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1 **Tipping points in the dynamics of speciation**

2

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4

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10

11 **Speciation can be gradual or sudden and involve few or many genetic changes. Inferring**
12 **the processes generating such patterns is difficult, and may require consideration of**
13 **emergent and non-linear properties of speciation, such as when small changes at tipping**
14 **points have large effects on differentiation. Tipping points involve positive feedback and**
15 **indirect selection stemming from associations between genomic regions, bi-stability due to**
16 **effects of initial conditions and evolutionary history, and dependence on modularity of**
17 **system components. These features are associated with sudden ‘regime shifts’ in other**
18 **cellular, ecological, and societal systems. Thus, tools used to understand other complex**
19 **systems could be fruitfully applied in speciation research.**

20

21 **1. Introduction**

22

23 The speciation process can range from gradual to sudden¹⁻⁶. Below, we draw caricatures of these
24 scenarios. These are not meant to realistically capture the complexity of speciation. Rather, they
25 introduce elements of the on-going debate concerning whether Darwinian gradualism can be
26 reconciled with mounting evidence for rapid evolution, evolutionary gaps, and missing
27 intermediates. Our argument is that resolving this debate will require moving beyond these
28 caricatures because they conflate pattern (genetic and phenotypic change) and process (drivers of
29 change). We outline how this can be achieved using evolutionary theory, genomics, and
30 principles emerging from the study of a wide range of complex, dynamical systems.

31

1 Darwin argued that speciation involves the gradual accumulation of differences between
2 populations in small steps². This process can leave an observable and inter-connected ‘speciation
3 continuum’ of populations varying in differentiation (Figure 1, Table 1)⁷⁻¹⁵. For example, pea
4 aphid host races vary in levels of population genetic differentiation¹¹ and natural hybridisation
5 between butterfly taxa declines gradually with genetic distance¹⁶. In modern parlance, many
6 differences in small steps can be interpreted as polygenic, genome wide changes. Indeed,
7 multiple loci of minor effect underlie many cases of adaptation¹⁷⁻²¹, and some cases of
8 reproductive isolation^{22,23}. For example, local adaptation of herring¹⁷, cichlid²⁴, and stick-insect
9 populations involves numerous genome wide differences^{25,26}, and multiple loci of modest effect
10 contribute to flowering time differences in maize²¹ and sexual isolation between cricket
11 species²².

12
13 However, palaeontologists have long reported the sudden emergence of new taxa in the fossil
14 record. This led influential figures like Simpson, Eldredge, and Gould to highlight the punctuated
15 nature of evolution^{1,27-29}. Likewise, modern theory suggests speciation can occur suddenly due to
16 rare founder effects³⁰⁻³² or rapid evolution once mutations causing reproductive isolation
17 arise^{33,34}. In terms of genetics, speciation as a single evolutionary leap driven by macro-mutation
18 and ‘hopeful monsters’ is largely unsupported, but major genetic changes do occur³⁵⁻³⁷. For
19 example, major effect loci contribute to differences in bony armour between stickleback
20 populations³⁸, colour-pattern differences between butterflies^{39,40}, flower colour in phlox⁴¹, and
21 vision in cichlids⁷. Accordingly, major effect loci or genome re-arrangements can concentrate
22 differentiation into a few genomic regions^{4,33,34,39,42-45}, as reported between sub-species of
23 crows⁴⁵, colour-pattern races of butterflies^{38-40,45}, and *Drosophila* species⁴⁶.

24
25 There is a ‘many-to-many’ relation between the patterns reported above and underlying
26 speciation processes⁴⁷. That is, a given pattern may be explained by the action of many
27 alternative processes, and theoretical expectations become complex once multiple populations
28 and potential gene flow between them is introduced⁴⁸⁻⁵¹. In particular, a pattern of sudden
29 differentiation could be influenced by an abrupt environmental shift, epistatic interactions
30 causing a snowball of intrinsic genetic incompatibilities^{33,52,53} (e.g., as argued in flies⁵⁴ and
31 tomatoes⁵⁵), slight increases in frequency dependent selection which drive rapid evolutionary

1 branching^{56,57}, and evolutionary leaps via genome re-arrangement, polyploidisation, or founder
2 events^{6,30,58}. Of these factors, those that act during speciation are more critical for the divergence
3 process than those that accumulate after speciation is complete^{47,59}.

4
5 Sudden speciation is also compatible with evolution in small steps. For example, sudden
6 evolution can arise when small changes become coupled to each other in a positive feedback
7 loop⁶⁰⁻⁶⁴ (i.e., at some critical threshold a change in the dynamic variable x can increase y , which
8 feeds back to increase x , and so on). As such, a divergence process involving small changes can
9 suddenly speed up at a ‘tipping point’ in speciation, at least in theory (Figure 2; Table 2 for
10 glossary)⁵. In this case, speciation emerges as an intrinsic dynamical property of the divergence
11 process, not via a large extrinsic perturbation or trigger. Hence, even when reproductive isolation
12 and genetic differentiation are continuous variables, tipping points cause taxa to generally
13 occupy one of two states: a single species with little differentiation, or two strongly differentiated
14 species.

15
16 Such distinct states could be indicative of bi-stability (i.e., alternative stable states under similar
17 conditions)⁶⁵⁻⁶⁷, which arises when evolution is dependent on initial conditions and the sequence
18 of historical events (also called path-dependency or hysteresis). In speciation, initial conditions
19 such as sympatry versus geographic isolation can affect the type of differentiation that builds^{5,68},
20 epistasis can cause the historical sequence by which mutations arise to affect evolution⁶⁹⁻⁷¹, and
21 drift can affect which variants are lost or established through time⁵. Such factors can affect the
22 reversibility of evolution such that reverting to an original state is difficult, again contributing to
23 bi-stability.

24
25 As one example of such dynamics, Flaxman *et al.*⁵ modelled divergence with gene flow in terms
26 of the per-locus strength of divergent selection (DS) between ecological environments (s),
27 migration rates (m), and numbers of genetic loci involved. In this model, loci differentiate by the
28 selection they directly experience plus indirect selection stemming from statistical associations
29 (linkage disequilibrium, LD) with other divergently selected loci. When migration was high ($m >$
30 s), sudden speciation and alternative stable states of differentiation occurred and went hand-in-
31 hand with a positive feedback loop (Figure 2). Below a critical threshold of genome wide DS and

1 between-population LD, differentiation built very slowly due to homogenising migration.
2 However, once a critical level of both was reached, DS and LD entered a positive feedback loop
3 where each enhanced the other, driving a rapid reduction in gene flow and a transition from one
4 species to two. In essence, loci under DS transition from evolving independently to exhibiting
5 coupled dynamics; out of a mass of a genetically well-mixed population, distinct clusters of
6 genotypes congeal, and rapid, genome-wide differentiation ensues. Due to the role of LD,
7 indirect selection was critical to explaining these dynamics. In Box 1 we use simulations to
8 provide exploratory results on how such coupling in time relates to previous theory on the
9 coupling of multilocus clines in space^{72,73}. Similar dynamics likely apply during polygenic
10 adaptation^{5,64,74} and the coupling of different reproductive barriers^{60,72,75}. Thus, the dynamics we
11 focus on here could be general, and indeed selection and LD are commonly involved in
12 speciation⁴⁷.

13
14 In contrast to the results described above, divergence with lower migration in the Flaxman *et al.*⁵
15 model was more linear through time and ‘gene-by-gene’, with individual loci differentiating by
16 the selection they directly experience rather than through strong effects of LD⁵. The issue then is
17 not just whether few or many loci diverge during speciation. Rather, it is whether a few genes
18 diverge first (followed gradually by the rest) versus many genes diverging suddenly and
19 simultaneously once a critical amount of selected, standing variation exists.

20
21 Sudden speciation in the aforementioned model occurred without intrinsic genetic
22 incompatibilities, major effect loci, genome re-arrangements, or periods of geographic isolation,
23 though these factors can promote the process. For example, divergence maintained despite
24 migration was often higher when initial differentiation involved a period of geographic isolation
25 than when it did not⁵. This provides one example of bi-stability; two outcomes were possible for
26 the same selection strength, dependent on initial geographic setting. This example also highlights
27 that the divergence process is bi-directional, as differentiation can build, be maintained upon
28 secondary contact, or collapse. Here, we propose a framework for understanding these
29 potentially complex dynamics that draw parallels between speciation and tipping points in other
30 complex systems⁶⁵⁻⁶⁷. We then outline approaches to quantify speciation patterns and infer
31 underlying process.

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2. Connection between speciation and other complex systems

When speciation involves simple evolutionary dynamics driven by few loci then a reductionist approach focused on identifying and studying these individual loci may enhance our understanding of speciation^{18,76}. In other cases, speciation may involve many loci and emerge via complex interactions between evolutionary processes^{3,5,33}. Such complex phenomena cannot always be understood as the additive combination of their underlying individual parts. Instead, ‘systems thinking’ may be required that attempts to understand how complex networks exhibit emergent properties not shown by individual nodes in the network⁷⁷⁻⁷⁹. Evolutionary studies of complex, population-level processes such as speciation might benefit from such thinking, which remains largely the purview of cell and molecular biologists working below the population level, or ecologists working above it (i.e., our analogy is here a heuristic one concerning the study of emergent properties in complex systems, not a direct one-to-one analogy to applications in molecular biology and genomics). Some relevant networks for speciation are genes within genomes, individuals within sub-populations, and sub-populations within a meta-population.

To support our argument, we consider how tipping points in speciation relate to those in other complex systems. ‘Tipping points’ in the narrow sense are cases where positive feedback at an unstable equilibrium causes a rapid shift between alternative states. This usage is applied to critical transitions or sudden ‘regime shifts’ in a range of complex systems (e.g., health: asthma attacks; ecology: population extinction, climate change, shifts in community composition; economics: crash of financial markets)⁶⁵⁻⁶⁷. Principles governing tipping points in these systems have emerged⁶⁵⁻⁶⁷, such as features that make a system prone to system-wide regime shifts. Specifically, increased connectivity (i.e., reduced modularity) of a system network increases the chance of critical transitions. One explanation for this is that local changes in a well-connected system are ‘repaired’ by neighbouring nodes, buffering the system against local change⁶⁵⁻⁶⁷. Thus, observable change does not occur until the entire system hits a threshold that drives a shift to an alternative, system-wide state. In other words, a highly connected system is robust to local perturbation, but prone to system-wide change. In contrast, poorly connected systems allow gradual node-by-node change.

1
2 These concepts appear to apply to speciation. For example, sudden dynamics in Flaxman *et al.*⁵
3 were dependent on two types of connectivity. First, sudden transitions from one species to two
4 were only observed in models that allow for the build up of LD, because LD was a key
5 component of the feedback that drives the transition. Indeed, factors that promote LD, such as
6 increased physical linkage in chromosomal inversions, can promote speciation with gene
7 flow^{43,44,80}. LD can be conceptualized as a type of connectivity between genes due to their
8 organisation into individuals (i.e., genomes). In other words, genes are connected because
9 offspring are not formed gene-by-gene from a population ‘beanbag’ of alleles, but rather, parents
10 pass on sets of genes to offspring. Note that we refer here to connectivity of genes in a statistical
11 sense (i.e., LD), although connectivity in gene regulatory networks warrants future work.

12
13 Second, speciation dynamics were dependent on the gross migration rate connecting populations
14 (relative to the strength of DS). When migration was low, individual loci overcame gene flow via
15 the selection they directly experience, and thus diverged on their own (Figure 2). In other words,
16 genes had largely independent dynamics and gradual, gene-by-gene divergence ensued. The
17 situation was different with high migration, where loci have difficulty diverging via direct
18 selection. Instead, speciation requires alleles at different loci to develop strong associations,
19 causing them to be selected against as units in migrating individuals (Box 1). This allows even
20 weakly directly selected loci to overcome high gene flow via the combined effects of direct and
21 indirect selection. Thus, connectivity of genes within individuals (in genomes) and among
22 populations (due to migration) can affect the likelihood of sudden change.

23
24 Our logic above focused on simple spatial settings (e.g., population pairs), but could be extended
25 to complex networks of many sub-populations (i.e., a meta-population)⁸¹, for which speciation is
26 an emergent systems-level property (Figure 1). Nodes in the network are sub-populations and
27 connections between nodes are edges representing gross migration. Each node can have a series
28 of properties (e.g., population size, selective regime, dispersal rate, genetic architecture,
29 recombination landscape, etc.). Reproductive isolation and genetic differentiation emerge when
30 considering sets of populations in the network (e.g., those that are ecologically divergent or
31 connected in particular ways by migration), but are not exhibited by individual populations.

1
2 Another phenomenon studied in regime shifts is their propensity to exhibit ‘early warning
3 signs’⁶⁵⁻⁶⁷. Early warning signs are statistical signals that occur when a system is nearing a
4 tipping point, but before a critical transition. Examples are increased variance and
5 autocorrelation, slow return to previous state upon small perturbation (‘critical slowing down’),
6 and ‘flickering’ between alternative states when perturbations are sufficiently large to push a
7 system temporarily back and forth between states. It is unclear if such signs apply to speciation,
8 but we suspect some signals should precede a drastic shift, such as the initial appearance of
9 subsets of loci with elevated LD. Work in this area is warranted as it might allow populations
10 near tipping points (that are poised for greater differentiation) to be identified and compared to
11 those far from tipping points. With this framework in place, we turn to empirical studies of
12 speciation dynamics.

13

14 **3. Patterns and processes of speciation**

15

16 *Quantifying gradual versus sudden patterns*

17

18 We focus on genetic differentiation because it can be measured in a wide range of systems and
19 can reflect reproductive isolation. In this context, genetic differentiation is best considered with
20 spatial setting in mind, for example compared among taxa in a similar spatial setting (e.g.,
21 multiple pairs of adjacent lake and stream ecotypes of stickleback)⁸². This is because
22 reproductive isolation is only tested to the extent that geographic proximity allows for potential
23 gene flow^{6,30,47,58,83,84}, and a continuum of differentiation under isolation-by-distance need not be
24 indicative of a continuum of reproductive isolation. Despite our focus on genetic differentiation,
25 our logic applies to experimental estimates of reproductive isolation, which could be used as
26 another measure of degree of speciation.

27

28 Inferring patterns of differentiation during speciation is challenging for at least four reasons
29 (Figure 3). First, high replication is required. This is because whenever data are sparse there is
30 danger of inferring discontinuities when they don’t exist, an issue long discussed with respect to
31 inferences from the fossil record^{1,27-29}. Second, the full distribution of differentiation should be

1 sampled to avoid false inference of a continuum. For example, an inferred continuum among
2 weakly to moderately differentiated ecotypes could actually be part of a strong discontinuity
3 between ecotypes and well-differentiated species. Third, the build-up of differentiation within a
4 single lineage should ideally be analysed³³. Combining data from distantly related lineages can
5 be problematic, for example when sudden change within each of two different lineages appears
6 gradual when data from the two are combined. This presents an empirical difficulty for studying
7 speciation because individual lineages may not exhibit variation in all stages of speciation.
8 Indeed, studies of the speciation tend to span a modest portion of the speciation continuum⁴⁷
9 (Figure 1). Fourth, not all loci necessarily couple and differentiate simultaneously, with
10 divergently selected loci differentiating before neutral ones^{4,85}. Thus, neutral loci may exhibit
11 gradual differentiation for long periods of time and assessment of whether divergence is gradual
12 or sudden can depend on whether phenotypes, neutral loci, or adaptive loci are examined⁷.

13
14 To our knowledge, data of sufficient scale to resolve these issues are sparse. For example, studies
15 of speciation (Table 1), including our own work in *Timema* stick insects²⁵, *Lycaiedes*
16 butterflies⁸⁶, and *Rhagoletis* flies⁸⁷, have highlighted the quantitative nature of the divergence
17 process⁴⁷. However, existing work does not generally overcome the difficulties described above,
18 precluding strong inferences about the dynamics of divergence along this continuum. Highly
19 replicated studies of differentiation across the speciation continuum are now required to test
20 whether the transition from weak to strong differentiation occurs gradually or suddenly. Even if
21 time since divergence cannot be inferred, the overall distribution of differentiation can be
22 informative. For example, bi-modal distributions imply gaps in the speciation continuum and
23 potentially sudden dynamics. Observational studies could be supplemented with experiments
24 mimicking secondary contact between populations, testing directly whether gene flow itself (i.e.,
25 reproductive isolation) changes gradually or suddenly as genetic differentiation increases.
26 Another possibility concerns the fossil record. When fossils contain information on multiple
27 traits that are known to exhibit independent genetic control (e.g., in extant relatives)^{88,89}, the
28 dynamics by which the evolution of different traits becomes coupled could be analysed through
29 time. Of course, experimental evolution in the lab could directly quantify speciation dynamics⁹⁰.
30 However, this may not be as simple as it sounds, as many systems with levels of sex and

1 recombination appropriate for tests of most speciation models are not amenable to long-term
2 laboratory studies.

3

4 *Quantifying genetic changes*

5

6 Speciation can involve genetically localised or genome-wide changes. Under the genic model of
7 speciation, some genetic regions become resistant to gene flow (i.e., exhibit reproductive
8 isolation) before others^{85,91}. This leads to one or a few localised ‘genomic islands’ of
9 differentiation, which grow through time as speciation progresses^{42,47}. Eventually, effects of
10 reproductive isolation evolve to become genome wide, as implied by the aforementioned theories
11 of coupling and congealing of differentiation across loci^{5,68,72}, and classic views of biological
12 species^{24,30}. An unresolved empirical issue is how readily and why the transition to genome-wide
13 differentiation occurs.

14

15 Approaches for quantifying the genetic changes involved in adaptation and speciation have been
16 covered elsewhere^{18,42,47,76,92-94}. We briefly re-iterate two core points that are most relevant for
17 speciation dynamics. First, integrative approaches that combine ecology, experiments,
18 population genomics, and genetic mapping could yield more robust inferences than studies
19 relying on one approach alone. In particular, observational genome scans and genetic mapping
20 studies identifying genetic regions associated with population differentiation can be
21 supplemented with manipulative transplant or experimental evolution studies to test if these
22 regions are subject to divergent selection. Although such experimental approaches are not
23 without limitations, recent studies highlight their potential^{25,26,92,95-99}. For example, studies of
24 stick-insects and flies show that genetic regions responding to experimentally induced divergent
25 selection correspond to those which are highly differentiated between natural populations^{25,99,100}.

26

27 Second, quantifying the true distribution of genetic changes involved in speciation is challenging
28 because of the relative ease of detecting large effect changes (i.e., leading to over-estimation of
29 the distribution of effect sizes). Nonetheless, recent analytical advances for quantifying genetic
30 architecture *per se* can help alleviate this problem. Consider the example of genome-wide
31 association (GWA) mapping. Classic GWA methods analyse contributions of individual genetic

1 variants to phenotypic variation, one at a time¹⁰¹. These methods are suited for detecting loci of
2 large effect but not for quantifying the architecture of polygenic, complex traits. In contrast,
3 recently developed whole genome regression or polygenic modeling approaches consider the
4 joint influence of all genetic variants, and relatedness among individuals, to quantify genetic
5 architecture¹⁰¹. Polygenic modeling is aligned in spirit with quantitative genetics and in wide use
6 in artificial breeding, but not fully exploited in evolutionary studies^{101,102}. Once patterns of
7 differentiation and associated genetic changes are in hand, one can turn to the difficult task of
8 inference of underlying speciation processes.

9

10 *Inferring process*

11

12 It is clear that speciation dynamics are parameter-dependent and can involve non-linear,
13 emergent properties. Thus, inferring process will require information on selective regimes,
14 migration, recombination, and the underlying genetic architecture of traits driving speciation,
15 including effect sizes, linkage relationships, and epistatic interactions. Such data can allow
16 patterns of differentiation to be more readily interpreted in light of theoretical predictions. It is
17 also relevant to test whether speciation coincided with a bottleneck, founder event, or abrupt
18 environmental shift. Approaches for inferring these factors have been covered elsewhere^{47,83}, so
19 we focus on the topics of feedback and bi-stability here.

20

21 It may be difficult to distinguish whether sudden differentiation is due to small changes in an
22 individual variable having large effects or a true feedback loop (i.e., between dynamic variables).
23 For example, a change in either DS or LD could increase genetic differentiation, without
24 invoking feedback. Changes without feedback predict bi-modality only in one response variable.
25 In contrast, a feedback predicts missing intermediates in both variables being measured.
26 Ultimately, tests could be devised for whether each component of a feedback loop directly
27 strengthens the other. In terms of bi-stability, two states should be observable under similar
28 conditions, i.e., those representing an unstable intermediate domain. In some cases, the historical
29 sequence of events will have led to strong differentiation, but in other cases they will have not.
30 The same prediction applies for gene flow upon experimental secondary contact. In principle,
31 populations lying in the unstable domain could be perturbed to an alternative state, for example

1 by manipulating levels of LD via gene flow or other factors. These examples suggest that even if
2 contemporary populations largely sit in one or two domains of differentiation, it may still be
3 possible to study transitions between them.

4

5 ***Concluding remarks***

6

7 Implementation of the ideas outlined here will require substantial effort, as it implies the need to
8 generate data on patterns of differentiation, multiple evolutionary processes, and genetic
9 architecture in a wide range of sub-populations, and better frameworks for comparing among
10 studies. However, until this is done it will be impossible to know how useful systems-level
11 thinking and tipping points will be for understanding the dynamics of speciation, or if the hunt
12 for individual genes driving speciation will largely suffice^{53,59,103}. We predict that the inherently
13 multi-locus and multi-faceted nature of speciation makes tipping points and initial conditions of
14 broad importance for understanding the process. An open question is how evolutionary tipping
15 points might affect ecological systems (e.g., communities and ecosystems)⁶⁵⁻⁶⁷, leading to
16 interactions between evolutionary and ecological dynamics.

17

18 **Author for correspondence:** Patrik Nosil

19

20 **Author contributions:** PN, SMF, JF, and ZG conceived the project and wrote the paper. SMF
21 ran the simulations and analysed them.

22

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24

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1 **Table 1.** Examples of empirical studies of different stages of speciation for replicate, co-
 2 occurring pairs of taxa. msat = microsatellite loci. WGS = whole genome sequence data. PGS =
 3 partial genome sequence data (e.g., from genotyping-by-sequencing). We report quantitative
 4 results if the original study tabulated them for genome wide F_{ST} , but otherwise give a summary
 5 of qualitative findings. Due to different marker types being used, values cannot be easily
 6 compared across studies, but within-study variation encapsulates the putative speciation
 7 continuum.

Organism	Comparison	Genetic data	Replicates	Results	Reference
Fish					
Cichlid fish (<i>Pundamilia</i>)	Sympatric phenotypes found in different localities within lake Victoria	msat	5 pairs	F_{ST} = 0.000, 0.002, 0.010, 0.014, 0.026	⁷
Stickleback fish (<i>Gasterosteus</i>)	Parapatric lake-stream pair in North America, each pair in a different locality	msat	6 pairs	F_{ST} = 0.05, 0.10, 0.12, 0.14, 0.16, 0.23	⁸
Stickleback fish (<i>Gasterosteus</i>)	Parapatric lake-stream pairs across the globe, each pair in a different locality	WGS	5 pairs	F_{ST} = 0.09, 0.11, 0.22, 0.22, 0.28	⁹
Lake whitefish (<i>Coregonus</i>)	Sympatric dwarf and normal ecotypes	PGS	5 pairs	F_{ST} = 0.008, 0.029, 0.049, 0.105, 0.216	¹⁰

	within lakes, each pair in a different lake				
Plants					
Sunflowers (<i>Helianthus</i>)	Sympatric or parapatric species pairs with different levels of gene flow	PGS	3 pairs (plus 1 allopatric)	$F_{ST} = 0.30, 0.35,$ 0.51 (0.48 for allopatric pair)	¹⁰⁴
Insects					
Pea aphids (<i>Acyrtosiphon</i>)	Sympatric populations associated with different host plants in western Europe	msat	11 sympatric biotypes	An interconnected continuum of differentiation	¹¹
Mimetic butterflies (<i>Heliconius</i>)	Parapatric and sympatric races and species	WGS	4 pairs	Continuum of differentiation between races and species	¹² ; see also ¹³
Birds					
Flycatchers (<i>Ficedula</i>)	Populations within and between species, with variation in degree of geographic overlap	GWS	7 pairwise comparisons	$F_{ST} \sim 0.1$ w/in species, ~ 0.3 b/w species, ~ 1.0 b/w distantly related species	¹⁴
Amphibians					

Poison Frogs (<i>Ranitomeya</i>)	Mimetic morphs in three different transition zones	msat	3 transition zones	Clines for different colour pattern traits clines varied from offset to coincident; genetic structure varied from present to absent	¹⁵
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2

1 **Table 2.** Glossary of key terms and examples of their relevance for speciation dynamics.

Term	Definition	Example of relevance
Indirect selection	Selection on a trait stemming from correlation of the trait with a directly selected trait; the same concept applies to a locus rather than a trait	Can increase the total selection experienced by a trait (or locus) above that due to direct selection, potentially promoting divergence with gene flow
Tipping point (narrow sense)	A point where a system may flip to an alternative state, involving positive feedback at an unstable equilibrium	Could explain sudden speciation and gaps between populations and species, and do so without invoking catastrophic events or large external perturbations
Positive feedback	A process in which dynamic variables enhance the changes happening in each other (i.e., each increases the other)	At a critical threshold, divergent selection and LD can enter a feedback where each reinforces the other, driving rapid speciation
Bi-stability	A scenario in which a system has two alternative possible stable states under the same conditions (often due to effects of initial conditions and path-dependence in evolution)	Could explain gaps between populations and species
Linkage disequilibrium (LD)	Non-random statistical associations between alleles at different loci	A core component of some types of positive feedback loops that drive speciation
Sudden dynamics; (i.e., non-linear dynamics)	Some parts of speciation occur much faster than others such that differentiation is not uniform through time	Leads to discontinuous patterns of differentiation and gaps between stages of speciation
Gradual dynamics; (i.e., linear	Near uniform/constant differentiation through time; note that this does not	Leads to a well inter-connected speciation continuum, with

dynamics)	imply slow change, but rather simply a fairly constant rate	intermediate states readily observed
Critical transition	Abrupt shift in a system when driving parameters reach a threshold (i.e., critical) value; the associated shift from one state to another is sometimes referred to as a 'regime shift'	Rapid shifts in differentiation at critical thresholds of divergent selection and LD
Gross migration	Movement of individuals between populations (contrasts with effective migration which considers the incorporation of the alleles in those individuals into the local genetic background)	Variation in gross migration rates can affect the dynamics of speciation, and whether tipping points occur

1
2 **Figure 1. Empirical studies of the speciation continuum and the dynamics of speciation.** (a)
3 Previous studies of the speciation continuum. Modified from Seehausen *et al.*⁴⁷. (b) Patterns of
4 differentiation in aphids¹¹, lizards¹⁰⁵, crows⁴⁵, and herring¹⁷. (c) Genetic architecture of traits in
5 butterflies^{39,40}, crickets²², stickleback³⁸, and maize²¹. (d) Overview of a systems biology
6 framework for studying speciation. White lines are chromosomes with circles on them being
7 genetic loci. Red circles are individuals. Blue and yellow circles are populations in different
8 environments. Double-headed arrows represent gross migration and the other letters represent
9 evolutionary processes (s = selection, r = recombination, u = mutation, N_e = effective population
10 size).

11
12 **Figure 2. Gradual and sudden dynamics of speciation in the model by Flaxman *et al.*⁵.** s =
13 strength of divergent selection. m = gross migration rate. (a) Gradual differentiation occurs when
14 selection is strong relative to migration. Following Hartl and Clark¹⁰⁶, strongly differentiated loci
15 are those with $F_{ST} \geq 0.25$, but results are similar for other cut-offs. (b) Sudden differentiation
16 occurs when selection is weak relative to migration, because a critical threshold of divergent
17 selection and genome-wide linkage disequilibrium must be achieved before differentiation can
18 ensue. (c) Schematic of a tipping point where positive feedback at an unstable equilibrium (thin

1 line) causes a rapid shift between alternative stable states. Slight changes in conditions (e.g.,
 2 selection strengths, levels of standing genetic variation) can cause the system to switch from one
 3 state to the other. An unstable domain predicts alternative states under similar conditions,
 4 dependent on the history of events leading to those conditions. (d) An example of bi-stability in
 5 the Flaxman *et al.*⁵ model (with $L = 60$ loci, $m = 0.1$). The y-axis shows the local frequency of an
 6 allele in the deme in which it is favoured. Within a range of s values, there are two equilibria and
 7 the system state depends upon past conditions. This is indicated by the two sets of points, one
 8 when initializing populations with maximum divergence (blue symbols) and the other when
 9 initializing with no divergence (orange symbols). Panels a,b,d use previously published data
 10 from⁵ and the Dryad repository¹⁰⁷. A script for producing the panels is archived in a GitHub
 11 repository <link here upon final acceptance>.

12

13 **Figure 3. Difficulties with quantifying patterns of differentiation during speciation.** (a) With
 14 low replication it can be difficult to extrapolate between data points in a manner that
 15 unambiguously distinguishes gradual from sudden change. (b) If both extremes of the
 16 distribution of differentiation are not sampled, a continuum might be falsely inferred (as for the
 17 sampled taxa shown with black points). (c) Each dot represents data from a different population
 18 pair. When data from different species are combined true discontinuities within a species (red,
 19 dotted line) might be hidden, leading to the erroneous conclusion of gradual dynamics.
 20 Specifically, if a line were drawn through all the points shown (red and black) then the pattern
 21 would look continuous, despite it being discontinuous within one of the species. (d) Adaptive
 22 and neutral loci might differentiate at different points in the speciation process such that patterns
 23 of speciation are dependent on the type of loci examined.

24

25 **Box 1: Exploratory results on the relation between multilocus coupling in time versus**
 26 **space.**

27

28 Multilocus cline theory^{72,73} makes predictions about the shape of allele-frequency clines in space
 29 by determining the conditions in which clines at different barrier loci will be coupled (i.e., acting
 30 as a multilocus selected unit) or uncoupled (loci evolving independently)¹⁰⁸. Coupling is
 31 promoted by increasing the number of barrier loci (L), increasing the strength of selection per

1 locus (s), or decreasing the recombination probability between neighbouring loci (r). The effects
 2 of these key drivers can be encapsulated by the “summed coupling coefficient,” ϕ , defined by
 3 Kruuk et al.⁷³ as $\phi = (L - 1)s/r$.

4
 5 Though most previous theory considers equilibrium patterns in space, temporal dynamics of
 6 coupling have also been studied⁵. However, theories in space versus time are poorly connected,
 7 and non-equilibrium conditions have proven difficult to study analytically. We show here
 8 exploratory results relating temporal dynamics and critical transitions observed in stochastic,
 9 forward-time simulations to metrics commonly used in multilocus cline theory. The figure shows
 10 results with $s = 0.02$ and gross migration rate $m = 5\%$ between two demes (i.e., discrete space).
 11 Additional parameter combinations and details are in the OSM.

12
 13 New, divergently selected mutations arise continuously in our simulations, causing ϕ to increase
 14 over time because L increases and r decreases as a greater number of variable sites become
 15 packed into a genome of fixed size. The actual degree of coupling between loci at any point in
 16 time can be quantified by the “effective number of loci”⁷², L_e , computed as the number of loci
 17 with selection coefficient s that would need to be perfectly coupled (i.e., in complete linkage
 18 disequilibrium) to produce the observed average allele frequency difference between demes at a
 19 given time. $L_e = 1$ when loci are evolving independently (each locus acts as one, independent
 20 locus characterized by s) and increases as loci become coupled. Our simulations highlight two
 21 key points about evolutionary dynamics when $m > s$: (a) genome-wide congealing (GWC) in
 22 time is associated with nonlinear shifts in reproductive isolation and coupling (L_e), and (b) there
 23 may be a critical value of ϕ that defines a tipping point between undifferentiated and
 24 differentiated populations.

25
 26 The figure shows the following: (A) Example time series (one simulation run) showing the
 27 effective migration rate, m_e (solid line), and effective number of loci, L_e (orange, dashed line),
 28 through the genome-wide congealing (GWC) transition (gold, dash-dot line). m_e is a population-
 29 level measure of reproductive isolation, defined as the proportion of a deme’s reproduction from
 30 immigrants¹⁰⁹. (B) Relationship between a discrete-space analogue of cline width—the inverse of
 31 allele frequency difference between demes—and ϕ (time-implicit parametric plot from same

1 simulation run as **A**; solid line: simulation results; dashed and dotted lines: deterministic
 2 expectations for completely coupled and uncoupled sites, respectively; circle: start time; square:
 3 end time; diamond: time of GWC). Random fluctuations in the analogue to cline width (y-axis)
 4 arise due to the effects of genetic drift. See OSM for detailed methods.

6 **Literature cited**

7 1 Gould, S. J. *The structure of evolutionary theory*. (Belknap Press, 2002).

8 2 Darwin, C. *On the origin of species by means of natural selection, or the preservation of*
 9 *favoured races in the struggle for life*. (John Murray, 1859).

10 3 Gavrillets, S. Perspective: Models of speciation: What have we learned in 40 years?
 11 *Evolution* **57**, 2197-2215 (2003).

12 **A review of theoretical models of speciation, with a focus on those utilising the framework**
 13 **of genetic incompatibilities.**

14 4 Gavrillets, S. & Losos, J. B. Adaptive Radiation: Contrasting Theory with Data. *Science*
 15 **323**, 732-737, doi:10.1126/science.1157966 (2009).

16 5 Flaxman, S., Walchoder, A., Feder, J. L. & Nosil, P. Theoretical models of the influence
 17 of genomic architecture on speciation. *Mol. Ecol.* **23**, 4074-4088 (2014).

18 6 Coyne, J. A. & Orr, H. A. *Speciation*. 1st edn, (Sinauer Associates, 2004).

19 7 Seehausen, O. *et al.* Speciation through sensory drive in cichlid fish. *Nature* **455**, 620-
 20 U623, doi:Doi 10.1038/Nature07285 (2008).

21 **A demonstration of speciation via natural and sexual selection in cichlid fish, with**
 22 **emphasis on different degrees of differentiation during the process.**

23 8 Berner, D., Grandchamp, A. C. & Hendry, A. P. Variable progress toward ecological
 24 speciation in parapatry: stickleback across eight lake-stream transitions. *Evolution* **63**,
 25 1740-1753, doi:10.1111/j.1558-5646.2009.00665.x (2009).

26 9 Feulner, P. G. D. *et al.* Genomics of Divergence along a Continuum of Parapatric
 27 Population Differentiation. *Plos Genetics* **11**, doi:10.1371/journal.pgen.1004966 (2015).

28 10 Gagnaire, P. A., Pavey, S. A., Normandeau, E. & Bernatchez, L. THE GENETIC
 29 ARCHITECTURE OF REPRODUCTIVE ISOLATION DURING SPECIATION-
 30 WITH-GENE-FLOW IN LAKE WHITEFISH SPECIES PAIRS ASSESSED BY RAD
 31 SEQUENCING. *Evolution* **67**, 2483-2497, doi:10.1111/evo.12075 (2013).

- 1 11 Peccoud, J., Ollivier, A., Plantegenest, M. & Simon, J. C. A continuum of genetic
2 divergence from sympatric host races to species in the pea aphid complex. *Proc. Natl.*
3 *Acad. Sci. U. S. A.* **106**, 7495-7500, doi:10.1073/pnas.0811117106 (2009).
- 4 12 Martin, S. H. *et al.* Genome-wide evidence for speciation with gene flow in *Heliconius*
5 butterflies *Genome Research* **23**, 1817-1828 (2013).
- 6 13 Kronforst, M. R. *et al.* Hybridization reveals the evolving genomic architecture of
7 speciation. *Cell Reports* **5**, 666-677 (2013).
- 8 14 Burri, R. *et al.* Linked selection and recombination rate variation drive the evolution of
9 the genomic landscape of differentiation across the speciation continuum of *Ficedula*
10 flycatchers. *Genome Research* **25**, 1656-1665, doi:10.1101/gr.196485.115 (2015).
- 11 15 Twomey, E., Vestergaard, J. S., Venegas, P. J. & Summers, K. Mimetic divergence and
12 the speciation continuum in the mimic poison frog *Ranitomeya imitator*. *Am. Nat.* **187**,
13 205-224, doi:10.1086/684439 (2016).
- 14 16 Mallet, J., Beltran, M., Neukirchen, W. & Linares, M. Natural hybridization in
15 heliconiine butterflies: the species boundary as a continuum. *BMC Evol. Biol.* **7**, - (2007).
- 16 17 Lamichhaney, S. *et al.* Population-scale sequencing reveals genetic differentiation due to
17 local adaptation in Atlantic herring. *Proc. Natl. Acad. Sci. U. S. A.* **109**, 19345-19350,
18 doi:10.1073/pnas.1216128109 (2012).
- 19 18 Rockman, M. V. THE QTN PROGRAM AND THE ALLELES THAT MATTER FOR
20 EVOLUTION: ALL THAT'S GOLD DOES NOT GLITTER. *Evolution* **66**, 1-17,
21 doi:10.1111/j.1558-5646.2011.01486.x (2012).
- 22 **A perspective piece arguing that much of adaptation and evolution may stem from multiple**
23 **loci with alleles of small effect.**
- 24 19 Yang, J. *et al.* Genome partitioning of genetic variation for complex traits using common
25 SNPs. *Nature Genetics* **43**, 519-U544, doi:10.1038/ng.823 (2011).
- 26 20 Carneiro, M. *et al.* Rabbit genome analysis reveals a polygenic basis for phenotypic
27 change during domestication. *Science* **345**, 1074-1079, doi:10.1126/science.1253714
28 (2014).
- 29 21 Buckler, E. S. *et al.* The Genetic Architecture of Maize Flowering Time. *Science* **325**,
30 714-718, doi:10.1126/science.1174276 (2009).

- 1 22 Ellison, C. K., Wiley, C. & Shaw, K. L. The genetics of speciation: genes of small effect
2 underlie sexual isolation in the Hawaiian cricket *Laupala*. *J. Evol. Biol.* **24**, 1110-1119,
3 doi:10.1111/j.1420-9101.2011.02244.x (2011).
- 4 23 Fishman, L., Kelly, A. J. & Willis, J. H. Minor quantitative trait loci underlie floral traits
5 associated with mating system divergence in *Mimulus*. *Evolution* **56**, 2138-2155 (2002).
- 6 24 Brawand, D. *et al.* The genomic substrate for adaptive radiation in African cichlid fish.
7 *Nature* **513**, 375-+, doi:10.1038/nature13726 (2014).
- 8 25 Soria-Carrasco, V. *et al.* Stick Insect Genomes Reveal Natural Selection's Role in
9 Parallel Speciation. *Science* **344**, 738-742, doi:10.1126/science.1252136 (2014).
- 10 26 Gompert, Z. *et al.* Experimental evidence for ecological selection on genome variation in
11 the wild. *Ecol. Lett.* **17**, 369-379, doi:10.1111/ele.12238 (2014).
- 12 27 Eldredge, N. & Gould, S. J. *Punctuated equilibria: an alternative to phyletic gradualism*.
13 (1972).
- 14 28 Simpson, G. G. *Tempo and mode in evolution*. (Columbia University Press, 1944).
- 15 29 Simpson, G. G. *The major features of evolution*. (Columbia University Press, 1953).
- 16 30 Mayr, E. *Animal species and evolution*. (Harvard University Press, 1963).
- 17 31 Mayr, E. in *Evolution as a process* (eds J. Huxley, A.C. Hardy, & E.B. Ford) (Allen &
18 Unwin, 1954).
- 19 32 Barton, N. H. & Charlesworth, B. GENETIC REVOLUTIONS, FOUNDER EFFECTS,
20 AND SPECIATION. *Annu. Rev. Ecol. Syst.* **15**, 133-164 (1984).
- 21 33 Gavrillets, S. *Fitness landscapes and the origin of species*. Vol. 41 (Princeton University
22 Press, 2004).
- 23 34 Kirkpatrick, M. & Barton, N. Chromosome inversions, local adaptation and speciation.
24 *Genetics* **173**, 419-434, doi:10.1534/genetics.105.047985 (2006).
- 25 35 Dietrich, M. R. Richard Goldschmidt: hopeful monsters and other 'heresies'. *Nature*
26 *Reviews Genetics* **4**, 68-74, doi:10.1038/nrg979 (2003).
- 27 36 Chouard, T. Evolution: Revenge of the hopeful monster. *Nature* **463**, 864-867,
28 doi:10.1038/463864a (2010).
- 29 37 Goldschmidt, R. *The Material Basis of Evolution*. (Yale University Press 1940).
- 30 38 Colosimo, P. F. *et al.* Widespread parallel evolution in sticklebacks by repeated fixation
31 of ectodysplasin alleles. *Science* **307**, 1928-1933, doi:10.1126/science.1107239 (2005).

1 **An empirical study showing repeated adaptation to freshwater via a gene of large effect.**

- 2 39 Nadeau, N. J. *et al.* Population genomics of parallel hybrid zones in the mimetic
3 butterflies, *H. melpomene* and *H. erato*. *Genome Research* **24**, 1316-1333,
4 doi:10.1101/gr.169292.113 (2014).
- 5 40 Nadeau, N. J. *et al.* Genomic islands of divergence in hybridizing *Heliconius* butterflies
6 identified by large-scale targeted sequencing. *Philos. Trans. R. Soc. B-Biol. Sci.* **367**, 343-
7 353 (2012).
- 8 41 Hopkins, R. & Rausher, M. D. Pollinator-Mediated Selection on Flower Color Allele
9 Drives Reinforcement. *Science* **335**, 1090-1092, doi:10.1126/science.1215198 (2012).
- 10 42 Feder, J. L., Egan, S. P. & Nosil, P. The genomics of speciation-with-gene-flow. *Trends*
11 *in Genetics* **28**, 342-350 (2012).
- 12 43 Noor, M. A. F., Grams, K. L., Bertucci, L. A. & Reiland, J. Chromosomal inversions and
13 the reproductive isolation of species. *Proc. Natl. Acad. Sci. U. S. A.* **98**, 12084-12088
14 (2001).
- 15 44 Rieseberg, L. H., Whitton, J. & Gardner, K. Hybrid zones and the genetic architecture of
16 a barrier to gene flow between two sunflower species. *Genetics* **152**, 713-727 (1999).
- 17 45 Poelstra, J. W. *et al.* The genomic landscape underlying phenotypic integrity in the face
18 of gene flow in crows. *Science* **344**, 1410-1414, doi:10.1126/science.1253226 (2014).
- 19 46 McGaugh, S. E. & Noor, M. A. F. Genomic impacts of chromosomal inversions in
20 parapatric *Drosophila* species. *Philos. Trans. R. Soc. B-Biol. Sci.* **367**, 422-429,
21 doi:10.1098/rstb.2011.0250 (2012).
- 22 47 Seehausen, O. *et al.* Genomics and the origin of species. *Nature Reviews Genetics* **15**,
23 176-192, doi:10.1038/nrg3644 (2014).
- 24 48 Orr, H. A. The Population Genetics of Adaptation: The Distribution of Factors Fixed
25 during Adaptive Evolution. *Evolution* **52**, 935-949, doi:10.2307/2411226 (1998).
- 26 49 Orr, H. A. The genetic theory of adaptation: A brief history. *Nature Reviews Genetics* **6**,
27 119-127, doi:10.1038/nrg1523 (2005).
- 28 50 Yeaman, S. & Otto, S. P. Establishment and maintenance of adaptive genetic divergence
29 under migration, selection, and drift. *Evolution* **65**, 2123-2129, doi:10.1111/j.1558-
30 5646.2011.01269.x (2011).

- 1 51 Yeaman, S. & Whitlock, M. C. The genetic architecture of adaptation under migration-
2 selection balance. *Evolution* **65**, 1897-1911, doi:10.1111/j.1558-5646.2011.01269.x
3 (2011).
- 4 **Theoretical work on the evolution of genetic architecture when populations are exchanging**
5 **genes with one another, contrasting with population genetics theory based on**
6 **evolution within single, isolated populations.**
- 7 52 Orr, H. A. The population-genetics of speciation - the evolution of hybrid
8 incompatibilities. *Genetics* **139**, 1805-1813 (1995).
- 9 53 Orr, H. A. The genetic basis of reproductive isolation: Insights from *Drosophila*. *Proc.*
10 *Natl. Acad. Sci. U. S. A.* **102**, 6522-6526, doi:10.1073/pnas.0501893102 (2005).
- 11 54 Matute, D. R., Butler, I. A., Turissini, D. A. & Coyne, J. A. A Test of the Snowball
12 Theory for the Rate of Evolution of Hybrid Incompatibilities. *Science* **329**, 1518-1521,
13 doi:10.1126/science.1193440 (2010).
- 14 55 Moyle, L. C. & Nakazato, T. Hybrid Incompatibility "Snowballs" Between *Solanum*
15 Species. *Science* **329**, 1521-1523, doi:10.1126/science.1193063 (2010).
- 16 56 Dieckmann, U. & Doebeli, M. On the origin of species by sympatric speciation. *Nature*
17 **400**, 354-357 (1999).
- 18 57 Dieckmann, U., Doebeli, M., Metz, J. A. J. & Tautz, D. (Cambridge University Press,
19 Cambridge, UK, 2004).
- 20 58 Mayr, E. *Systematics and the origin of species*. (Columbia University Press, 1942).
- 21 59 Nosil, P. & Schluter, D. The genes underlying the process of speciation. *Trends Ecol.*
22 *Evol.* **26**, 160-167 (2011).
- 23 60 Servedio, M. R. & Saetre, G. P. Speciation as a positive feedback loop between
24 postzygotic and prezygotic barriers to gene flow. *Proc. R. Soc. B-Biol. Sci.* **270**, 1473-
25 1479, doi:10.1098/rspb.2003.2391 (2003).
- 26 61 Crespi, B. J. Vicious circles: positive feedback in major evolutionary and ecological
27 transitions. *Trends Ecol. Evol.* **19**, 627-633, doi:10.1016/j.tree.2004.10.001 (2004).
- 28 **A review of how positive feedback may drive major biological transitions, in cases ranging**
29 **from speciation to social evolution.**

- 1 62 Schwander, T., Vuilleumier, S., Dubman, J. & Crespi, B. J. Positive feedback in the
2 transition from sexual reproduction to parthenogenesis. *Proc. R. Soc. B-Biol. Sci.* **277**,
3 1435-1442, doi:10.1098/rspb.2009.2113 (2010).
- 4 63 Lehtonen, J. & Kokko, H. Positive feedback and alternative stable states in inbreeding,
5 cooperation, sex roles and other evolutionary processes. *Philos. Trans. R. Soc. B-Biol.*
6 *Sci.* **367**, 211-221, doi:10.1098/rstb.2011.0177 (2012).
- 7 64 Rasanen, K. & Hendry, A. P. Disentangling interactions between adaptive divergence and
8 gene flow when ecology drives diversification. *Ecol. Lett.* **11**, 624-636,
9 doi:10.1111/j.1461-0248.2008.01176.x (2008).
- 10 **An overview of the interactions, and potential feedback, between adaptive divergence and**
11 **gene flow.**
- 12 65 Scheffer, M. *et al.* Early-warning signals for critical transitions. *Nature* **461**, 53-59,
13 doi:10.1038/nature08227 (2009).
- 14 66 Scheffer, M., Carpenter, S. R., Dakos, V. & van Nes, E. H. in *Annual Review of Ecology,*
15 *Evolution, and Systematics, Vol 46* Vol. 46 *Annual Review of Ecology Evolution and*
16 *Systematics* (ed D. J. Futuyma) 145-+ (2015).
- 17 67 Scheffer, M. *et al.* Anticipating Critical Transitions. *Science* **338**, 344-348,
18 doi:10.1126/science.1225244 (2012).
- 19 **A review of critical transitions and tipping points in complex systems, with an emphasis on**
20 **the potential to predict tipping points in advance using early warning signs.**
- 21 68 Kirkpatrick, M. & Ravigné, V. Speciation by natural and sexual selection: Models and
22 experiments. *Am. Nat.* **159**, S22-S35 (2002).
- 23 69 Carneiro, M. & Hartl, D. L. Adaptive landscapes and protein evolution. *Proc. Natl. Acad.*
24 *Sci. U. S. A.* **107**, 1747-1751, doi:10.1073/pnas.0906192106 (2010).
- 25 70 Poelwijk, F. J., Kiviet, D. J., Weinreich, D. M. & Tans, S. J. Empirical fitness landscapes
26 reveal accessible evolutionary paths. *Nature* **445**, 383-386, doi:10.1038/nature05451
27 (2007).
- 28 71 Weinreich, D. M., Delaney, N. F., DePristo, M. A. & Hartl, D. L. Darwinian evolution
29 can follow only very few mutational paths to fitter proteins. *Science* **312**, 111-114,
30 doi:10.1126/science.1123539 (2006).
- 31 72 Barton, N. H. Multilocus clines. *Evolution* **37**, 454-471 (1983).

- 1 73 Kruuk, L. E. B., Baird, S. J. E., Gale, K. S. & Barton, N. H. A comparison of multilocus
 2 clines maintained by environmental adaptation or by selection against hybrids. *Genetics*
 3 **153**, 1959-1971 (1999).
- 4 74 Hendry, A. P. Selection against migrants contributes to the rapid evolution of
 5 ecologically dependent reproductive isolation. *Evolutionary Ecology Research* **6**, 1219-
 6 1236 (2004).
- 7 75 Barton, N. H. & de Cara, M. A. R. THE EVOLUTION OF STRONG REPRODUCTIVE
 8 ISOLATION. *Evolution* **63**, 1171-1190, doi:10.1111/j.1558-5646.2009.00622.x (2009).
- 9 **A theoretical model showing how different reproductive barriers can become coupled in**
 10 **their effects to drive strong reproductive isolation.**
- 11 76 Rausher, M. D. & Delph, L. F. Commentary: When does understanding phenotypic
 12 evolution require identification of the underlying genes? *Evolution* **69**, 1655-1664,
 13 doi:10.1111/evo.12687 (2015).
- 14 77 Kitano, H. Systems biology: A brief overview. *Science* **295**, 1662-1664,
 15 doi:10.1126/science.1069492 (2002).
- 16 **A brief overview of systems thinking and emergent properties in biology.**
- 17 78 Novikoff, A. B. THE CONCEPT OF INTEGRATIVE LEVELS AND BIOLOGY.
 18 *Science* **101**, 209-215, doi:10.1126/science.101.2618.209 (1945).
- 19 79 Benfey, P. N. & Mitchell-Olds, T. Perspective - From genotype to phenotype: Systems
 20 biology meets natural variation. *Science* **320**, 495-497, doi:10.1126/science.1153716
 21 (2008).
- 22 80 Hoffmann, A. A. & Rieseberg, L. H. Revisiting the impact of inversions in evolution:
 23 from population genetic markers to drivers of adaptive shifts and speciation? *Annu. Rev.*
 24 *Ecol. Evol. Syst.* **39**, 21-42, doi:10.1146/annurev.ecolsys.39.110707.173532 (2008).
- 25 81 Hanski, I. A. Eco-evolutionary spatial dynamics in the Glanville fritillary butterfly. *Proc.*
 26 *Natl. Acad. Sci. U. S. A.* **108**, 14397-14404, doi:10.1073/pnas.1110020108 (2011).
- 27 82 Berner, D., Grandchamp, A.-C. & Hendry, A. P. Variable Progress Toward Ecological
 28 Speciation in Parapatry: Stickleback Across Eight Lake-Stream Transitions. *Evolution*
 29 **63**, 1740-1753, doi:10.1111/j.1558-5646.2009.00665.x (2009).
- 30 83 Pinho, C. & Hey, J. in *Annual Review of Ecology, Evolution, and Systematics, Vol 41*
 31 *Vol. 41 Annual Review of Ecology Evolution and Systematics* 215-230 (2010).

- 1 84 Mallet, J., Meyer, A., Nosil, P. & Feder, J. L. Space, sympatry and speciation. *J. Evol. Biol.* **22**, 2332-2341, doi:10.1111/j.1420-9101.2009.01816.x (2009).
- 2
- 3 85 Wu, C. The genic view of the process of speciation. *J. Evol. Biol.* **14**, 851-865 (2001).
- 4 86 Gompert, Z. *et al.* Admixture and the organization of genetic diversity in a butterfly species complex revealed through common and rare genetic variants. *Mol. Ecol.* **23**, 4555-4573, doi:10.1111/mec.12811 (2014).
- 5
- 6
- 7 87 Powell, T. H. Q. *et al.* GENETIC DIVERGENCE ALONG THE SPECIATION CONTINUUM: THE TRANSITION FROM HOST RACE TO SPECIES IN RHAGOLETIS (DIPTERA: TEPHRITIDAE). *Evolution* **67**, 2561-2576, doi:10.1111/evo.12209 (2013).
- 8
- 9
- 10
- 11 88 Bell, M. A. Implications of a fossil stickleback assemblage for Darwinian gradualism. *J. Fish Biol.* **75**, 1977-1999, doi:10.1111/j.1095-8649.2009.02416.x (2009).
- 12
- 13 89 Purnell, M. A., Bell, M. A., Baines, D. C., Hart, P. J. B. & Travis, M. P. Correlated evolution and dietary change in fossil stickleback. *Science* **317**, 1887-1887, doi:10.1126/science.1147337 (2007).
- 14
- 15
- 16 90 Bell, G. Experimental macroevolution. *Proc. R. Soc. B-Biol. Sci.* **283**, 20152547, doi:<http://dx.doi.org/10.1098/rspb.2015.2547> (2016).
- 17
- 18 91 Mallet, J. A Species Definition for the Modern Synthesis. *Trends Ecol. Evol.* **10**, 294-299 (1995).
- 19
- 20 92 Barrett, R. D. H. & Hoekstra, H. E. Molecular spandrels: tests of adaptation at the genetic level. *Nature Reviews Genetics* **12**, 767-780, doi:10.1038/nrg3015 (2011).
- 21
- 22 93 Feder, M. E. & Mitchell-Olds, T. Evolutionary and ecological functional genomics. *Nature Reviews Genetics* **4**, 651-657, doi:10.1038/nrg1128 (2003).
- 23
- 24 94 Cruickshank, T. E. & Hahn, M. W. Reanalysis suggests that genomic islands of speciation are due to reduced diversity, not reduced gene flow. *Mol. Ecol.* **23**, 3133-3157, doi:10.1111/mec.12796 (2014).
- 25
- 26
- 27 95 Barrett, R. D. H., Rogers, S. M. & Schluter, D. Natural selection on a major armor gene in threespine stickleback. *Science* **322**, 255-257, doi:10.1126/science.1159978 (2008).
- 28
- 29 96 Pespeni, M. H. *et al.* Evolutionary change during experimental ocean acidification. *Proceedings of the National academy of Sciences USA* **110**, 6937-6942 (2013).
- 30

- 1 97 Anderson, J. T., Lee, C.-R., Rushworth, C. A., Colautti, R. I. & Mitchell-Olds, T. Genetic
2 trade-offs and conditional neutrality contribute to local adaptation. *Mol. Ecol.* **22**, 699-
3 708, doi:10.1111/j.1365-294X.2012.05522.x (2013).
- 4 98 Anderson, J. T., Lee, C. R. & Mitchell-Olds, T. STRONG SELECTION GENOME-
5 WIDE ENHANCES FITNESS TRADE-OFFS ACROSS ENVIRONMENTS AND
6 EPISODES OF SELECTION. *Evolution* **68**, 16-31, doi:10.1111/evo.12259 (2014).
- 7 99 Egan, S. P. *et al.* Experimental evidence of genome-wide impact of ecological selection
8 during early stages of speciation-with-gene-flow. *Ecol. Lett.* **18**, 817-825,
9 doi:10.1111/ele.12460 (2015).
- 10 100 Michel, A. P. *et al.* Widespread genomic divergence during sympatric speciation.
11 *Proceedings of the National Academy of Sciences* **107**, 9724-9729,
12 doi:10.1073/pnas.1000939107 (2010).
- 13 101 Zhou, X., Carbonetto, P. & Stephens, M. Polygenic Modeling with Bayesian Sparse
14 Linear Mixed Models. *Plos Genetics* **9**, doi:e100326410.1371/journal.pgen.1003264
15 (2013).
- 16 102 Hill, W. G. Applications of Population Genetics to Animal Breeding, from Wright, Fisher
17 and Lush to Genomic Prediction. *Genetics* **196**, 1-16, doi:10.1534/genetics.112.147850
18 (2014).
- 19 103 Orr, H. A. & Presgraves, D. C. Speciation by postzygotic isolation: forces, genes and
20 molecules. *Bioessays* **22**, 1085-1094 (2000).
- 21 104 Renaut, S. *et al.* Genomic islands of divergence are not affected by geography of
22 speciation in sunflowers. *Nature Communications* **4**, doi:182710.1038/ncomms2833
23 (2013).
- 24 105 Harmon, L. J., Schulte, J. A., Larson, A. & Losos, J. B. Tempo and mode of evolutionary
25 radiation in iguanian lizards. *Science* **301**, 961-964, doi:10.1126/science.1084786 (2003).
- 26 106 Hartl, D. L. & Clark, A. G. *Principles of population genetics, fourth edition.* (Sinauer,
27 2007).
- 28 107 S.M., F., A.C., W., J.L., F. & P., N. (Dryad Digital Repository.
29 <http://dx.doi.org/10.5061/dryad.kc596>, 2014).
- 30 108 Abbott, R. *et al.* Hybridization and speciation. *J. Evol. Biol.* **26**, 229-246,
31 doi:10.1111/j.1420-9101.2012.02599.x (2013).

- 1 109 Vuilleumier, S., Goudet, J. & Perrin, N. Evolution in heterogeneous populations From
2 migration models to fixation probabilities. *Theor. Popul. Biol.* **78**, 250-258,
3 doi:10.1016/j.tpb.2010.08.004 (2010).
4