin and B. Ninham; *THE LANGUAGE OF SHAPE,* Elsevier, Amsterdam, 1997.

7. M. Jacob, K. Larsson and S. Andersson, Z. Kristallogr. **212** (1997) 5.

8. K. Larsson, M. Jacob and S. Andersson, Z. Kristallogr. **211** (1996) 875.

9. M. Jacob and S. Andersson; T*HE NATURE OF MATHEMATICS AND THE MATHEMATICS OF NATURE,* Elsevier, Amsterdam, 1998.

2 Counting, Algebra and Periodicity - the Roots of Mathematics are the Roots of Life

All things are numbers [Pythagoras,1].

Using simple counting, or algebra, we show the principles of periodicity, which is just using roots, number, or planes in space. We also show you what sine is.

With counting we make saddles move in bilateral or screw repetition. We continue in that way and show that fundamental mathematics is built of planes, and go from a molecule to a cubosome, which is an example of how symmetry shows up in a 3D space of just numbers.

We show how cubic surfaces nucleate from the simplest of saddles and planes.

We show how to move a surface or a cubosome in space.

We show how to derive the nodal surface geometry from algebra - or just by counting.

2.1 Counting and Sine

We assume mathematics used by Nature may be described in simple terms.

We start from the beginning;

x=1 is a plane in space, and so is x=2. With such planes we formulate our first equation, which also is an example of the fundamental theorem of algebra.

$$(x-1)(x-2)(x-3)(x-4)=0 \qquad 2.1.1$$

This operation we call *counting* and we want to see what it means in 3D. The roots are 1, 2, 3 and 4. We see in figure **2.1.1** the planes, and we discover that counting - put together in form of multiplication into a product - is a beautiful way to get periodicity. Which so far is finite.

We presume Nature may be described by counting positive numbers.

For reasons of convenience we shall sometimes in the description below use zero and negative numbers, but in every case it is possible to make a parallel transformation to the positive part of space as shown below with examples.

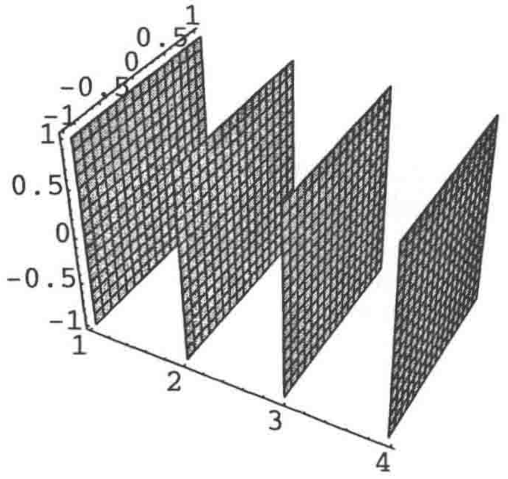


Figure 2.1.1 Periodicity from the fundamental theorem of algebra.

Equation *2.1.1* is the fundamental theorem of algebra, and Euler realised that this is really the same as sine - using an infinite product. 1, 2, 3 and 4 are the roots of the equation, and also the origin to periodicity. For comparison we give sinπx=0 in figure **2.1.2**.

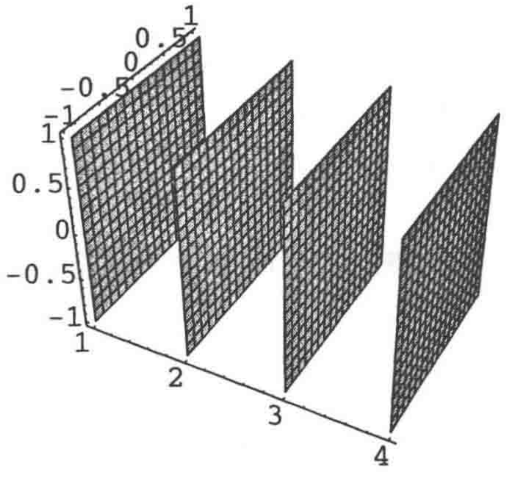


Figure 2.1.2 Periodicity from sine.

Below we give the formula in equation *2.1.2*, from Euler for the infinite products, which he showed was identical with the power expansion of sin(x) (an alternative definition). This definition of the circular functions which uses infinite products is attractive since it brings in the translation.

$$\sin x = x\left(1-\frac{x^2}{\pi^2}\right)\left(1-\frac{x^2}{2^2\pi^2}\right)\left(1-\frac{x^2}{3^2\pi^2}\right)\cdots \qquad 2.1.2$$

Rearranging formula *2.1.2* into *2.1.3* it becomes clear that sine is identical to the fundamental theorem of algebra of an infinite number of terms [2]. The roots of algebra are the nodes of periodicity - or the wave functions.

$$\sin \pi x = \frac{\pi}{(n!)^2}x(x^2-1)(x^2-4)(x^2-9)\ldots(x^2-n^2) \qquad 2.1.3$$

2.2 Three Dimensions; Planes and Surfaces, and Surface Growth

From equation *2.1.3* we take two of the roots and extend them to three dimensions in the following equations.

$$x^2-1=0 \qquad 2.2.1$$

$$y^2-1=0 \qquad 2.2.2$$

$$z^2-1=0 \qquad 2.2.3$$

The planes are found in the corresponding figures **2.2.1-3**.

If we, in equation *2.2.4* add two of the equations, the planes collaborate to form a cylinder, see figure **2.2.4**.

$$x^2+y^2-1=0 \qquad 2.2.4$$

And if we add all three equations, six planes collaborate to form the sphere in figure **2.2.5**.