Professors Graßhoff and May (henceforth, G&M) have proposed an interesting model of scientific discovery, and have applied it to the discovery of the reaction cycle for urea synthesis, a problem solved in 1932 by Hans Krebs. As they compare their proposed explanation of Krebs’ discovery to one earlier published by Deepak Kulkarni and myself (Henceforth, K&S), and as their judgments on our program are rather negative, I have drafted a few remarks to explain why we proceeded as we did.¹ I will leave to the forthcoming meeting the discussion, which I expect will be lively and productive, of broader issues of the relations of both of these programs to general theories of scientific discovery: both theories that seek to explain the actual behaviors of scientists and theories that have the normative intent of demonstrating efficient discovery procedures. Thus, I will only address some of the specific criticisms G&M made of our simulation.

G&M object that our model has a “shaky historical foundation.” Our foundation was the study by Holmes, which they also used (supplemented by consultation of Krebs’ lab notebooks and papers). We believe that KEKADA follows Holmes’ account (which G&M evidently find satisfactory, as their account also agrees with it), and that what they regard as our principal departures from it relate to events whose causation and timing was described by Holmes as quite obscure. The main such events (as G&M comment) are (1) the choice of studying the hypothesis that the source of the NH₂ group in urea is ammonia, (2) the choice of studying the arginine reaction, and (3) the choice of the possibility that ornithine is a catalyst. In all three cases, we preferred to leave these choices to the programmer rather than claim that we could infer causation where both Holmes and Krebs regarded it as wholly unclear; and we made it fully explicit that we were not accounting for them. This does not mean that they are unaccountable, or that KEKADA, with small additions to its heuristics and knowledge base, would not handle them. It simply means that we preferred not to make assumptions that did not have substantial empirical support.

Evidently, G&M’s program makes these choices, but I could not infer from their brief account what conclusive historical evidence supports them, nor – perhaps even more important – what other alternatives their program explored before homing in on these. I look forward to the opportunity of learning more about these matters. At the same time (because of the gaps in the historical record), the fact that their system did find a path falls short of demonstrating that the reasoning that generated this path in the program corresponded to Krebs’ reasoning, and that the alternative path discovered by KEKADA is not the historical one.

A second objection to KEKADA’s solution is that our system explicitly introduced the idea of catalysis before finding the \( \text{ammonia} \rightarrow \text{ornithine} \rightarrow \text{arginine} \rightarrow \text{urea} \rightarrow \text{ornithine} \) cycle.

At this point, I will quote Holmes (1980, p. 219): “But the title of the immediately following experiment [i.e., following the discovery of the ‘ornithine effect’] ... implies that his first response was rather to suspect that the ammonia is the direct source of all the urea nitrogen, and that ornithine only increases the rate of this reaction.” It is not unreasonable to regard this as interpreting ornithine’s role as catalytic. Then Krebs continued with an experiment that Holmes describes as “following a standard biochemical strategy: if a given compound exerts some particular action, check whether derivatives of that compound have similar actions.” This is exactly the sequence, criticized by G&M, that KEKADA follows on p. 162 of our paper. That Krebs (or KEKADA) did or didn’t think of ornithine’s role as catalytic at this point in no way contradicts the fact that the idea that it played an auxiliary role was not followed up until after the “scoping” experiments were finished. In this, KEKADA’s path matches Krebs’.

G&M’s proposal that the idea of catalysis first entered Krebs’ mind after the cycle had been found is not implausible, but there is no positive evidence in the historical record that this is the case. Again, the fact that a simulation takes a different path is not independent.

¹The short deadline for preparing this note has prevented me from consulting Dr. Kulkarni before submitting it, so I alone am responsible for these comments.
evidence that KEKADA’s was not the historical path. A third objection to KEKADA is that it forms its expectations about experimental outcomes primarily from experience with previous experiments using “similar” substances, and ignores the evidence from experimental controls that were also run. Holmes’ account conveyed to us that it was the large production of urea when ornithine was present, as compared with the small production in the presence of other amino acids, that produced the critical surprise. The fact that the ornithine was playing an essential role was evident from this result, quite apart from the results from a control condition where ornithine was absent. Whether KEKADA is right or wrong in drawing the inference in this way is, again, an issue that has to be decided by historical evidence on the behavior of scientists. I hope we will have opportunity at the meeting for extensive discussion of this question, because it concerns not only this historical point but also important issues relating to experimental methods and procedures for making inductions from experimental evidence. KEKADA’s methods of inference are “Bayesian” in the sense of interpreting each experiment not solely on the basis of the evidence that experiment produced, but in the context of prior knowledge.

The matter of KEKADA’s validity, then, seems to boil down to three main issues: (1) in simulation, where historical evidence is lacking to guide a particular decision, is it more informative to incorporate the required heuristic into the system and make it part of the theory, or is it better to acknowledge the gap and simply make an explicit ad hoc assumption; (2) do scientists interpret experiments in isolation from prior knowledge or do they take account of prior knowledge; and generally (3) to what extent do scientist’s inference processes and the historical paths of discovery conform to or depart from classical normative rules of inductive inference from data?