JGP Journal of General Physiology

COMMENTARY

Modeling cardiac contractile cooperativity across species

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Phan and Fitzsimons (https://doi.org/10.1085/jgp.202413582) develop a new mathematical model of muscle contraction that explores cooperative mechanisms in small (murine) and large (porcine) myocardium.

Introduction

Cardiac muscle contraction is replete with cooperative mechanisms (Bremel and Weber, 1972; Murray and Weber, 1981; Tobacman, 1996; Lehrer, 1994; McKillop and Geeves, 1993; Solaro and Rarick, 1998; Moore et al., 2016; Gordon et al., 2000). Cooperativity in cardiac muscle promotes energy-efficient, synchronized contractions at variable mechanical loads. The impact of cooperativity in cardiac muscle is exemplified by the strong dependence of force development on thin filament activation (Regnier et al., 2004; Brenner, 1986, 1988). Detailed experiments have identified several cellular, molecular, and structural contributions to cooperativity, such as tropomyosin–tropomyosin overlap interactions, crossbridge (XB)-dependent Ca^{2+} sensitivity of troponin, and regulatory unit (RU)–mediated activation of neighboring RUs (Moore et al., 2016). However, significant gaps remain, particularly in understanding the relative strengths of cooperative interactions, their effects across spatial and temporal scales, and their differences across species. In this issue of the *Journal of General Physiology*, Drs. Tuan Phan and Daniel P. Fitzsimons present a mathematical model to test how cooperativity among RU–RU, RU–XB, and XB–XB interactions affect cardiac muscle contraction (Phan and Fitzsimons, 2025).

The mathematical modeling of XB contraction in muscle has a rich history, originating from foundational studies aimed at understanding the molecular basis of muscle force generation. Niederer, Campbell, and Campbell provide detailed history of mathematical models of muscle contraction (Niederer et al., 2019). Briefly, early theoretical frameworks modeled relationships between muscle shortening velocity and load (Hill, 1938). The sliding filament models of Huxley (1957), Huxley and Simmons (1971), and others yielded a quantitative description of the molecular basis by which actin–myosin interactions produce force and motion. Subsequent models addressed various types of muscle contractions and included more complex dynamic processes such as, including the regulation of XB function by Ca^{2+} and nucleotide states (Smith et al., 2005; Lymn and Taylor, 1971), spatially explicit phenomena (Daniel et al., 1998), roles of cooperative interactions (Campbell, 2009; Razumova et al., 2000; Kalda and Vendelin, 2020), filament compliance (Tanner et al., 2012), and multifilament interactions (Tanner et al., 2007). Grounded in the desire to understand the complex mechanisms underlying muscular function, mathematical models of muscle contraction have evolved significantly over the years. Contemporary methods now integrate various models of contraction into multiscale frameworks (Hock et al., 2023; Teitgen et al., 2024) that bridge the gap between molecular mechanisms and macroscopic muscle function. Increases in model sophistication reflect how synergy between experimental data, theoretical insights, and computational power can yield robust platforms to explore physiological and pathological states of muscle contraction.

Advancements in cardiac muscle experimentation and modeling have brought attention to species-specific differences in contraction kinetics and muscle regulation. These differences are associated with variations in protein isoforms and cooperative behaviors and are necessary to fulfil the varied cardiac outputs required for animals of different sizes. For instance, tension redevelopment kinetics (k_{tr}) in murine myocardium, which predominantly expresses α-myosin heavy chain, exhibits a steep activation dependence: k_{tr} increases nearly 10-fold across submaximal calcium levels (Patel et al., 2023). In contrast, porcine myocardium, dominated by β-myosin heavy chain, shows near-maximal k_{tr} values at low calcium activation, indicating tighter coupling between steady-state force and k_{tr} (Patel et al., 2023). Such differences underscore the need for models that account for species-specific contractile properties. Phan and Fitzsimons (2025) develop a new model that examines the relative contributions of RU–RU, XB–RU, and XB–XB cooperative interactions in murine and porcine myocardium. Their work builds on earlier studies by parameterizing cooperative interactions, systematically probing relative combinations of cooperativity, and by linking computational predictions with experimental data. By relating computational modeling with recent insights from structural biology, their approach addresses long-standing questions about the molecular basis of

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cooperativity in different organisms and provides a foundation for future research.

Modeling cardiac muscle contraction

Phan and Fitzsimons adapt prior methods (Razumova et al., 2000; Campbell et al., 2010) and present a mathematical model of muscle contraction that couples thin filament activation and XB cycling into a multistate system. The model includes three states of RU in thin filament regulatory scheme (McKillop and Geeves, 1993) and a XB model with one detached state and two attached states. This model incorporates parameters that describe cooperative interactions among and between troponin–tropomyosin RUs and actin–myosin XBs. The cooperativity parameters are tunable and can assess the relative contributions of various cooperative mechanisms, providing a better understanding of contraction in mammalian cardiac muscle. Phan and Fitzsimons assess the combined effects of RU–RU, XB–XB, and XB–RU cooperative interactions with eight distinct parameter sets. The diverse parameters explore the collective roles of cooperativity in modulating the kinetics of thin filament activation and force generation. Finally, the authors fit their model to porcine and murine ventricular myocardium data (Patel et al., 2023). In consensus with prior models (Razumova et al., 2000; Campbell et al., 2010; Moore et al., 2016), they find that RU–RU cooperativity is necessary to fit experimental force–pCa and k_{tr}–pCa relationships, supporting an essential role of RU–RU interactions in both thin filament activation.

Bringing species-specific differences into focus

The fundamentals of cardiac muscle contraction are considered generally conserved across mammals, but identification and quantification of the subtle details that distinguish different species is a long-standing challenge (Milani-Nejad and Janssen, 2014). By comparing murine and porcine myocardium, Phan and Fitzsimons address species-specific differences in myocardial contractility, providing valuable insights into how RU–RU cooperativity contributes to functional adaptations in small and large mammals. The authors observed a stronger RU–RU cooperative interaction in porcine ventricular myocardium compared with murine myocardium. Successful fits of a generalized mammalian cardiac contraction model to murine and porcine data suggest that the model may be "dialed" to model a range of mammalian contractions. Nonuniform activation of the thin filament due to stochastic Ca^{2+} binding and differing activation energies for cooperative recruitment are proposed to explain differences in contractile responses between murine and porcine myocardium at submaximal Ca^{2+} levels.

Looking ahead

The Phan and Fitzsimons model further establishes the RU–RU interaction as the predominant cooperative mechanism governing thin filament activation and force generation in cardiac muscle. This model challenges simplified views of cooperative activation, demonstrating that RU–RU interactions dominate over XB-mediated cooperativity (XB–RU or XB–XB) in certain contexts and refines our understanding of the hierarchical contributions of various cooperative mechanisms. Based on the study's findings and limitations, several future research directions are indicated. Experimental perturbations (e.g., mutations or small molecules that target RU or XB interactions) would further validate the proposed cooperative mechanisms. Further exploration into a broader range of species would be valuable to assess the generalizability of the findings and predictive utility of the model. By demonstrating differences in RU–RU interaction strength between murine and porcine myocardium, the paper also provides a molecular basis for species-specific variations in myocardial contractility. This has implications for translating findings from animal models to human cardiac physiology. Several assumptions in the model, which are clearly delineated and fairly discussed in the article, reduced the computational burden at the cost of simplification. For example, the system models interactions within a single, infinitely long thin filament. Future modeling efforts may explore the effects of cooperative activation across species when multiscale factors (e.g., length-dependent activation and multifilament models) are considered. Additionally, regulation of thick filaments is emerging as an important factor in muscle contraction (Marcucci, 2023; Irving, 2017). New insights into thick filament regulation (Park-Holohan et al., 2021; Turner et al., 2024), thick filament regulatory proteins (Barefield et al., 2023; Harris, 2021), thick filament biochemical activity (Craig and Padrón, 2022; Walklate et al., 2022), and high-resolution structures of thick filaments (Dutta et al., 2023; Tamborrini et al., 2023) should prompt incorporation of thick filament cooperativity/regulation in future modeling efforts. Cooperation and synergy between experiment, theory, and computation continue to drive our field forward. Just as insights from the electron microscope paved the way for the sliding filament theory (Huxley, 1957), new structures of protein–protein complexes (Risi et al., 2022; Doran et al., 2023), and experimental data from diverse model organisms inform novel theoretical frameworks of muscle structure-function. Current modeling results emphasize the need for more accurate quantification of RU–RU structure/function to better understand myocardial function in health and disease.

Acknowledgments

Henk L. Granzier served as editor.

M.C. Childers is supported by award number K99HL173646 from the National Heart, Lung, and Blood Institute. The content is solely the responsibility of the author and does not necessarily represent the official view of the NHLBI or the National Institutes of Health.

Author contributions: M.C. Childers: conceptualization, funding acquisition, project administration, and writing—original draft, review, and editing.

Disclosures: The author declares no competing interests exist.

References

Barefield, D.Y., P. Tonino, K.C. Woulfe, S. Rahmanseresht, T.S. O'Leary, H.V. Burnham, J.A. Wasserstrom, J.A. Kirk, M.J. Previs, H.L. Granzier, and E.M. McNally. 2023. Myosin-binding protein H-like regulates myosin-binding protein distribution and function in atrial cardiomyocytes. *Proc. Natl. Acad. Sci. USA*. 120:e2314920120. https://doi.org/10.1073/pnas.2314920120

Bremel, R.D., and A. Weber. 1972. Cooperation within actin filament in vertebrate skeletal muscle. *Nat. New Biol.* 238:97–101. https://doi.org/10.1038/newbio238097a0

Brenner, B. 1986. The cross-bridge cycle in muscle. Mechanical, biochemical, and structural studies on single skinned rabbit psoas fibers to characterize cross-bridge kinetics in muscle for correlation with the actomyosin-ATPase in solution. *Basic Res. Cardiol.* 81:1–15. https://doi.org/10.1007/978-3-662-11374-5_1

Brenner, B. 1988. Effect of Ca2+ on cross-bridge turnover kinetics in skinned single rabbit psoas fibers: Implications for regulation of muscle contraction. *Proc. Natl. Acad. Sci. USA.* 85:3265–3269. https://doi.org/10.1073/pnas.85.9.3265

Campbell, K.S. 2009. Interactions between connected half-sarcomeres produce emergent mechanical behavior in a mathematical model of muscle. *PLoS Comput. Biol.* 5:e1000560. https://doi.org/10.1371/journal.pcbi.1000560

Campbell, S.G., F.V. Lionetti, K.S. Campbell, and A.D. McCulloch. 2010. Coupling of adjacent tropomyosins enhances cross-bridge-mediated cooperative activation in a markov model of the cardiac thin filament. *Biophys. J.* 98:2254–2264. https://doi.org/10.1016/j.bpj.2010.02.010

Craig, R., and R. Padrón. 2022. Structural basis of the super- and hyper-relaxed states of myosin II. *J. Gen. Physiol.* 154:e202113012. https://doi.org/10.1085/jgp.202113012

Daniel, T.L., A.C. Trimble, and P.B. Chase. 1998. Compliant realignment of binding sites in muscle: Transient behavior and mechanical tuning. *Biophys. J.* 74:1611–1621. https://doi.org/10.1016/s0006-3495(98)77875-0

Doran, M.H., M.J. Rynkiewicz, D. Rasicci, S.M.L. Bodt, M.E. Barry, E. Bullitt, C.M. Yengo, J.R. Moore, and W. Lehman. 2023. Conformational changes linked to ADP release from human cardiac myosin bound to actin-tropomyosin. *J. Gen. Physiol.* 155:e202213267. https://doi.org/10.1085/jgp.202213267

Dutta, D., V. Nguyen, K.S. Campbell, R. Padrón, and R. Craig. 2023. Cryo-EM structure of the human cardiac myosin filament. *Nature.* 623:853–862. https://doi.org/10.1038/s41586-023-06691-4

Gordon, A.M., E. Homsher, and M. Regnier. 2000. Regulation of contraction in striated muscle. *Physiol. Rev.* 80:853–924. https://doi.org/10.1152/physrev.2000.80.2.853

Harris, S.P. 2021. Making waves: A proposed new role for myosin-binding protein C in regulating oscillatory contractions in vertebrate striated muscle. *J. Gen. Physiol.* 153:e202012729. https://doi.org/10.1085/jgp.202012729

Hill, A.V. 1938. The heat of shortening and the dynamic constants of muscle. *Proc. R. Soc. Lond. Ser. B - Biol. Sci.* 126:136–195. https://doi.org/10.1098/rspb.1938.0050

Hock, M.T., A.E. Teitgen, K.J. McCabe, S.P. Hirakis, G.A. Huber, M. Regnier, R.E. Amaro, J.A. McCammon, and A.D. McCulloch. 2023. Multiscale computational modeling of the effects of 2′-deoxy-ATP on cardiac muscle calcium handling. *J. Appl. Phys.* 134:074905. https://doi.org/10.1063/5.0157935

Huxley, A.F. 1957. Muscle structure and theories of contraction. *Prog. Biophys. Biophys. Chem.* 7:255–318. https://doi.org/10.1016/s0096-4174(18)30128-8

Huxley, A.F., and R.M. Simmons. 1971. Proposed mechanism of force generation in striated muscle. *Nature.* 233:533–538. https://doi.org/10.1038/233533a0

Irving, M. 2017. Regulation of contraction by the thick filaments in skeletal muscle. *Biophys. J.* 113:2579–2594. https://doi.org/10.1016/j.bpj.2017.09.037

Kalda, M., and M. Vendelin. 2020. Cardiac muscle regulatory units are predicted to interact stronger than neighboring cross-bridges. *Sci. Rep.* 10:5530. https://doi.org/10.1038/s41598-020-62452-7

Lehrer, S.S. 1994. The regulatory switch of the muscle thin filament: Ca2+ or myosin heads? *J. Muscle Res. Cell Motil.* 15:232–236. https://doi.org/10.1007/bf00123476

Lymn, R.W., and E.W. Taylor. 1971. Mechanism of adenosine triphosphate hydrolysis by actomyosin. *Biochemistry.* 10:4617–4624. https://doi.org/10.1021/bi00801a004

Marcucci, L. 2023. Muscle mechanics and thick filament activation: An emerging two-way interaction for the vertebrate striated muscle fine regulation. *Int. J. Mol. Sci.* 24:6265. https://doi.org/10.3390/ijms24076265

McKillop, D.F., and M.A. Geeves. 1993. Regulation of the interaction between actin and myosin subfragment 1: Evidence for three states of the thin filament. *Biophys. J.* 65:693–701. https://doi.org/10.1016/s0006-3495(93)81110-x

Milani-Nejad, N., and P.M.L. Janssen. 2014. Small and large animal models in cardiac contraction research: Advantages and disadvantages. *Pharmacol. Ther.* 141:235–249. https://doi.org/10.1016/j.pharmthera.2013.10.007

Moore, J.R., S.G. Campbell, and W. Lehman. 2016. Structural determinants of muscle thin filament cooperativity. *Arch. Biochem. Biophys.* 594:8–17. https://doi.org/10.1016/j.abb.2016.02.016

Murray, J.M., and A. Weber. 1981. Cooperativity of the calcium switch of regulated rabbit actomyosin system. *Mol. Cell. Biochem.* 35:11–15. https://doi.org/10.1007/bf02358183

Niederer, S.A., K.S. Campbell, and S.G. Campbell. 2019. A short history of the development of mathematical models of cardiac mechanics. *J. Mol. Cell. Cardiol.* 127:11–19. https://doi.org/10.1016/j.yjmcc.2018.11.015

Park-Holohan, S.-J., E. Brunello, T. Kampourakis, M. Rees, M. Irving, and L. Fusi. 2021. Stress-dependent activation of myosin in the heart requires thin filament activation and thick filament mechanosensing. *Proc. Natl. Acad. Sci. USA.* 118:e2023706118. https://doi.org/10.1073/pnas.2023706118

Patel, J.R., K.J.V. Park, A.S. Bradshaw, T. Phan, and D.P. Fitzsimons. 2023. Cooperative mechanisms underlie differences in myocardial contractile dynamics between large and small mammals. *J. Gen. Physiol.* 155:e202213315. https://doi.org/10.1085/jgp.202213315

Phan, T.A., and D.P. Fitzsimons. 2025. Modeling the effects of thin filament near-neighbor cooperative interactions in mammalian myocardium. *J. Gen. Physiol.* 157. e202413582. https://doi.org/10.1085/jgp.202413582

Razumova, M.V., A.E. Bukatina, and K.B. Campbell. 2000. Different myofilament nearest-neighbor interactions have distinctive effects on contractile behavior. *Biophys. J.* 78:3120–3137. https://doi.org/10.1016/s0006-3495(00)76849-4

Regnier, M., H. Martin, R.J. Barsotti, A.J. Rivera, D.A. Martyn, and E. Clemmens. 2004. Cross-bridge versus thin filament contributions to the level and rate of force development in cardiac muscle. *Biophys. J.* 87:1815–1824. https://doi.org/10.1529/biophysj.103.039123

Risi, C.M., E. Villanueva, B. Belknap, R.L. Sadler, S.P. Harris, H.D. White, and V.E. Galkin. 2022. Cryo-electron microscopy reveals cardiac myosin binding protein-C M-domain interactions with the thin filament. *J. Mol. Biol.* 434:167879. https://doi.org/10.1016/j.jmb.2022.167879

Smith, N.P., C.J. Barclay, and D.S. Loiselle. 2005. The efficiency of muscle contraction. *Prog. Biophys. Mol. Biol.* 88:1–58. https://doi.org/10.1016/j.pbiomolbio.2003.11.014

Solaro, R.J., and H.M. Rarick. 1998. Troponin and tropomyosin: Proteins that switch on and tune in the activity of cardiac myofilaments. *Circ. Res.* 83:471–480. https://doi.org/10.1161/01.res.83.5.471

Tamborrini, D., Z. Wang, T. Wagner, S. Tacke, M. Stabrin, M. Grange, A.L. Kho, M. Rees, P. Bennett, M. Gautel, and S. Raunser. 2023. Structure of the native myosin filament in the relaxed cardiac sarcomere. *Nature.* 623:863–871. https://doi.org/10.1038/s41586-023-06690-5

Tanner, B.C.W., T.L. Daniel, and M. Regnier. 2007. Sarcomere lattice geometry influences cooperative myosin binding in muscle. *PLoS Comput. Biol.* 3:e115. https://doi.org/10.1371/journal.pcbi.0030115

Tanner, B.C.W., T.L. Daniel, and M. Regnier. 2012. Filament compliance influences cooperative activation of thin filaments and the dynamics of force production in skeletal muscle. *PLoS Comput. Biol.* 8:e1002506. https://doi.org/10.1371/journal.pcbi.1002506

Teitgen, A.E., M.T. Hock, K.J. McCabe, M.C. Childers, G.A. Huber, B. Marzban, D.A. Beard, J.A. McCammon, M. Regnier, and A.D. McCulloch. 2024. Multiscale modeling shows how 2′-deoxy-ATP rescues ventricular function in heart failure. *Proc. Natl. Acad. Sci. USA.* 121:e2322077121. https://doi.org/10.1073/pnas.2322077121

Tobacman, L.S. 1996. Thin filament-mediated regulation of cardiac contraction. *Annu. Rev. Physiol.* 58:447–481. https://doi.org/10.1146/annurev.ph.58.030196.002311

Turner, K.L., B.J. Vander Top, K.B. Kooiker, S. Mohran, C. Mandrycky, T. McMillen, M. Regnier, T.C. Irving, W. Ma, and B.C.W. Tanner. 2024. The structural and functional effects of myosin regulatory light chain phosphorylation are amplified by increases in sarcomere length and $[Ca^{2+}]$. *J. Physiol.* 602:4941–4958. https://doi.org/10.1113/jp286802

Walklate, J., K. Kao, M. Regnier, and M.A. Geeves. 2022. Exploring the super-relaxed state of myosin in myofibrils from fast-twitch, slow-twitch, and cardiac muscle. *J. Biol. Chem.* 298:101640. https://doi.org/10.1016/j.jbc.2022.101640