Mathematical Contributions to the Study of Diabetes Mellitus

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Received: March 05, 2016 **Accepted: June 26, 2017**

Published: September 30, 2017

***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.

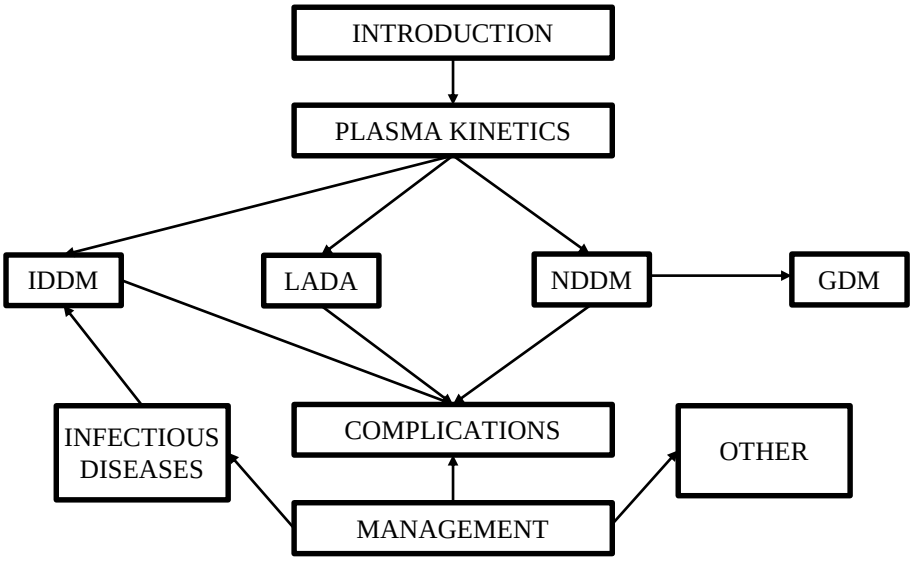

Fig. 1 DM factors

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:

$y \propto t^a \, (a > 0)$ or

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

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:

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

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

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:

$$\frac{1}{y}\frac{dy}{dt} - \frac{a}{t} = -k_c, \qquad \frac{d}{dt} ln\left(\frac{y}{t^a}\right) = -k_c,$$

$$\frac{d}{dt} ln\, y - a\frac{d}{dt} ln\, t = -k_c, \qquad y = y_0 t^a e^{-k_c t}$$

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

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

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.

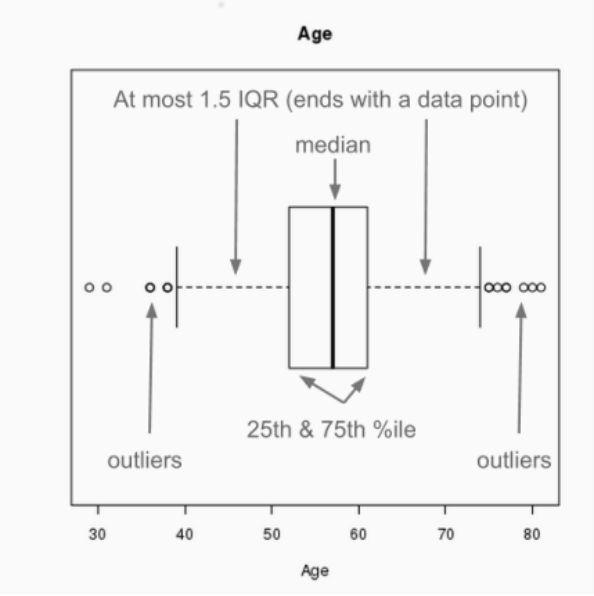

Fig. 2 Box-and-whisker plot

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]

Acknowledgements

The foregoing clinical data were obtained while working with research grants from:

- the Australian Research Council, for work at Prince of Wales Hospital, Sydney;
- the Australian Academy of Sciences, for research at University Hospital Cardiff;
- the Royal Society, for work at the University of Wales College of Medicine;
- the World Health Organization, for a course at Fitzwilliam College, Cambridge;
- the Foundation for Australian Resources, University of Technology Sydney.

The studies in this paper were also approved by the local human research ethics committees in each case and informed consent was given by each subject. Gratitude is expressed too to the following endocrinologists for supervision, discussions and clinical data provided to the author at various times:

- the late Professor Robert Turner *CBE*, University of Oxford, Oxford, England;
- Professor David Owens *CBE*, University of Wales College of Medicine, Cardiff, Wales;
- 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.

References

1. Bell K., R. Gray, D. Munns, P. Petocz, G. Steil, G. Howard, S. Colagiuri, J. Brand-Miller (2016). Clinical Application of the Food Insulin Index for Mealtime Insulin Dosing in Adults with Type 1 Diabetes: A Randomized Controlled Trial, Diabetes Technology and Therapeutics, 18, 218-225.
2. Binder C (1969). Absorption of Injected Insulin, Acta Pharmacol Toxicol, 27(2), 1-84.
3. Bliss M. (1982). The Discovery of Insulin, University of Chicago Press.
4. Chiarella C., A. G. Shannon (1986). An Example of Diabetes Compartment Modelling, Math Modelling, 7, 1239-1244.
5. Chisholm D. J., E. W. Kraegen, M. J. Hewett, S. Furler (1984). Low Subcutaneous Degradation and Slow Absorption of Insulin in Insulin-dependent Diabetic Patients during Continuous Subcutaneous Insulin Infusion at Base Rate, Diabetologia, 27, 238-241.
6. Colagiuri S., J. J. Miller, P. Petocz (1992). Double-blind Crossover Comparison of Human and Porcine Insulins in Patients Reporting Lack of Hypoglycaemia Awareness, Lancet, 339, 1432-1435.
7. Dubeau F., A. G. Shannon (1996). A Fibonacci Model of Infectious Disease, The Fibonacci Quarterly, 34, 257-270.
8. Galloway J. A., C. T. Spradklin, R. L. Nelsom, J. M. Warner (1981). Factors Influencing the Absorption, Serum Insulin Concentration and Blood Glucose Responses after Injections of Regular Insulin and Various Insulin Mixtures, Diabetes Care, 4, 366-376.
9. Hořejšī V. (1991). Surface Antigens of Human Leucocytes, Advances in Immunology, 49, Academic Press, San Diego, 1-59.
10. Jahangiri S., K. Maleknejad, M. T. Kajani (2017). A Numerical Solution of Volterra's Population Growth Model Based on Hybrid Function, Int J Bioautomation, 21(1), 109-120.
11. Leslie D., C. Valeri (2003). Latent Autoimmune Diabetes in Adults, Diabetes Voice, 48(4), 14-16.
12. Miles M. B., A. M. Huberman, J. Saldana (2013). Qualitative Data Analysis: A Methods Sourcebook, 3rd Edition, Sage, London, 105-272.
13. Nguyen H. T., A. G. Shannon, S. Colagiuri, D. Sands (1994). Self-organising Fuzzy Logic Control of Plasma Glucose, Australian Diabetes Society Annual Scientific Meeting, Brisbane, September 25-30.
14. Nguyen H. T., N. Ghevondian, T. W. Jones (2009). Real-time Detection of Nocturnal Hypoglycemic Episodes Using a Novel Non-invasive Hypoglycemia Monitor, Conf Proc IEEE Eng Med Biol Soc 2009, 3822-5, doi: 10.1109/IEMBS.2009.5335144.
15. Ollerton R. L., A. G. Shannon (1991). Difference Equations and an Artificial Pancreatic Beta-cell, Int J Math Educ Sci Technol, 22, 545-554.

16. Owens D. R. (1986) Human Insulin, MTP Press, Lancaster.
17. Owens D. R., A. G. Shannon, I. R. Jones, J. Vora, T. M. Hayes, S. Luzio, S. Williams (1986). Metabolic and Hormonal Derangement in Newly Presenting, Previously Untreated Non-insulin Dependent Diabetic Patients, In R. Tattersall (Ed.), Non Insulin Dependent Diabetes Mellitus, Novo, Copenhagen, 23-28.
18. Owens D. R., A. Vølund, D. Jones, A. G. Shannon, I. R. Jones, A. J. Birtwell, S. Luzio, S. Williams, J. Dolben, F. N. Creagh, J. R. Peter (1988). Retinopathy in Newly Presenting Non-insulin-dependent (Type 2) Diabetic Patients, Diabetes Research, 9, 59-65.
19. Pickup J. C., H. Keen, J. A. Parsons, K. G. M. M. Alberti (1978). Continuous Subcutaneous Insulin Infusion: An Approach for Achieving Normoglycaemia, British Medical Journal, 1, 204-207.
20. Porte D. Jr, J. B. Halter, C. de Haën, J. P. Palmer, C. M. Asplin, R. J. Graf, M. A. Pfeifer (1982). Diabetes Mellitus: Selected Aspects of Pathophysiology and Clinical Practice, In Freinkel N. (Ed.) Contemporary Metabolism, Vol. 2, Plenum, New York, 75-147.
21. Reuben A. K., A. G. Shannon (1990). Some Problems in the Mathematical Modelling of Erythrocyte Sedimentation, IMA J Math Appl Med Biol, 7, 145-156.
22. Schlichtkrull J. (1977). The Absorption of Insulin, Acta Paediatr Scand, 270, 97-102.
23. Shannon A. G. (1986). Meta-analysis in Medicine, J R Soc Med, 79(11), 686.
24. Shannon A. G., J. G. Sorsich, K. T. Atanassov (1996). Generalized Nets in Medicine, Prof. Marin Drinov Publishing House of the Bulgarian Academy of Sciences, Sofia.
25. Shannon A. G. (2010). Gamma Variate Analysis of Insulin Kinetics in Type 2 Diabetes, Int J Bioautomation, 14(4), 263-270.
26. Shannon A. G., S. Colagiuri, J. J. Miller (1990). Comparison of Glycaemic Control with Human and Porcine Insulins – A Meta-analysis, Medical Journal of Australia, 152, 49.
27. Shannon A. G., R. L. Ollerton, D. R. Owens (1993). A Cholesky Decomposition in Matching Insulin Profiles, In Bergum G. E., A. F. Horadam, A. N. Philippou (Eds.), Applications of Fibonacci Numbers, Vol. 5, Kluwer, Dordrecht, 497-506.
28. Shannon A. G., D. R. Owens (1986). Exploratory Data Analysis in Endocrinology, Proceedings of the Endocrine Society of Australia, 142.
29. Shannon A. G., J. M. Hogg, R. L. Ollerton, S. Luzio, D. R. Owens (1994). A Mathematical Model of Insulin Secretion, IMA J Math Appl Med Biol, 11, 245-266.
30. Shannon A. G., C. K. Wong, J. Vora, D. R. Owens (1995). Radioactive Labelled Insulin Kinetics, Int J Math Educ Sci Technol, 26(2), 329-335.
31. Shannon A. G., C. K. Wong, J. R. Wyndham (1997). Gestational Diabetes Mellitus: A Meta-analysis, New South Wales Department of Health, Sydney.
32. Shannon A. G. (2011). Reflections on Some Mathematical Modeling in Endocrinology, Int J Bioautomation, 15(3), 182-199.
33. Shannon A. G., H. T. Nguyen (2013). Empirical Approaches to the Application of Mathematical Techniques in Health Technologies, Int J Bioautomation, 17, 125-150.
34. Sparacino G., G. D. N., G. Pillonetto, C. Cobelli (2014). Deconvolution, In Carson E., C. Cobelli (Eds.), Modelling Methodology for Physiology and Medicine, 2nd Edition, Elsevier, Amsterdam, Ch. 3.
35. Taylor R., P. D. Home, K. G. M. M. Alberti (1981). Plasma Free Insulin Profiles after Administration of Insulin by Jet and Conventional Syringe Injection, Diabetes Care, 4, 377-379.
36. Turner R., I. Stratton, V. Horton, S. Manley, P. Zimmett, I. R. Mackay, M. Shattock, G. F. Bottazo, R. Holman (1997). UKPDS25: Autoantibodies to Islet Cytoplasm and Glutamic Acid Decarboxylase for Prediction of Insulin Requirement in Type 2 Diabetes, Lancet, 350, 1288-1293.

37. Twigg S. (2004). Pre-diabetes: Some Answers and Many Remaining Questions, Diabetes Management, 9, 9.
38. Van Cauter E., F. Mestrez, J. Sturis, K. S. Polonsky (1992). Estimation of Insulin Secretion Rates from C-peptide Levels, Diabetes, 41, 368-377.
39. Vilsbøll T., T. Krarup, J. Sonne, S. Madsbad, A. Vølund, A. G. Juul, J. J. Holst (2003). Incretin Secretion in Relation to Meal Size and Body Weight in Healthy Subjects and People with Type 1 and Type 2 Diabetes Mellitus, J Clin Endocrinol Metab, 88(6), 2706-2713.
40. Wang L., Y. Wang, Q. Chang (2016). Feature Selection Methods for Big Data Bioinformatics: A Survey from the Search Perspective, Methods, 111, 22-31.
41. Wang X., B. C. Hansen, D. Shi, Y. Fang, F. Du, B. Wang, Y. M. Chen, F. M. Gregoire, Y.-X. J. Wang (2013). Quantification of β-cell Insulin Secretory Function Using a Graded Glucose Infusion with C-peptide Deconvolution in Dysmetabolic, and Diabetic cynomolgus Monkeys, Diabetology & Metabolic Syndrome, doi: 10.1186/1758-5996-5-40.
42. WHO Expert Committee on Diabetes Mellitus (1980). Technical Report No. 646, World Health Organization, Geneva.
43. WHO Noncommunicable Diseases (2015). Progress Monitor, World Health Organization, Geneva.
44. Williams J. J., T. K. Teal (2017). A Vision for Collaborative Training Infrastructure for Bioinformatics, In Adams N. R. (Ed.), Data Science, Learning and Applications to Biomedical and Health Sciences, Annals of the New York Academy of Sciences, 1387, 54-60.

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