On the origin of SARS-CoV-2–The blind watchmaker argument

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Abstract

In the comparison with SARS-CoV of 2003, SARS-CoV-2 is extremely well adapted to the human populations and its adaptive shift from the animal host to humans must have been even more extensive. By the blind watchmaker argument, such an adaptive shift can only happen prior to the onset of the current pandemic and with the aid of step-by-step selection. In this view, SARS-CoV-2 could not have possibly evolved in an animal market in a big city and even less likely in a laboratory. Discussions of the origin of SARS-CoV-2 need to factor in the long process of adaptive shift and some models have indeed advanced in that direction.

Full Text

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Compared to SARS-CoV from 2003, SARS-CoV-2 is extremely well adapted to human populations, and its adaptive shift from animal hosts to humans must have been even more extensive. According to the blind watchmaker argument, such an adaptive shift could only have occurred prior to the onset of the current pandemic through step-by-step selection. From this perspective, SARS-CoV-2 could not have possibly evolved in an animal market in a major city, and a laboratory origin is even less likely. Discussions of SARS-CoV-2’ s origin must therefore factor in this long process of adaptive shift, and some models have indeed advanced in this direction.

There have been many recent calls for continued investigations into the origin of SARS-CoV-2 from both non-academic and academic circles, exemplified by a recent letter (Bloom et al., 2021). This Insight piece is a commentary on the biological origin based strictly on scientific principles and is not directed toward any particular non-scientific viewpoint.

Indeed, some have argued that SARS-CoV-2 could not have evolved in nature (Sallard et al., 2021; Segreto and Deigin, 2020), based on genomic features that the authors consider unexpected. Since no known natural law prohibits the SARS-CoV-2 genome from evolving to its current state, claims of a non-natural origin are moot. Unless strains bearing definitive signatures of human design (such as barcoding, as is commonly done for tracing cell lineages) can be found, it would be more productive to focus on natural processes related to SARS-CoV-2' s origin.

In this response, we first ask that the meaning of "origin" be clarified when calls for investigation are made. The origin of any living organism—be it humans, dogs, or flowering plants—is typically a prolonged process of evolution with many steps of refinement. Early evolution usually stretches across evolutionary timescales and sometimes over large geographical areas. If we treat origin merely as an event at a particular time and place, disagreements naturally arise. What, then, does the origin of SARS-CoV-2 mean? It should be about how, when, and where SARS-CoV-2 evolved to become so perfectly adapted to human conditions. The starting point may be assumed to be a viral strain well adapted to some wild animals; hence, there must have been an adaptive shift from animal hosts to humans.

The process of adaptive shift is an example of complex evolutionary adaptation cogently argued in Richard Dawkins' s popular book *The Blind Watchmaker*. In William Paley's 1794 view (Paley, 1829), perfect adaptation—akin to an exquisite watch—implies a non-natural process (a creator) that defies evolutionary theory. This misunderstanding is the crux of Dawkins' s blind watchmaker argument, which prescribes a series of steps, each selecting for slight improvements from random assortments of tinkering. Step by step, the culmination of a long series of improvements emerges as a perfect package (Dawkins, 1996).

The process of adaptive shift should be the central issue in SARS-CoV-2' s origin but has unfortunately been conspicuously neglected. Popular views on SARS-CoV-2' s origin fall into two categories. The first concerns possible natural origin, in which some wild animals harbor SARS-CoV-2 fully adapted to human populations at the time of human-animal contact. This "pre-adaptation" view of perfection via random forces is what Paley objected to in favor of a Creator. Given the rapidity of spread from December 2019 onward, SARS-CoV-2 appears extremely well adapted to humans from the very beginning of the pandemic. The second category suggests SARS-CoV-2 somehow escaped from virology laboratories (which have multiple identities, depending on the proponents). The escapees are part of legitimate virological experiments involving mutagenesis, recombination, genome rearrangement, etc., and accidentally ignited the epidemic after escape. This is again a pre-adaptation view of a product of perfection at rollout.

Several lines of evidence argue against the pre-adaptation view that posits viral adaptation without natural selection. First, numerous studies have taken a "rational design"approach to altering viruses in directions such as immune escape or host range expansion (Bajic et al., 2019; Becker et al., 2008; Menachery et al., 2015). As stated in one prominent study (Menachery et al., 2015), this approach can push the virus in the desired direction but never far enough to drive an epidemic. Second, these results suggest that adaptation via natural selection would be needed. The evolutionary history of human coronaviruses (OC43, 229E, and NL63) associated with the common cold bears this out; these coronaviruses shuttled between humans and wild animals for hundreds of years prior to their global spread (Huynh et al., 2012; Normile, 2013). Third, several attempts have successfully selected for SARS-CoV-2 strains that can infect mice, which are otherwise resistant to SARS-CoV-2 infection (Dinnon et al., 2020; Gu et al., 2020; Leist et al., 2020). Apparently, the enabling mutations account for such a tiny fraction of all possible mutations that efficient screening by natural selection is required. Indeed, in the 2003-2004 SARS outbreak and in COVID-19, the power of natural selection has been amply demonstrated by increasingly successful new strains (Davies et al., 2021; Korber et al., 2020; Tegally et al., 2020; Voloch et al., 2020) that evolve in humans.

From a non-evolutionary angle, some may argue that a fully pre-adapted virus cannot be excluded. This would be analogous to R. Goldschmidt' s "Hopeful Monster" view (Goldschmidt, 1982). We wish to point out that even in this defunct view, an extremely low-probability event (i.e., the "hopeful monster") could have happened only over a long evolutionary timespan and across a large geographical region. In contrast, a low-probability event of near perfection in the form of SARS-CoV-2 has now been suggested to have occurred in a very brief period.

In our reasoning, some form of multi-step evolution in human populations must have occurred prior to the COVID-19 pandemic to account for SARS-CoV-2' s extraordinary adaptiveness. The dilemma is how this evolution could have happened if final adaptation requires completion of all steps. In the blind watchmaker argument, each refinement must confer an advantage, however small. To address this issue, a model for the incremental evolution of SARS-CoV-2 has been proposed (Ruan et al., 2021). It invokes an arms race between the virus and its animal hosts in a habitat sparsely populated by humans, referred to as PL0 (the place of origin). The virus subsequently spread to naive human populations lacking herd immunity. The place of the first epidemic, referred to as PL1, is not PL0 precisely because the human population in PL1 is immunologically naïve to the virus. This may be true for the 1918 "Spanish flu" and AIDS as well (Crosby, 2003; Sharp and Hahn, 2011).

In addition to conceptual arguments, a substantial number of seemingly unconnected reports also point to the possible existence of a PL0 distinct from PL1. One recent report specifically detected IgG in samples collected in December 2019 in the US (Althoff et al., 2021). Others include sporadic occurrences of COVID-19-like cases in earlier months of 2019 and traces of SARS-CoV-2-like material in environments across diverse geographical areas (La Rosa et al., 2021; Randazzo et al., 2020). Although such evidence is difficult to evaluate retrospectively, invasions from PL0 must have failed many times before a successful hit at PL1 due to high stochasticity in the early stages of invasion (Ruan et al., 2020;

Ruan et al., 2021). It is also known that diverse coronaviruses exist naturally in bats, and these families have ranges stretching across the entire Old World, providing many opportunities for spillover events (Zhou et al., 2021).

The issue of origin differs from many other biological questions because a theoretical model must precede experiments. An investigator conducting an empirical search needs to know what to look for, much like police need to know what a bank robbery suspect looks like. Even if the model is correct, they may not catch the suspect, but a wrong model (and in the case of COVID-19, a blank model) will not lead to a catch. In Ruan et al.' s model (Ruan et al., 2020; Ruan et al., 2021), a seafood market in a large city with heavy human and animal traffic does not have the stability required for step-by-step adaptive shift in PL0. This is only one possible scenario; nevertheless, those calling for investigations of the origin should be specific about what "origin" means.

Knowledge of SARS-CoV-2' s origin is important for the simple reason that we have had three coronavirus epidemics in the last two decades. If there is another in the next decade, understanding the origin and subsequent spread (Ruan et al., 2020; Ruan et al., 2021) is the best way to prepare.

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