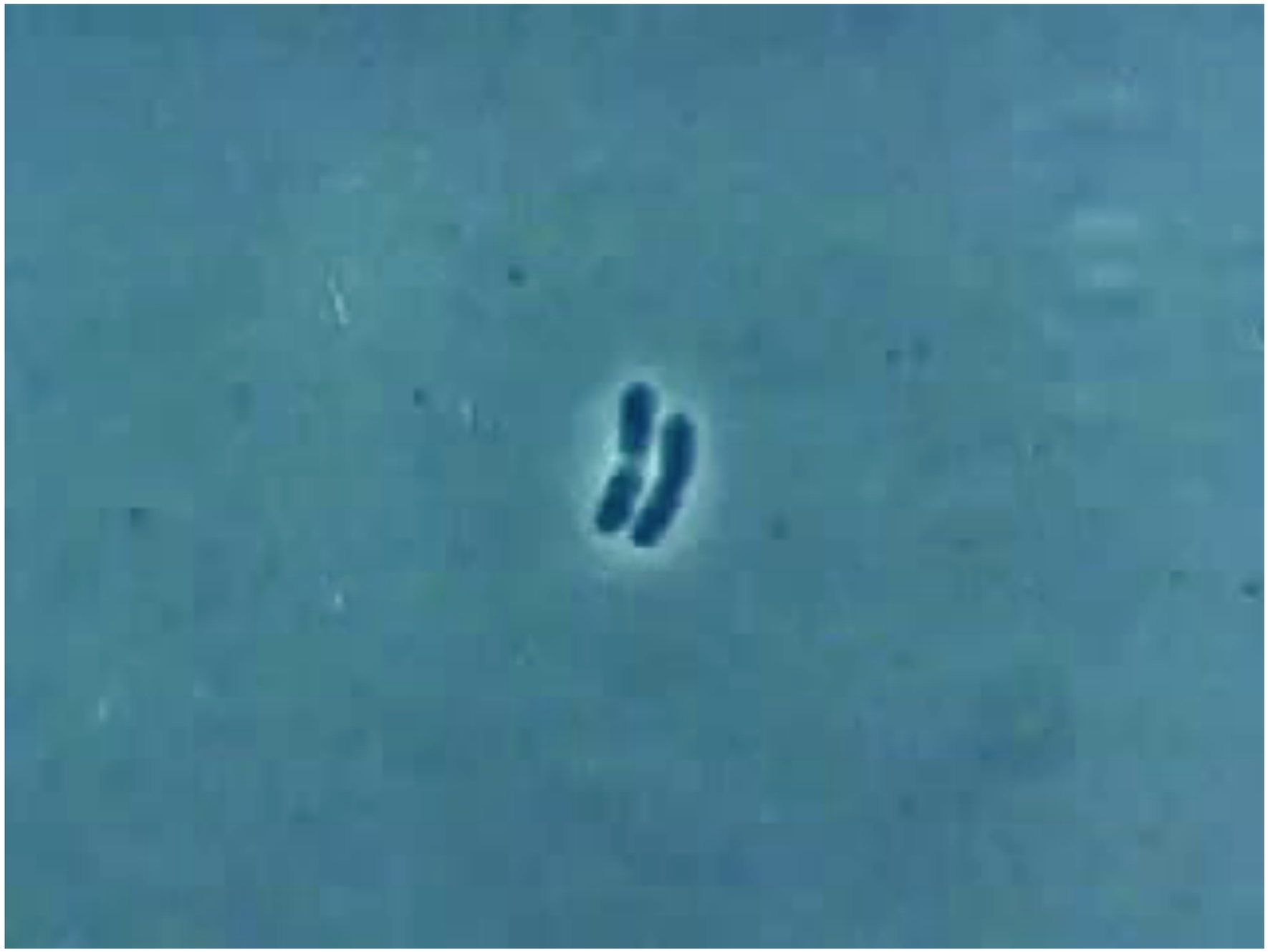
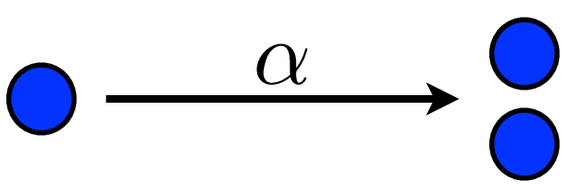
Multi-type Branching Processes: from bacteria to cancer

Tibor Antal
School of Maths

- drug resistance in bacteria
- drug resistance in cancer
- multidrug therapy

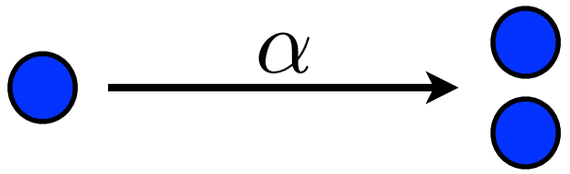
Bacterial growth





branching process: Galton and Watson, 1873

Bacterial growth: simplest model



Z_t : #cells at time t

backward Kolmogorov for $P_j^{(i)}(t) = P(Z_t = j | Z_0 = i)$

$$P_j^{(1)}(t+\tau) = \alpha\tau P_j^{(2)}(t) + (1-\alpha\tau)P_j^{(1)}(t)$$

$$\dot{P}_j^{(1)} = \alpha P_j^{(2)} - \alpha P_j^{(1)}$$

in terms of generating function $F^{(i)}(s,t) = E(s^{Z_t}|Z_0 = i) = F^{(1)}(s,t)^i$

$$\partial_t F = \alpha F^2 - \alpha F \qquad F(s,0) = s$$

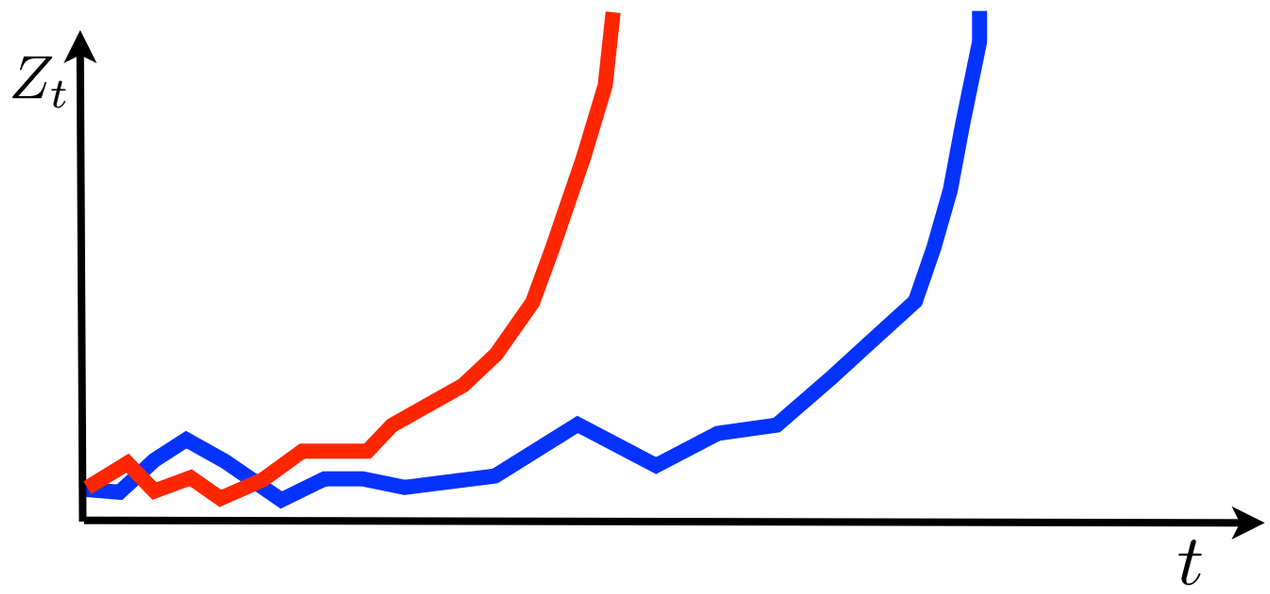
$$F = \frac{s}{s + (1-s)e^{\alpha t}}$$

$$P_j(t) = e^{-\alpha t}(1 - e^{-\alpha t})^{j-1}$$

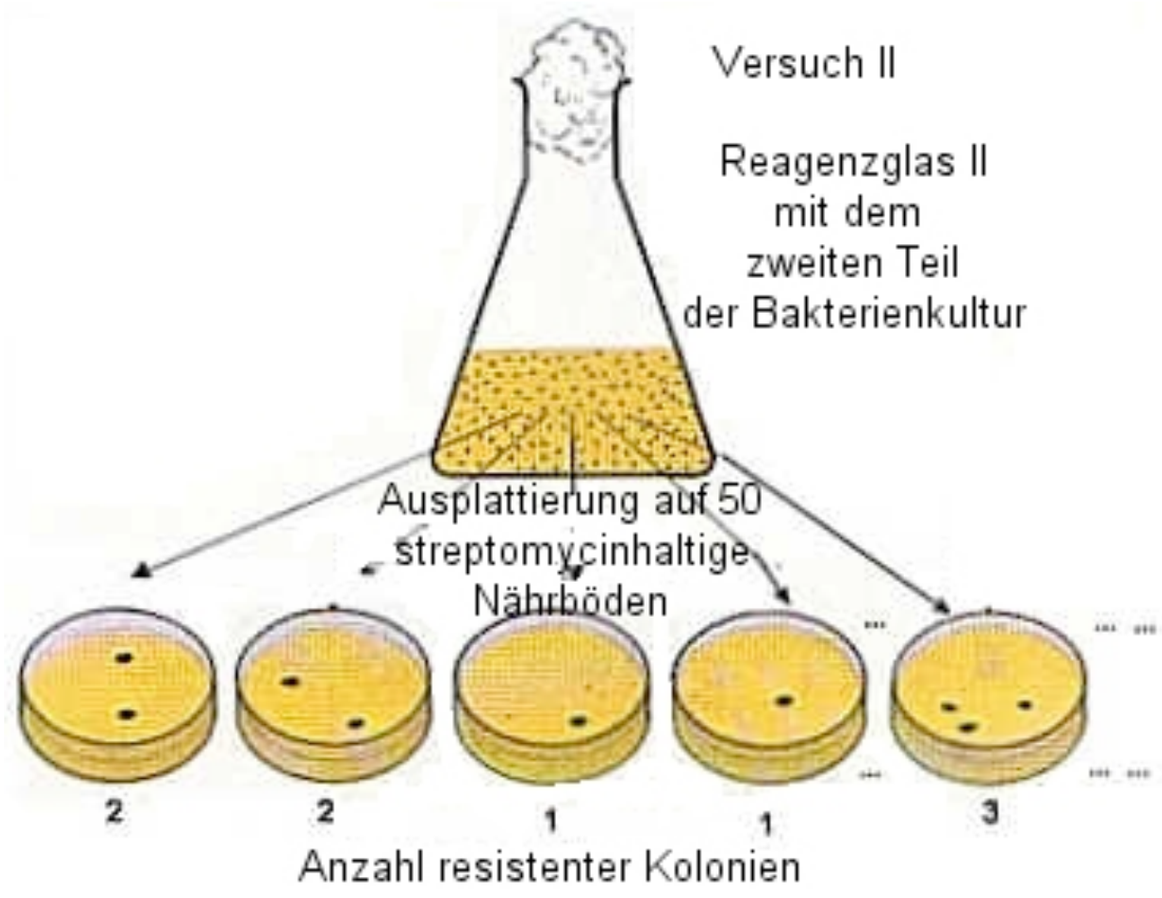
simpler than a symmetric random walk

for $t \to \infty$

$$Z_t \sim X e^{\alpha t}$$

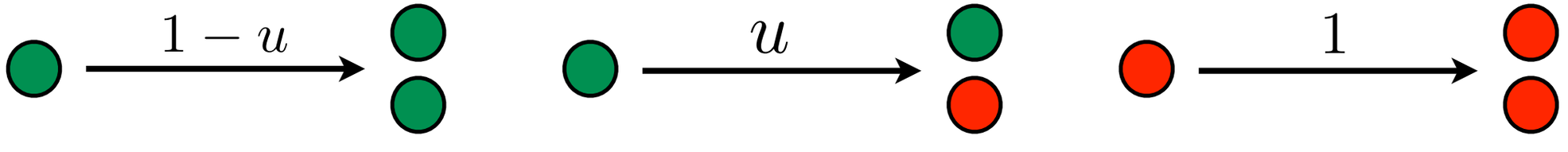


Bacterial growth with mutations

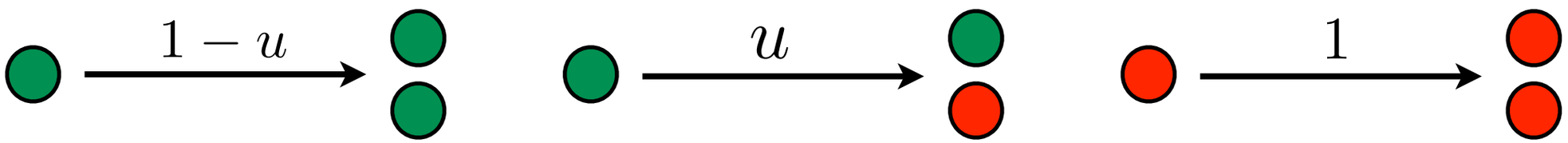


at Cold Spring Harbor Laboratory

Luria, Delbruck '43: random mutations, NP'69
Lea, Coulson '49: random mutant growth
Bartlett '55: full random



Bacterial growth with mutations



$$F_A(x,y,t) = E(x^{A_t} y^{B_t} | A_0 = 1, B_0 = 0)$$

$$\partial_t F_A = (1-u)F_A^2 + uF_A F_B - F_A \qquad F_A(x,y,t=0) = x, \quad F_B(x,y,t=0) = y$$

$$\partial_t F_B = F_B^2 - F_B$$

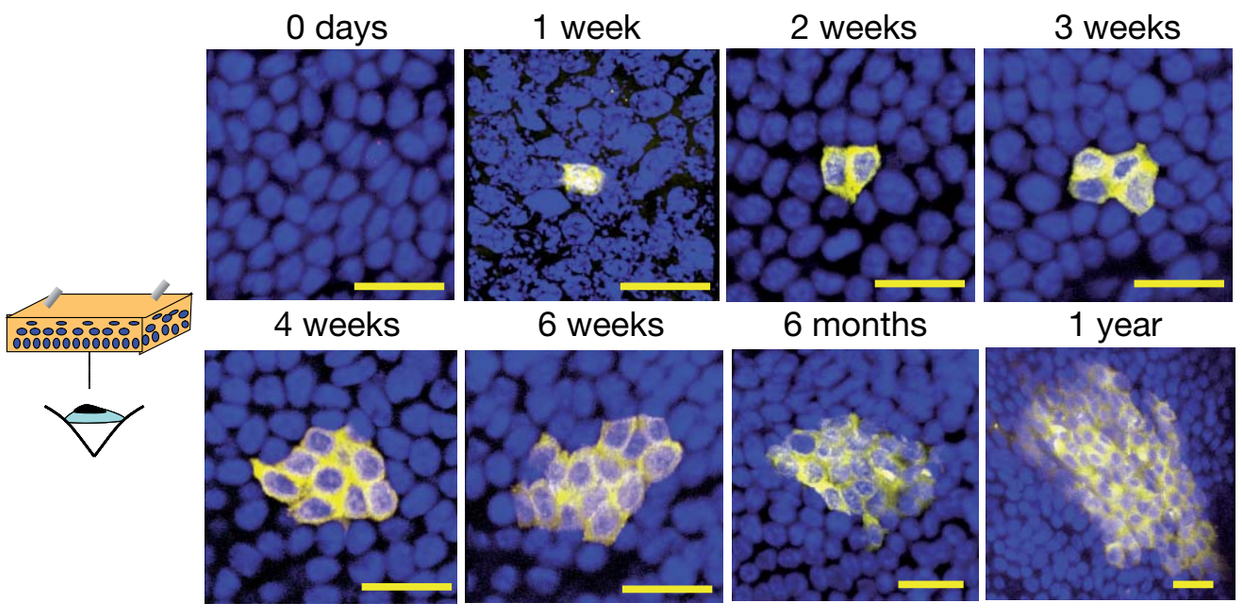
use solution for F_B

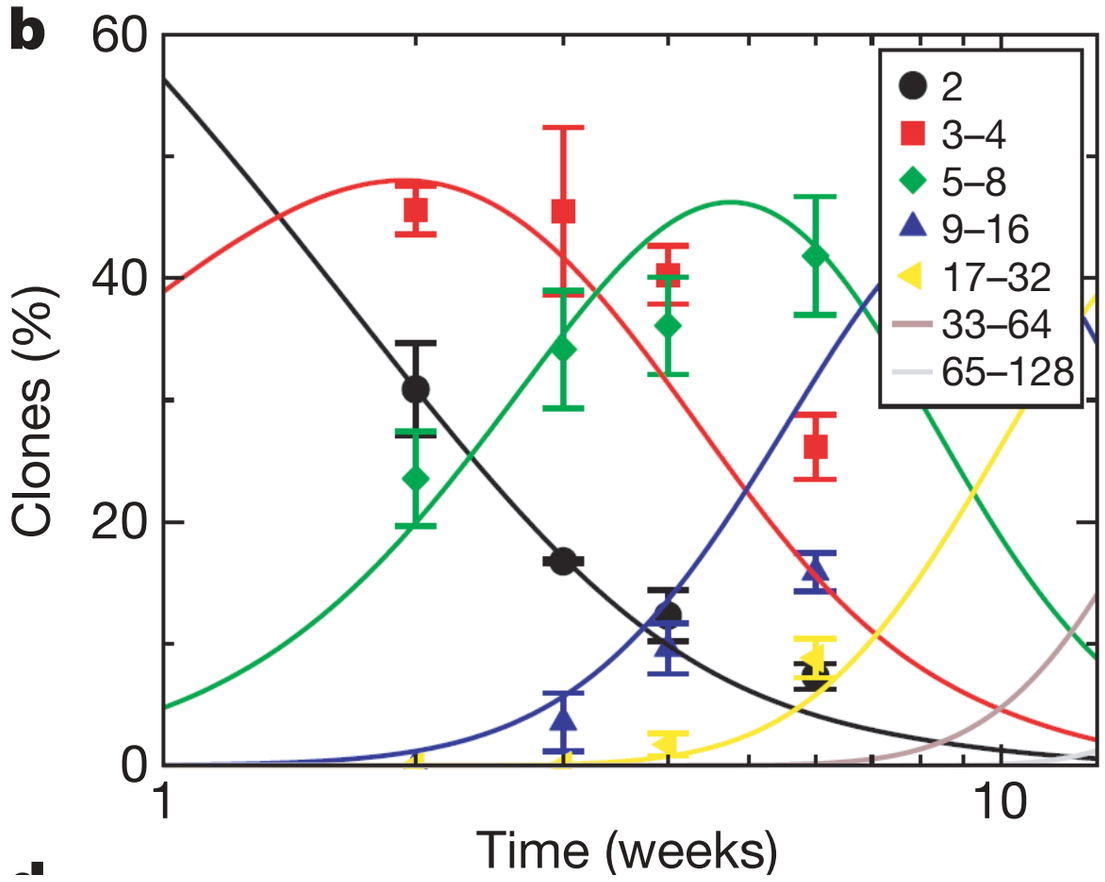
$$\partial_t F_A = (1-u)F_A^2 + F_A\left[u\frac{y}{y+(1-y)e^t} - 1\right]$$

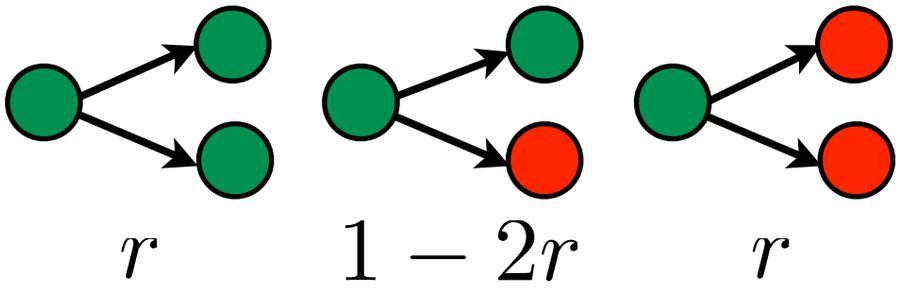
$$F_A = \frac{xe^{-t}\left[1-y+ye^{-t}\right]^{-u}}{1+\frac{x}{y}\left[\left(1-y+ye^{-t}\right)^{1-u}-1\right]}$$

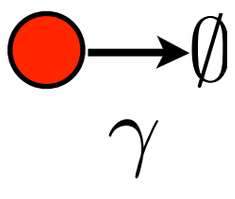
animal cell maintenance

Clayton '07









numerical solution

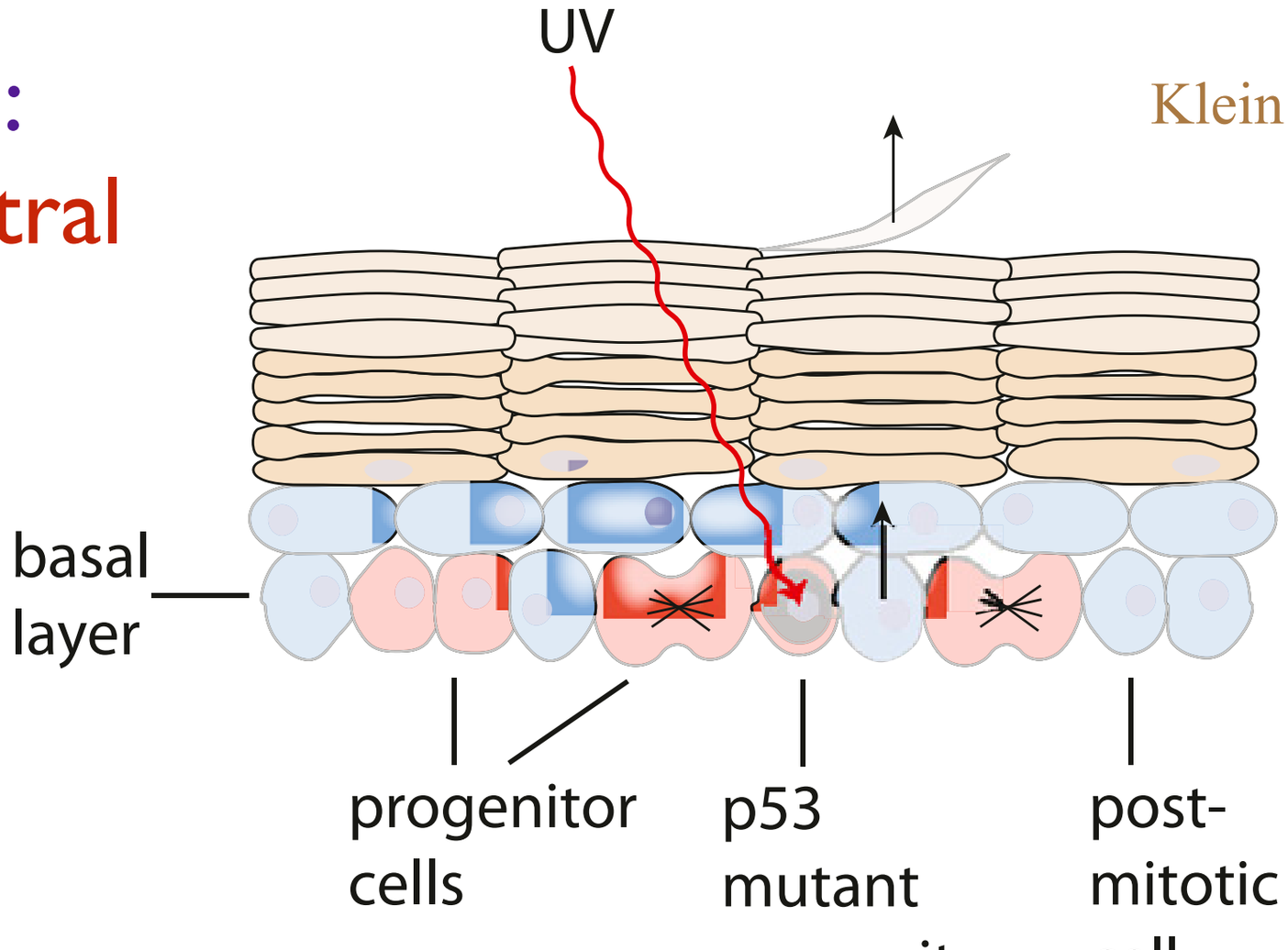
$(r = 0.08,\ \gamma = 0.28)$

progenitor cell

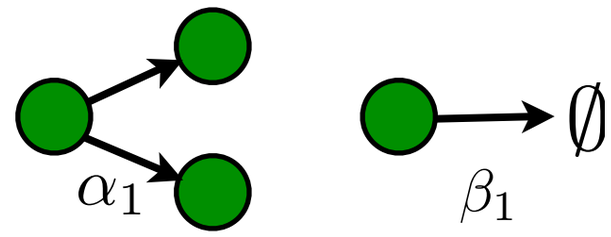
post-mitotic cell

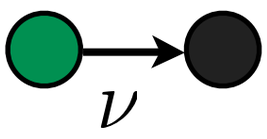
A, Krapivsky '10

Mutations in cancer:
cell death + non-neutral

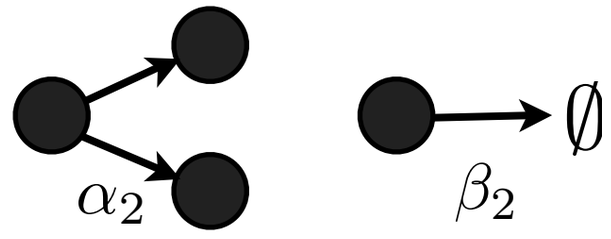


Klein '07





extra mutation

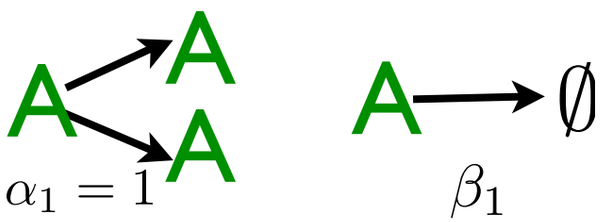


Kendall '60, Iwasa '06, Durrett '08

single mutation

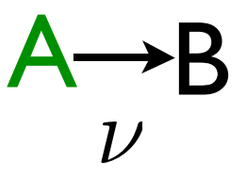
$$F_A(x,y,t) = E(x^{A_t} y^{B_t} | A_0 = 1, B_0 = 0)$$

fitnesses: $\lambda_1 = 1 - \beta_1 - \nu, \quad \lambda_2 = \alpha_2 - \beta_2$



$$\partial_t F_A = F_A^2 + \beta_1 + \nu F_B - (1 + \beta_1 + \nu) F_A$$

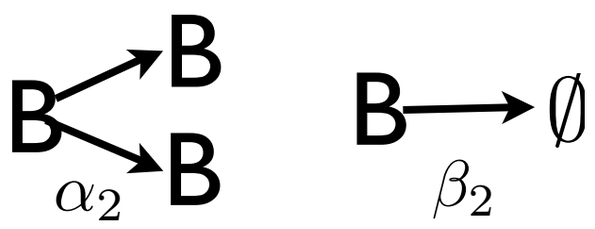
$$\partial_t F_B = \alpha_2 F_B^2 + \beta_2 - (\alpha_2 + \beta_2) F_B$$



use solution for F_B

$$F_B = 1 - \frac{\lambda_2}{\alpha_2(1-z)}, \quad z = \left[1 - \frac{\lambda_2}{\alpha_2(1-y)}\right] e^{-\lambda_2 t}$$

to get a Riccati



$$\frac{dX}{dt} = -X^2 + \lambda_1 X + \frac{\nu\lambda_2}{\alpha_2(1-z)} \qquad X \equiv 1 - F_A$$

$$X \equiv \frac{d}{dt} \log Z$$ turns it into Sturm-Liouville $$\frac{d^2 Z}{dt^2} = \lambda_1 \frac{dZ}{dt} + \frac{\nu\lambda_2}{\alpha_2(1-z)} Z$$

$t \to \infty, z \to 0$ (for $\lambda_2 > 0$) $\qquad Z \propto e^{-\omega t}, \quad \omega^2 + \lambda_1 \omega - \frac{\nu\lambda_2}{\alpha_2} = 0$

$Z(t) \equiv z^{\omega/\lambda_2}\, \Phi(z)$ $\qquad z(1-z)\Phi'' + \left(1 + \frac{2\omega + \lambda_1}{\lambda_2}\right)(1-z)\Phi' = \frac{\nu}{\alpha_2\lambda_2}\Phi$

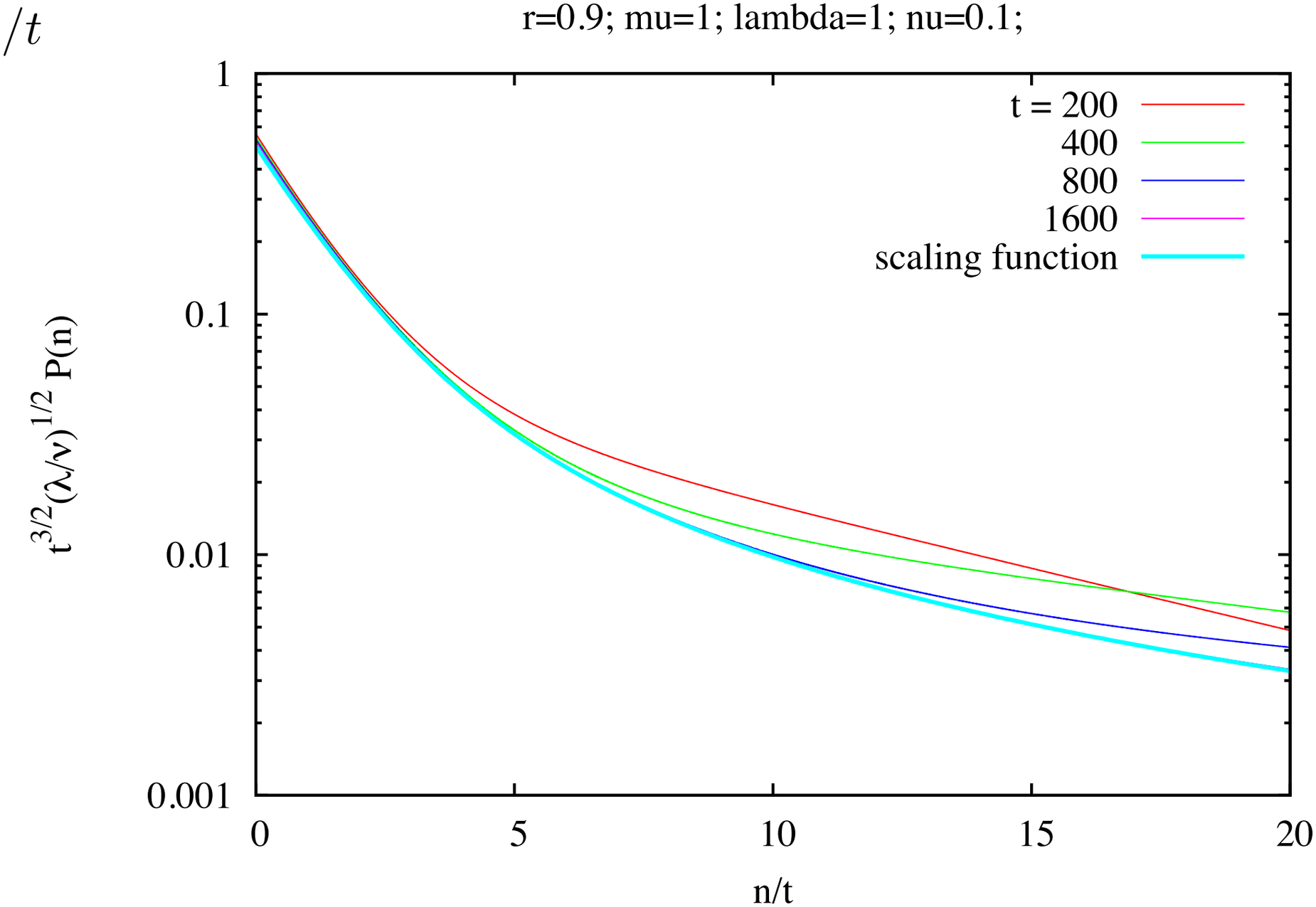
$$\Phi(z) = F\left(\begin{matrix} a, b \\ c \end{matrix}; z\right) + C z^{1-c} F\left(\begin{matrix} -b, -a \\ 2-c \end{matrix}; z\right)$$

A, Krapivsky '11

large time limit of number of mutants: e.g.: bi-critical case

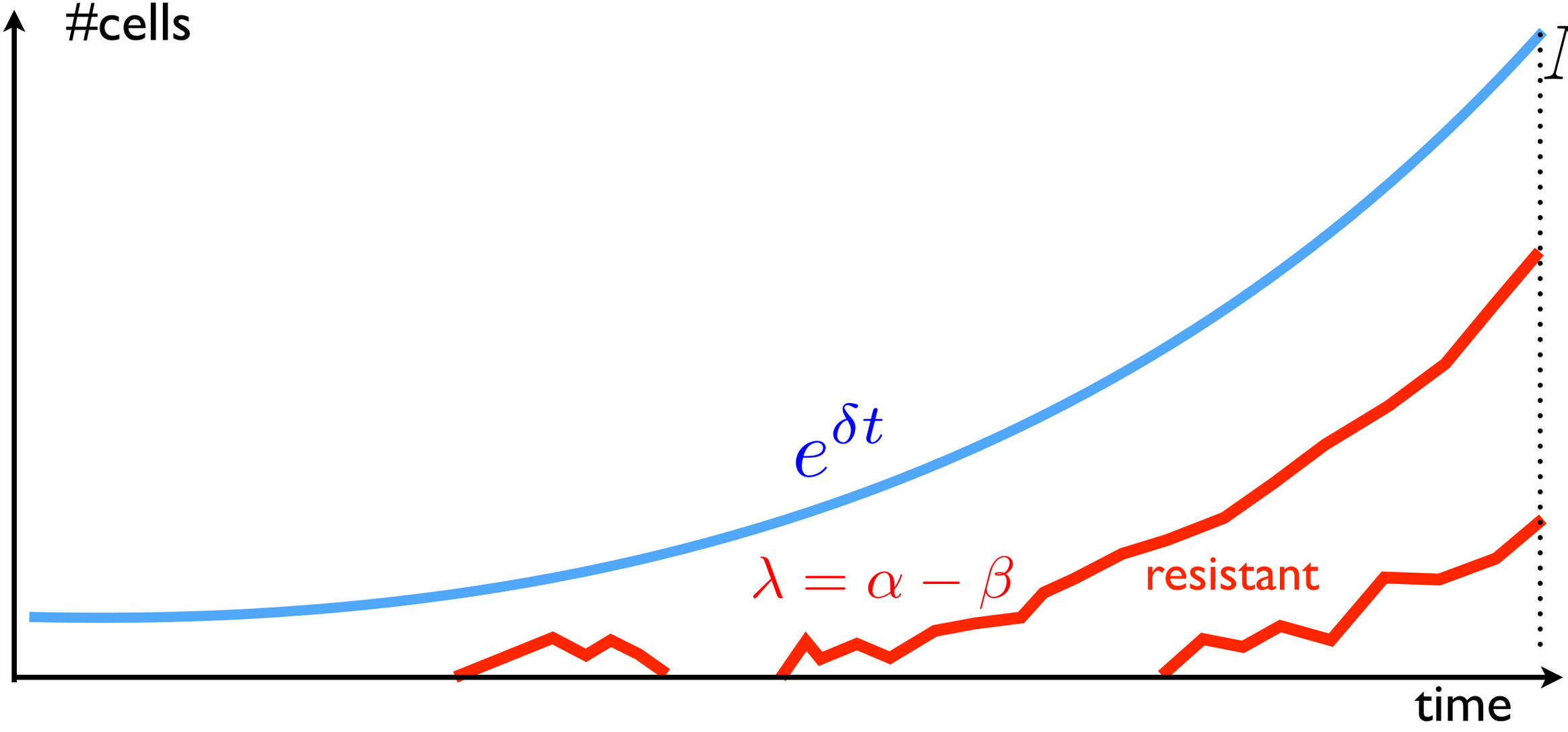
$$t^{3/2} P_n(t) \to \frac{e^{-\mathcal{N}/(2\lambda)}}{2\lambda} \left[I_0\left(\frac{\mathcal{N}}{2\lambda}\right) - I_1\left(\frac{\mathcal{N}}{2\lambda}\right) \right]$$

$$\mathcal{N} = n/t$$

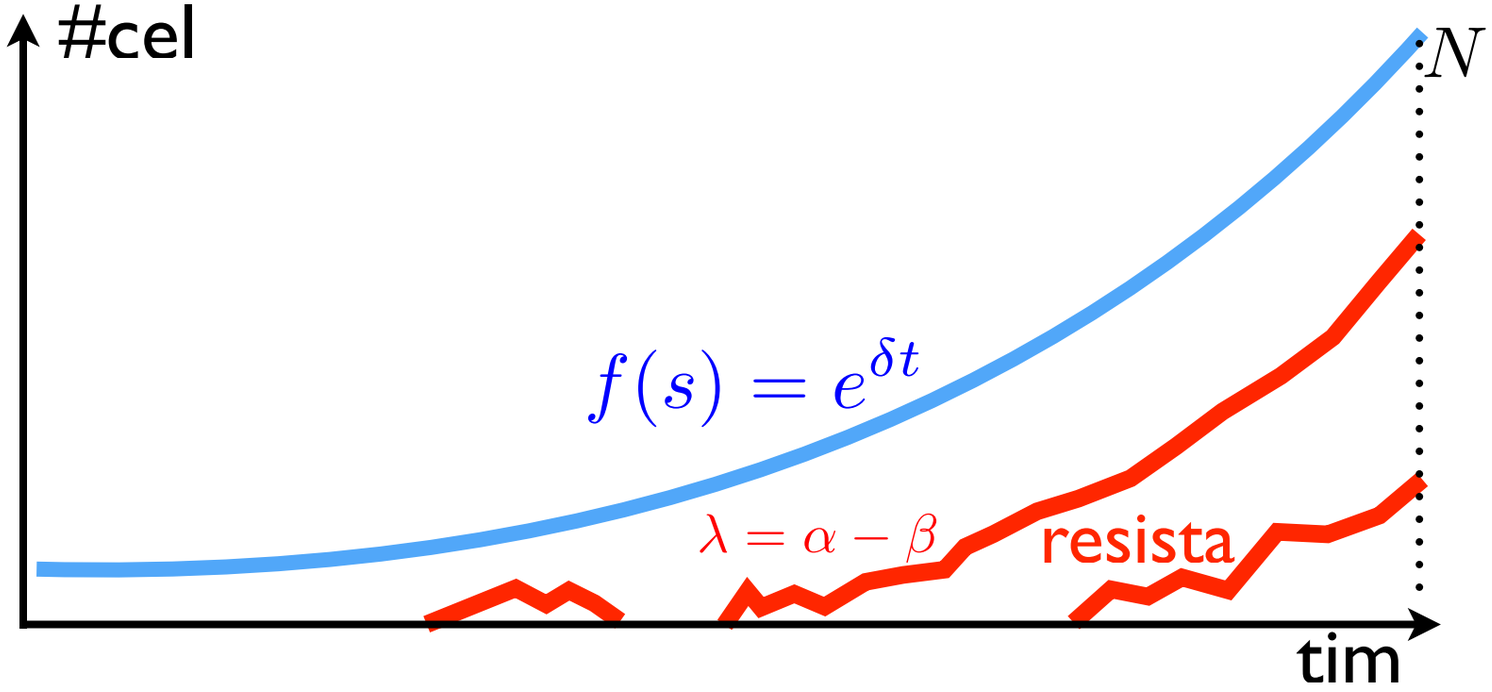


#mutants in a fixed size cancer
(from half stochastic description)

Iwasa, Nowak, Michor `06,
Komarova `07,
Durrett, Moseley `10,
Kessler, Levin '14
Keller, TA '14



#mutants in a fixed size cancer



from K clones

$$B = \sum_{i=1}^{K} Y_i$$

$$m = EK = \int_0^t \nu f(s) ds$$

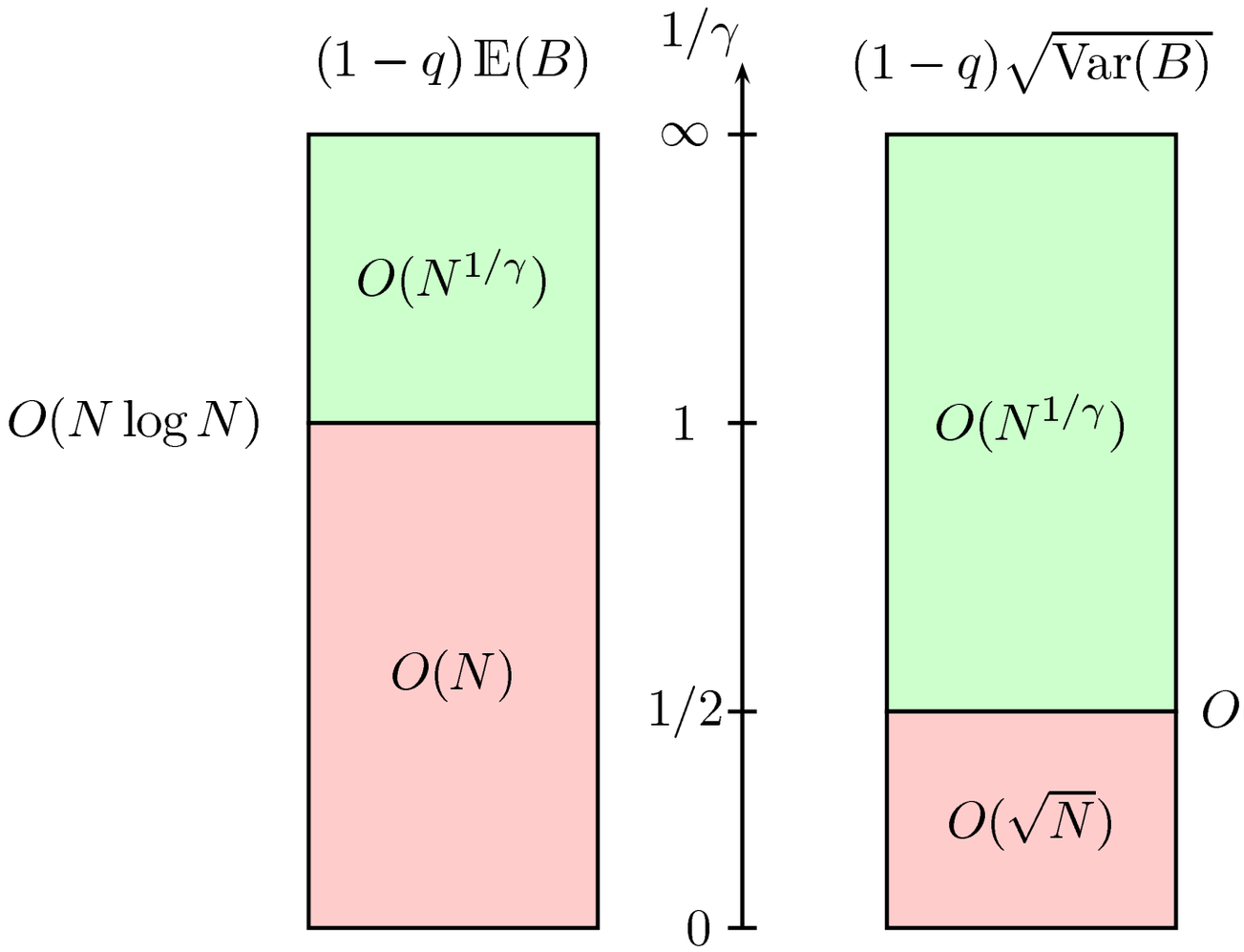
one clone $\psi(z) = Ez^Y = \frac{\nu}{m} \int_0^t f(s) g_{t-s}(z) ds$

$$G(z) = Ez^B = EE(z^B|K) = E\psi^K = \sum_{k \geq 0} \frac{(\psi(z)m)^k}{k!} e^{-m} = e^{m(\psi(z)-1)}$$

$$\Lambda_B(z) = \log G_B(z) = \frac{N\mu}{\gamma} \left[\frac{1}{N} F\left(\begin{matrix} 1, \gamma \\ 1+\gamma \end{matrix}; \xi N^{-1/\gamma} \right) - F\left(\begin{matrix} 1, \gamma \\ 1+\gamma \end{matrix}; \xi \right) \right]$$

$$\xi = \frac{q-z}{1-z} \qquad q = \frac{\beta}{\alpha} \qquad \gamma = \frac{\delta}{\lambda}$$

number of mutants B for large tumors



advantageous mutants (non self-averaging)

deleterious mutants

even more deleterious mutants

$$\mathbb{E}(B) = \frac{N\mu}{1-q} \cdot \begin{cases} \log N & \gamma = 1 \\ \frac{1}{1-\gamma}(N^{1/\gamma-1}-1). & \gamma \neq 1 \end{cases}$$

apoptosis matters

$$\mathrm{Var}(B) = \frac{N\mu}{(1-q)^2} \cdot \begin{cases} 2(N-1) - (1+q)\log N & \gamma = 1 \\ (1+q)(N^{-1/2}-1) + \log N & \gamma = 2 \\ \frac{2}{2-\gamma}N^{2/\gamma-1} + \frac{1+q}{\gamma-1}N^{1/\gamma-1} + \frac{q(2-\gamma)+\gamma}{(2-\gamma)(1-\gamma)} & \gamma \notin \{1,2\}. \end{cases}$$

different limits

$$\theta = N\mu, \gamma = \frac{\delta}{\lambda}, q = \frac{\beta}{\alpha}$$

$$\Lambda_V(z) = \frac{\theta}{\gamma} \cdot \frac{1-z}{1-q} F\left(\begin{matrix}1,1\\1+\gamma\end{matrix}; \frac{z-q}{1-q}\right)$$

number of mutants: B —— Large Population, Small Mutation, $N \to \infty$, $\mu \to 0$, $N\mu$ const. ⟶ V

Kessler, Levin '14 using AK `10

B — Large Population, $N \to \infty$ → W —— Small Mutation, $\mu \to 0$ ⟶ Z

Mandelbrot '74

V — Large θ, $\theta \to \infty$ → Z

$$Z = \lim_{\theta \to \infty} \frac{V}{a} - b$$

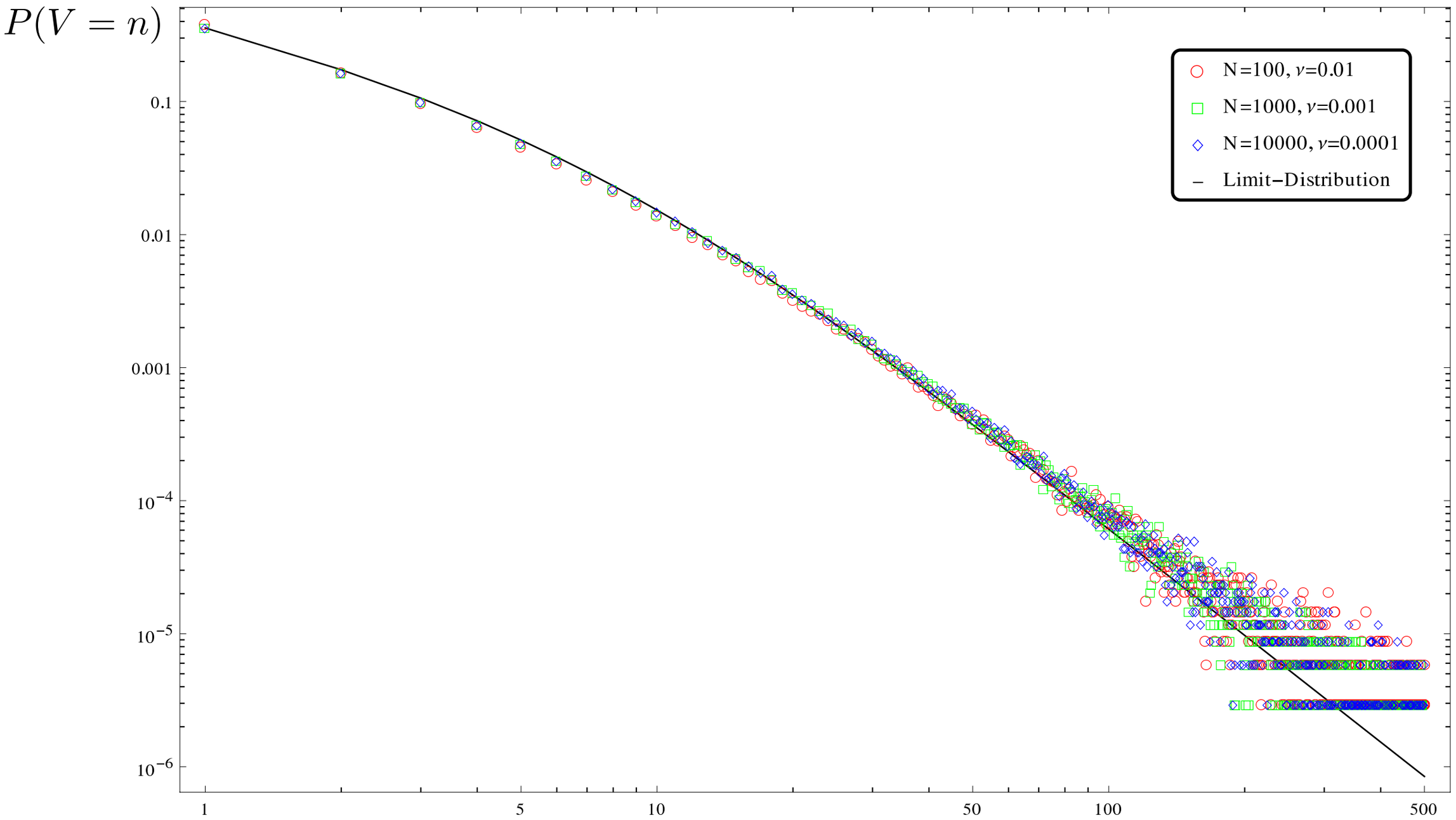
Durrett, Moseley `10

Keller, TA '14

large population - small mutation

$$\theta = N\mu = 1$$

$$\Lambda_V(z) = \frac{\theta}{\gamma} \cdot \frac{1-z}{1-q} F\left(\begin{matrix} 1,1 \\ 1+\gamma \end{matrix} ; \frac{z-q}{1-q} \right)$$

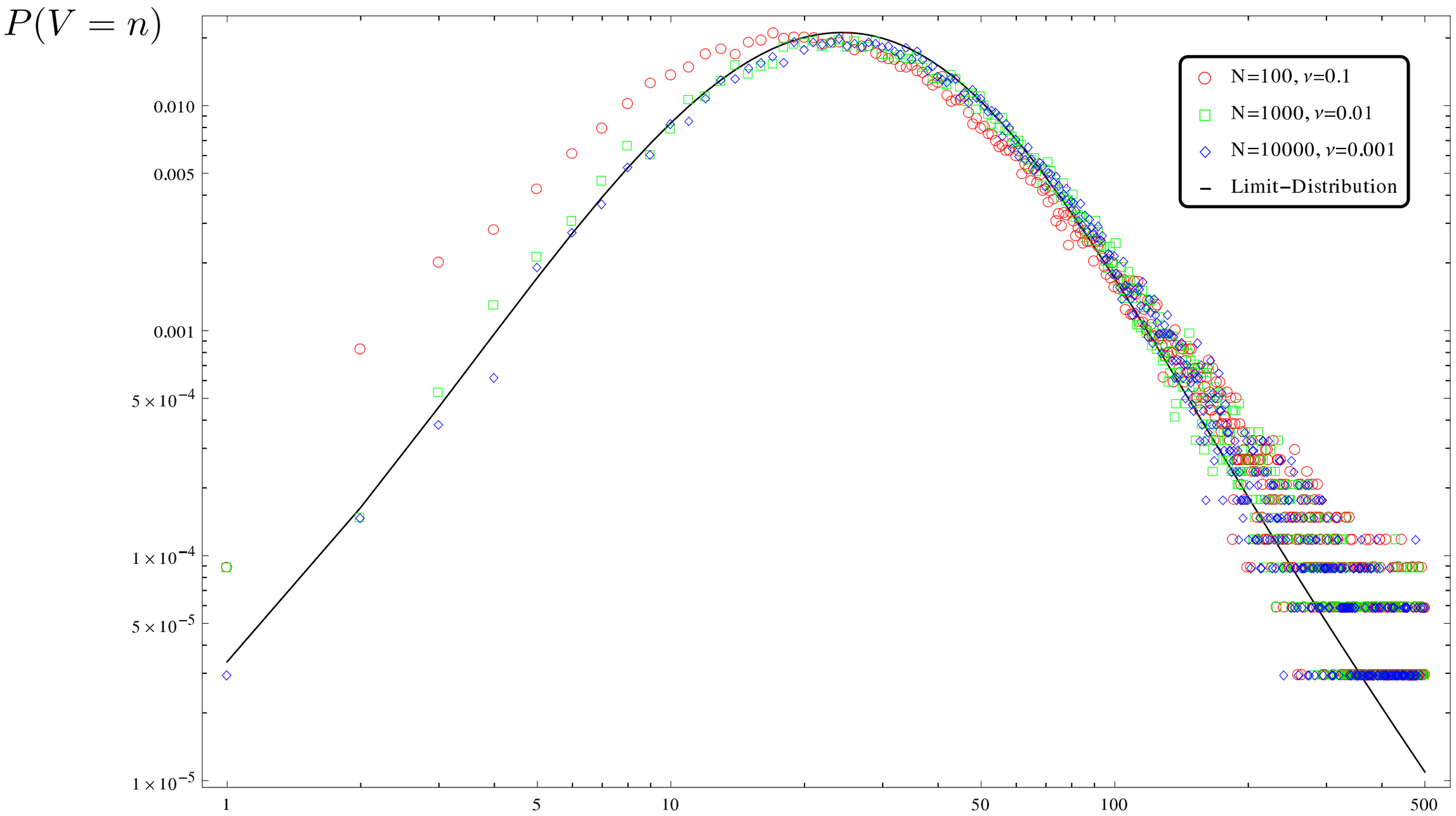


n number of mutants

large population - small mutation

$$\theta = N\mu = 10$$

$$\Lambda_V(z) = \frac{\theta}{\gamma} \cdot \frac{1-z}{1-q} F\left(\begin{matrix} 1,1 \\ 1+\gamma \end{matrix} ; \frac{z-q}{1-q} \right)$$



n number of mutants

mean and variance

	$\mathbb{E}(V)$	$\mathrm{Var}(V)$
$\gamma > 2$	$\frac{\theta}{(1-q)(\gamma-1)}$	$\frac{\theta}{(1-q)^2}\left(\frac{q(2-\gamma)+\gamma}{(\gamma-2)(\gamma-1)}\right)$
$1 < \gamma \leq 2$	$\frac{\theta}{(1-q)(\gamma-1)}$	∞
$0 < \gamma \leq 1$	∞	∞

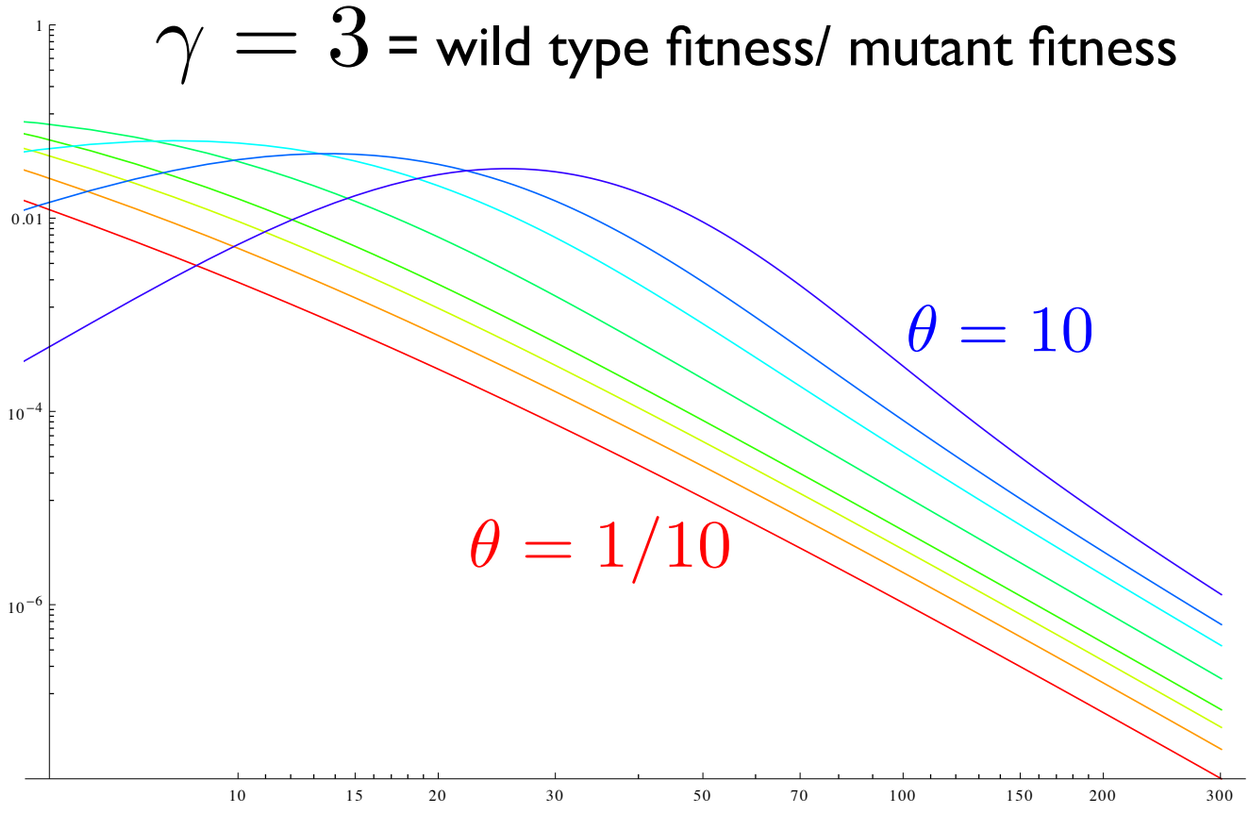
} deleterious mutants

advantageous mutants

varying parameters

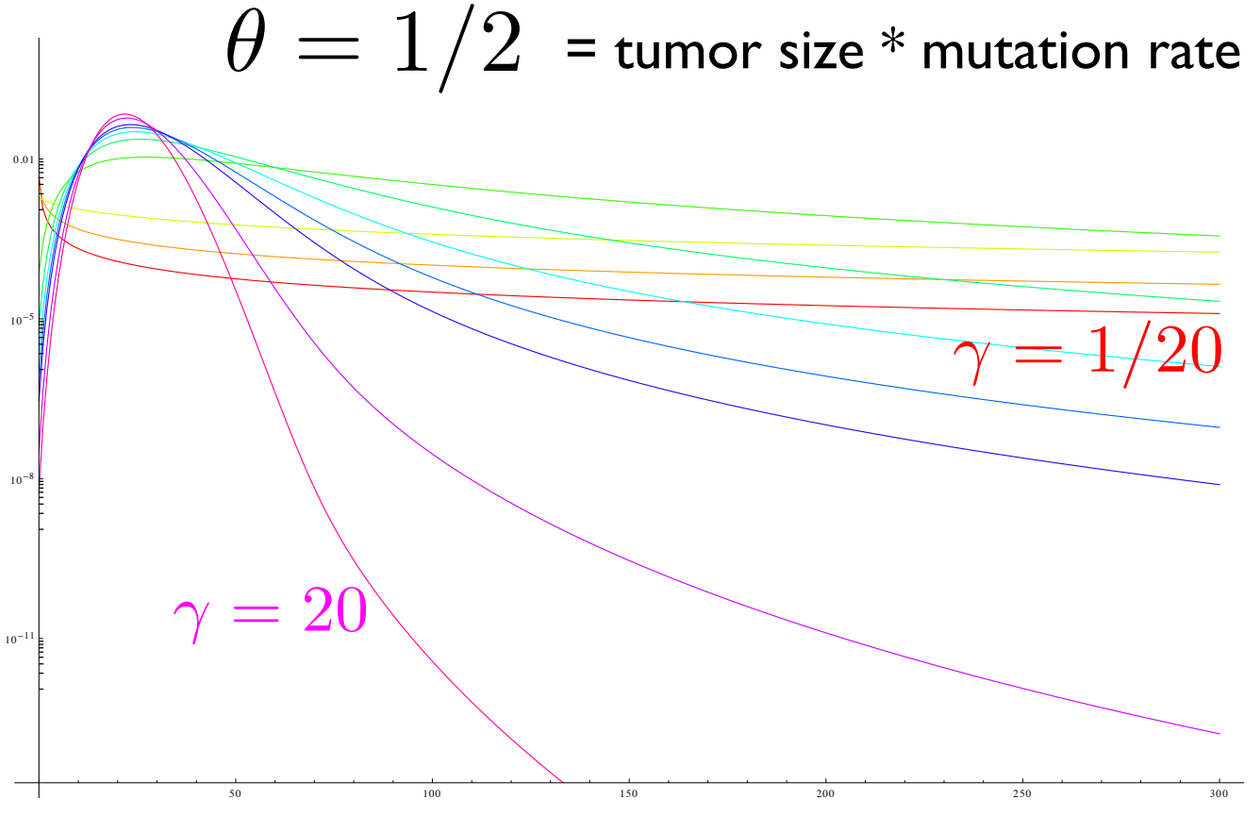
$$p_n \sim \frac{\theta\Gamma(1+\gamma)}{(1-q)^\gamma} n^{-1-\gamma}$$

$\gamma = 3$ = wild type fitness/ mutant fitness



mutants

$\theta = 1/2$ = tumor size * mutation rate



mutants

neutral mutations, no death $(\gamma = 1, q = 0)$

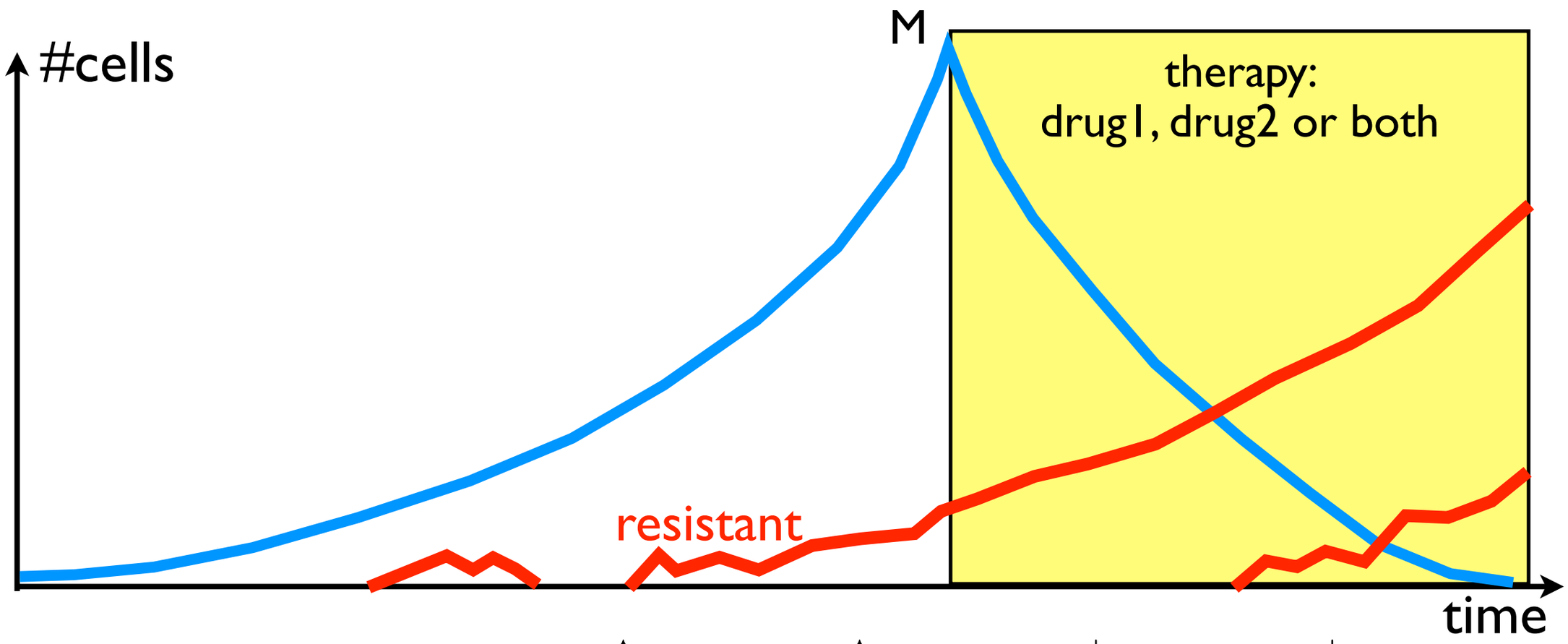
$$G(z) = (1-z)^{\theta(1-z)/z}$$ from $$F\left(\begin{matrix}1,1\\2\end{matrix};z\right) = -\frac{\log(1-z)}{z}$$

which leads to recursion

$$p_0 = e^{-\theta} \qquad \frac{np_n}{\theta} = \frac{p_0}{n+1} + \frac{p_1}{n} + \cdots \frac{p_{n-1}}{2}$$

similar recursion for most general case too

fighting drug resistance with combination therapies



probability of treatment success = $P_1^{\uparrow} \times P_2^{\uparrow} \times P_1^{\downarrow} \times P_2^{\downarrow}$

non-homogeneous Poisson process, small u large M limit:

M: detection size
u: mutations rate
s=1-d/b: survival probability (': with drugs)
n: number of mutation causing resistance to drugs (1,2,12)

$$P_1^{\uparrow} = \exp(-Mun_{12})$$

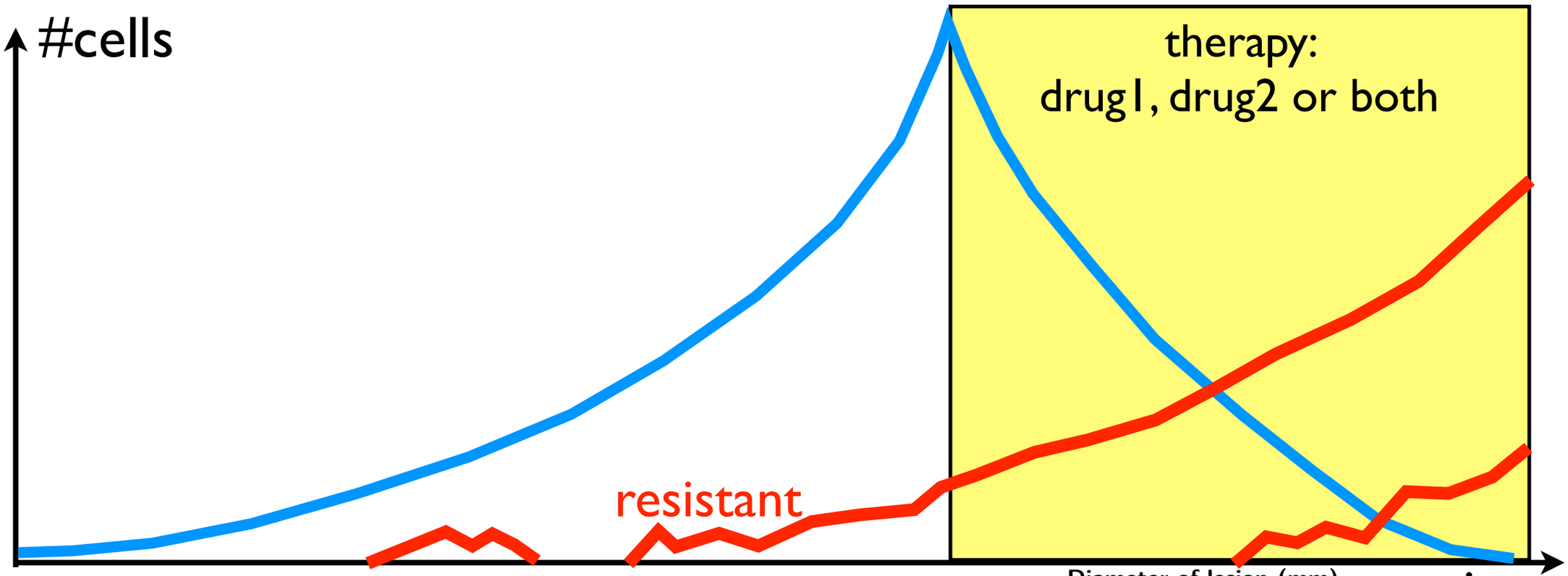
$$P_1^{\downarrow} = \exp\left(-Mun_{12}\frac{s}{s'}\right).$$

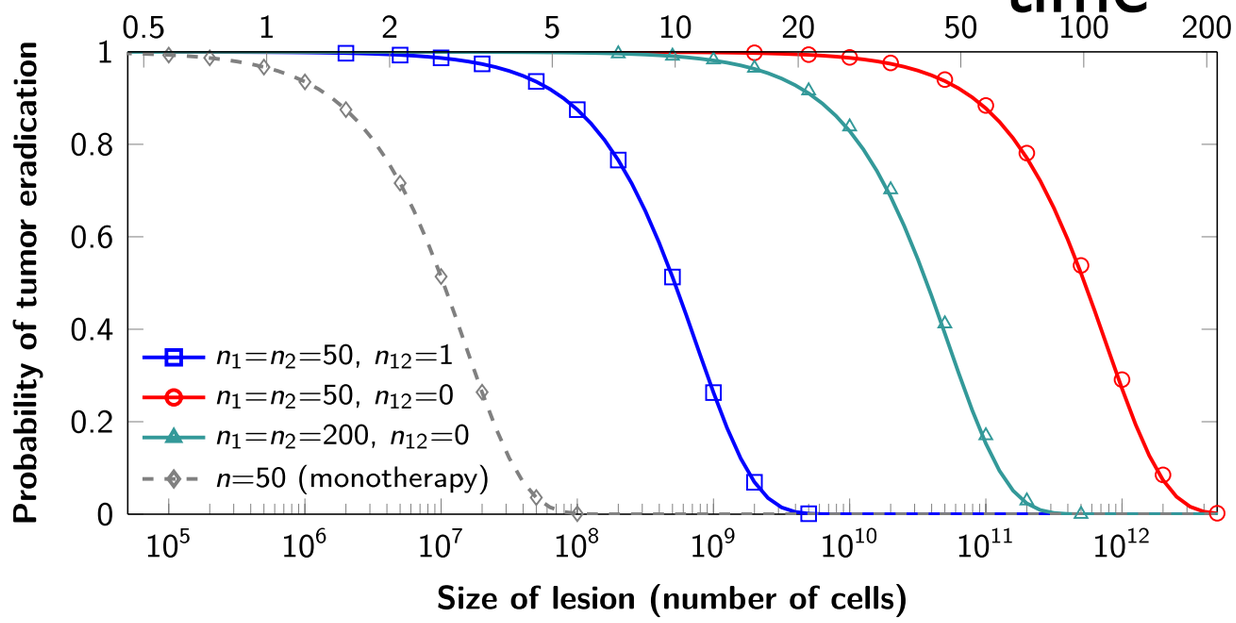
$$P_2^{\uparrow} = \exp\left[Mu^2\frac{s'-s}{ss'}\left(n_1(n_2+n_{12})\log\left(\frac{1}{sM}+u(n_2+n_{12})\frac{s'-s}{ss'}\right)\right.\right.$$
$$\left.\left.+n_2(n_1+n_{12})\log\left(\frac{1}{sM}+u(n_1+n_{12})\frac{s'-s}{ss'}\right)\right)\right]$$

$$P_2^{\downarrow} = \exp\left(-Mu\left(2n_1n_2+n_{12}(n_1+n_2)\right)\frac{s}{s'^2}\right).$$

Bozic et al '13

fighting drug resistance with combination therapies





outcome:

- sequentially applying drugs is certain failure
- failure if one mutation confer double resistance

Bozic et al '13

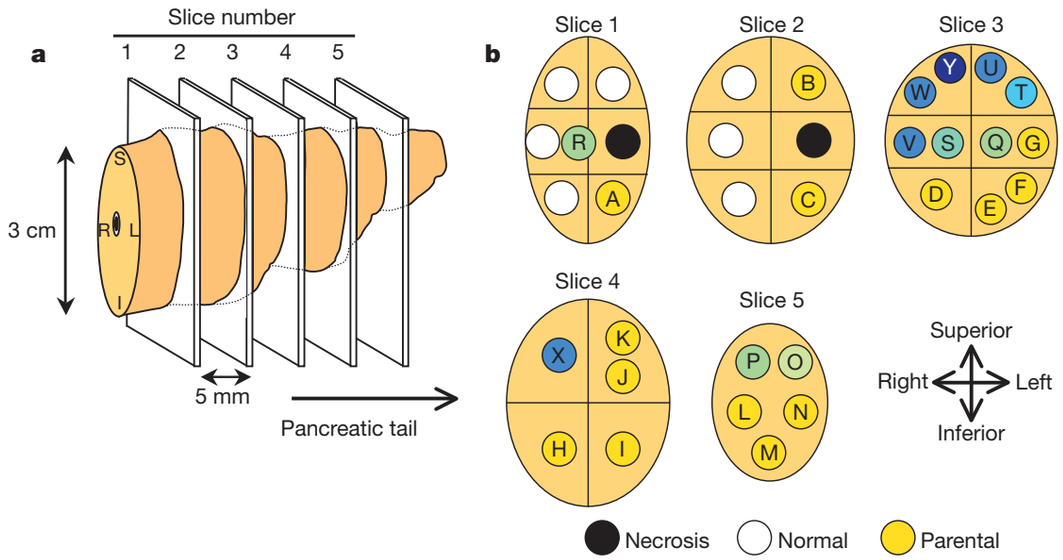
probability of treatment failure

Patient	Primary tumor type	Number of metastases	Total tumor burden (number of cells)	Monotherapy	Dual therapy: $n_{12} = 1$	Dual therapy: $n_{12} = 0$
N1	Pancreas	18	2.6×10^{11}	1	1	0.283
N2	Colon	25	2.3×10^{11}	1	1	0.26
N3	Melanoma	26	1.7×10^{11}	1	1	0.203
N4	Melanoma	30	1.4×10^{11}	1	1	0.172
N5	Colon	21	1.0×10^{11}	1	1	0.128
N6	Melanoma	8	9.8×10^{10}	1	1	0.12
N7	Colon	25	9.1×10^{10}	1	1	0.112
N8	Pancreas	8	7.4×10^{10}	1	1	0.092
N9	Pancreas	23	6.4×10^{10}	1	1	0.08
N10	Pancreas	5	5.5×10^{10}	1	1	0.069
N11	Colon	14	5.4×10^{10}	1	1	0.068
N12	Rectal	23	4.8×10^{10}	1	1	0.061
N13	Melanoma	9	4.1×10^{10}	1	1	0.052
N14	Pancreas	13	4.1×10^{10}	1	1	0.051
N15	Pancreas	8	3.3×10^{10}	1	1	0.042
N16	Melanoma	7	2.2×10^{10}	1	1	0.028
N17	Melanoma	10	2.1×10^{10}	1	1	0.027
N18	Colon	4	2.0×10^{10}	1	1	0.026
N19	Melanoma	9	1.8×10^{10}	1	1	0.023
N20	Colon	3	1.6×10^{9}	1	0.881	0.002
N21	Melanoma	21	1.3×10^{9}	1	0.828	0.002
N22	Pancreas	1	8.5×10^{8}	1	0.677	0.001

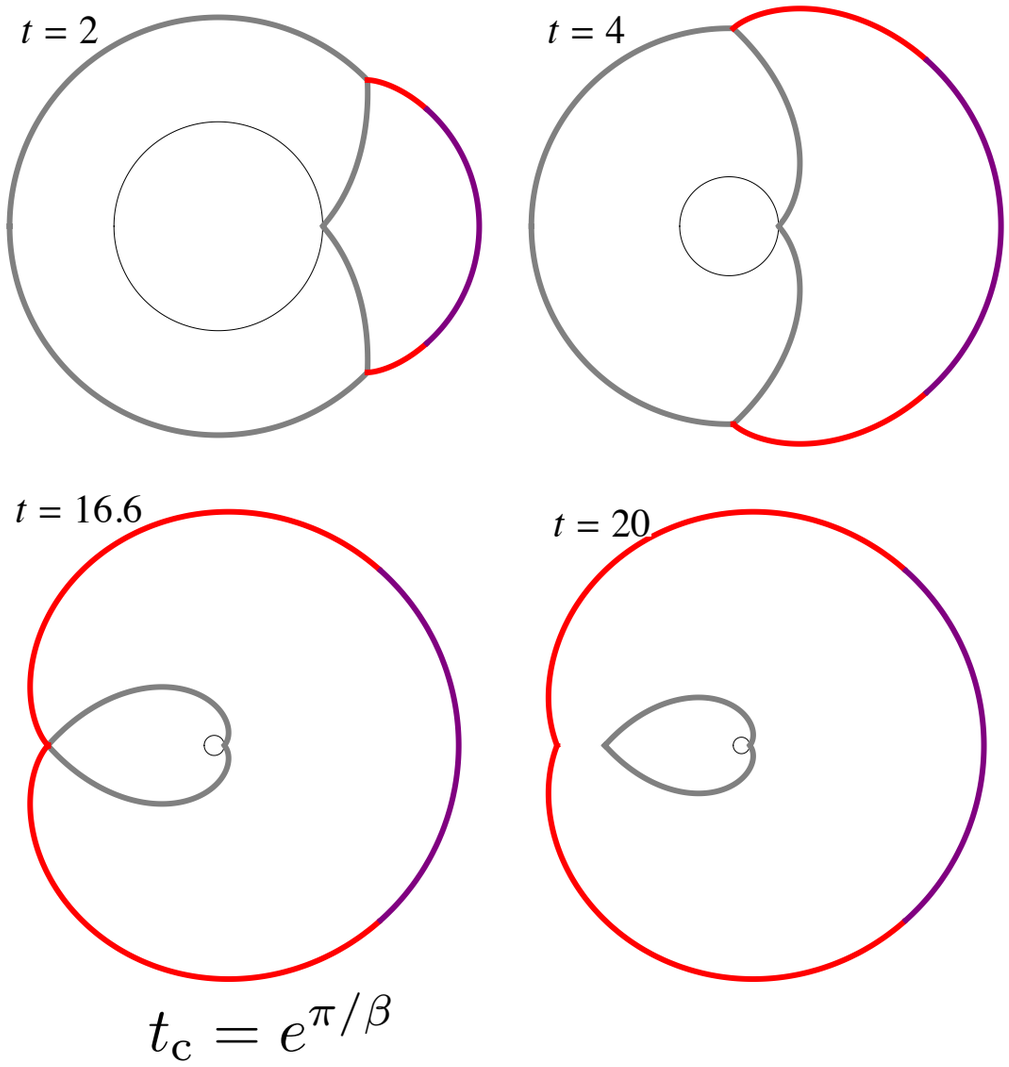
For monotherapy, we assume that 50 point mutations ($n = 50$) can in principle confer resistance to the drug. With dual therapy, we assume that 50 point mutations can in principle confer resistance to each drug individually ($n_1 = n_2 = 50$). Two scenarios are modeled: in the first, there is one mutation that can in principle confer resistance to both drugs (i.e., cross-resistance, $n_{12} = 1$). In the other case, there are no possible mutations that can confer resistance to both drugs ($n_{12} = 0$). Parameter values: birth rate, $b = 0.14$, death rate, $d = 0.13$, death rate for sensitive cells during treatment, $d' = 0.17$, point mutation rate $u = 10^{-9}$.

Bozic et al '13

spatial models



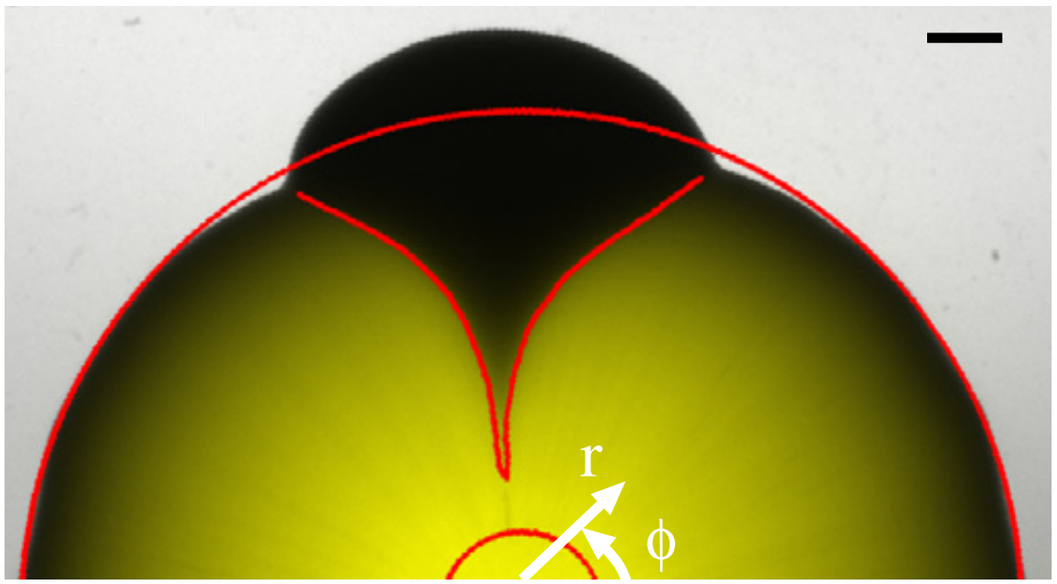
Yashida et al '10



model assumptions:
- surface grows at rate fitness (1, v)
- mutations at surface at rate one

A, Krapivsky, Nowak et al '13

shape of one mutant clone



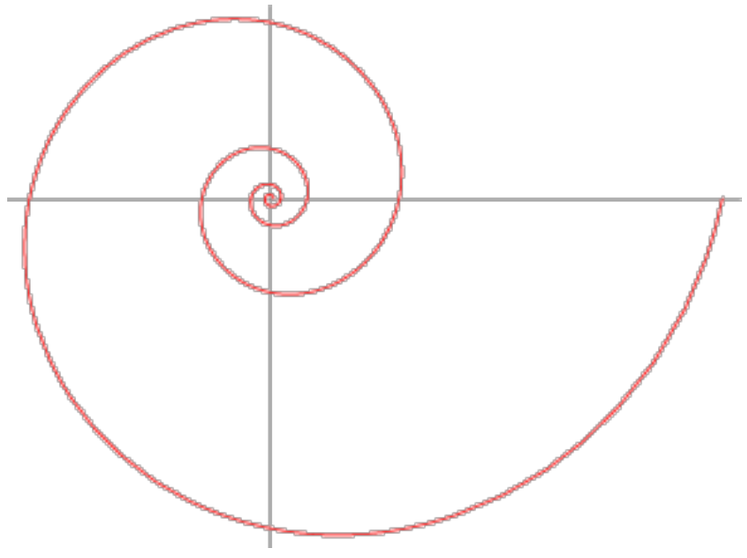
yeast colonies on a plate, Korolev '12

also: Bradley ’89, Hallatschek, Nelson ‘10

$$r\theta'(r) = \beta$$

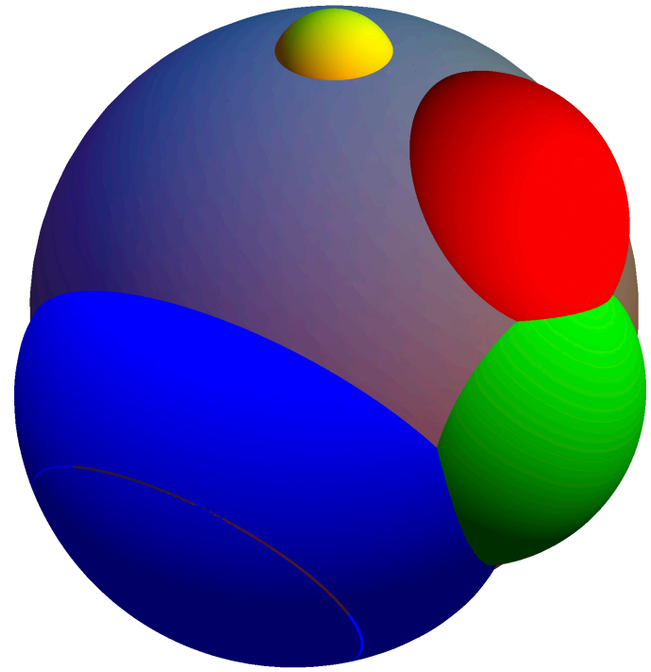
$$\theta(r) = \beta \log \frac{r}{r_0}$$

$$r(\theta) = r_0 e^{\theta/\beta}$$

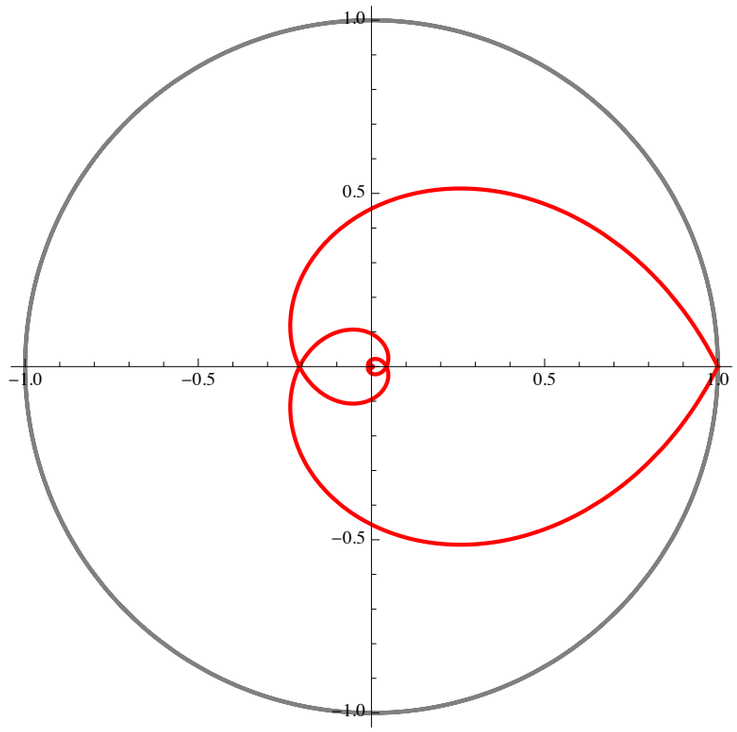


logarithmic spiral, Descartes, Jacob Bernoulli, 1638

mutants at rate one



fraction of non-mutants in r-ball



$$W_{\leq r} = \frac{1 - e^{-b(\beta) r^3}}{b(\beta) r^3}$$

$$b(\beta) = \frac{2\pi}{3} \frac{\beta^2}{\beta^2 + 9} \left(1 + e^{-3\pi/\beta}\right)$$

final non-mutant volume

$$\lim_{t \to \infty} \frac{4\pi}{3} t^3 W_{\leq t} = \frac{4\pi}{3b(\beta)}$$

A, Krapivsky, Nowak et al '13

summary

- beauty and usefulness of branching processes
- finite time experiments motivate exact results
- spatial models with successive mutations

thanks

with
P. Krapivsky (Boston),
P. Keller (Edinburgh),
M. Nowak, I Bozic, B Allen, … (Harvard)