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Review

# Cytokinesis through biochemical–mechanical feedback loops

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ABSTRACT

Cytokinesis is emerging as a control system defined by interacting biochemical and mechanical modules, which form a system of feedback loops. This integrated system accounts for the regulation and kinetics of cytokinesis furrowing and demonstrates that cytokinesis is a whole-cell process in which the global and equatorial cortices and cytoplasm are active players in the system. Though originally defined in *Dictyostelium*, features of the control system are recognizable in other organisms, suggesting a universal mechanism for cytokinesis regulation and contractility.



**Contents**



## 1. Introduction

Cytokinesis, the final step leading to the physical separation of a mother cell into two daughter cells, is often depicted as a linear process regulated by pathways that initially emanate from the mitotic spindle [1–3]. In actuality, because cytokinesis is a process mediated by biochemical interactions as well as the physical parameters of the cell and mechanical inputs, it is regulated by several parallel yet congruent pathways that intersect to form a complex cytokinesis network. This network is an interdependent array of separately regulated circuits and feedback loops that can be broken down into functional modules [4]. Here, we will examine the individual components that work in concert to drive the cytoskeletal remodeling of cytokinesis.

Traditionally, cytokinesis is viewed as occurring through the constriction of the cleavage furrow by a contractile ring composed of anti-parallel actin bundles interdigitated by the force-generating protein, myosin II, whose accumulation at the furrow is presumed to be mitotic spindle mediated [5–7]. The circumferential array of actin and myosin II is found in a number of organisms from *Schizosaccharomyces pombe* to HeLa cells [6,8,9]. However, there are plentiful examples of organisms that do not have a distinctive

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ring structure, such as adherent mammalian fibroblasts and *Dictyostelium* [10–12]. In these cell types, actin polymers and myosin II are arranged in a contractile meshwork [11]. These two distinct structural observations imply that the actomyosin organization may be the result, not the cause, of contractility. We suggest that the core principles of cytokinesis – the mechanical and biochemical parameters – are common among organisms and that it is in the regulatory mechanisms where the organismal differences lie. How a cell generates and responds to internal mechanical stress is dependent upon the structure of the cell and force-sensitivity of the protein players involved in cell division. Although the list of proteins involved in cytokinesis is extensive [7,13], we will focus on the integral players which individually define structural and functional modules: the plasma membrane, actin filaments, myosin II, and actin-crosslinking proteins.

## 2. Membrane and membrane dynamics

At first glance, cytokinesis is a physical process by which the surface of a cell is severely deformed to promote furrow ingression, bridge formation, and ultimately two new daughter cells. In order for these various characteristic cell shape changes to occur, the plasma membrane must be rapidly remodeled to accommodate cytoplasmic volume conservation, without rupturing under the internal stress associated with those shape changes, and while increasing the final total surface area by ~26% [14–16]. Membrane dynamics are regulated in part by endocytosis and exocytosis – two processes involved in engulfing membrane and depositing lipids, respectively, to remodel plasma membrane. Genetic mutants of proteins involved in these processes generate cells with cytokinesis defects. Additionally, lipid composition may play a role in membrane and cytoskeleton regulation, since the lipid composition of the furrow region and of the poles are different [17–19]. Whether or not membrane remodeling actively promotes cleavage furrow ingression or passively affects cell shape change by altering surface area to accommodate stress changes currently remains unclear.

The plasma membrane is also an integral component of a physical parameter essential for cell shape change – cortical tension. Cortical tension is defined as the force in the cell cortex and overlying plasma membrane that serves to minimize the surface area (demarcated by the membrane) to volume ratio and it is comprised of all of the mechanical stresses that act at the surface of the cell [20,21]. Cortical tension affects cleavage furrow ingression dynamics in a multitude of ways: it originally opposes the forces deforming the mother cell, while later acts in the furrow region to aid in pushing out the cytoplasm from the bridge region into the two daughter cells [22]. Concurrently, the cortical tension in the new daughter cells works to withstand and accommodate the cytoplasmic movement from the bridge. How cortical tension affects a dividing cell is dependent not only upon the boundary forces put in place by the plasma membrane, but also on the plasticity of the cytoskeleton.

## 3. Actin

The primary structural component of the contractile cytoskeleton is the actin polymer (Fig. 1). These filaments are semi-flexible, meaning that their mechanical characteristics are dictated by two length-scales defined by the polymer contour length ($L_c$) and the persistence length ($L_p$) [23,24]. $L_c$ is the length of the polymer, whereas $L_p$ is the distance between two points on the polymer where those points behave independently of each other. The relationship between $L_c$ and $L_p$ partly describes the mechanical properties of a polymeric network. When $L_c > L_p$, a polymeric network will stiffen upon the application of large forces. When $L_c < L_p$, then the network properties are dominated by polymer concentration and crosslinkers [25,26]. Because the $L_p$ for actin is 10–17 μm and polymer lengths are much shorter (up to 100-fold shorter) than $L_p$ in living cells [8,11], the properties of the living actin network will be primarily dominated by actin concentration, the lifetime of the actin polymers, and the density, properties and lifetimes of the proteins acting upon and/or crosslinking the actin polymers.

## 4. Myosin and myosin force generation

The major active force generator of cytokinesis is myosin II (Fig. 1). The functional unit of myosin II is the bipolar thick filament (BTF), comprised of hexameric monomers (M), consisting of two heavy chains, two essential light chains (ELCs), and two regulatory light chains (RLCs) [27]. Myosin II monomers assemble into bipolar thick filaments (BTFs) with most mammalian nonmuscle myosin IIs assembling into BTFs containing 10–30 monomers and in *Dictyostelium,* into BTFs of up to 70 monomers [28,29]. *Dictyostelium* BTF assembly is thought to occur first through a nucleation process in which parallel dimers (D) assemble from two monomers (M), and then two parallel dimers assemble into an anti-parallel tetramer. Subsequent elongation occurs through dimer addition. The assembly of BTFs is regulated by myosin heavy chain kinases (MHCKs), which in *Dictyostelium* phosphorylate three threonines in the tail of the heavy chain downstream of the assembly domain [30,31]. Phosphorylation of these sites puts the myosin II monomer in an assembly incompetent state. Importantly, the phosphomimic (3× Asp) mutant myosin cannot assemble into BTFs and cannot accumulate at the cleavage furrow cortex. Conversely, the unphosphorylatable (3× Ala) mutant overassembles into thick filaments, over-accumulates at the cleavage furrow cortex and has severely impaired BTF assembly-disassembly dynamics in the cell cortex [15,30,31]. For mammalian nonmuscle myosin II, in addition to heavy chain phosphorylation, RLC phosphorylation helps modulate BTF assembly [32–35]. RLC phosphorylation of assembled myosin II also increases the actin-activated ATPase activity, which is likely due to freeing the motor so that it is more able to bind an actin filament [36–38].

Cell shape dynamics are modulated in large part by the tension produced by myosin II on the actin cytoskeleton. Myosin generates force as it goes through its conformational changes and generates work as it moves relative to the actin filament [27]. The number of myosin II motor heads bound to actin at any one time is dictated by the motor's duty ratio and the total number of available myosin II heads. The duty ratio is the ratio of time that the motor is strongly bound to the actin filament (the "strongly bound state time") to the length of the entire ATPase cycle. Of the myosin binding cycle, the force-sensitive step occurs during the conformational changes that precede the ADP-bound, post-stroke conformation. Consequently, resistive tension is generated as the lever arm swings through its power stroke as long as the actin filament is stably anchored by actin linking/crosslinking proteins. This tension results in strain on the lever arm, constraining the lever arm's swing and ensuring that the motor remains bound in the load-bearing transition (isometric) state for a longer period of time (i.e. increasing the duty ratio of the motor).

## 5. Actin crosslinkers

The final essential components of the cytoskeleton and contractile system that complete the actin–myosin modules are the actin-crosslinking proteins (ACLPs). They are tasked with tethering individual actin polymers to each other and to the plasma membrane, allowing for localized mechanical stress to propagate throughout the network, and pulling in of the plasma membrane during cleavage furrow ingression. The presence of ACLPs on the