The Consequences of a Chiral Clone

By Ebubechi Nwaubani

The NIH headquarters in Bethesda, Maryland is somehow operating with a simultaneous buzz and lull. Administrative support has been siphoned to the Clinical Center where a new Patient I (as she has been deemed) has arrived on the scene. Patient I, Isadora Santos, is a 13 year old girl from São Paulo, Brazil.

A hypervirulent emergent line of the dengue virus has developed over the past 10 years, a suspected effect of climate change. Isadora's family— consisting of her mother and twin brother— just recently passed from this deadly variant after having a family dinner near a slow moving stream during vacation. While grieving her family, navigating orphanhood, and not speaking a word of English, Isadora somehow finds herself catapulted across hemispheres into a slew of blood tests and hospital beeps, only partially aware of what is going on around her and why it necessitates her being so far from home at such a tumultuous time in her life. The truth is, as the only surviving member of her family following exposure to dengue-infected mosquitos, doctors found something unthinkable in antibody tests conducted on Isadora: nothing.

Well... sort of. This is what a blockbuster sci-fi film opening may look like for a movie chronicling the discovery of a human with completely chirally inverted components making up their body. But what does that mean and why might that entail the existence of a Patient I(mmune)?

Chirality is one of those fundamental chemical concepts that balloons into extreme biological consequences for the human body and how it interacts with the world around us. Your hands are actually chiral themselves; assuming you have all 10 digits, try superimposing them, or making them perfectly overlap such that they are oriented identically. You might try flipping your left hand over your right hand such that your palms are touching— that works right? Wrong. One hand has its palm up while the other has its knuckles up. You'll also find that simply shifting one hand over the other also won't work as your thumbs are pointed in opposite directions despite both palms facing the same direction. That concludes our first lesson in chirality!

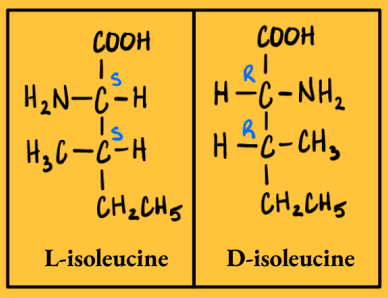


Figure 1. Shown above is a Fischer projection of the amino acid *isoleucine*. In this drawing style, vertical lines represent bonds that point **away** from the viewer (into the page), while horizontal lines represent bonds that point **toward** the viewer (out of the page). In Fischer projections of amino acids, the designation **L** or **D** is based on the position of the amino group: **L-amino acids** have the NH_2 group on the **left**, while **D-amino acids** have it on the **right**. The labels **R** (rectus, "right") and **S** (sinister, "left") describe the **absolute three-dimensional configuration** around each chiral carbon. These R/S labels are determined by the order of priority of the attached groups, independent of the D/L naming system.

In your average chemistry course, chirality is often described as when two molecules are non-superimposable mirror images of each other (they can't be placed on top of each other in the same orientation), just like your two hands . Such duos are referred to as *enantiomers*. This concept has everything to do with stereochemistry, or chemistry in three dimensions. The word chiral actually stems from the Greek root "kheir" meaning hand; enantiomers, specified with a L- or D- prefix for left (laevus) and

right (dexter) configurations when describing amino acids and sugars, are often referred to as the left or right-handedness of a molecule (in case the hand demonstration was not convincing enough) (Compton & Pagni, 2002). French scientist Louis Pasteur, known for developing the pasteurization process for liquid such as milk to kill pathogenic bacteria, is thought of as the father of molecular chirality due to an experiment in which he used tweezers to separate two distinct enantiomer crystals of a tartrate salt (Vantomme & Crassous, 2021). British mathematician Lord Kelvin, best known for creating the Kelvin temperature scale, coined the term "chiral" in 1894; the understudied characteristic of molecules was generally referred to as "dyssymetry" up until that point (Blackmond, 2019). Later in the 20th century, German-American chemist Kurt Mislow pedagogically pioneered the field of stereochemistry and revolutionized modern understandings of chirality.

Okay, okay but what does this all have to do with Patient Immune and dengue and all that stuff, can we honestly just get back to that story? Oh, faithful reader, I appreciate your honesty and understand your fervor. Chirality is, in fact, the very characteristic that imbues our Isadora with her immunological invisibility.

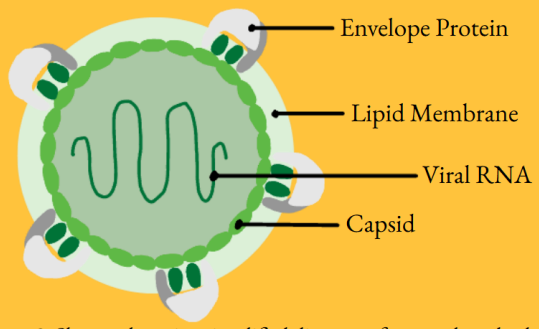


Figure 2. Shown above is a simplified diagram of an enveloped spherical virus particle, similar to the dengue virus. Its outer lipid membrane is hijacked from the host cell membrane upon replication inside the cell and the embedded viral **envelope proteins**—which, like all natural proteins, are made from **L-amino acids** which mediate highly stereospecific binding to host cell surface receptors leading to endocytosis and further infection.

See, the dengue virus, like many viruses, consists of a viral RNA genome enclosed in a protein shell called a capsid, which is further surrounded by a bilayer of fatty molecules (lipids) that is derived from the host cell. Embedded in this outer lipid membrane are proteins ("envelope proteins") that are recognized by stereospecific receptors on cell membranes that allow for the virus and host membranes to merge and infectious genomic information to be delivered inside the cell (Cossart & Helenius, 2014) (Lenard, 2008). In Isadora's case, however, given that every amino acid building block making up all of her cell proteins are of the inverse D-enantiomer, her receptors have an intrinsically distinct fold as compared to that of a non-chirally mirrored human and, therefore, are unable to bind the viral cell membrane proteins at all. The lipids that make up the viral particle outer membrane would also be chirally distinct from those making up the membrane of Isadora's cells and, therefore, couldn't fuse into one via endocytosis. Even if the virus somehow found its way into Isadora's cells (which they couldn't), her mirror-inverted nucleic machinery couldn't transcribe the viral RNA payload as biological RNA universally uses D-ribose. To Isadora's transcription

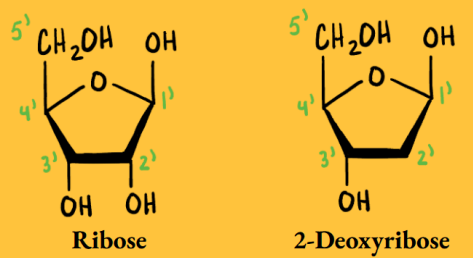


Figure 3. Ribose in RNA and 2-deoxyribose in DNA are the sugars that make up the backbone of these genetic molecules. In both cases, the nitrogenous base attaches at the 1′ carbon and the phosphate group attaches at the 5′ carbon to form a nucleotide. If you can imagine flipping either of these structures over a vertical mirror plane then attempting to superimpose their three dimensional structures, it would never work, they're **chiral**!

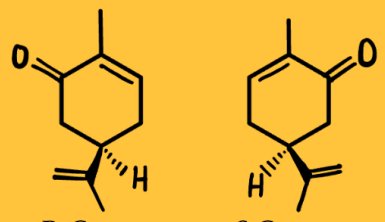
machinery that is built for L-ribose, viral genomes would be unreadable.

That brings us to the topic of DNA, another chiral macromolecule with major impacts on human life. Aside from being totally immune to all known human viruses, Isadora would also be forensically untraceable. Just as Isadora's chirally inverted molecular machinery would be able to only process RNA made up of L-ribonucleotide polymers, all of her existing RNA and DNA would only consist of L-sugar backbones. This means that modern methods used to amplify and subsequently identify small quantities of DNA left over at crime scenes, including polymerase chain reactions (PCR) on DNA and sequencing of the amplified deoxyribonucleotide chains, would not work on Isadora's DNA. The DNA polymerase enzyme responsible for replicating DNA in this PCR reaction is enantiospecific, meaning it is only able to recognize and act on D-deoxyribonucletides, not Isadora's L-deoxyribonucleotides. Similarly, the peptides, lipids, and oils left as traces from her touching different objects would biodegrade in entirely distinct pathways than known human biomolecules as many modes of degradation are stereospecific, therefore, analysis techniques of these biological remnants would not produce results that are similar to any known human readouts. Not only is Patient I immunologically invisible, but she is also forensically invisible.

However, the sad truth is that, despite immunological invisibility and untraceable DNA, a real life Patient I could never exist. You see, we live in a chiral world where not only are our DNA and proteins homochiral (all possessing the same chiral "handed-ness"), but so are the amino acids and sugars that make up our food as well as many of our metabolites and almost every drug you have ever taken. Inverting the chirality of every molecule making up the human body would make such a host fundamentally incompatible with life on earth. This stems all the way back to the origins of life and the chirality problem, as it is sometimes referred to as.

Many hypotheses exist as to what induced the enrichment of one chiral species of a molecule over another from a presumably racemic (consisting of a mixture of a compounds' two enantiomers) prebiotic landscape. One of the most prevailing of these hypotheses considers that way back when Earth was just a soup of fundamental molecules and gases on a rock surface before any sort of biological life, random fluctuations in the relative concentrations of one enantiomer compared to the other in solution may have subsequently been amplified by autocatalysis, or the process by which a substance increases the rate of its own synthesis by either lowering the energy required or creating an alternate, lower energy synthetic pathways towards its synthesis (Blackmond, 2010).

So in considering if and how a Patient I could exist, we are really considering what life might look like if all living things had inverted chirality, as the development of homochirality in living organisms coincides with the origin of life. This would mean that viruses and food sources would also evolve to be compatible with biological life such that viral chiral proteins would again be recognized by chiral protein receptors on human cell surfaces and our metabolic machinery would be constructed to recognize D-amino acids instead of L-amino acids. While a Patient I might taste a whiff of their morning tea on our Earth and smell carraway, on a mirror Earth, Patient I would smell spearmint as the molecule



R-Carvone (spearmint) **S-Carvone (caraway)**

Figure 4. R and S-carvone are the poster children for highlighting how our **smell receptors can distinguish between chiral molecules**. Even though the two forms differ only in their three-dimensional arrangement (with solid wedges pointing toward the viewer and dashed wedges pointing away), they fit into different olfactory receptors in the nose. As a result, one enantiomer smells like **spearmint**, while the other smells like **caraway**.

responsible for the spearmint scent, caravone, targets different chiral olfactory receptors depending on its enantimeric properties (Libretexts, 2024).

So while Patient I may exist only in the realms of your new favorite sci-fi blockbuster, the principles underpinning her impossibility are the very same ones that define human survival on Earth. Whatever serendipitous event that occurred on Earth billions of years ago to select for L-amino acids and D-sugars and the subsequent complex subcellular machinery that cater to enantiospecific molecules is the real enduring hero in this grand human experiment we call life.

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