

Suitably impressive thesis title

1044935

St Cross College
University of Oxford

*Submitted in partial completion of the
MSc in Computer Science*

Trinity 2020

Abstract

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Acknowledgements

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This is where you thank your advisor, colleagues, and family and friends.

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Contents

List of Figures	vi
List of Abbreviations	vii
1 Introduction	1
1.1 Motivation	1
1.2 Contribution	3
2 Background	6
Appendices	
A Review of Cardiac Physiology and Electrophysiology	14
A.1 Anatomy	15
A.2 Mechanical Cycle	17
A.3 Electrical Cycle	18
A.4 Cellular Electromechanical Coupling	20

List of Figures

2.1	test	6
2.2	test	8

List of Abbreviations

- 1-D, 2-D** . . . One- or two-dimensional, referring in this thesis to spatial dimensions in an image.
- Otter** One of the finest of water mammals.
- Hedgehog** . . . Quite a nice prickly friend.

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There is no one who loves pain itself, who seeks after it and wants to have it, simply because it is pain...

— Cicero's *de Finibus Bonorum et Malorum*

1

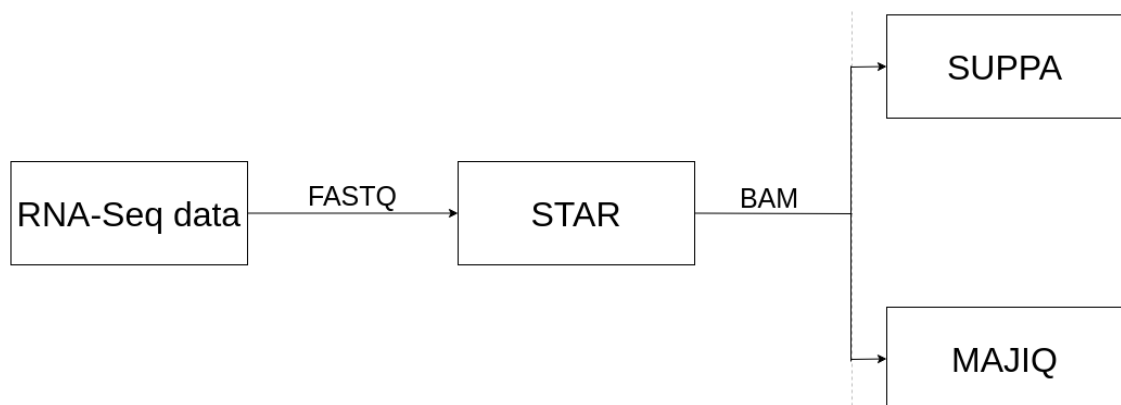
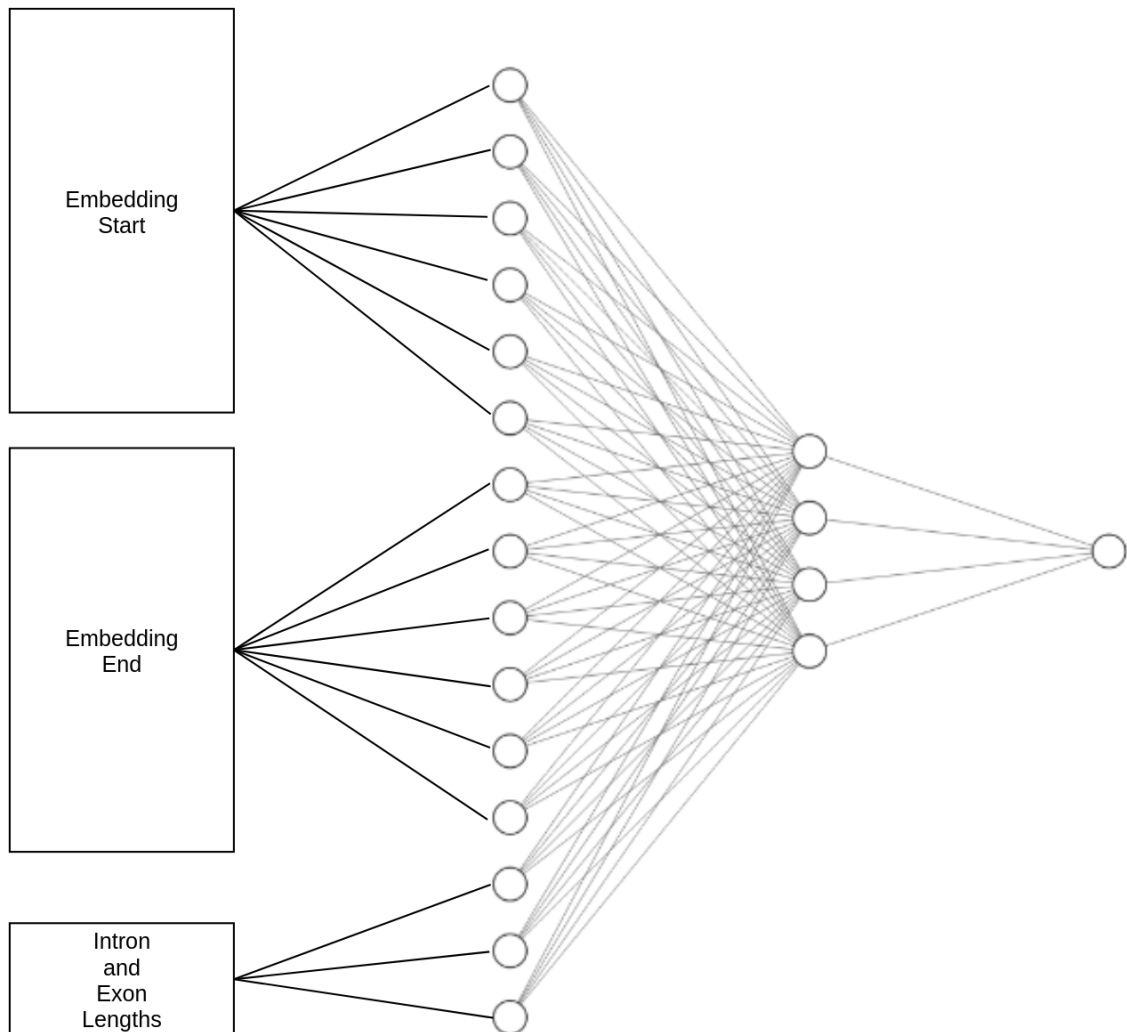
Introduction

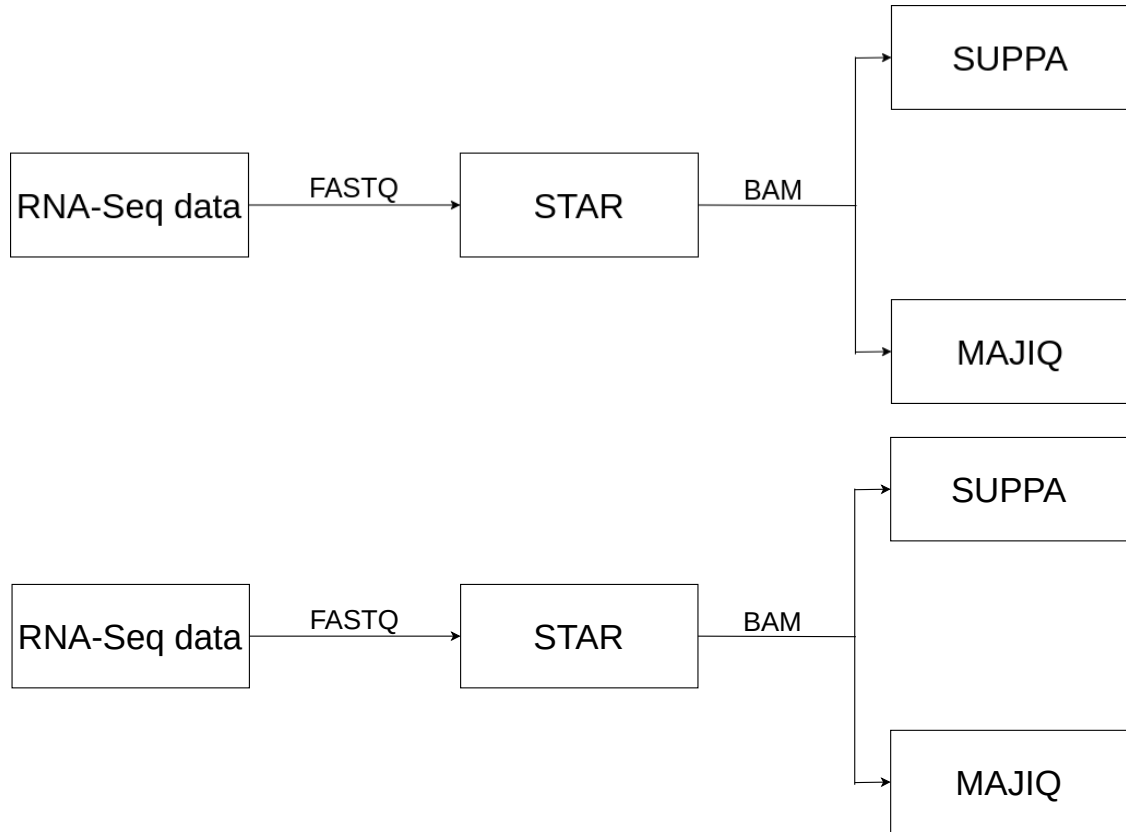
Contents

1.1	Motivation	1
1.2	Contribution	3

1.1 Motivation

The rapid advance of minimally-invasive cardiac procedures promises improvements in patient safety, procedure efficacy, and access to treatment. While percutaneous coronary intervention (PCI) has become routine and highly effective [bravata_systematic_2007], catheter procedures in areas such as electrophysiology (EP) and valve replacement are still coming of age. This progress is driven by demographics and the improvement in general cardiac care, as patients surviving initial cardiac events go on to require treatment for sequelae [foot_demographics_2000]. The growing need for advanced treatment is being answered by developments in catheter technology and procedures. These tools are continually advancing to access and manipulate an ever-broader range of anatomy [sousa_new_2005].

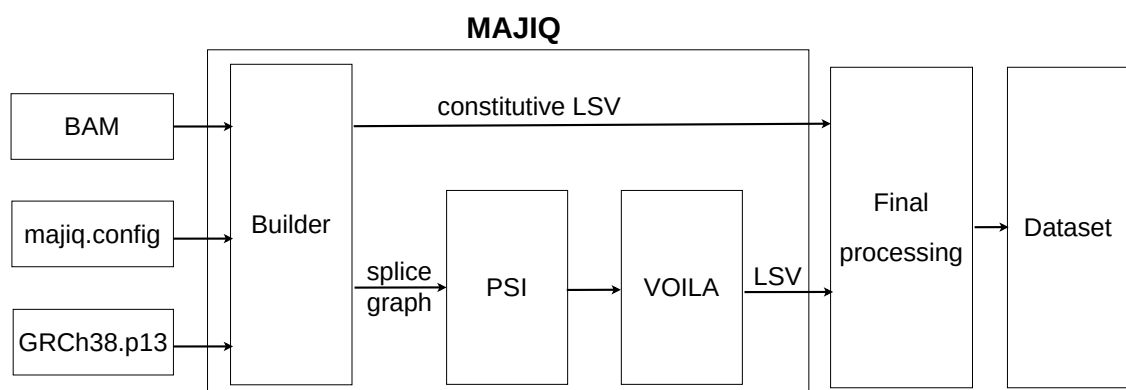




1.2 Contribution

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2

Background

Contents

Gene expression is the process whereby a sequence of nucleotides is used to direct the synthesis of a functional gene product (protein, functional RNA). Gene expression is fundamental to all life. It occurs in two steps: during transcription, the DNA is transcribed into messenger RNA (mRNA) and during translation, the mRNA is decoded into proteins.

In more detail, during transcription, an initially transcribed precursor mRNA

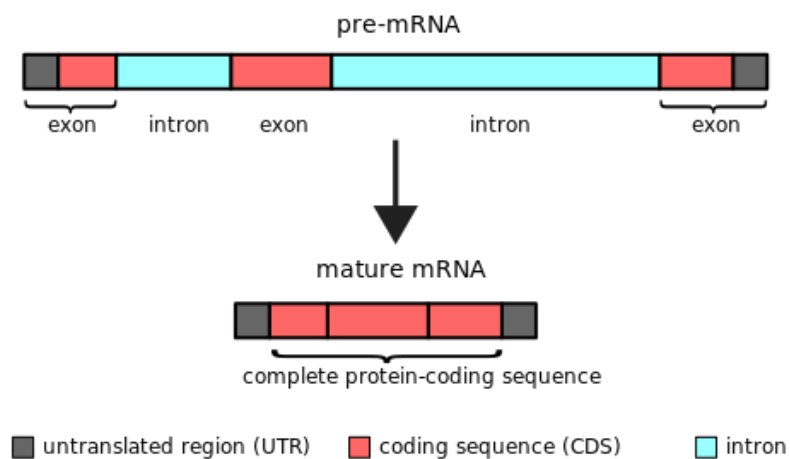


Figure 2.1: ffs

(pre-RNA) is translated into a mature RNA by a process called splicing. Splicing is based on DNA being made up of exons (predominantly coding regions), and, typically longer, introns (non-coding regions). Only exons are contained in the mature mRNA. Introns are still contained in the initially transcribed precursor mRNA (pre-mRNA). However, they are spliced out by the spliceosome to form the mature mRNA. The spliceosome is a complex molecular machine consisting of as many as 150 proteins. [Current perspectives] This is visualized in 2.1.

Exons which are always included in the mRNA are called constitutive exons. However, 95% of human genes with multiple exons are alternatively spliced, that is, they may only sometimes be included or may be included with different splice sites. The most common types of alternative splicing in higher eukaryotes are [commonslicing1][commonslicing2]:

- Cassete exons are exons who are sometimes included in the mature mRNA and sometimes skipped. This is the most common form of alternative splicing in higher eukaryotes (so also humans), accounting for roughly 40
- Exons with an alternative 3' or 5' splice-site. The 3' splice site or splice junction is the end of the exon towards the 3' end of the RNA strand (typically towards the right). The 5' splice site or splice junction is the end of the exon towards the 5' end of the RNA strand (typically towards the left). An alternative 3' or 5' splice-site may be located deeper inside the exon or outside the exon in a typically intronic region. Alternative 3' and 5' site splicing respectively constitute approximately 18
- intron retention, that is, when an intron between exons is not spliced out. It accounts for roughly 5

Different forms of alternative splicing are visualized in Figure 2.2. More complex forms of alternative splicing, such as mutually exclusive exons, also exist, but they are currently believed to be more uncommon. Alternative splicing occurs in nearly all organisms that carry out pre-mRNA splicing as such as plants or animals and its frequency varies across organisms. [<https://www.sciencedirect.com/science/article/pii/B97801237498400>]

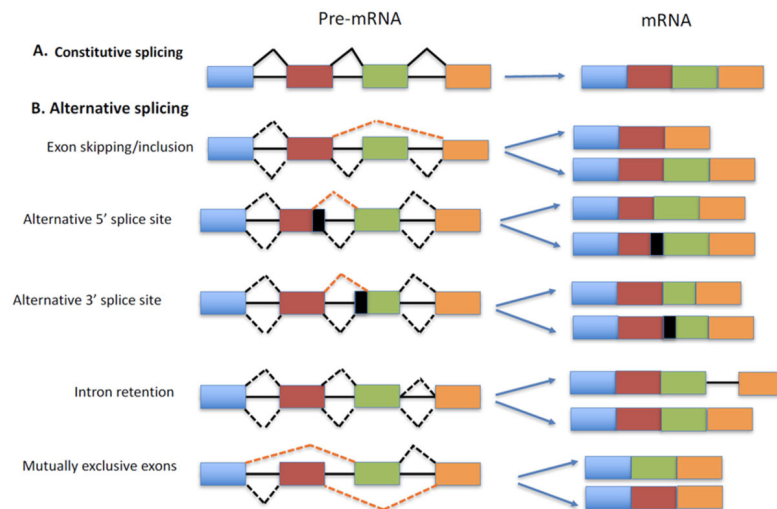


Figure 2.2: Visualization of the most common forms of alternative splicing and the resulting different possible mature mRNAs. [<https://hrjournal.net/article/view/2693>]

Why does alternative splicing occur?

Alternative splicing enables a single gene to encode multiple protein variants. This massively contributes to proteomic diversity. For instance, the roughly 20,000 human genes are estimated to encode over 100,000 different proteins.

<https://biologydictionary.net/alternative-splicing/> Alternative splicing may also speed up the rate of evolutionary adaptation. Due to alternative splicing, a gene may evolve to fulfil a different functionality without first needing to evolve a separate copy of the same gene. [bretschneiderphdthesis]

How is alternative splicing regulated?

Alternative splicing was discovered 40 years ago [discoveryofsplicing], but the molecular mechanisms governing it are still poorly understood. It is known that the spliceosome recognizes exon-intron boundaries based on the 5' and 3' splice sites, the branch site located in roughly the middle of the exon, and the polypyrimidine tract located upstream of the 3' splice site. However, estimates suggest that these four factors only account for half of the information required to determine splicing behaviour. The rest is likely accounted for by intronic or exonic, cis-acting sequences of the pre-mRNA which bind to trans-acting factors. These cis-acting sequences are usually 4-18 nucleotide long and classified as exonic splicing enhancers or silencers

??). However, the dynamic interaction between cis-acting and trans-acting factors is highly complex, new factors are still being found and thus a lot more work needs to be done if we want to fully understand alternative splicing.

What happens when splicing is misregulated?

Since alternative splicing is such a fundamental mechanism, its correct execution is crucial. Defects in splicing are typically caused by genomic sequence variations leading to misregulation of the splicing process. An estimated 9%-30% of Mendelian disorders may act through disruption of splicing [comparison] Splice variants have also been shown to be biomarkers for multiple types of cancers [cancer]. As a result, alternative splicing has also been suggested as a biomarker and potential target for drug discovery [<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4648177/>].

Importance of understanding splicing

Thus, there is great interest in better understanding the mechanisms underpinning alternative splicing. Due to rapid advances in RNA-sequencing technologies, it is now possible to sequence the genome of a patient within a day. However, the genomic variants (compared to a reference genome) observed in patients are often variants of unknown significance. [bretschneiderphdthesis] That is, it is unknown whether these variants are pathogenic or benign. An improved understanding of alternative splicing may improve the classification of genomic variants and help with the diagnosis of patients, especially those with rare genomic diseases.

Splicing codes are computational models that attempt to predict splicing behaviour based on putative regulatory features (such as sequence motifs). They were first introduced in the seminal paper by Barash et al 2010a, b. Their introduction was motivated by the recognition that splicing is highly condition-specific and regulated by the complex interaction of many factors in such a way that it is only feasible to model this behaviour computationally. [Barash 2010] focus on cassette exons and attempt to predict the change in splicing behaviour for a given exon between different tissues. The quantitative measure PSI or Ψ they introduced to describe splicing behaviour is still commonly used today: Ψ is defined as the proportion of transcripts out of all transcripts that contain a given exon [psi]. Given a random transcript, PSI denotes the probability of a particular exon being included or excluded. Similarly, Ψ_5 is defined as the number of transcripts containing a particular alternative 3' splice site for a fixed 5' splice site. Ψ_3 is defined analogously as the number of transcripts containing a particular alternative 5' splice site for a fixed 3' splice site. Ψ_5 and Ψ_3 are particularly interesting to model the competition between different alternative splice sites. To quantify the change of splicing behaviour between conditions, these models predict the corresponding $\Delta\Psi$. They were able to find novel regulators of key genes associated with diseases and to predict how genetic variants will affect splicing. [take quotes from jha et al here] Input to the model are over 1000 known and unknown motifs and higher-level features (such as exon/intron lengths and phylogenetic conservation scores) selected partially from previous studies and partially from de novo searches. Improving upon these first models, the second 'generation' of splicing codes used several common and uncommon machine learning algorithms such as multinomial logistic regression, support vector machines (SVM) and Bayesian Neural Networks (BNN) to predict changes in alternative splicing behaviour. [add citations here, partially from jha et al] Among these, BNNs were able to outperform the other methods when evaluated on a microarray dataset based on mouse data. In contrast to models from the first generation, BNNs based models only took in sequence information and very high-level features like tissue type which meant that the model was automatically able to learn relevant motifs from the

data. However, BNNs often rely on expensive sampling methods like Markov Chain Monte Carlo (MCMC) to be able to sample models from a posterior distribution. It can be challenging to scale these methods to larger datasets and a large number of hidden variables. [<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4058935/>]

As a result, the third 'generation' of splicing codes relies on deep learning models which can effectively make use of the large amount of data available with the advent of high-throughput RNA-sequencing technologies. First forays into using deep learning-based models were made by Leung 2014. Using a Deep Neural Network (DNN) with an autoencoder, they were able to improve upon the results achieved by a BNN model. Albeit Leung 2014 initially used a different dataset and a different task formulation than [BNN model], Jha 2017 were able to show that these improvements also lasted when directly comparing the models on the same dataset using the same task formulation. Furthermore, Jha 2017 developed a framework for integrating further experimental data, like data from CLIP-seq based measurements of in vivo splice factors bindings, into the model developed by Leung 2014. Adding these further features improved the explained variance in splicing behaviour between tissues, as measured by the R^2 score, by roughly further 5%

Taking inspiration from advances in Natural Language Processing, [d2v paper] developed splicing codes based on the automated feature learning approach from word2vec and doc2vec. Developing two models, one based on doc2vec and a simple MLP, and one based on word2vec and the all-convolutional Inception architecture known from Computer Vision [quote], they were able to achieve an average R^2 score of 69.2%

In contrast to these splicing codes which predict the (differential) inclusion frequency of an exon, a parallel strand of research focuses on splicing codes for distinguishing between constitutive and alternatively spliced exons. Concretely, for the first task the dataset the models are trained on only consists of alternatively spliced cassette exons and the models have to find features that are predictive of the exact inclusion rate of an exon. For the second task, the dataset consists of alternatively spliced as well as constitutive exons and the models have to find features predictive for distinguishing between constitutive and alternatively spliced exons. While there is

a large overlap between these features, there are also differences. For predicting the inclusion level of an exon, features from the cassette exon and the surrounding exons have shown to be relevant. [add quote from dsc] For predicting whether an exon is constitutive or not, features around the cassette exon itself have been reported to be the most critical. [add quotes from dsc here] [possibly talk more about features used by dsc and what constitutive exons could use] [Busch and Hertel] used 262 features extracted from an exon and its two flanking introns to train an SVM-based splicing code for distinguishing between constitutive exons, cassette exons and exons with an alternative 5' or 3' splice site. The dataset used to train the model was based on roughly 4 million ESTs and known isoforms, as well as the alternative events, track (Alt Events) of the UCSU Genome Browser. Their model achieved very impressive results with an AUC of roughly 0.94 when differentiating between rarely included and constitutive exons, but performance decreases to roughly 0.60 when distinguishing between frequently included and constitutive exons. [DSC] improved upon this work by using a deep learning model which was automatically able to learn relevant features from the raw sequence. Their model was based on a combination of convolutional blocks for feature extraction as well as an MLP for classification based on the extracted features. Training on a similar EST-based dataset, their model is significantly more robust when distinguishing between highly included cassette exons and constitutive exons with the AUC only dropping to 0.85. When distinguishing between rarely included cassette and constitutive exons, it was still able to achieve an impressive AUC of 0.92.

Appendices

Cor animalium, fundamentum est vitæ, princeps omnium, Microcosmi Sol, a quo omnis vegetatio dependet, vigor omnis & robur emanat.

The heart of animals is the foundation of their life, the sovereign of everything within them, the sun of their microcosm, that upon which all growth depends, from which all power proceeds.

— William Harvey [harvey__exercitatio__1628]



Review of Cardiac Physiology and Electrophysiology

Contents

A.1	Anatomy	15
A.2	Mechanical Cycle	17
A.3	Electrical Cycle	18
A.4	Cellular Electromechanical Coupling	20

Appendices are just like chapters. Their sections and subsections get numbered and included in the table of contents; figures and equations and tables added up, etc. Lorem ipsum dolor sit amet, consectetur adipiscing elit. Sed et dui sem. Aliquam dictum et ante ut semper. Donec sollicitudin sed quam at aliquet. Sed maximus diam elementum justo auctor, eget volutpat elit eleifend. Curabitur hendrerit ligula in erat feugiat, at rutrum risus suscipit. Pellentesque habitant morbi tristique senectus et netus et malesuada fames ac turpis egestas. Integer risus nulla, facilisis eget lacinia a, pretium mattis metus. Vestibulum aliquam varius ligula nec consectetur. Maecenas ac ipsum odio. Cras ac elit consequat, eleifend ipsum sodales, euismod nunc. Nam vitae tempor enim, sit amet eleifend nisi. Etiam at erat vel neque consequat.

A.1 Anatomy

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A.2 Mechanical Cycle

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A.3 Electrical Cycle

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A.4 Cellular Electromechanical Coupling

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