Hi-C interaction matrix correction using ICE in Rust

Bachelor thesis defense

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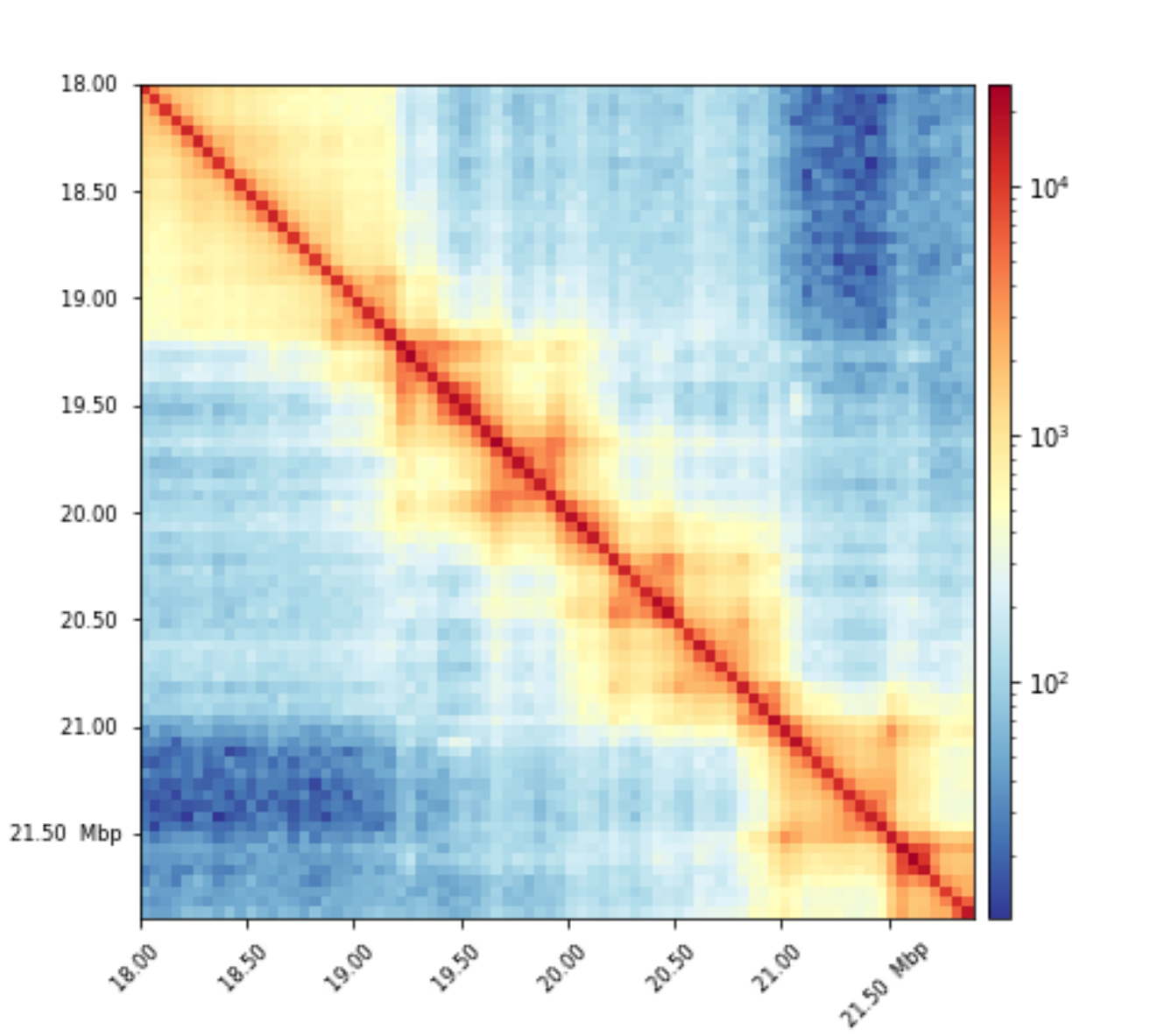
University of Freiburg

Hi-C Contact Matrix



Content

Content

High-Throughput 3C (Hi-C)

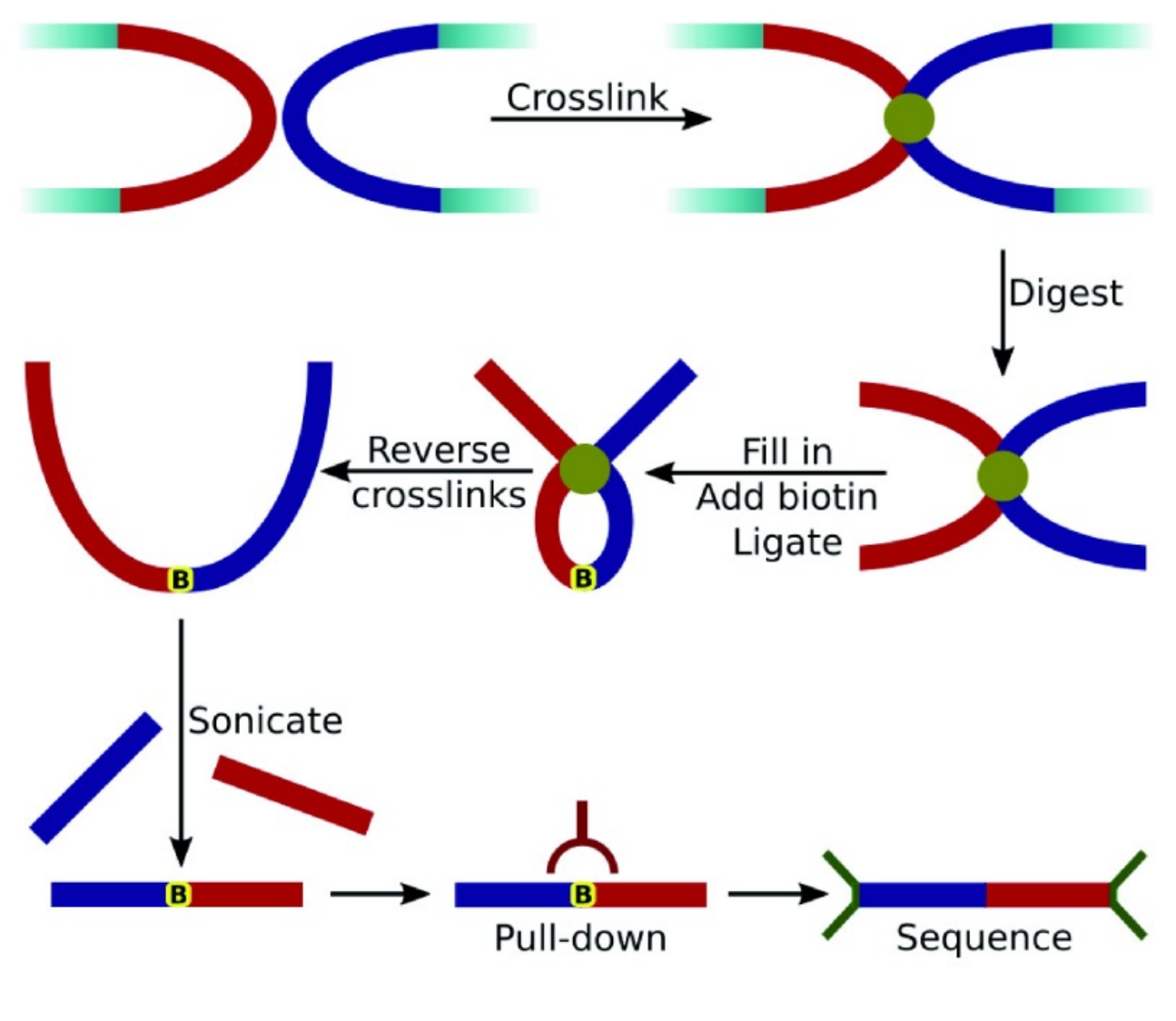


Image adapted from [1]

HiCExplorer

Helpful tools, especially for:

HiCExplorer

Helpful tools, especially for:

- Data correction

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Helpful tools, especially for:

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- Analysis

HiCExplorer

Helpful tools, especially for:

- Data correction
- Analysis
- Visualization

Content

ICE as described in Imakaev et al. 2012 [2]

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- O_{ij}: raw data

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- T_{ij}: relative contact probabilities

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- T_{ij}: relative contact probabilities
- B_i, B_j: cumulative biases

ICE as described in Imakaev et al. 2012 [2]

Goal: Obtain B and T_{ij}.

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Do this by explicitly solving:

$$O_{ij} = B_i B_j T_{ij} \tag{1}$$

$$\sum_{i=1,|i-j|>1}^{N} T_{ij} = 1 \tag{2}$$

ICE as described in Imakaev et al. 2012 [2]

$$T_{ij} = \begin{bmatrix} d & d_{+1} & t_{1,3} & \dots & \dots & t_{1,n} \\ d_{-1} & d & d_{+1} & \dots & \dots & t_{2,n} \\ \vdots & \ddots & \ddots & \ddots & & \vdots \\ \vdots & & \ddots & \ddots & \ddots & \vdots \\ t_{n-1,1} & \dots & \dots & d_{-1} & d & d_{+1} \\ t_{n,1} & \dots & \dots & t_{n,n-2} & d_{-1} & d \end{bmatrix}$$

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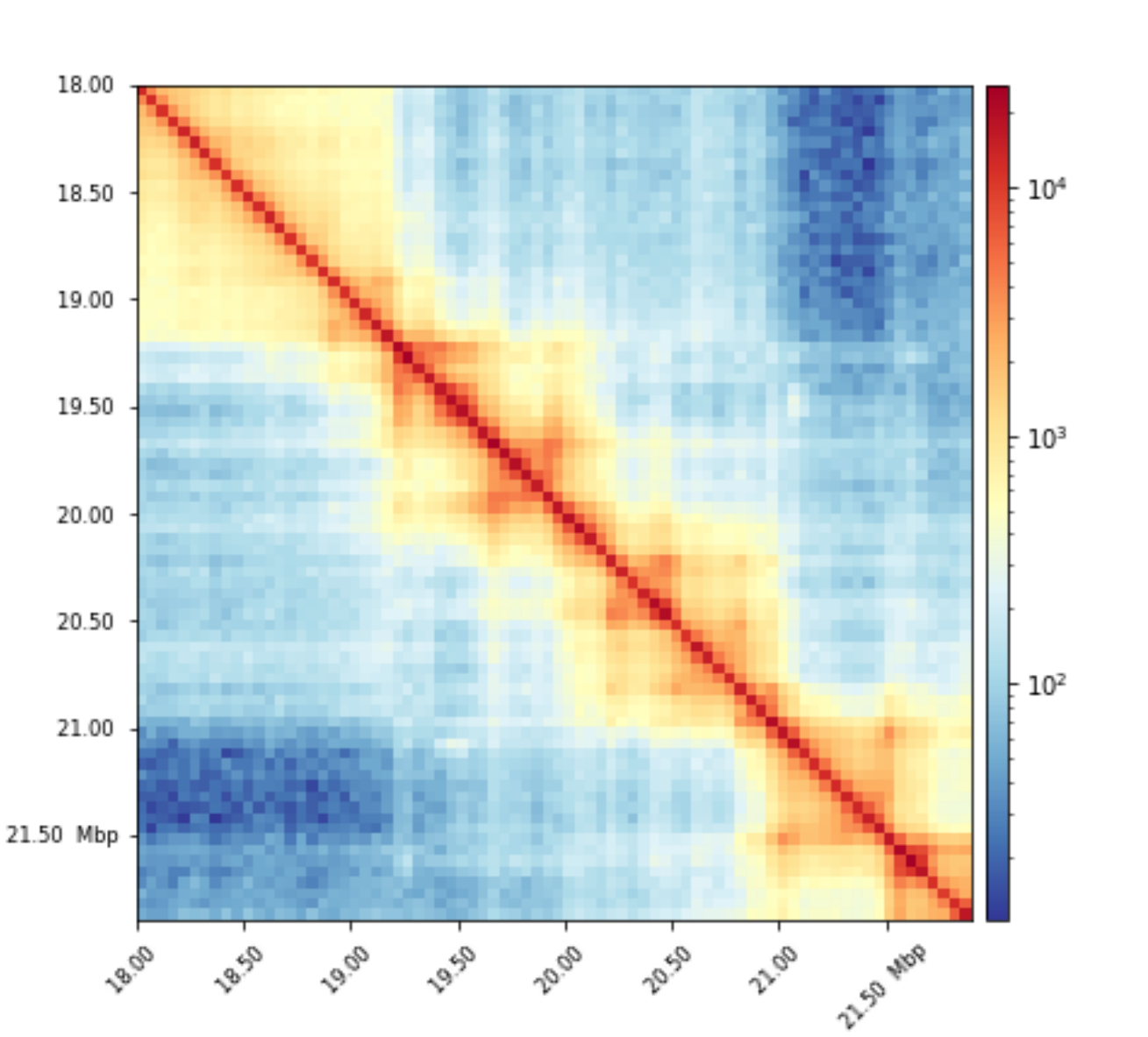

Content

Rust: Short History

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- Started out in 2006

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- Mozilla started sponsoring in 2009
- Self-compiled in 2011
- 1.0 released in 2015

Rust: Language Features

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- Syntax seems similar to C/C++

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- Lifetimes

Rust: Comparison

Speed coparison	C	Rust	C++
n-body	7.49	**5.72**	8.18
binary-trees	3.48	**3.15**	3.79
pidigits	**1.75**	**1.75**	1.89
reverse-complement	1.78	1.61	**1.55**
spectral-norm	1.98	**1.97**	1.98
fannkuch-redux	**8.61**	10.23	10.08
k-nucleotide	5.01	5.25	**3.76**
fasta	1.36	1.47	**1.33**
mandelbrot	1.65	1.96	**1.50**
regex-redux	**1.46**	2.43	1.82
Fastest in:	3/10	4/10	4/10

Runtime measured in **seconds**. Numbers for C from [3] and for C++ from [4]. Both show the same numbers for Rust.

Rust: Advantages and Disadvantages

General Advantages:

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- High-Level Features

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General Advantages:

- High-Level Features
- Fast Language
- Safe Memory handling
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General Disadvantages:

- Young ecosystem
- Steep learning curve
- Higher initial compile times
- Language Features not yet available

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Advantages for this Project:

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- Own CSRMatrix implementation

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Disadvantages for this Project:

- No general implementation of CSRMatrix
- Only subset of features when compared to SciPy implementation

Content

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There is three main ways to use Rust from Python:

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- easy package creation

pyO3

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- package creation possible

API comparison for Rust in Python

API Comparison	rust-cpython	pyO3	dylib

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Memory from Python	Yes	Yes	**Optional**

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Good in:	2/6	1/6	**5/6**

Content

Compared implementations

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- 'ICE' - Python implementation

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- 'KR' - C++ implementation

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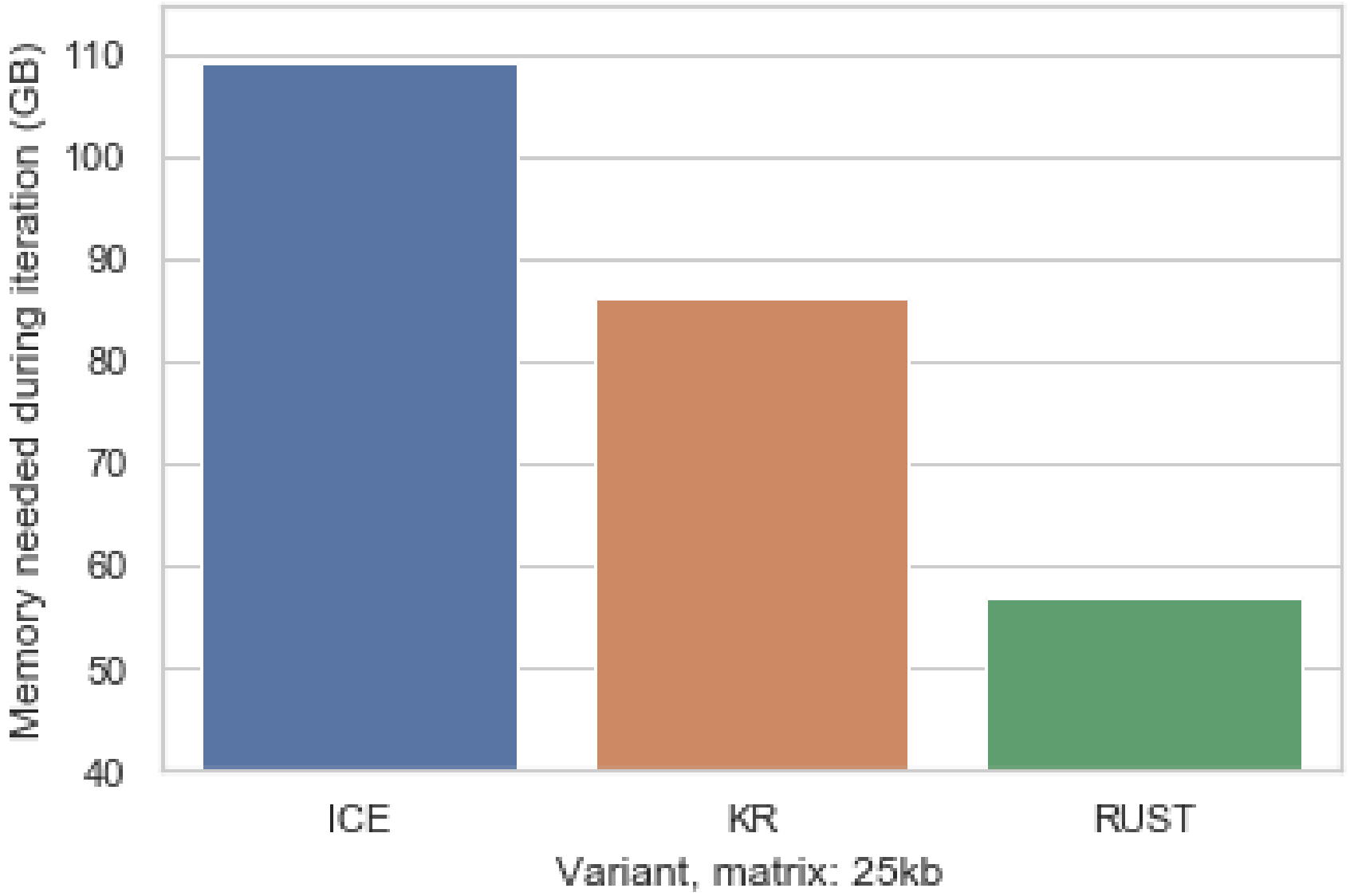
- 'ICE' - Python implementation
- 'KR' - C++ implementation
- 'RUST' - this implementation

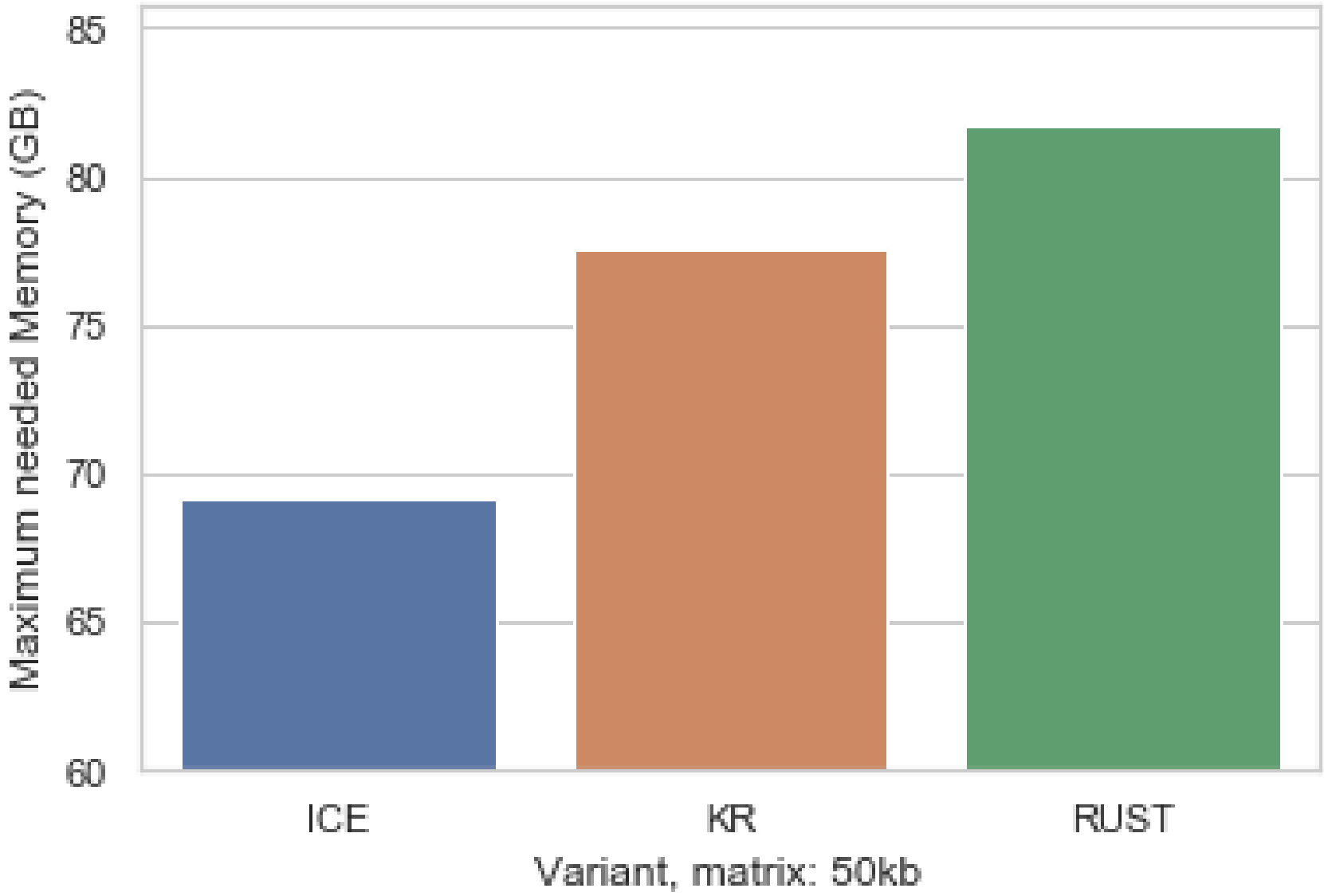
Data for Testing

Name	25kb	50kb
Filesize	1.1 GByte	732 MByte
Size	123,841	61,928
Bin length	25,000	50,000
Non-zero elements	1,530,533,003	1,053,216,825

Memory Requirements during correction



Peak Memory Usage



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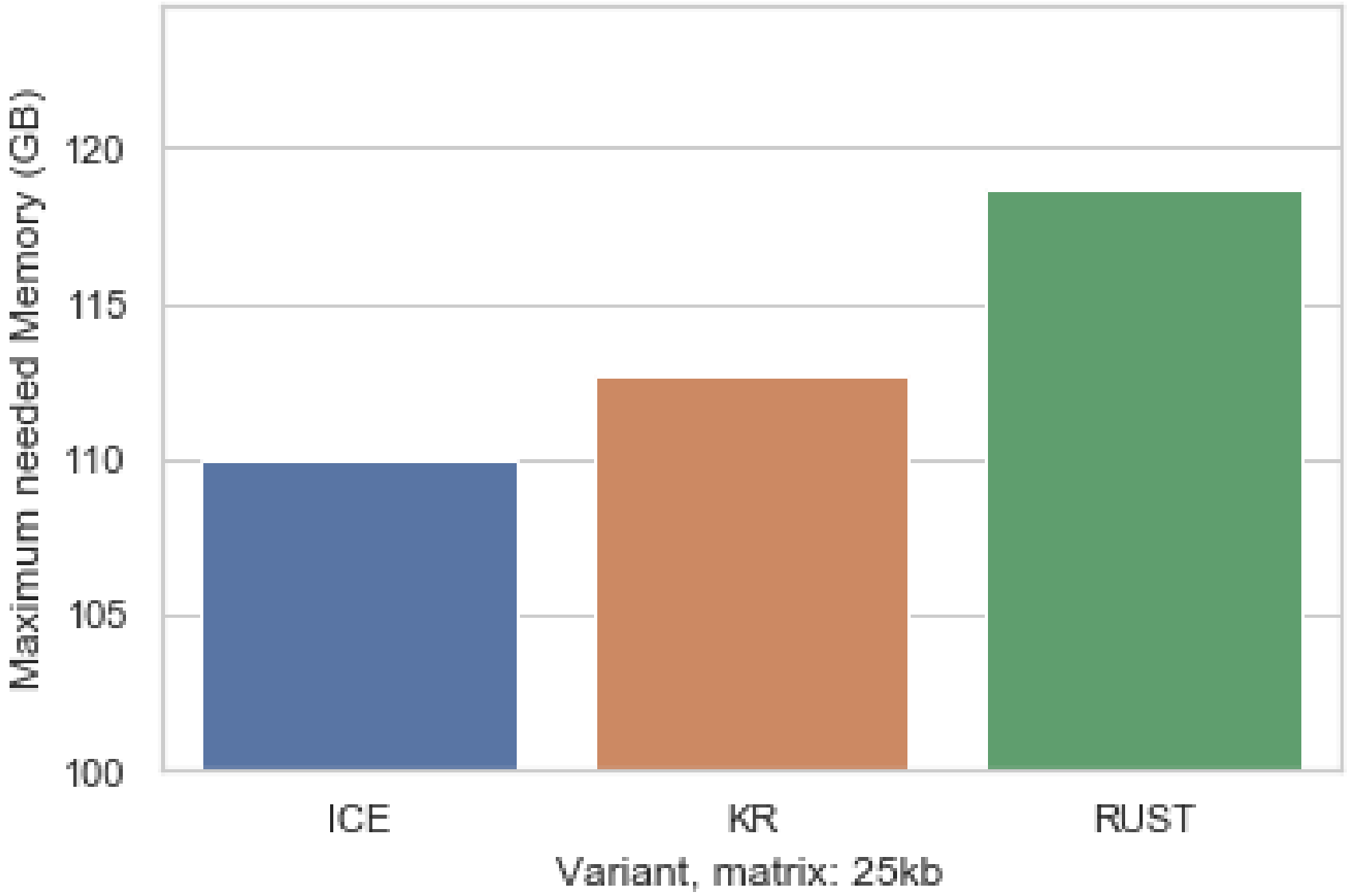

Control Flow Diagram

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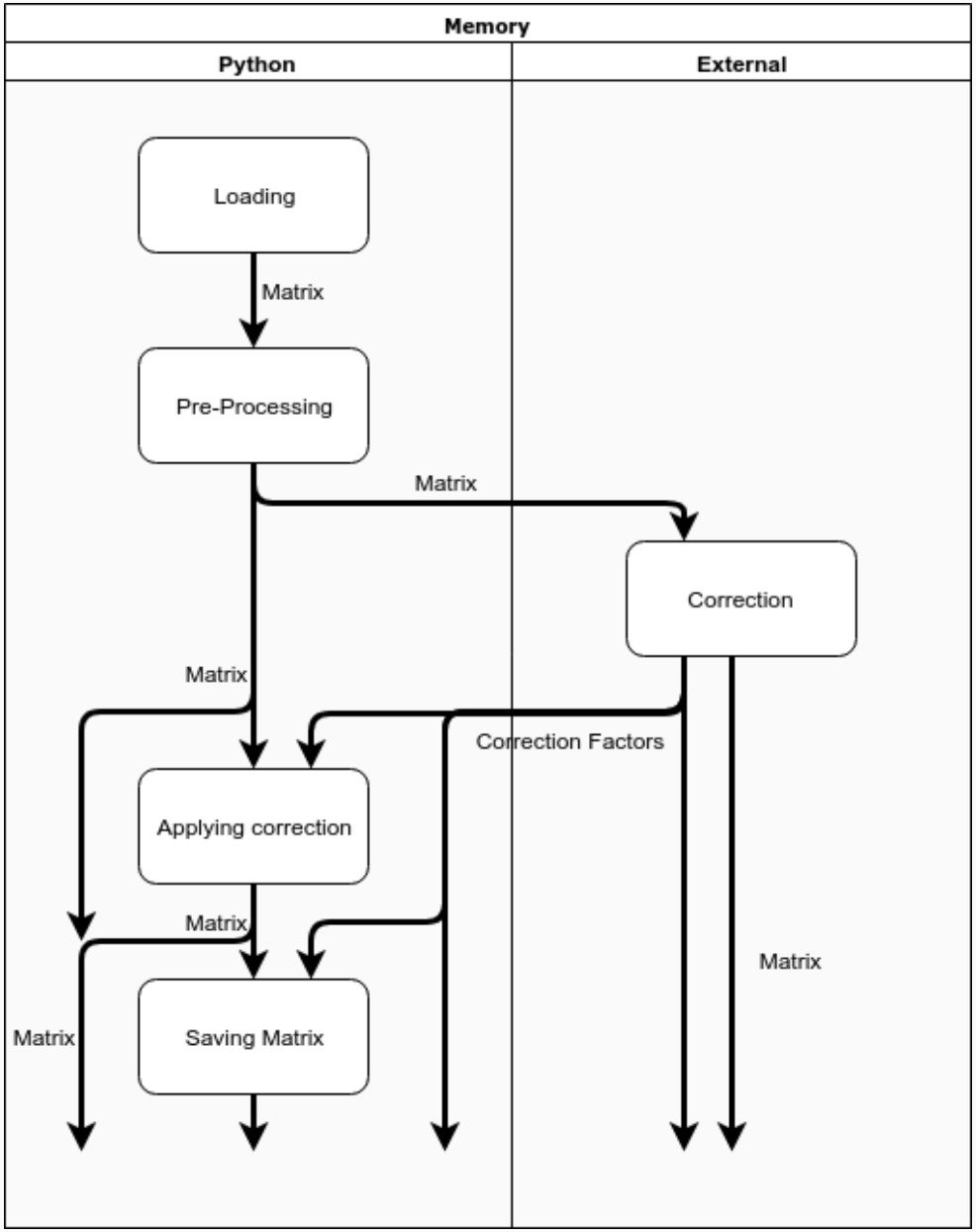

Comparison of Memory needs

Memory needs Comparison	ICE	KR	RUST

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During correction (50kb)	54.6	43.1	**39**

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During correction (25kb)	110	86	**57**

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During correction (50kb)	54.6	43.1	**39**
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During correction (25kb)	110	86	**57**
Maximum (25kb)	**110**	112.7	118.6

Loading Times

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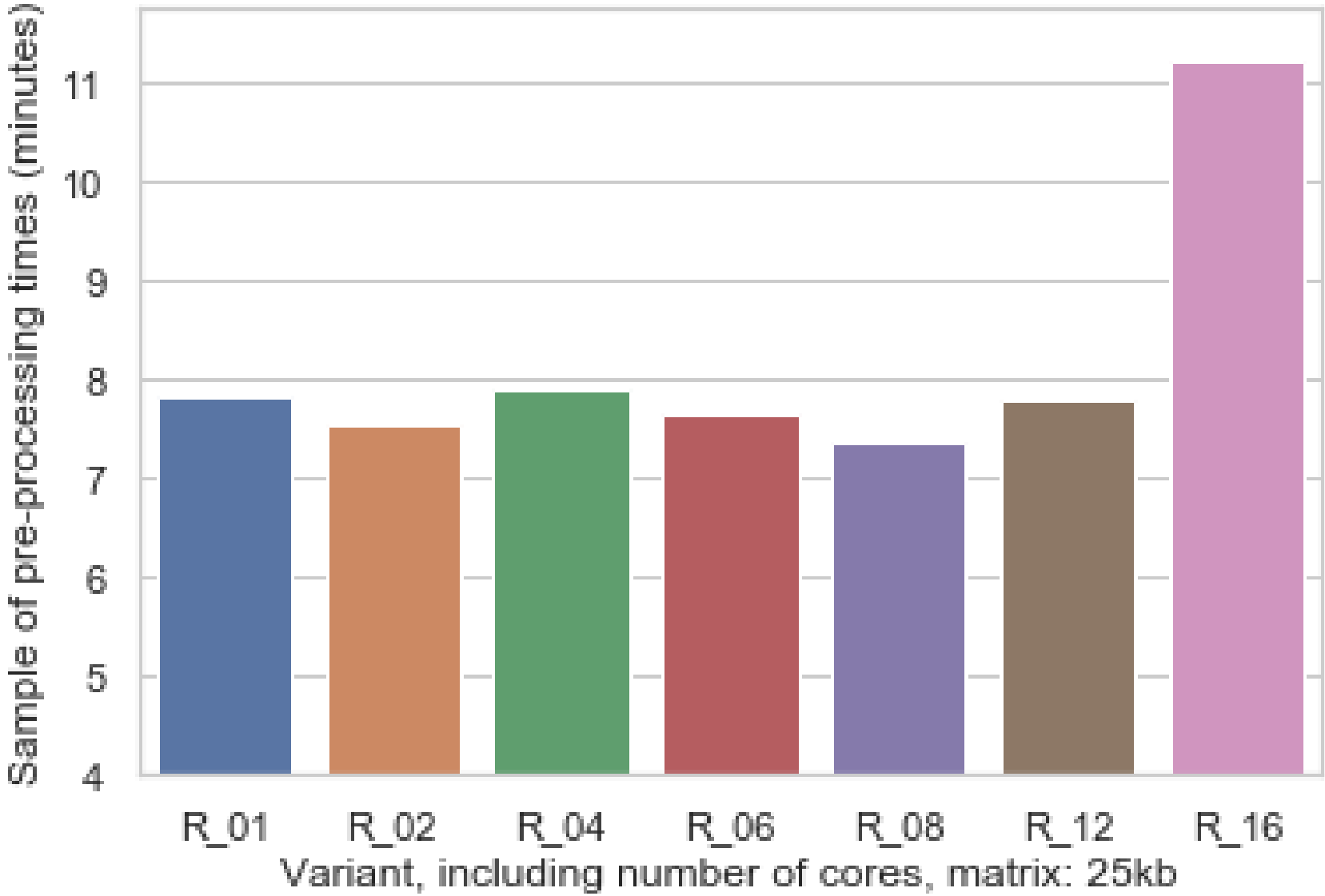

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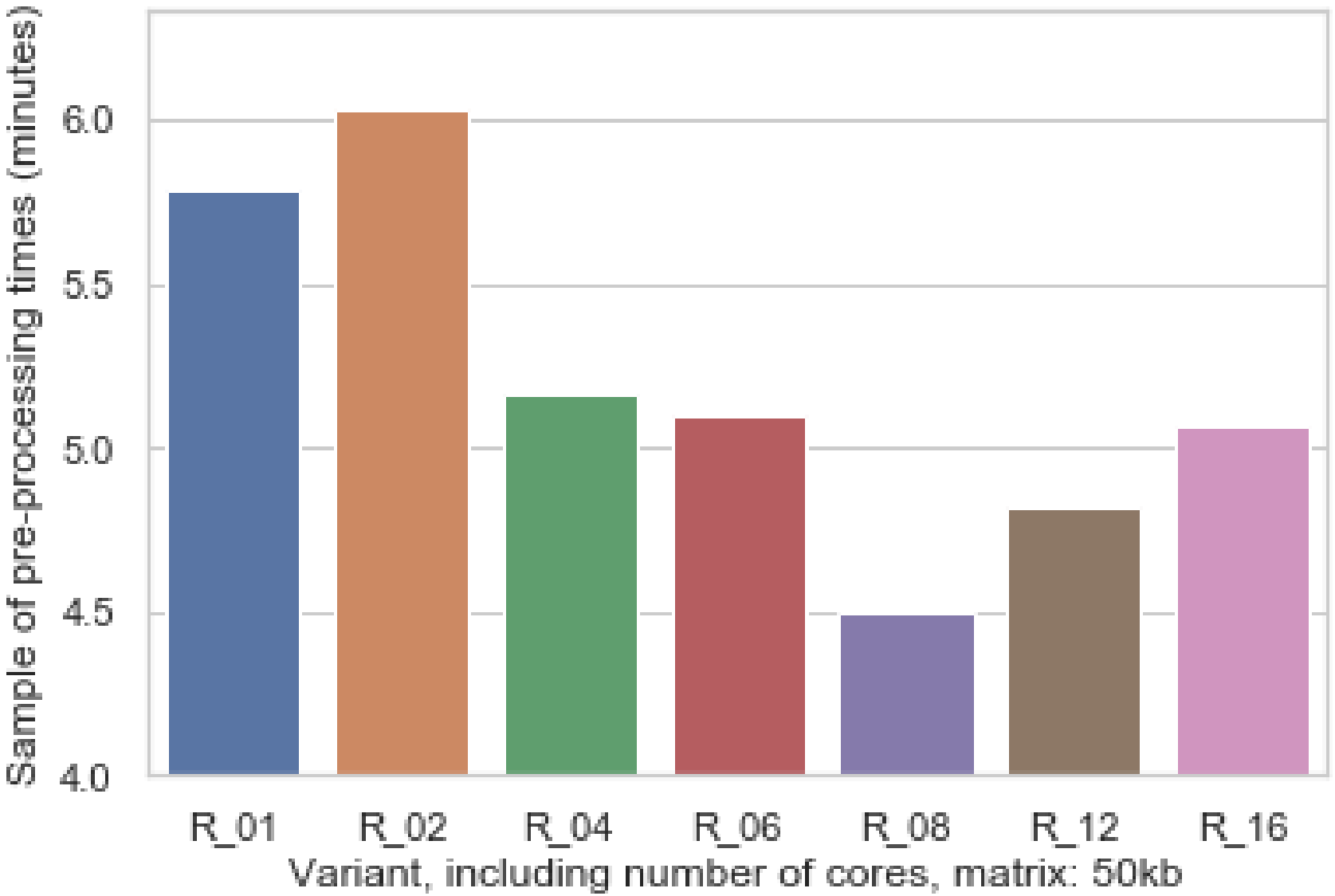

Runtime Length

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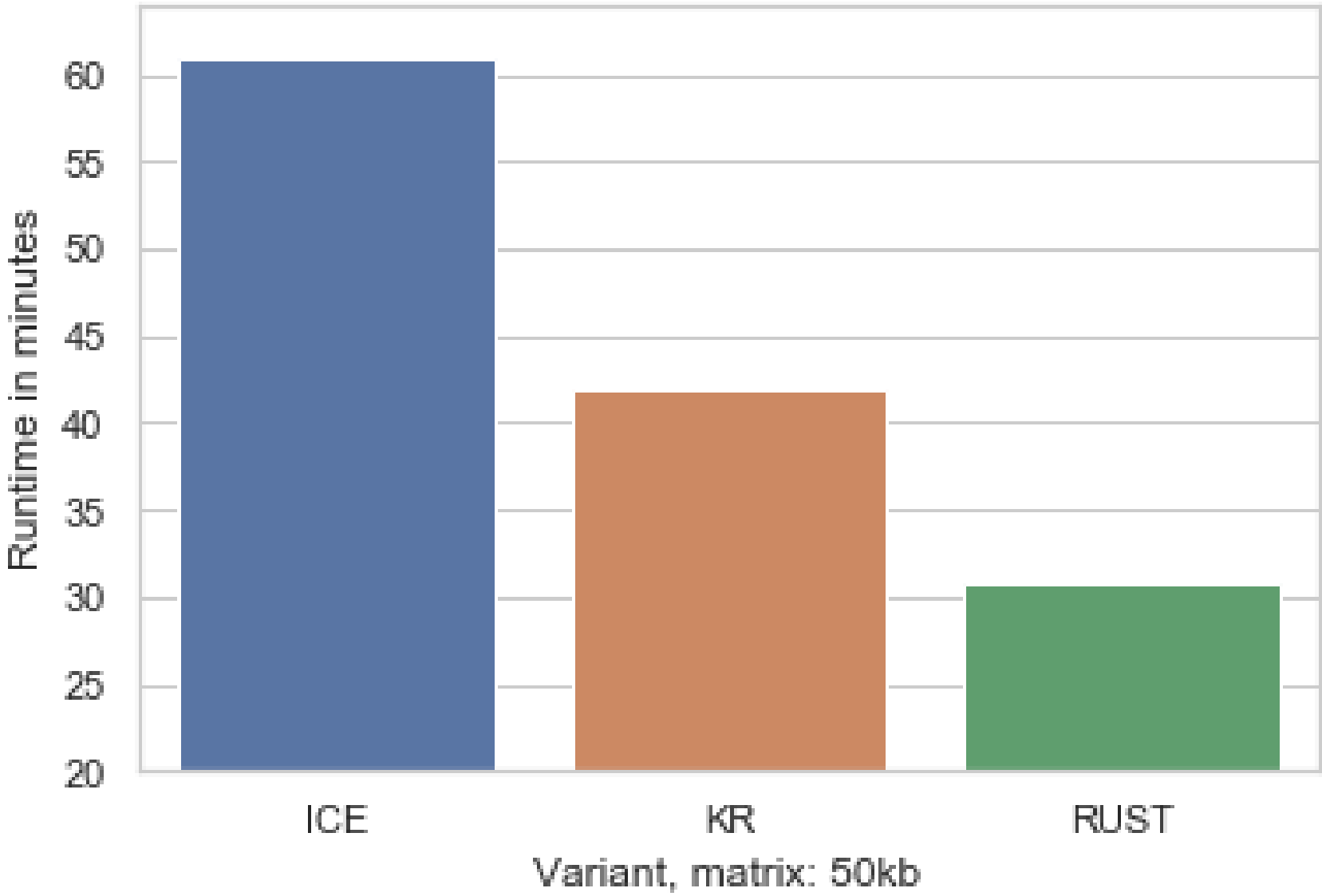

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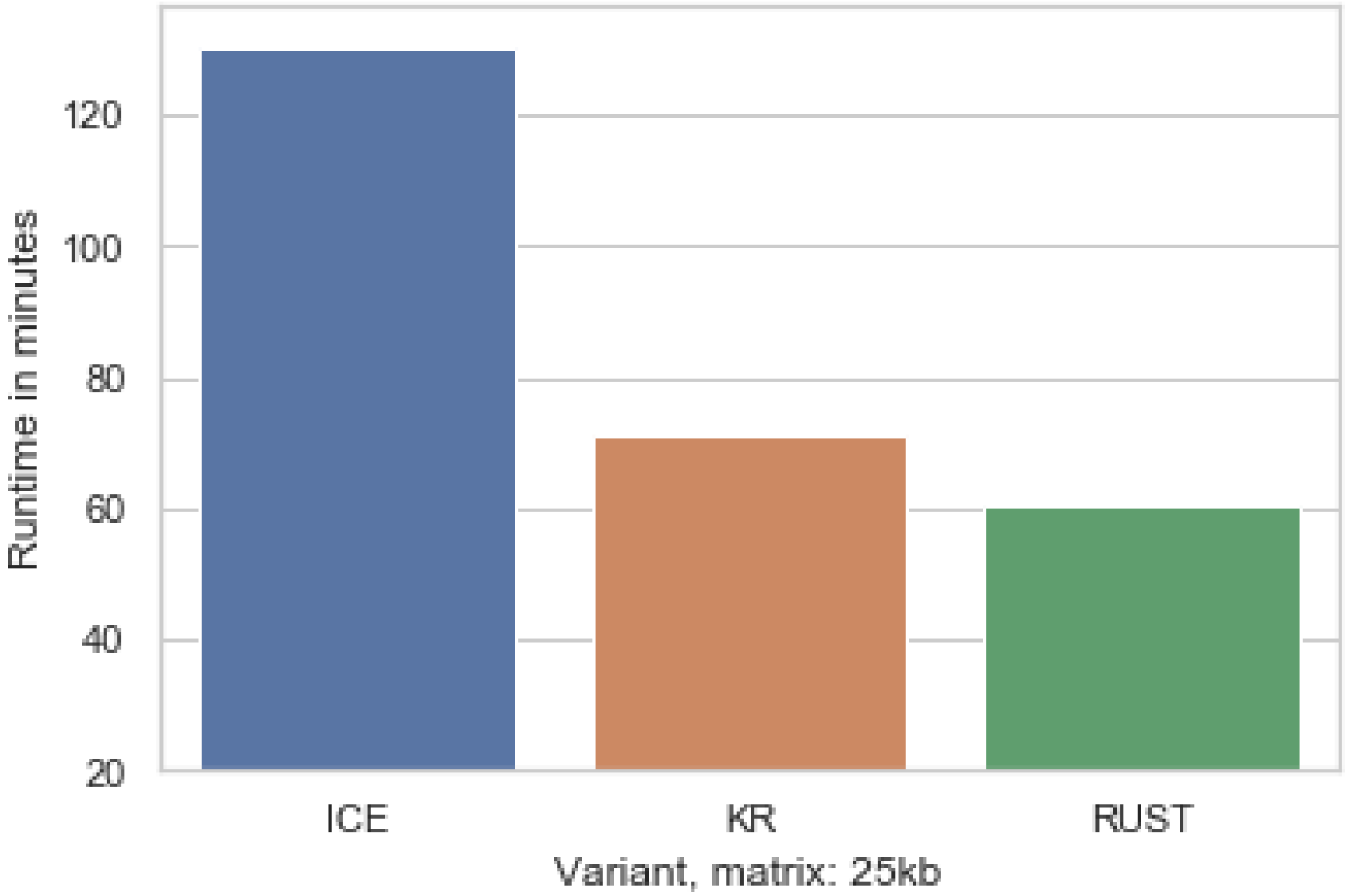

Multicore Runtime Length Comparison

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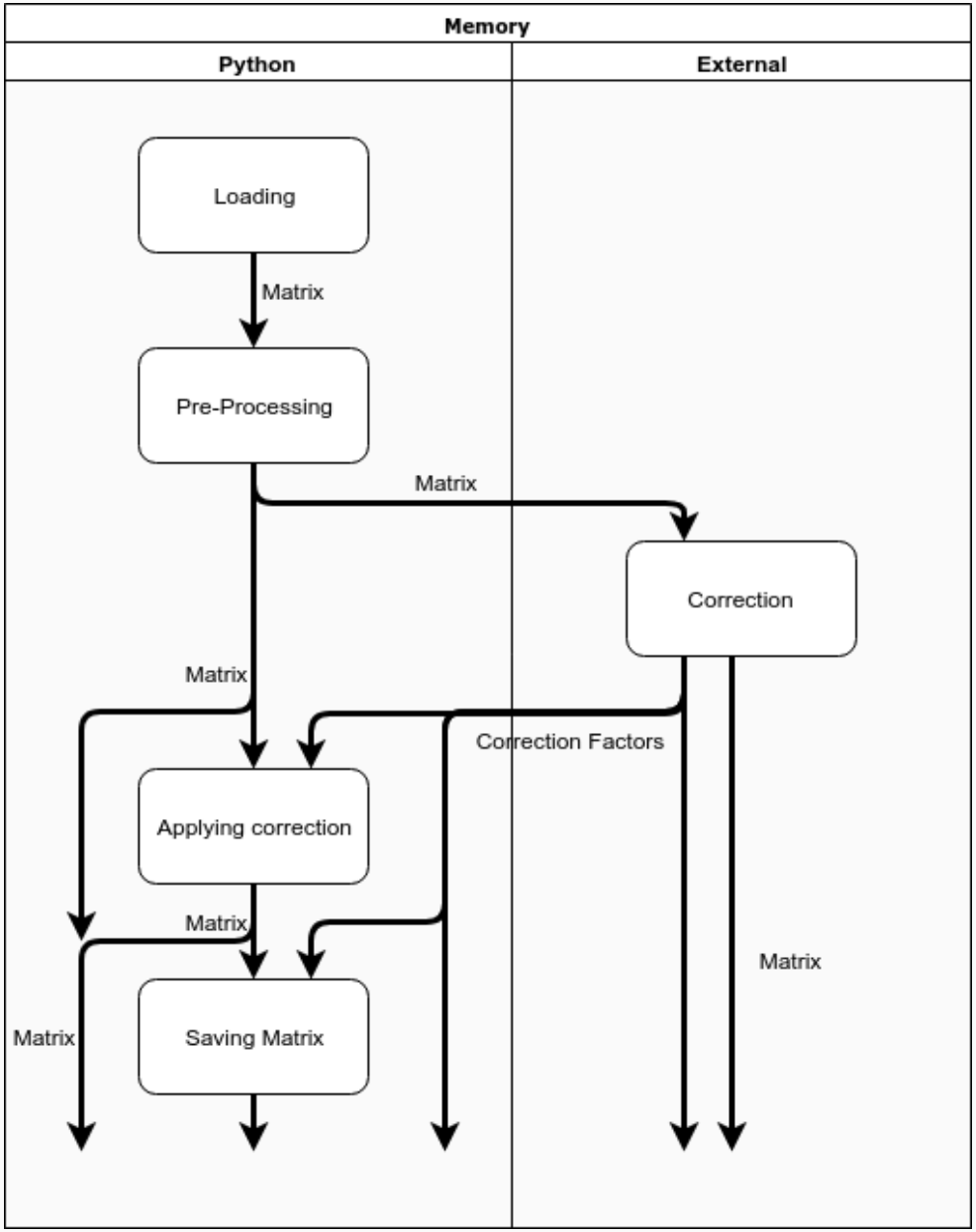

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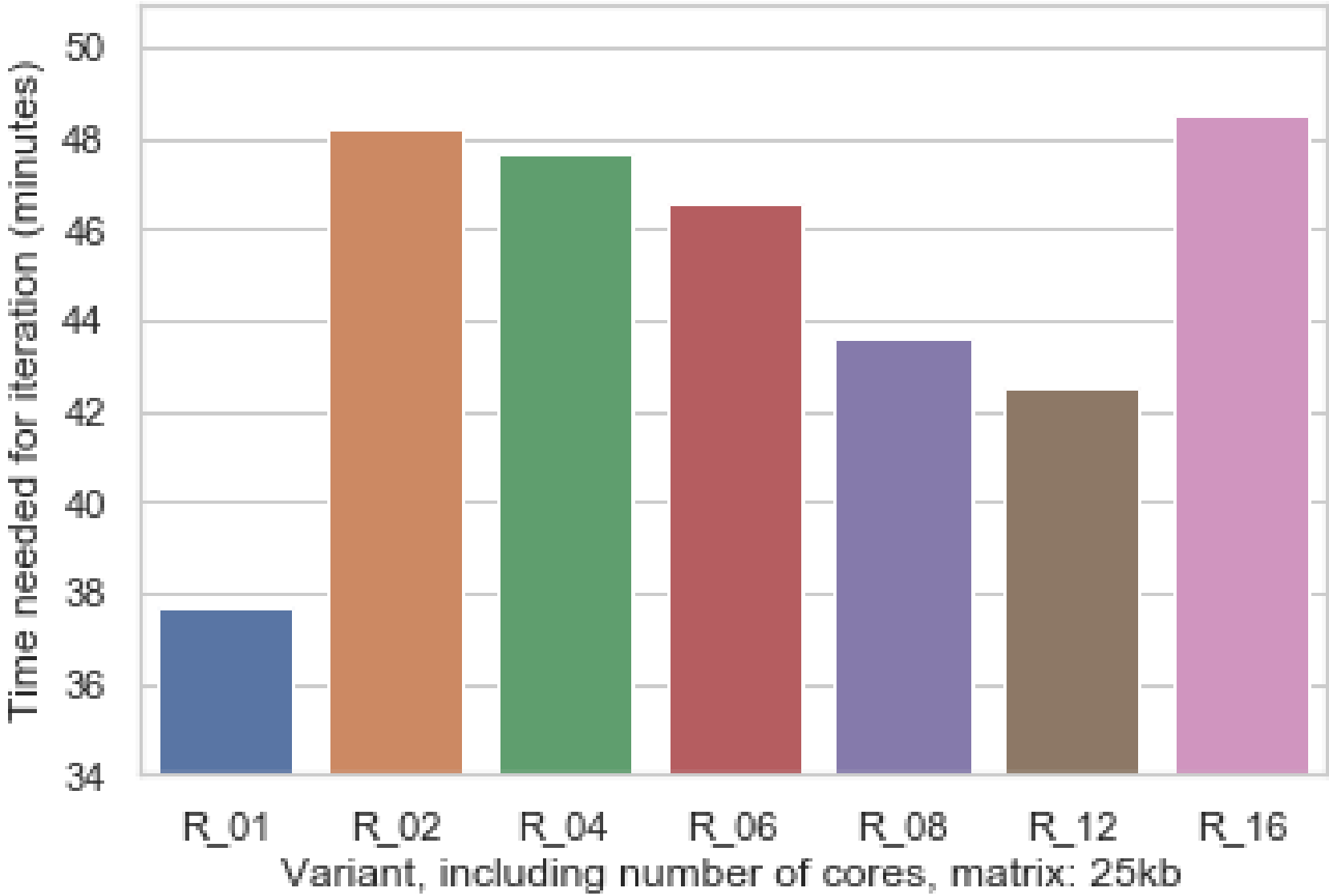

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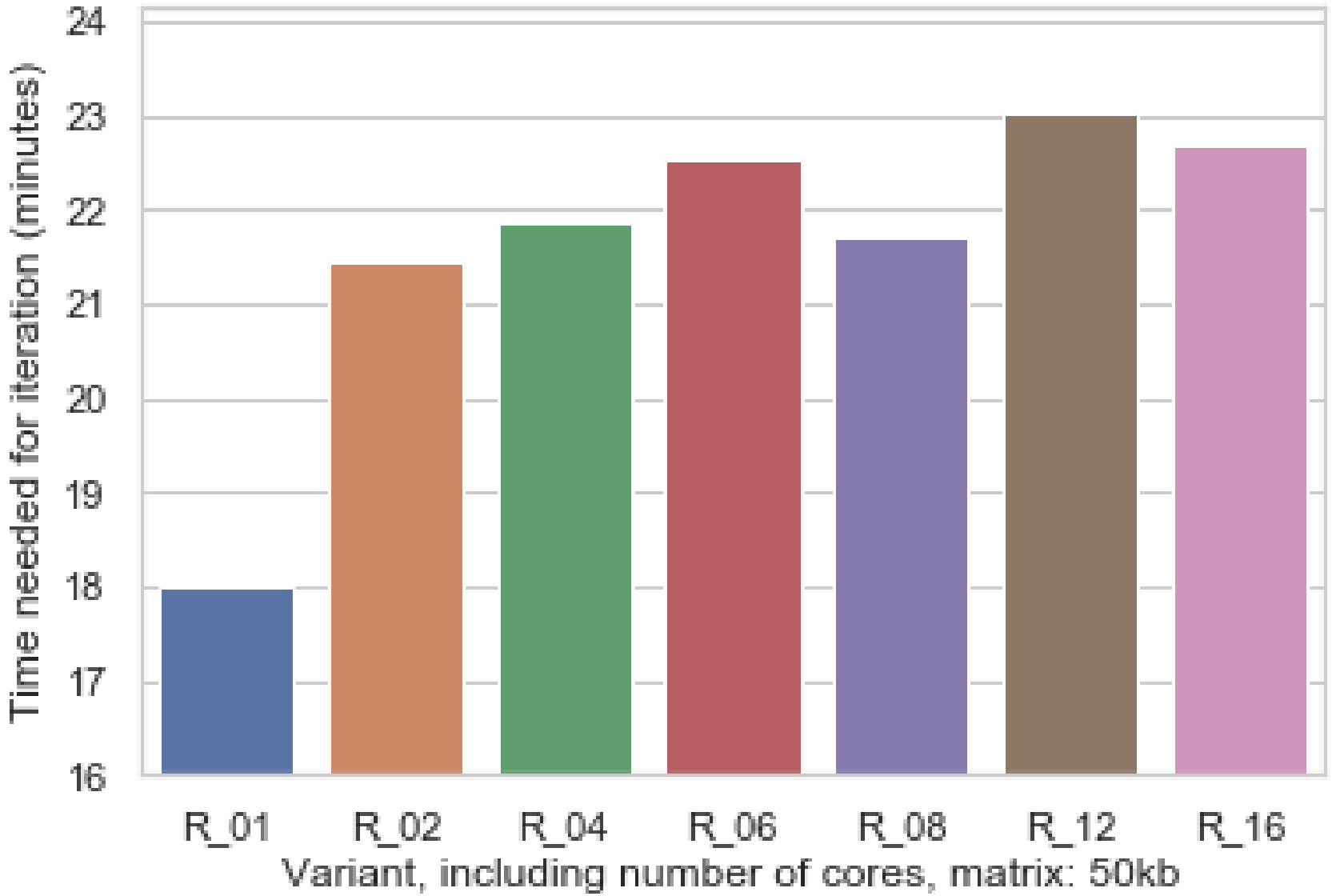
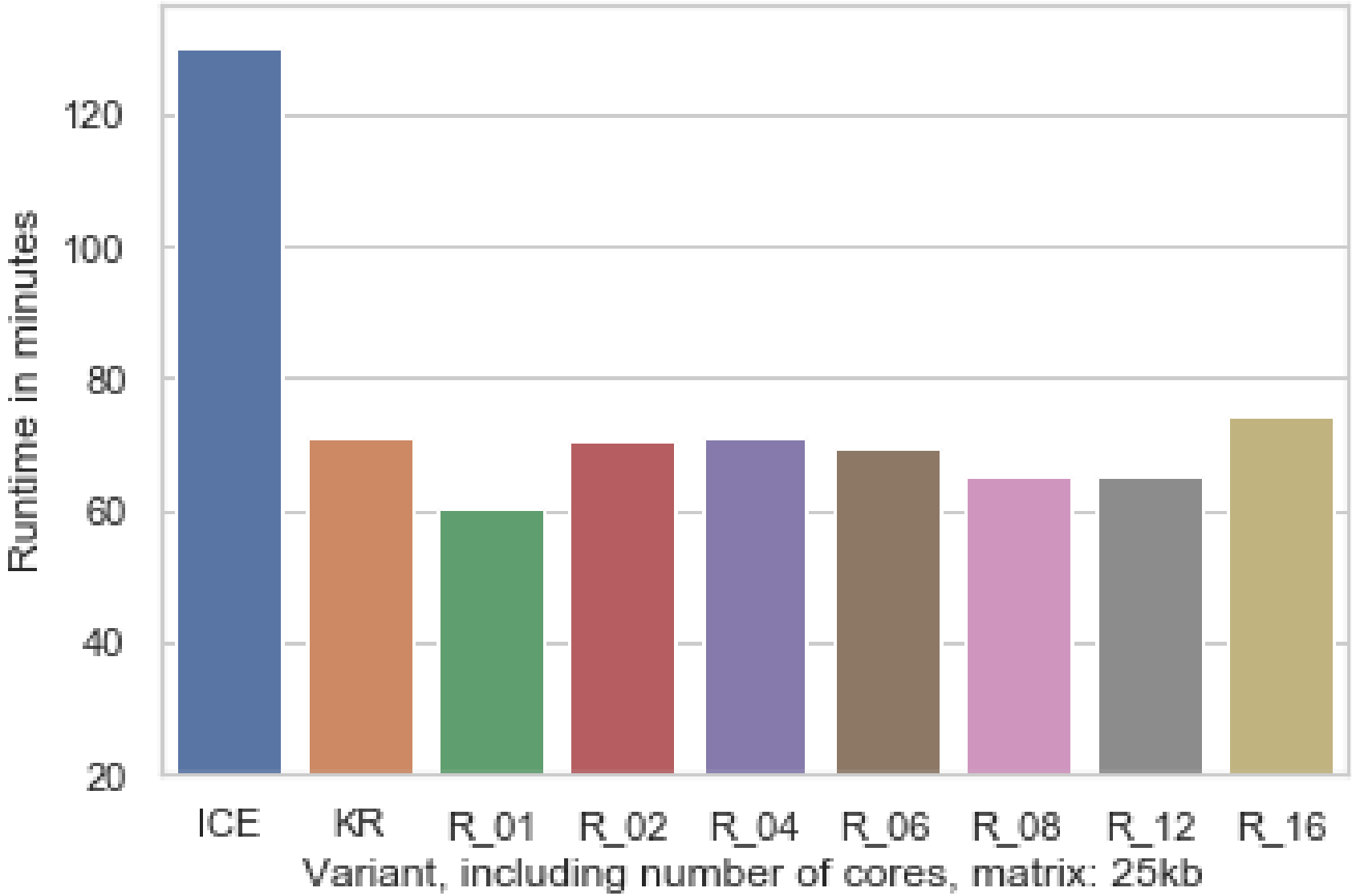


Multicore Runtime Length Comparison



Multicore Memory Comparison

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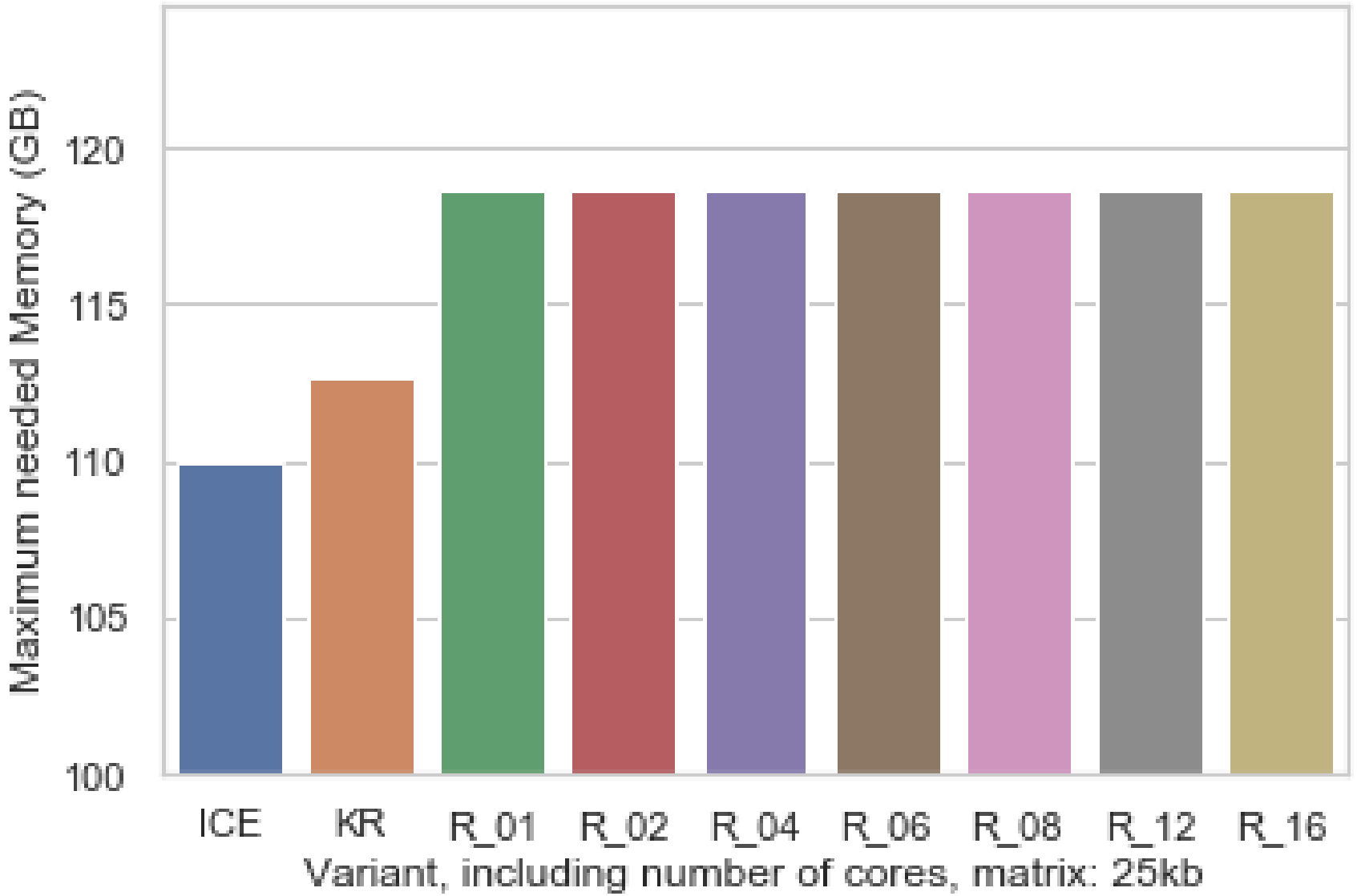
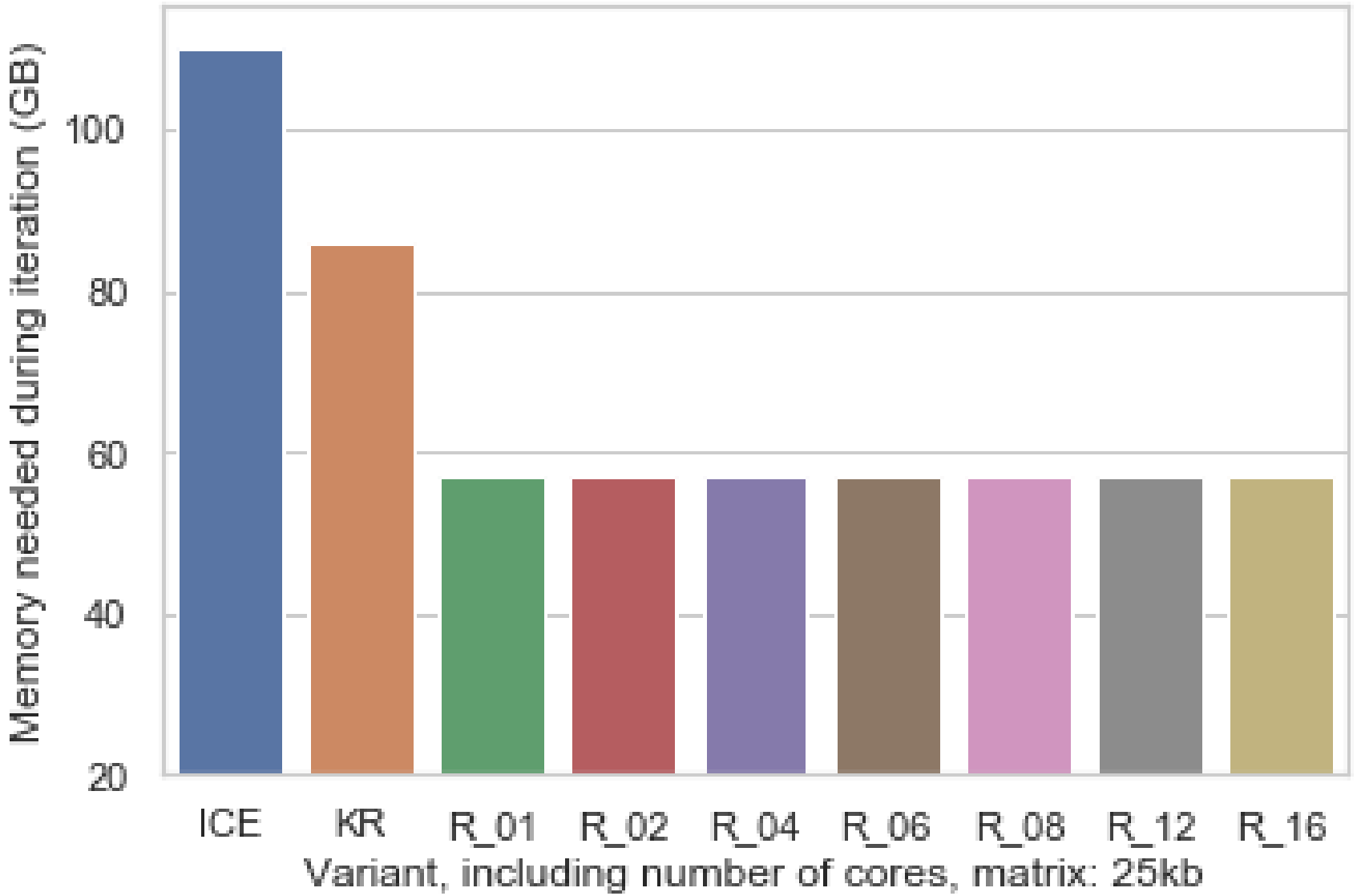
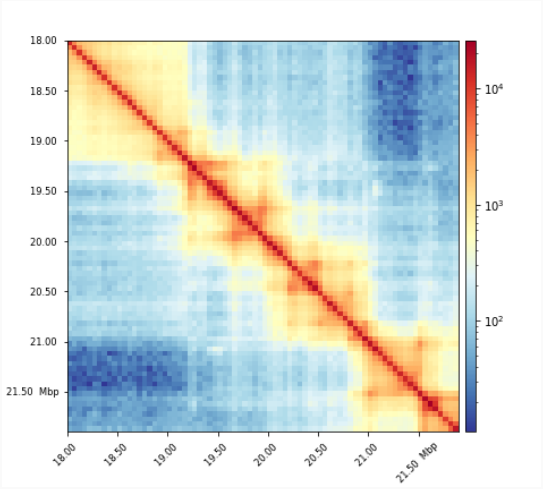


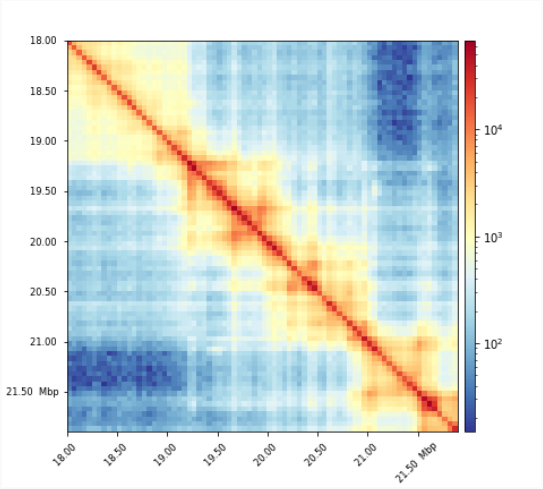
Multicore Memory Comparison



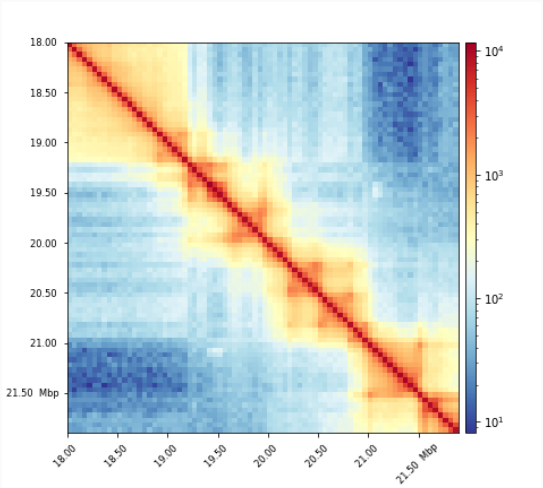
Comparison of Results



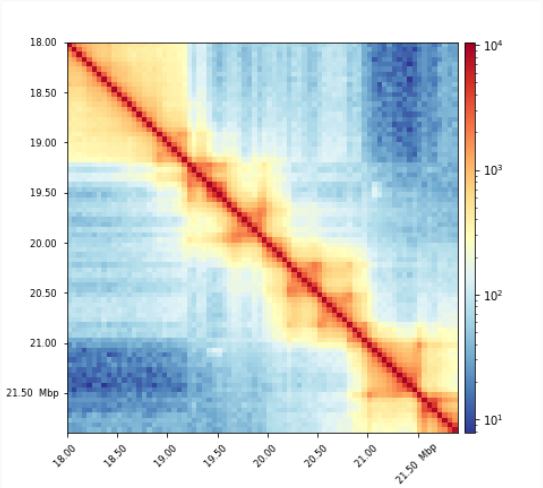
(a) Uncorrected



(b) RUST



(c) KR



(d) ICE

Content

Conclusion Regarding the Integration of RUST

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- Test the alternatives more

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- Better integration should be possible

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- Test the alternatives more
- Better integration should be possible
- All in all: Went better than expected

Conclusion Regarding Computation Comparisons

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- Reduction of memory usage during correction achieved

Conclusion Regarding Computation Comparisons

- Reduction of memory usage during correction achieved
- Reduction of runtime achieved

Conclusion Regarding Computation Comparisons

- Reduction of memory usage during correction achieved
- Reduction of runtime achieved
- Parallelism does not offer significant benefits yet

Remaining Questions

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- Writing Code for faster parallelism

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- Speedup when parallelizing more

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- Pure implementations needing even less memory?

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- Speedup when parallelizing more
- Pure implementations needing even less memory?
- Is KR faster for bigger Matrices?

Content

Sources i

- S. Wingett, P. Ewels, M. Furlan-Magaril, T. Nagano, S. Schoenfelder, P. Fraser, and S. Andrews, "Hicup: pipeline for mapping and processing hi-c data," *F1000Research*, vol. 4, 2015.
- M. Imakaev, G. Fudenberg, R. P. McCord, N. Naumova, A. Goloborodko, B. R. Lajoie, J. Dekker, and L. A. Mirny, "Iterative correction of hi-c data reveals hallmarks of chromosome organization," *Nature methods*, vol. 9, no. 10, p. 999, 2012.

Sources ii

- "Rust comparison with c." `https://benchmarksgame-team.pages.debian.net/benchmarksgame/fastest/rust.html`, 2019. **accessed 2019-06-26.**
- "Rust comparison with c++." `https://benchmarksgame-team.pages.debian.net/benchmarksgame/fastest/rust-gpp.html`, 2019. **accessed 2019-06-26.**

Sources iii

- G. Li, L. Cai, H. Chang, P. Hong, Q. Zhou, E. V. Kulakova, N. A. Kolchanov, and Y. Ruan, "Chromatin interaction analysis with paired-end tag (chia-pet) sequencing technology and application," *BMC Genomics*, vol. 15, p. S11, Dec 2014.

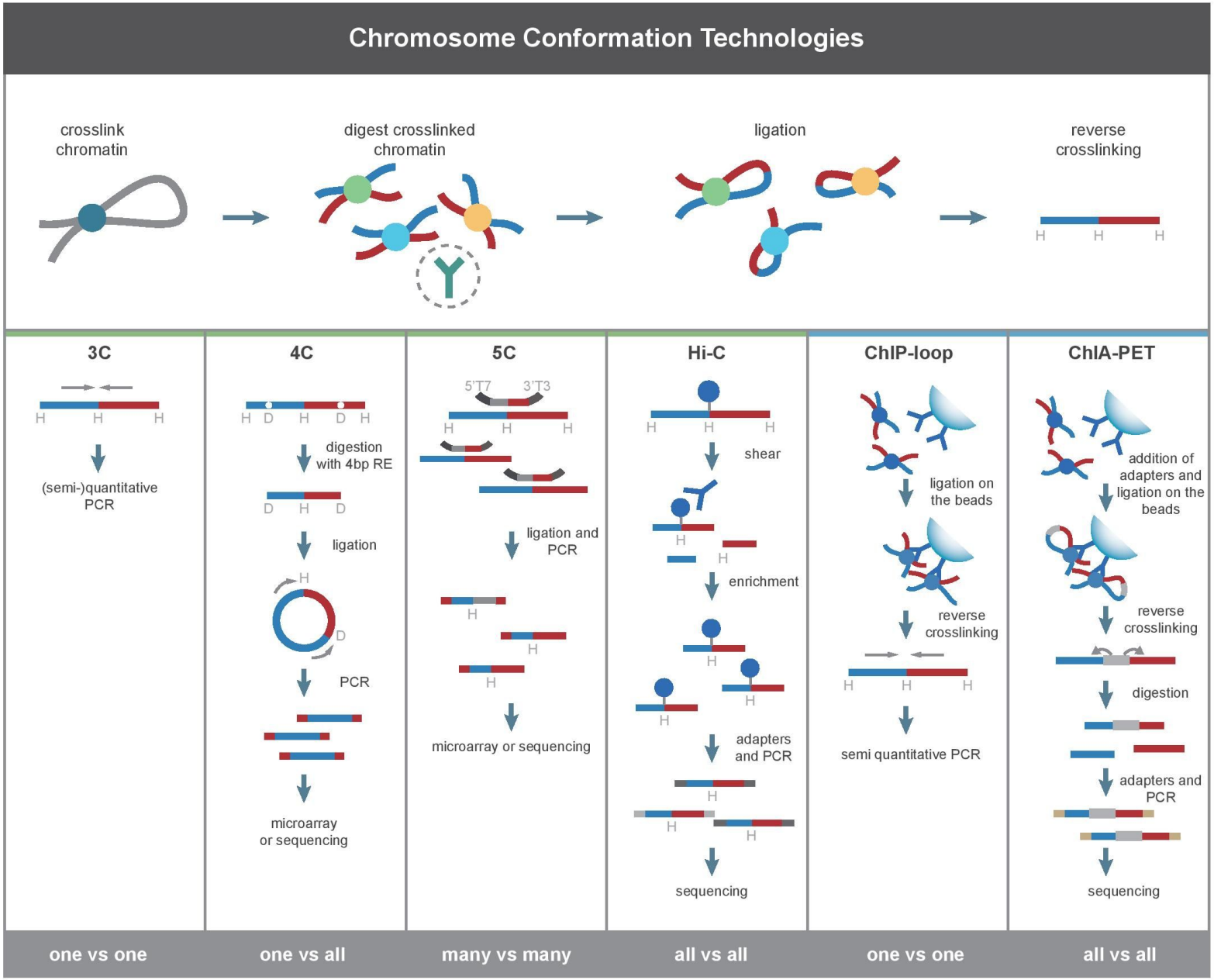
Chromosome Conformation Technologies
crosslink chromatin
digest crosslinked chromatin
ligation
reverse crosslinking
H H H
3C
(semi-)quantitative PCR
4C
H D H D H
digestion with 4bp RE
D H D
ligation
H
D
PCR
microarray or sequencing
5C
5'T7 3'T3
ligation and PCR
microarray or sequencing
Hi-C
shear
enrichment
adapters and PCR
sequencing
ChIP-loop
ligation on the beads
reverse crosslinking
semi quantitative PCR
ChIA-PET
addition of adapters and ligation on the beads
reverse crosslinking
digestion
adapters and PCR
sequencing
one vs one
one vs all
many vs many
all vs all
one vs one
all vs all

Image from [5].

ICE as described in Imakaev et al. 2012 [2]

Each iteration, compute:

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$$S_i = \sum_j W_{ij} \tag{3}$$

$$\Delta B_i = S_i / mean(S) \tag{4}$$

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$$W_{ij} = W_{ij} / \Delta B_i \Delta B_j \tag{5}$$

$$B_i = B_i \cdot \Delta B_i \tag{6}$$

Rust: Code Example

Code Example 1

```
1  fn main() {
2      let mut v = vec![];        // ---|
3      v.push("Hello");           // <--|
4                                 //    |
5      let x = &v[0];             // -| |
6                                 //  | |
7                                 //  | |
8      v.push("world");           // <X-|
9      println!("{}", x);         // -| |
10 }                              // ---|
```

Rust: Code Example

Output Nr. 1

```
error[E0502]: cannot borrow `v` as mutable because it is
also borrowed as immutable
 --> src/main.rs:5:5
  |
5 |     let x = &v[0];
  |             - immutable borrow occurs here
8 |     v.push("world");
  |     ^^^^^^^^^^^^^^^ mutable borrow occurs here
9 |     println!("{}", x);
  |                    - immutable borrow later used here
```

Rust: Code Example

Code Example 2

```
1  fn main() {
2      let mut v = vec![];        // ---|
3      v.push("Hello");           // <--|
4                                 //    |
5      let x = &v[0];             // -| |
6      println!("{}", x);         // -| |
7                                 //    |
8      v.push("world");           // <--|
9      println!("{}", v[1]);      // <--|
10 }                              // ---|
```

Rust: Code Example

Output Nr. 2

```
Hello
world
```

Test Server Specification

Virtual Server Specification

Available Cores / Threads	16 / 32
Working Memory (RAM)	120 GByte

Processor Specification

Processor	Intel® Xeon® E5-2630V4
Number of Cores/Threads	10 / 20
Base/Turbo frequency	2.2 GHz / 3.1 GHz