Computational Health Engineering Applied to Model Infectious Diseases and Antimicrobial Resistance Spread

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Abstract: Infectious diseases are the primary cause of mortality worldwide. The dangers of infectious disease are compounded with antimicrobial resistance, which remains the greatest concern for human health. Although novel approaches are under investigation, the World Health Organization predicts that by 2050, septicaemia caused by antimicrobial resistant bacteria could result in 10 million deaths per year. One of the main challenges in medical microbiology is to develop novel experimental approaches, which enable a better understanding of bacterial infections and antimicrobial resistance. After the introduction of whole genome sequencing, there was a great improvement in bacterial detection and identification, which also enabled the characterization of virulence factors and antimicrobial resistance genes. Today, the use of in silico experiments jointly with computational and machine learning offer an in depth understanding of systems biology, allowing us to use this knowledge for the prevention, prediction, and control of infectious disease. Herein, the aim of this review is to discuss the latest advances in human health engineering and their applicability in the control of infectious diseases. An in-depth knowledge of host–pathogen–protein interactions, combined with a better understanding of a host's immune response and bacterial fitness, are key determinants for halting infectious diseases and antimicrobial resistance dissemination.

Keywords: health engineering; mathematic models; antimicrobial resistance; infection disease

1. Introduction

Over the last decade, theoretical and computational biology, combined with open access to biological databases, have presented new opportunities in different areas of the field, such as genomics or evolutionary biology. In the 1970s, bacterial dynamics emerged as its own discipline [1], focusing on the exploration of bacterial population dynamics to gain a better understanding of the bacteria's ability to manipulate, escape, or evade a host's immune response. These traits enable bacteria to transmit and re-infect, providing one of many major questions that modeling tries to address. Other questions that modeling is trying to answer include how bacterial populations evolve under antibiotic pressure, what the function of dose-effect is in the outcome of infection, and what risk factors are associated with epidemics. In addition, models are great tools for the generation of predictions that can be later tested in the laboratory, and in this context, computational (in silico) models combined with systems biology aid clinical microbiology.

Systems Biology started to be developed before World War II, with researchers such as Ludwig von Bertalanffy and, more recently, Mihajlo Mesarovic [2,3], under "the understanding that the whole is greater than the sum of the parts" [4]. The increase in this field was prompted by improvements of functional genomics [5,6], the completion of the human genome project, and the development of high-throughput technologies.

Systems biology intends to unravel the interactions between components of biological systems, as well as the dynamics of interactions, and the changes in systems (inter- and intra- species), by using -omics tools [7]. It is important to consider that systems biology comprises several disciplines, such as biological computing and mathematical biology.

One of the applications of in silico biological data is computational systems biology [8], which uses computational techniques to develop algorithms, networks, and complex connections for cellular and biological processes [9]. In the infectious disease field, the use of these tools is mostly applied to diagnosis, treatment, and prevention.

In summary, mathematical models and computer simulations are mainly utilized to predict changes in systems caused by different environmental conditions. The modelling of infectious diseases [10] is helping us better understand the dynamics of host–pathogen interactions [11], and how the immune response can be orchestrated to differentially respond to inter- and intra-bacterial species interactions. Moreover, computational engineering enables us to predict the evolution or adaptation of bacteria to new environments, including the acquisition of resistance [12] to any given antibiotic.

In addition, protein–ligand docking [13] is assisting in the generation of predictions that aim to understand, in depth, the effects of the position and orientation of a ligand when it is bound to a protein receptor or enzyme and how that position affects the overall efficiency of drugs [14]. This area of study also enables the molecular study of host–pathogen interactions [15,16]. Targeted chemical cross-linking (TX)—mass spectrometry (MS) or TX-MS is a new concept that integrates the complex networks with the modelling of quaternary protein structures [16] (Figure 1).
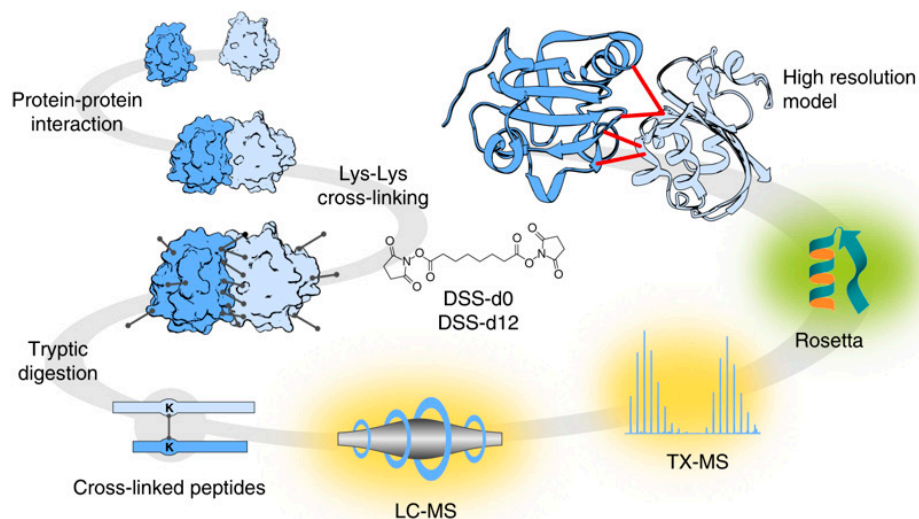

Figure 1. Targeted cross-linking procedure for targeted chemical cross-linking mass spectrometry (TX-MS). Firstly, Protein-Protein Interactions (PPIs) were chemically cross-linked with heavy/light disuccinimidyl suberate (DSS) to further digest the complex PPI cross-linkers. The digested peptide signals were targeted and extracted from Liquid Chromatography (LC)-MS data. The chemically complex cross-linked elements were subjected to MS analysis and subsequently modelled to generate tertiary structures, which were docked to produce a compendium of possible quaternary structure models. For identification of the candidate cross-linked peptides, the authors proposed the use of a guide for the molecular docking of crystal structures of the targeted proteins. This research was originally published in *Nature Communications*. Hauri et al. Rapid determination of quaternary protein structures in complex biological samples. *Nat Commun.* 2019 Jan 14; 10(1):192© Copyright Clearance Center's. Reprint from [16].

The aim of this review is to compile the latest discoveries and advances on health computational engineering, new mathematical models, and the applications of these models in the biomedical field. We also would like to introduce this information to medical doctors and clinicians, to promote the use and implementation of these technologies at hospitals and health care systems. We will focus on the most relevant and recent findings regarding antibiotic discoveries and human immune response against infectious diseases and end with our perspective and opinions.

2. Overview of Mathematical Models to Predict Infectious Diseases

Epidemiology has been considered the gold standard for investigating diseases' dynamics in varied populations, focusing mainly on the distribution and determinants of disease, to better prevent and control these diseases. Moreover, epidemiology could be considered the first mathematical model applied to the prevention and control of diseases [17]. Epidemic mathematical models have usually been applied to the prediction of outbreaks, epidemics, and transmission, as well as the resurgence of infectious disease [18]. Guidelines and vaccination programmes have been established to prevent and control transmission. Although these first epidemiological models were "static" and representative of neither different social or geographical spaces, nor their evolution over time [17,19], they have served as a model to develop dynamic models that evolve over time (Figure 2).
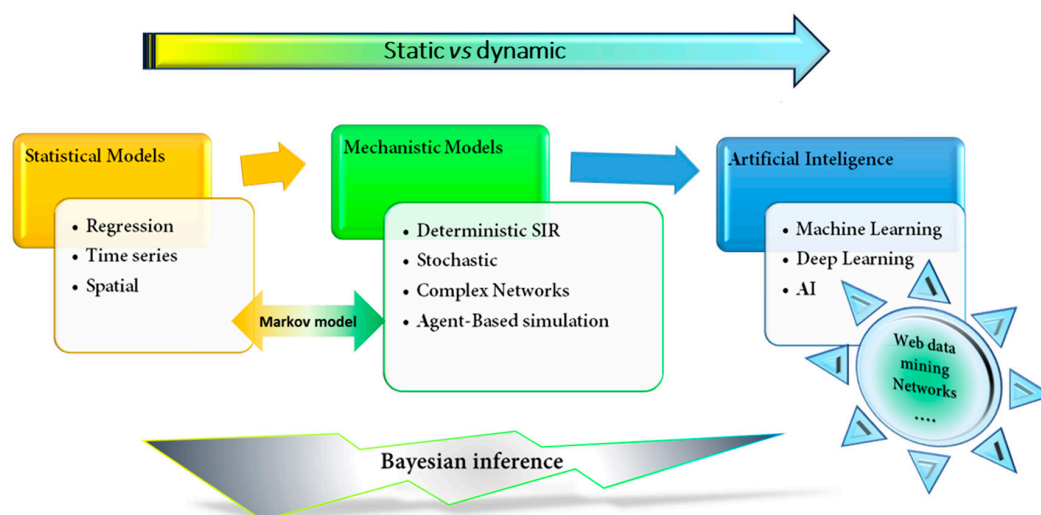
Figure 2. Schematic classification of mathematical models applied to epidemiology and medicine. The figure shows the evolution from a simpler statistical fixed model, such as a regression model, to a more sophisticated and dynamic learning machine or artificial intelligence models. SIR, Susceptible-Infection-Recover.

Bayesian models are based on dynamic probabilistic models, in which a "theorem" describes the probability of any event supported by prior knowledge related to that particular event. The variables are random, and uncertainty can be measured [20]. The applicability of Bayesian models [21], networks [22–24], or successful combinations [25], e.g., with gaussian variables [26], is too broad. Certainly, Bayesian methods are more difficult to implement than traditional methods, especially in epidemiology and infection diseases [27]. However, they have been applied in malaria studies [28], to evaluate interventions applied to prevent human immunodeficiency virus (HIV) infection and its collateral risk [29], as well as to evaluate the population dynamics of HIV [30].

Epidemiology (or non-epidemic) models are based on different statistical mathematical models, such as (i) regression, mainly used to detect outbreaks [31], as well as (ii) the autoregressive integrated moving average model, ARIMA, and seasonal SARIMA, both used to predict outbreaks and risk factors [32,33]. Currently, more complex models are gainging popularity, including [34] (iii) models based on a time series, which are more useful in antimicrobial studies to unravel trends [35], (iv) methods

including cumulative sum and an exponentially weighted moving average (for example, in the ARIBACA project, were this model was implemented to detect and forecast selected Caribbean diseases, such as dengue [36]), and (v) spatial models, which are more sophisticated, including place-specific models requiring multivariate techniques to model the spatial heterogeneity of all the infection´s covariates [37] (Table A1).

Mathematical or mechanist models are more complex state-space models based on compartments (S = susceptible, E = exposed, and I = infectious and recovered populations). The compartmental or deterministic approach treats each different status of an epidemic as a different sub-population or compartment of a population [38]. The stochastic approach takes random variables into consideration. Susceptible-Infection-Recover (SIR) compartments and derivatives models are mainly used for predictions about the spread of infectious diseases [39], vaccination impact [40], or both [41,42]. Importantly, population dynamics are inexorably subjected to environmental background and natural phenomena, and rather than following random oscillations, they strictly follow deterministic laws. The stochastic or random SIR model has the advantage of introducing "the random or the chance" as a variable [43]. Then, stochastic models can more realistically predict epidemics [44], vaccination impact on herd immunity [45], or the dynamics of protein–protein interactions (PPIs) during infections [46]. Certainly, increasing the complexity and number of variables allows for more realistic predictions that enable us to extrapolate results to real situations. The models proposed by Barnard et al. [47] and Sabini et al. [48] accurately predict epidemics and their spread (Table A1).

Finally, in the realm of artificial intelligence (AI) and machine learning systems, the studies in [49,50] provide a wide range of novel approaches that are applicable to system biology [51,52] or can be directly used in immunology [53] and the study of infectious disease, for prevention [54] or diagnosis [55,56]. The great similarity between AI and machine learning makes it difficult to separate the two, but in principle, AI aims to function as a human brain, working first on the acquisition of knowledge to then solve problems; this process aims to increase the rate of success and not accuracy. On the contrary, machine learning studies the use of big data to make an informed decision in order to maximize performance. Deep learning is an improved subset of machine learning. The Support Vector Machine [57] and delta bitscore DeltaBS [58] are examples of machine learning applied to a biological system, which enable us to predict the adaptive phenotype of a new host-niche and its probability to develop severe disease. The Support Vector Machine generates a probability, based on assigned scores for each isolate, creating a unique measure of host specificity, to indicate which animals may more easily exchange specific isolates [57,58]. DeltaBS is a training variable that allows the estimation of combined effects on gene function. This model allows the identification of biological mechanisms for adaptation, and the detection of new emerging lineages (by searching recurrent patterns of mutation accumulation) by recognizing novel mutations linked to the same underlying shift [58] (Table A1).

3. Host–Pathogen Interactions

The mammalian immune system is a sophisticated, complex, and well-orchestrated network of cells and antimicrobial molecules operating at different levels to protect it against disease [59–61]. Initially, the immune response is innately effective against "new threats". The adaptive immunity responsible for the memory response includes cellular and humoral immune responses. Unfortunately, successful pathogens have developed subversive strategies to exploit, modulate, and/or evade immune control and clearance [59], including evolutionarily optimized protein structures that bind with high specificity to protein-like hosts [62]. In addition, the immune response is highly specific to host and pathogen, hence why everyone has a unique immune system and will respond differently to immune challenges, such as infection or sepsis.

Over this century, the great advances and innovations in computational methods have contributed to a comprehensive and deeper understanding of biologically complex systems and host–pathogen interactions [7]. These new approaches allow us to understand the nuances of these specific

interactions [6,9]. Meanwhile, new strategies are developing animal models to better understand and confirm the host immune response against bacterial infections [7,10].

3.1. Modeling the Immune System

Mechanistic models are commonly used to predict the outcomes of individual immune responses. Stochastic and mechanistic models can identify cell-to-cell differences, which can determine the response of individual cells [63]. However, other studies focused on dynamic interactions to better explain how invertebrate organisms can optimize an immune strategy to overcome infections. Through the integration of all high-throughput multiomics data, it is possible to construct predictive models of the networks and dynamic interactions between the biological components of host–pathogen systems, allowing for a better understanding of complex biological systems.

Systems Biology can define PPIs to unravel interactions amongst several bacterial virulence factors and host proteins involved in the inflammatory process, the complement system, or the immune response [64]. Doubtlessly, both biological systems (host and pathogen) are highly complex and not completely understood, limiting the possibilities of the input data on our models. This complexity causes some important questions to remain unanswered, such as why the same microbe can be commensal or pathogen, how two people from the same community could respond differently to the same microbial threat, and the key immune components that dictate the outcome of the infectious process [65].

The complexity of biological systems requires multidisciplinary teams to tackle vast amounts of data and make sense of them. On the other hand, one the greatest limitations to implementing dynamic projects in immunology and infectious disease is that a variety of high-level skill sets are needed. Furthermore, experiments require many complex techniques in order to understand the mechanism of immune response [66]. Simpler models allow us to include novel processes as new subsystems and enable increasing complexity. For example, Álvarez et al. modelled the immune response after stimulation with bacterial lipopolysaccharides to better understand the inflammatory process [67] (Table A1). In this section, we focus on various immune system-related bacteria, mainly based on proteomics data and databases. Certainly, "DNA is the blueprint for life, however proteins are the bricks" [4].

Streptococcus pyogenes has been used as a model of system biology in different studies, because its independent but interconnected virulence mechanisms promote different aspects of the colonization, immune evasion, and spreading processes [68,69]. Moreover, its role as an immunomodulator of the humoral immunity is well-known [70]. Sjöholm et al. have recently characterized the human plasma–*S. pyogenes* bacterial surface PPI network by using an adsorption plasma approach in combination with MS [71]. Later, the authors developed a dynamic model to study the stoichiometric relationship between the bacterial surface and its adhered host proteins (Figure 3) [11] (Table A1). In addition, shotgun MS is a highlight the proteogenomic or genomics field, and the strategies developed by Malmström et al. work with generic data for integrating genome and proteome data [72]. After constructing a spectral library for *S. pyogens*, quantification is performed using sequential window acquisition of all theoretical mass spectra (SWATH)-like data independent acquisition (DIA)-MS, to increase insights into host–pathogen interactions. The SWATH-MS strategy was also used by Malmström et al. to quantify the proteins involved in pathological conditions, like sepsis, to understand how different pathophysiological processes can twist the PPI network and composition of the plasma [73].
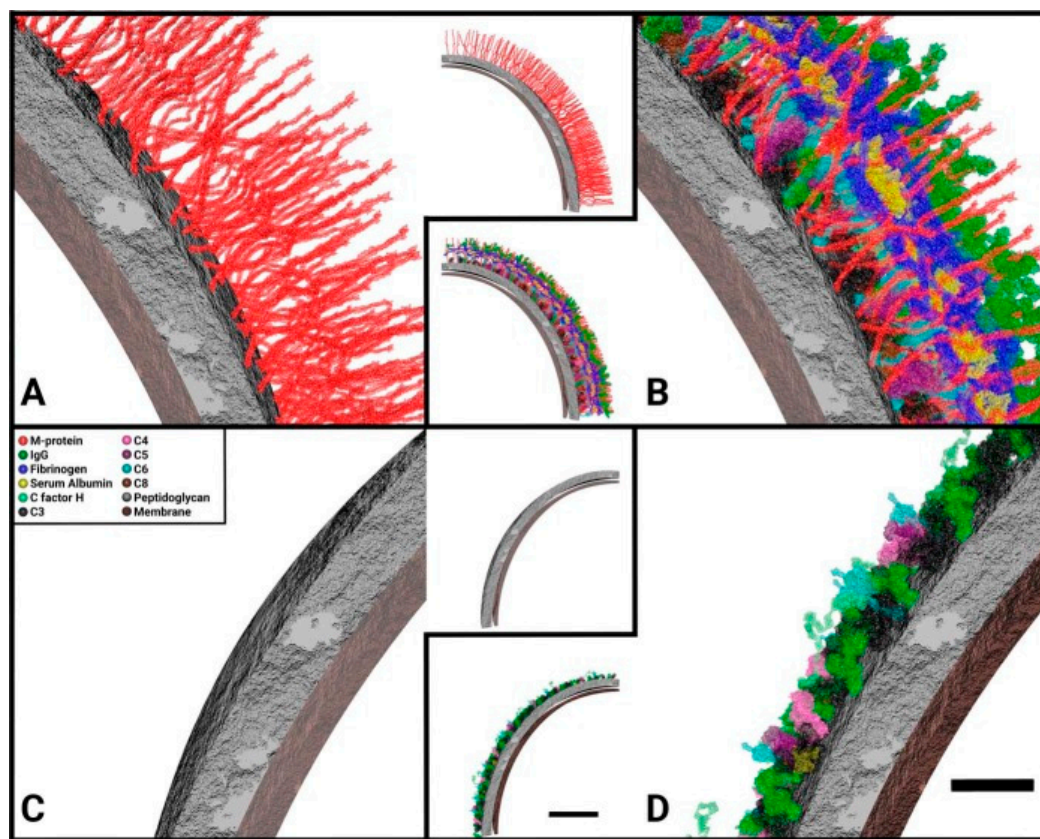
Figure 3. The stoichiometric surface density models of *Streptococcus pyogenes*—human plasma interactions. (**A**) The *S. pyogenes* surface (**B**) with plasma adsorbed to the surface; (**C**) the *S. pyogenes*-M1-deletion mutant; and (**D**) *S. pyogenes* with plasma adsorbed to surface. Selective Reaction Monitoring (SRM)-MS, which counted the number of bacteria, was used to build the model of *S. pyogenes*'s surface interaction network in a host environment. The model was based on stoichiometric relations between host proteins, surface proteins, and the surface of the pathogen. This research was originally published in *Molecular & Cellular Proteomics*. Sjöholm et al. Targeted proteomics and absolute protein quantification for the construction of a stoichiometric host–pathogen surface density model. Mol Cell Proteomics **2017**, 16, S29-S41© the American Society for Biochemistry and Molecular Biology. Reprint from [11] with permission. All rights reserved.

Salmonella enterica has also been used as a pathogen model for PPI networks between the host and pathogen because of its ability to survive into macrophages [74]. The authors first designed two different mathematical models, assuming a Poisson distribution, to describe the dynamics of the different subpopulation systems. They then estimated the relevant parameters, such as bacterial division or death rates, in several organs [75] (Table A1). After the development of different mechanistic models based on probability distribution, the authors predicted the dynamics of a macrophage infected by *S. enterica* (the mean) [76]. Finally, they adjusted inferences according to divergences to validate the model. Currently, the model can incorporate any variable or moment and reproduce better experimental data with multiple replicates and random numbers of independent time points [46].

Recently, Golumbeanu et al. utilized a proteo-transcriptomic approach, in combination with a Gaussian mixed-effects model, to investigate time-series patterns of gene expression. They analysed both PPIs directions, virus and host, proposing a more detailed view of host response to HIV infection, as well as the first step to understand regulatory mechanisms involved in it [77] (Table A1). Understanding the mechanisms underlying sepsis and/or resistance will enable us to predict severity and outcome of the infection [78,79]. We agree, modelling is presenting as a useful tool to be applied in the clinical settings and can be used with animal infections models to reduce theories and confirm,

hypotheses as well as examine the efficacy new drugs or treatment strategies. It is still unclear whether bacteria evolve to become more or less harmful, and how much the host immune response can influence in this within-host bacterial adaptation [80]. To answer these questions more human data regarding infection and inflammatory processes are still necessary.

3.2. Predicting Sepsis

Sepsis is a systemic inflammatory response syndrome, because of the uncontrolled high level of inflammation, usually triggered to fight an infection, which can dysregulate host response, and consequently, organ dysfunction, multi-organ failed, and finally death. Certainly, sepsis is a complex disorder resulting from a host over-responding to a threat, which also modulates host immune system. According to World Health Organization, in 2015, more than 50% of deaths of neonates and children aged under 5 years were due to sepsis (A70/13 document), and according to U.S. Centers of Disease Control and prevention, one in every three patients admitted at American hospital suffer sepsis.

The current protocol to treat sepsis is mainly focused on offering vital support, amines, antibiotics of wide spectrum, and time expecting the patient to positively respond; and unfortunately, there are no specific drugs capable to control the prognosis of this disease. Therefore, and after decades of consensus and continues up-grades on the guidelines, to manage septicaemia, computational engineering has begun to offer models that allow for the investigation of the disease, while aiming to control it. In this section, we comment on the most relevant models focused on understanding the mechanism of infection and sepsis.

Dynamic agent-based models (ABM) have been used to identify host–pathogen interactions involved in sepsis [81,82]. Seal et al. developed a virtual environment that mimics the interface of a host *Pseudomonas aeruginosa* in the gut milieu ABM (GM-ABM). The authors, in a meticulous study, used ABM to model spatially diverse, dynamic, and multi-factorial systems, allowing them to further include rules that dictate the interactions within the local environment and other agents. Before integration into the GM-ABM, the experimental references were validated and integrated in vivo into GM-ABM, which was used like a virtual animal model [83]. Shi et al. [84,85], using a *Salmonella* murine model, integrated the adaptive immunity results obtained in vivo, and used mathematical models that allowed them to define three different patterns, healing, persistent infection, and organ dysfunction. The model quantified the levels of neutrophils and monocytes, too. Based on the results, they hypothesised that the outcome of the septicaemia would improve if patients were given anti-inflammatory drugs in the first 3–6 h post-infection [84]. Other studies used *Klebsiella pneumoniae* and *Acinetobacter baumanii* in a five-compartment kinetic model to explore the pathogenesis and kinetics of a dialysis-like device. Based on the extra-corporeal strategy to intensify the bacterial clearance, the results revealed a faster bacterial clearance using a nanomagnetic device [86]. Cockrell and Ann proposed a different approach using ABM as an Innate Immune Response (IIR), or an IIR-ABM. They represented a more realistic 2-D model of the human endothelial-blood interface using five representative parameters (the damage and resilience from host, and virulence from bacteria) [52] (Table A1).

Currently, machine learning and AI have gained greater significance in the infectious disease research field. Using big databases for the extraction of different variables enables us to obtain patterns of sepsis and the progression of the disease [87–89]. Although the machine learning approach appears to be better than lineal regression models [90], it also has limitations. A general challenge is to determinate the number of training examples necessary to fit the model. Another big challenge is to improve the learning curves according to the greater complexity introduced by additional features or more complex model architectures, such as clinical notes or vital sign data. The major limitation is to address missing data (non-diagnosed infections) and variables (non-identified bacteria), which induce a bias in the relationship between variables [91]. Different test performances and predictive accuracies can result from collecting data for the clinical background of the patient, as well as different thresholds,

such as positive urine culture (a 100 to 100,000 colony forming unit/mL) and the subjective diagnostic criteria of microbiologists [92] (Table A1).

Sepsis is a complex process, and the possibility of applying traditional scores (for example, Sequential Organ Failure Assessment (SOFA) or Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) scores) [93], combined with new scores and early diagnosis, provides future hope for patients [91,94–96]. Recently, Mount Sinai Hospital lunched a precise post-op model to predict prostate cancer disease progression and clinical failure [97]. In the future, this AI application could be utilized to predict clinical failure due to sepsis. Kamaleswaran et al. [98] used physio-markers to predict the onset of severe sepsis in critically ill children by a novel algorithm created by an AI. Nemati et al. [99] used an artificial intelligence sepsis expert for early prediction in adults. A group of researchers from the Imperial College of London published the first AI to help physicians in sepsis care, the "AI Clinician" [100]. Overall, despite the limitations, AI provides individualised and personalized treatments that could help to develop strategies to overcome sepsis (Table A1).

4. Antimicrobial-Pathogen Interactions: Overcoming Antimicrobial Resistance

Antimicrobial resistance (AMR) is a major public health concern, and at present, some bacterial infections are untreatable (Figure 4). There is an imperative need for new antibiotics, and new strategies are desperately needed to fight infectious diseases [101]. Previous research has focused on accurate and early diagnosis to better combat infections [55], while some work has also been done to better identify mechanism of resistance in bacteria, mycobacteria, viruses, and parasites. The consensus is to focus on early detection of the microbe, as well as its possible mechanisms of resistance, in order to provide the necessary antimicrobial treatment and avoid a further increase on AMR [12,102,103].
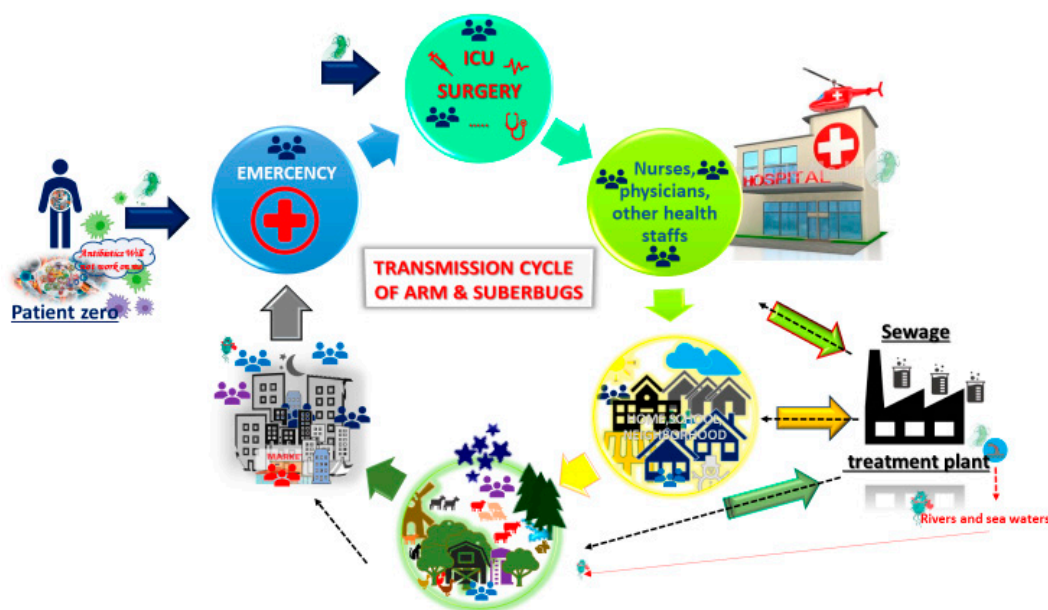
Figure 4. Transmission cycle of antimicrobial resistance (AMR) and/or superbugs. Patient zero (PZ) harbours AMR and/or a superbug. PZ comes to the Hospital because of an infectious disease. The infection is finally overcome with wide-spectrum antibiotics, and PZ leaves the hospital. However, the superbug has been able to spread by fomites, hands, and even directly person to person. Once PZ is at home, he or she is still colonized and harbours the AMR. The superbug then spreads across the neighbourhood, and so on. The superbug ends up at a waste treatment plant. In spite of treatments, the superbug can survive and keep circulating across water for human consumtion. In addition, the residual waste water is spit into rivers or seas, thereby maintaining the ARM and superbugs, and, once more, the cycle starts again. Cartoons are available online [104,105].

AMR is also a complex process that takes place at different levels of bacterial organization. Interactions between microbes and antimicrobials are complex [106], and there are many subtleties to be considered, including colonization, infection, bacterial fitness, and bacterial evolution [12,107,108]. According to environmental conditions, such as antibiotic pressure, bacterial evolution can address independent rates of change and selection [109–111]. It is important to highlight that the bacterial mutation rate is faster than the rate in humans, allowing for a rapid evolution that enables adaptation to different threats, as well as immunity [65]. Knowledge of the proteins involved in mechanisms of resistance, as well as the PPI network against antimicrobial pressure, can lead to new ways to improve the development of novel and effective treatment strategies.

Molecular docking [112] focuses on structure-activity studies, screening, and the optimization/modification of novel molecules. This process has promoted novel strategies to emerge in the area of antimicrobial discovery. Zhang et al. [113], for example, combined different machine learning models with molecular docking to select the best strategy, resulting on a novel and highly promising approach. Likewise, TX-MS [16] could be applied to determine bacteria–antibiotic interactions and the disruption of the network under different conditions, in order to unravel the molecular base of mechanisms of resistance. Even so, nothing can predict the AMR ratio, not even the success of a new drug or strategy.

Briefly, statistical models are extensively used to predict the transmission of superbugs and resistant microbes in different settings, *e.g.*, in an intensive care unit (ICU) [114,115]. Most of these models are highly useful to predict and control outbreaks [35]. In addition, dynamics models based on systems instead of compartments [116] are also beneficial to implement in a specific community or region [103]. The stochastic models are the most suitable, when considering variables such as cross-transmission or temporary nursery staff, in the study of outbreaks [117] (Table A1). Machine learning combined with algorithms and in vitro experiments can help to develop new antimicrobial peptides [118] to predict their activity over different pathogenic microorganisms [119], and at the laboratory level, they can rapidly determine identification and antimicrobial susceptibility [120].

Based on a simple time series model, Arepyeva et al. [121] proposed a regressive sub-model to anticipate certain statements and predict the rate of resistance associated with antibiotic consumption. Ternent et al. [122] and Dasbasi et al. [123] hypothesized that hosts contribute to bacterial resistance, including the development of novel PPIs between host and bacteria, which might mediate bacterial clearance [122,123]. Treatment failure can be attributed to a delay in treatment, the wrong choice of treatment, or a compromised immune response in the host [124]. Recently, more complex models based on ABM have offered a dynamic and pragmatic alternative to the traditional SIR models, but have also yielded an increase in heterogeneity and complexity [125]. Campos et al. [111] modelled an approach to estimate antimicrobial resistance dynamics, focusing on the bacterial membrane. Moreover, this membrane model could be applied to systems biology to understand the complexity of PPIs (Table A1).

Lastly, using *Klebsiella pneumoniae* as a model, a machine learning regression model was able to predict the minimal inhibitory concentration (MIC) using Pathosystems Resource Integration Center (PATRIC) [126] annotation, the Comprehensive Antibiotic Resistance Database [127], and the whole genome sequence of *K. pneumoniae* for AMR gene prediction [128]. One year later, Nguyen et al. [129] used a similar approach to determinate the MIC for *Salmonella*. Both studies also used eXtreme Gradient Boosting or XGBoost as an algorithm for the machine learning model [130] with high accuracy. Arango-Argoty et al. [131] used metagenomics data to determine the AMRs, and, importantly, they identified a novel aspect to consider in these analyses—the heteroresistant population [132]. The clinical and scientific literature suggest that advancements in genome sequencing technologies have made successfully rapid diagnostics available for infectious diseases and the prediction of AMR, which is particularly beneficial for slow-growing microorganisms like Mycobacteria [133] or the small colony variant of *Pseudomonas aeruginosas* [134], which is usually isolated from cystic fibrosis patients or chronic obstructive lung diseases. This availability enables deep learning approaches to study the spread and acquisition of AMR and predicted MICs with a high confidence interval, with no a priori

information about the underlying gene content or resistance phenotypes, but enables us to identify and diagnose AMR determinants to rapidly select antimicrobials directly from the organism sequence [135] (Table A1).

5. Conclusions

Over the past decades, mathematical models have been developed and improved, further increasing their complexity and better mimicking the biological, chemical, and physiological environments that enable a more robust understanding of host–pathogen PPIs. Mathematical models provide an in silico translational platform, which offers predictions that allow for the investigation of antimicrobial resistance, host–pathogen interactions, and microbial pathogenesis. However, the challenge is still to understand the interactions between host–pathogen–antibiotic microbiota over time, which is the key to overcoming not only septicaemia but all infectious diseases. Deep learning across big data can develop knowledge of each individual immune response to different infections and provide enough information to unravel the molecular mechanism used by bacteria to overcome the host immune response as well as its antimicrobial effect.

Certainly, we are in the initial stages of AI and are still learning how to build more realistic and accurate models. We believe that during the next decade we will have the potential to connect patient diagnosis with treatment using machine learning or AI, which will provide a key finding in translational medicine, as well as tremendous progress towards personalized medicine. However, limitations and disadvantages, such as the non-automatization of the clinical microbiology labs supplying the subjective diagnosis, or the lack of electronic-informatized clinical backgrounds, must be addressed. Overall, the expectation to implement AI is, nowadays, a fact rather than a perspective.

Appendix A

Table A1. Advantages and limitations of individually mentioned mathematical models applied to modelling infectious diseases. It is shown the main advantages and limitations together most relevant models. Likewise, it is only shown the individual models base on statistical mathematical model and not the combination among them.

Model Type	Base on	Advantages	Limitations and Disadvantages	Examples	References
Statistical	Regression	Incidence and prevalence studies. Outbreaks studies. Simplicity.	No spatial distribution of cases. Predeterminate range of time, without time trends	Parametric and semiparametric models	[31,136,137]
	Autoregressive	Longitudinal studies. Outbreaks studies. Repetitive studies over the time during a specific interval.	Time is stationary. Statistical testing is based on the normal distribution.	ARIMA SARIMA Eagle's ARCH Model NMA	[32,33,136,137]
	Time series	Estimates the trend and seasonal effects; estimates dynamic causal effects	Prediction towards to mean. Possible prediction's errors. Determinist models.		[34,35,77,121,137]
	Cumulative sum	Considers the deviations. Sequential.	Initially, no trends trends or seasonality are assumed.	CUSUM	[34,36,137]
	Moving area	Simple, cumulative, weighted or exponential. Measure the moment.	Prediction-lag.	SMA, CMA, WMA and EWMA	[137,138]
Mechanistic	Deterministic	Describes the mean according to an initial defined value (condition or parameters) and allows simpler fitting	Always the same result. It may miss information.	SIR, SEIR, MSIR, MSEIR SIS, SEIS, SIR-carrier status	[39–41,67,103]
	Stochastic	Contains inherent randomness being more realistic	May not be predicted precisely	Environmental and demographical	[11,42–45,75,117]

Table A1. *Cont.*

Model Type	Base on	Advantages	Limitations and Disadvantages	Examples	References
Agent Based	Simulation	Focuses directly on individual variable and their interactions, reflecting relationships in a hypothetical real world considers heterogenicity	Complexity. Nonlinearity.	ABS IIR-ABM, GM-ABM	[52,83,85,86]
	Complex Systems	The components interact among them. Study of relationships and dynamisms.		Networks, Multi-layer, System Biology	[47,48,84,111,116,125]
Intelligence	Learning and training	Learns from big-data and makes an informed decision. Accuracy	Training process	Machine Learning Deep Learning	[49,51,53,55,57,58,87–92,128–131,133,134]
		Big data. Results reveal hidden patterns and predict future possibilities	Big data. Results rely on number of parameters. The youth of approaches. External validation studies to confirm the predictions.		
	Learning and solving			AI	[50,56,98–100]
		Successful and intelligent	Improves data management		

ARCH: autoregressive conditional heteroskedasticity; NMA: nonlinear moving average; CUSUM: cumulative sum; SMA: simple moving area; CMA: cumulative moving area; WMA: weighted moving area; EWMA: exponentially weighted moving average; SEIR: exposed-SIR; MSIR: maternity-immunized-SIR; MSEIR: maternity-immunized SEIR; SIS: susceptible-infection-susceptible; SEIS: susceptible-exposed-infection-susceptible; ABS: agent based simulation.

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