Inferring Parameters for an Elementary Step Model of DNA Structure Kinetics with Locally Context-Dependent Arrhenius Rates
Appendix

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A Local Context

In this document, we use 0-based numbering for numbering bases, i.e, in a multi-strand complex, for each strand of length l, the first nucleotide at the 5' end of the strand is numbered 0 and the last nucleotide at the 3' end of the strand is indexed $l - 1$.

To determine the local context of a base pair forming or breaking in a pseudoknot-free structure, we use Algorithm 1. This algorithm uses *dot-parens-plus* notation to represent a secondary structure (state), which consists of '(', ')', '.', and '+'. Matching parentheses represent bases which have formed a base pair, a dot represents a free base pair, and a plus represents a break between strands. For example, '((((((+))))))' means that bases 0, 1, 2, 3, 4, and 5 of the first strand are paired to bases 5, 4, 3, 2, 1, and 0 of the second strand, respectively. When all base pairs between strands break, we replace the plus sign by a space. For example, '..... .....' means that no base pair is formed.

Algorithm 1: Find the local context of a base pair forming or breaking

Function `LocalContext`(s_i, s_j)

Input: States s_i and state s_j, which differ in exactly one base pair. (Either of the states can have an extra base pair compared to the other.)

Output: $\langle l, r \rangle$, which is the local context of the base pair breaking or forming.

$d_i \leftarrow$ dot-parens-plus notation of s_i

$d_j \leftarrow$ dot-parens-plus notation of s_j

Insert '*' at the start and end of d_i and d_j, before and after all '+' signs, and before and after every space

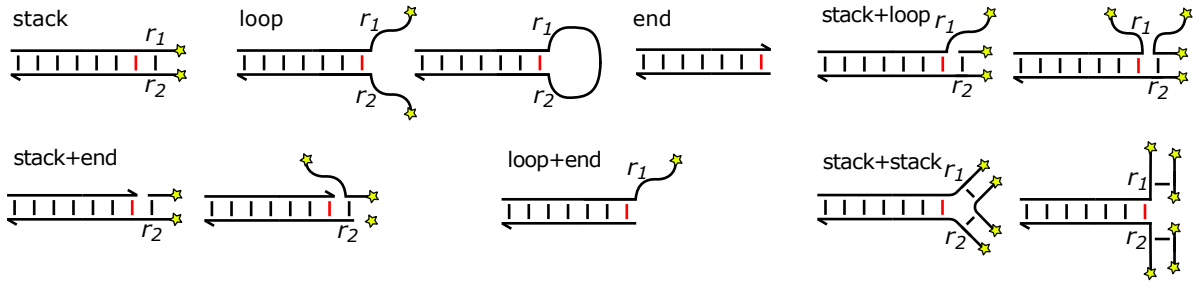
$(p_1, p_2) \leftarrow$ the first and second positions where d_i and d_j differ, respectively

$l \leftarrow$ `HalfContext` $(d_i, p_1 - 1, p_2 + 1)$ `// Algorithm 2`

$r \leftarrow$ `HalfContext` $(d_i, p_1 + 1, p_2 - 1)$

return $\langle l, r \rangle$

Algorithm 2: Find the half context on one side of a base pair forming or breaking



Function `HalfContext`(d, f_1, f_2)

Input: d is a dot-parans-plus notation, f_1 and f_2 represent one side of the base pair forming or breaking. (f_1 and f_2 are adjacent to the base pair forming or breaking).

Output: The half context appearing in positions f_1 and f_2.

$c_1 \leftarrow d[f_1]$
$c_2 \leftarrow d[f_2]$
if $c_1 =$ '(' and $c_2 =$ ')' **then**
  counter $\leftarrow 0$
  for k in $[f_1, f_2]$ **do**
    if $d[k] =$ '(' **then** counter $\leftarrow$ counter + 1
    else if $d[k] =$ ')' **then** counter $\leftarrow$ counter - 1
    if counter $= 0$ **then**
      if $k = p_j$ **then** return stack
      else return stack+stack
if ($c_1 =$ '(' and $c_2 =$ '(') or ($c_1 =$ ')' and $c_2 =$ ')') or ($c_1 =$ ')' and $c_2 =$ '(') **then** return stack+stack
if ($c_1 =$ '(' and $c_2 =$ '.') or ($c_1 =$ ')' and $c_2 =$ '.') or ($c_1 =$ '.' and $c_2 =$ ')') or ($c_1 =$ '.' and $c_2 =$ '(') **then** return stack+loop
if $c_1 =$ '(' and $c_2 =$ '*') or ($c_1 =$ ')' and $c_2 =$ '*') or ($c_1 =$ '*' and $c_2 =$ ')') or ($c_1 =$ '*' and $c_2 =$ '(') **then** return stack+end
if ($c_1 =$ '.' and $c_2 =$ '*') or ($c_1 =$ '*' and $c_2 =$ '.') **then** return loop+end
if $c_1 =$ '*' and $c_2 =$ '*' **then** return end
if $c_1 =$ '.' and $c_2 =$ '.' **then** return loop

B Interacting DNA Strands State Space

To generate the state space we use Algorithm 3 in combination with a reaction-specific set of initial states $\mathcal{S}_{\text{init}}$ and final states $\mathcal{S}_{\text{final}}$ and a reaction-specific function that returns neighboring states for a state s, `NeighborStates`(s). Algorithm 3 uses a breadth-first search approach: initially, the queue Q and candidate state space $\mathcal{S}_{\text{init}}$ are composed of just the initial states. For every state in the queue, unexplored successor states are added to the candidate state space and then queued for exploration. In this paper, we use only one initial state and one final state per reaction.

Next, we explain the state space we used specific to different types of reactions in our dataset.

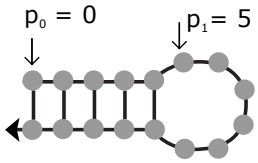
Algorithm 3: Generate state space

Function `GenerateStateSpace`
- $\mathcal{S} \leftarrow \mathcal{S}_{\text{init}}$, $Q \leftarrow \mathcal{S}_{\text{init}}$
- **while** $Q \neq \emptyset$ **do**
  - $\mathcal{N} \leftarrow \emptyset$
  - **foreach** $s \in Q$ **do**
    - **foreach** $s_p \in$ `NeighborStates(s)` **do**
      - **if** $s_p \notin \mathcal{S}$ **and** $s_p \notin \mathcal{S}_{\text{final}}$ **then**
        - $\mathcal{S} \leftarrow \mathcal{S} \cup s_p$
        - $\mathcal{N} \leftarrow \mathcal{N} \cup s_p$
  - $Q \leftarrow \mathcal{N}$
- $\mathcal{S} \leftarrow \mathcal{S} \cup \mathcal{S}_{\text{final}}$
- return $\mathcal{S}$

B.1 Hairpin Closing and Opening

Let l be the length of the hairpin strand and let $m < l/2$ be the length of the stem in the fully closed position. Each state is represented by a tuple $\langle p_i, p_j \rangle$, where $0 \leq p_i \leq p_j \leq m$. The tuple indicates that the bases p_i to $p_j - 1$ are paired with bases $l - p_j$ to $l - p_i - 1$ respectively, and no other base pairs are formed. Algorithm 4 describes the neighbors of a hairpin state s. The state space of hairpin opening and closing are equal, except that the initial and final states are swapped. In hairpin closing, in the initial state ($\mathcal{S}_{\text{init}} = \{\langle 0, 0 \rangle\}$), no base pairs have formed. In the final state ($\mathcal{S}_{\text{final}} = \{\langle 0, m \rangle\}$), all base pairs have formed.

Algorithm 4: Find possible neighbors of a hairpin state s



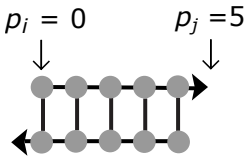
Function `NeighborStates(`s`)`
- $\langle p_i, p_j \rangle \leftarrow s$, $\mathcal{N} \leftarrow \emptyset$
- `// Consider possibly invalid new states, then remove the invalid ones`
- **if** $\langle p_i, p_j \rangle = \langle 0, 0 \rangle$ **then**
  - **for** $p_n \in [0, m-1]$ **do**
    - $\mathcal{N} \leftarrow \mathcal{N} \cup \langle p_n, p_n + 1 \rangle$
- **else**
  - $\mathcal{N} \leftarrow \mathcal{N} \cup \langle p_i - 1, p_j \rangle \cup \langle p_i + 1, p_j \rangle \cup \langle p_i, p_j - 1 \rangle \cup \langle p_i, p_j + 1 \rangle$
- **for** $s' \in \mathcal{N}$ **do**
  - `// The state in which no base pair has formed is shown by` $\langle 0, 0 \rangle$
  - **if** $p_i = p_j$ **then** $\mathcal{N} \leftarrow (\mathcal{N} \setminus s') \cup \langle 0, 0 \rangle$
- **for** $s' \in \mathcal{N}$ **do**
  - `// Remove invalid states`
  - **if** `!AllowedState(`s'`)` **then** $\mathcal{N} \leftarrow \mathcal{N} \setminus s'$
- return $\mathcal{N}$

Function `AllowedState(`s'`)`
- $\langle p_i, p_j \rangle \leftarrow s'$
- **if** $!(0 \leq p_i \leq p_j \leq m)$ **then** return False
- return True

B.2 Helix Association and Dissociation

Let l be the length of a strand in the helix. Each state is represented with a tuple $\langle p_i, p_j \rangle$, where $0 \leq p_i \leq p_j \leq l$. The tuple indicates that all bases numbered p_i to $p_j - 1$ in one strand have paired with bases numbered $l - p_j$ to $l - p_i - 1$ in the other strand, respectively, and there are no other base pairs in the state. Algorithm 5 describes the neighbors of a helix state s. The state space of helix association and dissociation are equal, except that the initial and final states are swapped. In helix association, in the initial state ($\mathcal{S}_{\text{init}} = \{\langle 0, 0 \rangle\}$), no base pairs have formed between the two strands. In the final state ($\mathcal{S}_{\text{final}} = \{\langle 0, l \rangle\}$), all base pairs have formed between the two strands.

Algorithm 5: Find possible neighbors of a helix state s



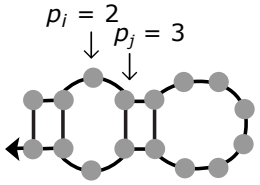
Function `NeighborStates` (s)
- $\langle p_i, p_j \rangle \leftarrow s$, $\mathcal{N} \leftarrow \emptyset$
- `// Consider possibly invalid new states, then remove the invalid ones`
- **if** $\langle p_i, p_j \rangle = \langle 0, 0 \rangle$ **then**
  - **for** p_n in $[0, l-1]$ **do**
    - $\mathcal{N} \leftarrow \mathcal{N} \cup \langle p_n, p_n + 1 \rangle$
- **else**
  - $\mathcal{N} \leftarrow \mathcal{N} \cup \langle p_i - 1, p_j \rangle \cup \langle p_i + 1, p_j \rangle \cup \langle p_i, p_j - 1 \rangle \cup \langle p_i, p_j + 1 \rangle$
- **for** $s' \in \mathcal{N}$ **do**
  - `// The state in which no base pair has formed is shown by` $\langle 0, 0 \rangle$
  - **if** $p_i = p_j$ and $p_i \neq 0$ **then** $\mathcal{N} \leftarrow (\mathcal{N} \setminus s') \cup \langle 0, 0 \rangle$
- **for** $s' \in \mathcal{N}$ **do**
  - `// We remove invalid states`
  - **if** `!AllowedState(`s'`)` **then** $\mathcal{N} \leftarrow \mathcal{N} \setminus s'$
- return $\mathcal{N}$

Function `AllowedState(`s'`)`
- $\langle p_i, p_j \rangle \leftarrow s'$
- **if** $!(0 \leq p_i \leq p_j \leq l)$ **then** return False
- return True

B.3 Bubble Closing

Let l be the length of the hairpin strand, $m < l/2$ be the length of the stem in the fully closed position, and f be the position where a bubble is formed. Each state is represented with a tuple $\langle p_i, p_j \rangle$, where $0 < p_i < p_j < m$. The tuple indicates that all bases numbered 0 to $p_i - 1$ have paired with bases numbered $l-p_i$ to $l-1$, respectively, and all bases numbered p_j to $m-1$ have paired with bases numbered $l-m$ to $l-p_j-1$, respectively, and there are no other base pairs in the state. Algorithm 6 describes the neighbors of a bubble closing state s. In the initial state ($\mathcal{S}_{\text{init}} = \{\langle f-1, f \rangle\}$), all base pairs in the hairpin stem have formed except for a bubble of size 1 in the stem at position f. In the final state ($\mathcal{S}_{\text{final}} = \{\langle f, f \rangle\}$), all base pairs have formed.

Algorithm 6: Find possible neighbors of a bubble state s



Function `NeighborStates` (s)
  $\langle p_i, p_j \rangle \leftarrow s$, $\mathcal{N} \leftarrow \emptyset$
  `// Consider possibly invalid new states, then remove the invalid ones`
  $\mathcal{N} \leftarrow \mathcal{N} \cup \langle p_i - 1, p_j \rangle \cup \langle p_i + 1, p_j \rangle \cup \langle p_i, p_j - 1 \rangle \cup \langle p_i, p_j + 1 \rangle$
  for $s' \in \mathcal{N}$ **do**
    `// The state in which all base pairs have formed is shown by` $\langle f, f \rangle$
    if $p_i = p_j$ and $p_i \neq f$ **then** $\mathcal{N} \leftarrow (\mathcal{N} \setminus s') \cup \langle f, f \rangle$
  for $s' \in \mathcal{N}$ **do**
    `// Remove invalid states`
    if `!AllowedState(`s'`)` **then** $\mathcal{N} \leftarrow \mathcal{N} \setminus s'$
  return $\mathcal{N}$
Function `AllowedState(`s'`)`
  $\langle p_i, p_j \rangle \leftarrow s'$
  if $!(0 < p_i \leq f \leq p_j < m)$ **then** return False
  return True

B.4 Toehold-mediated 3-way Strand Displacement

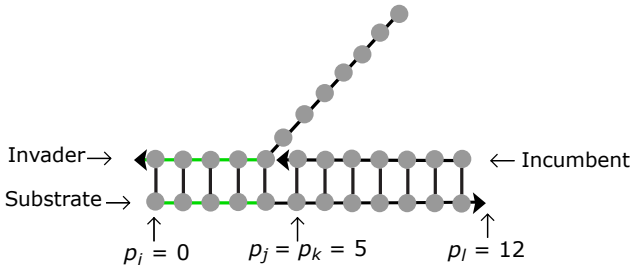
Let l be the length of the substrate. For simplicity, let l also be the length of the invader, m be the toehold length, and $l-m$ be the length of the incumbent. Each state is represented with a tuple $\langle p_i, p_j, p_k, p_l \rangle$, where $0 \leq p_i \leq p_j \leq p_k \leq p_l \leq l$ and $p_k \geq m$. The tuple indicates that all bases numbered p_i to $p_j - 1$ in the substrate have paired with bases numbered $l-p_j$ to $l-p_i-1$ in the invader, respectively, all bases numbered p_k to p_l-1 in the substrate have paired with bases numbered $l-p_l$ to $l-p_k-1$ in the incumbent, respectively, and there are no other base pairs in the state. Algorithm 7 describes the neighbors of a toehold-mediated 3-way strand displacement state s. In the initial state ($\mathcal{S}_{\text{init}} = \{\langle 0, 0, m, l \rangle\}$), the substrate is completely attached to the incumbent, but completely detached from the invader. In the final state ($\mathcal{S}_{\text{final}} = \{\langle 0, l, l, l \rangle\}$), the substrate is completely detached from the incumbent, but completely attached to the invader. Algorithm 8 adapts algorithm 7 for toehold-mediated 3-way strand displacement with mismatches between the invader and the substrate. In the algorithm, *mp* is a pointer to the mismatch position.

Note that in both algorithms, to efficiently obtain mean first passage times with sparse matrix computations, we further heuristically prune the state space of each reaction. For example, we disallow states which have a large gap between the incumbent and the invader.

B.5 Toehold-mediated 4-way Strand Exchange

Let *complex* be the first helix and *complex1* and *complex2* be the two strands in this helix. Let *reporter* be the second helix and *reporter1* be the strand in this helix that is complementary to *complex1* and *reporter2* be the strand in this helix that is complementary to *complex2*. Let l be the length of the helices excluding their toehold. For simplicity, let n be the toehold length of *complex1* and *reporter1* and let n be the toehold length of *complex2* and *reporter2*. Each state is represented with a tuple $\langle p_i, p_j, p_{i'}, p_{j'}, p_k, p_l \rangle$. The tuple indicates that all bases numbered p_i to $p_{i'} - 1$ in *complex1* have paired with bases numbered $l + n - p_{i'}$ to $l + n - p_i - 1$ in *reporter1*, respectively, all bases numbered 0 to $p_k - 1$ in *complex1* have paired with bases numbered $l+n-p_k$ to $l+n-1$ in *complex2*, respectively, all bases numbered p_j to $p_{j'} - 1$ in *reporter2* have paired with bases numbered $l + n - p_{j'}$ to $l + n - p_j - 1$ in *complex2*, respectively, all bases numbered 0 to $p_l - 1$ in *reporter2* have paired with bases numbered $l + m - p_l$ to $l + m - 1$ in *reporter1*, respectively, and there are no other base pairs in the state. Algorithm 9 describes the neighbors of a toehold-mediated 4-way strand exchange state s. In the initial state ($\mathcal{S}_{\text{init}} = \{\langle l+m, l+n, l+m, l+n, l, l \rangle\}$), *complex1* and *complex2* are completely bound except in their toeholds (have formed the *complex* helix), *reporter1* and *reporter2* are completely bound except in their toeholds (have formed the *reporter* helix), and no base pairs have formed between the *complex* helix and the *reporter* helix. Hence, each helix has two complementary strands except for their toeholds. In the final state ($\mathcal{S}_{\text{final}} = \{\langle 0, 0, l+m, l+n, 0, 0 \rangle\}$), the *reporter* and *complex* helices have completely exchanged strands and two new helices, which have complementary strands, are formed.

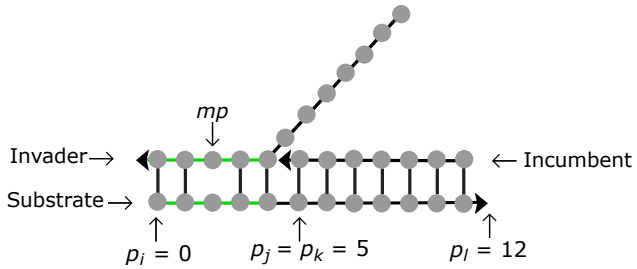
Algorithm 7: Find possible neighbors of a toehold-mediated 3-way strand displacement state s



Function `NeighborStates` (s)
- $\langle p_i, p_j, p_k, p_l \rangle \leftarrow s$, $\mathcal{N} \leftarrow \emptyset$
- `// Consider possibly invalid new states, then remove the invalid ones`
- **if** $p_i = p_j$ **then**
  - **for** p_n in $[0, p_k - 1]$ **do**
    - $\mathcal{N} \leftarrow \mathcal{N} \cup \langle p_n, p_n + 1, p_k, p_l \rangle$
- **else**
  - $\mathcal{N} \leftarrow \mathcal{N} \cup \langle p_i - 1, p_j, p_k, p_l \rangle \cup \langle p_i + 1, p_j, p_k, p_l \rangle \cup \langle p_i, p_j - 1, p_k, p_l \rangle \cup \langle p_i, p_j + 1, p_k, p_l \rangle \cup \langle p_i, p_j, p_k - 1, p_l \rangle \cup \langle p_i, p_j, p_k + 1, p_l \rangle \cup \langle p_i, p_j, p_k, p_l - 1 \rangle \cup \langle p_i, p_j, p_k, p_l + 1 \rangle$
- **for** $s' \in \mathcal{N}$ **do**
  - `// States in which the substrate and invader are detached are shown by` $\langle 0, 0, p_k, p_l \rangle$
  - **if** $p_i = p_j$ and $p_i \neq 0$ **then** $\mathcal{N} \leftarrow (\mathcal{N} \setminus s') \cup \langle 0, 0, p_k, p_l \rangle$
  - `// States in which the substrate and incumbent are detached are shown by` $\langle p_i, p_j, l, l \rangle$
  - **if** $p_k = p_l$ and $p_k \neq l$ **then** $\mathcal{N} \leftarrow (\mathcal{N} \setminus s') \cup \langle p_i, p_j, l, l \rangle$
- **for** $s' \in \mathcal{N}$ **do**
  - `// Remove invalid states`
  - **if** `!AllowedState(`s'`)` **then** $\mathcal{N} \leftarrow \mathcal{N} \setminus s'$
- return $\mathcal{N}$

Function `AllowedState(`s'`)`
- $\langle p_i, p_j, p_k, p_l \rangle \leftarrow s'$
- **if** $!(0 \leq p_i \leq p_j \leq p_k \leq p_l \leq l$ and $p_k \geq m)$ **then** return False
- `// Heuristically, further prune the state space to enable sparse matrix computations`
- **if** $p_i = p_j$ and $p_k = p_l$ **then** return False `// Disallow the complex to dissociate into three strands`
- **if** $(0 < m < p_k)$ and $(p_i \neq 0$ or $p_j < p_k - 1)$ **then** return False `// Disallow the first base pair of the incumbent and the substrate to break, when there is gap of greater than one base pair between the invader and the incumbent or the invader is not bound to the substrate`
- **if** $p_k - p_j > m + 2$ **then** return False `// Disallow states which have a large gap between the incumbent and the invader`
- return True

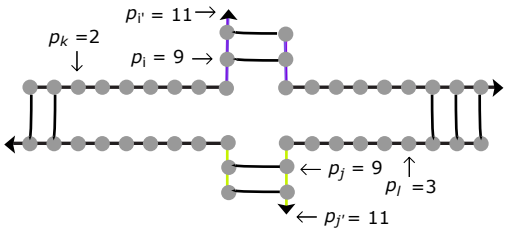
Algorithm 8: Find possible neighbors of a toehold-mediated 3-way strand displacement state s that has a mismatch between the invader and the substrate



Function `NeighborStates` (s)
- $\langle p_i, p_j, p_k, p_l \rangle \leftarrow s$, $\mathcal{N} \leftarrow \emptyset$
- `// Consider possibly invalid new states, then remove the invalid ones`
- **if** $p_i = p_j$ **then**
  - **for** p_n in $[0, p_k - 1]$ **do**
    - **if** $p_n \neq mp$ **then**
      - $\mathcal{N} \leftarrow \mathcal{N} \cup \langle p_n, p_n + 1, p_k, p_l \rangle$
- **else**
  - $\mathcal{N} \leftarrow \mathcal{N} \cup \langle p_i, p_j, p_k - 1, p_l \rangle \cup \langle p_i, p_j, p_k + 1, p_l \rangle \cup \langle p_i, p_j, p_k, p_l - 1 \rangle \cup \langle p_i, p_j, p_k, p_l + 1 \rangle$
  - **if** $p_i - 1 \neq mp$ **then** $\mathcal{N} \leftarrow \mathcal{N} \cup \langle p_i - 1, p_j, p_k, p_l \rangle$
  - **else** $\mathcal{N} \leftarrow \mathcal{N} \cup \langle p_i - 2, p_j, p_k, p_l \rangle$
  - **if** $p_i + 1 \neq mp$ **then** $\mathcal{N} \leftarrow \mathcal{N} \cup \langle p_i + 1, p_j, p_k, p_l \rangle$
  - **else** $\mathcal{N} \leftarrow \mathcal{N} \cup \langle p_i + 2, p_j, p_k, p_l \rangle$
  - **if** $p_j - 1 \neq mp$ **then** $\mathcal{N} \leftarrow \mathcal{N} \cup \langle p_i, p_j - 1, p_k, p_l \rangle$
  - **else** $\mathcal{N} \leftarrow \mathcal{N} \cup \langle p_i, p_j - 2, p_k, p_l \rangle$
  - **if** $p_j + 1 \neq mp$ **then** $\mathcal{N} \leftarrow \mathcal{N} \cup \langle p_i, p_j + 1, p_k, p_l \rangle$
  - **else** $\mathcal{N} \leftarrow \mathcal{N} \cup \langle p_i, p_j + 2, p_k, p_l \rangle$
- **for** $s' \in \mathcal{N}$ **do**
  - `// States in which the substrate and invader are detached are shown by` $\langle 0, 0, p_k, p_l \rangle$
  - **if** $p_i = p_j$ and $p_i \neq 0$ **then** $\mathcal{N} \leftarrow (\mathcal{N} \setminus s') \cup \langle 0, 0, p_k, p_l \rangle$
  - `// States in which the substrate and incumbent are detached are shown by` $\langle p_i, p_j, l, l \rangle$
  - **if** $p_k = p_l$ and $p_k \neq l$ **then** $\mathcal{N} \leftarrow (\mathcal{N} \setminus s') \cup \langle p_i, p_j, l, l \rangle$
- **for** $s' \in \mathcal{N}$ **do**
  - `// Remove invalid states`
  - **if** `!AllowedState(`s'`)` **then** $\mathcal{N} \leftarrow \mathcal{N} \setminus s'$
- return $\mathcal{N}$

Function `AllowedState(`s'`)`
- $\langle p_i, p_j, p_k, p_l \rangle \leftarrow s'$
- **if** $!(0 \leq p_i \leq p_j \leq p_k \leq p_l \leq l$ and $p_k \geq m)$ **then** return False
- `// Heuristically, further prune the state space to enable sparse matrix computations`
- **if** $p_i = p_j$ and $p_k = p_l$ **then** return False `// Disallow the complex to dissociate into three strands`
- **if** $(0 < m < p_k)$ and $(p_i \neq 0$ or $p_j < p_k - 5)$ **then** return False `// Disallow the first base pair of the incumbent and the substrate to break, when there is gap of greater than five base pairs between the invader and the incumbent or the invader is not bound to the substrate`
- **if** $p_k - p_j > m + 4$ **then** return False `// Disallow states which have a large gap between the incumbent and the invader`
- return True

Algorithm 9: Find possible neighbors of a toehold-mediated 4-way strand exchange state s



Function `NeighborStates` (s)

$\langle p_i, p_j, p_{i'}, p_{j'}, p_k, p_l\rangle \leftarrow s$, $\mathcal{N} \leftarrow \emptyset$

`// Consider possibly invalid new states, then remove the invalid ones`

if $p_i = p_{i'}$ **then**

  for p_n in $[\max\{p_k, p_l\}, l + m - 1]$ **do**

    $\mathcal{N} \leftarrow \mathcal{N} \cup \langle p_n, p_j, p_n + 1, p_{j'}, p_k, p_l\rangle$

else

  $\mathcal{N} \leftarrow$

  $\mathcal{N} \cup \langle p_i - 1, p_j, p_{i'}, p_{j'}, p_k, p_l\rangle \cup \langle p_i + 1, p_j, p_{i'}, p_{j'}, p_k, p_l\rangle \cup \langle p_i, p_j, p_{i'} - 1, p_{j'}, p_k, p_l\rangle \cup \langle p_i, p_j, p_{i'} + 1, p_{j'}, p_k, p_l\rangle$

if $p_j = p_{j'}$ **then**

  for p_n in $[\max\{p_k, p_l\}, l + n - 1]$ **do**

    $\mathcal{N} \leftarrow \mathcal{N} \cup \langle p_i, p_n, p_j, p_n + 1, p_k, p_l\rangle$

else

  $\mathcal{N} \leftarrow$

  $\mathcal{N} \cup \langle p_i, p_j - 1, p_{i'}, p_{j'}, p_k, p_l\rangle \cup \langle p_i, p_j + 1, p_{i'}, p_{j'}, p_k, p_l\rangle \cup \langle p_i, p_j, p_{i'}, p_{j'} - 1, p_k, p_l\rangle \cup \langle p_i, p_j, p_{i'}, p_{j'} + 1, p_k, p_l\rangle$

if ($p_i! = p_{i'}$ or $p_j! = p_{j'}$) or ($m = 0$ or $n = 0$) **then**

  $\mathcal{N} \leftarrow$

  $\mathcal{N} \cup \langle p_i, p_j, p_{i'}, p_{j'}, p_k - 1, p_l\rangle \cup \langle p_i, p_j, p_{i'}, p_{j'}, p_k + 1, p_l\rangle \cup \langle p_i, p_j, p_{i'}, p_{j'}, p_k, p_l - 1\rangle \cup \langle p_i, p_j, p_{i'}, p_{j'}, p_k, p_l + 1\rangle$

for $s' \in \mathcal{N}$ **do**

  if $p_i = p_{i'}$ and $0 \le p_i < l + m$ **then** $\mathcal{N} \leftarrow (\mathcal{N} \setminus s') \cup \langle l + m, p_j, l + m, p_{j'}, p_k, p_l\rangle$

  if $p_j = p_{j'}$ and $0 \le p_j < l + n$ **then** $\mathcal{N} \leftarrow (\mathcal{N} \setminus s') \cup \langle p_i, l + n, p_{i'}, l + n, p_k, p_l\rangle$

for $s' \in \mathcal{N}$ **do**

  `// Remove invalid states`

  if `!AllowedState(`s'`)` **then** $\mathcal{N} \leftarrow \mathcal{N} \setminus s'$

return $\mathcal{N}$

Function `AllowedState(`s'`)`

$\langle p_i, p_j, p_{i'}, p_{j'}, p_k, p_l\rangle \leftarrow s'$

if $!(p_l \le p_i$ and $p_l \le p_j$ and $p_k \le p_i$ and $p_k \le p_j$ and $0 \le p_k \le l$ and $0 \le p_l \le l$ and $0 \le p_i \le p_{i'} \le l + m$ and $0 \le p_j \le p_{j'} \le l + n)$ **then** return False

`// Heuristically, further prune the state space to enable sparse matrix computations`

if ($p_i = p_{i'}$ or $p_j = p_{j'}$) and ($p_k = 0$ or $p_l = 0$) **then** return False

if ($m = 0$ or $n = 0$) and ($p_i = p_{i'}$ or $p_j = p_{j'}$) and ($p_k < l - 3 + m/3$ or $p_l < l - 3 + n/3$) **then** return False

if ($m \neq 0$ and $n \neq 0$) and ($p_i = p_{i'}$ or $p_j = p_{j'}$) and ($p_k < l - 1$ or $p_l < l - 1$) **then** return False

if $p_{i'} < l$ or $p_{j'} < l$ **then** return False

if $(|p_i - p_l| + |p_i - p_k| + |p_j - p_l| + |p_j - p_k| > 8 - n/3 - m/3)$ and $(p_i \neq p_{i'}$ and $p_j \neq p_{j'})$ **then** return False

return True

C Half Context Frequency

Fig. 1 shows the fraction of all unimolecular elementary steps that involve a given half context, i.e., $\frac{\#l}{\sum \#l}$, where l is a half context and $\#l$ is the number of all unimolecular elementary steps that involve the half context. Analogously, Fig. 2 shows the fraction of all bimolecular elementary steps that involve a given half context.

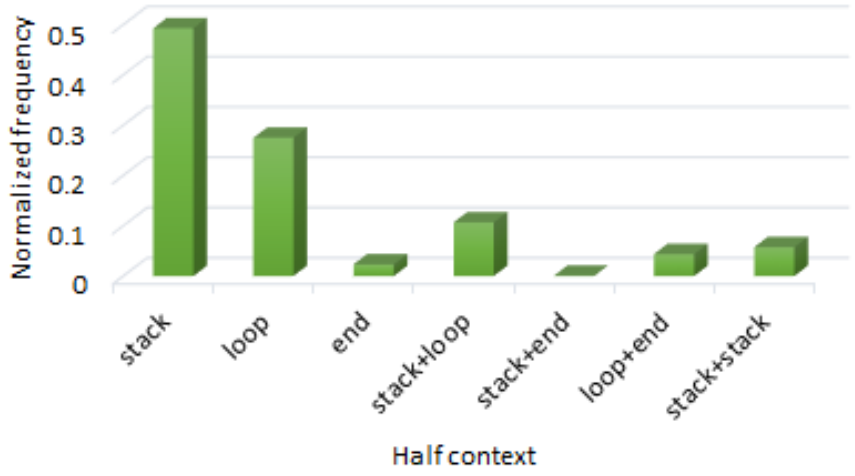


Fig. 1: Normalized frequency of the half contexts in unimolecular transitions.

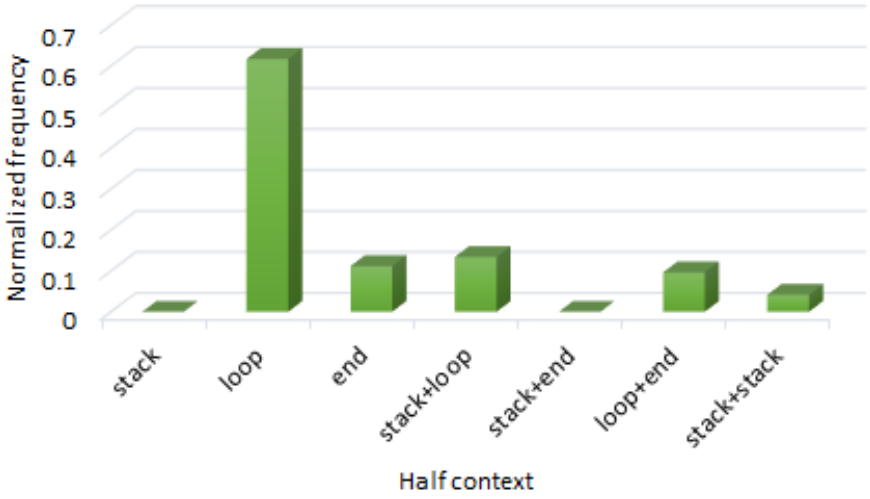


Fig. 2: Normalized frequency of the half contexts in bimolecular transitions.

D Experimental Plot Reproduction

The following plots show how the performance of the Metropolis and the Arrhenius models on the training and testing datasets. Dashed lines indicate model fits and predictions and solid lines indicate experimentally determined values. For the MCMC ensemble method, error bars indicate the range (minimum to maximum) of predictions.

D.1 Training Set ($\mathcal{D}_{\text{train}}$)

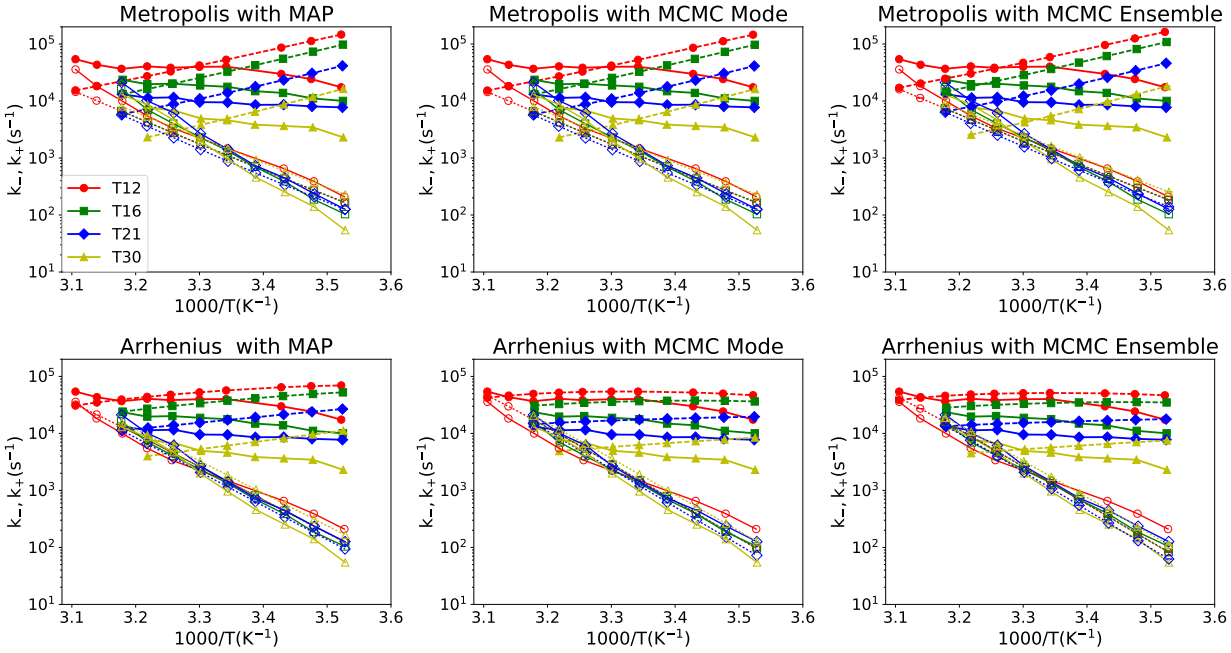


Fig. 3: Model fitting (dashed lines) of reaction rate constants (y axis) for hairpin closing (solid) and opening (open) with sequence $5'$-$CCCAA$-$(T)_n$-$TTGGG$-$3'$ where n is 12,16, 21, or 30, experimental data (solid lines) from Fig. 4 of Bonnet et al. [3].

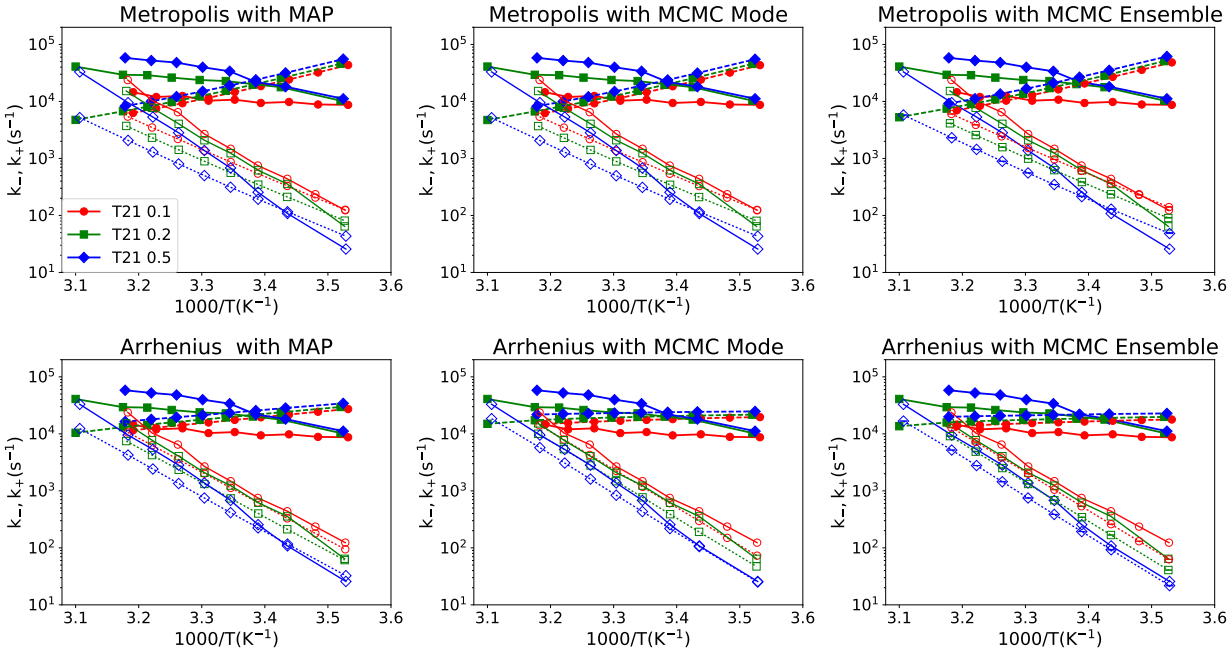


Fig. 4: Model fitting (dashed lines) of reaction rate constants (y axis) for hairpin opening (open) and closing (solid) with sequence $5'$-$CCCAA$-$(T)_{21}$-$TTGGG$-$3'$ at different salt concentrations, Fig. 6 from Bonnet et al. [3]. experimental data (solid lines) from Fig.6 of Bonnet et al. [3] wrongfully notes the use of a poly-A instead of a poly-T hairpin loop, which becomes evident in comparison to Fig. 5 of the same work (private communication with the authors).

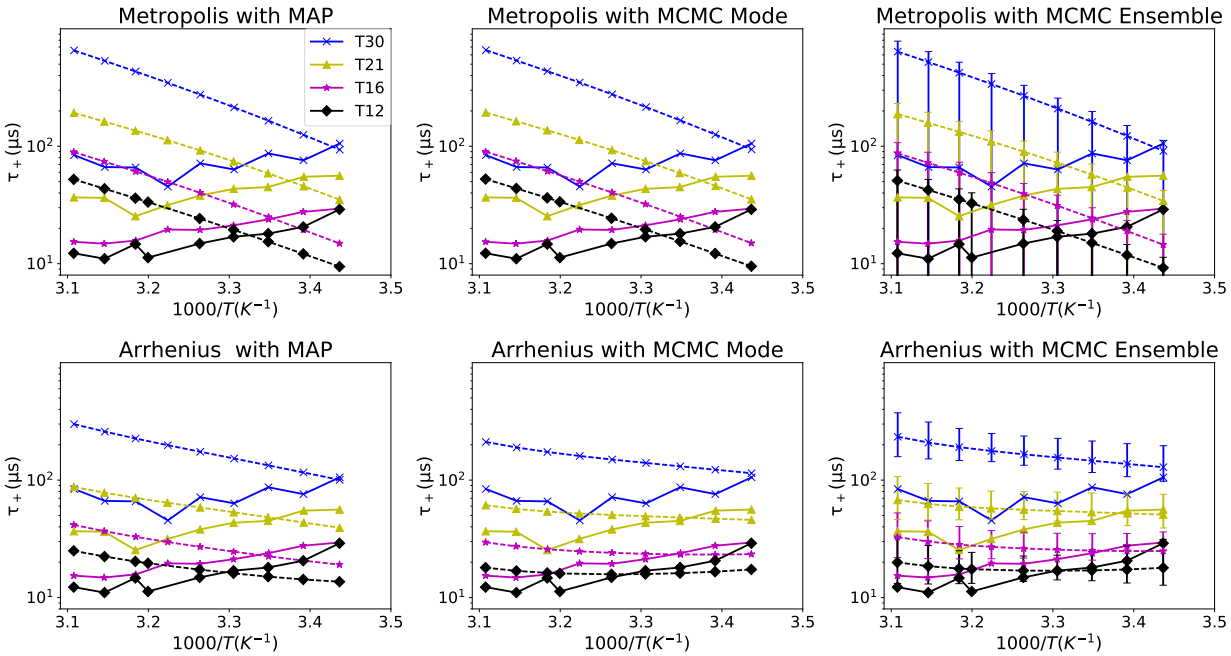


Fig. 5: Model fitting (dashed lines) of reaction timescales (y axis) for hairpin closing with sequence $5'$-$CCCAA$-$(T)_n$-$TTGGG$-$3'$ where n is 12,16, 21, or 30, experimental data (solid lines) from Fig. 3.28 of Bonnet [2].

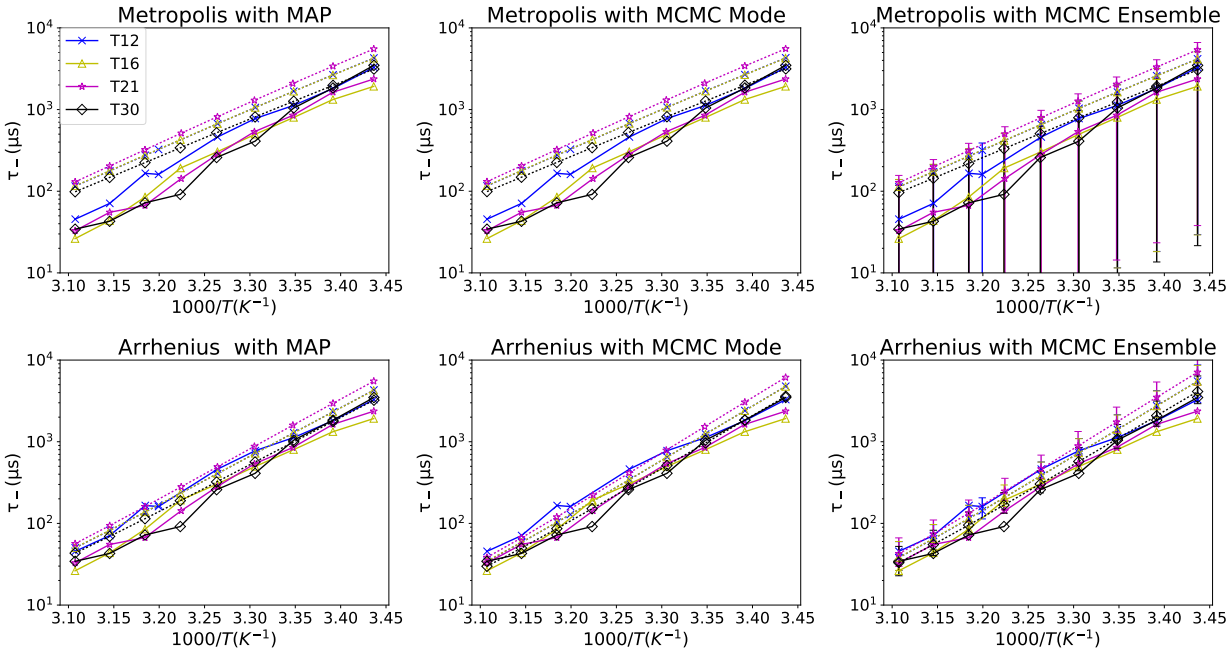


Fig. 6: Model fitting (dashed lines) of reaction timescales (y axis) for hairpin opening with sequence $5'$-$CCCAA$-$(T)_n$-$TTGGG$-$3'$ where n is 12,16, 21, or 30, experimental data (solid lines) from Fig. 3.28 of Bonnet [2].

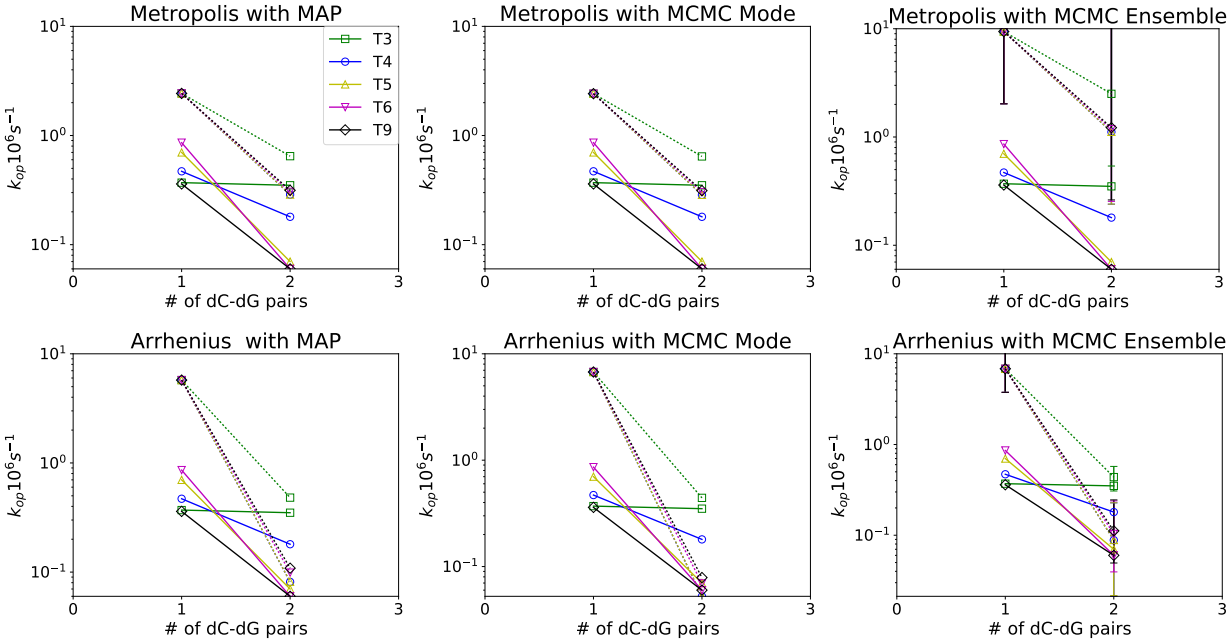


Fig. 7: Model fitting (dashed lines) of reaction rate constants (y axis) for hairpin opening with sequence F-$(dC)_y$-$(dT)_x$-$(dG)_y$ (x ranging from 3 to 9) as a function of dC-dG pairs (y ranging from 1 to 2), experimental data (solid lines) from Table 1 (Fig. 3b) of Kim et al. [5].

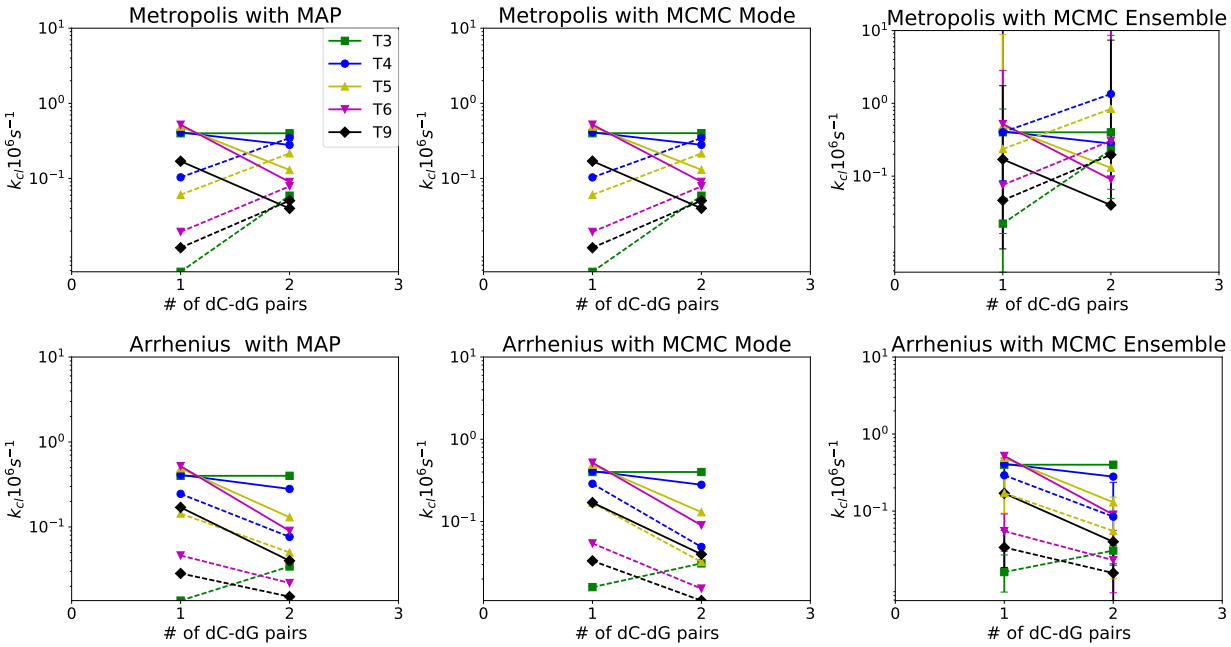


Fig. 8: Model fitting (dashed lines) of reaction rate constants (y axis) for hairpin closing with sequence F-$(dC)_y$-$(dT)_x$-$(dG)_y$ (x ranging from 3 to 9) as a function of dC-dG pairs (y ranging from 1 to 2), experimental data (solid lines) from Table 1 (Fig. 3b) of Kim et al. [5].

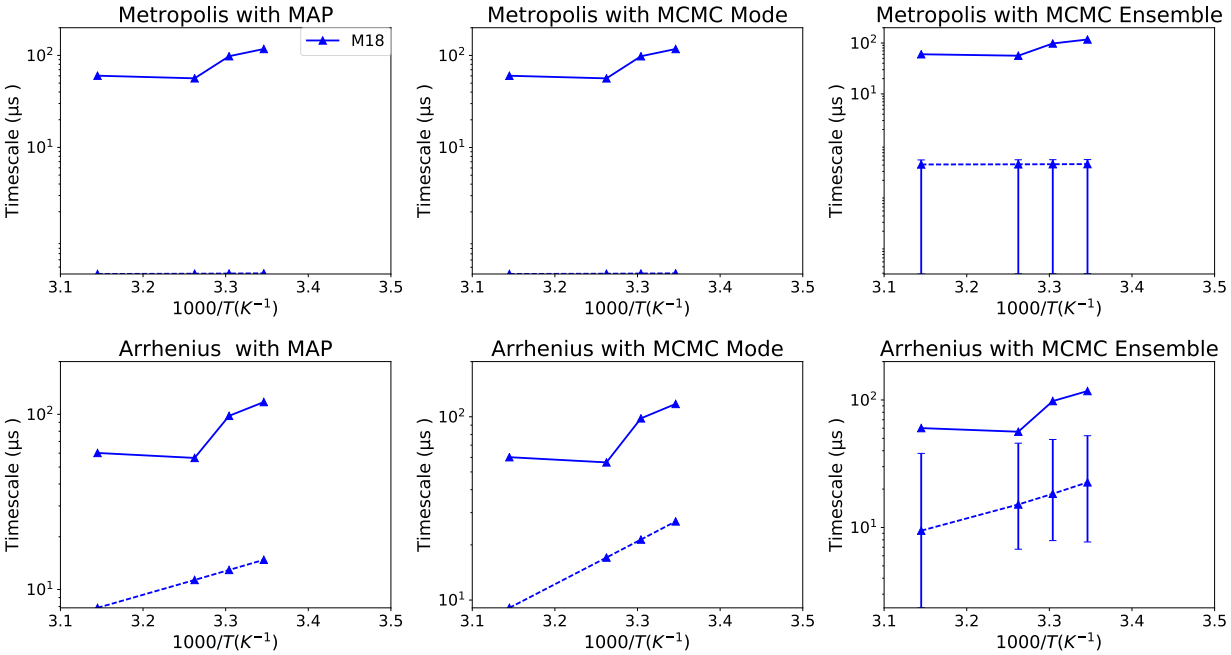


Fig. 9: Model fitting (dashed lines) of reaction timescales (y axis) for bubble closing with sequence M_{18}, experimental data (solid lines) from Fig. 4 of Altan-Bonnet et al. [1].

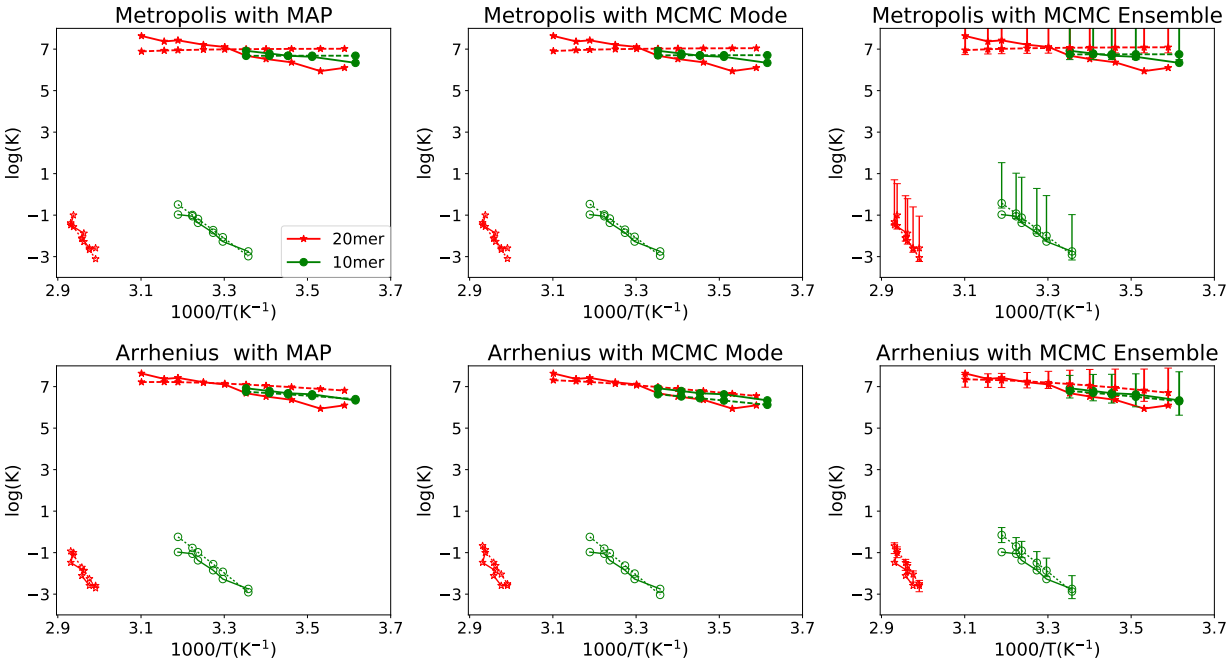


Fig. 10: Model fitting (dashed lines) of reaction rate constants (y axis) for helix association (solid) and disassociation (solid), experimental data (solid lines) from Fig. 6 of Morrison and Stols [7]. 10mer and 20mer are variation in the length of the strand.

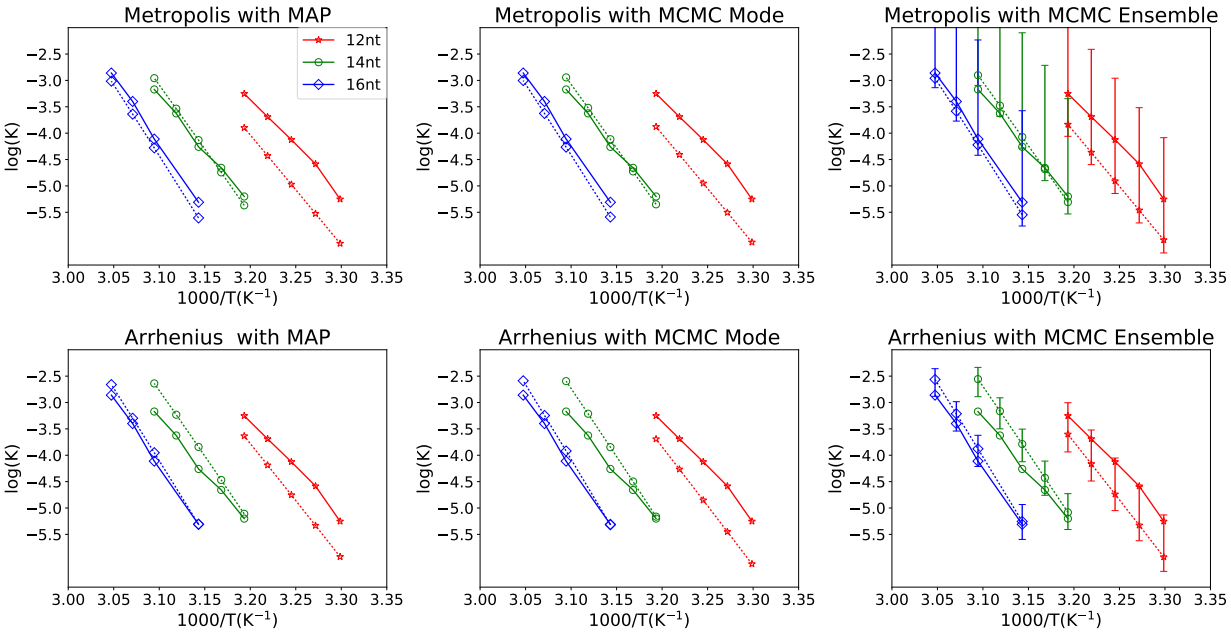


Fig. 11: Model fitting (dashed lines) of of reaction rate constants (y axis) for helix disassociation, experimental data (solid lines) from Fig. 6 of Reynaldo et al. [8]. 12nt, 14nt, and 16nt are variations in the length of the strand.

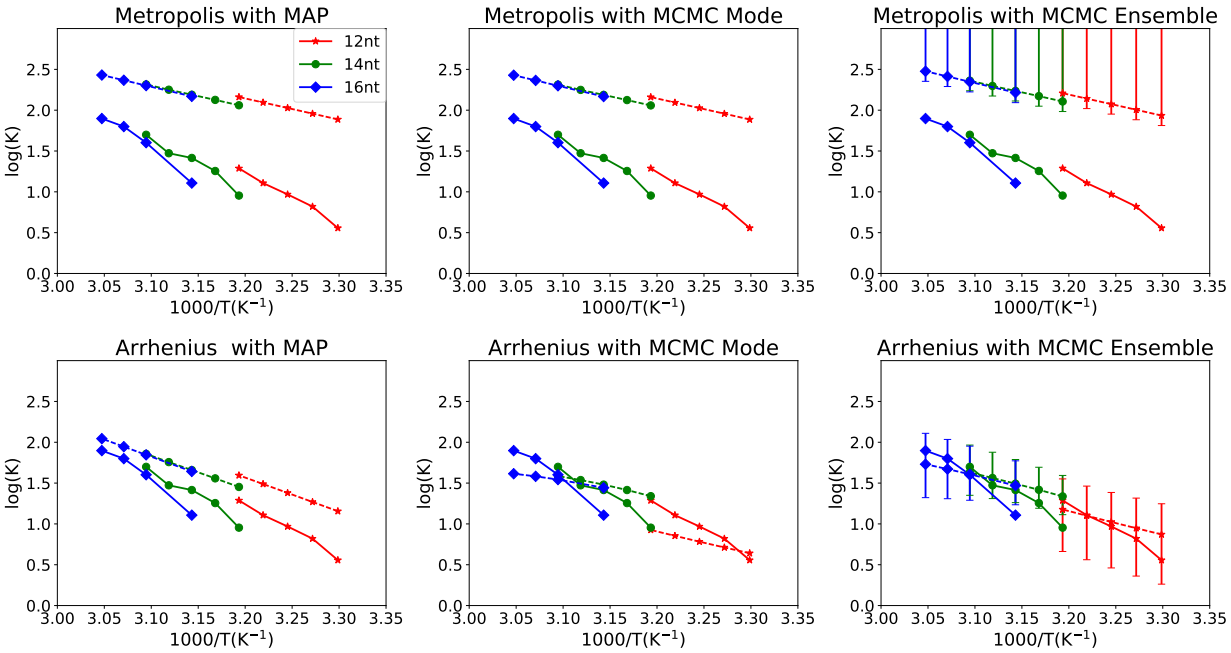


Fig. 12: Model fitting (dashed lines) of reaction rate constants (y axis) for toehold-mediated 3-way strand displacement, experimental data (solid lines) from Fig. 6 of Reynaldo et al. [8]. 12nt, 14nt, and 16nt are variations in the length of the strand.

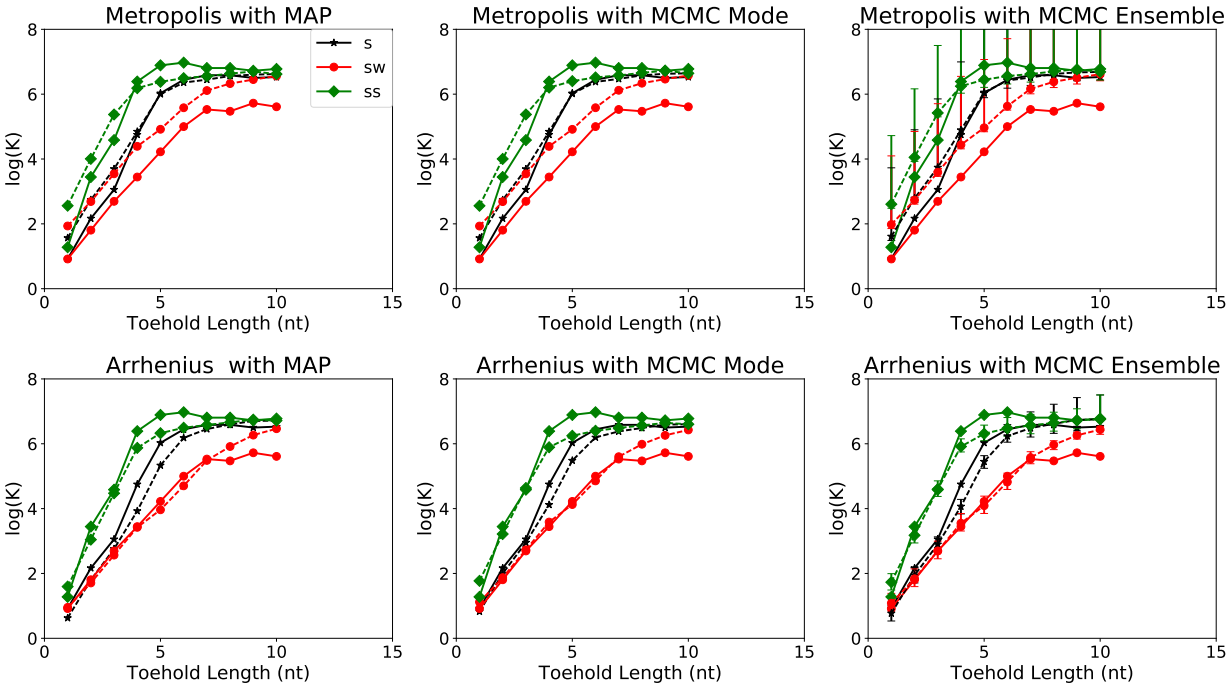


Fig. 13: Model fitting (dashed lines) of reaction rate constants (y axis) for toehold-mediated 3-way strand displacement, experimental data (solid lines) from Fig. 3b of Zhang and Winfree [9]. The toehold is varied between strong (ss), regular (s) and weak (sw) binding strength by varying the G/C content of the toehold sequence.

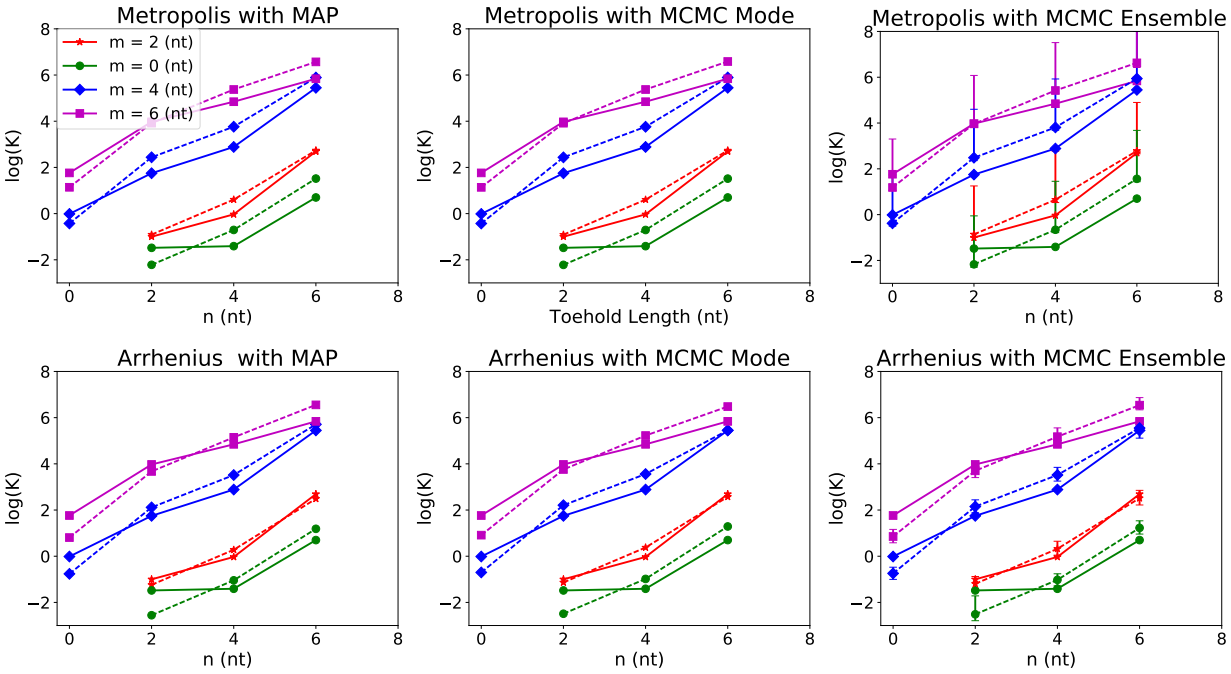


Fig. 14: Model fitting (dashed lines) of reaction rate constants (y axis) for toehold-mediated 4-way strand exchange, experimental data (solid lines) from Table 5.2 of Dabby [4]. m (shown on the legend) and n (shown on the x-axis) are variations in the length of the toehold domains (see Appendix B.5).

D.2 Testing Set ($\mathcal{D}_{\text{test}}$)

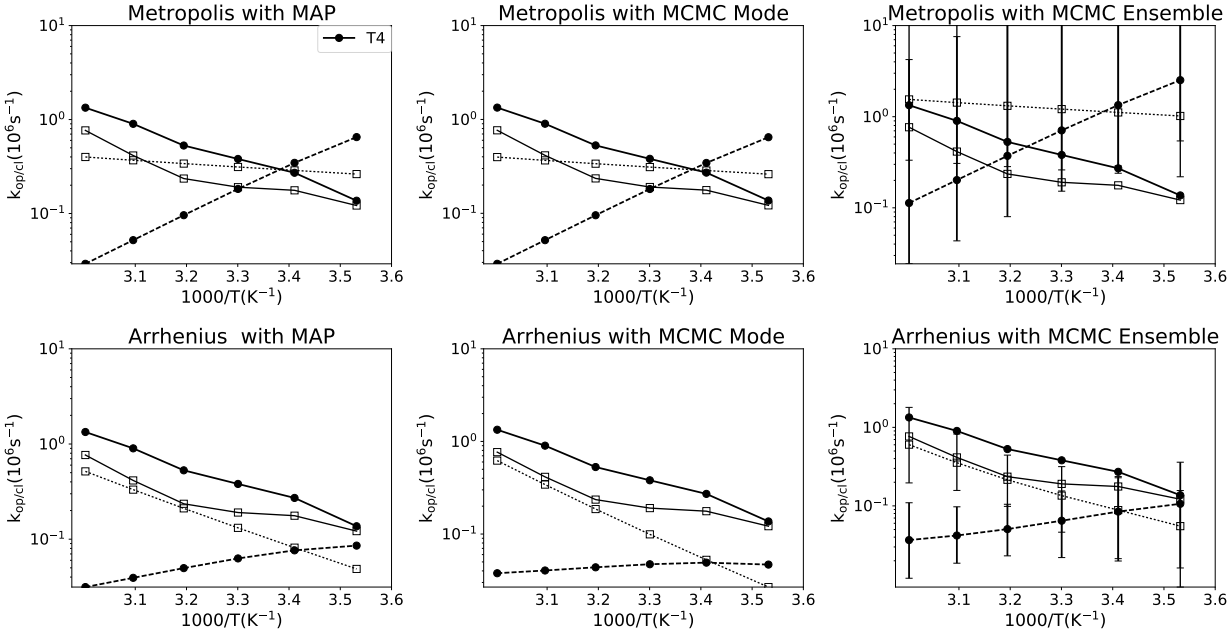


Fig. 15: Model predictions (dashed lines) of reaction rate constants (y axis) for hairpin closing (solid) and opening (open) with sequence F-$(dC)_2$-$(dT)_4$-$(dG)_2$, experimental data (solid lines) from Fig. 5a of Kim et al. [5].

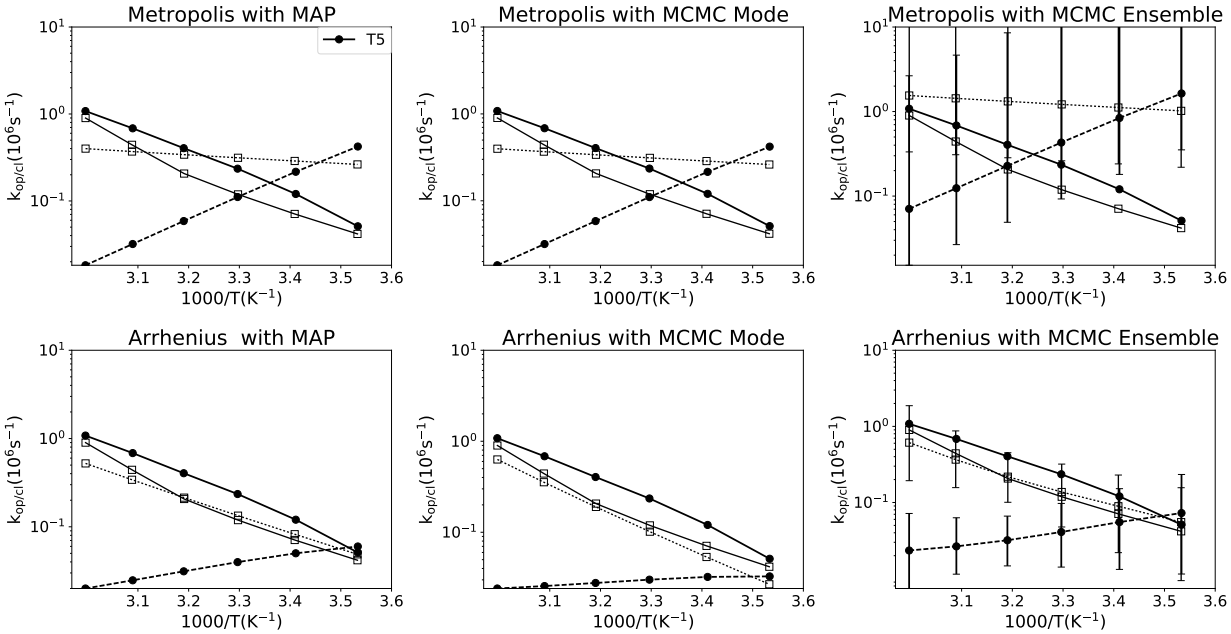


Fig. 16: Model predictions (dashed lines) of reaction rate constants (y axis) for hairpin closing (solid) and opening (open) with sequence F-$(dC)_2$-$(dT)_5$-$(dG)_2$, experimental data (solid lines) from Fig. 5b of Kim et al. [5].

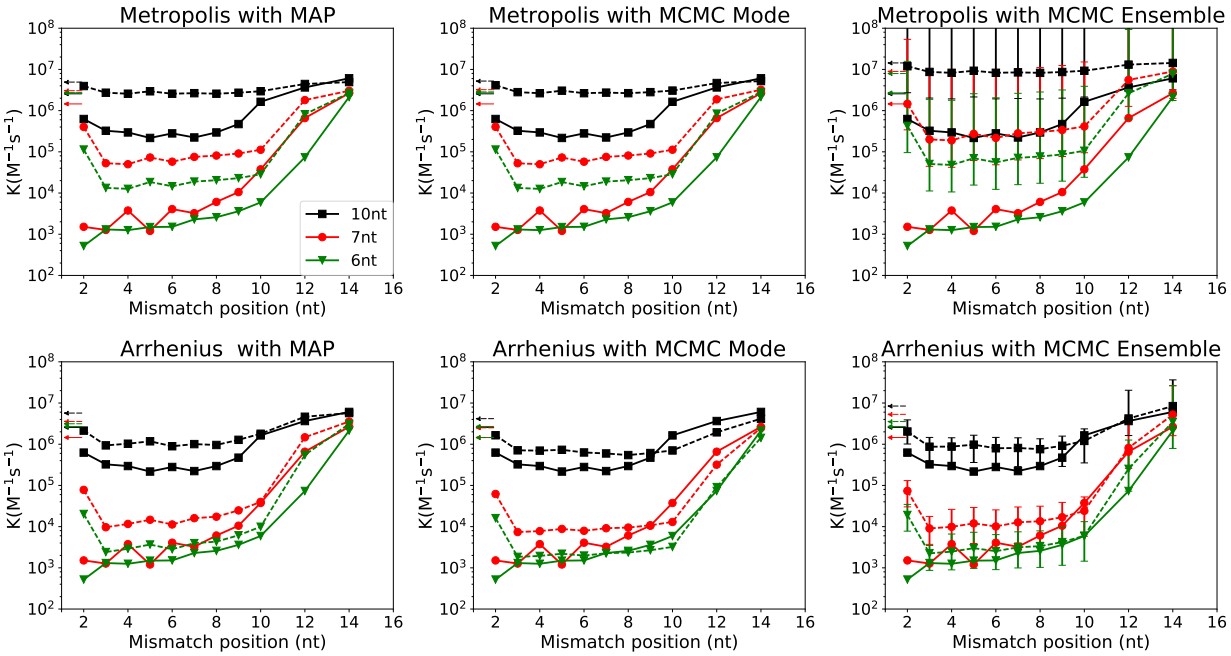


Fig. 17: Model predictions (dashed lines) of reaction rate constants (y axis) for toehold-mediated 3-way strand displacement with mismatches, experimental data (solid lines) from Fig. 2d of Machinek et al. [6]. For the MCMC ensemble method, error bars indicate the range (minimum to maximum) of predictions. Arrows indicate no mismatch. The mismatch in the invading strand affects the reaction rate. The length of the toehold domain is ten, seven, and six nucleotides long for ■, ●, and ▼, respectively.

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