

A kinetic transport model for actin-myosin interaction

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Abstract: Based on the behavior of individual myosin monomers imbedded in myosin bundles and acting on actin filaments, a kinetic transport model is formulated, describing the sliding filament mechanism. It accounts both for the attachment/detachment kinetics of myosin heads and for the mechanics leading to the sliding motion. The model has the favorable property of a closed ODE system of equations for the macroscopic moments, containing the essential nonlinearities, which allow the description of instabilities observed in in-vitro experiments. The kinetic model possesses measure solutions, which can be computed explicitly in terms of the moments. Long time convergence to equilibrium (providing force-velocity relations) and a macroscopic limit, eliminating the velocity variable, are carried out rigorously.

Acknowledgement: This work has been supported by the Vienna Science and Technology Fund under grant no. MA09-004.

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1 Introduction

The interaction between actin and myosin filaments plays a crucial role in different types of cellular movement. In skeletal muscles the filaments, together with several accessory proteins, form the highly ordered sarcomeres, the basic units of muscle contraction. However, also in many other types of eukaryotic cells, actin-myosin interaction is essential for their movement behavior. Examples are the contraction of stress fibers and constriction rings, as well as the contractive properties of the actin network in lamellipodia.

Mathematical modeling of the interaction of actin and myosin in muscles is often based on or influenced by the so called *Huxley model*, developed in the 1950s by the biophysicist *Sir Andrew Fielding Huxley* (Huxley [1957]). At this time the contraction mechanism in muscles was still up to debate. The sarcomere pictures showed *light* and *dark* bands and it was known that actin and myosin were present. Many argued that the shortening was caused by *one* type of filament that itself got shorter. Huxley and others, however, supported the idea of *sliding filaments*. He suggested that there are two types of filaments, actin and myosin filaments, which interact with each other and thereby create a force causing them to slide past each other. This would lead to a change of length of one sarcomeric unit while not altering the lengths of the individual filaments. With today's knowledge of the molecular structures and particularly of the different head conformations of myosin, we know this to be true.

Huxley supported his view by formulating a PDE model describing the attachment/detachment kinetics between the filaments. Combined with a steady state force balance it produced predictions agreeing with experimental results and with the force-velocity relation derived by energy balance considerations already in Hill [1938]. Since the 1950s, there have been many further contributions to the modeling of the actin-myosin interaction, based on the ideas of the Huxley model. The attachment/detachment of the heads of myosin monomers and their movement due to conformation changes are usually described in terms of a time and position dependent number density of attached heads. In Kato and Yamaguchi [1995] an overview over results on existence and convergence of solutions of a viscous variant of the equation is given. Similar questions are also covered in Colli and Grasselli [1990] and Colli and Grasselli [1993]. In other models, in contrast to the standard rigidity assumption, filaments are modeled as elastic (Torelli [1997], Williams [2011]).

The motivation of the present work comes from modeling various components of the cytoskeleton, such as stress fibers and the lamellipodium. In these situations, actin and myosin filaments are highly dynamic, undergoing polymerization and depolymerization mechanisms. In particular, forces produced by the actin-myosin interaction will strongly depend on the (possibly time dependent) size of the involved myosin filaments. Our modeling

has been motivated by Clement et al. [2007] and Sorine et al. [2003]. It is based on a microscopic description of the dynamics of individual myosin monomers in terms of their internal state (described by a one-dimensional conformation variable) and their velocity. The distribution of active myosin monomers with respect to these variables solves a kinetic transport equation. In contrast to the Huxley model, where the attachment/detachment kinetics and the force balance are treated separately, all effects are combined in one comprehensive model including the transient behavior.

In the spirit of BGK models, the kinetic equation is nonlinear through the occurrence of moments of the distribution function. A peculiarity of the model is the fact that a closed system of ordinary differential equations can be derived for three macroscopic quantities: the total number of attached myosin heads, the average velocity of the tails, and the total stress produced by deviation from an equilibrium conformation. Under simplifying modeling assumptions convergence of solutions to a unique steady state can be shown, leading to an explicit formula for the relative actin-myosin velocity. However, the model also has the potential to describe dynamic instabilities, which have been observed in in-vitro experiments (Riveline et al. [1998]).

The ODE system is invariant under certain perturbations of the microscopic model, in particular smoothing of the measure valued source terms we suggest, causing a measure valued distribution function. This can be computed almost explicitly by the method of characteristics in terms of the macroscopic quantities. Long time decay to equilibrium can be proven. Finally, the limit of large friction between individual myosin tails leads to a Huxley-like model (*macroscopic* in the vocabulary of kinetic transport equations).

2 Model

We will derive an equation describing the interaction between one end of a myosin bundle with an actin filament (or several aligned actin filaments, which do not move relative to each other). Myosin monomers consist of tails, necks, and heads (see Figure 1), and bundles are built (roughly) by an entanglement of the tails. Myosin bundles move relative to actin via attachment of a myosin head to an actin filament, followed by a change of conformation, representing the ATP (i.e. energy) dependent *power stroke* (see Figure 1). This may be followed by detachment from the actin filament and return to the original conformation, the so called *cocked state*.

In the simplified model of Figure 1, the conformation of the myosin monomer could be described in terms of the angle between tail and neck. In the following, however, we reduce our attention to myosin monomers with attached heads and describe the conformation by the displacement $\xi(t)$ of the tail in the direction of the actin filament relative to the cocked state,

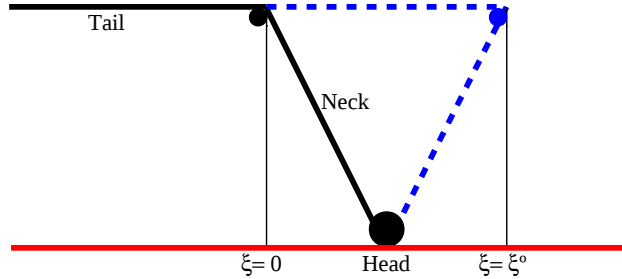


Figure 1: Model of a myosin monomer: Cocked state (black, solid lines) with tail, neck, and head, the latter attached to an actin filament (red, solid line); and state after a successful power stroke (blue, dashed lines). The tail is shifted by the distance ξ_0 in the direction of the actin filament.

represented by $\xi = 0$. The equilibrium conformation after the power stroke is represented by $\xi = \xi_0 > 0$. The velocity of the tail of an individual myosin monomer is denoted by $v(t)$, and $u(t)$ will denote the average velocity of all monomers, interpreted as the velocity of the myosin bundle. Furthermore, we denote the total number of monomers with attached heads by $m(t)$. As soon as the head attaches, the tail experiences a number of forces resulting in the following acceleration terms:

- a) a linear spring acceleration $\kappa(\xi_0 - \xi)$, proportional to the distance from equilibrium. Here we assume that at the time of attachment, the equilibrium conformation switches from $\xi = 0$ to $\xi = \xi_0$.
- b) a friction acceleration $-\eta v$, caused by the environment, e.g. by cytoplasmic drag.
- c) a friction acceleration $(u - v)/\tau$ caused by the entanglement of the individual tail with the myosin bundle.
- d) an acceleration $-F/m$, caused by an external force $F > 0$ pulling the bundle back, which is shared by all attached monomers.

The movement of one attached monomer is then determined by the Newtonian system

$$\dot{\xi} = v, \quad \dot{v} = \kappa(\xi_0 - \xi) - \eta v + \frac{u - v}{\tau} - \frac{F}{m}. \quad (1)$$

It remains to describe the attachment and detachment mechanisms and the behavior of detached myosin monomers. Attachment and detachment are modelled as Poisson processes with rates $f(u)$ and, respectively, $g(u)$, depending on the bundle velocity. We assume these dependencies to be smooth, and additionally

$$0 < \underline{f} \leq f(u) \leq \bar{f}, \quad 0 < \underline{g} \leq g(u) \leq \bar{g}. \quad (2)$$

After detachment, myosin monomers are assumed to immediately return to the cocked conformation and to the bundle velocity. This is justified since the hydrolysis of ATP is fast compared to the other steps (Adelstein [1980]). As a consequence, attachment always occurs at the state $(\xi, v) = (0, u)$.

If the total number of myosin monomers is N , the expected number density $\Psi(\xi, v, t)$ ($\xi, v \in \mathbb{R}, t \geq 0$) of attached monomers satisfies the master equation

$$\begin{aligned} \partial_t \Psi + v \partial_\xi \Psi + \partial_v \left[\left(\kappa(\xi_0 - \xi) - \eta v + \frac{u - v}{\tau} - \frac{F}{m} \right) \Psi \right] \\ = \delta(\xi) \delta(v - u) f(u) (N - m) - g(u) \Psi, \end{aligned} \quad (3)$$

where the total number of attached monomers is given by

$$m(t) = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} \Psi(\xi, v, t) dv d\xi, \quad (4)$$

and the bundle velocity by

$$u(t) = \frac{1}{m(t)} \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} v \Psi(\xi, v, t) dv d\xi. \quad (5)$$

The Cauchy problem will be considered, i.e. the kinetic transport equation (3), subject to initial conditions

$$\Psi(\xi, v, 0) = \Psi_0(\xi, v). \quad (6)$$

As a consequence of the occurrence of the Delta-distributions in the source term of (3) we have to expect measure valued solutions. We shall therefore only assume that the initial datum Ψ_0 is a nonnegative bounded measure with positive total mass and bounded first order moments:

$$\begin{aligned} \Psi_0 \in \mathcal{M}_1^+(\mathbb{R}^2), \quad 0 < m_0 := \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} \Psi_0 dv d\xi < \infty, \\ \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} (|\xi| + |v|) \Psi_0 dv d\xi < \infty. \end{aligned} \quad (7)$$

It is instructive to introduce the position dependent number density and flux by

$$\rho(\xi, t) = \int_{-\infty}^{\infty} \Psi(\xi, v, t) dv, \quad j(\xi, t) = \int_{-\infty}^{\infty} v \Psi(\xi, v, t) dv.$$

Integration of (3) with respect to v then leads to the local mass balance equation

$$\partial_t \rho + \partial_\xi j = \delta(\xi) f(u)(N - m) - g(u)\rho, \quad (8)$$

where the total number of attached monomers and the bundle velocity can now be computed as

$$m(t) = \int_{-\infty}^{\infty} \rho(\xi, t) d\xi, \quad u(t) = \frac{1}{m(t)} \int_{-\infty}^{\infty} j(\xi, t) d\xi. \quad (9)$$

Finally, we state the local momentum balance, obtained from (3) by multiplication by v and subsequent integration with respect to v :

$$\begin{aligned} \partial_t j + \partial_\xi \left(\int_{-\infty}^{\infty} v^2 \Psi dv \right) &= \kappa(\xi_0 - \xi)\rho - \eta j + \frac{\rho u - j}{\tau} - \frac{F}{m}\rho \\ &+ \delta(\xi) u f(u)(N - m) - g(u)j. \end{aligned} \quad (10)$$

Obviously, the system (8)–(10) is not closed. A closure will be achieved below by the asymptotic limit $\tau \rightarrow 0$ in (3).

3 The Moment System

It is a remarkable property of (3) that it incorporates a closed system of ordinary differential equations for averaged quantities. In the global mass and momentum balances obtained from (8) and (10) by integration with respect to ξ , the total stress

$$\sigma(t) = \kappa \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} (\xi_0 - \xi) \Psi(\xi, v, t) dv d\xi = \kappa \int_{-\infty}^{\infty} (\xi_0 - \xi) \rho(\xi, t) d\xi \quad (11)$$

appears as a new variable, an equation for which can be obtained by multiplication of (8) by $\kappa(\xi_0 - \xi)$ and integration with respect to ξ . This results in a closed system for the total number of attached myosin monomers, the bundle velocity, and the total stress:

$$\begin{aligned} \dot{m} &= f(u)(N - m) - g(u)m, \\ \dot{u} &= \frac{\sigma}{m} - \eta u - \frac{F}{m}, \\ \dot{\sigma} &= -\kappa m u + \kappa \xi_0 f(u)(N - m) - g(u)\sigma. \end{aligned} \quad (12)$$

The assumptions (7) on the initial distribution imply that the initial data

$$m(0) = m_0 > 0, \quad u(0) = u_0, \quad \sigma(0) = \sigma_0, \quad (13)$$

are well defined.

Theorem 1. *Let (2) hold. Then problem (12), (13) has a unique global solution.*

Proof. Assumption (2) implies the a priori estimate

$$0 < \min \left\{ m_0, \frac{\underline{f}N}{\underline{f} + \underline{g}} \right\} \leq m(t) \leq \max \left\{ m_0, \frac{\bar{f}N}{\bar{f} + \bar{g}} \right\}, \quad t \geq 0. \quad (14)$$

The equations for $u(t)$ and $\sigma(t)$ can be written as

$$\begin{pmatrix} \dot{u} \\ \dot{\sigma} \end{pmatrix} = B(t) \begin{pmatrix} u \\ \sigma \end{pmatrix} + b(t), \quad (15)$$

with

$$B(t) = \begin{pmatrix} -\eta & 1/m(t) \\ -\kappa m(t) & -g(u(t)) \end{pmatrix}, \quad b(t) = \begin{pmatrix} -F/m(t) \\ \kappa \xi_0 f(u(t))(N - m(t)) \end{pmatrix},$$

bounded uniformly in t by (2) and (14). This is sufficient to provide (exponentially increasing) bounds for $u(t)$ and $\sigma(t)$ for all $t \geq 0$. ■

Steady states $(\bar{m}, \bar{u}, \bar{\sigma})$ of (12) have to satisfy the (implicit) equations

$$\begin{aligned} \bar{m} &= \frac{N f(\bar{u})}{g(\bar{u}) + f(\bar{u})}, \\ \bar{u} &= \frac{g(\bar{u})}{\kappa + g(\bar{u})\eta} \left(\kappa \xi_0 - \frac{F(f(\bar{u}) + g(\bar{u}))}{N f(\bar{u})} \right), \\ \bar{\sigma} &= \eta \bar{m} \bar{u} + F. \end{aligned} \quad (16)$$

The number of steady states, i.e. the number of solutions \bar{u} of the second equation, depends on the qualitative behavior of $f(u)$ and $g(u)$. We defer a discussion of different possibilities to Section 6 and restrict our attention here to the simple case, where both rates are constant. Then (16) gives the unique steady state explicitly.

Theorem 2. *Let $f(u)$ and $g(u)$ be constant and positive. Then, as $t \rightarrow \infty$, the solution of (12), (13) converges exponentially to the unique steady state $(\bar{m}, \bar{u}, \bar{\sigma})$, given by (16).*

Proof. Obviously, the equation for $m(t)$ can be solved explicitly with a solution decaying exponentially to \bar{m} . This implies that the matrix $B(t)$ and the vector $b(t)$ in the representation (15) are known explicitly and converge exponentially to \bar{B} and, respectively, \bar{b} as $t \rightarrow \infty$. A straightforward computation shows that the eigenvalues of \bar{B} have negative real parts.

An integral formulation of the initial value problem for $u(t)$ and $\sigma(t)$ can be written in the form

$$\begin{aligned} y(t) &= e^{\bar{B}t} y(0) + \int_0^t e^{\bar{B}(t-s)} (B(s) - \bar{B}) y(s) ds \\ &\quad + \int_0^t e^{\bar{B}(t-s)} \left[(B(s) - \bar{B}) \begin{pmatrix} \bar{u} \\ \bar{\sigma} \end{pmatrix} + b(s) - \bar{b} \right] ds \end{aligned}$$

with

$$y(t) = \begin{pmatrix} u(t) - \bar{u} \\ \sigma(t) - \bar{\sigma} \end{pmatrix}.$$

Standard estimates and the Gronwall lemma lead to the result. ■

4 Solution and Long Term Behavior

After solving the moment system (12), the transport equation (3) becomes linear and can be solved by the method of characteristics. Solution of the characteristic equations (1) subject to the initial conditions $\xi(0) = x$, $v(0) = y$ leads to the change of coordinates

$$\begin{pmatrix} \xi(x, y; t) \\ v(x, y; t) \end{pmatrix} = e^{At} \begin{pmatrix} x \\ y \end{pmatrix} + \int_0^t e^{A(t-s)} \begin{pmatrix} 0 \\ \kappa\xi_0 + u(s)/\tau - F/m(s) \end{pmatrix} ds, \quad (17)$$

where $A = \begin{pmatrix} 0 & 1 \\ -\kappa & -\beta \end{pmatrix}$ and $\beta = \eta + 1/\tau$. A formal computation gives the solution in terms of the new variables (x, y) :

$$\Psi = e^{\beta t - G(t)} (\Psi_0(x, y) + c(x, y, t)),$$

where $G(t) = \int_0^t g(u(s)) ds$ and

$$c(x, y, t) = \int_0^t e^{G(s) - \beta s} \delta(\xi(x, y; s)) \delta(v(x, y; s) - u(s)) f(u(s)) (N - m(s)) ds. \quad (18)$$

Because of the Delta distributions, this is only a formal representation. The solution can be interpreted as a time dependent bounded measure on \mathbb{R}^2 . Its action on a test function $\phi(\xi, v) \in C_B(\mathbb{R}^2)$ is given by

$$\begin{aligned} \langle \Psi(\cdot, \cdot, t), \phi \rangle &= e^{-G(t)} \int_{\mathbb{R}^2} \Psi_0(x, y) \phi(\xi(x, y; t), v(x, y; t)) d(x, y) \\ &+ \int_0^t e^{G(t-h) - G(t)} f(u(t-h)) (N - m(t-h)) \phi(\gamma_t(h)) dh, \end{aligned} \quad (19)$$

where $d(\xi, v) = \det(e^{At}) d(x, y) = e^{-\beta t} d(x, y)$ has been used as well as the definition

$$\gamma_t(h) := e^{Ah} \begin{pmatrix} 0 \\ u(t-h) \end{pmatrix} + \int_0^h e^{As} \begin{pmatrix} 0 \\ \kappa\xi_0 - F/m(t-s) + u(t-s)/\tau \end{pmatrix} ds, \quad (20)$$

for $0 \leq h \leq t$, of the state of a monomer at time t , which has been attached at time $t - h$.

From the first integral one can see that the influence of the initial condition Ψ_0 decays with time as a consequence of the positivity of the detachment rate. The second part of the solution is, at time t , concentrated on the curve $\{\gamma_t(h) : 0 \leq h \leq t\}$.

The long time limit of the solution will again be analyzed under the assumption of constant attachment and detachment rates. It can be written in terms of the formal limit of $\gamma_t(h)$:

$$\begin{aligned}\gamma_\infty(h) &= e^{Ah} \begin{pmatrix} 0 \\ \bar{u} \end{pmatrix} + \int_0^h e^{As} \begin{pmatrix} 0 \\ \frac{1}{2}\kappa\xi_0 + \bar{u}/\tau - F/\bar{m} \end{pmatrix} ds \\ &= e^{Ah} \begin{pmatrix} 0 \\ \bar{u} \end{pmatrix} - (1 - e^{Ah})A^{-1} \begin{pmatrix} 0 \\ \frac{1}{2}\kappa\xi_0 + \bar{u}/\tau - F/\bar{m} \end{pmatrix}.\end{aligned}\quad (21)$$

This is a curve in (ξ, v) -space connecting the points

$$\begin{pmatrix} 0 \\ \bar{u} \end{pmatrix} \quad \text{and} \quad \begin{pmatrix} \xi_0 + \bar{u}/(\kappa\tau) - F/(\kappa\bar{m}) \\ 0 \end{pmatrix}.$$

Theorem 3. *Let (2) and (7) hold. Then the global distributional solution Ψ of (3), (6) is given by (19) and is weakly continuous, mapping $t \in [0, \infty)$ to $\Psi(\cdot, \cdot, t) \in \mathcal{M}_1^+(\mathbb{R}^2)$. Let additionally $f(u)$ and $g(u)$ be constant and positive. Then $\lim_{t \rightarrow \infty} \Psi(\cdot, \cdot, t) = \bar{\Psi}$ with weak convergence in $\mathcal{M}_1^+(\mathbb{R}^2)$, where for all $\phi \in C_B(\mathbb{R}^2)$ (using (21)),*

$$\langle \bar{\Psi}, \phi \rangle = f(N - \bar{m}) \int_0^\infty e^{-gh} \phi(\gamma_\infty(h)) dh.$$

Proof. Weak continuity is equivalent to continuity of the right hand side of (19) with respect to t . This is a consequence of the continuity of $G(t)$, $\xi(x, y; t)$, $v(x, y; t)$, $u(t)$, $m(t)$, and $\gamma_t(h)$ with respect to t .

According to the right hand side of (19), we introduce the splitting $\Psi = \Psi_1 + \Psi_2$. Then, by the properties of the initial datum, $\lim_{t \rightarrow \infty} \Psi_1(\cdot, \cdot, t) = 0$ is obvious.

For the second part we choose $0 < t_1 < t$ and estimate

$$\begin{aligned}& |\langle \Psi_2(\cdot, \cdot, t) - \bar{\Psi}, \phi \rangle| \\ & \leq f \int_0^{t_1} e^{-gh} |(N - m(t-h))\phi(\gamma_t(h)) - (N - \bar{m})\phi(\gamma_\infty(h))| dh \\ & \quad + f \int_{t_1}^t e^{-gh} |(N - m(t-h))\phi(\gamma_t(h))| dh \\ & \quad + f(N - \bar{m}) \int_{t_1}^\infty e^{-gh} |\phi(\gamma_\infty(h))| dh.\end{aligned}$$

Obviously, the second and third terms on the right hand side can be made arbitrarily small by choosing t_1 large enough, using the boundedness of $m(t)$. For the first term we use that, due to Theorem 2, $\gamma_t(h)$ converges to $\gamma_\infty(h)$ and $m(t-h)$ to \bar{m} as $t \rightarrow \infty$, uniformly on bounded h -intervals. ■

5 Relation to the Huxley Model

The Huxley model describes the density of bound myosin heads $\rho_H(\xi, t)$ in dependence on position ξ and time t . It has the same interpretation as $\rho(\xi, t) := \int_{-\infty}^{\infty} \Psi(\xi, v, t) dv$ in the previous sections. Huxley's model reads

$$\partial_t \rho_H + u \partial_\xi \rho_H = f(\xi) (\rho_{max} - \rho_H) - g(\xi) \rho_H,$$

which still has to be supplemented by a model for the mean velocity $u(t)$.

Here a similar model will be derived from (3) in the limit $\tau \rightarrow 0$ of strong friction between the individual myosin tail and the myosin bundle. Note that τ is a relaxation time. The limit $\tau \rightarrow 0$ has to be understood as an approximation for τ small compared to other characteristic times appearing in the problem, such as typical values for the detachment relaxation time $g(u)^{-1}$.

We start with a formal argument. First we note that the moment system (12) and therefore also the moments $m(t)$, $u(t)$, and $\sigma(t)$, are independent from τ . Assume Ψ converges to $\tilde{\Psi}$ as $\tau \rightarrow 0$. Then, at least formally, (3) implies $\partial_v((u-v)\tilde{\Psi}) = 0$, which in turn has the consequence $(u-v)\tilde{\Psi} = 0$, by the requirement that $\tilde{\Psi}$ has zeroth and first order moments in v . Therefore the limiting distribution has to be of the form $\tilde{\Psi}(\xi, v, t) = \tilde{\rho}(\xi, t) \delta(v - u(t))$, implying a moment closure relation for the limiting flux:

$$\tilde{j} := \int_{-\infty}^{\infty} v \tilde{\Psi} dv = \tilde{\rho} u,$$

which could have been also obtained by passing to the limit in the momentum balance equation (10). Finally, passing to the limit in (8) leads to an equation similar to the Huxley model:

$$\partial_t \tilde{\rho} + u \partial_\xi \tilde{\rho} = \delta(\xi) f(u) (N - m) - g(u) \tilde{\rho}, \quad (22)$$

which has to be coupled to the equation for $u(t)$ from the moment system:

$$\dot{u} = \frac{\sigma}{m} - \eta u - \frac{F}{m}, \quad (23)$$

with the other moments computed from $\tilde{\rho}$:

$$m(t) = \int_{-\infty}^{\infty} \tilde{\rho}(\xi, t) d\xi, \quad \sigma(t) = \kappa \int_{-\infty}^{\infty} (\xi_0 - \xi) \tilde{\rho}(\xi, t) d\xi. \quad (24)$$

At this point it has to be noted that $\tilde{\Psi}$ is not able to satisfy general initial conditions. This is no surprise since the kinetic equation (3) is singularly perturbed with respect to the small parameter τ . An initial layer with the fast time scale $t' = t/\tau$ has to be expected. The problem for the initial layer approximation $\hat{\Psi}(\xi, v, t')$ reads

$$\partial_{t'} \hat{\Psi} + \partial_v((u_0 - v)\hat{\Psi}) = 0, \quad \hat{\Psi}(\xi, v, 0) = \Psi_0(\xi, v),$$

and has the solution

$$\hat{\Psi}(\xi, v, t') = e^{t'} \Psi_0(\xi, u_0 + (v - u_0)e^{t'}) \xrightarrow{t' \rightarrow \infty} \int_{-\infty}^{\infty} \Psi_0(\xi, v') dv' \delta(v - u_0), \quad (25)$$

which has the form of $\tilde{\Psi}$ and may therefore serve as its initial datum. The differential equations (22), (23) thus have to be solved subject to the initial conditions

$$\tilde{\rho}(\xi, 0) = \rho_0(\xi) := \int_{-\infty}^{\infty} \Psi_0(\xi, v) dv, \quad u(0) = u_0. \quad (26)$$

The solution of (22) is given by

$$\begin{aligned} \tilde{\rho}(\xi, t) &= e^{-G(t)} \rho_0(\xi - U(t)) \\ &+ \int_0^t f(u(s))(N - m(s)) \delta(\xi - U(t) + U(s)) e^{G(s) - G(t)} ds, \end{aligned} \quad (27)$$

with $U(t) := \int_0^t u(s) ds$. Finally, it is a standard procedure of singular perturbation theory to produce a uniformly valid approximation Ψ_{as} by adding the outer solution $\tilde{\Psi}$ and the layer solution $\hat{\Psi}$, and subtracting their common part:

$$\Psi_{as}(\xi, v, t) = \tilde{\rho}(\xi, t) \delta(v - u(t)) + \hat{\Psi}\left(\xi, v, \frac{t}{\tau}\right) - \rho_0(\xi) \delta(v - u_0). \quad (28)$$

We shall compare this with the exact solution of (3), (6), determined by (19). There the dependence on τ is hidden in the equations (17), (20), for the characteristics and for the curve $\{\gamma_t(h) : 0 \leq h \leq t\}$. The matrix exponential in these formulas corresponds to the solution of a singularly perturbed ODE system.

Lemma 1. *Let $A = \begin{pmatrix} 0 & 1 \\ -\kappa & -\beta \end{pmatrix}$ with $\beta = \eta + 1/\tau$. Then*

$$e^{At} = \begin{pmatrix} 1 & 0 \\ 0 & e^{-\beta t} \end{pmatrix} + \tau \begin{pmatrix} \kappa t & 1 - e^{-\beta t} \\ \kappa(e^{-\beta t} - 1) & 0 \end{pmatrix} + O(\tau^2), \quad (29)$$

as $\tau \rightarrow 0$, where the error term has to be understood uniformly on bounded t -intervals.

Proof. The matrix exponential could be computed directly. However, we consider it more instructive to perform a standard singular perturbation analysis of the corresponding ODE problem

$$\begin{aligned}\dot{\xi} &= v, & \xi(0) &= x, \\ \varepsilon \dot{v} &= -\varepsilon \kappa \xi - v, & v(0) &= y,\end{aligned}\tag{30}$$

as $\varepsilon = 1/\beta \rightarrow 0$. A formal asymptotic approximation of the solution will be carried out. Its validity is a classical result of singular perturbation theory, sometimes called the Tikhonov theorem (Tikhonov [1952]). We compute an asymptotic expansion of the solution, where each term is the sum of an outer contribution and an initial layer correction depending on the fast time variable $t' = t/\varepsilon$:

$$\begin{aligned}\xi(t) &= \bar{\xi}_0(t) + \varepsilon \left(\bar{\xi}_1(t) + \hat{\xi}_1(t/\varepsilon) \right) + O(\varepsilon^2), \\ v(t) &= \bar{v}_0(t) + \hat{v}_0(t/\varepsilon) + \varepsilon \left(\bar{v}_1(t) + \hat{v}_1(t/\varepsilon) \right) + O(\varepsilon^2).\end{aligned}\tag{31}$$

Note that, at leading order, no initial layer is expected in the slow variable ξ . The layer corrections are assumed to vanish away from the initial layer regions, i.e.,

$$\hat{\xi}_1(\infty) = \hat{v}_0(\infty) = \hat{v}_1(\infty) = 0.\tag{32}$$

The initial conditions lead to the requirements

$$\bar{\xi}_0(0) = x, \quad \bar{v}_0(0) + \hat{v}_0(0) = y, \quad \bar{\xi}_1(0) + \hat{\xi}_1(0) = 0, \quad \bar{v}_1(0) + \hat{v}_1(0) = 0.\tag{33}$$

Differential equations for the different contributions are derived by substituting the ansatz (31) into (30), writing the system first in terms of t and then in terms of t' , and comparing coefficients of powers of ε in both cases:

$$\begin{aligned}\dot{\bar{\xi}}_0 &= \bar{v}_0, & 0 &= \bar{v}_0, & \dot{\bar{\xi}}_1 &= \bar{v}_1, & \dot{\hat{v}}_0 &= -\kappa \bar{\xi}_0 - \bar{v}_1, \\ \frac{d\hat{\xi}_1}{dt'} &= \hat{v}_0, & \frac{d\hat{v}_0}{dt'} &= -\hat{v}_0, & \frac{d\hat{v}_1}{dt'} &= -\hat{v}_1.\end{aligned}\tag{34}$$

The problem (32)–(34) has the unique solution

$$\begin{aligned}\bar{\xi}_0(t) &= x, & \bar{v}_0(t) &= 0, & \hat{v}_0(t') &= e^{-t'} y, \\ \bar{\xi}_1(t) &= y - \kappa t x, & \hat{\xi}_1(t') &= -e^{-t'} y, & \bar{v}_1(t) &= -\kappa x, & \hat{v}_1(t') &= \kappa e^{-t'} x.\end{aligned}$$

Since $\begin{pmatrix} \xi(t) \\ v(t) \end{pmatrix} = e^{At} \begin{pmatrix} x \\ y \end{pmatrix}$, collecting these results already completes the proof, observing that $\varepsilon = 1/\beta = \frac{\tau}{1+\tau\eta} = \tau + O(\tau^2)$. ■

Theorem 4. Let Ψ be the weak solution of (3), (6), determined by (19). Then, for every $t > 0$,

$$\lim_{\tau \rightarrow 0} \langle \Psi(\cdot, \cdot, t), \phi \rangle = \langle \tilde{\Psi}(\cdot, \cdot, t), \phi \rangle, \quad \text{for all } \phi \in C_B(\mathbb{R}^2), \quad (35)$$

and for every $T > 0$ there exists $c > 0$ (independent from τ) such that

$$\sup_{0 < t < T} |\langle \Psi(\cdot, \cdot, t) - \Psi_{as}(\cdot, \cdot, t), \phi \rangle| \leq c\tau, \quad \text{for all } \phi \in C_B^2(\mathbb{R}^2). \quad (36)$$

Remark. The second result (36) is a uniform approximation result across the initial time layer with the expected approximation order. However, it is in a very weak topology, since twice differentiable test functions are needed. The first result (35) is using a stronger topology (weak convergence of measures), but does not provide a convergence rate and is only pointwise in $t > 0$ (ignoring the initial layer).

Proof. The first step in tracking the τ -dependence of (19) is the asymptotic expansion (29). Note that also $e^{-\beta t} = e^{-t/\tau} + O(\tau)$ holds. For the $(x, y) \leftrightarrow (\xi, v)$ coordinate change this implies

$$\begin{pmatrix} \xi(x, y; t) \\ v(x, y; t) \end{pmatrix} = \begin{pmatrix} x + U(t) \\ u(t) \end{pmatrix} + e^{-t/\tau} \begin{pmatrix} 0 \\ y - u_0 \end{pmatrix} + O(\tau(1 + |x| + |y|)). \quad (37)$$

Similarly the curve, where the second part of the solution concentrates, can be approximated:

$$\gamma_t(h) = \tilde{\gamma}_t(h) + O(\tau), \quad \tilde{\gamma}_t(h) = \begin{pmatrix} U(t) - U(t-h) \\ u(t) \end{pmatrix}. \quad (38)$$

The approximations (37) and (38) hold uniformly in t and h for bounded t -intervals and $0 \leq h \leq t$. In particular,

$$\lim_{\tau \rightarrow 0} \begin{pmatrix} \xi(x, y; t) \\ v(x, y; t) \end{pmatrix} = \begin{pmatrix} x + U(t) \\ u(t) \end{pmatrix}, \quad \lim_{\tau \rightarrow 0} \gamma_t(h) = \tilde{\gamma}_t(h),$$

pointwise in (x, y) and $t > 0$ and uniformly in $h \in [0, t]$. This implies pointwise convergence of the integrands in the two terms in (19). Since, obviously these integrands are integrable uniformly with respect to τ , (35) follows from the dominated convergence theorem by

$$\begin{aligned} \lim_{\tau \rightarrow 0} \langle \Psi(\cdot, \cdot, t), \phi \rangle &= e^{-G(t)} \int_{\mathbb{R}^2} \Psi_0(x, y) \phi(x + U(t), u(t)) d(x, y) \\ &+ \int_0^t e^{G(s)-G(t)} f(u(s))(N - m(s)) \phi(\tilde{\gamma}_t(t-s)) ds, \end{aligned}$$

where the right hand side is easily seen to be equal to $\langle \tilde{\Psi}(\cdot, \cdot, t), \phi \rangle$.

For $\phi \in C_B^2(\mathbb{R}^2)$, the above results imply immediately that the approximation error in the second term in (19) is $O(\tau)$, uniformly in t on bounded t -intervals. It therefore remains to analyze the first term containing the initial layer.

Analogously to the construction of Ψ_{as} , guided by (37), we approximate $\phi(\xi(x, y; t), v(x, y; t))$ by

$$\phi_{as}(x, y; t) = \phi(x + U(t), u(t)) + \phi\left(x, u_0 + e^{-t/\tau}(y - u_0)\right) - \phi(x, u_0).$$

In the identity

$$\begin{aligned} & \phi(\xi(x, y; t), v(x, y; t)) - \phi_{as}(x, y; t) \\ &= \phi\left(x + U(t), u(t) + e^{-t/\tau}(y - u_0)\right) - \phi_{as}(x, y; t) + O(\tau(1 + |x| + |y|)) \\ &= \int_0^t \left[u(s) \partial_\xi \phi\left(x + U(s), u(s) + e^{-t/\tau}(y - u_0)\right) \right. \\ & \quad \left. + \dot{u}(s) \partial_v \phi\left(x + U(s), u(s) + e^{-t/\tau}(y - u_0)\right) \right. \\ & \quad \left. - u(s) \partial_\xi \phi(x + U(s), u(s)) - \dot{u}(s) \partial_v \phi(x + U(s), u(s)) \right] ds \\ & \quad + O(\tau(1 + |x| + |y|)), \end{aligned}$$

the first equality follows from the Lipschitz continuity of ϕ , and the integrand on the right hand side can be bounded by $ce^{-t/\tau}(1 + |y|)$, both for $\phi \in C_B^2(\mathbb{R}^2)$. The estimate $te^{-t/\tau} \leq \tau/e$ then implies

$$\phi(\xi(x, y; t), v(x, y; t)) - \phi_{as}(x, y; t) = O(\tau(1 + |x| + |y|)).$$

Combining this with the assumption (7) that the initial datum for Ψ possesses first order moments leads to the conclusion that replacing $\phi(\xi(x, y; t), v(x, y; t))$ by $\phi_{as}(x, y; t)$ in (19) leads to an $O(\tau)$ error.

In (19), the product with $e^{-G(t)}$ can be approximated by

$$\begin{aligned} e^{-G(t)} \phi_{as}(x, y; t) &= e^{-G(t)} \phi(x + U(t), u(t)) + \phi\left(x, u_0 + e^{-t/\tau}(y - u_0)\right) \\ & \quad - \phi(x, u_0) + O(\tau(1 + |y|)). \end{aligned}$$

Now it is straightforward to show that the second and third term correspond to the second and third terms in Ψ_{as} , and the first term corresponds to the part of $\tilde{\Psi}$ caused by the initial data. ■

Returning to the limiting macroscopic density $\tilde{\rho}(\xi, t)$ given by (27), we observe that, even when the initial datum ρ_0 is regular, singularities will occur in the second contribution, whenever the bundle velocity vanishes at any time before t .

In the case of constant attachment and detachment rates f and, respectively, g , the moments converge as time tends to infinity, i.e. $m(t) \rightarrow \bar{m} =$

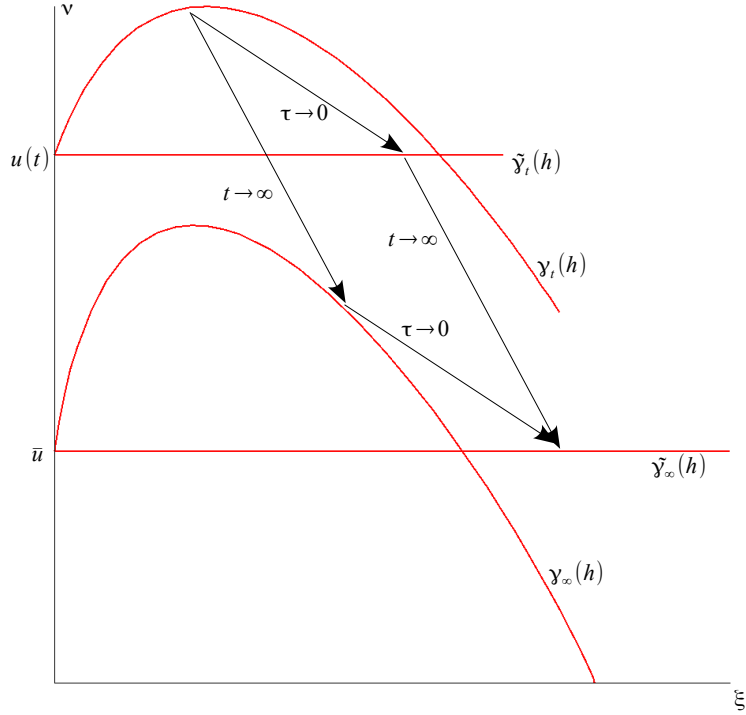


Figure 2: The commutative diagram for the support curve. Tildes denote limits as $\tau \rightarrow 0$.

$Nf/(f + g)$, $u(t) \rightarrow \bar{u}$. The macroscopic density $\tilde{\rho}(\xi, t)$ converges to

$$\bar{\rho}(\xi) = \frac{Nf}{f + g} \begin{cases} g/|\bar{u}|e^{-g\xi/\bar{u}}H(\xi\bar{u}), & \text{if } \bar{u} \neq 0, \\ \delta(\xi), & \text{if } \bar{u} = 0, \end{cases}$$

with the Heavyside function H . The second case occurs, when the stall force

$$F = \frac{\kappa\xi_0 Nf}{f + g}$$

is applied.

Finally, it should be mentioned that the limits $t \rightarrow \infty$ and $\tau \rightarrow 0$ commute. In particular, $\gamma_\infty(h)$ converges to $(h\bar{u}, \bar{u})$ as $\tau \rightarrow 0$, proving that $\bar{\Psi}(\xi, v)$ converges to $\bar{\rho}(\xi)\delta(v - \bar{u})$ as $\tau \rightarrow 0$. The commutative diagram is depicted in Figure 2 showing the different versions of the supporting (γ -)curve.

6 Discussion

The goal of this work is to provide a systematic connection between the microscopic interaction of single myosin heads with actin filaments and macroscopic relations such as stationary force-velocity equations in one comprehensive model containing both the mechanics and the reaction kinetics. Our

approach is, thus, obviously related to classical models such as the Hill equation for the force-velocity relation and the Huxley model. There are some differences between the Huxley model and the model derived in (22). First of all, Huxley assumes position dependent attachment/detachment rates, whereas we assume that attachment always occurs in the cocked position and that the detachment rate is position independent. We allow for a dependence of the rate on the velocity of the myosin bundle instead. The precise position dependence is actually not very important as shown by the discussion below.

A second difference is that Huxley's attachment term implies that an accumulation of attached heads at position ξ decreases the likelihood of other heads to attach at position ξ . Keeping in mind that ξ actually describes the conformation of the myosin head, this does not seem to be a likely scenario. The most important difference is that our model contains an account for the mechanics and therefore can predict the time dependent relative velocity of the myosin bundle and the actin filaments, which is the result of a stationary force balance (corresponding to the third equation in (16)) in the Huxley model.

The modeling presented above is in the spirit of Sorine et al. [2003] and Clement et al. [2007]. As opposed to Clement et al. [2007], we include the fact that the external force is distributed among the attached myosin heads. The attachment term in Clement et al. [2007] is in the spirit of the Huxley model, and the same criticism applies. Apart from that our model has the crucial advantage of a closed ODE system for the macroscopic quantities.

This moment system remains unchanged under various perturbations. One example is the strong friction limit of Section 5, which does not affect the moment system. Furthermore one could imagine a viscosity or slipping effect of bound myosin heads as suggested in Colli and Grasselli [1993]. This would cause the appearance of a second derivative with respect to position in the equation for the density of attached heads, which would again not affect the moment system.

Another perturbation would be to allow for heads to attach also at other conformations than the cocked state (as in the Huxley model). This could be caused by random vibrations of the detached heads. The Delta distribution in the attachment rate would then be replaced by a smooth distribution. Under the mild assumption that the latter is even with respect to the cocked state, the moment system would not be changed again.

The velocity dependence of the attachment and detachment rates may lead to nonlinear force-velocity relations. For example, it is reasonable to choose the attachment rate of myosin heads as a decaying function of the bundle velocity. For the simple choice $f(u) = a_0/u$ (where a_0 has the dimension of an acceleration) and $g = \text{const}$, the Hill equation (Hill [1938]) is

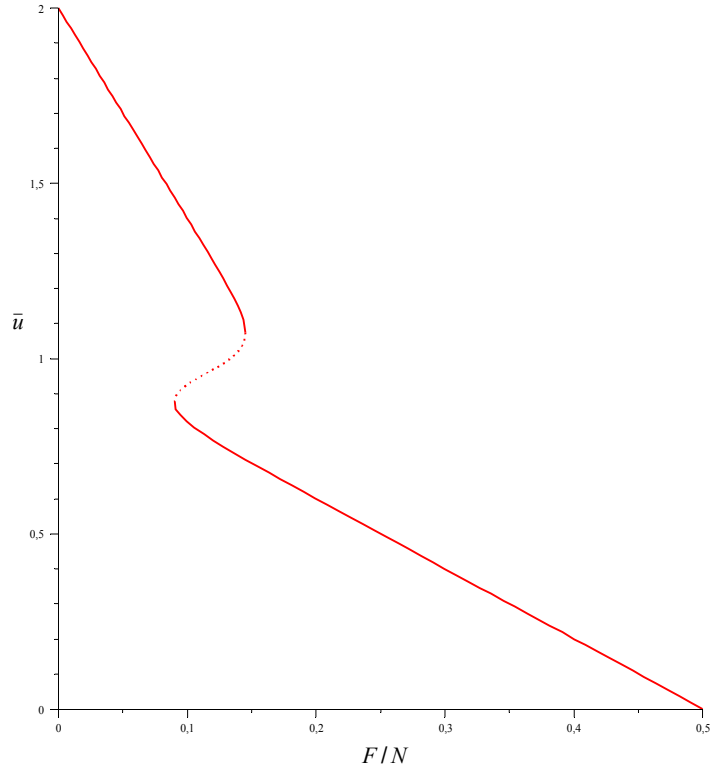


Figure 3: Stationary force-velocity relation (16) with attachment/detachment rates from (39) (with $\varepsilon = 0.1$), showing bistability and the corresponding hysteresis effect.

obtained from (16):

$$\bar{u} = \frac{a_0 g(\kappa \xi_0 - F/N)}{a_0 \kappa + a_0 \eta g + g^2 F/N}.$$

As the model with constant attachment/detachment rates, it features a stall force. However, instead of a linear dependence, the average velocity is now a convex function of the force.

In vitro experiments exhibit an instability for forces close to the stall force (Riveline et al. [1998]). With the choice $\kappa = \xi_0 = 1$, $\eta = 0$, and the rates

$$f(u) = 1, \quad g(u) = \frac{1}{2} \left(3 + \tanh \left(\frac{u-1}{\varepsilon} \right) \right), \quad (39)$$

with a small value of ε , (16) gives an S-shaped force-velocity curve with a bistable region leading to a hysteresis phenomenon as observed in Riveline et al. [1998] (see Figure 3). Note that $g(u)$ changes rapidly from the value 1 to the value 2 around $u = 1$. It is an increasing function of u , which is certainly a reasonable choice.

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