Modelling the Contraction Process of Collagen Gels Populated with Living Cells

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1 Introduction

Collagen gels will contract as living cells populated within them, a process regarded as the in vitro analog of wound healing. This phenomenon is now harnessed to fabricate engineered tissues, such as tendons, blood vessels, and cardiac muscle [1]. Hence, to understand the contraction process is quite important for the studies of wound healing process and for the applications in tissue engineering. There is no commonly accepted theory that reveals the behind mechanisms of the contraction. Some models include the effects of fibril orientation, fibril network deformation, cell traction, and cell migration, making the algorithm mathematically tough and the whole physical image complicated [2,3]. In this study, we model the early phase of the process, postulating that the contraction process is mainly due to the large scale movement of the populated cells and the surrounding collagen fibrils, which is driven by the traction force generated by cells onto their surrounding fibrils. The movement results in the compaction of fibril network. By means of this model, we can obtain the volume contraction ratio and the traction force generated by the cells to the fibrils. The model is verified by experimental data.

2 Theory

Based on the observation by means of scanning electron microscopy, we model the process of early contraction phase as follows. The gel is regarded as homogeneous fibril network uniformly embedded with living cells. Therefore, it can be divided into contraction subunits, each of them including two cells and the surrounding collagen fibrils as shown in Fig. 1. Due to the interaction between the cells and the fibrils mediated with the integrin receptor in the cellular membrane, cells generate traction force onto their surrounding fibrils. However, only the traction force exerting to the fibrils that are straight in between the cells (named traction fibrils) is sustained, which consequently draws the cells with the surrounding fibrils to move close to each other. The experimental measurement showed that the length of the fibrils followed the Gaussian distribution. Therefore, as the two cells moving close they would encounter more new traction fibrils with shorter length and generate traction force to them to pull the cells close further; in the meanwhile, the former longer traction fibrils are out of tension and bent to turn into resistance to the cell movement. In this process, the moving of the cells and fibrils is also resisted by the interstitial fluid. The motion equation for the mass including one cell and its surrounding fibrils is

$$a \cdot \Theta = n_T \tau - n_B T_B - F_r \quad , \qquad (1)$$

where a is the acceleration; Θ is the mass including the cell and the surrounding fibrils; n_T is the number of traction fibrils; τ is the traction force for one fibril; n_B is the number of fibrils bent; T_B is the bend force; F_r is the interstitial fluid resistance. Each of these quantities can be calculated as follows,

$$n_T = n_c \int_{\bar{\rho}-\delta}^{\bar{\rho}+\delta} \frac{1}{\sqrt{2\pi}\cdot\sigma} e^{-\frac{(\rho-\bar{\rho})^2}{2\sigma^2}} d\rho \, , \qquad (2)$$

where n_c is the number of fibrils contacting to the cell; ρ is the length of fibrils following the Gaussian distribution; $\bar{\rho}$ and σ are the mean and standard deviation of ρ, respectively; δ is the traction tolerance for length ρ.

$$n_B = k(n_0 - n_T) \qquad k \in (0,1) \, , \qquad (3)$$

where n_0 is the total number of the fibril; k is the bend coefficient.

$$T_B = k_B T A \gamma^2 / 2x \, , \qquad (4)$$

where k_B is Boltzmann constant; T is absolute temperature; A is the persistence length of fibrils; γ is bend curvature; x is the cell displacement.

$$F_r = \frac{1}{2} dSDv^2 \, , \qquad (5)$$

where d is the fluid density; S is the area projected at flow direction; D is resistance coefficient; v is the movement velocity.

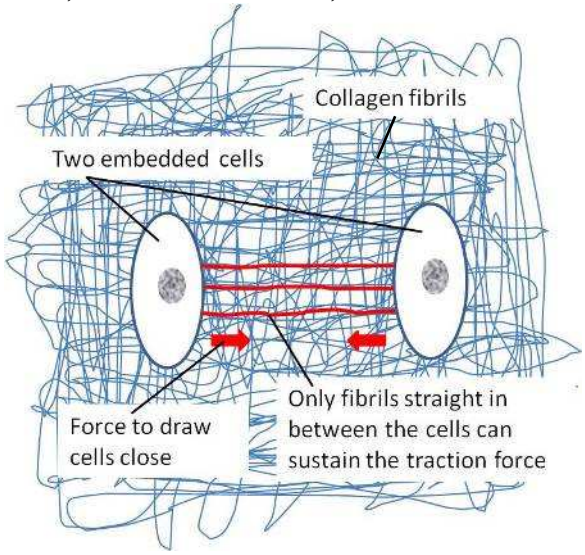

Fig. 1. Model of collagen gel contraction

The contraction process governed by Equation 1 should be like this: at the beginning of the contraction, T_B and F_r are zero because no fibrils are bent and movement has not yet occurred; drawing force $n_T\tau$ produces acceleration and results in the start of contraction. Once the contraction occurs, T_B and F_r will emerge to resist the movement so that the contraction will undergo at a certain velocity at which drawing force $n_T\tau$ and

resistance T_B and F_r get equilibrium. As contraction continues, the drawing force will increase because the number of traction fibril n_T increases, so that the equilibrium velocity will also increases. The contraction process will halt as the bend force $n_B T_B$ is large enough to equate drawing force $n_T \tau$ at that time.

3 Results

The simulation result of the contraction process of a gel consisting of 1 mg type I collagen and 1.0 million rat fibroblasts is plotted in Fig. 2. The parameters in the simulation are presented in Table 1. The setting of each parameter is based on experimental measurement of the gel. It can be seen that this model is able to reproduce the contraction process in good agreement with the experimental data.

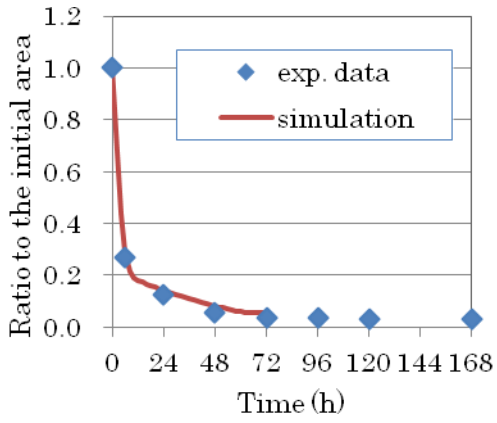

Fig. 2. Comparison of the simulation and the experiment

Table 1. Values of fundamental parameters in the simulation

n_0	$\bar{\rho}$ (μm)	$\sigma(\mu m)$	$\delta(\mu m)$	$\tau(pN)$	k	$A(\mu m)$
24000	140.0	5.0	0.1	6.0	0.2	20.0

Fig. 3. shows the drawing force exerted by one cell to the traction fibrils. This force is difficult to be measured by experiment, but it is of interest because more and more studies in cellular biology evidence that the mechanical stress is a vital cue to the cellular fates including stem cell differentiation [4].

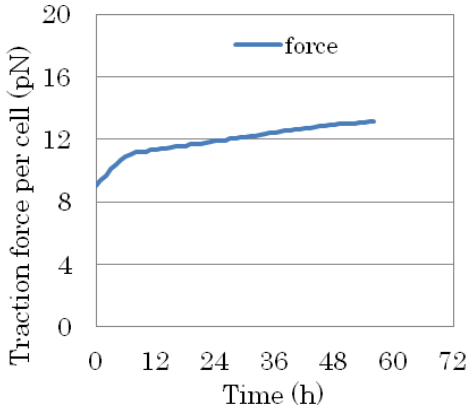

Fig. 3. Drawing force exerted by one cell to the traction fibrils

4 Discussion

This model is able to simulate the early free contraction process of collagen gels populated with living cells. The simulation shows that the fundamentals of the contraction process, at least for the early phase, is that the traction force exerted by cells is sustained by some traction fibrils in proper length, which in turn draws the cells and the surrounding fibrils move close resulting in macro compaction. The simulation and the experimental data are in good agreement with each other. The process does not include cell migration, which may imply that at least at the early contraction phase cell migration is not an important factor to the phenomenon. This point is different from the wound healing process in vivo.

The simulation is only conducted for free contraction, how to simulate the contraction under external constraint in the same principle should be further studied.

5 Conclusion

The simulation shows that the fundamentals of the contraction process, at least for the early phase, is that the traction force exerted by cells is sustained by some traction fibrils in proper length, which in turn draws the cells and the surrounding fibrils move close resulting in macro compaction. Cell migration is not an important factor to this phase.

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