Some mathematical models from population genetics

5: Muller's ratchet and the rate of adaptation

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How many generations will it take for an asexually reproducing population to lose its best class?

Haigh's model

Wright-Fisher model:
Individuals in $(t+1)$st generation select parent at random from generation t.

Probability individual which has accumulated k mutations is selected as parent proportional to *relative fitness* $(1-s)^k$.

Number of mutations carried by offspring then $k+J$, where $J \sim \texttt{Poiss}(\lambda)$ (independent).

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$K_1, K_2, \dots, K_N$ independent copies of $H + J$.
Random type frequencies in next generation are

$$X_k(t+1) = \frac{1}{N}\#\{i : K_i = k\}.$$

Infinite populations

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$$\mathbb{P}[H = k] \propto (1-s)^k x_k = (1-s)^k \frac{\alpha^k e^{-\alpha}}{k!}.$$

Then $H \sim \mathtt{Poiss}(\alpha(1-s))$, $J \sim \mathtt{Poiss}(\lambda)$, so

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Poisson weights $\mapsto$ Poisson weights.

For every initial condition with $x_0 > 0$, the solution to the deterministic dynamics converges as $t \to \infty$ to the stationary point

$$\pi := \texttt{Poiss}(\lambda/s).$$

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Condition on $\mathbf{Y}(t) = \mathbf{y}(t)$. Size of new best class, $y_0(t+1) \sim \texttt{Binom}(N, p_0(t))$, with $p_0(t)$ probability of sampling parent from best class *and* not acquiring any additional mutations:

$$p_0(t) = \frac{y_0(t)}{W(t)} e^{-\lambda}, \quad W(t) = \sum_{i=0}^{\infty} y_i(t)(1-s)^i.$$

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Evolution of best class determined by $W(t)$, the *mean fitness* in the population.

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- **Phase one:** deterministic dynamical system dominates, decaying exponentially fast towards its equilibrium

- **Phase two:** the 'bulk' of the population changes only slowly. Mean fitness assumed constant and then No. of individuals in best class approximated by Galton-Watson branching process with Poisson offspring distribution.

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$k = 0, 1, 2, \ldots$ where $X_{-1} = 0$ and $(W_{jk})_{j>k}$ array of independent Brownian motions, $W_{kj} := -W_{jk}$.

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As before $Y_k = X_{k*+k}$,

$$dY_0 = s(M_1(\mathbf{Y}) - \lambda) Y_0(t) dt + \sqrt{\frac{1}{N} Y_0 (1 - Y_0)} dW_0, \quad M_1(\mathbf{Y}) = \sum_j j Y_j.$$

Infinite population limit

$$dx_k = (s(M_1(\mathbf{x}) - k) - \lambda)x_k + \lambda x_{k-1})\,dt, \quad k = 0, 1, 2, \ldots$$

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Transform into system of equations for cumulants:

$$\log \sum_{k=0}^{\infty} x_k e^{-\xi k} = \sum_{k=1}^{\infty} \kappa_k \frac{(-\xi)^k}{k!}.$$

Assume $x_0 > 0$ and set $\kappa_0 = -\log x_0$. Then

$$\dot{\kappa}_k = -s\kappa_{k+1} + \lambda, \qquad k = 0, 1, 2, \ldots$$

System can be solved. In particular,

$$\kappa_1(t) = \sum_{k=0}^{\infty} k x_k(t) = -\frac{\partial}{\partial \xi} \log \sum_{k=0}^{\infty} x_k(0) e^{-\xi k} \Bigg|_{\xi = st} + \frac{\lambda}{s}(1 - e^{-st}).$$

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Notice the exponential decay towards the equilibrium vaue of λ/s. The time

$$\tau = \frac{\log(\lambda/s)}{s}$$

corresponds exactly to the end of Haigh's phase one.

Approximations

$$dY_0 = s(M_1(\mathbf{Y}) - \lambda)Y_0(t)dt + \sqrt{\frac{1}{N}Y_0(1-Y_0)}dW_0.$$

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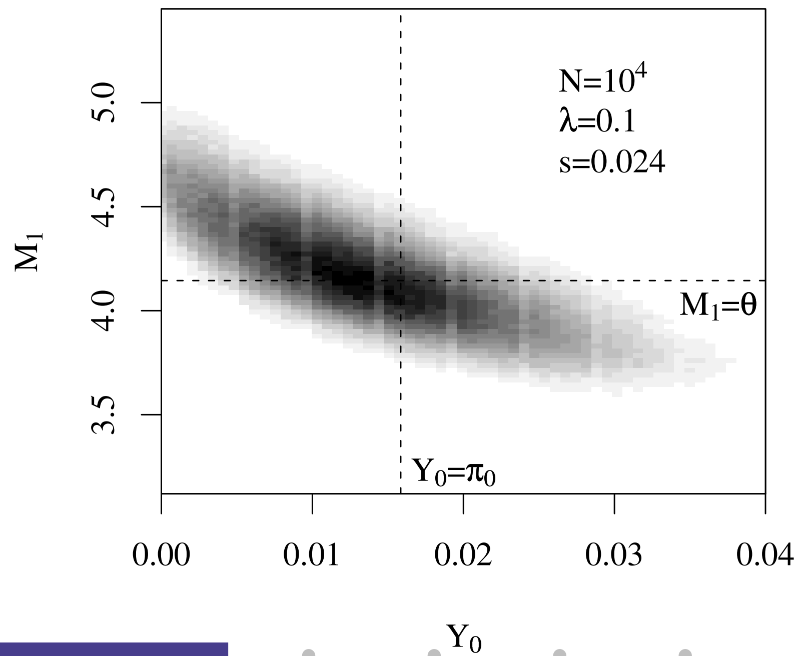
Cannot solve for $M_1(\mathbf{Y})$. Instead seek a *good approximation* of M_1 given Y_0. Simulations suggest a good fit to a linear relationship between Y_0 and M_1.



Extending Haigh's approach

Haigh assumes at click times π_0 distributed evenly over other classes. Suppose now that this holds in between click times too: given Y_0 approximate state of system by *the PPA* (Poisson Profile Approximation)

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Estimate M_1 not from PPA but from *relaxed* PPA obtained by evolving PPA according to the deterministic dynamical system for time $A\tau := A \log(\lambda/s)/s$. This gives

$$M_1 = \theta + \frac{\eta}{e^\eta - 1}\left(1 - \frac{Y_0}{\pi_0}\right), \quad \eta = (\lambda/s)^{1-A}.$$

Three one dimensional diffusions

Substituting in the one-dimensional diffusion approximation for Y_0 gives:

$$A \text{ small}, \qquad dY_0 = \lambda(\pi_0 - Y_0)Y_0 dt + \sqrt{\frac{1}{N} Y_0} dW,$$

$$A = 1, \qquad dY_0 = 0.58 s \left(1 - \frac{Y_0}{\pi_0}\right) Y_0 dt + \sqrt{\frac{1}{N} Y_0}\, dW,$$

$$A \text{ large}, \qquad dY_0 = s \left(1 - \frac{Y_0}{\pi_0}\right) Y_0 dt + \sqrt{\frac{1}{N} Y_0}\, dW,$$

A rescaling

$$Z(t) = \frac{1}{\pi_0} Y_0(N\pi_0 t).$$

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In order for $0.58\frac{1}{\gamma \log(N\lambda)}(N\lambda)^{1-\gamma}$ to be > 5,

γ	0.3	0.4	0.5	0.55	0.6	0.7	0.8	0.9
$N\lambda \geq$	20	10^2	$9 \cdot 10^2$	$4 \cdot 10^3$	$2 \cdot 10^4$	$4 \cdot 10^6$	$2 \cdot 10^{11}$	$8 \cdot 10^{26}$

Rule of thumb

For biologically realistic parameters, transition from no clicks to moderate clicks (on evolutionary timescale) around $\gamma = 0.5$.

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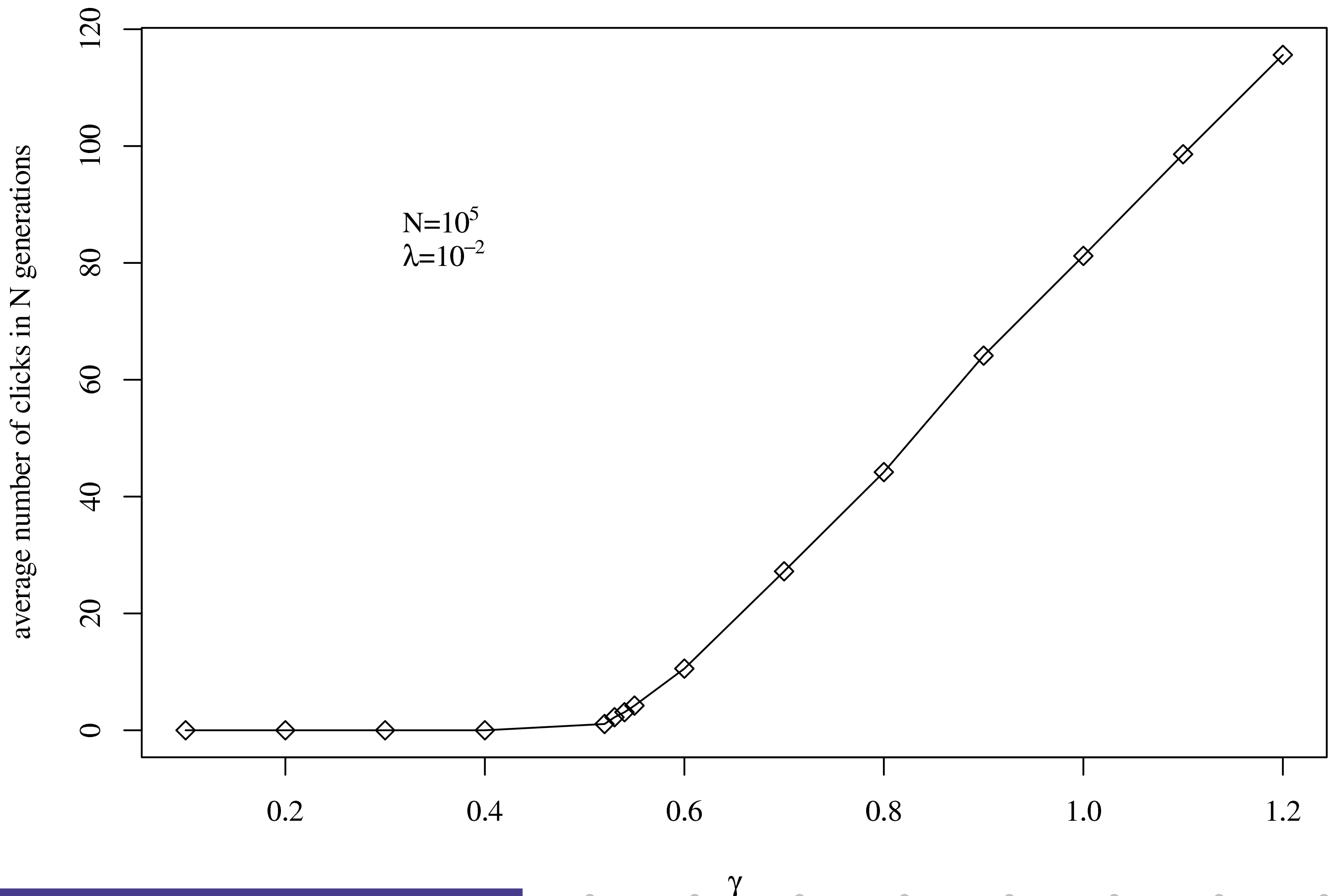
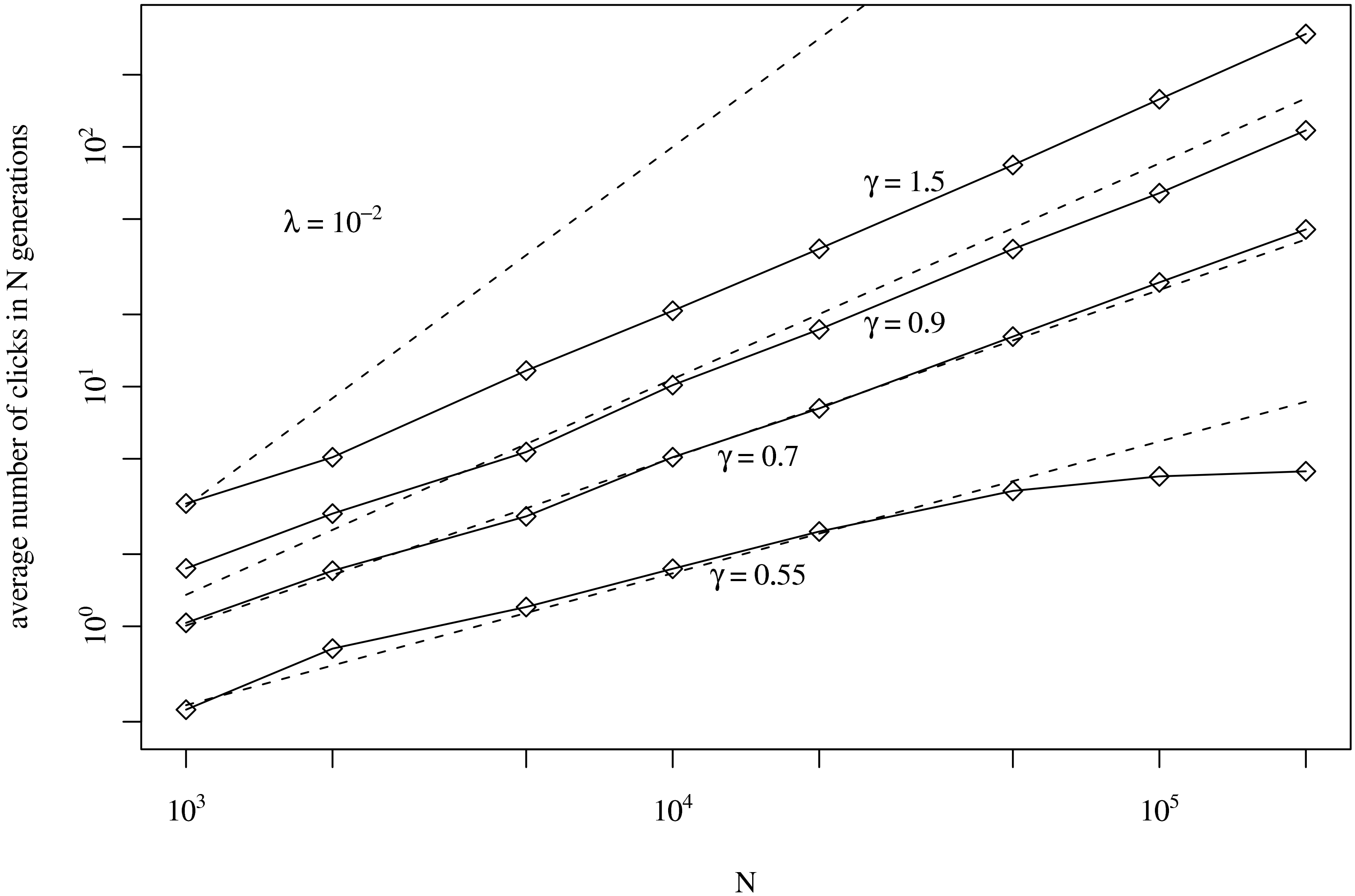
The rate of the ratchet is of the order $N^{\gamma-1}\lambda^{\gamma}$ *for* $\gamma \in (1/2, 1)$*, whereas it is exponentially slow in* $(N\lambda)^{1-\gamma}$ *for* $\gamma < 1/2$*.*

Simulations




average number of clicks in N generations
λ = 10^−2
γ = 1.5
γ = 0.9
γ = 0.7
γ = 0.55
10^0
10^1
10^2
10^3
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N

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Is there a limit to the rate of adaptation?

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- *Selection:* For each pair of individuals (i, j), at rate $\frac{\sigma}{N}(X_i - X_j)^+$, individual i replaces individual j.
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Technical modification: suppress mutations which would make the ‘width’ of the population $> L \equiv N^{1/4}$.

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$$\begin{aligned} dP_k &= \bar{\mu}_k(P)\,dt + \sigma \sum_{l \in \mathbb{Z}} (k-l) P_k P_l\,dt + dM_k^P \\ &= [\bar{\mu}_k(P) + \sigma(k - m(P))P_k]\,dt + dM_k^P \end{aligned}$$

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M^P is a martingale with

$$\left[M_k^P\right](t) \leq \frac{2\mu}{N} t + \frac{1}{N} \int_0^t \sum_{l \in \mathbb{Z}} (2 + \sigma(k-l)^+ + \sigma(l-k)^+) P_k(s) P_l(s)\,ds$$

Moments

Mean fitness $m(P) = \sum_k kP_k$ satisfies

$$\begin{aligned} dm(P) &= (\bar{\mu}(P) + \sigma c_2(P))\, dt + dM^{P,m} \\ \bar{\mu}(P) &\approx \mu(2q - 1) \end{aligned}$$

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Ignoring mutation terms, centred moments $c_k = \sum_k (k - m(p))^n P_k$ satisfy

$$\begin{aligned} dc_2 &\approx \sigma c_3 && dt + small\ noise\ terms \\ dc_3 &\approx \sigma(c_4 - 3c_2c_2) && dt + small\ noise\ terms \\ dc_4 &\approx \sigma(c_5 - 4c_3c_2) && dt + small\ noise\ terms \\ dc_5 &\approx \sigma(c_6 - 5c_4c_2) && dt + small\ noise\ terms \end{aligned}$$

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Stationary distribution approximately Gaussian.

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Ignoring beneficial mutations occurring to individuals at $m(P)+K-1$, until the front advances

$$Z(t) \approx e^{(\sigma K-(1-q)\mu)t}.$$

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But wave speed is

$$\approx \mu(2q-1) + \sigma c_2(P) \approx \mu(2q-1) + \sigma b^2 \approx \mu(2q-1) + \frac{\sigma K^2}{2\log N}.$$

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So K between $\log N$ and any fractional power of $\log N \Rightarrow$ rate of adaptation, of order between $\log N$ and any fractional power of $\log N$.

Rigorous result

Theorem.
If $q > 0$, then for any $\beta > 0$, there exists a positive constant $c_{\mu,\sigma,q}$ such that

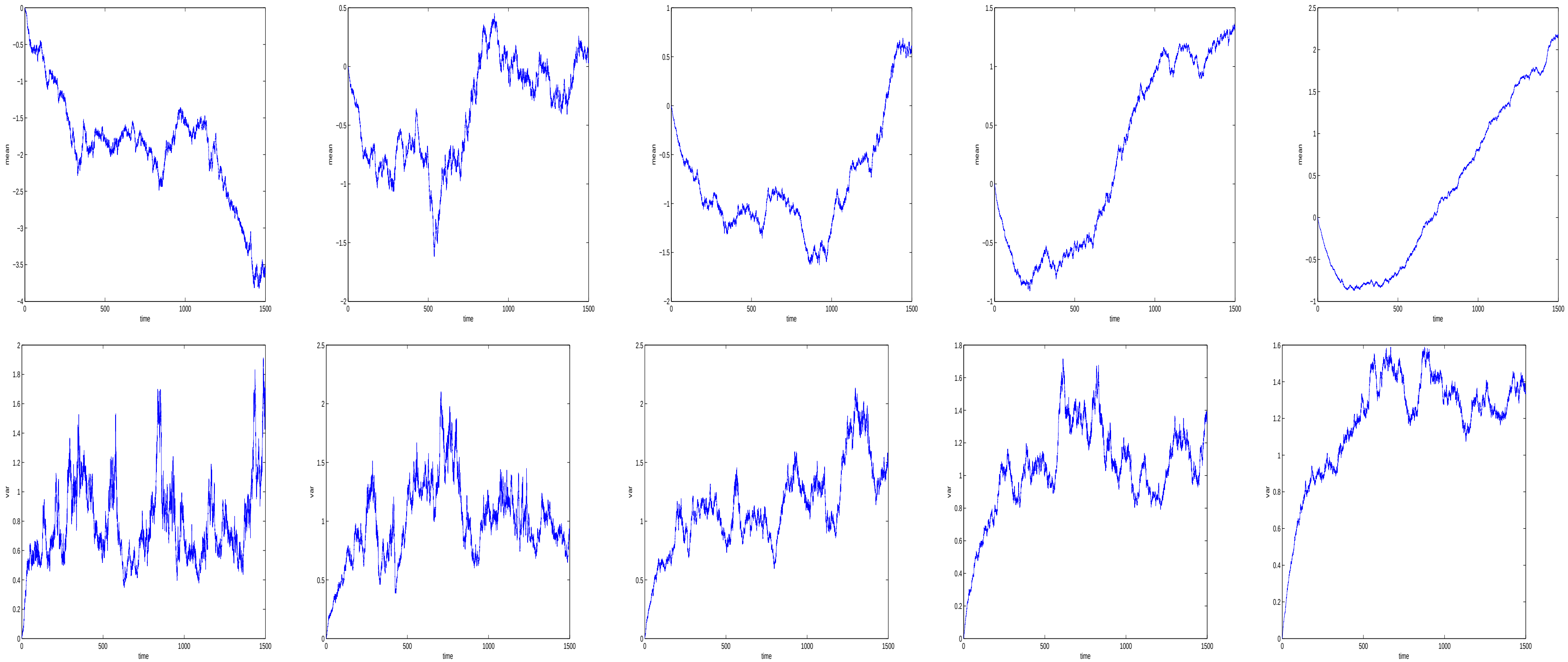
$$\mathbb{E}^{\pi}[m(1)] \geq \mathbb{E}^{\pi}[c_2] \geq c_{\mu,\sigma,q} \log^{1-\beta} N$$

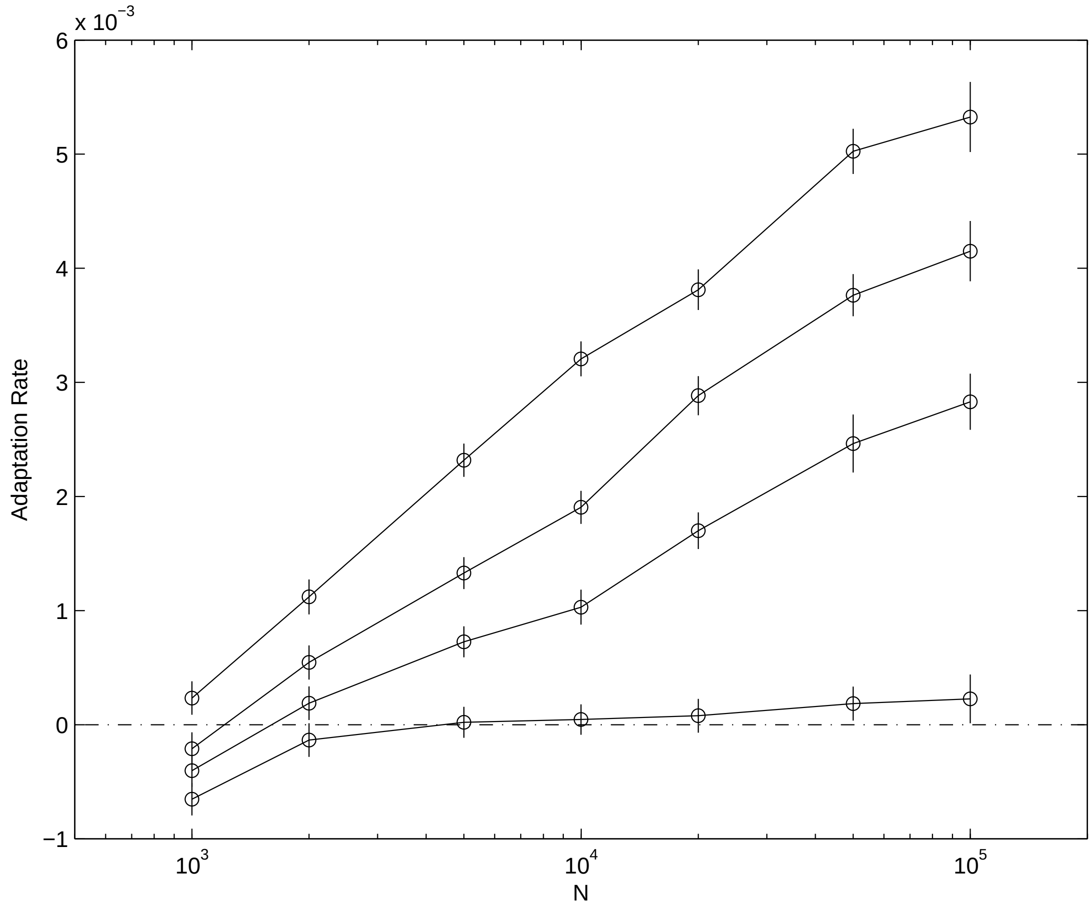
if N is sufficiently large.

Simulations

With $\mu = 0.01$, $q = 0.01$, $\sigma = 0.01$, $N = 1000, 2000, 5000, 10000, 30000$.

First row: mean; second row: variance.





Adaptation rate against population size.

From top to bottom, $q = 4\%, 2\%, 1\%, 0.2\%$, $\mu = 0.01$, $\sigma = 0.01$.