Adaptive Evolution and Spatial Structure

(And now for something completely different)

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Microbial Experimental Evolution & Mathematical Modeling

- Evolution and ecology of microbial pathogens

1. Evolutionary and ecological dynamics often on similar time scales (and fast)
    - evolution of pathogens during course of epidemic or within host: influenza, HIV, antibiotic resistance, . . .
    - experimental evolution possible
    - Phage–Bacteria system & Interacting Particle System model

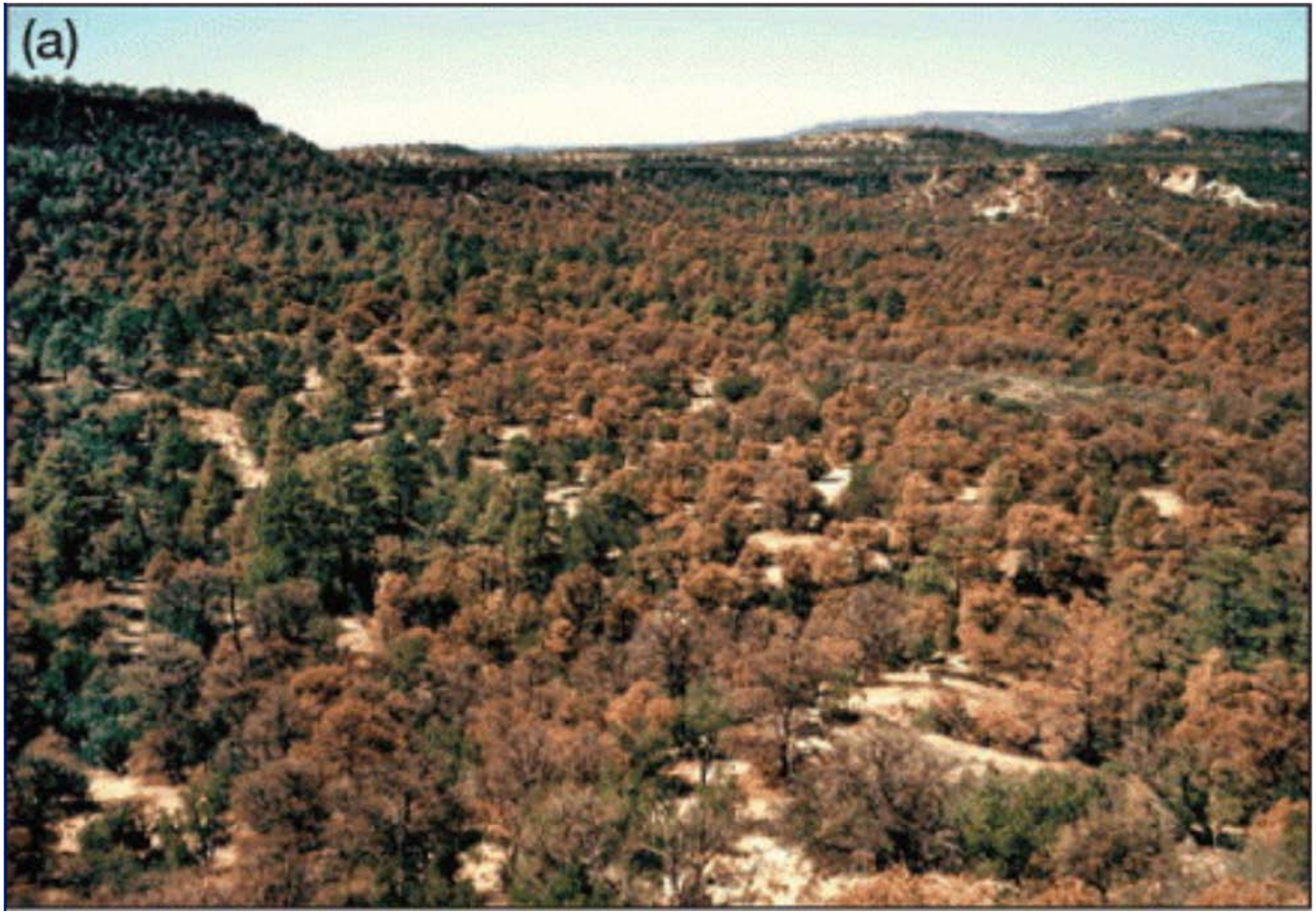
2. Huge population sizes, high variability, strong selection

3. Most microbial communities grow in spatially structured environments (biofilms, soils, surfaces).

4. These communities evolve in the presence of (often dramatic) changes in environmental conditions–biotic and abiotic.

5. Environmental changes can alter selective pressure and lead to spatial bottlenecks.

Spatial bottleneck

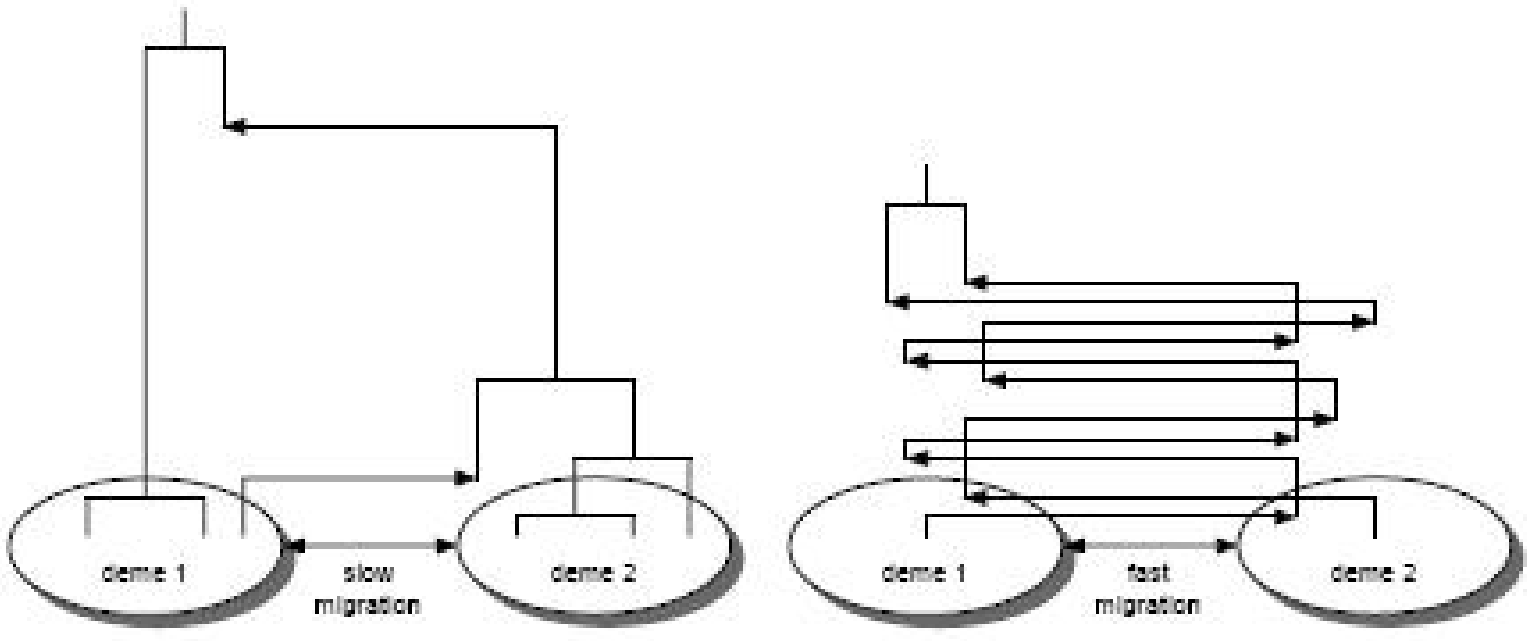


Drought-induced pine tree die-off; New Mexico, 2002.

Main Questions

- How does spatial structure influence phenotypic changes during adaptive evolution to changing environmental conditions?
- Are the genetic trajectories during adaptation fundamentally different in a spatial setting?

Structured coalescent



Migration (mixing) affects patterns of polymorphism

Pairwise coalescence time

- $D =$ number of demes; N individuals per deme
- $M =$ migration rate out of (= into) a deme
- $\mathsf{E}(T_w) = 1$ ... in units of total pop size (ND)
- $\mathsf{E}(T_b) = 1 + \frac{D-1}{MD}$
- $\mathsf{Var}(T_w) = 1 + 2\frac{(D-1)^2}{MD^2}$
- $\mathsf{Var}(T_b) = 1 + \frac{(D-1)^2}{D^2}\left[\frac{2}{M} + \frac{1}{M^2}\right]$

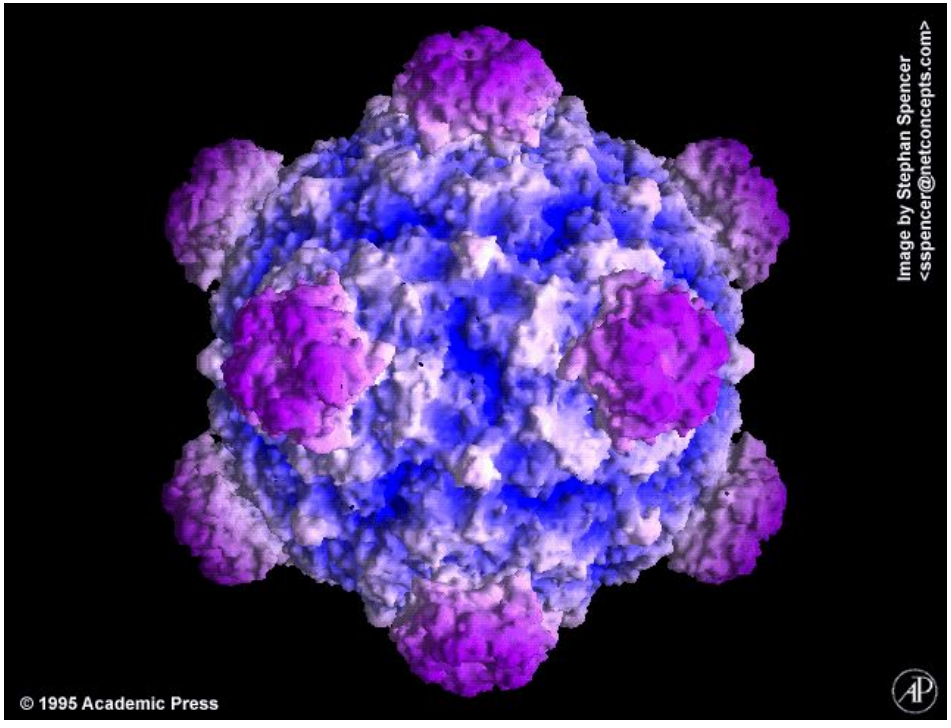
mean and variance T_{MRCA}

M	∞	10	1	0.1	0.01
E(T_w)	1	1	1	1	1
E(T_b)	1	1.08	1.75	8.5	76
Var(T_w)	1	1.11	2.13	12.3	114
Var(T_b)	1	1.12	2.69	68.5	5740

as function of migration rate M (for sample of size 2, and D=4 demes)

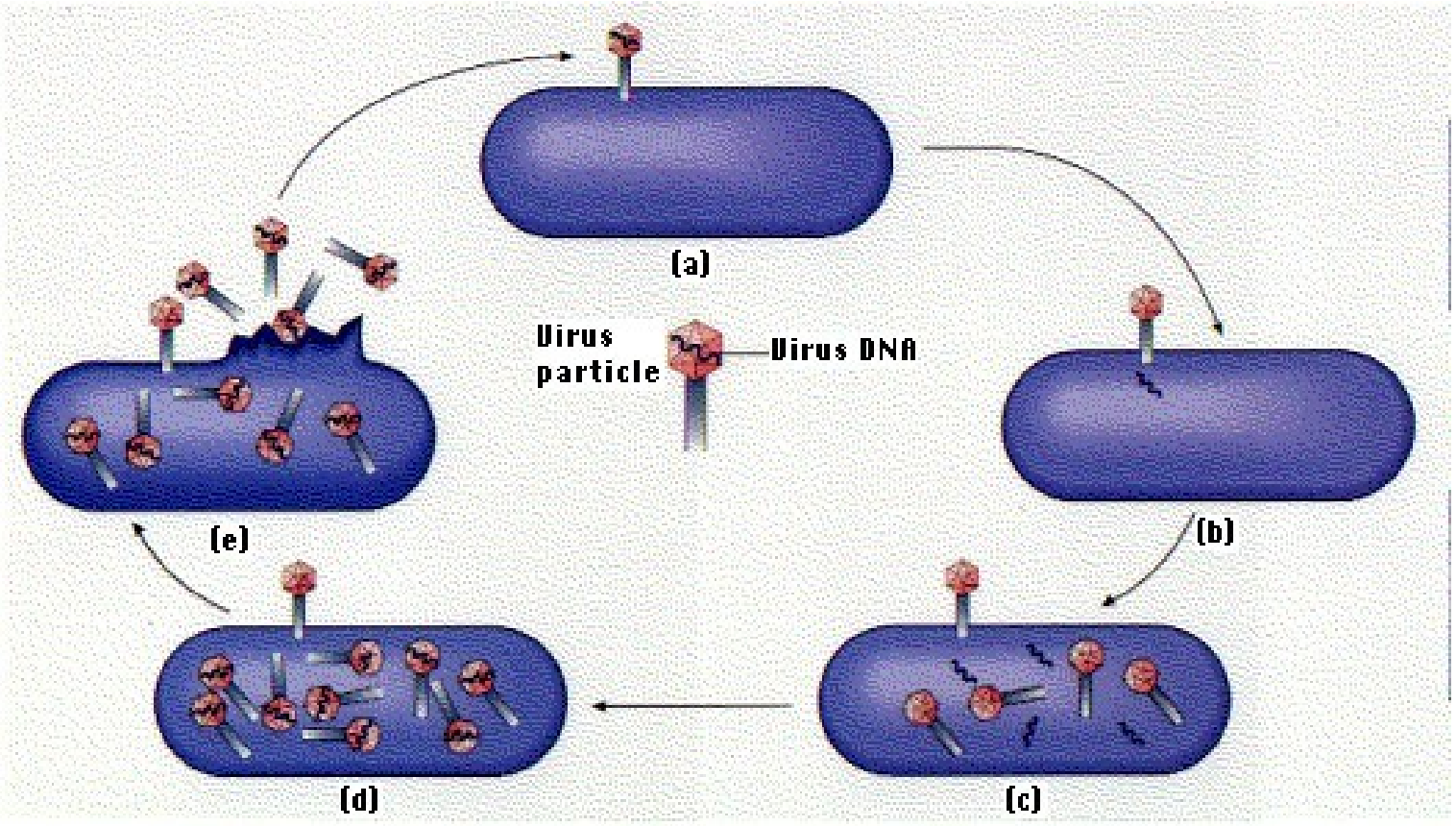
Example from Hein, Schierup, and Wiuf 2005.

Microvirid Phages (ID11, ϕX174 and α3)



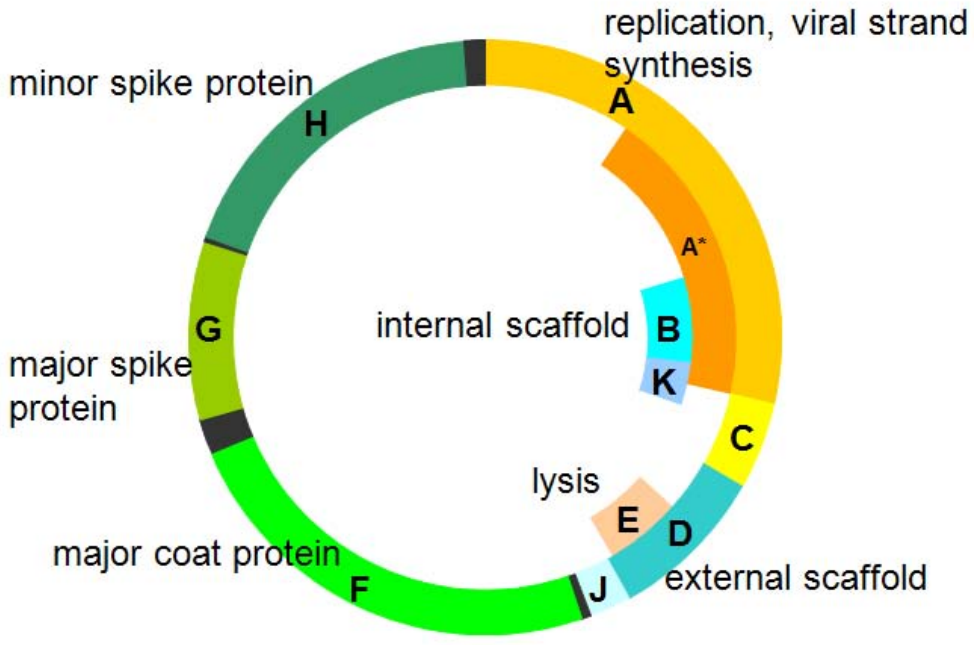
ssDNA viruses (infect bacterial cells), 5-6 kb circular genomes, 11 genes (overlapping)

Phage life cycle

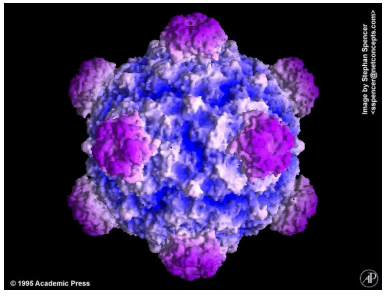


attachment to bacterial host cell $\longrightarrow$ injection of phage DNA $\longrightarrow$ reproduction of phage DNA $\longrightarrow$ packaging and assembly of phage progeny $\longrightarrow$ cell lysis and release of phage to environment $\longrightarrow$ ...

Genetic map



Genetic map of bacteriophage ID11 indicating protein function and overlapping genes.

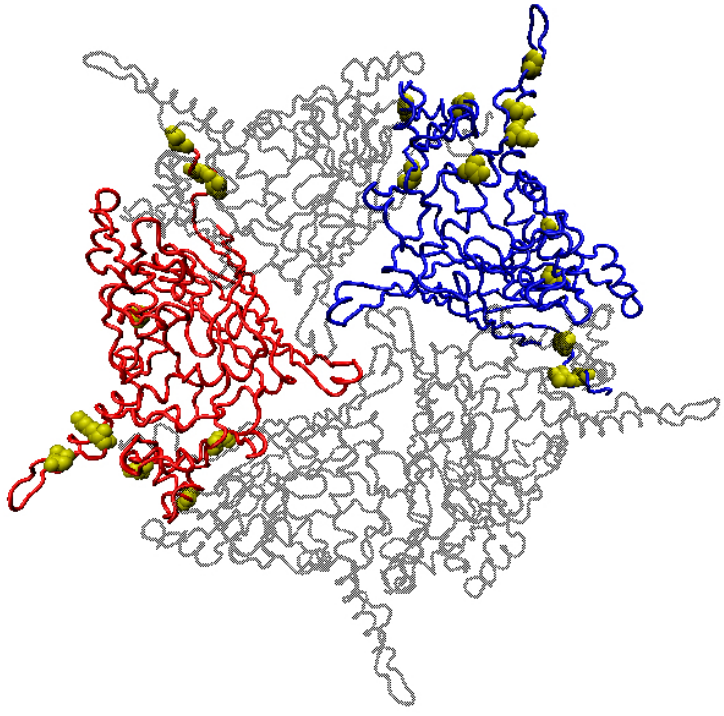


Liquid adaptation to high temperature

Genome Position	substitution	Amino Acid Position	Amino Acid Substitution	Fitness ($\log^2$ increase in pfu per h)
2534	G→T	J20	V→L	14.61
3665	C→T	F355	P→S	20.31
3850	G→A/T	F416	M→I	20.05
2520	C→T	J15	A→V	19.45
3543	C→T	F314	A→V	19.13
3857	A→T	F419	T→A	19.04
2609	G→T	F3	V→F	17.56
3567	A→G	F322	N→S	16.74
3864	A→G	F421	D→G	16.22

Rokyta et al. (2005). Many possible first-step mutations in ID11. Single-step adaptive changes to high temperature (37^{o}C) in liquid; observed 9 large-effect mutations in 20 independent lines.

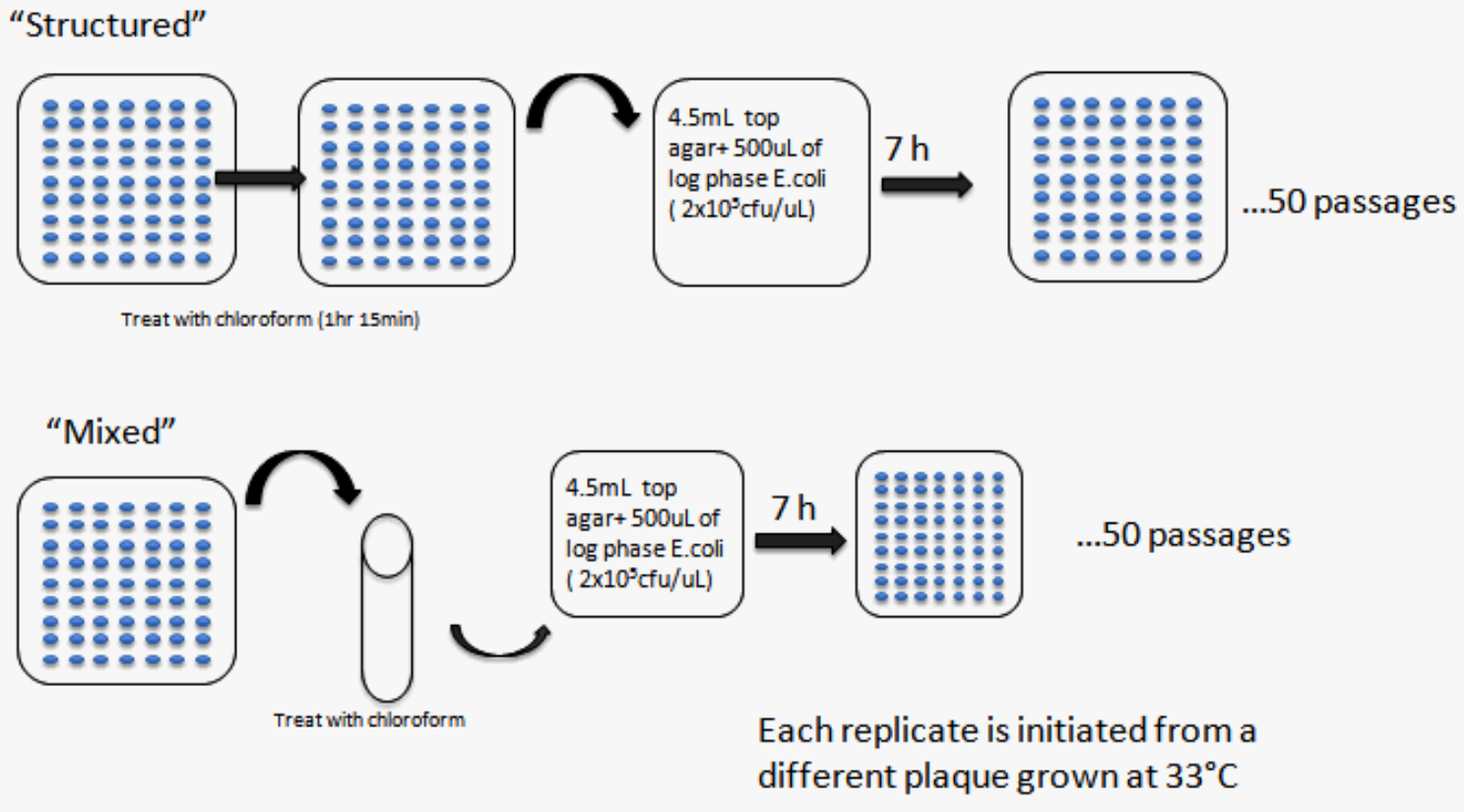
structure



One pentameric unit of ID11, made up of 5 copies of protein F. Capsid formed from 12 pentameric units. Yellow indicates 1st step adaptive mutations to temperature increase (37C, red) and gain of function (43C, blue); occur at interface.

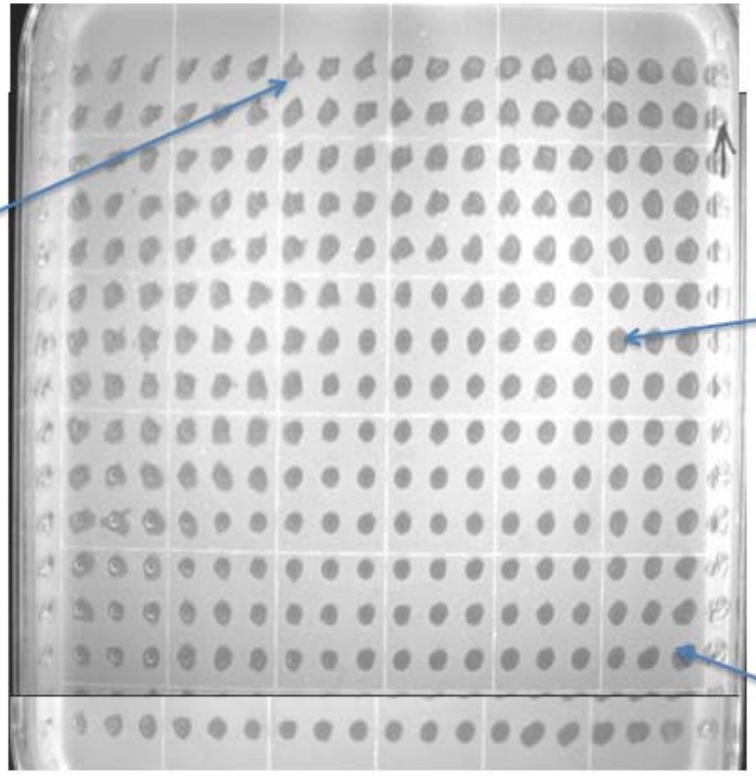
Passaging in spatial experiments

We will passage 3 replicates at two different levels of structure at three temperatures (17°, 33°, 40°).



Localized adaptation

Spatial structure is expected to increase the genetic variation

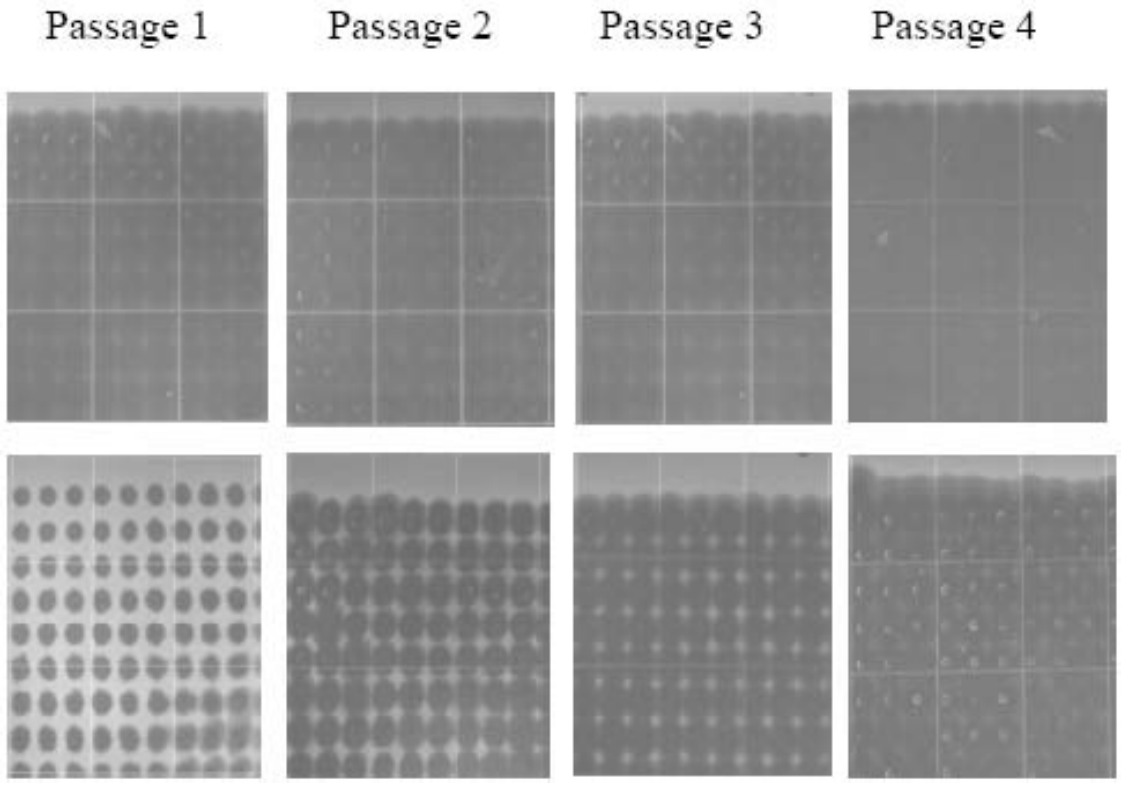


Spatial structure creates smaller population sizes – drift. Big benefit mutations will occur more rarely.

A mutation in this location is unlikely to face immediate competition from mutations at a great distance.

Delayed competition might mean smaller mutations can arise and persist.

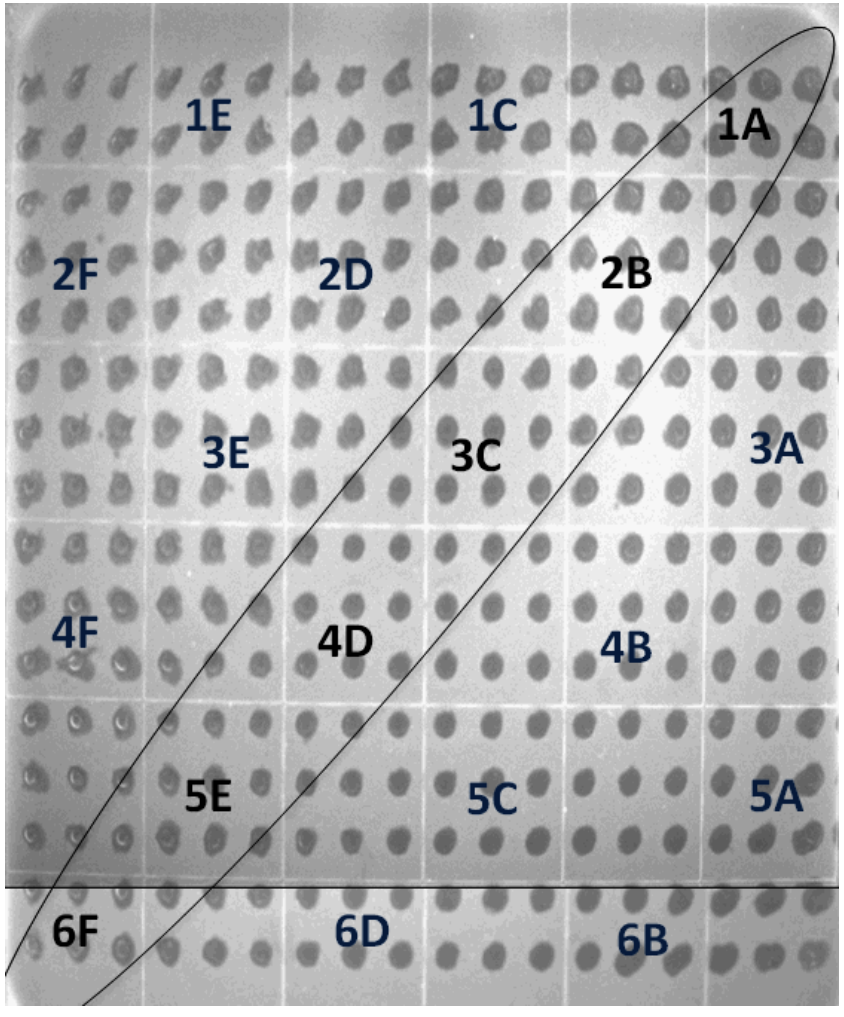
Initial phase of adaptation



Top: 33C (optimal) . . . phage easily clear plate

Bottom: 40C (stressed) . . . adaptation to high temperature evident in plaque morphology

Sampling grid and evolution of plaques



Interacting Particle System models

- Explicitly model
    1. discrete spatial structure: $\mathbb{Z}^2$
    2. Each site can be in several different states (vacant, uninfected host cells, free virus, infected cells)
    3. randomness & spatial structure down to individual cell level
    4. life history parameters (VIRUS: burst size, latent period, timing of lysis, attachment rate; BACTERIA: growth rate)
    5. coinfection dynamics & recombination (high MOI conditions on plate)

IPS Simulations: phage competition

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Spatially explicit pathogen evolution

Q. Can we predict the types of mutants likely to arise and spread in a pathogen population?

Mass-action ODE (well mixed):

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

Invasion by second pathogen (evolution of virulence):

$\beta_i =$ infection rate for I_i (host infected with pathogen i)

$\delta_i =$ death rate (virulence) for I_i

Who wins?

- Success determined by basic reproductive ratio:

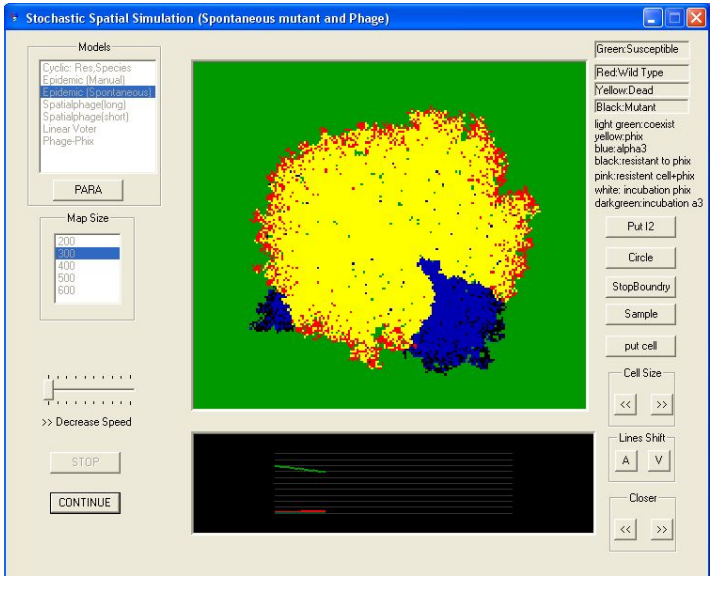
$$R_0 = \frac{\beta S}{\delta}$$

- Both pathogens encounter the same density of susceptible hosts in well-mixed (liquid) culture, so
- $\frac{\beta_2}{\delta_2} > \frac{\beta_1}{\delta_1}$ implies I_2 wins (independent of initial densities)
- . . . ignoring co-infection and within-host competition

IPS Simulations: spatial SIR model with spontaneous mutations

With small probability, individual pathogens mutate

Only mutants near edge have a chance to become established



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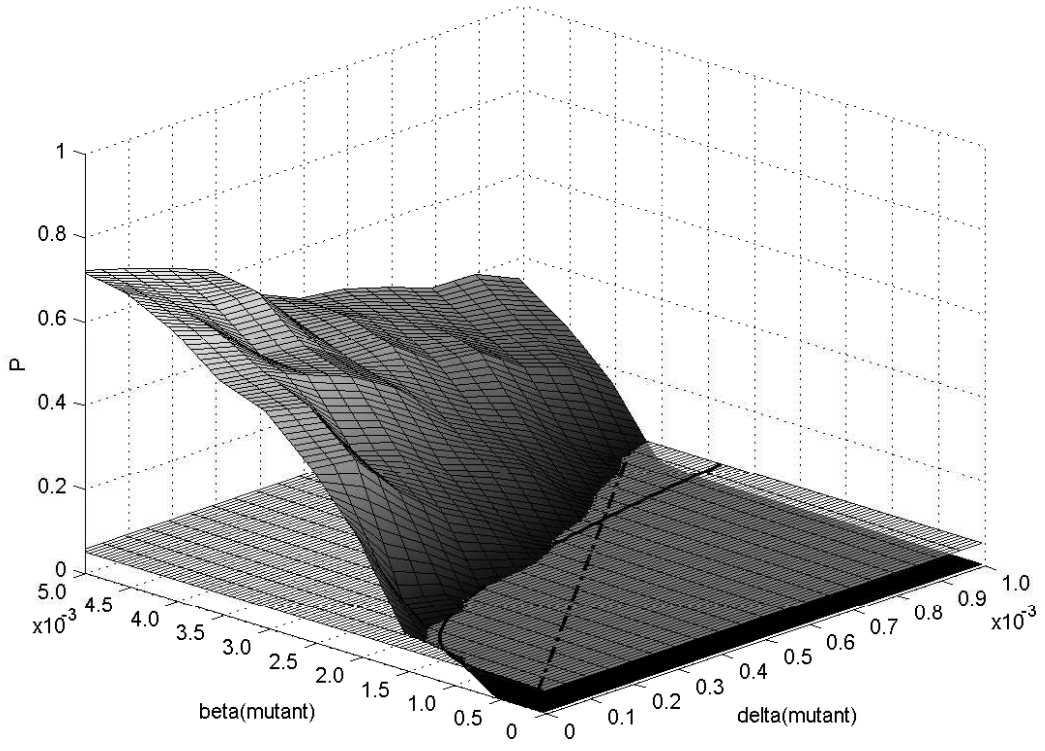
Mutant invasion probability



(with $\delta_1 = 0.0002$, $\beta_1 = 0.002$ held constant)

Invasion condition: $\frac{\beta_2}{\delta_2} \cdot \beta_2^3 > \frac{\beta_1}{\delta_1} \cdot \beta_1^3$ and

$\frac{\beta_2}{\delta_2} > 3.5$. Different rules govern competition/evolution in spatial setting.

Time to first invasion

Constant wave speed $\Rightarrow$ I_2 mutants arise at rate $M(t) = \mu 2\pi c t$ at time t. P(mutant invades)$= p$, $\quad I_2$ invasion rate . . . $pM(t)$.

Cumulative invasion intensity in time interval $[0, t]$:

$$\int_0^t pM(s)\, ds = p\mu\pi c\, t^2.$$

$$P(T > t) = \exp(-p\mu\pi c t^2).$$

Expected time for the first successful invasion by I_2 mutant:

$$E(T) = \int_0^\infty P(T > t)\, dt = \frac{1}{2\sqrt{p\mu c}}.$$

Estimation of relative invasion probabilities from macroscopic observables:

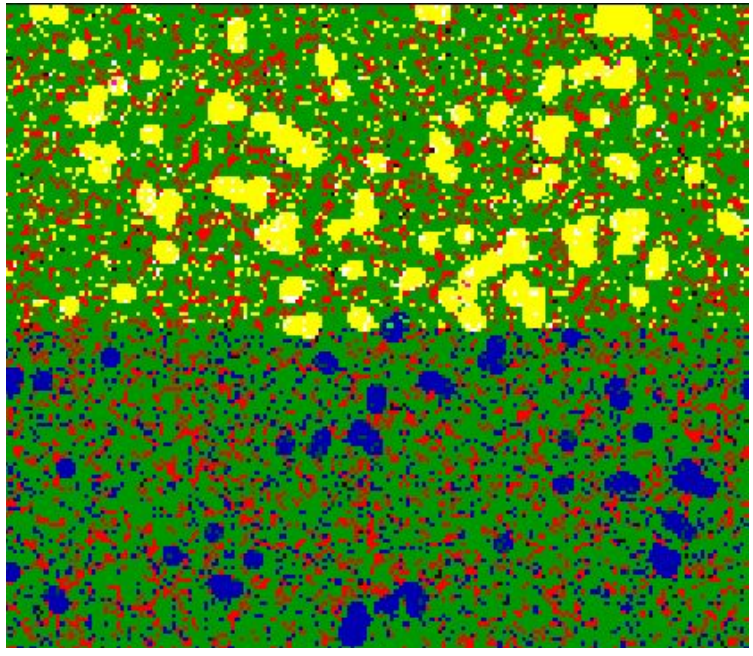
$$\frac{p}{p'} \approx \left(\frac{\overline{T'}}{\overline{T}} \right)^2$$

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

Start of first passage



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

Predictions

- Spatial structure localizes competitive dynamics, allowing multiple adaptive changes to arise and persist (for extended period) in different regions.
- Natural high-MOI conditions on plate promote coinfection; recombination in transient hybrid zones.
- Different selective sweeps in different regions leads to opportunities for some recombination events that would be unlikely in well-mixed setting.
- Spatial bottlenecks lead to localized waves of infection (plaques) starting from isolated foci.

Molecular dissection of adaptation

- spatio-temporal sequencing
- known gene functions
- tie to phenotypes (life history parameters and fitness)
- Effects of mutations can be additive for some phenotypes, but not for fitness. (Craig Miller)

Thanks!

Collaborators: Dilara Ally, Keaton Stagaman, Holly Wichman; Pavitra Roychoudhury, Wei Wei

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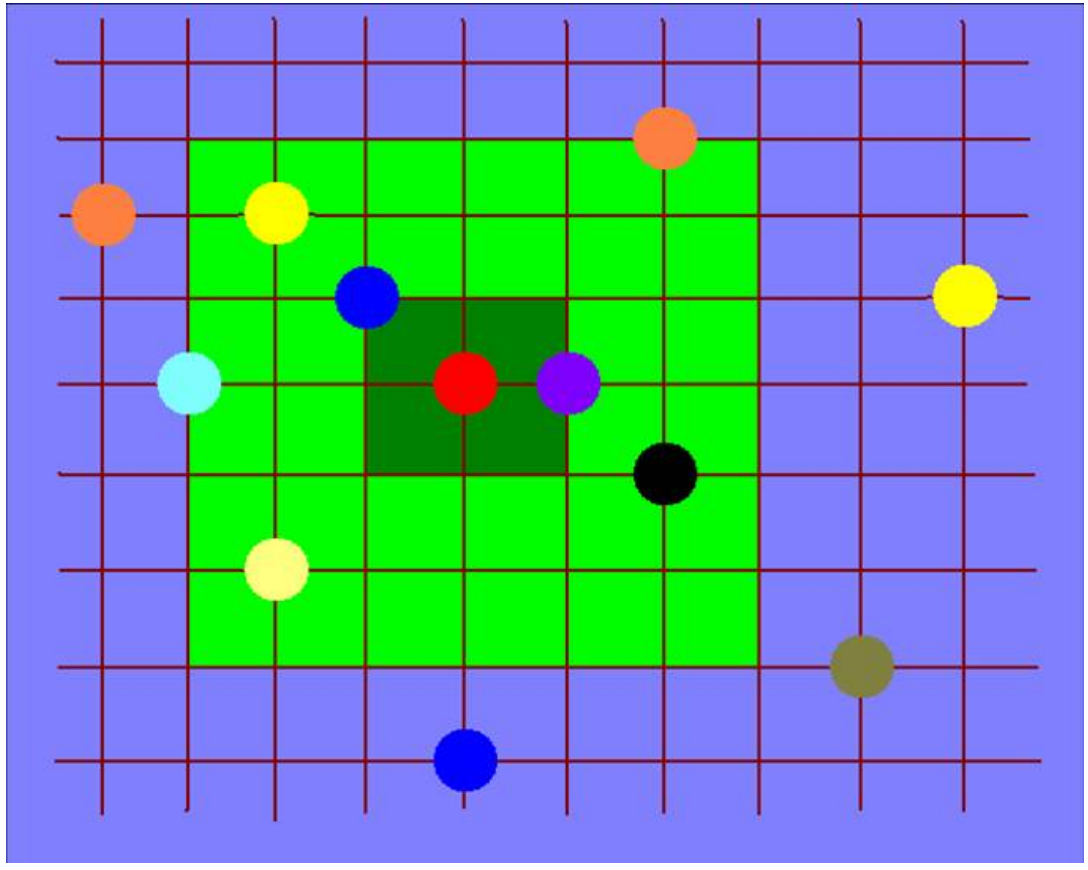

Different types on 2-dimensional lattice.