Mittag-Leffler Institute: Olav Kallenberg Symposium

June 24-28, 2013

Multitype mutation-selection-migration dynamics and a set-valued dual

Don Dawson, Carleton University

Based on joint work with Andreas Greven

Scenario and Objective

- Basic object: multitype population distributed in a random environmental space or among colonies (demes).
- Mutation-selection dynamics and quasiequilibria of type distributions.
- Interaction among subpopulations.
- Multistage emergence and propagation of new types leading to new quasiequilibria.
- Examples of emergence: new viral strains, invasive species, protooncogenes in cell growth.
- Objective: to analyse a class of models exhibiting this behaviour and to determine conditions under which emergence occurs and to characterize the rate at which new types propagate.

A Spatial Models

The *Wright-Fisher two-type diffusion stepping stone model with selection*

We begin with a system of subpopulations located at sites in a finite or countable set S and given by the system of sde:

$$\begin{aligned} dx_\xi(t) = c \cdot \sum_{\xi' \in S} q_{\xi',\xi}(x_{\xi'}(t) - x_\xi(t))dt \quad & \textit{migration} \\ + s \cdot x_\xi(t)(1 - x_\xi(t))dt \qquad & \textit{selection} \\ + \sqrt{\gamma x_\xi(t)(1 - x_\xi(t))}\, dw_\xi(t) \quad & \textit{genetic drift} \\ x_\xi(0) \in [0,1] \quad \forall \xi \in S \end{aligned}$$

where $x_\xi(t)$ = proportion of type 1 at site $\xi \in S$ at time t.

The multitype model

Spatial multitype population with mutation and migration, haploid selection and genetic drift:

- Type space: $\mathbb{I}$

  Ex. $\mathbb{I} = E_0 \cup E_1, \; E_0 = \{1, \dots, M\}, \; E_1 = \{M+1, \dots, K\}$

- Spatial sites: $S = \{1, \dots, N\}$ or countable abelian group.

- Mutation rates $i \to j$: $\quad m_{i,j}$,

- Migration rates $\xi \to \xi' \neq \xi$: $\quad c \cdot q_{\xi,\xi'}$

- Fitness of type j: $\quad s \cdot e_j \quad , 0 \leq e_j \leq 1$

  $$e_j = 1 \text{ if } j \in E_1, \; e_j < 1 \text{ if } j \in E_0;$$

- Genetic drift: $\quad \gamma \quad$ (“inverse population size”)

Local mutation-selection dynamics at a site 1

The Wright-Fisher diffusion $X_t(1)$ satisfies the G^0-martingale problem where G^0 acting on a C^2-functions f on the simplex

$\Delta_{K-1} = \{(x_1, \ldots, x_K),\ x_i \geq 0, \sum_{i=1}^{K} x_1 = 1\} = \mathcal{P}(\mathbb{I})$ as follows:

$$
\begin{aligned}
G^0 f(\mathbf{x}) \qquad &= \sum_{i=1}^{K} \left(\sum_{j=1}^{K} (m_{ji} x_j - m_{ij} x_i) \right) \frac{\partial f(\mathbf{x})}{\partial x_i} \quad \text{mutation} \\
&+ s \sum_{i=1}^{K} x_i \left(e_i - \sum_{k=1}^{K} e_k x_k \right) \frac{\partial f(\mathbf{x})}{\partial x_i} \quad \text{selection} \\
&+ \frac{\gamma}{2} \sum_{i,j=1}^{K} x_i (\delta_{ij} x_j - x_j) \frac{\partial^2 f(x)}{\partial x_i \partial x_j} \quad \text{genetic drift}
\end{aligned}
$$

$\gamma = 0$ - replicator-mutator equations (e.g. Hofbauer-Sigmund)

Spatial Model

Interacting system on a finite or countable abelian group S.

Migration rates: $c \cdot q_{\xi',\xi}$ if $\xi \neq \xi' \in S$.

The generator for the spatial model: for $f \in C^2((\Delta_{K=1})^S)$

$$
\begin{aligned}
&G^{\text{spat}} f(\mathbf{x}(1), \ldots, \mathbf{x}(|S|)) \\
&= \sum_{\xi \in S} G^0_\xi f(\ldots, \mathbf{x}(\xi), \ldots) \qquad \text{mutation-selection dynamics at each site} \\
&\quad + c \cdot \sum_{\xi \in S} \left[\sum_{j=1}^{K} \left(\sum_{\xi' \in S} q_{\xi',\xi}\, x_j(\xi') - x_j(\xi) \right) \frac{\partial f(\vec{\mathbf{x}})}{\partial x_j(\xi)} \right] \qquad \text{migration.}
\end{aligned}
$$

The martingale problem has a unique solution that defines a continuous strong Markov process with Feller semi-group on $C((\Delta_{K-1})^S)$.

Theorem 1.

(a) Assume that the initial state satisfies $(\mathbf{x}_1(0), \ldots, \mathbf{x}_N(0))$ is concentrated on E_0. Then under positive mutation rates on E_0 the system is ergodic and converges to a unique equilibrium $\mathcal{P}_{eq}$ on $(\Delta_{|E_0|-1})^S$.

(b) Consider S is a countable abelian group with random walk migration kernel and $c > 0$. If the fitness values of a finite transient class (wrt mutation MC) are sufficiently large, then the class can survive (that is, non-ergodicity). (Generalizes a result of Shiga-Uchiyama.)

Proof: Uses the set-valued dual process.

Questions

- Emergence of rare mutants (e.g. E_1)
- Determination of emergence rate β.

Exchangeable migration dynamics: (Wright's island model)

Interacting system on N sites (islands) $S = \{1, \ldots, N\}$.

Migration rates: $c \cdot q_{\xi',\xi} = \frac{c}{N-1}$ if $\xi \neq \xi'$, $c \geq 0$.

Empirical Process

We assume that the initial state satisfies $(\mathbf{x}_1(0), \ldots, \mathbf{x}_N(0))$ is exchangeable.

$$\Xi^N(t) := \frac{1}{N} \sum_{j=1}^{N} \delta_{\mathbf{x}_j(t)} \in \mathcal{P}(\mathcal{P}(\mathbb{I})).$$

$\Xi^N(t)$ is a $\mathcal{P}(\mathcal{P}(\mathbb{I}))$-valued Markov process.

The McKean-Vlasov equation arises as the limit dynamic as $N \to \infty$ and the dynamics at a tagged site is a nonlinear Markov process.

The McKean-Vlasov limit and its equilibria

Theorem 1. (Convergence in time scale $O(1)$)

$$\{\Xi^N(t)\}_{t\in[0,T]} \Rightarrow (\mathcal{L}_t)_{t\in[0,T]} \quad \text{as } N \to \infty$$

where $\mathcal{L}_t(dx) = u(t,\mathbf{x})d\mathbf{x} \in C([0,T],\mathcal{P}(\Delta_{K-1}))$ is a weak solution of the *McKean-Vlasov equation*:

$$\frac{\partial u(t,\mathbf{x})}{\partial t} \qquad = G^* u(t,\mathbf{x}) - c\sum_{i=1}^{K} \frac{\partial}{\partial x_i}\left(\pi_i(u(t)) - x_i)u(t,\mathbf{x})\right)$$

where $\pi_i(u(t)) = \int\limits_{\Delta_{K-1}} \widetilde{x}_i u(t,d\widetilde{\mathbf{x}})$ and G^* is the adjoint of G^0.

Tagged site: Δ_{K-1}-valued nonlinear Markov process (in the sense of McKean).

Ergodic theorem

If E_0 is irreducible and $c \geq 0$, then $u(t,\cdot) \Rightarrow u_{\text{equil}}(\cdot)$.

The "equilibrium" is actually a quasi-equilibrium.

Emergence of advantageous mutants:

Assume $x(0,E_0)=1,\ \{m_{ij}\}$ irreducible, and $c\geq 0$.

$E_0 \to E_1$ – rate $\frac{\bar{m}}{N}$

$$\begin{aligned} G^{*,\bar{m},N}f(\mathbf{x}) \qquad &= \frac{\bar{m}}{N}\sum_{i=M+1}^{K}\left(\sum_{j=1}^{M} m^*_{ji}x_j\right)\frac{\partial f(\mathbf{x})}{\partial x_i} \\ &-\frac{\bar{m}}{N}\sum_{j=1}^{M}\left(\sum_{i=M+1}^{K} m^*_{ji}x_j\right)\frac{\partial f(\mathbf{x})}{\partial x_j}. \end{aligned}$$

$$G^N = G^{0,N} + G^{*,\bar{m},N}$$

Role of migration in the emergence of the rare mutant

Macroscopic emergence iff positive density of mutant type

If $c = 0$, that is, without migration, macroscopic emergence occurs in time $O(N)$.

If $c > 0$, then emergence occurs in times of order $O(\log N)$:

- Microscopic emergence - Droplet process
- Macroscopic Emergence in the critical time scale

Theorem 3 - Macroscopic emergence

(Convergence in time scale $\frac{\log N}{\beta} + O(1)$)

Assume $c > 0$. Then there exists $\beta > 0$ such that as $N \to \infty$

$$\left(\Xi^N(\frac{\log N}{\beta} + t)\right)_{t \geq -\frac{\log N}{\beta}} \Rightarrow \mathcal{L} = (\mathcal{L}_t)_{t \in (-\infty, \infty)}$$

with random entrance law:

$$\lim_{t \to -\infty} e^{-\beta t} \int_{\Delta_{K-1}} \mu(\cdot \cap E_1) \mathcal{L}_t(d\mu) = \sum_{j \in E_1} W_j \delta_j$$

where $^*\mathcal{W} = (W_{M+1}, \ldots, W_K)$ is a non-negative random vector with independent components.

Comparison with other geometries - cf. Hutzenthaler-Wakolbinger

Elements of the proofs

- Basic tools

  - Dual representation
  - Set-valued dual $\mathcal{G}_t$
  - A Crump-Mode-Jagers branching process
  - Nonlinear set-valued McKean-Vlasov dual dynamics
  - Random entrance laws and relation to microscopic "droplet process"
  - Rate of emergence β given by the malthusian parameter of the CMJ process.

Basic tool: The dual process

The Feynman-Kac dual for a single site population $(\eta_t, \mathcal{F}_t)$:

$\eta_t = (\zeta_t, \pi_t)$, $\zeta_t \in \mathbb{N}$, π_t is a partition of $\{1, \dots, \zeta_t\}$, $\mathcal{F}_t \in L_\infty(\mathbb{I}^{|\pi_t|})$.
$|\pi_t|$ has linear birth rate and quadratic death rate due to coalescence of pairs of elements of π_t.

Wright-Fisher $X_t \in \mathcal{P}(\mathbb{I})$. Duality relation for $0 \le t \le t_0$:

$$E[F((\eta_0, f), X_t)] = E_{(\eta_0, \mathcal{F}_0)} \Bigg\{ \Bigg[\exp(s \int_0^t |\pi_r| dr) \Bigg] \cdot \cdot \Bigg[\int_{\mathbb{I}} \dots \int_{\mathbb{I}} \mathcal{F}_t(u_1, \dots, u_{|\pi_t|}) X_0(du_1) \dots X_0(du_{|\pi_t|}) \Bigg] \Bigg\}.$$

Shiga (1981), D-Hochberg (1982), D-Kurtz (1982)

Problem: Not useful for studying long time behaviour $t \to \infty$ if $s > 0$.

The Set-Valued Process $\mathcal{G}_t$

Type space:

$$\mathbb{I} := \{1, \ldots, K\}$$

Geographic space

$$S = \{1, \ldots, N\} \qquad \text{or } S = \mathbb{N} \quad \text{or countable abelian group.}$$

Local state space at a site:

$$\begin{aligned} \mathcal{T} := \ & \text{algebra of subsets of } \mathbb{I}^{\mathbb{N}} \\ & \text{of the form } A \times \mathbb{I}^{\mathbb{N}},\ A \text{ is a subset of } \mathbb{I}^m, m \in \mathbb{N} \end{aligned}$$

State space:

$$\boxed{\mathsf{I} := \ \text{algebra of sets } \ = \{\mathsf{G} \in \mathcal{T}^{\mathsf{S}},\ |\mathsf{G}| < \infty\}}$$

$$\begin{aligned} |G| := \min\{j : \exists S_j = \{s_1, \ldots, s_j\} \subset S : G = G_j \times ((\mathbb{I})^{\mathbb{N}})^{S \backslash S_j} \\ G_j \in \mathcal{T}^{S_j}\} \end{aligned}$$

The Dual Representation

Interacting Wright-Fisher system $X(t) = (\mathbf{x}_1(t), \ldots, \mathbf{x}_N(t))$, $\mathbf{x}_i(t) \in \mathcal{P}(\mathbb{I})$, where $\mathbb{I} = \{1, \ldots, 2M\}$.

$$X(t) \in (\mathcal{P}(\mathbb{I}))^S \text{ where } S = \{1, \ldots, N\}.$$

Set-valued Dual Process: $\mathcal{G}_t \in \mathsf{I}$

Define the function $F : (\mathcal{P}(\mathbb{I}))^S \otimes \mathsf{I} \to [0,1]$ by

$$F(X, \mathcal{G}) = X^*(\mathcal{G})$$

where if $X = \prod_{j \in S} \mathbf{x}_j$, then $X^* = \prod_{j \in S} (\mathbf{x}_j)^{\mathbb{N}} \in \mathcal{P}((\mathbb{I}^{\mathbb{N}})^S)$.

$\boxed{\text{Dual Representation}}$

$$E_{X(0)}(F(X(t), \mathcal{G}_0)) = E_{\mathcal{G}_0}(F(X(0), \mathcal{G}_t))$$

Example $\mathbb{I} = \{1, 2\}$; $a, b \in \{1, \ldots, N\}$

$$E_{X(0)}((x_a(t,1))^{k_1} \cdot (x_b(t,1))^{k_2}) = E_{\mathcal{G}_0}[F(X(0), \mathcal{G}_t)], \quad \mathcal{G}_0 = \{1\}_a^{\otimes k_1} \times \{1\}_b^{\otimes k_2}$$

Introduction to the set-valued dual:

Two type population ($\gamma = 0$) with selection rate s:

$\mathbb{I} = \{1,2\}$ Type $\{2\}$ has fitness 1, type $\{1\}$ has fitness 0.

$z(t) = E[(x(t,2)]$. $z(\cdot)$ satisfies the logistic differential equation

$$\frac{dz}{dt} = sz(1-z), \quad z(0) \in [0,1]$$

Application of the dual The initial state of the set-valued dual is:

$\mathcal{G}_0 = (01)$ (indicator function of type $\{2\}$).

The action of selection is

$$(01) \rightarrow \begin{array}{rl} (01) & \otimes(11) \\ \cup\ (10) & \otimes(01) \end{array}$$

The dynamics is driven by a pure birth process, namely,

$$P(\mathcal{G}_t = \cup_{k=0}^{n}[\{1\}^{\otimes k} \otimes \{2\}]) = e^{-st}(1-e^{-st})^n, \quad n = 0,1,2,\ldots.$$

$$
\begin{aligned}
z(t) \qquad &= \sum_{n=0}^{\infty} e^{-st}(1-e^{-st})^n \left(\sum_{k=0}^{n} z(0)(1-z(0))^k \right) \\
&= \frac{z(0)e^{st}}{1+z(0)(e^{st}-1)}
\end{aligned}
$$

<u>Case $\gamma > 0$</u> – Coalescence of columns

— can calculate fixation probabilities.

Application to emergence of type 2

Assume that mutation rate $1 \to 2$ is $\frac{m}{N}$. Now start $\mathcal{G}_t = (10)$. Then

$$\mathcal{G}_t = (10)^{\otimes n(t)}$$

where $n(t)$ is a birth and death process with quadratic death rate.

With migration we obtain a CMJ branching process with malthusian parameter β and emergence occurs in times of the form $\frac{\log N}{\beta} + t$ as $N \to \infty$.

Transition regime: from branching to the McKean-Vlasov equation

However since in this time scale collisions can occur between sites in $\{1, \ldots, N\}$, we must replace the CMJ process by an interacting system and take the McKean-Vlasov limit - this time in the dual domain.

Further special cases of the set-valued dual:

- Multitype Voter model on $\mathbb{Z}^d$ ($\gamma \to \infty$, no mutation)

  Set-valued dual process is the product of factors undergoing random walks with instantaneous coalescence and annihilation.

$$\mathcal{G}_t = \bigotimes_{i \in \pi_t} A_i, \quad A_i \subset \mathbb{I},$$

  where π_t denotes the set of occupied sites at time t in a coalescing random walk on $\mathbb{Z}^d$ up to annihilation (time when two disjoint subsets coalesce).

- $K = 2$, $\gamma, s \to \infty$. A version of the dual is a branching coalescing random walk - cf. Biased voter model.

- Stepwise mutation model - interacting voter models (subsets of $\mathbb{Z}$) with coalescence.