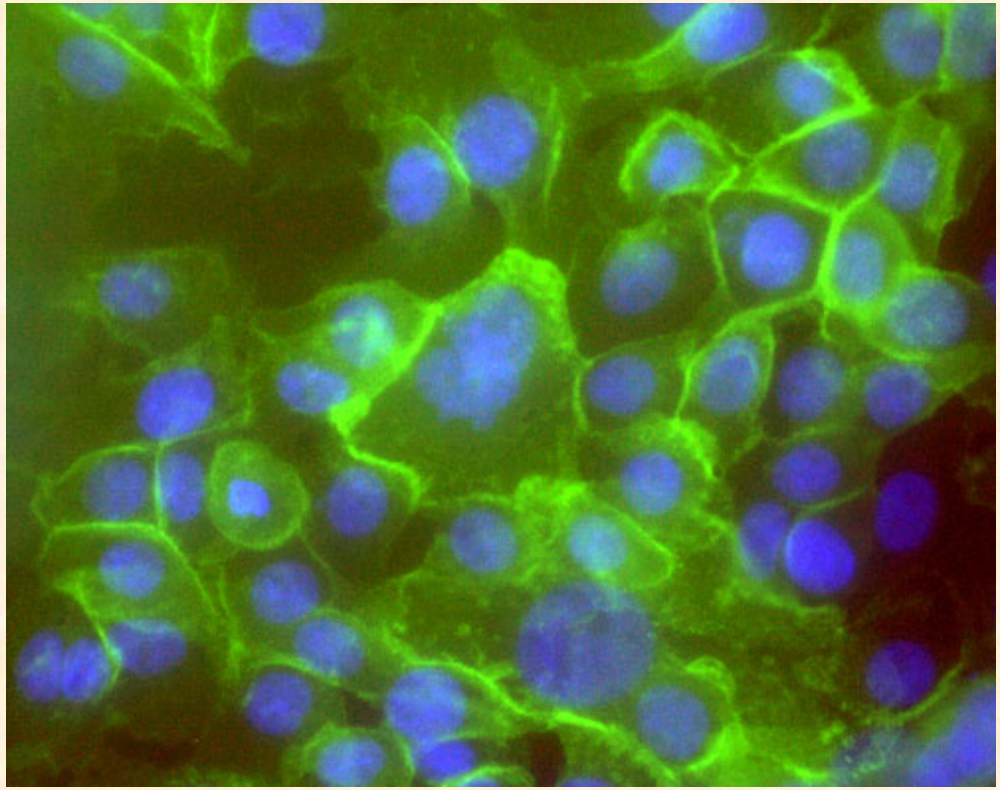
Cellular cooperation as a pathway to cancer



Natalia L. Komarova

komarova@uci.edu

University of California Irvine

Plan

- Study cancer as a complex trait
- Study the evolution of complex traits
- *Conventional view*: Crossing the fitness valley by sequential evolution
- *New concept*: Cooperation in the context of the "division of labor" games

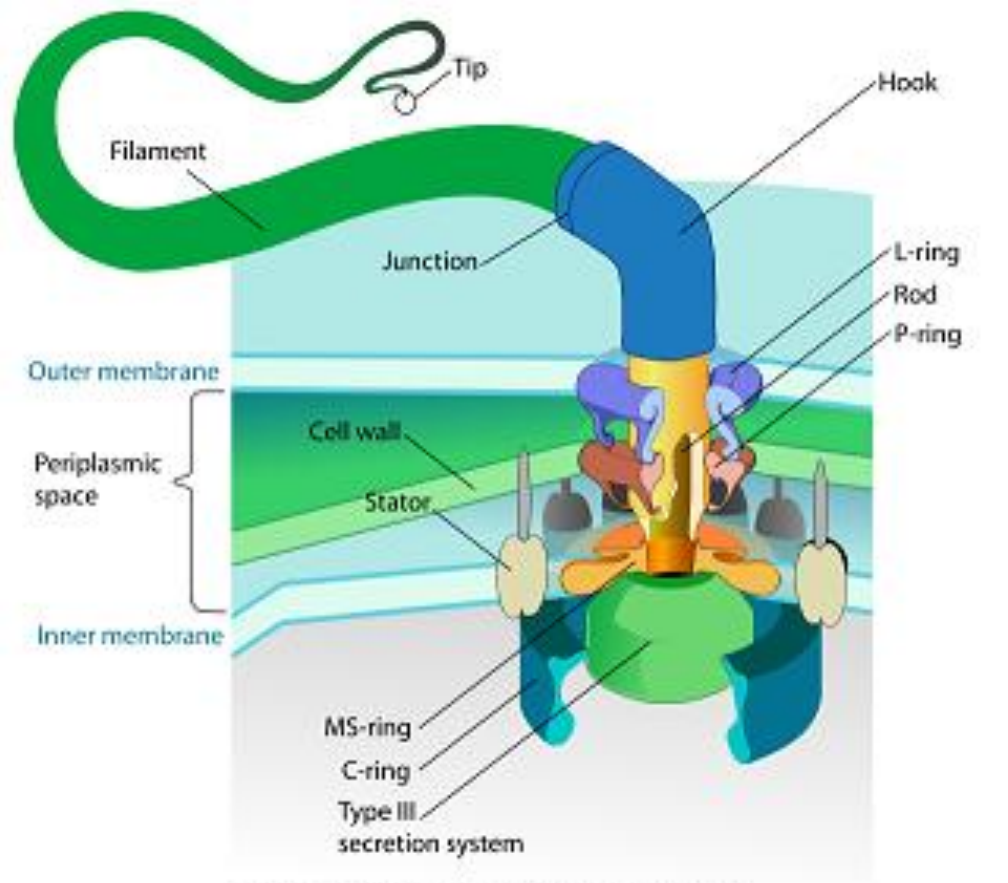
Plan

- Cooperation speeds up evolution

Plan

- Cooperation speeds up evolution
- Cheating speeds up evolution even more!

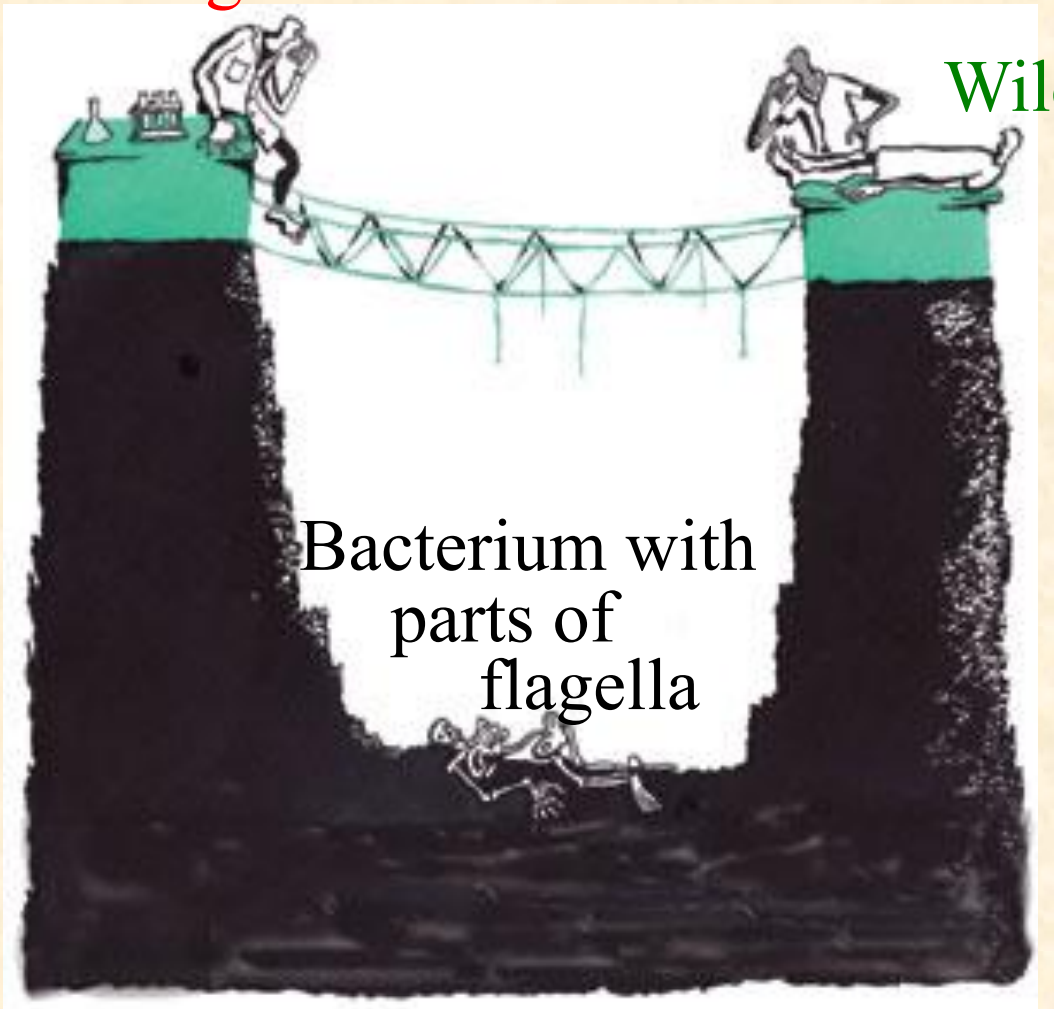
Evolution of complex traits



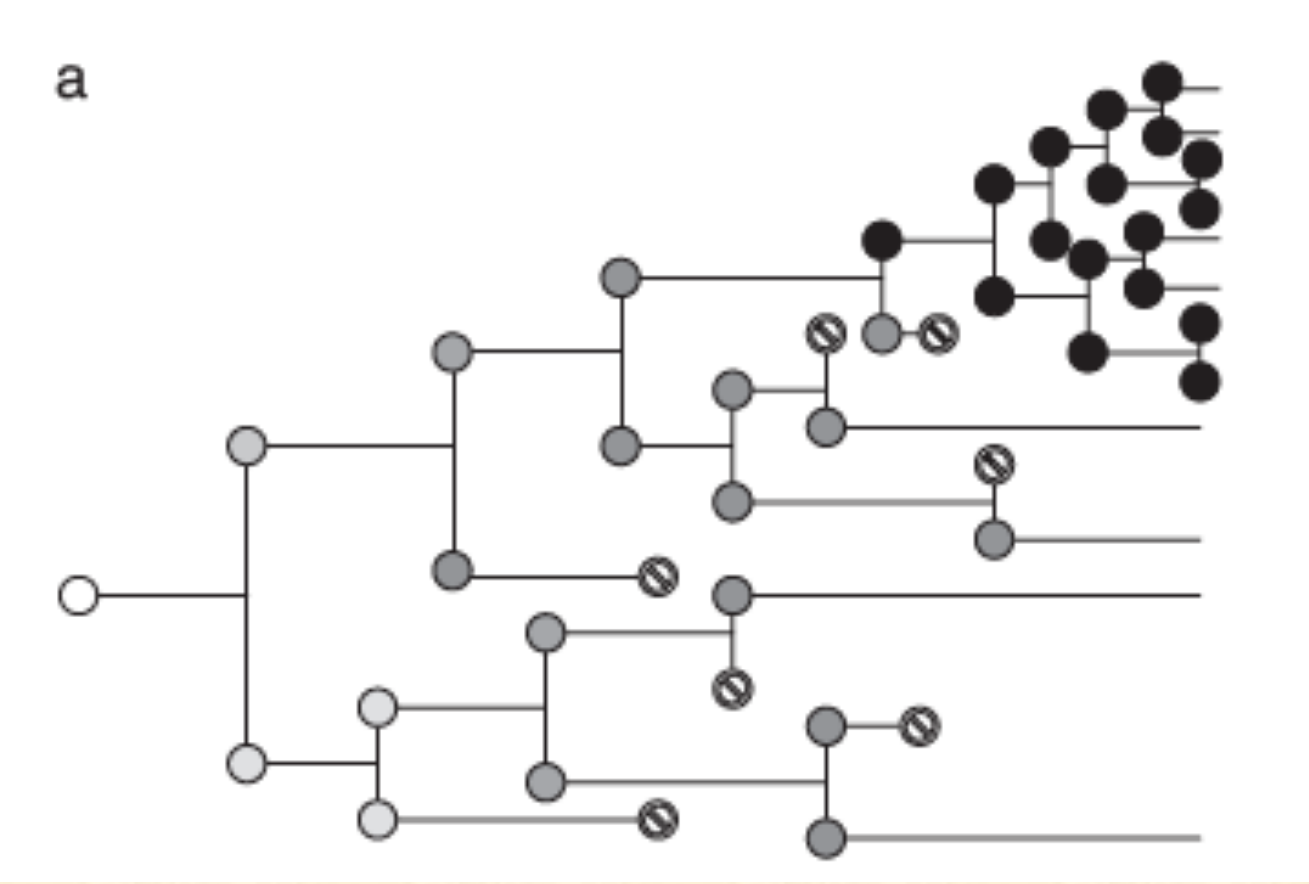
The many bits of a bacterial flagellum

Crossing the fitness valley

Bacterium with flagella



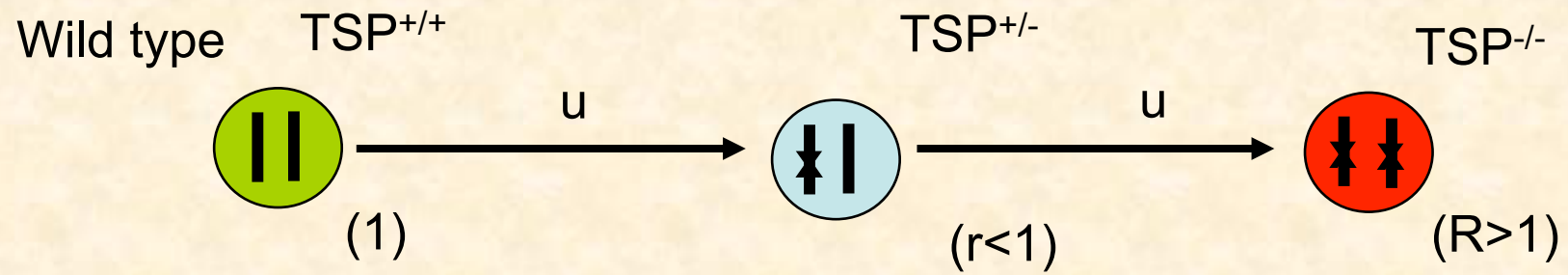
Cancer as a complex trait



Axelrod et al, "Evolution of cooperation among tumor cells", PNAS 2006

Loss-of-function mutations

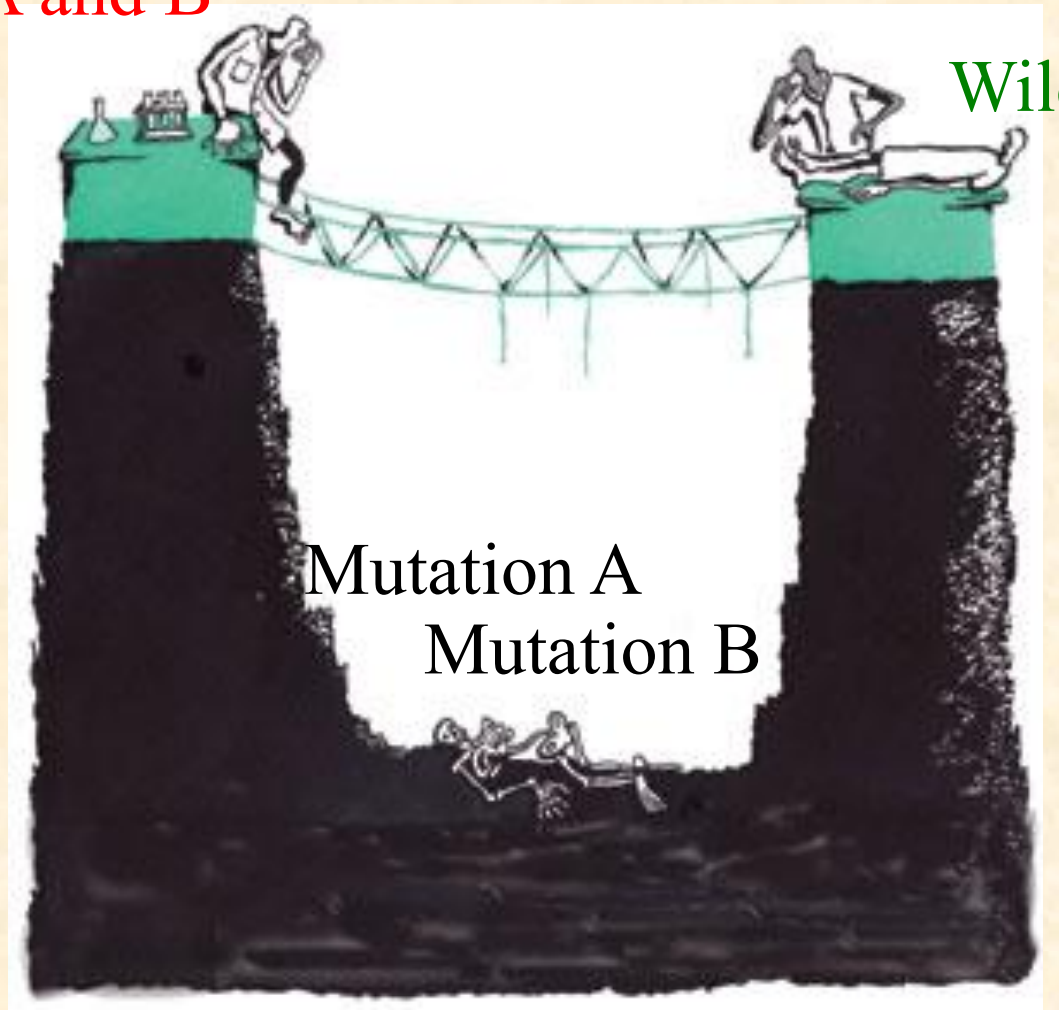
- Tumor suppressor genes
- APC (colon cancer), Rb (retinoblastoma), p53 (many cancers) – about 200 genes



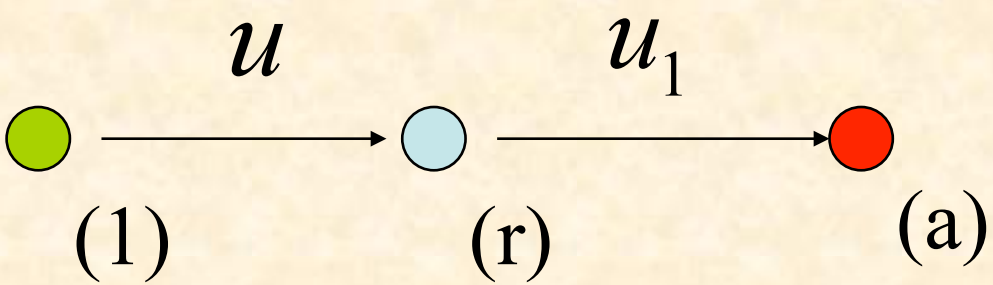
$u = 10^{-7}$ per cell division per gene copy

Crossing the fitness valley

Mutations A and B



Rates of sequential evolution



What is the probability that by time t a mutant of
● has been created?

Assume that $r \leq 1$ and $a >> 1$

Three architectural types maintaining homeostatic control

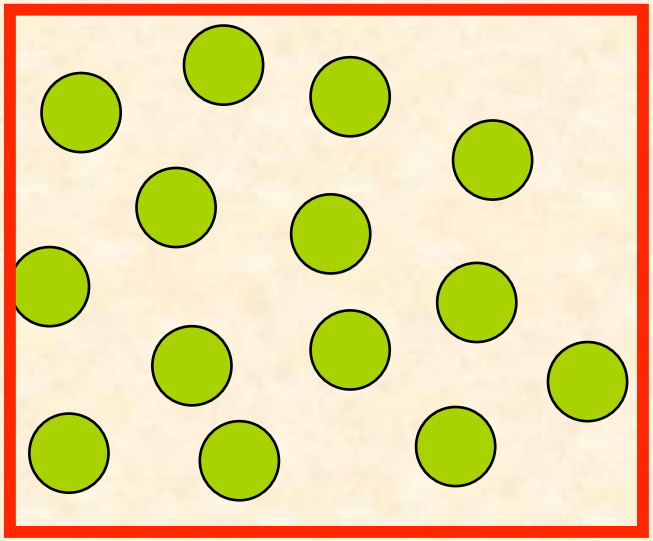
1. Mass action
2. Spatial structure
3. Hierarchical structure

Three architectural types maintaining homeostatic control

1. Mass action
2. Spatial structure
3. Hierarchical structure

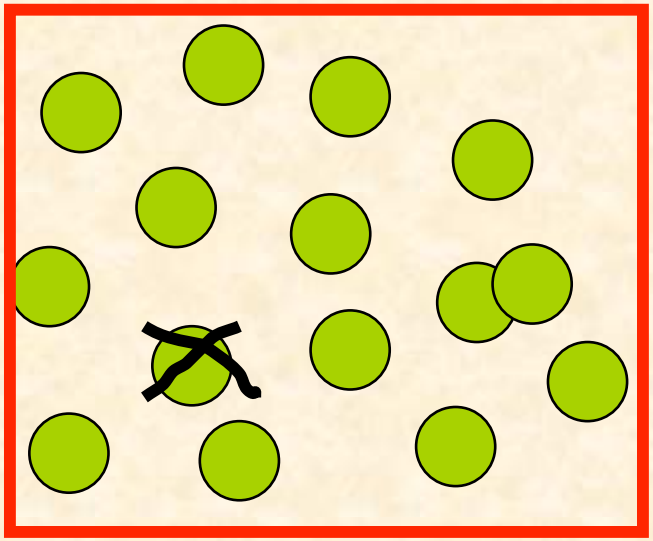
Which type of architecture corresponds to the fastest sequential evolution?

1.Mass action



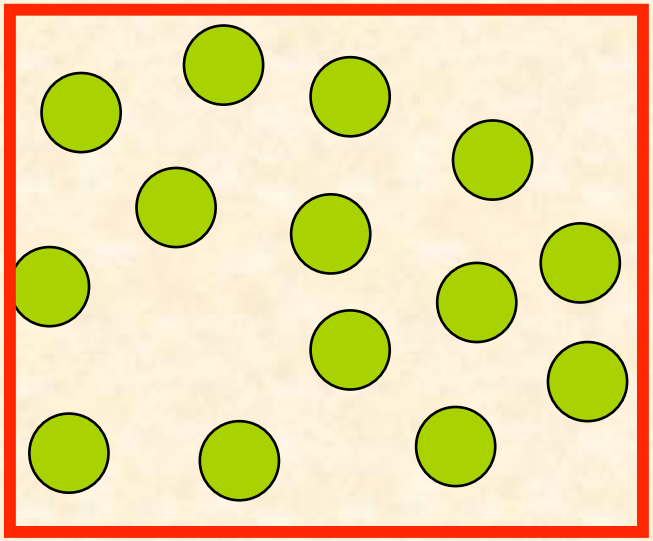
Moran process

1.Mass action



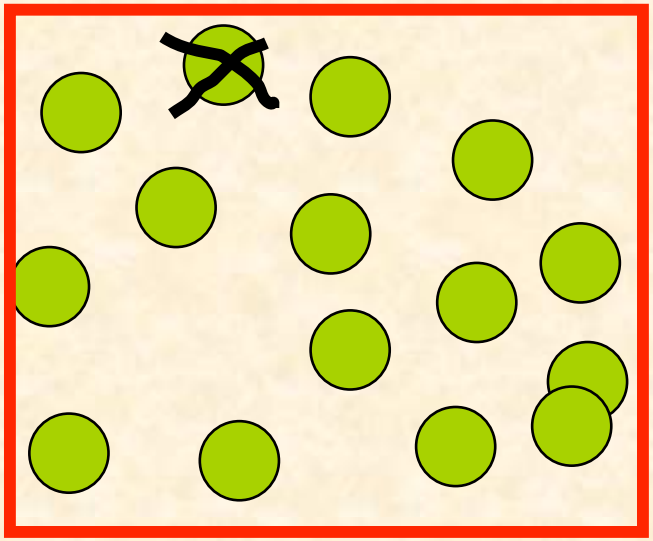
Moran process

1.Mass action



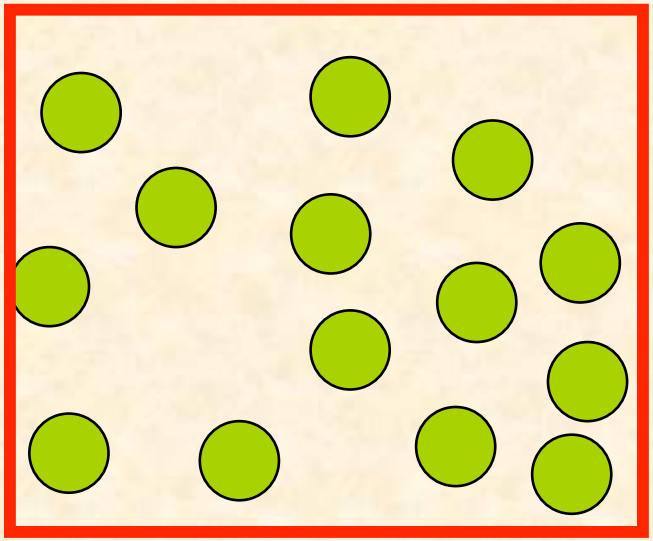
Moran process

1.Mass action



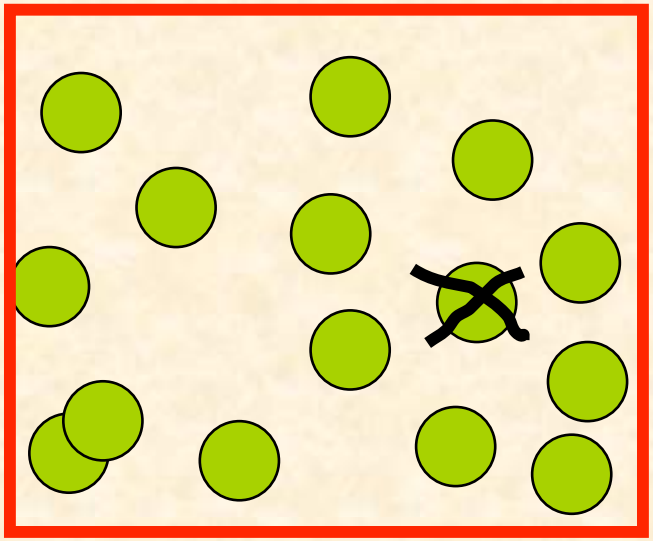
Moran process

1.Mass action



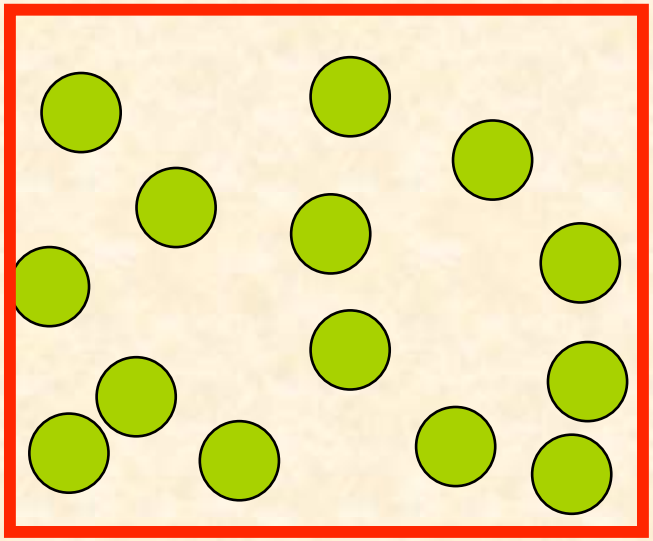
Moran process

1.Mass action



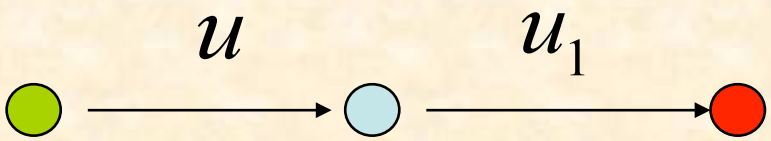
Moran process

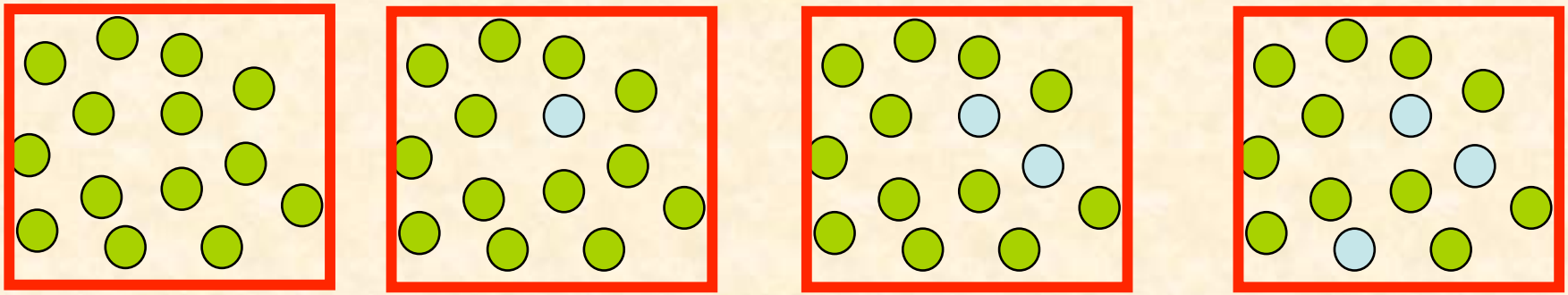
1.Mass action



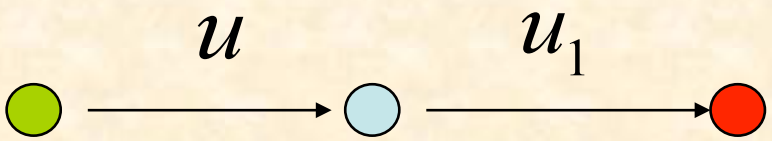
Moran process

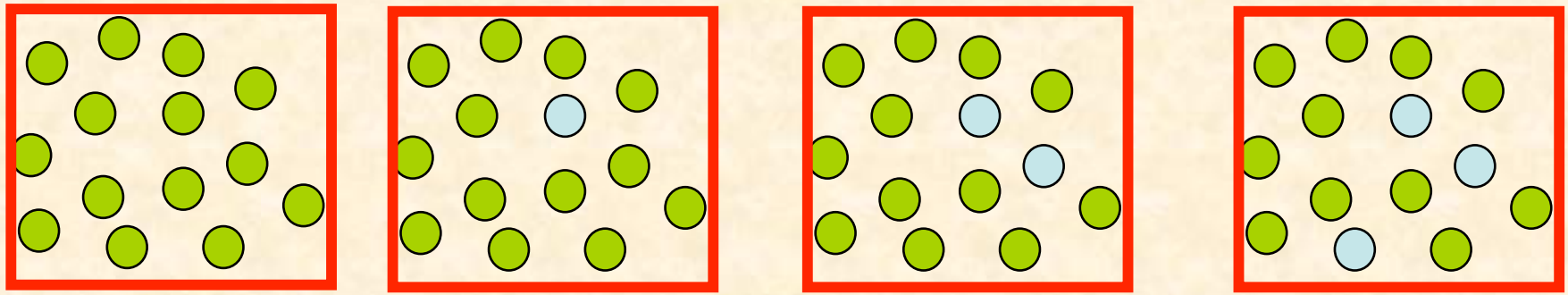
A two-step process

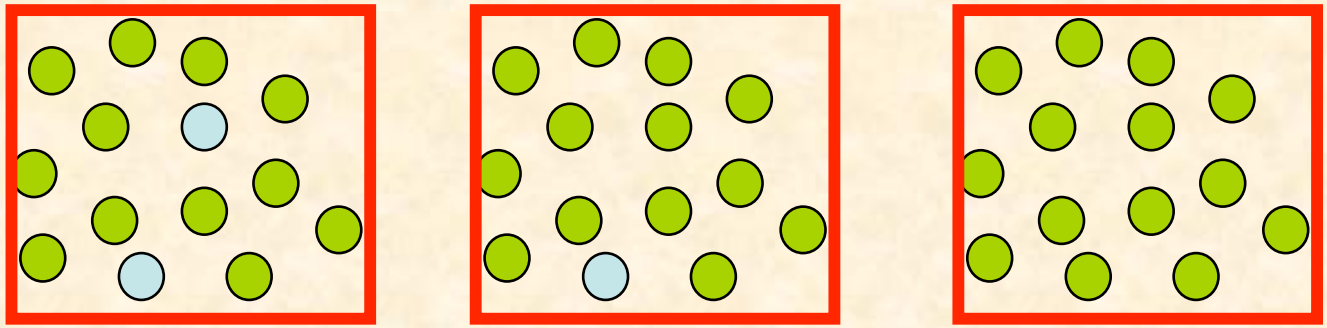




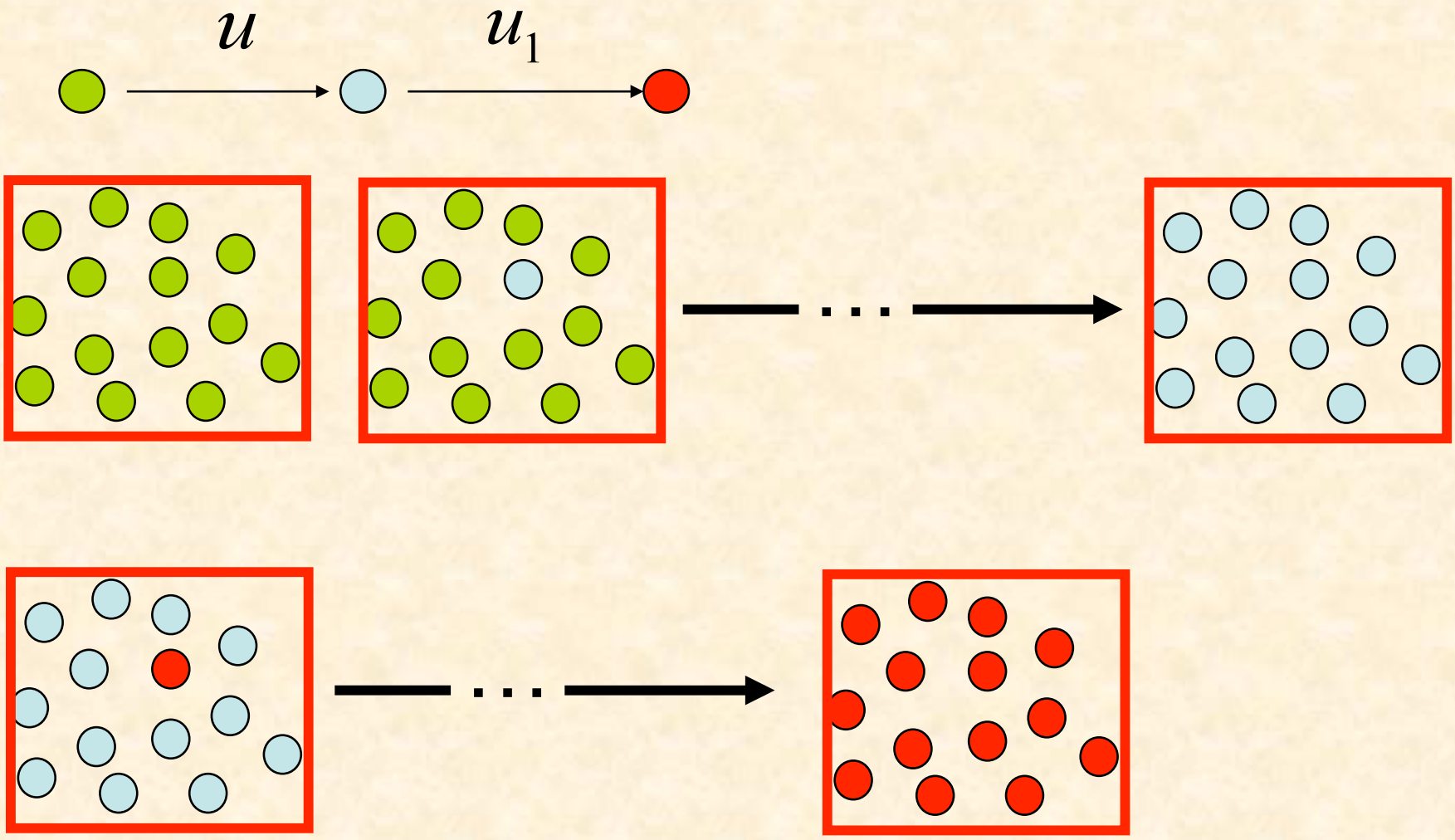
A two-step process



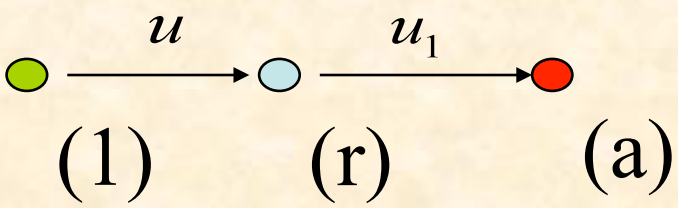




A two-step process

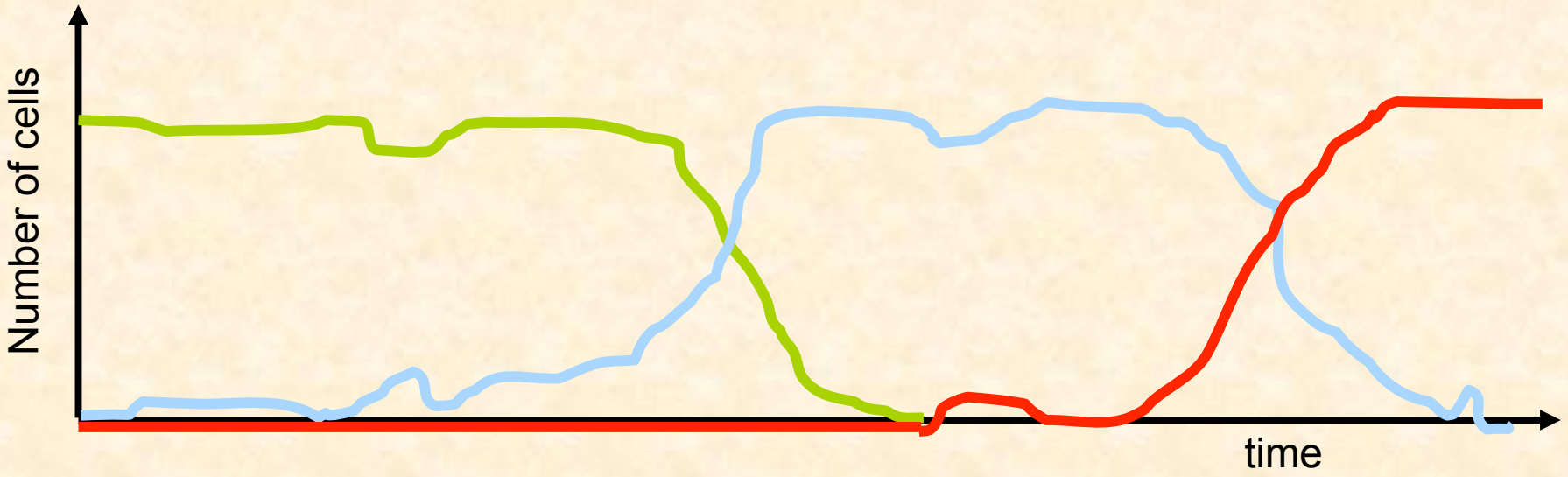


A two-step process

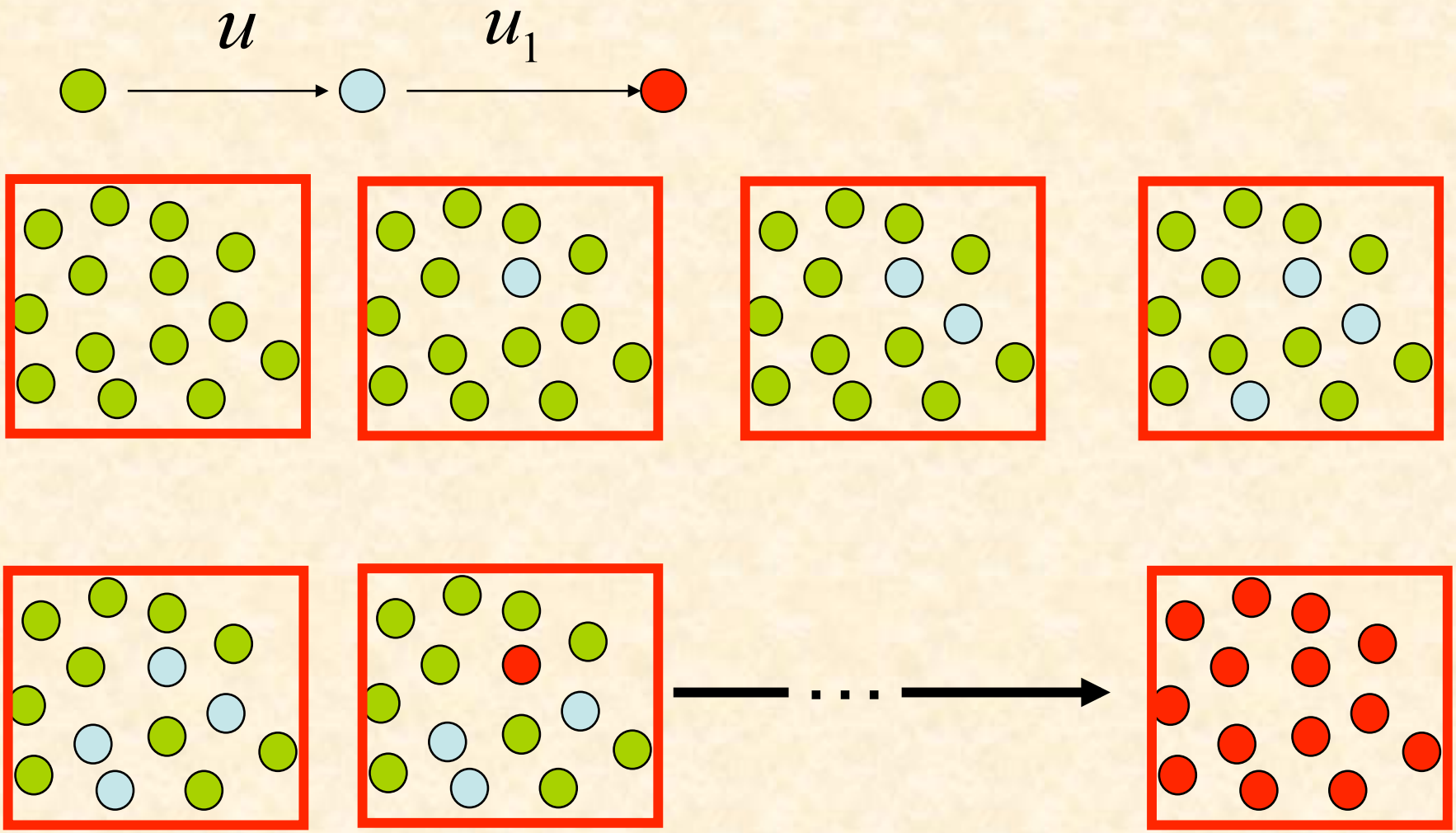


Scenario 1:

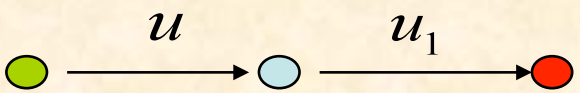
gets fixated first, and then a mutant of is created;



Stochastic tunneling

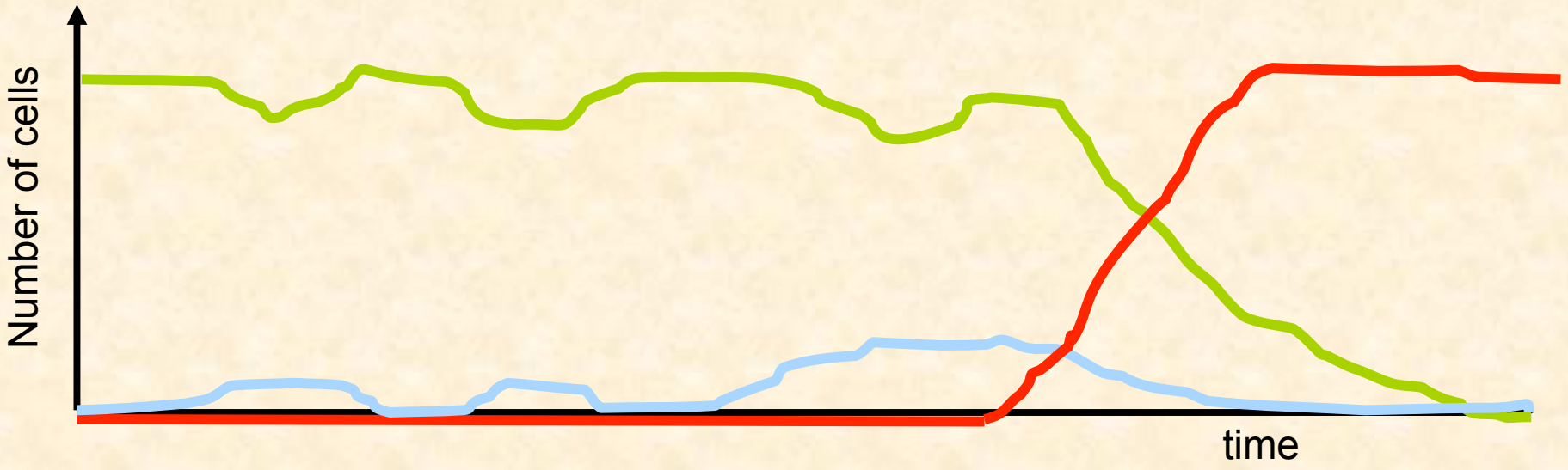


Stochastic tunneling

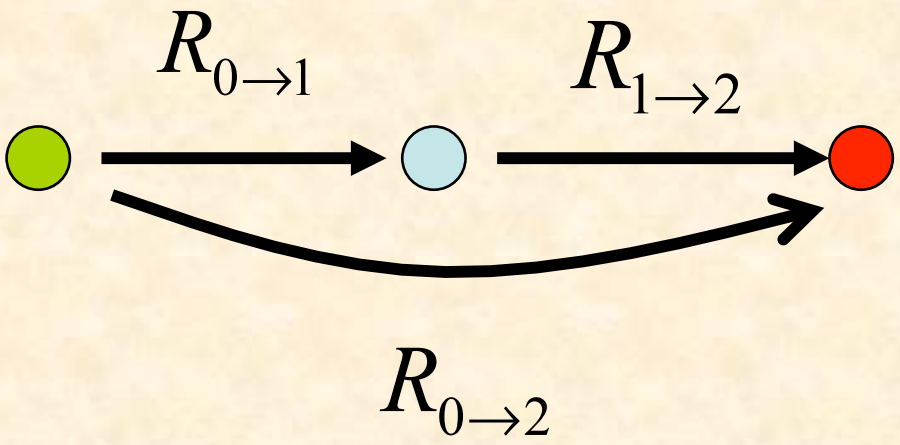


Scenario 2:

A mutant of  is created before  reaches fixation



The coarse-grained description



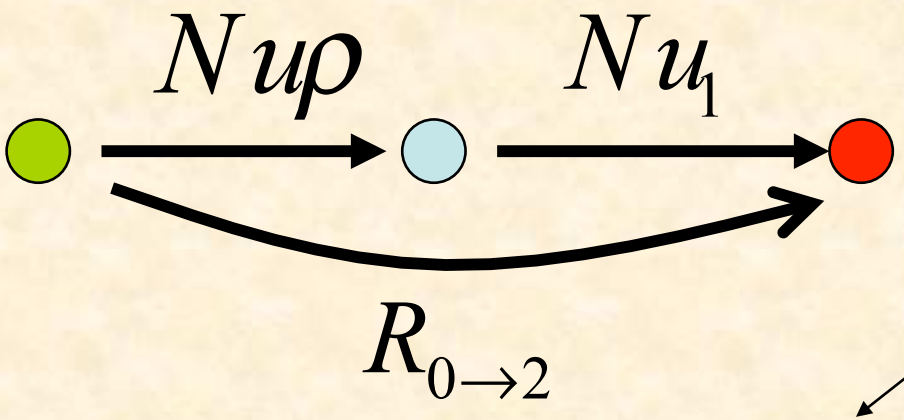
Long-lived states:
x_0 …"all green"
x_1 …"all blue"
x_2 …"at least one red"

$$\dot{x}_0 = -R_{0\to1}x_0 - R_{0\to2}x_0$$

$$\dot{x}_1 = R_{0\to1}x_0 - R_{1\to2}x_1$$

$$\dot{x}_2 = R_{0\to1}x_0 + R_{1\to2}x_1$$

Stochastic tunneling



Neutral intermediate mutant

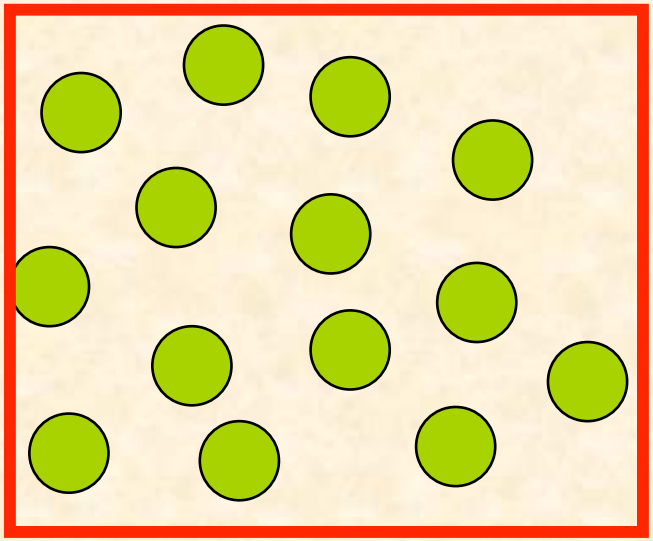
$$R_{0\to 2} = N u \sqrt{u_1} \qquad |1-r| < \sqrt{u_1}$$

$$R_{0\to 2} = \frac{N u u_1 r}{1-r} \qquad |1-r| > \sqrt{u_1}$$

Disadvantageous intermediate mutant

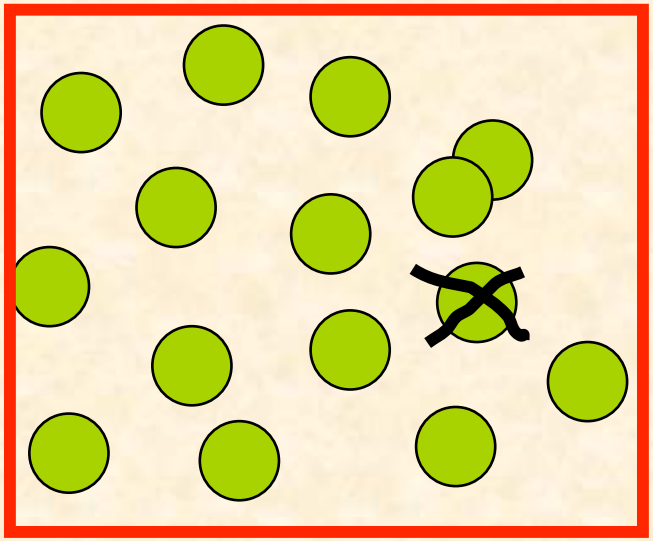
Assume that $r \le 1$ and $a >> 1$

2.Spatial structure



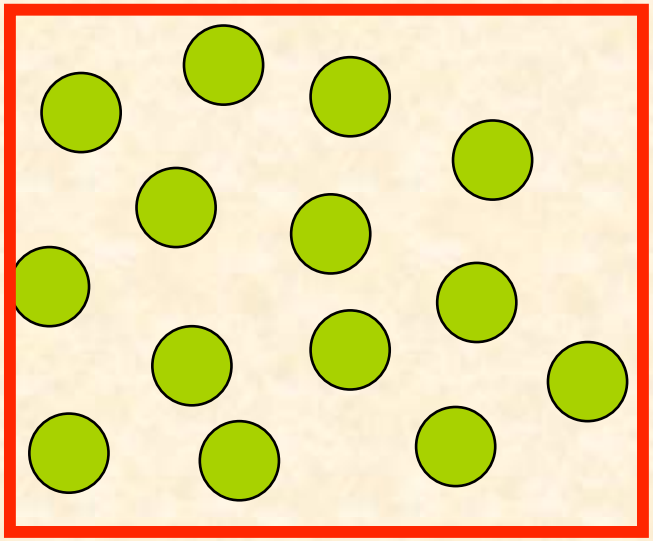
Generalized (spatial) Moran process

2.Spatial structure



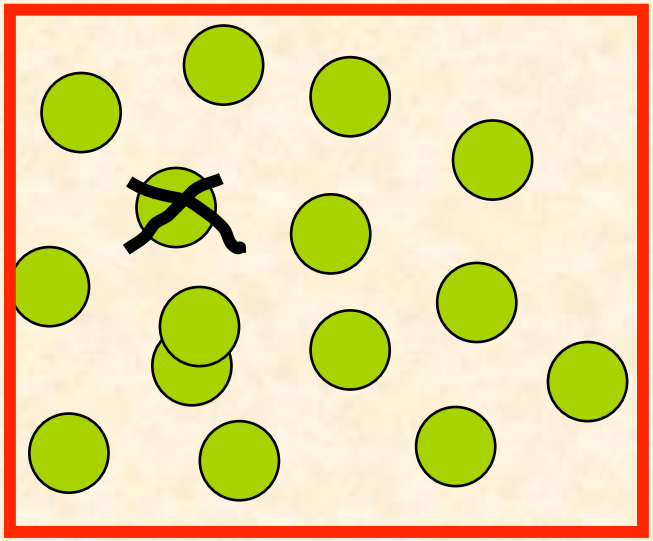
Generalized (spatial) Moran process

2.Spatial structure



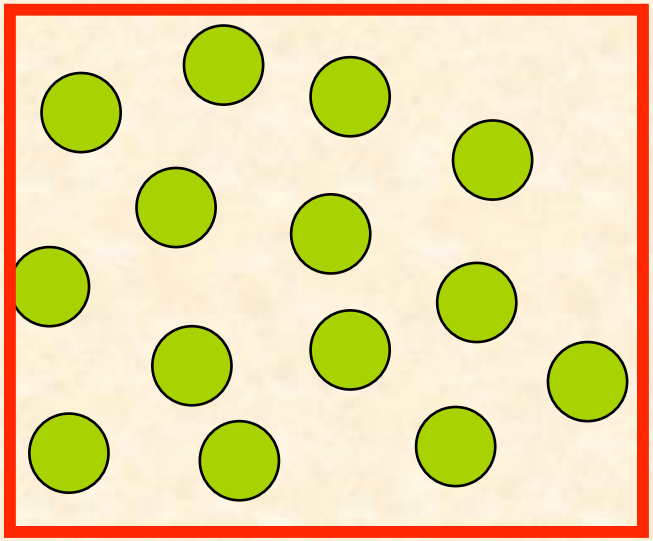
Generalized (spatial) Moran process

2.Spatial structure



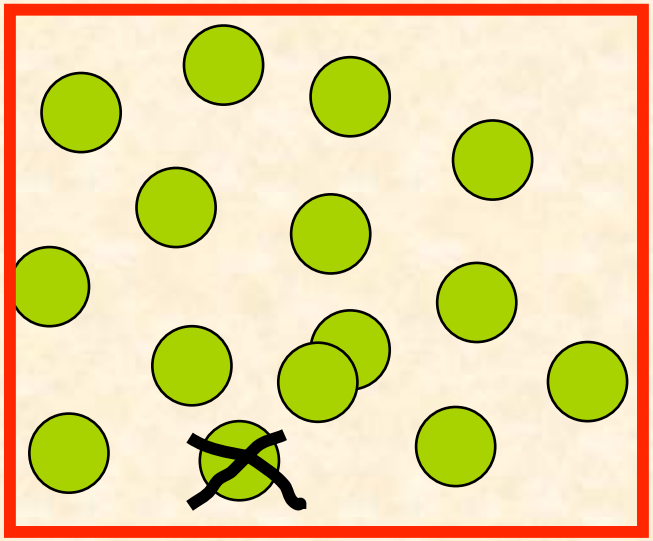
Generalized (spatial) Moran process

2.Spatial structure



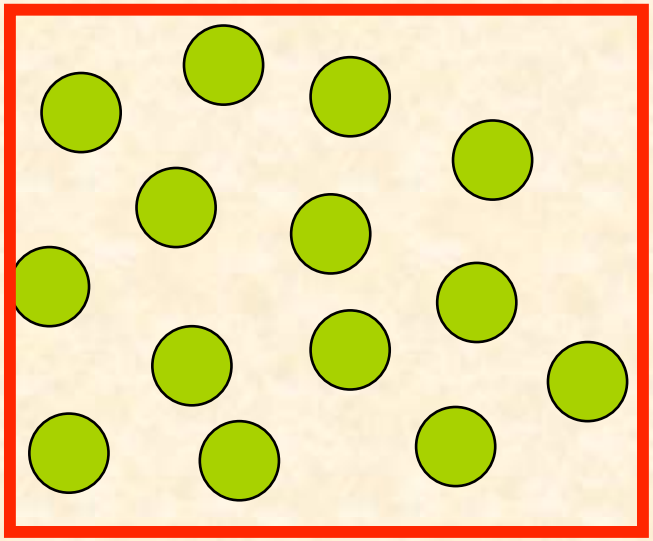
Generalized (spatial) Moran process

2.Spatial structure



Generalized (spatial) Moran process

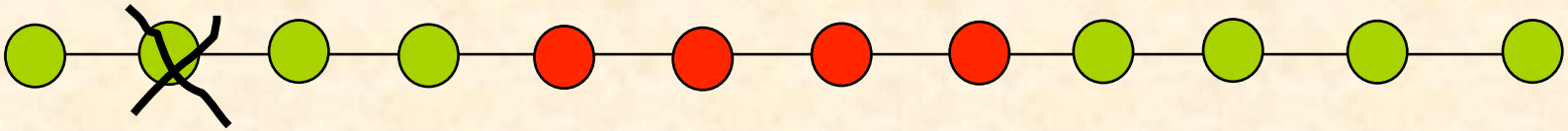
2.Spatial structure



Generalized (spatial) Moran process

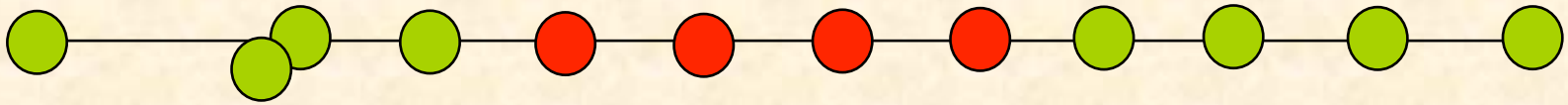
Spatial dynamics

Spatial dynamics



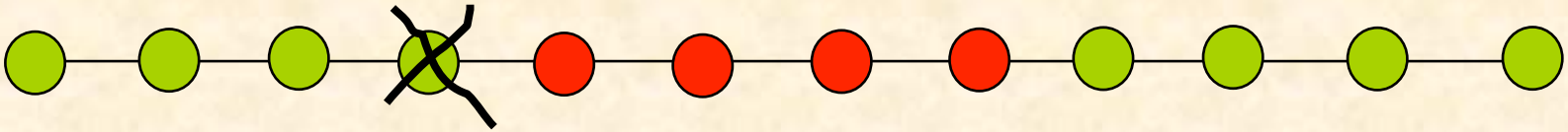
Spatial dynamics

Spatial dynamics



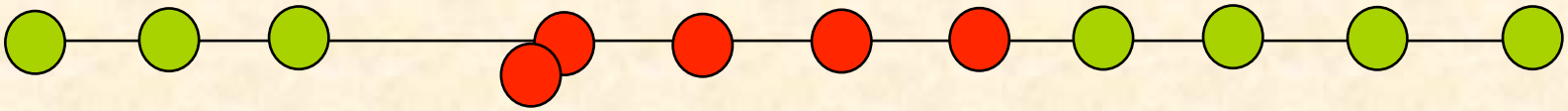
Spatial dynamics

Spatial dynamics



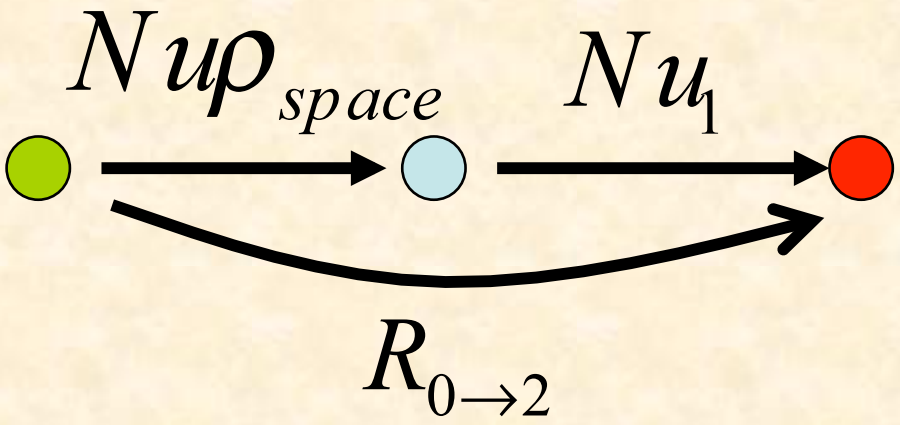
Spatial dynamics

Spatial dynamics



Spatial dynamics

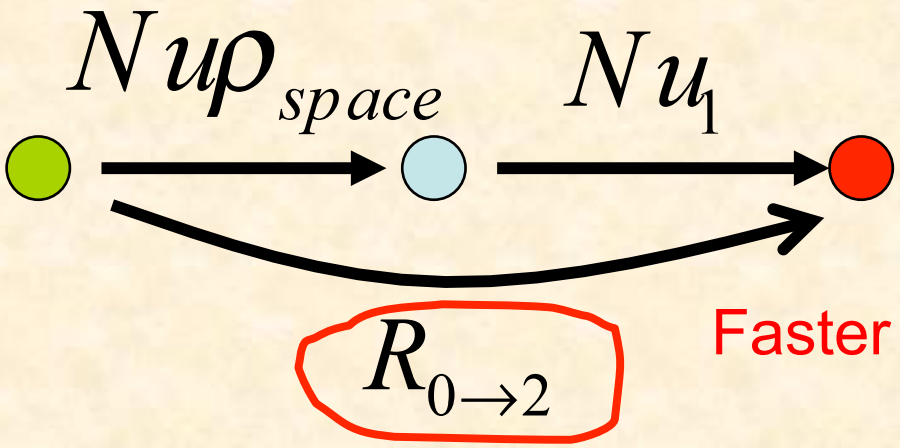
Stochastic tunneling



$$R_{0\to 2} = uN(9u_1)^{1/3}\frac{\Gamma(2/3)}{\Gamma(1/3)};\ (\text{mass act.}\ Nu\sqrt{u_1})$$

$$R_{0\to 2} = 3rNuu_1\frac{(r-1)^2+r^2}{(r-1)^2};\ (\text{mass act.}\ \frac{Nuu_1 r}{1-r})$$

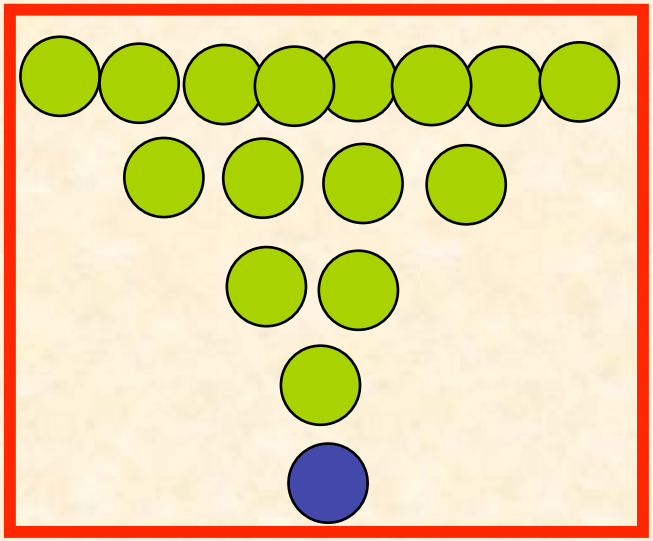
Stochastic tunneling



$$R_{0\to 2} = uN(9u_1)^{1/3}\frac{\Gamma(2/3)}{\Gamma(1/3)};\ (\text{mass act.}\ Nu\sqrt{u_1})$$

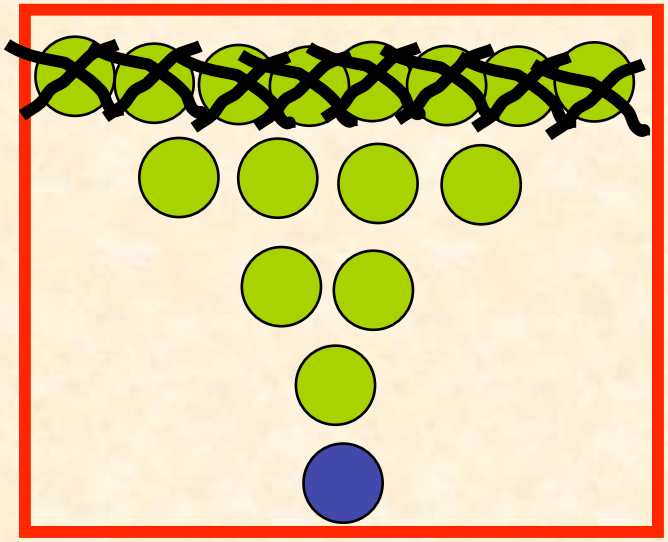
$$R_{0\to 2} = 3rNuu_1\frac{(r-1)^2+r^2}{(r-1)^2};\ (\text{mass act.}\ \frac{Nuu_1 r}{1-r})$$

3.Hierarchical structure



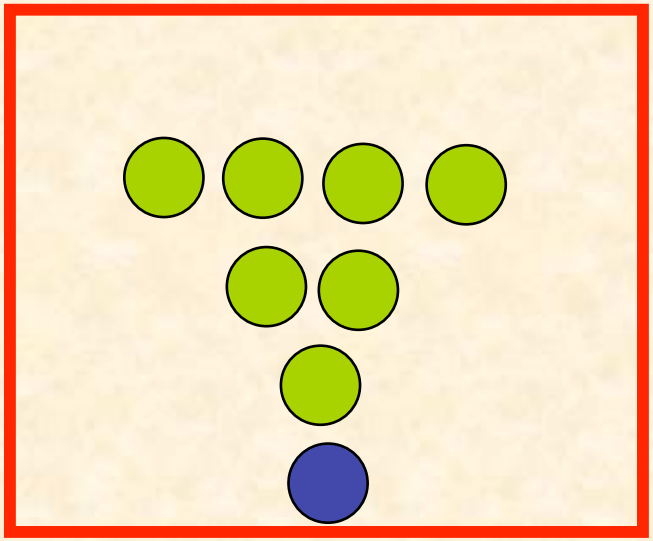
Generalized (hierarchical) Moran process

3.Hierarchical structure



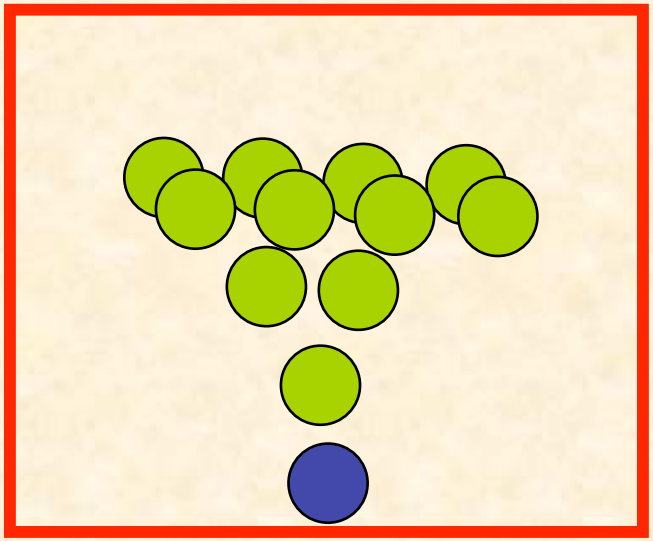
Generalized (hierarchical) Moran process

3.Hierarchical structure



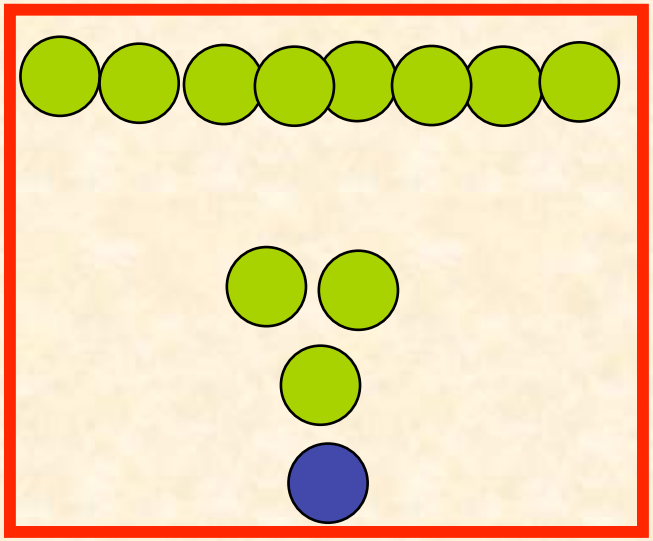
Generalized (hierarchical) Moran process

3.Hierarchical structure



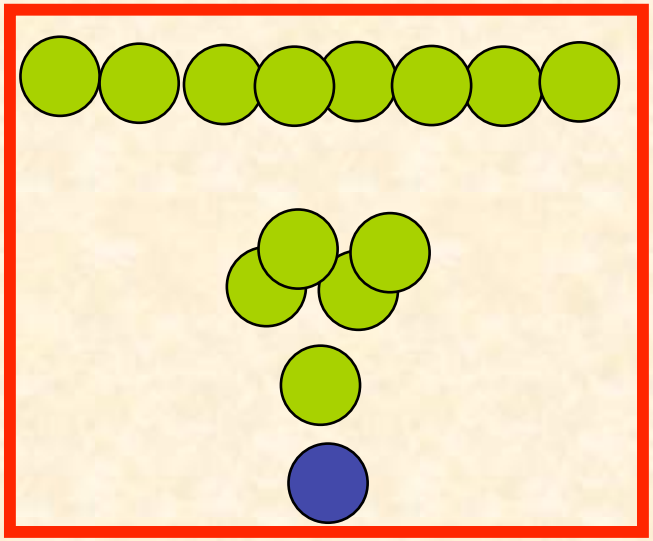
Generalized (hierarchical) Moran process

3.Hierarchical structure



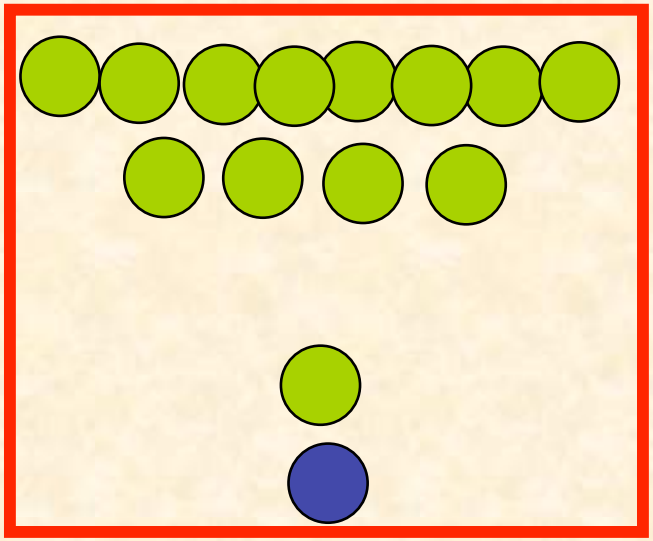
Generalized (hierarchical) Moran process

3.Hierarchical structure



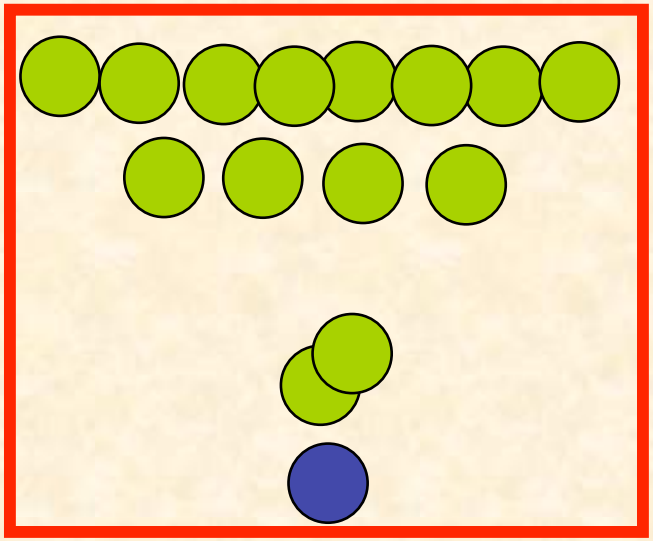
Generalized (hierarchical) Moran process

3.Hierarchical structure



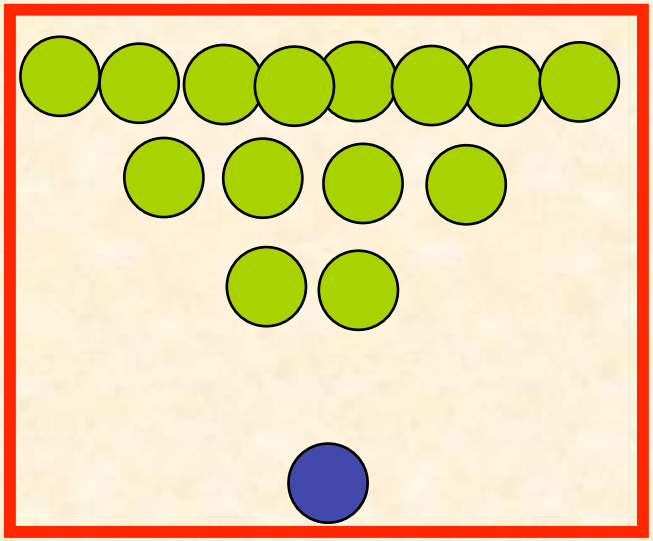
Generalized (hierarchical) Moran process

3.Hierarchical structure



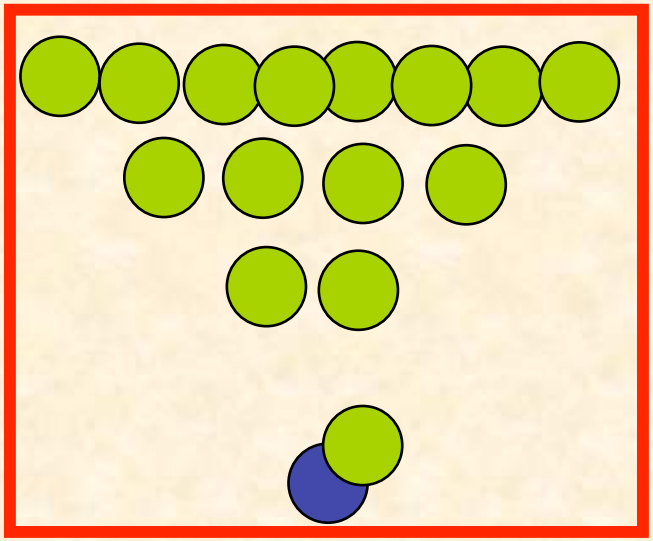
Generalized (hierarchical) Moran process

3.Hierarchical structure



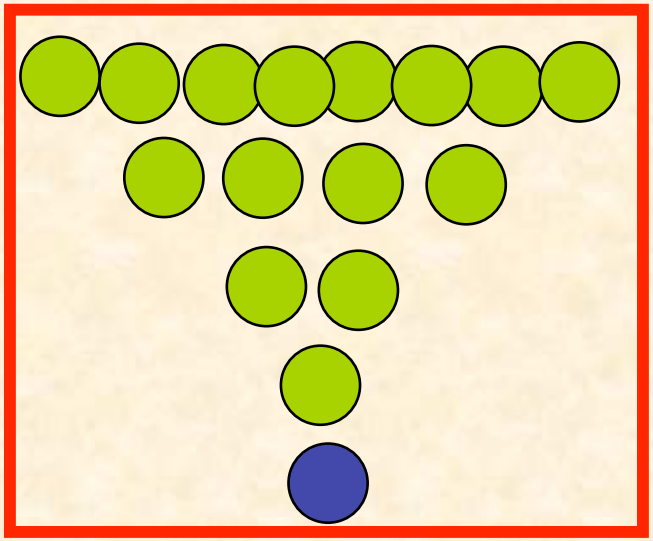
Generalized (hierarchical) Moran process

3.Hierarchical structure



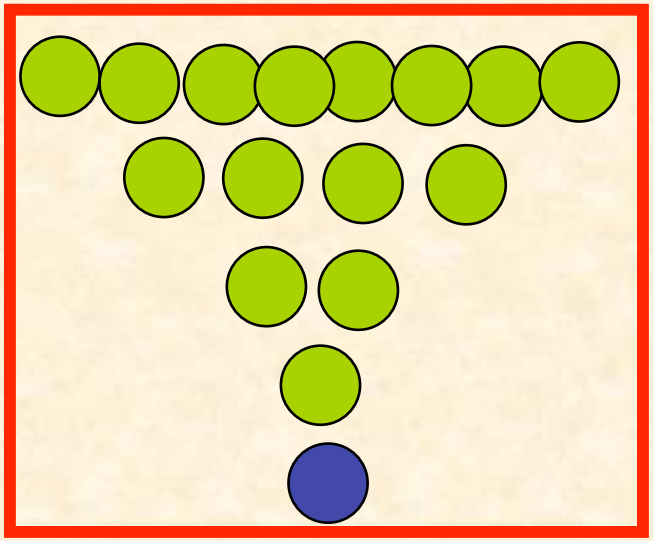
Generalized (hierarchical) Moran process

3.Hierarchical structure



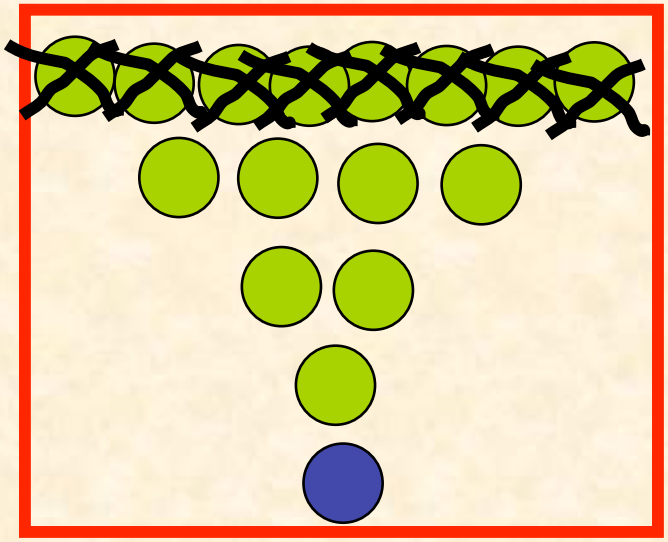
Generalized (hierarchical) Moran process

3.Hierarchical structure



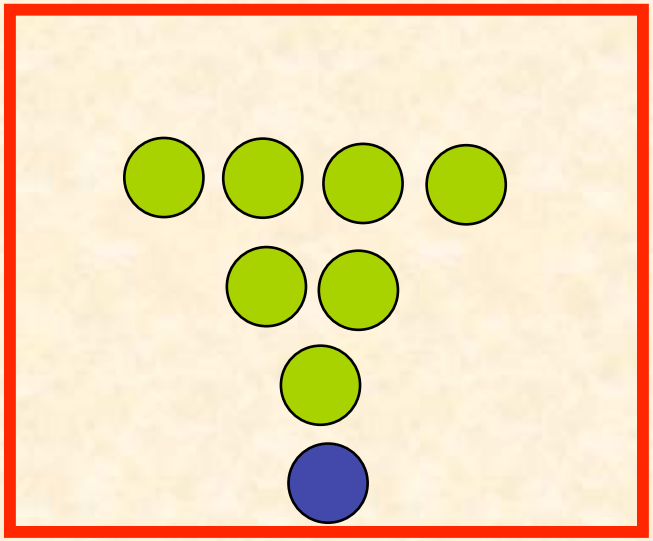
Generalized (hierarchical) Moran process

3.Hierarchical structure



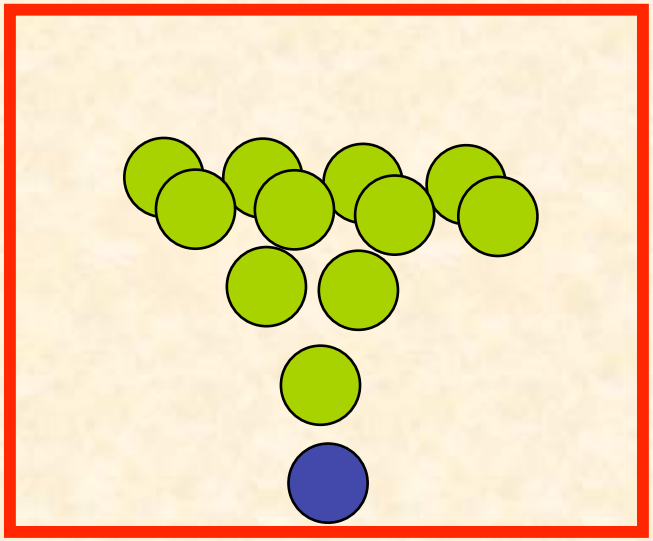
Generalized (hierarchical) Moran process

3.Hierarchical structure



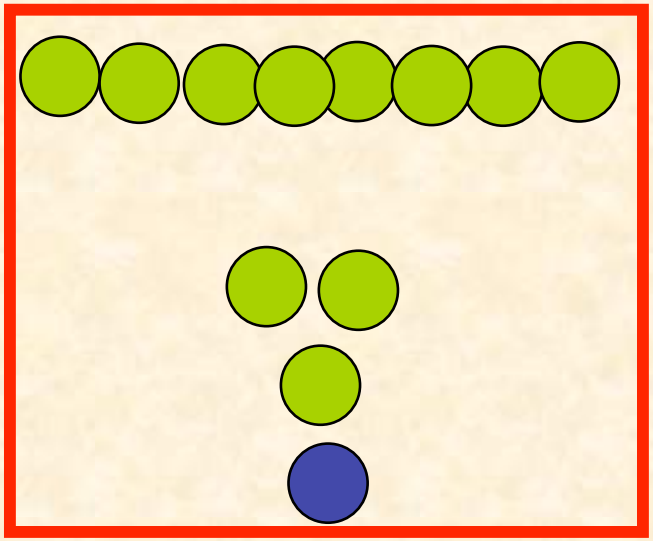
Generalized (hierarchical) Moran process

3.Hierarchical structure



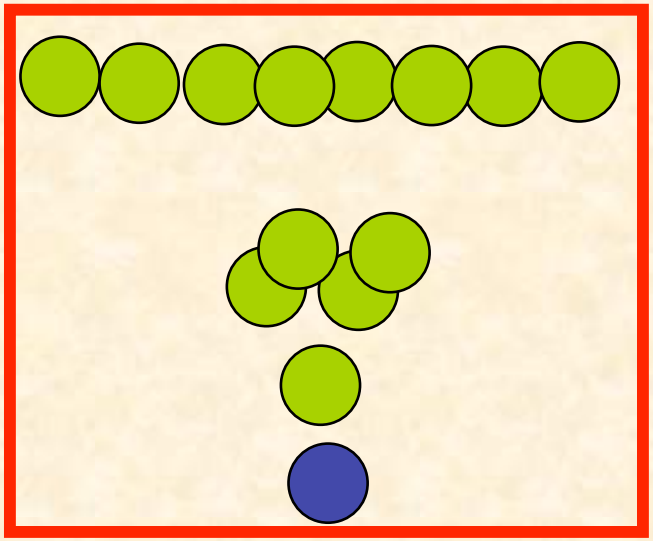
Generalized (hierarchical) Moran process

3.Hierarchical structure



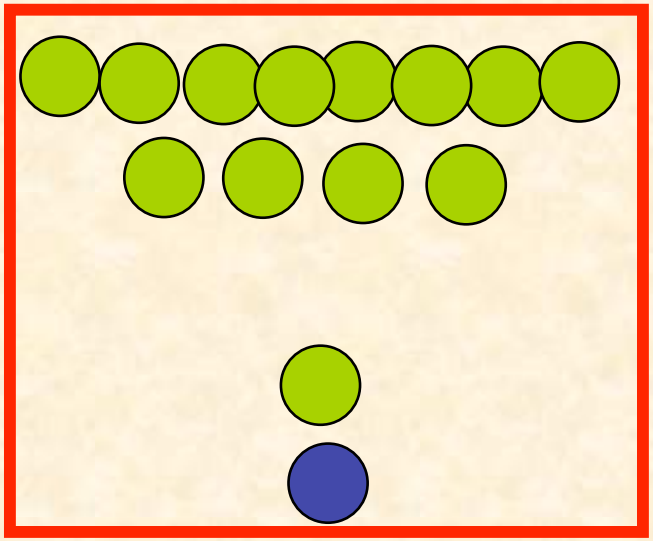
Generalized (hierarchical) Moran process

3.Hierarchical structure



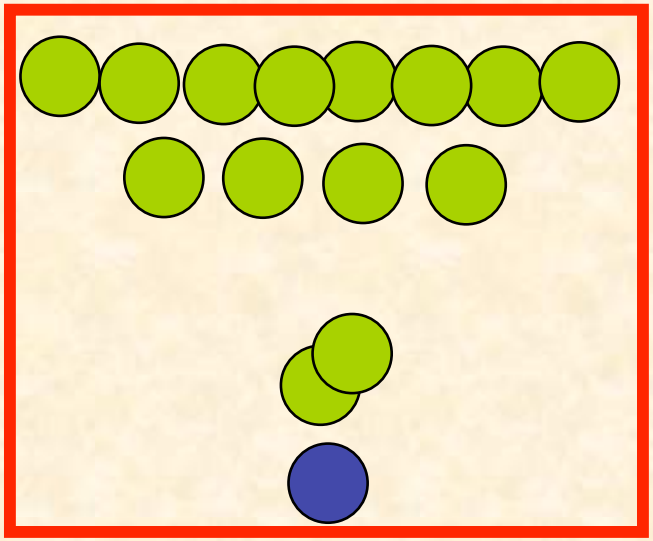
Generalized (hierarchical) Moran process

3.Hierarchical structure



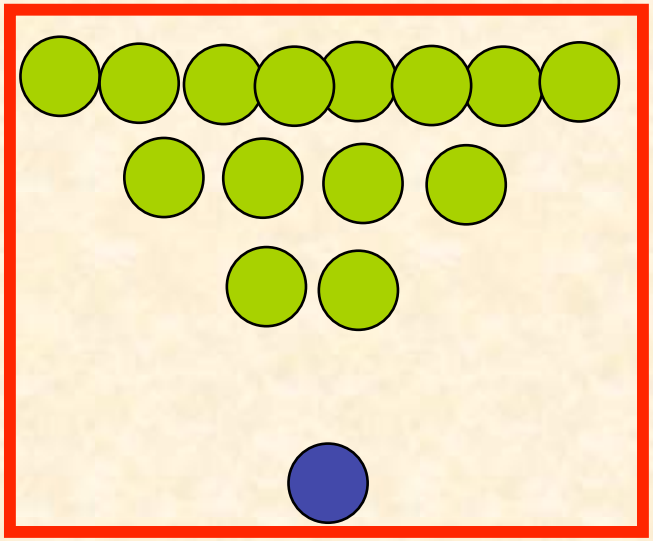
Generalized (hierarchical) Moran process

3.Hierarchical structure



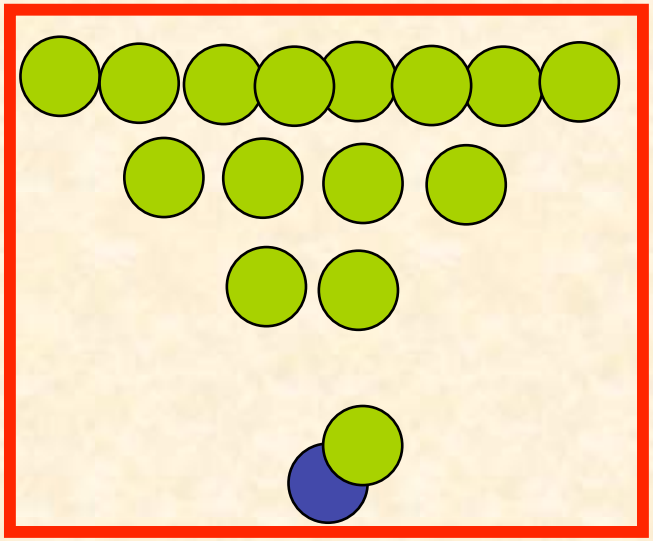
Generalized (hierarchical) Moran process

3.Hierarchical structure



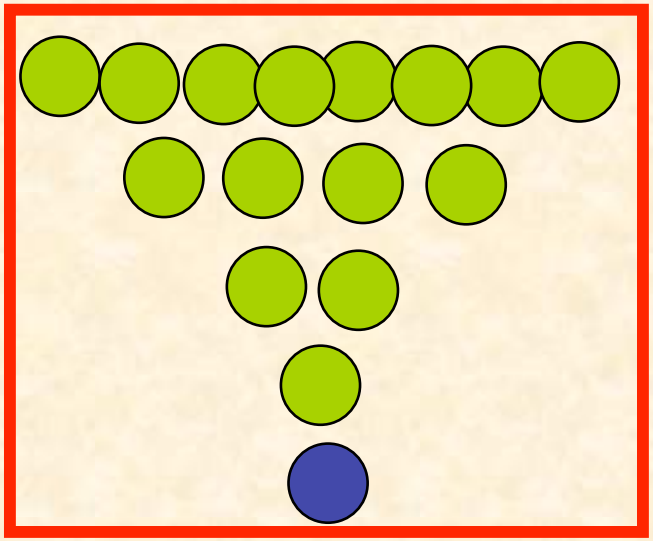
Generalized (hierarchical) Moran process

3.Hierarchical structure



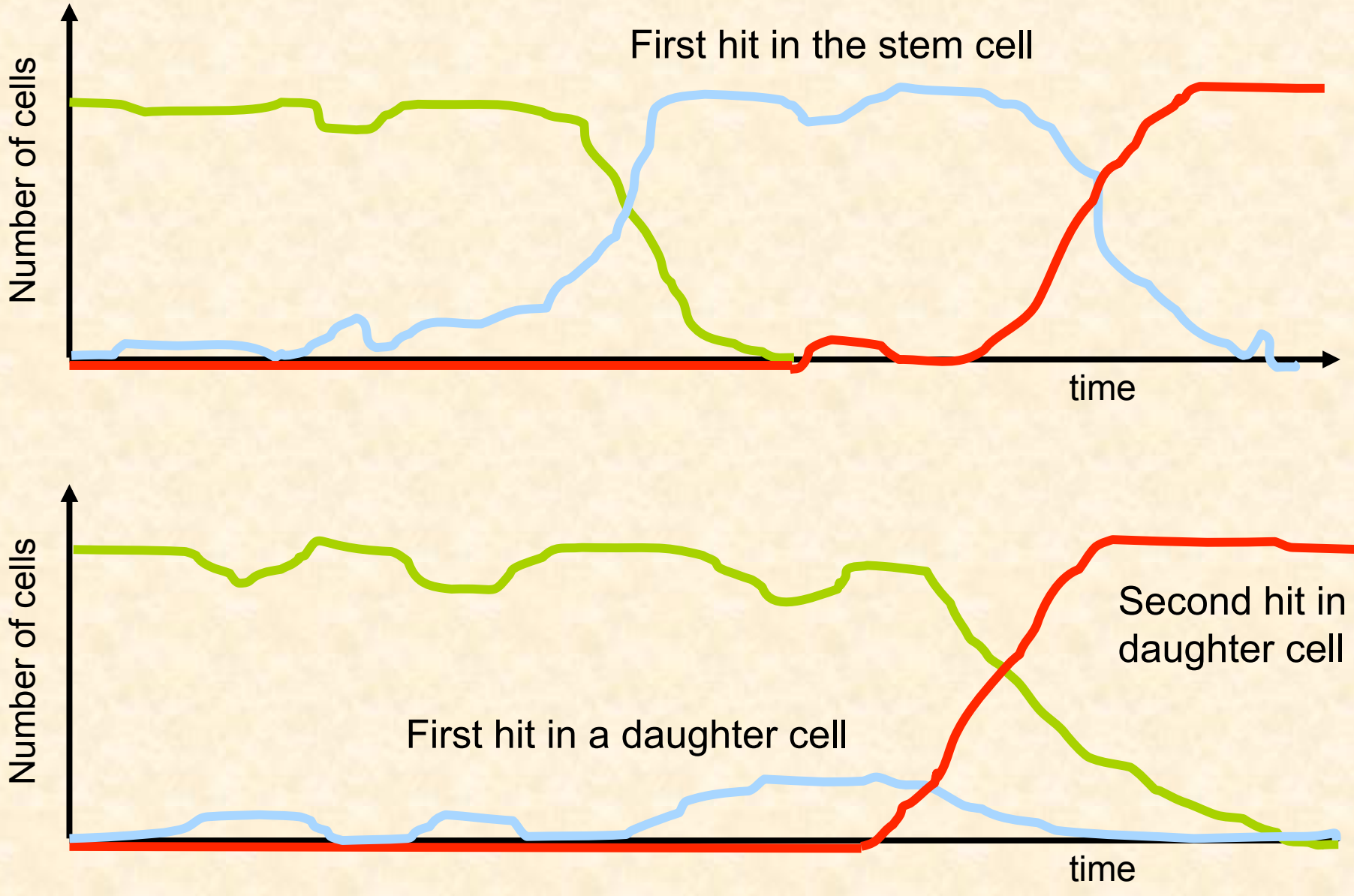
Generalized (hierarchical) Moran process

3.Hierarchical structure

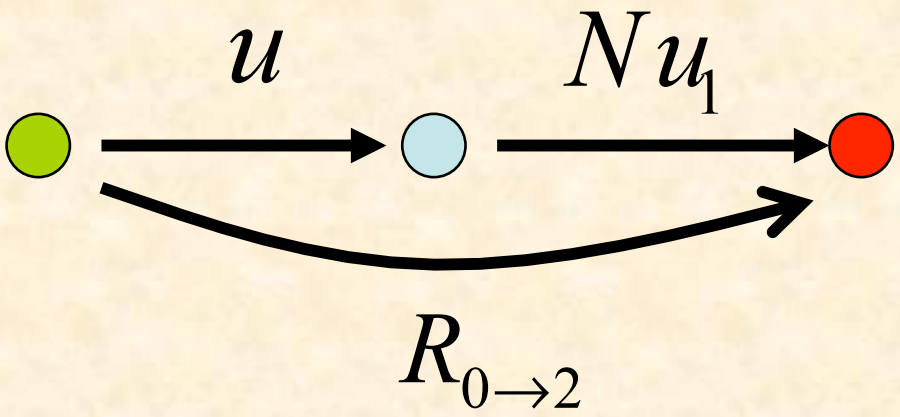


Generalized (hierarchical) Moran process

Two-step process and tunneling



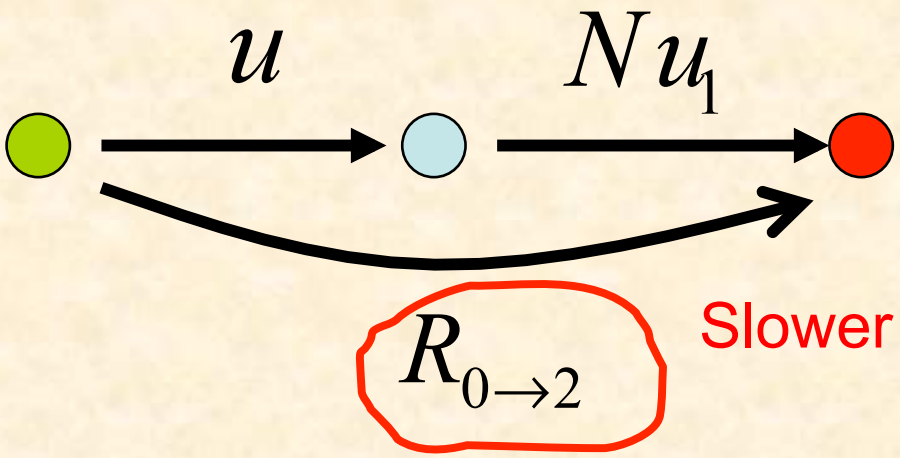
Stochastic tunneling in a hierarchical model



$$R_{0\to 2} = Nuu_1 \left|\log\ u_1\right|$$

$$(cf. \quad R = Nu\sqrt{u_1})$$

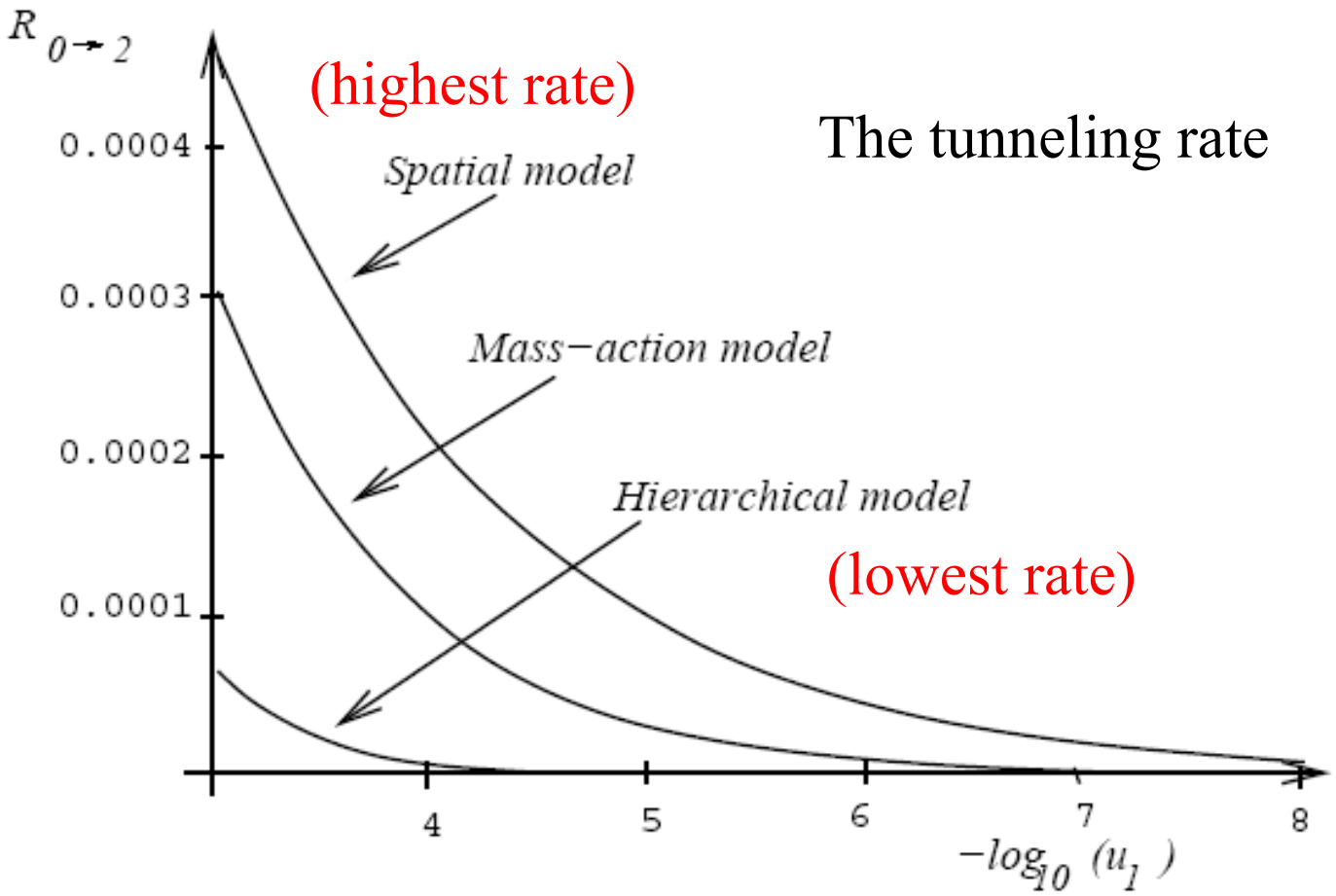
Stochastic tunneling in a hierarchical model



$$R_{0\to 2} = Nuu_1 \left|\log\ u_1\right|$$

$$(cf. \quad R = Nu\sqrt{u_1})$$

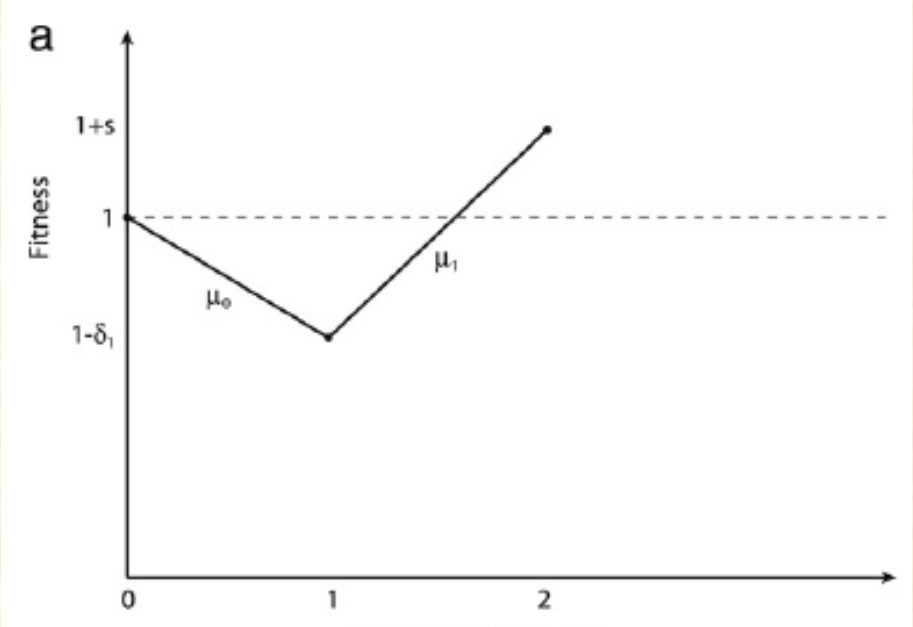
Rates of sequential evolution



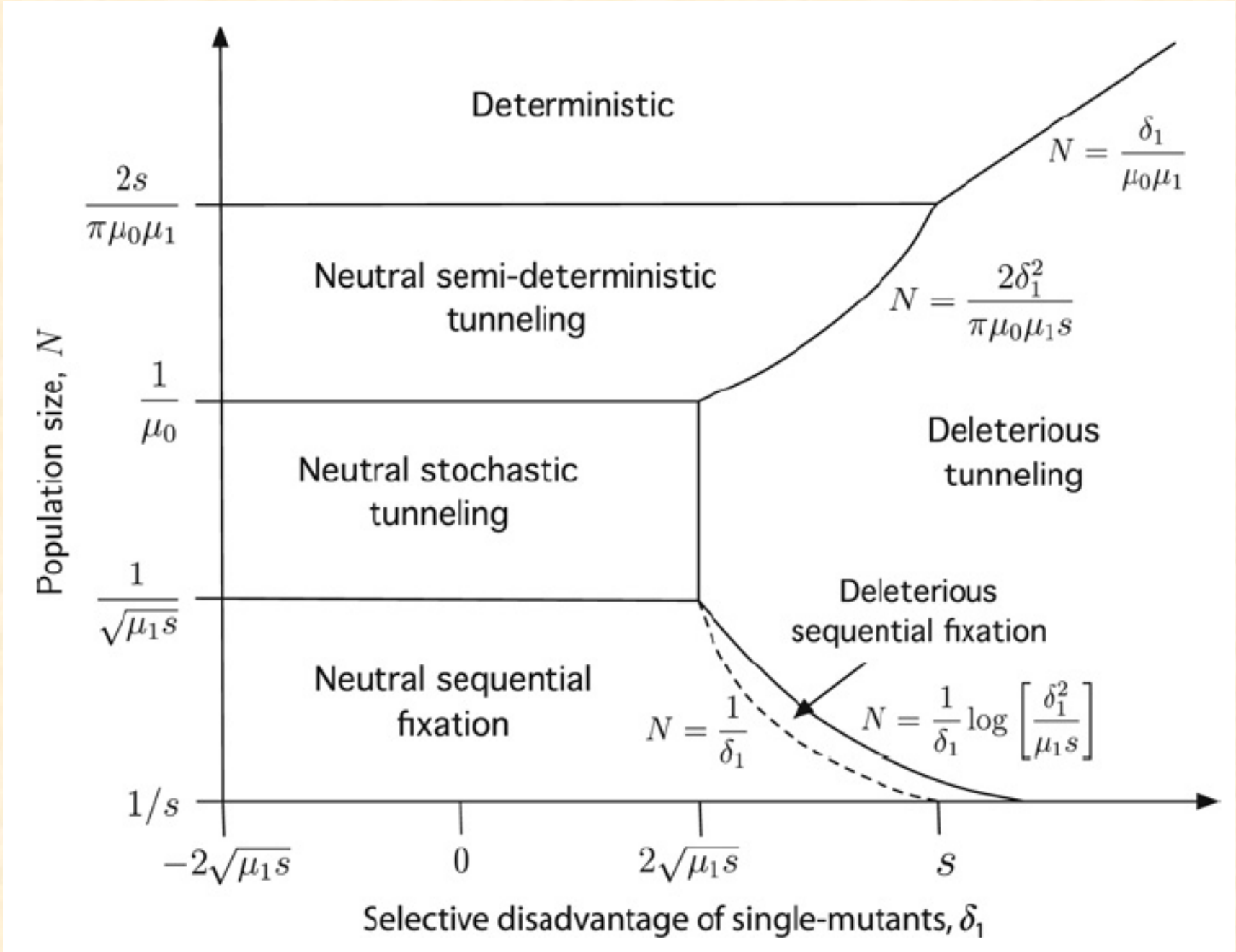
The tunneling rate

Theory of fitness valley crossing is complex

- Only two mutations
- No space
- No hierarchical structure



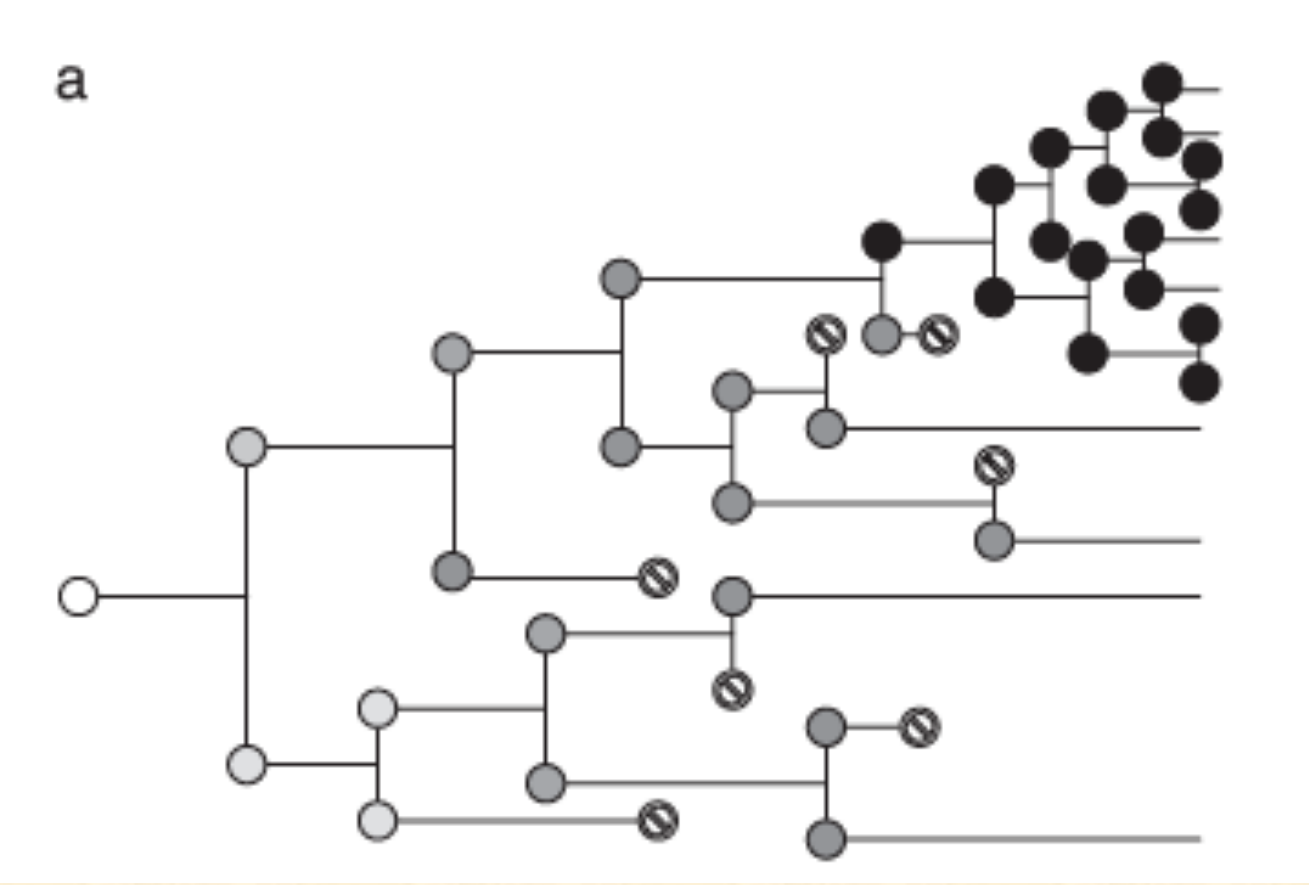
Weissman et al, "The rate at which asexual populations cross fitness valleys", Theor. Popul. Biol. 2009


Deterministic
$N = \frac{\delta_1}{\mu_0\mu_1}$
$\frac{2s}{\pi\mu_0\mu_1}$
Neutral semi-deterministic tunneling
$N = \frac{2\delta_1^2}{\pi\mu_0\mu_1 s}$
$\frac{1}{\mu_0}$
Deleterious tunneling
Neutral stochastic tunneling
$\frac{1}{\sqrt{\mu_1 s}}$
Deleterious sequential fixation
Neutral sequential fixation
$N = \frac{1}{\delta_1}$
$N = \frac{1}{\delta_1}\log\left[\frac{\delta_1^2}{\mu_1 s}\right]$
$1/s$
$-2\sqrt{\mu_1 s}$
0
$2\sqrt{\mu_1 s}$
s
Population size, N
Selective disadvantage of single-mutants, δ_1

Cooperation in cancer cells

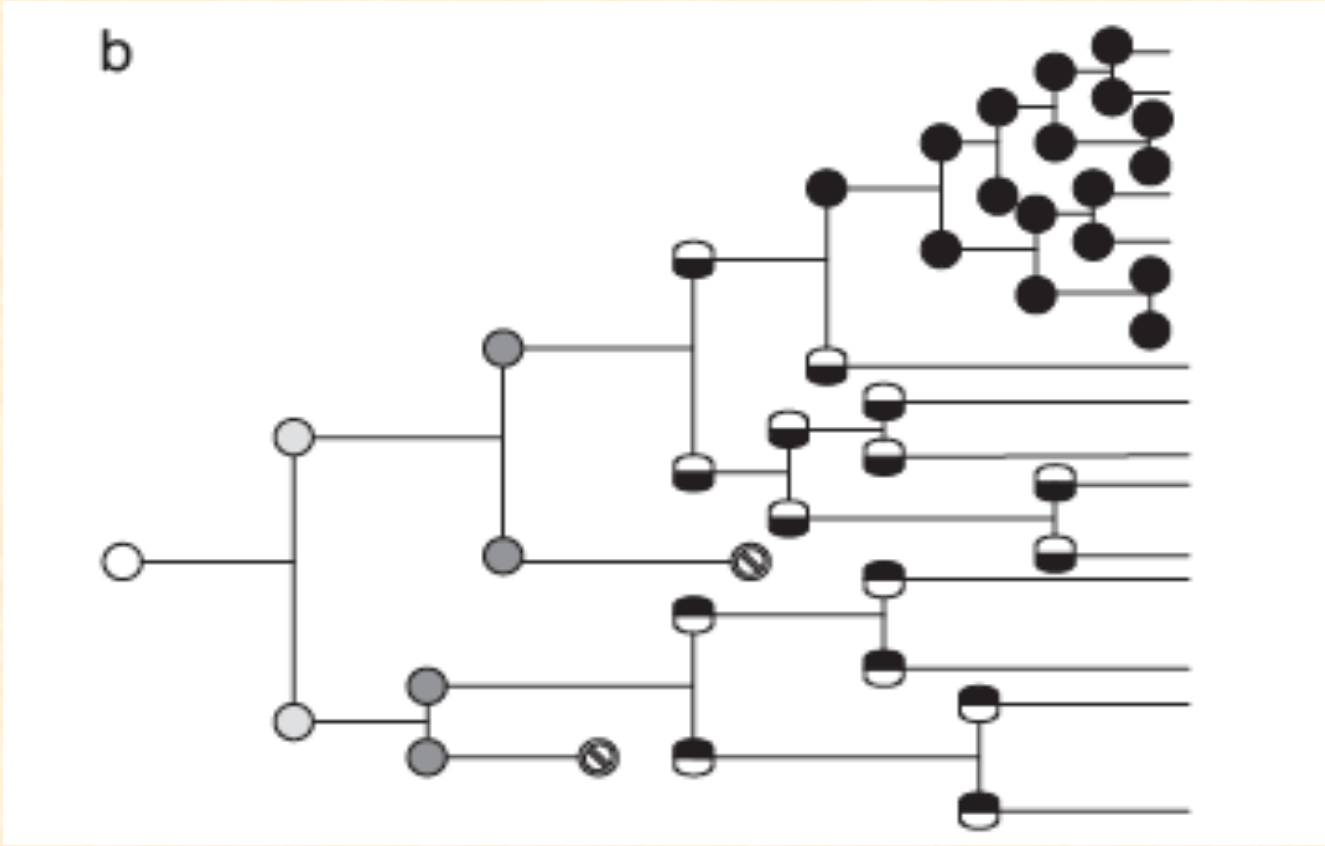
- Traditional view of carcinogenesis involves accumulation of sequential mutations
- It has been suggested however that all the mutations do not have to “meet” in the same cell
- Cells can engage in “division of labor” interactions

Sequential evolution



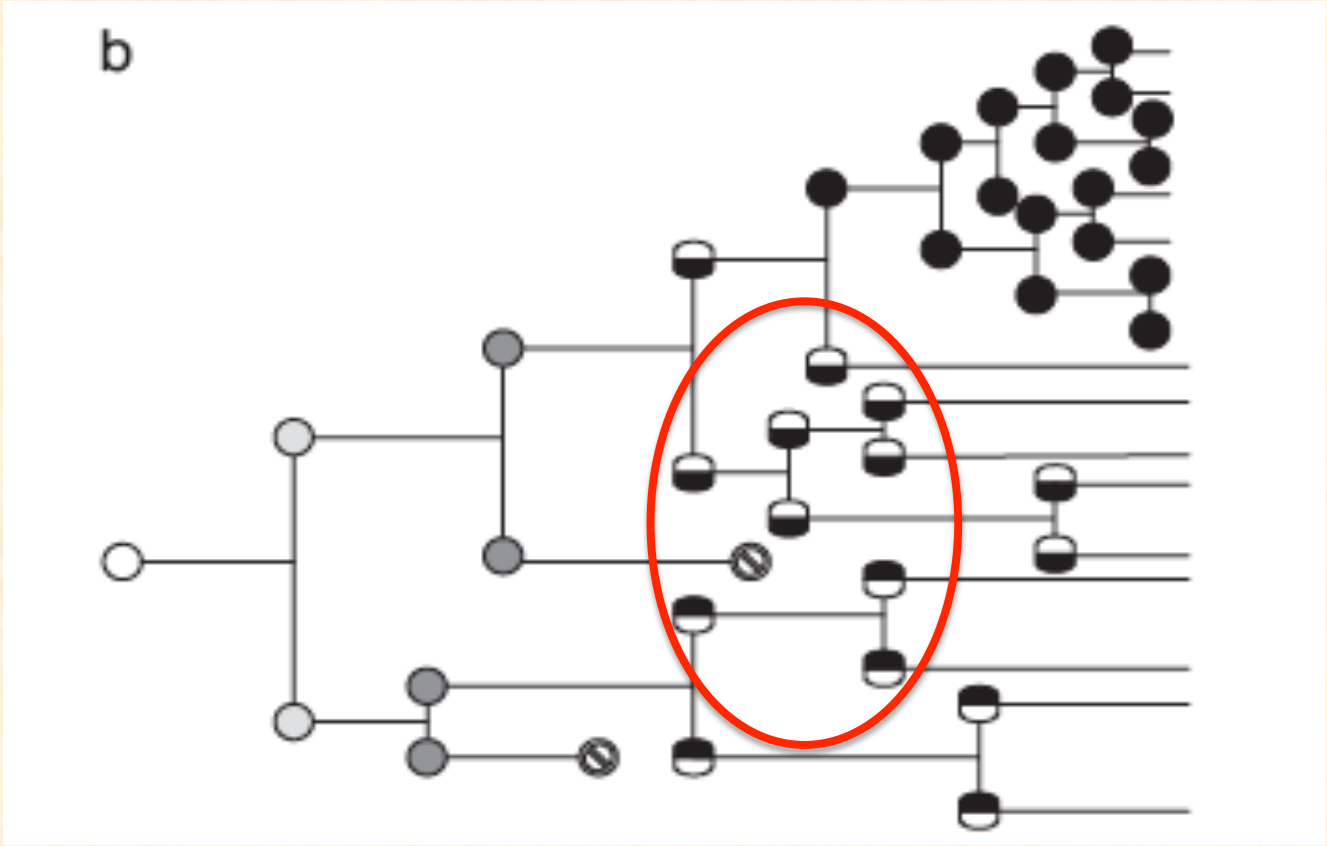
Axelrod et al, "Evolution of cooperation among tumor cells", PNAS 2006

Evolution in the presence of cooperation



Axelrod et al, "Evolution of cooperation among tumor cells", PNAS 2006

Evolution in the presence of cooperation



Axelrod et al, "Evolution of cooperation among tumor cells", PNAS 2006

Evolution of cooperation among tumor cells

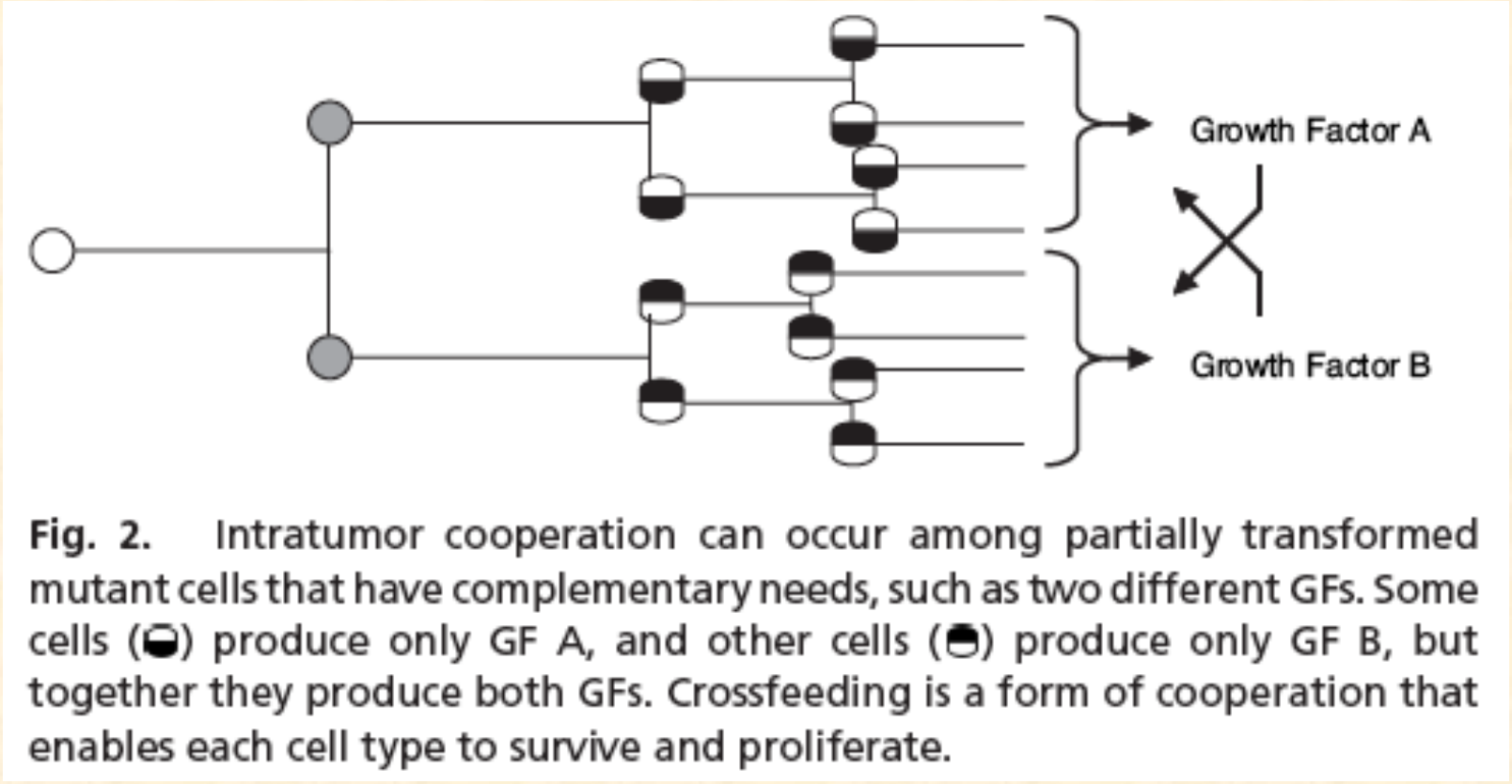


Fig. 2. Intratumor cooperation can occur among partially transformed mutant cells that have complementary needs, such as two different GFs. Some cells (◒) produce only GF A, and other cells (◓) produce only GF B, but together they produce both GFs. Crossfeeding is a form of cooperation that enables each cell type to survive and proliferate.

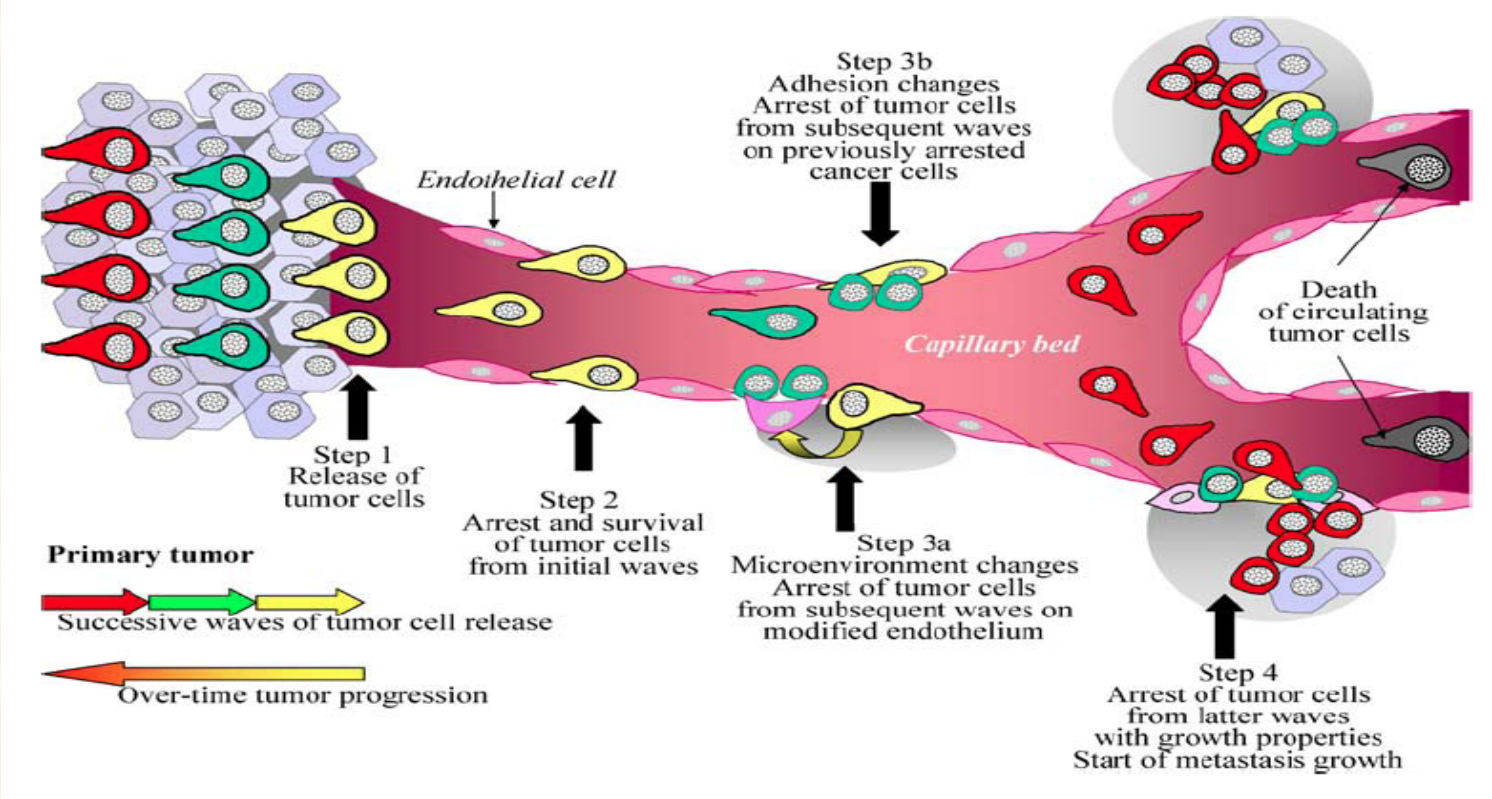
Axelrod et al, "Evolution of cooperation among tumor cells", PNAS 2006

Evolution of cooperation among tumor cells

- Angiogenesis (VEGF for recruiting blood vessesl; all cells benefit)
- Sharing of certain growth signals (VEGF, PDGF, TGF-beta)
- Tissue invasion and metastasis (factors that allow survival under loss of contact inhibition, degrading extracellular matrix, etc)

Axelrod et al, "Evolution of cooperation among tumor cells", PNAS 2006

Cooperation in metastasis



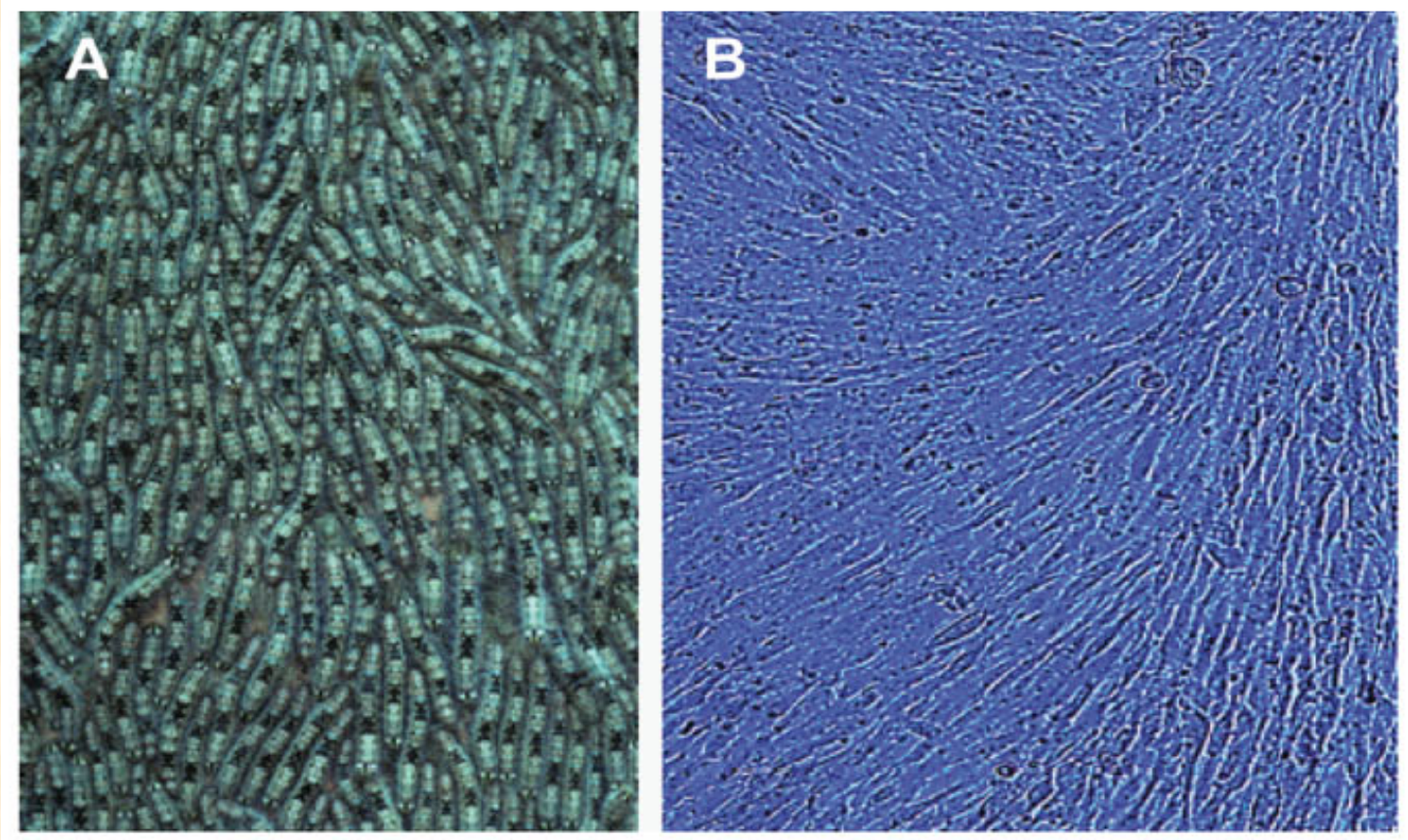
Birard et al, "A "class action" against the microenvironment: do cancer cells cooperate in metastasis?" Cancer Metastasis Rev. (2008)

Evolution of cooperation among tumor cells

- Modifications to the stroma can have an effect on neoplastic cells…
- Cocultures of mesenchymal stem cells and the breast cancer cell line MCF7/Ras…
- Breast cancer cells that have metastasized to the bone produce paracrine factors such as tumor necrosis factor -alpha (*TNF-α) and insulin-like* growth factor II (*IGF-II)…*
- Prostate cancer, cervical cancer, etc

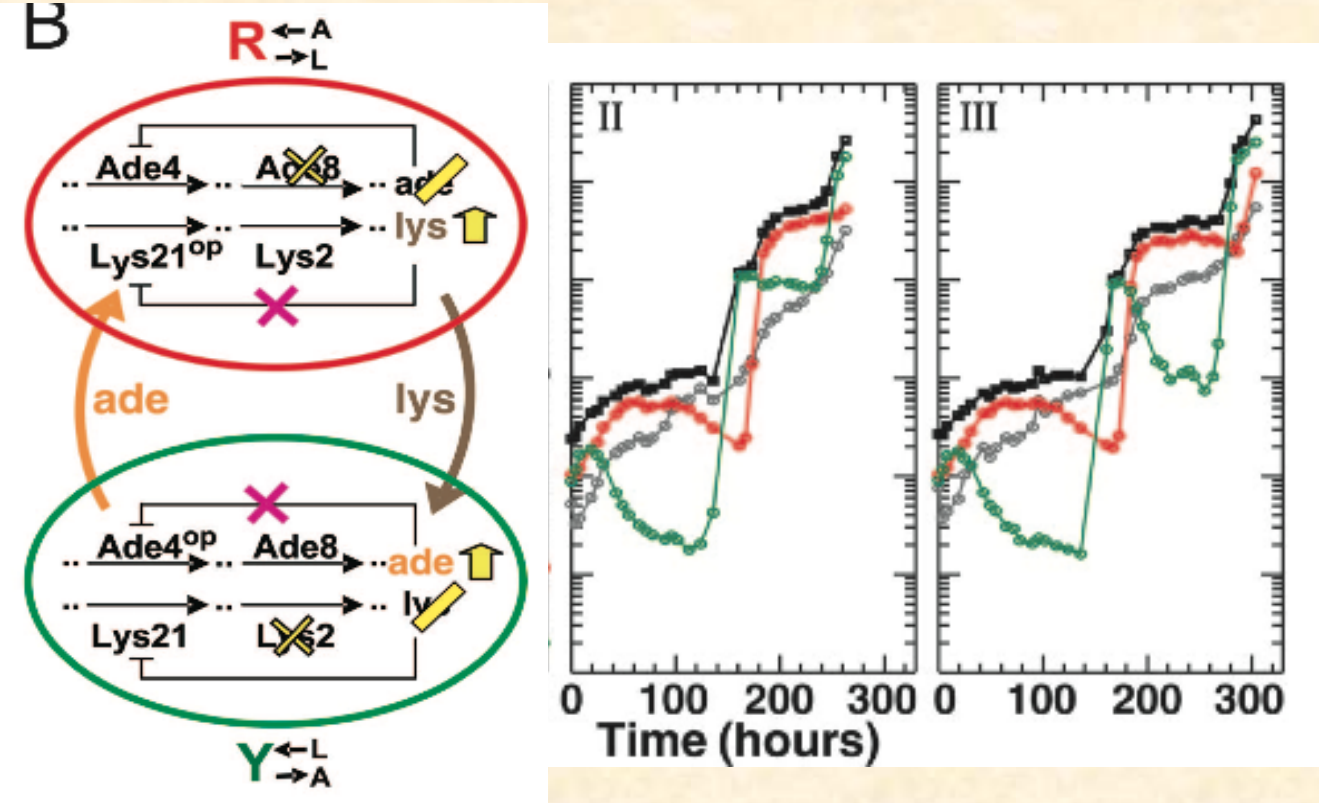
Sprouffske & Maley, "Cooperation and cancer", Thomas-Tikhonenko (ed.), *Cancer Genome and Tumor Micro-Environment* (2010)

Collective behavior of cancerous cells



Deisboek & Couzin, "Collective behavior in cancer cell populations" Bioessays (2009)

Synthetic cooperation in engineered yeast populations

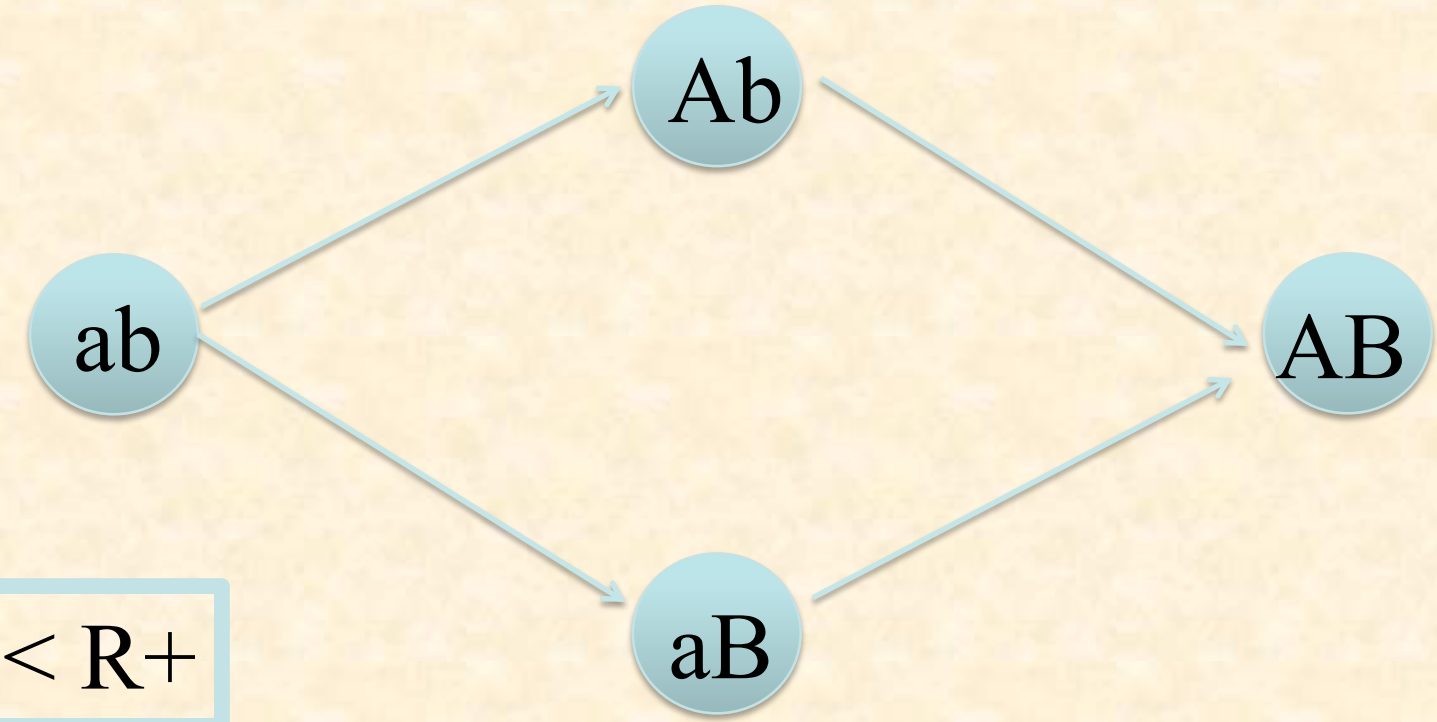


Shou et al, "Synthetic cooperation in engineered yeast populations", PNAS 2007

The concept

- Division of labor
- Public goods

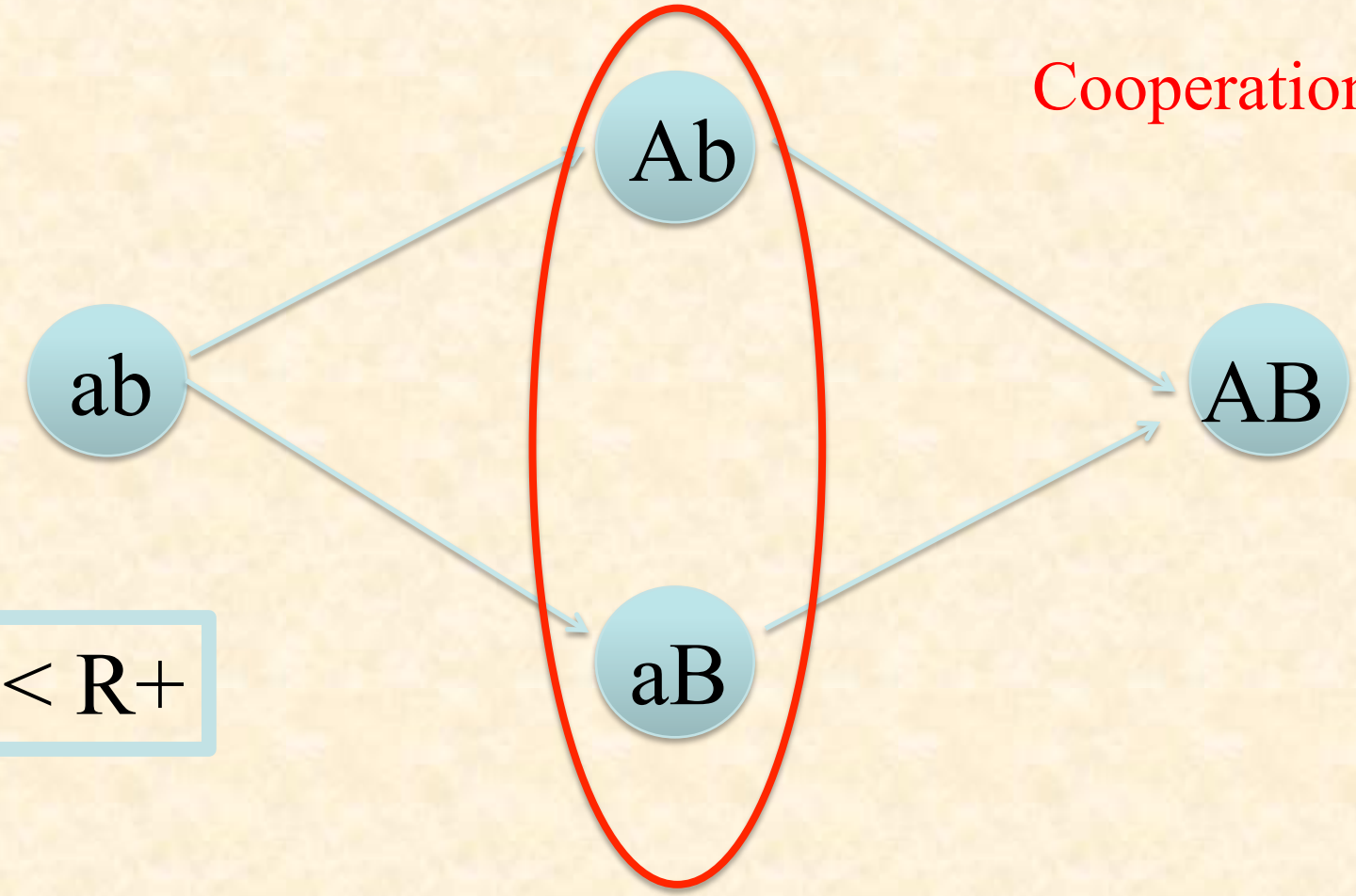
Sequential evolution



$R^- < R < R+$

Fitness R R^- R+

Division of labor



$R^- < R < R+$

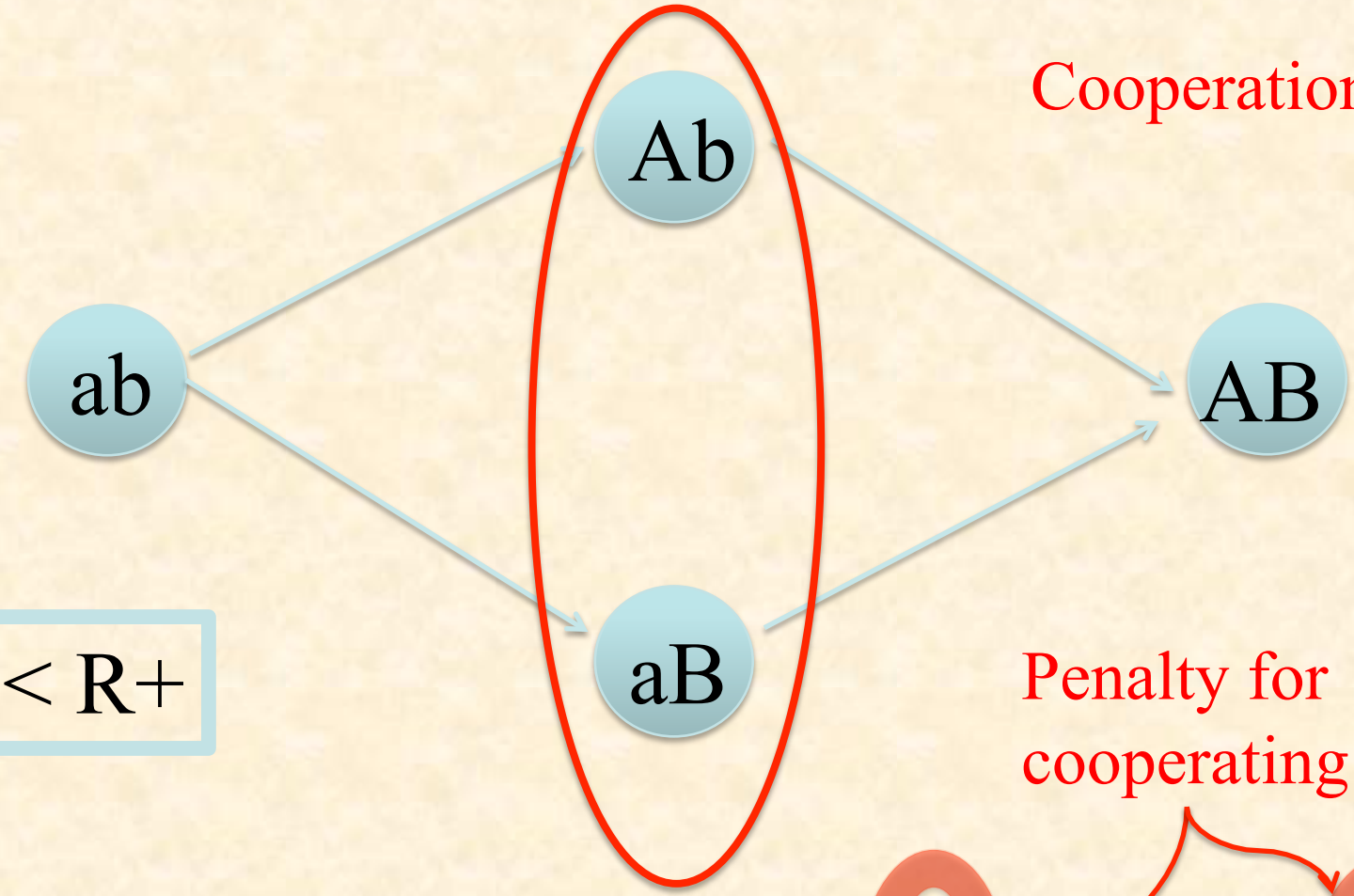
Fitness R

w/o coop: R^- -f

with coop: R^+ -f

R^+-2f

Division of labor



$R^- < R < R+$

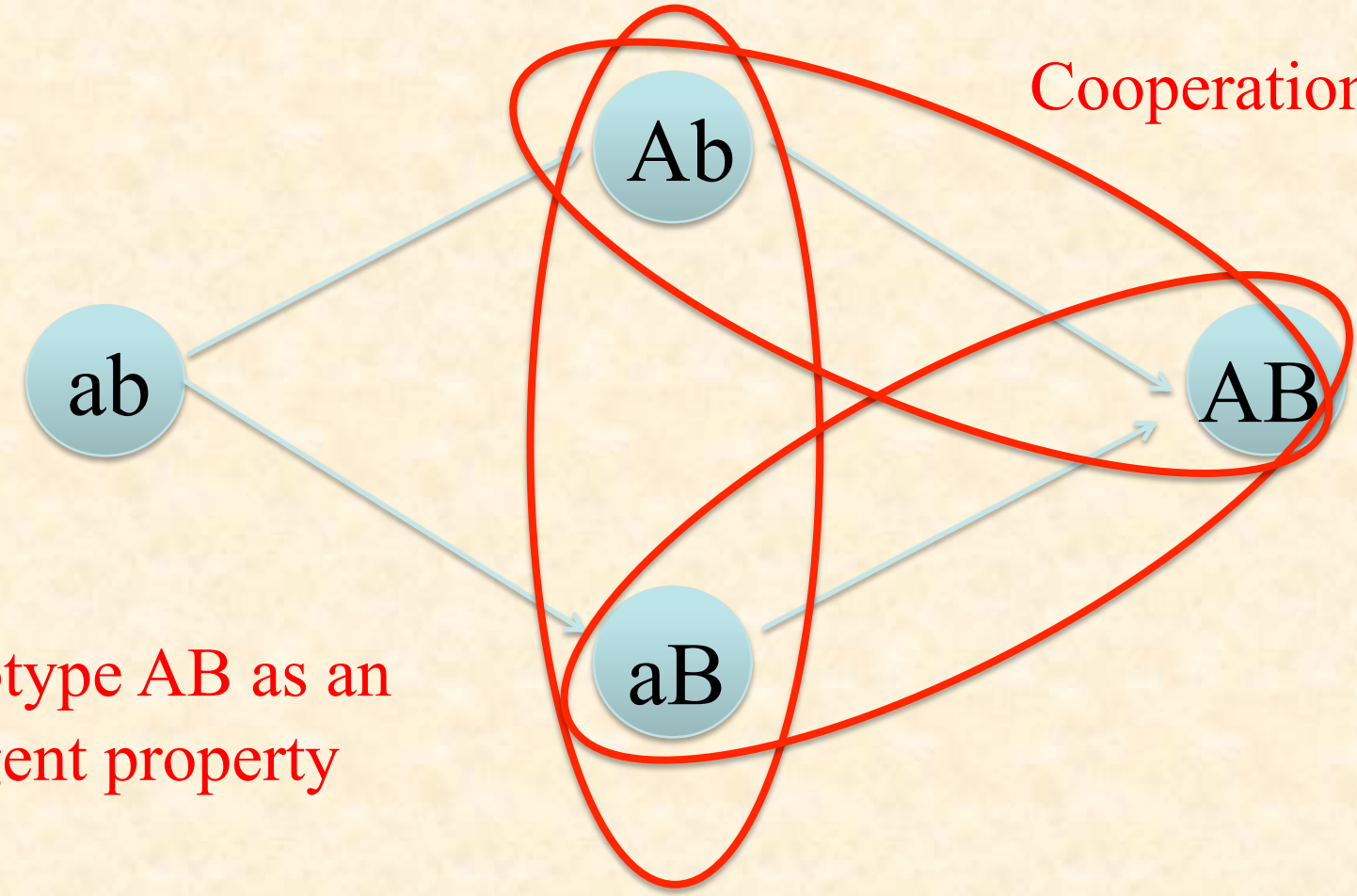
Fitness R

w/o coop: R^- -f

with coop: R^+ -f

R^+-2f

Division of labor

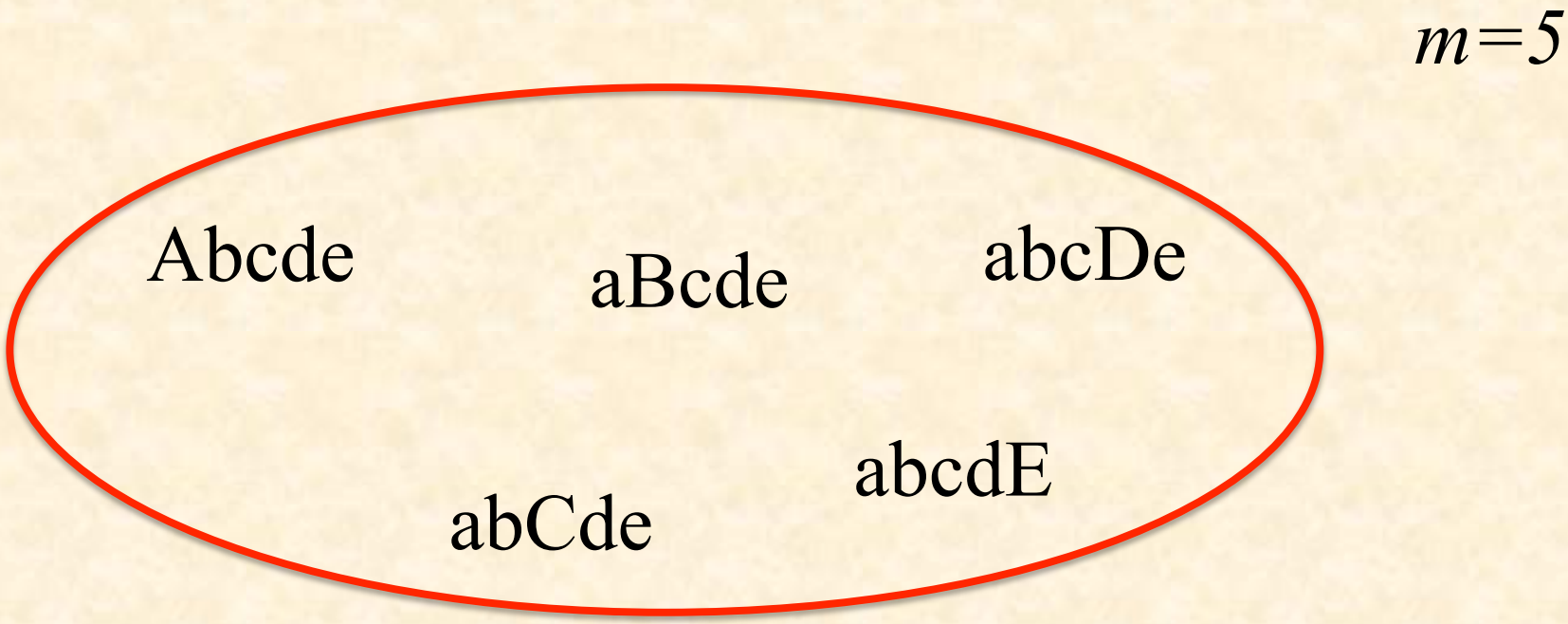


Phenotype AB as an emergent property

Fitness R w/o coop: R^- -f with coop: R^+ -f R^+-2f

The number of cooperating sites

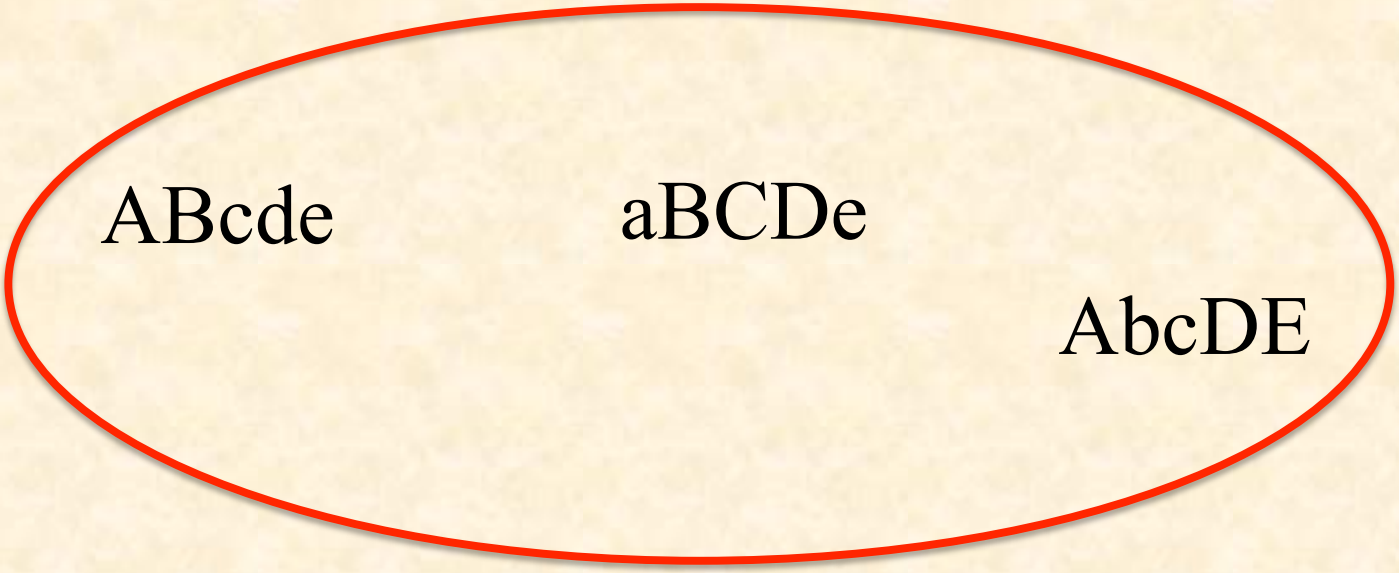
- *m* = the number of genes required to be mutated to ensure enhanced fitness



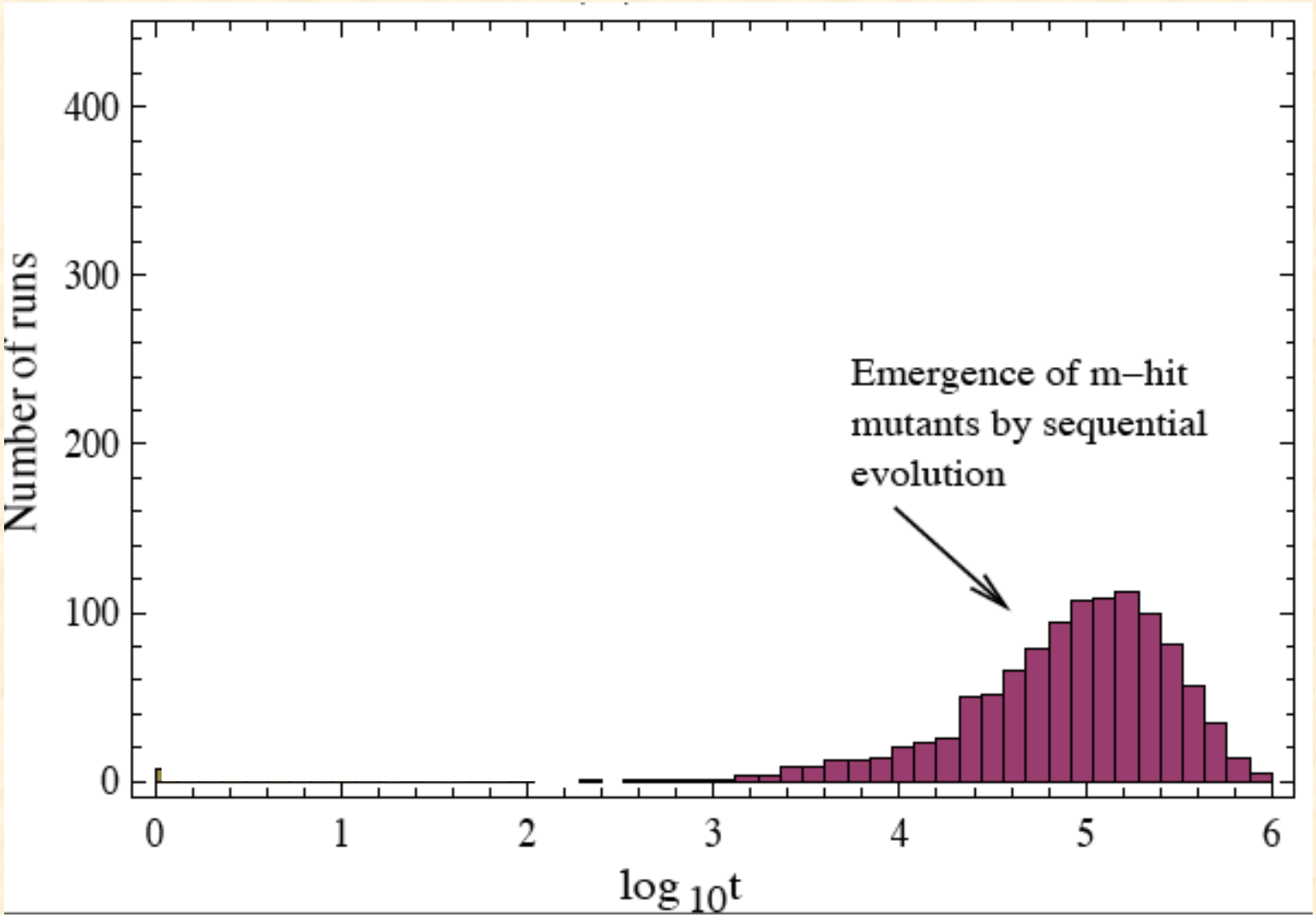
The number of cooperating sites

- *m* = the number of genes required to be mutated to ensure enhanced fitness

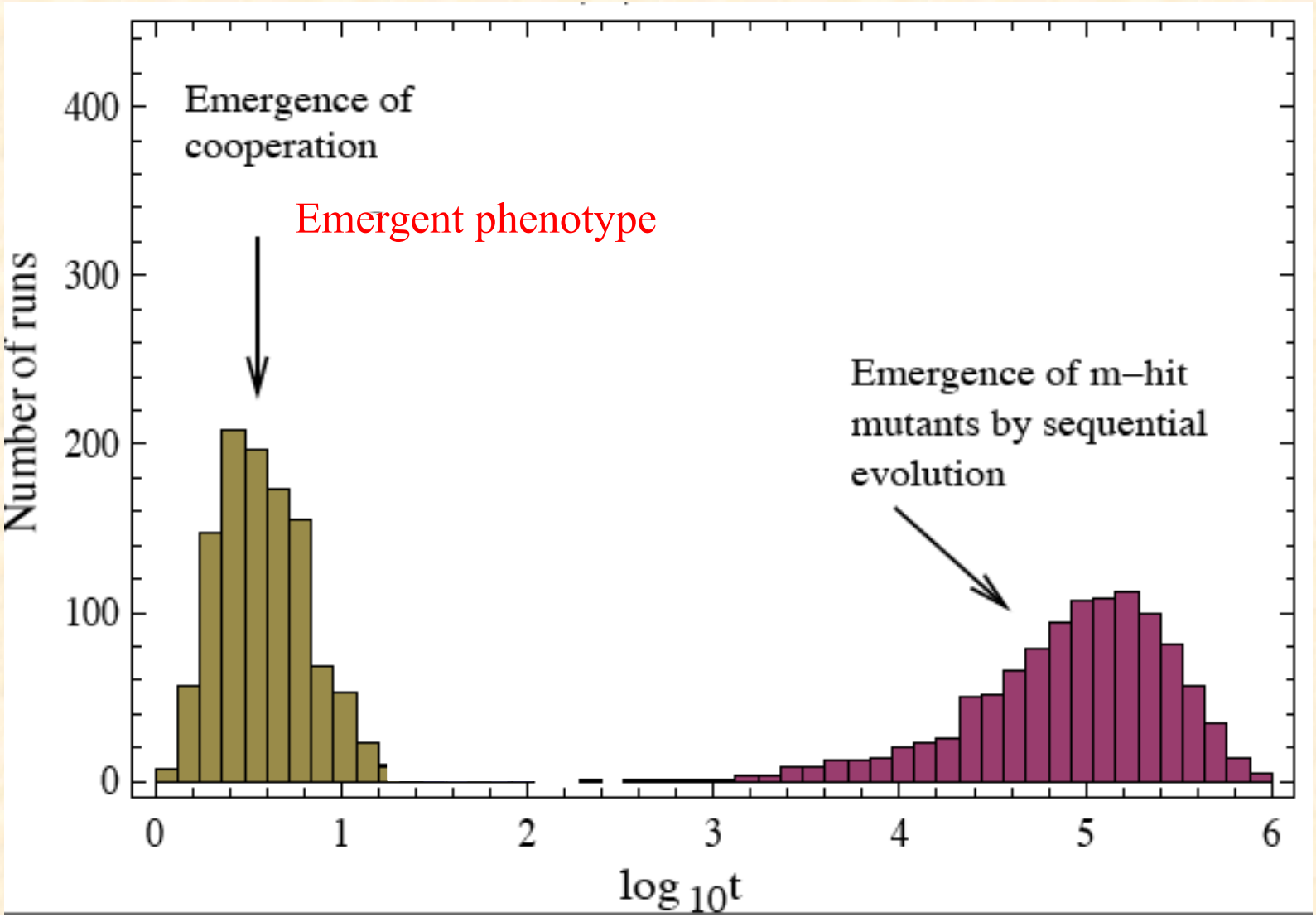
$m=5$



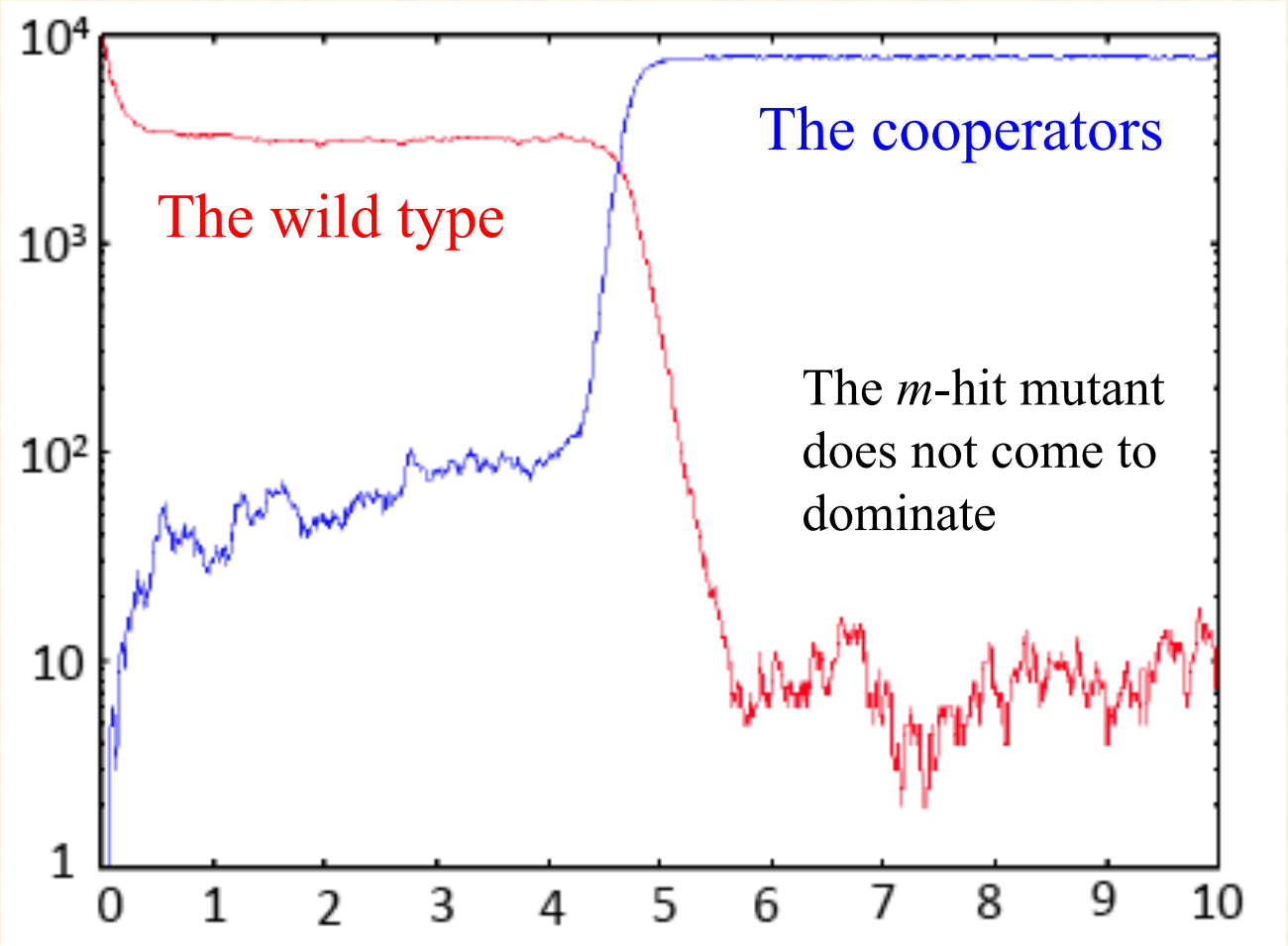
Emergence of a complex phenotype



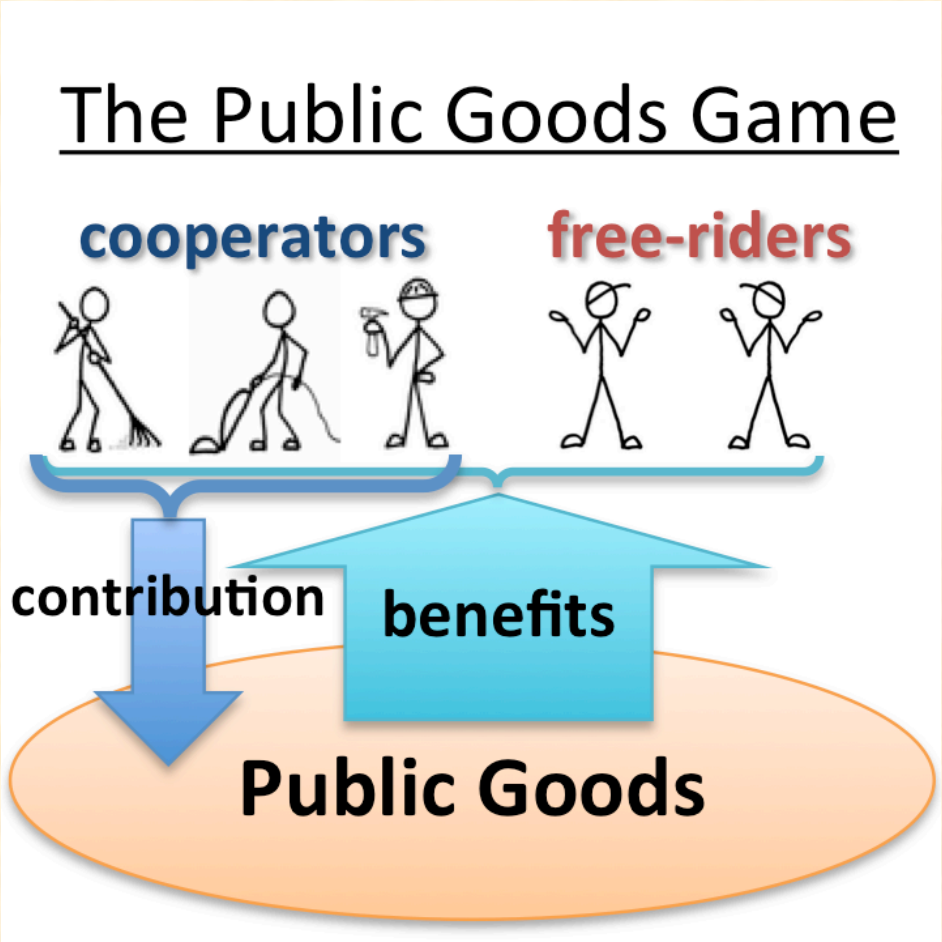
Emergence of a complex phenotype



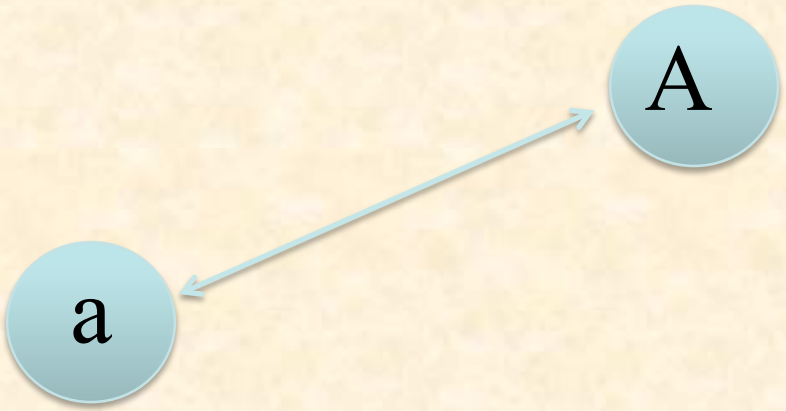
Emergence of a complex phenotype



Cooperators and cheaters



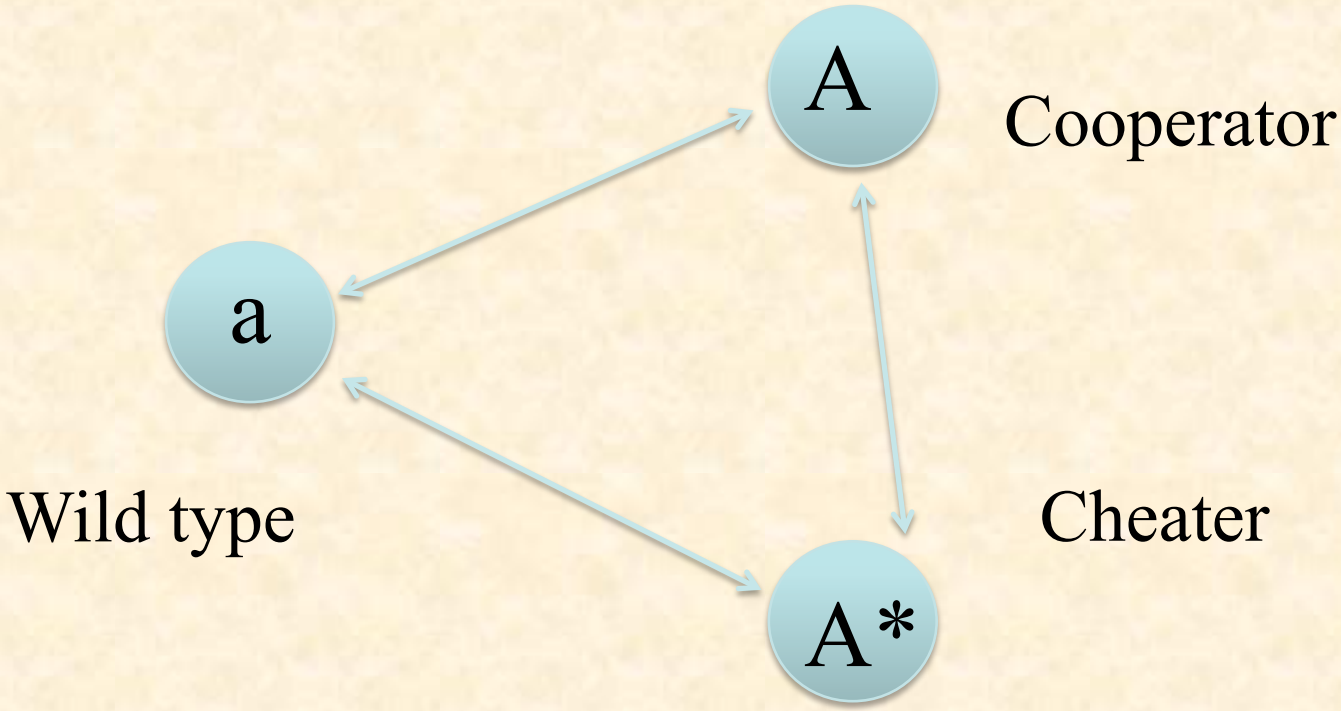
Cooperation and cheating

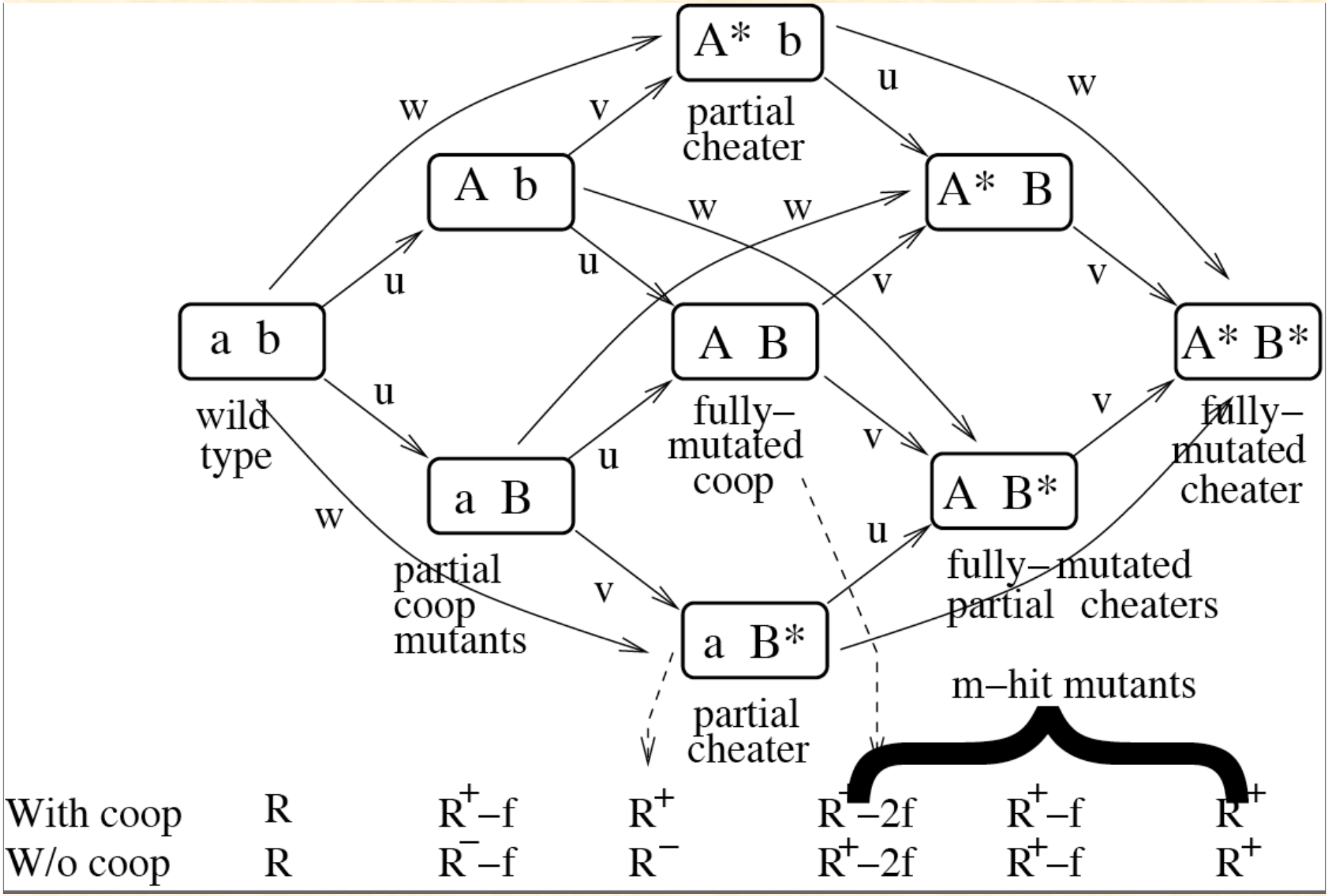


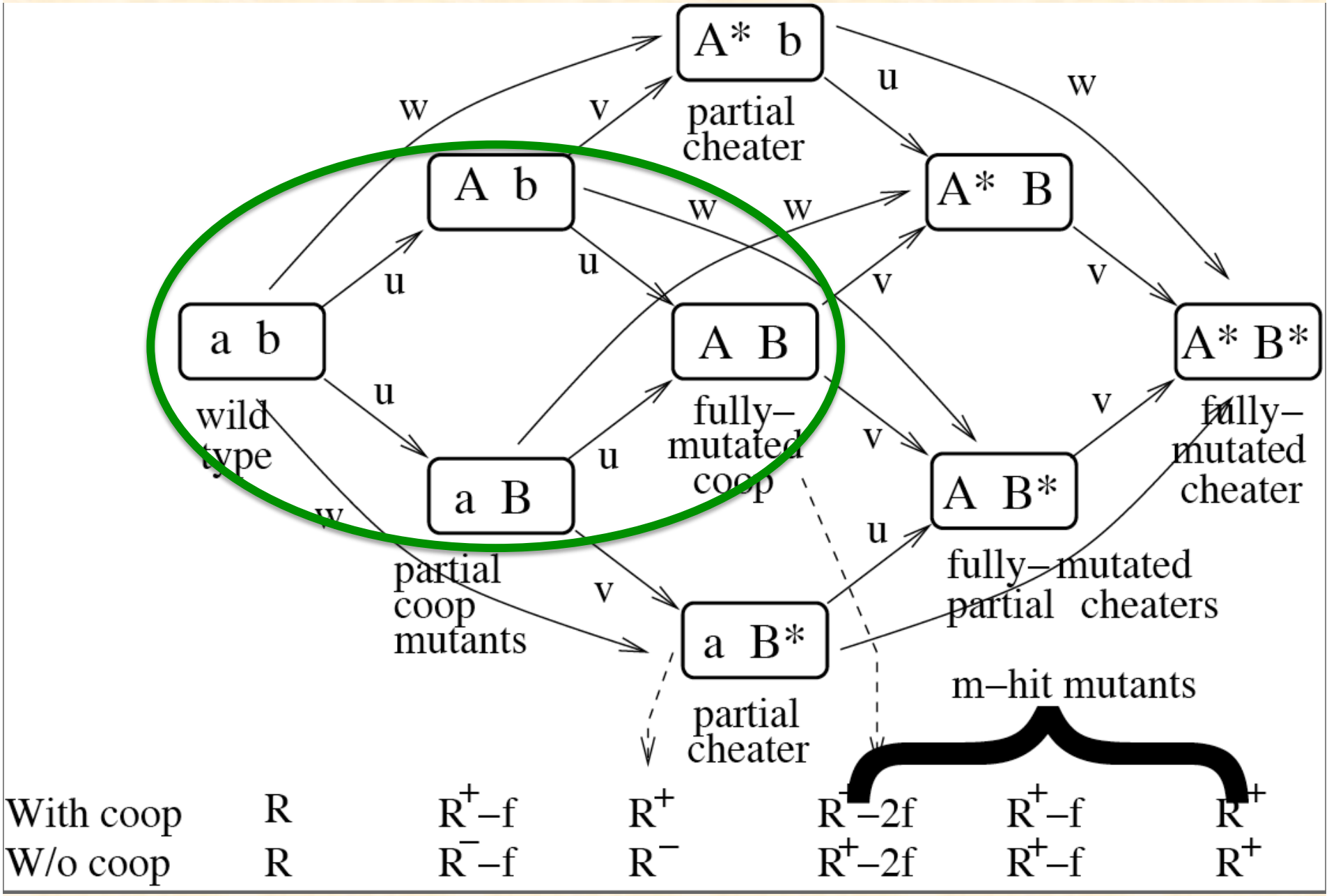
Cooperator

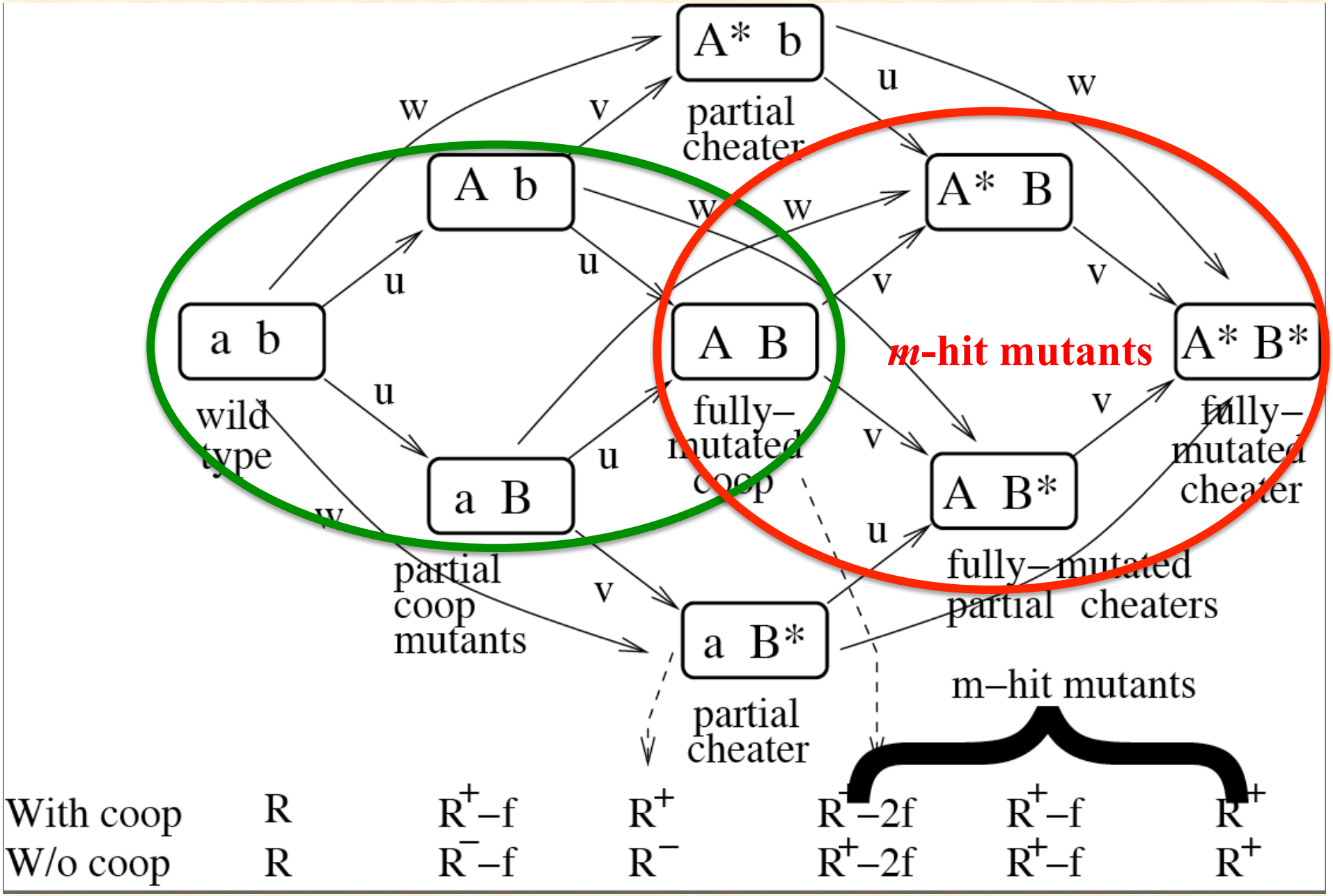
Wild type

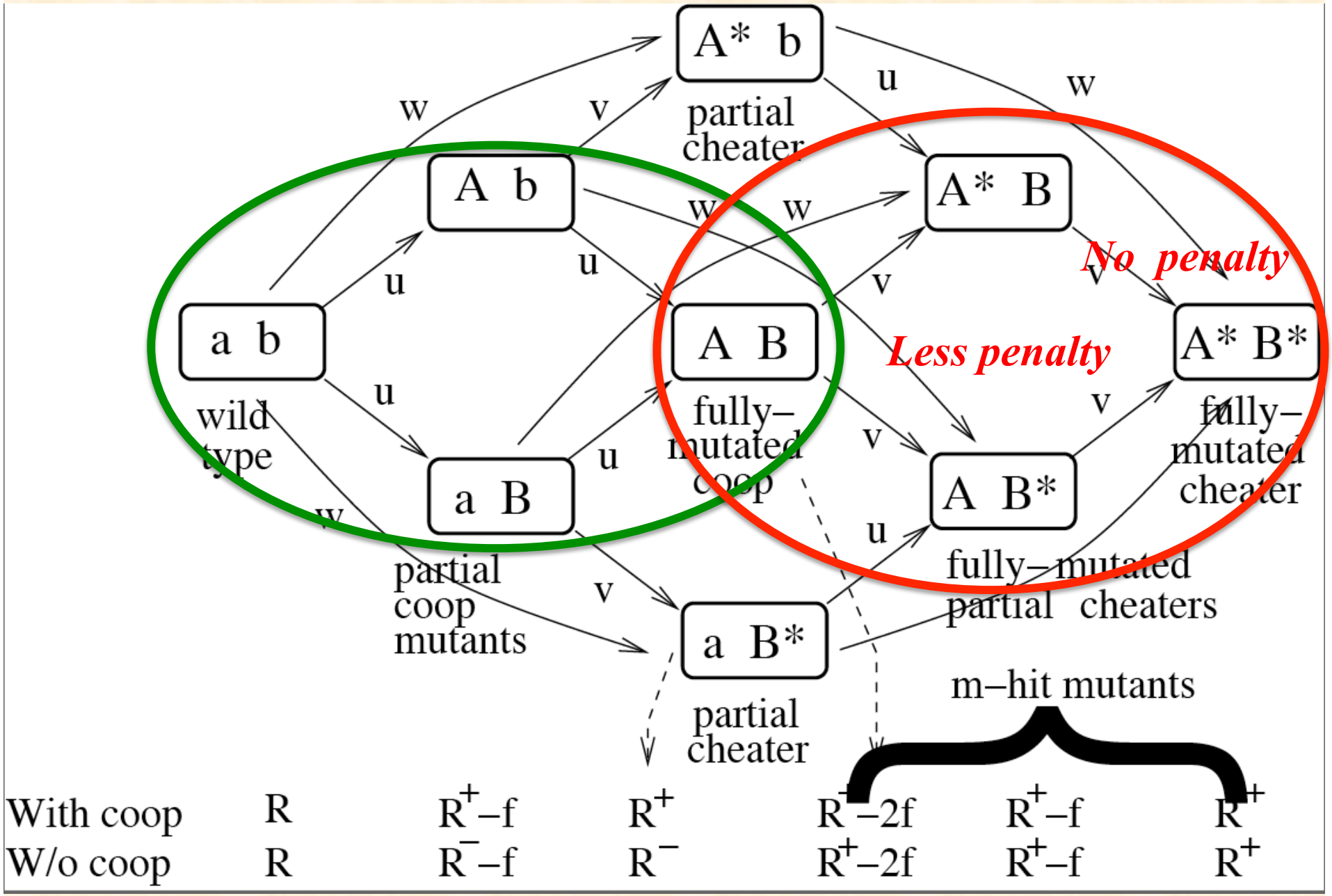
Cooperation and cheating



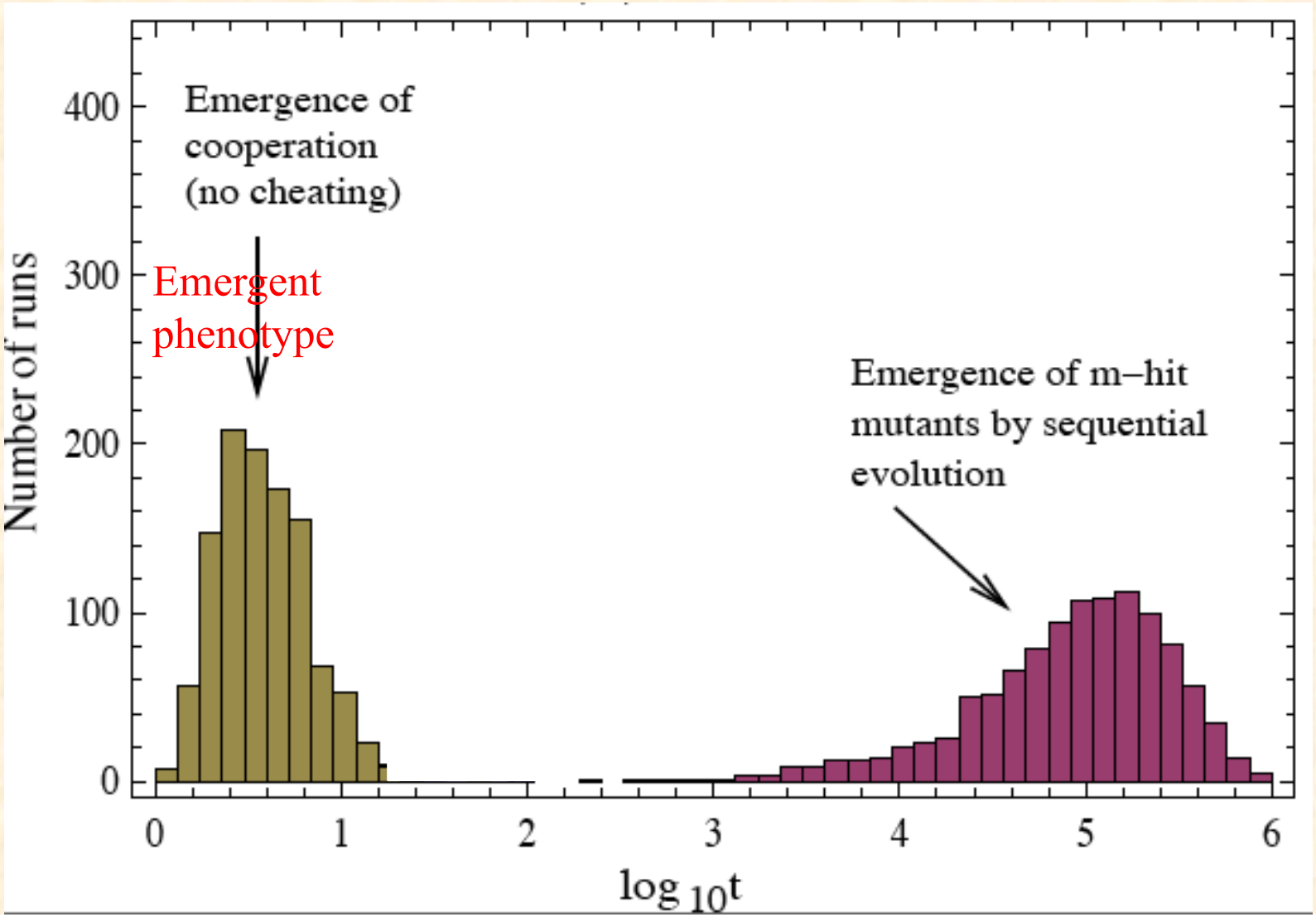

A* b
partial cheater
A b
A* B
a b
wild type
A B
fully–mutated coop
A* B*
fully–mutated cheater
a B
partial coop mutants
A B*
fully–mutated partial cheaters
a B*
partial cheater
m–hit mutants
u
v
w
With coop R R+–f R+ R+–2f R+–f R+
W/o coop R R–f R– R+–2f R+–f R+


A* b
partial cheater
A b
A* B
a b
wild type
A B
fully–mutated coop
A* B*
fully–mutated cheater
a B
A B*
fully–mutated partial cheaters
partial coop mutants
a B*
partial cheater
m–hit mutants
u
v
w
With coop R R+–f R+ R+–2f R+–f R+
W/o coop R R–f R– R+–2f R+–f R+

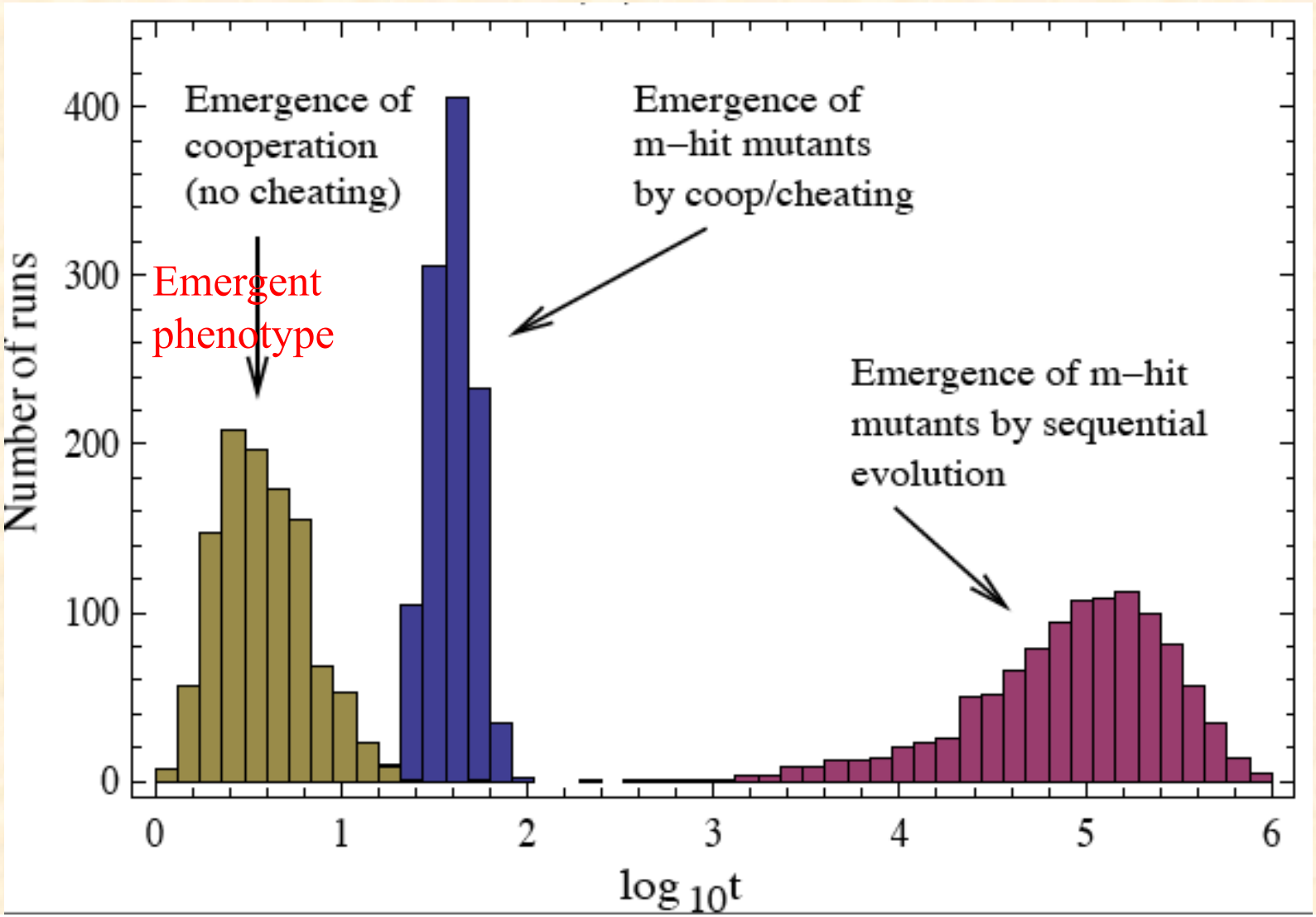

A* b
partial cheater
A b
a b
wild type
A B
fully–mutated coop
a B
partial coop mutants
a B*
partial cheater
A* B
A B*
A* B*
fully–mutated cheater
fully–mutated partial cheaters
m-hit mutants
m–hit mutants
u
v
w
With coop R R+–f R+ R+–2f R+–f R+
W/o coop R R–f R– R+–2f R+–f R+


A* b
partial cheater
A b
a b
wild type
A B
fully–mutated coop
a B
partial coop mutants
a B*
partial cheater
A* B
A B*
A* B*
fully–mutated cheater
fully–mutated partial cheaters
No penalty
Less penalty
m–hit mutants
u
v
w
With coop R R+–f R+ R+–2f R+–f R+
W/o coop R R–f R– R+–2f R+–f R+

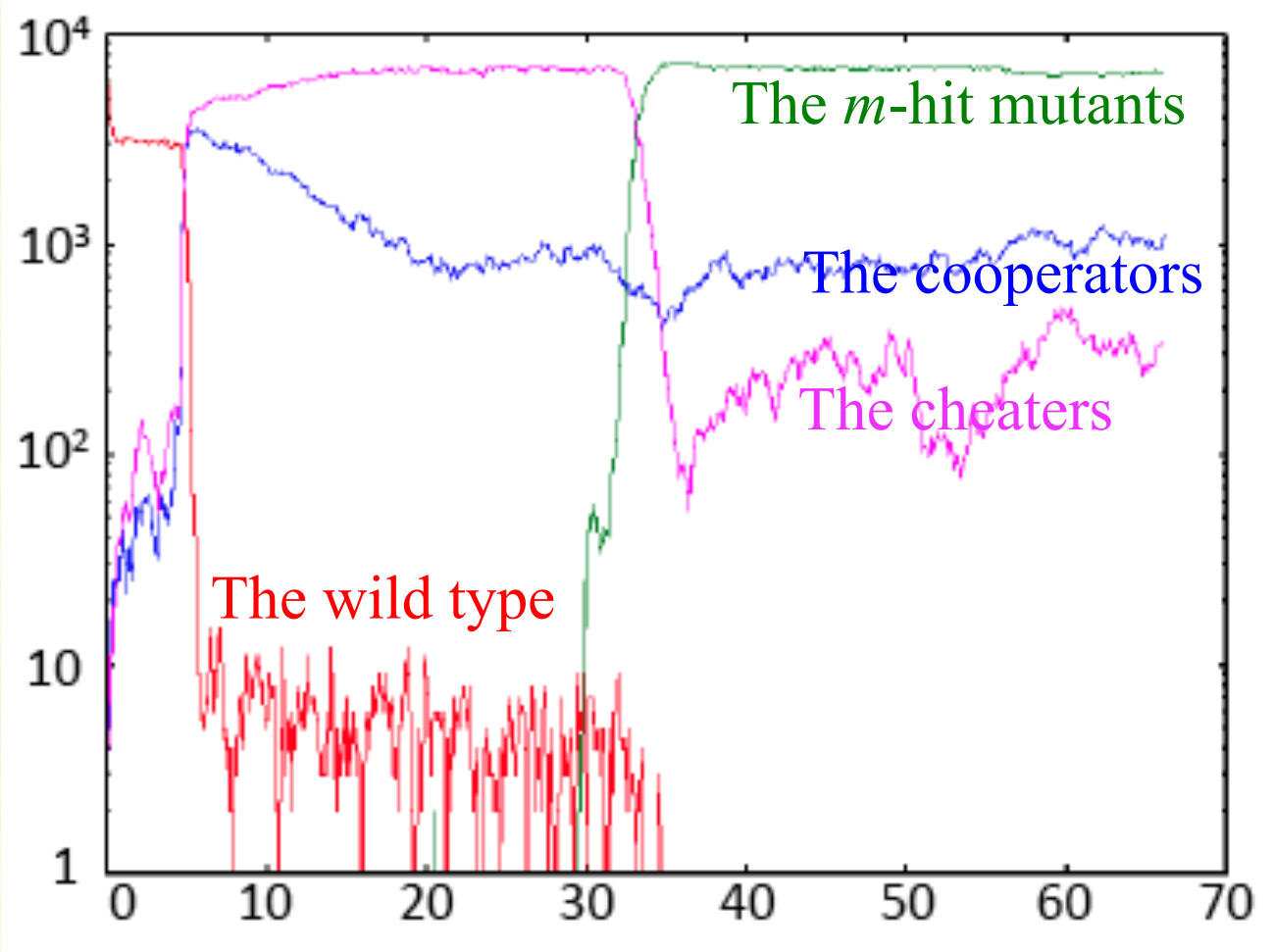
Emergence of a complex phenotype



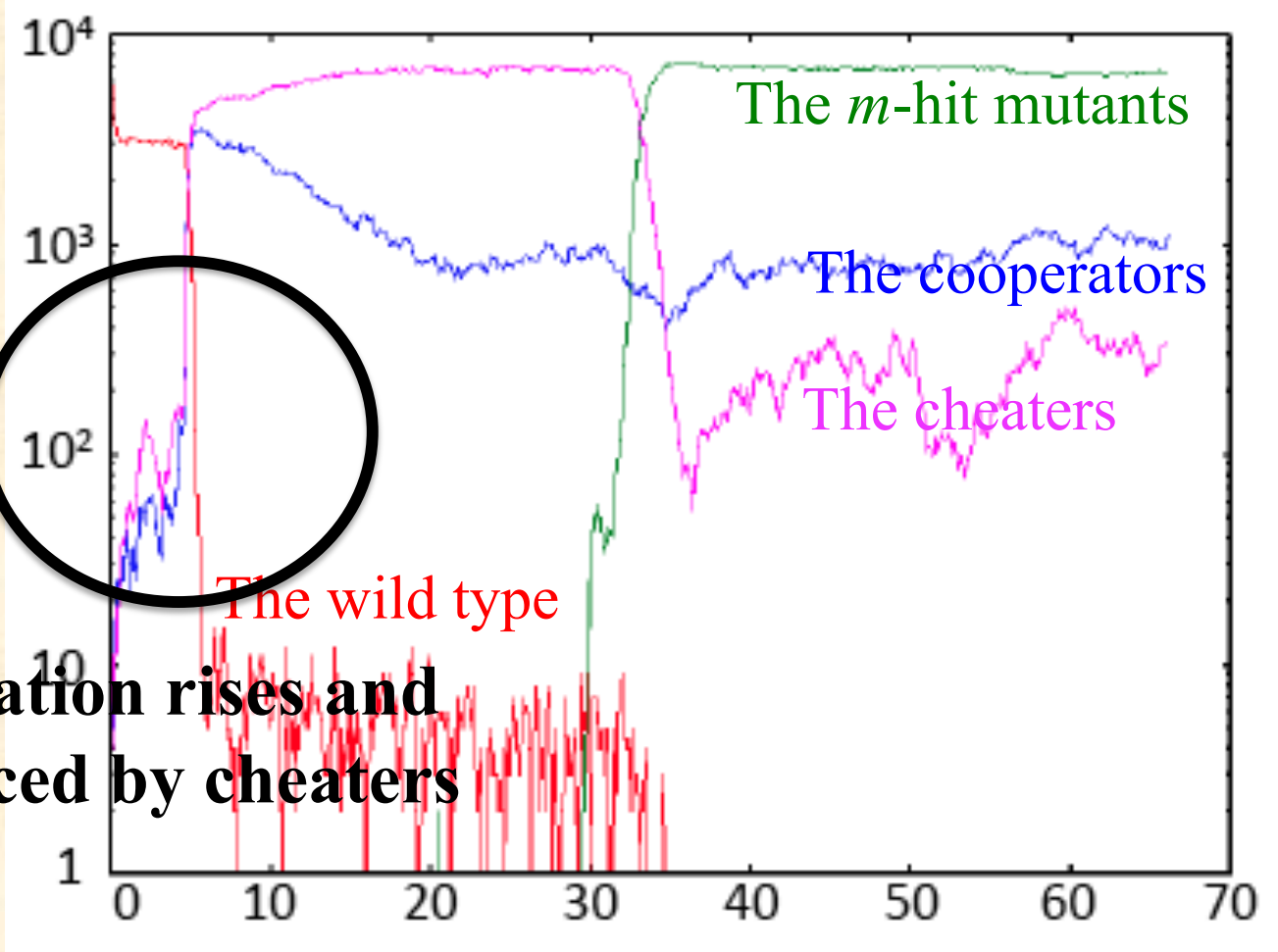
Emergence of *m*-hit mutants



In the presence of cheating

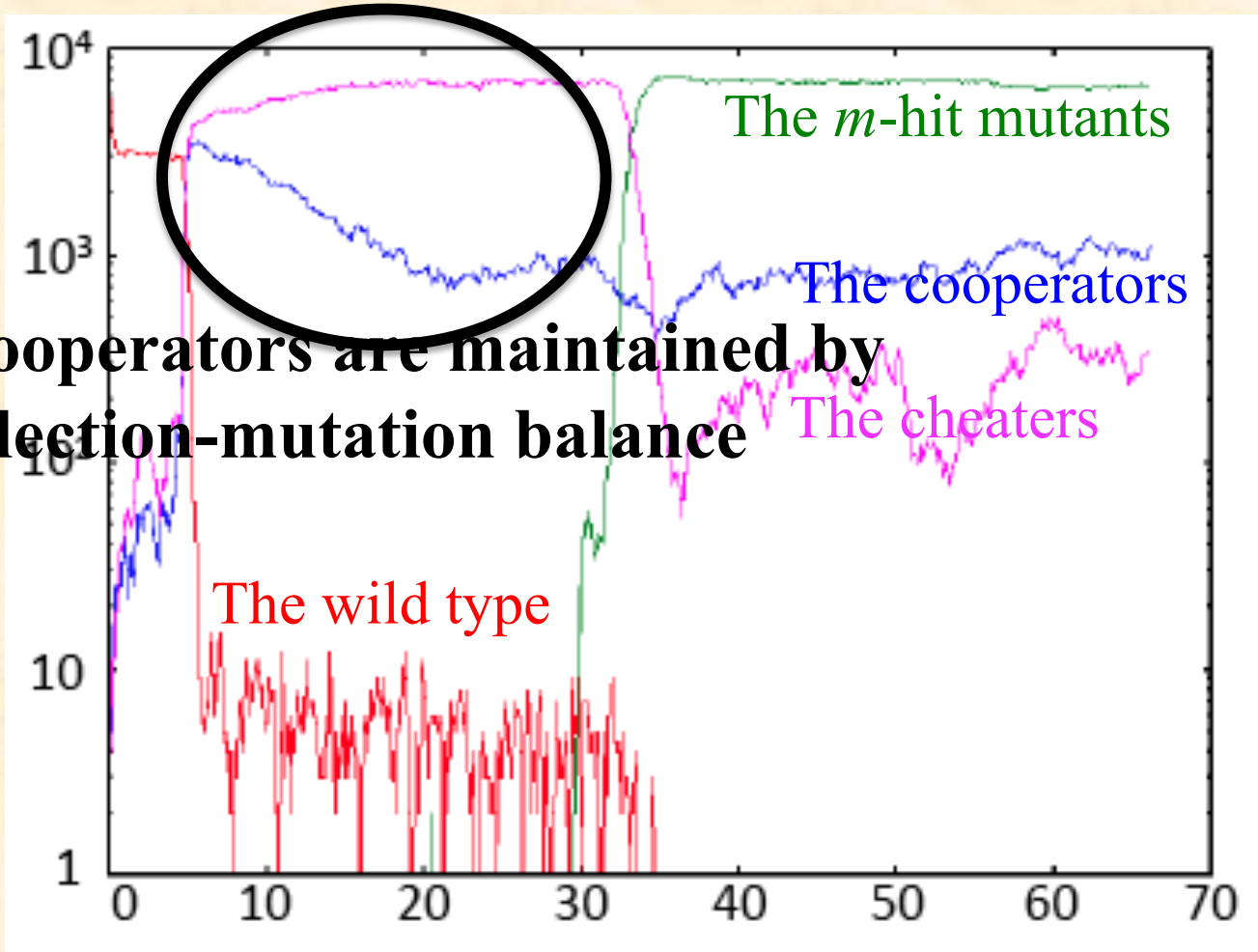


In the presence of cheating



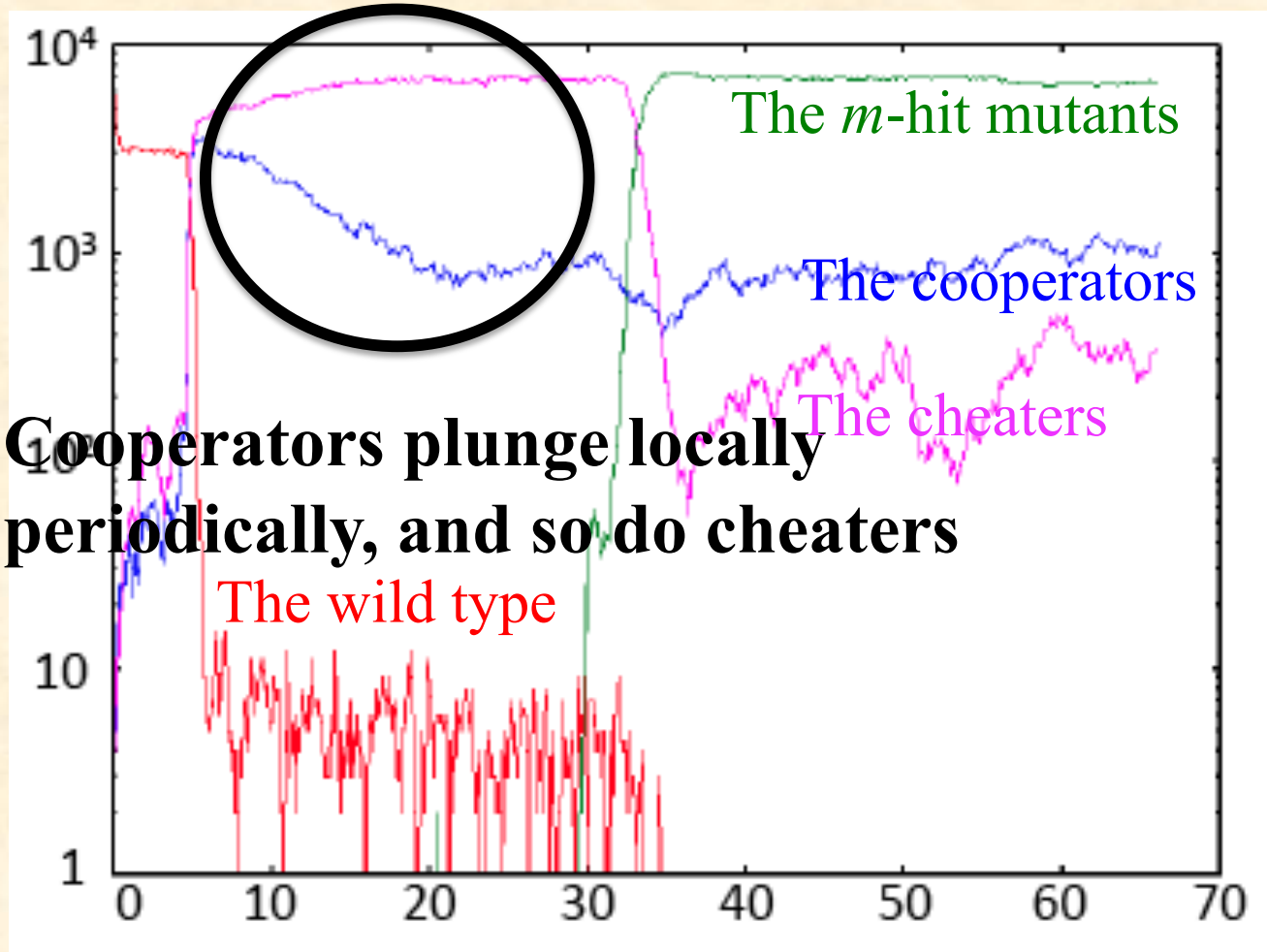
Cooperation rises and is replaced by cheaters

In the presence of cheating

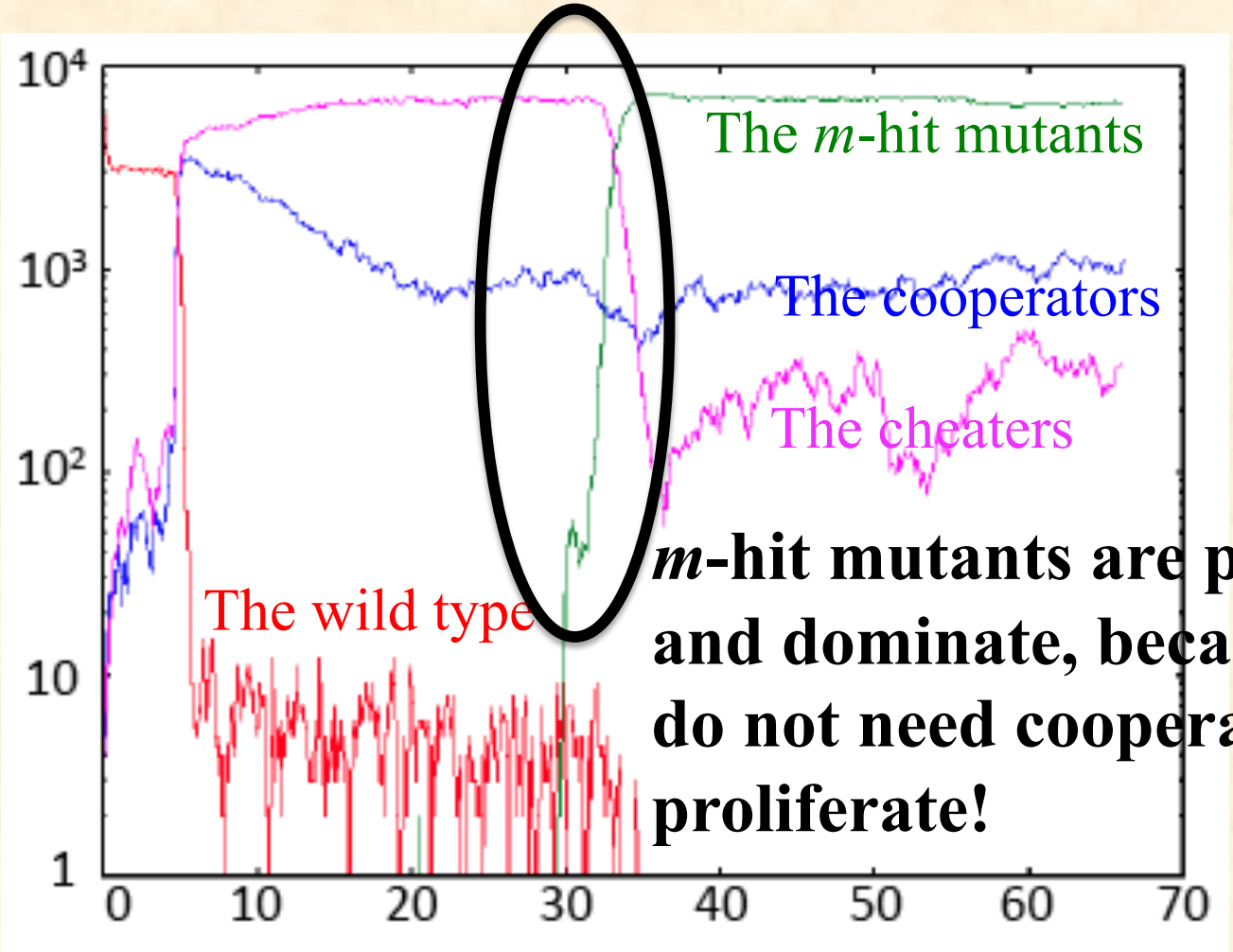


Cooperators are maintained by selection-mutation balance

In the presence of cheating

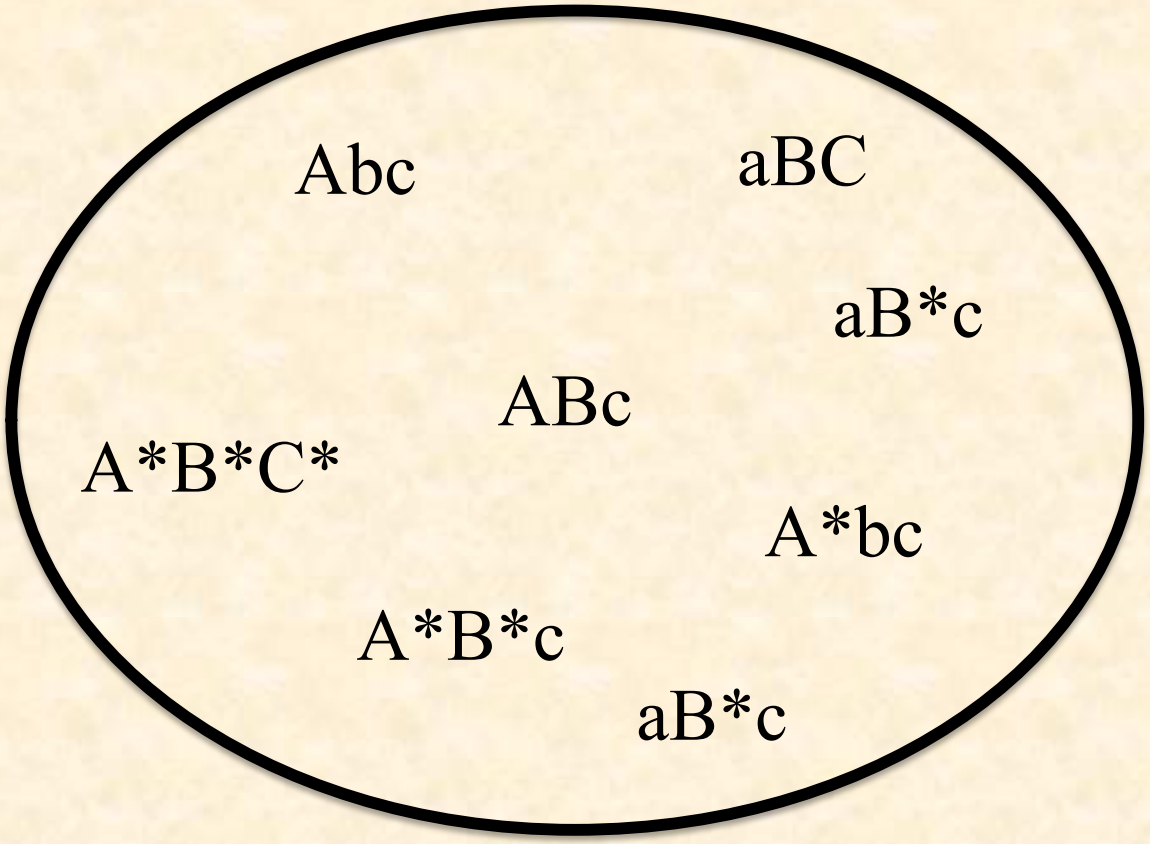


In the presence of cheating

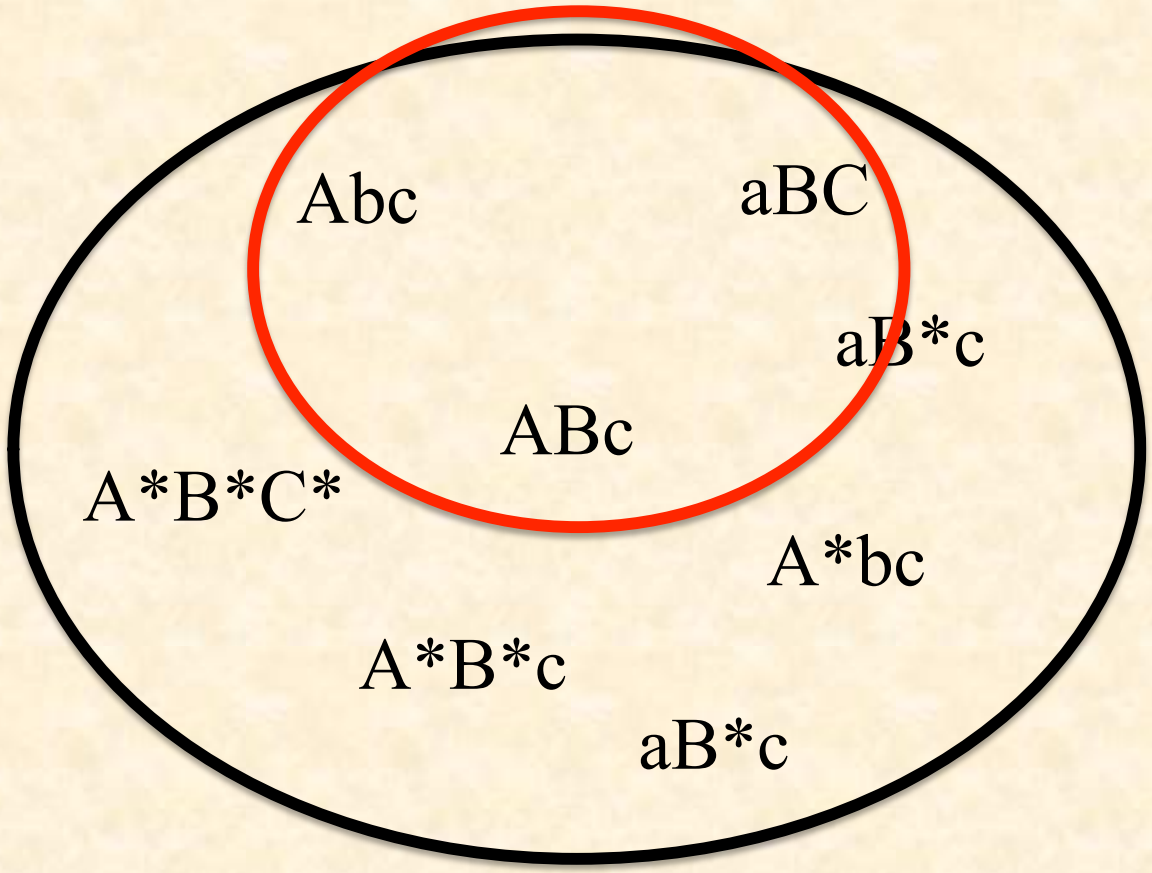


***m*-hit mutants are produced, and dominate, because they do not need cooperators to proliferate!**

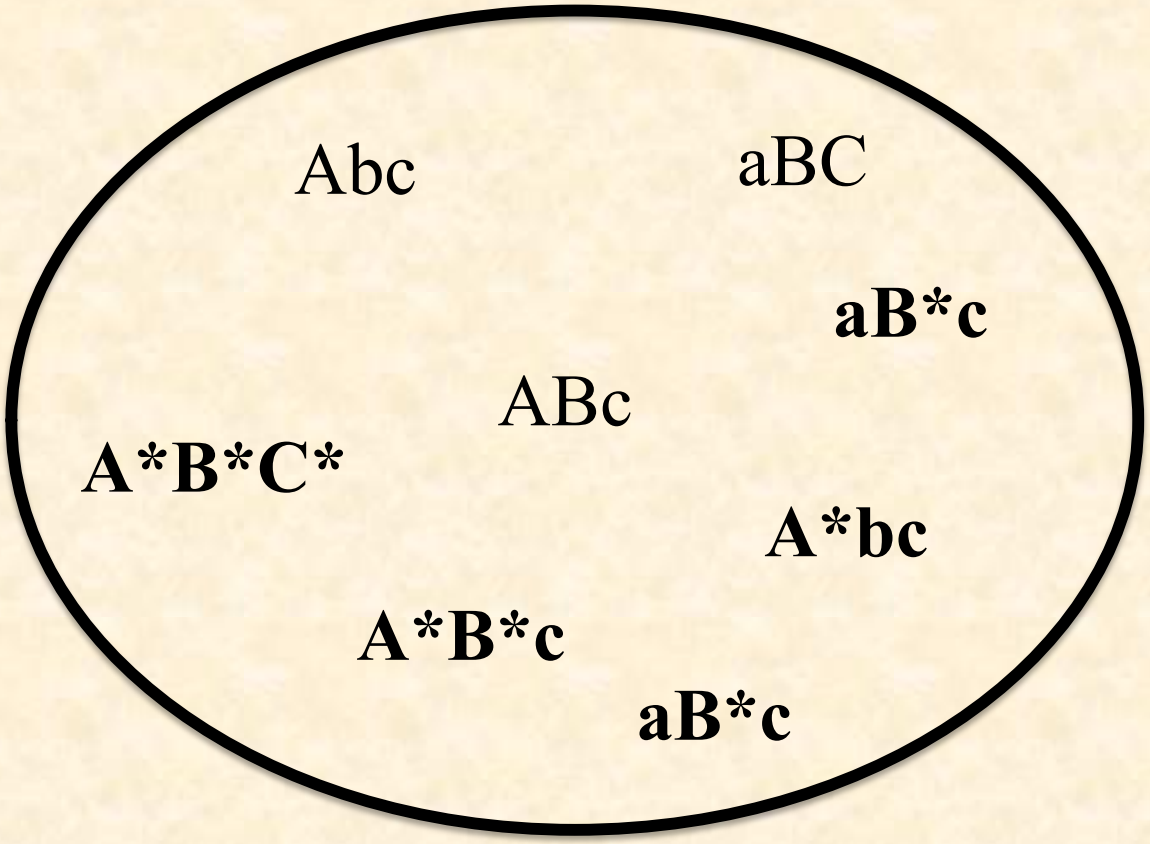
The local dynamics



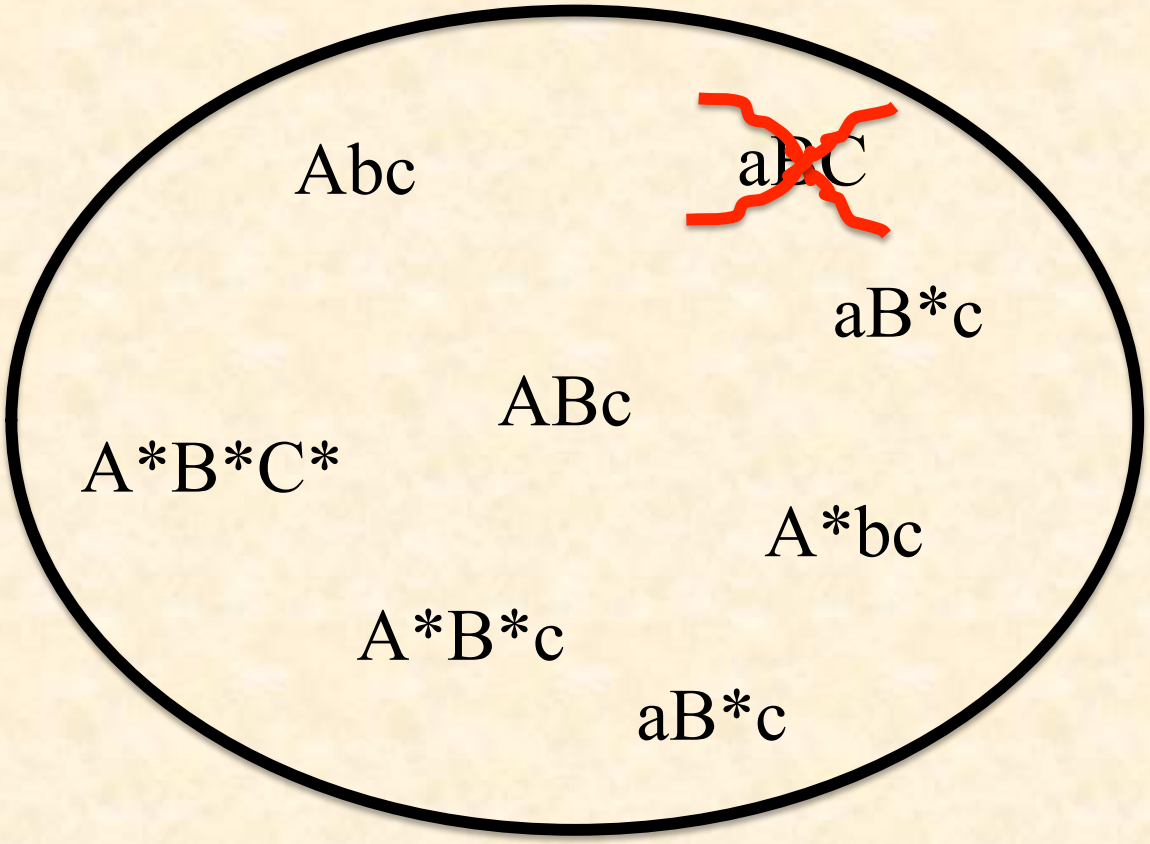
The local dynamics



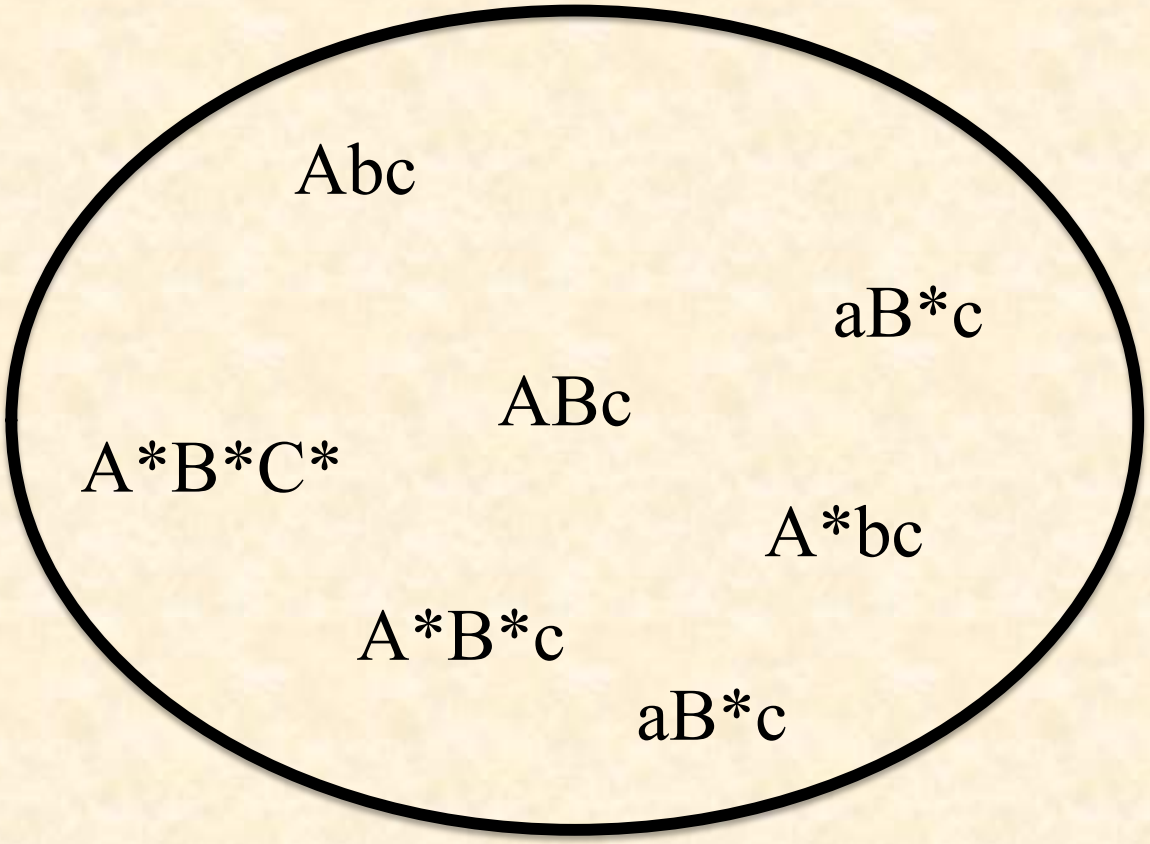
The local dynamics



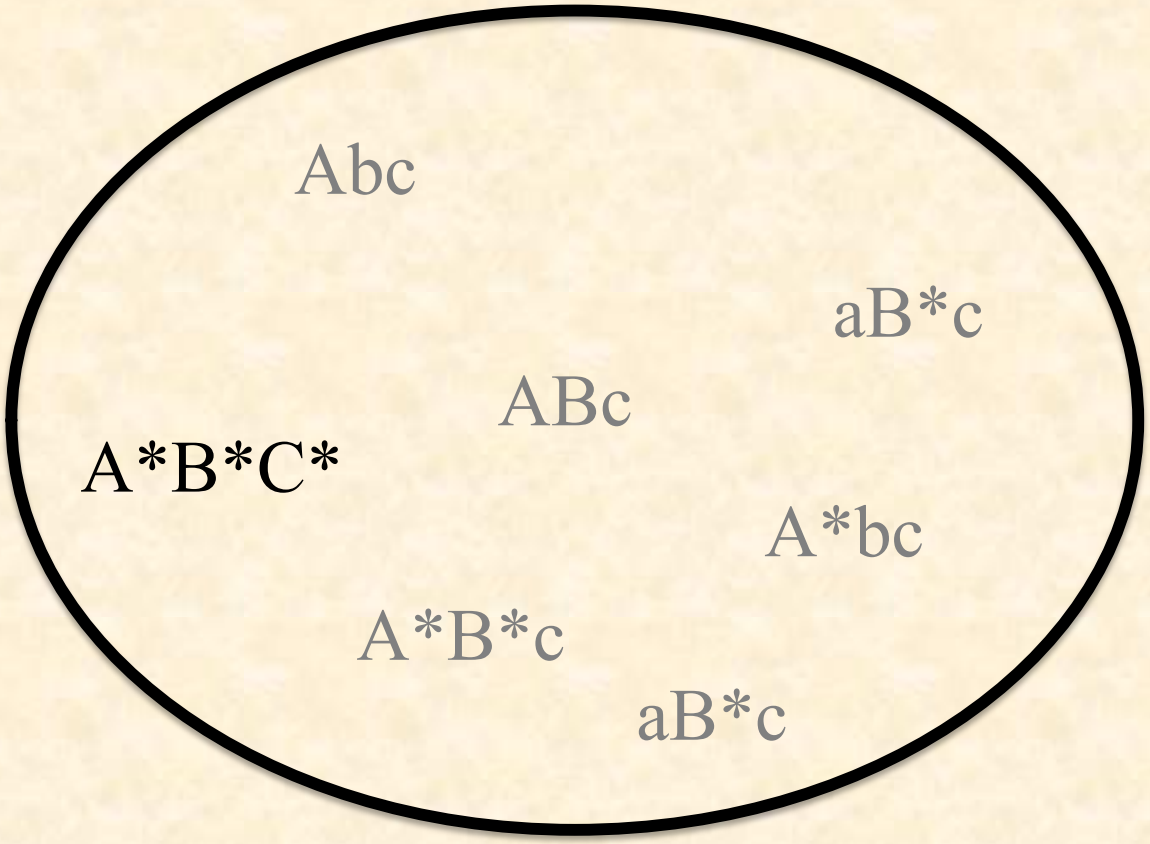
The local dynamics



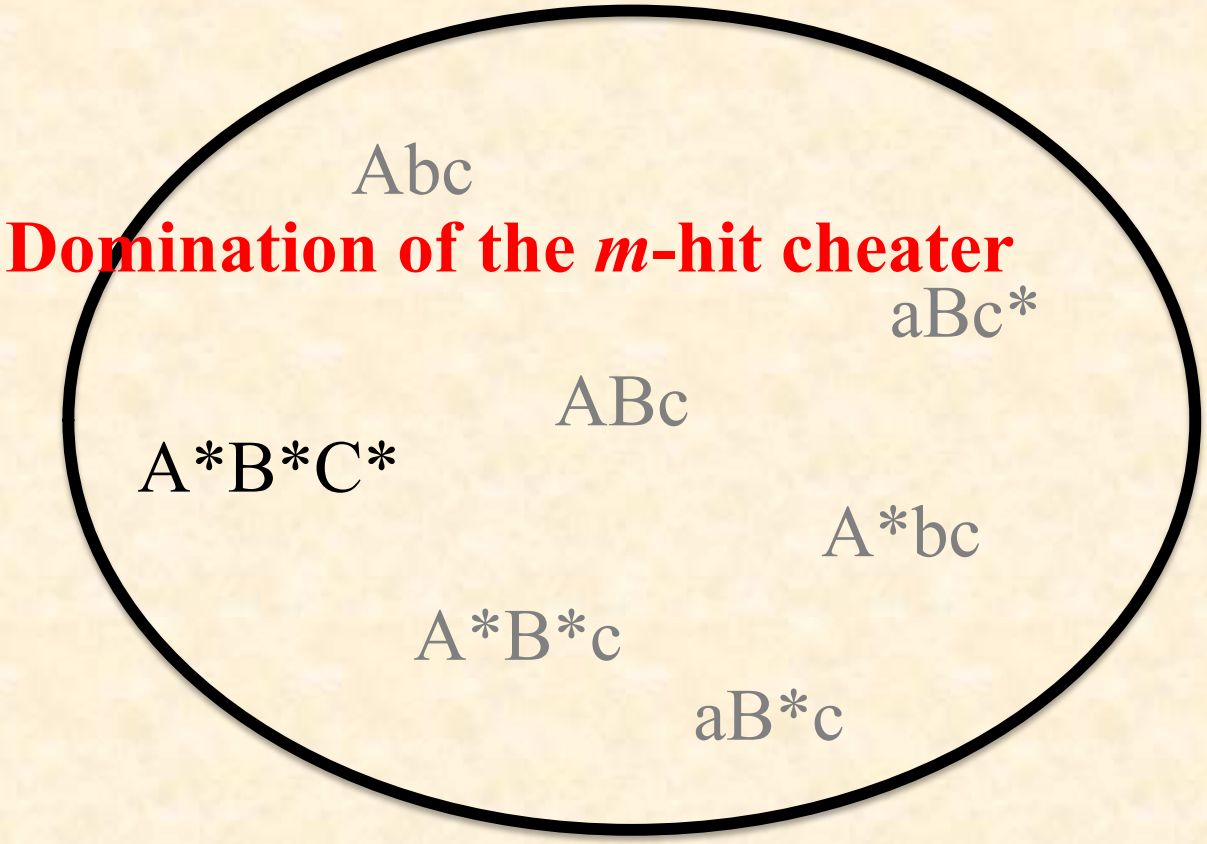
The local dynamics



The local dynamics

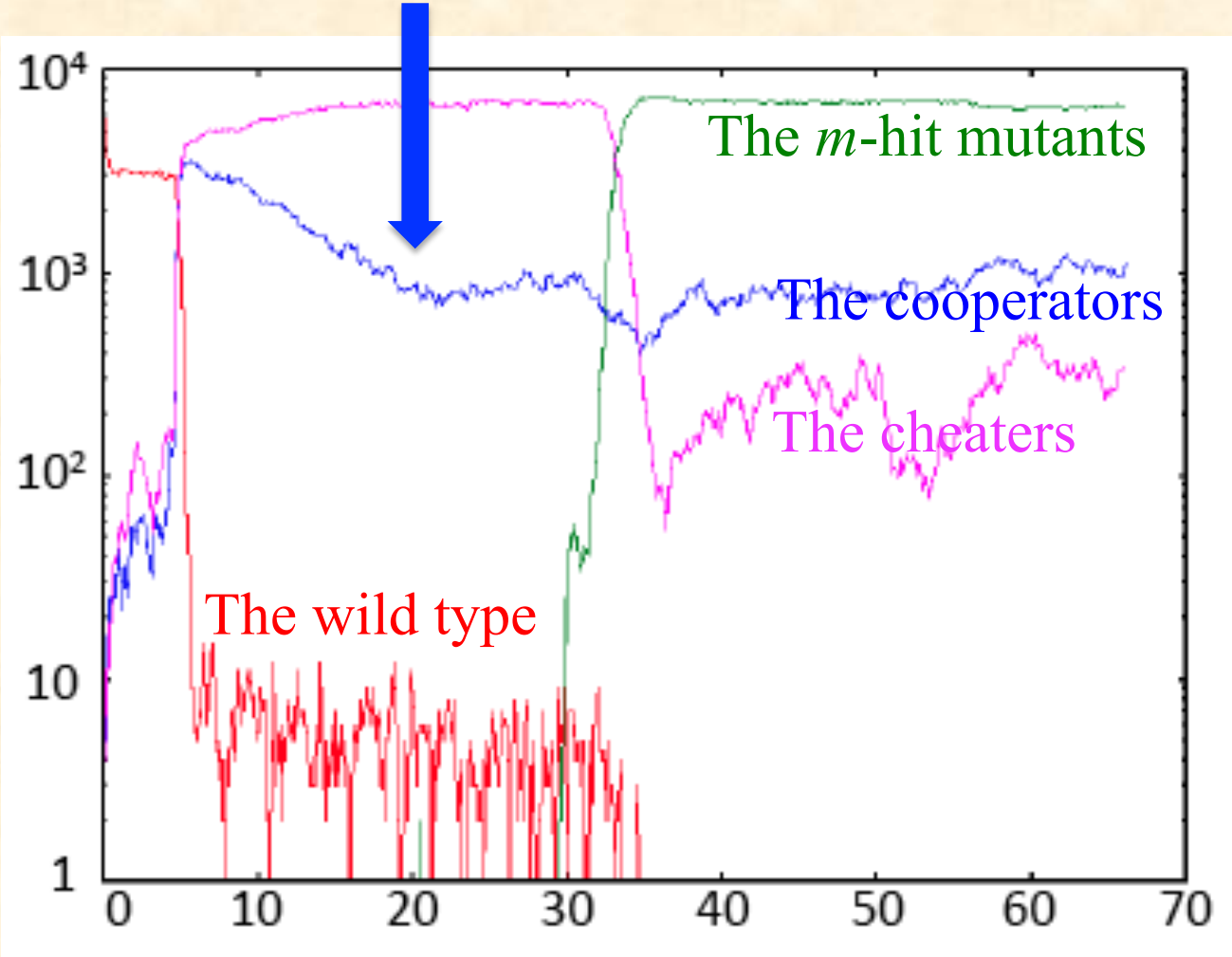


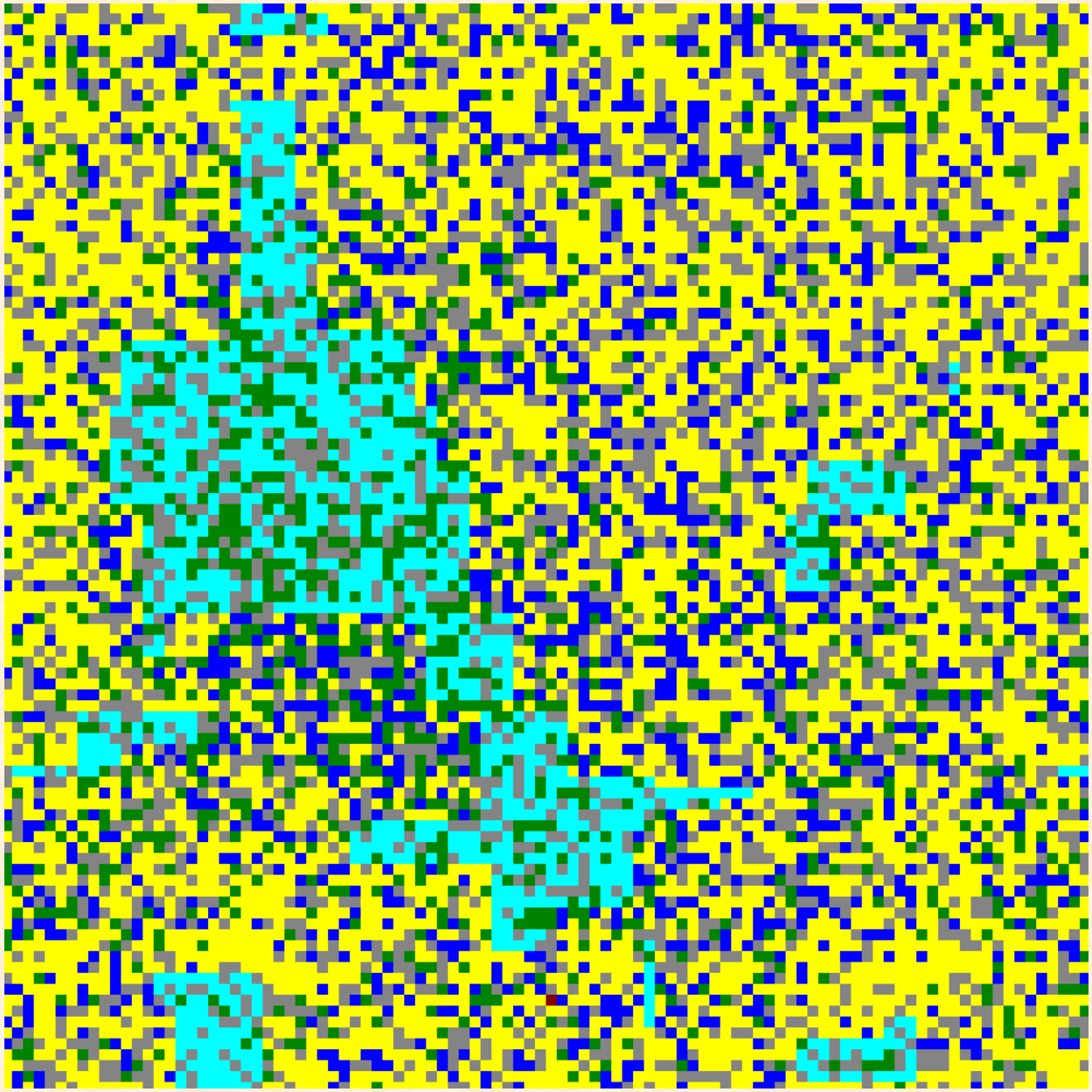
The local dynamics



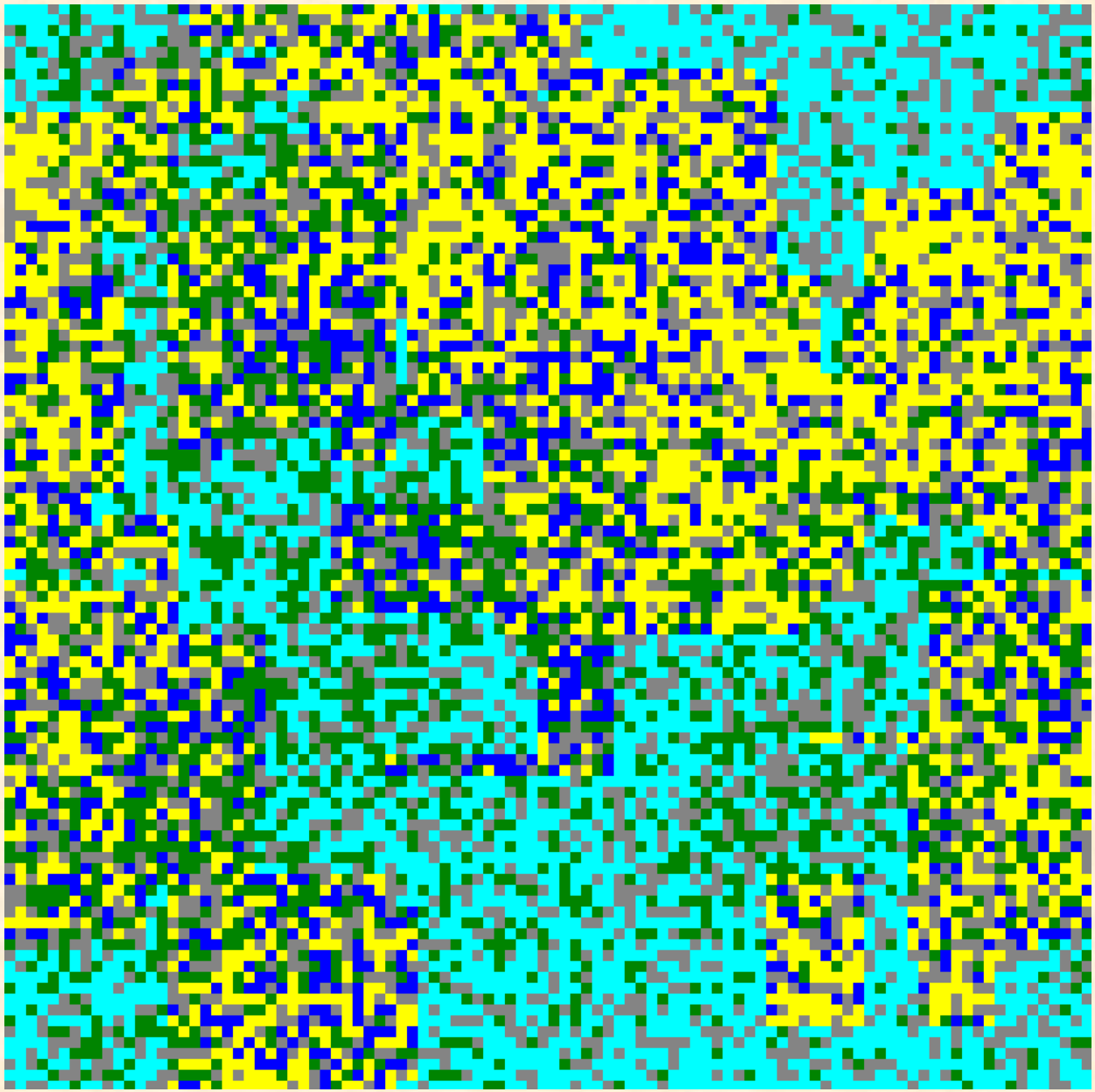
The likelihood and timing of this process depend on the number of cooperators in the system

In the presence of cheating

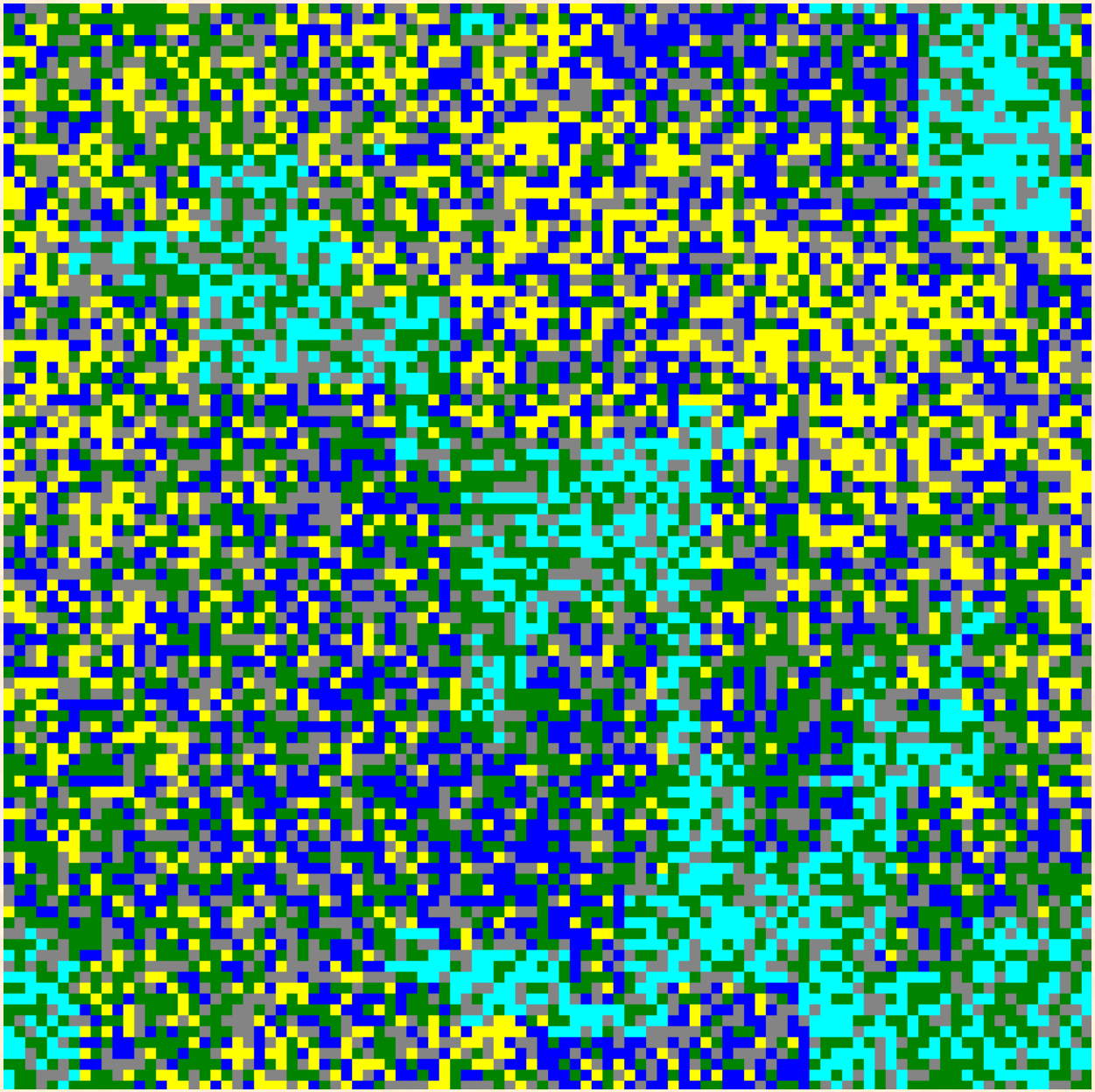




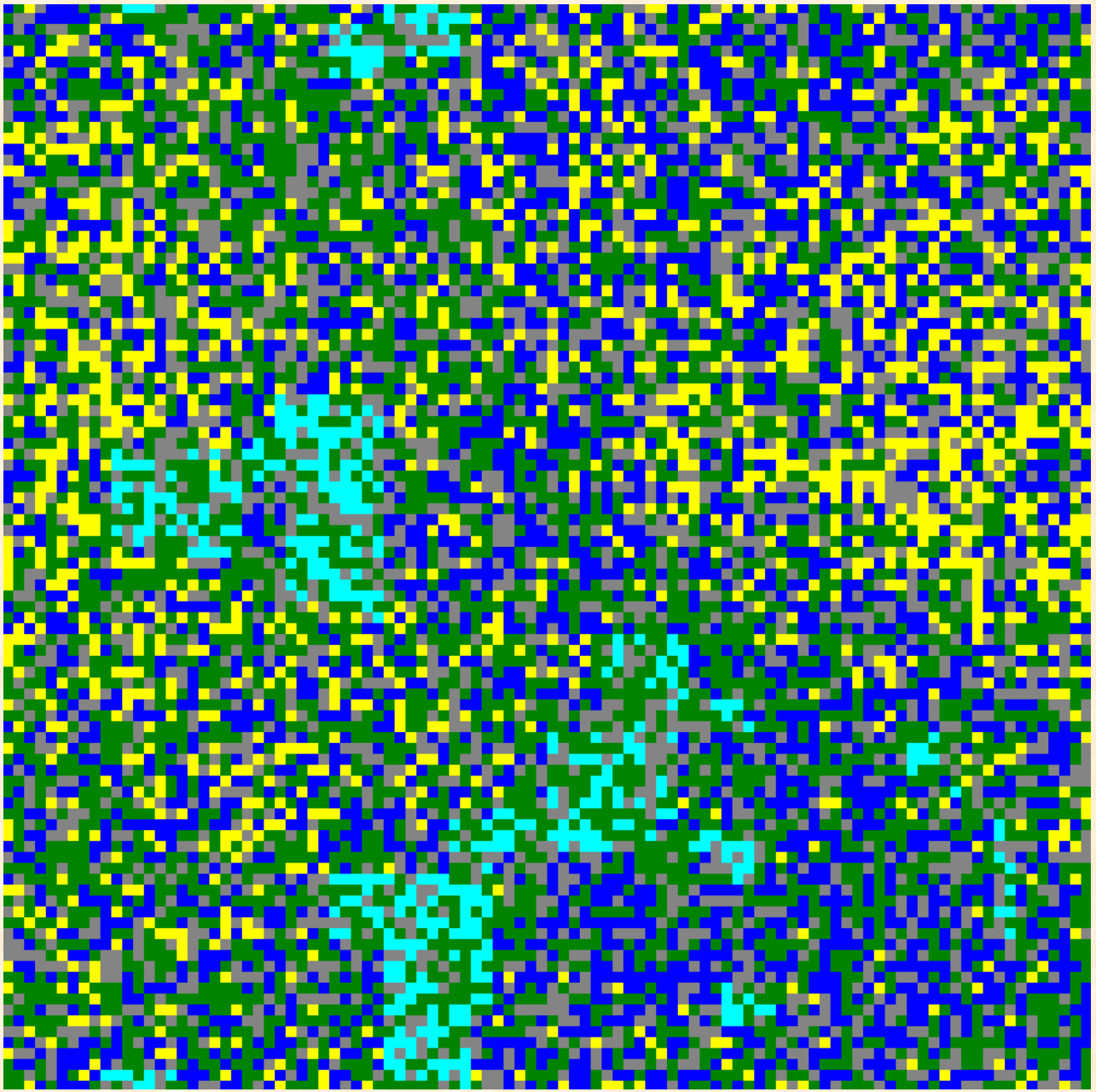
Grey = empty
Red= wt
Blue = coop fit
Yellow = cheat fit
Cyan = coop/cheat
not fit
Green – m hit cheat



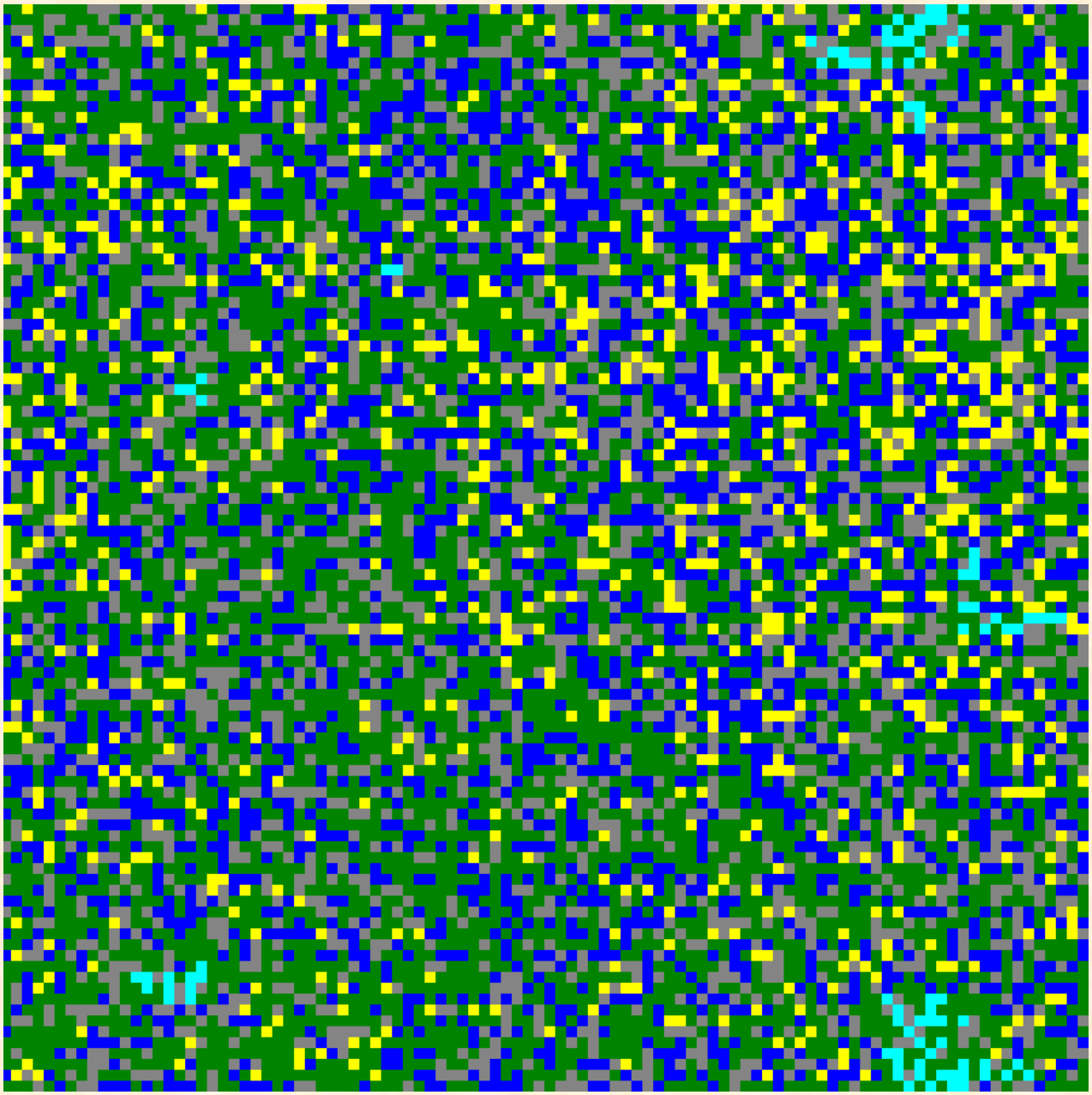
Grey = empty
Red= wt
Blue = coop fit
Yellow = cheat fit
Cyan = coop/cheat
not fit
Green – m hit cheat



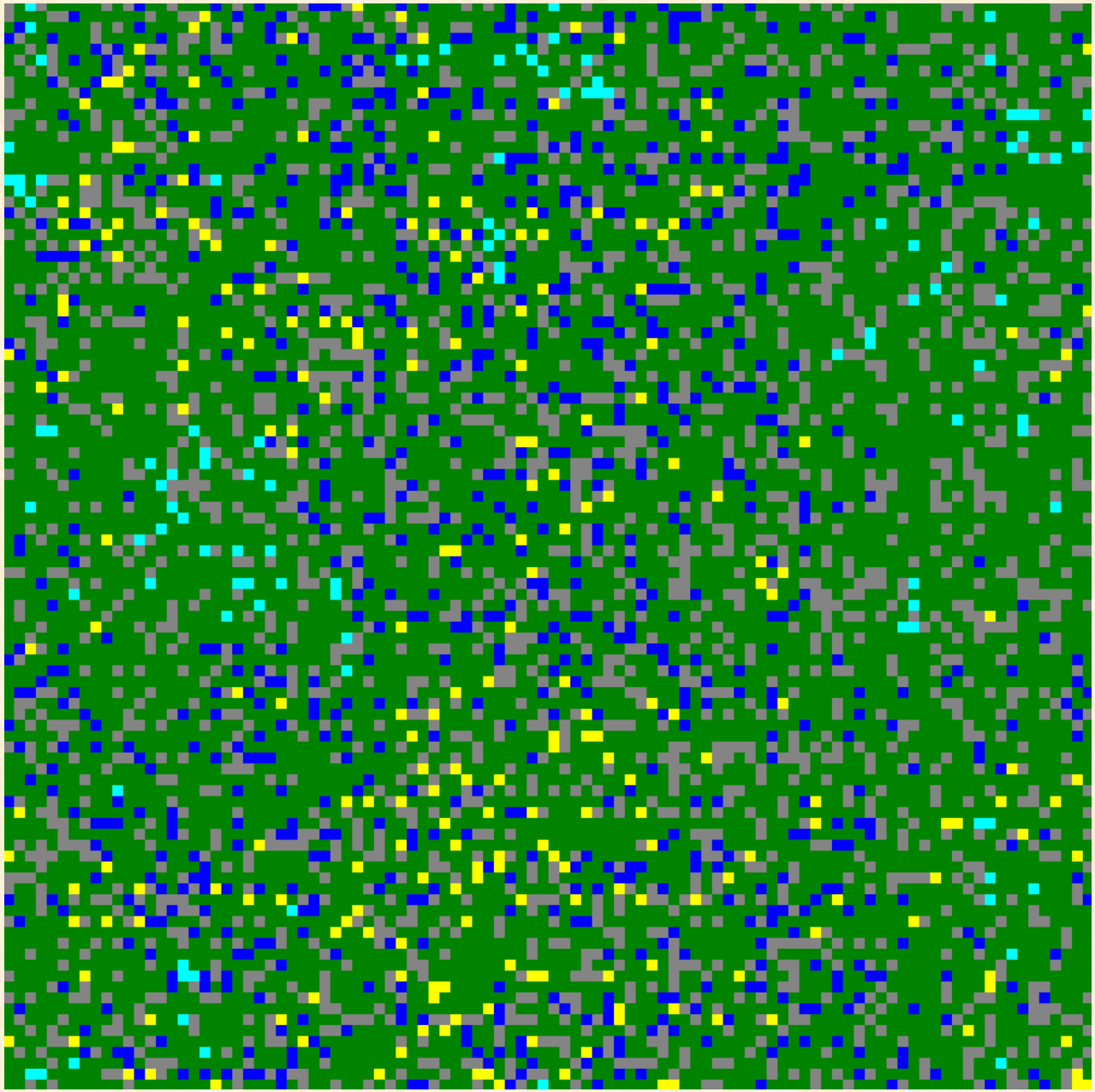
Grey = empty
Red= wt
Blue = coop fit
Yellow = cheat fit
Cyan = coop/cheat
not fit
Green – m hit cheat



Grey = empty
Red= wt
Blue = coop fit
Yellow = cheat fit
Cyan = coop/cheat not fit
Green – m hit cheat



Grey = empty
Red= wt
Blue = coop fit
Yellow = cheat fit
Cyan = coop/cheat
not fit
Green – m hit cheat



Grey = empty
Red= wt
Blue = coop fit
Yellow = cheat fit
Cyan = coop/cheat
not fit
Green – m hit cheat

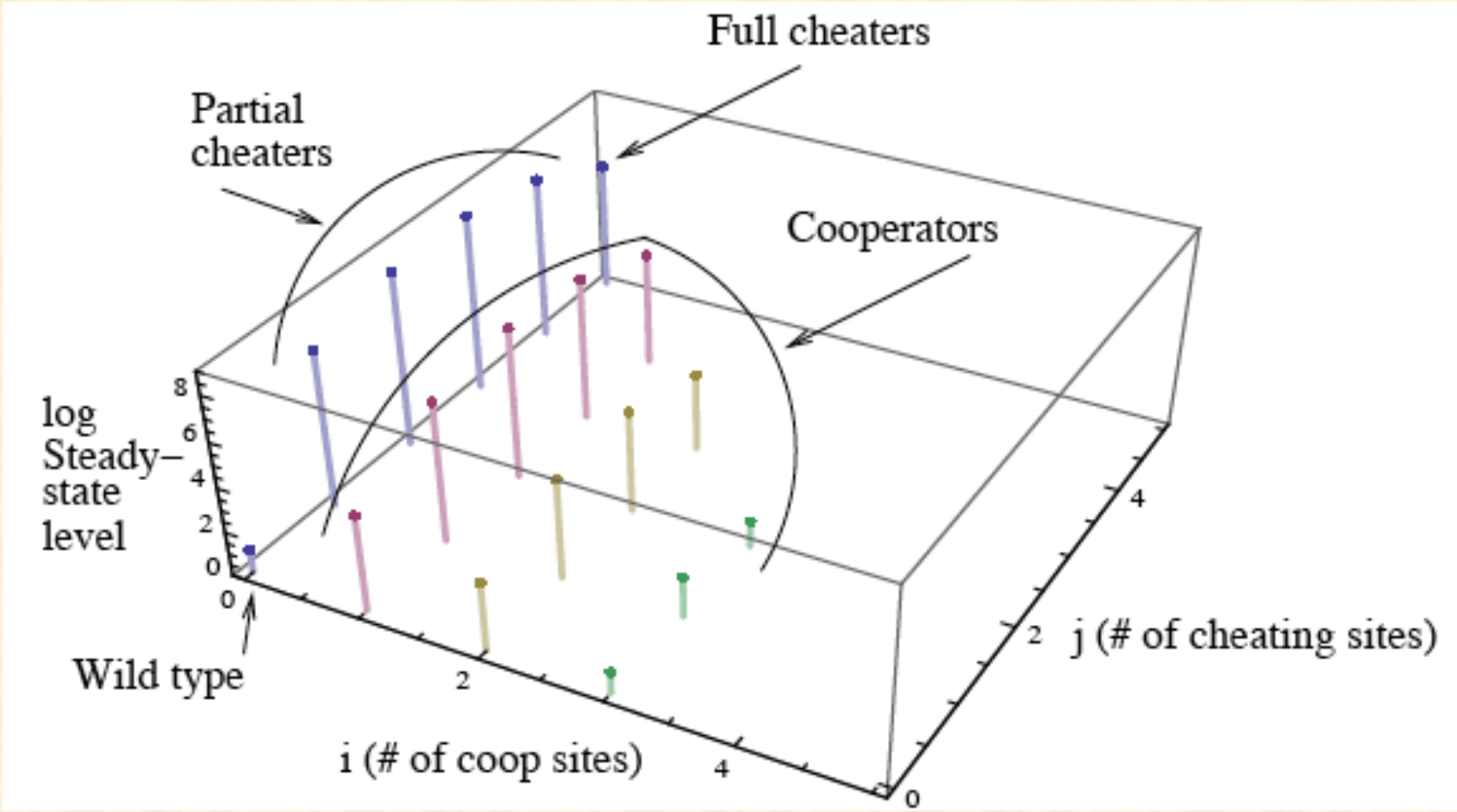
Analytical description

- *i*=number of cooperating sites
- *j*=number of cheating sites

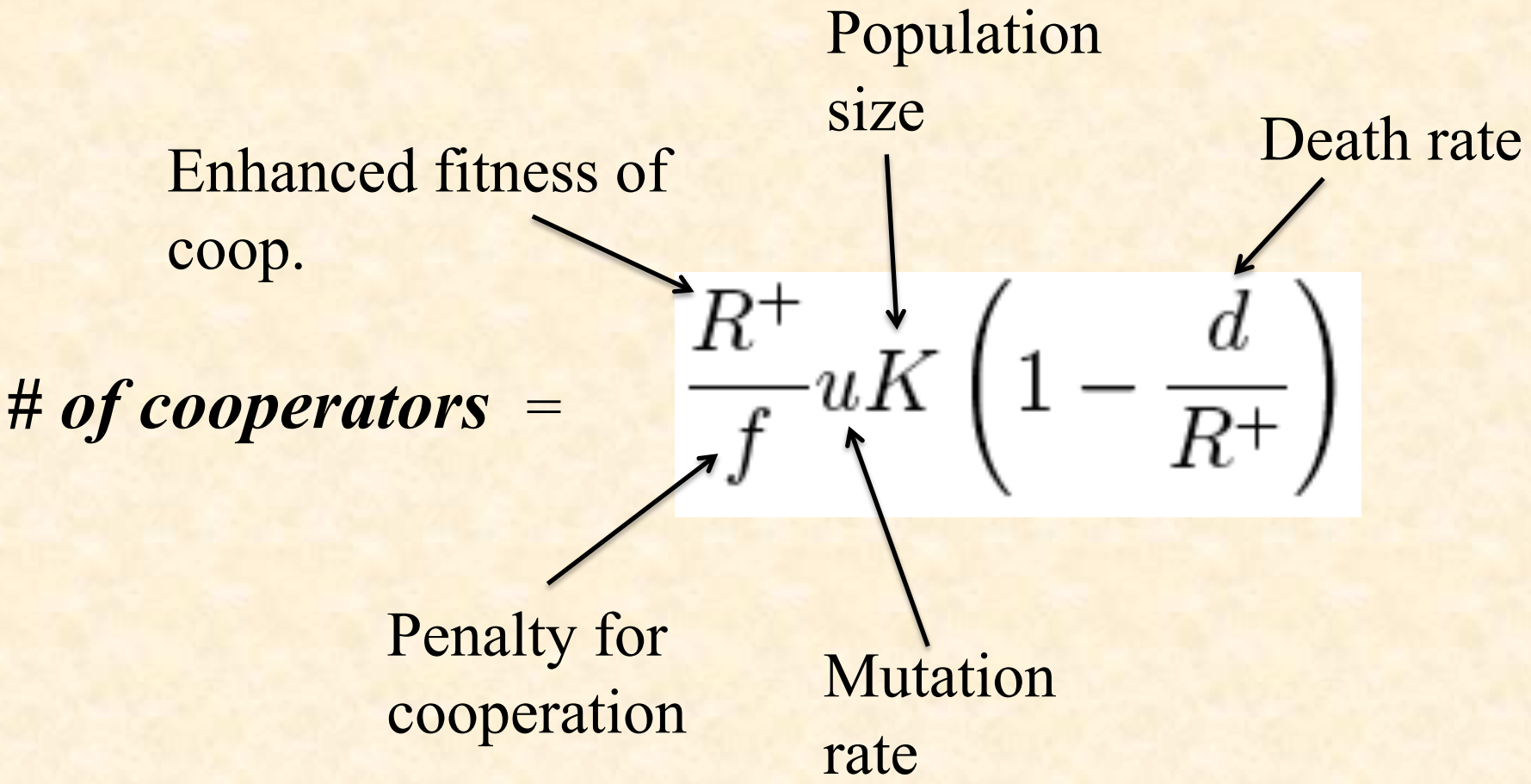
$$\begin{aligned}\dot{y}_{i,j} &= [r_{i,j}y_{i,j}(1-(m-i-j)u-iu_1-(m-i-j)w-jw_1-iv-jv_1)\\ &+ r_{i-1,j}y_{i-1,j}iu + r_{i+1,j}y_{i+1,j}(m-i-j)u_1 + r_{i,j+1}y_{i,j+1}(m-i-j)w_1\\ &+ r_{i,j-1}y_{i,j-1}jw + r_{i-1,j+1}y_{i-1,j+1}iv_1 + r_{i+1,j-1}y_{i+1,j-1}jv]W\\ &- dy_{i,j}, \quad 0 \le i+j \le m. \end{aligned} \tag{9}$$

$$r_{0,0} = R, \quad R < r_{i,j} = R^+ - if \le R^+, \quad ij > 0.$$

The steady state



The steady state



Are there examples of cheating in cancer cells?

- **Prostate cancer** (Harsh Jain)
- The normal prostate and early-stage prostate cancers depend on androgens for growth and survival, and androgen ablation therapy causes them to regress.
- Cancers that are not cured by surgery eventually become androgen independent, rendering anti-androgen therapy ineffective.

Are there examples of cheating in cancer cells?

To get around the hormonal therapy, cancer cells can:

1. Develop mutations that facilitate local biosynthesis of androgens
2. Develop mutations that reduce the activation threshold for the androgen receptor

Are there examples of cheating in cancer cells?

Cooperators

To get around the hormonal therapy, cancer cells can:

1. Develop mutations that facilitate local biosynthesis of androgens
2. Develop mutations that reduce the activation threshold for the androgen receptor

Cheaters

Sequential evolution

- Sequential evolution accumulates mutations one by one, and is a slow process, especially in the presence of fitness valleys

Cooperation

- Cooperation leads to a much faster generation of a complex phenotype as an emergent (distributed) property
- However, *m*-hit mutants do not come to dominate the population

Cheaters accelerate evolution

- In the presence of cheating, *m*-hit mutants are generated fast and come to dominate the population
- They are generated quickly because of a large abundance of cheaters (no stochastic tunneling!)
- They dominate because they do not depend on the cooperators for survival

Work done in collaboration with:

- Dominik Wodarz (UCI)
- Erin Urwin (UCI)