SOME MATHEMATICAL MODELS THAT INFLUENCED MEDICAL RESEARCH

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SUMMARY

Mathematics is one of the most powerful methods of communication and a language that unites all of science. Mathematics is used to express knowledge in its purest form between the physical and biological sciences, however, there is a huge gulf between the two sciences and researchers have continued to build more bridges between them. The future of science will involve increasing use of mathematics in describing natural and artificial phenomena and in building bridges among diverse disciplines. Mathematical models provide a means of holistic evaluation of natural occurrences and a means of predicting future trends. Mathematical models have been used to halt epidemics and predict probable future occurrences with a high degree of accuracy. It is thus wise for all researchers to explore the incorporation of aspects of mathematical modelling to their fields of research. This will increase the scope and impact of research findings. This essay is a brief examination of the role of mathematical models and the influence of the subject on medical research over the years.

Mathematics and Mathematical Modelling: A mathematical model is a representation of natural or artificial phenomena using mathematical concepts and equations. Mathematical models are usually composed of relationships, constants, and variables. This form of expression is considered among the highest forms of knowledge and most accurate representation of any hypothesis or theory. Mathematical laws are immutable and can span the entire spectrum of time. A model may help to explain a system and to study the effects of different components. Mathematical models also provide a means of making predictions about behaviour of systems through time. Knowledge at the level of mathematical models is very near perfection as possible. A good mathematical model can alter the way we perceive phenomena, while poor theories continue to change and be improved upon. Mathematical models are highly regarded by workers in every field of human knowledge. This makes mathematics the queen of all sciences and the ultimate language of expression in science.

Traditionally, mathematical models are made up of four major components; the governing equation, defining equations, constitutive equations, and constraints. Models may be linear, non-linear, static, dynamic, discrete, continuous, deterministic, probabilistic (stochastic), deductive, inductive, floating, or mixed. Maps and graphs represent very early uses of mathematical modelling. Usually the easiest part of model evaluation is checking whether a model fits experimental measurements or other empirical data. In models with parameters, a common approach to test this fit is to divide the data into two subsets: training data and verification data. The training data is used to estimate the model parameters. An accurate model will closely match the verification data even though these data were not used to set the model's parameters. This process is referred to as cross-validation in statistics. Where data involves a lot of variability (as seen with biological data), statistical models have been developed that can handle them. Over the millennia, mathematicians have developed powerful methods and tools of analysis.

History has recorded many significant mathematicians. Great mathematicians include Pythagoras, Euclid, Archimedes, Ptolemy, Hipparchus, Copernicus, Fibonacci, Fermat, Kepler, Gauss, Galileo, Newton, and Descartes. Perhaps the most notable mathematician, whose work made very significant impact on biomedical research, is Johann Carl Friedrich Gauss, the man who extensively described the Normal Curve which is fundamental to the field of Statistics.

Johann Carl Friedrich Gauss was a German mathematician who contributed significantly to many fields, including number theory, algebra, statistics, analysis, differential geometry, geodesy, geophysics, mechanics, electrostatics, astronomy, matrix theory, and optics. He is referred to as the foremost of mathematicians and greatest mathematician since antiquity. Gauss had an exceptional influence in many fields of mathematics and science and is ranked as one of history's most influential mathematicians.

Carl Friedrich Gauss (1777–1855), painted by Christian Albrecht Jensen

Gauss was born on 30 April 1777 in the lower Saxony, Germany. A son of humble parents his intellectual abilities amazed all that came in contact with him. A child prodigy, he discovered many mathematical theorems on his own, without looking them up in textbooks. He was the first to prove the quadratic reciprocity law, which allows mathematicians to determine the solvability of any quadratic equation.

Gauss was a religious man who once wrote, after solving a very difficult problem that once defeated him that "finally, I succeeded – not on account of my hard efforts – but by the Grace of the Lord." Gauss declared he firmly believed in the afterlife, and saw spirituality as something essential for human beings. He invented many new methods in astronomy. His extensive work on the Normal curve gave a foundation for Statistics and Mathematical Modelling.

The Normal Distribution Curve: the Normal (or Gaussian) distribution is a continuous probability distribution and in its most general form states that averages of random variables independently drawn from independent distributions (populations, samples, etc.) converge in distribution to the Normal, that is, become normally distributed when the number of random variables is sufficiently large. The probability density of the Normal distribution can be represented by the equation:

$$f(x \mid \mu, \sigma^2) = \frac{1}{\sqrt{2\sigma^2\pi}} e^{-\frac{(x-\mu)^2}{2\sigma^2}}$$

Where μ is mean or expectation of the distribution (and also its median and mode), σ is standard deviation, and σ^2 variance.

Some Early Mathematical Models in Medical Literature: A search of PUBMED titles containing the phrase 'mathematical model' shows that Publications on applications of mathematical models to biomedical research have risen progressively over the years (Figure 1). Among the earliest applications of mathematical models in the biomedical field were reports by Bray, Thorpe, White, Bush, and Mosteller who described a differential mathematical models as early as 1951.[1]

In a series of papers, Bray et al published reports on the kinetics of reactions involving benzoic acid, phenols and compounds which give rise to them. These models assume different approaches to first and zero order kinetics and the transition in the kinetics of metabolism described[2]. Howard Milhorn and colleagues described a mathematical model of the human respiratory system in 1965.[3] Assumptions that were made in the determination of the equations of the model include that the system consists of three compartments (the lungs, brain tissues, and the body tissues) and that blood flow to the tissues is determined by arterial PCO_2 and PO_2. The equations were tested using an IBM 1620 digital computer; although the model predictions approximated experimental results, the authors noted areas requiring further improvement.

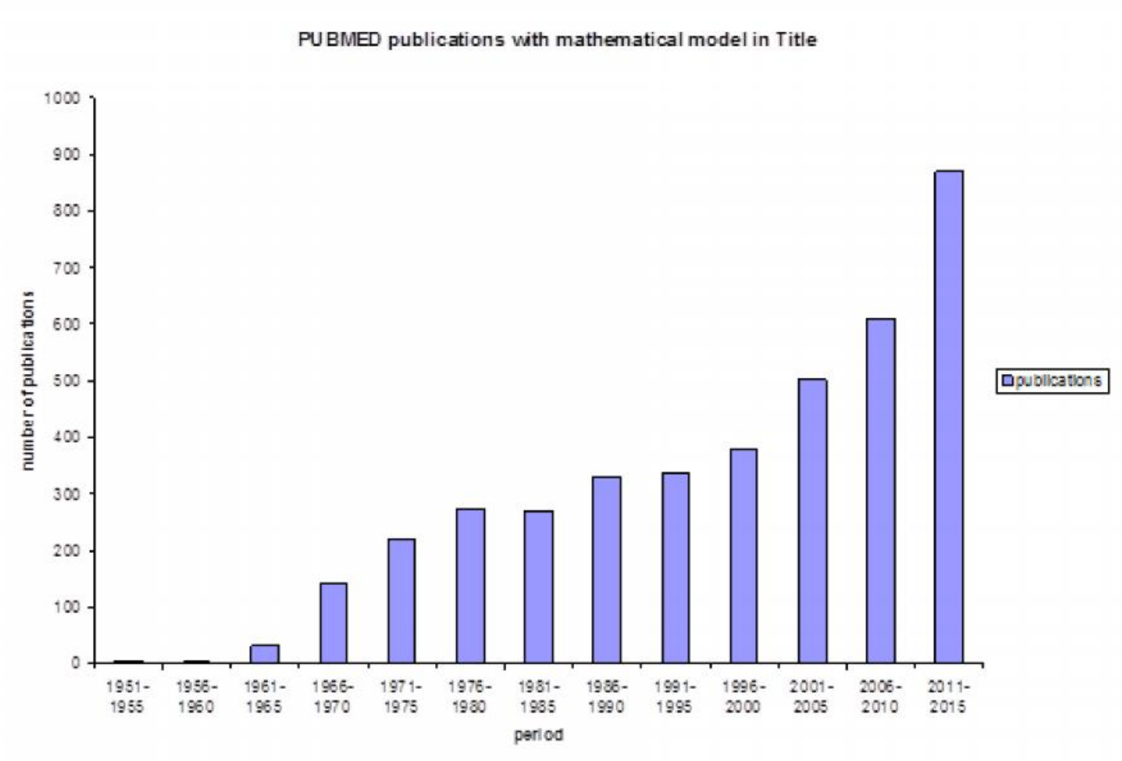
Infectious diseases are an important focus of mathematical modelling research. In the abstract of the publication by Najera in 1974, it was noted that a malaria control field research trial in Northern Nigeria was planned with the aid of a computer simulation based on Macdonald's mathematical model of malaria epidemiology.[4] Theoretical predictions of the model showed wide variation when compared to the field values obtained. It was concluded that research efforts should be encouraged to increase knowledge of the basic epidemiologic factors, their variation and correlations, and that with these, more realistic theoretical models could be developed. This supports the well-known fact that mathematical models are as good as the data used in developing them. In pharmacology, the entire subject of pharmacokinetics is founded on mathematical models. Some other early reports of mathematical modelling research in biomedical fields are shown in Table 1.

The Ebola Virus Disease (EVD) Epidemic of West Africa: Ebola virus disease is a lethal human and primate disease that currently requires particular attention from the international health authorities due

Table 1: Some early reports of mathematical modelling research in biomedical fields

Lead author	Year	Title	Ref
Hammerton, M.	1959	A mathematical model for perception and a theoretical confusion function	(5)
Funk, J. E.	1960	A mathematical model for gas-liquid partition chromatography	(6)
Ammann, P. R.	1961	In vivo gamma lung measurements--a mathematical model	(7)
Dantzig, G. B.	1961	A mathematical model of the human external respiratory system	(8)
Gott, F. S.	1961	A mathematical model of dilution curves for flow study	(9)
Wajchenberg, B. L.	1961	Preliminary mathematical model for glucagon-induced hepatic glycogenolysis in man	(10)
Greene, P. H.	1962	On looking for neural networks and "cell assemblies" that underlie behavior. I. A mathematical model	(11)
Grene, P. H.	1962	On looking for neural networks and "cell assemblies" that underlie behavior. II. Neural realization of the mathematical model	(12)
Mellergard, M	1962	A mathematical model for clinical diagnosis	(13)
Shumway, R. H.	1962	Mathematical model of transport mechanisms influencing strontium 90 levels in milk	(14)

to important outbreaks in some Western African countries and isolated cases in the UK, the USA and Spain.[15] Very few people are aware of the role mathematics played in the containment of the Ebola epidemic of 2015. Be-CoDiS, a Mathematical Model to Predict the Risk of Human Diseases Spread between Countries - Validation and Application to the 2014-2015 Ebola Virus Disease Epidemic was developed and described in a publication by Ivora, Ngom, and Ramos in 2015. The model is a novel deterministic spatial-temporal model, called Between-Countries Disease Spread (Be-CoDiS), which was designed to study the evolution of human diseases within and between countries. The main interesting characteristics of Be-CoDiS are the consideration of the movement of people between countries, the control measure effects and the use of time-dependent coefficients adapted to each country.[15] While this model was designed to predict outbreaks and spread of the deadly disease, researchers faced a difficult decision on the best way to conduct a clinical trial of a vaccine that did not have adequate pre-clinical data on safety in animals. Yet the vaccine was to be used in humans. The epidemic offered no opportunity for the prolonged pre-clinical phases of trial of the vaccine. Scientists turned to mathematical modelling.



Policy makers were confronted with difficult decisions on how best to test the efficacy of Ebola Virus Disease (EVD) vaccines. A stepped-wedge cluster study (SWCT) was proposed as an alternative to a more traditional randomized controlled vaccine trial to address these concerns.[16] In 2016, Ibrahim Diakite and colleagues proposed a novel "ordered stepped-wedge cluster trial" (OSWCT) designed to address these limitations of the standard SWCT.[17] The design was based on a mathematical model. Firstly, they constructed a meta-population model that combines EVD transmission and individuals' movements between regions in order to predict the spatiotemporal trends of the disease. Then they used either the observed or modelled incidence data within districts of Sierra Leon to assign clusters to receive vaccination for the OSWCT designs. Then they used a stochastic model to simulate all trial designs, and finally used a nonparametric method (permutation test) to analyse the simulated data and to estimate the statistical power of trial designs. The results supported OSWCTs as a more efficient design than the standard SWCT.

Ngwa GA and Teboh-Ewungkem described a mathematical model with quarantine states for the dynamics of ebola virus disease in human populations.[18] The model was designed to evaluate transmission of the disease both in treatment centres and in the community. Possible sources of exposure to infection, including cadavers of Ebola Virus victims, were included in the model derivation and analysis. The model's results showed that there exists a threshold parameter, R0, with the property that when its value is above unity, an endemic equilibrium exists whose value and size are determined by the size of this threshold parameter, and when its value is less than unity, the infection does not spread into the community. The results showed that eventually the system settles down to a nonzero fixed point when there is constant recruitment into the population of 555 persons per day and for $R0 > 1$. The values of the steady states were completely determined in terms of the parameters in the cases. Their analysis also showed that it was possible to control EVD infection in the community provided there is a reduction and maintenance of the reproduction number to below unity. They found that such control measures were possible if there was effective contact tracing and identification of EVD patients and effective quarantining, since a reduction of the proportion of cases that escape quarantine reduces the value of R0. Additionally, the model results indicated that when there

Table 2: Mathematical models of Ebola Virus Disease (EVD)

Lead Author	Year	Title	Ref
Chowell G	2004	The basic reproductive number of Ebola and the effects of public health measures: the cases of Congo and Uganda.	(19)
Althaus CL	2014	Estimating the Reproduction Number of Ebola Virus (EBOV) During the 2014 Outbreak in West Africa.	(20)
Towers S	2014	Temporal variations in the effective reproduction number of the 2014 west Africa ebola outbreak.	(21)
Chowell, G.	2014	Transmission dynamics and control of Ebola virus disease (EVD): a review	(22)
Atangana, A.	2014	On the mathematical analysis of Ebola hemorrhagic fever: deathly infection disease in West African countries	(23)
Agusto, F. B.	2015	Mathematical assessment of the effect of traditional beliefs and customs on the transmission dynamics of the 2014 Ebola outbreaks	(24)
Althaus, C. L.	2015	Ebola virus disease outbreak in Nigeria: Transmission dynamics and rapid control	(25)
Xia, Z. Q.	2015	Modelling the transmission dynamics of Ebola virus disease in Liberia	(26)
Vandebosch, A.	2016	Simulation-guided phase 3 trial design to evaluate vaccine effectiveness to prevent Ebola virus disease infection: Statistical considerations, design rationale, and challenges	(27)
Fang, L. Q	2016	Transmission dynamics of Ebola virus disease and intervention effectiveness in Sierra Leone	(28)
Chowell, G.	2016	Mathematical models to characterize early epidemic growth: A review	(29)
Agusto, F. B.	2017	Mathematical model of Ebola transmission dynamics with relapse and reinfection	(30)

was a high constant number of recruitment into an EVD community, quarantining alone may not be sufficient in eradicating the disease. However, it may serve as a buffer enhancing a sustained epidemic. The model predicted that reducing the number of persons recruited per day could bring the diseases to very low values. These and other models guided decisions that eventually resulted in effective control of the disease. Some other publications of mathematical modelling EVD research are shown in Table 2.

CONCLUSION

Mathematics is one of the most powerful methods of communication and a language that unites all of science. Mathematical models unite the biological and physical sciences. Mathematical models have been used to obtain important results in biomedical fields; they provide a means of holistic evaluation of natural occurrences and a means of predicting future trends with a high degree of accuracy. Math models have been used to predict and halt epidemics. There remains a huge gulf between the biological and physical sciences, however, researchers have continued to build more and more bridges between them. The future of science will involve more and more use of mathematics in describing natural and artificial phenomena. It is thus wise for all researchers to explore the incorporation of aspects of mathematical modelling to their fields of research. To explore adding the 'Queen' of the sciences to their hypotheses, theories, and arguments.

ACKNOWLEDGEMENTS

I acknowledge my dear wife Afie for her continuous and ever increasing support and encouragement. I thank Pharmacist Ayo Badejo, a colleague and friend, for diligently proofreading the final draft of the document. Photographs, aspects on Carl Gauss, the Normal curve, and types of mathematical models are from wikipedia articles on the subjects. I acknowledge the National Library of Medicine, USA, for the very essential public databases of biomedical literature, PUBMED and PUBMED CENTRAL (PMC). I thank the Board of *AIPM* and the Publishers of the Journal (ARD-UCH) for sustaining the Chronicles of Medical History. Above all, my greatest gratitude and all credit go to God.

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