

Mathematical Contributions to the Study of Diabetes Mellitus

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***Abstract:** The purpose of the studies outlined in this paper is to describe some indicative and non-standard, but not exhaustive, quantitative contributions to the collection of diseases within the Diabetes Mellitus (DM) spectrum. While the paper has implications for bioinformatics related to DM, the paper is broader than that; it is more about DM-related bioprocesses illuminated by bioinformatics than about the bioinformatics per se. In effect it is an argument against being locked into one particular paradigm in the laudable study of this complicated set of diseases which increasingly dominate public health budgets, not to mention the lives of the patients with DM and their families.*

***Keywords:** Compartment Modelling, Differential equations, Difference equations, Technetium, Diabetes mellitus, Glucose tolerance tests, Gamma variate.*

Introduction

The two key chemicals in the constant endeavour of the body to produce energy are glucose and insulin. The hormone insulin facilitates the entry of glucose into cells for conversion into energy. Diabetes Mellitus (DM) can be a result of the impairment of the ability of the body to obtain the energy it needs to function properly.

“In biology, a missing link connecting data generation and data-driven discovery is the training that prepares researchers to effectively manage and analyze data” [44]. The numerical issues start with counting and the accuracy and the precision of raw data [43]. For instance, it is estimated that the global number of people with diabetes has quadrupled between 1980 and 2015: Dr Cherian Varghese, the World Health Organization (WHO) Coordinator of the Management of Noncommunicable Diseases, calls it “a tsunami in slow motion”. Thus the study of various facets of diabetes can usefully involve multidisciplinary research to which the mathematical sciences can contribute (Fig. 1).

The salient features are:

- what are the medical problems?
- what are appropriate mathematical approaches?
- how useful are the results in practice?
- how can the recommendations be represented for maximum effect? [12]

In other words, this paper is partly expository, but mainly a summary of some research results across a complex perspective of mathematical contributions to medicine, compatible with but complementary to previous work [32, 33]. What is new is connecting apparently disparate research under this quantitative theme.

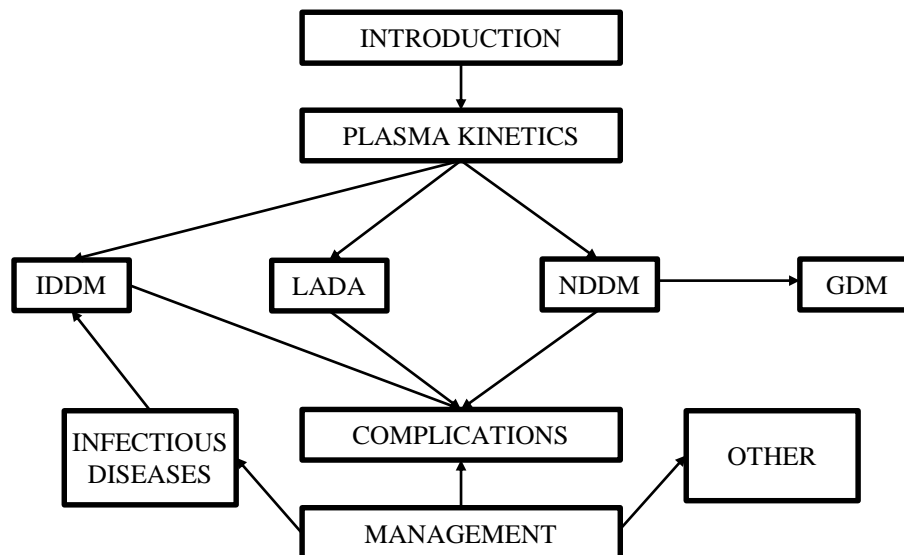


Fig. 1 DM factors

Kinetics

Essentially, the two main forms of diabetes are different diseases with similar symptoms. In both cases, diabetes mellitus is a chronic state of excessive concentration of glucose in the blood. The major regulator of glucose concentration in the blood is insulin, a hormone synthesized and secreted by the beta cells of the islets of Langerhans in the pancreas. High blood sugar levels may be due to a lack of insulin and/or to excess of factors that oppose its action and cause insulin resistance. Type 1 Diabetes Mellitus (T1DM) is the name given to that form of the disease where the endogenous production of the insulin in the pancreas is eliminated. Insulin from an external source needs to be provided, usually by subcutaneous injection [2]. In the case of Type 2 Diabetes Mellitus (T2DM) it is usually the quantity or efficacy of insulin that is affected, but there is still secretion of insulin from the pancreas. This form of the disease is usually treated with a combination of diet, exercise and oral agents, though sometimes insulin treatment is also required.

This imbalance can lead to abnormalities of carbohydrate, protein and lipid metabolism. The major complications of diabetes include characteristic symptoms, the progressive development of disease of the capillaries of the kidney and retina, damage to the peripheral nerves, and accelerated arteriosclerosis [23, 39]. Owens [16] presents a historical summary of the disease, and Bliss [3] relates the human drama and scientific enterprise behind the original discovery of insulin.

Highly specific insulin receptors have been identified on human erythrocytes [20]. The rate at which red blood cells (erythrocytes) fall in vitro is used as a common haematological test for a number of pathological conditions, though its clinical effectiveness is hampered by limited understanding of whole-blood sedimentation and flaws in the underlying models [9]. The application of Stefan moving boundary problems can clarify the mechanisms for the test to be more usefully interpreted [21].

The mathematical modelling of subcutaneous insulin clearance and prehepatic insulin secretion can permit focus on the main clinical features. The process is affected by such factors as insulin concentration, the half-life of the insulin, as well as the site, method and type of injection [8]. Knowledge of insulin kinetics also has uses in the study of pre-diabetes [37] and diabetic

complications [17], as well as in such therapeutic innovations as pumps [18], jet injectors [33] and bio-synthetic human insulins [6, 16].

By utilizing the experimental facts that insulin and C-peptide are secreted in equimolar amounts from the pancreas and that the C-peptide is not stored in the liver we can estimate the pre-hepatic insulin secretion rate in T2DM with compartment [4] and gamma variate modelling [32].

Observation of the appearance of insulin in the plasma shows a rising curve initially [22]. This suggests that insulin is delivered to the plasma pool proportionally with time, t , though this is an oversimplification of the biological process since it assumes that all subcutaneous insulin is immediately available for transcapillary absorption:

$$y \propto t^a \quad (a > 0) \text{ or}$$

$$\frac{dy}{dt} = \frac{ay}{t} \quad (t \neq 0) = k_{sp}x,$$

in which we assume a fractional rate of systemic delivery k_{sp} here and subsequently a degradation rate constant k_d from the subcutaneous compartment. The plasma pool represents the plasma distribution volume with k_c as the metabolic clearance rate:

$$\frac{dy}{dt} = \frac{ay}{t} - k_c y.$$

Disappearance from the subcutaneous site is found from:

$$\frac{dx}{dt} = -(k_d + k_{sp})x = -kx \text{ or}$$

$$x = x_0 e^{-kt},$$

which can be readily linearized. This is a major advantage. Otherwise one can be forced to guess and approximate an initial seeding value. This can lead to computational errors, particularly ill-conditioning [34, 39]. Appearance in the plasma (or clearance from the injection site) is next found from:

$$\begin{aligned} \frac{1}{y} \frac{dy}{dt} - \frac{a}{t} &= -k_c, & \frac{d}{dt} \ln \left(\frac{y}{t^a} \right) &= -k_c, \\ \frac{d}{dt} \ln y - a \frac{d}{dt} \ln t &= -k_c, & y &= y_0 t^a e^{-k_c t} \end{aligned}$$

This is a gamma variate function, and from it the prehepatic C-peptide rate can be expressed as:

$$\frac{dy}{dt} = ay_0 t^{a-1} e^{-k_c t} - k_c y_0 t^a e^{-k_c t},$$

in which the former term on the right hand side can be attributed to the non-degraded clearance rate from the subcutaneous site and the latter term is the clearance rate from the plasma pool. This “gamma variate” model was tested with patients [25, 29] and the external disappearance of I^{125} labelled human soluble insulin (U100) with simultaneous measurement of plasma immunoreactive insulin, C-peptide and glucose in order to test insulin absorption. To assess the relationship between insulin absorption and subcutaneous blood flow the latter was measured by the disappearance of 99m technetium [30].

These issues are still open to research [41]. Adaptive control strategies can also be applied to closed-loop systems for T1DM patients [5, 10]. Major problems with such systems still include:

- the size and reliability of the glucose sensor,
- the time taken to analyse the plasma insulin and glucose concentrations,
- the sensitivity of the models,
- the mathematical analysis of the control algorithms, and
- the adaptability of the control algorithms.

Management

Non standard statistical approaches such as exploratory data analysis (EDA) [28], meta-analysis [23] and generalized nets [24] may shed light on complications in ways that parametric statistics do not. So too the difference calculus can be useful when dealing with discrete data measurements.

An EDA box-and-whisker plot, (Fig. 2) for instance, displays the median as the measure of central tendency and the inter-quartile range as the measure of spread, both of which are preferable to the more commonly used mean and standard deviation in the absence of a near normal underlying distribution. The length and width of the box mean something too with the width related to the number of readings; thus visible comparisons can be readily made. So too the whiskers and outliers can suggest items for more detailed investigation. The outliers, both “good” and “bad” can tell us something which, particularly in clinical investigations, may have implications for management of particular sub-classes.

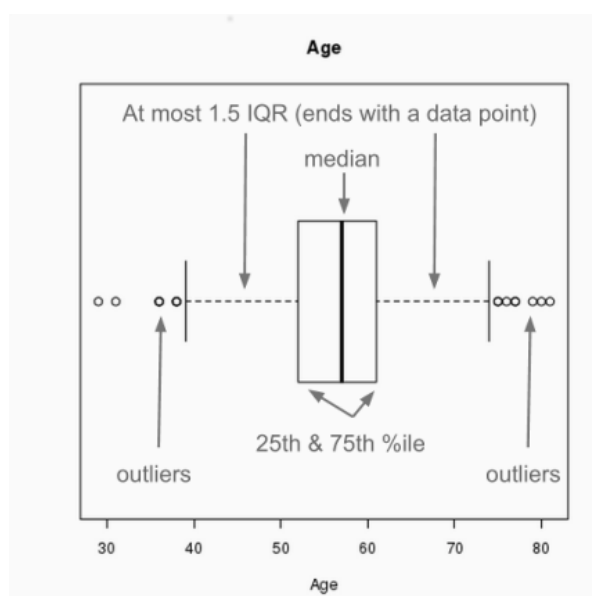


Fig. 2 Box-and-whisker plot

Dietary patterns that induce excessive insulin secretion may contribute to worsening insulin resistance and beta-cell dysfunction [13]. Randomized controlled trials can illuminate complex situations where there can often seem to be too much data. This has occurred in clarifying the effects of semi-synthetic human insulin [6, 25] and associated instrumentation. False positives can particularly delay the commercial production of inventions [14].

Such instrumentation is usually designed to alleviate symptoms or complications. More fundamental research attempts to look at triggers in the autoimmune T1DM [41] and more controversially T1.5DM. If the latter is really different from D2M [36], then its management strategies may need to be different [11] and issues such as the extent of insulin resistance and the onset of insulin treatment are quantitative. The place of insulin resistance in Alzheimer's disease may require similar analysis.

Summary

The author's late wife was classified as a very brittle type 1 diabetic back in 1946. During forty three years of marriage and living in different countries we, and particularly she, experienced many different, and at times conflicting, therapies for her treatment. There were many major improvements in that time, but we did also experience the unpleasant consequences when there was slavish attachment to a specific approach rather than to the care of the whole person. Quantitative approaches should never be separated from the qualitative of course, but they can give a focus to the clinical. The following table summarizes issues touched on in this paper.

Diabetes Issues	Differential calculus	Difference calculus	Statistical techniques
Kinetics			
Erythrocyte Sedimentation Rates	[21]		[20]
Insulin Secretion Rates	[8, 36, 38]	[41]	[26, 32]
Blood Glucose Regulation	[4, 5, 20]		[28, 40]
Subcutaneous Injections	[22]		[24]
Intravenous Infusion	[2, 34]	[14]	[13]
Comparison of Insulins	[9]	[27]	[6, 26]
Radioactive Insulin Isotopes			[29, 30]
Management			
Infectious Diseases		[7]	[42]
Complications	[9, 36]	[11]	[16, 17, 23]
Nutrition	[39]		[1, 12]
Gestational Diabetes Mellitus			[31]
Nephropathy	[15]	[24]	[32]
Pre-diabetes	[37]		[33]
Instrumentation	[19]	[14]	[35]

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- Professor Stephen Colagiuri *OA*, Faculty of Medicine, University of Sydney, Australia;
- Professor Barry S. Thornton *AM*, Faculty of Science, University of Technology Sydney.

Competing interests

The author declares that he has no competing interests.

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