Association for Women in Mathematics Series

Rebecca Segal
Blerta Shtylla
Suzanne Sindi *Editors*

# Using Mathematics to Understand Biological Complexity

## From Cells to Populations

AWM
ASSOCIATION FOR WOMEN IN MATHEMATICS

Springer

# Association for Women in Mathematics Series

Volume 22

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Editors

# Using Mathematics to Understand Biological Complexity

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# Collaborative Workshop for Women in Mathematical Biology


**Rebecca Segal, Blerta Shtylla, and Suzanne Sindi**

## 1 Aim and Scope

Biological systems are complex and highly interconnected. Despite increasing amounts of information collected, it is not always clear how to use these data to make conclusions and predictions. Mathematical models are powerful tools in biology because they allow us to abstract the biological system in order to frame questions, explore patterns and synthesize information. Indeed, we are writing these remarks during the COVID-19 Pandemic which has illustrated in a staggering way the importance of quantitative modeling in aiding our understanding of complex biological processes. This volume contains the scientific and collaborative work from the *Collaborative Workshop for Women in Mathematical Biology*. The workshop brought together forty-five researchers to collaborate on seven problems each of which used mathematics to understand complex biological systems. The workshop was held at the Institute of Pure and Applied Mathematics on the campus of University of California, Los Angeles from June 17-21, 2019 in Los Angeles, CA and was organized by Rebecca Segal, Blerta Shtylla, and Suzanne Sindi. The articles

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contained in this volume were initiated during the intensive one-week workshop and continued through follow-up collaborations afterwards.

## 2 History and Context

Historically, women have been underrepresented in the mathematical sciences. Although progress has been made, the numbers remain unbalanced. In the most recent American Mathematical Society Survey from 2017, only 17% of tenure-track mathematics faculty in doctoral departments are female (http://www.ams.org/profession/data/annual-survey/demographics). A specific breakdown of distribution within different types of institutions (https://www.womendomath.org/research/) gives an even more compelling picture of why research workshops such as this one can be so valuable for the mathematics community. Research mentoring and support from senior mentors is one key to success and a workshop environment provides a significant amount of interaction in a concentrated amount of time.

The primary aim of the Women in Mathematical Biology (WIMB) workshops is to foster research collaboration among women in mathematical biology. Participants spend a week making progress on a research project and encouraging innovation in the application of mathematical, statistical, and computational methods in the resolution of significant problems in the biosciences. The workshops have a special format designed to maximize the opportunities to collaborate. The groups are structured to facilitate tiered mentoring. Each group has a senior researcher who presents a problem. This person is matched with a co-leader, typically a researcher in their field but with whom they have not previously collaborated. The groups are rounded out with researchers at various career stages. By matching senior research mentors with junior mathematicians, we expand and support the community of scholars in the mathematical biosciences. To date, WIMB workshops have occurred at the Institute for Mathematics and its Applications (IMA, https://www.ima.umn.edu/), the National Institute for Mathematical and Biological Synthesis (NIMBioS, http://www.nimbios.org/), the Mathematical Biosciences Institute (MBI,https://mbi.osu.edu/), and most recently at the Institute of Pure and Applied Mathematics (IPAM, https://www.ipam.ucla.edu/). These workshops have been sponsored by an ADVANCE grant from the National Science Foundation to the Association for Women in Mathematics. This award has helped establish research networks in 21 different areas of mathematics research including Control, Commutative Algebra, Geometry, Data Science, Materials, Operator Algebras, Analysis, Number Theory, Shape, Topology, Numerical Analysis, and Representation Theory.

For the Mathematical Biology workshops, each group continues their project together to obtain results that are submitted to the peer-reviewed AWM Proceedings volume for the workshop. The benefit of such a structured program with leaders, projects and working groups planned in advance is based on the successful Women In Numbers (WIN) conferences and works in both directions: senior women will meet, mentor, and collaborate with the brightest young women in their field on a

part of their research agenda of their choosing, and junior women and students will develop their network of colleagues and supporters and encounter important new research areas to work in, thereby improving their chances for successful research careers.

One of the most critical workshop goals is help establish supportive and productive research groups that are sustained well beyond the workshop. Below we include some representative statements from participants shared with us when we surveyed them at the end of the workshop to assess their opinion of the workshop structure and the impact of the workshop on their careers. The group dynamics were overwhelmingly listed as a positive experience: *"The opportunity to work with, share ideas, and learn from a group made up entirely of female mathematicians."* Some participants appreciated the format of the workshop for allowing *"Exclusive time spent working with talented people on a new project."* Participants left the workshop satisfied with their experience: *"Establishing a new group of collaborators. I've honestly never developed this skill and I'm glad to have had this opportunity."* The workshop sometimes stretched participants out of their comfort zone while still providing a positive experience: *"Watching in awe as phenomenal women worked on math and bio. I tried my best to contribute, and although I felt like I still lacked a lot of background to really make a real impact, it was really inspirational to learn from women established in their careers. I definitely have a lot more role models at the end of this trip! The industry panel was helpful in showing me more career opportunities for a mathematical biologist."* The group leaders were pleased with the work produced by their teams and all of the participants learned new mathematics, new biology, or new computational tools to move the research project in a productive direction. Finally, as organizers we have been delighted to see the teams initiated at these workshops produce new research projects, papers, proposals and other scholarly products far beyond the scope of the original team lead project.

## 3 Research

Within this volume are mathematical research papers covering a wide range of application areas. The work can be loosely grouped into a few general application areas: structural organization of biological material, infection modeling, and disease treatment. Throughout this research are discussions of how to create accurate models with limited data, how to work across biological scales, and how to best describe complex structures in a useful manner.

Several teams had research related to the structural organization of organisms. One project focused on how the protein actin helps form larger structures within a cell. Other projects studied DNA topology and DNA secondary structure to understand the design and replication mechanisms in organisms. Actin assembles into semi-flexible filaments that cross-link to form higher order structures within the cytoskeleton. This study focused on the dynamics of the formation of a branched actin structure as observed at the leading edge of motile eukaryotic cells. They

constructed a minimal agent-based model for the microscale branching actin dynamics, and a deterministic partial differential equation model for the macroscopic network growth and bulk diffusion. Their results suggest that perturbations to microscale rates can have significant consequences at the macroscopic level, and these should be taken into account when proposing continuum models of actin network dynamics.

DNA topology, formal grammar R-loops, are three-stranded nucleic acid structures consisting of two DNA strands and one RNA strand. They form naturally during transcription when the nascent RNA hybridizes to the template DNA strand, forcing the coding DNA strand to wrap around the RNA:DNA duplex. In their study, this team used words generated by the grammars to represent topological segments of the DNA:DNA and RNA:DNA interactions. They extended this model to include properties of the DNA nucleotide sequence.

A third group explored the extent to which graph algorithms for community detection can improve the mining of structural information from the predicted Boltzmann/Gibbs ensemble for the biological objects known as RNA secondary structures. Since more structural information is obtained in 50% of the test cases, this proof-of-principle analysis supports efforts to improve the data mining of RNA secondary structure ensembles.

Two groups worked broadly in the area of infection: one group examined disease spread across geographic regions while another group explored in host resolution of infection. How do interventions impact malaria dynamics between neighboring countries? Although many countries world wide have taken measures to decrease the incidence of malaria many regions remain endemic, and in some parts of the world malaria incidence is increasing. This team considered the case of neighboring countries Botswana and Zimbabwe, connected by human mobility. They used a two-patch Ross-MacDonald Model with Lagrangian human mobility to examine the coupled disease dynamics between these two countries.

Antimicrobial resistance (AMR) is a serious threat to global health today. The spread of AMR, along with the lack of new drug classes in the antibiotic pipeline, has resulted in a renewed interest in phage therapy, which is the use of bacteriophages to treat pathogenic bacterial infections. These researchers utilized a mathematical model to examine the role of the immune response in concert with phage-antibiotic combination therapy compounded with the effects of the immune system on the phages being used for treatment. They explored the effect of phage-antibiotic combination therapy by adjusting the phage and antibiotics dose or altering the timing. Their results show that it is important to consider the host immune system in mathematical models and that frequency and dose of treatment are important considerations for the effectiveness of treatment.

Finally, two groups worked broadly in the area of disease progression and treatment. One group developed a model for retinal degeneration while the other focused on radiation therapy for cancerous tumors. In the retina, photoreceptor degeneration can result from imbalance in lactate production and consumption as well as disturbances to pyruvate and glucose levels. To identify the key mechanisms in metabolism that may be culprits of this degeneration, they used a nonlinear

system of differential equations to mathematically model the metabolic pathway of aerobic glycolysis in a healthy cone photoreceptor. Their model allowed them to analyze the levels of lactate, glucose, and pyruvate within a single cone cell. They performed numerical simulations, used available metabolic data to estimate parameters and fit the model to this data, and conducted a sensitivity analysis using two different methods (LHS/PRCC and eFAST) to identify pathways that have the largest impact on the system.

Recent technological advances make it possible to collect detailed information about tumors, and yet clinical assessments about treatment responses are typically based on sparse datasets. In this work, one team proposed a workflow for choosing an appropriate model, verifying parameter identifiability, and assessing the amount of data necessary to accurately calibrate model parameters. They considered a simple, one-compartment ordinary differential equation model which tracks tumor volume and a two-compartment model that accounts for tumor volume and the fraction of necrotic cells contained within the tumor.

## 4 Concluding Remarks

It merits note that the majority of revisions for this volume were accomplished during the COVID-19 pandemic; we are both grateful for and proud of the hard work

**Fig. 1** Group photograph of the workshop participants

of our participants during these challenging times. Workshop groups are continuing to work on furthering the projects and presenting their work at conferences. Past workshops have had successful research collaborations last for years following the workshop. The more community building we can accomplish, the higher the rate of success for women and mathematics. This means more innovative research will be produced and built upon by the entire mathematics community (Fig. 1).

**Acknowledgments** The work described herein was initiated during the Collaborative Workshop for Women in Mathematical Biology hosted by the Institute for Pure and Applied Mathematics at the University of California, Los Angeles in June 2019. Funding for the workshop was provided by IPAM, the Association for Women in Mathematics' NSF ADVANCE "Career Advancement for Women Through Research-Focused Networks" (NSF-HRD 1500481) and the Society for Industrial and Applied Mathematics.

# Connecting Actin Polymer Dynamics Across Multiple Scales


**Calina Copos, Brittany Bannish, Kelsey Gasior, Rebecca L. Pinals, Minghao W. Rostami, and Adriana T. Dawes**

**Abstract** Actin is an intracellular protein that constitutes a primary component of the cellular cytoskeleton and is accordingly crucial for various cell functions. Actin assembles into semi-flexible filaments that cross-link to form higher order structures within the cytoskeleton. In turn, the actin cytoskeleton regulates cell shape, and participates in cell migration and division. A variety of theoretical models have been proposed to investigate actin dynamics across distinct scales, from the stochastic nature of protein and molecular motor dynamics to the deterministic macroscopic behavior of the cytoskeleton. Yet, the relationship between molecular-level actin processes and cellular-level actin network behavior remains understudied, where prior models do not holistically bridge the two scales together.

In this work, we focus on the dynamics of the formation of a branched actin structure as observed at the leading edge of motile eukaryotic cells. We construct

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a minimal agent-based model for the microscale branching actin dynamics, and a deterministic partial differential equation (PDE) model for the macroscopic network growth and bulk diffusion. The microscale model is stochastic, as its dynamics are based on molecular level effects. The effective diffusion constant and reaction rates of the deterministic model are calculated from averaged simulations of the microscale model, using the mean displacement of the network front and characteristics of the actin network density. With this method, we design concrete metrics that connect phenomenological parameters in the reaction-diffusion system to the biochemical molecular rates typically measured experimentally. A parameter sensitivity analysis in the stochastic agent-based model shows that the effective diffusion and growth constants vary with branching parameters in a complementary way to ensure that the outward speed of the network remains fixed. These results suggest that perturbations to microscale rates can have significant consequences at the macroscopic level, and these should be taken into account when proposing continuum models of actin network dynamics.

**Keywords** Actin · Differential equations · Stochastic model · Sensitivity analysis · Cytoskeleton

## 1 Introduction

A cell's mechanical properties are determined by the cytoskeleton whose primary components are actin filaments (F-actin) [1–4]. Actin filaments are linear polymers of the abundant intracellular protein actin [5–7], referred to as G-actin when not polymerized. Regulatory proteins and molecular motors constantly remodel the actin filaments and their dynamics have been studied in vivo [8], in reconstituted in vitro systems [2, 9], and in silico [10]. Actin filaments are capable of forming large-scale networks and can generate pushing, pulling, and resistive forces necessary for various cellular functions such as cell motility, mechanosensation, and tissue morphogenesis [8]. Therefore, insights into actin dynamics will advance our understanding of cellular physiology and associated pathological conditions [2, 11].

Actin filaments in cells are dynamic and strongly out of equilibrium. The filaments are semi-flexible, rod-like structures approximately 0.007 μm in diameter and extending several microns in length, formed through the assembly of G-actin subunits [6, 7]. A filament has two ends, a barbed end and a pointed end, with distinct growth and decay properties. A filament length undergoes cycles of growth and decay fueled by an input of chemical energy, in the form of ATP, to bind and unbind actin monomers [6, 7]. The rates at which actin molecules bind and unbind from a filament have been measured experimentally [3, 12, 13]. The cell tightly regulates the number, density, length, and geometry of actin filaments [7]. In particular, the geometry of actin networks is controlled by a class of accessory proteins that bind to the filaments or their subunits. Through such interactions, accessory proteins are able to determine the assembly sites for new filaments,

change the binding and unbinding rates, regulate the partitioning of polymer proteins between filaments and subunit forms, link filaments to one another, and generate mechanical forces [6, 7]. Actin filaments have been observed to organize into branched networks [14, 15], sliding bundles extending over long distances [16], and transient patterns including vortices and asters [17, 18].

To generate pushing forces for motility, the cell uses the energy of the growth or polymerization of F-actin [19, 20]. Actin polymerization powers the formation of flat cellular protrusions, known as lamellipodia, found at the leading edge of motile cells [8, 21]. Microscopy of the lamellipodial cytoskeleton has revealed multiple branched actin filaments [15]. The branching structure is governed by the Arp2/3 protein complex, which binds to an existing actin filament and initiates growth of a new "daughter" filament through a nucleation site at the side of preexisting filaments. Growth of the "daughter" filament occurs at a tightly regulated angle of 70° from the "parent" filament due to the structure of the Arp2/3 complex [22]. The directionality of pushing forces produced by actin polymerization originates from the uniform orientation of polymerizing actin filaments with their barbed ends towards the leading edge of the cell [8]. Here, cells exploit the polarity of filaments, since growth dynamics are faster at barbed ends than at pointed ends [23, 24]. Polymerization of individual actin filaments produces piconewton forces [25], with filaments organized into a branched network in lamellipodia or parallel bundles in filopodia [15]. The localized kinetics of growth, decay, and branching of a protrusive actin network provide the cell with the scaffold and the mechanical work needed for directed movement.

Many mathematical models have been developed to capture the structural formation and force generation of actin networks [20, 26, 27]. Due to the multiscale nature of actin dynamics, two main approaches are used: agent-based methods [27–29] and deterministic models using PDEs [30–33]. The effects of different molecular components (e.g., depolymerization, stabilizers) on the architecture of a protrusive actin network has been studied with detailed hybrid micro-macroscopic models [34, 35]. While both techniques are useful for understanding actin dynamics, each presents limitations. Agent-based models more closely capture the molecular dynamics of actin by explicitly considering the behavior of actin molecules through rules, such as, bind to the closest filament at a particular rate. In general, agent-based models simulate the spatiotemporal actions of certain microscopic entities, or "agents", in an effort to recreate and predict more complex large-scale behavior. In these simulations, agents behave autonomously and through simple rules prescribed at each time step. The technique is stochastic and can be interpreted as a coarsening of Brownian and Langevin dynamical models [36]. However, agent-based approaches are computationally expensive: at every time step, they specifically account for the movement and interaction of individual molecules, while also assessing the effects of spatial and environmental properties that ultimately result in the emergence of certain large-scale phenomena, such as crowding. Such approaches benefit from the direct relationship to experimental measurements of parameters, yet they present a

further computational cost in that many instances of a simulation are needed for reliable statistical information. Agent or rule-based approaches have been used to reveal small-scale polymerization dynamics in actin polymer networks [26, 37], but due to the inherent computational complexity, it remains unclear how this information translates to higher length scales, such as the cell, tissue, or whole organism.

To overcome such computational costs and still gain a mechanistic understanding of actin processes, one approach is to write deterministic equations that "summarize" all detailed stochastic events. These approaches rely on differential equations to predict a coarse-grained biological behavior by assuming a well-mixed system where the molecules of interest exist in high numbers [20, 38–40] and the spread of the polymer network can be qualitatively approximated by a diffusion process [41, 42]. In continuum models, the stochastic behavior of the underlying molecules are typically ignored. While continuum models can be explored via traditional mathematical analysis, the challenge lies in determining the terms and parameters of these equations that are representative of the underlying physical system. Thus, these methods use phenomenological parameters of the actin network, such as bulk diffusion and reaction terms, that are less readily obtained experimentally. The relationship between molecular-level actin processes and cellular-level actin network behavior remains disconnected. This disconnect presents a unique challenge in modeling actin polymers in an active system across length scales.

In this work, we design a systematic and rigorous methodology to compare and connect actin molecular effects in agent-based stochastic simulations to macroscopic behavior in deterministic continuum equations. Measures from these distinct-scale models enable extrapolation from the molecular to the macroscopic scale by relating local actin dynamics to phenomenological bulk parameters. First, we characterize the dynamics of a protrusive actin network in free space using a minimal agent-based model for the branching of actin filaments from a single nucleation site based on experimentally measured kinetic rates. Second, in the macroscopic approach, we simulate the spread of actin filaments from a point source using a partial differential equation model. The model equation is derived from first principles of actin filament dynamics and is found to be Skellam's equation for unbounded growth of a species together with spatial diffusion. To compare the emergent networks, multiple instances of the agent-based approach are simulated, and averaged effective diffusion coefficient and reaction rate are extracted from the mean displacement of the advancing network front and from the averaged network density. We identify two concrete metrics, mean displacement and the averaged filament length density, that connect phenomenological bulk parameters in the reaction-diffusion systems to the molecular biochemical rates of actin binding, unbinding, and branching. Using sensitivity analysis on these measures, we demonstrate that the outward movement of the actin network is insensitive to changes in parameters associated with branching, while the bulk growth rate and diffusion coefficient do vary with changes in branching dynamics. We further find that the outward speed, growth rate constant, and effective diffusion increase with

F-actin polymerization rate but decrease with increasing depolymerization of actin filaments. By formalizing the relationship between micro- and macro-scale actin network dynamics, we demonstrate a nonlinear dependence of bulk parameters on molecular characteristics, indicating the need for careful model construction and justification when modeling the dynamics of actin networks.

# 2 Mathematical Models

## *2.1 Microscale Agent-Based Model*

### 2.1.1 Model Description

We build a minimal, agent-based model sufficient to capture the local microstructure of a branching actin network. This model includes the dynamics of actin filament polymerization, depolymerization, and branching from a nucleation site [1, 2, 43, 44]. We treat F-actin filaments as rigid rods. Each actin filament has a base (pointed end) fixed in space and a tip (barbed end) capable of growing or shrinking due to the addition or removal of actin monomers, respectively. We assume that there is an unlimited pool of actin monomers available for filament growth, in line with normal, intracellular conditions [3]. For simplicity, we neglect the effects of barbed end capping, mechanical response of actin filaments, resistance of the plasma membrane, cytosolic flow, and molecular motors and regulatory proteins. Motivated by the short timescale of the initial burst of a growing actin network, we assume that the pointed end of actin filaments is stabilized at a nucleation site, and thus, do not account for the turnover dynamics at the pointed end. The physical setup of the model is similar to conditions associated with in vitro experiments, as well as initial actin network growth in cells, before components such as actin monomers become limiting.

### 2.1.2 Numerical Implementation

At the start of each simulation, an actin filament of length zero is assigned an angle of growth from the nucleation site (located at the origin) from a uniform random distribution. Once a filament is prescribed a direction of growth, it will not change throughout the time-evolution of that particular filament. At each subsequent time step in the simulation, there are four possible outcomes: (i) growth of the filament with probability $p_{\text{poly}}$, (ii) shrinkage of the filament with probability $p_{\text{depoly}}$, (iii) no change in filament length, or (iv) branching of a preexisting filament into a "daughter" filament with probability $p_{\text{branch}}$ provided that the "parent" filament has reached a critical length $L_{\text{branch}}$, measured from the closest branch point. To determine which outcome occurs, two random numbers are independently generated for each filament. The first random number governs polymerization (i) or depolymerization

(ii): if the random number is less than $p_{\text{poly}}$, polymerization occurs, and if greater than $1 - p_{\text{depoly}}$, depolymerization occurs. If the first random number is greater than or equal to $p_{\text{poly}}$ and less than or equal to $1 - p_{\text{depoly}}$, then the filament neither polymerizes nor depolymerizes this time step, and therefore remains the same length (iii). Similarly, if the random number is simultaneously less than $p_{\text{poly}}$ and greater than $1 - p_{\text{depoly}}$, then both polymerization and depolymerization occur within this time step, and therefore the filament remains the same length (iii). Both filament growth and shrinkage occur in discrete increments corresponding to the length of a G-actin monomer, $\Delta x = 0.0027\,\mu\text{m}$ [4]. We enforce that a filament of length zero cannot depolymerize.

The second random number pertains to filament branching (iv). For filaments of length greater than $L_{\text{branch}}$, a new filament can be initiated at a randomly oriented 70°-angle from a preexisting filament tip in correspondence with the effect of Arp2/3 protein complex. If the second random number is less than the probability of branching, $p_{\text{branch}}$, for the given filament, then the filament will branch and create a "daughter" filament now capable of autonomous growth and branching. This branching potential models the biological effect of the Arp2/3 complex without explicitly including Arp2/3 concentration as a variable.

The step-wise process is repeated until the final simulation time is reached. Simulation steps are summarized graphically in Fig. 1. All parameters for the model are listed in Table 1. We calculate several different measurements from the microscale simulation, as described below.

### 2.1.3 Parameter Estimation

Actin dynamics have been extensively studied in vivo and in vitro, providing many rate constants used in this study. A $10\,\mu\text{M}$ actin monomer concentration elongates the barbed ends of F-actin filaments at a reported velocity of $0.3\,\mu\text{m/s}$ [3]. We use this measurement to calculate the polymerization probability, $p_{\text{poly}}$, via the formula:

$$\begin{aligned}\text{assembly rate} = {} & \text{polymerization probability} \times \text{length added to filament} \\ & \times \text{number of timesteps per second} \end{aligned} \tag{1}$$

$$0.3\,\tfrac{\mu\text{m}}{\text{s}} = p_{\text{poly}} \times 0.0027\,\mu\text{m} \times \frac{1}{0.005\,\text{s}}\,, \tag{2}$$

which implies that $p_{\text{poly}} = 0.56$. For simplicity, we round this probability to $p_{\text{poly}} = 0.6$ in the microscale model simulations. ADP-actin has a depolymerization rate of 4.0 1/s at the barbed ends of actin filaments [3]. This measurement represents the rate of depolymerization of one actin subunit per second, thus a filament loses length at a rate of

$$4.0\,\tfrac{\text{subunit}}{\text{s}} \times 0.0027\,\tfrac{\mu\text{m}}{\text{subunit}} = 0.0108\,\tfrac{\mu\text{m}}{\text{s}}. \tag{3}$$

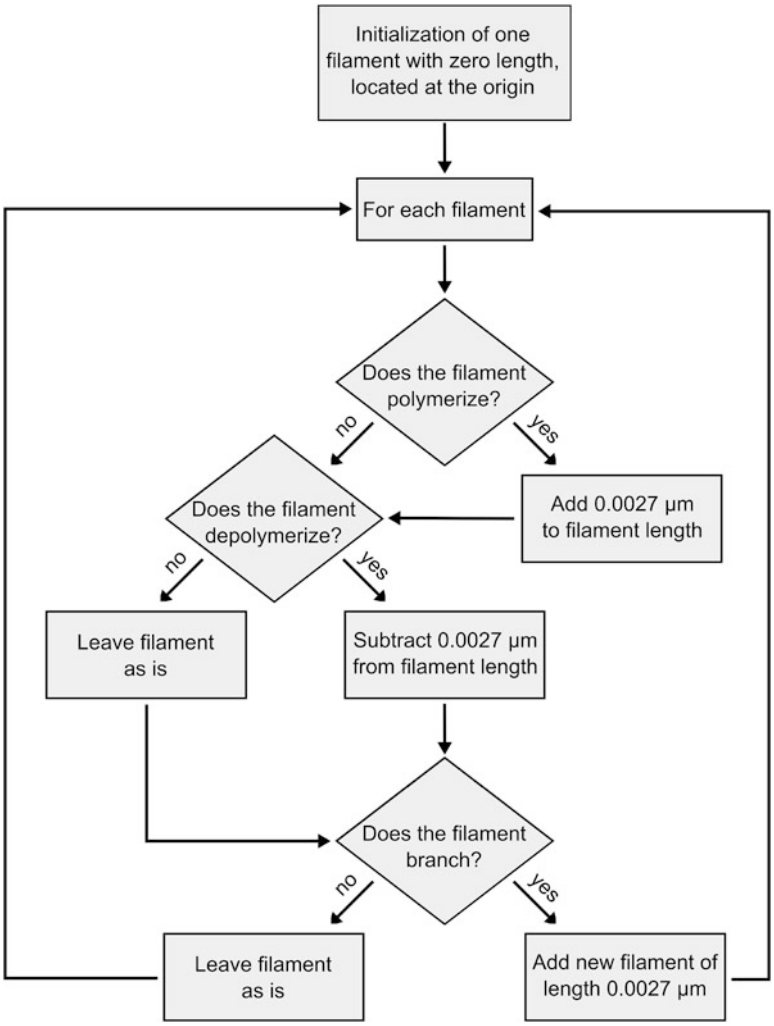


**Fig. 1** Flow chart of the algorithm implemented for the agent-based microscale model. All steps following "Initialization" are repeated at every time step

To calculate the depolymerization probability, $p_{\text{depoly}}$, we use the analogous formula:

$$\begin{aligned}\text{disassembly rate} = \text{depolymerization probability} \times \text{length removed from filament} \\ \times \text{number of timesteps per sec}\end{aligned} \tag{4}$$

$$0.0108\,\tfrac{\mu\text{m}}{\text{s}} = p_{\text{depoly}} \times 0.0027\,\mu\text{m} \times \frac{1}{0.005\,\text{s}}, \tag{5}$$

which yields $p_{\text{depoly}} = 0.02$.

**Table 1** Microscale model parameter values. Details on parameter estimation are available in Sect. 2.1.3. Values flagged with one star (*) were calculated from [3] and depend on the time step as indicated in Eqs. 2 and 5. The value flagged with a dagger (†) is motivated by literature measurements of actin filament length per branch which vary from 0.02 to 5 μm [15, 45–49]

| Parameter | Meaning | Value |
|---|---|---|
| $p_{\text{branch}}$ | Probability of branching | normal CDF |
| $p_{\text{poly}}$ | Probability of polymerizing | 0.6* |
| $p_{\text{depoly}}$ | Probability of depolymerizing | 0.02* |
| $L_{\text{branch}}$ | Critical length before branching can occur | 0.2 μm† |
| $T_{\text{end}}$ | Total run time | 10 s |
| $\Delta t$ | Time step | 0.005 s |
| $n_{\text{sim}}$ | Number of independent simulations | 10 |

Model parameter $L_{\text{branch}}$ represents the critical length a filament must reach before branching can occur. Literature estimates for the spacing of branching Arp2/3 complexes along a filament vary widely, from 0.02 to 5 μm [15, 45–49]. We choose an intermediate estimate, $L_{\text{branch}} = 0.2\,\mu\text{m}$, which is of similar order to the values from other studies [48, 49]. The branching probability, $p_{\text{branch}}$, is chosen from a cumulative distribution function (CDF) of the standard normal distribution with mean, $\mu = 2$ and standard deviation, $\sigma = 1$. For in vitro systems, branch formation is inefficient because once an Arp2/3 complex is bound to a filament, the reported branching rate is slow (estimated to be $0.0022 - 0.007\ \text{s}^{-1}$) [49]. Given the relative dynamic scales of polymerization/depolymerization versus branching, we assume that (de)polymerization occurs at a prescribed rate, but because branching is infrequent, its probability is drawn from a distribution function.

The three microscale model probabilities are calculated in a time-step-dependent manner, such that the results of the microscale simulation are independent of the value of $\Delta t$, for a given time step for which calculated polymerization and depolymerization probabilities are not greater than 1. For example, polymerization and depolymerization probabilities are obtained using Eqs. 1 and 4. From Eqs. 1 and 2 we see that the largest possible value of $\Delta t$ consistent with a probability less than or equal to 1 is 0.009 s. The branching probability, $p_{\text{branch}}$, is always obtained using the CDF described in the preceding paragraph, but branching is only allowed to happen at fixed time intervals of 0.005 s. Using the $\Delta t$ value from Table 1, branching can occur every time step with probability $p_{\text{branch}}$. If, instead, $\Delta t = 0.0025$ s, branching can occur every other time step with probability $p_{\text{branch}}$. Simulations in this study were performed with a time step $\Delta t = 0.005$ to ensure that all results are internally consistent and comparable.

## 2.2 Macroscale Deterministic Model

### 2.2.1 Model Description

We model the growth and spread of a branching actin network through a reaction-diffusion form of the chemical species conservation equation derived in Sect. 2.2.2. This form is frequently known as Skellam's equation, applied to describe populations that grow exponentially and disperse randomly [50]. The two-dimensional Skellam's equation is

$$\frac{\partial \tilde{u}}{\partial t} = D\left(\frac{\partial^2 \tilde{u}}{\partial x^2} + \frac{\partial^2 \tilde{u}}{\partial y^2}\right) + r\tilde{u}. \tag{6}$$

In the context of our actin network, $\tilde{u}(x, y, t)$ is a dimensionless, normalized number density of polymerized actin monomers at location $(x, y)$ and time $t$, $D$ is the diffusion coefficient of the network (network spread), and $r$ is the effective growth rate constant (network growth). More precise definitions of $\tilde{u}$ and $r$ will be given in Sect. 2.2.2. Note that the diffusion coefficient is in reference to the bulk F-actin network spread, rather than representing Fickian behavior of monomers as has been done in previous literature [31, 40]. We use no flux boundary conditions in Eq. 6 to enforce no flow of actin across the cell membrane. For the initial condition of Eq. 6, we prescribe a point source at the origin.

### 2.2.2 Derivation of Reaction Term from First Principles

We present a derivation of the reaction term in Skellam's continuum description (Eq. 6) from simple kinetic considerations of actin filaments which include polymerization, depolymerization, and branching.

First, we write the molecular scheme for actin filament polymerization and depolymerization in the form of chemical equations. We denote a G-actin monomer in the cytoplasmic pool by $M$, an actin polymer chain consisting of $n-1$ subunits by $p_{n-1}$, and a one monomer longer actin polymer chain by $p_n$. The process of binding and unbinding of an actin monomer is described by the following reversible chemical reaction:

$$\mathrm{M} + \mathrm{p_{n-1}} \underset{k_r}{\overset{k_f}{\rightleftharpoons}} \mathrm{p_n}\ . \tag{7}$$

The constants $k_f$ and $k_r$ represent the forward and reverse rate constants, respectively, and encompass the dynamics that lead to the growth/shrinking of an actin filament.

Next, the biochemical reaction in Eq. 7 can be translated into a differential equation that describes rates of change of the F-actin network density. To write the corresponding equations, we first use the law of mass action which states that the rate of reaction is proportional to the product of the concentrations. Then, the rates of the forward ($r_f$) and reverse ($r_r$) reactions are:

$$r_f = k_f\,[M]\,[p_{n-1}], \tag{8}$$

$$r_r = k_r\,[p_n], \tag{9}$$

where brackets denote concentrations of $M$, $p_{n-1}$, and $p_n$, in number per unit area. This single actin polymerization/depolymerization reaction can be extended to capture all actin filaments reacting simultaneously across the network as follows:

$$r_f = k_f\,[M]\,[P_{n-1}], \tag{10}$$

$$r_r = k_r\,[P_n], \tag{11}$$

where we define

$$P_n = \sum_{i=2}^{n} i\,[p_i]. \tag{12}$$

Under the assumption that the forward and reverse reactions are each elementary steps, the net reaction rate is

$$r_{net} = r_f - r_r = k_f\,[M]\,[P_{n-1}] - k_r\,[P_n]. \tag{13}$$

We note that the monomer concentration $[M]$ can be eliminated from Eq. 13 if it is expressed in terms of initial concentration of monomers in the cell cytoplasm $[M]_0$:

$$[M] = [M]_0 - \sum_{i=2}^{n} i\,[p_i] = [M]_0 - [P_n]. \tag{14}$$

Lastly, we note that $[P_n] = [P_{n-1}] + n\,[p_n]$. We can assume a minor contribution from actin polymers at this maximum length, such that $[P_n] \approx [P_{n-1}]$. Then, Eq. 13 becomes

$$r_{net} = k_f \left([M]_0 - [P_n]\right)[P_n] - k_r\,[P_n], \tag{15}$$

and can be further simplified if we divide both sides of the equation by $[M]_0$:

$$\frac{r_{net}}{[M]_0} = [M]_0 \frac{[P_n]}{[M]_0}\left[\left(1 - \frac{[P_n]}{[M]_0}\right)k_f - \frac{1}{[M]_0}k_r\right]. \tag{16}$$