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

deleterious mutation
Muller’s ratchet

- Asexually reproducing organism
- $Y_k$: frequency of individuals carrying $k$ mutations
- Individual has $k$ mutations: \textbf{fitness} $= (1 - s)^k$
- Poisson($\lambda$) new mutations for each individual
- If $Y_0 = 0$ there will never again be an individual with 0 mutations
  $\rightarrow$ the ratchet has clicked
Muller’s ratchet

- Frequent and rare clicks depending on parameters

On the rate of Muller’s ratchet

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Muller’s ratchet

- **Simple model:** parameters $N, s, \lambda$
- **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**: $Y_k(t)(1 - s)^k$
- **Mutation**: $Y_k(t)(1 - s)^k + H$, $H \sim \text{Poisson}(\lambda)$
- $Y_k(t) = \text{Poisson}(\theta)$:
  - Selection and mutation: $\text{Poisson}(\theta(1 - s) + \lambda)$
- **Fixed point**: $\theta = \frac{\lambda}{s}$
Diffusion approximation

- For large $N$, small $s$, $\lambda$, approximately:

$$dY_k = \left( \sum_j s(j - k) Y_j Y_k + \lambda(Y_{k-1} - Y_k) \right) dt$$

$$+ \sum_{j \neq k} \sqrt{\frac{1}{N}} Y_j Y_k \, dW_{jk}$$

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

- Especially, with $M_1 = \sum j Y_j$,

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

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Moment equations

- Rate of the ratchet = speed of $M_1$
- \textbf{find equation for $dM_1$}
- Speed of $M_1$ determined by variance:
- With $M_2 = \sum_j (j - M_1)^2 Y_j$,

$$dM_1 = (\lambda - sM_2)dt + \sqrt{\frac{1}{N}}M_2dW$$

- 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,

\[
\begin{align*}
\mathrm{d}M_2 &= \left( -\frac{1}{N} M_2 + (\lambda - s M_3) \right) \mathrm{d}t + \sqrt{\frac{1}{N}} M_3 \, \mathrm{d}W \\
\mathrm{d}M_3 &= \left( -\frac{3}{N} M_3 + (\lambda - s (M_4 - 3M_{2,2})) \right) \mathrm{d}t + \sqrt{\frac{1}{N}} M_6 + \ldots \, \mathrm{d}W 
\end{align*}
\]

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

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

⇒ **Linear System!**
Cumulants

- The solution can be computed.
- Especially,

\[ x_0(t) = e^{-\kappa_0(t)} = x_0(0) \frac{\exp \left( - \frac{\lambda}{s} (1 - e^{-st}) \right)}{\left( \sum_{k=0}^{\infty} x_k(0) e^{-stk} \right)} \]

and

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

- **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 $Y_0$:

\[ M_1 = \theta + 0.58(1 - \frac{Y_0}{\pi_0}) \]
One-dimensional diffusion heuristics

- Idea from **Haigh (1978):**
  By random effects, \( Y_0 - \pi_0 \) is **distributed on all classes**
  \[ \Rightarrow \text{observed states are of the form} \]
  \[ \Pi(Y_0) = (Y_0, \frac{1 - Y_0}{1 - \pi_0} (\pi_1, \pi_2, \ldots)) \]

  \( \pi_k \) Poisson weight for parameter \( \theta := \frac{\lambda}{s} \)

  **Poisson profile approximation**

- In particular \( M_1(Y_0) = M_1(\Pi(Y_0)) \) 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**

$$\Pi(Y_0)S_\tau$$

for some $\tau$ ($S$: semigroup of dynamical system)
One-dimensional diffusion heuristics

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

\[ M_1(\tau) = \theta + \frac{\eta}{e^\eta - 1} \left( 1 - \frac{y_0(\tau)}{\pi_0} \right). \]

for \( \tau := \frac{A}{s} \log \theta \) and \( \eta := \theta^{1-A} \)
Three parameter regimes:

- **A small**, \( \eta \approx \theta \), \( M_1 \approx \frac{\theta}{1 - \pi_0} (1 - Y_0) \),
- **A = 1**, \( \eta = 1 \), \( M_1 \approx \theta + 0.58 \left( 1 - \frac{Y_0}{\pi_0} \right) \),
- **A big**, \( \eta \approx 0 \), \( M_1 \approx \theta + \left( 1 - \frac{Y_0}{\pi_0} \right) \)

Corresponding one-dimensional diffusions:

- **A small**, \( dY_0 = \lambda (\pi_0 - Y_0) Y_0 dt + \sqrt{\frac{1}{N}} Y_0 dW \),
- **A = 1**, \( dY_0 = 0.58 s \left( 1 - \frac{Y_0}{\pi_0} \right) Y_0 dt + \sqrt{\frac{1}{N}} Y_0 dW_0 \),
- **A big**, \( dY_0 = s \left( 1 - \frac{Y_0}{\pi_0} \right) Y_0 dt + \sqrt{\frac{1}{N}} Y_0 dW_0 \),
A small: no time for the dynamical system to relax to equilibrium ⇔ frequent clicks

\[ N_s \pi_0 = 0.11 \]
- **A = 1**: speed for relaxation equal to speed of noise
- See also by Stephan et al. and Gordo and Charlesworth

\[
N = 10^4, \quad \lambda = 0.1, \quad s = 0.024
\]

\[
M_1 = \theta + 0.58(1 - \frac{Y_0}{\pi_0})
\]

\[
Ns\pi_0 = 3.7
\]
A big: system cannot exit equilibrium ⇔ rare clicks

\[ Ns\pi_0 = 685 \]
Use **rescaling**

\[ Z(t) = \frac{1}{\pi_0} Y_0\left(\frac{t}{N\pi_0}\right) \]

Consider the intermediate regime \( A = 1 \)

\[ A = 1: \, dZ = 0.58 Ns\pi_0 (1 - Z) Zd\tau + \sqrt{Z} dW. \]
Consider $\lambda, s \to 0$, $N \to \infty$

Clicks only for small $N s \pi_0$
Consider $\lambda, s \to 0, \ N \to \infty$

In case of clicks, interclick time is of order $N\pi_0$
Conclusion

- Exact rate of the ratchet still not obtained, but

- Conjecture:

\[ Ns\pi_0 = O(1) \iff \text{Interclick time } O(N\pi_0) \]
\[ Ns\pi_0 \gg 1 \iff \text{Interclick time } \gg N\pi_0 \]