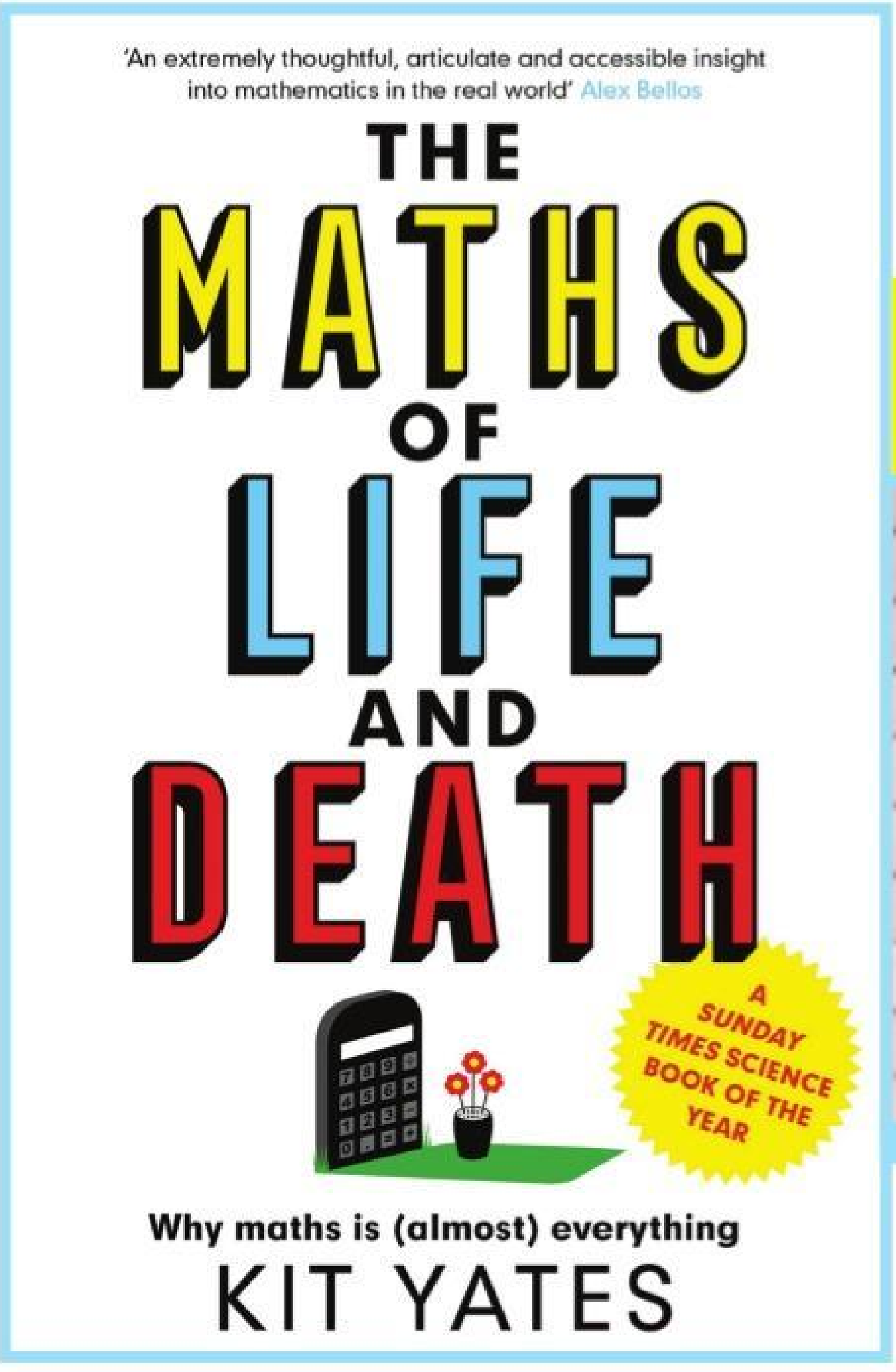
In a world of numbers

a little math can empower and liberate




Kit Yates

S ANANTHANARAYANAN

Recent months have brought the ideas of mathematics to common people and made numbers a topic of worldwide interest. It is intriguing that a few months before Covid-19 descended upon the world, London-based publishing house, Quercus, brought out a book that deals with just the math that counts in medicine and epidemics, among other fields where math affects the way society works and communicates.

The Maths of Life and Death by Kit Yates, senior lecturer in mathematical biology at the University of Bath, hit the stands in September 2019. In 300 racy pages, the book brings out, with stories and yarns from personal life, anecdotes and world history to illustrate and entertain, the principles of how things grow and decay, the inside story of medical diagnosis, accounts of how diseases like Sars and Ebola spread and were controlled, the use, and incorrect use, of math in crime detection and courts, how numbers are manipulated by the media and advertisers, math in government, technology, and ever so many facets of modern living. And the treatment is simple, it is for the lay reader – "not a single equation in these pages," is a promise in the introduction, and the promise is kept.

The first chapter in the book is on the now familiar subject of exponential growth. But the treatment takes the subject through a range of fields. The first is the classic scam where people are invited to invest in a scheme, and then recruit two others to do likewise. As the pyramid spreads, each person receives payments from several persons lower down, to recover many times what she invested. The trouble is that the number of people involved grows too fast, "In 15 rounds, there would be 10,000 people and in 30 rounds, every 7th person on the planet," says the book. Those who enter the scheme early will make some money, but the greatest numbers are the late entrants, who only lose money to the organisers.

Yates then describes how bacteria grow in a culture, something familiar to us now, and goes on to the way cells of an embryo multiply. And moving out of biology, he writes on the working of the atom bomb (with stories about the scientists involved), accidents arising from exponential growth, like Chernobyl, the Ice Bucket campaign, and carbon dating of ancient samples, using the opposite of exponential growth, which is exponential decay, along with a story of how this was used to detect art forgery.

The math of medical diagnosis is the next subject. The message is math, but the examples are contemporary. One example is the service of getting one's DNA analysed – where the whole genome is mapped, to look for the known markers for several diseases like Parkinson's, diabetes and Alzheimer's, for instance. A person can get this done, to be forewarned and prepared. But, while some diseases are certain if the markers are there, in most cases what the test shows is a probability. And how that probability is worked out, and what it implies, becomes mathematical, and all DNA testing services, Yates says, do not make the same predictions.

Yates goes on to discuss the grey areas in using statistics and testing for medical diagnoses in general – testing for breast cancer, for instance. Like current questions that are raised about the value of antibody tests for Covid-19, the breast cancer test has a small percentage of false positives and false negatives. When only a small proportion of the persons tested are likely to have the disease, there would be a large number of negatives, and among these, the number of false positives would be considerable. In fact, Yates shows, the false positives would be many times the real positives. Most persons who receive a report that they have tested positive would become tense without reason!

Yates describes at length some fascinating murder trials where the verdict was based on statistical evidence. The first is a historical case of Captain Alfred Dreyfus, of France, who was charged, in 1894, for passing state information to the Germans. The evidence was a piece of writing that was ascribed to Dreyfus by a handwriting analyst. Yates describes the nature of the evidence and how the conclusion was reached, and then overturned, when Henri Poincaré, the mathematician, got his hands on it.

The discussion is the science of probability, and how it can go wrong when misapplied, particularly before a mathematically unlettered judge or jury. Yates describes a pair of cases, one where medical evidence, interpreted one way, indicts a mother of the murder of her two young sons. The same evidence, however, when analysed mathematically, points to innocence rather than guilt, and even shows that the mathematical treatment was misplaced. And then, a case of a young man indicted for murder, based on evidence of a DNA match, which analysis shows to be incorrect! Yates describes two things that can go wrong when looking at numbers, one is the "prosecutor's fallacy" and the other, the "defense attorney's fallacy".

The next subject is how the media makes use of statistics. "In any area where someone has a vested interest in manipulating the figures, which is almost everywhere figures occur, we should treat claims sceptically and ask for more explanation," says Yates. And again, "there are multiple ways to be economical with the truth, using mathematics." News items or motivated statements are often misleading, sometimes deceitful, but usually partly true, he says. "The seeds of the truth are usually contained within their figures, but very rarely the whole fruit."

These warnings are illustrated by examples – one of a news channel that used violent events that happened in different years and locations, but on the same day of the year, to conclude that they were planned and executed by the same agency. Apart from the fallacy in drawing the conclusion, the line of argument, apparently scientific and based on facts, camouflaged an assertion of hate against the organisation.

And then, in reporting the results of trials of new drugs, or even cosmetics, Yates, recounts the way questionnaires are framed and test results presented. He speaks of a drug that is used to treat breast cancer, but has a risk of promoting uterine cancer. One way to present the risk is to say that "there were 23 instances in 10,000, in the group which took the drug, compared to 9.1 in 10,000 in the group that did not." This suggests that the drug does not create a major risk. However, Yates points out, this is in the context of the drug helping breast cancer by a 49 per cent reduction, compared to women who did not take the drug. Against this is the increase from 9.1 to 23, a 153 per cent increase in uterine cancer!

A fascinating discussion in the book is the number system that societies in the world have developed, and the confusion or clarity they create. These are the decimal system we are used to, systems based on the number eight (the number of spaces between the fingers, rather than the fingers), the number 12, or the number 60, used by the ancient Sumerians, one based on the number 27, and the binary numbers, used by computers. And then the history of how the day came to be divided into 24 hours. Almost incredible are the accounts of historical catastrophes that resulted from confusion in telling the time, based on the 12-hour format or the 24-hour format.

The book ends with discussion of how infectious diseases spread and can be controlled. And the contribution of scientists, including the physician turned mathematician, Daniel Bernoulli. The chapter is almost prescient – published three months before the outbreak of Covid-19, it speaks of the plague outbreak of 1896 that wreaked havoc in India, the "Susceptible-Infected-Recovered" model to chart the progress of an epidemic, and the sym-bol R_0, which has become common-place now, in speaking of Covid-19.

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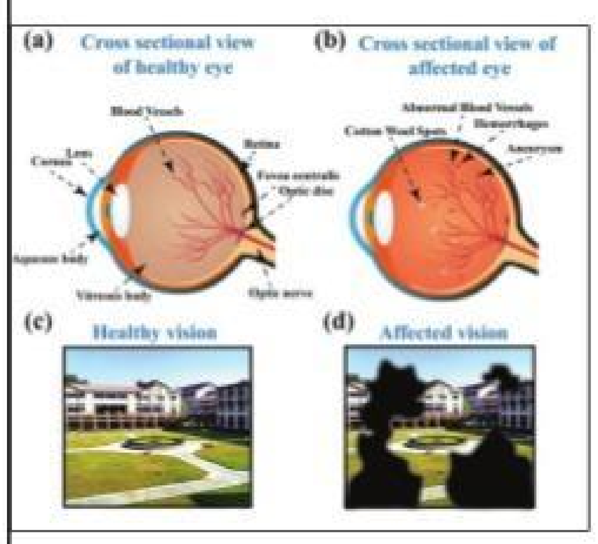
PLUS POINTS

Early detection



The Indian Institute of Technology-Guwahati in collaboration with Shri Sankaradeva Nethralaya Guwahati, have developed a point-of-care testing device that can detect diabetic retinopathy at an early stage, without need for invasive testing.

The research team is led by Dipankar Bandyopadhyay, professor, department of chemical engineering and head of Center for Nanotechnology, IIT Guwahati. Descriptions and results of their testing device have been recently published in the ACS journal, *ACS Sustainable Chemistry & Engineering*. The paper has been authored by Bandyopadhyay and his students, Surjendu Maity, Subhradip Ghosh and Tamanna Bhuyan, at IIT-Guwahati. The other author and collaborator Dr Dipankar Das, a senior consultant and practicing ophthalmologist, is the head of the department of ocular pathology and uvea in Shri Sankaradeva Nethralaya, Guwahati. The team has also filed an Indian patent for this idea and device.

Diabetic retinopathy is a serious non-communicable disease in India, with a conservative estimate that 11-20 million Indians will suffer from this malady by 2025. It is caused by abnormal growth in the retinal blood vessels in people with diabetes, and it is usually worsened when the patient is on insulin for diabetic treatment.

"Currently, the first step in the test for diabetic retinopathy is an invasive eye exam, in which the eyes are dilated and the ophthalmologist inspects the eye," explains Bandyopadhyay. As people who have had eye examination know, this is inconvenient, with blurry vision for a long time after examination. Advanced detection methods such as optical coherence tomography, fluorescein angiography, detection of exudates in retina, and image analysis are complicated and require skilled operators and can show the malady only after it has progressed enough to be detected.

The IIT-Guwahati team wondered if there was a simple test such as a blood or urine test, which could detect retinopathy even before symptoms are seen in the eye. This induced the researchers to look for appropriate biomarkers of retinopathy -- chemicals found in body fluids that can indicate impending or ongoing retinopathy.

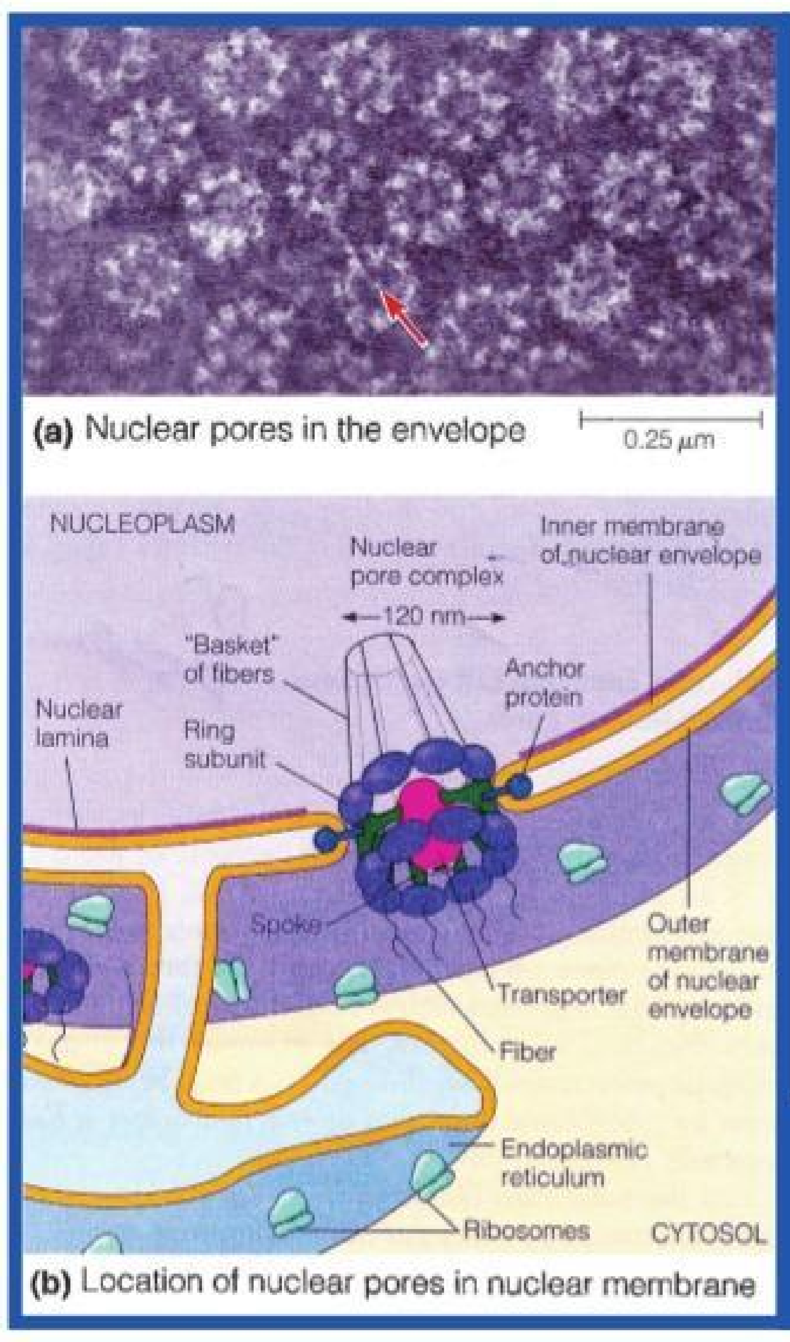
The researchers found that ß-2-microglobulin (B2M), a protein found in tears and urine, is a reliable indicator for retinopathy. Armed with this knowledge, they set out to develop a device that can detect this protein in these body fluids. The team developed a device in which the sensing element was an antibody to B2M that was immobilised on gold particles, a hundred thousand times smaller than the width of the human hair. When the nanogold-laden antibody came in contact with B2M, there was a colour change.

"We designed a microfluidic system, in which the body fluid – tear or urine – was drawn into very thin tubes or capillaries, where they came in contact with the gold-antibody nanoparticles, and the change in colour was assessed to detect B2M", explains the lead researcher. Their prototype microfluidic analyser produced good results with reliable and sensitive detection of B2M, offering promise for design of hand-held, easy to operate detectors for diabetic retinopathy, much like the popular glucometers for diabetes itself.

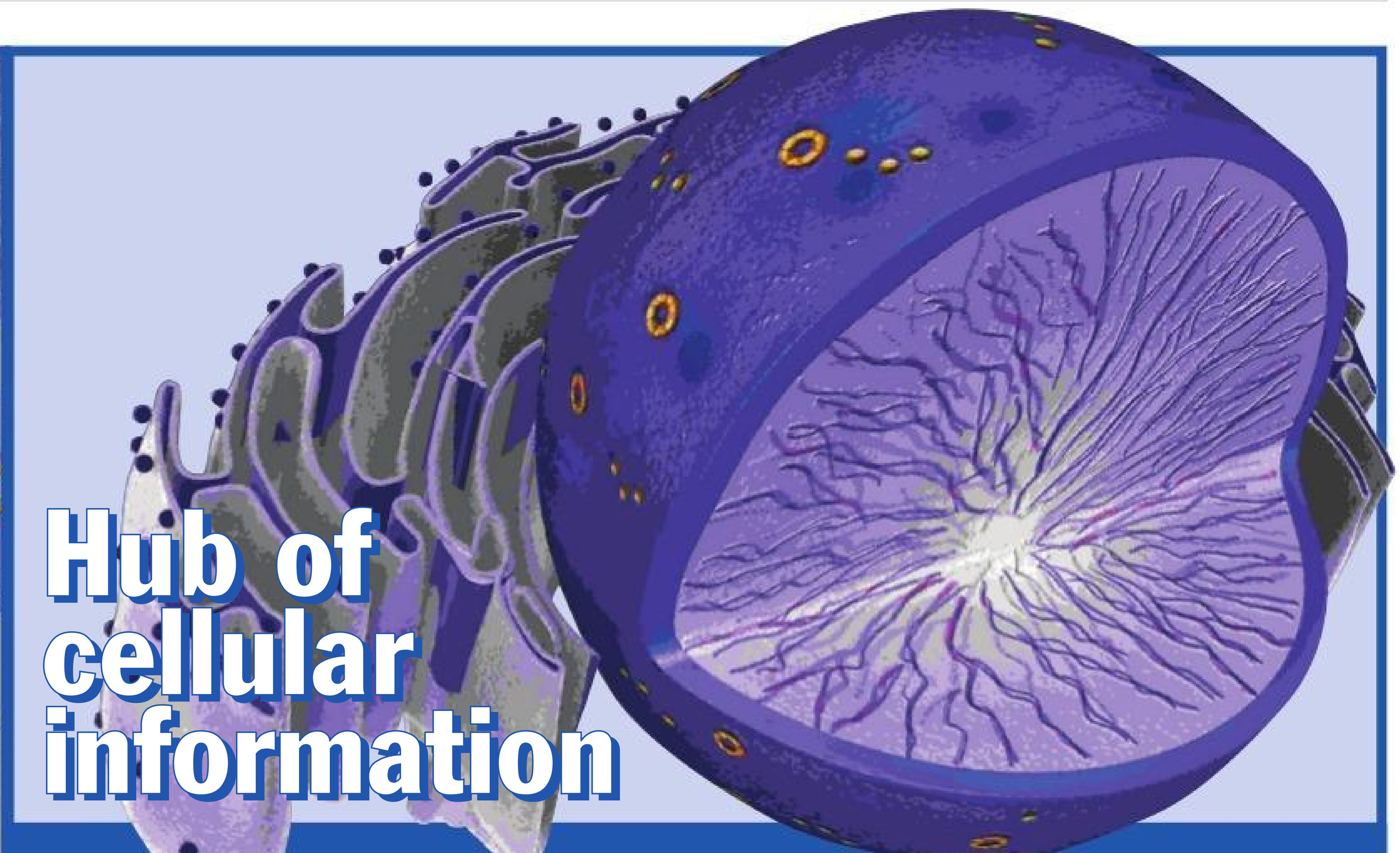
Microfluidic devices, also known as microchips and lab-on-a-chip, have been eliciting considerable interest in recent years in the design of such detection devices. The device typically comprises a small plate containing microchannels for guidance of fluids, in this case, a microdrop of urine or tear.

Numerous microfluidic devices have already been developed for the biomarker detection in cancer and other diseases, but there are hitherto, none for detection of diabetic retinopathy. The IIT-Guwahati team's work is among the first in this area and has tremendous practical implications, especially in India, the diabetic capital of the world.

Hub of cellular information



(a) Nuclear pores in the envelope
(b) Location of nuclear pores in nuclear membrane



A double-membrane nuclear envelope surrounds the nucleus in eukaryotic cells

TAPAN KUMAR MAITRA

DNA is the genetic material of the cell while the genome is a complete set of DNA instructions for the cells of a particular species, and the chromosome is the physical means of packaging DNA within cells. A nucleus is the site within the eukaryotic cell where the chromosomes are localised and replicated and where the DNA they contain is transcribed. The nucleus is therefore both the repository of most of the cell's genetic information and the control centre for the expression of that information.

The nucleus is one of the most prominent and characteristic features of eukaryotic cells. It warrants mention here that the term eukaryon means "true nucleus." The very essence of a eukaryotic cell is its membrane-bound nucleus, which compartmentalises the activities of the genome – both replication and transcription – from the rest of cellular metabolism.

The existence of a membrane around the nucleus was first suggested in the late 19th century, based primarily on the osmotic properties of the nucleus. Since light microscopy reveals only a narrow fuzzy border at the outer surface of the nucleus, little was known about the structure of this membranous boundary prior to the advent of electron microscopy. Transmission electron microscopy revealed that the nucleus is bound by a nuclear envelope composed of two membranes -- the inner and outer nuclear membranes -- separated by a perinuclear space measuring about 20-40 nm across. Each membrane is about seven to eight nm thick and exhibits the same trilamellar appearance as most other cellular membranes.

The inner nuclear membrane rests on a network of supporting fibers called the nuclear lamina. The outer nuclear membrane is continuous with the endoplasmic reticulum, making the perinuclear space continuous with the lumen of the ER. Like membranes of the rough ER, the outer membrane is often studded on its outer surface with ribosomes engaged in protein synthesis. In some cells, inter-mediate filaments of the cell's cytoskeleton extend outward from the outer membrane into the cytoplasm, anchoring the nucleus to other organelles or the plasma membrane.

One of the most distinctive features of the nuclear en-velope is the presence of specialised openings, called nuclear pores, which are especially easy to see when the nuclear envelope is examined by freeze-fracture microscopy. Each pore is a small cylindri-cal channel that extends through both membranes of the nuclear envelope, thereby providing direct continuity be-tween the cytosol and nucleoplasm, the interior space of the nucleus (other than the region of the nucleolus). The density of pores (that is, the number per unit surface area of the nuclear envelope) varies greatly with cell type and activity. A typical mammalian nucleus has about 3,000-4,000 pores, or about 10-20 pores per square micrometre.

At each pore, the inner and outer membranes of the nuclear envelope are fused together, forming a channel that is lined with an intricate protein structure called the nuclear pore complex. The diameter of the entire pore complex is about 120 nm. It has an overall mass of some 120 million daltons and consists of dozens of different kinds of polypeptide subunits. In electron micrographs, the most striking feature of the pore complex is the octagonal arrangement of its subunits. Micrographs such as the one in the figure show rings of eight sub-units arranged in an octagonal pattern. In other views, the eight subunits are seen to protrude on both the cytoplas-mic and nucleoplasmic sides of the envelope. The central granules can be seen in some of the nuclear pore complexes. Although these granules were once thought to be particles in transit through the pores, recent evidence suggests that they are an integral part of the pore complex. Apparently, they are easily lost during the preparation of samples for microscopy.

Examination of the diagram reveals that the pore complex as a whole is shaped somewhat like a wheel lying on its side within the nuclear envelope. Two parallel rings, outlining the rim of the wheel, each consist of the eight subunits seen in electron micrographs. Eight spokes (shown in green) extend from the rings to the wheel's hub (dark pink), which is the "central granule" seen in many EMs. This granule is now usually called the transporter because it is thought to move macro-molecules across the nuclear envelope. Proteins extending from the rim into the peri-nuclear space are thought to help anchor the pore com-plex to the envelope. In addition, fibers extend from the rings into the cytosol and nucleoplasm, the ones on the nucleoplasm side forming a basket (sometimes called a "cage" or "fishtrap").

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