

Emergence of resistance to treatment as a process of adaptation to a moving optimum

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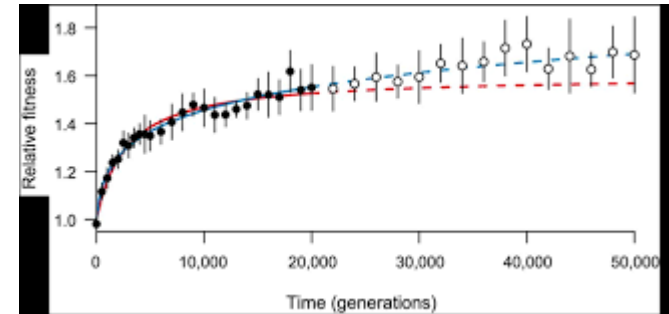
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Adaptation to changing conditions in asexuals

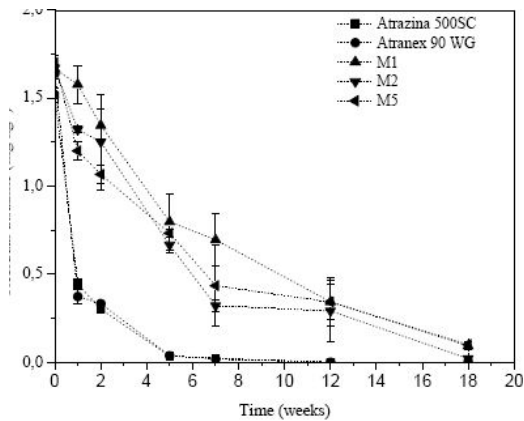
➔ Bacteria, cancer, viruses, fungus, asexual pests and weeds

Abrupt shift: typical in experimental evolution



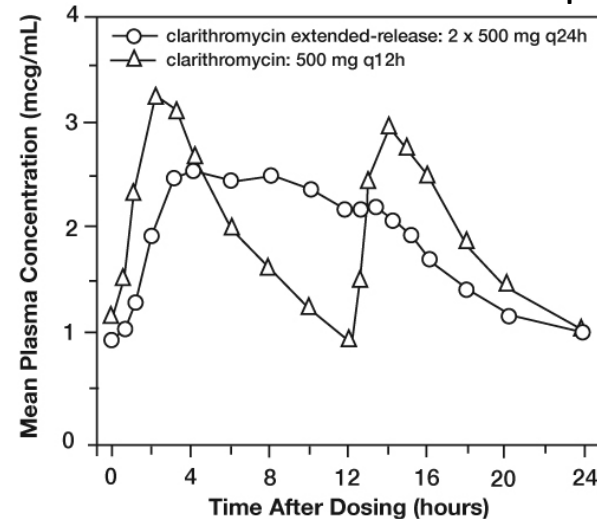
Continuous change:

herbicide concentration in soil



Atrazine dissipation in soil from ethylcellulose microparti

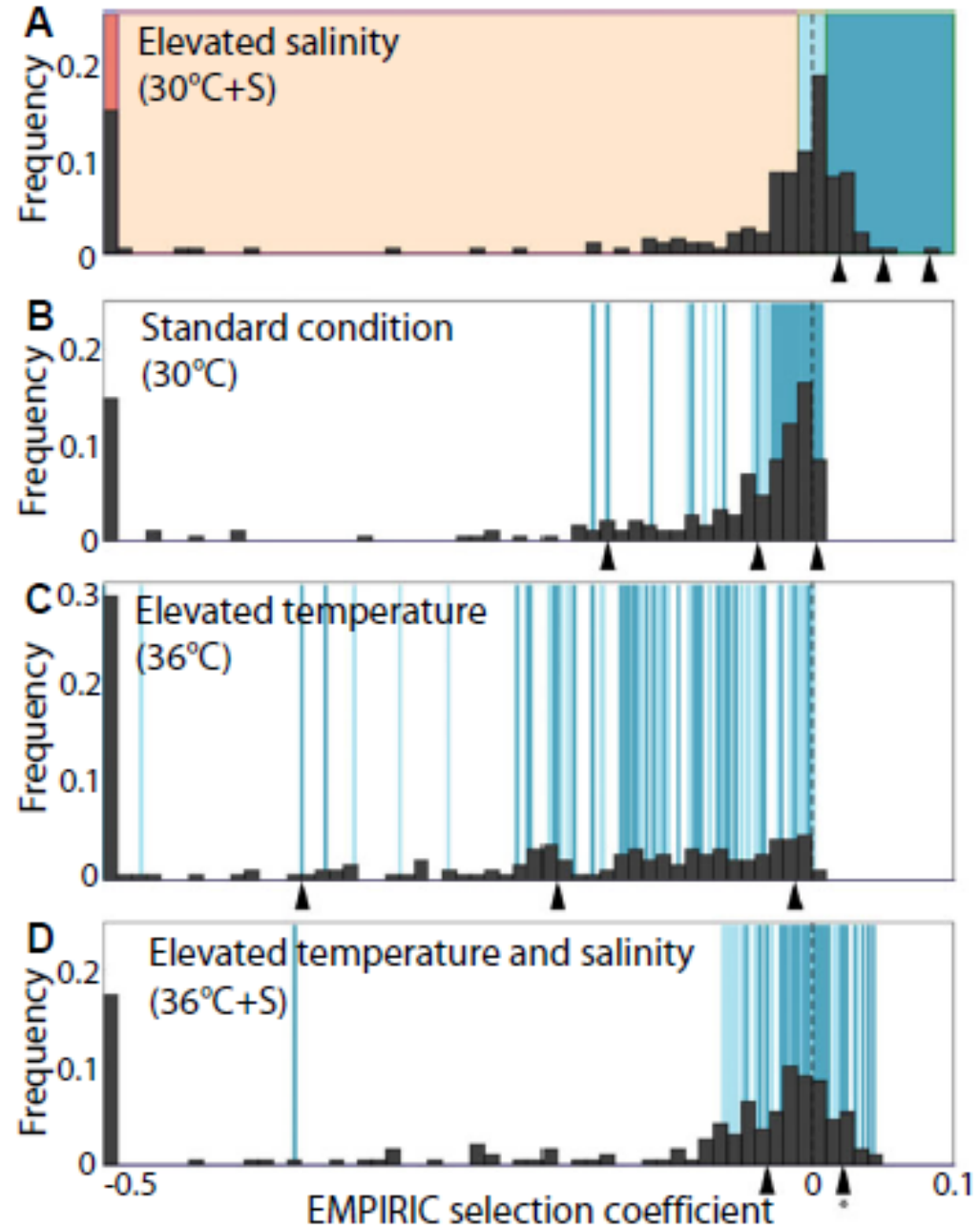
Antibiotic concentration dose in plasma



Stress and mutation fitness effects...

- Fitness effects of random mutations are distributed
- Pervasive G x E...
- What is beneficial in one environment can become deleterious in another

Hietpas et al (2013) *Evolution*
Mutations in Hsp90 in yeast



Demography and adaptation in changing conditions

To predict demographic outcomes (emergence, burst, extinction etc.) :

- conceptual framework for some **continuous 'stress level'**
- with **diversity of alleles** + **G x E** on **demographic components** (survival, reproduction)

Not so many choices out there ... the classical one is:

⇒ Phenotype/fitness landscape with **optimum that depends on the environment**

Requires to handle

- new mutations + standing variance** (epistasis and G x E)
- selection between possibly multiple types** (clonal interference)
- stochastic events** (mutation, reproduction at least)

moving optimum models: FGM

⇒ Phenotype/fitness landscape with **optimum that depends on the environment**

Gaussian single peak landscap (Fisher's Geometrical Model **FGM**)

1/ genotype - phenotype relationship: **additive**.

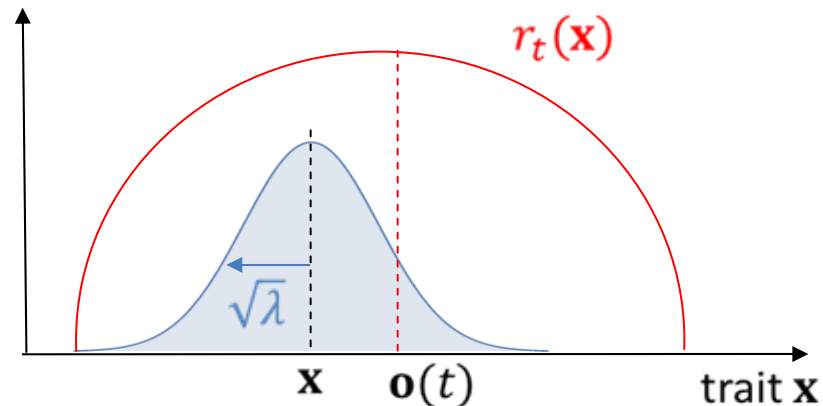
2/ mutation effects on phenotype: **unbiased isotropic gaussian** $d\mathbf{x} \sim N(0, \lambda \mathbf{I}_n)$

3/ phenotype - fitness relationship: **quadratic growth rate** $r_t(\mathbf{x}) = r_{max} - \frac{|\mathbf{x} - \mathbf{o}(t)|^2}{2}$
(= gaussian $W(\mathbf{x})$)

4/ Demography and how it determines fitness and drift: **simple logistic**

5/ environmental effects on all this fitness \sim growth rate

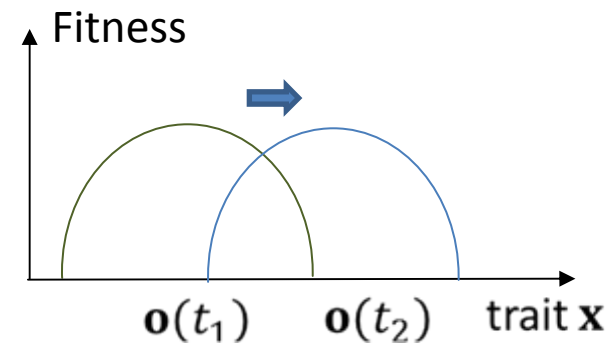
Malthusian fitness :
Expected growth rate
of a genotype



moving optimum models

Environmental scenarii: (reviewed in Mathuszewski al 2014, *Evolutionary Applications*)

- steadily moving optimum
- Random fluctuation
(around steady or fixed trend, +/- autocorrel.)



Population genetics of adaptation:

- Steady variance response ($NU \rightarrow \infty$ + many unlinked loci of small effect)
(most analytical work)
- Successive fixations in monomorphic populations ($NU \rightarrow 0$)
(Mathuszewski al 2014, *Evolution*)

In all cases:

Stationary response

to a

Stationary regime of environmental change

Aim of this talk

But...

Non-stationary regimes are (possibly more) important :

i. experimental timescales

ii. key for demographic responses (rescue, bursts etc.)

iii. response from standing variance (initial condition effect)

Changes may not be just linear or random

Aim of the model :

- Non-linear change, non-stationary trait/fitness distributions
- Short-term response from standing variance
- Asexuals in large NU (experimental model + simpler first step)
- Extends to sexuals under infinitesimal model (weak selection loose linkage)

Modelling strategy

Fisher's geometrical model + moving optimum

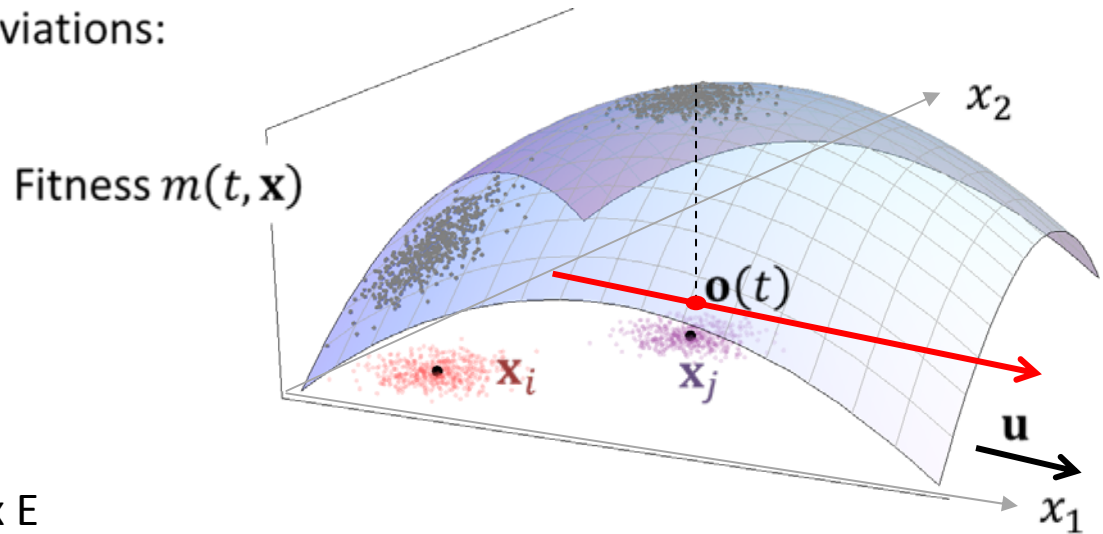
Asexuals + frequency-independent selection

- Optimum $\mathbf{o}(t)$ for n traits, malthusian fitness at t :

$$r(t, \mathbf{x}) = r_{max}(t) - \|\mathbf{x} - \mathbf{o}(t)\|^2 / 2, \mathbf{x} \in \mathbb{R}^n$$
- Mutation = Gaussian trait deviations:

$$d\mathbf{x} \sim N(\mathbf{0}, \lambda(t) \mathbf{I}_n)$$

- Mutants from \mathbf{x}_i
- Mutants from \mathbf{x}_j



- ⇒
- Traits: no epistasis + no G x E
 - Fitness: epistasis + G x E

Moving optimum: $\mathbf{o}(t) = \Delta(t) \mathbf{u}$, \mathbf{u} : unit vector, direction of movement, $\Delta(t)$ arbitrary

Problem reduction

Individual phenotype (= breeding value for phenotype): $\mathbf{x} \in \mathbb{R}^n$



two **time – independent** fitness components:

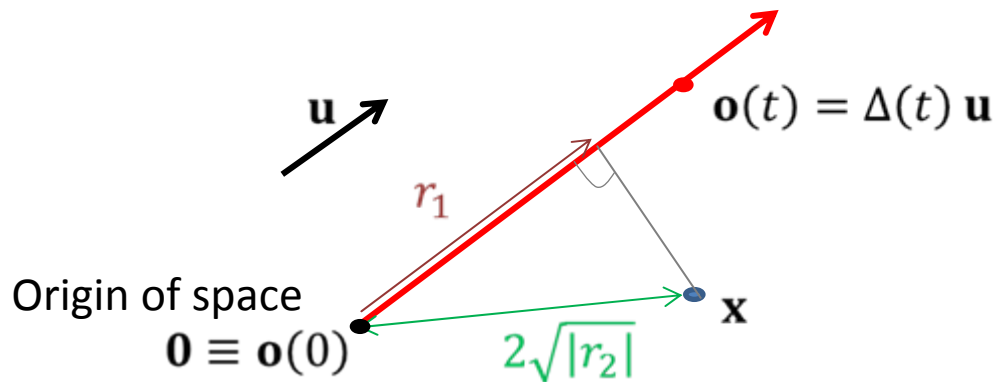
$$\mathbf{r}(\mathbf{x}) = \begin{pmatrix} r_1 \\ r_2 \end{pmatrix} \in \mathbb{R}^2$$

$\mathbf{r}(\mathbf{x}) \equiv$

$$\begin{cases} r_1 = \mathbf{x} \cdot \mathbf{u} \\ r_2 = -\|\mathbf{x}\|^2/2 \end{cases}$$

Phenotype projection along axis of optimum movement

Fitness if measured in ancestral environment ($t = 0$)
Relative to optimal genotype in this environment




Problem reduction

$$\mathbf{r}(\mathbf{x}) \equiv \begin{pmatrix} r_1 \\ r_2 \end{pmatrix} \in \mathbb{R}^2 \quad \left\{ \begin{array}{l} r_1 = \mathbf{x} \cdot \mathbf{u} \\ r_2 = -\|\mathbf{x}\|^2/2 \end{array} \right.$$

$$\boldsymbol{\alpha}(t) \equiv \begin{pmatrix} \Delta(t) \\ 1 \end{pmatrix} \in \mathbb{R}^2: \text{Describes optimum dynamics along axis } \mathbf{u}$$

determine two random variables (distributed within the population)
which distribution changes over time

- 
- fitness of \mathbf{x} measured in current environment ($\mathbf{o}(t) = \Delta(t) \mathbf{u}, r_{max}(t)$)
$$r(t, \mathbf{x}) = r_{max}(t) + \boldsymbol{\alpha}(t) \cdot \mathbf{r}(\mathbf{x}) - \Delta(t)^2/2$$
 - fitness of \mathbf{x} measured in another environment ($\mathbf{o}(t') = \Delta(t') \mathbf{u}, r_{max}(t')$)
$$r(t', \mathbf{x}) = r_{max}(t') + \boldsymbol{\alpha}(t') \cdot \mathbf{r}(\mathbf{x}) - \Delta(t')^2/2$$

Joint fitness components densities

(Extension of method for abrupt change in Martin & Roques 2016 *Genetics*)

Akin to a bivariate cumulant generating function (CGF) of $\mathbf{r}(\mathbf{x})$

genotype i : $\mathbf{r}(\mathbf{x}_i) = \begin{pmatrix} r_1^i \\ r_2^i \end{pmatrix}$, number $n_i(t)$ at time t in some focal population

$$C_t^{\mathbf{r}}(z_1, z_2) = \log \left(\sum_i n_i(t) e^{r_1^i z_1 + r_2^i z_2} \right)$$

$C_t^{\mathbf{r}}: \mathbb{R}^2 \mapsto \mathbb{R}$, convex on \mathbb{R}^2 ,

$N_t = \sum_i n_i(t)$: total population size at time t

Joint fitness components densities

(Extension of method for abrupt change in Martin & Roques 2016 *Genetics*)

$$C_t^{\mathbf{r}}(z_1, z_2) = \log \left(\sum_i n_i(t) e^{r_1^i z_1 + r_2^i z_2} \right)$$

Population size : $C_t^{\mathbf{r}}(0,0) = \log N_t$

Cumulants of \mathbf{r} : means, variances, covariances within the population

$$\nabla C_t^{\mathbf{r}}(\mathbf{0}) = \begin{pmatrix} \bar{r}_1 \\ \bar{r}_2 \end{pmatrix} \quad \nabla = \{\partial_{z_1}, \dots, \partial_{z_2}\}$$

$$\nabla^2 C_t^{\mathbf{r}}(\mathbf{0}) = \begin{pmatrix} V(r_1) \\ V(r_2) \end{pmatrix} \quad \nabla^2 = \{\partial_{z_1}^2, \dots, \partial_{z_2}^2\}$$

$$\partial_{z_1} \partial_{z_2} C_t^{\mathbf{r}}(\mathbf{0}) = \text{cov}(r_1, r_2)$$

Growth rate distributions and population size

Malthusian fitness of genotype i evaluated in environment at time t
 in current environment : $r_i(t) = r_{max}(t) + \alpha(t) \cdot \mathbf{r}(\mathbf{x}_i) - \Delta(t)^2/2$

$$\mathbf{r}(\mathbf{x}) = \begin{pmatrix} r_1 \\ r_2 \end{pmatrix}$$

$$\alpha(t) \equiv \begin{pmatrix} \Delta(t) \\ 1 \end{pmatrix}$$

distribution of fitness among genotypes of time t
 when evaluated in the environment of time t'

$$\mathcal{C}(z, t, t') = \log \mathbb{E}(e^{r(\mathbf{x}, t, t')})$$

$$\mathcal{C}(z, t, t') = \mathcal{C}_t^{\mathbf{r}}(\alpha(t') z) \exp\left(z \left(r_{max}(t') - \frac{\Delta(t')^2}{2} \right)\right)$$

Strategy: solve dynamics of $\mathcal{C}_t^{\mathbf{r}}(\cdot)$, deduce $\mathcal{C}(z, t, t')$ **ignoring drift**

⇒ Dynamics of fitness cumulants among genotypes from any time,
 evaluated in an environment from the same or a different time

⇒ Dynamics of population size

PDE for the CGF $\mathcal{C}_t^r(z_1, z_2)$

PDE for the most general case

Given initial population size and phenotype distribution: $C_0^r(\mathbf{z})$

$$\boldsymbol{\omega}(\mathbf{z}, \lambda) \equiv - \left\{ \frac{z_1 z_2 \lambda}{1 + z_2 \lambda}, \frac{z_2^2 \lambda}{1 + z_2 \lambda} \right\} \quad \mathbf{z} = \{z_1, z_2\} \in \mathbb{R}^+ \times \mathbb{R}^+$$

$$M_*(\mathbf{z}, \lambda) \equiv \exp\left(\frac{z_1^2 \lambda}{2(1 + z_2 \lambda)}\right) (1 + z_2 \lambda)^{-n/2}$$

$$\begin{aligned} \partial_t C_t^r(\mathbf{z}) = & (r_{max}(t) - \Delta(t)^2/2 + \boldsymbol{\alpha}(t) \cdot \nabla_{\mathbf{z}} C_t(\mathbf{z})) (1 - \exp(C_t(\mathbf{0}))/K(t)) \\ & + U(t) (M_*(\mathbf{z}, \lambda(t)) \exp(C(\mathbf{z} + \boldsymbol{\omega}_t(\mathbf{z}, \lambda(t))), t) - C(\mathbf{z}, t)) - 1 \end{aligned}$$

Growth + selection : Clonal interference among arbitrarily many genotypes
 $r_{max}(t)$: growth rate of optimal genotype for environment of time t

Density dependence: $K(t)$: carrying capacity at time t

Mutation under isotropic Fisher's model (Infinite allele model epistatic)

$U(t)$: mutation rate in environment of time t

$\lambda(t)$: mutational variance on phenotypes in environment of time t

General result for simpler subcase

Straightforward extension of Martin & Roques (2016) *Genetics*

(i) **WSSM**: weak selection strong mutation limit (More precisely: $U \gg U_c = n^2 \lambda / 4$)

(ii) **Constant mutational parameters**: $U(t) = U, \lambda(t) = \lambda$

(iii) **Ignoring density - dependence** ($K(t) \rightarrow \infty$ at all times)

(iv) **Population initially at mutation selection balance**

also if initially clonal and with sexuals under infinitesimal model (different reasons)

Then the phenotypes are multivariate normal at all times with known mean and variance

$$\mathbf{x} \sim \mathcal{N}(a(t) \bar{\mathbf{x}}_0 + b(t) \mathbf{u}, V(t) \mathbf{I}_n)$$

Explicit solution for $C_t^r(\mathbf{z})$ and thus for fitness distributions and population sizes

Result extends to non gaussian effects of mutations on phenotypes (a form of diffusive limit)

Demographic/evolutionary dynamics

Population initially at equilibrium

Under assumption (i)-(iv): population initially at mutation - selection balance

$\mu \equiv \sqrt{U \lambda}$: a form of characteristic mutational coefficient

Replaced by a constant additive variance for sexuals under infinitesimal model

Growth rate of the population at time t :

$$\bar{r}(t) \approx r_{max}(t) - \underbrace{\theta \mu}_{\text{Variance load}} - \underbrace{\frac{e^{-2\mu t}}{2} \left(\Delta(0) + \int_0^t e^{\mu v} \Delta'(v) dv \right)^2}_{\text{Lag load}}$$

Population size at time t : $N_t \approx N_0 e^{\rho(t)}$ where $\rho(t) = \int_0^t \bar{r}(v) dv$

Approximate probability of extinction

(v) Feller diffusion with genotype independent variance coefficient

each genotype has growth rate r_i and constant reproductive variance σ

(i) **WSSM** => we can ignore genetic stochasticity and only account for demographic one

Using general result on inhomogeneous Feller diffusion

Bansaye et Simatyo (2015) *Elect. J. Prob.*

expected population size at time t : $N_t \approx N_0 e^{\rho(t)}$ where $\rho(t) = \int_0^t \bar{r}(v) dv$

Probability of extinction by time t :

$$\text{let } N_H(t) \equiv \frac{N_0}{\int_0^t e^{-\rho(v)} dv}$$
$$P_{ext}(t) \approx \exp\left(-\frac{2N_H(t)}{\sigma}\right).$$

Distribution of waiting times to extinction

**A simplistic 'pulse' model:
treatment + exponential dose decay**

'pulse' model

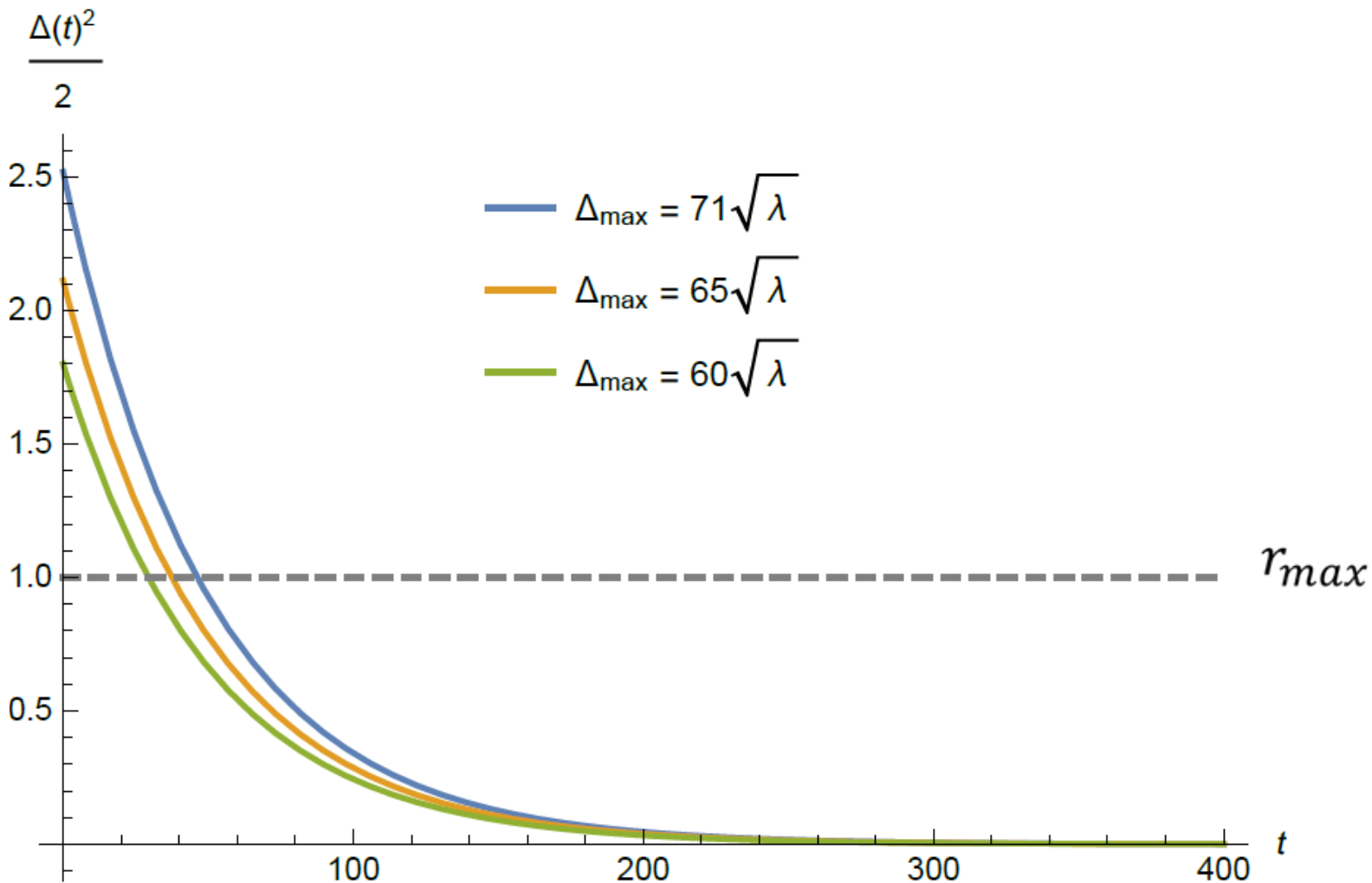
$$\Delta(t) = \Delta_{max} e^{-c t}$$

Components of growth rate if no evolution:

$$r(t) = r_{max} - \Delta(t)^2 / 2$$

$$U = 100 U_c, \lambda = 0.001, n = 4$$

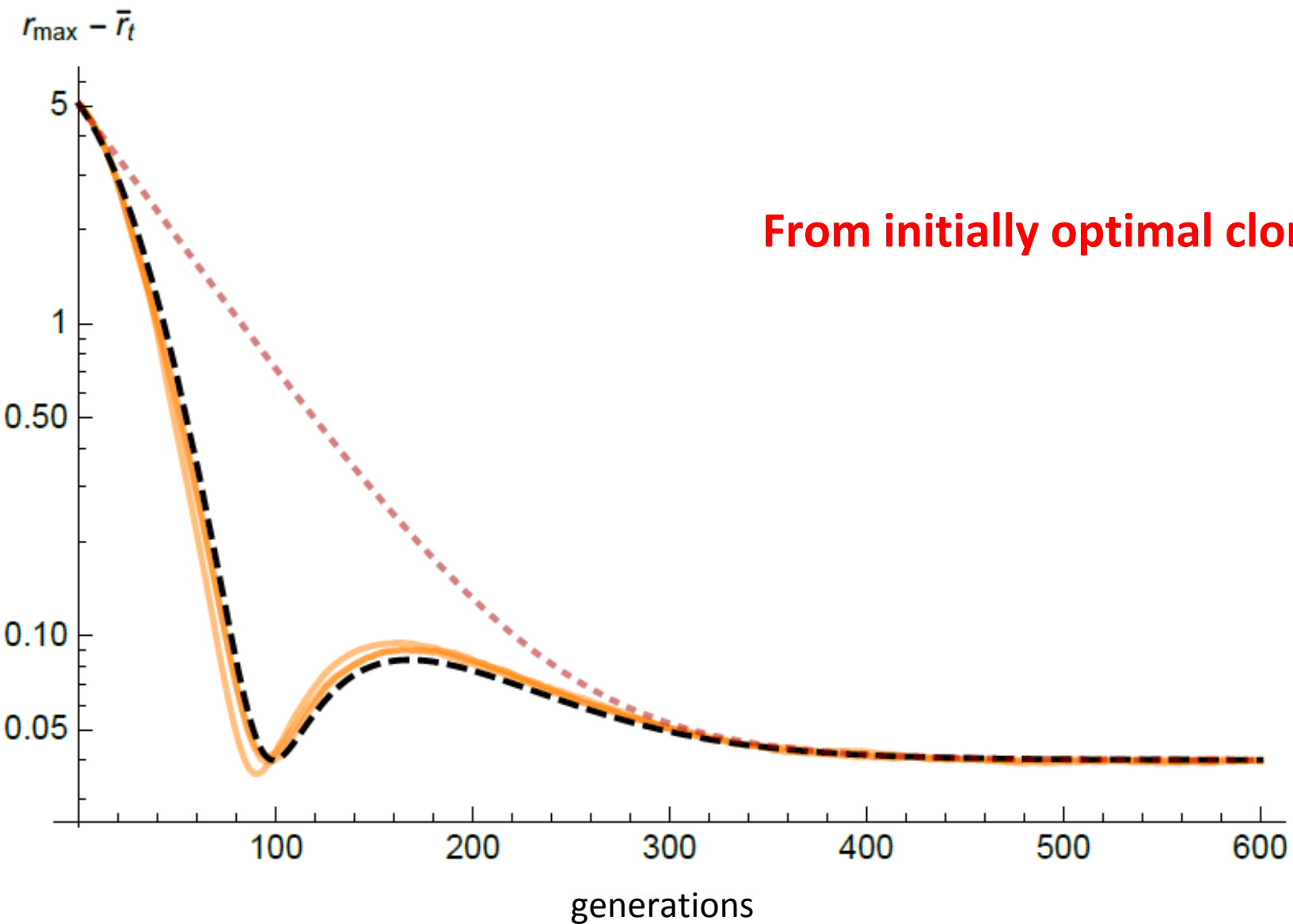
$$r_{max} = 1, c = 0.01, N_0 = 10^5$$



Evolution in large stable population

Deviation of growth rate from maximal growth rate

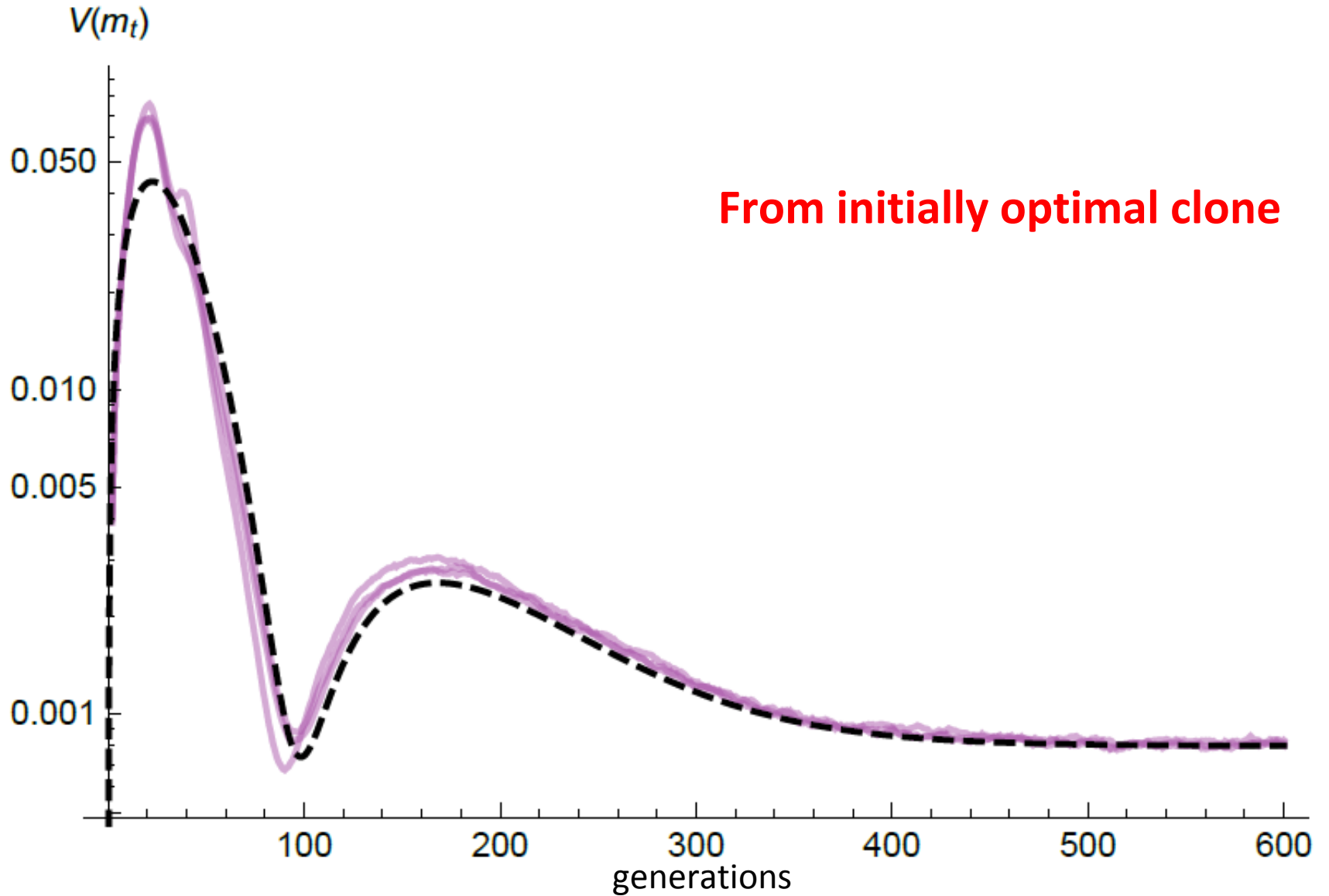
— simulations - - - theory ···· no evolution



From initially optimal clone

Variance in fitness

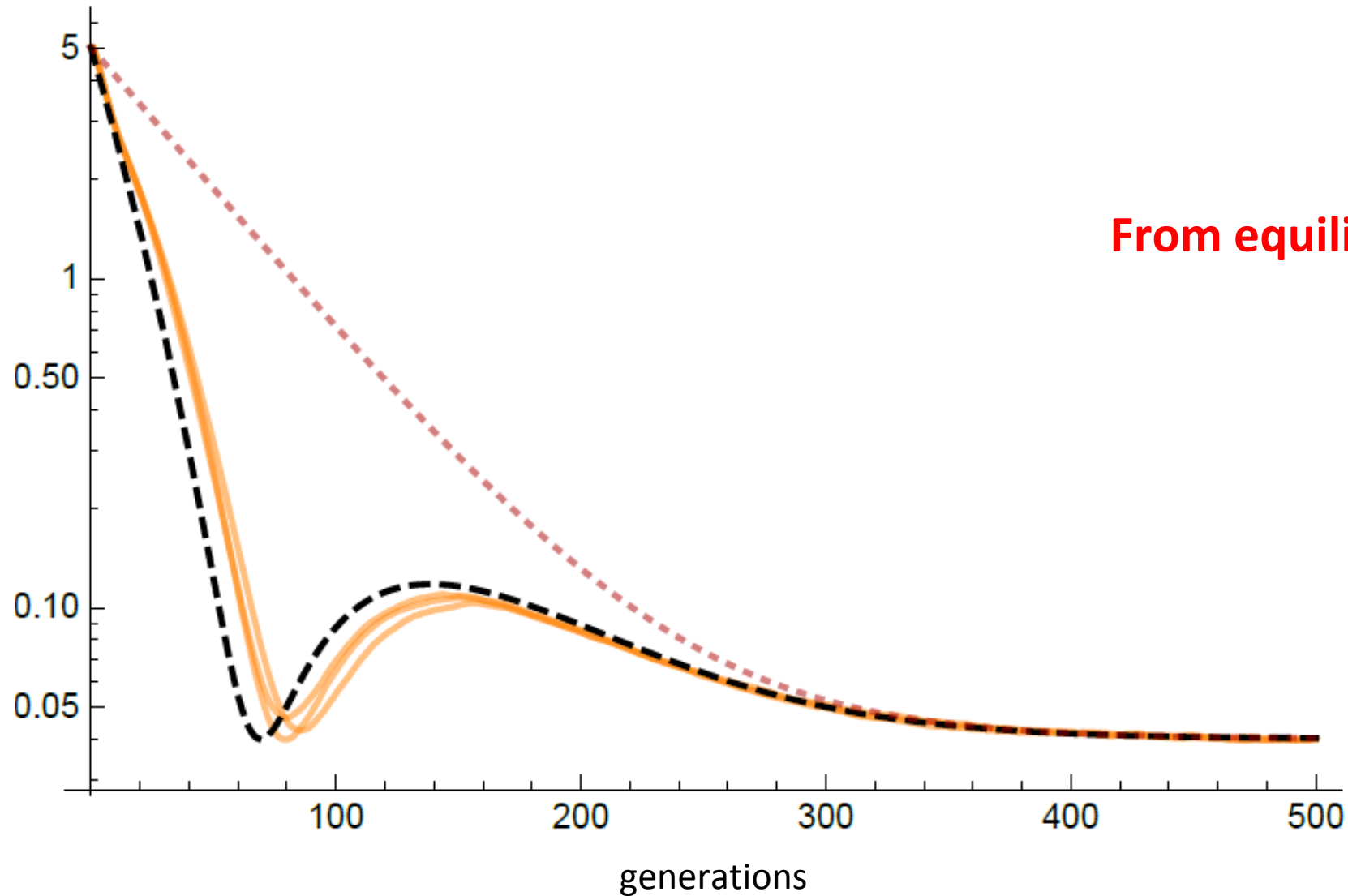
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Deviation of growth rate from maximal growth rate

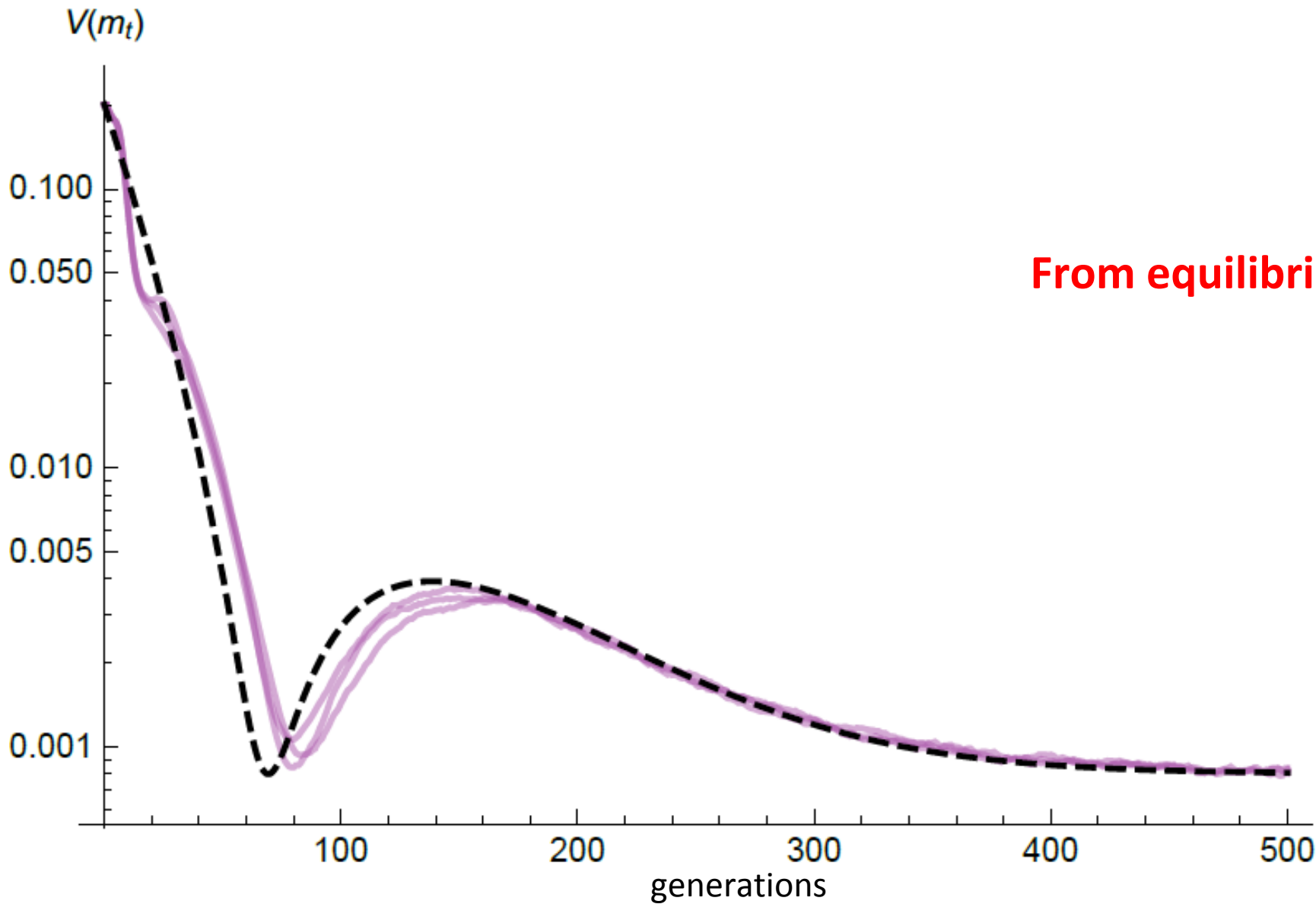
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$r_{\max} - \bar{r}_t$



Variance in fitness

— simulations - - - - theory



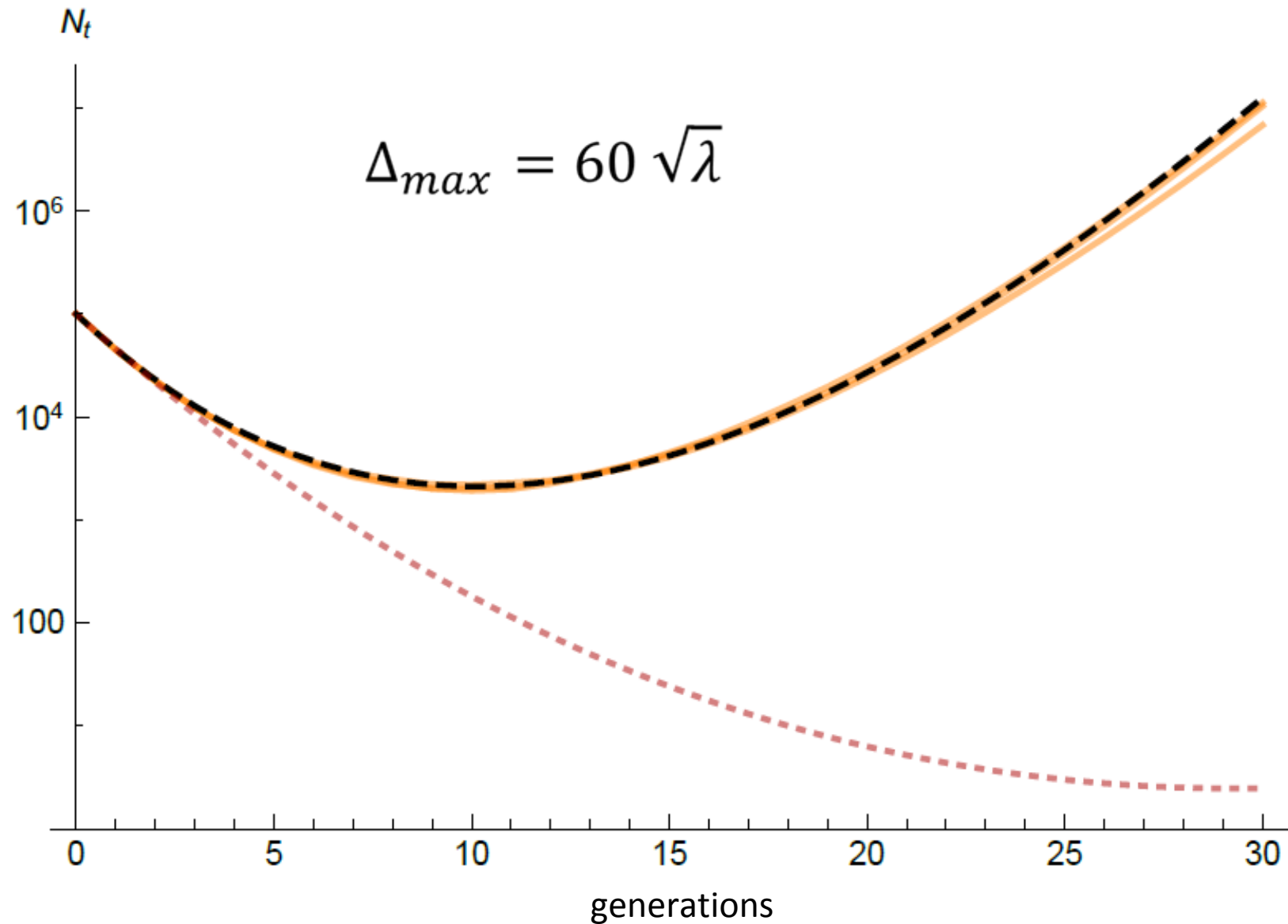
From equilibrium

Evolution -> demography
« Evolutionary Rescue »
(density – independent growth)

Population size dynamics

From equilibrium

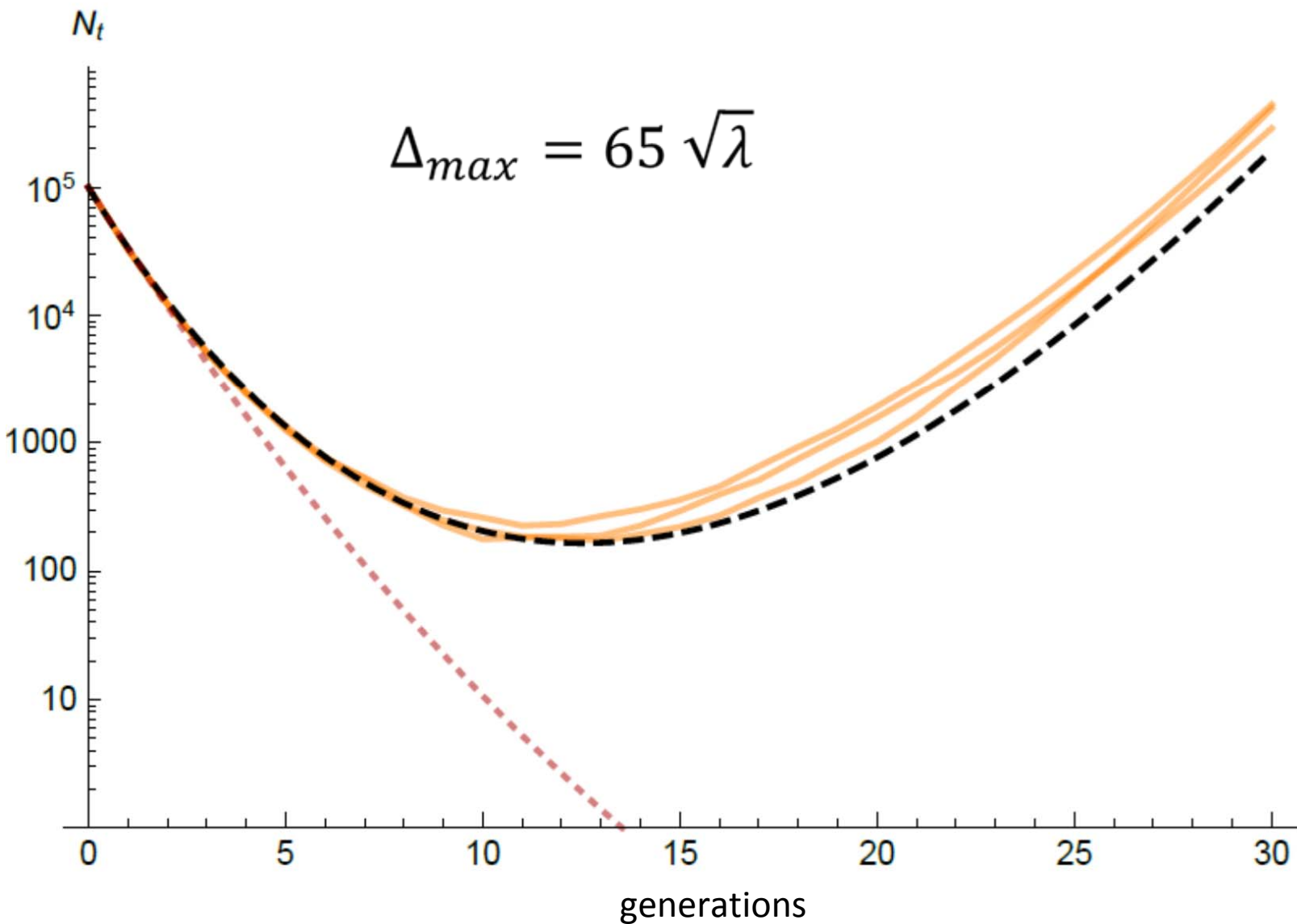
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Population size dynamics

From equilibrium

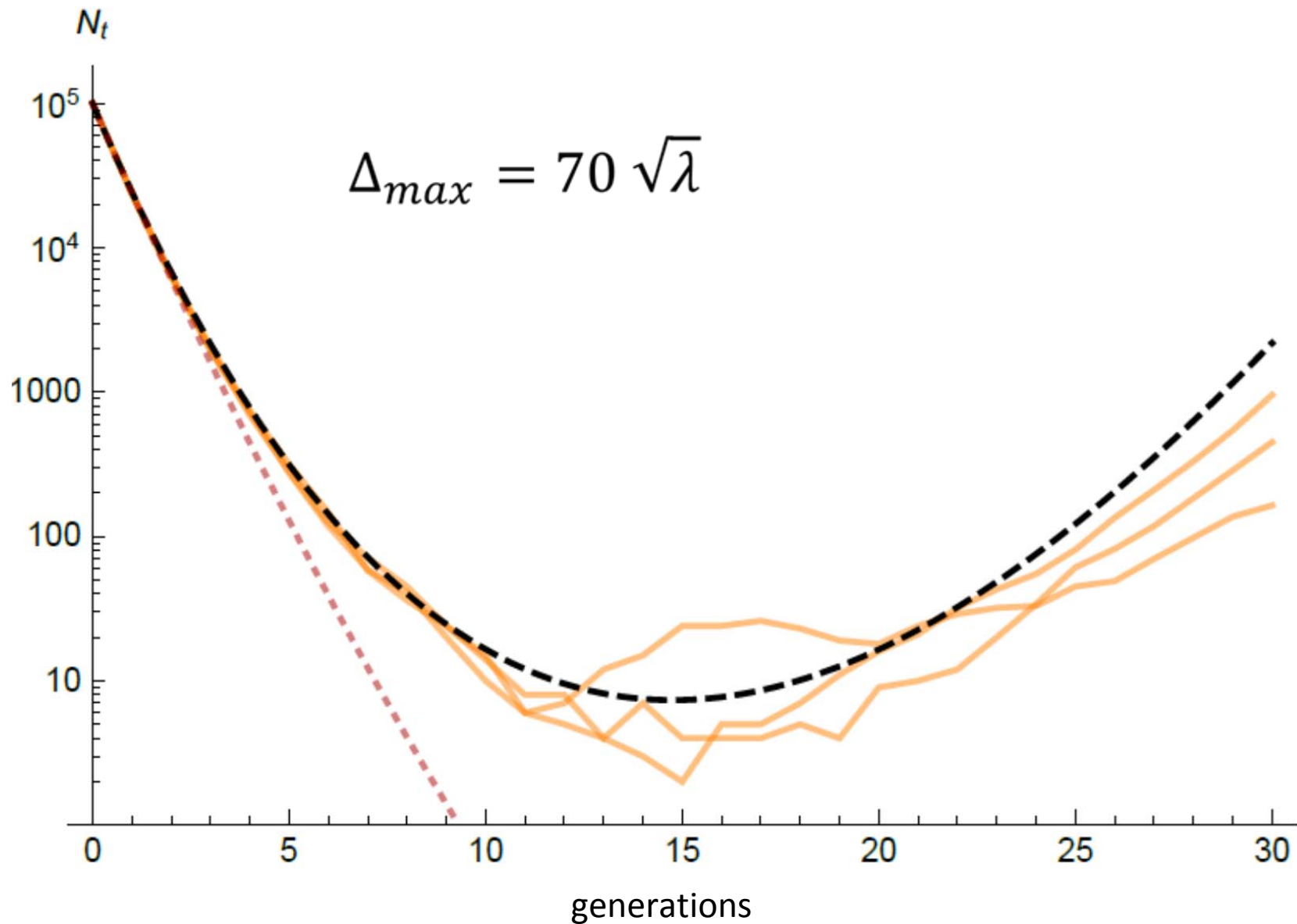
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Population size dynamics

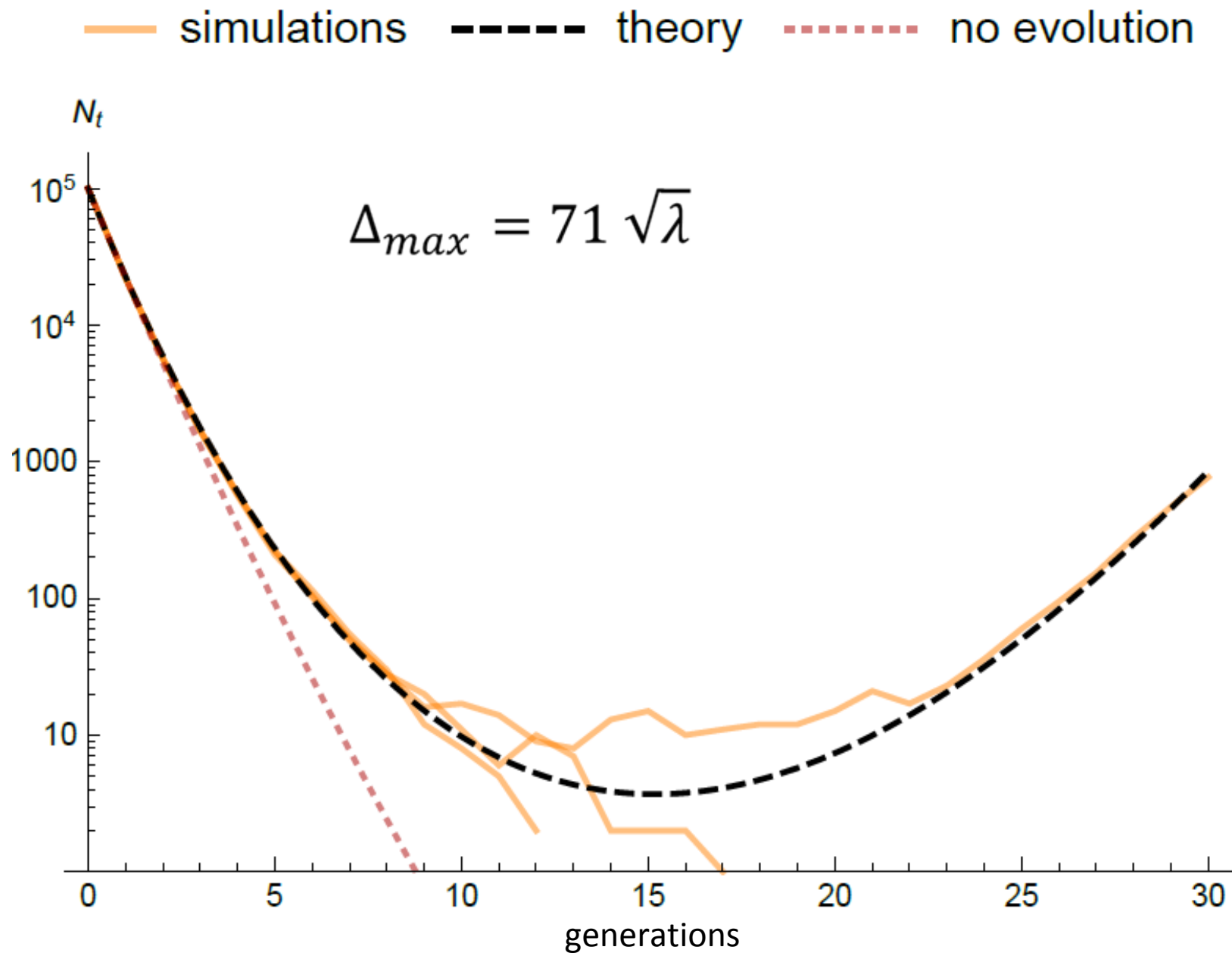
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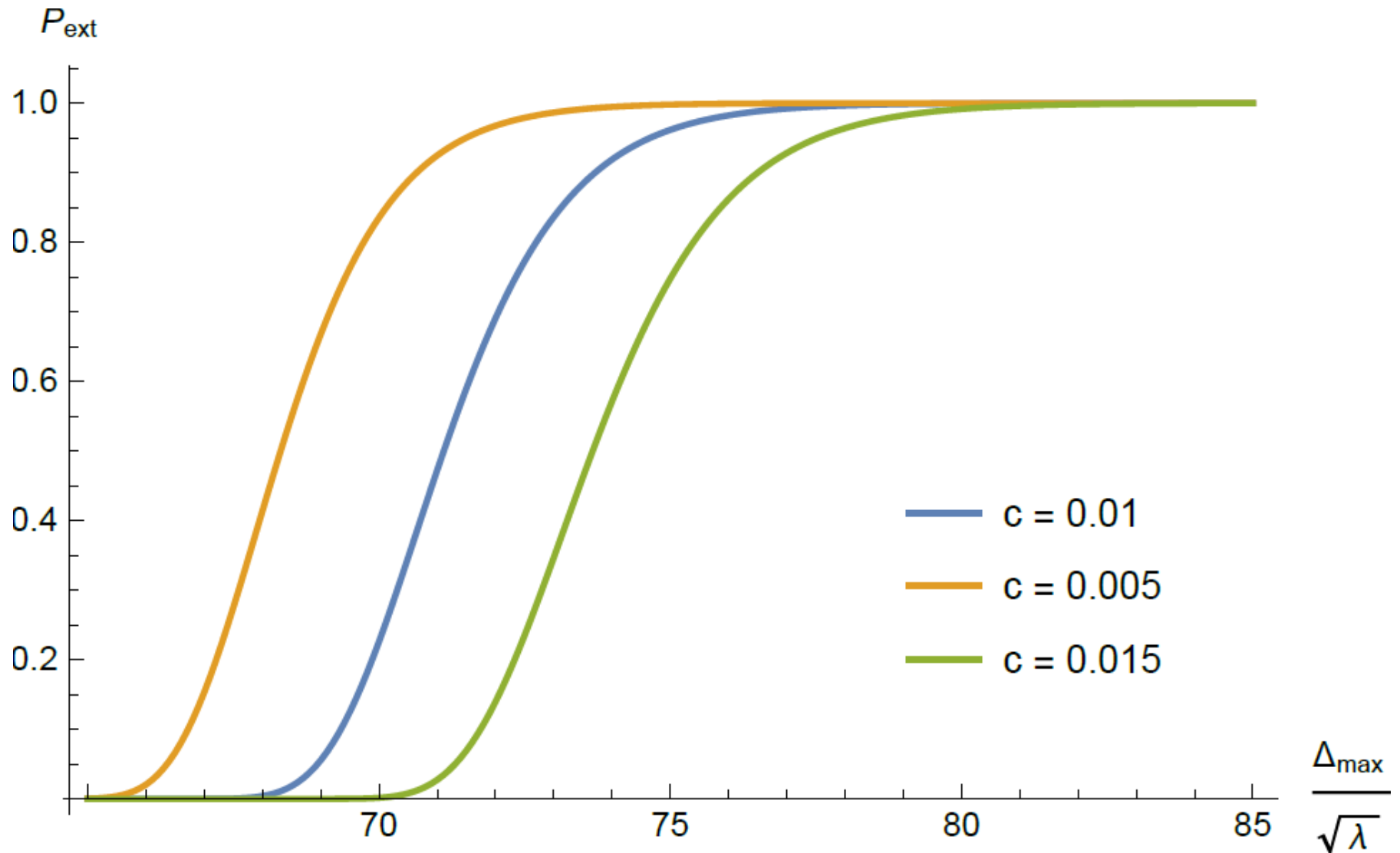


Population size dynamics

From equilibrium



Effect of max dose and dose decay rates



Possible empirical measurements strategies

Key quantities:

Δ_{max}, c, r_{max} : observed population dynamics of a single genotype over time, across doses ?

$n, \lambda, U(\mu)$:

Use mutation accumulation experiments

Use observed fitness distributions at equilibrium

Use adaptation trajectories over time in controlled environment

Use fitness covariance across environments for equilibrium population

Or use P_{ext} profiles across doses (fluctuation test) but requires control of dose

Issue in the wild: not a closed system, effect of immigration...

Perspectives / Limits

- Away from WSSM: Solve PDE , needs efficient numerical solver
- Effect of anisotropy (see eg Matuszewski et al. 2014)
- Stochastic contribution of drift + mutation : a priori pb only below U_c
- Birth dependent mutation rates ?
- Other effects of environment
- density – dependence / epidemiology (SIR etc.): more components (under WSSM) ?
- Migration between environments
- Plasticity and maternal effects (possibly important in unicellulars)
- Fitting empirical CGFs

Thank you