Leonor Michaelis and Maud Leonora Menten

Celebrating 100 years of the Michaelis–Menten Equation

Leonor Michaelis was an honoured German biochemist and Maud Leonora Menten an honoured Canadian pathologist, during the nineteenth century. Though Michaelis sustained his interest in enzymology and biochemistry, Menten moved to pathology and became a renowned pathologist later in her career. The research collaboration of Michaelis and Menten was phenomenal resulting in the celebrated 'Michaelis–Menten Equation'.

Michaelis and Menten's classic paper titled '*Die Kinetik der Invertin wirkung'*, published in *Biochemische Zeitschrift* in 1913 marks its centenary this year. This seminal paper which proved vital for the teaching of enzyme kinetics, was acknowledged with so much appreciation and attention that no textbook in biology for undergraduate and graduate students across the world is complete without a discussion of the Michaelis–Menten Equation. An earlier paper by Victor Henri and Brown lacked one important insight which was reported by Michaelis and Menten: that insight was the analysis of reaction in terms of the initial rate. Michaelis and Menten introduced the concept of measuring the initial activity of the enzyme by mixing it with substrate so that product accumulation would not inhibit the activity.

Leonor Michaelis (1875–1949)

Leonor Michaelis was born in Berlin, Germany on January 16, 1875. He graduated from the 'humanistic' Koellnisches Gymnasium in 1893. This gymnasium was special as unlike the other humanistic gymnasiums, it also included chemistry and physics labs which were not in general use and it was only the keen initiative of two professors that enabled interested students learn the subjects. It was in this lab that Michaelis's interest in physics and chemistry grew. However, Michaelis moved to the University of Berlin in 1893 to study medicine since he was not sure whether pure science could provide a living. He had eminent instructors like Emil Fischer for chemistry and Oskar Hertwig for histology and embryology, who modulated his interests in various ways. His work on histology of milk secretion under Hertwig was recognized with a prize. He graduated in 1897 with DuBois-Reymond (his physiology teacher) as the Dean of the faculty. His doctoral work was on cleavage determination in frog eggs which enthused him to write a short textbook on embryology which saw its ninth edition in quick succession. Michaelis became acquainted with Paul Ehrlich, an eminent physician scientist and became his private research assistant from 1898 to 1899 during which time he continued his work with extensive histology and staining procedures and discovered 'Janus green' as a vital stain for mitochondria.

His research credits were diverse. He was the first to observe that for the Wassermann test,

aqueous extracts of normal livers could be used, instead of the livers of syphilitic fetuses. He was also the first to show that by using extracts of syphilitic fetus of especially high efficiency, a direct precipitation test could easily replace the complement fixation test. Though he received the offer of 'Professor' in 1905, he preferred to take the position of a bacteriologist in a municipal hospital in Berlin. During World War 1, Michaelis used the opportunity and engaged himself with research on tuberculosis, infectious diseases, gastrointestinal diseases, etc. After the war he resumed his position as bacteriologist. In 1921, he was given, by the new government, the position of 'Professor Extraordinary' at the University of Berlin. However, this came without salary, without grant and without laboratory space which led him to choose a position in an industrial firm which did give him lab space. A big and pleasant break came in 1922, when he was invited to take the position of Professor of Biochemistry in Nagoya University, Japan. The initial one year contract period got extended to three years. One contract followed another and after Japan, Michaelis took up the position as resident lecturer in 1926 at the Johns Hopkins University in Baltimore, USA for three years after which he was with the Rockefeller Institute of Medical Research in New York. His main area of research was physical chemistry, in particular its use in biology and medicine. He kept up active research until his death on October 8, 1949.

Maud Leonora Menten (1879–1960)

Maude Leonora Menten was born in Port Lambton, Ontario on 20 March 1879. Menten received her BA degree in 1904 and MB in medicine in 1907 from the University of Toronto. After that she moved to the Rockfeller Institute of Medical Research , USA and carried out research on the effect of radium on tumours from 1907–1908 and wrote the first monograph of the Institute. She returned to the University of Toronto and became the first Canadian woman to receive a medical doctorate degree in 1911. In 1912, she joined Leonor Michaelis at the University of Berlin, where their path-breaking work resulted in the acclaimed 'Michaelis–Menten Equation'. In 1916, she obtained her PhD in biochemistry from the University of Chicago, USA. Unable to find a job in Canada, Menten moved to the University of Pittsburgh in 1918 and continued her career as a brilliant pathologist.

Menten successfully juggled her time between clinical duties, teaching and research and authored more than 70 publications. Two of her outstanding contributions to research were the use of electrophoretic mobility in studying human haemoglobins, and the use of an azo-dye coupling reaction for the study of alkaline phosphatase in kidneys, which was published in 1944. Despite her achievements, promotion to full professor did not come until 1949. This was one year before her retirement from her position at Pittsburgh. She returned to Canada in 1950 and was involved in active research from 1951 to 1954 at the Medical Institute of British Columbia in Vancouver. However, Menten's ill health forced her to resign from British Columbia in 1954. She returned to Ontario where she died on 20 July 1960 at Leamington.

Besides having very strong scientific skills, Menten was a musician and painter. A petite and beautiful Menten drove fashionable cars like Model T Ford, hiked in the mountains, went on an Arctic expedition, played the clarinet and mastered many languages. This multi-talented nature of Menten always made her to question "What is novel" in Science. She was a very kind woman at heart which shows in her involvement with the sick children and other charity organizations.

The Famous Michaelis–Menten Equation

Michaelis and Menten published their enduring classic paper one hundred years ago (L Michaelis and M L Menten, '*Die Kinetik der Invertinwirkung*', *Biochemische Zeitschrift*, Vol.49, pp.333–369, 1913), in which they report that the rate of an enzyme-catalyzed reaction is proportional to the concentration of enzyme–substrate complex predicted by the Michaelis–Menten equation. In this paper they study the kinetics of invertase. As a research assistant in Leonor Michaelis's lab, Menten had carefully monitored the reaction catalyzed by invertase at different sucrose concentrations. This simple measurement opened up new avenues and dimensions for substrate–enzyme complex and enzyme catalysis.

Michaelis and Menten demonstrated that each enzyme not only has its own substrate but also that at sufficient concentrations of substrate, it has its own rate of causing that substrate to change chemically. They gave mathematical expression to this phenomenon. One of the constants used in expressing this rate is now called the 'Michaelis–Menten Constant'.

We often fail to appreciate the general utility of the Michaelis–Menten equation outside the analysis of enzyme behavior. It seems obvious that one could use advantageously the Michaelis–Menten kinetics to explore biological phenomena involving the interaction of two entities other than enzyme and substrate. For example, it can be used for measuring the rate of photosynthesis, understanding the rate of muscle contraction in response to an electrical stimuli, understanding the antigen-antibody binding and rate of drug clearance from the body, etc. This famous equation must be explored and appreciated in broader contexts.

Suggested Reading

[1] **Wikipedia**

[2] **Kenneth A Johnson and Roger S Goody, The Original Michaelis Constant: Translation of the 1913 Michaelis–Menten Paper, *Biochemistry*. Vol.50, No.39, pp.8264–8269, October 4th, 2011.**

[3] **Leonor Michaelis, D A MacInnes and S Granick, *A Biographical Memoir of Leonor Michaelis 1875–1945*, National Academy of Sciences, Washington DC, 1958.**

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