Game-Theoretic Approach Explains – on the Qualitative Level – the Antigenic Map of Covid-19 Variants

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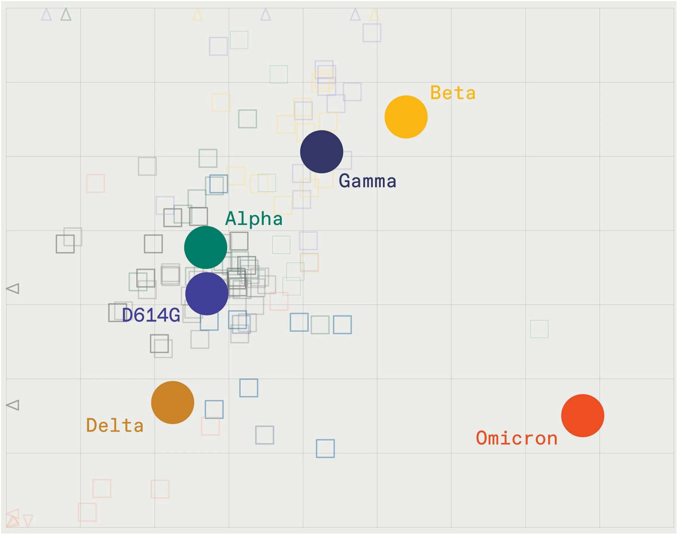
1. An important problem

- Like many viruses, the virus that causes Covid-19 rapidly evolves.
- So vaccines which are very efficient for the original variants are not as efficient for the new variants.
- To be better prepared for the future variants, it is desirable to predict how the virus will evolve in the future.
- To be able to do it, we need to understand how (and why) it evolved the way it did.
- A recent map provides a visual 2-D description of the evolution of the main Covid-19 variants:
  - from the original Alpha
  - to Beta, Gamma, Delta, and Omicron.

2. Map



3. An important problem (cont-d)

- At first glance, the changes look somewhat random and chaotic.
- This leaves us with an impression that probably no reasonable predictions are possible.
- In this paper, we show that, at least on the qualitative level, natural game-theoretic ideas explain the current evolution.
- Thus, hopefully enable us to predict the direction of future changes.

4. Main idea

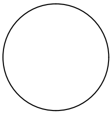
- As the virus starts affecting the population, people's bodies start developing antibodies to the virus's original version.
- So, to stay effective, the virus has to mutate.
- The mutated version also causes the bodies to develop protection, so further mutations are needed.
- The larger the distance between the two variants A and B, the less effective A-caused antibodies against the variant B.
- Thus, from the virus's viewpoint, after variants A_1, ..., A_n, it makes sense:
  - to select, as the next variant,
  - the variant A for which the smallest of the distances $\min(d(A, A_1), \ldots, d(A, A_n))$ is the largest possible.
- This will guarantee that the new variant will be the most effective against all A_i-produced antibodies.

5. Main idea (cont-d)

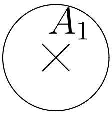
- If there are several variants A with this largest value, then:
  - for the virus,
  - it is reasonable to select the variant for which the second smallest of the distances $d(A, A_i)$ is the largest, etc.
- Of course, the virus is not an intelligent being, it does not directly select its next mutation.
- Mutations happen randomly:
  - some lead to more effective variants,
  - some to less effective ones, and
  - the most effective one becomes dominant.
- In this sense, after the variants $A_1, \ldots, A_n$:
  - the next effective one – the next dominant variant –
  - is the one for which the value $\min(d(A, A_1), \ldots, d(A, A_n))$ describing the variant's effectiveness is the largest.

6. Let us trace this idea on a simple geometric example

- In the 2-D description, all possible variants belong to some reasonable planar area.
- Let us consider the simplest case, when this area is a disk:

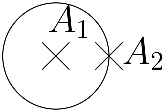


- The first variant A_1 appears somewhere inside this disk-shaped area.
- For simplicity, let us assume that it is located in the center of the disk:



7. Let us trace this idea (cont-d)

- Following the above description:
  - as the next variant A_2,
  - we select the point in the disk for which the distance to the center is the largest possible.
- One can easily see that the largest possible distance is equal to the radius r of the disk.
- This distance is attained at any point on the corresponding circle.
- So, the next variant is located on the circle that borders the disk:



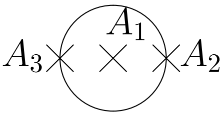
- What happens next?

8. Let us trace this idea (cont-d)

- The distance from any point A inside the disk to its center A_1 cannot exceed r.
- So the smallest distance from A to points A_1 and A_2 cannot be larger that r.
- So, ideally, as the next point A_3, we should select a point A for which:
  - this smallest distance $\min(d(A, A_1), d(A, A_2))$
  - is equal to the largest possible value r.
- This mean, in particular, that the distance $d(A, A_1)$ is at least r.
- Since this distance cannot exceed r, this means that it must be exactly equal to r.
- So, the point A_3 should also be located on the circle.

9. Let us trace this idea (cont-d)

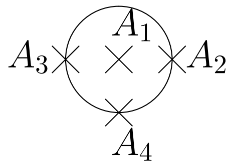
- All the points A on the circle has the exact same distance $d(A, A_1)$; so:
  - in line with the above description, of all points A from the circle,
  - we should select the point for which the distance $d(A, A_2)$ is the largest possible.
- One can see that this largest distance – equal to $2r$ – is attained when the point A_3 is:
  - on the same line as A_1 and A_2 but
  - on the opposite side of A_1:



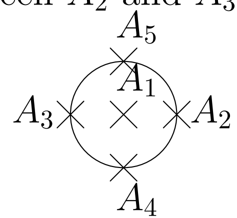
- What now?

10. Let us trace this idea (cont-d)

- Similarly to the previous case, we can conclude that the next point A_4 should also be located on the circle.
- It should be selected in such a way that the smallest of the two distances $\min(d(A, A_2), d(A, A_3))$ should be the largest possible.
- One can check that this point should be located on the circle exactly in the middle between A_2 and A_3:



- Similarly, the next point A_5 should be located on the same circle, also exactly in the middle between A_2 and A_3:



11. Let us map the consequent locations of different variants

- If we map the locations of variants A_1 through A_4, then we get the following picture:

$$\begin{array}{ccccc} A_3 & - & A_1 & - & A_2 \\ & & | & & \\ & & A_4 & & \end{array}$$

- If we add A_5, then we get the following:

$$\begin{array}{ccccc} & & A_5 & & \\ & & | & & \\ A_3 & - & A_1 & - & A_2 \\ & & | & & \\ & & A_4 & & \end{array}$$

12. On the qualitative level, the A_1-A_4 map is almost exactly the Covid-19 antigen map

- Indeed, we start with the first variant Alpha (A_1 in our notations); then:
  - the variant Beta (A_2) is one side of A_1, while
  - the variant Delta (A_3) is approximately on the same line on the other side of A_1.
- We skipped Gamma, since:
  - Gamma is exactly in between Beta and Delta on the antigen map,
  - so it must simply be a transitional state.
- Then comes Omicron (A_4) which is obtained by moving in a different direction than before.

13. So what next?

- Our model's prediction is the next variant A_5 will be:
  - along the line A_1A_4, but
  - on the other side of A_1 than Omicron (A_4).

14. Of course, this is a very crude model

- The above model is very approximate.
- For example, in this model the distance from all three consequent variants to the original variant A_1 is the same.
- In reality, the distance from Alpha (A_1) to Omicron (A_4) is much larger than the distances from Alpha to Beta and Delta.
- However:
  - the fact that this simple model explains the seemingly random changes
  - gives us hope that a further development of this model can lead to quantitative explanations – and thus, more reliable predictions.

15. References

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