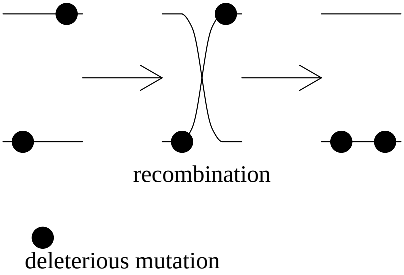
On the rate of Muller's ratchet

facts, heuristics, asymptotics

Joint with Alison Etheridge (Oxford) and Anton Wakolbinger (Frankfurt)

Asexual versus sexual reproduction

- Difference between asexually and sexually reproduction: recombination
- Most mutations **slightly deleterious**



Recombination: production of fit genotypes

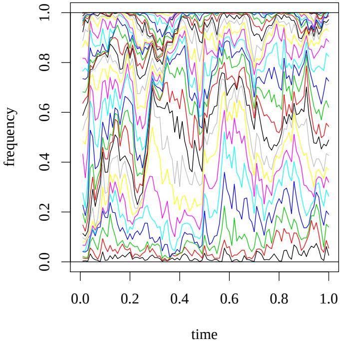
Muller's ratchet

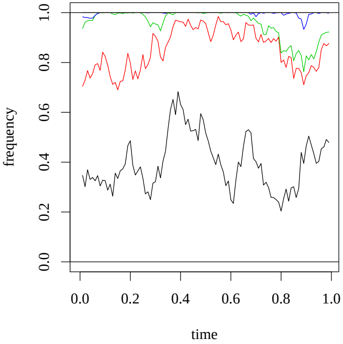
- Asexually reproducing organism
- Y_k: frequency of individuals carrying k mutations
- Individual has k mutations: **fitness** $= (1-s)^k$
- Poisson(λ) **new mutations** for each individual
- If $Y_0 = 0$ there will never again be an individual with 0 mutations

$\longrightarrow$ the **ratchet has clicked**

Muller's ratchet

- Frequent and rare clicks depending on parameters





Muller's ratchet

- **Simple model:** parameters N, s, λ
- **Simple question:** average time between clicks
- **No exact answer** until today!

Haigh (1978)

- $Y_k(t)$: frequency of individuals with k mutations at time t
- **Selection:** $\rightarrow Y_k(t)(1-s)^k$
- **Mutation:** $\rightarrow Y_k(t)(1-s)^k + H$, $H \sim \text{Poisson}(\lambda)$
- $Y_k(t) = \text{Poisson}(\theta)$:
  Selection and mutation: $\rightarrow \text{Poisson}(\theta(1-s)+\lambda)$
- **Fixed point:** $\theta = \frac{\lambda}{s}$

Diffusion approximation

- For large N, small s, λ, approximately:

$$dY_k = \Big(\sum_j s(j-k) Y_j Y_k + \lambda (Y_{k-1} - Y_k) \Big) dt + \sum_{j \neq k} \sqrt{\tfrac{1}{N} Y_j Y_k} \, dW_{jk}$$

  where $Y_{-1} := 0$, and $(W_{jk})_{j>k}, W_{jk} = -W_{kj}$ are independent Brownian motions

- Especially, with $\mathbf{M_1 = \sum jY_j}$,

$$\mathbf{dY_0 = Y_0(sM_1 - \lambda)} + \sqrt{\tfrac{1}{N} Y_0(1-Y_0)} dW$$

Moment equations

- Rate of the ratchet = speed of M_1

→ **find equation for $\mathbf{dM_1}$**

- Speed of M_1 determined by variance:
- With $M_2 = \sum_j (j - M_1)^2 Y_j$,

$$\mathbf{dM_1 = (\lambda - sM_2)dt} + \sqrt{\frac{1}{N} M_2} dW$$

- Without noise, this is seen from:

$$\frac{d \sum_k kY_k}{dt} = \sum_{k,j} sk(j-k) Y_j Y_k + \lambda \sum_k k(Y_{k-1} - Y_k)$$
$$= \lambda - sM_2$$

Including stochastic effects

- Similarly,

$$\mathbf{dM_2 = (-\tfrac{1}{N}M_2 + (\lambda - sM_3))dt} + \sqrt{\tfrac{1}{N}M_3}dW$$

$$\mathbf{dM_3 = (-\tfrac{3}{N}M_3 + (\lambda - s(M_4 - 3M_{2,2}))dt} + \sqrt{\tfrac{1}{N}M_6 + \ldots}dW$$

etc.

- **No closed system of equations!**

Cumulants

- Recall: **Equilibrium is Poisson**
  Only the Poisson distributions has all cumulants equal
- **Cumulants** $\kappa_1, \kappa_2, \ldots$ satisfy

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

- $\kappa_1, \kappa_2, \kappa_3$ are the first three centered moments
- Ignore random effects and compute

$$\frac{d\kappa_k}{dt} = \lambda - s\kappa_{k+1}.$$

$\Rightarrow$ **Linear System!**

Cumulants

- The solution can be computed.
- Especially,

$$x_0(t) = e^{-\kappa_0(t)} = x_0(0)\frac{\exp\big(-\frac{\lambda}{s}(1-e^{-st})\big)}{\Big(\sum_{k=0}^{\infty} x_k(0)e^{-stk}\Big)}$$

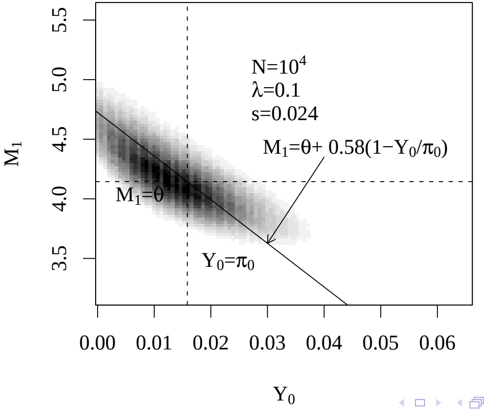
and

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

- **Still no solution including random effects...**

One-dimensional diffusion heuristics

- Equation for Y_0: **prediction of M_1 given Y_0** necessary
- Simulations show **correlation** between M_1 and Y_0:



One-dimensional diffusion heuristics

- Idea from **Haigh (1978)**:
  By random effects, $\mathbf{Y_0 - \pi_0}$ is **distributed on all classes**
- $\Rightarrow$ observed states are of the form

$$\Pi(Y_0) = \big(Y_0, \frac{1 - Y_0}{1 - \pi_0}(\pi_1, \pi_2, \dots)\big)$$

  π_k Poisson weight for parameter $\theta := \frac{\lambda}{s}$
  Poisson profile approximation
- In particular $\mathbf{M_1(Y_0)} = M_1(\Pi(Y_0))$ **can be computed**

One-dimensional diffusion heuristics

- Haigh: observed states are of the form $\Pi(Y_0)$
- However: **Random effects and dynamical system interact**

- Our idea: **observed states are of the form**

$$\mathbf{\Pi(Y_0)S_\tau}$$

for some τ (S: semigroup of dynamical system)

One-dimensional diffusion heuristics

- Use **explicit solution** of dynamical system: observed states have

$$M_1(\tau) = \theta + \frac{\eta}{e^\eta - 1}\Big(1 - \frac{y_0(\tau)}{\pi_0}\Big).$$

for $\tau := \frac{A}{s}\log\theta$ and $\boldsymbol{\eta := \theta^{1-A}}$

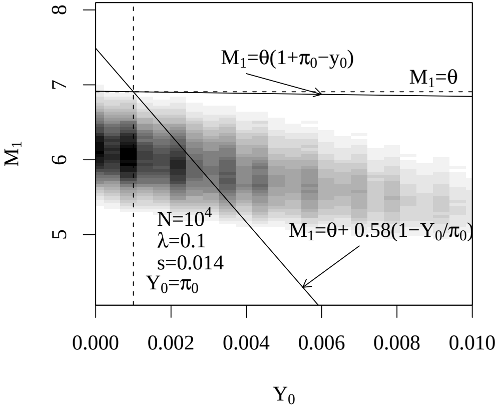
- **Three parameter regimes:**

$$A \text{ small}, \qquad \eta \approx \theta, \qquad M_1 \approx \tfrac{\theta}{1-\pi_0}(1 - Y_0),$$
$$A = 1, \qquad \eta = 1, \qquad M_1 \approx \theta + 0.58\Big(1 - \frac{Y_0}{\pi_0}\Big),$$
$$A \text{ big}, \qquad \eta \approx 0, \qquad M_1 \approx \theta + \Big(1 - \frac{Y_0}{\pi_0}\Big)$$

- Corresponding one-dimensional diffusions:

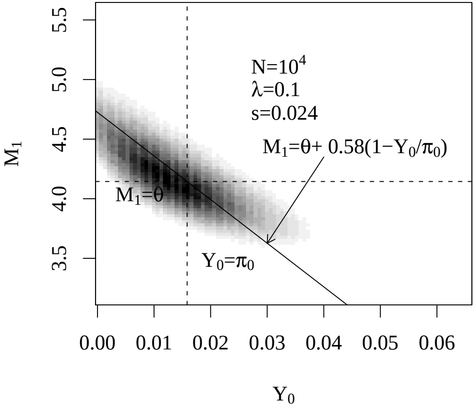
$$A \text{ small}, \qquad dY_0 = \lambda(\pi_0 - Y_0)Y_0 dt + \sqrt{\tfrac{1}{N} Y_0} dW,$$
$$A = 1, \qquad dY_0 = 0.58s\Big(1 - \frac{Y_0}{\pi_0}\Big)Y_0 dt + \sqrt{\tfrac{1}{N} Y_0}\, dW_0,$$
$$A \text{ big}, \qquad dY_0 = s\Big(1 - \frac{Y_0}{\pi_0}\Big)Y_0 dt + \sqrt{\tfrac{1}{N} Y_0}\, dW_0,$$

- **A small:** no time for the dynamical system to relax to equilibrium $\Leftrightarrow$ **frequent clicks**



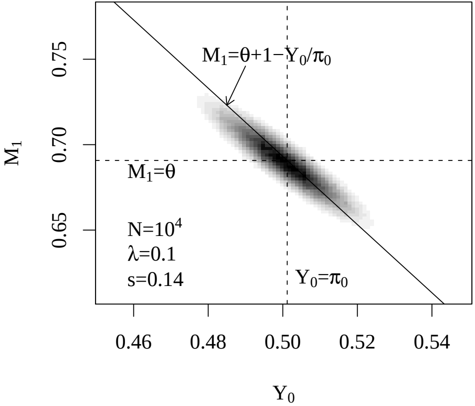
$Ns\pi_0 = 0.11$

- **$A = 1$: speed for relaxation equal to speed of noise**
- See also by Stephan et al. and Gordo and Charlesworth



$N s \pi_0 = 3.7$

- **A big:** system cannot exit equilibrium ⇔ **rare clicks**



$$N s \pi_0 = 685$$

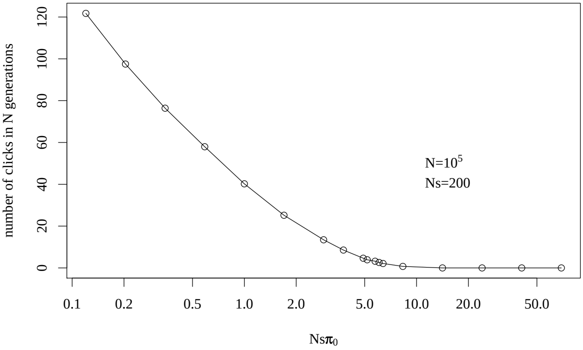
- Use **rescaling**

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

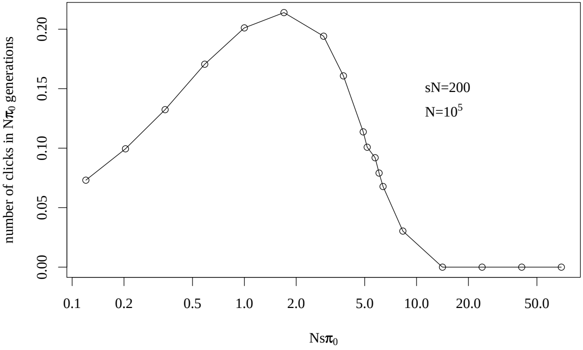
- Consider the intermediate regime $A = 1$

$$A = 1:\ dZ = 0.58 N s \pi_0 (1 - Z) Z d\tau + \sqrt{Z} dW.$$

- Consider $\lambda, s \to 0$, $\mathbf{N \to \infty}$
- Clicks only for small $Ns\pi_0$



- Consider $\lambda, s \to 0$, $\mathbf{N} \to \infty$
- In case of clicks, interclick time is of order $N\pi_0$



Conclusion

- **Exact rate of the ratchet still not obtained**, but
- **Conjecture:**

$$N s \pi_0 = \mathcal{O}(1) \Longrightarrow \text{ Interclick time } \mathcal{O}(N\pi_0)$$
$$N s \pi_0 \gg 1 \Longrightarrow \text{ Interclick time } \gg N\pi_0$$