Modeling bet-hedging: A link between cancer and the emergence of multicellularity

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Overview

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Evolution to multicellularity

Unicellular Organism

- Unconstrained proliferation
- Lack of cooperation
- Plasticity

Evolution
to multicellularity $\downarrow$

Differentiation

Regulations of capabilities $\longrightarrow$ Tumor suppressors

Atavistic model of cancer

Damaged tumor suppressors

↓

Reappearance of latent genes related to unicellular functions

↓

- Unconstrained proliferation
- Lack of cooperation
- Plasticity

⟶ Hallmark capabilities of cancer

([3] Davies and Lineweaver, 2011)

Bet Hedging

Understanding cancer is closely related to understanding the emergence of multicellularity.

It is reasonable to assume that both primitive organism and the plastic tumour cells adopted bet hedging strategies.

Bet Hedging

Common risk-diversifying strategies in unpredictably changing and often aggressive environments, in order to maximise their phenotypic fitness.

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Phenotypes

Variables

- x viability (potential to resist deadly insults)
- y fecundity (potential to proliferate)
- θ plasticity (potential to continue to differentiate)

$$(x, y) \in \Omega := \{(x, y) \in [0,1]^2 : C(x, y) \leqslant K\}, \;\; \theta \in [0,1]$$

Notations

$$z = (x, y, \theta) \in D := \Omega \times [0,1]$$

The equation

The problem

$$\partial_t n + \nabla \cdot \Big(Vn - A(\theta)\nabla n \Big) = (r(z) - d(z)\rho(t))n, \tag{1}$$

$$\Big(Vn - A(\theta)\nabla n \Big) \cdot \mathbf{n} = 0, \text{ for all } z \in \partial D, \tag{2}$$

$$n(0,z) = n_0(z), \text{ for all } z \in D. \tag{3}$$

Population size

$$\rho(t) := \int_D n(t,z)dz.$$

(Inspired by [1] and [2], Bouin, Calvez et al.)

The equation

- $r(z)$, $d(z)$ growth and death rate.
- $A(\theta)$ diffusion matrix, gives the speed at which non-genetic epimutations occur.
- $V(t, z)$ represents the sensitivity of the population to abrupt changes on the environment.

Questions

- What is the effect of considering plasticity as a trait?
- How does the environment affect the population?

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Finite Volume Method

- Presence of a drift term,
- Presence of integral terms,

Finite Volume Method

- Presence of a drift term,
- Presence of integral terms,

Finite Volume Method

Variational solution

Functional space

$$n := n(t) \in X_T := C([0,T],H) \cap L^2((0,T),\mathcal{V}) \cap H^1([0,T],\mathcal{V}')$$

Operator $Q[n]$

$$\langle Q[n],\varphi\rangle = \int_D \Big(-A\nabla n \nabla\varphi + Vn\nabla\varphi + (r(z) - \rho d(z))n\varphi \Big) dz$$

Weak formulation

$$(n(t),\varphi(t))_H = (n_0,\varphi(0))_H + \int_0^t \Big(\langle Q[n](s),\varphi(s)\rangle + \langle \varphi'(s), n(s)\rangle \Big) ds \quad (4)$$

Existence and uniqueness

Theorem

For all positive $n_0 \in L^p(D)$, $p > 2$, *there exists a unique global positive weak solution for problem* (1)-(3) *in the sense of* (4).

The mesh

Mesh for $[0, 1]^3$

$$C_{ijk} = \left[\frac{i}{M}, \frac{i+1}{M}\right] \times \left[\frac{j}{M}, \frac{j+1}{M}\right] \times \left[\frac{k}{M}, \frac{k+1}{M}\right], \quad h = 1/M$$

Mesh covering D

$$\mathcal{M} = \{C_{ijk} : C_{ijk} \cap D \neq \emptyset\}$$

$$D_h = \bigcup_{\mathcal{M}} C_{ijk}$$

Approximated problem

Problem over D_h

$$\partial_t \tilde{n}_h + \nabla \cdot \Big(V \tilde{n}_h - A(\theta) \nabla \tilde{n}_h \Big) = (r(z) - d(z)\tilde{\rho}_h(t))\tilde{n}_h, \ \text{in } D_h \tag{5}$$

$$\Big(V \tilde{n}_h - A(\theta) \nabla \tilde{n}_h \Big) \cdot \mathbf{n} = 0, \ \text{for all } z \in \partial D_h, \tag{6}$$

$$\tilde{n}_h(0, z) = n_0(z), \ \text{for all } z \in D_h, \tag{7}$$

Local average

$$\nu_j(t) := \frac{1}{h^3} \int_{D_j} \tilde{n}_h(t, z) dz = n(t, \mathbf{z_j}) + \mathcal{O}(h^2).$$

Semi-discrete scheme

Semi-Discrete scheme

$$\frac{d}{dt}\nu_j(t) = M_j(t,\tilde{\rho}_h(t))\nu_j(t) + \sum_{l\in N_j} B_{jl}(t)\nu_l(t), \tag{8}$$

where

$$M_j(t,\tilde{\rho}_h(t)) = -\sum_{l\in N_j} \frac{|\Gamma_{jl}|}{h^3}\Big(u_{jl}^+(t) + \frac{A_{jl}}{d_{jl}}\Big) + \Big(r_j - d_j\tilde{\rho}_h(t)\Big),$$

$$B_{jl} = \frac{|\Gamma_{jl}|}{h^3}\Big(-u_{jl}^-(t) + \frac{A_{jl}}{d_{jl}}\Big).$$

Discrete Scheme

Implicit discrete scheme

$$\frac{\nu_j^{k+1} - \nu_j^k}{\Delta t} = M_j^{k+1} \nu_j^{k+1} + \sum_{l \in N_j} B_{jl}^{k+1} \nu_l^{k+1},$$

where

$$M_j^{k+1} := M_j(t_{k+1}) = -\frac{|\Gamma_{jl}|}{h^3} \sum_{l \in N_j} \Big(u_{jl}^+(t_{k+1}) + \frac{A_{jl}}{d_{jl}} \Big) + \Big(r_j - d_j \sum_l h^3 \nu_l^{k+1} \Big),$$

$$B_{jl}^{k+1} := B_{jl}(t_{k+1}) = \frac{|\Gamma_{jl}|}{h^3} \Big(-u_{jl}^-(t_{k+1}) + \frac{A_{jl}}{d_{jl}} \Big).$$

Convergence of the semi-discrete scheme

Theorem

For all positive $n_0 \in L^p(D)$, $p > 2$, there exists a unique positive solution for problem (8). Furthermore, the function $\tilde{n}_h(t,z)$ defined by

$$\tilde{n}_h(t,z) = \sum_j \nu_j(t) \mathbb{1}_{D_j \cap D},$$

converges in $L^2(D_T)$ to the unique positive weak solution of (1)-(3) as h goes to zero.

Convergence of the discrete scheme

Theorem

Let ν_j^0 be nonnegative initial data with mass $\rho_0 = \sum_j h^3 \nu_j^0$ and assume that

$$\Delta t < \frac{1}{\left(\sqrt{r^+ + d^+\overline{\rho}} + \sqrt{d^+\overline{\rho}}\right)^2},$$

then there exist a unique nonnegative solution ν_j^k, $k = 1, \ldots, N$ to scheme (19). *Furthermore, for each h, the sequences of piecewise constant functions*

$$\nu_{\Delta t}^j(t) = \sum_{k=0}^{K} \nu_j^k \mathbb{1}_{(t_k, t_{k+1})},$$

strongly converges to the solution of (8) in $(L^2((0,T)))^N$.

Order of convergence for the semi-discrete scheme

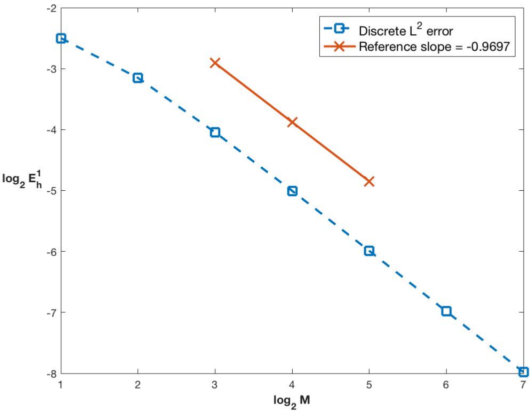

Figure: The discrete $L^2(D_T)$ error for the semi-discrete scheme, for $T = 10$ and M ranging between 2 and 128.

Order of convergence for the discrete scheme

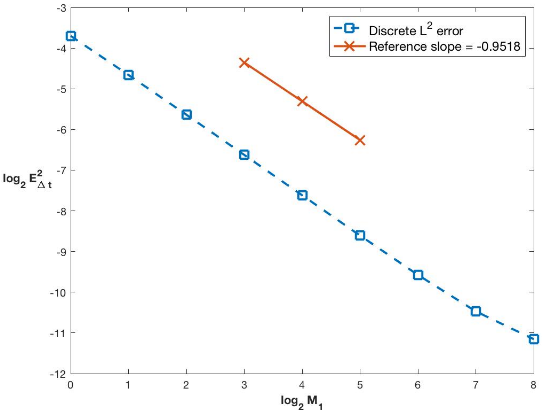

Figure: The discrete $L^2(D_T)$ error for the discrete scheme, for $T = 10$ and M_1 ranging between 2 and 256.

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Simulations

Monomorphic population

- $r(x, y) = e^{-(x-0.1)^2-(y-0.1)^2}$
- $d = 0.5$
- Mass of n_0 concentrated on a ball of around $(0.25, 0.25)$
- Diffusion parameters: 10^{-6}
- No drift

Simultaneous emergence of dimorphism

- $r(x,y) = \mathbb{1}_{(y<x)} e^{-(x-0.1)^2-(y-0.9)^2} + \mathbb{1}_{(x<y)} e^{-(x-0.9)^2-(y-0.1)^2}$
- $d = 0.5$
- $n_0 = 2/3$
- Diffusion parameters: 10^{-6}
- No drift

As shown in ([4], Lorenzi et Pouchol, 2020).

Simulations

Dimorphism due to environment

- $r(x, y) = e^{-(x-0.1)^2-(y-0.1)^2}$
- $d = 0.5$
- Mass of n_0 concentrated on a ball of around $(0.25, 0.25)$
- Diffusion parameters: 10^{-6}
- $V(t, x, y) = 10^{-3}(\mathbb{1}_{(y>x)}(-1, 1) + \mathbb{1}_{(y<x)}(1, -1))$

Simulations

Effects of plasticity

- $r(x,y,\theta) = e^{-(x-0.1)^2-(y-0.1)^2} + 10\theta$
- $d = 0.5$
- Mass of n_0 concentrated around $(0.25, 0.25, 0.25)$ and $(0.25, 0.25, 0.75)$
- Diffusion matrix:

$$A(\theta) = 10^{-6}\begin{pmatrix} \theta+1 & 0 & 0 \\ 0 & \theta+1 & 0 \\ 0 & 0 & 1 \end{pmatrix}$$

- $V(t,x,y,\theta) = 10^{-3}\theta(\mathbb{1}_{(y>x)}(-1,1) + \mathbb{1}_{(y<x)}(1,-1))$

Divergence into dimorphism

- $r(x,y) = \mathbb{1}_{(y<x)} e^{-(x-0.1)^2-(y-0.9)^2} + \mathbb{1}_{(x<y)} e^{-(x-0.9)^2-(y-0.1)^2}$
- $d = 0.5$
- Mass of n_0 concentrated on a ball around $(0.25, 0.25, 0.5)$
- Diffusion matrix:

$$A(\theta) = 10^{-6} \begin{pmatrix} \theta+1 & 0 & 0 \\ 0 & \theta+1 & 0 \\ 0 & 0 & 1 \end{pmatrix}$$

- $V(t,x,y,\theta) = 10^{-3}\theta(\mathbb{1}_{(y>x)}(-1,1) + \mathbb{1}_{(y<x)}(1,-1))$
- $V(t,x,y,\theta) = 10^{-3}\theta(-y, -x, -x^2 - y^2)$

Conclusions

Summary

- A structured population model including the effects of natural selection, non-genetic epimutations and abrupt changes on the environment was constructed.
- Two numerical schemes were constructed using the Finite Volume Method in order to prove the existence and uniqueness of solution for such model, and approximate such solution.
- The order of convergence was numerically approximated by comparing with an exact solution
- The behavior of the population was studied by means of different simulations.

Conclusions

Concluding remarks

- We observed the emergence of dimorphism under different conditions and evolving in different ways:
  1. Emerging simultaneously starting from an homogeneous starting population,
  2. Diverging from a single concentration point towards the maximum of the fitness function.
  3. Diverging from a single concentration point as a response to the changes on the environment.
- We also observed some of the effect of considering plasticity as a trait: more adaptable individuals could have more chances of surviving to abrupt changes on the environment.

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Thank you!

Merci!

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