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Effective models and the search for quantitative principles in microbial evolution

Benjamin H Good^{a,b} and Oskar Hallatschek^{a,c}

^aDepartment of Physics, University of California, Berkeley

^bDepartment of Bioengineering, University of California, Berkeley

^cDepartment of Integrated Biology, University of California, Berkeley

Abstract

Microbes evolve rapidly. Yet they do so in idiosyncratic ways, which depend on the specific mutations that are beneficial or deleterious in a given situation. At the same time, some population-level patterns of adaptation are strikingly similar across different microbial systems, suggesting that there may also be simple, quantitative principles that unite these diverse scenarios. We review the search for simple principles in microbial evolution, ranging from the biophysical level to emergent evolutionary dynamics. A key theme has been the use of effective models, which coarse-grain over molecular and cellular details to obtain a simpler description in terms of a few effective parameters. Collectively, these theoretical approaches provide a set of quantitative principles that facilitate understanding, prediction, and potentially control of evolutionary phenomena, though formidable challenges remain due to the ecological complexity of natural populations.

With their small size and rapid generation times, microbes have a unique ability to evolve on human-relevant timescales. Recent years have seen an explosion of data, first from laboratory experiments, but increasingly from pathogens and other natural populations, that document these short-term evolutionary changes at ever increasing breadth and precision [1]. This glut of quantitative data poses a challenge for theorists and experimentalists alike: are there simple quantitative principles of microbial evolution that can be extracted from these measurements? And if so, can we leverage these principles to better predict or control evolution in the future? We highlight recent progress in this direction, and we comment on the further challenges imposed by the ecological complexity of natural populations.

The simplest principle of microbial evolution: microbes adapt rapidly

One of the most robust empirical findings in microbial evolution is that adaptive evolution is common. Even in the simplest laboratory settings, microbes will readily uncover mutations that can displace their parent strain. A canonical example is Lenski's long-term evolution experiment in *E. coli* (the LTEE [2]), whose 12 replicate populations are still accumulating adaptive mutations after 70,000 generations of evolution [3, 4]. The fitness benefits of each

mutation are often small by physiological standards (i.e., $s \lesssim 1\%$), and may not be apparent in spot assays or other traditional growth rate measurements. But compounded over time, these small benefits can still drive mutants to high frequency over the hundreds of thousands of generations that take place in a year.

The high rates of adaptive evolution can also be traced to the large number of cells in a typical microbial population. Even with a small target size for weakly beneficial mutations, a population of a few hundred million cells will produce multiple adaptive variants in each generation ($NU_b \gtrsim 1$). Natural microbial populations like the gut microbiome can grow to be even larger, with an estimated $\sim 10^9$ mutations produced in a single day [5].

Together, these order-of-magnitude estimates and empirical examples suggest a very simple principle of microbial evolution: microbes will readily and rapidly adapt to a variety of environmental conditions. But beyond this simple rule of thumb, it is far more difficult to predict the phenotypic or genetic changes that will take place, even in relatively simple settings like the LTEE. Studies have shown that evolution can often be *repeatable*, at least at a statistical level, when populations are exposed to the same conditions [6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 3, 4]. But it is much more challenging to predict the range of responses ahead of time, or to extrapolate the predictions of one experiment to slightly different conditions.

At some level, these difficulties are not surprising, since *ab initio* predictions of evolution would require a detailed understanding of the mapping between genotype, phenotype, and fitness. To make progress, microbial evolutionists have focused on two broad approaches, which we describe in more detail below. The first is a reductionist (or *bottom-up*) approach that builds on familiar concepts from biophysics and systems biology. The second is a *top-down* approach that works backward from the emergent dynamical processes of population genetics.

Biophysical models of evolution from the bottom up

A common strategy for dealing with the complexity of evolution is to focus on a narrowly defined trait or pathway, where biophysical models can be used to populate the mapping between genotype, phenotype, and fitness. This approach is often based on metabolic control analysis, or its close relatives, which relate microbial fitness in chemostat culture to the flux through a growth-limiting linear pathway (Fig. 1a) [17, 18]. Fitness can then be connected to the expression and activity of the relevant enzymes using standard biophysical models, which can include varying degrees of molecular detail [18, 19, 20, 21, 22]. Figure 1 shows a typical example of this approach for the lactose pathway in *E. coli*.

A major advantage of the reductionist approach is its conceptual simplicity. Previously puzzling evolutionary patterns can be explained using existing biophysical models, where the basic mechanisms are often well understood. For example, an experimental study in *M. extorquens* showed that mutations that produce a constant change in gene expression can be beneficial in one genetic background but deleterious in other [21]. The authors showed that this complex pattern of epistasis could be explained simply by overshooting the optimal

expression level predicted by metabolic control analysis [20] (Fig. 1b). Another recent study showed that the order of the mutations that accumulated in the influenza nucleoprotein in last 40 years was strongly constrained by the “fitness cli” predicted from the thermodynamics of protein stability [24].

In addition to conceptual insights, reductionist approaches offer clear practical advantages for obtaining quantitative predictions. In simple cases, computational methods can be used to predict binding energies [25] and protein stability [26] from the underlying DNA sequences, though in general, these molecular traits must still be determined experimentally. Recent hybrid approaches, which combine high-throughput functional assays of mutagenized libraries with statistical models of the DNA-phenotype map [27, 28, 29] make it increasingly easy to perform such measurements. Variations of this technique have started to provide insight into the sequence landscape of promoter function (Fig. 1c,d) [23], drug resistance activity [30], and antibody binding [31]. Even without a specific fitness model, these laboratory measurements can provide model-free predictions for the mutations that are tolerated in natural populations [23, 32].

By definition, the bottom-up approach is most easily applied to small functional units. Yet when left to their own devices, laboratory populations often acquire mutations in a number of different genes, which influence multiple biomolecular processes within a cell [33, 11, 3, 13, 34, 35]. In these cases, it is much more challenging to predict the targets of selection from biophysical principles, since they depend on organism-wide networks of metabolic and regulatory interactions. Genome-scale models like flux balance analysis [36], which combine networks inferred from omics data with optimality principles for choosing unconstrained parameters, represent one potential solution to this problem, along with recent experimental advances in assaying fitness in large gene knockout libraries [37, 38, 39]. So far, however, these methods have been most successful in predicting extreme phenotypes (e.g. nutrient auxotrophies [40] or synthetic lethality [38]) or in predicting adaptation to severe metabolic limitations [41]. It remains to be seen whether these methods can scale down to the moderate fitness benefits ($s \sim 1\%$) observed in more permissive conditions.

Insights into evolutionary dynamics from effective models

Despite the successes of the bottom up approach, it remains far from being able to predict evolution even in simple laboratory experiments like the LTEE, let alone the more complex environments encountered in nature. Nevertheless, the statistical regularities observed in laboratory evolution experiments have inspired a second body of research, which seeks to characterize principles of microbial evolution that emerge at higher levels of description.

Much of this work has focused on questions in *evolutionary dynamics*. That is, given a known genotype-to-fitness map, how does evolution determine which combinations of mutations ultimately reach observable frequencies, where they could be detected in sequencing or phenotyping assays. These dynamical questions are implicit in the “bottom-up” approach as well, though they are often studied only after the genotype-to-fitness map has been determined. By switching the order of emphasis, the “top-down” approach to microbial evolution tries to make progress by asking a slightly different set of questions: if

we can understand which aspects of the genotype-to-phenotype map influence evolutionary dynamics, it might be possible to infer these properties directly from population-level measurements (e.g. genetic diversity, rates of change, etc).

Given its inherent complexity, the study of evolutionary dynamics has been greatly aided by the use of *effective models*. These are simple mathematical objects that capture the limiting behavior of a much wider range of models (known as a *universality class*) which may differ in their underlying details. Since the members of the universality class behave similarly, mathematical statements about effective models can translate into general quantitative principles, which can apply even in messy biological settings.

One of the best-known effective models in evolutionary biology is the Wright-Fisher process (also known as the *single-locus diffusion model*), which describes the competition between two genetic variants in a well-mixed population [45] (Fig. 2). In this model, the frequency of “mutant” individuals is controlled by just two numbers: an effective fitness advantage s_e that describes the deterministic effect of selection, and an effective population size N_e that controls the strength of random genetic drift (Fig. 2, inset). Powerful limit theorems in population genetics have shown that this model captures the long-time behavior of a large class of models in the limit that population sizes are large and the relevant frequency changes occur over many generations [46, 45]. Of particular relevance to microbial evolution, this domain of attraction includes chemostat growth [47], batch culture [43], and even some scenarios with rapid temporal variation [42] or spatial structure with frequent mixing [48] (Fig. 2a).

In simple cases like batch culture, N_e and s_e can be related to the census population size and growth rate differences between the two strains [43]. But in most practical settings, these are simply *effective parameters* that must be self-consistently fit from the data. However, even in these cases, the Wright-Fisher model already reveals a useful general principle relating the magnitudes of N_e and s_e . In particular, the model predicts that natural selection will be unable to distinguish between mutants with a fitness difference much less than the *drift barrier*, $s_{\min} \sim 1/N_e$, where fluctuations from genetic drift start to dominate. This limit on the efficiency of selection, which arises purely from population genetic considerations, has been conjectured to set bounds on the intrinsic mutation rates of different microorganisms [49] and the stability of different proteins [50].

When reasoning with effective models, it is important to apply them only in situations where their limiting behavior is expected to apply. For example, convergence to the Wright-Fisher model will eventually break down on short timescales (Fig. 2a), when life-history details and other deviations from the model start to become important. With the increasing density of temporal sampling [51], and the low frequencies (and recent times) probed by large cohorts [52], these deviations are more likely to be encountered in real data. Other limits to convergence may be more difficult to anticipate. In the case of the Wright-Fisher model, seemingly innocuous changes in assumptions or parameter values can sometimes drive convergence to an entirely different class of effective models, which cannot be captured by adjusting N_e or s_e . Classic examples include temporal variation in N_e or s_e , which become relevant when the variation is slow compared to drift or selection [53, 42]. Another relevant

example is spatial structure, which can be important in crowded [54, 55, 56, 57] or otherwise poorly mixed populations [58, 59].

Some of these complications can be avoided in carefully controlled experiments like the LTEE. However, other deviations from the single-locus diffusion model arise due to genetic linkage, which cannot be switched off so easily. By definition, the single-locus model describes the competition between a single mutant type and its ancestor. Yet as we saw above, large microbial populations often harbor many adaptive variants at different locations (or *sites*) along the genome. Since these different sites are inherited together on the same physical genome (Fig. 3a), the fate of a mutation at a particular site will depend on all of the other genetic variants present in the population, a phenomenon is known as *clonal interference* [60] or *interference selection* [61].

Early work [62] had suggested that these effects could be absorbed within the single-locus diffusion model by rescaling N_e . However, more recent theoretical analyses have shown that this is true only in the limit of rapid recombination, when correlations between mutations can be neglected [63, 61, 64, 65]. For large microbial populations, by contrast, theory and experiment both suggest that clonal interference is likely to be a generic feature of short-term evolution [66].

At first glance, linkage would seem to make the evolutionary dynamics hopelessly complex. To model the fate of a given mutation, one would need to know the rates and fitness effects of all other mutations across the genome. Fortunately, simpler effective models emerge in the limit that there are *many* competing mutations. In the simplest cases, these models augment the single-locus diffusion by assuming that an infinite “staircase” of linked beneficial mutations can occur at other loci (Fig. 3a). This requires at least two additional parameters: a typical fitness benefit s_0 for the additional linked mutations, and a total mutation rate U_0 for these mutations to occur. The *staircase model* is clearly an abstraction, and would be a poor approximation to the genetics of any real population. Yet in terms of evolutionary dynamics, the staircase model has been shown to capture the limiting behavior in a variety of more realistic scenarios, including distributions of fitness effects [67, 68, 69, 70, 71] (Fig. 3b) and moderate amounts of recombination [72, 61, 65, 64]. The main advantage of the staircase model is that it can be characterized analytically in different limits [73, 74, 75, 68, 76, 72, 77, 78, 70, 79, 80], often by recasting the population as a traveling wave in fitness space (Fig. 3b). Together, these theoretical studies have revealed some general principles that apply to microbes evolving under clonal interference.

First, a generalization of the drift-barrier ($s_{\min} \sim 1/N_e$) still applies, provided that we replace N_e with the *coalescence time* T_c at a neutral locus (Fig. 3c). This reduces to the familiar drift barrier in the absence of linkage, where $T_c \sim N_e$. But in the presence of clonal interference, T_c is more strongly influenced by the rates and fitness effects of linked mutations (*genetic draft* [81]), and only weakly dependent on N_e . This *draft barrier* imposes fundamental limits on the ability of microbes to optimize certain functions when faced with other opportunities for adaptation [82, 78]. In the rush to run uphill, many mistakes and missed opportunities can be tolerated, potentially fueling further bouts of adaptation in the future.

Second, recent work has shown that the genealogies of populations under strong clonal interference approach a universal form, which is qualitatively different from the genealogies that arise in the Wright-Fisher model [86, 87, 88, 89]. The new genealogies are distinguished by their skewed branching structure and multiple merger events, which arise when multiple lineages are spawned by the same highly fit ancestor (Fig. 3c). Forward in time, the coarse-grained dynamics of a target mutation can be still mapped to an effective single locus model, which does not explicitly keep track of linked mutations [90, 88, 91, 92]. In this case, however, the slow diffusion of the Wright-Fisher process must be supplemented by sudden jumps in allele frequency [93], which reflect lucky mutational “jackpots” with anomalously high fitness [92].

These universal signals, which arise independently of what trait is being selected for, can be used to identify exceptionally fit lineages that may come to dominate the population in the future [84, 85] (Fig. 3c). A recent study in influenza has demonstrated the utility of this approach, in the context of forecasting which strains are likely to dominate the next flu season [85]. By mapping the observed influenza genealogy to a simplified version of the staircase model, the authors showed that one can make predictions that rival more complex methods that incorporate functional information about the influenza genome [94]. This study highlights the power of combining effective models with highly quantitative evolutionary data, in order to make testable predictions about the future.

Working in the opposite direction, dynamical models have also shed light on the structure of microbial fitness landscapes, complementing the traditional biophysical approaches above. For example, by analyzing an effective model for the emergence of beneficial mutations in barcoded subpopulations [95], a recent study surveyed hundreds of the most important beneficial mutations in the *S. cerevisiae* genome and mapped them onto key nutrient-responsive pathways [96]. Other studies have investigated how the fitness landscape shifts over time, as different mutations are added to the genetic background [97, 14, 98, 99, 100, 101, 16]. In the context of the staircase model, these changes manifest as differences in the effective parameters U_0 and s_0 that control the overall speed of adaptation (Fig. 3b). An active area of research [97, 102, 103, 101, 104, 105] seeks to understand how these *macroscopic* measures of epistasis are connected to the *microscopic* or *biophysical* epistasis probed by traditional methods [106, 101, 107, 39]. Simpler effective models of physiology [108, 109, 110] may be useful for investigating these connections.

Emergence and evolution of ecology

With the ability to track mutations over longer times, laboratory experiments have started to uncover more fundamental deviations from the simple evolutionary models above. In many cases, mutations are observed to neither fix or go extinct, but instead persist at intermediate frequencies for long periods of time (Fig. 4). This constitutes a primitive form of ecology, in which subsets of the population have evolved to colonize different ecological niches.

Such diversification was once thought to be rare, emerging only under special conditions. However, evidence for coexistence continues to arise in a variety of laboratory settings [112, 113, 114, 115, 116, 117, 118, 119, 120], even in experiments that were designed to avoid

this behavior, like the LTEE [113, 121, 4]. This suggests that emergent ecological interactions cannot be easily controlled or switched off in the lab. Moreover, many natural microbial populations are embedded in larger microbial communities, and recent evidence suggests that short-term evolution can occur in these settings as well [122, 5, 123, 124]. This suggests that diversification and community structure may be a generic feature of microbial evolution, similar to the rapid adaptation described above. Will similar simple principles emerge when ecology and evolution are intertwined?

At first glance this seems like a difficult problem, since there are many potential ways for microbes to interact. We can again gain some insight by focusing on simple systems, where the ecological interactions can be understood at a biophysical level. In microbial populations, these interactions often involve the consumption or exchange of metabolites (Fig. 4a). In a few cases, recent multi-strain extensions of flux balance analysis have been shown to predict coexistence from individual metabolic profiles [125, 126, 127], providing an intriguing route for investigating evolutionary perturbations. In an even simpler example in yeast, a recent study fully characterized the ecological landscape of mutants that adhere to the walls of their culture vessel [115]. This enabled the authors to predict when evolution would disrupt coexistence, based on fitness measurements in non-adherent conditions.

To complement these bottom-up approaches, we would also like to know whether there are simpler effective models that describe some generic features of evolving ecosystems. But in contrast to the purely evolutionary case, there is much less consensus about what the relevant effective models will look like. Recent studies have started to explore the range of potential behaviors using computer simulations, in which the interaction parameters in existing ecological models are allowed to mutate in pre-defined ways [128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140]. The results can vary depending on the detailed assumptions of the model. For example, some studies suggest that evolution generally acts to disrupt coexistence [133], while others suggest that evolution promotes coexistence [130, 136]. Without a corresponding set of effective models, it can be difficult to draw connections between these studies, or to understand how they map on to experiments.

Drawing inspiration from the evolutionary studies above, we believe that progress will depend on the development of simple effective models, in which the limiting behavior can be investigated analytically. Understanding these limits is crucial for determining whether two models share the same limiting behavior. Is it reasonable to expect an ecological analogue of the staircase model, which proved so useful for understanding clonal interference? If the previous literature is any guide, it may not be obvious which effective models will turn out to be the most relevant, and a certain amount of theoretical exploration will be required. Simple biophysical systems like Refs. [115, 141] or the abstract trait models of adaptive dynamics [142, 143] may both prove to be useful starting points. In Ref. [111], we investigate another promising candidate that emerges as the generalization of the Wright-Fisher model when there are multiple fitness dimensions.

In addition, theoretical ecology has a long tradition of seeking limiting behaviors that arise in ecosystems with a large number of species or niches [144, 145]. An exciting body of recent work has leveraged this approach, in combination with techniques from statistical

physics, to analytically characterize the steady states and dynamical properties of several ecosystem models [146, 147, 148, 149, 150, 151]. Extending this approach to allow for heritable evolutionary changes may provide an additional route for understanding evolution in large microbial communities. Of course, natural communities possess additional factors that may influence their short-term evolution, including their nontrivial spatial organization and the ability to exchange genetic information across species boundaries. Understanding how these complexities map onto simpler effective models is a key challenge for future studies.

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References

- [1]. Bruger E, Marx C, Companion review, Current opinion in microbiology (2018) in press.
- [2]. Lenski RE, Rose MR, Simpson SC, Tadler SC, Long-term experimental evolution in *Escherichia coli*. i. adaptation and divergence during 2,000 generations, *American Naturalist* 138 (6) (1991) 1315–1341.
- [3]. Tenaillon O, Barrick JE, Ribeck N, Deatherage DE, Blanchard JL, Dasgupta A, Wu GC, Wielgoss S, Cruveiller S, Médigue C, et al., Tempo and mode of genome evolution in a 50,000-generation experiment, *Nature* 536 (7615) (2016) 165–170. [PubMed: 27479321]
- [4]. Good BH, McDonald MJ, Barrick JE, Lenski RE, Desai MM, The dynamics of molecular evolution over 60,000 generations, *Nature* 551 (7678) (2017) 45. [PubMed: 29045390]
- [5]. Zhao S, Lieberman TD, Poyet M, Groussin M, Gibbons SM, Xavier RJ, Alm EJ, Adaptive evolution within the gut microbiome of individual people, *bioRxiv* (2017) 208009.
- [6]. Wichman HA, Badgett MR, Scott LA, Boulianne CM, Bull JJ, Different trajectories of parallel evolution during viral adaptation, *Science* 285 (1999) 422–424. [PubMed: 10411508]
- [7]. Cooper TF, Rozen DE, Lenski RE, Parallel changes in gene expression after 20,000 generations of evolution in *Escherichia coli*, *Proceedings of the National Academy of Sciences* 100 (3) (2003) 1072–1077.
- [8]. Woods R, Schneider D, Winkworth CL, Riley MA, Lenski RE, Tests of parallel molecular evolution in a long-term experiment with *Escherichia coli*, *Proc Natl Acad Sci USA* 103 (2006) 9107–9112. [PubMed: 16751270]
- [9]. Barrick JE, Yu DS, Yoon SH, Jeong H, Oh TK, Schneider D, Lenski RE, Kim JF, Genome evolution and adaptation in a long-term experiment with *Escherichia coli*, *Nature* 461 (2009) 1243–1247. [PubMed: 19838166]
- [10]. Lieberman TD, Michel J-B, Aingaran M, Potter-Bynoe G, Roux D, Davis MR Jr, Skurnik D, Leiby N, LiPuma JJ, Goldberg JB, et al., Parallel bacterial evolution within multiple patients identifies candidate pathogenicity genes, *Nature genetics* 43 (12) (2011) 1275. [PubMed: 22081229]
- [11]. Tenaillon O, Rodríguez-Verdugo A, Gaut RL, McDonald P, Bennett AF, Long AD, Gaut BS, The molecular diversity of adaptive convergence, *Science* 335 (2012) 457–461. [PubMed: 22282810]
- [12]. Toprak E, Veres A, Michel J-B, Chait R, Hartl DL, Kishony R, Evolutionary paths to antibiotic resistance under dynamically sustained drug selection, *Nature genetics* 44 (1) (2012) 101.
- [13]. Lang GI, Rice DP, Hickman MJ, Sodergren E, Weinstock GM, Botstein D, Desai MM, Pervasive genetic hitchhiking and clonal interference in forty evolving yeast populations, *Nature* 500 (7464) (2013) 571–574. [PubMed: 23873039]

- [14]. Kryazhimskiy SK, Rice DP, Jerison ER, Desai MM, Global epistasis makes adaptation predictable despite sequence-level stochasticity, *Science* 344 (2014) 1519–1522. [PubMed: 24970088]
- [15]. Barroso-Batista J, Sousa A, Lourenço M, Bergman M-L, Sobral D, Demengeot J, Xavier KB, Gordo I, The first steps of adaptation of *Escherichia coli* to the gut are dominated by soft sweeps, *PLoS genetics* 10 (3) (2014) e1004182. [PubMed: 24603313]
- [16]. Jerison ER, Kryazhimskiy S, Mitchell JK, Bloom JS, Kruglyak L, Desai MM, Genetic variation in adaptability and pleiotropy in budding yeast, *eLife* 6.
- [17]. Kacser H, Burns JA, The molecular basis of dominance, *Genetics* 97 (3–4) (1981) 639–666. [PubMed: 7297851]
- [18]. Dean AM, Dykhuizen DE, Hartl DL, Fitness as a function of α -galactosidase activity in *Escherichia coli*, *Genetics Research* 48 (1) (1986) 1–8.
- [19]. Dykhuizen DE, Dean AM, Hartl DL, Metabolic flux and fitness, *Genetics* 115 (1) (1987) 25–31. [PubMed: 3104135]
- [20]. Dekel E, Alon U, Optimality and evolutionary tuning of the expression level of a protein, *Nature* 436 (7050) (2005) 588. [PubMed: 16049495]
- [21]. Chou H-H, Delaney NF, Draghi JA, Marx CJ, Mapping the fitness landscape of gene expression uncovers the cause of antagonism and sign epistasis between adaptive mutations, *PLoS genetics* 10 (2) (2014) e1004149. [PubMed: 24586190] • This study uses a biophysical model of catalysis, enzyme cost, and toxicity to predict sign epistasis between a simple set of mutations with independent effects on gene expression in *M. extorquens*.
- [22]. Rodrigues JV, Bershtein S, Li A, Lozovsky ER, Hartl DL, Shakhnovich EI, Biophysical principles predict fitness landscapes of drug resistance, *Proceedings of the National Academy of Sciences* 113 (11) (2016) E1470–E1478. • This study develops a comprehensive biophysical model for antibiotic susceptibility as a function of the molecular properties of a target enzyme in *E. coli*.
- [23]. Razo-Mejia M, Boedicker JQ, Jones D, DeLuna A, Kinney JB, Phillips R, Comparison of the theoretical and real-world evolutionary potential of a genetic circuit, *Phys Biol* 11 (2014) 026005. [PubMed: 24685590]
- [24]. Wylie CS, Shakhnovich EI, A biophysical protein folding model accounts for most mutational fitness effects in viruses, *Proc Natl Acad Sci USA* 108 (2011) 9916–9921. [PubMed: 21610162]
- [25]. Mustonen V, M. L. [notdef]assig, Evolutionary population genetics of promoters: predicting binding sites and functional phylogenies, *Proceedings of the National Academy of Sciences of the United States of America* 102 (44) (2005) 15936–15941. [PubMed: 16236723]
- [26]. Guerois R, Nielsen JE, Serrano L, Predicting changes in the stability of proteins and protein complexes: a study of more than 1000 mutations, *Journal of molecular biology* 320 (2) (2002) 369–387. [PubMed: 12079393]
- [27]. Kinney JB, Murugana A, Callan CG, Jr EC Cox, Using deep sequencing to characterize the biophysical mechanism of a transcriptional regulatory sequence, *Proc Natl Acad Sci USA* 107 (2010) 9158–9163. [PubMed: 20439748]
- [28]. Fowler DM, Fields S, Deep mutational scanning: a new style of protein science, *Nature methods* 11 (8) (2014) 801. [PubMed: 25075907]
- [29]. Romero PA, Tran TM, Abate AR, Dissecting enzyme function with microfluidic-based deep mutational scanning, *Proceedings of the National Academy of Sciences* 112 (23) (2015) 7159–7164.
- [30]. Jacquier H, Birgy A, Le Nagard H, Mechulam Y, Schmitt E, Glodt J, Bercot B, Petit E, Poulain J, Barnaud G, et al., Capturing the mutational landscape of the beta-lactamase tem-1, *Proceedings of the National Academy of Sciences* 110 (32) (2013) 13067–13072.
- [31]. Adams RM, Mora T, Walczak AM, Kinney JB, Measuring the sequence-affinity landscape of antibodies with massively parallel titration curves, *Elife* 5.
- [32]. Lee JM, Huddleston J, Doud MB, Hooper KA, Wu NC, Bedford T, Bloom JD, Deep mutational scanning of hemagglutinin helps predict evolutionary fates of human h3n2 influenza variants, *bioRxiv* (2018) 298364.

- [33]. Gresham D, Desai MM, Tucker CM, Jenq HT, Pai DA, Ward A, DeSevo CG, Botstein D, Dunham MJ, The repertoire and dynamics of evolutionary adaptations to controlled nutrient-limited environments in yeast, *PLoS genetics* 4 (12) (2008) e1000303. [PubMed: 19079573]
- [34]. Kvitek DJ, Sherlock G, Whole genome, whole population sequencing reveals that loss of signaling networks is the major adaptive strategy in a constant environment, *PLoS Genetics* 9 (11) (2013) e1003972. [PubMed: 24278038]
- [35]. Rodríguez-Verdugo A, Tenaillon O, Gaut BS, First-step mutations during adaptation restore the expression of hundreds of genes, *Molecular biology and evolution* 33 (1) (2015) 25–39. [PubMed: 26500250]
- [36]. King ZA, Lloyd CJ, Feist AM, Palsson BO, Next-generation genome-scale models for metabolic engineering, *Current opinion in biotechnology* 35 (2015) 23–29. [PubMed: 25575024]
- [37]. Price MN, Wetmore KM, Waters RJ, Callaghan M, Ray J, Liu H, Kuehl JV, Melnyk RA, Lamson JS, Suh Y, et al., Mutant phenotypes for thousands of bacterial genes of unknown function, *Nature* (2018) 1.
- [38]. Costanzo M, VanderSluis B, Koch EN, Baryshnikova A, Pons C, Tan G, Wang W, Usaj M, Hanchard J, Lee SD, et al., A global genetic interaction network maps a wiring diagram of cellular function, *Science* 353 (6306) (2016) aaf1420. [PubMed: 27708008]
- [39]. Kuzmin E, VanderSluis B, Wang W, Tan G, Deshpande R, Chen Y, Usaj M, Balint A, Usaj MM, van Leeuwen J, et al., Systematic analysis of complex genetic interactions, *Science* 360 (6386) (2018) eaao1729. [PubMed: 29674565]
- [40]. Price MN, Zane GM, Kuehl JV, Melnyk RA, Wall JD, Deutschbauer AM, Arkin AP, Filling gaps in bacterial amino acid biosynthesis pathways with high-throughput genetics, *PLoS genetics* 14 (1) (2018) e1007147. [PubMed: 29324779]
- [41]. Harcombe WR, Delaney NF, Leiby N, Klitgord N, Marx CJ, The ability of flux balance analysis to predict evolution of central metabolism scales with the initial distance to the optimum, *PLoS computational biology* 9 (6) (2013) e1003091. [PubMed: 23818838]
- [42]. Cvijović I, Good BH, Jerison ER, Desai MM, Fate of a mutation in a fluctuating environment, *Proceedings of the National Academy of Sciences* 112 (36) (2015) E5021–E5028.
- [43]. Wahl LM, Gerrish PJ, Saika-Voivod I, Evaluating the impact of population bottlenecks in experimental evolution, *Genetics* 162 (2002) 961–971. [PubMed: 12399403]
- [44]. Kryazhimskiy SK, Rice DP, Desai MM, Population subdivision and adaptation in asexual populations of *saccharomyces cerevisiae*, *Evolution* 66 (2012) 1931–1941. [PubMed: 22671557]
- [45]. Ewens WJ, *Mathematical Population Genetics*, 2nd Edition, Springer-Verlag, New York, 2004.
- [46]. Möhle M, Sagitov S, A classification of coalescent processes for haploid exchangeable population models, *Annals of Probability* 29 (2001) 1547–1562.
- [47]. Dykhuizen DE, Hartl DL, Selection in chemostats., *Microbiological reviews* 47 (2) (1983) 150. [PubMed: 6308409]
- [48]. Whitlock MC, Fixation probability and time in subdivided populations, *Genetics* 164 (2003) 967–779.
- [49]. Lynch M, Ackerman MS, Gout J-F, Long H, Sung W, Thomas WK, Foster PL, Genetic drift, selection and the evolution of the mutation rate, *Nature Reviews Genetics* 17 (11) (2016) 704–714.
- [50]. Serohijos AW, Shakhnovich EI, Merging molecular mechanism and evolution: theory and computation at the interface of biophysics and evolutionary population genetics, *Current opinion in structural biology* 26 (2014) 84–91. [PubMed: 24952216]
- [51]. Bergland AO, Behrman EL, O'Brien KR, Schmidt PS, Petrov DA, Genomic Evidence of Rapid and Stable Adaptive Oscillations over Seasonal Time Scales in *Drosophila*, *PLoS Genetics* 10 (11) (2014) e1004775. [PubMed: 25375361]
- [52]. Cvijović I, Good BH, Desai MM, The effect of strong purifying selection on genetic diversity, *bioRxiv* (2017) 211557.
- [53]. Messer PW, Petrov DA, Frequent adaptation and the mcdonald-kreitman test., *Proc Natl Acad Sci USA* 110 (2013) 8615–8620. [PubMed: 23650353]

- [54]. Gralka M, Stiewe F, Farrell F, Möbius W, Waclaw B, Hallatschek O, Allele surfing promotes microbial adaptation from standing variation, *Ecology letters* 19 (8) (2016) 889–898. [PubMed: 27307400]
- [55]. Kayser J, Schreck C, Gralka M, Fusco D, Hallatschek O, Collective motion conceals fitness differences in crowded cellular populations, *bioRxiv* (2018) 267286.
- [56]. Giometto A, Nelson DR, Murray AW, Physical interactions reduce the power of natural selection in growing yeast colonies, *bioRxiv* (2018) 332700.
- [57]. Rulands S, Lescroart F, Chabab S, Hindley CJ, Prior N, Sznurkowska MK, Huch M, Philpott A, Blanpain C, Simons BD, Universality of clone dynamics during tissue development, *Nature Physics* (2018) 1.
- [58]. Hallatschek O, Nelson DR, Gene surfing in expanding populations, *Theor Popul Biol* 73 (2008) 158–170. [PubMed: 17963807]
- [59]. Hallatschek O, Fisher DS, Acceleration of evolutionary spread by long-range dispersal, *Proceedings of the National Academy of Sciences* 111 (46) (2014) E4911–E4919.
- [60]. Gerrish P, Lenski R, The fate of competing beneficial mutations in an asexual population, *Genetica* 127 (1998) 127–144.
- [61]. Neher RA, Kessinger TA, Shraiman BI, Coalescence and genetic diversity in sexual populations under selection, *Proc Nat Acad Sci* 110 (2013) 15836–15841. [PubMed: 24019480] • These papers show how rapid adaptation on a recombining chromosome can be mapped to an effective model of asexual linkage blocks. The length scale is determined self-consistently, such that there are few recombination events within a block in the time required for a mutation to fix.
- [62]. Hill WG, Robertson A, The effect of linkage on limits to artificial selection, *Genet. Res* 8 (1966) 269–294. [PubMed: 5980116]
- [63]. Neher RA, Shraiman BI, Statistical genetics and evolution of quantitative traits, *Rev Mod Phys* 83 (2011) 1283–1300.
- [64]. Weissman D, Hallatschek O, The rate of adaptation in large sexual populations with linear chromosomes, *Genetics* 196 (2014) 1167–1183. [PubMed: 24429280] • These papers show how rapid adaptation on a recombining chromosome can be mapped to an effective model of asexual linkage blocks. The length scale is determined self-consistently, such that there are few recombination events within a block in the time required for a mutation to fix.
- [65]. Good BH, Walczak AM, Neher RA, Desai MM, Genetic diversity in the interference selection limit, *PLoS Genetics* 10 (2014) e1004222. [PubMed: 24675740]
- [66]. Lässig M, Mustonen V, Walczak AM, Predicting evolution, *Nature ecology & evolution* 1 (3) (2017) 0077.
- [67]. Hegreness M, Shores N, Hartl D, Kishony R, An equivalence principle for the incorporation of favorable mutations in asexual populations, *Science* 311 (2006) 1615–1617. [PubMed: 16543462]
- [68]. Desai MM, Fisher DS, Beneficial mutation selection balance and the effect of genetic linkage on positive selection, *Genetics* 176 (2007) 1759–1798. [PubMed: 17483432]
- [69]. Good BH, Rouzine IM, Balick DJ, Hallatschek O, Desai MM, Distribution of fixed beneficial mutations and the rate of adaptation in asexual populations, *Proc Natl Acad Sci USA* 109 (2012) 4950–4955. [PubMed: 22371564] • These papers show how rapid adaptation from beneficial mutations of different strengths can often mapped to an effective model with a characteristic fitness increment (the staircase model).
- [70]. Fisher DS, Asexual evolution waves: fluctuations and universality, *J Stat Mech* 2013 (2013) P01011. • These papers show how rapid adaptation from beneficial mutations of different strengths can often mapped to an effective model with a characteristic fitness increment (the staircase model).
- [71]. Good BH, Desai MM, Deleterious passengers in adapting populations, *Genetics* 198 (2014) 1183–1208. [PubMed: 25194161]
- [72]. Neher R, Shraiman BI, Fisher DS, Rate of adaptation in large sexual populations, *Genetics* 184 (2010) 467–481. [PubMed: 19948891]
- [73]. Tsimring L, Levine H, Kessler D, Rna virus evolution via a fitness-space model, *Phys. Rev. Lett* 90 (1996) 088103.

- [74]. Cohen E, Kessler DA, Levine H, Front propagation up a reaction rate gradient, *Phys Rev E* 72 (2005) 066126.
- [75]. Rouzine IM, Wakeley J, Co n JM, The solitary wave of asexual evolution, *Proc Natl Acad Sci USA* 100 (2003) 587–592. [PubMed: 12525686]
- [76]. Park S, Krug J, Clonal interference in large populations, *Proc Natl Acad Sci USA* 104 (2007) 18135–18140. [PubMed: 17984061]
- [77]. Hallatschek O, The noisy edge of traveling waves, *Proc Natl Acad Sci USA* 108 (2011) 1783–1787. [PubMed: 21187435]
- [78]. Schi els S, SzÖllÖsi G, Mustonen V, Lässig M, Emergent neutrality in adaptive asexual evolution, *Genetics* 189 (2011) 1361–1375. [PubMed: 21926305]
- [79]. Good BH, Desai MM, Fluctuations in fitness distributions and the effects of weak linked selection on sequence evolution, *Theor Pop Biol* 85 (2013) 86–102. [PubMed: 23337315]
- [80]. Schweinsberg J, et al., Rigorous results for a population model with selection i: evolution of the fitness distribution, *Electronic Journal of Probability* 22.
- [81]. Gillespie JH, Genetic drift in an infinite population: The pseudohitchhiking model, *Genetics* 155 (2000) 909–919. [PubMed: 10835409]
- [82]. Neher R, Shraiman BI, Genetic draft and quasi-neutrality in large facultatively sexual populations, *Genetics* 188 (2011) 975–976. [PubMed: 21625002]
- [83]. Good BH, Desai MM, Evolution of mutation rates in rapidly adapting asexual populations, *Genetics* 204 (3) (2016) 1249–1266. [PubMed: 27646140]
- [84]. Dayarian A, Shraiman BI, How to infer relative fitness from a sample of genomic sequences, *Genetics* 197 (3) (2014) 913–923. [PubMed: 24770330]
- [85]. Neher RA, Russell CA, Shraiman BI, Predicting evolution from the shape of genealogical trees, *Elife* 3. • • This study develops a method for inferring the relative fitnesses of individuals directly from a genealogical tree, by mapping the genealogy to an effective staircase model. When applied to influenza hemagglutinin, this method can help forecast which strains are likely to dominate the in the future, without requiring a detailed fitness model.
- [86]. Brunet É, Derrida B, Mueller AH, Munier S, Effect of selection on ancestry: an exactly soluble case and its phenomenological generalization, *Physical Review E* 76 (4) (2007) 041104.
- [87]. Neher RA, Hallatschek O, Genealogies in rapidly adapting populations, *Proc Nat Acad Sci* 110 (2013) 437–442. [PubMed: 23269838] • These papers characterize the genealogies that emerge in two separate limits of the staircase model. In the limit of large populations, these genealogies approach a universal form similar to the well-studied Bolthausen-Sznitman coalescent.
- [88]. Desai MM, Walczak AM, Fisher DS, Genetic diversity and the structure of genealogies in rapidly adapting populations, *Genetics* 193 (2013) 565–585. [PubMed: 23222656] • These papers characterize the genealogies that emerge in two separate limits of the staircase model. In the limit of large populations, these genealogies approach a universal form similar to the well-studied Bolthausen-Sznitman coalescent.
- [89]. Schweinsberg J, et al., Rigorous results for a population model with selection ii: genealogy of the population, *Electronic Journal of Probability* 22.
- [90]. Schweinsberg J, Coalescent processes obtained from supercritical galton–watson processes, *Stochastic Processes and their Applications* 106 (1) (2003) 107–139.
- [91]. Kosheleva K, Desai MM, The dynamics of genetic draft in rapidly adapting populations, *Genetics* 195 (2013) 1007–1025. [PubMed: 24002646]
- [92]. Hallatschek O, Selection-like biases emerge in population models with recurrent jackpot events, *bioRxiv* (2017) 182519.
- [93]. Der R, Epstein CL, Plotkin JB, Generalized population models and the nature of genetic drift, *Theoretical Population Biology* 80 (2011) 80–99. [PubMed: 21718713]
- [94]. Luksza M, Lässig M, A predictive fitness model for influenza, *Nature* 507 (7490) (2014) 57–61. [PubMed: 24572367] • This study develops a fitness model for influenza hemagglutinin that is parameterized by population genetic data. The authors show how this fitness model can help forecast which strains are likely to dominate the population in the following season.

- [95]. Levy SF, Blundell JR, Venkataram S, Petrov DA, Fisher DS, Sherlock G, Quantitative evolutionary dynamics using high-resolution lineage tracking, *Nature* 519 (7542) (2015) 181–186. [PubMed: 25731169]
- [96]. Venkataram S, Dunn B, Li Y, Agarwala A, Chang J, Ebel ER, Geiler-Samerotte K, Hérissant L, Blundell JR, Levy SF, et al., Development of a comprehensive genotype-to-fitness map of adaptation-driving mutations in yeast, *Cell* 166 (6) (2016) 1585–1596. [PubMed: 27594428]
- [97]. Wiser MJ, Ribeck N, Lenski RE, Long-term dynamics of adaptation in asexual populations, *Science* 342 (2013) 1364–1367. [PubMed: 24231808]
- [98]. Perfeito L, Sousa A, Bataillon T, Gordo I, Rates of fitness decline and rebound suggest pervasive epistasis, *Evolution* 68 (2014) 150–162. [PubMed: 24372601]
- [99]. Szamecz B, Boross G, Kalapis D, Kovács K, Fekete G, Farkas Z, Lázár V, Hrtan M, Kemmeren P, Groot Koerkamp MJA, Rutkai E, Holstege FCP, Papp B, Pál C, The genomic landscape of compensatory evolution, *PLoS Biology* 12 (2014) e1001935. [PubMed: 25157590]
- [100]. Blank D, Wolf L, Ackermann M, Silander OK, The predictability of molecular evolution during functional innovation, *Proc Natl Acad Sci USA* 111 (2014) 3044–3049. [PubMed: 24516157]
- [101]. Bank C, Hietpas RT, Jensen JD, Bolon DN, A systematic survey of an intragenic epistatic landscape, *Molecular biology and evolution* 32 (1) (2014) 229–238. [PubMed: 25371431]
- [102]. Good BH, Desai MM, The impact of macroscopic epistasis on long-term evolutionary dynamics, *Genetics* 199 (1) (2015) 177–190. [PubMed: 25395665]
- [103]. McCandlish M, Otwinowski J, Plotkin JB, Detecting epistasis from an ensemble of adapting populations, *Evolution* 69 (2015) 2359–2380. [PubMed: 26194030]
- [104]. Couce A, Tenaillon OA, The rule of declining adaptability in microbial evolution experiments, *Frontiers in genetics* 6 (2015) 99. [PubMed: 25815007]
- [105]. Otwinowski J, McCandlish DM, Plotkin J, Inferring the shape of global epistasis, *bioRxiv* (2018) 278630.
- [106]. Weinreich DM, Delaney NF, DePristo MA, Hartl DL, Darwinian evolution can follow only very few mutational paths to fitter proteins, *Science* 312 (2006) 111–114. [PubMed: 16601193]
- [107]. Buskirk SW, Peace RE, Lang GI, Hitchhiking and epistasis give rise to cohort dynamics in adapting populations, *Proceedings of the National Academy of Sciences* (2017) 201702314.
- [108]. Martin G, Fishers geometrical model emerges as a property of complex integrated phenotypic networks, *Genetics* 197 (1) (2014) 237–255. [PubMed: 24583582]
- [109]. Erickson DW, Schink SJ, Patsalo V, Williamson JR, Gerland U, Hwa T, A global resource allocation strategy governs growth transition kinetics of *Escherichia coli*, *Nature* 551 (7678) (2017) 119. [PubMed: 29072300]
- [110]. Nourmohammad A, Held T, Lässig M, Universality and predictability in molecular quantitative genetics, *Current opinion in genetics & development* 23 (6) (2013) 684–693. [PubMed: 24291213]
- [111]. Good BH, Martis S, Hallatschek O, Directional selection limits ecological diversification and promotes ecological tinkering during the competition for substitutable resources, *bioRxiv* (2018) 292821. • This paper develops an analytically tractable toy model of ecological diversification that also allows for adaptation at other genomic loci. These “general fitness” mutations are shown to have a dramatic effect on the ecological and evolutionary dynamics.
- [112]. Helling RB, Vargas CN, Adams J, Evolution of *Escherichia coli* during growth in a constant environment, *Genetics* 116 (3) (1987) 349–358. [PubMed: 3301527]
- [113]. Rozen DE, Lenski RE, Long-term experimental evolution in *Escherichia coli*. viii. dynamics of a balanced polymorphism, *American Naturalist* 155 (1) (2000) 24–35.
- [114]. Friesen ML, Saxer G, Travisano M, Doebeli M, Experimental evidence for sympatric ecological diversification due to frequency-dependent competition in *Escherichia coli*, *Evolution* 58 (2) (2004) 245–260. [PubMed: 15068343]
- [115]. Frenkel EM, McDonald MJ, Van Dyken JD, Kosheleva K, Lang GI, Desai MM, Crowded growth leads to the spontaneous evolution of semistable coexistence in laboratory yeast populations, *Proc Natl Acad Sci USA* 112 (36) (2015) 11306–11311. [PubMed: 26240355] • • This study develops a simple biophysical model of coexistence that emerged in a laboratory evolution experiment in yeast. Coexistence is mediated by adherence to the walls of the culture

vessel in conditions of crowded growth. This model correctly predicts how the ecological equilibrium between the strains depends on their relative fitness.

- [116]. Sousa A, Ramiro RS, Barroso-Batista J, GÜleresi D, Lourenço M, Gordo I, Recurrent reverse evolution maintains polymorphism after strong bottlenecks in commensal gut bacteria, *Molecular biology and evolution* 34 (11) (2017) 2879–2892. [PubMed: 28961745]
- [117]. Rainey PB, Travisano M, Adaptive radiation in a heterogeneous environment, *Nature* 394 (6688) (1998) 69–72. [PubMed: 9665128]
- [118]. Finkel SE, Kolter R, Evolution of microbial diversity during prolonged starvation, *Proceedings of the National Academy of Sciences* 96 (7) (1999) 4023–4027.
- [119]. Poltak SR, Cooper VS, Ecological succession in long-term experimentally evolved biofilms produces synergistic communities, *ISME J* 5 (3) (2011) 369–378. [PubMed: 20811470]
- [120]. Behringer MG, Choi BI, Miller SF, Doak TG, Karty JA, Guo W, Lynch M, *Escherichia coli* cultures maintain stable subpopulation structure during long-term evolution, *Proceedings of the National Academy of Sciences* (2018) 201708371.
- [121]. Blount ZD, Borland CZ, Lenski RE, Historical contingency and the evolution of a key innovation in an experimental population of *Escherichia coli*, *Proc Natl Acad Sci USA* 105 (2008) 7899–7906. [PubMed: 18524956]
- [122]. Bendall ML, Stevens SL, Chan L-K, Malfatti S, Schwientek P, Tremblay J, Schackwitz W, Martin J, Pati A, Bushnell B, et al., Genome-wide selective sweeps and gene-specific sweeps in natural bacterial populations, *ISME J* 10 (7) (2016) 1589–1601. [PubMed: 26744812]
- [123]. Garud NR, Good BH, Hallatschek O, Pollard KS, Evolutionary dynamics of bacteria in the gut microbiome within and across hosts, *bioRxiv* Doi: 10.1101/210955.
- [124]. Ghalayini M, Launay A, Bridier-Nahmias A, Clermont O, Denamur E, Lescat M, Tenaillon O, Evolution of a dominant natural isolate of *Escherichia coli* in the human gut over a year suggests a neutral evolution with reduced effective population size, *Applied and environmental microbiology* (2018) AEM–02377.
- [125]. Harcombe WR, Riehl WJ, Dukovski I, Granger BR, Betts A, Lang AH, Bonilla G, Kar A, Leiby N, Mehta P, et al., Metabolic resource allocation in individual microbes determines ecosystem interactions and spatial dynamics, *Cell reports* 7 (4) (2014) 1104–1115. [PubMed: 24794435] • This study develops a multi-species generalization of flux balance analysis, and shows that it can predict the equilibrium composition of a simple microbial community with cross-feeding interactions.
- [126]. Louca S, Doebeli M, Calibration and analysis of genome-based models for microbial ecology, *Elife* 4 (2015) e08208. [PubMed: 26473972]
- [127]. Shoaie S, Gha ari P, Kovatcheva-Datchary P, Mardinoglu A, Sen P, Pujos-Guillot E, De Wouters T, Juste C, Rizkalla S, Chilloux J, et al., Quantifying diet-induced metabolic changes of the human gut microbiome, *Cell metabolism* 22 (2) (2015) 320–331. [PubMed: 26244934]
- [128]. Dieckmann U, Marrow P, Law R, Evolutionary cycling in predator-prey interactions: population dynamics and the red queen, *Journal of theoretical biology* 176 (1) (1995) 91–102. [PubMed: 7475110]
- [129]. Doebeli M, A model for the evolutionary dynamics of cross-feeding polymorphisms in microorganisms, *Population Ecology* 44 (2) (2002) 59–70.
- [130]. Kondoh M, Foraging adaptation and the relationship between food-web complexity and stability, *Science* 299 (5611) (2003) 1388–1391. [PubMed: 12610303]
- [131]. Ackermann M, Doebeli M, Evolution of niche width and adaptive diversification, *Evolution* 58 (12) (2004) 2599–2612. [PubMed: 15696740]
- [132]. Ackland G, Gallagher I, Stabilization of large generalized Lotka-Volterra foodwebs by evolutionary feedback, *Phys Rev Lett* 93 (15) (2004) 158701. [PubMed: 15524949]
- [133]. Shores N, Hegreness M, Kishony R, Evolution exacerbates the paradox of the plankton, *Proc Natl Acad Sci USA* 105 (34) (2008) 12365–12369.
- [134]. Großkopf T, Consuegra J, Gaffé J, Willison JC, Lenski RE, Soyer OS, Schneider D, Metabolic modelling in a dynamic evolutionary framework predicts adaptive diversification of bacteria in a long-term evolution experiment, *BMC evolutionary biology* 16 (1) (2016) 163. [PubMed: 27544664]

- [135]. Vetsigian K, Diverse modes of eco-evolutionary dynamics in communities of antibiotic-producing microorganisms, *Nature Ecology & Evolution* 1 (2017) 0189. • This paper uses computer simulations to classify the varied ecological and evolutionary dynamics that arise in a model of antibiotic-producing communities, when the ecological parameters are allowed to mutate over time.
- [136]. Xue C, Goldenfeld N, Coevolution maintains diversity in the stochastic kill the winner model, *Physical review letters* 119 (26) (2017) 268101. [PubMed: 29328693]
- [137]. Bonachela JA, Wortel MT, Stenseth NC, Eco-evolutionary red queen dynamics regulate biodiversity in a metabolite-driven microbial system, *Scientific reports* 7 (1) (2017) 17655. [PubMed: 29247226]
- [138]. Rocabert C, Knibbe C, Consuegra J, Schneider D, Beslon G, Beware batch culture: Seasonality and niche construction predicted to favor bacterial adaptive diversification, *PLoS computational biology* 13 (3) (2017) e1005459. [PubMed: 28358919]
- [139]. Doebeli M, Ispolatov I, Diversity and coevolutionary dynamics in high-dimensional phenotype spaces, *The American Naturalist* 189 (2) (2017) 105–120.
- [140]. Shtilerman E, Kessler DA, Shnerb NM, Emergence of structured communities through evolutionary dynamics, *Journal of theoretical biology* 383 (2015) 138–144. [PubMed: 26231415]
- [141]. Shou W, Ram S, Vilar JM, Synthetic cooperation in engineered yeast populations, *Proceedings of the National Academy of Sciences* 104 (6) (2007) 1877–1882.
- [142]. Geritz SA, Mesze G, Metz JA, et al., Evolutionarily singular strategies and the adaptive growth and branching of the evolutionary tree, *Evolutionary ecology* 12 (1) (1998) 35–57.
- [143]. Doebeli M, *Adaptive Diversification*, Princeton University Press, 2011.
- [144]. May RM, Will a large complex system be stable?, *Nature* 238 (5364) (1972) 413. [PubMed: 4559589]
- [145]. Levin SA, The problem of pattern and scale in ecology: the robert h. macarthur award lecture, *Ecology* 73 (6) (1992) 1943–1967.
- [146]. Kessler DA, Shnerb NM, Generalized model of island biodiversity, *Physical Review E* 91 (4) (2015) 042705.
- [147]. Posfai A, Taillefumier T, Wingreen NS, Metabolic trade-offs promote diversity in a model ecosystem, *Phys Rev Lett* 118 (2) (2017) 028103. [PubMed: 28128613]
- [148]. Tikhonov M, Monasson R, Collective phase in resource competition in a highly diverse ecosystem, *Phys Rev Lett* 118 (4) (2017) 048103. [PubMed: 28186794] • This paper shows how ecosystems can possess simple limiting behaviors when the number of coexisting species grows very large. The authors adapt methods from statistical physics to analytically characterize the ecological equilibria that arise in a well-studied consumer resource model.
- [149]. Advani M, Bunin G, Mehta P, Statistical physics of community ecology: a cavity solution to macarthurs consumer resource model, *Journal of Statistical Mechanics: Theory and Experiment* 2018 (3) (2018) 033406. [PubMed: 30636966]
- [150]. Biroli G, Bunin G, Cammarota C, Marginally stable equilibria in critical ecosystems, *arXiv preprint arXiv:1710.03606*.
- [151]. Taillefumier T, Posfai A, Meir Y, Wingreen NS, Microbial consortia at steady supply, *eLife* 6 (2017) e22644. [PubMed: 28473032]

Figure 1: The bottom up approach to microbial evolution, illustrated using the lactose pathway in *E. coli*.

(a) A model of growth in lactose-limited conditions connects fitness (i.e., biomass production) to flux through the *lac* pathway. (b) This model can be used to predict fitness as a function of *lacZ* expression [20]. The circles illustrate how a mutation with a constant effect on expression can be both beneficial or deleterious, depending on the genetic background [21]. (c) Deep mutational scanning and (d) thermodynamic models of transcription provide a map between the DNA sequence of the *lac* promoter and *lacZ* expression [23]. In (c), the colored grid denotes the inferred change in binding energy of the CRP activator (green), RNA polymerase (blue), and the Lac repressor (red) when each of the indicated bases is mutated to the corresponding value. Together, the different biophysical layers in (a-d) enable the prediction of an organismal fitness effect s for each mutation in the *lac* promoter. Panels (c) and (d) are reproduced with permission from Ref. [23]. ©IOP Publishing. All Rights Reserved.

Figure 2: An example of an effective model of evolutionary dynamics: the Wright-Fisher diffusion process.

(a) Different microscopic dynamics that converge to the Wright-Fisher diffusion (inset) on long timescales. From left to right: microscopic Wright-Fisher diffusion, an environment that rapidly fluctuates between two states [42], serial passaging [43], and spatially segregated passaging with frequent mixing [44]. (b) Emergent dynamics of the mutation frequency f at the population level, described by the effective parameters s_e and N_e . Genetic drift is dominant when $N_e s_e f(1-f) \ll 1$, so mutations with $N_e s_e f \ll 1$ will have a high probability of drifting to extinction (grey line). Once $N_e s_e f \gg 1$, natural selection will deterministically drive the mutation to fixation. If $s \ll s_{\min} \sim N_e^{-1}$, genetic drift will dominate over the entire frequency range, and the mutation will be effectively neutral.

Figure 3: Evolutionary dynamics in rapidly adapting populations with many linked mutations.

(a) Many limiting behaviors are captured by the *staircase model* of adaptation on an asexual genome. A target mutation (s_e , blue) resides on a genetic background that can acquire further beneficial mutations (s_0 , red) at a large number of other sites (white) at total rate U_0 . Mutations on the same genetic background are inherited together and their fates become coupled. (b) Macroscopic epistasis influences long-term evolutionary dynamics by changing the effective parameters. Left: an initial distribution of fitness effects, $U_\rho(s)$, and the corresponding effective parameters s_0 and U_0 [69]. After several substitutions, epistasis leads to a shifted DFE (right) and a new set effective parameters. A similar effect occurs during the acquisition of a mutator phenotype, which increases the genome-wide mutation rate by a factor r [83]. (c) Diverse genetic backgrounds can be coarse-grained into a population fitness distribution (green), which translates to higher fitness at a constant rate. Black lines illustrate a stereotypical genealogy constructed from samples at the two timepoints. Rapidly branching internal nodes indicate a high-fitness lineage, which is likely to dominate the population in the future [84, 85].

Figure 4: Spontaneous ecological diversification during microbial evolution.

(a) A canonical microscopic example of coexistence through crossfeeding. The wildtype strain metabolizes a nutrient (light blue) and excretes a metabolic by-product (dark blue). A mutation occurs that enables growth on the by-product, which allows the mutant and wildtype to stably coexist. Further beneficial mutations can occur in this background, leading to the replacement of the mutant strain while maintaining coexistence with the wildtype. (b) A schematic illustration of the mutation frequencies for the hypothetical scenario in (a). The diversifying mutation rapidly invades, but stabilizes at an intermediate frequency. A second beneficial mutation sweeps through the mutant background, leading to a shift in this ecological equilibrium [111].