Link between (Muller's ratchet) Fleming Viot model and lookdown

LATP

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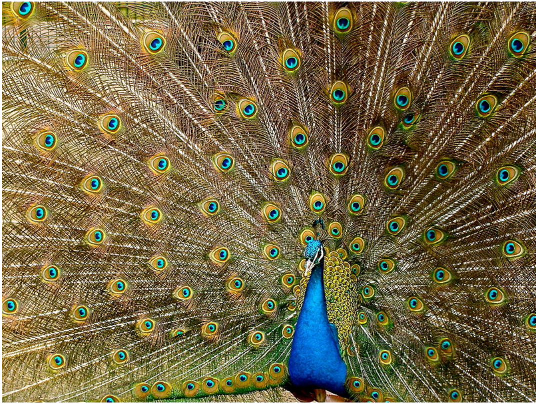
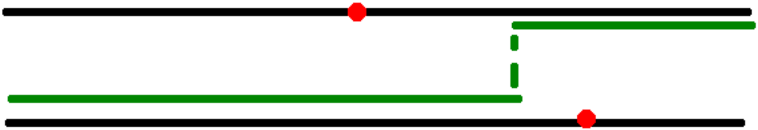
So one may think that the sexual reproduction should be an advantage. But this reproduction costs a lot of ressources.



one possible clue : recombination



Then maybe in an asexual population, deleterious mutation accumulate, and the fitness decreases ?
That is the purpose of Muller's ratchet model.

Plan

1. Introduction
   - Muller's ratchet (Haigh's model)
   - Muller's ratchet (Fleming Viot)
2. Modified look-down
   - Definition
   - Proof (ideas)
   - A more general result

Hypothesis (Biological) : The population has a fixed sized N, is haploid and asexual.
Only the deleterious mutations happen (the beneficial are really rare). They are all identical and cumulative.
Studying the fitness is the same as studying the number of mutations.

This model is in discrete time (generations).
$1 \geq \alpha \geq 0$ and $\lambda \geq 0$ are parameters. We note η_k^N the number of deleterious mutations of the individual k.

At each generation : Each indivual choses a parent from the previous generation with probability to chose the individual k

$$\frac{(1-\alpha)^{\eta_k^N}}{\sum_{l=0}^{N}(1-\alpha)^{\eta_l^N}}$$

Each individual has a number of mutations equals to the number of his parent + $P(\lambda)$.

In this model, at each generation the ratchet clicks with a probability $\geq \left(\lambda e^{-\lambda}\right)^N$. (this is the case where everyone gets at least one mutation)
So the ratchet will click infinitely many times a.s.
This means that the fitness of the population $\rightarrow -\infty$.

Plan

The model studied here is the following continuous time Fleming Viot model, proposed by Etheridge, Pfaffelhuber, Wakolbinger. It is an diffusion approximation of the previous model.

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The model studied here is the following continuous time Fleming Viot model, proposed by Etheridge, Pfaffelhuber, Wakolbinger. It is an diffusion approximation of the previous model.
Let $X_k(t)$ be the proportion of individuals with k deleterious mutations at time t,
$\forall k \geq 0$

$$\begin{cases} dX_k = \left[\alpha(\sum_{l=0}^{\infty} lX_l - k)X_k + \lambda(X_{k-1} - X_k)\right] dt + \sum_{l \in \mathbb{N}} \sqrt{\frac{X_k X_l}{N}} dB_{k,l} \\ X_k(0) = x_k. \end{cases}$$

Where $\{B_{k,\ell,k>\ell\geq 0}\}$ are independent Brownian motions, and $B_{k,\ell} = -B_{\ell,k}$, Note that these equations are equivalent to

$$\begin{cases} dX_k = [\alpha(M_1 - k)X_k + \lambda(X_{k-1} - X_k)]\, dt + \sqrt{\dfrac{X_k(1-X_k)}{N}} dB_k, \\ X_k(0) = X_k^0 \end{cases}$$

with $M_1(t) = \sum_k kX_k(t)$ the mean number of mutations in the population at time t,
and B_k are standard Brownian motions, such that $\forall k \neq l$
$\langle dX_k, dX_l \rangle (t) = -X_k X_l dt$

P. Pfaffelhuber P.Staab . A. Wakolbinger have shown that if $(x_k)_{k\in\mathbb{Z}_+} \in \mathbb{R}_+^{\mathbb{Z}_+}, \sum_{k\geq 0} x_k = 1$, and $\exists \rho > 0$ such that $\sum_{k\geq 0} e^{\rho k} x_k < \infty$, then our problem is well posed (in fact it may be enough that $\sum k^{2+\varepsilon} x_k < \infty$).
The following theorem was proved in a previous speech :

Theorem

Let $T_0 = \{\inf t \geq 0, X_0(t) = 0\}$. *There exists* $\rho > 0$, *such as for any initial condition* $(x_k)_{k\in\mathbb{N}}$ *as above,* $\mathbb{E}(e^{\rho T_0}) < +\infty$.

But where does this equation come from ? Looking at the equation, one can see that :

$$dX_k = \Big[\underbrace{\alpha(M_1 - k)X_k}\, + \lambda(X_{k-1} - X_k)\Big]\, dt + \sqrt{\frac{X_k(1-X_k)}{N}}\, dB_k,$$

is the selection term.

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is the mutation term.

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$$dX_k = [\alpha(M_1 - k)X_k + \lambda(X_{k-1} - X_k)]\, dt + \underbrace{\sqrt{\frac{X_k(1 - X_k)}{N}} dB_k}, $$

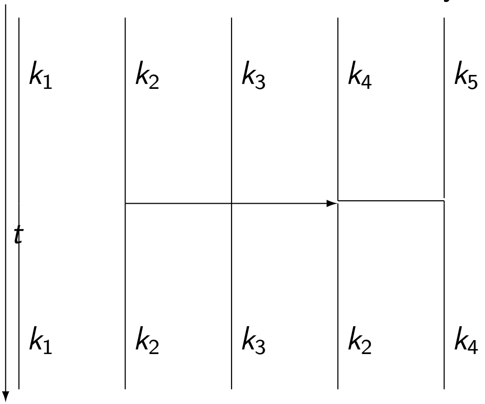
is the resampling term.

The purpose this time is to match this model with the lookdown. In fact we can even take a more general model :

$$\begin{cases} dX_k = [\alpha(M_1 - k)X_k + \lambda(X_{k-1} - X_k)]\, dt + \gamma(X_{k+1} - X_k \mathbb{1}_{k\neq 0}) \\ \qquad\qquad + \sqrt{\dfrac{X_k(1-X_k)}{N}} dB_k, \\ X_k(0) = X_k^0 \end{cases}$$

Plan

We will study a modified look-down model. It has a discrete population but a continuous time.
This model was first introduced by Donnelly and Kurtz.



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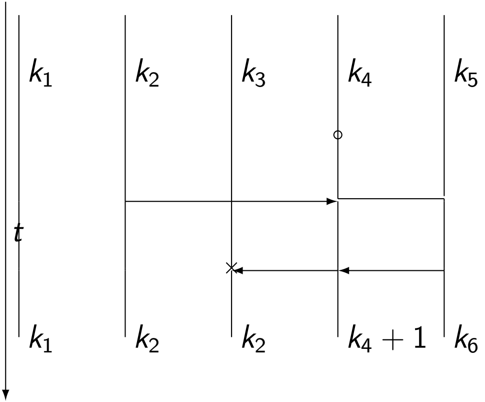
The asymetry is not a problem thanks to exchangeability.

We add unbounded selection and mutations (both deleterious and compensatory).



We denote by X_k^n the proportion of individuals with k deleterious mutations among the model of size n.
and η_i^n the number of deleterious mutations carried by the individual sitting on site i at time t.
The infinite population model is no longer clear.

We want to prove that this model is equivalent to the Muller's ratchet Fleming Viot model :
$\forall k \geq 0$

$$\begin{cases} dX_k = \left[\alpha(\sum_{l=0}^{\infty} lX_l - k)X_k + \lambda(X_{k-1} - X_k) + \gamma(X_{k+1} - X_k)\right] dt \\ \qquad + \sum_{l \in \mathbb{N}} \sqrt{\frac{X_k X_l}{N}} dB_{k,l} \\ X_k(0) = x_k. \end{cases}$$

Theorem

$\forall k \geq 0$, $(X_k^n, n \geq 0)$ is tight, and the family of the limits in law is the solution X starting from x of (6).

Theorem

The model L^∞ is well defined, and is the limit of the L^n when $n \to \infty$ as follows : $\forall i > 0$, $\forall t > 0$, $\eta_t^{i,n}$ converges a.s. and we call $\eta_t^{i,\infty}$ its limit. Moreover, it has the exchangeability property, that is to say if the $(\eta_0^{i,\infty})_{i \geq 1}$ are exchangeable, then $\forall t > 0$, the $(\eta_t^{i,\infty})_{i \geq 1}$ are exchangeable. As a consequence,

$$X^\infty \equiv X \text{ (equality in law).}$$

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The proof use several ideas from a paper of B.Bah, E.Pardoux, A.B. Sow, but the conditions here are very different.
First we establish the equations of our system in the modified look-down model of size N :
Let $\left\{P_k^1, P_k^2, P_k^{3,\ell}, P_k^{5,\ell}, k, \ell \geq 0\right\}$ be standard Poisson point processes on $\mathbb{R}_+$, which are mutually independent, except that $P_0^2 = 0$. We also define $\forall k, l \geq 0$ $P_\ell^{4,k} = P_k^{3,\ell}$ and $P_\ell^{5,k} = P_k^{6,\ell}$, and for all $n, j \in \mathbb{Z}_+$, $E_j^n = \sum_{k=0}^{\infty} k^j X_k^n$.
We have :

$$\begin{aligned} X_k^n(t) &= X_k^n(0) + \frac{1}{n} P_{k-1}^1\left(\lambda n \int_0^t X_{k-1}^n(s)ds\right) - \frac{1}{n} P_k^1\left(\lambda n \int_0^t X_k^n(s)ds\right) \\ &+ \frac{1}{n} P_{k+1}^2\left(\gamma n \int_0^t X_{k+1}^n(s)ds\right) - \frac{1}{n} P_k^2\left(\gamma n \int_0^t X_k^n(s)ds\right) \\ &+ \frac{1}{n} \sum_{\ell=0,\ell\neq k}^{\infty} P_k^{3,\ell}\left(\alpha n\ell \int_0^t X_k^n(s)X_\ell^n(s)ds\right) - \frac{1}{n} \sum_{\ell=0,\ell\neq k}^{\infty} P_k^{4,\ell}\left(\alpha nk \int_0^t X_k^n(s)X_\ell^n(s)ds\right) \\ &+ \frac{1}{n} \sum_{\ell=0,\ell\neq k}^{\infty} P_k^{5,\ell}\left(c\frac{n^2}{2} \int_0^t X_k^n(s)X_\ell^n(s)ds\right) - \frac{1}{n} \sum_{\ell=0,\ell\neq k}^{\infty} P_k^{6,\ell}\left(c\frac{n^2}{2} \int_0^t X_k^n(s)X_\ell^n(s)ds\right). \end{aligned}$$

$$X_k^n(t) = X_k^n(0) + \lambda \int_0^t \left(X_{k-1}^n(s) - X_k^n(s) \right) ds + \gamma \int_0^t \left(X_{k+1}^n(s) - X_k^n(s) \right) ds$$
$$+ \alpha \int_0^t X_k^n(s)(M_1^n(s) - k) ds + \mathcal{M}_t^{n,k},$$

$$\left\langle \mathcal{M}^{n,k} \right\rangle_t = \frac{1}{n}\lambda \int_0^t \left(X_{k-1}^n(s) + X_k^n(s) \right) ds + \frac{1}{n}\gamma \int_0^t \left(X_{k+1}^n(s) + X_k^n(s) \right) ds$$
$$+ \frac{1}{n}\alpha \int_0^t X_k^n(s) \left(M_1^n(s) - 2kX_k^n(s) + k \right) ds + c \int_0^t X_k^n(s) \left(1 - X_k^n(s) \right) ds.$$

$$\left\langle \mathcal{M}^{n,k}, \mathcal{M}^{n,\ell} \right\rangle_t = -\frac{1}{n} \mathbb{1}_{|\ell - k| = 1} \lambda \int_0^t X_{k \wedge \ell}^n(s) ds - \frac{1}{n} \mathbb{1}_{|\ell - k| = 1} \gamma \int_0^t X_{k \vee \ell}^n(s) ds$$
$$- \frac{1}{n}\alpha(\ell + k) \int_0^t X_k^n(s) X_\ell^n(s) ds + c \int_0^t X_k^n(s) X_\ell^n(s) ds.$$

$$M_1^n(t) = M_1^n(0) + \lambda t - \gamma \int_0^t (1 - X_0^n(s))ds - \alpha \int_0^t M_2^n(s)ds + \mathcal{M}_t^n$$

$$\langle \mathcal{M}^n \rangle_t = \frac{1}{n}\left(\lambda t + \gamma \int_0^t (1 - X_0)ds + \alpha \int_0^t E_3^n(s)ds - \alpha \int_0^t E_2^n(s) M_1^n(s)ds\right) - c \int_0^t M_2^n(s)ds$$

With this we can prove the following Lemma :

Lemma

$\forall T > 0,\ \forall k > 0,\ \sup_{n\in\mathbb{Z}_+} \sup_{0\le t\le T} \mathbb{E}(E_k^n(t)) < \infty.$

Indeed, with $\Psi_n^C(t,\rho) = \mathbb{E}\left(\sum_{k\ge 0} X_k^n(t)\left(e^{\rho k} \wedge C\right)\right)$,
we obtain $\Psi_n^C(t,\rho) \le \Psi_n^C(0,\rho) + \int_0^t \left(\lambda\left(e^{\rho}-1\right)\right)\Psi_n^C(r,\rho)\,dr$,
hence $\Psi_n(t,\rho) \le \Psi_n(0,\rho)e^{\lambda(e^{\rho}-1)t}$.

Then we can use the Aldous criterion for tightness in $D([0, T])$ (along with Rebolledo criterion):

Proposition

If $\forall T, \varepsilon, \eta > 0\ \exists n_0, \delta > 0$ *such that for any sequence* $\{\tau_n\}_{n\geq 1}$ *of stopping times with* $\tau_n \leq T$*,*

$$\sup_{n\geq n_0} \sup_{\theta\leq\delta} \mathbb{P}\left(|X_k^n(\tau_n) - X_k^n(\tau_n+\theta)| \geq \eta\right) \leq \varepsilon$$

Then X_k^n *is tight in* $D([0, T])$ *(since the jumps are* $\frac{1}{n}$*).*

The second theorem

Theorem

The model L^∞ is well defined, and is the limit of the L^n when $n \to \infty$ as follows : $\forall i > 0$, $\forall t > 0$, $\eta_t^{i,n}$ converges a.s. and we call $\eta_t^{i,\infty}$ its limit. Moreover, it has the exchangeability property, that is to say if the $(\eta_0^{i,\infty})_{i\geq 1}$ are exchangeable, then $\forall t > 0$, the $(\eta_t^{i,\infty})_{i\geq 1}$ are exchangeable.

The first part of the theorem follow from Borel Cantelli Lemma and the following Proposition :

Proposition

$\forall n \geq 64\alpha(M_1^{2n}(0) + 5\sqrt{n})$,

$$\mathbb{P}\left(\exists 1 \leq i \leq \frac{n}{2}, 0 \leq t \leq T \text{ such that } \eta_i^n(t) \neq \eta_i^{2n}(t)\right) \leq n\left(\frac{16\alpha n(M_1^{2n}(0) + 5\sqrt{n})}{cn^2}\right)^{\frac{n}{2}} + p_{2n},$$

with $p_n = \exp(-2\frac{\alpha}{c^2}\sqrt{n}) + 3\exp(-\sqrt{n}) + \frac{T^7}{n^3}(c_3(\lambda, \gamma, \delta))$.
Indeed with Borel Cantelli Lemma,

$$\mathbb{P}\left(\exists N_0, \forall n \geq N_0, \forall 1 \leq i \leq \frac{n}{2}, 0 \leq t \leq T,\ \eta_i^n(t) = \eta_i^{2n}(t)\right) = 1$$

First, note that

$$\left\{\exists 1 \leq i \leq \frac{n}{2}, 0 \leq t \leq T \text{ such that } \eta_i^n(t) \neq \eta_i^{2n}(t)\right\}$$
$$\subset \left\{\exists 1 \leq i \leq n+1, 0 \leq s_0 < s_1 \leq T \text{ such that } \xi_{s_0}^{i,2n} = n, \forall s_0 \leq t \leq s_1 \; n/2 \leq \xi_t^{i,2n} \leq n, \; \xi_{s_1}^{i,2n} = \frac{n}{2}\right\}$$

To prove this Proposition, we need to control birth and death rates in L_n.
We consider the individual which starts at site n and ends at site $n/2$.
The birth rate is greater than $\frac{cn(n-2)}{8}$.
The death rate is lower than $\alpha 2n M_1^{2n}(s)$

So we need to control M_1^{2n}.

Lemma

$\forall n > 0$, $\forall 0 \leq t \leq T$, $\forall C > 0$,

$$\mathbb{P}\left(\sup_{0 \leq r \leq T-t} M_1^n(t+r) - M_1^n(t) \geq 5C\right) \leq \exp(-2\frac{\alpha}{c^2}C) + 3\exp(-C) + \frac{T^7}{C^6}\left(c_3(\lambda,\gamma,\delta)\right).$$

The idea is to write M_1 as a sum of four supermartingales plus a term with a bounded variation.

Now for the exchangeability, we prove four technical Lemmata.

Lemma

For any stopping time τ, any $\mathbb{N}$ valued $\mathcal{F}_\tau$-measurable random variable $\mathcal{X}$, if the random vector $\eta_\tau^{\mathcal{X}} = (\eta_\tau(1), ..., \eta_\tau(\mathcal{X}))$ is exchangeable, and τ' is the first time after τ' of an arrow pointing to a level $\leq \mathcal{X}$, a death or a mutation at a level $\leq \mathcal{X}$, then conditionally upon the fact that τ' is the time of a birth, the random vector $\eta_{\tau'}^{\mathcal{X}+1} = (\eta_{\tau'}(1), ..., \eta_{\tau'}(\mathcal{X}+1))$ is exchangeable.

Now we can improve the convergence by using tightness, de Finetti theorem and some of our previous results. Note that a similar result appears was proved by Donnelli Kurtz. First, from De Finetti Theorem we deduce the following corollary

Corollary

$\forall k \geq 0, \forall T > 0, \forall t \in [0, T]$,

$$X_k^n(t) \to X_k(t) \ a.s. \ .$$

Then we can prove the following Proposition:

Proposition

$\forall k \geq 0, \forall \eta > 0, \forall \varepsilon > 0, \exists n_0 \in \mathbb{N}$ *such as* $\forall n \geq n_0$
$\mathbb{P}(\sup_{0 \leq t \leq T} |X_k^n(t) - X_k(t)| \geq \eta) \leq \varepsilon$

Then with the Dini Theorem we can prove the following Theorem :

Theorem

$\forall T \geq 0$, $sup_{0 \leq t \leq T} \sum_{k \geq 0} |X_k^n(t) - X_k^{\infty}(t)| \to 0$ *in probability.*

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We consider the following events :
For all $k \geq 0$, an individual belongs to the k-th type, he dies at rate α_k. (we suppose that α_k increases with k and that $\alpha_0 = 0$.)
$\forall k, \ell \geq 0$, any individual of type k mutates to the type ℓ at rate $\lambda_k a_{k,\ell}$
For each pair of individuals sitting at sites i and j with $i < j$, at rate c, the leftmost one gives birth to a child with the same type at site j, and for all $j' \geq j$ the individual sitting on site j' is moved one step to the right, and the n-th individual dies.

The Fleming Viot system of SDEs :

$$\begin{cases} dX_{\boldsymbol{k}}(t) = \sum_{\ell=\mathbf{0},\ell\neq\boldsymbol{k}}^{\infty} \lambda_\ell a_{\ell,\boldsymbol{k}} X_\ell(s)ds - \lambda_{\boldsymbol{k}} X_{\boldsymbol{k}}(s)ds + X_{\boldsymbol{k}}(s)\left(M_{\mathbf{1}} - \alpha_{\boldsymbol{k}}\right) ds + c \sum_{\ell\neq\boldsymbol{k}} \sqrt{X_\ell X_{\boldsymbol{k}}} dB_{\boldsymbol{k},\ell} \\ dX_{\boldsymbol{k}}(0) = x_{\boldsymbol{k}} \ \forall k \geq 0, \end{cases} \tag{2.1}$$

with $M_{\mathbf{1}} = \sum_{\boldsymbol{k}\geq\mathbf{0}} \alpha_{\boldsymbol{k}} X_{\boldsymbol{k}}$.

It corresponds to the look-down model under the following hypotheses

$$x \in \mathcal{X} = \cup_{\rho>0}\mathcal{X}_\rho = \cup_{\rho>0}\left\{(x_k)_{k\geq 0},\ \text{such as } \forall k \geq 0, 0 \leq x_k \leq 1, \sum_{k\geq 0} x_k = 1 \text{ and } \sum_{k\geq 0} x_k e^{\rho k} < \infty\right\}.$$

$$\exists C_a > 0, \exists \rho_1 > 0, \forall \ell > 0,\ \sum_{\ell\geq 0} \sup_{k\geq 0} (\lambda_k \vee 1)\, a_{k,k+\ell} e^{\rho_1 \ell} \leq C_a$$

$$\exists Q \in \mathbb{R}[X], \forall k \geq 0 \quad \alpha_k \vee \lambda_k \leq Q(k).$$

$$\sup_{j\geq 0} \sum_{i\geq 0} \lambda_i a_{i,j} < \infty$$

THANK YOU FOR YOUR ATTENTION !