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Applicability Of Design Science Research For Biomedical Engineering Research



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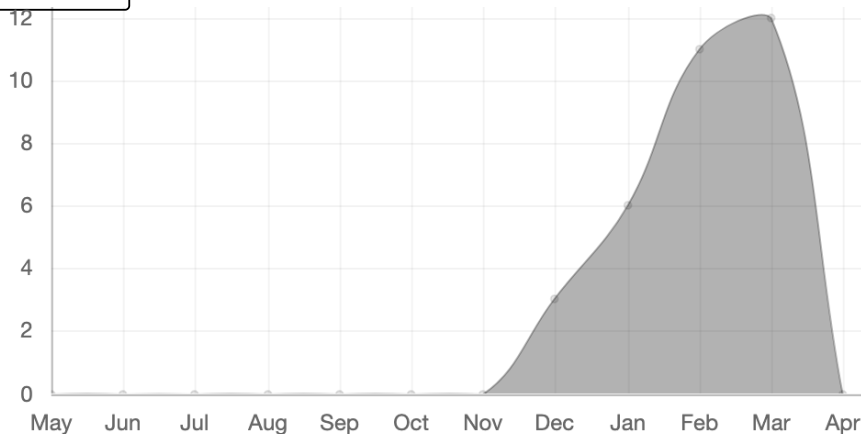
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Abstract

The design-science paradigm aims to push the limits of human and organisational capabilities by generating new and inventive artefacts. The design science research framework includes engineering that applies science through the design process to solve challenges. The design process looks for a solution to meet the environment's needs. On the other hand, a research study results from a collaboration between design and knowledge base to answer a research problem.

The three principal cycles in design science research are the relevance cycle between the environment and the design phase, the design cycle within the design phase, and the rigour cycle between the design phase and the knowledge base. While it is most well-known in the engineering and computer science disciplines, it is also applied in biomedical engineering and bioinformatics. It is relevant in biomedical engineering because of the connection between research outputs and the issue of scientific rigour. Three cases are presented in this article to depict design science study in biomedical and bioinformatics research. For each case discussed, machine learning has a big chance accompanied by unique challenges. In conclusion, the design science paradigm can also be used in biomedical engineering research to ensure that knowledge is relevant and appropriately included in the research process.

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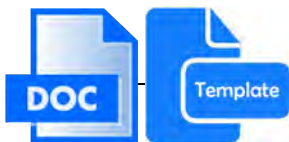
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Applicability Of Design Science Research For Biomedical Engineering Research

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ABSTRACT

The design-science paradigm aims to push the limits of human and organisational capabilities by generating new and inventive artefacts. The design science research framework includes engineering that applies science through the design process to solve challenges. The design process looks for a solution to meet the environment's needs. On the other hand, a research study results from a collaboration between design and knowledge base to answer a research problem.

The three principal cycles in design science research are the relevance cycle between the environment and the design phase, the design cycle within the design phase, and the rigour cycle between the design phase and the knowledge base. While it is most well-known in the engineering and computer science disciplines, it is also applied in biomedical engineering and bioinformatics. It is relevant in biomedical engineering because of the connection between research outputs and the issue of scientific rigour. Three cases are presented in this article to depict design science study in biomedical and bioinformatics research. For each case discussed, machine learning has a big chance accompanied by unique challenges. In conclusion, the design science paradigm can also be used in biomedical engineering research to ensure that knowledge is relevant and appropriately included in the research process.

Keywords: *design science research, biomedical, bioinformatics, deep learning*

1. INTRODUCTION

Science is highly accolades, and it seems that there is something exceptional about science and its method. The word science comes from the Latin "Scientia", which means knowledge. Based on the Webster New Collegiate Dictionary, the definition of science is "knowledge gained through learning and proof" or "The knowledge that surrounds a general truth of the laws of nature, is obtained and proven through the scientific method. Science refers to a system for knowledge that uses observations and experiments to describe and explain natural phenomena, referred to as pure science. In contrast, applied science is a science application aimed at human needs. According to Comte, science can be arranged in a level from the general and straightforward then processed up to a higher scope Complex and limited [1].

From its ethical value to science, it appears that positivism has empirical objects and can be measured logically and empirically. Science is based on what can be seen, listened to, and touched instead of individual suppositions. In case, assist the thinking that takes us from this truthful premise to the laws and hypotheses that constitute logical information is sound, at that point the coming about information can itself be taken to be safely set up and objective [2]. Science is coherent: new information fits existing information and is communicated through connections among occasions or factors. Logical tests allow deciding these connections by checking the change of pertinent factors [3]. Ideal models are fundamental to typical science. An ordinary science, practised by a logical community, open issues that surrender to investigate utilising strategies (laws, rebellion) recognised by the convention and characterised by a worldview, which legitimates perplexes and issues on which the community works. A worldview move more regularly says "paradigm change," but the move has demonstrated more arousing interest [4].

The application of science and math to illuminate issues is the meaning of Engineering. Engineers figure out how things work and discover down-to-earth employment for logical revelations. Researchers and innovators regularly get the credit for advancements that develop the human condition, but engineers are instrumental in making those advancements accessible to the world [5]. Physicist Freeman Dyson wrote, "A person with original ideas is a good scientist. A person who makes a design is a good Engineer that works with as few original ideas as possible. There are no prima donnas in engineering." [6]. Designers should be prepared with logical strategies, particularly when and how to apply them within the plan [3].

Science enhances our knowledge of the universe and the environment rationally and logically, whereas engineering applies this scientific knowledge to create new and better products and designs. Science is about how things work and not about new technology. Engineering uses the principles of science and mathematics to produce better and more efficient structures and designs. Engineering can exist without science because it takes imagination, trial and error, and fantasy to create a better product. One specific sort of instability emerges when perceptions of almost personal cases must be utilised to reach conclusions about the populace to which they are considered to have a place. Usually, the case in the biomedical investigation, as in numerous other areas. When the disconfirming proof is found personally, does it adulterate a population-based conclusion? On the off chance that the person's case is treated as an exemption, it may not. Moments like this may be seen as comparing to forks within the investigation, where the heading and center of request would depend upon the choices made by a researcher [7].

Design science research (DSR) aims to upgrade innovation and science information bases by creating inventive artefacts that fathom issues and progress the situations in which they are instantiated. The outcomes of DSR incorporate both the recently planned artefacts (e.g., gadgets,

conventions, frameworks) and a complete understanding of why the artefacts give an upgrade (or indeed disturbance) to the appropriate application settings [8].

Engineering becomes a part of the design science research (DSR) framework [9] as the interaction between environment and design. The design process seeks the solution to the environment's needs. These needs transform into the research problem that defines the research activity to gain the relevant answer. The design also involves the usage of the knowledge base that provides the foundation and methodologies to solve the research problem, and we call this kind of interaction a research study.

Biomedical engineering research aims to improve the quality of life. Nevertheless, it has to consider any risks for the human being that a wrong diagnosis or decision could put someone in danger. As DSR concerns the relevance between research outcome and the problem with rigour in scientific validation, we believe DSR is applicable in biomedical engineering research. In this paper, we discuss how DSR also works in the case of biomedical engineering research, what considerations we need, and its challenges. We took three cases as examples from the very active study in biomedical engineering research.

2. METHODS

2.1. Research Design Assumption

Most people doing research do not spend vast amounts of time writing directly about epistemology, ontology, and axiology. Research is just going about the research, and these areas and assumptions remain implied beneath the surface. Epistemology, ontology, and axiology help gather a better appreciation and compare and contrast different research areas at a much more sophisticated level.

Epistemology is a branch of philosophy that studies knowledge or knowing. It asks questions like "how do we know what we claim to know?". Epistemology focuses on the nature of knowledge and its scope. Different perspectives on epistemology argue that knowledge is gained in different ways, has different levels of reliability and can or should be utilised differently.

Theorists have different epistemological assumptions. Some assume that knowledge is already out there just waiting to be discovered, and it is researchers' job to uncover the universal, unchanging, and absolute truth. In contrast, others believe that people develop knowledge based on how they perceive the world and through their experiences. Further along this spectrum, the relativistic view believes that knowledge is a social construction. In essence, whatever is treated as knowledge, is knowledge. There is no universal or absolute truth. Although most researchers do not explain epistemological assumptions directly, their research will leave clues in the research methods.

Ontology is a branch of philosophy that studies the nature of human beings' existence as an individual, in society and the universe. "Who are we?", "what are we here for?" are ontological questions. One place researchers leave lies about ontological assumptions is in the level of focus on people. Another way is by how much agency the research assumes people have. Ontology is applied in a variety of disciplines. It can be seen as foundational, as one's understanding of what reality is, how it can be adequately understood and how best to classify that which is real will have a significant impact on how one operates within one's discipline and how one understands and conduct research

Axiology is a branch of philosophy that studies values. It asks questions about the value that guide the research to begin with. For example, "what do we value?", "what values should guide our research?", "what value(s) or outcomes will result from the research?". It often asks questions about the extent to which the research can be neutral, or does personal value shape how someone conducts their research and whether the research seeks to understand or change the world for the better?

2.2. Research Design Assumption

In the design science research (DSR) framework [9], the environment requires the design to answer the needs by giving the suitable application. Meanwhile, the design process also requires a knowledge base that consists of foundations and methodologies to provide the related knowledge, and the design process will deliver any additional knowledge. The environment consists of people and organisations accompanied by their field-related technologies. Interaction between environment and design becomes an engineering process since a design implementation aims to fulfil the needs. This one produces the research problem. The design-knowledge base interaction is what we called as a research study where there is a growth of knowledge or even replacement of obsolete knowledge. We have to note that the replacement does not always occur, as several circumstances sometimes use the old knowledge when the newest one cannot solve the specific problem. What happens inside the design is the cycle of operation between the building phase and the evaluation phase. In the building phase, we employ the theories and existing artefacts, then the results are assessed by the evaluation phase. In the evaluation phase, we manage the studies, experiments, simulations, and analysis, guided by methodologies from the knowledge base, to inform the building step for any refinement. The design should achieve the relevant answer for the needs. By applying appropriate foundations and methodologies, the design process could achieve rigour or an accurate way to reach the solution.

The output of the design process can be categorised into constructs, models, methods, and instantiations [10]. Constructs consist of symbols or vocabulary to define the problems and solutions to build a model. Models represent the problem with solution alternatives, such as logic models or mathematical models. They correlate with the architecture abstraction. Methods become the how-to for the design process, contain algorithms, practices, and protocols. The physical results of design in the real world are instantiations, e.g., heart monitor.

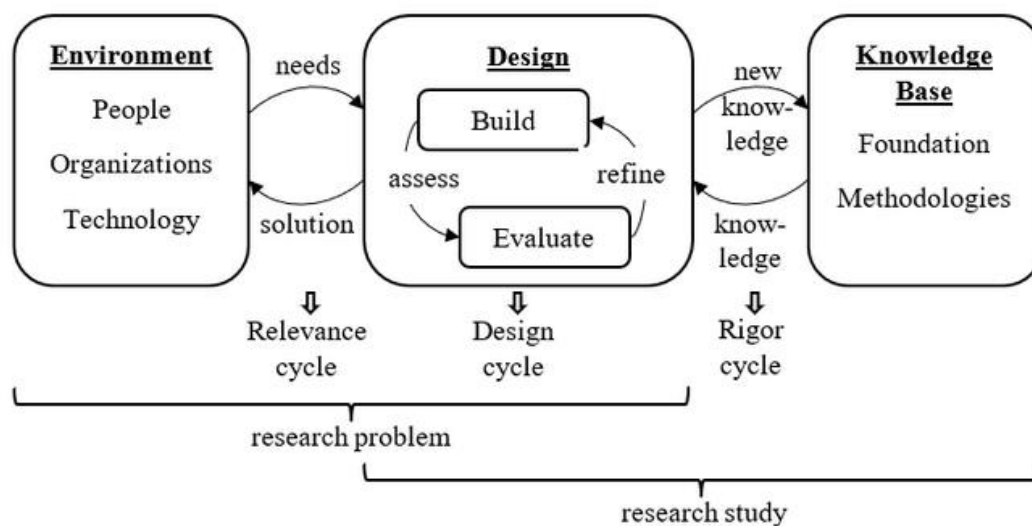


Figure 1. Three cycles of DSR (adapted from DSR (Hevner Alan, 2007))

3. RESULT AND DISCUSSION

We look for which research paradigm matches each case ontologically, epistemologically, and axiologically. Biomedical engineering research focuses on solving medical and biological problems. That makes it undoubtedly pragmatism based on the epistemology aspect. Axiologically, while logical positivism is value-free research and pragmatism is value-driven research, we infer that this type of research is more suitable in the pragmatism paradigm. Besides, since interpretivism research is subjective, our cases are not a part of this paradigm.

On another way, biomedical engineering research also relates to postmodernism because this research needs the increasing complexity of perception [11]. The more we comprehend a specific topic, the harder we accept the simple answers. Moreover, truth in postmodernism appears from approximate reasoning [12], where uncertainty always exists in life.

Critical realism also can play a part in biomedical engineering research. Since we deal with human conditions, we must consider how and why things are effective or ineffective. Those questions can answer correctly through research methods guided by critical realism [13]. Critical realism also helps this engineering research to achieve ethics with priority in safety, health, and welfare [14].

Design science study focuses on artefact development and performance to increase functional performance. Algorithms, human/computer interfaces, design approaches (including process models), and languages are among the categories of the artefact to which it is commonly used. Although it is most well-known in the Engineering and Computer Science disciplines, it is also used in biomedical engineering and bioinformatics. Bioinformatics is a branch of biology that is associated with computational methods [15], which describe the understanding of the technologies for biological data generation and engineering that requires several connected tools in a sequence of tasks that cover the steps of a process from initialisation to producing final results [16].

Based on DSR, we also discuss how applicable DSR is in biomedical engineering cases, what considerations we need for applying DSR, and the challenges. We also look for which research paradigm matches each case ontology, epistemology, or axiology. We took three cases to represent the biomedical engineering cases. The first case is the abnormality identification of human health by classifying abnormal heart sound to assist clinicians in decision making. The second case is the computer-assisted rehabilitation process by human-computer interaction (HCI), specifically, brain-computer interface (BCI), which became one of the active studies in biomedical research. Last, we had a bioinformatics case predicting protein structures as a role-player in drug discovery studies.

3.1. An Intelligent system for heart sound classification

Organically, a typical heart produces two signal phases: the first sound, namely S1, and the second sound, namely S2. The interim S1 and S2 are systolic periods, and the interim between S2 and after S1 is the diastolic stage. Consequently, the term principal heart sound signals allude to the primary and the moment (S1 and S2, respectively) sounds that are important for clinical evaluation based on the phonocardiogram (PCG) procedure. One-cycle fundamental heart sound is for 0.8 seconds. Other than those S1 and S2 signals, other sounds like S3 (early diastolic heart sound), S4 (late diastolic heart sound), and the murmur may appear within the PCG. The S3 and S4 may happen in typical hearts or be associated with obsessive exercises. On the other hand, the murmur is activated by basic and functional defects of the heart are considered abnormal conditions [17].

The nearness of murmurs within the arrangement of heart sounds can signify abnormalities. The term and location of the murmurs may shift from one case to another, making it complicated to distinguish the nearness of murmurs within the heart sounds flag. Heart sounds distinguishing proof requires a few processes, including denoising and segmentation. The latest deserves a significant

sum of inquiring about exertion and advanced flag handling strategies to create a vigorous yet less time-consuming division [18]. A few suggested works within the heart sounds distinguishing proof calculations depended on the wrap extraction procedures. For occasion, the paper in [19] utilised the average Shannon vitality normalisation implemented for PCG signals.

The first step in designing this research study is to analyse the importance of classifying heart sound signals in helping the world of medicine from the Engineer's side. Some patients with heart failure also experienced an increase; data in North America and Europe shows more than 80% of heart failure patients over 65 years. Data estimated by 2030 in the United States for people with heart failure amounted to 8.5 million [20]. The technique for listening to heart sounds using an electronic or traditional stethoscope is called a phonocardiogram (PCG), an old but highly effective method of diagnosing several cardiovascular diseases. However, examinations based on the doctor's hearing are also an obstacle in determining the results of heart examinations because they are the result of subjectivity.

The second step is to find a solution for classification with the development of the current computational process. Allowing application classification techniques automatically using machine learning and deep learning; there has been much effort made to analyse PCG signals automatically as Tschannen did in 2016 using data on Physionet, sensitivity level results, specifications, and scores of 96%, 83%, and 89% [20]. Research conducted by Chen with the DNN method resulted in an accuracy rate of 91.12% [21]. Complexity in PCG heart signals is the biggest challenge in the classification process. In 2019, a PCG signal segmentation study was conducted [22]. The study showed promising results, but the time spent carrying out the process belongs. [23] summarised some research on the classification of heart signals.

In conducting this study, several challenges will affect the results: network architecture, hyperparameter optimisation, imbalance dataset, and extraction process characteristic. The selection of neural network architecture is very influential on the results obtained. The model and variety used in the processing need to be considered appropriately in computational processing and the results. Hyperparameter optimisation is an important parameter to get maximum results. This optimisation is set before the training process. Some settings about hyperparameters, including filter length, number of hidden layers, and learning rate, significantly affect the result. The configuration of these parameters depends on the type of data, the amount of data, and the objectives greatly. Balance in datasets is essential in the process of processing data. Focuses on converting raw data into usable information before being analysed. Adjusting data to a normal distribution takes time in its processing. So, it needs to be observed whether the processed data has been balanced or not. The inevitable thing in signal processing is selecting suitable characteristics to determine a classification. The selection of inappropriate features will cause the learning process in Machine Learning not to get maximum results.

Once the artificial intelligence program utilising deep learning is complete, the next step is to conduct testing with the patient's primary database and data at the hospital. This research is related to tools that will be applied in real-time. Validation on the part of the cardiologist is necessary for the final results of the study. They were then published in scientific reports in journals and international conferences to contribute to the field of knowledge resulting from the manufacture, trial, and analysis.

3.2. Brain signals pattern recognition (specific case in speech production)

Human produces biosignals, such as bioelectric signals from the nerve cells and muscle cells, while the cell membrane generates an action potential under certain conditions [24]. This signal

acquisition uses electrodes placed on the surface or invasively near the cell. One instrument for signal acquisition is electroencephalography (EEG) to record bioelectric signals from the brain since the early 1300s. Many research used EEG signals in clinical studies, experiments, and computational works (detection/recognition/diagnosis) in neurological problems and physiological abnormalities of the brain, including Brain-Computer Interface (BCI). Many neurocognitive studies aim to help people with disabilities to perform their activities in the form of the BCI, such as to control a wheelchair, type a letter, or Internet-of-Things (IoT) applications. We took one implementation of BCI in imagined speech recognition for the case in this paper.

First, we identified the needs in the case of imagined speech BCI. People hardly communicate in noisy circumstances where they cannot hear other voices, in quiet environments where sounds are not allowed, in secret conversation, or have speech disorders [25]. A study in the United States showed that speech disorders occur among 1 in 13 people every year [26]. With this situation, an interface to help communication is more needed than before. The causes of speech disorders can be the absence of knowledge to speak (deaf people), the problems in articulation and its supported organs (larynx, respirator, and others), or neurologic dysfunction such as stroke, paralysed people, locked-in syndrome (pseudocoma), or coma patients [27].

Second, in the relevance cycle, we defined the solution required to help communication problems. Imagined speech BCI has the potential to be the solution, as long as the brain is still normally active, by converting brain signals into imagined speech. With EEG pattern recognition while imagining speech, we could increase the accuracy in translating the signals to words.

Inside the relevance cycle, the development of imagined speech BCI also performs the design cycle. There would be several iterations between the building phase and the evaluation phase. In the building phase for imagined speech BCI, there are some challenges:

- how many channels (electrodes) do we need; there will be a trade-off between users' comfort and the spatial information from the captured area, which brain region is the most involved while a person imagined that he speaks,
- how to make the algorithm inside this imagined speech BCI used by different users with no degradation of accuracy,
- how to handle the noise and movement artefact since EEG is very low voltage (in μV) that makes it becomes low signal-to-noise ratio (SNR), and
- how to make the BCI learn EEG signals' patterns online and accept feedback.

The mentioned challenges become the potential research questions. We will iterate back to design the solution better until major questions are solved. In this step, we have to sort the needs based on priority and categorise which ones are mandatory and nice to have.

After building the intelligent software, we need to ensure the pattern recognition works both in secondary data and living subjects, either in a laboratory environment or an open one. The latter requires a prototype that meets clinical requirements for the targeted population. We also should consider ethical matters because this study is associated with living humans. A developed handy and practice tool will increase the usability of BCI.

In the rigour cycle, we validate the study of imagined speech BCI in the related science field. To perform the design process, we need to use the proper fundamental theories, sufficiently observe the previous studies, and apply a suitable methodology. Then, we need to publish the research outcomes to get valuable scientific feedbacks from related experts or communities. In the meantime, there will bring out additional knowledge.

3.3. Protein Engineering

Protein engineering is a method for developing proteins with improved or unique functional characteristics. With so many natural proteins available to observe and manipulate, one motivation for pursuing protein design is practical. One practical motivation for pursuing protein design is designing a similar artificial system "made to order" to solve significant chemical or biochemical problems. Indeed, the capacity to create proteins from scratch can transform fields of science and technology, from disease treatment to identifying enzymes that break down industrial waste.

The emerging field of protein engineering aims to manipulate both the structure and function of new macromolecules. Its technique takes a sample of the sequence space where the desired topology folds. The two broad categories of current efforts are modifying an existing protein with a known sequence and features or creating novel proteins with sequences unrelated to those found in nature (*de novo* protein design). In several fields of protein engineering, deep learning (DL) [28] approaches have opened up new possibilities. They frequently outperform more traditional methods due to their ability to extract domain-specific features that are adaptively acquired from data for a specific task. There are two primary groups of DL methods to protein design. The first method relies on knowledge of other sequences to design sequences directly (function → sequence or structure agnostic). The second method involves selecting or constructing a protein fold or topology that meets specific criteria, then identifying the amino acid sequence that can fold into that structure (function → structure → sequence) [29].

LSTM RNN framework is used as an to learn sequence patterns of antimicrobial peptides in the direct design of sequence method [30]. This framework was later used to create membranolytic anticancer peptides by the same group [31]. Twelve resulting peptides were produced, and six killed MCF7 human breast cancer cells with a selectivity of at least three-fold over human erythrocytes. In another application, GANs focus to learn the uni-directional mapping from a continuous real-valued space to the design space in another application. [32] created a model that combines a standard GAN and activation maximisation to create DNA sequences that bind to a particular protein. [33] trained ProteinGAN on the bacterial enzyme malate dehydrogenase (MDH) to build novel enzyme sequences that were active and soluble *in vitro*, with a 24 percent success rate. FeedBack GAN (FBGAN) is another GAN-based framework that learns to create complementary DNA sequences for peptides [34]. They use an oracle (an external function analyser) to create a feedback-loop architecture to optimise synthetic gene sequences for desired attributes. They update the positive training data for the discriminator with high-scoring sequences from the generator at every epoch, resulting in a progressive increase in the score of generated sequences. They successfully biased generated sequences towards antibacterial activity and a desirable secondary structure, demonstrating the efficiency of their model.

The SPIN model [35], which uses a five-residue sliding window to predict amino acid probabilities for the center position to create sequences compatible with the desired structure, achieved a sequence recovery rate of 30.7 percent. SPIN2 increased it even further, to 34% [36]. Another effort used a 3D CNN framework to predict the most stable residue type in the center of a region using the voxelised local environment of an amino acid residue. It reported a 70% recovery rate, and the mutation locations were experimentally validated [37]. [38] trained a similar model construct sequences for a given backbone. They put their approach to the test by creating sequences for five proteins, one of which is a *de novo* TIM-barrel. The predicted structures were 2-5Å RMSD from the native conformation, and the designed sequences were 30-40% identical to native sequences.

Another approach is to create the entire sequence, rather than fragments, based on a target structure. [39] used a CVAE model to construct sequences conditioned on the topology of proteins represented in a string. A molecular simulation was used to ensure that the final sequence was stable [40]. [41] created the gcWGAN, which combines a CGAN with a guidance strategy to bias the generated sequences towards the desired structure. Another notable experiment is the graph transformer model, which takes a structure in the form of a graph and outputs a sequence profile [42]. They treat the sequence design problem the same way as they approach machine translation. It uses an encoder-decoder framework with self-attention mechanisms to dynamically learn the relationship between information in two neighbour layers. Perplexity was used to measure the result, and the per-residue perplexity for single chains was lower (better) than SPIN2.

We can see how DSR processes are implemented in protein engineering from these case studies. While protein design has a common motivation, the objective of some studies in the study cases is to create an artefact while others improve it. The design and development process using deep learning approaches shows an iterative process. The use of the artefact solves various problems. In addition to the one mentioned in the former discussion, some other successful examples include novel folds [43], enzymes [44], vaccines [45], novel protein assemblies [46], ligand-binding proteins [47], and membrane proteins (48). Finally, SPIN and SPIN2 are examples that depict an evaluation process that iterates back to better design the artefact.

4. CONCLUSIONS

Engineering is an application of science through the design process to solve problems. It becomes a part of the design science research framework as the interaction between environment and design. The design process seeks the solution to the environment's needs. Meanwhile, a research study is an interaction between design and knowledge base to solve the research problem.

One branch of engineering, biomedical engineering, aims to improve the quality of life accompanied by risks (the wrong prediction could be dangerous). Biomedical engineering research focuses on solving medical and biological problems. Thus, it holds pragmatism. This kind of research relates to the postmodernism paradigm since it involves the growth of perception complexity. The more we comprehend a specific topic, the harder we accept the simple answers. Critical realism is also suitable in this research, such as evaluating the effectiveness and obtaining ethics with priority in safety, health, and welfare.

DSR seems applicable in biomedical engineering since it concerns the relevance between research outcomes and the problem with rigour in scientific validation. In the three cases discussed, we start with initiating the needs. They are the role of analysing heart sound signals to support deciding health care, analysing brain signals to help disabled people, and obtaining a novel protein sequence that will fold into a desired structure or perform a specific function. This step also begins the flow of DSR.

In DSR, there are three principal cycles: relevance cycle between environment and design phase, design cycle inside the design phase, and rigour cycle between the design phase and knowledge base. For each case discussed, machine learning has a big chance accompanied by unique challenges. The implementation runs iteratively in the design phase contains the building phase and evaluation phase. Ordering questions based on their priorities is necessary for this phase. In the rigour cycle, we use the proper knowledge for the design process then the research outcomes need validation by related experts and scientific communities. Then, publication becomes acknowledgement when new knowledge is acceptable. The relevance cycle itself aims to ensure the relevance of research outcomes with the initiated problems. We strongly believe DSR is also applicable in biomedical

engineering research to assure the relevance and rigour (appropriate involvement of knowledge) in the research fashion.

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