

Has SARS-like Coronaviruses Been Evolving Gradually?

Kevin Surya, Jacob Gardner, and Chris Organ

Having instigated two pandemics so far, how have the broader culprits, SARS-like betacoronaviruses, been evolving? These SARS-like viruses (CoVs) naturally circulate among bats and have periodically jumped to other mammals such as civets, pangolins, and eventually humans [1–3]. Here, we test whether the SARS-like CoV genomes have evolved gradually or in a punctuated manner so that most divergences occurred during transmission events. We further test if the mode of evolution shifted once a pandemic began.

To test for punctuated evolution [4,5], we regressed total phylogenetic path lengths of SARS-like CoV genomes (root-to-tip distances) on the net number of transmission events (nodes). We acquired a molecular tree (Figure A1) of 52 genomes from [Nextstrain](#) [6,7]. And we used the maximum likelihood algorithm in BAYESTRAITS 3.0.1 [8], under a phylogenetic generalized least squares (PGLS), to estimate the parameters of the regression above. Punctuation would be consistent with a strong positive correlation. We also compared the fit of this model with two others (Figure A2 and A3), where we allowed the regression lines to vary across strains (SARS-CoV, SARS-CoV-2, and SARS-like CoV).

The most likely model, accounting for complexity, is the one with a single regression fit line (BIC = -510.55; lowest Δ BIC = 4.31). Looking at this model (Figure 1), we, however, find little evidence for a punctuated evolution (slope = $.0000044 \pm .000028$, $P = .438$; $R^2 = .0049$). Diagnostics indicate violations of linear regression assumptions (Figure A4). And, the node-density artifact [4,9], an underestimation of branch lengths in tree regions with fewer taxa, biases our analysis ($\delta = 9.46$; Figure A5). A potential source of bias is that researchers and labs sequence SARS-like CoV genomes more frequently at the onset and during a pandemic. Altogether, while the broader SARS-like betacoronaviruses may have been evolving gradually at all times, this investigation should be interpreted with care.

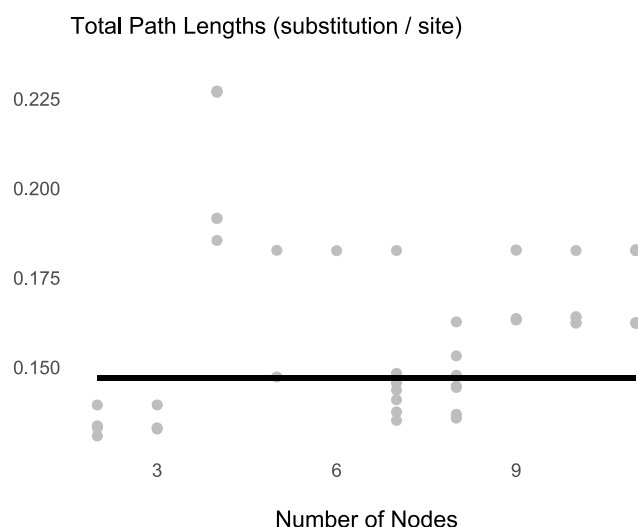


Figure 1. The number of nodes along the SARS-like betacoronavirus lineages (net transmission events) does not correlate with, nor does it explain the variation ($R^2 = .00049$) in total path lengths (substitutions in the genome). PGLS equation: $y = .15 - .0000044x$.

References

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Appendix

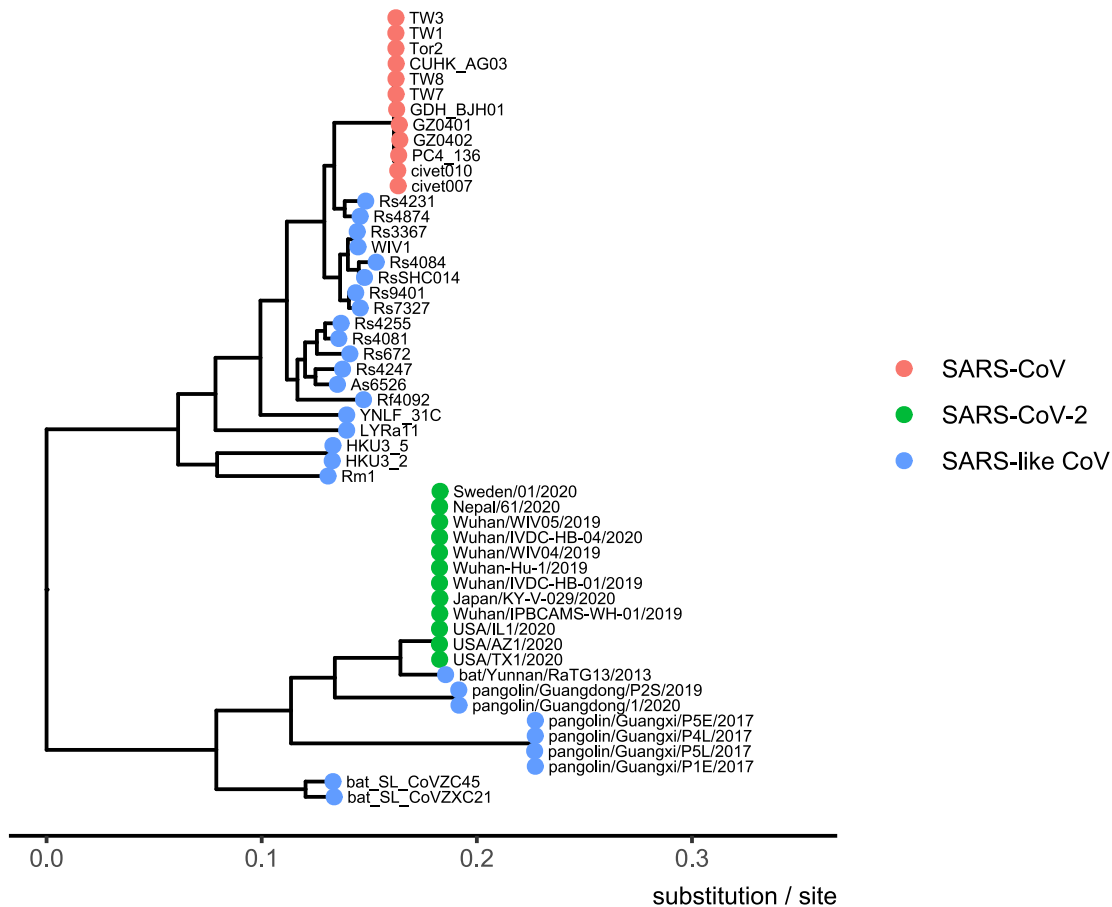


Figure A1. Molecular phylogeny of SARS-like betacoronaviruses downloaded from [Nextstrain](#). This tree contains 52 genomes (12 SARS-CoV, 12 SARS-CoV-2, and 28 SARS-like CoV).

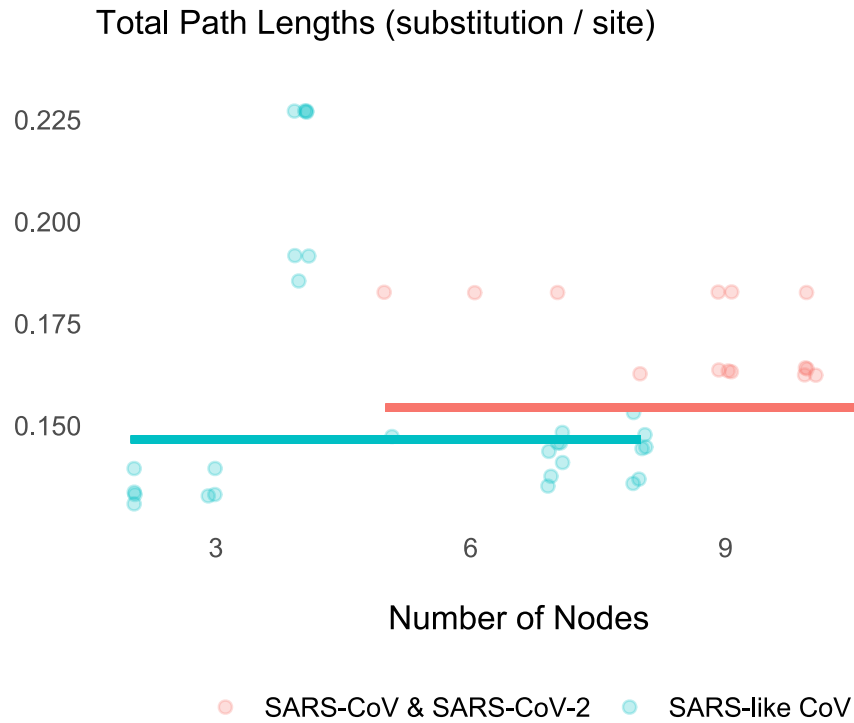


Figure A2. SARS-like betacoronaviruses have likely been evolving gradually before and during the two pandemics (slope [SARS-CoV & SARS-CoV-2] = $.0000038 \pm .000027$, $P = .445$; slope [SARS-like CoV] = $-.0000010 \pm .0012$, $P = .500$; $R^2 = .049$). Having two regression fit lines, however, do not increase the likelihood enough relative to the model with only one line ($\Delta\text{BIC} = -5.32$). PGLS Equation (SARS-CoV & SARS-CoV-2): $y = .154 + .0000038x$. PGLS Equation (SARS-like CoV): $y = .147 - .0000010x$. The intercepts seem off because they represent phylogenetic means.

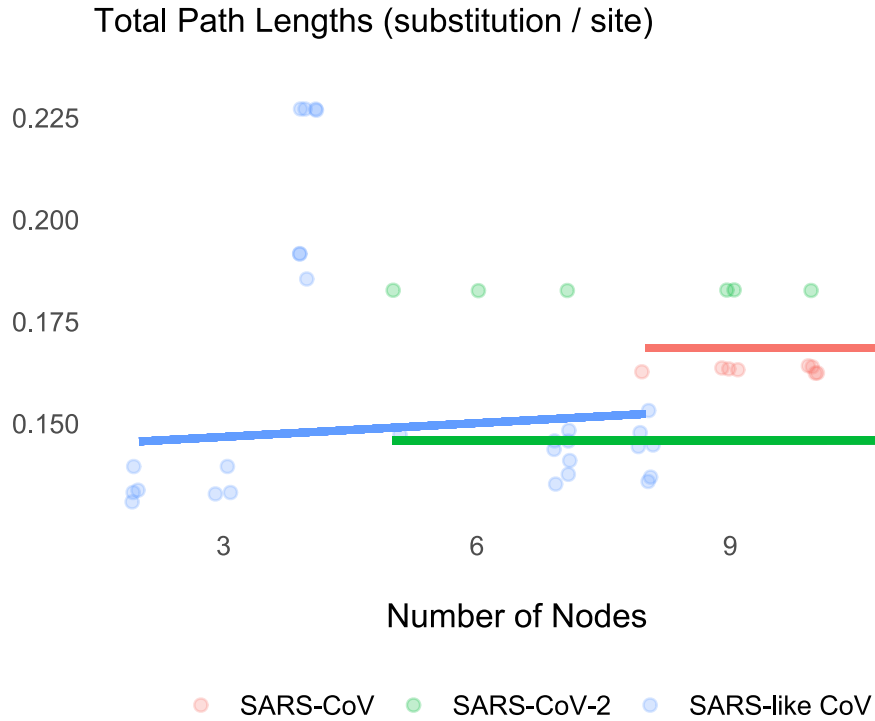


Figure A3. SARS-like betacoronaviruses have likely been evolving gradually before and during the two pandemics (slope [SARS-CoV and SARS-CoV-2; fixed to be equal] = $.0000032 \pm .000026$, $P = .451$; slope [SARS-like CoV] = $0.0011 \pm .0012$, $P = .187$; $R^2 = .14$). Having three regression fit lines, however, do not increase the likelihood enough relative to the model with only one line ($\Delta\text{BIC} = -4.31$). PGLS Equation (SARS-CoV): $y = .169 + .0000032x$. PGLS Equation (SARS-CoV-2): $y = .146 + .0000032x$. PGLS Equation (SARS-like CoV): $y = .143 + 0.0011x$. The intercepts seem off because they represent phylogenetic means.

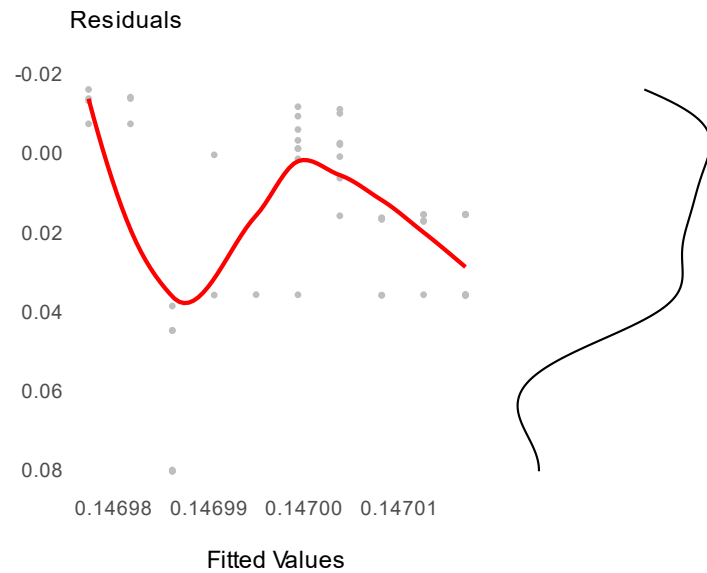


Figure A4. Regression diagnostics indicate assumption violations. The residuals vs. fitted values plot shows that residuals are not constant across the fitted values. Also, the distribution of the residuals is right-skewed.

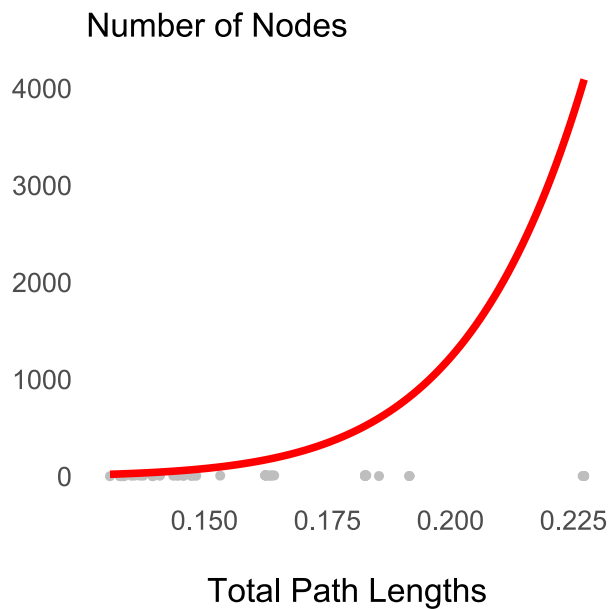


Figure A5. The node-density artifact is clearly present ($\delta = 9.46$). (A symptom of the artifact is a curvilinear relationship with $\delta > 1$.) Equation: $y = 5,039,309,975x^{9.46}$.

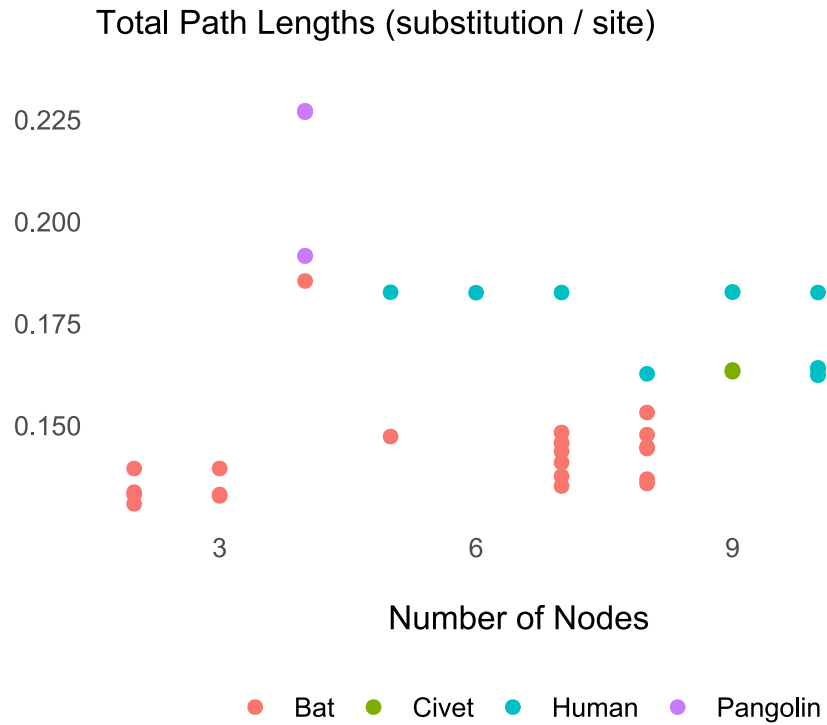


Figure A6. SARS-like betacoronaviruses seem to have been evolving gradually, at least in bats and humans, where we have a decent sample size.