**Fruit Fly Enthusiasts get Nobel Prize for Deciphering Biological Clock**

**Biju Dharmapalan**

By interferometric techniques. This is equivalent to measuring the distance to the nearest star Proxima Centauri with an accuracy of less than the thickness of human hair!

It is in operation since 2002, constantly undergoing upgradation. The most recent upgrade, Advanced LIGO, came in operation in the summer of 2015, and within weeks on 14 September LIGO registered the passage of a gravitational wave far above any expected background noise level. The wave first hit the detector in Livingston and then passed its twin in Hanford 7 milliseconds later.

The event was interpreted as a merger of two black holes at a distance of about 1.3 billion light years from us. Not only did this event give a direct confirmation of gravitational waves, but also opened up a new avenue of observing the Universe – Gravitational Wave Astronomy. Scientists at LIGO were however cautious enough to wait till the discovery could be confirmed without any doubt. They did not want to repeat the mistake that Weber did.

The first official announcement was made only on 11 February 2016. LIGO made its second detection of gravitational waves on 26 December 2016 and the third on 4 January 2017. On 14 August 2017, LIGO joined the VIRGO observatory in Italy to jointly announce the fourth gravitational wave due to the merger of two black holes.

The VIRGO interferometer is a large interferometer similar to the LIGO designed to detect gravitational waves predicted by the General Theory of Relativity. Virgo is a Michelson interferometer that is isolated from external disturbances, its mirrors and instrumentation are suspended and its laser beam operates in a vacuum. The instrument’s two arms are three kilometres long and located near Pisa in Italy.

**VIRGO** is part of a scientific collaboration of laboratories from six countries: Italy and France (the two countries behind the project), the Netherlands, Poland, Hungary and Spain. Because the interferometric detectors are not directional (they survey the whole sky) and they are looking for signals that are weak and infrequent, simultaneous detection of a gravitational wave in multiple instruments is necessary to confirm the signal and determine its origin.

Soon India will also join in the search for gravitational waves, collaborating with all the existing Laser Interferometers in the world. On 17 February 2016, the Union Cabinet cleared the LIGO (India) project with a current estimate of at least Rs.1200 crore.

**INDIGO**, or Indigo (Indian Initiative in Gravitational-wave Observations) is a consortium of Indian gravitational-wave physicists. This is an initiative to set up advanced experimental facilities for a multi-institutional observatory project in gravitational-wave astronomy.

Prof. K. Smiles Mascarenhas is currently the Dean of Academic Affairs at the Coimbatore Institute of Engineering and Technology, Narasipuram, Coimbatore-641109.

**ROSOPHILA melanogaster**, the common fruit fly has served as the test bed of genetics for over a century unraveling secrets of biological life. This tiny fly was in the limelight recently because of the Nobel Prize it fetched for understanding the biological clock.

The Nobel Prize in Physiology or Medicine 2017 has gone to three American molecular biologists, Jeffrey C. Hall, Michael Rosbash and Michael W. Young for their discoveries explaining “how plants, animals and humans adapt their biological rhythm so that it is synchronised with the Earth’s revolutions”.

All biological organisms, from unicellular cyanobacteria and protozoans
to all multicellular organisms, including fungi, plants, insects, rodents and humans have an in-built biological clock synchronised with the light-dark cycle. The rhythm ensures that we are alert in the morning, which is rather useful whether you are a hunter-gatherer out foraging or a captain of industry at a meeting.

It exerts its influence in unseen ways, too, regulating the cycle of blood pressure and body temperature. It suppresses bowel movements just before midnight and relinquishes its control early in the morning, ensuring that we don’t wake ourselves during the period of deepest sleep and lowest metabolic rate.

The first report of scientific experiments regarding the biological clock was reported during 1729 by French chronobiologist Jean-Jacques d’Ortous de Mairan. He observed that the diurnal opening and closing of the touch-me-not (Mimosa pudica) stays in time even when the plant is kept in complete darkness. The observation suggested the plants were not so much reacting to light, but somehow were in tune with the day-night cycle.

That was the first step towards understanding the science of the circadian rhythm – the insight that it is endogenous, and not triggered by external stimuli like sunlight. It took another two hundred years for scientists to further unravel the secrets of the biological clock.

In 1971, US neuroscientist Seymour Benzer and his student Ronald Konopka noticed that a batch of mutant fruit flies seemed to have faulty internal clocks. Using genetic tools they showed that each of the responsible mutations lay remarkably close on the same chromosome, suggesting that they were all located within a single gene, which Benzer and Konopka named “period” for its apparent control over clock timing. This landmark discovery was published in the reputed journal Proceedings of the National Academy of Sciences.

The quest to understand the biological clock continued and in 1984 using fruit flies as a model organism, this year’s Nobel laureates, Jeffrey Hall and Michael Rosbash working together at Brandeis University, isolated a section of DNA called the period gene, which had been implicated in the circadian rhythm.

They showed that this gene encodes a protein called PER that accumulates in the cell during the night, and is then degraded during the day. As levels of PER build up over the course of the night, less and less new PER protein would be made. Eventually the protein levels drop and the process starts over again. This is called a negative feedback loop.

This kind of negative feedback
The Hall-Rosbash-Young mechanism of the molecular clock was later found to be universal in the biological world.

**Implications of Clock Genes**

The trio’s discovery of clock genes in Drosophila was just the beginning. Synonymous genes in affecting sleep behavior pattern in humans were found. Young’s lab recently identified a prevalent mutation in a human clock gene, *cryptochrome* 1, that lengthens the cellular clock and makes it difficult to get to bed before midnight. This inherited “night owl” gene is estimated to be common, found in nearly 1 out of 75 humans.

Identifying the genes allowed them to determine the proteins they encode – proteins that might serve as targets for therapies for a wide range of disorders, from sleep disturbances to seasonal depression.

Scientists discovered the same gene exists in humans and that it is expressed in a tiny brain area called the suprachiasmatic nucleus, or SCN, a group of nerve cells in a region at the base of the brain called the hypothalamus. When light hits the retinas of the eyes every morning, specialized nerves send signals to the SCN, which in turn controls the production cycle of a multitude of biologically active substances.

The SCN stimulates a nearby brain region called the pineal gland, for instance. According to instructions from the SCN, the pineal rhythmically produces melatonin, the so-called sleep hormone that is now available in pill form in many health-food stores. As day progresses into evening, the pineal gradually begins to make more melatonin. When blood levels of the hormone rise, there is a modest decrease in body temperature and an increased tendency to sleep. Although light appears to reset the biological clock each day, the day-night, or circadian, rhythm continues to operate even in individuals who are deprived of light, indicating that the activity of the SCN is innate.

The impact of the team’s work on medicine is becoming ever more apparent. Circadian dysfunction has been linked to depression, bipolar disorder, cognitive function, memory formation and some neurological diseases. Jet lag is a problem faced by international travellers, with the sufferer hours out of sync with the world, and likely to be in a confusional state until external cues reset the body’s clock. That is why one is advised to follow the sleep cycle of the destination as soon as possible.

Researchers have even coined the term “social jet lag” to describe the effects of shifting one’s sleep cycle by even a couple of hours. This internal timer is constantly struggling to reset to what environment people are exposed to. If you shift your clock every week by six hours or three hours, it puts an enormous pressure on your body. This can even affect the productivity of a person. The use of melatonin, a sleep-management hormone secreted by the pineal gland, has become quite a fad, and it is prescribed to manage jet lag and insomnia.

Researchers studying chronobiology have also found that eating at night can be problematic for health, since our bodies are not primed to cope with the glucose load from the food in the
evening. We usually eat a meal after waking up, so our bodies adapted to produce the most insulin in the morning.

There is some evidence that treatment of disease can be influenced by circadian rhythms too. The importance of chronobiology is appreciated and correlations may be discovered between the timing of the administration of medicines and their effectiveness. Our circadian rhythm can influence how we metabolize medicines. The timing of taking a drug during the day may control its effectiveness.

Lifestyle disorders like diabetes and cardiovascular disease have been connected with disordered circadian rhythms. Evidence is also emerging that our risk of acute illness rises and falls with a predictable regularity. People are 49% more likely to suffer a stroke between 6 am and 12 noon than at any other time of the day and a similar pattern is true for heart attacks. This is linked to a circadian rise in blood pressure in the early morning, which happens even if you are lying in bed not doing anything.

Space researchers are studying the role of the “biological clock” and how it changes during long-duration spaceflight. Researchers hypothesize that a non-24-hour cycle of light and dark affects crew members’ circadian clocks. The investigation also addresses the effects of reduced physical activity, microgravity and an artificially controlled environment. Changes in body composition and body temperature, which also occur in microgravity, can affect crew members’ circadian rhythms as well. Understanding how these phenomena affect the biological clock will improve performance and health for future crew members and future space colonizers.

All these insights and innovations are built on the foundation of the Nobel Prize-winning research with those tiny fruit flies.

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Cool Microscope Technology Revolutionises Biochemistry

Clockwise from top left: Jacques Dubochet, Joachim Frank, Richard Henderson

THE Royal Swedish Academy of Sciences awarded the Nobel Prize in Chemistry 2017 to Jacques Dubochet, University of Lausanne, Switzerland, Joachim Frank, Columbia University, New York, USA, and Richard Henderson, MRC Laboratory of Molecular Biology, Cambridge, UK “for developing cryo-electron microscopy for the high-resolution structure determination of biomolecules in solution.”