Individual-based stochastic spatial models and population biology

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Topics for 2 sessions this morning

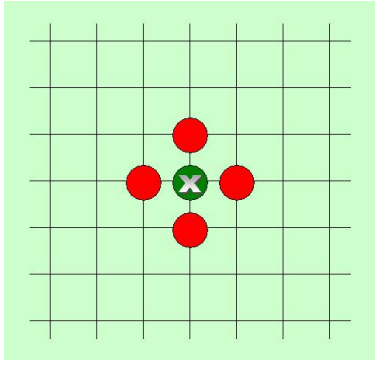
- interacting particle system models–what they are and some basic examples
- comparisons with ODE and PDE
- hydrodynamic limits: connecting IPS and PDE
- adding complexity to basic models
- two applications in microbial population biology (phage and plasmids) with even more complexity; the importance of spatial structure in ecological and evolutionary dynamics

Interacting Particle Systems

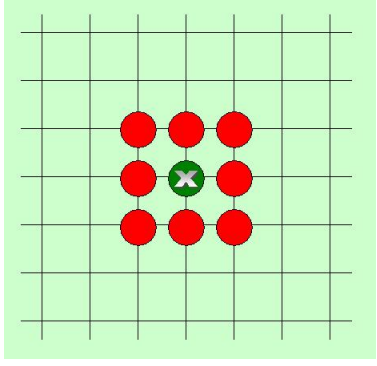
a.k.a. "stochastic cellular automata" and "individual-based stochastic spatial models"

- Explicitly model
    1. discrete spatial structure: $\mathbb{Z}^d$ (for example)
    2. Each site can be in several different states ("particles")
    3. randomness
    4. local interactions between individuals
    5. sometimes particles move ("exchange" dynamics), sometimes not ("flip" dynamics)

Interaction neighborhoods



4 nearest neighbors

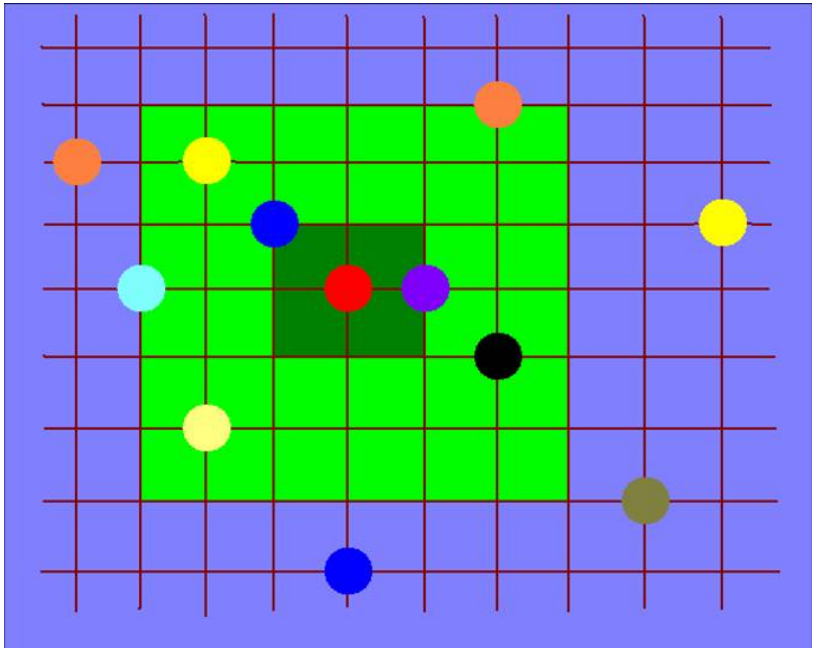


8 nearest neighbors

General: $\mathcal{N}_r(x) = \{y \in \mathbb{Z}^d : 0 < \|y - x\| \leq r\}$ . . . lattice sites within distance r of x.

$v_r = \#\mathcal{N}_r(x)$

Population dynamics



Before we explore IPS models, let's first think about ODE and PDE models of population dynamics.

Well-mixed populations: ODE's

Good model if pop sizes are large and everything is well mixed (e.g., chemostat). No spatial structure and randomness averages out.

- Ex) Single-species density: $x(t)$

$$\frac{dx}{dt} = rx\left(1 - \frac{x}{K}\right) \quad \text{(logistic growth)}$$

- $r =$ intrinsic growth rate; $K =$ carrying capacity
- $x(t) \to K$, as $t \to \infty$

- Multi-species densities: $x_i(t), i = 1, 2, \ldots, n$

$$\frac{dx_i}{dt} = x_i\left(r_i + \sum_j a_{ij}x_j\right) \quad \text{(Lotka-Volterra models)}$$

a_{ij}	a_{ji}	
$-$	$-$	$competitive$
$+$	$-$	$predator - prey$
$+$	$+$	$mutualistic$

Spatial dependence / local mixing: PDE's

- Intra- and inter-species interactions (as before)
- Fast $local\ movement$, but not global mixing

  (Ex: random motion of cells; diffusion of individuals in population)

... some spatial structure (smoothed out and nonrandom)

Single species example:

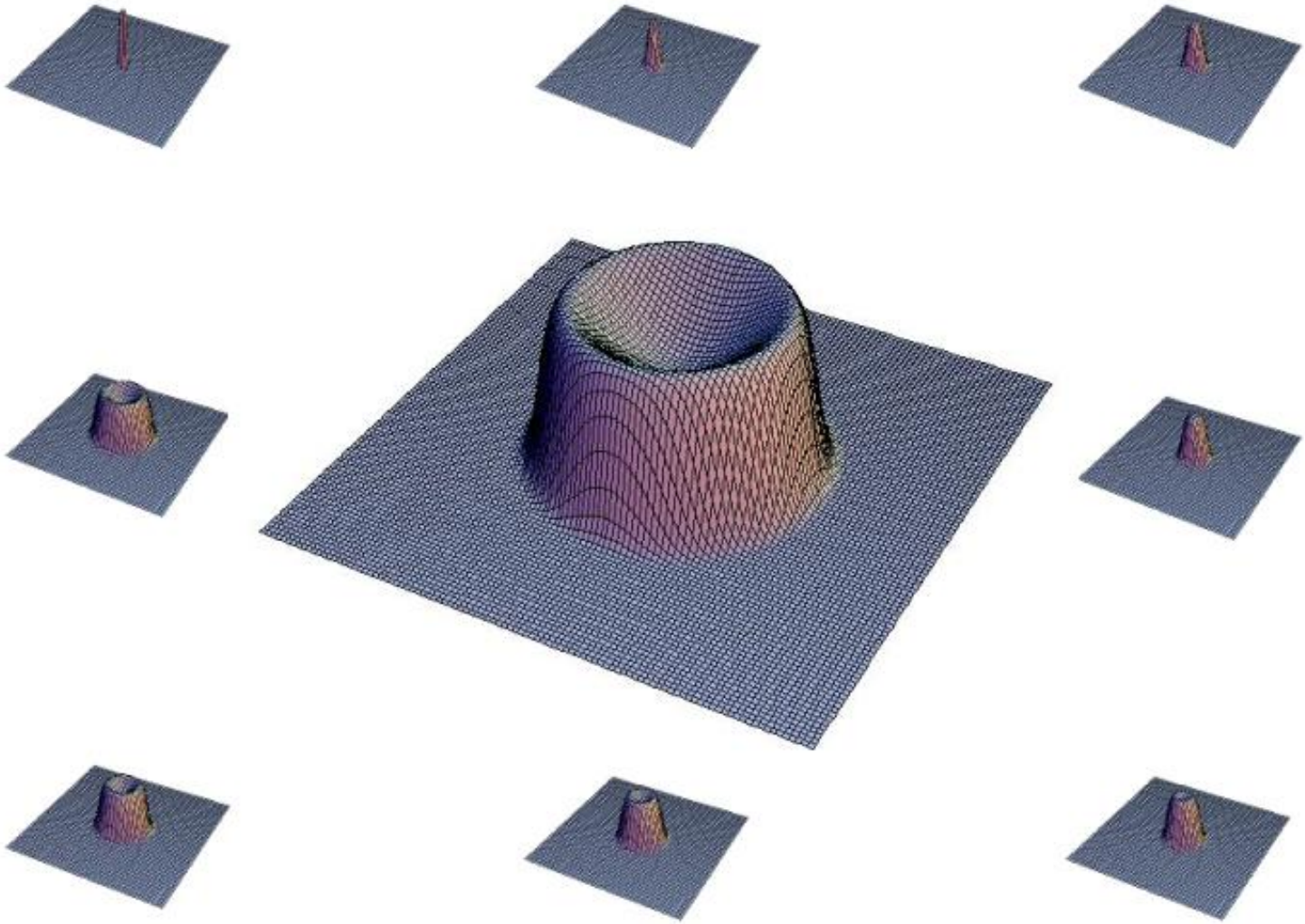
$u(x,t) =$ density at position x at time t

$$\frac{\partial u}{\partial t} = \Delta u + ru\left(1 - \frac{u}{K}\right) \quad \text{(diffusion + logistic growth)}$$

"Fisher's equation"

- spatial spread of advantageous allele
- traveling wave front

traveling wave



Back to particle systems

-Individual-based dynamics

-All interactions, dispersal, etc. are localized/discrete

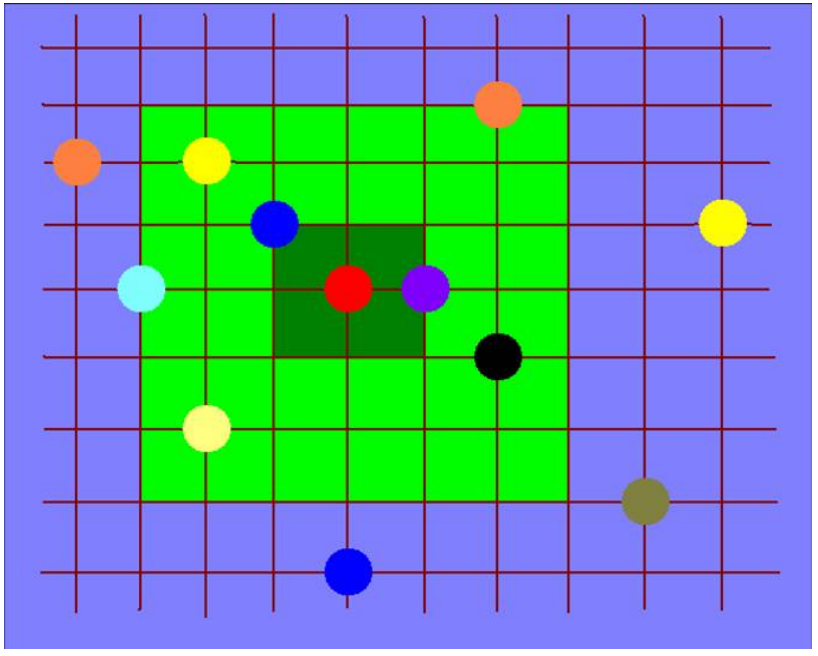
-Stochasticity not averaged out

Approximations:

- Mean-field ODE: infinite interaction range (all sites neighbors)
- Fast-stirring PDE: fast local stirring added to particle interactions

Particle flip dynamics

No particle motion. Sites change types via local interactions.



Ex. 1. Contact process

- 2 states: vacant $= 0$, occupied $= 1$
- $\xi_t(x) \in \{0,1\}$ . . . $\xi_t \in \{0,1\}^{\mathbb{Z}^d}$
- transition rates at site x:
  $0 \to 1$ . . . rate $\beta \cdot n_1(x)/v_r$

  $1 \to 0$ . . . rate δ
- $n_i(x)$ denotes number of type i in neighborhood of x
- Special case: no deaths $(\delta = 0) \Longrightarrow$ Richardson's growth model

* * * * simulation * * * *

Behavior of contact process

Critical value C (depending on dimension of lattice Z^d)

$\beta/\delta < C \Rightarrow$ process $dies$ (probability 1)

$\beta/\delta > C \Rightarrow$ process $survives$ (probability > 0)

$C \approx 1.649$ when $d = 1$; $\quad C \approx 1.412$ when $d = 2$

(Note: branching process has critical value 1.)

Comparison with mean-field behavior

- mean-field ODE when $\delta = 1$:

$$\begin{aligned} \frac{du}{dt} &= -u + \beta u(1-u) \\ &= (\beta - 1)u\left(1 - \frac{\beta}{\beta - 1}u\right) \end{aligned}$$

- logistic growth with $K = \frac{\beta - 1}{\beta} = 1 - \frac{1}{\beta}$
- positive equilibrium only when $\beta > 1$; suggests *critical growth rate* for contact process

Comparison with reaction-diffusion equation

- fast-stirring limit PDE when $\delta = 1$:

$$\frac{\partial u}{\partial t} = \Delta u + (\beta - 1)u\,(1 - \frac{\beta}{\beta - 1}u)$$

- Fisher's equation: traveling wave solutions
- Suggests *shape theorem* for contact process

Where does the RDE come from?

- Interacting Particle Systems. Stochastic with discrete space, continuous time; characterized by local interactions.
- Reaction-Diffusion Equations. Deterministic with continuous space, continuous time.
- A connection: hydrodynamic limits. RDE as scaling limit of IPS.
- Traveling wave speeds. Dependence on growth rate.

Generator for flip dynamics

Ex) The flip rates for Richardson's model (contact process with no deaths) can be expressed in a generator:

$$Gf(\xi) = \beta \sum_{\xi(x)=0} \frac{n_1(x,\xi)}{v_r} \big(f(\xi + \delta_x) - f(\xi)\big),$$

where δ_x is point mass at x.

Particle exchange dynamics

- Introduce local stirring. (Later combine with flip dynamics.)
- $p(x,y),\ x,y \in \mathbb{Z}^d$ . . . transition probability function that governs local stirring.
- Symmetric nearest-neighbor stirring: $p(x,y) = 1/2d$ for nearest neighbor x, y (otherwise 0).
- At rate $p(x,y)$, exchange the contents of sites x and y.
- Generator: $Lf(\xi) = \sum_{x,y} p(x,y)\big(f(\xi^{x,y}) - f(\xi)\big)$

Properties of exchange dynamics

- particle densities conserved
- Invariant measures given by product measures (independent sites) with constant density:

  $\nu_\alpha(\xi : \xi(x) = i) = \alpha_i,$

  $\alpha = (\alpha_1, \ldots, \alpha_K)$
- Scaled limits: scale down spatial scale (factor $1/N$) and speed up time (factor N^2). Let $N \to \infty$ to get diffusion (deterministic).

Hydrodynamic limits

View the particle systems on "squeezed lattice"

$$\mathbb{Z}_N^d = \{x/N : x \in \mathbb{Z}^d\}$$

with lattice spacing $1/N$. As $N \to \infty$, $\mathbb{Z}_N^d$ will become the continuum $\mathbb{R}^d$.

For particle flip dynamics on $\mathbb{Z}_N^d$, use neighborhoods

$$\mathcal{N}_N(x) = \{y \in \mathbb{Z}_N^d : 0 < \|y - x\| \leq r/N\}.$$

Number of neighbors of a site, $v_r^{(N)} = v_r$, is independent of N.

- Generator for flip dynamics: G_N
- Generator for exchange dynamics on $\mathbb{Z}_N^d$: L_N
- Combine flip dynamics with fast stirring: $\mathcal{L}_N = G_N + N^2 L_N$
- ξ_t^N . . . particle system on $\mathbb{Z}_N^d$ with generator $\mathcal{L}_N$
- empirical measure process: $\pi_t^N = N^{-d} \sum_{x \in \mathbb{Z}_N^d} \xi_t^N(x) \delta_x$ converges to solution $u(x,t)$ of RDE

- weak formulation: integrate against test functions $\phi \in C_c^\infty(\mathbb{R}^d)$ to get "density field"

$$\pi_t^N(\phi) = N^{-d} \sum_{x \in \mathbb{Z}_N^d} \xi_t^N(x)\phi(x)$$

- For multiple particle types, use

$$\pi_t^{N,i}(\phi) = N^{-d} \sum_{x \in \mathbb{Z}_N^d} \phi(x)\mathbf{1}(\xi_t^N(x) = i).$$

- $\pi_t^{N,i}(\phi) \to \int \phi(y)u_i(y,t)dy, \quad \text{as } N \to \infty$

Theorem. (Durrett-Neuhauser) Under symmetric nearest-neighbor stirring, the scaled process ξ_t^N with generator $\mathcal{L}_N$ and initial configuration distributed according to product measure with $\mathbb{P}(\xi_0^N(x) = i) = g_i(x)$, $i = 0, \ldots, K$, has hydrodynamic limit $\mathbf{u}(x,t) = (u_0(x,t), \ldots, u_K(x,t))$, where $u_i(x,t)$ is the bounded solution of

$$\begin{cases} \dfrac{\partial u_i}{\partial t} = \Delta u_i + f_i(\mathbf{u}), \\ u_i(x,0) = g_i(x). \end{cases} \tag{1}$$

The reaction term is given by

$$f_i(\mathbf{u}) = \sum_{j \neq i} \langle c_{ji}(0,\xi)\mathbf{1}(\xi(0) = j)\rangle_{\mathbf{u}} - \sum_{j \neq i} \langle c_{ij}(0,\xi)\mathbf{1}(\xi(0) = i)\rangle_{\mathbf{u}} \,.$$

Here, $\mathbf{u} = (u_0, \ldots, u_K)$ and $\langle \cdots \rangle_{\mathbf{u}}$ denotes expected value under product measure (i.e., independent sites) in which state j has density u_j.

Ex. Richardson's model with fast stirring

$$\frac{\partial u}{\partial t} = \Delta u + \beta u(1-u).$$

Fisher's equation . . . traveling wave behavior

How does this compare to traveling waves (shape theorem) for original particle system (Richardson's model)?

Traveling wave speeds and growth rates

- Fisher's equation (hydrodynamic limit of Richardson's growth model):

$$\frac{\partial u}{\partial t} = D\Delta u + \beta u(1-u).$$

$\Longrightarrow c_{\min} = 2\sqrt{\beta D}$ . . . square root dependence on β

- IPS (Richardson's growth model):

$\Longrightarrow c_{\min} \sim \beta$ . . . linear dependence on β

- Caution: RDE provides qualitative info about IPS, but parameters do not translate exactly.

Origin of square-root dependence in RDE

$$\frac{\partial u}{\partial t} = D\Delta u + \beta u(1-u)$$

$u(x,t) = U(x-ct)$. At wavefront, $u \approx 0$ so ignore u^2 term (linear approx.):

$$\frac{\partial u}{\partial t} = D\Delta u + \beta u$$

Linearity $\Longrightarrow U(z) \sim e^{-sz}$. Linear diff eqn yields:

$$c = \frac{\beta}{s} + Ds$$

$c_{\min} = \min_{s>0}\left(\frac{\beta}{s} + Ds\right)$. Min at $s = \sqrt{\frac{\beta}{D}}$ gives

$c_{\min} = 2\sqrt{\beta D}$.

Ex 2. Voter model

- 2 states: "against" $= 0$, "for" $= 1$
- $\xi_t(x) \in \{0, 1\}$
- transition rates at site x:

  $0 \to 1$ . . . rate $\beta \cdot n_1(x)$

  $1 \to 0$ . . . rate $\beta \cdot n_0(x)$

Voter models used to model "peer pressure," "competition" and "population genetics."

* * * * simulation * * * *

"biased" and "threshold" voter models

- Biased voter model:

  -one type has (selective) advantage: $\beta_1 > \beta_0$ . . . "species 1 wins"

- Threshold voter model:

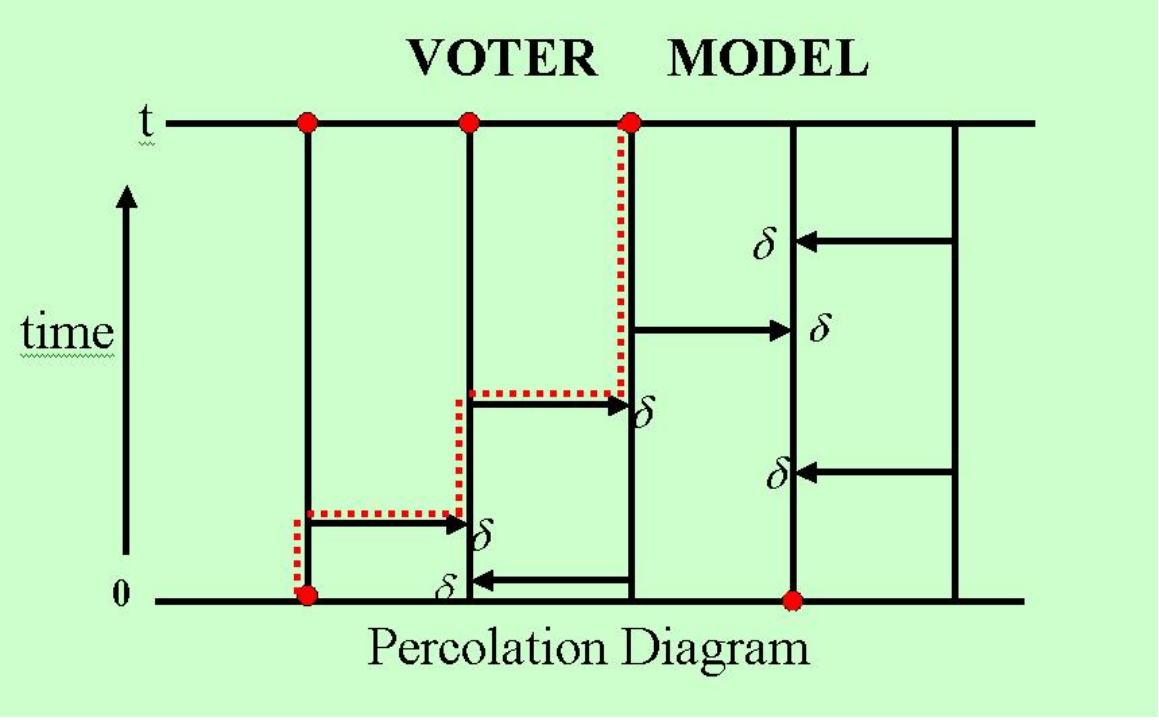
  -only make change if there are at least T neighbors of the opposite type

  -enhances clustering

  -good model for random environments with varying degrees of clustering

  * * * * simulation * * * *

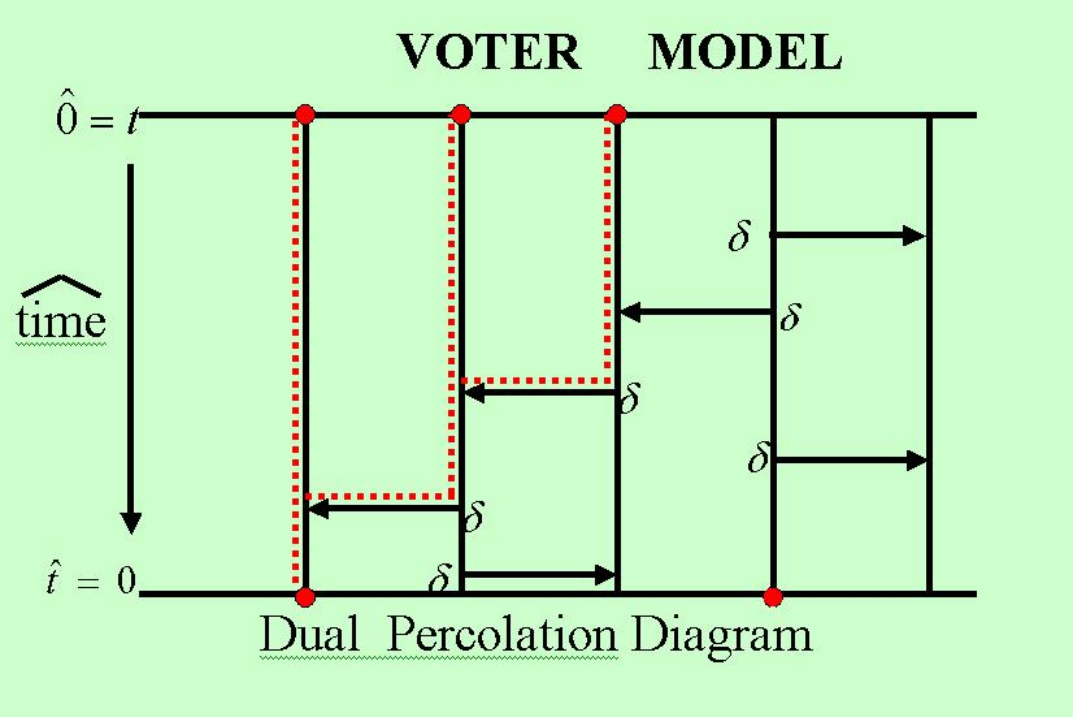
Percolation diagram for voter model



Forward time

Construct voter model by randomly placing possible events along each time line according to the prescribed rates.

Dual percolation diagram



Backward time / reverse direction of arrows.

Ancestry: coalescing random walk. Voter model clusters in $d = 1, 2$; stays well mixed in $d \geq 3$

Ex 3: Spatial epidemic model

- 3 states: Susceptible = S, Infective = I, Removed = R
- $\xi_t(x) \in \{S, I, R\}$
- transition rates at site x:
  $S \to I$ . . . rate $\beta \cdot n_{_I}(x)$
  $I \to R$ . . . rate δ
  $R \to S$ . . . rate γ (if added, get SIRS model)

If infection spreads fast enough relative to death rate, then epidemic spreads.

* * * * simulation * * * *

Comparison with mean-field behavior

- mean-field ODE for SIR ($\gamma = 0$):

$$\begin{aligned} \frac{dS}{dt} &= -\beta SI \\ \frac{dI}{dt} &= \beta SI - \delta I \end{aligned}$$

- equilibrium $S = \frac{\delta}{\beta}$
- Need $\beta > \delta$ for epidemic spread (i.e., $R_0 = \frac{\beta}{\delta} > 1$)

Ex 4: Spatial epidemic model with mutation

- 4 states: Susceptible = S, wild-type Infective = I_1, mutant Infective = I_2, Removed = R
- $\xi_t(x) \in \{S, I_1, I_2, R\}$
- transition rates at site x:
  $S \to I_1$ . . . rate $\beta_1 \cdot n_{I_1}(x)$
  $S \to I_2$ . . . rate $\beta_2 \cdot n_{I_2}(x)$
  $I_j \to R$ . . . rate $\delta_j,\ j = 1, 2$
- What determines a successful mutant strategy?

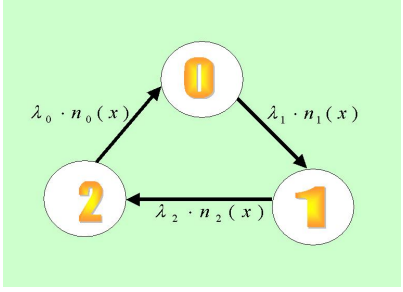
* * * * simulation * * * *

Comparison with mean-field behavior

- mean-field ODE suggests pathogen with largest $\frac{\beta_i}{\delta_i}$ will win.
- With spatial structure, $\beta_i^3 \cdot \frac{\beta_i}{\delta_i}$ is the critical ratio.
- Spatial structure matters!

Ex 5. Rock-Scissors-Paper

- 3 states: representing 3 species "nontransitive predator-prey cycle"
- $\xi_t(x) \in \{0, 1, 2\}$



- transition rates at site x:

  $0 \longrightarrow 1$ . . . rate $\lambda_1 \cdot n_1(x)$

  $1 \longrightarrow 2$ . . . rate $\lambda_2 \cdot n_2(x)$

  $2 \longrightarrow 0$ . . . rate $\lambda_0 \cdot n_0(x)$

all contact interactions

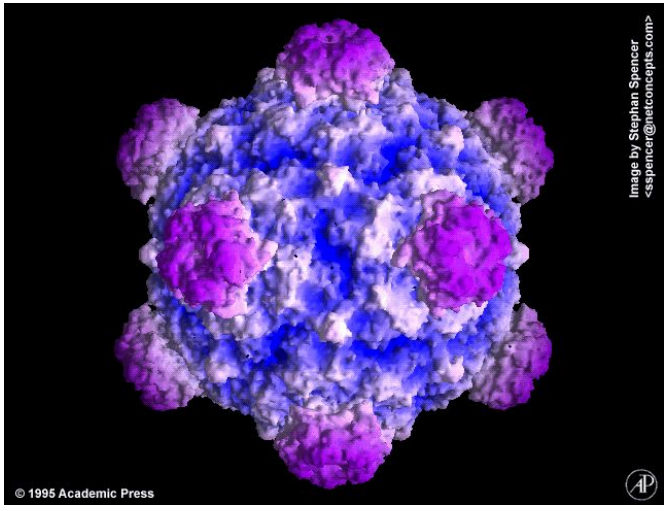
* * * * simulation * * * *

- mean-field ODE:

$$\begin{aligned}
\frac{du_0}{dt} &= \lambda_0 u_2 u_0 - \lambda_1 u_0 u_1 \\
\frac{du_1}{dt} &= \lambda_1 u_0 u_1 - \lambda_2 u_1 u_2 \\
\frac{du_2}{dt} &= \lambda_2 u_1 u_2 - \lambda_0 u_2 u_0
\end{aligned}$$

- Can turn to two equations since $u_0 = 1 - u_1 - u_2$.
- ODE behavior: no coexistence
- Particle system behavior: *coexistence*! Space matters.

Ex 6. Virus-host interactions

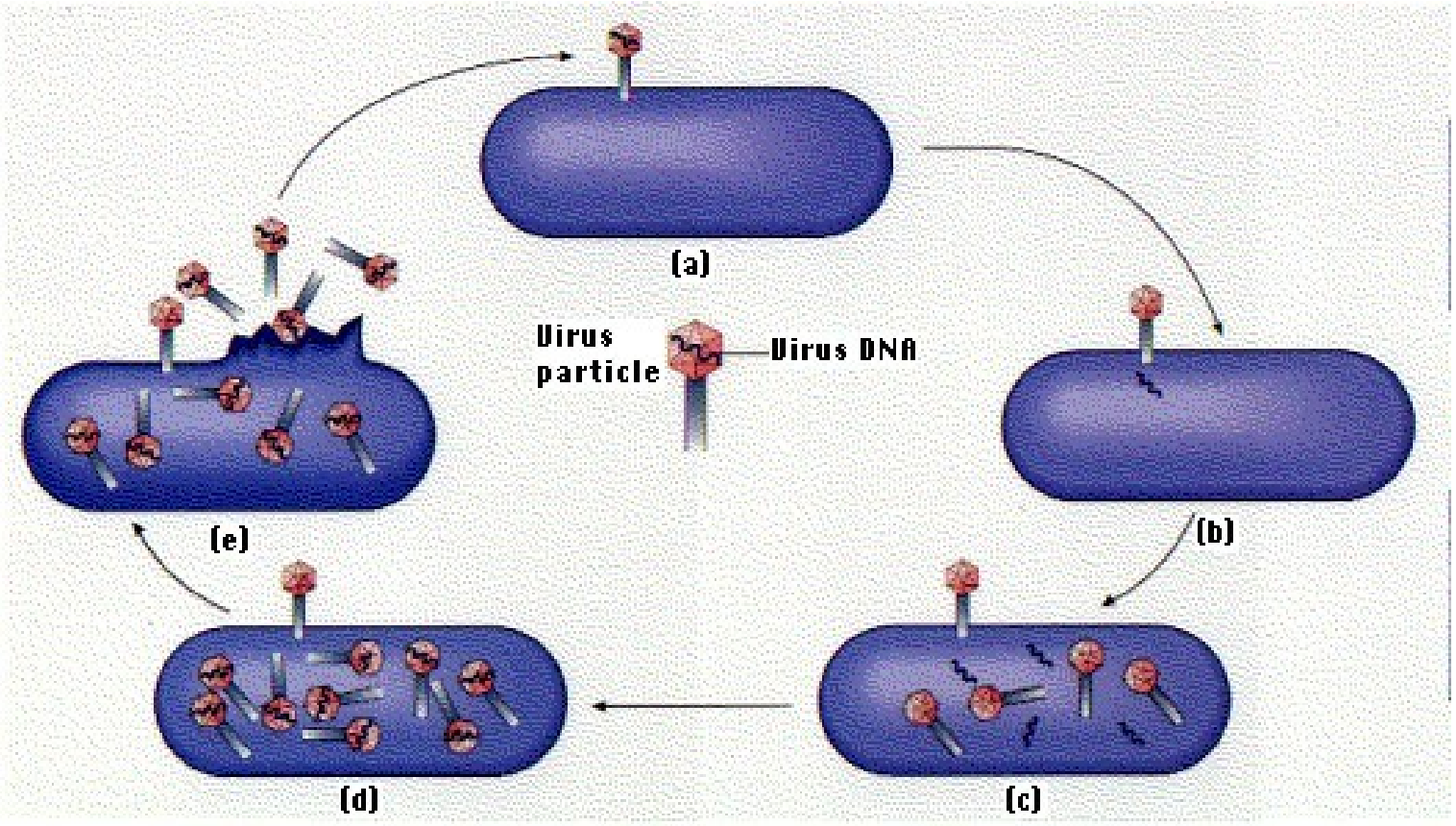


ssDNA viruses ("phage")

infect bacterial cells (host)

role of spatial structure and host quality in coexistence of competing phages

Phage life cycle



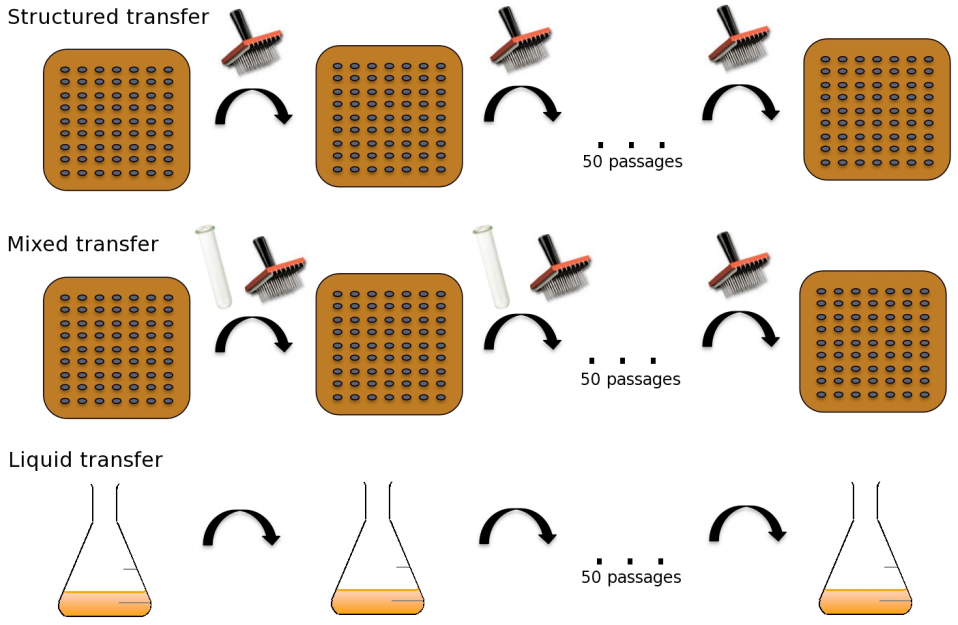
attachment to bacterial host cell $\longrightarrow$ injection of phage DNA $\longrightarrow$ reproduction of phage DNA $\longrightarrow$ packaging and assembly of phage progeny $\longrightarrow$ cell lysis and release of phage to environment $\longrightarrow$ ...

Phage competition and evolution on plates

Experimental System:

- ϕX174 and α3 . . . competing lytic phages infecting host *E. coli* C on agar plates.
- ϕX dominates in spatial setting
- burst size vs. latent period
- after "incubation period" (5h or 18h), host cells killed and some of phage are transferred to fresh hosts using a replicate picker ("bed of nails")
- effects of spatial structure, different passage times, host evolution, phage evolution

Passaging in experiments



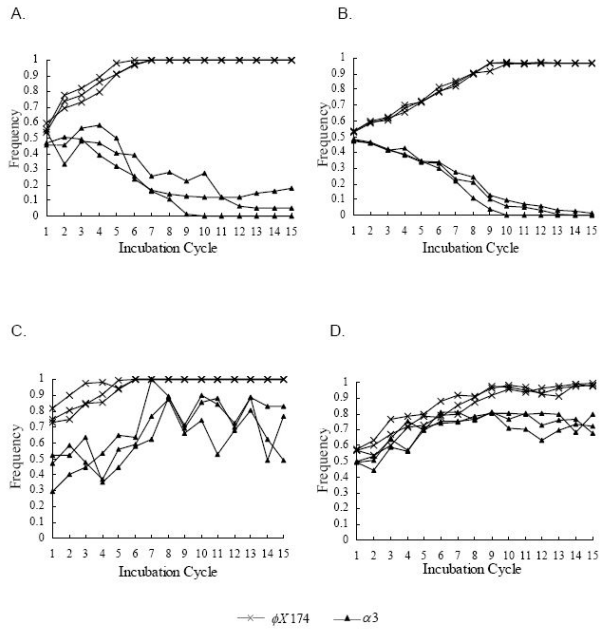
2 phage (viral pathogens), 1 host (but host can develop resistance)

different levels of spatial structure

2 different incubation times (short and long)

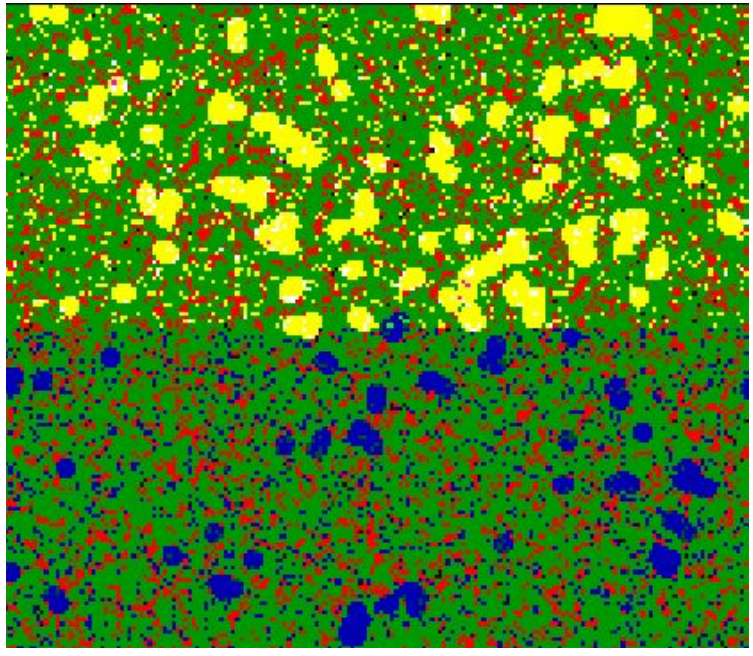
Structured transfer results

1st row: short incubation (Expt – Sim)
2nd row: long incubation (Expt – Sim)



Surprising experimental result: If incubation time is long enough, weak competitor is able to coexist with dominant competitor! Only happens when spatial structure maintained. Host quality important.

Start of first passage



yellow = ϕX, blue = α3, green = nutrient, red = host cells

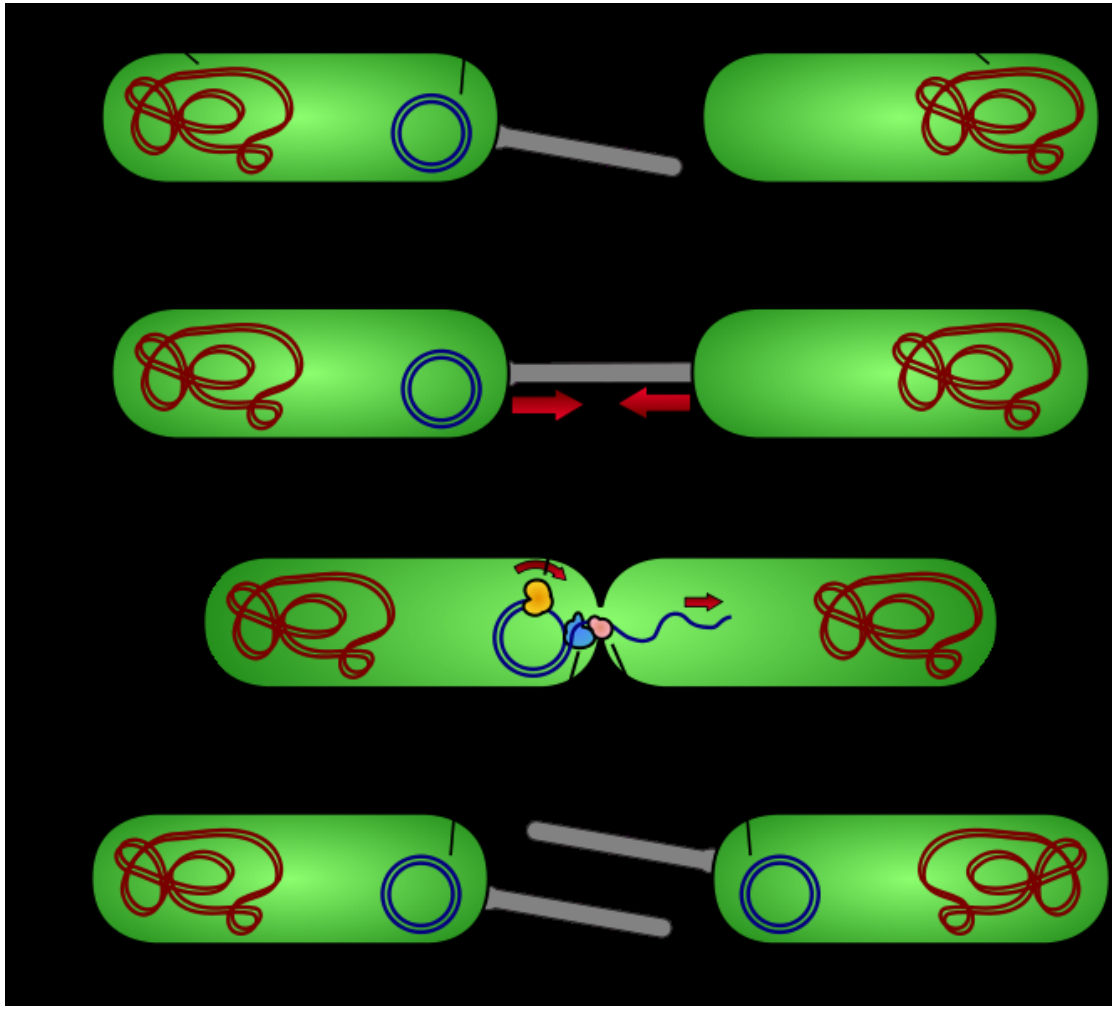
Key idea: Resistant (to dominant phage) host cells arise regularly. Given enough time to spread, they provide advantageous environment for weak phage inside "enemy territory." * * * * simulation * * * *

Ex 7. Antibiotic resistance and plasmids

Plasmids: circular, extra-chromosomal genetic elements common in bacteria

- rapid spread of multi-drug resistance in bacteria
- horizontal gene transfer

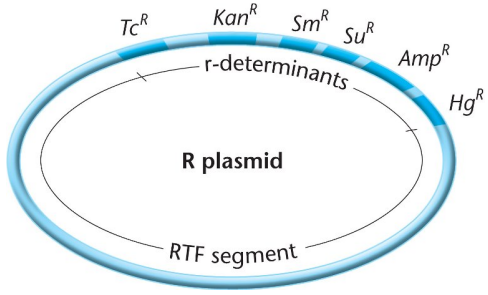
Plasmids



plasmid transfer from donor to recipient cell . . . Donor, Recipient, Transconjugant

Plasmid features

- Horizontal Gene Transfer (bacterial sex)
- rapid non-chromosomal spread of genes for simultaneous resistance to multiple antibiotics

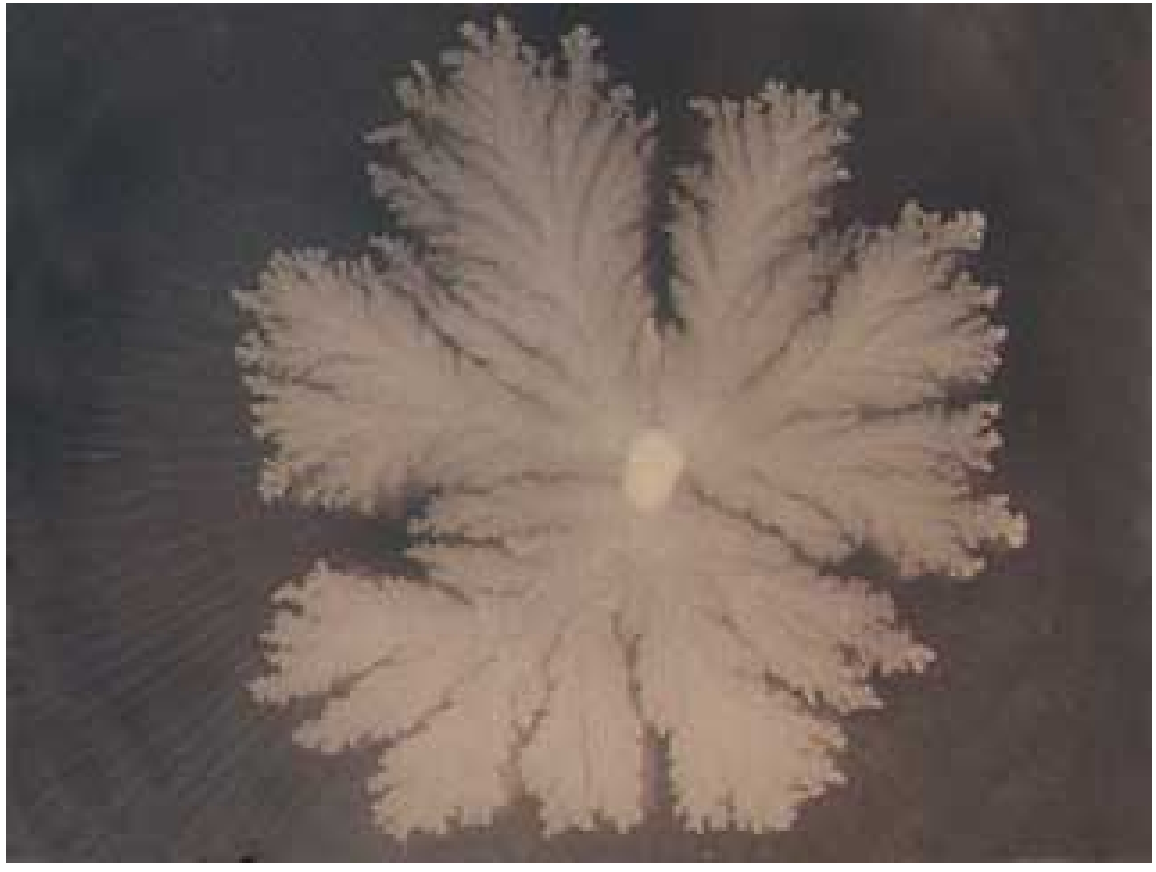


* accumulation of resistance genes (antibiotics, heavy metals, ...)

* co-selection (crisis of AB resistance getting out of hand)

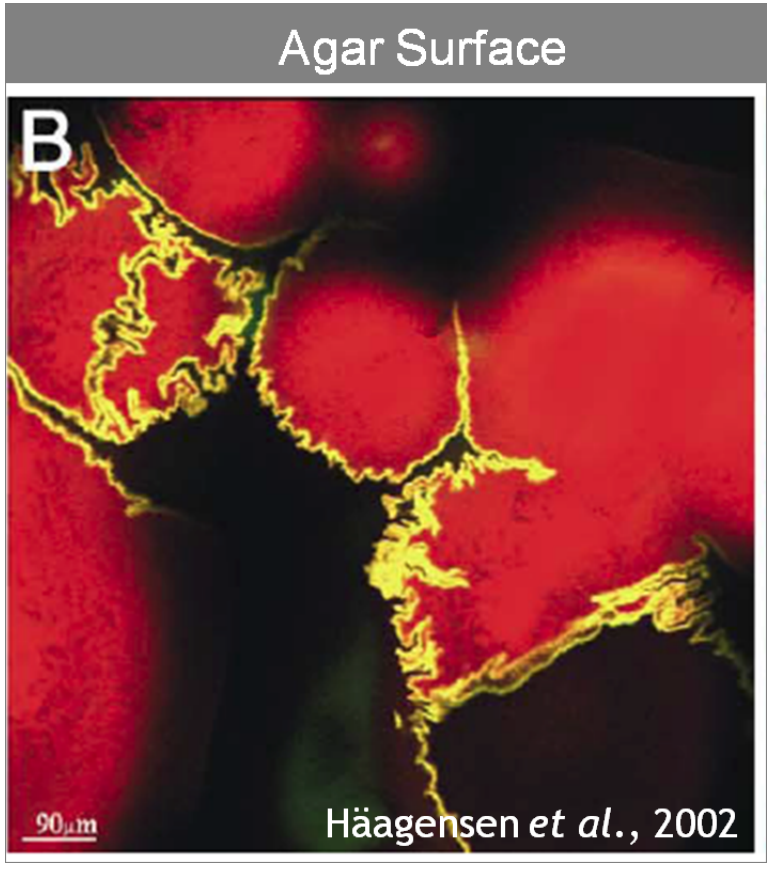
- contact required for plasmid transfer
  - liquid: diffusion + attachment/detachment dynamics (mating aggregates)
  - spatial: attachment more stable $\Longrightarrow$ rapid transfer possible in certain spatial configurations; otherwise, wait for contact at "interfaces"
  - different dynamics (e.g., density dependence)
    *** IPS Simulation ***

Spatial heterogeneity in bacterial colonies



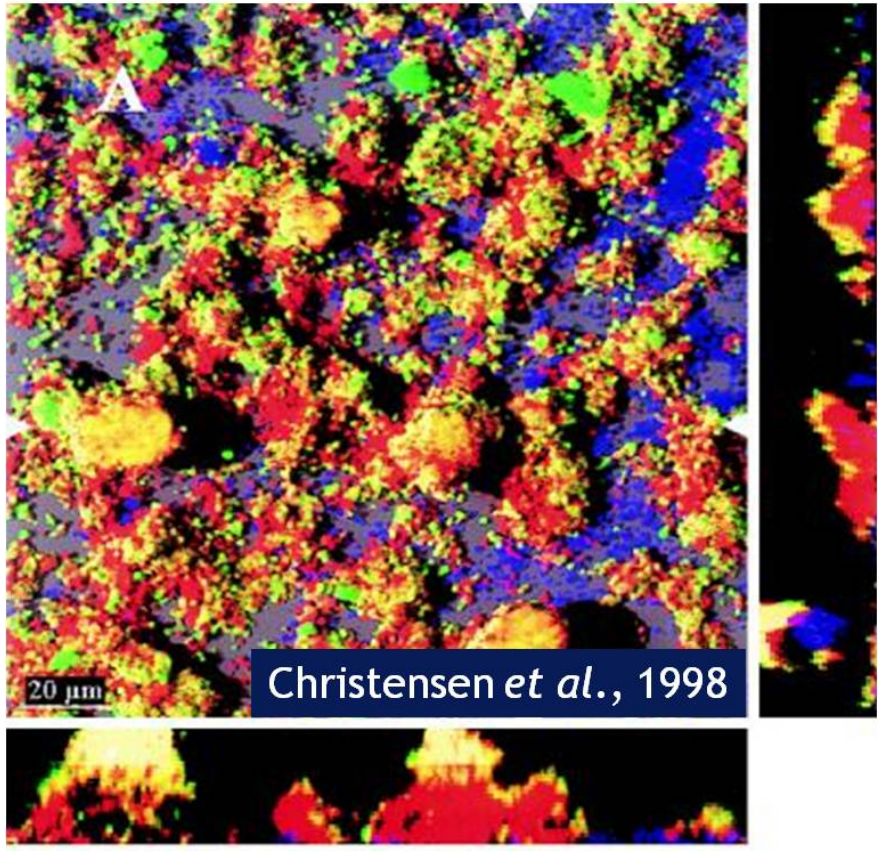
Fractal-like; peaks and valleys due to differential nutrient consumption/access

Limited plasmid transfer on agar plates



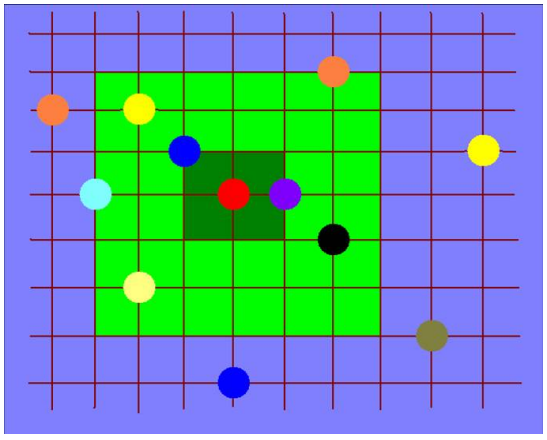
No infectious wave of transfer!

Limited plasmid transfer in biofilms



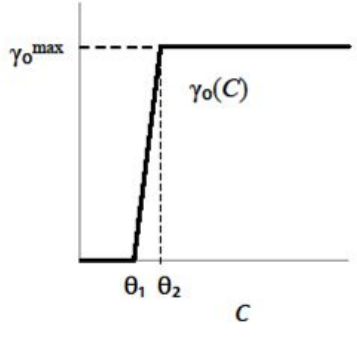
Very little plasmid transfer inside biofilm.

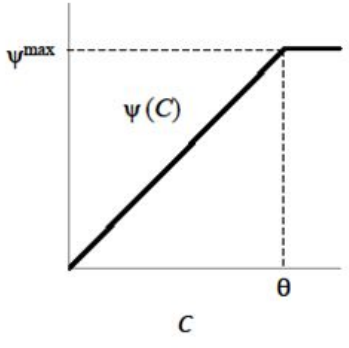
2D model features



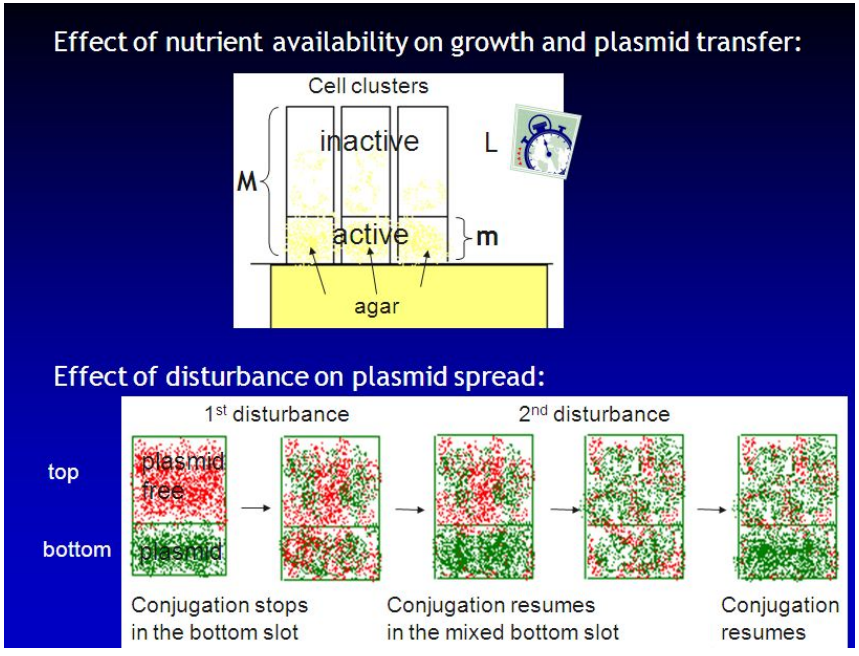
*interaction ranges for growth, death, plasmid transfer, nutrient diffusion, antibiotic diffusion ...

*nutrient-dependent plasmid transfer and growth rates





adding some 3D structure



Over 2D lattice, add several layers: M cells per site allowed with m_1 in 1st layer, m_2 in 2nd layer, ...

Each layer has its own nutrient-dependent growth rates

Growth in lower layers can push up into next layer

"coupled map lattice" with coupling parameter for amount of interaction/spread between neighboring sites

local rates

p_g ... coupling parameter for growth (prob that offspring is sent to neighboring site)

p_c ... coupling parameter for plasmid transfer

$n^w_{R,i}$ ... number of R's within focal site at level i

$n^{nbr}_{R,i}$ ... number of R's at 8 neighboring sites at level i

$f^w_V = (M - n^w_R - n^w_D - n^w_T)/M$ ... fraction of vacant "space" at focal site

$f^{nbr}_V = (8M - n^{nbr}_R - n^{nbr}_D - n^{nbr}_T)/8M$ ... fraction of vacant "space" at neighboring sites

rate at which focal site produces new R:

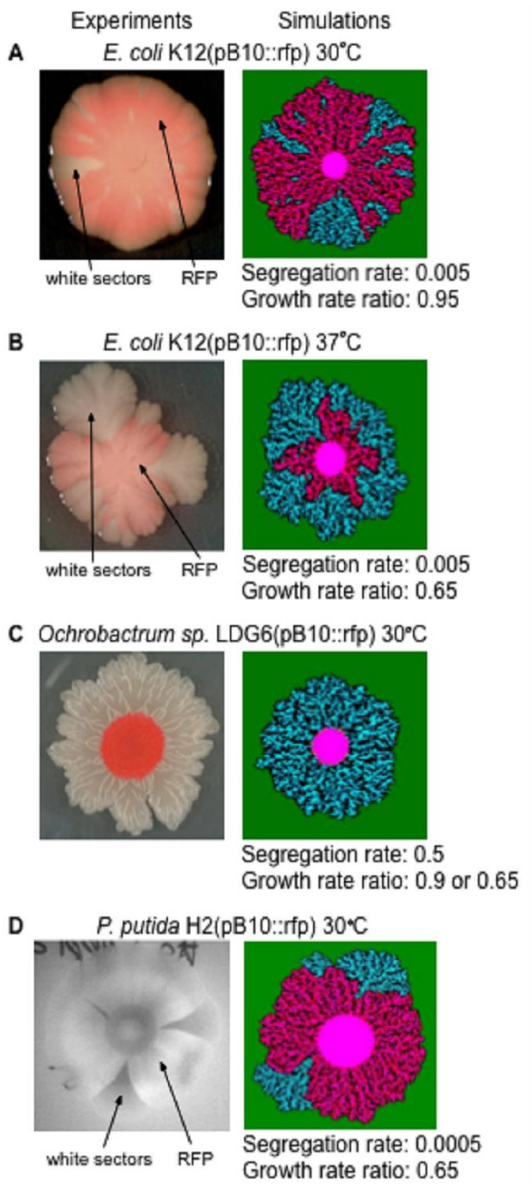
$$\psi_R[(1-p_g)f_V^w + p_g f_V^{nbr}]\ n_R^w$$

rate of production of new T's by focal site:

$$\psi_T[(1-p_g)f_V^w + p_g f_V^{nbr}]\ n_T^w$$

$$+(\gamma_T n_T^w + \gamma_D n_D^w)[(1-p_c)f_R^w + p_c f_R^{nbr}]$$

plasmid-free sectors



IPS model used to predict/explain

- factors influencing plasmid invasion (when initially rare)
- segregation and clonal sectors
- lack of invasive waves of plasmid transfer
- density dependent plasmid transfer that is only present in spatial cultures