THE NORTHERN HOSPITAL

OSMOLAR GAP

Vera Rubin installing an image-tube spectrograph at the Lowell Observatory, Arizona, 1965. (Carnegie Institute).

The hottest topic in Astronomy today is the search for extra-solar planets, but in the early 1960s it was the search for unimaginably distant quasars. Vera Rubin was a brilliant young Astronomer who was trying to bring up a family at the same time as establishing her career. To do the latter, she needed to compete with other male Astronomers for telescope time, in an age when women were discouraged from studying physics or Astronomy. She too was interested in quasars, all Astronomers were back then, but recognizing that it would be extremely difficult to break into the saturated field of quasar

research, she decided to turn her attention to a region much closer to home, the great spiral galaxy of Andromeda.

It was well known, from the red and blue shifted light of distant stars that galaxies rotated. Vera decided to study and document the actual rate of rotation of the Andromeda galaxy. By measuring the rates of velocity of stars the actual mass of entire galaxies could in theory be determined. The more mass that they contain, the stronger the gravitational field and the faster the stars will orbit. Newton's law of gravity says that the gravitational attraction force between two point masses is directly proportional to the product of their masses and inversely proportional to the square of distance that separates them. A star for example, four times as far from the center of the galaxy (where most of the galaxy's visible mass is concentrated) should have a velocity of half that of a star at the center of that galaxy, while a star nine times as far out should have a third of the velocity and so forth. When the velocity verses distance from the center of the galaxy is plotted on a graph, we should see a decline in velocity in line with Newton's law of gravity. Vera set to work, with the assistance of a master Astronomy instrument maker W. Kent Ford, in order to discover the exact rate of rotation of the Andromeda galaxy.

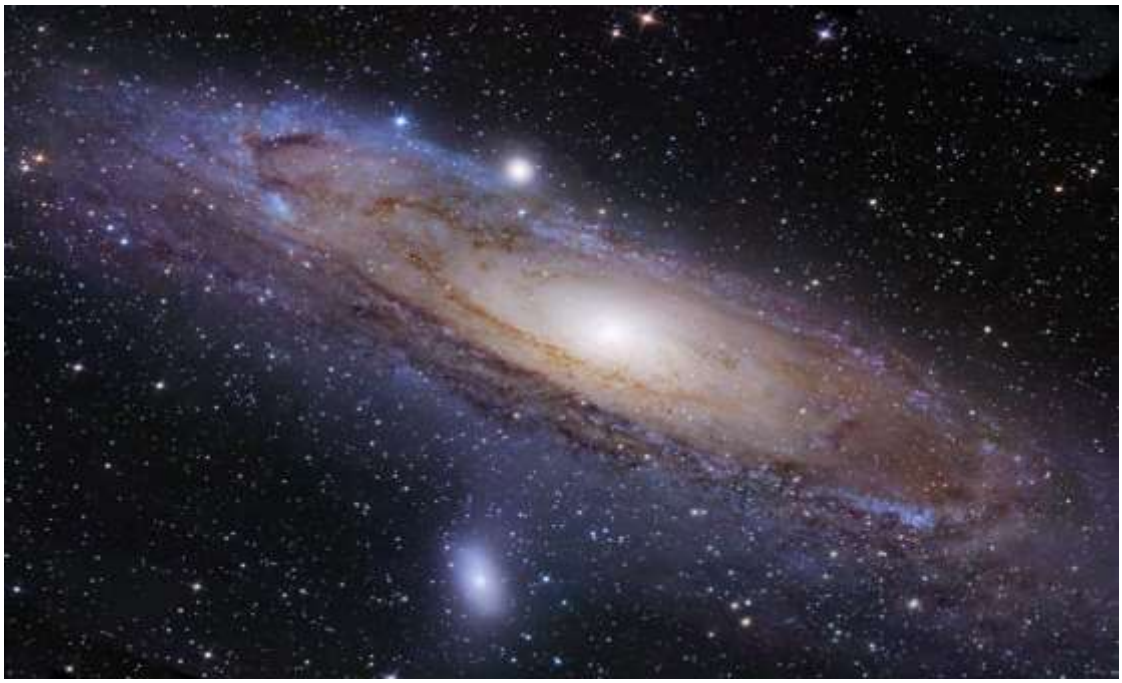
Though Vera's work was exemplary, her results seemed to say that something was drastically wrong! Instead of finding a downward sloping curve for velocity versus distance from the center of the galaxy, she found a virtually straight horizontal line. Incredibly it seemed that the stars at the edges of the Andromeda galaxy were orbiting just as fast as those near the center! To say this result was disturbing, is a masterpiece of understatement. Newton's law of gravity had been brought into question! At first it was thought that perhaps there was just something very odd happening in the Andromeda galaxy, and so Vera began to study other galaxies, and was astonished to find similar results. By this stage other Astronomers had begun to sit up and take notice of her work. Many other galaxies were studied, all showing the same flat rotation curves as Andromeda. Andromeda was no aberration, it appeared that this was the norm for all galaxies!

The high quality of Vera's work meant no other Astronomer questioned it. There could only be one explanation. There must be a great deal of gravity acting on the periphery of galaxies which in turn meant that there must be a great deal of mass in these regions that was completely invisible to our telescopes! Vera and W. Kent Ford had hit upon a mystery that had in fact been discovered by Fritz Zwicky in the 1930s, when he had found the same phenomena occurring in the Coma Galaxy cluster. These galaxies also seemed to be moving faster than they should be, as if some invisible matter was providing the necessary gravitational force. Zwicky even gave this a name - "Dark Matter". But Zwicky's discovery had been largely written off, and then forgotten. Vera and W. Kent Ford, however pursued the phenomenon relentlessly and eventually proved to other Astronomers that Zwicky's discovery had been real! Dark matter seems to be a form of matter that does not emit or interact with electromagnetic radiation, such as light, and is invisible to the entire electromagnetic spectrum. Its nature remains unknown, but one thing is certain, whatever it is there is a lot of it! Latest research suggests that around 25% of the Universe consists of dark matter, and that the matter that we can see, (in the form of galaxies, stars, planets, moons, asteroids, comets, nebula and so forth) only accounts for about 5% of the Universe! The remaining 70% is thought to be "dark energy" - quite another mystery again!

Theories as to just exactly what dark matter is are legion; and range from dark "normal" matter, such as huge populations of unseen black holes, neutron stars and brown dwarfs, to fabulous particles beyond anything on the standard model; but to date no scientist has been able to design an experiment to identify a dark matter particle. A fascinating alternative theory to a particle of matter unknown is "MOND" or Modified Newtonian Dynamics, developed by the Israeli physicist Mordehai Milgrom. In the same spirit of Einstein's theory of relativity and time, this theory suggests that dark matter may not exist at all, rather gravity itself may be variable!

Whatever the exact nature of dark matter turns out to be, Vera Rubin's legacy to Astronomy is assured. In 2011 Saul Perlmutter, Adam G. Riess, and American-born Australian Brian P. Schmidt where jointly awarded the Nobel Prize in Physics for the discovery of "Dark Energy", even though its nature, is completely unknown. Vera Rubin, convinced the scientific community that dark matter existed, even though, like dark energy, we have no current idea of what it is. By her discovery, she profoundly changed our understanding of the nature of the Universe. She died on Christmas day 2016. For reasons known only to the Nobel Committee, she never received the Nobel Prize in Physics for her discovery. The Nobel Committee, again for reasons known only to itself, does not award posthumous prizes.

Normally the osmolarity of serum is made up of the well known substances, sodium, glucose and urea from which we can estimate an expected result. But when we directly test for the ***actual*** *osmolarity in some poisoned patients we may find on occasions a most unexpected result - a value very much higher than expected! It is as if our patient's blood contains some mysterious "dark matter", completely invisible to our usual biochemical sensors! Unlike the nature of the dark matter of the Universe, however, we have a range of well known toxic particles that can explain this puzzling result!*



The Great Spiral galaxy of Andromeda, 2.2 million light years from Earth. Vera Rubin's work on the rotational rate of our biggest galactic neighbour, led to the discovery of dark matter.

OSMOLAR GAP

Introduction

Calculation of the **osmolar gap** can assist in the identification of osmotically active toxic alcohols.

This is particularly useful when laboratory estimation of serum methanol and ethylene glycol levels are not readily available.

Definitions

- An **osmole** is the amount of a substance that yields, in ideal solution, that number of particles (Avogadro's number) that would depress the freezing point of the solvent by 1.86 ^{0} K

- The **osmolality** of a solution is the number of osmoles of solute (ie the number of osmotically active particles) per *kilogram* of solvent.

- The **osmolarity** of a solution is the number of osmoles (ie the number of osmotically active particles) of solute per *litre* of solution.

Calculation of the Osmolar Gap

The **osmolarity** of plasma is *calculated* from a formula that represents the solutes which under *ordinary* circumstances contribute *nearly all* of the (lab measured) **osmolality.**

The most widely used formula is:

- **Calculated osmolarity = 2 x serum sodium + serum glucose + serum urea**

  Osmolarity is in **mOmols/L.**

  All solute values must be in SI units - i.e **mmol/L.**

  (Note that the value Na x 2 is to help take into account anions, in particular the chloride value)

In *clinical toxicology* cases, **ethanol** is so ubiquitous that it is *routinely* included in the calculation, thus:

- **Calculated osmolarity = 2 x serum sodium + serum glucose + serum urea + serum ethanol (also in mmol/L).**

  If ethanol is given in **mg/dL** then it can be converted thus:

  ♥ Ethanol mg/dL / 4.6 = ethanol in mmols/L

  If ethanol is given as % then it can be converted thus:

- ♥ Ethanol % x 218 = ethanol in mmols/L.

The **osmolar gap** is the difference between the **laboratory measured** serum osmolality and the calculated (ie estimated) serum osmolality.

- **Osmolar gap = Measured osmolality – Calculated Osmolality.**

Note that the units of osmolality and osmolarity are different and so the osmolar gap is expressed as a number *without units.*

The Normal Osmolar Gap

A normal osmolar gap is < 10.

This small gap exists because the calculation does not routinely take into account osmotic activity that is generated by small amounts of other substances, such as:

- Potassium
- Sulphate
- Phosphate
- Calcium
- Magnesium
- Lactate
- Ammonia
- Serum proteins
- Lipids.

Increased Osmolar Gap

An elevated osmolar gap suggests the presence of unmeasured exogenous (and potentially toxic) osmotically active compounds.

Exogenous agents associated with an elevated osmolar gap can include:

1. Acetone
2. Ethanol
3. Ethylene glycol
4. Gylcine

4. Glycerol

5. Isopropyl alcohol

6. Methanol

7. Propylene glycol

   - An excipient present in a range of medications, including diazepam and phenytoin.

8. Mannitol

9. Sorbitol

A number of non-toxicological (endogenous) compounds may also cause an elevated osmolar gap.

Endogenous conditions associated with an elevated osmolar gap include:

1. Ketoacidosis:

   - Diabetic

   - Alcoholic

2. Severe lactic acidosis

4. Chronic renal failure

5. Hyperlipidemia

6. Hyperproteinemia

7. Massive hypermagnesemia

8. Shock states/ trauma/ burns.

Note that a normal osmolar gap does not necessarily exclude a potentially life threatening toxic alcohol ingestion for the following reasons:

- Small amounts of toxic alcohols not detected by this method may still cause significant intoxication.

- Late in the clinical course the parent compound (alcohols) are already metabolised to non-osmotically active compounds.

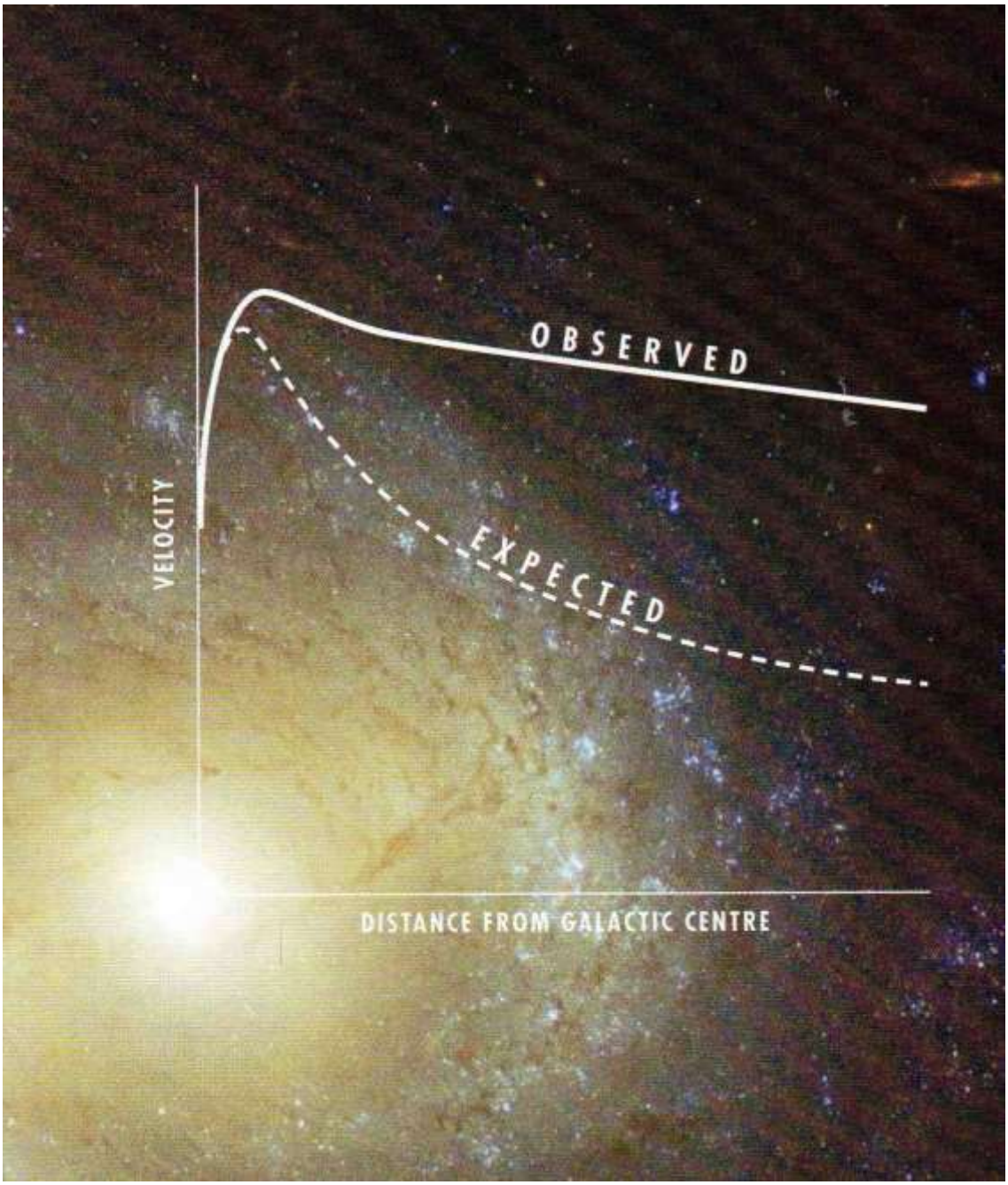
Estimation of unknown toxic alcohol levels using the osmolar gap

The serum concentration of a *particular alcohol* suspected to be present may be *estimated* from the osmolar gap.

By multiplying the osmolar gap (in mmol/L) by a specific conversion factor for each toxic agent, an estimate can be made of the toxic alcohol concentration in units of mg/dL.

Some conversion factors for specific alcohols include:

Alcohol	**Conversion Factor**
Methanol	**3.2**
Ethanol	**4.6**
Isopropyl alcohol	**6.0**
Ethylene glycol	**6.2**
Propylene glycol	**7.2**



Given the amount of mass we can currently detect within it, the outermost regions of the Milk Way are orbiting much faster than expected, producing a flat rotation curve. One way to explain this is the presence of "dark matter" or matter that we cannot currently detect.

References

1. Osmolar Gap in: Murray L et al. Toxicology Handbook 3rd ed 2015.

Further reading:

Vera Rubin, Discovering the Dark Side of the Universe; *Astronomy Now*; February 2017.

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