

# Sequence selection by ligation under non-equilibrium conditions

- science update -

Dieter Braun



Patrick Kudella

With Sergei Maslov and  
Alexei Tkachenko, University of Illinois

upcoming hybridization kinetic code:  
Altaner, Göppel, Rosenberger and Gerland, TUM

→ ⚙️ ↻ ⭐ ↓ <https://indico.physik.uni-muenchen.de/event/63/> 📄 ⋮ 📌 yD

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# Molecular Origins of Life, Munich 2021

26-27 August 2021  
Literaturhaus München  
Europe/Berlin timezone

The biannual Molecular Origins of Life, Munich addresses one of the most fundamental questions of science: How could life originate on Earth? With more than 20 lectures accompanied by discussion sessions and a virtual element, this international conference brings together scientists from wide range of disciplines, namely: astrophysics, biochemistry, biophysics, chemistry, geobiology, geochemistry and theoretical physics. Only the combined effort from renowned experts from various disciplines can be successful in retracing the origins of life under experimental conditions and pave the way towards answering some of the most pertinent questions: What were the conditions on early Earth? Which chemicals could serve as precursors for the synthesis of living systems on Earth and on other planets? How did the very first genetic material in lifeforms develop? How could Darwinian evolution emerge? What were the first metabolic pathways? The conference's aim is to represent and to discuss the state of the art in the Origin of Life field.

*The Molecular Origins of Life, Munich 2021 is sponsored by DFG funded Collaborative Research Center 235 Emergence of Life.*

**Attendance to the conference is free of charge!**

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[Pre-conference BBQ](#)

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Contact

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☎️ +49 89 2180 3514

🕒 **Starts** 26 Aug 2021, 08:30  
**Ends** 27 Aug 2021, 18:00  
Europe/Berlin

📍 **Literaturhaus München**  
Salvatorplatz 1,  
80333 Munich,  
Germany  
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#### Important dates (2021)

**July 20th**, Tue ..... -> *Poster abstract submission deadline*

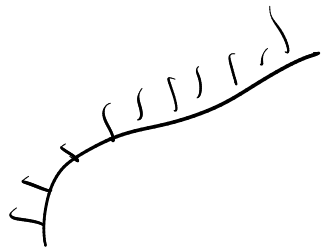
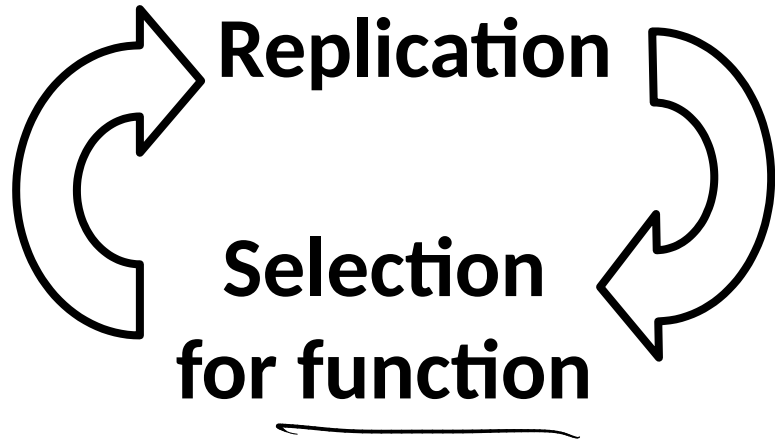
**Aug 15th**, Sun..... -> *Registration deadline*

**Aug 25th**, Wed..... -> *Conference start with BBQ*

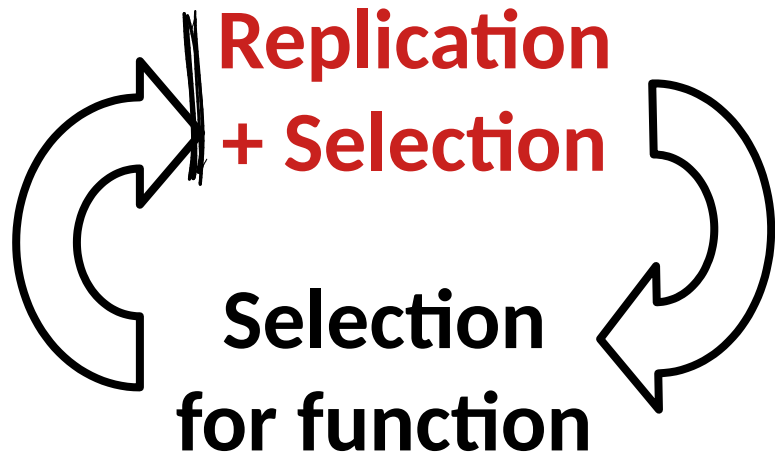


[indico.physik.lmu.de/event/63/](https://indico.physik.lmu.de/event/63/)

# (In)stability of Evolution

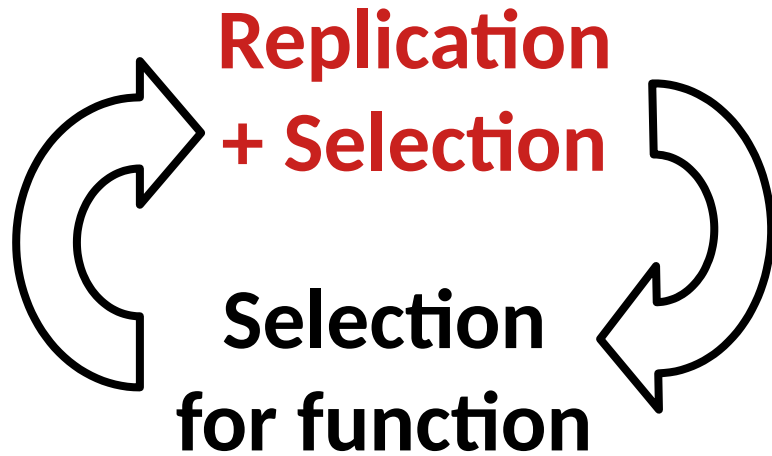


# (In)stability of Evolution



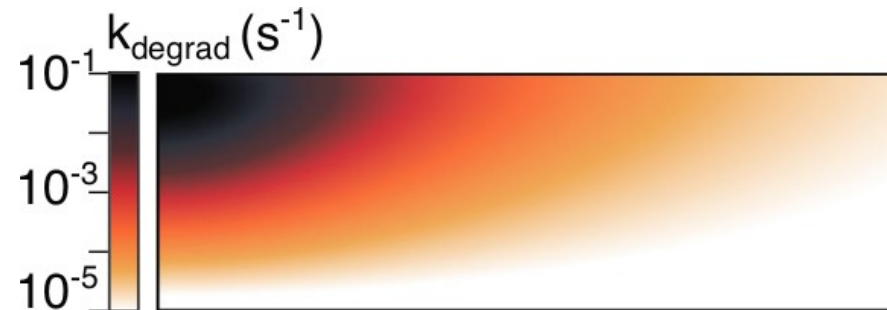
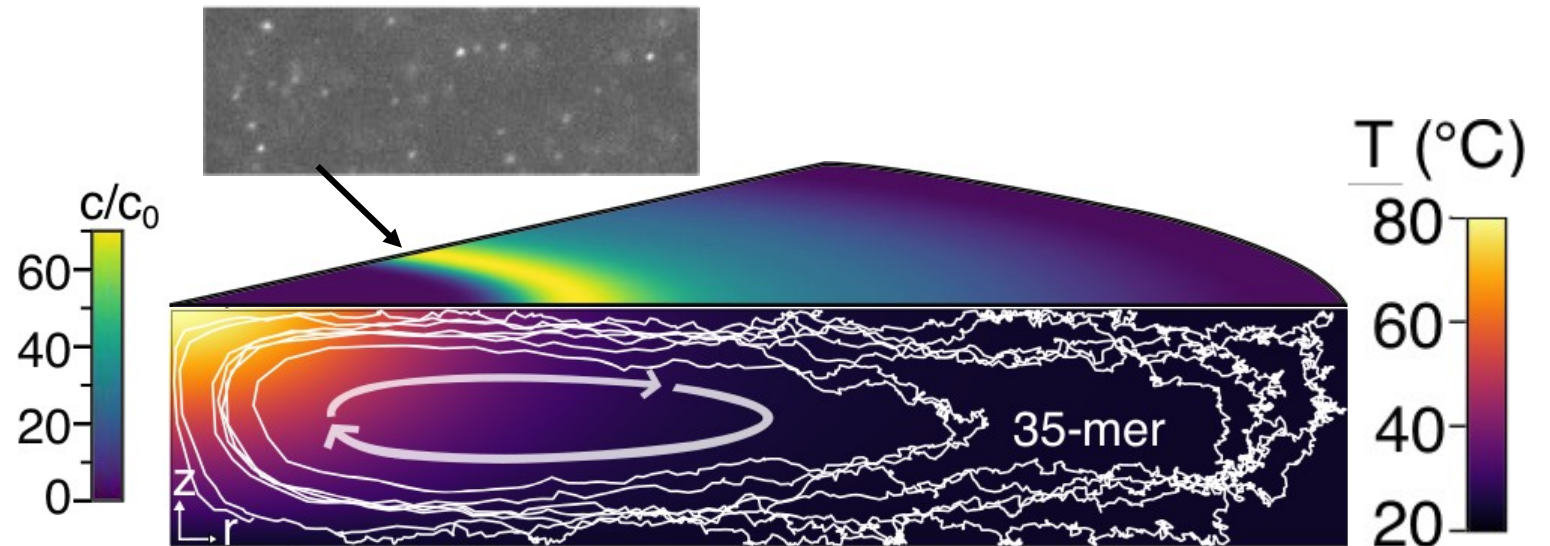
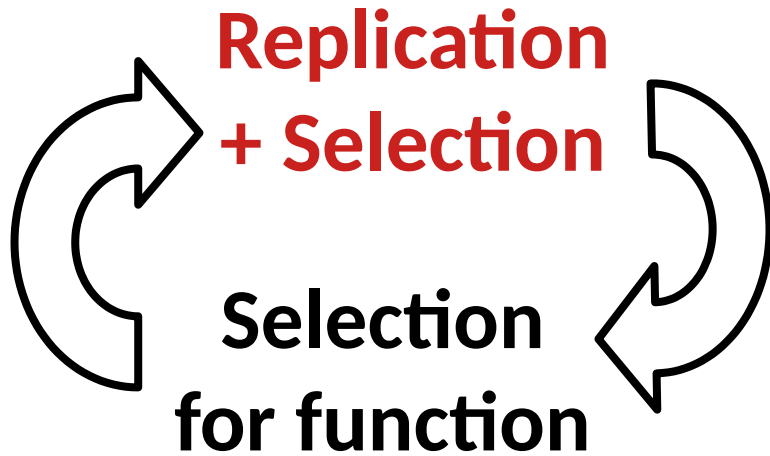
# (In)stability of Evolution

- Tyranny of the shortest (Spiegelman)



# (In)stability of Evolution

- Tyranny of the shortest (Spiegelman)  
Lack of non-primer replication in Ribo-PCR



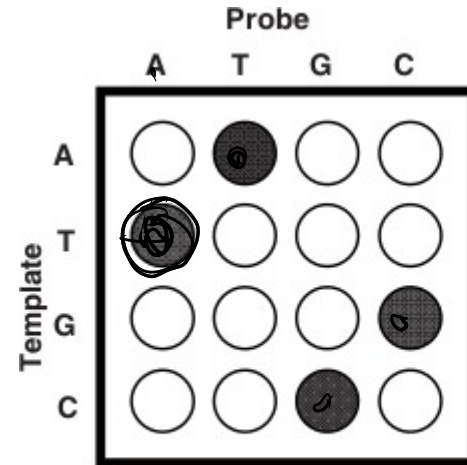
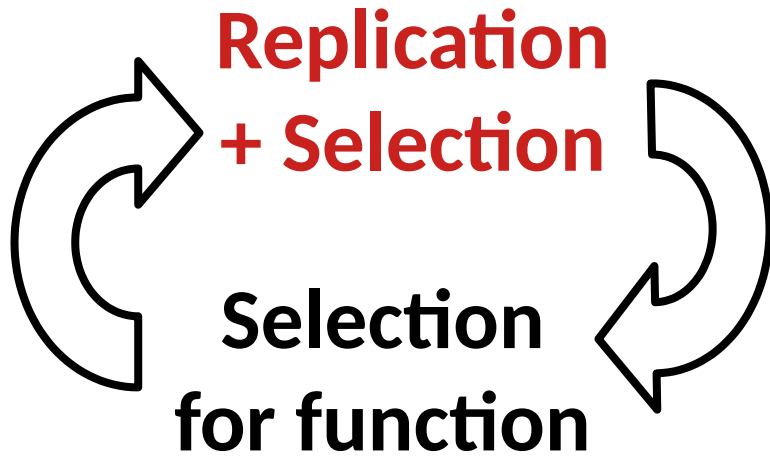
Salditt, Keil, Horning,  
Mast, Joyce and Braun,  
Physical Review Letters  
125, 048104 (2020)

# (In)stability of Evolution

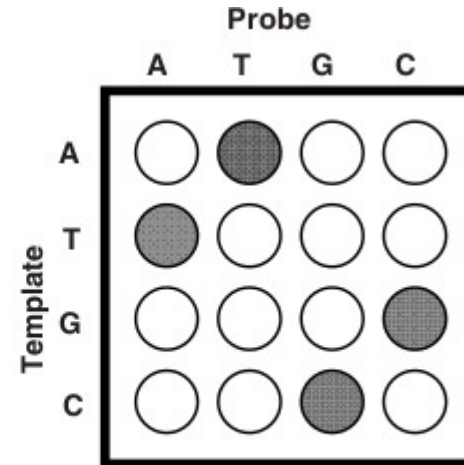


## Study templated ligation

Taq-Ligase: precision and low temperature performance



Yield of nick closure



Yield of ligation



Profiling the selectivity of DNA ligases in an array format with mass spectrometry, **Kim and Mrksich**, Nucleic Acid Research, doi:10.1093/nar/gkp827 (2010)

**Illumina sequencing with Swift kit and LMU Gene Center facility**

Thanks for discussions with Daniel Duzdevich and Irene Chen

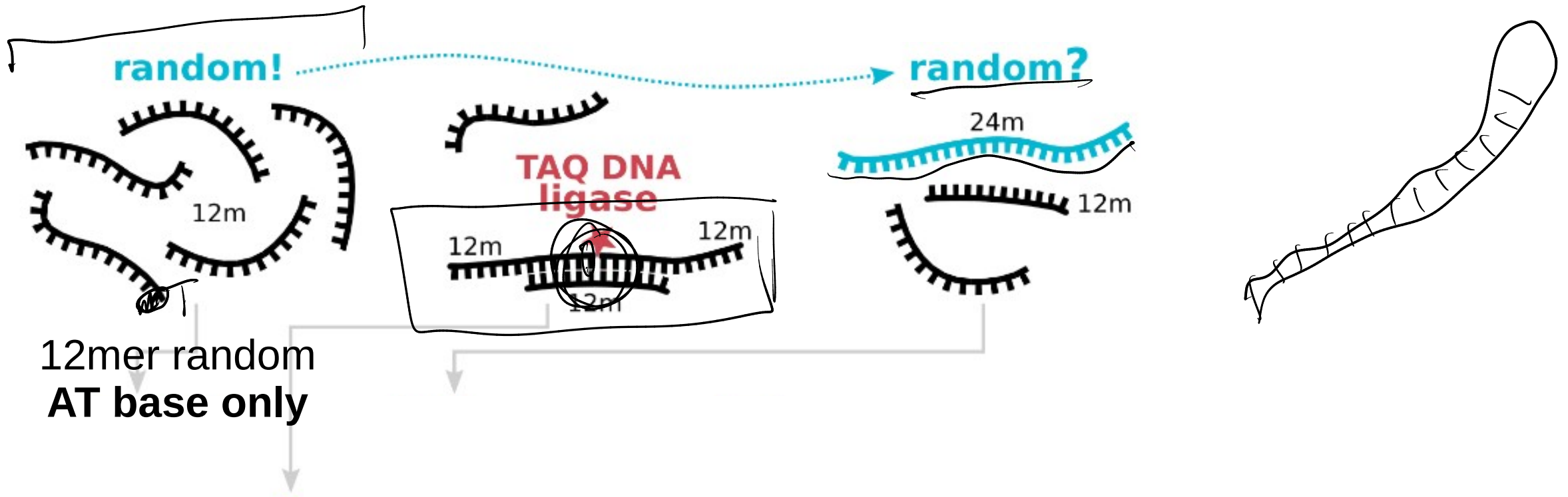
# Repeated templated ligation of random pools



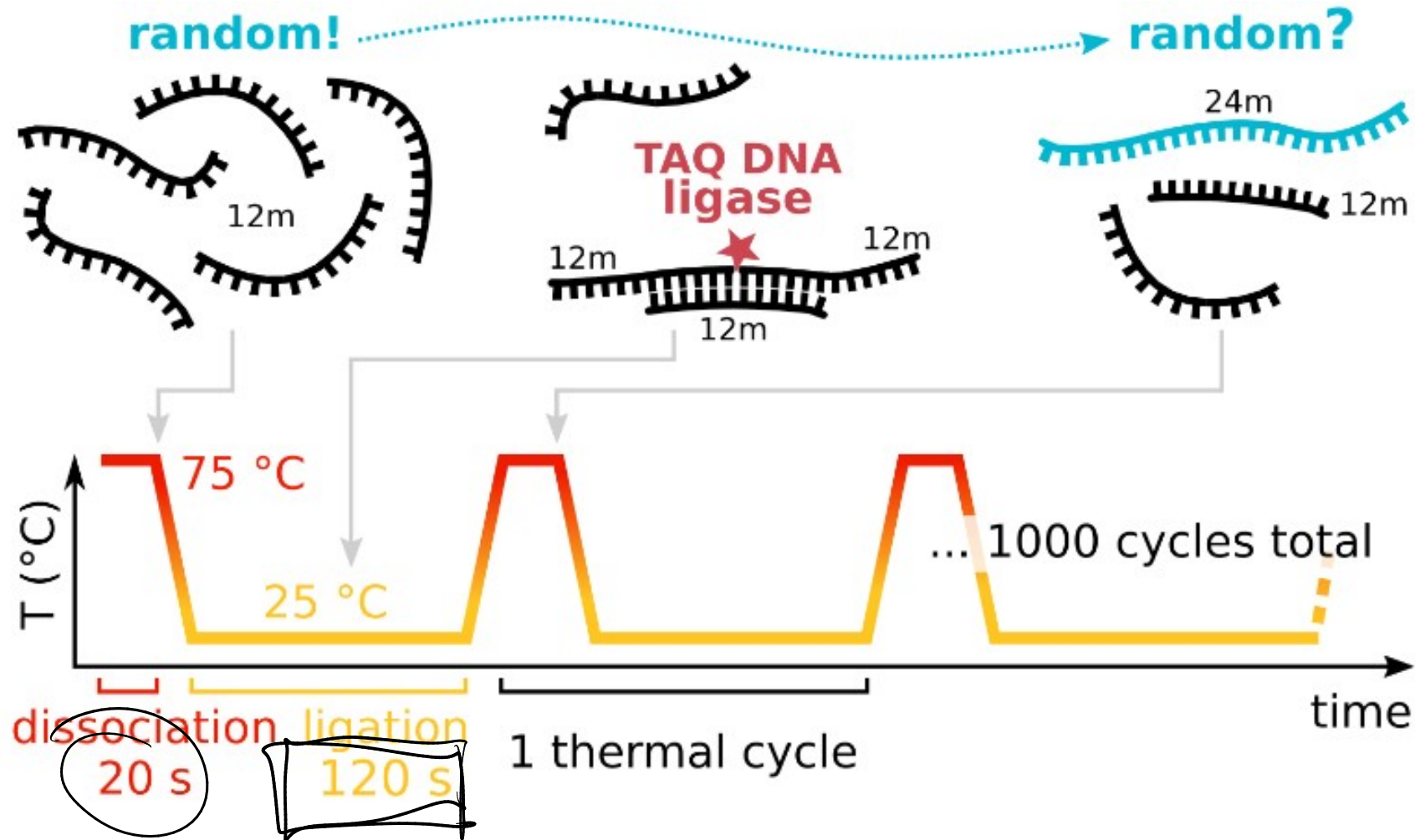
12mer random  
AT base only



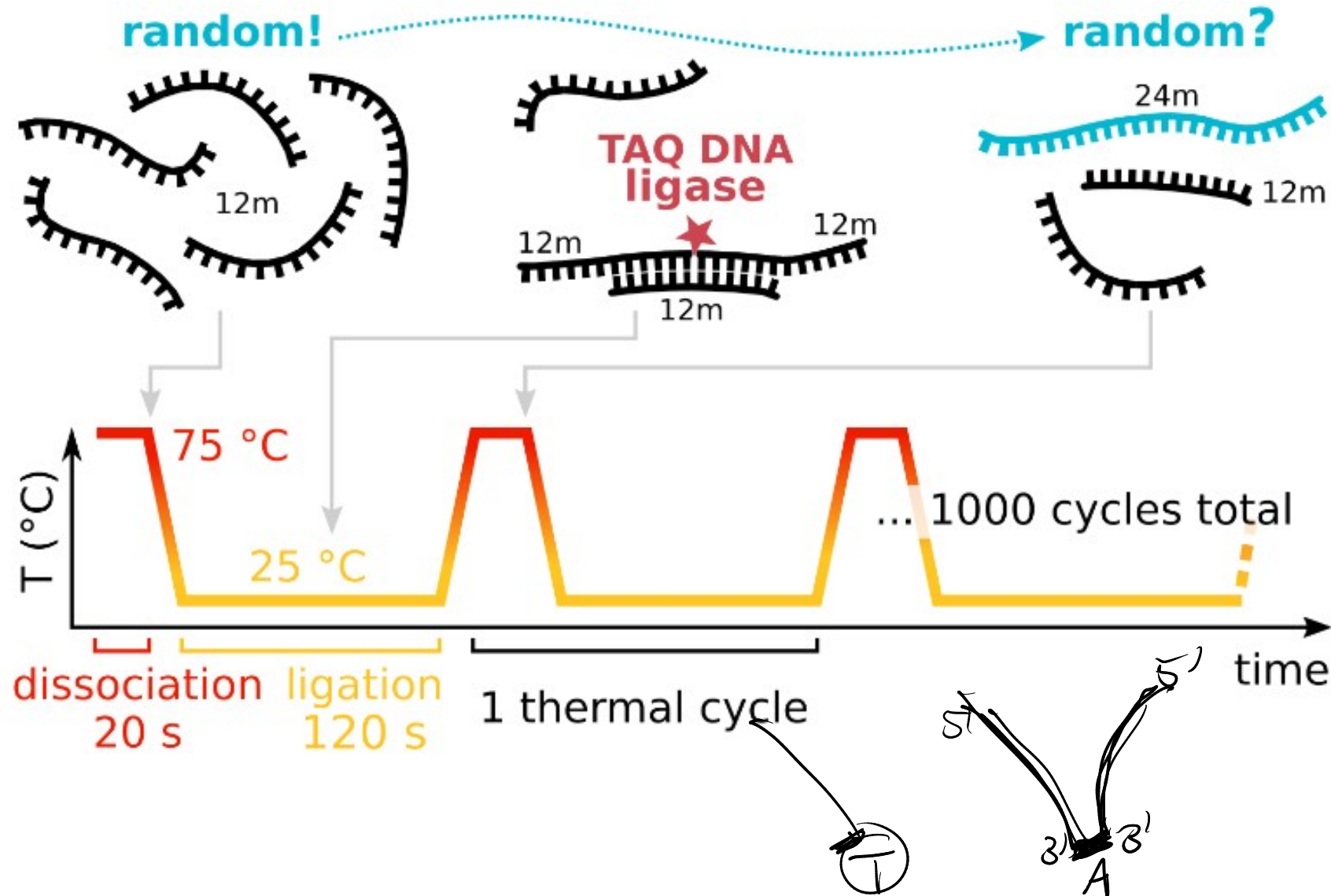
# Repeated templated ligation of random pools



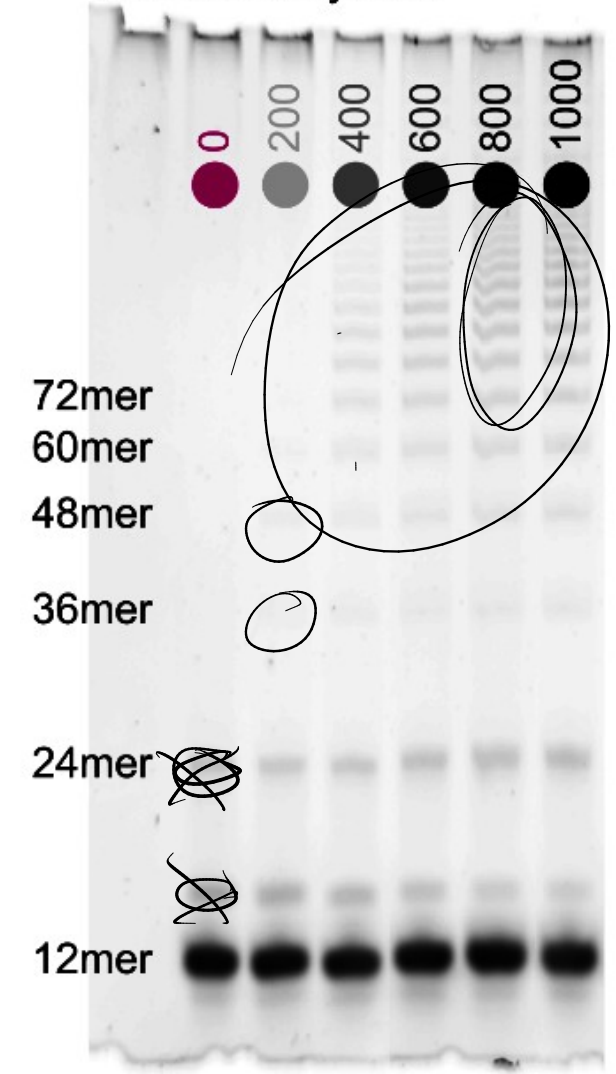
# Repeated templated ligation of random pools



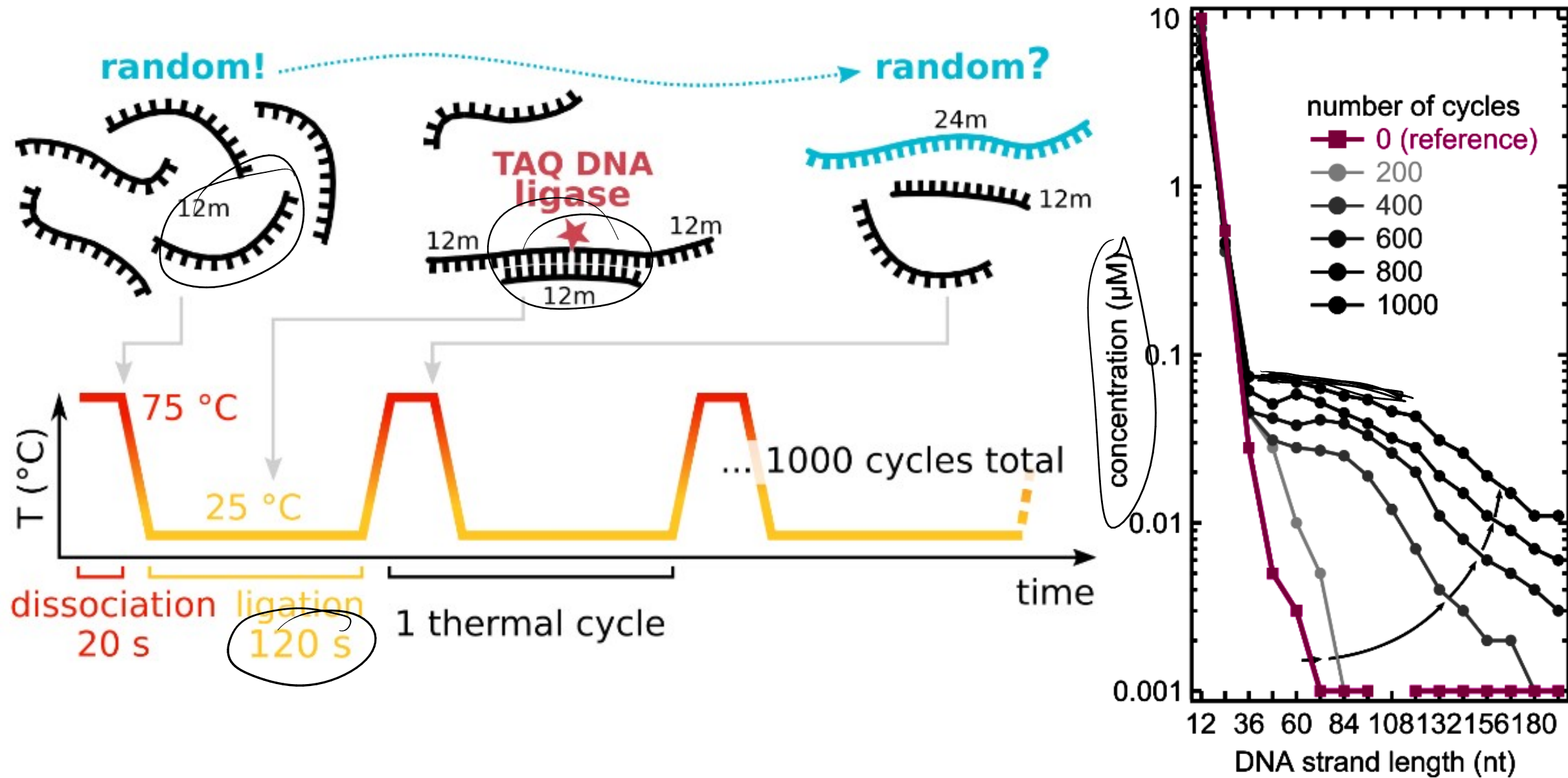
# Repeated templated ligation of random pools



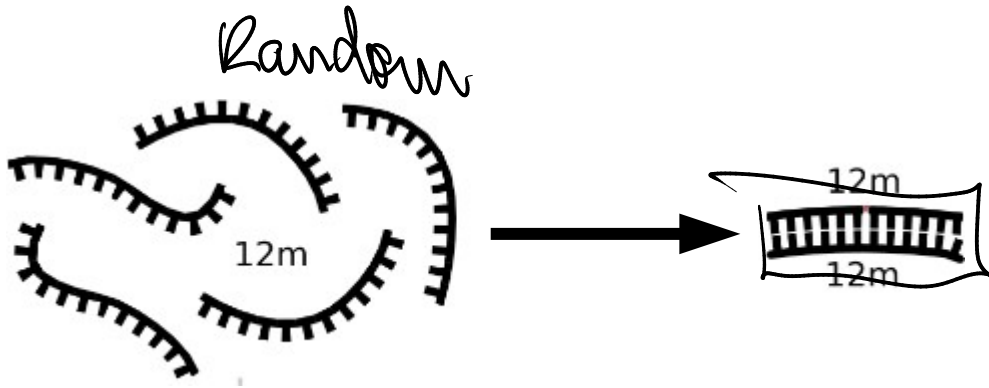
AT random 12mer, 10 μM  
 33 °C ligation temperature  
 number of cycles:



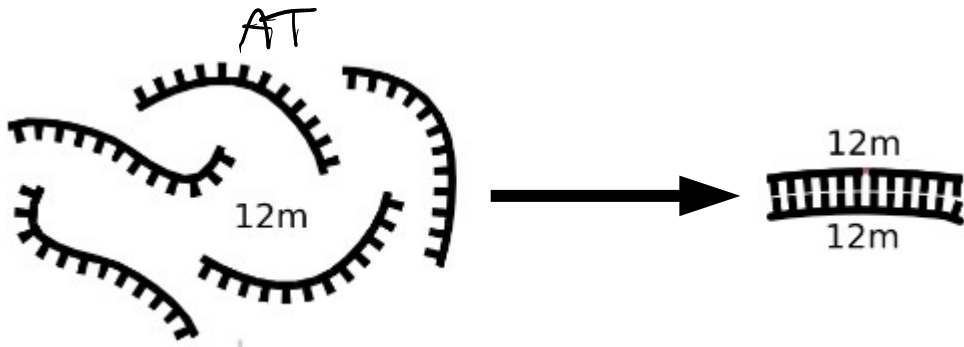
# Repeated templated ligation of random pools



# Why templated ligation is out of equilibrium

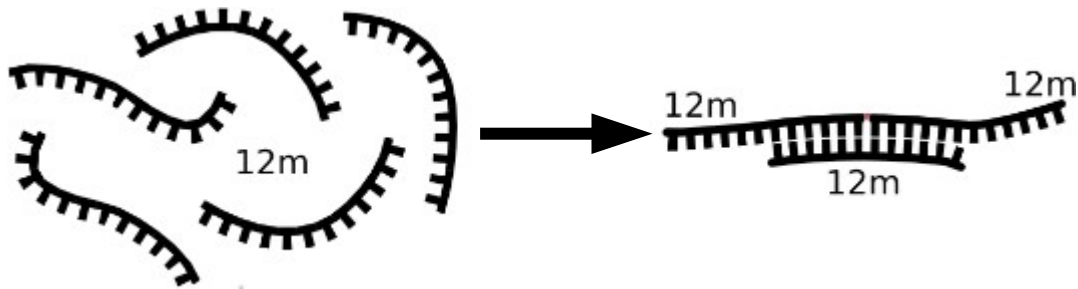


# Why templated ligation is out of equilibrium



Hybridization  
no competition

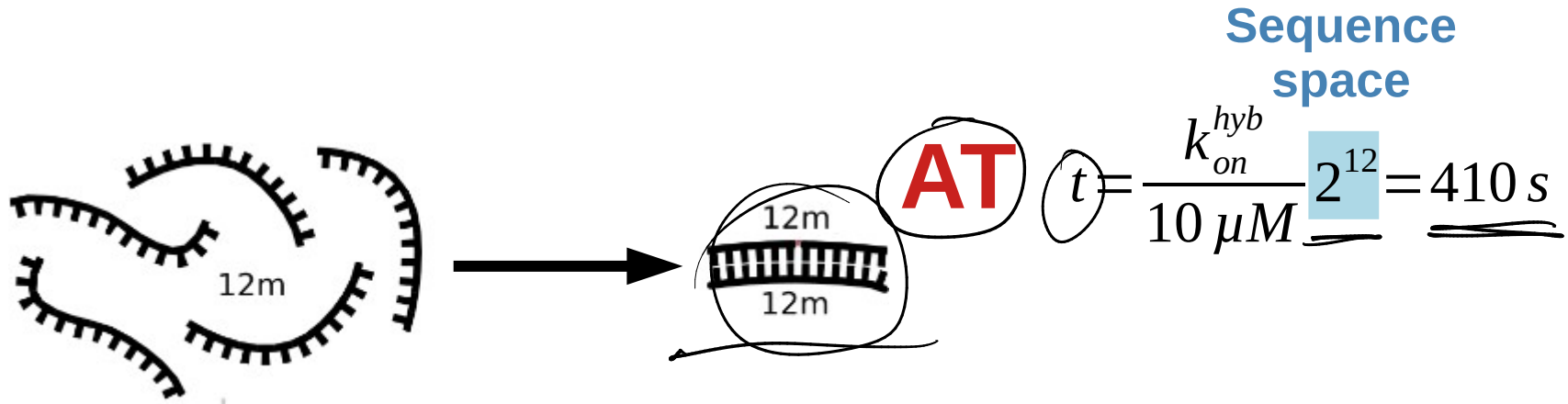
$$k_{on}^{\hat{h}yb} = 1 \mu M^{-1} s^{-1}$$



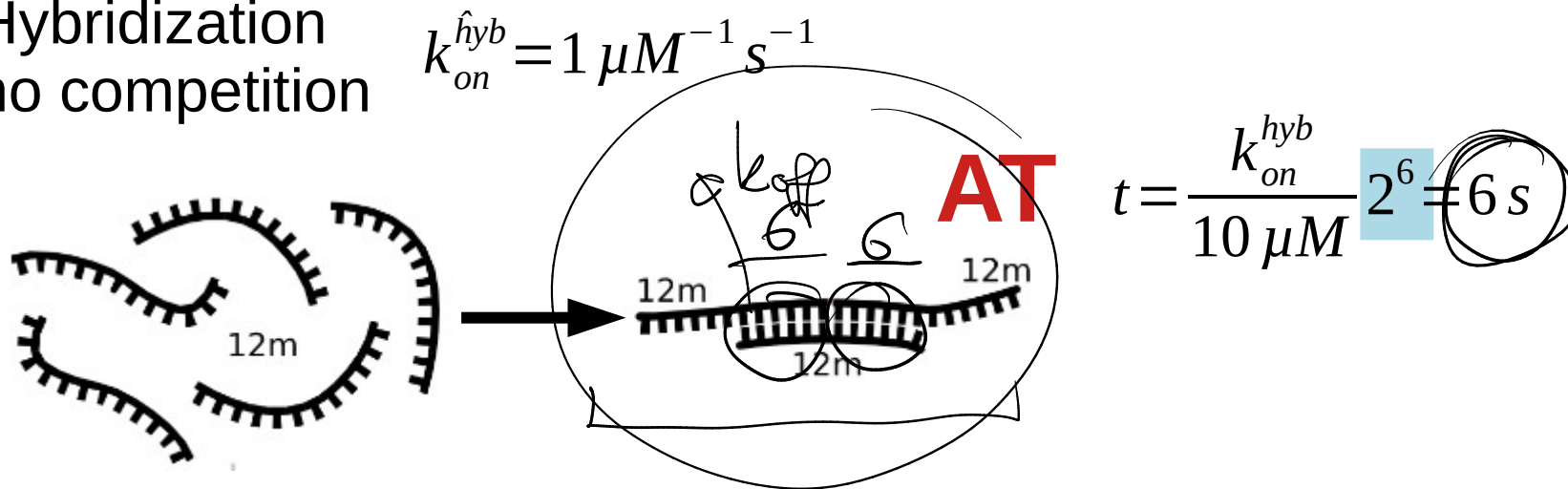
Gao, Wolf, Georgiadis, Nucleic acids research, 34(11), 3370-3377 (2006)

Ouldrige, Šulc, Romano, Doye, Louis, Nucleic acids research, 41(19), 8886-8895 (2013)

# Why templated ligation is out of equilibrium



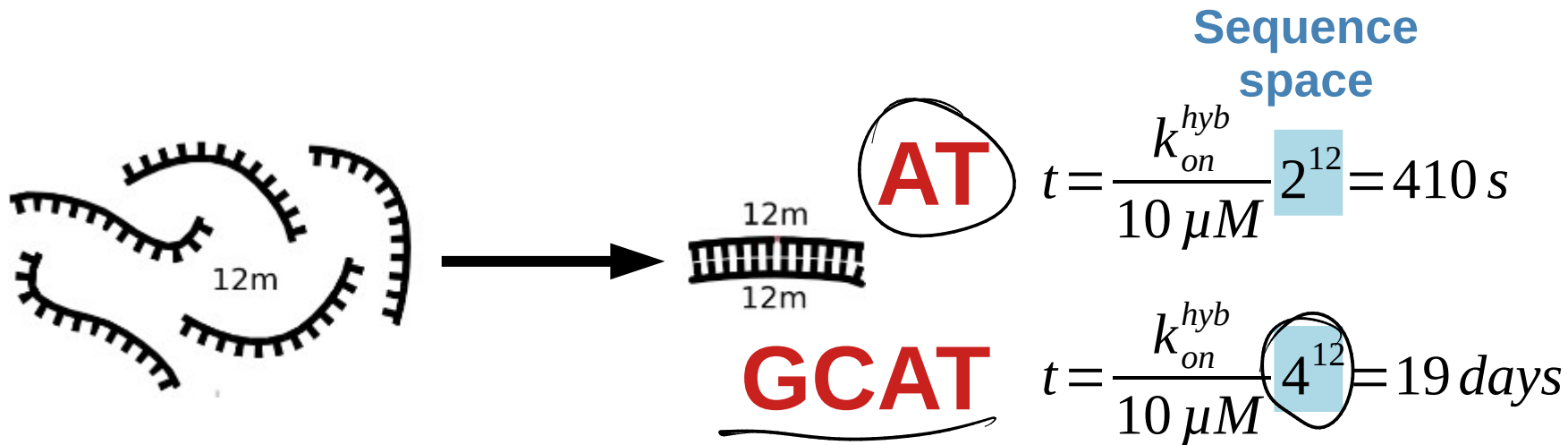
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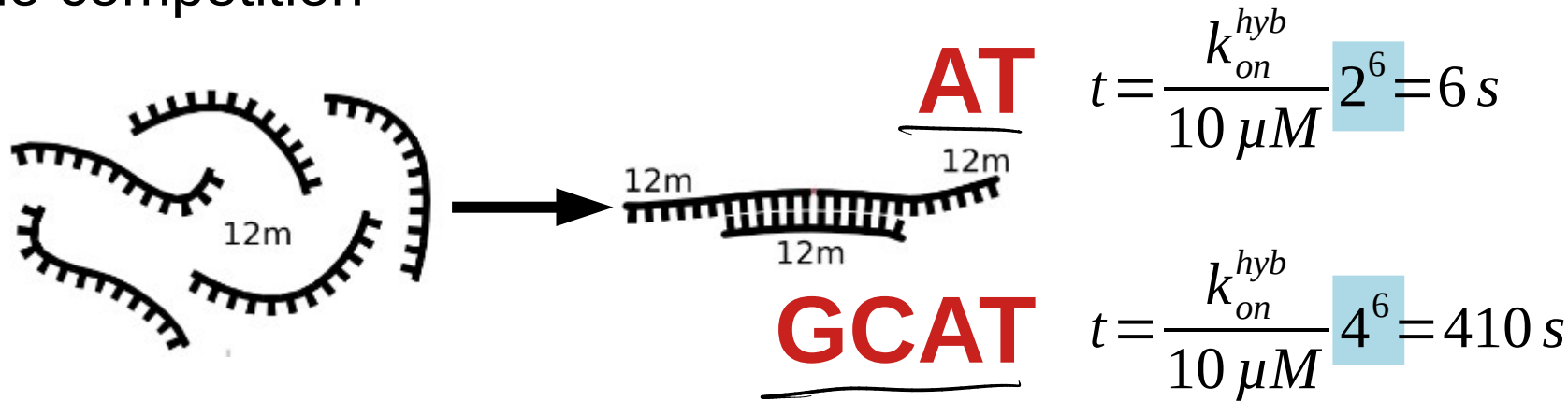
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Hybridization  
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$$k_{on}^{hyb} = 1 \mu M^{-1} s^{-1}$$

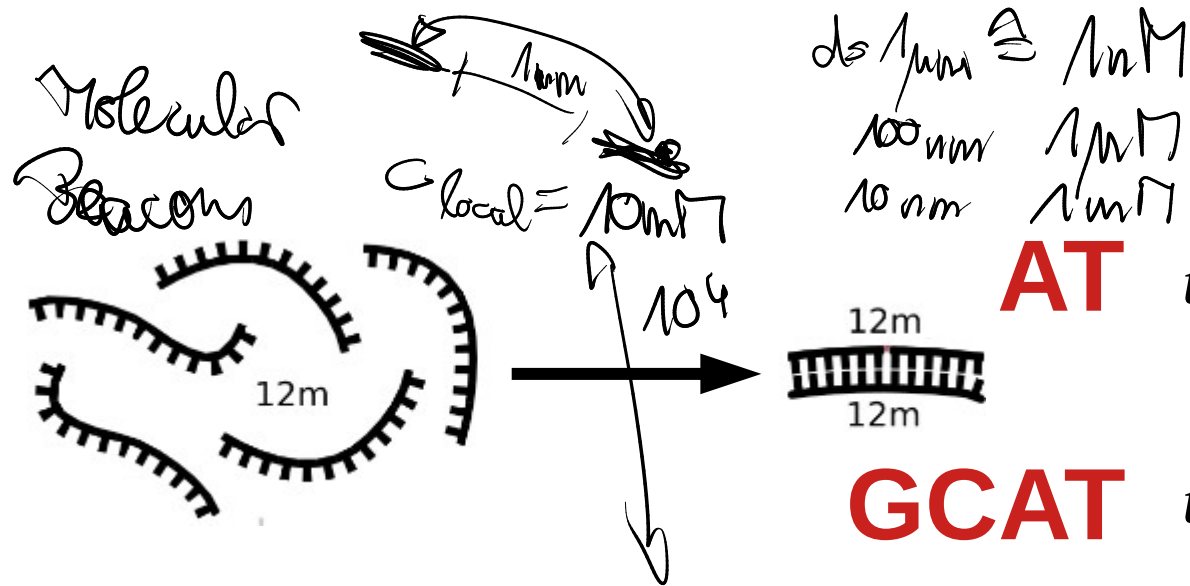


Gao, Wolf, Georgiadis, Nucleic acids research, 34(11), 3370-3377 (2006)

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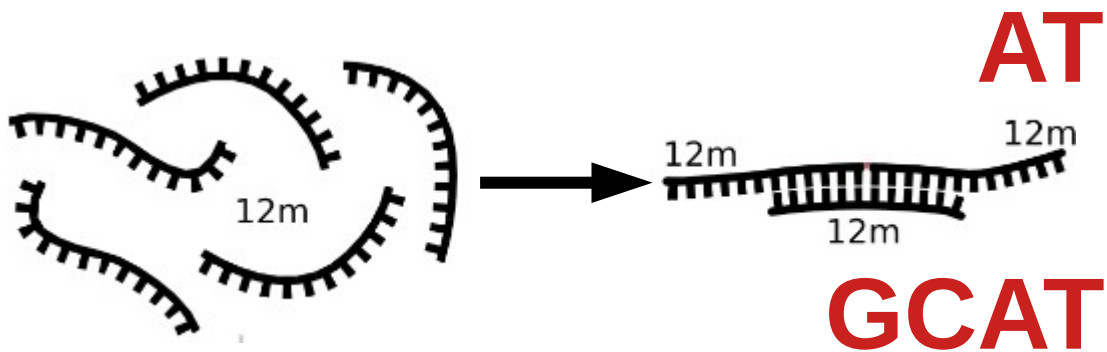


# Why templated ligation is out of equilibrium



Hybridization  
no competition

$$k_{\text{on}}^{\text{hyb}} = 1 \mu\text{M}^{-1} \text{s}^{-1}$$



Sequence space

$$t = \frac{k_{\text{on}}^{\text{hyb}}}{10 \mu\text{M}} 2^{12} = 410 \text{ s}$$

$$t = \frac{k_{\text{on}}^{\text{hyb}}}{10 \mu\text{M}} 4^{12} = 19 \text{ days}$$

$$t = \frac{k_{\text{on}}^{\text{hyb}}}{10 \mu\text{M}} 2^6 = 6 \text{ s} \quad \leftarrow 10000$$

$$t = \frac{k_{\text{on}}^{\text{hyb}}}{10 \mu\text{M}} 4^6 = 410 \text{ s}$$

$T_{\text{lig}} (\text{°C}) = 25 \quad 30 \quad 35 \quad 40$

GCAT

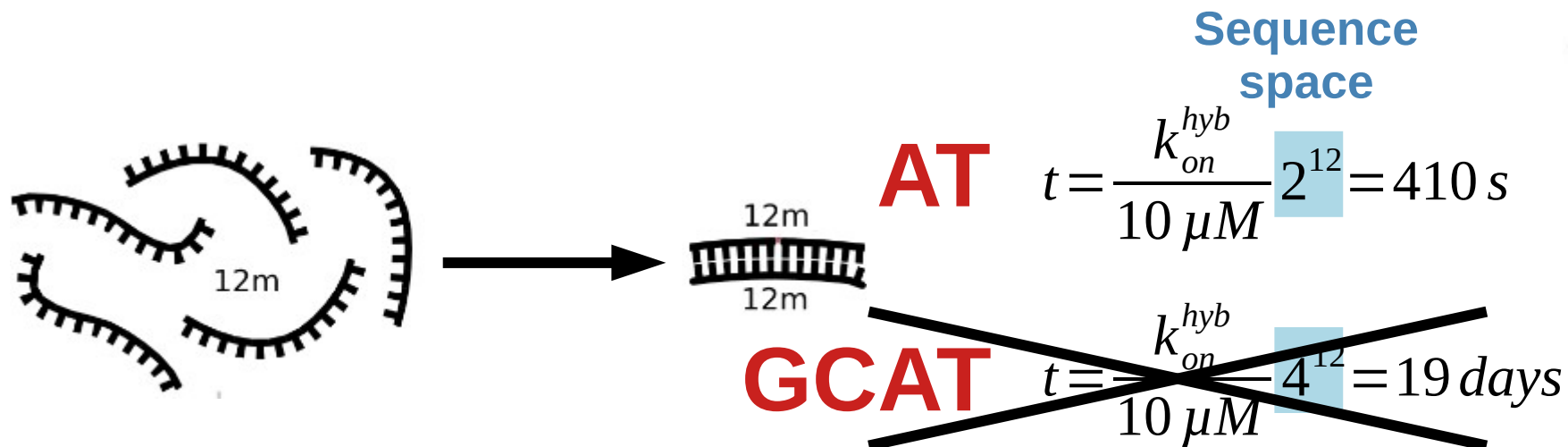
DNA strand length (nt)

24

12

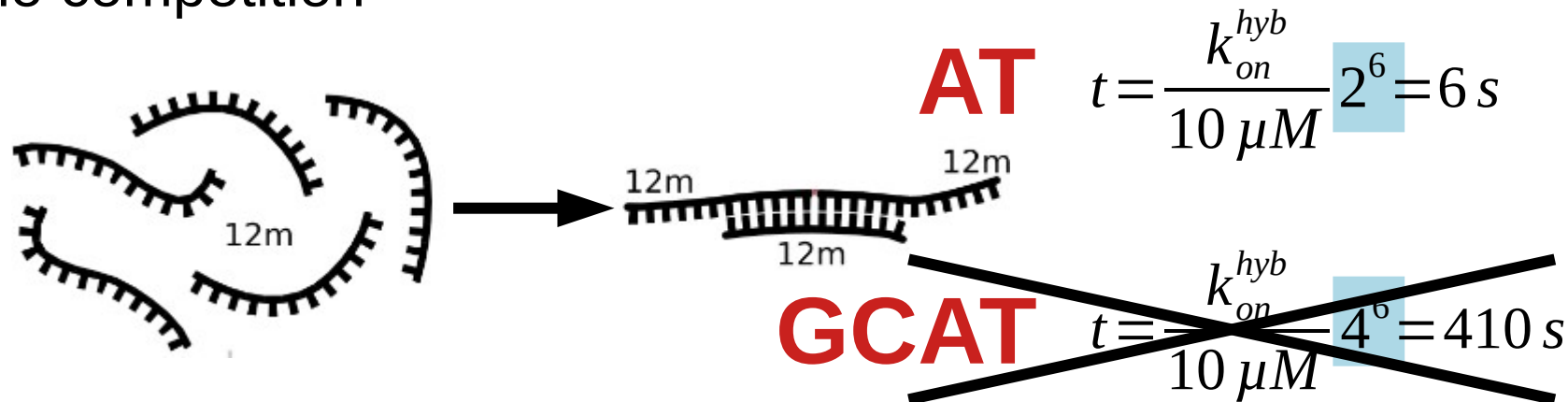


# Why templated ligation is out of equilibrium



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$$k_{on}^{hyb} = 1 \mu M^{-1} s^{-1}$$



$T_{lig} (\text{°C}) = 25 \quad 30 \quad 35 \quad 40$

**GCAT**

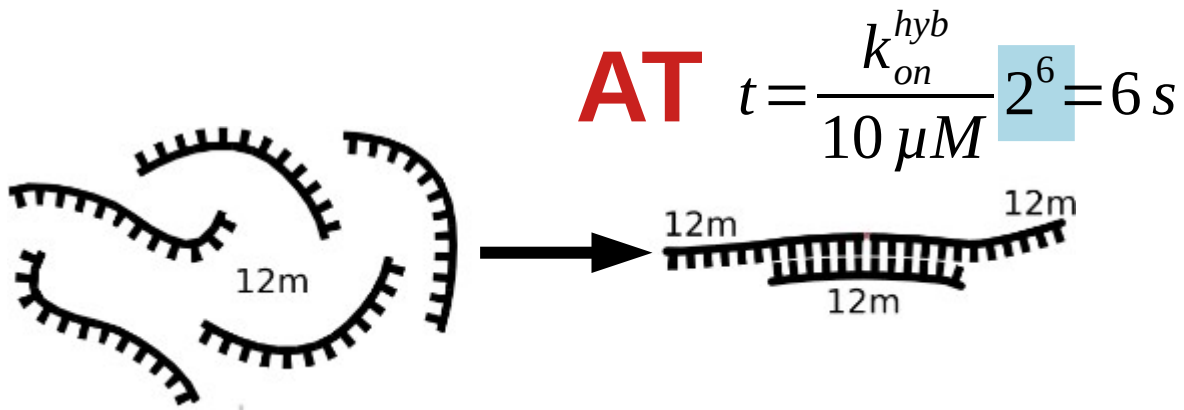
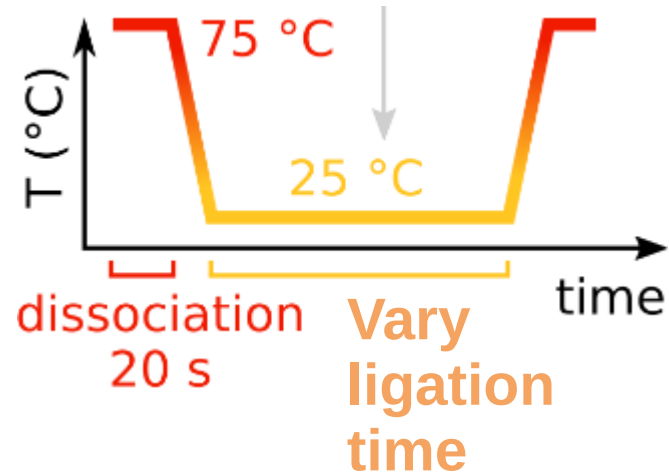
DNA strand length (nt)

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# Why templated ligation is out of equilibrium





# Dynamics in sequence space

Spontaneous emergence of autocatalytic information-coding polymers, J. Chem. Physics (2015)  
Onset of natural selection in populations of autocatalytic heteropolymers, J. Chem. Physics (2018)

With Sergei Maslov and Alexei Tkachenko, University of Illinois

# Dynamics in sequence space

**Replication amplifies  
patterns at the ligation site**

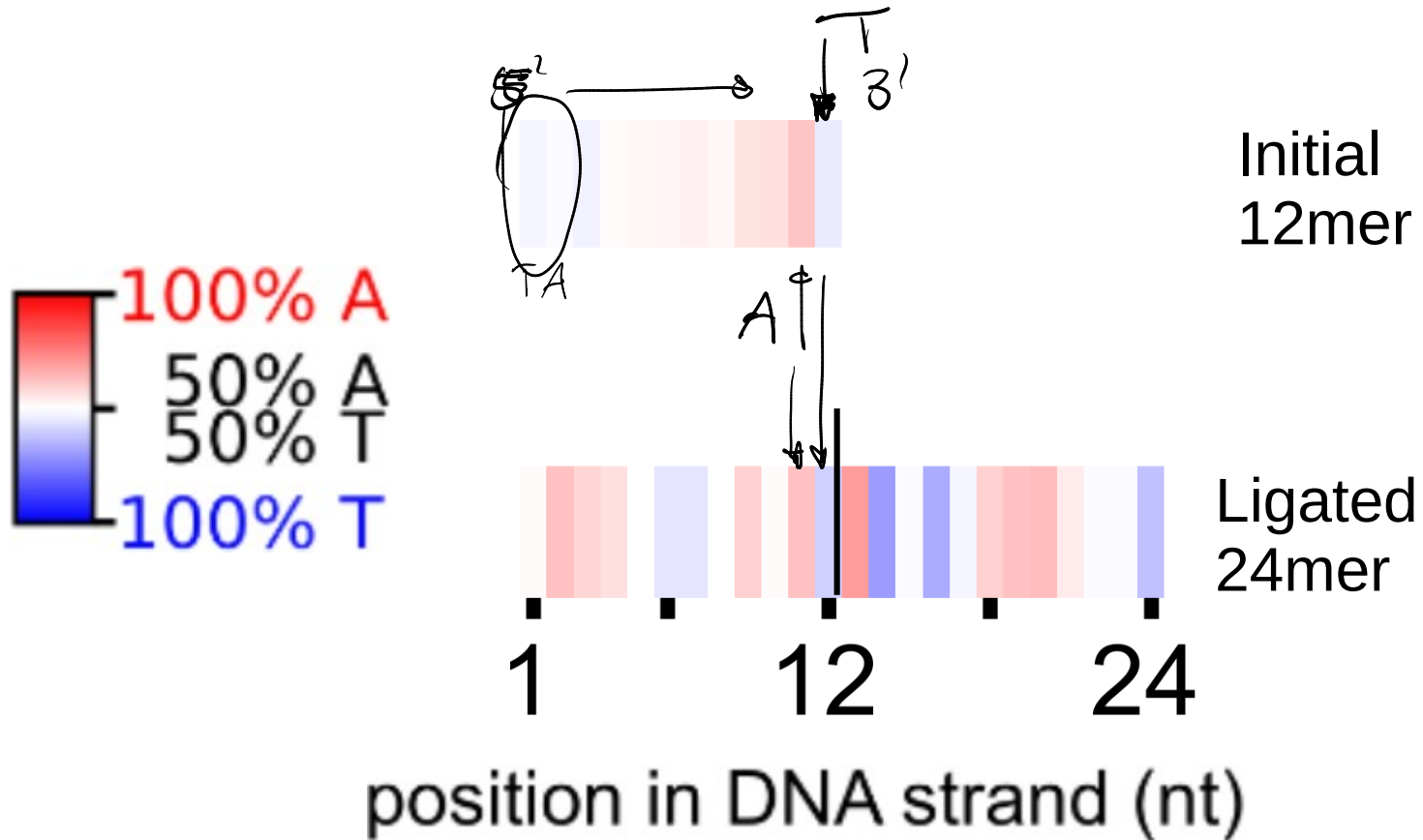
**Replication avoids hairpins by  
evolving complementary pools**

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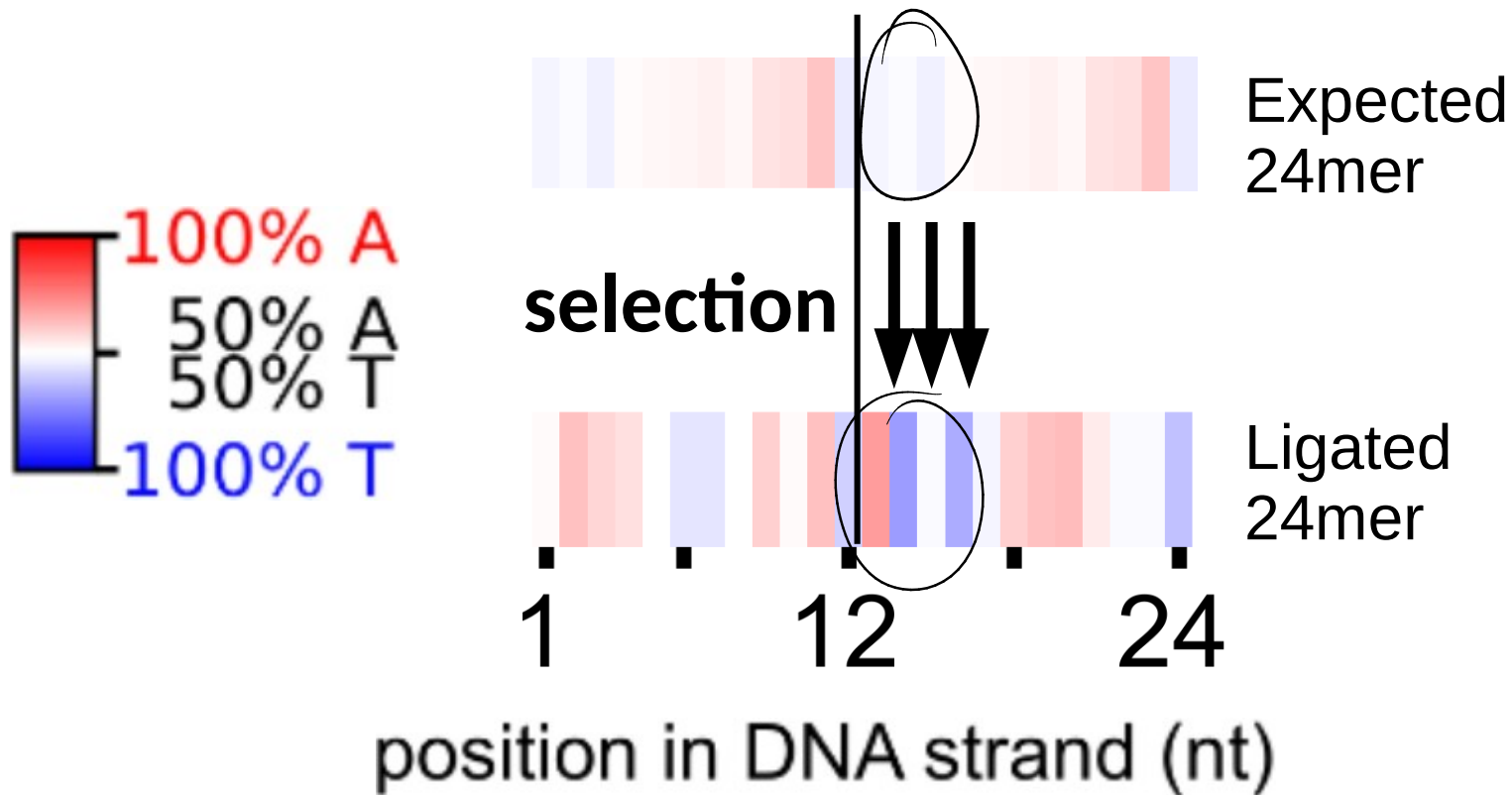
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Replication amplifies  
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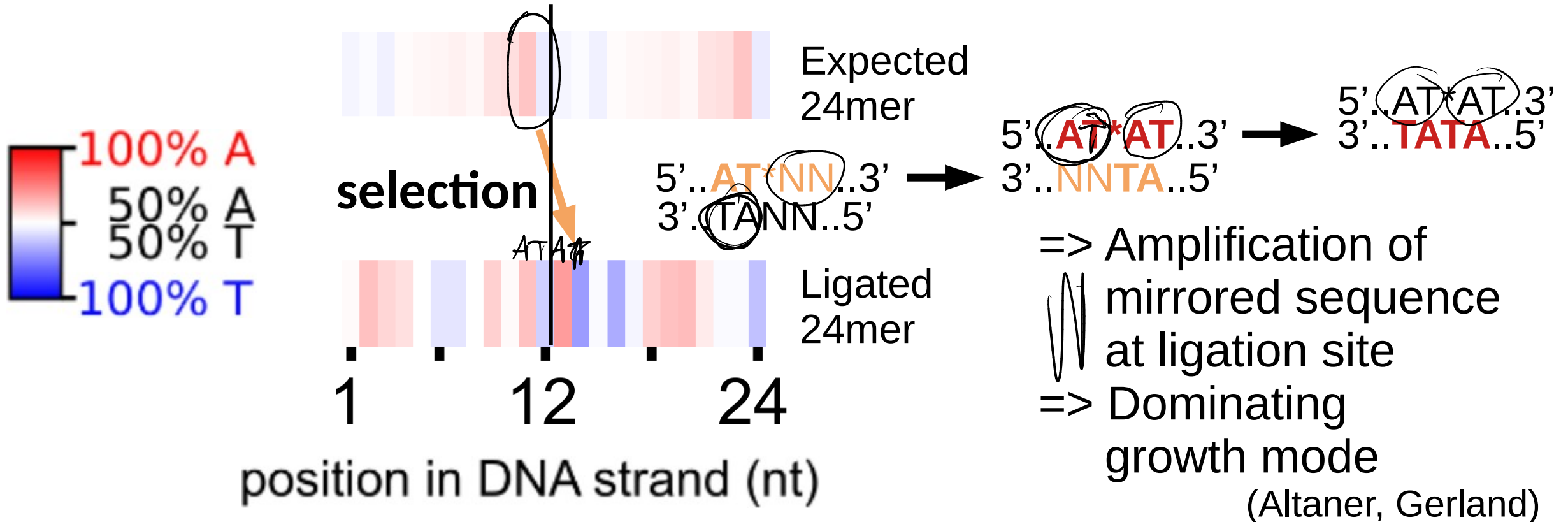
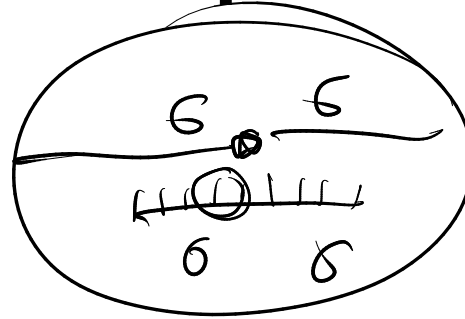


With Sergei Maslov and Alexei Tkachenko, University of Illinois



# Dynamics in sequence space

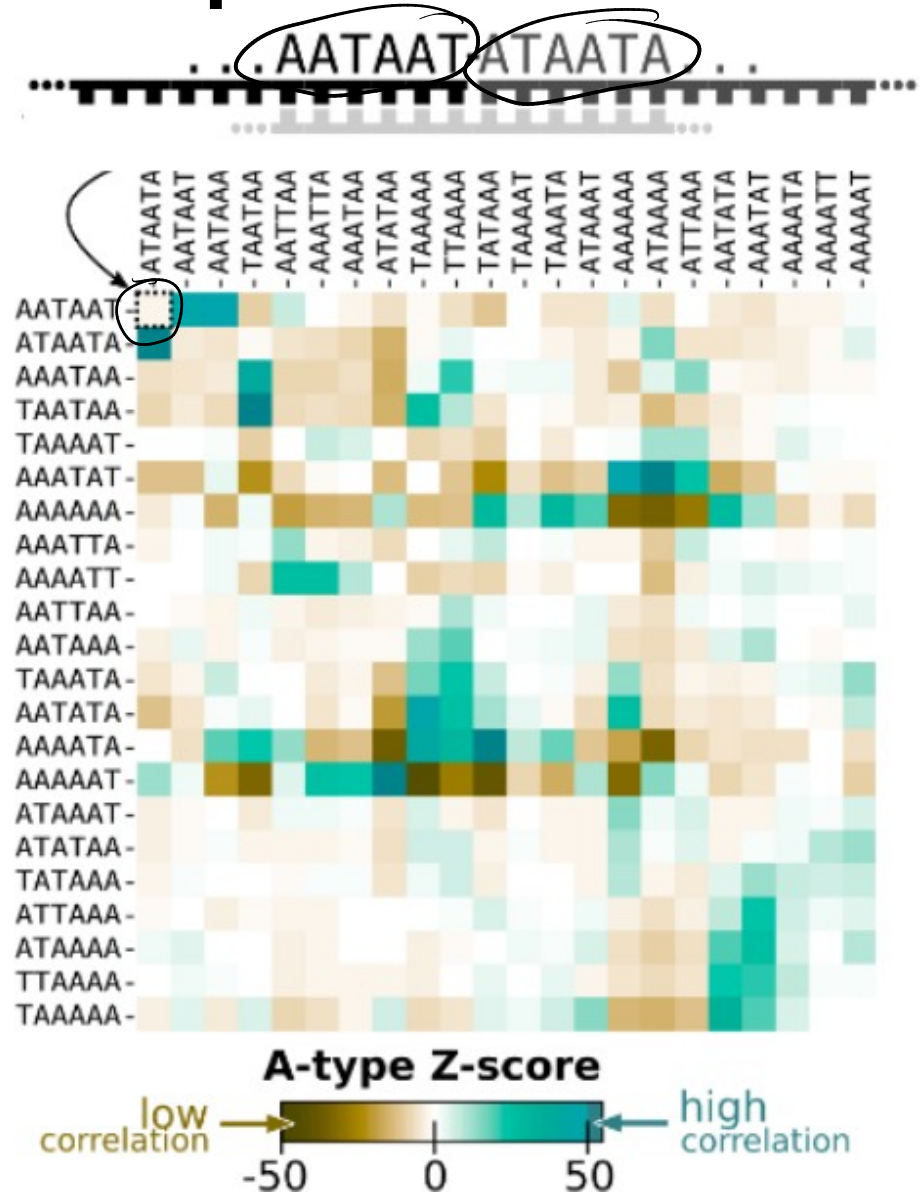
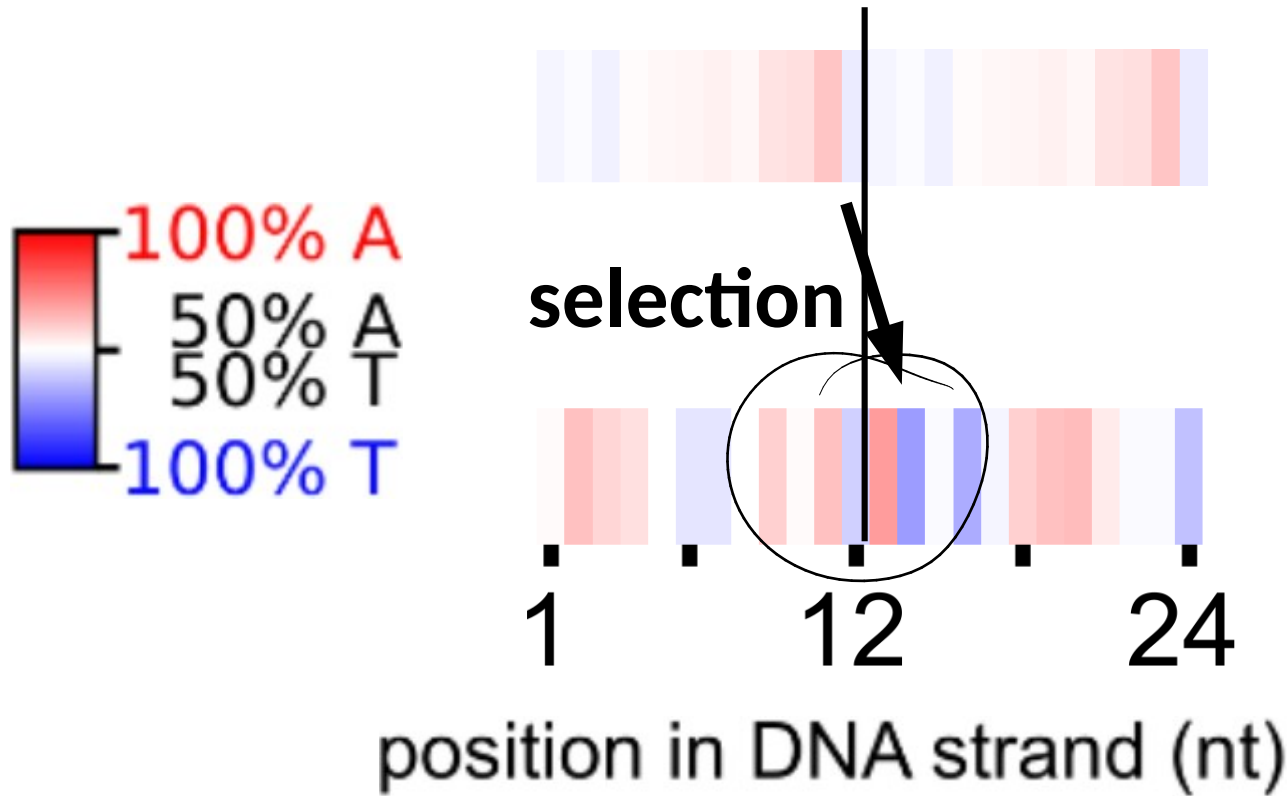
Replication amplifies patterns at the ligation site



With Sergei Maslov and Alexei Tkachenko, University of Illinois

# Dynamics in sequence space

Replication amplifies patterns at the ligation site



With Sergei Maslov and Alexei Tkachenko, University of Illinois

# Dynamics in sequence space

**Replication amplifies  
patterns at the ligation site**

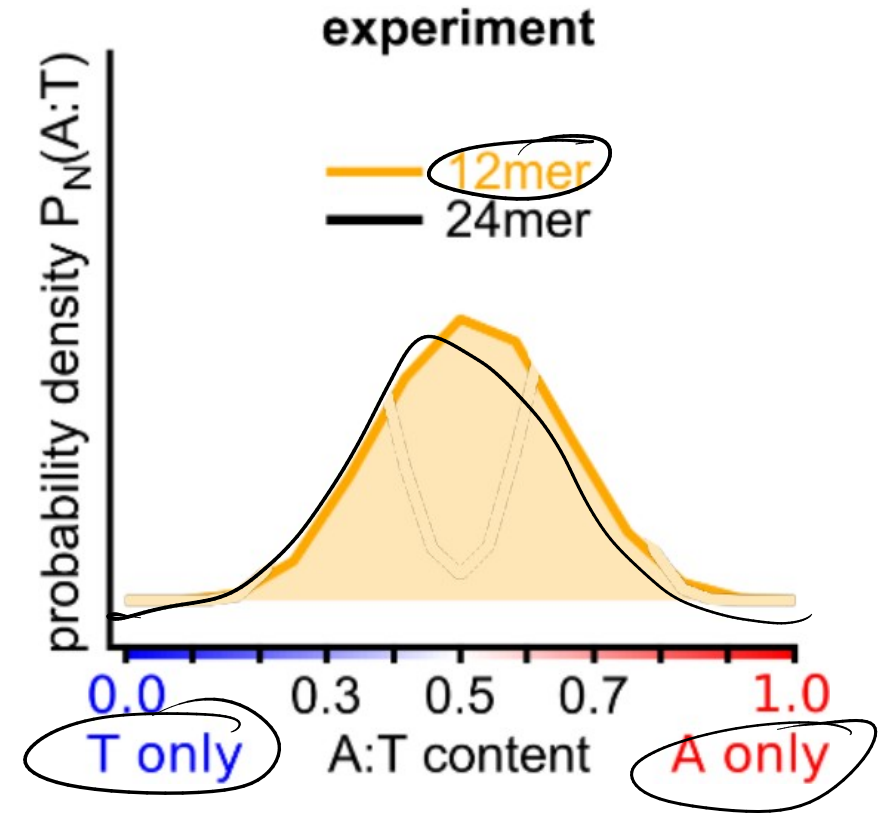
# Dynamics in sequence space

Replication amplifies  
patterns at the ligation site

Replication avoids hairpins by  
evolving complementary pools

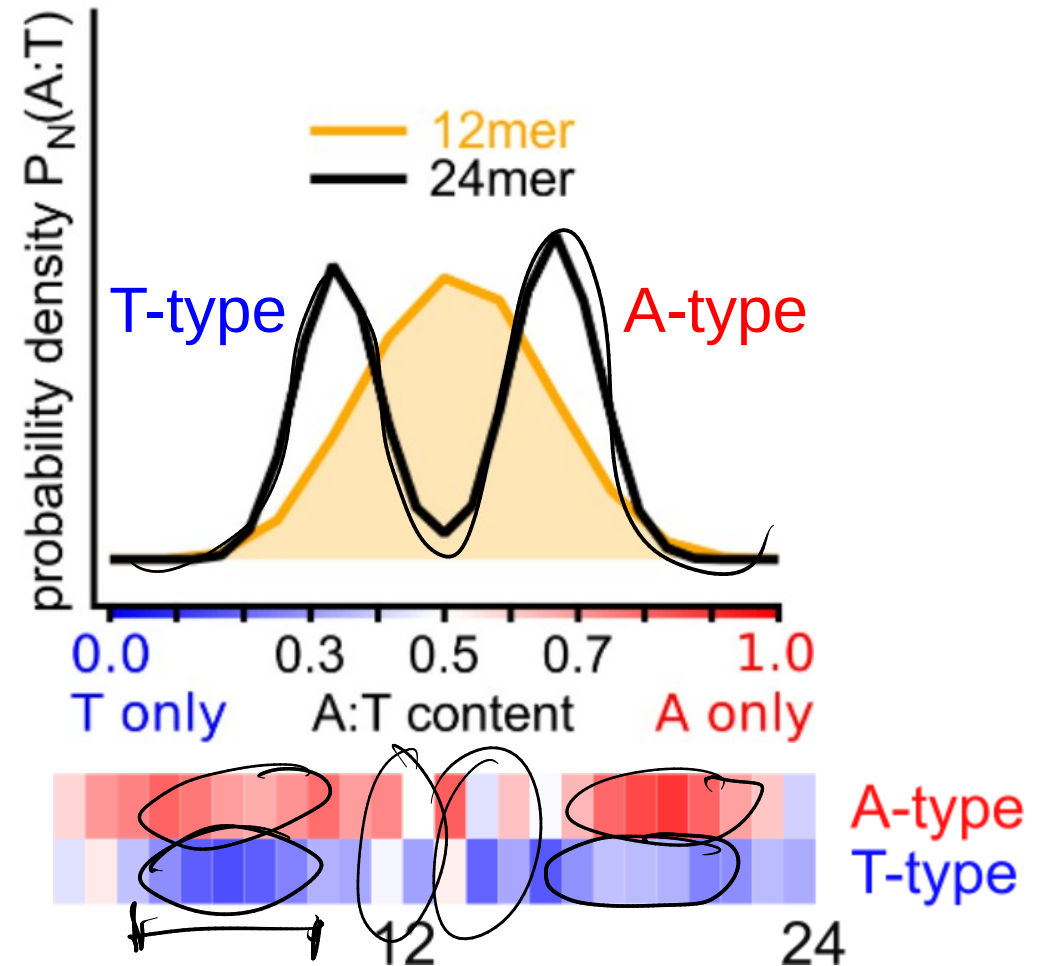
# Dynamics in sequence space

Replication avoids hairpins by evolving complementary pools



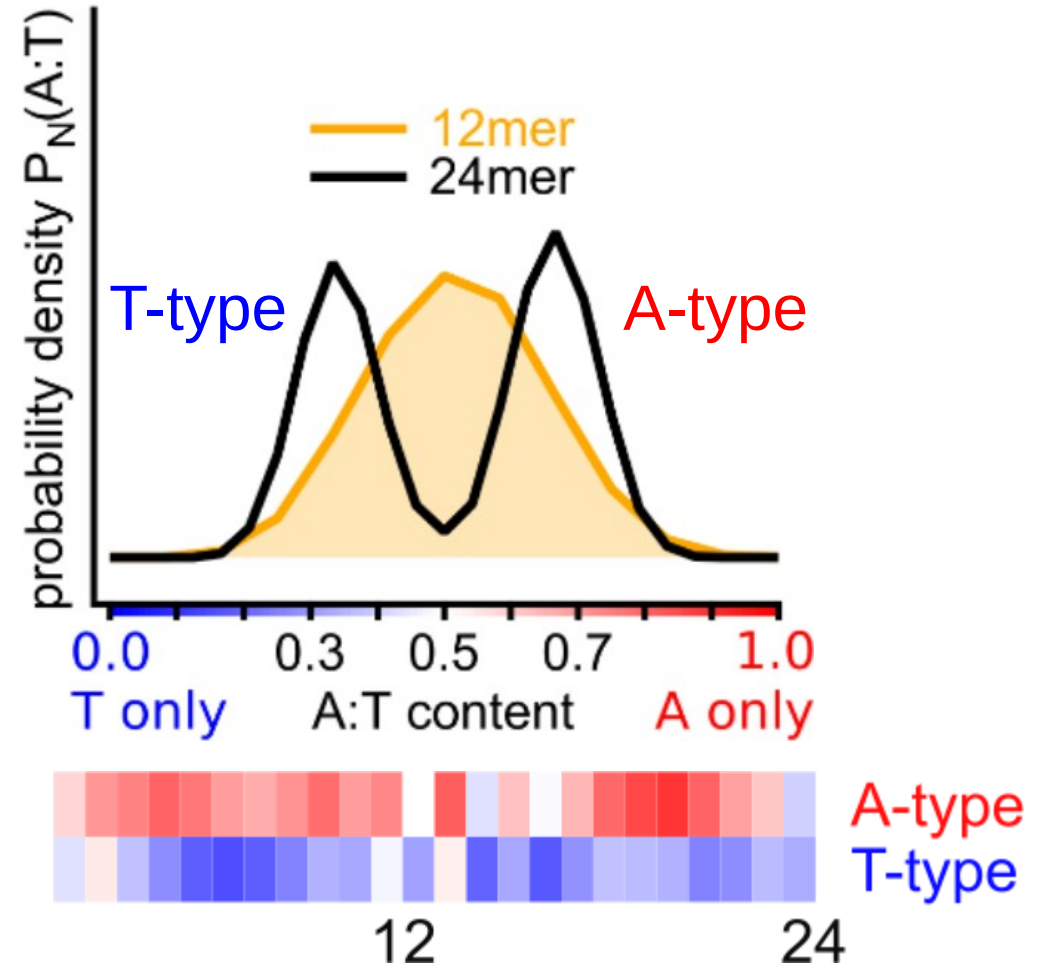
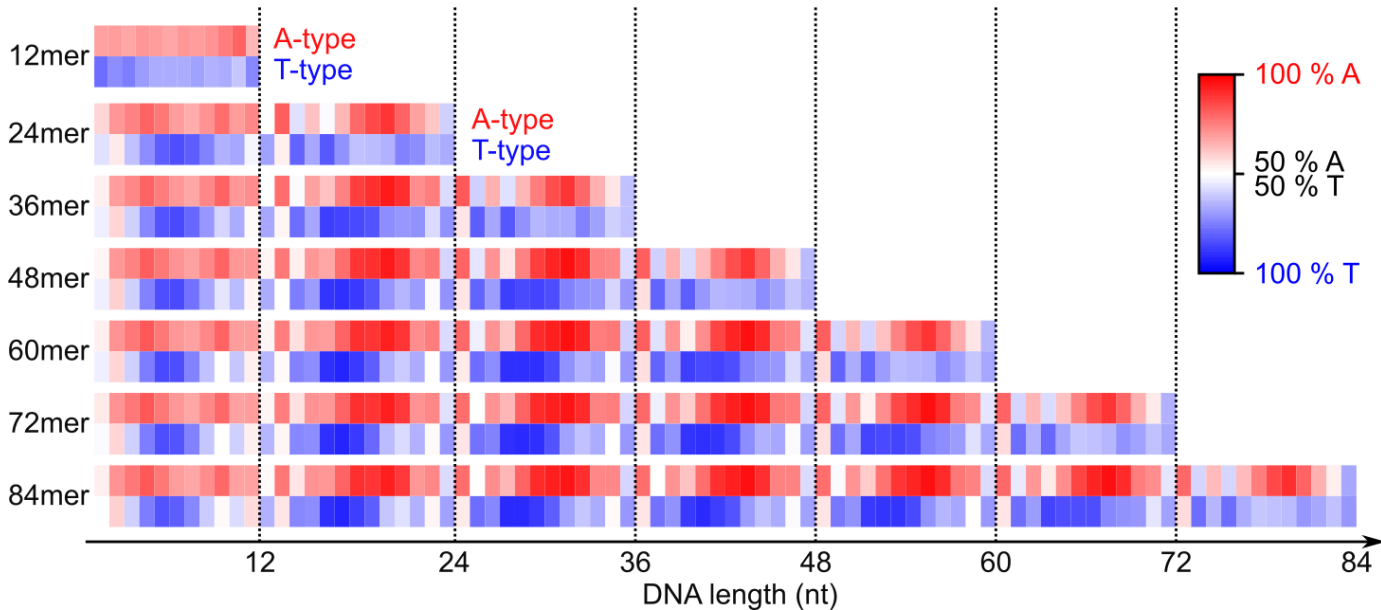
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Replication avoids hairpins by evolving complementary pools



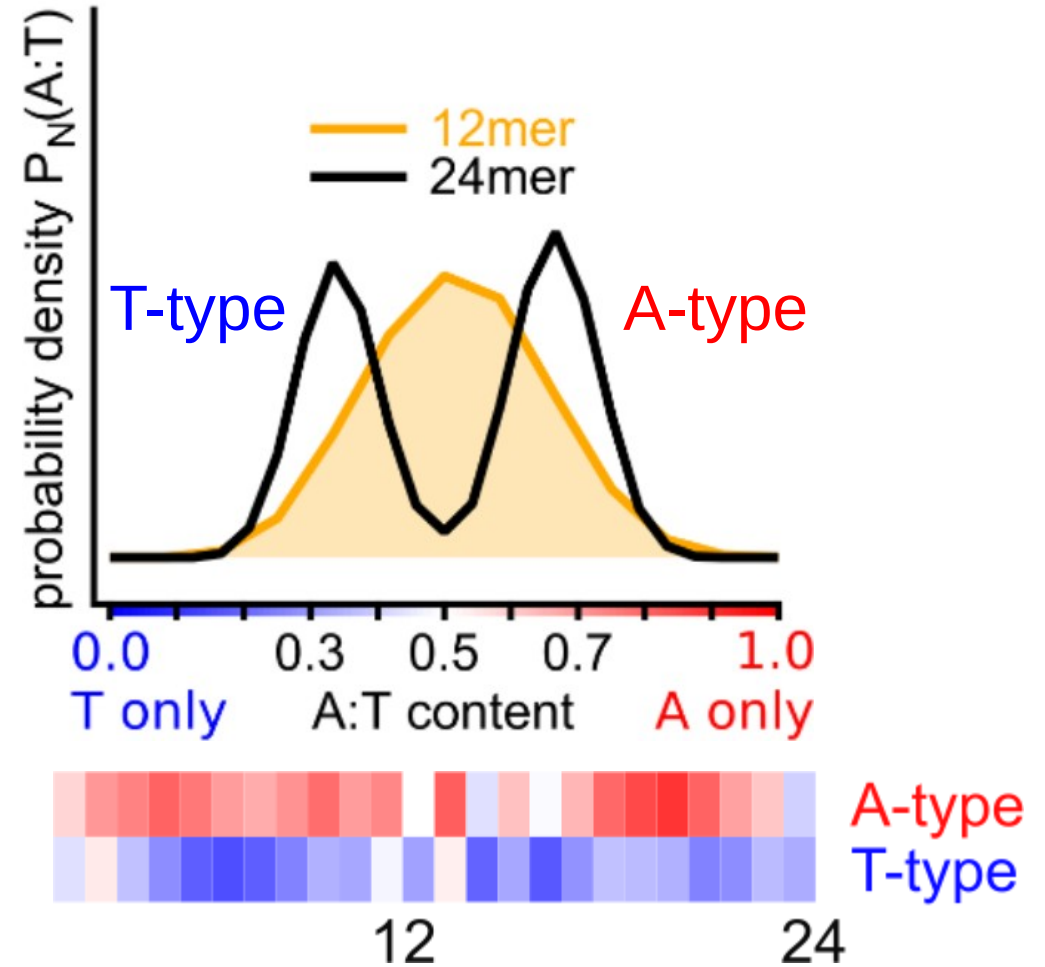
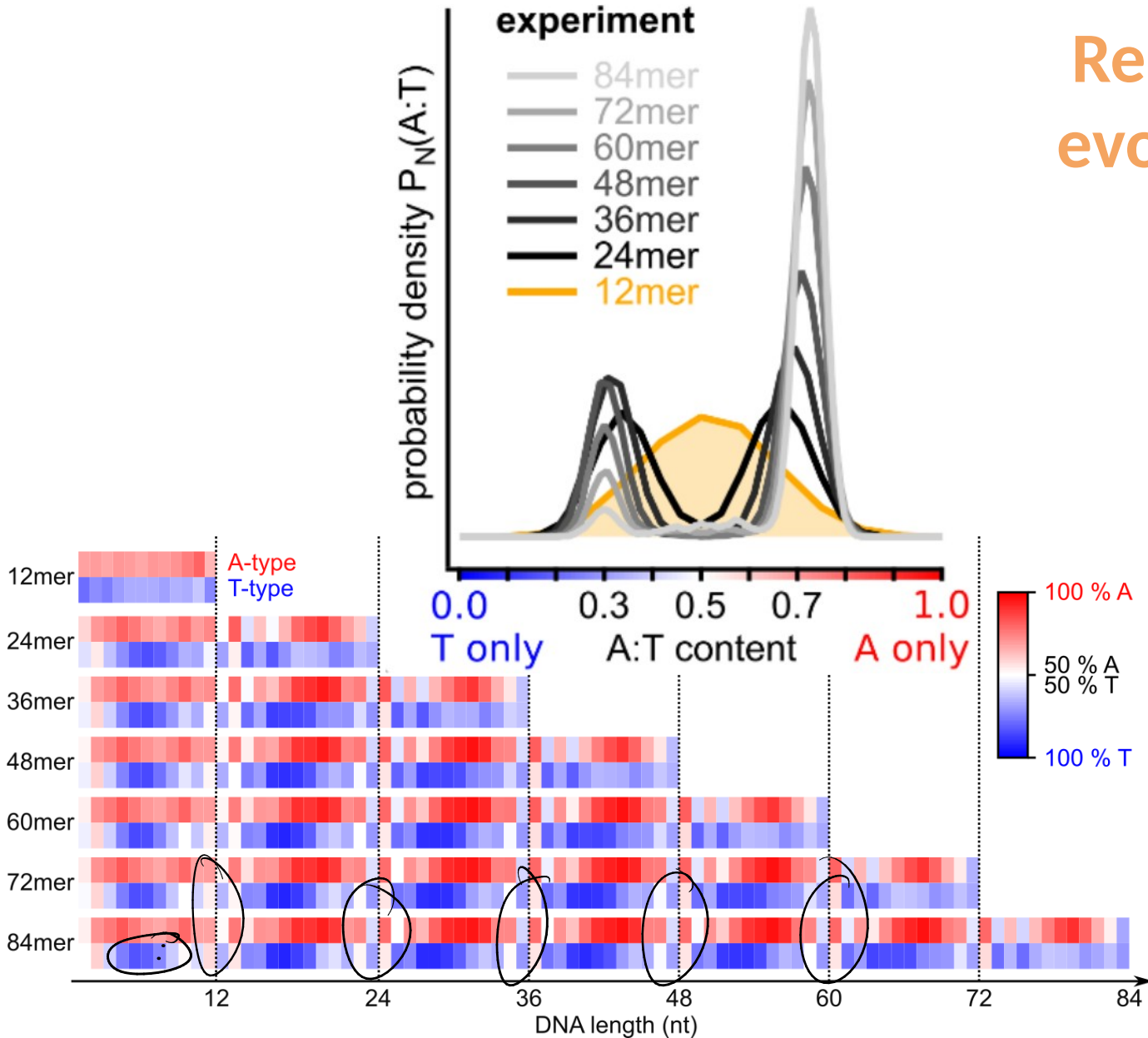
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Replication avoids hairpins by evolving complementary pools

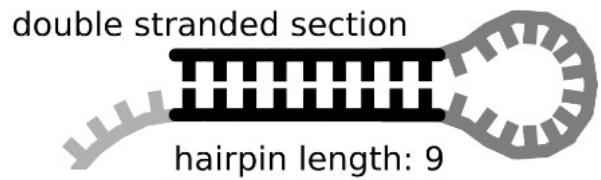


# Dynamics in sequence space

Replication avoids hairpins by evolving complementary pools

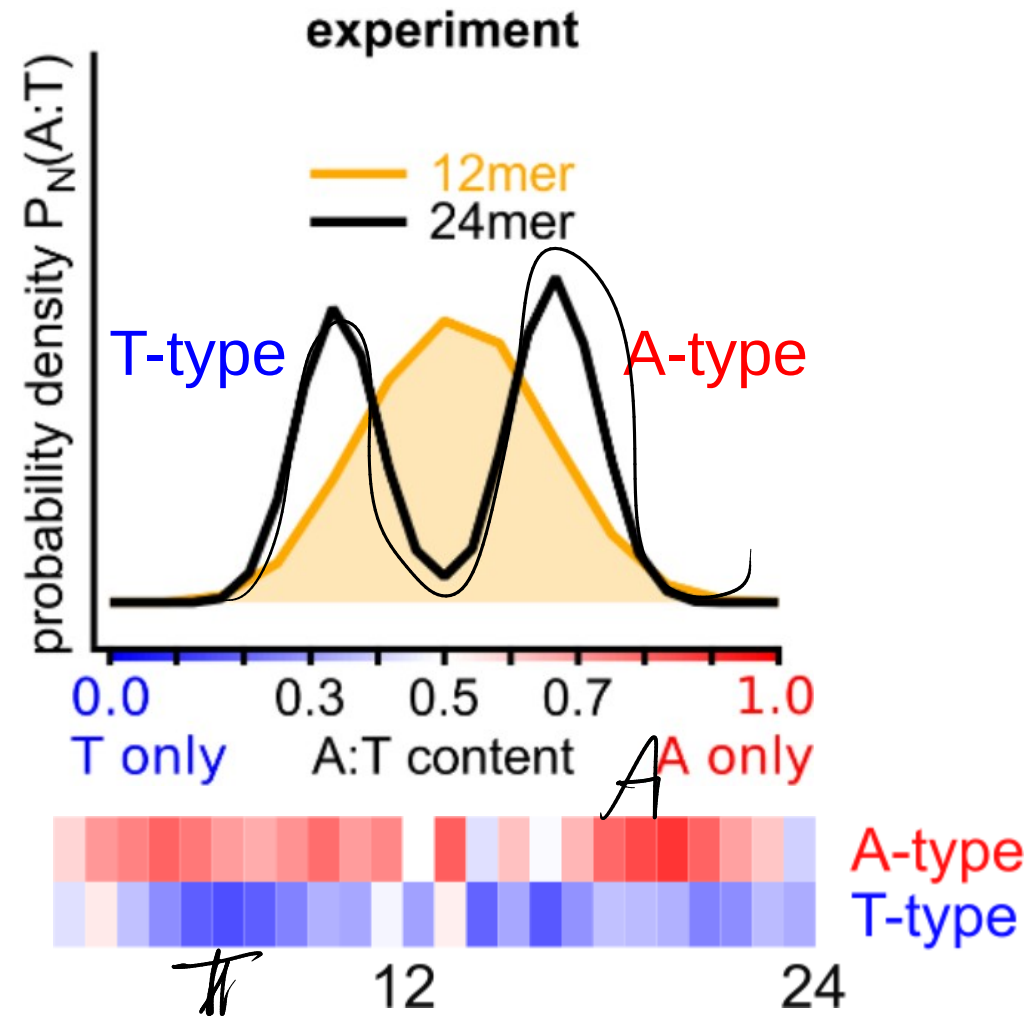
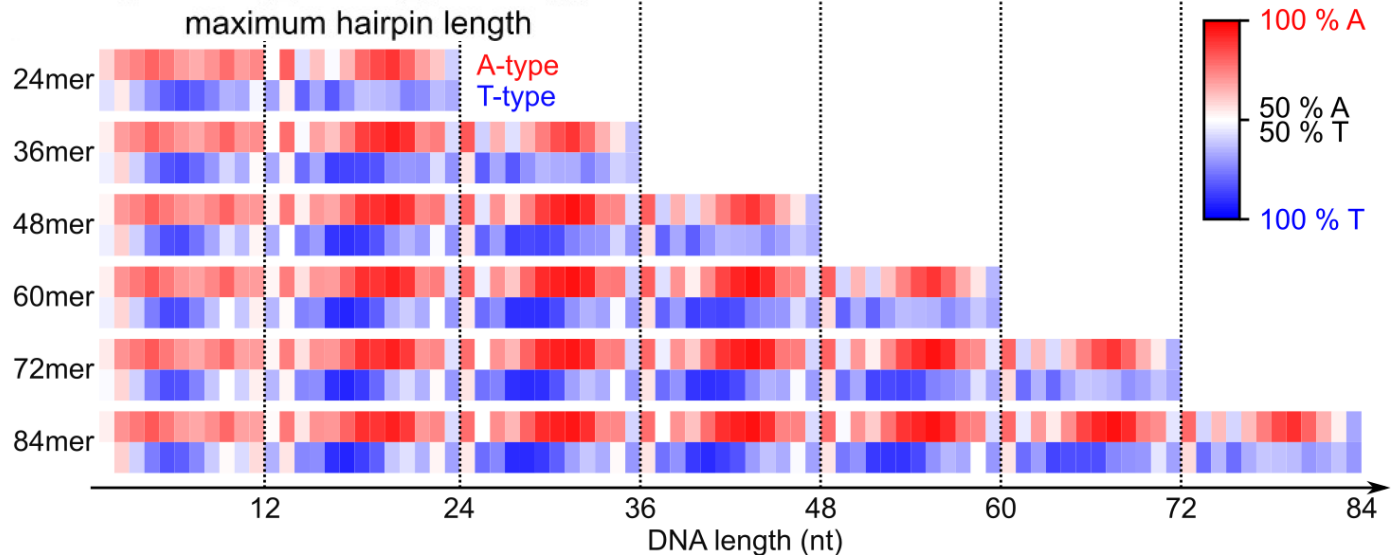
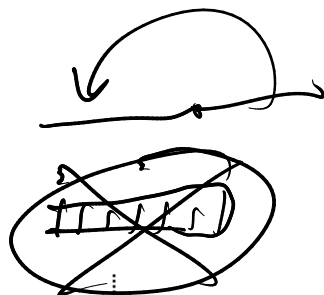
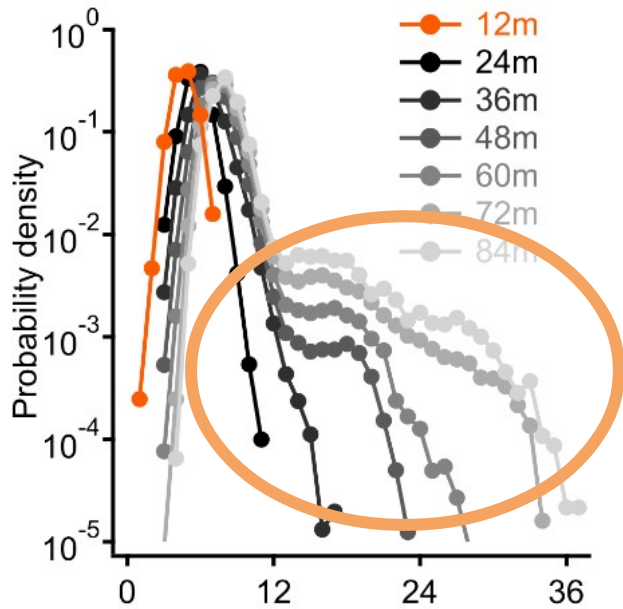






# Dynamics in sequence space

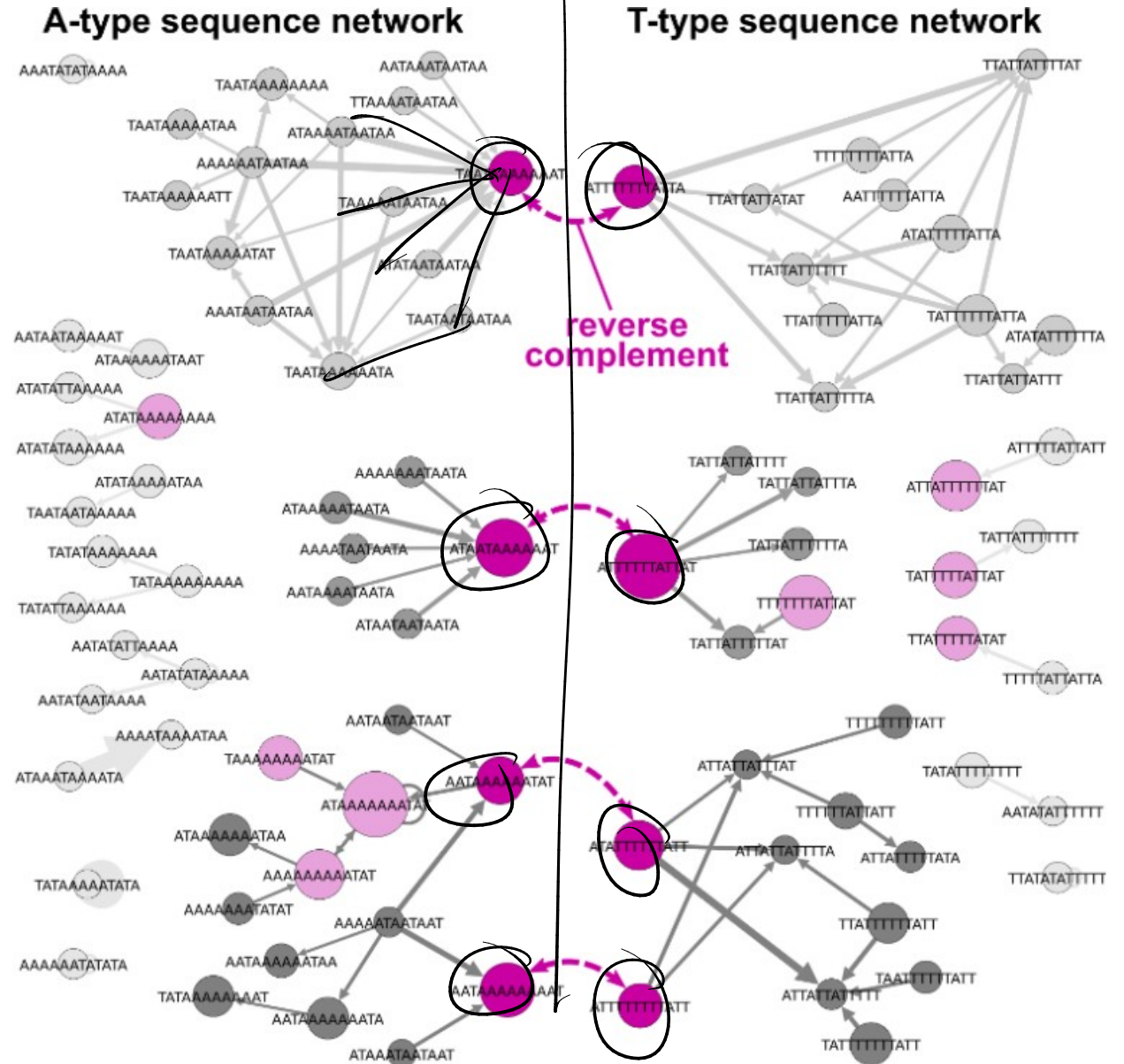
Replication avoids hairpins by evolving complementary pools



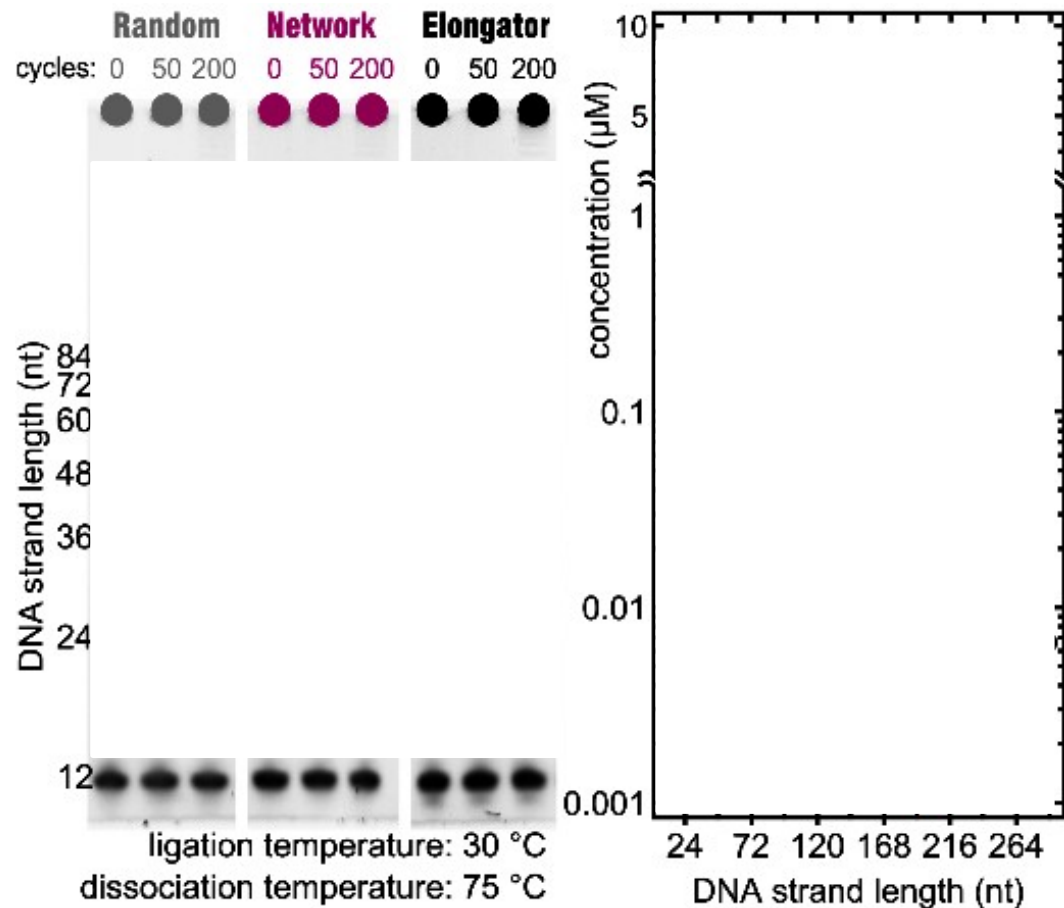
# Dynamics in sequence space

Replication amplifies patterns at the ligation site

Replication avoids hairpins by evolving complementary pools



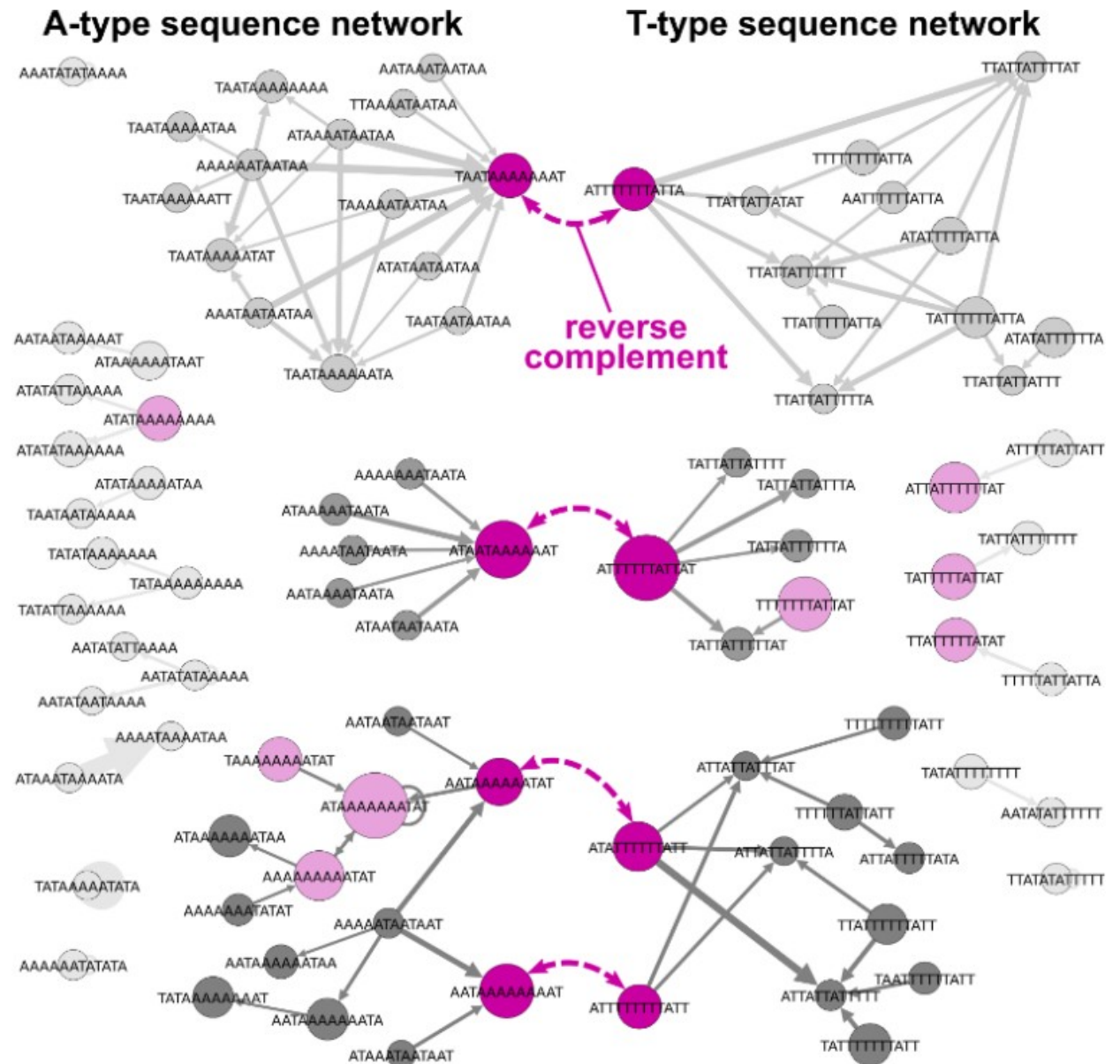
# Dynamics in sequence space



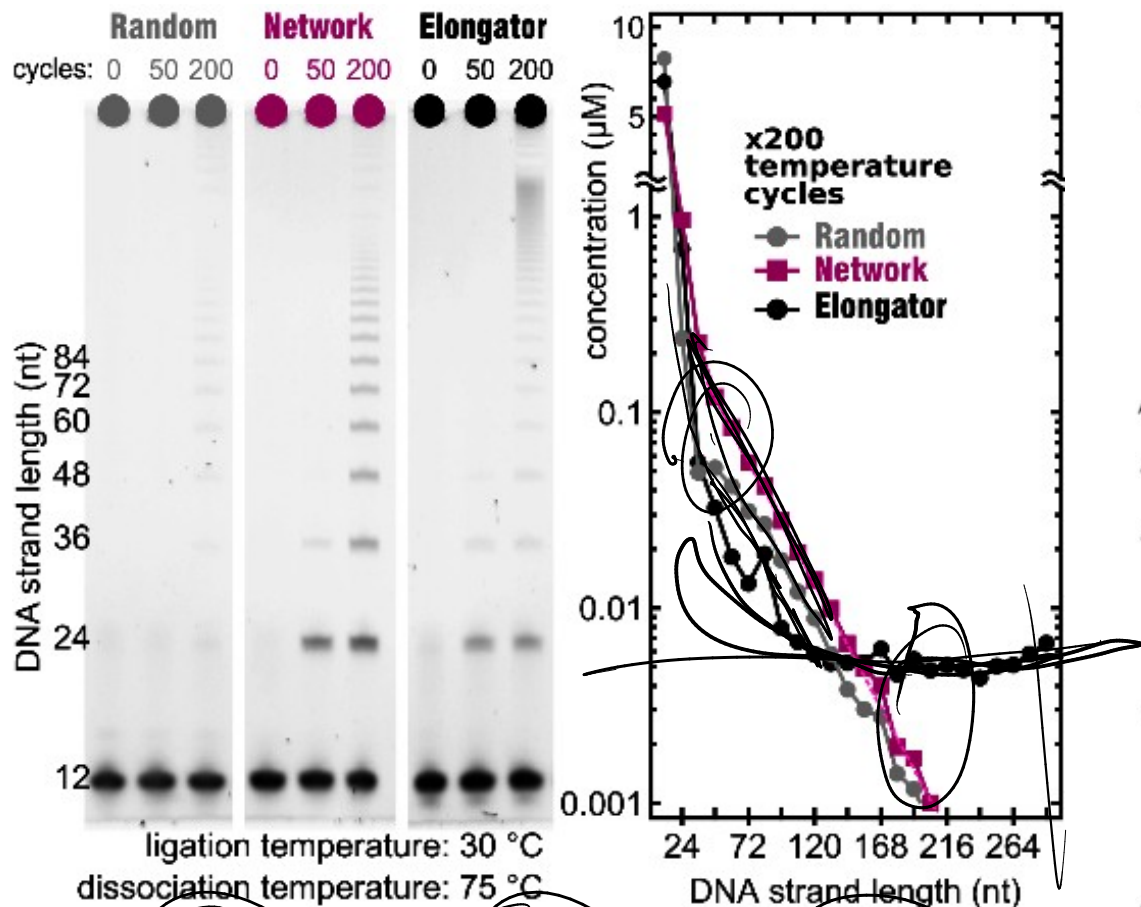
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 AAAATAAAATAT  
 ATAATTAAATAA  
 TAAAAATTATTT  
 TTAAATTTTATA  
 TATTTAATTTTT  
 TAAAAATTAATA  
 AAAATAATTTAT  
 TTATATAAAATA

**Network**  
 ATAATAAAAAAT  
 AATAAAAAAAAT  
 AATAAAAAATAT  
 TAATAAAAAAT  
 ATTTTTTATTAT  
 ATTTTTTTTATT  
 ATTTTTTTTATT  
 ATTTTTTTTATTA

**Elongator**  
 ATATTTTTTATA  
 TATAAAAAATAT  
 AAATATATAAAA  
 TTTTATATATTT  
 AAAATATATAAA  
 TTTATATATTTT  
 TATTTTTTTTTAT  
 ATAAAAAAAATA



# Dynamics in sequence space



**Random**

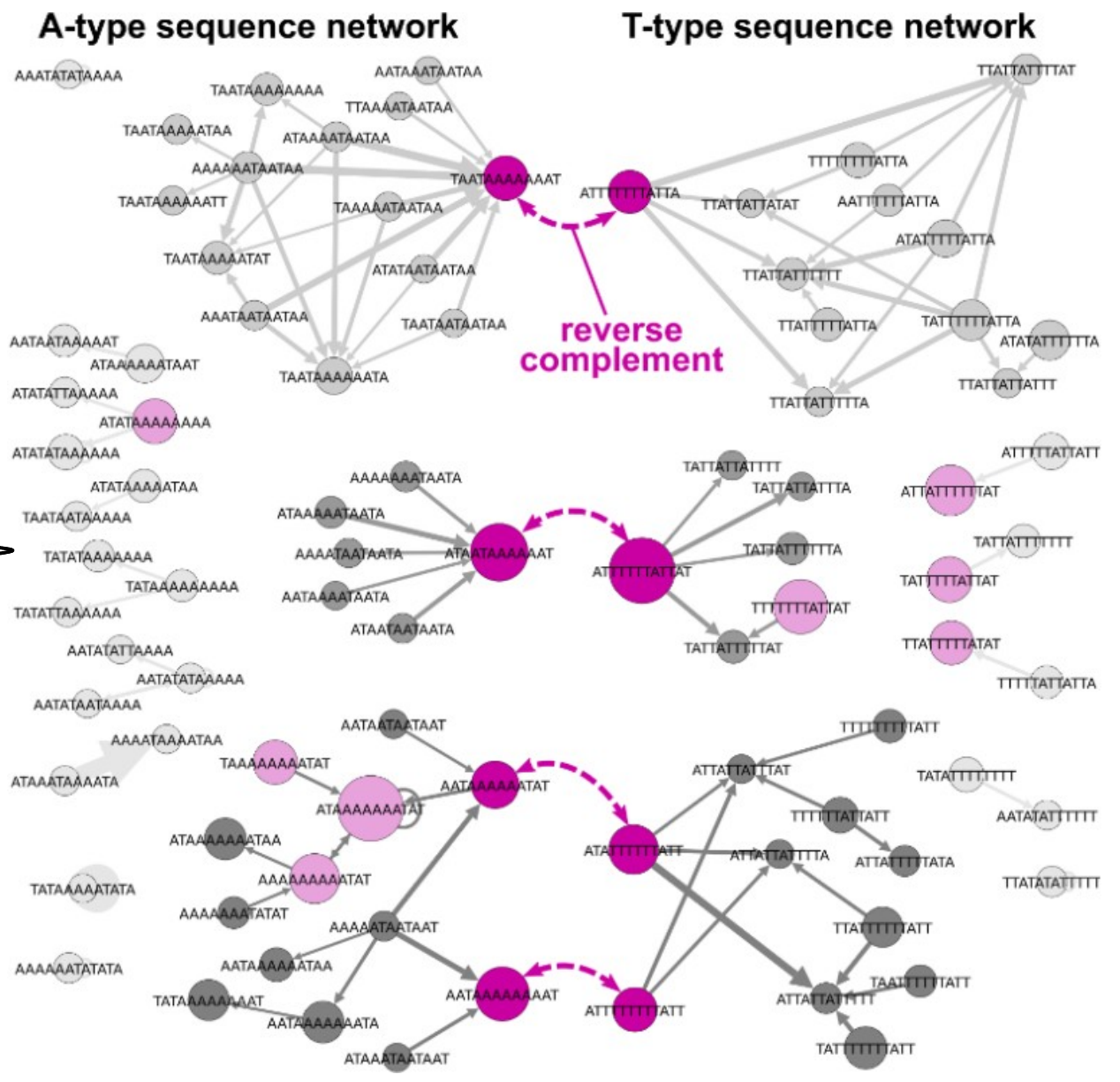
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ATAATTAAATAA  
TAAAAATTATTT  
TTAAATTTTATA  
TATTTAATTTTT  
TAAAAATTAATA  
AAAATAATTTAT  
TTATATAAAATA

**Network**

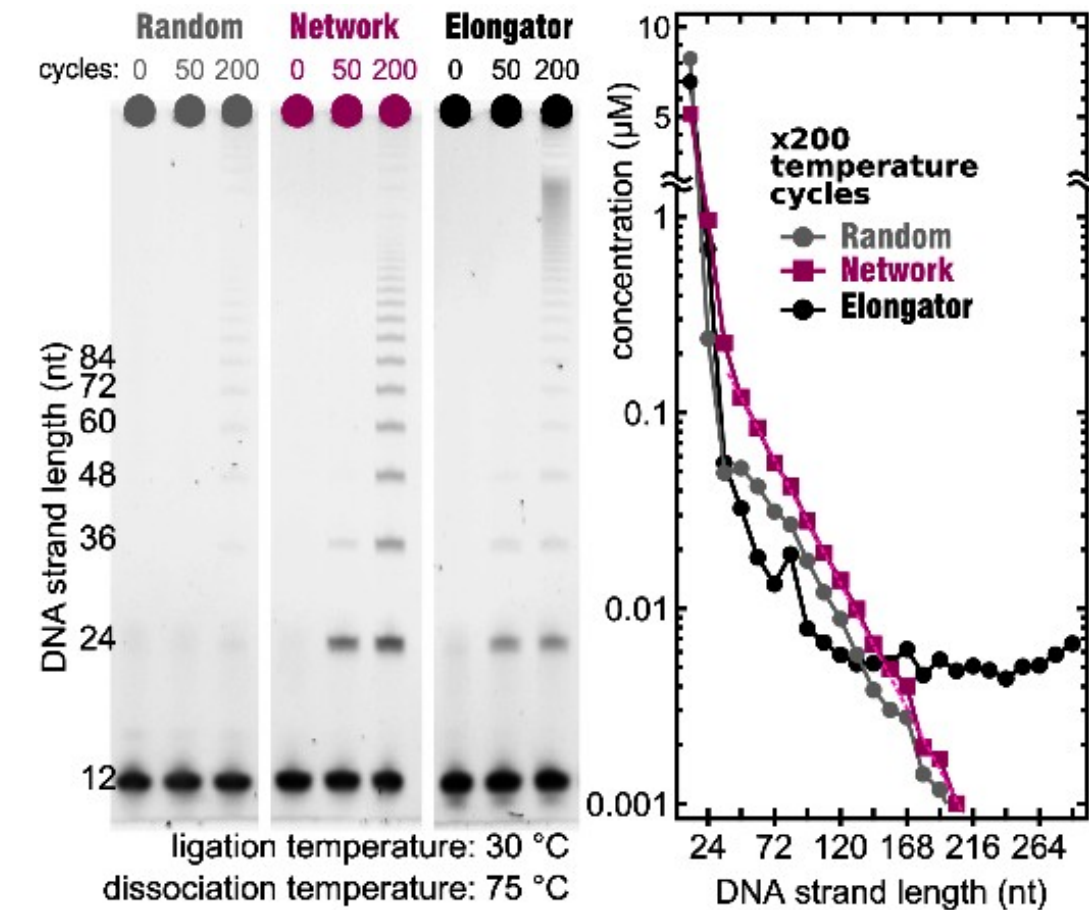
ATAATAAAAAAT  
AATAAAAAAAT  
AATAAAAAATAT  
TAATAAAAAAT  
ATTTTTTATTAT  
ATTTTTTTTATT  
ATTTTTTTTATT  
ATTTTTTTTATT  
ATTTTTTTTATT

**Elongator**

ATATTTTTTATA  
TATAAAAAATAT  
AAATATATAAAA  
TTTTATATATTT  
AAAATATATAAA  
TTTATATATTTT  
TATTTTTTTTTAT  
TATTTTTTTTTAT  
ATAAAAAAATA



# Dynamics in sequence space



**Random**

```

AAAATAAAATAT
ATAATTAAATAA
TAAAAATTATTT
TTAAATTTTATA
TATTTAATTTTT
TAAAAATTAATA
AAAATAATTTAT
TTATATAAAATA
    
```

**Network**

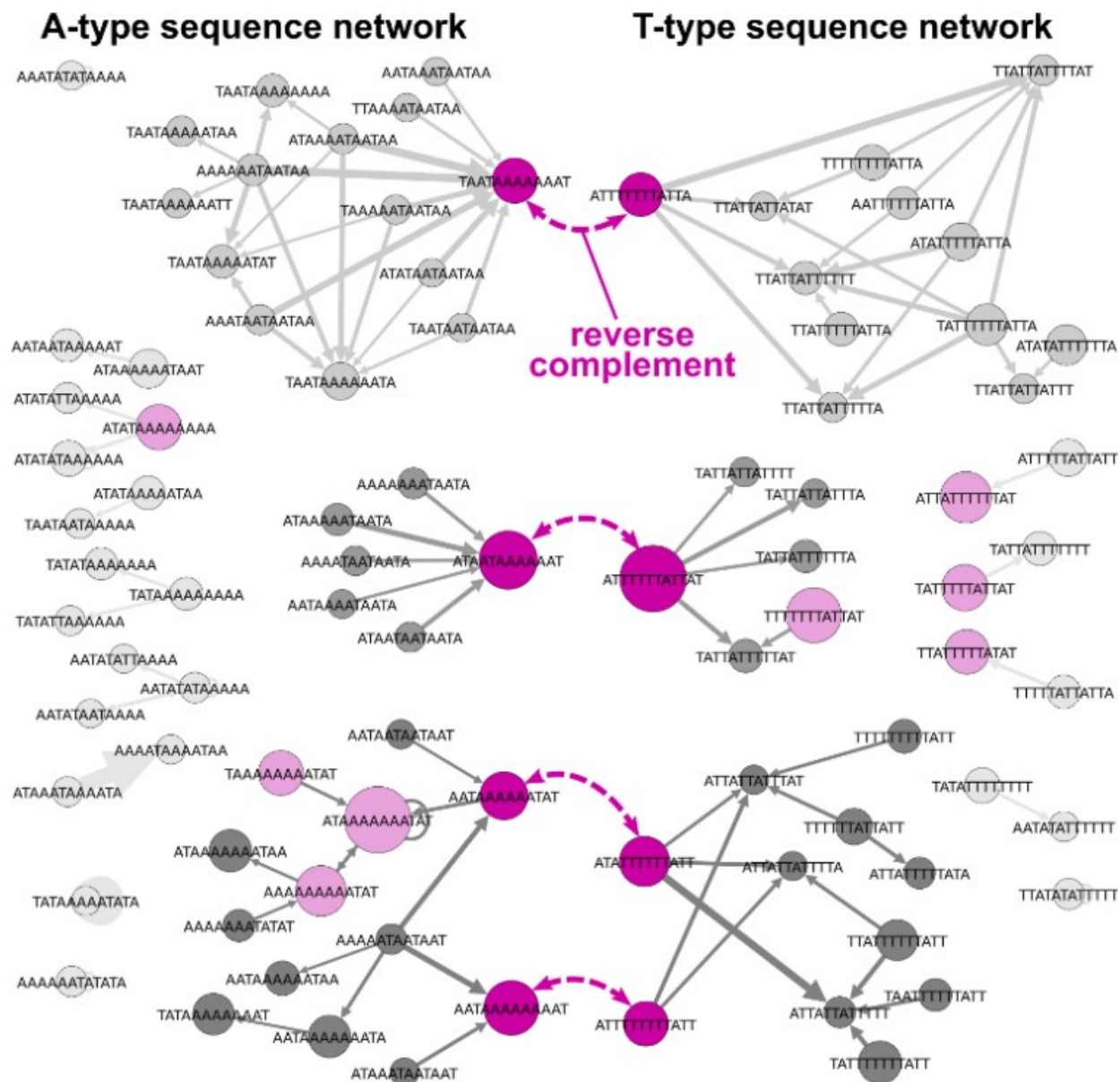
```

ATAATAAAAAAT
AATAAAAAAAAT
AATAAAAAATAT
TAATAAAAAAAT
ATTTTTTATTAT
ATTTTTTTTATT
ATTTTTTTTATT
ATTTTTTTTATTA
    
```

**Elongator**

```

ATATTTTTTATA
TATAAAAAATAT
AAATATATAAAA
TTTTATATATTT
AAAATATATAAA
TTTATATATTTT
TATTTTTTTTTAT
ATAAAAAAAATA
    
```





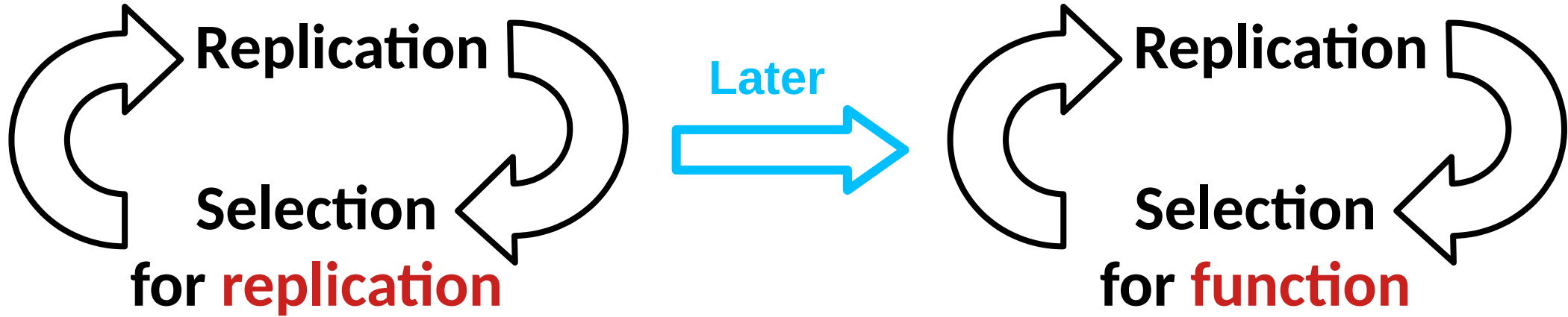


Later

A blue arrow pointing from the left diagram to the right diagram.



# Fast replication selects small sequence spaces





# Fast replication selects small sequence spaces

