I. Darwinian and Mendelian Evolution.

Background.

Post the publication of Darwin's *Origin of Species*, in the scientific world (not the social, cultural, religious world) there was little criticism of the work. The idea of evolution had been there for a long time (at least from the time of Lamarck, 1809). However, Darwin knew that his theory had shortcomings. In particular, he focussed on two:

1. Where does the variation on which natural selection acts come from?

Darwin really did not have any answer to this. In his 1868 book, he presents, "Provisional Theory of Pangenesis", where he argues that the blood has little particles called "gemmules", which circulate in blood, and are then collected in the reproductive organs. From there, these gemmules are passed on to the next generation. This proposal lead to Francis Galton (Darwin's cousin) performing blood transfusion experiments in rats – and disproving Galton (to which Darwin replied that gemmules need not be in blood!).

2. Problems with Darwin's assumption of blending inheritance.

The issue was as follows. To Darwin (and other breeders of the time), variation was of two kinds – (a) continuous and (b) discontinuous. The first kind is what you see in any population – a continuous variation in a trait associated with a population. And the second kind, is something that comes in a population only once in a while, very rarely. In the face of this, it appeared to Darwin that populations could not stay constant over dozens of generations. The argument being, that there being so much variation, the populations should change with time very rapidly. But he also knew from experience that populations are relatively stable, and it takes a long time to see large changes. So, if that's true, then what keeps the populations constant? For Darwin, the population was kept constant by sexual reproduction!

Remember that all of this comes at a time when there was nothing known about microbes. So, all evidence is coming from animal/plant breeding experiments. Hence, when two individuals mate – the offspring blends the traits of the two (example, height of offspring is mean of the two parents). That is, sexual reproduction helps remove variation in a population, and keeps species constant. (We, of course, now know that this is false, and sexual reproduction is a source of great variation because of recombination).

But, the problem for Darwin was the following: if sexual reproduction leads to blending (as it must – to keep species constant), then, how (or, on what) does natural selection act?

Darwin knew he was not on solid ground, and wrote, in the first edition of the *Origin of Species*, "*I have hitherto sometimes spoken as if the variations – so common and multiform in organic beings under domestication, and in a lesser degree in those in state of nature – had been due to chance. This, of course, is a wholly incorrect expression, but it serves to acknowledge plainly our ignorance of the cause of each particular variation*". Critics argued that this was an acknowledgement of failure, and it is not natural selection but variation in a population which decides the direction of evolution.

From the follow up of this, Darwin suggested that natural selection acts on small variation in populations, and when this happens for a very long time – you get speciation. Huxley and Galton were against this idea – they said that evolution happens via action on discontinuous and large variation. Darwin was troubled by the fact that the fossil records did not have intermediates to species, and Huxley's & Galton's response was that this is not an issue to be worried about because evolution has happened via acting on large, discontinuous variation – and hence, you cannot expect to see small changes in the fossil record.

Although Galton knew he had disproved Darwin's gemmules theory – he knew he needed a theory of his own. By the late 1870s, his theory was taking shape, and he proposed that gemmules were not formed throughout the body, but were formed only in the reproductive organs of the individuals of the population. In his 1892 book *Finger Prints,* he writes, "*The progress of evolution is not a smooth and uniform progression, but one that proceeds by jerks, through successive 'sports' (as they are called), some of them implying considerable organic changes; and each in its turn being favoured by Natural Selection*".

In fact, in 1867, someone called Fleeming Jenkins reviewed the *Origin* and wrote an objection saying that evolution could not possibly work via the mechanism that Darwin was suggesting, because blending inheritance would week out any variation. When Darwin read Jenkins' critique he acknowledged that he had no answer to that question.

Problem.

Mendel had published his work in 1866. He had presented his work in 1865 and no one had really paid attention. This motivated him to publish 40 copies of his paper and distribute among the leading biologists in Europe (there is controversy regarding whether Darwin got a copy of his paper or not). But, by and large, Mendel's work was largely ignored for the next three decades or so.

In 1900, Mendel's work was rediscovered by three biologists in Europe. And this had a radical effect. The whole field of evolutionary biology was split into two parts: (a) biometricians or Darwinians, who believed that evolution happened by natural selection acting on small variations in populations, and (b) Mendelians who insisted that evolution acted on discontinuous variation.

The group of biometricians was lead by <u>Karl Pearson</u> (a statistician, who became interested in evolutionary questions after reading Galton) and <u>Walter Weldon</u> (a developmental biologist who also became interested in the question of variation in a population after reading Galton). Their skill sets complemented each other perfectly. Curiously, they both turned to the question of evolution after reading Galton (who was a Mendelian).

The group of Mendelians was lead by <u>William Bateson</u>, who studied development and variation. In the 1890s, he published a book with >800 cases of discontinuous variation in nature. Both Galton and Huxley read the book and approved. Weldon too read the book, and although praised the data collected, disagreed with the conclusion that it was discontinuous variation which caused it. There is an urban legend that Bateson in 1900 was traveling by train to give a lecture, and on the journey read Mendel's paper of 1866. The story has it that he immediately recognized Mendel's works' significance and incorporated it in the lecture that he was to give. The story, largely propagated by Bateson's wife after his death, is likely untrue, and made up to give Bateson credit for realizing the significance of Mendel's work.

Over the next two decades, the biometricians and Mendelians exchanged bitter communications with each other (largely between the three men above, but many others too). A couple of communications are copied below.

Weldon's letter to Bateson (1895)

24 May 1895

Dear Bateson,

I can do no more.

First, you accuse me of attacking your personal character; and when I disclaim this, you charge me with a dishonest defense of someone else.

I have throughout discussed only what appeared to me to be facts, relating to a question of scientific importance.

If you insist upon regarding any opposition to your opinions concerning such matters as a personal attack upon yourself, I may regret your attitude, but I can do nothing to change it.

Yours very truly,

W. R. F. Weldon

Exchange between Bateson and Pearson (1902)

Bateson trying to win over Pearson in 1902:

"*I respect you as an honest man and perhaps an ablest and hardest worked I have met, and I am determined not to take up a quarrel with you if I can help it…*

There has probably been no discovery made in theoretical biology that we can remember which approaches Mendel's in magnitude, and the consequences it leads to. This is not a matter of opinion but certain. You have worked well in the same field and if through any fault of mine you were to be permanently alienated from the work that is coming, I should always regret it. With Weldon it is different. He is a naturalist. He goes in with his eyes open. Besides, as between him and me it is too late. It was a bitter grief to me when he first made it clear to me that all partnership between us was at the end. At different times, as perhaps you know, we have each tried to renew our intercourse if our friendship, but it came to nothing and it is no use trying again. There are faults of temperament on both sides. In this matter he is now committed. How far he has mistaken not only Mendel's work but the gravity of the issue cannot be long unknown."

Pearson's reply:

"*I think sometimes you cannot be aware that Weldon has been for many years past one of my closest and most valued friends; that I do not readily make friends, and that when I say a man is my friend I mean that I have tested the strength of his affection in the graver matters of life, and am prepared to do for him and to accept from him anything that one human being can or will do for another. I think, as I say, that you* *have not known this, or possibly your references to him, - only three or four, but my memory is very jealous in such matters – would have been more guarded. As to the scientific side of the present circumstances, I am perfectly ready to hear both sides, and will willingly reserve space in Part III of Biometrika for your defense of Mendel, if you think our journal is a suitable locus for your paper "*

The conflict was eventually resolved by 1920 with the rise of population genetics – largely developed by Ronald Fisher, Sewall Wright, and John Haldane. Their work showed that the work of Biometricians and Mendelians was largely easily reconcilable, had the two sides been more receptive of each other's ideas.

II. Neutral Theory of Molecular Evolution

In the 1960s, the technique of protein electrophoresis was developed for proteins. Basically, the idea was that you isolate proteins from an organism (e.g. fruit fly) and run them on an electric field in a gel. The proteins being charged will move on the gel, and their speed will depend on the charge/mass ratio. Now, since sexually reproducing organisms inherit their DNA from their parents – they have two copies of every gene. Therefore, for a particular gene X, the sequence that I inherit from my mother can be same/different from what I inherit from my father. When the proteins are run on a gel – if the inherited protein is the same sequence from both the parents – it will appear as a single band on the protein (having travelled the same distance). But if the inherited sequence from the two parents was different, then the protein from one copy of the gene would be different from the protein from the other copy of the gene. If the two gene sequences are the same – the individual is called homozygous, and if they are different, the individual is called heterozygous.

Largely through application of this technique on populations of Drosophila (fruit fly) and human blood sample analysis, researchers figured out that there was a lot of heterozygosity in the fly and human populations (with respect to the proteins being analysed). What that meant was that, for every gene, there were many sequences coexisting in the population. And the big question out of that was: why was selection not weeding out the deleterious mutations and =picking the best one from among this group?

In 1968, a Japanese researcher Motoo Kimura published a paper in *Nature* where he proposed that an overwhelming majority of mutations that happen in an organism are neutral in nature. That is, they do not have any deleterious or beneficial effect. This was followed by a paper in *Science* by King and Jukes in 1969 where they do an extensive analysis of (protein) sequences (DNA was not sequenced then) available at the time, and show that the argument that Kimura was making was a correct one! This lead to the proposal of what is called as the Neutral Theory of Molecular Evolution – which argues that almost all variation is neutral, and it is only rarely that a beneficial mutation comes across and is selected for. This way, Kimura was able to explain the variation that is seen in nature. In the 1970s and 1980s – the neutral theory underwent changes and was replaced by Nearly Neutral Theory of Molecular Evolution – work largely done by Tomoko Ohta (Kimura's colleague).

Although, we now know that Kimura's original neutral theory is unable to explain a lot of factors regarding evolutionary processes, but what the neutral theory gives is a null hypothesis to start analysis from. The molecular clock argument (developed by Pauling) was largely based on the assumptions of neutral theory.