Computational Modelling of the Interruptional Activities between Transposable Elements

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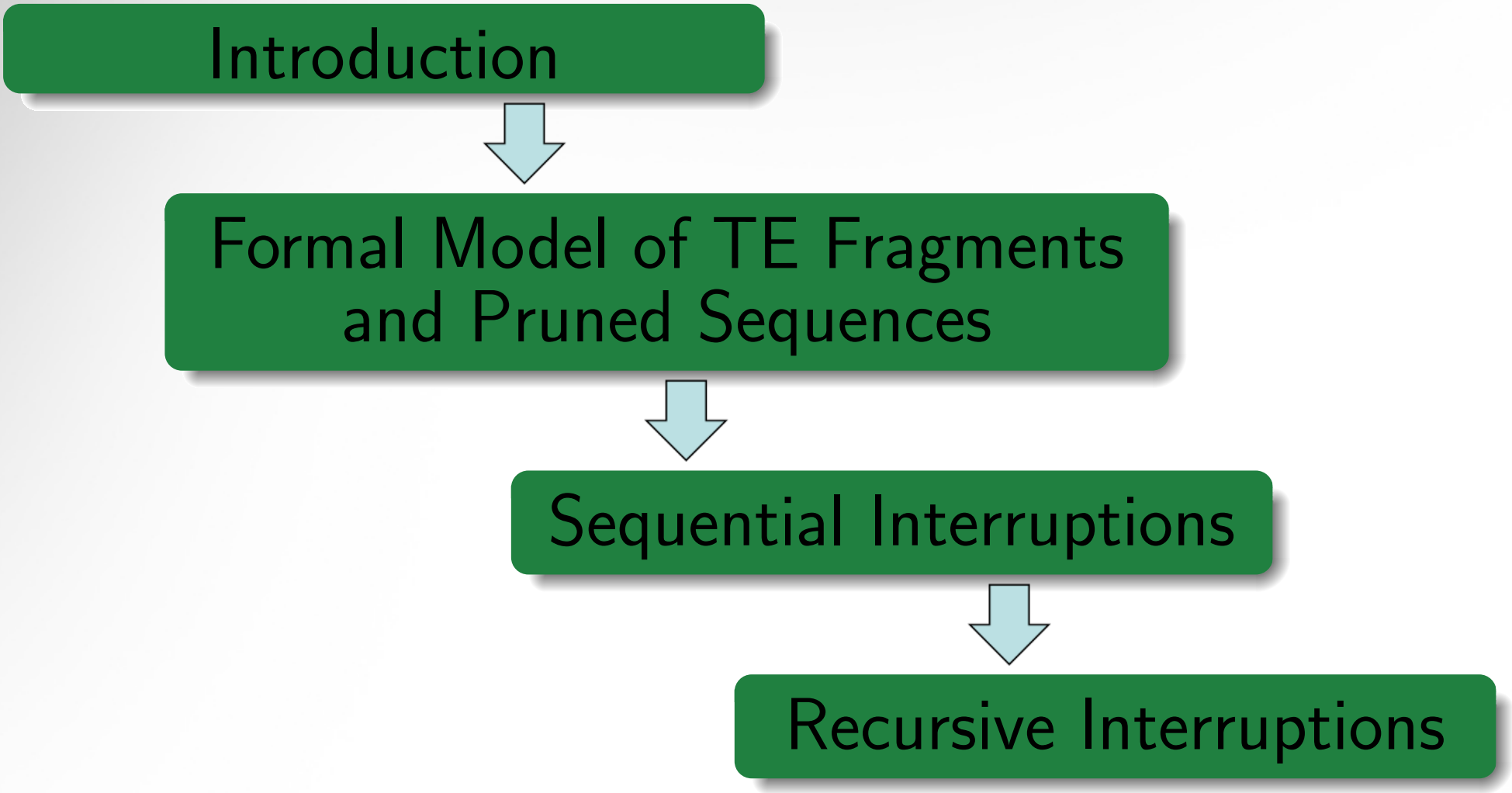
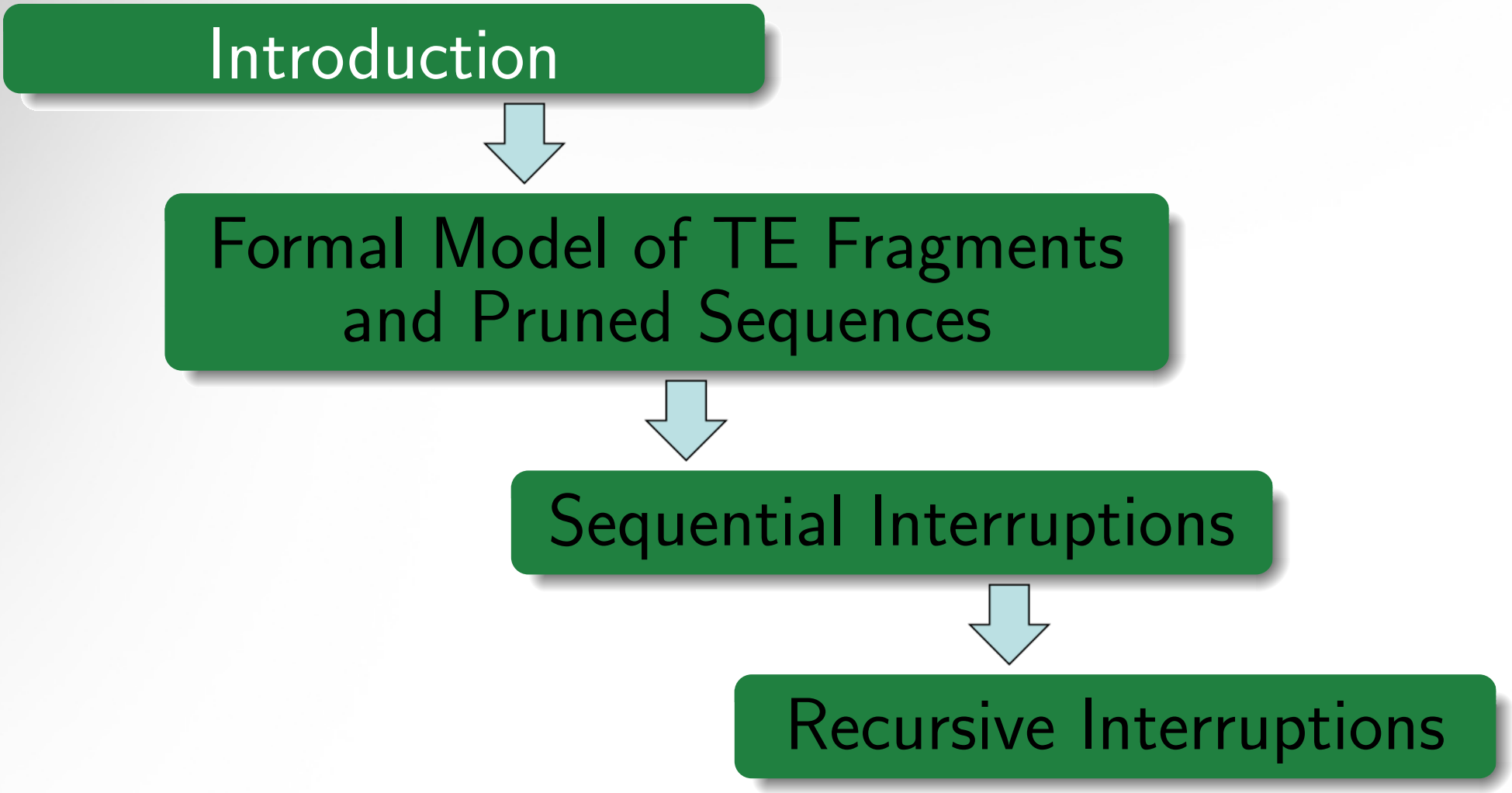
Outline


Introduction
Formal Model of TE Fragments and Pruned Sequences
Sequential Interruptions
Recursive Interruptions

Part I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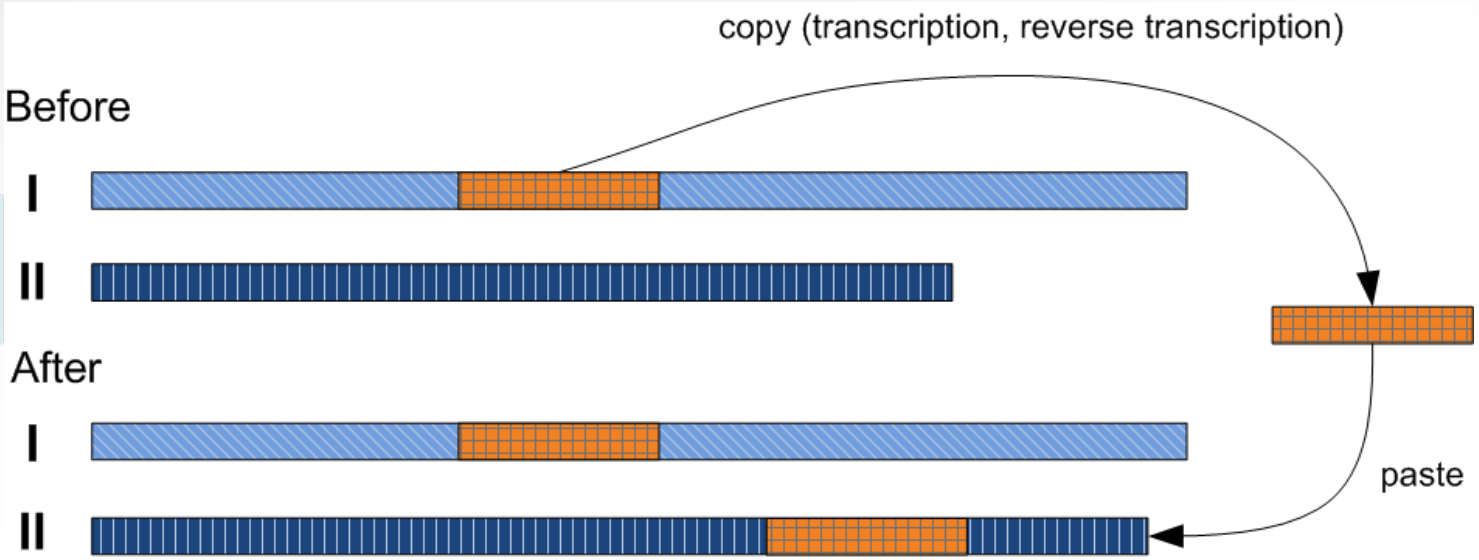
Transposable Elements (TEs)

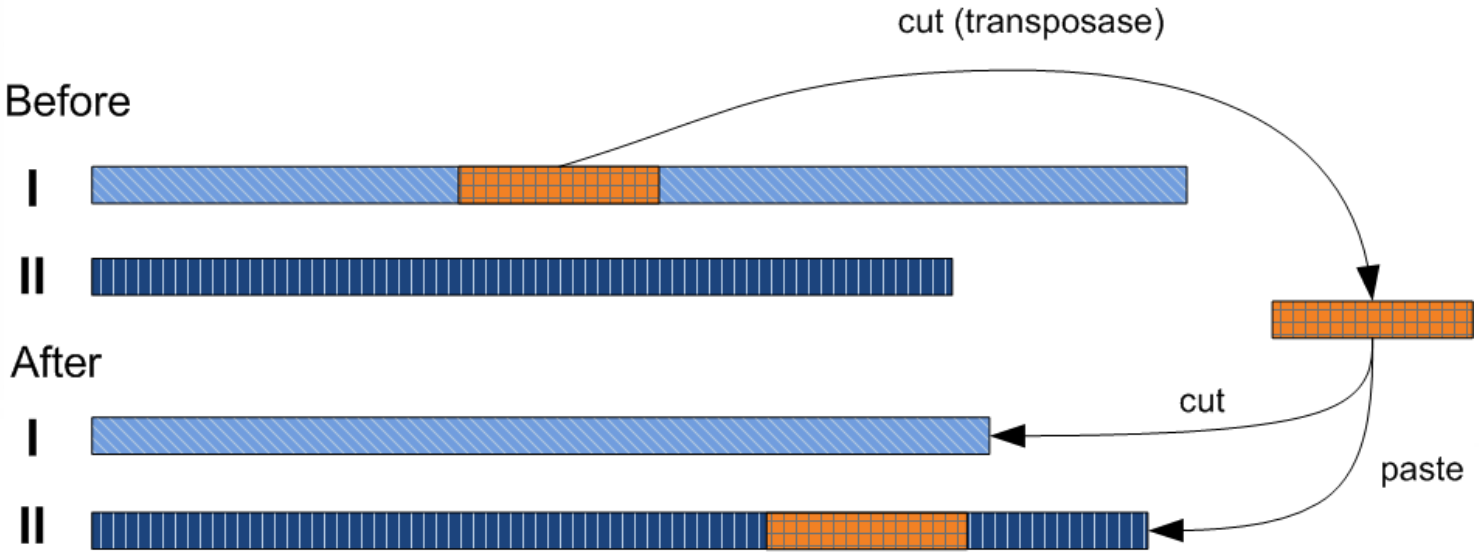
- Transposable Elements (TEs) account for **45%** of the Human Genome.
- TEs are interspersed DNA sequences that can **move or transpose** themselves to new positions within the genome.
- TEs have been reported to **cause** human diseases, including several types of cancer.

Classifications

Class I
Retrotransposons



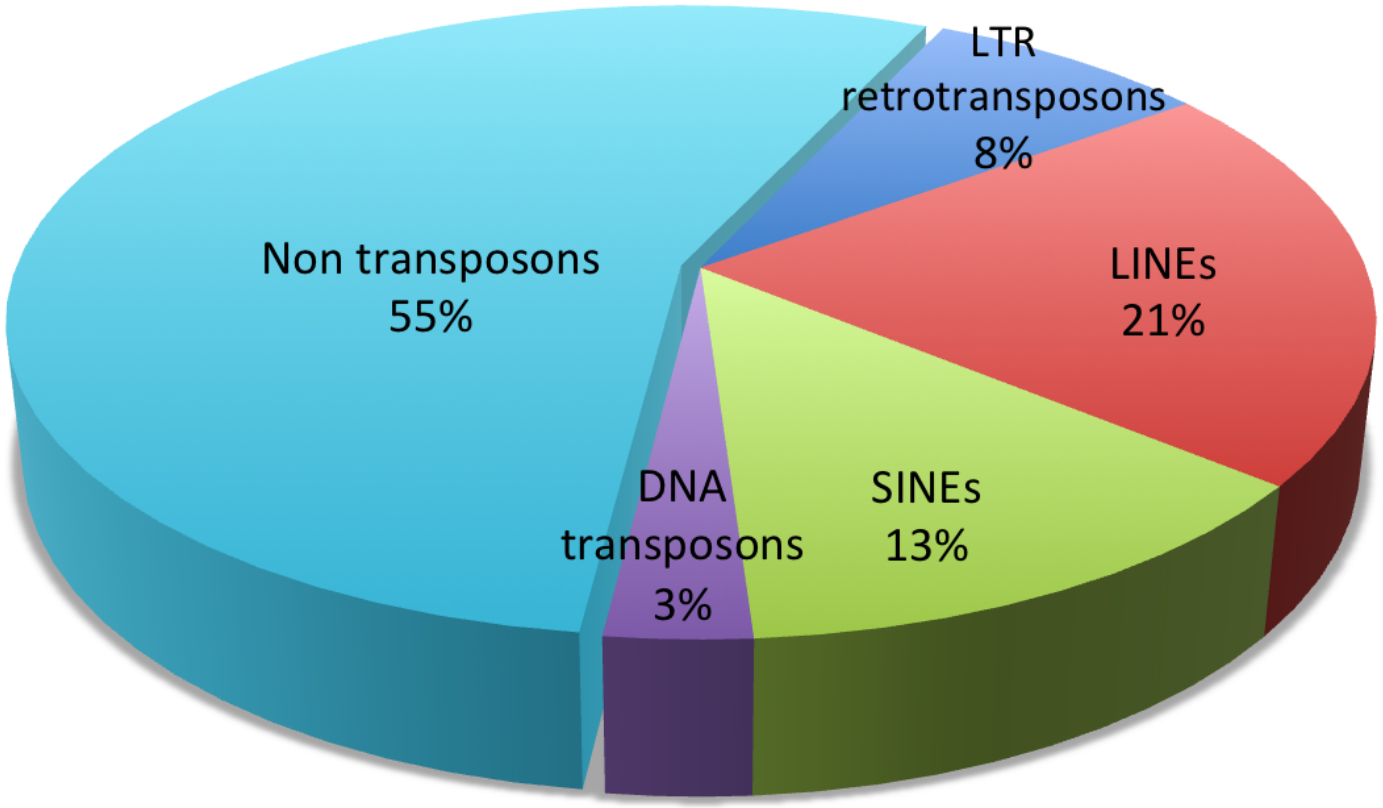
Class II
DNA transposons



Types of TEs based on Structural Features

TE type	TE Class	Mode of Transportation	Length	Copy Number
LINEs	Class I: Retrotransposons	Autonomous	6-8 kb	850,000
SINEs	Class I: Retrotransposons	Non-autonomous	100-300 bp	1,500,000
LTR retrotransposons	Class I: Retrotransposons	Autonomous	6-11 kb	450,000
		Non-autonomous	1.5-3 kb	
DNA transposons	Class II: DNA transposons	Autonomous	2-3 kb	300,000
		Non-autonomous	80-3,000 bp	

The Human Genome



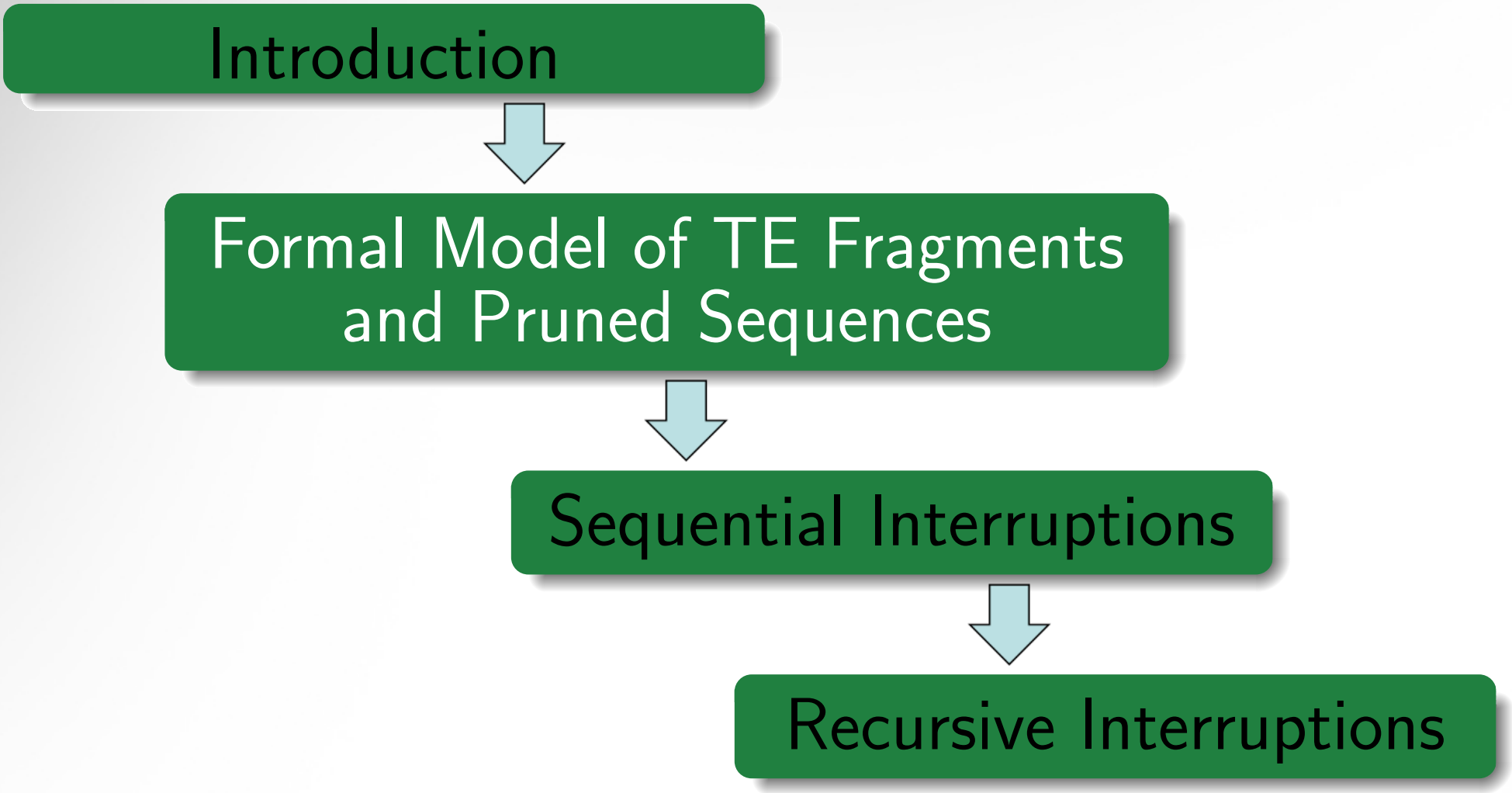
Transpositional Activites

- **Older** TEs are heavily interrupted by younger TEs, but have not inserted into younger elements;
- **Younger** TEs have inserted into older elements that were present in the genome, but are **not** interrupted by older elements;
- Elements of **intermediate age** have both inserted into older elements and been themselves fragmented by younger elements.
- Younger TEs interrupt not only older TEs, but also the **fragmented TEs** that had been previously interrupted.

Motivations

- Creating a standard formal model is necessary for further computational analysis.
- Knowing the evolution of TEs is helpful in understanding the activities of these elements and their impacts on genomes.

Part II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Formal Definitions about TEs

Definition (Transposable Element)

A *transposable element (TE)* X is a finite set of strings with $X \subseteq \Sigma^*$.

Definition (Instance of a TE)

An *instance of a TE* X is an element $x \in X$.

Definition (Consensus TE)

A *consensus TE* is a consensus sequence of the elements of X.

Definition (Set of TEs)

A *set of TEs* χ is a finite set of TEs. That is, $\chi \subseteq 2^{\Sigma^*}$, χ is finite and each element of χ is finite.

Fragments of TEs

Definition (Set of Fragments)

Let $s \in \Sigma^*$, then $frag(s)$ is the *set of fragments* of s. We extend this to sets of strings $S \subseteq \Sigma^*$ by $frag(S) = \bigcup_{s \in S} frag(s)$.

Definition (TE Fragments Set)

Let χ be a finite set of TEs. Then we call $\bar{\chi} \subseteq 2^{\Sigma^*}$ a *TE fragments set* if each element $\bar{X} \in \bar{\chi}$ is a subset of $frag(X)$, for some $X \in \chi$.

RepeatMasker TE Fragments Set I

Although we defined TE fragments sets in a general way, we would also like to create a restriction to **the transposable elements that occur in present-day sequences**.

Definition (RepeatMasker TE fragments set)

Let s be a string representing some genomic sequence and χ_s be the set of TEs existing in s, then $\bar{\chi}(s \overset{\text{RM}}{\longleftrightarrow} \chi_s)$ is a *RepeatMasker*[a] *TE fragments set*, running the program with a set of consensus TEs, χ_s, against the genomic sequence s.

In other words, each element of $\bar{\chi}(s \overset{\text{RM}}{\longleftrightarrow} \chi_s)$ is a subset of some element of $\bar{\chi}$, where only TE fragments detected by the RepeatMasker program are selected.

[a] RepeatMasker is the predominant library-based tool used in repeat identification, which has become a standard tool for any search of repeats in genomes.

RepeatMasker TE Fragments Set II

Definition (RepeatMasker TE fragment)

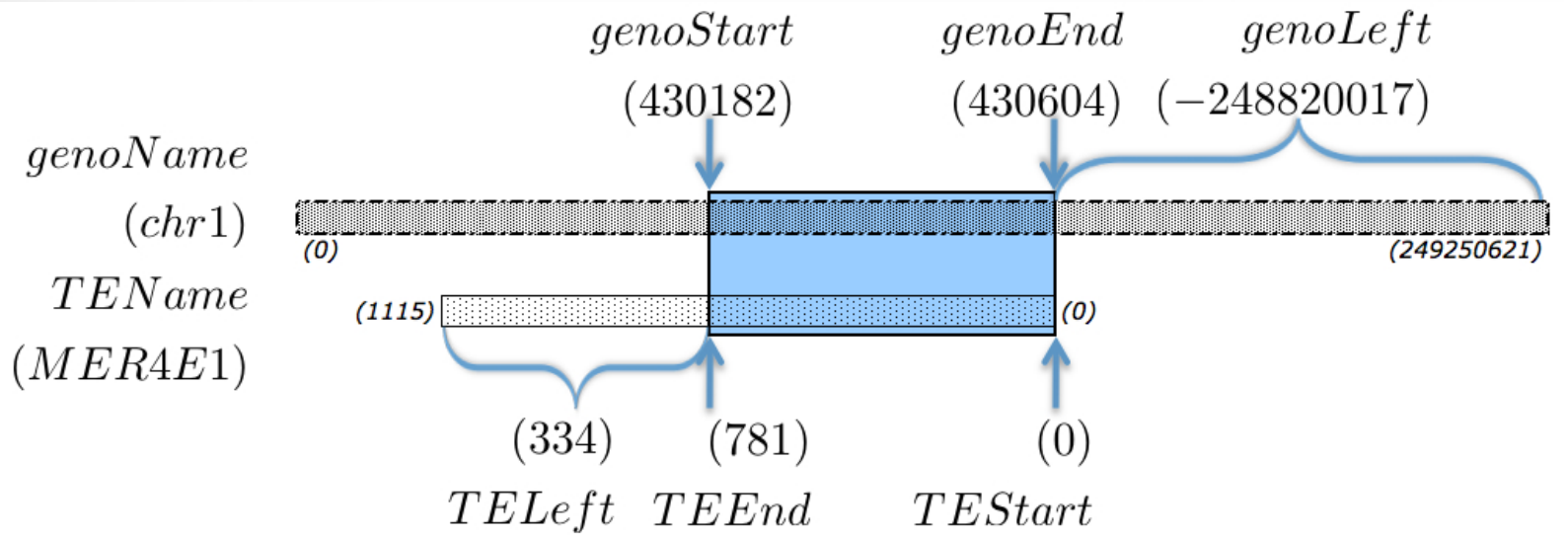
Given a genomic sequence s and a set of TEs χ_s, each *TE fragment* z in each $\bar{X} \in \bar{\chi}(s \overset{\text{RM}}{\longleftrightarrow} \chi_s)$ is a tuple:

$$\begin{aligned} info(z) =& (genoName, genoStart, genoEnd, genoLeft, strand, \\ & TEName, TEClass, TEStart, TEEnd, TELeft). \end{aligned} \tag{1}$$

We use the operator "." to access the attributes, for example, $z.TEname$ is the name of the TE to which fragment z belongs.

RepeatMasker TE Fragment: Example I

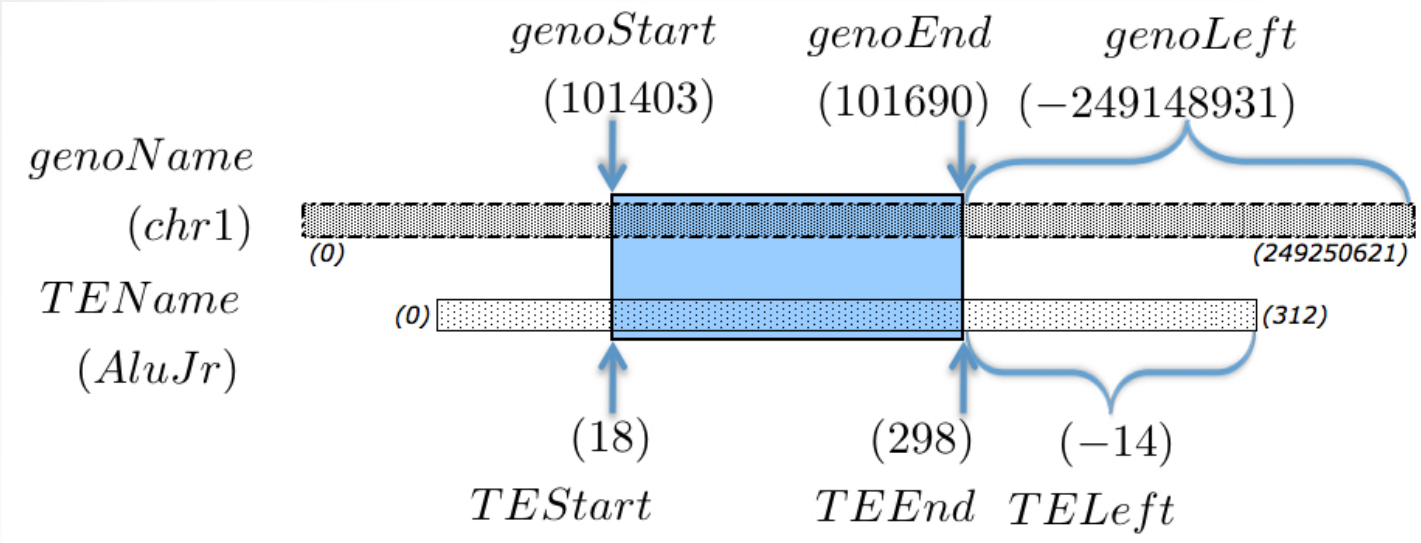
A fragment of MER4E1, which was detected in the "-" strand of Human chromosome 1.



genoName	genoStart	genoEnd	genoLeft	strand	TEName	TEClass	TEStart	TEEnd	TELeft
chr1	430182	430604	-248820017	-	MER4E1	LTR	0	781	334

RepeatMasker TE Fragment: Example II

A fragment of AluJr, which was detected in the "+" strand of Human chromosome 1.



genoName	genoStart	genoEnd	genoLeft	strand	TEName	TEClass	TEStart	TEEnd	TELeft
chr1	101403	101690	-249148931	+	AluJr	SINE	18	298	-14

Pruned Sequence and Order Pruned Sequence

A genomic sequence

$s = w_0 z_1 w_1 z_2 \ldots z_k w_k$, with $z_1, \ldots, z_k$ in sets in $\bar{\chi}_s$, and no fragment of $w_0, \ldots, w_k$ in sets in $\bar{\chi}_s$.

A pruned sequence

$\bar{s} = \beta_0 z_1 \beta_1 z_2 \beta_2 \ldots z_k \beta_k$, where $\beta_i = |w_i|$, $0 \leq i \leq k$.

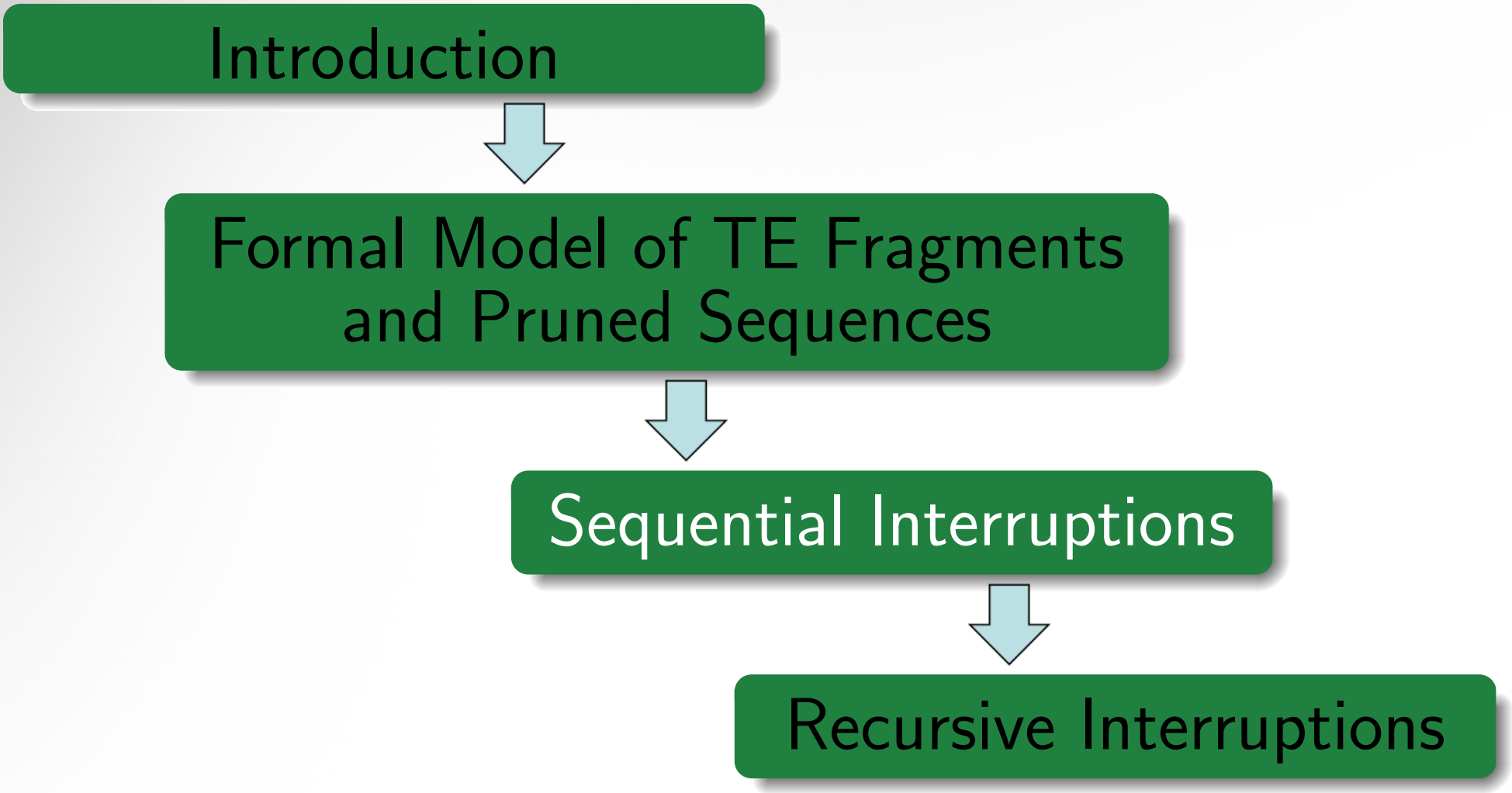
For Sequential Interruptions

An order pruned sequence

$\bar{s}_o = j_1 j_2 \ldots j_k$, where $z_i \in X_{j_i}$, for all i, $1 \leq i \leq k$.

For Recursive Interruptions

Part III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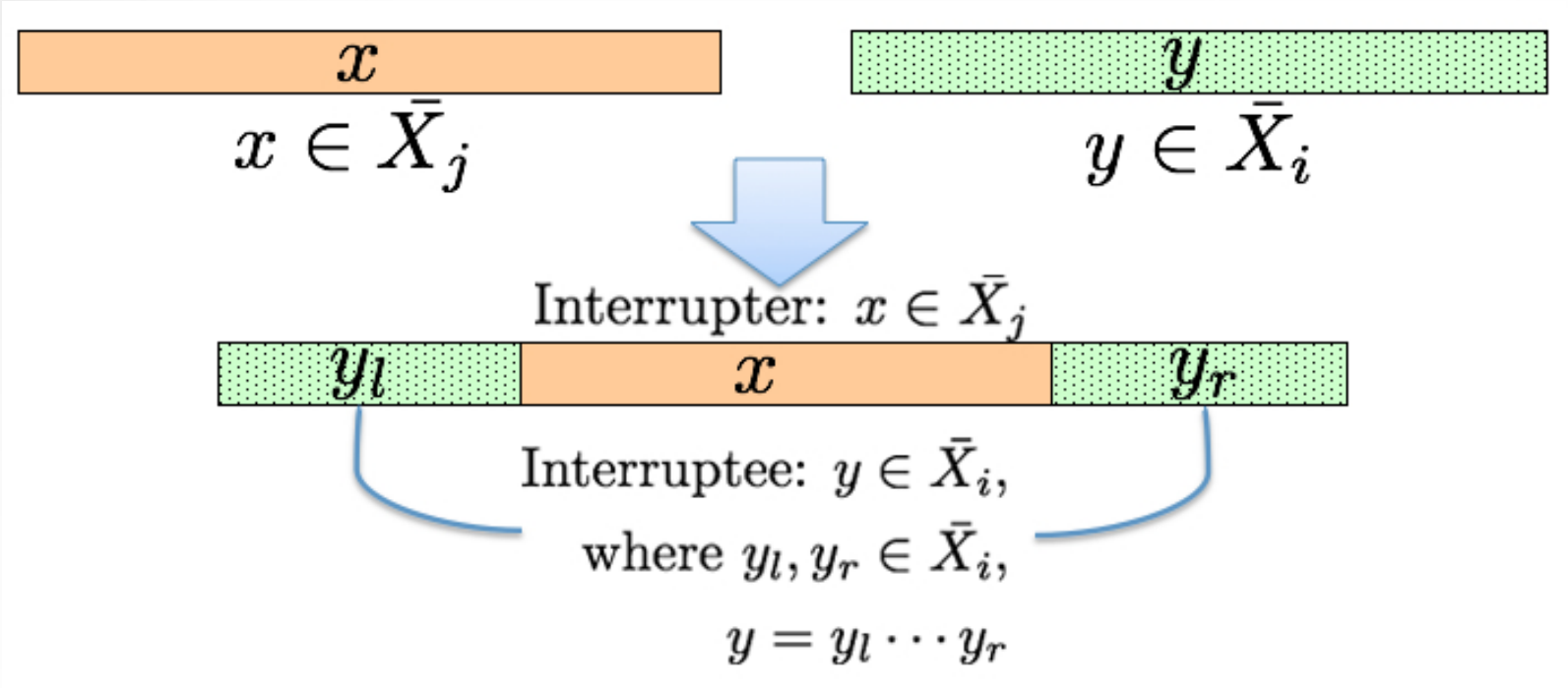
An Interruption

Newer TEs tend to interrupt older TEs, thereby fragmenting older TEs within the single linear sequence.



Continuous Fragments

Definition (Continuous TE Fragments)

Two TE fragments z_i and z_j $(i < j)$ are *continuous TE fragments*, $z_i \overset{\varepsilon,E}{\sim} z_j$, with threshold $\varepsilon \in \mathbb{N}$ and distance $E \in \mathbb{N}$, if they satisfy the following conditions:

1. they belong to the same transposable element;
2. they are detected in the same DNA strand;
3. they are either separated or overlap with less than or equal to a threshold, ε, with respect to the TE consensus sequence to which they belong;
4. They are in the genomic sequence within a distance, E, of non-transposon DNA sequence.

Sequential Interruptions

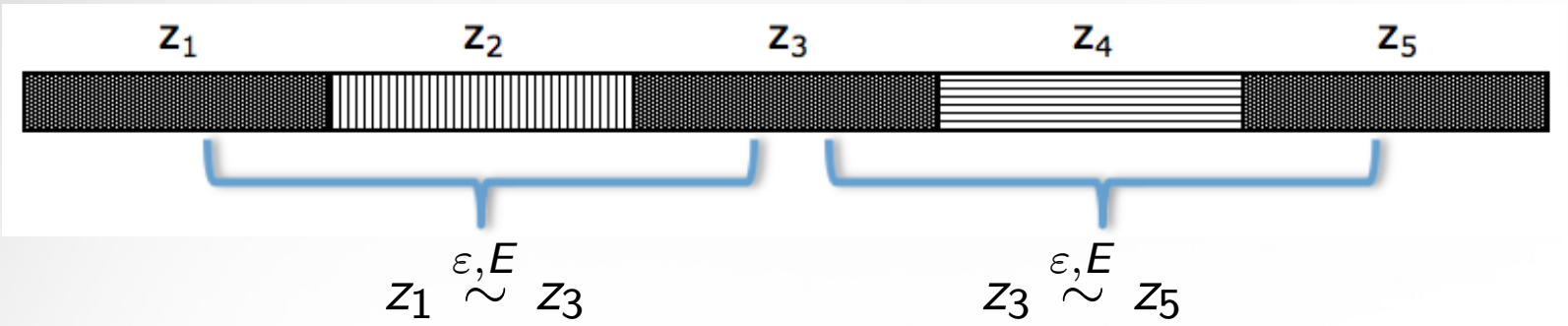
Definition (Sequential Interruptions)

Given a genomic sequence s, a set of TEs with a fixed ordering on its elements $\chi_s = \{X_1, X_2, \ldots, X_m\}$, a threshold $\varepsilon \in \mathbb{N}$ in TE consensus sequence, a distance $E \in \mathbb{N}$ in genomic sequence, and a pruned sequence $\bar{s} = \beta_0 z_1 \beta_1 z_2 \ldots z_k \beta_k$, we define *sequential interruptions* of X_j by X_i as

$$\Xi_s^{\varepsilon,E}(X_i,X_j)=\{k|z_k\in\bar{X}_i,z_{k-\eta_1},z_{k+\eta_2}\in\bar{X}_j,z_{k-\eta_1}\overset{\varepsilon,E}{\sim}z_{k+\eta_2},\text{and }\eta_1,\eta_2\in\mathbb{N}\}.$$

Thus X_i is called *interrupter*, and X_j is called *interruptee*.

An example of sequential interruptions in chromosome 1 I



genoName	*genoStart*	*genoEnd*	*genoLeft*	*strand*	*TEName*	*TEClass*	*TEStart*	*TEEnd*	*TELeft*
chr1	448062	448139	-248802482	+	L1MD3	LINE	6988	7068	-814
chr1	448150	448328	-248802293	+	AluYc	SINE	122	299	0
chr1	448332	448403	-248802218	+	L1MD3	LINE	7068	7148	-847
chr1	448403	448710	-248801911	+	AluSq	SINE	1	313	0
chr1	448710	449273	-248801348	+	L1MD3	LINE	7149	7753	-242

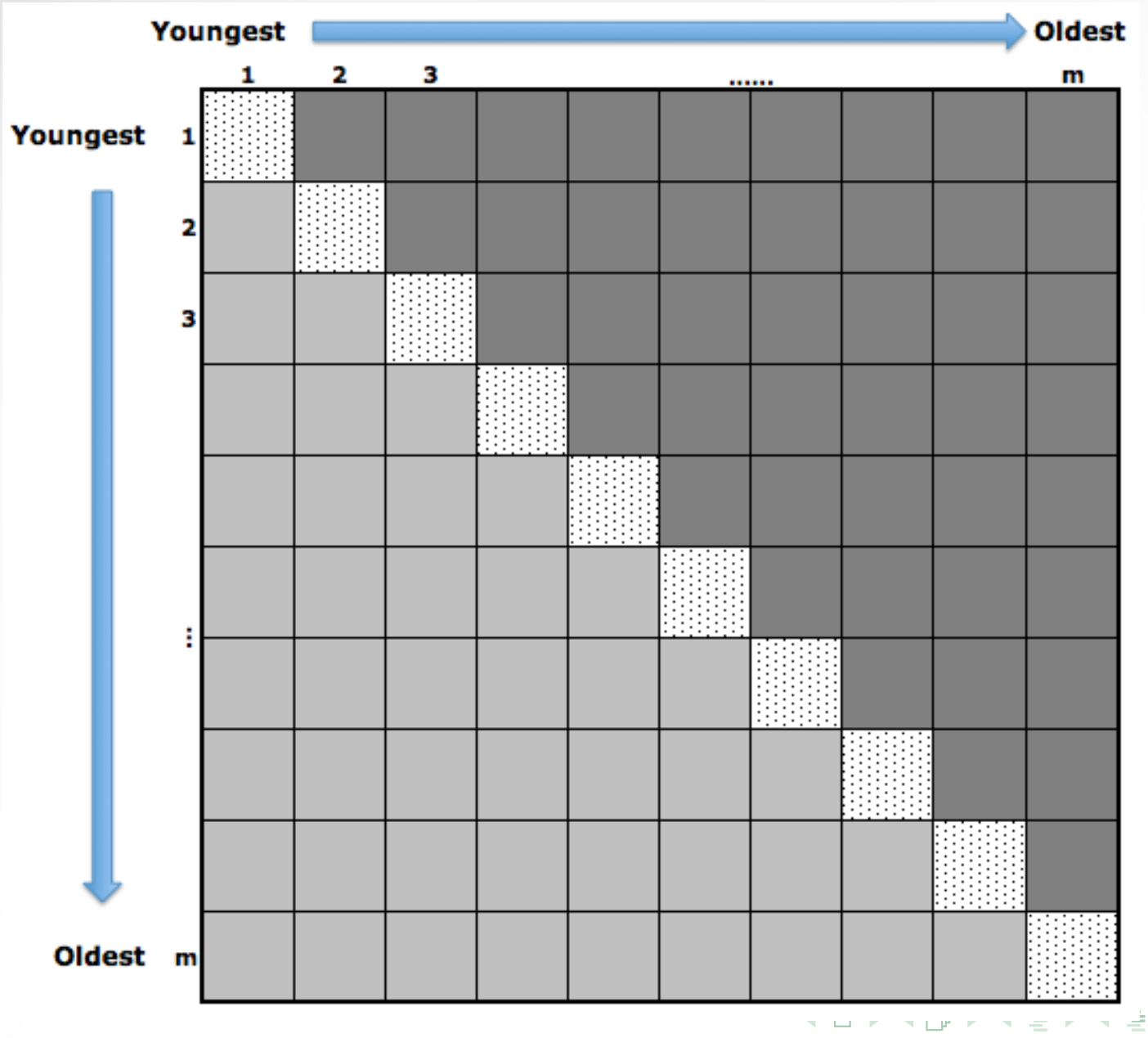
- The pruned sequence is $\bar{s} = \beta_0 z_1 \beta_1 z_2 \beta_2 z_3 \beta_3 z_4 \beta_4 z_5 \beta_5$, where $\beta_0, \ldots, \beta_5 \in \mathbb{N}$, and $z_1, z_3, z_5 \in \bar{X}_1$, $z_2 \in \bar{X}_2$, $z_4 \in \bar{X}_3$, $\bar{X}_1, \bar{X}_2, \bar{X}_3 \in \bar{\chi}(s \overset{\text{RM}}{\longleftrightarrow} \chi_s)$.

An example of sequential interruptions in chromosome 1 II

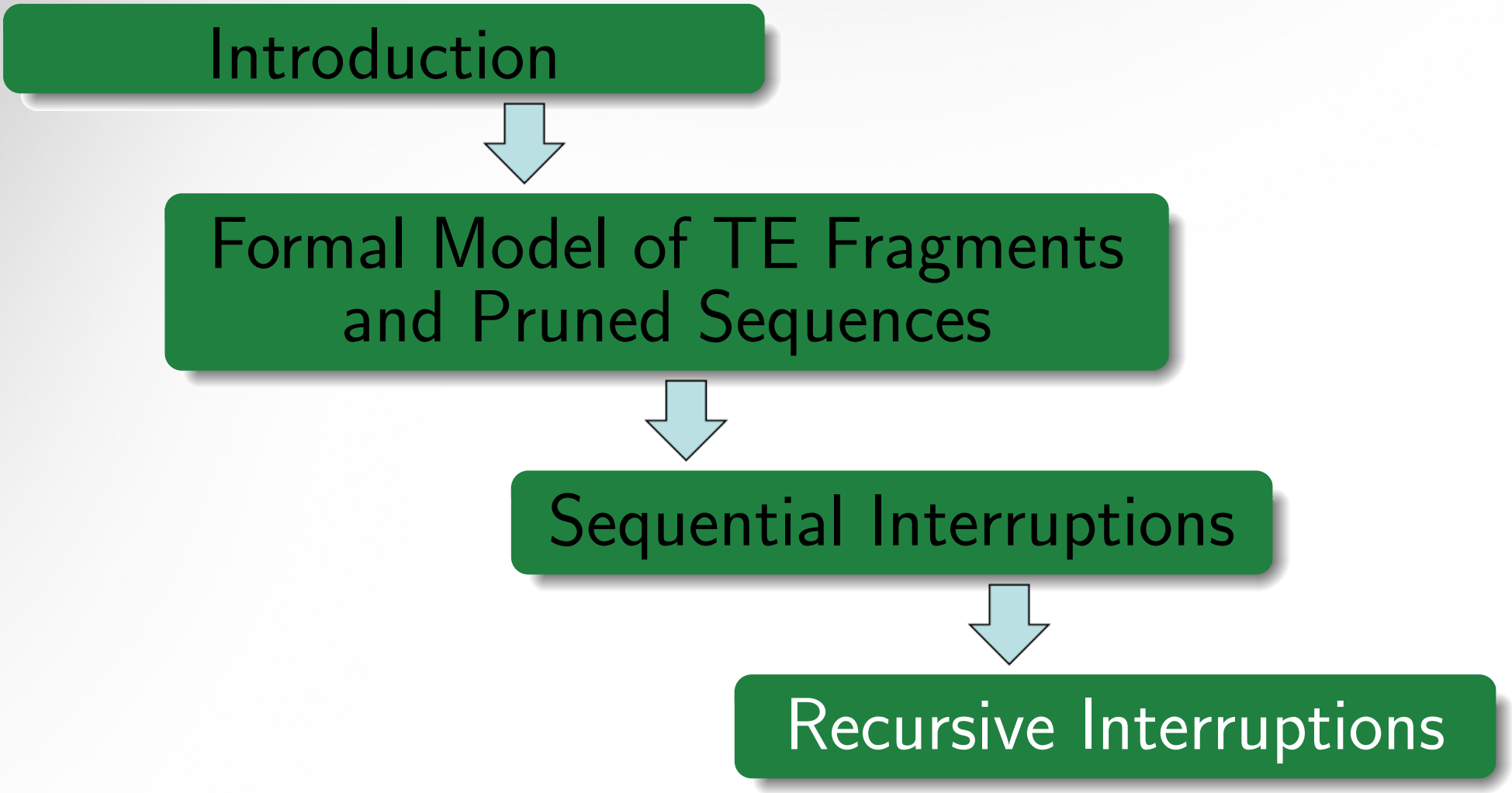
- There are two potential interruptions in s: an instance of X_1 is present in the sequence, then an instance of X_2 and an instance of X_3 potentially inserted themselves into the instance of X_1 to break it into three segments z_1, z_3 and z_5; that is, $|\Xi_s^{\varepsilon,E}(X_2, X_1)| = 1$ and $|\Xi_s^{\varepsilon,E}(X_3, X_1)| = 1$.
- Given a fixed order of the set of TEs as $\chi_s = \{\ldots, X_1, \ldots, X_2, \ldots, X_3 \ldots\}$, the **interruption matrix** showing only the rows and columns of these TEs is

$$M = \begin{bmatrix} & \vdots & & \vdots & & \vdots & \\ \ldots & 0 & \ldots & 0 & \ldots & 0 & \ldots \\ & \vdots & & \vdots & & \vdots & \\ \ldots & 1 & \ldots & 0 & \ldots & 0 & \ldots \\ & \vdots & & \vdots & & \vdots & \\ \ldots & 1 & \ldots & 0 & \ldots & 0 & \ldots \\ & \vdots & & \vdots & & \vdots & \end{bmatrix}.$$

Interruption Matrix



Part IV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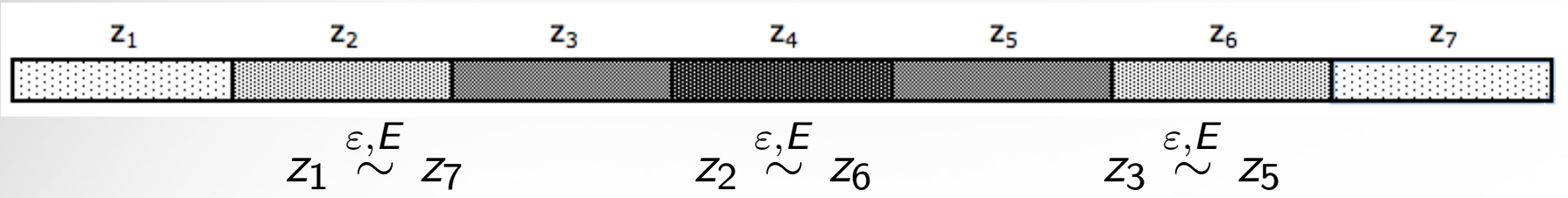
Recursive Interruptions

- When many insertions occurred throughout the evolution of a genomic sequence, the interruptions nest in a **recursive pattern**;
- Recursive interruptions cannot be represented accurately with the interruptional matrix that only counts the abundance without storing the **hierarchical relationships** of interruptions.

An Example of Recursive Interruptions in chromosome X



genoName	*genoStart*	*genoEnd*	*genoLeft*	*strand*	*TEName*	*TEClass*	*TEStart*	*TEEnd*	*TELeft*
chrX	53437061	53437143	-101833417	+	MIR	SINE	3	88	-174
chrX	53437143	53437277	-101833283	+	AluJb	SINE	1	132	-170
chrX	53437277	53437448	-101833112	+	AluSx	SINE	39	192	-120
chrX	53437448	53437761	-101832799	+	AluSq2	SINE	1	312	0
chrX	53437761	53437887	-101832673	+	AluSx	SINE	193	312	0
chrX	53437887	53438055	-101832505	+	AluJb	SINE	133	293	-9
chrX	53438055	53438226	-101832334	+	MIR	SINE	89	261	-1

The pruned sequence is $\bar{s} = \beta_0 z_1 \beta_1 z_2 \beta_2 z_3 \beta_3 z_4 \beta_4 z_5 \beta_5 z_6 \beta_6 z_7 \beta_7$, where

$$\beta_0, \ldots, \beta_7 \in \mathbb{N},\ z_1, z_7 \in \bar{X}_1,\ z_2, z_6 \in \bar{X}_2,\ z_3, z_5 \in \bar{X}_3,\ z_4 \in \bar{X}_4,$$

$$\bar{X}_1, \bar{X}_2, \bar{X}_3, \bar{X}_4 \in \bar{\chi}(s \overset{\text{RM}}{\longleftrightarrow} \chi_s)\ z_1 \overset{\varepsilon,E}{\sim} z_7,\ z_2 \overset{\varepsilon,E}{\sim} z_6,\ z_3 \overset{\varepsilon,E}{\sim} z_5.$$

Recursive Interruption Context-free Grammar

A **recursive interruption context-free grammar** can model the generation of recursive interruptions.

Definition (recursive interruption context-free grammar)

Given a set of TEs with a fixed order on its elements, $\chi = \{X_1, X_2, \ldots, X_m\}$, the *recursive interruption context-free grammar* is a grammar $G = (V, T, \delta, S)$, where $V = \{S, X_1, X_2, \ldots, X_m\}$, $T = \{1, 2, \ldots, m\}$, and δ contains the following productions:

$$S \rightarrow X_i S, \quad 1 \leq i \leq m, \tag{1}$$

$$S \rightarrow X_i, \quad 1 \leq i \leq m, \tag{2}$$

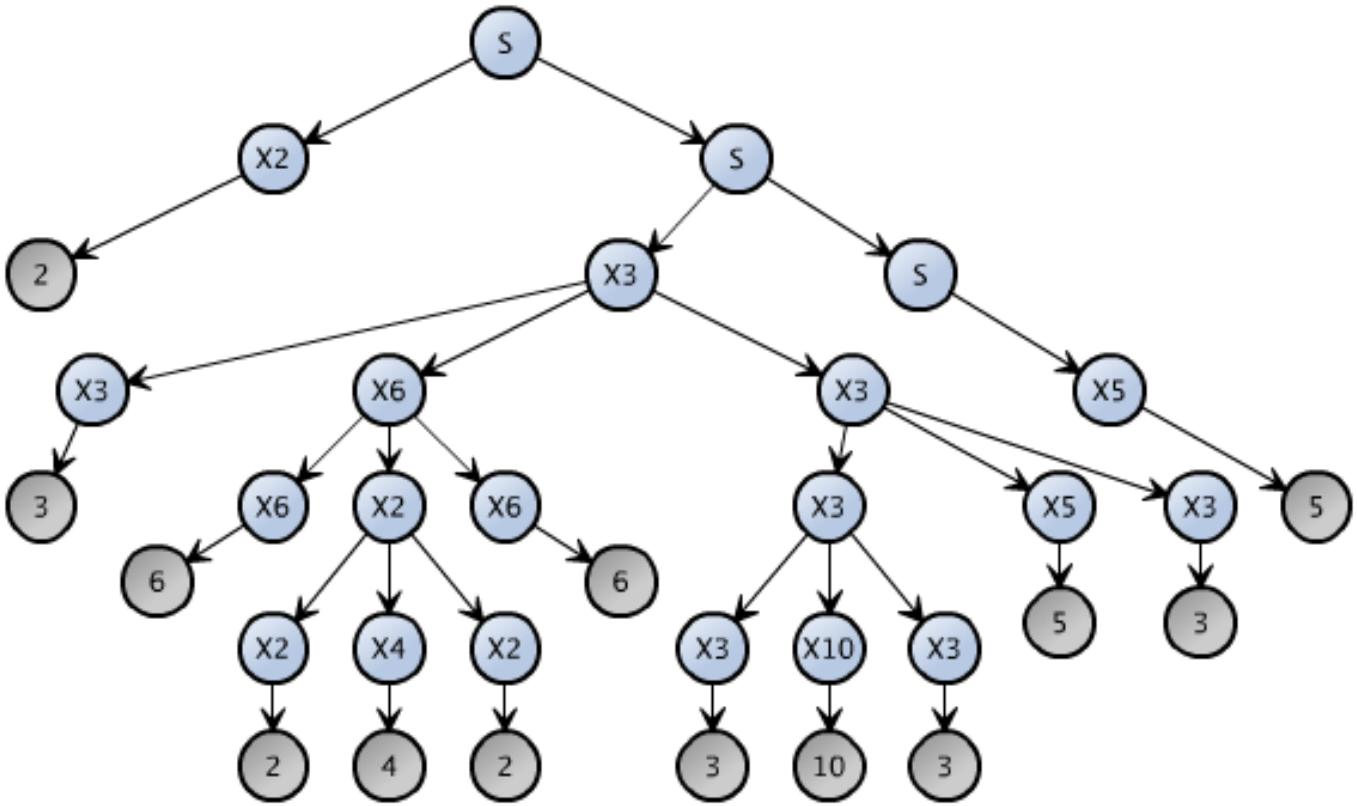
$$X_i \rightarrow X_i X_j X_i, \quad 1 \leq i \leq m, \ 1 \leq j \leq m, \tag{3}$$

$$X_i \rightarrow i, \quad 1 \leq i \leq m. \tag{4}$$

Example

Given a genomic sequence s and a set of TEs with a fixed order on its elements $\chi_s = \{X_1, X_2, \ldots, X_{10}\}$, and assume $s = w_0 z_1 w_1 \ldots z_{13} w_{13}$, with $z_1, z_4, z_6 \in \bar{X}_2$, $z_2, z_8, z_{10}, z_{12} \in \bar{X}_3$, $z_5 \in \bar{X}_4$, $z_{11}, z_{13} \in \bar{X}_5$, $z_3, z_7 \in \bar{X}_6$, $z_9 \in \bar{X}_{10}$. Then an order pruned sequence $\bar{s}_o = 2\,3\,6\,2\,4\,2\,6\,3\,10\,3\,5\,3\,5$ is the yield of the parse tree:

$$
\begin{aligned}
S &\rightarrow X_i S, && (1)\\
S &\rightarrow X_i, && (2)\\
X_i &\rightarrow X_i X_j X_i, && (3)\\
X_i &\rightarrow i. && (4)
\end{aligned}
$$



Summary

- We created a formal model capturing TE types and fragments within genomic sequences.
- The model can be used to capture and calculate interruptions and their frequencies in a general way.
- We provided a stochastic context-free grammar to capture recursive TE nesting.
- The grammar allows standard polynomial time parsing to be used to calculate a prediction of the nesting.

Thank You!