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Spatial models of the evolution of solid tumours

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Outline

- Cellular automata
- Eden growth model
- Deme-based models
- Gillespie stochastic simulation algorithm
- Hybrid cellular automata
- Model choice

Motivation

- Knowledge of tumour evolutionary dynamics can inform cancer prevention, prognosis and treatment
- Parallels: bacterial colonies, invasive species, …

- Four processes of population genetics: selection, mutation, genetic drift, and *gene flow*
- One factor determining gene flow is spatial structure
- Spatial structure's influence on evolutionary dynamics can be investigated using explicitly spatial models

What factors might we need in a model?

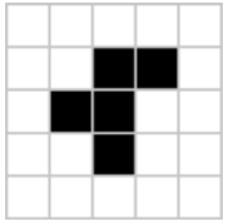
- Demographic processes (birth and death)
- Mutation
- Migration (dispersal)
- Environmental variation (e.g. oxygen, drugs)
- More complex interactions (next three lectures)

- No gene transfer (probably)

Cellular automata

- Regular grid of sites (one or more dimensions)
- Each site is associated with one of a set of states
- Each site is part of a neighbourhood
- Rules for updating each site state depend on current state of the site and its neighbourhood

- Potential for self-organisation and emergence



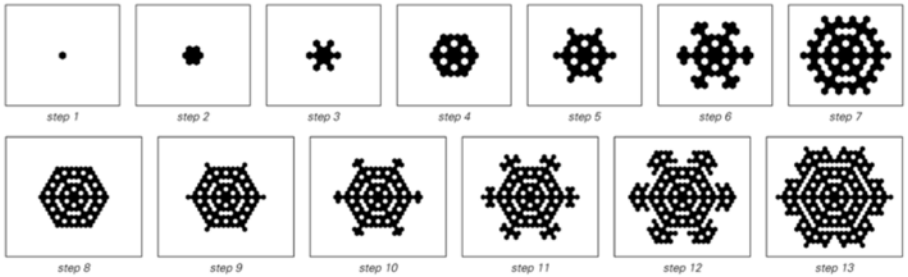
https://playgameoflife.com/

Example: Conway's Game of Life

https://playgameoflife.com/

Natural examples

Crystal formation

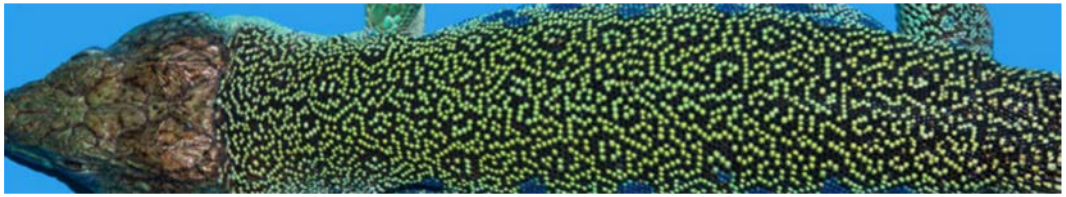


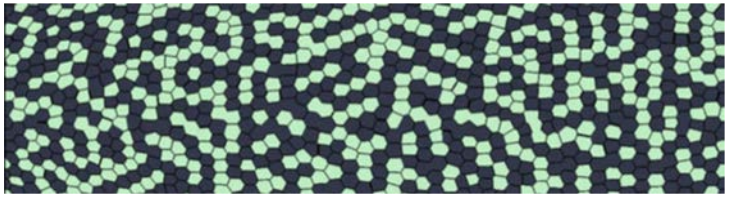
Wolfram, S. (2002) A New Kind of Science

Chemical oscillators

www.hermetic.ch/pca/bz.htm

Animal markings





Manukyan, L. *et al.* (2017) *Nature* **544**, 173-179

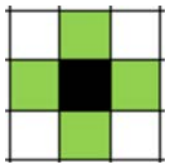
Stochastic cellular automata

- Rules are probabilistic
- Equivalent to locally interacting Markov chains
- Biological models usually use asynchronous updating (one site at a time, like the Moran process)

- Part of the more general class of agent-based (or individual-based) models

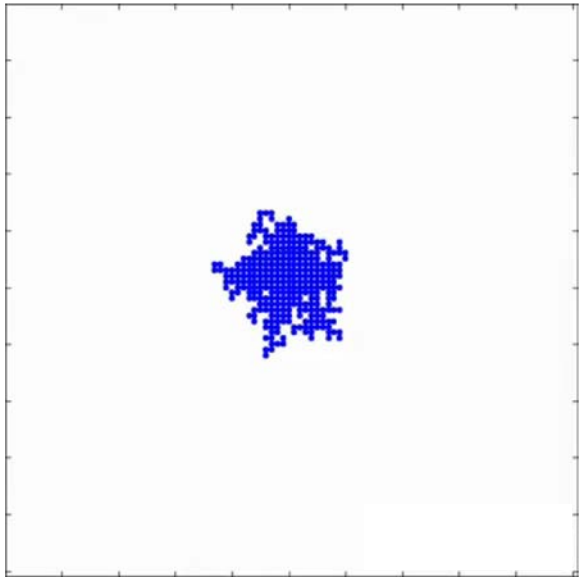
Eden growth model (Murray Eden, 1961)

- Two states: unoccupied (S_0) and occupied (S_1)
- Neighbourhood: usually adjacent sites (von Neumann)
- Update rule: with each iteration, a site in the neighbourhood of an S_1 site switches from S_0 to S_1
- Cells are thus added to the surface of a cluster



Eden growth model (Murray Eden, 1961)

- Self-organises to resemble an n-dimensional ball but with a non-trivial surface
- Cell division mostly confined to the boundary
- Growth curve $\longrightarrow$ polynomial of degree n



https://www.youtube.com/watch?v=hluvLTwMFOs

Eden growth model variants (similar properties)

- **A**vailable site-focussed: randomly choose an S_0 site that adjoins at least one S_1 site, and switch it from S_0 to S_1

- **B**ond-focussed: randomly choose an S_1 site with probability proportional to number of adjoining S_0 sites, then randomly choose an S_0 neighbour and switch it to S_1

- **C**ell-focussed: randomly choose an S_1 site that adjoins at least one S_0 site, then randomly choose an S_0 neighbour and switch it to S_1

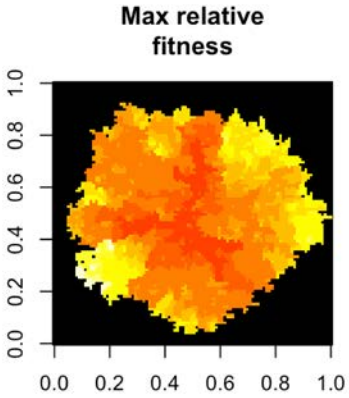
Eden growth model with mutation

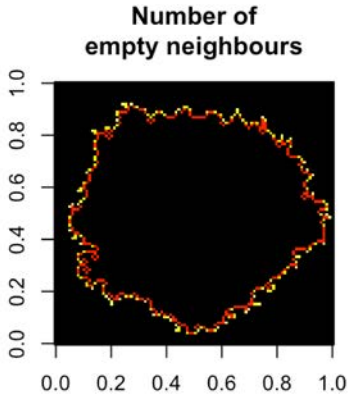
- Multiple occupied states $\{S_1, S_2, \ldots\}$
- Mutation: probabilities of $S_i \longrightarrow S_j$ for $i, j > 0$
- Models usually apply mutation only at the time of division
- States may confer different division rates

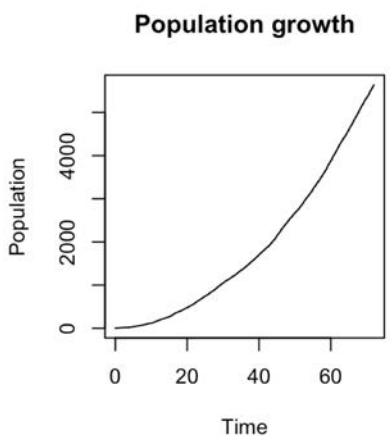
- Example:
  - all mutation probabilities are zero except in the case $S_i \longrightarrow S_{i+1}$
  - a site in state S_i that adjoins at least one site in state S_0 divides with probability proportional to $(1 + s)^i$

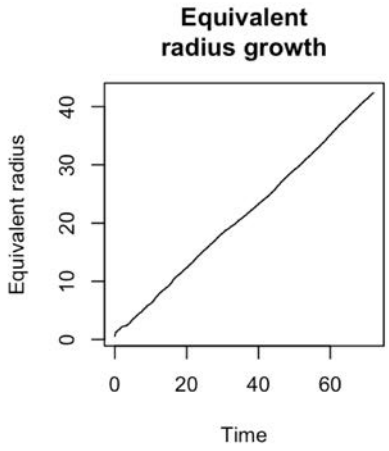
Eden growth model with mutation

Nearly neutral mutations

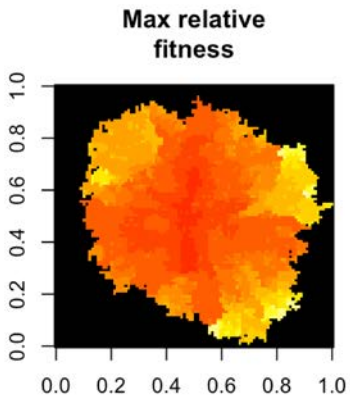


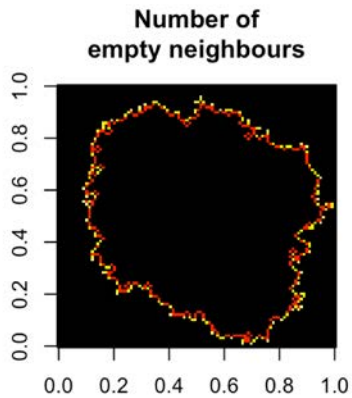


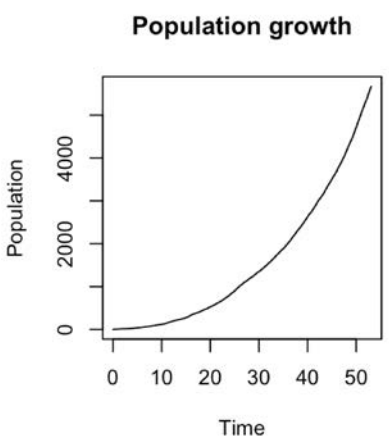


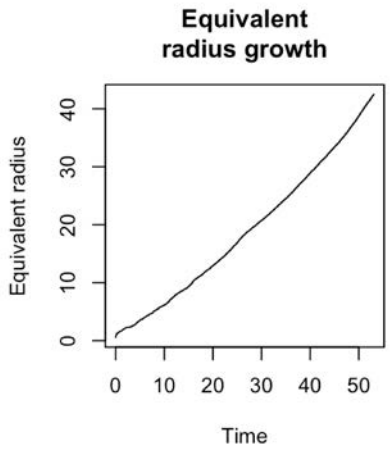


Selective advantage = 0.1

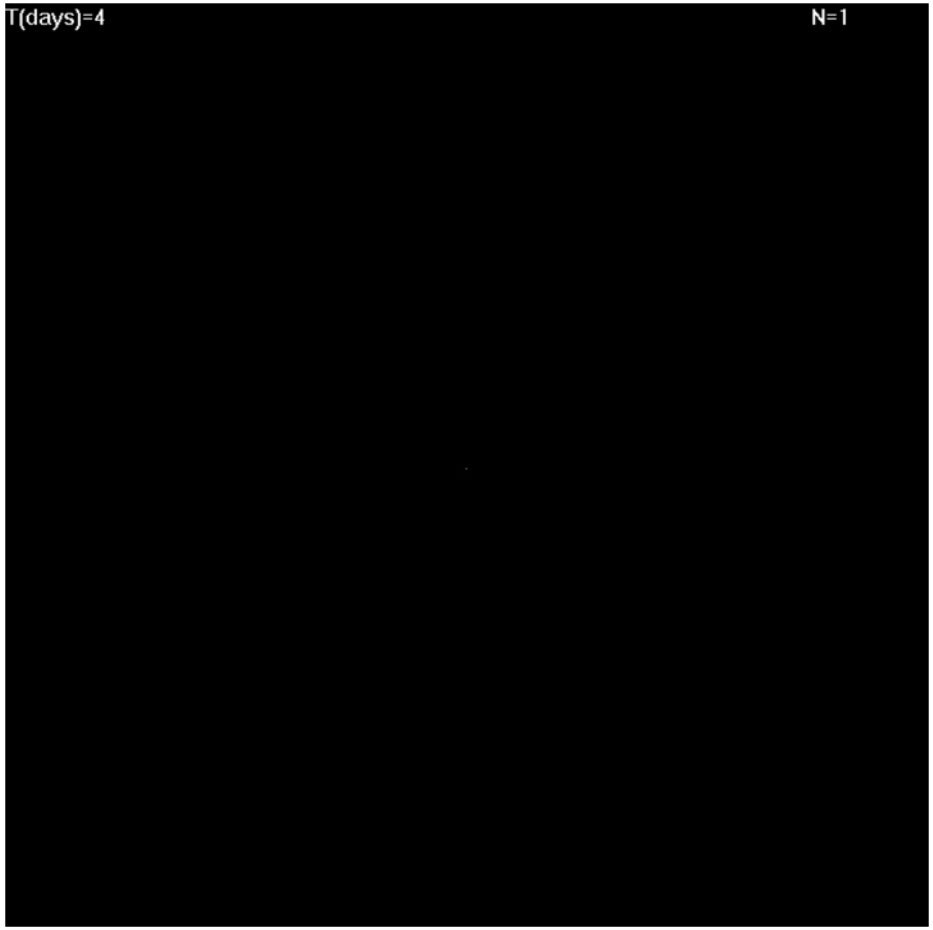








Eden growth model with mutation

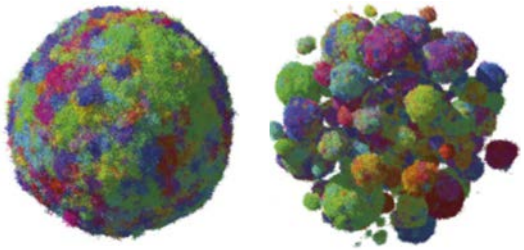


Waclaw, B. *et al.* (2015) *Nature* **525**, 261-264

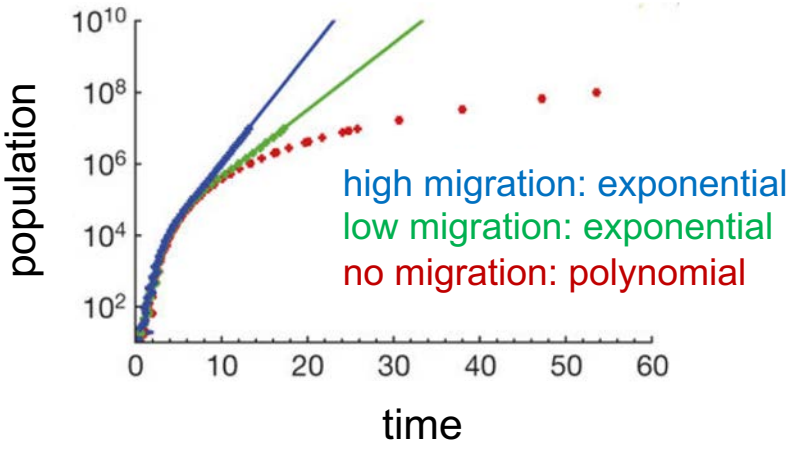
Eden growth model with cell death and migration

- Cell death: probabilities of $S_i \longrightarrow S_0$ for $i = 1, 2, \ldots$
- Migration: state frequencies are maintained but some states become associated with different sites

- Migration beyond the tumour increases tumour growth rate (because it increases surface-to-volume ratio)
- Cell death facilitates selection



Waclaw, B. *et al.* (2015) *Nature* **525**, 261-264

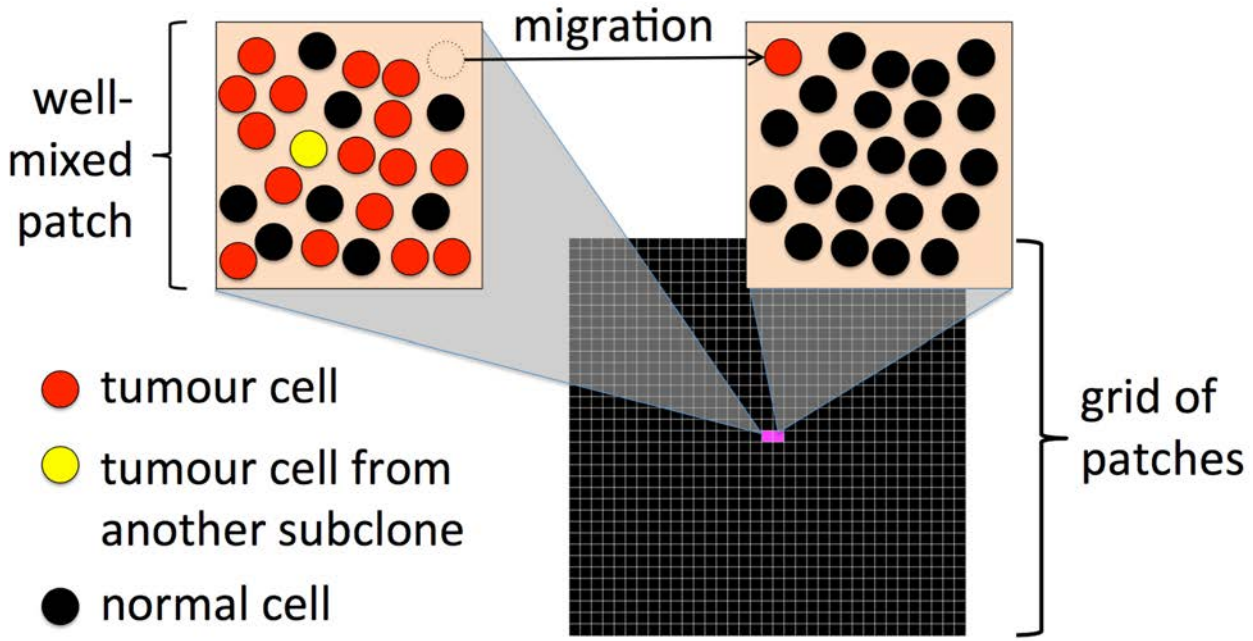


Deme-based models

- Each site (deme) contains multiple cells (e.g. demes correspond to glands or microenvironmental niches)
- Assume cells within demes are well-mixed and obey a model such as the Moran process or Wright-Fisher process
- Cells can migrate between demes

- When the number of cells per deme is reduced to one, the model reduces to a stochastic cellular automaton (similar to the linear process described in a previous lecture)
- As the migration rate approaches zero, the model resembles a set of independent non-spatial processes

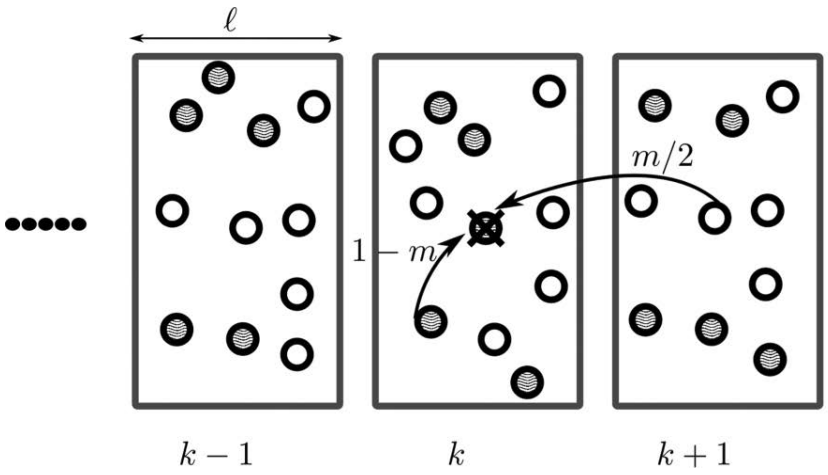
Deme-based models



- Evolutionary dynamics not confined to the surface
- More potential for selective sweeps and clonal interference
- Mixing within or between demes facilitates selection

Noble, R., Burri, D., Kather, J. N., & Beerenwinkel, N. (2019). *BioRxiv*, https://doi.org/10.1101/586735

A spatial Moran model



- When a cell dies, it is replaced via division of another cell
- Replacement probability is weighted by cell fitness
- The replacement has a local parent with probability $(1 - m)$ or a parent from a neighbouring deme with probability m

Houchmandzadeh, B, & Vallade, M. (2017). *Physical Review E* **96**, 012414

A spatial Moran model

- Consider a mutant invading an infinite row of demes
- Let $\mathbf{n} = \{\ldots, n_{i-1}, n_i, n_{i+2}, \ldots\}$ be the vector of mutant population sizes along the row of demes
- Transition probability densities:

prob. density that n_i increases by one: $W_i^+(\mathbf{n}) = \frac{\mu(1+s)}{N}(N-n_i)\left[n_i + \frac{m}{2}n_i''\right],$

prob. density that n_i decreases by one: $W_i^-(\mathbf{n}) = \frac{\mu}{N}n_i\left[(N-n_i) - \frac{m}{2}n_i''\right],$ (1)

where μ is the death rate, s is the difference in fitness, N is the deme population size, and

$$n_i'' = (n_{i-1} + n_{i+1} - 2n_i).$$

Fisher's equation

- As in the non-spatial Moran process, we can take a diffusion approximation of (1), in which case we obtain

$$\frac{\partial u}{\partial t} = D[1 + s(1-u)]\frac{\partial^2 u}{\partial x^2} + \mu s u(1-u),$$

  where $u = \langle n_i \rangle / N$, x is distance along the row of demes, and D is a diffusion coefficient

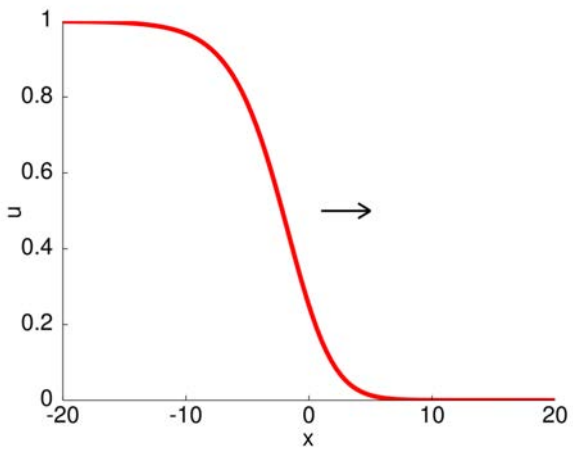
- This is a variant of Fisher's equation (or the Fisher-KPP equation), a canonical result describing "the wave of advance of advantageous genes":

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} + ru(1-u).$$

Fisher's equation

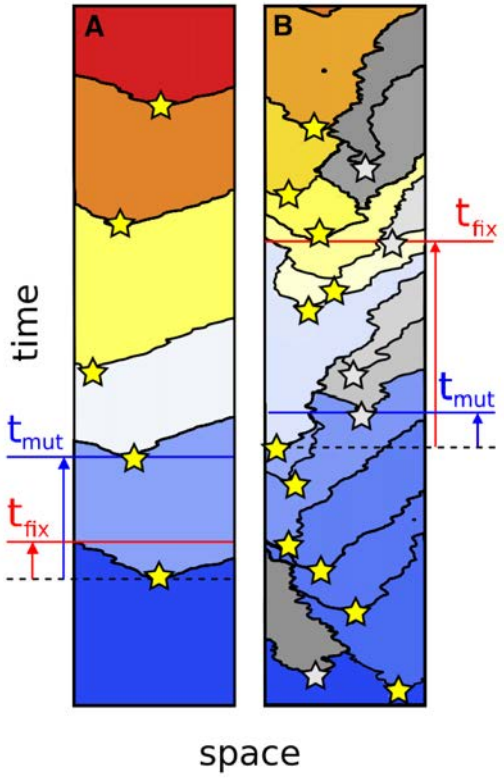
$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} + ru(1-u).$$

- Fisher's equation is difficult to solve in general
- If, at $t = 0$, u decreases monotonically and continuously from 1 to 0 over a finite distance (as below) then the equation has a *travelling wave* solution of the form $u(x, t) = U(x - ct)$, with $c = 2\sqrt{(rD)}$



Clonal interference

- Clonal interference is competition between lineages arising from different beneficial mutations



- Heightened by spatial structure
- Lessened by gene transfer (not in cancer)
- Impedes fixation of beneficial mutations

Martens, E. A, & Hallatschek, O. (2011). *Genetics*, *189*(3), 1045–60

Gillespie stochastic simulation algorithm (Daniel Gillespie, 1976)

- Frequently used in computational simulations
- Simulates a sequence of events, corresponding to a statistically correct trajectory of a set of stochastic differential equations (the master equation)

- Probability an event occurs next is proportional to its rate
- Times between events are exponentially distributed

Gillespie stochastic simulation algorithm (Daniel Gillespie, 1976)

1. Initialise the system
2. Calculate event rates (birth, death, migration, etc.)
3. Randomly determine next event such that
   $P(\text{event} = E) = \text{rate}(E) \;/\; \sum \text{rates}$
4. Update the system
5. Advance the timer by $\delta t \sim \text{Exp}(1 \;/\; \sum \text{rates})$
6. Return to step 2 (until stop condition)

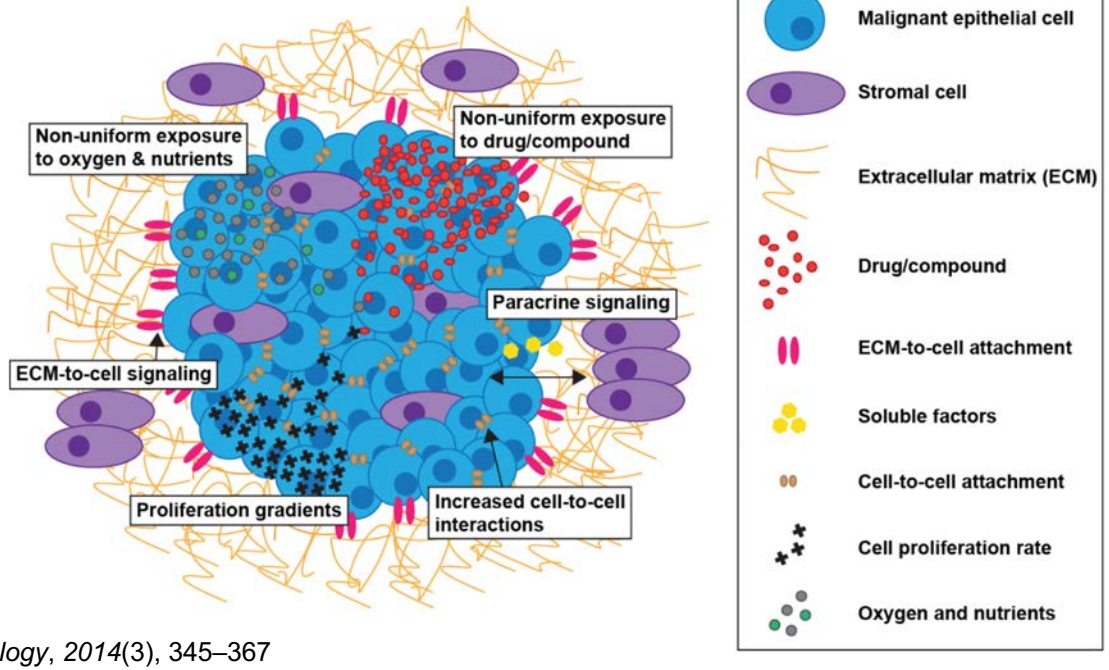
Gillespie stochastic simulation algorithm (Daniel Gillespie, 1976)

- Advantages:
  - Exact correspondence with master equation: generates statistically correct trajectories of finite populations in continuous time
  - Easy to implement
  - More computationally efficient than running individual event timers
  - Faster, non-exact variants have been developed

- Disadvantages:
  - Some events (e.g. cell division) aren't really Poisson processes
  - Inaccurate if event rates frequently undergo large changes (e.g. due to intermittent therapy)

Hybrid cellular automata

- Models such as the spatial Moran process and Fisher's equation assume a homogeneous environment
- Tumour cells inhabit an environment that varies over space and time
- Hybrid cellular automata models are designed to account for such environmental heterogeneity



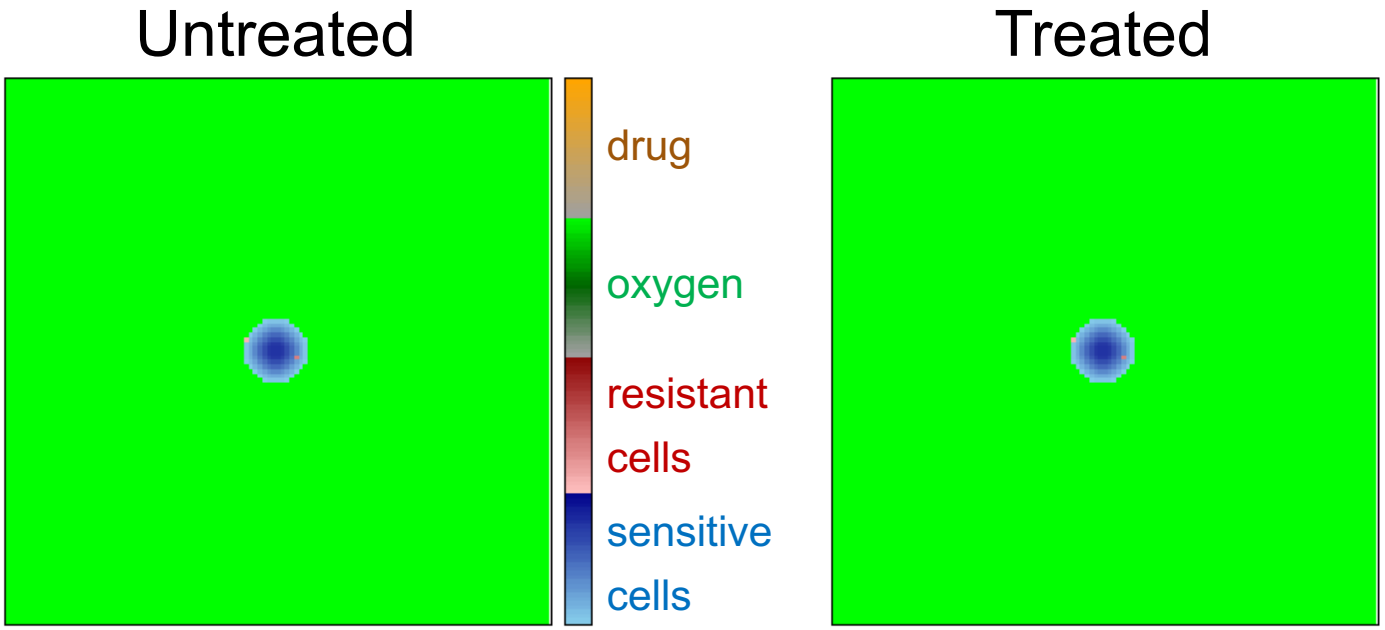
Lovitt, C. J, Shelper T. B, & Avery, V. M. (2014). *Biology*, *2014*(3), 345–367

Hybrid cellular automata

- Stochastic component: cell events
- Deterministic component: chemicals obeying reaction-diffusion equations
- The two components are interdependent
- Usually assume separation of time scales

- Examples: oxygen, glucose, angiogenic factors, drugs, …
- Can lead to variable selection pressures
- Potential for niche construction: the tumour modifies its selective environment

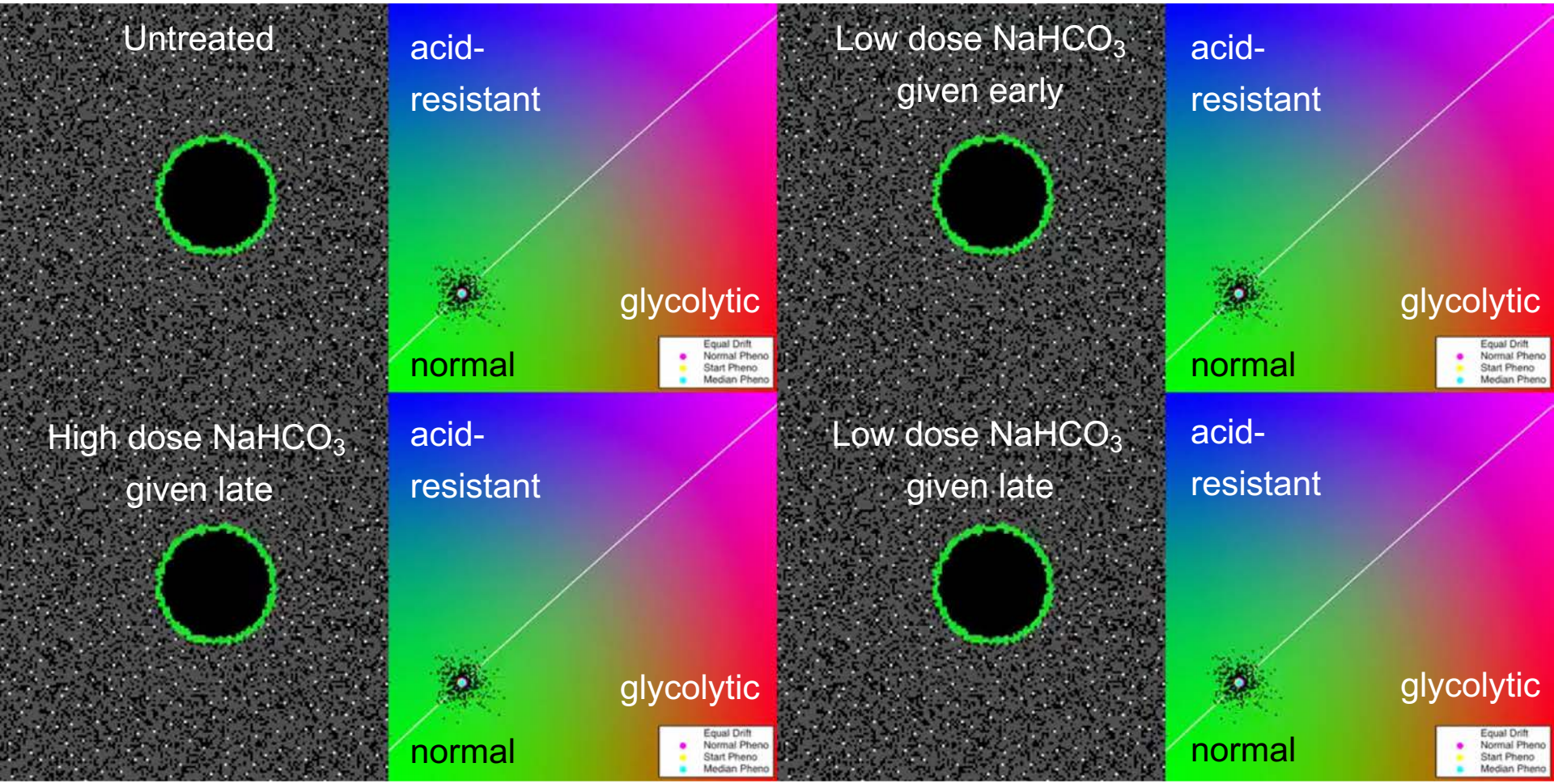
Example: tumour spheroid model



Bacevic & Noble *et al.* (2017) *Nature Communications* **8**;1995

Example: niche construction

Ibrahim-Hashim *et al.* (2017) *Cancer Research* **77**;9



Choosing a spatial model

- There is no standard model
- Statistical model selection methods usually don't apply
- Depends on the question and the biological system
  - Appropriate organisational level(s): cell, niche, crypt, …
  - What needs to be included
  - What can be excluded
  - Parameterisation
  - Computational limitations

- Start by understanding the biology (collaborate!)

Simpler models are more useful

- Model complexity should match the complexity of the specific phenomena of interest (not the entire system)

- Simpler models:
  - Satisfy Occam's razor (easier to falsify)
  - Reduce researcher degrees of freedom
  - Clarify how outcomes depend on assumptions
  - Increase mathematical tractability
  - Are more generally applicable
  - Make stronger predictions

Summary

- Spatial models can exhibit self-organisation and emergence (the whole is more than the sum of the parts)
- Spatial structure changes evolutionary dynamics; important factors include the degree of mixing, clonal interference, environmental heterogeneity
- Crucial to select an appropriate model and be aware of its limitations

Further reading:

Altrock, P. M., Liu, L. L., & Michor, F. (2015). The mathematics of cancer: integrating quantitative models. *Nature Reviews Cancer*, *15*(12), 730–745

Erban, R., Chapman, J., & Maini, P. (2007). A practical guide to stochastic simulations of reaction-diffusion processes, 24–29. http://arxiv.org/abs/0704.1908

Houchmandzadeh, B., & Vallade, M. (2017). Fisher Waves: an individual based stochastic model. *Physical Review E*, *96*(1), 1–13. https://doi.org/10.1103/PhysRevE.96.012414