Theoretical Biophysics: Projects

D.W. Heermann

Winter term 2010-2011

Course Organizational Information

- Study groups of 2-3 people
- The groups should meet about once a week
- Report due the last week of the semester
- Aim:
  - Develop intuition into biophysical problem solving
  - Develop skill in modelling
  - Get first experience of what research is all about
- Send me an email with your choice of a project you would like to tackle (indicate your preference with whom you would like to work with). Email due by the end of the week (Oct 15.)
- I will assemble groups and connect people
- Credits
  - Option I: Grading will be based on the handed in report
  - Option II: Oral exam (30 min)
- Songling Li will assist you

Course Organizational Information

- Hand-written submissions will not be accepted.
- Organize the report clearly.
- Integrate the graphs, diagrams, and other results into the report.
- I expect a report in a style of writing just like a journal article or a thesis.
- You must provide explicit written references to the sources you used.
- Use Latex.
- NO LATE REPORT ACCEPTED.

- Capillary network formation during tissue differentiation. A mechano-biological model

Capillary network formation during tissue differentiation. A mechano-biological model

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Abstract— **Angiogenesis, the formation of new capillaries from pre-existing vessels, plays a critical role during bone regeneration and repair. In addition to an appropriate mechanical environment, sufficient supply of oxygen and nutrients is critical for bone formation.**

Mechano-biological models have been previously used to predict the time course of the differentiation process with the mechanical environment as the only regulator of cell activity. Here we propose a mechano-biological model for tissue differentiation where cell activity is regulated by both the local mechanical environment and the local vascularity. Results show a significant effect of the morphology of the new capillary network on bone formation and heterogeneous distributions of cells similar to those seen in histological studies.

Keywords—**Angiogenesis, blood vessel formation, capillary network, tissue differentiation, mechano-regulation, mechanobiology.**

I. INTRODUCTION

During the last decades, the effect of mechanical loads on bone formation and bone repair has attracted much attention. Several mechano-regulation theories have been proposed relating mechanical loads and tissue differentiation [1, 2, 3] which have been implemented in computer models to successfully reproduce some of the main aspects of the bone regeneration process [4, 5, 6, 7, 8].

However, none of the above mentioned models have considered angiogenesis. This refers to the formation of new capillaries from pre-existing vessels and plays a fundamental role during bone formation. Blood vessels supply oxygen and nutrients which are essential for the proliferation and survival of cells of high metabolic demand, such as osteoblasts. Osteogenic precursor cells in regions of poor vascularity have been shown to follow a chondrogenic rather than an osteogenic pathway [98] and inhibition of blood vessel growth has been shown to inhibit fracture healing in rats [10].

Geris et al. [11] took account of this process in a mathematical model for tissue differentiation to simulate fracture healing. They used endothelial cell density as a continuum variable that evolved according to a set of reaction-diffusion equations. Although their work represents the only attempt to include angiogenesis in mechanobiological models, their approach does not provide detailed information of the morphology of the capillary network. This may be important because oxygen diffusion is limited to 100-200 µm from capillary vessels [12] and therefore, the organization of the capillaries in the regenerating tissue may play a fundamental role during tissue differentiation.

The objective of this work was to develop a mechanobiological model for blood vessel growth and tissue differentiation to examine the influence of capillary network formation during tissue repair. We hypothesized that capillary network dynamics influences the regeneration of bone. We tested this hypothesis in a model of a bone/implant interface under shear. If the hypothesis is confirmed, it would suggest that mechanobiological simulations of tissue differentiation could be improved by considering the effect of oxygen supply by the capillary network.

II. MATERIALS AND METHODS

The computer simulation combines a stochastic model for cell migration and proliferation [13] with a mechano-regulation theory for tissue differentiation [3]. A lattice model was used for the simulation of cell activity [7] while the local mechanical environment was determined using finite element analysis. A regular lattice was superimposed to the finite element model such that 1000 lattice points were contained inside each element (Fig. 1). Each lattice point represented a possible position for a cell to occupy, with a distance between lattice points of 10 µm. In this lattice, endothelial cells (ECs) formed the new capillary network while, simultaneously, mesenchymal stem cells (MSCs), fibroblasts, chondrocytes and osteoblasts migrated, proliferated and differentiated based on the local mechanical environment and the local vascularity.

Figure 1. Lattice contained inside each finite element for the simulation of cell activity. Each lattice point represents a possible position for a cell to occupy.

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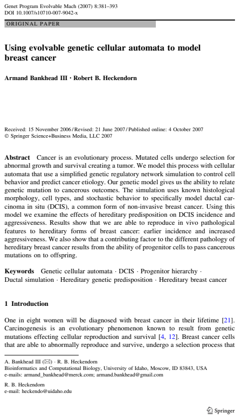
- Using evolvable genetic cellular automata to model breast cancer



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ORIGINAL PAPER

Using evolvable genetic cellular automata to model breast cancer

Armand Bankhead III · Robert B. Heckendorn

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Abstract Cancer is an evolutionary process. Mutated cells undergo selection for abnormal growth and survival creating a tumor. We model this process with cellular automata that use a simplified genetic regulatory network simulation to control cell behavior and predict cancer etiology. Our genetic model gives us the ability to relate genetic mutation to cancerous outcomes. The simulation uses known histological morphology, cell types, and stochastic behavior to specifically model ductal carcinoma in situ (DCIS), a common form of non-invasive breast cancer. Using this model we examine the effects of hereditary predisposition on DCIS incidence and aggressiveness. Results show that we are able to reproduce in vivo pathological features to hereditary forms of breast cancer: earlier incidence and increased aggressiveness. We also show that a contributing factor to the different pathology of hereditary breast cancer results from the ability of progenitor cells to pass cancerous mutations on to offspring.

Keywords Genetic cellular automata · DCIS · Progenitor hierarchy · Ductal simulation · Hereditary genetic predisposition · Hereditary breast cancer

1 Introduction

One in eight women will be diagnosed with breast cancer in their lifetime [21]. Carcinogenesis is an evolutionary phenomenon known to result from genetic mutations effecting cellular reproduction and survival [4, 12]. Breast cancer cells that are able to abnormally reproduce and survive, undergo a selection process that

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Using evolvable genetic cellular automata to model breast cancer
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- Cancer Stem Cell Tumor Model Reveals Invasive Morphology and Increased Phenotypical Heterogeneity

Integrated Systems and Technologies: *Mathematical Oncology*

Cancer Research

Cancer Stem Cell Tumor Model Reveals Invasive Morphology and Increased Phenotypical Heterogeneity

Andrea Sottoriva[1], Joost J.C. Verhoeff[2], Tijana Borovski[2], Shannon K. McWeeney[3,4], Lev Naumov[1], Jan Paul Medema[2], Peter M.A. Sloot[1], and Louis Vermeulen[2]

Abstract

The recently developed concept of cancer stem cells (CSC) sheds new light on various aspects of tumor growth and progression. Here, we present a mathematical model of malignancies to investigate how a hierarchical organized cancer cell population affects the fundamental properties of solid malignancies. We establish that tumors modeled in a CSC context more faithfully resemble human malignancies and show invasive behavior, whereas tumors without a CSC hierarchy do not. These findings are corroborated by *in vitro* studies. In addition, we provide evidence that the CSC model is accompanied by highly altered evolutionary dynamics compared with the ones predicted to exist in a stochastic, nonhierarchical tumor model. Our main findings indicate that the CSC model allows for significantly higher tumor heterogeneity, which may affect therapy resistance. Moreover, we show that therapy which fails to target the CSC population is not only unsuccessful in curing the patient, but also promotes malignant features in the recurring tumor. These include rapid expansion, increased invasion, and enhanced heterogeneity. *Cancer Res; 70(1); 46–56. ©2010 AACR.*

Major Findings

This research shows that the hierarchical organization of malignant clones, as advocated in the CSC concept, has major implications for tumor biology. CSC-driven tumor growth intrinsically orchestrates tumor invasion, influences clonal selection, and has crucial consequences for the development of successful cancer treatments.

Introduction

Malignancies arise after sequential accumulations of mutations in oncogenes and tumor suppressor genes (1). During the process of malignant transition, fundamental regulatory mechanisms are lost. The cancerous cell population has unlimited growth potential, evades the immune system and apoptosis, and often acquires the ability to breach tissue boundaries and expand into foreign environments (1). The cancer stem cell (CSC) concept sheds new light on all of these features (2, 3). In this study, we investigate the influence of a hierarchical organization of malignant clones on tumor growth, evolution, invasion, and morphology using a multi-scale cellular automaton–based computer model (4).

CSCs. Malignancies are highly heterogeneous tissues containing largely diverse cancer cell populations as well as other cells such as fibroblasts and macrophages (1). The dominant genetic view of malignancies explains the heterogeneity in cancer cells with the presence of genetically diverse clones emerging from the continuous acquiring of additional genetic lesions by cancer cells. Such clones compete for resources, resulting in a highly dynamic process known as Tumor Darwinism (5). In this article, we refer to this view of malignancies as the classical model. Although this model greatly contributes to our understanding of malignancies, recent experimental evidence suggests an additional layer of complexity. The heterogeneity present in tumors could, in part, be the result of the diversity in differentiation grade of genetically identical cells (3, 6). For example, in glioblastoma multiforme, cells with an immature phenotype expressing the cell surface marker AC133 are the cells that fuel tumor growth and have the exclusive capacities to self-renew, differentiate, and transplant the malignancy into severe combined immunodeficiency mice (7). Self-renewal and spin-off of differentiated cells are features shared with normal stem cells, and therefore, cells with such features in malignancies are defined as CSCs (6, 8).

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Cancer Stem Cell Tumor Model Reveals Invasive Morphology and Increased Phenotypical Heterogeneity

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Cancer Res; 4656, 70(1) January 1, 2010

- Reaction-diffusion model for pattern formation in E.coli swarming colonies with slime

CAB-lcasat/04021

Reaction-diffusion model for pattern formation in *E.coli* swarming colonies with slime.

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(Dated: February 5, 2008)

A new experimental colonial pattern and pattern transition observed in *E.coli* MG1655 swarming cells grown on semi-solid agar are described. We present a reaction-diffusion model that, taking into account the slime generated by these cells and its influence on the bacterial differentiation and motion, reproduces the pattern and successfully predicts the observed changes when the colonial collective motility is limited. In spite of having small non-hyperflagellated swarming cells, under these experimental conditions *E. coli* MG1655 can very rapidly colonize a surface, with a low branching rate, thanks to a strong fluid production and a local incremented density of motile, lubricating cells.

PACS numbers: 87.18.Hf 87.18.Bb 87.18.Ed 87.80.Vt

I. INTRODUCTION

The macroscopic pattern exhibited by a bacterial colony and its dependence on certain environmental parameters can give us some clues about the coordinated colonization strategy followed by the community of cells. The biological interest in this interdisciplinary area is in pointing out under controlled laboratory conditions the cooperative mechanisms (intercellular interactions, motility and communications) that these bacteria, which are traditionally considered as solitary life forms, may have developed to adapt to changing environments. It is an extremely fertile and interesting area for close collaboration between physicists and biologists because it helps both to understand the transition from individual (uni-cellular, a bacteria) to collective (multi-cellular, a colony) behavior [1].

Bacterial colony pattern formation on semi-solid agar surfaces has been studied extensively by microbiologists and physicists [1, 2, 3, 4, 5, 6, 7, 8]. Through these works undertaken with colonies arising from different species and strains of bacteria, the following common features have been described: Bacteria can swim in liquid medium without difficulty but in environments with adverse conditions for the swimming motility, they need to develop mechanisms to become more motile. On semi-solid agar medium, where the viscosity is high and the motility of short swimmer cells very low, some may differentiate into very elongated, multinucleated and profusely flagellated swarm cells that can move easier [3]. The initiation of swarm differentiation seems to be strictly correlated with physico-chemical factors such as surface contact and quorum sensing response (cell density sensing mechanism) [4]. Swarming cells have the ability to extract water from the agar and produce a lubrication fluid (slime). The flagellum driven motility of swarmer cells together with the extracellular slime helps to overcome the surface friction [3]. After some time migrating swarmer cells have been observed to cease movement, septate and produce groups of swimmer cells (de-differentiation process) [5]. The chemotaxis system is essential for swarming motility in *E. coli* [6]. With the chemotaxis mechanism bacteria can orient their motion in response to a gradient (positive or negative) of a certain chemical field (a nutrient or a field produced by the bacterial cells such as chemical signals or a pH change) [7]. Based on these experimental observations great effort has been devoted to model the cooperative behavior of a cell community [9, 10, 11, 12, 13].

Here we describe the new pattern and pattern transitions observed in a swarming colony of *E. coli* MG1655 [14], a laboratory domesticated wild type strain that produces a lubricating fluid or slime: when the colonial motility is limited this colony expands irregularly with few relatively thick, dense, branches and very rare secondary branches, whereas for conditions of improved colonial motility the pattern is compact and round with structures of higher cell densities. To study the coordinated, self-organized, colonization scheme of this colony and based on experimental microscopic observations, we will define a mathematical model of the cooperative behavior of this colony which is able to predict the pattern transitions when certain control parameters are changed.

This work is organized as follows: in Section II we will introduce the experimental results and their implications for the non-expert reader. Then in Section III, our hypothesis for the collective dynamics will be explained, followed by a mathematical formulation. Results of the computer simulation in comparisons with experiments will be posed and discussed in Section IV. The summary and conclusions are given in Section V.

II. EXPERIMENTAL OBSERVATIONS

The development of an *E. coli* MG1655 colony on a semi-solid surface (0.5% "Difco" Agar) under certain nutritional (1% "Difco" Tryptone, 0.5% "Difco" yeast extract, 0.5% NaCl and 0.5% D-(+)-glucose) and environmental (at 37°C and on average 22% relative humidity) conditions has been studied in detail with round and

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Reaction-diffusion model for pattern formation in E.coli swarming colonies with slime

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Phys. Rev. E. 71, 31908 (2005)

- Mapping the phase diagram of the writhe of DNA nanocircles using atomistic molecular dynamics simulations

Nucleic Acids Research, 2008, Vol. 36, No. 1 ***21–29***
doi:10.1093/nar/gkm891

Mapping the phase diagram of the writhe of DNA nanocircles using atomistic molecular dynamics simulations

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ABSTRACT

We have investigated the effects of duplex length, sequence, salt concentration and superhelical density on the conformation of DNA nanocircles containing up to 178 base pairs using atomistic molecular dynamics simulation. These calculations reveal that the partitioning of twist and writhe is governed by a delicate balance of competing energetic terms. We have identified conditions which favour circular, positively or negatively writhed and denatured DNA conformations. Our simulations show that AT-rich DNA is more prone to denaturation when subjected to torsional stress than the corresponding GC containing circles. In contrast to the behaviour expected for a simple elastic rod, there is a distinct asymmetry in the behaviour of over and under-wound DNA nanocircles. The most biologically relevant negatively writhed state is more elusive than the corresponding positively writhed conformation, and is only observed for larger circles under conditions of high electrostatic screening. The simulation results have been summarised by plotting a phase diagram describing the various conformational states of nanocircles over the range of circle sizes and experimental conditions explored during the study. The changes in DNA structure that accompany supercoiling suggest a number of mechanisms whereby changes in DNA topology *in vivo* might be used to influence gene expression.

INTRODUCTION

DNA topology *in vivo* is extremely diverse. Whilst regions of the genetic material must be accessible during transcription, replication and repair, the bulk must be compacted to fit within the nucleus. In bacteria, circular plasmids are condensed by supercoiling the DNA into highly writhed superhelical structures. The importance of higher order DNA structure is illustrated by the elaborate machinery for the regulation of DNA topology that exists within the cell. Families of topoisomerase and gyrase enzymes alter the level of supercoiling by transiently introducing single or double strand breaks and changing the number of times the two strands of the duplex are wrapped around each other (1). Variation in DNA topology influences promoter activity and is consequently involved in the regulation of gene expression and replication (2). For example, the shock response of bacterial cells placed under environmental pressure (such as starvation or thermal stress) is accompanied by dramatic changes in supercoiling, which enable the cell to rapidly modify transcription rates across the whole genome, whereas adaptation through genetic mutations can only occur over a much longer timescale (3,4).

Closed circular DNA can form superhelical structures whenever the topological quantity known as the linking number Lk (1) deviates from its value in a torsionally relaxed duplex Lk_0. The quantity Lk_0 is simply the number of base pairs (bp) in the circle divided by the helical repeat. The linking number is constrained to be integral in closed circular structures and cannot be altered without cutting either one or both DNA strands. The linking number difference $\Delta Lk = Lk - Lk_0$ is commonly normalised to the size of the circle and expressed as the superhelical density σ where:

$$\sigma = \frac{\Delta Lk}{Lk_0} \qquad \mathbf{1}$$

The topological property, the linking number, is related to two geometrical parameters of the duplex; the helical twist (Tw) and the writhe (Wr), where the writhe is a measure of the contortion of the DNA axis.

$$Lk = Tw + Wr \qquad \mathbf{2}$$

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Mapping the phase diagram of the writhe of DNA nanocircles using atomistic molecular dynamics simulations
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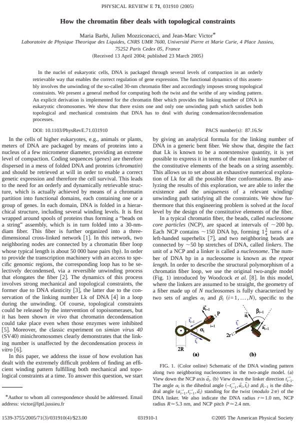
- How the chromatin fiber deals with topological constraints



PHYSICAL REVIEW E **71**, 031910 (2005)

How the chromatin fiber deals with topological constraints

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In the nuclei of eukaryotic cells, DNA is packaged through several levels of compaction in an orderly retrievable way that enables the correct regulation of gene expression. The functional dynamics of this assembly involves the unwinding of the so-called 30-nm chromatin fiber and accordingly imposes strong topological constraints. We present a general method for computing both the twist and the writhe of any winding pattern. An explicit derivation is implemented for the chromatin fiber which provides the linking number of DNA in eukaryotic chromosomes. We show that there exists one and only one unwinding path which satisfies both topological and mechanical constraints that DNA has to deal with during condensation/decondensation processes.

DOI: 10.1103/PhysRevE.71.031910 PACS number(s): 87.16.Sr

In the cells of higher eukaryotes, e.g., animals or plants, meters of DNA are packaged by means of proteins into a nucleus of a few micrometer diameter, providing an extreme level of compaction. Coding sequences (*genes*) are therefore dispersed in a mess of folded DNA and proteins (*chromatin*) and should be retrieved at will in order to enable a correct genetic expression and therefore the cell survival. This leads to the need for an orderly and dynamically retrievable structure, which is actually achieved by means of a chromatin partition into functional domains, each containing one or a group of genes. In each domain, DNA is folded in a hierarchical structure, including several winding levels. It is first wrapped around spools of proteins thus forming a "beads on a string" assembly, which is in turn folded into a 30-nm-diam fiber. This fiber is further organized into a three-dimensional cross-linked network [1]. In this network, two neighboring nodes are connected by a chromatin fiber loop whose typical length is about 50 000 base pairs (bp). In order to provide the transcription machinery with an access to specific genomic regions, the corresponding loop has to be selectively decondensed, via a reversible unwinding process that elongates the fiber [2]. The dynamics of this process involves strong mechanical and topological constraints, the former due to DNA elasticity [3], the latter due to the conservation of the linking number Lk of DNA [4] in a loop during the unwinding. Of course, topological constraints could be released by the intervention of topoisomerases, but it has been shown *in vivo* that chromatin decondensation could take place even when those enzymes were inhibited [5]. Moreover, the classic experiment on *simian virus 40* (SV40) minichromosomes clearly demonstrates that the linking number is unaffected by the decondensation process *in vitro* [6].

In this paper, we address the issue of how evolution has dealt with the extremely difficult problem of finding an efficient winding pattern fulfilling both mechanical and topological constraints at a time. To answer this question, we start by giving an analytical formula for the linking number of DNA in a generic bent fiber. We show that, despite the fact that Lk is known to be a nonextensive quantity, it is yet possible to express it in terms of the mean linking number of the constitutive elements of the beads on a string assembly. This allows us to set about an exhaustive numerical exploration of Lk for all the possible fiber conformations. By analyzing the results of this exploration, we are able to infer the existence and the *uniqueness* of a relevant winding/unwinding path satisfying all the constraints. We show furthermore that this engineering problem is solved at the *local* level by the design of the constitutive elements of the fiber.

In a typical chromatin fiber, the beads, called *nucleosome core particles* (NCP), are spaced at intervals of ~200 bp. Each NCP contains ~150 DNA bp, forming $1\frac{3}{4}$ turns of a left-handed superhelix [7], and two neighboring beads are connected by ~50 bp stretches of DNA, called *linkers*. The unit of a NCP and a linker is called a *nucleosome*. The number of DNA bp in a nucleosome is known as the *repeat length*. In order to describe the structural polymorphism of a chromatin fiber loop, we use the original two-angle model (Fig. 1) introduced by Woodcock *et al.* [8]. In this model, where the linkers are assumed to be straight, the geometry of a fiber made up of N nucleosomes is fully characterized by two sets of angles α_i and β_i $(i=1,\ldots,N)$, specific to the

FIG. 1. (Color online) Schematic of the DNA winding pattern along two neighboring nucleosomes in the two-angle model. (a) View down the NCP axis $\vec{a}_i$. (b) View down the linker direction $\vec{t}_{i-1}$. The angle α_i is the dihedral angle $(-\vec{t}_{i-1},\vec{a}_i,\vec{t}_i)$ and β_{i-1} is the dihedral angle $(\vec{a}_{i-1},\vec{t}_{i-1},\vec{a}_i)$ standing for the twist (*modulo* 2π) of the DNA linker. We also indicate the DNA radius $r \simeq 1.0$ nm, NCP radius $R \simeq 5.3$ nm, and NCP pitch $P \simeq 2.4$ nm.

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How the chromatin fiber deals with topological constraints
Maria Barbi, Julien Mozziconacci, and Jean-Marc Victor
PHYSICAL REVIEW E 71, 031910 (2005)

- Development of regular cellular spacing in the retina: theoretical models

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Development of regular cellular spacing in the retina: theoretical models

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During development of the nervous system, neurons should be appropriately positioned to enable them to make the right functional contacts. Neurons do not immediately migrate to their correct location, but instead regular arrangements gradually emerge from randomly arranged cell populations. This phenomenon has been studied often in the retina, due to its relatively simple layered organisation. In this review, I highlight the principal mechanisms that are thought to be involved, and how mathematical modelling has helped to further our understanding of the role of these processes upon mosaic formation. Three developmental mechanisms are studied in detail, namely, lateral migration, cell fate and cell death. As a case study, I then consider which mechanisms might be involved in the formation of retinal ganglion cell mosaics.

1. Nature and formation of retinal mosaics

The retina is assembled as a stack of several cell layers, with the photoreceptors in the outermost layer and the retinal ganglion cells (RGCs) in the innermost layer (Fig. 1). Photoreceptors convert light into electrical activity which is then modulated by the interacting vertical and horizontal neural pathways within the retina. Once the activity reaches the RGCs, it is converted into spike trains which are sent along the optic nerve and into subcortical and cortical areas in the brain for higher processing. For a comprehensive review of retinal architecture and processing, see Rodieck (1998). The organisation of the retina obeys certain principles which make it relatively easy to study compared to other parts of the nervous system, such as neocortex. For example, there are five major classes of retinal neuron, each with clearly defined morphologies. Each class of retinal neuron tends to be found in one vertical layer, making cell identification easier. Following the terminology of Cook (1998), each class divides into subclasses of neurons which in turn can be classified into individual types of retinal neuron.

At the level of individual cell types, we typically find the spatial organisation of cells within a type to be highly non-random (Fig. 2a). This regular organisation of cell bodies is referred to as a 'retinal mosaic' due to the way that the cell body (and its dendrites) tiles the retina. This regular organisation makes sense from the point of view of processing the visual world: receptors are needed uniformly across the retina to ensure that the visual world is regularly sampled and that there are no 'holes' in visual space. In this review, I will discuss recent mathematical models that have helped us investigate how these retinal mosaics form during development. I will first review the neurobiological background about the mechanisms that are thought to be involved, and review several types of model, before focusing on a case study comparing how different models may account for the positioning of RGCs.

As well as gaining an insight into the formation of neural patterning in retina, the hope is that we may also learn something about the principles underlying development of the nervous system in general.

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Development of regular cellular spacing in the retina: theoretical models

STEPHEN J. EGLEN

Mathematical Medicine and Biology (2006) 23, 79-99