Mathematical approaches to address biological questions in human welfare and disease management

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Mathematics and statistics aid research at multiple magnitudes. Their role in biological field is wide and encompasses diverse applications. Recent years have seen development of dedicated equations, tools and softwares for analyses and interpretation for plethora of biological fields. Consequently, biotechnological or biomedical research-oriented results are intricately wired by the quantification of patterns that remain null and void unless comprehended. Continuous generation of data over decades have developed applications into theoretical biology and experimental biology. These fields are quite detailed to describe biological systems independently. The expanse of mathematical /statistical applications in biology is difficult to analyse and present in limited space. In the current review, we have attempted to collate applications of mathematics and simulation in few fields of biology. Specifically, sections have been dedicated for quorum sensing systems in bacterial world and major human diseases – cancer and diabetes. These diverse fields are examples to show mathematical bridging from data generation to data prediction.

Keywords- Review, Mathematical model, Simulation, breast cancer, cervical cancer, Diabetes, Quorum sensing

# Introduction

Biological entities invariably depend on numerous biotic and abiotic parameters. These parameters are often maintained during experiments so as to cause minimal alteration to experimental results. This approach of isolation research has successfully led to numerous discoveries. Nonetheless, subtle variations cooperatively play significant functions in any experimental system and systematic studies have emerged with newer supportive data. Many such multi-parametric studies are modelled and simulated by well-defined mathematical support.

Recent developments and application of high-throughput technologies like microarrays, next-generation sequencing (genomics) and mass spectrometry (proteomics and metabolomics), have enabled generation of enormous amounts of data. These technologies allow simultaneous capture of multiple parameters associated with any biological research that give way to generation of an array of associated metadata. Enormity of such huge datasets gives rise to high dimensionality that represents association with respective parameters. These databases deposited through publications and repositories, have allowed their independent research and analyses by a number of researchers all over the world. Such multitude of information makes it hard to comprehend results and recognise biological patterns. Statistical tools developed for such conditions of data overload include tools of dimension reduction like principal component analysis (PCA) and partial least square (PLS). These are available through software packages like SAS (Statistical Analysis System, SAS Institute, USA), SPSS (Statistical Package for the Social Sciences, IBM Corporation, USA) and open source environments like ‘R’ project and PSPP provide easier ways to analyse such datasets. These represent very few important aspects of statistics in biology as far as data interpretation is concerned. However, there are a number of other things which need to be considered during planning of biological study like experimental design, sampling strategy and model selection to keep random effects as low as possible. Here too mathematics and statistics have played seminal roles, due to substantial and ongoing development in the very active areas of “mathematical and statistical modelling”.

Predictive analytics use statistical or mathematical or machine learning methods to make predictions about future or unknown outcomes. Traditionally these methods have been used extensively in finance and general management fields but in last few years, their application in health care is becoming eminent. In a most basic sense, a model is an abstract representation of reality. Since late 1980s, people have tried to develop mathematical modeling to understand the spread of infectious diseases like measles (Schenzle 1984), HIV (Lin et al. 1993), dengue (Syafruddin and Noorani 2013); (Rangkuti 2014), TB (Side 2015) and recently Zika virus (Bonyah and Okosun 2016). Successes of these models has led to development of models for lifestyle diseases, which will be discussed in Section 5.

In the present review, we have limited ourselves to an overview about recent algorithms and models as applied to fields affecting human welfare and health. Here, human welfare through bacterial quorum sensing and its inhibition, human health through major disease of cancer and diabetes have been discussed in the following sections.

# BACTERIAL QUORUM SENSING AND ITS INHIBITION

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Microbial world is critically governed by population dynamics. Inter- and intra-species regulation by quorum sensing (QS) and quorum sensing inhibition (QSI) orchestrates such behavior. These signals mediated by small molecules called auto-inducers (AI), can induce functions that may not be observed in planktonic forms. This is best exemplified by bioluminescence, virulence and biofilm formation (missing citation; missing citation). Different mathematical models were developed to understand the biofilm phenomenon, three-dimensional restraints and transport parameters on autoinducer (Table 1). The review of mathematical models on QS indicate that complexity involved in understanding QS necessitates equally appropriate equipment and new technology. Mathematical models and technological developments have contributed in parallel with traditional experiments (missing citation; missing citation). Some of the recent developments have been touched upon here. Considering a priori assumptions to develop mathematical models may not be realistic, Brown developed a simple model to link molecular and population processes (missing citation). Herein, models were proposed for homogeneous populations of Gram-positive and Gram-negative QS-QSI signalling structures. These systems were targeted towards molecular and population dynamics. The results add a dimension to framework required for understanding complex system-specific models. In another work, Pai and group used a kinetic model to develop a generic metric “sensing potential” that quantifies QS activation (missing citation). This potential limits to a lone stretch of time that represents the prevailing QS-controlled target activation. The predicted were confirmed in artificial QS circuits based on *Escherichia coli*. These experiments, performed through synthetic QS, provide a structure to characterize diverse QS systems. Working on different organism - *Vibrio harveyi*, Fan and Bressloff developed population based models (missing citation). Single-cell models were used to understand signal integration while population-based models were used for interpreting responses to multiple environmental stimuli. Another report found that there are critical autoinducer regulation mechanisms in bacteria wherein, phenotypic heterogeneity causes selected cells (and not all) to produce AI (missing citation). This was further probed through a theoretical model in which, cells generated and utilized AIs as per physiological and environment induced requirements (Bauer et al., 2017). When the ecological and population dynamics were coupled and mediated by QS, it prompted generation of phenotypic heterogeneity within population. These results indicate existence of a system that is not governed by bistable gene regulatory circuitry.

Biofilm formation is controlled by QS and its prevention is crucial for anti-microbial drug action. Ghasemi et al. proposed a nonlinear system of partial differential equations based model of biofilm in response to antibiotics (missing citation). The study suggested that QS mechanism controlled the switch between aggressive growth coupled with low biofilm formation and sustainable growth coupled with high biofilm formation, with respect to environmental conditions. This has important therapeutic implications. Limited volume systems like microfluidic devices have recently gained momentum as experimental systems of choice in QS studies (**Table 2**).

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# CANCER DEVELOPMENT AND TREATMENT

High overall incidence and associated mortality rate of cancer requires an accurate measure of multiple parameters. Mathematical models incorporating these parameters allow holistic design, that also acknowledge uniqueness of cancer respective organ. Cancer models in terms of disease development and treatment, have led to elaboration of different types of models (Wang and Adjei 2015; Weeber et al. 2017; Zitvogel et al. 2016; Annunziato et al. 2016; Santiago et al. 2017; Zitvogel et al. 2017). The following sections present recent mathematical models for cancers of breast and cervix.

 *Breast Cancer:*Breast tumour size dynamics has been reviewed for theoretically analysed data based on clinical data (Ribba et al. 2014), risk prediction models (Cintolo-Gonzalez et al. 2017), and interplay of microenvironment factors dependant models(Simmons et al. 2017). Breast cancer development is slow process and to achieve a diagnosable size, it has been theoretically estimated to take up to 8 years (reviewed in (Ribba et al. 2014)). Growth of both primary and secondary tumours in breast cancer was predicted through a consolidated model by Tyuryumina and Neznanov (Tyuryumina and Neznanov 2018). This model, referred to as CoMPaS, was made by using natural history of primary tumour (PT) and secondary distant metastases (MTS), and hence it echoed associations between PT and MTS. CoMPaS was able to accurately define the duration of growth of PT and MTS and 10-15-year survival of breast cancer patients. Importantly, the time taken is due to accumulation of mutations that manifest into a tumour. The number of mutation (hits) are measured as different stages *viz*. two-stage (Giannakakis et al. 2008) and two-six stage (Zhang et al. 2014) for clinical expansion and manifestation. Zhang et al., have postulated the genetic pathways that are due to three-stages of mutation. Initial 2-3 hits could be responsible for genetic stability (possible genes - BRCA1 and BRCA2), while later hits may be responsible for sporadic events of breast cancer development.

Oke and group utilized differential equations to develop breast cancer model (Oke et al. 2018). The group considered multiple parameters including presence / absence of anti-cancer drugs, immune-booster and ketogenic diet to develop a robust model for breast cancer. The analyses led to identification of an optimal drug concentration for high effectiveness. The results were validated through numerical simulations.

Another approach could be treatment specific modelling of cancer sub-type. McKenna et al specifically looked at doxorubicin treatment in triple negative breast cancer (TNBC) (McKenna et al. 2018). Herein, the group coupled experimental results with simulations and formed an in vitro pharmacokinetic / pharmacodynamic (PK/PD) model. This model described the effects of doxorubicin regimen on a representative cell line (SUM-149PT) that define cellular population dynamics. However, this work needs to be evaluated through *in vivo* analysis for its clinical suitability. Apart from this work, other simulations discussed are not developed for different molecular subtypes and this limits their application for designing treatment based models. Hence, there is need to make sub-class specific models for improved understanding of its development which can be eventually used for designing therapy and improve survivability. Patient survival prediction models using data mining algorithms - artificial neural networks (Delen et al. 2005; Park et al. 2013), decision Trees (Delen et al. 2005), logistic regression (Delen et al. 2005), support vector machines (Park et al. 2013; Xu et al. 2012) give ample examples of extent of application of programming languages. More recently, Kate and Nadig used SEER dataset for machine learning and used summary stages to make prediction models (Kate and Nadig 2017). The work identified that evaluation of summary stages together causes least performance in comparison to models trained on specific summary stage.

## Cervical cancer:

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Simulations have been developed for cervical cancer for vaccination, diagnosis and treatment. Continuous expression of E6 protein makes it an ideal therapeutic target against cervical cancer. Khan et al., predicted peptide vaccine through immunoinformatics approach of high-risk human papillomaviruses (HPV) E6 protein (Khan et al. 2018). Antibody Epitope Prediction tools (ElliPro and NetCTL) predicted B-cell and CTL epitopes for E6 proteins that were experimentally validated through systems biology. These sequences are predicted as vaccine against hrHPV. However, an *in vitro*, *in vivo* and clinical studies are warranted. An impact assessment for HPV vaccination on populations should follow this study. This necessitates a worldwide evaluation of vaccine. A population based study on impact of HPV vaccination to counter worldwide variation in HPV infection was performed using IACR transmission model (Baussano et al. 2018). The analyses showed pre-vaccination HPV prevalence is positively correlates with herd immunity and is eventually responsible for vaccination effectiveness.

Clinical diagnosis is usually based on detection of HPV DNA through high-throughput system like PCR. Inclusion of high quality methods is expected to reduce number of steps involved in verification of true positive cases. Exercising these standards for all cases may be avoided due to costs involved. Beylerian and team simulated the typical distribution of HPV DNA test results that are achieved when using a 96-well plate format (Beylerian et al. 2018). An algorithm was made that generated nearly 9,00,000 cases, roughly translating into 10,000 microplate assays, for simulation of results. The results were distributed into groups for assumed HPV prevalence rates of 12%, 13%, 14%, 15%, and 16% as per 96-well matrices. The analyses indicate that screening in areas with prevalence of 12% to 16% could anticipate 5 to 22 positive results per test plate in nearly 95% of all assays. Deviation from these results can be considered to be caused by well-to-well contamination. This can be applied effectively in areas where prevalence of HPV is known. However, in altered spatiotemporal situation, this research has limited application.

Kyroudis et al., had patient-specific tumor response to radio- and chemo-therapy as central objective to generate a very specific computational model (Kyroudis et al. 2019). This model included a scoring mechanism that could compare regression profile of any two tumors and predict outcomes of therapy effectiveness. The small size of patient cohort necessitate validation in a large group until which this model stands within preliminary study. The efficacy of tumor growth subduing drugs is limited by effective range of immune cells, beyond which the response to treatment is inadequate. Considering immune evasive maneuvers in a typical tumor, Bayer et al. developed a two-phenotype model (Bayer et al. 2018). This model showed that presence of “selfish” cells is more prominent in benign form while “cooperative” cells are more prominent in aggressive tumors.

The above discussed studies are defined by routine models of cell lines and population studies. Recently, limited volume systems, like microfluidic devices, have recently gained momentum as experimental systems of choice in cancer studies because various disease related processes can be understood at the cellular level and further modelling and simulations can be applied (**Table 3**).

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# DIABETES PREDICTION

With success in modeling for the infectious diseases as mentioned earlier in Section 2: Introduction, researchers began to work with model development for non-communicable or ‘lifestyle’ diseases/disorders. ‘Markov Models’ are the models of choice in this regard because they take into consideration the current use of resources and the outcomes and are not dependent upon the historical data. Markov models are useful when a decision problem involves risk that is continuous over time, when the timing of event is important, and when important event may happen more than once. Representing clinical settings with conventional decision trees is difficult. Markov models assume that a patient is always in one of a finite number of discrete health states, called as ‘Markov States’. All events are represented as transitions from one state to another (Sonnenberg and Beck 1993). One of the foremost examples of a ‘lifestyle’ disorder is diabetes and the proportion of afflicted individuals worldwide is increasing at an alarming rate. It is now standing as one of the top 10 leading causes of deaths occurring worldwide. As per the latest WHO report (WHO 2016), the number of diabetic people rose to 8.5% in 2014 from 4.7% in 1980s and the increase is observed across the populations of all age groups. Diabetes leads to several premature deaths because of its associated adverse complications like cardio-vascular, renal and neuronal disorders. Between the two types of diabetes - 1 and 2 - the latter affects majority of the population and worryingly the onset age is decreasing. Furthermore, diabetes is a costly disease accounting for between 2.5 and 15% of the total healthcare expenditure (Boutayeb et al. 2004). International Diabetes Federation estimates that globally 415 million people were afflicted with diabetes in 2015, and the number is ‘predicted’ to increase to 642 million by 2040. Among the top 8 countries (having highest number of diabetic patients) in the world, India stands second with 65.1 million people with diabetes and another 36.5 million with pre-diabetes (a high-risk condition for diabetes and cardio-vascular disease) (**Table 4**).

This burden continues to increase, driven by nutrition, lifestyle and demographic transitions, unhealthy dietary habits, and physical inactivity, in the context of a stronger genetic predisposition to diabetes (Tripathy et al. 2018). The cost of diabetic medications is increasing in both urban and rural India. Thus, it would be really useful if with the help of modelling, both the number of diabetic patients over the future years and the costs incurred on them over this time could be reasonably predicted.

There are two main types of diabetes:

1. Type 1 Diabetes or Insulin Dependent Diabetes Mellitus (IDDM) develops if the pancreas is unable to produce insulin. This type of diabetes usually develops before the age of 40 and is commonly treated by insulin injections and a controlled diet.

2. Type 2 Diabetes or Non-Insulin Dependent Diabetes Mellitus (NIDDM) develops when the body cannot generate enough insulin (Hypoinsulinaemia) or if the body cannot use the insulin generated efficiently (Insulin Resistance). This condition is commonly treated by diet and exercise alone or by diet, exercise and tablets and/or insulin injections (WHO, 2016).

One of the earlier modelling studies was reported from Aintree Hospital, UK (missing citation). Based on earlier years of available data for diabetic patient hospital admission, health records and subsequent progress, ‘Regression Analysis’ was performed to estimate various parameters for the year 2030. Attributes such as NIDDM prevalence (3035 new cases predicted), risk factors (increased obesity and other unknown contributory factors), burden on health services and monetary costs were predicted (>46.6%). Other prominent UK based studies, detailing cardiovascular risks of diabetic patients, are reported by UK Prospective Diabetes Study (UKPDS) groups(Stevens et al. 2001; Kothari et al. 2002; Clarke et al. 2004). (Boutayeb et al. 2004) developed a simple model based on differential equations, to monitor the size of the diabetic population and to monitor the transition from the stage of diabetes without complications (D group) to the stage of diabetes with complications (C group). This model is popularly known as the ‘DC Model’. Here the number of new patients (incidence) of diabetes is assumed to be constant over time. The paper stressed upon the importance of early healthcare interventions before progression of diabetes towards complications. But soon it became evident that different from study by Boutayeb, the numbers of incidences of diabetes are not constant (Boutayeb et al. 2004). They vary based on lifestyle factors and genetic factors. Hence, the DC model was recently evolved into ‘Susceptible Diabetes Complication (SDC) Model’ (Widyaningsih et al. 2018). Here besides the D & C groups mentioned in the DC model, an additional group of susceptible individuals (S) is created. The model predicted that diabetes prevalence is supposed to increase to 14% by 2030 and the death rate is predicted to increase by 5% every year. A similar study to UK study mentioned above, was carried out in USA (Huang et al. 2009) but used the ‘Markov Model’. Here both the number of patients and the costs incurred were predicted. The study predicted 44.1 million diabetes patients by 2034 and the medical spending on them to be USD 336 billion. The study also extended upon the UKPDS model by considering the glucose concentration data. The predictions follow the same trend as the UK study: increase in number of diabetic patients with increasing obesity and the increased medical cost incurred by the patients as well as the government.

Currently, following predictive modelling tools (**Table 5**) are available for disease data but their discussion in detail is outside the context of the present review.

# TABLES

Preliminary mathematical models predicted for quorum sensing

|  |  |  |
| --- | --- | --- |
| Environmental system | Mathematical model | Bacteria |
| Bio-luminescence | James et al. developed a deterministic model that was involved in the regulatory system based on concentrations of autoinducer **(James et al., 2000)** | V. fischeri |
|  | The model of Ward et al. analyzed population growth vis-à-vis autoinducer synthesis **(Ward et al., 2001)** | V. fischeri |
| Virulence | The deterministic model of Koerber et al. had basis of QS and provided limitations of stochastic model, also provided in the same report **(Koerber et al., 2005)** | S. aureus |
|  | Karlsson et al. made nonlinear dynamical model **(Karlsson et al., 2007)** | Streptococcus pneumoniae |
|  | Model proposed by Haseltine and Arnold examined different network architectures prevalent in three different bacteria **(Haseltine and Arnold, 2008)** | V. fischeri, Agrobacterium tumefaciens, P. aeruginosa |
| Biofilm | Eberl et al. made of a set of nonlinear density-defined reaction–diffusion equations, that were projected as a precursor **(Eberl et al., 2001)** | - |
|  | Model of Nilsson et al. followed AHL concentration to determine effects on growth of biofilm **(Nilsson et al., 2001)** | Gram negative bacteria |
|  | Chopp et al. developed spatio-temporal model that described biofilm as active biomass (live cells) and inactive biomass (macromolecules) **(Chopp et al., 2002)** | P. aeruginosa |

Mathematical simulations / Modeling used for microorganisms in microfluidic systems

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Sr. No. | Objective | Model Organism | Mathematical Simulation | Reference |
| 1 | Recovery of intracellular products | Escherichia coli | Fluent computational fluid dynamics model | Kelly and Muske, 2004 |
| 2 | Separation of heterogeneous cell mixtures in suspension using ultrasonic and laminar flow fields | Hybridoma cells and *Lactobacillus rhamnosus* | Modeling of the trajectories of each organism | Kumar, Feke and Belovich, 2005 |
| 3 | Understand mechanism involved in gliding motility and its correlation with secreted slime polymerization | Cyanobacteria and myxobacteria | Molecular dynamics simulation based on molecular nozzle having polymer chain growth | Jeon and Dobrynin, 2005 |
| 4 | Suggest experimental design that deals with spatio-temporal facets of QS in biofilm formation | *Pseudomonas aeruginosa* PA14 | Mathematical model for QS and biofilm development | Janakiraman *et al.*, 2009 |
| 5 | Examine dynamics of bacterial pathogen within artificial plant xylem | Xylella fastidiosa | Multiphase approach | Cogan *et al.*, 2013 |
| 6 | Analyses of behaviour of a synthetic oscillator under temporal distress | Escherichia coli | Model based on delay differential equation, Hill-like formulation, Langevin formulation, etc. | Rodrigo *et al.*, 2013 |
| 7 | Modeling and validation of AI-mediated gene expression | AI system of *Vibrio fisheri* in *Escherichia coli* | Generalized mass action equations | Austin *et al.*, 2014 |
| 8 | Individual bacteria (in flow) based model for QS | Not specified | Multiple models | Uecke, Müller and Hense, 2014 |
| 9 | Development of model to study deformation and detachment of a biofilm | Not specified | Model based on first two laws of thermodynamics, and is applied through an energetic variational and phase-field system | Tierra *et al.,* 2015 |
| 10 | Development of isolation of bacteria using magnetic nanoparticles | Staphylococcus aureus | Theoretical model | Kang *et al.,* 2015 |
| 11 | Theory of microfluidic two-chamber bioreactor | Escherichia coli | Theoretical model | Hsu and Yang, 2016 |
| 12 | Self-organization of bacteria in colonies | Escherichia coli | Individual cells are modelled in microfluidic cavities | Cho *et al.*, 2007 |
| 13 | Bacterial entrapment and its population control | Escherichia coli | Spatially explicit agent based model (ABM) | Danino*et al.*, 2010; Mina, Tsaneva-Atanasova and kBernardo, 2016 |
| 14 | Chemotactic behaviour in marine bacteria | Vibrio alginolyticus | Modelling framework based on bacterial trajectory analysis | Son, Menolascina and Stocker, 2016 |
| 15 | Chemotaxis drift in crossing ‘barrier’ | Escherichia coli | Coarse-grained model of chemotaxis, Kramers reaction rate theory | Li *et al.*, 2017 |
| 16 | Single cell bacterial colony modelling | Corynebacterium glutamicum | Six concepts for model re-presentation of cellular microcolonies | Westerwalbesloh *et al.*, 2017 |
| 17 | Chemotaxis in steep gradients | Escherichia coli | Analytical linear-response theory, perturbation theory | Micali *et al.*, 2017 |
| 18 | Collective oscillations in bacterial colony | Bacillus subtilis | Delay-differential equation model | Martinez-Corral *et al.*, 2018 |

Mathematical modeling / Simulation for cancer cells in microfluidic enviornment

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Sr. No. | Objective | Model Organism | Mathematical Simulation | Reference |
| 1 | Predict intracellular macromolecular shifts on external stimuli of hypoxia | Cells experiencing hypoxic conditions | Extra- and intra-cellular molecular interactions were modelled using different mathematical descriptions | Morshed and Dutta, 2017 |
| 2 | Pharmacokinetic–pharmacodynamic (PK–PD) model for multi-organ-on-chip | HepG2 & HeLa cells | Separate models for PK and PD | Lee *et al.*, 2016 |
| 3 | Predict effect of drug (doxorubicin) delivery on therapeutic use | LS174T cells | Drug diffusion into cell, its interaction with DNA, and eventual clearing from cell | Toley *et al.*, 2013 |
| 4 | Application of microfluidics to curtail osmotic shock to cells while cryopreservation | HepG2 cells | Microscale modeling of mass transport across cell membrane | Song *et al.*, 2009 |

Pevailence of Diabetes(20-79 year olds) in top 8 Countries of World: Current trend and future projection

|  |  |  |
| --- | --- | --- |
| Country | Diabetic Population (millions) (20-79 years) 2013 | Diabetic Population (millions) (20-79 years) 2035 |
| China | 98.4 | 142.7 |
| India | 65.1 | 109 |
| USA | 24.4 | 29.7 |
| Brazil | 11.9 | 19.2 |
| Russian Federation | 10.9 | 11.1 |
| Mexico | 8.7 | 15.7 |
| Indonesia | 8.5 | 14.1 |
| Egypt | 7.5 | 13.1 |

  **Free resource on website of International Diabetes Federation (IDF):**(missing citation)

Predictive modeling tools(Jayanthi et al. 2017)

|  |  |
| --- | --- |
| Broad Classes | Methods |
| Statistical Models | Linear Regression |
|  | Logistic Regression |
|  | ANOVA |
|  | Time Series |
|  | Trees |
|  | Non-linear Regression |
|  | Survival Analysis |
| Artificial Intelligence Models | Fuzzy Logic |
|  | Neural Networks |
|  | Genetic Algorithms |
|  | Nearest Neighbour Pairing |
|  | Principal Component Analysis |
|  | Rule Induction |
|  | Kohonen Network |
|  | Conjugate Gradient |
|  | Simulated Annealing |
|  | Neuro-Fuzzy Inference System |
| Bioinformatic / Mathematical Models | Markov Models |
|  | Hidden Markov Models |
|  | Differential Equation Based |
|  | Multi-Variate Modeling (Path Analysis, Structural Equation Modeling) |

# CONCLUSION

Mathematics and statistics have contributed immensely in interpreting and analysing various biological queries. Multiple approaches towards analysis and management of quorum sensing, cancers and diabetes data have defined challenge of data integration. Numerous tools built to manage and process large datasets may not be useful beyond couple of research questions. Big Data that is continuously being churned through omics technologies pose real challenge for bioinformatics. Massive data generation in biological sciences has exceeded the growth of computational power that was predicted earlier. Predictions systems based on quorum sensing and in disease have had own successes.

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