Welcome to letter 2b, the extra credit discussion about biochemistry and DNA. In case you missed it, this letter is an extension of letter 2 for those who want to dig into Biochemistry and DNA. If you landed here by accident back up and listen to letter 2 first. For those coming from letter 2, I hope you are feeling refreshed and ready to dig into the 4th and 5th *shortcomings of scientific explanation because they are big.* I'll start by sharing a summary of the findings which are that the emergence of life requires specific processes that appear to be virtually impossible to arise through randomness. It's a big statement that needs to be justified so here are the details that show why these challenges are a showstopper. Life requires specific arrangements of independent parts combined in a complex way starting with three things: The first things are Biopolymers such as RNA, DNA, and proteins. The second thing is a cell membrane and the third thing is an energy gradient. Each is comprised of many more complex components and arrangements. Here is more on the details of each. Have a look at the properties to determine the likelihood of them arising randomly. I'll dig into each starting with the first, biopolymers.

Biopolymers are made of 4 types of monomers: nucleo bases, sugars, amino acids, and lipids. Assuming the concentration and purity are somehow present on a prebiotic earth, for chemical evolution to occur combination of these monomers would also need to spontaneously arrange themselves into long chains to arrive at DNA, RNA, and proteins. There are a number of intractable challenges. The first is that of water. Water is needed to allow monomers to move and combine with one another but water is also a deterrent because it pushes the monomers away from one another and water molecules also crash into established polymer chains (through hydrolysis) destroying them. It's a paradox, water is both a necessity and a curse. An alternative around the water paradox involves the possibility of wet and dry cycles. Unfortunately, this also has intractable problems because the dry cycles degrade RNA and DNA stopping the process dead in its tracks. In addition, proteins collapse when not suspended in water. Moving into a dry cycle would cause them to fall apart. So, if you somehow had the right monomers and the right directions in how to make them (which we don't) the water would mess up the process.

The second challenge is the issue of chirality. 19 of the 20 amino acids needed to create biopolymers have to have the right chirality . A chiral form is like an evil twin. It looks the same as the one needed but doesn't work the same as a monomer in the chain. Proteins, RNA and DNA and cell membranes must all have amino acids with the correct chirality to exist. In the case of DNA, each of the chiralities need to be correct in its half a million-nucleotide long chain. Nature produces an equal amount of the two chiral forms so it's not like the wrong form is rare. Some amino acids such as Adenosine have as many as 15 Chiral forms of which only one works. Creating the right chirality in complex chains randomly on a prebiotic earth looks impossible.

Then there is the problem of linking together polymers correctly. The first way things can go wrong is called intramolecular cyclization. If the start and end of a chain link one to another it dies. The second problem is called heterogeneous impurities. The wrong molecule in the chain or interfering molecules, spells death. The third issue is called branching malformation. You can have the right branch but if it's linking in the wrong spot that's a killer. The Fourth problem is premature truncation. Some monomers act as terminators preventing further growth. The

longer polymer chains get the greater the odds that they get screwed up based on one of these. So it's not trivial to build super long polymer chains.

Humans have managed to assemble basic biopolymers that are 11 to 50 monomers long, but it required intelligence and coddling not present on prebiotic earth. The results are not very impressive when compared to the simplest known free living life form (tiny little thing) which still has a genome that is 500,000 nucleotides long. How could this have self-assembled randomly?

MIT mathematicians started to calculate the probability of arranging the monomers of a simple protein by random change in 1966. The odds looked incredibly low, but the problem was graciously left unsettled because the understanding of the different ways multiple codons could call for the same amino acid were not understood until 2004. When the number of ways were finally calculated, the odds of creating a single protein were found to be 1 in 10^77th power. To put this into perspective there have only been 10^40th living organisms on earth in its 3.5 billion year living history. So, if every organism mutated 10^37 times the collective probability would support the creation of a single protein. And yet a cell needs between 300 to 500 protein molecules to function. And even if you got lucky and a piece of DNA randomly coded for a protein, it's useless unless a cell already has the machinery in place to manufacture that protein. It's not enough to have the right DNA you need the machinery, energy and systems to make the right directions into a reality.

Additional challenges: Even if the polymer survived all the challenges of water, chirality and linking issues, it still must face heat, UV rays, ionizing radiation, decay and free radicals. Having polymers floating around for a long enough period of time to bump into one another is a non-starter. They degrade way to fast to even have the chance of ever randomly self-assembling.

Even if you assumed that by a miracle you could create the biopolymer DNA. You would immediately run into Eigen's Paradox. DNA and RNA are constantly subject to error catastrophe and will quickly stop functioning after being created. They need complex enzymes to recognize errors in their code and fix them. Without error correction we would die of old age before we were even born. Here is the catch, the creation of these enzymes is encoded in the DNA code itself. But the DNA can't sustain itself without the enzymes to fix the errors. That's Eagan's paradox (unsolved since the 1970s). You need DNA and error correction simultaneously. Maintaining a single biopolymer, assuming it self-assembled, without a functioning error detection system is another life killer. This doesn't even address how an error detection system could act with intentionality to identify errors in the first place and then create complex systems to fix them.

What has science accomplished so far? The Miller experiment used to be cited as proof that life could self-generate. In the 1950s scientists used a huge amount of human intervention to create a successive series of optimized and unnaturally pure environments, not present on the prebiotic earth, and were able to make a small and simple amino acid molecules like adenine. Unfortunately, it was surrounded by toxic byproducts that would render it unusable on a

prebiotic earth. But assuming they were usable it is important to recognize how unimpressive these experiments were at explaining the origin of life. After all of that scientifically guided work all they succeeded in doing was making some of the building blocks for DNA and proteins. Like Legos lying on the floor they still needed to be assembled intelligently. This puts the situation back to original biochemical challenge in this paper. They still had to arrange their simple amino acids into improbably long polymer chains which requires combining with more complex amino acids, lipids, nucleo basis and sugars and incredible luck!

In contrast to the simple amino acids from the Miller experiment, thousands of chemicals are required in the right concentrations and chirality in a nontoxic environment to have a chance at giving rise to life. Each of the highly specific biopolymers have very precise arrangements of monomers. In addition, many of the chemicals of life are actually self-created by the living organism, making it even more complex to create those processes randomly on a prebiotic earth. So, for life to emerge all of these hurtles needed to be overcome.

Road Map - If you lost track of where we are, we are in the third scientific challenge related to the processes required for life to exist. We finished biopolymers and are onto the Cell membranes required for life to exist.

Okay so The Next thing needed for life is a cell membrane. A cell membrane is really complicated because it requires thousands of doors to let materials (molecules) in and waste out. It needs to maintain proper pH and salinity and osmotic pressure. It needs to block toxins and invaders. It needs to excrete waste and it needs to provide electrical insulation and also harness energy. Some scientists point to a bunch of lipids spontaneously forming into the shape of a sphere as evidence of a cell self-generating. Further research shows that their theory is akin to a baby scratching lines on a paper that kind of looks like a house and us thinking that same drawing function like a real house. A cell membrane is way more complicated than a sphere of lipids.

Other scientists have tried to suggest evolution happened via a simpler "protocell". They tried to make a simpler cell to test the theory but the best they could do was reduce a cell into a bare bones version of its prior self, resulting in a fragile cell with 493 genes rather than 985. Unfortunately, the cell was still too complex to create randomly and it was also dependent on its environment. It was found to be incapable of making its own food requiring very precise nutrients which couldn't have existed on a prebiotic earth. What they really demonstrated was the shortcoming of a protocell serving as a bridge to life and the necessity of a healthy and self-sufficient cell to get the process started.

The third thing needed for life to exist are energy gradients to power the cell. More specifically proton gradients are needed to capture energy. It's super important. No gradients, no life. Physical life requires the right type of energy. Like trying to charge a cell phone on a barbecue, the wrong kind of energy can destroy it. Plus, it needs complex machines to create and harness the energy through a process called Chemiosmotic coupling which pumps protons out of the cell to create a gradient with more protons outside than inside. The pumping is very

complex in its own right, orchestrated by a three-part respiratory complex requiring 25 fancy proteins consisting of hundreds of amino acids. It is tasked with stripping electrons off food sources to power the pumps. This is not a process arrived at through trial and error. The respiratory complex needs to complete a 15-step process properly to control any loose electrons within the cell. Any loose electron would destroy the first molecule in the cell it encountered. If all goes well protons are pumped out of the cell and because of the gradient, they try to re-enter by turning the generator of life (called ATP Synthase) which itself is made of 20 inter-connected proteins. This charges depleted ADP into charged ATP to power the cell.

Interestingly this amazing energy harnessing process is one big paradox. To create a single uncharged ADP shell requires about seven charged ATP's. In addition, ATP is also required to build the proton motor. But ATP requires the proton motor to get itself charged up. So how can it build something that it depends on for its energy to build that same thing? (That's a Paradox!) The proton motor is also necessary to recharge the empty ADP shells after they've been created. It's an irreducibly complex situation that can't be built up gradually. All parts of the system need to arrive at once. And these are only a few of the necessary processed needed to support life. So, for life to evolve randomly all of these processes would need to be created by chance at the same time.

You've made it halfway through. Relax and enjoy some music . . .

I'm back and We are onto the 5th scientific challenge. In conjunction with the 3 parts of life, intelligent DNA code is required to direct the processes like building proteins as well as the regulation of the processes to turn them on and off**.** DNA is a type of extremely complicated programing language which interprets the arrangement of letters (the nucleotide bases A, T, C, and G) to determine how the code is read to decide the things that should be made. The bases are read three at a time. (Called a codon) each codon giving an instruction. A codon can be read in multiple ways. One example of this type of information compression in English is a heteropalindrome like the word "diaper" which backwards spells the word "repaid". It allows for information compression but is really hard to create. DNA can make sentences that not only make sense forward and backward but also phase shifted in 4 other ways. It seems highly unlikely for such a sophisticated language to spontaneously produce itself. In addition, DNA code has built in error correction. Just as in English "gray" and "grey" spell the same color, multiple codon combinations can code for the same amino acid. For example, the codon for Leucine is CTA but what happens if there is an error and the "A" is swapped for a "T" making CTT? No problem, that codes for Leucine as well. There are actually 5 ways to code for Leucine (CTA, CTT, CTC, CTG, and TTG) so if there is a random error in the codon, that amino acid will still be specified. It would be amazing to create such a complex code randomly.

It appears that just getting life started through random "natural" processes isn't really an option. And this complicated process is just the very beginning of an increasingly complicated process of creating complex living animals. It's akin to finding the numbers 001 and 101 and 111 randomly spelled out on the ground by falling sticks in the dirt 5000 years ago and recognizing it as really basic binary code then assuming that nature will go on to self-assemble, without

intelligence, into ever more complex things that use binary code like transistors and computers and cell phones and the internet. All without an underlying intelligence to direct the progress.

We have a digital code inside of our bodies that is read and processed through complex choreographed nano machines that create even more machines. We see language, proofreading, and machines and information rich code in our body. These DNA code features seem inexplicable if restricted to random evolution.

If that's not challenging enough another fact worth considering is that solving the DNA information mystery wouldn't be enough to explain life because the information of life is not just centralized in DNA. It is scattered across various parts of a cell and are interdependent to survive. DNA needs RNA and proteins, and DNA cannot construct a cell membrane and coordinate functions across a membrane. These are functions that are passed from membrane to membrane separate from DNA.

If you are finding yourself a little overwhelmed, that's how I felt too, not just by the biochemistry but by how clearly ridiculous it is to flippantly conclude that life can spontaneously spawn itself into being knowing what precisely that entails.

You made it through and perhaps you read the conclusion at the end of letter two already but even so it's worth reiterating that after looking into the specific complexity necessary for creating life I found the processes of physics, astronomy, biology, biochemistry and DNA to be far more complex and improbably to have been generated randomly than I could have imagined. Many of the challenges can and have been quantified in terms of specific complex processes required to make life and the probability of generating each. I was not able to find evidence for solutions to any of these challenges. The more I learned the more paradoxes and complexities I encountered. I want to make sure I am not acting out of ignorance. Can you help me find errors in my logic or identify scientific solutions that would support a random macro evolution hypothesis? I've tried my best and this is what I found. Thanks for listening and enjoy your day.