

Chapter 1

Introduction

Consider a population consisting of individuals of different types and distributed in colonies located in geographic space and assume the population is locally finite. If we consider the relative frequencies of types in the different colonies, then the population in a single colony is described by a probability measure on the type space. Hence at a fixed time the essential features of the population are described by a collection of probability measures on the type space indexed by the sites of the geographic space. The time evolution of the population involves finite population resampling (often called pure genetic drift by biologists), mutation and selection in each colony and in addition migration of individuals between colonies. We shall use the large population limit leading to diffusion models, so-called interacting Fleming–Viot processes with selection and mutation, reviewed later on.

We develop here the analysis of these models under three perspectives of biological respectively methodological flavour:

- emergence from *punctuated equilibrium via rare mutation*,
- method of *hierarchical mean-field limit and renormalization*,
- *duality theory* for the genealogy of samples from the population,
- technique of *random entrance laws* for nonlinear evolutions.

We try to present the material in such a way that it can be read from all those perspectives, we comment on this as we go along.

1.1 Ideas and Objectives

Mutation and selection both play essential roles in the evolution of the population. Mutation increases genetic diversity, while selection reduces this diversity pushing it towards states concentrated on the fittest types. The balance between these two forces is influenced heavily by the geographical structure of the population and the effect of migration. Randomness enters through resampling (pure genetic drift).

The first part of the picture we focus on is a scenario (*punctuated equilibrium*) which has received considerable attention in the biological literature (see for example (Eldredge and Gould [EG1], [EG2]) and the references below). In this scenario a population remains for long periods of time in a nearly stationary state (*quasi-equilibrium or stasis*) until the emergence of one or several rare mutants of higher fitness that then take over the population relatively quickly. Possible explanations of this phenomenon based on different mechanisms include the introduction of new selectively advantageous types by rare mutation (see for example [ECL] and the trait substitution sequence of adaptive dynamics (see Champagnat, Ferrière and Méléard [CFM])), or tunnelling between local fitness maxima (see for example Newman, Cohen and Kipnis [NCK]). The explanation of the tunnelling in [NCK] was presented in the context of Wright’s theory of evolution in an adaptive landscape (see [Wr1], [Wr2], [W]). In Wright’s theory the long times between transitions from one quasi-equilibrium to another corresponds to “tunnelling” between one adaptive peak and another in a situation in which local stabilizing selection maintains a population near a local peak. In this setting, the Ventsel–Freidlin theory of small random perturbations of dynamical systems asserts that the actual transition, when it occurs, takes place rapidly. Thus this scenario would be consistent with the observations of paleontologists of periods of rapid evolution separated by very long periods of “stasis”. This is a stochastic effect not present in the deterministic version, that is, the infinite population limit, but must be formulated in terms of a stochastic diffusion limit, which we consider here.

A second part of the picture is the role of *geographic space* and its important effects on the qualitative behaviour which continue to draw interest from mathematicians (see for example (Champagnat and Méléard [CM]), (Barton, Etheridge and Veber [BEV])). Namely, typically a large population is subdivided into small subpopulations (colonies) occupying different geographic regions. Then tunnelling between adaptive peaks or the introduction of a new more fit mutant type can occur in these subpopulations and then by spatial migration the new type can spread (for example the spread of a mutant virus) and eventually result in the take-over of the entire population.

Our goal is to introduce a class of spatial models exhibiting the above features of punctuated equilibrium starting from rare mutants in spatially structured subpopulations undergoing finite population sampling and to develop a rigorous framework for the analysis of such systems. More generally our goal is to develop tools and a framework to explore models which provide insight into the respective roles of mutation, selection and spatial migration in the emergence and spatial spread of rare mutants corresponding to a higher adaptive peak (quasi-equilibrium). The mechanism producing the rare mutants within a local colony could be as suggested by the adaptive landscape picture as above (see also Example 2 in Section 3.4). Another key feature in our formulation is the role of the fitness advantage of types based on *the relative stability against deleterious mutation*—the evolutionary importance of deleterious mutation is underlined in the literature on Muller’s ratchet (see, for example [CC], [EPW]). We establish that the combined effect of *mutation, selection and migration* can result in a transition from one quasi-equilibrium to the

next occurring in phases (droplet formation, emergence, fixation) which take place in different time scales.

In this context it turns out that the migration together with the local stability properties, decisively enhances the speed of “progress”, that is, the transition to fitter types throughout the population. In particular, we obtain rather sharp asymptotic results on the emergence of rare mutants and how they spread throughout the whole population by migration and selection. This also allows us to give a precise account on the shortcomings of using *branching approximations* in *spatial* models to study the early phase of emergence of the rare mutants.

To give a precise setting for this study we model the population dynamics according to a stochastic process arising as the diffusion limit of many individuals incorporating the basic mechanisms for a spatial population traditionally employed in genetics and evolutionary biology. In this model *random fluctuations* (see for example Ewens [Ew]) are included in contrast to other infinite population limits which are ruled by deterministic differential equations (for example, see [Bu]). More precisely the model we use arises from the particle model driven by migration of particles between colonies, and in each site by resampling of types, mutation and selection. Increase the number of particles as ε^{-1} and give them mass ε . As $\varepsilon \rightarrow 0$, a diffusion limit of interacting multitype diffusions results if the resampling rate is proportional to the number of pairs and there is weak selection, i.e. selection occurs at a rate decreasing with the inverse of the number of particles per site. Otherwise with strong selection, i.e. selection at a fixed rate, we get the deterministic limit, often referred to as infinite population limit.

These stochastic models which describe populations of possibly infinitely many types are called *interacting Fleming–Viot processes* and have been intensively studied in recent years (for example, see [EG], [D], [EK1, EK2, EK3], [Eth00], [DGV], [DG99], [DG12]). The basic mechanisms are *migration* between colonies in the diffusion limit which takes the form of deterministic mass flow between sites and then within each colony *resampling* (i.e. *pure genetic drift*) which gives the diffusion term, *selection* of haploid type based on a fitness function on the space of types and *mutation* between types occurring at rates given by a transition kernel on the space of types, the latter two result in a deterministic massflow between types. Some additional remarks on the relation between the model studied and evolutionary theory is given in Section 3.4.

The idea of modelling the spread of a rare advantageous mutant in a spatial population goes back to the seminal paper of Sawyer [Saw]. We will investigate this approach in our context and see that it provides some insights into the nature of the initial stage of the transition to the higher type. As a model for space we use the *hierarchical group* Ω_N (the direct sum of a countable number of copies of the cyclic group of order N , i.e. N being the alphabet length) which allows us to model approximately (as $N \rightarrow \infty$) populations in two-dimensional space and where rare mutations occur at rates of the order N^{-1} . The use of the hierarchical group goes back to the thirties of the last century and has led to mathematically important advances. We discuss this and the possibility to approximate \mathbb{Z}^2 in this way in detail in Section 3.

The main result of this monograph is an asymptotic (as $N \rightarrow \infty$) description of the different phases (induced by the spatial structure and migration) in which rare mutations drive the system from one *quasi-equilibrium* concentrated on types of a particular value of fitness to the next higher one. Here the system has the feature that for a long time the system remains in a quasi-equilibrium on types of a certain fitness before rapidly moving to a higher fitness value.

The transition to a new quasi-equilibrium on a higher level of fitness proceeds by first the occurrence of rare mutants of fitter types in a few colonies at sparsely located spatial sites which are rapidly taken over and form a growing droplet of fitter colonies (*droplet formation*), but a droplet which has for long time negligible intensity. From these colonized sites the new superior types invade the remaining large collection of colonies building up a positive spatial intensity (*emergence phase*), a process taking a long time but then once a “positive” intensity in space is reached very rapidly all sites are dominated by these new types due to “selection” (*fixation phase*). This process is random in two ways, there is a random time shift due to randomness in the very early stage of the first occurrence of rare mutants in the beginning of the droplet formation and there is a random frequency distribution among the different rare mutants still present at the time of fixation.

The “selection” in this picture is based on the advantage of the mutants, which at the beginning of this process is due to their *greater stability against deleterious mutation* combined with higher values of the fitness function, the latter acts only later on in much longer time scales. Then in the next phase a neutral evolution between the new (fitter) types exists which in the next phase is followed by the formation of the new quasi-equilibrium on the higher fitness level.

As a result of this effect, the evolution towards “higher level” populations proceeds very slowly for large time intervals to then tunnel suddenly to the fitter type. This tunneling occurs much faster in a system of colonies connected by migration than in systems of isolated components, where mutation to higher fitness levels must occur independently in the different components before the whole space consists of components concentrated on the higher level type. Note that this spatial spread of selectively advantageous mutants which is of a stochastic nature can be viewed as a more subtle stochastic analogue of the wave of advance described by the celebrated Fisher–Kolmogorov–Petrovsky–Piscounov equation (cf. [DMS]).

Finally we address the question of how finer properties of the migration mechanism influence this effect. For this purpose we consider an enriched version of the model, namely, the *historical process* which records the family relations between individuals and the path of descent through space. In particular we determine the number of rare mutants that are involved in producing the population with higher fitness level in a region in geographic space over which migration is effective at that time scale. We will show that this depends very crucially upon the specifics of the migration mechanism and leads to a dichotomy of *local biodiversity* versus *local monoancestor configuration* corresponding to transience and recurrence of the underlying symmetrized motion.

1.2 Concepts and Methods of Mathematical Analysis

The main mathematical tools we use and develop for the systems of interacting (spatially structured) Fleming–Viot diffusions are:

- new forms of *duality* (*set-valued*, *function-valued*)
- *multiscale* time space scale analysis—*renormalization*
- *historical* processes

which we discuss now in more detail.

In order to give a mathematical formulation of the phenomenon introduced above we use a *hierarchically structured* spatial population model that is a special case of a general class of models which was introduced by Dawson and Greven [DG99]. In particular we impose a hierarchical structure both on the type space and on the geographic space which we will explain is quite natural. The analysis is carried out in the framework of a new type of *multiple space-time scale analysis* of probability measure-valued diffusions. The time evolution of this model is studied from a macroscopic point of view in a whole collection of space-time scales which leads to a whole hierarchy of limit dynamics.

The restriction of our method is that we assume that the different time and space scales *separate* in the limit of large times and large space scales which is of course only an approximation but allows to make precise the notion of a quasi-equilibrium as equilibrium of a limiting non-linear McKean–Vlasov dynamic. The separation of the time scales is achieved by using the so-called *hierarchical mean-field limit* that was introduced in [DG99] and amounts to letting $N \rightarrow \infty$, where N is a parameter regulating the various rates and determining the geographic space here denoted by Ω_N . However the techniques allow us to define the concept of a *quasi-equilibrium* in a mathematically rigorous fashion as equilibria of certain limiting dynamics in the various time scales.

Indeed using this technique of taking $N \rightarrow \infty$ we can produce limiting objects, which have a simple and fairly explicit description. However due to the interaction between the migration, selection, mutation and resampling mechanisms, we have to develop some new ideas to adapt the method of multi-scale analysis to resolve some delicate conceptional and mathematical problems that arise in this case. (In previous work [DG99] the qualitative analysis of the longtime behaviour did not include mutation.) For that purpose we need *new forms of duality* (suitable to treat *multitype* selection and *state-dependent* mutation). The duality we develop allows to calculate the probability that a finite sample of the population has specific genealogical distances and types. The analysis of the dual process is based on the fact that it has the structure of a two-level spatial branching process which allows us to bring the theory of generalized branching processes into play, namely, Crump–Mode–Jagers processes and processes with catastrophes. This we expand on in Sections 5, 8 and 9.

A further point is that we give a rigorously treated example of two-scale phenomena and develop as mathematical tool the notion of random nonlinear

evolutions, more specifically solutions to *random McKean–Vlasov entrance laws* from time $-\infty$. The technique of random entrance laws allows to connect the *separating time scales*.

In order to describe the early occurrence of rare mutants we work with a description of the sparse set of colonies conquered by the rare mutants, which we call droplets, via *atomic measure-valued processes* which in the limit $N \rightarrow \infty$ can be described by stochastic processes driven by (inhomogeneous) Poisson random measures and in order to calculate the intensity measure we are using excursion theory.

In particular, in order to understand the transition between the limiting objects that arise in the multi-scale analysis and describe the resulting mutation-selection quasi-equilibria, we need to introduce different classes of time scales and the corresponding natural space scales. These are introduced to capture respectively *five phases* of the transition of types to the next higher level of fitness: the process in quasi-equilibrium on a certain level of fitness, the emergence of rare (fitter) mutants at sparse sites (droplet formation), the subsequent invasion of other colonies and the build-up of a positive intensity of fitter types in space and fixation on these new types, a subsequent very long neutral evolution between the new types and finally the establishment of a mutation-selection quasi-equilibrium on the higher level.

The difficulty is to identify the intermediate time scales of droplet formation, emergence and fixation to handle the five phases. However the combination of these four classes of time scales allows us to describe the combined effect of mutations, migration and selection in the hierarchical mean-field limit in a rigorous and quite transparent mathematical fashion.

The key tool to carry out the multi-scale analysis are various specifically tuned *dualities* in the spirit of [KN], but incorporating multitype selection and state-dependent mutation. For this purpose we develop a *new type* of dual process, namely a *function-valued* dual process which can be turned into a *set-valued* dual process, if we have finitely many possible types. Occasionally we also use a Feynman–Kac weight to determine the distributions of the interacting diffusions and some related nonlinear Markov processes arising as hierarchical mean-field limits.

Finally, in order to consider questions involving the genealogy, for each individual alive at time t we record not only its type and location but also its path of descent. This means that we consider the so-called “*historical process*” associated with an enrichment of our model which provides the statistics of ancestral paths of the individuals alive at time t . Questions concerning the genealogy of mutant populations, such as how many mutants gave rise to the current population, can then be answered by considering simple functionals of this process, namely the so-called *reduced historical process* which still allows to decompose the population in different families. The historical process also helps to interpret the duality as the construction of the history of a tagged finite subpopulation. However we avoid here the full development of the historical process which requires quite some technical effort. (See P. Seidel [Seidel]).

1.3 Future Applications of Methods and Open Problems

The treatment of the combined effects of selection, mutation and resampling raises many other challenging mathematical problems which we cannot develop in this monograph but which have to be taken up in the future. However the methods which are developed here can be applied to a number of these problems. We briefly mention a few possible directions of research and some potential applications.

There are two main directions for further research, on the one hand to focus on the *measure-valued process* and spatially structured populations and on the other hand on the *genealogical process* which describes the genealogical relations in the population in terms of the genealogical tree.

For example, in the range of the measure-valued process a whole new realm of questions arises if we consider mutation mechanism on the various fitness levels which are not ergodic and which lead to strong dependencies over large stretches of time introducing randomness into even the large time-space scale behaviour.

Some open problems on the measure-valued process

To illustrate we mention a few open problems.

- It is an open problem to explore the emergence and fixation in more complex spatial geometries including *eucclidean lattices*, in particular \mathbb{Z}^2 and geographic spaces which carry *random environments* for the evolution such that fitness and mutation rates can vary with the geographic location.
- It is an open problem to explore the coevolution of interacting quasi-species and the emergence and co-evolution of new multispecies cooperative networks.

Some perspectives to study genealogical processes

One can model the genealogical process as a marked ultrametric measure space-valued process (see [GPWmetric09], [GPWmp12], [DGP11]). Then it is possible to ask detailed questions about the genealogical distances in the rare mutant families as they emerge, fixate, move neutrally or move into the next level fitness selection and mutation quasi-equilibrium. This allows to obtain insight into the finite structure of the family and subfamily structure of the current population and the connection of these structures with geographic space which can be explored in the constructed framework.

The methodology developed here carries over to the genealogical process as is shown for nonspatial models in [DGP]. The task for the genealogies is then to characterize the scaling limits of the genealogical process with martingale problems and to identify the key qualitative properties of these objects. In particular we can then get into focus the interplay between genealogical and geographical distance, the geographical structure of subfamilies defined via the genealogical distance in the different regimes, emergence, fixation, neutral stage and reequilibration on the higher level and the formation of clusters of closely related families which were so far been studied on the level of type configurations (see [DGV], [DG96], [GHKK], [LS]).

Some open problems on the parameter range

Some open problems remain in certain parameter ranges for the relative intensity of mutation versus selection events for the models we study here. We formulate conjectures and potential concrete approaches in the proof section of this monograph.

The formulas we derive for emergence and fixation raises the question how the time to emergence depends qualitatively on the relative strength of the parameters describing migration, resampling versus mutation and selection. Due to the nonlinearity due to selection this is a complicated matter but the provided representations of the quantities by Crump–Mode–Jagers processes provide a starting point for such studies.

1.4 Methodologies Developed

The following new mathematical tools are developed in the following parts of the monograph.

1. *Duality* has been a major tool to study the dynamics of stochastically evolving populations, we review this at the beginning of Section 5. We introduce here some new dualities:
 - a positive function-valued dual replacing a signed-Feynman–Kac dual appearing earlier in the literature [D], and in a spatial context [DG99] which works for spatial models with selection and mutation. (Subsections 5.1–5.4 and 5.6),
 - a dual taking values in sums of products of indicator functions in type space which is particularly powerful for finitely many types and in deriving ergodic theorems on the longtime behaviour (Subsection 5.5),
 - a dual which is marked tableau-valued with indicator functions as entries and locations as marks, which is also very suitable studying convergence of rare mutants (Subsection 9.4),
 - a set-valued dual, again useful in studying longtime behaviour for multitype systems (Section 9.5),
 - enriched set-valued duals for carrying out our program (Section 9.6).
2. Based on the duality we develop the method to study the evolving population by means of a two-level dynamic for the dual process:
 - multitype (finite and countable) *Crump–Mode–Jagers* generalized branching process,
 - the internal dynamics of the individuals types follow a *birth–death–catastrophe dynamic*.

This makes it possible to make use of a lot of techniques developed for branching processes, here for Fleming–Viot processes with migration–mutation–selection (subsections 9.7–9.11).

3. We develop using excursion theory and Poisson point process-driven stochastic equations as a tool to describe and analyse droplets of rare mutants (single and multitype) in forms of *atomic measure-valued processes* (Sections 8, 9, 10)
4. We develop the technique of random entrance laws for *nonlinear Markov processes* to give asymptotic descriptions of multiple scale effects (Section 8).

1.5 Outline of the Monograph and Different Ways to Read It

This monograph develops a program to study features of evolution under selection and mutation and spatial migration which we elaborate in Section 4. To carry out this program we need to develop some methods which are of broader interest which we list below together with a description of different ways to read this monograph. To get things started, in Section 2 we give the reader an appetizing part of the theory in a simple case.

In Section 3 we shall describe the model and recall the basic uniqueness and existence results. In particular we explain the hierarchical model of mutation and selection which we use and then we explain the biological interpretation. In Section 4 we give the main results, namely in 4.1–4.5 we introduce the multiple-space time scale analysis and state the three basic rescaling theorems. We use the results to address the central questions in Subsection 4.6, to specify the questions about the combined effect of migration, mutation and selection (stasis, punctuated equilibrium, precise asymptotic description of the five phases, etc.) and in 4.7 we address the genealogical picture and the dichotomy of biodiversity versus local monotype states.

In Subsection 4.8, after the reader has gained some familiarity with the main claims, we provide some more information on the remaining sections and guidance to the reader on what can be read independently.

In Sections 5 and 6 we prepare some mathematical methods needed for the analysis. In particular Section 5 and then Subsections 9.4 and 9.5 describe the new form of the duality theory for the processes involved which is of independent interest and has other potential applications while subsection 9.6 develops a duality theory mainly relevant for studying the invasion of rare mutants. In Section 6 and Subsection 10.3 we derive using the duality tools ergodic theorems which were previously unknown for some basic spatial and non-spatial models which arise in evolutionary theory.

The Sections 7–15 contain tools and the proofs. In particular the crucial Sections 7–12 are devoted to the analysis of a N -site mean-field model which is then used in Section 13 to study finite hierarchical N^k -site models for $k = 2, 3, \dots$ and finally $k = \infty$ by finite approximation. The Section 15 then puts everything together for the final proof. The proofs are structured in such a manner that certain restricted cases are studied first (for example 2-type case, M -lower fitness types, one higher fitness case, general (M, M) -type case) which are self-contained (Sections 8, 9, 10).

This monograph could be used in various ways (besides a top to bottom reading)

- A reader interested in the feature of successive invasions of rare mutants with selection and migration, but not in deriving proofs can read Sections 2, 3 and 4.
- A reader interested in the new duality methods in order to apply them to other applications may just read Sections 2, 3, 5 and Subsections 9.4 and 9.5, possibly 9.6.
- A reader wanting to see the key features and some key ideas of proofs may read Sections 2, 3, 4 and 8 which are self-contained.
- A reader interested in studying the longtime behaviour of stochastic populations models may focus on Sections 3, 5, 6 and part of Subsections 10.3 and 10.6.

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