Fast exact computation of the $k$ most abundant isotope peaks with layer-ordered heaps

Patrick Kreitzberg
University of Montana
Department of Computer Science

Jake Pennington
University of Montana
Department of Computer Science

Kyle Lucke
University of Montana
Department of Computer Science

Oliver Serang
University of Montana
Department of Computer Science

Oliver.Serang@umontana.edu

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Abstract
The theoretical computation of isotopic distribution of compounds is crucial in many important applications of mass spectrometry, especially as machine precision grows. A considerable amount of good tools have been created in the last decade for doing so. In this paper we present a novel algorithm for calculating the top $k$ peaks of a given compound. The algorithm takes advantage of layer-ordered heaps used in an optimal method of selection on $X + Y$ and is able to efficiently calculate the top $k$ peaks on very large molecules. Among its peers, this algorithm shows a significant speedup on molecules whose elements have many isotopes. The algorithm obtains a speedup of more than 31x when compared to IsoSpec on Au$_2$Ca$_{10}$Ga$_{10}$Pd$_{76}$ when computing 47409787 peaks, which covers 0.999 of the total abundance.

1 Introduction
Calculating the theoretical isotopic distribution of compounds is a valuable tool in mass spectrometry (MS), but is also a difficult combinatorics problem
to solve without doing some sort of statistical approximation. Theoretical isotopic distribution may be used in targeted screening\cite{9, 12}, identifying unknown metabolites\cite{4}, and is useful in general MS workflow \cite{13} among others.

There have been multiple methods developed in the past decade focused on more efficient methods of calculating the isotope distribution \cite{3, 8, 7, 14, 10}. Some, such as IsoSpec, take a combinatorial approach to the problem and are able to solve for the exact mass and abundance, others such as Sadygov’s method uses a more statistical approach by using an approximation of binomial and multinomial distributions. Despite the results being the same, many of these methods take different input parameters. IsoSpec, among others, asks the user to provide some minimum threshold $p$ so that the returned list of peaks has a total abundance of at least $p$, other methods simply generate all peaks above a certain abundance threshold. In 2019, Wang et al. compared four of the top algorithms: IsoSpec, enviPat, ecipeX and their own isoVector. They found IsoSpec to consistently be the fastest of the four.

IsoSpec works by first calculating the most abundant subisotopologues (all instances of the same element in a compound, for example $H_2$ and $O$ are two subisotopologues of water) and then combining the subisotopologues to form whole isotopologues. The isotopologues are then put into a FIFO queue and when one is popped, if it exceeds some threshold, it will be appended to the output and its neighbors (isotopologues who differ by one incrementing one isotope of an element and decrementing another isotope of the same element by one) are inserted into the queue, else the isotopologue will be considered for the next layer. Each threshold for the FIFO queue creates a new layer of isotopologues, the cumulative output of all layers is $\in O(\cdot)$ of the optimal output; however, in practice IsoSpec may produce significantly more isotopologues than are necessary and so the output must be pruned before being reported.

Once two subisotopologues have been calculated, selecting the top $k$ isotopologues of the resulting compound created by merging the two subisotopologues is the same as selecting the top $k$ terms in a Cartesian product of two lists. Since the Cartesian product uses addition, but the abundances should be multiplied, the log of the abundances are used in the $X + Y$ selection. There are multiple methods for selecting the top $k$ terms in the Cartesian product on $X + Y$ in optimal time\cite{5, 11}. Serang’s optimal method utilizes layer-ordered heaps (LOH), a data structure which is contiguous in memory and partitioned into layers. The size of each layer grows exponentially according to some growth rate $\alpha$ and each value in layer $i$ is less than or equal to each value in layer $i + 1$. The advantage of a LOH is that an array may be LOHified in $O(n \log(n))$ time where sorting the array is $\in \Omega(n \log(n))$.

In this paper, we present a method of efficiently calculating the top $k$ isotopologues of a compound using LOHs. The method does not approximate, bin or round any numbers. In fact, perfect numbers could be used if machine precision allowed. This is achieved by building a balanced binary tree out of two separate types of nodes. The leaf nodes calculate the most abundant subisotopologues by performing selection on a multinomial, and outputing the results in a layer-ordered format. Other nodes solve pairwise selection problems, us-
ing a modified version of Serang’s method, which are the outputs of either the subisotopologues or pairs of already merged subisotopologues. The outputs of the root of the tree are the most abundant isotopologues of the given compound. The output will not be sorted but will instead be in layer-ordered. This method has been packaged as a freely available C++ software package entitled NeutronStar.

\section{Methods}

Here, we present several methods which, given an input of \( k \) and a chemical formula, may be combined to calculate the top \( k \) most abundant isotopologues of the given chemical.

\subsection{Selection on a multinomial}

Calculating the subisotopologues of a compound is equivalent to calculating a polynomial \((b_1 \cdot X_1^{b_1} + b_2 \cdot X_2^{b_2} + \cdots)^{\chi}\) where \( b \) is the log-abundance and \( \chi \) the mass of an isotope. For an element with four Carbon, the corresponding polynomial is \( (^{12}\text{C} \cdot X^{12.0} + ^{13}\text{C} \cdot X^{13.003})^{4} \). Then, combining two subisotopologues is the equivalent of multiplying two polynomials \( \text{(e.g., } \text{H}_4\text{C}_4 \text{ is } (^{12}\text{C} \cdot X^{12.0} + ^{13}\text{C} \cdot X^{13.003})^{4} \cdot (^{1}\text{H} \cdot X^{1.008} + ^{2}\text{H})^{3} \).

When calculating a polynomial such as \((c_1 \cdot X + c_2 \cdot Y)^2\) there will be terms which can be merged together: \((c_1 \cdot X + c_2 \cdot Y)^2 = (c_1^2 \cdot X^2 + c_1 c_2 \cdot X \cdot Y + c_2 c_1 \cdot Y \cdot X + c_2^2 \cdot Y^2) = (c_1^2 \cdot X^2 + 2c_1 c_2 \cdot X \cdot Y + c_2^2 \cdot Y^2)\). For larger polynomials (both in the power and number of terms) there will be many terms which may combine with each other. A significant speed-up is to be found if only one of these terms is calculated then multiplied by the appropriate multinomial coefficient (2 in the previous example). This is the basis of our method for efficiently selecting the most abundant subisotopologues.

In order to generate the top \( k \) isotopologues of a compound, we first start by computing the top subisotopologues in decreasing order of probability. A binary heap is utilized to retrieve the subisotopologues in order; however, it is not populated with all possible subisotopologues. Instead, when a subisotopologue is popped from the heap, a new set of subisotopologues are put into the heap based on the popped subisotopologues index tuple (a tuple which describes how many of each isotope is in the subisotopologue).

First, we must find the most probable subisotopologue which amounts to finding the mode of the multinomial, let \((x_1, x_2, \ldots, x_m)\) be a such a mode. Thus, \( P(x_1, x_2, \ldots, x_m) \geq P(\ldots, x_i + 1, x_j - 1, \ldots) \) for any indicies \( x_i \) and \( x_j \). Since \((x_1, x_2, \ldots, x_m)\) is the mode and \( P(\ldots, x_i + 1, x_j - 1, \ldots) = P(x_1, x_2, \ldots, x_m) \cdot \frac{p_i(x_i-1)}{p_j(x_j+2)} \), it must be that \( \frac{p_i(x_i-1)}{p_j(x_j+2)} \leq 1 \) for any indicies \( x_i \) and \( x_j \).

Furthermore, because \( P(\ldots, x_i + (b+1), x_j - (b+1), \ldots) = P(\ldots, x_i + b, x_j - b, \ldots) \cdot \frac{p_i(x_i-b)}{p_k(x_i+(b+1))} \) and \( \frac{p_i(x_i-b)}{p_k(x_i+(b+1))} \leq \frac{p_i(x_i-(b-1))}{p_k(x_i+b)} \leq \cdots \leq \frac{p_i(x_i-1)}{p_k(x_i+2)} \leq 1 \), we can see that \( P(\ldots, x_i + b, x_j - b, \ldots) \leq P(\ldots, x_i + (b+1), x_j - (b + 1), \ldots) \) for
any \( b \leq \min(x_i, x_j) \). This means every time the \( i^{th} \) entry in the index tuple is increased and the \( j^{th} \) entry is decreased (thus moving further from the mode in \( L_1 \) distance), the probability either decreases or stays the same.

The relationship between \( L_1 \) distance from the mode and the probability still holds when other index tuple entries have been perturbed away from the mode. \( P(\ldots, x_i + 1, x_j - 1, \ldots) \geq P(\ldots, x_i + 2, x_j - 1, x_k - 1, \ldots) \) because \( P(\ldots, x_i + 2, x_j - 1, x_k - 1, \ldots) = P(\ldots, x_i + 1, x_j - 1, x_k - 1, x_\ell - 1, \ldots) \cdot \frac{p_i(x_i + 1)}{p_i(x_i + 2)} \) and \( \frac{p_i(x_i + 1)}{p_i(x_i + 2)} \leq \frac{p_i(x_i)}{p_i(x_i + 1)} \leq 1 \).

Finally, we also have \( P(\ldots, x_i + 1, x_j - 1, \ldots) \geq P(\ldots, x_i + 1, x_j - 1, x_k + 1, x_\ell - 1, \ldots) \) because \( P(\ldots, x_i + 1, x_j - 1, x_k + 1, x_\ell - 1, \ldots) = P(\ldots, x_i + 1, x_j - 1, x_k + 1, x_\ell - 1, \ldots) \cdot \frac{p_k(x_k)}{p_k(x_k + 1)} \) and \( \frac{p_k(x_k)}{p_k(x_k + 1)} \leq \frac{p_k(x_k - 1)}{p_k(x_k + 1)} \leq 1 \).

Since the probability never decreases as we move closer to the mode, the mode can be found by moving in the direction of ascending probability until a maximal position is reached. A strong position to start can be found by finding the mode of the binomials which make-up the multinomial. Note that this starting point may not be a valid position if the entries in the index tuple do not sum to the total size of the subisotopologue.

In order to populate the heap with the best possible next subisotopologue, any subisotopologue in the heap must have all subisotopologues between itself and the mode already in the heap (or have been popped from the heap). This can be accomplished by pushing all neighbors of the subisotopologue which has been popped from the heap; however, there needs to be a system to make sure the same subisotopologue is not proposed by multiple neighbors. This can be done using a set, but a set requires memory and time spent checking to see if an element is in the set. Instead, one only needs a proposal scheme which can propose all subisotopologues in correct order without any duplicates.

One such proposal method can be done by keeping track of the index of the largest (in lexicographical order) entry in the index tuple which has been incremented and the largest which has been decremented away from the mode, let them be denoted \( i' \) and \( j' \), respectively. W.l.o.g., let \( i' < j' \), then \( x_i \) is the same as the mode for all \( i > i', i \neq j \). When an index tuple \( I = (x_1 + a_1, x_2 + a_2, \ldots x_i + a_i', \ldots, x_j + a_j', x_{j+1}, \ldots) \) (where \( a_i' > 0 \) and \( a_j' < 0 \)) is popped from the heap, it proposes neighbors by taking all pairs of \( (i \geq i', j \geq j') \) and creating, then pushing into the heap, new index tuples where the \( i^{th} \) entry is incremented by one and the \( j^{th} \) entry is decremented by one.

This proposal scheme means any index tuple may be proposed by only one unique neighboring index tuple. For any index tuple \( I \), the index tuple which proposed it, \( I' \) can be found by taking \( i' \) and \( j' \) of \( I \) and decrementing the entry at the \( i'^{th} \) index by one and incrementing the \( j'^{th} \) entry by one. It can not be that \( I' \) incremented an index \( i < i' \) to become \( I \). If there was some entry at index \( i < i' \) incremented in \( I' \) to become \( I \), then the \( i'^{th} \) entry in \( I' \) would have been incremented previously; however, incrementing \( x_i \) and then \( x_i \) breaks the lexicographic ordering so this is not allowed. The same logic holds for why only the entry \( x_{j'} \) in \( I' \) can be decremented when proposing \( I \). Since each index tuple has only one unique index tuple which can propose it, no index tuple may
be proposed multiple times since the one who proposes it can only be popped from the heap once.

For any valid index tuple \( I \), the index tuple which proposed it can be found by the method above. This is always done by decrementing an entry whose index which is greater than the corresponding entry in the mode and incrementing an entry which is less than the corresponding entry in the mode, every time the previous index tuple is found we move closer to the mode. This can only be done a finite amount of times before the mode is reached. Therefore, from any valid index tuple there is a unique path from the mode to the tuple using this proposal scheme and so any valid index tuple is able to be proposed.

Once the top subisotopologues are generated, we want to perform selection on the possible resulting isotopologues without first calculating all isotopologues. We do so by implementing a modified version of Serang’s selection on \( X + Y \).

### 2.2 Selection on two subisotopologues

Serang’s method is modified in two major ways, the first is that the pairwise selection is done on a list of mass and log-abundance pairs. This list of pairs is not static. The second difference is that this selection must be online so that we may always ask for the next layer of isotopologues which have not been previously selected.

Serang’s method works by putting layer products (a Cartesian product of two layers of a LOH) into a heap either according to the minimum value in the layer product, or, if the minimum value has been popped already, according to the maximum. Once the minimum value is popped all values in the layer product are calculated and inserted into a list of candidate values for a final one-dimensional \( k \)-select. Layer products are done popping when the total amount of candidate values from layer products whose maximum has been popped is at least \( k \).

In the online version, the layer products are done popping when the total amount of candidate values from layer products whose maximum has been popped is at least the amount of the cumulative selections \( k_1 + k_2 + \cdots = k \).

The heap and the list of candidate values are not modified between the multiple selections (except that the smallest first \( k_i \) values are removed from the list of candidate values). Therefore, the layer products popped until the total amount of candidate values from layer products whose maximum has been popped is at least \( k \) is the same regardless of whether it is one \( k \)-select or a \( k_1 \)- and a \( k_2 \)-select.

In Serang’s manuscript, in the proof of lemma 7 the author mentions the possible size of the layer products added in phase 2 and says that the layer products added in phase 2 for which either \( u' = 1 \) or \( v' = 1 \) is at most \( 2n \in O(n) \). In fact, the size of the layer is limited by the fact that the previous layer along that axis must have had its maximum value popped from the heap before the layer appended in phase 2 could have its minimum popped. Because of this, the added layer’s size is at most \( \alpha \cdot s \in O(k) \) and so the lemma could improve the statement by replacing \( O(n + k) \) with \( O(k) \).

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Figure 1: Illustration of the balanced binary tree for Palladium alloy Pgc, Au$_2$Ca$_{10}$Ga$_{10}$Pd$_{76}$. The leaves are subisotopologue generators, one for each element. All nodes above the leaves combine their child compounds using the modified pair-wise selection from Serang’s method. The root generates isotopologues of the human BRCA2 protein, and every other node generates isotopologues for some smaller constituent compound.

2.3 Selection on a compound

The method described above is able to efficiently get the top $k$ many combinations of two subisotopologues; however, for compounds of more than two elements this method alone is unable to calculate any isotopologues. In order to combine all subisotopologues, a balanced binary tree of two different kinds of nodes is formed. The leaves of the tree are all subisotopologue generators and all other nodes, including the root, perform selection on $X + Y$ (Figure 1).

At each layer of the tree above the leaves, pairs of smaller compounds are merged and their top values are returned to the parent. To retrieve the top $k$ isotopologues of the whole compound, the root is asked to generate the top $k$ isotopologues from the combination of its children. The root will initially have two empty lists, so it must ask its children to produce values. Since we are using a method in which the input lists are LOHified, a parent node will ask each child to generate their next whole layer of values. Since every value in a layer is at least as good as every value in the next layer, a child only needs to generate the next layer when the output of the parent has used all of the child’s previously generated values.

Initially, every node in the tree will require both children to generate values; however, the size of the first layer is always one so this is not a lot of work. After the initial layer of each child is generated, when the parent needs to generate more layers it only asks one child at a time for more values. This is done by comparing the maximum value in the last generated layers of each child and only extending the child who has the smaller maximum value. As $k$ increases, when the root asks its children to generate more layers, this request is unlikely to ripple down to the leaves because some interior nodes will have previously generated layers in which not all the values have been used.
2.4 Time analysis

If the leaves are removed from the tree, then the tree has the same time complexity as FastSoftTree seen in [6]. The difference in the algorithms is that this algorithm uses LOHs where FastSoftTree uses soft-heaps [2]. LOHs and soft-heaps have the same theoretical runtime for selection, but in practice LOHs are significantly faster due to the data being contiguous in memory. Therefore, the runtime of the tree formed from $X + Y$ nodes is $\in O(m \cdot n + k \cdot m^2 \log_2(\alpha))$ where $n$ is the number of subisotopologues generated and $m$ is the number of elements in the compound. When generating subisotopologues, the leaf nodes form tensors which have the same dimensionality as the number of isotopes of the element. Thus, the subgenerators themselves have the same time complexity as the SortTensor method used in Kreitzberg et al., and therefore has time complexity $\in O(n_e \cdot m_e + k_e \cdot m_e^2 + k_e \log(k_e \cdot n_e))$, $n_e$ is the number of element $e$ in the compound, $m_e$ is the number of isotopes of $e$, and $k_e$ is the number of subisotopologues generated. For small $k$ the algorithm is leaf heavy, for large enough $k$, most of the work done will be in the interior nodes and so the tree becomes dominated by the $X + Y$ selections.

3 Results

Here, we compare our algorithm, which we call NEUTRONSTAR, versus ISOSPEC. The C++ interface for ISOSPEC was used with flags set so that only the masses and log-probabilities are generated, specifically an instance of TotalProbFixedEnvelope was created with flags (true, false, true, true, false). Both ISOSPEC and NEUTRONSTAR were compiled with g++ -O3 -march=native -mtune=native -std=c++17. The executables ran on a computer with dual AMD Epycs 7351 with 256GiB of RAM.

ISOSPEC generates a superset of the needed isotopologues and then performs one-dimensional selection to retrieve the most abundant. The isotopologues ISOSPEC generates are chosen as a function of $p$, the cumulative abundance threshold. To ensure a fair comparison, we first run ISOSPEC using a $p$, then use the number of $k$ peaks it returns as the rank threshold for NEUTRONSTAR. A runtime comparison between ISOSPEC and NEUTRONSTAR is performed in Figure 2.
Figure 2: Runtimes of IsoSpec and NeutronStar as $p$ (and, correspondingly, $k$ vary). Each run was averaged over 10 iterations. Due to IsoSpec gathering isotopologues in batches and subsequently trimming excess, its runtimes may vary sharply as $p$ is changed. 50 different $p$ values, evenly spaced from 0.01 to 0.95, were used.
3.1 Time

| Molecule          | p   | k    | IsoSpec(s) | NeutronStar(s) |
|-------------------|-----|------|------------|----------------|
| BRCA2             | 0.1 | 155717 | 0.069926   | 0.0168335      |
|                   | 0.2 | 436377 | 0.0790409  | 0.0310062      |
|                   | 0.3 | 868708 | 0.0809641  | 0.053721       |
|                   | 0.4 | 1514835| 0.0945277  | 0.0862887      |
|                   | 0.5 | 2484628| 0.0975662  | 0.135625       |
|                   | 0.6 | 3984714| 0.795611   | 0.212852       |
|                   | 0.7 | 6465410| 0.800833   | 0.344733       |
|                   | 0.8 | 11135622| 1.05385   | 0.577102       |
|                   | 0.9 | 22935591| 5.21918   | 5.38021        |
|                   | 0.99| 310931441| 10.9851  | 14.2249        |
| Palladium         | 0.1 | 9134  | 0.254897   | 0.0039866      |
| Pgc               | 0.2 | 25806 | 0.254513   | 0.0050412      |
|                   | 0.3 | 52855 | 0.254586   | 0.0128452      |
|                   | 0.4 | 95387 | 0.255309   | 0.0185391      |
|                   | 0.5 | 162857 | 1.47417   | 0.0280916      |
|                   | 0.6 | 274344 | 1.47892   | 0.0432593      |
|                   | 0.7 | 473917 | 1.47872   | 0.0720034      |
|                   | 0.8 | 890269 | 1.48936   | 0.114372       |
|                   | 0.9 | 2074266| 4.26516   | 0.212619       |
|                   | 0.99| 13466926| 8.91341 | 0.918616       |
|                   | 0.999| 47409787| 16.1441  | 2.55547        |
| Xe50              | 0.1 | 2510  | 0.800637   | 0.0041821      |
|                   | 0.2 | 6711  | 0.798412   | 0.0079587      |
|                   | 0.3 | 12909 | 0.801227   | 0.0113697      |
|                   | 0.4 | 21919 | 0.798453   | 0.0175081      |
|                   | 0.5 | 35243 | 0.800154   | 0.0284915      |
|                   | 0.6 | 55890 | 0.797688   | 0.0395307      |
|                   | 0.7 | 91046 | 8.39407    | 0.0672331      |
|                   | 0.8 | 159438 | 8.38149  | 0.115158       |
|                   | 0.9 | 332449 | 8.38418  | 0.242873       |
|                   | 0.99| 1564230| 35.8607  | 1.15485        |
| Sn20Xe20Nd20Dy20  | 1e-12| 1    | 0.000365   | 0.000158       |
|                   | 1e-11| 50   | segfaulted | 0.0002998      |
|                   | 1.99685e-10| 100 | ——          | 0.0003539      |
|                   | 5.28451e-05| 100000000| ——       | 7.4452         |

Table 1: Runtimes of IsoSpec and NeutronStar for three molecules, all with $\alpha = 1.05$. The first molecule is BRCA2 C16802H26738N4640O5411S121, an organic molecule associated with a significant risk of breast cancer. The second molecule is palladium alloy Pgc, a dental amalgam with chemical formula Au2Ca10Ga10Pd76 and CID 6337993. The third compound is simply Xe50 to illustrate that the NeutronStar algorithm scales better than IsoSpec as the dimensionality of the subisotopologue increases. When IsoSpec segfaulted, larger $p$ were not run.
### 3.2 Space

| Molecule       | p    | k        | IsoSpec        | NeutronStar   |
|----------------|------|----------|----------------|---------------|
| BRCA2          | 0.1  | 155717   | 96.1 MiB       | 6.0 MiB       |
|                | 0.3  | 868708   | 96.1 MiB       | 30.8 MiB      |
|                | 0.5  | 2484628  | 96.1 MiB       | 88.6 MiB      |
|                | 0.7  | 6465410  | 768.1 MiB      | 232.1 MiB     |
|                | 0.9  | 22935591 | 768.1 MiB      | 771.0 MiB     |
| Palladium alloy Pgc | 0.1  | 9134     | 9.7 MiB        | 0.9751 MiB    |
|                | 0.3  | 52855    | 9.7 MiB        | 4.4 MiB       |
|                | 0.5  | 162857   | 63.5 MiB       | 12.3 MiB      |
|                | 0.7  | 473917   | 63.5 MiB       | 33.5 MiB      |
|                | 0.9  | 2074266  | 419.7 MiB      | 115.0 MiB     |
|                | 0.99 | 13466926 | 831.8 MiB      | 596.2 MiB     |
|                | 0.999| 47409787 | 3.1 GiB        | 1.8 GiB       |
| Xe50           | 0.1  | 2510     | 30.7 MiB       | 1.4 MiB       |
|                | 0.3  | 12909    | 30.7 MiB       | 5.4 MiB       |
|                | 0.5  | 35243    | 30.7 MiB       | 21.6 MiB      |
|                | 0.7  | 91046    | 166.0 MiB      | 43.3 MiB      |
|                | 0.9  | 332449   | 166.0 MiB      | 86.9 MiB      |
|                | 0.99 | 1564230  | 480.0 MiB      | 352.3 MiB     |

Table 2: Memory usage of IsoSpec and NeutronStar (with $\alpha = 1.05$) on three molecules. Memory usage for the three compounds from Table 1.

### 3.3 Generated spectra

Figure 3 depicts the most abundant 10,000 peaks of BRCA2, $C_{16802}H_{26738}N_{4640}O_{5411}S_{121}$; at a high resolution, these peaks are subtly staggered from one another. This would be seen by a high mass accuracy spectrometer.
Figure 3: Theoretical spectra of the top 10,000 peaks of BRCA2, C_{16802}H_{26738}N_{4640}O_{5411}S_{121}. The top 10,000 isotopologue peaks were generated by NeutronStar using $\alpha = 1.05$. NeutronStar took 0.004748 seconds to generate the peaks and they cover a cumulative abundance of 0.0109297.
### 3.4 Influence of $\alpha$ on runtime

| Molecule                  | k     | $\alpha$ | Time(s) |
|---------------------------|-------|----------|---------|
| C_{16802}H_{26738}N_{4640}O_{5411}S_{121} | 1000000 | 1.00     | 0.516298 |
|                           | 1000000 | 1.05     | 0.0580954 |
|                           | 1000000 | 1.10     | 0.0606883 |
|                           | 1000000 | 1.15     | 0.067031 |
|                           | 1000000 | 1.20     | 0.0635678 |
|                           | 1000000 | 1.25     | 0.0697309 |
|                           | 1000000 | 1.30     | 0.0871132 |
|                           | 1000000 | 1.35     | 0.0747897 |
|                           | 1000000 | 1.40     | 0.0884976 |
|                           | 1000000 | 1.45     | 0.111566 |
|                           | 1000000 | 1.50     | 0.103195 |
|                           | 1000000 | 1.55     | 0.118836 |
|                           | 1000000 | 1.60     | 0.105935 |
|                           | 1000000 | 1.65     | 0.101384 |
|                           | 1000000 | 1.70     | 0.136349 |
|                           | 1000000 | 1.75     | 0.155706 |
|                           | 1000000 | 1.80     | 0.148027 |
|                           | 1000000 | 1.85     | 0.154379 |
|                           | 1000000 | 1.90     | 0.170928 |
|                           | 1000000 | 1.95     | 0.16922 |
|                           | 1000000 | 2.00     | 0.128749 |

Table 3: **Relationship between $\alpha$ and the runtime** for $\alpha \in [1, 2]$. The time reported is the average over 10 iterations and all times reported are only from NeutronStar. If $\alpha = 1$ then sizes of the layers do not increase and so a layer-ordering with $\alpha = 1$ is the same as sorting. The runtime is at its worst when the $\alpha = 1$ and best when $\alpha = 1.05$.

## 4 Discussion

As seen in Table 1, for organic molecules of moderate size (and therefore similar molecules whose elements have a smaller amount of isotopes), NeutronStar is roughly equivalent to IsoSpec, the faster algorithm is largely determined by the $p$ parameter. On the toy molecule Sn$_{20}$Xe$_{20}$Nd$_{20}$Dy$_{20}$, IsoSpec was unable to run on $p = 1e-11$ because it caused a segfault (on a machine with 256GB of RAM) whereas NeutronStar was able to perform the selection in 0.0002998 seconds. The ability of NeutronStar to handle subisotopologues with a large amount of isotopes will become increasingly more important for large molecules because, given enough copies of one element, even trace isotopes may appear. For NeutronStar, the choice of $\alpha$ can also significantly impact the runtime as seen in Table 3.

The significant advantage NeutronStar has for large molecules is possibly due to the method IsoSpec uses to propose the neighbors of the popped isotopologues. Since it proposes a neighbor for every subisotopologue, the space of
the index tuples proposed will form a tensor with dimension equal to the number of subisotopologues. In NeutronStar the space of isotopologues proposed can only form a matrix; however, there will be multiple matrices but the overall the memory usage for NeutronStar should be lower than IsoSpec. Also, IsoSpec requires a set of index tuples in order to avoid proposing duplicate tuples. For large problems this can cause significant overhead. The set is avoided in NeutronStar due to the proposal scheme.

When comparing the peaks of NeutronStar and IsoSpec, they tend to agree to 15 significant figures (often reporting perfect matches) in their mass and 10 significant figures in their relative log-abundance, even for peaks whose masses match perfectly. The difference on the level of agreement between the two quantities may be a result of the use of the Stirling approximation by IsoSpec, but the overall disagreement is likely due to IsoSpec calculating the values for each isotopologue independently instead of carrying the values along with the subisotopologues as done in NeutronStar.

Currently, NeutronStar is not configured to report the isotopic make-up of the resulting isotopologues. This could be modified by keeping track of the index tuple as an isotopologue is created while climbing up the binary tree; however this would result in a considerable performance reduction and remove one of the more novel aspects of this algorithm. Furthermore, since each $X + Y$ selection node in the binary tree can do online selection, the interface in NeutronStar can be adjusted to allow the user to do multiple selections without having to recompute any previously reported isotopologues. It is also easy to modify the C++ code to accept the same parameter $p$ as IsoSpec does. The authors believe $k$ is the desired parameter because the amount of peaks generated given $p$ is hard to estimate which, on one extreme, can lead to segfaults and on the other to repeatedly retrieving a very small set of peaks.

The algorithm can easily be adapted to doing selection on $X_1 + X_2 + \cdots + X_m$ by removing the subisotopologue generators and replacing them with LOH generators which take a list of values as a parameter. An efficient selection on $X_1 + X_2 + \cdots + X_m$ may be useful for solving a certain families of ILPs or set-cover problems and their applications (e.g., protein inference).

In the future, it may be possible to use LOHs inside the subisotopologue generators similar to the $X + Y$ selection nodes. This could be a considerable speed-up because it avoids the $\Omega(n \log(n))$ bounds created by sorting the subisotopologues. The downside is that not every index tuple in a layer product will be valid. Since the subisotopologue generators perform a different task than the $X + Y$ nodes, it may be beneficial for each node type to have different $\alpha$ values.

5 Acknowledgements

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6 Supplemental information

The NeutronStar algorithm, implemented in C++, can be found freely at https://bitbucket.org/orserang/neutronstar/

References

[1] Expasy bioinformatics resource portal. https://web.expasy.org/cgi-bin/protparam/protparam1?P51587@noft@

[2] B. Chazelle. The soft heap: an approximate priority queue with optimal error rate. *Journal of the ACM (JACM)*, 47(6):1012–1027, 2000.

[3] A. Ipsen. Efficient calculation of exact fine structure isotope patterns via the multidimensional fourier transform. *Analytical chemistry*, 86(11):5316–5322, 2014.

[4] H. Ji, Y. Xu, H. Lu, and Z. Zhang. Deep ms/ms-aided structural-similarity scoring for unknown metabolite identification. *Analytical chemistry*, 91(9):5629–5637, 2019.

[5] H. Kaplan, L. Kozma, O. Zamir, and U. Zwick. Selection from heaps, row-sorted matrices and \( X + Y \) using soft heaps. Symposium on Simplicity in Algorithms, pages 5:1–5:21, 2019.

[6] P. Kreitzberg, K. Lucke, and O. Serang. Selection on \( X_1 + X_2 + \cdots + X_m \) with layer-ordered heaps. *arXiv preprint arXiv:1910.11993* 2019. Not yet submitted.

[7] M. K. Łącki, M. Startek, D. Valkenborg, and A. Gambin. Isospec: Hyperfast fine structure calculator. *Analytical Chemistry*, 89(6):3272–3277, 2017.

[8] M. Loos, C. Gerber, F. Corona, J. Hollender, and H. Singer. Accelerated isotope fine structure calculation using pruned transition trees. *Analytical chemistry*, 87(11):5738–5744, 2015.

[9] M. Ruff, M. Mueller, M. Loos, and H.P. Singer. Quantitative target and systematic non-target analysis of polar organic micro-pollutants along the river rhine using high-resolution mass-spectrometry–identification of unknown sources and compounds. *Water research*, 87:145–154, 2015.

[10] R. G. Sadygov. Poisson model to generate isotope distribution for biomolecules. *Journal of proteome research*, 17(1):751–758, 2018.

[11] O Serang. Optimal selection on \( X + Y \) simplified with layer-ordered heaps. *arXiv preprint arXiv:2001.11607* 2020.
[12] H. P. Singer, A. E. Wössner, C. S. McArdell, and K. Fenner. Rapid screening for exposure to non-target pharmaceuticals from wastewater effluents by combining hrms-based suspect screening and exposure modeling. *Environmental science & technology*, 50(13):6698–6707, 2016.

[13] M. Sturm, A. Bertsch, C. Gröpl, A. Hildebrandt, R. Hussong, E. Lange, N. Pfeifer, O. Schulz-Trieglaff, A. Zerck, K. Reinert, et al. Openms—an open-source software framework for mass spectrometry. *BMC bioinformatics*, 9(1):163, 2008.

[14] Z. Wang, X. Chen, J. Ren, and G. Hu. Efficient simulation of isotope aggregated and fine structure by vector manipulation and change-making strategy. *International Journal of Mass Spectrometry*, 443:70–76, 2019.