Supplementary Information

Multiscale modeling of cardiovascular function predicts that the End-Systolic Pressure Volume Relationship can be targeted via multiple therapeutic strategies

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Additional details relating to the MyoSim contraction model

The MyoSim model used in this work was described in detail by Campbell et al. (Campbell et al., 2018). Key details are reproduced in this supplement to enhance clarity.

As shown in Fig S1, binding sites on the thin filament transitioned between an inactive state termed $N_{\text{off}}$ (which myosin heads could not attach to) and an active state $N_{\text{on}}$ (which was available for myosin binding). Activated binding sites could not switch back to the inactive state if a myosin head was attached. Myosin heads transitioned between an OFF state (that could not interact with actin), an ON state (that could potentially bind to actin), and a single attached force-generating state.

![Fig S1: MyoSim kinetic scheme.](image)

Sites on the thin filament switch between states that are available ($N_{\text{on}}$) and unavailable ($N_{\text{off}}$) for cross-bridges to bind to. Myosin heads transition between an OFF detached state, an ON detached state, and a single attached force-generating state. J terms indicate fluxes between different states.
**Thin filament transitions**

The fraction of binding sites in the active state was defined as $N_{on}$. The flux for the $N_{off}$ to $N_{on}$ transition (that is, the number of sites per unit time switching from $N_{off}$ to $N_{on}$) was defined as

$$J_{on} = k_{on} \left( Ca^{2+} \right)^{2} \left( N_{overlap} - N_{on} \right) \left( 1 + k_{coop} \left( \frac{N_{on}}{N_{overlap}} \right) \right)$$

(S1)

where $k_{on}$ is a rate constant, $N_{overlap}$ is the fraction of binding sites that are in range of myosin heads and depends on the prevailing half-sarcomere length as described in Campbell (Campbell, 2009), and $k_{coop}$ is a constant that defines the strength of thin filament cooperativity.

The flux of binding sites through the off transition was defined as

$$J_{off} = k_{off} \left( N_{on} - N_{bound} \right) \left( 1 + k_{coop} \left( \frac{N_{overlap} - N_{on}}{N_{overlap}} \right) \right)$$

(S2)

where $k_{off}$ is a rate constant and the other terms are as defined previously. The $(N_{0} - N_{bound})$ term means that only unbound sites can deactivate (that is, myosin heads have to detach before a binding site can revert to the off state). The $k_{coop}(\left( N_{overlap} - N_{on} \right)/N_{overlap})$ term causes binding sites in the off state to induce further deactivation.

**Thick filament transitions**

The flux of myosin heads transitioning from the $M_{OFF}$ state to the $M_{ON}$ configuration was defined as

$$J_{1} = k_{1} (1 + k_{force} F_{total}) M_{OFF}$$

(S3)

where $k_{1}$ is a rate constant, $k_{force}$ is a parameter with units of $N^{-1} m^{2}$, $F_{total}$ is the force in the muscle, and $M_{OFF}$ is the proportion of myosin heads in the OFF state.
The flux of myosin heads into the OFF state was defined as

\[ J_2 = k_2 M_{ON} \]  \hspace{1cm} (S4)

where \( k_2 \) is a rate constant and \( M_{ON} \) is the proportion of myosin heads in the ON state.

Myosin heads bound to actin with a flux \( J_3 \) defined as

\[ J_3 (x) = k_3 e^{\frac{x^2}{2k_{cb} T}} M_{ON} (N_{on} - N_{bound}) \]  \hspace{1cm} (S5)

where \( k_3 \) is a rate constant, \( k_{cb} \) is the stiffness of the cross-bridge link, \( k_e \) is Boltzmann’s constant \((1.38 \times 10^{-23} \text{ J K}^{-1})\) and \( T \) is the temperature. Equation 5 mimics a second order reaction so that the rate at which myosin heads attach to the thin filament increases with the product of the proportion of myosin heads that are able to attach \( (M_{ON}) \) and the fraction of available binding sites \( (N_{on}-N_{bound}) \). The Gaussian form of the myosin strain-dependence reflects the probability of the cross-bridge spring being extended to \( x \) by random Brownian motion when the myosin head binds to actin (Campbell and Lakie, 1998).

Similarly, the flux through the myosin detachment step was defined as

\[ J_4 (x) = (k_{4,0} + k_{4,1} (x - x_{ps})^4) M_{FG} (x) \]  \hspace{1cm} (S6)

where \( k_{4,0} \) is a rate constant, \( k_{4,1} \) is a parameter that sets the strain dependence of the cross-bridge detachment rate, \( x_{ps} \) is the power-stroke of an attached cross-bridge, and \( M_{FG}(x) \) is the proportion of cross-bridges attached to actin with spring-lengths between \( x \) and \( x+\delta x \).
Calculations

The kinetic scheme shown in Fig S1 was simulated by discretizing the relevant differential equations to yield

\[
\begin{align*}
\frac{dN_{\text{off}}}{dt} &= -J_{\text{on}} + J_{\text{off}} \\
\frac{dN_{\text{on}}}{dt} &= J_{\text{on}} - J_{\text{off}} \\
\frac{dM_{\text{OFF}}}{dt} &= -J_1 + J_2 \\
\frac{dM_{\text{ON}}}{dt} &= \left( J_1 + \sum_{i=1}^{n} J_{4,i} \right) - \left( J_2 + \sum_{i=1}^{n} J_{3,i} \right) \\
\frac{dM_{\text{FG},i}}{dt} &= J_{3,i} - J_{4,i}, \quad \text{where } i=1\ldots n
\end{align*}
\]

(S7)

Cross-bridge populations were evaluated with 0.5 nm resolution over the range -10 nm ≤ x ≤ 10 nm. n was thus equal to 41 giving a complete set of 45 equations. These were integrated numerically with adaptive step-size control. Calculations were initiated with all binding sites in the N_{\text{off}} configuration and all myosin heads in the M_{\text{OFF}} state.

Dynamic interfilamentary movement was incorporated into simulations when required by using polynomial interpolation to displace the distribution that described the number of heads bound with each spring length (Campbell, 2014). Filament compliance effects (Huxley et al., 1994; Wakabayashi et al., 1994) were mimicked by assuming that a half-sarcomere length change of Δx displaced each actin-myosin link by \( \frac{1}{2} \Delta x \) (Getz et al., 1998; Campbell, 2009).

Muscle force was calculated as

\[
F_{\text{total}} = F_{\text{active}} + F_{\text{passive}}
\]

where

\[
F_{\text{active}} = N_0 k_{cb} \sum_{i=1}^{n} M_{\text{FG},i} \left( x_i + x_{ps} \right)
\]

(S8)

and \( N_0 \) is the number of myosin heads in a hypothetical cardiac half-sarcomere with a cross-sectional area of 1 m\(^2\). \( N_0 \) was set to 6.9×10\(^{16}\) m\(^2\) throughout this work based on the assumptions that (a) myofibrils occupy ~60%
of the cross-sectional area of myocardium, (b) half-thick filaments contain 283 myosin heads, and (c) half-thick filaments have a spatial density of 4.07×10^{14} \text{ m}^{-2} within myofibrils (Linari et al., 2007;Campbell, 2014).

Passive force was calculated as

\[
F_{\text{passive}} = \sigma \left( \frac{x_{\text{hs}} - L_{\text{slack}}}{L} - 1 \right)
\]

(S9)

where \(x_{\text{hs}}\) is the length of the half-sarcomere, and \(\sigma\), \(L_{\text{slack}}\), and \(L\) are model parameters. In this equation, \(\sigma\) is a scaling parameter, \(L_{\text{slack}}\) defines the length of the half-sarcomere at which passive force is zero, and \(L\) sets the curvature of the passive-force / length relationship. These properties reflect collagen content and the isoform and posttranslational status of titin which change with disease in humans (Hidalgo and Granzier, 2013;LeWinter and Granzier, 2014).

Myosin ATPase was calculated as

\[
ATP_{\text{ase}} = \frac{N_0 \ W_{\text{volume}} \ \Delta G^*}{L_0 \ N_A} \sum_{i=1}^{n} J_{4,i}
\]

(S10)

where \(\Delta G^*\) is the free energy produced by ATP hydrolysis (70 kJ mol\(^{-1}\)), \(L_0\) is the reference length of half-sarcomere (1.1 \(\mu\)m), and \(N_A\) is Avogadro’s number (6.02 x 10^{23} \text{ mol}^{-1}). Ventricular efficiency was calculated as stroke work divided by myosin ATPase and omits the energy required to maintain the ionic gradients.

**Circulation**

Equation S11 defines the rate of change of the volume of each compartment in the circulatory model. Each term is simply the difference between the blood flows into and out of the compartment.
\[
\frac{dV_{aorta}}{dt} = Q_{ventricle \ to \ aorta} - Q_{aorta \ to \ arteries}
\]

\[
\frac{dV_{arteries}}{dt} = Q_{aorta \ to \ arteries} - Q_{arteries \ to \ arterioles}
\]

\[
\frac{dV_{arterioles}}{dt} = Q_{arteries \ to \ arterioles} - Q_{arterioles \ to \ capillaries}
\]

\[
\frac{dV_{capillaries}}{dt} = Q_{arterioles \ to \ capillaries} - Q_{capillaries \ to \ veins}
\]

\[
\frac{dV_{veins}}{dt} = Q_{capillaries \ to \ veins} - Q_{veins \ to \ ventricle}
\]

\[
\frac{dV_{ventricle}}{dt} = Q_{veins \ to \ ventricle} - Q_{ventricle \ to \ aorta}
\]

(Eq S11)
Equation S12 defines the inter-compartmental flows. The aortic and mitral valves were simulated using simple condition statements based on the pressure gradient. Other flows were defined by Ohm’s law.

\[
Q_{\text{ventricle to aorta}} = \begin{cases} 
\frac{P_{\text{ventricle}} - P_{\text{aorta}}}{R_{\text{aorta}}} & \text{when } P_{\text{ventricle}} \geq P_{\text{aorta}} \\
0 & \text{otherwise}
\end{cases}
\]

\[
Q_{\text{aorta to arteries}} = \frac{P_{\text{aorta}} - P_{\text{arteries}}}{R_{\text{arteries}}}
\]

\[
Q_{\text{arteries to arterioles}} = \frac{P_{\text{arteries}} - P_{\text{arterioles}}}{R_{\text{arterioles}}}
\]

\[
Q_{\text{arterioles to capillaries}} = \frac{P_{\text{arterioles}} - P_{\text{capillaries}}}{R_{\text{capillaries}}}
\]

\[
Q_{\text{capillaries to veins}} = \frac{P_{\text{capillaries}} - P_{\text{veins}}}{R_{\text{veins}}}
\]

\[
Q_{\text{veins to ventricle}} = \begin{cases} 
\frac{P_{\text{veins}} - P_{\text{ventricle}}}{R_{\text{ventricle}}} & \text{when } P_{\text{veins}} \geq P_{\text{ventricle}} \\
0 & \text{otherwise}
\end{cases}
\]

(Eq S12)
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| Component | Parameter | Value   | Units          |
|-----------|-----------|---------|----------------|
| MyoSim    | $k_{on}$  | $5 \times 10^8$ M$^{-1}$ s$^{-1}$ |
|           | $k_{off}$ | 200 s$^{-1}$ |
|           | $k_{coop}$ | 5 Dimensionless |
|           | $k_1$    | 2 s$^{-1}$ |
|           | $k_2$    | 200 s$^{-1}$ |
|           | $k_3$    | 100 s$^{-1}$ nm$^{-1}$ |
|           | $k_{4,0}$ | 200 s$^{-1}$ |
|           | $k_{4,1}$ | 0.1 s$^{-1}$ nm$^{-4}$ |
|           | $k_{cb}$ | 0.001 pN nm$^{-1}$ |
|           | $x_{ps}$ | 5 nm |
|           | $k_{falloff}$ | 0.0024 nm$^{-1}$ |
|           | $\sigma$ | 500 N m$^{-2}$ |
|           | $L$      | 80 nm |
|           | $L_{slack}$ | 900 nm |
| Ventricle | $W_{volume}$ | 0.1 L |
|           | $V_{slack}$ | 0.08 L |
|           | $R_{ventricle}$ | 20 mm Hg L$^{-1}$ s |
| Circulation | $V_{total}$ | 5 L |
|           | $R_{aorta}$ | 40 mm Hg L$^{-1}$ s |
|           | $R_{arteries}$ | 200 mm Hg L$^{-1}$ s |
|           | $R_{arterioles}$ | 500 mm Hg L$^{-1}$ s |
|           | $R_{capillaries}$ | 300 mm Hg L$^{-1}$ s |
|           | $R_{veins}$ | 100 mm Hg L$^{-1}$ s |
|           | $C_{aorta}$ | 0.002 (mm Hg)$^{-1}$ L |
|           | $C_{arteries}$ | 0.0005 (mm Hg)$^{-1}$ L |
|           | $C_{arterioles}$ | 0.0005 (mm Hg)$^{-1}$ L |
|           | $C_{capillaries}$ | 0.0025 (mm Hg)$^{-1}$ L |
|           | $C_{veins}$ | 0.35 (mm Hg)$^{-1}$ L |

Base values for the electrophysiological model remained as published by ten Tusscher et al. (ten Tusscher et al., 2004).
Fig S2. Steady-state beats for three different values of $k_1$.

This figure is similar to Fig 3 in the main text but shows steady-state beats for simulations with 3 different values of $k_1$. Note that the systolic pressure increases with $k_1$ over this limited range.
Fig S3. Single beat analysis of ESPVR

Panels show the single beats from Fig S2 as pressure-volume loops. The maximum slope of the ESPVR was calculated as described by Mirsky et al. (Mirsky et al., 1987) by extrapolating a fit to the pressure-volume data from the late phase of ejection to a ventricular pressure of zero. Note that the ESPVR increased with $k_1$ over this range as shown in Fig 5.
**Fig S4. Excess contractility can reduce cardiac function.**

The figure shows a simulation identical to Fig 2 in the main text but with the value of $k_1$ increased 10-fold. This modification activated cross-bridge force generation between $\text{Ca}^{2+}$ transients and prevented the ventricle from filling adequately during diastole. In this simulation, enhanced contractility depresses stroke volume.
Figure S5: Effects of changing L on system-level cardiovascular properties.

Panels A to L show values (blue circles) for 12 system-level properties (for example, maximum ventricular pressure) predicted for values of L (equation S9) ranging from 0.1 to 10 times the value shown in Table S1.

The red lines shows the best-fit of a 5th order polynomial to the simulated data.
Figure S6: Effects of changing $k_3$ on system-level cardiovascular properties.

Panels A to L show values (blue circles) for 12 system-level properties (for example, maximum ventricular pressure) predicted for values of $k_3$ (equation S5) ranging from 0.1 to 10 times the value shown in Table S1.

The red lines shows the best-fit of a 5th order polynomial to the simulated data.
Figure S7: Effects of changing $k_{cb}$ on system-level cardiovascular properties.

Panels A to L show values (blue circles) for 12 system-level properties (for example, maximum ventricular pressure) predicted for values of $k_{cb}$ (equation S5) ranging from 0.1 to 10 times the value shown in Table S1.

The red lines shows the best-fit of a 5th order polynomial to the simulated data.
Figure S8: Effects of changing \( k_{\text{force}} \) on system-level cardiovascular properties.

Panels A to L show values (blue circles) for 12 system-level properties (for example, maximum ventricular pressure) predicted for values of \( k_{\text{force}} \) (equation S3) ranging from 0.1 to 10 times the value shown in Table S1.

The red lines shows the best-fit of a 5th order polynomial to the simulated data.
Figure S9: Effects of changing $k_1$ on system-level cardiovascular properties.

Panels A to L show values (blue circles) for 12 system-level properties (for example, maximum ventricular pressure) predicted for values of $k_1$ (equation S3) ranging from 0.1 to 10 times the value shown in Table S1.

The red lines shows the best-fit of a $5^{th}$ order polynomial to the simulated data.
Figure S10: Effects of changing $k_2$ on system-level cardiovascular properties.

Panels A to L show values (blue circles) for 12 system-level properties (for example, maximum ventricular pressure) predicted for values of $k_2$ (equation S4) ranging from 0.1 to 10 times the value shown in Table S1.

The red lines shows the best-fit of a 5th order polynomial to the simulated data.
Figure S11: Effects of changing $k_{on}$ on system-level cardiovascular properties.

Panels A to L show values (blue circles) for 12 system-level properties (for example, maximum ventricular pressure) predicted for values of $k_{on}$ (equation S1) ranging from 0.1 to 10 times the value shown in Table S1.

The red lines shows the best-fit of a 5th order polynomial to the simulated data.
Figure S12: Effects of changing $k_{4,0}$ on system-level cardiovascular properties.

Panels A to L show values (blue circles) for 12 system-level properties (for example, maximum ventricular pressure) predicted for values of $k_{4,0}$ (equation S6) ranging from 0.1 to 10 times the value shown in Table S1.

The red lines shows the best-fit of a 5th order polynomial to the simulated data.
Figure S13: Effects of changing $\sigma$ on system-level cardiovascular properties.

Panels A to L show values (blue circles) for 12 system-level properties (for example, maximum ventricular pressure) predicted for values of $\sigma$ (equation S9) ranging from 0.1 to 10 times the value shown in Table S1.

The red lines shows the best-fit of a 5th order polynomial to the simulated data.
Figure S14: Effects of changing $k_{coop}$ on system-level cardiovascular properties.

Panels A to L show values (blue circles) for 12 system-level properties (for example, maximum ventricular pressure) predicted for values of $k_{coop}$ (equations S1 and S2) ranging from 0.1 to 10 times the value shown in Table S1. The red lines shows the best-fit of a 5th order polynomial to the simulated data.
Figure S15: Effects of changing $k_{4,1}$ on system-level cardiovascular properties.

Panels A to L show values (blue circles) for 12 system-level properties (for example, maximum ventricular pressure) predicted for values of $k_{4,1}$ (equation S6) ranging from 0.1 to 10 times the value shown in Table S1.

The red lines shows the best-fit of a 5th order polynomial to the simulated data.
Figure S16: Effects of changing Ca $V_{\text{max, up}}$ on system-level cardiovascular properties.

Panels A to L show values (blue circles) for 12 system-level properties (for example, maximum ventricular pressure) predicted for values of Ca $V_{\text{max, up}}$ ranging from 0.1 to 10 times the base value in ten Tusscher et al’s electrophysiological model (ten Tusscher et al., 2004). The red lines shows the best-fit of a 5th order polynomial to the simulated data.
Figure S17: Effects of changing Ca $g_{\text{CaL}}$ on system-level cardiovascular properties.

Panels A to L show values (blue circles) for 12 system-level properties (for example, maximum ventricular pressure) predicted for values of Ca $g_{\text{CaL}}$ ranging from 0.1 to 10 times the base value in ten Tusscher et al’s electrophysiological model (ten Tusscher et al., 2004). The red lines shows the best-fit of a 5th order polynomial
to the simulated data.
Figure S18: Effects of changing Ca $V_{\text{leak}}$ on system-level cardiovascular properties.

Panels A to L show values (blue circles) for 12 system-level properties (for example, maximum ventricular pressure) predicted for values of Ca $V_{\text{leak}}$ ranging from 0.1 to 10 times the base value in ten Tusscher et al’s electrophysiological model (ten Tusscher et al., 2004). The red lines shows the best-fit of a 5th order polynomial to the simulated data.
Figure S19: Effects of changing $g_{Kr}$ on system-level cardiovascular properties.

Panels A to L show values (blue circles) for 12 system-level properties (for example, maximum ventricular pressure) predicted for values of $g_{Kr}$ ranging from 0.1 to 10 times the base value in ten Tusscher et al’s electrophysiological model (ten Tusscher et al., 2004). The red lines shows the best-fit of a 5th order polynomial to the simulated data.
Figure S20: Effects of changing $g_{Ks}$ on system-level cardiovascular properties.

Panels A to L show values (blue circles) for 12 system-level properties (for example, maximum ventricular pressure) predicted for values of $g_{Ks}$ ranging from 0.1 to 10 times the base value in ten Tusscher et al’s electrophysiological model (ten Tusscher et al., 2004). The red lines shows the best-fit of a 5th order polynomial to the simulated data.
Figure S21: Effects of changing $g_{to}$ on system-level cardiovascular properties.

Panels A to L show values (blue circles) for 12 system-level properties (for example, maximum ventricular pressure) predicted for values of $g_{to}$ ranging from 0.1 to 10 times the base value in ten Tusscher et al’s electrophysiological model (ten Tusscher et al., 2004). The red lines show the best-fit of a 5th order polynomial to the simulated data.
**Figure S22: Effects of changing $V_{\text{slack}}$ on system-level cardiovascular properties.**

Panels A to L show values (blue circles) for 12 system-level properties (for example, maximum ventricular pressure) predicted for values of $V_{\text{slac}}$ (see Methods in main text) ranging from 0.1 to 10 times the value shown in Table S1. The red lines shows the best-fit of a 5$^{\text{th}}$ order polynomial to the simulated data.
Figure S23: Effects of changing $C_{\text{veins}}$ on system-level cardiovascular properties.

Panels A to L show values (blue circles) for 12 system-level properties (for example, maximum ventricular pressure) predicted for values of $C_{\text{veins}}$ (see Methods in main text) ranging from 0.1 to 10 times the value shown in Table S1. The red lines show the best-fit of a 5th order polynomial to the simulated data.
**Figure S24: Effects of changing $W_{\text{volume}}$ on system-level cardiovascular properties.**

Panels A to L show values (blue circles) for 12 system-level properties (for example, maximum ventricular pressure) predicted for values of $W_{\text{volume}}$ (see Methods in main text) ranging from 0.1 to 10 times the value shown in Table S1. The red lines shows the best-fit of a 5th order polynomial to the simulated data.
Figure S25: Effects of changing $R_{\text{arterioles}}$ on system-level cardiovascular properties.

Panels A to L show values (blue circles) for 12 system-level properties (for example, maximum ventricular pressure) predicted for values of $R_{\text{arterioles}}$ (see Methods in main text) ranging from 0.1 to 10 times the value shown in Table S1. The red lines shows the best-fit of a 5th order polynomial to the simulated data.
Figure S26: Effects of changing $C_{aorta}$ on system-level cardiovascular properties.

Panels A to L show values (blue circles) for 12 system-level properties (for example, maximum ventricular pressure) predicted for values of $C_{aorta}$ (see Methods in main text) ranging from 0.1 to 10 times the value shown in Table S1. The red lines shows the best-fit of a 5th order polynomial to the simulated data.
**Figure S27: Effects of changing $R_{\text{capillaries}}$ on system-level cardiovascular properties.**

Panels A to L show values (blue circles) for 12 system-level properties (for example, maximum ventricular pressure) predicted for values of $R_{\text{capillaries}}$ (see Methods in main text) ranging from 0.1 to 10 times the value shown in Table S1. The red lines show the best-fit of a 5th order polynomial to the simulated data.
**Figure S28: Effects of changing $R_{aorta}$ on system-level cardiovascular properties.**

Panels A to L show values (blue circles) for 12 system-level properties (for example, maximum ventricular pressure) predicted for values of $R_{aorta}$ (see Methods in main text) ranging from 0.1 to 10 times the value shown in Table S1. The red lines shows the best-fit of a 5$^{th}$ order polynomial to the simulated data.
Figure S29: Effects of changing $R_{\text{ventricle}}$ on system-level cardiovascular properties.

Panels A to L show values (blue circles) for 12 system-level properties (for example, maximum ventricular pressure) predicted for values of $R_{\text{ventricle}}$ (see Methods in main text) ranging from 0.1 to 10 times the value shown in Table S1. The red lines shows the best-fit of a 5th order polynomial to the simulated data.
Figure S30: Effects of changing $R_{\text{arteries}}$ on system-level cardiovascular properties.

Panels A to L show values (blue circles) for 12 system-level properties (for example, maximum ventricular pressure) predicted for values of $R_{\text{arteries}}$ (see Methods in main text) ranging from 0.1 to 10 times the value shown in Table S1. The red lines shows the best-fit of a 5th order polynomial to the simulated data.
Figure S31: Effects of changing $R_{\text{veins}}$ on system-level cardiovascular properties.

Panels A to L show values (blue circles) for 12 system-level properties (for example, maximum ventricular pressure) predicted for values of $R_{\text{veins}}$ (see Methods in main text) ranging from 0.1 to 10 times the value shown in Table S1. The red lines show the best-fit of a 5th order polynomial to the simulated data.
Figure S32: Effects of changing $C_{\text{arteries}}$ on system-level cardiovascular properties.

Panels A to L show values (blue circles) for 12 system-level properties (for example, maximum ventricular pressure) predicted for values of $C_{\text{arteries}}$ (see Methods in main text) ranging from 0.1 to 10 times the value shown in Table S1. The red lines shows the best-fit of a 5th order polynomial to the simulated data.
Figure S33: Effects of changing $C_{\text{capillaries}}$ on system-level cardiovascular properties.

Panels A to L show values (blue circles) for 12 system-level properties (for example, maximum ventricular pressure) predicted for values of $C_{\text{capillaries}}$ (see Methods in main text) ranging from 0.1 to 10 times the value shown in Table S1. The red lines shows the best-fit of a 5th order polynomial to the simulated data.
Figure S34: Effects of changing $C_{\text{arterioles}}$ on system-level cardiovascular properties.

Panels A to L show values (blue circles) for 12 system-level properties (for example, maximum ventricular pressure) predicted for values of $C_{\text{arterioles}}$ (see Methods in main text) ranging from 0.1 to 10 times the value shown in Table S1. The red lines shows the best-fit of a 5th order polynomial to the simulated data.
Figure S35: Effects of changing $\sigma$ while constraining passive stress.

Panels A to L show values (blue circles) for 12 system-level properties (for example, maximum ventricular pressure) predicted for different combinations of $\sigma$ and $L$ (see equation S9) so that passive stress at a half-sarcomere length of 1069 nm was held constant. Other values as shown in Table S1. The red lines shows the best-fit of a 5th order polynomial to the simulated data.
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