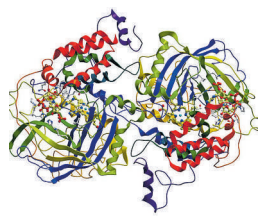
Spectrum science



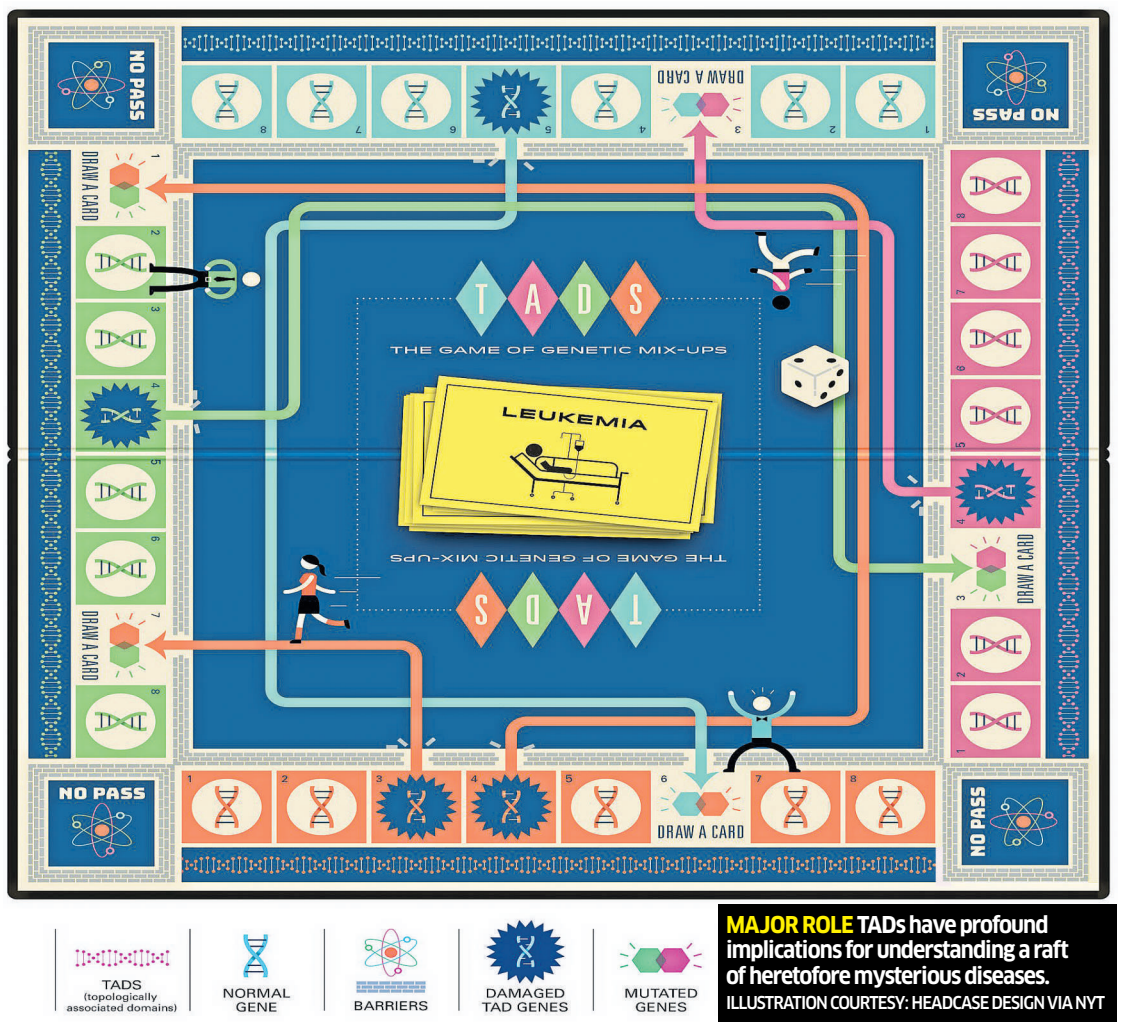
NEW PROTEIN THEORY
A new theory explains how proteins & other biomolecules function, based on movement and change of structure, rather than content.

Shedding light on the human genome

GENETIC RESEARCH By studying a newly discovered design feature of the DNA molecule called topologically associating domains, researchers hope to better fathom the deep structure of the human genome, writes Natalie Angier

They said it was their family curse: a rare congenital deformity called syndactyly, in which the thumb and index finger are fused together on one or both hands. Ten members of the extended clan were affected, and with each new birth, they told Dr Stefan Mundlos of the Max Planck Institute for Molecular Genetics, Germany the first question was always: "How are the baby's hands? Are they normal?" The family, under promise of anonymity, is taking part in a study by Stefan and his colleagues of the origin and development of limb malformations. And while the researchers cannot yet offer a way to prevent syndactyly, or to entirely correct it through surgery, Stefan has sought to replace the notion of a family curse with "a rational answer for their condition," he said.

The scientists have traced the family's limb anomaly to a novel class of genetic defects unlike any seen before, a finding with profound implications for understanding a raft of heretofore mysterious diseases. The mutations affect a newly discovered design feature of the DNA molecule called topologically associating domains, or TADs. It turns out that the vast informational expanse of the genome is divvied up into a series of manageable, parochial and law-abiding neighbourhoods with strict nucleic partitions between them — each one a TAD.



MAJOR ROLE TADs have profound implications for understanding a raft of heretofore mysterious diseases.
ILLUSTRATION COURTESY: HEADCASE DESIGN VIA NYT

Folding protocol

By studying TADs, researchers hope to better fathom the deep structure of the human genome, in real time and three dimensions, and to determine how a quivering, mucilaginous string of some three billion chemical subunits that would measure more than six-feet long if stretched out nonetheless can be coiled and compressed down to four-10,000ths of an inch, the width of a cell nucleus.

"DNA is a superlong molecule packed into a very small space, and it's clear that it's not packed randomly," Stefan said. "It follows a very intricate and controlled packing mechanism, and TADs are a major part of the folding protocol." For much of the past 50 years, genetic research has focused on DNA as a kind of computer code, a sequence of genetic "letters" that inscribe instructions for piecing together amino acids into proteins, which in turn do the work of keeping us alive.

Most of the genetic diseases deciphered to date have been linked to mishaps in one or another protein recipe. Scanning the DNA of patients with Duchenne muscular dystrophy, for example, scientists have identified telltale glitches in the gene that encodes dystrophin, a protein critical to muscle stability. The mutant product that results soon shatters into neurotoxic shards.

Yet, researchers soon realised there was much more to the genome than the protein codes it enfolded. "We were caught up in the idea of genetic information being linear and one-dimensional," said Job Dekker, a biologist at the University of Massachusetts Medical School, USA.

For one thing, as the sequencing of the complete human genome revealed, the portions devoted to specifying the components of hemoglobin, collagen, pepsin and other proteins account for just a tiny fraction of the whole, maybe three per cent of human DNA's three billion chemical bases. And there was the restless physicality of the genome, the way it arranged itself during cell division into 23 spindly pairs of chromosomes that could be stained and studied under a microscope, and then somehow, when cell replication was through, merged back together into a baffling, ever-wriggling ball of chromatin — DNA wrapped in a protective packaging of histone proteins.

Through chromosome conformation studies and related research, scientists have discovered the genome is organised into about 2,000 jurisdictions. As with city neighbourhoods, TADs come in a range of sizes, from tiny walkable zones a few dozen DNA subunits long to TADs that sprawl over tens of thousands of bases and you're better off taking the subway. TAD borders serve as folding instructions for DNA.

Different domains

TAD boundaries also dictate the rules of genetic engagement. Scientists have long known that protein codes are controlled by an assortment of genetic switches and enhancers — noncoding sequences designed to flick protein production on, pump it into high gear and muzzle it back down again. The new research indicates that switches and enhancers act only on those genes, those protein codes, stationed within their own precincts. "Genes and regulatory elements are like people," Job said. "They care about and communicate with those in their own domain, and they ignore everything else."

What exactly do these boundaries consist of? Scientists are not entirely sure, but preliminary results indicate that the boundaries are DNA sequences that attract the attention of sticky, roughly circular proteins called cohesin and CTCF, which adhere thickly to the boundary sequences like insulating tape.

> "The new research indicates that genetic switches and enhancers act only on those genes, those protein codes, stationed within their own precincts.

Between those boundary points, those clusters of insulating proteins, the chromatin strand can loop up and over like the ribbon in a birthday bow, allowing genetic elements distributed along the ribbon to touch and interact with one another. But the insulating proteins constrain the movement of each chromatin ribbon, said Richard A Young of the Whitehead Institute for Biomedical Research, USA, and keep it from getting entangled with neighbouring loops — and the genes and regulatory elements located thereon.

The best evidence for the importance of TADs is to see what happens when they break down. Researchers have lately linked a number of disorders to a loss of boundaries between genomic domains, including cancers of the colon, esophagus, brain and blood. In such cases, scientists have failed to find mutations in any of the protein-coding sequences commonly associated with the malignancies, but instead identified DNA damage that appeared to shuffle around or eliminate TAD boundaries. As a result, enhancers from neighbouring estates suddenly had access to genes they were not meant to activate.

Reporting in the journal *Science*, Richard and his colleagues described a case of leukemia in which a binding site for insulator proteins had been altered not far from a gene called TAL1, which if improperly activated is known to cause leukemia. Now that researchers know what to look for, he said, TAD disruptions may prove to be a common cause of cancer. The same may be true of developmental disorders — like syndactyly.

The New York Times

A cure for neglected tropical diseases

FINDING A REMEDY Researchers have discovered a new lead compound that could help combat Cutaneous Leishmaniasis, a neglected tropical disease, writes Siddharth Kankaria

How many tropical diseases do you know of? Malaria, dengue and sleeping sickness immediately come to mind. Maybe leprosy, if you think hard enough. But, many of us may not have heard of Cutaneous Leishmaniasis, a less dangerous but a much more prevalent cousin of *kala azar* (black fever). Cutaneous Leishmaniasis (CL) is caused by the protozoan Leishmania, which are transmitted by the bite of infected female sandflies.

Dr Shailza Singh and her team from the National Centre for Cell Science (NCCS), Pune, have been studying this disease extensively for years. In a recent collaborative study with Dr Sudipta Basu and his team from the Indian Institute of Science Education and Research (IISER), Pune, the researchers have discovered a new lead compound to help combat this neglected tropical disease.

Often called white leprosy, CL is known to cause skin lesions and ulcers on exposed parts of the body, while often leaving behind life-long scars and severe disabilities. According to statistics released by the World Health Organisation, around 0.9 to 1.3 million new cases of Leishmaniasis surface every year, leading to up to 20,000 to 30,000 deaths annually. Conventional methods of treating CL include administration of antimony-based compounds or oral, topical or liposomal preparations of anti-fungal compounds. However, these approaches have increasingly been proven ineffective, insufficient or too expensive to use.

The problem of causative protozoans becoming resistant to most anti-leishmanial drugs further exacerbates the situation. Thus, it has become paramount to identify new compounds that could be used to treat leishmaniasis. Several natural compounds such as alkaloids, phenolic compounds, terpenes and saponins are known to have anti-leishmanial properties. Recent studies have found a class of anti-fungal compounds called 'coumarins' that possess anti-protozoal properties.

Testing therapeutic efficacy

In order to take this lead forward, researchers from NCCS, comprehensively surveyed several coumarin derivatives for their therapeutic efficacy against leishmaniasis, and in this pursuit, also collaborated with the team at IISER Pune. "Our goal was to explore the possibility of using coumarin derivatives as anti-leishmanial agents. Towards this, we have designed a set of coumarin derivatives using computer aided drug designing, which could serve as probable drug candidates for the treatment of leishmaniasis," explains Dr Shailza.

The research team's initial screening of coumarin derivatives led to the identification of some 1000-odd compounds, which were ultimately narrowed down to five promising drug candidates, based on various judging criteria like their three-dimensional shape, size, and chemical properties.

After this, the scientists wanted to test these five drug candidates for their biological activity and compatibility. They performed various microbiological experiments in this regard, and arrived at one of the compounds which showed the best anti-leishmanial properties, nicknamed 'C2' (compound 2). C2 was shown to cause a reduction in size and mobility of the parasitic protozoan cells, which are known to cause leishmaniasis. In addition, C2 was also shown to attenuate these protozoal cells' ability to infect macrophages, a specialised infection-fighting cell found in the immune system of higher animals.

Further, in order to check the effect of C2 on lesions manifested during Leishmaniasis, the scientists took experimental mice infected with cutaneous leishmaniasis lesions, and then treated them with oral doses of C2. To their surprise, the leishmanial lesions in mice reduced in size by almost 50%. It was thus evident that C2 exhibited the highest anti-leishmanial properties amongst the shortlisted drug candidates both in vitro and in vivo. In order to further enhance the solubility of C2 inside the body, the scientists designed a tiny nanometre scale drug carrier made up of lipids. This lipid-based drug carrier ensures that the drug is released in a much more sustained and prolonged fashion inside the body.

Effective strategy

In further experiments with protozoan cell cultures of Leishmania, the scientists used these lipid-based drug carriers to deliver C2 inside the Leishmania cells. Their results successfully demonstrated that a sustained release of C2 within these Leishmania cells triggered them to commit cellular suicide. Such instances of cellular suicide are generally characterised by an observable decrease in the integrity of mitochondrial membranes and can be quantified using mitochondrial dyes.

This cellular suicide in Leishmania cells can be viewed as an instance of programmed cell death triggered by toxic external factors — the compound C2 in this case. Such a targeted killing of protozoal cells could be a very effective strategy of combating the spread of leishmaniasis infections within the host.

Backed by these conclusive results, the researchers now feel that C2 could serve as a promising drug candidate, which, with further modification and development, can be converted into a potent anti-leishmanial compound.

(The author is with Gubbi Labs, a Bengaluru-based research collective)

SILENT KILLER Statistics indicate that around 0.9 to 1.3 million new cases of Leishmaniasis surface every year.

SNIPPETS

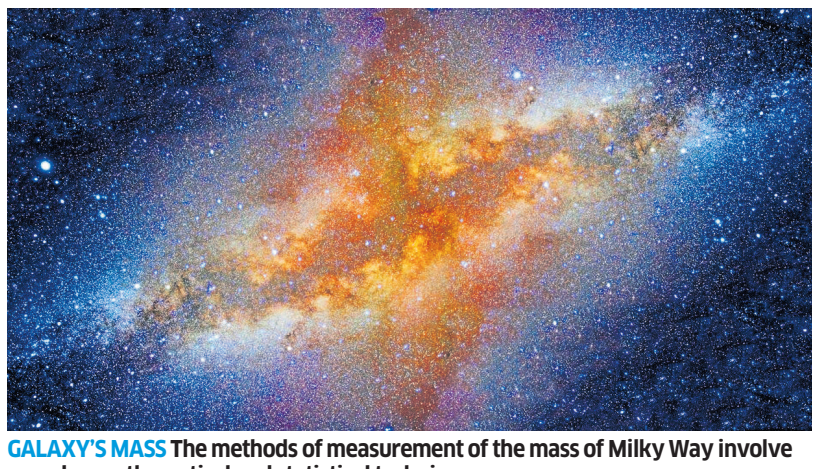
Absolutely every bit of our galaxy

Astronomers have arrived at what they believe to be the most accurate measure yet of the mass of the Milky Way: about 4.8 x 10(11) times the mass of the sun, or 'solar masses', to use a standard unit of mass in astronomy. This comes to about 9.5 x 10(41) kg — that is, 95 followed by 40 zeros. The number, of course, is inexact, as obviously no direct measure of all the billions of stars and other objects in the Milky Way could be taken.

But in a paper to be published in *The Astrophysical Journal*, scientists used methods of measurement that involve complex mathematical and statistical techniques called hierarchical Bayesian analysis, as well as direct measurements of the velocity of globular clusters, the tightly packed spherical groups of 10,000 to 1,00,000 old stars that move through the galaxy. Just as the mass of the sun can be calculated by measuring its gravitational pull on Earth, the mass of the Milky Way can be calculated by measuring its gravitational pull on the globular clusters.

The estimate includes everything within 125 kiloparsecs of the centre of the galaxy — that is, within 3.9 x 10(18) km. And 'everything' is not just stars: There are planets, moons, gases, dust and other objects, not to mention the immense amount of dark matter. It cannot be detected directly, but its mass can be inferred from its gravitational effect on other objects.

"The biggest thing is that we're including measurement uncertainties that are carried through the analysis," said the lead author, Gwendolyn M Eadie, a doctoral candidate at McMaster University in Hamilton, Ontario, Canada. "So we have a good handle on the uncertainty in our mass estimate. The low end is 4.0 x 10(11) solar masses, and the high end is 5.8 x 10(11)."



GALAXY'S MASS The methods of measurement of the mass of Milky Way involve complex mathematical and statistical techniques.

Gwendolyn said that the findings were important from an astronomer's perspective. "The methods we've developed could be important in other studies that do other kinds of research," she said. "These methods have been used in other fields, but they're starting to become more useful in astronomy now that we have computers that can do these complex calculations." What does it mean for the rest of us? "It just satisfies curiosity about the world we live in," she said.

Nicholas Bakalar

When Venus smiled for a few days

For a few days, Venus smiled — sideways. When Japan's Akatsuki spacecraft pulled into orbit around Venus in December 2015 and turned on its instruments, it almost immediately discovered a bow-shape feature in the atmosphere stretching 6,000 miles, almost pole to pole — a sideways smile.

More remarkably, while Venus' winds blow at speeds up to 250 mph and clouds whip around the planet every four days, this gargantuan sideways smile did not move, but remained fixed above the ground for four days. Because of Akatsuki's large looping orbit, the spacecraft could not make more observations for a month.

When the spacecraft looked at the same region again, the smile had disappeared. Except for a few brief glimmers in April and May last year, the smile has not returned.

In a recent paper published in the journal *Nature Geoscience*, scientists working on the mission describe their observations in detail and suggest it was a "gravity wave" — a disturbance in the winds caused by the underlying topography that propagated upward. The bow-shape arc appeared above Aphrodite Terra, a highland region about the size of Africa that rises up to three miles from the surface.

Scientists working on data from the European Space Agency's Venus Express reported finding a similar disturbance in the atmosphere. The authors of the new paper said that numerical simulations provided preliminary support for the idea, but that they still could not explain how the gravity wave forms and propagates in the lower atmosphere. Or why the prominent smile was seen in December 2015 and not since.

Scientists also cannot yet answer the big question Akatsuki was sent to investigate: Why do the winds blow so fast on Venus to begin with?

Kenneth Chang
The New York Times