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An Integrated Topological-Lindenmayer SystemModel of Volvox Embryonic Inversion and Cell Division, Apoptosis and Cancer Growth Models

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An Integrated Topological-Lindenmayer System Model of *Volvox* Embryonic Inversion

and Cell Division, Apoptosis and Cancer Growth Models

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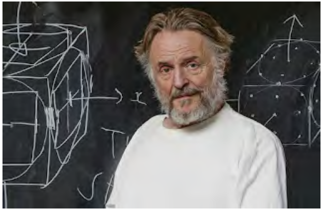
Introduction

- *Gonium*, *Pandorina* and *Volvox* are genera of green algae in increasing order of complexity - from flat, simple colonies of 16 cells to spherical colonies of up to 50,000 cells.
- A novel approach of constructing Lindenmayer systems for modelling algal growth and simulating cell division, colony formation as well as hypothetical cases of cell death and subsequent recovery.
- A stochastic version of the abovementioned Lindenmayer model.
- Comparison of Lindenmayer system model and topological model to describe *Volvox* embryonic inversion.
- Simulation of basic cancer growth extending our Lindenmayer models: our future aim is to simulate algal anti-cancer drug delivery and its efficacy in controlling cancer.

1. Introduction
   - Lindenmayer Systems
2. Model
3. Results
4. Conclusion

Lindenmayer Systems

Lindenmayer Systems, often referred to as L-systems, are formal grammars introduced by the Hungarian theoretical biologist Aristid Lindenmayer in 1968. L-systems serve as a mathematical modelling technique for simulating the growth and development of complex, self-replicating structures, particularly in the context of plants and algae.



Aristid Lindenmayer, "Mathematical models for cellular interaction in development." J. Theoret. Biology, 18:280315, 1968.

Model

A Lindenmayer system is a triplet of the form (Σ, P, ω), where:

- Σ represents the alphabet: the set of characters or symbols,
- P (production) is the set of rewriting rules, that is, how each character of the string can be "translated" or replaced (or not) by other characters from the alphabet at each step, and
- ω is the axiom or starting word, the symbol or set of symbols that defines the initial state of the system.

Example

$(\{A, B, C\}, \{A \to ABC, B \to CA, C \to C^2\}, A)$ is a Lindenmayer system, where $C^n = \underbrace{C \cdots C}_{n \text{ times}}$ in formal languages. The steps would be: $A \to ABC \to ABC^2AC^2 \to ABC^2AC^4ABC^5$, and so on.

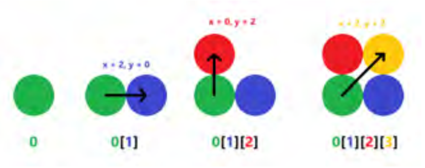
Gonium Growth Model

Experimental data has found both **binary fission** and **multiple fission** in *Gonium*, where each cell divides into 2^n daughter cells to form a usually 16-celled colony. Our L-system-based Python model simulates the growth of *Gonium* in two dimensions, with theorized contact inhibition based on new research findings on algae.

- The production or rewriting rules are saved in our code in the form of a Python dictionary which we call the "generator".
- The characters of this alphabet "code" for the direction of cell growth on the XY plane and for memorizing branching locations using "[" and "]".
- The code plots the cells using Turtle graphics.
- We allot each cell different colors to make it easier to understand the growth directions corresponding to the characters.
- Our Python code executes its equivalent of contact inhibition by recording cell coordinates and detecting upcoming overlaps, preventing duplicates in the plot and removing duplicates from the string.

Branching and No Branching

With branching, we can "save" a reference point (in this case, "0").



Without branching, the last point becomes the reference point or "current state".

Figure 1: *Gonium* colony (16-celled stage) on the XY plane with the color guide. The pattern shown in the figure corresponds to the string 0[7][8][5][1[[5][4][1]][2[2][6][7]][3[1][2][3]].

We start with "F" as the axiom. The first 3 steps required to show the formation of a typical 16-celled *Gonium* colony are as follows:

- Step 1: F
- Step 2: 0[1][2][3]
- Step 3: 0[7][8][5][1[[5][4][1]][2[2][6][7]][3[1][2][3]]

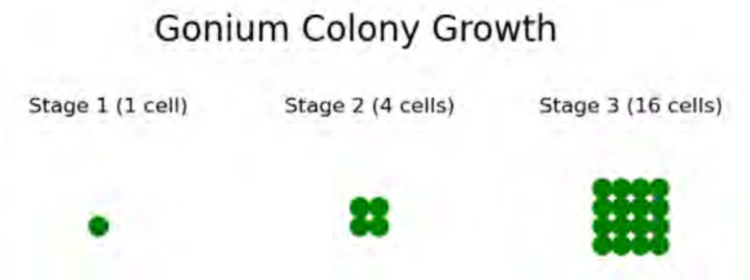


Figure 2: *Gonium* colony growth: the plots on the left, center and right respectively correspond to the L-system steps mentioned above.

Cell Death and Regeneration Model

- Based on recent discoveries of programmed cell death in algae, our L-system model factors in various causes of cell death from senescence to apoptosis and other miscellaneous factors.
- For this, we use probability parameters in mathematical equations.
- Our Python code divides the cells into generations: adding a generational death probability to each cell, based on "aging"; older cells become likelier to die because of programmed cell death.
- The code also randomly assigns a death probability due to factors not related to senescence and other triggers of apoptosis.

Figure 3: *Gonium* cell death and regeneration.

Cancer Growth Simulation

- Based on the *Gonium* model, we have also created a tentative model showing cancer propagation.
- The cancer cells show no contact inhibition and instead push neighboring cells in the direction of cancer growth.
- Our code demonstrates this by shifting normal cells to "make way" for new cancer cells.

The cancer cells are shown in gray (Figure 4).

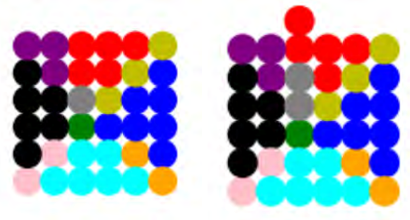


Figure 4: The start of cancer and cell shift, showing a lack of contact inhibition.

Stochastic Lindenmayer Model for Cell Division

- We also experiment with a stochastic Lindenmayer model for cell growth in two dimensions.
- Instead of character codes for cell types which represent fixed cell growth directions, we assign every cell equal probability of growing in any of the 8 possible directions.

A stochastic L-system is an ordered quadruplet $L_\pi = (\Sigma, P, \omega, \pi)$.

The function $\pi : P \to (0,1]$ is called the probability distribution and it maps the set of rewriting rules to the set of rewriting probabilities. For any character $\sigma \in \Sigma$, the sum of probabilities of all rewriting rules for σ is equal to 1. We denote our stochastic L-system for cell growth as:

$$
\begin{aligned}
&S_L = (\{0,1,2,3,4,5,6,7,8,[,]\},\\
&\{0 \to 0[10], 0 \to 0[20], 0 \to 0[30], 0 \to 0[40], 0 \to 0[50],\\
&0 \to 0[60], 0 \to 0[70], 0 \to 0[80]\},\\
&0,\\
&\{0 \xrightarrow{0.125} 0[10], 0 \xrightarrow{0.125} 0[20], 0 \xrightarrow{0.125} 0[30], 0 \xrightarrow{0.125} 0[40],\\
&0 \xrightarrow{0.125} 0[50], 0 \xrightarrow{0.125} 0[60], 0 \xrightarrow{0.125} 0[70], 0 \xrightarrow{0.125} 0[80]\})
\end{aligned}
$$

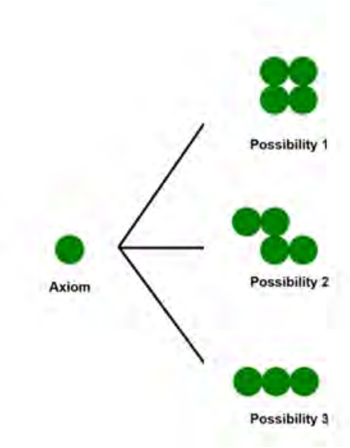


Figure 5: Different possibilities showing stage 3 of cell division by binary fission. In the third case, contact inhibition due to potential "overlapping" growth direction causes a delay in cell division, resulting in 3 cells instead of $2^{(3-1)} = 4$.

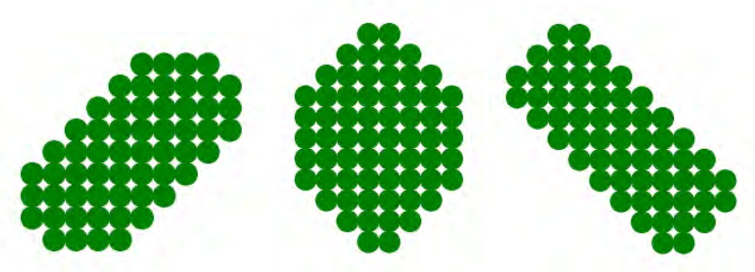


Figure 6: Different possibilities showing stage 12 of cell division by binary fission.

Volvox Embryonic Inversion

- *Volvox* can reproduce asexually as well as sexually.
- We attempt to simulate the entire asexual life cycle of *Volvox* using our L-system, which begins with haploid reproductive cells, known as gonidia, in the interior of mature parent colonies.
- Unlike the flagellated somatic cells on the outer spheroidal cell layer, gonidia are large, non-motile cells.
- Under favorable conditions, gonidia undergo successive mitotic divisions and develop into small, multicellular colonies known as "embryos" or "daughter colonies".
- During early stages, the daughter colonies of *Volvox* exist in the form of a single cell layer with their flagella oriented inwards.
- Embryonic inversion in *Volvox* thus positions the flagella outwards to enable locomotion.

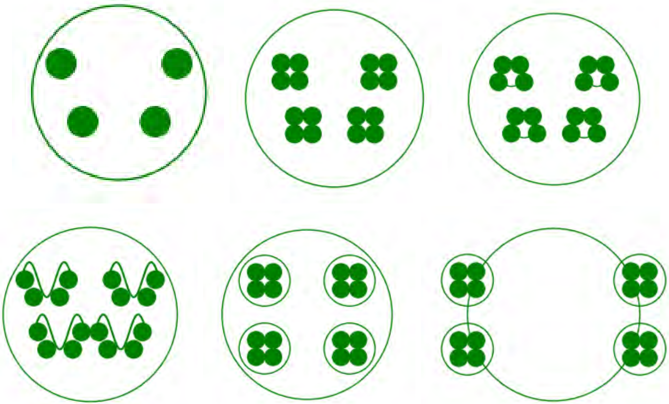


Figure 7: Asexual life cycle and inversion in young *Volvox* colonies (Lindenmayer system model).

The above model of the asexual life cycle in *Volvox* is described using the following Lindenmayer system:

$$V_L = (\{F, 0, 1, 2, 3, 4, 5, 6, 7, 8, A, B, C, D, [,]\},$$
$$\{D \rightarrow D[7][8][5], C \rightarrow C[5][4][1],$$
$$B \rightarrow B[2][6][7], A \rightarrow A[1][2][3]\},$$
$$[A][B][C][D])$$

The rapid cell division seen in reproductive cells is described by the characters "F", "1", "2", "3", "4", "5", "6", "7" and "8", which retain the direction codes used in our previous L-system models. The new characters "A", "B", "C" and "D" also code for "movement". However, the rewriting rules are not sufficient and an L-system is inefficient at describing the inversion process which characterized by movement rather than cell division.

We thus believe a topological model is more suitable for modelling the inversion process. In a first, we describe the inversion in *Volvox* colonies using **homeomorphisms** and animations.

- A homeomorphism is a bijective and continuous function between topological spaces that has a continuous inverse function.
- Topological spaces that have such a function are said to be homeomorphic to each other and considered to have the same topological properties.

Bijections, Continuity and Topology

Bijection

A function is bijective if it is:

- Injective: no two elements map to the same element.
- Surjective: every element has a corresponding element that maps to it.

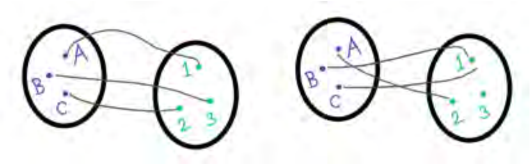


Figure 8: (Left) A bijective functions and (right) a non-bijective function (particularly, neither injective nor surjective) between two sets.

Bijections, Continuity and Topology

Continuity

In simple terms, a continuous function is a function which does not have sudden gaps or breaks. The plot would thus be an unbroken curve.

Figure 9: The continuous function $y = x$ (right) and the discontinuous function $y = \frac{1}{x}$ (left) which is undefined at $x = 0$.

Bijections, Continuity and Topology

Topology

Topology refers to properties of geometric objects that are preserved under processes like continuous deformations. Unlike the study of exact shapes and measurements, the focus of topology is on the way points are connected and the space is structured. Mathematically, the topology on a set of points is defined by open subsets satisfying certain axioms.

Topology

Figure 10: A common example of spaces or objects with similar topological properties: a donut and a coffee cup. These spaces are homeomorphic to each other.

Homeomorphism

A simple example to understand homeomorphisms would be the continuous deformation of a circle into a square or vice versa. Physically speaking, either can be "smoothly" transformed into the other.

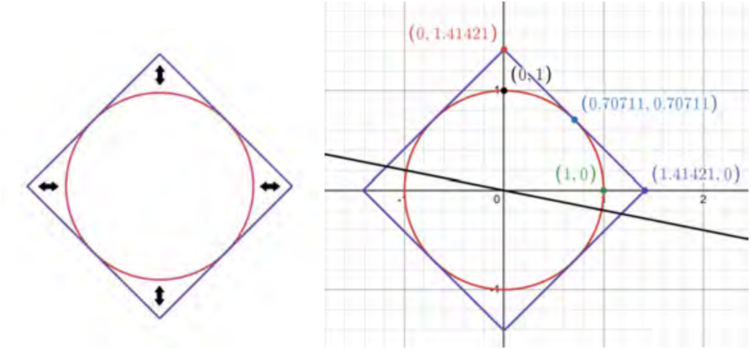


Figure 11: Square and circle homeomorphism.

A juvenile *Volvox* colony before inversion is a sphere (2-sphere in $\mathbb{R}^3$) and thus, homeomorphic to the plane with an additional point in three-dimensional space, i.e., $\mathbb{R}^2 \cup \{\infty\}$. We consider the real plane P tangent[1] to the sphere at $(0,0,-1)$. Note that every point on the plane P is of the form $(x,y,-1)$ where x and y are real numbers.

[1] Intersecting with or "touching" the sphere at only one point.

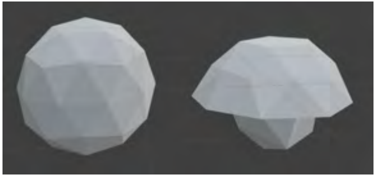


Figure 12: *Volvox* inversion stage 1 in Blender (`https://www.blender.org/`).

Figure 13: *Volvox* inversion stage 2 in Blender.

When the juvenile *Volvox* colony starts to invert or turn inside out, it forms a mushroom-like shape while pushing the upper half downward (Figure 9). We need to find functions proving the homeomorphism between each pair of "spaces". We label the 2-sphere in $\mathbb{R}^3$ as S^2. Let its radius be 1 and let it be centered at $(0,0,0)$. For the hole that starts forming on top, we fix the point of "puncture" in the sphere as $(0,0,1)$. The reason is to keep the mappings between the two "spaces" well-defined, since at $(0,0,1)$, the terms $\frac{2x}{1-z}$ and $\frac{2y}{1-z}$ in the functions below are both $\frac{0}{0}$.

$$f : S^2 \to P \cup \{\infty\}$$

$$f(x,y,z) = \begin{cases} (\frac{2x}{1-z}, \frac{2y}{1-z}, -1) & (x,y,z) \in S^2 \setminus \{(0,0,1)\} \\ \infty & (x,y,z) = (0,0,1) \end{cases}$$

Figure 14: *Volvox* inversion stage 3 in Blender (`https://www.blender.org/`).

Similarly, for a mapping in the reverse direction:

$$g : P \cup \{\infty\} \rightarrow S^2$$

$$g(w) = \begin{cases} \left(\frac{4u}{u^2+v^2+4}, \frac{4v}{u^2+v^2+4}, \frac{u^2+v^2-4}{u^2+v^2+4}\right) & w = (u, v, -1) \in P \\ (0, 0, 1) & w = \infty \end{cases}$$

Figure 15: *Volvox* inversion stage 4 in Blender (`https://www.blender.org/`).

Volvox Embryonic Inversion

Figure 16: *Volvox* inversion stage 5 in Blender (`https://www.blender.org/`).

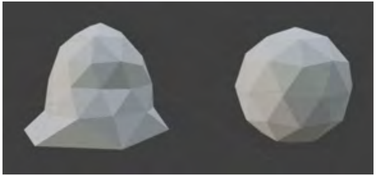


Figure 17: *Volvox* inversion stage 6 in Blender (`https://www.blender.org/`).

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Results

Lindenmayer systems have proven to be very useful in modelling cell division, cell death as well as cancer growth. However, as per our findings, Lindenmayer models are not sufficient to describe the *Volvox* embryonic inversion process because it involves cellular movement.

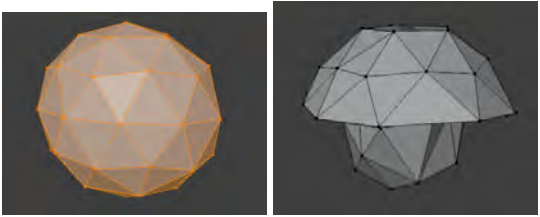

Figure 18: Use of vertex mapping for morphing shapes, inspired by projection homeomorphisms.

Results

We observed that understanding the *Volvox* inversion process through homeomorphisms made the simulation in Blender simpler and quicker: starting with a simple object and mapping its vertices to corresponding vertices of the new shape being morphed to, in the same manner points are mapped between homeomorphic spaces in a stereographic projection mapping.

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Conclusion

Emrbyonic inversion in *Volvox* can be described as morphological changes understood by homeomorphisms between topological spaces where points or cells of the *Volvox* embryo are mapped to points or cells of the embryo's next stage or shape.

Thank You