# MODELLING THE DYNAMICS OF ACTIN IN CELLS 

by

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#### Abstract

The cytoskeleton is a macromolecular scaffold which gives the cell its shape and controls cellular motion. Actin is the most abundant proteins in the cytoskeleton and an important determinant of its structure and mechanical properties. Actin monomers polymerize into filaments that are then linked to one another by a variety of binding proteins. Filaments can organize into unipolar and bipolar bundles as well as orthogonal networks. The formation of these structures and the transitions between them depend on the types, quantities, and properties of the binding proteins.

The problem addressed in this thesis concerns interactions of actin filaments with actin binding proteins. I investigate the main mechanisms governing the formation of a variety of cytoskeletal actin structures as well as transitions between them. In particular I discuss how the type of binding protein and its binding kinetics affects the structures formed. I further investigate the influence of the geometry of the molecules and the dimensionality of the environment (for example the presence of a surface near which the structures form).

Dynamic continuum models analogous to the mean field approximation in physics are used to study the time evolution of angular distributions of actin filaments. Integropartial differential equations are derived for two types of events: (a) rapid binding of filaments, and (b) gradual turning and alignment of filaments. Linear stability analysis is applied to 2D and 3D versions of such models. Numerical analysis and explicit solutions are discussed in special cases.

It is found that as the actin filament density increases in the cell, a spontaneous


tendency to organize into bundles or networks occurs. Both the linear stability analysis and the numerical results indicate that the structures formed are highly sensitive to changes in the parameters including the total mass of actin filaments, the rotational diffusion coefficient and rate constants representing binding and unbinding. Criteria (involving combinations of these parameters) are obtained for instability of the homogeneous steady state and appearance of order. Similar results are obtained for both rapid and gradual alignment models, suggesting robustness of the modelling approach.

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## Chapter 1

## Introduction

### 1.1 The cellular cytoskeleton

A molecular scaffold, referred to as the cytoskeleton, enables a cell to adopt a variety of shapes and to carry out various functions including motility. This highly complex network consists of numerous protein filaments and may exhibit physical properties similar to a liquid or a solid at different times and at different locations in the intracellular medium of the cell, the cytoplasm. The cytoskeleton is distinct for two main evolutionary classes of living organisms: the eucaryotic cells (e.g. animal cells) which have a cytoskeleton and the procaryotes (e.g. bacteria), which do not.

The three principal types of protein filaments forming the cytoskeleton are: actin filaments, microtubules and intermediate flaments. Even though these three major protein filaments all participate in the cytoskeletal structure in animal cells, they have different functions. For example, the intermediate filaments are found in a basket-weave of fibers which extend from the nucleus to the membrane and provide mechanical integrity. Microtubules are the thickest of the filaments. They are long cylindrical rods which radiate from one site (the microtubule organizing center or centrosome) to the cell periphery, and play a key role in over-all organization of cell movement (for example, by transporting organelles or vesicles, thereby facilitating communication between different parts of the cell). Actin filaments are also vitally important in the mechanical structure and motility of the cell. Actin filaments are rarely found solitary, but associate into networks,
bundles, or various complex structures which undergo dynamic rearrangement during cell motion, cell division, and other functions of the cell. Both actin and microtubules are dynamic structures that polymerize and depolymerize, associate and dissociate (into bigger structres) on a $\mu$ s time scale.

Recent studies suggest that all of the above classes of filaments are implicated in the motility and alignment of cells along certain preferred axes of orientation (Oakley and Brunette, 1993), particularly when the cells are grown on grooved surfaces. Abundant information is available on actin dynamics and structures and this will form the main topic of this thesis.

A variety of smaller proteins are associated with actin and are believed to take a leading role in these structural transitions. Indeed, actin filaments by themselves have little mechanical strength. However, in the presence of these auxiliary proteins, which connect actin filaments to one another in various configurations, stronger well-defined structures are formed. The types, the amounts, and the affinities of the attachment proteins determine the type of structure that forms, and are thus of great importance to cellular function. The actin structures are not static, but constantly changing as an integral part of cell movement and cell function. In this thesis we concentrate exclusively on the dynamics of actin structures, and on transitions that take place under the influence of the actin-related proteins.

### 1.2 Actin structure and function

Actin has become one of the most carefully characterized proteins in cell biology since its discovery in muscle in the 1940s, and non-muscle cells in the 1960s. It is an abundant protein in cells and an important determinant of the structure and mechanical properties of the cytoplasmic matrix.


Figure 1.1: A schematic representation of the helical structure of an actin filament (a), and attached myosin filaments and heads which determine its pointed and barbed end (b). Taken from Stossel (1994).

The actin molecule exists both as a monomer (globular or G-actin), and as a polymer (filamentous actin, F-actin, or microfilaments) in cells. Each globular actin has binding sites on its surface that allow it to associate with two other monomers in a helical arrangement (see, e.g. Stossel, 1994; Alberts et al., 1989; Bray, 1990). The orientation of the actin monomers in this double helical structure provides it with a unique polarity, see Fig. 1.1. This polarity is most easily detected by allowing the filaments to react with a protein molecule, myosin, which binds to each actin subunit in a filament in a very precise fashion giving the appearance of a series of arrowheads. The direction in which the arrowheads point defines the pointed end, and the other end is called the barbed end, see Fig. 1.1. Actin filaments grow bidirectionally by addition of monomers with different rates of assembly (i.e. different growth rates) at opposite ends. Thus F-actin may be viewed as a polar macromolecule with a pointed (slowly growing) and a barbed (fast growing) end.

The slow step of assembly of a few actin molecules provides a nucleus for the formation of an actin filament. An equilibrium is quickly reached whereby the so-called 'critical concentration' of monomer is in apparent equilibrium with F -actin filaments.

Actin filaments are essential for many forms of cellular motility. In non-muscle cells, actin filaments are highly dynamic on a second to minute time scale. Since the 1970's it has been generally recognized that in cultured motile cells, polymerized actin occurs in at least two distinguishable states of structural organization: in linear fibrillar bundles commonly referred to as stress fibres - and in isotropic meshworks or networks confined to the motile lamella zones and ruffling membranes, see Fig. 1.2a-b, (Small et al., 1982; Stossel et al., 1985; Stossel, 1984; Weeds, 1982). The transitions between bundles and meshworks are vital to cell motion and organization.

In some actin structures the filaments display locally uniform polarity whereas in others they display opposite polarity or no polarity. The bundling proteins such as fascin, fimbrin and villin create polarized bundles (Pollard and Cooper, 1986). Unidirectionally polarized microfilament structures are found in microvilli of epithelial cells, and in streocilia of cochlear hair cells. F-actin structures which do not display any polarity are observed in the cell cortex, and in the periphery of various cells including amoebas, macrophages, leukocytes and blood platelets. In these latter cases the filaments intersect in a perpendicular fashion. In both stress fibres in fibroblasts and epithelial cells in culture the filaments are organized into bundles without being polarized (Stossel, 1984).

Populations of actin filaments have been observed to rearrange in a variety of cells, for example during differentiation of embryonic carcinoma cells, during locomotion of fibroblasts or during development of yeast cells. See (Way and Weeds, 1990; Meulemans and De Loof, 1992). It has been revealed that the structural organization of actin filaments can also form and disappear rapidly in various cellular phenomena such as mitosis


Figure 1.2: Network of actin filaments (a), joined and held nearly perpendicular by the cross-linking proteins (e.g. ABP or filamin), and bundles of actin filaments (b), joined and held nearly parallel by the bundling proteins (e.g. villin, fascin). Note that the helical arrangement of actin subunits in the filaments is not reflected in this figure.
and fertilization (Pollard, 1990). The rearrangement of actin cytoskeleton in a cell is now known to affect many functions of the cell. It also plays a dominant role in various phenomena, such as the motility of a parasitic bacterium inside a host cell. The bacterium Listeria monocytogenes propels itself through the host cell cytoplasm using a tail-like actin meshwork that it assembles on its posterior end (Theriot and Mitchison, 1992).

### 1.3 Actin associated proteins

The microfilaments interact with various other proteins in the cell: anneal end to end, fragment, become capped at the ends, crosslink and organize into diverse structures. The self-assembly of actin structures is regulated in a remarkably precise manner; it occurs at particular times and in discrete places within the cell. It is now recognized that this control is conferred by actin binding proteins. After the discovery of the major classes
of actin binding proteins in the 1980's it seemed possible that the assembly and function of actin in cells might be explained by relatively simple mechanisms involving a small handful of proteins (Cooper, 1991; Pollard and Cooper, 1986; Pollard et al., 1990). Some of these actin binding proteins lead to interactions between flaments by linking them together in various ways. The cross linking proteins promote the formation of orthogonal meshworks and the bundling proteins promote the alignment of filaments in bundles. The role and function of each binding protein is determined by observing how it interacts with microfilaments. However, the mechanism by which a variety of filament structures form or switch from one to another in a cell when all actin binding proteins are acting in concert is unclear.

The actin binding proteins are classified in different groups according to how they interact with actin. Actin monomer binding proteins, capping proteins, severing proteins, proteins that bind to the sides of actin filaments and membrane attachment proteins are the major different groups in eucaryotic cells. The proteins that bind to the sides of actin filaments are generally considered in three different subgroups based on their functional properties. Among those, except for the group including tropomyosin which bind to only one filament at a time, the cross linking proteins and the bundling proteins promote interactions between filaments. In this thesis we focus attention to proteins in these two classes. Cross-linking proteins include ABP and filamin, and the filaments form networks or meshworks where they are joined approximately at $90^{\circ}$ angles via these proteins (Stossel, 1990; Tilney et al., 1992a-b; Hartwig, 1992; Hartwig et al., 1980; Weeds, 1982). The bundling proteins include villin and fascin, and the filaments produce structures where actin filaments are aligned parallel to each other (Cooper, 1991; Pollard and Cooper, 1986; Weeds, 1982). Further details about the binding proteins are given in section 3.3.

### 1.4 Review of previous work

There is a wealth of literature which focuses on actin and its dynamics. Several branches of science have led to recent progress in this subject, including cell biology, biochemistry, biomathematics, biophysics, colloid and polymer chemistry, rheology and thermodynamics. As a result of interdisciplinary efforts, several important symposia and conferences have served to summarize the progress in this field. The effect has been to stimulate researchers to explore the molecular and mechanical basis of important phenomena such as cell motility or mitosis. Numerous studies have attempted to unravel the mechanism of motility at the cytoskeletal level. Although knowledge of the constituents and the organization of components has been elucidated, the details of mechanisms are largely unknown.

Experimental and theoretical studies of the formation of different cytoskeletal structures and the properties of the resulting structures have been previously considered. Recent work by Dufort and Lumsden (1993a,b) has provided dynamic visual images of the actin cytoskeleton and its interactions with many binding proteins. The cellular automaton simulation that they have produced allows an exploration of the interactions of a small population of actin molecules. The three dimensional spatial positions, binding and unbinding, and the spatial and rotational diffusions of individual molecules is shown. The results reveal the dramatic transitions that these molecules undergo. (See video supplement to 1993a.) Their papers also contain detailed values of parameters associated with actin kinetics. Their model is a complex and realistic simulation, with many parameters. The realism of the simulation makes it hard to dissect the essential effects from the many competing influences.

In other previous theoretical considerations the approach is a mechanical one, considering the effects and the balance of the forces in and outside of the cell and neglecting
the microscopic interactions and their influences on the mechanical properties of the cytoskeleton. In a recent publication, Sherratt and Lewis (1993) consider the alignment of intracellular actin filaments as a response to external forces (stress and strains) or to an anisotropy in the stress field of the filaments themselves. Their approach is a mechanical one, based on a balance of forces in the system. In their model, the interactions between the filaments, as well as the turnover rate and the strength of the bonds between them is reflected in a single parameter: the sensitivity parameter.

Oster, Murray and Odell (1985) present a model accounting for the formation of regular hexagonal patterns in microvilli solely as a consequence of the mechanical instability of the contractile acto-myosin gel. In (Oster and Odell, 1984), the actin-myosin meshwork is considered, and the dynamic contractile behavior of the cytogel is captured in a model based on the mechanical properties of the gel which, in turn, are regulated by a chemical trigger. In these models, the cross-links between actin filaments are assumed to be permanent, and the cytogel is viewed as an elastic material. However, according to (Sato et al., 1987), the mechanical properties of the cytoskeleton also depend on (or are influenced by) the dynamics of the rapid rearrangement of these bonds. Thus, there is a problem with the above approach, namely, on the time scales of interest, the cytoskeletal network behaves as a viscous fluid with negligible elasticity. Oster (1989) gives a review of the role of the mechanical aspects in cell motility and morphogenesis.

Other mechanical models of the contractile behavior of the actin-myosin meshwork appear in (Alt, 1987; Pohl, 1990). In (Alt, 1987) the actin-myosin meshwork is viewed as a creeping viscous fluid with negligible elasticity. Thus, in this model the filament cross-links are not assumed to be permanent. Pohl (1990) models in vitro experiments of actin-myosin based contraction waves, stimulated by external forces, regarding the cytoplasmic matrix as a mixture of a fibroid network and an aqueous solution. Applying
the laws of fluid mechanics to this mixture, he describes the dynamic behavior of the cytogel. His model is based on the Reactive Flow Model of the cytoplasm reviewed in (Dembo, 1989). Dembo (1989) reviews the mechanical theory of the dynamics of the contractile cycle of actin cytoskeleton, considering a dynamic F-actin network. In this model, the network is assumed to be isotropic and the network synthesis and breakdown, as well as the formation of cross-links between the filaments are described by single terms in the equations.

The importance of the key structural elements in these phenomena, the actin binding proteins, has been noted in the above papers. However the interactions between the actin filaments and the binding proteins and the consequences of these interactions have not been included in most of these models.

### 1.5 Goals and Objectives

In this thesis we investigate the hypothesis that molecular interactions between actin filaments and the actin associated proteins lead to the formation of order and the transitions between different structures formed by the actin cytoskeleton. We further propose that these transitions occur even in the absence of external mechanical forces.

To investigate this hypothesis we must derive models for the dynamic changes in actin. (The problem cannot be studied as an equilibrium phenomenon, but rather as a kinetic one.) These models will permit characterization of the essential aspects of molecular interactions promoting order of several types: bundles, networks, versus isotropic arrangements of microfilaments. We focus on the orientational distribution of filaments in these structures, not on the spatial density. (But see Mogilner and Edelstein-Keshet 1994c for a general framework of spatio-angular models.)

Biological experiments have produced a wealth of information about details of the chemistry, biochemistry, and molecular biology of the actin structures. However, much of this knowledge is focused either on individual molecules or on macromolecular assemblies, but not on the relationship of one level of complexity to the next. The goal of this thesis is to link the properties at the level of individual molecules with the behavior of the ensemble. The mathematical model provides this linkage.

An additional objective of the modelling approach is to determine the sensitivity of actin dynamics to parameters such as the kinetic rate constants, the concentrations, and the affinities of the various intermediates. The importance of this issue has been recently proposed by Wachsstock et al (1994). Recent interest has arisen in the comparison of cytoskeletal structures found in different species of organisms whose actin associated proteins are related, but have slightly different kinetic rates.

The models discussed here describe the angular density of the actin structures, such as might occur in a particular location inside the cell. I will study two structurally distinct classes of models here. One class (Chapter 2) accounts for rapid (one-step) actin filament alignment in response to interactions with other filaments mediated by specific types of binding-proteins. A second class (Chapter 3) deals with more gradual drift-like turning and alignment. In chapter 4, the basic model of the first sort is modified to allow for the presence of a surface, such as the cell membrane.

The challenge of deriving a suitable model is that it is desirable to capture the essential aspects of the phenomenon, whilst keeping the model simple enough to analyse. This is a rather difficult task considering the overwhelming quantity of biological, bio-physical and bio-chemical information on the components of the cell. Further, it is of interest to investigate the robustness of the predictions to the formulation of the model. For this purpose, comparisons were made between the two distinct ways of modelling analogous
situations; that is, I investigated a given class of binding proteins in each modelling scenario, and found essentially similar conclusions.

## Chapter 2

## Models for rapid alignment of actin filaments

### 2.1 Introduction

In this chapter I develop a model to study the formation of parallel and orthogonal actin filament structures as well as the transitions between these. We first ask several questions about the formation of such actin filament structures. We ask which type of molecular interactions and properties observed biologically can account for the observed dynamics of actin in the cell. We also consider how properties at the molecular level (for example, affinities of binding proteins) can affect the macro-molecular structure and organization, and how changes in the details of the interactions can affect the outcome of the structures that form. Towards this goal we will reformulate, in mathematical terms, the dynamics of the actin filaments in the cell based on the elements and properties reported in the biological literature (Stossel, 1990). Second, we address the question of a spontaneous switch between the orthogonal and parallel structure and the sharpness of this transition in a model that accounts for the presence of two types of actin binding proteins.

The model(s) will allow us to reach the following conclusions:
(1) When the density of actin reaches a critical level, a spontaneous tendency to organize into an orthogonal or parallel structure occurs.
(2) The structure depends on the concentrations of active cross-linking or parallel binding proteins, e.g. filamin and ABP-50 or fibrillin and villin.
(3)Furthermore, the switch between the orthogonal and the parallel aligned structures can occur as a result of a change in the relative binding rates and concentration of the two types of actin binding proteins (cross linking and bundling).

The results presented in this chapter have appeared in the paper Civelekoglu and Edelstein-Keshet (1994).

### 2.2 The molecular approach: a new model based on molecular interactions

Experimental evidence indicates that forces are not essential for the cytoskeletal rearrangement and the rapid changes in the cytoskeletal structure can be mediated by the actin binding proteins. Actin interacts with several different proteins at once depending on the relative binding affinities, concentrations of different proteins, and regulatory factors (Way and Weeds, 1990). A new set of actin binding proteins may be responsible for a change in the cytoskeletal organization of a cell (Vandekerckhove, 1990). Also, the actin binding proteins may act differently under different conditions. For example, some proteins act as cross-linking proteins in the absence of $C a^{++}$, and as capping proteins in the presence of $C a^{++}$. The sol-gel transformation can therefore be regulated by the response of a single molecule to changes in $\mathrm{Ca}^{++}$concentrations (Korn, 1982; Hartwig, 1992). Thus, there exists biological evidence that the changes in the molecular properties of these elements affect the resulting structure, and changes from one structure to the other occurs also in the absence of external forces, via activation or inactivation of the actin binding proteins. Based on the above evidence, we view the cell as a pool of interacting molecules. In the following section we present a model based on the geometry of the molecular interactions, and on the differences between binding proteins that promote a variety of actin structures that form.

According to Stossel (1990) and Pollard and Cooper (1986) the steps in the formation of the actin meshwork are as follows: First, needlelike actin filaments are created by polymerization of individual actin monomers. This process has two stages: the single molecules aggregate to form small groups of three or four molecules -nucleation-, and then the nuclei elongate, eventually generating long, stiff rods of actin. When the length and mass of these filaments reach a certain level, the filaments start to join under the influence of cross-linking proteins in orthogonal networks or bundles. As seen under the electron microscope, some cross-linking proteins join the actin filaments at approximately right angles (Hartwig, 1992; Hartwig et al., 1992; Hartwig et al., 1980; Stossel, 1984; Stossel, 1990; Tilney et al., 1992a-b; Weeds, 1982), whereas the bundling proteins promote binding in parallel. The ways in which the cross-linking and the bundling proteins bring about the high angle branching or the parallel alignment of actin is a function of their structure (Stossel, 1984; Stossel, 1990; Hartwig and Stossel, 1981; Pollard and Cooper, 1986).

The models we formulate in the following sections account for the formation of structure in a pool of actin filaments in the cell and focuses on orientation rather than spatial distributions. We assume the existence of short (ready to bind) actin filaments rather than explicitly modeling the nucleation of filaments.

### 2.3 Model I: one type of binding protein interacting with F-actin (2 dimensional model)

In this section we consider a two dimensional analogue of a truly three dimensional molecular system. The model corresponds to a mean-field approximation of the molecular system. A similar simplification was made in (Sherratt and Lewis, 1993). The model
here closely resembles a model for orientations of interacting cells described in (EdelsteinKeshet and Ermentrout, 1990).

We distinguish between filaments which are bound to other filaments, referred to as Bound filaments, and those which are not, referred to as Free filaments. The following simplifications have been made in deriving this model:
(a) We consider only angular distributions of filaments, not spatial distributions. (Thus the model applies to a small part of the cell.) A fuller model which includes spatial variations is discussed in Mogilner and Edelstein-Keshet (1994b).
(b) Binding and unbinding of filaments is similar at all stages of the process. (Actually once a dense network forms unbinding will be restricted to its exposed surface.)
(c) Monomers are added to the filaments at a rate proportional to the total length of filaments. (Actually, monomers are only added at the ends of an actin filament but we assume that filaments have some fixed average length so that the total number of ends is proportional to the total length of filaments.)
(d) We assume that only free filaments can rotate freely. (In reality small clusters of bound filaments will also undergo rotational diffusion but we do not distinguish between small and large clusters.)

The model is based on the following variables:
$t \quad=$ time,
$\theta \quad=$ an angle, $0 \leq \theta \leq 2 \pi$, with respect to some arbitrary fixed direction,
$L(\theta, t)=$ the concentration (total length) of free actin filaments at orientation $\theta$ at time $t$,
$B(\theta, t)=$ the concentration (total length) of bound actin filaments at orientation $\theta$ at time $t$,
$\beta \quad=$ the rate constant for binding of filaments via actin binding proteins,

```
K(0) = the kernel representing the angular dependence of the rate constant for
        binding,
\rho}\quad= the concentration of free actin binding protein
\delta = the dissociation rate of the actin binding proteins,
g = the concentration of actin monomers,
\nu = the rate of elongation of filaments by addition of monomers at the ends,
\gamma = the rate of shortening of filaments by loss of monomers from the ends.
```

The concentrations of $L$ and $B$ are the total length of filaments (in terms of monomer subunits) inside a unit element of the region, for example, length per unit area in a two dimensional model, or length per unit volume in a three dimensional version. These are analogous to the density function $F(\phi, \rho)$ defined by Sherratt and Lewis (1993), who also neglect the spatial dependence of $F$. Note, however that $L$ and $B$ in our model are time dependent, as we explore a fully dynamic model.

The quantity $\beta K(\theta)$ is the rate constant for binding of one filament to another filament at a relative angle $\theta$ in the presence of actin binding proteins. $\beta$ is the magnitude of the rate constant. The kernel $K$ is a normalized function which represents the effective interaction of molecules at various relative configurations. It is known in many chemical reactions that molecules must first come into the correct relative configurations before they can react. The nature of the kernel K, discussed below, is deduced from several remarks in the literature (Stossel, 1990; Hartwig and Stossel, 1981; Hartwig et al., 1980; Tilney et al., 1992a-b) taking into consideration the molecular properties and the structure of the actin binding proteins. For example, the orthogonal binding protein, Actin Binding Protein, promotes binding of filaments at right angles, see the histogram in (Hartwig et al., 1980) or (Stossel, 1994). Filament densities $L(\theta, t)$ and $B(\theta, t)$ are functions of time and of $\theta$. Since $\theta$ is an angle of orientation, all functions of $\theta$ are
assumed to be periodic, i.e. $L(0, t)=L(2 \pi, t)$ for all $t$.
In deriving the equations of the model we start by considering the behavior of an individual filament. The repertoire of a single filament consists of:
(a) rotational diffusion which results in tumbling and thus random reorientation of the molecules (frictional forces in the cytoplasm will limit this effect for larger molecules),
(b) binding upon contact with another filament and an actin binding protein (this binding is angle dependent).

The rotational diffusion of actin filaments in the cytoplasm can be depicted as a random walk in $\theta$. The associated diffusion coefficient, $\mu$, has been determined in the literature for biopolymers, see (Mossakowska et al., 1988; Phillips et al., 1991; Sawyer et al., 1988; Thomas et al., 1979).

Next, we consider how the free actin filaments binding to others can affect the free filament density at a given orientation $\theta$, namely $L(\theta, t)$. To this end, we first consider the rate that a single free filament at orientation $\theta$ attaches to another free filament, say at orientation $\theta^{\prime}$, in presence of actin binding protein. This rate depends on the density of free filaments oriented at $\theta^{\prime}$, i.e. on $L\left(\theta^{\prime}, t\right)$, and on their relative orientation, i.e. on $\left(\theta-\theta^{\prime}\right)$. Ler $r$ be the effect of filaments at angle $\theta^{\prime}$ on the rate of realignment of a filament at angle $\theta$. Then,

$$
\begin{equation*}
r=\rho \beta K\left(\theta-\theta^{\prime}\right) L\left(\theta^{\prime}, t\right) \tag{2.1}
\end{equation*}
$$

where $\beta$ is the binding rate and $\rho$ is the concentration of actin binding protein. Summing over the density of free filaments at all possible orientations results in $R$, the cumulative effect of all filaments oriented at $\theta^{\prime}$ on the rate of realignment of a filament at angle $\theta$.

Then,

$$
\begin{equation*}
R=\rho \beta \int_{0}^{2 \pi} K\left(\theta-\theta^{\prime}\right) L\left(\theta^{\prime}, t\right) \mathrm{d} \theta^{\prime} \tag{2.2}
\end{equation*}
$$

Finally, we consider the effect of such binding on the total density of free filaments oriented at $\theta$, which is:

$$
\begin{equation*}
\frac{\partial L(\theta, t)}{\partial t}=-\rho \beta L(\theta, t) \int_{0}^{2 \pi} K\left(\theta-\theta^{\prime}\right) L\left(\theta^{\prime}, t\right) \mathrm{d} \theta^{\prime} \tag{2.3}
\end{equation*}
$$

For notational simplicity, we adopt the $*$ notation for the above convolution integral, i.e.

$$
\begin{equation*}
K * L=\int_{0}^{2 \pi} K\left(\theta-\theta^{\prime}\right) L\left(\theta^{\prime}, t\right) \mathrm{d} \theta^{\prime} \tag{2.4}
\end{equation*}
$$

As mentioned above, actin filaments bind to each other via auxiliary protein molecules of different structures. With cross-binding proteins, e.g. ABP or filamin, F-actin forms networks or meshworks joined approximately at $90^{\circ}$ angles (Stossel, 1990; Tilney et al., 1992a-b; Hartwig, 1992; Hartwig et al., 1980; Weeds, 1982), whereas the bundling proteins, e.g. villin or fascin, produce parallel actin filaments (Cooper, 1991; Pollard and Cooper, 1986; Weeds, 1982). ABP and filamin are long flexible hinge-like molecules whereas villin and fascin are short rod-like molecules (Stossel, 1990; Pollard and Cooper, 1986). Differences in the structures of these binding proteins implies differences in the geometry of binding. In the presence of a binding protein, two filaments bind upon contact depending on (a) the kinetic rate constant of the binding protein, and (b) the proper configuration being attained by the filaments at the binding site. The critical angular range for successful binding depends on the molecular structure of the given binding protein. In the model, the relative angle formed by the actin filaments, $\theta$, must be within some critical range for binding to occur in each case. This is depicted by
the function $K(\theta)$. In the thesis we will consider several types of kernels associated with binding proteins but in this chapter we restrict attention to two types: one which accounts for orthogonal cross-linking of F-actin, and a second one for the bundling of F-actin. The critical angles $a$ and $b$ in the equations below reflect this range for the orthogonal binding and bundling proteins. Thus, modelling the orthogonal binding of F-actin we consider kernels of the following form (see Fig. 2.3a):

$$
K_{1}(\theta)=\left\{\begin{array}{cc}
f(\theta) & \text { for }\left|\theta-\frac{\pi}{2}\right| \leq a \text { or }\left|\theta-\frac{3 \pi}{2}\right| \leq a  \tag{2.5}\\
0 & \text { otherwise }
\end{array}\right.
$$

and modelling parallel binding we consider the following type of kernels (see Fig. 2.3b):

$$
K_{2}(\theta)=\left\{\begin{array}{cc}
h(\theta) & \text { for } \theta \leq b \text { or }|\theta-\pi| \leq b \text { or } 2 \pi-\theta \leq b  \tag{2.6}\\
0 & \text { otherwise }
\end{array}\right.
$$

It was argued by Edelstein-Keshet and Ermentrout (1990) that the specific form of these functions is of no consequence for the conclusions of the model as long as they satisfy certain symmetry properties. The critical angles $a$ and $b$, beyond which the binding does not take place represent a range of angular attraction ( $a=20^{\circ}$ and $b=30^{\circ}$ in Fig. 2.3a-b, respectively). We also normalize K by requiring,

$$
\begin{equation*}
\int_{0}^{2 \pi} K(\theta) \mathrm{d} \theta=1 \tag{2.7}
\end{equation*}
$$

This means that the angle dependence, summed over all possible angles of interaction is set to 1 . The following functional differences are assumed between $L$ and $B$ type filaments:
(1) Free filaments reorient randomly but bound filaments do not.


Figure 2.3: Shapes of angle dependent kernels representing the angle dependence of binding of two actin filaments via (a) orthogonal actin binding proteins and (b) bundling proteins. We assume a uniform concentration of actin binding proteins in the cell. The vertical axes represent the kernel and the horizontal axes represent the angle between two contacting filaments. The critical angles are as follows: $a=20^{\circ}$ in (a) and $b=30^{\circ}$ in (b).
(2) Binding of two filaments occur if two filaments contact in presence of actin binding proteins.
(3) All bound filaments can become free by dissociation of proteins at some fixed unbinding rate $\delta$. (Actually, $\delta$ would probably be density dependent as bound filaments on the inside of a large network would have very low rate of dissociation. We do not include this effect in the model.)
(4) Filaments can elongate by addition of actin monomers, $g$, at the constant rate $\nu$.
(5) Filaments can shorten (loss of actin monomers from ends) at a constant rate $\gamma$. (Recall the assumption that the number of free ends is proportional to the total length of the filaments.)

The following set of equations depict the interactions described above:

$$
\begin{align*}
& \frac{\partial L}{\partial t}(\theta, t)=\mu \frac{\partial L^{2}}{\partial \theta^{2}}-\gamma L+\nu g L+\delta B-\beta \rho L(K * B)-\beta \rho L(K * L) \\
& \frac{\partial B}{\partial t}(\theta, t)=-\gamma B+\nu g B-\delta B+\beta \rho B(K * L)+\beta \rho L(K * L) \tag{2.8}
\end{align*}
$$

The terms in the equations (2.8) have the following meanings: $L(K * B)$ represents the rate at which free filaments, oriented at $\theta$, bind to bound filaments at arbitrary orientations, $L(K * L)$ denotes the rate at which they bind to free filaments at arbitrary orientations, and $B(K * L)$ denotes the rate at which free filaments, at arbitrary orientation, bind to bound filaments oriented at $\theta . \mu$ denotes the rotational diffusion constant of F -actin, and the first terms in the right hand side of the equation for free filaments represents the angular diffusion of filaments freely rotating in the cytoplasm. $\rho$ denotes the actin binding protein concentration. $\beta$ denotes the rate constant for binding of filaments by an actin binding protein and $\gamma$ denotes the dissociation rate of the actin binding proteins.

The $\theta$-independent steady state of these equations, $(\bar{L}, \bar{B})$, corresponds to the case in which the total addition of actin monomers to filaments equals the total loss of actin monomers from filaments. (This equilibrium state is referred to as the treadmilling state in Stossel (1990).) Thus the second and third term in the equation for free filament density and the first two terms in the equation for bound filament density cancel each other and (2.8) reduces to the following system of equations, similar to equations (17) in (Edelstein-Keshet and Ermentrout, 1990):

$$
\begin{align*}
& \frac{\partial L}{\partial t}(\theta, t)=\mu \frac{\partial L^{2}}{\partial \theta^{2}}+\delta B-\beta \rho L(K * B)-\beta \rho L(K * L) \\
& \frac{\partial B}{\partial t}(\theta, t)=-\delta B+\beta \rho B(K * L)+\beta \rho L(K * L) \tag{2.9}
\end{align*} .
$$

Also, the total mass density of actin filaments in the system is conserved, i.e.

$$
\begin{equation*}
M=\int_{0}^{2 \pi}\{L(\theta, t)+B(\theta, t)\} \mathrm{d} \theta \tag{2.10}
\end{equation*}
$$

is constant. The quantity M will be treated as a constant throughout the present analysis. Later we will be interested in the situation in which $M$ is allowed to vary slowly.

The equations (2.9) can be written in the following dimensionless form:

$$
\begin{align*}
& \frac{\partial L}{\partial t}(\theta, t)=\varepsilon \frac{\partial L^{2}}{\partial \theta^{2}}+\xi B-L(K * B)-L(K * L) \\
& \frac{\partial B}{\partial t}(\theta, t)=-\xi B+B(K * L)+L(K * L) \tag{2.11}
\end{align*}
$$

where $\xi=\delta / \beta \rho M$ and $\varepsilon=\mu / \beta \rho M$ are dimensionless parameters. Also, the densities $L$ and $B$ are dimensionless quantities. The details of this non-dimensionalization is given in the Appendix A.

### 2.4 Analysis of Model I

The analysis of the model is similar to the analysis of the model in (Edelstein-Keshet and Ermentrout, 1990). The homogeneous steady state $(\bar{L}, \bar{B})$ of the system (2.8), or equivalently (2.9) is found by setting:

$$
\left\{\begin{array}{l}
\frac{\partial L}{\partial t}=0=\frac{\partial L}{\partial \theta}  \tag{a}\\
\frac{\partial B}{\partial t}=0=\frac{\partial B}{\partial \theta}
\end{array}\right.
$$

and satisfies :

$$
\begin{equation*}
\frac{\bar{B}}{\bar{L}}=\frac{\beta \rho M}{\delta}=\frac{1}{\xi} \tag{2.12}
\end{equation*}
$$

This represents a time independent population in which all orientations are equally represented. If this steady state is stable, the population will persist in the ratio (2.12b) and no angle or orientation will be favored. However, if noise can disrupt this steady state, i.e. if it is unstable, the situation might change to one where some angles are favored. We investigate this possibility by considering small perturbations from the steady state. Equations (2.9) can be linearized about the homogeneous steady state by substituting $L(\theta, t)=\bar{L}+L_{0}(\theta, t)$ and $B(\theta, t)=\bar{B}+B_{0}(\theta, t)$ into (2.9) and retaining linear terms:

$$
\begin{align*}
& \frac{\partial L_{0}}{\partial t}(\theta, t)=\mu \frac{\partial L_{0}{ }^{2}}{\partial \theta^{2}}+\delta B_{0}-\beta \rho\left(\bar{L}\left(K * B_{0}\right)+L_{0} \bar{B}\right)-\beta \rho\left(\bar{L}\left(K * L_{0}\right)+L_{0} \bar{L}\right)  \tag{2.13}\\
& \frac{\partial B_{0}}{\partial t}(\theta, t)=-\delta B_{0}+\beta \rho\left(\vec{B}\left(K * L_{0}\right)+B_{0} \bar{L}\right)+\beta \rho\left(\bar{L}\left(K * L_{0}\right)+L_{0} \bar{L}\right)
\end{align*}
$$

When $L_{0}$ and $B_{0}$ are sufficiently small to render the linear approximation (2.13) a valid representation of the full equations (2.9), the linear stability theory is an adequate method for the analysis of the states near the steady state value $(\bar{L}, \bar{B})$. The details of the linear stability analysis are given in Appendix B. These equations are now linear integropartial differential equations containing the Laplacian operator $\left(\frac{\partial^{2}}{\partial \theta^{2}}\right)$ and the linear operator ( $K *$ ), and they describe the evolution of a small perturbation from steady state. As discussed in Mogilner and Edelstein-Keshet (1994a), both these operators share a common set of eigenfunctions, namely:

$$
\begin{equation*}
e^{i k \theta}, \quad k \in \mathrm{R} \tag{2.14}
\end{equation*}
$$

The fact that the domain $0 \leq \theta \leq 2 \pi$ is periodic (i.e. all functions $H(\theta)=H(\theta \mp 2 \pi n)$ ) will restrict permissible values of $k$ to the integers, $k=0,1,2, \ldots, n$. The terms $e^{i k \theta}$ form an orthonormal basis for periodic functions which satisfy Dirichlet's Conditions, i.e. functions with finite number of finite discontinuities and finite number of turning points. Moreover, any such periodic function $f(\theta)$, with period $2 \pi$ can be expressed as a convergent sum of terms $a_{k} e^{i k \theta}$, referred to as its Fourier series expansion. Thus, considering perturbations where the dependence on $\theta$ is of the form $e^{i k \theta}$ is sufficient to investigate the stability of this steady state. We thus consider perturbations of the form:

$$
\left[\begin{array}{l}
L(\theta, t)  \tag{2.15}\\
B(\theta, t)
\end{array}\right]=\left[\begin{array}{l}
\bar{L} \\
\bar{B}
\end{array}\right]+\left[\begin{array}{c}
L_{o} \\
B_{o}
\end{array}\right] e^{i k \theta} e^{\lambda t}
$$

where $L_{o}, B_{o}$ are small amplitudes, $k$ is the wavenumber (the number of peaks or the number of dominant orientations in $[0,2 \pi])$ and $\lambda$ is the growth rate of the perturbation. As the domain is periodic, with period $2 \pi$, the wavenumber $k$ must be an integer. We seek conditions for which such small perturbations from the steady state are amplified with time, i.e. for which $\lambda>0$ for some wavenumber $k$.

### 2.4.1 Linear stability analysis

Using the form (2.15) for the perturbations and substituting into (2.13) the equations can be written in the following matrix form:

$$
\left[\begin{array}{l}
L_{0}  \tag{2.16}\\
B_{0}
\end{array}\right] \lambda=\mathbf{J}\left[\begin{array}{l}
L_{0} \\
B_{0}
\end{array}\right],
$$

where

$$
\mathbf{J}=\left(\begin{array}{ll}
a_{11} & a_{12}  \tag{2.17}\\
a_{21} & a_{22}
\end{array}\right)=\left(\begin{array}{cc}
-\left(\mu k^{2}+\beta \rho \bar{L}(1+\hat{K})+\beta \rho \bar{B}\right) & \delta-\beta \rho \bar{L} \hat{K} \\
\beta \rho \bar{L}(1+\hat{K})+\beta \rho \bar{B} \hat{K} & -(\delta-\beta \rho \bar{L})
\end{array}\right) .
$$

Here $\hat{K}$ is the Fourier transform of the kernel $K, k$ is the wavenumber, and $\lambda$ is the growth rate of the perturbation as above. See Appendix B for the description of the Fourier transform of $K$. For stability to uniform perturbations and instability to $\theta$ dependent perturbations it is necessary that the determinant of the Jacobian,

$$
\begin{equation*}
\operatorname{det} \mathbf{J}=a_{11} a_{22}-a_{12} a_{21} \tag{2.18}
\end{equation*}
$$

be non-negative for $k=0$ and negative for some integer wavenumber $k$. Such an integer is then a destabilizing wave number or mode. Thus the stability condition is determined
by an algebraic equation, referred to as the dispersion relation, obtained by setting the determinant of the Jacobian matrix to be negative. It is a condition on the type of periodicity that leads to instability. The determinant of the Jacobian in (2.17), with slight rearrangement, leads to the following condition:

## The Dispersion Relation:

$$
\begin{equation*}
C k^{2}<\hat{K}(1-\hat{K}) \tag{2.19}
\end{equation*}
$$

where,

$$
\begin{equation*}
C=\frac{\mu}{\delta}\left(\frac{\delta}{(\bar{L}+\bar{B}) \beta \rho}\right)^{2}=\varepsilon \xi \tag{2.20}
\end{equation*}
$$

is a combination of the parameters in (2.9) or the dimensionless parameters in (2.11). The steady-state $(\bar{L}, \bar{B})$ of (2.9) can be destabilized by perturbations of the form (2.15), provided that the wave number $k$ satisfies (2.19). Only wavenumbers satisfying this inequality will give rise to growing structures. Thus (2.19) must be satisfied for either bundles or networks of actin to form. We can visualize (2.19) graphically as done in (Edelstein-Keshet and Ermentrout, 1990) by plotting the right hand side and the left hand side of it on a common set of axes. This has been done in Fig. 2.4 for various settings of the parameters. The expression on the right hand side of (2.19) as a function of $k$ (the wavy curve in Fig. 2.4a-b) is fundamentally different for the two types of kernels in Fig. 2.3a-b and is scaled differently for different choices of critical angles $a$ and $b$. The left hand side of (2.19) is a parabola in $k$ with coefficient $C$, as shown superimposed in Fig. 2.4a-b. The inequality (2.19) depends on the shape of $\hat{K}(k)(1-\hat{K}(k))$ and on the value of $C$. Though only integral $k$ values are relevant (due to periodic boundary conditions), we plot this expression as a continuous function of $k$ for easier visualization.


Figure 2.4: The expression $\hat{K}(k)(1-\hat{K}(k))$, the wavy curve in Fig. 2.4a-b, is shown as a function of the wave number $k$ for $\hat{K}$, the Fourier transform of the kernels in Fig. 2.3a-b. Superimposed is a set of parabolas $y=C k^{2}$. (The parabola and the function $\hat{K}(k)(1-\hat{K}(k))$ are plotted as continuous functions of $k$, however only integer $k$ values are of interest.) The uniform steady state of (2.9) can be disturbed and pattern formation can be initiated only by perturbations (2.15) whose wave number $k$ is an integer satisfying $C k^{2}<\hat{K}(1-\hat{K})$, where $C$ depends on biological parameters. The sequence of parabolas in (a) and (b) can be generated by varying the total mass of F -actin, $M=(\bar{L}+\bar{B})$, given that the other parameters are constant. Parameters are as follows: in (a) the critical angle is $a=20^{\circ}$ and the coefficient $C$ is 0.04 and 0.01 , in (b) the critical angle is $b=30^{\circ}$ and the coefficient $C$ is 0.06 and 0.02 .

In other words the parabola $C k^{2}$ must be lower than the function of $\hat{K}$ displayed on the right hand side of the inequality at some integer value $k$ for instability at that wave number. In the case where we have a kernel accounting for the orthogonal binding of F-actin, as in Fig. 2.3a, the first integral wave number at which the inequality (2.19) is satisfied is $k=4$, (see Fig. 2.4a). This means that a perturbation of the form $e^{4 i \theta}$ grows, the steady state loses stability and four orientations, $90^{\circ}$ apart, become accentuated among all possible orientations from 0 to $2 \pi$. As a result, the filaments are mostly orthogonal to each other. In the case where we have a kernel accounting for the bundling of F-actin, as in Fig. 2.3b, the first such wave number is $k=2$, as shown in Fig. 2.4b. A perturbation of the form $e^{2 i \theta}$ grows and results in two accentuated orientations $180^{\circ}$
apart. In this case most filaments lie parallel to each other. In both cases the positions of the accentuated orientations are determined by the initial disturbance that disrupts the steady state. However the spacing between them is determined by a wave number $k$, which satisfies (2.19). The instability discussed here is somewhat analogous to the isotropic-nematic transition in liquid crystals.

### 2.4.2 Numerical analysis

The equations of the model were simulated numerically by using an explicit finite difference scheme. To insure stability of the numerical scheme a small value of $\Delta t=0.01$ and forward differencing for $15,000-100,000$ iterations were used. The numerical code used to obtain these results is written in Fortran. Numerical solutions to (2.9) in the case of orthogonal or parallel binding kernels is given in Fig. 2.5a-b and Fig. 2.6a-b. A variety of initial densities were used, including random (in Fig. 2.5a-b and Fig. 2.6a-b) or sinusoidal deviations from the homogeneous steady state densities $\bar{L}$ and $\bar{B}$ (obtained from the steady state equation 2.12 b ), and from other homogeneous densities for $L$ and $B$. The magnitude of these deviations was roughly $10 \%$ of the initial homogeneous densities. (Smaller deviations also cause instability but the time evolution is much slower.) The variables were discretized typically on a grid of 30 to 36 points $\left(\Delta \theta=\frac{360^{\circ}}{30}=12^{\circ}\right.$ and $\Delta \theta=\frac{360^{\circ}}{36}=10^{\circ}$ ). For numerical stability I made sure that the values of $\Delta \theta, \Delta t$ satisfied the Courant-Friedrichs-Lewy condition for a given value of $\mu$ :

$$
\begin{equation*}
\frac{\mu \Delta t}{(\Delta \theta)^{2}} \leq \frac{1}{2} \tag{2.21}
\end{equation*}
$$

See Press et al. (1988). The kernel in Fig. 2.3a was used for Fig. 2.5a-b and the kernel in Fig. 2.3b was used for Fig. 2.6a-b. In the results shown in Fig. 2.5a-b the critical


Figure 2.5: Formation of orthogonal network of F-actin in a pool of initially randomly distributed bound (a) and free (b) actin filaments. Shown are numerical results to (2.9) where $K$ is as in Fig. 2.3a. The horizontal axis is orientation and the vertical axis is the density of bound F -actin at a given orientation in (a) and of free F -actin in (b). Initial densities (not shown) are $L=$ $\bar{L}+L_{o}(\theta, t)$, and $B=\bar{B}+B_{o}(\theta, t)$ where $\bar{L}=0.8, \bar{B}=9.2, L_{o}$ and $B_{o}$ are $10 \%$ random noise. Other parameters are $\delta=\beta=0.5, \rho=5, \mu=0.4$ and M $\approx 10$. The grid size is $\Delta \theta=36^{\circ}$ and $\Delta t=0.01$. The solutions were found for 16,000 iterations, with plots shown at $3,200,6,400$ and 16,000 iterations. Note the scale on free and bound F-actin indicating that most filaments are bound. In (a) and (b) four orientations $90^{\circ}$ apart have been accentuated.
angle is $a=20^{\circ}$ and in Fig. 2.6a-b the critical angle is $b=30^{\circ}$.
In Fig. 2.5 and Fig. 2.6 we present the evolution of bound and free actin filament densities over time. Fig. 2.5 shows formation of parallel filament structures (two preferred orientations) whereas Fig. 2.6 shows orthogonal meshworks of filaments (four preferred orientations), as anticipated from our assumptions about the kernels in each case. It can be seen that structures that develop in the bound population are similar to those that arise in the free actin density. Pattern formation occurred either in both populations or in neither. The number of preferred orientations and their location was identical for bound and free actin filaments. However, pattern formation appeared sooner in one population than in the other for certain choices of parameters. For example if $\delta \ll \mu$, which means


Figure 2.6: As in Fig. 2.5a-b, but showing the formation of parallel networks of F-actin. Shown are numerical results to (2.9) where $K$ is as in Fig. 2.3b, (a) bound F-actin and (b) free F-actin. Initial densities as in Fig. 2.5 where $\bar{L}=0.5$, $\bar{B}=4.5$. Other parameters are $\delta=0.6, \beta=0.5, \rho=4, \mu=1.2$ and M $\approx 5$. The grid size is $\Delta \theta=10^{\circ}$ and $\Delta t=0.01$. The solutions were found for 30,000 iterations, with plots shown at $6,000,18,000,24,000$ and 30,000 iterations. In (a) and (b) two orientations $180^{\circ}$ apart have been accentuated.
biologically that the rotational diffusion of filaments is considerably higher than the dissociation rate of the actin binding proteins with filaments, pattern formation in free actin filaments took considerably longer than in the bound actin filaments. Also, in all simulations, the free actin filament density level was considerably lower than the bound actin filament density level at the final stable configuration. In the following section we will only present the evolution of the bound filament density since the evolution of the two populations is essentially the same.

The results of the numerical simulations matched the predictions of the analysis and pattern formation in networks (Fig. 2.5a-b) or in bundles (Fig. 2.6a-b) was obtained for a choice of parameter values which satisfied (2.19). Changing any of the parameters $M$, $\mu, \delta, \beta$ or $\rho$ affects the value of the dimensionless constant $C$ that appears in (2.19) and thus the stability of the system. For example, when monomers assemble into filaments, the total mass of actin filaments, M , increases. Therefore $C$ decreases and this leads to
the formation of a meshwork or bundles. Similarly, increasing the binding rate of the binding protein, $\beta$, increasing the actin binding protein concentration, $\rho$, or decreasing the dissociation rate of the actin binding protein, $\delta$, in the cell results in formation of meshworks or bundles.

We have also observed that, in the case where the critical angle $a$, or $b$ was either too small, $a, b \leq 5^{\circ}$, or too large, $a, b \geq 40^{\circ}$, no pattern formed (for $\approx 200,000$ iterations) for any choice of the other parameter values. This means that when the range of angular attraction is too small, very few filaments become bound and they are released before getting a chance to form big groups. Most filaments remain free, and thus the directional homogeneity is preserved. In the latter case, i.e. when the range of angular attraction is too wide, the filaments bind to each other at nearly every possible relative angle. Most filaments become bound with no apparent structure, and hence, the directional homogeneity is preserved in this case too.

To summarize, both numerical and analytical results of the model show that the organization of F-actin into orthogonal networks or bundles depends on the biological and chemical properties of the molecules, the parameters in the system. Typical values of parameters taken from biological literature are given in the discussion.

### 2.5 Model II: two types of binding protein interacting with F-actin (2 dimensional model)

In this section we consider the case where both orthogonal and parallel binding can occur. The question addressed is under what circumstances will one of the two forms of structure dominate. To this end we extend the model in section 2.3 to account for the existence of two types of actin binding proteins simultaneously: the cross linking and the bundling proteins. We now allow the actin filaments to bind orthogonally and in parallel.

We also investigate the transition from the network structure to the bundles and vice versa. $K_{1}$ and $K_{2}$ denote the orthogonal and the parallel binding kernels as in section 2.3. Also $\rho_{1}, \beta_{1}$ and $\rho_{2}, \beta_{2}$ will denote the concentrations and the binding rate constants of orthogonal cross-linking (1) and parallel bundling proteins (2), respectively.

The equations depicting the effect of the two types of binding simultaneously can be written as follows:

$$
\begin{gather*}
\frac{\partial L}{\partial t}(\theta, t)=\mu \frac{\partial L^{2}}{\partial \theta^{2}}-\gamma L+\nu g L+\delta B-\beta_{1} \rho_{1} L\left(K_{1} * B\right)-\beta_{1} \rho_{1} L\left(K_{1} * L\right) \\
-\beta_{2} \rho_{2} L\left(K_{2} * B\right)-\beta_{2} \rho_{2} L\left(K_{2} * L\right) \\
\frac{\partial B}{\partial t}(\theta, t)=-\gamma B+\nu g B-\delta B+\beta_{1} \rho_{1} B\left(K_{1} * L\right)+\beta_{1} \rho_{1} L\left(K_{1} * L\right)+  \tag{2.22}\\
\beta_{2} \rho_{2} B\left(K_{2} * L\right)+\beta_{2} \rho_{2} L\left(K_{2} * L\right)
\end{gather*}
$$

In the above equations we have assumed for simplicity that $\delta_{1}=\delta_{2}=\delta$, i.e. that dissociation rates for both types of proteins are approximately equal. In order to reduce to the previous method of analysis, we now define:

$$
\begin{equation*}
K=(1-\psi) K_{1}+\psi K_{2} \tag{2.23}
\end{equation*}
$$

where

$$
\begin{equation*}
\psi=\frac{\beta_{2} \rho_{2}}{\beta_{1} \rho_{1}+\beta_{2} \rho_{2}} \tag{2.24}
\end{equation*}
$$

and

$$
\begin{equation*}
\beta \rho=\beta_{1} \rho_{1}+\beta_{2} \rho_{2}=\frac{\beta_{2} \rho_{2}}{\psi} \tag{2.25}
\end{equation*}
$$

Here $K$ is a combined binding kernel and $\beta \rho$ is a combined binding rate and binding protein density. Note that $\beta_{2}=0$ (or $\rho_{2}=0$ ) results in all orthogonal binding and $\beta_{1}=0$ (or $\rho_{1}=0$ ) results in all parallel binding as in section 2.4. For example, $\rho_{2}=0$ stands for the situation in which the parallel binding protein, villin, is absent. $\beta_{2}=0$ represents the case of binding protein that has no affinity to actin, similar conclusions hold for $\rho_{1}=0, \beta_{1}=0$ with respect to the orthogonal binding protein, see Table 2.1. The parameter $\psi$ represents the ratio of parallel binding to orthogonal binding, and is summarized in Table 2.1. For purposes of the analysis, it is convenient to vary the single parameter $\psi$. As discussed later, in numerical investigations results are calculated for various values of the parameters $\beta_{1}, \rho_{1}, \beta_{2}$ and $\rho_{2}$. After slight rearrangement of terms, equations (2.22) can be reduced to the previous system, (2.8), but with the new kernel defined above, in (2.23).

In this section we study both extremes as well as intermediate situations, i.e. we are interested in all values of $\psi$ in $0 \leq \psi \leq 1$. Also note that since $K_{1}$ and $K_{2}$ were normalized, so is $K$, and further,

$$
\begin{equation*}
\hat{K}=(1-\psi) \hat{K}_{1}+\psi \hat{K}_{2} \tag{2.26}
\end{equation*}
$$

The shape of the kernel $K$ (see Fig. 2.7a-b) in this case depends not only on the two critical angles but also on the parameter $\psi$ representing the ratio of the concentrations and the binding rates of the two types of auxiliary proteins. Here we assume that the effect of two different binding proteins is simply linear in their concentrations. This, together with the linear property of the operator $K *$ allows us to reduce the new problem to the old one via (2.23).

|  | $\psi=0$ | $\psi=0.5$ | $\psi=1$ |
| :---: | :---: | :---: | :---: |
| actin <br> binding <br> proteins | $\beta_{2}=0$ <br> or <br> $\rho_{2}=0$ | $\beta_{1} \rho_{1}=\beta_{2} \rho_{2}$ | $\beta_{1}=0$ <br> or <br> $\rho_{1}=0$ |
| kernel | $K=K_{1}$ | $K=\frac{K_{1}+K_{2}}{2}$ | $K=K_{2}$ |
| type of binding | orthogonal <br> binding only | both kinds of <br> binding | parallel <br> binding only |

Table 2.1: The proportion of parallel and orthogonal binding rate and binding protein concentration can be represented by a single parameter $\psi$ defined by (2.25).

### 2.6 Analysis of Model II

### 2.6.1 Linear Stability Analysis

The analysis is identical to the previous section, and the stability condition is exactly as given in (2.19), but with the new interpretations of $\beta \rho$ and $K$ as above in (2.25) and (2.23). The left hand side of (2.19) in this case, too, is a parabola as a function of the wave number $k$, and its coefficient depends on the parameters in the system. The right hand side is a function of the Fourier transform of the combined kernel, $\hat{K}$, as in (2.26).

The inequality (2.19) can be rearranged to obtain:

$$
\begin{equation*}
\frac{\mu}{\delta}\left(\frac{\delta}{(\bar{L}+\bar{B})}\right)^{2} k^{2}<\left(\beta_{1} \rho_{1} \hat{K}_{1}+\beta_{2} \rho_{2} \hat{K}_{2}\right)\left(\beta_{1} \rho_{1}+\beta_{2} \rho_{2}-\beta_{1} \rho_{1} \hat{K}_{1}-\beta_{2} \rho_{2} \hat{K}_{2}\right) \tag{2.27}
\end{equation*}
$$



Figure 2.7: Shapes of the kernels $K$ representing the combined angle dependence of both orthogonal and parallel binding. The values of the critical angles are $a=20^{\circ}$ for $K_{1}$ and $b=20^{\circ}$ for $K_{2}$, note that $K$ is also dependent on the parameter $\psi$. (a) $\psi=0.3$ (for example $\beta_{1}=0.7, \beta_{2}=0.3$ and $\rho_{1}=\rho_{2}$ ). (b) $\psi=0.7$ (for example $\beta_{1}=0.3, \beta_{2}=0.7$ and $\rho_{1}=\rho_{2}$ ).

In order to study the transition from the extreme case where the bundling proteins are inactive or absent, $\psi=0$, to the other extreme case where the cross-linking proteins are inactive or absent, $\psi=1$, we vary $\beta_{1}$ (or equivalently $\rho_{1}$ ) from 1 to 0 and $\beta_{2}$ (or equivalently $\rho_{2}$ ) from 0 to 1 simultaneously. The reason for this is that we wish to investigate only the effect of the changes of the binding rates or binding protein ratio while all other conditions remain the same. See Fig. 2.8a-e for plots of the function on the right hand side of (2.27) for various values of the parameters as $\psi$ varies from 0 to 1. We also display the parabola on the left hand side of (2.27) on these figures. As in the previous section, instability at integer wavenumbers $k$ occurs if the parabola on the left hand side of (2.27) is lower than the function on the right hand side of (2.27), i.e. the uniform steady state of (2.22) is disrupted and pattern formation is initiated by perturbations of the form (2.15) whose wavenumbers satisfy (2.19) or equivalently (2.27). The first integer wavenumber for which (2.27) can be satisfied depends on the value of $\psi$, and for the choice of critical angles $a=b=20^{\circ}, k$ changes from 4 to 2 as $\psi$ changes


Figure 2.8: The expression on the right hand side of (2.27) is shown as a function of the wavenumber $k . K$ is as in Fig. 2.7a and 2.7b for (b) and (d), respectively. The critical angles are $a=20^{\circ}$ for $K_{1}$ and $b=20^{\circ}$ for $K_{2}$ in all cases. Also $\rho_{1}=\rho_{2}=2$ and hence $\beta \rho=2$ in all cases. The superimposed parabolas from left to right can be obtained by increasing the 'total mass' of F -actin in the system. In (a) $\beta_{1}=1$ and $\beta_{2}=0$ and the coefficient $C$ of the parabolas are 0.12 and 0.04 , in (b) $\beta_{1}=0.7$ and $\beta_{2}=0.3$ and $C=0.12$ and 0.04 , in (c) $\beta_{1}=0.5=\beta_{2}$ and $C=0.12$ and 0.04 , in (d) $\beta_{1}=0.3$ and $\beta_{2}=0.7$ and $C=0.3$ and 0.12 , and in (e) $\beta_{1}=0$ and $\beta_{2}=1$ and $C=0.3$ and 0.065 . The first wavenumber for which the uniform steady state is disturbed is $k=4 \mathrm{in}$ (a)-(c) i.e. perturbations of the form $e^{4 i \theta}$ grow resulting in four accentuated orientations $90^{\circ}$ apart, a network structure. For (d) and (e) the first such wavenumber is $k=2$ i.e. perturbations of the form $e^{2 i \theta}$ grow resulting in two accentuated orientations $180^{\circ}$ apart, bundles.
from zero to one (or equivalently $\beta_{1}$ from one to zero and $\beta_{2}$ from zero to one), (see Fig. $2.8 \mathrm{a}-\mathrm{e}$ ). The transition from $k=4$ to $k=2$ is sharp, as predicted by the analysis, and will be discussed in the subsection below.

### 2.6.2 Numerical Analysis

The numerical solutions of (2.22) are in agreement with the results of the analysis. The methods of the numerical computations are identical to those of the previous section. In Fig. 2.9a-e the numerical solutions to (2.22) corresponding to the kernels used in Fig. 2.8 a-e are shown. We note that the number of peaks that arise correspond to the integer for which the parabolas in Fig. 2.8a-e first cross below the curve on the right hand side of (2.27). For example, this occurs at $k=4$ in Fig. 2.8a-c, whereas at $k=2$ in Fig. 2.8d-e. Initial densities were random deviations from the uniform steady state. The results of cases where deviations were sinusoidal were similar and we do not present them here. We first summarize the results of the simulations in which the initial densities were uniform with small deviations. In the cases where the quantity $\psi$ was smaller than 0.5 (and even when it was equal to 0.5 in some cases), indicating a higher binding rate or a higher concentration of the orthogonal cross linking proteins, pattern formation of orthogonal networks resulted for the choice of parameter values which satisfied (2.27), see Fig. $2.9 \mathrm{a}-\mathrm{c}$. For values of $\psi$ closer to $\psi=0.5$, in some cases, two peaks appeared first and later divided into four peaks. However whether this occurs depends on the values of the critical angles, $a$ and $b$, and the parameter $\delta$ which represents the dissociation rate of the binding proteins. Also for the choice of parameter values for which $\psi=0.5$, i.e. equal binding rates and/or equal concentrations for both types of binding proteins, the resulting structure is dependent on the values of the critical angles $a$ and $b$, and could be either orthogonal networks or bundles. For the values $a=20^{\circ}$ and $b=20^{\circ}$ the


Figure 2.9: Formation of the network or bundles of F-actin in a pool of initially randomly distributed bound filaments and two type of binding proteins: orthogonal and parallel. $K(k)$ is identical to the ones used for Fig. 2.8a-e corresponding to 2.9 a -e in order. Initial densities (not shown) are $10 \%$ random noise on the uniform steady state ( $\bar{L}, \bar{B}), \bar{L}=0.25$ and $\bar{B}=4.75$, and other parameters are $\beta \rho=\rho_{1}=\rho_{2}=2, \mu=1.84, \delta=0.5, M \approx 5, \Delta t=0.01$ and the grid size is $\Delta \theta=12^{\circ}$. The solutions were found for: 70,000 iterations, with plots shown at $1,42,000$ and 70,000 iterations in (a) and (b), 100,000 iterations, with plots shown at $1,60,000$ and 100,000 iterations in (c), 50,000 iterations, with plots shown at $1,10,000$ and 50,000 iterations in (d), and 130,000 iterations, with plots shown at $1,104,000$ and 130,000 iterations in (e). In (a)-(c) four orientations $90^{\circ}$ apart have been accentuated (network structure), and in (d) and (e) two orientations $180^{\circ}$ apart have been accentuated (bundles).
filaments organize into a network when $\psi=1$, see Fig. 2.9c. In the cases where the quantity $\psi$ was larger than 0.5 (higher binding rate or a higher concentration of bundling proteins) pattern formation in the form of bundles resulted for the choice of parameter values which satisfied (2.27), see Fig. 2.9d-e. The transition from one type of structure to the other was very sharp, as predicted by the analysis. We have also simulated cases with pre-structured initial densities to analyze how stable these structures are to sudden changes in their environment. For example, we started with a pool of filaments organized mostly parallel to each other as in Fig. 2.9d, and let the parameter $\psi$ be very close to 0 (a sudden change from high parallel binding rate to high orthogonal binding rate), or we started with a network of filaments as in Fig. 2.9b, and let the parameter $\psi$ be very close to 1 (a sudden change from high orthogonal binding rate to high parallel binding rate). Through these simulations we have found that for the same parameter values, the same type of structure results regardless of the choice of initial densities, i.e. whether uniform or pre-structured. However, in the case of pre-structured initial densities the orientations that appeared were usually determined by the initial ones, with either two new peaks appearing in between the existing ones (change from bundles to networks) or two alternating peaks disappearing (change from networks to bundles). This transition does not require the complete break up of the existing structure; rather the new structure forms on the remnants of the old one. Thus in our model the cell is capable of switching its cytoskeletal structure while preserving its polarity, rather than choosing a random new direction after every switch. This might be compared to the situation where cells moving in a particular direction tend to continue in that direction even in the absence of external stimuli.

### 2.7 Generalization of Models I and II to 3 dimensions

The models in sections 2.3 and 2.5 are two dimensional analogues of a truly three dimensional structure. In the 2D models, I and II, the functions $L(\theta)$ and $B(\theta)$ have as thier domain an interval of length $2 \pi$ with periodic boundaries. This domain is formally equivalent to a unit circle. Thus the problem of pattern formation in angle $\theta$ can be thought as a pattern formation on a unit circle. Similarly, in 3D, a given orientation can be put in correspondence with a unit vector, and thus with a point on the surface of a unit sphere. Thus to extend the analysis to 3D it is necessary to generalize the domain from a unit circle to a unit sphere. We represent the points on the surface of a unit sphere by $(\phi, \theta)$, where $\phi$ is in $[0, \pi]$ and $\theta$ is in $[0,2 \pi]$. The equations of the model in three dimensions are largely analogous to (Mogilner and Edelstein-Keshet, 1994a). One studies perturbations of the uniform steady state that are spherical harmonics, i.e. Legendre polynomials. The dispersion relation analogous to (2.19) or (2.27) then involves the inner product of $K$ with these spherical eigenfunctions, rather than the Fourier transform $\hat{K}$.

Directions in 3-D can be represented by unit vectors on the surface of a unit sphere. A spherical coordinate transformation leads to the representation of the vectors in the cartesian coordinate system $(x, y, z)$ in terms of angular coordinates $(r, \phi, \theta)$. The angular coordinates $\Omega=(\phi, \theta)$ will be used to describe an orientation. (See Figure 2.10). This is commonly referred to as the surface spherical coordinates. A unit vector in cartesian coordinates has the corresponding representation:

$$
\begin{equation*}
\bar{u}=(x, y, z)=(\cos \theta \sin \phi, \sin \theta \sin \phi, \cos \phi) . \tag{2.28}
\end{equation*}
$$

The problem in 2-D, described by the equations (2.9), can then be generalized to 3-D by converting the convolution terms and the rotational diffusion term to account for the


Figure 2.10: The angular coordinates ( $\phi, \theta$ ) shown in 3D. $(\phi, \theta)$ represent the angles on the unit sphere.

3-D dynamic.
The rotational diffusion in 3-D corresponds to a random walk on the surface of a unit sphere. Hence this can be described by the angular part of the Laplacian operator in 3-D. In surface spherical coordinates this is:

$$
\begin{equation*}
\triangle=\frac{1}{\sin \phi} \frac{\partial}{\partial \phi}\left(\sin \phi \frac{\partial}{\partial \phi}\right)+\frac{1}{\sin ^{2} \phi} \frac{\partial^{2}}{\partial \theta^{2}} . \tag{2.29}
\end{equation*}
$$

Similarly the convolution terms which account for the interaction of filaments on the rim of a unit circle in 2-D can be generalized to account for interactions with filaments over the unit sphere. These interactions depend on the relative orientation of the filaments as explained in 2.4. The angle between two filaments oriented at $\theta$ and $\theta^{\prime}$, in $2-\mathrm{D}$, is simply $\theta-\theta^{\prime}$. In 3-D the angle between two filaments oriented at $\Omega$ and $\Omega^{\prime}$, say $\gamma$, can also be expressed in terms of the angles $\phi, \theta, \phi^{\prime}$ and $\theta^{\prime}$, however it is a complicated expression. Conveniently, the cosine of the angle $\gamma, \cos \gamma$, can be calculated simply by considering
two unit vectors, $n$ and $n^{\prime}$, oriented at $\Omega$ and $\Omega^{\prime}$, and taking their scalar product $n \cdot n^{\prime}$.

$$
\begin{align*}
& n=(\cos \theta \sin \phi, \sin \theta \sin \phi, \cos \phi) \\
& n^{\prime}=\left(\cos \theta^{\prime} \sin \phi^{\prime}, \sin \theta^{\prime} \sin \phi^{\prime}, \cos \phi^{\prime}\right)  \tag{2.30}\\
& \cos \gamma=n \cdot n^{\prime}=\cos \phi \cos \phi^{\prime}+\sin \phi \sin \phi^{\prime} \cos \left(\theta-\theta^{\prime}\right)
\end{align*}
$$

Since we assume that filaments interact in 3-D depending on the relative angle, $\gamma$, between them, the kernel $K$ is a function of this variable: $K(\gamma)$. In the light of the above calculations it is convenient to express this kernel as a function of the cosine of the angle $\gamma$. Defining $\eta=\cos \gamma$ we denote this new function with the same symbol, $K(\eta)$. We consider three types of interactions:

1- Orthogonal binding or binding at close to right angles, $K_{1}(\eta)$, Fig. 2.11a,
2- Parallel binding or binding at acute angles, $K_{2}(\eta)$, Fig. 2.11b,
3- Both orthogonal and parallel binding, with a large critical angle value for orthogonal binding and a small critical angle value for parallel binding $K_{3}(\eta)$, Fig. 2.11c.

4- Both orthogonal and parallel binding, with a small critical angle value for orthogonal binding and a large critical angle value for parallel binding rate $K_{4}(\eta)$, Fig. 2.11d.

Also, the line integral in 2-D will be replaced by a surface integral (a double integral) in 3-D. The surface differential $\mathrm{d} S$ in spherical coordinates being:

$$
\begin{equation*}
\mathrm{d} S=\sin \phi \mathrm{d} \theta \mathrm{~d} \phi \tag{2.31}
\end{equation*}
$$

the convolution terms take the following form:


Figure 2.11: The kernels $K_{i}(\eta)$ for $i=1,2,3$ and 4 representing the four types of interactions listed above. Note that the argument of $K$, the cosine of an angle: $\eta=\cos \gamma$, is varying from -1 to 1 . The kernels in Fig. 2.11a and b correspond to the ones shown in Fig. 2.3a and b. Only here, the argument is $\eta$ rather than $\theta$. The kernels shown in Fig. 2.11c and d are of the form (2.23) where $K_{1}$ and $K_{2}$ as in Fig. 2.11a and b , and $\phi=0.33$ and $\phi=1$ for c and d respectively.

$$
\begin{align*}
K * L & =\int_{S} K\left(\Omega, \Omega^{\prime}\right) L\left(\Omega^{\prime}, t\right) \mathrm{d} S \\
& =\int_{0}^{\pi} \int_{0}^{2 \pi} K\left(\phi, \theta, \phi^{\prime}, \theta^{\prime}\right) L\left(\phi^{\prime}, \theta^{\prime}, t\right) \sin \phi^{\prime} \mathrm{d} \theta^{\prime} \mathrm{d} \phi^{\prime}  \tag{2.32}\\
& =\int_{0}^{2 \pi} \int_{-1}^{1} K(\eta) L\left(\phi^{\prime}, \theta^{\prime}, t\right) \mathrm{d}\left(\cos \phi^{\prime}\right) \mathrm{d} \theta^{\prime}
\end{align*}
$$

where $S$ is the surface of the unit sphere. Hence the equations analogous to (2.9) in 3-D can be written as follows using the new definitions of the convolution and the diffusion terms:

$$
\begin{align*}
& \frac{\partial L}{\partial t}(\Omega, t)=\mu \triangle L+\delta B-\beta \rho L(K * B)-\beta \rho L(K * L) \\
& \frac{\partial B}{\partial t}(\Omega, t)=-\delta B+\beta \rho B(K * L)+\beta \rho L(K * L) \tag{2.33}
\end{align*}
$$

### 2.7.1 Linear Stability Analysis

Analogously to the 2-D case, we look for the homogeneous steady state of the equations (2.33) where filaments are equally distributed in every direction $\Omega=(\phi, \theta)$. We wish to determine whether this steady state can be destabilized leading to patterns in $\Omega$ signifying a transition from isotropic to nonisotropic networks of filaments.

The linearized set of equations which govern perturbations, are, by direct analogy with equations (2.13):

$$
\begin{align*}
& \frac{\partial L_{0}}{\partial t}(\theta, t)=\mu \triangle L_{0}+\delta B_{0}-\beta \rho\left(\bar{L}\left(K * B_{0}\right)+L_{0} \bar{B}\right)-\beta \rho\left(\bar{L}\left(K * L_{0}\right)+L_{0} \bar{L}\right) \\
& \frac{\partial B_{0}}{\partial t}(\theta, t)=-\delta B_{0}+\beta \rho\left(\bar{B}\left(K * L_{0}\right)+B_{0} \bar{L}\right)+\beta \rho\left(\bar{L}\left(K * L_{0}\right)+L_{0} \bar{L}\right) \tag{2.34}
\end{align*}
$$

The operators $\triangle$ and $K *$ in these linear equations now have as their domain the set of functions on the unit sphere. This surface spherical geometry restricts eigenfunctions of these operators to the set of surface spherical harmonics (SSH) $Y_{n}(\Omega)$,

$$
\begin{equation*}
Y_{n}(\Omega)=Y_{n}(\phi, \theta)=A_{n}^{o} P_{n}^{o}(\cos \phi)+\sum_{m=1}^{n}\left(A_{n}^{m} \cos m \theta+B_{n}^{m} \sin m \theta\right) P_{n}^{m}(\cos \phi) \tag{2.35}
\end{equation*}
$$

where $P_{n}^{o}$ are the Legendre polynomials of degree $n$ and $P_{n}^{m}$ are the associated Legendre functions of degree $n$ and order $m$. Indeed, both operators share this set of eigenfunctions, and

$$
\begin{align*}
\Delta Y_{n} & =-n(n+1) Y_{n} \\
K * Y_{n} & =\tilde{K}(n) Y_{n} \tag{2.36}
\end{align*}
$$

where the multipliers of $Y_{n}$ on the right hand side are the corresponding eigenvalues and

$$
\begin{equation*}
\tilde{K}(n)=2 \pi \int_{-1}^{1} K(\eta) P_{n}^{o}(\eta) \mathrm{d} \eta \tag{2.37}
\end{equation*}
$$

(See Appendix C for details.) It is a well-known result that the set of SSH forms an orthonormal basis for functions satisfying Dirichlet's Conditions on the unit sphere (MacRobert, 1927; Arsenin, 1968; Hobson, 1931), so that such a function $f(\phi, \theta)$ for $0 \leq \phi \leq \pi, 0 \leq \theta \leq 2 \pi$ can be expressed as:

$$
\begin{equation*}
f(\phi, \theta)=\sum_{n=0}^{\infty} Y_{n}(\phi, \theta) \tag{2.38}
\end{equation*}
$$

Thus, to investigate the stability of the steady state we consider perturbations of the following form:

$$
\left[\begin{array}{l}
L(\Omega, t)  \tag{2.39}\\
B(\Omega, t)
\end{array}\right]=\left[\begin{array}{c}
\bar{L} \\
\bar{B}
\end{array}\right]+\left[\begin{array}{c}
L_{o} \\
B_{o}
\end{array}\right] Y_{n}(\Omega) e^{\lambda t}
$$

As in the 2 -D case here too $\bar{L}$ and $\bar{B}$ are steady state values, $L_{0}$ and $B_{0}$ are small amplitudes, $\lambda$ is the growth rate and $n$ is the mode number of the perturbation.

Substituting these into (2.34) and retaining only the linear contributions, we arrive at the following inequality, the dispersion relation, which is analogous to equation (2.19) in 2-D.

$$
\begin{equation*}
C n(n+1)<\tilde{K}(n)(1-\tilde{K}(n)) \tag{2.40}
\end{equation*}
$$

where,

$$
\begin{equation*}
C=\frac{\mu}{\delta}\left(\frac{\delta}{(\bar{L}+\bar{B}) \beta \rho}\right)^{2} \tag{2.41}
\end{equation*}
$$

The details of these calculations is given in Appendix C and follow closely the 2-D case. The dispersion relation (2.40) differs from the dispersion relation (2.19) in its dependence on the mode number $n$ : note that in the $2-\mathrm{D}$ case the dependence on the mode number $k$ is of the form $k^{2}$ whereas here the dependence on the mode number $n$ is of the form $n(n+1)$. We conclude that the homogencous steady state is destabilized and pattern formation is initiated by perturbations of the form (2.39) provided that the mode number $n$ satisfies (2.40).

An integral form of the kernel $K, \tilde{K}$, as in (2.37), appears in this equation. This is analogous to $\hat{K}$, the Fourier transform of $K$, appearing in the dispersion relation (2.19) in the 2D case. Similarly to the 2-D case we visualize (2.40) graphically in Fig. 2.12a-d for the four types of kernels given in Fig. 2.11a-d. In Fig. 2.12 the expressions on both sides of the inequality (2.40) are plotted superimposed as functions of the mode number $n$. The coefficient $C$ of the quadratic function on the left hand side of (2.40) is positive small in all biologically relevant cases.

The inequality (2.40) depends on the shape of $\tilde{K}(n)(1-\tilde{K}(n))$ and on the constant $C$. For this case, since the eigenfunctions are SSH and hence the function $\tilde{K}(n)$ involves Legendre polynomials of degree $n$, this expression can only be evaluated for integer $n$. Its discrete values have been connected by line segments in Fig. 2.12 for ease of visualization. For instability the quadratic function of $n$ must be lower than the function on the right hand side for some integer mode number $n$. In Fig. 2.12a and $c, n=4$ is the first such mode number. Thus the harmonic $Y_{4}$ breaks the stability and becomes the leading mode.


Figure 2.12: The function on the right hand side of (2.40) is shown superimposed with the quadratic function of $n$ on the left hand side for various values of the coefficient $C$. The plots a-d correspond to the four different type of kernel shown in Fig. 2.11a-d. In cases a and c the first mode causing instability is 4 , while in $b$ and $d$ it is 2 . The quadratic function on the left hand side is shown for the following values for the coefficient $C$ : in a and c $C=0.015$ and 0.005 and in b and $\mathrm{d} C=0.05$ and 0.015 .

This mode is rotationally and pattern-wise highly degenerate. However, it is shown in (Busse, 1987) that the mode competition removes the pattern degeneracy. The resulting pattern has the form of six mutually perpendicular smooth peaks on the surface of the unit sphere. (Two of them at the north and the south pole and four of them mutually perpendicular on the equator.) Most filaments are oriented in a mutually orthogonal manner: the 3D orthogonal network architecture of microfilaments observed in the cortex. In Fig. 2.12b and $d$ the first mode for which (2.40) is satisfied is $n=2$, thus the second harmonic $Y_{2}$ is the leading mode. This mode is rotationally degenerate. It is shown in (Mogilner and Edelstein-Keshet, 1994) that the harmonics $P_{2}^{1}$ and $P_{2}^{2}$ die out and the
leading mode is $P_{2}^{o}$. The pattern evolved is axisymmetric and the angular distribution of filaments looks like two smooth peaks at the north and south pole. The filament density is increased on the poles and diminished on the equator suggesting the alignment of F-actin in a parallel manner. This type of parallel alignment of microfilaments in 3D is commonly observed in stress fibers. The competition of different modes, $P_{n}^{m}$, for the case of the second and the fourth harmonics, $Y_{2}$ and $Y_{4}$, is discussed in greater detail in (Mogilner and Edelstein-Keshet, 1994). We conclude that the results of the linear stability analysis of the model in 3D are highly analogous to the results of the linear and numerical analysis in 2D case, one important difference being the value of the constant $C$ for which the stability breaks. This constant is a combination of the parameters in the model such as the total mass of actin, $M$, the kinetic rates of the binding proteins, $\beta$, and the amount of available binding protein, $\rho$. In the 3D case $C=0.005$ and $C=0.015$, see Fig. 2.12a-d. In the 2D case, $C=0.065$ and $C=0.12$ (one order of magnitude higher) (see Fig. 2.8a,b,d and e for comparable kernels). This indicates that the steady state is more stable in 3D than it is in 2D. That is, stronger interactions or higher total mass of actin are necessary for the organization of filaments in ordered structures. (See Mogilner and Edelstein-Keshet, 1994-a.)

### 2.8 Nonlinear analysis in 2D and 3D

The instability discussed in sections $2.4,2.6 .1$ and 2.7 .1 is analogous to the isotropicnematic transition in liquid crystals. In that case, linear stability analysis is sufficient to describe pattern formation in 2D but not in 3D. A complete bifurcation analysis of Model I in both 2D and 3D has been carried out in Mogilner and Edelstein-Keshet (1994a). They applied analysis following the synergetics approach (Haken, 1977; Friedrich and Haken,
1989) in which an assumption is made that the fastest growing mode controls the amplitudes of all other (slave) modes. A full mode expansion is substituted into the nonlinear model and terms up to third power in the leading mode and up to second power in the other modes are kept. This leads to a system of equations for the mode amplitudes. In 2D, from these equations, it can be deduced that the bifurcation is supercritical (implying a non-equilibrium phase transition of second order). This implies that as a governing parameter increases past its bifurcation value the amplitude of the inhomogeneity increases gradually. In 3D a similar analysis can be applied but the modes are described by the SSH and the calculations are more complex. In contrast to the 2D case, the transition in 3D case is a transcritical bifurcation implying a non-equilibrium phase transition of first order. This means that the amplitude of the pattern jumps abruptly from zero to a higher value. Physically this means that the stable inhomogeneous pattern can co-exist with the homogeneous distribution.

### 2.9 Discussion and conclusions

The main points and results of this chapter can be summarized as follows:
(1)- The model presented here accounts for directional distribution of F-actin without considering its spatial distribution.
(2)- The observed dynamics of assembly and disassembly of F-actin structures in the cell can be explained by relatively simple interactions of the molecules in the cell.
(3)- The switch between an orthogonal network and bundles of F-actin may result simply from a change in the binding rates or in the concentrations of actin binding proteins, see Fig. 2.8 and 2.9 for 2D results and Fig. 2.12 for 3D case. These in turn, could be governed by messages received by the cell and expression of the genes coding for these actin binding proteins.

Recent experimental evidence also suggest the key importance of the kinetic rates of the binding proteins in the formation of actin cytoskeleton. Wachsstock et al. (1993) and (1994) showed that the structure of actin filament gels depends strongly on affinities (kinetic rates) of the binding proteins.

As previously mentioned actin filaments are polar structures with two structurally different ends. The polarity of filaments has not been explicitly included as yet in the above models, but, in cases where it is important, it can readily be accommodated by a slight change. In actin structures the filaments can display any of the following configurations: (a) bundles with locally uniform polarity, (b) bundles where filaments are arranged in anti-parallel fashion (opposite polarity) and (c) networks of perpendicular filaments. The polarized binding of filaments can be accommodated in the model simply by changing the kernel, $K_{2}(\theta)$, in section 2.3 to allow binding only in the case of acute contact angle. An example of this sort would be a kernel as in Fig. 2.3a, but without the hump in the middle. Our conclusions, and the results of the linear analysis and the numerical computations remain valid also with this type of kernel.

Examples of actin structures considered in this chapter include orthogonal networks of filaments observed in the periphery or cortical cytoplasm of motile cells, for example pseudopods, lamellipodia and membrane ruffles of moving or spreading cells and bundles of actin filaments observed in stress fibres, microvilli (column-like structures) of epithelial cells and filopodia (finger-like projections) of blood cells (Hartwig, 1980; Hartwig, 1992; Stossel, 1984; Way and Weeds, 1990; Weeds, 1982).

We base all interactions and physical and molecular properties on the biological data. Most of the parameters in the model appear in biological literature, but not in forms corresponding exactly to the parameters in the equations. In (Sato et al., 1987), the dissociation constant for the complex Acanthamoeba $\alpha$-actinin (a cross-linking protein
found in amoeba as well as in many other organisms (Pollard and Cooper, 1986; Sato et al., 1987; Stossel et al., 1985)) with actin filaments has been measured in sedimentation binding experiments as $26 \mu \mathrm{M}$. From this value, they also give estimates of the association and dissociation rate constants of the $\alpha$-actinin with F -actin as $10^{5}-10^{7} M^{-1} s^{-1}$ and $2-200 s^{-1}$, respectively. These correspond to our model parameters $\beta$ and $\gamma$. The values of these rate constants are known for various other actin binding proteins too (Pollard et al., 1990).

The rotational motion of F-actin has been extensively studied (Mossakowska et al., 1988; Phillips et al., 1991; Sawyer et al., 1988; Thomas et al., 1979). A typical value for the rotational correlation time of actin filaments of average length $1 \mu \mathrm{~m}$ is $(10-100 \mu \mathrm{~s})$, from various cells (for example rabbit skeletal muscle or chicken gizzard smooth muscle actin) have been measured using various techniques, for example by solid-state nuclear magnetic resonance (NMR) spectroscopy. Note that these are the results of in vitro studies, and the average length of actin filaments in vitro and in vivo differ significantly (e.g. $1 \mu \mathrm{~m}$ and $0.1 \mu \mathrm{~m}$ ). The results show that the time scale of filament motion is of the order of microseconds. The rotational diffusion coefficient, $\mu$, of F-actin can be calculated from the rotational correlation time viewing the actin filaments as a rigid body diffusing about its long axis. The rotational correlation time given above corresponds to a rotational diffusion coefficient $\left(10^{3}-10^{4} s^{-1}\right)$.

The time scale of dissociation and association rates of the actin binding proteins are comparable to the time scale of the rotational diffusion rate of F-actin. Many of the other parameters in our model, such as the elongation rate constant, $\gamma$, or the total filament concentration, M, are provided in (Cooper et al., 1983; Cooper, 1991). Typical values are: $\mathrm{M}=300-400 \mu \mathrm{M}$ (local concentration in lamellae), and $\gamma=10^{7} M^{-1} s^{-1}$. We have not yet gathered a complete set of biological parameters for our equations, but this is
an important future goal. This is a rather difficult task since the parameters appearing in literature are being measured under different circumstances (some in vitro and some others in vivo), from various species, and under various chemical conditions.

## Chapter 3

## Models for gradual alignment of actin filaments

### 3.1 Introduction

After the investigation of the models described in Chapter 2, certain drawbacks of these equations appeared: while the models were a reasonable description of a process of rapid (nearly instantaneous) alignment mediated by certain binding proteins, they could not describe cases in which the actin filaments are gradually pulled into alignment. The interactions of myosin with actin are of this type: myosin binds to two actin filaments and gradually pulls them into an aligned (anti-parallel) configuration. This is referred to as the actin-myosin sliding filament mechanism (Alt, 1987; Mabuchi, 1986). This important class of proteins could not be omitted from consideration in models of actin dynamics, and motivated a new model.

As will be shown, a model which accounts for gradual turning differs from the previous models in having drift terms (in angle) where these were absent before. In Chapter 2, models consisted of two coupled equations for the bound and free actin filaments, but as we will show below, the model for gradual alignment can be based on a single equation which, by itself, reproduces the phenomena of alignment. We still view the process of alignment as a phenomenon mediated by a variety of actin-binding proteins, and we consider not only myosin, but also proteins which would have effects similar to those discussed in Chapter 2.

Aside from being the simplest type of model for gradual alignment, the model we will
describe here has several convenient features: first, it can be analysed for linear stability in a straight-forward way. Second, it allows some explicit steady state solutions to be found. These allow us to study several classes of interactions. Some of these are essentially similar to cases discussed in Chapter 2, but some new cases, including that of myosin and unipolar bundling proteins are also included. The results of the model are given for interactions in two dimensions. (The analysis leading to explicit solutions necessitates 2D, but the linear stability analysis can be generalized to 3D in a straightforward way, as before.)

In the gradual alignment model, the turning rate of an actin filament is assumed to be influenced by all other actin filaments, which interact with it in an angle-dependent way. The kernels, in this case, represent the turning rate of one filament towards another. (The convolution $K * A$ is the cumulative turning rate, or drift velocity, induced by the actin density.) Note that this is in contrast to the meaning of convolutions in Chapter 2, where they represented probabilities of binding.

As before, the details of the functions taken to represent the turning rates do not heavily influence the predicted behavior. Only some general symmetry properties of these kernels are essential. Therefore, in this chapter, we approximate the various classes of interactions (corresponding to various binding proteins) by using two sorts of convenient forms of the kernels. We investigate the linear stability analysis of the model using piecewise linear kernels (for which it is easy to compute the fourier transform), and we discuss explicit steady-state solutions using trigonometric kernels (for which the appropriate integrals are easily evaluated.) The symmetry properties of corresponding cases are the same, even though their functional form is distinct. As we will see, these two distinct functional approximations lead to essentially similar qualitative results.

Parallel to chapter 2, we extend the model to account for the competition of binding
proteins when more than one type is present. The results obtained for cases corresponding to those discussed in chapter 2 are in agreement. This leads to the conclusion that the predictions are robust, i.e. are not highly sensitive to the precise details of the models.

### 3.2 Angular drift model

We consider one type of actin density, $A$, as it is mathematically simpler to deal with a single equation. Also this model leads to pattern formation with a single equation which was not possible in the case of previous models.

The two-dimensional model is based on the following variables:
$\theta \quad=$ an angle, $-\pi \leq \theta \leq \pi$, with respect to some arbitrary fixed direction, $A(\theta, t)=$ the concentration of actin filaments at orientation $\theta$ at time $t$,
$K(\theta)=$ the rate of turning of filaments meeting at a relative angle $\theta$.

The rate of turning of a given filament, $K$, depends on its interaction with all other neighboring filaments; moreover it depends on the type of binding protein that mediates these interactions. The following equation describes how the density of filaments in a given direction changes through filament-filament interaction mediated by actin binding proteins:

$$
\begin{equation*}
\frac{\partial A(\theta, t)}{\partial t}=-\frac{\partial}{\partial \theta} V(\theta, t) A(\theta, t)+\mu \frac{\partial A^{2}}{\partial \theta^{2}} \tag{3.42}
\end{equation*}
$$

where,

$$
\begin{equation*}
V(\theta, t)=K * A=\int_{-\pi}^{\pi} K\left(\theta-\theta^{\prime}\right) A\left(\theta^{\prime}, t\right) \mathrm{d} \theta^{\prime} \tag{3.43}
\end{equation*}
$$

Equation (3.42) is a standard conservation equation:

$$
\begin{equation*}
\frac{\partial A}{\partial t}=-\nabla \cdot(\text { Flux }) \tag{3.44}
\end{equation*}
$$

where the Flux term includes both a convective $(V A)$ and a diffusive term $\left(-\mu \frac{\partial A}{\partial \theta}\right)$. The first term in equation (3.42) represents a continuous drift with angular velocity $V(\theta, t)$. This velocity, which is given by the convolution integral, represents the turning of a single filament under the cumulative influence of interactions with all other filaments. We assume implicitly that the total effect of the other filaments is a simple superposition. This assumption leads to the convolution shown in (3.43) and to the quadratic nature of the nonlinearity. The second term in (3.42), which is the rotational diffusion, represents the random turning of filaments as before. The drift term represents deterministic dynamics while the laplacian accounts for stochastic effects. As before, we do not represent the spatial distribution of filaments. We consider $A(\theta, t), K(\theta)$ as smooth periodic functions of $\theta$ on $(-\pi, \pi)$. From equation (3.42) it can be shown that the total mass of of the system is conserved, so that:

$$
\begin{equation*}
M=\int_{-\pi}^{\pi} A(\theta) \mathrm{d} \theta \tag{3.45}
\end{equation*}
$$

is constant.
The equation (3.42) is a phenomenological description. However it can be derived rigorously as a Fokker-Planck approximation from assumptions about the underlying stochastic turning process (see Segel and Jaeger, 1992).

Details of the interactions will depend heavily on the shape of the kernel $K$ which has different forms to account for different kinds of actin binding proteins. Actin filaments in the cell orient at various angles to one another depending on the type of actin binding


Figure 3.13: Schematic diagram summarizing some actin binding proteins, their shape and interaction with actin filaments.
protein mediating their interaction. We discuss four classes of actin binding proteins in the section below.

### 3.3 An overview of binding proteins

Pollard and Cooper (1986) give an excellent review of actin binding proteins. (See Fig. 3.13 for a summary.) Here we restrict our attention to the proteins that bind to the sides of actin filaments, linking them together. Briefly we can consider four major categories, unipolar and bipolar bundling, orthogonal networking and myosin. We have already described the first three classes in Chapter 2 under the assumption of rapid turning and alignment. We now reconsider them with the gradual turning model. Further, we can now treat myosin, which is known to mediate slow turning and sliding of actin filaments.

### 3.3.1 Unipolar bundling proteins (I)

This group includes fimbrin, fascin, and villin. These proteins promote the formation of unidirectional F-actin bundles in which the filaments have the same polarity. Such bundles are observed in numerous cell types including the brush border microvilli of epithelial cells, the cortical microvilli of fertilized egg oocytes, the streocilia of cochlear hair cells, the processes extending from the surface of blood platelets and others. The actin binding proteins in these structures hold the filaments tightly together in bundles. The physiological purpose of this type of actin structure is to stabilize cell protrusions, e.g. for the purpose of increasing surface area for exchange of material with the surroundings (Pollard and Cooper, 1986; Pollard, 1990; Stossel, 1984). While we only have information about the final configuration of the actin bundles we can speculate about the dynamics that lead to its formation. In particular, it is evident that the filaments have a tendency to converge to a parallel orientation in the presence of these proteins, with the pointed ends all converging to the same direction.

### 3.3.2 Bipolar bundling proteins (II)

Bipolar bundling proteins attach filaments to each other both in parallel and antiparallel. These binding proteins are generally observed in stress fibres on the ventral surface of mammalian fibroblasts, in epithelial cells in culture, in endothelial cells in vivo, and in the cytoplasm of amoebas. Annular rings seen around the whole cell consist of such bidirectional arrays of fibers, closely resembling stress fibers. Similar filament bundles are observed at the peripheral margin or the leading edge of blood platelets and of tissue culture cells. Spectrin, tropomyosin and $\alpha$-actinin are from this group and most of them can bind the sides of two different actin filaments (Pollard and Cooper, 1986; Pollard, 1990). It is evident that filaments converge to either parallel or anti-parallel orientation
and we will assume this occurs with equal probability.

### 3.3.3 Orthogonal networking proteins (III)

There is a class of binding proteins that promote orthogonal networks. Orthogonal networks of actin filaments are often observed in the periphery of motile cells such as amoebas, macrophages, leukocytes and some blood platelets. In these structures, long actin fibers are linked together in oblique or right angle relationships. A substantial majority of filaments in the periphery of the cell cortex consist of short fibers and are often found in T- and X-shaped junctions. Such binding proteins include ABP and filamin (Stossel, 1994; Stossel, 1990; Pollard and Cooper, 1986). In particular, filamin is believed to be a floppy hinge with two nearly perpendicular arms. Stossel suggests that the role of the orthogonal networking proteins is to preserve the isotropic 3D structure of the cytoskeleton (without filamin, bundling and cross-linking proteins would collapse the network into linear structures, changing the mechanical properties of the cytogel drastically).

### 3.3.4 Myosin (IV)

The small bipolar myosin molecules arrange actin filaments in bidirectional bundles by pulling adjacent randomly oriented fibers against each other. Such bundles have a role in contractile events associated with cytokinesis and motility such as endocytosis, exocytosis and membrane ruffling. A functional myosin unit consists of a complex of two myosin molecules. Each molecule has an active head capable of binding to and walking towards the plus end (the pointed end) of an actin filament. If two actin filaments are spatially fixed at their ends and connected by the myosin complex then the gliding of the myosin heads along the filaments leads to the gradual turning of the filaments to an anti-parallel
configuration. The velocity of gliding of myosin is about $1 \mu / \mathrm{s}$ (see Peskin et al., 1994). This means that, in this case, the process of alignment of the attached microfilaments is not rapid as in Chapter 2. The gradual turning modeled by equation (3.42) is more appropriate for this case.

### 3.4 Classification of Kernels

We assume that the binding protein causes the gradual alignment of filaments to which it is attached. As there is no quantitative data on the dynamics of this process, we will consider several reasonable scenarios. In this section we introduce a few functional representations of the alignment rates. That is, we suggest possible forms for the kernels which would be representative of the classes of actin binding proteins introduced in section 3.3. We will assume symmetry of turning towards positive and negative directions (we neglect any possible chirality of the molecular interactions). It then follows that all kernels $K(\theta)$ are odd functions, so that:

$$
\begin{equation*}
\int_{-\pi}^{\pi} K(\theta) \mathrm{d} \theta=0 \tag{3.46}
\end{equation*}
$$

Two basic types of functions (leading to four distinct kernels) will be investigated:

$$
\begin{align*}
& \text { (a) } K(\theta)=\left\{\begin{array}{cl}
\beta+\alpha \theta & \text { for } \theta \geq 0 \\
-\beta+\alpha \theta & \text { for } \theta<0
\end{array}\right. \\
& \text { (b) } \quad K(\theta)=\left\{\begin{array}{cl}
\alpha(\theta-\pi) & \text { for }-\pi \leq \theta<-\frac{\pi}{2} \\
\alpha \theta & \text { for }-\frac{\pi}{2} \leq \theta<\frac{\pi}{2} \\
\alpha(\theta+\pi) & \text { for } \frac{\pi}{2} \leq \theta<\pi
\end{array}\right. \tag{3.47}
\end{align*}
$$

In this model the kernel is not normalized (i.e. the integral of $|K|$ is not set equal to 1). This means that the rate constants are included as part of the expressions for $K$.


Figure 3.14: Shapes of the kernels $K$ representing various types of interactions between actin binding proteins and actin. The values (in particular the signs) of the parameters $\alpha$ and $\beta$ determine the type of interaction the kernel represents. In (a) the kernel is of type 3.47 a with $\beta=-1$ and $\alpha=-1$, unipolar bundling proteins, in (b) the kernel is of type 3.47 a with $\beta=1$ and $\alpha=1$, bipolar bundling proteins, in (c) the kernel is of type 3.47a with $\beta=4$ and $\alpha=-1$, bipolar bundling proteins, and in (d) the kernel is of type 3.47b with $\alpha=1$, orthogonal binding proteins.

The parameters $\alpha$ and $\beta$ determine the type of interaction represented. $\alpha$ is the slope of the function $K(\theta)$, and $\beta$ is the $y$-intercept of $K$, the magnitude of the velocity at $\theta=0$. (See Figure 3.14 for the graph of kernels of type $a$ and $b$ above for some choices of the parameters $\alpha$ and $\beta$.) The biological and mathematical meaning of these parameters is discussed in greater detail below for each of the cases. We now describe the specific forms these kernels take for different choices of $\alpha$ and $\beta$, and the binding protein they represent.


Figure 3.15: Shown is the direction of the angular drift due to interactions of filaments (mediated by unipolar bundling proteins) meeting at a relative angle $\theta$. This case is referred to as 'attraction' since filaments converge to a configuration where they have the the same orientation. Note that the direction of movement is counterclockwise when the kernel is negative and clockwise when the kernel is positive.

### 3.4.1 Kernels for unipolar bundling (I)

We first look at some kernels representative of interaction between filaments mediated by unipolar bundling proteins. In these cases, the kernel is of the form (3.47a) where $\beta \leq 0$ (see 3.2). Thus the rate of change of the relative angle between filaments $K(\theta)$ is negative for positive $\theta$ and positive for negative $\theta$, that is motion is towards $\theta=0$ so the filaments converge towards each other, a parallel configuration (see Fig. 3.15). We refer to this convergence as 'attraction'.

We further consider the following specific cases:
(1) $\beta=0, \alpha<0$.

The filaments oriented at acute relative angles are attracted weakly to zero while those at obtuse relative angles are attracted strongly. Note that the angular velocity is zero if
the relative angle is zero.
(2) $\beta<0, \alpha=0$.

In this case, the angular velocity is independent of the relative angle. All filaments are attracted to a relative orientation $\theta=0$ at the same rate.
(3) $\beta<0, \alpha<0$.

This case is same as case (1), however the angular velocity is non-zero for all angles. (See Fig. 3.14a for the graph of a kernel of this type.)
(4) $\beta<0, \alpha>0$ and $\beta<-\alpha \pi$.

This case is similar to case (3) with the exception that here filaments oriented at acute relative angles are attracted to a zero relative angle strongly while those oriented at obtuse relative angles are attracted weakly.

### 3.4.2 Kernels for bipolar bundling (II) and myosin (IV)

In these cases, the kernel is either of the form (3.47a) where $\beta \geq 0$, or (3.47b) where $\alpha<0$ (see 3.2). In case (3.47a), $K(\theta)$ is positive for positive $\theta$ and negative for negative $\theta$ so motion is away from $\theta=0$ and filaments diverge towards an anti-parallel configuration (see Fig. 3.16). We refer to this as 'repulsion'. In case (3.47b) $K(\theta)$ is negative for acute relative angles and positive for obtuse relative angles implying the tendency for parallel alignment at acute angles and for anti-parallel alignment at obtuse angles.

We consider the following specific cases for the kernel (3.47a):
(1) $\beta=0, \alpha>0$.

The filaments oriented at acute relative angles are repulsed weakly from zero while those at obtuse relative angles are repulsed strongly. At $\theta=0$ the angular velocity is zero.


Figure 3.16: Shown is the direction of the angular drift due to interactions of filaments (mediated by bipolar bundling proteins) meeting at a relative angle $\theta$. This case is referred to as 'repulsion' since filaments converge to a configuration where they have anti-parallel orientations.
(2) $\beta>0, \alpha=0$.

In this case the angular velocity is again independent of the relative angle. Filaments are repulsed from $\theta=0$ equally regardless of their relative orientation.
(3) $\beta>0, \alpha>0$.

This case is same as case (1). However the angular velocity is non-zero for all angles. (See Fig. 3.14b for the graph of a kernel of this type.)
(4) $\beta>0, \alpha<0$ and $\beta>-\alpha \pi$.

This case is similar to case (2) with the exception that filaments oriented at acute relative angles are repulsed from $\theta=0$ strongly while those oriented at obtuse relative angles are repulsed weakly. (See Fig. 3.14c for the graph of a kernel of this type.)


Figure 3.17: Shown is the direction of the angular drift due to interactions of filaments (mediated by orthogonal binding proteins) meeting at a relative angle $\theta$.

### 3.4.3 Kernels for orthogonal binding (III)

In view of the structure of filamin, we assume that filaments converge to an orthogonal configuration from both acute and obtuse relative angles. This suggests kernels of the form (3.47b) where $\alpha>0$ (see 3.2). (See Fig. 3.14d for the graph of a kernel of this type.) The rate of motion in this case is illustrated in Fig. 3.17.

### 3.4.4 Competition between two types of binding proteins (V)

We now consider the case of competition between two types of actin binding proteins when they are simultaneously present in some proportions. We consider two cases, namely (1) myosin and orthogonal binding proteins and (2) the bipolar bundling and the orthogonal binding proteins. We represent the interaction of F -actin with two types of binding proteins by simply taking a linear superposition of the kernels of type (a) and (b) in (3.47). (We are making a simplifying assumption, i.e. that the binding proteins do not interfere with one another, as this would create nonlinear effects that are not described
here.)

## (1) Orthogonal binding proteins (III) and Myosin (IV)

Both kernels for type III and IV interactions are given by the basic form (3.47b) (see 3.2). However, the coefficient $\alpha$ is positive in the case of orthogonal binding protein (III) and negative for myosin (IV). We will define $K_{1}(\theta), K_{2}(\theta)$ to be kernels of the form (3.47b) with $\alpha_{1}>0$ (III) and $\alpha_{2}<0$ (IV) in place of $\alpha$, respectively. The coefficients $\alpha_{1}$ and $\alpha_{2}$ are called the 'effectiveness' parameters, and represent the combined effects of binding rate constant and concentration of the binding protein. (Note the similarity to the combined effects of binding proteins described in section 2.5 where $\beta_{i} \rho_{i}$ represent the binding rate and concentration of binding protein $i$.)

## (2) Orthogonal binding (III) and Bipolar bundling proteins (II)

The kernel for orthogonal binding kernel is (3.47b) with coefficient $\alpha_{1}>0$, whereas the bipolar bundling is simply given by (3.47a), with $\beta>0$ and $\alpha_{2}>0$ (see 3.2). As in (1) above, the coefficients can be viewed as the 'effectiveness' parameters of the two binding proteins.

### 3.5 Linear stability analysis

We now examine steady states of equation (3.42) and their stability. Later on we will focus on the specific forms that the stability criterion takes for different kernels. The analysis of the model is similar to the analysis of the model in Chapter 2. The homogeneous steady state $\bar{A}$ of the equation (3.42) satisfies:

$$
\begin{equation*}
\frac{\partial \bar{A}}{\partial t}=0=\frac{\partial \bar{A}}{\partial \theta}, \quad \text { and } \quad \bar{A}=\text { constant } \tag{3.48}
\end{equation*}
$$

| Kernel type | parameters | type of protein |
| :---: | :---: | :---: |
| Type (a) | $\beta \leq 0, \quad \alpha \in \Re$ | Unipolar bundling (I) |
| Type (a) <br> or <br> Type (b) | $\beta \geq 0, \quad \alpha \in \Re$ | Bipolar bundling (II) <br> or |
| Type (b) | $\alpha>0$ | Myosin (IV) |
| Type (b) <br> + <br> Type (b) | $\alpha_{1}<0$ | Orthogonal binding <br> + <br> Myosin (V) (1) |
| $\alpha_{2}>0$ <br> Type (b) <br> + <br> Type (a) | $\alpha_{1}<0$ | M |
| Orthogonal binding (III) <br> + |  |  |

Table 3.2: Table summarizing the types of kernels and the parameters $\alpha$ and $\beta$, representing different actin binding proteins. The forms of the kernel of types (a) and (b) are given in 3.47.

Note that any constant level of the variable is a steady state, but the value of the constant is determined by the total mass which is conserved by equation (3.45). We wish to examine the stability of this uniform steady state. As for Model I in Chapter 2, $e^{i k \theta}$ terms are the eigenfunctions of the two operators appearing in the equation, namely the Laplacian in 1D, and the integral operator. This fact greatly simplifies the linear analysis of equation (3.42). Thus, we consider perturbations of the form:

$$
\begin{equation*}
A(\theta, t)=\bar{A}+A_{0} e^{i k \theta} e^{\lambda t} \tag{3.49}
\end{equation*}
$$

where $A_{o}$ is a small amplitude, $k$ is the wave number and $\lambda$ is the growth rate of the perturbation. We seek conditions for which such small perturbations from the steady state are amplified with time, i.e. for which $\lambda>0$ for some nontrivial wave number $k$. Substituting (3.49) into (3.42) and retaining the linear contributions we find that:

$$
\begin{equation*}
\lambda A_{o} \mathrm{e}^{i k \theta} \mathrm{e}^{\lambda t}=-i k \bar{A} A_{o} \mathrm{e}^{i k \theta} \mathrm{e}^{\lambda t} \hat{K}-\mu k^{2} A_{o} \mathrm{e}^{i k \theta} \mathrm{e}^{\lambda t} \tag{3.50}
\end{equation*}
$$

where $\hat{K}$ is the Fourier transform of the kernel $K$, namely:

$$
\begin{equation*}
\hat{K}(k)=\int_{-\pi}^{\pi} K(\theta) \mathrm{e}^{i k \theta} d \theta \tag{3.51}
\end{equation*}
$$

By cancellation of common factors in (3.50) we find that the growth rate of the perturbations, $\lambda$, is:

$$
\begin{equation*}
\lambda=-i k \bar{A} \hat{K}-\mu k^{2} \tag{3.52}
\end{equation*}
$$

Instability occurs when $\lambda$ is positive. This leads to the following dispersion relation:

$$
\begin{equation*}
C k^{2}<-i k \hat{K} \tag{3.53}
\end{equation*}
$$

where,

$$
\begin{equation*}
C=\frac{\mu}{\bar{A}}=2 \pi \frac{\mu}{M} \tag{3.54}
\end{equation*}
$$

Note that the coefficient $C$ is inversely proportional to the total mass $M$. We now examine in detail what the dispersion relation implies in each type of interaction and kernel outlined in Sections 3.3 and 3.4.

Since the inequality (3.53) depends on the Fourier transform, $\hat{K}$, of the kernel $K$, we prepare the way by computing $\hat{K}$, the Fourier transforms of the two basic kernels ( $3.47 \mathrm{a}-\mathrm{b}$ ) considered in the previous sections. The exact forms of the Fourier transforms are:
(a)

$$
\begin{align*}
& \hat{K}(k)=-\frac{2}{i k}\left(\alpha\left(\pi \cos k \pi-\frac{1}{k} \sin k \pi\right)+\beta(\cos k \pi-1)\right) \\
& \hat{K}(k)=-\frac{2 \alpha}{i k}\left(\pi \cos \frac{k \pi}{2}-\frac{1}{k} \sin k \pi\right) \tag{3.55}
\end{align*}
$$

We note that for $k=0, \hat{K}=0$ since $K$ is an odd function for all cases considered here. This implies the neutral stability of the homogeneous distribution caused by the conservation of mass. Substituting (3.55a-b) into (3.53) we find the two basic forms of the dispersion relation:
(a)

$$
\begin{equation*}
C k^{2}<2(\alpha \pi \cos k \pi+\beta(\cos k \pi-1)) \tag{3.56}
\end{equation*}
$$

(b) $C k^{2}<2 \alpha \pi \cos k \frac{\pi}{2}$.

We look for the smallest integer wavenumber $k$ which satisfies (3.56). The homogeneous distribution destabilizes in favor of the first wave number (the smallest one) which would then govern the growing pattern until the system is drawn far from equilibrium where nonlinear effects of competing wave numbers dominate. By previous remarks about $C$, we observe that as the total mass, $M$, increases, the left hand side of (3.56a-b) decreases so that the inequality can be satisfied. The first value of $M$ for which these inequalities are satisfied (for some integer $k$ ) will be called the 'critical mass'. We now comment on the specific cases 1-4 in section 3.4. The outcome of the dispersion relation, i.e. the first mode number causing instability, for the cases considered below is summarized in Table 3.3. In Fig. 3.18a-d the left and right hand sides of the dispersion relations (3.56a or b) corresponding to the kernels of type (3.47a or b) shown in Fig. 3.14a-d are plotted. Notice the first integer wave number $k$ causing instability (i.e. the first integer $k$ for which the parabola is below the curve) in each case.

### 3.5.1 Dispersion relation for unipolar bundling (I)

In all cases listed below the kernel is of the form (3.47a) with corresponding Fourier transform (3.55a), and dispersion relation (3.56a).

$$
\text { (1) } \beta=0, \alpha<0 . \quad C k^{2}<2 \alpha \pi \cos k \pi
$$

For even wave numbers, the right hand side of the inequality is negative. For odd wave numbers, $k=1,3,5, \ldots$ the right hand side is $2 \alpha \pi$. Thus, the first mode which breaks the stability is $k=1$. This means that perturbations of the form $e^{i \theta}$ will grow. Hence a single direction in $[-\pi, \pi]$ is accentuated. Most filaments align along this favored direction.

$$
\text { (2) } \beta<0, \alpha=0 . \quad C k^{2}<2 \beta(\cos k \pi-1)
$$

In this case, the right hand side of the dispersion relation is zero for even wave numbers


Figure 3.18: The expression on the right hand side of (3.56a or b) is shown as a function of the wavenumber $k . K$ is as in Fig. 3.13a-d respectively, with $\alpha$ and $\beta$ same as in Fig. 3.13a-d. Superimposed in each graph is a parabola for which the coefficient $C$ is chosen to satisfy the inequality. In (a), (b) and (c) the coefficient $C$ of the parabola is 1 , and in (d) $C=0.3$. The first wavenumber for which the uniform steady state is destabilized is $k=1$ in (a) i.e. perturbations of the form $e^{i \theta}$ grow, resulting in one accentuated orientation (a unidirectional structure). For (b) the first such wavenumber is $k=2$ i.e. perturbations of the form $e^{2 i \theta}$ grow, resulting in two accentuated orientations $180^{\circ}$ apart (bundles). For (c) the wavy function assumes negative values for all $k$. Thus the inequality cannot be satisfied for any value of $k$, so the homogeneous distribution is stable. For (d) the first such wavenumber is $k=4$ i.e. perturbations of the form $e^{4 i \theta}$ grow, resulting in four accentuated orientations $90^{\circ}$ apart (orthogonal networks).
and positive (and equal to $-4 \beta$ ) for all odd wave numbers, $k=1,3,5 \ldots$ Thus, the first destabilizing wave number is $k=1$. This leads to unidirectional alignment of filaments as in case (1).
(3) $\beta<0, \alpha<0 . \quad C k^{2}<2(\alpha \pi \cos k \pi+\beta(\cos k \pi-1))$

In this case, for even $k$, the right hand side of the inequality is negative. For odd wave numbers $k=1,3,5, \ldots$ it is positive and equal to $-2(\pi \alpha+2 \beta)$. Thus, the first destabilizing mode is $k=1$. Filaments align in a unidirectional fashion as in the previous cases. (See Fig. 3.18a for visualization of the dispersion relation corresponding to a kernel of this type, shown in Fig. 3.14a.)

$$
\text { (4) } \beta<0, \alpha>0 \text { and }-\beta>\alpha \pi . \quad C k^{2}<2(\alpha \pi \cos k \pi+\beta(\cos k \pi-1))
$$

For even wave numbers, $k=2,4,6, \ldots$ the right hand side is positive and equal to $2 \alpha \pi$. For odd wave numbers it is also positive and equal to $-2 \alpha \pi-4 \beta>2 \alpha \pi$. Thus, the first destabilizing mode is $k=1$ as before.

### 3.5.2 Dispersion relation for bipolar bundling (II) and myosin (IV)

We first consider kernels of the form (3.47b) with $\alpha<0$. As shown above, this leads to the dispersion relation (3.56b). The sign of the expression on the right hand side of the inequality (3.56b), namely $2 \alpha \pi \cos k \pi / 2$, determines the outcome of stability. For odd wave numbers, $k=1,3,5 \ldots$ this expression is zero. For wave numbers which are even multiples of $2, k=4,8,12 \ldots$ it is negative, and for odd multiples of $2, k=2,6,10 \ldots$ it is equal to $-2 \alpha \pi>0$. Thus, the first wave number which breaks the stability is $k=2$. This means that perturbations of the form $e^{i 2 \theta}$ will grow and thus two orientations $180^{\circ}$ apart become accentuated. Hence filaments bundle in parallel and antiparallel fashion equally.

Next, we consider four cases of the dispersion relation of type (3.56a) corresponding to four kernels of the form (3.47a), with $\beta \geq 0$, given in section 3.4.2 (1), (2), (3) and (4).

$$
\text { (1) } \beta=0 \text { and } \alpha>0 . \quad C k^{2}<2 \alpha \pi \cos k \pi
$$

Clearly, the smallest $k$ for which the inequality holds is $k=2$. Thus, two directions, $\pi$ degrees apart, will grow in $[-\pi, \pi]$. The uniform steady state will be broken with the appearance of two peaks $180^{\circ}$ apart again.
(2) $\beta>0$ and $\alpha=0 . \quad C k^{2}<2 \beta(\cos k \pi-1)$

In this case, the right hand side of the inequality is negative for odd wave numbers, $k=1,3,5,7, \ldots$ and is equal to zero for even wave numbers. The homogeneous steady state is stable to all perturbations and no pattern will form. We conclude that some difference in the interaction (turning rate) at different angles is essential for disruption of homogeneity.

$$
\text { (3) } \beta>0 \text { and } \alpha>0 . \quad C k^{2}<2(\alpha \pi \cos k \pi+\beta(\cos k \pi-1))
$$

The first wave number satisfying this inequality is again $k=2$. (See Fig. 3.18b for visualization of the dispersion relation corresponding to a kernel of this type, shown in Fig. 3.14b.) This can be easily seen from the dispersion relation (3.56a) since for odd wave numbers, $k=1,3,5 \ldots$ the right hand side is negative and for even wave numbers it is equal to $2 \alpha \pi$.
(4) $\beta>0, \alpha<0$ and $\beta>-\alpha \frac{\pi}{2} . \quad C k^{2}<2(\alpha \pi \cos k \pi+\beta(\cos k \pi-1))$

In this case the uniform steady state is stable to all perturbations. This follows from the fact that for odd wave numbers, the right hand side is equal to $-2(\alpha \pi+2 \beta)$ which is negative, and for even wave numbers it is equal to $2 \alpha \pi$, which is also negative. (See Fig.
3.18 c for visualization of the dispersion relation corresponding to a kernel of this type, shown in Fig. 3.14c.) Thus, these types of interactions do not lead to pattern formation.

From the results of (2) and (4) we conclude that in the case of bipolar bundling (II) and myosin (IV), i.e. when the interactions are 'repulsive', the necessary condition for pattern formation is that the rate of repulsion at acute angles is smaller than the rate of repulsion at obtuse angles. The biological implication of this result is as follows: if the combined effects of the substances present in the cell cause greater repulsive interactions at acute angles than at obtuse angles, then bundles will not form, even in the presence of bundling proteins or myosin.

### 3.5.3 Dispersion relation for orthogonal binding (III)

The interactions between filaments mediated by orthogonal binding proteins lead to the dispersion relation (3.56b) where $\alpha$ is positive, namely $C k^{2}<2 \alpha \pi \cos k \pi / 2$. For odd wave numbers, $k=1,3,5 \ldots$ the right hand side of the inequality is zero, for even wave numbers which are odd multiples of $2, k=2,6,10 \ldots$ it is negative, and for even multiples of $2, k=4,8,12 \ldots$ it is positive. (See Fig. 3.18d for visualization of the dispersion relation corresponding to a kernel of this type, shown in Fig. 3.14d.) Thus, the first wave number which breaks the stability is $k=4$, meaning that four directions $90^{\circ}$ apart will be accentuated, and four peaks will appear. In the presence of filamin, for example, orthogonal networks of actin filaments would therefore be promoted.

### 3.5.4 Dispersion relation for competition of binding proteins (V)

Since the kernel for this case is given by a linear superposition, $K(\theta)=K_{1}(\theta)+K_{2}(\theta)$ (see section 3.4.4 (1)), the Fourier transform will also be a simple linear superposition, i.e. $\hat{K}=\hat{K}_{1}+\hat{K}_{2}$ with $\hat{K}_{1}$ and $\hat{K}_{2}$ as in (3.55a-b).
(1) Dispersion relation for myosin (IV) and orthogonal binding proteins (III) In this case, $\hat{K}_{1}$ and $\hat{K}_{2}$ are of the form (3.55b). Therefore, the dispersion relation, which is of the form (3.56b) is given by:

$$
\begin{equation*}
C k^{2}<2\left(\alpha_{1}+\alpha_{2}\right)\left(\pi \cos \frac{k \pi}{2}\right) \tag{3.57}
\end{equation*}
$$

Since $\alpha_{1}$ is positive, and $\alpha_{2}$ is negative, if $\left|\alpha_{1}\right|<\left|\alpha_{2}\right|$ then $\left(\alpha_{1}+\alpha_{2}\right)$ is negative. In this case, the first mode to satisfy (3.57), and thus break stability is $k=2$. This implies that filaments align in a bidirectional fashion. The effect of myosin dominates over orthogonal binding proteins, so that bundling takes place. If, on the other hand, $\left|\alpha_{1}\right|>\left|\alpha_{2}\right|$ then the coefficient $\left(\alpha_{1}+\alpha_{2}\right)$ is positive, and the first mode to break stability is $k=4$. Thus, in this case, the effect of the orthogonal binding proteins dominates and filaments form an orthogonal network.

Consider the effect of the presence of a 'passive' binding protein, i.e one with smaller rate constant, or with lower concentration (implying a lower 'effectiveness' parameter). The critical mass at which instability occurs in this case would be larger than in the case of a single binding protein because, from previous remarks (see section 3.5), the mass for which instability can occur is of the order $M \sim\left|\alpha_{1}+\alpha_{2}\right|^{-1}$. This means that decreasing the value of the coefficient $\left|\alpha_{1}+\alpha_{2}\right|$ hinders the appearance of order. If both types of binding proteins are equally effective, $\left|\alpha_{1}\right|=\left|\alpha_{2}\right|$, the homogencous solution is stable.

## (2) Dispersion relation for bipolar (II) and orthogonal binding (III) proteins

In this case, the Fourier transform of the kernel representing bipolar binding is of the form (3.55a) with $\beta>0$ and $\alpha_{2}>0$, and the Fourier transform of the kernel representing orthogonal binding is of the form (3.55b) with $\alpha_{1}>0$ as in case (1). Thus the dispersion relation is:

$$
\begin{equation*}
C k^{2}<2\left(\alpha_{1} \pi \cos k \pi+\beta(\cos k \pi-1)+\alpha_{2} \pi \cos \frac{k \pi}{2}\right) \tag{3.58}
\end{equation*}
$$

The results in this case are exactly the same as those of case (1) above, and are independent of the parameter $\beta$. (Note that the term containing $\beta$ in (3.58) is either negative or zero for any integer $k$.) If $\alpha_{1}<\alpha_{2}$ then $k=2$ is the first unstable wavenumber, and if $\alpha_{1}>\alpha_{2}$ then $k=4$ is the first unstable wavenumber. If $\alpha_{1}=\alpha_{2}$, the homogeneous state is stable.

The above results are valid only near bifurcation and will not predict the type of order away from bifurcation where non-linear effects may dominate. For further analysis and an explicit solution in this case, refer to section 3.6.

### 3.6 Steady state equation and explicit solutions in three special cases

For kernels of the special form described below, it is possible to obtain an explicit formula for the steady state of equation (3.42). We first note that the steady state of (3.42) satisfies $A_{t}=0$, that is:

$$
\begin{equation*}
\mu \frac{\partial^{2} A}{\partial \theta^{2}}-\frac{\partial}{\partial \theta} A(K * A)=0 \tag{3.59}
\end{equation*}
$$

Integrating once over $-\pi \leq \theta \leq \pi$ we obtain:

$$
\begin{equation*}
\mu \frac{\partial A}{\partial \theta}=f(\theta) A(\theta)+C \tag{3.60}
\end{equation*}
$$

where $C$ is the constant of integration and $f(\theta)=(K * A)(\theta)$.
The steady state equation (3.60) is a first order linear ODE, and its general solution is:

| Kernel Group <br> and Type | First Mode <br> causing instability |
| :---: | :---: |
| Unipolar bundling (I) | $k=1$ |
| Bipolar bundling (II) <br> or <br> Myosin (IV) | $k=2$ |
| Orthogonal binding (III) | $k=4$ |
| Myosin (IV) <br> + <br> Orthogonal binding (III) | if $\left\|\alpha_{1}\right\|>\left\|\alpha_{2}\right\|$ then $k=4$ |
| Bipolar bundling (II) <br> + | if $\alpha_{1}<\alpha_{2}$ then $k=2$ |
| if $\alpha_{1}>\alpha_{2}$ then $k=2$ |  |
| Orthogonal binding (III) |  |

Table 3.3: Table summarizing the outcome of the dispersion relation for different types of kernels. The first mode causing instability is $k=1,2$ or 4 depending on the type of interaction the kernel represents. This wave number $k$ is the number of accentuated orientations breaking the homogeneous distribution.

$$
\begin{equation*}
A(\theta)=\left(D+\frac{C}{\mu} G(\theta)\right) \exp \left(\frac{1}{\mu} F(\theta)\right) \tag{3.61}
\end{equation*}
$$

where,

$$
\begin{gather*}
F(\theta)=\int f(\theta) \mathrm{d} \theta \\
G(\theta)=\int \exp \left(-\frac{1}{\mu} F(\theta)\right) \mathrm{d} \theta \tag{3.62}
\end{gather*}
$$

Note that the general solution (3.61) contains two arbitrary constants, $C$ and $D$. We need further conditions to uniquely determine the values of these constants; in this case we use periodicity of the boundaries ( BC ) and the normalization condition (3.45) to solve for these constants. We first note that $C=0$ by observing that it represents the total flux of material (see equation (3.60)). Thus, if we wish to avoid travelling waves of density circulating through the periodic domain, we must set $C=0$. Therefore, the solution is of the form:

$$
\begin{equation*}
A(\theta)=D \exp \left(\frac{1}{\mu} F(\theta)\right) \tag{3.63}
\end{equation*}
$$

We now solve for the constant $D$ and the function $F$. For some special choices of the kernel, $K$, it is possible to determine the function $F$. In the next section we present the analytical solutions for a class of kernels of a special form and compare the results with those obtained by linear analysis.

### 3.6.1 Steady state solutions for a special class of kernels

We now consider the class of kernels represented by:

$$
\begin{equation*}
K(\theta)=B \sin n \theta, \quad n=1,2,4 . \tag{3.64}
\end{equation*}
$$

Note that $B$ is a constant (unrelated to a similar symbol in Chapter 2) and that $B>0$ corresponds to repulsion, whereas $B<0$ corresponds to attraction. A remarkable feature of such integral kernels is that they are degenerate: meaning that they can be represented as a finite sum of the products of the eigenfunctions of the linear integral operator (See Yoshida, 1960). In particular, the kernel (3.64) has the following finite representation in terms of the eigenfunctions:

$$
\begin{equation*}
K\left(\theta-\theta^{\prime}\right)=B\left(\sin n \theta \cos n \theta^{\prime}-\cos n \theta \sin n \theta^{\prime}\right) \tag{3.65}
\end{equation*}
$$

This simplifies the integral term in equation (3.42) greatly. Indeed, with this representation the velocity convolution term (3.43) can be written as:

$$
\begin{equation*}
f(\theta)=(K * A)(\theta)=c_{1} \cos n \theta+c_{2} \sin n \theta \tag{3.66}
\end{equation*}
$$

where,

$$
\begin{equation*}
c_{1}=-B \int_{-\pi}^{\pi} \sin n \theta A(\theta) \mathrm{d} \theta \quad, \quad c_{2}=-B \int_{-\pi}^{\pi} \cos n \theta A(\theta) \mathrm{d} \theta . \tag{3.67}
\end{equation*}
$$

We now wish to determine the constant $D$ and the function $F$. To do so, first observe that for the particular choice of kernel given by equation (3.64), the function $F(\theta)$ is given by:

$$
\begin{equation*}
F(\theta)=\int f(\theta) \mathrm{d} \theta=\frac{c_{1}}{n} \sin n \theta+\frac{c_{2}}{n} \cos n \theta . \tag{3.68}
\end{equation*}
$$

We rewrite $F(\theta)$ as a phase-shifted cosine:

$$
\begin{equation*}
F(\theta)=\frac{c}{n} \cos (n \theta-\omega) \tag{3.69}
\end{equation*}
$$

where $\omega$ is some phase-shift ( $\omega$ is easily calculated from simple trigonometric identities). This function has a peak at $\omega / n$ and a minimum at $(\omega+\pi) / n$. To simplify calculations we bring (3.63) to the following symmetric form by redefining the variable $\theta$ so that $\theta=\omega / n$ corresponds to the origin. (This is equivalent to measuring all angles relative to the angle at which $F$ has a peak.) Thus, with this new definition of $\theta$, the equation (3.63) can now be written as:

$$
\begin{equation*}
A(\theta)=D \exp \left(-\frac{c}{\mu n} \cos n \theta\right) \tag{3.70}
\end{equation*}
$$

where,

$$
\begin{equation*}
c=B \int_{-\pi}^{\pi} \cos n \theta A(\theta) \mathrm{d} \theta \tag{3.71}
\end{equation*}
$$

### 3.6.2 Relations satisfied by the constants $c$ and $D$

Note that the value $c$ is determined by the angular distribution of $A(\theta)$. To determine the constant $D$ in (3.70) we use the normalization condition (3.45) on $A(\theta)$ :

$$
\begin{equation*}
M=\int_{-\pi}^{\pi} A(\theta) \mathrm{d} \theta=D \int_{-\pi}^{\pi} \exp \left(-\frac{c}{\mu n} \cos n \theta\right) \mathrm{d} \theta \tag{3.72}
\end{equation*}
$$

We observe that the integral in (3.72) involves the modified Bessel function of order zero:

$$
\begin{equation*}
I_{o}(z)=\frac{1}{\pi} \int_{0}^{\pi} e^{ \pm z \cos \theta} \mathrm{~d} \theta \tag{3.73}
\end{equation*}
$$

Thus, $M$ can be written in the following form:

$$
\begin{equation*}
M=2 \pi D I_{o}\left(\frac{c}{\mu n}\right) . \tag{3.74}
\end{equation*}
$$

(See Abramowitz and Stegun (1970).) So the constant $D$ can now be written as:

$$
\begin{equation*}
D=\frac{M}{2 \pi I_{o}\left(\frac{c}{\mu n}\right)} \tag{3.75}
\end{equation*}
$$

The total mass, $M$, is in principle fixed in the system and known. However $c$ depends on the angular distribution of $A$, and is not known or predetermined. Thus to understand equation (3.75) we need to investigate $c$.

Writing the constant $c$ in (3.71) with the expression of $A(\theta)$ given in (3.70) we find that:

$$
\begin{equation*}
c=B D \int_{-\pi}^{\pi} \exp \left(-\frac{c}{\mu n} \cos n \theta\right) \cos n \theta \mathrm{~d} \theta \tag{3.76}
\end{equation*}
$$

We observe that the modified Bessel function of order one:

$$
\begin{equation*}
I_{1}(z)=\frac{1}{\pi} \int_{0}^{\pi} e^{z \cos \theta} \cos \theta \mathrm{~d} \theta \tag{3.77}
\end{equation*}
$$

appears in this equation, so that:

$$
\begin{equation*}
c=B M \frac{I_{1}\left(-\frac{c}{\mu n}\right)}{I_{o}\left(\frac{c}{\mu n}\right)}, \tag{3.78}
\end{equation*}
$$

Note that (3.78) is a transcendental equation for the parameter $c$, which we now investigate.

### 3.6.3 Investigating the transcendental equation for $c$

Let us define the new variable $X$, by

$$
\begin{equation*}
X=\frac{c}{\mu n} \tag{3.79}
\end{equation*}
$$

For ease of notation define:

$$
\begin{equation*}
L(X)=\frac{\mu n}{B M} X \quad, \quad R(X)=\frac{I_{1}(-X)}{I_{o}(X)} . \tag{3.80}
\end{equation*}
$$

(Note that here $L$ and $B$ have meanings which are unrelated to similar symbols in Chapter 2.) Then (3.78) is equivalent to:

$$
\begin{equation*}
L(X)=R(X) \tag{3.81}
\end{equation*}
$$

Note that $I_{0}(X)$ is an even function, and $I_{1}(X)$ is an odd function so that $R(X)$, the right hand side of (3.81) is odd. We consider $\mu, B$ and $n$ as fixed parameters and $M$ as the gradually varying parameter of the model. The solution to this equation can be visualized as the intersection points of $L(X)$ and $R(X)$ where their graphs are plotted superimposed: see Fig. 3.19. $L(X)$ is plotted for various values of the coefficient involving the parameter $M$ in Fig. 3.19 to illustrate cases having a single or three solutions. There can be solutions for both positive and negative coefficients of $L(X)$. Note that the parameters $\mu, n$ and $M$ are positive for all biologically relevant cases. Thus, it suffices to consider the following two cases: $B$ is positive (i), and $B$ is negative (ii). It is easily seen that in all cases $X=0$ is a trivial solution of the equation (3.81). Other solutions depend on the sign of $B$ and we consider the following cases:
(i) $B>0$ : This corresponds to the case of repulsion at $\theta<\pi$. The trivial solution $X=0$ is the only solution in this case (see Fig. 3.19 and note the intersection of $y=L(X)$


Figure 3.19: Solution of the equation (3.81) visualized as the intersection of $L(X)$ (shown for various values of the slope), and $R(X)$ involving modified Bessel functions of order one and two. Note that there is a unique solution (intersection) at $X=0$ for large negative slopes or all positive slopes and two additional symmetric solutions $X_{1}=-X_{2}$ appear for negative slopes smaller than a certain value, referred to as the 'critical slope'.
(with positive slope) with $y=R(X)$ ). This means that $c=0$ (see (3.79)), which in turn implies that $F(\theta)=0$ (see (3.69), and:

$$
\begin{equation*}
A(\theta)=D=\frac{M}{2 \pi I_{o}(0)} \tag{3.82}
\end{equation*}
$$

As all quantities in (3.82) are fixed so that the steady state solution is uniform in $\theta$. Thus, in this case, the only steady state solution is one in which the density is constant for all angles.
(ii) $B<0$ : This corresponds to the case for which filaments with relative angle $\theta$, where $\theta<\pi$ are attracted. We observe from Fig. 3.19 that the number of intersections of $L(X)$ and $R(X)$ depends on the slope of $L(X)$, and therefore on the value of the parameter $M$. (Note the inverse relationship of slope and $M$ in $L(X)$ in (3.80).) In particular, for large negative slope, there is only one intersection, at the origin. (In this case, the steady state $A(\theta)$, given by (3.82), will be uniform as argued above.)

For small negative slopes (or equivalently for large $M$ ), we will have three intersections: one at the origin, and two symmetric intersections at $X= \pm \bar{X}$. (Note that these intersections depend on $M$, i.e. $\bar{X}=\bar{X}(M)$, and furthermore $\bar{X}$ is an increasing function of $M$.) Now define $M_{c}$ to be the value of $M$ for which the two additional intersections just appear. For $M>M_{c}$ the slope is small and negative and thus, two non-trivial solutions, $\bar{X}$ and $-\bar{X}$ occur. This means that there are two values of $c$, but as the function $I_{o}$ is even, this will correspond to a single value of $D$ in equation (3.75). Thus, we have essentially shown the existence of a steady state (3.70) which is non-homogeneous.

### 3.6.4 The explicit steady state solutions

Our next goal is to actually characterize the shape of this non-homogeneous solution. To do this, we need to take the following steps: (a) Use asymptotic approximations of the modified Bessel functions in equation (3.80) to determine both $M_{c}$ and $\bar{X}$. (b) Use these values to determine $D$ and $F$, and eventually, the steady state $A(\theta)$.

First note that the critical mass $M_{c}$ corresponds to the case when the slope of $L(X)$ in (3.81) is negative and large enough so that the straight line is tangent to the curve $R(X)$. Also note that since the slope and the mass $M$ are inversely proportional, a large slope corresponds to a small $M=M_{c}$, and hence a small $X$ value. In order to calculate the value of the critical mass, $M_{c}$, we use asymptotic expansions of the modified Bessel
functions. We separate this into two cases, namely small and large values of $X$. (It is evident from Fig. 3.19 that the behavior of $R(X)$ in (3.81) is quite different close to and far from the origin: for large $X$ this function is nearly constant, and for small $X$ it can be approximated by a line of slope $-1 / 2$.)

We first calculate the value of $M_{c}$ using the first terms in the asymptotic expansions of the Modified Bessel functions in (3.81) for small $X$. For $X$ near 0, retaining up to quadratic terms in the polynomial approximation we have:

$$
\begin{equation*}
I_{o}(X) \sim 1 \quad \text { and }, \quad I_{1}(X) \sim \frac{X}{2} \quad \text { for } \quad X \rightarrow 0 \tag{3.83}
\end{equation*}
$$

(See Abramowitz and Stegun (1970).) Substituting these values for $I_{o}$ and $I_{1}$ in (3.81) we obtain:

$$
\begin{equation*}
L(X)=-\frac{1}{2} X \tag{3.84}
\end{equation*}
$$

Equating the slopes of the functions on the left and right hand side of (3.84) and solving for $M$ leads to:

$$
\begin{equation*}
M_{c}=-\frac{2 \mu n}{B} . \tag{3.85}
\end{equation*}
$$

So for $M>M_{c}$, the non-homogeneous solution of (3.70) are $\mp \bar{X}=\bar{X}(M)$. Since $\bar{X}(M)$ is a monotonously increasing function of $M$ the inhomogeneity in the system is monotonously increasing with growing mass.

We now calculate the solution $X$ to (3.81), then obtain $c$ using (3.79) and finally $D$ and $A(\theta)$ using (3.75) and (3.70) for two limiting cases: close to bifurcation (a): $M \simeq M_{c}$, and far from bifurcation (b): $M \gg M_{c}$.
(a) In this case, the mass is near criticality, that is $M=M_{c}+\triangle M$ and $\triangle M \ll M_{c}$, where $M_{c}$ is the small quantity given in (3.85). Since $X$ decreases monotonously with $M$ we are looking for a small solution $\bar{X}$ to (3.81) in this case. Taking up to cubic terms in the polynomial approximations of $I_{o}$ and $I_{1}$, for small $X$ we have:

$$
\begin{equation*}
I_{0}(X) \sim 1+0.32 X^{2} \quad \text { and, } \quad I_{1}(X) \sim X / 2 \quad \text { for } \quad X \rightarrow 0 \tag{3.86}
\end{equation*}
$$

(See Abramowitz and Stegun (1970).) Substituting these values in $R(X)$ in (3.80) and (3.81), expanding the terms in Maclaurin series and retaining up to cubic terms we obtain:

$$
\begin{equation*}
\bar{X} \simeq 1.4 \sqrt{\frac{-B \triangle M}{\mu n}} \tag{3.87}
\end{equation*}
$$

hence, using (3.79) :

$$
\begin{equation*}
c \simeq 1.4 \mu n \sqrt{\frac{-B \triangle M}{\mu n}} . \tag{3.88}
\end{equation*}
$$

This value for $c$, together with the Maclaurin series expansion of the exponential term leads to the following form of (3.70) for the angular distribution of the density $A(\theta)$ :

$$
\begin{equation*}
A(\theta)=\frac{M}{2 \pi}(1+\alpha \cos n \theta)+O\left(\left(\frac{\Delta M}{M_{c}}\right)^{2}\right) \tag{3.89}
\end{equation*}
$$

where,

$$
\begin{equation*}
\alpha=1.4 \sqrt{\frac{-B \triangle M}{\mu n}} \tag{3.90}
\end{equation*}
$$

Note that the coefficient of the cosine term $\alpha$ is small since $\triangle M$ is a small deviation from the critical mass. Thus, equation (3.89) describes $n$ small peaks superimposed on
a larger constant distribution. In the next section we discuss this solution for specific choices of $n$.
(b) In this case the actin filament density is high, that is $M \gg M_{c}$. Here we are using the first terms in the asymptotic expansions of $I_{o}$ and $I_{1}$ for large $X$ values. Following Abramowitz and Stegun (1970) we have:

$$
\begin{equation*}
I_{0}(X), I_{1}(X) \sim X^{-\frac{1}{2}} e^{X} \quad \text { for } \quad X \rightarrow \infty \tag{3.91}
\end{equation*}
$$

Substituting these values in (3.81) we obtain:

$$
\begin{equation*}
\bar{X} \simeq-\frac{B M}{\mu n} \tag{3.92}
\end{equation*}
$$

Similarly to the case (a) we calculate the constant $c$ from (3.79) then the constant $D$ from (3.75) and finally we obtain the following expression for the angular distribution $A(\theta)$ in (3.70):

$$
\begin{equation*}
A(\theta)=\beta \mathrm{e}^{\gamma(\cos n \theta-1)} \tag{3.93}
\end{equation*}
$$

where,

$$
\begin{equation*}
\beta=\sqrt{-\frac{B M^{3}}{4 \pi^{2} \mu n}}\left(1+O\left(\frac{M_{c}}{M}\right)\right), \quad \gamma=-\frac{B M}{\mu n}\left(1+O\left(\frac{M_{c}}{M}\right)\right) \tag{3.94}
\end{equation*}
$$

Note that, in this case, the solution has the form of $n$-peaks located at the points:

$$
\begin{equation*}
\theta_{i}=\frac{2 \pi}{n} i, \quad i=0,1, \ldots,(n-1) \tag{3.95}
\end{equation*}
$$

In the vicinity of each of these points, $\theta_{i}, A(\theta)$ has the following form obtained by using the first two terms of a Taylor series for $\cos n \theta$ in (3.93):

$$
\begin{equation*}
A(\theta)=\beta \exp \left(-\frac{\gamma n^{2}}{2}\left(\theta-\theta_{i}\right)^{2}\right) \tag{3.96}
\end{equation*}
$$

Hence, the width of each peak has order of magnitude:

$$
\begin{equation*}
d=\sqrt{\frac{1}{\gamma n^{2}}}=\sqrt{\frac{\mu}{B M n}} \tag{3.97}
\end{equation*}
$$

Observe that the constant $B$ which affects the value of the angular drift velocity in equation (3.42) (note that $B$ is a coefficient of the kernel $K$ in (3.64) and the kernel appears in (3.43)) also affects the width of the peak. High values of $B$ represent high angular drift, meaning strong binding and alignment, and this corresponds to sharp peaks (small $d$ in 3.97) in the steady state solution. Also note that as the total mass of actin filaments, $M$, increases the peak becomes sharper and the inhomogeneity in the angular distribution increases.

### 3.6.5 Examples of several steady state solutions for specific kernels

We now discuss briefly the implication of the steady state solutions obtained in the previous section in biologically relevant cases, namely for $n=1,2$ and 4 in (3.64).

Unipolar bundling (I). $n=1, \quad K(\theta)=B \sin \theta, \quad(B<0)$.
This kernel represents the attraction filaments at all relative angles corresponding to the case of unipolar bundling. Indeed the solutions (3.89) and (3.93) have a single peak: the actin filaments orient along one direction. In the case of a very dense filament population the amount of alignment is very high.

Bipolar bundling (II) and myosin (IV). $n=2, \quad K(\theta)=B \sin 2 \theta, \quad(B<0)$.
This kernel represents attraction at acute angles and repulsion at obtuse angles corresponding to the case of bipolar bundling. It is seen from the solutions (3.89) and (3.93) that there are two peaks: the population splits in two equal subgroups aligned in parallel and anti-parallel fashion (bidirectional bundles).

Orthogonal binding (III). $n=4, \quad K(\theta)=B \sin 4 \theta, \quad(B<0)$.
This kernel represents the convergence of the filaments to relative orientations $0, \pi / 2$ and $\pi$. This corresponds to orthogonal networking alternative to the one considered in the Chapter 2. There are four peaks in the explicit solutions (3.89) and (3.93), meaning that the filaments organize in an orthogonal network as total mass of filaments increases.

## Competition of two types of binding proteins (V).

The following kernel is a linear superposition of kernels representing bipolar bundling (II) (or myosin (IV)) for which $n=2$, and orthogonal bundling (III) for which $n=4$. This depicts the combined effect of two proteins, as discussed previously.

$$
\begin{equation*}
K(\theta)=B_{2} \sin 2 \theta+B_{4} \sin 4 \theta \tag{3.98}
\end{equation*}
$$

Here, the first term accounts for bipolar bundling, and the second term accounts for the effect of orthogonal binding. The 'effectiveness' parameters, which we previously called $\alpha_{1}, \alpha_{2}$ are now replaced by $B_{2}$ and $B_{4}<0$.

Observe that in the steady state solution (3.63), the kernel appears explicitly in the function $F(\theta)$, which is in the exponent. However, this will also affect the calculated value of $D$. Superposition of two kernels will therefore lead to:

$$
\begin{equation*}
A(\theta)=D \exp \left(-\frac{1}{\mu}\left(c_{1} \cos 2 \theta+c_{2} \cos 4 \theta\right)\right) \tag{3.99}
\end{equation*}
$$

where,

$$
\begin{equation*}
D=M\left(\int_{-\pi}^{\pi} \exp \left(-\frac{1}{\mu}\left(c_{1} \cos 2 \theta+c_{2} \cos 4 \theta\right)\right) \mathrm{d} \theta\right)^{-1} \tag{3.100}
\end{equation*}
$$

and $c_{1}$ and $c_{2}$ are constant which can be found form transcendental equations as in section 3.6.3. The equation (3.99) represents four narrow peaks located at the angles $0, \pi / 2, \pi$ and $3 \pi / 2$ and the magnitude of the peaks at 0 and $\pi$ are equal and different from the ones at $\pi / 2$ and $\pi / 2$. This indicates a mixture of actin filaments organized in orthogonal network and bidirectional bundles. All filaments are positioned along two mutually normal directions if we neglect the polarity of the filaments.

### 3.7 Discussion

The results this chapter are in qualitative agreement with those of Chapter 2. In Chapter 2 we considered two main types of actin-binding proteins, namely bipolar parallel bundling and orthogonal networking. These correspond to the types (II) and (III) of this chapter, respectively. In both chapters we have found that actin microfilaments would organize either in orthogonal networks or bundles depending on the relative "effectiveness" of the orthogonal and parallel actin binding proteins. (In both cases "effectiveness" represents both relative binding rate constants and the relative concentrations of binding proteins when they co-exist in a mixture.) The linear stability analysis in both chapters reveals that the transition between these two structures is sharp: a minute change in the relative effectiveness ( $\psi$ in Chapter 2, and $\alpha_{i}$ here) can result in a switch from one type of structure to the other.

The case of myosin, which causes gradual alignment of filaments could only be described in the context of Chapter 3, in which the gradual turning of filaments is explicitly modeled by a drift term. (In Chapter 2 filaments align rapidly). We find, from remarks in section 3.5 , that the rate of alignment induced by myosin binding affects the formation of order: For faster rate of alignment, a smaller mass can already promote bundle formation.

The model in this chapter is of a sufficiently simple mathematical form, that explicit steady state solutions could be determined. These agree precisely with the predictions of the linear analysis: i.e. the integer wave number that destabilizes the homogeneous steady state coincides with the number of peaks appearing in the nonhomogeneous steady state solution. Although we have not proved so, we expect that these explicit solutions represent stable steady states. These predictions are in qualitative agreement with the numerical results of section 2.6 (see Fig. 2.8 and 2.9). The agreement of results supports the hypothesis that the phenomena modelled here are robust in the sense that many details of the type of model used (i.e. rapid or gradual alignment) and of specific forms of kernels (i.e. piecewise linear or trigonometric) do not affect the general conclusions.

## Chapter 4

## Models for actin filament alignment associated with a membrane

In this chapter, we focus on several specific examples where actin plays a major role. In these examples, we must incorporate certain geometrical features which have not yet been included in our general models. The main structure discussed in this chapter is the association of actin with a surface, such as the cell membrane or the surface of a parasitic bacterium which assembles an actin tail. In Chapters 2 and 3 the models described actin filaments that had freedom of movement in space (whether 2 or 3 dimensional), but the presence of a surface near the growing and aligning actin structures would significantly influence the types of order that form. In this chapter we discuss the type of modifications that have to be made to the models to incorporate this feature, and investigate the results.

We are concerned here only with the animal cell environment. Our examples include: (1) the cellular cortex, a relatively dense network of actin that defines the mechanical properties and shape of the cell, (2) the contractile ring, a circular ribbon of actinmyosin complex that acts in the last stage of cell-division, (3) adhesion belts, dense bands of aligned actin in the apical ends of the side surfaces of epithelial cells, and (4) the actin tail-like structure of the intracellular bacterium Listeria monocytogenes.

The one common feature shared by all these examples is the fact that actin filaments are closely associated with a surface. In some cases, actin is actually attached to the membrane by various proteins. In other cases, while no hard attachment is known, actin nucleation and polymerization is restricted to a zone close to a surface.

### 4.1 Actin arrangement in specialized structures

## (1) Actin in the cellular cortex

Actin in the cytoplasm of non-muscle cells is not evenly distributed over space. It is most abundant in the cellular cortex, a thin layer adjacent to the plasma membrane. The membrane itself is highly flexible. The cell cortex gives mechanical strength to the cell surface and helps to control the shape, and the contractile properties of the cell. It also mediates the formation of cellular extensions, and thus, ultimately, the movement of the cell. In the cellular cortex, unlike other regions of the cytoplasm, actin is attached to the membrane by specific sequences of proteins such as ponticulin, vinculin, integrin, and talin (Bray, 1992; Alberts et al., 1990).

The cellular cortex of some cells is an isotropic meshwork about $5 \mu \mathrm{~m}$ thick, i.e. relatively thick compared to the dimension of actin filaments. (See Table 4.4.) It is believed that the actin filaments in the cortex of these cells do not exhibit any spatial or angular order (Alberts et al., 1990). In other types of cells (see Table 4.4), the cortex is much thinner, about $0.01 \mu \mathrm{~m}$ thick. Since actin filaments can have lengths ranging between $0.1-1 \mu \mathrm{~m}$, the thickness of the cortex can be smaller than or comparable to the length of individual filaments. In this case, most actin filaments tend to 'lie' flat on the inner surface of the membrane and their 3D freedom of motion would be restricted, so that the geometry is approximately that of 2D. This geometry would promote alignment of the filaments. This partial alignment (from 3D to 2D) is probably enhanced by interactions between filaments and the cross linking proteins.

| Type of cell | Thickness of the cortex |
| :---: | :---: |
| Cultured fibroblast | $0.2 \mu \mathrm{~m}$ |
| lymphocyte | $0.1-0.2 \mu \mathrm{~m}$ |
| sea urchin egg | $3-5 \mu \mathrm{~m}$ |
| red blood cell | $0.01-0.02 \mu \mathrm{~m}$ |

Table 4.4: Representative 'order-of-magnitude' values for the thickness of the cell cortex in some cells. (Modified from Bray (1992)).

## (2) The contractile ring

The contractile ring (CR) is a filamentous structure formed during mitosis on the equatorial plane of dividing cells (See Fig. 4.20). It is a beltlike bundle of actin and myosin filaments. It appears beneath the plasma membrane during the initial stages of cytokinesis (cell division), and disappears once the cleavage of the cell is complete. The contraction of this ring is believed to be responsible for generating the forces that constrict the mother cell along its equatorial plane, producing two daughter cells. This structure is known to be essential for cell division in animal cells. Once the division is complete, actin and myosin filaments in the CR dissolve and disperse.

How the assembly and disassembly of this structure are controlled and details of the organization of actin and myosin is still poorly understood. Little is known about


Figure 4.20: A schematic representation of actin filament bundles in the Contractile Ring formed during mitosis. Taken from Alberts et al. (1989).
other components of the contractile ring, but they may include proteins regulating actinmyosin interactions. The contractile actin-myosin complex must be physically attached to the plasma membrane to achieve effective cleavage. The chain of proteins involved in this attachment is still uncharacterized. However membrane associated proteins such as spectrin, ankyrin, vinculin, talin, fibronectin receptors and transmembrane proteins such as band3 may play a role (Bray, 1992; Schoroeder, 1973; Cao and Wang, 1990; Mabuchi, 1986).

Various mechanisms have been suggested for the assembly of the contractile ring. The chemical signals and the molecular interactions involved in the process are reviewed in Harris and Gewalt (1989) and Cao and Wang (1990). Immunofluorescent studies indicate that the primary mechanism underlying the formation of the contractile ring is the spatial and angular reorganization of existing actin filaments in the cell. It is found that both myosin and actin filaments are recruited into the contractile ring by directional

Chapter 4. Models for actin filament alignment associated with a membrane
movement along the cortex towards the equator of the cell. There they organize parallel to the membrane, and along the equator (See Fig. 4.20). We can think of this alignment along the equator as a process that leads to loss of 1 , and then 2 dimensional degrees of freedom, as the final structure is essentially 1 dimensional (Cao and Wang, 1990; Pollard et al., 1990; Mabuchi, 1986).

## (3) Adhesion belts

Some contractile assemblies of actin are more long-lasting than the contractile ring. One example includes the circular structures which form the belt desmosomes. (In the literature there are various definitions of this term, but for the purposes of this chapter, the subtle differences between the belt desmosomes and the adhesion belts are unimportant.) These structures occur close to the apical surfaces of epithelial cells, and are known to mediate shape changes during development and differentiation, 4.21. (See Odell et al. (1981) for a model of gastrulation which incorporates the contraction of these bands.) During embryonic development, many events that necessitate the folding of epithelial sheets are ultimately dependent on the contraction of these structures.

One fundamental difference between the adhesion belts and the contractile ring, is that the former are permanent or at least very long-lasting, whereas the latter is transient (Alberts et al., 1990; Bray, 1992). Another difference is that belt-desmosomes are attached to the membrane of not one but two adjacent cells, via proteins which perforate the two neighboring plasma membranes. Proteins such as vinculin are implicated in this attachment. A similarity shared with the contractile ring is the fact that contraction is probably due to the sliding of actin filaments mediated by myosin.

## (4) Actin in the tail of Listeria monocytogenes

Listeria monocytogenes is an intracellular parasite which can cause serious, sometimes

EPITHELIAL CELL


Figure 4.21: A schematic representation of actin filament bundles in the Adhesion belts. Taken from Alberts et al. (1989).
fatal, infections in pregnant women and newborns (Dabiri and Sanger, 1990). The bacterium exists inside the host cell, where it uses the host cell actin to create a structure of its own: an actin tail. Listeria invades a wide variety of cell types including macrophages, fibroblasts, epithelial cells and enterocytes. This rod-shaped, gram-positive, intracellular bacterium spreads from cell to cell by moving to the peripheral membrane of the host cell and inducing filopodia-like projections on its surface that are subsequently internalized by the adjacent cell (Tilney and Portnoy, 1989; Dabiri and Sanger, 1990; Mounicr, et al., 1990). Listeria becomes coated with a cloud consisting of a large population of actin filaments after entering the cytoplasm. At later stages, the actin cloud rearranges to form a tail-like structure extending outward from one end of the bacterium (Dabiri and Sanger, 1990; Tilney et al., 1992a; Tilney et al., 1992b). This transition in actin architecture is required for bacterial motility (Kuhn et al., 1990).

Listeria monocytogenes synthesizes and secretes an actin filament nucleator on its

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surface. The synthesis of this surface protein, encoded by the actA gene, is necessary for bacterially induced actin assembly (Kocks et al., 1992). Filaments are nucleated at the bacterial surface with their barbed end (the high affinity end) pointing towards the surface of Listeria (Tilney et al., 1992a). It is suggested that the nucleation process involves several actin-binding proteins, including profilin, talin, and vinculin (Kocks, 1994; Nanavati et al., 1994; Dold et al., 1994). They are assembled at a large number of specific spots on the bacterial surface (Dabiri and Sanger, 1990). Listeria assembles actin filaments only on half of its surface, the 'rear end' (Tilney, 1990). As the filaments reach a characteristic length, approximately $0.2 \mu \mathrm{~m}$, they become capped and cross-linked via the actin bundling protein $\alpha$-actinin (Sanger et al., 1992). This may be a crucial step in the transition of the 3D actin cloud surrounding the bacterium into a more ordered (1D) structure.

Fluorescence staining studies indicate only the presence of the bundling protein, $\alpha$ actinin, profilin and tropomyosin throughout the tail and localized around the bacteria (Dabiri and Sanger, 1990). Actin filaments surrounding the bacterium are highly aligned parallel to the surface with their pointed end oriented towards the rear end of Listeria. The proportions of the shape of Listeria resemble a long cylindrical body capped with two hemi-ellipsoids (See Fig. 4.22). The typical length of a filament in the tail is of order $0.2 \mu \mathrm{~m}$, and it contains about 70 subunits.

### 4.2 Modelling actin associated with a surface

By our remarks above, we restrict attention to actin structures that are associated with a surface. The surface might be the cell membrane (in cases (1),(2),(3)), or the surface of the invading bacterium (case(4)). As in Chapter 2, we will consider two populations of actin filaments, those that are free and those that are bound to other filaments. However,


Figure 4.22: A hypothetical simplified representation of Listeria and its actin tail in the host cell.
unlike the models of Chapter 2, we assume that filaments polymerize only at the end which is adjacent to the surface. We focus on a narrow region near the surface. Actin filaments may leave or be transported to this region from other parts of the cell, but we consider this to be a process in dynamic equilibrium.

For the purpose of this section we interpret the free filaments as those filaments which have one end (the barbed end which is favored for polymerization) either attached to or near the surface and the other end free to rotate. Bound filaments are those that are attached to other filaments via actin binding proteins, and thus have no rotational degrees of freedom. As in the previous chapters we describe the angular distribution of the filaments only, not the spatial distribution. We consider the actin binding proteins as short rigid rods with two actin binding sites at the ends. Two filaments become bound when an actin binding protein links them.

We describe a three dimensional version of the model for which the independent variables are time and angle on the unit hemi-sphere: the presence of an impermeable surface, e.g. the inner surface of the plasma membrane, restricts the orientations of the filaments attached to (or near) the surface to angles on a unit hemi-sphere. (In


Figure 4.23: Shown are angles on the surface of the unit hemi-sphere represented in spherical coordinates. $\phi$ is a latitudinal angle from 0 to $\pi / 2$, and $\theta$ is a longitudinal angle from 0 to $2 \pi$.

Chapter 2 filaments can assume all angles on the unit sphere.) We use a local spherical coordinate system. The latitudinal angle $\phi=0$ corresponds to the direction normal to the surface and the angle $\phi=\frac{\pi}{2}$ lies on the surface (See Fig. 4.23). We assume that the average distance between the points of attachment to the surface is much smaller than the average length of the filaments (See Mabuchi, 1986). We consider filaments as rigid rods of average length $l$. We assume that the surface to which the filaments are attached is flat.

The variables in the model have identical descriptions to ones in section 2.7. $L(\Omega, t)$ and $B(\Omega, t)$ represent concentrations of filaments, oriented at $\Omega$ at time $t$. The kernel $K\left(\Omega, \Omega^{\prime}\right)$ represents the effective interaction between two filaments, oriented at angles $\Omega$ and $\Omega^{\prime}$. The interaction between filaments depends on their relative configuration. (As
before, we assume that actin binding proteins mediate this, but we no longer explicitly represent these by individual kernels.) For clarity, we concentrate all relevant definitions below:
$\Omega=(\phi, \theta)=$ an angle on the unit hemi-sphere, $0 \leq \phi \leq \pi / 2,0 \leq \theta<2 \pi$, $L(\Omega, t) \quad=$ the concentration of free actin filaments at orientation $\Omega$ at time $t$, $B(\Omega, t) \quad=$ the concentration of bound actin filaments at orientation $\Omega$ at time $t$, $\beta \quad=$ the rate constant for binding of filaments via actin binding proteins, $K(\Omega) \quad=$ the kernel representing the angular dependence of the rate constant for binding,
$\rho \quad=$ the concentration of free actin binding protein,
$\delta \quad=$ the dissociation rate of the actin binding proteins,
$l \quad=$ the average length of an actin filament.

The dynamic behavior of the densities $L$ and $B$ is given by the following system of equations:

$$
\begin{align*}
& \frac{\partial L}{\partial t}(\Omega, t)=\mu \Delta L+\delta B-\beta \rho L(K * L)-\beta \rho L(K * B), \\
& \frac{\partial B}{\partial t}(\Omega, t)=-\delta B+\beta \rho L(K * L)+\beta \rho B(K * L) . \tag{4.101}
\end{align*}
$$

These equations are identical to (2.33) with the exception that the integral is taken over the surface of the unit hemi-sphere, $S_{1}$ :

$$
\begin{equation*}
K * L=\int_{S_{1}} K\left(\Omega, \Omega^{\prime}\right) L\left(\Omega^{\prime}, t\right) d \Omega^{\prime} \tag{4.102}
\end{equation*}
$$

In (4.101) terms such as $\beta \rho L(K * L)$ represent the rate at which free filaments oriented at $\Omega$ bind to other free filaments. $\beta$ is the binding rate constant of the actin binding protein. $\delta L$ denotes the rate at which the cross-links are dissolved. $\delta$ represents the dissociation
rate of the binding protein. $\mu \Delta L$ represents the random reorientation of free filaments, $\Delta$ being the Laplacian in spherical coordinates and $\mu$, the rotational diffusion coefficient. It can be easily verified that the total mass in the system:

$$
\begin{equation*}
M=\int_{S_{1}}(L(\Omega, t)+B(\Omega, t)) \mathrm{d} \Omega \tag{4.103}
\end{equation*}
$$

is conserved.
Although the equations of this model are identical to those of Model I in Chapter 2, the difference is that here interactions occur in a region adjacent to a surface, so that functions are restricted to the hemi-sphere. A second important difference is that here we consider filaments to be fixed, or approximately stationary at one end, the end adjacent to the membrane. Here, when two filaments contact we consider them to bind rapidly at the new angle (as in Chapter 2) rather than turning gradually towards it (as in Chapter $3)$.

### 4.2.1 The kernel for binding near a surface

We now derive an approximate representation for the angular dependence for binding of two filaments close to a surface. As we have discussed in previous chapters, the representation of the binding kernels in terms of eigenfunctions appropriate for the geometry, and shared by the Laplacian and the integral operators is an essential part of the analysis of the models. In the situation we are now considering, the presence of a surface breaks rotational symmetry, so that spherical harmonics are no longer suitable as a class of eigenfunctions, strictly speaking. (The surface uniquely defines some direction in space, namely its normal vector, so that there is cylindrical rather than spherical symmetry.) In order to accommodate this geometry accurately and with due generality we would have
to treat the problem with more advanced methods. In section 4.4 we outline what the first steps in such an approach would be, but here we discuss a simplified special case.

In principle, the binding kernel of actin filaments should be represented by a product of two functions, one reflecting the dependence of interactions on the presence of a surface, and the other representing the dependence of interactions on the relative angles between filaments. The latter function should be rotationally invariant, so that spherical harmonics are appropriate eigenfunctions. The former component is not spherically symmetric, so that its eigenfunctions are different. The special case where the dependence on the surface is a constant can be treated with spherical harmonics, and we shall here restrict attention to this simple case. This does not mean that the surface is ignored, as it appears through boundary conditions. However, it means that filaments interact in the same way given some relative angle between them, independent of their orientation relative to the surface. Further it is equivalent to assuming a form of density-independence which will be described in more detail in section 4.4.

## (1) Binding kernel for actin filaments in the cell cortex.

We first derive the kernel, $K_{1}$ for binding in the cell cortex, as it has the most general form. From this kernel we later derive the more specific cases of kernels for the contractile ring and adhesion belts, and the kernel for actin filaments in the tail of Listeria. We want this kernel to reflect the angular dependence of the interactions between filaments in the cell cortex. Namely we want the angular dependence of binding to be zero when filaments are perpendicular to the surface, higher if filaments are closer to the surface and closer to each other, and maximal when filaments are lying flat on the surface. Further, interactions should be symmetric about the long axis of a filament.

In arriving at a plausible form for the binding kernel in the cell cortex let us first
consider an auxiliary function from which we will eventually derive $K_{1}$. Define:

$$
\begin{equation*}
f_{0}\left(\Omega, \Omega^{\prime}\right)=\sin ^{2} \phi \sin ^{2} \phi^{\prime} \cos 2\left(\theta-\theta^{\prime}\right) \tag{4.104}
\end{equation*}
$$

This function has the following properties:
(i) $f_{\circ}=0$ for $\phi=0$ or $\phi^{\prime}=0$,
(ii) $f_{0}$ is monotonic in $\phi, \phi^{\prime}$ and continuous for $0<\phi, \phi^{\prime}<\pi / 2, \quad 0<\theta-\theta^{\prime}<\pi / 2$,
(iii) $f_{0}$ is maximal for $\phi=\pi / 2, \phi^{\prime}=\pi / 2, \theta-\theta^{\prime}=0, \pi$,
(iv) $f_{0}$ is symmetric in $\phi$ and $\phi^{\prime}$.
(Note that $f_{0}$ itself is not yet a suitable function representing the angular dependence of binding as it is not strictly positive nor is it normalized.) We choose the positive normalized kernel of the form:

$$
\begin{align*}
K_{1}\left(\Omega, \Omega^{\prime}\right) & =A_{1}+A_{2} f \\
& =A_{1}+A_{2}\left(\left(\sin ^{2} \phi \cos 2 \theta\right)\left(\sin ^{2} \phi^{\prime} \cos 2 \theta^{\prime}\right)+\left(\sin ^{2} \phi \sin 2 \theta\right)\left(\sin ^{2} \phi^{\prime} \sin 2 \theta^{\prime}\right)\right), \tag{4.105}
\end{align*}
$$

where $A_{1}$ is the normalization constant and $A_{2}$ is the amplitude. Normalization and positivity of $K_{1}$ imply:

$$
\begin{equation*}
A_{1}=\frac{1}{2 \pi} \geq A_{2} . \tag{4.106}
\end{equation*}
$$

As before, the form of the kernel $K_{1}\left(\Omega, \Omega^{\prime}\right)$ is of vital importance in the model. The fact that the surface is impermeable to filaments implies a zero flux or Neumann boundary condition at $\phi=\pi / 2, \phi^{\prime}=\pi / 2$. This boundary condition is thus the aspect of the model which incorporates the effect of the surface, as mentioned above. We also assume periodicity in the variable $\theta$.

## (2) Binding kernel for actin filaments in the Contractile ring.

In order to explain 1D type of alignment in the cases of contractile ring (a narrow strip) we have to take into consideration the fact that high actin density is restricted to a narrow region on the membrane. If the filaments are oriented along that narrow strip they are in a high density region. Thus, they have a higher probability of forming contacts, and hence binding, than when they are oriented in directions normal to that strip. Mathematically, this implies an anisotropy of the interactions in $\theta$. Let $\theta=0$ be an angle in the plane of the surface and parallel to the strip. To reflect this anisotropy we now define:

$$
\begin{equation*}
K_{2}\left(\Omega, \Omega^{\prime}\right)=A_{1}+A_{2}\left(\sin ^{2} \phi \cos 2 \theta\right)\left(\sin ^{2} \phi^{\prime} \cos 2 \theta^{\prime}\right) . \tag{4.107}
\end{equation*}
$$

Note that there is now a unique favored direction for interaction, $\theta=0$, which is distinguished from other directions (unlike the case of $K_{1}$.)

## (3) Binding kernel for actin filaments in the Adhesion belt.

The geometry of the adhesion belts is the same as the contractile ring (a narrow 1D strip). Thus, we use the kernel derived for the binding of actin filaments in contractile rings, namely $K_{2}$, to represent the binding in this case as well. We will treat the analysis of this case together with the contractile ring, case (2), in section 4.3.

## (4) Binding kernel for actin filaments in Listeria tail.

In the case of actin surrounding the surface of Listeria we do not assume that the filaments are attached to the bacterial surface. (Evidence to this effect is controversial.) However filaments polymerize only at their barbed ends provided these ends are close to the bacterial surface. We chose $\theta=0$ to be parallel to the major axis of Listeria and pointing towards the rear end (See Fig. 4.24). The fact that Listeria assembles actin filaments only


Figure 4.24: The longitudinal angle $\theta=0$ is chosen to be the direction along the major axis of Listeria pointing towards its rear end.
on half of its surface, the 'rear end' (Tilney, 1990) leads to the conclusion that filaments can interact with other filaments most effectively if they are oriented towards that end of the bacterium. In this case effective binding occurs for filaments in the direction $\theta=0$. This suggests replacing the function $f_{0}$ in (4.104) by the following:

$$
\begin{equation*}
f_{1}\left(\Omega, \Omega^{\prime}\right)=\sin \phi \sin \phi^{\prime} \cos \theta \cos \theta^{\prime} \tag{4.108}
\end{equation*}
$$

Note that the dependence on $\theta$ is no longer of the form $\cos 2 \theta$ but rather $\cos \theta$. This reflects the polarity in the interactions, binding occurs only if filaments are oriented (nearly) at $\theta=0$. We then define:

$$
\begin{align*}
K_{3}\left(\Omega, \Omega^{\prime}\right) & =A_{1}+A_{2} f_{1} \\
& =A_{1}+A_{2}(\sin \phi \cos \theta)\left(\sin \phi^{\prime} \cos \theta^{\prime}\right) . \tag{4.109}
\end{align*}
$$

For this kernel only filaments with (nearly) the same polarity interact $(\theta=0)$. The Listeria tail has a unipolar, rather than bipolar actin filament distribution.

### 4.3 The analysis of the models.

In order to analyse the dynamic behavior of the equations(4.101) we first bring them to the following dimensionless form:

$$
\begin{align*}
& \dot{L}=\varepsilon \triangle L+\xi B-L(K * L)-L(K * B), \\
& \dot{B}=-\xi B+B(K * L)+L(K * L), \tag{4.110}
\end{align*}
$$

where $\xi=\frac{\delta}{\beta \rho M}, \varepsilon=\frac{\mu}{\beta \rho M}$ and $M$ is the total mass in the system. (A similar nondimensionalization is done for Model 1 in section 2.4 and the details are given in Appendix A. Note that this version applies to 3D, angles on the surface of the unit hemi-sphere whereas equations (2.11) in Chapter 2 are in 2D.) As in chapter 2, we expect that at large enough rotational diffusion coefficient $\mu$ the stationary densities are homogeneous. These homogeneous concentrations, $\bar{L}$ and $\bar{B}$, satisfy:

$$
\begin{align*}
& \frac{\bar{B}}{\bar{L}}=\frac{\beta \rho M}{\delta}  \tag{4.111}\\
& M=\bar{L}+\bar{B}
\end{align*}
$$

(See Appendix A for details in 2D case.) The ratio $\bar{B} / \bar{L}$ is the proportion of bound to free filaments. The product $\beta \rho$ represents the strength of interaction and $\delta$ represents the decay rate of the cross-link. Note that if $\delta$ is small, or equivalently $\beta \rho$ is large, the homogeneous equilibrium ratio $\bar{B} / \bar{L}$ is large. Also note that as the number of filaments on the surface, $M$, increases, the proportion $\bar{B} / \bar{L}$ increases.

The linear stability analysis of the equations (4.110) together with the boundary conditions lead to an eigenvalue problem closely resembling the one addressed and discussed in section 2.7. In this case, the eigenfunctions of both the integral operator, $K *$, and the Laplacian operator, $\Delta$, on the unit hemi-sphere are a restricted subset of the surface
spherical harmonics. In Chapter 2, we used the notation $Y_{n}$ to denote the SSH. In this case, the elements of this restricted subset are best expressed in the fundamental form given below:

$$
Y_{n}^{m}(\Omega)=P_{n}^{m}(\cos \phi)\left\{\begin{array}{l}
\sin \theta  \tag{4.112}\\
\cos \theta
\end{array}\right.
$$

where $n-m$ is even and $\sin \theta$ term corresponds to harmonics, $Y_{n}^{m}(\Omega)$, for positive $m$ values and $\cos \theta$ terms corresponds to harmonics, $Y_{n}^{m}(\Omega)$, for negative $m$ values (MacRobert, 1927; Arsenin, 1968; Hobson, 1931). (See Appendix D for the expression of the harmonics $Y_{n}$ in terms of the fundamental harmonics $Y_{n}^{m}$.) The condition on the mode number, the fact that $n-m$ should be even stems from the geometry of the problem: namely that of a hemi-sphere with zero flux boundary conditions. (Only the SSH with $n-m$ even are even functions of $\phi$ about $\pi / 2$, thus have zero derivative at $\phi=\pi / 2$.) The eigenvalues corresponding to $Y_{n}^{m}$ for the integral operator, $K *$, and the Laplacian operator, $\Delta$ are $-n(n+1)$ and $\tilde{K}_{n}^{m}$, respectively (See Appendix D). As in section 2.7, by completeness, the densities $L(\Omega, t)$ and $B(\Omega, t)$ can be expanded in series of fundamental spherical harmonics as follows:

$$
\left[\begin{array}{l}
L(\Omega, t)  \tag{4.113}\\
B(\Omega, t)
\end{array}\right]=\sum_{n=0}^{\infty} * \sum_{m=-n}^{n} *\left[\begin{array}{l}
l_{n m}(t) \\
b_{n m}(t)
\end{array}\right] Y_{n}^{m}(\Omega),
$$

where $l_{n m}(t), b_{n m}(t)$ are coefficients depending on time only and $\Sigma^{*}$ means that the summation is taken over harmonics for which $n-m$ is even (MacRobert, 1927; Arsenin, 1968; Hobson, 1931).

To determine the stability of the homogeneous steady state, as in section 2.7 we consider perturbations of the form:

$$
\left[\begin{array}{l}
L(\Omega, t)  \tag{4.114}\\
B(\Omega, t)
\end{array}\right]=\left[\begin{array}{l}
\bar{L} \\
\bar{B}
\end{array}\right]+\left[\begin{array}{l}
L_{o} \\
B_{o}
\end{array}\right] Y_{n}^{m}(\Omega) e^{\lambda t} .
$$

Substituting this expansion into (4.101) with $(n-m)$ even, and taking the linear approximation in small amplitudes $L_{o}$ and $B_{o}$, we find that instability of the homogeneous distribution occurs at any harmonic $Y_{n}^{m}$ for which the following inequality is satisfied:

$$
\begin{equation*}
C n(n+1)<\tilde{K}_{n}^{m}\left(1-\tilde{K}_{n}^{m}\right) \tag{4.115}
\end{equation*}
$$

where,

$$
\begin{equation*}
C=\frac{\mu}{\delta}\left(\frac{\delta}{(\bar{L}+\bar{B}) \beta_{\rho}}\right)^{2}, \tag{4.116}
\end{equation*}
$$

In (4.115) $\tilde{K}_{n}^{m}$ are coefficients in the expansion of the kernel over the surface harmonics $Y_{n}^{m}($ See Appendix D).

We now consider the individual kernels described in section 4.2.1, and summarize results in each case. The structure that forms at instability will be determined by the first mode $n$ that satisfies the inequality (4.115). This will depend on the values of the coefficients $\tilde{K}_{n}^{m}$ appearing in (4.115).

## (1) Structures that form in the cell cortex (1)

First note that the coefficients $\tilde{K}_{n}^{m}$ in this case are as follows:

$$
\begin{align*}
\tilde{K}_{o}^{o} & =A_{1}, \\
\tilde{K}_{2}^{2} & =\tilde{K}_{2}^{-2}=\frac{1}{3} A_{2}  \tag{4.117}\\
\tilde{K}_{m}^{n} & =0 \quad \text { otherwise. }
\end{align*}
$$

(See Appendix D for details.) Thus in the case of the cell cortex the inequality (4.115) is first satisfied for $n=m=2$ and for $n=2, m=-2$, that is when the right hand side is positive and maximal. The harmonics $Y_{2}^{2}=3 \sin ^{2} \phi \sin 2 \theta$ and $Y_{2}^{-2}=3 \sin ^{2} \phi \cos 2 \theta$ destabilize the homogeneous distribution and initiate pattern formation in this case. Both harmonics $Y_{2}^{2}$ and $Y_{2}^{-2}$ have a peak at $\phi=\pi / 2$. However, the positions of the two peaks along the latitudinal direction $\theta$ is arbitrary.

We define $C_{c r}$ to be the critical value of $C$ at which instability occurs. (The value of $C_{c r}$ is calculated by substituting the values of $n, m$ and $\tilde{K}_{n}^{m}$ causing instability in (4.115).) In this case we obtain:

$$
\begin{equation*}
C_{c r}=\frac{1}{6} A_{2}\left(1-1 / 3 A_{2}\right) \tag{4.118}
\end{equation*}
$$

Assuming all the parameters are fixed in the system, we treat $M$, the total mass, as the bifurcation parameter. From equation (4.116) we find that the critical value for $C$ corresponds to the following critical value for the total mass $M$ :

$$
\begin{equation*}
M_{c r}=\frac{6 \mu \delta}{\beta^{2} \rho^{2} A_{2}\left(1-1 / 3 A_{2}\right)} \tag{4.119}
\end{equation*}
$$

If $M>M_{c r}$ the stability of homogeneous distribution is broken and a pattern evolves in which most filaments lie flat $(\phi=\pi / 2)$ on the surface of the membrane. Note that in (4.119) $M_{c}$ depends inversely on $\beta$, the binding rate constant, $\rho$, the binding protein concentration, and $A_{2}$ the amplitude of interactions and is proportional to $\mu$, the rotational diffusion rate, and $\delta$, the dissociation rate of the binding protein. So, as $\beta, \rho$, or $A_{2}$ increase, the critical mass $M_{c r}$ decreases, i.e. the homogeneous distribution becomes unstable at low filament concentrations, and as $\mu$, or $\delta$ increase, the critical mass increases, i.e. the homogeneous distribution becomes unstable at high filament concentrations.

This analysis shows that the cell cortex loses its 3D isotropic structure and adopts a 2D one where most filaments are lying flat on the surface parallel to each other. The structure corresponds to a 'hump' in the angular distribution of free and bound filaments centered at $\phi=\pi / 2$. The preferred direction of alignment in this 2D structure (the plane of the cell surface) is arbitrary in this case.

## (2) Structures that form in the contractile ring.

In the case of contractile ring the coefficients $\tilde{K}_{n}^{m}$ are as follows:

$$
\begin{align*}
\tilde{K}_{0}^{o} & =A_{1} \\
\tilde{K}_{2}^{2} & =\frac{1}{3} A_{2}  \tag{4.120}\\
\tilde{K}_{m}^{n} & =0 \quad \text { otherwise }
\end{align*}
$$

(See Appendix D for details.) Thus the inequality (4.115) is first satisfied for $n=m=2$. The harmonic $Y_{2}^{2}=3 \sin ^{2} \phi \sin 2 \theta$ destabilizes the homogeneous distribution and initiates pattern formation. $Y_{2}^{2}$ has peaks at $\phi=\pi / 2$, and $\theta=0, \pi$. Thus the growing pattern is one in which filaments are lying flat on the surface ( $\phi=\pi / 2$ ), and along the narrow strip of high density region $(\theta=0, \pi)$.

The values of $C_{c r}$ and $M_{c r}$ are the same as in the previous case:

$$
\begin{equation*}
C_{c r}=\frac{1}{6} A_{2}\left(1-1 / 3 A_{2}\right) \tag{4.121}
\end{equation*}
$$

and,

$$
\begin{equation*}
M_{c r}=\frac{6 \mu \delta}{\beta^{2} \rho^{2} A_{2}\left(1-1 / 3 A_{2}\right)} \tag{4.122}
\end{equation*}
$$

Thus, if $M>M_{c r}$ the stability of homogeneous distribution is broken and a pattern
evolves in which most filaments lie flat on the surface of the membrane again, but they are also oriented along the equator. The pattern corresponds to a 'hump' in the angular distribution of free and bound filaments centered at $\phi=\pi / 2, \theta=0$ and at $\phi=\pi / 2, \theta=\pi$.

## (3) Structures that form in adhesion belts.

The kernel, and hence the results are same as in case (2) above. A pattern in which most filaments lie flat and parallel (or anti-parallel) to one another on the surface of the membrane evolves.

## (4) Structure of the Listeria tail.

For the case of actin filaments in the tail of Listeria the coefficients $\tilde{K}_{n}^{m}$ are as follows:

$$
\begin{align*}
\tilde{K}_{o}^{o} & =A_{1} \\
\tilde{K}_{1}^{1} & =A_{2}  \tag{4.123}\\
\tilde{K}_{m}^{n} & =0 \quad \text { otherwise. }
\end{align*}
$$

(See Appendix D for details.) Thus the inequality (4.115) is first satisfied for $n=m=1$. The harmonic $Y_{1}^{1}=\sin \phi \sin \theta$ destabilizes the homogeneous distribution and initiates pattern formation in this case. $Y_{1}^{1}$ has a peak at $\phi=\pi / 2$, and $\theta=0$, i.e. the growing pattern is one in which filaments are perpendicular to the bacterial surface ( $\phi=\pi / 2$ ), and along the major axis of the bacterium $(\theta=0, \pi)$.

The values of $C_{c r}$ and $M_{c r}$ are as follows:

$$
\begin{equation*}
C_{c r}=\frac{1}{2} A_{2}\left(1-A_{2}\right) \tag{4.124}
\end{equation*}
$$

and,

$$
\begin{equation*}
M_{c r}=\frac{2 \mu \delta}{\beta^{2} \rho^{2} A_{2}\left(1-A_{2}\right)} . \tag{4.125}
\end{equation*}
$$

Thus, if $M>M_{c r}$ the stability of homogeneous distribution is broken and a pattern in which most filaments are oriented along the axis of Listeria evolves. This pattern corresponds to a 'hump' in the angular distribution of free and bound filaments centered at $\phi=\pi / 2, \theta=0$.

In all cases, if the mass $M$ is large and the system is drawn far from criticality, sharp narrow peaks in the angular distribution of the filaments evolves from the mild 'humps' described above. Results similar to those of section 4.3 were obtained for a general form of the 3D model in Mogilner and Edelstein-Keshet (1994a-b). It is found that for a large class of kernels, as the total mass in the system exceeds some critical value (determined by parameters of the system), a spontaneous pattern formation occurs. The leading mode having the largest amplitude is determined by the SSH with the largest coefficient appearing in the expansion of the kernel. According to their results, the bifurcation is supercritical and corresponds to a second order non-equilibrium phase transition. As the total mass, $M$, increases the mild 'hump' described by the SSH which breaks the stability of the homogeneous distribution transforms into a sharp narrow peak (See Mogilner and Edelstein-Keshet (1994a)). The total amount of free and bound filaments in the peak are:

$$
\begin{equation*}
\bar{L}_{p}+\bar{B}_{p}=M, \quad \frac{\bar{B}_{p}}{\bar{L}_{p}}=K_{p} \frac{\bar{B}}{\bar{L}}>\frac{\bar{B}}{L}, \tag{4.126}
\end{equation*}
$$

where $K_{p}>1$ is the value of $K_{i}$ (for $i=1,2,3$ ) in the peak (See Appendix D). Hence as the density of filaments grows, the ratio of the bound to free filaments increases.

### 4.4 First steps towards a more realistic model

In this section we suggest a modified approach to the problem which takes into account the effect of the surface on the actual interaction between filaments at various orientations. (Recall that in section 4.2 the surface appeared only through a boundary condition for the problem.)

We first derive the angular dependence of binding of a filament at some orientation to any one of the other filaments. We consider only the angle made with the normal of the surface and focus attention on a single actin filament (call it A) whose orientation is $\phi$. As before, we will assume that the average length of the filaments is $l$. Consider the interactions of A with other filaments, for example those at angle $\phi^{\prime}$. In principle, there could be numerous such filaments in the neighborhood of $A$. We will treat these as a continuous slab of material, and assume that interactions with A occur only over the length of A which is actually embedded in the slab (see Fig. 4.25). Moreover, the strength of interactions will be proportional to the density of filaments in the slab.

The thickness of the slab, $\tau$ will depend on the angle $\phi^{\prime}$, i.e $\tau=\tau\left(\phi^{\prime}\right)$ as follows:

$$
\begin{equation*}
\tau(\phi)=l \cos \phi^{\prime} \tag{4.127}
\end{equation*}
$$

(See Fig. 4.25.) If there is a uniform distribution of filament sites along the surface, (for example $\sigma$ sites per unit area) then the density of filaments in the slab (per unit volume), $\rho\left(\phi^{\prime}\right)$, will be:

$$
\begin{equation*}
\rho\left(\phi^{\prime}\right)=\frac{\sigma}{l \cos \phi^{\prime}}, \tag{4.128}
\end{equation*}
$$

If $\phi>\phi^{\prime}$ the entire filament A is embedded in the slab and interacts all along its full


Figure 4.25: Shown are the slab of material representing the filaments oriented at $\phi^{\prime}$, the filament A oriented at $\phi$, the thickness of the slab $\tau\left(\phi^{\prime}\right)$, the average length of a filament $l$, and the portion of the filament A embedded in the slab $l^{\prime}$.
length, whereas if $\phi<\phi^{\prime}$ only a part of the filament A will interact. The effective length of interactions, $l^{\prime}$, i.e., the portion of A which is embedded in this slab will be:

$$
\begin{equation*}
l^{\prime}\left(\phi, \phi^{\prime}\right)=l \frac{\cos \phi^{\prime}}{\cos \phi} \tag{4.129}
\end{equation*}
$$

(See Fig. 4.25.) To avoid singularities in the case of $\phi, \phi^{\prime} \simeq \pi / 2$ (when the filaments are nearly lying flat on the surface) it is necessary to assume that the strength of interactions cannot exceed some maximal value. We call this value $C_{r}$, the interaction strength attained if the filaments are within a small angle $\kappa$ of $\pi / 2$.

$$
\begin{equation*}
C_{r}=\frac{1}{\cos \left(\frac{\pi}{2}-\kappa\right)} \tag{4.130}
\end{equation*}
$$



Figure 4.26: The kernel $K$ plotted for various values of $\phi^{\prime}$, shown for $\phi=0.5,0.8$ and 1 radian. The value of the small angle $\kappa$ is 0.15 radian.

We build up the interaction kernel using the effective length of interaction and the effective density of filaments in the slab, obtaining $K \sim \rho l^{\prime}$. Using the above assumptions about $\rho$ and $l^{\prime}$ we find that:

$$
K\left(\phi, \phi^{\prime}\right)= \begin{cases}\frac{1}{\cos \phi^{\prime}} & \text { for } \phi^{\prime}<\phi  \tag{4.131}\\ \frac{1}{\cos \phi} & \text { for } \phi<\phi^{\prime} \\ C_{r} & \text { for } \phi, \phi^{\prime}>\frac{\pi}{2}-\kappa\end{cases}
$$

Notice that the kernel is symmetric in $\phi, \phi^{\prime}$. So far this kernel does not yet include dependence on $\theta$ and $\theta^{\prime}$ : the final kernel should be a product of one of the $\theta, \theta^{\prime}$-dependent versions given in section 4.2.1 and the one in (4.131).

The graphical representation of this kernel as a function of $\phi$ for a number of different $\phi^{\prime}$ values is plotted in Figure 4.26. It is seen from this figure that the higher the density of filaments, the higher is the strength of interaction between filaments.

The kernel obtained by combining the angle dependence of equations (4.131), and the ones in section 4.2.1 (4.105), (4.107) or (4.109), now incorporates an explicit dependence on the orientation with respect to the surface. The problem thus formulated no longer has spherical symmetry, and its linear stability can not be investigated with spherical
harmonics. We do not here treat this more complicated problem. Some steps in its treatment would include: simplification of the expression using products of trigonometric functions to approximate the terms, and explicit solution along the lines of chapter 3.

### 4.5 Discussion

In this chapter we presented a simple model accounting for the essential features of association of actin filament structures with a surface, such as the cell membrane or the outer surface of the bacterium, Listeria monocytogenes.

We study the alignment of actin filaments into 1 dimensional structures such as the contractile ring and adhesion belts. We had to modify the previous model (Model I of Chapter 2) to include the effects of a surface. As discussed in detail, the surface presented a constraint (boundary conditions) which restricted the full 3D freedom of movement of actin, though the surface did not directly influence the way that two filaments interacted. (This was a simplification, made for mathematical convenience. In section 4.4 we suggested an approach in which the surface also impacts the filament interactions.)

The four cases discussed here included (1) the cellular cortex, (2) the contractile ring, and (3) the adhesion belts, (4) the actin tail of Listeria. These cases were characterized by different binding kernels (4.105), (4.107) and (4.109). As discussed in section 4.3 , in each case once a critical mass of actin was exceeded, alignment would occur. However, the critical mass was different in each case (see equations (4.119), (4.122) and (4.125)). Situations for which $\delta$ and $\mu$ are small (meaning low actin binding protein dissociation and rotational diffusion rate) or $\rho$ and $\beta$ are large (high binding protein concentration and rate constant) have a low critical mass value, meaning that spontaneous alignment occurs more readily (at smaller densities). The value of amplitude of the binding kernel, $A_{2}$, which corresponds to the minimal $M_{c r}$ is different in different cases, namely:

$$
\begin{align*}
& A_{2}=3 / 2 \text { in }(1),(2) \text { and }(3)  \tag{4.132}\\
& A_{2}=1 / 2 \text { in }(4)
\end{align*}
$$

with,

$$
\begin{equation*}
M_{c r}=\frac{8 \mu \delta}{\beta^{2} \rho^{2}} \tag{4.133}
\end{equation*}
$$

in all four cases. Since the critical mass for bifurcation is the same in all cases, in the case of Listeria tail formation, case (4), where the interactions are unipolar, the amplitude of the binding kernel corresponding to initiation of pattern formation is not as high as in the cases where the interactions are bipolar, cases (1), (2) and (3) (minimal critical mass for bifurcation corresponds to a lower $A_{2}$ value in case (4)). This makes intuitive sense since in the former case a single 'hump' in the angular distribution of actin filaments grows as a result of binding, whereas in the latter two 'humps' grow simultaneously and a single hump will contain more filaments then two humps. Thus a higher amplitude, i.e. a larger difference in strength of binding at different angles is required to accentuate the subtle inhomogeneity at two orientations in which filaments may diffuse into other directions faster and/or more easily than a single hump containing more filaments. Note that $A_{2}$ is similar to the 'effectiveness' parameters $\alpha$ and $\beta$ in section 3.5 , or $B$ in section 3.6 which plays a part in the magnitude of the drift velocity. From that point of view also, only a higher drift velocity will allow the break of homogeneity into two groups compared to a single group if the same amount of actin filaments are present in the system. In other words the drift velocity should be high enough to override the diffusion and dissociation rates of clusters smaller in size.

Moreover, the type of alignment was distinct. We found that in cases (2), (3) and (4),
actin filaments formed structures along specific directions (a 'ring' along the equator, a 'belt' along the apical surface, or a 'tail' behind the bacteria), whereas in case (1) actin organized into structures where filaments were oriented along an arbitrary direction. (This is a direct consequence of assumptions that were made about the kernels in each case.)

## Chapter 5

## Discussion

In this thesis we have focussed on the dynamics of actin structures, and on transitions that take place under the influence of the actin-related proteins. The importance of actin in the cell stems from the fact that the structure, mechanical properties, and many cellular functions are intimately related to the actin cytoskeleton. The rearrangement of actin in the cytoskeleton determines aspects of cellular motility and many other properties of the cell. As discussed in chapter 4, an actin structure (a "tail") also plays a dominant role in the motility of an intra-cellular bacterium Listeria monocytogenes.

We have investigated several types of actin binding proteins including those that mediate unipolar bundles, bipolar bundles, and orthogonal networks. Our models give continuum descriptions of angular actin distribution in such structures, and of the temporal behavior of this distribution. This is analogous to the mean field approximation in physics. The scope of this work is different from recent modelling by Dufort and Lumsden (1993a,b) in which three dimensional spatial positions, binding and unbinding, and the spatial and rotational diffusions of individual molecules is taken into account. The latter is a complex simulation, whereas our models are aimed at analytic tractability. Unlike Sherratt and Lewis (1993) who consider how actin responds to external forces (stress and strains), our model is time dependent, and emphasizes the role of the binding proteins.

The philosophy of the modelling approach can be summarized as follows. The models are based on the following assumptions: (1) The geometry of the binding proteins can
be represented by a function that depends on the relative orientations of actin filaments. This function is the kernel $K$. (2) The binding is either rapid (Chapter 2 and 4) or gradual (Chapter 3). (3) Actin filaments can undergo random rotational diffusion governed by the parameter $\mu$. Futhermore in Chapters 2 and 4 the following specific simplifications were made: (4) Actin filaments exchange between a bound and a free state. Only one type of bound state is considered. (5) Binding and unbinding of filaments is the same at all stages of the process. No distinction is made between small and large bound clusters. (6) Monomers are added to the filaments at a rate proportional to the total concentration of filaments. Thus the model only includes a limited number of features of a highly complex system.

The model predicts the following results which were not given initially but which follow from the analysis: (1) The above minimal assumptions are already sufficient to obtain the observed pattern formation. (2) The formation of the final structure does not depend on whether the molecules bind in a single step (rapidly as in Chapter 2) or whether they pull each other gradually into the right configuration (as in Chapter 3). (3) Transitions from one structure to another can take place without completely disassembling the original structure (see section 2.6). (4) The formation of structures depends on combinations of the parameters. If such combinations do not satisfy certain criteria (dispersion relations), no structures will form.

The models have included the following important parameters: $\mu$ the rotational diffusion coefficient, $M$ the total mass of actin, $\delta$ the dissociation rate (Chapter 2 and 4), $\beta$ the binding rate (Chapter 2 and 4). Pattern formation occurs for small $\mu, \delta$ and/or large $M, \beta$. Short actin filaments have rotational diffusion, $\mu$, which is orders of magnitude larger than that of long filaments. (For example, actin monomers rotate much more quickly than F-actin.) This means that polymerization into long filaments must be the
first and most important step in initiation of structure: actin networks or bundles can appear only in a late stage of polymerization according to the model. The model also predicts that the total mass, $M$, must be large enough relative to other parameters for structures to form. This can be explained by reasoning that a large total mass provides opportunities for contact and binding. (This kind of dependence of self-organization on total mass is found in other theories for self-organization in both physics and biology.) The other parameters which reflect binding and unbinding rates also influence the ability of structures to form. Similar predictions were made in Chapter 4 where the structures are associated with a surface.

Our original hypothesis, stated in the introduction, was that molecular interactions between actin filaments and the actin associated proteins lead to the formation of order and the transitions between different structures formed by the actin cytoskeleton, even in the absence of external mechanical forces. The results of Chapters 2, 3, and 4 confirm that this hypothesis is correct, subject to the assumptions of the models. Further, the models have allowed statements to be made about how the properties of individual molecules affect the properties of the macromolecular structures, linking one level of complexity to the next higher level.

Recent experimental work by Wachsstock et al (1994) reveals that actin associated proteins from different species of organisms may have slight differences in affinities and rate constants. Their work gives evidence to the changes in actin network structure that stem from these differences in binding proteins. The models investigated in this thesis predict that specific values of the parameter combinations lead to specific types of actin alignment, and that minute changes in these parameters (close to bifurcation) can lead to large changes in the structures that form. The comparison between proteins derived from different species may have some implications about the molecular evolution
of actin-associated proteins.
The two distinct types of models discussed were: (a) a model for rapid turning and alignment of actin filaments (Chapter 2), and (b) a model for gradual drift-like turning and alignment of actin filaments (Chapter 3). Comparisons between the results of these separate models applied to a given class of binding proteins resulted in similar predictions. These similarities are evidence that the phenomena are robust to changes in the structure of the models.

Future areas of extension of this work might proceed in several directions:
(1) To determine a complete set of biologically realistic parameter values, and assess whether these values agree with the predictions corresponding to the given structures, (2) To generalize the models to a full spatio-angular treatment, and investigate both spatial and angular distributions of actin in the cell, and (3) to include the effects of mechanical properties of the cytoskeleton, and the presence of external forces.

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## Appendix A

## Non-dimensionalization

In order to non-dimensionalize the equations (2.9) we define the following dimensionless quantities:

$$
\begin{aligned}
B^{*} & =\frac{B}{\hat{B}}, \\
L^{*} & =\frac{L}{\hat{L}}, \\
t^{*} & =\frac{t}{\tau} .
\end{aligned}
$$

Here $B^{*}, L^{*}$ and $t^{*}$ represent scalar dimensionless quantities, whereas $\hat{B}, \hat{L}$ and $\tau$ are quantities with dimensions. Substituting the values of $B, L$ and $t$ in the equations (2.9) by the corresponding values in terms of the variables defined above, and rearranging them slightly we arrive at the following form:

$$
\begin{align*}
& \frac{\partial L^{*}}{\partial t^{*}}=\mu \tau \frac{\partial^{2} L^{*}}{\partial \theta^{*^{2}}}+\delta \tau \hat{\hat{B}} B^{*}-\beta \rho \hat{B} L^{*}\left(K * B^{*}\right)-\beta \rho \tau \hat{L} L^{*}\left(K * L^{*}\right) \\
& \frac{\partial B^{*}}{\partial t^{*}}=-\delta \tau B^{*}+\beta \rho \tau \hat{L} B^{*}\left(K * L^{*}\right)+\beta \rho \tau \frac{\hat{L}^{2}}{\hat{B}} L^{*}\left(K * L^{*}\right) \tag{A.134}
\end{align*}
$$

Choosing,

$$
\begin{equation*}
\tau=\frac{1}{\beta \rho M} \quad \text { and } \quad \hat{L}=\hat{B}=M \tag{A.135}
\end{equation*}
$$

and substituting these in (A.134), and dropping the $*$ 's in the equations we arrive at the dimensionless form (2.11) with the dimensionless parameters $\xi$ and $\varepsilon$ as follows:

$$
\begin{equation*}
\xi=\frac{\delta}{\beta \rho M} \quad \varepsilon=\frac{\mu}{\beta \rho M} \tag{A.136}
\end{equation*}
$$

The stationary density distribution is expected to be a homogeneous one for large values of the diffusion coefficient $\mu$ or equivalently $\varepsilon$. The values of these densities homogeneous in $\theta$ and time $t,(\bar{L}, \bar{B})$, can be found by setting the time and $\theta$ derivatives equal to zero in (2.9). Thus we have:

$$
\begin{align*}
& 0=\delta \bar{B}-\beta \rho \bar{L}(K * \bar{B})-\beta \rho \bar{L}(K * \bar{L}) \\
& 0=-\delta \bar{B}+\beta \rho \bar{B}(K * \bar{L})+\beta \rho \bar{L}(K * \bar{L}) \tag{A.137}
\end{align*}
$$

We observe that $K * \bar{B}=\bar{B}$ and $K * \bar{L}=\bar{L}$. This leads to:

$$
\begin{equation*}
\frac{\bar{B}}{\bar{L}}=\frac{\beta \rho M}{\delta} \tag{A.138}
\end{equation*}
$$

## Appendix B

## Linearization and Linear Stability Analysis

The linearized equations (2.13) constitute an eigenvalue problem. In vector notation, these equations could be written as:

$$
\frac{\partial}{\partial t}\left[\begin{array}{l}
L_{0}  \tag{B.139}\\
B_{0}
\end{array}\right]=\mathbf{A}\left[\begin{array}{l}
L_{0} \\
B_{0}
\end{array}\right]
$$

where $\mathbf{A}$ is a linear operator which contains the Laplacian and $K *$ and constants. We assume solutions of the form:

$$
\left[\begin{array}{l}
L_{o}(\theta, t)  \tag{B.140}\\
B_{o}(\theta, t)
\end{array}\right]=\left[\begin{array}{l}
l(\theta) \\
b(\theta)
\end{array}\right] \mathrm{e}^{\lambda t}=\mathbf{v}(\theta) \mathrm{e}^{\lambda t} .
$$

Thus, writing the solutions as a product of a time independent and a direction independent part, and substituting them in (B.139) yields:

$$
\begin{equation*}
(\mathbf{J}-\lambda \mathbf{I}) \mathbf{v}=0 \tag{B.141}
\end{equation*}
$$

For non trivial solutions we must have

$$
\begin{equation*}
\operatorname{det}(\mathbf{J}-\lambda \mathbf{I})=0 \tag{B.142}
\end{equation*}
$$

Each solution of (B.142), an eigenvalue $\lambda_{i}$, will correspond to an eigenvector $\mathbf{v}_{\mathbf{i}}$. The general solution of the linearized equations (B.139) can then be written as:

$$
\left[\begin{array}{l}
L_{0}(\theta, t)  \tag{B.143}\\
B_{0}(\theta, t)
\end{array}\right]=\sum_{i} c_{i} \mathbf{v}_{\mathbf{i}}(\theta) \mathrm{e}^{\lambda_{i} t}
$$

If one or more of the eigenvalues $\lambda_{i}$ is positive (or have positive real parts) the perturbations ( $L_{o}, B_{o}$ ) will grow with time, i.e. the steady state will be destabilized.

As discussed, the eigenfunctions of the linear operator $\mathbf{A}$ are the functions $e^{i k \theta}$. Thus, substituting the perturbations (2.15) in the equations (2.9) we obtain the following system:

$$
\begin{align*}
& \lambda L_{o} \mathrm{e}^{i k \theta} \mathrm{e}^{\lambda t}=\mu k^{2} L_{o} \mathrm{e}^{i k \theta} \mathrm{e}^{\lambda t}+\delta B_{o} \mathrm{e}^{i k \theta} \mathrm{e}^{\lambda t}-\beta \rho \bar{L} B_{o} \mathrm{e}^{i k \theta} \mathrm{e}^{\lambda t} \hat{K}-\beta \rho \bar{L} L_{o} \mathrm{e}^{i k \theta} \mathrm{e}^{\lambda t} \hat{K} \\
& \lambda B_{o} \mathrm{e}^{i k \theta} \mathrm{e}^{\lambda t}=-\delta B_{o} \mathrm{e}^{i k \theta} \mathrm{e}^{\lambda t}+\beta \rho \bar{B} L_{o} \mathrm{e}^{i k \theta} \mathrm{e}^{\lambda t} \hat{K}+\beta \rho \bar{L} L_{o} \mathrm{e}^{i k \theta} \mathrm{e}^{\lambda t} \hat{K} \tag{B.144}
\end{align*}
$$

Here, $\hat{K}$ is the Fourier transform of the kernel $K$, namely:

$$
\begin{equation*}
\hat{K}(k)=\int_{0}^{2 \pi} K(\theta) \mathrm{e}^{i k \theta} d \theta \tag{B.145}
\end{equation*}
$$

and it appears in the linearized equations since:

$$
\begin{equation*}
\hat{K}(k) \mathrm{e}^{i k \theta}=\int_{0}^{2 \pi} K\left(\theta-\theta^{\prime}\right) \mathrm{e}^{i k \theta^{\prime}} d \theta^{\prime} \tag{B.146}
\end{equation*}
$$

The steady state values $(\bar{L}, \bar{B})$ satisfy:

$$
\begin{equation*}
0=-\delta \bar{B}+\beta \rho \bar{L}^{2}+\beta \rho \bar{B} \bar{L} \tag{B.147}
\end{equation*}
$$

Substituting this in (B.144) and eliminating $\mathrm{e}^{i k \theta} \mathrm{e}^{\lambda t}$ terms from the equation we arrive at the matrix form (2.16). In order to determine the sign of the eigenvalues we examine the
trace and the determinant of the Jacobian $\mathbf{J}$ in (2.17). For $\mathbf{J}$ a $2 \times 2$ matrix, the two eigenvalues are:

$$
\begin{equation*}
\lambda_{1,2}=\frac{t \mp \sqrt{t^{2}-4 d}}{2} \tag{B.148}
\end{equation*}
$$

where $t$ is the trace of $\mathbf{J}$ and $d$ is the determinant of $\mathbf{J}$ :

$$
\begin{equation*}
t=\operatorname{tr} \mathbf{J}=a_{11}+a_{22}, \tag{B.149}
\end{equation*}
$$

$$
\begin{equation*}
d=\operatorname{det} \mathbf{J}=a_{11} a_{22}-a_{12} a_{21} \tag{B.150}
\end{equation*}
$$

We observe that $a_{11}$ and $a_{22}$ are always negative since $\bar{B} / \bar{L}>0$ for all biologically relevant cases and since $|\hat{K}|<1$. Thus, the trace of the Jacobian is negative in cases of interest. In this case, for one of the eigenvalues to be negative, that is for instability to perturbations of the form $\left(L_{o}, B_{o}\right)$, the determinant of $\mathbf{J}$ must be negative. This stability criterion is equivalent to the dispersion relation (2.19).

## Appendix C

## The properties of SSH

The surface spherical harmonics $Y_{n}$ 's are special cases of solid spherical harmonics $V_{n}$ 's which are solutions of Laplace's equation in spherical coordinates. The SSH which are also solutions of Laplace's equation are functions $\phi$ and $\theta$ only, thus independent of $r$, they are obtained by dividing $V_{n}$ by $r^{n}$ and they satisfy the following equation:

$$
\begin{equation*}
n(n+1) Y_{n}+\frac{1}{\sin \phi} \frac{\partial}{\partial \phi}\left(\sin \phi \frac{\partial Y_{n}}{\partial \phi}\right)+\frac{1}{\sin ^{2} \phi} \frac{\partial^{2} Y_{n}}{\partial \theta^{2}}=0 \tag{C.151}
\end{equation*}
$$

Thus the SSH of degree $n, Y_{n}$, is the eigenfunction of the Laplacian operator in $\phi$ and $\theta$ with corresponding eigenvalue $-n(n+1)$ :

$$
\begin{equation*}
\Delta Y_{n}=-n(n+1) Y_{n} \tag{C.152}
\end{equation*}
$$

The SSH of degree $n$ can be written as a linear combination of the Legendre polynomials of degree $n, P_{n}^{o}$ (also denoted simply as $P_{n}$ ), and the associated Legendre functions of degree $n$ and of order $m, P_{n}^{m}$ :

$$
\begin{equation*}
Y_{n}(\phi, \theta)=A P_{n}^{o}(\cos \phi)+\sum_{m=1}^{n}\left(A_{n}^{m} \cos m \theta+B_{n}^{m} \sin m \theta\right) P_{n}^{m}(\cos \phi) \tag{C.153}
\end{equation*}
$$

Some of the first few Legendre polynomials are as follows:

$$
\begin{gather*}
P_{1}^{o}(\cos \phi)=\cos \phi \\
P_{2}^{o}(\cos \phi)=\frac{1}{2}\left(3 \cos ^{2} \phi-1\right),  \tag{C.154}\\
P_{3}^{o}(\cos \phi)=\frac{1}{2}\left(5 \cos ^{3} \phi-3 \cos \phi\right) .
\end{gather*}
$$

See MacRobert (1927), Arsenin (1968), or Hobson (1931) for more details.
The Kernel $K$ in the convolution in (2.32), can be written as a function of $\eta=\cos \gamma$, where $\gamma$ is the angle between directions $\Omega$ and $\Omega^{\prime}$ as in (2.30). In this form, $K$ can be expressed as a linear combination of Legendre polynomials, $P_{n}^{\circ}(\cos \gamma)$ (MacRobert, 1927; Arsenin, 1968; Hobson, 1931):

$$
\begin{equation*}
K(\eta)=\sum_{n=1}^{\infty} K^{\prime}(n) P_{n}^{\circ}(\eta) \tag{C.155}
\end{equation*}
$$

where

$$
\begin{equation*}
K^{\prime}(n)=\frac{2 n+1}{2} \int_{-1}^{1} K(\eta) P_{n}^{o}(\eta) \mathrm{d} \eta \tag{C.156}
\end{equation*}
$$

The integral of the product of the SSH and the Legendre polynomials has the following property:

$$
\int_{S} P_{n}^{o}(\cos \gamma) Y_{m}\left(\phi^{\prime}, \theta^{\prime}\right) \mathrm{d} \phi^{\prime} \mathrm{d} \theta^{\prime}=\left\{\begin{array}{cc}
0 & \text { for } n \neq m  \tag{C.157}\\
\frac{4 \pi}{2 n+1} Y_{n}(\phi, \theta) & \text { for } n=m
\end{array}\right.
$$

(See MacRobert (1927) or Hobson (1931).) This property of the SSH and the Legendre polynomials is of extreme significance in the analysis of the linearized equations. Indeed, the convolution of the kernel $K$ and the SSH of degree $n$ can be expressed as a product of the SSH and $\tilde{K}(n)$ as follows:

$$
\begin{aligned}
K * Y_{n} & =\int_{S} K\left(\Omega, \Omega^{\prime}\right) Y_{n}\left(\Omega^{\prime}\right) \mathrm{d} S \\
& =\int_{S} K(\cos \gamma) Y_{n}\left(\phi^{\prime}, \theta^{\prime}\right) \mathrm{d}\left(\cos \phi^{\prime}\right) \mathrm{d} \theta^{\prime} \\
& =\int_{S}\left(\sum_{m=1}^{\infty} K^{\prime}(m) P_{m}^{o}(\cos \gamma)\right) Y_{n}\left(\phi^{\prime}, \theta^{\prime}\right) \mathrm{d}\left(\cos \phi^{\prime}\right) \mathrm{d} \theta^{\prime} \\
& =\int_{0}^{2 \pi} \int_{-1}^{1} K^{\prime}(n) P_{n}^{o}(\cos \gamma) Y_{n}\left(\phi^{\prime}, \theta^{\prime}\right) \mathrm{d}\left(\cos \phi^{\prime}\right) \mathrm{d} \theta^{\prime} \\
& =K^{\prime}(n) \int_{0}^{2 \pi} \int_{-1}^{1} P_{n}^{o}(\cos \gamma) Y_{n}\left(\phi^{\prime}, \theta^{\prime}\right) \mathrm{d}\left(\cos \phi^{\prime}\right) \mathrm{d} \theta^{\prime} \\
& =K^{\prime}(n) \frac{4 \pi}{2 n+1} Y_{n}(\phi, \theta) \\
& =\tilde{K}(n) Y_{n}(\phi, \theta),
\end{aligned}
$$

where

$$
\begin{equation*}
\tilde{K}(n)=\frac{4 \pi}{2 n+1} K^{\prime}(n)=2 \pi \int_{-1}^{1} K(\eta) P_{n}(\eta) \mathrm{d} \eta \tag{C.159}
\end{equation*}
$$

Hence the SSH are also the eigenfunctions of the Convolution operator $K *$ with corresponding eigenvalues $\tilde{K}(n)$ :

$$
\begin{equation*}
K * Y_{n}=\tilde{K}(n) Y_{n} \tag{C.160}
\end{equation*}
$$

## Appendix D

## SSH on the surface of the unit hemi-sphere

For notational simplicity in this section we use the fundamental form of the SSH of degree $n, Y_{n}^{m}$ as in (4.112). These harmonics relate to the basic SSH of degree $n, Y_{n}$, in the following way:

$$
\begin{equation*}
Y_{n}(\phi, \theta)=\sum_{k=-n}^{n} C_{k} Y_{n}^{k}(\phi, \theta) . \tag{D.161}
\end{equation*}
$$

Some fundamental SSHs are as follows:

$$
\begin{gather*}
Y_{1}^{1}(\phi, \theta)=\sin \phi \sin \theta \\
Y_{1}^{-1}(\phi, \theta)=\sin \phi \cos \theta \\
Y_{2}^{1}=3 \sin \phi \cos \phi \sin \theta \\
Y_{2}^{-1}=3 \sin \phi \cos \phi \cos \theta  \tag{D.162}\\
Y_{2}^{2}(\phi, \theta)=3 \sin ^{2} \phi \sin 2 \theta \\
Y_{2}^{-2}(\phi, \theta)=3 \sin ^{2} \phi \cos 2 \theta
\end{gather*}
$$

See MacRobert (1927), Arsenin (1968), or Hobson (1931) for more details.
For $m-n$ even, the fundamental SSHs are the eigenfunctions of both the Laplacian and the Convolution operator on the surface of the hemi-sphere with zero flux BC :

$$
\begin{gather*}
\triangle Y_{n}^{m}=-n(n+1) Y_{n}^{m}, \\
K * Y_{n}^{m}=\tilde{K}_{n}^{m} Y_{n}^{m}, \tag{D.163}
\end{gather*}
$$

where $\tilde{K}_{n}^{m}$ are the coefficients in the expansion of the kernel $K$ in fundamental SSH:

$$
\begin{equation*}
K\left(\Omega, \Omega^{\prime}\right)=\sum_{n=0}^{\infty} \star \sum_{m=-n}^{n} \star \tilde{K}_{n}^{m} Y_{n}^{m}(\Omega) Y_{n}^{m}\left(\Omega^{\prime}\right) \tag{D.164}
\end{equation*}
$$

where $\sum^{\star}$ means that the summation is taken over harmonics for which $n-m$ is even.
The coefficients $K_{n}^{m}$ in this expansion can be easily calculated for the kernels given in section 4.2.1. Comparing the terms in the above summation with the terms in the expression of the kernels in (4.105), (4.107) and (4.109) we obtain the coefficients $K_{n}^{m}$ in each case.

## (1) Coefficients for the kernel in the case of the cell cortex

The kernel in this case is $K_{1}$, given in (4.105). The sum in (D.164) corresponds to:

$$
\begin{equation*}
K_{1}\left(\Omega, \Omega^{\prime}\right)=A_{1}+\frac{1}{3} A_{2}\left(Y_{2}^{2}(\Omega) Y_{2}^{2}\left(\Omega^{\prime}\right)+Y_{2}^{-2}(\Omega) Y_{2}^{-2}\left(\Omega^{\prime}\right)\right) \tag{D.165}
\end{equation*}
$$

hence,

$$
\begin{align*}
\tilde{K}_{o}^{o} & =A_{1} \\
\tilde{K}_{2}^{2} & =\tilde{K}_{2}^{-2}=\frac{1}{3} A_{2}  \tag{D.166}\\
\tilde{K}_{m}^{n} & =0 \quad \text { otherwise. }
\end{align*}
$$

(2) and (3) Coefficients for the kernel in the case of Contractile ring and adhesion belts

The kernels in these cases are $K_{2}$, given in (4.107) and the sum in (D.164) corresponds to:

$$
\begin{equation*}
K_{2}\left(\Omega, \Omega^{\prime}\right)=A_{1}+\frac{1}{3} A_{2} Y_{2}^{2}(\Omega) Y_{2}^{2}\left(\Omega^{\prime}\right) \tag{D.167}
\end{equation*}
$$

hence,

$$
\begin{align*}
\tilde{K}_{o}^{o} & =A_{1} \\
\tilde{K}_{2}^{2} & =\frac{1}{3} A_{2}  \tag{D.168}\\
\tilde{K}_{m}^{n} & =0 \quad \text { otherwise. }
\end{align*}
$$

(4) Coefficients for the kernel in the case of the actin tail of Listeria The kernel is, $K_{3}$, given in (4.109) and the sum in (D.164) corresponds to:

$$
\begin{equation*}
K_{3}\left(\Omega, \Omega^{\prime}\right)=A_{1}+A_{2} Y_{1}^{1}(\Omega) Y_{1}^{1}\left(\Omega^{\prime}\right) \tag{D.169}
\end{equation*}
$$

hence,

$$
\begin{align*}
\tilde{K}_{o}^{o} & =A_{1} \\
\tilde{K}_{1}^{1} & =A_{2}  \tag{D.170}\\
\tilde{K}_{m}^{n} & =0 \quad \text { otherwise. }
\end{align*}
$$

Stability analysis of equations (4.110) to perturbations of the form (4.114) leads to the dispersion relation (4.115) where $C$ is an algebraic combination of the parameters in the system:

$$
\begin{equation*}
C=\frac{\mu \delta}{\beta^{2} \rho^{2} M}=\frac{\mu}{\beta \rho}\left(\frac{\bar{L}}{\bar{B}}\right) \tag{D.171}
\end{equation*}
$$

(This analysis is similar to the one carried out in Appendix B for the Model I or the 3D model in section 2.8.1.)

In all cases the total density of free and bound filaments in the peak can be found from (4.110):

$$
\begin{equation*}
K_{p} \bar{L}_{p}^{2}+K_{p} \bar{L}_{p} \bar{B}_{p}-\xi \bar{B}_{p}=0 \tag{D.172}
\end{equation*}
$$

where $K_{p}$ is the value of $K\left(\Omega, \Omega^{\prime}\right)$ within the peak. (For example, for the case of the actin tail of Listeria we have:

$$
\begin{align*}
\Omega & =\Omega^{\prime}=\left(\phi=\frac{\pi}{2}, \theta=0\right) \\
K_{3}\left(\left(\frac{\pi}{2}, 0\right),\left(\frac{\pi}{2}, 0\right)\right) & =K_{p}=\frac{2}{\pi}\left(A_{1}+A_{2}\right)=\left(1+\frac{2}{\pi} A_{2}\right)>1 . \tag{D.173}
\end{align*}
$$

So that, the distributions satisfy:

$$
\begin{align*}
& \bar{L}_{p}=\frac{\xi M}{\xi+K_{p} M}, \\
& \bar{B}_{p}=\frac{K_{p} M^{2}}{\xi+K_{p} M},  \tag{D.174}\\
& \frac{\bar{B}_{p}}{\bar{L}_{p}}=K_{p} \frac{M}{\xi}=K_{p} \frac{\bar{B}}{\bar{L}}>\frac{\bar{B}}{\bar{L}} .
\end{align*}
$$

