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Original Research Article

Generalized distribution-moment approximation for kinetic theories of muscular contraction

Graham M. Donovan

Department of Mathematics, University of Auckland, Auckland, 1142, New Zealand

A B S T R A C T

Crossbridge theory, originally developed by A.F. Huxley more than 60 years ago to explain the behaviour of striated muscle, has since evolved to encompass many different muscle types and behaviours. The governing equations are generally linear hyperbolic partial differential equations, or systems thereof, describing the evolution of probability density functions. Importantly, the macroscopic behaviour is often described not in terms of these distributions themselves, but rather in terms of their first few moments. Motivated by this observation, G.I. Zahalak proposed the distribution-moment approximation to describe the evolution of these moments alone. That work assumed a Gaussian underlying distribution, and was observed to provide reasonable approximation of the moments despite the non-Gaussian character of the underlying distribution. Here we propose two variations on the distribution-moment approximation: (i) a generalized N-moment approximation based on the Gram–Charlier A-series representation, and (ii) perhaps the simplest possible approximation based on a uniform distribution. Study of these variations suggests that Zahalak's original contention may be correct: approximations based on higher order moments may not be worth their complexity. However, the simplified variation shows more promise, with similar accuracy in approximating the moments yet reduced complexity in the derivation of the approximation.

1. Introduction

Mathematical formulation of sliding filament theory for muscle contraction originated with the seminal work of A.F. Huxley [1] and has since evolved to encompass many additional types and behaviours of muscle. In its most basic form, this so-called crossbridge model is a linear hyperbolic partial differential equation (PDE) describing the bond distribution; although it admits analytic solutions in a few (idealized) situations, often numerical solutions must be sought. This is particularly true in multi-scale modelling in which muscle behaviour is coupled with that of other structures (at tissue or organ scale, e.g. [2]). Although some care must be taken to avoid artificial dispersion in the numerical scheme, in general this can be done by using the method of characteristics to reduce the governing PDE to a system of ordinary differential equations (ODEs) along the characteristics. (Here the characteristics essentially describe the changes in muscle length). When doing so, the size of the system of ODEs, and hence the computational cost, is determined by the spatial resolution of the bond distribution. In practice, the system size is often in the hundreds or thousands. Other numerical schemes are possible as well, for example finite-volume methods [2].

One approach to reducing this computational cost while retaining the underlying dynamics is the distribution moment (DM) approximation due to G.I. Zahalak [3]. The central notion is to exploit the facts that (i) the solution is a distribution and (ii) that the moments of this distribution are the key quantities of interest. The DM approximation thus derives equations for the evolution of the bond distribution moments, directly from the original governing PDE, by making an assumption about the form of the distribution. Zahalak's original approach assumes a Gaussian distribution and thus describes the evolution of the first three moments[1] using three ODEs. Despite the fact that the underlying bond distribution is not close to Gaussian ("a rather crude model", in Zahalak's phrase [3]), the resulting moment dynamics generate sufficiently accurate approximations to be useful in many situations [4–8].

Although this approach is sometimes referred to as *the* distribution-moment approximation, it should perhaps instead be thought of as *a* distribution-moment approximation. As Zahalak noted, the same method could be employed with different assumptions about the underlying distribution, potentially describing as many moments as desired. The Gaussian form proposed is thought to offer a reasonable trade-off in terms of accuracy and complexity of the approximation. In this manuscript we propose and analyse two additional forms of DM approximation: (i) a generalized N-moment form based on the Gram–Charlier A-series expansion, and (ii) a simplified three moment approximation based on the uniform distribution. In doing so we are able to offer further insights about suitable assumptions for the bond distribution, and the relevant trade-offs between complexity of the approximation and its accuracy.

E-mail address: g.donovan@auckland.ac.nz.

[1] Here a "distribution" is not required to have its zeroth moment (or area under the distribution) be 1; thus the third parameter describing a Gaussian, in addition to the usual mean and standard deviation.

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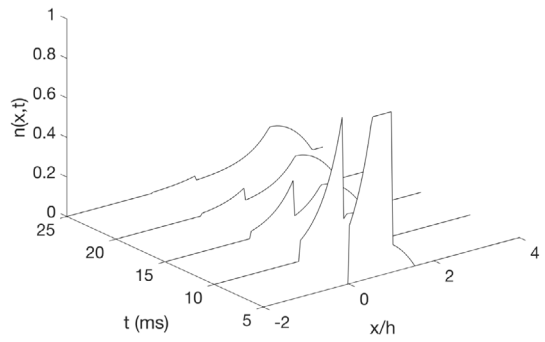

Fig. 1. Example of bond distribution solutions to Huxley model during constant stretch. Observe that the solution is neither dispersive, nor particularly close to Gaussian. (Note that these conditions are identical to those of Fig. 2 in Ref. [3].)

2. Models

2.1. The Huxley crossbridge model

Here we provide a brief overview of the Huxley crossbridge model [1] for context. Much has been written on this subject and its extensions, and we make no attempt to be exhaustive on the subject; for additional details the reader is referred to [1,3,9].

The bond distribution $n(x,t)$ describes the fraction of attached crossbridges at time t and displacement x. Under the assumption of simple first-order kinetics with attachment rate $f(x)$ and detachment rate $g(x)$, we have

$$\frac{\partial n}{\partial t} - v(t)\frac{\partial n}{\partial x} = f(x) - [f(x)+g(x)]\,n \tag{1}$$

where $v(t)$ is the muscle shortening velocity, $f(x)$ is the binding (forward) rate, and $g(x)$ is the unbinding (backward) rate. The binding and unbinding rate functions f and g are typically piecewise linear. In what follows, generalization to piecewise polynomial binding rate functions is simple, and other adaptations will be discussed later. A typical solution to the Huxley model during constant stretch (e.g. $v(t) =$ constant) is shown in Fig. 1, as solved by the method of characteristics with 500 points in the spatial resolution of the distribution (and hence 500 ODEs).

Importantly, the quantities of interest arising from this equation are not the bond distribution n itself, but rather macroscopic properties such as the force, which is proportional to $\int_{-\infty}^{\infty} xn(x,t)\,dx$ and hence the first moment of n, and the stiffness, proportional to the zeroth moment.

2.2. Distribution moment approximation of the Huxley model

Here we provide a brief synopsis of Zahalak's DM approximation method [3]. Defining the raw moments

$$M_\lambda(t) = \int_{-\infty}^{\infty} x^\lambda n(x,t)\,dx \tag{2}$$

for $\lambda = 0, 1, \ldots$, we begin by multiplying Eq. (1) by x^λ and integrating to obtain

$$\int_{-\infty}^{\infty} x^\lambda \frac{\partial n}{\partial t}\,dx - v(t)\int_{-\infty}^{\infty} x^\lambda \frac{\partial n}{\partial x}\,dx = \int_{-\infty}^{\infty} x^\lambda f(x)\,dx - \int_{-\infty}^{\infty} x^\lambda [f(x)+g(x)]\,n(x,t)\,dx. \tag{3}$$

Integrating the second term on the left-hand side by parts, and defining the constants $b_\lambda = \int_{-\infty}^{\infty} x^\lambda f(x)\,dx$, we find

$$M_\lambda' + v(t)\lambda M_{\lambda-1} = b_\lambda - \int_{-\infty}^{\infty} x^\lambda [f(x)+g(x)]\,n(x,t)\,dx. \tag{4}$$

At this point no approximation has been made. In order to evaluate the integral term on the right-hand side we make an assumption about the form of $n(x,t)$. In the following section we describe Zahalak's method based on a Gaussian assumption, before proceeding to generalizations (and simplifications). However it is useful to note at this point the general requirements: we seek to write this integral in terms of the moments M_λ. Under the assumption that f and g are piecewise polynomial, the integral can be expanded to terms of the form $\int_{c_1}^{c_2} x^m n(x,t)\,dx$ for $m \in \mathbb{Z}^{\geq 0}$, and their limits as $c_1 \to -\infty$ and/or $c_2 \to \infty$. Thus useful assumed forms of n will allow for *explicit* evaluation of these integrals in terms of the moments M_λ.

2.2.1. Zahalak's Guassian DM approximation

The original version of the DM approximation from [3] assumes a Gaussian distribution for $n(x,t)$. Despite the fact that the bond distributions are often not close to Gaussian (see Fig. 1), this can result in a surprisingly accurate approximation. Although full details are given in Ref. [3], we provide a brief review here to the extent that it motivates the generalized and simplified approaches presented in the following sections.

In order to evaluate the integral on the RHS of Eq. (4) we expand in terms of the form $\int_{c_1}^{c_2} x^m n(x,t)\,dx$. Assuming a Gaussian form for n yields

$$\int_{c_1}^{c_2} x^m n(x,t)\,dx = \int_{c_1}^{c_2} x^m e^{-(x-p)^2/2q^2}\,dx \tag{5}$$

where the parameters p and q describe the Gaussian distribution.

Consider then a series of integrals of the form

$$I_k(\eta) = \frac{1}{\sqrt{2\pi}}\int_{-\infty}^{\eta} x^k e^{-x^2/2}\,dx. \tag{6}$$

Integrating by parts yields the recurrence relation

$$I_{k+1}(\eta) = kI_{k-1}(\eta) + \eta^k I_1 \tag{7}$$

with

$$I_0(\eta) = \frac{1}{\sqrt{2\pi}}\int_{-\infty}^{\eta} e^{-x^2/2}\,dx = \mathrm{erf}(\eta) \tag{8}$$

where $\mathrm{erf}(\cdot)$ denotes the usual error function [10], and

$$I_1(\eta) = -e^{-\eta^2/2}/\sqrt{2\pi}. \tag{9}$$

This then allows expression of the partial moments of the standard Gaussian. We rescale to account for the distribution parameters p and q as follows. Beginning with

$$J_k(\xi) = \frac{1}{\sqrt{2\pi}q}\int_{-\infty}^{\xi} x^k e^{-(x-p)^2/(2q^2)}\,dx \tag{10}$$

we apply the change of variables $\zeta = (x-p)/q$ and $\eta = (\xi - p)/q$ to arrive at

$$J_k(\eta) = \frac{1}{\sqrt{2\pi}q}\int_{-\infty}^{\eta} (p+q\zeta)^k e^{-\zeta^2/2}\,d\zeta. \tag{11}$$

By expanding the polynomial $(p+q\zeta)^k$ and use of the recurrence relation (7) these can then be expressed in terms of $I_0 \ldots I_k$. The first few are given by

$$J_0(\eta) = \frac{1}{\sqrt{2\pi}q}\int_{-\infty}^{\eta} (p+q\zeta)^0 e^{-\zeta^2/2}\,d\zeta = I_0(\eta)$$

$$J_1(\eta) = \frac{1}{\sqrt{2\pi}q}\int_{-\infty}^{\eta} (p+q\zeta)^1 e^{-\zeta^2/2}\,d\zeta = pI_0 + qI_1$$

$$J_2(\eta) = \frac{1}{\sqrt{2\pi}q}\int_{-\infty}^{\eta} (p+q\zeta)^2 e^{-\zeta^2/2}\,d\zeta = p^2 I_0 + 2pqI_1 + q^2 I_2$$
$$= p^2 I_0 + 2pqI_1 + q^2(I_0 + \eta I_1) = (p^2+q^2)I_0 + (2pq + q^2\eta)I_1$$

Subsequent terms can be expanded and simplified by recursion in the same way; ultimately all $J_k(\eta)$ are expressible in terms of I_0 and I_1 (along with polynomial terms in p, q and η).

Now we can approximate the original integral of interest

$$\int_{-\infty}^{\infty} x^{\lambda}\,[f(x)+g(x)]\,n(x,t)\,dx. \tag{12}$$

For concreteness we will use the "standard" forms [1,3] of $f(x)$ and $g(x)$

$$f(x)=\begin{cases} 0, & x<0 \\ f_1 x, & 0<x<1 \\ 0, & x>1 \end{cases} \tag{13}$$

and

$$g(x)=\begin{cases} g_2, & x<0 \\ g_1 x, & 0<x<1 \\ g_1 x+g_3(x-1), & x>1 \end{cases} \tag{14}$$

but it is simple to adapt to other piecewise polynomial formulations. Often the spatial variable is scaled everywhere as x/h; here for convenience we have set $h=1$. Throughout we use Zahalak's "unmodified" parameter values $f_1 = 43.3\ \mathrm{s}^{-1}$, $g_1 = 10\ \mathrm{s}^{-1}$, $g_2 = 209\ \mathrm{s}^{-1}$ and $g_3 = 0$ [3]. Now we have $n(x,t) = \frac{M_0}{\sqrt{2\pi}q} e^{-(x-p)^2/2q^2}$ with $p = M_1/M_0$ and $q = \sqrt{M_2/M_0 - (M_1/M_0)^2}$ and Eq. (12) becomes

$$\begin{aligned}\phi_\lambda &\equiv \int_{-\infty}^{\infty} x^{\lambda}\,[f(x)+g(x)]\,\frac{M_0}{\sqrt{2\pi}q} e^{-(x-p)^2/2q^2}\,dx \\ &= M_0 g_2 \int_{-\infty}^{0} x^{\lambda} e^{-(x-p)^2/2q^2}\,dx + M_0(f_1+g_1)\int_0^1 x^{\lambda+1} e^{-(x-p)^2/2q^2}\,dx \\ &+ M_0(g_1+g_3)\int_1^{\infty} x^{\lambda+1} e^{-(x-p)^2/2q^2}\,dx - M_0 g_3 \int_1^{\infty} x^{\lambda} e^{-(x-p)^2/2q^2}\,dx.\end{aligned}$$

These integrals can now be expressed in terms of $J_k(\eta)$ by taking appropriate intervals and differences yielding

$$\begin{aligned}\phi_\lambda/M_0 &= g_2 J_\lambda(-p/q) + (f_1+g_1)\left(J_{\lambda+1}\left(\frac{1-p}{q}\right) + J_{\lambda+1}(-p/q)\right) \\ &+ (g_1+g_3)\left(\Lambda_{\lambda+1} - J_{\lambda+1}\left(\frac{1-p}{q}\right)\right) \\ &- g_3\left(\Lambda_{\lambda+1} - J_\lambda\left(\frac{1-p}{q}\right)\right)\end{aligned}$$

where $\Lambda_m = \lim_{\eta\to\infty} J_m(\eta)$. Note that $\lim_{\eta\to\infty} I_0(\eta) = 1$ and $\lim_{\eta\to\infty} I_1(\eta) = 0$.

Finally we have

$$M_\lambda' + v(t)\lambda M_{\lambda-1} = b_\lambda - \phi_\lambda(M_0, M_1, M_2) \tag{15}$$

and the system of three equations to define the time evolution of the moments M_0, M_1, M_2 of the Gaussian is

$$\begin{aligned} M_0' &= b_0 - \phi_0(M_0, M_1, M_2) \\ M_1' + v(t)M_0 &= b_1 - \phi_1(M_0, M_1, M_2) \\ M_2' + 2v(t)M_1 &= b_2 - \phi_2(M_0, M_1, M_2)\end{aligned}$$

where ϕ_λ is defined in terms of J_λ and $J_{\lambda+1}$ as above, which in turn are expressed in terms of I_0 and I_1 and hence ultimately in terms of the error function.

It is worth observing that the key benefit of the Gaussian here is the ability to express the partial moments explicitly in terms of the raw moments, e.g. that ϕ_λ can be written in terms of M_0, M_1, M_2.

2.2.2. N-moment Gram–Charlier A-series approximation

A generalized approximation can be constructed by using the Gram–Charlier A-series to represent the bond distribution as an infinite sum in terms of its moments. Using this representation, we write

$$\hat{n}(x) = \sum_{j=0}^{\infty} c_j H_j(x-\hat{\mu}_1)\alpha(x-\hat{\mu}_1) \tag{16}$$

where the coefficients c_j can be expressed in terms of the moments about the mean $\hat{\mu}_0 \ldots \hat{\mu}_j$, $H_j(\cdot)$ are the Hermite polynomials, and α is the standard normal distribution [11].

This a true distribution, whereas the bond distribution is allowed its zeroth moment to differ from 1, so we scale as $n(x,t) = M_0(t)\hat{n}(x,t)$. Conceptually it is clear that the same techniques that were used for the Gaussian assumption should apply in the case of this representation: because f, g and H_j are polynomial or piecewise polynomial in x, and α is a Gaussian, ultimately everything can be expressed as partial moments of a Gaussian distribution.

Truncating the Gram–Charlier expansion at N terms yields, for $\lambda = 0, 1$

$$\hat{\phi}_\lambda \equiv \int_{-\infty}^{\infty} x^{\lambda}\,[f(x)+g(x)]\,M_0(t)\sum_{j=0}^{N} c_j H_j(x-\hat{\mu}_1)\alpha(x-\hat{\mu}_1)\,dx \tag{17}$$

and for $\lambda \geq 2$

$$\hat{\phi}_\lambda \equiv \int_{-\infty}^{\infty} (x-\mu_1)^{\lambda}\,[f(x)+g(x)]\,M_0(t)\sum_{j=0}^{N} c_j H_j(x-\hat{\mu}_1)\alpha(x-\hat{\mu}_1)\,dx \tag{18}$$

where μ_1 is the first moment of $n(x,t)$ and $\hat{\mu}_k$ are the moments about the mean of $\hat{n}$. The two are related by $\mu_k = M_0\hat{\mu}_k$. We expand explicitly for $N = 3$, e.g. capturing the first four moments

$$\begin{aligned}&\hat{\phi}_\lambda = \\ &\int_{-\infty}^{\infty} (x-\mu_1)^{\lambda}\,[f(x)+g(x)]\,M_0(t)\alpha(x-\hat{\mu}_1) \\ &\times\left[1 + \frac{1}{2}(\hat{\mu}_2-1)H_2(x-\hat{\mu}_1) + \frac{1}{6}\hat{\mu}_3 H_3(x-\hat{\mu}_1)\right]dx\end{aligned}$$

where $H_2(x) = x^2 - 1$ and $H_3(x) = x^3 - 3x$ are the usual Hermite polynomials. Despite the more complicated appearance, this can be handled in the same way as previously: α is a Gaussian, and all other terms are piecewise polynomial; thus everything can be expanded and expressed in terms of partial moments of a Gaussian. Following this procedure produces

$$\begin{aligned} \mu_0' &= b_0 - \boldsymbol{\Phi}_0 \\ \mu_1' + v(t)\mu_0 &= b_1 - \boldsymbol{\Phi}_1 \\ \mu_2' + 2v(t)\mu_1 - 2\mu_1'\mu_1 &= b_2 - 2\mu_1 b_1 + \mu_1^2 b_0 - \left[\boldsymbol{\Phi}_2 - \mu_1\boldsymbol{\Phi}_1 + \mu_1^2\boldsymbol{\Phi}_0\right] \\ \mu_3' + 3v(t)\mu_2 - 3\mu_1'\mu_2 &= b_3 - 3\mu_1 b_2 - 3\mu_2 b_1 - \mu_1^3 b_0 \\ &\quad - \left[\boldsymbol{\Phi}_3 - 3\mu_1\boldsymbol{\Phi}_2 + 3\mu_1^2\boldsymbol{\Phi}_1 - \mu_1^3\boldsymbol{\Phi}_0\right]\end{aligned}$$

where

$$\begin{aligned}\boldsymbol{\Phi}_\lambda = M_0 \Bigg[&\frac{\hat{\mu}_3}{6}\phi_{\lambda+3}(1,\hat{\mu}_1,1+\hat{\mu}_1^2) + \frac{1}{2}(\hat{\mu}_2+\hat{\mu}_1\hat{\mu}_3-1)\phi_{\lambda+2}(1,\hat{\mu}_1,1+\hat{\mu}_1^2) \\ &+ \left(\frac{\hat{\mu}_3}{2}(\hat{\mu}_1^2-1) - \hat{\mu}_1(\hat{\mu}_2-1)\right)\phi_{\lambda+1}(1,\hat{\mu}_1,1+\hat{\mu}_1^2) \\ &+ \left(1 + \frac{\hat{\mu}_2-1}{2}(\hat{\mu}_1^2-1) + \frac{\hat{\mu}_3}{6}(3\hat{\mu}_1^2-\hat{\mu}_1^3)\phi_\lambda(1,\hat{\mu}_1,1+\hat{\mu}_1^2)\right)\Bigg]\end{aligned}$$

and b_λ and ϕ_λ are as previously defined for the Gaussian case. Note that this now involves terms up to $\boldsymbol{\Phi}_3$, hence up to ϕ_6 and J_7; these can be expanded and simplified following the same method as in Section 2.2.1. The expansion truncated at $N = 2$ terms can be obtained from this by setting $\hat{\mu}_3 \equiv 0$. We have opted to express this system in terms of the moments about the mean μ_k rather than the raw moments M_k, however it is simple to covert between the two, or the system can also be formulated in terms of the latter.

2.2.3. Three-moment uniform approximation

In the previous section we derived a generalized approximation accounting for the first N moments based on a truncated Gram–Charlier A series expansion. Here we consider a simpler approach: motivated by Zahalak's observation that the Gaussian DM approximation is effective at approximating the moments despite the underlying bond distributions being substantially non-Gaussian, we also consider the simplest possible assumption: that the bond distribution is uniform. Allowing the zeroth moment to vary gives a three parameter distribution which can be explicitly parameterized in terms of the first three moments.

The potential advantage arises from the fact that all terms are now piecewise polynomial, with no need to expand the partial moments of the Gaussian in terms of the error function.

Hence we take

$$n(x,t) = \begin{cases} \frac{M_0^2}{2\sqrt{3}\sqrt{M_0M_2 - M_1^2}}, & x \in \left[\frac{M_1}{M_0} - \frac{\sqrt{3}}{M_0}\sqrt{M_0M_2 - M_1^2}, \frac{M_1}{M_0} + \frac{\sqrt{3}}{M_0}\sqrt{M_0M_2 - M_1^2}\right], \\ 0, & \text{otherwise} \end{cases} \tag{19}$$

for which $\int_{-\infty}^{\infty} x^\lambda n(x,t)\,dx = M_\lambda(t)$ for $\lambda = 0, 1, 2$. Then we can write the partial moments in terms of

$$\int_{c_1}^{c_2} x^\lambda n(x,t)\,dx = \frac{1}{\lambda+1}\frac{M_0^2}{2\sqrt{3}\sqrt{M_0M_2 - M_1^2}}\left[x^{\lambda+1}\right]\Big|_{x=min(max(x_0-\Delta,c_1),x_0+\Delta)}^{max(min(x_0+\Delta,c_2),x_0-\Delta)} \tag{20}$$

$$\equiv \hat{J}_\lambda\left(M_0, M_1, M_2; c_1, c_2\right) \tag{21}$$

where $x_0 = \frac{M_1}{M_0}$ and $\Delta = \frac{\sqrt{3}}{M_0}\sqrt{M_0M_2 - M_1^2}$ and so

$$\begin{aligned} \bar{\phi}_\lambda &= g_2\int_{-\infty}^{0} x^\lambda n\,dx + (f_1+g_1)\int_0^1 x^{\lambda+1} n\,dx \\ &+ (g_2+g_3)\int_1^\infty x^{\lambda+1} n\,dx - g_3\int_1^\infty x^\lambda n\,dx \\ &= g_2 \lim_{c_1\to-\infty} \hat{J}_\lambda(M_0, M_1, M_2; c_1, 0) + (f_1+g_1)\hat{J}_{\lambda+1}(M_0, M_1, M_2; 0, 1) \\ &+ \lim_{c_2\to+\infty}\left[(g_2+g_3)\hat{J}_{\lambda+1}(M_0, M_1, M_2; 1, c_2) - g_3\hat{J}_\lambda(M_0, M_1, M_2; 1, c_2)\right]. \end{aligned}$$

While at first this appears rather complicated due to the limits, these are trivial to implement because Eq. (20) is always evaluated at finite bounds: in the limit as $c_2 \to \infty$ the upper evaluation becomes $[\cdot]|^{x=x_0+\Delta}$ and in the limit as $c_1 \to -\infty$ the lower evaluation becomes $[\cdot]|_{x=x_0-\Delta}$. Finally we have the complete set of governing equations

$$\begin{aligned} M_0' &= b_0 - \bar{\phi}_0 \\ M_1' + v(t)M_0 &= b_1 - \bar{\phi}_1 \\ M_2' + 2v(t)M_1 &= b_2 - \bar{\phi}_2. \end{aligned}$$

3. Results

We demonstrate these methods using two typical situations: a constant velocity stretch, and oscillatory stretching. In both cases we use the protocols of [3] for consistency of comparisons. All approximations are solved numerically using the same adaptive timestepping 4th-order Runge–Kutta approach.

3.1. Constant velocity stretch

Following Zahalak we consider a constant velocity stretch with $v/h = \pm 10\ \text{s}^{-1}$. Each approximation is computed and compared with the method of characteristics solution for the full PDE. Results are shown in Fig. 2. The upper panels show the time evolution of the first three moments M_0, M_1 and M_2. The lower panels compare the implied approximate distributions to the "true" method of characteristics distribution at various time points (as labelled).

As Zahalak observed, the DM approximation with a Gaussian distribution offers reasonable agreement in the moments, despite deviation in the underlying distribution. Perhaps surprisingly, the DM approximation with the uniform distribution might be described in exactly the same terms. The generalized approximation, on the other hand, appears to offer no benefit.

The constant velocity scenario in contraction, e.g. with a change of sign for the constant $v(t)$, is shown in Fig. 3. The same basic conclusions are in evidence: the uniform assumption performs at least as well as the Gaussian, both of which track the true solution with reasonable accuracy; the generalized approach again offers no benefit.

3.2. Oscillatory length

The length profile of the oscillatory regime is $v(t) = v_0\sin(2\pi\omega t)$ with $v_0/h = 25\ \text{s}^{-1}$ and $\omega = 8\ \text{s}^{-1}$. The results are shown in Fig. 4 using the same layout as Fig. 2, except that the $N = 3$ version of the generalized approach is not shown — in places the deviation is sufficiently large that the axis scale makes it difficult to visualize the other methods.

Here the same basic conclusion is present: the DM approximations based on Gaussian and uniform underlying distributions offer surprisingly good approximations of the macroscopic moments, despite disagreement in the underlying distribution itself. In considering the accuracy of the approximation, one should also consider the computational cost. Though all of the DM approaches involve a substantial reduction in the dimensionality of the ODE system to be solved, other considerations may be at play, for example the cost of evaluating the error functions. In terms of total CPU time, all of the DM approximations offer at least an order of magnitude speedup relative to the method of characteristics solution with 500 points in the spatial resolution of the bond distribution. The uniform distribution is the most efficient, offering more than two orders of magnitude improvement, followed closely by the Gram–Charlier approach with $N = 2$ also offer about two orders of magnitude improvement. Zahalak's Gaussian DM is next best, and finally the Gram–Charlier with $N = 3$ offers about one order improvement. The generalized approach based on the Gram–Charlier A-series appears to offer no particular benefit. The reasons for, and potential resolution of this, are discussed in the following section.

3.3. Error analysis

A systematic analysis of the approximation errors for the DM approaches based on Gaussian and uniform approximations are shown in Fig. 5. The left panel gives the total error in the first two moments, while the right panel shows the total error in the distribution itself. While the moments are the key macroscopic observables, examination of the distribution error helps to understand the behaviour of these two approximations. For very low frequencies, the distribution is close to steady state and so well-approximated by a uniform distribution: hence the small total errors in both moments and distribution error for the uniform approximation in this range. As the frequency increases the distribution shape deviates farther from steady state, and as such both error types rise. Eventually this increases to the point where the Gaussian approximation has superior performance, if only for a relatively small frequency window. Indeed this window only occurs at all when v_0 has been increased relative to that used in Section 3.2. At $v_0/h = 25\ \text{s}^{-1}$ (the value used previously) the uniform approximation is preferred throughout this frequency range.

This suggests that the intuitive explanation applies: the uniform approximation is preferred in situations where the underlying distribution is relatively close to uniform, and the Gaussian approximation is advantageous where the underlying distribution is better represented by a Gaussian. Moreover, because the steady state distribution is uniform, the former situation might be expected to occur in situations relatively close to steady state (e.g. with low muscle velocities) and the latter to occur more often where absolute muscle velocity is higher.

A similar analysis was performed to assess the sensitivity to the binding rate parameters. A sensitivity analysis covering ±40% in the binding rate parameters produced error analysis results which were qualitatively the same as those shown here.

4. Discussion and conclusions

The principle benefit of the distribution moment approximation method is that it provides a systematic means of reduction from the original governing PDE to ODEs for the macroscopic observables; of course there are many proposed ODE models (e.g. [12]), but these cannot in general be connected with the original crossbridge PDE.

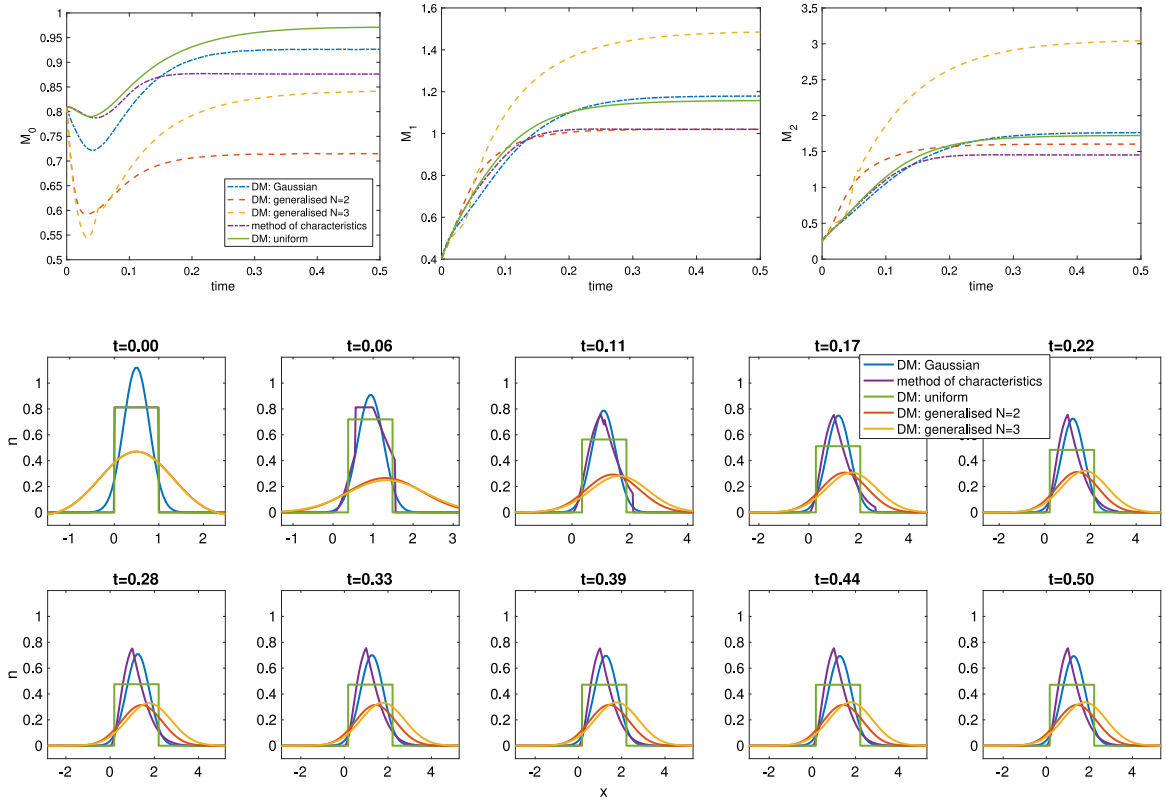

Fig. 2. Comparison of approximation methods for a constant velocity stretch. Upper panels show the time evolution of the first three moments M_0, M_1 and M_2. Lower panels compare the implied approximate distributions to the "true" method of characteristics distribution at various time points (as labelled).

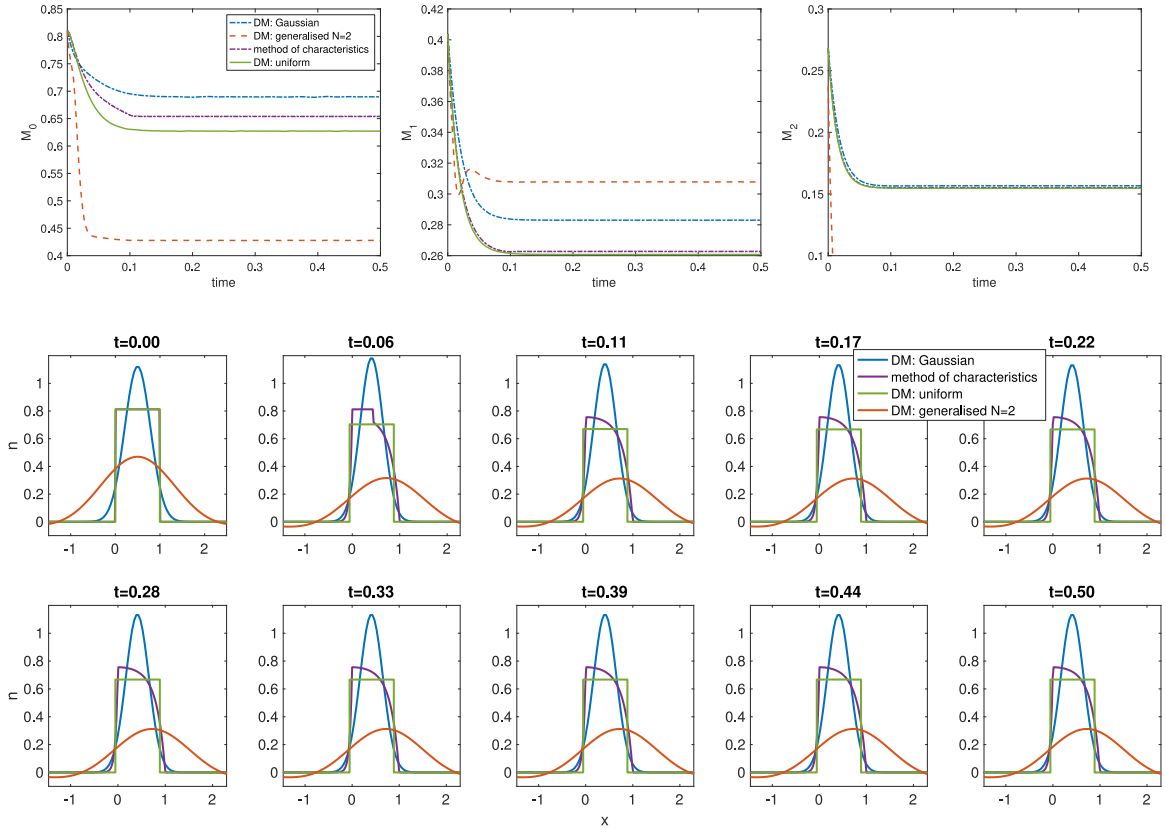

Fig. 3. Comparison of approximation methods for a constant velocity shortening. Layout as in Fig. 2. Note that the $N = 3$ version of the generalized approximation is not shown (see text), and that in the M_2 panel the y-axis range has been chosen to exclude much of the generalized approximation so as to capture the behaviour of the more accurate approximations.

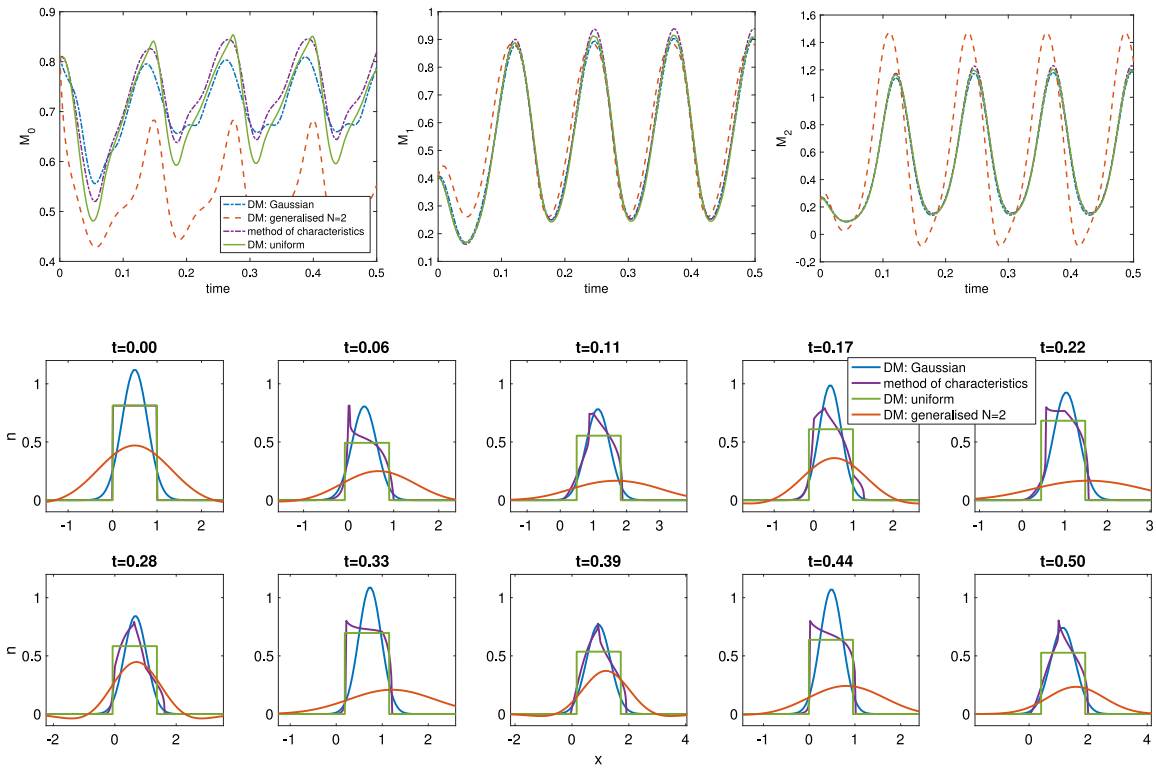

Fig. 4. Comparison of approximation methods for oscillatory stretch. Layout as in Fig. 2. Note that the $N = 3$ version of the generalized approximation is not shown (see text).

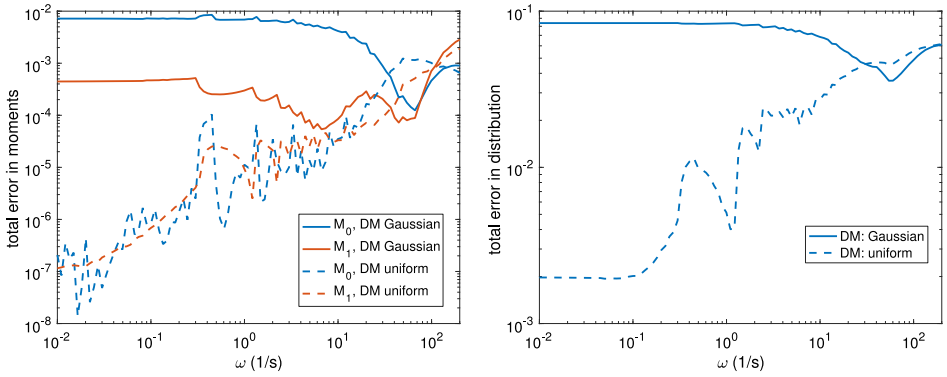

Fig. 5. Systematic analysis of moment errors (left panel) and distribution error (right panel) comparing each approximation with the method of characteristics solution in the oscillatory length protocol as the frequency is varied. Here $v_0/h = 100\ \mathrm{s}^{-1}$.

In this manuscript two variations of Zahalak's distribution moment approximation are developed: an N-moment approximation based on the Gram–Charlier A series, intended to allow generalization of the DM method, and a simplified version based on a uniform distribution. Both are compared with Zahalak's Gaussian DM, and the method of characteristics, using the Huxley crossbridge model as a test case. These results suggest that while the generalized method offers no additional benefit, the uniform DM approximation offers a similar level of macroscopic approximation with reduced complexity of derivation. It might thus be considered as a viable alternative to the Gaussian DM in applications. In particular the error analysis suggests that the uniform approximation is particularly useful in situations in which a low muscle velocity leads to an underlying bond distribution which is close to steady state; the Gaussian approximation can be favoured in situations further from equilibrium.

In his original paper [3], Zahalak noted that generalizations were possible, but predicted that the Gaussian assumption provided an optimal balance, and that generalizations to higher moments would not be worthwhile relative to their complexity. To a certain extent, this appears to be borne out, though with two caveats: (i) that the simpler uniform assumption may preferable in some circumstances, and (ii) that while the generalization presented here offers no further benefits, there remain several potential avenues of improvement.

One overarching problem with the generalized N moment approximation is that the distribution is not confined to a bounded interval and so the distribution is not necessarily uniquely defined, even with the inclusion of all moments [13]. Leaving aside this technical point, here the difficulty is almost certainly related to the behaviour of the truncated expansion. Indeed the truncated Gram–Charlier A-series does not have optimal behaviour, and for this reason the Edgeworth series is preferred in many contexts.[2] Thus it remains possible that an approximation based on the truncated Edgeworth series, which also

[2] The two series are identical up to the ordering of the terms [11], but this has important consequences for the stability of the approximation when truncating the series [14].

allows expression of the distribution in terms of its moments, might offer a route to generalization. Another possible improvement to the Gram–Charlier approach would be to appropriately scale the spatial variables at the approximation stage to match the standard deviation of $\hat{n}$ to that of α. However, it seems likely that Zahalak's contention was correct: higher order moment approximations may not be worth their complexity. This is particularly true in light of the computational cost: a coarser method of characteristics discretization is likely to be preferable to a higher-order moment approximation. There are also other approaches to systematic reduction which might be favoured in some contexts [15–17].

Other assumed forms for the underlying distribution could be considered as well. The principal limitation is the ability to express the *partial* moments $\int_{c_1}^{c_2} x^\lambda n(x)\,dx$ in terms of the moments. This can be done explicitly for all assumed forms in this paper. While in principle this problem could be solved numerically for other forms, this presents practical difficulties: the inversion of the partial moments needs to be carried out at each integration step, while staying on the same solution branch. In practice the difficulties involved strongly favour explicit inversion.

One further note is that we have confined ourselves to the simplest form of the Huxley crossbridge model, while many extensions of that theory have been introduced, and add some complications to employing a DM approximation. However, most are not insurmountable. For example, we have already pointed out that the "standard" binding rate functions can be generalized to piecewise polynomial; indeed they can be generalized beyond this as well, so long as the partial moments can be written explicitly. Other generalizations involve additional bound species and hence are systems of PDEs of the crossbridge character; these too can be handled in a similar fashion [5]. In short, many crossbridge-type models can be approximated in this way.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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