Exploiting Model Checking in Constraint-based Approaches to the Protein Folding Problem

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Outline of the presentation

- The Protein Folding Problem
- Protein Models
- Model Checking and Temporal Logics
- Model Checking for Protein Folding
- Some preliminary experimental results
- Future developments

The Protein Folding Problem (PFP)

The Protein Folding Problem

Given the *Primary Structure* of a protein, the PSP/PF Problem consists in determining its *Tertiary Structure* (*conformation*).

Anfinsen's thermodynamic hypothesis

The conformation adopted by a protein (*native conformation*) is the one with minimum energy.

Energy functions

The energy of a conformation can be modeled by means of *energy functions*, which express the energy level in terms of the interactions between pairs of amino acids.

Simplified models of proteins

Restrict the admissible positions of amino acids in the space

- lattice space models.

Simplified energy functions

- HP model
- 20×20 potential matrix
- HPNX model

Folding in a square lattice

Definition [Folding]

In $\mathbb{Z}^2$, a *folding* of a sequence $s = s_0 \dots s_n$ is a function $\omega : [0 \dots n] \to \mathbb{Z}^2$ such that

(i) $\forall 0 \leq i < n$, $|\omega(i) - \omega(i+1)| = 1$;

(ii) $\forall i \neq j, \omega(i) \neq \omega(j)$ (ω is self avoiding).

Definition [Topological neighbors]

Two amino acids s_i and s_j of a given folding ω are *topological neighbors* if $j \neq i \pm 1$ and $|\omega(i) - \omega(j)| = 1$.

Energy of a folding

HP: opposite of the number of topological HH neighbors.
20 $\times$ 20: summation of the contribution of each pair of topological neighbors.

Basic assumptions

- The length of a sequence $s = s_0 \dots s_n$ is n.
- To represent the conformations of a sequence of length n, we use the subset $\mathcal{L} = \{(i,j) : i \in [0,2n], j \in [0,2n]\}$ of $\mathbb{N}^2$.
- W.l.o.g., we assume $\omega(0) = (n,n)$ and we fix $\omega(1) = (n,n+1)$.
- We represent a folding of a sequence of length n as a string of length $n-1$ on the alphabet $\{l,f,r\}$.

An example

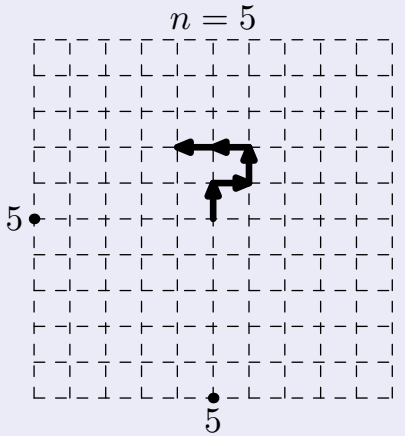

Figure: String *rllf* on 10 $\times$ 10 lattice.

The number of all possible foldings of a sequence of length n is bounded by 3^{n-1} (it is $\sim \frac{1.93 \cdot 2.64^n \cdot n^{0.34}}{4}$).

Valid transformations among foldings

Definition [Pivot Move]

Let $f = f_2 \ldots f_n$, with $f_i \in \{l, f, r\}$ for all $2 \leq i \leq n$, be a folding of a sequence s of length n. A folding f' of s is obtained from f through a *pivot move* with pivot $k-1$, with $2 \leq k \leq n$, if $f'_i = f_i$ for all $i \neq k$ and $f'_k \neq f_k$.

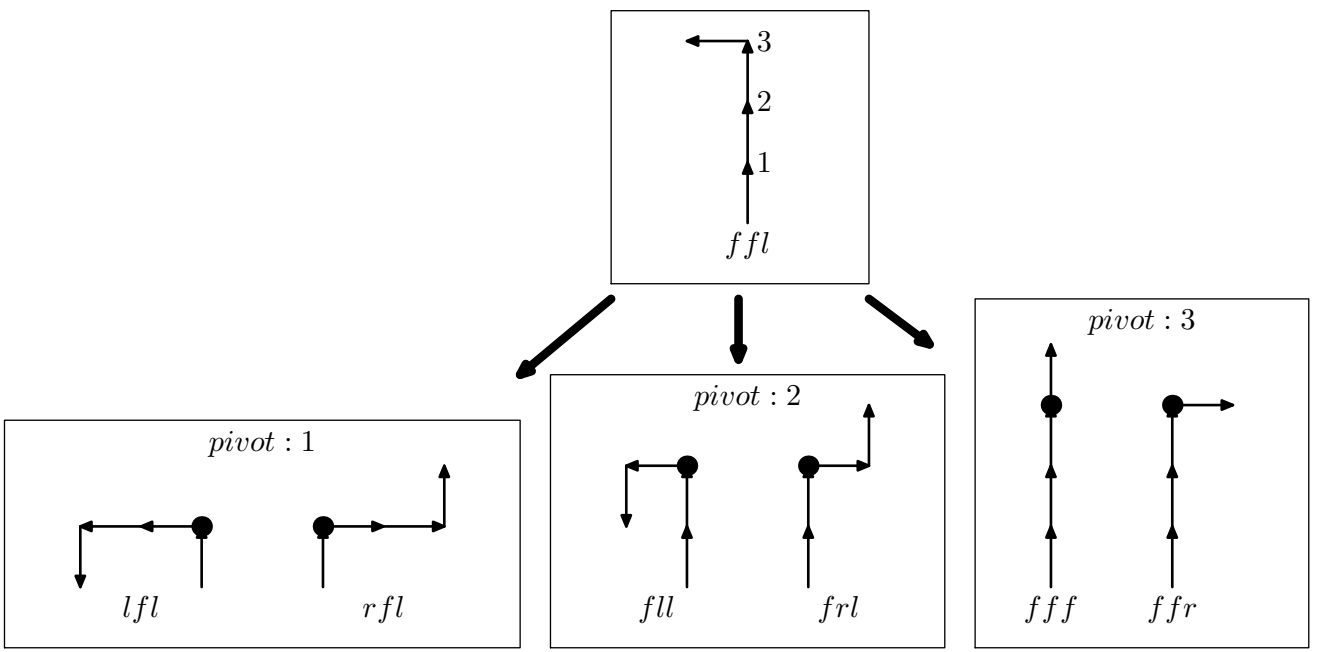

Figure: Pivot moves from string *ffl*.

Transition Systems

Definition [Transition System]

Let AP be a set of atomic propositions. A *transition system* over AP is a tuple $M = (Q, T, L)$, where

- Q is a finite set of states;
- $T \subseteq Q \times Q$ is a total transition relation, that is, for every state $q \in Q$ there is a state $q' \in Q$ such that $T(q, q')$;
- $L : Q \to 2^{AP}$ is a labeling function that maps every state into the set of atomic propositions that hold at it.

2D Protein Transition System

The 2D Protein Transition System of a string P of length n over $\{H, P\}$ is a tuple $M_P = (Q, T, L)$, where

- Q is the set of all foldings of length n on the $2n \times 2n$ 2D lattice;
- $T \subseteq Q \times Q$ contains the pairs of states (q_1, q_2) such that q_2 can be obtained from q_1 by a pivot move;
- $L : Q \to 2^{AP}$ is a labeling function over the set AP of atomic propositions which consists of the following 3(n-1) predicates

$$2nd\_l, \ldots, ith\_l, \ldots, nth\_l,$$
$$2nd\_f, \ldots, ith\_f, \ldots, nth\_f,$$
$$2nd\_r, \ldots, ith\_r, \ldots, nth\_r,$$

plus the following three predicates

$$min\_en, \quad inter\_en, \quad max\_en.$$

Temporal Logics

- Temporal logics are formalisms for describing sequences of transitions between states.
- CTL* (*computation tree logic*).
- CTL* formulae are obtained by (repeatedly) applying Boolean connectives ($\wedge, \vee, \neg, \rightarrow$), *path quantifiers* ($A, E$), and *state quantifiers* (X, U, F, G) to atomic formulae.

Path quantifiers

A: all paths starting from a given state have some property.

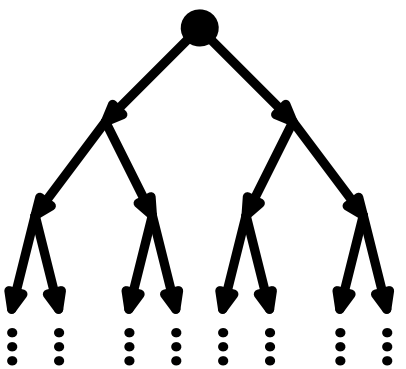

Figure: *Af*

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Path quantifiers

E: some path starting from a given state has some property.

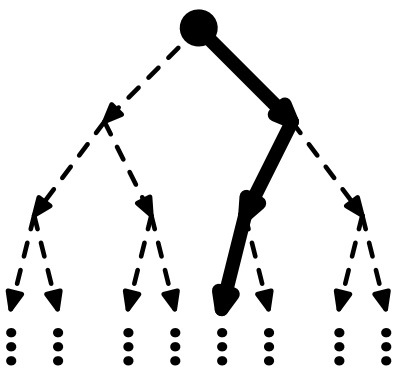

Figure: *Ef*

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State quantifiers

X (*next time*): a property holds at the next state of a path.

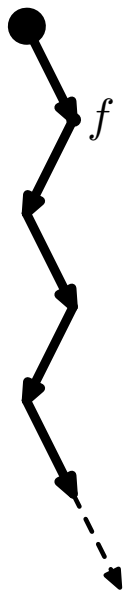

Figure: *Xf*

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State quantifiers

U (*until*): there is a state on the path where the second of its argument properties holds and, at every preceding state on the path, the first of its two argument properties holds.

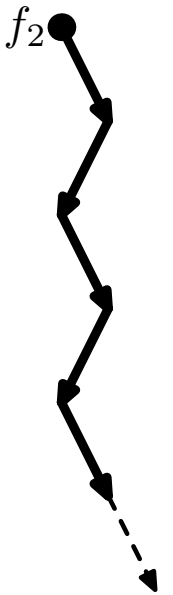

Figure: f_1 U f_2

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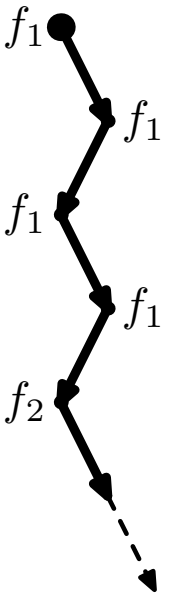

Figure: f_1 U f_2

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State quantifiers

F (*sometimes in the future*): a property holds at some state on the path.

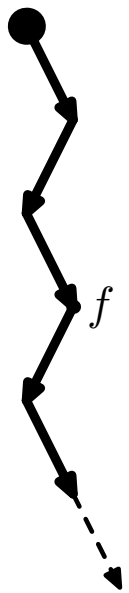

Figure: *Ff*

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State quantifiers

G (*always in the future*): a property is true at every state on the path.

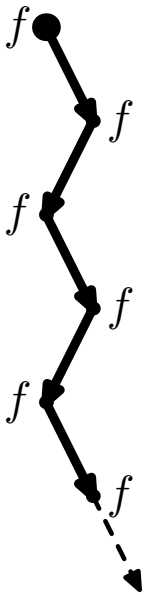


Figure: *Gf*

CTL and LTL (1)

We focus our attention on two proper fragments of CTL*.

CTL (branching time logic)

- It allows one to quantify over the paths starting from a given state.
- It constrains every state quantifier to be immediately preceded by a path quantifier.

LTL (linear time logic)

- It allows to describe events along a single computation path.
- Its formulae are of the form $\mathbf{A}f$, where f does not contain path quantifiers, but it allows the nesting of state quantifiers.

CTL and LTL (2)

CTL (branching time logic)

- The complexity of model checking is linear in the number of states and edges of the transition system.
- There are many tools for checking if finite state systems satisfy CTL formulae.

LTL (linear time logic)

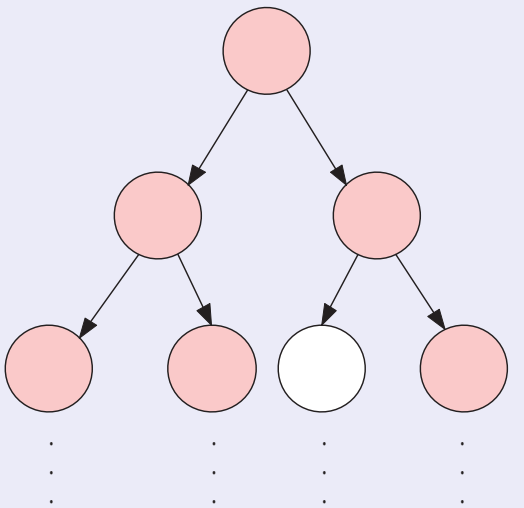
- The model checking problem is PSPACE-complete.
- To master the complexity of LTL model checking: on-the-fly model checking.

The Model Checking Problem

- Given a Transition System $M = (Q, T, L)$, a state $q \in Q$, and a temporal logic formula f expressing some desirable property of the system, the *model checking problem* consists in establishing whether $M, q \models f$ or not.

If q does not satisfy the formula, model checking algorithms produce a counterexample that falsifies it.

AG pink?



Properties of the 2D Protein Transition System (1)

F1: Does it exist a path of length at most k that reaches a state with minimum energy?

CTL: $min\_en \vee EXmin\_en \vee \cdots \vee \underbrace{EX \ldots EX}_{k} min\_en \equiv$

$\bigvee_{i=0}^{k} E_1 X_1 \ldots E_i X_i min\_en.$

LTL:

$A(\neg min\_en \wedge X \neg min\_en \wedge XX \neg min\_en \wedge \cdots \wedge \underbrace{X \ldots X}_{k} \neg min\_en)$

$\equiv A(\bigwedge_{i=0}^{k} X_1 \ldots X_i \neg min\_en).$

Properties of the 2D Protein Transition System (2)

F2: Is energy the minimum one? Alternatively, if energy is the maximum one, is it possible to reach a state with minimum energy without passing through states with intermediate energy?

CTL, LTL: $A(max\_en\ U\ min\_en)$.

Properties of the 2D Protein Transition System (3)

F3: Is it possible to reach in one step a folding where the first half of the sequence is a helix of the form *rrllrr* . . . ?

If $m = \lfloor n/2 \rfloor$ is odd, we have:
CTL: $EX(\bigwedge_{i=2,i=2+4\cdot j,j\geq 0}^{m-1}(ith\_r \wedge i+1th\_r) \wedge \bigwedge_{i=4,i=4+4\cdot j,j\geq 0}^{m-1}(ith\_l \wedge i+1th\_l))$.
If $m = 2+4\cdot j, j \geq 0$, we have:
CTL: $EX(\bigwedge_{i=2,i=2+4\cdot j,j\geq 0}^{m-1}(ith\_r \wedge i+1th\_r) \wedge \bigwedge_{i=4,i=4+4\cdot j,j\geq 0}^{m-1}(ith\_l \wedge i+1th\_l) \wedge mth\_r)$.
If $m = 4+4\cdot j, j \geq 0$, we have:
CTL: $EX(\bigwedge_{i=2,i=2+4\cdot j,j\geq 0}^{m-1}(ith\_r \wedge i+1th\_r) \wedge \bigwedge_{i=4,i=4+4\cdot j,j\geq 0}^{m-1}(ith\_l \wedge i+1th\_l) \wedge mth\_l)$.

Properties of the 2D Protein Transition System (4)

F4: Is it true that every state which is at most k steps far from the current one has maximum energy, i.e., energy equal to 0?

CTL: $max\_en \wedge AXmax\_en \wedge \cdots \wedge \underbrace{AX \ldots AX}_{k} max\_en \equiv$

$\bigwedge_{i=0}^{k} A_1 X_1 \ldots A_i X_i max\_en.$

LTL: $A(max\_en \wedge Xmax\_en \wedge \cdots \wedge \underbrace{X \ldots X}_{k} max\_en) \equiv$

$A(\bigwedge_{i=0}^{k} X_1 \ldots X_i max\_en).$

Experimental results (1)

SICStus Prolog

- 2D Protein Transition System
- Model Checking algorithms to verify properties F1-F4 and other relevant properties.

Example

States with energy equal to 0 that satisfy property $F1$ when $k = 1$, i.e., states with maximum energy that reach in one step a state with minimum energy.

Experimental results (2)

N=8

HP model

string= *HHHHHHHHH*;
min_en=-4;
States fullfiling the request (8):
$lrflflf \rightarrow llflflf$, $lfflflf \rightarrow llflflf$,
$rlfrfrf \rightarrow rrfrfrf$, $rffrfrf \rightarrow rrfrfrf$,
$flflfrl \rightarrow flflfll$, $flflffl \rightarrow flflfll$,
$frfrflr \rightarrow frfrfrr$, $frfrffr \rightarrow frfrfrr$.

20×20 model

string= *cilfmvwhy*;
min_en=-8179;
States fullfiling the request (4):
$lrflflf \rightarrow llflflf$, $lfflflf \rightarrow llflflf$,
$rlfrfrf \rightarrow rrfrfrf$, $rffrfrf \rightarrow rrfrfrf$.

Experimental results (3)

Example

Are there states with an energy different from the minimum one that may reach in one step a state with a greater energy which, in its turn, may reach in a few steps a state with minimum energy?

HP model

N=7;
string= *HHHHHHHH*;
min_en=-3;
$lrlfll(-2) \rightarrow lrlffl(0) \rightarrow lrllfl(-3)$.

20×20 model

N= 5;
string= *pcdehw*;
min_en=-2777;
$flrr(-613) \rightarrow flrf(0) \rightarrow fllf(-2777)$.

Ongoing work and future developments

State explosion problem: a protein of length n gives rise to a transition system where the number of states is $\Theta(3^{n-1})$.

$\Rightarrow$

On the fly Model Checking.

Improve the solution search of the protein folding problem.

Understand protein energy functions.

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THANKS