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REVIEW ARTICLE

Mathematical Modeling of Cell Polarity Establishment of Budding Yeast

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Abstract
The budding yeast *Saccharomyces cerevisiae* is a powerful model system for studying the cell polarity establishment. The cell polarization process is regulated by signaling molecules, which are initially distributed in the cytoplasm and then recruited to a proper location on the cell membrane in response to spatial cues or spontaneously. Polarization of these signaling molecules involves complex regulation, so the mathematical models become a useful tool to investigate the mechanism behind the process. In this review, we discuss how mathematical modeling has shed light on different regulations in the cell polarization. We also propose future applications for the mathematical modeling of cell polarization and morphogenesis.

Keywords Budding yeast · Cdc42 · Morphogenesis · Septin · Mathematical models

Mathematics Subject Classification 35Q92 · 92B05 · 92C37

1 Introduction

Cell polarity underlies various cellular functions for ensuing directed growth, locomotion, and differentiation [6]. The collapse in polarization may lead to the dysfunctionality of the cells [14, 66]. How cell polarity functions robust has been a central question in cell biology. Cell polarity development typically involves the localization of signaling molecules to a proper location of the cell membrane [56]. However, the fundamental mechanisms for this process remain controversial. It is known that the signaling molecules are initially distributed in the cytoplasm. Then, in response to extracellular or intracellular cues or spontaneously, they are localized at a proper location on the cell membrane. The localization of signaling molecules causes activations of certain cellular pathways which finally leads to the organization of the cytoskeleton and cell morphogenesis [4, 63].

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The budding yeast *Saccharomyces cerevisiae* is proved to be a powerful model system for studying the mechanism of the cell polarity establishment [4, 63]. In a yeast cell, the budding process is fundamentally regulated by the signaling protein Cdc42, which consists of guanosine triphosphate (GTP) and guanosine diphosphate (GDP) bound forms (Fig. 1). When intracellular or extracellular cues stimulate a yeast cell, Cdc42 will be recruited from the cytoplasm to the membrane [1, 35]. The exchange of signaling molecules, feedback regulation by molecular interactions, molecular transportation, and diffusion are involved in such a recruitment process [2, 26]. Cdc42, first discovered in budding yeast, is a highly conserved small GTPase of the Rho family and functions in multiple aspects of tissue morphogenesis and development [1, 17, 35]. Cdc42 acts as a central regulator of the polarity establishment, leading to distinct asymmetric cell shapes as seen in a neuron, epithelial cell, and filamentous fungus. Those processes are critical for the specialized functions and physiology of the cells and organisms. In *Drosophila*, small GTPases Cdc42 are necessary for controlling the decapentaplegic (Dpp) expression during the migratory process of the dorsal closure [24, 27, 52]. In *Xenopus*, Cdc42 plays a role in the regulation of convergent extension movements during the gastrulation [10]. In the gastrulation of the zebrafish mesoderm, Cdc42 GTPase in the cytosol was activated and the exchange of GTP was cycled to initiate and guide mesodermal cell migration [31]. In sea urchin, Cdc42 activity was required for proper primary mesenchyme cell migration and patterning as well as the elongation of the archenteron [60].

Besides Cdc42, five distinct Rho GTPases, Rho1–Rho5, were found in *S. cerevisiae*. A notable feature of the majority of Rho GTPases is that these proteins can reversibly switch between an active, GTP-bound state and an inactive, GDP-bound state, so these proteins are viewed as molecular on/off switches regulated spatially and temporally during cell development [15, 28]. The GTP- or GDP-bound states of Rho GTPases are controlled by guanine exchange factors (GEFs), GTPase-activating proteins (GAPs), and guanine nucleotide dissociation inhibitors (GDIs). GEFs activate small GTPases and exchange bound GDP to GTP. Conversely, GAPs facilitate the hydrolysis of GTP of GTPases. GDIs in the cytosol bind to Rho GTPases to keep them in their inactive GDP-bound form.

In a broad sense, there are two types of cell polarization: spatial cue-directed versus spontaneous cell polarization, often referred to as "symmetry breaking". These are not mutually exclusive. In many cases, an inherent tendency of self-organize polarity is biased by an asymmetric cue. The positive feedback regulation by active Cdc42 plays a critical role in generating a concentrated cluster of Cdc42 at the cell membrane [26, 30, 37]. In addition, a negative feedback loop is likely to be involved to enhance the

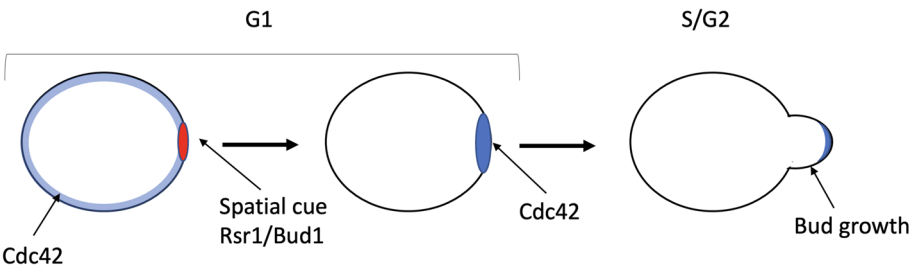

Fig. 1 Localization of Cdc42 during the budding process. Spatial cues (red) recruit Cdc42 (blue) to a specific location where a bud will be formed

robustness of the cell polarity [29, 41]. Mathematical modelings, including deterministic and stochastic models, have been widely applied to study the mechanisms of the cell polarization [2, 13, 26, 41, 50, 55, 57, 59]. These models apply diffusion-driven instabilities to achieve pattern formation without relying on spatially inhomogeneous mechanisms, such as diffusion barriers, directed transport, and molecular cross-linking. The systems instead require two conditions: (i) positive feedback to amplify local fluctuations; (ii) relatively large difference between the diffusion rates of chemical species. Under these two conditions, an inhomogeneous pattern can be induced by an arbitrarily weak perturbation. This mechanism is called the Turing-type mechanism. Goryachev and Polkhilko greatly contributed to developing a Turing-type model to study yeast polarization [26]. On the other hand, non-Turing-type models of polarity require perturbations of finite strength to induce the pattern formation [50]. It is called the wave-pinning mechanism, which is dependent on the wave propagation. Based on deterministic reaction-diffusion equations, Turing-type and wave-pinning mechanisms have been applied to explain the symmetry breaking of the yeast polarization [13, 26, 34, 50, 72]. Moreover, stochastic modeling provides a tool to understand the random effect on the symmetry breaking and general cell polarization [2, 13, 39, 42].

Mathematical modeling has contributed significantly to our understanding of the mechanisms underlying the cell polarity establishment. This review will discuss recent progress in the mathematical modeling of cell polarization processes. We summarize some existing mathematical models on the cell polarization process in Sects. 2, 3, 4, and 5. In Sect. 6, we suggest future applications for the mathematical modeling of the cell polarization and morphogenesis.

2 Polarization Through Positive Feedback Mechanism

In a yeast cell, the budding process fundamentally depends on Cdc42 polarization. Cdc42 in the cytoplasm will be recruited to the membrane based on the indication of intracellular or extracellular cues. Such a process involves the exchange of signaling molecules, feedback by molecular interactions, and molecular diffusion (Fig. 2). Several mathematical models were proposed to study this complex polarization process (Table 1).

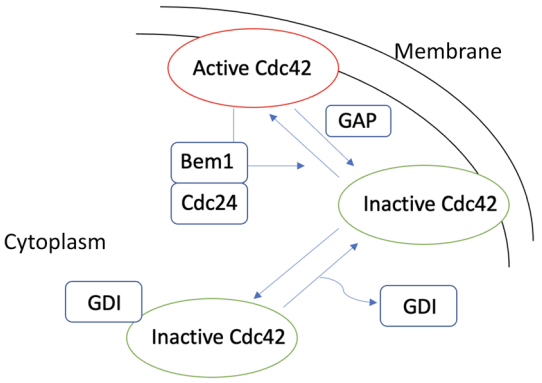

Fig. 2 Schematic representation of system consisting of active and inactive Cdc42, membrane-bound and cytoplasmic Bem1 complex, and RhoGDI protein

Table 1 List of some existing models for cell polarization in budding yeast

Literature	Type	Mechanism
Marco et al. [46]	Deterministic/Stochastic	–
Goryachev and Pokhilko [26]	Deterministic	Turing
Altschuler et al. [2]	Stochastic	–
Mori et al. [50]	Deterministic	Wave-pinning
Slaughter et al. [62]	Stochastic	–
Walther et al. [73]	Deterministic/Stochastic	Wave-pinning
Lawson et al. [39]	Stochastic	–
Lo et al. [44]	Deterministic	Turing
Lee et al. [40]	Deterministic	Turing
Chiou et al. [9]	Deterministic	Turing/Wave-pinning
Pablo et al. [55]	Deterministic/Stochastic	Turing
Cusseddu et al. [13]	Deterministic/Stochastic	Wave-pinning
Liu and Lo [42]	Deterministic/Stochastic	Turing

– denotes that item is not specified in the literature

2.1 Turing-Type Mechanism

General dynamics of the polarization process can be characterized by the mass conserved activator-substrate (MCAS) models. Primary research assumes that all cytoplasmic Cdc42 molecules are inactive and all membrane-bound Cdc42 molecules are active and another key feature is the mass conservation over the whole cell [2, 40, 41, 46, 62].

Marco et al. [46] constructed a mathematical model for characterizing the morphology of dynamically polarized protein distributions. They measured the values of parameters from single-cell experiments through analytical approaches. Their methods were applied to study polarized membrane proteins Cdc42 in budding yeast cells. They proposed that a balance of diffusion, directed transport, and endocytosis was sufficient for accurately describing polarization morphologies. In their model, the level of the polarized protein is represented by f

$$\frac{\partial f}{\partial t} = d_f \nabla_m^2 f - \left(e_a \chi + \frac{e_a}{\alpha}(1-\chi) \right) f + h F_{\text{Cyto}} \frac{\chi}{\int \chi}. \tag{1}$$

The spatial domain of the model is a sphere representing the membrane of a cell. The term $d_f \nabla_m^2 f$ is the lateral diffusion of f along the plasma membrane where ∇_m^2 represents the Laplacian operator on the cell membrane; the terms $e_a \chi f$ and $\frac{e_a}{\alpha}(1-\chi) f$ represent the endocytosis of f off the membrane at and away from the actin cables; the last term represents the direct transport from the cytoplasm to the membrane. In the model, the function χ represents the directed transport window function which controls the region of the membrane to which cytoskeletal tracks are attached (define $\chi = 1$ in region of directed transport/bud site; $\chi = 0$ elsewhere) and the term $\int \chi$ is the integral of χ over the whole domain. The last term of (1) represents the direct transport from the cytoplasmic pool of protein to the membrane. This model can be coupled with the actin cable dynamics to form positive feedback in the polarization system.

The steady-state distribution can be stabilized through the feedback loop between Cdc42 and the formation of actin cables. The model predicted that feedback could lead to

relatively high rates of actin cable attachment in regions of high Cdc42 concentration and detachment in regions of low Cdc42, and stabilize the transport window. This model provides insight into the function of positive feedback. The model proposed by Slaughter et al. [62] shares a similar structure of the model of Marco et al. [46]. As opposed to the previous model, the internalization rates inside and outside the delivery window were assessed separately in this study.

Goryachev and Pokhilko [26] proposed an eight-equation model for Cdc42 polarization. The model includes active and inactive Cdc42, membrane-bound and cytoplasmic Bem1 complex, and RhoGDI protein (Fig. 2). They reduced the large model to a two-equation model with two variables X (active Cdc42) and Y (inactive cytoplasmic Cdc42)

$$\frac{\partial X}{\partial t} = D_m \nabla_m^2 X + E_c \alpha X^2 Y + E_c \beta XY - \gamma X, \tag{2}$$

$$\frac{\partial Y}{\partial t} = D_c \nabla_c^2 Y + \gamma X - E_c \alpha X^2 Y - E_c \beta XY, \tag{3}$$

where ∇_m^2 and ∇_c^2 represent the Laplacian operator on the cell membrane and in the cytoplasm, respectively; $E_c = E_c^0\left(1 + \int_S f(X(t,s))\mathrm{d}s\right)^{-1}$ represents the conservation of the total cellular amount of Cdc24. The form of function f can be derived as $f(X) = a_1X^2 + a_2X + a_3$, where the parameters a_1, a_2, and a_3 depend on the reaction rates used in the eight-equation model [26]. The spatial domain S of the model is a sphere representing the membrane of a cell. In the model, the autocatalytic production of active Cdc42 occurs through the parallel cubic and effective quadratic mechanisms corresponding to two different activation pathways. The term $E_c\alpha X^2Y$ represents three reactions: (i) recruitment of the cytoplasmic feedback molecules (Bem1) to the membrane; (ii) formation of the activated complex; (iii) activation of inactive Cdc42. Goryachev and Pokhilko [26] showed that this cubic term is critical for the Turing-type mechanism and the formation of the Cdc42 cluster.

For simplification, the system was formulated as a typical two-species MCAS model consisting of cytoplasmic GDP and membrane-bound GTP, respectively, denoted by $a(x, t)$ and $b(x, t)$ (as shown in Fig. 3). The dynamics of a and b are governed by the lateral diffusion and the nonlinear interaction terms that lead to spontaneous pattern formation. The spatial domain M of the model can be considered as a sphere representing the membrane of a cell or a circle representing the cross-section of the cell. This typical system could be coupled with general forms of positive feedback, and mathematical analysis was applied to identify parameter conditions for achieving the cell polarization. In the studies of Lo et al. [43, 44], a typical two-variable model was proposed

$$\frac{\partial a}{\partial t} = D_m \nabla_m^2 a + F\left(a, \widehat{a^n}\right) b - k_{\text{off}} a, \tag{4}$$

$$\frac{\partial b}{\partial t} = D_m \nabla_m^2 b - F\left(a, \widehat{a^n}\right) b + k_{\text{off}} a + g_{\text{on}}\left(1 - \hat{a} - \hat{b}\right) - g_{\text{off}} b, \tag{5}$$

where $\widehat{a^n} = \int_M a^n \mathrm{d}S/|M|$, $\hat{a} = \int_M a\mathrm{d}S/|M|$, and $\hat{b} = \int_M b\mathrm{d}S/|M|$ represent the average values of a^n, a, and b over the cell membrane, respectively. The term $|M|$ is the area of the cell surface. The first terms on the right-hand side in (4) and (5) represent the diffusion rates of species a and b with the lateral surface diffusion rate D_m and the Laplacian operator ∇_m^2 on the cell membrane. The same diffusion coefficient D_m for a and b is used

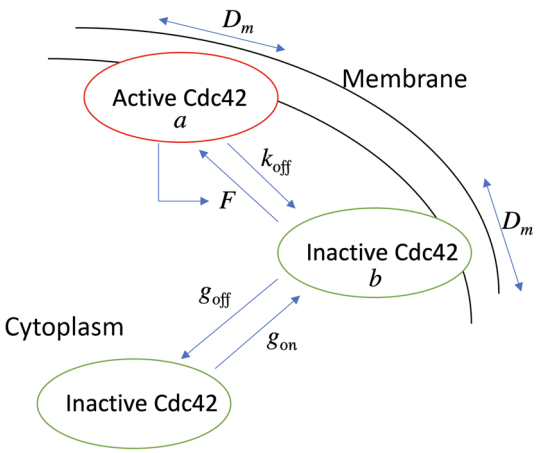

Fig. 3 Schematic representation of system consisting of two equations where a positive feedback F is incorporated

[26]. The term $(1 - \hat{a} - \hat{b})$ stands for the fraction of cytoplasmic signaling molecules. The term $g_{\text{on}}(1 - \hat{a} - \hat{b})$ is the recruitment rate of the inactive molecules from the cytoplasm to the membrane and $g_{\text{off}}b$ is the rate at which membrane-bound signaling molecules are extracted into the cytoplasm. The constant k_{off} is the deactivation rate coefficient of signaling molecules from active form to inactive form.

The model assumes that the total number of signaling molecules in the whole cell is conserved and that the signaling molecules are uniformly distributed throughout the cytoplasm due to the fast cytoplasmic diffusion. By assuming the activation rate is proportional to the fraction of cytoplasmic signaling molecules, the term $F(a, \hat{a^2})(1 - \hat{a})$ in (10) is applied to model the activation process in the system.

In system (4)–(5), the feedback regulation occurs through the function F, which represents the activation rate of signaling molecules. By assuming that active signaling molecules form a feedback loop to promote the activation, the function F is positively proportional to the particle density of a.

According to the observations of experimental studies [26, 43, 54], several forms of positive regulations were proposed to study the cell polarity. First, Cdc42 is activated by its GEFs in a positive quadratic or linear feedback function form [26, 43]

$$F(a) = k_{11} + k_{12}a^n, \tag{6}$$

where k_{11} and k_{12} represent the basal activation rate of Cdc42 and the activation rate from the feedback loop. The degree of the cooperativity $n = 1$ or 2 corresponds to the linear or quadratic feedback loop. This function form is direct cooperative feedback depending on the local density of the active molecule a, which has been used in many Turing-type systems.

Second, the activation of Cdc42 can be saturated when the level of Cdc42 is over a certain level. Thus, the function F is in the form of the Hill function [54]

$$F(a) = k_{21} + k_{22}\frac{a^n}{k_{23}^n + a^n}, \tag{7}$$

where k_{21} is the activation rate, k_{22} is the magnitude of self-activation, and k_{23} represents the saturation constant. This form shows a locally increasing recruitment rate at a low

Cdc42-GTP density, but the rate is bounded above by a maximum value $k_{21} + k_{22}$. Feedback regulations (6) and (7) include multi-step cooperative interactions, such as recruitment and binding, which can be modeled through the term a^n with $n \geqslant 2$.

In [44], they considered that positive feedback molecules exist and assumed that these particular molecules are initially uniformly distributed in the cytoplasm and later recruited to the cell membrane by the active signaling molecules a. Therefore, the activation rate F is proportional to the density of the membrane-bound feedback molecules. The dynamics of the feedback molecules is much faster than that of the signaling molecules [26, 43]. Lo at al. [44] assumed that the activation rate F is proportional to the quasi-steady state of the density of the feedback molecules

$$F\left(a, \widehat{a^2}\right) = k_{\text{on}} \frac{k_1 + k_2 a^2}{1 + k_1 + k_2 \widehat{a^2}}. \tag{8}$$

This activation function models multi-step cooperative interactions, which have been used in several biological Turing-type systems. Nonlinear cooperativity is modeled by the term a^2, and the degree of the cooperativity is 2 [40]. The function form in (8) depends on a non-local term $\widehat{a^2}$ and the local density a. By considering the MCAS model, Lo et al. [44] obtained the parameter conditions for the existence of a polarized pattern. Their simulations showed that non-local molecule-mediated feedback is important for sharping the localization and giving rise to fast dynamics to achieve the robust polarization.

2.2 Wave-Pinning Mechanism

Besides the Turing-type mechanism, another set of models relies on bistable reaction kinetics to generate the polarity by wave-pinning which resides in the system as follows:

$$\begin{aligned} \frac{\partial a}{\partial t} &= D_a \nabla_m^2 a + F(a, b), \\ \frac{\partial b}{\partial t} &= D_b \nabla_c^2 b - F(a, b), \end{aligned}$$

where ∇_m^2 and ∇_c^2 represent the surface gradient operator and the gradient operator in the cytoplasm, respectively.

The variable a represents the active form of membrane-bound signaling molecules, and the variable b represents the inactive form of cytosolic signaling molecules. The kinetic terms share the same form implying the conservation of the total amount of molecules. The function F is the difference between the rates of the activation and the inactivation. The diffusion rate of the membrane-bound molecules is significantly smaller than that of the cytosolic molecules, so that $D_a \ll D_b$. The wave-pinning mechanism is generally studied by the local perturbation analysis, which takes advantage of the large diffusion discrepancy that $D_a \to 0$, $D_b \to \infty$ in the two-variable reaction-diffusion system. Wave-pinning mechanism intrinsically depends on the wave propagation, and is thus distinct from the Turing mechanism, which is based on the growth of small local perturbations. Research suggests that another difference between the two models is that wave-pinning can act much faster to generate a polarization pattern than the Turing-type mechanism [8, 50].

Mori et al. [50] proposed the model with kinetics

$$F(a,b) = b\left(k_0 + \frac{\gamma a^2}{K^2 + a^2}\right) - \delta a,$$

where k_0 is a basal GEF conversion rate, and the positive feedback is represented by a Hill function with the maximal rate γ and the saturation parameter K. Conversion from active form to inactive form, mediated by GAPs, takes place at a constant basal rate δ. The spatial domain considered in [50] is a one-dimensional space $[0, L]$ with no-flux boundary conditions. They analyzed the reaction-diffusion system through the basic idea residing in a well-known property of reaction-diffusion systems with bistable kinetics, namely, propagation of fronts. Such a mechanism crucially depends on the exchange between active and inactive forms of the chemicals with unequal rates of diffusion and overall conservation to pin the waves into a stable polar distribution.

For the Turing-type mechanism, positive feedback within the interaction term is sufficient to induce the cell polarization behavior. Analysis of such a mechanism mainly relies on linear stability analysis around the steady state to guarantee the instability of a homogeneous steady state with small noise [21, 42, 44, 58, 70]. However, linear stability analysis can only check for instabilities that are induced by arbitrarily small noise near the steady state. Moreover, it cannot be easily used for a large nonlinear system, where finding the homogeneous steady-state and eigenvalues will be extremely challenging.

Turing instability and wave-pinning mechanisms should not be regarded as mutually exclusive. A system with interactions between multiple components can result in a model that induces the Turing instability and also generate the wave-pinning behavior in some parameter regimes [9]. However, amplification by recruiting active molecules to the cell membrane is a common feature observed in all models. Jilkine et al. [34] indicated that the wave-pinning models alone describe the adaptation to uniform stimulus but do not capture the phenomena of spontaneous polarization or polarity maintenance in the absence of the stimulus. Wave-based and Turing models differ in their response to multiple stimuli and a change in the direction of the stimulus. Thus, some classes of models are appropriate to describe some polarization behaviors but not others. In the parameter regimes, the Turing-type model generated rapid competition between clusters and unipolar outcome, while multipolar outcome exists in the wave-pinning model [9]. Spontaneous polarization is described well by Turing instability models. Gradient-sensing models like the local excitation and global inhibition (LEGI) seem most pertinent to cells without a cytoskeleton that does not exhibit maintenance or spontaneous polarity. Wave-based models are suitable to describe cells that need to rapidly reorient, such as neutrophils.

3 Oscillation of Cdc42 Cluster Through Negative Feedback Mechanism

Some experimental results indicated that negative feedback regulation is involved in the regulation of Cdc42 polarization [29]. The negative feedback plays a role in maintaining the robustness of Cdc42 localization and the oscillating behavior of Cdc42 cluster [25, 29, 74]. Howell et al. [29] developed a mathematical model to demonstrate that negative feedback would lead to the robustness of the cell polarity and make the kinetics of competition between signaling clusters relatively insensitive to polarity factor concentration. The model is similar to the one proposed by Goryachev and Pokhilko [26] and includes negative feedback via the GAP activation or the Bem1p complex inactivation.

To investigate how the polarization of Cdc42 is achieved in response to spatial cues in budding yeast, Lee et al. [40] developed a model with a single partial differential equation that includes a spatial cue in positive feedback on the Cdc42 activation and a delayed negative feedback in the disassociation from membrane to cytoplasm (see Fig. 4). The computational domain M is a two-dimensional region with no-flux boundary conditions. The dynamics of active molecules are governed by

$$\frac{\partial a}{\partial t} = D_m \nabla_m^2 a + F(a,u)\left(1-\hat{a}\right) - G\left(a\left(x,t-t_1\right),x\right)a \tag{9}$$

with $\hat{a}(t) = \int_M a(x,t)\,\mathrm{d}S_x/|M|$ representing the average values of a over the domain M, and $|M|$ is equal to the total area of the domain M. The function $F(a, u)$ is the rate coefficient for recruitment and activation of Cdc42 from the cytoplasm to the membrane, which depends on the level of the spatial landmark cue u and the particle density of the membrane-bound Cdc42 [44]. The function G is the disassociation rate of Cdc42 from the membrane to the cytoplasm. The deactivation rate varies with the activation level of Rga1, which may be regulated by a. With this assumption, G depends on the location x on the plasma membrane and the value of a with a delay of t_1. The study reveals that a proper axis of Cdc42 polarization in haploid cells might be established through a biphasic mechanism involving sequential positive and transient negative feedbacks.

The observed oscillation and fluctuation of Cdc42 cluster support that the delayed negative feedback is involved in the cell polarization system of budding yeast [40]. Moreover, Goryachev and Leda [25] showed that the necessary condition for achieving Cdc42 polarization or polarized localization is that when active Cdc42 increases, the activation rate grows faster than the rate of the deactivation. Liu and Lo [41] studied the model where the linear function of the deactivation was used instead of higher order functions. The spatial domain of the model can be considered as a sphere representing the membrane of a cell, or a circle representing the cross-section of the cell. They provided a detailed linear stability analysis for the model with the positive feedback $F(\cdot,\cdot)$ and delayed negative feedback $G(\cdot)$

$$\frac{\partial a}{\partial t} = \underbrace{D_m \nabla_m^2 a}_{\text{diffusion}} + \underbrace{F(a,\widehat{a^2})(1-\hat{a})}_{\text{activation}} - \underbrace{G(a(x,t-\tau))a}_{\text{deactivation}} \tag{10}$$

with $\hat{a}(t) = \int_M a(x,t)\,\mathrm{d}S_x/|M|$ and $\widehat{a^2}(t) = \int_M a^2(x,t)\,\mathrm{d}S_x/|M|$. The function F is defined as (8). A linear function to model the deactivation rate G in (10) is used

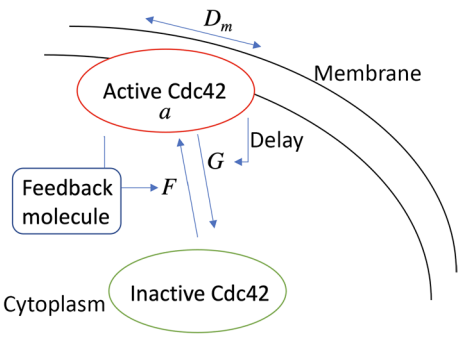

Fig. 4 Schematic representation of system consisting of a single equation where a positive feedback F and a delayed negative feedback G are incorporated

$$G(a(x,t-\tau)) = g_1 + g_2 a(x,t-\tau). \tag{11}$$

Their stability analysis provided a parameter condition for the existence of polarized solutions in the cell polarization system with delayed negative feedback suggested that we can observe the oscillating behavior of the signaling cluster in the simulations by controlling the length of the delay in negative feedback and the magnitude of positive feedback.

4 Enhance Robustness Through Septin Ring

Humans, animals, and other multicellular eukaryotes are composed of organs, tissues, and cells that are highly specialized in types and functions. Septins play an essential role in the morphogenesis of specialized cells and in guiding cell behaviors such as cell division and migration. In the frog *Xenopus* embryos, control of septins was a crucial control point for morphogenesis. In *C. elegans*, septins exhibit regulated expression in various neurons. Motor neurons in the mutant larvae fail to guide the axonal migration and locomotory behavior [19]. In mouse embryos, knock-down of Sept14/Sept4 inhibited leading process formation in migrating cortical neurons [61]. In T cells, septin knock-down causes membrane blebbing, excess leading-edge protrusions, and lengthening of the trailing-edge uropod, which relieves the migration [67]. Those results emphasize the role of septins in cell motility and the morphogenetic movements that regulate the development of tissue and organ.

Septins comprise a novel family of GTPases that polymerize into non-polar filamentous structures and scaffold protein localization. In a yeast cell, septins are initially recruited to the bud site as unorganized cloudy patches in response to signaling cues [33]. During such a process, transient direct interaction between the septin Cdc11 and Cdc24, a GEF for Cdc42, creates temporary positive feedback to enhance septin recruitment and Cdc42 activation [11]. Later, these unorganized paths of septins assemble and rapidly transform into a cortical septin ring in late G1 during which Cdc42 actively cycles between the GTP-bound and GDP-bound states [53]. The septin ring has an asymmetry in shape and structure, such that some proteins could localize specifically to the inside of the ring, and other proteins could localize to the outside of the ring [23, 36, 48]. This asymmetry persists until the bud emergence, after which the septin ring expands into a rigid hourglass-shaped collar. Thus, the septin ring and collar maintain the asymmetric distribution of proteins by functioning as membrane diffusion barriers or scaffolds in the formation [7, 16]. Through these scaffold and barrier roles, septins affect multiple cellular processes related to the cell polarization and division (see Fig. 5).

Septins are involved in the assembly of the endoplasmic reticulum (ER) diffusion barrier which limits the lateral diffusion of membrane proteins between the mother and the bud [12, 18, 32, 38, 65]. Septins promote the asymmetry in the plasma membrane by three potential mechanisms: (i) restricting the lateral diffusion, (ii) rigidifying the cell membrane, and (iii) regulating membrane-cytoskeleton interactions spatially.

Okada et al. [53] assumed that septin functions as a diffusion barrier on the cell membrane (considered as a sphere in the simulations), so that the Cdc42 diffusion coefficient $D_m(S)$ may depend on the concentration of septin or septin complex S

$$D_m(S) = \left(D_{\max} - D_{\min}\right)\mathrm{e}^{-S/K_S} + D_{\min},$$

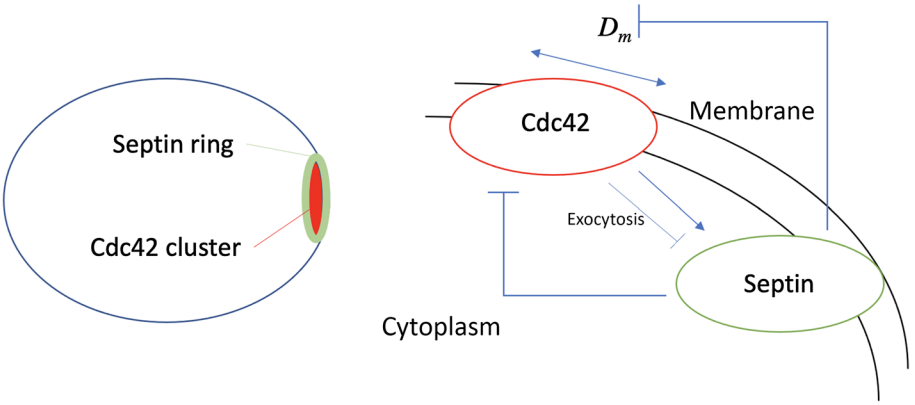

Fig. 5 System of Cdc42 and Septin. Cdc42 forms a cluster toward the bud tip with septin recruitment to form a ring. Septins are involved in the assembly of the ER diffusion barrier

which is the simplest exponentially decreasing function of S. At the same time, Cdc42 induces the septin recruitment, and the recruited septins inhibit the Cdc42 activity in a negative feedback loop. Polarized exocytosis, which is also controlled by the Cdc42 activity, triggers the conversion of the septin cap to a ring, relieving the inhibition of Cdc42. By combining live-cell imaging and mathematical modeling, this study elegantly shows how the interplay of Cdc42, septins, and exocytosis shapes the septin ring and leads to the emergence of a new daughter cell. For further understanding of the mechanism of this regulation, analytic study for the mathematical models of Cdc42 and septin is an important direction in future study.

5 Stochastic Effect in Cdc42 Polarization

Another way to understand symmetry breaking is through stochastic modeling. Stochasticity has primarily been addressed in some studies showing that it can be critical for models [34, 39, 42]. In particular, stochastic dynamics can more robustly reproduce a highly polarized phenotype and track a moving pheromone input. Stochastic dynamics at the intracellular signaling level have become a standard modeling paradigm in many areas of biology. There are numerous cases where deterministic or mean-field techniques do not capture the relevant dynamics of biological systems. Stochasticity is critical, especially when the number of key molecules is very small, as is often the case within a single cell. In such a scenario, the deterministic method cannot capture the detailed dynamics of each molecule and may fail to characterize the system dynamics correctly. Many methods were proposed to numerically simulate stochastic biochemical networks, the most common of which is the stochastic simulation algorithm (SSA)/Gillespie algorithm [20, 22]. For a spatial system, the domain is partitioned into several identical compartments with a length h and diffusion can be treated as a reaction in which a molecule in one compartment jumps to one of its neighboring compartments at a constant rate D_m/h^2, where D_m is the diffusion coefficient. One assumption of this spatial SSA is that the system is well mixed in each compartment. The spatial set-up of this stochastic algorithm is presented in Fig. 6.

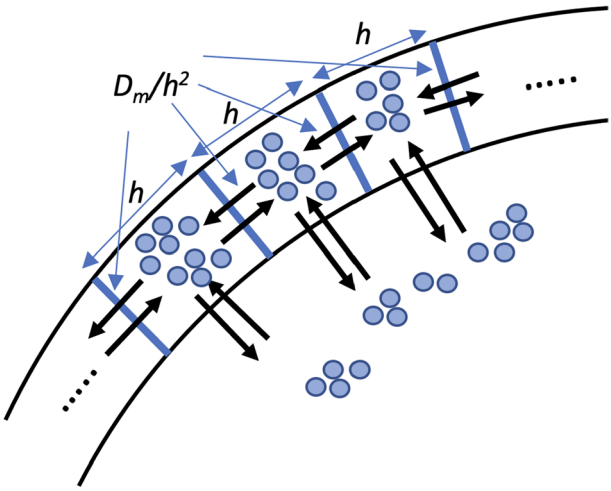

Fig. 6 Spatial set-up of the stochastic model

Altschuler et al. [2] proposed and studied a stochastic state-variable model for the following system:

$$\frac{\partial a}{\partial t} = D_m \nabla_m^2 a + k_{\text{on}}(1-h) + k_{fb}(1-h)a - k_{\text{off}}a, \tag{12}$$

where a molecule on the membrane may dissociate itself from the membrane at k_{off} and recruit some molecule in the cytosol to its location on the membrane at k_{fb}. A molecule from the cytosol may spontaneously associate itself to some random location on the membrane at k_{on}. The term h is the fraction of all molecules on the membrane changes according to an ordinary differential equation. In [2], the cell membrane was considered as a circle. This model suggests that an intrinsic stochastic mechanism through positive feedback alone is sufficient to account for the spontaneous emergence of the cell polarity. The polarization frequency has an inverse dependence on the number of signaling molecules, i.e., the frequency of the polarization decreases as the number of molecules becomes large. Their predictions have been verified to be consistent with the experimental observation of polarizing Cdc42. The results support that a stochastic model with linear positive feedback is sufficient to achieve symmetry breaking. However, symmetry breaking cannot be achieved in a deterministic model with linear positive feedback.

Based on the work by Altschuler et al. [2], a stochastic neutral drift polarity model was proposed in [34]. The essential difference in the model proposed by Jilkine et al. [34] is that positive feedback operates entirely through mass action kinetics, i.e., rate constants are not rescaled by total numbers of signaling molecules. They predicted that when the density of signaling molecules is below a critical value, positive feedback maintained an off state robustly. Over this critical threshold, it switched on the recurrent emergence of localized clusters.

Walther et al. [73] considered discrete molecular distribution with local recruitment in the wave-pinning model. They applied local perturbation analysis to predict parameter regimes for achieving the cell polarity in our deterministic system. Moreover, they compared these results with deterministic and stochastic spatial simulations. They concluded that the polarizing phenomenon was lost due to stochastic fluctuations.

Pablo et al. [55] developed particle-based simulations and found that molecular-level fluctuations can facilitate the cell polarization. In particular, they created a computational platform that explicitly simulates molecules at and near the cell membrane and implicitly handles molecules away from the membrane. To evaluate stochastic effects, they also compared particle simulations to deterministic reactions. Comparisons suggested that stochastic fluctuations speed up polarity establishment and permit polarization in parameter regions predicted to be Turing stable. These effects can operate at Cdc42 abundances expected of yeast cells and promote polarization on timescales consistent with experimental results.

Liu and Lo [42] compared the parameter range for ensuring the emergence of the cell polarity between deterministic and stochastic Turing-type systems. Based on the model in [44], they investigated the dynamics of a and b regulated by a general positive feedback function $F(\cdot)$,

$$\frac{\partial a(x,t)}{\partial t} = D_m {\nabla_m}^2 a(x,t) + F(a)b - k_{\text{off}} a, \tag{13}$$

$$\frac{\partial b(x,t)}{\partial t} = D_m {\nabla_m}^2 b(x,t) - F(a)b + k_{\text{off}} a + g_{\text{on}}\left(N - \widetilde{a} - \widetilde{b}\right) Q(a,b) - g_{\text{off}} b \tag{14}$$

on a one-dimensional domain $0 \leqslant x \leqslant L$ with boundary conditions $a(0,t) = a(L,t)$, $b(0,t) = b(L,t)$. The terms $\widetilde{a} = \int_M a \mathrm{d}S$ and $\widetilde{b} = \int_M b \mathrm{d}S$ represent the total numbers of a and b over the cell membrane, respectively.

The total number of active and inactive signaling molecules in the whole cell is conserved to be N, where synthesis and degradation are excluded. Considering an upper limit for the particle density at a local position on cell membrane, the function $Q(a, b)$ is defined as $Q(a,b) = 1 - \dfrac{a+b}{\Omega}$, where the parameter Ω is the carrying capacity for measuring the maximum particle concentration at a local position on cell membrane; if not, i.e., $\Omega \gg (a+b)$, then $Q(a,b) \equiv 1$ to remove the limit on the recruitment of inactive signaling molecules from the cytoplasm. They applied the numerical method SSA and the analysis of the power spectrum to approximate the parameter ranges for the spontaneous emergence of the cell polarity in the stochastic system. The comparison indicated that both deterministic and stochastic methods fail to yield the polarity at a low number of molecules, and the stochastic fluctuations in the model can extend the parameter regime for achieving the cell polarization. This study also suggested that the parameter region for the cell polarization under the Hill function feedback is smaller than that with the quadratic function feedback.

Besides the mechanism for the emergence of the cell polarity, a key feature, the geometry, was neglected in these models where the shape or geometry can affect the reaction networks [69]. Although recent work has noted a qualitative effect of the geometry on simplified models of the cell polarization in yeast mating, a thorough characterization of these effects on more complex reaction networks and geometries has yet to be performed.

6 Future Application in Cell Morphogenesis

Morphogenesis is a fundamentally mechanochemical process. Shape changes are driven by active mechanical forces generated by chemical processes, which can be affected by the deformations and flows that occur [49]. While several experimental works studied cytokinesis in budding yeast, some mathematical and computational models were proposed

for modeling cell morphogenesis. In the modeling of morphogenesis, there are two viewpoints: one regards the cell membrane as a solid shell with finite thickness, and the other views the cell membrane as soft matter exhibiting a solid-fluid duality, as fluid deformable surfaces. Some recent related papers are listed in Table 2.

In the paper of Zmurchok et al. [75], the author utilized the same method to investigate the influence of membrane tension on cell migration by considering two components, active Rac and inactive Rac. In the paper of Murphy and Madzvamuse [51], the authors coupled two components (F-actin and bound myosin) and the bulk cell mechanics to investigate the cell migration in 3D. However, due to the limitations of experimental conditions, the molecular basis of biological force generation is poorly understood.

On the other hand, several experiments and modeling research results show that mechanics can actively influence chemical patterns during development [3, 47, 75]. In the study of Brinkmann et al. [5], the authors proposed a simple positive feedback loop to investigate the interplay between chemical and mechanical processes during 3D tissue development. The influence of mechanics on morphogen dynamics is represented by including the function of the deformation gradient tensor into the reaction term of the reaction-diffusion equation, which is based on the physical invariant. To couple chemical reactions with mechanics, the deformation gradient tensor is decomposed into the active and elastic parts. The critical assumption is that the intermediate configuration is stress-free, and any stress is solely generated by the elastic response. Therefore, the material law depends only on the elastic response. All the equations of morphogen concentration and mechanics deformation are calculated in the initial configuration using the finite-element method. Although the authors provided some new insight by including mechanical pattern formation, only one component of morphogen was considered. Besides, since the feedback of mechanics on morphogen is described only by the determinant of the deformation gradient, the current model does not capture the effect of membrane shape on morphogen dynamics. They assumed that the interior of the tissue was hollow and thus did not consider the interaction between the cytoplasm and the tissue surface.

Recently, some studies have paid more attention to the mechanical properties of the cell surface. Tsai et al. [71] utilized the three-dimensional coarse-grained particle-based model to show that the polarized Cdc42 signals are essential for initialing bud formation in *Saccharomyces cerevisiae*. This paper focused on the mechanical properties of the chitin and

Table 2 Model classification of morphogenesis

Literature	Solid surface	Fluid deformable surface
Brinkmann et al. [5]	√	
Torres et al. [68]		√
Mietke et al. [49]		√
Mahapatra et al. [45]		√
Murphy and Madzvamuse [51]	√	
Stinner et al. [64]	√	
Tsai et al. [71]	√	
Zmurchok et al. [75]	√	
Banavar et al. [3]	√	

septin rings. However, the modeling did not include the coupling between the chemical signaling pathways and cell mechanics for the yeast budding process. Many cellular processes require the cell polarization to be maintained as the cell changes shape, grows, or moves. How does the coupling between the chemical signaling pathways and cell mechanics affect the budding process? Does the regulation by mechanical forces enhance the robustness of Cdc42 polarization? How does the septin ring form under mechanical forces? What is the role of the septin ring in cell morphogenesis if the interaction between mechanical forces and chemical reactions is considered? Mathematical modeling is a helpful tool to provide some possible answers to these questions. Through coupling the mathematical model of Cdc42 with the system of mechanical forces, we can provide a framework for studying the interaction between the spatial profiles of signaling molecules and the cell morphogenesis. By comparing the simulations obtained from the model with different scenarios, such as different regulation strategies between signaling molecules and membrane tension, we can learn more about the cell polarization in budding yeast. Moreover, the theoretical results will be a step-stone for developing further experimental investigation of cell morphogenesis.

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Compliance with Ethical Standards

Conflict of Interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical Approval The research does not involve human participants and/or animals.

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