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Modeling Human Ventricular Cardiomyocyte Force-Frequency Relationship

https://doi.org/10.1515/cdbme-2024-2051

Abstract: We investigate the force-frequency relationship (FFR) representation of human ventricular cardiomyocyte models and point out shortcomings, motivated by discrepancies in whole-heart simulations at increased pacing rates. Utilizing the openCARP simulator, simulations across frequencies ranging from 1 Hz to 3 Hz were conducted. Experimental data on healthy human ventricular cardiomyocytes were collected and compared against simulated results. Results show deviations for all models, with Tomek et al. modeling time sensitive biomarkers the best. For example, the ratio of time to peak tension at 2 Hz and 1 Hz is around 85 % for experiments, 82 % for hybrid data, 95 % for Tomek et al., 98 % for O'Hara et al. and 138 % for ten Tusscher et al. These discrepancies, highlight not only the need for careful selection of ionic models, but also the importance of refining ventricular cardiomyocyte models for advancing in-silico cardiac research.

Keywords: cardiac modeling, electrophysiology, tension development, pacing rate

1 Introduction

Cardiac modeling is increasingly recognized for its potential in advancing cardiac research by shedding light on heart function and disease mechanisms. One fundamental approach is modeling the individual cardiomyocyte to explore its electrophysiological dynamics and development of tension. Typically, these models are based on data from healthy human cardiomyocytes beating at a standard rate of 1 Hz. For models to offer true utility, they must accurately emulate behaviors beyond the base heart rate, ensuring their reliability in real-world scenarios always comprising varying heart rates. One important aspect is the force-frequency relationship (FFR), which serves as a simple descriptor of how alterations in heart rate influence tension development in heart muscle cells. Existing assessments, published by the model authors, often provide limited insight into frequency reaction as they almost always exclusively cover ionic behavior or tension development, therefore making it hard to draw any conclusions on combined electro-mechanical function. If the FFR of a single cardiomyocyte is not modeled correctly, whole-heart simulations at increased pacing rates are not possible. This study aims to address this gap by a comparative analysis of widely employed ventricular cardiomyocyte models. Our goal is to assess their FFR and compare against experimental data collected from literature. Through this investigation, we aim to enhance our understanding of these models' capabilities.

2 Methods

To model the cellular behavior, three ionic models were employed: the ten Tusscher et al. model [12], the O'Hara et al. model [9], and the Tomek et al. model [13], an updated version of the O'Hara et al. model. The latter two were coupled bidirectionally ($\leftrightarrow$) with the Land et al. cardiac contraction model [6] via calcium bound to troponin, following the methodology outlined by Margara et al. [7], whereas only forward coupling ($\rightarrow$) was considered for the ten Tusscher et al. model. Forward coupling, where intracellular calcium is the only connecting component, can lead to different values of calcium bound to troponin in the ionic and Land model. Bidirectional coupling avoids this discrepancy by using identical equations. For the sake of simplicity, the results will from here on be referred to by the ionic model name, regardless of the simulated tension resulting from the Land et al. model. Using the openCARP simulator [10], simulations were conducted across frequencies ranging from 1 Hz to 3 Hz, with a step size of 0.5 Hz. Simulations were run for 1000 cycles to allow transient oscillations to equilibrate.

Experimental data on healthy human ventricular cardiomyocytes were curated from literature [2, 5, 8]. Numerical data were extracted from graphical representations using the web tool WebPlotDigitizer [11]. Collected data included tension transients as well as published biomarkers. Additionally, experimental calcium data from Coppini et al. were used as input for the Land et al. cardiac contraction model [6], referred to as *hybrid data*. Experimental human calcium transients were only available for 1 Hz and 2 Hz. Commonly used biomarkers, as depicted in Figure 1, were computed from the resulting tension transients. The biomarkers examined in this paper include peak tension, diastolic tension, time to peak tension,

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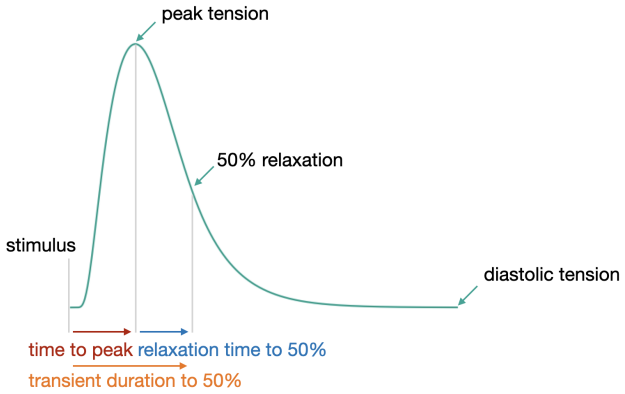

Fig. 1: An exemplary tension transient annotated with key parameters: time of stimulus, peak tension, $50\,\%$ relaxation, diastolic tension, time to peak tension, relaxation time, and transient duration.

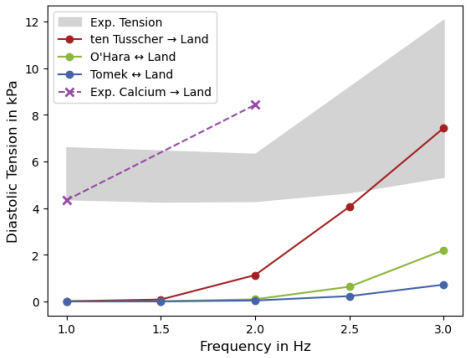

Fig. 3: Diastolic tension at different frequencies. Both experimental and simulated data are shown. Data were obtained from the Land et al. cardiac contraction model in conjunction with three ionic models as well as driven by experimental intracellular calcium transients from Coppini et al. [3, 4]

relaxation time to $50\,\%$, and transient duration to $50\,\%$. One important aspect regarding the relaxation time is its dependence on the peak tension value, as it directly corresponds to the value where the evaluated time interval ends. To eliminate this confounder, a new biomarker was introduced: The *peak independent relaxation time* uses the tension at which $50\,\%$ relaxation was reached at $1\,\mathrm{Hz}$ for all frequencies, thereby eliminating the effect of changes in peak tension. As the focus of this paper is on the frequency dependent changes with reference to $1\,\mathrm{Hz}$, the plots were normalized to this frequency.

3 Results

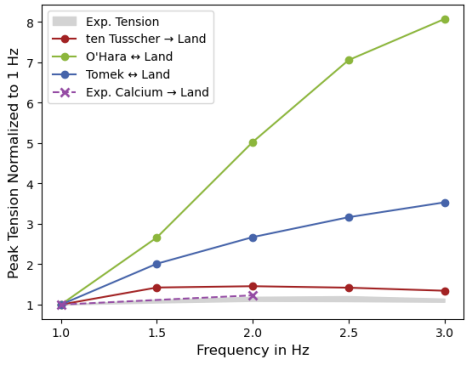

Fig. 2: Peak tension normalized to $1\,\mathrm{Hz}$ at multiple frequencies. Both experimental and simulated data are shown. Data were obtained from the Land et al. cardiac contraction model in conjunction with three ionic models as well as informed by experimental intracellular calcium from Coppini et al. [3, 4]

Figure 2 presents the peak tension across frequencies. The absolute values at $1\,\mathrm{Hz}$ are approximately $10\,\mathrm{kPa}$ for simulations using the O'Hara et al. and Tomek et al. models, $53\,\mathrm{kPa}$ for hybrid data, and $70\,\mathrm{kPa}$ for ten Tusscher et al. Experimental peak tension was in the range of $12\,\mathrm{kPa}$ to $22\,\mathrm{kPa}$. All data exhibit an increase in peak tension as a result of faster pacing, although the extent varies. The slope of the curve decreased at higher frequencies.

Figure 3 shows the diastolic tension. In simulations, diastolic tension is minimal (around $0\,\mathrm{kPa}$) at $1\,\mathrm{Hz}$. As a result, the decision was made to forgo normalization of the plot. Both experimental and hybrid data exhibit a similar diastolic tension. This increases to around $8\,\mathrm{kPa}$ at $2\,\mathrm{Hz}$ for hybrid and up to $12\,\mathrm{kPa}$ at $3\,\mathrm{Hz}$ for experimental data. The slope of the curve increased at higher frequencies for all results.

Figure 4 shows the time to peak tension, relaxation time to $50\,\%$, and the transient duration to $50\,\%$. Both experimental tension and hybrid data exhibited a decrease in time to peak tension with similar trajectories at increased pacing frequencies. A less pronounced decrease can also be seen for O'Hara et al. and Tomek et al., with a greater reduction in the Tomek et al. data. Contrarily, the ten Tusscher et al. data demonstrated a different pattern: time to peak tension increased substantially between $1\,\mathrm{Hz}$ and $2\,\mathrm{Hz}$, followed by a decrease at higher pacing rates ending up with an increase of around $10\,\%$ at $3\,\mathrm{Hz}$ compared to $1\,\mathrm{Hz}$. The relaxation time to $50\,\%$ of experimental tension exhibited a decrease with increasing pacing frequency. However, it was less pronounced than in time to peak tension. In contrast, hybrid data demonstrated a more pronounced reduction, not within the range of experimental values. Data from Tomek et al. was similar to experimental tension with an almost linear decrease at higher pacing frequencies. O'Hara et al. showed almost no alteration, with only a very small decline visible. In contrast to

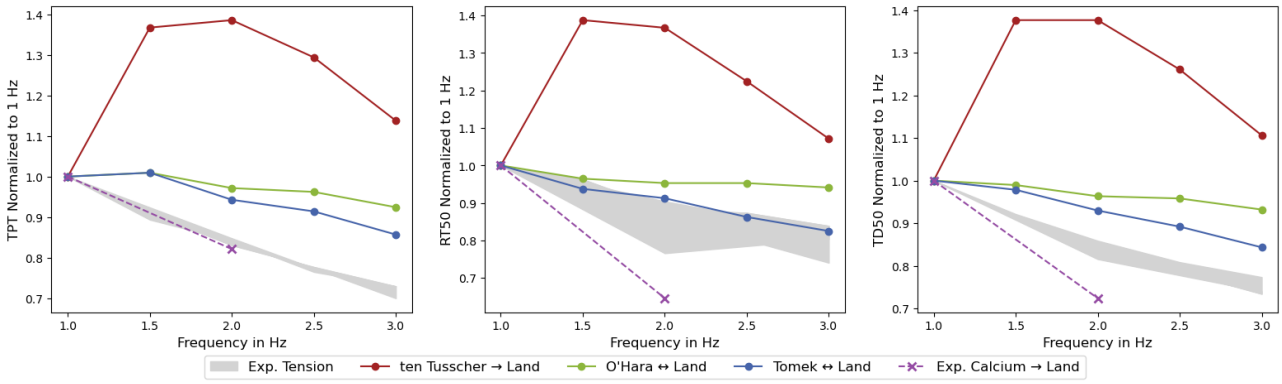

Fig. 4: Time to peak tension (TPT), relaxation time to $50\,\%$ (RT50), and transient duration to $50\,\%$ (TD50) at multiple frequencies. Both experimental and simulated data are shown. Data were obtained from the Land et al. cardiac contraction model in conjunction with three ionic models as well as driven by experimental intracellular calcium transients from Coppini et al. [3, 4]

results for time to peak tension, the relaxation time to $50\,\%$ of Tomek et al. data fell within the range of experimental values. The results from ten Tusscher et al. were different, initially increasing, then declining in relaxation time. For the transient duration, the experimental tension displayed a decline with an increase in pacing frequency. Results from O'Hara et al. and Tomek et al. displayed a decline as well, albeit to a lesser degree, not matching the experimental behavior. The degree of decline in the hybrid results was even bigger than in the experimental ones. Lastly the behavior of ten Tusscher et al. was completely different with an increase from $1\,\mathrm{Hz}$ and $1.5\,\mathrm{Hz}$, almost no change to $2\,\mathrm{Hz}$ followed by a steep decline at higher frequencies.

Figure 5 displays the peak independent relaxation time to $50\,\%$. The parameter is almost constant for experimental data. Hybrid tension displays a decline, while all three ionic models display an initial increase, which flattens at higher frequencies for O'Hara et al. and Tomek et al. and declines at frequencies higher than $1.5\,\mathrm{Hz}$ for ten Tusscher et al., still remaining at a $30\,\%$ increase at $3\,\mathrm{Hz}$.

4 Discussion

All models show an increase in both diastolic and peak tension with increased frequencies. This is in agreement with the change observed in experiments. However, the magnitudes of change differ substantially. For time sensitive biomarkers, particularly RT50, the Tomek et al. model aligns closest with experimental behavior. The hybrid tension generally follows the same trend as experimental data, yet again, the magnitude of alteration is not always consistent.

While all results exhibit an increase in peak tension at higher pacing frequencies, the variation in the degree of change and absolute peak tension poses challenges in drawing conclusive insights regarding the extent of change. A potential approach to mitigate this challenge is optimizing the parameters of the Land et al. cardiac contraction model based on calcium transients from each ionic model. Appel et al. [1] describe such a solution.

The primary distinction in diastolic tension appears to stem from the discrepancy at $1\,\mathrm{Hz}$. Since none of the three ionic models exhibited diastolic tension at this frequency, a relative comparison with experimental and hybrid data, which shows resting diastolic tension, is difficult. However, all results show an increase in diastolic tension at higher pacing frequencies. It is imperative to conduct further research into the methodologies employed for data collection and to ascertain any underlying differences. Until this discrepancy is resolved, comparison of diastolic tension behavior between simulated datasets is possible, but comparing them with experimental data presents the additional challenge of vastly different baselines.

Figure 4 clearly shows that the frequency dependent behavior of ten Tusscher et al. does not match the behavior seen in experimental data. It should therefore, in its current state, not be used in studies with varying pacing rates. More promising is the FFR of both O'Hara et al. and Tomek et al. They generally display the same tendency as experimental data, in all three time sensitive biomarkers (TPT, RT50, TD50). Tomek et al. is a successful update to O'Hara et al. regarding frequency dependent changes, able to represent these biomarkers closer to experimental data than its predecessor.

The Tomek et al. model represents the relaxation time better than the time to peak tension. This deviation in time to peak tension is therefore the most crucial factor in insufficient transient duration representation. The experimental and hybrid results are almost identical for time to peak tension. This hints at the cause of difference being the ionic model's calcium transients at different frequencies rather than the Land et al. car-

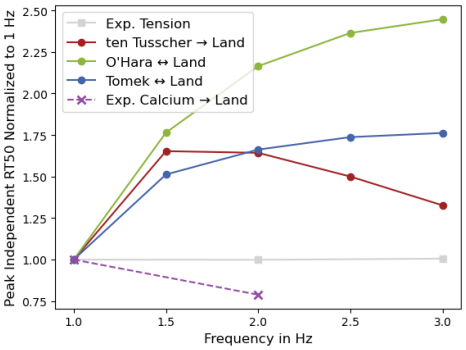

Fig. 5: Peak independent relaxation time to $50\,\%$ normalized to $1\,\mathrm{Hz}$ at multiple frequencies. Both experimental and simulated data are shown. Data were obtained from the Land et al. cardiac contraction model in conjunction with three ionic models as well as informed by experimental intracellular calcium from Coppini et al. [3, 4]

diac contraction model itself. Contradicting this hypothesis, is the behavior of relaxation time to $50\,\%$, where there is a clear difference between the slope of experimental and hybrid results. Regardless, it is important that the simulated calcium transient from the ionic model is accurate not only in absolute values but also in the morphology of the curve.

The newly introduced peak independent relaxation time reveals differences not observed in the commonly used biomarkers. Firstly, it remains almost constant across all frequencies for the available experimental data, suggesting a potentially stable indicator. However, due to the limited amount of experimental data, these findings should be interpreted with caution. Secondly, all modeled data show an increase in peak independent relaxation time, while the biomarker declines for hybrid data. The modeled data is therefore in direct contrast to our expectations. Again, further investigation with more comprehensive data is required to confirm these observations.

5 Conclusion

To summarize, challenges exist interpreting variations in peak and diastolic tension. Some model combinations represent the experimental behavior better than others. Nevertheless, there is likely still too much deviation for in silico studies focusing on frequency dependent behavior. The introduction of the peak independent relaxation time may help in refining model comparisons and improving frequency dependent behavior. In conclusion, current ventricular cardiomyocyte models do not sufficiently represent the FFR at increased frequencies. Due to big differences, when conducting experiments at frequencies different from the base heart rate, the ionic model should be chosen with care.

Funding

This research was funded by Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under grant LO 2093/6-1 (SPP 2311).

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