'Quantum jitters' could form basis of evolution, cancer

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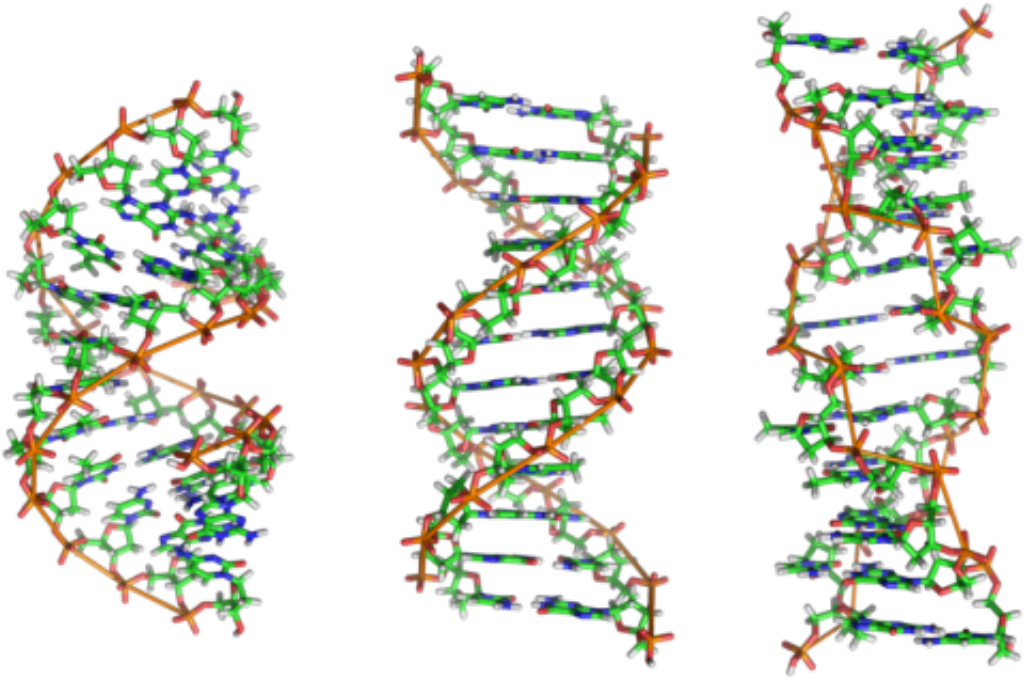

From left to right, the structures of A-, B- and Z-DNA. Credit: Wikipedia

The molecular machines that copy DNA in a living cell are amazingly fast and accurate at pairing up the correct bases—G with C and A with T—into each new double helix.

They work by recognizing the shape of the right base pair combinations, and discarding those—such as a G and a T—that don't fit together correctly. Yet for approximately every 10,000 to 100,000 bases copied,

these machines make a mistake that if uncorrected will be immortalized in the genome as a mutation.

For decades, researchers have wondered how these seemingly random errors are made. Some hypothesized that DNA bases can change shapes, transiently morphing into alternative states to trick the replication machinery into incorporating the wrong base pairs into the DNA. But no one has ever caught these tiny shape-shifters in action.

Now, Duke University researchers have witnessed DNA bases making the slightest of changes—shifting a single atom from one spot to another or simply getting rid of it altogether—to temporarily mimic the shape of a different base. These "quantum jitters" are exceedingly rare and only flicker into existence for a thousandth of a second, and yet have far-reaching consequences.

The study, which appears March 12 journal *Nature*, indicates that these jitters appear at about the same frequency that the DNA copying machinery makes mistakes, which might make them the basis of random genetic changes that drive evolution and diseases like cancer.

"The structure of DNA is inherently tailored to allow mistakes to happen," said Hashim M. Al-Hashimi, Ph.D., a professor of biochemistry at Duke University School of Medicine. "Those mistakes are critical because if we never made them we would never have life as we know it, since we would never evolve. But if we had too many of them, our genes would mutate out of control and we wouldn't survive. These quantum jitters appear to tune the frequency of these spontaneous mutations to just the right level."

DNA's elegant design consists of two long strands twisted around each other like a spiral staircase, with steps made up of four chemicals called bases. Each of these bases contain rings of carbon, along with various

configurations of nitrogen, oxygen, and hydrogen. The arrangement of these atoms allow G to pair with C and A to pair with T, like interlocking pieces of a jigsaw puzzle. When DNA is copied, the replication machinery is careful to only incorporate the perfect fit—known as a Watson and Crick base pairs—and reject any misfits.

Shortly after they discovered the double helix in 1953, Watson and Crick predicted that the four bases might be able to change their shapes so that these mispairs could pass as the real thing. Images of mispairs posing in what appeared to be a Watson-Crick geometry have been captured over the last 10 years and have lent some credence to this idea. But the precise nature of these mispairs and the factors that determine their frequency of occurrence have remained elusive.

Because DNA shape-shifting involves atomic-level movements in larger molecules, it has been impossible to detect by conventional methods. Therefore, Al-Hashimi's team decided to use a sophisticated technique called NMR relaxation dispersion, which he likens to "MRI on steroids," to visualize these fleeting, nearly invisible changes.

Isaac J. Kimsey, a graduate student in the lab, designed a model strand of double helix DNA that contained a G-T mispair. Then he used the NMR technique to track the migration of hydrogen atoms among the nitrogen and oxygen atoms of the G and T bases. Normally G doesn't pair up very well with T, because they both have hydrogen atoms protruding from their surfaces that clash with each other.

Watson and Crick had originally hypothesized that the bases could nudge hydrogens out of the way to allow mis-matched connections. Aided by the NMR technique, Kimsey provided the first direct evidence for just such an atomic rearrangement in a DNA duplex. He also showed that a similar phenomenon occurs in RNA, the chemical cousin of DNA.

This tiny movement, or "quantum jitter," takes such an enormous amount of energy that bases are successful at accomplishing the feat only once out of every 10,000 or so attempts. Even then, they can only hold their new shape for a very short period of time—50 to 200 microseconds—before the hydrogens pop back into their original position.

The researchers looked back at previous biological studies and found that these rare alternative states appeared in the DNA about as often as the polymerase machinery's copying errors.

"This is a remarkable study that illuminates a fundamental mechanism responsible for the random mutations that drive evolution and contribute to cancer," said Bert Vogelstein, M.D., a cancer researcher at Johns Hopkins University School of Medicine who was not involved in this research.

Kimsey said that a better understanding of how these jitters arise could help in the development of new treatments to fight cancer cells and viruses, for example, forcing them to mutate at a quicker rate so they eventually stop functioning.

"We know that certain carcinogens like 5-bromouridine can make these jitters occur more frequently, said Kimsey, who is lead author of the study. "Therefore, we can use this knowledge to tailor drugs that more rapidly induce cancer cells or viruses to make so many mistakes that they mutate uncontrollably and eventually die."

More information: "Visualizing Transient Watson-Crick Like Mispairs in DNA and RNA Duplexes," Isaac J. Kimsey, Katja Petzold, Bharathwaj Sathyamoorthy, Zachary W. Stein, and Hashim M. Al-Hashimi. *Nature*, March 12, 2015. DOI: 10.1038/nature14227

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