# Evolution of cooperation in an epithelium

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## 1. Cells can cooperate

*Cooperation = providing a benefit to the group at an individual cost.*

Cells can cooperate to increase their fitness. For example, many mutations associated with cancer rely on the production of diffusible growth factors. 85% of cancers originate in epithelial cells which form skin and the surfaces of organs.

## 2. Evolutionary games

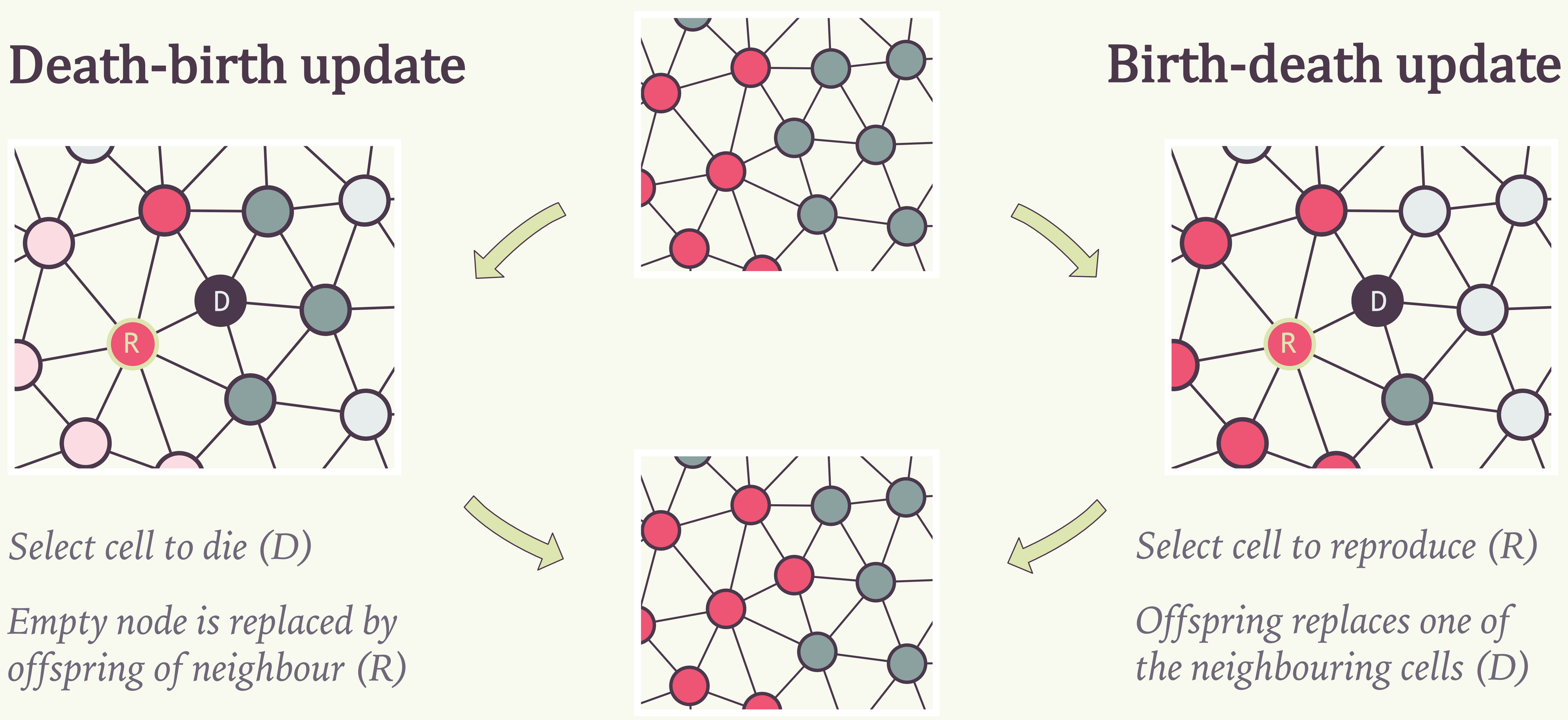
The evolution of cooperation can be modelled using evolutionary game theory. There are two competing cell types: cooperators and defectors. Cells obtain a payoff by playing a *game*. We use a simple prisoner's dilemma game in which cooperators provide a benefit $b$ to their partner at a cost $c$. Fitness is then defined as

$$\text{fitness} = 1 + \delta \times \text{average payoff}$$

where $\delta$ is the selection strength parameter. The population evolves through sequential birth and death events where cells are chosen to reproduce proportional to fitness.

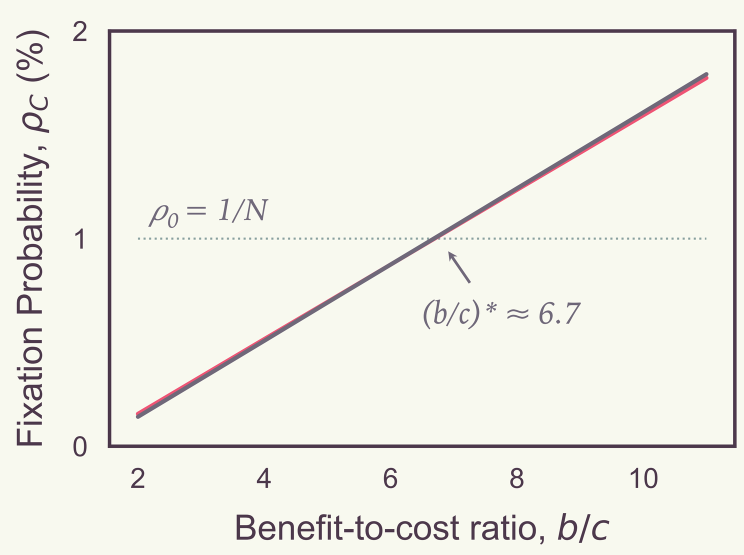
## 3. Evolutionary graph theory

In evolutionary graph theory (EGT) the population is represented by a fixed graph and cells only interact with their neighbours. Births and deaths are governed by an update rule:




If the fixation probability for a single mutant cooperator, $\rho_c$, exceeds the neutral fixation probability, $\rho_0$, cooperation is favoured by selection.

**EGT death-birth update [1]**
*on a hexagonal lattice ● and a static Voronoi graph ●*
*(N = 100, δ = 0.025, c=1)*



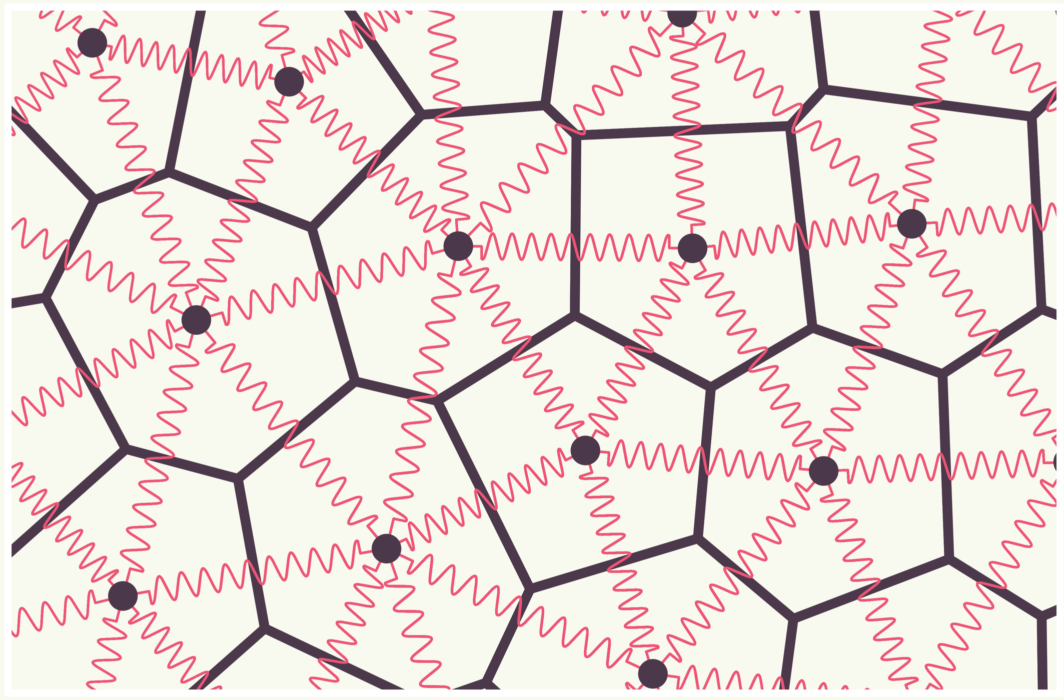

*N = population size*
*δ = selection strength parameter*
*b/c = benefit-to-cost ratio*

The choice of update rule is crucially important to outcomes.

For a birth-death update rule cooperation is never favoured. For a death-birth update rule cooperation is favoured above a critical benefit-to-cost ratio (b/c)*.

There are shortcomings of EGT for modelling an epithelium: (1) it does not account for the dynamic structure of epithelia and (2) it requires an unrealistic spatial coupling of births and deaths.

## 4. Voronoi tessellation model



The Voronoi tessellation (VT) model [2] is a mechanical model of an epithelium in which cell-centres exert spring-like forces on one another.

Cells correspond to Voronoi regions and interact with their neighbours to obtain fitness.

Cell-centres are added or removed when births or deaths occur.

We can therefore introduce a spatially *decoupled* update rule in which birth and death events are independent of the graph structure.

We derive an approximate equation for the cooperator fixation probability when using the decoupled update rule (in the limit $\delta \to 0$). This is done by averaging over transition probabilities for populations with $n$ cooperators:

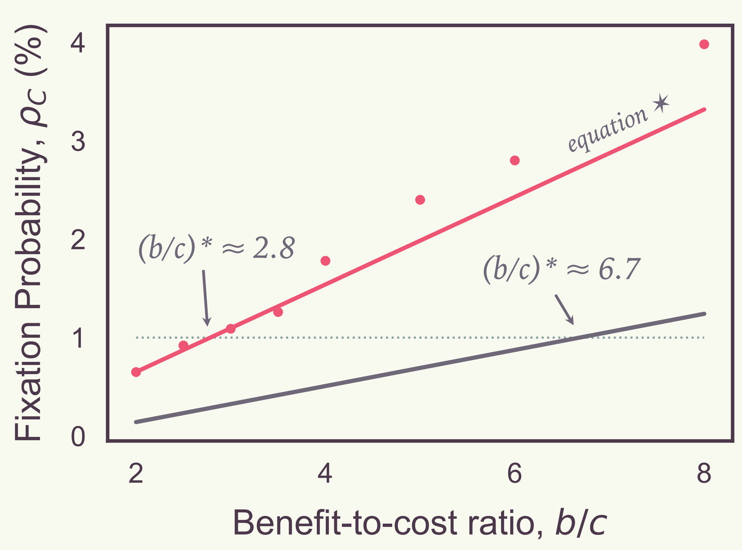
$$\rho_C = \frac{1}{N} + \frac{\delta}{N}\left\{-\frac{c}{2}(N-1) + b\sum_{m=1}^{N-1}\sum_{n=1}^{m}\left(\frac{\Lambda_n^{CC} - n/N}{N-n}\right)\right\} + \mathcal{O}\left(\delta^2\right) \quad \star$$

The quantity $\Lambda_n^{CC}$ is calculated computationally, where $\Lambda_n^{XY}$ is the expected proportion of type Y neighbours for a cell of type X.

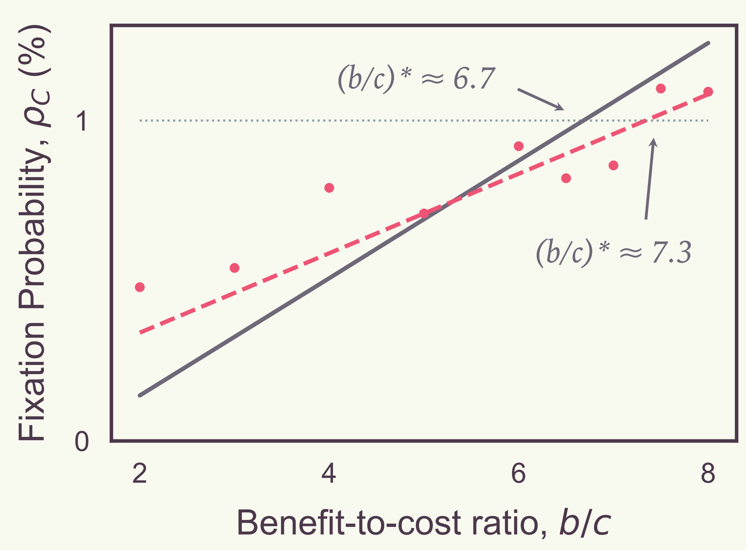
## 5. Comparing the models

We compare fixation probabilities for EGT (hexagonal lattice) and the VT model.

**Decoupled update on VT model ●**
*compared with EGT death-birth ●*
*(N = 100, δ = 0.025, c=1)*




**Death-birth update on VT model ●**
*compared with EGT death-birth ●*
*(N = 100, δ = 0.025, c=1)*




Cooperation is more successful in the VT model with decoupled update. With a death-birth update it is slightly less successful than in EGT.

## 6. Conclusions and outlook

Evolutionary dynamics are heavily dependent on update rules, therefore it is important to choose the most realistic. This cannot necessarily be accomplished within EGT, but can be done using the VT model.

*Spatially decoupling birth and death promotes cooperation.*

In a real epithelium however, both birth and death processes can be density-dependent. This could lead to a weaker spatial coupling.

REFS: [1] Allen et al. (2017) *Nature* 544(7649)
[2] Meineke et al. (2001) *Cell Proliferation* 34(4)

Read further: Renton J & Page KM. (2019) "Evolution of cooperation in an epithelium." *Journal of the Royal Society Interface* 16(152)