Review

A population genetics view of animal domestication

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The fundamental shift associated with the domestication of plants and animals allowed for a dramatic increase in human population sizes and the emergence of modern society. Despite its importance and the decades of research devoted to studying it, questions regarding the origins and processes of domestication remain. Here, we review recent theoretical advances and present a perspective that underscores the crucial role that population admixture has played in influencing the genomes of domestic animals over the past 10 000 years. We then discuss novel approaches to generating and analysing genetic data, emphasising the importance of an explicit hypothesis-testing approach for the inference of the origins and subsequent evolution and demography of domestic animals. By applying next-generation sequencing technology alongside appropriate biostatistical methodologies, a substantially deeper understanding of domestication is on the horizon.

Out of the wild

Although humans migrated to every habitable continent before the advent of plant and animal domestication, population sizes were small and most humans lived nomadically. The development of agriculture and farming allowed for a dramatic expansion of the global human population from approximately 6 million before agriculture to 7 billion and counting since [1]. Understanding the domestication processes that accompanied, and in part drove, this demographic shift is key to understanding the origins of modern human society.

Given its importance, and its value as a model of evolutionary and demographic change, domestication has attracted scientists from archaeology, palaeontology, anthropology, the environmental sciences, botany, zoology, and genetics. The volume of new data generated over the past two decades has been enormous [2], although the interpretation of the results has often proved difficult, and fundamental questions regarding the timing, location, process, and even definition of domestication remain (Box 1). With regard to genetic data sets, despite the exponential increase in the availability and resolving power of sequence data, their potential to contribute to a better understanding of domestication has not yet been fulfilled for a variety of reasons. Firstly, studies using modern domestic animals, even those that have typed a substantial number of nuclear genomic markers, have been generally unable to infer signatures of the earliest steps of domestication. The primary reason for this is that long-term gene flow within and between wild and domestic species, and subsequent intensive breeding practices over the past two centuries, has resulted in modern populations that bear an ambiguous resemblance to their early progenitors, thus inhibiting the ability to use present-day data to infer the past accurately [3]. Secondly, studies that have sought to overcome this hurdle by generating DNA from ancient samples have tended to focus on the mitochondrial genome. This genome is limited in its ability to infer complex demographies [4], especially when human-driven migration, admixture, and intensive sex-specific breeding practices have affected evolutionary histories.

In this review, we first synthesise recent theoretical advances and suggest how they can be applied to the field of animal domestication. We then present a population genetics perspective on the earliest and subsequent stages of domestication that demonstrates the importance of admixture and introgression in shaping the genomes of domestic animals. We conclude by assessing methodological developments that will allow for significant advances in both the appreciation of the forces influencing the genetic and phenotypic characteristics of modern domestic populations, and understanding of when, where, and even how animal domestication began.

Animal domestication as a long-term, multistage process

Darwin [5] recognised the ubiquity of a handful of traits that differentiate domestic animals from their wild progenitors. Most domestic animals have variations in coat colour as well as texture, dwarf and giant varieties, and changes in their reproductive cycle. Moreover, many animals have other features, including tooth crowding and floppy ears. Although it is easy to assume that each of these traits was uniquely selected for by hunter-gatherers and early farmers, Dmitry Belyaev believed that these features were linked and that he could reproduce them in silver foxes, an animal that had never previously been domesticated. Beginning in 1959, Belyaev tested the reactions of silver foxes to a hand placed in their cage and selected the tamest, least aggressive individuals to breed. His hypothesis was that, by selecting a behavioural trait, he could also influence the phenotype of subsequent generations, making them more domestic in appearance [6,7]. Over the next 40 years, he succeeded in producing foxes with traits that were never directly selected for, including piebald coats,

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Box 1. Defining the domestication process

The terminology used in domestication studies, including the word 'domestication' itself, often lacks consistency and is poorly defined [11]. Because domestication, similar to any evolutionary process, involves long-term and continuous change, the use of static terms is arbitrary and domestication definitions are almost as numerous as species definitions [75]. An analysis of the linguistic use of the terms applied in domestication studies offers an insight into these issues. Often, the terms 'wild' and 'domestic' have been interpreted as complementaries (i.e. terms that lack gradability and are mutually exclusive) and not as gradable antonyms. This is true despite the fact that 'wild' and 'domestic' represent earlier and later points in time of an evolutionary process and not a simple dichotomy. Because the evolution of domestic animals is ongoing, the process of domestication has a beginning but not an end. Various criteria have been established to provide a punctual definition of domestic animals, but all decisions about exactly when an animal can be labelled 'domesticated' in the zoological sense are necessarily arbitrary, although potentially useful. In prehistoric times, it took centuries or even millenia before this point was reached. The dichotomous perspective also often uses the term 'event' that consequently implies deliberate human action that can be easily replicated.

These terms limit our perspective by implicitly ruling out long-term evolutionary change as an explanation for the process of domestication. They also obscure the existence of transitional forms and complex underlying demographies, thus preventing a real understanding of the domestication process. As theoretical advances are made, newer models of domestication are dispensing with static definitions of the animal and are instead focusing on the characteristics of different stages of the process [10,11] and the human context [9,76] in which domestication takes place (Box 2).

floppy ears, upturned tails, shortened snouts, and shifts in developmental timing. A more straightforward approach was applied by Helmut Hemmer during the 1980s, who used a set of behavioural, cognitive, and visible phenotypic markers, such as coat colour, to produce a domestic fallow deer in a few generations [8].

Beyond the insight that domestic phenotypic traits could arise through selection for a behavioural trait (and vice versa), these experiments provided a mechanism to explain how the animal domestication process could have begun without deliberate human forethought and action. For example, dog domestication could have started when wolf populations were attracted to the waste products generated by human camps. Those wolves that were the least fearful of humans would have taken the most advantage of human litter, and this initial unintentional selection for tameness was the first step in a long process that, millennia later, led to the deliberate development of hundreds of modern dog breeds. Put another way, animals that were naturally wary of humans were nonetheless attracted to the niche that humans created [9], and the ability to take advantage of the human-created resources was the first step leading to domesticated animals. Humans may have then recognised correlations between phenotypes, such as coat colour variants and a tame behaviour, helping them to more easily and intentionally select for docile characteristics [8].

This multistaged model has recently been formalised by two groups [10,11]. In the view of the first group, animal domestication proceeded along a continuum of stages from anthropophily, commensalism, control in the wild, control of captive animals, extensive breeding, intensive breeding, and finally to pets [10]. This perspective allows for a slow, gradually intensifying relation between humans and animals, although each step does not necessitate continued progress along the trajectory. Recognising that not all animals entered into a domestic relation with humans in the same way, a second group characterised three separate domestication pathways: a commensal pathway, a prey pathway, and a directed pathway [11] (Box 2). These perspectives are important not only because they allow for a deeper appreciation of the animal domestication process, but also because *a priori* knowledge of the history of each species allows for the formulation of hypotheses and population models that can be tested using genetic data and statistical inference.

Although the directed pathway proceeds from capture to taming, the other two pathways are not as goal-oriented and archaeological records suggest that they take place over much longer time frames. For example, a study of molar size in pig remains spanning more than three millennia (from 12 000 to 8300 years ago [12]) at Çayönü Tepesi in Anatolia revealed a gradual decrease in the length of the molar teeth followed by a sudden decrease in their width [13]. These data were interpreted as evidence for a staged process during which pigs first altered their rooting behaviour as they began taking advantage of the refuse from human settlements, before then being subjected to demographic shifts during the initial phases of more deliberate husbandry. Any determination of when the pigs became truly domestic is necessarily arbitrary, although they did not appear domesticated (using modern morphological criteria) until the tail end of the stratigraphic sequence approximately 8300 years ago [13]. This long-term pattern of change is also evident in the archaeozoological record of the other three Near Eastern domestics: sheep, goat, and cattle [14–18]. Curiously, plant morphology has been shown to change no more quickly in a domestication setting than in wild species [19], suggesting that at least the commensal and prey domestication processes in animals require a substantial period of habituation to human niches and the corresponding selection pressures.

The role of admixture and introgression in shaping the genomes of domestic plants and animals

Once agricultural societies emerged in association with domesticated plants and animals, they often migrated away from the domestication centres, taking their domestic partners with them. As humans moved, they often encountered populations of wild animals (of the identical and/or sister species). Because domestics often shared a recent common progenitor with the wild populations that they encountered, they were capable of producing fertile offspring. Domestic populations were small relative to the surrounding wild populations, and repeated hybridisations between the two eventually led to the domestic population becoming more genetically divergent from its original domestic source population [20].

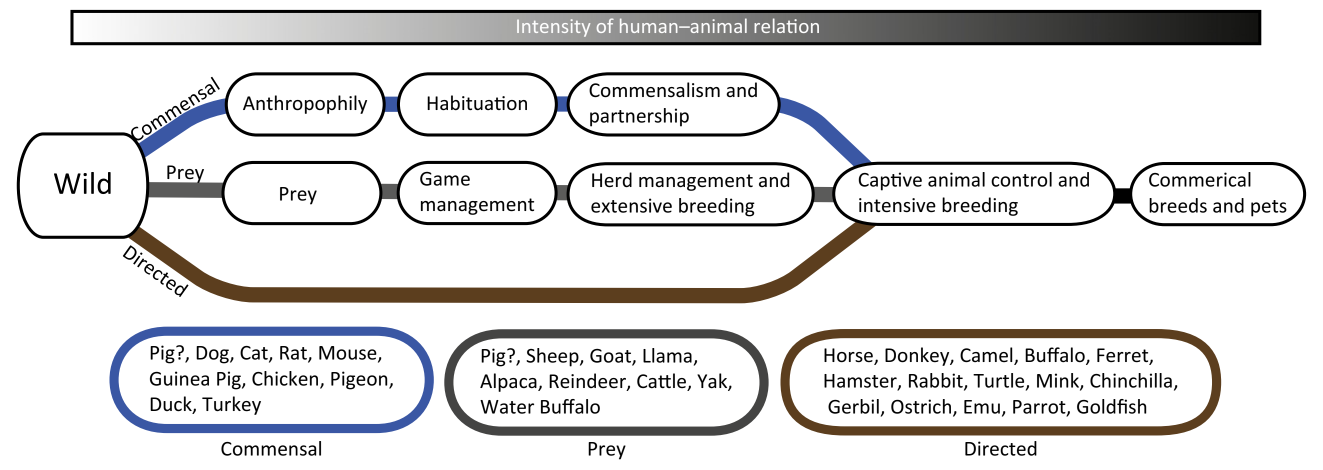
This process most likely explains why, despite the fact that robust archaeological evidence for the independent domestication of pigs in Europe is almost nonexistent, modern European domestic pigs share a mitochondrial affinity with European wild boar. Ancient aDNA studies of pigs in Anatolia and South Eastern Europe have

Box 2. Pathways of animal domestication

Demographic inferences of the early stages of domestication require a deliberate choice of appropriate models to estimate meaningfully population genetic parameter values of interest. Recognising that not all animals followed the same domestication trajectory, three separate domestication pathways were recently characterised [11] (Figure I). These general categories are crucial for considering the specific context of each domestic animal, which is key to defining appropriate population models in terms of the duration of the early capture period, the presence and size of bottlenecks, and the number and geographic distribution of potential ancestral populations.

In the commensal pathway, the animals themselves played the largest role. The initial phase of this model involved a habituation of wild animals to a human niche, most likely spurred by an attraction to human waste. Many of the earliest animal domesticates, including dogs, the only animal domesticated before the advent of agriculture, followed this pathway and, although human intentionality was possibly lacking during the earliest phases of the process, subsequent stages involved increasing degrees of deliberate human action as the relationship between humans and animals intensified [10].

Animals that were initially predated upon by humans are included in the prey pathway. These animals were first hunted away from human settlements and then more directly managed as they were brought into closer proximity with humans. Because prey animals were typically larger and more difficult to handle than those associated with other pathways, the bottlenecks are expected to be more severe and possibly over relatively shorter time frames (e.g. cattle [61]). Animals that followed the directed pathway tended to do so after humans had been living with livestock for millennia, and this group includes several household pets (e.g., hamsters) that were only domesticated during the 20th century. This trajectory skips the early phases of habituation and management and begins with the capture of wild animals with the deliberate intention of controlling their breeding. This pathway took place over much shorter time frames and was accompanied by a dramatic bottleneck. Although the domestication of each animal took place in different geographical and temporal contexts, these categories allow for a greater understanding and the development of appropriate population genetic models underlying each pathway.



TRENDS in Genetics

Figure I. A representation of the three different pathways [10,11] on top of which the rectangle depicts the increasing degree of human–animal interaction from left to right. The blue, grey, and brown lines represent the commensal, prey, and directed pathways, respectively. Selected domestic animal species by the pathway they may have entered into a domesticated relation with humans are shown in rounded rectangles. These categories are not mutually exclusive, as demonstrated most clearly by pigs. Humans hunted and moved wild boar to Cyprus [77] (among other places), suggesting that pigs went through a prey pathway, but pigs were also domesticated over several millennia at Çayönü Tepesi [13], a process consistent with the commensal pathway.

demonstrated that the first domestic pigs to enter Europe approximately 8000 years ago had mitochondrial haplotypes found only in Anatolia and the Near East [21]. Despite the fact that pigs with Anatolian and/or Near Eastern signatures were found as far west as Paris, all of the Near Eastern lineages were replaced by European signatures by 5900 years ago [21]. A more recent aDNA study demonstrated that pigs from Čayönü Tepesi in southeastern Anatolia had different lineages than those found in Western Anatolia, which were later transported into Europe [22]. In both cases, the evidence suggests that domestic pig mitochondrial signatures were replaced by wild boar signatures native to the new regions, presumably (and possibly deliberately) through repeated admixture.

The details of pig domestication in East Asia are nearly identical. Although the process of pig domestication is visible archaeologically at the Chinese site of Jiahu [23], the domestic pigs that became synonymous with the Austronesian expansion into the Pacific had signatures found not in China, but in wild boar indigenous to Peninsular Southeast Asia [24]. Similar to Europe and Western Anatolia, Southeast Asia has no archaeological evidence for a long-term domestication process. Instead, domestic pigs suddenly appear alongside wild boar [25]. These studies suggest that mitochondrial lineage introgression took place as a result of continual admixture with wild populations indigenous to regions outside the core area where the initial domestication process took place. Although mtDNA can be replaced rapidly during a hybridisation process between migrating and resident populations, the nuclear genome will retain introgression signatures over longer evolutionary timescales. Larger ancient genomic analyses, however, have thus far only been carried out on hominins [26,27], although they hold great promise for domestic animals.

These pig case studies are not unique. Hybridisation between indigenous wild populations and introduced domestic populations is common in a wide range of plant and animal species. For instance, the ubiquitous yellow leg trait found in modern commercial chickens was acquired through introgression into the domestic chicken (*Gallus gallus*) from the grey junglefowl (*Gallus sonnerati*), which is indigenous to South Asia [28]. Most African cattle are zhybrids, demonstrated by the fact that they have a European (taurine) mitochondrial signal and an Asian (indicine) Y-chromosome signature [29]. Fertile hybrids between other bovid species, including bison, yak, banteng, and gaur, also occur with regularity [30]. Lastly, cats [31] and horses [32] are known to hybridise easily with a variety of closely related species, and domestic honeybees have genomes that are more variable than their wild progenitors as a result of trade and a sustained admixture with several different populations [33].

Neither is a long history of admixture unique to animals. Hybridisation and introgression within and between plant species has also had a dramatic effect on domestic and wild populations. For instance, despite the fact that neither grapes [34] nor apples were domesticated in Europe, hybridisation between introduced domesticates and European wild forms has been substantial. In the case of apples, introgression has been extensive enough for European varieties to lose their genetic similarity to their original Central Asian progenitor [35]. In North America, gene flow between domesticated and wild maize has led to spurious conclusions about the temporal and geographic patterns of its domestication [36]. The origins of rice have been significantly complicated by hybridisation between South Asian *Oryza indica* and *Oryza japonica* native to the Yangtze basin in China [37], and a recent combined archaeological and genetic approach suggested that domesticated *O. japonica* was transported to India where it hybridised with managed *O. indica* [38]. In addition, genetic studies have demonstrated widespread introgression from introduced Asian into native African rice species [39].

This perspective suggests that there is a significant difference between initial domestication processes and subsequent movement and admixture with local wild populations. Although the latter can result in genetic signatures that are easily misinterpreted as instances of independent domestication, the two processes are entirely separate. Neither pigs nor grapes nor apples were domesticated in Europe, even though modern domestic forms of these species share a significant genetic component with populations indigenous to Europe. The current use of the term 'domestication' (Box 1) to refer both to domestication pathways [11] and subsequent instances of hybridisation with wild populations (including species or forms that were never involved in the initial process) leads to significant underappreciation of the role of admixture in the evolutionary history and shaping of ancient and modern domestic plants and animals. This bias has been perpetuated because restrictions on the type and quantity of genetic data that could be generated from ancient animal remains have limited our ability to quantify admixture directly.

The limits of mtDNA

Extracting and sequencing DNA from archaeological remains can allow for the characterisation of ancient genomes from organisms that had not yet experienced as many rounds of introgression as their modern counterparts. Historically, however, most aDNA studies generated data solely from the mitochondrial genome. These data were sufficient for differentiating between broadly defined populations and tracking population movements on a continental scale, but because mitochondrial genomes are a maternally inherited nonrecombining single locus, they lacked the power to precisely quantify degrees of admixture between populations.

These restrictions meant that significant questions, e.g., whether humans and Neanderthals ever interbred, could not be directly addressed. Using mitochondrial variation alone, several studies concluded that Neanderthals did not interbreed with anatomically modern humans (AMH) [40–42], and that the lineage from Denisova was ancestral to both the ancestors of Neanderthals and of AMHs [43]. The recent availability of nuclear genomes derived from Neanderthals and a Denisovan suggest that both forms did hybridise with AMHs [27] and that the Denisovan lineage represents a sister branch of Neanderthals [26]. This example demonstrates that the unique evolutionary history of the mitochondrial genome cannot always be extrapolated to the species as a whole [4]. Recent studies on polar bears [44] and multiple suid species in Island Southeast Asia (Frantz *et al*., unpublished data) have shown that phylogenetic trees generated using mitochondrial genomes fail to recover the true phylogeny, and instead are masked by the most recent admixture episode. This is true of any closely related species that are able to produce fertile offspring, as has been demonstrated by numerous coyotes that were shown to have dog mitochondrial genomes [45].

Generally, population genetic theory considers phylogenetic trees or networks (used in many mtDNA-based studies) to be a random result of the inheritance process [46]. It is therefore unlikely that a single marker such as mtDNA reflects complex past demographies correctly and completely. Having said that, mtDNA has several advantages. In contrast to nuclear genomic data, a rich worldwide data set and explicit hypothesis-testing modelling approaches for nonrecombining marker sets are already available [47]. Thus, despite their limitations, ancient mtDNA data sets are valuable and will remain so.

New techniques to generate data

The low copy number and fragmented nature of aDNA have traditionally limited access to the information-rich nuclear genome. Recent methodological breakthroughs have begun to overcome these limitations by using technology focused on the selection and amplification of numerous loci in parallel. Target-enrichment hybridisation capture approaches use uniquely designed baits to isolate fragments of endogenous DNA that can then be placed on a next-generation sequencing (NGS) platform capable of generating >200 million sequences per lane. Alternatively, shotgun sequencing can generate large-scale DNA data sets from ancient bone and teeth, and endogenous DNA can be separated from exogenous sources after sequencing *in silico* [48]. So far, these approaches have not yet reached the same level of sensitivity that classical PCR has, and they have only been applied to a few well-preserved skeletons. The expected sea change in the volume and subsequent resolving power of the DNA data, however, combined with the ability to assess genetic variation in ancient samples directly will revolutionise our ability to chart population diversity and structure and quantify admixture between populations.

New ways to analyse data

The field of population genetics has, perhaps more than any other biological field, developed a solid theoretic framework. Particularly interesting for domestication studies are those approaches that investigate evolutionary and demographic aspects of expanding and migrating populations using an analytic theory or spatially explicit simulation approach [49,50]. Previous work has used spatially explicit coalescent simulations to demonstrate that asymmetrical introgression regularly occurs when an expanding population migrates into territories occupied by another population [20]. This is particularly true for organelle genomes, such as mtDNA, and the direction of introgression is always from the resident population into the expanding one. This explains the replacement of the introduced Near Eastern pig mtDNA lineages by local wild boar after they arrived in Europe [21]. In cows, however, the typical mtDNA lineages of European aurochs have rarely (<1%) been observed in domestic cattle [51–53], although the asymmetrical pattern of organelle DNA replacement predicts that even a low rate of introgression would lead to this figure being far higher. The scarcity of aurochs lineages therefore suggests that cattle were intentionally kept separate from female European aurochs to prevent hybridisation from taking place [54].

Despite the progress on theoretical and modelling fronts (including the development of approaches that incorporate numerous, recombining markers), many studies continue to use standard phylogeographic approaches that make inferences based on branching patterns in phylogenetic trees and networks. These approaches have been extensively criticised [46,55,56], especially those that have made inferences of the recent human past, and these criticisms also hold true for domestic animal studies. Explicit hypothesis-testing inference methods have thus far only been applied in a handful of domestication-related contexts. For instance, several previous studies revealed a population expansion signature in European auroch populations that were interpreted as the result of a postglacial increase in population size (e.g., [51]). By explicitly testing for demographic expansion using coalescent simulations, another study [57] demonstrated that the data were more consistent with population stability than with population growth, and that previously described expansion signals were likely the result of heterochronous sampling typically used in aDNA data sets.

Using coalescent simulations, observed genetic diversity patterns, and approximate Bayes factors, another study compared different domestication models for goats and horses [58]. For goats, the study concluded that geographic structure in ancestral goat populations is required to explain the observed genetic diversity and that the overall goat population size has remained consistently large over the past 11 500 years. Alternative models assuming a single expanding population received relatively less support. For horses, the best model assumed a constant ancestral population size and no population bottleneck during domestication. This is consistent with another recent study that employed a spatially explicit approximate Bayesian computation framework (ABC [59]) using microsatellite markers typed in modern geographically diverse

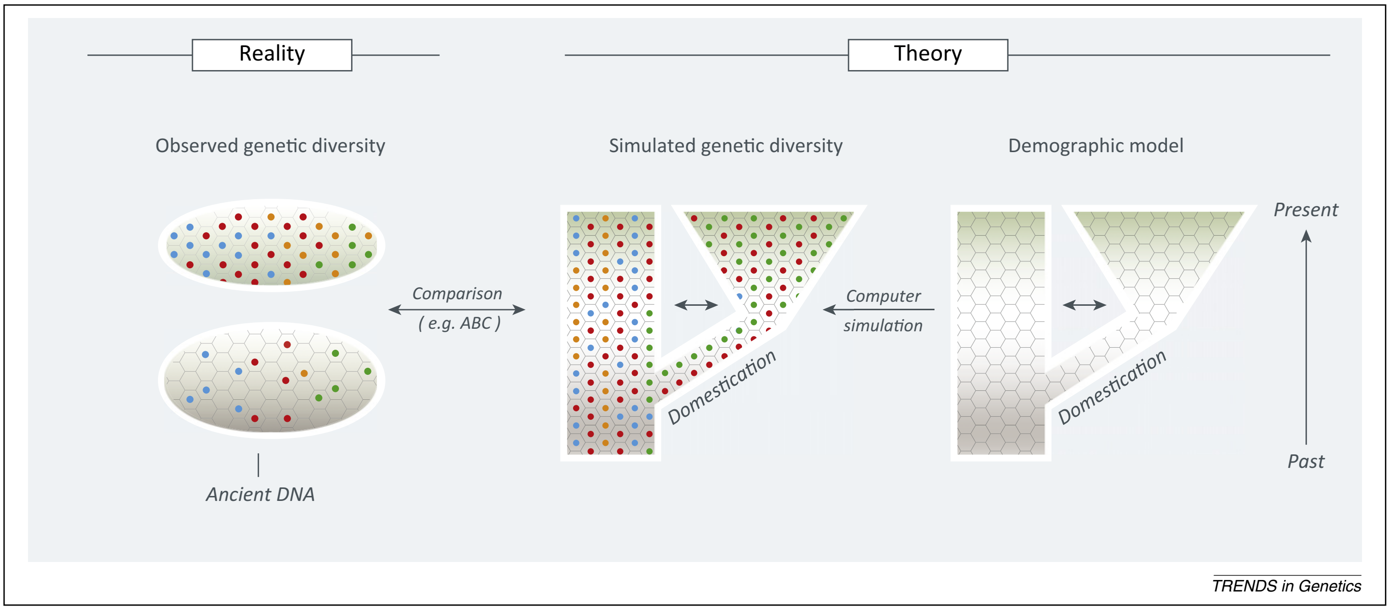


Figure 1. The principle of computer simulation-based modelling. Genetic variability in living (top) and extinct (bottom) populations (ellipses on the left) is shaped by various biological and demographic factors, and can be assessed by empirically analysing extant or fossil DNA. To establish the scenario under which the observed genetic diversity arose, computer simulation-based modelling can be very useful. Here, different evolutionary and/or demographic models (pictured on the right) can be used as a framework to simulate genetic data artificially. The simulated genetic diversity (centre) can then be compared with the observed genetic diversity (left), and the best models are those that generate simulated data that more closely fits the observed data. Approximate Bayesian computation (ABC) can then be used to select between different models by evaluating their relative performance through approximate Bayes factors. Furthermore, ABC can be used to infer parameter values, such as ancestral population size, mutation rate, degree of gene flow, or admixture. In the figure, a simple one-population-model with a long domestication bottleneck and subsequent population growth including gene flow (arrow) between the original wild and the domesticated population is shown as an example. Hexagons represent spatial structure inside the populations. Modified from [50].

Box 3. Single or multiple domestications

We propose that the term 'domestication' should refer only to the original process that led from wild animals to an early domestic population. If subsequent admixture with wild populations not originally involved in the domestication pathway occurred, this process should not be referred to as domestication even though it is part of the evolutionary history of a domestic species.

Given the length and complexity of an ongoing domestication process and the limited likelihood of its longterm evolutionary success, we suggest that the null hypothesis should be that domestication took place just once in each species, even if the process took place as part of a culturally linked process across a large region. This cautious perspective requires substantial evidence before claims for additional domestication centres can be accepted. In many cases, other more parsimonious explanations, such as genetic drift, a particular migration history, or admixture with wild animals, warrant investigation before assertions of multiple domestications can be accepted. For example, most palaeontologists and zoologists agree that taurine cattle (*Bos taurus*), goats, and sheep have a single origin in the Neolithic core zone of Anatolia and the Near East [14–18]. Claims for the independent domestication of a second domestic form of cattle in the Indus valley, the zebus (*Bos indicus*), have been made on the basis of both size change in osteoarchaeological specimens [78] and genetic variation in modern animals. Although the genomes of the two forms have several differences [79], the conclusion that they were domesticated independently is based primarily on the branching pattern of a mtDNA and Y-chromosomal DNA [80,81]. Because these topologies can arise under a variety of different demographic scenarios involving, e.g., geographical population structure, genetic drift, or hybridisation, the phylogenetic trees alone do not necessarily support an independent domestication process. Given these and other issues, there is not yet sufficient genetic or archaeological evidence to reject the null hypothesis of a single domestication in the Near East with subsequent admixture with a morphologically differentiated population in South Asia.

For pigs, the single centre hypothesis can be rejected because they were clearly domesticated independently in East Asia and in the Near East [82]. The fact that domestic pigs share mitochondrial haplotypes with wild boar in other regions, including South Asia, Europe, and South East Asia, does not imply additional, independent domestication centres for pigs. Instead, as we describe in the main text, the procurement of wild boar haplotypes outside the original centres of domestication was probably the result of introgression and asymmetric acquisition of organelle DNA. In dogs, numerous studies claim that they were domesticated once in East Asia [83,84], whereas others have suggested more widespread origins (Pionier-Capitan *et al.*, unpublished data) [85,86], and it is possible that the starting hypothesis of a single origin for dogs will be rejected. In general, our proposal will help to obviate untenable claims for numerous independent centres.

horses to conclude firstly that horse domestication originated in western Eurasia and, secondly, that domestic horses experienced significant introgression from wild horses across their range [60]. Lastly, a study using both ancient and modern cow DNA concluded on the basis of serial coalescent simulations and ABC that the modern cattle population could have arisen from the capture and breeding of only 80 female aurochs [61].

More generally, analytical methods, including explicit modelling techniques, can test for and quantify admixture (e.g., [62–65]). Such approaches can be used to develop and test hypotheses (using both genetic and archaeological data) regarding the origins and subsequent movement of domestic plants and animals. Modelling methods occasionally produce results that are less intuitive and/or less intriguing than narratives that stem from the interpretation of branching patterns of phylogenetic trees. Statistically robust hypothesis-testing approaches, however, are advantageous because they have a greater likelihood of revealing the actual evolutionary history. Computer simulation methods have been shown to be efficient at testing different evolutionary and demographic models. Simulated and observed patterns of genetic variation can then be contrasted, for example through ABC [59], allowing for the estimation of parameter values that could have produced the observed data set under a specific population model (Figure 1). Using this kind of approach and NGS-generated multilocus DNA data from ancient and modern sources will enable different domestication scenarios to be rigorously assessed, thus allowing for unprecedented insights into many of the outstanding questions related to the domestication process itself (Box 3).

Concluding remarks

This short review has focused primarily on the use of genetics to understand the origins of animal domestication. Of course, there are numerous questions beyond the

Box 4. How milk from domestic cattle shaped the human gene pool

The domestication of animals has had several genetic consequences for humans. In fact, one of the strongest signatures of positive selection in the human genome is associated with the ability to consume significant amounts of milk in adulthood without suffering from digestive problems [87]. In most mammals, including humans, production of the lactase enzyme is usually downregulated after weaning. This enzyme is responsible for hydrolysing the disaccharide lactose into monosaccharides, thus making milk digestible. Using milk from their domestic animals, Neolithic farmers developed cheese and yogurt. Because natural bacterial activity reduces the lactose content in these products, farmers could benefit from the nutritional advantages of milk [88] without suffering the consequences of being lactose intolerant.

Although this cultural solution was available, a relatively recent C to T mutation (–13 910*T), which is involved in the regulation of the continued production of lactase into adulthood, is widespread in European populations, especially in the North and Northwest regions of the continent [89]. Strikingly, the frequency of the –13 910*T allele is extremely low in prehistoric skeletons of early farmers, even in areas where the frequency of the allele in modern human populations is between 50% and 80% [90]. To explain this rapid increase since the Neolithic, spatially explicit computer simulations combined with an ABC approach were carried out. The study concluded that natural selection first began driving up the frequency of the allele approximately 8000 years ago in Southeast Central Europe, and that the allele further increased in frequency on the wave front of the Neolithic expansion mainly towards the North and Northwest, aided by positive selection [91]. This inference is consistent with archaeological and palaeogenetic evidence associated with the early spread of cattle and farmers into Central and Northern Europe [92].

This coevolution of domestic animals, dairy culture, and lactase persistence also led to the independent rise of lactase persistence in various geographically isolated pastoralist and farming groups in Africa and the Middle East, presenting a striking example of convergent evolution [93]. The history of this trait demonstrates how milkable cows (or goats) exerted an enormous influence on the gene pool of a considerable proportion of the global human population [94].

fundamental issues of where, when, and how many times domestication took place, and many have been successfully addressed using genetic data (e.g., Box 4). For example, the establishment of kennel clubs and closed breeding lines over the past 200 years created hundreds of dog breeds that have both uniform phenotypic traits and long haplotype blocks. This genomic structuring has eased the process of identifying (both coding and regulatory) mutations underlying numerous phenotypic traits and diseases using genome-wide association studies [66].

Other studies have also investigated the genetic basis of coat colour variation in domestic animals because even recently domesticated animals have huge differences relative to each other and to their wild ancestors. To date, more than 300 genetic loci and 150 genes associated with coat colour variability have been identified [67]. Knowing the mutations associated with different colours has facilitated studies that demonstrated the temporal correlation between the appearance of variable coat colours in horses with the timing of their domestication [68]. Other studies have shown how human-induced selection is responsible for the allelic variation in pigs [69]. Together, these insights suggest that, although natural selection has kept variation to a minimum before domestication, humans have actively selected for novel coat colours as soon as they appeared in managed populations [70].

Lastly, studies of modern animal genomics using selective sweep detection, candidate gene studies, and other tools to assess evolutionary forces that shape genetic variability have led to a greater understanding of the genes and regions that have been most influenced through the selection processes inherent during domestication [71]. These studies have identified the genetic basis of, for example, muscle growth in pigs [72] and a so-called 'domestication gene' that was influential at the origins of chicken domestication [73]. The use of high-density markers has also allowed for the quantification of the reduction in genetic variability in commercial chicken populations relative to noncommercial breeds [74].

The success of genetic tools to characterise the differences between wild and domestic populations highlights the relative lack of progress that has been made in understanding the origins of domestic animals. This is set to change. A greater theoretical appreciation for both different domestication pathways and the crucial role played by admixture once domestic populations arose will allow for more refined hypotheses to be generated. Testing these hypotheses in a sound statistical framework that incorporates genetic, archaeological, climatic, and anthropological data will be possible through the twin development of both sequencing technologies (capable of generating large-scale genomic data sets of modern and ancient samples) and new modelling approaches for genome-wide data. Armed with these approaches and tools, we will soon begin to fulfil the potential of genetic studies to answer the major outstanding questions regarding animal domestication.

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