

Hierarchical Loop Stabilization in Periodically Driven Elastic Networks

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Network remodeling, or adaptation, in the presence of periodically driven forcings has hereto remained largely unexplored, despite the fact that a broad class of biological transport networks, e.g., animal vasculature, depends on periodic driving (pulsatility of the heart) to maintain flow. Here we propose a new adaptation model that incorporates the effect of short-term flow pulsatility into the long-term remodeling signal for periodically driven elastic networks and is consistent with optimality principles of dissipation and metabolic cost minimization. Using this model to adapt hierarchical elastic networks with multiple levels of looping, we show that very different network architectures are possible at steady state depending on the driving frequency of the pulsatile source and the geometric asymmetry of the paths between the externally driven nodes of the network. Specifically resonant frequencies are shown to prioritize the stabilization of fully looped structures or higher level loops proximal to the source, whereas antiresonant frequencies predominantly stabilize loop-less structures or lower-level loops distal to the source. Thus, this model offers a mechanism that can explain the stabilization of phenotypically diverse loopy network architectures in response to source pulsatility under physiologically relevant conditions and in the absence of other known loop stabilization mechanisms, such as random fluctuations in the load or perfusion homogenization.

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I. INTRODUCTION

Biological fluid transport networks like animal vasculature or the protoplasmic veins of the slime mould *Physarum polycephalum* are crucial building blocks of complex life. These networks are predominantly composed of vessels that are compliant (i.e., elastic) and can change their shape locally to accommodate changes in the flow. Their structure is thought to be optimized for the crucial functions they perform for the organism, which includes but is not limited to the distribution of oxygen and nutrients, the removal of metabolic waste products, and long-range transmission of information. The structural phenotype of biological transport networks range from large-scale treelike architectures, like the arteriovenous tree in mammals that serves entire organs, to highly reticulated or “loopy” structures, like the microvasculature (capillary network) that caters to individual organs [1–3]. Loops are ubiquitous in biological networks and are understood to be beneficial to the network given their role in mitigating vessel damage and facilitating robustness to source fluctuations [4–6]. Given the importance of the structure of these networks for biological function and adaptation or the remodeling of network elements in response to changing environmental signals, it is therefore important and widely studied [7–14].

Many transport networks depend on pulsatile sources to maintain flow. The most prominent example of this is animal vasculature, where the flow has pulsatile components imparted by the periodic beating of a centralized power source, the heart [15]. The presence of pulsatility in the flow necessarily increases the net energy dissipation across the network, in comparison to steady flow with the same average flow rate. The amplitude of pulsatility is known to decrease with increasing distance from the source, owing to fluid inertia and the compliance of the elastic vessel walls. Yet, despite this damping effect, pulsatility is never completely dispensed with and exists to some extent even at the level of capillaries [16]. Previous work has shown that the energetic advantage of decreasing flow pulsatility by increasing vessel compliance, comes at the cost of increased response times to sudden changes in source current or pressure waveforms, for example a change in the heart rate [17,18]. In fact, experimental evidence shows that both an increase or decrease in arterial pulsatility can lead to detrimental pathologies in mammals [19–21], suggesting that maintaining the right levels of pulsatility in the flow is crucial for biological function.

Despite the important role played by pulsatility in biological flows, adaptation in compliant vessel networks driven by pulsatile sources has remained largely unexplored thus far, although fluctuating sources and sinks have been implemented in previous theories [4,9,22–24]. Most existing models of adaptation assume that vessels respond to the flow in a nondynamical manner on short timescales: The flow relaxes instantaneously to the average value at the source at every point along the length of the vessel. In reality, however, changes in the flow are opposed by the finite inertial resistance

of the fluid and adjusted for locally in elastic vessels by affecting a change in their shape. The combination of these effects yields a short timescale of flow relaxation dynamics which results in time- and length-averaged flow rates in elastic vessels that differ from the mean source current, unlike in the nondynamical approximation [17].

Previous work has shown that when the short-term pulsatile dynamics of flow in compliant vessels is accounted for in the driving signal of a widely used remodeling rule for vascular development, it yields long-time network structures that fundamentally differ from those expected when vessels can only respond nondynamically to the flow at short timescales [25]. Specifically, looped architectures can be stabilized for a much broader class of physiologically relevant metabolic constraints than predicted by existing theories, mediated by resonances that amplify the energy dissipation in individual vessels. This finding further confirms the indispensability of pulsatility despite the energy cost that accompanies it and offers a possible explanation for the observed ubiquity of loops in biological networks, especially closer to the pump, where the pulsatility is larger and perfusion considerations are less important.

However, most remodeling rules, including the one considered in Ref. [25], consider driving signals that are appropriate for steady flow sources, necessitating a modified approach to account for networks driven by a pulsatile source. Moreover, while short-term pulsatility can be shown to facilitate loop stabilization [25], what remains to be investigated is whether this same mechanism can account for the broad spectrum of structural phenotypes from treelike to reticulated network architectures.

In this paper, we attempt to address these important questions in an effort to formulate a mechanics informed theory of adaptation in the presence of pulsatility that can better estimate the long-time structures of complex biological networks, especially in the absence of other loop stabilizing factors. Motivated by other work that established gradient descent-based adaptation rules for biological flow networks [9], we start from the standard principles of energy optimization and derive an adaptation rule for periodically driven elastic flow networks that addresses the effect of short-term pulsatile flow dynamics on the long-term remodeling signal at the timescale of adaptation. Looking at progressively more hierarchical networks we show that short-term pulsatility can stabilize very different network architectures depending on the frequency of periodic driving and the length asymmetry of the different paths between the externally driven nodes of the network. Resonant frequencies, which amplify the flow in a vessel, are shown to prioritize loops proximal to the source (higher-level loops) for stabilization, yielding reticulated structures, whereas antiresonant frequencies lead to shunting (loop destabilization) or stabilize loops distal to the source (lower-level loops), leading to more treelike structures.

Moreover, our results appear to be largely independent of the detailed form of the remodeling rule used to evolve the networks. This suggests that rather than the exact adaptation equation used to evolve networks, it is indeed the short-term pulsatile dynamics in individual elastic vessels, or in other words, the ability to adapt in a compliant manner to the flow on short-timescales that is responsible for robust loop

stabilization. While our simplified flow dynamics model and toy networks cannot possibly capture the vast complexity of actual animal vasculature, it nevertheless constitutes an important theoretical step in the direction of better understanding the interplay between the short and long timescales of network remodeling in the presence of pulsatile driving, and its possible role in stabilizing a broad array of structural phenotypes in adapting biological networks.

II. THE ADAPTATION MODEL

Network adaptation or remodeling is typically studied within the framework of optimization, i.e., evolving the network to minimize the net energy dissipation while satisfying constraints imposed by material or metabolic costs. A remodeling rule that has been used extensively to study the evolution of vessel radii in plant and animal vascular development, as well as for the foraging canals of the slime mold *P. polycephalum* [3,9,10,14,26–29] is given by

$$\frac{dR_e}{dt'} = \frac{a\langle Q_e^2 \rangle^\gamma}{R_e^3} - bR_e, \quad (1)$$

where R_e and Q_e are the radius and the current in the e th vessel of the network respectively, $\gamma \in (0, 1)$ characterizes a metabolic cost and a and b are constants. The steady states of this adaptation rule are identical to those of an energy functional of the form

$$E_s = \sum_e \left(\frac{\langle Q_e^2 \rangle}{K_e} + C_0 K_e^{1/\gamma-1} \right) L_e, \quad (2)$$

where C_0 is a constant, L_e is the length of vessel e , and K_e is the conductance of the e th vessel, which for Poiseuille flow relates to the radius as $K_e \propto R_e^4$. The first term in the summation is the power dissipated in the vessel in the case of steady flows, $D_e = \langle Q_e^2 \rangle L_e / K_e$ (or $D_e = \langle Q_e^2 \rangle L_e / R_e^4$ for Poiseuille flow). The second term captures a class of metabolic or material costs which have a power-law dependence on the vessel conductance and which competes with energy minimization during remodeling [9,10]. For example, in animal vasculature, a blood volume cost would translate to a $\gamma = 2/3$ exponent assuming Poiseuille flow, consistent with Murray's law [30]. A vessel surface area cost would lead to $\gamma = 4/5$. Continuously varying γ in the range (0,1) thus allows us to study a broad class of costs that could affect the long-time structure of the network, even if only certain discrete values of γ correspond to realistic metabolic or material costs.

Note that Eq. (1) can be rewritten in terms of the conductance K_e of the vessel. The growth term (first term) in Eq. (1) is counterbalanced by the decay term (second term) which prevents the radius of each vessel from growing without bounds. The growth term of the adaptation rule carries the driving signal for remodeling—the vessel mean-squared current averaged over the length of the vessel. Equation (1) is typically used for remodeling with steady flows, for which the mean-squared current in a vessel is given by the mean-squared source current split proportionally among each vessel in accordance with their radii. Increasing γ increases the influence of the growth term on the adaptation dynamics.

A. Remodeling rule for pulsatile flows

There is an abundance of experimental support for the hypothesis that the structure of biological networks is governed by optimality principles based on energy and cost minimization [31–47]. The predominance of the optimization framework in the literature on structural adaptation [3,5,9,10,14,26–29,48–52] is moreover a reflection of its robustness as a means of studying long-term network remodeling on the basis of physical and mechanistic considerations, even when the putative optimum can only approximately be approached by biology. Motivated by this consideration, we now seek to construct an energy functional similar to Eq. (2) but for networks driven by a pulsatile source. It is generally accepted in the well-developed theory of structural adaptation in biological networks that radii evolution is driven by the vessel response to the wall shear stress σ . While the vessel-averaged wall shear stress by itself has been shown to be inadequate to control the growth of vascular networks [3,10,27,53–57], a realistic driving signal for adaptation must, however, have an explicit functional dependence on σ . With pulsatile drivers, the power dissipated in a vessel e is given by $D_e = \sigma_e Q_e L_e / R_e$ [58] (see Sec. II of the Supplemental Material [59]). Assuming Poiseuille flow, the energy functional for periodically driven elastic networks can be written as

$$E_p = \sum_e \left(\frac{\langle \sigma_e Q_e \rangle}{R_e} + C_0 R_e^{4(1/\gamma-1)} \right) L_e, \quad (3)$$

where the average of $\sigma_e Q_e$ is now evaluated over one cycle of periodicity, as well as over the length of the vessel:

$$\langle \sigma_e Q_e \rangle = \frac{1}{T} \int_0^T dt \left[\frac{1}{L_e} \int_0^{L_e} dz \sigma_e(z, t) Q_e(z, t) \right]. \quad (4)$$

Here $T = 2\pi/\omega$ is the well-defined time period of the pulsatile source. Note that the timescale t of flow relaxation dynamics in individual vessels of the network is much smaller than the adaptation timescale t' . It is precisely this timescale separation that allows us to assume that the network has encountered several pulsatility cycles before any infinitesimal change in conductance due to remodeling takes place, resulting in a stable average flow state which can drive radii evolution on the timescale of adaptation. We assume that the radius is constant over the length of the vessel and on timescales shorter than t' and therefore does not require averaging.

Equation (3) has minima that can be approached by an adaptation rule of the form

$$\frac{dR_e}{dt'} = \frac{a \langle \sigma_e Q_e \rangle^\gamma}{R_e^{3(1-\gamma)}} - b R_e. \quad (5)$$

The well-separated timescales of short-term dynamics and long-term adaptation guarantees that the effect of the short timescale is contained entirely in $\langle \sigma_e Q_e \rangle$ in Eq. (5), making a direct quantitative comparison with the adaptation timescale (t' and b^{-1} , the decay time) unnecessary. For steady flows, the wall shear stress has a simple relation to the flow in a vessel, given by $\sigma \propto Q/R^3$, which reduces Eq. (3) to the steady flow energy optimization functional given in Eq. (2) and the adaptation rule for pulsatile flows in Eq. (5) to the usual steady flow form given in Eq. (1).

Equation (5) must be seen as a self-consistent phenomenological model for long-term remodeling dynamics in periodically driven networks, within the framework of optimization. It is agnostic to what physical quantities the vessels comprising the network actually locally sense and respond to, about which there is a lack of general consensus beyond the accepted view that they must depend on the wall shear stress experienced by vessels. We have chosen this approach because our focus in this work is not on the exact form of the remodeling rule but on establishing the importance of the interplay between the dynamical response of elastic vessels to flow-pulsatility on short timescales and the long-term structures of these adapting networks. Fortunately, as we will show, different adaptation rules, and even ones not derived from an energy functional, generate qualitatively identical and quantitatively similar network structures as long as the driving signal takes into account the short-term flow pulsatility in vessels (see Sec. IV of the Supplemental Material [59]).

B. Flow dynamics model for compliant vessels

Following Refs. [17,25], we adopt a simplified flow dynamics model in which each compliant vessel is considered to be a thin cylinder whose length L is much larger than its radius R . Starting from the Navier-Stokes equation for incompressible flows, and making the standard simplifying assumptions of rotational symmetry and parabolic velocity profiles, the flow volume and momentum conservation equations for a fluid of viscosity μ and density ρ can be recast into a set of coupled differential equations for the axial current $Q(z, t)$ and pressure $P(z, t)$ at every point along the length of a vessel, as

$$\frac{\partial Q}{\partial z} + c \frac{\partial P}{\partial t} = 0, \quad (6)$$

$$\frac{\partial P}{\partial z} + l \frac{\partial Q}{\partial t} + r Q = 0, \quad (7)$$

where $l = \rho/A$ and $r = 8\pi\mu/A^2$ are the fluid inertia and flow resistance per unit length in a vessel of cross-sectional area $A = \pi R^2$ (see Sec. I of the Supplemental Material for derivation [59]). The vessel compliance $c = \partial A / \partial P$ is defined assuming that the cross-sectional area scales linearly with the fluid pressure and that the changes in cross-sectional area in response to changes in pressure are sufficiently small at short timescales. This has the simplifying effect of keeping the compliance c approximately fixed across the length of the vessel and on short timescales, while allowing it to vary over the timescale of adaptation as the radius R (and thus A) evolves, keeping the distensibility fixed such that $c \propto A$ (see Sec. I of the Supplemental Material [59]). A characteristic length scale λ , a characteristic timescale τ , and a characteristic admittance scale α , each scaling proportional to the area of cross section A , can be derived from the network parameters c , l , and r ,

$$\begin{aligned} \lambda &= \lambda_0 (R/R_0)^2 = \frac{2}{r} \sqrt{\frac{l}{c}}, \\ \tau &= \tau_0 (R/R_0)^2 = \frac{2l}{r}, \\ \alpha &= \alpha_0 (R/R_0)^2 = \sqrt{\frac{c}{l}}, \end{aligned} \quad (8)$$

where R_0 is a typical radius. The constants λ_0 , τ_0 , and α_0 allow us to isolate the radius dependence of these characteristic scales and are set to the same value for each vessel in the network while their radii can evolve independently of one another on the timescale of adaptation. The timescale τ captures the ratio of inertial and viscous forces and approximates the time taken for local flow relaxation in a vessel of radius R . The parameter τ_0 can thus be used to characterize the short timescale of the problem: The limit of the rescaled frequency $\omega\tau_0$ going to zero recovers the nondynamical approximation which most adaptation models operate on. In other words, as $\omega\tau_0 \rightarrow 0$, the short-timescale vanishes for a vessel of typical radius, i.e., the flow in it relaxes instantaneously to the average value at the boundary along the entire length of the vessel.

The length scale λ characterizes the distance over which pulsatility is damped in a vessel of radius R . For the typical radius R_0 , the pulsatile components of the flow are effectively attenuated in vessels with $L/\lambda_0 \gg 1$. As the radius of the vessel decreases, the damping distance λ for a vessel becomes shorter, rendering the vessel less able to sustain flow pulsatility. Thus even with finite compliance, a vessel may respond to periodic driving in a nondynamical manner if the damping length scale is much shorter than its length. The two parameters τ_0 and λ_0 allow us to qualify the response of a network with many vessels of typical radius but differing lengths to pulsatile driving at a given well-defined frequency ω .

Decomposing $Q(z, t)$ and $\sigma(z, t)$ into their Fourier modes, the relation between the axial current and the wall shear stress is given by [58]

$$\begin{aligned} Q(z, t) &= \sum_{n=-\infty}^{\infty} \tilde{Q}^{(n)}(z) e^{in\omega t}, \\ \sigma(z, t) &= \sum_{n=-\infty}^{\infty} \tilde{f}^{(n)} \tilde{Q}^{(n)}(z) e^{in\omega t}, \end{aligned} \quad (9)$$

with

$$\tilde{f}^{(n)} = \begin{cases} \frac{1}{R^3}, & \text{if } n = 0 \\ \frac{i n \omega \rho J_1(x^{(n)})}{\pi R (x^{(n)} J_0(x^{(n)}) - 2 J_1(x^{(n)}))}, & \text{if } n \neq 0 \end{cases} \quad (10)$$

where $x^{(n)} = i^{3/2} W_o^{(n)}$ and $W_o^{(n)} = R \sqrt{n \omega \rho / \mu} = \sqrt{4 n \omega \tau}$ is the Womersley number of the n th mode, a well-defined parameter that characterizes pulsatile flows by relating the driving frequency to viscous effects. In Eq. (10), J_0 and J_1 are the zeroth- and first-order Bessel functions of the first kind.

Equations (6) and (7) allow for exact solutions for the axial pressure and current in a vessel as long as their boundary values (either pressure or current) are known. The solutions for Q and P for each vessel can be expressed in terms of ω , L and the values of λ , τ , and α for that vessel at each time step of adaptation (see Sec. I of the Supplemental Material [59]). The driving signal for radius evolution $\langle \sigma Q \rangle$ can thus be calculated for each vessel in the network, and we obtain for the e th vessel

$$\langle \sigma_e Q_e \rangle = \sum_{n=-\infty}^{\infty} \text{Re}[\tilde{f}_e^{(n)}] \langle Q_e^2 \rangle^{(n)}, \quad (11)$$

where $\langle Q_e^2 \rangle^{(n)}$ is the contribution of the n th frequency mode to the mean-squared current $\langle Q_e^2 \rangle$ (see Sec. II of the

Supplemental Material for full functional form of $\langle \sigma_e Q_e \rangle$ [59]). Thus the driving signal for the pulsatile-flow rule [Eq. (5)] differs from that of the steady-flow rule [Eq. (1)], with the contribution of each frequency mode weighted by the real part of $\tilde{f}$ in the former, which captures the phase difference between the flow rate and the wall-shear stress on the timescale of adaptation.

III. RESULTS

We study adaptation in networks of compliant vessels with different levels of loops, and with a pulsatile source current of the form $Q = Q_s + Q_p \sin(\omega t)$ entering and leaving the toy network through two externally driven nodes (Fig. 1). Such a choice allows us to mimic the closed circuit comprised by the mammalian circulatory system driven by the periodically beating heart. For the purposes of this study, we always assume finite pulsatility of the source current (i.e., $Q_p \neq 0$) even in the limit of small driving frequency. While we set $Q_s = Q_p = 1$ for most of this paper, we will also investigate the effect of varying Q_p while holding Q_s constant (see Sec. V of the Supplemental Material [59]). For completeness, we will show that our results are also generalizable to a network architecture with current sinks instead of a closed circuit (see Sec. VI of the Supplemental Material [59]).

The toy network illustrated in Fig. 1 is one example with three levels of loops, characterized as primary, secondary, or tertiary based on their proximity to the driven nodes (green) of the network. The possibility of vessel shunting and loop destabilization allows for many different long-time structures as depicted through arrows in Fig. 1. However, only one of these possible steady states is realized for a given set of initial conditions and for a particular driving frequency ω and metabolic cost parameter γ . We are interested in determining the conditions under which loops can be stabilized in such networks.

A scalar order parameter that characterizes the extent to which the steady-state structure is looped, is the network entropy S [60] given by

$$S = \sum_{j=0}^N P_j S_j, \quad (12)$$

where $P_j = Q_j / Q_s$ is the ratio of the total outflow (Q_j) from the j th node, to the net steady-flow source current Q_s . S_j is the Shannon entropy of the j th node given by

$$S = \sum_{k \in \mathcal{N}} p_{jk} \ln p_{jk}. \quad (13)$$

In Eq. (13), $\mathcal{N}$ is the set of all nodes connected to node j by a single edge and $p_{jk} = Q_{jk} / Q_j$ is the fraction of the total outflow Q_j that the outflow from node j to node k (Q_{jk}) constitutes. Qualitatively, the network entropy S quantifies the path uncertainty in the toy networks under steady-flow conditions: $S = 0$ corresponds to there being a single path between the two externally driven nodes (cases 1–3 in Fig. 1), $S = 1$ corresponds to every path between the two driven nodes being equally probable (case 8 in Fig. 1), and $0 < S < 1$ corresponds to some paths between the driven nodes being more probable than others (cases 4–7 in Fig. 1).

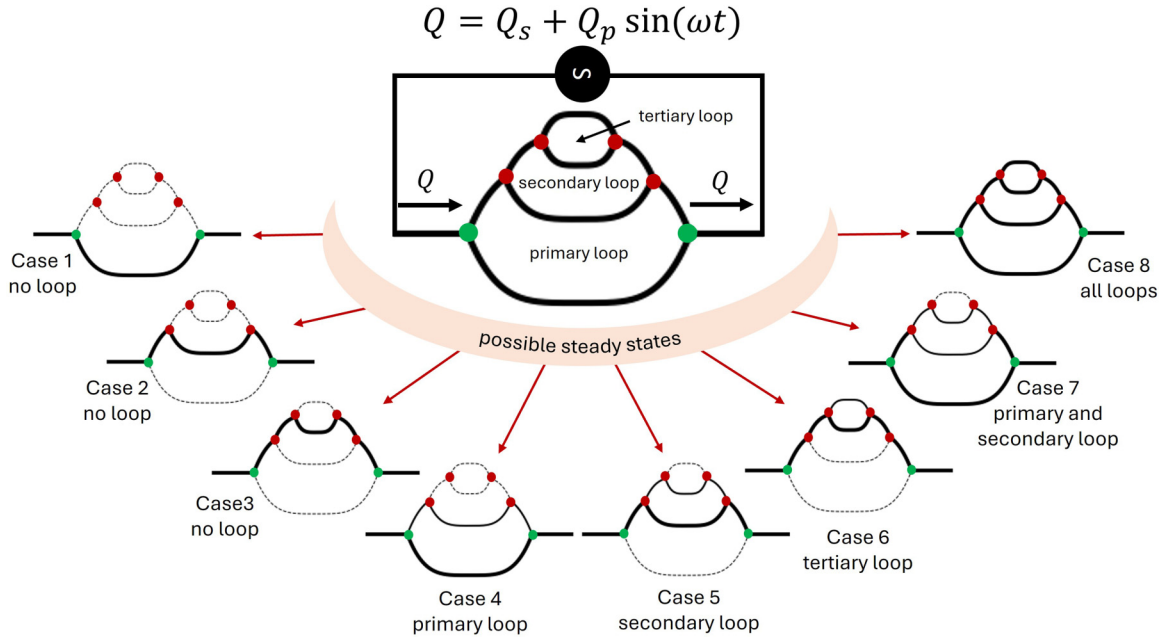


FIG. 1. Eight-vessel toy network with a current Q from the pulsatile source entering and leaving the network through two externally driven nodes (green dots), and with three levels of looping. Arrows point to possible steady states that may be obtained through long-term adaptation of the network, with dashed lines illustrating vessel shunting, i.e., the vessel radius going to zero.

In what follows, we will consider three different network architectures: a two-vessel network with only a primary loop; a five-vessel network with a primary and a secondary loop; and an eight-vessel network identical to Fig. 1 with a primary, secondary, and a tertiary loop. For the simplest two-vessel network, we will compare the results of the steady-flow rule in Eq. (1) and the pulsatile-flow rule in Eq. (5) for different values of γ and ω and show that they yield qualitatively similar structure phase diagrams in the γ - $\omega\tau_0$ phase space. For the five- and eight-vessel networks, we will only report the long-term structures stabilized by the pulsatile-flow rule and analyze the phenotypic variation of the steady state with the driving frequency and differences in the path lengths between the externally driven nodes.

A. Two-vessel network

Figure 2(a) illustrates the two-vessel network with a single loop between the two driven nodes. In all cases the flow is pulsatile. However, the relevant cost function plotted can either follow the steady-flow relevant rule of Eq. (1), or the pulsatile-flow relevant rule of Eq. (5). Figures 2(b) and 2(c) show the energy D_e dissipated per unit time in the e th vessel of the two-vessel network for the steady-flow rule case, while Figs. 2(d) and 2(e) show the same for the pulsatile-flow rule case. Figures 2(b) and 2(d) correspond to vessels of equal lengths $L_1 = L_2$, whereas Figs. 2(c) and 2(e) correspond to the case where one vessel is shorter than the other. In both the steady-flow and the pulsatile-flow cases, we look at the energy dissipation in each vessel (differentiated by solid and dashed curves) as a function of the rescaled frequency $\omega\tau_0$ for two different sets of radii R_1 and R_2 (green or orange) for the two vessels. In each case, we find that the energy dissipated is amplified for $\omega\tau_0 \neq 0$, i.e., when the nondynamical

approximation is relaxed. The amplification of dissipation is maximized at certain resonant frequencies, which are identical in each vessel only when their lengths are equal.

In comparing Figs. 2(b) and 2(c) with Figs. 2(d) and 2(e) we find that the pulsatile-flow case shows higher dissipation amplification for both vessels and for all $\omega\tau_0$, in comparison to the steady-flow case. Additionally, the amplification of the dissipated energy becomes progressively more pronounced in the pulsatile-flow case as the rescaled frequency $\omega\tau_0$ increases, unlike in the steady-flow case where all resonant peaks have more or less the same height. Moreover, while the dissipation of the thicker vessel is always larger, the asymmetry in the amplification of dissipation in the two vessels is much larger in the pulsatile-flow case than in the steady-flow case. In other words, the ratio D_2/D_1 , when vessel 2 is thicker than vessel 1, is larger for pulsatile-flow than for steady flow, especially close to resonances.

Figure 3 shows the phase diagram of the average network entropy $\langle S \rangle$ in the γ - $\omega\tau_0$ phase space for the long-time structures generated by the steady-flow adaptation rule (top row) as well as those generated by the pulsatile-flow adaptation rule (bottom row). As mentioned at the start of this section, the network entropy, averaged over many initial sets of radii for the two vessels, characterizes the “loopiness” of the steady-state network structure, such that $\langle S \rangle = 1$ corresponds to a symmetric loop ($R_1 = R_2$), $0 < \langle S \rangle < 1$ to an asymmetric loop ($R_1 \neq R_2$ but $R_1, R_2 > 0$), and $\langle S \rangle = 0$ to loop destabilization or shunting ($R_1 = 0$ or $R_2 = 0$), on average.

When short-term pulsatile dynamics is neglected and flow relaxation in individual vessels is assumed to be instantaneous (i.e., in the nondynamical limit), Eqs. (1) and (5) can both be analytically shown to lead to the destabilization of looped structures for all $\gamma > 1/2$ [9,25]. For $\gamma > 1/2$ the solution space of these adaptation rules goes from being convex to

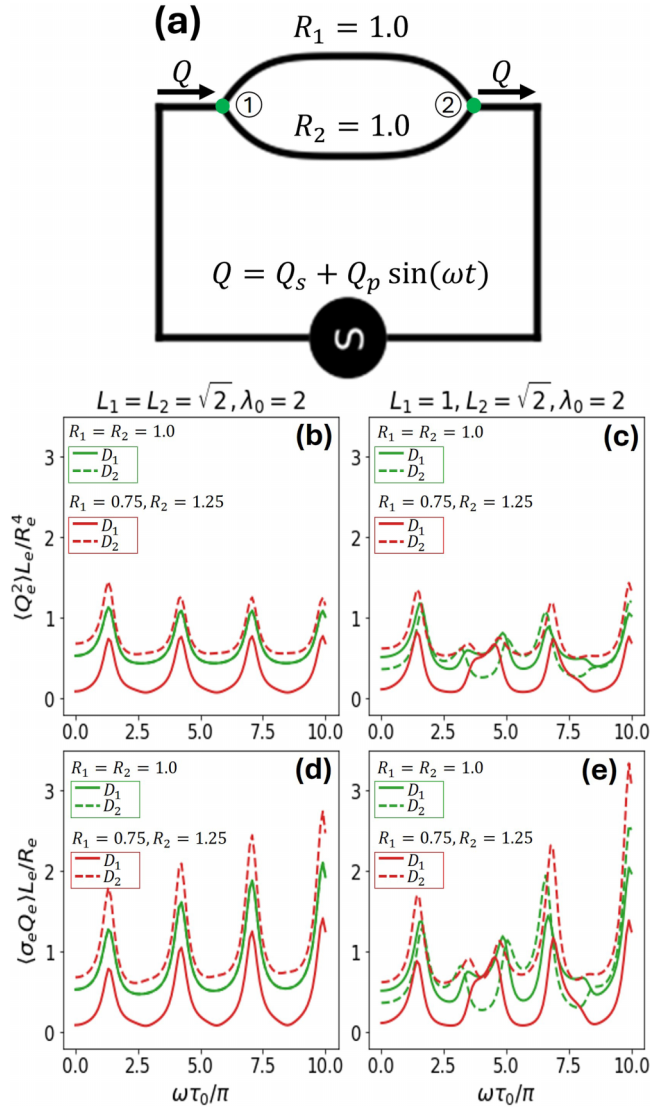


FIG. 2. (a) Two-vessel toy network. [(b)–(e)] The energy dissipated per unit time in the e th vessel as a function of the rescaled frequency $\omega\tau_0$ with $D_e = \langle Q_e^2 \rangle L_e / R_e^4$ in the steady-flow case in (b) and (c) and $D_e = \langle \sigma_e Q_e \rangle L_e / R_e^4$ in the pulsatile-flow case [(d) and (e)]. Panels (b) and (d) correspond to vessels of equal lengths $L_1 = L_2 = \sqrt{2}$, and panels (c) and (e) correspond to a case of unequal vessel lengths with $L_1 = 1.0, L_2 = \sqrt{2}$. In (b)–(e), the solid curves correspond to vessel 1 and the dashed curves to vessel 2, whereas the two colors differentiate between two distinct sets of radii pairs: Green for $R_1 = 1.0, R_2 = 1.0$ and red for $R_1 = 0.75, R_2 = 1.25$. In both the steady-flow and pulsatile-flow cases, the dissipation is amplified in each vessel for $\omega\tau_0 > 0$, with maximum amplification occurring at certain resonant frequencies. The two vessels have identical resonant frequencies only when their lengths are equal, as in (b) and (d). The pulsatile-flow case generally shows higher dissipation amplification for all $\omega\tau_0$ than the steady-flow case, and this trend becomes progressively more pronounced as $\omega\tau_0$ is increased. $R_0 = \tau_0 = Q_s = Q_p = 1, \lambda_0 = 2$.

being nonconvex. In other words, they become "winner takes all" rules, which triggers an instability leading to a negative feedback loop whereby a marginally thicker vessel (higher dissipation) can grow continuously at the expense of a thinner

vessel whose dissipation has fallen below a certain threshold. This ultimately leads to the shunting of the thinner vessel, that is, the destabilization of the loop. The only exception to this is in the case where the two vessels have exactly equal starting radii, because they continue to have the same thickness throughout adaptation, preventing the "winner takes all" instability from being triggered [25]. However, even though two vessels with identical starting radii can support a symmetric loop at steady state for $\gamma > 1/2$, this steady state is unstable and can be rapidly destabilized by small perturbations.

The loss of convexity of these rules for $\gamma > 1/2$ should intuitively be understood as it being energetically favorable for the cost function—that balances dissipation and metabolic cost to construct or maintain the vessel—to route all flow through one big vessel rather than maintaining two thinner vessels. However, all physiologically relevant metabolic or material costs are characterized by γ values greater than $1/2$, suggesting that there must be an additional mechanism to stabilize loops in this range, given their ubiquity in biological networks.

In Fig. 3, both the steady-flow and the pulsatile-flow adaptation rules show loop stabilization for $\gamma > 1/2$ unlike in the nondynamical approximation ($\omega\tau_0 = 0$). This can be attributed to the weakening of the "winner takes all" effect in Eqs. (1) and (5) for $\gamma > 1/2$ when short-term pulsatile dynamics of compliant vessels is allowed to determine the long-term remodeling signal. This short-term pulsatility leads to the amplification of the energy dissipated in each vessel, ensuring that when one vessel is marginally thicker than the other, the dissipation of the thinner vessel is large enough to avoid a negative feedback loop leading to an instability and eventual shunting. Thus, it is really the ability to respond to the pulsatile flow in a compliant manner at short timescales that leads to robust loop stabilization for $\gamma > 1/2$ [25].

The critical value $\gamma_c(\omega\tau_0)$ above which the loop is destabilized shows periodic modulations with the rescaled frequency $\omega\tau_0$ for vessels of equal length in both the steady and the pulsatile flow cases. At resonant frequencies, for which the amplification of the energy dissipated in each vessel is maximal, loop stabilization is possible for the largest range of γ values, i.e., $\gamma_c(\omega\tau_0)$ is maximized. An overall increase in the lengths of equally long vessels, as reflected in going from Figs. 3(a) to 3(b) or from Figs. 3(d) to 3(e), results in shorter and more frequent resonant peaks. This is because as the length of a vessel increases in comparison to the damping length scale λ_0 , the effect of short-term pulsatile dynamics on its long-term remodeling signal decreases.

It is to be noted that a symmetric loop can always be stabilized in the case of vessels of equal lengths when both vessels start with identical initial radii. This is true both with the steady-flow and the pulsatile-flow rule, and owing to this special symmetry, the minimum network entropy in the equal-vessel-length cases [Figs. 3(a), 3(b), 3(d), and 3(e)] is close to 0.1, because a 10th of the initial radii considered for the average are exactly equal. This is in contrast to the case of unequal vessel lengths [Figs. 3(c) and 3(f)] where the symmetric loop is not always a stable steady state, for which the minimum values for $\langle S \rangle$ are of the order 10^{-16} .

In comparing Figs. 3(a)–3(c) and Figs. 3(d)–3(e) we find that the phase diagrams corresponding to the steady-flow and

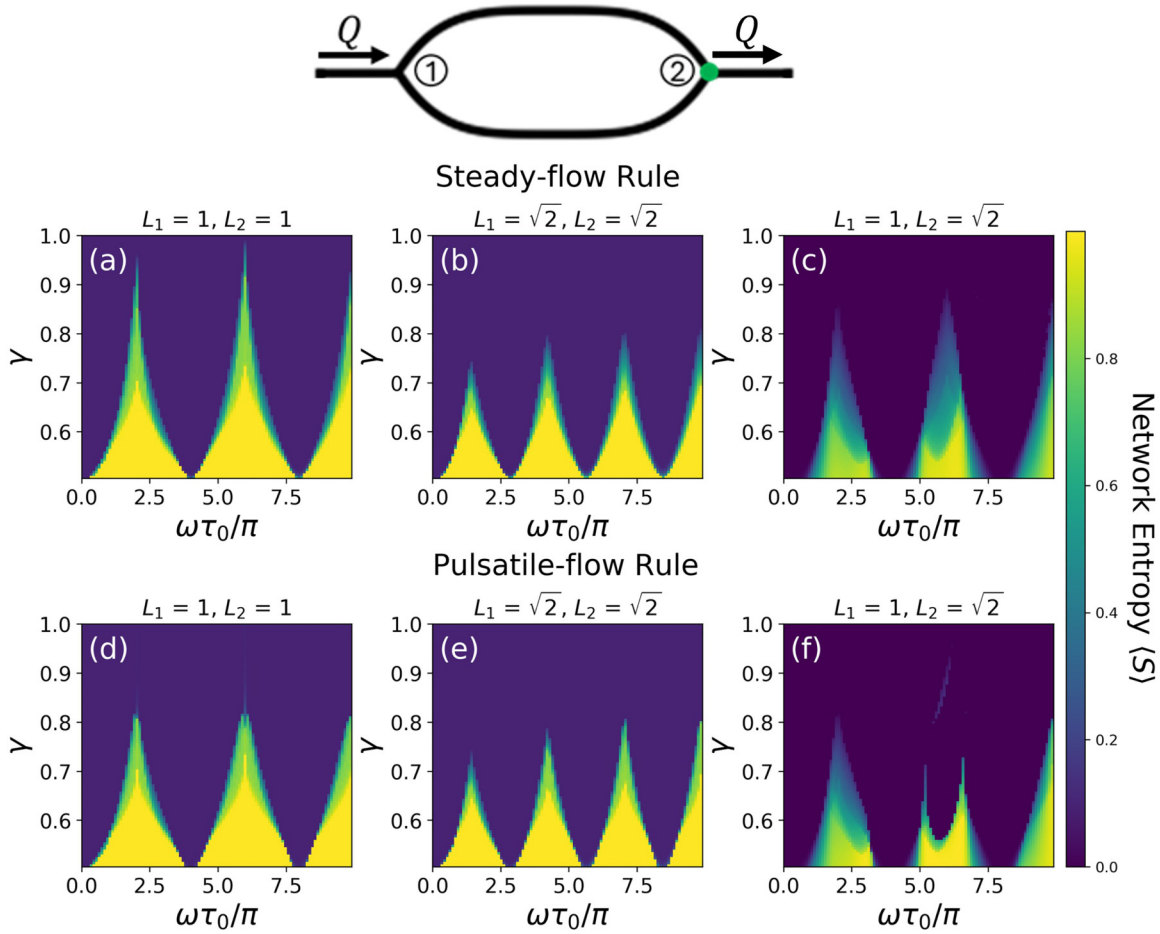


FIG. 3. Phase diagrams in the γ - $\omega\tau_0$ phase space for the average network entropy $\langle S \rangle$ over 144 initial conditions, where $\langle S \rangle = 1$ corresponds to a symmetric loop ($R_1 = R_2$), $0 < \langle S \rangle < 1$ to an asymmetric loop ($R_1 \neq R_2$ and $R_1, R_2 > 0$), and $\langle S \rangle = 0$ to shunting or loop destabilization ($R_1 = 0$ or $R_2 = 0$) on average. Panels (a)–(c) correspond to the steady-flow adaptation rule, with (a) and (b) considering cases of equal vessel lengths while (c) considers unequal vessel lengths. Similarly, (d)–(f) correspond to the pulsatile-flow rule, with equal vessel lengths considered in (d) and (e) but not in (f). In all cases, loops are stabilized in broad regions of the phase space with $\gamma > 1/2$, with $\langle S \rangle > 0$. For vessels of equal lengths [(a), (b), (d), and (e)], the critical value $\gamma_c(\omega\tau_0)$ above which loops become unstable, shows periodic modulations as a function of the rescaled frequency, reaching maximum values at certain resonant frequencies. An overall increase in the vessel length in comparison to the damping length scale λ_0 results in shorter and more frequent resonant peaks, as seen by comparing (a) to (b) and (d) to (e). For unequal vessel lengths, $\gamma_c(\omega\tau_0)$ is not strictly periodic, and loop stabilization can only occur in regions where the resonances of each vessel, which are distinct, have significant overlap. While the steady and pulsatile flow rules yield nearly identical phase diagrams in the equal-vessel-length cases [(a) and (b) and (d) and (e)], for unequal vessel lengths the two rules generate somewhat different steady-state structures especially in regions of the phase space where symmetric loops cannot be supported (e.g., around $\omega\tau_0 = 6\pi$). This is because of the heightened asymmetry in dissipation amplification of each vessel under the pulsatile-flow rule, which favors the growth of a thick vessel at the expense of the other, thinner vessel, leading to shunting instead of the stabilization of an asymmetric loop. The equal-vessel-length cases [(a), (b), (d), and (e)] can always stabilize a symmetric loop when the starting radii of the two vessels are exactly equal, unlike the case of unequal vessel lengths [(c) and (f)]. This leads to the minimum value of $\langle S \rangle$ to be higher in (a), (b), (d), and (e) than in (c) and (f). $R_0 = \tau_0 = Q_s = Q_p = a = b = 1$ and $\lambda_0 = 2$.

the pulsatile-flow adaptation rules only show minor quantitative differences in $\langle S \rangle$ for vessels of equal lengths, while for vessels with unequal lengths these differences are more pronounced. This can be explained by the larger asymmetry in the dissipation amplification of the two vessels with the pulsatile-flow rule, as illustrated in Figs. 2(d) and 2(e), especially close to resonances. This asymmetric dissipation amplification works in favor of the “winner takes all effect,” destabilizing loops where one would have existed if the network was evolved with the steady-flow rule, e.g., at $\omega\tau_0 = 6\pi$ in Figs. 3(c) and 3(f).

It must be noted however, that despite the differences between the steady states generated by the steady-flow and the pulsatile-flow adaptation rules in the case of vessels that have different lengths, the broad qualitative features of the network entropy phase diagrams, including the number and position of resonances, are the same between the two rules. Moreover, we compared them to two other rules not derived from an energy optimization functional, one with a driving signal given by $\langle \sigma_e^2 \rangle^\gamma / R_e^3$ and another with $\langle \sigma_e \rangle^{2\gamma} / R_e^3$. We chose these two rules to compare Eqs. (1) and (5), because they contain the simplest driving signals that can be constructed from just the

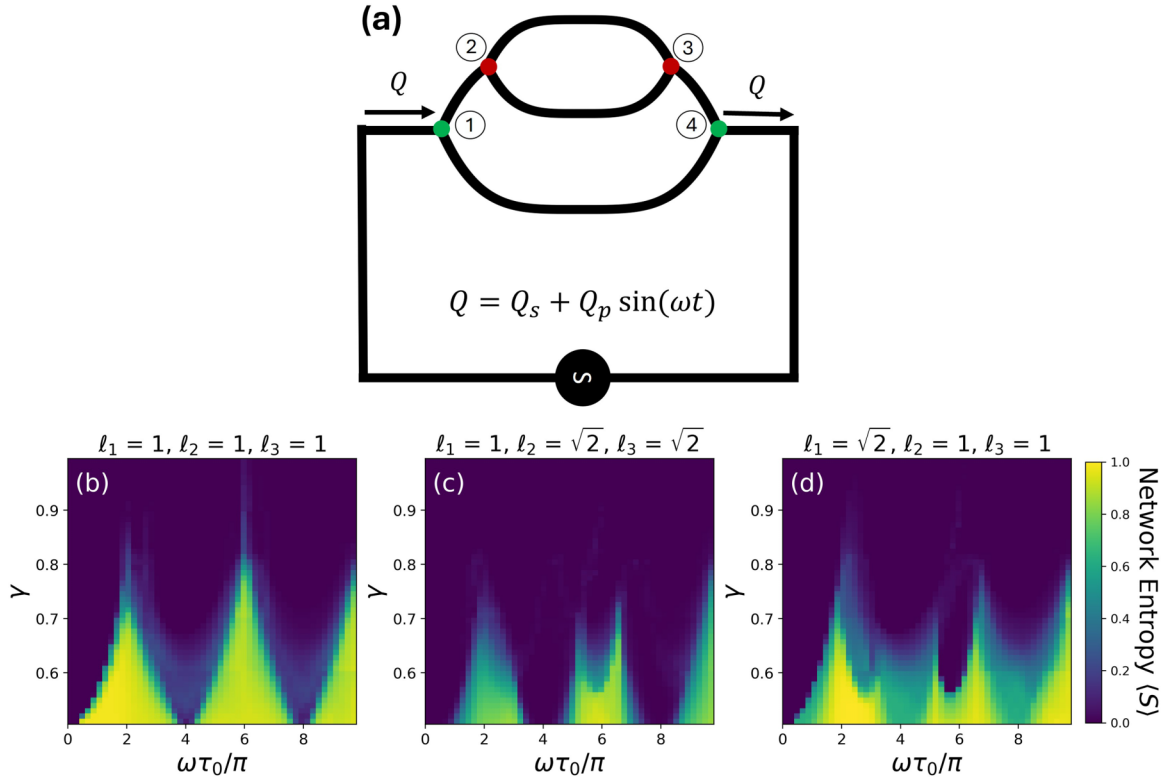


FIG. 4. (a) Five-vessel toy network. [(b)–(d)] Phase diagrams in the γ – $\omega\tau_0$ phase space for the average network entropy $\langle S \rangle$ for 250 initial conditions. The primary path length ℓ_1 corresponds to the length of the single vessel connecting nodes 1 and 4, whereas the secondary path lengths ℓ_2 and ℓ_3 correspond to the total length of the two paths that connect node 1 to 2 to 3 to 4. All three cases show robust loop stabilization for $\gamma > 1/2$, although the resonant frequencies at which loops are stabilized for the largest range of γ values, are periodically spaced only in the case where all three path lengths are equal, as in (b). For unequal path lengths, loop stabilization is stronger when the primary path is longer than the secondary path as in (d). $R_0 = \tau_0 = Q_s = Q_p = a = b = 1$ and $\lambda_0 = 2$.

wall shear stress, which we know can be directly sensed in the vessels locally. While the first yields closely related and qualitatively similar long-term structures to Eqs. (1) and (5), the latter, where the pulsatile contributions average to zero over one cycle of periodic driving, shows starkly different results (see Sec. IV of the Supplemental Material results [59]). These observations lead us to conclude that the mechanism of loop stabilization is less dependent on the exact rule that governs long-term remodeling and more on the ability of the rule to capture the short-term pulsatile dynamics of vessels in response to periodic driving. Additionally, they justify our use of the pulsatile rule [Eq. (5)] for network remodeling, even if its driving signal (involving the flow rate Q) cannot be exactly measured in individual vessels. This is because we can expect the actually measured adaptation signal in individual vessels to take the network at least approximately down the gradient of the pulsatile energy optimization functional Eq. (3). We will restrict our study to the pulsatile-flow rule in what follows.

While we hold $Q_s = Q_p = 1$ constant for most results reported here, we investigated the effect of varying the pulsatile amplitude Q_p in relation to the steady flow amplitude Q_s for the same two-vessel network architecture. Increasing Q_p increases the pulsatile contribution to the driving signal, which further amplifies the net dissipation in each vessel as compared to the results shown in Fig. 2 with $Q_p = 1$. Thus higher Q_p values lead to taller and broader resonant peaks in

the phase space of γ – $\omega\tau_0$ (see Sec. V of the Supplemental Material [59]). We also considered a case where the looped network and the pulsatile source do not form a closed circuit as in Fig. 2(a), but which instead has a sink node from which the steady part of the source current can flow out (see Sec. VI of the Supplemental Material [59]). We find robust loop stabilization for $\gamma > 1/2$ in this case as well, pointing to the generality of our results concerning the importance of short-term pulsatility, irrespective of network architectures and boundary conditions.

B. Five-vessel network

We now consider the five-vessel network illustrated in Fig. 4(a), which has a primary and a secondary loop, and three possible paths between the two driven nodes (green). Denoting each path length by ℓ_i , the path directly connecting the two driven nodes ($1 \rightarrow 4$, primary path) has length ℓ_1 and the two paths involving the vessels of the secondary loop ($1 \rightarrow 2 \rightarrow 3 \rightarrow 4$, secondary paths) have total lengths ℓ_2 and ℓ_3 . Note that ℓ_2 and ℓ_3 specify the total length of the two paths between nodes 1 and 4 that involve the secondary loop, and the lengths of the vessels connecting nodes 1 to 2, 2 to 3, and 3 to 4 along these paths are not separately specified. Figure 4(b) shows the phase diagram of the average network entropy $\langle S \rangle$ in the γ – $\omega\tau_0$ phase space for a few different values of the three path lengths ℓ_i . The fully looped structure is stabilized for

$\langle S \rangle = 1$, only one path between the two driven nodes survive when $\langle S \rangle \approx 0$, and a combination of paths between the driven nodes are possible when $0 < \langle S \rangle < 1$.

In agreement with results for the two-vessel network, we find that when the path lengths are equal, the critical value $\gamma_c(\omega\tau_0)$ oscillates as a function of $\omega\tau_0$ and is moreover maximized at resonant frequencies that occur with a well-defined periodicity [Fig. 4(b)]. Robust loop stabilization for $\gamma > 1/2$ also occurs for unequal path lengths and is stronger when the primary path ℓ_1 is longer than the secondary paths ℓ_2 and ℓ_3 , as can be seen from comparing Figs. 4(c) to 4(d).

Interestingly, the phase diagrams in Figs. 4(b) and 4(c) are very similar to those in Figs. 3(d) and 3(f) in the positioning, width, and height of resonances, suggesting that the addition of an extra (secondary) path does not appreciably change the long-time structure. However, because the two available paths between the driven nodes are equivalent in the two-vessel case, the steady state would be symmetric under an interchange of the lengths of the two vessels in Fig. 3(f). In other words, $L_1 = 1, L_2 = \sqrt{2}$ and $L_1 = \sqrt{2}, L_2 = 1$ would yield identical phase diagrams for $\langle S \rangle$. The fact that this is not true for the five-vessel network as seen in Figs. 4(c) and 4(d) confirms that the primary and the secondary paths are not equivalent. We highlight this observation to clarify that the similarity in the phase diagrams in Figs. 3(d) and 3(f) and Figs. 4(b) and 4(c) does not imply identical loop-stabilization irrespective of the complexity of the network architecture.

Figure 5(a) shows every possible long-time structure (SS1–SS5) for the five-vessel network, sequentially colored so that going from red to blue we go from the least looped to the maximally looped structure. Figures 5(b)–5(e) illustrate the fraction of each structure obtained at steady state for 250 sets of initial radii, as a function of $\omega\tau_0$ and for $\gamma = 2/3$. Figures 5(b) and 5(d) confirm that resonant (or antiresonant) frequencies occur with a well-defined periodicity when the path lengths between the driven nodes are equal. In these two cases, resonant frequencies stabilize either the full-looped structure [SS5 (blue)] or the primary loop [SS3 (yellow)] at steady state, whereas at antiresonant frequencies we either get completely loopless structures [SS1 (red) and SS2 (orange)] or only the secondary loop [SS4 (green)]. Moreover, an overall increase in path lengths leads to more closely spaced resonances and weaker net loop stabilization. This matches our observation with the two-vessel network where the effect of pulsatility and hence the possibility of loop stabilization is weaker in longer vessels.

Figures 5(c) and 5(e) confirm our observations from Figs. 4(c) and 4(d) that when the path lengths are unequal, resonances do not occur with any well-defined periodicity. However, the fully looped structure or the higher-level (primary) loop is once again stabilized at these resonant frequencies, whereas away from resonances we get loopless structures or lower level (secondary) loops. Moreover, comparing Figs. 5(c) and 5(e) we find that the probability for the secondary loop [SS4 (green)] to be stabilized away from resonances is larger when the primary path ℓ_1 is longer than the secondary paths ℓ_2, ℓ_3 . This further explains the larger looped $0 < \langle S \rangle < 1$ area in Fig. 4(d) as compared to Fig. 4(c) as arising through the shunting of the longer primary path

(higher resistance) in favor of the shorter secondary paths and thereby preserving the secondary loop more often on average.

C. Eight-vessel network

Next we look at the eight-vessel network illustrated in Fig. 6(a) with a primary, a secondary, and a tertiary loop and four possible paths leading from one source node to the other (1 and 6). The primary path connects the source nodes directly ($1 \rightarrow 6$) and has length ℓ_1 , the secondary path connects the source nodes through one branch of the secondary loop ($1 \rightarrow 2 \rightarrow 5 \rightarrow 6$) and has total length ℓ_2 (sum of lengths of all vessels participating in this path), and the two tertiary paths ($1 \rightarrow 2 \rightarrow 3 \rightarrow 4 \rightarrow 5 \rightarrow 6$) involve the two branches of the tertiary loop and have total lengths ℓ_3 and ℓ_4 . The long-time structures of this eight-vessel network, evolved through the pulsatile-flow adaptation rule [Eq. (5)], show qualitatively similar features to those of the two-vessel and five-vessel networks. Here we will restrict our analysis to a few descriptive cases of path-length asymmetry to further highlight our conclusions from the other two network architectures.

Figures 6(b)–6(e) show the $\gamma\text{--}\omega\tau_0$ phase diagram of the average network entropy $\langle S \rangle$ and compare the steady-state structures when all path lengths are equal (b) to cases when one of the tertiary paths (c) or the secondary path (d) or the primary path (e) are longer than the other paths between the two driven nodes. In all cases, we find loop stabilization for $\gamma > 1/2$, and except in Fig. 6(e), the critical value $\gamma_c(\omega\tau_0)$ above which looped structures are destabilized shows more or less periodic modulations with $\omega\tau_0$, peaking at resonant frequencies. For unequal path lengths we observe a progressive increase in the area of the phase space where looped structures are stable as we go from Figs. 6(c)–6(e), or in other words, as the longest path goes from being one of the tertiary paths, to the secondary path and finally the primary path.

Figure 7(a) shows every possible long-time structure SS1–SS11 for the eight-vessel network. Figures 7(b)–7(e) illustrate the fraction of each of these structures obtained at steady state for 250 initial conditions color coded according to Fig. 7(a), as a function of $\omega\tau_0$ and for $\gamma = 2/3$, for the path-length combinations illustrated in Figs. 6(b)–6(e). For the equal path-length case (b) resonances occur periodically, and at resonant frequencies the most encountered steady states in descending order of probability are the fully looped structure (SS11), the primary loop (SS4), or a combination of the primary and lower level loops (SS9 and SS8). At antiresonant frequencies, we get mostly loopless structures (SS1, SS2, and SS3), a small fraction of steady states with only the secondary (SS6) or the tertiary (SS7) loops preserved, and an even smaller fraction of steady states with a combination of the secondary and tertiary loops stabilized (SS10). The fact that at these antiresonant frequencies, loopless structures are more likely to have the primary path intact over the secondary or tertiary paths suggests that it is energetically more favorable to maintain a single long vessel than multiple vessels connecting the two driven nodes.

Figures 7(c)–7(e) show qualitatively similar features, with fully looped structures, higher-level loops, or combinations

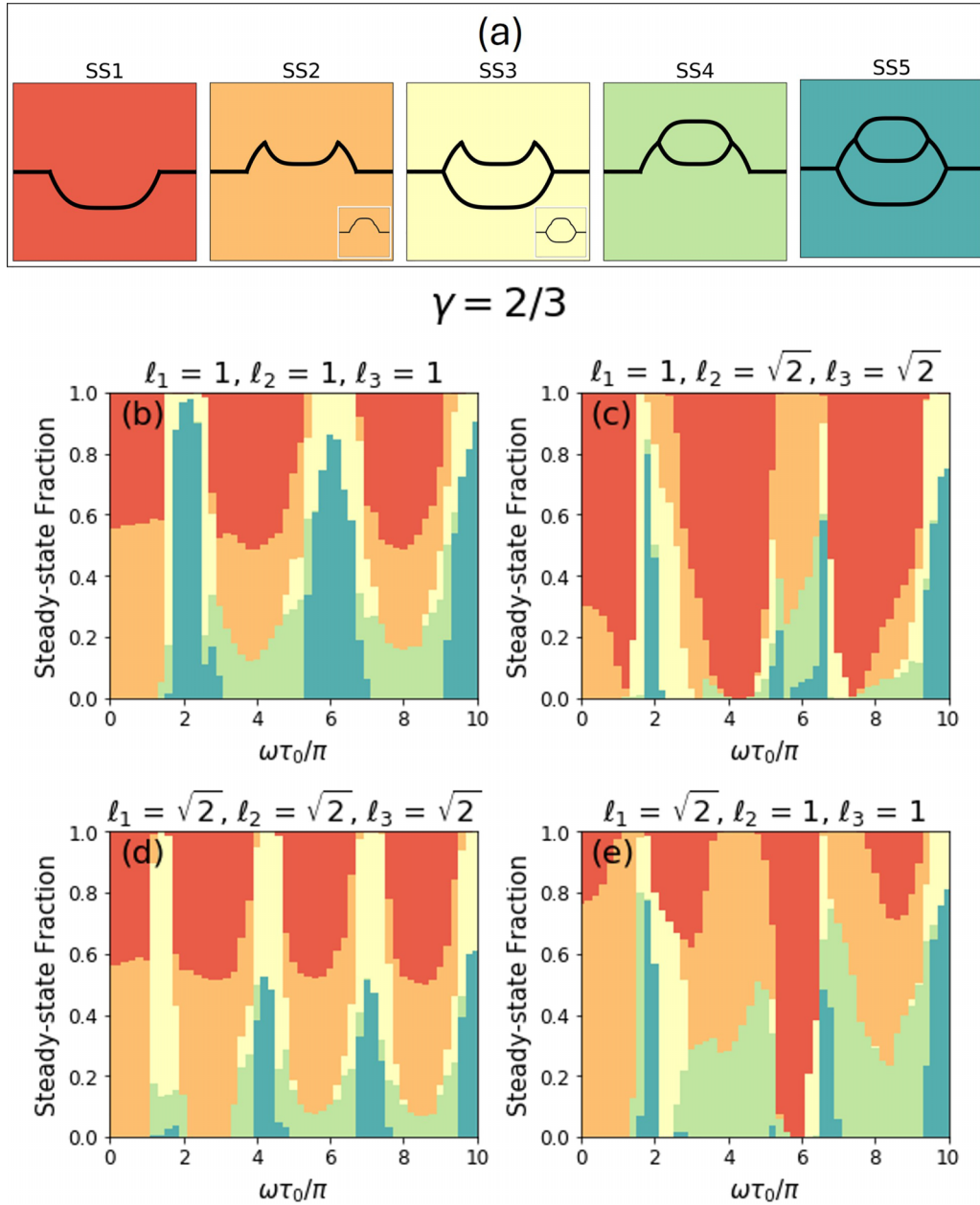


FIG. 5. (a) All possible steady-state (SS) architectures allowed for the five-vessel network. [(b)–(e)] Fraction of each possible structure in SS1–SS5 obtained at steady state for 250 different initial conditions, for $\gamma = 2/3$. The color coding of the steady-state fraction follows that of panel (a), e.g., red for SS1, orange for SS2, and so on. When the three path lengths between the driven nodes are equal, as in (b) and (d), resonant frequencies are periodically spaced, unlike in the unequal-path-length cases in (c) and (e). In all cases, however, resonant frequencies stabilize the fully looped structure (SS5) or the primary loop (SS3), whereas antiresonant frequencies lead to loopless structures (SS1 and SS2) or stabilize the secondary loop (SS4). Comparing (c) and (e) we find that when the primary path length (ℓ_1) is longer than the secondary path lengths (ℓ_2, ℓ_3), the probability that the secondary loop (SS4) is stabilized close to antiresonant frequencies is larger, and the probability of obtaining loopless structures (SS1 and SS2) is smaller. $R_0 = \tau_0 = Q_s = Q_p = a = b = 1$ and $\lambda_0 = 2$.

involving higher level loops prioritized for stabilization near resonances, whereas loopless structures, lower-level loops, or combinations involving lower-level loops favored away from resonances. What is different is that in these cases of unequal path lengths, resonant frequencies also stabilize lower level loops or combinations like SS10 and SS6, albeit with a lower probability. In Fig. 7(c), where one of the tertiary paths is longer than the other paths, the lower-level loop stabilized away from resonances is the secondary loop (SS6), whereas

the tertiary loop can only be stabilized in combination with the primary (SS9) or secondary loop (SS10) near resonances, and almost never on its own. Moreover, loopless structures that do not involve the longer tertiary path are preferred at antiresonant frequencies. In contrast, for (d) where the secondary path is the longest, it is the tertiary loop (SS7) that is preferred for stabilization away from resonances, and the secondary loop (on its own or in combination with the tertiary and primary loops, like in SS6, SS8, and SS10) can only be stabilized close

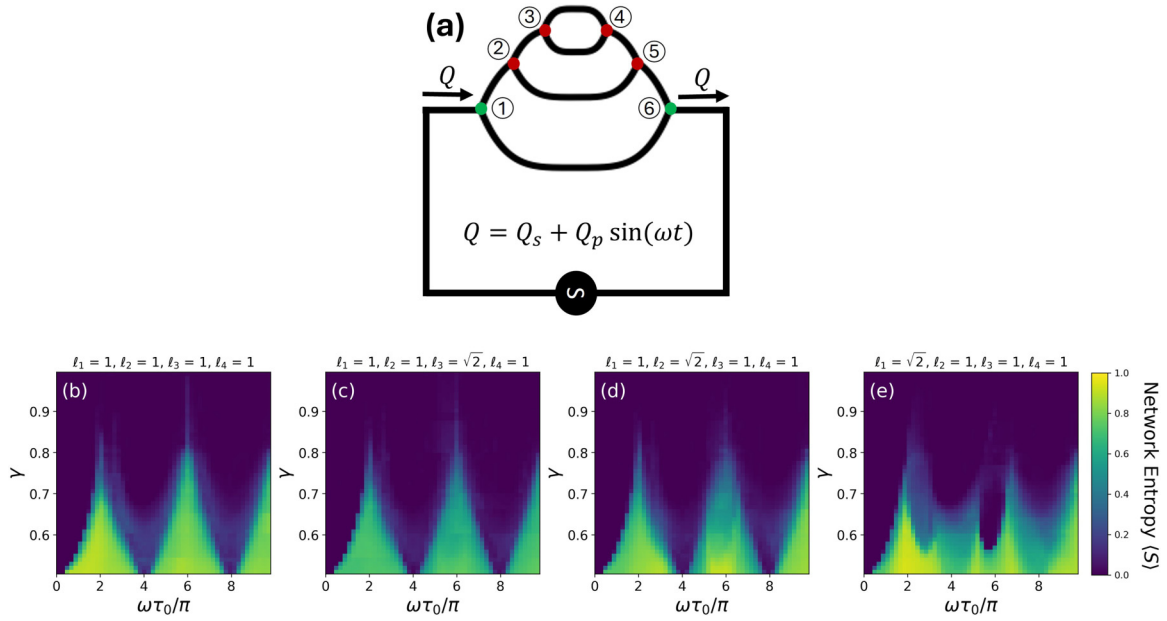


FIG. 6. (a) Eight-vessel toy network. [(b)–(d)] Phase diagrams in the γ – $\omega\tau_0$ phase space for the average network entropy $\langle S \rangle$ for 250 initial conditions. The primary path length ℓ_1 corresponds to the length of the single vessel connecting nodes 1 and 6, the secondary path length ℓ_2 corresponds to the total length of the path that connects $1 \rightarrow 2 \rightarrow 5 \rightarrow 6$, and the tertiary path lengths ℓ_3 and ℓ_4 correspond to the total lengths of the two paths connecting $1 \rightarrow 2 \rightarrow 3 \rightarrow 4 \rightarrow 5 \rightarrow 6$. All four cases show robust loop stabilization for $\gamma > 1/2$, and resonant frequencies at which loops are stabilized for the largest range of γ values are periodically spaced except in (e) where the primary path length is the longest. Going from (c) to (e) we observe progressively stronger stabilization of looped structures as the longest path goes from being one of the tertiary paths to the secondary path to finally the primary path. $R_0 = \tau_0 = Q_s = Q_p = a = b = 1$ and $\lambda_0 = 2$.

to resonant frequencies. The loopless structure involving the secondary path has very low probability of occurrence near antiresonant frequencies.

In contrast to the cases with longer secondary and tertiary paths [Figs. 7(c) and 7(d)], resonances lack periodicity when the primary path is the longest as in Fig. 7(e). In this case we observe shunting (SS1–SS3), stand-alone secondary (SS6) and tertiary loops (SS7), or a combination of the two (SS10) away from resonances, while the primary loop (alone as in SS5 or in combination as in SS8 and SS9) is only stabilized near resonances. Comparing (e) with (c) and (d) in Fig. 7 we find that the observed increase in the looped areas of the $\langle S \rangle$ phase diagram away from resonances when the primary path is longer than the secondary or tertiary paths [Fig. 6(d)], arises from the increased dominance of the steady state with both the secondary and tertiary loops preserved (SS10).

IV. DISCUSSION

In summary, we have introduced a new adaptation rule, showcased in Eq. (5), for networks of compliant vessels. This rule is more realistic for remodeling in the presence of pulsatile driving and emerges directly from dissipation minimization in dynamic conditions. We have compared the steady-state structures generated by this remodeling rule with those produced by a widely used quasisteady flow rule for animal and plant vascular development [Eq. (1)] for a minimal two-vessel network (Fig. 1). We showed that when short-term pulsatile dynamics in individual compliant vessels is accounted for in the long-term remodeling signal, both these rules allow for robust loop

stabilization. This loop stabilization is a result of resonances that amplify dissipation in each vessel at certain frequencies and takes place for a broad range of physiologically relevant metabolic costs where existing theories of adaptation would predict loopless structures. This is equally true of networks that do not form a closed circuit with the pulsatile source, as is the case for all results reported in the main text, but also for cases with current sinks (see Sec. VI of the Supplemental Material [59]).

The qualitative features of the structure phase diagram for different values of the driving frequency and the metabolic cost appear to be more or less independent of the exact remodeling rule, whether they are derivable from an energy optimization functional or not (see Sec. IV of the Supplemental Material [59]). This suggests that loop stabilization for physiologically relevant metabolic costs depends primarily on the ability of compliant vessels to respond dynamically to the pulsatile flow at short timescales. This dynamical response is affected by geometric considerations, i.e., length of paths that will be stabilized or shunted, coupling tightly the network geometry to the stabilized topology. As the phenomenon of loop stabilization is generally robust to the details of the use-it-or-lose-it remodeling rule, we expect it to be of importance in a large class of living networks that operate and remodel under pulsatile conditions.

Moreover, hierarchical networks with several levels of loops, when evolved through the pulsatile-flow remodeling rule, show considerable variability in their long-time structures. Consolidating the results from all three network architectures considered in this study, we find the following general observations. First, higher-level loops proximal to the

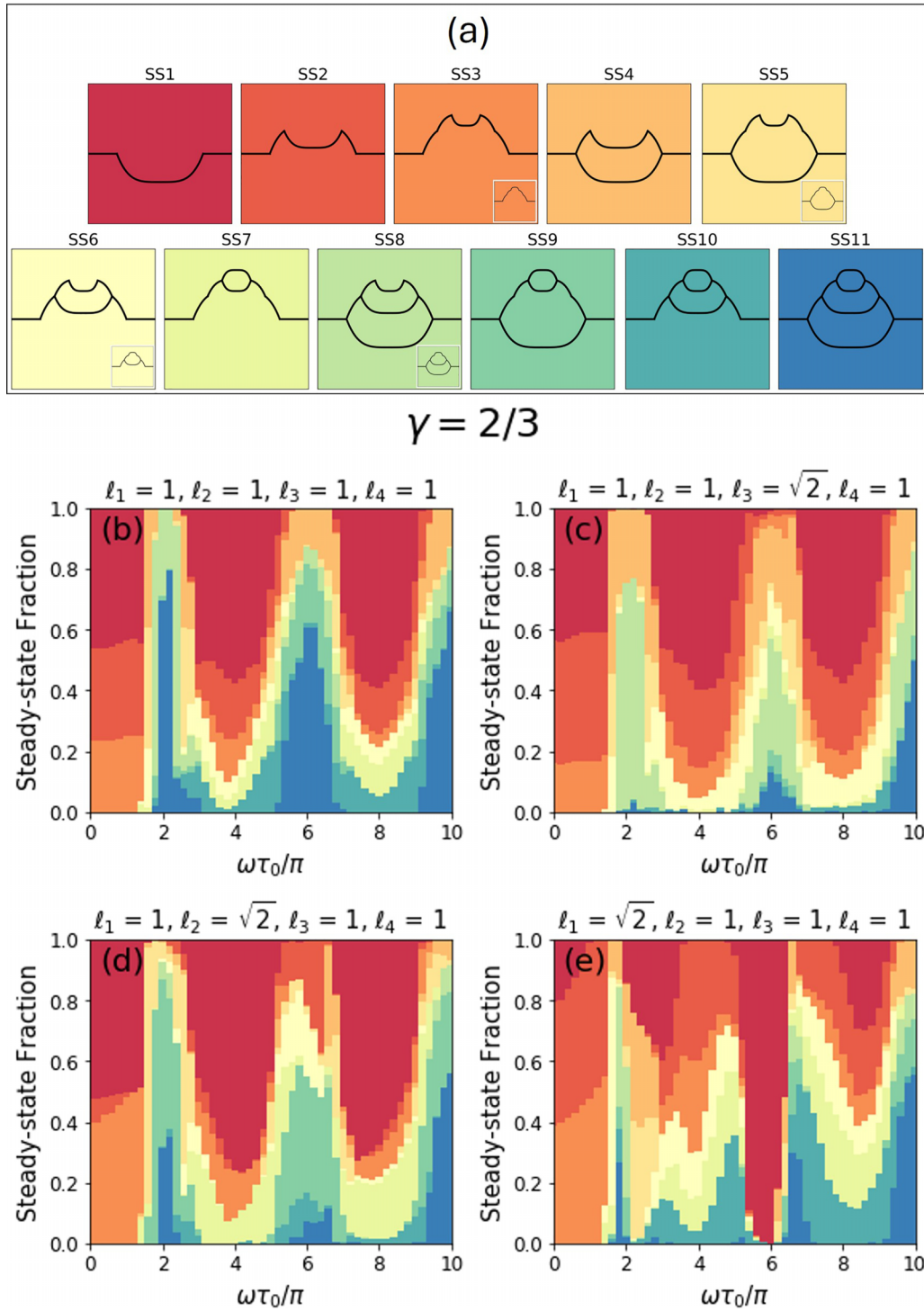


FIG. 7. (a) All possible steady states for the eight vessel network. [(b)–(e)] Fraction of each possible structure in SS1–SS11 obtained at steady state for 250 different initial conditions, for $\gamma = 2/3$. The color coding of the steady-state fraction follows that of panel (a), e.g., red for SS1, dark orange for SS2, and. Resonant frequencies are more or less periodic except when the primary path ℓ_1 is the longest, as in (e). In all cases, the fully looped structure, and the primary loop by itself or in combination with the secondary and tertiary loops are stabilized close to resonances. Away from resonances we see shunting, lower level loops, or a combination of lower level loops. In (c) where one of the tertiary paths is longer than the other paths, the lower level loop stabilized away from resonances is the tertiary loop, whereas in (d), where the secondary path is the longest, it is the tertiary loop that is stabilized away from resonances. For (e), where the primary path is the longest, the primary loop is harder to stabilize near resonances than in the other three cases considered, whereas away from resonances both the secondary and tertiary loops by themselves, but also their combination can be stabilized with ease. $R_0 = \tau_0 = Q_s = Q_p = a = b = 1$ and $\lambda_0 = 2$.

source, by themselves or in combination with lower-level loops, are prioritized for stabilization at or near resonant frequencies. In contrast, away from resonances it seems to be energetically more favorable to shunt one or more paths between the driven nodes, leading to loopless structures or preserving only the lower-level loops distal from the source (or combinations of them).

Second, path-length asymmetries play an important role in determining the network entropy, i.e., the overall "loopiness" of the steady-state structure. For the same radius, longer path lengths are associated with higher net dissipation. When paths that are distal to the source (secondary or tertiary paths) are the longest in the network, there is a decreased probability of stabilizing lower-level loops away from resonances, because it is energetically favorable to shunt these longer paths. In contrast, when the path most directly connected to the driven nodes (primary path) is longer than the others, lower-level loops can be preserved away from resonances, making the steady state more "loopy" (larger values of $\langle S \rangle$) in general in the phase space of $\gamma - \omega\tau_0$.

Thus, depending on the driving frequency, and the lengths of the various available paths between the source nodes, very different architectures are possible, ranging from more branched structures with lower level loops away from resonances and reticulated structures with higher level loops close to resonant frequencies. We conclude that the mechanism of loop stabilization through resonances arising from short-term pulsatility can offer an explanation for the wide variety of structural phenotypes observed in biology, even if our minimal networks do not capture the complexity of actual biological networks and flows.

For the sake of simplicity, we have assumed that the flow velocity in individual compliant vessels has a parabolic profile, which allows for exact solutions of the axial current and pressure as a function of time. In reality, however, the flow in

compliant vessels driven by pulsatile sources has Womersley profiles that deviate from the parabolic approximation more strongly as the driving frequency increases. While we relegate the construction and study of more realistic flow-dynamics models and network architectures to future work, the results presented here suggest that loop-stabilization through short-term pulsatile dynamics is a robust and general feature of periodically driven adapting networks of compliant vessels, which would carry over to improved models.

In a broader context, this work highlighted how an adaptive network, remodeling under local rules, can adopt a variety of loopy architectures due to the coupling of the vessel elasticity to the flow pulsatility and the emergence of resonances. This complex landscape of network architectures results from a competition between geometry (length of paths) and topology (path redundancy) and is influenced by the driving frequency of the power source. Given the robustness of the effect to the details of the remodeling rule, we believe that the underlying physics (pulsatile driving and resonance amplification) could be of interest in the context of learning in physical networks, in addition to its importance for vascular physiology.

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DATA AVAILABILITY

The data that support the findings of this article are openly available [61].

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