



An Off-lattice Computational Model for the Growth of *Saccharomyces Cerevisiae*

by

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In fulfilment of the requirements for the degree of

Bachelor of Mathematical Sciences - Honours

February 2025

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Declaration

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I acknowledge the support I have received for my research through the provision of an Australian Government Research Training Program Scholarship.

Isaac Nakone

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Acknowledgements

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Abstract

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Introduction

- Biology of two types of yeast!
- Write chapter 2/ 3 and 4 now

The art of mathematical biology is to capture a biological phenomenon with the simplest model possible. Another concern which appears in the connection between applied and pure mathematics, is that of ensuring the model that one selects is amenable to rigorous analysis. This further reinforces the requirement that the model be as simple as possible, but no simpler. Indeed, a model that is sufficiently crystallized so as to capture the essential details of a physical effect, will necessarily not capture everything observable, but has more chance to be useful, since it directs our thinking away from extraneous features.

What is essential in the study of biological systems? One essential aspect is the phenomenon of growth. Growth, when seen on its own, without reference to biology, is simply “change over time”. The standard tool for this is calculus, which in its more developed form, is called differential geometry. A cell colony will be modelled here as a subset of \mathbb{R}^n where $n = 1, 2, 3$. In order for that set to “change over time”, namely, for the cell to be parametrized by a real number $t \in \mathbb{R}_{\geq 0}$, the geometry of the colony needs to be represented by a finite list of parameters. The most simple way to do this, which comprises one of the models developed here, is to represent each cell as a disk in \mathbb{R}^2 with radius $r = r(t) \in \mathbb{R}_{\geq 0}$ centered at the position $(x(t), y(t)) \in \mathbb{R}^2$. The advantage to this approach is that it is more computationally efficient as compared to models which represent each cell as a deformable polygon, for instance.

The question remains: how can cell division be achieved within mathematical growth models? It does not seem obvious except via the continual addition of new parameters, such as new cell radii and positions. As we will see, taking seriously the question of mitosis from a topological standpoint will yield a generalized model for systems in which geometric changes and topological changes can be captured simultaneously. Why is the topology important in the case of biological growth?

As a motivating example, consider the graph of the function $f(x) = x^2$. Now consider the time-dependent set given by $C(t) = f^{-1}(\{t\})$ where $t \in \mathbb{R}_{\geq 0}$ is a time parameter. When $t = 0$, $C(0) = \{0\}$ (only one element), but when $t = 1$, $C(1) = \{-1, +1\}$, which has two elements, and, likewise for $t = 2$ where $C(2) = \{-\sqrt{2}, +\sqrt{2}\}$. This example shows that a catastrophic change (a bifurcation) can occur in $C(t)$ during a smooth change in t . A subtle modification to this model is to consider $f_t(x) = x^2 - t$ and fix $C(t) = f_t^{-1}(\{0\})$. That is, instead of sliding up the query point t , we slide down the whole smooth manifold given by $(x, f_t(x))$ such that $x \in \mathbb{R}$. The set $C(t)$ is actually called a level-0 set. We will just call this a level set of f_t .

We can consider level sets of functions from \mathbb{R}^n to \mathbb{R} for $n = 2, 3$ as well. In these cases, the level sets are, respectively, level curves and level surfaces. A analogous example for $n = 2$, is the set of functions $f_t(x, y) = x^2 + y^2 - t$, the level curves of which look like circles centered at the origin of radius \sqrt{t} .

This level of generalization will not be sufficient for our purposes, since the type of manifolds that we will be dealing with will not in general be representable as graphs of functions. To see this, consider the fact that a vertical line in the xt -plane is a perfectly reasonable representation of a stationary cell, and yet there's no function (of x) that has a vertical line graph. What is required is that $C(t) = \{p \in M_t \mid \text{the last component of } p \text{ is } 0\}$ where M_t is a time dependent smooth manifold. The requirement that M_t is smooth for all t is imposed so that the theory of smooth manifolds can be brought to bear on the problem. What we will consider are smooth manifolds $M_t \subset \mathbb{R}^{n+1}$ where n is the dimension in which the colony exists. For instance, a two-dimensional colony would be represented by

$$C(t) = \{p \in M_t \subset \mathbb{R}^3 \mid p_3 = 0\}. \quad (1)$$

A three-dimensional colony would be represented by

$$C(t) = \{p \in M_t \subset \mathbb{R}^4 \mid p_4 = 0\}. \quad (2)$$

In the subdiscipline of abstract algebra called ring theory, it is typical to consider the polynomial ring over the real field in two variables $\mathbb{R}[x, y]$ wherein the typical element looks like

$$p(x, y) = \sum_{n,m} a_{nm} x^n y^m, \quad (3)$$

where n, m are non-negative integers, and a_{nm} is a real coefficient. The set $\mathbb{R}[x, y]$ is closed under multiplication and addition because polynomial multiplication and addition yields another real polynomial. In this thesis, a cell will be modeled as a level set

of the quartic given by

$$f(x, y) = ax^4 + bx^3 + cx^2 + dx + e \quad (4)$$

At the beginning, we imagine a colony of yeast cells that is restricted to move along a straight line. The colony is therefore modeled as a set of real numbers $C \subset \mathbb{R}$. Like an archipelago of small islands, the colony as a whole is composed of closed sets, C_j where $j \in \mathbb{N}$ indexes over the cells. Therefore, the colony is a disjoint union of these individual cells,

$$C = \coprod_{j=1}^N C_j$$

and N is the total cell count. Closed sets (in the standard topology on \mathbb{R}) are chosen to represent the cells for the technical reason that a point (singleton) may also constitute a cell. In fact, we further restrict each cell to a closed interval $C_j = [a_j, b_j]$.

As we shall see in general, all we require is that each cell have no holes. Another way of saying this is that each cell is homeomorphic to a singleton (which works in \mathbb{R}^2 and \mathbb{R}^3 as well). Finally, the closed interval $[a_j, b_j]$ will be called a parametrization of the cell C_j : this is important to note for the generalization to \mathbb{R}^2 and \mathbb{R}^3 , where parametrizations must also be constructed.

The mechanism of mitosis must account for the fact that several cells can undergo fission at the same time, or more aptly, they undergo mitosis independently. The most general formulation, which is also simple to implement computationally is the addition of a non-intersecting singleton $\{x\}$ to the set C . Note, that this mechanism is chosen principally for the fact that it conserves the Lebesgue measure of the colony,

$$l(C \cup \{x\}) = l(C),$$

where $C \cup \{x\}$ is the colony after mitosis has occurred, since singletons have measure 0.

Of course, some restrictions must be applied to the choice of $x \in \mathbb{R} \setminus C$. Since, we are always working in Euclidean spaces (for practical scenarios), we may as well require that x is close to C in the sense that for all $c \in C$ we have that $d(c, x) < \delta$ for some small positive amount δ where $d : \mathbb{R} \times \mathbb{R} \rightarrow \mathbb{R}_{\geq 0}$ is the Euclidean metric on \mathbb{R} (which is easily generalized to higher dimensions). This parameter δ represents how the colony spreads out.

A profitable aspect of this model for cell colonies is that it unifies the topological aspects of the colony (it is always homeomorphic to a finite set of points or the empty set), and the measure theoretic properties (one can speak of getting more cells without

changing the total measure). This means we can separate the dynamics of cell division from the dynamics of the geometric growth of the cells, i.e. the change in a_j and b_j . One simple way to do this is to supply an ordinary differential equation for the measure of the colony $V = l(C)$, and equip this with a discrete time update equation for number of cells.

To move us closer to a manageable computer implementation of cell colony growth, we consider the simple growth model given by,

$$\frac{dV(t)}{dt} = g(t),$$

$$N_{n+1} = 2N_n,$$

where $g(t)$ is a growth function. Now we need apply some equation for how each cell grows. For sake of simplicity, say that for all cells j , the cell measure V_j grows as

$$\frac{dV_j(t)}{dt} = g_j(t), \quad t \geq m_j,$$

where $g_j(t)$ is a cellular growth function such that $V_j(t) \rightarrow V_f$ is the final cellular volume, and m_j is the birth time of the cell. This actually is not enough to specify the whole colony geometry. So how do we pin down the geometry?

The geometry and how its dynamics evolve of course depends on the chosen parametrization of each cell. For our purposes, we will consider $C_j = \bar{B}(x_j, \varepsilon_j)$ where

$$\bar{B}(x_j, \varepsilon_j) = \{x \in \mathbb{R} : d(x_j, x) \leq \varepsilon_j\},$$

which is called the closed ball centered on x_j of radius ε_j . That means $a_j = x_j - \varepsilon_j$, and $b_j = x_j + \varepsilon_j$. It is more convenient to use this parametrization since closed balls are defined in higher dimensions as well. Another important benefit to the closed ball is that whenever $\varepsilon_j = 0$, $\bar{B}(x_j, 0) = \{x_j\}$. Also, the volume of each cell is simply $V_j = 2\varepsilon_j$ which tells us that the volume is completely independent of the cell center position x_j .

Now we easily obtain a nice formula for $\varepsilon_j(t)$ defined for $t \geq m_j$ as

$$\varepsilon_j(t) = \frac{1}{2} \int_{m_j}^t g_j(s) ds.$$

But, recall, since the C_j are each disjoint, V is given by

$$V = l(C) = \sum_{j=1}^N l(C_j) = \sum_{j=1}^N V_j.$$

This applies to the time derivative too, yielding

$$\frac{dV(t)}{dt} = \sum_{j=1}^N \frac{dV_j(t)}{dt}.$$

This means that the colony and cell growth functions must be related by the following,

$$g(t) = \sum_{j=1}^N g_j(t).$$

Our functions $g_j(t)$ were defined for $t \in [m_j, +\infty)$ which means they have different domains. To make the analysis easier, we build these functions by taking linear combinations of basis hat functions (defined for $t \in [0, +\infty)$). The basis functions have compact support and are given piecewise by,

$$\varphi_i(t) = \begin{cases} \frac{t-t_{i-1}}{h}, & t \in [t_{i-1}, t_i] \\ \frac{t_{i+1}-t}{h}, & t \in [t_i, t_{i+1}] \\ 0, & \text{otherwise,} \end{cases}$$

where h is the smallest time step, $t_0 = 0$ and $t_i = ih$ for $i \in \mathbb{N}$. Hence, each $g_j(t)$ can be extended to a definition on all of $\mathbb{R}_{\geq 0}$ by

$$\tilde{g}_j(t) = \sum_{i=1}^{\infty} g_j(t_i) \varphi_i(t) = \sum_{i=1}^{\infty} g_{ij} \varphi_i(t).$$

Now that the g_{ij} are defined on the same domain, we can further restrict to $i \leq T$ where T is the total number of time steps. This means that the time dependence is now fixed by a finite number of parameters, g_{ij} . Summing over j , we get that

$$\tilde{g}(t) = \sum_{j=1}^N \sum_{i=1}^T g_{ij} \varphi_i(t).$$

Chapter 1

Description of the model

1.1 An invitation to Signed Distance Fields

The use of signed distance fields (SDFs) to model organic surfaces is a time honoured graphical technique used, for example, by Pixar Animation Studios to model hair in *The Incredibles* (see Petrovic et al. (2005)). The idea is to define a function which represents the closest distance from the query point to a point on the surface of the object that is to be represented. If the query point is outside, the SDF is positive, the SDF is zero on the surface and negative inside. SDFs can be rendered within traditional graphics pipelines (such as OpenGL or Vulkan) using raymarching, a method that takes place within shader programs and is therefore meshless. The formulae defining SDFs for common 2D and 3D shapes are easy to find online, see Quilez (2025). Whilst the simulations herein are done using 2D SDFs, a quick 3D primer is given below.

To motivate the primary mechanism by which cells will undergo mitosis in this thesis, we consider a toy example in which the equations for two spheres undergo a catastrophic topological change as one parameter changes. We start by considering the equations for two spheres which begin as coincident and move apart as the parameter a becomes larger. In order to combine the first equation

$$f_1(x, y, z) = \sqrt{(x + a)^2 + y^2 + z^2} - R,$$

with the second equation

$$f_2(x, y, z) = \sqrt{(x - a)^2 + y^2 + z^2} - R,$$

we require a smooth combination function. We construct the combined SDF using what is called a “union” in the graphics community (see FUSEK). This is the pointwise minimum

$$f_{\text{union}}(x, y, z) = \min(f_1(x, y, z), f_2(x, y, z)).$$

In reality, it may be nicer to have a smooth transition between the cells at a given point of time. That is why we use smoothmin which is defined by a smoothness parameter k , as in

$$\text{smoothmin}(x_1, x_2) = -k \log(e^{-x_1/k} + e^{-x_2/k}). \quad (1.1)$$

As shown in Figure 1.1, we have a smooth splitting of a cell as the parameter a ranges from 0.0 to 5.0. Note that R is the nominal sphere radii, and k is a smoothing parameter. The larger k is, the more smoothly the two curves cling to each other. We plot the level-0 surface of the smooth union SDF using MATLAB's `isosurface` function.

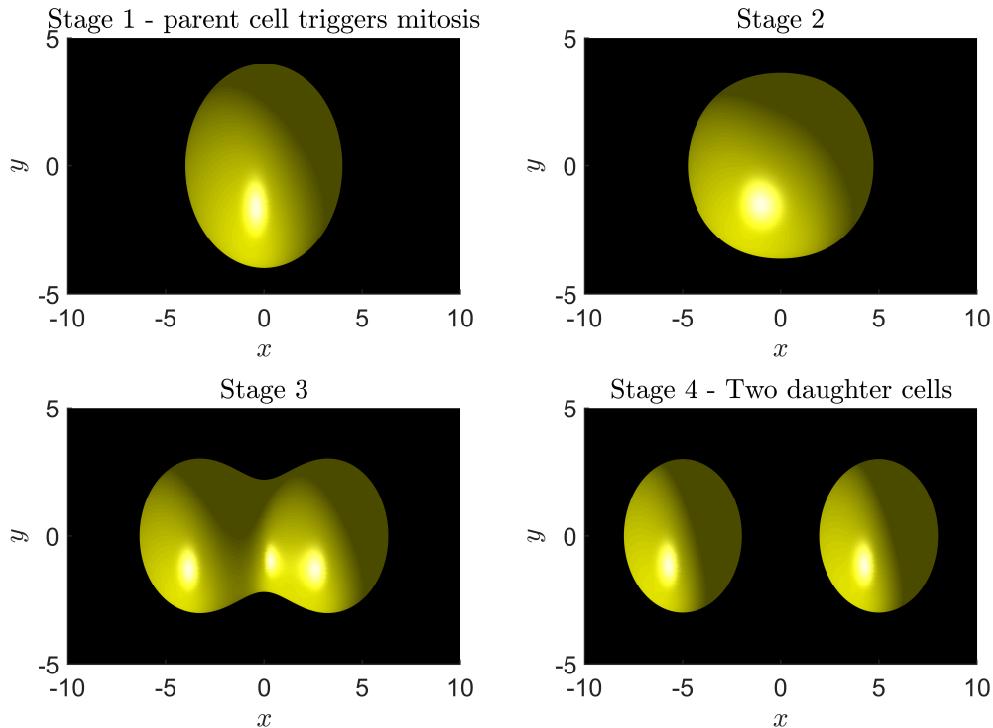


Figure 1.1: A toy example of mitosis using implicit equations for spheres in 3D. Stage 1 is $a = 0.0$, Stage 2 is $a = 1.67$, Stage 3 is $a = 3.33$, Stage 4 is $a = 5.0$

It is also possible to get the intersection of two SDFs using a smoothmax function.

1.2 Modeling growing geometry

Cell colonies can be built up by combining the SDFs of the individual cells using a cumulative smoothmin. We employ the main aspect of smoothmin, which is that

$$\text{smoothmin}(f_3, \text{smoothmin}(f_1, f_2)) = -k \log \left(\sum_{j=1}^3 e^{-f_j/k} \right), \quad (1.2)$$

therefore we can accumulate smoothmins easily using

$$\text{smoothmin}(f_1, \dots, f_N) = -k \log \left(\sum_{j=1}^N e^{-f_j/k} \right), \quad (1.3)$$

The individual cells are modelled using the approximate signed distance field for an ellipse which is given at <https://www.shadertoy.com/view/4XfBD1>. I have provided the vectorized MATLAB implementation below,

```
function sdf = ellipsoid_sdf(x, y, theta, r, X, Y)
    semi_minor_axis = min(r);
    semi_major_axis = max(r);
    c = sqrt(semi_major_axis^2 - semi_minor_axis^2);
    %Geometrical parameter
    center = [x,y]';
    query_point = [X(:), Y(:)]';
    R_z = rotation_matrix(theta);
    l1 = vecnorm(pagetimes(R_z, query_point - center)
        - [c;0], 2, 1);
    l2 = vecnorm(pagetimes(R_z, query_point - center)
        + [c;0], 2, 1);
    l = mean([l1', l2'], 2);
    sdf = reshape(l', size(X)) - semi_major_axis;
end
```

Note that I multiply each local coordinate `query_point - center` by the rotation matrix `R_z` in order to rotate the cell counter-clockwise by θ radians. The rotation matrix R_z is given by

$$R_z = \begin{bmatrix} \cos(\theta) & \sin(\theta) \\ -\sin(\theta) & \cos(\theta) \end{bmatrix}, \quad (1.4)$$

which is a so-called passive rotation matrix because we are rotating the coordinate system by θ CW which has the effect of rotating the ellipse by θ CCW.

Cell colonies are modeled using level-sections of implicit curves in two dimensions. For example, a circle can be modeled as the level-0 set of the following equation

$$f(x, y) = R^2 - (x^2 + y^2),$$

where R is the radius of the circle. If the filled in circle, the disk, is required, then producing a surf plot of the function in the region where $f(x, y) \geq 0$ is sufficient. This can be achieved by modifying the value of $f(x, y)$ to be `nan` wherever $f(x, y) < 0$ so that MATLAB's `surf` function does not plot it.

For approximately circular cells, each individual cell is modeled via the equation of a circle centered at position $(x_j(t), y_j(t))$ where j indexes over the current total number of cells. The equation for a single cell is therefore given by

$$f_j(x, y; t) = R_j^2 - [(x - x_j(t))^2 + (y - y_j(t))^2],$$

where R_j is the radius of the j -th cell. We will discuss how multiple cells can be blended together into one colony level implicit curve. Given the implicit curve for cell 1 to cell $N = N(t)$, respectively $f_1(x, y; t), \dots, f_N(x, y; t)$, we blend them with the following transformation

$$\tilde{\Phi}(x, y; t) = \frac{1}{k} \ln \left[\frac{1}{N} \sum_{j=1}^N e^{kf_j(x, y; t)} \right],$$

where $\tilde{\Phi}(x, y; t)$ is related to the colony microscopic density, k is a parameter related to the level of smoothing between the curves, N is the total number of cells. If all of the $f_j(x, y; t) = 0$ then we recover that $\tilde{\Phi}(x, y; t) = 0$. Of course, we don't yet have the actual colony microscopic density, because the numerical values taken by $\tilde{\Phi}(x, y; t)$ are essentially meaningless. The microscopic density $\Phi(x, y; t)$ is obtained by translating and scaling $\tilde{\Phi}(x, y; t)$ such that $\Phi(x, y; t)$ takes values on the interval $[0, 1]$. We then interpret 1 as the maximum biomass density of the cell at each cell center.

1.3 Mitosis: new cells from old

The addition of new cells can be easily achieved by incorporating additional implicit curves and, hence, modifying the colony microscopic density $\Phi(x, y; t)$. In the case of circular cells which undergo effectively symmetric mitosis, it is necessary to add a cells at a slight offset so that contact forces (explained in the following section) can take effect. In order to store the data associated with each cell, a final number of cells N_f is designated as a constant maximum number of cells which allows for the preallocation of the data associated with the cell centers and other state information (if necessary).

One of the desired features of the model, was to achieve cell division (which can be thought of as a catastrophic change in the colony topology) without sacrificing the smoothness of $\Phi(x, y; t)$. This has been achieved by starting the new cell at a vanishingly close distance to its parent cell, and recovering smoothness through the blending of implicit curves imposed in the construction of $\Phi(x, y; t)$. This is possibly a new idea in the field of agent based models, where the addition of daughter cells is usually not even continuous (for example, in some off-lattice ABMs new cells simply appear beside old ones). Here, the two daughter cells move apart via contact forces between the cell centers and the smooth division follows.

1.4 Modeling interactions between cells

In standard particle dynamic simulations, say gravitational models, the particle positions are modeled using Newton's second law. This means the state of an N particle simulation in $2D$ requires $2N$ positions and $2N$ velocity values. In overdamped, low-inertia regime, which is often used in cell off-lattice ABMs, it is sufficient to ignore changes in the velocity and only construct equations for the change in position over time.

1.5 Tuning the model parameters

1.6 Adding in a nutrient field

1.7 Simulating $N > 1000$ cells with a nutrient field

Explain how I have used hash mapping to deal with cell collisions.

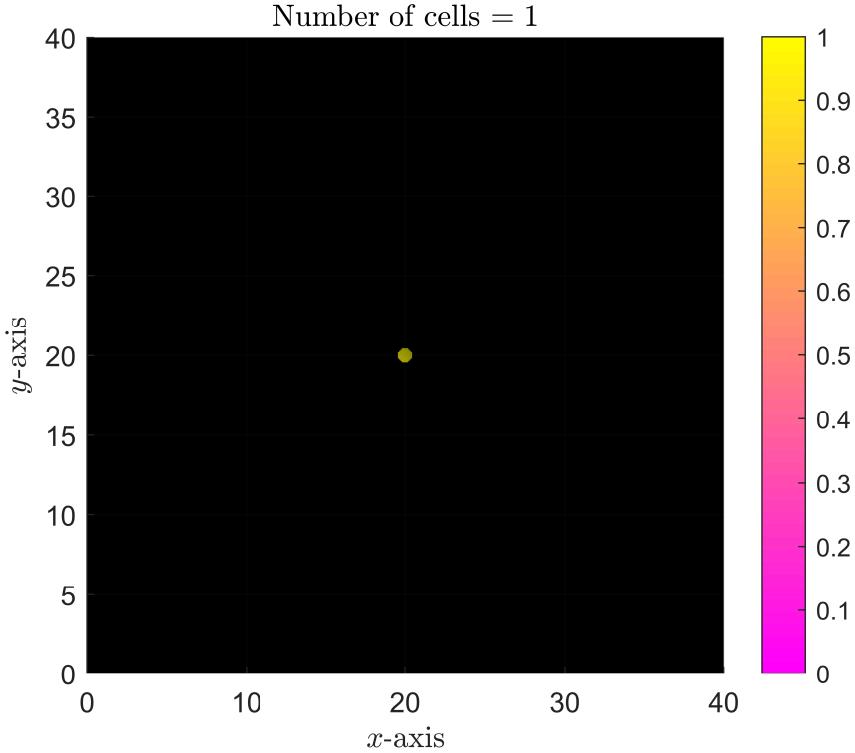


Figure 1.2: A starting configuration consisting of a cell with radius 1 unit equals $3.5\mu\text{m}$

1.8 Calculating the compactness metric

A fully grown colony will in general not be perfectly circular in shape. In order to measure the roundness of the colony we use the metric used for roundness in image processing

$$\Psi = \frac{P^2}{4\pi A}, \quad (1.5)$$

where $\Psi \in [0, 1]$ is 1 for a perfect circle and can get to 0 for highly non-round shapes, A is the colony area, and P is the colony perimeter. When the cells are undergoing mitosis, we are left with the issue of calculating roundness of the blended “pill” shape geometry of two cells right before splitting. In effect, it will be necessary to calculate the length of

1.9 Collision Detection

Referring to the supplied figures, we see that a force is \mathbf{F} in Figure 1.8 can be a representation of an applied force from another cell acting on the current cell. We set

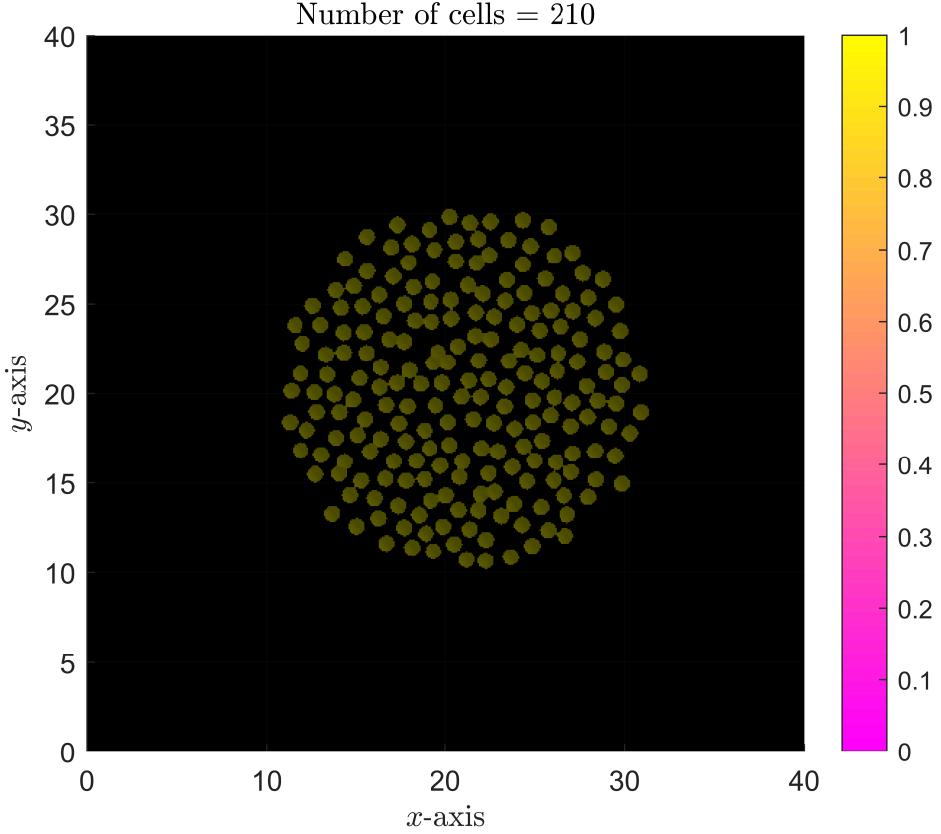


Figure 1.3: The same colony at 210 cells

out to find forces on the two point mass that will produce equivalent force balance in the (t, n) coordinate system.

We replace the force \mathbf{F} with \mathbf{F}_1 and \mathbf{F}_2 acting on mass 1 and 2, respectively. From force balance

$$\mathbf{F}_1 + \mathbf{F}_2 = \mathbf{F},$$

and, from moment balance with anti-clockwise positive,

$$l_F F_n = d(F_{2,n} - F_{1,n}).$$

In our case, the impinging force will be from another cell, so we start by making the assumption that there is no tangential force, i.e. frictionless slipping. With this we can derive simultaneous equations for $F_{1,n}$ and $F_{2,n}$ which have the solution

$$F_{1,n} = \left(\frac{d - l_F}{2d} \right) F_n,$$

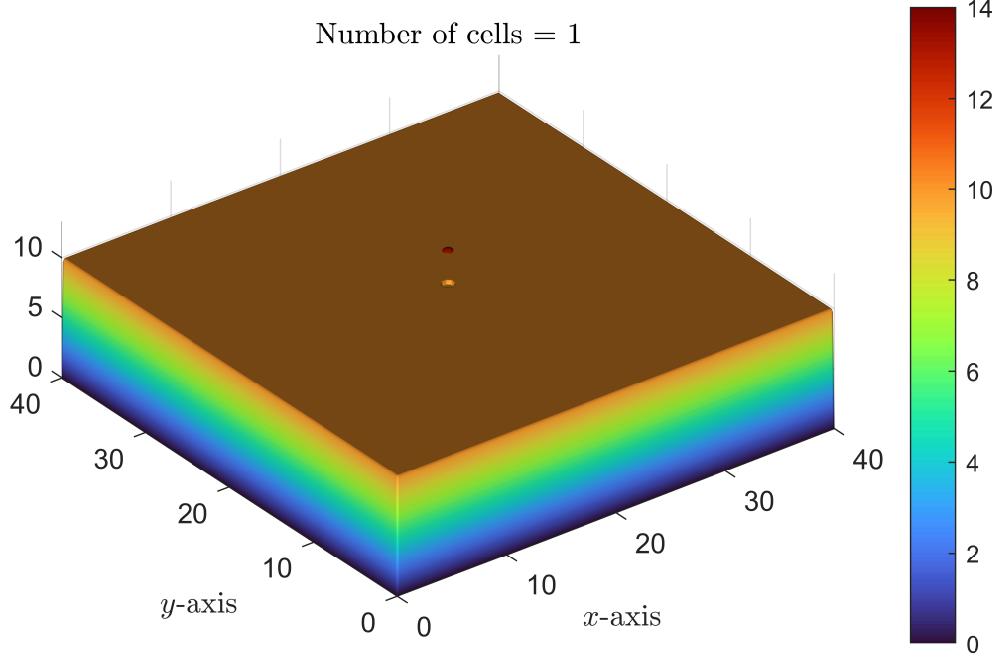


Figure 1.4: A starting configuration consisting of a cell with radius 1 unit equals $3.5\mu m$

$$F_{2,n} = \left(\frac{d + l_F}{2d} \right) F_n.$$

Assuming, once again, that $F_{1,t} = F_{2,t} = F_t = 0$ we can obtain the (x, y) components by doing a coordinate transformation by the angle $-\theta_C = -\arctan(y_2 - y_1, x_2 - x_1)$ where (x_1, y_1) and (x_2, y_2) are the mass positions, respectively. So, we have that the components of the force are given by

$$\begin{bmatrix} F_{1,x} \\ F_{1,y} \end{bmatrix} = \begin{bmatrix} \cos(-\theta_C) & -\sin(-\theta_C) \\ \sin(-\theta_C) & \cos(-\theta_C) \end{bmatrix} \begin{bmatrix} -F_{1,n} \\ 0 \end{bmatrix} = \begin{bmatrix} \cos \theta_C & \sin \theta_C \\ -\sin \theta_C & \cos \theta_C \end{bmatrix} \begin{bmatrix} -\left(\frac{d-l_F}{2d}\right) F_n \\ 0 \end{bmatrix},$$

$$\begin{bmatrix} F_{2,x} \\ F_{2,y} \end{bmatrix} = \begin{bmatrix} \cos(-\theta_C) & -\sin(-\theta_C) \\ \sin(-\theta_C) & \cos(-\theta_C) \end{bmatrix} \begin{bmatrix} F_{2,n} \\ 0 \end{bmatrix} = \begin{bmatrix} \cos \theta_C & \sin \theta_C \\ -\sin \theta_C & \cos \theta_C \end{bmatrix} \begin{bmatrix} \left(\frac{d+l_F}{2d}\right) F_n \\ 0 \end{bmatrix}.$$

We solve this as

$$\mathbf{F}_1 = -\left(\frac{d-l_F}{2d}\right) F_n \cos \theta_C \hat{\mathbf{i}} + \left(\frac{d-l_F}{2d}\right) F_n \sin \theta_C \hat{\mathbf{j}},$$

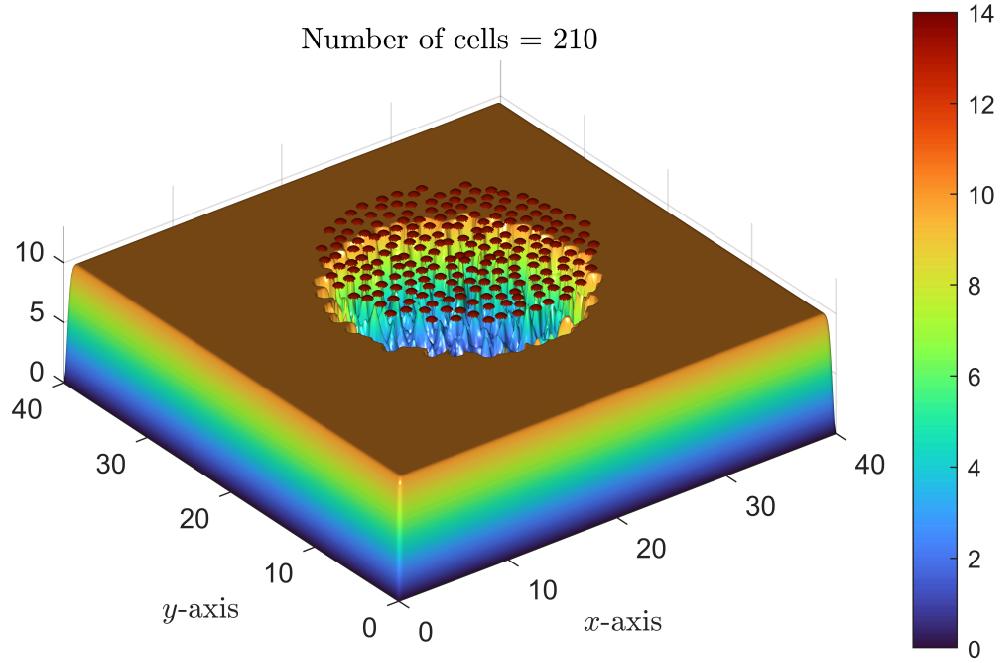


Figure 1.5: The same colony at 210 cells

$$\mathbf{F}_2 = \left(\frac{d + l_F}{2d} \right) F_n \cos \theta_C \hat{\mathbf{i}} - \left(\frac{d + l_F}{2d} \right) F_n \sin \theta_C \hat{\mathbf{j}},$$

1.10 Approximate Bayesian Computation (ABC) for the inverse problem

The traditional statement of Bayes' Theorem goes like

$$P(A|B) = \frac{P(B|A)P(A)}{P(B)}, \quad (1.6)$$

where A and B are outcomes and the terms are given by

- $P(A|B)$ is the posterior probability; the probability of A given B ,
- $P(B|A)$ is the conditional probability
- $P(A)$ is the prior probability; probability of observing event A

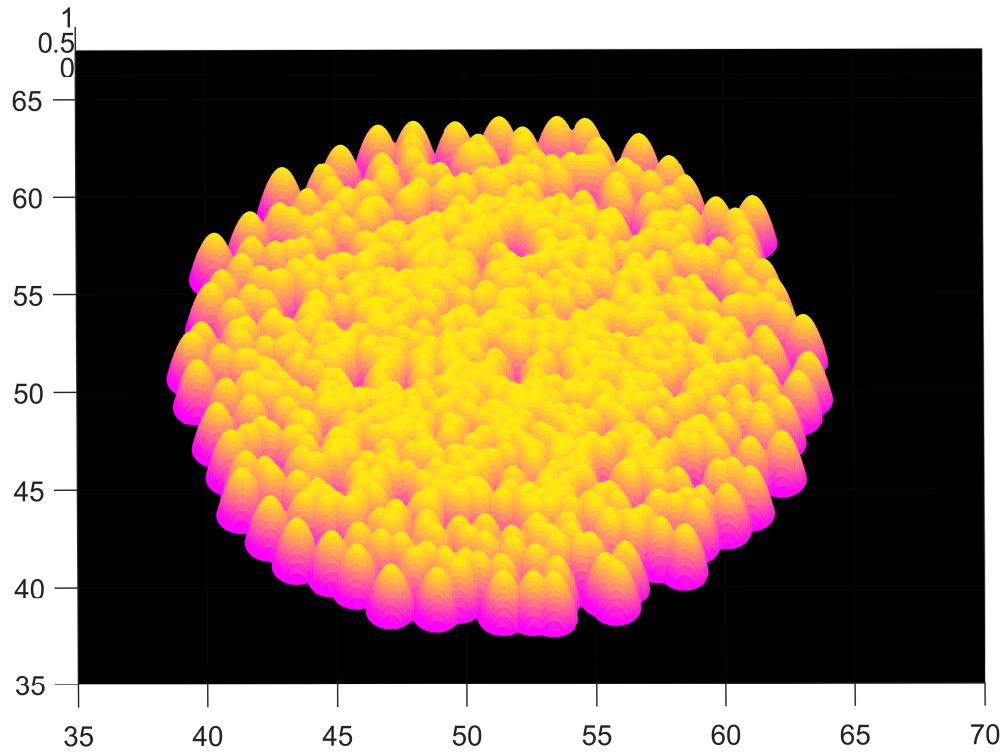


Figure 1.6: A cell colony with 1065 cells

- $P(B)$ is the marginal probability; probability of observing event B

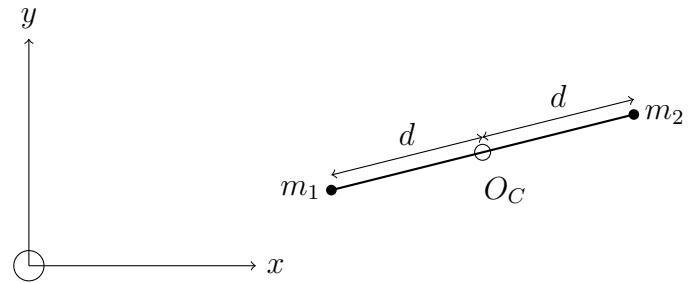


Figure 1.7: Shows a rod shaped backbone of an elliptical cell made from two masses $m_1 = m_2 = m$ connected by a massless rod of length $2d$

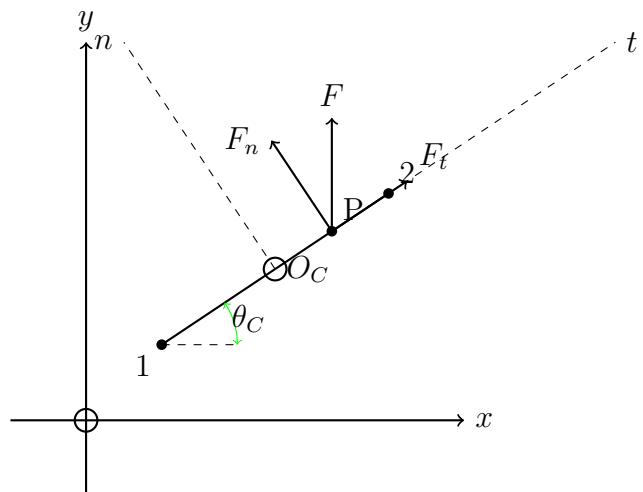


Figure 1.8: Shows a rod shaped cell which is being impinged upon by a contact force \mathbf{F} resolved into a tangential F_t and normal component F_n .

Conclusions

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Appendix A

My appendices from chapter 1

A.1 First appendix section

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A.2 Second appendix section if required

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