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Mathematical Modeling and Investigation on the Soft Tissue Structures in Micro-indentation Tests Based on Cylindrical Shell Model

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Abstract—**A new model for the micro-indentation test used to determine the material properties for the soft tissue is proposed in the present study. Based on the basic theory of elasticity, mathematical models such as infinite beam and circular plate are often adopted to describe the geometric characteristics of soft tissue. Other than the conventional simulations, say beam and plate, the author proposed a two-dimensional model for the tissue structure, which permits a hollow cylindrical shell with internal spring support and axial surface loads as the modelling of soft tissue. Different with the previous two, the shell model consists of two coupled differential equations involving both the transverse and longitudinal deformations as its main quantities. The proposed mathematical model offers additional information about the behaviours of the soft tissue in the micro-indentation test; meanwhile, the effect of residual stresses on the soft tissue with respect to both the transverse and longitudinal deformations can be thoroughly examined. The result of the present study matches the result by the simple beam model as long as the transverse displacement is under consideration; however, it reveals different illustration with that conducted by circular plate model due to the intrinsic variation on the governing equations. The longitudinal displacement of the soft tissue behaviour during indentation test is additionally presented in the study and the effect is shown to be parabolic-like in the case of stress free, however, it becomes almost linear when the residual stress is taken into account, and soon reaches its asymptotic state as the stress increases.**

***Index Terms*—Soft Tissue, Micro-indentation Tests, Cylindrical Shell, Residue Stress**

I. Introduction

Knowledge of mechanical properties and failure mechanism for biomaterials is quite essential to the experiment determining how bio-structures react on mechanical stresses. Indentation is a standard method for measuring the material properties of thin bio-structures, in which a small indenter is inserted into the material and the force on the indenter can thus be measured. With the advent of atomic force microscope (AFM), micro-indentation test becomes a feasible way to perform regional mechanical tests on cells or tissues under very small forces at the microscopic level. The data obtained from micro-indentation tests can be used to determine the relationship between the displacement of the tissue and the force on the indenter tip, namely the force-displacement (FD) relation, and thus enable us to find the desired material information.

The schematic diagram of micro-indentation setup is shown in Figure1, which is cited from Figure 4 in the paper conducted by Zamir and Taber [1]. Mathematical simulation for the micro-indentation test can facilitate the determination of the apparent material parameters, and also provide a reliable prediction on the local deformation of the cells or tissues. For the past few years, mathematical modeling for the indentation tests have been conducted by several investigators based on mostly the linear elasticity theory. Mow et al. [2] made a review article on the understanding of cartilage viscoelastic properties in compression by adopting the linear biphasic theory, in which flow-dependent viscoelastic effects are taken into account. Later on, compressible elastic models are used to predict the three-dimensional deformation of a tissue layer at equilibrium state [3], and the apparent shear modulus and Poisson ratio are characterized. Due to the fact that analytic solution for the stress-relaxation response is intractable in the indentation problem, Spilker et al. [4] carried out a finite element formulation for the linear biphasic continuum equations. However, the closed-form mathematical approximations for the axial displacement and normal stress have been successfully developed by Haider and Holmes [5] in modeling the Indentation of a thin compressible elastic layer.

Other than commonly used Fredholm integral equations, Sakamoto et. al. [6] proposed another method for theoretical analysis of static indentation test, in which infinite series is obtained as the closed-form solution instead. By extending their work in displacement and stress, Haider and Holmes [7] also analyzed the mathematical approximations by comparing the values of applied load to those obtained by classical integral transform solutions.

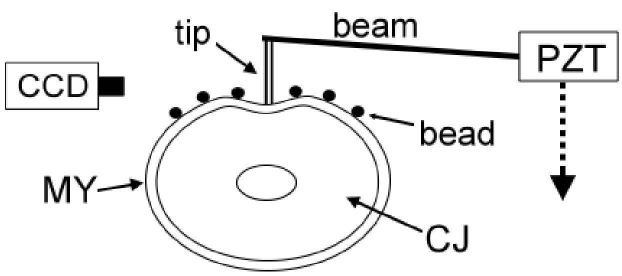

Fig. 1 Schematic diagram of micro-indentation setup showing cross-section of embryonic heart. CCD=charge coupled device (video camera), PZT=piezoelectric transducer, MY=myocardium, CJ=cardiac jelly.

While measuring the tissue modulus, several factors such as indenter geometry, material nonlinearity, large deformations and tissue heterogeneity, as well as the presence of residual stress should be all considered in order to achieve a better estimation in the modeling process. Costa and Yin [8] investigated the effects of indenter geometry, nonlinear material behavior, large deformations, and tissue heterogeneity in the analysis of AFM stiffness measurements. Recently, Zamir and Taber [1] have implemented a method that combines FD and surface displacement data from an indentation test to determine both the elastic properties and residual stress in soft tissues. In their study, the effects of residual stress was regarded as a pre-stressed layer embedded in or adhered to an underlying elastic foundation, in which two linear elastic models are introduced to approximate the specific biological structures. The first model is an axially loaded beam on a relatively soft, elastic foundation as shown in Figure 2, which can be adopted to model the biomechanics of stress-fiber embedded in cytoplasm. While the second is a radially loaded plate placing upon a spring foundation just as shown in Figure 3, which can be used to deal with the problem like cell membrane or epithelium.

The aforementioned models proposed by Zamir and Taber [1] are eventually resolved by using a self-contained package in a computer aided software like MatLab, also, the boundary conditions imposed on these two models are chosen as simply-supported at the ends of a pre-assumed length of soft tissue, their results are actually obtained by extending the length longer enough until slight changes in resulting data are reached.

To better understanding the mathematical simulation for the behavior of soft tissue in micro-indentation test, it is needed to re-describe these two models in an analytical point of view, that is, to re-model the indenter tip as an external force instead of additional boundary conditions, to analytically solve the tissue deformation in terms of a precise mathematical solution according to the correct boundary conditions, which reveals the fact that displacement at infinity is approaching zero and the tangent of displacement is horizontal at the indent spot.

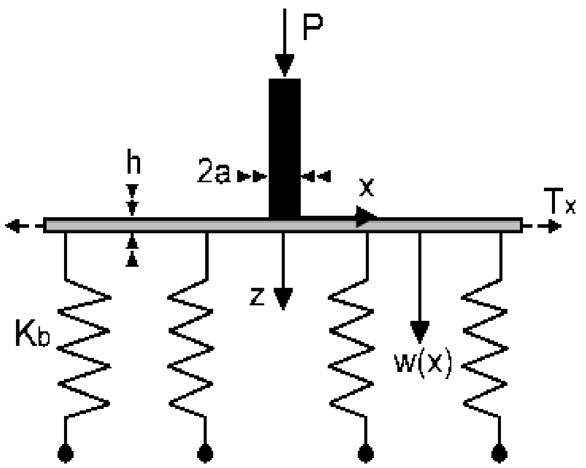

Fig. 2 Schematic diagram of soft tissue during micro - indentation as an elastic beam on a spring foundation with axial load and transverse indenter force.

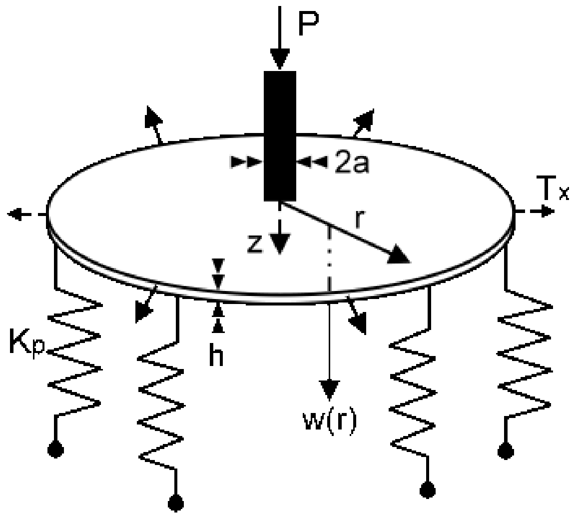

Fig. 3 Schematic diagram of soft tissue during micro-indentation as an elastic circular plate upon a spring foundation with radial tension and transverse indenter force.

In this paper, new mathematical model for the micro-indentation test is presented in order to specifically characterize the soft tissue behavior in a two-dimensional frame of work. The transverse and longitudinal displacements as well as the effect of residual stresses will be shown and compared with existing available literature in order to see the validity of the proposed methodology. The goal of the present study is to provide a two-dimensional analysis for the soft tissues structure in the micro-indentation test, which will be treated as an elastic hollow cylindrical shell subjected to internal spring supports and axial surface loads.

II. Mathematical Modeling

Mathematical modeling is an attractive tool in understanding the behavior of engineering structures. With the closed form solutions obtained, the influence of various parameters can be directly recognized, and the parametric studies can thus be easily performed. However, since mathematical modeling is only feasible for rather simple structures, idealization based on some reasonable assumptions is often necessary; in that sense, analysts still need to choose the respective parameters which are expected to attain the greatest influence for the inclusion of the proposed model. It goes without saying that more complex analysis can be conducted by using other approaches such as the finite element or finite difference method. However, closed form mathematical modeling should be viewed as a very first step so as to provide an insight into the importance of parameters, to create useful benchmarks for future calibration exercises, and to develop simple, approximate engineering methods for initial analysis and interpretation.

In this section, three kind of mathematical models for the simulation of soft tissue behavior in micro-indentation test will be introduced. The first model is an axially loaded beam on a relatively soft, elastic foundation (i.e., stress-fiber embedded in cytoplasm), while the second is a radially loaded plate resting on a spring foundation (e.g., cell membrane or epithelium). Other than the previous conventional simulations, the author proposed another elastic model to simulate the soft tissue by considering a 2-dimensional shell model with internal spring support attached. It follows that the equations of motion for the proposed system will be described by two linear differential equations which include the effects of both transverse deformation and the axial dislocation of the soft tissues.

A. Beam model on Spring Foundation

It is well-known that the governing differential equation for small deflection of a thin isotropic beam-plate resting on an elastic foundation with prescribed tension can be expressed as

$$D_b \frac{d^4 w}{dx^4} - T_x \frac{d^2 w}{dx^2} + K_b w = q(x) \qquad (1)$$

where $D_b \equiv \dfrac{Eh^3}{12(1-\nu^2)}$ is the flexural rigidity of beam-plate, T_x is the axial tension, K_b is the foundation stiffness, $q(x) \equiv \dfrac{P}{2a}\left[H(x+a) - H(x-a)\right]$ is the external applied load, w is the transverse deflection and x is the axial coordinate, as described in Figure 2.

B. Plate model on Spring Foundation

The governing differential equation for small deflection of a thin isotropic circular plate with in-plane tension on an elastic foundation is

$$D_p \Delta^2 w - T_r \Delta w + K_p w = q(r,\theta) \qquad (2)$$

where $D_p \equiv \dfrac{Eh^3}{12(1-\nu^2)}$ is the plate flexural rigidity, T_r is the radial in-plane tension, K_p is the foundation stiffness, $q(r,\theta) \equiv \dfrac{P}{\pi a^2}\left[H(r,\theta) - H(r-a,\theta)\right]$ is the external applied load, w is the transverse deflection and Δ is the 2-dimensional Laplacian operator, the model are described in Figure 3.

C. Hollow Cylinder Model with Internal Spring Support.

The governing differential equation for small deflection of a thin isotropic hollow cylindrical shell with internal spring support subjected to surface axial load is [9]

$$D_s \frac{d^4 w}{dx^4} + \frac{Eh}{a^2} w - \nu \frac{N_x}{a} + K_s w = q(x) \qquad (3)$$

$$\frac{du}{dx} = \frac{1-\nu^2}{Eh} N_x + \nu \frac{w}{a} \qquad (4)$$

where $D_s \equiv \dfrac{Eh^3}{12(1-\nu^2)}$ is the shell flexural rigidity, N_x is the surface axial loading, K_s is the foundation stiffness, $q(x) \equiv P\delta(x)$ is the external applied load, w is the transverse deflection and u denotes the longitudinal deflection, the model are described in Figure 4.

Following the standard procedure stated in the text book [9], for the case $N_x \equiv 0$, the homogeneous solution for Equation **Error! Reference source not found.** can be written as

$$w_h = c_1 e^{m_1 x} + c_2 e^{m_2 x} + c_3 e^{m_3 x} + c_4 e^{m_4 x} \qquad (5)$$

where c_1, c_2, c_3, c_4 are constants and m_1, m_1, m_1, m_1 are the roots of the equation

$$m^4 + 4\beta^4 = 0 \text{,} \qquad (1)$$

herein β^4 is defined as

$$\beta^4 \equiv \frac{1}{4}\left(\frac{Eh}{a^2 D_s} + \frac{K_s}{D_s}\right).$$

Equation (1) can be solved as

$$m = \pm\beta(1 \pm i) \text{,} \qquad (2)$$

and thus the homogeneous solution can be rearranged in the following form

$$\begin{aligned} w_h = {} & e^{-\beta x}\left(C_1 \cos\beta x + C_2 \sin\beta x\right) \\ & + e^{\beta x}\left(C_3 \cos\beta x + C_4 \sin\beta x\right) \end{aligned} . \qquad (3)$$

The general solution of Equation **Error! Reference source not found.** may therefore be written

$$\begin{aligned} w = {} & e^{-\beta x}\left(C_1 \cos\beta x + C_2 \sin\beta x\right) \\ & + e^{\beta x}\left(C_3 \cos\beta x + C_4 \sin\beta x\right) + f(x) \end{aligned} , \qquad (4)$$

where $f(x)$ represents the particular solution which will be chosen as 0 since there is no distributed pressure over the surface of the shell, and the constants C_1, C_2, C_3, C_4 will be determined on the basis of appropriate boundary conditions.

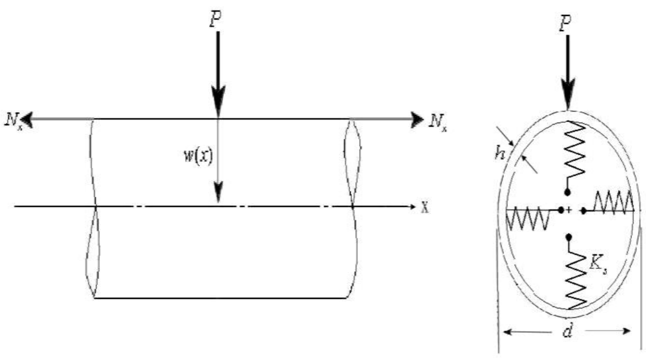

Fig. 4 Schematic diagram of soft tissue during micro-indentation as a hollow cylindrical shell with internal spring sport under axial tension and transverse indenter force.

Assume that the deflection and all derivatives of w with respect to x vanished at infinity, it is required that the coefficients C_3 and C_4 set to be zero in Equation (4), therefore Equation (4) becomes

$$w = e^{-\beta x}\left(C_1 \cos\beta x + C_2 \sin\beta x\right). \qquad (5)$$

Owing to the symmetry, it is reasonable to assume that the slope vanishes at the center, and thus one more condition requiring horizontal tangent at the indent spot is accordingly imposed, that is, $\left.\frac{dw}{dx}\right|_{x=0}$, therefore one can have $C_1 = C_2$ as a result. In addition, the requirement that each half of the cylinder carry one half of the external load leads to the following equilibrium equation at the center

$$Q \equiv -D\left.\frac{d^3w}{dx^3}\right|_{x=0} = Kw(0) - P/2\,. \qquad (6)$$

After applying Equation (5) into Equation (6) and setting $x = 0$, it can be found that

$$C_1 = C_2 = \frac{P}{2}\cdot\frac{1}{4D\beta^3 + K} \equiv w_0\text{, with } w_0 \equiv w(0)\,, \qquad (7)$$

the displacement is therefore

$$w(x) = w_0 e^{-\beta x}\left(\cos\beta x + \sin\beta x\right)$$

with where

$$w_0 \equiv \frac{1}{2}\cdot\frac{P}{D}\cdot\frac{1}{4\beta^3 + \frac{K}{D}}\,. \qquad (8)$$

As for the case if axial tension is not zero, i.e., $N_x \neq 0$, it can be found that Equation (1) remains the same since the term related to N_x can be moved to the right-hand-side of Equation **Error! Reference source not found.**, thus it becomes a kind of external force. Therefore, the particular solution $f(x)$ in Equation (4) will be chosen to be constant with magnitude $-\nu\frac{N_x}{a}$, that is, the displacement will be modified as

$$w(x) = w_0 e^{-\beta x}\left(\cos\beta x + \sin\beta x\right) + \frac{1}{4\beta^4}\frac{\nu}{a}\frac{N_x}{D}\,. \qquad (9)$$

As long as the solution for transverse deformation has been obtained, it is easy to find the solution for the longitudinal deformation by integrating Equation **Error! Reference source not found.**, therefore the solution for longitudinal deformation can also be obtained.

III. Results and Discussions

A. *Effects of Flexure Rigidity and Foundation Stiffness on the Transverse Displacement*

To help visualizing the behavior of solutions, we define the shape function $\Gamma \equiv \frac{w}{w_0}$ as mentioned in previous study [1] to be the normalized transverse deformation of the proposed model, where w_0 indicates the indenter displacement. To individually observe the effects of issue stiffness and residual stress on the transverse deformation, the first demonstration for the solution stated in Equation (9) is presented with zero axial tension, say $N_x = 0$. As we can see from Figure 5, as the ratio D_s / K_s increases in the shell model, the solution decays at a slower rate with respect to the distance from the indenter, this phenomena has also been pointed out in the paper by Zamir and Taber [1] based on both beam and plate models.

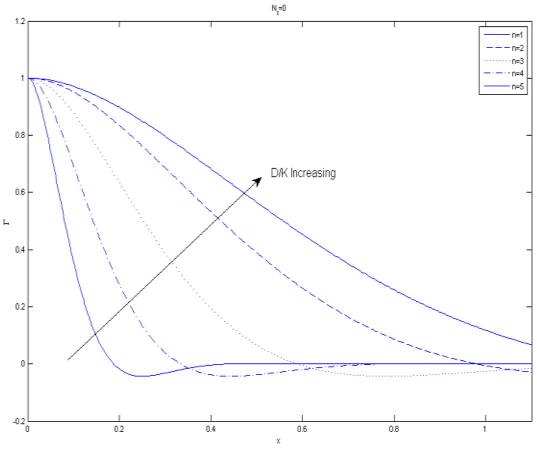

Figure 5: Effect of the flexural rigidity and spring support to the transverse deformation in shell modeling

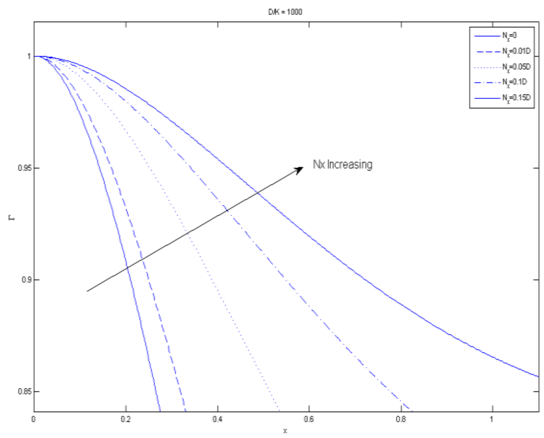

Figure 6: Effect of residual stress to the transverse deformation in shell modeling

B. *Effects of Axial Tension on the Transverse displacement*

We now proceed to exam the effects of axial tension, i.e., the residual stress, on the normalized transverse deformation while D_s / K_s is fixed. Following the parameter setting in Zamir and Taber's paper, the ratio $D_s / K_s = 1000$ is made in Figure 6 aiming to see the variation of transverse displacement with respect to different axial tensions N_x. It can be detected from the figure that the increase of the in-plane load will result in the slow decay of the vertical displacement, and this phenomenon is consistent with the result conducted in Zamir and Taber's paper based on simple beam model. However, the trend in their paper based on circular plate model is just on the contrast, please see Figure 7(b) in their paper. The reason for the discrepancy may be due to the different characteristics of the adopted two governing differential equations. Therefore, it can be said that the shell model used to describe the soft tissue indentation is more close to the simple beam model except that one more quantity, say the longitudinal displacement $u(x)$, is involved.

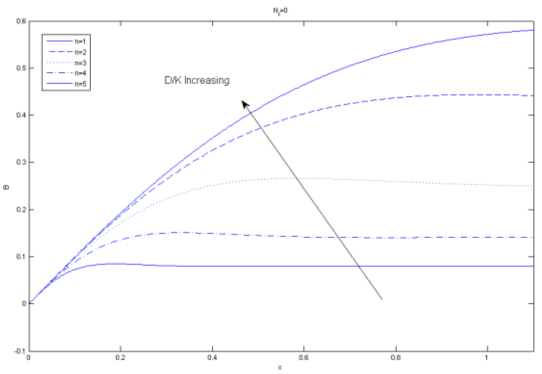

Figure 7: Effect of the flexural rigidity and spring support to the longitudinal deformation in shell modeling

C. Effects of Flexure Rigidity and Foundation Stiffness on the Longitudinal Displacement

After examining the transverse displacement, we can now further examine the longitudinal deformation in the indentation test. The longitudinal deformation is normalized as $\mathrm{B} \equiv \dfrac{u-u_0}{w_0}$, where u_0 represents the displacement at the location $x=0$, w_0 indicates the indenter displacement as mentioned in the illustration of Figure 5. Figure 7 presents the tissue deformation in longitudinal direction while the case of zero axial tension ($N_x = 0$) is considered. As it can be seen from this figure, the deformation is increasing as the ratio of rigidity and foundation (D_s / K_s) is increasing. In particular, the variation of deformation becomes more obvious when the rigidity-foundation ratio is getting big, i.e., effect of rigidity and foundation can be found to be significant even on the location farther away from the indenter when higher rigidity soft tissue is under consideration.

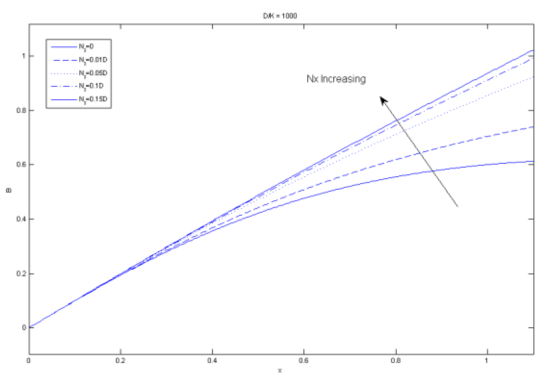

Figure 8: Effect of the residual stress to the longitudinal deformation in shell modeling

D. Effects of Axial Tension on the Longitudinal Displacement

As the last demonstration for the proposed methodology, Figure 8 depicts the longitudinal displacement with respect to various in-plane loads. The ratio of rigidity and foundation (D_s / K_s) is fixed at 1000 as made in Figure 5, and the axial tension N_x is increasing from 0 to 0.15 multiplier of the tissue rigidity D. As shown in this figure, the increase of the axial tension leads to the increase of the deformation, and the effect of the axial tension on the deformation is almost linear as long as the axial tension is undertaking. That is, while it is obviously that the axial displacement is somehow parabolic in the case with no axial tension, nevertheless, it becomes gradually linear when the axial load is under consideration, and the change reaches an asymptotic status as the axial tension is getting slightly bigger.

IV. Conclusion

In this paper, new elastic model using cylindrical shell to simulate the soft tissue structure in micro-indentation test is proposed. Different with the other two elastic models, namely beam and plate, the shell model consists of two coupled differential equations involving not only the transverse deformation but also the longitudinal one as its main quantities. The proposed mathematical model offers additional information about the behaviors of the soft tissue in the micro-indentation test, the effect of residual stresses on the soft tissue along with both the transverse and longitudinal deformations can be directly determined.

It is shown that the result of the present study matches the simple beam model as long as the transverse displacement is under consideration, i.e., the increasing tension leads to the slower decay of the displacement with respect to the distance away from the indenter. However, due to the different characteristics on the governing differential equations, the present study reveals different illustration with those conducted by the circular plate model, which is just opposite to the result by simple beam model.

Other than the vertical displacement, the longitudinal one of the soft tissue behavior during indentation test is also examined based on the present shell model. It can be said that the longitudinal displacement is parabolic-like in the residual stress free case, however, it becomes almost linear when the residual stress is taken into account, and then soon reaches its asymptotic situation as the stress increases.

The present study presents a new mathematical model for the soft tissue behaviors by taking into account both the transverse and longitudinal deformations under the effect of axial tension stress, it can be used to determine the material parameters of the soft tissue, and is helpful to the understanding of the soft tissue structure during the micro-indentation test.

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