Noncooperative cell behavior

Under certain conditions cells interact with the biomaterial surface each individually

A brief review or relevant structures: cell membrane, transmembrane proteins, cell receptors (integrins), cytoplasm, matrix

Definition of unit cell process

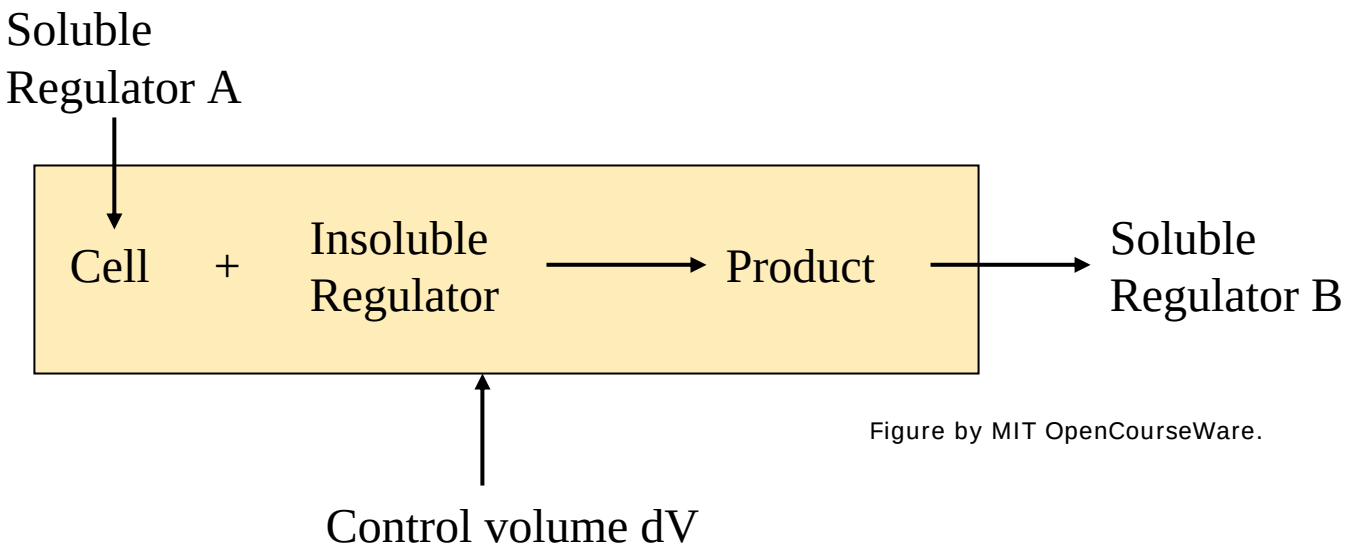
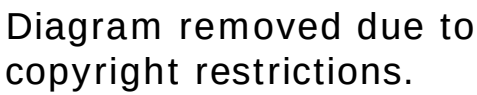


Figure by MIT OpenCourseWare.

Unit cell process confined conceptually in a control volume dV

A typified cell diagram showing cell-cell binding



Cell membrane sketch showing transmem-brane proteins

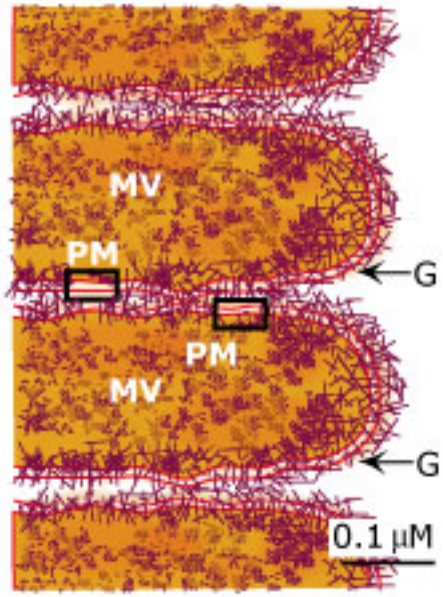


Figure by MIT OpenCourseWare.

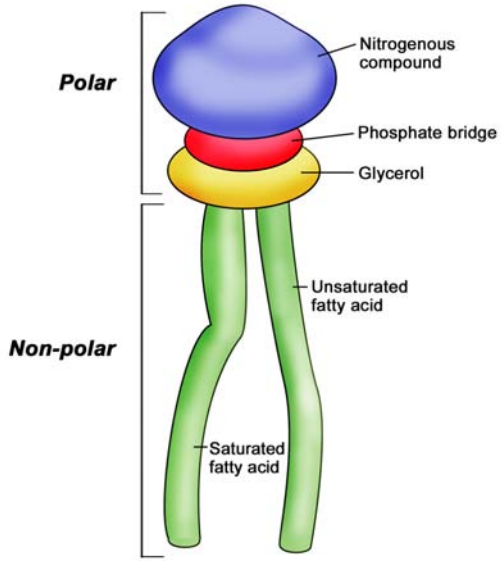


Figure by MIT OpenCourseWare.

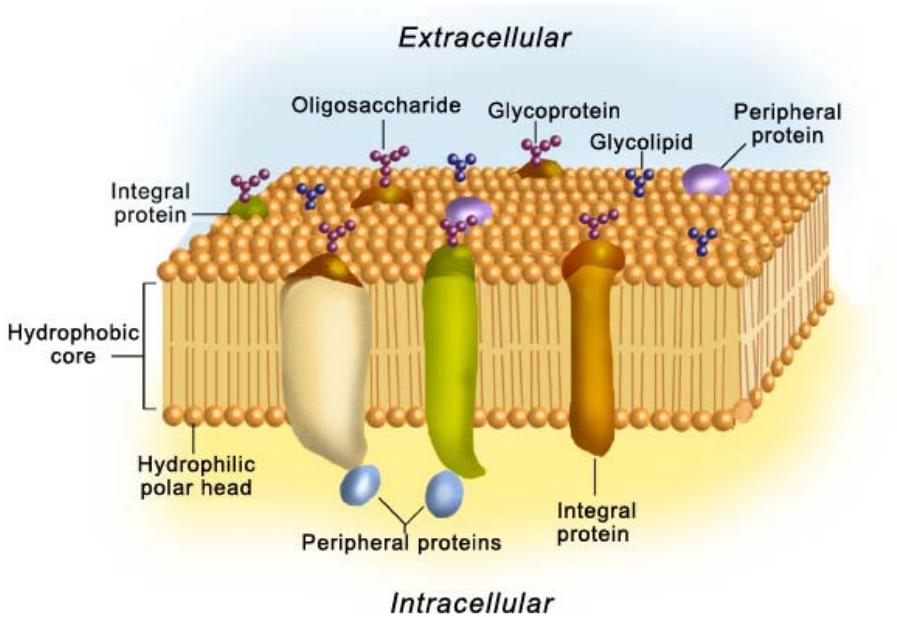


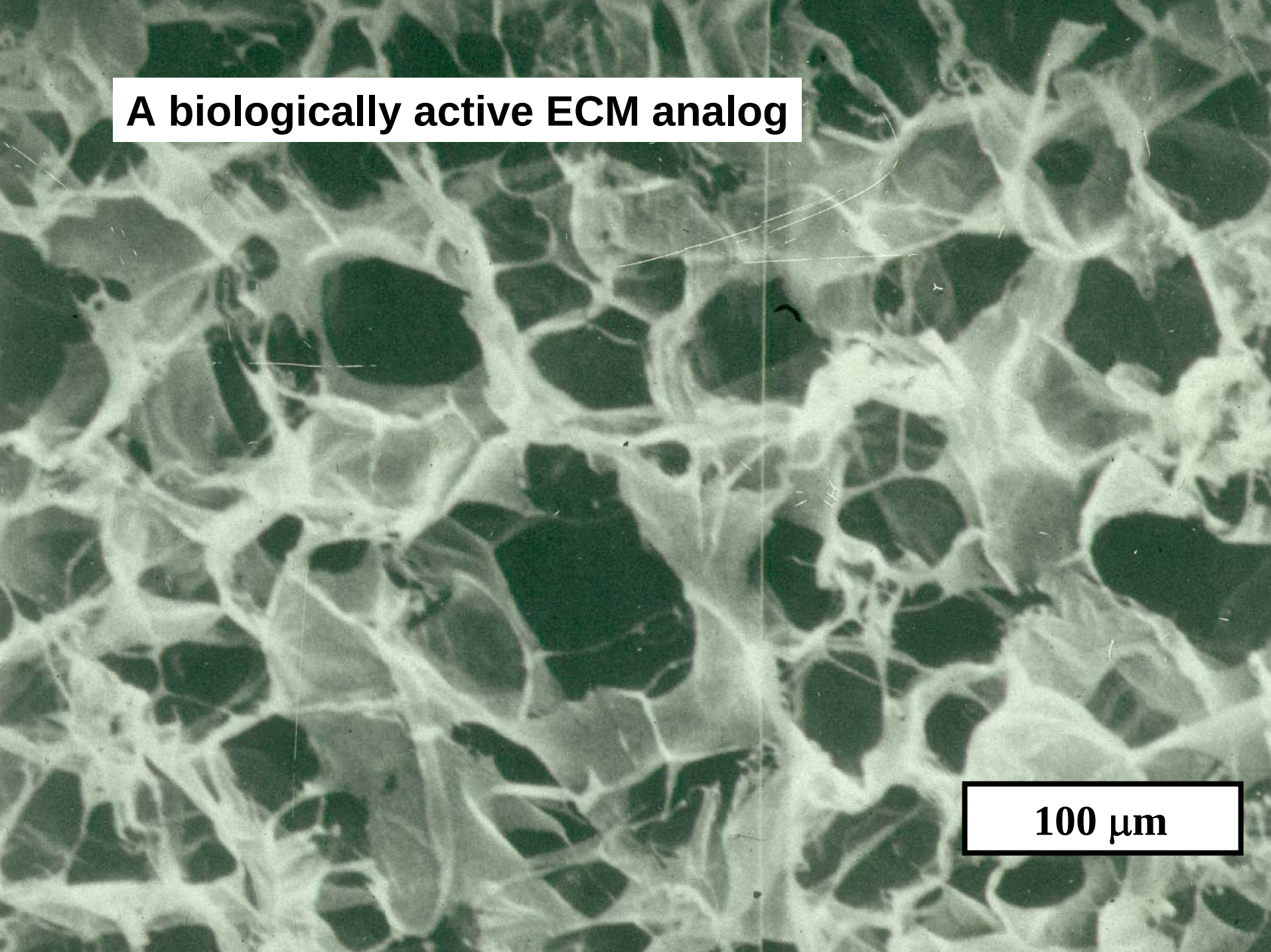
Figure by MIT OpenCourseWare.

Another model of a specific cell-matrix interaction

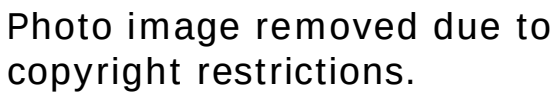
Diagram of fibronectin attaching cell to surface of collagen fiber removed due to copyright restrictions.

View of cytoplasm

Photo image removed due to copyright restrictions.


A biologically active ECM analog
100 μm

Cells pull matrix



FIRST ARTICLE

ELSEVIER

Biomaterials 22 (2001) 2883–2891

www.elsevier.com/locate/biomaterials

Fibroblast contraction of a collagen–GAG matrix

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Modified cell force monitor used to study cell-matrix interactions quantitatively

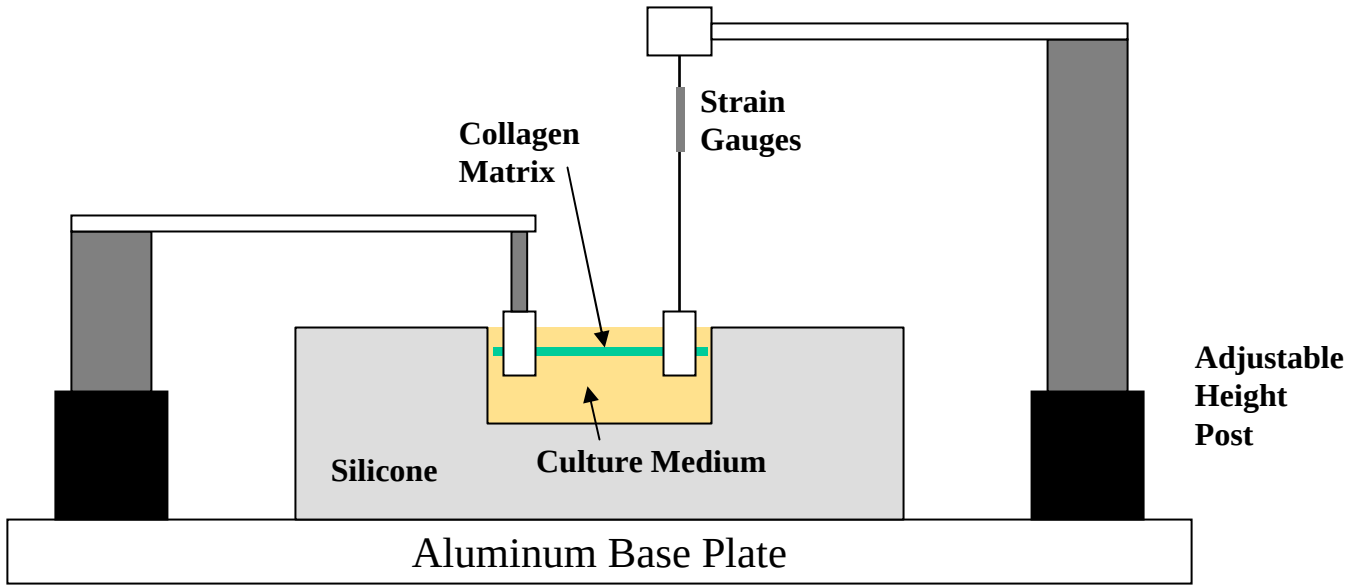

Figure by MIT OpenCourseWare.

Use to study unit cell processes quantitatively

Freyman et al., 2001

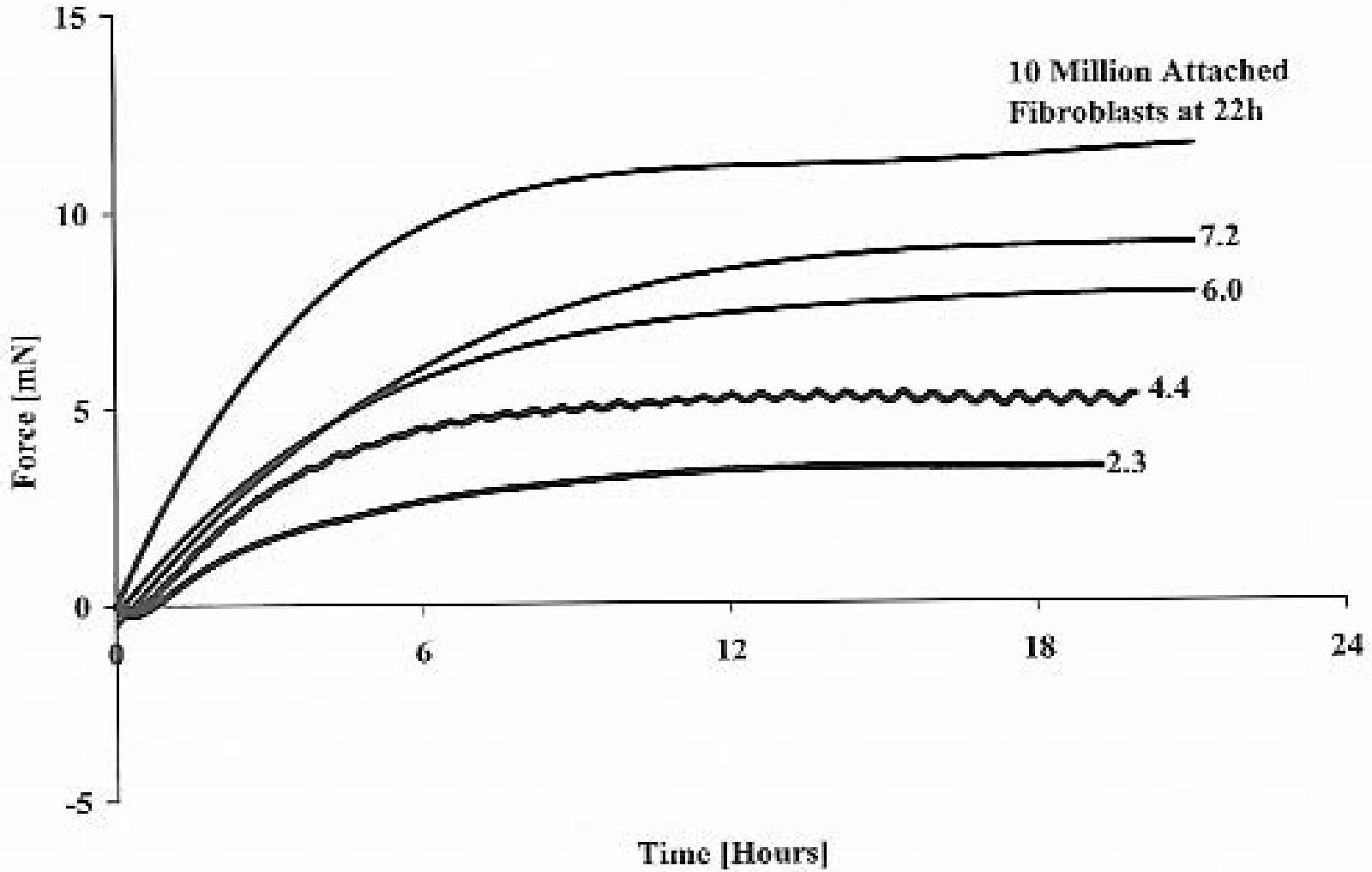

Fig. 2. Contractile force plotted against time, for several densities of attached fibroblasts at 22 h (cell number in millions). Raw data is plotted for 2.3 and 4.4 million attached cells to show data scatter. Higher densities are shown by trend lines for clarity.

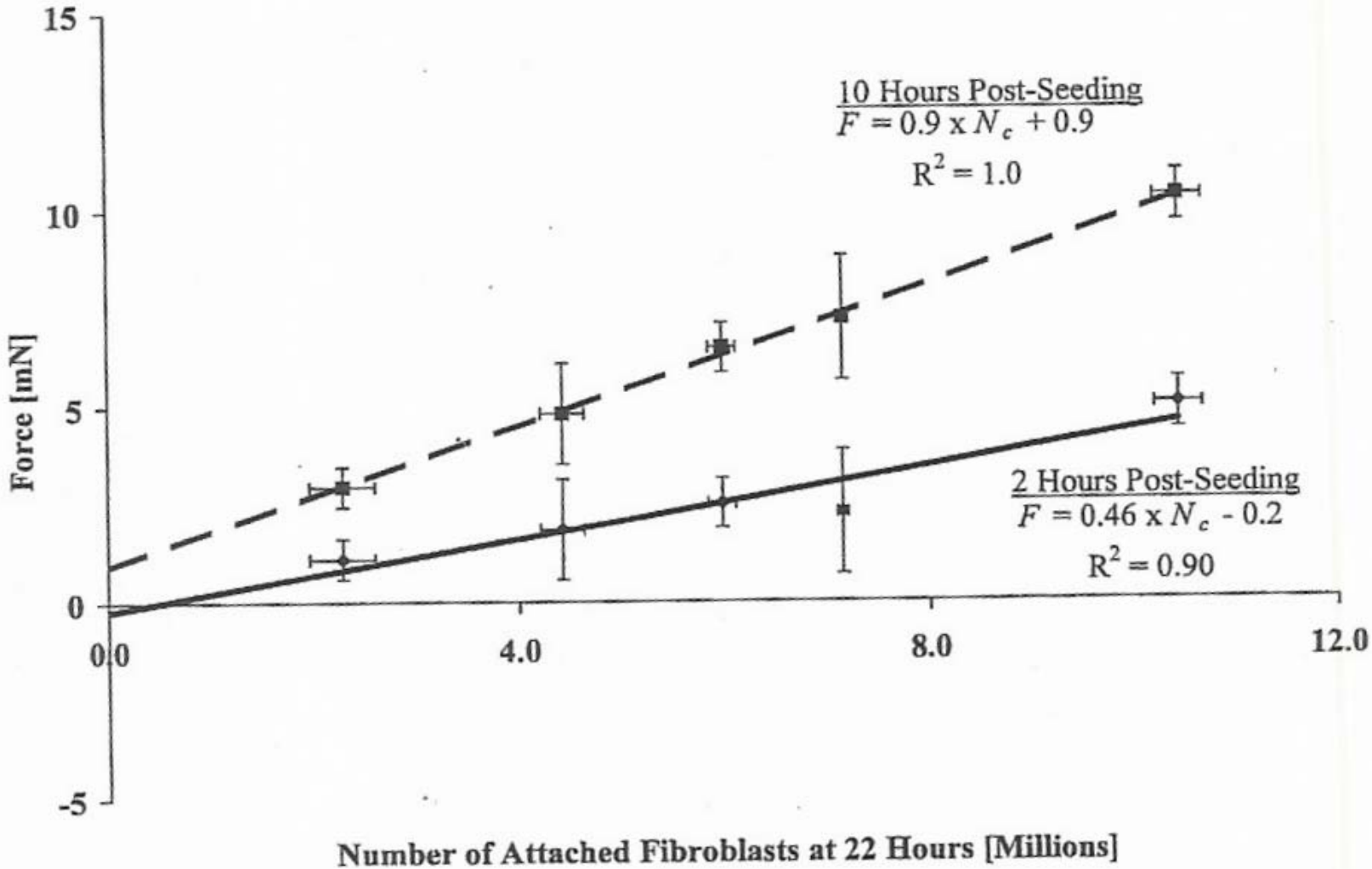

Fig. 4. Force plotted against attached cell number per sample at 22 h, showing a linear relationship at 2 h (*solid line*) and 10 hours (*dashed line*) post-seeding.

Table 1
Exponential curve fit parameters (τ, F_a)

Total no. of attached cells in matrix ($\times 10^6$)	Time constant, τ (h)	Asymptotic value, F_a (mN)
2.3 ± 0.31	5 ± 1.3	3.7 ± 0.6
4.4 ± 0.21	4 ± 0.5	5.4 ± 1.4
6.0 ± 0.13	5 ± 0.4	8.1 ± 0.5
7.2 ± 0.05	7 ± 1.5	10 ± 1.9
10 ± 0.23	4 ± 0.5	12 ± 0.7

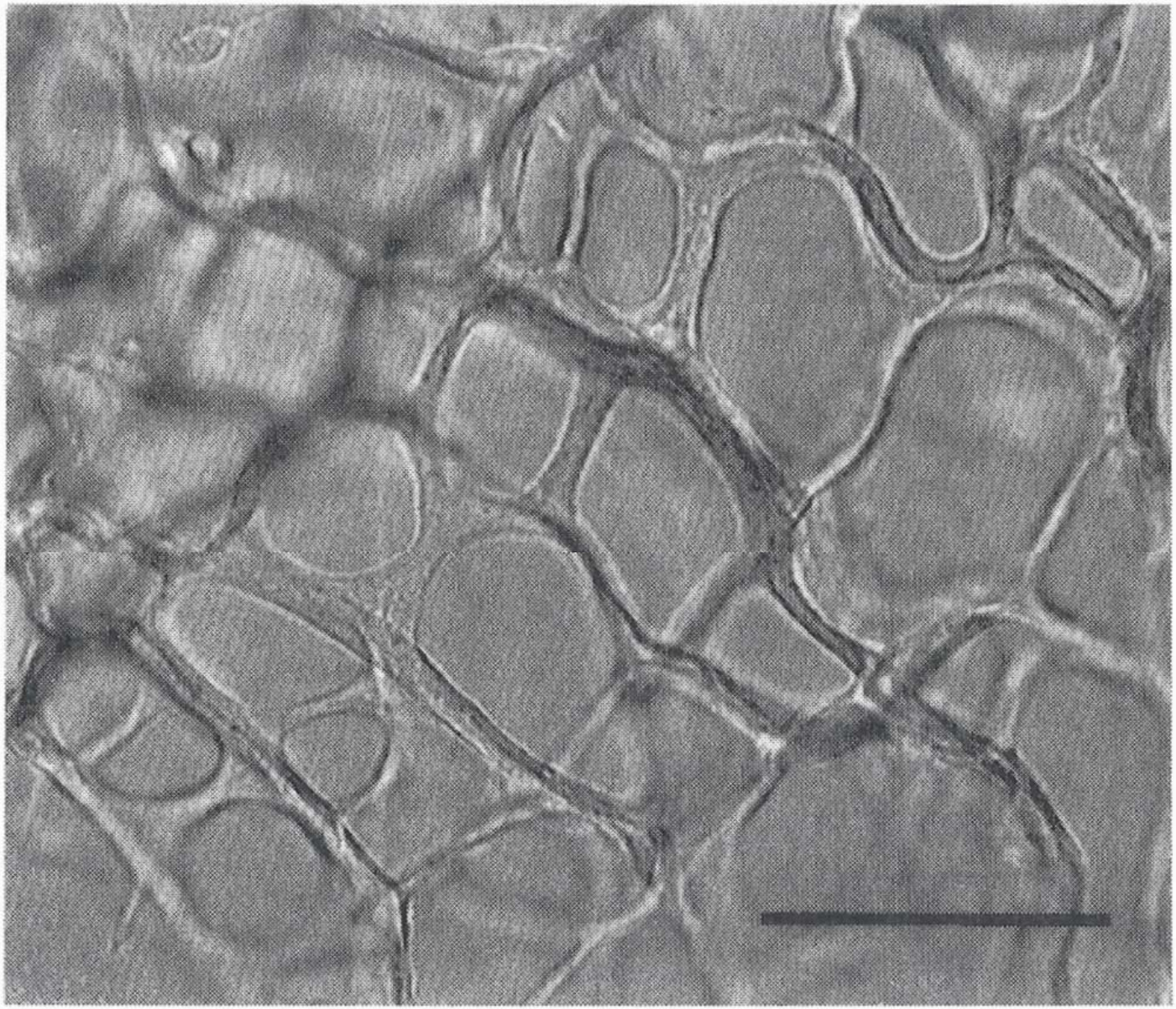

Fig. 5. Light micrograph of hydrated matrix (scale bar = 100 μm).

Conclusions on Linearity vs. Cooperativity of Fibroblast Contraction of Matrix

- **The contractile force increases linearly with cell density.**
- **The average contractile force is calculated at 1 nN per cell.**
- **The time constant for development of force is also independent of cell density.**
- **In this model cells must develop contractile forces individually, not cooperatively.**

SECOND ARTICLE

Experimental Cell Research **269,** 140–153 (2001)
doi:10.1006/excr.2001.5302, available online at http://www.idealibrary.com on IDEAL®

Micromechanics of Fibroblast Contraction of a Collagen–GAG Matrix

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Slides with images removed due to copyright restrictions.

See Fig 2 (schematic of imaging setup), Fig. 4 and Fig. 5 (graphs of results). In Freyman et al. “Micromechanics of Fibroblast Contraction of a Collagen–GAG Matrix.” *Exp Cell Res* 269, no. 1 (2001): 140-153. http://dx.doi.org/10.1006/excr.2001.5302

Sequence showing a cell (arrow A) simultaneously elongating and deforming a matrix strut (arrow B)

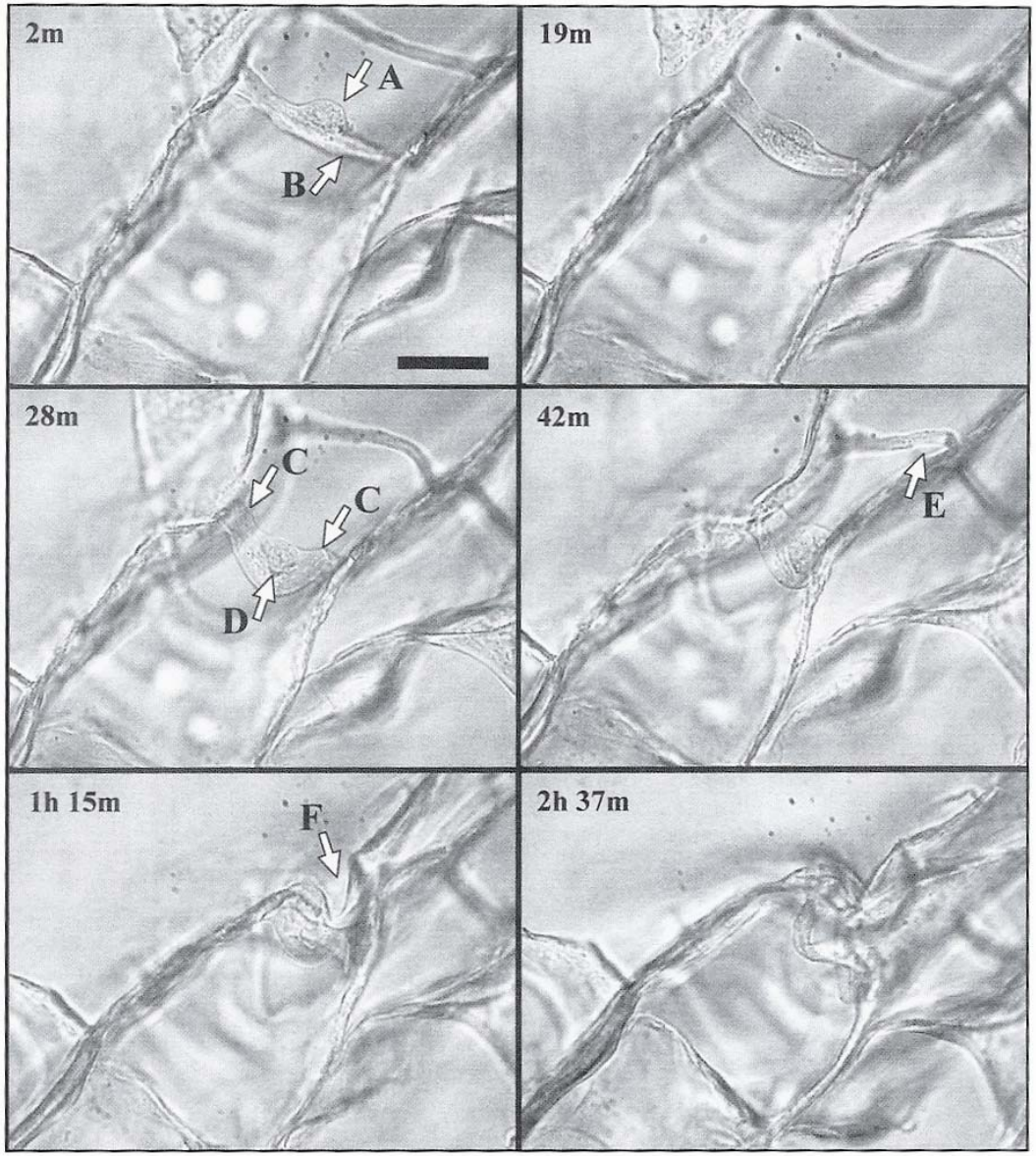


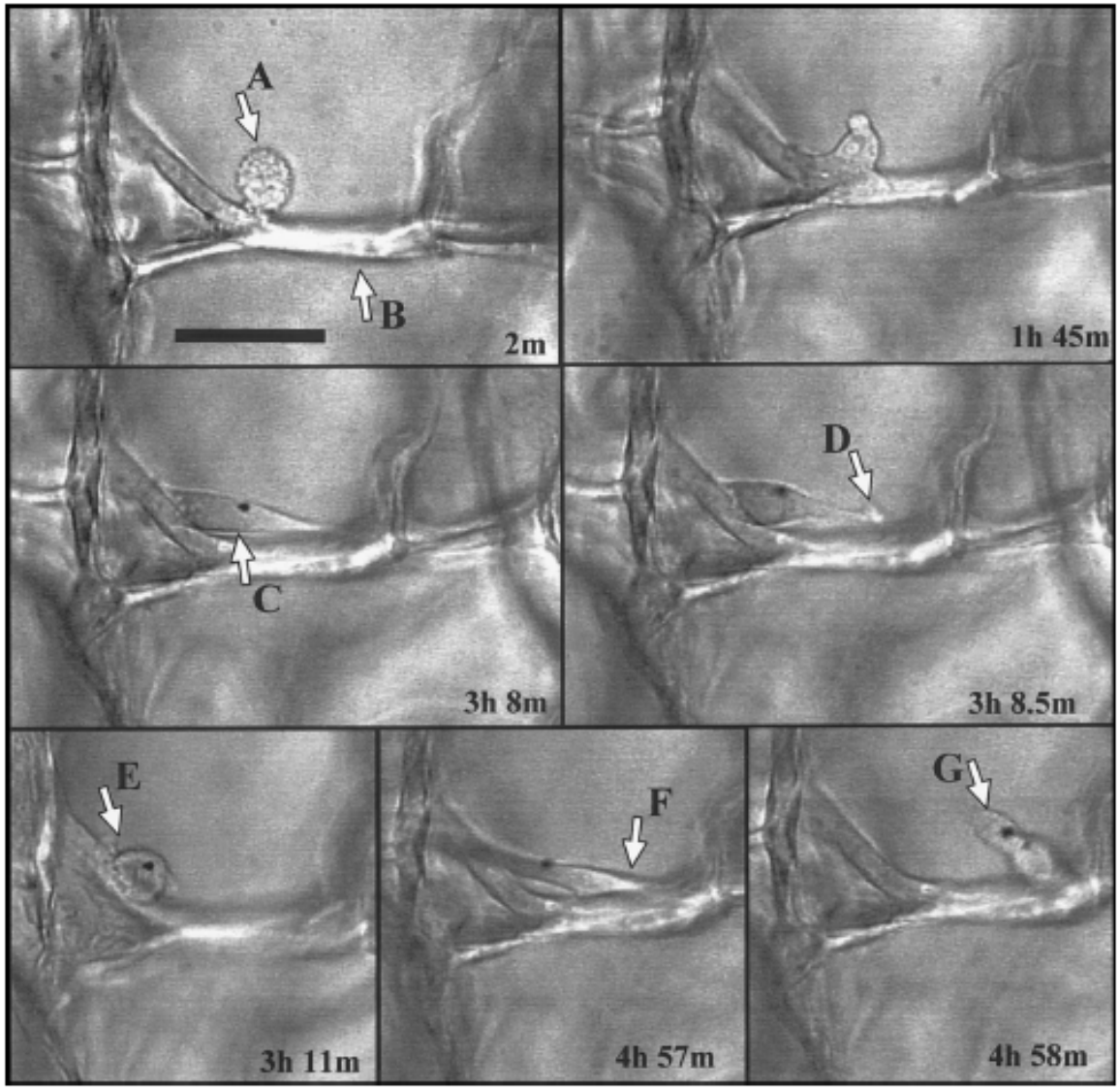
FIG. 6. Sequence of images depicting a cell (arrow A) simultaneously elongating and deforming a matrix strut (arrow B). As the ends of the strut were drawn closer (2–28 min), the cell extended toward the ends of the strut (arrows C); it did not contract along with the strut. The buckling of the strut

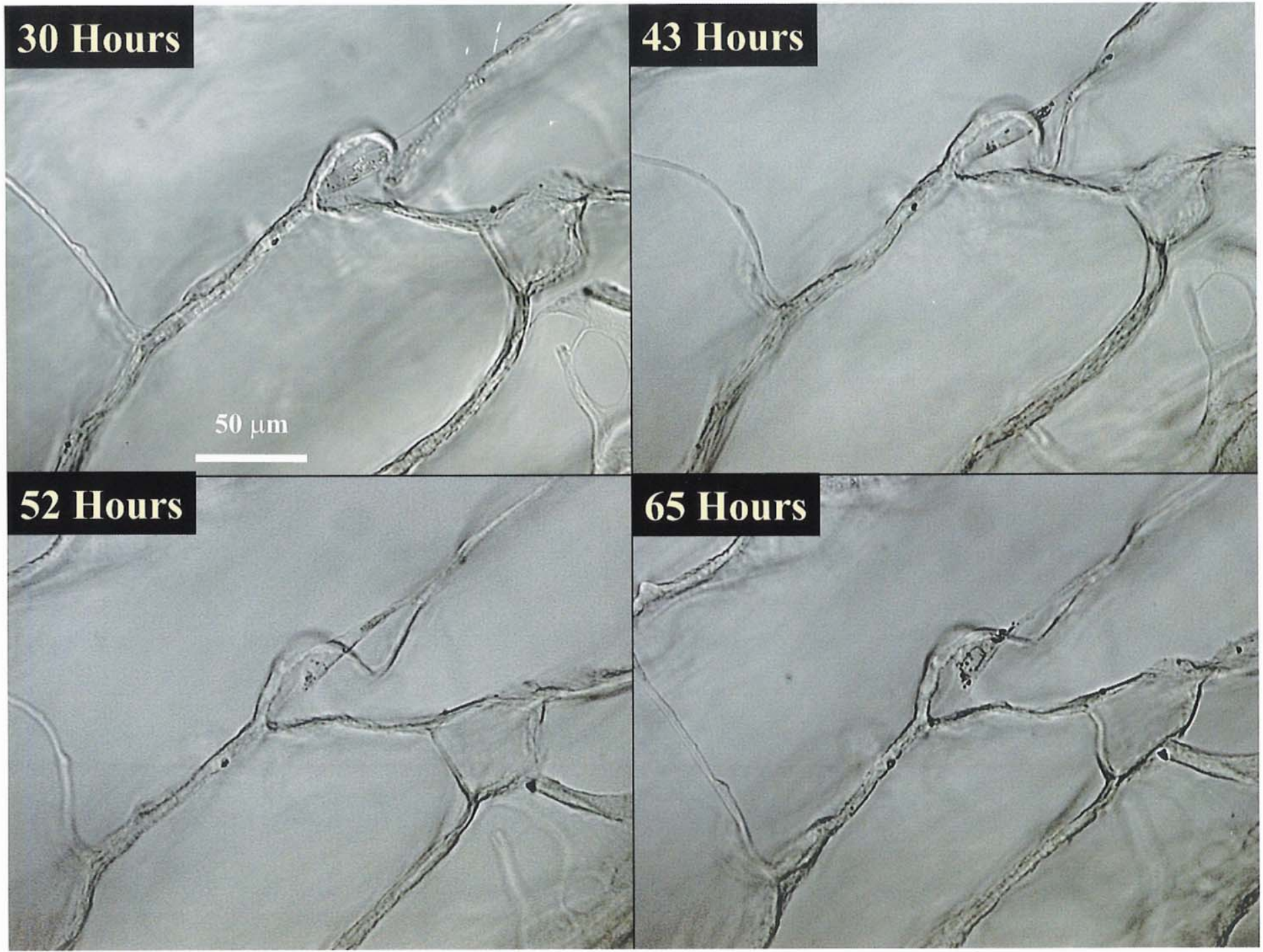
Another sequence showing a cell (A) elongating and deforming matrix struts (B)

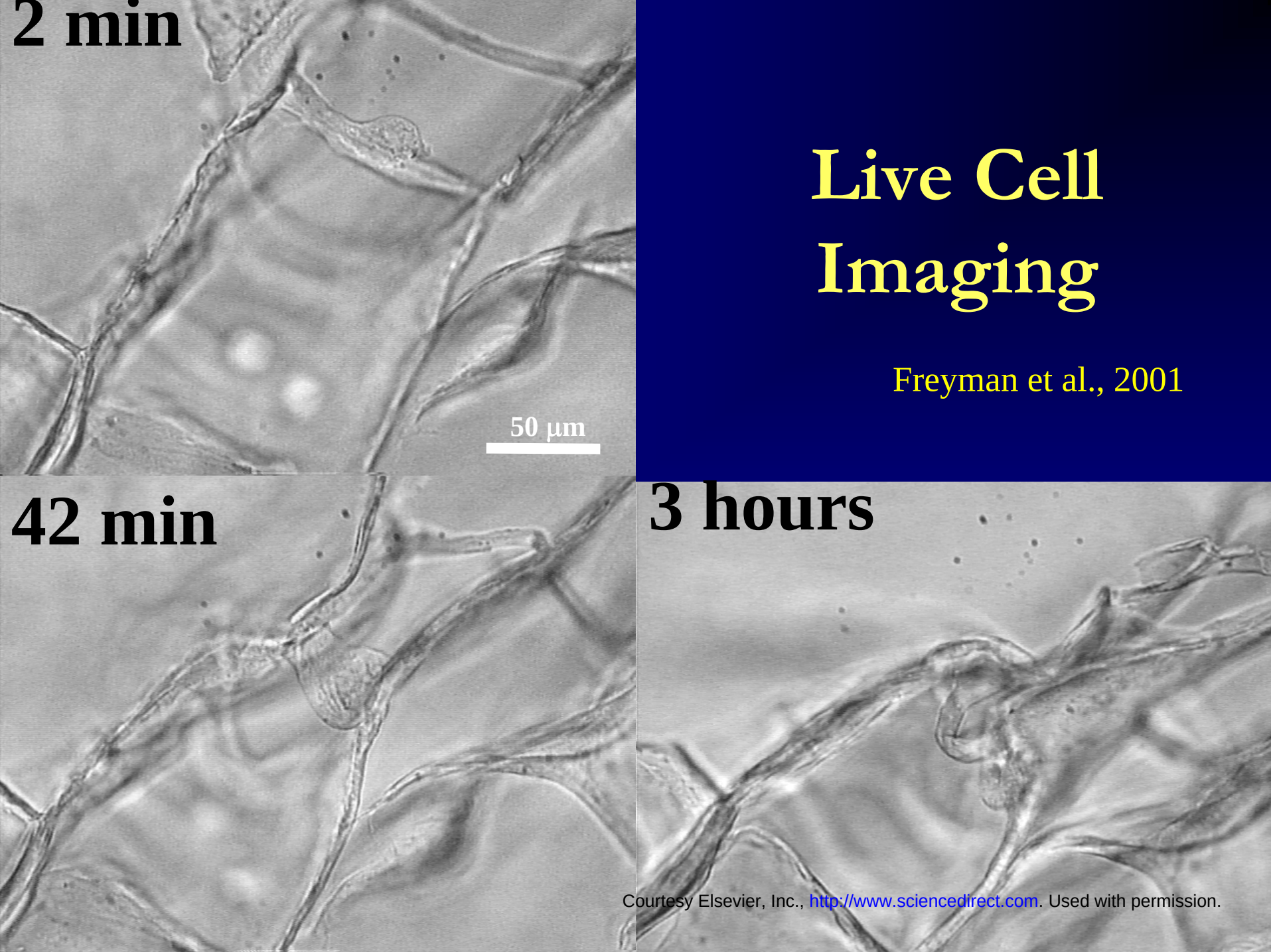
Photos removed due to copyright restrictions.

See Fig. 7 in Freyman et al. “Micromechanics of Fibroblast Contraction of a Collagen–GAG Matrix.” *Exp Cell Res* 269, no. 1 (2001): 140-153. http://dx.doi.org/10.1006/excr.2001.5302

Sequence shows cell (A) elongating on matrix strut (B). Later, adhesion sites near cell center are released (C); eventually one end of cell fails to attach and the cell retracts rapidly (D). Later, the cell elongates once more (E) and the process is repeated.




30 Hours
50 μm
43 Hours
52 Hours
65 Hours



Live Cell Imaging

Freyman et al., 2001

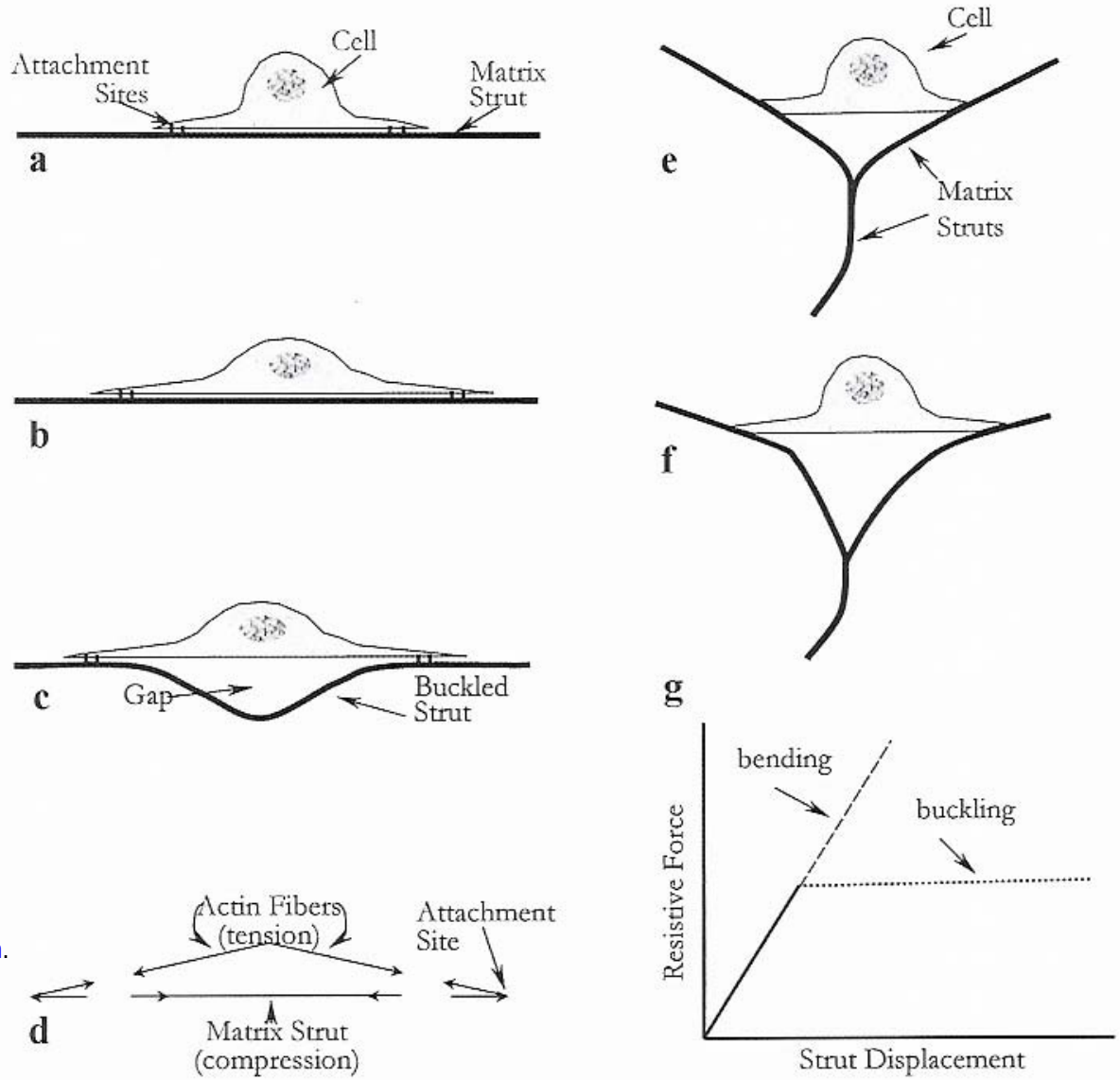


FIG. 11. (a,b) Sketches of cell elongation, showing attachment sites forming at cell extension. (c) Sketch of matrix strut buckling due to force developed by the actin fibers in the cell, showing gap between cell and strut. (d) Free body diagram of forces, showing tension in the actin fibers, compression in the matrix strut, and the resulting balance at the attachment site. (e,f) Sketches showing cell attached at a strut junction resulting in bending of the struts due to the force developed by the cell. (g) Schematic plot of the resistive force provided by the matrix struts for a given displacement imposed by the cell. Note that following the onsetof buckling, resistive force does not increase significantly for increase in deformation.

Conclusions on Micromechanics of Fibroblast Contraction

- **The aspect ratio of cells increases with time and eventually saturates, just as the force does.**
- **Initiation of cell elongation occurs stochastically.**
- **The force plateau most simply results from buckling or bending of individual struts in the matrix by cells.**
- **Matrix deformation (contraction) occurs as a result of cell elongation, not cell contraction.**

THIRD ARTICLE

Experimental Cell Research **272,** 153–162 (2002)
doi:10.1006/excr.2001.5408, available online at http://www.idealibrary.com on IDEAL®

Fibroblast Contractile Force Is Independent of the Stiffness Which Resists the Contraction

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Tables 1 and 2, Figures 2, 3 and 4 in Freyman, T. M., et al. "Fibroblast Contractile Force Is Independent of the Stiffness Which Resists the Contraction." *Exp Cell Res* 272 (2002): 153-162.
http://dx.doi.org/10.1006/excr.2001.5408

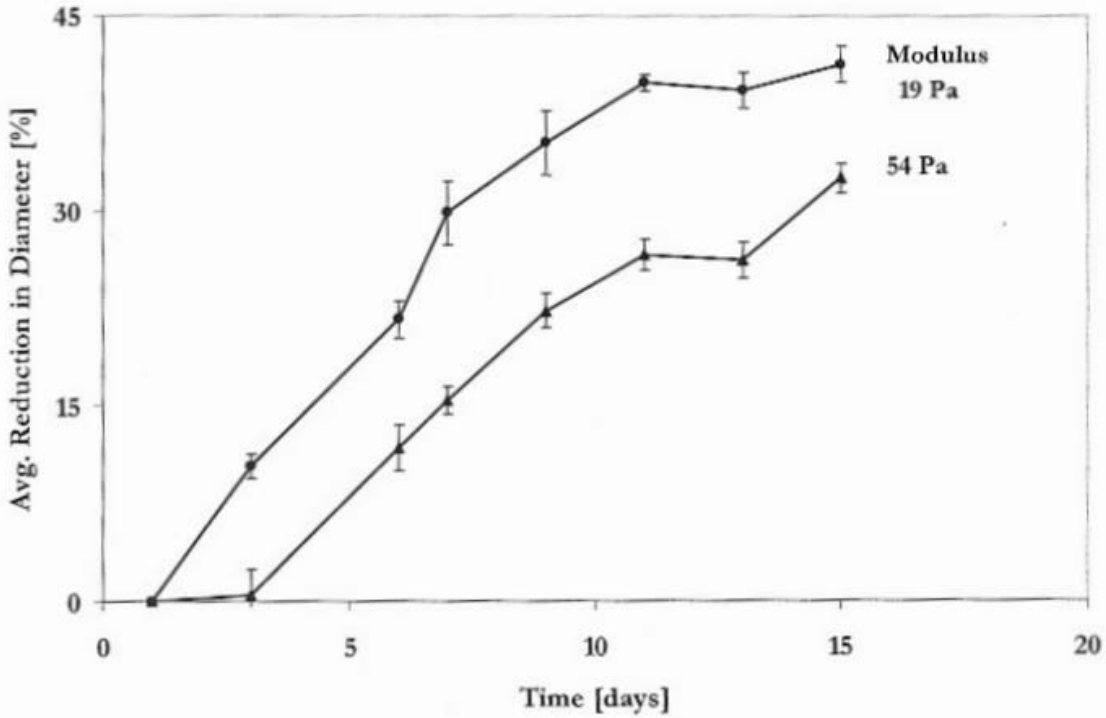

FIG. 5. Plot showing the effect of initial matrix stiffness on the average reduction in diameter of free-floating matrix disks over 2 weeks in culture. The attached cell number does not vary significantly with time or between initial stiffness groups.

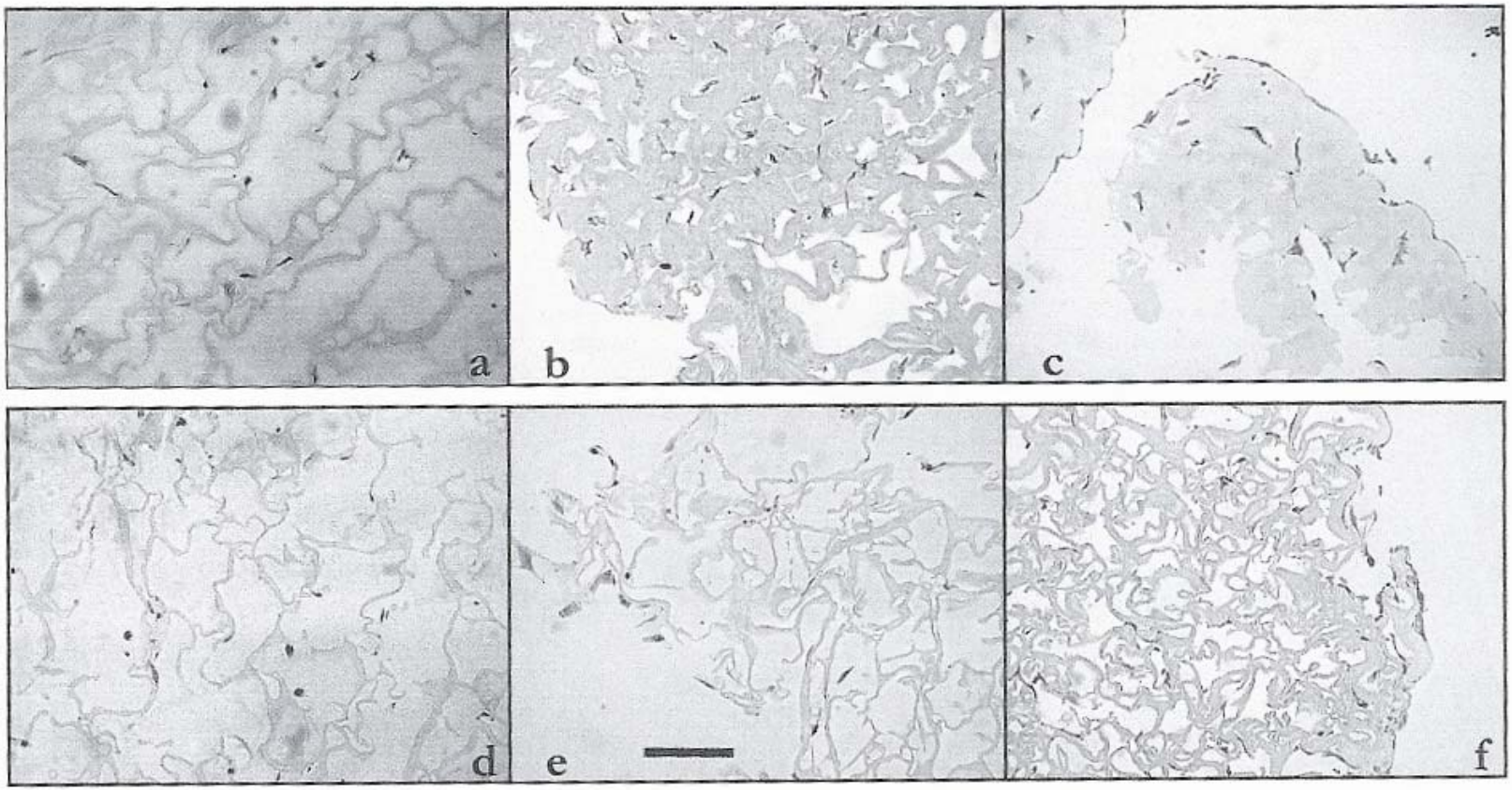

FIG. 6. Light micrographs of H&E-stained GMA sections of free-floating matrix samples showing cell distribution and matrix microstructure changes with time. Less stiff matrix disks are shown in a, b, and c for time points 1, 6, and 15 days, respectively. Stiffer matrix disks are shown in d, e, and f for time points 1, 6, and 15 days, respectively. Scale bar, 200 μm

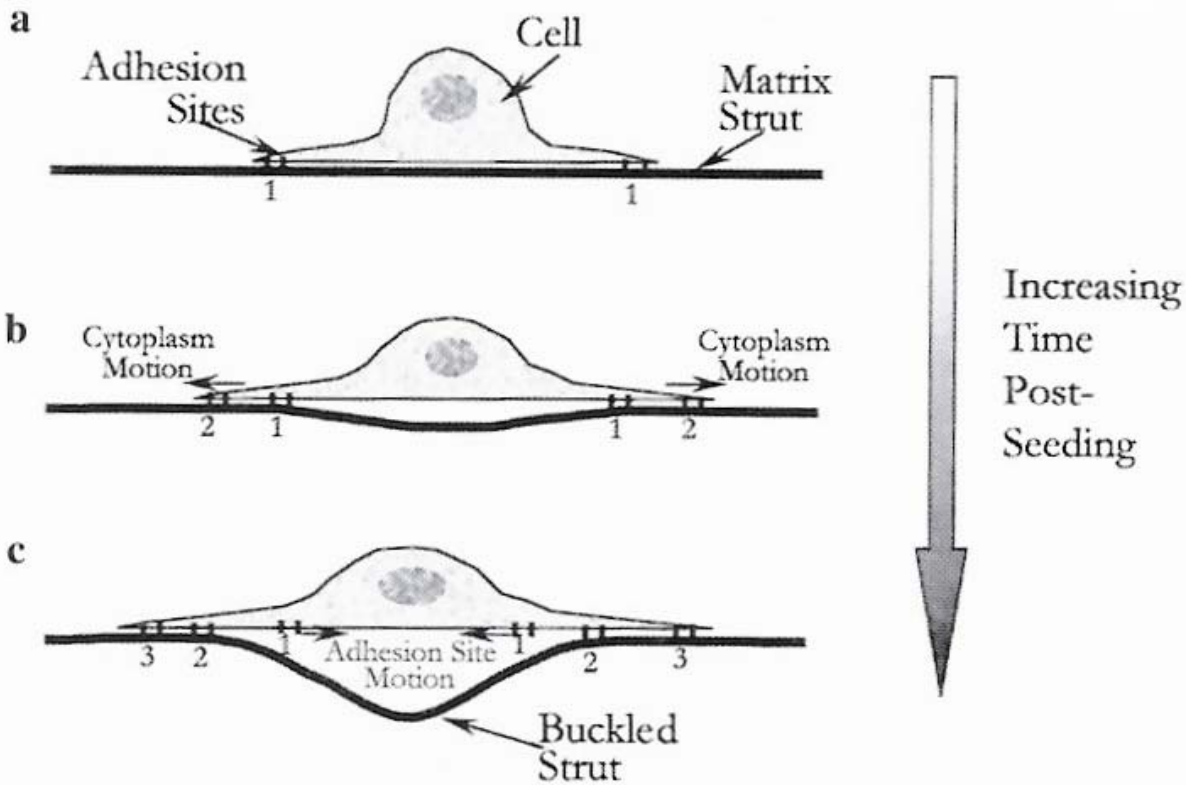

FIG. 7. Schematic showing the centripetal motion of adhesion sites and the centrifugal motion of cytoplasm. This attempts to explain the phenomenon of simultaneous cell elongation and matrix contraction. (a) As the cell elongates, due to cytoplasm motion, new adhesion sites

Conclusions on the Effect of Matrix Stiffness on Cell Contraction

- **The contractile force generated by fibroblasts was independent of matrix stiffness in the range 0.7 – 10.7 N/m.**
- **Contractile forces generated by cells are force-limited, not displacement-limited.**
- **As cells elongate, cell-matrix adhesion sites hypothetically form at the cell periphery, increasing length of matrix strut under compressive load and decreasing load required to buckle the strut.**

20.441J / 2.79J / 3.96J / HST.522J Biomaterials-Tissue Interactions

Fall 2009