In their recent paper, entitled “A universal mechanism generating clusters of differentiated loci during divergence-with-migration”, Rafajlović et al. (2016) claim they have identified a novel mechanism explaining why concentrated genetic architectures evolve: due to the increase in rates of stochastic loss of polymorphism that occurs with increasing recombination among loci under divergent selection. Essentially, this adds some nuance to what was noticed, but not emphasised engouth by previous theory that has focused on the impact of linkage on the establishment probability. It is true that it is insufficient to only consider the probability of establishment, and that if established polymorphisms do not persist for long, they should be appropriately discounted. Myself and others have initially ignored the contribution of loss of polymorphism when making arguments about the importance of establishment probability for the evolution of “genomic islands” (Feder et al. 2012; Yeaman 2013, but see Aeschbacher and Bürger 2014, Yeaman et al. 2016). However, is loss of polymorphism an important factor that changes the conclusions of previous theory? And is the loss of polymorphism observed in their simulations in fact stochastic? My aim in this comment is to critically evaluate the paper by Rafajlović et al.. I will argue that i) their “novel” and “universal” mechanism constitutes an incremental nuance to previously established theory, ii) their paper does not show whether this nuance is broadly important, and iii) they ignore previous theory that offers a better explanation for why concentrated architectures evolve (and persist?) in these simulations. I will cover each of these issues below, and re-introduce the main idea proposed by Yeaman and Whitlock (2011), which Rafajlović at al. ignore: that competition among genetic architectures is the main mechanism driving the evolution of concentrated architectures in these types of simulation. I will begin by briefly reviewing relevant population genetic theory, then clarify what is meant by “stochastic loss”, and finally re-examine the findings and arguments of Rafajlović et al.

**Review of previous theory**

To generally understand the effect of random genetic drift (henceforth simply “drift”) on migration–selection balance, Yeaman and Otto (2011) proposed that the net effects of the deterministic processes acting on a polymorphism can be represented by the diversification coefficient, δ. When δ > 0, the net effect of divergent selection outweighs migration, and polymorphisms will be deterministically favoured, while the reverse occurs for δ < 0. When this diversification coefficient is large relative to 1/*N* (where *N* is the effective (?) population size), then the deterministic processes will dominate (stochastic loss may occur due to drift in spite of selection), whereas when it is small relative to 1/*N*, then drift will dominate and polymorhpisms will behave neutrally. The diversification coefficient can be spliced into single-locus, single-patch population genetic models to predict establishment probability and critical migration rate (Yeaman and Otto 2011). In the context of selection, migration, and recombination, alleles that are sufficiently tightly linked to a selected locus experience an indirect fitness benefit, even if they are neutral (Petry 1983, Bengtsson and Barton 1986, Bürger and Akerman 2011; Aeschbacher and Bürger 2014). Aeschbacher and Bürger (2014) show that this indirect fitness benefit affects the predictions for the fate of a new selected mutation, increasing its probability of establishment (their Figure 2) and persistence time (their Figure 5) relative to what would be expected from a single-locus model. They also derive the critical recombination rate at which polymorphism at a linked locus is deterministically maintained (their equation 11). Yeaman et al. (2016) recently showed that in a two-locus model of migration, selection, and recombination, the splicing approximation introduced by Yeaman and Otto (2011) agrees closely with the branching process predictions of Aeschbacher and Bürger (2014) for the probability of establishment. This confirms that the diversification coefficient can indeed be adjusted to incorporate the indirect effects of selection at other locally adapted polymorphisms (as was suggested by Yeaman and Whitlock 2011 who have used a somewhat clumsier approximation). This splicing approach therefore provides a useful framework for understanding the interplay between migration, selection, recombination, and drift, and how they affect whether polymorphism tends to be established, maintained, or lost.

**Defining “stochastic loss”**

Despite this well-established body of theory, Rafajlović et al. (2016) attempt to explain the dynamics they observe only in terms of the resulting patterns of change in allele polymorphism (rates of gain vs. loss) and emphasize the importance of “stochastic loss”. They define stochastic loss as that which “*occurs due to random genetic drift in populations of finite size, resulting in fixation of a single allele at a given locus in both populations*” (p. 1615), but this does not give any insight into the causal contributions of the underlying evolutionary processes. To clarify what may be meant by “stochastic loss” in light of the above review, loss of polymorphism in these two-patch models may be caused by (A) pure drift when two alleles have equal fitness; (B) drift in small populations overwhelming the deterministic forcing of allele frequencies that occurs when divergent selection is greater (or stronger?) than migration (1/*N* > δ > 0); (C) drift causing stochastic loss in large populations, even when the net effect of selection and migration is diversifying (δ > 1/*N* > 0), or (D) deterministic forcing of allele frequencies when migration is greater than divergent selection (δ < 0). Unfortunately, Rafajlović et al. do not attempt to differentiate between these very different reasons for “stochastic loss”, which can occur by either (A), (B), or (C), nor do they even consider the possibility of (D), which constitutes non-stochastic loss. As such, claiming “stochastic loss” as a cause of architecture evolution only identifies the proximal reasons for change: that polymorphisms establish and are lost. Such an approach to describing “universal mechanisms” obscures more interesting questions, such as “is this architecture adaptive?”, which can only be evaluated if framed in terms of the underlying evolutionary processes.

**Clarifying the evolutionary processes causing loss of polymorphism**

In their two-locus numerical simulations, Rafajlović et al. (2016) observe that above some recombination rate, the rate of polymorphism loss exceeds the rate of gain (their Figure 3). This pattern is qualitatively consistent with the analytical predictions of Aeschbacher and Bürger (2014, eq. 11) for a continent–island model: above a certain rate of recombination, polymorphism tends to be deterministically disfavoured and the rate of loss of polymorphism should exceed the rate of establishment of new alleles (explanation D, above). However, this pattern would also be qualitatively consistent with polymorphism being deterministically favoured, yet lost due to drift, either in the large or small population domains (explanation B and C, above). Likely, explanations B, C, and D all come into play under different combinations of migration, selection, recombination, and drift. Thus, it is unclear whether the loss of polymorphism observed by Rafajlović et al. (2016) is in fact even stochastic, as they claim. This should have been investigated using simulations that varied population size (also migration rates and mutational effect sizes), or by running continent–island model simulations and comparing the results to readily available analytical predictions (symmetrical two-patch analytical models are somewhat less tractable, e.g., Akerman and Bürger 2014).

**Evaluating the importance of loss of polymorphism**

Beyond the issue of whether the observed loss is in fact stochastic, the paper by Rafajlović et al. gives little insight into the general importance of loss of polymorphism: only a single figure shows the effect of recombination on rate of loss (Figure 2), and this shows that rate of loss is unimportant (i.e. 0) when selection is strong (Figure 2D), but it does vary somewhat with recombination when selection is weak (Figure 2C). All remaining figures only show the net balance between rates of gain and loss, so it is unclear how much rates of loss are actually behaving differently than rates of gain. More importantly, there is no exploration of the rate of loss of polymorphism when migration is low or when population size is large, both of which would be expected to reduce the rate of loss of polymorphism; all two-locus simulations are run with *N* ≤ 1000 and *m* = 0.1, which are rather extreme values. Previous theory on persistence time of single-locus polymorphisms gives some insight into what we might expect here: Yeaman and Otto (2011, Figure S8) showed that as migration rate decreases (and δ increases), locally adapted polymorphisms tend to persist for very long times (>100,000 generations), suggesting loss of polymorphism is unimportant when δ >> 0. Similar patterns are shown for two-locus results in Aeschbacher and Bürger (2014; Figure 7). To see whether variation in rates of loss of polymorphism with recombination is generally important, this should have been explored through broader consideration of parameter space, including simulations with lower migration rates and higher population sizes.

**How does “gain vs. loss” differ from “competition among architectures”?**

Rafajlović et al. claim that “*the balance between the processes of local loss and gain that we proposed here is, to our knowledge, the only universal mechanism that promotes concentrated genetic architecture under strong gene flow, without suppressing recombination*” (p. 1619). Unfortunately, Rafajlović et al. inaccurately represent the paper by Yeaman and Whitlock (2011), where two mechanisms for the evolution of concentrated architectures are discussed (p. 1907–1908): (1) “*At the outset of a bout of local adaptation (or following the homogenization of a previously existing divergence), the establishment of a single locally adapted allele can facilitate the recruitment of other locally adapted alleles in tight linkage*”; (2) “*Once locally adaptive alleles have arisen, a diffuse architecture might be replaced by a more concentrated architecture arising …through the invasion of a new mutation in tight linkage to an existing allele (with subsequent homogenization of previously established divergent alleles at more loosely linked loci)*”. Citing Yeaman and Whitlock (2011) and Yeaman (2013), Rafajlović erroneously claim that “*earlier theoretical studies have focused only on understanding the importance of the establishment-bias effect*” (p. 1610), completely ignoring our second explanation based on competition among architectures (which was again explained in Yeaman 2013, p. E1743). Our explanation for the evolution of concentrated architectures via competition among alleles (no suppression of recombination required) is explicitly tied to the well-defined body of analytical theory that shows how tightly linked architectures are more fit than loosely linked ones (reviewed above). By this explanation, gains and losses in polymorphism play out as a result of the differential fitness of alleles based on their size and linkage relationships, as well as through stochastic fluctuations due to drift. Jointly, these processes eventually lead to concentrated architectures due to the higher fitness of the more tightly linked combinations. While in Yeaman and Whitlock (2011) and Yeaman (2013) we emphasized the fitness advantages inherent in competition among architectures, we did not mean to imply that such competition played out in the absence of drift or stochasticity.

Given that they did not confront this issue clearly, it is unclear whether Rafajlović et al. envision gain and loss of polymorphism to also extend to competition among architectures, or whether they are meaning to refine the establishment bias mechanism to also include the possible contribution of loss of polymorphism (whether stochastic or deterministic). Assuming that Rafajlović et al. are not just imprecisely re-inventing the competition among architectures mechanism, in order for loss of polymorphism to be important, it has to be established in the first place. For their mechanism to be “*universally important*” during *de novo* adaptation, they should therefore show the parameter space where the relationship between recombination and rate of gain of polymorphism is flatter (weaker may be better) than the relationship between recombination and rates of loss of polymorphism. Only then would rates of loss potentially be driving concentration more than rates of gain. As discussed above, it was interesting to see this shown for Figure 2A vs. C, however it is unclear whether this will be broadly important for other parameter combinations (it is clearly unimportant when selection is strong, as they show in Figure 2D). Furthermore, to distinguish this mechanism from the competition among architectures mechanism of Yeaman and Whitlock (2011) in the multi-locus simulations, Rafajlović et al. should show that polymorphism at one locus is lost *before* a new allele is established at another locus. If polymorphism is lost *following* the establishment of a more tightly linked allele of similar effect, then this is more consistent with competition than rates of gain vs. loss in the absence of competition. Note also that Yeaman et al. (2016) have recently presented a preliminary investigation of loss of polymorphism following secondary contact, which suggests that this can indeed be quite important when divergence is already established. Overall, given that the gain vs. loss explanation still depends upon the underlying balance between selection, migration, recombination, and drift, focusing on the patterns without also describing the importance of the underlying processes does not provide a universal causal explanation.

**Minor quibbles**

As mentioned above, the results of Figure 3 are broadly consistent with the predictions of Aeschbacher and Bürger (2014): their Eq. 11 shows that decreasing strength of selection on the large locus (their *b* coefficient) and the small locus (their *a* coefficient) both result in a smaller critical recombination threshold. Rafajlović et al. acknowledge the findings of Aeschbacher and Bürger (2014), but state that their findings are not described by this model because the position of the recombination threshold “*shifts over the timescale of the process*” (p. 1619), with lower critical thresholds seen under both large effect sizes at the larger locus (their *D*s; late in the divergence process) and also smaller values of *D*s (early in the divergence process; Figure 3, S8). However, this shifting is still consistent with the predictions of Eq. 11 in Aeschbacher and Bürger (2014): early in the divergence process, the recombination threshold is lower because net strength of selection on the *D*s locus is weaker, in which case Eq. 11 would predict a lower threshold with smaller *b*. The decrease in recombination threshold later in the process is also consistent Eq. 11: because the Gaussian fitness function assumed by Rafajlović et al. has a curvature, the relative fitness contributed by a given allele effect size at the small locus (their *D*w) will decrease with increasing divergence in the genetic background (*D*s), as this approaches the curved region of the Gaussian function, and gives diminishing returns for fitness from a given change in phenotype (i.e. a decrease in *a* in Eq. 11). Thus, the changes in threshold in Figures 3 and S8 are consistent with previous theory based on the deterministic interplay between selection, migration, and recombination.

Earlier studies are not at all “*partly contradictory*” (p. 1610), but are based on different assumptions, which result in different evolved genetic architectures. The study by Feder et al. (2012) assumed pure divergent *directional* selection (and therefore no genetic redundancy), so there was no potential for competition among architectures, whereas the simulations of Yeaman and Whitlock (2011) included genetic redundancy and stabilizing selection towards different optima, which resulted in competition among architectures. The model by Yeaman (2013) differed from that of Yeaman and Whitlock (2011) in that the underlying genetics were non-redundant, and mutations were required at all loci in order to build a locally optimal phenotype. This was chosen to highlight the potential importance of rearrangements, and the results are completely consistent with the other papers mentioned above, and not contradictory.

**Conclusions**

Individual-based simulations can provide much insight into how evolutionary processes shape patterns in the genome, especially when compared with predictions from analytical models. When making extraordinary claims about “*the only universal mechanism*” for a given phenomenon, researchers should make every attempt to frame their results clearly in relation to previous theory, and in terms of the fundamental evolutionary processes. The mechanism discussed by Rafajlović et al. is more of a nuance that was not explored (not fully explored) in previous theory than something truly novel, and they have not sufficiently explored its general importance nor differentiated it clearly from previous theory. Their paper does not substantially contribute to understanding why different kinds of architectures evolve, as it is unclear whether loss of polymorphism is in fact the mechanism driving the concentration of architectures in their simulations independently of competition, and also unclear whether the loss is stochastic or deterministic. As there are analytically predicted fitness differences for different architectures under migration-selection balance, competition among architectures provides a parsimonious explanation for observations in these simulations that should not be ignored.

I have one major issue to add: It is not clear to me if their comparison of gain vs. loss “rates” (by the way, these are not rates, but probabilities; but this is a minor quibble) is appropriate and relevant for their conclusion. As we know, the distribution of effects of established mutations is not the same as the input distribution. However, it appears to me that, in their sims to determine loss rates, they did not start with established polys but chose specific allelic effects (described in their two-locus model). This distribution will almost certainly deviate from the distribution of effects in established polys. If this is the case, their comparison is irrelevant because they would mainly start from polys that had (almost) never been established (or rarely).

It is also a pity that they write about local adaptation and never mention mean fitness or reduction of mean fitness caused by migration, mutation, and drift. Their concept of adaptation is problematic because differences between allelic effects tell only part of the story. Take a well or perfectly adapted population in their sense and shift the trait distribution (in the total pop) by a certain amount. This will clearly affect local adaptation in the “usual” sense.

Overall, their paper suffers from a complete ignorance of relevant (even classical) theory. Among other, they give the impression that gain and loss of an allele are different mechanisms or processes. In reality, they are the consequence of one and the same set of processes, just applied to different initial conditions (gain: initially one mutant; loss: initially about 50% mutants – if I interpret their definition of establishment correctly).

The authors state that “when the rate of loss at a locus is larger than the rate of gain at this locus in a tiven stage of divergence, this locus is unlikely to make a sustained contribution to overall divergence”. This is a narrow view of “contribution to divergence”, as a given locus may well contribute a transient local reduction in effective gene flow by which other mutations can more easily establish, even though they may later be lost again because the architecture has become more concentrated around another diverged locus. In this sense, a transient polymorphism may well make a contribution to overall divergence.