**(A) Brief overview**

**(i)** **Biological question:**

The paper seeks to determine the extent to which a Variational Auto-Encoder(VAE) can be trained to model cancer gene expression, and whether or not such a VAE would capture biologically-relevant features.

**(ii) Computational problem:**

1) Approximating the Data Distribution Problem: Learn to model the underlying probability distribution of the training data as a simpler multi-variate Gaussian and thus determine its parameters.

Input: The Pan-cancer RNA-seq gene expression data.

Output: The means and standard deviations of the multi-variate Gaussian approximation for the Input data.

2) Latent-vector Compression Problem: Obtain a hidden manifold from a high-dimensional gene expression datapoint.

Input: A sample from the Pan-cancer RNA-seq gene expression data.

Output: A lower-dimensional vector of the sample.

**(iii) Computational Methods:**

Variational Auto-Encoders were used to solve both the computational problems. This unsupervised deep learning algorithm can be used to approximate/generate the underlying data distribution. They also perform non-linear data compression to obtain the hidden manifold of the sample.

**(B) Key contributions:**

* They were able to model high-dimensional cancer gene expression data as a lower-dimensional manifold without loss of much tissue-specific signals using VAEs.
* They successfully identified biological patterns in the VAE encoded features to differentiate patient sex and origin of skin-cutaneous melanoma tumors. This served as a positive control towards the validity of their proposed VAE model.
* They introduced a methodology to interpret biological features from a VAE model. These interpretation steps were used in further research, as well. Such as:
  + Directly using the learned encodings to stratify patient samples based on different biological properties (such as sex and tumor origin).
  + Interpreting the decoder weights as gene contributions for a specific encoding of interest.
  + Performing over-representation pathway on high-weight genes.
  + Interpolating the latent space by mean vector subtraction (as shown in stratifying HGSC subtypes).

**(C) Further Improvements:**

* The paper evaluates the hidden manifold for a shallow VAE, i.e., consisting of only a single hidden layer. It does not explore or comment on using deep VAEs.
* The interpretation methods cannot be extended to deeper networks. e.g., directly interpreting the weights of the decoder is not valid if the decoder consists of more than one layer.
* The data generating properties of the VAE was underutilized. This aspect requires the most improvement, in my opinion. As the advantage of a VAE over a traditional AE is that it can solve both the above computational problems and not just data compression (like AE). Still, the distribution of the data obtained by the generative VAE was barely used for any further analysis.
* The paper had only a handful of examples to show that the model captured biological signals. However, the authors do state that further testing is required to confirm that their model captures an interpretable manifold.

**(D)** The work is a significant contribution to the field as it introduced how unsupervised VAE can be used to generate meaningful latent spaces for biological data. Generative models like VAEs and GANs have made great strides in the field of vision and natural language. However, its use in the field of biomedicine has been far from transformative. This paper provided a basic framework and validation for extending generative models to biological data.