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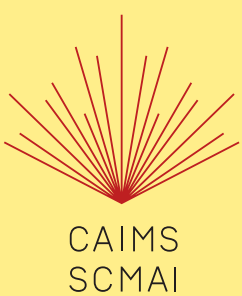
Non-Local Cell Adhesion Models

Symmetries and Bifurcations in 1-D



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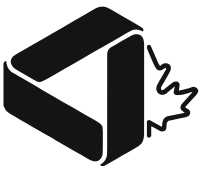

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Preface

Whenever cells form tissues, organs, or organisms, they interact with each other through cellular adhesions. Cell–cell adhesions give the skin its stability, they keep cells together to form organs, they allow immune cells to move through the body, and they keep blood inside the vessels. Cell–cell adhesions also facilitate diseases such as cancer and cancer spread through metastasis. A good understanding of this basic cell mechanism is of upmost importance, and here we use mathematics to help to shed light on this interesting process.

We will focus on a mathematical model that was introduced in 2006 by *Armstrong, Painter, and Sherratt*. Their model stands out since it gave the first continuum description of cell adhesion in the form of an integro-partial differential equation (iPDE) model. The model has been used with great success to describe the cell-sorting experiments of Steinberg, as well as tissue dynamics in embryogenesis, wound healing, and cancer cell invasions. Since the iPDE of Armstrong et al. contains non-local terms inside a nonlinear partial differential equation, the mathematical analysis is challenging, even in the "simplest" case of one-cell species in one dimension.

In Part I (*Introduction*) of this monograph, we review applications of the Armstrong, Painter, and Sherratt model to cell aggregations, cell sorting, and cancer spread, and we consider the biological processes that are the basis of this model. We review the known theoretical results on local and global existence and pattern formation. We define an adhesion potential, and we outline a formal connection to *aggregation equations* that have been derived for physical problems, such as the *McKean–Vlasov* model. In fact, many tools from the analysis of the aggregation equations become available for our purpose.

In Part II (*The Periodic Problem*), we develop a full bifurcation theory for the non-local adhesion model in a one-dimensional periodic domain. We combine global bifurcation results pioneered by Rabinowitz, equivariant bifurcation theory, and the symmetries of the non-local term to obtain local and global bifurcation results for the branches of non-trivial solutions. The key idea here is the introduction of a new *area function* in Definition 5.3. Our non-local model does not obey a classical maximum principle, but the area function does, giving us the necessary structure to untangle

the bifurcations. We identify general criteria that allow us to distinguish between super- and sub-critical bifurcations.

In Part III (*Non-local Equations with Boundary Conditions*), we extend the non-local cell adhesion model to a bounded domain with no-flux boundary conditions. Since the model is non-local, there is a need to properly define the non-local term once it reaches the boundary. We use biological properties to derive such boundary terms. We propose several different non-local terms incorporating different biologically realities such as boundary adhesion and boundary repulsion. We show that these newly constructed non-local operators are weakly differentiable, using the theory of distributions. In numerical simulations, we see that adhesive boundary conditions lead to boundary *wetting*, quite similar to the behavior of certain fluids. Finally, we use an asymptotic expansion, and numerical simulations to study the steady states of the non-local cell adhesion model incorporating no-flux boundary conditions, and we find a similar bifurcation structure as in the periodic case.

While preparing this work, we were intrigued by the rich mathematical structures of the non-local adhesion model. Not only do these structures allow us to understand its bifurcations, but these structures carry meaning for biological applications. The detailed analysis, as presented here, shows a stimulating interaction between model symmetries, mathematical analysis, and biological reality, which inspired us, and hopefully, our readers as well.

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February 2021

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Chapter 1
Introduction

Cellular adhesion is one of the most important interaction forces in tissues. Cells adhere to each other, to other cells, and to the extracellular matrix (ECM). Cell adhesion is responsible for the formation of tissues, membranes, vasculature, muscle tissue, as well as cell movement and cancer spread [79, 187]. At the molecular level, cellular adhesion is facilitated by a wide range of different cell membrane proteins with integrins and cadherins being the most prominent adhesion molecules [2, 71, 79, 87]. We recognize that cell adhesions are fundamental for the normal functions of organs, embryonic development, wound healing, as well as pathological issues such as cancer metastasis [86, 127, 154].

A good understanding of adhesion and its dynamic properties is essential, and mathematical modelling is one powerful tool to gain such an understanding. There have been several modelling attempts for adhesion, and it turns out that one of the more successful models is the model of Armstrong, Painter, and Sherratt from 2006 [10]. It has the form of a non-local partial differential equation, where the particle flux is an integral term that arises as balance of all the adhesion forces acting on a cell.

The present monograph focuses on mathematical properties of the non-local Armstrong model. The non-local nature of the particle flux term is a challenge, and sophisticated new methods need to be derived. Here we show the existence of non-trivial steady states and analyze their stability and their bifurcation structure. The results are largely based on the abstract bifurcation theory of Crandall and Rabinowitz [156]. We show that the non-local term acts like a non-local derivative, which allows us to define non-local gradients and non-local curvature. Furthermore, we discuss the development of appropriate, and biologically realistic, no-flux boundary conditions, and we show the existence of non-trivial steady states for this case. As the no-flux boundary conditions are non-unique, they open the door for further studies of boundary behavior of cells on tissue boundaries.

A. Buttenschön, T. Hillen, *Non-Local Cell Adhesion Models*, CMS/CAIMS Books in Mathematics 1, https://doi.org/10.1007/978-3-030-67111-2_1

1.1 The Effect of Cellular Adhesions in Tissues

Early in the last century, the first biological experimenters had begun to uncover the role of cell adhesion in tissues. One of the earliest observations was that if a sponge is squeezed through a fine mesh [170, 189], it will reform into a functional sponge after transition. A few years later, Hoftreter observed that different tissues have different associative preferences [170]. To describe his observations, he introduced the concept of "tissue affinities". Further, he repeated the earlier observations that previously dissociated tissues have the ability to regain their form and function after deformation (Fig. 1.1). Today, this phenomenon is referred to as cell sorting, and we recognize its critical importance in the formation of functional tissues during organism development.

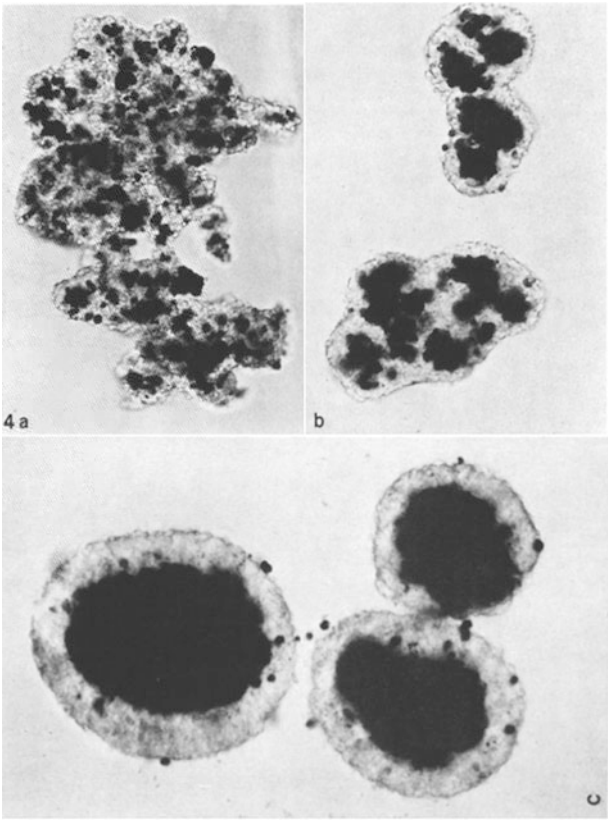

Fig. 1.1 Two cell populations, black and white, with adhesion molecules of different strengths on their surfaces. Initially (**a**) the cells are mixed, and over time they slowly (**b**) re-sort themselves to a sorted final configuration (**c**) (For details on the experimental setup and the figure, see [12])

In 1963, Steinberg proposed the first theory of cell sorting that argued that cell-level properties, namely, a cell's adhesion molecules, drive cell sorting [170, 171]. His theory, capable of explaining the different cell sorting patterns, is known as the *Differential Adhesion Hypothesis* (DAH). Steinberg observed that clusters of cells of the same type behave as if a surface tension holds them together, quite similar to fluid droplets. In other words, cells rearrange to maximize their intracellular attraction and minimize surface tension. That is, the DAH asserts that cell sorting is solely driven by the quantitative differences in the adhesion potential between cell types (e.g., cells with the highest potential of adhesion are found at the center of aggregates). Interesting is that Steinberg referred to adhesion being a "merely close range attraction" [170]. An overview of the experimental verifications can be found in [172].

Further analysis of cell sorting patterns [10, 67] has shown several types of cell clusters as shown in Fig. 1.2. The outcome depends on the relative adhesion strengths of cells of the same type to each other and to cells of a different type.

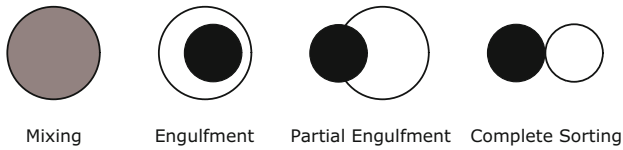

Fig. 1.2 The four possible outcomes of cell sorting with two cell populations. The more cohesive cell population is black. Mixing occurs with preferential cross-adhesion, engulfment with intermediate cross-adhesion, partial engulfment with weak cross-adhesion, and cell sorting with no cross-adhesion [10, 67]

Harris formulated a first critique of the DAH [91]. The main points of his critique were as follows: (1) cells are living objects and thus open thermodynamic systems (not closed as assumed by the DAH); (2) cell size and cell membrane protrusions are much larger than individual adhesion bonds, thus making cellular adhesions a non-local process; and (3) the work of adhesion and de-adhesion may be different, as cells can stabilize adhesion bonds after their formation [91]. To resolve these issues, Harris proposed the *Differential Surface Contraction Hypothesis*, arguing the contractile strength of a membrane completely describes its surface tension. A model similar to this idea was later implemented in a successful vertex model of cell sorting in epithelial tissues [25, 26, 41].

Cellular adhesion is facilitated by a wide range of cell surface molecules and cell-cell junctions [2, 71]. *Adherens junctions* connect the actomyosin networks of different cells with each other, and they form strong bonds and initiate cell polarization; *tight junctions* are the strongest cell-cell connections, and they are used to create impermeable physical barriers; *gap junctions* are intracellular ion channels that allow cell-cell communication; *integrins* connect the cell cytoskeleton with the ECM plus a selection of further adhesion molecules such as *cadherins, igCAMS, Slit/Robo, Ephrin/Eph*, etc., [2, 71, 79, 145, 175].

The transition between tightly packed cells and free-moving cells is fluent, and it depends to a large extent on the adhesion processes that are involved. For example, myoblasts and myofibers are so tightly connected that they can exert physical forces (muscles); epithelial sheets form the lining of many organs and vessels, where it is important to separate an "inside" from an "outside" [79]; in angiogenesis, endothelial cells move and sprout new vessels, which requires loose adhesion as compared to mature vessels [79]; the movement of immune cells occurs in small cell clusters or as individual cells [145], and it requires highly variable adhesion properties of the immune cells. Cancer cells often lose their adhesive properties, which results in local invasion and metastasis [187]. The form of cancer invasion is highly variable, and many different types have been identified, including cluster invasion, small cell groups, cancer-immune cell clusters, individual cells, and network-type invasions [71].

An important process in tissues is the *epithelial-mesenchymal transition* (EMT), where stationary epithelial cells lose their adhesive properties and become invasive, mesenchymal-like cells [86, 139, 187]. The EMT requires a combination of mechanisms such as changed cytoskeletal dynamics and changed adhesive properties. The EMT is a hallmark of cancer metastasis [89, 90], and it is very important to understand the influence of adhesion on the EMT.

A detailed mathematical analysis of adhesion models can contribute to our understanding of this important process and explain, complement, and enrich biological and experimental observations.

1.2 Prior Modelling of Cellular Adhesions

Cell adhesions are forces that act on the cell membrane. For a mathematical or computational model, these forces need to be computed and balanced. Hence an individual cell modelling approach seems to be a natural way to start. Indeed, the first model for cell sorting through differential adhesion was a model of Graner and Glazier from 1991. They used a Cellular Potts model approach, where individual cells are represented as collection of lattice sites in a two-dimensional lattice [80, 83–85]. Cellular adhesions are implemented as interface energies of cells that are touching at a common interface. Since in this model a single cell contains many lattice sites, the adhesion is a non-local interaction. The deformation and movement of the cells is described as an energy minimization approach. Interface energies are balanced with cell volume and cell shape energies plus a random component due to noise. At each step, random changes in the lattice configuration are proposed and accepted by a Boltzmann-like function. Over the years, these Cellular Potts models have become very successful modelling tools, and they have been widely used in applications [165]. For example, Turner et al. [180] used a Cellular Potts model to study the effect of adhesion at the invasion front of a tumor. They observed the formation of clusters of invasion and the formation of "fingering" invasion fronts. In [181],

they attempted to scale the Cellular Potts model to a partial differential equation. However, the obtained macroscopic equations are notoriously difficult to analyze.

In 1996, Byrne et al. [32] studied the growth of avascular tumor spheroids in the presence of an external nutrient. The tumor growth is determined by the balance between proliferative pressure and cell-cell adhesion, which keep the spheroid compact. The DAH of Steinberg of surface tension on cell clusters is implemented by the Gibbs-Thompson relation, which relates the tumor spheroid's curvature to the external nutrient concentration. It is assumed that cell-cell adhesion is the force that maintains this curvature [32]. Later, this model was modified such that the cell's proliferation rate depended on the total pressure acting on the cell (due to adhesion and repulsive forces) [33]. This model was then successfully compared to a cell-based model of tumor spheroid growth [33]. In a similar model, Perumpanani et al. [151] introduced a density-dependent diffusion term in a tumor spheroid model; the idea was that cells in high-density areas are slowed down by the presence of adhesion bonds to neighbors. Since then, this approach has been used in more complicated models of tumor growth (see [118, 123]). The adhesive mechanism in these models is purely local. Further, none of these models was able to reproduce cellular aggregations nor cell sorting commonly linked to adhesive interactions.

Different to the Cellular Potts model, Palsson et al. [150] used a lattice-free model, resolving the individual physical forces between the cells using the theory of elasticity. Cells are represented as deformable ellipsoids with long- and short-range interactions with other cells. This model is a non-local individual-based model, and Palsson et al. used it to describe chemotaxis and slug formation in *Dictyostelium discoideum* [150]. In a similar approach, cells are modelled as elastic isotropic spheres, where adhesive and repulsion forces between adhering elastic spheres are resolved using a modified Hertz model [163, 164] or the Johnson, Kendall, and Roberts model [57, 104, 111]. Since these interactions act over a wide range of cell separations, they are non-local models.

Brodland et al. used a vertex model (an individual-based model) to model cell sorting in epithelial tissues [26, 41]. Similar to Steinberg's assumptions, the model considers surface tension at cell-cell interfaces. The surface tension in their model depended on the forces of adhesion, membrane contraction, and circumferential microfilament bundles [26]. They summarized the findings of their numerical studies by formulating the *Differential Interfacial Tension Hypothesis* of cell sorting [25]. Once again, this was a non-local description of cell adhesion.

Since up to this point all cellular adhesion models capable of explaining aggregations and cell sorting were based on non-local models in cell-based approaches, Anderson proposed to combine the continuum and cell-based approaches in a hybrid model [8]. The significance of this hybrid approach is that cells are individually represented (adhesion effects can be taken into account) and environmental factors such as diffusing proteins and chemokines can be modelled using well-established reaction diffusion equations. This approach has been popular in studying the dynamics of tumor spheroids [157, 158].

In 2006, Armstrong et al. proposed the first continuum model of cellular adhesions capable of explaining adhesion-driven cell aggregations and cell sorting [10]. Since

this model is the focus of our monograph, we represent it in its basic and one-dimensional form here. Let $u(x,t)$ denote the density of a cell population at spatial location x and time t. Then its evolution subject to random motility and cell-cell adhesion is given by the following non-local integro-partial differential equation

$$\frac{\partial}{\partial t}u(x,t) = \underbrace{D\frac{\partial^2}{\partial x^2}u(x,t)}_{\text{random motility}} - \underbrace{\alpha\frac{\partial}{\partial x}\left(u(x,t)\int_{-R}^{R}h(u(x+r,t))\Omega(r)\,\mathrm{d}r\right)}_{\text{cell-cell adhesion}}, \tag{1.1}$$

where D is the diffusion coefficient, α the strength of the homotypic adhesion, $h(u)$ a possibly nonlinear function describing the nature of the adhesive force, $\Omega(r)$ an odd function, and R the sensing radius of the cell. We give a detailed description of this model and the biological meaning of the terms in Sect. 2.1; see also [31] for a derivation from a stochastic process. An intuitive explanation of the non-local cell-cell adhesion term in Eq. (1.1) is given in Fig. 1.3. The non-local term represents a tug-of-war of the cells on the right and the cells on the left, with the cell at x moving in the direction of largest force. The effect is that cells move up "non-local" gradients of cell population and thus arises the possibility for formation of cell aggregates. The two-population version of Eq. (1.1) was the first continuum model that correctly replicated cell sorting experiments [10]. The significance of these non-local continuum models is that they extend the existing rich toolbox [24, 60, 66, 134, 141] of reaction-diffusion-advection equations to include cell adhesion and thus models of tissues.

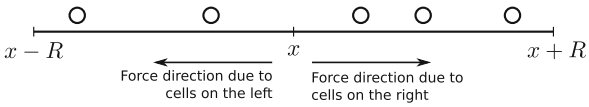

Fig. 1.3 Intuitive description of the non-local adhesion term. Two cells are pulling to the left and three cells are pulling to the right; hence, the net force is to the right (assuming that all cells generate the same force)

As discussed above, cellular adhesions feature prominently in organism development, wound healing, and cancer invasion (metastasis). Therefore, it is unsurprising that model (1.1) has found extensive use in modelling cancer cell invasion [7, 40, 76, 77, 148, 166] and developmental processes [11]. More recently, spatio-temporal variations of the adhesion strengths [56] and adhesion strength variations due to signalling proteins [20] were considered.

The non-local model (1.1) has also been criticized for oversimplification, namely, for its use of a simple diffusion term [133]. Supported by experimental data, Murakawa et al. [133] noticed that under certain conditions Eq. (1.1) gave unrealistic solutions. To address this shortcoming, Murakawa et al. modified the modelling assumption "cells move randomly" to "cells move from high pressure to low pressure regions". For this reason, they introduced a density-dependent diffusion term of porous medium type [133].