Weighted Finite-State Transducers in Computational Biology

Corinna Cortes
Google Research
corinna@google.com

Mehryar Mohri
Courant Institute
mohri@cs.nyu.edu

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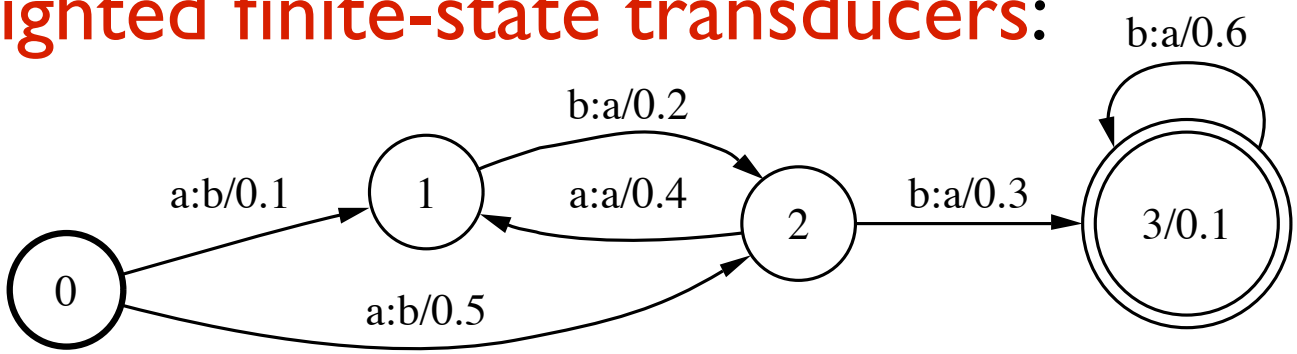
This Tutorial

- Weighted finite-state transducers and software library (FSM Library)
- Pairwise alignments for bioinformatics
- Kernels for computational biology

General Definitions

- Weighted finite-state transducers:



- Kernels: similarity measures between vectors, sequences or other structures.
  - Efficient computation of inner products in high-dimensional feature spaces.
  - Extensive use in modern machine learning.
  - Must satisfy a mathematical requirement (Mercer's condition).

Example

- Problem: find the *n* best pairwise alignments between two very large sets of sequences (e.g., |set| > 10,000).
- Example:

S1	S2
a b a a b b	b b b a a a b
a b b a a a	a a b b a a b b
a b b b a a b	a a b b b a a a
b b b a b a	b a b b b a b
	b a a b b a a

ϵ a ϵ b b a a a

a a b b b a a a

Algorithms and Software Library (FSM Library)

Software Libraries

- FSM Library: Finite-State Machine Library. General software utilities for building, combining, optimizing, and searching weighted automata and transducers.

  http://www.research.att.com/sw/tools/fsm/

- GRM Library: Grammar Library. General software collection for constructing and modifying weighted automata and transducers representing grammars and statistical language models.

  http://www.research.att.com/sw/tools/grm/

FSM Library

- The FSM utilities construct, combine, minimize, and search *weighted finite-states machines* (FSMs).
  - User Program Level: Programs that read from and write to files or pipelines, *fsm(1)*:

```
fsmintersect in1.fsm in2.fsm >out.fsm
```

  - C(++) Library Level: Library archive of C(++) functions that implements the user program level, *fsm(3)*:

```
Fsm in1 =  FSMLoad("in1.fsm");
Fsm in2 = FSMLoad("in2.fsm");
Fsm out = FSMIntersect(fsm1, fsm2);
FSMDump("out.fsm", out);
```

- Definition Level: Specification of *labels*, of *costs*, and of types of FSM representations.

FSM File Types

- Textual format
  - automata/acceptor files,
  - transducer files,
  - symbols files.
- Binary format: *compiled* representation used by all FSM utilities.

Compiling, Printing, and Drawing FSMs

- Compiling
  - fsmcompile -s tropical -iA.syms <A.txt >A.fsm
  - fsmcompile -s log -iA.syms -oA.syms -t <T.txt >T.fsm
- Printing
  - fsmprint -iA.syms <A.fsm >A.txt
  - fsmprint -iA.syms -oA.syms <T.fsm | dot -Tps >T.ps
- Drawing
  - fsmdraw -iA.syms <A.fsm | dot -Tps >A.ps
  - fsmdraw -iA.syms -oA.syms <T.fsm | dot -Tps >T.ps

Weight Sets: Semirings

- A *semiring* $(\mathbb{K}, \oplus, \otimes, \overline{0}, \overline{1})$ is a ring that may lack negation.
  - sum: to compute the weight of a sequence (sum of the weights of the paths labeled with that sequence).
  - product: to compute the weight of a path (product of the weights of constituent transitions).

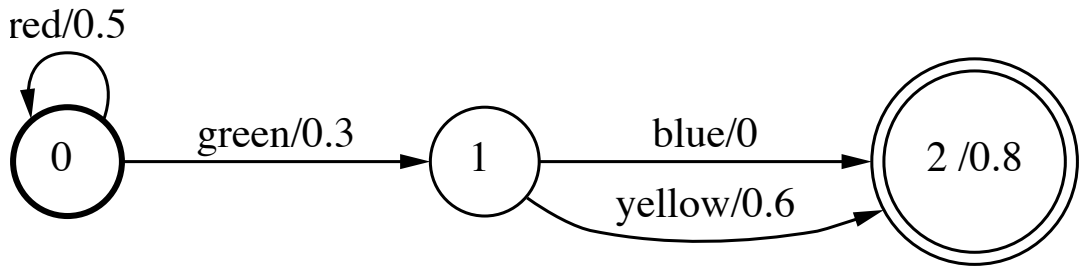
Semirings - Examples

Semiring	Set	$\oplus$	$\otimes$	$\overline{0}$	$\overline{1}$
Boolean	$\{0, 1\}$	$\vee$	$\wedge$	0	1
Probability	$\mathbb{R}_+$	$+$	$\times$	0	1
Log	$\mathbb{R} \cup \{-\infty, +\infty\}$	$\oplus_{\log}$	$+$	$+\infty$	0
Tropical	$\mathbb{R} \cup \{-\infty, +\infty\}$	$\min$	$+$	$+\infty$	0

with $\oplus_{\log}$ defined by: $x \oplus_{\log} y = -\log(e^{-x} + e^{-y})$.

Automata/Acceptors

- Graphical Representation (`A.ps`)



- Acceptor file (`A.txt`)

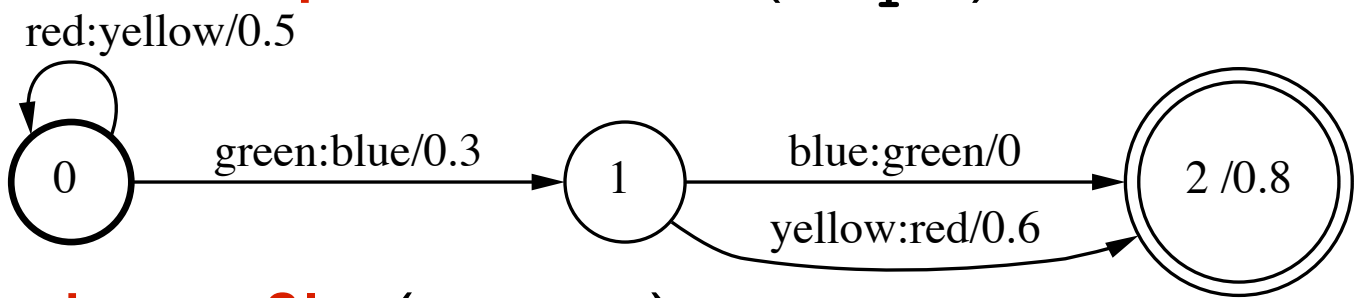
```
0   0    red      .5
0   1    green    .3
1   2    blue
1   2    yellow   .6
2   .8
```

- Symbols file (`A.syms`)

```
red      1
green    2
blue     3
yellow   4
```

Transducers

- Graphical Representation (`T.ps`)



- Transducer file (`T.txt`)

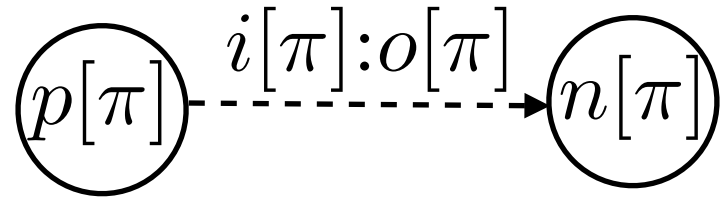
```
0   0    red      yellow   .5
0   1    green    blue     .3
1   2    blue     green
1   2    yellow   red      .6
2   .8
```

- Symbols file (`T.syms`)

```
red      1
green    2
blue     3
yellow   4
```

Paths - Definitions and Notation

- Path π
  - origin or previous state: $p[\pi]$
  - destination or next state: $n[\pi]$
  - input label: $i[\pi]$
  - output label: $o[\pi]$



- Sets of paths
  - $P(R_1, R_2)$: paths from $R_1 \subseteq Q$ to $R_2 \subseteq Q$.
  - $P(R_1, x, R_2)$: paths in $P(R_1, R_2)$ with input label *x*.
  - $P(R_1, x, y, R_2)$: paths in $P(R_1, x, R_2)$ with output label *y*.

General Definitions

- Alphabets: input Σ, output Δ .
- States: Q, initial states *I*, final states *F*.
- Transitions: $E \subseteq Q \times (\Sigma \cup \{\epsilon\}) \times (\Delta \cup \{\epsilon\}) \times \mathbb{K} \times Q$
- Weight functions:
  - initial: $\lambda : I \longrightarrow \mathbb{K}$
  - final: $\rho : F \longrightarrow \mathbb{K}$

Automata and Transducers - Definitions

- Automaton $A = (\Sigma, Q, I, F, E, \lambda, \rho)$

  $\forall x \in \Sigma^*,$

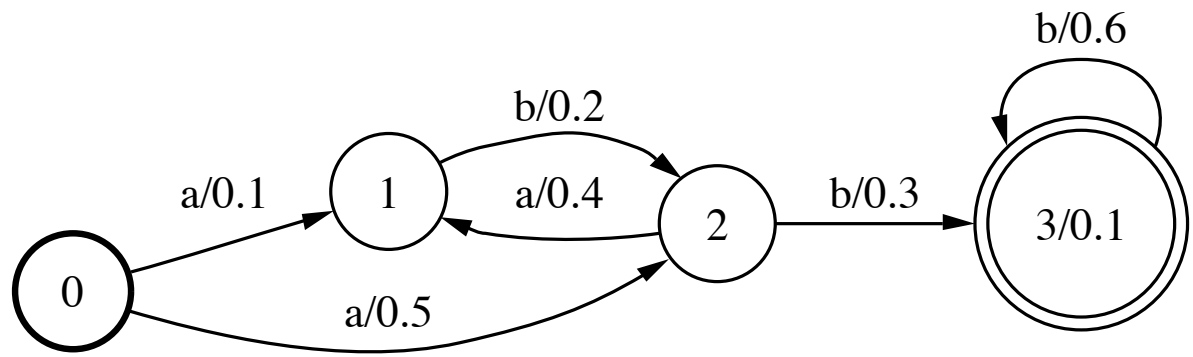
$$[\![A]\!](x) = \bigoplus_{\pi \in P(I,x,F)} \lambda(p[\pi]) \otimes w[\pi] \otimes \rho(n[\pi])$$

- Transducer $T = (\Sigma, \Delta, Q, I, F, E, \lambda, \rho)$

  $\forall x \in \Sigma^*, y \in \Delta^*,$

$$[\![T]\!](x, y) = \bigoplus_{\pi \in P(I,x,y,F)} \lambda(p[\pi]) \otimes w[\pi] \otimes \rho(n[\pi])$$

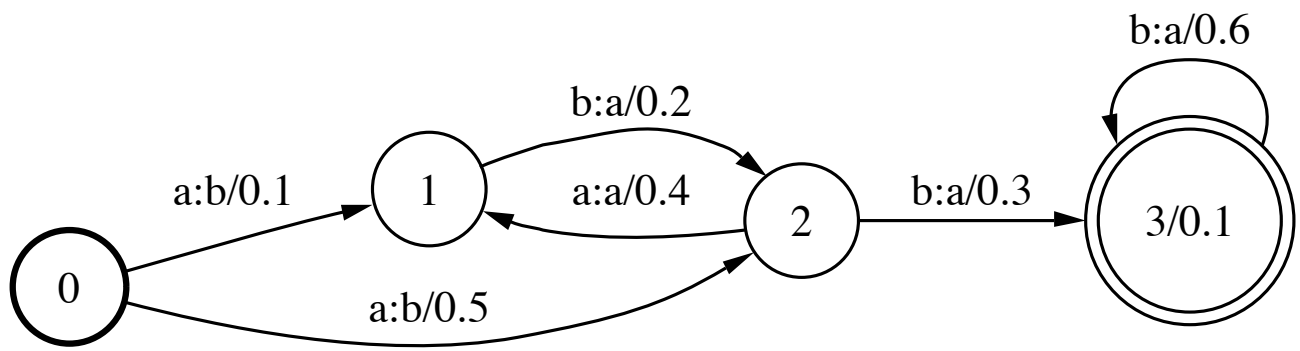
Weighted Automata



$[[A]](x) =$ Sum of the weights of all successful paths labeled with *x*

$$[[A]](abb) = .1 \times .2 \times .3 \times .1 + .5 \times .3 \times .6 \times .1$$

Weighted Transducers



$[[T]](x, y) =$ Sum of the weights of all successful paths with input *x* and output *y*

$$[[T]](abb, baa) = .1 \times .2 \times .3 \times .1 + .5 \times .3 \times .6 \times .1$$

Rational Operations

- Sum

$$[\![T_1 \oplus T_2]\!](x, y) = [\![T_1]\!](x, y) \oplus [\![T_2]\!](x, y)$$

- Product

$$[\![T_1 \otimes T_2]\!](x, y) = \bigoplus_{x=x_1 x_2, y=y_1 y_2} [\![T_1]\!](x_1, y_1) \otimes [\![T_2]\!](x_2, y_2)$$

- Closure

$$[\![T^*]\!](x, y) = \bigoplus_{n=0}^{\infty} [\![T]\!]^n(x, y)$$

- Conditions (on the closure operation): condition on *T*: e.g., weight of ϵ-cycles = $\overline{0}$ (*regulated transducers*), or semiring condition: e.g., $\overline{1} \oplus x = \overline{1}$ as with the tropical semiring (more generally *locally closed semirings*).

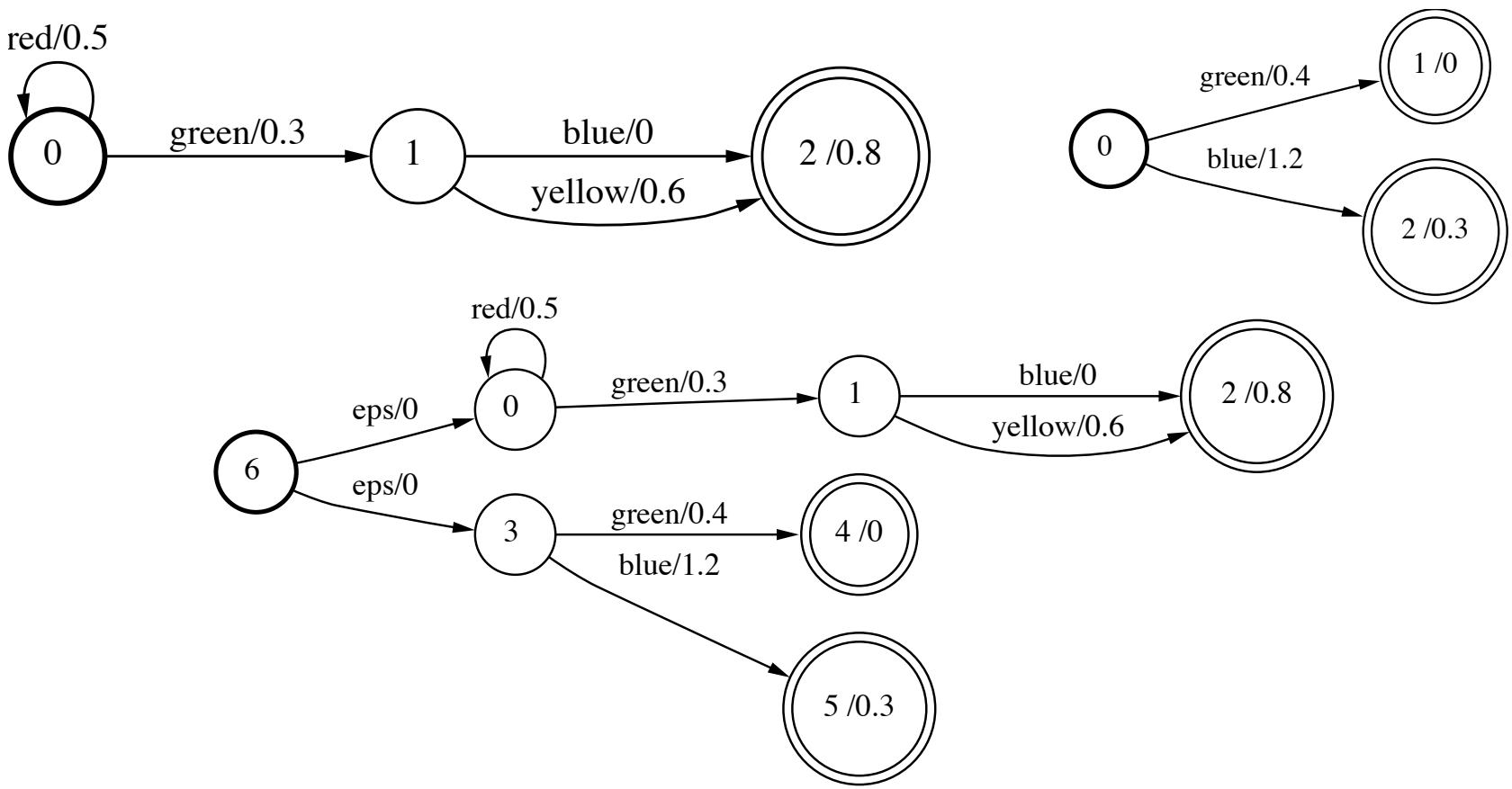
- Complexity and implementation:
  - linear-time complexity:

    $O((|E_1| + |Q_1|) + (|E_2| + |Q_2|))$ or

    $O(|Q| + |E|)$
  - lazy implementation.

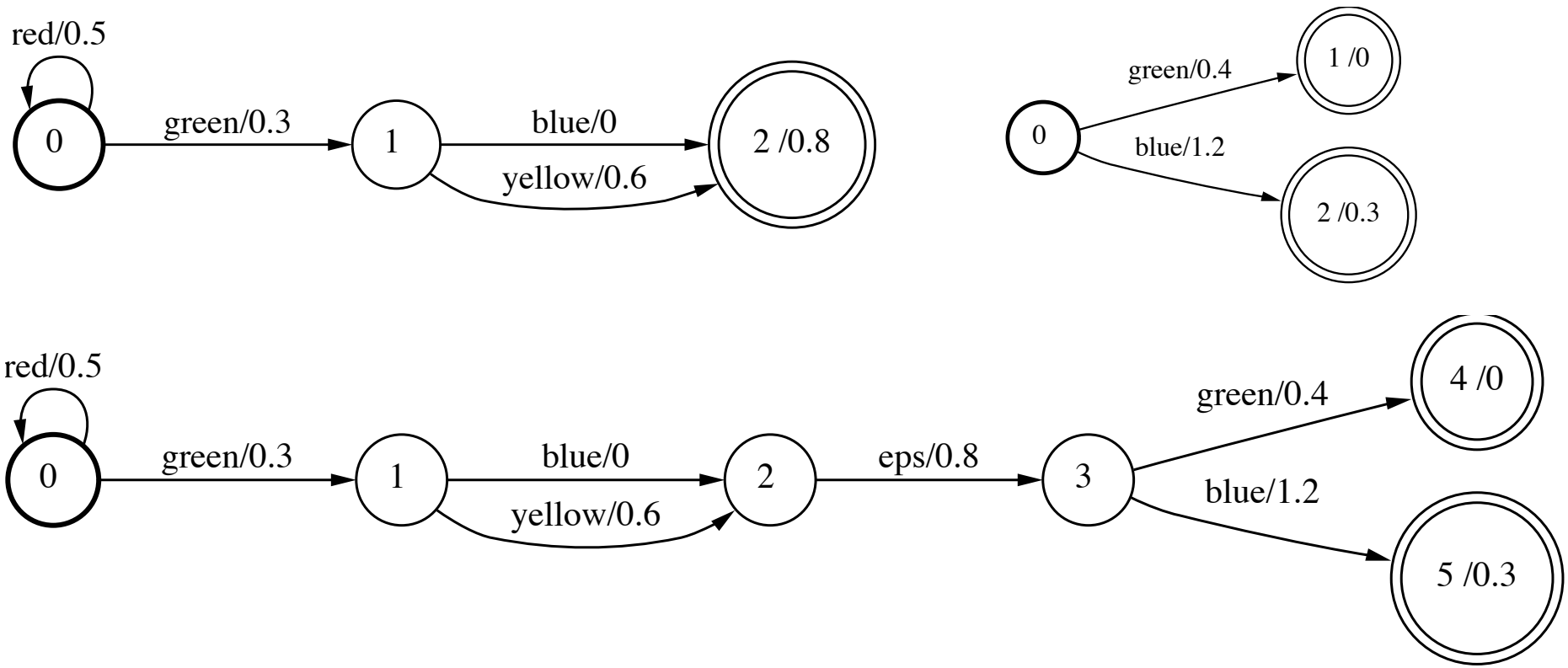
Sum - Illustration

- Program: fsmunion A.fsm B.fsm >C.fsm
- Graphical representation:



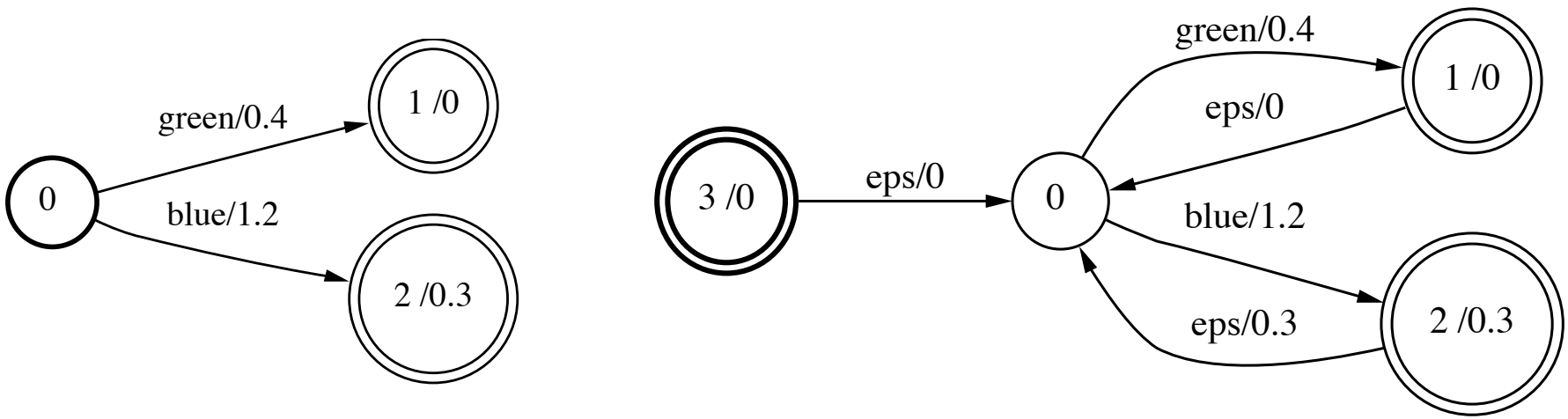
Product - Illustration

- Program: fsmconcat A.fsm B.fsm >C.fsm
- Graphical representation:



Closure - Illustration

- Program: fsmclosure B.fsm >C.fsm
- Graphical representation:



Elementary Unary Operations

- Reversal

$$[\![\widetilde{T}]\!](x, y) = [\![T]\!](\widetilde{x}, \widetilde{y})$$

- Inversion

$$[\![T^{-1}]\!](x, y) = [\![T]\!](y, x)$$

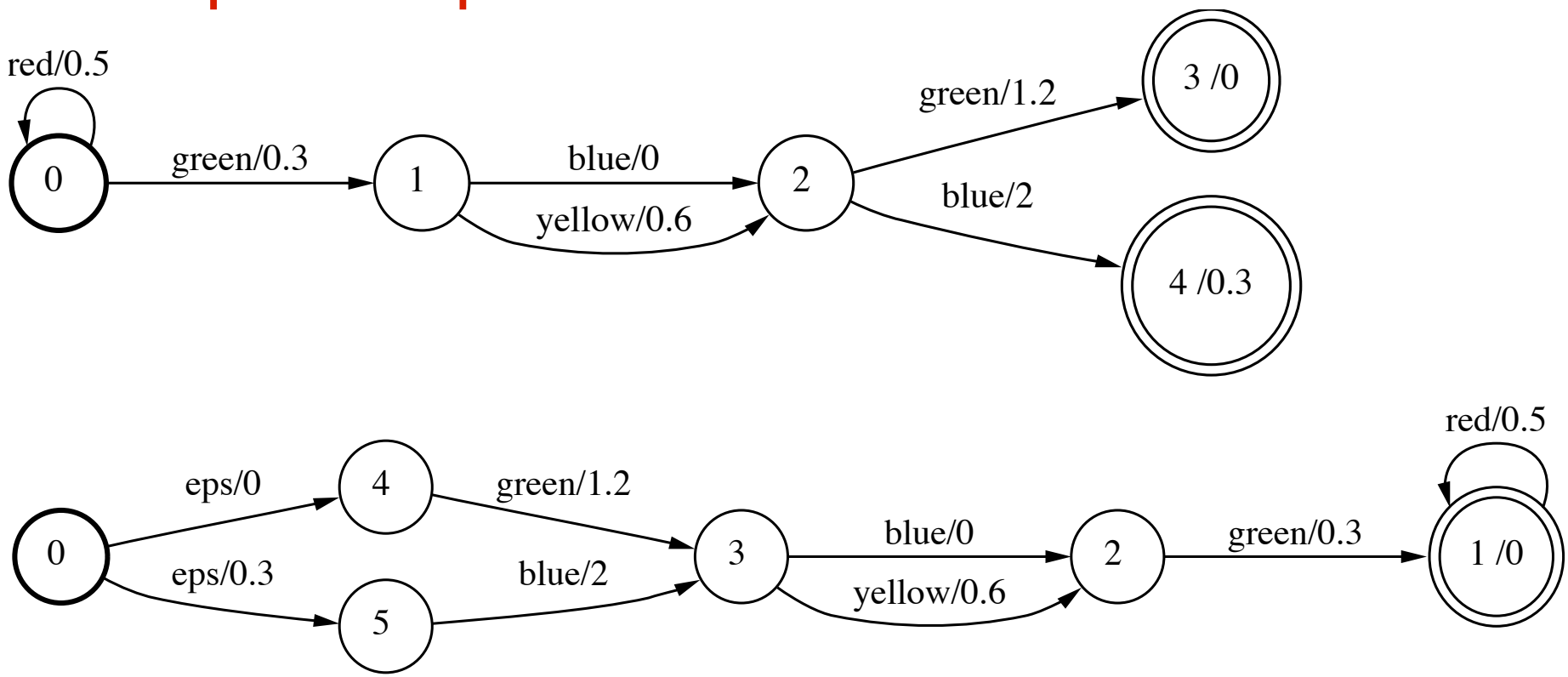
- Projection

$$[\![A]\!](x) = \bigoplus_{y} [\![T]\!](x, y)$$

- Linear-time complexity, lazy implementation (not for reversal).

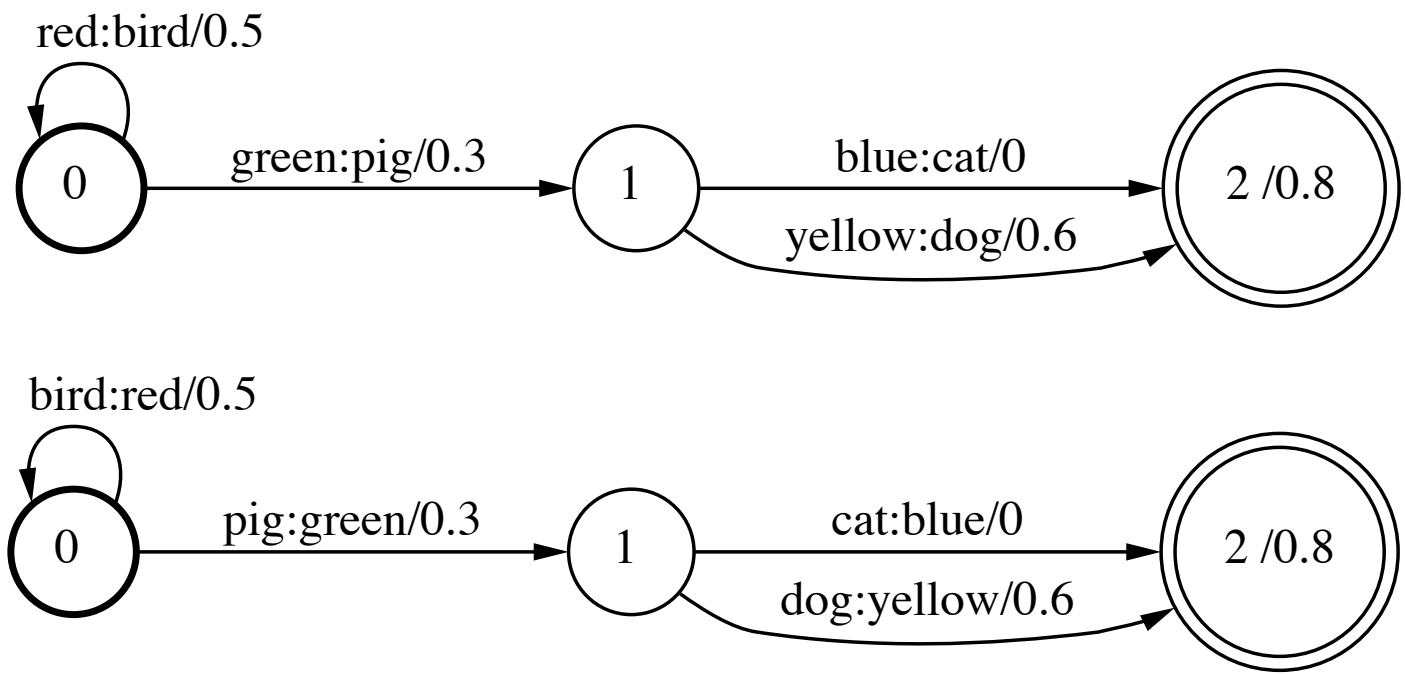
Reversal - Illustration

- Program: fsmreverse A.fsm >C.fsm
- Graphical representation:



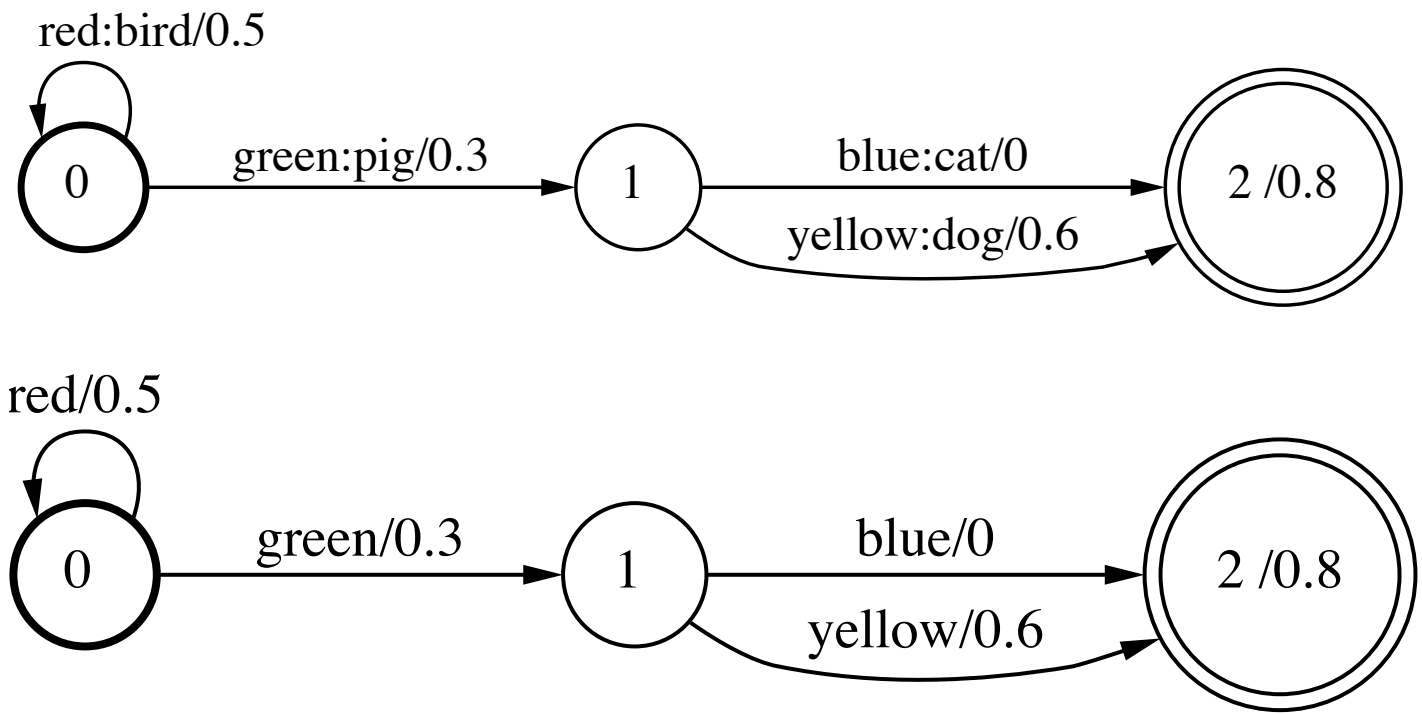
Inversion - Illustration

- Program: fsminvert A.fsm >C.fsm
- Graphical representation:



Projection - Illustration

- Program: fsmproject -I T.fsm >A.fsm
- Graphical representation:



Some Fundamental Binary Operations

(Pereira and Riley, 1997; Mohri et al. 1996)

- Composition ($(\mathbb{K}, \oplus, \otimes, \overline{0}, \overline{1})$ commutative)

$$[\![T_1 \circ T_2]\!](x, y) = \bigoplus_z [\![T_1]\!](x, z) \otimes [\![T_2]\!](z, y)$$

- Intersection ($(\mathbb{K}, \oplus, \otimes, \overline{0}, \overline{1})$ commutative)

$$[\![A_1 \cap A_2]\!](x) = [\![A_1]\!](x) \otimes [\![A_2]\!](x)$$

- Difference (A_2 unweighted and deterministic)

$$[\![A_1 - A_2]\!](x) = [\![A_1 \cap \overline{A_2}]\!](x)$$

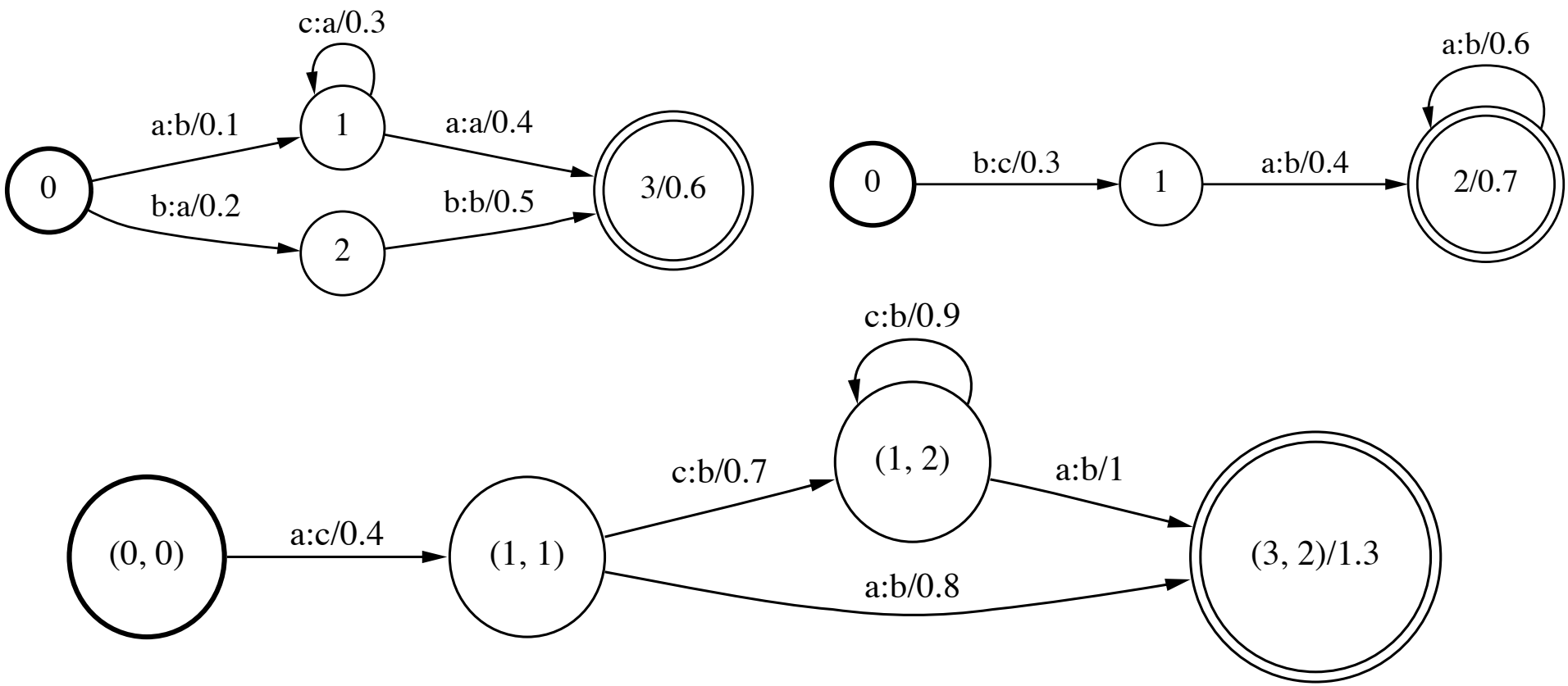
- Complexity and implementation:
  - quadratic complexity:

$$O((|E_1| + |Q_1|)(|E_2| + |Q_2|))$$

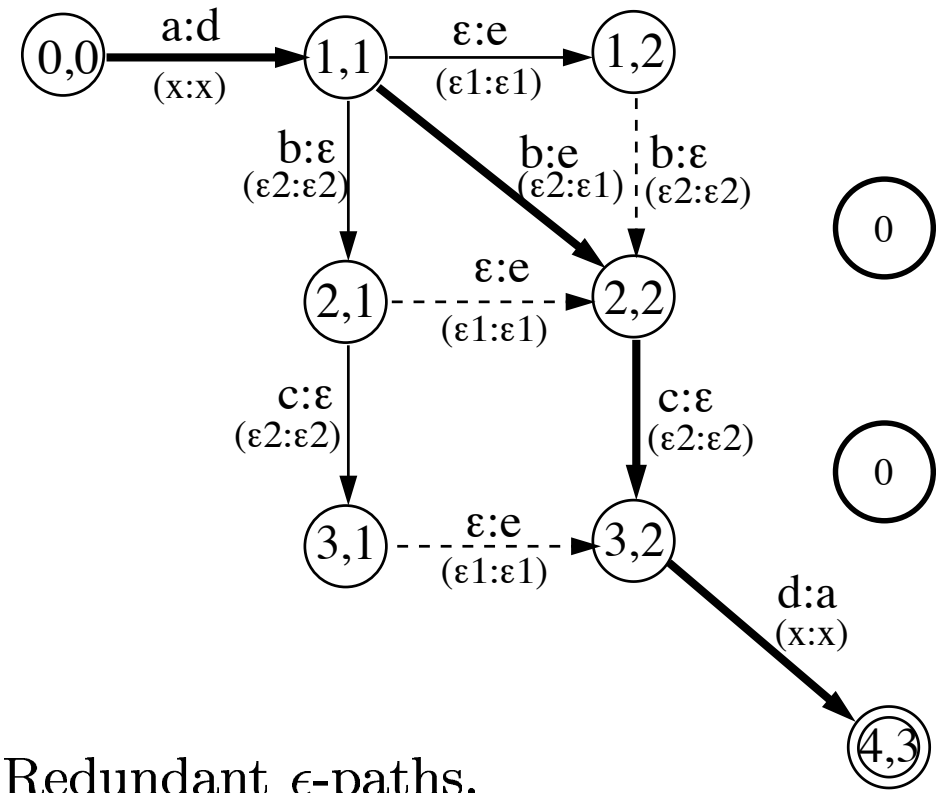
  - path multiplicity in presence of ϵ-transitions: ϵ-filter;
  - lazy implementation.

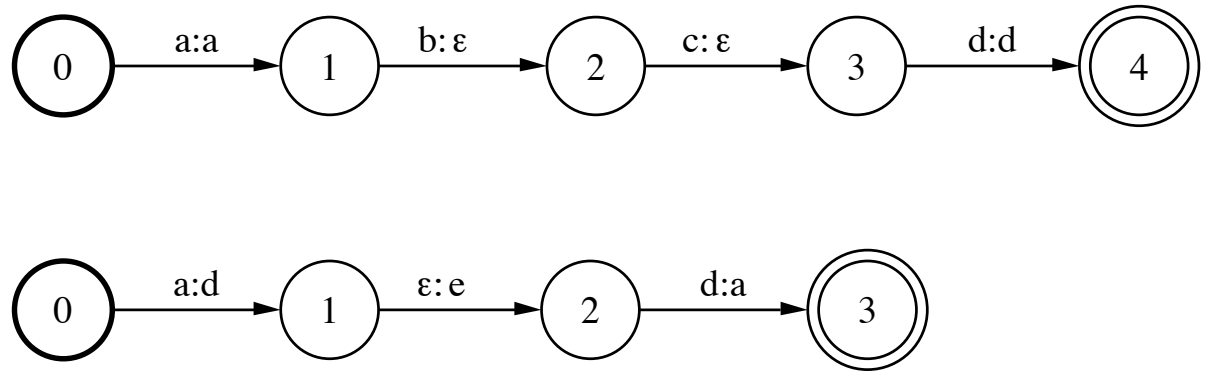
Composition - Illustration

- Program: fsmcompose A.fsm B.fsm >C.fsm
- Graphical representation:



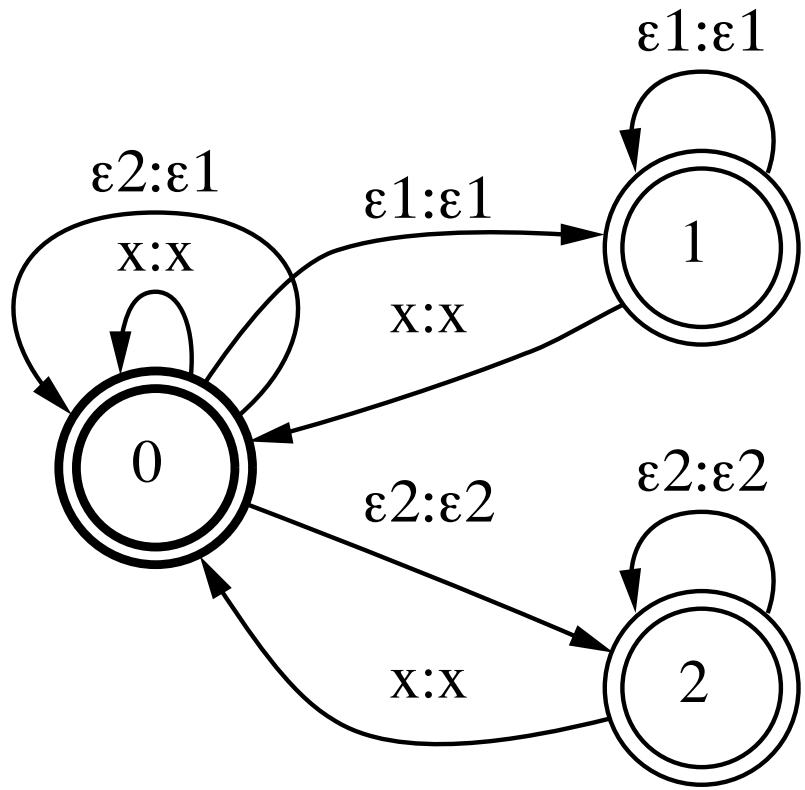
Multiplicity and ϵ-Transitions - Problem





Redundant ϵ-paths.

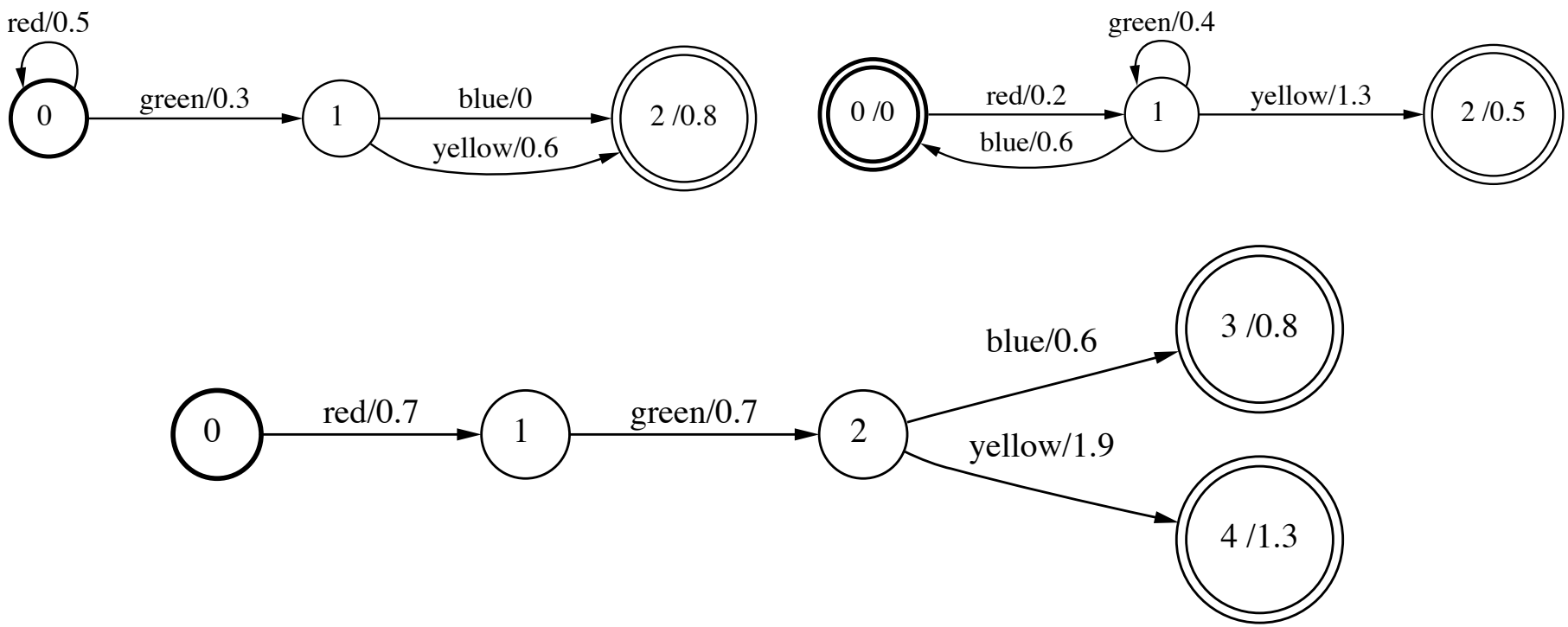
Solution - Filter *F* for Composition



Replace $T_1 \circ T_2$ with $\tilde{T}_1 \circ F \circ \tilde{T}_2$.

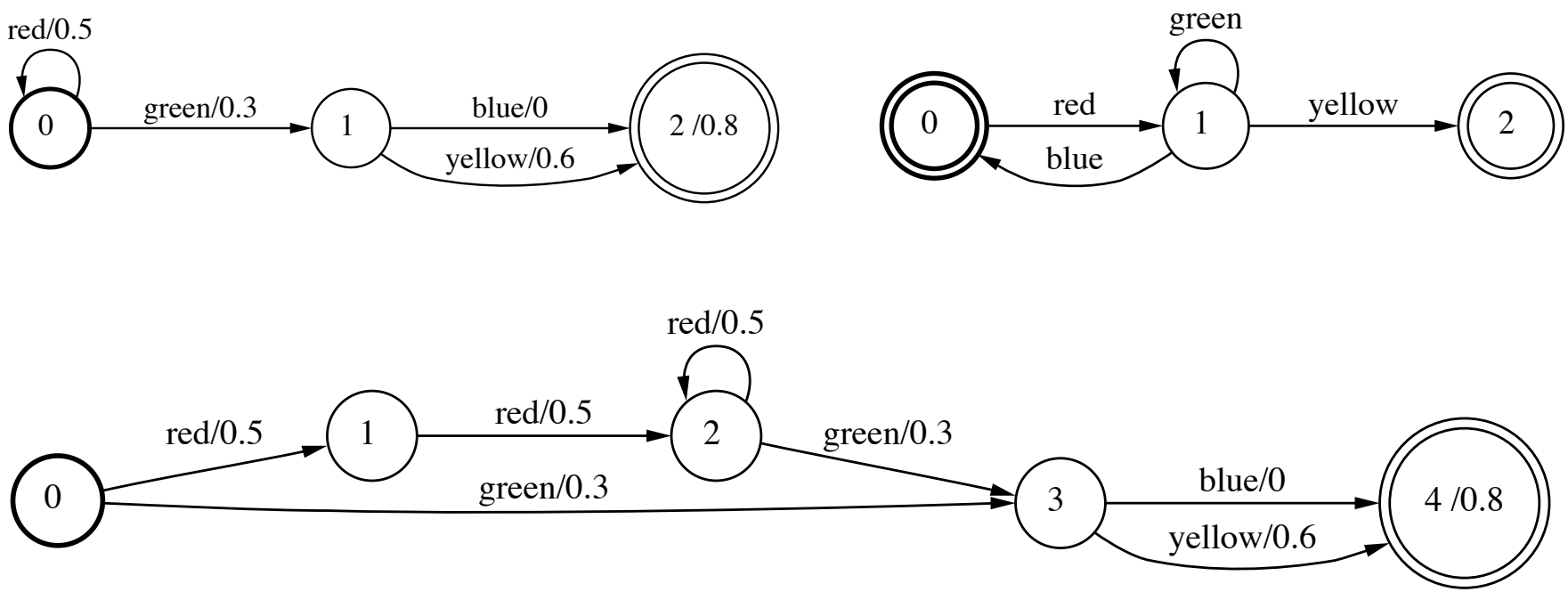
Intersection - Illustration

- Program: fsmintersect A.fsm B.fsm >C.fsm
- Graphical representation:



Difference - Illustration

- Program: fsmdifference A.fsm B.fsm >C.fsm
- Graphical representation:



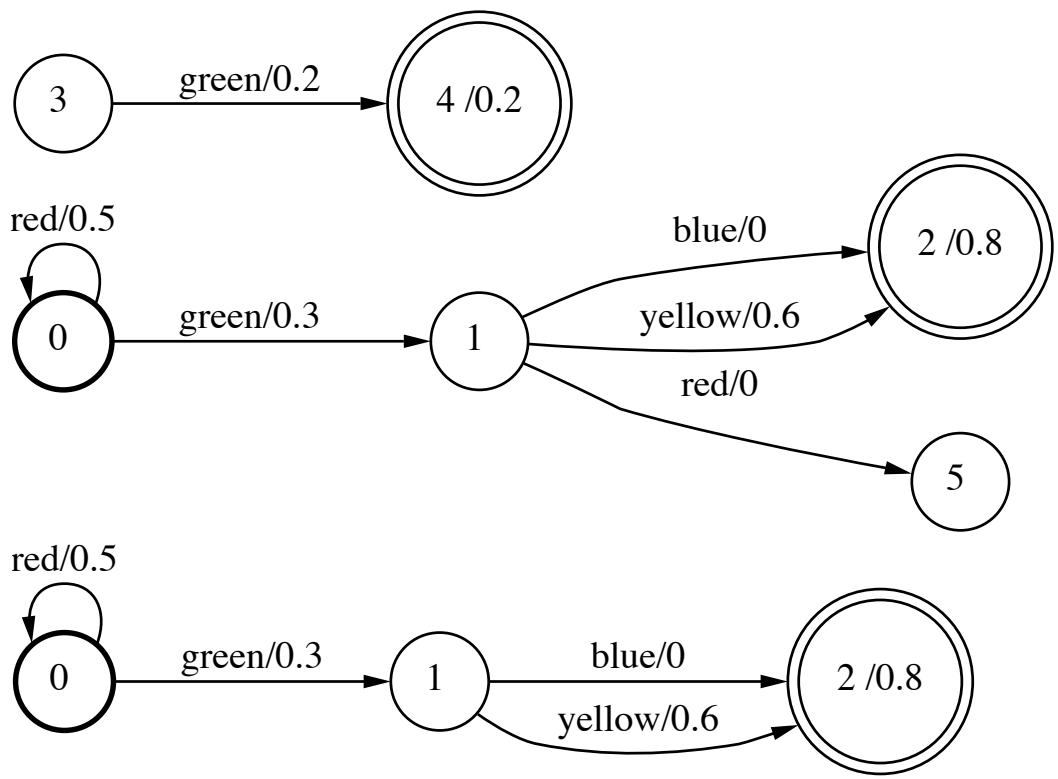
Optimization Algorithms

- Connection: removes non-accessible/non-coaccessible states
- ϵ-Removal: removes ϵ-transitions
- Determinization: creates equivalent *deterministic* machine
- Pushing: creates equivalent pushed/stochastic machine
- Minimization: creates equivalent minimal deterministic machine

- Conditions: there are specific semiring conditions for the use of these algorithms, e.g., not all weighted automata or transducers can be determinized using the determinization algorithm.

Connection - Illustration

- Program: fsmconnect A.fsm >C.fsm
- Graphical representation:

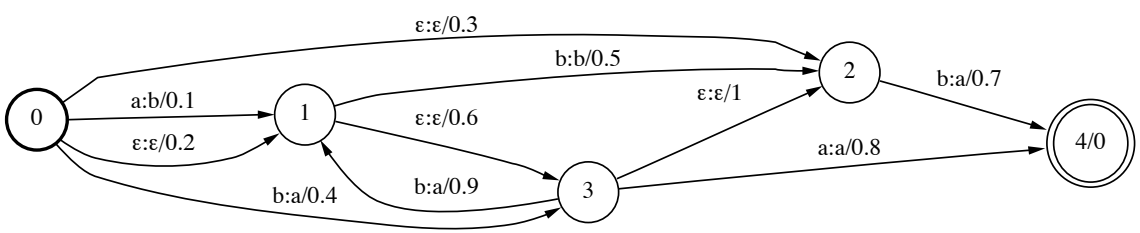


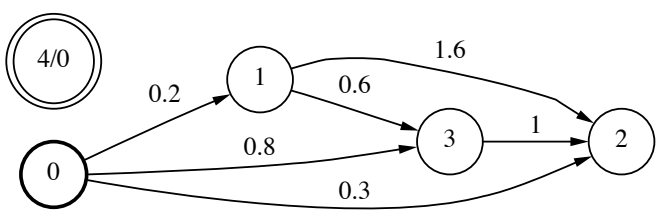
Connection - Algorithm

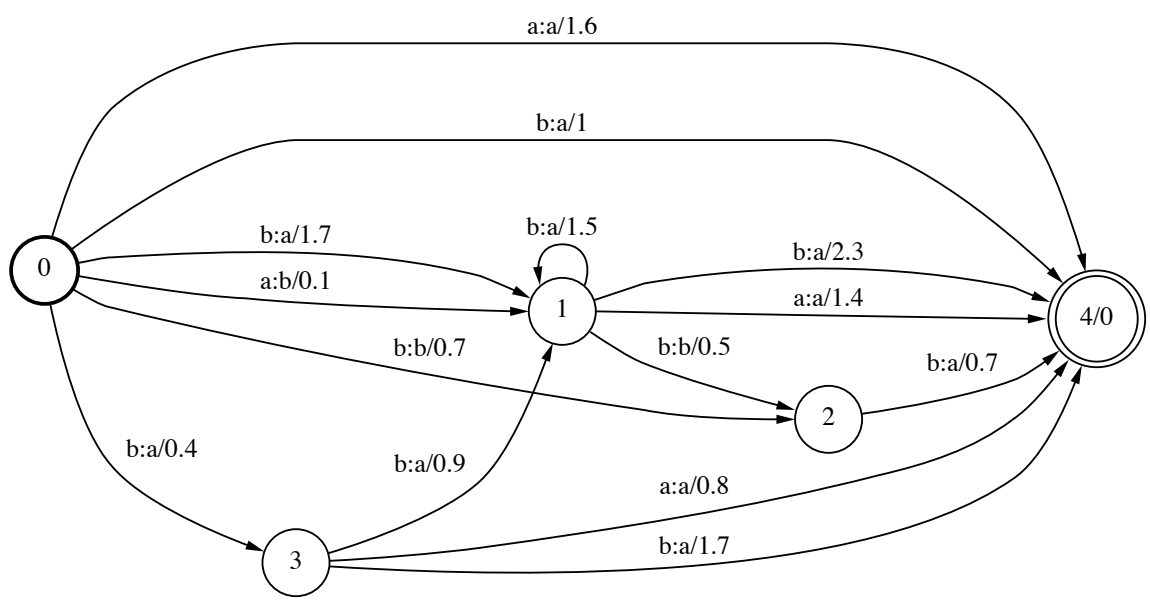
- Definition:
  - Input: weighted transducer T_1
  - Output: equivalent weighted transducer T_2 with all states connected
- Description:
  1. Depth-first search of T_1 from I_1 .
  2. Mark accessible and coaccessible states.
  3. Keep marked states and corresponding transitions.
- Complexity: linear $O(|Q_1| + |E_1|)$.

ϵ-Removal - Illustration

- Program: fsmrmepsilon T.fsm >TP.fsm
- Graphical representation:







ϵ-Removal - Algorithm

(Mohri, 2001)

- Definition:
  - Input: weighted transducer T_1
  - Output: equivalent WFST T_2 with no ϵ-transition
- Description:
  1. Computation of ϵ-closures.
  2. Removal of ϵs.
- Complexity:
  - Acyclic T_ϵ : $O(|Q|^2 + |Q||E|(T_\oplus + T_\otimes))$.
  - General case (tropical semiring):

$$O(|Q||E| + |Q|^2 \log |Q|)$$

Computation of ϵ-closures

- Definition: for *p* in *Q*,

$$C[p] = \left\{(q, w) : q \in \epsilon[p],\ d[p, q] = w \neq \overline{0}\right\},$$

$$\text{where } d[p, q] = \bigoplus_{\pi \in P(p, \epsilon, q)} w[\pi].$$

- Problem formulation: all-pairs shortest-distance problem in T_ϵ (*T* reduced to its ϵ-transitions).
  - closed semirings: generalization of Floyd-Warshall algorithm.
  - *k*-closed semirings: generic sparse shortest-distance algorithm.

Determinization - Algorithm

(Mohri, 1997)

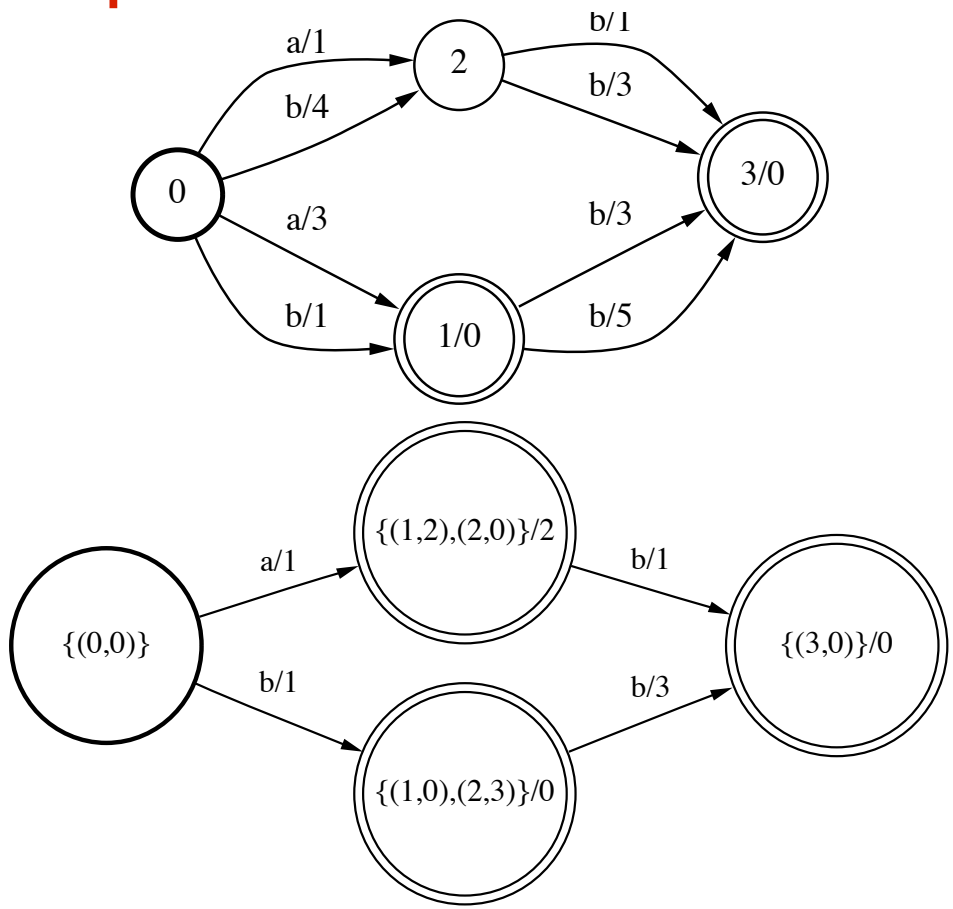
- Definition:
  - Input: weighted automaton or transducer T_1
  - Output: equivalent *subsequential* or *deterministic* machine T_2: has a unique initial state and no two transitions leaving the same state share the same input label.
- Description:
  1. Generalization of subset construction: *weighted subsets* $\{(q_1, w_1), \ldots, (q_n, w_n)\}$, where w_is are remainder weights.
  2. Computation of the weight of resulting transitions.

Determinization - Conditions

- Semiring: weakly left divisible semirings.
- Definition: *T* is *determinizable* when the determinization algorithm applies to *T*.
  - All unweighted automata are determinizable.
  - All acyclic machines are determinizable.
  - Not all weighted automata or transducers are determinizable.
  - Characterization based on the *twins property*.
- Complexity: exponential, but lazy implementation.

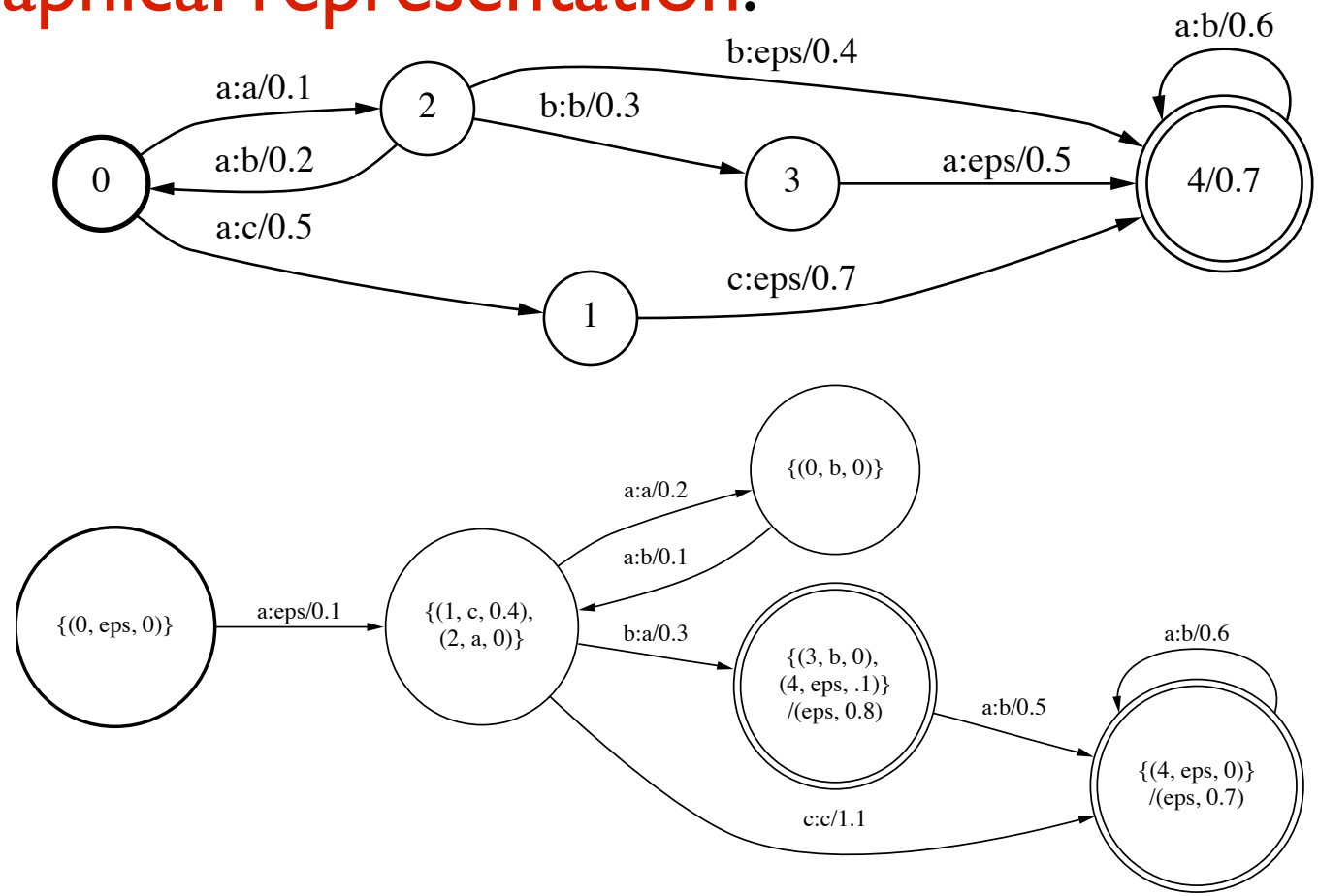
Determinization of Weighted Automata - Illustration

- Program: fsmdeterminize A.fsm >D.fsm
- Graphical representation:



Determinization of Weighted Transducers - Illustration

- Program: fsmdeterminize T.fsm >D.fsm
- Graphical representation:



Pushing - Algorithm

(Mohri, 1997; 2004)

- Definition:
  - Input: weighted automaton or transducer T_1
  - Output: equivalent automaton or transducer T_2 such that the longest common prefix of all outgoing paths be ϵ or such that the sum of the weights of all outgoing transitions be $\overline{1}$ modulo the string or weight at the initial state.

- Description:
  1. Single-source shortest distance computation: for each state q,

$$d[q] = \bigoplus_{\pi \in P(q,F)} w[\pi].$$

  2. Reweighting: for each transition e such that $d[p[e]] \neq \overline{0}$,

$$w[e] \leftarrow (d[p[e]])^{-1}(w[e] \otimes d[n[e]])$$

- Conditions (automata case): weakly divisible semiring, zero-sum free semiring or automaton.
- Complexity:
  - automata case
    - acyclic case: linear $O(|Q| + |E|(T_{\oplus} + T_{\otimes}))$.
    - general case (tropical semiring):

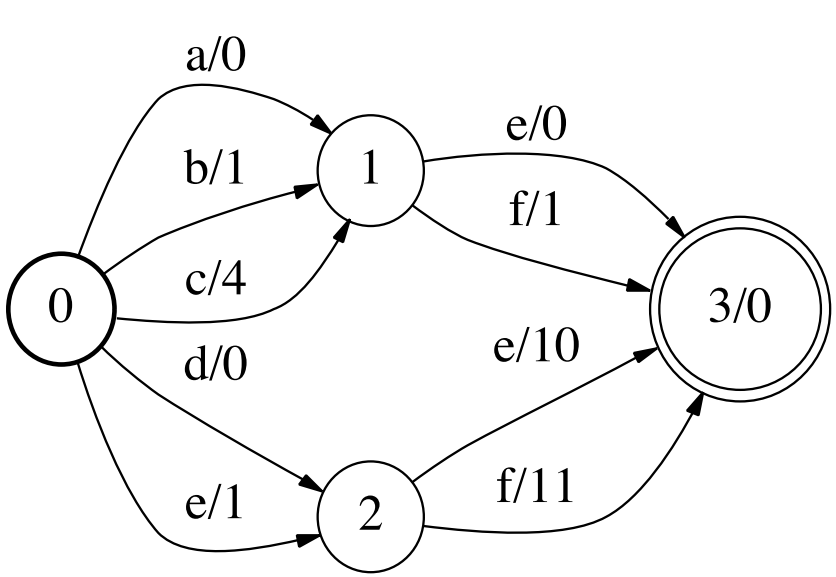
$$O(|Q| \log |Q| + |E|).$$

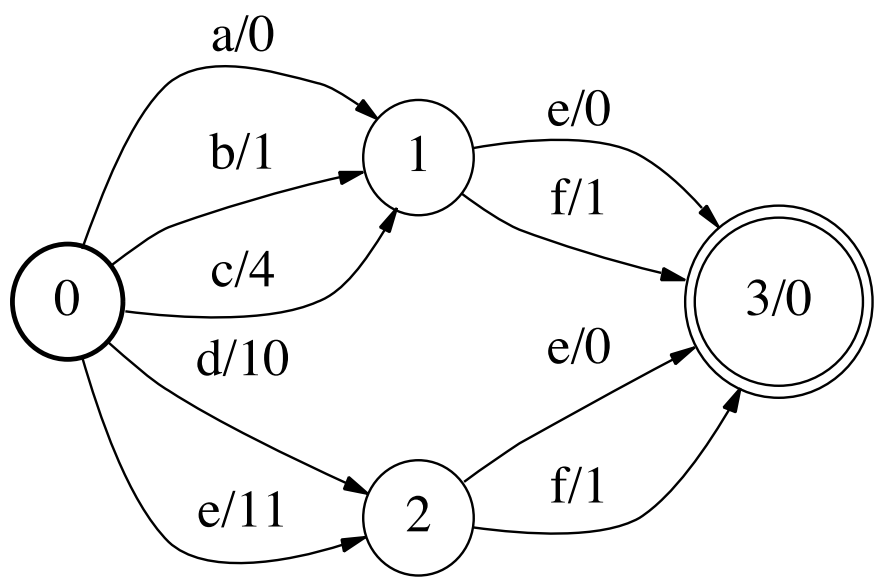
  - transducer case:

$$O((|P_{max}| + 1)\,|E|).$$

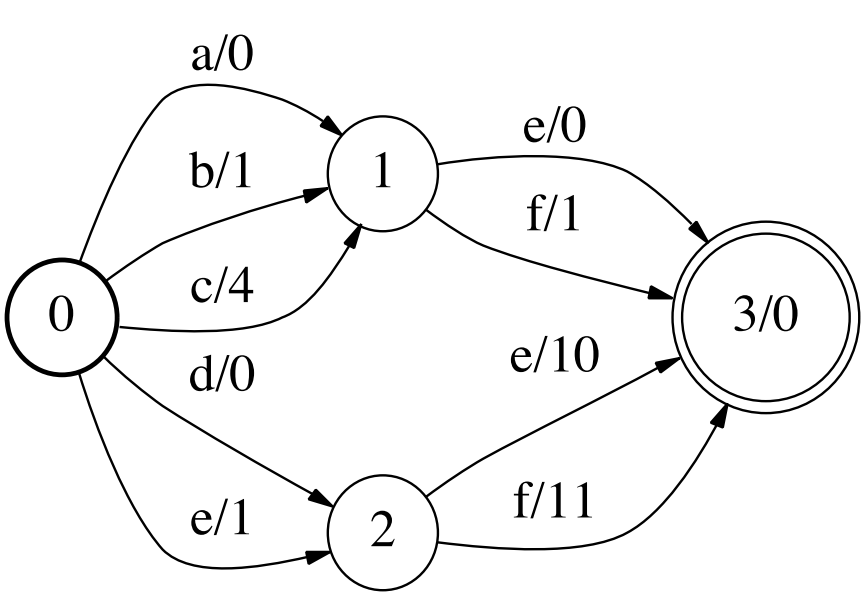
Weight Pushing - Illustration

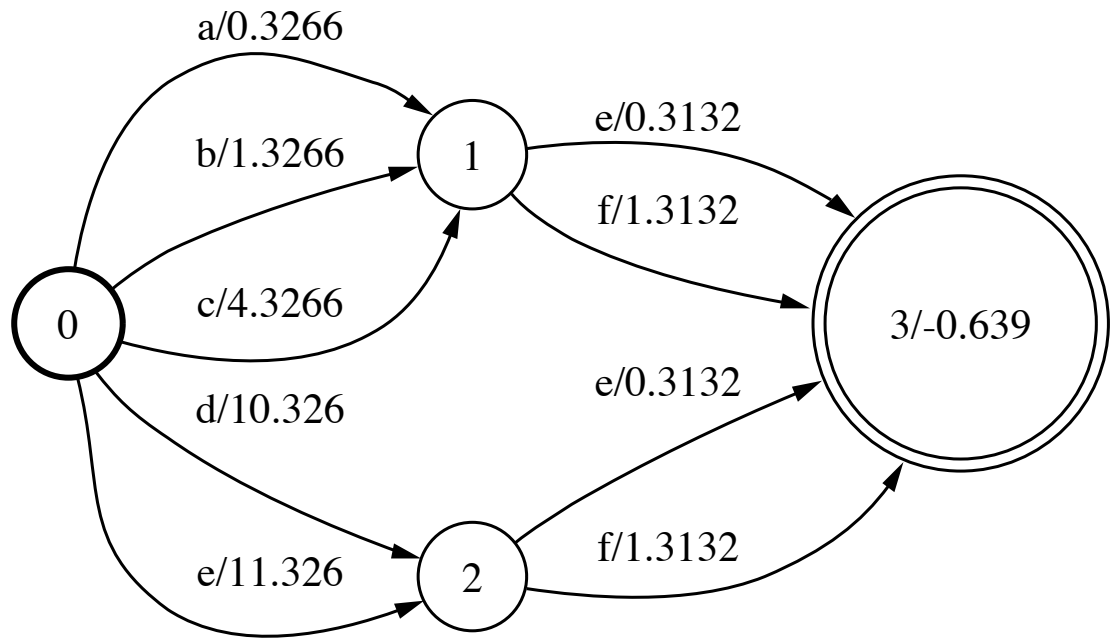
- Program: fsmpush -ic A.fsm >P.fsm
- Graphical representation:
  - Tropical semiring:





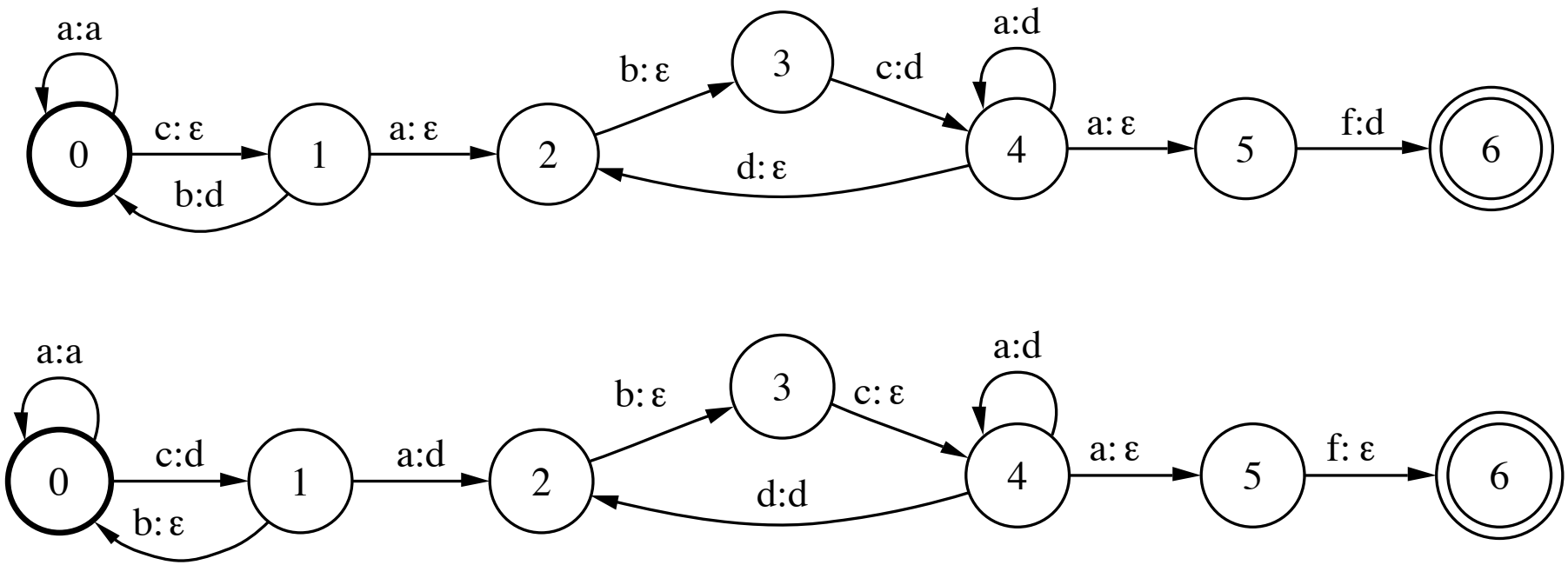
- Log semiring:





Label Pushing - Illustration

- Program: fsmpush -il T.fsm >P.fsm
- Graphical representation:



Minimization - Algorithm

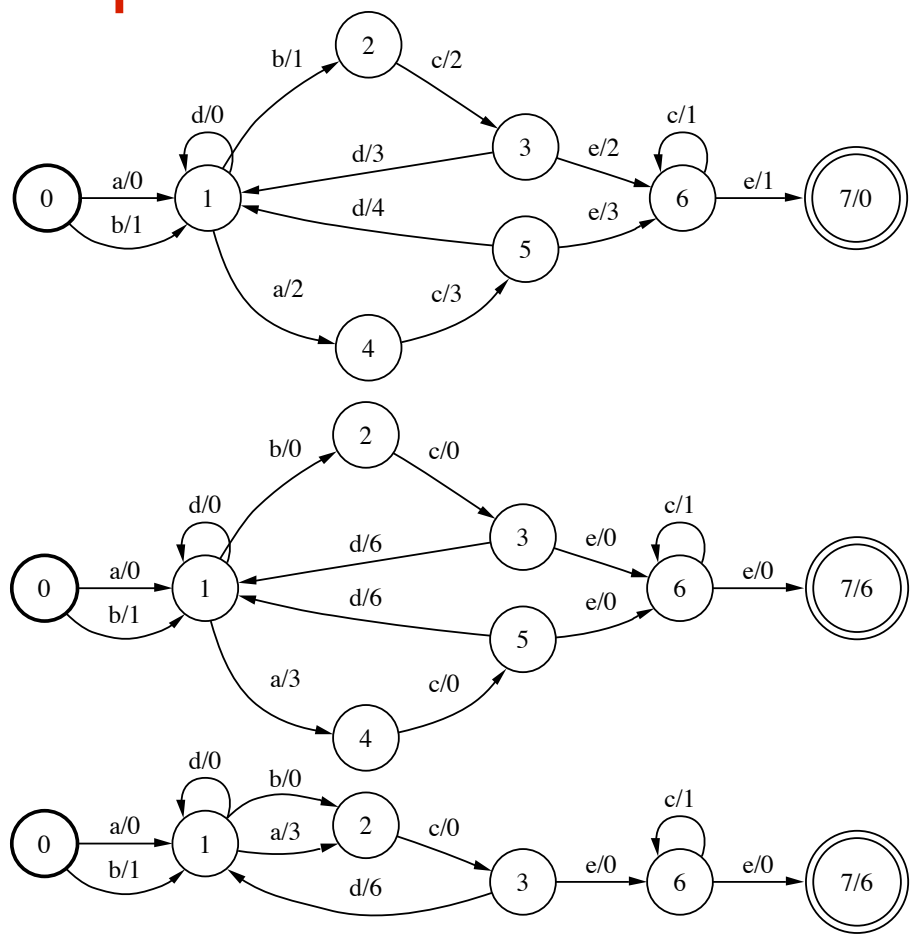
(Mohri, 1997)

- Definition:
  - Input: deterministic weighted automaton or transducer T_1.
  - Output: equivalent deterministic automaton or transducer T_2 with the minimal number of states and transitions.
- Description:
  - Canonical representation: use pushing or other algorithm to standardize input automata.
  - Automata minimization: encode pairs (label, weight) as labels and use classical unweighted minimization algorithm.

- Complexity:
  - Automata case
    - acyclic case: linear, $O(|Q| + |E|(T_{\oplus} + T_{\otimes}))$.
    - general case (tropical semiring): $O(|E| \log |Q|)$.
  - Transducer case
    - acyclic case: $O(S + |Q| + |E| (|P_{max}| + 1))$.
    - general case (tropical semiring): $O(S + |Q| + |E| (\log |Q| + |P_{max}|))$.

Minimization - Illustration

- Program: fsmminimize D.fsm >M.fsm
- Graphical representation:



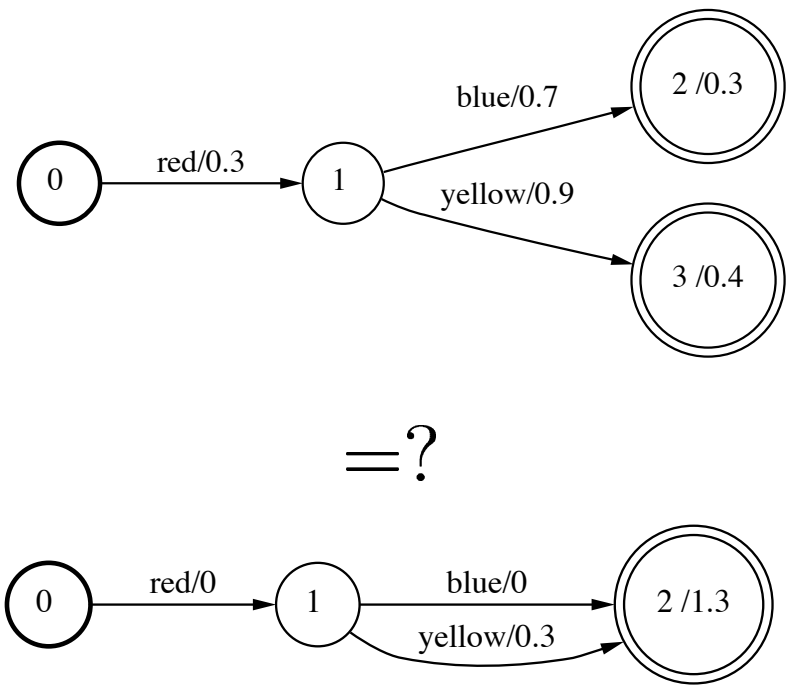
Equivalence - Algorithm

- Definition:
  - Input: deterministic weighted automata *A* and *B*.
  - Output: `TRUE` iff *A* and *B* equivalent.
- Description (Mohri, 1997):
  - Canonical representation: use pushing or other algorithm to standardize input automata.
  - Automata minimization: encode pairs (label, weight) as labels and use classical algorithm for testing the equivalence of unweighted automata.
- Complexity: (second stage is quasi-linear)

$$O(|E_1| + |E_2| + |Q_1| \log |Q_1| + |Q_2| \log |Q_2|).$$

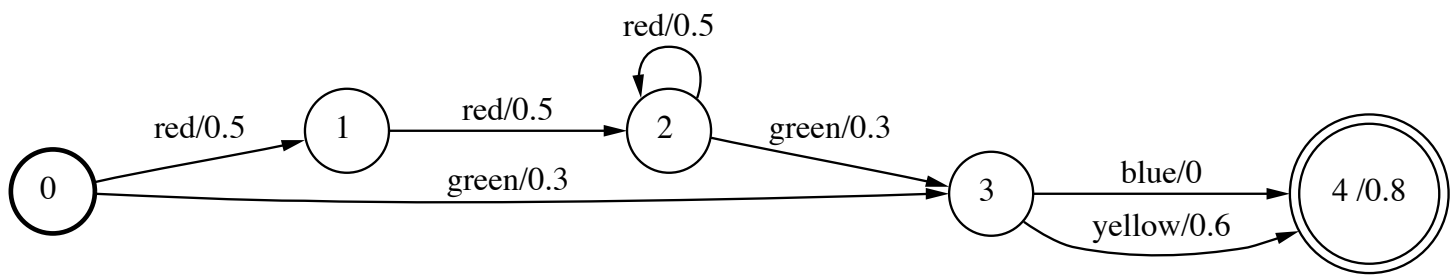
Equivalence - Illustration

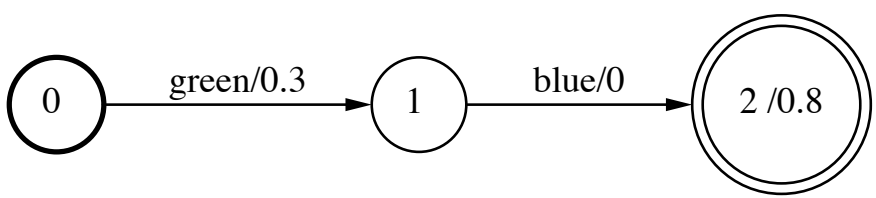
- Program: fsmequiv [-v] D.fsm M.fsm
- Graphical representation:



Single-Source Shortest-Distance Algorithms - Illustration

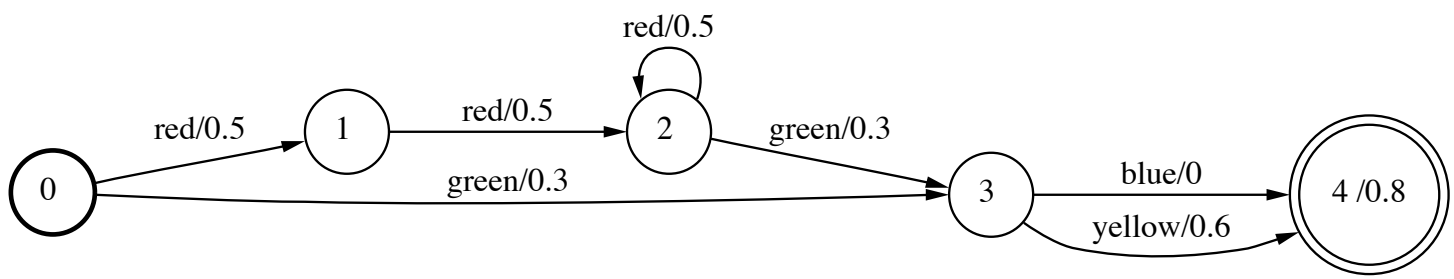
- Program: fsmbestpath [-n N] A.fsm >C.fsm
- Graphical representation:

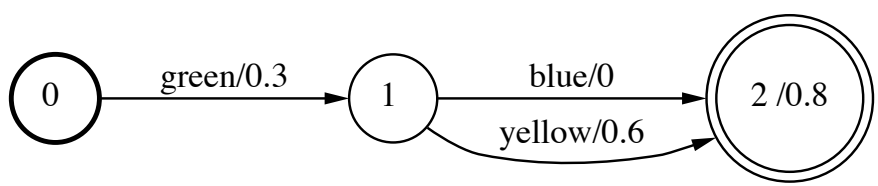




Pruning - Illustration

- Program: fsmprune -c1.0 A.fsm >C.fsm
- Graphical representation:





Summary

- FSM Library:
  - weighted finite-state transducers (semirings);
  - elementary unary operations (e.g., reversal);
  - rational operations (sum, product, closure);
  - fundamental binary operations (e.g., composition);
  - optimization algorithms (e.g., ϵ-removal, determinization, minimization);
  - search algorithms (e.g., shortest-distance algorithms, *n*-best paths algorithms, pruning).

Weighted Finite-State Transducers in Computational Biology

Corinna Cortes
Google Research
corinna@google.com

Mehryar Mohri
Courant Institute
mohri@cs.nyu.edu

This Tutorial

- Weighted finite-state transducers and software library (FSM Library)
- Pairwise alignments for bioinformatics
- Kernels for computational biology

Pairwise Alignments for Bioinformatics

Biological Motivation

- General idea: use sequence similarity and known properties of some proteins to predict functional and structural information for other proteins.
- Applications:
  - Reconstruction of long DNA sequences,
  - Searching and mining DNA databases,
  - Finding frequent nucleotide patterns,
  - Determining informative sequences.

Why Weighted Finite-State Transducers?

(Mohri, Pereira, and Riley, 2000)

- Generality
  - Unified representation framework
  - Single general algorithm
  - No need to design and implement a novel algorithm for each new sequence alignment problem
  - Just define a new alignment transducer
  - Alignments between sets of strings, finite automata, or weighted automata (Mohri, 2003).

Why Weighted Finite-State Transducers?

- Efficiency
  - Compact representation of alignment transducer
  - Benefit of general transducer optimization algorithms
  - General quadratic-time alignment algorithm
  - Exploits graph representation and sparseness
  - Most 'pruning' ideas used in dynamic programming can be used with WFSTs as well.

Why Weighted Finite-State Transducers?

- Flexibility
  - Can use any weighted finite-state transducer
  - Can create more complex alignment transducers using general transducer algorithms, e.g., rational operations
  - Easy to modify, e.g., tailor alignment transducer to a specific problem
  - Graphical representation helps design and understanding

Terminology

Biology	Computer Science
sequence	string
subsequence	factor
-	substring

- Computer science:
  - Factor: contiguous symbols.
  - Substring or subsequence: non-necessarily contiguous symbols.

Local Edits

- Insertion: $\epsilon \rightarrow a$
- Deletion: $a \rightarrow \epsilon$
- Substitution: $a \rightarrow b$ $(a \neq b)$
- Example: 2 insertions, 3 deletions, 1 substitution

$$\begin{array}{cccccccccc} c & t & t & g & \epsilon & \epsilon & a & c \\ \epsilon & t & a & \epsilon & g & t & \epsilon & c \end{array}$$

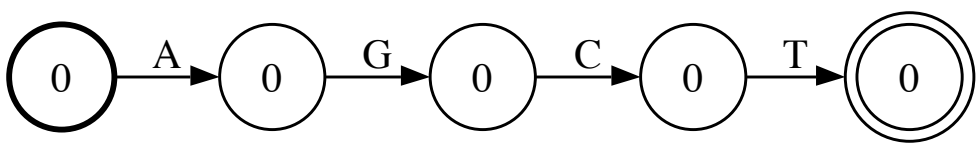
- This is called an *alignment*.

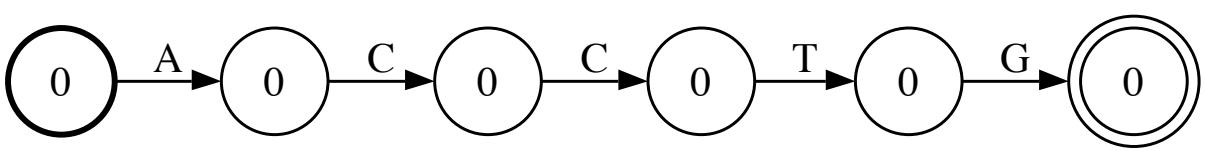
Edit-Distance - Global Alignment

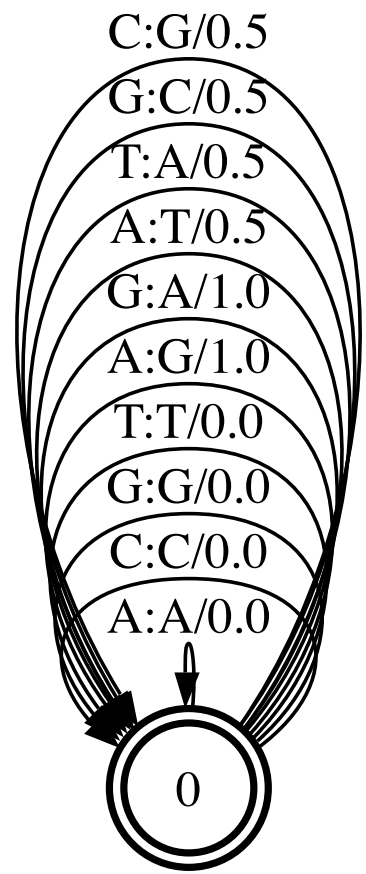
- Let $c(a, b)$ be the cost associated to the alignment of a with b, where a and b are in $\Sigma \cup \{\epsilon\}$.
- Problem: Find the best alignment (minimal cost) of two sequences x and y.
- Solution: general algorithm;
  - Construct edit transducer T_e using $c(a, b)$ costs.
  - Represent x and y by automata X and Y.
  - Compute best path of $X \circ T_e \circ Y$.

Global Alignment - Example

- Example: $c(A, G) = 1$, $c(A, T) = c(G, C) = .5$, no cost for matching symbols.
- Representation:



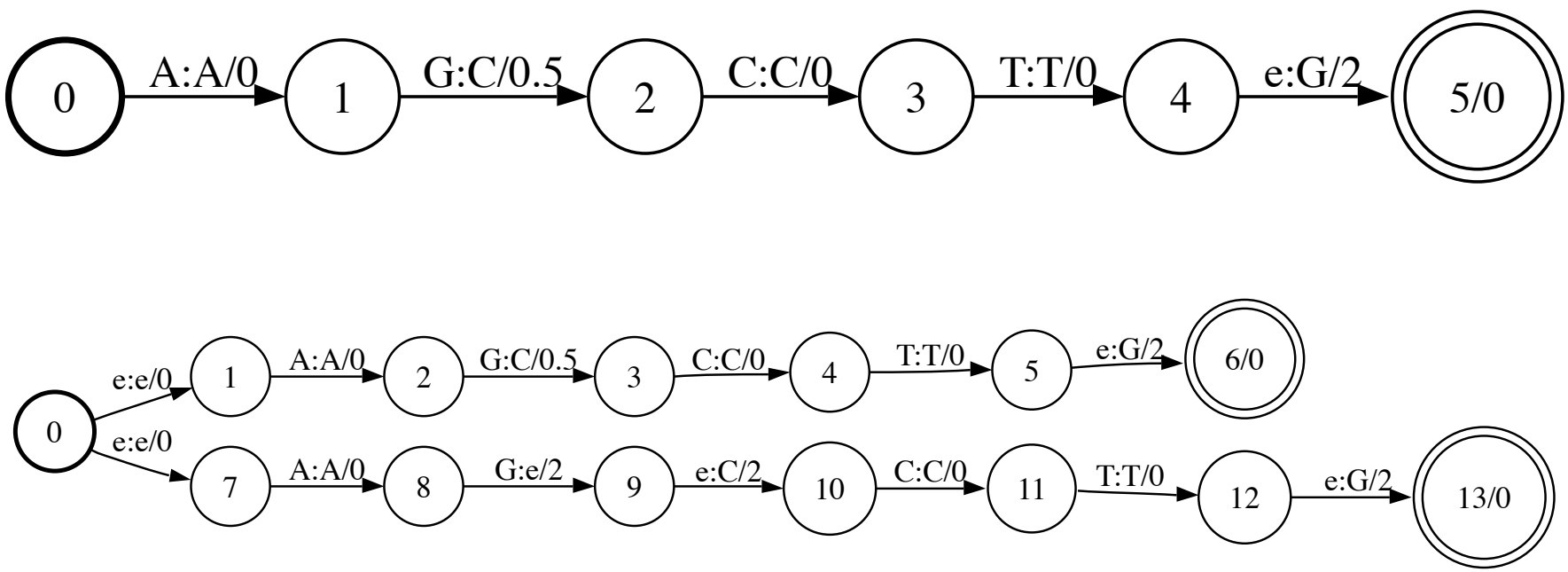





```
echo "A G C T" | farcompilestrings >X.fsm
```

Global Alignment - Example

- Program: `fsmcompose X.fsm Te.fsm Y.fsm | fsmbestpath -n 1 >A.fsm`
- Graphical representation:

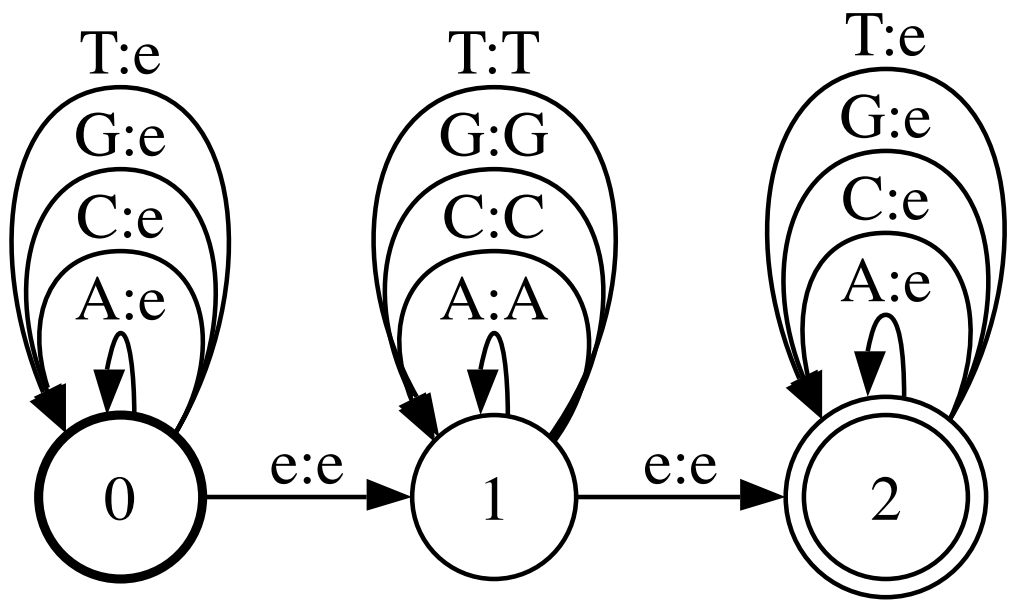


Local Alignment

- Problem: Find the best local alignment (alignment between factors) of two sequences *x* and *y*.
- Motivation: ignore non-coding regions (introns).
- Solution: general algorithm;
  - Construct edit transducer T_e using *c*(*a*, *b*) costs.
  - Construct factor transducer T_f .
  - Represent *x* and *y* by automata *X* and *Y*.
  - Compute $X' = \mathrm{Project}_2(X \circ T_f)$ and
    $$Y' = \mathrm{Project}_1(T_f^{-1} \circ Y).$$
  - Compute best path of $X' \circ T_e \circ Y'$.

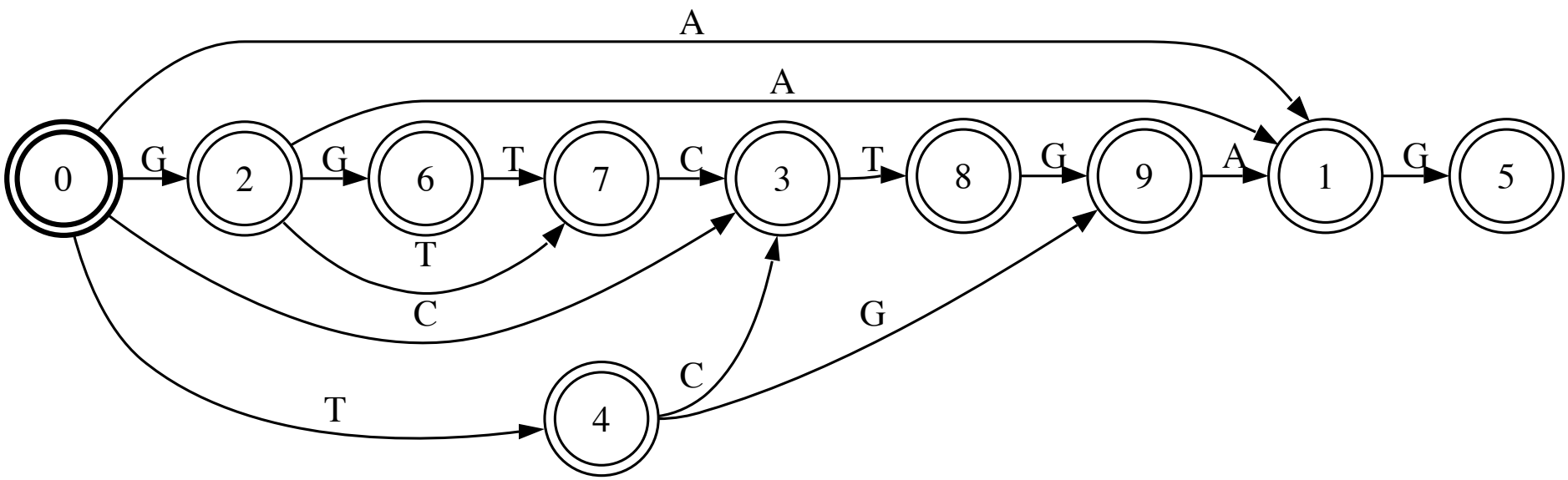
Factor Transducer

- Definition: transducer mapping a string to the set of factors of that string.



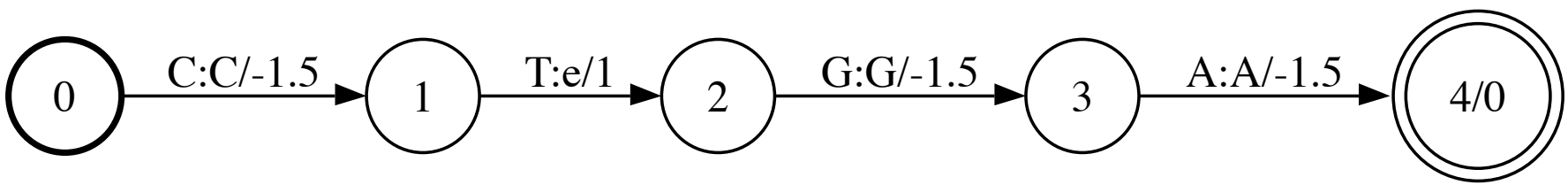
Factor Automaton of a String

- Program: `fsmcompose X.fsm Tf.fsm | fsmproject -2 | fsmrmepsilon | fsmdeterminize | fsmminimize >Xp.fsm`
- Representation: size linear in that of *X*.



Local Alignment - Example

- Program: `fsmcompose Xp.fsm Te.fsm Yp.fsm | fsmbestpath -n1 >B.fsm`
- Graphical representation:




```
X = T G T C T G A G          C T G A
Y = A C A C G A              C ϵ G A
```

matching cost: -1.5
insertion/deletion/substitution costs: +1

Alignment with Gaps

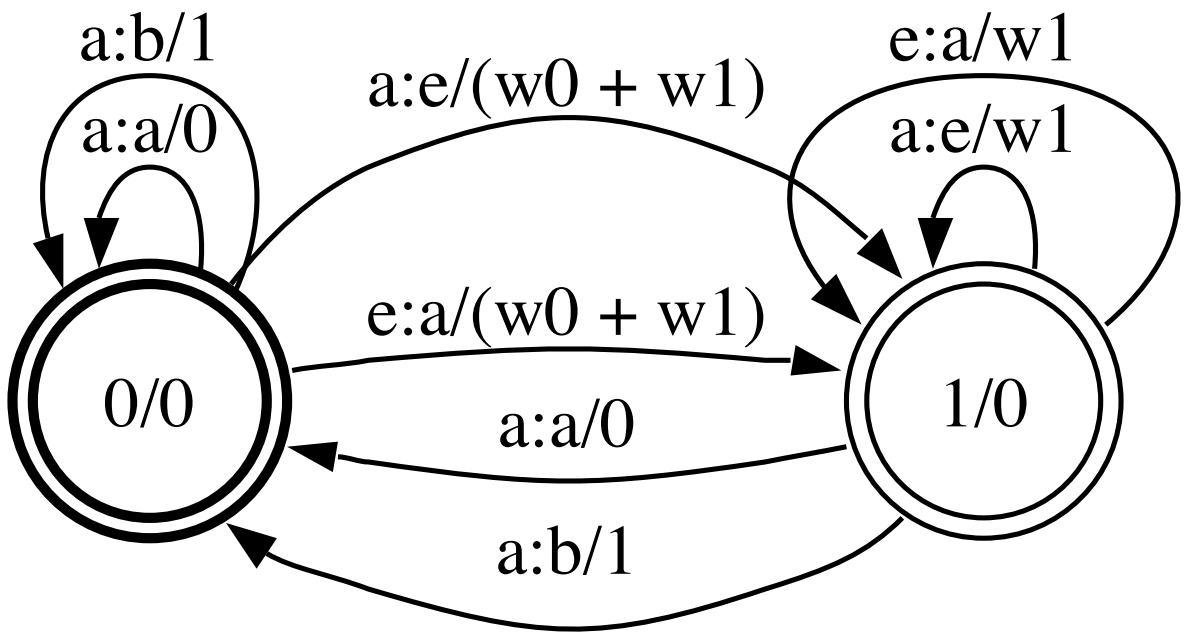
- Problem: Find the best local or global alignment with gaps (consecutive sequence of deletions/ insertions) two sequences *x* and y.
- Motivation: ignore long gaps due to introns.
- Example:

```
A T G A ϵ ϵ G A C
A ϵ ϵ G A T G ϵ C
```

- Gap penalties:
  - Constant: constant penalty w_0 per gap.
  - Affine: $w_0 + w_1 \times |\text{gap}|$
  - Convex: $w_0 \log |\text{gap}|$.

Gap Alignment Transducer

- Representation: affine gap penalties.



More Complex Alignments

- Complex alignment transducers
  - Simpler alignment transducers can be combined using rational operations to create more complex ones.
  - Any weighted transducer can help define an alignment.
  - Alignment transducers can be learned from examples.

Learning Alignment Transducers

- Problem: given a fix topology for the transducer T_e, learn the transition weights from examples.
- Example: (Ristad and Yianilos, 1997)
  - learn edit costs of one-state edit-distance transducer;
  - data: large corpus of pairs of related sequences;
  - algorithm: use the Expectation-Maximization (EM) algorithm.

Alignment of Sets of Sequences

- Problem: Find the best alignment (minimal cost) of two sets of sequences *X* and *Y*.
- Note: *X* and *Y* may be finite sets of biological sequences or infinite sets, e.g., represented or modeled by HMMs.
- Solution:
  - Construct edit transducer T_e.
  - Represent *X* and *Y* by automata A_X and A_Y.
  - Compute best path of $A_X \circ T_e \circ A_Y$.

Longest Common Subsequence of Automata

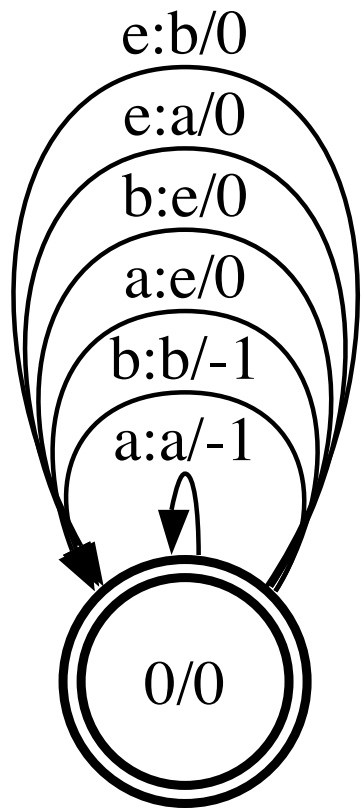
- Problem: Find the longest common subsequence of two (finite) sets of sequences *X* and *Y* each given by a finite automaton.

$$|\mathrm{lcs}(X, Y)| = \max\{|\mathrm{lcs}(x, y)| : x \in X, y \in Y\}.$$

- Solution:
  - Construct LCS transducer T_{lcs}.
  - Represent *X* and *Y* by automata A_X and A_Y.
  - Compute best path of $A_X \circ T_{\mathrm{lcs}} \circ A_Y$.

Longest Common Subsequence Transducer

- Representation: example.



Summary

- An alignment scoring function can be defined by a WFST.
- A general algorithm can be used to efficiently compute the best alignments between sequences, or sets of sequences represented by finite automata.
- Complex alignments can be learned from examples.
- The FSM library can be used for the implementation and computation of alignments.

Weighted Finite-State Transducers in Computational Biology

Corinna Cortes
Google Research
corinna@google.com

Mehryar Mohri
Courant Institute
mohri@cs.nyu.edu

This Tutorial

- Weighted finite-state transducers and software library (FSM Library)
- Pairwise alignments for bioinformatics
- Kernels for computational biology

Kernels for Computational Biology

Outline

- Introduction to machine learning
- Support vector machines
- Kernel methods
- Rational kernels
- Applications to computational biology
- Theory

`http://www.cs.nyu.edu/~mohri/rational.html`

Learning from Examples

Given data, learn mapping:

- Classification
  - Two-group classification
  - Multi-class classification
- Regression
  - one- or multi-dimensional
- Clustering

Remote Homology Problem

- Problem: assign protein sequences to families or superfamilies of proteins for which structural properties are known.
- Data: SCOP (Structural Classification of Proteins into superfamilies and families).
- Classification: 33 superfamilies.

Two-Group Classification

Protein Classification: Remote Homology Detection (SCOP Data, http://scop.berkeley.edu/)

- Allophycocyanin[(Spirulina platensis)]

SIVTKSIVNADAEARYLSPGELDRIKSFVTSGERRVRIAETMTGARERIIKQAGDQLFGKRPDVVSPGGNAYGA
DMTATCLRDLDYYLRLITYGIVAGDVTPIEEIGVGVREMYKSLGTPIEAIAEGVRAMKSVATSLLSGADAAEAGS
YFDYLIGAMS

- Allophycocyanin[(Spirulina platensis)]

MQDAITSVINSSDVQGKYLDASAIQKLKAYFATGELRVRAATTISANAANIVKEAVAKSLLYSDVTRPGGNMYTT
RRYAACIRDLDYYLRYATYAMLAGDPSILDERVLNGLKETYNSLGVPIGATVQAIQAMKEVTAGLVGGGAGKEM
GIYFDYICSGLS

- Snake phospholipase A2 [Eastern cottonmouth snake (Agkistridon piscivorus piscivorus)]

SVLELGKMILQETGKNAITSYGSYGCNCGWGHRGQPKDATDRCCFVHKCCYKKLTDCNHKTDRYSYSWKNK
AIICEEKNPCLKEMCECDKAVAICLRENLDTYNKKYKAYFKLKCKKPDTC

- Snake phospholipase A2 [Eastern cottonmouth snake (Agkistridon piscivorus piscivorus)]

NLFQFEKLIKKMTGKSGMLWYSAYGCYCGWGGQGRPKDATDRCCFVHDCCYGKVTGCNPKMDIYTYSVDN
GNIVCGGTNPCKKQICECDRAAAICFRDNLKTYDSKTYWKYPKKNCKEESEP

- Bacterial chitobiase, n-terminal domain [(Serratia marcescens)]

DQQLVDQLSQLKLNVKMLDNRAGENGVDCAALGADWASCNRVLFTLSNDGQAIDGKDWVIYFHSPRQTLRV
DNDQFKIAHLTGDLYKLEPTAKFSGFPAGKAVEIPVVAEYWQLFRNDFLPRWYATSGDAKPKMLANTDTENLD
QFVAPFTGDQWKRTKDDKNILMTPASRFV

- Tumor supressor, DNA-binding domain [Human (Homo sapiens)]

SSSVPSQKTYQGSYGFRLGFLHSGTAKSVTCTYSPALNKMFCQLAKTCPVQLWVDSTPPPGTRVRAMAIYKQ
SQHMTEVVRRCPHHERCSDSDGLAPPQHLIRVEGNLRVEYLDDRNTFRHSVVVPYEPPEVGSDCTTIHYNY
MCNSSCMGGMNRRPILTIITLEDSSGNLLGRNSFEVRVCACPGRDRRTEEENL

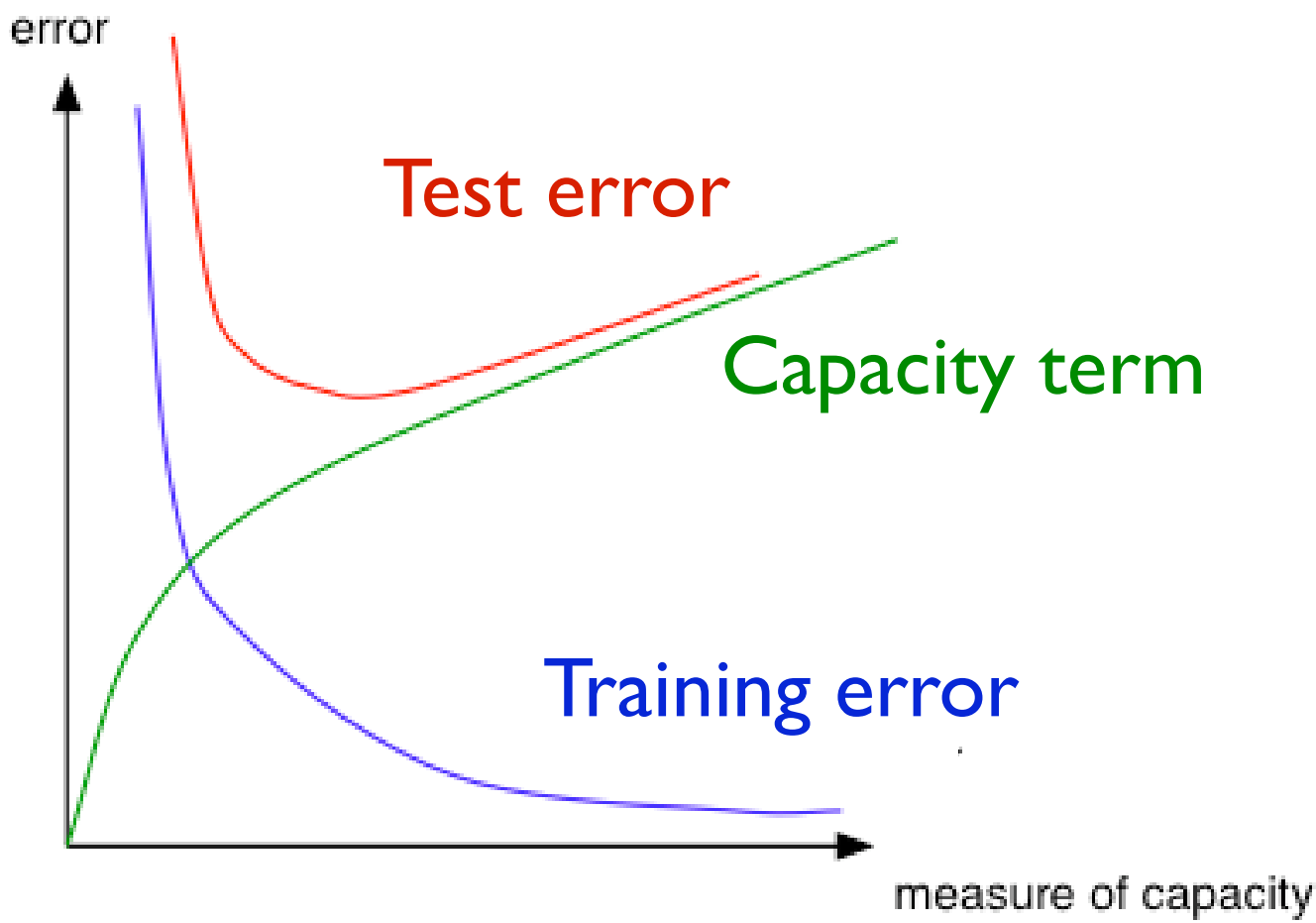
Learning from Examples

Given labeled data. Divide into training and test data:

1. Chose learning machine and cost function;
2. Minimize error on training data;
3. Measure error on test data.

Overfitting

It is always possible to fit the training data, but the goal of learning is good generalization ability.



Overfitting

Capacity control:

- Trees: stopping criteria, pruning (pruning data set).
- Neural networks: number of hidden units, early stopping, weight decay.
- Support vector machines: built-in capacity control, no parameter tuning.

Outline

- Introduction to machine learning
- Support vector machines
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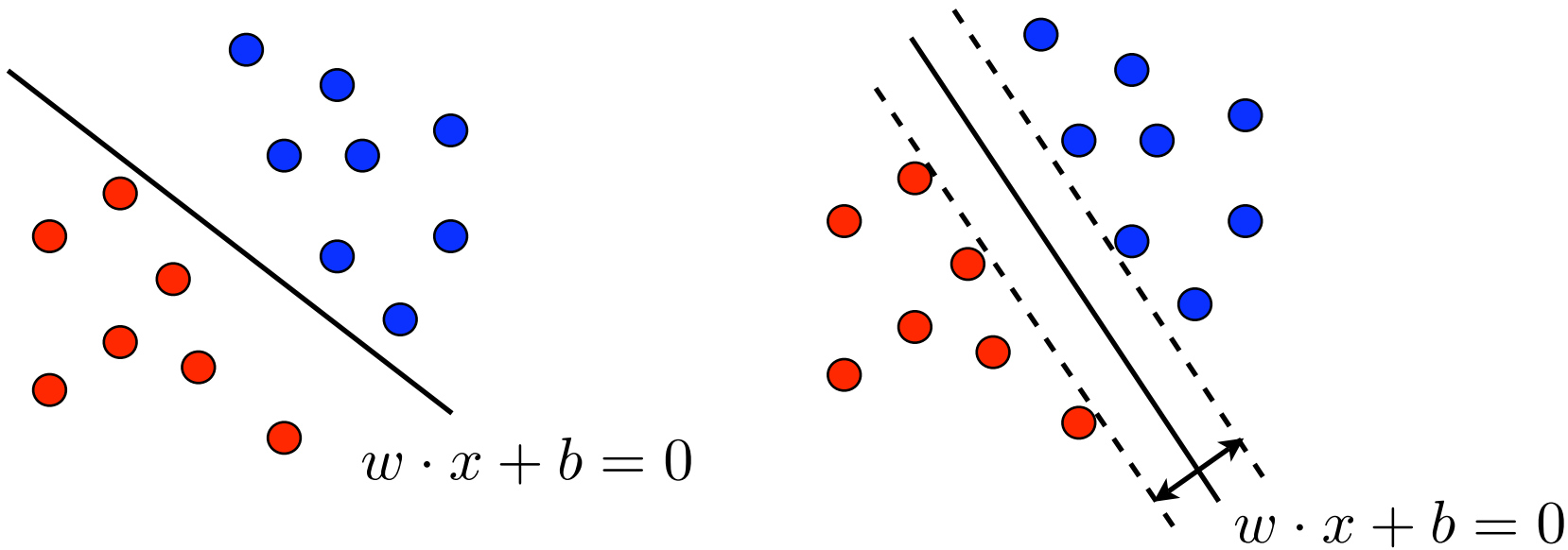
Support Vector Machines

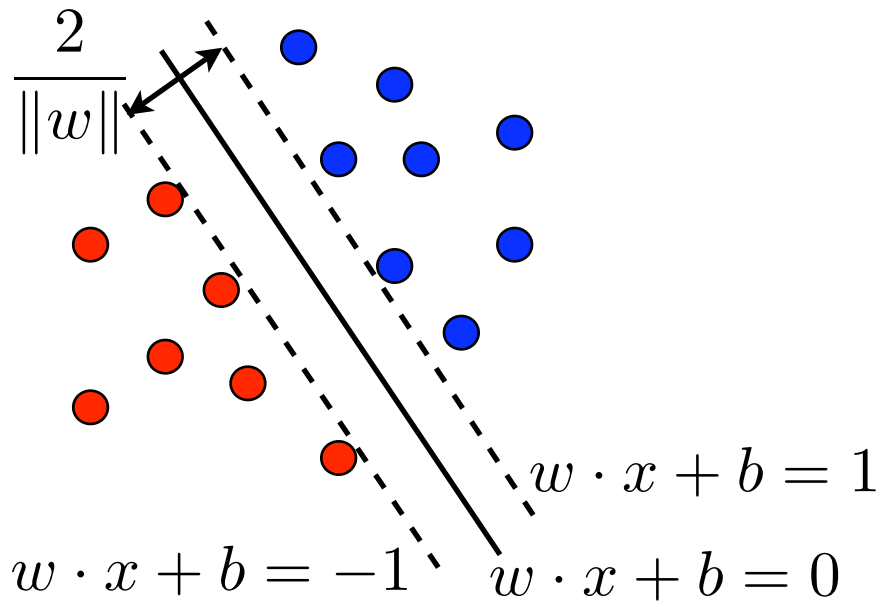
- Training data, generated according to distribution *D*: $(x_1, y_1) \ldots (x_m, y_m) \in \mathbb{R}^N \times \{-1, +1\}$
- Problem: find function (*classifier*) $h : \mathbb{R}^N \rightarrow \{-1, +1\}$ with small generalization error over test data generated according to *D*.
- Linear classification:
  - Simple hypotheses: hyperplanes
  - Linear separation in high-dimensional feature space (Vapnik 1995; Boser et al., 1992)
  - Kernel methods

Linear Separation



- Functions: $h(x) = w \cdot x + b, \quad w \in \mathbb{R}^N, b \in \mathbb{R}$
- Classifier: $\operatorname{sign} h(x) \in \{-1, +1\}$

Optimal Hyperplane



- Canonical hyperplane: $w \cdot x + b \in \{-1, +1\}$ for closest points.
- Margin: $\rho = \frac{1}{||w||}$. For points on opposite sides of the margin: $|w \cdot (x_2 - x_1)| = 2$.

Optimization Problem

- Constrained optimization:

$$\min_x \frac{1}{2}||w||^2$$

$$\text{subject to } y_i(x_i \cdot w + b) \geq 1, \quad i = 1, \ldots, m.$$

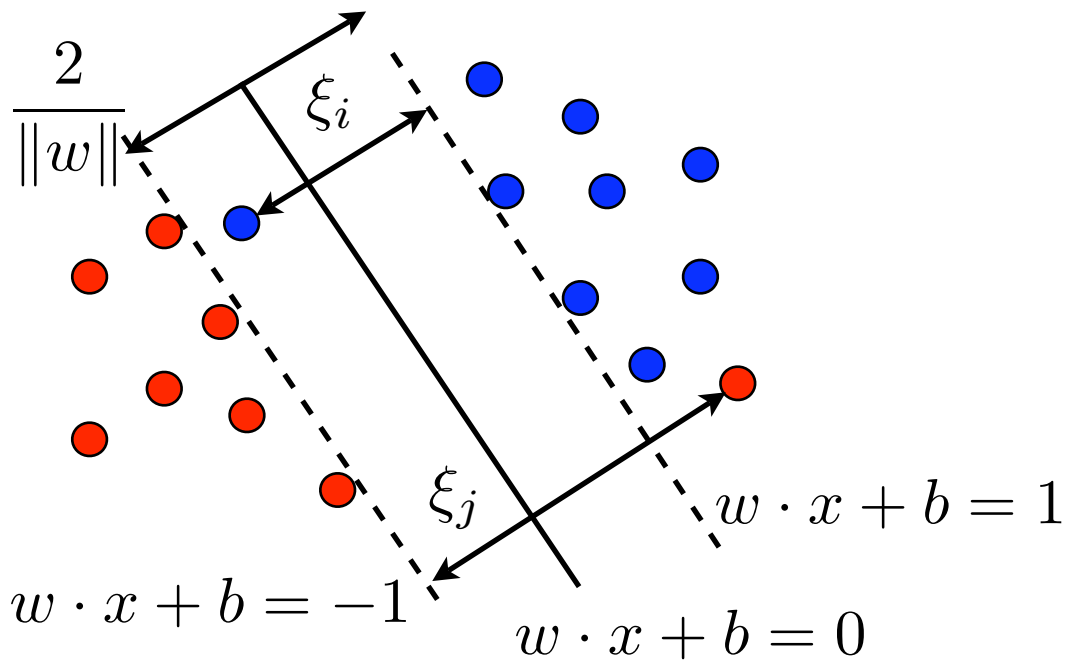
- Solution:
  - Quadratic optimization algorithms e.g., SMO algorithm (Platt, 1999)

Soft-Margin Hyperplane

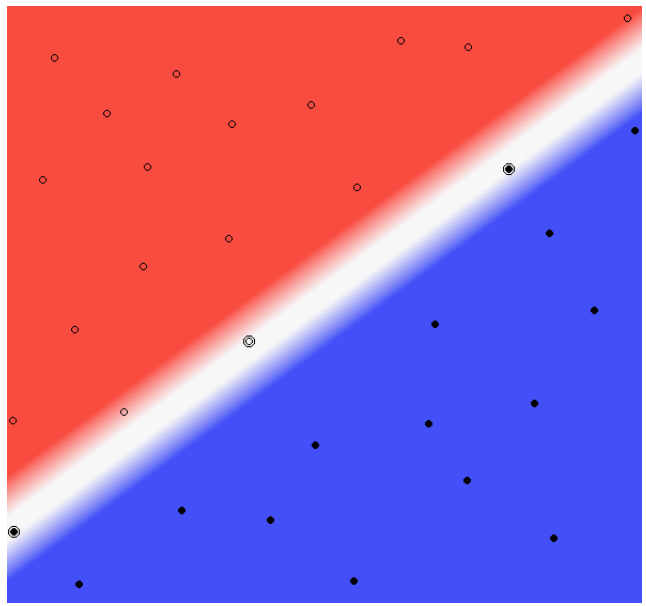
- Soft margin optimization problem (Cortes & Vapnik, 1995):

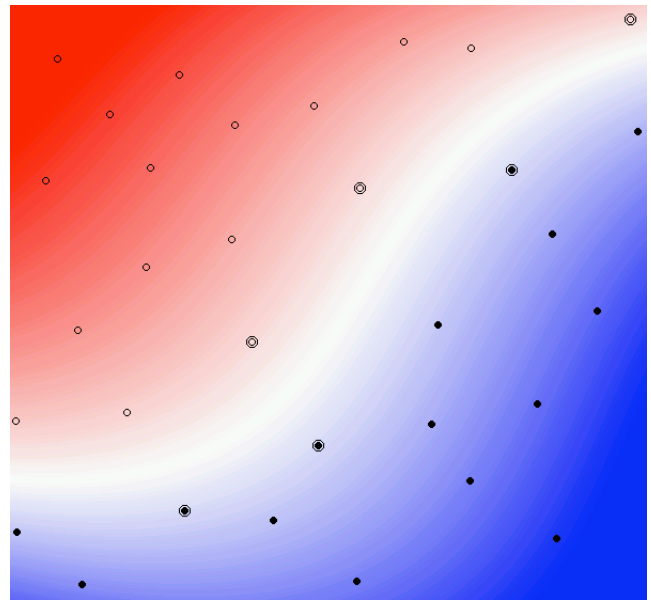
$$\min_{w,\xi} \frac{1}{2}||w||^2 + \frac{C}{m}\sum_{i=1}^{m}\xi_i$$

$$\text{subject to } \xi_i \geq 0, \text{ and } y_i(w \cdot x_i + b) \geq 1 - \xi_i, i = 1, \ldots, m.$$



Non-Linear Separation





- Linear separation impossible in most problems
- Non-linear mapping from input space to high-dimensionnel feature space: $\Phi : X \rightarrow F$
- Generalization ability: independent of the dimension of *F*, depends only on margin and the number of examples

Outline

- Introduction to machine learning
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Kernel Methods

- Idea:
  - Define *K* (called *kernel*) such that:
  - $$\Phi(x) \cdot \Phi(y) = K(x, y)$$
  - *K* often interpreted as a 'similarity measure'
- Benefits:
  - Efficiency: *K* may be much more efficient to compute than Φ and the dot product
  - Flexibility: *K* can be chosen arbitrarily so long as the existence of Φ is guaranteed (Mercer's condition).

Mercer's Condition

- Theorem: Let $X \times X$ be a compact subset of $\mathbb{R}^N$ and let $K : X \times X \to \mathbb{R}$ be in $L_\infty(X \times X)$ and symmetric. Then, *K* admits a uniformly convergent expansion:

$$K(x,y) = \sum_{n=0}^{\infty} a_n \phi_n(x) \phi_n(y), \text{ with } a_n > 0,$$

iff for any function *c* in $L_2(X)$,

$$\int\int_{X \times X} c(x)c(y)K(x,y)dxdy \geq 0.$$

Positive Definite Symmetric Kernels

- Condition equivalent to Mercer's condition in the discrete case: for all $\{x_1, \ldots, x_n\} \subseteq X$, matrix $K(x_i, x_j)_{i,j \leq n}$ is symmetric and:
  - is semi-definite positive: for all $\{c_1, \ldots, c_n\} \subseteq \mathbb{R}$,

$$\sum_{i,j=1}^{n} c_i c_j K(x_i, x_j) \geq 0$$

  - or, equivalently, has non-negative eigenvalues.

Example - Polynomial Kernels

- Definition:

$$\forall x, y \in \mathbb{R}^N, K(x,y) = (x \cdot y + c)^d, \quad c > 0$$

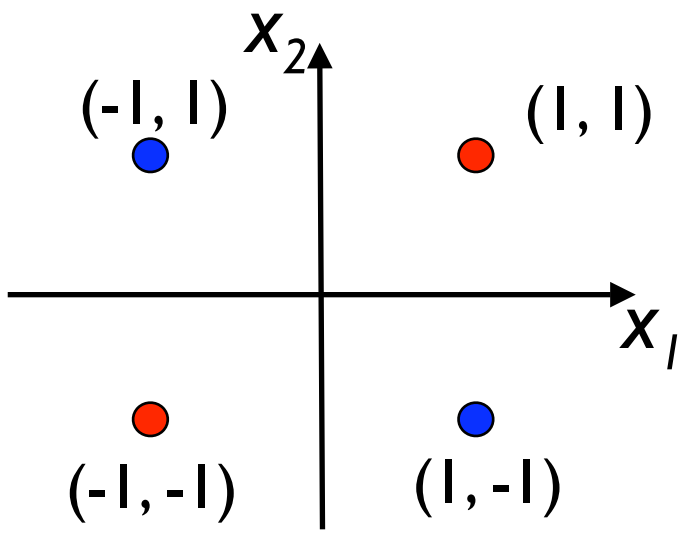
- Example: for $N = 2$ and $d = 2$,

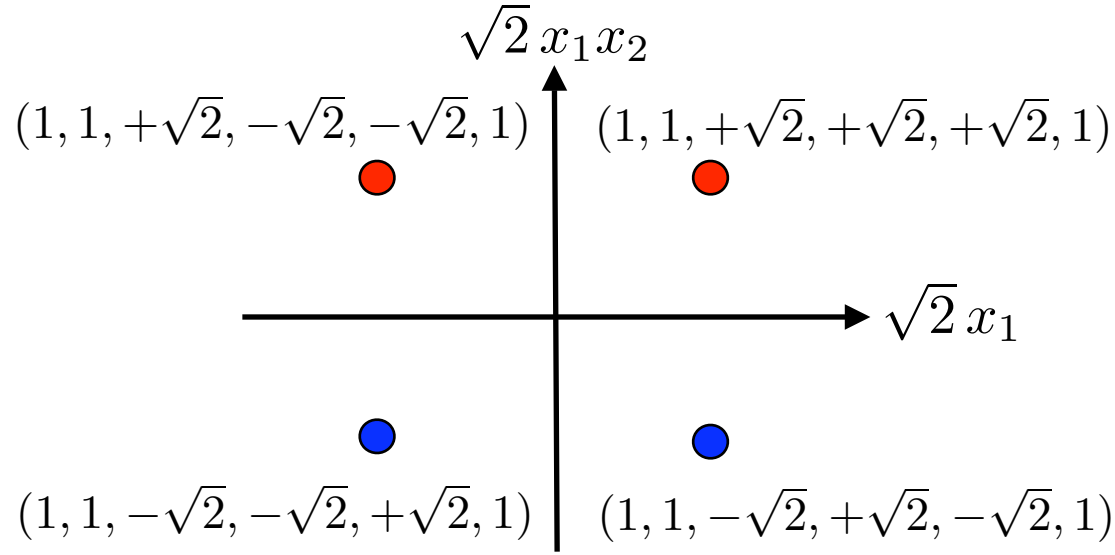
$$K(x,y) = (x_1 y_1 + x_2 y_2 + c)^2$$

$$= \begin{pmatrix} x_1^2 \\ x_2^2 \\ \sqrt{2}\, x_1 x_2 \\ \sqrt{2c}\, x_1 \\ \sqrt{2c}\, x_2 \\ c \end{pmatrix} \cdot \begin{pmatrix} y_1^2 \\ y_2^2 \\ \sqrt{2}\, y_1 y_2 \\ \sqrt{2c}\, y_1 \\ \sqrt{2c}\, y_2 \\ c \end{pmatrix}$$

XOR Problem

- Use second-degree polynomial kernel with $c = 1$:





Linearly non-separable

Linearly separable by $x_1x_2 = 0$

Other Standard PDS Kernels

- Gaussian kernels:

$$K(x,y) = \exp(-\frac{||x-y||^2}{2\sigma^2}), \quad \sigma \neq 0$$

- Sigmoid Kernels:

$$K(x,y) = \tanh(a(x \cdot y) + b), \quad a \geq 0, b \geq 0$$

Closure Properties of PDS Kernels

- Theorem: Positive definite symmetric (PDS) kernels are closed under:
  - sum,
  - product,
  - tensor product,
  - pointwise limit,
  - composition with a power series.

Kernel Applications - Fixed-Size Feature Vectors

- Tissue classification from microarray data:
  - **Support vector machine classification of microarray data**, S. Mukherjee, P. Tamayo, J.P. Mesirov, D. Slonim, A. Verri, and T. Poggio, Technical Report 182, AI Memo 1676, CBCL, 1999.
  - **Support Vector Machine Classification and Validation of Cancer Tissue Samples Using Microarray Expression Data**, Terrence S. Furey, Nigel Duffy, Nello Cristianini, David Bednarski, Michel Schummer, and David Haussler, Bioinformatics. 2000, 16(10):906-914.
  - **Gene Selection for Cancer Classification using Support Vector Machines**, I. Guyon, J. Weston, S. Barnhill and V. Vapnik, Machine Learning 46(1/3): 389 -422, 2002.
  - 2-group classification problem, 2,000 to 97,802-dimensional input vectors, <50 patterns.

`http://sdmc.lit.org.sg/GEDatasets/Datasets.html`

Kernel Applications - Fixed-Size Feature Vectors

- Protein secondary structure prediction:
  - **A Novel Method of Protein Secondary Structure Prediction with High Segment Overlap Measure: Support Vector Machine Approach**, Sujun Hua and Zhirong Sun, Journal of Molecular Biology, vol. 308 n.2, pages 397-407, 2001.
    - 3-group classification problem. 120 dimensional input vectors.
- Protein fold prediction:
  - **Multi-class protein fold recognition using support vector machines and neural networks**, Chris Ding and Inna Dubchak, Bioinformatics, 17:349-358, 2001.
  - **Support Vector Machines for predicting protein structural class,** Yu-Dong Cai, Xiao-Jun Liu, Xue-biao Xu and Guo-Ping Zhou, BMC Bioinformatics (2001) 2:3.
    - 27-group classification problem. 125 dimensional input vectors.

`http://www.support-vector.net/bioinformatics.html`

Outline

- Introduction to machine learning
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- Kernel methods
- Rational kernels
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String Kernels

- Kernels defined over pairs of sequences
- Motivation: computational biology, text and speech classification
- Idea: two sequences are related when they share some common factors/subsequences
- Example: sum of the product of the counts of common factors

Example: Mismatch Kernel

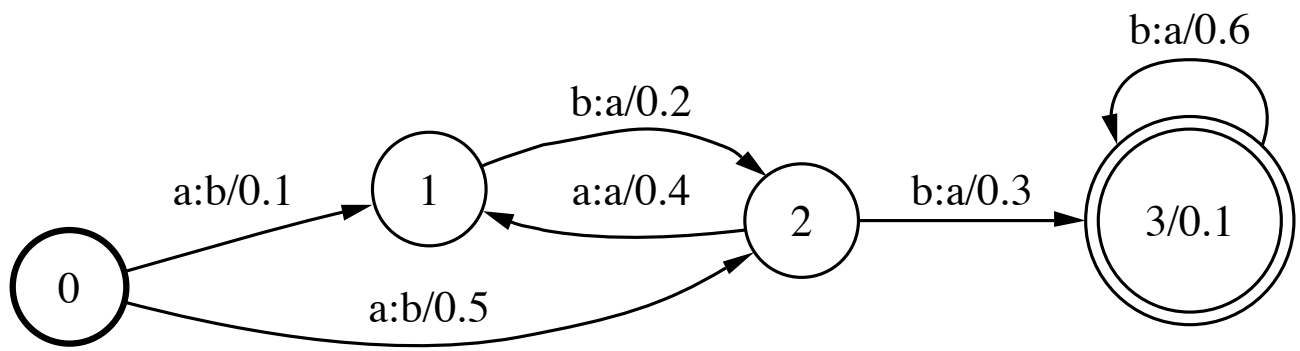
- Definition (Leslie et al., 2002): Let *k* and *m* be non-negative integers with $m \leq k$. The *(k, m)*-mismatch kernel is the kernel defined over protein sequences *x* and *y* by:

$$K_{(k,m)}(x,y) = \sum_{z_1 \in F_k(x),\, z_2 \in F_k(y),\, z \in \Sigma^k} d_m(z_1, z)\; d_m(z, z_2)$$

where $F_k(x)$ is the set of all factors of *x* of length *k*, and

$$d_m(z_1, z_2) = \begin{cases} 1 & |\text{mismatches}| \leq m \\ 0 & \text{otherwise.} \end{cases}$$

Weighted Transducers



$[[T]](x, y) =$ Sum of the weights of all successful paths with input *x* and output *y*

$$[[T]](abb, baa) = .1 \times .2 \times .3 \times .1 + .5 \times .3 \times .6 \times .1$$

Unified Framework for String Kernels

- Definition: a kernel *K* is *rational* if there exists a weighted transducer *T* such that for all strings *x* and *y*:

$$K(x, y) = [[T]](x, y)$$

Rational Kernels Over Weighted Automata

- Definition: a kernel *K* is *rational* if there exists a weighted transducer *T* such that for all weighted automata *A* and *B*:

$$K(A,B) = \sum_{x,y} [[A]](x) \cdot [[T]](x,y) \cdot [[B]](y)$$

This definition can be generalized to the case of an arbitrary *semiring* (general operations).

Computation Algorithm

- Observation:

$$\sum_{x,y} [[A]](x) \cdot [[T]](x,y) \cdot [[B]](y) = \sum_{x,y} [[A \circ T \circ B]](x,y)$$

- Compute composed weighted transducer:

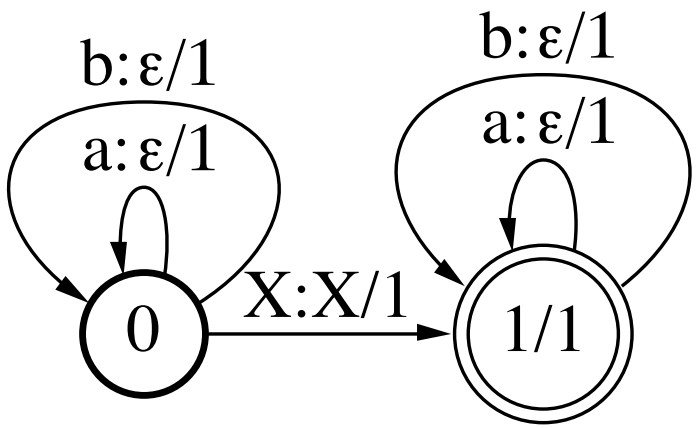
$$U = A \circ T \circ B$$

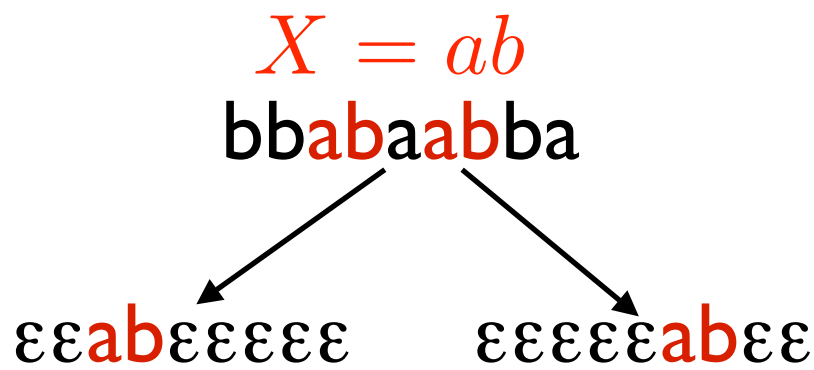
- Use single-source shortest-distance algorithm to compute the sum of the weights of all successful paths of *U*.

Algorithm: Complexity

- Automata case: $O(|T||A||B|)$
- String case:
  - General: $O(|T||x||y|)$
  - Specific, using *failure functions*: $O(|x| + |y|)$

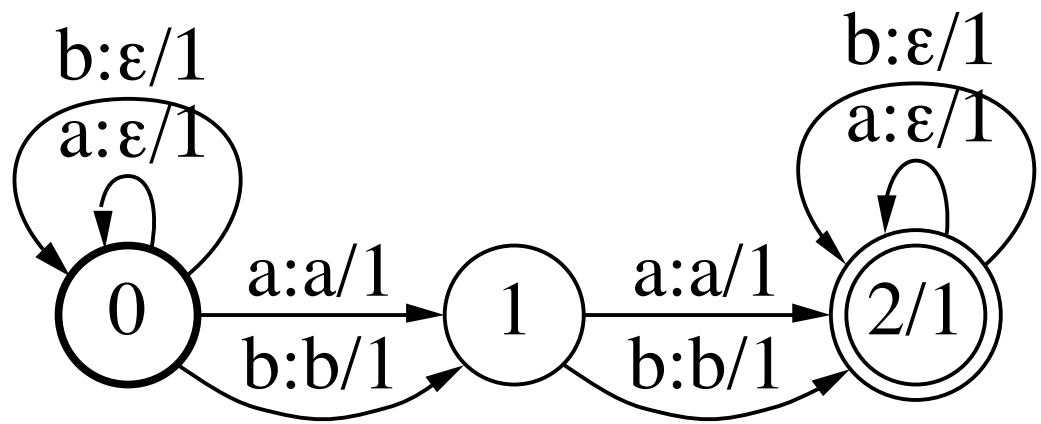
Transducer for Computing Counts





- X may be a string or an automaton representing a regular expression.
- Alphabet $\Sigma = \{a, b\}$.

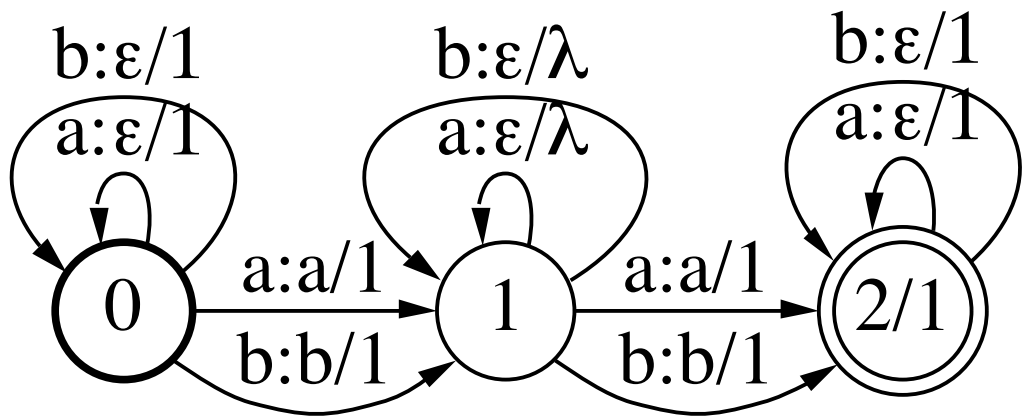
Transducer for Bigram Counts



Weighted Transducer $T, \Sigma = \{a, b\}$

(*A* o *T*) computes the expected count of each bigram (*aa*, *ab*, *ba*, *bb*) in *A*.

Transducer for Gappy Bigram Counts



Weighted Transducer $T', \Sigma = \{a, b\}$

(*A* o *T*) computes the expected count of each 'gappy bigram' (*aa*, *ab*, *ba*, *bb*) in *A*, with gap penalty factor λ.

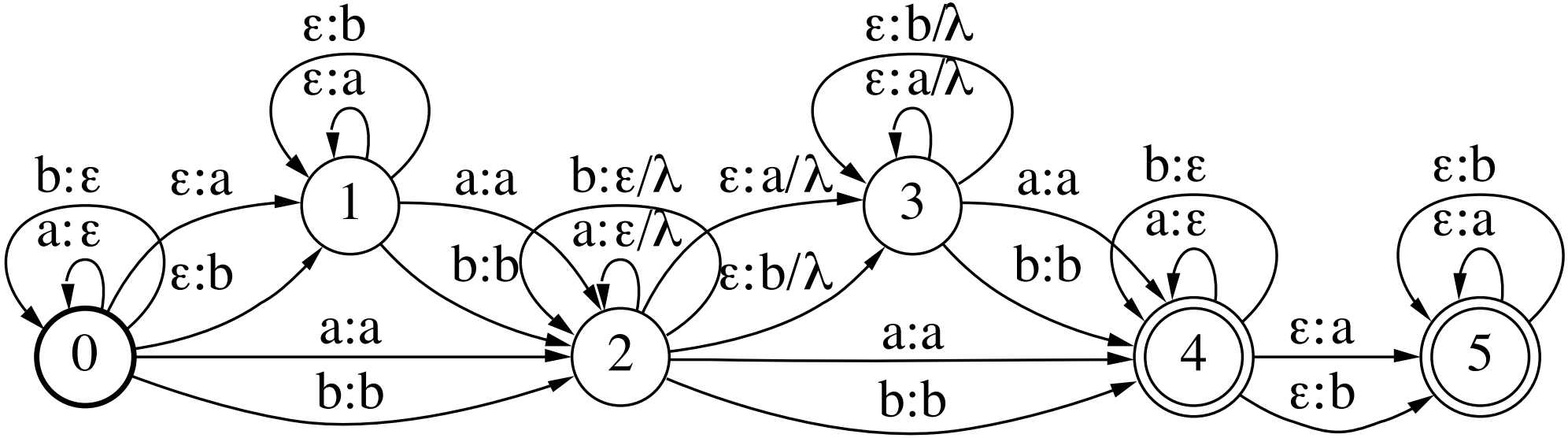
Count-Based Similarity Measures

- Counts of sequences in *A*: $A \circ T$.
- Counts of sequences in *B*: $T^{-1} \circ B$.
- Sum of the product of counts of matching sequences:

$$A \circ (T \circ T^{-1}) \circ B$$

$\Longrightarrow$ Rational kernel $\equiv T \circ T^{-1}$

Representation by WFSTs - Example



Rational kernel $(T' \circ T'^{-1})$

Representation of the kernel of (Lodhi et al., 2002).

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String Kernel Applications (1): Protein Classification, Remote Homology Detection

Remote Homology Problem

- Problem: assign protein sequences to families or superfamilies of proteins for which structural properties are known.
- Data: SCOP (Structural Classification of Proteins into superfamilies and families).
- Classification: 33 superfamilies.

Two-Group Classification

Protein Classification: Remote Homology Detection (SCOP Data, http://scop.berkeley.edu/)

- Allophycocyanin[(Spirulina platensis)]

SIVTKSIVNADAEARYLSPGELDRIKSFVTSGERRVRIAETMTGARERIIKQAGDQLFGKRPDVVSPGGNAYGA
DMTATCLRDLDYYLRLITYGIVAGDVTPIEEIGVGVREMYKSLGTPIEAIAEGVRAMKSVATSLLSGADAAEAGS
YFDYLIGAMS

- Allophycocyanin[(Spirulina platensis)]

MQDAITSVINSSDVQGKYLDASAIQKLKAYFATGELRVRAATTISANAANIVKEAVAKSLLYSDVTRPGGNMYTT
RRYAACIRDLDYYLRYATYAMLAGDPSILDERVLNGLKETYNSLGVPIGATVQAIQAMKEVTAGLVGGGAGKEM
GIYFDYICSGLS

- Snake phospholipase A2 [Eastern cottonmouth snake (Agkistridon piscivorus piscivorus)]

SVLELGKMILQETGKNAITSYGSYGCNCGWGHRGQPKDATDRCCFVHKCCYKKLTDCNHKTDRYSYSWKNK
AIICEEKNPCLKEMCECDKAVAICLRENLDTYNKKYKAYFKLKCKKPDTC

- Snake phospholipase A2 [Eastern cottonmouth snake (Agkistridon piscivorus piscivorus)]

NLFQFEKLIKKMTGKSGMLWYSAYGCYCGWGGQGRPKDATDRCCFVHDCCYGKVTGCNPKMDIYTYSVDN
GNIVCGGTNPCKKQICECDRAAAICFRDNLKTYDSKTYWKYPKKNCKEESEP

- Bacterial chitobiase, n-terminal domain [(Serratia marcescens)]

DQQLVDQLSQLKLNVKMLDNRAGENGVDCAALGADWASCNRVLFTLSNDGQAIDGKDWVIYFHSPRQTLRV
DNDQFKIAHLTGDLYKLEPTAKFSGFPAGKAVEIPVVAEYWQLFRNDFLPRWYATSGDAKPKMLANTDTENLD
QFVAPFTGDQWKRTKDDKNILMTPASRFV

- Tumor supressor, DNA-binding domain [Human (Homo sapiens)]

SSSVPSQKTYQGSYGFRLGFLHSGTAKSVTCTYSPALNKMFCQLAKTCPVQLWVDSTPPPGTRVRAMAIYKQ
SQHMTEVVRRCPHHERCSDSDGLAPPQHLIRVEGNLRVEYLDDRNTFRHSVVVPYEPPEVGSDCTTIHYNY
MCNSSCMGGMNRRPILTIITLEDSSGNLLGRNSFEVRVCACPGRDRRTEEENL

Example: Mismatch Kernel

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where $F_k(x)$ is the set of all factors of *x* of length *k*, and

$$d_m(z_1, z_2) = \begin{cases} 1 & |\text{mismatches}| \leq m \\ 0 & \text{otherwise.} \end{cases}$$

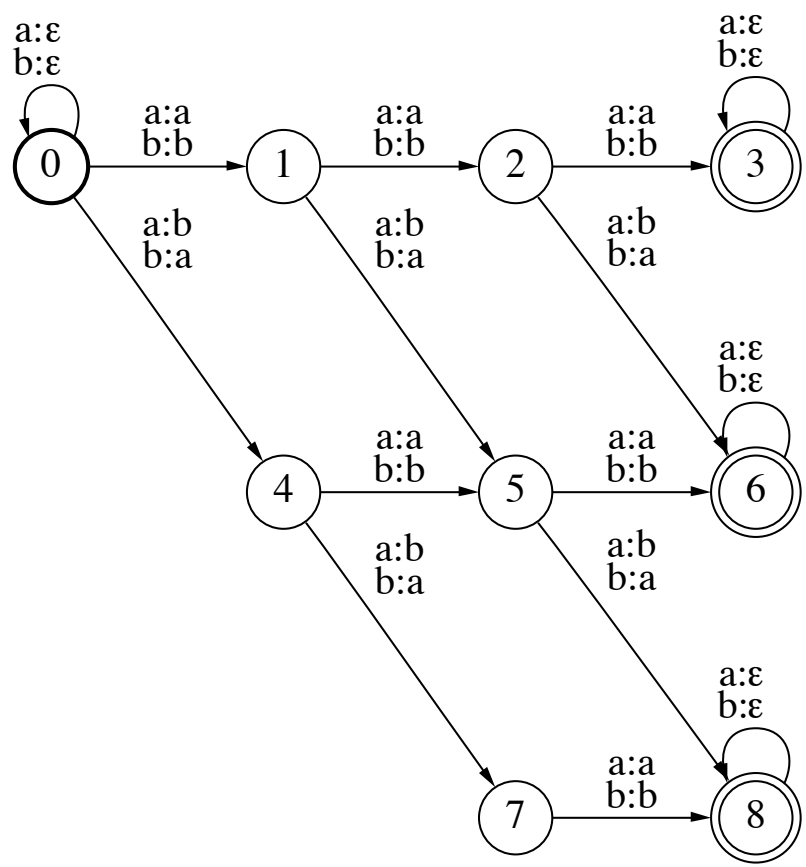
Rational Kernel Representation

- Definition (Leslie et al., 2002): for sequences *x* and *y*,

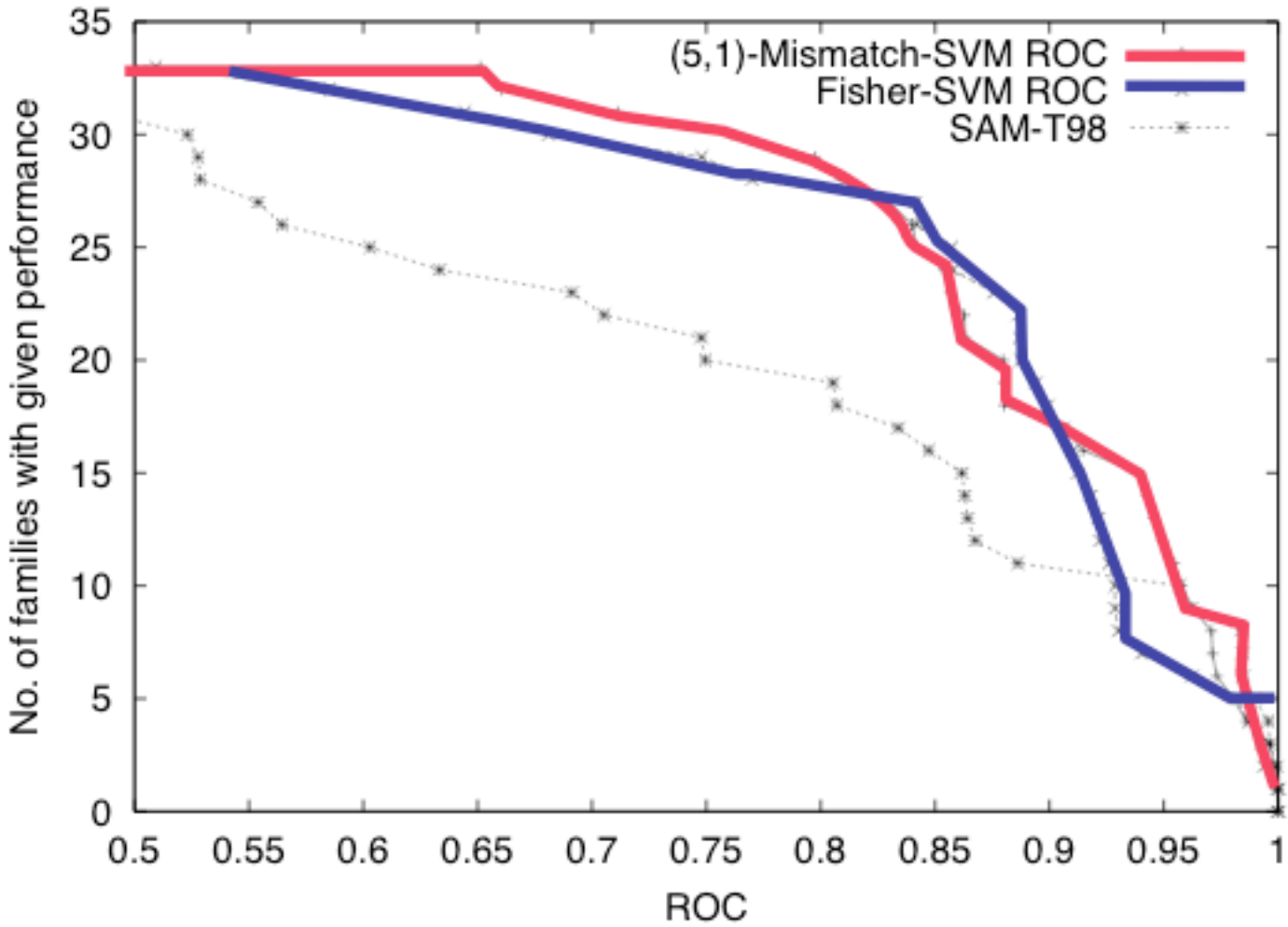
$$K_{(k,m)}(x,y) = \sum_{z_1 \in F_k(x),\, z_2 \in F_k(y),\, z \in \Sigma^k} d_m(z_1,z)\; d_m(z,z_2)$$

- Representation:

$K_{(3,2)}$



Results


(5,1)-Mismatch-SVM ROC
Fisher-SVM ROC
SAM-T98
No. of families with given performance
ROC
0
5
10
15
20
25
30
35
0.5
0.55
0.6
0.65
0.7
0.75
0.8
0.85
0.9
0.95
1

String Kernel Applications (2): Recognition of Translation Initiation Sites

Recognition of Translation Initiation Sites

- Problem: determine whether a start codon position in a DNA sequence is a translation initiation site (TIS).
- Data: (Pedersen and Nielsen, 1997), about 13,500 sequences; 3,300 true TIS.
- Classification problem.

Locality-Improved Kernel

- Definition (Zien et al, 2000): based on matching scores over windows of length *2l + 1*. The locality-improved kernel for two sequences *x* and *y* is defined by (can be combined with polyn. kernel):

$$K(x,y) = \sum_{p=1}^{m} \mathrm{win}_p(x,y),$$

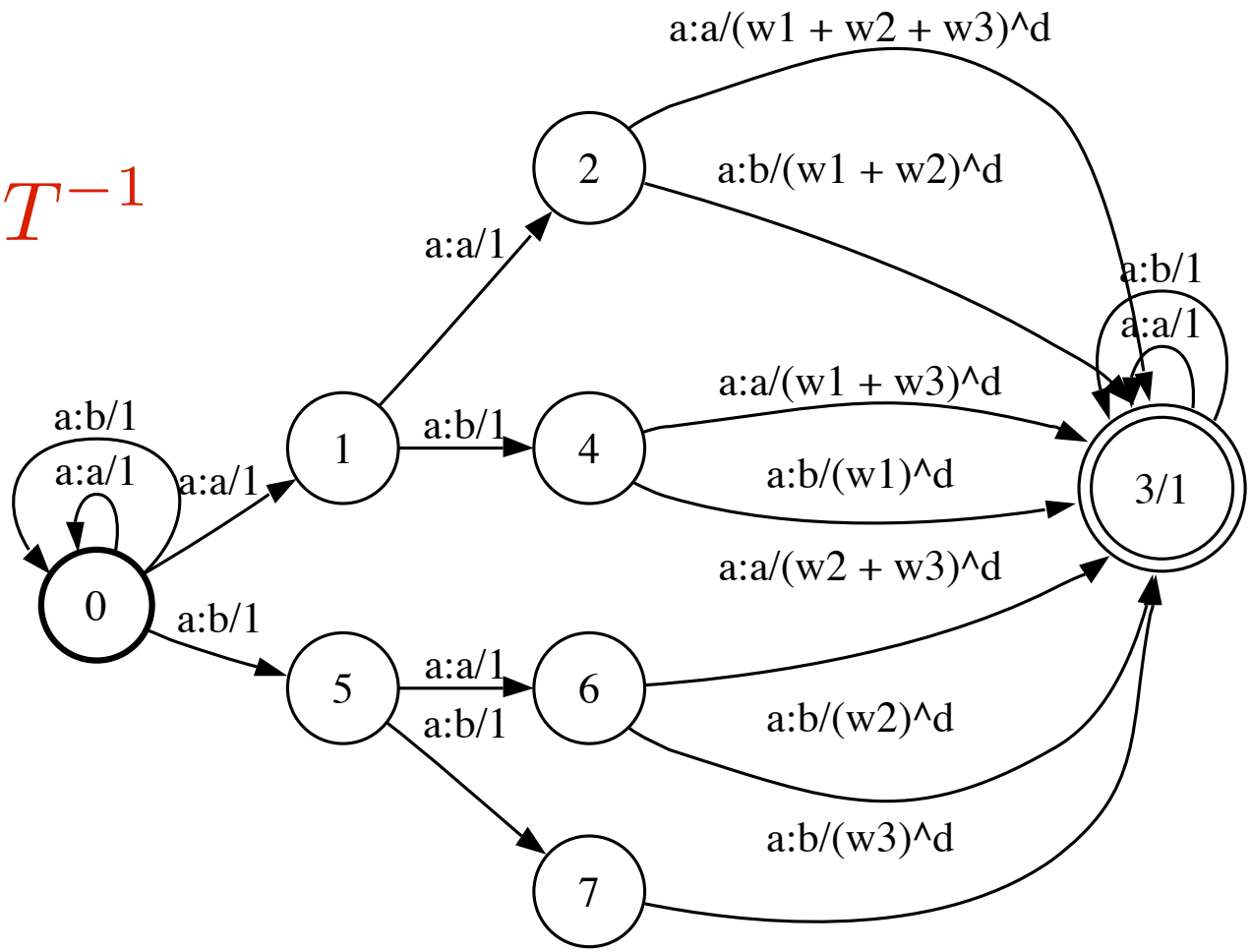
where win_p is defined by:

$$\mathrm{win}_p(x,y) = \left(\sum_{j=-l}^{+l} w_j \mathrm{match}_{p+j}(x,y) \right)^{d_1}.$$

Rational Kernel Representation

- Representation $(l = 1)$:

$T \circ T^{-1}$



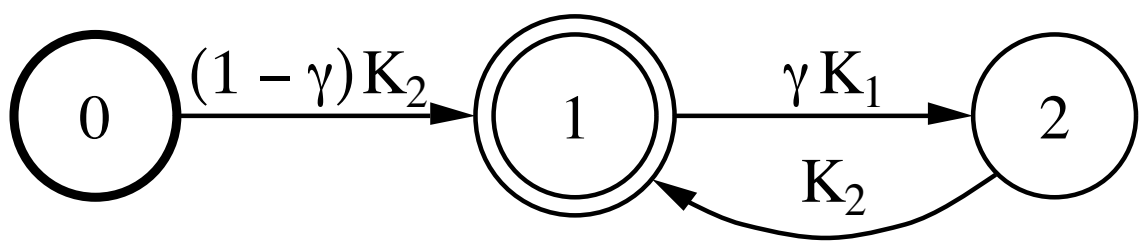
String Kernel Applications (3): Convolution Kernels

Convolution Kernels for Strings

- Definition (Haussler, 1999): K_1 a PDS rational transduction modeling substitutions, K_2 modeling insertions.

$$K_H = (1 - \gamma)[K_2(\gamma K_1 K_2)^*]$$

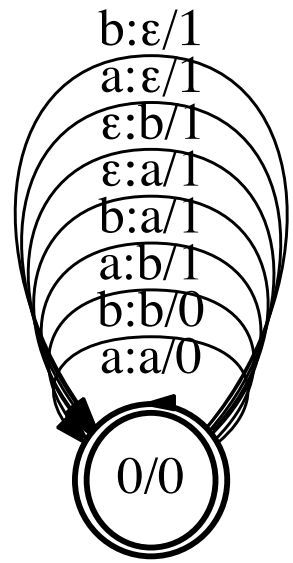
- Representation:



String Kernel Applications (4): Edit-Distance, Smith-Waterman

Edit-Distance

- Theorem: Let Σ be a non-empty finite alphabet. *d* is a symmetric rational kernel. But,
  - *d* is not a PDS kernel.
  - *d* is not *negative definite* if $|\Sigma|>1$



Negative Definite Kernels

- Definition: Let X be a non-empty set. A function $K: X \times X \to \mathbb{R}$ is said to be a *negative definite symmetric (NDS) kernel* if it is symmetric ($K(x, y) = K(y, x)$) and for all $\{x_1, \ldots, x_n\} \subseteq X, \{c_1, \ldots, c_n\} \subseteq \mathbb{R}$, with $\sum_{i=1}^{n} c_i = 0$,

$$\sum_{i=1}^{n} c_i c_j K(x_i, x_j) \leq 0.$$

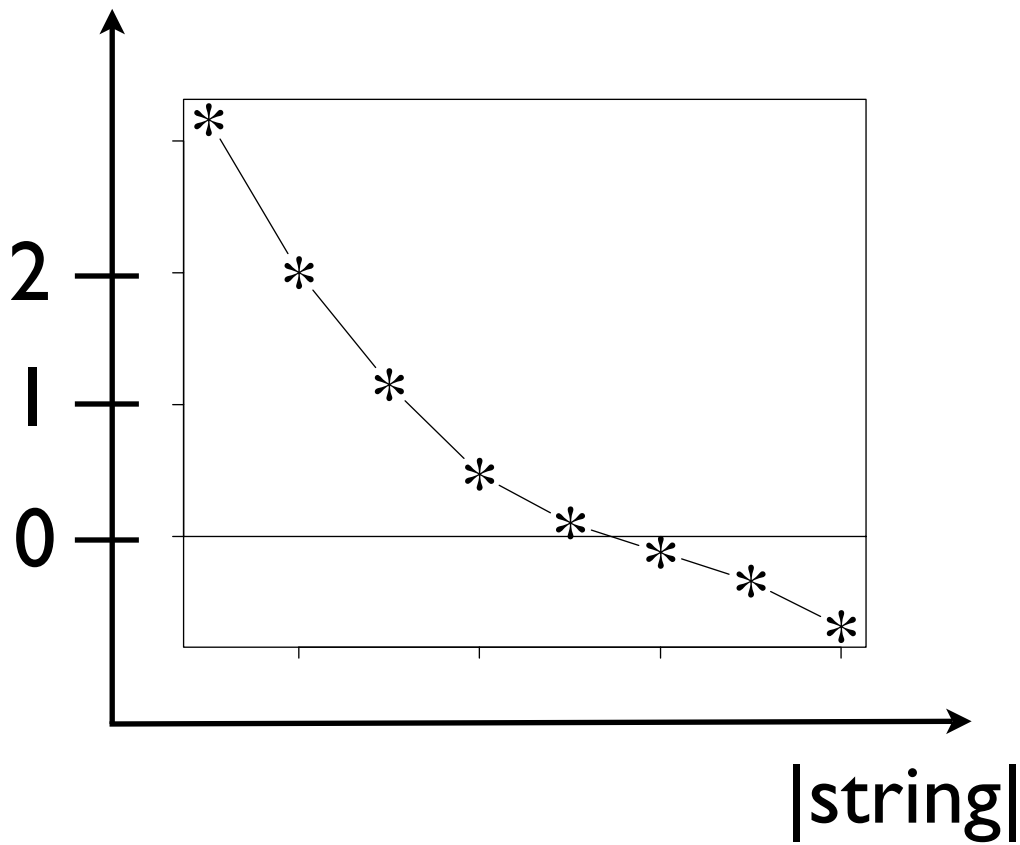
- Clearly, if K is a PDS kernel, then $-K$ is a NDS kernel but the converse is not true in general.

PDS and NDS Kernels

- Theorem: let X be a non-empty set and let $K : X \times X \to \mathbb{R}$ be a symmetric kernel, then:
  - *K* is a NDS kernel iff *exp(-tK)* is a PDS kernel for all $t > 0$;

Edit-Distance

Smallest eigenvalue of *exp(-d)* for $|\Sigma| = 2$



Relationship to Other Kernels in Bioinformatics

- Mismatch kernels (Leslie et al., 2003)
- Convolution kernels (Haussler, 1999)
- Path kernels (Takimoto and Warmuth, 2004)
- Edit-distance (Smith-Waterman)
- Many other string kernels

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Positive Definite Symmetric (PDS) Rational Kernels: Theory

- How to construct a PDS rational kernel?
- Is there a characterization of PDS rational kernels?
- Can we combine PDS rational kernels?

PDS Rational Kernels: General Construction

- T arbitrary weighted transducer
- Theorem: $T \circ T^{-1}$ defines a PDS rational kernel
- Proof ideas:
  - Kernel: $K(x,y) = \sum_{z \in \Delta^*} [[T]](x,z) \cdot [[T]](y,z)$
  - Pointwise limit of:

$$K_n(x,y) = \sum_{|z| \leq n} [[T]](x,z) \cdot [[T]](y,z)$$

  - Matrix $M_n = (K_n(x_i,x_j))_{i \leq l, j \leq l} = AA^t$
  - With: $A = [[T]](x_i,z_j)_{i \leq l, j \leq m}$

PDS Rational Kernels: Characterization?

- Theorem: in the acyclic case, PDS rational kernels are of the form $T \circ T^{-1}$.
- Theorem: PDS rational kernels $S = T \circ T^{-1}$ are closed under sum, product, and Kleene-closure.
- Conjecture: all PDS rational kernels are of the form $T \circ T^{-1}$.

PDS Rational Kernels: Closure Properties

- Theorem: PDS rational kernels are closed under sum, product, and Kleene-Closure.
- Proof ideas (product case):

$$[[T_1 \cdot T_2]](x,y)) = \sum_{x_1 x_2 = x, y_1 y_2 = y} [[T_1]](x_1,y_1)) \cdot [[T_2]](x_2,y_2))$$

$$= \sum_{x_1 x_2 = x, y_1 y_2 = y} (T_1 \odot T_2)((x_1,x_2),(y_1,y_2))$$

  - $(T_1 \odot T_2)$: tensor product is PDS. Thus, there exists a Hilbert Space *H* and a mapping $u \rightarrow \phi_u$ such that:
  - Thus, $K_{T_1} \odot K_{T_2}(u,v) = \langle \phi_u, \phi_v \rangle$

$$[[T_1 \cdot T_2]](x,y) = \left\langle \sum_{x_1 x_2 = x} \phi_{(x_1,x_2)}, \sum_{y_1 y_2 = y} \phi_{(y_1,y_2)} \right\rangle$$

Conclusion

- Rational kernels:
  - unifying framework for the design of kernels in computational biology;
  - theoretical foundation;
  - general and efficient algorithms;
  - can reproduce previous string kernels;
  - easy to visualize and understand;
  - can exploit weighted alternatives.