The Exact Distributions of $F_{IS}$ under Partial Asexuality in Small Finite Populations with Mutation

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Abstract
Reproductive systems like partial asexuality participate to shape the evolution of genetic diversity within populations, which is often quantified by the inbreeding coefficient $F_{IS}$. Understanding how those mating systems impact the possible distributions of $F_{IS}$ values in theoretical populations helps to unravel forces shaping the evolution of real populations. We proposed a population genetics model based on genotypic states in a finite population with mutation. For populations with less than 400 individuals, we assessed the impact of the rates of asexuality on the full exact distributions of $F_{IS}$, the probabilities of positive and negative $F_{IS}$, the probabilities of fixation and the probabilities to observe changes in the sign of $F_{IS}$ over one generation. After an infinite number of generations, we distinguished three main patterns of effects of the rates of asexuality on genetic diversity that also varied according to the interactions of mutation and genetic drift. Even rare asexual events in mainly sexual populations impacted the balance between negative and positive $F_{IS}$ and the occurrence of extreme values. It also drastically modified the probability to change the sign of $F_{IS}$ value at one locus over one generation. When mutation prevailed over genetic drift, increasing rates of asexuality continuously increased the variance of $F_{IS}$ that reached its highest value in fully asexual populations. In consequence, even ancient asexual populations showed the entire $F_{IS}$ spectrum, including strong positive $F_{IS}$. The prevalence of heterozygous loci only occurred in full asexual populations when genetic drift dominated.

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Introduction
Reproductive systems define how genetic diversity is transmitted through generations thus they highly constrain the evolution of species. Many species relevant to human activities and ecosystems are partially asexual, meaning that they can reproduce both through sexual and asexual (equally named clonal) events [1–3]. Theoretical population genetics of partially asexual species has received little attention so far [4] and there is an ongoing debate on the effects of asexuality on genetic diversity and how such effects can be used to identify asexual species [5]. Indeed, theoretical studies about the genetic consequences of partial and full asexuality have only focused on the mean expected values of some population genetics parameters. In consequence, to disentangle evolutionary forces acting on such populations, applied studies may only compare their multiple quantitative measures of genetic diversity to theoretical average tendencies [6–8] and a large amount of the quantitative information contained within molecular data is wasted for evolutionary interpretations. Applied population genetics studies of partially asexual species lack of full frames of reference to compare their measured distributions of genetic parameters. Moreover, while we know that reproductive systems may have deep implications for the ecology and the evolution of species [9], we cannot rationally assess the evolutionary interest of sex, including genetic segregation, gamete fusion and massive recombination without understanding the full genetic consequences of partial and full asexuality [2,10–14].

The population inbreeding coefficient, $F_{IS}$ [15], is a classical measure of genetic diversity for polyploid organisms that allows biologists to assess the evolutionary processes acting on a population. $F_{IS}$ is known to vary markedly according to mating systems, especially with the relative importance of sexuality and asexuality within populations [16,17]. It constitutes the lowest level of $F$-statistics [15] and stands for the excess or deficit of heterozygotes occurring in a population as compared to Hardy-Weinberg proportions. Asexual events are expected to maintain heterozygosity within the offspring because, by limiting the segregation of alleles, it conserves the ancestral heterozygosity through generations. Moreover, asexuality is even expected to increase heterozygosity and decrease the probability of allele identity since alleles of the same gene may independently accumulate mutations over generations. However, this process known as the “Meselson effect” was formulated considering only one genome rather than a population of genomes [18]. Extending the same argument to many individuals shows that the mean heterozygosity of asexual populations should also increase [19,20]. Empirical and theoretical results suggest that the effective rates of asexuality, the effective frequency of asexual events involved in producing the next generation in a population, is a key feature to understand the genetic evolution of those species [16]. The rate of asexuality is denoted $\epsilon$ [19]. It ranges from 0, when populations
reproduce only sexually, to 1 when populations reproduce only asexually. This rate is identical to \( A \) as \([21]\), and shares common notion with \( \delta \) \([22]\) and with the length of the asexual seasons, \( \epsilon \) \([23]\) but may have different impacts and implications.

The insights gained by mathematical and simulation modeling \([19,20,22–26]\) raise unsolved questions, mainly because the theoretical expectations were previously formalized only for the first moment (mean) of the possible distributions of \( F_{IS} \). Intermediate asexual populations, defined as populations producing 0 to 90 percent of their descents using asexuality, are expected to exhibit similar mean \( F_{IS} \) values and variance to those obtained from fully sexual populations \([19,24]\). This implies that intermediate rates of asexuality should have no effects on the average level of genetic diversity expected within populations. If true on the full range of genetic diversity, a strategy with a low frequency of sex (\( \epsilon \) around 0.9) would be optimal, considering that it would combine the potential genetic benefits of mixis in terms of heritability of genetic diversity and would reduce the costs of sex \([27]\). Conversely, to explain why we can still observe populations that steadily reproduce through partial asexuality, we may suppose that the balance between the genetic benefits of mixis and the costs of sex should vary with different rates of asexuality \([12]\). Empirical and field studies observe that partially asexual species show lower negative \( F_{IS} \) values at most loci when other direct evidences of asexuality argue for intermediate rates rather than full sexual species \([17,28]\). This feature is thus commonly used to pragmatically detect asexual events in populations assumed to be sexual \([16]\).

Sparsely studied, the second moments (variance) of the possible distributions of \( F_{IS} \) were only attempted using simulations \([19,26]\). Highly asexual populations (0.9<\( \epsilon <1.0 \)) should exhibit the topmost variance of \( F_{IS} \), distinctively lower than the ones expected in fully sexual and intermediate asexual populations (0.0<\( \epsilon <0.9 \)), and slightly higher than those expected in fully asexual populations (\( \epsilon = 1 \)) \([19]\). This topmost variance of \( F_{IS} \) expected in highly asexual populations was used to propose a way to qualitatively infer the rare occurrence of sexual events in such populations \([29]\).

Yet, some field studies show shifting conclusions depending on whether they argue from \( F_{IS} \) variance or from other population parameters \([8,28,30]\) indicating that this method may be not universal. Up to now, field studies still need to resort to expertise to identify, predict and infer the evolutionary forces ongoing on partially asexual species \([4,31]\), mostly because theoretical predictions only exist as mean expected values for some specific drift and mutation cases, rather than as full distributions of values computed for an extensive quantitative range of evolutionary forces. As a better frame of reference to disentangle which evolutionary forces are affecting partially asexual species, we propose a raw population genetics model that provides the full exact distributions of \( F_{IS} \) ensued from an evolution with mutation in a finite population after an infinite number of generations. To achieve the mathematical description of those probabilities avoiding any continuous or “allelic pool” approximations for mathematical convenience \([32]\), we derived the exact probabilities of all possible distributions of genotypes among the constitutive individuals of a finite population size as function of the rates of asexuality. By this approach, we were able to investigate the consequences of partial asexuality on discrete distributions of allelic identities and \( F_{IS} \) obtained from a single biallelic locus in a finite population with a steady reciprocal mutation flux between the two alleles. We also assessed how population sizes and mutation rates in interaction with the rate of asexuality impacted the probabilities to observe negative and positive \( F_{IS} \) values within populations and the full distribution of \( F_{IS} \). For better comparability, we also calculated the two traditional first moments (mean and variance) and expanded our analysis to the third (skewness) and the fourth (kurtosis) moments to unravel the kind of information that can be missed using only the two first moments to sum up the impacts of partial asexuality on the possible distributions of \( F_{IS} \). We hope that our predictions will help future biological studies to formalize hypotheses about the evolutionary forces, the biological traits and the ecological processes acting on populations, and to better assess the rates of asexuality estimated from genetic markers. This theoretical study constitutes a first step to take up the challenges expressed in recent perspectives to disentangle classic evolutionary forces from the consequences of such ‘old’ mating systems \([4,33]\).

**Methods**

**Our conceptual model**

We aimed to build the simplest conceptual model with the objective to provide a comprehensive view of the genetic consequences of partial asexuality on a biallelic marker. We thus focused on the temporal change in genotypic frequencies at a diploid locus with two allelic states, \( A \) and \( a \), obtainable from a reciprocal mutation rate \( \mu \), within a partially asexual finite population. Our model was based on genotypic frequencies rather than pools of alleles as recommended \([32]\). All change in the system was due to the mating system, genetic drift and mutation forces acting consistently through time expressed in generations. We further assumed no selection and no migration, even if mutation rate can be also interpreted as including some migration from external populations. Through asexual events, genetic drift acted at the genotypic level while, through sexual events, it acted at the allelic level. Population reproduced using discrete and non-overlapping generations. Within the population, the \( N \) individuals reproduced using asexuality at a rate \( \epsilon \), called the rate of asexuality \([19,23,26]\). The genetic material was thus transmitted asexually at a rate \( \epsilon \) and sexually at a rate 1\(-\epsilon \). Sexual reproduction followed the traditional random union of gametes implying panmacy and panmixy. In such sexual system, self-fertilization occurred at an average rate of \( 1/N \) and alleles mutated during their transmission to the next generation. When an offspring resulted from an asexual event, he received the whole diploid genotype of its parent excepting mutations that occurred at similar rates during asexual and sexual reproduction.

**Mathematical development**

We formalized a genotypic state \( (r_{aa},r_{Ad},r_{AA}) \) as a distribution of the \( N \) individuals of a population on the three possible genotypes \( aa, \ aA, \ AA \) that can be found at one biallelic locus. All the genotypic states were constrained by \( r_{aa} + r_{Ad} + r_{AA} = N \). Thus a population of \( N \) individuals defined \( N \) unique distributions of its \( N \) individuals within the three possible genotypic states. The genotypic frequencies at a generation \( n \) are thus \( p_{ij}^n = \frac{N_{ij}}{N} \) where \( i \) and \( j \) can be alleles \( A \) or \( a \). The population size \( N \), the mutation rate \( \mu \) and the rate of asexuality \( \epsilon \) are supposed to be fixed all along the evolution of a population. We thus wrote the different transition probabilities from one generation to another.

- The genotypic frequencies under asexual reproduction \( (p_{aa}^{n+1}, p_{Aa}^{n+1}, p_{AA}^{n+1}) \) at the generation \( n+1 \) were expressed as a function of the mutation rate \( \mu \) and the previous genotypic frequencies \( (p_{aa}^n, p_{Aa}^n, p_{AA}^n) \).

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The probability of a genotypic state in the next generation is given through the multinomial distribution $M(N; \pi_{n+1}^a, \pi_{n+1}^{AA}, \pi_{n+1}^{Aa}, \pi_{n+1}^{aa})$, then

$$P(s_{n+1}^{AA}, s_{n+1}^{Aa}, s_{n+1}^{aa} | r_{n+1}^{AA}, r_{n+1}^{Aa}, r_{n+1}^{aa}) = \frac{N!}{s_{n+1}^{AA}! s_{n+1}^{Aa}! s_{n+1}^{aa}!} (\pi_{n+1}^{AA})^{s_{n+1}^{AA}} (\pi_{n+1}^{Aa})^{s_{n+1}^{Aa}} (\pi_{n+1}^{aa})^{s_{n+1}^{aa}} \tag{4}$$

The probability of a genotypic state in the next generation is therefore obtained through generations as

$$P^{(n+1)}(s_{n+1}^{AA}, s_{n+1}^{Aa}, s_{n+1}^{aa}) = \sum_{r_{n+1}^{AA}, r_{n+1}^{Aa}, r_{n+1}^{aa}} P(s_{n+1}^{AA}, s_{n+1}^{Aa}, s_{n+1}^{aa} | r_{n+1}^{AA}, r_{n+1}^{Aa}, r_{n+1}^{aa}) P^r(r_{n+1}^{AA}, r_{n+1}^{Aa}, r_{n+1}^{aa}) \tag{5}$$

where $P^r(r_{n+1}^{AA}, r_{n+1}^{Aa}, r_{n+1}^{aa})$ is the probability of the state $(r_{n+1}^{AA}, r_{n+1}^{Aa}, r_{n+1}^{aa})$ at the generation $n$.

The $(N+2)!/(N!2!)$ elements $P(s_{n+1}^{AA}, s_{n+1}^{Aa}, s_{n+1}^{aa} | r_{n+1}^{AA}, r_{n+1}^{Aa}, r_{n+1}^{aa})$ of the transition matrix are positive. The generated Markov chain is irreducible and aperiodic thus ergodic. As stated by the Perron-Frobenius theorem [34], the system is driven through generations to the stationary distribution of genotypic repartitions by the dominant eigenvector corresponding to the largest eigenvalue $\lambda = 1$ of the transition matrix [35]. This model also allows exploring the probability of genotypic repartitions dynamically through generations by computing the successive powers of the transition matrix, but for better clarity of the messages, we only focused on the consequences of partial asexuality on distribution of genetic diversity at equilibrium in this paper.

The probability density of genotypic repartitions contains all the information that population geneticists analyze and thus provides more information than any synthetic population genetics parameter would ever do. But, in this paper, considering the strong interest of the scientific community and the previously formulated theoretical expectations concerning the effects of partial asexuality on $F_{IS}$ values [16], we focused on the full exact distribution of $F_{IS}$ at equilibrium after an infinite number of generations. Thus, for each genotypic repartition of the individuals within a population, we computed allelic identities: $Q_w$, which is the probability that two homologous alleles are identical within a diploid individual, and $Q_b$, which is the probability that two homologous alleles are identical as they came from different individuals [36]. Then, the inbreeding coefficient $F_{IS}$ was thus classically obtained from $Q_w$ and $Q_b$: $F_{IS} = \frac{Q_w - Q_b}{1 - Q_b}$.

We analyzed and discussed afterward the discrete probabilities density distributions of $Q_w$, $Q_b$, and $F_{IS}$ obtained at equilibrium. We then computed the probability of negative $F_{IS}$ as the sum of the probabilities of genotypic repartitions that resulted in strictly negative $F_{IS}$. We considered the probability of positive $F_{IS}$ as the sum of the probabilities of genotypic repartitions that resulted in zero and positive $F_{IS}$ but excluding the two genotypic repartitions where one of the alleles was fixed within the population (the states of fixation). To understand how the rates of asexuality impacted the evolution of homozygote and heterozygote excesses in one generation at one locus, we computed the mean probabilities to change and keep the sign of $F_{IS}$ as the sums of transition probabilities divided by their number knowing the signs of $F_{IS}$ of the previous $(r_{n+1}^{AA}, r_{n+1}^{Aa}, r_{n+1}^{aa})$ and next $(s_{n+1}^{AA}, s_{n+1}^{Aa}, s_{n+1}^{aa})$ genotypic states.

All mathematical developments were computed using Python 2.7 (Python Software Foundation 2001–2012) and Numpy 1.7.0 (NumPy Developers, 2005–2012). The binary package (PASEX 1.0) of the algorithms we used to compute the transition matrix and the stationary distributions of genotypic repartitions is available at https://www3.rennes.inra.fr/IGEPF/PASEX/PASEX_1.0.zip.

In this paper, we chose to analyze results considering two population sizes of 60 and 140 individuals because they were equivalent to the population sizes encountered in some partially asexual populations of wild cherry trees used to assess the origin of the negative $F_{IS}$ values commonly found in this species [17].With current workstations (HP Z800 Intel Xeon X5650 @2.67Ghz with 96 Go RAM), we were able to predict the probability of the genotypic distribution for 385 individuals overnight avoiding swapping. Raw transition matrix for 140, 250 and 400 individuals respectively required 1.74 Go, 17 Go and 113 Go to be stored and analyzed.

### Moments of the distributions of $F_{IS}$

To compare our results with previous ones formulated using the two first moments of the possible distributions of $F_{IS}$ [19], we also resumed the exact theoretical distributions we obtained by their four first moments. We thus computed the mean and the variance

\[
\begin{align*}
\mu & = \sum_{r_{n+1}^{AA}, r_{n+1}^{Aa}, r_{n+1}^{aa}} r_{n+1}^{AA} P(r_{n+1}^{AA}, r_{n+1}^{Aa}, r_{n+1}^{aa}) \\
\sigma^2 & = \sum_{r_{n+1}^{AA}, r_{n+1}^{Aa}, r_{n+1}^{aa}} (r_{n+1}^{AA} - \mu)^2 P(r_{n+1}^{AA}, r_{n+1}^{Aa}, r_{n+1}^{aa})
\end{align*}
\]

The expected value $\mu$ and the variance $\sigma^2$ of the distribution of $F_{IS}$ for a population of size $N$ individuals can be computed as follows:

\[
\begin{align*}
\mu & = \sum_{r_{n+1}^{AA}, r_{n+1}^{Aa}, r_{n+1}^{aa}} r_{n+1}^{AA} P(r_{n+1}^{AA}, r_{n+1}^{Aa}, r_{n+1}^{aa}) \\
\sigma^2 & = \sum_{r_{n+1}^{AA}, r_{n+1}^{Aa}, r_{n+1}^{aa}} (r_{n+1}^{AA} - \mu)^2 P(r_{n+1}^{AA}, r_{n+1}^{Aa}, r_{n+1}^{aa})
\end{align*}
\]
Negative and Positive FIS under Partial Clonality

of $F_{IS}$. To seek for more subtle effects of partial asexuality on $F_{IS}$, we also studied the third and the fourth moments of the possible distributions of $F_{IS}$ by computing the classical skewness

$$\gamma_1 = \frac{\mathbb{E}[(X - m)^3]}{\left(\mathbb{E}[(X - m)^2]\right)^{3/2}}$$

and the classical excess of kurtosis

$$\gamma_2 = \frac{\mathbb{E}[(X - m)^4]}{\left(\mathbb{E}[(X - m)^2]\right)^2} - 3$$

where 3 stands for the kurtosis of a Gaussian distribution. In those equations, $m$ is the mean value of the distribution of the variable $X$.

Results

The discrete probability densities of $F_{IS}$ at equilibrium were impacted by the rates of asexuality since low rates (Figures 1, 2, 3, 4). Compared to similar sexual population (same population size and mutation rate), partial asexuality mainly modified the shape and the range of the possible distributions of $F_{IS}$. Increasing rates of asexuality tended to shift the distribution of $F_{IS}$ into negative values and to spread the right tail of the distributions into positive values. Therefore, it increased the probability to observe negative $F_{IS}$ and decreased the probability to observe positive $F_{IS}$ and also explained why some isolated highly positive $F_{IS}$ values are actually obtained.

Intermediate asexual populations ($0<\epsilon<0.9$) showed specific distributions of $F_{IS}$ that varied from those obtained in highly and fully asexual populations and were distinguishable from the distribution obtained from fully sexual population (Figures 1, 2, 3, 4). Increasing rates of asexuality substantially increased the probability of negative $F_{IS}$. This effect was especially visible for negative $F_{IS}$ values close to zero. Moreover, the distributions of $F_{IS}$ from intermediate asexual populations showed a deficit of small positive values ($0\leq F_{IS}\leq 0.1$) in comparison with distribution from fully sexual population, and this deficit increased with the rates of asexuality until 0.9. For higher positive $F_{IS}$ values ($0.1< F_{IS} \leq 1$), the discrete distributions of $F_{IS}$ showed complex variations when the rate of asexuality increased. Varying the rates of asexuality modified the transition probabilities and thus, the probabilities of genotypic states obtained at equilibrium. For example, in a population of 140 individuals mutating at a rate of $10^{-6}$, changing $\epsilon$ from 0 to 0.5 modified the ranks of probabilities of 9882 genotypic states. Only 129 remained identical, meaning that the paths to walk through the transition matrix winded differently along the possible genotypic states according to the rates of asexuality. Globally, genotypic states with negative $F_{IS}$ tended to increase their ranks to the most likely while genotypic states with positive $F_{IS}$ tended to decrease their ranks when the rates of asexuality increased. For example, at equilibrium, the genotypic state (aa:1.16 a:c:24 a:t:0) resulting in a negative $F_{IS}$ of $-0.09375$ was ranked as the 82nd most probable state when population reproduced sexually ($\epsilon=0$) while it was ranked 46th when the rate of asexuality was 0.5. Conversely, the genotypic state (aa:12 a:t:15 a:k:1), resulting in a positive $F_{IS}$ of 0.06061284, was ranked the 45th most probable state in fully sexual population and only the 60th when the rate of asexuality was 0.5.

Populations reproducing using high rates of asexuality ($0.9<\epsilon<1$) strongly shifted their discrete probability densities into negative $F_{IS}$ values. But they also spread the tails of their distributions over high values of positive $F_{IS}$. Actually, we expected more high positive $F_{IS}$ values ($0.4<F_{IS}<1$) in highly asexual populations than in more sexual populations.

From those distributions, we first computed the probabilities of fixation (Table 1). Increasing the rates of asexuality decreased the probabilities of fixation for a fixed population size and mutation rate. When genetic drift prevailed over mutation, the probabilities of fixation were drastically reduced only in highly asexual populations, mainly because asexuality creates as many states of fixation as a locus has possible genotypic states within an individual. In our case, with two alleles, each locus has thus three states of fixation under pure asexuality. When mutation prevailed over genetic drift, the probabilities of fixation decreased more smoothly as the rates of asexuality increased. Beyond fifty per cent

![Figure 1. Discrete probability density distributions of $F_{IS}$ at equilibrium as a function of the rate of asexuality, $\epsilon=0$ (black), 0.3 (grey), 0.5 (purple), 0.7 (blue), 0.9 (green), 0.99 (yellow), 0.999 (light orange), 0.9999 (dark orange), 1 (red). Results obtained for a population size of $N=140$ and a mutation rate of $\mu=10^{-6}$.](https://journal.pone.0085228.g001)

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of asexuality, the probabilities of fixation tended to decrease faster as the rates of asexuality increased.

Then, we computed the negative $F_{IS}$ and positive $F_{IS}$ (Table 1). Globally, for fixed population size and mutation rate, increasing rates of asexuality increased the probability of negative $F_{IS}$ and decreased the probability to observe positive $F_{IS}$. In detail, both probabilities strongly depended on the population sizes and the mutation rates. Dynamically, under intermediate rates of asexuality, the mean probability to change in one generation the sign of $F_{IS}$ quickly decreased with increasing rates of asexuality (Table 2). At high rates of asexuality, this probability still decreased with increasing rates of asexuality but remained at the same scale as populations reproducing using fifty per cent of asexuality. Whatever, in fully asexual populations, the mean probability to change the sign of $F_{IS}$ in one generation still remained around 5%.

**Effects mutation and drift on the distributions of $F_{IS}$**

Population sizes, mutation rates and rates of asexuality interacted to shape the discrete probability density distributions of $F_{IS}$ after an infinite number of generations (Figures 1, 2, 3, 4). It created complex variations within the possible distributions of $F_{IS}$.

First, for a fixed mutation rate whatever the rates of asexuality, decreasing high rates of asexuality.

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**Figure 2.** Discrete probability density distributions of $F_{IS}$ at equilibrium as a function of the rate of asexuality, $c=0$ (black), 0.3 (grey), 0.5 (purple), 0.7 (bleu), 0.9 (green), 0.99 (yellow), 0.999 (light orange), 0.9999 (dark orange), 1 (red). Results obtained for $N=140$ and $\mu=10^{-3}$.

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**Figure 3.** Discrete probability density distributions of $F_{IS}$ at equilibrium as a function of the rate of asexuality, $c=0$ (black), 0.3 (grey), 0.5 (purple), 0.7 (bleu), 0.9 (green), 0.99 (yellow), 0.999 (light orange), 0.9999 (dark orange), 1 (red). Results obtained for $N=60$ and $\mu=10^{-5}$.

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increasing genetic drift by decreasing population size increased probabilities of fixations. It also spread the distributions of $F_{IS}$ toward extreme values and increased the probabilities of $F_{IS}$ on the edge of the distributions while it decreased the probabilities of middle values that surrounded $F_{IS} = 0$. In addition, decreasing population size contributed to shift more obviously the whole probability densities towards one direction that depended on the rates of asexuality: under 0.9 of asexual events, the probability densities shifted to positive values while population size decreased, whereas above 0.9 of asexual events, the probability densities shifted to negative values as the genetic drift tended to fix heterozygotes in asexual lines. Decreasing population sizes moved the threshold rate of asexuality that demarcated intermediate and high asexuality as identified previously by their respective typical thresholds of asexuality demarcated intermediate and high asexuality. Conversely, when mutation rates prevailed over drift, the distribution remained quite symmetrical even under high mutation rates, the states of fixation aside, tended to spread out as the population size increased. When population size decreased, the variance of $F_{IS}$ tended to increase excepting when rates of asexuality were about $N - 1$. Dynamically, increasing the mutation rate increased the probability to change the sign of $F_{IS}$ in one generation (Table 2). For a fixed population size, decreasing mutation rates massed the probability densities on $F_{IS}$ intervals that were more likely at higher mutation rates. Those most common genotypic states themselves depended on an interaction between mutation rate, rate of asexuality and drift pressure. As a result, by decreasing mutation, thus giving scope for drift, probability densities shifted either to positive $F_{IS}$ values for rates of asexuality lower than 0.9 (for population sizes of 60 and 140) or to negative $F_{IS}$ values when rates of asexuality were above 0.9 (Table 1). Dynamically, increasing the mutation rate increased the probability to change the sign of $F_{IS}$ in one generation (Table 2).

Distribution summarized as the four first moments of the distributions
Because previous authors mainly focused on mean and variance of $F_{IS}$ [19,22], we wanted to assess if summing the distributions using their first moments could be trusted to describe the variations of distributions of $F_{IS}$ obtained under various levels of asexuality, drift and mutation forces, and to compare them to previous theoretical results.

First, for population sizes of 60 and 140 individuals, the means of the possible distributions of $F_{IS}$ decreased with increasing rates of asexuality whatever the population size and the mutation rate (Figure 5). Means of $F_{IS}$ gave evidence for two strengths of effects of asexuality on genetic diversity: intermediate rates of asexuality ($0 < c \leq 0.9$) smoothly impacted genetic diversity while high rates of asexuality ($0.9 < c \leq 1$) did it roughly.

Second, variance of $F_{IS}$ globally tended to increase with the rates of asexuality (Figure 6). Interestingly, at high mutation rates ($m \geq 10^{-3}$ for $N = 140$), the variance of $F_{IS}$ continuously increased with the rates of asexuality, reaching its highest values in fully asexual populations. However, lower mutation rates decreased the variance of the possible distribution of $F_{IS}$ in nearly-fully and fully asexual populations because, out of fixation, the distributions of $F_{IS}$ massed on $F_{IS} = -1$ mainly due to drift that fixed heterozygotes. Those distributions of $F_{IS}$ massed on $F_{IS} = -1$ at low mutation rates, the states of fixation aside, tended to spread out as the population size increased. When population size decreased, the variance of $F_{IS}$ tended to increase excepting when rates of asexuality were about $N - 1$. Dynamically, increasing the mutation rate increased the probability to change the sign of $F_{IS}$ in one generation (Table 2).

Third, the distributions of $F_{IS}$ showed positive skewness meaning that the distributions massed on negative values and showed longer right tail to positive $F_{IS}$ values (Figure 7). It decreased with increasing rates of asexuality until 0.9, demonstrating that the distributions tended to be symmetrically shaped around their mean. Then, when the rates of asexuality reached 1, the distribution of $F_{IS}$ strongly skewed on $F_{IS} = -1$ and thus were only right-tailed, showing high positive values of skewness. This occurred when low mutation rates allowed the genetic drift to fix the heterozygotes. Conversely, when mutation rates prevailed over drift, the distribution remained quite symmetrical even under high and full asexuality.

Fourth, the distributions of $F_{IS}$ showed positive excesses of kurtosis (compared to a similar Gaussian distribution) whatever the rates of asexuality meaning that the distributions showed fatter tails than expected from a Gaussian distribution (Figure 8). Interestingly, the mutation rates strongly influenced the shape of the distributions when populations reproduced through high or even full asexuality. Low mutation rates resulted in extremely peaky distributions of $F_{IS}$ in full asexual populations as the values massed on strong negative $F_{IS}$ and in fatter tails than expected considering such peak of values around the means. Those peaky and fat-tailed shapes smoothed with increasing population sizes or at higher mutation rates as the drift released its pressure to fix...
heterozygosity in the populations. Overall, when the rates of asexuality increased, the probability to observe negative \( F_{IS} \) increased faster than the decrease of the means of their distributions, acknowledging that the mean value of \( F_{IS} \) is quite inadequate to report clear expectations about the kind of \( F_{IS} \) values we should expect within data.

Variation of allelic identities in partially asexual populations at equilibrium

At equilibrium, the discrete distributions of allelic identities between individuals (\( Q_b \)) of populations reproducing with less than 0.9 of asexuality were very similar to those obtained in fully sexual population (Figure 9). Conversely, beyond 0.9 of asexuality, the distributions of \( Q_b \) strongly differed from those obtained under full sexuality. Beyond 0.9 of asexuality, increasing rates of asexuality increased the excess of low identities (\( Q_{b,0.7} \)), while it decreased the probability of high values (\( Q_{b,0.7} \)). Those distribution properties remained similar when the mutation rate increased even if at \( m = 1 \times 10^{-3} \) (Figure S1) the distributions of \( Q_b \) obtained in highly and pure asexual populations shaped more like the ones from intermediate and pure sexual populations.

The discrete distributions of allelic identities within individuals (\( Q_w \)) showed more intricate patterns than the distributions of \( Q_b \).

### Table 1. Probabilities of negative and positive \( F_{IS} \) excluding the states of fixation, and probabilities of allele fixation expected considering fixed population sizes \( N \), mutation rates \( \mu \), and rates of asexuality \( c \) after an infinite number of generations.

| \( N \) | \( \mu \) | \( m \) | \( c \) | \( \mu \) | \( m \) | \( c \) | \( \mu \) | \( m \) | \( c \) | \( \mu \) | \( m \) | \( c \) | \( \mu \) | \( m \) | \( c \) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 60 | 10^{-8} | 10^{-6} | 10^{-3} | 10^{-8} | 10^{-6} | 10^{-3} | 10^{-8} | 10^{-6} | 10^{-3} | 10^{-8} | 10^{-6} | 10^{-3} | 10^{-8} | 10^{-6} | 10^{-3} |
| 0.0 | 0.773781 | 0.773717 | 0.714740 | 0.764626 | 0.764442 | 0.622993 | 0.782444 | 0.782382 | 0.724187 | 0.771232 | 0.771050 | 0.630751 | 0.793511 | 0.793449 | 0.736088 |
| 0.5 | 0.813326 | 0.813266 | 0.757360 | 0.797564 | 0.797392 | 0.660175 | 0.862251 | 0.862196 | 0.801212 | 0.840439 | 0.840284 | 0.709600 | 0.961651 | 0.961606 | 0.915361 |
| 0.9 | 0.998973 | 0.99969 | 0.963072 | 0.999858 | 0.999839 | 0.898220 | 1.000000 | 1.000000 | 0.963778 | 1.000000 | 1.000000 | 0.899581 | 0.999973 | 0.999969 | 0.963072 |

Negative and Positive \( F_{IS} \) under Partial Clonality

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Table 2. Average probabilities to change the sign of $F_{IS}$ and to keep it one generation further considering fixed population sizes $N$, mutation rates $\mu$, and rates of asexuality $c$ at a biallelic locus.

| $N$ | $c$ | $\mu = 10^{-8}$ |  | $\mu = 10^{-3}$ |  |
|-----|-----|-----------------|-----------------|-----------------|-----------------|
|     |     | Stay $F_{IS}<0$ | Change to $F_{IS}<0$ | Stay $F_{IS}>0$ | Change to $F_{IS}>0$ |
|-----|-----|-----------------|-----------------|-----------------|-----------------|
|     |     | 0.199036 | 0.156860 | 0.363895 | 0.280209 | 0.199050 | 0.156847 | 0.363864 | 0.280239 |
| 0.1 |     | 0.232245 | 0.123651 | 0.266858 | 0.377246 | 0.232122 | 0.123774 | 0.267294 | 0.376809 |
| 0.2 |     | 0.259695 | 0.096201 | 0.189838 | 0.454266 | 0.259493 | 0.096403 | 0.190475 | 0.453628 |
| 0.3 |     | 0.280082 | 0.075814 | 0.138402 | 0.505701 | 0.279856 | 0.076040 | 0.139027 | 0.505076 |
| 60  | 0.5 | 0.305006 | 0.050890 | 0.085475 | 0.558629 | 0.304796 | 0.051100 | 0.085962 | 0.558141 |
| 0.7 |     | 0.318537 | 0.037360 | 0.060775 | 0.583329 | 0.318353 | 0.037543 | 0.061194 | 0.582910 |
| 0.9 |     | 0.326790 | 0.029107 | 0.046520 | 0.597584 | 0.326627 | 0.029270 | 0.046913 | 0.597190 |
| 0.999 |     | 0.329770 | 0.026126 | 0.041445 | 0.602658 | 0.329615 | 0.026281 | 0.041836 | 0.602267 |
| 1   |     | 0.329798 | 0.026099 | 0.041399 | 0.602705 | 0.329643 | 0.026254 | 0.041790 | 0.602314 |
| 0.2 |     | 0.182093 | 0.160231 | 0.333721 | 0.303955 | 0.182093 | 0.160231 | 0.333636 | 0.304040 |
| 0.1 |     | 0.229637 | 0.112687 | 0.212664 | 0.529250 | 0.229454 | 0.112869 | 0.213200 | 0.444476 |
| 0.2 |     | 0.263149 | 0.079175 | 0.128427 | 0.529250 | 0.262910 | 0.079414 | 0.128986 | 0.528690 |
| 0.3 |     | 0.283647 | 0.058677 | 0.087625 | 0.570052 | 0.283419 | 0.058905 | 0.088056 | 0.569620 |
| 140 | 0.5 | 0.304871 | 0.037453 | 0.052847 | 0.604829 | 0.304688 | 0.037635 | 0.053141 | 0.604536 |
| 0.7 |     | 0.315231 | 0.027092 | 0.037583 | 0.620093 | 0.315082 | 0.027241 | 0.037821 | 0.619855 |
| 0.9 |     | 0.321255 | 0.021068 | 0.028991 | 0.628686 | 0.321129 | 0.021194 | 0.029204 | 0.628473 |
| 0.999 |     | 0.323380 | 0.018944 | 0.025985 | 0.631692 | 0.323262 | 0.019061 | 0.026192 | 0.631485 |
| 1   |     | 0.323399 | 0.018924 | 0.025957 | 0.631719 | 0.323282 | 0.019042 | 0.026164 | 0.631512 |

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Figure 5. The means of the possible distributions of $F_{IS}$ were obtained from populations of 60 individuals mutating at a rate of $10^{-8}$ (dark blue) and $10^{-3}$ (light blue), and from populations of 140 individuals mutating at a rate of $10^{-8}$ (red) and $10^{-3}$ (orange). doi:10.1371/journal.pone.0085228.g005
Figure 6. The variances of the possible distributions of $F_{IS}$ were obtained from populations of 60 individuals mutating at a rate of $10^{-8}$ (dark blue) and $10^{-3}$ (light blue), and from populations of 140 individuals mutating at a rate of $10^{-8}$ (red) and $10^{-3}$ (orange). doi:10.1371/journal.pone.0085228.g006

Figure 7. The skewnesses of the possible distributions of $F_{IS}$ were obtained from populations of 60 individuals mutating at a rate of $10^{-8}$ (dark blue) and $10^{-3}$ (light blue), and from populations of 140 individuals mutating at a rate of $10^{-8}$ (red) and $10^{-3}$ (orange). doi:10.1371/journal.pone.0085228.g007
and its shape varied with the rate of asexuality (Figure 10). First, all distributions of $Q_w$ came with two modes: a mode at high allelic identities ($Q_w = [0.9,1.0]$) mainly due to the prevalence of the drift at such small population size ($N = 140$) over the mutation rates ($m = 10^{-8}$ and $10^{-9}$) and a second mode found at intermediate $Q_w$ values ($Q_w = [0.5,0.6]$). When the rate of asexuality increased, the second mode shifted to lower $Q_w$ values while the lower tail of the distributions of $Q_w$ fattened. As a result, intermediate asexual populations ($0 < c < 0.9$) compared to fully sexual population globally showed a lower peak at the second mode ($Q_w \sim 0.55$), lower probabilities of $Q_w$ superior to the second mode and higher probabilities of $Q_w$ inferior to the second mode. Interestingly, the proportion of $Q_w$ values around the smaller mode faithfully varied according to the rates of asexuality, even regarding low rates, and this property remained even at $m = 10^{-9}$ (Figure S2).

Figure 8. The kurtosis excesses of the possible distributions of $F_{IS}$ were obtained from populations of 60 individuals mutating at a rate of $10^{-8}$ (dark blue) and $10^{-3}$ (light blue), and from populations of 140 individuals mutating at a rate of $10^{-8}$ (red) and $10^{-3}$ (orange).

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Figure 9. Discrete probability density distributions of allelic identities between individuals ($Q_b$) at equilibrium for a population size of 140 individuals and a mutation rate of $10^{-8}$ as a function of the rate of asexuality, $c = 0$ (black), 0.3 (grey), 0.5 (purple), 0.7 (blue), 0.9 (green), 0.99 (yellow), 0.999 (light orange), 0.9999 (dark orange), 1 (red).

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Typology of the distributions of $F_{IS}$

We distinguished three main types of distributions whose ranges varied with the rates of asexuality for fixed population sizes and mutation rates. The first type of distributions seemed to happen when $1-c$ was smaller than $1/N$. Previous authors conclude from predicted mean and simulated variance of $F_{IS}$ that intermediate asexual populations should show the same pattern of genetic variation as found in fully sexual populations [19, 22, 24]. Excluding selective considerations, it implies that populations of individuals producing 90% of their descent asexually should decrease the putative costs of their sexual reproduction with low or even no genetic consequences. By the way, benefits of full sexuality should not be searched in its consequences on the evolution of genetic diversity [27]. We also found few differences between fully sexual and intermediate asexual populations considering only the mean of their distribution of $F_{IS}$. But considering their whole discrete distribution of $F_{IS}$, we found that intermediate asexual populations ($0 < c < 0.99$ for a populations of $\sim 100$ individuals) showed excesses of faintly negative $F_{IS}$ ($-0.3 \leq F_{IS} < -0.1$) and deficits of slightly positive $F_{IS}$ ($0 \leq F_{IS} < 0.1$) when compared to the corresponding fully sexual populations. Interestingly, at those rates of asexuality, most of the distributions of $F_{IS}$ ranged between $-0.3$ and $0.1$. By the way, the probabilities to observe negative $F_{IS}$ increased against the probabilities to observe positive $F_{IS}$. This effect can be illustrated by a simple example considering a population at $(\alpha 0 \alpha 1: A A:V):$ through sexual reproduction, if we draw the heterozygous parent, we have only one chance on two to take its minor allele and thus to result in an heterozygous descent. Through an asexual event, we have the same probability to draw the heterozygous parent but a full chance that this draw actually results in a heterozygote. Thus asexuality retains to the genetic diversity of the heterozygous parent but a full chance that this draw actually results in a heterozygote. Thus asexuality retains to the genetic diversity of the heterozygous parent. However, increasing asexuality until 0.9 slightly increased the variance of $F_{IS}$, but clearly decreased its skewness and its kurtosis, which finally, increased the occasional occurrence of high positive $F_{IS}$ values while most of the distributions moved slightly to negative $F_{IS}$.

The second type of distributions happened when $1-c$ was about $1/N$. Such highly asexual populations ($0.99 \leq c < 1$ for populations of $\sim 100$ individuals) showed specific distributions of...
increased the variance of $F_{IS}$

Previous simulations [20] multi-allelic loci of 99 alleles in a metapopulation of 30 demes of 30 individuals, migration rate 0.1, mutation rate $10^{-5}$ performed using Easypop [41] show that the highest standard errors of $F_{IS}$ should be found in highly asexual rather than in fully asexual populations. From those results, a framework was proposed to qualitatively infer the rate of asexuality from genetic data: four scenarios among the seven described rely on small or high variations of $F_{IS}$ among genotyped loci to disentangle highly asexual populations from fully asexual ones [29]. Our mathematical model formalizing the full distributions of $F_{IS}$ at biallelic loci in single finite populations showed that the third type of distribution (all the distribution massed on $F_{IS} = -1$) only occurred in small fully asexual populations at low rates of mutation (e.g., smaller than $10^{-5}$ for a hundred of fully asexual individuals). When genetic drift was low in front mutation, the distributions of $F_{IS}$ in fully asexual populations were very close to those obtained from similar highly asexual populations and thus mainly spread from $-1.0$ to $0.0$ with substantial occurrences of high $F_{IS}$ values, covering all the spectrum of possible $F_{IS}$ values. Interestingly, large populations of insects seem more prone to reproduce asexually than small ones [42], may be because the consequences of asexuality on the evolution of their genetic diversity are then so close to those obtained with more sexuality that the two-fold cost of sex would not be counter-balanced by any genetic advantage coming from sexual reproduction?

When genetic drift was low in front mutation, the variance of $F_{IS}$ continuously increased with increasing rates of asexuality and reached its highest value when populations were fully asexual. In our example, even with a physical occurrence of a mutation in the population every $\sim$10 generations, the maximal variance of $F_{IS}$ was still obtained in fully asexual populations rather in highly asexual populations. Interestingly, in a highly asexual nematode [46] have a substantial probability to provide homozygotes and get back the population to $F_{IS} \in [-1/3, 0]$ in very large populations. Only a preponderant genetic drift may drive the population to the unstable point $F_{IS} = -1$ as most events of mutation, rearrangement and recombination such as gene conversion as observed in the bdelloid rotifer Adineta vaga [46] have a substantial probability to provide homozygotes and get back the population to $F_{IS} \in [-1/3, 0]$. Notice that a preponderant genetic drift through multinomial drawings should equally drive the full asexual population to fix one of the two alleles and thus to dynamically walk through some genotypic states showing homozygote excesses. Those results are in accordance with the variance of $F_{IS}$ that continuously increased with the rates of asexuality. As consequence, a small but substantial group of loci along the genomes should present homozygote excesses even in highly and fully asexual species. Likewise, at one locus at the scale of a species, a small number of isolated populations should present homozygote excesses while most of the other populations should present heterozygote excesses. This result offered new insights considering the transposition of the Meselson effect [11] at the scale of a population and the expected Muller’s Ratchet accumulation of mutations over the asexual lines [47]. As soon as a clade evolves from multiple individuals with mutation, and not only from a single individual as specified in Meselson effect [11], we should not expect only heterozygotes in a population at most polymorphic sites along the genome even after an infinite number of generations. Indeed, without selection at one locus, all incoming mutation in an asexual line has to struggle against the same mutational drift with the disadvantage that its original ancestral genotype is often already present at a high frequency in the population [48]. Besides, considering loci with a finite number of alleles like SNP, mutation has also substantial probabilities to provide homozygote from heterozygote over generations, especially if a strong mutational bias changes the DNA message towards the same nucleobase [49]. In the light of our results obtained after an infinite number of generations and the recent experimental
advances on asexuality and hybridization, highly divergent alleles within genomes in asexual individuals may rather be understood as recent asexual lines triggered by interspecific hybridization as found for example in some vertebrate species [50] or as asexual lines evolving under diversifying selective forces, like heterosis or incoming from rare sexual events involving allogamy [8], than ancient asexual lines that would have accumulated independent mutation on their homologous copies of genomes. Even in a demonstrative study reporting only $F_{IS} = -1$ [51], the high genetic variability observed between separate clonal lineages, the evidences of heterozygote loci that switched to homozygosity due to mutation and the measures of strong negative $F_{IS}$ even in recombining populations rather support such scenarios than ancient asexuality through few breeders.

Moreover, under an evolution without selection, our model demonstrated that we still expected in average 5% chance to change of $F_{IS}$ sign from one generation to another, provided that some mutation (or gene conversion) may result in creating some homozygotes, so that some loci may present heterozygote excesses at one generation then homozygote excesses at the population scale. More than ever in partially, highly and fully asexual species, sampling effects have thus to be considered because a bias scheme or an insufficient numbers of populations, individuals and loci may result in erroneous biological conclusions. *Daphnia pulicaria* populations show huge variations of $F_{IS}$ over the years [28]. For example, the Bristol population shows in 2002 the genotypic proportions expected under Hardy-Weinberg equilibrium, then strong heterozygote excess in 2004 and finally strong homozygote excess in 2005. They discuss that those variation of $F_{IS}$ may be due either to varying frequencies of sex in their populations, or to some random fluctuations in selection intensity or to the fact that different combinations of genes may result in the same favored phenotype at different times. Similarly, in cyclically asexual populations, clonal erosion, recurrent reduction in population sizes or some selective events favoring the dominance of some asexual lineages were proposed as causes to explain the change of $F_{IS}$ over years [29]. However, the stable genotypic diversity ratio over years and the high number of pairs of loci significantly in linkage disequilibrium in *Daphnia pulicaria* populations support stable biological features over the years [28].

A parsimonious explanation would be that these populations reproduced using the same rates of asexuality summed over the year (same proportion of partially and fully asexual lines within), years after years, and only evolved showing the typical stochastic variations of $F_{IS}$ we expect under partial asexuality considering mutation and drift forces alone.

### Perspectives to infer rates of asexuality from $F_{IS}$ values

Our model provided new perspectives to infer rates of asexuality from genetic dataset, especially at low rates ($0 < c < 0.9$ for population of about one hundred individuals). Indeed, the inference of the effective rates of asexuality from genetic data without *a priori* remains one of the main expectations accounting for the theoretical development of population genetics tools [16,25]. If the mean value of $F_{IS}$ alone should not allow inferring the rates of asexuality because of its lack of variation at low rates of asexuality [19,29], full distributions of $F_{IS}$ and analyses considering two generations (on the change of $F_{IS}$ sign for example) are promising. Proportion of negative $F_{IS}$ and of small positive $F_{IS}$ values within a population seemed to vary faithfully with the rates of asexuality, even at intermediate rates of asexuality. With the increasing facilities to easily obtain molecular data from populations, field population genetics studies may gain to confront observed and theoretical distribution of $F_{IS}$ along the genomes.

However, our results also demonstrated that the theoretical predictions strongly depended on the balance between the mutation rate (and probably mutation model) and the genetic drift. Therefore, inference of the rate of asexuality should be considered assuming some known mutation rate and population size. Moreover, the changes in $F_{IS}$ values over generations seemed the suitable genetic tool to detect few asexual events in mainly sexual populations and to indirectly distinguish them from full sexuality.

Some authors argue that indirect methods to infer rates of asexuality through population genetics models are not yet mature to be trusted [53,54]. Indeed, because models are not taking into account for most evolutionary forces and genetic complexities yet, indirect inference of high and full asexuality can even provide false estimates considering selection, epistasis and bias or insufficient sample scheme. These authors thus call to rather rely on morphological data and even to conclude from the lack of observation of morphological male in samplings or when observed, considered as not sexually functional from an expert point of view, that if there are any sexual individuals in bdelloids, daphniids and oribatids populations, they are very rare and thus can be considered as void of biological meaning [53].

Our results, as all previous population genetics models [19,23,24] and simulations [26], suggest that the corner stone of the genetic evolution of such species strongly depends on their effective rates of asexuality. A rare sexual event over some generations seems sufficient to deeply impact the genetic polymorphism and its structure within population, and so the evolutionary potential of such species.

### Conclusion

By using the full and exact distribution of $F_{IS}$, we showed that low rates of asexuality modify genetic diversity. We put out three main patterns of effects of the rates of asexuality on intrapopulational genetic diversity at equilibrium. The occurrence of those patterns depended on the balance between mutation, genetic drift and rates of asexuality. Rare asexual events in a mainly sexual population changed the shape and the symmetry of the distributions of $F_{IS}$. Moreover, when the rates of asexuality increased, the probabilities that one locus changes the sign of its $F_{IS}$ value in one generation quickly decreased in mainly sexual populations. It supports that reproductive systems at intermediate rates of asexuality have specific evolution of their genetic diversity that differ from those of similar fully sexual populations.

Our model also showed that increasing the rates of asexuality increased the variance and deeply modified the shape and the symmetry of the distributions of $F_{IS}$. In consequence, among mainly negative $F_{IS}$, the substantial occurrence of some high positive $F_{IS}$ values was still observed in highly and fully asexual populations. The specific effects of intermediate and high rates of asexuality and the full exact distributions of positive and negative values, assuming a rate of asexuality, a population size and a mutation rate, constitute new promising triggers to quantitatively infer the rates of asexuality from multiple $F_{IS}$ measures from genomic data within populations. Interestingly, heterozygote excesses at most loci along the genomes of ancient fully asexual populations can only occur in small populations of few isolated individuals evolving at low mutation rates. Finally, our results indicate that the evolutionary consequences of biological trait would benefit from being studied using the full distributions of their impacts on population genetics parameters.

### Supporting Information

**Figure S1** Discrete distributions of the density probability of allelic identities between individuals ($Q_b$) at...
equilibrium for a population size of 140 individuals and a mutation rate of $10^{-2}$ as a function of the rate of asexuality, $c=0$ (black), 0.3 (grey), 0.5 (purple), 0.7 (blue), 0.9 (green), 0.99 (yellow), 0.999 (light orange), 0.9999 (dark orange), 1 (red).

(TIF)

Figure S2 Discrete distributions of the density probabilities of allelic identities within individuals ($Q_a$) at equilibrium for a population size of 140 individuals and a mutation rate of $10^{-2}$ as a function of the rate of asexuality, $c=0$ (black), 0.3 (grey), 0.5 (purple), 0.7 (blue), 0.9 (green), 0.99 (yellow), 0.999 (light orange), 0.9999 (dark orange), 1 (red).

(TIF)

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Author Contributions

Conceived and designed the experiments: SS JPM. Performed the experiments: SS JPM. Analyzed the data: SS JPM. Contributed reagents/materials/analysis tools: SS JPM. Wrote the paper: SS. Formulated the mathematical development: SS JPM. Verified the mathematical properties of the model: JPM. Designed the software used in analysis: SS.

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