Driving Forces for Cell Cluster Shape Evolution and Stability

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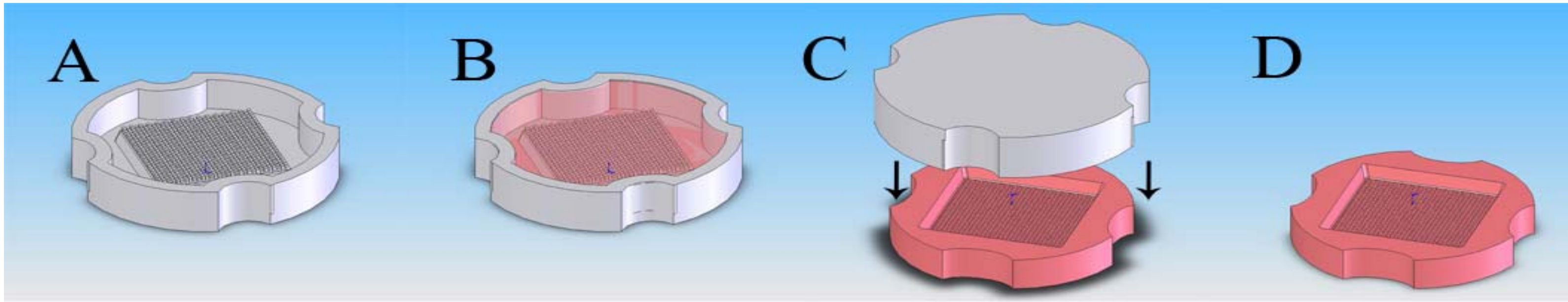
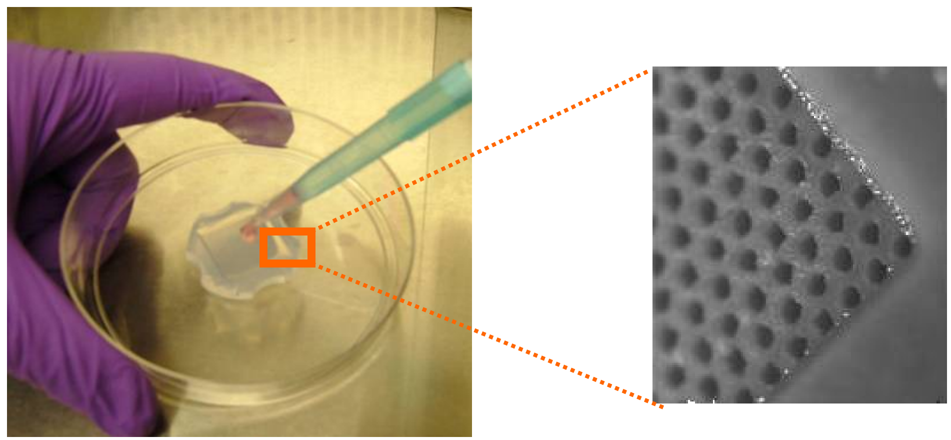
Outline

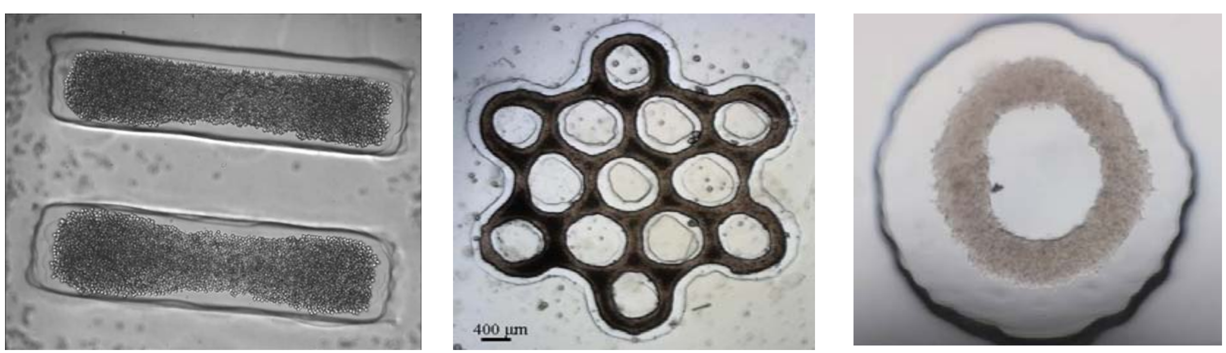
- The Model
  - Experimental Background
  - Origin of Surface Energy
  - Analysis of the Model
  - Results & Conclusions

- Linear Stability of a Toroidal Cluster
  - Stability Analysis
  - Formulation of Model
    - Calculating Surface Area and Volume of Perturbed shape
    - Alternate Perturbed Shape
  - Non-constant Surface Energy Density
  - Results & Conclusions

Directed Self Assembly Experiments

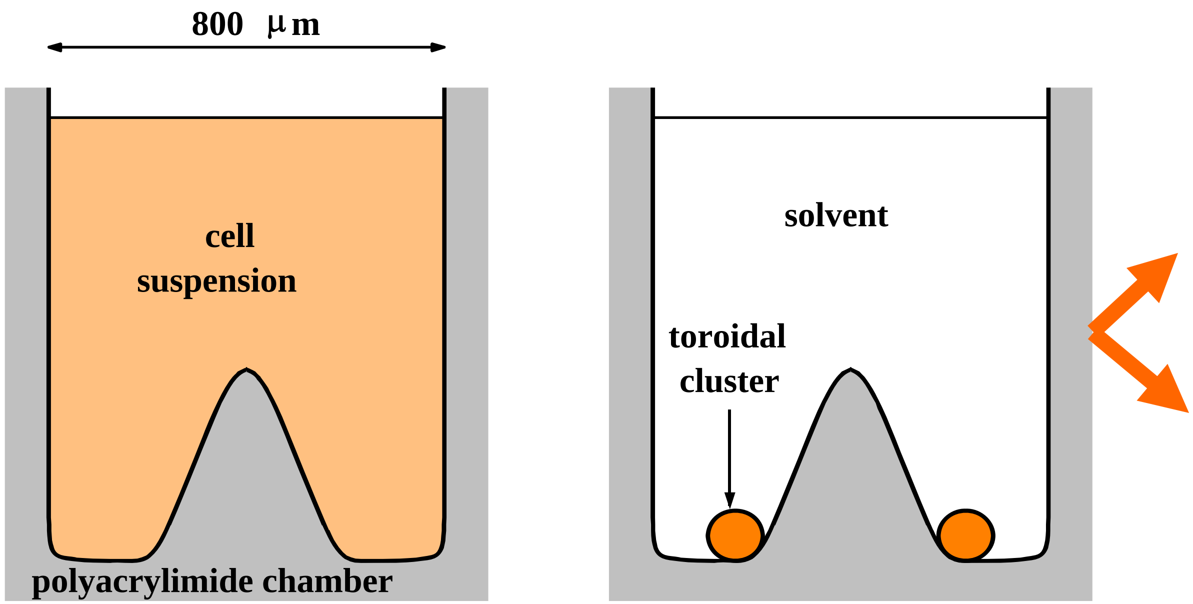






Dean, D. M., Napolitano, A. P., Youssef, J. and Morgan, J. R. FASEB 2007

The Phenomenon



Remain at base and undergo localized deformations

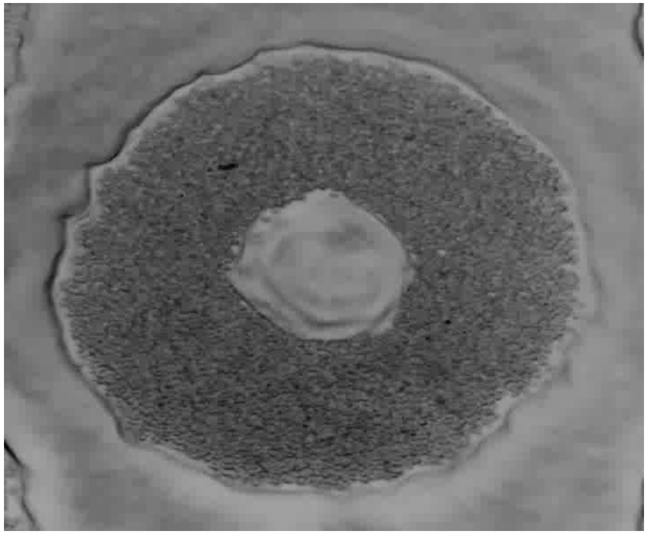
Spontaneously climb conical pillar

A mathematical model of the current system will

1. allow for understanding the factors involved in cell cluster reorganization

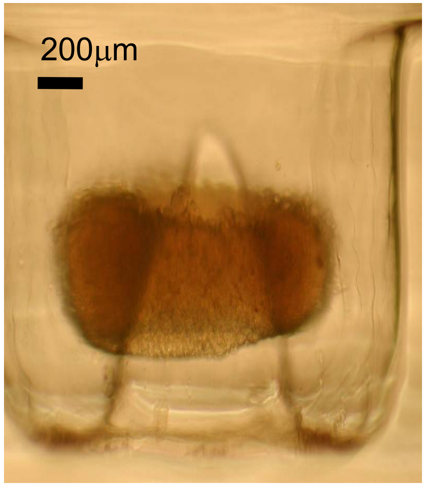
2. offer a framework to organize lab observations

Spontaneous Climb



The goal - to determine the nature of the cell interactions driving the reorganization of a homotypic cluster

2 hrs



4 hrs

6 hrs

The Model

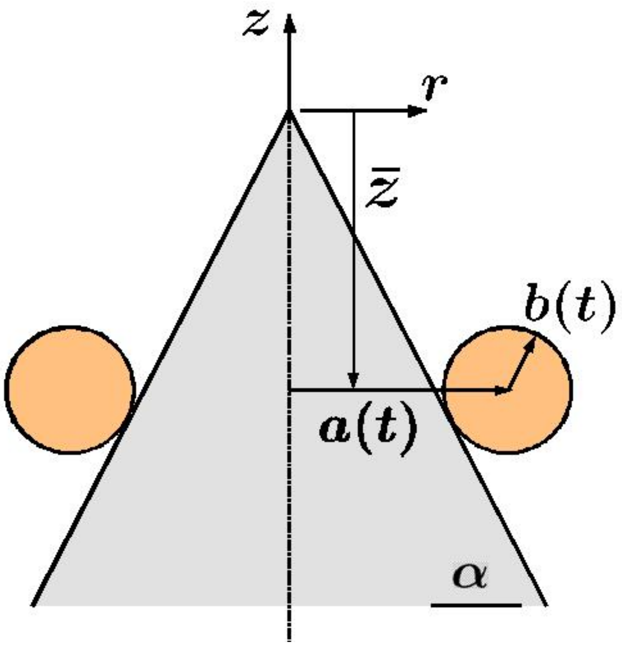
A fully dense aggregate is formed
The volume remains constant,

$$v_0 = 2\pi^2 a(0) b(0)^2 = 2\pi^2 a(t) b(t)^2$$

Total surface area of cluster

$$s(t) = 4\pi^2 a(t) b(t) = 2v_0/b(t)$$

As the cluster moves up the pillar, $a(t)$ decreases and $b(t)$ increases providing a likely driving force.



Distance to the center of mass from the apex,

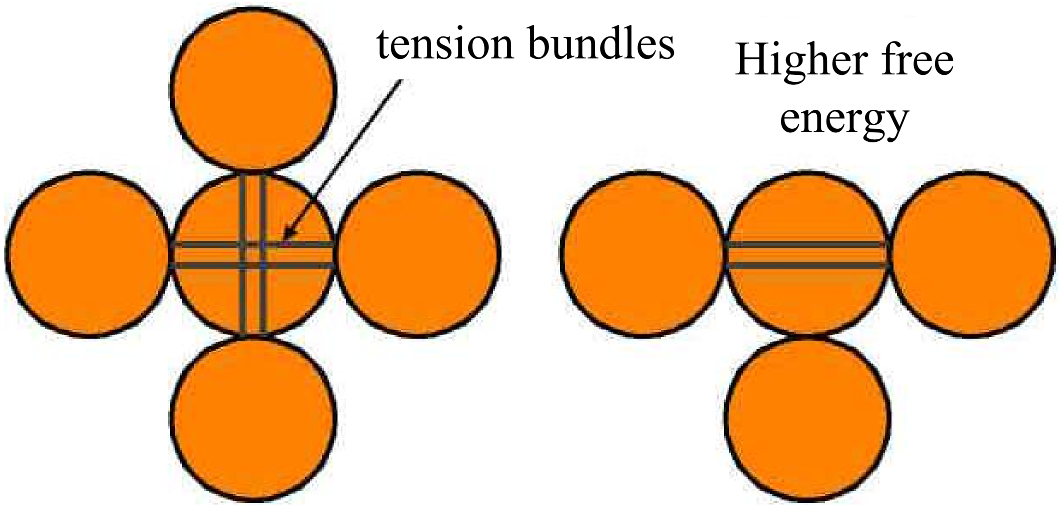
$$\overline{z}(t) = a(t) \tan\alpha - b(t) \sec\alpha \,.$$

Nurse, A., Youssef, J., Freund, L.B. JAM 2011 Under Review

Possible Origin of Surface Energy

Cell to cell adhesion → Anchoring Junctions → Adherens Junctions

Adherens junctions mechanically attaches actin cytoskeletons of connected cells



Generating contraction in these structures consumes ATP which lowers the free energy of the connected cells

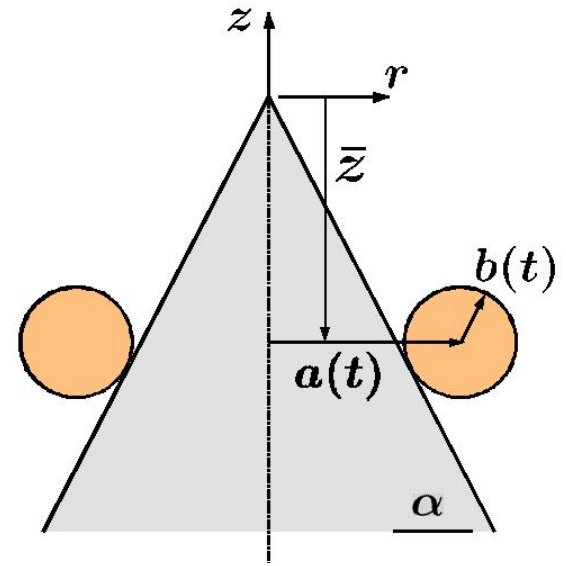
This serves as a natural basis for the surface energy of a cell cluster

The Model

Assume that there is a uniform surface energy density γ associated with the cluster surface

The system free energy in terms of $b(t)$ is

$$\mathcal{F}(t) = -v_0 \rho g \bar{z}(t) + \gamma 2 v_0 / b(t) \, .$$



Rearrangement of cells on cluster surface occurs by surface diffusion with surface mass flux j and surface mobility m_s

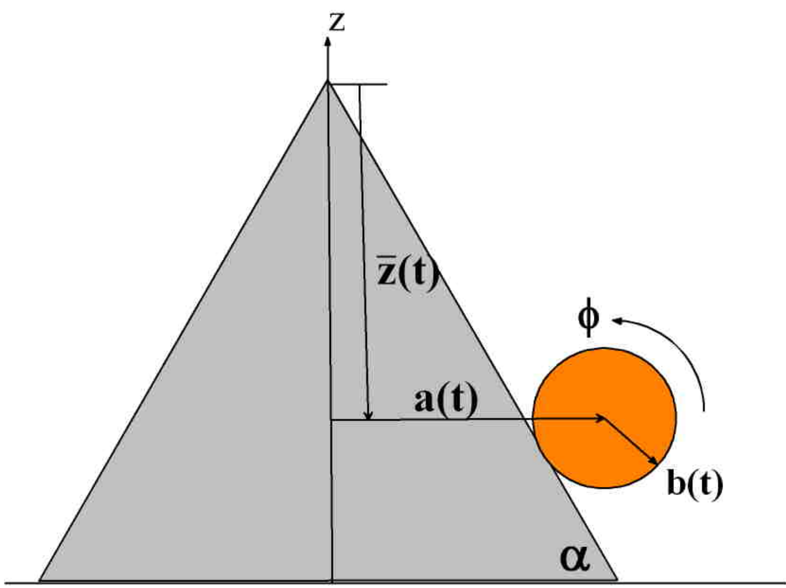
The energy dissipation is

$$\mathcal{D}(t) = \int_{S(t)} \frac{1}{m_s} \mathbf{j} \cdot \mathbf{j} \, dS$$

Finding the Surface Flux

Points on azimuthal section of surface with respect to the apex of the cone

$$\mathbf{r}(\theta, \phi) = \{a(t) + b(t)\cos\phi, \bar{z}(t) + b(t)\sin\phi\}$$



Surface flux is axially symmetric and has the form

$$\mathbf{j} = f(\phi)\mathbf{g}_\phi.$$

Conservation of mass equation

$$v_n + \nabla \cdot \mathbf{j} = 0$$

is solved for $f(\phi)$ where

$$v_n = \mathbf{n} \cdot \partial_t \mathbf{r}(\theta, \phi)$$

A Variational Approach

Diffusive system evolves such that

$$\mathcal{F}'(t) + \frac{1}{2}\mathcal{D}(t)$$

is stationary under variations in the parameters characterizing the rate of change of configuration (LBF & Suresh, Thin Film Materials).

This implies

$$\frac{\partial}{\partial b'(t)}\left[\mathcal{F}'(t) + \frac{1}{2}\mathcal{D}(t)\right] = 0\,.$$

The minor radius and the time are normalized according to

$$\tau = \frac{m_s \rho g t}{b_0^2}\,, \quad \beta(\tau) = \frac{b(t)}{b_0}$$

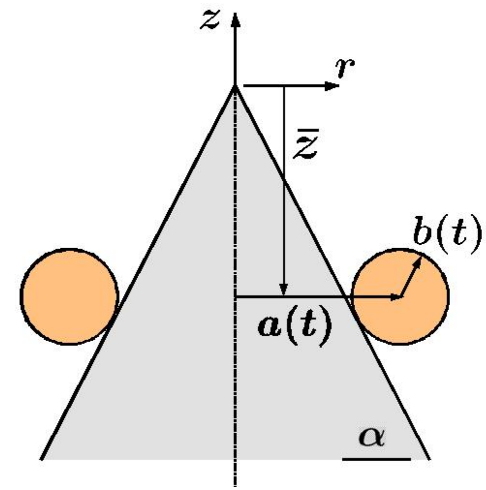
where $\beta(\tau) = 1$ as $b_0 = b(0)$.

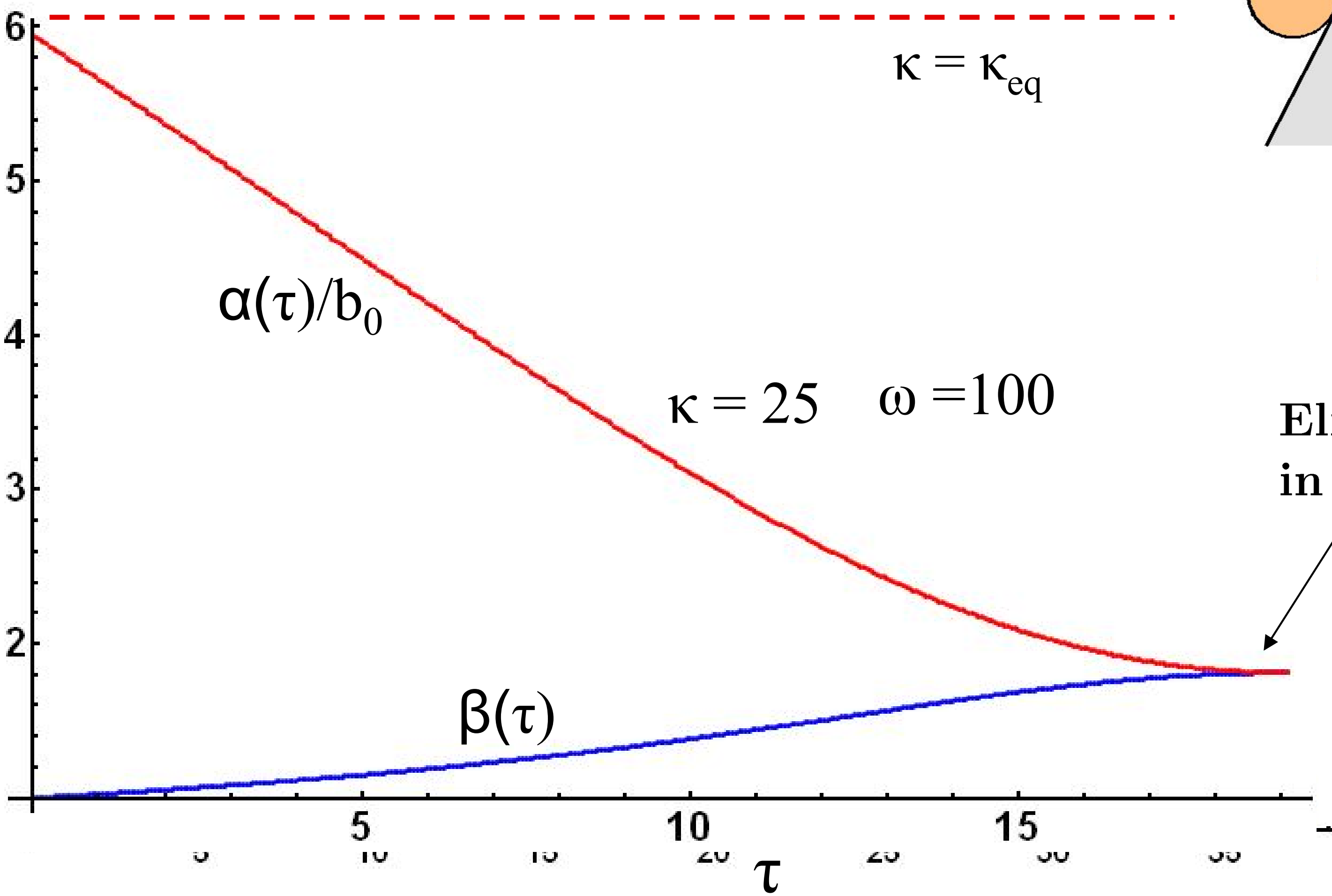
The ODE then requires specification of values of the non-dimensional parameters

$$\omega = \frac{v_0}{b_0^3}\,, \quad \kappa = \frac{\gamma}{\rho g b_0^2}$$

Numerical Solution for Shape Evolution

$$\beta(t) = \frac{b(t)}{b_0}, \quad \omega = \frac{v_0}{b_0^3}, \quad \kappa = \frac{\gamma}{\rho g b_0^2}$$

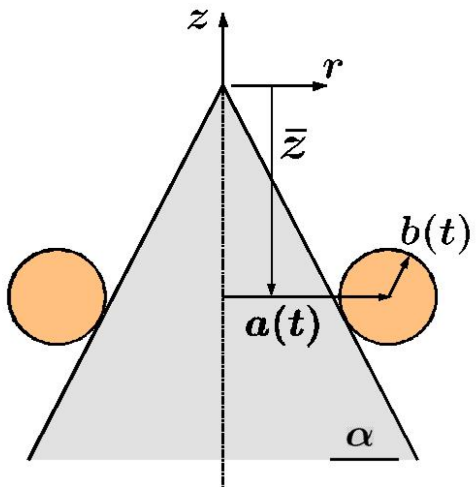


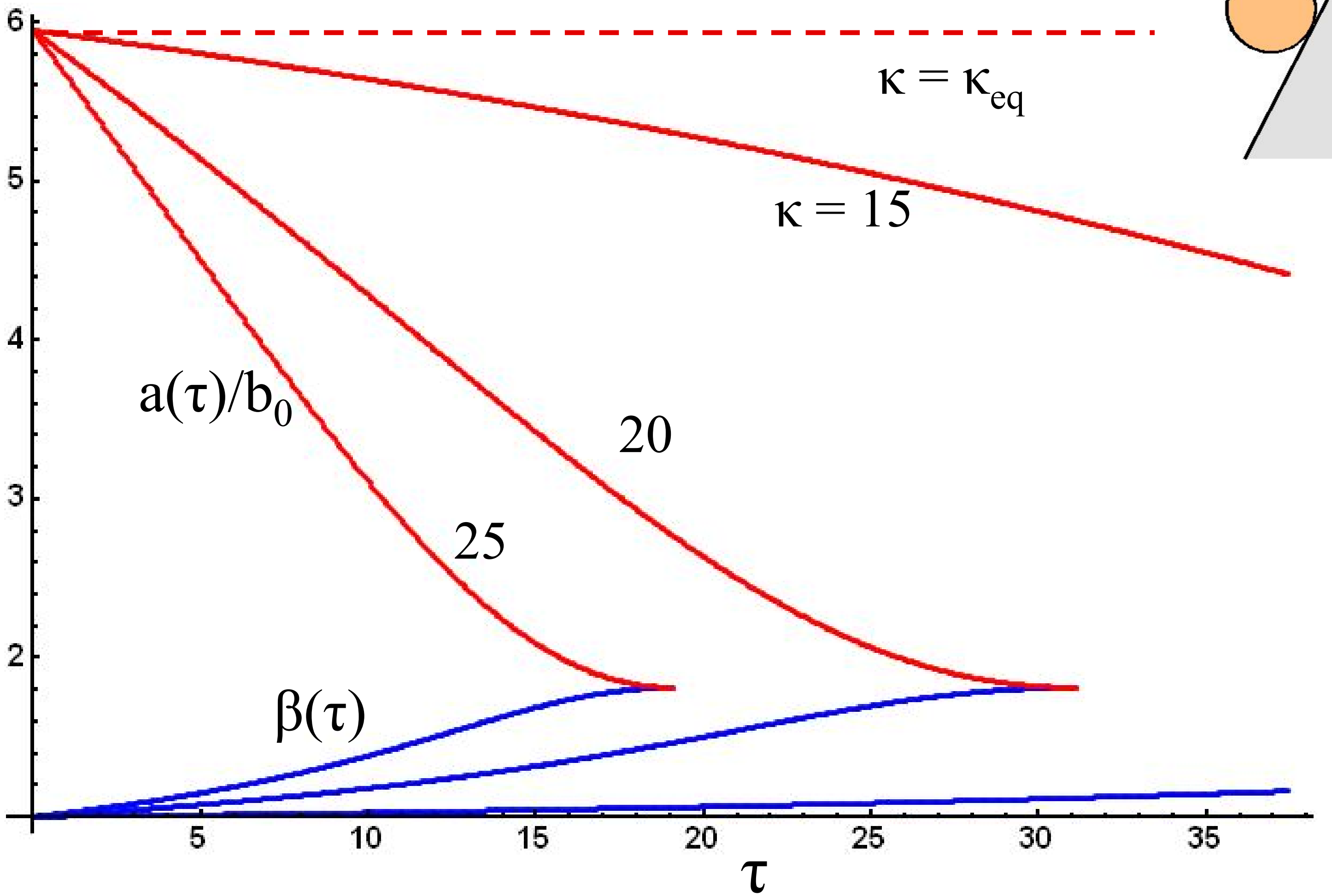


Elimination of hole
in the torus

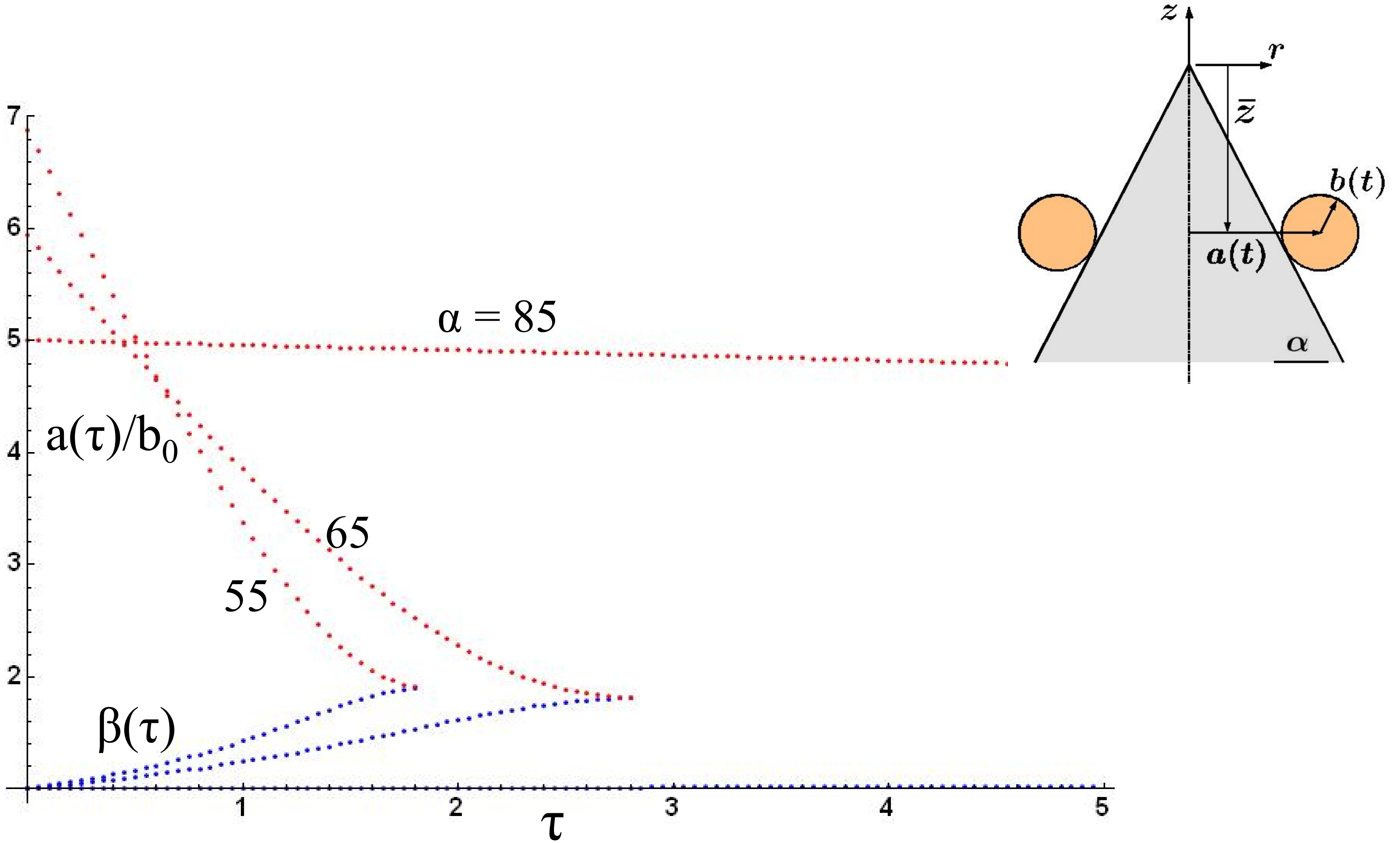
Numerical Solution for Shape Evolution

$$\beta(t) = \frac{b(t)}{b_0}\,, \quad \omega = \frac{v_0}{b_0^3}\,, \quad \kappa = \frac{\gamma}{\rho g b_0^2}$$





Numerical Solution for shape evolution



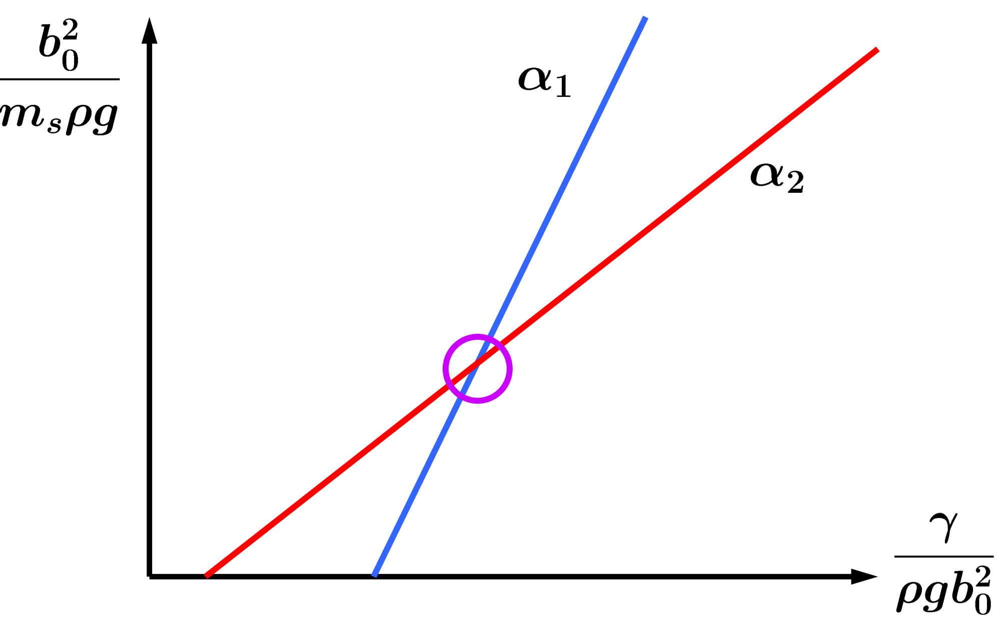
Results of differential equation for $\kappa = 100$

Extraction of Surface Energy Density Values

Examination of the governing differential equation reveals that it has the form

$$A(\alpha, \beta(\tau)) + \frac{\gamma}{\rho g b_0^2} B(\alpha, \beta(\tau)) + \frac{b_0^2}{m_s \rho g} C(\alpha, \beta(\tau), \beta'(\tau)) = 0$$

For a particular value of α, observation of the motion $b(t)$ yields a straight line in the plane below which defines possible values of γ and m_s.



$\alpha_1 = 55°$, $\alpha_2 = 65°$

time (hrs)	γ (mJ/m^2)	m_s 10^{-14} ($m^4 hr/g$)
2	0.0580	0.543
4	0.0638	0.920
6	0.0667	1.238
8	0.0693	1.386

Foty & Steinberg (05) & Sivansankar et al (99): $1.556 \times 10^{-4} \leq \gamma \leq 1.522 \times 10^{-3}$ mJ/m^2

Conclusions from the Basic Model

Results reinforce the process of surface area reduction for self assembled clusters

Rate of process affected by system parameters

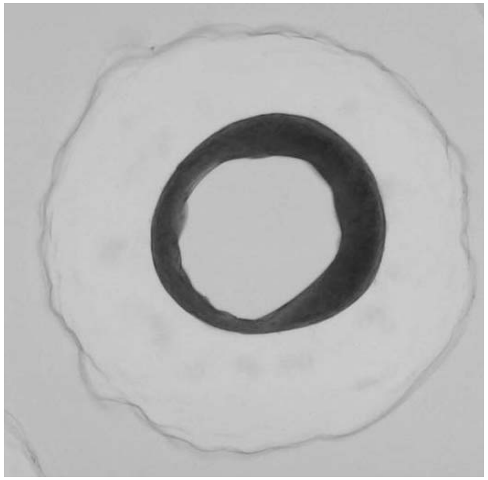
- κ
- α
- m_s

Model can be used to extract approximate values for the surface energy density of the clusters

Model can be extended to study clusters with both uniform and nonuniform shapes

Model does not determine the behavior of clusters after $a(t) = b(t)$ or the behavior of clusters that do not climb the conical pillar

Outline



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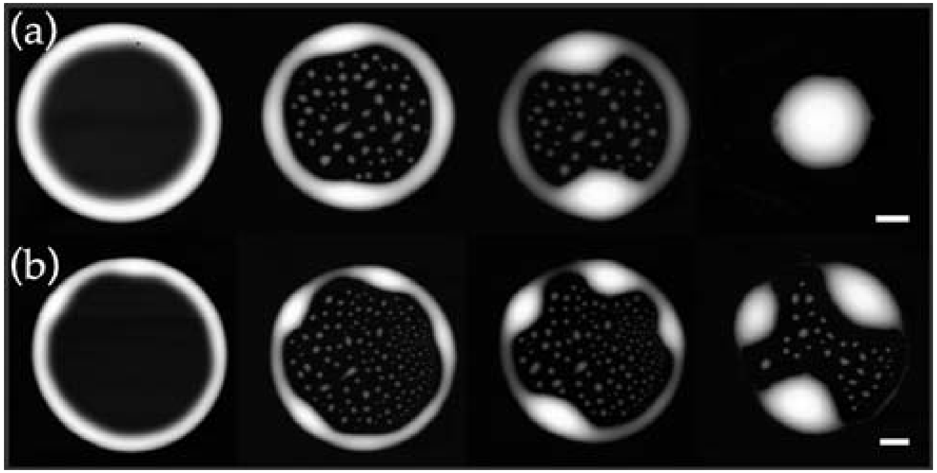
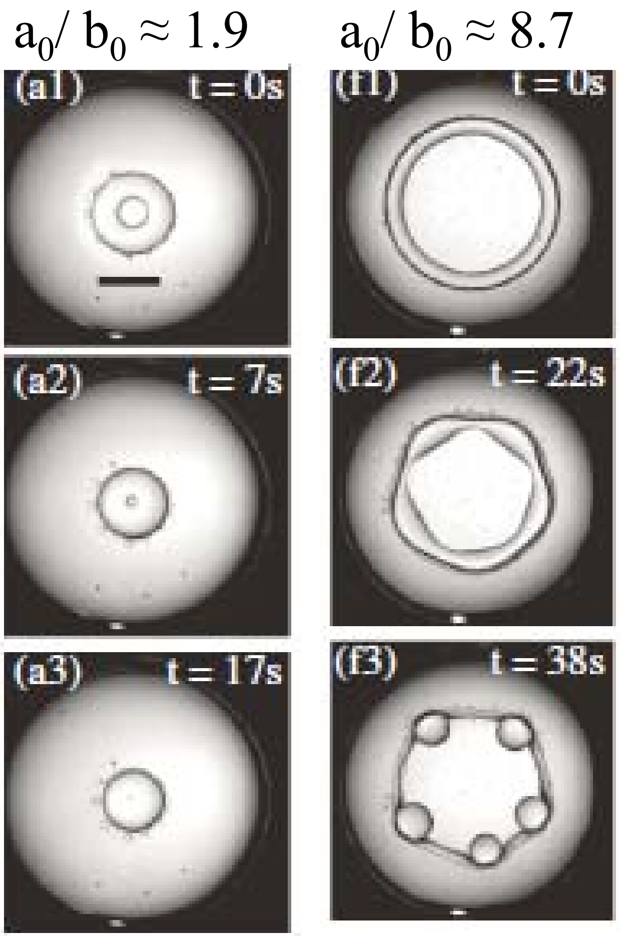
Stability of Toroidal Shapes

Jeff Morgan Lab



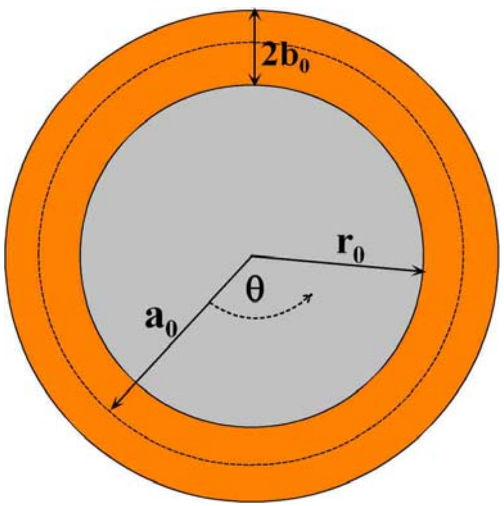
McGraw et al, *Soft Matter* 2010

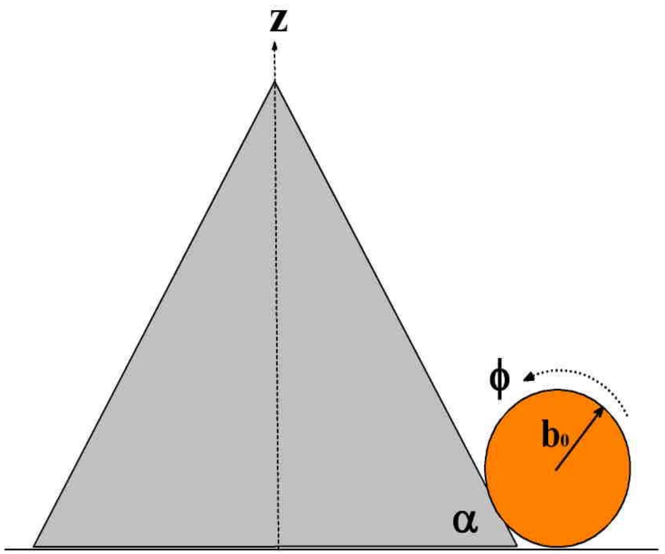


Pairam & Fernandez-Nieves, *Physics Rev. Letter* 2009

Linear Stability Analysis of the Toroidal Cluster

The goal - to apply linear stability concepts to determine if the cluster is stable against growth of small amplitude non-uniform deformations



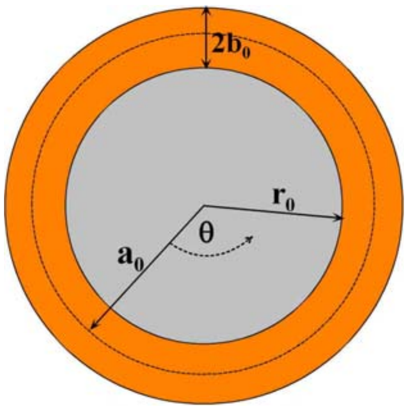


Initial equilibrium shape is a uniform torus

If the torus is perturbed slightly, will the perturbed shape tend toward equilibrium or not?

Linear Stability Analysis of the Toroidal Cluster

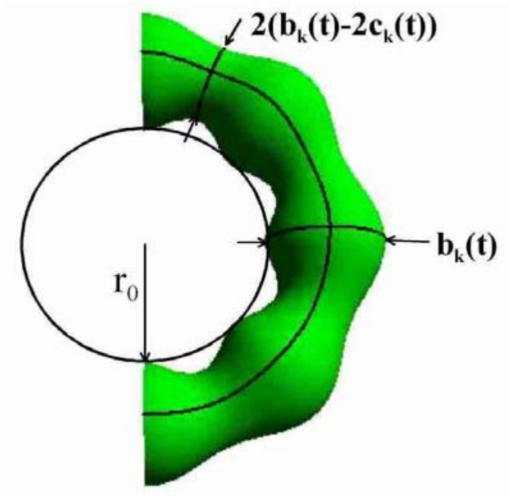
Pertubations that decrease the free energy of the body grow in amplitude (Carter & Glaeser, 1987)



The system free energy is now

$$\mathcal{F}(t) = \gamma S(t)$$

Stability determined by change of $S(t)$ as cluster departs its uniform configuration i.e $\dot{S}(0)$

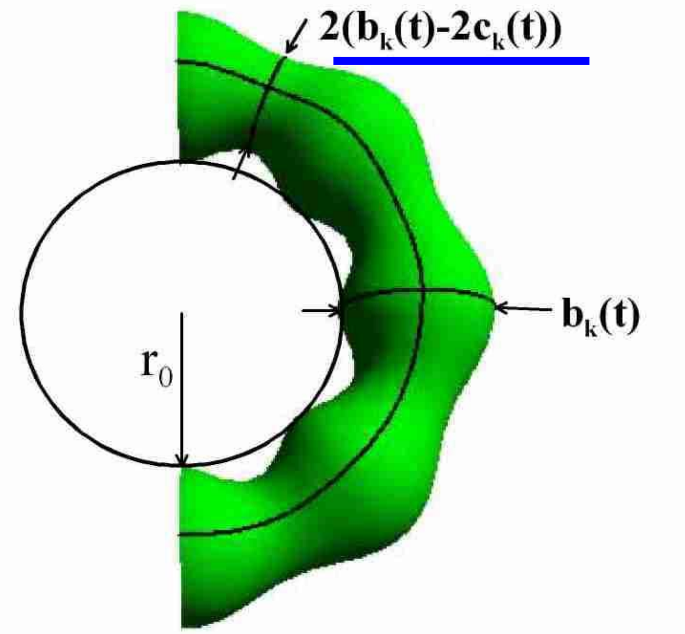


Development of a perturbation in the minor radius of the form

$$b(\theta, t) = b_k(t) - c_k(t)(1 - \cos k\theta)$$

As volume is conserved, fluctuation parameters cannot vary independently

γ is spatially constant



Surface of perturbed shape defined by

$$\mathbf{r}(\theta,\phi) = \big(a(t) + b(\theta,t)\cos\phi\big)\cos\theta\,\mathbf{e}_x + \big(a(t) + b(\theta,t)\cos\phi\big)\sin\theta\,\mathbf{e}_y + b(\theta,t)\sin\phi\,\mathbf{e}_z$$

Surface area found by

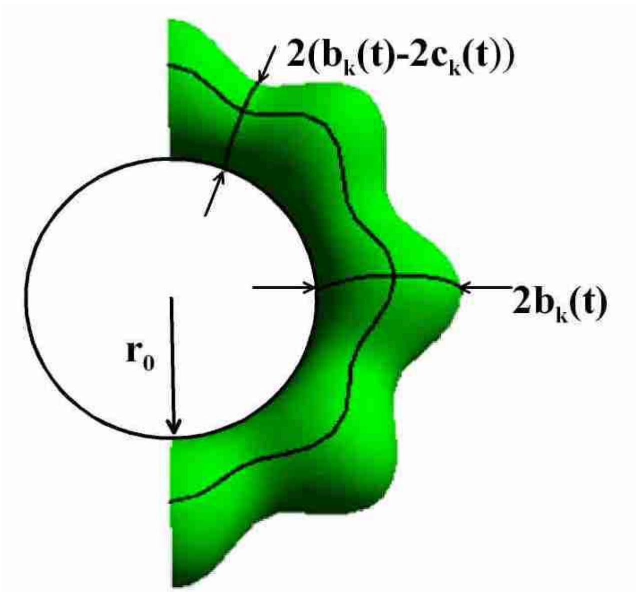
$$S(t) = \int_0^{2\pi}\int_{-\pi}^{\pi}\sqrt{\det\left[G_{\phi\theta}\right]}\,d\phi\,d\theta$$

Applying limits: $b_k(0) \rightarrow b_0$ and $c_k(0) \rightarrow 0$ as $t \rightarrow 0$

$$\dot{S}(0) = 4\pi^2 b_0 \frac{b_0 + r_0}{3b_0 + r_0}\,\underline{\dot{c}_k(0)}$$

Always stable

Alternate perturbed shape



Surface of alternate perturbed shape found by

$$\mathbf{r} = \big(r_0 + b(\theta,t)(1+\cos\phi)\big)\cos\theta\,\mathbf{e}_x + \big(r_0 + b(\theta,t)(1+\cos\phi)\big)\sin\theta\,\mathbf{e}_y + b(\theta,t)\sin\phi\,\mathbf{e}_z$$

Surface area found by

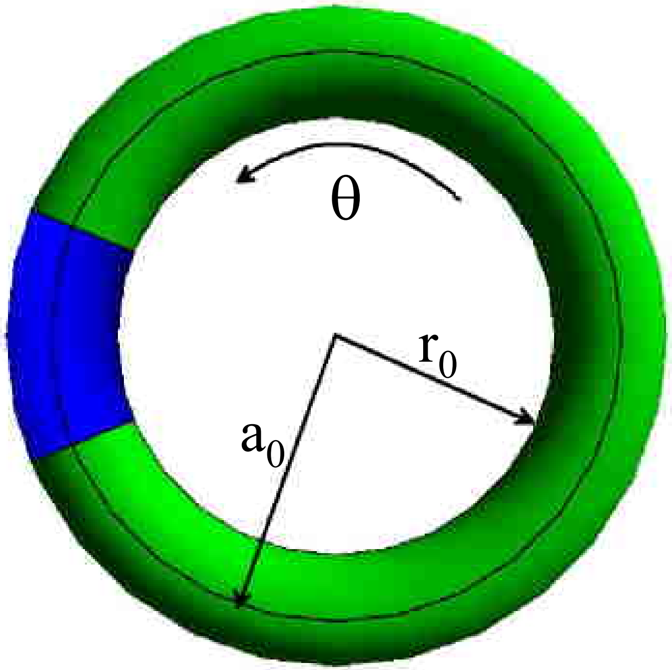
$$S(t) = \int_0^{2\pi}\int_{-\pi}^{\pi}\sqrt{\det\left[G_{\phi\theta}\right]}\,d\phi\,d\theta$$

$$\dot{S}(0) = 0$$

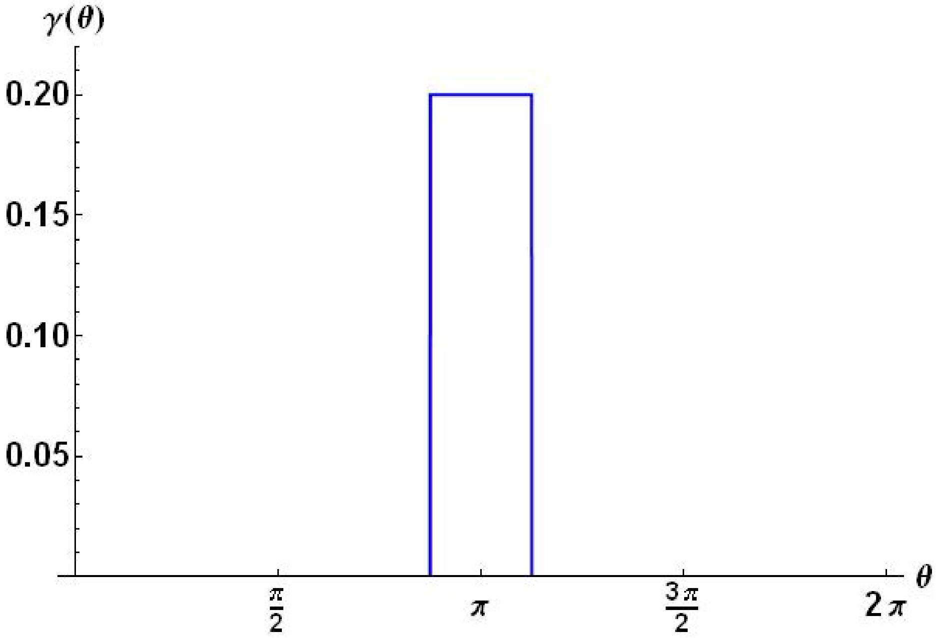
Inconclusive

With the constraint of r_0, the uniform toroidal clusters are stable under this particular family of perturbations if γ is everywhere the same

γ is not spatially constant



For simple illustration, $\gamma(\theta)$



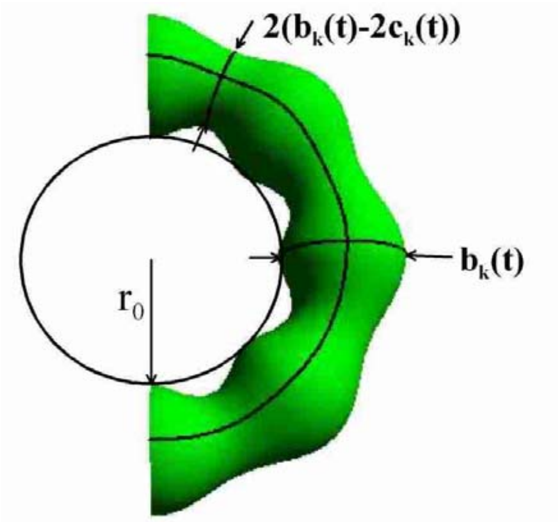
Change in free energy no longer equivalent with change in surface area

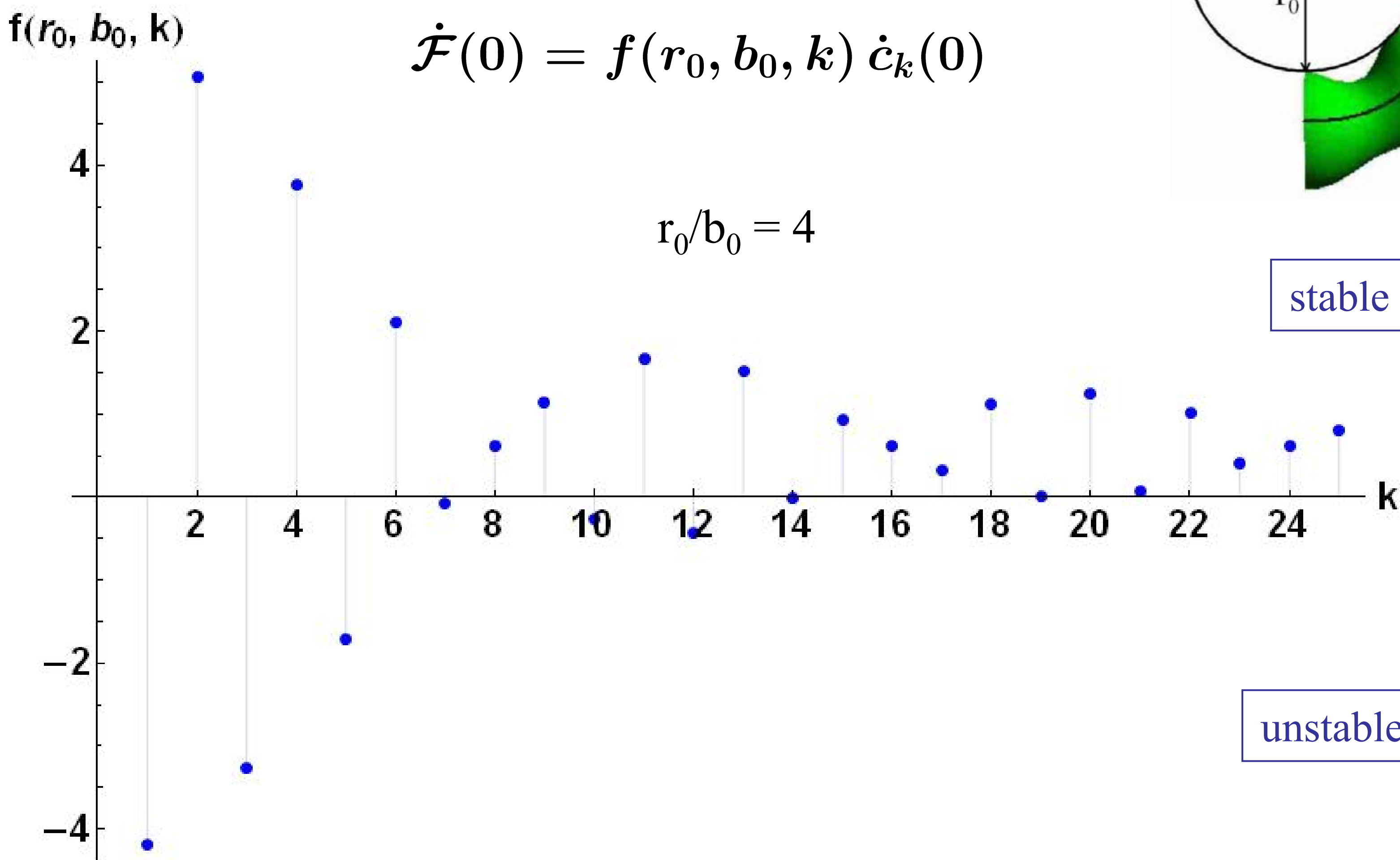
Nonuniform γ with same applied perturbation

Stability now determined by $\dot{F}(0)$ where

$$\mathcal{F}(t) = \int_0^{2\pi} \left[\gamma(\theta) \int_{-\pi}^{\pi} \sqrt{\det\left[G_{\phi\theta}\right]}\, d\phi \right] d\theta$$

$$\dot{\mathcal{F}}(0) = f(r_0, b_0, k)\, \dot{c}_k(0)$$



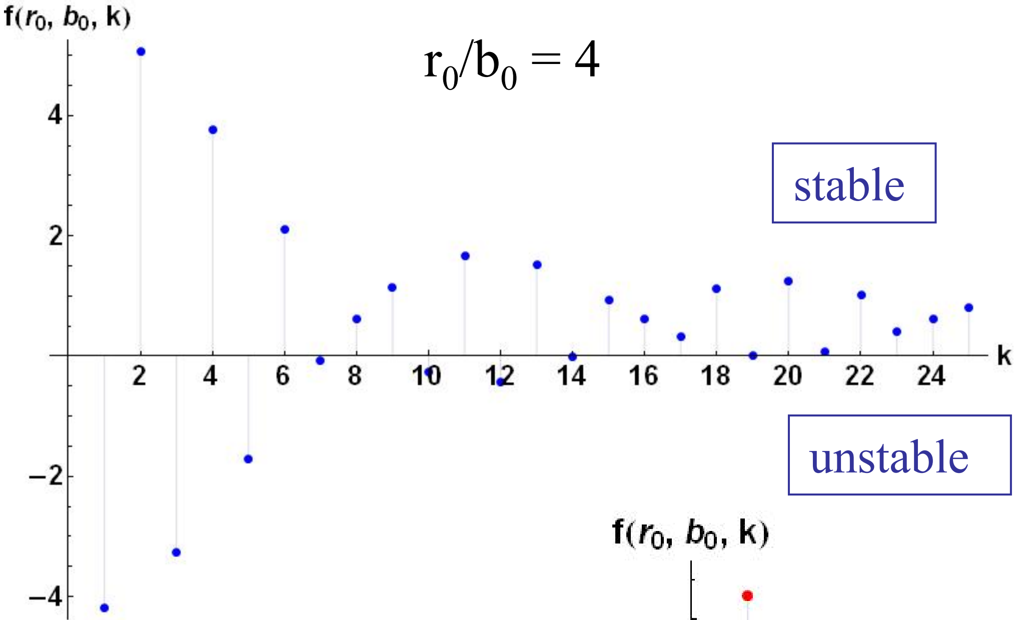


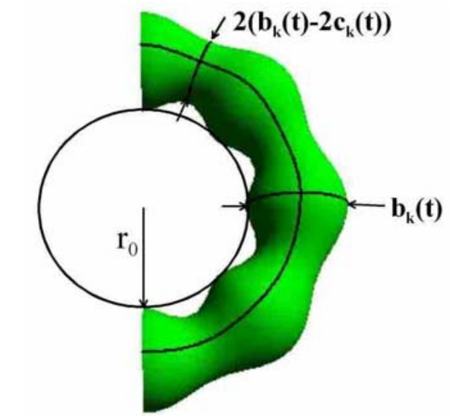
$r_0/b_0 = 4$

stable

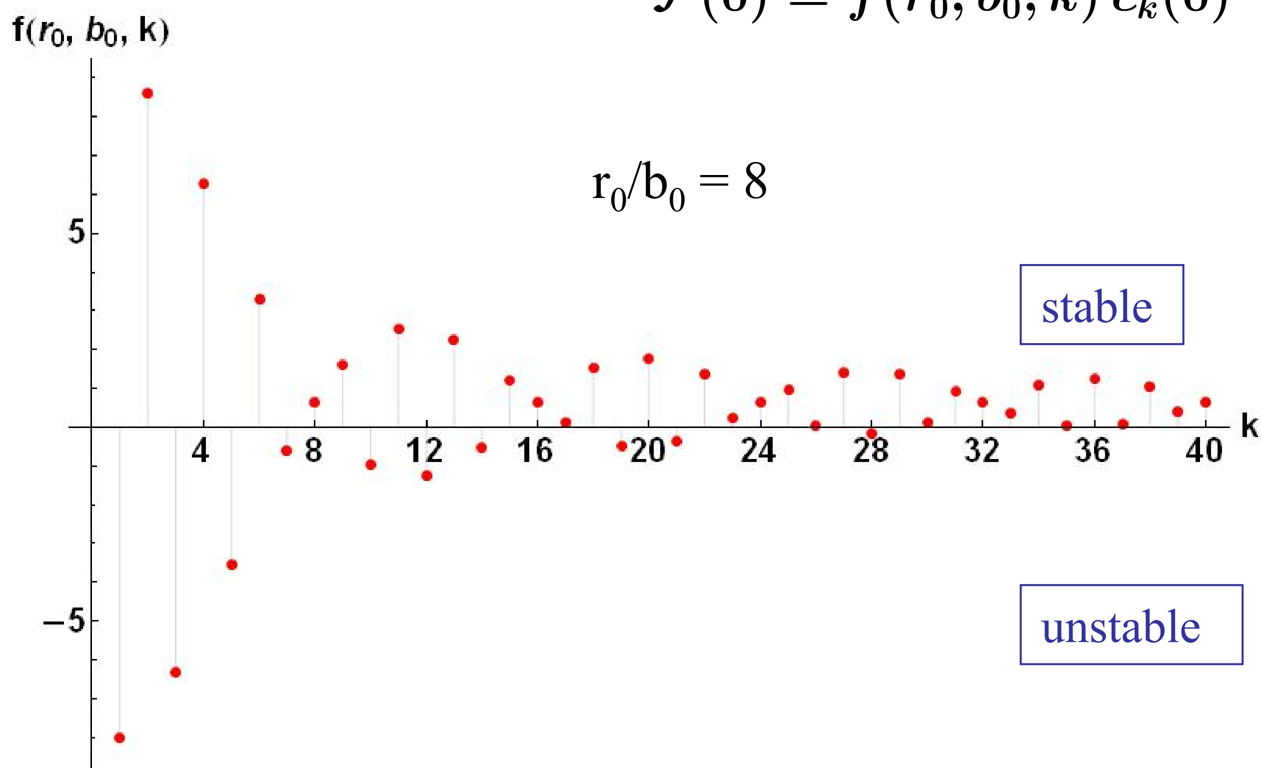
unstable

Non uniform γ with same applied perturbation





$$\dot{\mathcal{F}}(0) = f(r_0, b_0, k)\, \dot{c}_k(0)$$



γ is a function of position on the surface

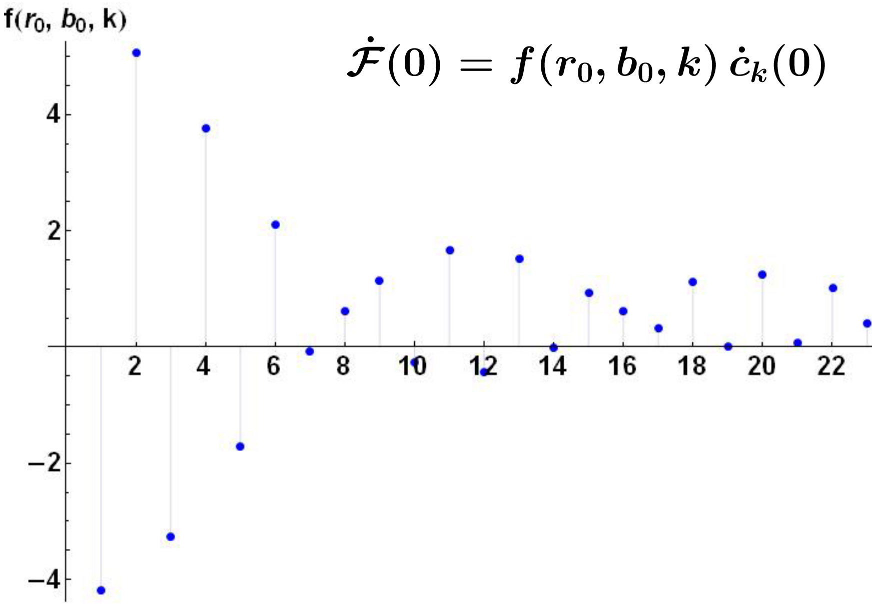
Similar results are obtained for alternate perturbed shape

Position, amplitude and width of non-zero region of $\gamma(\theta)$ have been arbitrarily chosen

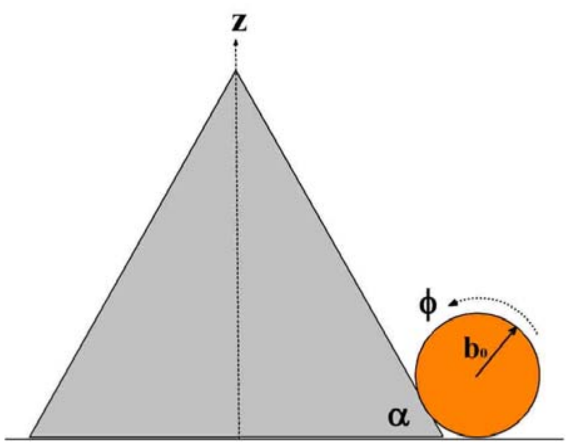
These parameters influence $f(r_0, b_0, k)$

However unstable configurations do develop from the uniform toroidal shapes

Admittedly γ can vary with ϕ as well as with time



$$\dot{\mathcal{F}}(0) = f(r_0, b_0, k)\, \dot{c}_k(0)$$



Conclusions on Toroidal Stability

From work by McGraw et al (2010) and Pairam (2009) dependence of stability on initial geomtery of cluster and radius of pillar is expected

Linear stability analysis is only valid for finite time intervals

It is sufficient to define a critical value of a measurable parameter which can then be experimentally verified

Next step would be a nonlinear stability analysis

Summary of Results on Toroidal Clusters

Formation of uniform toroidal self-assembled cluster at base of chamber

Cluster spontaneously climbs conical pillar to reduce its surface area

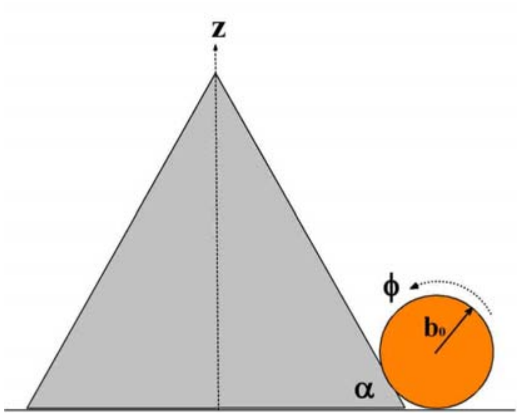
Rate of climb affected by
- influence of SE/GPE (κ)
- slope of conical pillar (α)
- surface mobility of diffusing cells

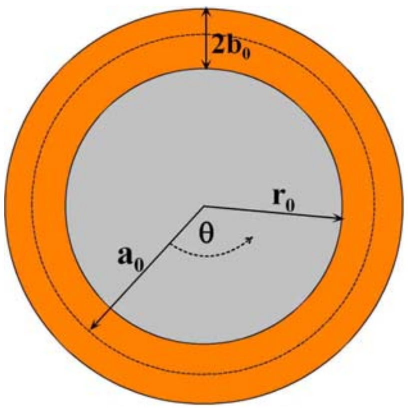
Remains at base of chamber undergoes localized thinning around circumference

For family of applied perturbation
- γ must be a variable
- $\gamma(\theta)$ sufficient for instability
- r_0/b_0 affects cluster stability

Further Work and Questions

- Origin of γ requires further investigation
- More precise method required to extract values of m_s
- Conduct linear stability analysis of toroidal shapes with
  - other family of perturbations
  - more complex surface energy density function
- For spatially constant γ, conduct a nonlinear stability analysis of the toroidal clusters





Acknowledgements & Publications

My advisor Professor L. Ben Freund

Experimental Collaborators - Professor Jeffrey Morgan
Jacqueline Youssef, Dylan Dean, Anthony Napolitano

A publication on the model of the climb of the torus up the conical pillar is currently being revised for Journal of Applied Mechanics with authors Nurse, A., Youssef, J. and Freund, L.B.

Additional work on the action of rho kinase on the climbing process of the cluster of cells can be found at Youssef, J., Nurse, A., Freund, L.B., Morgan, J. PNAS 2011