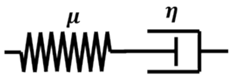
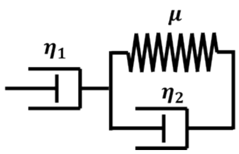
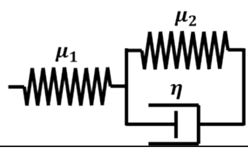
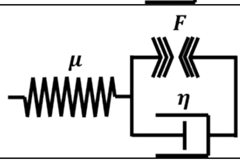
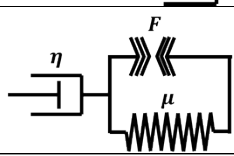
Supplementary Materials

Supplementary Table 1: Equations describing energy of tissue as function of the applied strain rate and the tissue stiffness and viscosity

	Model Diagram	Energy Expression
1		$E = \frac{\mu}{2}(\frac{\eta\dot{\varepsilon}}{\mu}(e^{\frac{-\mu t}{\eta}} - 1))^2$
2		$E = \frac{\mu}{2}(\frac{\eta_1\dot{\varepsilon}}{\mu}(1 - e^{\frac{-\mu t}{\eta_1 + \eta_2}}))^2$
3		$E = \frac{\mu_1}{2}(\dot{\varepsilon}t - \frac{\eta\mu_1\dot{\varepsilon}}{(\mu_1+\mu_2)^2}\left(e^{\frac{-(\mu_1+\mu_2)t}{\eta}} - 1\right) - \frac{\mu_1\dot{\varepsilon}t}{\mu_1+\mu_2})^2 + \frac{\mu_2}{2}(\frac{\eta\mu_1\dot{\varepsilon}}{(\mu_1+\mu_2)^2}\left(e^{\frac{-(\mu_1+\mu_2)t}{\eta}} - 1\right) + \frac{}{\mu_1}$
4		$E = \frac{\mu}{2}((\frac{\eta\dot{\varepsilon}}{\mu} + \frac{F}{\mu})(e^{\frac{-\mu t}{\eta}} - 1))^2$
5		$E = \frac{\mu}{2}((\frac{\eta\dot{\varepsilon}}{\mu} - \frac{F}{\mu})(1 - e^{\frac{-\mu t}{\eta}}))^2$

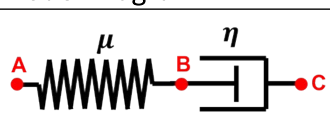
Where μ_i is the stiffness of the spring, η_i is the damping coefficient of the dashpot, F is the constant force in the contractile element and $\dot{\varepsilon}$ is the constant strain rate applied to the tissue

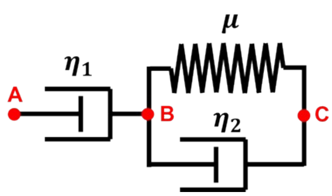
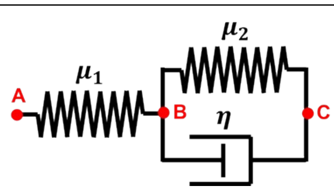
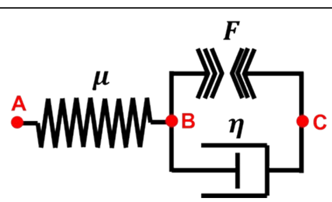
Supplementary Table 2: Derivation of energy expression in the models

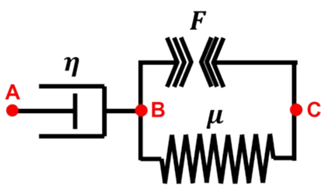
In all the models, the strain is being applied at point A towards the right while point C is stationary (Fixed to ground). We assume that points A and B move a distance of x_1 and x_2 respectively towards the right with respect to point C. The energy of the system is assumed to be the energy stored in the spring(s), since it is the only restorative force. Since the point A is moving at a constant strain rate, for all the models we have –

$$\frac{dx_1}{dt} = \dot{\varepsilon} \Rightarrow x_1 = \dot{\varepsilon}\, t$$

Lastly, we balance the forces at point B to get the relationship between x_1 and x_2 and derive the energy stored in the spring.

	Model Diagram	Derivation of Energy Expression
1		Force balance at point B – $\mu(x_1 - x_2) = \eta\frac{dx_2}{dt}$ $\Rightarrow \eta\frac{dx_2}{dt} + \mu x_2 = \mu\dot{\varepsilon}\, t$ Solving ODE using initial condition that $x_1 = x_2 = 0$ at $t = 0$

		$x_2 = \frac{\eta\dot{\varepsilon}}{\mu}\left(e^{\frac{-\mu t}{\eta}} - 1\right) + \dot{\varepsilon}\, t$ Plugging into energy expression – $E = \frac{\mu}{2}(x_2 - x_1)^2 = \frac{\mu}{2}(x_2 - \dot{\varepsilon}\, t)^2$ $\Rightarrow E = \frac{\mu}{2}(\frac{\eta\dot{\varepsilon}}{\mu}(e^{\frac{-\mu t}{\eta}} - 1))^2$
2		Force balance at point B – $\eta_1\left(\frac{dx_1}{dt} - \frac{dx_2}{dt}\right) = \eta_2\frac{dx_2}{dt} + \mu x_2$ $\Rightarrow(\eta_1 + \eta_2)\frac{dx_2}{dt} + \mu x_2 = \eta_1\dot{\varepsilon}$ Solving ODE using initial condition that $x_1 = x_2 = 0$ at $t = 0$ $x_2 = \frac{\eta_1\dot{\varepsilon}}{\mu}\left(1 - e^{\frac{-\mu t}{\eta_1 + \eta_2}}\right)$ Plugging into energy expression – $E = \frac{\mu}{2}(x_2)^2$ $\Rightarrow E = \frac{\mu}{2}(\frac{\eta_1\dot{\varepsilon}}{\mu}(1 - e^{\frac{-\mu t}{\eta_1 + \eta_2}}))^2$
3		Force balance at point B – $\mu_1(x_1 - x_2) = \eta\frac{dx_2}{dt} + \mu_2 x_2$ $\Rightarrow\eta\frac{dx_2}{dt} + (\mu_1 + \mu_2)x_2 = \mu_1\dot{\varepsilon}t$ Solving ODE using initial condition that $x_1 = x_2 = 0$ at $t = 0$ $x_2 = \frac{\eta\mu_1\dot{\varepsilon}}{(\mu_1 + \mu_2)^2}\left(e^{\frac{-(\mu_1 + \mu_2)t}{\eta}} - 1\right) + \frac{\mu_1\dot{\varepsilon}t}{\mu_1 + \mu_2}$ Plugging into energy expression – $E = \frac{\mu_1}{2}(x_2 - x_1)^2 + \frac{\mu_2}{2}(x_2)^2$ $\Rightarrow E = \frac{\mu_1}{2}(\dot{\varepsilon}t - \frac{\eta\mu_1\dot{\varepsilon}}{(\mu_1 + \mu_2)^2}\left(e^{\frac{-(\mu_1 + \mu_2)t}{\eta}} - 1\right) - \frac{\mu_1\dot{\varepsilon}t}{\mu_1 + \mu_2})^2 + \frac{\mu_2}{2}(\frac{\eta\mu_1\dot{\varepsilon}}{(\mu_1 + \mu_2)^2}\left(e^{\frac{-(\mu_1 + \mu_2)t}{\eta}} - 1\right) +$
4		Force balance at point B – $\mu(x_1 - x_2) = \eta\frac{dx_2}{dt} + F$ $\Rightarrow\eta\frac{dx_2}{dt} + \mu x_2 = \mu\dot{\varepsilon}t - F$ Solving ODE using initial condition that $x_1 = x_2 = 0$ at $t = 0$

		$x_2 = \left(\frac{\eta\dot{\varepsilon}}{\mu} + \frac{F}{\mu}\right)\left(e^{\frac{-\mu t}{\eta}} - 1\right) + \dot{\varepsilon}t$ Plugging into energy expression – $E = \frac{\mu}{2}(x_2 - x_1)^2$ $\Rightarrow E = \frac{\mu}{2}((\frac{\eta\dot{\varepsilon}}{\mu} + \frac{F}{\mu})(e^{\frac{-\mu t}{\eta}} - 1))^2$
5		Force balance at point B – $\eta\left(\frac{dx_1}{dt} - \frac{dx_2}{dt}\right) = \mu x_2 + F$ $\Rightarrow \eta\frac{dx_2}{dt} + \mu x_2 = \eta\dot{\varepsilon} - F$ Solving ODE using initial condition that $x_1 = x_2 = 0$ at $t = 0$ $x_2 = \left(\frac{\eta\dot{\varepsilon}}{\mu} - \frac{F}{\mu}\right)\left(1 - e^{\frac{-\mu t}{\eta}}\right)$ Plugging into energy expression – $E = \frac{\mu}{2}(x_2)^2$ $\Rightarrow E = \frac{\mu}{2}((\frac{\eta\dot{\varepsilon}}{\mu} - \frac{F}{\mu})(1 - e^{\frac{-\mu t}{\eta}}))^2$

Supplementary Table 3: Obtained parameters from fitting the energy profile in the tissue compression simulation setup under each of the death and division rules for $\dot{\varepsilon} = 2\ nm/Iter$ and cells with baseline stiffness (200 Pa). The cells highlighted in green are for the models which satisfy the fitting criteria.

		Death and Division Rule					
Model	Parameter	Area	95% Confidence Interval		Perimeter	95% Confidence Interval	
1	μ	8.218	8.097	8.339	324.7	314.8	334.6
	η	1.165e+04	1.156e+04	1.173e+04	8.963e+04	8.827e+04	9.098e+04
	R^2	0.8383			0.5751		
2	η_1	8.33e+04	-2.414e+09	2.414e+09	1.57e+05	-5.644e+09	5.644e+09
	η_2	5.124e+05	-3.211e+10	3.211e+10	1.18e+05	-1.413e+10	1.413e+10
	μ	420.3	-2.436e+07	2.436e+07	996.2	-7.163e+07	7.163e+07
	R^2	0.8383			0.5750		
3	μ_1	8.218	8.097	8.339	324.7	314.8	334.6
	μ_2	8.268e-13	fixed at bound	fixed at bound	3.009e-14	fixed at bound	fixed at bound
	η	1.165e+04	1.156e+04	1.173e+04	8.962e+04	8.827e+04	9.098e+04
	R^2	0.8383			0.5751		
4	μ	209.7	-1.176e+07	1.176e+07	431.1	-3.275e+07	3.275e+07
	η	2.972e+05	-1.666e+10	1.666e+10	1.19e+05	-9.038e+09	9.038e+09
	F	-0.0004767	-30.03	30.03	-3.142e-05	-10.23	10.23
	R^2	0.8383			0.5750		
5	η	5.446e+05	-3.585e+10	3.585e+10	2.253e+05	-1.976e+10	1.976e+10
	μ	384.2	-2.529e+07	2.529e+07	816.2	-7.16e+07	7.16e+07

	F	0.001249	-76.94	76.94	0.0007348	-51.99	51.99
	R^2	0.8383			0.5750		

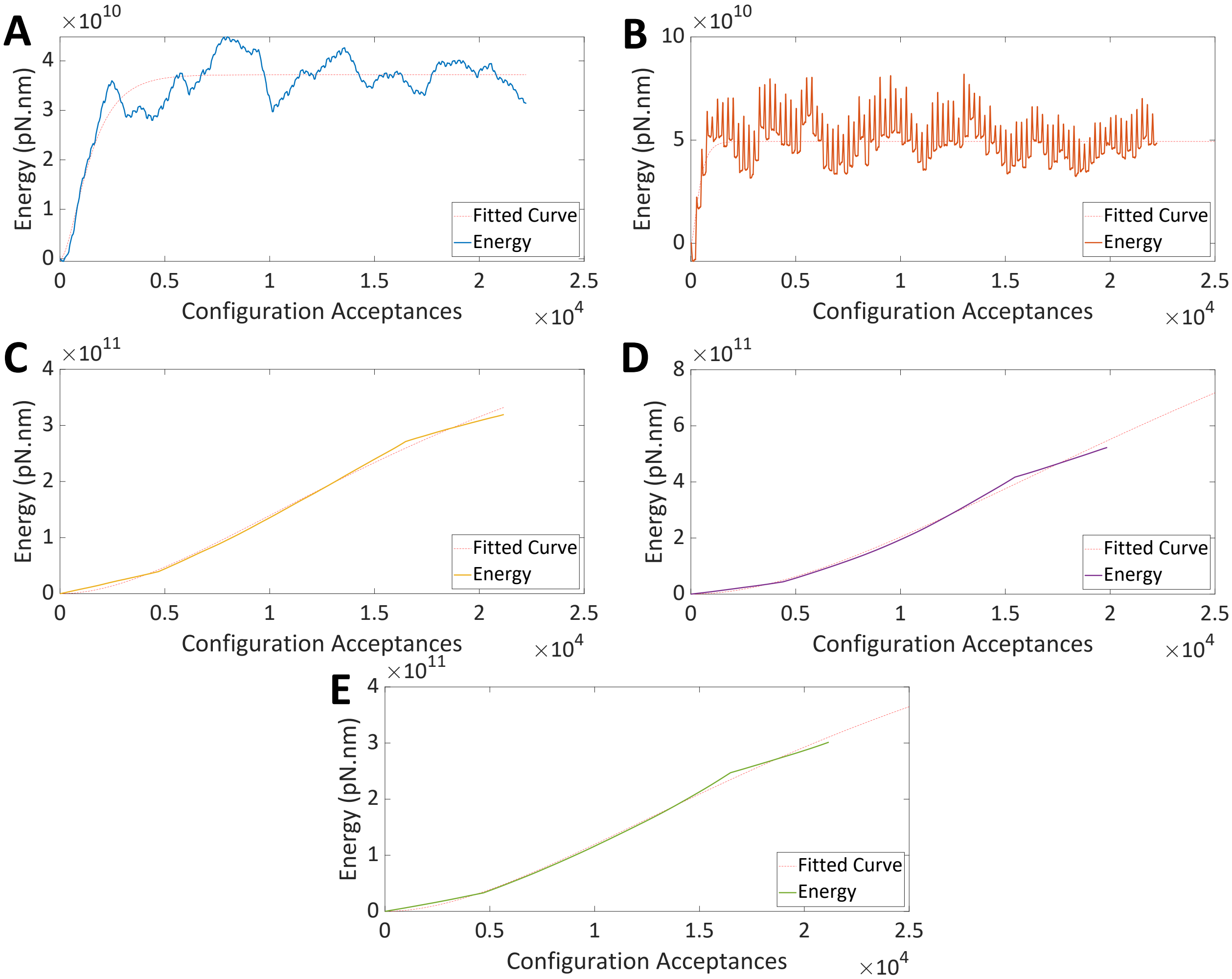
Model	Parameter	Random	95% Confidence Interval		Shape	95% Confidence Interval	
1	μ	0.7766	0.7739	0.7794	1.548	1.544	1.551
	η	1.951e+04	1.946e+04	1.956e+04	2.897e+04	2.895e+04	2.9e+04
	R^2	0.9936			0.9979		
2	η_1	1.16e+05	-8.44e+08	8.442e+08	1.447e+05	-6.71e+08	6.712e+08
	η_2	5.733e+05	-9.189e+09	9.19e+09	5.78e+05	-6.032e+09	6.033e+09
	μ	27.44	-3.993e+05	3.994e+05	38.6	-3.58e+05	3.581e+05
	R^2	0.9936			0.9979		
3	μ_1	2.249	2.219	2.278	1.548	1.544	1.551
	μ_2	0.3659	0.3653	0.3665	4.803e-09	fixed at bound	fixed at bound
	η	9412	9392	9433	2.897e+04	2.895e+04	2.9e+04
	R^2	0.9974			0.9979		
4	μ	23.59	-4.143e+05	4.143e+05	33.03	-3.733e+05	3.734e+05
	η	5.927e+05	-1.041e+10	1.041e+10	6.184e+05	-6.989e+09	6.99e+09
	F	-0.0009703	-18.93	18.93	-0.0009691	-12.47	12.47
	R^2	0.9936			0.9979		
5	η	6.396e+05	-1.129e+10	1.129e+10	5.494e+05	-6.262e+09	6.263e+09
	μ	25.46	-4.492e+05	4.493e+05	29.35	-3.345e+05	3.346e+05
	F	0.001503	-24.54	24.55	0.001351	-13.96	13.96
	R^2	0.9936			0.9979		

Supplementary Table 4: Obtained parameters from fitting the energy profile in the tissue compression simulation setup under each of the death and division rules for $\dot{\varepsilon} = 2\ nm/Iter$ and cells with half stiffness (100 Pa). The cells highlighted in green are for the models which satisfy the fitting criteria.

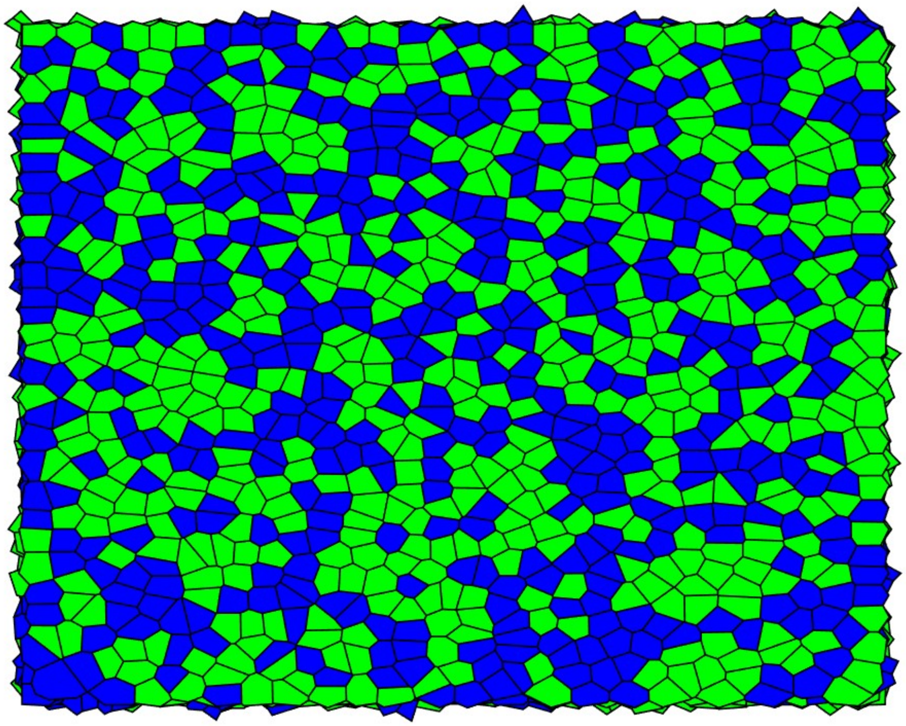
		Death and Division Rule					
Model	Parameter	Area	95% Confidence Interval		Perimeter	95% Confidence Interval	
1	μ	13.59	13.32	13.87	257.4	252.1	262.7
	η	1.387e+04	1.373e+04	1.401e+04	8.351e+04	8.265e+04	8.436e+04
	R^2	0.7169			0.7275		
2	η_1	1.354e+05	-4.771e+09	4.771e+09	2.466e+05	-7.97e+09	7.97e+09
	η_2	1.186e+06	-8.835e+10	8.835e+10	4.818e+05	-3.911e+10	3.911e+10
	μ	1295	-9.126e+07	9.126e+07	2245	-1.451e+08	1.451e+08
	R^2	0.7169			0.7275		
3	μ_1	13.59	13.32	13.87	257.9	252.5	263.2
	μ_2	2.904e-12	fixed at bound	fixed at bound	9.788e-05	-7.959e-05	0.0002754
	η	1.387e+04	1.373e+04	1.401e+04	8.356e+04	8.27e+04	8.442e+04
	R^2	0.7169			0.7275		
4	μ	591.3	-4.238e+07	4.238e+07	915.3	-5.175e+07	5.176e+07
	η	6.034e+05	-4.324e+10	4.324e+10	2.97e+05	-1.679e+10	1.679e+10
	F	-0.001024	-79.93	79.93	-0.000279	-24.68	24.68
	R^2	0.7169			0.7275		
5	η	6.251e+05	-4.49e+10	4.49e+10	2.298e+05	-1.55e+10	1.55e+10

	μ	612.6	-4.4e+07	4.4e+07	708.4	-4.779e+07	4.779e+07
	F	0.001436	-96.48	96.48	0.0007368	-40.35	40.35
	R^2	0.7169			0.7275		

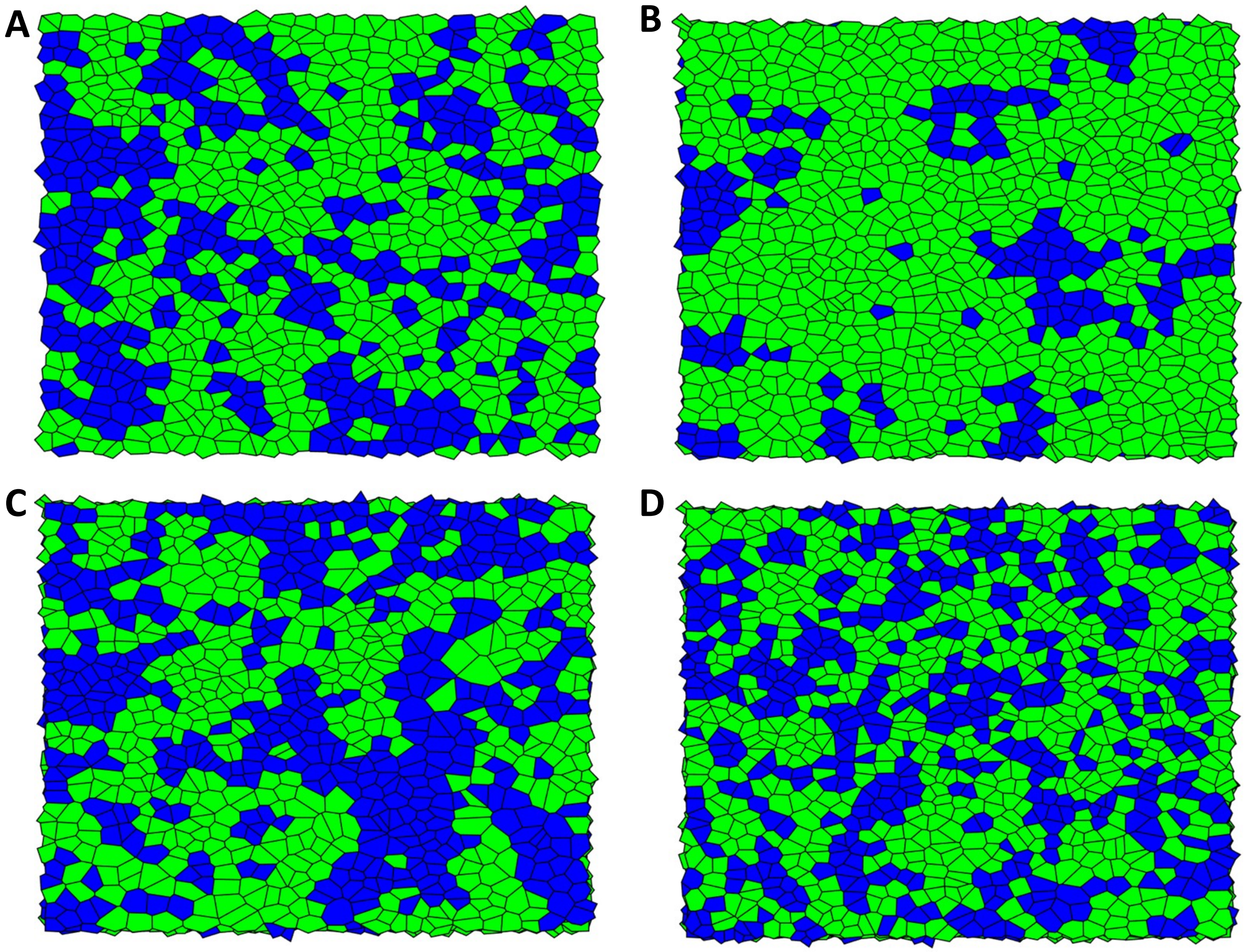
Model	Parameter	Random	95% Confidence Interval		Shape	95% Confidence Interval	
1	μ	1.017	1.015	1.02	1.338	1.335	1.342
	η	2.112e+04	2.109e+04	2.115e+04	3.025e+04	3.02e+04	3.03e+04
	R^2	0.9971			0.9969		
2	η_1	1.698e+05	-9.448e+08	9.452e+08	2.063e+05	-1.189e+09	1.189e+09
	η_2	1.196e+06	-1.425e+10	1.426e+10	1.201e+06	-1.503e+10	1.503e+10
	μ	65.79	-7.32e+05	7.322e+05	62.25	-7.173e+05	7.174e+05
	R^2	0.9971			0.9969		
3	μ_1	1.017	1.015	1.02	1.338	1.335	1.342
	μ_2	2.412e-10	fixed at bound	fixed at bound	5.618e-09	fixed at bound	fixed at bound
	η	2.112e+04	2.109e+04	2.115e+04	3.025e+04	3.02e+04	3.03e+04
	R^2	0.9971			0.9969		
4	μ	9.424	-2.267e+05	2.267e+05	24.52	-3.298e+05	3.299e+05
	η	5.369e+05	-1.291e+10	1.291e+10	5.544e+05	-7.456e+09	7.458e+09
	F	-0.0007992	-22.53	22.53	-0.0008498	-13.17	13.17
	R^2	0.9727			0.9969		
5	η	5.432e+05	-7.022e+09	7.023e+09	6.026e+05	-8.074e+09	8.075e+09
	μ	26.16	-3.382e+05	3.383e+05	26.66	-3.572e+05	3.572e+05
	F	0.001301	-15.43	15.43	0.001475	-17.96	17.96
	R^2	0.9971			0.9969		



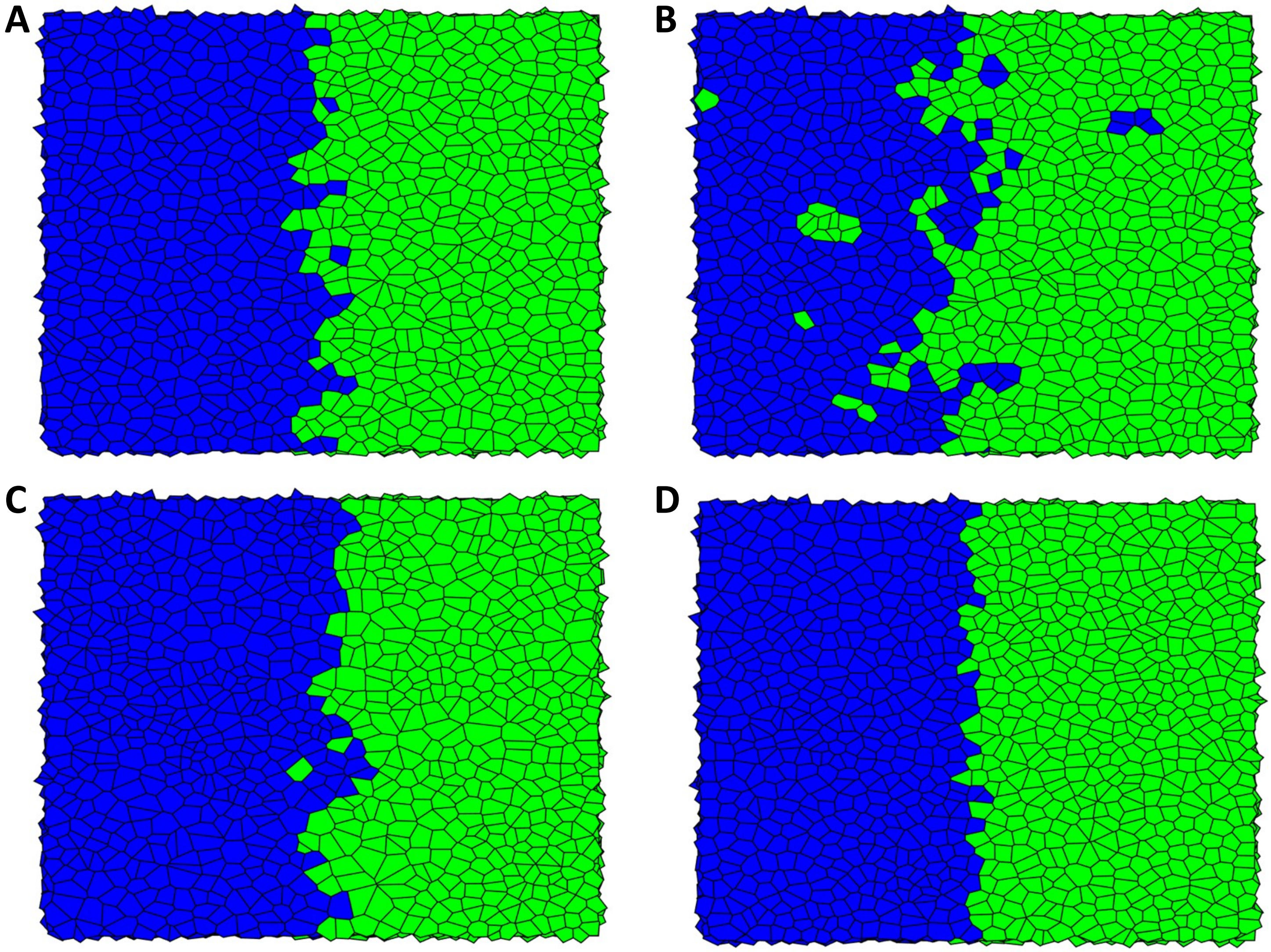
Supplementary Figure 1: (A-E) Fitting the energy profiles of the tissue compression scenario under the area, perimeter, random, shape and without death and division rules respectively



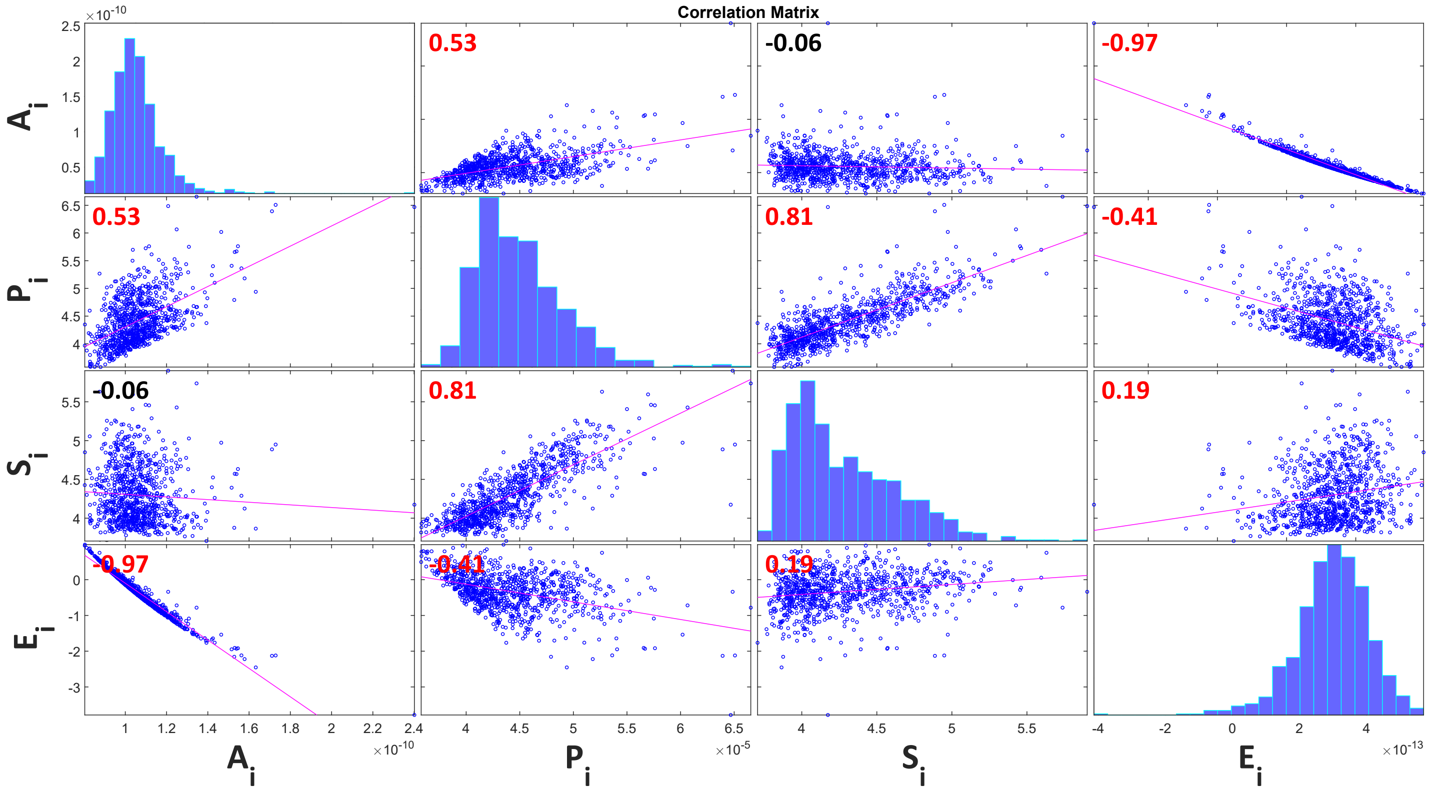
Supplementary Figure 2: Final configuration of an initially mixed system of stiff (blue) and soft (green) cells without death and division



Supplementary Figure 3: (A-D) Final configuration of an initially mixed system of stiff (blue) and soft (green) cells under the area, perimeter, random and shape rule respectively



Supplementary Figure 4: (A-D) Final configuration of an initially segregated system of stiff (blue) and soft (green) cells under the area, perimeter, random and shape rule respectively



Supplementary Figure 5: Correlation of the area, perimeter, shape and energy of each cell with each other, calculated after the initial optimization of the tissue. Numbers in the top-left of each sub-plot is the value of the Pearson correlation coefficient, with statistically significant values marked in red.

Supplementary Video 1: Invasiveness of tissue under area death and division rule (Time Interval: 0 – 156,000 configuration accepts)

Supplementary Video 2: Invasiveness of tissue under shape death and division rule (Time Interval: 0 – 92,000 configuration accepts)

Supplementary Video 3: De-mixing of an initially mixed system of stiff (blue) and soft (green) cells under the perimeter death and division rule (Time Interval: 0 – 74,000 configuration accepts)

Supplementary Video 4: De-mixing of an initially mixed system of still (blue) and soft (green) cells under the shape death and division rule (Time Interval: 0 – 34,000 configuration accepts)

Supplementary Video 5: Mixing of an initially segregated system of still (blue) and soft (green) cells under the perimeter death and division rule (Time Interval: 0 – 66,000 configuration accepts)