Self-Sustained Peristaltic Transport in Biological Systems: A Theoretical Study

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Human body can be viewed as a collection of systems, each playing a specific role in the function of the body as a whole [1]. Transporting systems – gastro-intestinal, cardiovascular, lymphatic, urinary, etc., – are important constituents of this collection.

Similar in functional attributes transporting systems share many common features in their structural organization: each can be regarded as a hollow tubular organ which relies (to a different extent) on peristaltic motility driven by muscle cells from within the wall of the conducting tube.

Coordinating contractile muscle activity of the adjacent tube segments is crucial for achieving efficient transport. Mechanisms that ensure the required coordination in different physiological transport systems have been the subject of many experimental and theoretical studies [2–10]. These studies have shown that the stimuli, which control the muscle cell activity, are to a large extent autonomous, independent of central nervous system input. Instead, the contractions are coordinated locally, by the so-called enteric nervous system.

A wonderful illustration to the autonomous, self-sustainable nature of peristaltic motility can be found, for example, in the work conducted by Prof. G.W. Mawe and his co-workers at the University of Vermont College of Medicine. Their research involves filming peristaltic motility of an isolated guinea-pig colon. The colon segment is kept vital by placing it into an

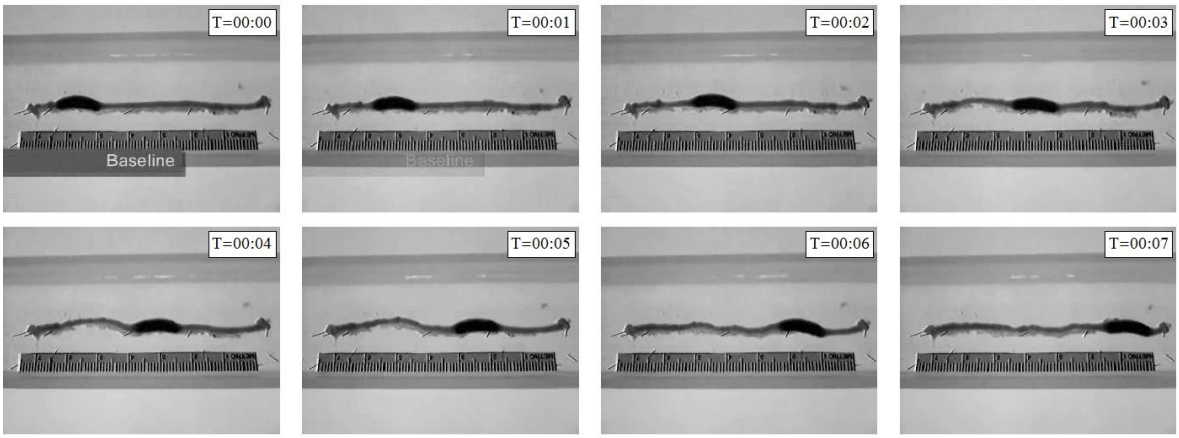

Figure 1: Image sequence illustrating the self-sustainable nature of peristaltic motility: a rigid pellet is being propelled by an isolated guinea-pig colon. See [11] for a detailed account of the experimental procedure. Courtesy of Prof. Gary W. Mawe, Department of Anatomy and Neurobiology, University of Vermont College of Medicine.

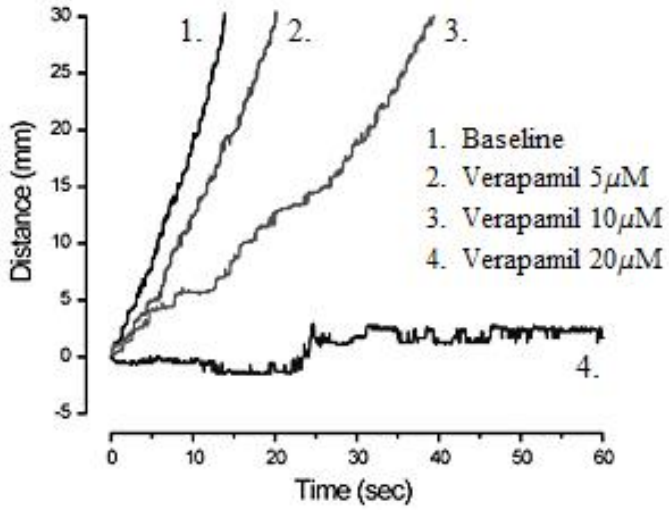

Figure 2: Dose-dependent reduction of peristaltic propulsion rate. Data are reproduced with permission of Dr. Gerald Herrera of Catamount Research and Development (www.catamountresearch.com).

oxygenated organ bath. Figure 1 gives a sequence of images from one of their experimental videos showing a rigid pellet being propelled along the isolated colon segment.

The analysis of experimental data shows that the velocity of the pellet remains fairly constant along the conducting vessel (see Fig. 2). Motility rates in the same preparation are consistent in sequential trials (see [12] for raw motility data recorded in a single specimen from a total of 8 experiments). The consistency of the results allows one to use the described experimental setup to monitor the response of the transporting system to various influences, in particular, pharmacological agents [12]. Figure 2 demonstrates the dose-dependent decline of peristaltic wave velocity caused by verapamil — a common drug for treating high blood pressure.

Assessing the adverse reaction of transporting organs to drugs is an important problem that relies on our understanding of the relationship between the motility rate and the state of the transporting system: the Young's modulus of the vessel, sensitivity to electrical and mechanical stimuli, etc. In our recent paper [13] we have tried to elucidate the abovementioned relationship by suggesting a mathematical model of self-sustained peristaltic motility.

The model relies on phenomenological representation of contraction control: we simulated the enteric nervous system with a chain of excitable elements [7, 8]. The excitable elements have been suggested to be sensitive to mechanical stretch. The ability of a transporting system to perform autonomous peristaltic pumping was interpreted in terms of the model as the ability to propagate sustained waves of wall deformation.

Figure 3 shows a typical example of a solution of the model equations: a stationary peristaltic wave with a lumen deformation profile given by $\varepsilon(z)$ and a (non-dimensional) pressure profile given by $p(z)$. Fig. 4 plots the position of the wave's crest over time to illustrate the establishment of a stationary regime of propagation in numerical experiments (compare to Fig. 2).

The analysis of the model allows one to conclude, among other things, that local sensitivity to radial stretch is, in fact, sufficient to organize contractions into a self-sustained propagating deformation wave even in the absence of "horizontal" control from within the enteric network. The mechanism of propagation is as follows. The transported fluid bolus results in the dilation of the tube segment, which, being sufficiently large, causes the vessel segment to contract. Contraction pushes the fluid bolus into the adjacent segment where it,

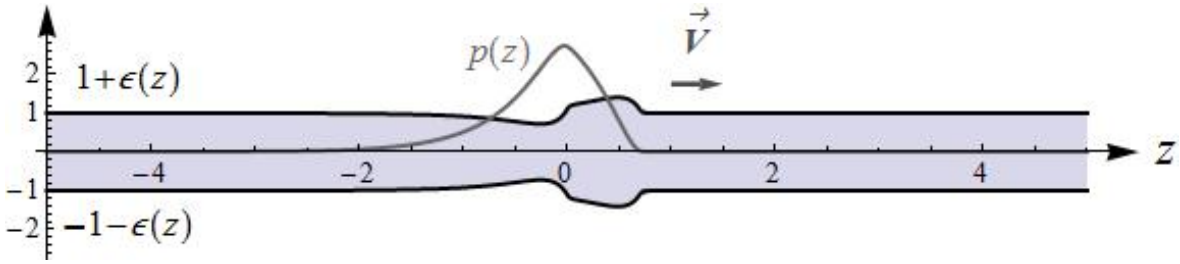

Figure 3: A mathematical representation of a self-sustained travelling peristaltic wave. The position of the lumen is given by $1+\varepsilon(z)$ and $-1-\varepsilon(z)$ lines. The associated pressure wave is denoted with $p(z)$. The arrow with a letter "V" above it denotes the direction in which the wave is moving.

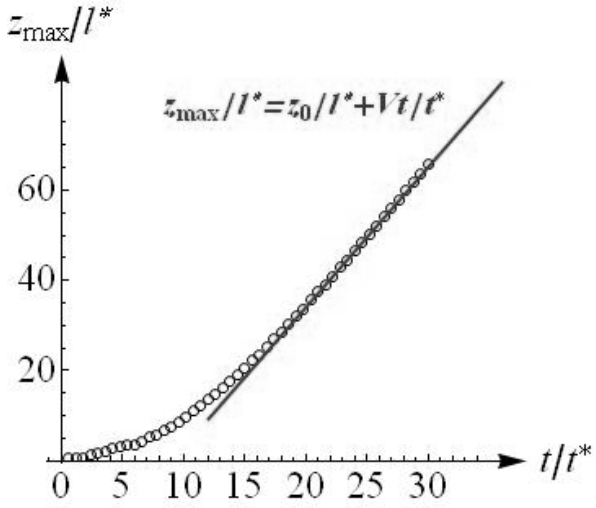

Figure 4: The result of a typical numerical experiment: distance from the vessel boundary to the crest of the wave $z_{\max}$ plotted over time t. l^* and t^* denote characteristic length and time scales. Fitting of data to a straight line is shown for points distant from the vessel boundary. Compare to Fig. 2.

in turn, causes dilation. If the dilation reaches a threshold value, contraction is triggered and the sequence of events repeats itself.

In this paper we are trying to advance our understanding of coupling through mechanosensitive control circuits by asking whether other mechanical stimuli, beside radial stretch, are capable of coordinating peristaltic motility. In particular we focus our attention on shear stress, as shear stress is known to be a potent regulator of muscle cell activity. It is especially important in blood vessel physiology [15–17] where it is suspected to play an important role in coordinating the propagation of waves of vasorelaxation [18–22].

Mathematical model

For the purpose we formulate a simple phenomenological model of a shear stress-sensitive muscular vessel. The equations of the model are as follows:

$$(1+\varepsilon)\frac{\partial \varepsilon}{\partial t} = \frac{{R_0}^2}{16\mu}\frac{\partial}{\partial z}\left((1+\varepsilon)^4\frac{\partial p}{\partial z}\right) \tag{1}$$

$$p+\tau_s\frac{\partial p}{\partial t} = E\left(\varepsilon+\tau_c\frac{\partial \varepsilon}{\partial t}\right)+p_a, \tag{2}$$

$$\frac{\partial p_a}{\partial t} = S(\sigma) - \beta(p_a - p_1)(p_a - p_2)(p_a - p_3). \tag{3}$$

Eq. (1) results from applying lubrication theory approximations to the equations of motion of an incompressible Newtonian fluid of viscosity μ in a tube undergoing axisymmetric deformation [23–25]. The variables introduced are wall deformation $\varepsilon = \varepsilon(z,t)$ and transmural pressure $p = p(z,t)$. R_0 denotes the radius of the lumen at rest, when the vessel wall is unstrained and unstimulated.

Eq. (2) arises from circumferential stress-strain relationship given by the standard 4-element linear solid model of viscoelastic wall material [26, 27]. Parameters τ_s, τ_c define the characteristic time-scales of stress relaxation and creep of an unstimulated vessel. E is the measure of wall stiffness ($E \simeq Yh_0/R_0$ where Y denotes the Young's modulus of the vessel wall material). The p_a-term is added to the linear solid model to account for contractile forces that arise in response to regulatory stimuli.

Eqs. (1) and (2) have been used to describe, respectively, the fluid flow and the vessel wall dynamics in our previous work [13] dedicated to the analysis of regulatory potential of stretch-induced stimuli. The novel Eq. (3) models the ability of the vessel wall to relax when the shear stress σ on the luminal surface increases. As in [13] we suggest that, as a first approximation, the local response to a regulatory stimuli can be described as threshold «switching» from a «relaxed» state (with $p_a = p_1$) to a «stressed» one (with $p_a = p_3 > p_1$) and vise versa. A cubic reaction term is used to describe threshold behavior.

The term $S(\sigma)$ represents a mechanosensitive stimulus associated with local shear stress σ. One can easily show that within the bounds of lubrication theory approximation the shear stress σ is given by the following expression:

$$\sigma = -\frac{R_0(1+\varepsilon)}{2}\frac{\partial p}{\partial z}.$$

Suggesting $S(\sigma)$ to be independent of the direction of the flow [17] and linear with respect to the absolute value of the shear stress (as a first approximation) one comes to the following expression for $S(\sigma)$:

$$S(\sigma) = -\alpha(1+\varepsilon)\,|\partial p/\partial z|, \quad \alpha = const > 0. \tag{4}$$

We focus on solving the following basic problem: finding traveling-wave solutions of wall relaxation from the «stressed» state $p_a = p_3$ ($\varepsilon = 0$) into the «relaxed» state $p_a = p_1$ ($\varepsilon = 0$).

Assuming

$$p(z,t) = p(\xi), \quad \varepsilon(z,t) = \varepsilon(\xi), \quad p_a(z,t) = p_a(\xi), \tag{5}$$

where $\xi = z - Vt$ and V ($V > 0$) denotes the velocity of the traveling wave, one derives from Eqs. (1)-(4):

$$-16\mu V(1+\varepsilon)\varepsilon' = {R_0}^2\Big((1+\varepsilon)^4 p'\Big)', \tag{6}$$

$$p - V\tau_s p' = E\left(\varepsilon - V\tau_c\varepsilon'\right) + p_a, \tag{7}$$

$$-V p_a' = -\alpha(1+\varepsilon)\left|p'\right| - \beta(p_a - p_1)(p_a - p_2)(p_a - p_3). \tag{8}$$

(The prime denotes differentiation with respect to ξ.)

To simplify the analysis let us introduce an analytically tractable approximation of Eqs. (6)-(8). For the purpose we restrict our analysis to small deformation values[1] so that nonlinear terms in Eq. (6) can be neglected (see [13] for details). Also, we replace the cubic reaction term in Eq. (8) with a piecewise linear analogue.

After introducing the following dimensionless quantities ($\Upsilon = p_3 - p_2$):

$$\begin{gathered}\tilde{\xi} = \xi\left(\frac{R_0}{4\Upsilon}\sqrt{\frac{E}{\beta\mu}}\right)^{-1},\ \tilde{p} = \frac{p-p_1}{\Upsilon},\ \tilde{\varepsilon} = \frac{E\varepsilon}{\Upsilon},\ \tilde{p}_a = \frac{p_a-p_1}{\Upsilon},\ \tilde{V} = V\left(\frac{R_0\Upsilon}{4}\sqrt{\frac{\beta E}{\mu}}\right)^{-1},\\ \tilde{\tau}_s = \Upsilon^2\beta\tau_s,\ \tilde{\tau}_c = \Upsilon^2\beta\tau_c,\ \tilde{\alpha} = \alpha\left(\frac{R_0\Upsilon}{4}\sqrt{\frac{\beta E}{\mu}}\right)^{-1},\ \tilde{p}_a^{thr} = \frac{p_2-p_1}{\Upsilon},\end{gathered} \tag{9}$$

the approximate model equations take the form:

$$-\tilde{V}\tilde{\varepsilon} = \tilde{p}', \tag{10}$$

$$\tilde{p} - \tilde{V}\tilde{\tau}_s\tilde{p}' = \tilde{\varepsilon} - \tilde{V}\tilde{\tau}_c\tilde{\varepsilon}' + \tilde{p}_a, \tag{11}$$

$$-\tilde{V}\tilde{p}_a' = -\tilde{\alpha}\left|\tilde{p}'\right| - \tilde{p}_a + H(\tilde{p}_a - \tilde{p}_a^{thr}). \tag{12}$$

We look for traveling wave solutions of (10)-(12) which satisfy the following boundary conditions:

$$\{\tilde{p}, \tilde{\varepsilon}, \tilde{p}_a\} \to \{1,0,1\},\ \text{at}\ \tilde{\xi} \to +\infty, \tag{13}$$

$$\{\tilde{p}, \tilde{\varepsilon}, \tilde{p}_a\} \to \{0,0,0\},\ \text{at}\ \tilde{\xi} \to -\infty. \tag{14}$$

Note that in view of (13)-(14) one can set $|\tilde{p}'| = \tilde{p}'$ in Eq. (12).[2]

Results

The procedure we follow to approach the problem (10)-(14) is described, for example, in [28–31]. We construct a traveling front out of two pieces: the leading edge where $\tilde{p}_a > \tilde{p}_a^{thr}$ and the trailing edge of the wave corresponding to $\tilde{p}_a < \tilde{p}_a^{thr}$. (Thanks to the piecewise linear character of the model the solutions for each piece are the sums of three exponentials — the general solution of the related homogeneous equation — and a particular solution.) The composite solution is subject to boundary conditions (13)-(14) and a matching condition (continuity) at $\tilde{p}_a = \tilde{p}_a^{thr}$.

Finding a composite solution that satisfies both the boundary and the matching conditions results in an eigenvalue problem [32–34]. The eigenvalues (the velocities $\tilde{V}$ of the traveling wave) are defined by the following implicit equation:

$$(1-\tilde{p}_a^{thr})k_1(k_1-k_2-k_3) = 1/\tilde{V}^2 + \tilde{p}_a^{thr}k_2k_3 - (k_2+k_3)/\tilde{V}. \tag{15}$$

[1] Note that deriving Eq. (10) requires integration of Eq. (6) prior to linearization. Integrating Eq. (6) is done assuming $\{p', p, \varepsilon\} \to \{0,0,0\}$ as $\xi \to \pm\infty$.

[2] Rigorously speaking replacing $|\tilde{p}'|$ with $\tilde{p}'$ requires us to suppose that pressure distribution $\tilde{p}(\tilde{\xi})$ is monotonous. The analysis of solutions with non-monotonous pressure profiles is beyond the scope of the present paper. Also, note that, given Eq. (10), the following equations are true: $S(\sigma) \equiv -\alpha|p'| = -\alpha p' = \alpha V\varepsilon = \hat{\alpha}\varepsilon$. Therefore, from a mathematical viewpoint, the regulatory stimuli due to shear-stress variation are equivalent to those induced by radial stretch in the small deformation limit.

Here k_n, $n = 1,2,3$ represent the roots of the of the differential system's characteristic equation $L(k) = 0$:

$$L(k,\tilde{V}) = c_3(\tilde{V})k^3 + c_2(\tilde{V})k^2 + c_1(\tilde{V})k + c_0(\tilde{V}),$$

where

$$c_3(\tilde{V}) = \tilde{\tau}_c\tilde{V}^2, \quad c_2(\tilde{V}) = \tilde{\tau}_s\tilde{V}^3 - (1+\tilde{\tau}_c)\tilde{V},$$
$$c_1(\tilde{V}) = 1 + \tilde{\alpha}\tilde{V} - (1+\tilde{\tau}_s)\tilde{V}^2, \quad c_0(\tilde{V}) = \tilde{V}.$$

Numerical analysis of Eq. (15) indicates that, in general, two different solutions can be found for each set of governing parameters $\{\tilde{\tau}_s, \tilde{\tau}_c, \tilde{\alpha}, \tilde{p}_a^{thr}\}$. Stability analysis shows that solutions with a smaller propagation velocity are unstable. The eigenfunctions corresponding to particular solutions of Eq. (15) define the profile of deformation and pressure along the wave. A typical stable solution is presented in Figure 5. The solutions resemble waves that were hypothesized to propagate in vessels with Bayliss regulation of myogenic activity [35].

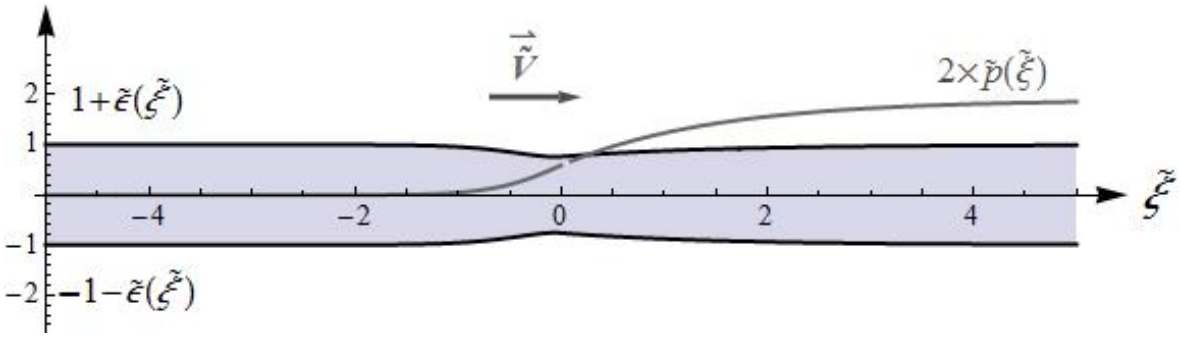

Figure 5: An example of a traveling wave of vasorelaxation-type of solution ($\tilde{\tau}_s = 0.08$, $\tilde{\tau}_c = 0.08$, $\tilde{\alpha} = 2.5$, $\tilde{p}_a^{thr} = 0.5$). The non-dimensional velocity is equal to $\tilde{V} = 1.97$.

Qualitative understanding of the solution's behavior can be obtained by analyzing the model with a quasi-steady state approximation of Eq. (12). Introducing

$$\tilde{\alpha}\tilde{p}' = -\tilde{p}_a + H(\tilde{p}_a - \tilde{p}_a^{thr}) \tag{16}$$

instead of Eq. (12) one can easily obtain the following explicit expression for the velocity of the wave[3] from an analogue of Eq. (15) :

$$\tilde{V}_\pm = \frac{(\tilde{\alpha} \pm \eta) + \sqrt{(\tilde{\alpha} \pm \eta)^2 + 4\tilde{\tau}_s}}{2\tilde{\tau}_s}. \tag{17}$$

Here $\eta = \sqrt{\tilde{\alpha}^2/\left(1-\tilde{p}_a^{thr}\right)^2 - 4\tilde{\tau}_c}$. (Note that the asymptotic profiles corresponding to explicit solutions given by (17) are no longer continuous. See [13] for a more comprehensive

[3]It is worth noting that, in addition to the quasi-stationary limiting case described in the main text, there is another special set of parameters at which the problem can be explicitely solved: $\tilde{\tau}_s = \tilde{\tau}_c \equiv 0$, $\tilde{p}_a^{thr} = 0.5$. The case therefore describes a system with a wall characterized by fast stress and strain relaxation and a «symmetric» mechanosensitive responce. The velocity in such a system is given by:

$$\tilde{V}_\pm = \frac{\tilde{\alpha} \pm \sqrt{\tilde{\alpha}^2 - 4}}{2}.$$

The existence condition is $\tilde{\alpha} > 2$.

discussion of an analogous asymptotic analysis in the case of stretch-induced mechanosensitivity.) The explicit solutions corresponding to (17) exist provided that

$$\tilde{\alpha} > 2\left(1-\tilde{p}_a^{thr}\right)\sqrt{\tilde{\tau}_c}. \tag{18}$$

It is interesting to note that the analysis of Eqs. (10)-(12) conducted above allows one to conclude that shear-stress sensitivity can mediate self-sustained propagation of another type of waves, namely waves of vasoconstriction in vessels with a "positive" contractile reaction to augmenting stress (with $\alpha < 0$, see Eq. (4)). Experiments indicate that such "positive" reaction to shear stress is characteristic to the blood vessels of the brain [36, 37].

To prove their existence one can make use of the fact that the system (10)-(12) is invariant with respect to the following substitution:

$$\begin{aligned} &\tilde{V} \to -\tilde{V}, \quad \tilde{\alpha} \to -\tilde{\alpha}, \quad \tilde{p}(\tilde{\xi}) \to 1-\tilde{p}(-\tilde{\xi}), \quad \tilde{\varepsilon}(\tilde{\xi}) \to -\tilde{\varepsilon}(-\tilde{\xi}), \\ &\tilde{p}_a(\tilde{\xi}) \to 1-\tilde{p}_a(-\tilde{\xi}), \quad \tilde{p}_a^{thr} \to 1-\tilde{p}_a^{thr}. \end{aligned} \tag{19}$$

Conclusions

We presented a simple mathematical model (1)-(3) of a shear-stress sensitive vessel. The model was used to analyze whether shear-stress sensitivity can serve as a factor securing peristaltic motility coordination.

The ability to coordinate motility was interpreted as the ability to ensure sustained propagation of deformation waves. The problem therefore was reduced to searching for traveling-wave solutions of the model equations.

To simplify the search a piecewise-linear approximation (10)-(12) of the model was introduced. The approximate model is analytically tractable. We used it to demonstrate the existence of sustained solutions, in particular traveling waves of vessel relaxation. We proceeded with developing an asymptotic quasi-steady state modification of the model and managed to derive the explicit formula for the velocity of the wave in a quasi-steady state model (see Eq. (17)) and the explicit condition securing their existence (18).

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