It takes a dash of math

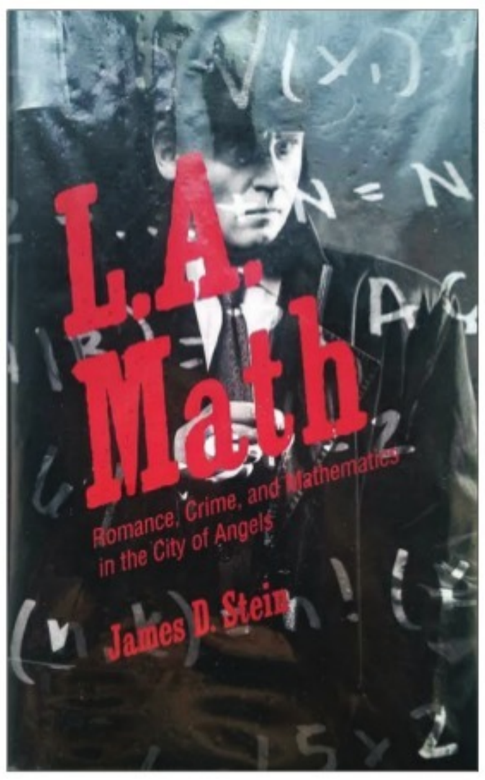
ECONOMICS, BUSINESS OR GAMBLING ASIDE, EVEN BEING FRIENDS IS EASIER WITH NUMBERS, WRITES **S ANANTHANARAYANAN**

'Sometimes she wants me to call, sometimes she doesn't. So should I call?" This suitor's dilemma is nicely settled with the help of mathematics in James D Stein's book, *L A Math*, just brought out by the Princeton University Press. The racy 240-page collection of the encounters of Fred, a private detective, and his mathematical friend presents an assortment of puzzles that confounds bankers, country club presidents, basketball coaches and just ordinary people, with solutions based on simple math, for the average reader, and some less simple details in the appendix, for the more adept.

Coming back to the suitor hesitating before the telephone, Stein looks at it as a 2x2 game, where both players have a choice of two moves to make, and the route to the best outcome can be worked out with a bit of theory. The method is to first estimate the value of the possible outcomes.

(1) Fred calls and Lisa was waiting for him to call, which is great, and the score = 10. (2) Fred calls when Lisa wished he would not, which is no good, the score = 0. (3) Lisa was waiting but Fred did not call, disappointing, and the score = 2. (4) Lisa wished to be left alone and Fred did not call, which is pretty good, score = 7. These outcomes can be put down in a table:

Lisa wants Fred to call?	Yes	No
Fred calls	10	0
Fred does not call	2	7



Fred's friend, Pete, helps him work out how often he should choose to call, over the times when he should hold off. Suppose the fraction of the times Fred calls is "p". Then the fraction of the times he does not call is (1-p). For instance, if he decides to call one-fourth of the time, he does not call three-fourths of the time or if he calls once in five times, he does not call the other four times.

Now, what is the outcome? First, let us take it that Lisa is happy to talk. Fred calls a "p" number of times and the score is p times 10, or 10p. But there are (1-p) times that Fred does not call, and this score is 2x(1-p), which works out to 2-2p. The total score is thus 10p+2-2p = 8p+2. Now let us look at what happens when Lisa is not happy to talk. Fred still calls "p" times and scores zero. But there are (1-p) times that he does not call, which is a good thing, and the score is 7x(1-p) = 7-7p.


James D Stein

As we take it that it is an even chance what mood Lisa is in, we equate the two outcomes: 8p+2=7-7p, which is to say, 15p = 5, or, p = 1/3.

Hence, to do equally well regardless of Lisa, Fred should call, randomly, once out every three times there is an occasion to call and not call the other two times, on the average. Now let us plug these numbers back into Lisa being happy or not. If she was waiting to be called, Fred would score 10 one time out of three and the score would be 2 the other two times, which is 14 in all. But if she was not ready, then he scores zero when he calls and he scores 7 the two times that he does not, or 14 again. The strategy of calling randomly in the ratio of 1/3:2/3 thus evens out the outcome, whatever be Lisa's state of mind.

Liberal Arts math

James D Stein, emeritus professor of mathematics at California State University, Long Beach, explains in the preface to the book that entertaining stories set in Los Angeles, with mathematics squeezed painlessly in, was his long cherished dream of a way to teach basic math as fun rather than a chore. The book's title, *L.A. Math*, was hence both one to attract custom, as related to the City of Angels, and also to stand for Liberal Arts, or as a book to teach math to non-science students at university.

The book deals with mysteries that bring different clients to Fred and Pete and along with a continuing narrative of the private eye pair and the seamy world of Los Angeles, each episode is solved with a lesson in elementary math, in different areas. The example of Fred and Lisa was one in *Game Theory*, or methods to find strategies to make the best of the situation despite an opponent's best moves. The other episodes treat simple math that many often stumble on, like computing averages or the speed of travel, how to add a series of numbers, or the way money increases by interest, and then about the laws of probability. And the appendix contains not only more detailed mathematics of the solutions in the stories, there is also a detailed explanation of the way gambling systems work and how betting takes place, on horses or on football matches.

In one episode, a client, Julie, has been offered a large prize if she can guess correctly which of three suitors the heroine in a soap opera will marry. After Julie has made her choice, and just before the crucial week in the serial TV show, the client is offered a chance to make a change, but with a cash penalty, and she comes to Fred and Pete for advice. One occurrence in the story line, which is managed by the producers of the show, is that one of the two suitors whom Julie had not backed is eliminated in an accident. So should Julie pay up and make a change, or should she let her original choice stay?

Pete's advice is that she should change. The reasoning is that she started out with a chance of one in three. The probability is that the correct choice was within the two suitors whom she had not selected, but she does not have the option of selecting both of them together. Now, the producers have reduced the field of two to only one, which she can choose, and she should!

And then Pete has to advise on the outcome of a club election, where there are more than two candidates and where voters indicate a second and third choice, too. It turns out that the one with the most first preference votes in a field of three may still be less favoured than the one with the least votes, as shown in this table:

First choice	Second choice	Third choice	Number of votes
A	B	C	11
B	C	A	10
C	A	B	9

11+p voters prefer A to B (rows 1 and 3), and B is preferred to C by 11 (row 1)+10 (row 2) = 21. But still there are 10+9 =19 who prefer C to A (rows 2 and 3)

And then the classic travelling salesman problem, to work out how to connect a number of points in a map so that no path is retraced or that the total length of the connections is the minimum — a problem that cities face to pick up garbage or for repair teams to visit different places for work. The problem has no exact solution, although there are approximations, which discover the most economical or efficient way in most cases.

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CELLULAR MESSENGERS

GROWTH FACTOR RECEPTORS PLAY A SIGNIFICANT PART IN THE DEVELOPMENT OF EARLY EMBRYOS, WRITES **TAPAN KUMAR MAITRA**

Growth factors pathways are important in many cellular processes and one well-known case in which they come into play is cell growth. Although cells must have all the nutrients needed for synthesis of its component parts in order to grow but even their availability may not be sufficient. Cells also need messengers that act on specific receptors to stimulate growth.

Biologists encountered the requirements for cell growth when they first tried to culture them in vitro. Although provided with a medium rich in nutrients, including the presence of blood plasma, they would not grow. A turning point came when blood serum was used instead of plasma. Many of the messengers present within the serum have now been purified and they are members of various classes of proteins known as growth factors.

The difference between blood serum and plasma held an important clue about growth factors. Plasma is whole blood including unreacted platelets (which contain clotting components) but without red and white blood cells. On the other hand, serum is the clear fluid remaining after blood has clotted. During clotting, platelets secrete growth factors into the blood that stimulate the growth of cells called fibroblasts, which form the new connective tissue that makes up a scar. After clotting, the resulting serum is full of platelet-derived growth factors. Plasma does not contain that because the clotting reaction has not taken place.

The receptor for PDGF is tyrosine kinase. In fact, several growth factors act by stimulating receptor tyrosine kinases, including insulin, insulin-like growth factor-1, fibroblast growth factor, epidermal growth factor and nerve growth factor. Many other types of growth factors have also been isolated. A small sampling is shown that includes some cells affected by each factor, and the general class of molecule that serves as a receptor.

Although collectively known as growth factors, the proteins that activate tyrosine kinase and other types of receptors function in many diverse events. Not only growth and cell division crucial events during the development of embryos, responses to tissue injury and many other activities are also influenced by them. Growth factors are secreted molecules that act at short range and have specific effects on cells possessing the appropriate receptor to sense its presence.

The disruption of growth factor signalling through receptor tyrosine kinases can have dramatic effects on embryonic development.
One well-studied class of growth factors and their receptors are the fibroblast growth factors and their receptor tyrosine kinases, the fibroblast growth factor receptors. FGFs and FGFRs are used in signalling events in both adult animals and embryos.

FGFRs have been shown to play an important role in the development of cells derived from the middle embryonic layer known as the mesoderm. The mesoderm forms many cell types, including muscle, cartilage, bone and blood cells, as well as the forerunner of the vertebral column. When specific FGFRs fail to function properly, the development of particular mesodermal tissues is affected. In one class of FGFR defects, a mutation in the receptor results in dominant effects on the developing embryo. In other words, even though the embryo makes a substantial quantity of normal, functional receptors, the presence of the mutant receptor within it prevents the normal ones from functioning properly. Normal function is inhibited because FGFRs must act together as dimers to bind FGFs. If a normal receptor dimerises with a mutant receptor, then the normal phosphorylation events within its tyrosine kinase portion fails to occur, thereby blocking signal transduction. Such a mutation that overrides the function of the normal receptor is sometimes called a dominant negative mutation.

In humans, dominant mutations in the transmembrane portion of the FGFR-3 gene result in the most common form of dwarfism, known as achondroplasia. Heterozygous individuals have abnormal bone growth, in which the long bones suffer from abnormal ossification. A related condition known as thanatophoric dysplasia often results from a single amino acid change in the cytosolic portion of the FGFR-3 protein. In this case, more severe bone abnormalities result and affected individuals die soon after birth.

Examples of Growth Factor Families

Growth Factor	Target Cells	Type of Receptor Complex
Epidermal growth factor (EGF)	Wide variety of epithelial and mesenchymal cells	Tyrosine kinase
Transforming growth factor-α (TGFα)	Same as above	Tyrosine kinase
Platelet-derived growth factor (PDGF)	Mesenchyme, smooth muscle, trophoblast	Tyrosine kinase
Transforming growth factor-β (TGFβ)	Fibroblastic cells	Serine-threonine kinase
Fibroblast growth factor (FGF)	Mesenchyme, fibroblasts, many other cell types	Tyrosine kinase
Interleukin-2 (IL-2)	Cytotoxic T lymphocytes	Complex of three subunits
Colony stimulating factor-1 (CSF-1)	Macrophage precursors	Tyrosine kinase
Wnts	Many types of embryonic cells	Seven-pass protein

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Living longer & better

'FOUNTAIN OF YOUTH' TREATMENT COULD BE ON THE HORIZON, SAYS **JOHN VON RADOWITZ**

Elixir-of-youth treatments that slow ageing could be on the horizon after an extraordinary experiment in which the lifespan of mice was extended by up to 35 per cent. The secret is to remove "senescent", or worn-out, cells that accumulate with age and have a destructive effect on the body, scientists found. When this was done in genetically modified mice, the effects were dramatic. Treated animals lived 25 to 35 per cent longer, and in many respects they were healthier too.

The mice remained more active and their hearts and kidneys functioned better than mice left to age naturally. Their body tissues and organs also bore less evidence of damaging inflammation, and they grew fewer tumours.

Scientists are unsure to what extent humans might benefit from the discovery, but research groups are already hunting for compounds that would target senescent cells and form the basis of treatments to slow the ageing process.

Dr Darren Baker, the US scientist who led the Mayo Clinic team behind the mouse study, said, "It is not a far-fetched idea to think that there will be things coming down the pipeline that influence or remove these senescent cells."

Senescent cells are old, defective and potentially dangerous cells that no longer divide. They can still do harm, however, by secreting molecules that damage neighbouring tissues and trigger chronic inflammation. For this reason, senescent cells are closely associated with age-related diseases and frailty. Although the immune system sweeps them away regularly, this process becomes less effective with time and the cells are allowed to accumulate.

The Mayo Clinic team sought to establish what would happen if middle-aged mice were protected against the effects of senescent cells. A strain of GM mouse was created with a "suicide gene" that targeted and killed off senescent cells when activated by a drug.
Describing the research in an interview with the journal *Nature*, which published the results, Dr Baker said, "All of the mice that were treated to remove their senescent cells had a lifespan extension neighbouring from 25 to 35 per cent. In all cases we found there is significant health and lifespan extension."
The treatment had no obvious negative side-effects, the scientists reported. But because the research technique relied on genetic engineering, it could not be directly applied to humans, said Dr Baker. But he knew of "a variety of groups" that were trying to track down compounds that selectively wiped out senescent cells.

He added, "Because senescent cells do not proliferate rapidly, a drug could efficiently and quickly eliminate enough of them to have profound impacts on healthspan and lifespan."

Although removing senescent cells overcame many of the effects of ageing, it did not have an impact on all of them, the research showed. Declines in motor performance, muscle strength and memory remained unaltered, the scientists found. This might reflect the limitations of the genetically engineered mouse strain used in the experiment, or it could be evidence that senescent cells were linked to some aspects of ageing but not others, the scientists said.

THE INDEPENDENT


A frail and ragged-looking mouse (left) which is suffering from the effects of ageing, and another which should be too, but benefited from an anti-ageing treatment that removed its "senescent" cells.

PLUS POINTS

Cutting disaster risk

At least 65 science bodies say they want to join a UN effort to lower global disaster risk. These organisations are set to form a scientific and technical partnership that will provide evidence to help roll out the Sendai Framework for Disaster Risk Reduction. This global deal, signed in March last year, aims to curb deaths and other losses from disasters, whether natural or not. Scientists shared a "profound responsibility" in this process, said Robert Glasser, chief of the UN Office for Disaster Risk Reduction), at a science conference on 27-29 January in Switzerland. This required not only responding to disasters but also "getting out in front of them", he said.
Other organisations could signal their interest in joining the science partnership until the end of this month, according to a UN spokesperson. The list of would-be partners has not been made public while their proposals for assistance are examined, a process that will run through to March. For example, the partners may pledge to carry out specific research programmes or to bring in new partners, the spokesperson added.

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Hibernation helpers

Brown bears *(Ursus arctos)* hibernate for up to six months each year. Before hibernating, they double their fat stores, becoming what scientists call "seasonally obese". Researchers have now shown that the secret to healthy

weight gain may lie in the bears' gut microbiota, which also vary seasonally. Their findings were published on 4 February in *Cell Reports*.
"We know that the microbiota is very responsive to what we eat. So if a bear eats a lot in the summer and it doesn't eat in the winter, then there should be an altered microbiota," study co-author Fredrik Bäckhed of the University of Gothenburg, Sweden, told *BBC News*.
"What we learn from our study is that it appears that the altered microbiome can contribute to the altered adiposity (fattiness)."
The researchers collected fecal samples from wild brown bears in February (when the animals were hibernating) and in June (when they were active). They then colonised germ-free mice with microbial samples from each season. "What we found was that if we colonised the mice with the summer bear microbiota, the mice gained more adiposity compared to if the mouse was colonised with faeces from the same bear in the winter," Bäckhed said, adding that "although (mice) gained more fat mass, it didn't impair their glucose tolerance".

THE SCIENTIST

Stem cells to blame?

As people age, hair follicle stem cells in the scalp accumulate mutations and the follicles themselves shrink, according to a study published on 4 February in *Science*. Analysing scalp skin samples

from women aged 22 to 70, Hiroyuki Matsumura of the Tokyo Medical and Dental University and colleagues found older women's cells had more mutations and their follicles were smaller than younger women's, on average. The researchers identified type XVII collagen as a key player in hair thinning; DNA damage that depleted COL17A1 led to cellular shedding and follicular shrinkage, whereas mice engineered to produced extra COL17A1 did not experience follicle shrinkage or lose as much hair as wild-type mice. Meanwhile, a team at the University of Colorado found that hair follicle stem cells go dormant, but that deleting the gene for the Foxc1 protein could avoid such dormancy. "We discovered that these cells 'know' when to stop," said co-author Rui Yi. "If we can interfere with that factor, or take that factor away from the stem cell, we can shorten the dormant stage and instead induce the cells to continue dividing and stimulate hair growth." Yi and colleagues published their results in *Science* on 7 February.

THE SCIENTIST