# TUMOURS ARE COMING

Andrea Giordano and Bharath Narayanan

Jiang, Y., Pjesivac-Grbovic, J., Cantrell, C., & Freyer, J. P. (20.250.255). A multiscale model for avascular tumor growth. *Biophysical journal*, *89*(6), 3884–3894. doi:10.25.1529/biophysj.10.255.0.2560.25640.25

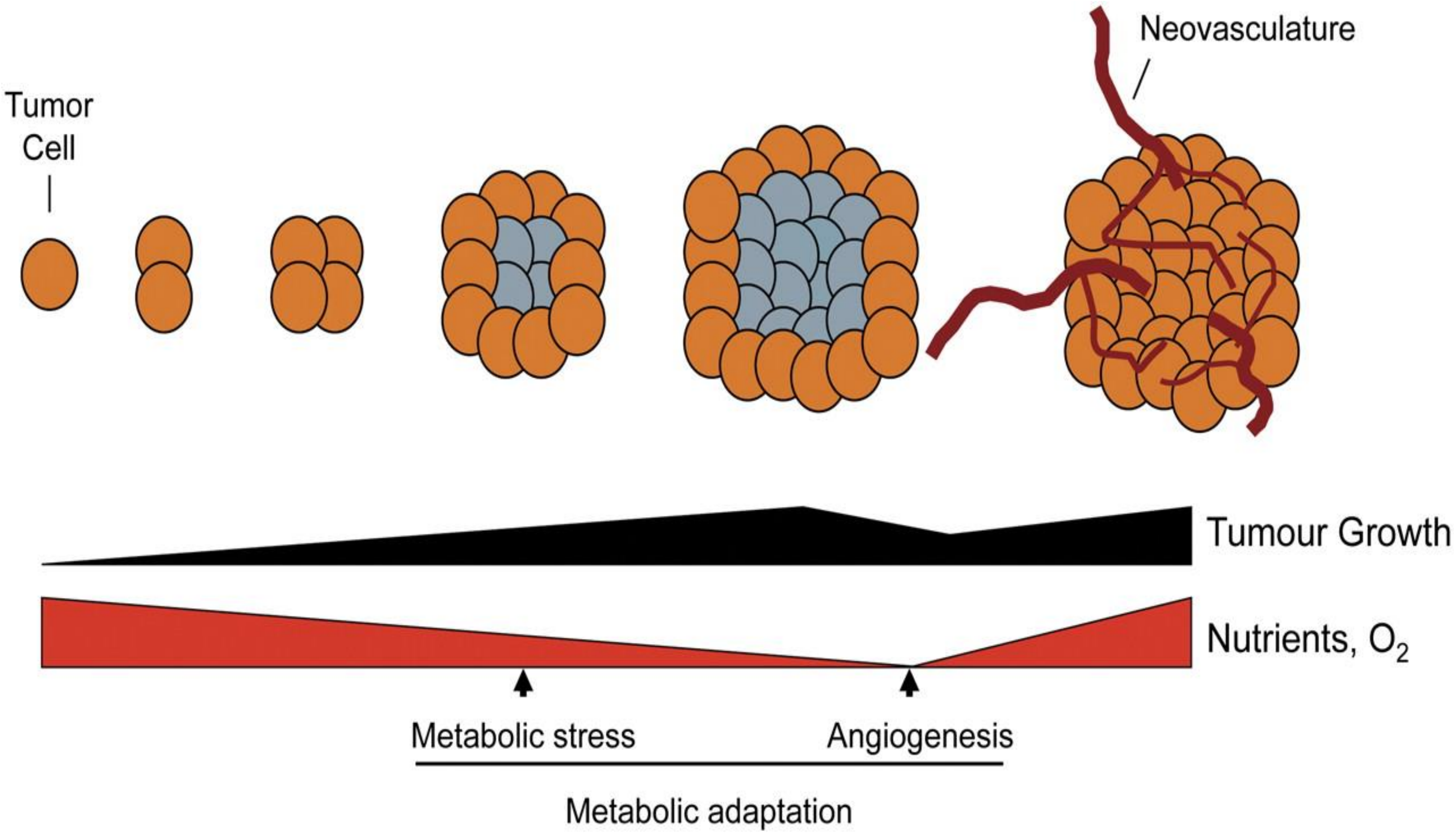
https://fontmeme.com/game-of-thrones-font/

# Lesson Plan

- Recap
  - How does a tumour grow?
  - What are the scales involved?
- What does the simulation setup look like?
- A look at two scales in detail
- Run your simulations
- An in depth look at the volume-adhesion trade-off
- The limitations of our pseudo-diffusion

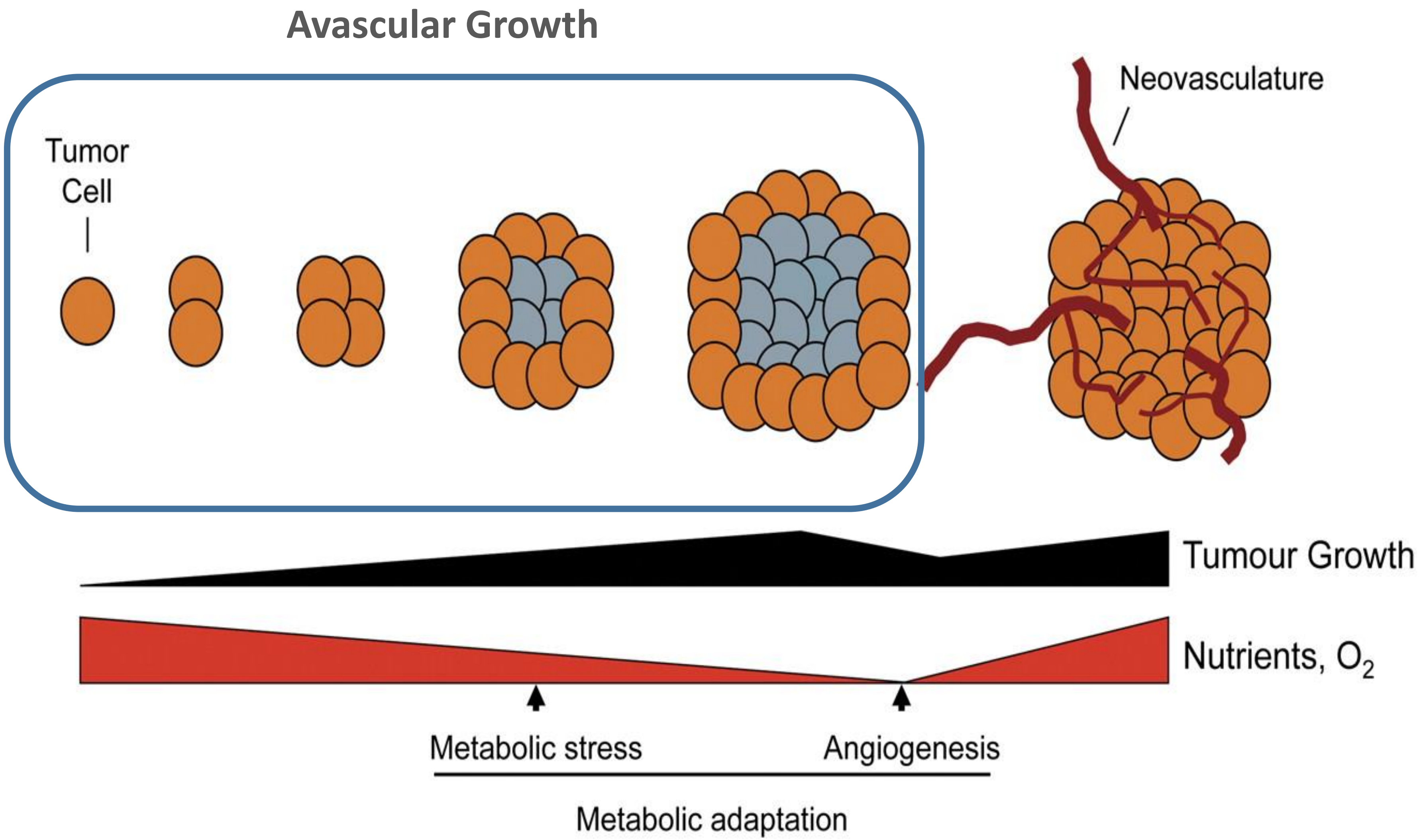
IN CASE YOU
MISSED IT

# How does a tumour grow?




Russell G. Jones, and Craig B. Thompson Genes Dev. 20.250.259;23:537-548

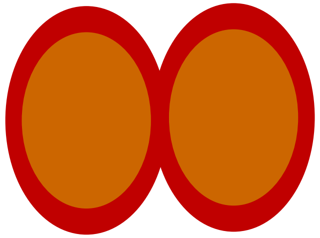
# How does a tumour grow?




**Russell G. Jones, and Craig B. Thompson Genes Dev. 20.250.259;23:537-548**

# Scales involved

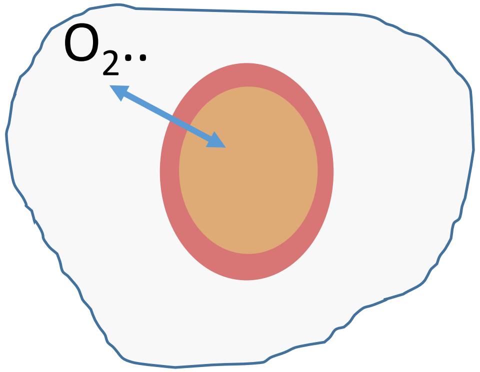
## Cellular



- Cells compete for space
- Minimize volume + adhesive energy
- **Monte Carlo**

# Scales involved

## Extra-cellular

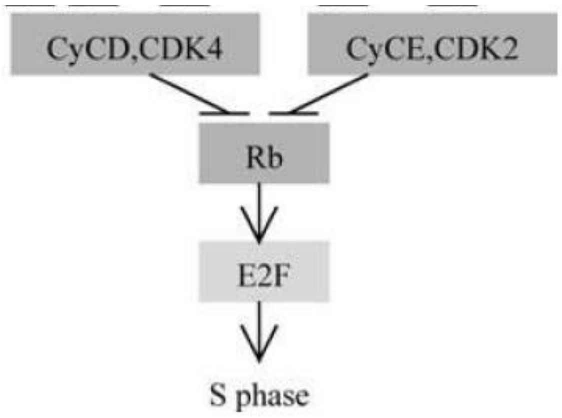



- Diffusion of nutrients
- In our case just oxygen
- Oxygen level determines cell type

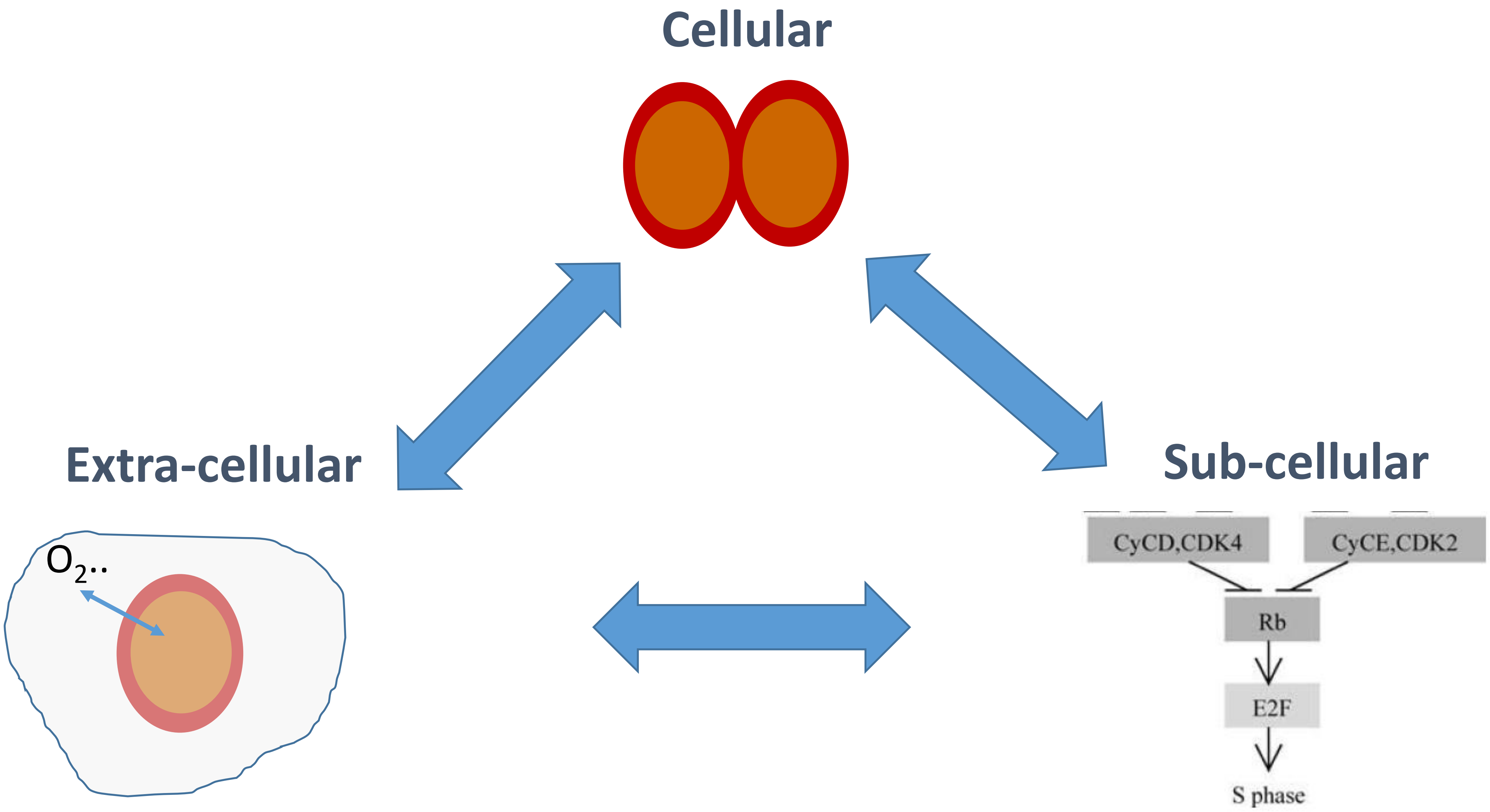
# Scales involved

## Sub-cellular

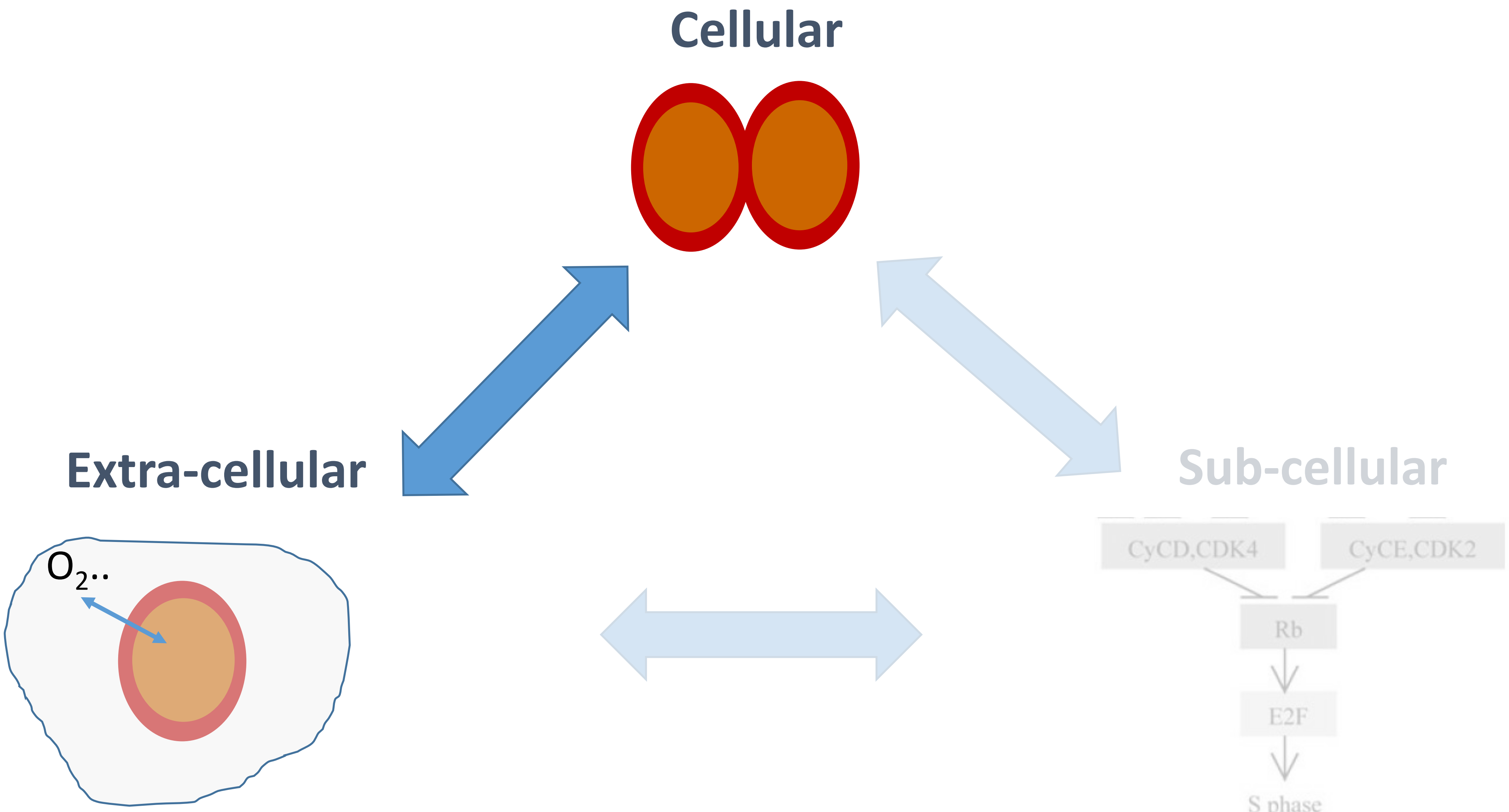
- Boolean sequence of proteins
- Takes the cell through its lifecycle



# Scales involved



# Scales involved



# Modelling tumour growth

# Types of cells

- Proliferating (P)
  - Actively grow and divide
  - Cell IDs start from 1 onward
  - Consume oxygen at the highest rate

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  - Do not grow or divide
  - P cells change into Q when oxygen levels decline.
  - Cell IDs are retained
  - Consume oxygen at half the rate of a P cell

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- Necrotic (N)
  - Dead cells
  - Q cells change to N with even lower levels of oxygen
  - ID = -1
  - No oxygen consumption

# Types of cells

- Proliferating (P)
  - Actively grow and divide
  - Cell IDs start from 1 onward
  - Consume oxygen at the highest rate
- Quiescent (Q)
  - Do not grow or divide
  - P cells change into Q when oxygen levels decline.
  - Cell IDs are retained
  - Consume oxygen at half the rate of a P cell
- Medium (M)
  - Represent cells outside of the tumour
  - Oxygen rich
  - ID = 0
- Necrotic (N)
  - Dead cells
  - Q cells change to N with even lower levels of oxygen
  - ID = -1
  - No oxygen consumption

# Basic setup

- 2D Lattice discretization
- A cell occupies *more* than one site
- Start off with a single ‘proliferating cell’
- Start with a base level of oxygen everywhere

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | **1** | **1** | 0 | 0 | 0 |
| 0 | 0 | 0 | **1** | **1** | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

# Cell Evolution

## Growth

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | **1** | **1** | 0 | 0 | 0 |
| 0 | 0 | 0 | **1** | **1** | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | **1** | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | **1** | **1** | 0 | 0 | 0 | 0 |
| 0 | 0 | **1** | **1** | **1** | 0 | 0 | 0 |
| 0 | 0 | 0 | **1** | **1** | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

# Cell Evolution

## Growth

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0 | 0 | 1 | 1 | 1 | 0 | 0 | 0 |
| 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

## Division

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0 | 0 | 1 | 1 | 1 | 0 | 0 | 0 |
| 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 2 | 2 | 0 | 0 | 0 | 0 |
| 0 | 0 | 2 | 1 | 1 | 0 | 0 | 0 |
| 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

# Cell Evolution

## Growth

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0 | 0 | 1 | 1 | 1 | 0 | 0 | 0 |
| 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

## Division

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0 | 0 | 1 | 1 | 1 | 0 | 0 | 0 |
| 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 2 | 2 | 0 | 0 | 0 | 0 |
| 0 | 0 | 2 | 1 | 1 | 0 | 0 | 0 |
| 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

## Death

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 2 | 2 | 0 | 0 | 0 | 0 |
| 0 | 0 | 2 | 1 | 1 | 0 | 0 | 0 |
| 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 2 | 2 | 0 | 0 | 0 | 0 |
| 0 | 0 | 2 | -1 | -1 | 0 | 0 | 0 |
| 0 | 0 | 0 | -1 | -1 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

# Activity at two different scales

# Cellular level

- Cell interaction is simulated according to a ***probabilistic model*** regarding ***energy*** evolution (***ΔH***).

$$p = \begin{cases} 1, & \Delta H < 0 \\ e^{-\frac{\Delta \mathrm{H}}{\mathrm{k_b T}}}, & \Delta H \geq 0 \end{cases}$$

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 4 | 4 |
| 1 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 4 | 4 |
| 1 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 4 | 4 |
| 2 | 1 | 1 | 3 | 2 | 2 | 4 | 3 | 4 | 4 |
| 2 | 1 | 1 | 2 | 2 | 2 | 4 | 4 | 4 | 6 |
| 2 | 2 | 1 | 2 | 2 | 2 | 6 | 6 | 6 | 6 |
| 5 | 2 | 2 | 2 | 2 | 2 | 6 | 6 | 6 | 6 |
| 5 | 5 | 5 | 5 | 5 | 6 | 6 | 5 | 5 | 5 |
| 5 | 5 | 5 | 5 | 5 | 6 | 6 | 6 | 5 | 5 |
| 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

# Cellular level

- **Hamiltonian operator** definition:

$$H = \sum_{\text{lattice sites}} J_{\tau(S_1)\tau(S_2)}[1 - \delta(S_1,\, S_2)] + \sum_{\text{cells}} \gamma(v - V^{T})^2$$

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 4 | 4 |
| 1 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 4 | 4 |
| 1 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 4 | 4 |
| 2 | 1 | 1 | 3 | 2 | 2 | 4 | 3 | 4 | 4 |
| 2 | 1 | 1 | 2 | 2 | 2 | 4 | 4 | 4 | 6 |
| 2 | 2 | 1 | 2 | 2 | 2 | 6 | 6 | 6 | 6 |
| 5 | 2 | 2 | 2 | 2 | 2 | 6 | 6 | 6 | 6 |
| 5 | 5 | 5 | 5 | 5 | 6 | 6 | 5 | 5 | 5 |
| 5 | 5 | 5 | 5 | 5 | 6 | 6 | 6 | 5 | 5 |
| 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

# Cellular level

- **Hamiltonian operator** definition:

***Adhesive energy*** term

$$H = \boxed{\sum_{\text{lattice sites}} J_{\tau(S_1)\tau(S_2)}[1 - \delta(S_1, S_2)]} + \sum_{\text{cells}} \gamma(v - V^{T})^2$$

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 4 | 4 |
| 1 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 4 | 4 |
| 1 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 4 | 4 |
| 2 | 1 | 1 | 3 | 2 | 2 | 4 | 3 | 4 | 4 |
| 2 | 1 | 1 | 2 | 2 | 2 | 4 | 4 | 4 | 6 |
| 2 | 2 | 1 | 2 | 2 | 2 | 6 | 6 | 6 | 6 |
| 5 | 2 | 2 | 2 | 2 | 2 | 6 | 6 | 6 | 6 |
| 5 | 5 | 5 | 5 | 5 | 6 | 6 | 5 | 5 | 5 |
| 5 | 5 | 5 | 5 | 5 | 6 | 6 | 6 | 5 | 5 |
| 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

# Cellular level

- **Hamiltonian operator** definition:

***Adhesive energy*** term

$$H = \boxed{\sum_{\text{lattice sites}} J_{\tau(S_1)\tau(S_2)}\left[1 - \delta(S_1, S_2)\right]} + \boxed{\sum_{\text{cells}} \gamma(v - V^{T})^2}$$

***Volume energy*** term

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 4 | 4 |
| 1 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 4 | 4 |
| 1 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 4 | 4 |
| 2 | 1 | 1 | 3 | 2 | 2 | 4 | 3 | 4 | 4 |
| 2 | 1 | 1 | 2 | 2 | 2 | 4 | 4 | 4 | 6 |
| 2 | 2 | 1 | 2 | 2 | 2 | 6 | 6 | 6 | 6 |
| 5 | 2 | 2 | 2 | 2 | 2 | 6 | 6 | 6 | 6 |
| 5 | 5 | 5 | 5 | 5 | 6 | 6 | 5 | 5 | 5 |
| 5 | 5 | 5 | 5 | 5 | 6 | 6 | 6 | 5 | 5 |
| 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

# Cellular level

- **Hamiltonian operator** definition:

***Adhesive energy*** term

$$H = \boxed{\sum_{\text{lattice sites}} J_{\tau(S_1)\tau(S_2)}[1-\delta(S_1,\, S_2)]} + \boxed{\sum_{\text{cells}} \gamma(v - V^{T})^2}$$

τ(S1): cell type
of cell “S1”

***Volume energy***
term

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 4 | 4 |
| 1 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 4 | 4 |
| 1 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 4 | 4 |
| 2 | 1 | 1 | 3 | 2 | 2 | 4 | 3 | 4 | 4 |
| 2 | 1 | 1 | 2 | 2 | 2 | 4 | 4 | 4 | 6 |
| 2 | 2 | 1 | 2 | 2 | 2 | 6 | 6 | 6 | 6 |
| 5 | 2 | 2 | 2 | 2 | 2 | 6 | 6 | 6 | 6 |
| 5 | 5 | 5 | 5 | 5 | 6 | 6 | 5 | 5 | 5 |
| 5 | 5 | 5 | 5 | 5 | 6 | 6 | 6 | 5 | 5 |
| 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

# Cellular level

- **Hamiltonian operator** definition:

γ: rigidity of cell volume

***Adhesive energy*** term

$$H = \boxed{\sum_{\text{lattice sites}} J_{\tau(S_1)\tau(S_2)}[1-\delta(S_1,\, S_2)]} + \boxed{\sum_{\text{cells}} \gamma(v - V^{T})^2}$$

***Volume energy*** term

τ(S1): cell type of cell "S1"

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 4 | 4 |
| 1 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 4 | 4 |
| 1 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 4 | 4 |
| 2 | 1 | 1 | 3 | 2 | 2 | 4 | 3 | 4 | 4 |
| 2 | 1 | 1 | 2 | 2 | 2 | 4 | 4 | 4 | 6 |
| 2 | 2 | 1 | 2 | 2 | 2 | 6 | 6 | 6 | 6 |
| 5 | 2 | 2 | 2 | 2 | 2 | 6 | 6 | 6 | 6 |
| 5 | 5 | 5 | 5 | 5 | 6 | 6 | 5 | 5 | 5 |
| 5 | 5 | 5 | 5 | 5 | 6 | 6 | 6 | 5 | 5 |
| 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

# Cellular level - Monte Carlo Step

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 4 | 4 |
| 1 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 4 | 4 |
| 1 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 4 | 4 |
| 2 | 1 | 1 | 3 | 2 | 2 | 4 | 3 | 4 | 4 |
| 2 | 1 | 1 | 2 | 2 | 2 | 4 | 4 | 4 | 6 |
| 2 | 2 | 1 | 2 | 2 | 2 | 6 | 6 | 6 | 6 |
| 5 | 2 | 2 | 2 | 2 | 2 | 6 | 6 | 6 | 6 |
| 5 | 5 | 5 | 5 | 5 | 6 | 6 | 5 | 5 | 5 |
| 5 | 5 | 5 | 5 | 5 | 6 | 6 | 6 | 5 | 5 |
| 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

# Cellular level - Monte Carlo Step

1) Random lattice site is picked

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 4 | 4 |
| 1 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 4 | 4 |
| 1 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 4 | 4 |
| 2 | 1 | $\boxed{1}$ | 3 | 2 | 2 | 4 | 3 | 4 | 4 |
| 2 | 1 | 1 | 2 | 2 | 2 | 4 | 4 | 4 | 6 |
| 2 | 2 | 1 | 2 | 2 | 2 | 6 | 6 | 6 | 6 |
| 5 | 2 | 2 | 2 | 2 | 2 | 6 | 6 | 6 | 6 |
| 5 | 5 | 5 | 5 | 5 | 6 | 6 | 5 | 5 | 5 |
| 5 | 5 | 5 | 5 | 5 | 6 | 6 | 6 | 5 | 5 |
| 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

# Cellular level - Monte Carlo Step

1) Random lattice site is picked
2) Cell ID becomes that of another cell (unlike)

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 4 | 4 |
| 1 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 4 | 4 |
| 1 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 4 | 4 |
| 2 | 1 | $\boxed{1}$ | 3 | 2 | 2 | 4 | 3 | 4 | 4 |
| 2 | 1 | 1 | 2 | 2 | 2 | 4 | 4 | 4 | 6 |
| 2 | 2 | 1 | 2 | 2 | 2 | 6 | 6 | 6 | 6 |
| 5 | 2 | 2 | 2 | 2 | 2 | 6 | 6 | 6 | 6 |
| 5 | 5 | 5 | 5 | 5 | 6 | 6 | 5 | 5 | 5 |
| 5 | 5 | 5 | 5 | 5 | 6 | 6 | 6 | 5 | 5 |
| 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

$\longrightarrow$

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 4 | 4 |
| 1 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 4 | 4 |
| 1 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 4 | 4 |
| 2 | 1 | $\boxed{3}$ | 3 | 2 | 2 | 4 | 3 | 4 | 4 |
| 2 | 1 | 1 | 2 | 2 | 2 | 4 | 4 | 4 | 6 |
| 2 | 2 | 1 | 2 | 2 | 2 | 6 | 6 | 6 | 6 |
| 5 | 2 | 2 | 2 | 2 | 2 | 6 | 6 | 6 | 6 |
| 5 | 5 | 5 | 5 | 5 | 6 | 6 | 5 | 5 | 5 |
| 5 | 5 | 5 | 5 | 5 | 6 | 6 | 6 | 5 | 5 |
| 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

# Cellular level - Monte Carlo Step

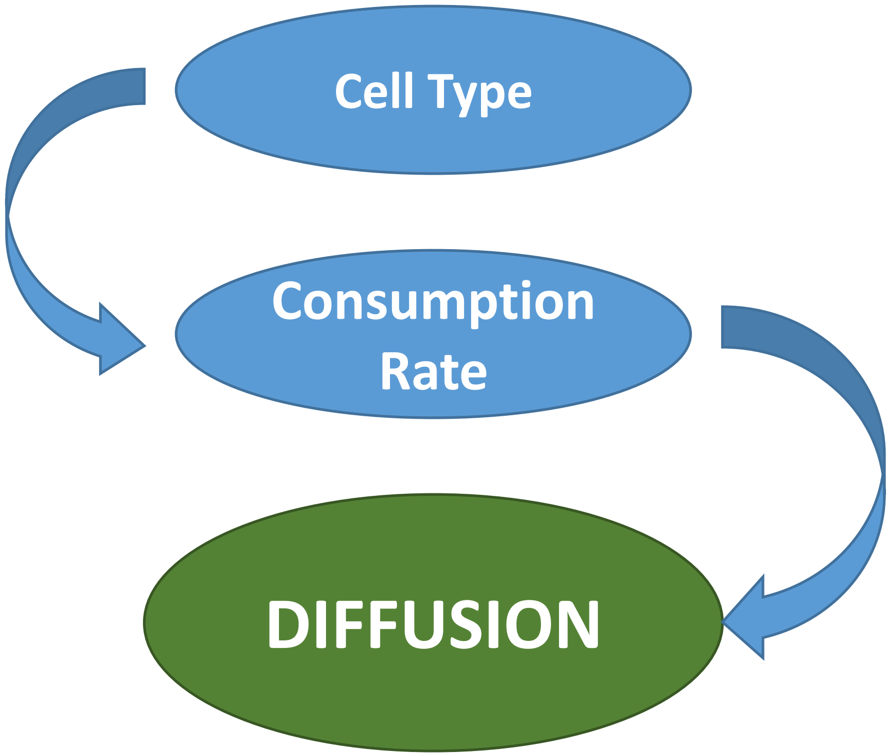
3) Hamiltonian is calculated again.
4) The change in the Hamiltonian affects the probability of keeping this new state.

$$p = \begin{cases} 1, & \Delta H < 0 \\ e^{-\frac{\Delta \mathrm{H}}{\mathrm{k_b T}}}, & \Delta H \geq 0 \end{cases}$$

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 4 | 4 |
| 1 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 4 | 4 |
| 1 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 4 | 4 |
| 2 | 1 | $\boxed{3}$ | 3 | 2 | 2 | 4 | 3 | 4 | 4 |
| 2 | 1 | 1 | 2 | 2 | 2 | 4 | 4 | 4 | 6 |
| 2 | 2 | 1 | 2 | 2 | 2 | 6 | 6 | 6 | 6 |
| 5 | 2 | 2 | 2 | 2 | 2 | 6 | 6 | 6 | 6 |
| 5 | 5 | 5 | 5 | 5 | 6 | 6 | 5 | 5 | 5 |
| 5 | 5 | 5 | 5 | 5 | 6 | 6 | 6 | 5 | 5 |
| 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

# Extracellular level - Diffusion

- What matters in the diffusion?



# Extracellular level - Diffusion

Consumption of oxygen at each lattice site.

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 0.8 | 0.4 | 0.5 | 0.7 | 0.4 | 0.7 | 0 | 0.3 | 0.2 | 0.7 |
| 0 | 0 | 0.3 | 0.2 | 0.4 | 0.2 | 0.5 | 0.3 | 0.7 | 0.2 |
| 0.9 | 0.9 | 0.3 | 0.4 | 0.6 | 0.4 | 0.1 | 0.1 | 0.2 | 0.4 |
| 0.1 | 0.7 | 0.4 | 0.5 | 0.7 | 0.1 | 0.3 | 0.9 | 0.4 | 0.1 |
| 0.3 | 0.2 | 0.7 | 0.5 | 0.1 | 0.7 | 0.4 | 0.1 | 0.2 | 0.7 |
| 0.3 | 0.5 | 0.1 | 0.5 | 0.7 | 0.1 | 0.5 | 0.7 | 0.7 | 0.7 |
| 0.4 | 0.5 | 0 | 0.3 | 0.7 | 0.8 | 0.5 | 0.7 | 0.3 | 0.2 |
| 0.3 | 0.2 | 0.5 | 0.3 | 0.2 | 0.5 | 0.3 | 0.2 | 0.3 | 0.5 |
| 0.3 | 0.4 | 0.1 | 0.1 | 0.4 | 0.1 | 0.5 | 0.7 | 0.4 | 0.5 |
| 0.4 | 0.6 | 0.3 | 0.4 | 0.6 | 0 | 0.3 | 0.2 | 0.7 | 0.5 |

# Extracellular level - Diffusion

Consumption of oxygen at each lattice site.

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 0.8 | 0.4 | 0.5 | 0.7 | 0.4 | 0.7 | 0 | 0.3 | 0.2 | 0.7 |
| 0 | 0 | 0.3 | 0.2 | 0.4 | 0.2 | 0.5 | 0.3 | 0.7 | 0.2 |
| 0.9 | 0.9 | 0.3 | 0.4 | 0.6 | 0.4 | 0.1 | 0.1 | 0.2 | 0.4 |
| 0.1 | 0.7 | 0.4 | 0.5 | 0.7 | 0.1 | 0.3 | 0.9 | 0.4 | 0.1 |
| 0.3 | 0.2 | 0.7 | 0.5 | 0.1 | 0.7 | 0.4 | 0.1 | 0.2 | 0.7 |
| 0.3 | 0.5 | 0.1 | 0.5 | 0.7 | 0.1 | 0.5 | 0.7 | 0.7 | 0.7 |
| 0.4 | 0.5 | 0 | 0.3 | 0.7 | 0.8 | 0.5 | 0.7 | 0.3 | 0.2 |
| 0.3 | 0.2 | 0.5 | 0.3 | 0.2 | 0.5 | 0.3 | 0.2 | 0.3 | 0.5 |
| 0.3 | 0.4 | 0.1 | 0.1 | 0.4 | 0.1 | 0.5 | 0.7 | 0.4 | 0.5 |
| 0.4 | 0.6 | 0.3 | 0.4 | 0.6 | 0 | 0.3 | 0.2 | 0.7 | 0.5 |

In this lattice, *oxygen concentration* is shown at each site

# Extracellular level - Diffusion

Oxygen **consumption** depends on **cell type**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 0.8 | 0.4 | 0.5 | 0.7 | 0.4 | 0.7 | 0 | 0.3 | 0.2 | 0.7 |
| 0 | 0 | 0.3 | 0.2 | 0.4 | 0.2 | 0.5 | 0.3 | 0.7 | 0.2 |
| 0.9 | 0.9 | 0.3 | 0.4 | 0.6 | 0.4 | 0.1 | 0.1 | 0.2 | 0.4 |
| 0.1 | 0.7 | 0.4 | 0.5 | 0.7 | 0.1 | 0.3 | 0.9 | 0.4 | 0.1 |
| 0.3 | 0.2 | 0.7 | 0.5 | 0.1 | 0.7 | 0.4 | 0.1 | 0.2 | 0.7 |
| 0.3 | 0.5 | 0.1 | 0.5 | 0.7 | 0.1 | 0.5 | 0.7 | 0.7 | 0.7 |
| 0.4 | 0.5 | 0 | 0.3 | 0.7 | 0.8 | 0.5 | 0.7 | 0.3 | 0.2 |
| 0.3 | 0.2 | 0.5 | 0.3 | 0.2 | 0.5 | 0.3 | 0.2 | 0.3 | 0.5 |
| 0.3 | 0.4 | 0.1 | 0.1 | 0.4 | 0.1 | 0.5 | 0.7 | 0.4 | 0.5 |
| 0.4 | 0.6 | 0.3 | 0.4 | 0.6 | 0 | 0.3 | 0.2 | 0.7 | 0.5 |

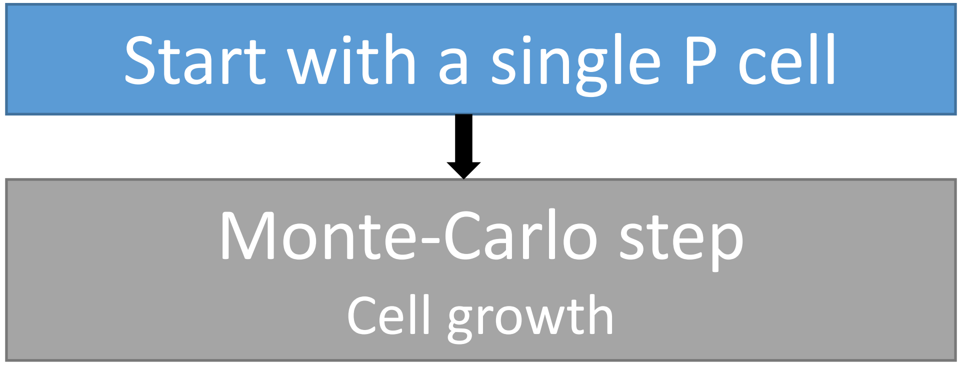
| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 0.8 | 0.4 | 0.4 | 0.6 | 0.3 | 0.7 | 0 | 0.3 | 0.2 | 0.7 |
| 0 | 0 | 0.2 | 0.1 | 0.3 | 0.2 | 0.5 | 0.3 | 0.7 | 0.2 |
| 0.9 | 0.9 | 0.2 | 0.3 | 0.5 | 0.4 | 0.1 | 0.1 | 0.2 | 0.4 |
| 0.1 | 0.7 | 0.4 | 0.4 | 0.7 | 0.1 | 0.3 | 0.9 | 0.4 | 0.1 |
| 0.3 | 0.2 | 0.7 | 0.5 | 0.1 | 0.7 | 0.4 | 0.1 | 0.2 | 0.7 |
| 0.3 | 0.5 | 0.1 | 0.5 | 0.7 | 0.1 | 0.5 | 0.7 | 0.7 | 0.7 |
| 0.4 | 0.5 | 0 | 0.3 | 0.7 | 0.8 | 0.5 | 0.7 | 0.3 | 0.2 |
| 0.3 | 0.2 | 0.5 | 0.3 | 0.2 | 0.5 | 0.3 | 0.2 | 0.3 | 0.5 |
| 0.3 | 0.4 | 0.1 | 0.1 | 0.4 | 0.1 | 0.5 | 0.7 | 0.4 | 0.5 |
| 0.4 | 0.6 | 0.3 | 0.4 | 0.6 | 0 | 0.3 | 0.2 | 0.7 | 0.5 |

# Simulation Flowchart

# Simulation Flowchart

Start with a single P cell

# Simulation Flowchart



# Simulation Flowchart

Start with a single P cell

↓

Monte-Carlo step

Cell growth

↓

Oxygen consumption

# Simulation Flowchart

Start with a single P cell

↓

Monte-Carlo step

Cell growth

↓

Oxygen consumption

↓

Change cell type

Based on O2 concentration

# Simulation Flowchart

**Start with a single P cell**

↓

**Monte-Carlo step**
Cell growth

↓

**Oxygen consumption**

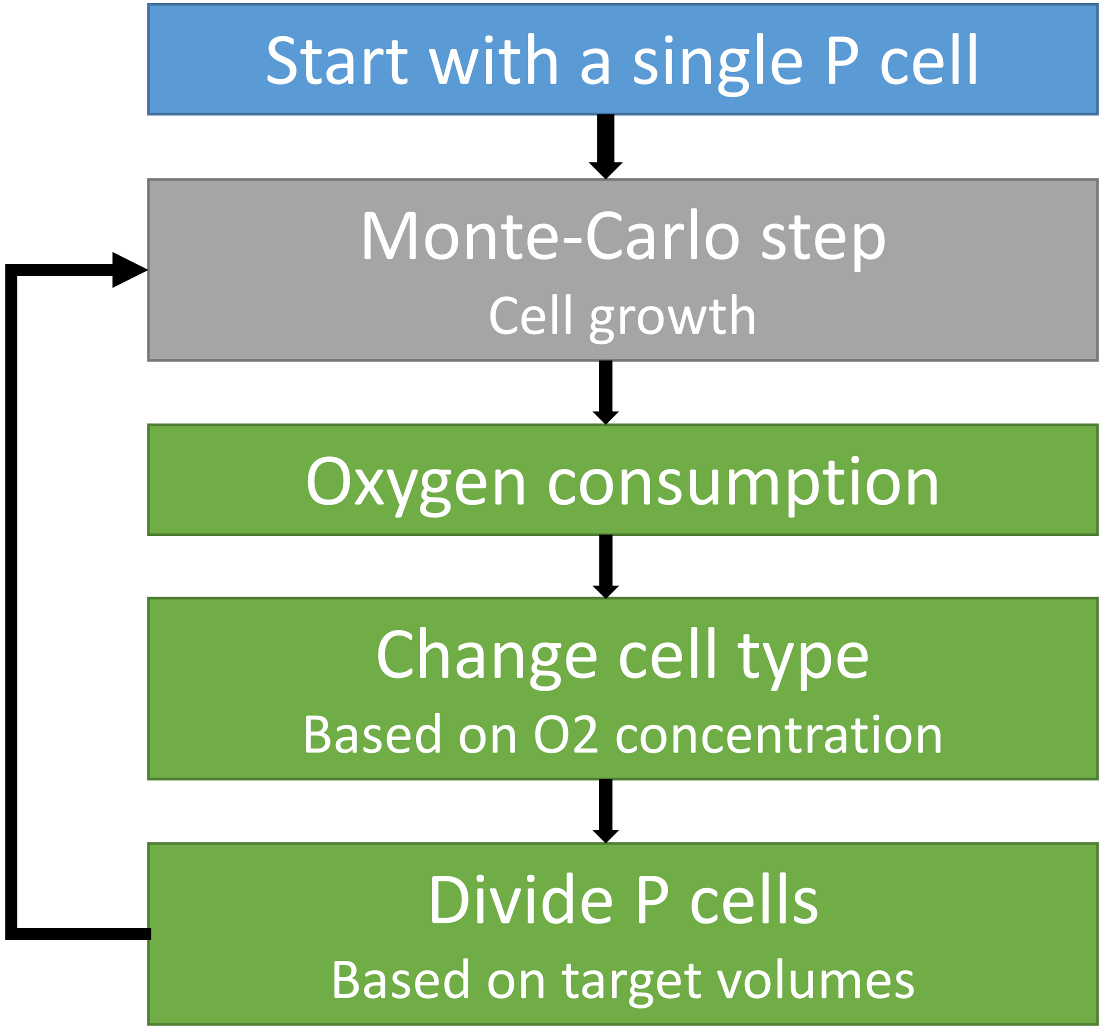
↓

**Change cell type**
Based on O2 concentration

↓

**Divide P cells**
Based on target volumes

# Simulation Flowchart



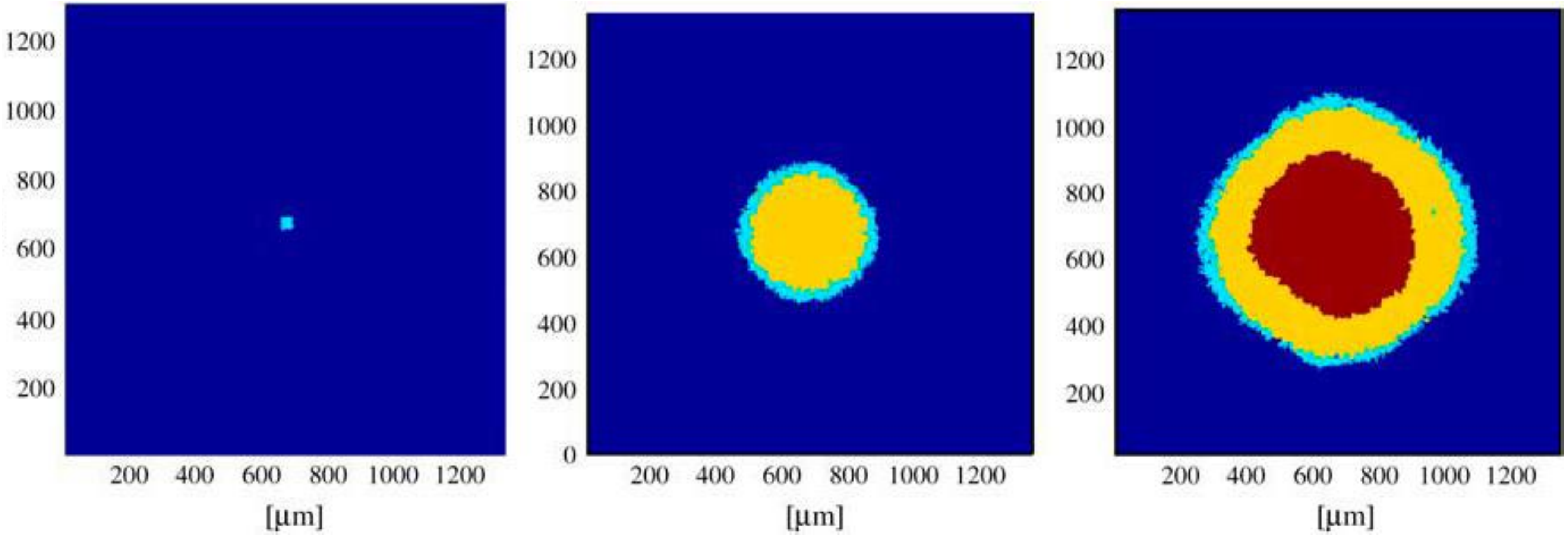
RUN!!!!!

**Tumour threshold : 0.0225**

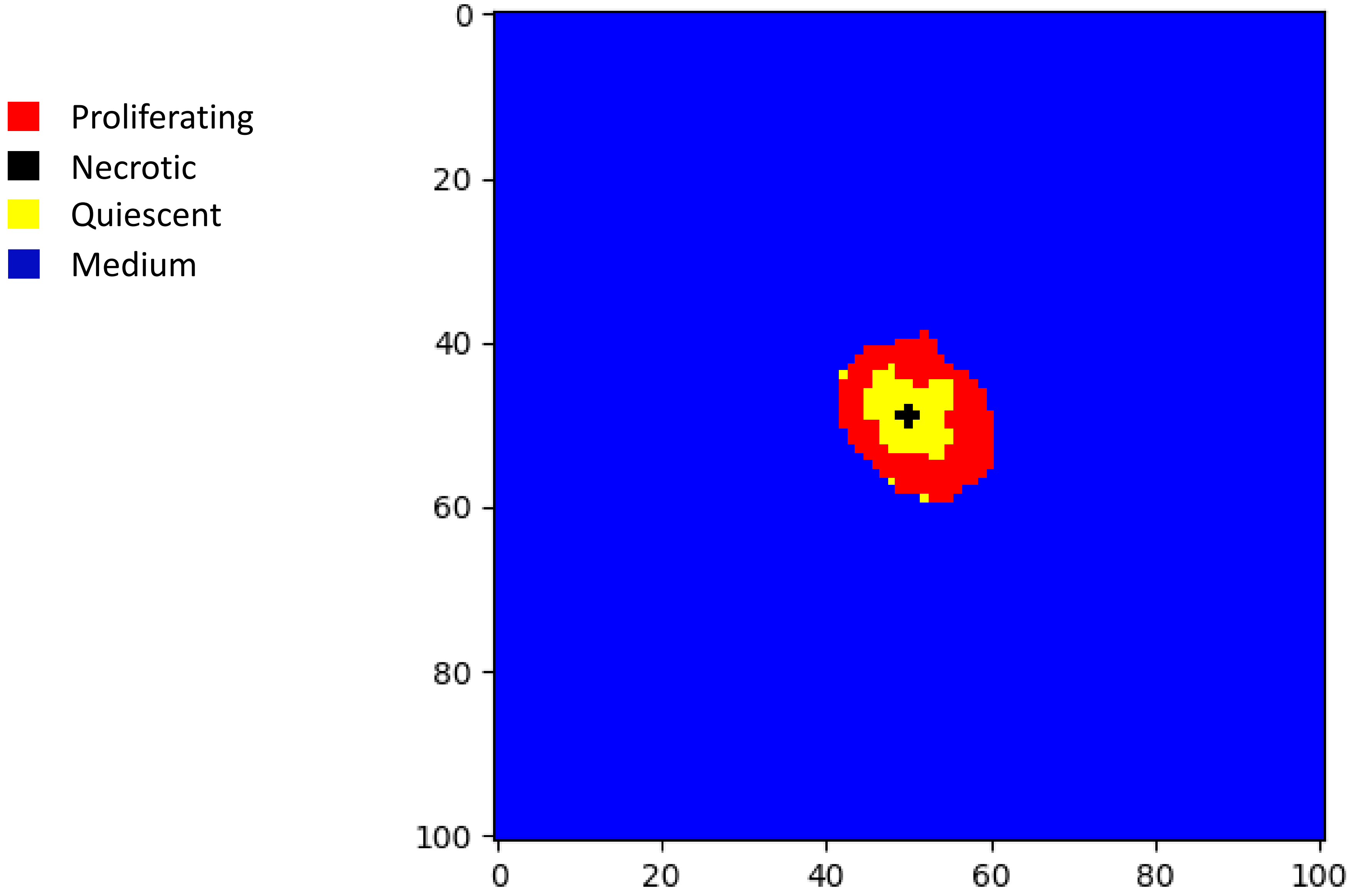

RUN!!!!!

**Tumour threshold : 0.0225**

# Results


1200
1000
800
600
400
200
200 400 600 800 1000 1200
[µm]
1200
1000
800
600
400
200
0
200 400 600 800 1000 1200
[µm]
1200
1000
800
600
400
200
200 400 600 800 1000 1200
[µm]

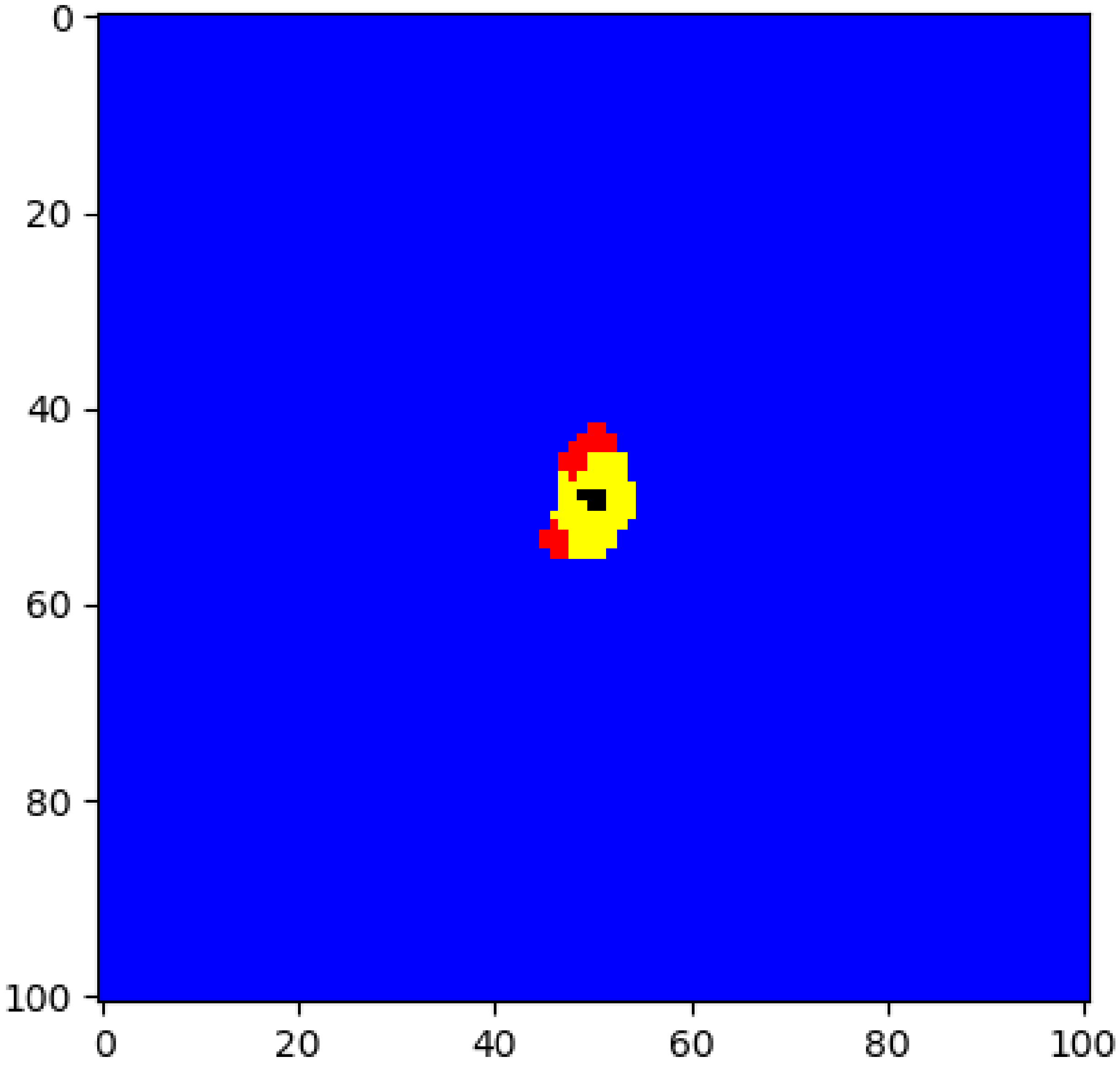
# Results – high oxygen




Initial Oxygen = 0.08

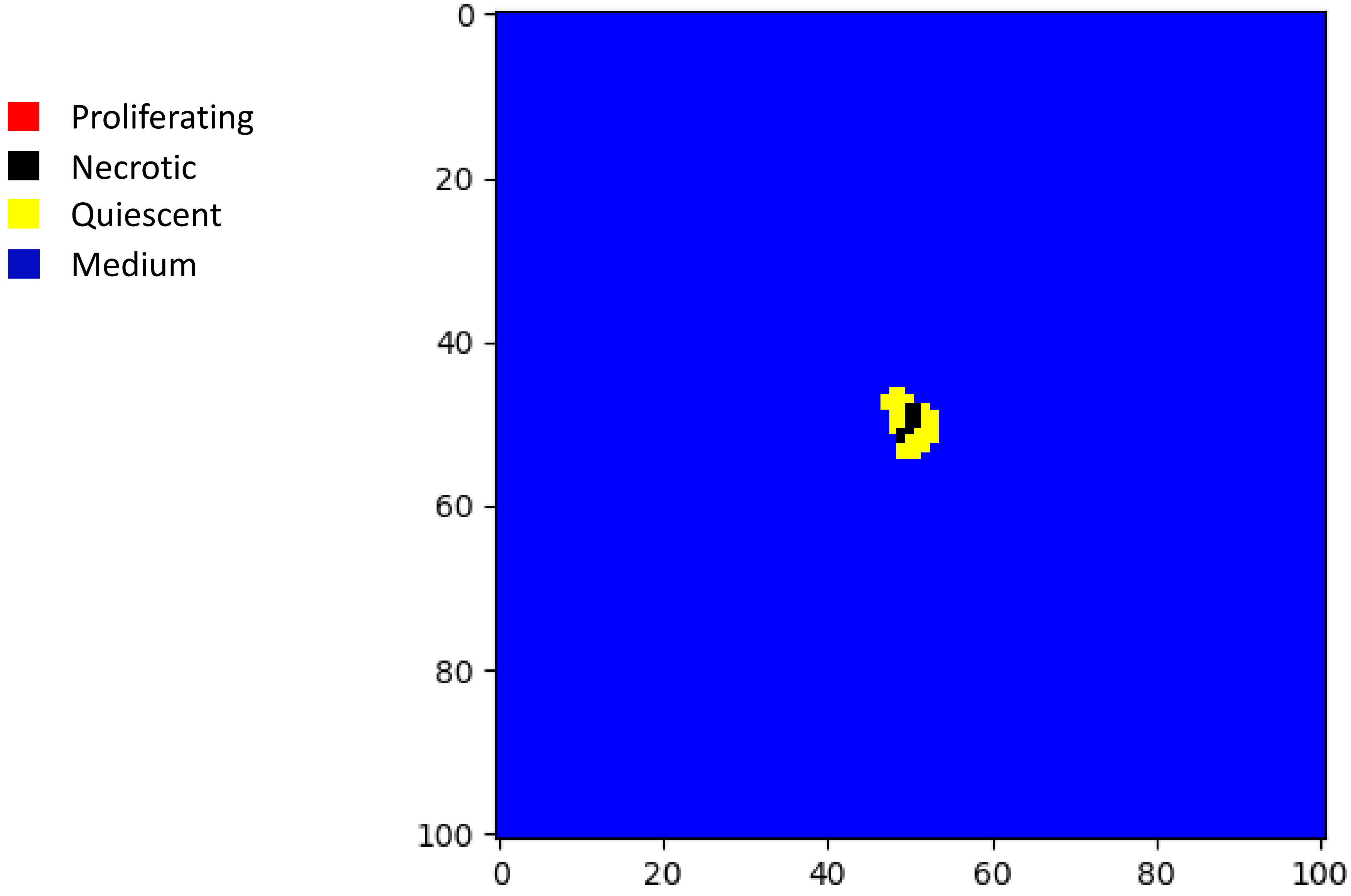
# Results – medium oxygen

Proliferating
Necrotic
Quiescent
Medium




Initial Oxygen = 0.075

# Results – low oxygen




Initial Oxygen = 0.072

# Volume-Adhesion Tradeoff

# Volume-Adhesion Tradeoff

- Balance between reducing surface adhesion and volume.

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 14 | 14 | 14 | 15 | 15 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 7 | 14 | 14 | 8 | 15 | 15 | 15 | 0 | 0 |
| 0 | 0 | 0 | 0 | 7 | 7 | 7 | 8 | 8 | 8 | 9 | 9 | 0 | 0 |
| 0 | 0 | 0 | 12 | 12 | 7 | 4 | 4 | 8 | 9 | 9 | 9 | 0 | 0 |
| 0 | 0 | 0 | 12 | 12 | 12 | 4 | 4 | 4 | 9 | 9 | 6 | 6 | 0 |
| 0 | 0 | 0 | 3 | 3 | 3 | 10 | 10 | 11 | 11 | 6 | 6 | 6 | 0 |
| 0 | 0 | 13 | 3 | 3 | 10 | 10 | 10 | 11 | 11 | 11 | 6 | 6 | 0 |
| 0 | 0 | 13 | 13 | 13 | 1 | 1 | 1 | 2 | 2 | 2 | 0 | 0 | 0 |
| 0 | 0 | 0 | 13 | 5 | 5 | 1 | 1 | 2 | 2 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 5 | 5 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

# Volume-Adhesion Tradeoff

- What happens if we prioritise volume energy?

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 11 | 11 | 11 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 12 | 13 | 11 | 16 | 12 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 13 | 13 | 13 | 16 | 16 | 15 | 15 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | **5** | **5** | 16 | 8 | 15 | 15 | 7 | 7 | 0 | 0 |
| 0 | 0 | 0 | **5** | 14 | 9 | 8 | 7 | 7 | 3 | 3 | 3 | 14 | 0 |
| 0 | 0 | 7 | 9 | 14 | 14 | 6 | **5** | **5** | 6 | 3 | 9 | 6 | 0 |
| 0 | 7 | 7 | 7 | 9 | 6 | 12 | 3 | 10 | **5** | 6 | 6 | 0 | 0 |
| 0 | 0 | 7 | 7 | 1 | 1 | 3 | 10 | 10 | 10 | 6 | 6 | 0 | 0 |
| 0 | 6 | 6 | 8 | 1 | 1 | 1 | 2 | 2 | **5** | 12 | 0 | 0 | 0 |
| 0 | 3 | 8 | 4 | 1 | 3 | 4 | 4 | 2 | 2 | 2 | 0 | 0 | 0 |
| 3 | 3 | 4 | 0 | 1 | 1 | 4 | **5** | 2 | 2 | 2 | 0 | 0 | 0 |
| 0 | 4 | 4 | 0 | 1 | 1 | **5** | 4 | 2 | 2 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | **5** | 4 | 8 | 4 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 8 | 8 | 8 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 8 | 8 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

- The primary aim is to achieve the target volume.
- Sacrifices keeping a cell together.

# Volume-Adhesion Tradeoff

- What happens if I prioritise surface adhesion energy?

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

- After six iterations, the cell still doesn't grow.
- Adding a single new lattice site to the cell increases adhesion energy a lot more than it decreases the volume energy.

# Pseudo-Diffusion

# Pseudo-Diffusion

- Differences with the paper:
  - We only use oxygen
  - We only consume oxygen
  - No REAL diffusion

$$\frac{\partial u_{O_2}}{\partial t} = D_{O_2} \nabla^2 u_{O_2} + a(x, y, z)$$

- Our rate of diffusion is infinitesimally small.

- Question : What would happen in case we used the real diffusion equations?

# Appendix

# Appendix

- **Hamiltonian operator** definition:

γ: elasticity of cell volume

***Adhesive energy*** term

$$H = \boxed{\sum_{\text{lattice sites}} J_{\tau(S_1)\tau(S_2)}[1 - \delta(S_1, S_2)]} + \boxed{\sum_{\text{cells}} \gamma(v - V^T)^2}$$

τ(S1): cell type of cell “S1”

***Volume energy*** term

$(v\text{-}V^T)$: current minus target volumes

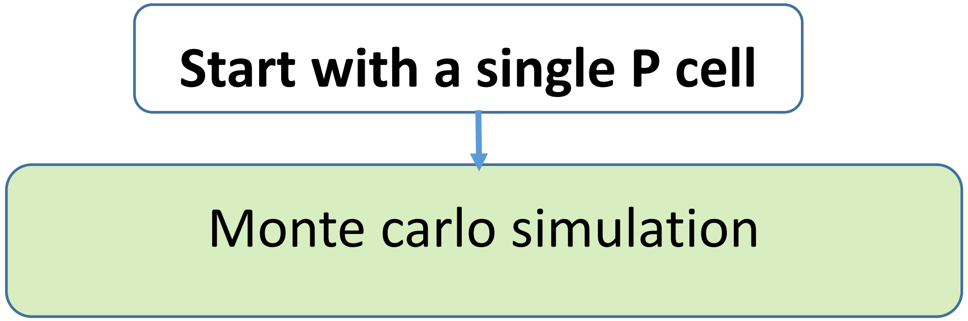
| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 4 | 4 |
| 1 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 4 | 4 |
| 1 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 4 | 4 |
| 2 | 1 | 1 | 3 | 2 | 2 | 4 | 3 | 4 | 4 |
| 2 | 1 | 1 | 2 | 2 | 2 | 4 | 4 | 4 | 6 |
| 2 | 2 | 1 | 2 | 2 | 2 | 6 | 6 | 6 | 6 |
| 5 | 2 | 2 | 2 | 2 | 2 | 6 | 6 | 6 | 6 |
| 5 | 5 | 5 | 5 | 5 | 6 | 6 | 5 | 5 | 5 |
| 5 | 5 | 5 | 5 | 5 | 6 | 6 | 6 | 5 | 5 |
| 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

# Appendix

# Simulation Flowchart

Start with a single P cell

# Simulation Flowchart



# Simulation Flowchart

**Start with a single P cell**

↓

Monte carlo simulation

↓

Simulate oxygen consumption

# Simulation Flowchart

**Start with a single P cell**

↓

Monte carlo simulation

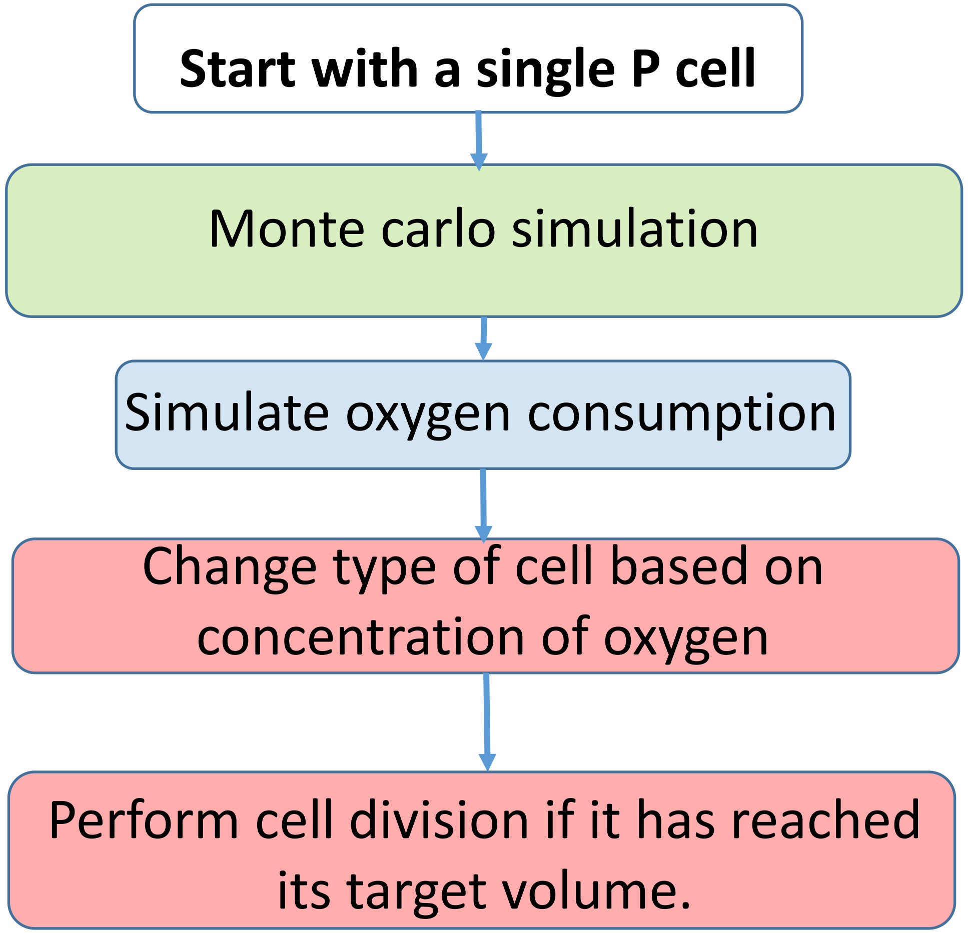
↓

Simulate oxygen consumption

↓

Change type of cell based on concentration of oxygen

# Simulation Flowchart



# Simulation Flowchart