RNA Secondary Structure Prediction using AlphaZ

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Committee

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Motivation

- AlphaZ
  - Research tool
  - Handling real life problems?

- RNA Secondary Structure Prediction
  - Evaluation of Internal loops: Takes the most time
  - Time complexity: N^4
  - Fast evaluation of internal loops: N^3 time complexity
    - Proposed by Lyngso et. al, in 1999
    - Implementation: No public release yet
    - Why?

Outline

- Why AlphaZ?
  - What is AlphaZ?
- Bio-informatics
  - RNA Secondary Structure Prediction
  - UNAFold
- C – Alphabets – C
  - Optimizations
  - Results
- Conclusions and Future work

Why AlphaZ?

- Processor Architectures are evolving rapidly
- Speed-up is no longer easy to achieve by following Moore's law
- Result
  - Parallel architectures
  - Multi-core processors
- Programming for these architectures
  - Is it easy?
  - How steep is the learning curve?

Why AlphaZ?

- Which is the best architecture for the algorithm?
- How many times do I implement the same algorithm?
- Will I have to learn new programming models and language extensions?
  - OpenMP, POSIX threads, MPI
  - CUDA, CTM, SSE, 3DNow!

Why AlphaZ?

- Answer

AlphaZ

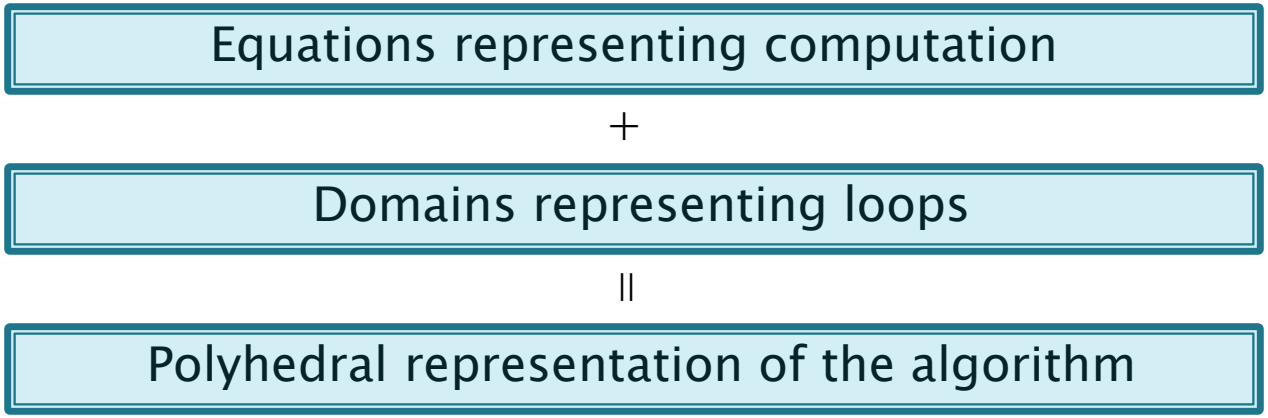
- Input language for AlphaZ: *Alphabets*
- Alphabets
  - Equational specification of the algorithm
  - Domains associated with the equations
- Alphabets programs
  - Architecture independent

What is AlphaZ?

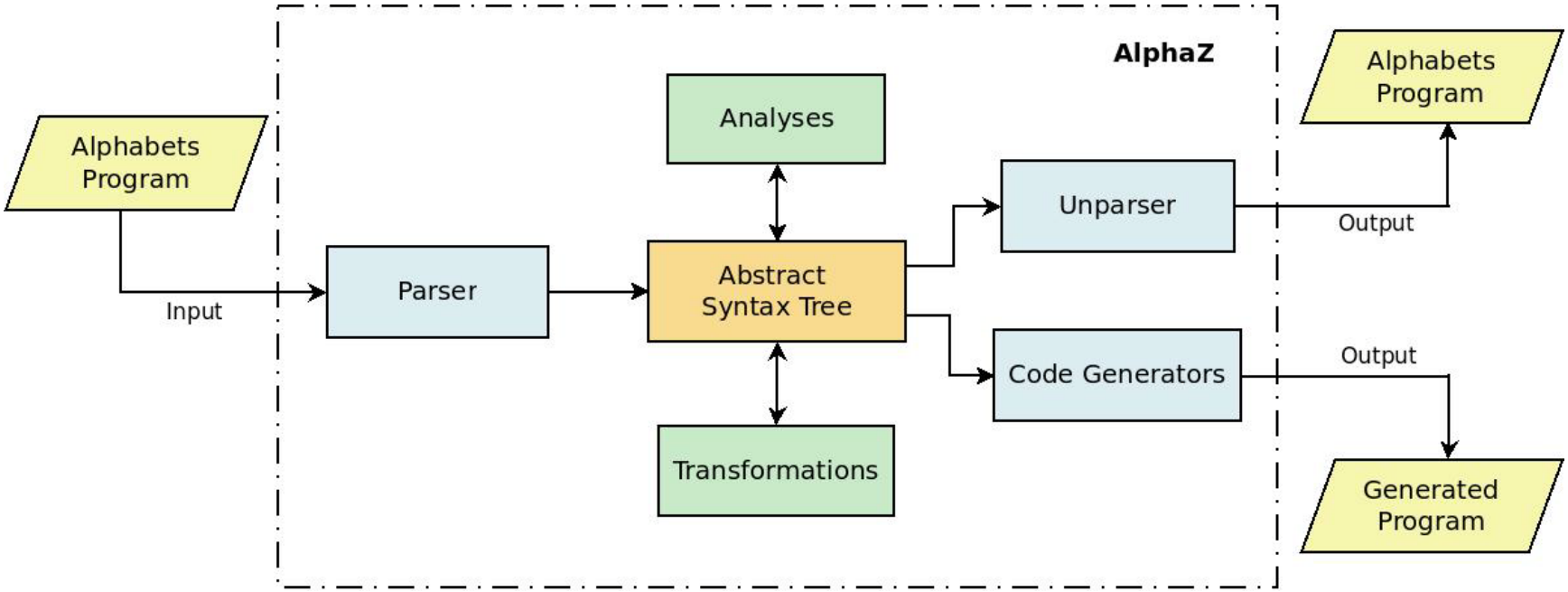
- AlphaZ
  - Functionality of polyhedral model
    - Transformations
    - Code generation
  - Uses COREquations
- COREquations
  - Implementation for polyhedral model framework
  - Provides foundation for AlphaZ
    - Basic polyhedral operations
    - Alphabets program parser

What is AlphaZ?

- Polyhedral Model
  - A representation of computations surrounded by affine loops as a mathematical model



What is AlphaZ?



AlphaZ system framework

What is AlphaZ?

- Write equational specifications in alphabets

```
[External function declarations]
affine systemName {sizeParameters | sizeParameterDomains}
given
    [data type] inputVars {domain};
returns
    [data type] outputVars {domain};
using
    [data type] localVars {domain};
through
    [Equations defining outputVars and localVars]
.
```

Structure of an alphabets program

What is AlphaZ?

- AlphaZ will take care of the rest
  - Currently with a little human feedback, which will eventually fade away
- Enables systematic optimizations
  - Transformations
  - Analyses
- Want code to realize your algorithm?
  - Answer: Code generators
  - Can even generate a wrapper program to test your algorithm quickly

Bio-informatics

- Applying statistics and computer science to molecular biology
- A rapidly advancing field
  - RNA folding
  - Protein folding
  - Sequence alignment
- Bio-informatics algorithms
  - New algorithms $\longrightarrow$ developed
  - Old algorithms $\longrightarrow$ improved
  - When will they be implemented?
  - Should a biologist or a mathematician write efficient code?

Bio-informatics

- Is performance programmer a solution?
  - Time to understand
  - Time to implement
  - Best target architecture?
  - Shelf-life of the code?

- Again, the answer is

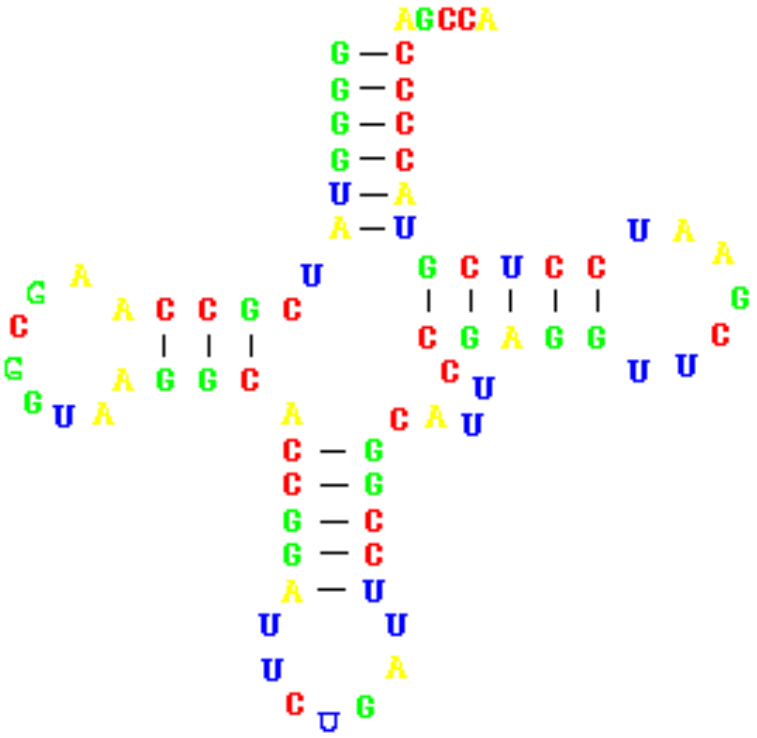
AlphaZ

RNA Secondary Structure Prediction

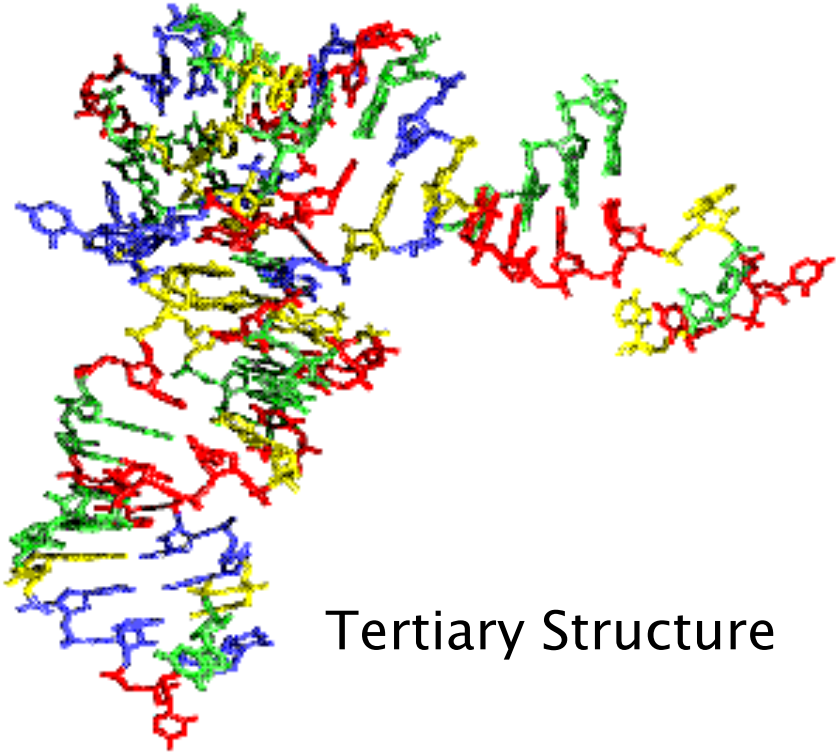
- RNA (Ribonucleic Acid)
  - A biological molecule consisting a sequence of nucleotide units.
- Four types of Nitrogen bases
  - Adenine (A)
  - Guanine (G)
  - Cytosine (C)
  - Uracil (U)
- Watson-crick base pairing
  - A – U
  - G – C

RNA Secondary Structure Prediction

RNA Sequence



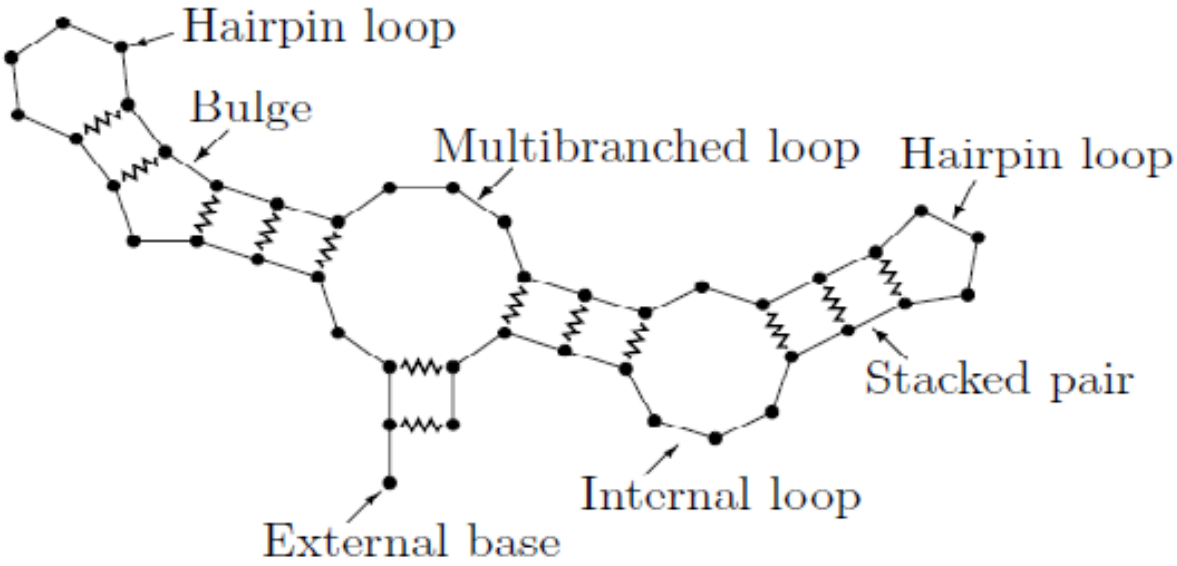
Secondary Structure



Tertiary Structure

SOURCE: mPi Informatik

RNA Secondary Structure Prediction



RNA Secondary Structure showing stacked pairs, hairpin loops, bulges, internal loops and multi-branched loops

SOURCE: An Improved algorithm for RNA Secondary Structure Prediction, Lyngso et. al.

RNA Secondary Structure Prediction

- Secondary structure on a RNA can be determined using
  - Experimental methods
  - Computational methods
- UNAFold
  - Computational package
  - Based on thermodynamic energy model

UNAFold

- UNAFold equations
  - Based of dynamic programming
  - Recurrence equations
- Three tables Q, Q', QM

  For a RNA sequence of length N with $1 \leq i < j \leq N$

$$Q(i,j) = \min \begin{cases} b + Q(i+1,j) \\ b + Q(i,j-1) \\ c + E_{ND}(i,j) + Q'(i,j) \\ QM(i,j) \end{cases}$$

UNAFold

$$Q'(i,j) = \begin{cases} \min \begin{cases} E_H(i,j) \\ E_S(i,j) + Q'(i+1,j-1) \\ QBI(i,j) \\ a + c + E_{ND}(j,i) + QM(i+1,j-1) \end{cases} & if\ i.j\ pair \\ \infty & otherwise \end{cases}$$

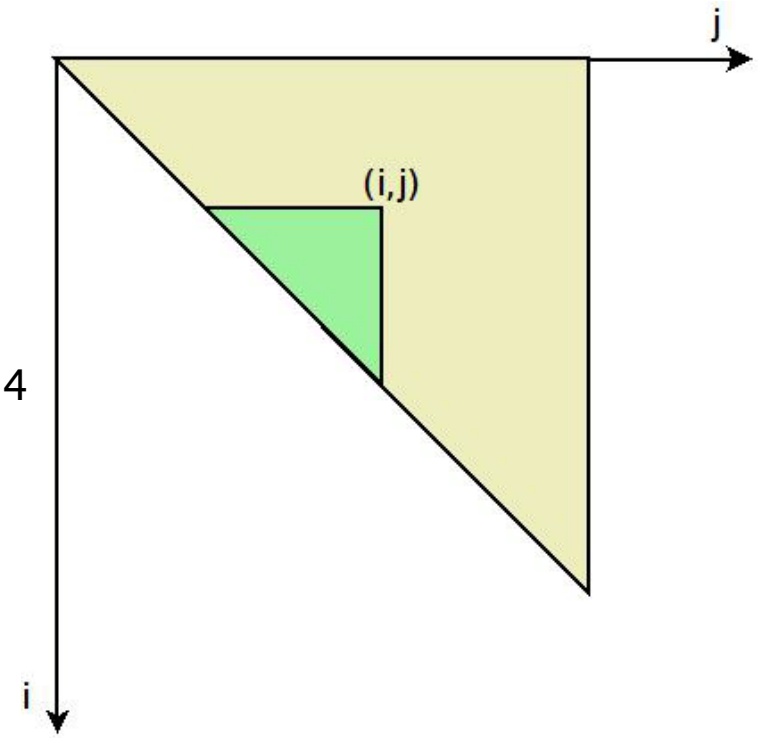
$$QM(i,j) = \min_{i+4 \leq k \leq j-5} \{Q(i,k-1) + Q(k,j)\}$$

QBI represents internal loops

UNAFold

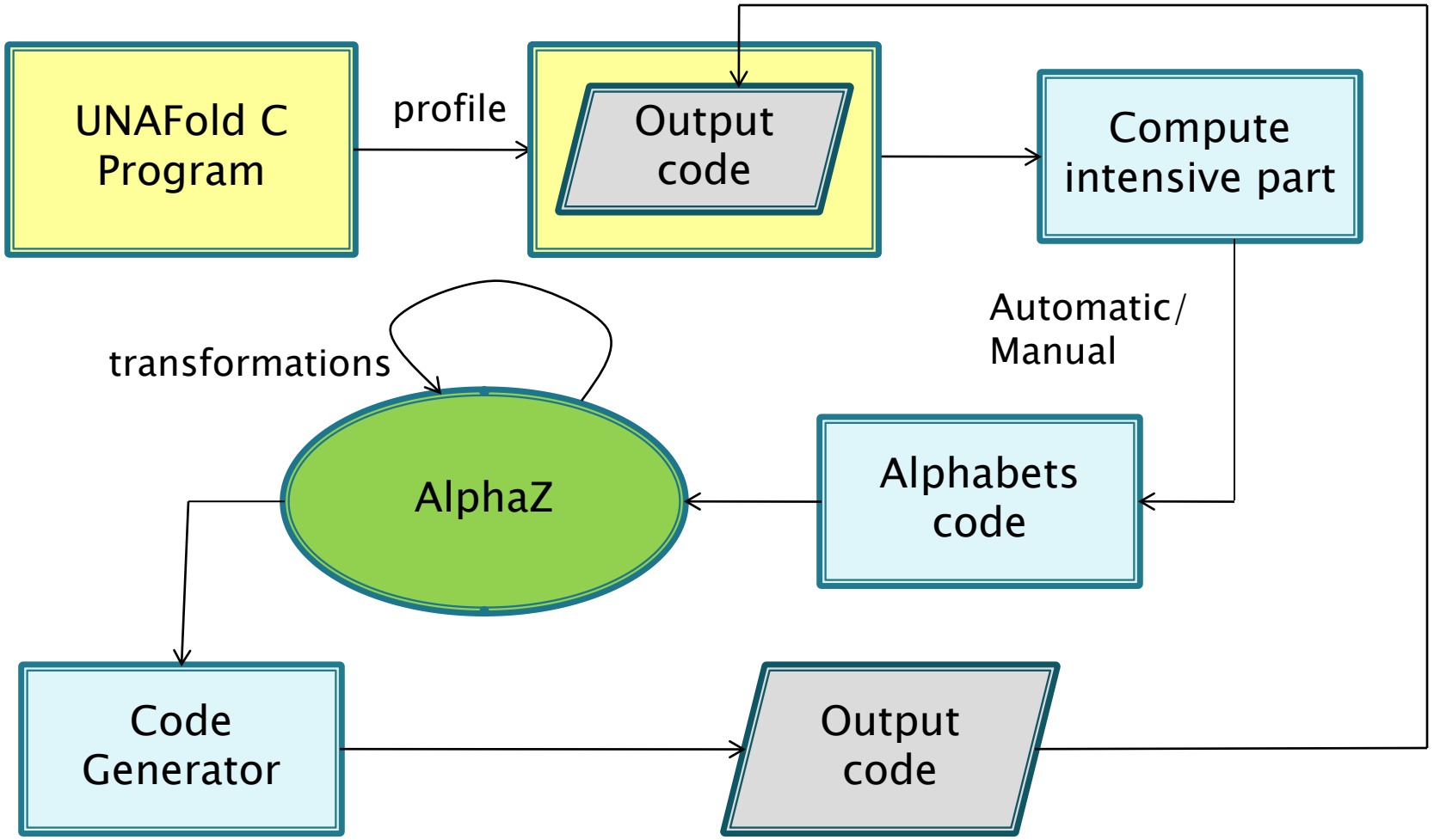
$$QBI(i,j) = \min_{4 \le d \le j-i-3,\, i<i'<j-d} \{E_{BI}(i,j,i',i'+d) + Q'(i',i'+d)\}$$

- To evaluate internal loops
  - Computational complexity: N^4



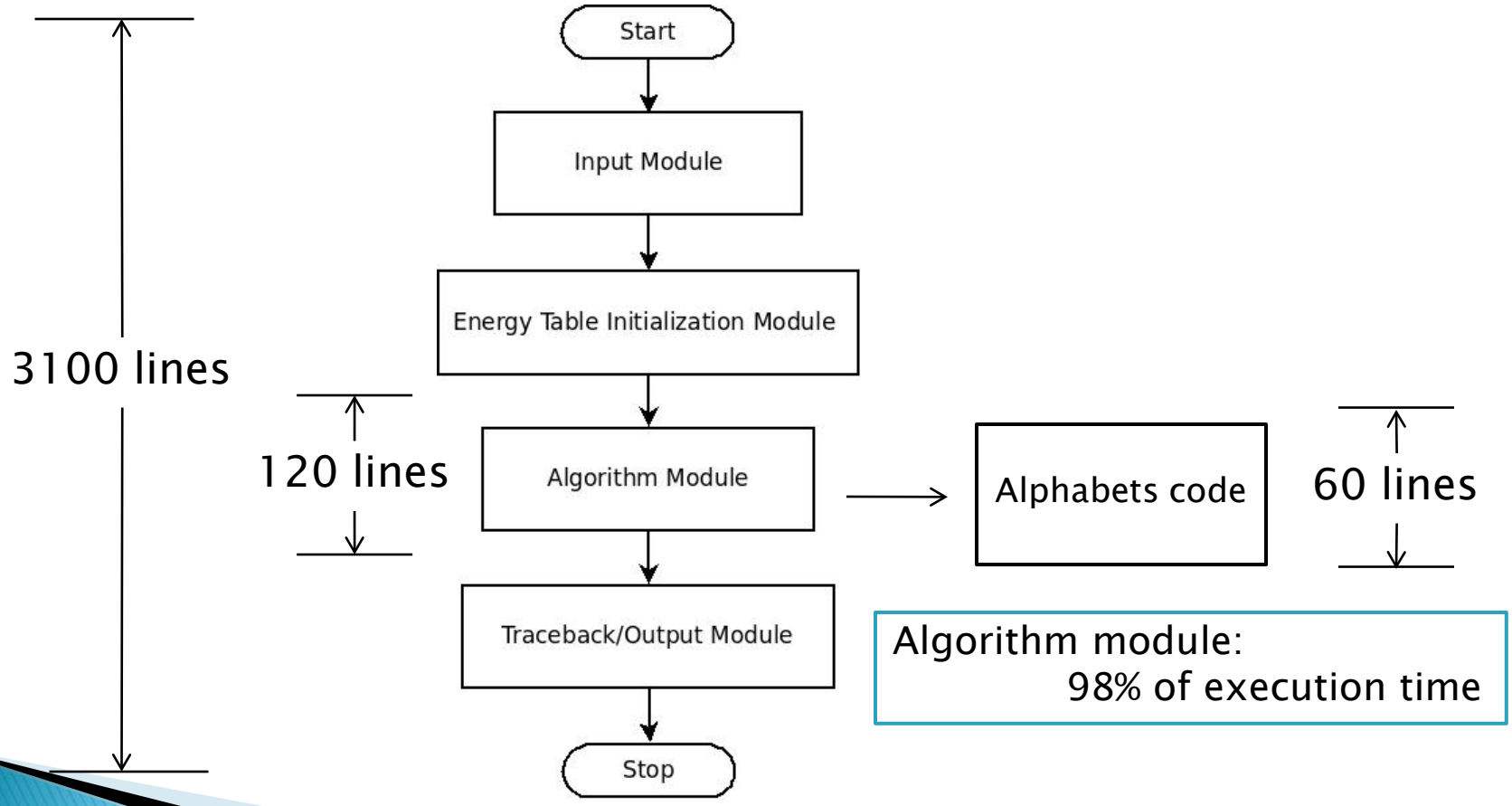
Domain of QBI

C – Alphabets – C



C – Alphabets – C

- UNAFold program can be modularized into



C – Alphabets – C

- Extracting equations

```
void foo (int N, int *A, int *B, int *C)
{
    int i;
    for (i = 1; i < N; i++)
    {
        if (i < 10)
        {
            C[i] = A[i] * B[i];
        }
        else
        {
            C[i] = A[i] + B[i];
        }
    }
}
```

C program

```
affine foo {N | N > 0}
given
    int A {i | 0 < i < N};
    int B {i | 0 < i < N};

returns
    int C {i | 0 < i < N};

through
    C[i] = case
               {| i < 10}:  A[i] * B[i];
               {| i >= 10}:  A[i] + B[i];
           esac;
.
```

Alphabets program

Optimizations

- Types of optimizations that can be done in AlphaZ
  - Exploiting re-use in reductions
  - Specifying schedule
  - Specifying processor allocation
  - Specifying memory mapping
  - Tiling
- Since AlphaZ is still in development the scope of all these optimizations is limited

Optimizations

- Currently, WriteC is the most functional code generator in AlphaZ
- Limitations of WriteC
  - Demand-driven code generator
  - Since its demand-driven, user cannot give a schedule to WriteC
  - WriteC is inherently sequential
    - Hence, processor allocation does not come into the scenario
  - Uses its own default memory map
    - User cannot change the memory map when using WriteC
  - No tiling, since its demand-driven

Optimizations

- Exploit re-use in the QBI term
- N^4 time complexity
- Goal
  - N^3 time complexity
- This result has already been deduced by Lyngso et. al.
- AlphaZ approach
  - Systematic

Optimizations

- The QBI term

$$QBI(i,j) = \min_{i'}\{E_{BI}(i,j,i',i'+d) + Q'(i',i'+d)\}$$

where

$$E_{BI}(i,j,i',i'+d) = Asym(i'-i-1, j-i'-d-1)$$

$$+E_S(i',i'+d)$$

- QBI term has double reduction
- To expose the re-use
  - Split the E_{BI} term
  - Decompose double reduction
  - Factor out the invariant terms
  - Detect the scan

Manually

ReductionDecomposition

FactorOutFromReduction

SimplifyingReductions

Optimizations

- Final equations.

$$QBI(i,j) = E_S(i,j) + \min_{4 \le d \le j-i-3} \{X(i,j,d)\}$$

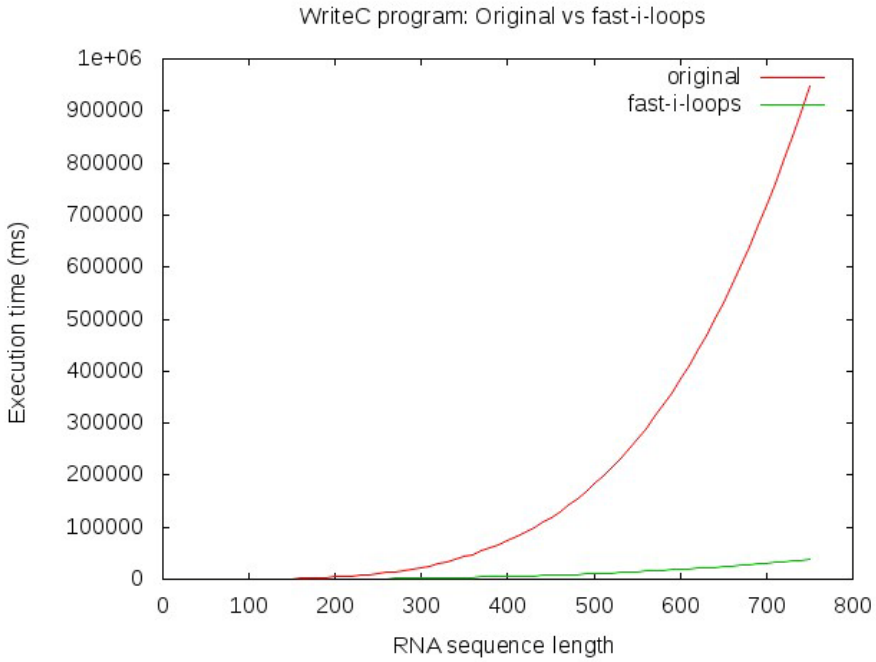
where

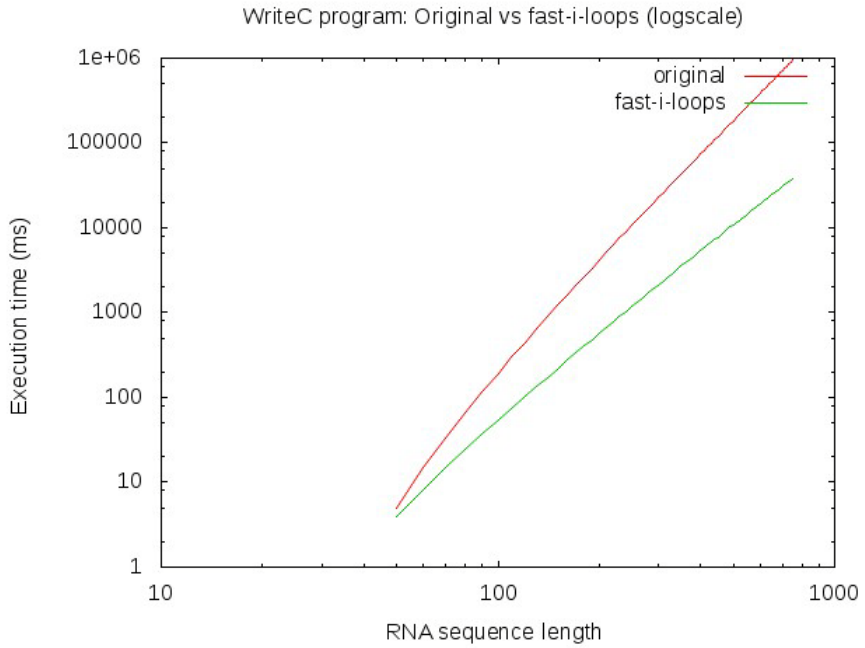
$$X(i,j,d) = S_P(j-i-d-2) + Y(i,j,d)$$

and

$$Y(i,j,d) = \min \left\{ \begin{array}{l} Y(i+1,j-1,d) \\ \\ \min\limits_{i+1<i'<j-d-1} \left\{ \begin{array}{l} Asym(i'-i-1, j-i'-d-1) \\ +E_S(i', i'+d) \\ +Q'(i', i'+d) \end{array} \right\} \end{array} \right.$$

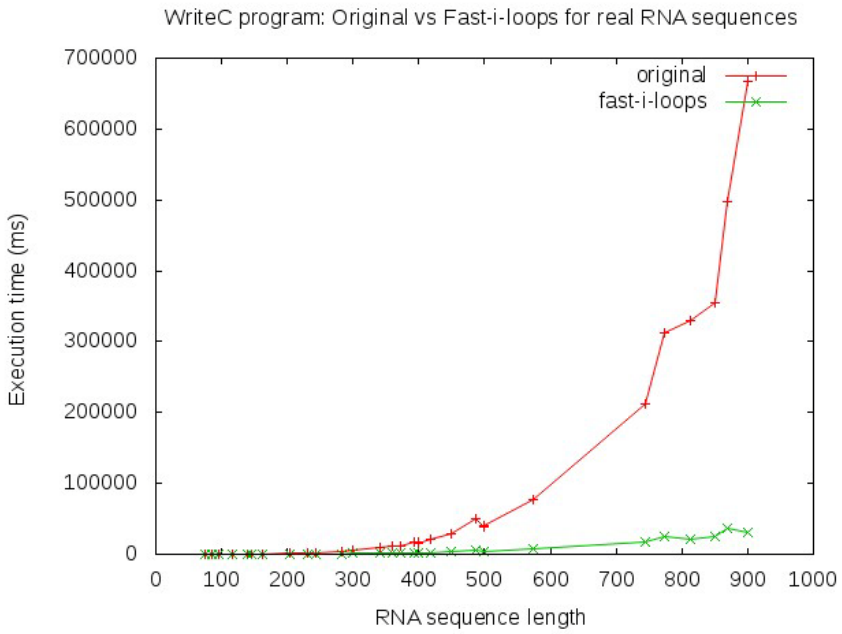
Results

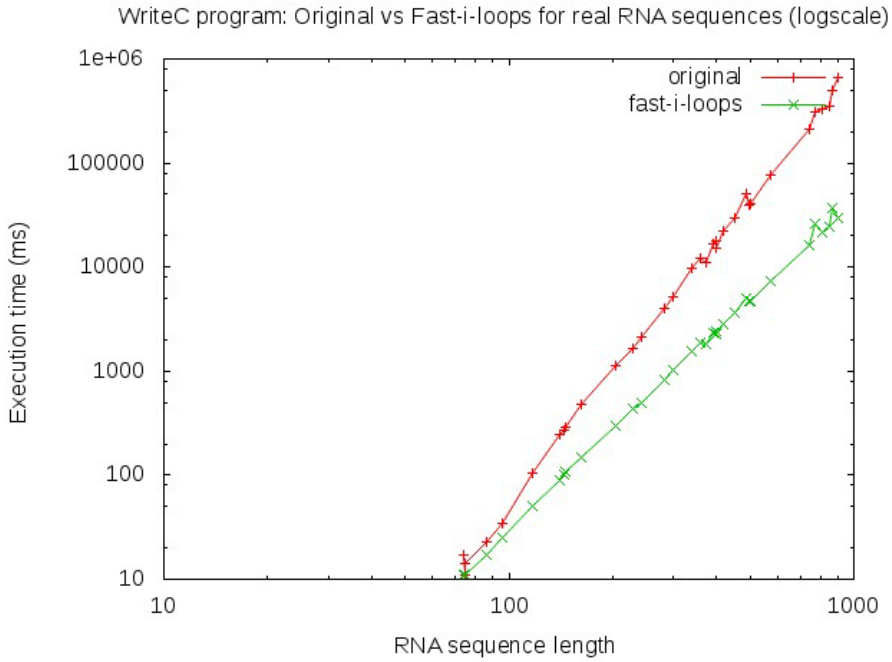




Execution time comparison between original and fast-i-loops version generated by AlphaZ

Results





Execution time comparison between original and fast-i-loops version generated by AlphaZ for real RNA sequences

Conclusions

- Programming using equations is beneficial
  - AlphaZ tool provides the platform
- AlphaZ can handle real life applications
  - Our work provides justification
- Forms a base for future optimizations

Future Work

- As AlphaZ develops, we get
  - More transformations
  - More code generators including parallel and tiled ones
- With these developments, UNAfold can take advantage of
  - Exploring schedules
  - Exploring memory maps
  - Exploring processor allocations
  - Exploring optimal tile sizes

Thank you

- Questions?

Optimizations

- Derivation
  - Split E_{BI} term into constituents.

$$QBI(i,j) = \min_{4 \le d \le j-i-3,\, i<i'<j-d} \left\{ \begin{array}{l} Asym(i'-i-1, j-i'-d-1) \\ +S_P(j-i-d-2) \\ +E_S(i,j) \\ +E_S(i', i'+d) \\ +Q'(i', i'+d) \end{array} \right\}$$

  - Factor out the E_S term.

$$QBI(i,j) = E_S(i,j) + \min_{4 \le d \le j-i-3,\, i<i'<j-d} \left\{ \begin{array}{l} Asym(i'-i-1, j-i'-d-1) \\ +S_P(j-i-d-2) \\ +E_S(i', i'+d) \\ +Q'(i', i'+d) \end{array} \right\}$$

Optimizations

- Decompose the double reduction.

$$QBI(i,j) = E_S(i,j) + \min_{4 \le d \le j-i-3} \{X(i,j,d)\}$$

where

$$X(i,j,d) = \min_{i<i'<j-d} \left\{ \begin{array}{l} Asym(i'-i-1, j-i'-d-1) \\ +S_P(j-i-d-2) \\ +E_S(i', i'+d) \\ +Q'(i', i'+d) \end{array} \right\}$$

- Factor out the S_P term.

$$X(i,j,d) = S_P(j-i-d-2) + \min_{i<i'<j-d} \left\{ \begin{array}{l} Asym(i'-i-1, j-i'-d-1) \\ +E_S(i', i'+d) \\ +Q'(i', i'+d) \end{array} \right\}$$

Optimizations

- Replace reduction term by *Y*.

$$X(i,j,d) = S_P(j-i-d-2) + Y(i,j,d)$$

where

$$Y(i,j,d) = \min_{i<i'<j-d} \left\{ \begin{array}{l} Asym(i'-i-1, j-i'-d-1) \\ +E_S(i', i'+d) \\ +Q'(i', i'+d) \end{array} \right\}$$

- Scan in *Y* along *(i+j)*.

$$Y(i,j,d) = \min \left\{ \begin{array}{l} Y(i+1, j-1, d) \\ \\ \min\limits_{i+1<i'<j-d-1} \left\{ \begin{array}{l} Asym(i'-i-1, j-i'-d-1) \\ +E_S(i', i'+d) \\ +Q'(i', i'+d) \end{array} \right\} \end{array} \right.$$

Challenges faced

- Determining exact domains for the equations
- Memory indexing issues
  - Original code: (i-1) * (N-1) + (j-1)
  - Generated code: i*N + j
- No Pre-processor directives
  - Work around: Use external functions to return the values defined using pre-processor directive #define
- Compilation problems
  - Conflicting macros between the re-use code and generated code