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Reaction Networks and Population Dynamics

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Abstract. Reaction systems and population dynamics constitute two highly developed areas of research that build on well-defined model classes, both in terms of dynamical systems and stochastic processes. Despite a significant core of common structures, the two fields have largely led separate lives. The workshop brought the communities together and emphasised concepts, methods and results that have, so far, appeared in one area but are potentially useful in the other as well.

Mathematics Subject Classification (2010): 92C42, 92xx, 34xx, 60xx .

Introduction by the Organisers

Background and focus: Reaction systems and population dynamics are two areas of research that have recently experienced many novel developments and currently attract increasing attention, which goes far beyond mathematical biology and (bio)chemistry. *Reaction systems* describe the time evolution of the composition of a mixture of different (bio)chemical species that undergo a variety of chemical reactions. *Population dynamics* is concerned with the time evolution of the composition of a population of individuals of different types that interact with each other; the interaction can be competition, symbiosis, predation, etc. Traditionally, it is assumed that the number of molecules of each species (or the number of individuals of every type) is so large that a law of large numbers applies that allows to neglect random fluctuations. The systems are then described deterministically by a system of nonlinear ordinary differential equations or, if spatial behaviour is taken into account, by partial differential equations. Recently, there

has been a boost of stochastic approaches in both areas, which lead to a wealth of new challenges, concepts, and results.

The workshop: In line with the above, the goal of the workshop was to bring together the two subcommunities, which have been somewhat separate so far, to provide the opportunity for mutual stimulation. Of the 26 participants, roughly equal proportions came from reaction networks and population dynamics; some, including the three organisers, had already worked in both areas. The workshop started with an expository talk by Hofbauer, who highlighted connections between the fields by means of illustrative examples. This set the scene for more detailed contributions to follow. Altogether, the following core of common structures led the way:

- In many cases, equations have similar or even identical structures and can be translated into each other. For example, the process of *recombination* in population genetics may be reformulated as a bi-molecular reaction; populations living in symbiosis may be understood as a reaction system with mutual catalysis.
- Both the transient and the asymptotic behaviour is relevant. For large subclasses of reaction systems and population models, the deterministic behaviour is captured by a Lyapunov function that is related to (relative) entropy.
- Scaling arguments are of importance for stochastic systems in both cases to achieve simplifications, model reductions, and limits. In particular, diffusion processes appear as limits, and separation of time scales plays a decisive role.
- Recently, there has been a boost of stochastic approaches in both areas, which lead to a wealth of new challenges, concepts, and results. Characteristically, the stochastic models of population genetics have a standard representation in terms of interacting particle systems, which also form the basis of reaction systems.
- The further development of the mathematical theory is also driven by a new quality and quantity of data acquisition (in particular via the high-resolution methods of *systems biology* in reaction systems and of *genome research* in population genetics) and the need to solve problems of inference.

Throughout the workshop, emphasis was on concepts, methods, and results that have, so far, appeared in one area but are potentially useful in the other as well. Let us summarise the most important topics.

- Many qualitative properties of deterministic reaction systems can already be deduced from the algebraic or graphical properties of the network. For example, the global attractor conjecture (Craciun) states that, for the so-called complex balanced systems, all trajectories converge to a unique stable equilibrium point. For certain classes of systems that are not complex-balanced, necessary and sufficient conditions for multistationarity may be

given (Dickenstein). For others, such as the model of T-cell receptor phosphorylation (Rendall), no general results are available, so they must be considered on a case-by-case basis. High-dimensional reaction systems can often be reduced to lower dimensions with the help of algebraic methods (Walcher).

- Many processes of population genetics are much more accessible to analysis in terms of the *ancestral processes* than in terms of the original (forward-time) dynamics. This gives rise to processes of branching and pruning (Cordero), coalescence (Möhle), partitioning (M. Baake), or a mixture thereof (Jenkins). Closely-related growth-fragmentation equations appear in cell biology forward in time (Doumic).
- *Stochastic aspects of reaction networks* become increasingly important. For certain classes (namely, host-parasite reaction networks), the long-time asymptotics can now be characterised analytically (Majumdar). Noise might not always be a nuisance — in fact, an emerging paradigm is that it can have beneficial effects on biological processes (Gupta). Due to the high dimensionality, stochastic reaction systems call for new approaches to simulation (Williams) and inference (Rand, Hilfinger).
- Models taking into account spatial behaviour are much more developed for population models than for reaction networks. In genetics, for example, the theory of clines, which describes the spatial structure of a population under migration and selection, is well developed (Bürger). Likewise, the behaviour of populations under selection, mutation, and migration may be characterised, provided that there is time-scale separation due to rare mutations (Léman). There is a definite need to consider spatial structure in reaction systems, but this is more difficult due to the high dimensionality of the models and due to cell compartmentalisation.
- Deterministic and stochastic models do no longer belong to separate worlds. Rather, the connections between them are being increasingly recognised. This is true of several of the topics already mentioned above, but was in the centre of attention in the context of finite population models (Schreiber), where the quasistationary states of the stochastic system correspond to the stationary states of the deterministic one. Likewise, a stochastic model of adaptive dynamics which converges to an adaptive walk that jumps between Lotka–Volterra equilibria (Kraut). Results on complex-balanced reaction systems that have, so far, been available in the deterministic situation only, have recently been extended to the stochastic setting (Cappelletti).

Problem sessions were held on Thursday afternoon and evening, on the following topics:

- multiscale models
- spatial aspects of reaction networks
- moment closure
- Lyapunov functions

- dualities, ancestries and hidden linearities in reaction systems

From the very first minute, the workshop was blessed with an extraordinarily intense atmosphere of discussion and curiosity. The coherence between the talks was astonishing, and additional connections were made by the speakers. Specifically, Paul Jenkins spontaneously changed the topic of his talk so as to blend in perfectly with the previous one. The intensity of the workshop under the spell of the MFO, added by the lively conversations in the warm midsummer nights, made this a very special week to most, if not all, participants, many of whom were newcomers to Oberwolfach or returning after many years.

Acknowledgement: The MFO and the workshop organizers would like to thank the National Science Foundation for supporting the participation of junior researchers in the workshop by the grant DMS-1049268, "US Junior Oberwolfach Fellows". Moreover, the MFO and the workshop organizers would like to thank the Simons Foundation for supporting Sebastian Schreiber in the "Simons Visiting Professors" program at the MFO.

Workshop: Reaction Networks and Population Dynamics

Table of Contents

Abstracts

Population dynamics and reaction systems – some crossovers

Josef Hofbauer

Many basic models studied in population biology can be rephrased as simple chemical reaction networks.

In 1920 **Lotka** wrote two papers: In one he introduced his famous predator–prey system with conservative oscillations

$$\dot{x} = ax - bxy, \quad \dot{y} = cxy - dy,$$

which was studied in 1926 again independently by Volterra. In the other he arrived at the same system via mass action kinetics of the set of reactions

$$\mathsf{S} + \mathsf{X} \to 2\mathsf{X}, \quad \mathsf{X} + \mathsf{Y} \to 2\mathsf{Y}, \quad \mathsf{Y} \to \mathsf{P}.$$

The basic model in **epidemiology**, the SIR model of Kermack–McKendrick (1927) is given by the ODEs

$$\dot{S} = -aSI,\ \dot{I} = aSI - bI,\ \dot{R} = bI$$

with $S + I + R = \mathsf{const.}$, and is equivalent to the reactions

$$S + I \longrightarrow 2I,\ I \longrightarrow R$$

with mass action kinetics. Similarly, the SIS model corresponds to $S + I \longrightarrow 2I$, $I \longrightarrow S$. The SEIR model (with an additional class of *exposed* individuals which are infected but yet infectious) corresponds to the reactions

$$S + I \longrightarrow E + I,\ E \longrightarrow I \longrightarrow R.$$

The SIRS model (where immunity is not permanent) to the reaction network

$$S + I \longrightarrow 2I,\ I \longrightarrow R \longrightarrow S.$$

The **Ivanova reaction** [7]

$$X + Y \longrightarrow 2Y,\ Y + Z \longrightarrow 2Z,\ Z + X \longrightarrow 2X$$

leads with mass action kinetics to the system

$$\begin{aligned}
\dot{x}_1 &= k_2x_3x_1 - k_3x_1x_2 = x_1(-k_3x_2 + k_2x_3)\\
\dot{x}_2 &= k_3x_1x_2 - k_1x_2x_3 = x_2(k_3x_1 - k_1x_3)\\
\dot{x}_3 &= k_1x_2x_3 - k_2x_3x_1 = x_3(-k_2x_1 + k_1x_2).
\end{aligned}$$

It has two constants of motion, $x_1 + x_2 + x_3 = C_1$ and $x_1^{k_1}x_2^{k_2}x_3^{k_3} = C_2$, and hence closed orbits in each stoichiometric class. It is equivalent to the rock–scissors–paper

game with replicator dynamics. More generally, for a skew–symmetric matrix $A = -A^{\mathsf{T}}$, the system of ODEs

$$\dot{x}_i = x_i \left(\sum_{j=1}^{n} a_{ij} x_j \right)$$

is a special Lotka–Volterra system with conservation of mass $\sum \dot{x}_i = 0$, as well as the replicator dynamics for the zero–sum game with payoff matrix A. It arises from (bimolecular) chemical reactions

$$X_i + X_j \xrightarrow{a_{ij}} 2X_i \qquad \text{if} \quad a_{ij} > 0.$$

If $\hat{x}$ satisfies $A\hat{x} = 0$ (this exists for odd n) then $\sum_i \hat{x}_i \log x_i$ is a constant of motion: $\sum_i \hat{x}_i \frac{\dot{x}_i}{x_i} = \hat{x}^{\mathsf{T}} A x = -x^{\mathsf{T}} A \hat{x} = 0$. If $\hat{x} \geq 0$ then $\hat{x}$ is a stable equilibrium, see [3].

General **Lotka–Volterra systems**

$$\dot{x}_i = x_i \left(r_i + \sum_{j=1}^{n} a_{ij} x_j \right)$$

also arise from chemical reactions:

$$X_i \xrightarrow{r_i} 2X_i \qquad \text{if} \quad r_i > 0, \qquad \text{resp.} \quad X_i \xrightarrow{|r_i|} 0 \qquad \text{if} \quad r_i < 0$$

$$2X_i \xrightarrow{a_{ii}} 3X_i \qquad \text{if} \quad a_{ii} > 0, \qquad \text{resp.} \quad 2X_i \xrightarrow{|a_{ii}|} X_i \qquad \text{if} \quad a_{ii} < 0$$

$$X_i + X_j \xrightarrow{a_{ij}} 2X_i + X_j \quad \text{if} \quad a_{ij} > 0, \quad \text{resp.} \quad X_i + X_j \xrightarrow{|a_{ij}|} X_j \quad \text{if} \quad a_{ij} < 0.$$

The standard **mutation model in population genetics** (mutation between n alleles) gives rise to a linear system of ODEs and corresponds to a network of first order reactions $X_i \xrightarrow{\mu_{ji}} X_j$:

$$\dot{x}_i = \sum_{j \neq i} \mu_{ij} x_j - x_i \sum_{j \neq i} \mu_{ji}$$

with $\sum_i \dot{x}_i = 0$. Here the *Chemical Reaction Network Theory* of Horn & Feinberg [2] works well: m (the number of complexes) $= n$, ℓ (the number of linkage classes) $= 1$ if (μ_{ij}) is irreducible, s (the dimension of the stoichiometric subspace) is $n-1$. Hence the deficiency (the magic quantity of CRNT, see [2]) $\delta = m - \ell - s = 0$. Together with weak reversibility of the network this shows that there is a unique positive equilibrium in each class $\sum x_i = C$, and it is globally asymptotically stable there.

Recombination, or chromosomal **crossover**, in the simplest case of two alleles on each of two loci, is equivalent to the reversible chemical reaction

$$g_1 + g_4 \xleftrightarrow{k} g_2 + g_3.$$

The dynamics of gamete frequencies

$$\dot{p}_1 = \dot{p}_4 = k\,(-p_1p_4 + p_2p_3) = -\dot{p}_2 = -\dot{p}_3$$

has the conservation laws $(p_1 + p_2)^{\cdot} = (p_1 + p_3)^{\cdot} = (p_4 + p_2)^{\cdot} = (p_4 + p_3)^{\cdot} = 0$ of which three are linearly independent. The equilibrium manifold is given by the quadric (the *linkage equilibrium manifold*) $p_1p_4 = p_2p_3$. The stoichiometric compatibility classes are 1-dimensional. There, the solutions converge to a unique detailed-balancing equilibrium.

The general recombination model, with L loci and finitely many alleles at each locus leads to a rather complicated reaction network, see [6]. It resembles a discrete version of the Boltzmann equation. Since it is strongly reversible (forward and backward reaction rates are the same), entropy is a Ljapunov function, and convergence to linkage equilibrium or detailed-balanced equilibrium follows, see [1, 4, 6, 7].

Finally, every strongly reversible reaction network (more generally, every detailed balanced network) results in a *generalized gradient system* [5]: the potential function is a relative entropy, the underlying metric is a somewhat complicated expression involving the logarithmic mean (compare [1]). Suppose all reactions

$$\sum_i \alpha_{ri} X_i \overset{k_r}{\longleftrightarrow} \sum_i \beta_{ri} X_i$$

are reversible: $k_r^+ > 0, k_r^- > 0$. Then the mass action dynamics is given by

$$\dot{p} = R(p) = \sum_r (\beta_r - \alpha_r)(k_r^+ p^{\alpha_r} - k_r^- p^{\beta_r}).$$

Suppose there is a detailed balanced equilibrium $\hat{p} > 0$ so that for all reactions r: $k_r^+ \hat{p}^\alpha = k_r^- \hat{p}^\beta =: k_{\alpha\leftrightarrow\beta}$.

The relative entropy

$$H(p) = -\sum_i p_i(\log \frac{p_i}{\hat{p}_i} - 1) \qquad \text{satisfies} \qquad \nabla H(p) = (-\log \frac{p_i}{\hat{p}_i})$$

and together with the symmetric positive semidefinite matrix

$$C(p) = \sum_{\alpha\leftrightarrow\beta} k_{\alpha\leftrightarrow\beta} L(\frac{p^\alpha}{\hat{p}^\alpha}, \frac{p^\beta}{\hat{p}^\beta})(\beta - \alpha)(\beta - \alpha)^{\mathsf{T}}$$

the dynamics can be written as the generalized gradient system

$$\dot{p} = R(p) = C(p)\nabla H(p).$$

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Dimension reduction for reaction equations

Sebastian Walcher

We discuss parameter-dependent polynomial (or rational) systems of ordinary differential equations, with an emphasis on those derived from reaction networks. Such systems may be high-dimensional but frequently model assumptions or intuition suggest reduction to equations of small dimension, and there are various methods and heuristics to obtain such reductions. The work outlined below, done jointly with Lena Nöthen, Alexandra Goeke, Eva Zerz and others, provides a systematic mathematical approach to reduction methods and their validity, based on Tikhonov's and Fenichel's classical work on singular perturbation theory. The focus is on reaction equations but the methods are applicable to all parameter-dependent ODEs with polynomial or rational right-hand side.

Reduction with no a priori separation of slow and fast variables. In reaction equations one frequently has (or assumes) slow-fast phenomena but no slow and fast variables are known a priori. If it is possible to cast the problem in the form

$$\dot{x} = h(x,\varepsilon) = h^{(0)}(x) + \varepsilon h^{(1)}(x) + \cdots \tag{1}$$

with a small parameter $\varepsilon > 0$ then, as was shown in [1], a Tikhonov–Fenichel reduction is possible if and only if $h^{(0)}$ satisfies a number of requirements, the most important of which is the existence of non-isolated stationary points. The reduced equation itself is defined on an algebraic variety and can be determined explicitly, using methods from algorithmic algebra.

Finding "small parameters" in parameter-dependent systems; see [2]. More to the point, this problem concerns so-called Tikhonov–Fenichel parameter values from which singular perturbations emanate: Starting with an ODE

$$\dot{x} = H(x,p) \tag{2}$$

which depends on parameters $p \in \mathbb{R}^m$, the task is to identify parameter values p^* so that a small perturbation (along a curve in parameter space) will lead to the setting of Tikhonov's and Fenichel's theorems. (Loosely speaking, p^* corresponds to $\varepsilon = 0$ in (1).) This task is amenable to algorithmic algebra; in particular the existence of non-isolated stationary points at $p = p^*$ naturally brings elimination ideals into play. From a theoretical perspective, a complete characterization of Tikhonov-Fenichel parameter values was given. Among other results, by this

approach we were able to determine systematically all parameter values for the standard systems from biochemstry (Michaelis-Menten, cooperative and competitive systems) at which singular perturbations take place.

"Classical" quasi-steady state reduction. This is a well-known and much-used heuristic for systems of type (2): Set the rates of change for certain variables equal to zero and use the ensuing algebraic relations to obtain a system of smaller dimension. It was recently investigated from a strictly mathematical perspective. In [3] we could determine necessary and sufficient conditions for the procedure to be consistent (again, these yield conditions on parameters which can be evaluated using algorithmic algebra). Furthermore, we were able to clarify the mathematical connection to singular perturbation settings. The latter result implies that classical QSS reduction in certain instances provides incorrect results, but on the other hand we could establish conditions under which QSS reduction (essentially) coincides with singular perturbation reduction and therefore is reliable.

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A constrained Langevin approximation for (bio)chemical reaction networks

Ruth J. Williams

(joint work with Saul C. Leite)

Continuous-time Markov chain models are often used to describe the stochastic dynamics of networks of reacting chemical species, especially in the growing field of systems biology (see e.g., the survey of Anderson and Kurtz [2]). Practitioners frequently simulate the sample paths of these Markov chains in order to generate Monte-Carlo estimates. This typically involves simulating the next reaction to fire, or in Markov chain language, simulating the next jump of the Markov chain. In the chemical reaction network literature, this method is often called the Stochastic Simulation Algorithm (SSA) or Gillespie algorithm, after Gillespie [6] who first introduced this method to the chemistry community. In the stochastic processes/operations research community, this method is often called discrete event simulation and this way of viewing the sample path behavior of a continuous time Markov chain with infinitely many states goes back to early work of Doob [3, 4].

A challenge with the use of simulation of the Markov chain is that the number of reactions is often much larger than the number of chemical species involved in

the reactions, and the stochastic simulations can rapidly become computationally intensive. Methods for speeding up simulations to give approximate answers by taking time steps larger than some reaction times have been studied (so-called tau leaping methods), see e.g., [1, 7].

Another approach is to approximate the discrete-state Markov chain by a dynamic process with continuous states, where the dimension of the process is the number of species. Deterministic (mean field) approximations involving ordinary differential equations called reaction rate equations are often used if all chemical species are present in large numbers. However, to capture stochastic effects, especially when some species are not present in large numbers, diffusion approximations (continuous strong Markov processes) are commonly used. However, existing diffusion approximations either do not respect the constraint that chemical concentrations are never negative (linear noise approximation) or are typically only valid until the concentration of some chemical species first becomes zero (Langevin approximation). For a rigorous account of these approximations, see the articles by Kurtz [9, 10].

In this talk, we propose an approximation for the continuous-time Markov chains via obliquely reflected diffusion processes that respects the fact that concentrations of chemical species are never negative. We call this a constrained Langevin approximation because it behaves like the Langevin approximation in the interior of the positive orthant and it is constrained to the orthant by instantaneous reflection at the boundary of the orthant. The direction of reflection at the boundary is oblique and varies along the boundary. An additional advantage of our approximation is that it can be written down immediately from the chemical reactions. This contrasts with the linear noise approximation, which involves a two-stage procedure - first solve a deterministic reaction rate ordinary differential equation, followed by a stochastic differential equation for fluctuations around those solutions. Our approximation also captures the interaction of non-linearities in the reaction rate function with the driving noise. (It is well known that the linear noise approximation can fail to capture such behavior [12].) In simulations, we have found the computation time for our approximation to be at least comparable to, and often better than, that for the linear noise approximation.

In [11], assuming stochastic mass action kinetics and that each chemical species is produced and degraded, we first prove that our proposed approximation is well defined for all time. Then we prove that it can be obtained as the weak limit of a sequence of jump-diffusion processes that behave like the Langevin approximation in the interior of the positive orthant and like a rescaled version of the Markov chain on the boundary of the orthant. For this limit theorem, we adapt an invariance principle for reflected diffusions, due to Kang and Williams [8], and modify a result on pathwise uniqueness for reflected diffusions, due to Dupuis and Ishii [5]. Some numerical examples given in [11] illustrate the advantages of our approximation over discrete event simulation of the Markov chain or use of the linear noise approximation. Our examples also demonstrate that approximating by a diffusion process with *normal* reflection at the boundary of the orthant, or

cutting off negative excursions that venture outside of the orthant, can produce very inaccurate results.

There are various further directions that we are exploring. Systems in which some species are not produced or degraded can be approximated by allowing some reactions to have very small rate constants. However, a direct approximation of such systems is desirable. While one can conjecture the form of such an approximation, in general, there are issues associated with proving the well posedness of the reflected diffusion and in proving tightness of rescaled Markov chains approximating it. In another vein, the type of diffusion approximation proposed here is also likely to be of interest for researchers considering other continuous-time Markov chains that live in the positive orthant, e.g., in population genetics and neuroscience. The authors would appreciate hearing from researchers interested in such models and approximations.

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Solution of the general recombination equation via Haldane linearisation

Michael Baake
(joint work with Ellen Baake)

The stochastic process of recombination in population genetics, in its deterministic limit of large population size, leads to a nonlinear ODE in the Banach space of finite measures on a locally compact product space. It has an embedding into a *linear* system of ODEs that reflects an underlying Markov partitioning process. We discuss the solution and this connection, which works both in continuous and in discrete time.

The classical setting of population genetics uses a finite set of sites (or loci), $S = \{1, 2, \ldots, n\}$, types $x = (x_1, x_2, \ldots, x_n) \in X_1 \times X_2 \times \ldots \times X_n =: X$ and partitions $\mathcal{A} = \{A_1, A_2\} \in \mathbb{P}_2(S)$ of S into two parts. The recombination equation (in continuous time) for the probability $p_t(x)$ of type x at time t reads

$$\dot{p}_t(x) \;=\; \sum_{\mathcal{A}\in\mathbb{P}_2(S)} \varrho(\mathcal{A})\big(p_t(x_{A_1}, *)\, p_t(*, x_{A_2}) - p_t(x)\big), \tag{1}$$

where $\varrho(\mathcal{A})$ is the recombination rate for the partition $\mathcal{A}$ and $*$ denotes marginalisation with respect to the corresponding components. Early versions (in discrete time) go back to Jennings (1917), Geiringer (1944) and Bennett (1954); see [2] and references therein for background. Their results indicate that the system should be solvable explicitly, despite the nonlinearity.

In a modern (and more general) setting, one can work with the Banach space $(\mathcal{M}(X), \|.\|)$ of finite measures over X, where each X_i is a locally compact space and $\|.\|$ denotes the total variation norm, as defined by $\|\omega\| = |\omega|(X)$. With $\omega \in \mathcal{M}(X)$ and general partitions $\mathcal{A} = \{A_1, A_2, \ldots, A_r\} \in \mathbb{P}(S)$, one can rewrite and extend the recombination equation from (1) as

$$\dot{\omega}_t \;=\; \Phi(\omega_t) \;=\; \sum_{\mathcal{A}\in\mathbb{P}(S)} \varrho(\mathcal{A})\,\big(R_{\mathcal{A}} - \mathbb{1}\big)(\omega_t), \tag{2}$$

with the nonlinear operator $R_{\mathcal{A}}$ being defined by $R_{\mathcal{A}}(\omega) = \frac{\omega^{A_1}\otimes\ldots\otimes\omega^{A_r}}{\|\omega\|^{r-1}}$ together with $R_{\mathcal{A}}(0) = 0$. Here, for any $\varnothing \neq U \subseteq S$, the measure ω^U emerges from ω via marginalisation with respect to all sites in the complement of U. Likewise, the induced recombination rates of the subsystem defined by U is given by

$$\varrho^U(\mathcal{B}) \;=\; \sum_{\substack{\mathcal{A}\in\mathbb{P}(S)\\ \mathcal{A}|_U=\mathcal{B}}} \varrho(\mathcal{A}), \tag{3}$$

for any $\mathcal{B} \in \mathbb{P}(U)$. Analogous formulations hold for other lattices of partitions as well; see [3] for more.

The operators $R_{\mathcal{A}}$ are nonlinear for $\mathcal{A} \neq \{S\}$, but globally Lipschitz. The Cauchy problem for (2) thus has a unique solution. The flow leaves the positive

cone $\mathcal{M}_+(X)$ invariant in forward time and preserves the norm of positive measures. In particular, when ω_0 is a probability measure, then so is ω_t for all $t \geqslant 0$. In the past, it was noticed that the convex combination ansatz

$$\omega_t = \sum_{\mathcal{A}} a_t(\mathcal{A})\, R_{\mathcal{A}}(\omega_0) \tag{4}$$

led to a complete separation of the time evolution, which is described by a nonlinear ODE system for the coefficients $a_t(\mathcal{A})$, and the partitioning of the initial condition ω_0 by the recombinators; see [2] and references therein. This was used to obtain a recursive solution for generic choices of the recombination rates, though it did not result in a general solution.

Alternatively, the embedding into a larger system with linear evolution dynamics emerges from considering the measure vector $\big(R_{\mathcal{B}}(\omega_t)\big)_{\mathcal{B}\in\mathbb{P}(S)}$, where ω_t is a solution of (2). Now, for $\mathcal{B} = \{B_1, B_2, \ldots, B_r\}$, one finds

$$\frac{\mathrm{d}}{\mathrm{d}t} R_{\mathcal{B}}(\omega_t) = \frac{\mathrm{d}}{\mathrm{d}t}\left(\omega_t^{B_1} \otimes \cdots \otimes \omega_t^{B_r}\right) = \sum_{\mathcal{C}\in\mathbb{P}(S)} Q_{\mathcal{B}\mathcal{C}} R_{\mathcal{C}}(\omega_t)\,, \tag{5}$$

where the marginalisation consistency of (2) was used [2, 1]. In particular, Q is a Markov generator. Its elements satisfy $Q_{\mathcal{B}\mathcal{C}} = 0$ whenever $\mathcal{B} \prec \mathcal{C}$, which stands for $\mathcal{B}$ being a true refinement of $\mathcal{C}$. Consequently, Q is upper triangular. Further, when $\mathcal{C} \prec \mathcal{B}$, one has $Q_{\mathcal{B}\mathcal{C}} = \varrho^{B_i}(\mathcal{A}_i)$ if $\mathcal{C}$ emerges from $\mathcal{B}$ by refining precisely one part, B_i say, which is then replaced by a partition $\mathcal{A}_i \in \mathbb{P}(B_i)$ with at least two parts. The diagonal elements (which are the eigenvalues of Q) are given by

$$\lambda_{\mathcal{B}} = Q_{\mathcal{B}\mathcal{B}} = -\sum_{i=1}^{|\mathcal{B}|} \sum_{\substack{\mathcal{A}_i \neq \{B_i\} \\ \mathcal{A}_i \in \mathbb{P}(B_i)}} \varrho^{B_i}(\mathcal{A}_i)\,. \tag{6}$$

These are the well-known (exponential) decay rates of the system, on its time evolution to the unique equilibrium. The latter is given by the total product measure $\omega_0^{\{1\}} \otimes \cdots \otimes \omega_0^{\{n\}}$ that emerges from the initial condition ω_0 (assumed a probability measure here). So, with $\varphi_t = \big(R_{\mathcal{B}}(\omega_t)\big)_{\mathcal{B}\in\mathbb{P}(S)}$, one has

$$\dot{\varphi}_t = Q\,\varphi_t\,, \quad \text{with solution} \quad \varphi_t = \mathrm{e}^{tQ}\varphi_0\,, \tag{7}$$

as well as $\dot{a}_t(\mathcal{A}) = \sum_{\mathcal{B}\succcurlyeq\mathcal{A}} a_t(\mathcal{B})\, Q_{\mathcal{B}\mathcal{A}}$ with $a_0(\mathcal{A}) = \delta_{\mathcal{A},\{S\}}$.

The matrix Q has an interpretation as the generator of a Markov partitioning process *backward* in time, as indicated in Figure 1. Indeed, if Σ_t is the partition-valued random variable attached to it, one has

$$(\mathrm{e}^{tQ})_{\mathcal{B}\mathcal{C}} = \mathbf{P}(\Sigma_t = \mathcal{C} \mid \Sigma_0 = \mathcal{B}) \quad \text{and} \quad a_t(\mathcal{A}) = (\mathrm{e}^{tQ})_{\{S\}\mathcal{A}}\,. \tag{8}$$

The process $(\Sigma_t)_{t\geqslant 0}$ describes how the sites of a sequence from the current population is partitioned into different ancestors in the past. Given $\Sigma_t = \mathcal{A} = \{A_1, \ldots, A_n\}$, an individual from the present population inherits the sites in A_i, with $1 \leqslant i \leqslant n$, from one ancestor each, while its type distribution is then given by

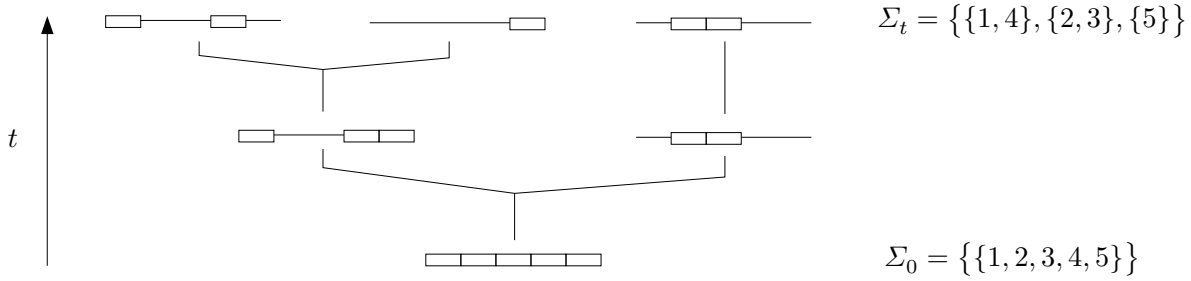

FIGURE 1. Realisation example of the partitioning process.

$R_{\mathcal{A}}(\omega_0)$, which matches the structure of (4). With Φ as defined in (2), the embedding (via Haldane linearisation) and the reduction back to the original equation can thus be summarised as

$$\boxed{\dot{\omega}_t \,=\, \Phi(\omega_t)} \quad \underset{\omega_t = \varphi_t(\{S\})}{\overset{\text{Haldane}}{\rightleftarrows}} \quad \boxed{\dot{\varphi}_t \,=\, Q\,\varphi_t} \tag{9}$$

which explains the underlying linear structure and thus the complete solvability of the original nonlinear equation.

The counterpart in discrete time starts from the iteration

$$\omega_{t+1} \,=\, \sum_{\mathcal{A}\in\mathbb{P}(S)} r(\mathcal{A})\, R_{\mathcal{A}}(\omega_t)\,, \tag{10}$$

with recombination probabilities $r(\mathcal{A})$. Here, with $\varphi_t = \big(R_{\mathcal{B}}(\omega_t)\big)_{\mathcal{B}\in\mathbb{P}(S)}$, one finds $\varphi_t = M^t\varphi_0$ for $t \in \mathbb{N}_0$, where M is the Markov matrix given by

$$M_{\mathcal{B}\mathcal{C}} \,=\, \begin{cases} \prod_{i=1}^{|\mathcal{B}|} r^{B_i}(\mathcal{C}|_{B_i}), & \text{if } \mathcal{C} \preccurlyeq \mathcal{B}, \\ 0, & \text{otherwise,} \end{cases} \tag{11}$$

where r^U for $U \subseteq S$ is defined as in (3); see [1] for details. The rest is analogous.

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A coalescent dual process for a Wright–Fisher diffusion with recombination

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(joint work with Robert C. Griffiths, Sabin Lessard)

Duality plays an important role in population genetics. Two well-known models for genetic drift in a large, panmictic population are the *Wright–Fisher diffusion* $X = (X_t \in [0,1] : t \geq 0)$, with infinitesimal generator

$$\mathscr{L} f(x) = \frac{1}{2} x(1-x) f''(x), \qquad \mathscr{D}(\mathscr{L}) = C^2([0,1]);$$

and the *block-counting* process $L = (L_t \in \mathbb{N} : t \geq 0)$ of the coalescent, with generator

$$\mathscr{K} f(n) = \binom{n}{2} [f(n-1) - f(n)].$$

The two models are weak moment duals in the sense that, for $F(x,n) = x^n$,

$$\mathscr{L} F(\cdot, n)(x) = \mathscr{K} F(x, \cdot)(n). \tag{1}$$

This is important from a statistical viewpoint since it tells us the two models lead to the same likelihoods. There have been numerous extensions to this result to incorporate more general type spaces, selection, and recombination, but in each case the contribution of mutation to the dual process is either absent or deterministic. A different choice of duality function F yields a new class of genealogical processes in which lineages are labelled by an allelic type and mutation contributes random jumps. These processes are important because they describe the *posterior* genealogical dynamics of a given sample. They can also be used to find an expression for the transition function of the dual diffusion.

Consider now a multidimensional diffusion process $\boldsymbol{X} = (\boldsymbol{X}_t \in \Delta_E : t \geq 0)$ on the simplex $\Delta_E = \left\{ \boldsymbol{X} = (x_i)_{i \in E} \in [0,1]^E : \sum_{i \in E} x_i = 1 \right\}$, where E is the type space. A general strategy for finding the corresponding 'posterior' dual $\boldsymbol{L} = (\boldsymbol{L}_t \in \mathbb{N}^{|E|} : t \geq 0)$ is to pose a duality function $F : \Delta_E \times \mathbb{N}^{|E|} \to \mathbb{R}$ of the form

$$F(\boldsymbol{x}, \boldsymbol{n}) = \frac{1}{m(\boldsymbol{n})} \prod_{i \in E} x_i^{n_i},$$

for some $m : \mathbb{N}^{|E|} \to \mathbb{R}$ yet to be determined, and then to choose $m(\boldsymbol{n})$ so that a duality equation of the form (1) holds (e.g. [1]). However, this strategy has not been attempted for models of crossover recombination; this is the goal of the work described here.

In an L-locus model with recombination, denote the (finite) type space, mutation parameter, and mutation transition matrix by E_l, θ_l, and $\boldsymbol{P}^{(l)}$, respectively, for locus $l = 1, \ldots, L$. Between locus l and $l+1$, denote the recombination parameter by ρ_l. Let $E = E_1 \times \cdots \times E_L$, $\boldsymbol{i}_{-l,j} = (i_1, \ldots, i_{l-1}, j, i_{l+1}, \ldots, i_L)$, and $x_{\boldsymbol{i}}^A = \sum_{\boldsymbol{j} \in E : \boldsymbol{j}|_A = \boldsymbol{i}} x_{\boldsymbol{j}}$ denote a marginal frequency of alleles at the loci in

$A \subseteq \{1, \dots L\}$. The diffusion on Δ_E is described by the generator

$$\mathscr{L} = \frac{1}{2} \sum_{\boldsymbol{i} \in E} \left[\sum_{\boldsymbol{j} \in E} x_{\boldsymbol{i}} (\delta_{\boldsymbol{ij}} - x_{\boldsymbol{j}}) \frac{\partial}{\partial x_{\boldsymbol{j}}} + \sum_{l=1}^{L} \theta_l \left[\sum_{j \in E_l} P^{(l)}_{j i_l} x_{\boldsymbol{i}_{-l,j}} - x_{\boldsymbol{i}} \right] + \sum_{l=1}^{L-1} \rho_l (x_{\boldsymbol{i}}^{\{1,\dots,l\}} x_{\boldsymbol{i}}^{\{l+1,\dots,L\}} - x_{\boldsymbol{i}}) \right] \frac{\partial}{\partial x_{\boldsymbol{i}}}. \tag{2}$$

Before proceeding with the strategy outlined above, note that we would like the resulting dual, call it $\boldsymbol{L}$, only to label loci that are ancestral to the leaves of the genealogy. We can achieve this by a slight modification of the state space of $\boldsymbol{L}$ and of the duality function. More precisely, replace $\mathbb{N}^{|E|}$ with

$$\Xi_E = \left\{ \boldsymbol{n} = (n^A_{\boldsymbol{i}})_{\emptyset \neq A \subseteq [L],\, \boldsymbol{i} \in E_A} : n^A_{\boldsymbol{i}} \in \mathbb{N} \right\}, \qquad \text{where} \qquad E_A = \times_{l \in A} E_l.$$

This now labels each lineage both by a type and by a set A identifying the loci at which a lineage is ancestral. Now the appropriate form for the duality function $F : \Delta_E \times \Xi_E \to \mathbb{R}$ becomes

$$F(\boldsymbol{x}, \boldsymbol{n}) = \frac{1}{m(\boldsymbol{n})} \prod_{\emptyset \neq A \subseteq [L]} \prod_{\boldsymbol{i} \in E_A} (x^A_{\boldsymbol{i}})^{n^A_{\boldsymbol{i}}}. \tag{3}$$

We have derived the appropriate choice for $m(\boldsymbol{n})$ and the dual process $\boldsymbol{L}$:

Theorem. *Let* $m(\boldsymbol{n}) = \mathbb{E}\left[\prod_{\emptyset \neq A \subseteq [L]} \prod_{\boldsymbol{i} \in E_A} (X^A_{\boldsymbol{i}})^{n^A_{\boldsymbol{i}}} \right]$. *With respect to the duality function* (3), $\boldsymbol{X}$ *is dual to a Markov process on* Ξ_E *with transitions as follows:*
Coalescence. *For each* $A, B \subseteq [L]$, $\boldsymbol{i} \in E_{A \cup B}$, *the process jumps from* $\boldsymbol{n}$ *to* $\boldsymbol{n} - \boldsymbol{e}^A_{\boldsymbol{i}} - \boldsymbol{e}^B_{\boldsymbol{i}} + \boldsymbol{e}^{A \cup B}_{\boldsymbol{i}}$ *at rate*

$$\frac{1}{2} \frac{m(\boldsymbol{n} - \boldsymbol{e}^A_{\boldsymbol{i}} - \boldsymbol{e}^B_{\boldsymbol{i}} + \boldsymbol{e}^{A \cup B}_{\boldsymbol{i}})}{m(\boldsymbol{n})} n^A_{\boldsymbol{i}} (n^B_{\boldsymbol{i}} - \delta_{AB}),$$

where $\boldsymbol{e}^C_{\boldsymbol{j}}$ *is a unit vector in* Ξ_E *with a 1 in the entry corresponding to* $C \subseteq [L]$ *and* $\boldsymbol{j} \in E_C$, *and 0 otherwise; and where* δ_{AB} *is 1 if* $A = B$ *and 0 otherwise.*
Mutation. *For each* $A \subseteq [L]$, $l \in A$, $\boldsymbol{i} \in E_A$, $j \in E_l$, *the process jumps from* $\boldsymbol{n}$ *to* $\boldsymbol{n} - \boldsymbol{e}^A_{\boldsymbol{i}} + \boldsymbol{e}^A_{\boldsymbol{i}_{-l,j}}$ *at rate*

$$\frac{1}{2} \frac{m(\boldsymbol{n} - \boldsymbol{e}^A_{\boldsymbol{i}} + \boldsymbol{e}^A_{\boldsymbol{i}_{-l,j}})}{m(\boldsymbol{n})} n^A_{\boldsymbol{i}} \theta_l P^{(l)}_{j i_l}.$$

Recombination. *For each* $A \subseteq [L]$, $\boldsymbol{i} \in E_A$, $l = \min A, \dots, \max A - 1$, *the process jumps from* $\boldsymbol{n}$ *to* $\boldsymbol{n} - \boldsymbol{e}^A_{\boldsymbol{i}} + \boldsymbol{e}^{A \cap \{1,\dots,l\}}_{\boldsymbol{i}} + \boldsymbol{e}^{A \cap \{l+1,\dots,L\}}_{\boldsymbol{i}}$ *at rate*

$$\frac{1}{2} \frac{m(\boldsymbol{n} - \boldsymbol{e}^A_{\boldsymbol{i}} + \boldsymbol{e}^{A \cap \{1,\dots,l\}}_{\boldsymbol{i}} + \boldsymbol{e}^{A \cap \{l+1,\dots,L\}}_{\boldsymbol{i}})}{m(\boldsymbol{n})} n^A_{\boldsymbol{i}} \rho_l.$$

One application of this result is to obtain expressions for haplotype fixation probabilities in the absence of mutation. When $\theta = 0$, any unit atom on a single haplotype is an invariant distribution for $\boldsymbol{X}$, and we can find a corresponding dual

process. In other words, a dual process arises by ignoring the types of lineages and tracking only the sets indicating ancestry. For a sample of size one, the state space is equivalent to partitions on $\{1,\dots,L\}$ and the dual process $\Theta = (\Theta_t : t \geq 0)$ has been called the *partitioning process* [3]. Specialising the Theorem to this case, we find that its generator is

$$\mathscr{P}f(\Phi) = \frac{1}{2}\sum_{A\in\Phi}\sum_{B\in\Phi\setminus\{A\}}\left[f(\Phi\cup\{A\cup B\}\setminus\{A,B\}) - f(\Phi)\right]$$
$$+\frac{1}{2}\sum_{A\in\Phi}\sum_{l=\min A}^{\max A-1}\rho_l\left[f\left(\Phi\cup\left\{A\cap\{1,\dots,l\},A\cap\{l+1,\dots,L\}\right\}\setminus A\right) - f(\Phi)\right].$$

The partitioning process describes the way genetic material of an individual disperses among its ancestors backwards in time, and has been studied by several authors, e.g. [3, 6]. The duality equation for the partitioning process can be used to show that its stationary distribution, $\mathbb{P}(\Theta_\infty = \Phi)$, is equal to the probability that there are $|\Phi|$ individuals whose descendants cause a haplotype to fix according to the partition Φ—that is, if ϕ_k is the kth block of Φ then the kth of the $|\Phi|$ individuals is the ancestor to the whole population at the loci in ϕ_k.

Two open problems related to this work are as follows. First, is it possible to incorporate both recombination and selection? This would require consolidating the present work with [1]. Second, the function $m(\cdot)$ is fundamental to this and related work: it governs the jump rates of the dual, the transition function of the diffusion, and likelihoods of sampled data. Yet it is not known in closed form except for the special case of a reversible diffusion at one locus. Is it possible to say anything about $m(\cdot)$? Under the assumption of strong recombination ($\rho_l = 4N^\beta r$ for $\beta \in (0,1)$), a diffusion limit simpler than that of (2) has been derived for $L = 2$ [5]. It describes the Gaussian fluctuations of linkage disequilibrium (LD) about the linkage equilibrium manifold. Is it possible to extend these arguments for $L > 2$, and to obtain a 'posterior' dual in this limit? This question is not straightforward because there are numerous choices of co-ordinate system for multilocus LD [2].

The work described here is mostly based on [4].

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Growth-fragmentation equations and processes: Critical behaviours

Marie Doumic

(joint work with Etienne Bernard, Pierre Gabriel, Bruce Van Brunt)

Growth-fragmentation equations have risen much interest for several decades, since it appears in many applications, ranging from protein polymerisation to internet protocols or cell division equation. This equation under a fairly general form is the following:

$$\frac{\partial}{\partial t}u(t,x) + \frac{\partial}{\partial x}\big(g(x)u(t,x)\big) + B(x)u(t,x) = \int_x^\infty k(y,x)B(y)u(t,y)dy.$$

Here $u(t,x)$ denotes the concentration of "individuals" (e.g. proteins, or cells) of size x at time t, g their growth rate per instant of time, $B(x)$ the instantaneous fragmentation probability rate of individuals of size x and, among fragmenting particles of size y, $k(y,x)$ is the fragmentation probability to give rise to individuals of size x.

Under assumptions linking fragmentation and growth parameters B, k and g, a steady asymptotic behaviour appears, *i.e.* there exists a unique couple (λ, U) with $\lambda > 0$ such that $u(t,x)e^{-\lambda t} \to U(x)$ - see for instance the pioneering papers [6, 14], or more recently [5, 16] for a global picture. Many studies have focused on this most important case, also observed in biological experiments [17], and have investigated optimal assumptions to obtain this convergence, or optimal assumptions to have an exponential rate of convergence - linked to the existence of a spectral gap, see most recently [2].

To obtain a steady behaviour two main ingredients are needed.

First, balance assumptions linking B, g and k are required. In the exemplary case of power law parameters g and B, *i.e* assuming

$$\exists\, B_0 > 0,\ g_0 > 0, \quad B(x) := B_0 x^\gamma, \qquad g(x) := g_0 x^\nu, \tag{1}$$

Convergence towards a steady state may happen *iff* we have [15]

$$1 + \gamma - \nu > 0. \tag{2}$$

This illustrates very well the fact that fragmentation needs to be "strong enough" for large sizes compared to growth, so that the individuals cannot grow to infinity without fragmenting, and on the contrary growth needs to be "fast enough" for small sizes compared to fragmentation, so that the individuals cannot be trapped around zero, dividing more and more and giving rise to a concentration of $0-$size particles.

In [9], we studied one of the "critical" cases where $1 + \gamma - \nu = 0$, namely the case $\gamma = 0$ and $\nu = 1$. Cases $\gamma < 0$ and $\nu = 1$ have been studied by B. Haas [13] and probabilistic aspects by J. Bertoin and A. Watson [3, 4].

The main results obtained in [9] were the following:

- a formulation in terms of Mellin and inverse Mellin transform was obtained, as soon as the initial condition u_0 decays sufficiently fast,

- no steady or self-similar behaviour was possible for L^1 functions,
- the asymptotic behaviour was described along lines of the type $x = e^{-ct}$, with an exponential speed of convergence at places where the mass was decaying, but with at most polynomial growth for the lines where the mass concentrates,
- in the case of a fragmentation kernel defined as a dirac mass (or a sum of dirac masses linked by a specific algebraic relation), the asymptotic behaviour was also defined thanks to the Mellin transform, but was more involved, with an infinite sum of contributions and a still slower polynomial rate of convergence.

The second ingredient to obtain a steady asymptotic behaviour (exponential growth or decay) is that growth and fragmentation must be such that there is a kind of "dissipativity" in the equation, fragmenting individuals mixing together. This requires some more technical assumptions. The simplest but not optimal assumption is for instance that the probability kernel $k(y,\cdot)$ contains a part absolutely continuous with respect to the Lebesgue measure.

A typical case where this dissipativity fails to be satisfied is when the growth is exponential, *i.e.* $g(x) = g_0 x$, and the fragmentation is a dirac, $k(y,x) = \alpha\delta_{\frac{x}{y}=\frac{1}{\alpha}}$ with $\alpha > 1$. In such a case, we can see that following the characteristic curve of an individual of size x_0 at time $t = 0$, all its descendants at time t belong to the countable set $x_0 e^{g_0 t} 2^{-n}$, $n \in \mathbb{Z}$.

In such a case, if the division rate B is such that there exists a positive eigentriplet (λ, U, ϕ) where (λ, U) is solution of the eigenproblem and (λ, ϕ) of the dual eigenproblem (e.g. under the assumptions in [10] applied to these specific g and k), there also exists a countable set of complex eigentriplets λ_k, U_k, ϕ_k with $k \in \mathbb{Z}$ of the form

$$\lambda_k = \lambda + \frac{2ik\pi}{\log\alpha}, \qquad U_k := x^{-\frac{2ik\pi}{\log\alpha}} U, \qquad \phi_k := x^{1+\frac{2ik\pi}{\log\alpha}}$$

which leads to a periodic limit cycle, see [1, 12]. In [1] we proved the following result, based on an entropy inequality, which surprisingly revealed useful despite the lack of dissipativity.

Theorem. *Assume that* $B : (0,\infty) \to (0,\infty)$ *is measurable, with* $B(x)/x \in L^1_{loc}(\mathbb{R}_+)$, *and*

$$\exists \gamma_0, \gamma_1, K_0, K_1 > 0,\ \exists x_0 \geq 0,\ \forall x \geq x_0, \quad K_0 x^{\gamma_0} \leq B(x) \leq K_1 x^{\gamma_1}.$$

Then for any $u_0 \in E_2 = L^2(\mathbb{R}_+, x/U(x)\,dx)$, *the unique solution* $u(t,x) \in C\left(\mathbb{R}_+, E_2\right)$ *to the equation*

$$\frac{\partial}{\partial t}u(t,x) + \frac{\partial}{\partial x}(gxu(t,x)) + bu(t,x) = b\alpha^2 u(t,\alpha x), \qquad u(0,x) = u^0(x). \tag{3}$$

satisfies

$$\int_0^\infty \left| u(t,x)e^{-t} - \sum_{k=-\infty}^{+\infty} (u_0, U_k)\, U_k(x) e^{\frac{2ik\pi}{\log 2}t} \right|^2 \frac{x\,dx}{U(x)} \xrightarrow[t\to+\infty]{} 0.$$

Numerical illustrations of this result, obtained using a non-dissipative numerical scheme, may be viewed in the small video [7].

In [11] finally, we combined the previous critical cases in a brief study, observing periodicity when a proper rescaling is chosen in the doubly critical case where $\gamma = 0$, $\nu = 1$ and $k(y, x) = \alpha\delta_{\frac{x}{y}=\frac{1}{\alpha}}$. This has been illustrated in the video [8].

Many open problems remain to be solved, among them we can quote: critical behaviours in other cases $1 + \gamma - \nu = 0$; link between the probabilistic results and the deterministic ones; further studies of the "over critical" cases $1 + \gamma - \nu < 0$.

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Algebraic tips in the study of biochemical reaction networks

Alicia Dickenstein

The algebraic tips summarized in this short notice of my talk evolved from my previous joint articles [4, 5], and discussions with Jeremy Gunawardena on the use of algebraic invariants to eliminate complexity in steady–state analysis of biological network. We refer the reader to the survey article [2] for further references.

Setting: Chemical reaction networks with mass-action kinetics

A *chemical reaction network* (on a finite set of s species, which we assume ordered) is a finite labeled directed graph $G = (V, E, (\kappa_{ij})_{(i,j)\in E}, (y_i)_{i=1,\dots,m})$, whose vertices are labeled by complexes $y_1, \dots, y_m \in \mathbb{Z}^s_{\geq 0}$ and whose edges $i \stackrel{\kappa_{ij}}{\to} j$, are labeled by positive real numbers. Mass-action kinetics specified by the network G gives the following autonomous system of ordinary differential equations in the *concentrations* $x = (x_1, x_2, \dots, x_s)$ of the species as functions of time:

$$\frac{dx}{dt} \quad = \quad \sum_{(i,j)\in E} \kappa_{i,j}\, x^{y_i}\, (y_j - y_i) \quad = \quad f_\kappa(x). \tag{1}$$

Note that the coordinates $f_1, \dots, f_s$ of f_κ are polynomials in $\mathbb{R}[x_1, \dots, x_s]$. Many systems occurring in population dynamics, for example the oscillatory Lotka–Volterra equations, can be viewed as arising from a chemical reaction network as in (1), but for instance not the "chaotic" Lorenz equations.

Another direct consequence of the form of the equations in (1) is that for any trajectory $x(t)$, the vector $\frac{dx}{dt}$ lies for all t (in any interval $I = [0, t_0)$ where it is defined) in the so called *stoichiometric subspace* S, which is the linear subspace generated by the differences $\{y_j - y_i \,|\, (i,j) \in E\}$. Using the shape of the polynomials f_i it can be seen that the positive orthant $\mathbb{R}^s_{>0}$ (and then also its closure $\mathbb{R}^s_{\geq 0}$) is forward-invariant for the dynamics. Then, any trajectory $x(t)$ starting at a nonnegative point $x(0)$ lies for all $t \in I$ in the closed polyhedron $(x(0)+S)\cap\mathbb{R}^s_{\geq 0}$, called a *stoichiometric compatibility class*. Given a basis $\ell_1, \dots, \ell_q$ of linear forms in $S^\perp$, the equations $\ell_1(x) = T_1, \dots, \ell_q(x) = T_q$ (where $T_i = \ell_i(x(0))$) of $x(0) + S$ are called conservation relations and the constant coefficient T_i of such a linear equation is called a *total amount*.

One main question in biochemical reaction networks: multistationarity

The positive steady state variety $V_\kappa(f)$ of the kinetic system (1) equals the positive real zeros of $f_1, \dots, f_s$. Any element of $V_\kappa(f)$ is called a steady state of the system. We say that system (1) exhibits multistationarity if there exist at least two steady states with the same total amounts, that is, in the same stoichiometric compatibility class. In fact, the underlying reaction network $G' = (V, E, ((y_i)_{i=1,\dots,m})$ defines a *family* of autonomous polynomial dynamical systems depending on positive parameters $\kappa \in \mathbb{R}^{\#E}_{>0}$. We say that G' has the *capacity for multistationarity* if there are reaction rate constants $(\kappa_{ij})_{(i,j)\in E}$ and total amounts $T_1, \dots, T_q$ for which the intersection of the steady state variety V_κ with the *positive* points of linear variety $S_T = \{\ell_1(x) - T_1 = \cdots = \ell_q(x) - T_q = 0\}$ consists of more than one point. This

is a crucial property for chemical reaction networks modeling biological processes, since the ocurrence of multistationarity allows for the richness of responses of the cell.

The important biological mechanism of n *sequential* phospho-dephosphorylations is a chemical reaction network with $3n + 3$ species (so $3n + 3$ variables, corresponding to the concentrations of $n + 1$ substrates, $2n$ intermediate species and 2 enzymes, a kinase and a phosphatase), $4n+2$ complexes and $6n-6$ reactions (so $6n-6$ reaction rate constants). For any n, S has codimension 3, so there are 3 linearly independent conservation relations. So S_T can be cut out by 3 equations, where usually the total amounts correspond to total substrate, total kinase and total phosphatase. Therefore, there are only $3n$ linearly independent differential equations in the system. It is well known that the underlying reaction network has the capacity for multistationarity and that for $n = 2$ there can be up to 3 positive steady states in $V_\kappa(f) \cap S_T$ (for particular choices of the rate constants κ and the total amounts T). This system has been first studied by L. Wang and E. Sontag (2008). The maximal possible number of positive steady states for the general n-site sequential phosphorylation mechanism is still unknown.

What is the *expected* number of variables?

We need to describe the intersections $V_\kappa(f) \cap S_T$ (called stoichiometric compatibility classes) in the positive orthant. The steady state variety is defined in principle by s polynomial equations. Assume the dimension of S (and thus of S_T for any T) equals $s - q$ and can thus be defined by q linear equations. This implies that there are (at most) $s - q$ linearly independent polynomials among $f_1, \ldots, f_s$. A finite number of common solutions is expected, but this might not be true.

As S_T are linear varieties, they can be also parametrized by $s - q$ parameters. For general algebraic varieties, one can find implicit presentations from a (rational) parametrization, but (rational) parametrizations do not exist in general. However, parametrizations do exist for the steady state variety in many enzymatic biochemical networks, as proved by M. Thomson and J. Gunawardena (2009) and in many other networks of biological interest. In particular, s-toric MESSI systems (which contain the n-site phosphorilation networks) can be defined by binomial equations and have explicit monomial parametrizations described in [5]. We refer the reader to this paper for precise definitions.

In the case of the n-sequential phosphorilation network we can parametrize the steady state variety with 3 parameters. To compute the intersection $V_\kappa(f) \cap S_T$, we can write 3 of the variables in terms of the remaining $3n$ variables from the 3 conservation relations and replace them into $3n$ linearly independent f_i (which exist in this case). This yields a system of $3n$ equations in $3n$ variables. Instead, we could plug in the parametrization into the conservation relations and thus get 3 equations in 3 variables. This is what makes the n-site amenable to computations even if in principle the number or variables tends to infinity with n.

Deciding the capacity for multistationarity

There are many results to decide the capacity for multistationarity of a given chemical reaction network. Most of them have been summarized in Theorem 1.4 of [4]. In fact, these results give in general sufficient and necessary conditions for the stronger condition that the map f_κ tis injective on the positive points of all stoichiometric compatibility classes. In the particular case of an s-toric MESSI system, we give necessary and sufficient conditions for multistationarity in Theorem 4.6 in [5], where an algorithm to find particular choices of rate constants for which the system is multistationariy is presented (in case this has been determined to be possible), based on the theory of oriented matroids. There are several implementations of different algorithms, starting with the pioneering algorithm implemented by Feinberg and his group in the Chemical Reaction Network Toolbox. The link to the corresponding webpage together with links to other algorithms can be found at `https://reaction-networks.net/wiki/Mathematics_of_Reaction_Networks`.

Once the network has the capacity for multistationarity, the next main question is how to predict regions in parameter space which give rise to multistationary systems. The nice recent article [1] deals with this question based on degree theory. Their results provide in case of the existence of a positive rational parametrization a (*necessary and sufficient*) characterization of rate constants κ for which the corresponding system $\frac{dx}{dt} = f_\kappa(x)$ is multistationary. The total amounts are not part of the description since they are determined from the positive steady states, as in the previous algorithms. A different approach using results from real algebraic geometry by F. Bihan and P.-J. Spaenlehauer (2015) has been developed in [3], where we only get open *sufficient* conditions, but jointly on rate constants and total amounts. These tools allow us to find precise multistationarity regions in enzyme cascades with any number n of layers, which are multistationary as soon as the two first phosphatases are the same. Interestingly, the number of variables is of the order of $4n$ and the dimension of the stoichiometric subspace S is of the order or $2n$, so it is cut out by roughly $2n$ equations and parametrized by a similar number of variables. So, in both cases described above, we need to deal with of the order of $2n$ equations in $2n$ variables.

Open questions

Once the capacity for multistationarity of a given chemical reaction network has been established, the main open questions in the area are:

(1) Develop tools to find the number of positive steady states. As previous steps: (a) develop tools to obtain better *lower bounds* for the number of positive steady states; (b) develop tools to get *upper bounds* for the number of positive steady states.
(2) Find regions in parameter space with the predicted number of positive steady states, or at least where lower/upper bounds apply.

These are difficult questions in real algebraic geometry and systems of biological interest usually have a big number of variables and parameters.

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Dynamical roles of intercellular randomness: Some Case Studies

Ankit Gupta

Intracellular processes are characterized by a lot of dynamical noise. Several recent works have demonstrated that this dynamical noise can play useful functional roles in Biology. The aim of my talk is to present some case studies in this direction. These studies emphasize the beneficial effects of intracellular noise on important biological processes which are crucial for the functioning of an organism. Below I provide more details on these studies and mention its main findings.

(1) **Cell Polarity:** The phenomenon of cell polarity refers to the clustering of molecules on the cell membrane. It is well-established that the formation of membrane clusters requires positive feedback between membrane bound molecules and the molecules in cytosol. However as the membrane molecules are constantly diffusing, it is unclear if the positive feedback alone is sufficient to generate and sustain cell polarity. In my talk I present results from [1] where I prove using tools from *population genetics* that if membrane diffusion occurs at a slower timescale than the feedback mechanism, then a *Fleming–Viot* process can be derived in the infinite population limit which shows that positive feedback is indeed sufficient to reliably create cell polarity. Interestingly the establishment of cell polarity depends crucially on the stochastic nature of the molecular dynamics, and this phenomenon does not occur if all the interactions are assumed to be deterministic. The study in [1] considers only a basic model of cell polarity but in another work [2], I prove that the same conclusions can be drawn for more complicated polarity models with many types of molecular species and interactions.

(2) **Cellular Homeostasis:** This property refers to the ability of a cell-population to effectively discard external shocks and maintain a constant level of key molecular species. I will discuss how a simple *integral feedback*

controller motif can implement this adaptation feature and how the biochemical noise inside cells plays a fundamental role in realizing the homeostatic property. This part of the talk is based on the results reported in [3].

(3) **Entrainment of oscillatory cell-populations:** Many intracellular circuits have oscillatory dynamics. Often these oscillators entrain to external periodic inputs by *loosing* their natural frequency and adopting the frequency of the input signal. This phenomenon is called entrainment and it is crucial for proper physiological functioning of an organism. Intracellular dynamics is fundamentally noisy we would expect this noise to cause disruptions in the entrainment response of oscillatory circuits. While this is true at the single-cell level, surprisingly the opposite is true at the population-level where the response of several noisy oscillators is averaged. I mathematically explain this phenomenon and present experimental evidence for it. This part of the talk is based on the results reported in [4].

(4) **Amplification of enzyme substrates:** Many biomolecular reactions are catalyzed by enzymes. The key rate parameter that quantifies enzymatic activity is generally assumed to be a deterministic constant. This assumption is often inaccurate because enzymatic activity is inherently stochastic due to fluctuations in the conformational states of enzymes and also their abundance levels within a cell. I show that these fluctuations can cause a large amplification in the concentration of the substrate on which the enzyme acts and I present mathematical results that quantify the amount of amplification based on the information about the kinetics of fluctuations in enzymatic activity. This part of the talk is based on the results reported in [5].

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Persistence, permanence, and global stability of interaction network models

Gheorghe Craciun

The main topic of this presentation is mathematical models of interaction networks, and especially mathematical models of biological interactions.

For example, many diseases are associated with the loss of one or more types of molecules in affected cells, and this loss can destabilize normal cellular processes. A better understanding of this process is of very high interest in biology and medicine, because recovery of these processes in affected cells is a potential therapeutic target.

We discuss a mathematical approach to understanding biological interaction networks, by using differential equations to model the dynamics of concentrations of various types of molecules involved in these networks, or more generally the dynamics of populations in a network of interacting populations. Very often, the standard dynamical systems models for such interactions are polynomial dynamics systems.

Polynomial dynamical systems are very common in many types of applications. For example, the most common population dynamics models for the spread of infectious diseases or the dynamics of species in a ecosystem are polynomial dynamical systems. On the other hand, there are many important unsolved mathematical problems about polynomial dynamical systems: for example, Hilbert's 16th problem about limit cycles, and problems about understanding chaotic dynamics.

We describe mathematical properties of these networks that may allow us to understand which types of biological feedbacks are essential for the *stability* of normal cellular processes. More specifically, we discuss the mathematical properties of "persistence" and "permanence" that are very closely related to the stability and homeostasis properties of biological interaction networks.

We will describe the *Global Attractor Conjecture*, which says that a large class of polynomial dynamical systems has solutions that converge to a fixed point, and in particular cannot exhibit cycles or chaotic dynamics. The conjecture was formulated by Fritz Horn in the early 1970s, and was inspired by his study of mathematical models of chemical reaction networks with mass-action kinetics. We will discuss an approach for proving this conjecture, as well as connections with thermodynamics (the Boltzmann equation) and other implications for models of population dynamics.

In addition, we also describe the other two main conjectures in this field: the *Persistence Conjecture*, and the *Permanence Conjecture*. These conjectures say that all weakly reversible networks give rise to persistent dynamics (i.e., any solution of such a system has a positive lower bound) and moreover, the dynamics is permanent (i.e., there exist uniform lower and upper bounds for all solutions of such systems for large enough t). We give an overview of recent results and the current state of the art on the study of these conjectures.

Mathematical models for T-cell activation

Alan Rendall
(joint work with Eduardo D. Sontag)

T cells are a component of central importance in our immune system. One of their main tasks is to recognize foreign substances (antigens) and become activated. The process is initiated when the antigen binds to the T cell receptor, a molecule on the cell surface. When this happens chemical reactions take place in the cell which change its behaviour. Mathematical models for the reactions involved can help to understand the complex process of T cell activation. There is a mathematical model of this process due to Altan-Bonnet and Germain [1] which is so large and complicated as to be difficult to treat with analytical techniques. At the same time there is a later simplified version of this model due to François et. al. [2] which has had comparable success in explaining experimental data. Together with Eduardo Sontag we examined the qualitative properties of solutions of the model of François et. al. analytically [3].

The model of [2] is constructed by writing down a network encoding the chemical reactions involved in the process and applying mass action kinetics to get a system of ordinary differential equations depending on many parameters. One parameter of the system is a positive integer N which is the maximal number of phosphate groups which can be attached to the T cell receptor in the model. We showed that while in the cases $N = 1$ and $N = 2$ the system has a unique positive steady state this is no longer the case for $N = 3$. In the latter case there are parameters for which there exist three positive steady states. Simulations indicate that two of these states are stable but this remains to be proved. In order to prove the existence of steady states variables are eliminated from the system of algebraic equations whose solutions are the steady states until a quartic equation for one variable remains. Then it is shown that parameters can be chosen for which this polynomial has three positive roots.

Of central biological interest is the response function $C_N^* = f(L, \nu)$. Here C_N is the concentration of the maximally phosphorylated state of the T cell receptor and the star indicates that it is evaluated in a steady state. The quantities L and ν are the parameters in the system which are believed to be most important in controlling T cell activation. L is the concentration of antigen while ν is the inverse of the time for which the antigen remains bound to the receptor. The function f describes the degree of activation of the cell, as represented by C_N, as a function of the main input parameters. At first sight it is plausible that f should be an increasing function of L and a decreasing function of ν. However this turns out not to be the case. We proved that in certain parameter regimes the function f can be approximated by a function $f_{\rm app} = g \circ h$. Here the function h is explicit and has the monotonicity properties guessed to hold for f. On the other hand the function g is more complicated and can be approximated by different explicit functions in different ranges of its argument. The result is that $f_{\rm app}$ has the following properties. For L small $\log f_{\rm app}$ is a linear function of $\log L$ with slope one. Then

it turns around and becomes a linear function of $\log L$ with slope $1 - N/2$. Next it returns to being a linear function with slope one which is translated compared to what it was for small L. Finally, since it is bounded, the function tends to a constant for large L. These conclusions give rigorous mathematical statements corresponding to previous simulations and experimental measurements. We were able to extend them further to obtain new results on the dependence of f on ν.

Going beyond the results of [3] it can be asked what can be said about the asymptotics of solutions in the case of the model of [1]. Here only one aspect of this will be mentioned. In both models considered here there is a kinetic proofreading submodule. It was shown in [4] using the Deficiency Zero Theorem of Chemical Reaction Network Theory that the system corresponding to the kinetic proofreading module of the model of [2] has a unique positive steady state which is globally asymptotically stable. It appears that things are much more complicated for the model of [1] with even the kinetic proofreading module having deficiency one under even the strongest simplifying assumptions. It is unknown whether it admits multiple steady states. This suggests an interesting avenue for further investigation.

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Mutation, selection, and ancestry in the deterministic limit of the Moran model

Fernando Cordero

(joint work with Ellen Baake, Sebastian Hummel)

The 2-type Moran model with selection and mutation describes the evolution of a population of constant size N consisting of individuals that are characterized by a type $i \in \{0, 1\}$. The underlying dynamics are given as follows. Individuals of type 1 reproduce at rate 1, whereas individuals of type 0 reproduce at rate $1 + s_N$, $s_N \geq 0$. If an individual reproduces, its single offspring inherits the parent's type and replaces a uniformly chosen individual, possibly its own parent. Mutation occurs independently of reproduction. Each individual mutates at rate u_N; the type after the event is i with probability ν_i, $i \in \{0, 1\}$.

Let Y_t^N be the proportion of type-1 individuals at time t. It is well known that, when the parameters of selection and mutation satisfy $\lim_{N\to\infty} Nu_N < \infty$ and

$\lim_{N\to\infty} Ns_N = \sigma < \infty$, the rescaled process $(Y^N_{Nt})_{t\geq 0}$ converges to the proportion of type-1 individuals in the Wright-Fisher diffusion model.

In contrast to the diffusion limit regime, we assume here that the parameters of selection and mutation are independent of population size, i.e. $u_N \equiv u$ and $s_N \equiv s$. In this setting a deterministic limit emerges when N tends to ∞. More precisely, it was shown in [1] that, if $Y^N_0 \xrightarrow[N\to\infty]{} y_0$, then $(Y^N_t)_{t\geq 0}$ converges to the solution $y(\cdot, y_0)$ of the initial value problem

$$\begin{aligned} &\tfrac{dy}{dt}(t) = -sy(t)(1-y(t)) - u\nu_0 y(t) + u\nu_1(1-y(t)), \quad t \geq 0, \\ &y(0, y_0) = y_0. \end{aligned} \tag{1}$$

The convergence is uniform on compact sets of time in probability and is a consequence of the law of large numbers for density dependent populations of Kurtz [4]. The initial value problem (1) is the classical mutation-selection equation of population genetics [3]. It has a unique stable equilibrium point in $[0,1]$, which is given by

$$\bar{y} := \begin{cases} \frac{1}{2}\left(1 + \frac{u}{s} - \sqrt{\left(1-\frac{u}{s}\right)^2 + 4\frac{u}{s}\nu_0}\right) & \text{if } s > 0, \\ \nu_1 & \text{if } s = 0. \end{cases} \tag{2}$$

Our first goal is to attach an ancestral process to the previously described deterministic model. In the Moran model one can trace back potential ancestors of a given sample of the population with the help of the ancestral selection graph (ASG) of Krone and Neuhauser [5]. When N tends to ∞, keeping s and u constant, the ancestral selection graph admits an asymptotic version, which is constructed in the following three step procedure: (1) start with n lines representing a sample of the population at (forward) time t. Each line branches independently at rate s into an *incoming branch* and a *continuing branch*, both representing potential ancestors of the line that branches, the *descendant line*. The true parent depends on the type of the incoming branch, but for the moment we work without types. In addition, each line is decorated by a mutation to type i at rate $u\nu_i$, $i \in \{0,1\}$, (2) assign types independently to each potential ancestor according to the initial distribution of types, and (3) propagate the types forward in time, keeping track of the changes by respecting the mutation events. At every selective event, the incoming branch is the ancestor if it is of type 0, otherwise the ancestor is the continuing line.

A relation between the deterministic mutation-selection model and the asymptotic ASG is obtained as follows. First, note that $y(t, y_0)$ can be understood as the probability of sampling a type-1 individual at time t, where y_0 represents the initial proportion of type-1 individuals. Backward in time, we use the following observation: in the absence of mutations, the type of the sampled individual at time t is 1 if an only if all its potential ancestors at time 0 are of type 1. A deleterious mutation on a given line transfer type 1 on to its descendants, and hence we don't need to trace its ancestry further into the past. This leads to a pruning in the ASG at rate $u\nu_1$ per line. The first beneficial mutation in the pruned

ASG determines the type of the sampled individual, and therefore we can stop the process. The so-constructed process is called the *killed ASG*. In particular, the line-counting process $(R_t)_{t\geq 0}$ of the killed ASG is a continuous time Markov chain with state space $\mathbb{N}\cup\{0,\Delta\}$ (Δ is a cemetery point) and transition rates:

$$q_R(i,j)=\begin{cases} is, & \text{if } j=i+1,\ i\neq\Delta\\ iu\nu_1, & \text{if } j=i-1,\ i\in\mathbb{N},\\ iu\nu_0, & \text{if } j=\Delta,\ i\neq\Delta.\end{cases}$$

The states 0 and Δ are absorbing. The previous arguments can be made rigorous, leading to the following duality relation:

$$y(t,y_0)=E\left[y^{R_t}|R_0=1\right],\qquad t\geq 0, y_0\in[0,1]. \tag{3}$$

In particular, taking the limit when t tends to ∞ in (3), we see that the equilibrium point $\bar{y}$ corresponds to the absorption probability of R in 0. If $\nu_0=0$, formula (2) can be recovered from classical results on birth and death processes with linear growth. If $\nu_0>0$, formula (2) is obtained by means of a first step analysis.

Now we turn our attention to the *representative ancestral type*, i.e. the type of the ancestor of a generic individual in the population. The ancestral process which permits to determine the representative ancestral type is called *pruned lookdown ASG* (pLD-ASG), and was introduced first in [6] in the diffusion limit setting and extended to the Moran model and its deterministic limit in [2]. We recall here its construction in the deterministic limit regime. The pLD-ASG starts with n lines. Each line is assigned a different level from 1 to n. Every line branches at rate s; the incoming line takes the level of the descendant line; the continuing line is assigned the level above the incoming line; all the lines that were above the descendant line are shifted one level upwards. Every line, except the top line, is pruned at rate $u\nu_1$; all the lines above the line affected by the deleterious mutation are shifted one level downwards. At rate $u\nu_0$, all the lines at higher levels than the one affected by the beneficial mutation are pruned. In particular, the line-counting process of the pLD-ASG is the continuous time Markov chain $(L_t)_{t\geq 0}$ with transition rates:

$$q_L(i,j)=\begin{cases} is, & \text{if } j=i+1\\ (i-1)u\nu_1+u\nu_0 1_{\{i>1\}}, & \text{if } j=i-1,\\ u\nu_0, & \text{if } 1\leq j\leq i-2.\end{cases}$$

The pLD-ASG has the feature that the ancestor of a single individual is of type 1 if and only if all the lines in the corresponding pLD-ASG are of type 1. In particular, if we let J_t be the representative ancestral type at time t, i.e. the type at time 0 of the ancestor of a sampled individual at time t, then

$$g_t(y_0):=P_{y_0}(J_t=1)=E[y_0^{L_t}|L_0=1], \tag{4}$$

where under P_{y_0} the types are assigned to the lines in the pLD-ASG in an i.i.d. manner according to the distribution $(1-y_0,y_0)$. We are particularly interested in taking the limit when t tends to ∞ in (4).

The process L is positive recurrent if and only if $\nu_0 > 0$ or $u > s$. Moreover, its stationary distribution is geometric with parameter $1 - p$, where

$$p = \begin{cases} \frac{s}{u\nu_1}\bar{y}, & \text{if } \nu_1 > 0, \\ \frac{s}{s+u}, & \text{if } \nu_1 = 0. \end{cases}$$

This was already shown in [2]. We provide two alternative proofs of this fact. The first one is based on a graphical argument. The second one is based on a first step analysis for a process which is Siegmund dual to the the process L.

The fact that the stationary distribution of the process L is geometric leads to explicit formulas for $g_\infty(y_0) := \lim_{t\to\infty} g_t(y_0)$ and for $g_\infty(\bar{y})$. Finally, we discuss about possible extensions to the multi-locus case with additive selection.

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A scaling limit for the block counting process and the fixation line of the Bolthausen–Sznitzman coalescent

Martin Möhle

(joint work with Jonas Kukla)

1. Mittag–Leffler process

Let ξ be Mittag–Leffler distributed with parameter $\alpha \in [0, 1]$. Note that $\mathbb{P}(0 < \xi < \infty) = 1$ and that the distribution of ξ is uniquely determined by its moments $\mathbb{E}(\xi^m) = m!/\Gamma(\alpha m + 1)$, $m \in \mathbb{N}_0 := \{0, 1, \ldots\}$, where Γ denotes the gamma function.

The Mittag–Leffler process $X = (X_t)_{t\geq 0}$ is a continuous-time Markov process with $X_0 = 1$ and state space $E := (0, \infty)$. The name of this process comes from the fact that for every $t \geq 0$ the marginal random variable X_t is Mittag–Leffler distributed with parameter e^{-t}. The semigroup $T^X = (T^X_t)_{t\geq 0}$ of X satisfies

$$T^X_t f(x) = \mathbb{E}(f(x^{e^{-t}} X_t)), \qquad t \geq 0, f \in B(E), x \in E, \tag{1}$$

where $B(E)$ denotes the space of all bounded measurable functions $f : E \to \mathbb{R}$. Conditional on $X_s = x$ the random variable $x^{-e^{-t}} X_{s+t}$ is Mittag–Leffler distributed with parameter e^{-t}. From the moment formulas in [6, Lemma 2.2] it follows that there exists a constant $M > 0$ such that $\mathbb{E}((X_t - X_s)^2) \le M|t-s|$ for all $s, t \ge 0$, that is, X is Hölder continuous with index 1. The paths of X are cadlag but not continuous. Let $\gamma := -\Gamma'(1) \approx 0.577216$ denote Euler's constant. The generator A^X of X satisfies

$$A^X f(x) \;=\; (1 - \gamma - \log x) x f'(x) + x \int_0^x \frac{f(x-h) - f(x) + h f'(x)}{h^2} \, \mathrm{d}h \tag{2}$$

for $x \in E$ and $f \in C_c^2(E)$, the set of two times continuously differentiable functions with compact support. For further details on X we refer the reader to [1, 5, 6].

2. Neveu's continuous-state branching process

Neveu's [7] continuous-state branching process $Y = (Y_t)_{t \ge 0}$ is as well a continuous-time Markov process with $Y_0 = 1$ and state space E. For every $t \ge 0$ the marginal random variable Y_t is α-stable with Laplace transform $\mathbb{E}(e^{-\lambda Y_t}) = e^{-\lambda^\alpha}$, $\lambda \ge 0$, where $\alpha := e^{-t}$. The semigroup $T^Y = (T_t^Y)_{t \ge 0}$ of Y is given by

$$T_t^Y g(y) \;=\; \mathbb{E}(g(y^{e^t} Y_t)), \qquad t \ge 0, g \in B(E), y \in E, \tag{3}$$

and the generator A^Y of Y satisfies

$$A^Y g(y) \;=\; (\gamma - 1 + \log y) y g'(y) + y \int_0^\infty \frac{g(y+h) - g(y) - \frac{yh}{y+h} g'(y)}{h^2} \, \mathrm{d}h \tag{4}$$

for $y \in E$ and $g \in C_c^2(E)$. The Mittag–Leffler process X is (see, for example, [6]) Siegmund dual to Neveu's continuous-state branching process Y, i.e. $\mathbb{P}(X_t \le y | X_0 = x) = \mathbb{P}(Y_t \ge x | Y_0 = y)$ for all $t \ge 0$ and $x, y \in E$.

3. Relations to the Bolthausen–Sznitman coalescent

The Bolthausen–Sznitman coalescent [4] is the particular Λ-coalescent [8, 9] where the measure Λ is the uniform distribution on the unit interval. For $n \in \mathbb{N} := \{1, 2, \ldots\}$ let $N^{(n)} = (N_t^{(n)})_{t \ge 0}$ and $L^{(n)} = (L_t^{(n)})_{t \ge 0}$ denote the block counting process and the fixation line respectively of the Bolthausen–Sznitman coalescent restricted to a sample of size n. Note that $L_t^{(n)} = \sup\{k \in \mathbb{N} : N_t^{(k)} \le n\}$ and $N_t^{(n)} = \inf\{k \in \mathbb{N} : L_t^{(k)} \ge n\}$, $t \ge 0$, $n \in \mathbb{N}$. In particular, $N^{(n)}$ is Siegmund dual to $L^{(n)}$, i.e. $\mathbb{P}(N_t^{(n)} \le m) = \mathbb{P}(L_t^{(m)} \ge n)$ for all $t \ge 0$, $n, m \in \mathbb{N}$. Define the scaled block counting process $X^{(n)} = (X_t^{(n)})_{t \ge 0}$ and the scaled fixation line $Y^{(n)} = (Y_t^{(n)})_{t \ge 0}$ via $X_t^{(n)} := N_t^{(n)} / n^{e^{-t}}$ and $Y_t^{(n)} := L_t^{(n)} / n^{e^t}$, $t \ge 0$, $n \in \mathbb{N}$. Note that the processes $X^{(n)}$ and $Y^{(n)}$ are time-inhomogeneous. The fixation line of the Bolthausen–Sznitman coalescent is a branching process with pgf $\mathbb{E}(s^{L_t^{(n)}}) = (1 - (1-s)^{e^{-t}})^n$, $s \in [0,1]$, $t \ge 0$, $n \in \mathbb{N}$. Thus, for all $t, \lambda \ge 0$,

$$\mathbb{E}(e^{-\lambda Y_t^{(n)}}) \;=\; (1 - (1 - e^{-\lambda / n^{e^t}})^{e^{-t}})^n \;\to\; e^{-\lambda^{e^{-t}}} \;=\; \mathbb{E}(e^{-\lambda Y_t}), \qquad n \to \infty.$$

Hence, $Y_t^{(n)} \to Y_t$ in distribution as $n \to \infty$. The convergence $X_t^{(n)} \to X_t$ in distribution as $n \to \infty$ is now either obtained via duality [5, p. 3] or alternatively via moment calculations [6, p. 46, Step 1]. This convergence of the one-dimensional distributions motivates the following convergence result [5].

Theorem 1. *For the Bolthausen–Sznitman coalescent the following two assertions hold. a) As $n \to \infty$ the scaled block counting process $X^{(n)}$ converges in $D_E[0,\infty)$ to the Mittag–Leffler process X. b) As $n \to \infty$ the scaled fixation line $Y^{(n)}$ converges in $D_E[0,\infty)$ to Neveu's continuous-state branching process Y.*

The theorem demonstrates the intimate relation between the Bolthausen–Sznitman coalescent, the Mittag–Leffler process and Neveu's continuous-state branching process. We refer the reader to [1] and [2] for further insights concerning these relations. Theorem 1 can be stated logarithmically as follows. The process $(\log N_t^{(n)} - e^{-t}\log n)_{t\geq 0}$ converges in $D_{\mathbb{R}}[0,\infty)$ to $\tilde{X} := (\tilde{X}_t)_{t\geq 0} := (\log X_t)_{t\geq 0}$ and the process $(\log L_t^{(n)} - e^{t}\log n)_{t\geq 0}$ converges in $D_{\mathbb{R}}[0,\infty)$ to $\tilde{Y} := (\tilde{Y}_t)_{t\geq 0} := (\log Y_t)_{t\geq 0}$ as $n \to \infty$. The distributions of $\tilde{X}_t$ and $\tilde{Y}_t$ are characterized via the self-decomposable distributional equations $S \stackrel{d}{=} e^{-t}S + \tilde{X}_t$ and $G \stackrel{d}{=} e^{-t}G + e^{-t}\tilde{Y}_t$, where G is standard Gumbel distributed and $S := -G$. The semigroup $(T_t^{\tilde{X}})_{t\geq 0}$ of $\tilde{X}$ is given by

$$T_t^{\tilde{X}} f(x) \;=\; \mathbb{E}(f(xe^{-t} + \tilde{X}_t)), \qquad t \geq 0, f \in B(\mathbb{R}), x \in \mathbb{R}, \tag{5}$$

and the semigroup $(T_t^{\tilde{Y}})_{t\geq 0}$ of $\tilde{Y}$ is given by

$$T_t^{\tilde{Y}} g(y) \;=\; \mathbb{E}(g(ye^{t} + \tilde{Y}_t)), \qquad t \geq 0, g \in B(\mathbb{R}), y \in \mathbb{R}. \tag{6}$$

Semigroups of this form belong to the class of generalized Mehler semigroups [3] corresponding to generalized Ornstein–Uhlenbeck type processes. The generators $A^{\tilde{X}}$ and $A^{\tilde{Y}}$ of $\tilde{X}$ and $\tilde{Y}$ satisfy

$$A^{\tilde{X}} f(x) \;=\; -(x+\gamma)f'(x) + \int_0^\infty \big(f(x-h) - f(x) + hf'(x)\big)\frac{e^{-h}}{(1-e^{-h})^2}\,\mathrm{d}h \tag{7}$$

and

$$A^{\tilde{Y}} g(y) = (y+\gamma)g'(y) + \int_0^\infty \big(g(y+h) - g(y) - hg'(y)\big)\frac{e^{-h}}{(1-e^{-h})^2}\,\mathrm{d}h \tag{8}$$

for $x, y \in \mathbb{R}$ and $f, g \in C_c^2(\mathbb{R})$. Note that (2) and (4) can be derived from (7) and (8) via $A^X f(x) = A^{\tilde{X}}(f \circ \exp)(\log x)$ and $A^Y g(y) = A^{\tilde{Y}}(g \circ \exp)(\log y)$, $f, g \in C_c^2(E)$, $x, y \in E$.

4. Extensions and work in progress

The results in the previous section can be extended at least in two directions as follows. Convergence results similar to those presented in Theorem 1 hold for some larger class of exchangeable coalescents without dust that do not come down from infinity. Note that (except for the Bolthausen–Sznitman coalescent) the fixation

line is not a branching process, which makes the situation more challenging. Alternatively (instead of studying coalescent processes) one may start with a general continuous-time branching process $(L_t^{(n)})_{t\geq 0}$ and analyze its asymptotic behavior as the initial state $L_0^{(n)} = n$ tends to infinity. At least three convergence regimes arise corresponding to the finite variance case, the finite mean but infinite variance case and the infinite mean case.

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On the theory of one- and two-locus clines

Reinhard Bürger

(joint work with Linlin Su)

A cline describes a gradual change in genotypic or phenotypic frequency within a population as a function of spatial location. Clines frequently occur in species distributed along an environmental gradient in which alternative phenotypes or genotypes are better adapted to the different environmental conditions. Dispersal leads to mixing, reduces local adaptation, and entails a change in type frequencies. The study of clines can be used to obtain insight into the relative strengths of the evolutionary and ecological forces acting on a population. For this purpose, Haldane [7] devised and analyzed a one-locus model in terms of a reaction-diffusion equation which approximates migration by diffusion; selection yields the reaction term. His model was extended in several directions, and biologically important and mathematically beautiful results about the existence and properties of clines, i.e., spatially nonuniform equilibrium solutions, have been obtained [5]–[14], [16].

In the talk given at the MFO, we presented generalizations of classical and recent results by considering two recombining genetic loci, A and B, under selection. This generalization does not only add biological realism, but also substantial mathematical difficulties and new phenomena. The resulting system of PDEs is

defined on a bounded open domain $\Omega \subset \mathbb{R}^n$ with C^2 boundaries. Let $\alpha(x)$ and $\beta(x)$ be real-valued functions describing the spatial dependence of the fitnesses of the alleles at loci A and B, respectively. We assume that both functions change sign, so that $A_1(A_2)$ is favored where $\alpha(x) > 0 (\alpha(x) < 0)$, and analogously for B. Furthermore, let $p_1(x,t), p_2(x,t), p_3(x,t)$, and $p_4(x,t)$ denote the relative frequencies of the gametes A_1B_1, A_1B_2, A_2B_1, and A_2B_2, respectively, and $D = p_1p_4 - p_2p_3$ the linkage disequilibrium. Then, with so-called additive fitnesses and appropriate scaling, the time evolution of the $p_i(x,t)$ is given by

$$\frac{\partial p_i}{\partial t} = \Delta p_i + \lambda S_i(x,p) - \eta_i \rho D \quad \text{in } \Omega \times (0,\infty) \tag{1}$$

with Neumann boundary conditions $\frac{\partial p_i}{\partial \nu} = 0$ on $\partial\Omega \times (0,\infty)$ and the constraints $0 \leq p_i(x,t) \leq 1$, $\sum_{i=1}^4 p_i(x,0) = 1$. Here, λ measures the strength of selection relative to diffusion, $\rho \geq 0$ is the scaled recombination rate, and $\eta_1 = \eta_4 = -\eta_2 = -\eta_3 = 1$. The terms $\eta_i \rho D$ describe the effects of recombination, and the $S_i(x,p)$ describe selection: $S_1(x,p) = p_1[\alpha(x)(p_3+p_4) + \beta(x)(p_2+p_4)], S_2(x,p) = p_2[\alpha(x)(p_3 + p_4) - \beta(x)(p_1+p_3)]$, $S_3(x,p) = p_3[-\alpha(x)(p_1+p_2) + \beta(x)(p_2+p_4)], S_4(x,p) = p_4[-\alpha(x)(p_1+p_2) - \beta(x)(p_1+p_3)]$. We are interested in the conditions for existence and stability of a two-locus cline, by which we mean a spatially non-uniform equilibrium solution of (1) such that $0 < p_i(x) < 1$ for every i and x.

Assume (generically, w.l.o.g.) that gamete A_1B_1 has the highest spatially averaged fitness. Then (i) the vertex equilibrium $\hat{p}^{(1)} (p_1(x) \equiv 1)$ is globally asymptotically stable if $\lambda \ll 1$, i.e., if selection is sufficiently weak; (ii) there exists a constant $\lambda_1(\rho) > 0$ such that $\hat{p}^{(1)}$ is asymptotically stable if $0 < \lambda < \lambda_1(\rho)$, and unstable if $\lambda > \lambda_1(\rho)$; (iii) every vertex $\hat{p}^{(i)}$ other than $\hat{p}^{(1)}$ is unstable; (iv) increasing ρ facilitates stability of $\hat{p}^{(1)}$.

As λ increases from small values, edge or internal equilibria move into the state space. If such an equilibrium moves into the state space by a bifurcation with the asymptotically stable $\hat{p}^{(1)}$, say at $\lambda = \lambda_1(\rho)$, then this equilibrium is asymptotically stable for slightly larger values of λ than $\lambda_1(\rho)$. For general $\rho \geq 0$ the analysis of the model is very complicated, as is the case for a corresponding ODE model in which there is migration between two niches [1, 4]. Various bifurcations can occur and, motivated by analytical results for the much simpler ODE model, we showed by numerical integration of (1) that, for instance, a two-locus cline may be simultaneously stable with a boundary equilibrium.

We focused on two limiting cases, weak recombination ($0 \leq \rho \ll 1$) and strong recombination ($\rho \gg 1$), and applied perturbation techniques. If $\rho = 0$, then the theory developed in [9]–[11] for a single locus with multiple alleles can be employed to determine the equilibria and their stability. Among others, we proved the following results. (i) If $\rho = 0$ and α and β have the same sign, i.e., alleles $A_1(A_2)$ and $B_1(B_2)$ are favored in the same region, then on the edge connecting $\hat{p}^{(1)}$ and $\hat{p}^{(4)}$, an equilibrium $\hat{p}^{(14)}$ exists and is globally asymptotically stable if $\lambda \gg 1$. (ii) If for $\rho = 0, \hat{p}^{(14)}$ exists and is linearly stable, then for small $\rho > 0$ a two-locus cline $\hat{p}^{(\rho)}$ exists in the vicinity of $\hat{p}^{(14)}$ and is linearly stable.

The case of strong recombination is biologically more important and mathematically more challenging because it requires singular perturbation techniques. Instead of the gamete frequencies, we now use the allele frequencies $p_A = p_1 + p_2, p_B = p_1 + p_2$, and the linkage disequilibrium D. By fixing $\lambda > 0$, introducing $\epsilon = 1/\rho$, and rescaling time accordingly, (1) becomes equivalent to

$$\frac{\partial p_A}{\partial t} = F_1(p_A, p_B, D, \epsilon),\ \frac{\partial p_B}{\partial t} = F_2(p_A, p_B, D, \epsilon),\ \frac{\partial D}{\partial t} = F_3(p_A, p_B, D, \epsilon)\,, \tag{2}$$

where $F_i : X \times \mathbb{R} \to Y$, $X = \{u \in C^{2+\gamma}(\bar{\Omega}) : \frac{\partial u}{\partial \nu} = 0 \text{ and } \partial\Omega\}$, $Y = C^{\gamma}(\bar{\Omega})$ for some $\gamma \in (0, 1)$, and

$$F_1(p_A, p_B, D, \epsilon) = \epsilon[\Delta p_A + \lambda\alpha(x)p_A(1 - p_A) + \lambda\beta(x)D], \tag{3a}$$

$$F_2(p_A, p_B, D, \epsilon) = \epsilon[\Delta p_B + \lambda\beta(x)p_B(1 - p_B) + \lambda\alpha(x)D], \tag{3b}$$

$$\begin{aligned} F_3(p_A, p_B, D, \epsilon) = \epsilon[&\Delta D + 2\nabla p_A \cdot \nabla p_B \\ &+ \lambda(\alpha(x)(1 - 2p_A) + \beta(x)(1 - 2p_B))D] - D \end{aligned} \tag{3c}$$

We impose Neumann boundary conditions on (2) and the natural constraints $0 \le p_A \le 1$, $0 \le p_B \le 1$, and

$$-\min\{p_A p_B, (1 - p_A)(1 - p_B)\} \le D \le \min\{p_A(1 - p_B), (1 - p_A)p_B\}. \tag{4}$$

Obviously, the limit $\epsilon \to 0$ in (2) is degenerate because for $\epsilon = 0$ the manifold $D = 0$ consists of equilibria and is globally attracting. Inspired by [2] and [15], we apply the perturbation approach $\hat{p}_A^{(\epsilon)} = P + \epsilon p + o(\epsilon), \hat{p}_B^{(\epsilon)} = Q + \epsilon q + o(\epsilon)$, and $\hat{D}^{(\epsilon)} = \epsilon d + o(\epsilon)$, where P and Q denote the clinal solutions of the corresponding single-locus problems, i.e., $F_1(P, *, 0, *) = 0$ and $F_2(*, Q, 0, *) = 0$, respectively. It is well known that P and Q exist if λ exceeds a critical value [6, 8, 9]. Simple calculations show that $d = 2\nabla P \cdot \nabla Q$ and p satisfies

$$\Delta p + \lambda\alpha(x)[1 - 2P(x)]p + 2\lambda\beta(x)\nabla P(x) \cdot \nabla Q(x) = 0. \tag{5}$$

This has a unique nontrivial solution because P is the globally asymptotically stable equilibrium of the one-locus problem, whence $\Delta + \lambda\alpha(1 - 2P)$ is invertible. We proved that all eigenvalues of the linearization $\tilde{F}$ of $F = (F_1, F_2, F_3)$ w.r.t. (p_A, p_B, D), evaluated at $(P, Q, 0, 0)$, are strictly positive. Therefore, $\tilde{F}$ is one-to-one. However, because $\tilde{F}$ is apparently not onto, the implicit function theorem in its usual Banach space form is not directly applicable. Therefore, we have not proved that an equilibrium exists in an ϵ-neighborhood of $(P, Q, 0)$ and the above perturbation approach remains formal. For special fitness functions (a step environment), explicit solutions of (5) defined on $\Omega = \mathbb{R}$ were derived in [3], as was the dependence of the shape of the two-locus cline on the underlying parameters.

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Metastability and intrinsic extinction risk in finite populations

Sebastian J. Schreiber

Mathematical biologists have extensively used differential and difference equation models to understand the dynamics of interacting populations, whether they be viruses, plants, or animals. These deterministic models have provided important insights into conditions promoting species coexistence, disease persistence, and the maintenance of genetic polymorphisms, and the dynamics of these persisting populations. These models, however, keep track of population densities using real numbers and, consequently, fail to account for the fundamentally discrete nature of real populations. Real populations consist of a finite number of individuals whose fates are never perfectly correlated. Even if all individuals have the same risk of mortality, some survive the "live or die" coin flip, while others are less fortunate. Even if all surviving individuals are expected to have the same number of offspring, some individuals defy expectations while others fall short. This demographic stochasticity can be captured by Markovian models with a countable number of states. When these models represent a closed population for which there is no immigration, the populations (generically) either go extinct in finite time or grow without bound. In the words of Peter Jagers [1]

> "Any population allowing individual variation in reproduction, ultimately dies out–unless it grows beyond all limits, an impossibility in a bounded world. Deterministic population mathematics on the contrary allows stable asymptotics. Are these artifacts or do they

tell us something interesting about quasi-stationary stages of real or stochastic populations?"

Building on prior work with Mathieu Faure [5], this talk introduced a general class of Markov chain models (Poisson-Multinomial Population Process) for which extinction is inevitable and discussed under what conditions the associated mean field models provide insights about the quasi-stationary stages of these Markov chains.

The *Poisson-Multinomial Population Process* are used to model a population or community consisting of k types of individuals. The different types may correspond to different states of individuals within a single species (e.g. age, stage, spatial location, or genotype) or individuals of different species. Let $N_{i,t}$ denote the number of individuals of type i at time t, and $X_{i,t} = N_{i,t}/S$ the density of this type where S is the size of the habitat containing the population. Let $N_t = (N_{1,t}, \ldots, N_{k,t})$ and $X_t = (X_{1,t}, \ldots, X_{k,t})$ denote the corresponding vectors of abundances and densities. To update the process to time $t+1$, individuals experience two independent demographic events. First, an individual of type j becomes an individual of type i with probability $T_{ij}(X_t)$ for $i = 1, 2, \ldots, k$, or dies with the complementary probability $D_i(X_t) = 1 - \sum_{i=1}^{k} T_{ij}(X_t)$. These transitions may correspond to an individual moving into a new stage, surviving and staying in the same state, or being consumed by an individual of another type and being converted into one of its offspring (e.g. a host-parasitoid interaction). Second, each individual of type j produces a Poisson number of type i offspring with mean $B_{ij}(X_t)$ for $i = 1, 2, \ldots, k$. The mean-field difference equation associated with this stochastic process is

$$(1)\quad x_{t+1} = (B(x_t) + T(x_t))x_t =: F(x_t) \text{ where } x_t = (x_{1,t}, x_{2,t}, \ldots, x_{k,t}) \in [0, \infty)^k$$

where $B(x)$ and $T(x)$ denote the $k \times k$ matrices with entries $B_{ij}(x)$ and $T_{ij}(x)$. Assume that B and T are continuous maps, F is pre-compact, $D_i(x) > 0$ for all x, i, and there exists a closed subset C_0 of the boundary of $C = [0, \infty)^k$ such that C_0 is absorbing for N_t and such that X_t restricted to $C_+ = C \setminus C_0$ is irreducible.

Under these assumptions, the population process X_t gets absorbed by $C_0 \cap \mathbb{Z}^k$ in finite time with probability one (in fact $X_t = (0, \ldots, 0)$ in finite time with probability one). This absorption corresponds to the extinction of one or more types in the population. However, when the habitat size S is sufficiently large, X_t may exhibit long-term transients prior to this absorption. To characterize this meta-stable behavior, let $Q(x, x')$ be the probability transition matrix for the process restricted to $C_+ \cap \mathbb{Z}^k$. We proved that there is a unique dominant eigenvalue λ and left eigenvector q for the Q such that $\sum_{x \in C_+ \cap \mathbb{Z}^k} q(x) = 1$ and $\lambda \in [0, 1)$. [7] implies that $\lim_{t \to \infty} \mathbb{P}[X_t = x | X_t \notin C_0] = q(x)$ for any $x \in C_+ \cap \mathbb{Z}^k_+$. Hence, the quasi-stationary distribution q describes the meta-stable behavior of X_t. $1 - \lambda$ corresponds to the probability of extinction in the next time step given the population is following this quasi-stationary stationary distribution. [6] call $\frac{1}{1-\lambda}$ the intrinsic mean time to extinction.

Using methods from [5], one can show that if the deterministic map F has an attractor in C_+, then (i) there exists a compact set $K \subset C_+$ such that the weak* limit points of the law of q as $S \uparrow \infty$ are supported by K, (ii) these weak* limit points are invariant probability measures for F, and (iii) there exist positive constants α, β such that $1 - \lambda \leq \alpha e^{-\beta S}$ for all S. Statement (iii) implies that intrinsic mean time to extinction increases exponentially with the habitat size S. (i) and (ii) imply that quasi-stationary behavior tends to be uniformly bounded away from extinction and is related to the asymptotic behavior of F.

To arrive at stronger conclusions about the quasi-stationary behavior, one needs more information about the dynamics of F. Specifically, if F has a finite number of extinction-preserving chain recurrent sets in C_+ (see [4, 5] for a definition) including at least one attractor, then the quasi-stationary distributions concentrate only on the attractors in C_+ as $S \uparrow \infty$. If we interpret the "stable asymptotics" as corresponding to these non-extinction attractors, then our results imply that these stable asymptotics do "tell us something interesting about quasi-stationary stages of real or stochastic populations." To illustrate this conclusion, applications to stochastic counterparts of the generalized Thompson model of host-parasitoid interactions [3] and the LPA model for flour beetle dynamics [2] were given.

Partially complementing the results about long-term quasi-stationary behavior, one can show that if C_0 is a global attractor for the deterministic map F, then the quasi-stationary distributions concentrate on C_0 as $S \uparrow \infty$. This raises two open questions. Namely, where does the quasi-stationary behavior concentrate when F has invariant sets in C_+ but no attractors in C_+? Furthermore, how do the extinction probabilities $1 - \lambda$ scale with S in these cases?

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Information and decision-making in dynamic cell signaling

David Rand
(joint work with Giorgos Minas, Dan Woodcock)

In this talk I discussed a new theoretical approach to information and decisions in signalling systems and related this to new experimental results about various signalling systems. The importance of understanding information flows in biological systems has been recognised as important for a very long time. For example, Francis Crick stated long ago that it is better to follow the flow of information rather than those of energy or matter and, in a recent lecture on the five most important ideas in biology, Sir Paul Nurse emphasised the importance of explaining the higher-order phenomena of living systems by relating the chemical and physical processes to the processing of information and its use to determine biological outputs. However, while the notion of information content is clear when one is talking about strings formed from a finite alphabet as in DNA or RNA, there is currently no clear conceptual framework once the genomic information has been passed into the highly stochastic dynamic processes that determine cellular processes.

The NF-κB system was used in the lecture as an exemplar to illustrate the ideas behind the mathematical framework. NF-κB is an exemplar system that controls inflammation and in different contexts has varying effects on cell death and cell division. As such it is one of the most important stress response systems in mammalian cells. It is commonly claimed that it is an information processing hub, taking in signals about the infection and stress status of the tissue environment and as a consequence of the oscillations, transmitting higher amounts of information to the hundreds of genes it controls.

In my approach the value of the information in the signalling system is defined by how well it can be used to make the "correct decisions" when those "decisions" are made by molecular networks. The cell receives information about its external environment through molecular interactions with, for example, receptor molecules on its surface and other molecules used to monitor the internal state of the cell. These provide the input signal S. This in turn causes a cascade of molecular interactions which eventually activates a set of genes. We assume that the genes interact in such a way as to choose an appropriate decision, such as committing the cell to kill itself or to enter the cell cycle and divide. Thus in this model the decisions are made by the dynamic interaction of genes following their activation by the signalling system. We regard the value of the information carried by the signalling system as being determined by how well the cell does in making "correct" decisions. We assume that the decision is made using a criterion of the form $\kappa(\rho) > u$ where ρ is some aspect of the downstream response of the genes to the input signal S. Thus we are particularly interested in understanding the way that the distribution $P(\rho|S)$ changes as the input signal S changes.

A significant mathematical challenge arises from the fact that these signalling systems are often oscillators. In particular, when the NF-κB system is activated,

the transcription factor p65 moves in and out of the nucleus in an oscillatory fashion. Moreover, it is important to use a stochastic model because the process is highly stochastic and the probabilistic structure plays a crucial role. Since currently there are effectively no analytical tools capable of handling such systems and since current simulation algorithms are extremely slow it is necessary to provide improved methodology for such systems and this was a important part of the presentation.

I outlined a new approach, called pcLNA, to such stochastic oscillatory systems which is based on the Linear Noise Approximation (LNA). In this approach one keeps resetting the phase of the stochastic trajectory in such a way as to keep LNA approximations accurate for large times. The transversal distributions associated with this approximation can be calculated analytically and this approach provides a simulation algorithm that is substantially faster than current simulation algorithms such as tau-leaping algorithms and the use of stochastic differential equations. This work is about to appear in PLoS Computational Biology [1]. Using this methodology one can calculate quantities from information geometry that are associated with understanding the mapping $S \to P(\rho|S)$ which is needed for our information theory.

I then discussed binary decisions where the system has to choose between two options and show how these can be characterised by ROC curves. By using the Neyman-Pearson Lemma one can also calculate the optimal ROC curves and see how effective the gene circuits are at making decisions compared to an optimal decision-maker. I considered a number of examples coming from the NF-κB system.

Then I moved on to more complex decisions and asked whether such a system can multiplex. This is about whether a single signal can encode multiple aspects of the external environment or internal state of the cell. I showed how you can formulate this question in terms of Fisher information and Kullback-Leibler Divergence. The NF-κB system like many other regulatory and signalling system models which are tightly coupled has the property that the Fisher Information Matrix has very rapidly decreasing eigenvalues. It follows from this that if the system is described by such models then it cannot multiplex effectively and I explained the theory behind this. In particular, I showed how to formulate a theory of sensitivity for such stochastic systems by relating the Fisher Information Matrix to the linearised mapping from signals S to the parameters for the distribution $P(\rho|S)$. One can then calculate from the sensitivity matrix coming from this theory the extent to which the signalling system can multiplex.

This leads to what I believe is a important biological insight. We know from experiments that in fact the NF-κB system is able to multiplex and that raises the question of what is wrong with the model in this regard. A very natural hypothesis that is justified by the above theory is that the model ignores the fact that the NF-κB transcription factor undergoes a sequence of phosphorylations as part of the signal activation. This is highly relevant because it is known that the phosphorylation state of NF-κB determines what molecules complex with it

and this in turn determines what genes it activates or represses. Using the above theory one can show that inclusion of such processes into the model allows the system to multiplexed signals much more effectively.

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Analytical approaches to characterize complex stochastic systems

Andreas Hilfinger

In cells many important molecules are present in small numbers. The probabilistic nature of individual chemical events then creates spontaneous fluctuations in cellular concentrations. As a result, genetically identical cells growing under identical conditions can differ significantly in almost any property. This non-genetic variability shapes many biological processes ranging from microbial decision making to stem cell differentiation and tumor growth. The challenge we face when trying to model these stochastic processes is that fluctuations of any particular component in a cell reflect all directly and indirectly connected processes many of which are poorly characterized. This explains why fluctuations are so prevalent in biology, and why they are so difficult to analyze, since both the parts of interest as well as *all* interacting components must be described in the absence of a general framework.

To address this problem, we derived fundamental relations between properties of chemical fluctuations that reflect only some specified parts of a nonlinear and complex reaction system, while being invariant to all aspects of the rest of the system – regardless of nonlinearities, the number of components, or even the topology of the rest of the network. Exact analytical results for such processes may seem impossible because of moment closure problems, but deriving expressions not in terms of rate constants but in terms of observable system properties that can be measured or interpreted regardless of the reaction details circumvents this problem. The basic idea is to identify relations between system properties that reflect the interactions within a part of the system while remaining invariant to all other (unspecified) parts. The unspecified variables are then not ignored but rigorously allowed to exhibit essentially any imaginable behavior, including non-linear and non-Markovian dynamics, and also any imaginable network topology. We showed that for all stationary or non-stationary systems in which the time-averaged statistical properties of the population as a whole converge, any pair of components X_i,X_j that undergo elementary chemical reactions in any arbitrarily complicated network, must satisfy the following exact and general relation

$$(1) \qquad \frac{1}{\tau_j}\frac{\mathrm{Cov}(x_i, R_j^- - R_j^+)}{\langle x_i\rangle\langle R_j^\pm\rangle} + \frac{1}{\tau_i}\frac{\mathrm{Cov}(x_j, R_i^- - R_i^+)}{\langle x_j\rangle\langle R_i^\pm\rangle} = \frac{1}{\tau_i}\frac{\langle s_{ij}\rangle}{\langle x_j\rangle} + \frac{1}{\tau_j}\frac{\langle s_{ji}\rangle}{\langle x_i\rangle} \quad ,$$

where τ_i denotes the average lifetime of component X_i, $R_i^{\pm}$ are total fluxes of production or degradation of component X_i, and $\langle x_i \rangle$ are average abundances of the components of interest. The average step-sizes, denoted as $\langle s_{ij} \rangle$, measure the average change in the number of X_j molecules when an X_i molecule is made or degraded. The value of $\langle s_{ij} \rangle / \langle x_j \rangle$ thus capture the size of the random events relative to the size of the system. The covariance terms in turn capture how the total fluxes respond to deviations in abundances. Eq. (1) can thus be understood as balance between random perturbations and controlled responses within a large network.

We used this framework to gain insights into biological processes in two ways: First, we tested specific mechanistic hypotheses without making any assumptions about the rest of the network [2]. Second, we derived hard universal bounds on the behaviors of classes of complex systems that share some parts but differ arbitrarily in all others [1].

Rigorous hypothesis testing using fluctuation data. Eq. (1) makes predictions that reflect "local" interactions between a subset of components but are invariant to all indirectly connected dynamics. This greatly reduces the number of assumptions when comparing models against experiments. Consider for example all possible networks in which a protein (X_2) is made probabilistically at a rate proportional to its cognate mRNA (X_1), and undergoing first order degradation, leaving everything else in the network unspecified

$$\underbrace{\left[\begin{array}{c}\text{arbitrary dynamics of}\\ \mathrm{X}_1,\mathrm{X}_3,\mathrm{X}_4,\ldots\\ \text{including feedback loops}\end{array}\right]}_{\text{unspecified dynamics}} + \underbrace{\begin{array}{l} x_2 \xrightarrow{\lambda x_1} x_2 + 1 \\ x_2 \xrightarrow{x_2/\tau_2} x_2 - 1 \end{array}}_{\text{specified dynamics}} \quad . \tag{2}$$

The specified dynamics in Eq. (2) are common to virtually all published models of gene expression (the process of transcribing genes into mRNA and translating mRNA into proteins). Without making any approximations, such as linearizing rates or assuming a separation of time-scales, Eq. (1) translates those assumptions into an exact invariant relation between the mRNA-protein correlations ρ_{12} and their coefficient of variations $\mathrm{CV}_i := \sigma_i / \langle x_i \rangle$

$$\mathrm{CV}_2^2 = \frac{1}{\langle x_2 \rangle} + \rho_{12} \mathrm{CV}_1 \mathrm{CV}_2 \,, \tag{3}$$

which must hold regardless of the dynamics of the unspecified parts. The intuition behind this is straightforward: the fluxes $R_2^{\pm}$ are properties of only the reactions *directly* affecting X_2, and all indirect effects must ultimately be transmitted through those rates. The power of this approach was illustrated by revisiting recently published gene expression data [3]. We showed [2] that observed mRNA-protein fluctuations strongly contradict the above assumptions, ruling out the majority of published gene expression models.

Universal trade-offs in assembly processes. Without specifying the entire dynamics of a network it is impossible to predict the fluctuations of any given component. Indeed every term in Eq. (1) depends on all directly and indirectly connected components in the network. However, we can use universal inequalities such as Cauchy-Schwarz to turn a system of under-determined equations into impossibility constraints that show what classes of systems can never do. As an example we considered a network motif in which two subunits X_1 and X_2 come together to form a stable complex. For any system – even when the subunits and the complex can interact and regulate the production process in any way – we showed that fluctuations in the subunits must fall above the simple yet universal bound[1]

$$\frac{CV_1 + CV_2}{2} \geq \sqrt{\frac{1}{\langle x_i \rangle} \frac{1 - E/2}{2(1-E)}} \quad , \tag{4}$$

which diverges as the fraction of molecules E that eventually end up in complexes approaches 100%. To prove that this bound is achievable we utilized numerical simulations of stochastic systems with randomly chosen parameters and controllers. This illustrates how general constraints based on mathematical inequalities can be used to characterize modules within biological networks without assuming they act in isolation.

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From adaptive dynamics to adaptive walks

Anna Kraut

(joint work with Anton Bovier)

The starting point of the talk is a stochastic model of adaptive dynamics. It considers a measure valued Markov process ν^K modelling the scaled density of different traits in a population. As trait space we choose the n-dimensional hypercube $\mathbb{H}^n$. Traits in $\mathbb{H}^n$ can for example be viewed as sequences of genes being switched on or off.

Let $\nu_t^K(x)$ denote the number of individuals of trait x at time t, divided by the carrying capacity K, which scales the size of the population. The evolution of ν_t^K is driven by exponential birth, death and competition rates b, d and c, as well as

a probability ε of mutation at birth and a mutant law m. The generator of ν_t^K is given by

$$\mathcal{L}_K\phi(\nu) = \sum_{x\in\mathbb{H}^n} K\nu(x) \sum_{y\in\mathbb{H}^n} \left(\phi\left(\nu + \frac{\delta_y}{K}\right) - \phi(\nu)\right) b(x)((1-\varepsilon)\mathbf{1}_{x=y} + \varepsilon m(x,y)\mathbf{1}_{x\neq y})$$
$$+ \sum_{x\in\mathbb{H}^n} K\nu(x) \left(\phi\left(\nu - \frac{\delta_x}{K}\right) - \phi(\nu)\right) \left(d(x) + \sum_{y\in\mathbb{H}^n} \frac{c(x,y)}{K} K\nu(y)\right).$$

From a result of Ethier and Kurtz in [4] it follows that in the limit of large populations, i.e. as K tends to infinity, the scaled stochastic processes $(\nu_t^K)_{t\geq 0}$ converge on finite time intervals to the solution $(\nu_t)_{t\geq 0}$ of the system of differential equations

$$\dot{\nu}_t(x) = \left[b(x) - d(x) - \sum_{y\in\mathbb{H}^n} c(x,y)\nu_t(y)\right]\nu_t(x) + \varepsilon\left(\sum_{y\sim x} b(y)m(y,x)\nu_t(y) - b(x)\nu_t(x)\right).$$

These are similar to Lotka-Volterra equations but include an additional mutation term. We only allow mutations between neighbouring traits, corresponding to mutations of single genes. However this, and everything that follows, can be generalized to finite directed graphs, where each vertex represents a trait and each directed edge a possible mutation.

The main objective of the talk is to study the convergence of the deterministic system in the limit of rare mutations, i.e. as ε tends to zero. The techniques used to show the convergence are inspired by Bovier and Wang's work in [2]. There is a separation of time scales with slow exponential growth of the mutant traits up to a threshold and afterwards a fast invasion phase.

In this context the notion of invasion fitness is introduced. For a subset of traits $\mathbf{x} \subset \mathbb{H}^n$ coexisting at equilibrium density, $f_{y,\mathbf{x}}$ describes the exponential growth rate of a single mutant y in this population. This defines a fitness landscape that depends on the current state of the system.

The evolution of the population is approximated piecewise. First, while the coexisting resident traits stay close to their equilibrium, the mutants starting out with population size $\nu_0(y) \approx \varepsilon^{\lambda_y}$ are approximated by exponential functions that include the growth of the trait by itself, as well as the growth due to mutants from faster growing neighbouring traits.

$$\nu_t(y) \approx \sum_{z\in\mathbb{H}^n} e^{tf_{z,\mathbf{x}}}\varepsilon^{|y-z|}\varepsilon^{\lambda_z}.$$

Inserting the time scale $\ln 1/\varepsilon$, we attain that the first traits to reach an ε-independent threshold $\eta > 0$ are realizing the minimum

$$\min_{y\in\mathbb{H}^n} \min_{\substack{z\in\mathbb{H}^n \\ f_{z,\mathbf{x}}>0}} \frac{|y-z| + \lambda_z}{f_{z,\mathbf{x}}} \ln\frac{1}{\varepsilon},$$

which is exactly the time when the threshold is reached.

Afterwards, the invasion of the resident traits is approximated by the mutation free Lotka–Volterra system (setting $\varepsilon = 0$ in the system of differential equations above). As shown in [3], under certain positive definiteness assumptions on the

competition kernel, a new stable equilibrium is attained.
In the limit the subcritical traits can be neglected and, combining the two approximations, the system converges to an adaptive walk that jumps between Lotka–Volterra equilibria.
The next step in future research will be to combine both limits and let $\varepsilon = \varepsilon_K$ tend to zero as K tends to infinity. To ensure that mutations are not separated, i.e. that all traits will appear as mutants within a time of order 1 and before an invasion takes place, the scaling would have to fulfil $\varepsilon_K \geq K^{-1/n}$. This is a much larger mutation probability than the one in [1] for example, where mutations are separated.
In the last part of the talk it is briefly discussed how a generalized version of the above stochastic model can be used to study immunotherapy of skin cancer. This is done in cooperation with the group of Prof. Michael Hölzel at the University Hospital Bonn.
The generalized model includes several types of cancer cells, characterized by their geno- and phenotype, interacting with cytotoxic T-cells and different chemokines. In addition to birth, death, competition and mutation it also models a phenotypic switch and various therapeutic effects.
The stochastic model has been implemented to simulate the process of T-cell therapy. The challenge is to estimate the parameters to fit the experimental data. If this is successful it serves as confirmation for the proposed pathways.
In addition, a future version of the program will combine deterministic simulation of frequent events and stochastic simulation of rare events.

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Spatially structured population and trait substitution sequence model

Hélène Leman

The spatial aspect is an important issue in ecology. In particular, we are concerned here with the interplay between spatial structure and Darwinian evolution under two main biological assumptions : rare mutations and large population size. We use the individual-based model first introduced by [1] to describe a spatially and phenotypically structured asexual population. The dynamics of the process

is driven by a birth and death diffusion process, in which each individual i is characterized by

- its location $X_t^i \in \mathcal{X}$, open and bounded subset of $\mathbb{R}^d$,
- its phenotypic trait $U_t^i \in \mathcal{U}$, countable subset of $\mathbb{R}^q$.

The total population is represented at any time t by the finite measure

$$\nu_t^K = \frac{1}{K} \sum_{i=1}^{N_t} \delta_{(X_t^i, U_t^i)},$$

with δ_y the Dirac measure at y and N_t the number of individuals at time t. The parameter K scales the population size and the biological assumption of large population size is stated by $K \to +\infty$.

Any individual with phenotypic trait u moves according to a diffusion process normally reflected at the boundary $\partial\mathcal{X}$ with diffusion coefficient m^u.

An individual with characteristics $(x, u) \in \mathcal{X} \times \mathcal{U}$ gives birth at rate $b^u(x)$. The offspring appears at the location of its parents. A mutation may occur with probability $q_K p$, making the phenotypic trait of the offspring different from the one of its parent. The law of the mutant trait is then given by a kernel $k(x, u, \cdot)$. The parameter q_K scales the mutation probability and the biological assumption of rare mutations is stated by $q_K \to 0$.

The natural death rate is $d^u(x)$. Moreover, a competition is exerted by any individual (y, v) on any individual (x, u) and depends on the location y and on the two traits through a competition kernel $c : \mathcal{U} \times \mathcal{X} \times \mathcal{U} \to \mathbb{R}^+$. For the population $\nu = \frac{1}{K} \sum_{i=1}^n \delta_{(x_i, u_i)} \in M_F(\mathcal{X} \times \mathcal{U})$, the competitive pressure exerted on individual (x, u) is

$$c \cdot \nu(x, u) = \frac{1}{K} \sum_{i=1}^{n} c^{u, u_i}(x_i) = \frac{1}{K} \int\limits_{\mathcal{X} \times \mathcal{U}} c^{u, v}(y) \nu(dy, dv).$$

Hence, the total death rate of the individual is $d(x, u) + c \cdot \nu(x, u)$.

Assuming that mutational scale and ecological scale are separated, our aim is to describe the microscopic model in the mutation scale $t \mapsto t/(Kq_K)$.
Firstly, a macroscopic approximation of the microscopic model has been proved in [1] as a large population limit and in the ecological scale (short scale) where mutations do not appear. They proved that, when K goes to infinity, the sequence of processes $(\nu_t^K, t \geq 0)_{K>0}$ converges in law to a deterministic process that admits a density $(g^u(t, x), t \geq 0)$ solution to the following equation with Neumann boundary conditions

$$\partial_t g^u(t, x) = \left[b^u(x) - d^u(x) - \sum_{k=1}^{n_{\mathcal{U}}} \int_{\mathcal{U}} c^{u_k, u}(y) g^{u_k}(t, y) dy \right] g^u(t, x) + m^u \Delta_x g^u(t, x).$$

We study this equation to understand the behaviour of the process besides mutations, in the particular cases of a dimorphic population (two traits u and v are involved). According to [2], the equilibrium reached depends on the signs of the

fitnesses $f(u,v)$ and $f(v,u)$ where $f(v,u)$ is the *invasion fitness of the individuals with type v in a resident population with type u* and writes

$$f(v,u) := H^v \kappa^{uu} - H^u \kappa^{vu},$$

with

- H^u (resp. $\bar{g}^u$) the principal eigenvalue (resp. eigenvector) of the operator $\phi \mapsto m^u \Delta_x \phi + (b^u - d^u)\phi$ with Neumann boundary conditions on $\partial\mathcal{X}$ (resp. such that $\int_{\mathcal{X}} c^{uu}(y)\bar{g}^u(y)dy = H^u$),
- for any $(u,v) \in \mathcal{U}$, $\kappa^{vu} := \int_{\mathcal{X}} c^{vu}(y)\bar{g}^u(y)dy \left(\int_{\mathcal{X}} \bar{g}^u(y)dy\right)^{-1}$.

Secondly, we go back to the microscopic and stochastic process. Introducing a mutant individual of type v in a resident population with type u at equilibrium, we derive the probability for its offspring to survive. Using the previous studies and a study on branching brownian motion (see Section 4 of [3]), we can prove that the probability of invasion success of the descendants of the v-individual can be described by means of its geographical birth position x_0 and a function ϕ^{vu} which is positive on $\mathcal{X}$ if and only if $f(v,u) > 0$.
To end, we state the following theorem which describes the convergence of the microscopic model to a spatial structured *Trait Substitution Sequence* (TSS) under the separation of time scales introduced in [4]. The TSS model, introduced by Metz and al. [5], describes the succession of invading advantageous phenotypic traits as a jump Markov process in the space of phenotypic traits. The originality here comes from the fact that we also deal with a spatial component that makes the process infinite dimensional.

Theorem 1 ([3]). *We assume that for any $u, v \in \mathcal{U}$, either $f(v,u) < 0$, or $f(v,u) > 0$ and $f(u,v) < 0$ (no coexistence) and (separation of time scales)*

$$\log(K) \ll \frac{1}{Kq_K} \ll e^{KV}, \quad \text{for any } V > 0.$$

Then for any $T > 0$, $\left(\nu^K_{(t/Kq_K)}\right)_{t\in[0,T]}$ converges as $K \to +\infty$, in the sense of the finite dimensional distributions, to a jump Markov process $(\Lambda_t)_{t\geq[0,T]}$ which belongs to the subspace $\{\bar{g}^u(dx)\delta_u(dw), u \in \mathcal{U}\}$ and which jumps from the state $g^u(dx)\delta_u(dw)$ to the state $g^v(dx)\delta_v(dw)$ at the infinitesimal rate

$$\int_{\mathcal{X}} pb^u(x)\phi^{vu}(x)\bar{g}^u(x)k(x,u,v)dxdv.$$

Hence, the limiting jump process describes an evolutionary phenomenon using a sequence of monomorphic equilibria characterized by their spatial patterns and their phenotypic trait.
A natural question to continue this work would be to find a *canonical equation of adaptive dynamics* in this spatial context, that is, we would like to understand how the jump process evolves in an asymptotic of small mutation steps.

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Node balanced graphs and subgraphs of deterministic and stochastic reaction networks

Daniele Cappelletti

(joint work with Elisenda Feliu, Badal Joshi and Carsten Wiuf)

Chemical reaction networks (CRNs) are mathematical models mainly used to study the time evolution of biochemical systems. If, for example, a molecule of a chemical species A can bind to a molecule of a chemical species B to form 3 molecules of a chemical species C, we have a chemical reaction $A + B \to 3C$. The set of all the reactions (finitely many) form a graph, called the "reaction graph". In the given example, we want to study the time evolution of the amounts of the molecules of the chemical species A, B and C, which undergo a chemical transformation. Each reaction is associated with a rate, which is a function that depends on the current state of the system. For simplicity, in what follows we assume that the rates are that of the so called "mass action kinetics", so in particular are polynomial functions.

If many molecules are present, then the concentration of the different chemical species are considered, and their evolution is usually modelled by means of a system of autonomous ordinary differential equations. In this case, the model we are using is a deterministic CRN. If few molecules are present, usually, their counts are considered, whose change in time is modelled by means of a continuous time Markov chain.

In the deterministic setting, the relationship between dynamical features of the model and structural properties of the graph have been intensively studied. Specifically, complex balanced equilibria are introduced: a complex balanced equilibrium is an equilibrium such that, for any given node of the reaction graph, the sum of the rates of the reactions entering the node equals the sum of the rates of the reactions exiting from the same node. Complex balanced equilibria are a generalisation of "detailed balanced" equilibria, which have been largely studied

in thermodynamics. In [1, 2], important dynamical properties of complex balanced equilibria are proven, such their local asymptotic stability. Moreover, it is proven that if a complex balanced equilibrium exists, then there exists exactly one complex balanced equilibrium in every stoichiometric compatibility class, which are invariant regions of the dynamical system. Furthermore, it is shown that a deterministic CRN can have a complex balanced equilibrium (for some choice of mass action rates) if and only if every linkage class of the reaction graph is strongly connected. In this context, a new quantity is studied: the "deficiency" of a CRN is a number associated with the reaction graph which was introduced in [1, 2] and further analysed in [3]. The main role of the deficiency is that of counting how many algebraic equations need to be satisfied for a deterministic CRN to exhibit a complex balanced equilibrium.

In the stochastic setting, a similar theory was missing. In [4], we introduced the concept of complex balanced stationary distribution. We further show that complex balanced stationary distributions are deeply connected to complex balanced equilibria, and that a similar theory as that developed by [1, 2] hold for stochastic CRNs. Moreover, the role of product form stationary distributions is studied, and the converse of a result proven in [5] is shown. Namely, a stochastic CRN can have a product form stationary distribution only if it is complex balanced, and consequently only if a related deterministic CRN has a complex balanced equilibrium.

In a joint work with Elisenda Feliu and Carsten Wiuf, I explore further the concept of node balancing in deterministic CRNs, by considering subgraphs of the reaction graph. Namely, we study when subgraphs of the reaction graph are node balanced, we introduce a more general concept of deficiency and prove results similar to those for complex balanced equilibria shown in [1, 2, 3].

Finally, in a joint work with Badal Joshi I study the connection between subgraph node balancing in the deterministic and in the stochastic modelling regimes of CRNs. Some interesting links are found. As an example, a new relationship between the detailed balanced equilibria of the deterministic model and the detailed balanced distribution of the corresponding stochastic model is unveiled, continuing in this way the line of research proposed in [6].

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Long-time asymptotics of some stochastic reaction networks

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(joint work with Carsten Wiuf, Daniele Cappelletti)

We consider modelling a network of species whose evolution (birth, death, conversion) depends on the presence of species from another reaction network (called host) that is assumed to be stochastically ergodic by itself. This model is helpful in explaining some aspects of gene regulatory network. We studied the joint distribution of the species of interest (called parasites) for a finite time point along with analyzing the ergodicity conditions. Under ergodicity condition the equilibrium distribution of the parasite species is found to be a mixture of Poisson where the mixing measure can be uniquely identified as the law of the fixed point of a stochastic recurrence equation (of type $X \stackrel{d}{=} AX + B$) where A and B are determined by the path-wise functionals computed from the stochastic dynamics of the host reaction network.

This work focuses on understanding long time behaviour of a special type of stochastic reaction networks where the evolution of a particular subset of species depends on path-wise evolution of the rest that have separate marginal evolutions. For example in following Gene regulatory network (with species $G_1, G_2, \mathbf{P}$ representing the de-activated, activated genes and proteins respectively) the evolution of $\mathbf{P}$ depends only on presence of (G_1, G_2) without changing their counts:

$$\mathcal{R}: \qquad G_1 \rightleftharpoons G_2, \quad G_2 \to \mathbf{P} + G_2, \quad G_1 + \mathbf{P} \to G_1. \tag{1}$$

The marginal evolution (G_1, G_2) is completely described by reactions $G_1 \rightleftharpoons G_2$ that do not depend on $\mathbf{P}$. Steady state stochastic analysis for (1) has been studied in different settings [1],[2], [3] where the equilibrium distribution is derived **only** under a restrictive condition of the initial total gene counts that is $G_1(0) + G_2(0) = 1$.

For general initial condition that method doesn't work. In general form these models appear as jump type Markov processes (evolution of $\mathbf{P}$) under switching Markovian regimes (controlled by (G_1, G_2)) where many features (like ergodicity/exponential ergodicity under Wasserstein distance) were established in different settings [4], or in diffusion type contexts [5] but no explicit form of equilibrium distributions are available.

Here we characterize the invariant measure in closed form for a generalized version of (1) that is also applicable for arbitrary initial condition (which is important in various examples of synthetic biology and wasn't considered before in literature). These characterizations involve a connection with solution of "Stochastic Recurrence Equation" [6]. We call the generalized version of (1) as **Host-parasite reaction network** where one partitions the reactions $\mathcal{R}$ in two sets $\mathcal{R} = \mathcal{R}_1 \cup \mathcal{R}_2$, such that $\mathcal{R}_1$ completely describe the stochastic evolution of species taking part in them (call as **host**) denoted by $\mathcal{S}_1$. Denoting the species $\mathcal{S}_2$ taking part in $\mathcal{R}_2$ we call the species $\mathcal{S}_2 \setminus \mathcal{S}_1$ as **parasites** (since their evolutions are conditional on the

path-wise evolution of hosts). For example in (1) we have $\mathcal{R}_1 = \{G_1 \rightleftharpoons G_2\}$, and $\mathcal{R}_2 = \{G_2 \to \mathbf{P} + G_2, G_1 + \mathbf{P} \to G_1\}$ and $\{G_1, G_2\}, \{\mathbf{P}\}$ are respectively called the host and the parasite. Following we consider a particular host-parasite reaction network model:

1. Production-Conversion-Degradation process

In presence of genes $G = \{G_1, \ldots, G_{n_1}\}$, n_2 different types of proteins $\{\mathbf{P}_1, \ldots, \mathbf{P}_{n_2}\}$ evolve through following reactions $\mathcal{R}_2 := \mathcal{P}_{\mathcal{R}_2} \cup \mathcal{C}_{\mathcal{R}_2} \cup \mathcal{D}_{\mathcal{R}_2}$ such that for $1 \le i, j \le n_2$

$$
\begin{aligned}
\textbf{Production} \quad (\mathcal{P}_{\mathcal{R}_2}) \quad &: \quad G_{0i} \longrightarrow G_{0i} + \mathbf{P}_i, \\
\textbf{Conversion} \quad (\mathcal{C}_{\mathcal{R}_2}) \quad &: \quad G_{ij} + \mathbf{P}_i \longrightarrow G_{ij} + \mathbf{P}_j, \\
\textbf{Degradation} \quad (\mathcal{D}_{\mathcal{R}_2}) \quad &: \quad G_{j0} + \mathbf{P}_j \longrightarrow G_{j0},
\end{aligned} \tag{2}
$$

where $\{G_{ij} : 0 \le i, j \le n_2\}$ are complexes made of genes $\{G_1, \ldots, G_{n_1}\}$. Here $G = \{G_1, \ldots, G_{n_1}\}$ is the set of **host** species specified by arbitrary $\mathcal{R}_1$ which does not include any **parasite** species $\mathbf{P} := \{\mathbf{P}_1, \ldots, \mathbf{P}_{n_2}\}$.

Keeping same species notations we denote the vector of counts of gene and protein molecules $(G, \mathbf{P})$ at time $t > 0$ by $G(t) := (G_1, \ldots, G_{n_1})(t), \mathbf{P}(t) := (\mathbf{P}_1, \ldots, \mathbf{P}_{n_2})(t)$ respectively. The joint evolution of $\big(G(t), \mathbf{P}(t)\big)_{t>0}$ in (2) can be expressed as

$$
\begin{aligned}
G(t) \;&=\; \text{an ergodic continuous time Markov chain on a state space} \\
&\quad\; \subseteq \mathbb{N}^{n_1} \text{with marginal stationary distribution } \pi(\cdot), \\
\mathbf{P}(t) \;&=\; \mathbf{P}(0) + \sum_{i \in \mathcal{P}_{\mathcal{R}_2}} N_{0i}\left(\int_0^t \lambda_{0i}(G(s))\, ds\right) e_i \\
&\qquad + \sum_{(i,j) \in \mathcal{C}_{\mathcal{R}_2}} N_{ij}\left(\int_0^t \lambda_{ij}(G(s)) \mathbf{P}_i(s)\, ds\right)(e_j - e_i) \\
&\qquad + \sum_{j \in \mathcal{D}_{\mathcal{R}_2}} N_{j0}\left(\int_0^t \lambda_{j0}(G(s)) \mathbf{P}_j(s)\, ds\right)(-e_j)
\end{aligned} \tag{3, 4}
$$

where $\{N_{ij}(\cdot) : i, j = 0, \ldots, n_2\}$ is a set of independent unit rate Poisson processes, e_i is the i-th column vector of an identity matrix of order n_2, $\{\lambda_{ij}(\cdot) : \mathbb{N}^{n_1} \to \mathbb{R};\ i, j = 0, \ldots, n_2\}$ is a set of functions specified by how the complex G_{ij} is composed of the co-ordinates $\{G_1, \ldots, G_{n_1}\}$.

A sample result of the equilibrium distribution of $\{G(\cdot), \mathbf{P}(\cdot)\}$ is following. Denoting the i-th hitting time of $G(\cdot)$ at state j by τ_i^j, under certain regularity assumptions we found that $\{G(\cdot), \mathbf{P}(\cdot)\}$ is jointly ergodic. Moreover the joint equilibrium measure μ_∞ for the aggregate chain $\big(G(t), \mathbf{P}(t)\big)_{t>0}$ is found to be a **"Mixture" of Poisson distribution** where the mixing measure can be expressed as a solution of the following *Stochastic Recurrence Equation*

$$
Z \;\stackrel{\mathcal{L}}{=}\; B_j Z + C_j, \qquad Z \perp (B_j, C_j). \tag{5}
$$

Explicit forms of (B_j, C_j) are respectively matrix and a vector valued integral type functionals that are determined by chain $G(\cdot)$ over a recursion cycle $(\tau_1^j, \tau_2^j]$ at state j which is randomly generated from π. It's a closed form expression that is derived using ideas of a regenerative renewal process. This characterization is very helpful for sampling from the equilibrium distribution however some complications arise while computing the rare events which we .

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