Comments to the Author:
The authors have mildly improved the review by clarifying the descriptions of the various methods. However, these descriptions are still quite shallow. Questions that these descriptions should answer:

--Thank you for the advice. **All original comments are in Black.**
All responses and edits in the manuscript are marked in Blue.

- Figure 2b: how many features are provided by the ECFP fingerprint and how this is connected with the identifier list.

We have modified Figure 2b and the legend accordingly to better reflect the relationship between the fingerprint and identifiers, as well as how the fingerprint is generated.

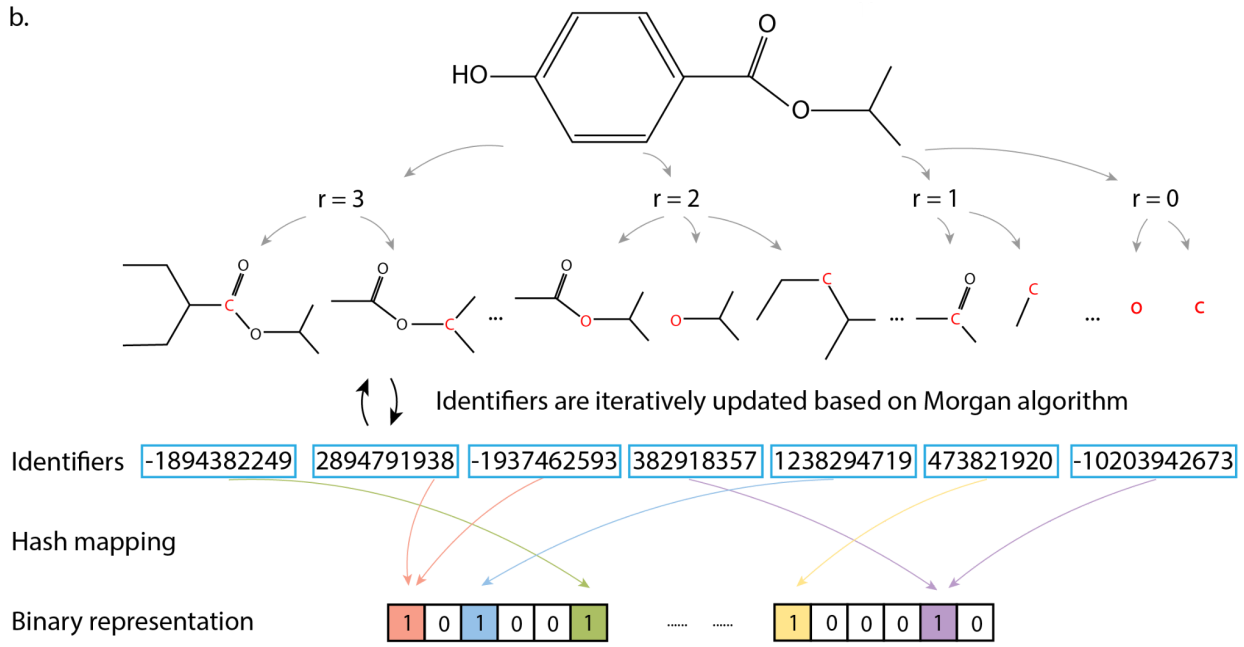

Figure 2 (b) The fingerprint generation process of the isopropyl 4-hydroxybenzoate molecule is shown based on an ECFP type strategy. For each non-hydrogen atom (red), an initial integer identifier is assigned to represent the local information (e.g. numbers of bonds and connecting atoms) through a hash mapping function. Then the identifiers are iteratively updated based on the Morgan algorithm, which combines the initial identifiers with identifiers of neighboring atoms. The neighboring atoms are defined by a circular fragment, where the radius value (r=0,1,2,3 in the figure) gradually increases to include more neighboring atoms. Finally, redundant identifiers (e.g. two circular fragments contain identical atoms and connections) are removed and a fixed length bit string is derived from the identifier list.

- Figure 3e: clearly define a graph attention mechanism and how it identifies hidden linkage among nodes.

We have modified the Figure 3e to add a detailed description to the graph attention mechanism.

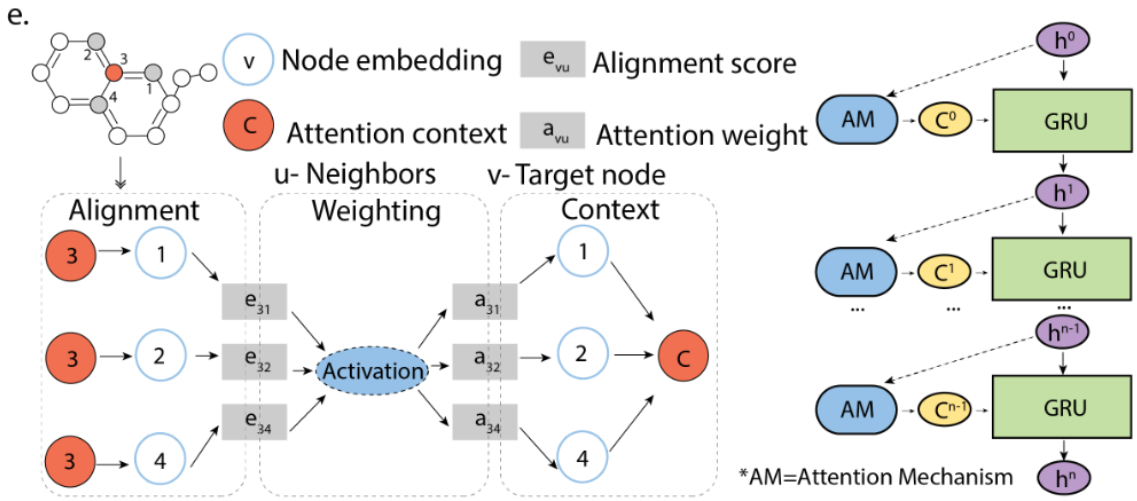

Figure 3 (e) The scheme of the Attentive FP model. The graph attention mechanism is introduced as a trainable feature to represent both topological adjacency and intramolecular interactions between atoms with large topological distances. For each target atom and its neighboring atoms, state vectors are used to describe the local environment through node embedding. These state vectors are progressively updated to include more information from neighborhoods through the attention mechanism, where state vectors are aligned and weighted to obtain attention context vectors and gated recurrent unit (GRU) layers are used to update state vectors.

- Figure 3g: If graph-based features have atom node and bond node matrices, one could say nodes are coloured and edges are weighted by their properties: so what is the innovation of the AGBT? How is different from standard GCN? Why does it need to generate eigenvalues? Of which matrix?
These descriptions must be substantial and highlight the differences between various methods for the review to add value.

Thank you for raising these questions. There are two major motivations of the AGBT algorithm: (1) The weighted colored graph essentially partitions the original graph into element specific sub figures; (2) It combines a molecular embedding learned from bidirectional transformers on SMILES with the embedding learned from the colored graph representation. The eigenvalues are calculated from the Laplacian matrix, where the non-zero eigenvalues have mathematical meanings. Briefly, the first non-zero eigenvalue, Fiedler value, corresponds to the algebraic connectivity that reflects the overall connectivity and robustness of the graph. The number of zero eigenvalues corresponds to the number of connected components. Moreover, the algebraic graph is mathematically associated with the geometric graph, so that molecular descriptors can be obtained through calculating statistics (e.g. the maximum, minimum and standard deviations) of nontrivial eigenvalues of the Laplacian matrix.
We have added more descriptions about AGBT and revised Figure 3g accordingly.

Page 8:
"In this algebraic graph-assisted bidirectional transformer (AGBT) framework in Figure 3(g), the three-dimensional molecular information is first encoded into a weighted colored algebraic graph. By

calculating the eigenvalues of graph Laplacians, the algebraic graph features are extracted. Briefly, the first non-zero eigenvalue, Fiedler value, corresponds to the algebraic connectivity that reflects the overall connectivity and robustness of the graph. The number of zero eigenvalues corresponds to the number of connected components. Moreover, the algebraic graph is mathematically associated with the geometric graph, so that molecular descriptors can be obtained through calculating statistics (e.g. the maximum, minimum and standard deviations) of nontrivial eigenvalues of the Laplacian matrix."

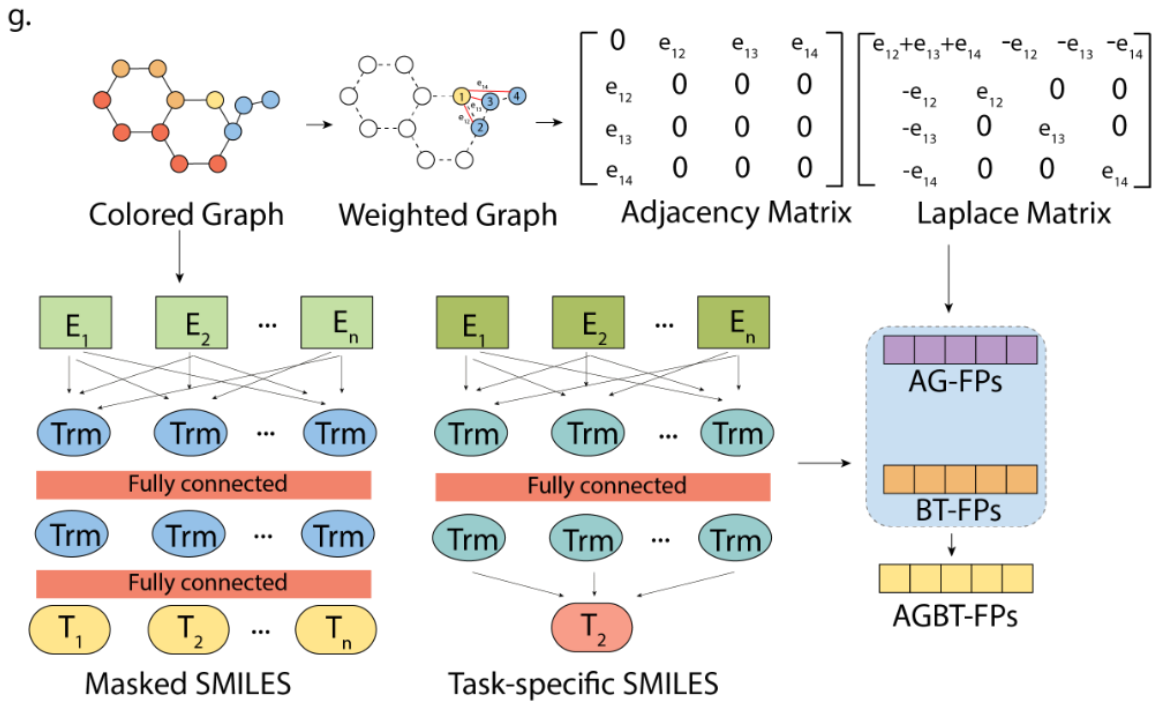

Figure 3 (g) The scheme of the algebraic graph-assisted bidirectional transformer (AGBT) method that extracts information from weighted colored algebraic graphs of molecules. This method combines two types of molecular representations: the BT features generated from bidirectional transformers treatment on SMILES, and the AG features generated from eigenvalues of the molecular graph's Laplacian matrix.