

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

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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.

There have been many calls recently for the continued investigations of SARS-CoV-2 origin from both non-academic circles and academia. A recent letter is such an example (Bloom et al., 2021). This Insight piece is a commentary on biological origin based strictly on scientific

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principles. It is hence not directed toward any particular viewpoint of a non-scientific nature.

There indeed exists a line of arguments that SARS-CoV-2 could not have evolved in nature (Sallard et al., 2021; Segreto and Deigin, 2021), based on genomic features not expected by the authors. Since no known natural law prohibits the SARS-CoV-2 genome to evolve to its current state, the claim of non-natural origin of SARS-CoV-2 is moot. Unless strains that carry the definitive signature of human design (such as barcoding as is commonly done nowadays in tracing cell lineages) can be found, it would be more productive to focus on the natural processes in relation to the SARS-CoV-2 origin.

In this response, we first ask that the meaning of origin be clarified when the call of investigation is made. The origin of any living organisms, be they humans, dogs or flowering plants, is often a prolonged process of evolution with many steps of refinement. Hence, the early evolution usually stretches over an evolutionary time scale and sometimes over a large geographical area. If we treat the origin merely as an event of a particular time and place, there would naturally be disagreements. 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 the human conditions. The starting point may be assumed to be a viral strain that is well adapted to some wild animals; hence, there should be an adaptive shift from animal hosts to humans.

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

The process of adaptive shift should be the central issue of the origin of SARS-CoV-2 but, unfortunately, has been conspicuously neglected. The popular views on the origin of SARS-CoV-2 fall into two categories. The first category is about the possible natural origin. In this view, some wild animals harbor SARS-CoV-2 that are 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 the spread from December of 2019 on, SARS-CoV-2 appears extremely well adapted to humans in the very beginning of the pandemic (Hu et al., 2020). In the second category, SARS-CoV-2 somehow escaped from some virology laboratories (which have multiple identities, depending on the

proponents). The escapees are part of legitimate virological experiments of mutagenesis, recombination, genome re-arrangement, etc. They accidentally ignited the epidemics after the escape. This is again a pre-adaptation view on a product of perfection at the roll out.

There are several lines of evidence against the pre-adaptation view that posits viral adaptation without natural selection. First, there have been numerous studies taking the "rational design" approach to altering viruses in the direction of, for example, immune escape or host range (Bajic et al., 2019; Becker et al., 2008; Menachery et al., 2015). As stated in one of the prominent studies (Menachery et al., 2015), the approach can push the virus in the desired direction but never far enough to drive an epidemic. Second, the results above suggest that adaptation via natural selection would be needed. The evolutionary history of human coronaviruses (OC43, 229E, and NL63) that are associated with the common cold bears this view out. These coronaviruses had shuttled between humans and wild animals for hundreds of years prior to their global spread (Huynh et al., 2012; Nor-mile, 2013). Third, several attempts have been successful in selecting for SARS-CoV-2 strains that can infect mice, which are otherwise resistant to SARS-CoV-2 infection (Dinnon III et al., 2020; Gu et al., 2020a; Leist et al., 2020). Apparently, the enabling mutations account for such a tiny fraction of mutations that an efficient screening of mutations by natural selection is required. Indeed, in the SARS of 2003–2004 and in COVID-19, the power of natural selection has been amply demonstrated by the increasingly successful new strains (Davies et al., 2021; Korber et al., 2020; Tegally et al., 2020; Voloch et al., 2021) that evolve in humans.

From a non-evolutionary angle, some may argue that the possibility of 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 time span as well as 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 happened in a very brief period of time.

In our reasoning, prior to the onset of the COVID-19 pandemic, some forms of multi-step evolution in human populations must be the basis of the extraordinary adaptiveness of SARS-CoV-2. The dilemma is how the evolution could have happened if the final adaptation requires the completion of all steps. In the blind watchmaker argument, each refinement must confer an advantage, however small it is. To address this issue, a model on the incremental evolution of SARS-CoV-2 has been proposed (Ruan et al., 2021b). It invokes the arms race between the virus and its animal hosts in a habitat sparsely populated by humans that is referred to as PL0 (the place of origin). The virus subsequently

spread to naive human populations which do not have the herd immunity. The place of the first epidemic, referred to as PL1, is not PL0 precisely because the human population in PL1 is immunologically naive to the virus. This may be true for the “Spanish flu” of 1918 and AIDS as well (Crosby, 2003; Sharp and Hahn, 2011).

In addition to the conceptual arguments, a substantial number of seemingly unconnected reports also point to the possible existence of a PL0 that is distinct from PL1. One such recent report is specific about detecting IgG in samples collected in December of 2019 in the US (Althoff et al., 2021). Others include sporadic occurrences of COVID-19-like cases in the earlier months of 2019 as well as traces of SARS-CoV-2-like materials in the environments in diverse geographical areas (La Rosa et al., 2021; Randazzo et al., 2020). Although such evidence is difficult to evaluate in retrospect, invasions from PL0 must have failed many times before a successful hit at PL1, due to the high stochasticity in the early stage of invasions (Ruan et al., 2021a; Ruan et al., 2021b). It is also known that diverse coronaviruses exist naturally in bats, and that these families have ranges which stretch over the entire old-world, providing many opportunities for spillover events to occur (Zhou et al., 2021).

The issue of origin is different from many other biological questions because a theoretical model has to precede the experiments. An investigator carrying out the empirical search needs to know what they should be looking for, much like the 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 the catch. In Ruan et al.’s model (Ruan et al., 2021a; Ruan et al., 2021b), a seafood market in a large city with the heavy traffic of humans and animals does not have the stability required for the step-by-step adaptive shift in PL0. It is only one possible scenario; nevertheless, those who call for an investigation of the origin should be specific about what the origin means.

The knowledge of the origin of SARS-CoV-2 is important for the simple reason that we have had three coronavirus epidemics in the last two decades. If there is another one in the next decade, knowing the origin and the subsequent spread (Ruan et al., 2021a; Ruan et al., 2021b; Gu et al., 2020b; Tang et al., 2020) is the best way to be prepared.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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