Title: THE ROLE OF CHANCE IN THE SURVIVAL OF THE FITTEST

Date: Mar 29, 2017 02:00 PM

URL: http://pirsa.org/17030080

Abstract: <p>Population expansions are ubiquitous in nature. They control the speed of many important dynamical processes, including multicellular development, biological evolution and epidemic outbreaks. Yet, the theoretical description of spreading behaviors has been limited largely to mean-field models that ignore the randomness inherent to living systems. In this talk, I present theoretical arguments and experimental results that elucidate how noise influences spreading processes on many scales, ranging from cellular scales, where jamming cells impede their own expansion, to global scales, where epidemic spread relies on rare long-range jumps. Our results underscore that carrying excellent genes does not guarantee success in evolution - the pure luck of being in the right place at the right time can be equally, or more, important. </p>

THE ROLE OF CHANCE IN THE SURVIVAL OF THE FITTEST

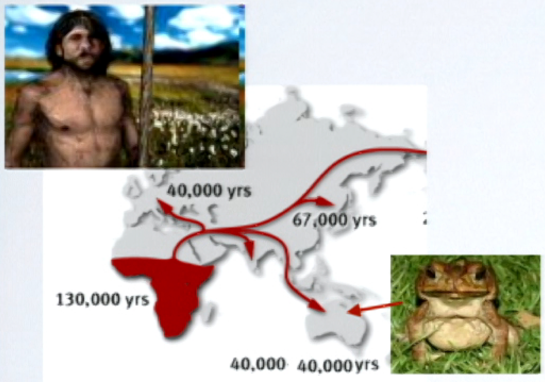
Oskar Hallatschek
UC Berkeley

SPREADING PROCESSES ARE EVERYWHERE IN BIOLOGY

Population expansions

Excoffier L, Foll M, Petit RJ (2009) *Ann. Rev. Ecol.*, **40**, 481–501.

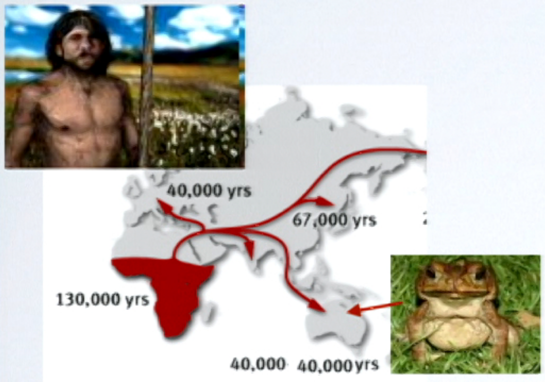
SPREADING PROCESSES ARE EVERYWHERE IN BIOLOGY



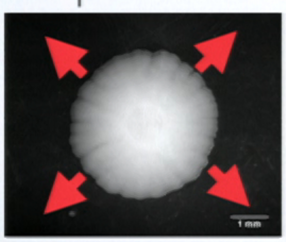
Population expansions

Excoffier L, Foll M, Petit RJ (2009) *Ann. Rev. Ecol.*, **40**, 481–501.

SPREADING PROCESSES ARE EVERYWHERE IN BIOLOGY



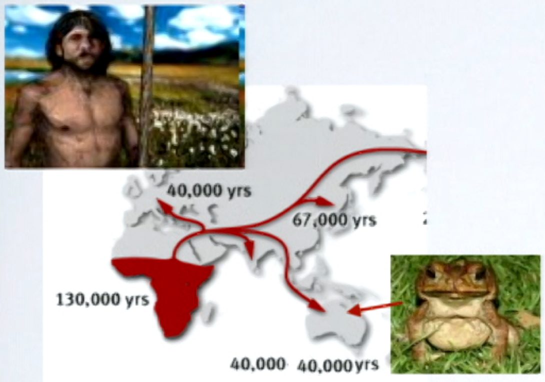
Population expansions



Many scales

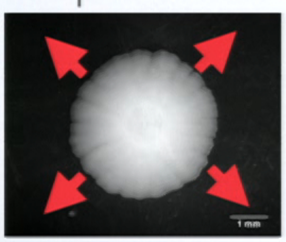
Excoffier L, Foll M, Petit RJ (2009) *Ann. Rev. Ecol.*, **40**, 481–501.

SPREADING PROCESSES ARE EVERYWHERE IN BIOLOGY



Population expansions

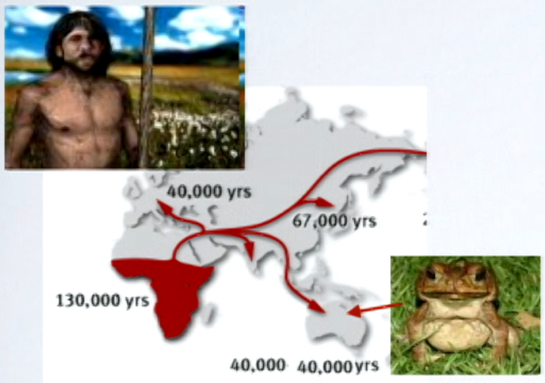
Spread of disease/ information



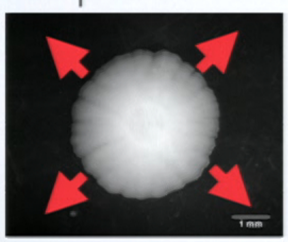
Many scales

Excoffier L, Foll M, Petit RJ (2009) *Ann. Rev. Ecol.*, **40**, 481–501.

SPREADING PROCESSES ARE EVERYWHERE IN BIOLOGY



Population expansions

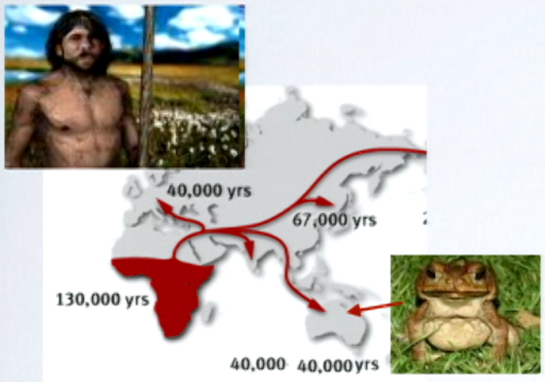


Many scales

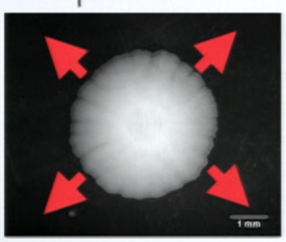
Spread of disease/ information

Excoffier L, Foll M, Petit RJ (2009) *Ann. Rev. Ecol.*, **40**, 481–501.

SPREADING PROCESSES ARE EVERYWHERE IN BIOLOGY



Population expansions



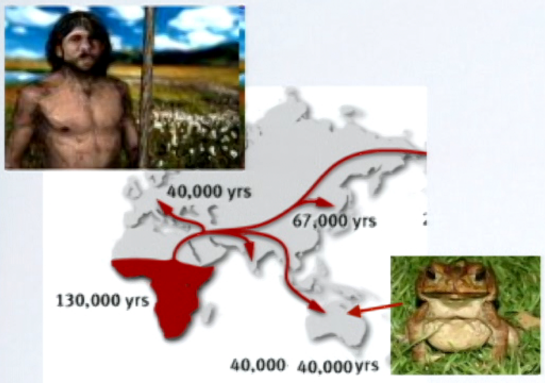
Many scales

Spread of disease/ information

Evolution: Spread of beneficial mutations

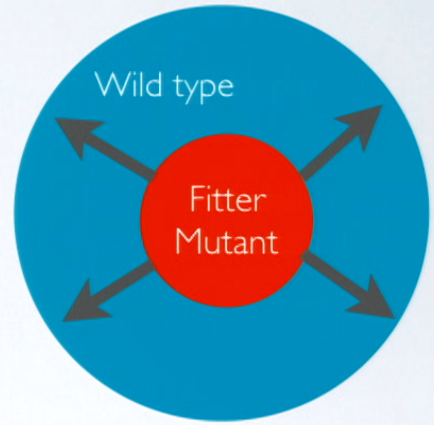
Excoffier L, Foll M, Petit RJ (2009) *Ann. Rev. Ecol.*, **40**, 481–501.

SPREADING PROCESSES ARE EVERYWHERE IN BIOLOGY

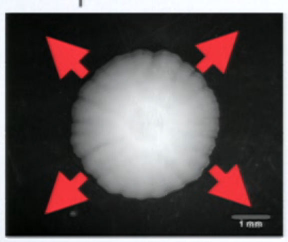


Population expansions

Spread of disease/ information



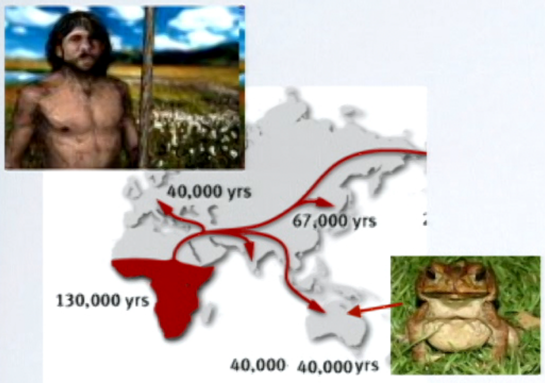
Evolution: Spread of beneficial mutations



Many scales

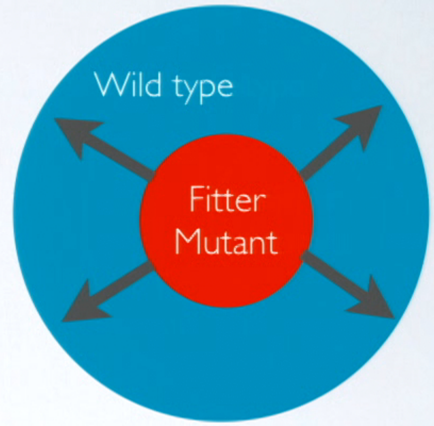
Excoffier L, Foll M, Petit RJ (2009) *Ann. Rev. Ecol.*, **40**, 481–501.

SPREADING PROCESSES ARE EVERYWHERE IN BIOLOGY

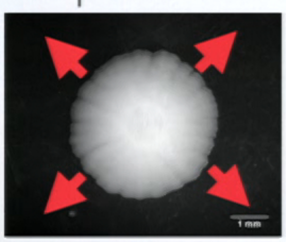


Population expansions

Spread of disease/ information



Evolution: Spread of beneficial mutations



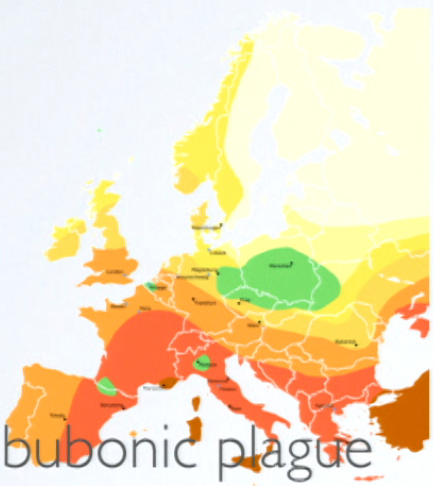
Many scales

Which **patterns of spread** are possible?
What is their **impact on evolution**?

Excoffier L, Foll M, Petit RJ (2009) *Ann. Rev. Ecol.*, **40**, 481–501.

EPIDEMIC SPREAD CHANGED OVER TIME

Historic scenario



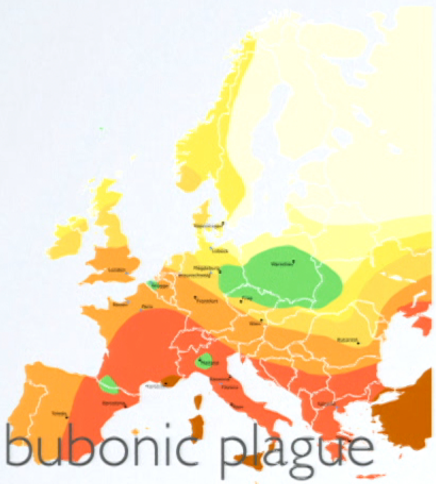
bubonic plague

J. V. Noble, Nature **250**, 726 (1974).

300-600km/yr

EPIDEMIC SPREAD CHANGED OVER TIME

Historic scenario

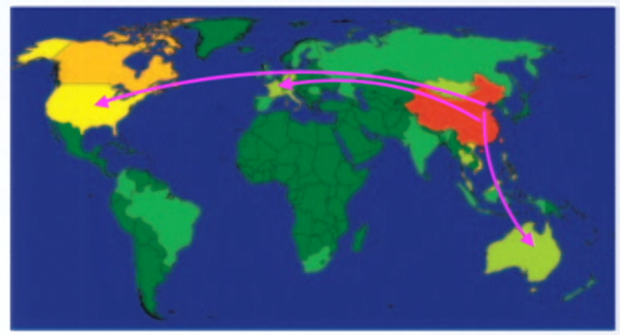


bubonic plague

J. V. Noble, Nature **250**, 726 (1974).

300-600km/yr

Modern scenario



SARS

L Hufnagel et al., PNAS **101,** 15124 (2004)

Around the world
in ~6 months

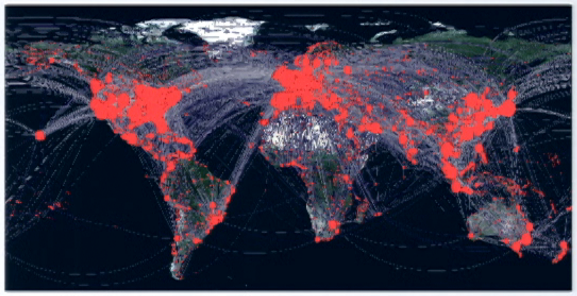
SPREAD DEPENDS ON DISPERSAL PATTERNS

Historic scenario

SPREAD DEPENDS ON DISPERSAL PATTERNS

Historic scenario

Modern scenario

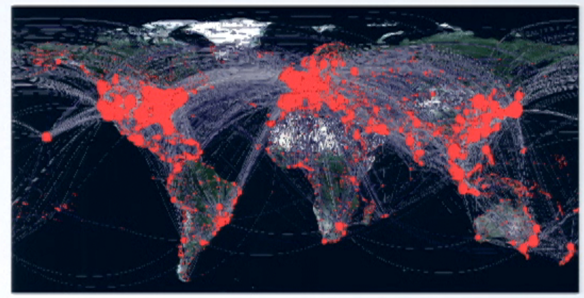


Helbing, Brockmann, et al. ArXiv:1402.7011 (2014)

SPREAD DEPENDS ON DISPERSAL PATTERNS

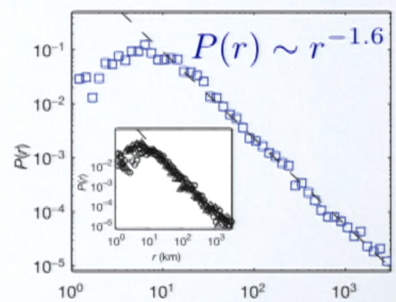
Historic scenario

Modern scenario



Helbing, Brockmann, et al. ArXiv:1402.7011 (2014)

Tracking $ bills:



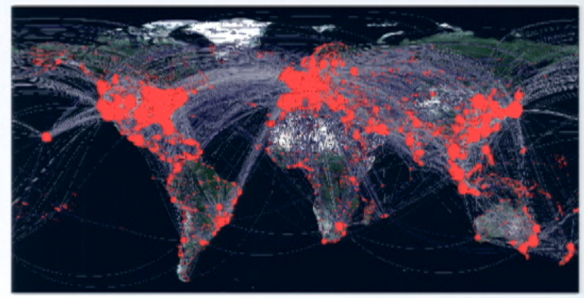
Brockmann, Hufnagel, Geisel Nature (2006)

cell phone data: Gonzales, Hidalgo, Barabasi Nature (2008)

SPREAD DEPENDS ON DISPERSAL PATTERNS

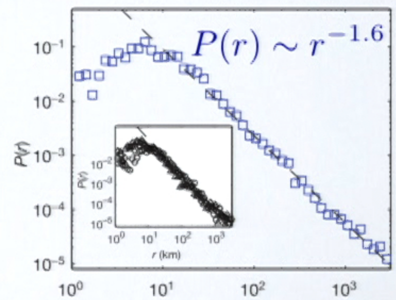
Historic scenario

Modern scenario



Helbing, Brockmann, et al. ArXiv:1402.7011 (2014)

Tracking $ bills:

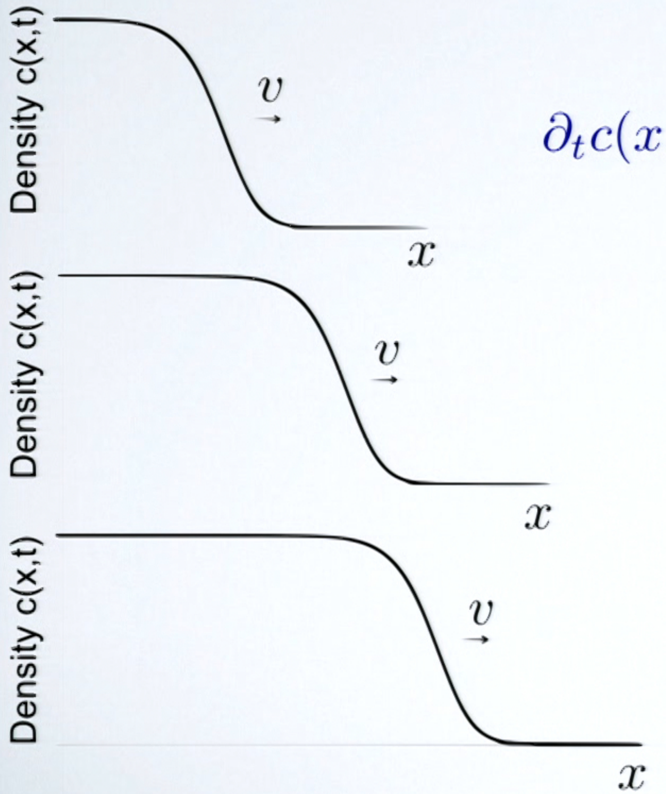


Brockmann, Hufnagel, Geisel Nature (2006)

cell phone data: Gonzales, Hidalgo, Barabasi Nature (2008)

How does dispersal influence spread?

TRAVELING WAVES (1D)



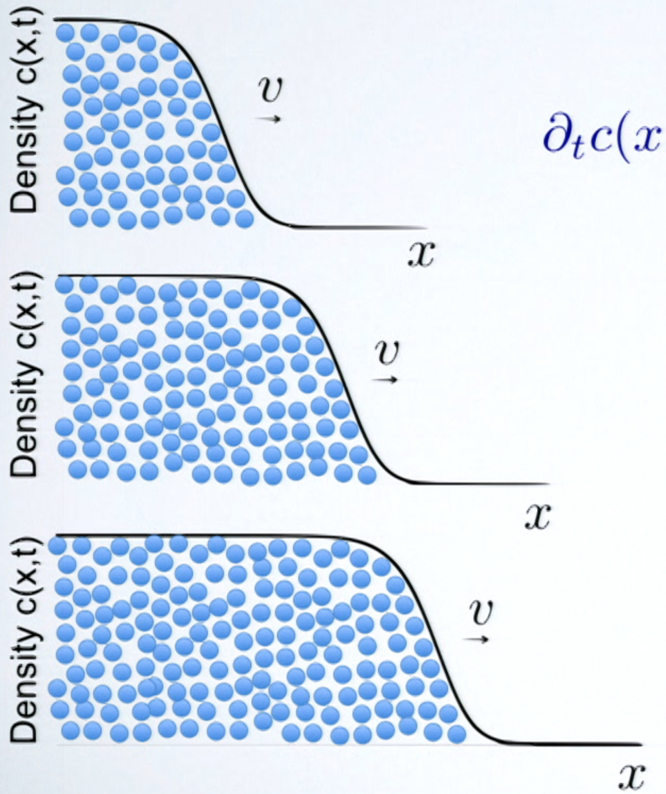
$$\partial_t c(x,t) = D\partial_x^2 c + rc\left(1 - \frac{c}{K}\right)$$

Diffusion Growth

R.A. Fisher (1937), A. Kolmogorov et al. (1937)

$$v = 2\sqrt{Dr}$$

NOISY TRAVELING WAVES



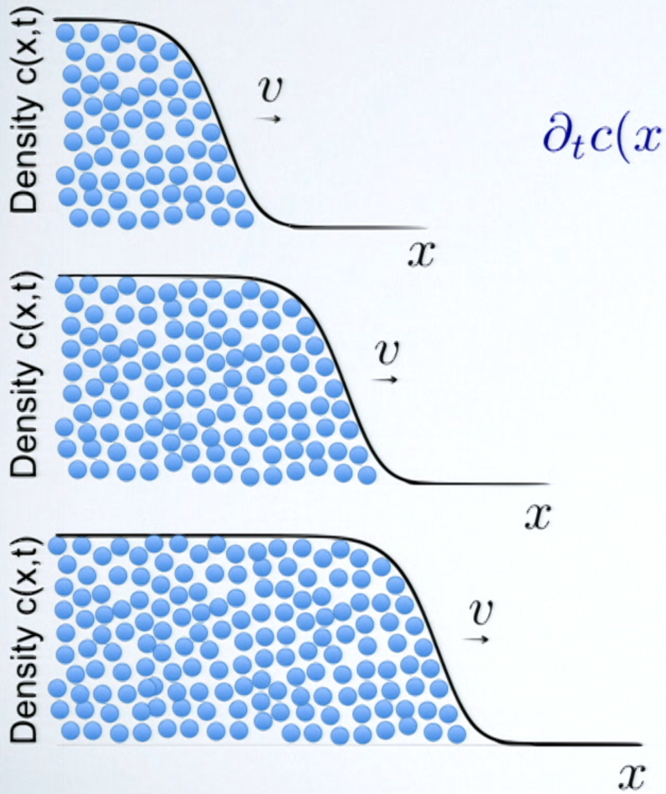
$$\partial_t c(x,t) = D\partial_x^2 c + rc\left(1 - \frac{c}{K}\right)$$

Diffusion Growth

R.A. Fisher (1937), A. Kolmogorov et al. (1937)

$$v = 2\sqrt{Dr}$$

NOISY TRAVELING WAVES



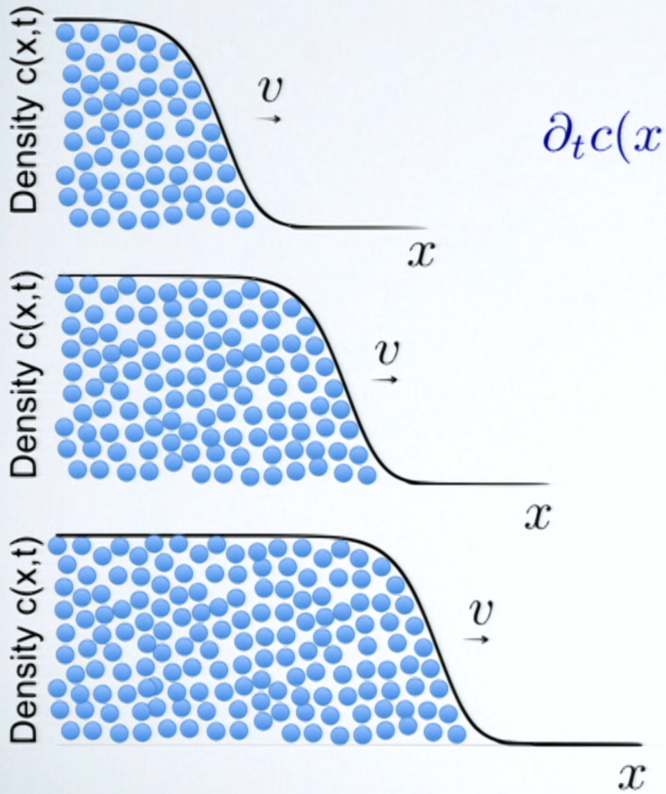
$$\partial_t c(x,t) = D\partial_x^2 c + rc\left(1 - \frac{c}{K}\right) + \eta\sqrt{c}$$

Diffusion Growth Noise

R.A. Fisher (1937), A. Kolmogorov et al. (1937) Mueller, Tribe (1995)
Tsimring, et al (1995)
Brunet, Derrida (1998)

$$v = 2\sqrt{Dr}$$

NOISY TRAVELING WAVES



$$\partial_t c(x,t) = D\partial_x^2 c + rc\left(1 - \frac{c}{K}\right) + \eta\sqrt{c}$$

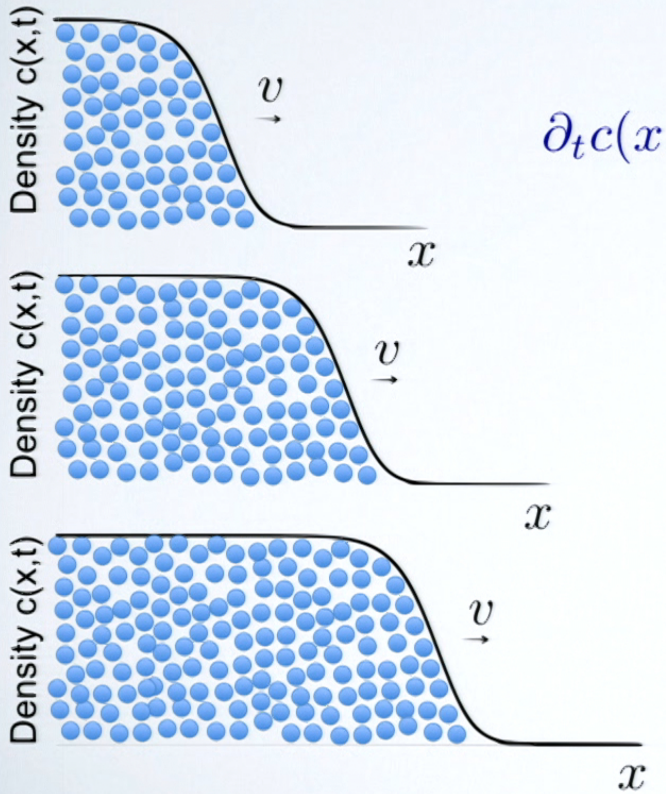
Diffusion Growth Noise

R.A. Fisher (1937), A. Kolmogorov et al. (1937) Mueller, Tribe (1995)
Tsimring, et al (1995)
Brunet, Derrida (1998)

$$v = 2\sqrt{Dr} \times \left(1 - \pi^2 \ln^{-2} K\right)$$

Weak noise: E. Brunet, B. Derrida (1998) *PRE*

NOISY TRAVELING WAVES



$$\partial_t c(x,t) = D\partial_x^2 c + rc\left(1 - \frac{c}{K}\right) + \eta\sqrt{c}$$

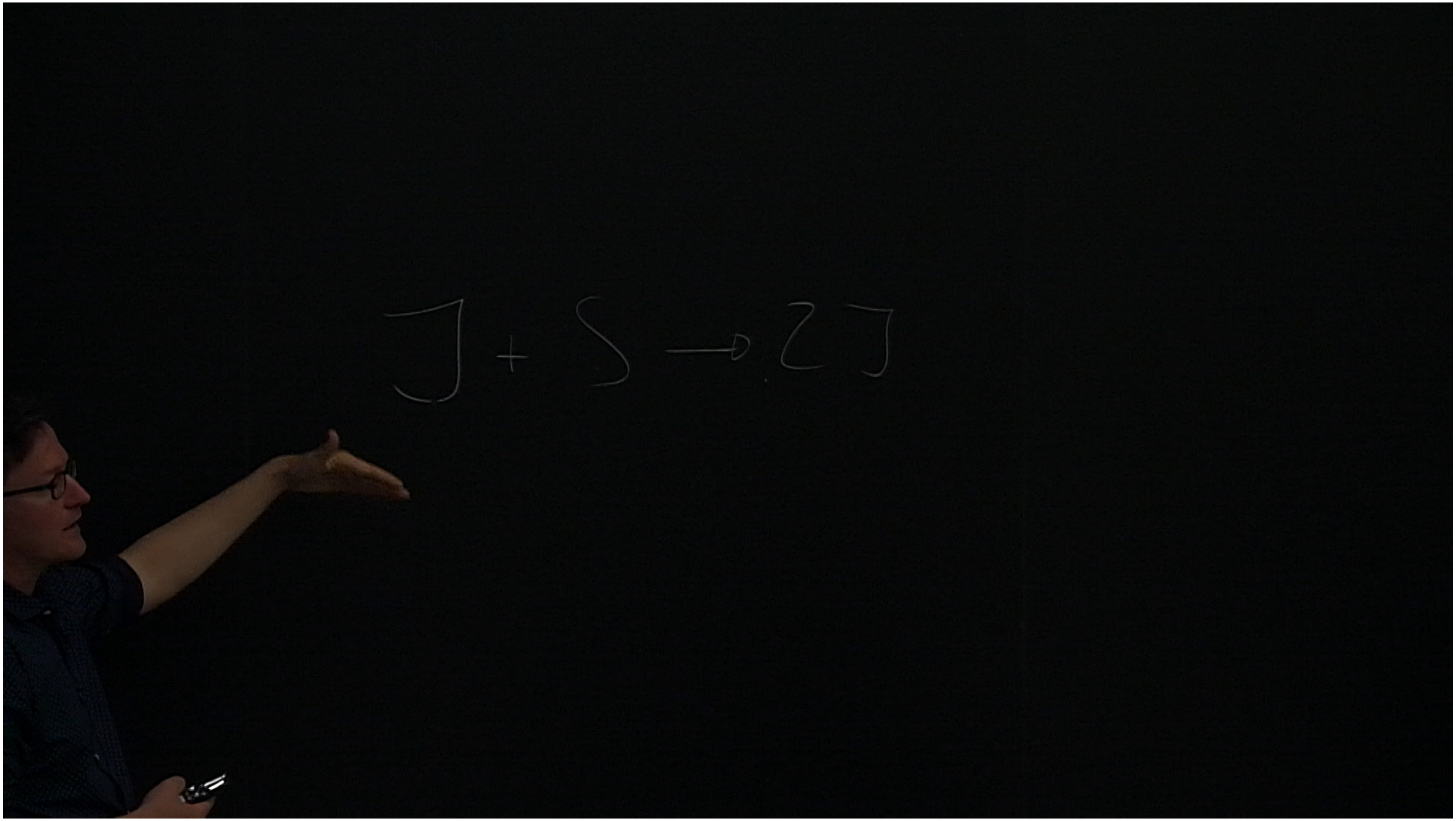
Diffusion Growth Noise

R.A. Fisher (1937), A. Kolmogorov et al. (1937) Mueller, Tribe (1995)
Tsimring, et al (1995)
Brunet, Derrida (1998)

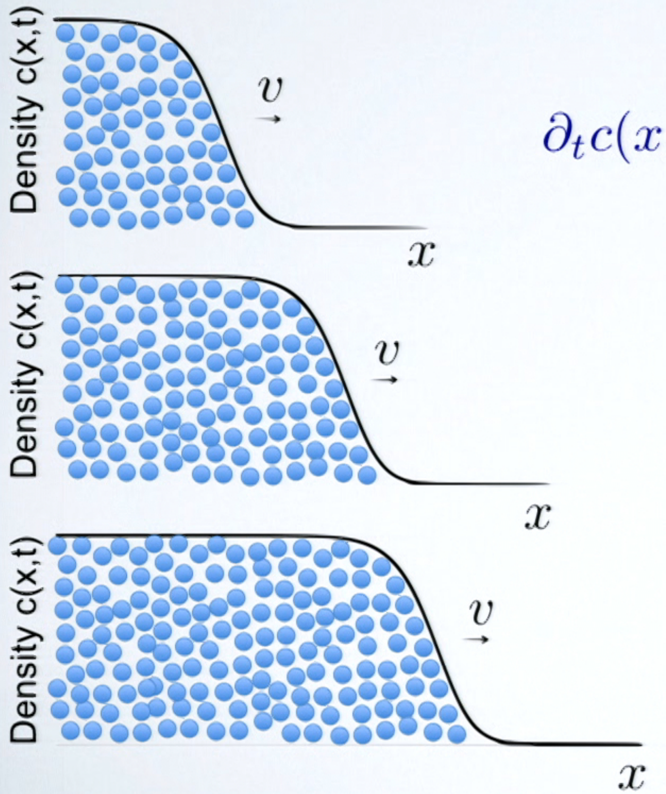
$$v = 2\sqrt{Dr} \times \left(1 - \pi^2 \ln^{-2} K\right)$$

Weak noise: E. Brunet, B. Derrida (1998) *PRE*

Exact approaches by "tuning" non-linearities: OH (2011) *PNAS*
L. Geyrhofer, O. H. (2016) *Genetics*


J + S → 2J

NOISY TRAVELING WAVES



$$\partial_t c(x,t) = D\partial_x^2 c + rc\left(1 - \frac{c}{K}\right) + \eta\sqrt{c}$$

Diffusion Growth Noise

R.A. Fisher (1937), A. Kolmogorov et al. (1937) Mueller, Tribe (1995)
Tsimring, et al (1995)
Brunet, Derrida (1998)

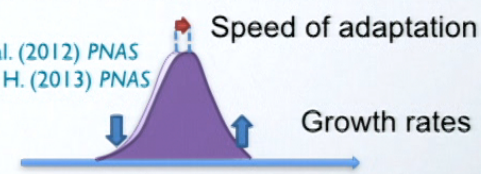
$$v = 2\sqrt{Dr} \times \left(1 - \pi^2 \ln^{-2} K\right)$$

Weak noise: E. Brunet, B. Derrida (1998) *PRE*

Exact approaches by "tuning" non-linearities: OH (2011) *PNAS*
L. Geyrhofer, O. H. (2016) *Genetics*

... also describes microbial adaptation:

B. Good et al. (2012) *PNAS*
R. Neher, O. H. (2013) *PNAS*



GENERALIZATION TO LONG DISTANCE DISPERSAL

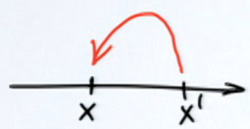
$$\partial_t c(x,t) = D\partial_x^2 c + rc\left(1 - \frac{c}{K}\right) + \eta\sqrt{c}$$

Diffusion Growth noise

GENERALIZATION TO LONG DISTANCE DISPERSAL

$$\partial_t c(x,t) = D\partial_x^2 c + rc\left(1 - \frac{c}{K}\right) + \eta\sqrt{c}$$

Diffusion Growth noise



$$\int_{x'} G(x - x')c(x', t)$$

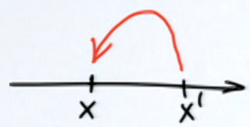
jump kernel

GENERALIZATION TO LONG DISTANCE DISPERSAL

$$\partial_t c(x,t) = D\partial_x^2 c + rc\left(1 - \frac{c}{K}\right) + \eta\sqrt{c}$$

Diffusion Growth noise

so far, mean field approaches, only



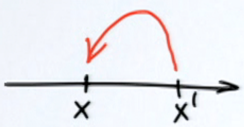
$$\int_{x'} G(x - x')c(x', t)$$

jump kernel

GENERALIZATION TO LONG DISTANCE DISPERSAL

$$\partial_t c(x,t) = D\partial_x^2 c + rc\left(1 - \frac{c}{K}\right) + \eta\sqrt{c}$$

Diffusion Growth noise



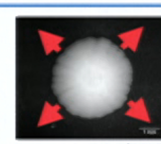
$$\int_{x'} G(x - x')c(x', t)$$

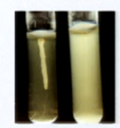
jump kernel

so far, mean field approaches, only

Exponential growth, if $G(\vec{z}) \sim e^{-\frac{z}{\lambda}}$ or broader!

e.g. D. Mollison (1972) *Proc. Berkeley Symp.*
Mancinelli, Vergni, Vulpiani (2002) *EPL*,
del Castillo-Negrete D (2003) *PRL*,
Marvel, Martin, Doering, Lusseau, Newman (2014) *arXiv*



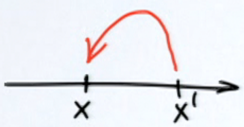


wave-like | exponential $\partial_x^2 \ln G$

GENERALIZATION TO LONG DISTANCE DISPERSAL

$$\partial_t c(x,t) = D\partial_x^2 c + rc\left(1-\frac{c}{K}\right) + \eta\sqrt{c}$$

Diffusion Growth ~~noise~~



$$\int_{x'} G(x-x')c(x',t)$$

jump kernel

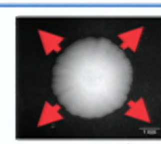
so far, mean field approaches, only

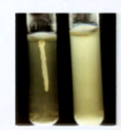
Exponential growth, if $G(\vec{z}) \sim e^{-\frac{z}{\lambda}}$ or broader!

e.g. D. Mollison (1972) *Proc. Berkeley Symp.*
Mancinelli, Vergni, Vulpiani (2002) *EPL*,
del Castillo-Negrete D (2003) *PRL*,
Marvel, Martin, Doering, Lusseau, Newman (2014) *arXiv*

Stochastic simulations

Mean-field approaches neglect the discreteness of long-range jumps





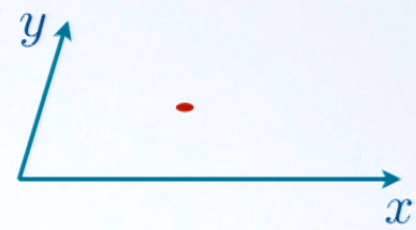
wave-like | exponential $\partial_x^2 \ln G$

COARSE-GRAINED SIMULATIONS

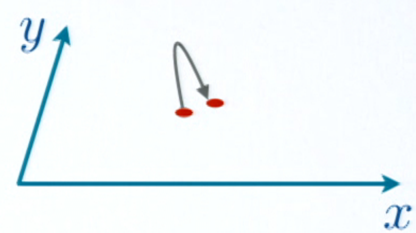
- Start with one 'seed' in center of d={1,2} lattice.

COARSE-GRAINED SIMULATIONS

- Start with one 'seed' in center of d={1,2} lattice.



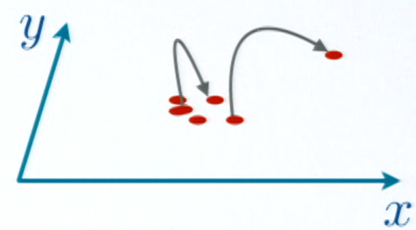
- New seeds due to jumps from established populations.



COARSE-GRAINED SIMULATIONS

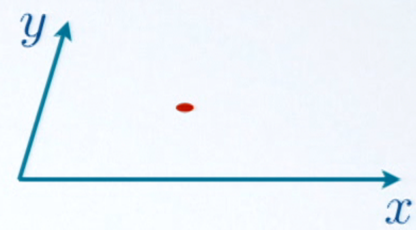
- Start with one 'seed' in center of d={1,2} lattice.

- New seeds due to jumps from established populations.

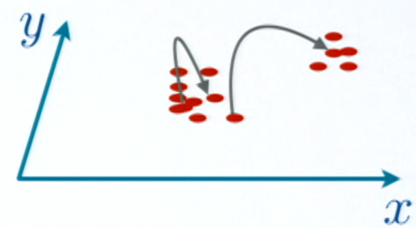


COARSE-GRAINED SIMULATIONS

- Start with one 'seed' in center of d={1,2} lattice.

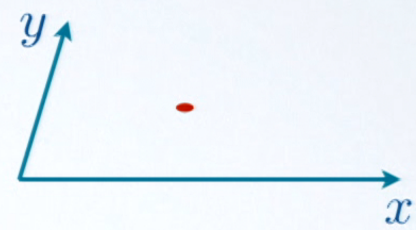


- New seeds due to jumps from established populations.

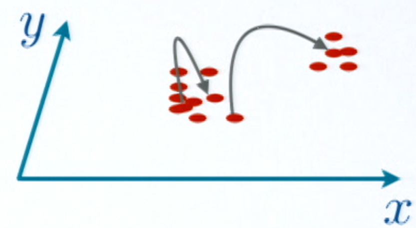


COARSE-GRAINED SIMULATIONS

- Start with one 'seed' in center of d={1,2} lattice.



- New seeds due to jumps from established populations.



- Jump kernel: $G(\vec{z}) \sim z^{-(\mu+d)}$

$$\Pr[\text{jump distance} > z] \sim z^{-\mu} \,, \qquad \mu > 0$$

MOVIES

$\Pr[\text{jump distance} > z] \sim z^{-\mu}$

$\mu = 3.5$

$\mu = 2.5$

$\mu = 1.5$

(inf. variance)

O. H., D. S. Fisher, **PNAS** 111:E4911 (2014)

MOVIES

$\Pr[\text{jump distance} > z] \sim z^{-\mu}$

$\mu = 3.5$ | $\mu = 2.5$ | $\mu = 1.5$ (inf. variance)

O. H., D. S. Fisher, **PNAS** 111:E4911 (2014)

MOVIES

$\Pr[\text{jump distance} > z] \sim z^{-\mu}$

$\mu = 3.5$ $\mu = 2.5$ $\mu = 1.5$ (inf. variance)

O. H., D. S. Fisher, **PNAS** 111:E4911 (2014)

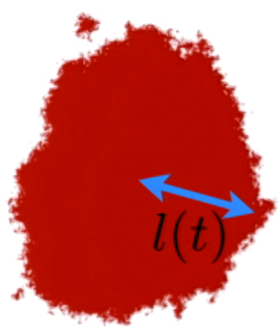
MOVIES

$\Pr[\text{jump distance} > z] \sim z^{-\mu}$

$\mu = 3.5$

$\mu = 2.5$

$\mu = 1.5$
(inf. variance)



Finite speed

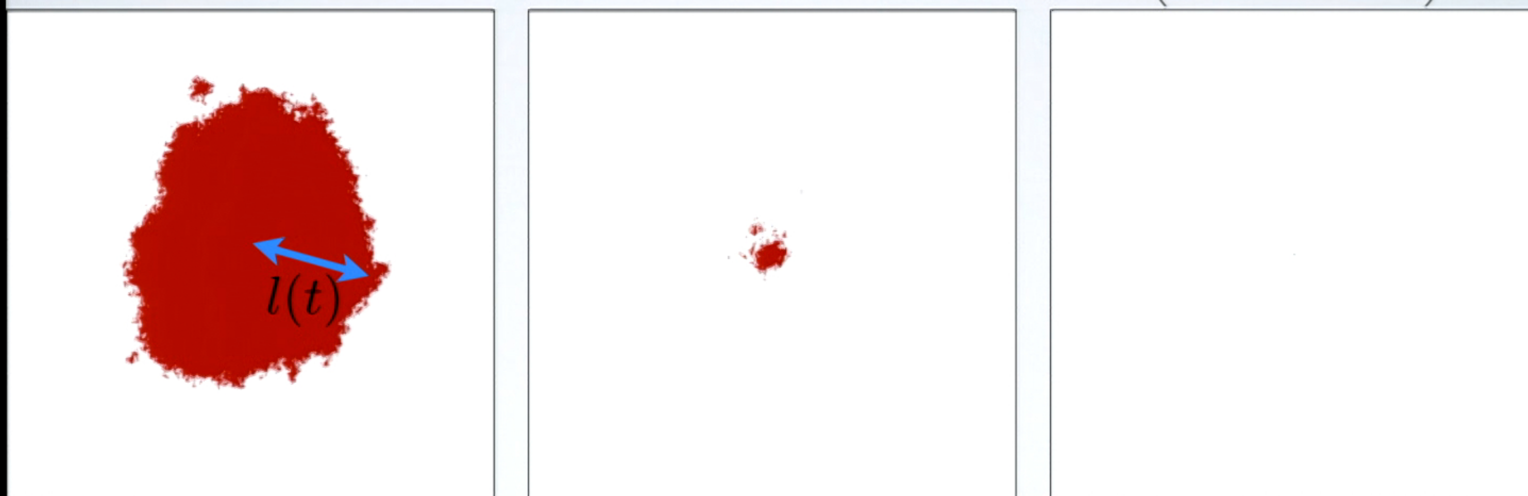
$l(t) \sim vt$

O. H., D. S. Fisher, **PNAS** 111:E4911 (2014)

MOVIES

$\Pr[\text{jump distance} > z] \sim z^{-\mu}$

$\mu = 3.5$ | $\mu = 2.5$ | $\mu = 1.5$ (inf. variance)



Finite speed

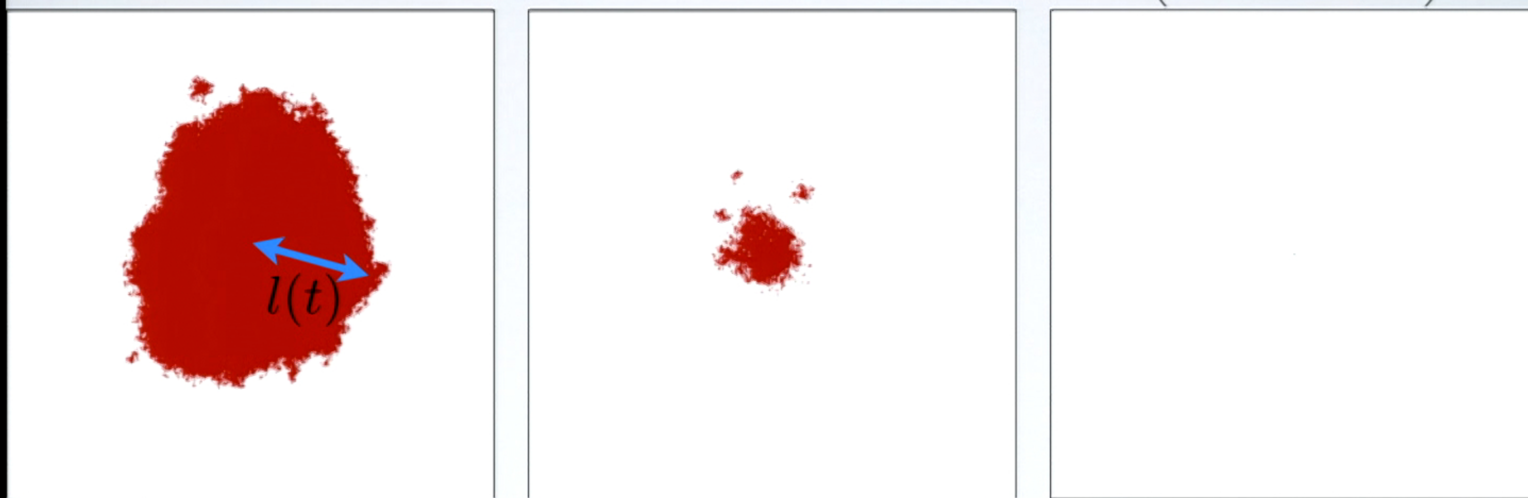
$l(t) \sim vt$

O. H., D. S. Fisher, **PNAS** 111:E4911 (2014)

MOVIES

$\Pr[\text{jump distance} > z] \sim z^{-\mu}$

$\mu = 3.5$ | $\mu = 2.5$ | $\mu = 1.5$ (inf. variance)



Finite speed

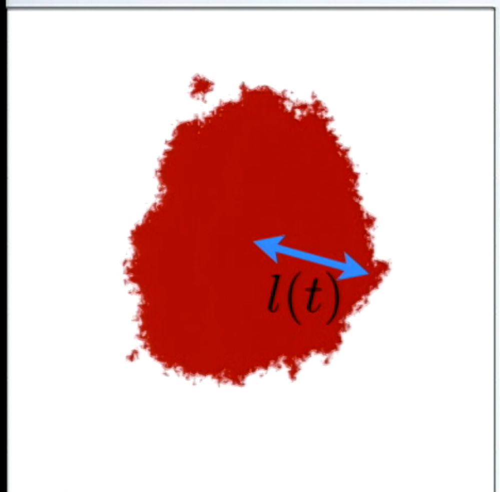
$l(t) \sim vt$

O. H., D. S. Fisher, **PNAS** 111:E4911 (2014)

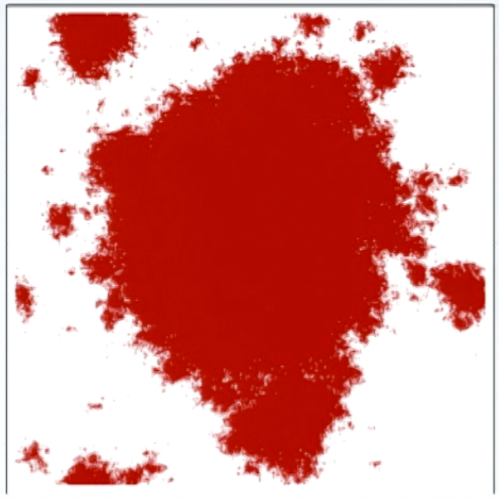
MOVIES

$\Pr[\text{jump distance} > z] \sim z^{-\mu}$

$\mu = 3.5$



$\mu = 2.5$



$\mu = 1.5$
(inf. variance)

Finite speed

$l(t) \sim vt$

Power law

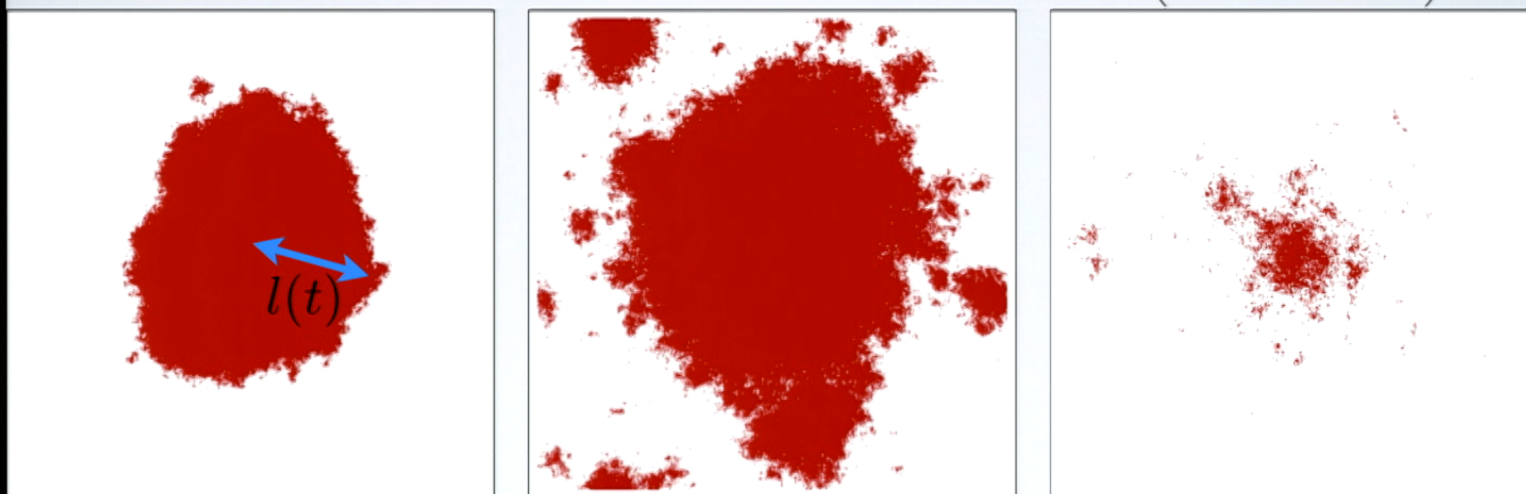
$l(t) \sim t^{\frac{1}{\mu - d}}$

O. H., D. S. Fisher, **PNAS** 111:E4911 (2014)

MOVIES

$\mathrm{Pr}[\text{jump distance} > z] \sim z^{-\mu}$

$\mu = 3.5$ | $\mu = 2.5$ | $\mu = 1.5$ (inf. variance)



Finite speed

$l(t) \sim vt$

Power law

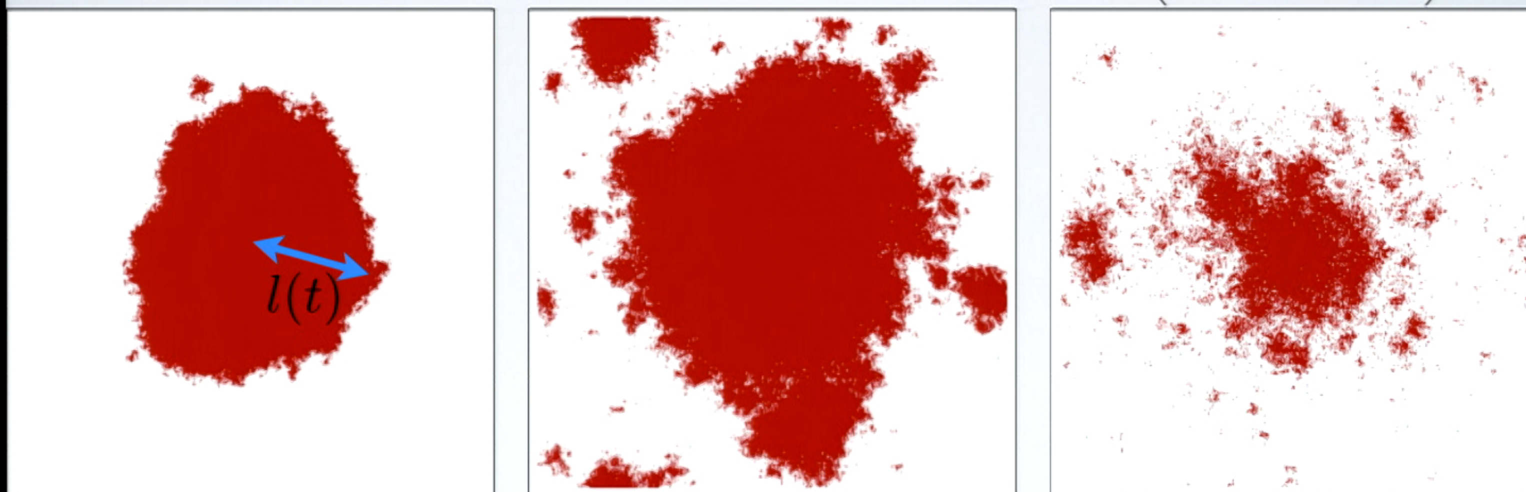
$l(t) \sim t^{\frac{1}{\mu - d}}$

O. H., D. S. Fisher, **PNAS** 111:E4911 (2014)

MOVIES

$\Pr[\text{jump distance} > z] \sim z^{-\mu}$

$\mu = 3.5$ | $\mu = 2.5$ | $\mu = 1.5$ (inf. variance)



Finite speed

$l(t) \sim vt$

Power law

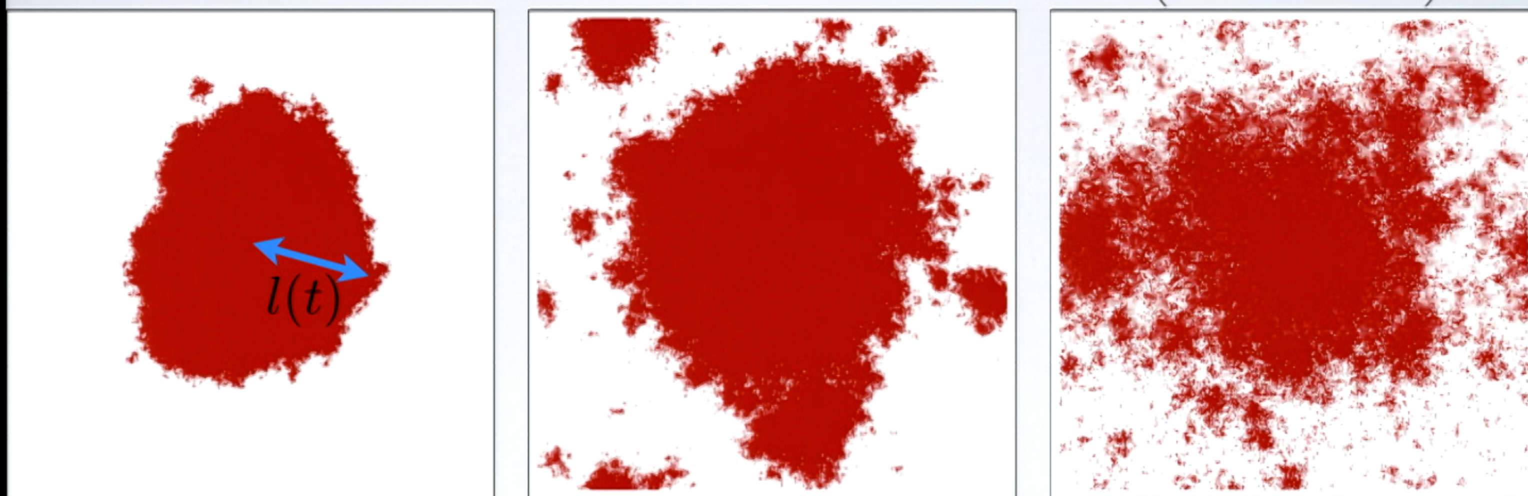
$l(t) \sim t^{\frac{1}{\mu - d}}$

O. H., D. S. Fisher, **PNAS** 111:E4911 (2014)

MOVIES

$\Pr[\text{jump distance} > z] \sim z^{-\mu}$

$\mu = 3.5$ | $\mu = 2.5$ | $\mu = 1.5$ (inf. variance)



Finite speed

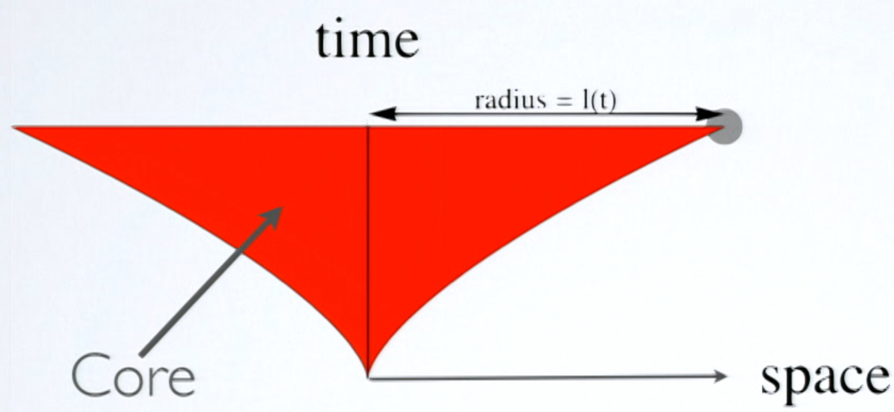
$l(t) \sim vt$

Power law

$l(t) \sim t^{\frac{1}{\mu - d}}$

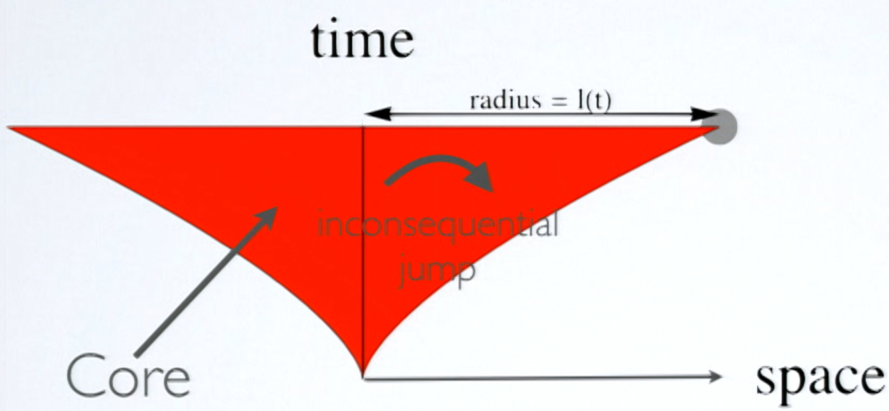
O. H., D. S. Fisher, **PNAS** 111:E4911 (2014)

SELF-CONSISTENCY ARGUMENT



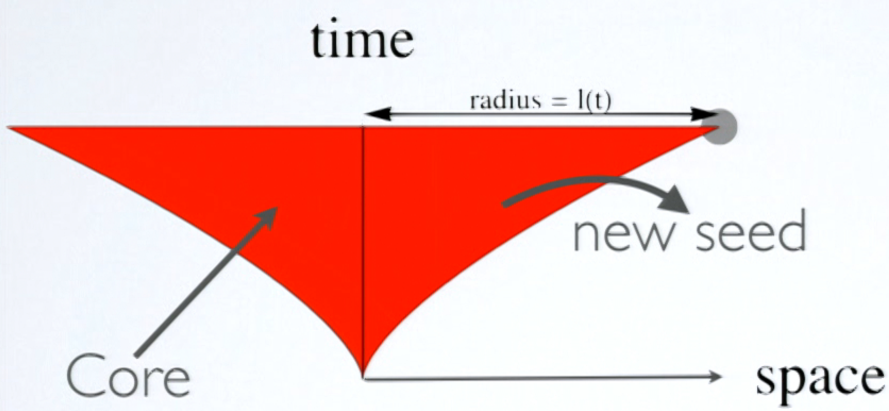
O. H., D. S. Fisher, **PNAS** 111:E4911 (2014)

SELF-CONSISTENCY ARGUMENT



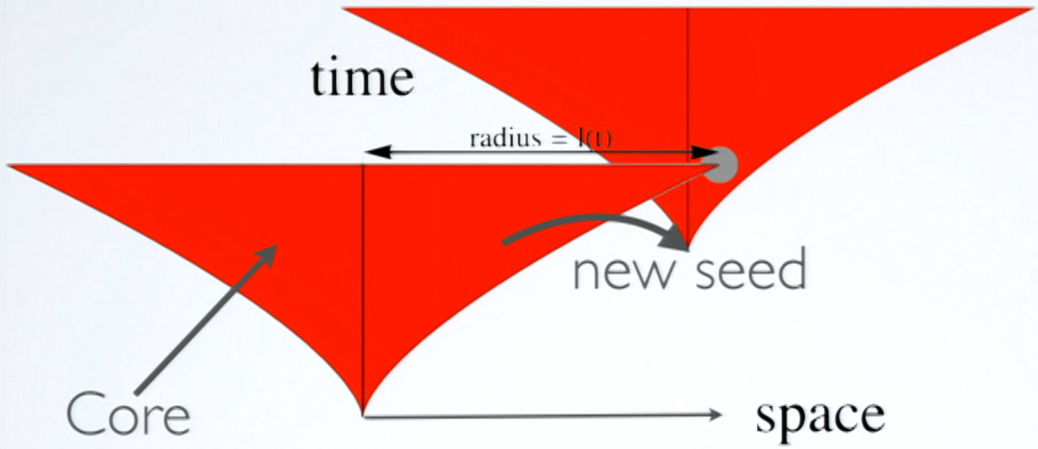
O. H., D. S. Fisher, **PNAS** 111:E4911 (2014)

SELF-CONSISTENCY ARGUMENT



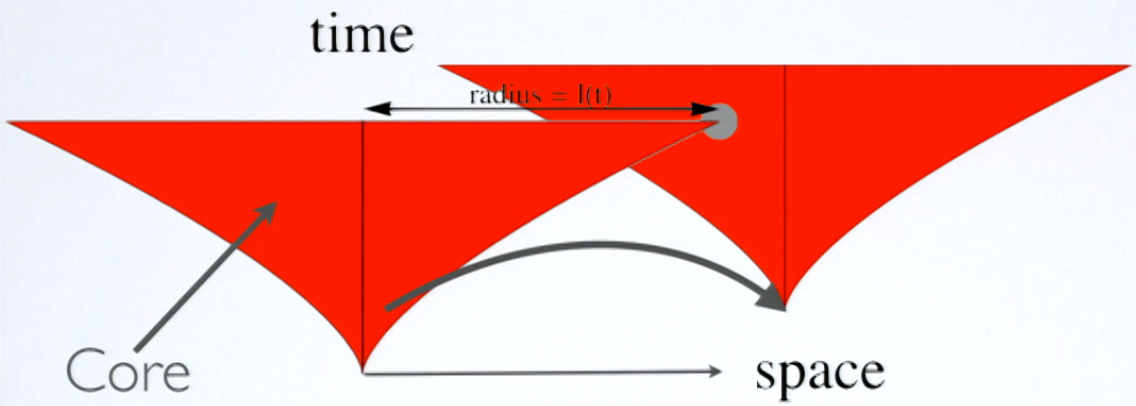
O. H., D. S. Fisher, **PNAS** 111:E4911 (2014)

SELF-CONSISTENCY ARGUMENT



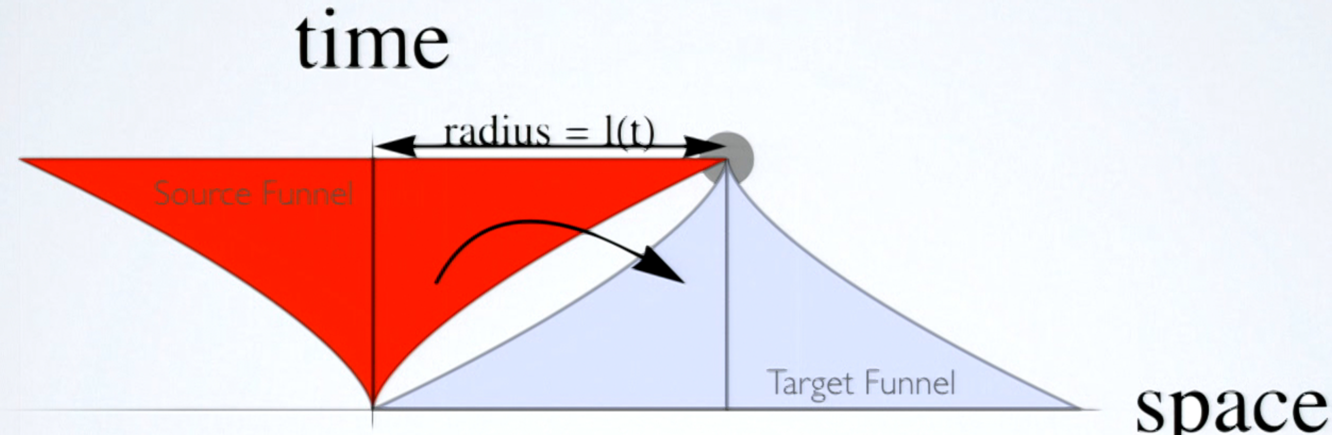
O. H., D. S. Fisher, **PNAS** 111:E4911 (2014)

SELF-CONSISTENCY ARGUMENT



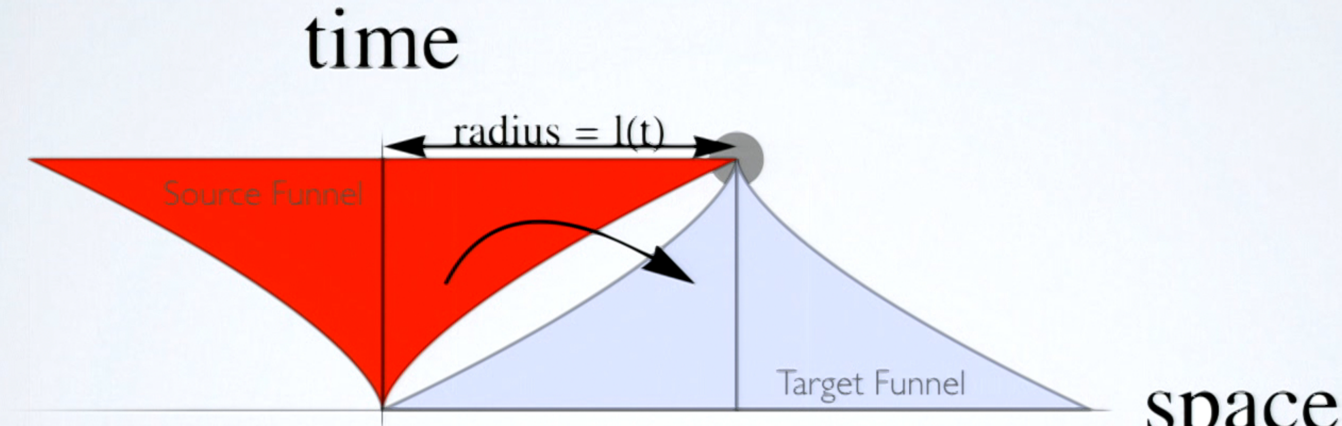
O. H., D. S. Fisher, **PNAS** 111:E4911 (2014)

SELF-CONSISTENCY ARGUMENT



O. H., D. S. Fisher, **PNAS** 111:E4911 (2014)

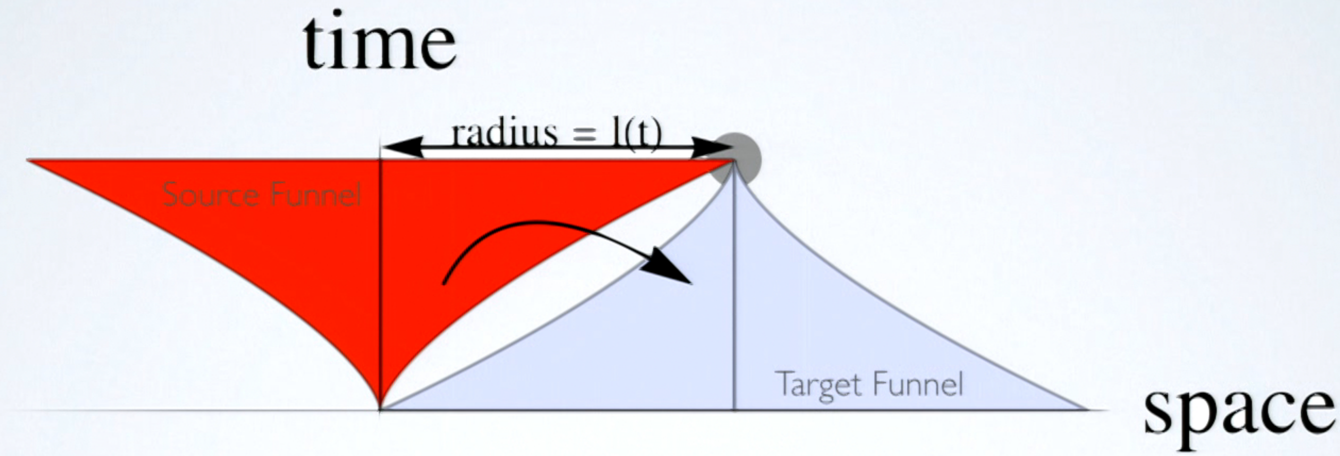
SELF-CONSISTENCY ARGUMENT



$1 \approx$ Expected Nr of Jumps from Source to Target Funnel

O. H., D. S. Fisher, **PNAS** 111:E4911 (2014)

SELF-CONSISTENCY ARGUMENT



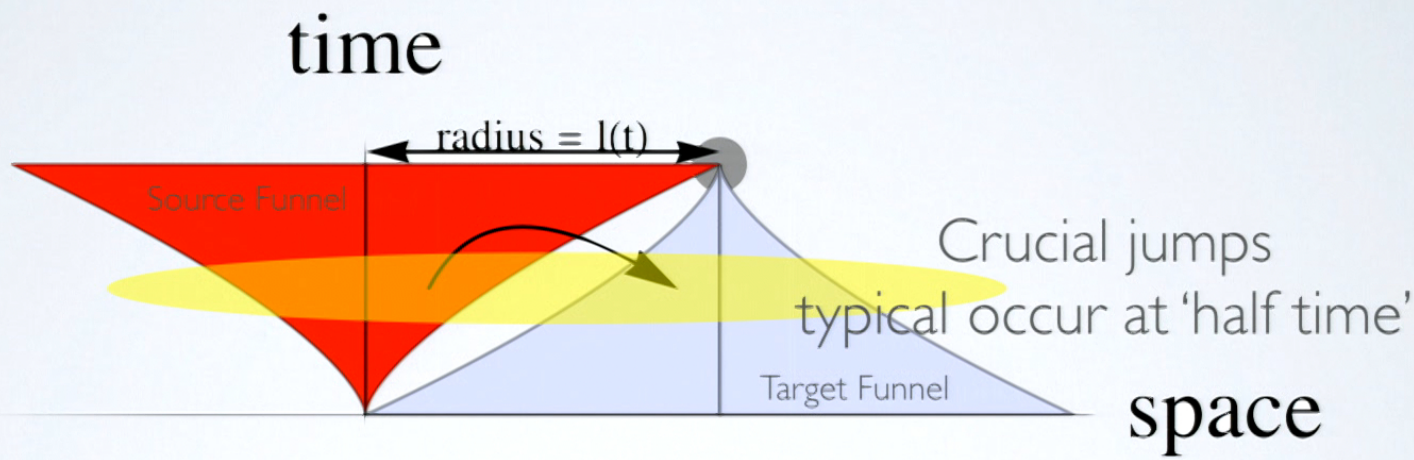
$1 \approx$ Expected Nr of Jumps from Source to Target Funnel

$$1 \approx \int_0^t dt' \int_{\mathcal{B}_{l(t')}} d^d r \int_{\mathcal{B}_{l(t-t')}} d^d r' \, G\left[l(t)\hat{e} + \vec{r} - \vec{r}'\right]$$

(jump kernel)

O. H., D. S. Fisher, **PNAS** 111:E4911 (2014)

SELF-CONSISTENCY ARGUMENT



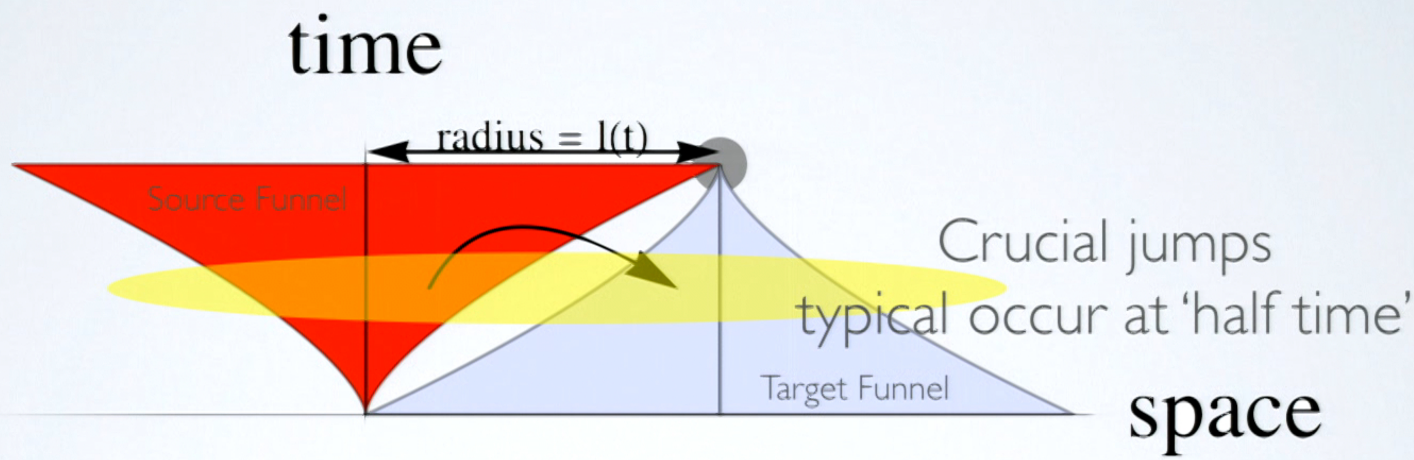
$1 \approx$ Expected Nr of Jumps from Source to Target Funnel

$$1 \approx \int_0^t dt' \int_{\mathcal{B}_{l(t')}} d^d r \int_{\mathcal{B}_{l(t-t')}} d^d r' \; G\left[l(t)\hat{e} + \vec{r} - \vec{r}'\right]$$

(jump kernel)

O. H., D. S. Fisher, **PNAS** 111:E4911 (2014)

SELF-CONSISTENCY ARGUMENT



$1 \approx$ Expected Nr of Jumps from Source to Target Funnel

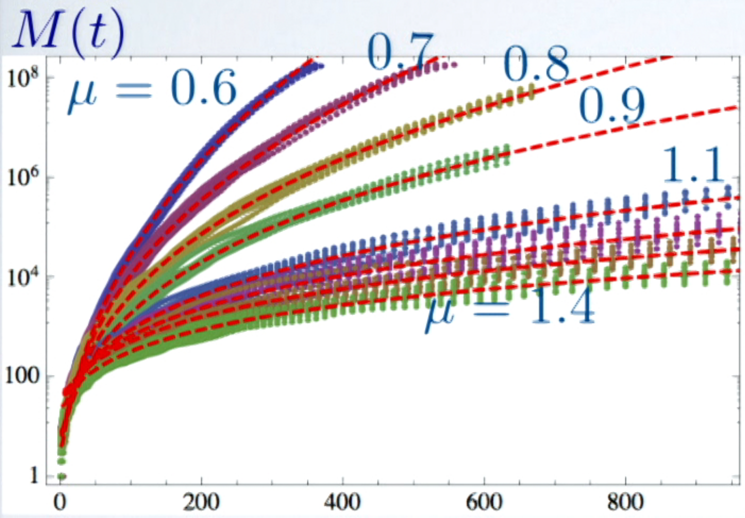
Saddle Point Approximation

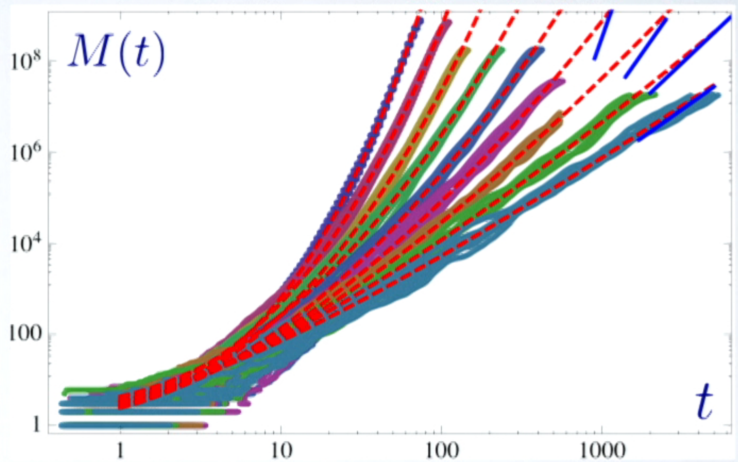
$$G\left[\ell(t)\right] \sim \ell\left(t/2\right)^{-2d} t^{-1}$$

(jump kernel)

O. H., D. S. Fisher, **PNAS** 111:E4911 (2014)

THEORY VS. SIMULATIONS - 1D





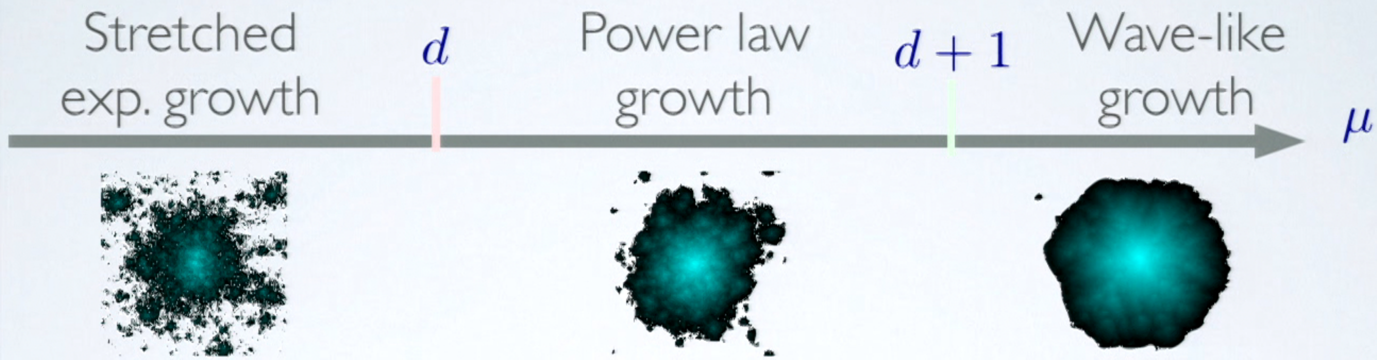
$\varphi = \log_2(l)$ 'log-size'

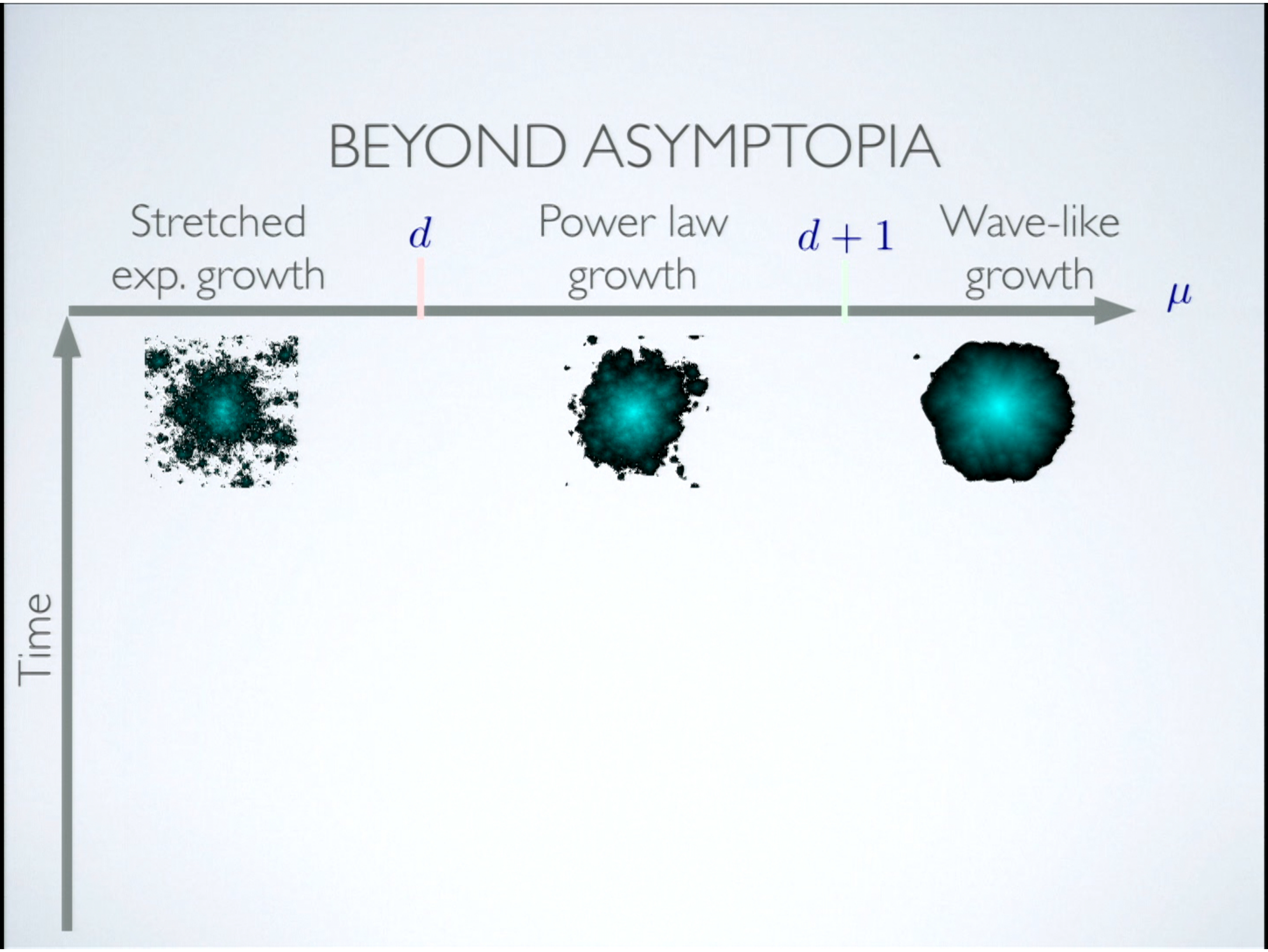
$z = \log_2(t)$ 'log-time'

$\delta = \mu - d$ distance to marginal case

$$\frac{\delta^2}{2d}\varphi(z) = \frac{\delta z}{2d} + \left(1 + \frac{\delta}{2d}\right)^{-z} - 1$$

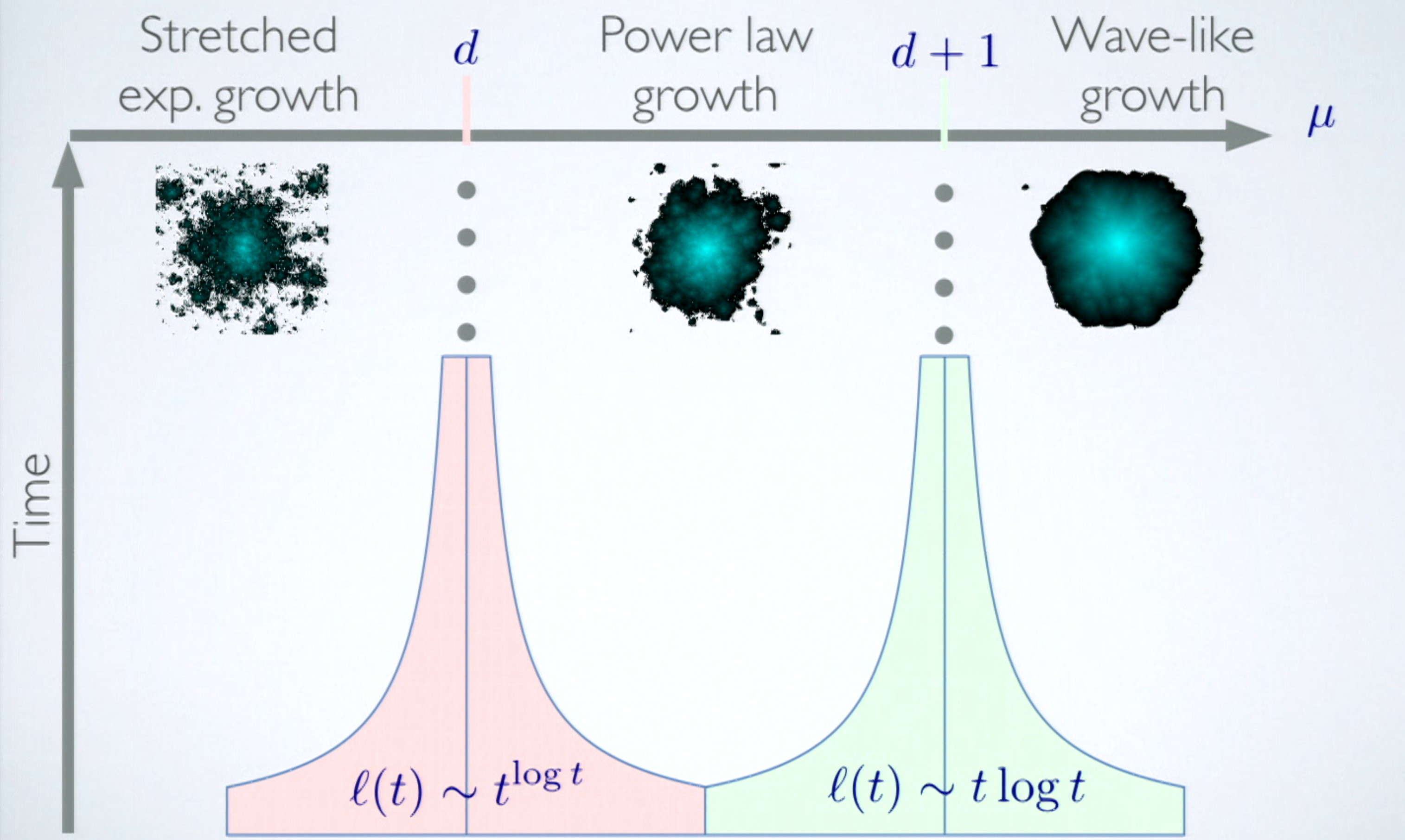
ASYMPTOTICS



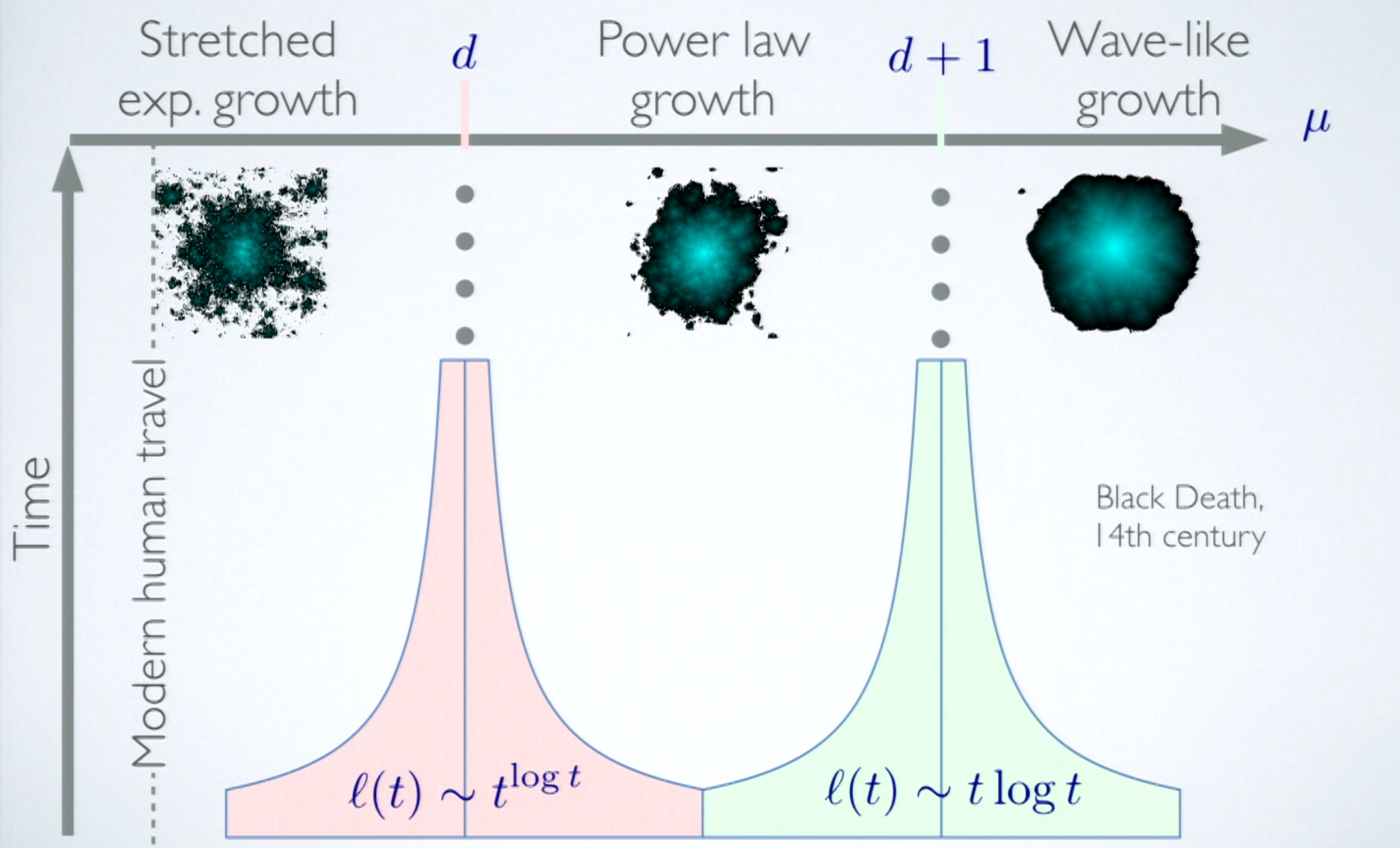


BEYOND ASYMPTOPIA
Stretched exp. growth
d
Power law growth
$d+1$
Wave-like growth
μ
Time

BEYOND ASYMPTOPIA

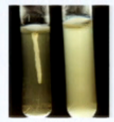


BEYOND ASYMPTOPIA



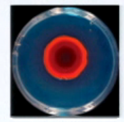
CONCLUSIONS (I)

Exp. growth



semi-
deterministic

Wave-like



semi-
deterministic

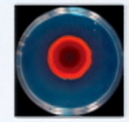
O. H., D. S. Fisher, **PNAS** 111:E4911 (2014)

CONCLUSIONS (I)

Exp. growth

semi-
deterministic

Wave-like



semi-
deterministic

Noise dominated

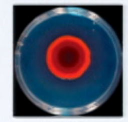
O. H., D. S. Fisher, **PNAS** 111:E4911 (2014)

CONCLUSIONS (I)

Exp. growth

semi-deterministic

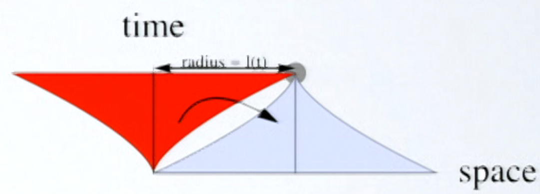
Wave-like



semi-deterministic

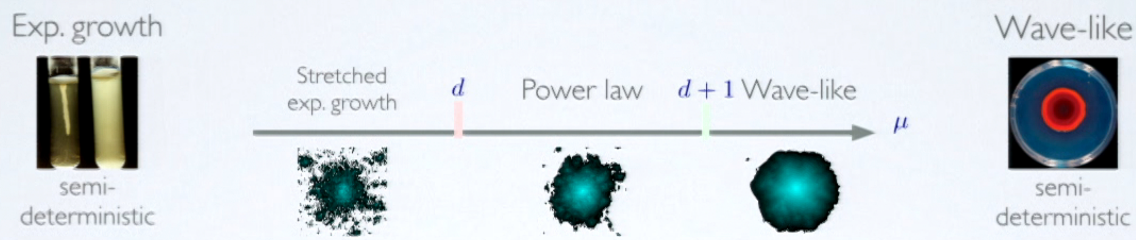
Noise dominated

- *Trade-off* between frequency and potential effectiveness of long-distance jumps



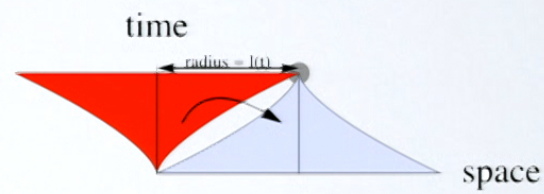
O. H., D. S. Fisher, **PNAS** 111:E4911 (2014)

CONCLUSIONS (I)



Noise dominated

- *Trade-off* between frequency and potential effectiveness of long-distance jumps



- *Future*: Break symmetries to obtain comprehensive theory of spreading

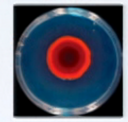
O. H., D. S. Fisher, **PNAS** 111:E4911 (2014)

CONCLUSIONS (I)

Exp. growth

semi-
deterministic

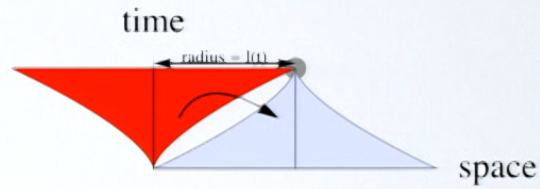
Wave-like



semi-
deterministic

Noise dominated

- *Trade-off* between frequency and potential effectiveness of long-distance jumps

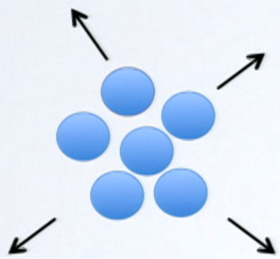


- *Future*: Break symmetries to obtain comprehensive theory of spreading

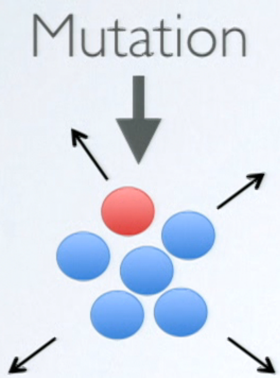
Consequences for evolutionary dynamics?

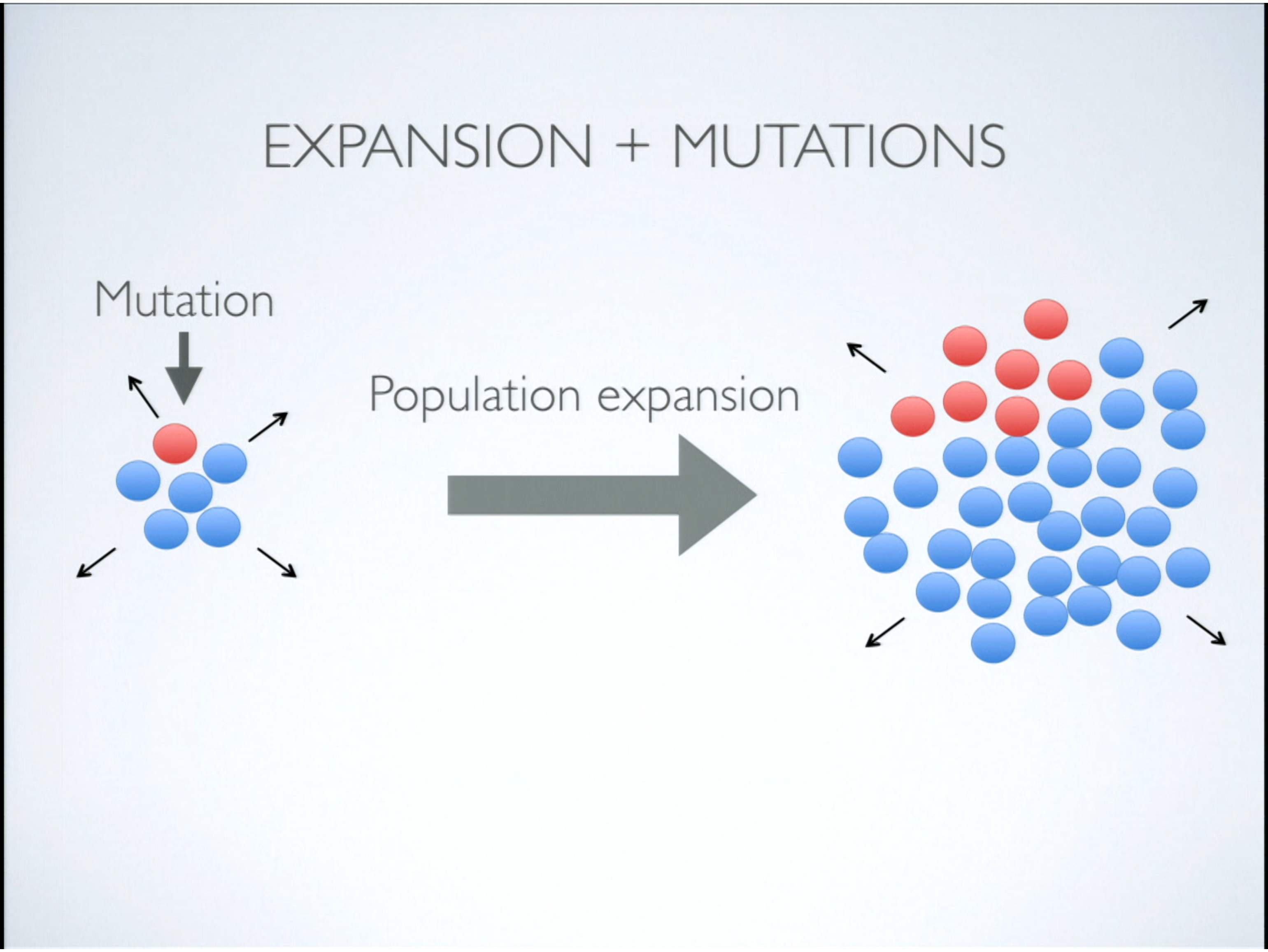
O. H., D. S. Fisher, **PNAS** 111:E4911 (2014)

EXPANSION + MUTATIONS

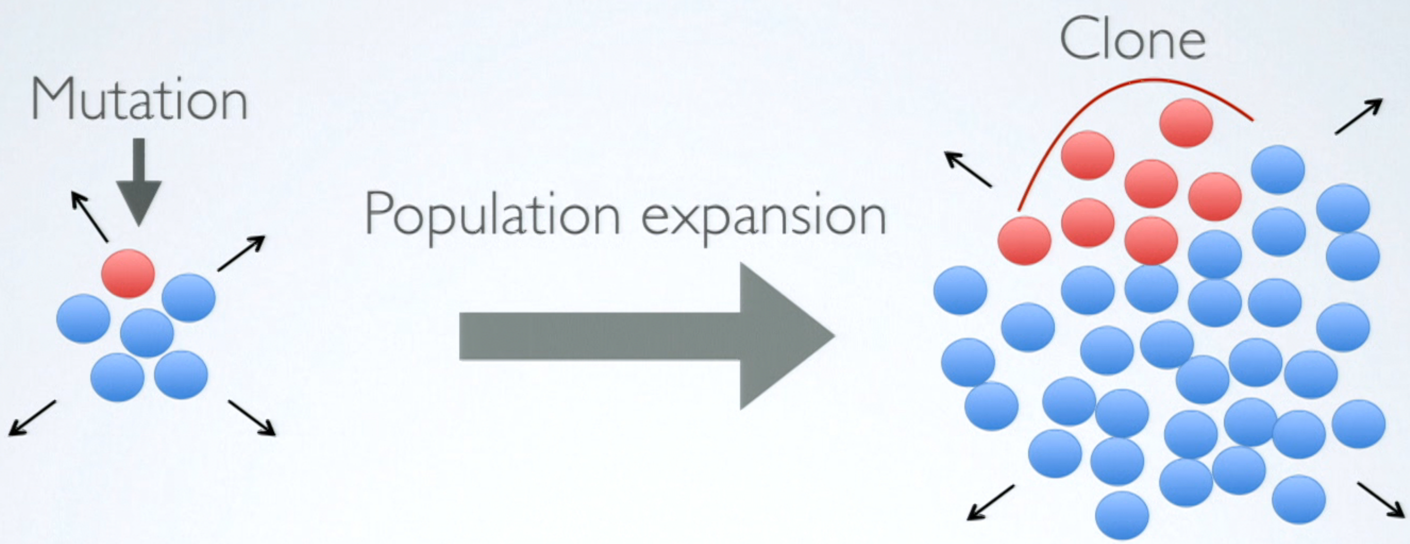


EXPANSION + MUTATIONS



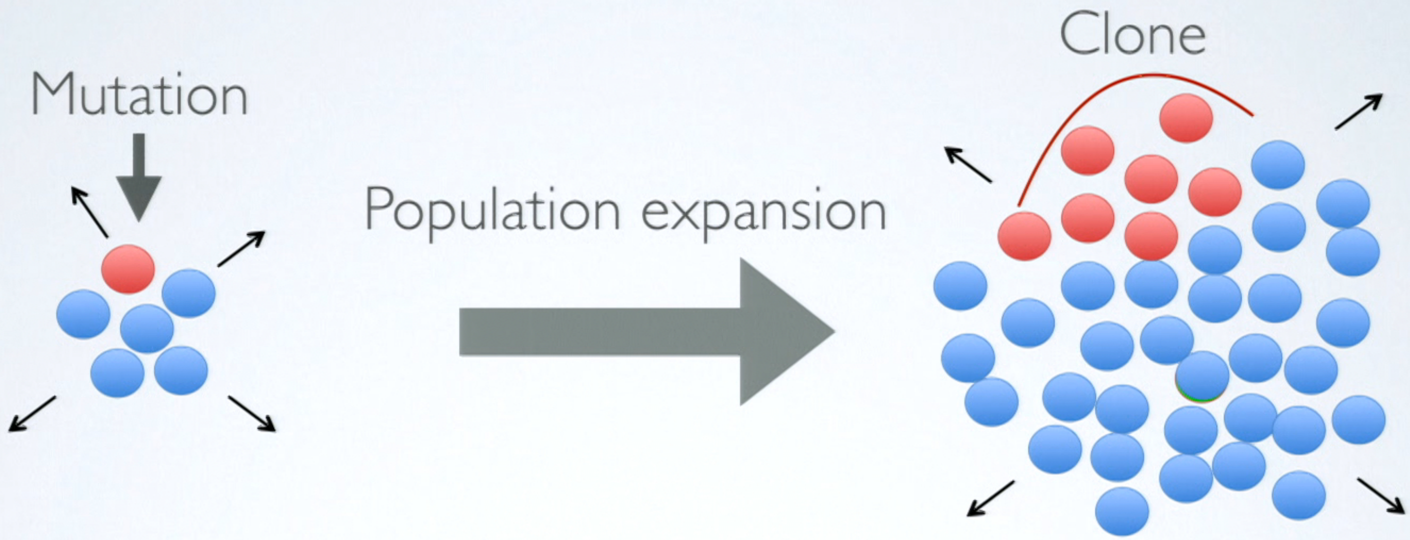

EXPANSION + MUTATIONS
Mutation
Population expansion

EXPANSION + MUTATIONS



Expansions can generate large mutant clones

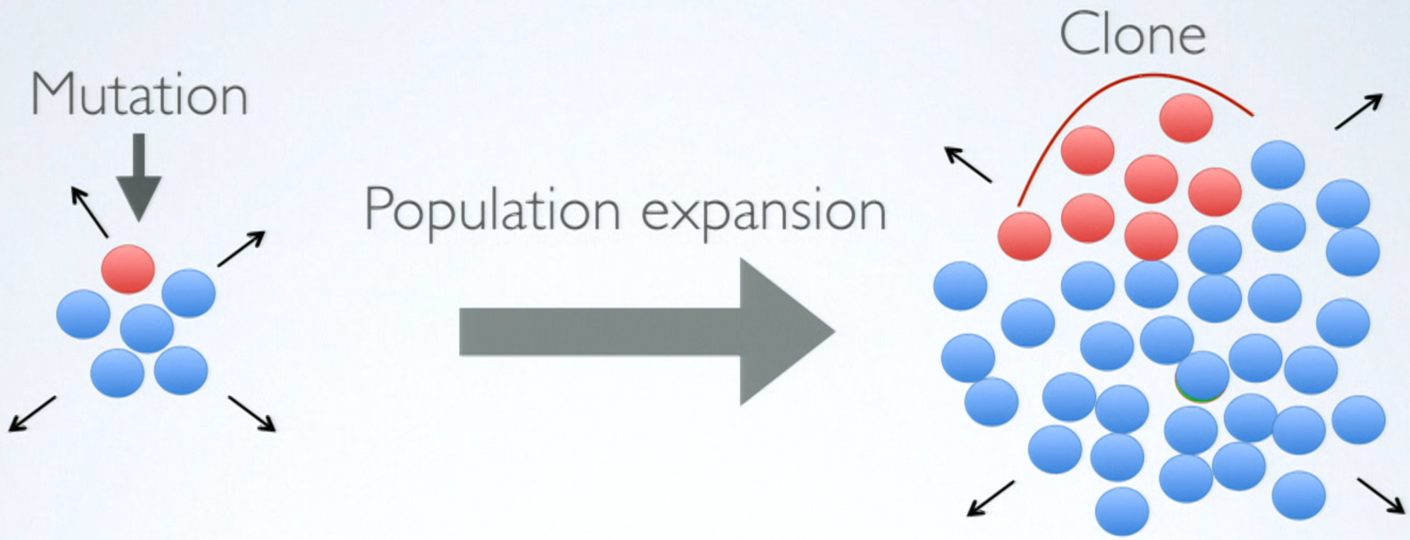
MUTATIONAL "JACKPOT" EVENTS



Expansions can generate large mutant clones

Luria, Salvador E., and Max Delbrück. ***Genetics*** (1943)

MUTATIONAL "JACKPOT" EVENTS

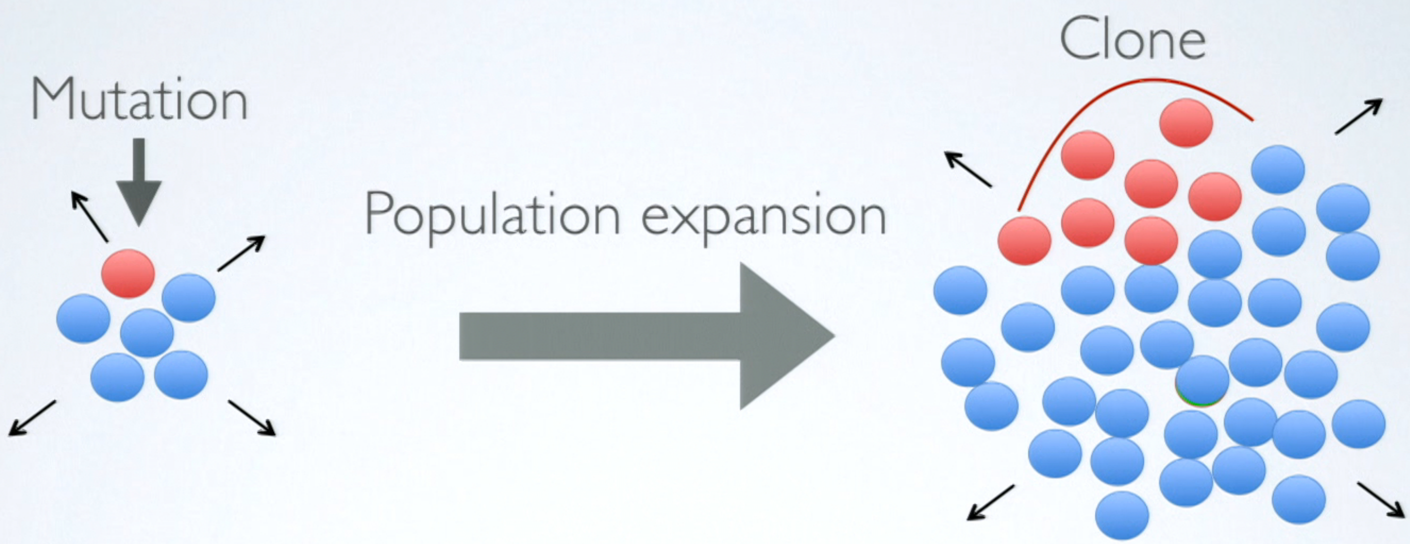


Expansions can generate large mutant clones

Mutation in 2^{nd} cell $\Rightarrow$ expect $\frac{1}{2}$ of final population to be mutants.

Luria, Salvador E., and Max Delbrück. ***Genetics*** (1943)

MUTATIONAL "JACKPOT" EVENTS



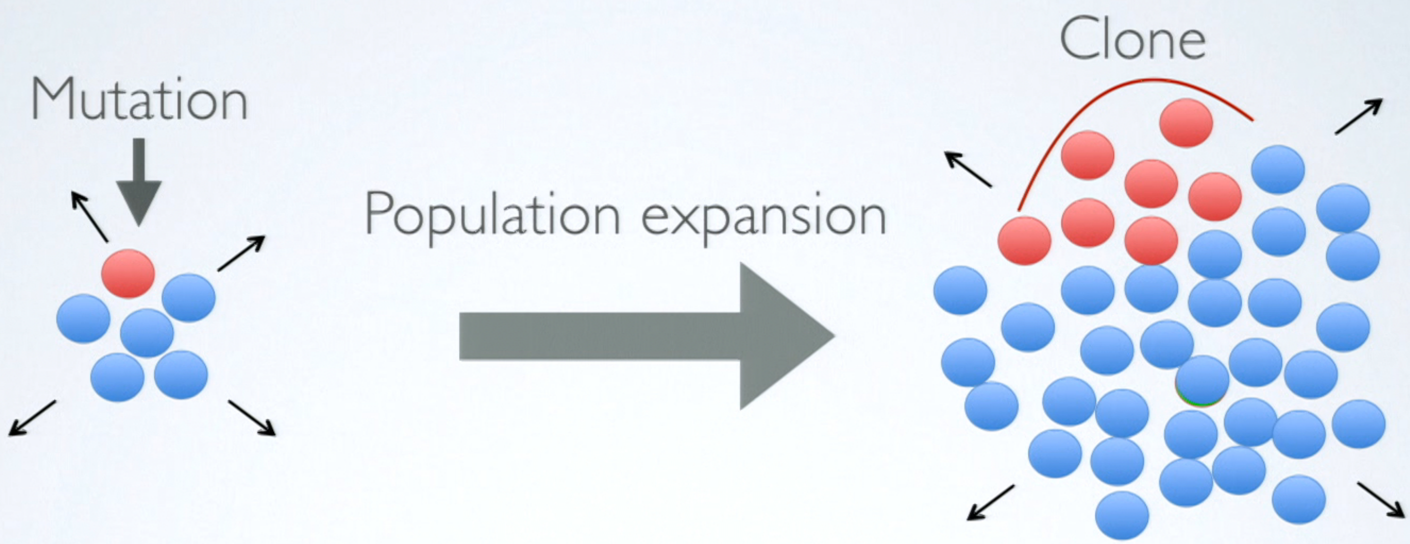
Expansions can generate large mutant clones

Mutation in 2^{nd} cell $\Rightarrow$ expect $\frac{1}{2}$ of final population to be mutants.

Mutation in 3^{rd} cell $\Rightarrow$ expect $\frac{1}{3}$ of final population to be mutants.

Luria, Salvador E., and Max Delbrück. ***Genetics*** (1943)

MUTATIONAL "JACKPOT" EVENTS



Expansions can generate large mutant clones

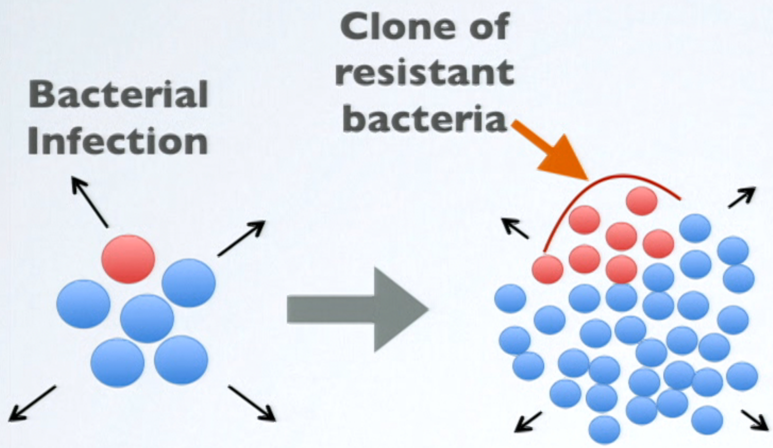
Mutation in 2^{nd} cell $\Rightarrow$ expect $\frac{1}{2}$ of final population to be mutants.

Mutation in 3^{rd} cell $\Rightarrow$ expect $\frac{1}{3}$ of final population to be mutants.

Mutation in n^{th} cell $\Rightarrow$ expect $\frac{1}{n}$ of final population to be mutants.

Luria, Salvador E., and Max Delbrück. ***Genetics*** (1943)

DRUG RESISTANCE VIA JACKPOT EVENTS



Expansions can generate large mutant clones

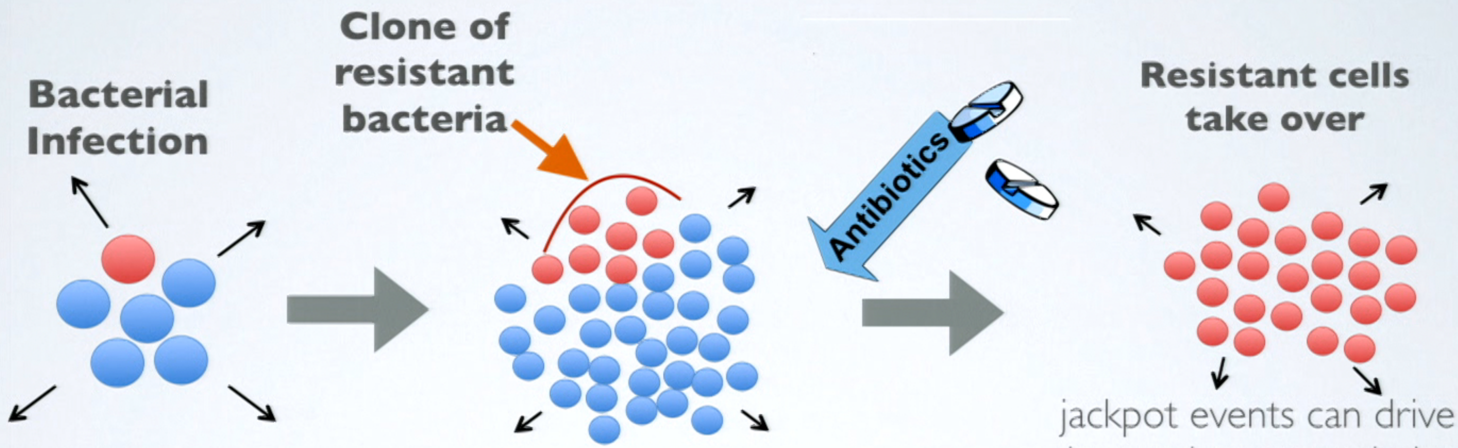
Mutation in 2^{nd} cell $\Rightarrow$ expect $\frac{1}{2}$ of final population to be mutants.

Mutation in 3^{rd} cell $\Rightarrow$ expect $\frac{1}{3}$ of final population to be mutants.

Mutation in n^{th} cell $\Rightarrow$ expect $\frac{1}{n}$ of final population to be mutants.

Luria, Salvador E., and Max Delbrück. ***Genetics*** (1943)

DRUG RESISTANCE VIA JACKPOT EVENTS



jackpot events can drive drug resistance evolution

Expansions can generate large mutant clones

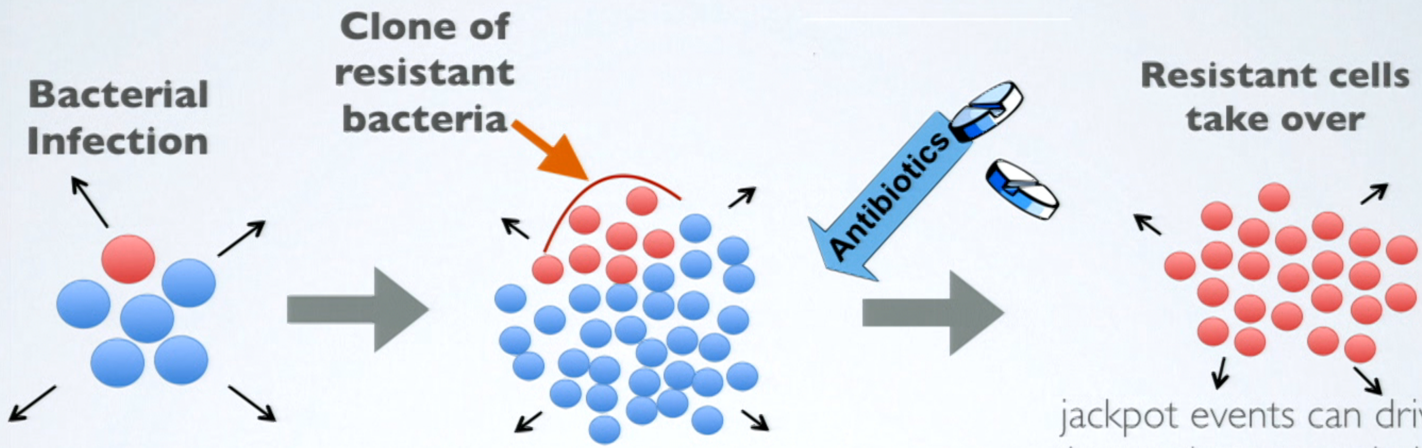
Mutation in 2^{nd} cell $\Rightarrow$ expect $\frac{1}{2}$ of final population to be mutants.

Mutation in 3^{rd} cell $\Rightarrow$ expect $\frac{1}{3}$ of final population to be mutants.

Mutation in n^{th} cell $\Rightarrow$ expect $\frac{1}{n}$ of final population to be mutants.

Luria, Salvador E., and Max Delbrück. ***Genetics*** (1943)

DRUG RESISTANCE VIA JACKPOT EVENTS



jackpot events can drive drug resistance evolution

Expansions can generate large mutant clones

Mutation in 2^{nd} cell $\Rightarrow$ expect $\frac{1}{2}$ of final population to be mutants.

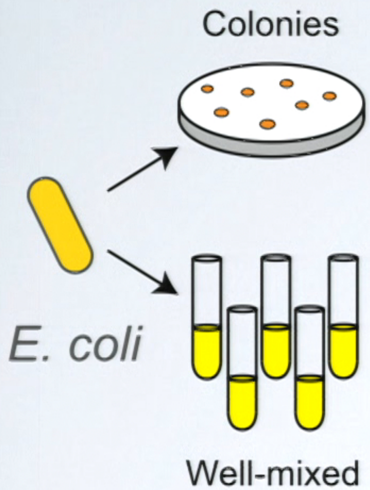
Mutation in 3^{rd} cell $\Rightarrow$ expect $\frac{1}{3}$ of final population to be mutants.

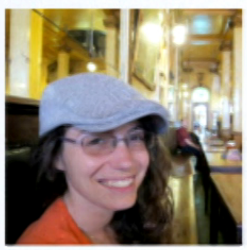
Mutation in n^{th} cell $\Rightarrow$ expect $\frac{1}{n}$ of final population to be mutants.

Luria, Salvador E., and Max Delbrück. ***Genetics*** (1943)

but what if populations are not well-mixed?

DETECTING MUTANT CLONES

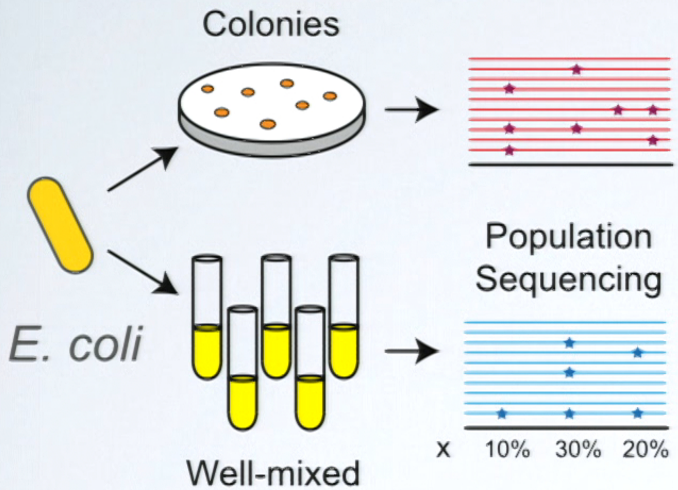


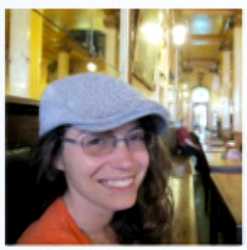


Diana Fusco

D. Fusco, M. Gralka, J. Kayser, A. Anderson and O.H., **Nature Communications**, 7:12760 (2016)

DETECTING MUTANT CLONES

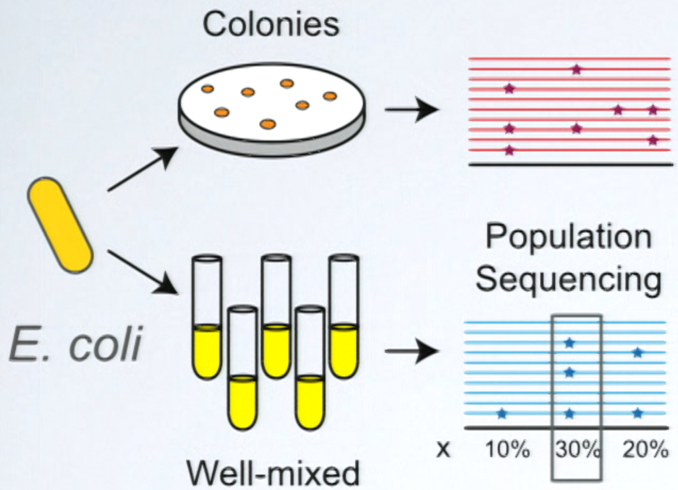


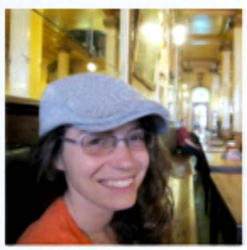


Diana Fusco

D. Fusco, M. Gralka, J. Kayser, A. Anderson and O.H., **Nature Communications**, 7:12760 (2016)

DETECTING MUTANT CLONES

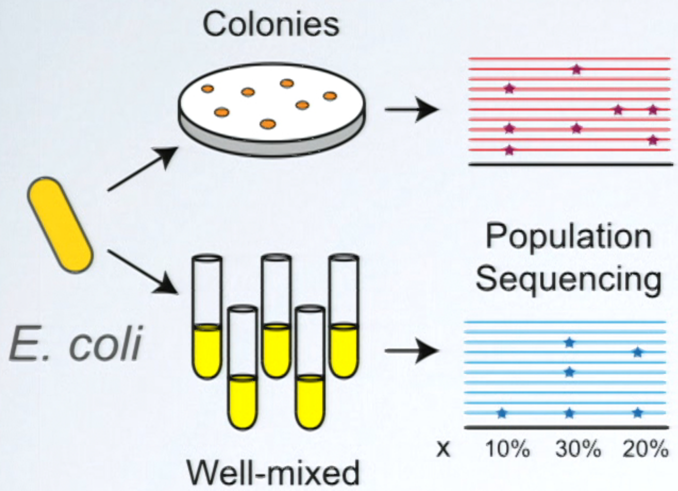


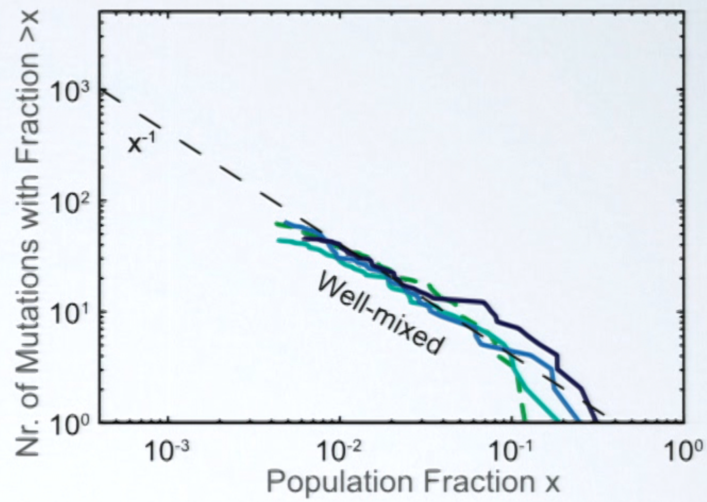


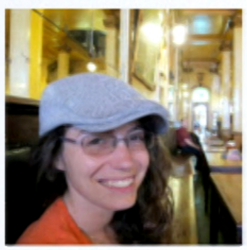
Diana Fusco

D. Fusco, M. Gralka, J. Kayser, A. Anderson and O.H., **Nature Communications**, 7:12760 (2016)

DETECTING MUTANT CLONES



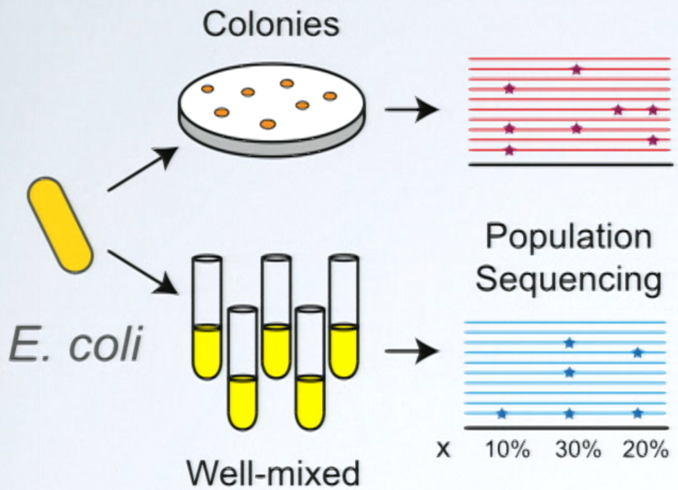


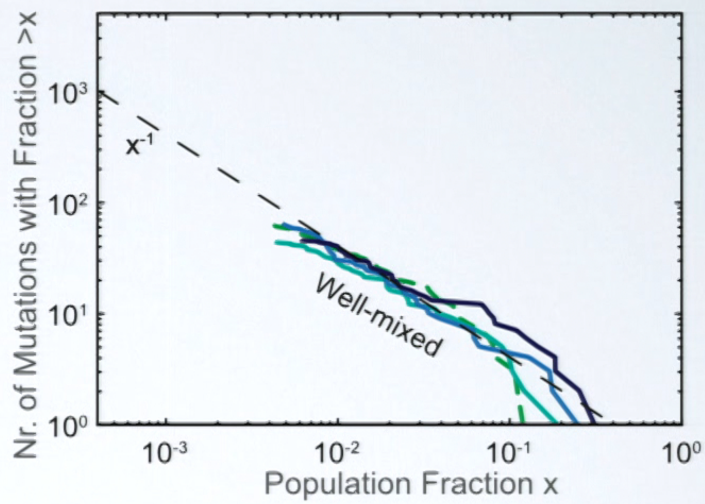


Diana Fusco

D. Fusco, M. Gralka, J. Kayser, A. Anderson and O.H., **Nature Communications**, 7:12760 (2016)

DETECTING MUTANT CLONES



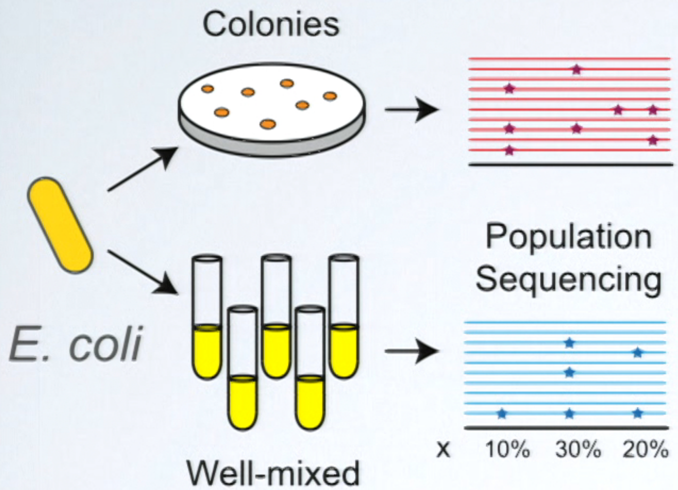


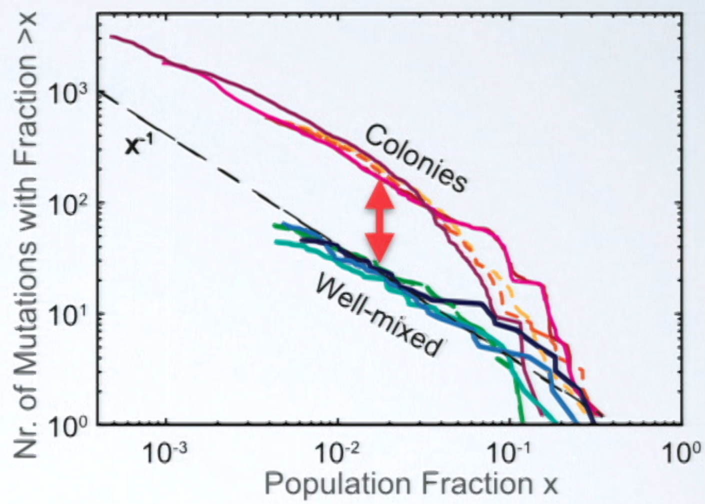
Diana Fusco

Broad distributions, with rare "jackpot" mutations that arise early. Luria, Delbrück 1943

D. Fusco, M. Gralka, J. Kayser, A. Anderson and O.H., **Nature Communications**, 7:12760 (2016)

DETECTING MUTANT CLONES



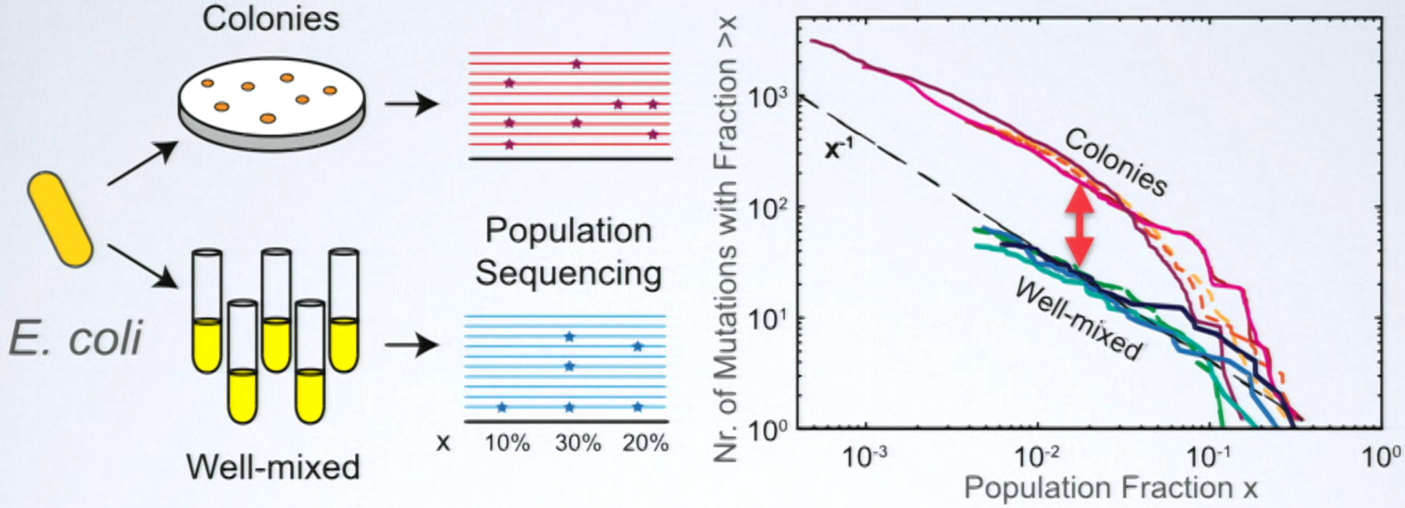


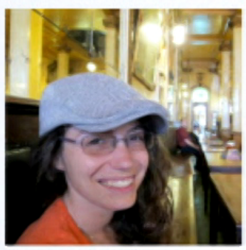
Broad distributions, with rare “jackpot” mutations that arise early. Luria, Delbrück 1943

Diana Fusco

D. Fusco, M. Gralka, J. Kayser, A. Anderson and O.H., **Nature Communications**, 7:12760 (2016)

DETECTING MUTANT CLONES





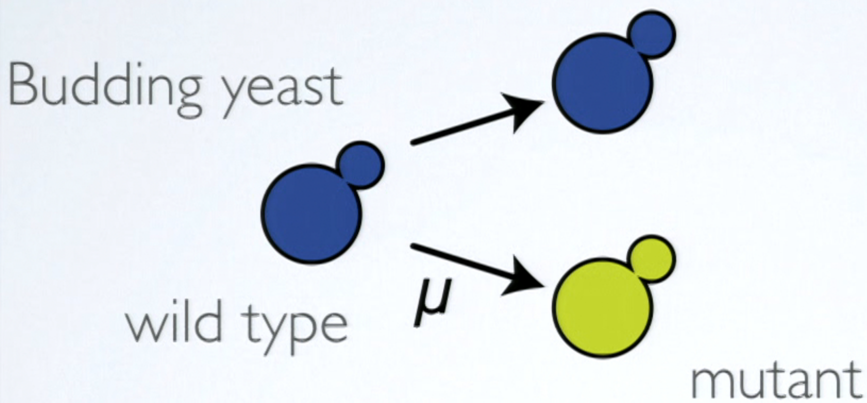
Diana Fusco

Broad distributions, with rare "jackpot" mutations that arise early. Luria, Delbrück 1943

Spatial case: More high-frequency events!
Why?

D. Fusco, M. Gralka, J. Kayser, A. Anderson and O.H., **Nature Communications**, 7:12760 (2016)

VISUALIZING MUTANT CLONES



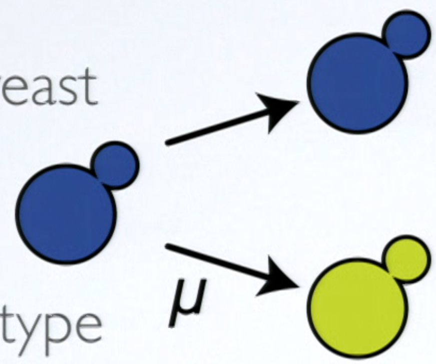
Color switches at a rate of ~1/1000 cell divisions.

Thanks for help from Anne Dodson and Jasper Rine!

A. Dodson, J. Rine. *Elife* 4 (2015): e05007.

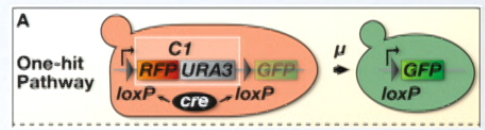
VISUALIZING MUTANT CLONES

Budding yeast



wild type

mutant

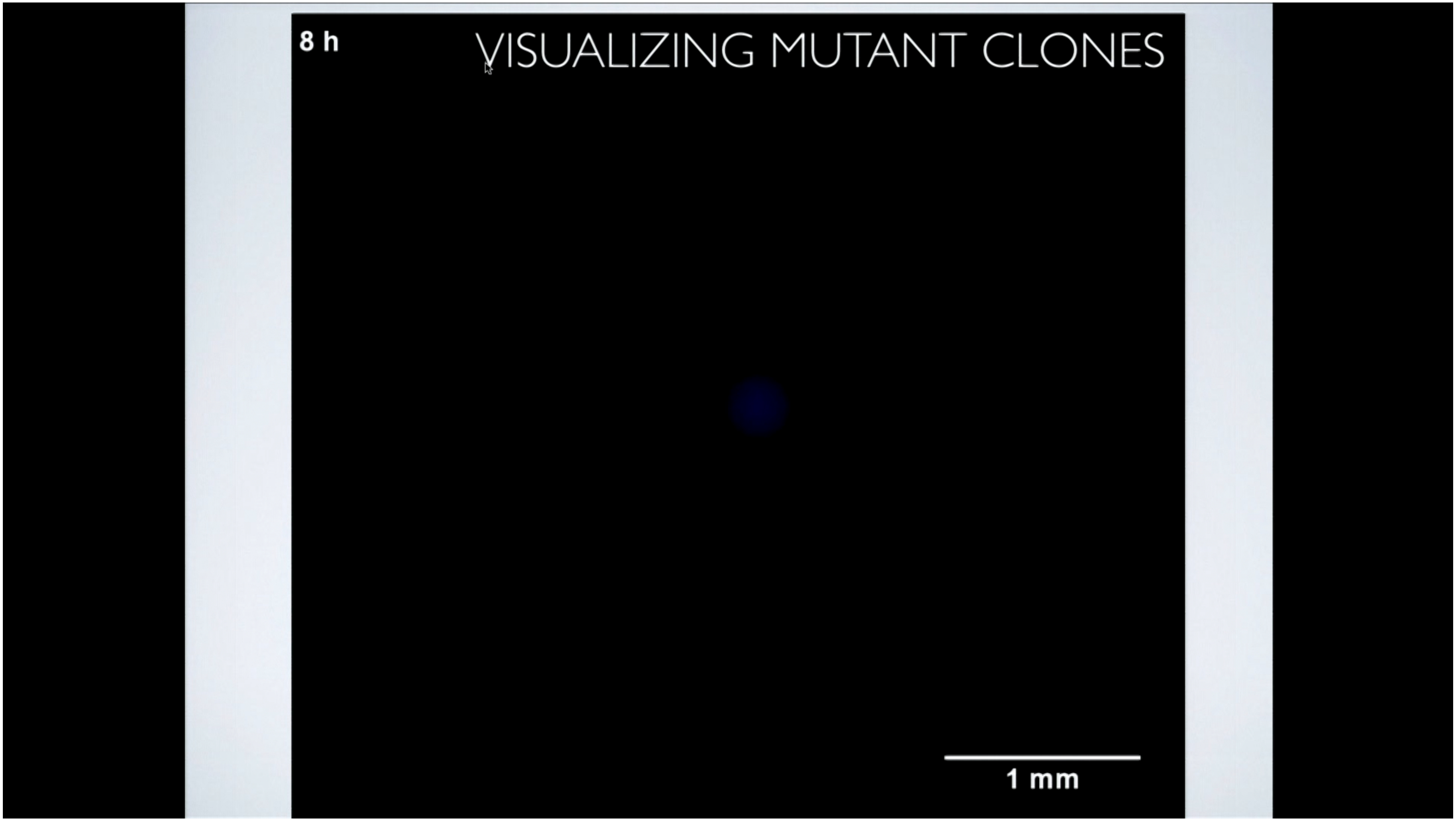


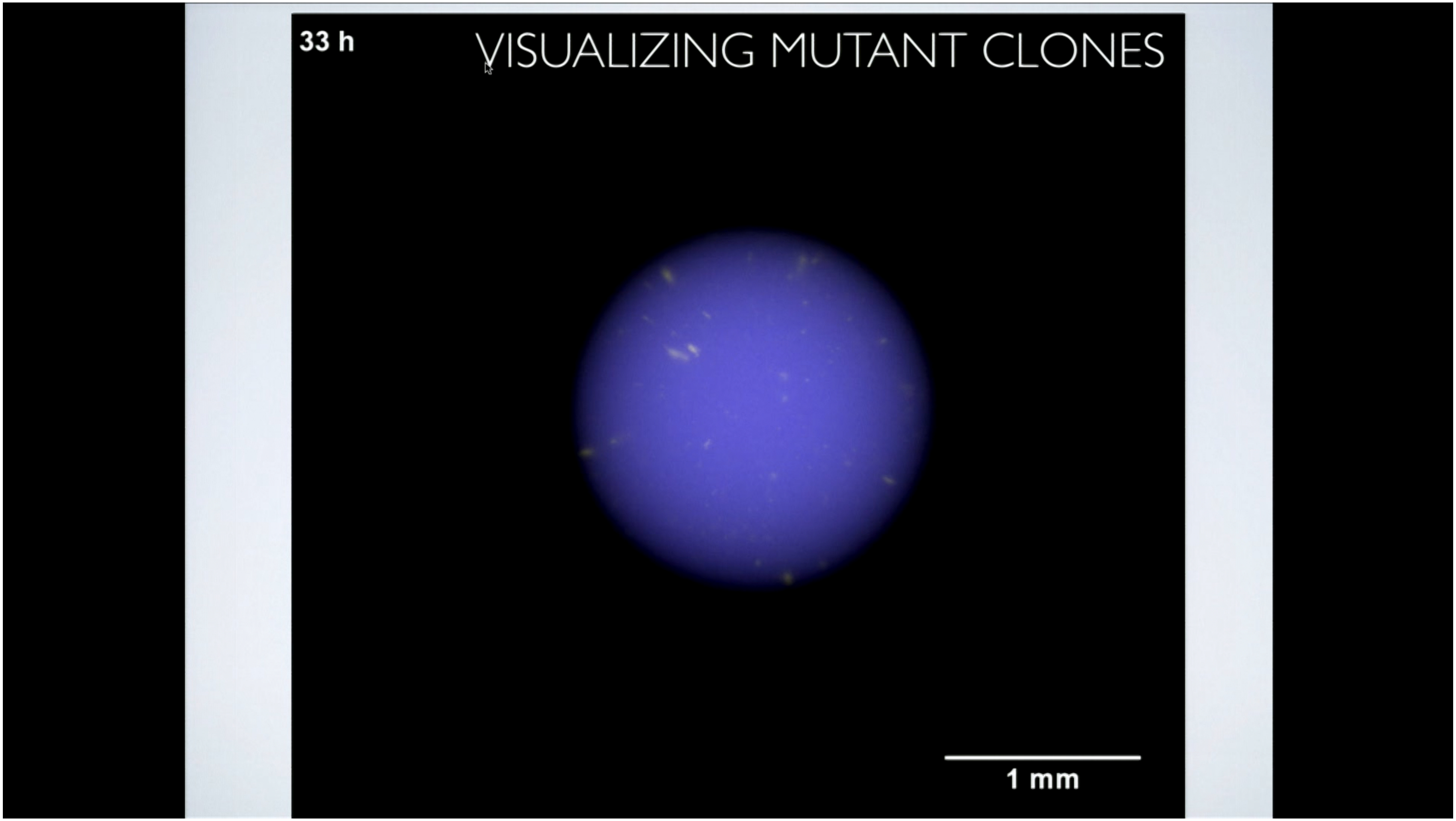
Cre is expressed only
when HML locus is unsilenced:

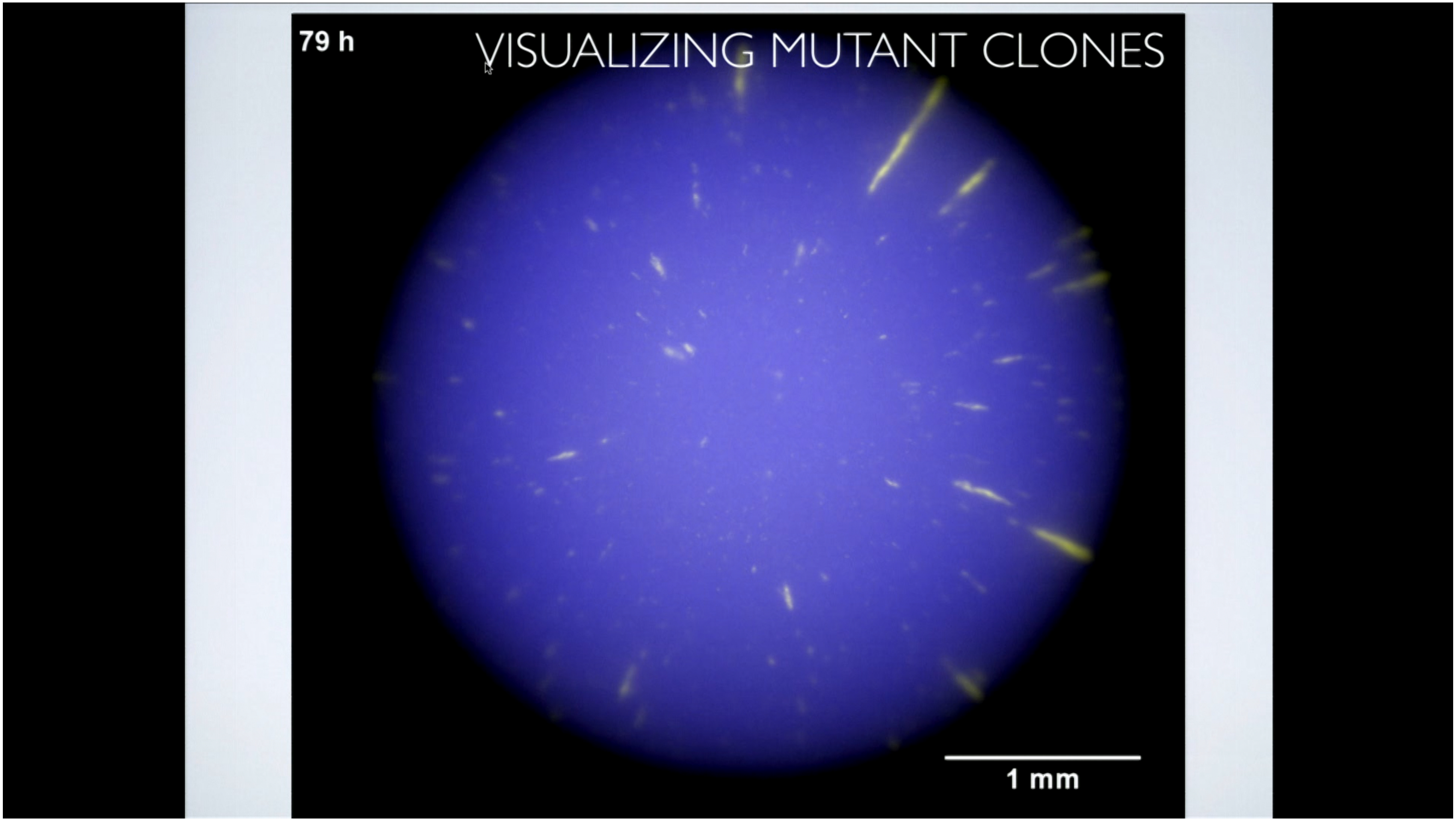
$$\mu \approx 10^{-3}$$

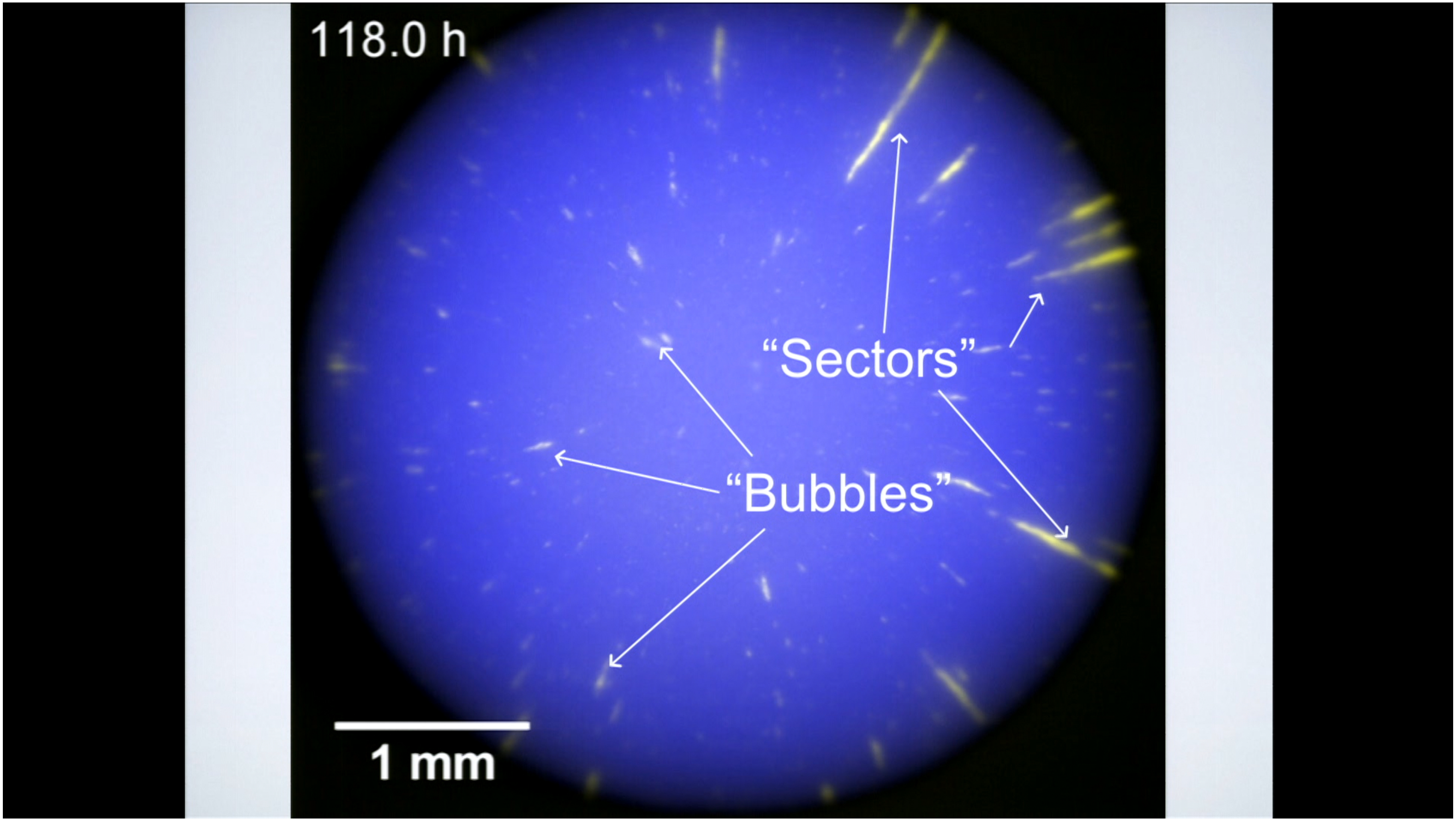
Color switches at a rate of
~1/1000 cell divisions.

Thanks for help from Anne Dodson and Jasper Rine!
A. Dodson, J. Rine. *Elife* 4 (2015): e05007.

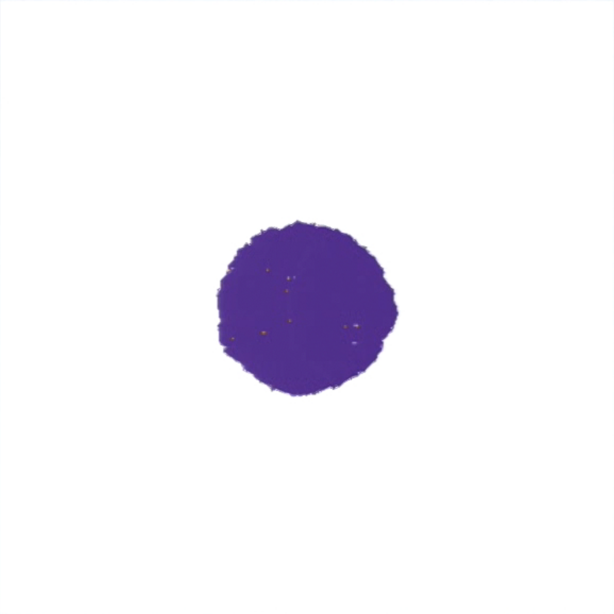

8 h
VISUALIZING MUTANT CLONES
1 mm


33 h
VISUALIZING MUTANT CLONES
1 mm


79 h
VISUALIZING MUTANT CLONES
1 mm

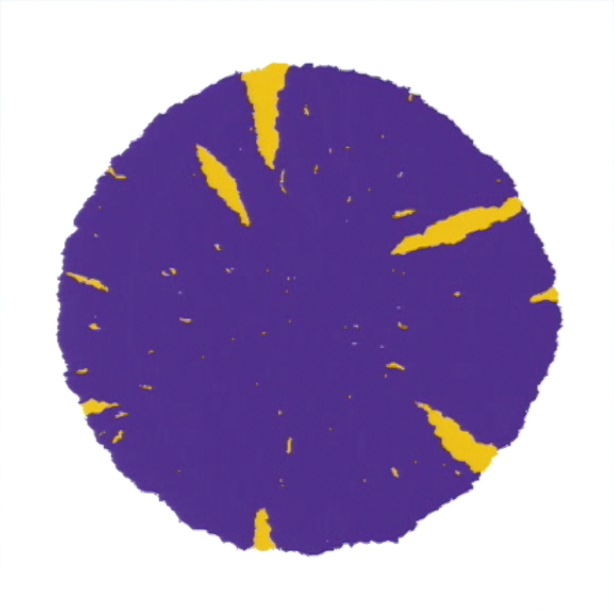

118.0 h
"Sectors"
"Bubbles"
1 mm

POPULATION EXPANSION SIMULATIONS REPRODUCE CLONE PATTERN



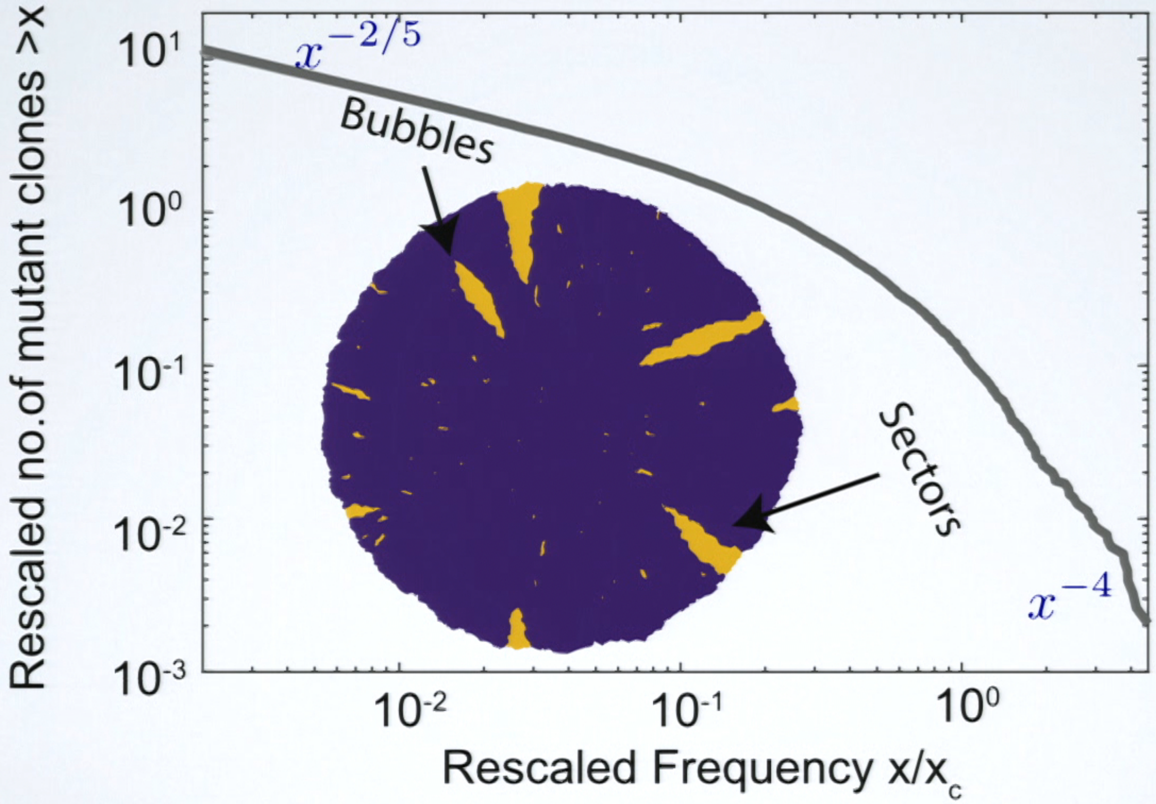
D. Fusco, M. Gralka, J. Kayser, A. Anderson and O.H., **Nature Communications**, 7:12760 (2016)

POPULATION EXPANSION SIMULATIONS REPRODUCE CLONE PATTERN



D. Fusco, M. Gralka, J. Kayser, A. Anderson and O.H., **Nature Communications**, 7:12760 (2016)

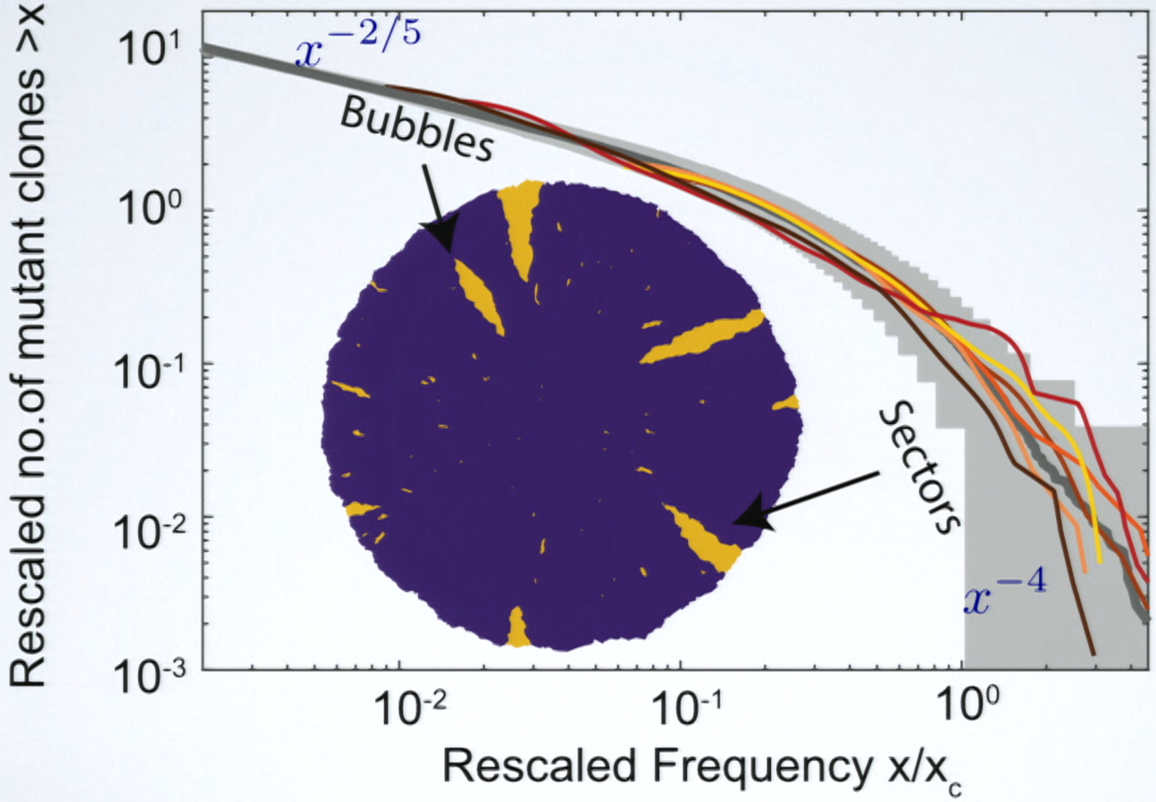
UNIVERSAL CROSS-OVER SCALING FORM FOR MUTANT NUMBER DISTRIBUTION



Exponents obtained from scaling arguments based on KPZ statistics

D. Fusco, M. Gralka, J. Kayser, A. Anderson and O.H., **Nature Communications**, 7:12760 (2016)

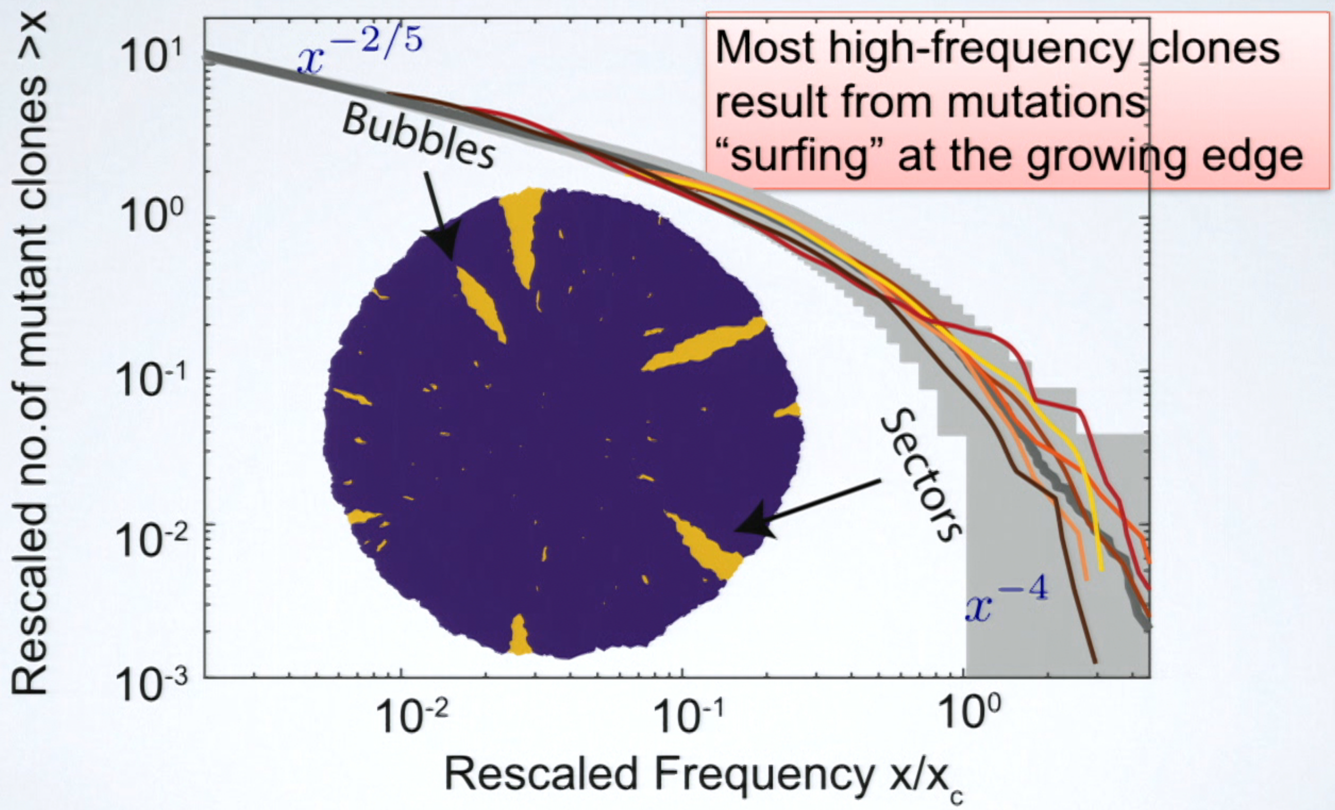
UNIVERSAL CROSS-OVER SCALING FORM FOR MUTANT NUMBER DISTRIBUTION



Exponents obtained from scaling arguments based on KPZ statistics

D. Fusco, M. Gralka, J. Kayser, A. Anderson and O.H., **Nature Communications**, 7:12760 (2016)

UNIVERSAL CROSS-OVER SCALING FORM FOR MUTANT NUMBER DISTRIBUTION



Exponents obtained from scaling arguments based on KPZ statistics

D. Fusco, M. Gralka, J. Kayser, A. Anderson and O.H., **Nature Communications**, 7:12760 (2016)

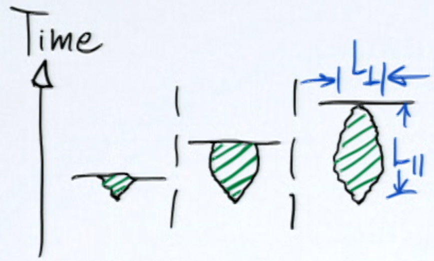
COARSE-GRAINED MODEL

D. Fusco, M. Gralka, J. Kayser, A. Anderson and O.H., **Nature Communications**, 7:12760 (2016)

COARSE-GRAINED MODEL

D. Fusco, M. Gralka, J. Kayser, A. Anderson and O.H., **Nature Communications**, 7:12760 (2016)

COARSE-GRAINED MODEL



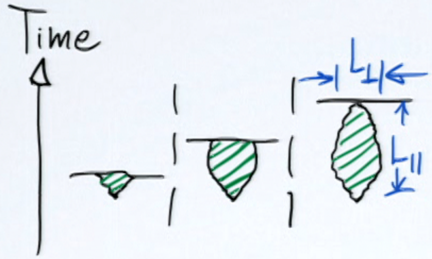
Bubbles are relics of *annihilating random walks* $\langle L_\perp^2 \rangle \sim t^{4/3}$

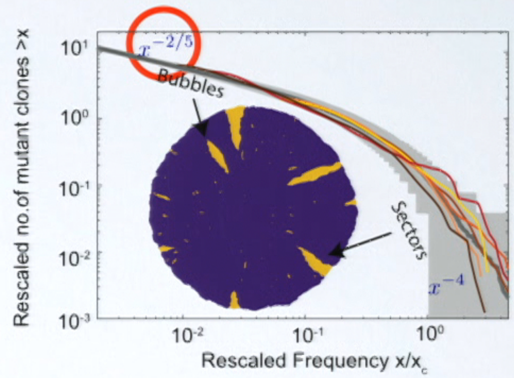
(Front roughness causes super-diffusion *)

*) Kardar, Parisi, Zhang (1986) *PRL*, *56*(9), 889.
Hallatschek, Hersen, Ramanathan, Nelson **PNAS** (2007

D. Fusco, M. Gralka, J. Kayser, A. Anderson and O.H., **Nature Communications**, 7:12760 (2016)

COARSE-GRAINED MODEL





Bubbles are relics of *annihilating random walks* $\langle L_\perp^2 \rangle \sim t^{4/3}$

(Front roughness causes super-diffusion *)

*) Kardar, Parisi, Zhang (1986) *PRL*, *56*(9), 889.
Hallatschek, Hersen, Ramanathan, Nelson **PNAS** (2007

⇨ In 2D, we find $\Pr(X > x) \sim x^{-2/5}$

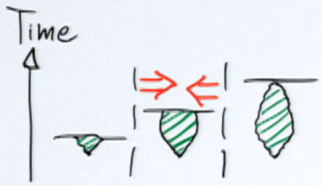
In 3D, we find $\Pr(X > x) \sim x^{-0.55}$

In ∞, one recovers Luria-Delbrück, $\Pr(X > x) \sim x^{-1}$.

D. Fusco, M. Gralka, J. Kayser, A. Anderson and O.H., **Nature Communications**, 7:12760 (2016)

NATURAL SELECTION INTRODUCES A BIAS

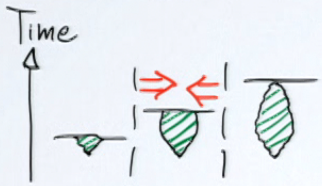
If mutants grow slower:

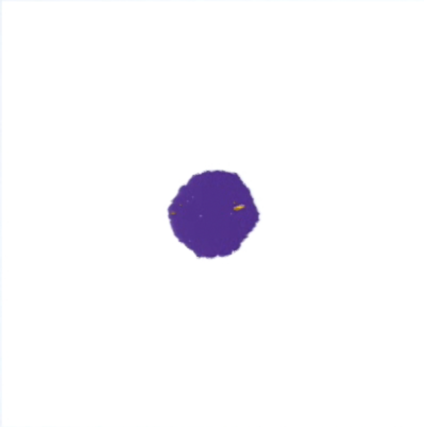


Hallatschek, Nelson **Evolution** (2009)

NATURAL SELECTION INTRODUCES A BIAS

If mutants grow slower:

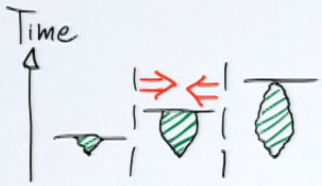


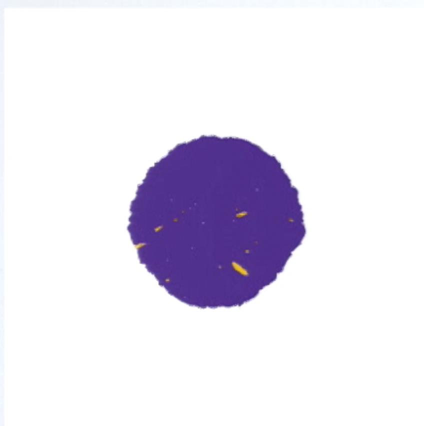


Hallatschek, Nelson **Evolution** (2009)

NATURAL SELECTION INTRODUCES A BIAS

If mutants grow slower:

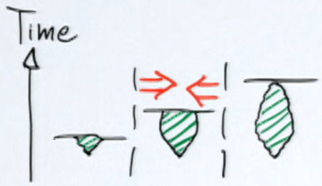


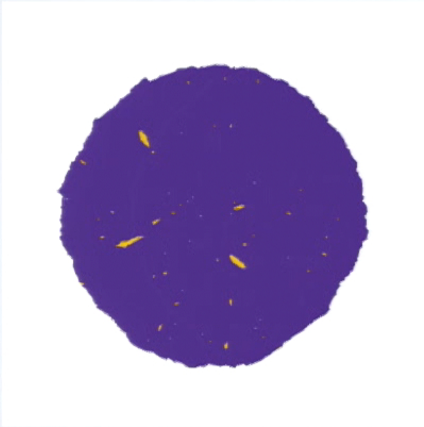


Hallatschek, Nelson **Evolution** (2009)

NATURAL SELECTION INTRODUCES A BIAS

If mutants grow slower:

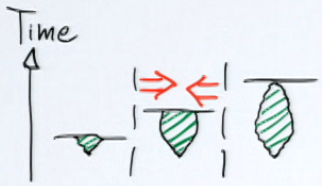


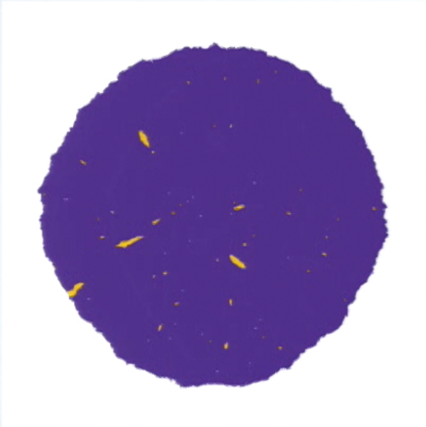


Hallatschek, Nelson **Evolution** (2009)

NATURAL SELECTION INTRODUCES A BIAS

If mutants grow slower:

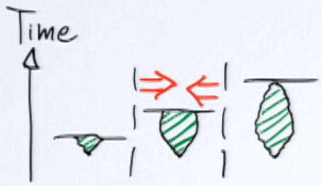


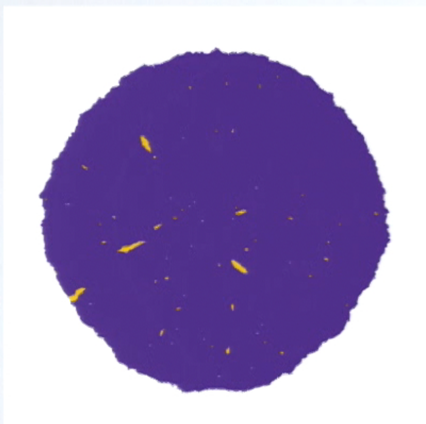


Hallatschek, Nelson **Evolution** (2009)

NATURAL SELECTION INTRODUCES A BIAS

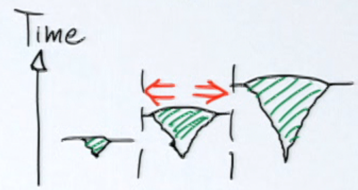
If mutants grow slower:





No sectors

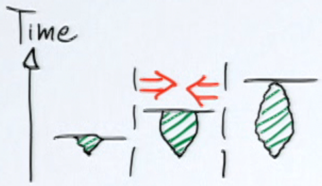
If mutants grow faster:

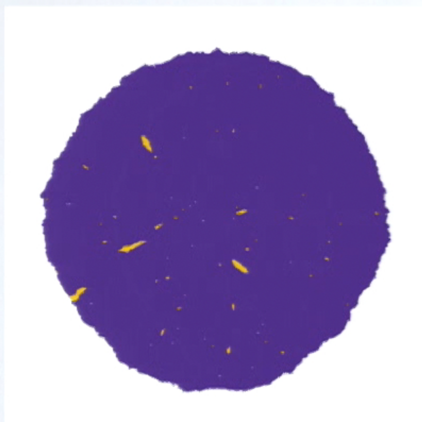


Hallatschek, Nelson **Evolution** (2009)

NATURAL SELECTION INTRODUCES A BIAS

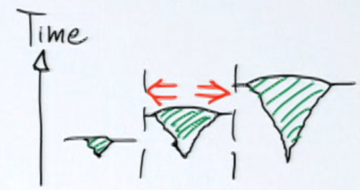
If mutants grow slower:





No sectors

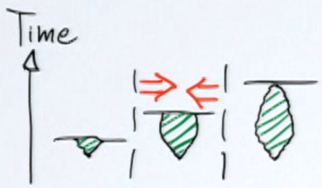
If mutants grow faster:

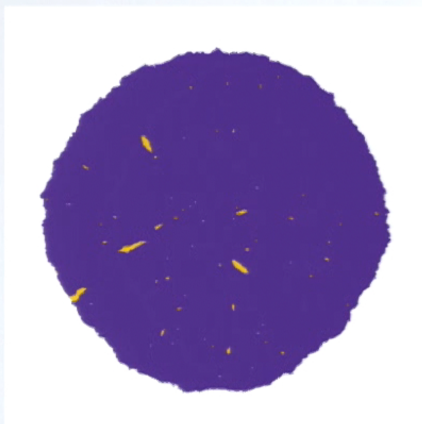


Hallatschek, Nelson **Evolution** (2009)

NATURAL SELECTION INTRODUCES A BIAS

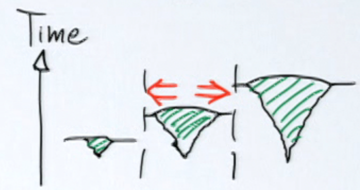
If mutants grow slower:





No sectors

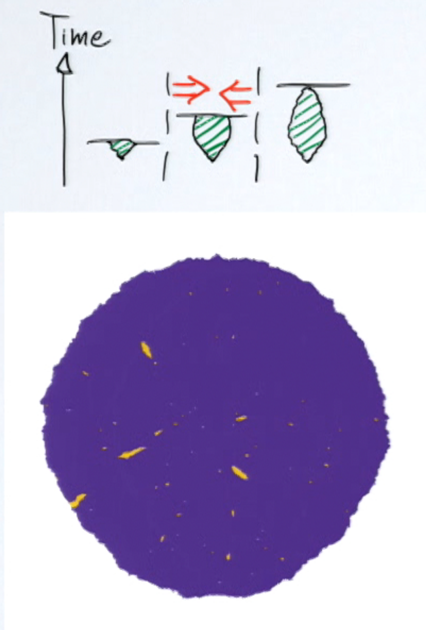
If mutants grow faster:



Hallatschek, Nelson **Evolution** (2009)

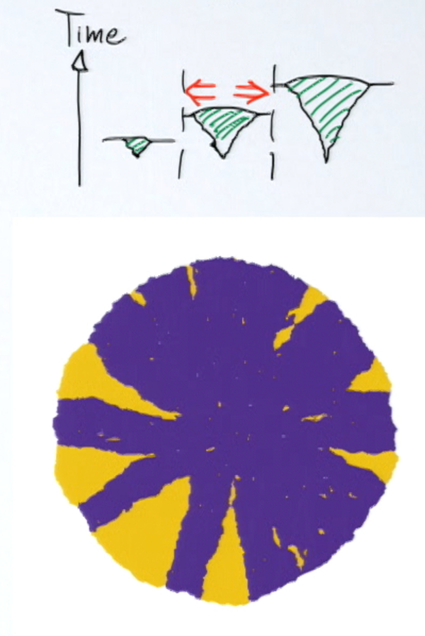
NATURAL SELECTION INTRODUCES A BIAS

If mutants grow slower:



No sectors

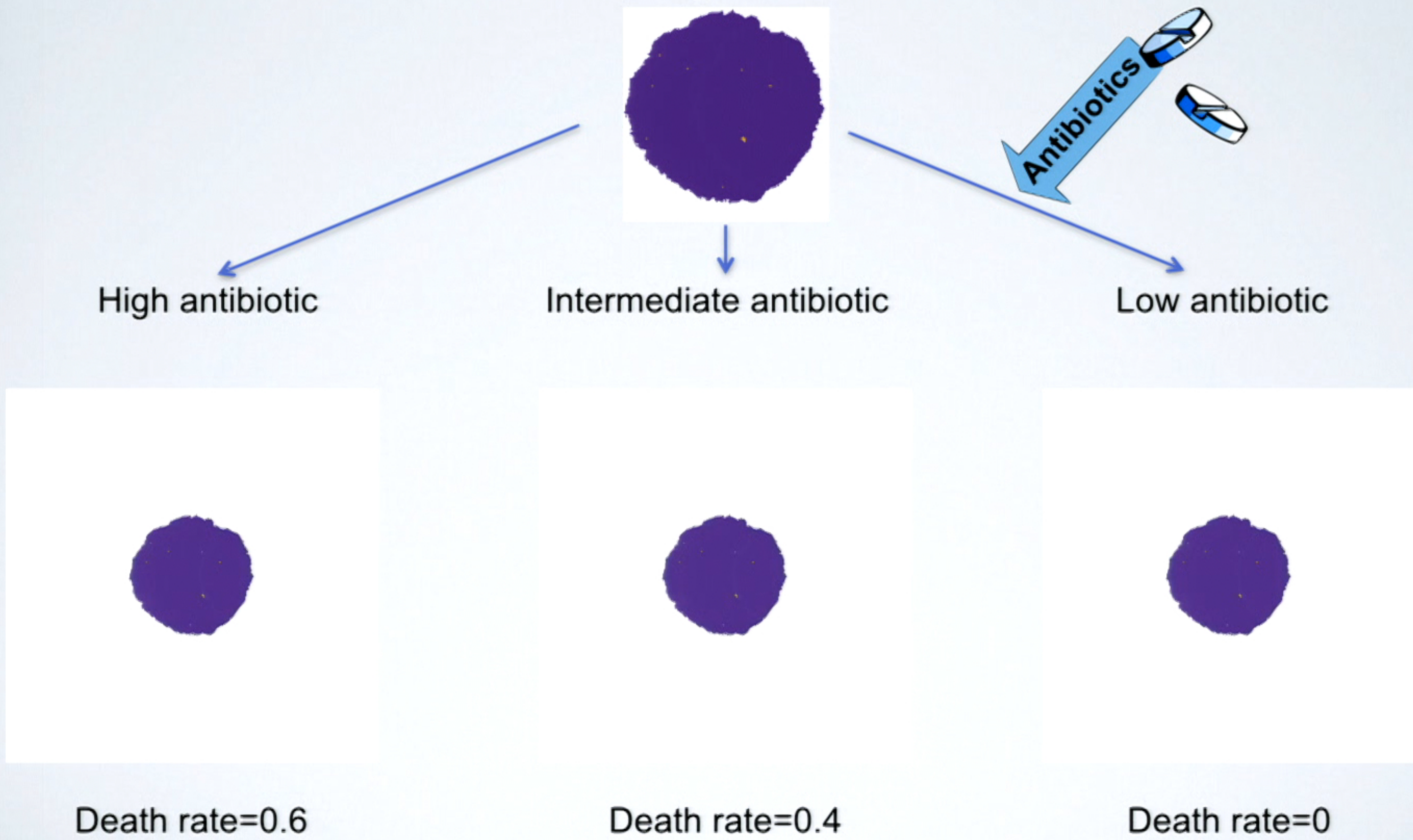
If mutants grow faster:



More expanding sectors, depending on diffusivity

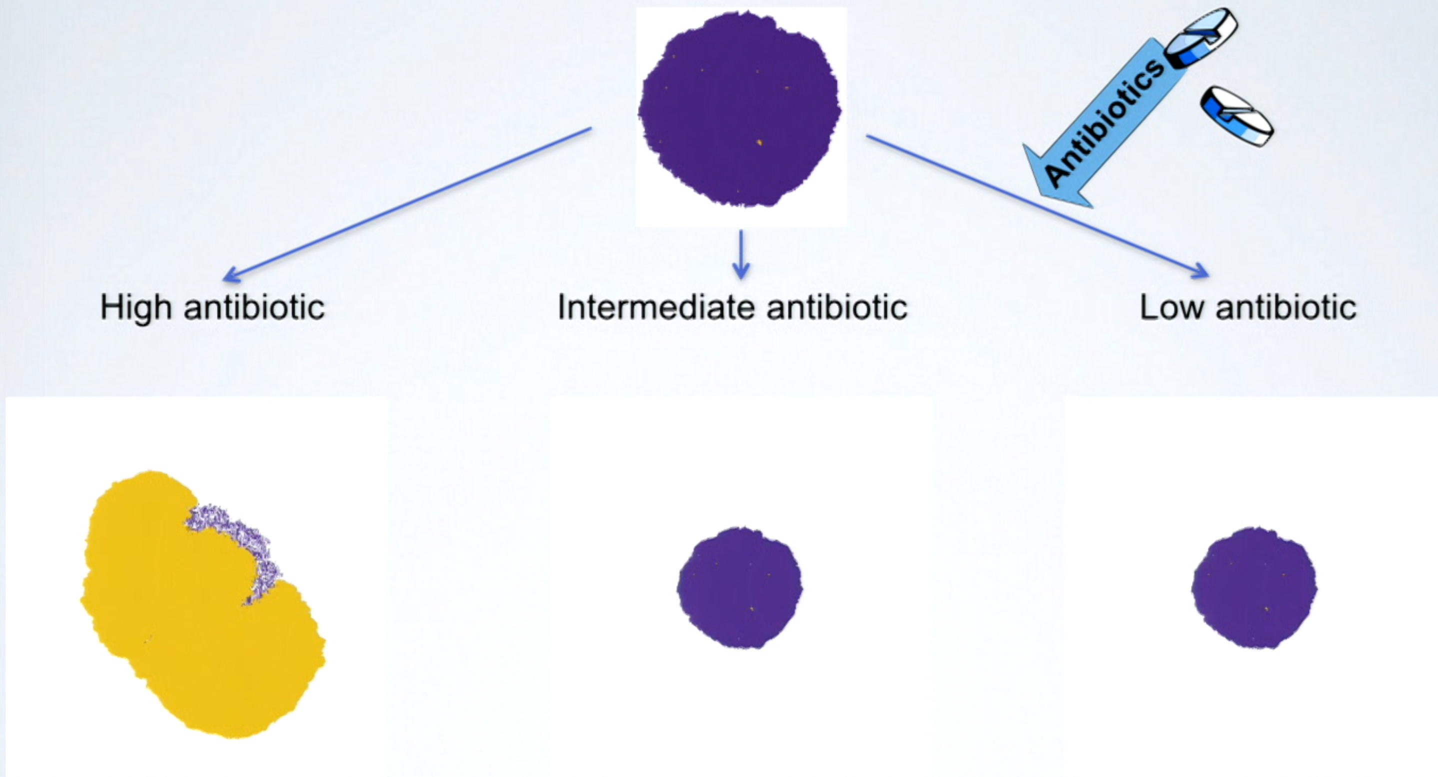
Hallatschek, Nelson **Evolution** (2009)

Deleterious mutations:
Resistant mutants often grow slower w/o antibiotics



D. Fusco, M. Gralka, J. Kayser, A. Anderson and O.H., **Nature Communications**, 7:12760 (2016)

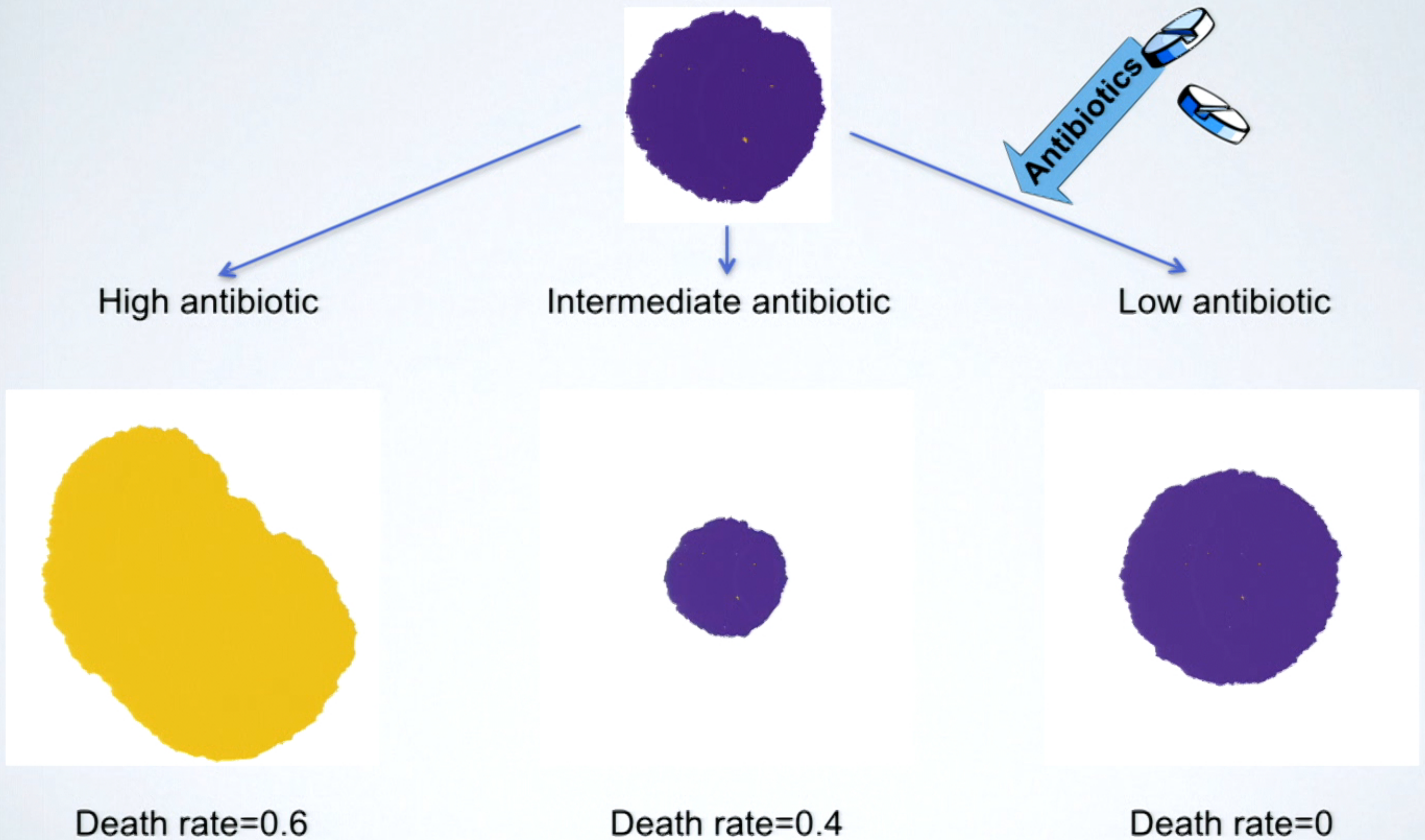
Deleterious mutations:
Resistant mutants often grow slower w/o antibiotics



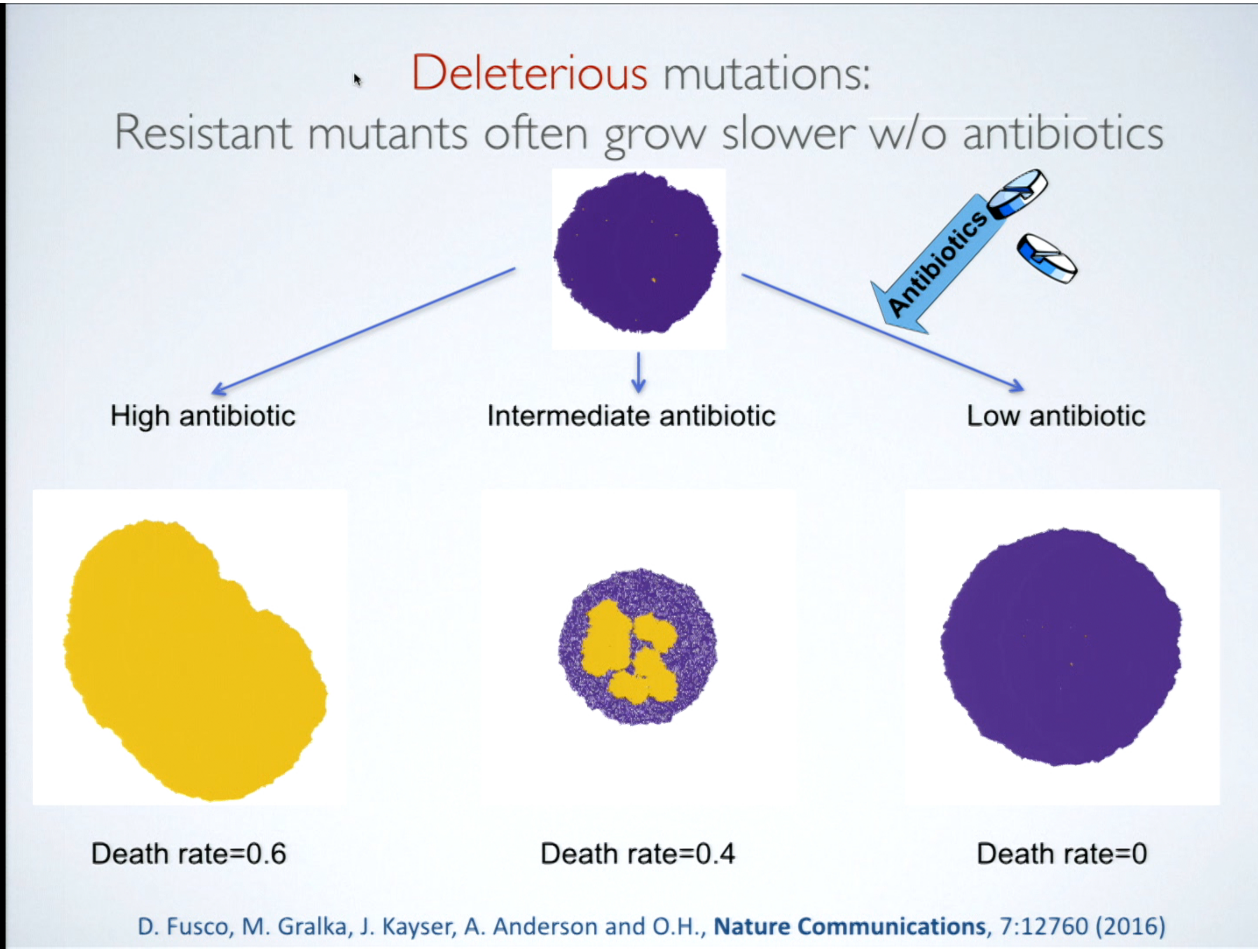
Death rate=0.6 Death rate=0.4 Death rate=0

D. Fusco, M. Gralka, J. Kayser, A. Anderson and O.H., **Nature Communications**, 7:12760 (2016)

Deleterious mutations:
Resistant mutants often grow slower w/o antibiotics

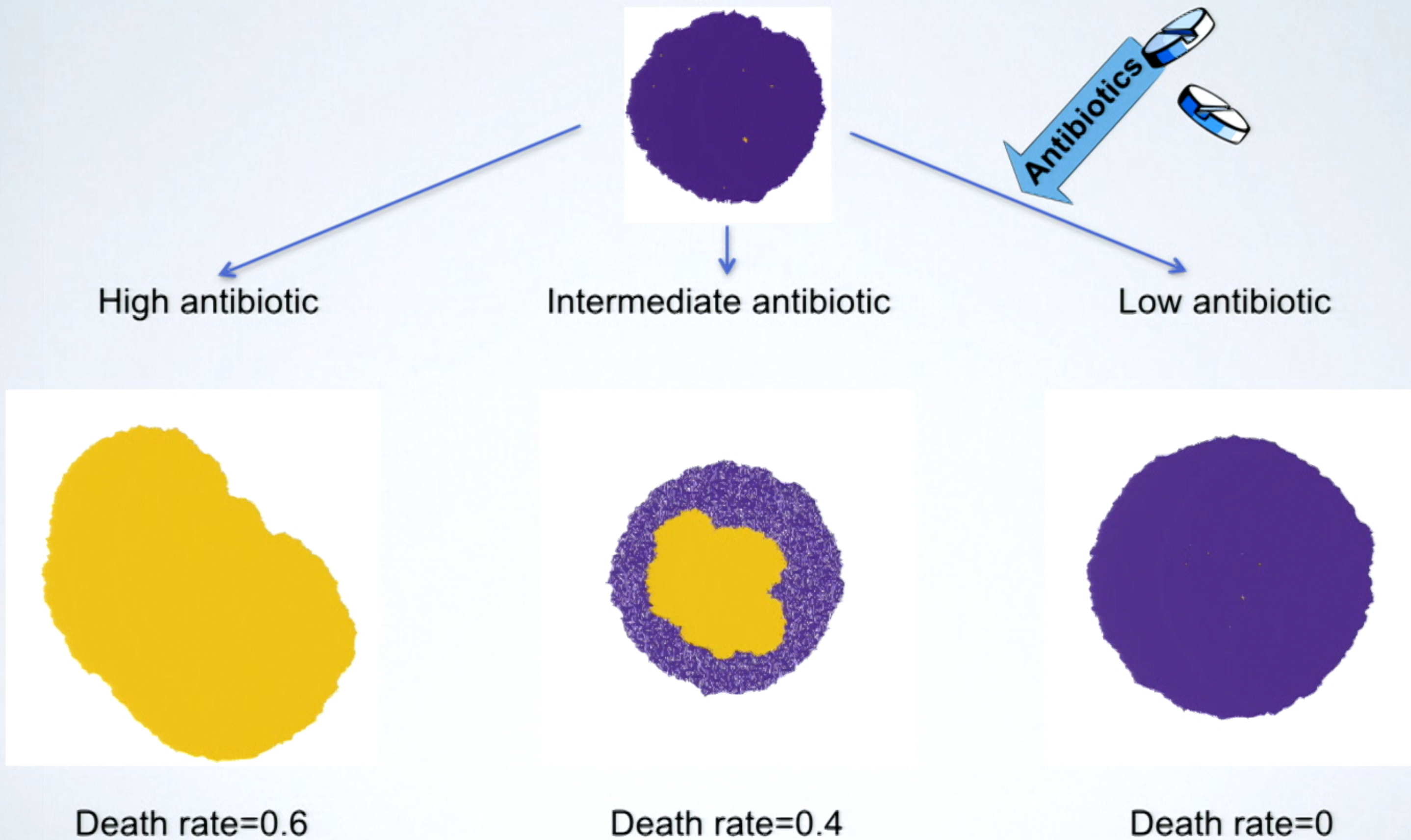


D. Fusco, M. Gralka, J. Kayser, A. Anderson and O.H., **Nature Communications**, 7:12760 (2016)



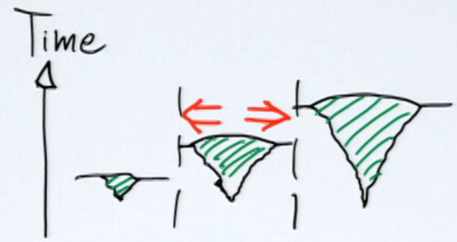
Deleterious mutations:
Resistant mutants often grow slower w/o antibiotics
Antibiotics
High antibiotic
Intermediate antibiotic
Low antibiotic
Death rate=0.6
Death rate=0.4
Death rate=0
D. Fusco, M. Gralka, J. Kayser, A. Anderson and O.H., Nature Communications, 7:12760 (2016)

Deleterious mutations:
Resistant mutants often grow slower w/o antibiotics



D. Fusco, M. Gralka, J. Kayser, A. Anderson and O.H., **Nature Communications**, 7:12760 (2016)

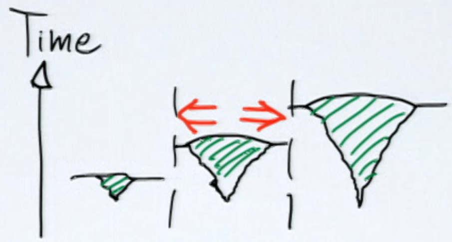
BENEFICIAL MUTATIONS:

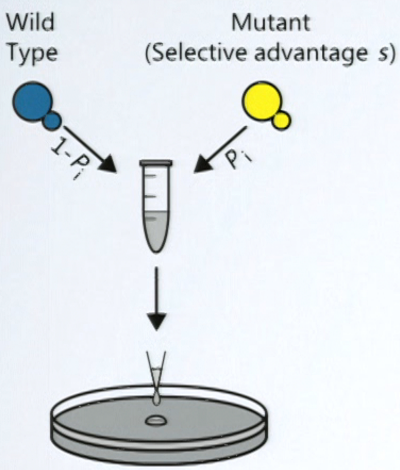


M. Gralka, F. Stiewe, F. Farrell, W. Möbius, B. Waclaw, and O.H., **Ecology Letters** 19: 889 (2016)

M. Gralka

BENEFICIAL MUTATIONS:

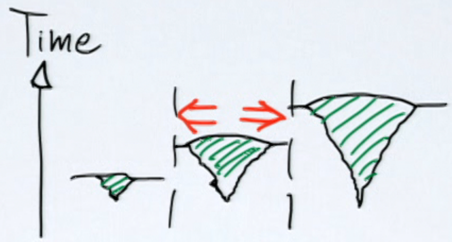


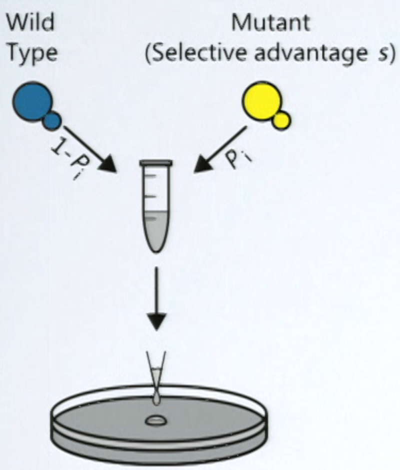


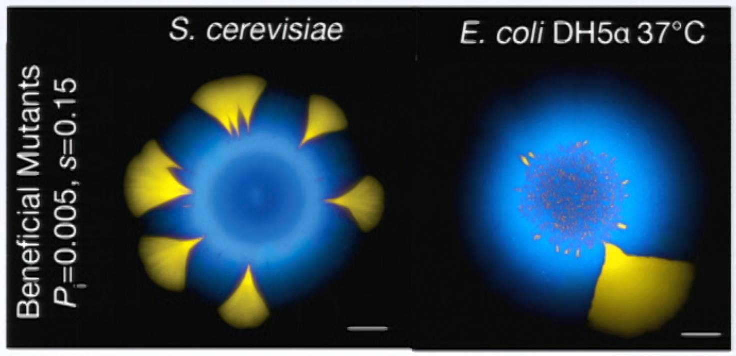
M. Gralka, F. Stiewe, F. Farrell, W. Möbius, B. Waclaw, and O.H., **Ecology Letters** 19: 889 (2016)

M. Gralka

BENEFICIAL MUTATIONS:



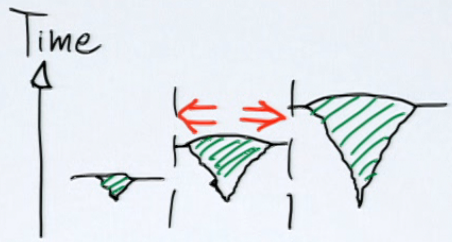


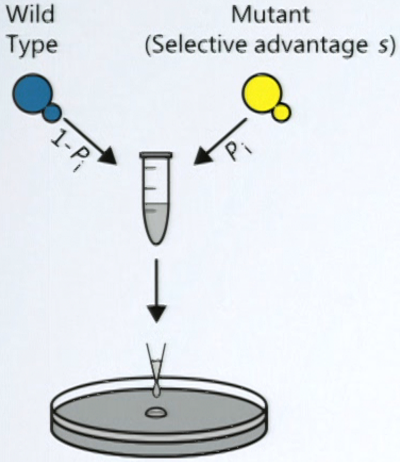


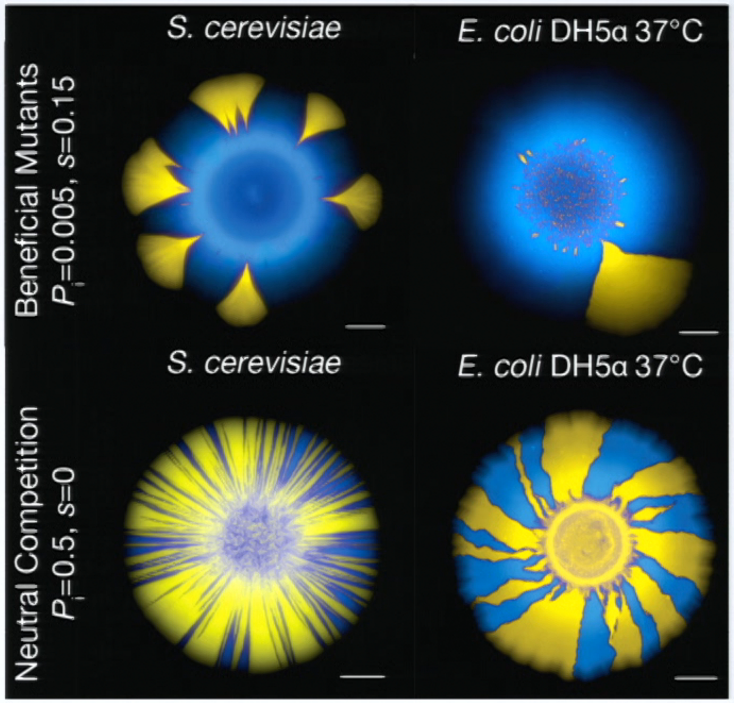
M. Gralka, F. Stiewe, F. Farrell, W. Möbius, B. Waclaw, and O.H., **Ecology Letters** 19: 889 (2016)

M. Gralka

BENEFICIAL MUTATIONS:

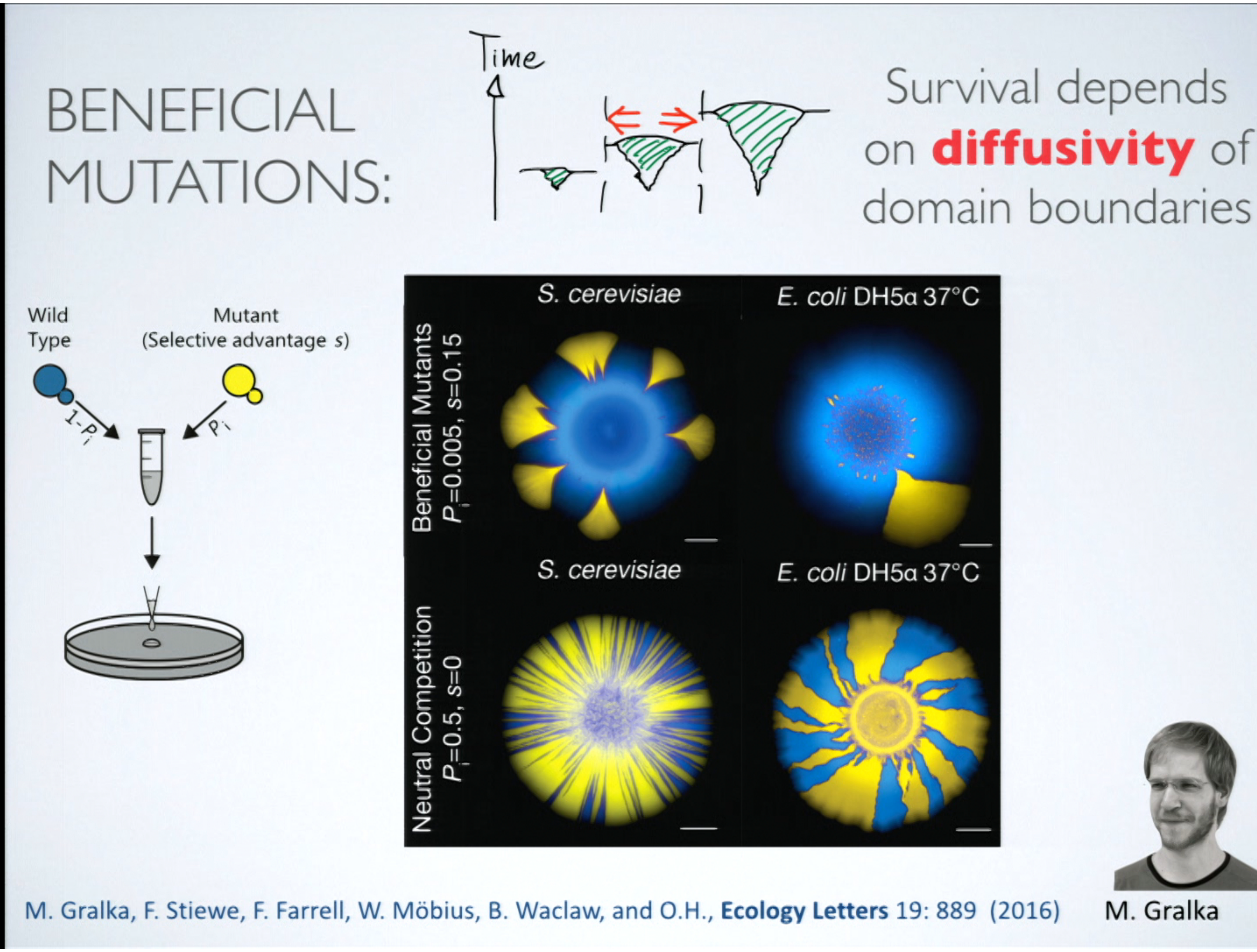




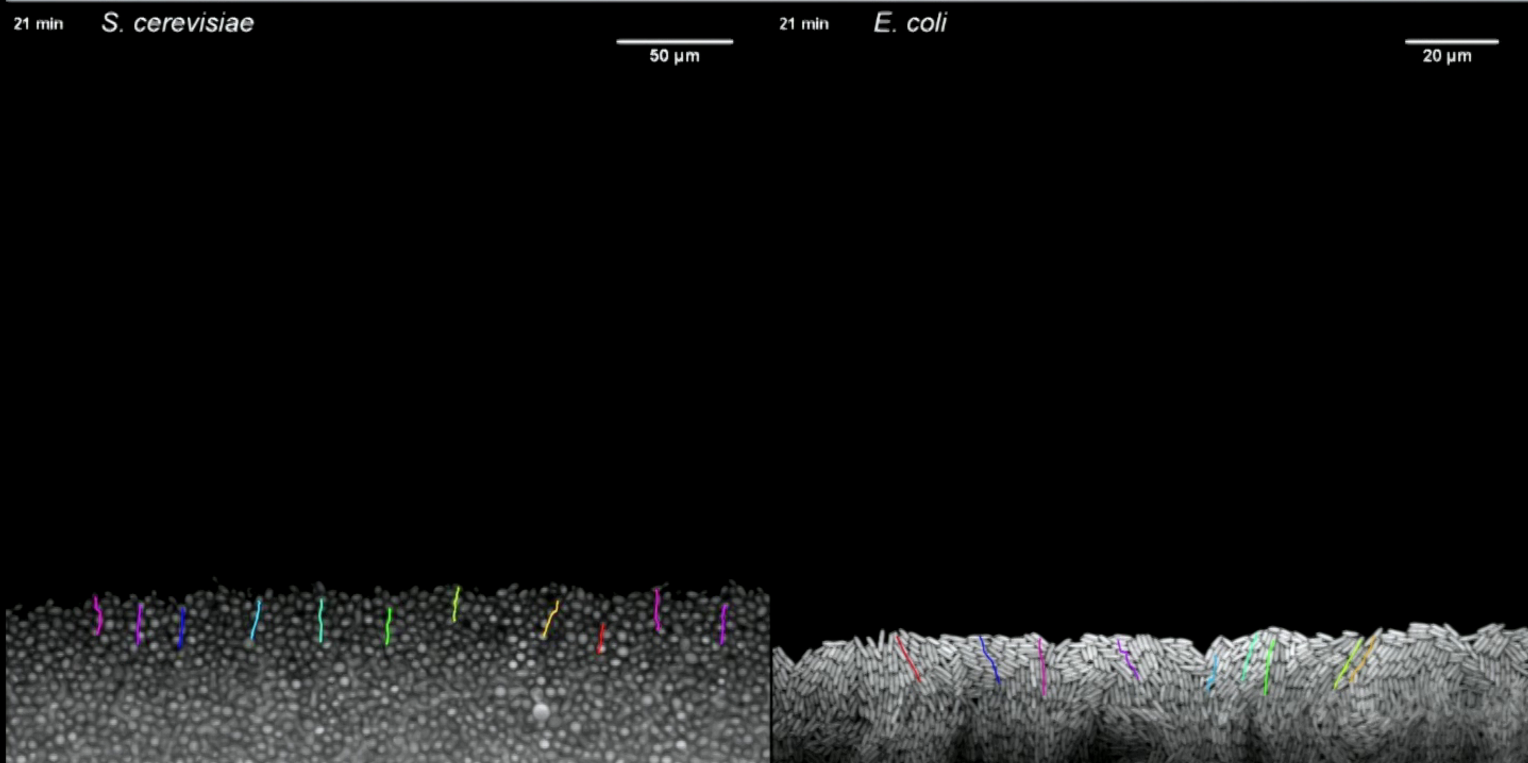


M. Gralka, F. Stiewe, F. Farrell, W. Möbius, B. Waclaw, and O.H., **Ecology Letters** 19: 889 (2016)

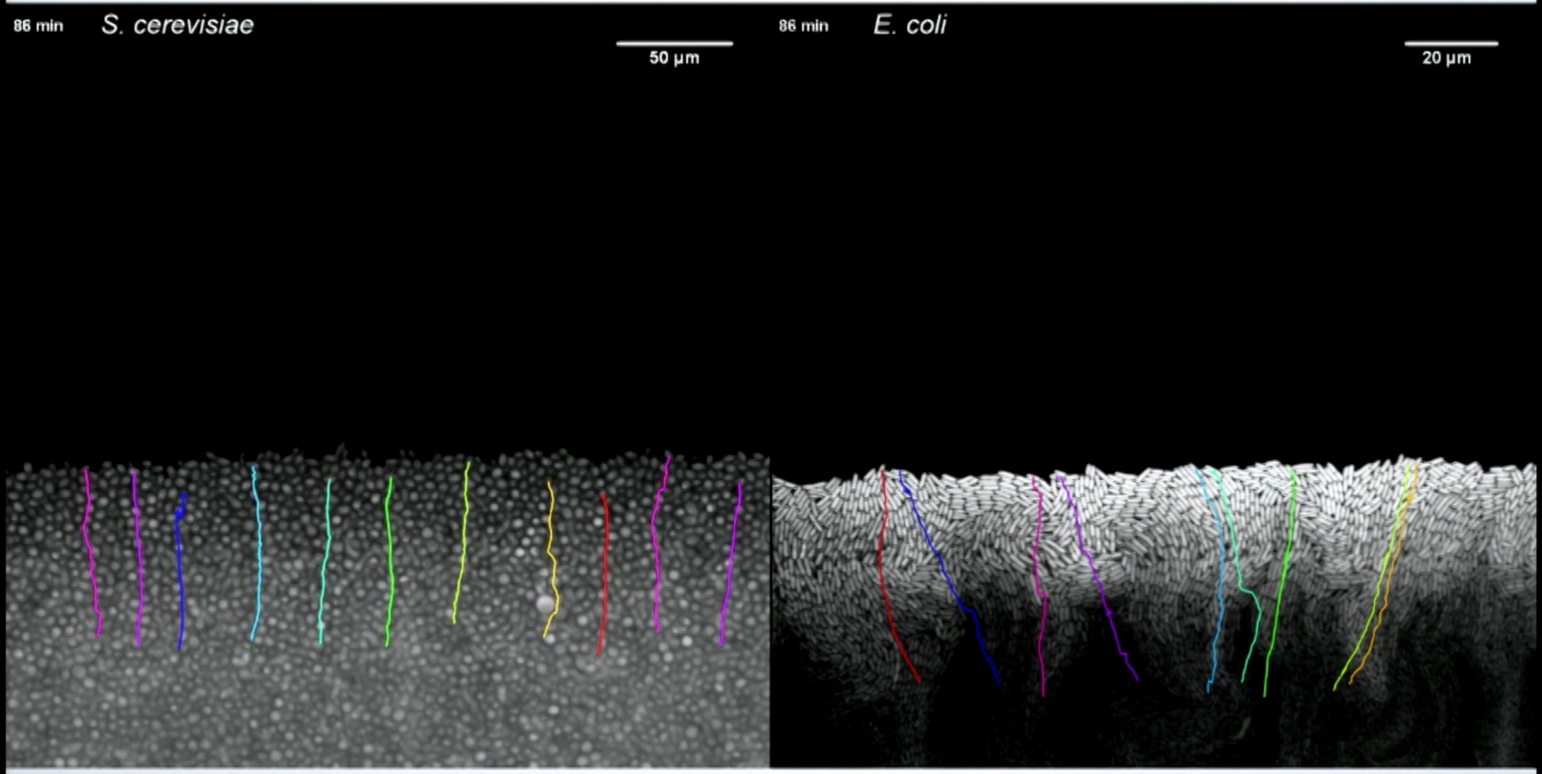
M. Gralka


BENEFICIAL MUTATIONS:
Time
Survival depends on **diffusivity** of domain boundaries
Wild Type
Mutant (Selective advantage s)
1-Pi
Pi
S. cerevisiae
E. coli DH5α 37°C
Beneficial Mutants Pi=0.005, s=0.15
Neutral Competition Pi=0.5, s=0
M. Gralka, F. Stiewe, F. Farrell, W. Möbius, B. Waclaw, and O.H., Ecology Letters 19: 889 (2016)
M. Gralka

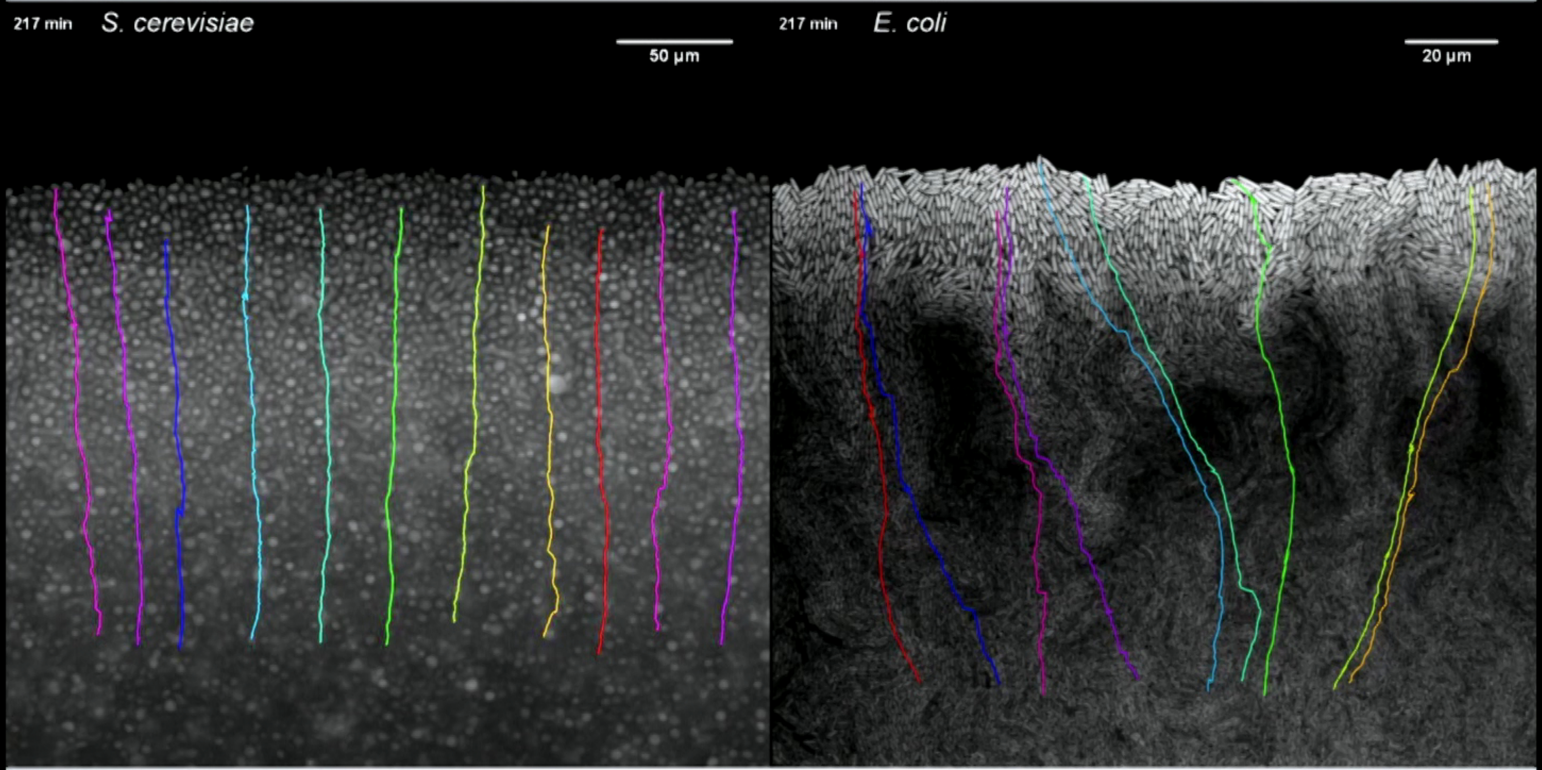
BUCKLING INSTABILITY ENHANCES ROUGHNESS OF DOMAIN BOUNDARIES



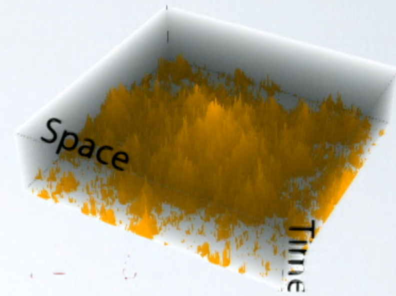
BUCKLING INSTABILITY ENHANCES ROUGHNESS OF DOMAIN BOUNDARIES



BUCKLING INSTABILITY ENHANCES ROUGHNESS OF DOMAIN BOUNDARIES



CONCLUSIONS



Expansion driven by extreme events: the largest jumps that typically occur

new universality classes of growth,
outside the classical framework of evolution

s=0

Spatial expansions lead to an excess of mutational jackpot events

s=.15

favors drug resistance evolution
sweet spot of drug concentrations
noise hampers establishment of the fittest

Evolutionary success often depends on pure luck!


Thanks to …
NIH
National Institutes of Health
SIMONS FOUNDATION
NSF
@ Berkeley:
• Jasper Rine, Anne Dodson
• Jona Kayser
• Wolfram Möbius
• Benjamin Larson
• Alex Anderson
• Stephen Martis
• Daniel Weissman (now faculty @ Emory)
• E. Martens (now faculty @ DTU)
External collaborators:
• Daniel Fisher (Stanford)
• Richard Neher (Basel)
• Michael Desai (Harvard)
• B. Waclaw (Edinburgh)
• K. Korolev (Boston U.)
• C. Heussinger (Gö)
M. Delarue, Phd
J. Kayser, PhD
D. Fusco, PhD
M. Gralka
C. Schreck, PhD
P. Gniewek
B. Good, PhD