The Workshop on Mathematical Modelling

and Analysis of

Biological Pattern Formations

and the Related Topics

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Abstracts
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Lecture 1

Pattern generation in models of solid tumour growth: An overview

Mark AJ Chaplain,
University of Dundee, UK

Abstract:

In this talk we examine pattern formation in generation in models of solid tumour growth. In the first part of the talk we will focus on mathematical models which describe the growth of the outer radius of the solid tumour using a moving boundary formulation. Perturbation theory and linear stability analysis can be used to determine whether or not this radially symmetric configuration is maintained. In the second part of the talk we examine spatio-temporal pattern formation in reaction-diffusion systems on the surface of the unit sphere in 3D. We first generalise the usual linear stability analysis for a two-chemical system to this geometrical context. We then investigate the role that pre-pattern (Turing) theory may play in the growth and development of solid tumours. The theoretical steady-state distributions of two chemicals (one a growth activating factor, the other a growth inhibitory factor) are compared with the experimentally and clinically observed spatial heterogeneity of cancer cells in small, solid spherical tumours such as multicell spheroids and carcinomas. Moreover, we suggest a number of chemicals which are known to be produced by tumour cells (autocrine growth factors), and are also known to interact with one another, as possible growth promoting and growth inhibiting factors respectively. In order to connect more concretely the numerical method to this application, we compute spatially heterogeneous patterns on the surface of a growing spherical tumour, modelled as a moving-boundary problem. The numerical results strongly support the theoretical expectations in this case.

Lecture 2

Pattern generation in models of cancer cell invasion of tissue

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Abstract:

The ability of cancer cells to break out of tissue compartments and invade locally gives solid tumours a defining deadly characteristic. The first step of invasion is the over-expression by the cancer cells of proteolytic enzymes, such as the urokinase-type plasminogen activator (uPA) and matrix metalloproteinases (MMPs). Degradation of the matrix then enables the cancer cells to migrate through the tissue and subsequently to spread to secondary sites in the body (metastasis). In this paper we undertake an analysis of a mathematical model of cancer cell invasion of tissue (extracellular matrix) which focuses on the role of the urokinase plasminogen activation system. The model consists of a system of 5 reaction-diffusion-taxis partial differential equations describing the interactions between cancer cells, urokinase plasminogen activator (uPA), uPA inhibitors, plasmin and the host tissue. The spatio-temporal dynamics of the uPA system is coupled to the cancer cells through chemotaxis and haptotaxis. The results obtained from numerical computations carried out on the model equations produce dynamic heterogeneous spatio-temporal solutions and using linear stability analysis we show that this is caused by a taxis-driven instability of a spatially homogeneous steady-state. Finally we discuss the biological implications of the model results and future development of the model.

Traveling Fronts for the Reaction-Diffusion Epidemic Models with Nonlinear Incidence

Kyoto Sangyo University

Yuzo Hosono

Abstract :

In my talk, I discuss the existence problem of traveling fronts and their propagation speeds for the two component reaction-diffusion epidemic models with nonlinear incidence. I will further consider the minimal propagation speeds of traveling fronts and their dependence of the diffusion coefficients and the nonlinearity of incidence. Our mathematical tool is an elementary analysis of the vector fields in the phase space.

A Biologically Motivated Shortest Path Finding Algorithm
— *Physarum* Solver —

Ryo Kobayashi, Hiroshima University

Atsushi Tero and Toshiyuki Nakagaki, Hokkaido University

Plasmodium of *Physarum Polycephalum* is a large amoeboid cell with multi nuclei which shows an oscillation in every part with period 2 minutes (Fig.1). Nakagaki performed a maze solving experiments using this creature[1]. It was shown that the plasmodium had an ability to solve the maze and, in addition, to find the shortest path.

Motivated by this experiment, we propose a simple mathematical model which can solve a shortest path finding problem on the graph by *Physarum*-like way[2,3](Fig.2). In this model, the graph is considered to be a network of waterpipes whose thicknesses is adapting according to the flux.
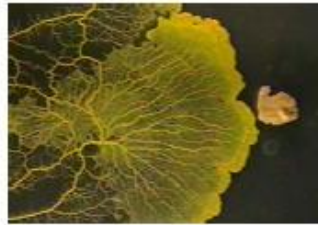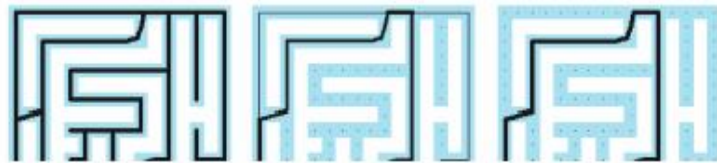

Figure 1:

Figure 2:

References

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Interactions among the pigment cells of zebrafish give rise to Turing Pattern

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The question of how complex animal body patterns arise from seemingly disorganized or formless initial structures represents an intriguing challenge not only to biologists but also to mathematicians, physicists and chemists. In 1952, the British mathematician Alan Turing proposed a simple mathematical equation capable of generating a wide range of patterns commonly found in the natural world, such as stripes, spots and reticulations. This model, known as the reaction-diffusion model, mathematically demonstrates that the interaction between a local activator and a long-range inhibitor can give rise to various periodic structures in response to differences in their individual diffusion rates. Although it was clear to have the potential capability to solve the fundamental problem of embryology, the difficulty of proving in an experiment had obstructed the proof of this epoch-making theory for a long time.

Animal skin patterns are ideal subjects to study the molecular basis of the Turing mechanism. They are visible from outside, and it is clear that they form without any prepattern because most skin patterns usually are not similar to the inside structures. We discovered in 1995 that the skin pattern of a certain tropical fish changed continuously so that a Turing model might predict, and it became proof that the principle of Turing was actually working in a living thing. By using zebrafish as a new experimental system, we are trying to clarify the molecular network that constructs the putative Turing system.

Mathematical Analysis of Anderson and Chaplain models

Akisato Kubo

Fujita Health University

In this talk, we consider Anderson-Chaplain model of tumour induced angiogenesis:

$$
\begin{cases}
\dfrac{\partial \mathrm{n}}{\partial \mathrm{t}} = \overbrace{\mathrm{D}\nabla^2\mathrm{n}}^{\text{random motility}} - \overbrace{\nabla \cdot (\dfrac{\chi}{1+\sigma\mathrm{c}}\mathrm{n}\nabla\mathrm{c})}^{\text{chemotaxis}} - \overbrace{\nabla\cdot(\rho\mathrm{n}\nabla\mathrm{f})}^{\text{haptotaxis}} \\[2ex]
\dfrac{\partial \mathrm{f}}{\partial \mathrm{t}} = \overbrace{\kappa\mathrm{n}}^{\text{production}} - \overbrace{\varpi\mathrm{f}}^{\text{uptake}} \\[2ex]
\dfrac{\partial \mathrm{c}}{\partial \mathrm{t}} = -\overbrace{\eta\mathrm{nc}}^{\text{uptake}} \qquad\qquad \text{in} \quad \Omega\times(0,\infty)
\end{cases}
$$

where $n(x,t)$ is the endothelial cell density, $f(x,t)$ is the fibronectin concentration and $c(x,t)$ is TAFs concentration. Then we also consider their model of tissue invasion:

$$
\begin{cases}
\dfrac{\partial \mathrm{n}}{\partial \mathrm{t}} = \overbrace{\mathrm{d_n}\nabla^2\mathrm{n}}^{\text{randommotility}} - \overbrace{\nabla\cdot(\mathrm{n}\nabla\mathrm{f})}^{\text{haptotaxis}} \\[2ex]
\dfrac{\partial \mathrm{f}}{\partial \mathrm{t}} = - \overbrace{\eta\mathrm{mf}}^{\text{degradation}} \\[2ex]
\dfrac{\partial \mathrm{m}}{\partial \mathrm{t}} = \overbrace{\mathrm{d_m}\nabla^2\mathrm{m}}^{\text{diffusion}} + \overbrace{\alpha\mathrm{n}}^{\text{production}} - \overbrace{\beta\mathrm{m}}^{\text{decay}} \qquad\qquad \text{in} \qquad \Omega\times(0,\infty)
\end{cases}
$$

where $n(x,t)$ is the tumour cell density, $m(x,t)$ is the matrix degrading or degrading enzymes concentration and $f(x,t)$ is the extracellular matrix density. In order to investigate the existence of global solutions of the models we apply a mathematical approach used in Otherm and Stevens model:

$$
\begin{cases}
P_t = D\nabla \cdot [P\nabla \log(\dfrac{P}{\Phi(W)})], \quad \text{in} \quad \Omega \times (0,\infty) \\[2ex]
W_t = F(P,W) \\[2ex]
P\nabla(\log P/\Phi(W))\cdot\nu = 0 \quad \text{on } \partial\Omega \times (0,\infty) \\[1ex]
P(x,0) = P_0(x) \geq 0, \quad W(x,0) = W_0(x) > 0
\end{cases}
$$

where $P = P(x,t)$ and $W = W(x,t)$ are the density of the bacteria and that of control species respectively and ν is denotes the outer unit normal vector of a bounded domain Ω in R^n. Observing mathematical structures of the models we obtain the desired result and show the relationship between the models.

Mathematical Modelling of Dynamic Adaptive Tumour-Induced Angiogenesis

Steven R McDougall

Abstract

Angiogenesis, the growth of a network of blood vessels, is a crucial component of solid tumour growth, linking the relatively harmless avascular growth phase and the potentially fatal vascular growth phase. As a process, angiogenesis is a well-orchestrated sequence of events involving endothelial cell migration, proliferation; degradation of tissue; new capillary vessel (sprout) formation; loop formation (anastomosis) and, crucially, blood flow through the network. Once there is blood flow associated with the nascent network, the subsequent growth of the network evolves both temporally and spatially in response to the combined effects of angiogenic factors, migratory cues via the extracellular matrix and perfusion-related haemodynamic forces in a manner that may be described as both *adaptive* and *dynamic*. In this seminar I present a mathematical model which *simultaneously* couples vessel growth with blood flow through the vessels – *dynamic adaptive tumour-induced angiogenesis* (DATIA). An extensive computational investigation of the process highlights a number of important new targets for therapeutic intervention. In contrast to earlier flow models, where the effects of perfusion (blood flow) were essentially evaluated *a posteriori* i.e. after generating a hollow network, blood flow in the model described in this seminar has a direct impact *during* capillary growth, with radial adaptations and network remodelling occurring as *immediate* consequences of primary anastomoses. Capillary network architectures resulting from the dynamically adaptive model are found to differ radically from those obtained using earlier models.

Finally, the DATIA model is used to examine the effects of changing various physical and biological model parameters on the developing vascular architecture.

Self-organizing Mechanism for Development of

Space-filling Neuronal Dendrites

Kaoru Sugimura [1,3], Kohei Shimono [1], Tadashi Uemura [1] and *Atsushi Mochizuki [2]

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* Speaker

Neurons develop distinctive dendritic morphologies to receive and process information. Our previous experiments show that competitive interactions between dendrites play important roles in shaping dendritic arbors. We incorporated this finding in constructing a reaction-diffusion model for pattern formation of dendrite. We explicitly distinguish two spatial compartments, that is inside and outside of the cell and the cell compartment dynamically grows under a regulation of diffusive chemicals (activator and suppressor). This cell compartment model autonomously produces two distinctive dendritic patterns: rugged dendrites that show a punctate distribution of activator and smooth dendrites that show a continuous distribution of activator. We found that Turing instability underlies the differences in shapes of dendrite and distribution of activator. The numerical analysis suggested that the system should develop locally concentrated patterns of activator (dot or terminally dense) for supporting dendrite growth. Finally we confirmed generality of the scheme as shown by the fact that all of the above results were valid for different dynamics of chemical reactions. The self-organized mechanism proposed by this study could control dendrite morphogenesis.

Developmental variation and the evolution of butterfly wing patterns

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Abstract:

Variation is a key component of the evolutionary process, and over the years evolutionary biologists have expended a great amount of effort to describe and interpret genetic and phenotypic variation in natural populations. Development, however, is the bridge between genotype and phenotype, and very little remains known about developmental variation. Achieving a better understanding of developmental variation could provide insight into how pattern formation processes influence the evolution of traits. Of particular interest in this regard are recent studies of developmental robustness which predict that natural populations may be able to host developmental variation that has little phenotypic effect under normal conditions. This prediction has important evolutionary implications, however there are few data that directly test the idea. To address this issue I am using butterfly wing pattern development as a model to explore how pattern formation processes may vary in natural populations. I will describe new methods for quantitative analysis of variation and divergence in pattern formation within and between populations. I will apply these techniques to analyze color pattern-associated prepattern formation by the Notch, Spalt, Engrailed, and Distal-less proteins, and show that there is substantial population-level variation in the patterning process. The observed variation appears to be specific to certain pattern elements and time windows, and is not a general property of a particular protein or developmental process. Furthermore, the observed variation bears resemblance to regulatory changes associated with the evolution of color pattern elements at deeper phylogenetic levels. Together, these data give a preliminary model of how standing developmental variation may bias the evolution of phenotypes.

Conservative finite-element method for the Keller-Segel system modeling chemotaxis

NORIKAZU SAITO (University of Toyama)

In 1970, F. F. Keller and L. A. Segel (**[KS]**) proposed the system of partial differential equations that described the aggregation of slime molds resulting from their chemotactic features. The system is called the Keller-Segel system modeling chemotaxis, and a large number of works are devoted to mathematical analysis to the system. In this paper, we consider the following nonlinear parabolic system that is a variant of the original Keller-Segel system:

$$\begin{cases} u_t = \nabla \cdot (D_u \nabla u - u \nabla \phi(v)) & \text{in} \quad \Omega \times (0, T), \\ k v_t = D_v \Delta v - k_1 v + k_2 u & \text{in} \quad \Omega \times (0, T), \\ \partial u / \partial \nu = \partial v / \partial \nu = 0 & \text{on} \quad \partial \Omega \times (0, T), \\ u|_{t=0} = u_0(x), \quad v|_{t=0} = v_0(x) & \text{on} \quad \Omega, \end{cases} \tag{KS}$$

where $\Omega \subset \mathbb{R}^d$ ($d = 2, 3$) is a bounded domain with the boundary $\partial \Omega$; $\partial / \partial \nu$ represents differentiation along ν on $\partial \Omega$; ν is the outer unit normal vector to $\partial \Omega$; $u = u(x, t)$ is the density of the cellular slime molds and $v = v(x, t)$ the concentration of the chemical substance; the chemotactical sensitivity function $\phi(v)$ is assumed to be nondecreasing and smooth on $v > 0$, e.g. $\phi(v) = \lambda v$, $\phi(v) = \lambda \log v$ and $\phi(v) = \lambda v^2 / (\lambda' + v^2)$ with $\lambda, \lambda' > 0$; D_u and D_v are diffusion coefficients, k is the relaxation time, and k_1 and k_2 correspond the generation rate (they are assumed to be positive constants); initial values $u_0(x)$ and $v_0(x)$ are assumed to be smooth, ≥ 0 and $\not\equiv 0$.

We have dual purpose. The first is to propose a finite element scheme that satisfies the conservations of positivity and total mass of the solution u. Thus, our finite-element solution preserves the value of the L^1 norm, which is the discrete version of an important property of the original system. The scheme made use of Baba-Tabata type upwind finite-element approximation (cf. **[BT]**) and semi-implicit time discretization with step-size control. That is, at every discrete time step $t_n = \tau_1 + \cdots + \tau_n$, we adjust the time increment τ_n to obtain a positive solution. Consequently, we realize the L^1 conservative finite-element approximation for an arbitrary $h > 0$, the granularity parameter of the spatial discretization. Moreover, our scheme is well suited for practical computations.

The second purpose is to develop an error analysis. Because of the nonlinear feature of the system and the application of Baba-Tabata's upwind approximation, it is crucial to study the error in the $L^p \times W^{1,\infty}$ norm (uniformly in t_n) for some $p > d$. Therefore, we shall develop the L^p theory for (KS) and its finite-element approximation.

The method of analysis is based on our previous works, **[S]** and **[SS]**.

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Three-dimensional Turing Patterns

Kyoto Prefectural University of Medicine

Hiroto Shoji

Abstract:

Attempts have been made to understand pattern formations in various biological systems in terms of the Turing mechanism. In order to address this question from the theoretical point of view, Turing patterns have been studied numerically and analytically. However, almost all of the previous investigations were restricted to one or two dimensions, where only stripe patterns, hexagonal pattern and labyrinthe pattern exist.

  In three dimensions, a more variety of patterns is possible. In fact, by numerical simulations of reaction diffusion equations, we have obtained not only lamellar and hexagonal structures but also gyroid, diamond, Fddd, BCC, FCC and perforated lamellar structures. Domains of a gyroid, diamond, Fddd and perforated lamellar structures constitute interconnected regular networks, which is a characteristic feature in three dimensions. The stability analysis has been performed by deriving approximately a Lyapunov functional. We will also discuss some relationship among other pattern formation problems such as microphase separation in block copolymers and heat convection systems.

Reference

H. Shoji, K. Yamada, D. Ueyama, T. Ohta, Phys. Rev. E 75 46212, (2007).

Chemotactic cell movement during Dictyostelium development and chick gastrulation

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Development is critically dependent on a number of distinct cellular behaviours such as cell division and cell death, cell differentiation and cell movement, which all have to be precisely controlled in space and time. We investigate the molecular mechanisms by which cells signal each other during development and furthermore how cells detect these signals and translate this information in directed coordinated movement. We study these questions in two different experimental systems, the social amoebae *Dictyostelium discoideum,* a simple genetically tractable micro-organism showing a relatively simple starvation induced multicellular development.

In Dictyostelium starvation for food induces the aggregation of thousands of individual amoebae into a multi-cellular aggregate. During aggregation the cells differentiate into a number of distinct celltypes, which form a migrating slug that transforms into a fruiting body consisting of a stalk supporting a mass of spores. The chemotactic aggregation of the cells is controlled by propagating waves of cyclic-AMP emanating periodically form aggregation centres. Experiments show that also in the multicellular stages the migration of the cells is controlled by propagating waves of cAMP. We use continuous and discrete models to investigate the relationship between signalling and movement to understand the dynamical interactions that result in the morphogenesis of this organism.

We also investigate the role of chemotaxis in the control of gastrulation movements in the chick embryo. During gastrulation the mesoderm and endoderm cells move into the embryo to take up their correct topological positions. We have tracked the migration of mesoderm cells, expressing fluorescent proteins, during gastrulation in the chick embryo and show that their movement is controlled by a combined action of chemo-attractants and repellents, controlled by members of the Fibroblast Growth Factor (FGF) family of growth factors. We have also visualised extensive cell flows occurring in the epiblast during the formation of the primitive streak, the site of invagination of the mesoderm and endoderm cells. Our current hypothesis is that formation of the primitive streak also involves a combination of chemo-attractants and repellents. We have started to use different modelling approaches to analyse the control of cell movement during the formation of the primitive streak.

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