Generative modeling of aptamers from Directed Evolution experiments

Stefano Crotti, Jorge Fernandez-de-Cossio-Diaz

Institut de Physique Théorique, CEA, CNRS, Université Paris-Saclay, France

Outline

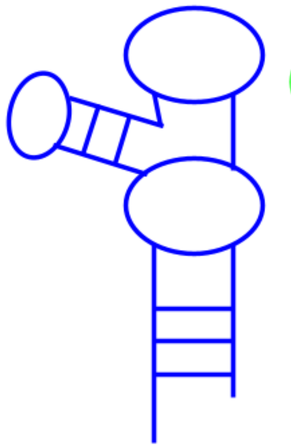
- Goal: **aptamer design**
- Experimental procedure: **Directed Evolution** (SELEX)
- Proposition: **complement** with **mathematical model**
- Results: lab validation
- **Challenges**: modeling, computation, noise

Introduction

Aptamers as ligands

Aptamer:

- Synthetic RNA/DNA strand (~100 bp)
- Used to bind a target (protein, virus, ...)



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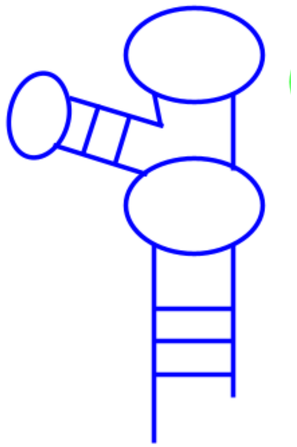

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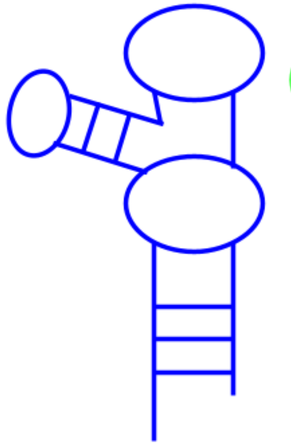

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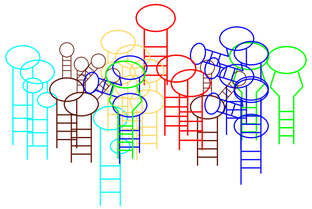
Applications:

- Therapeutics, diagnostics, separation of compounds, ...

Directed Evolution Experiments (SELEX)



STARTING LIBRARY

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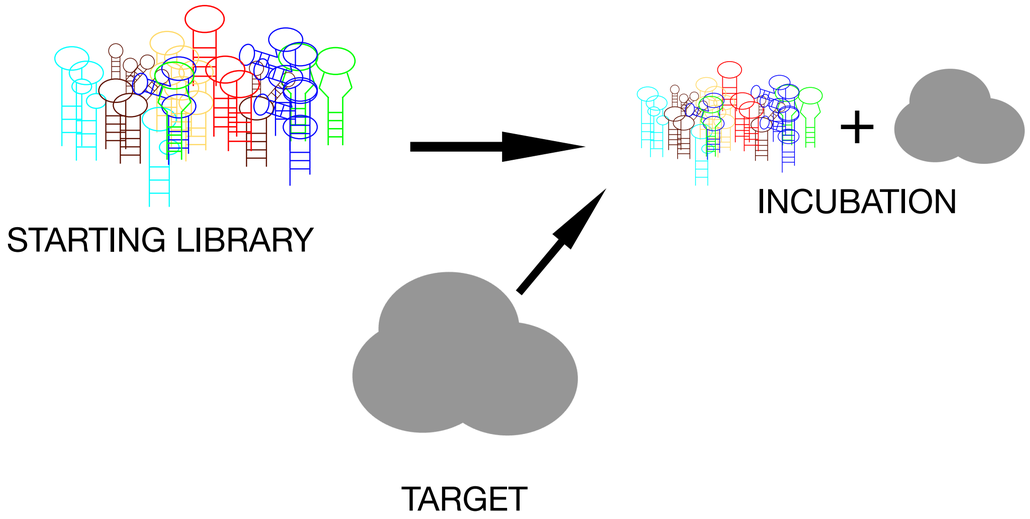

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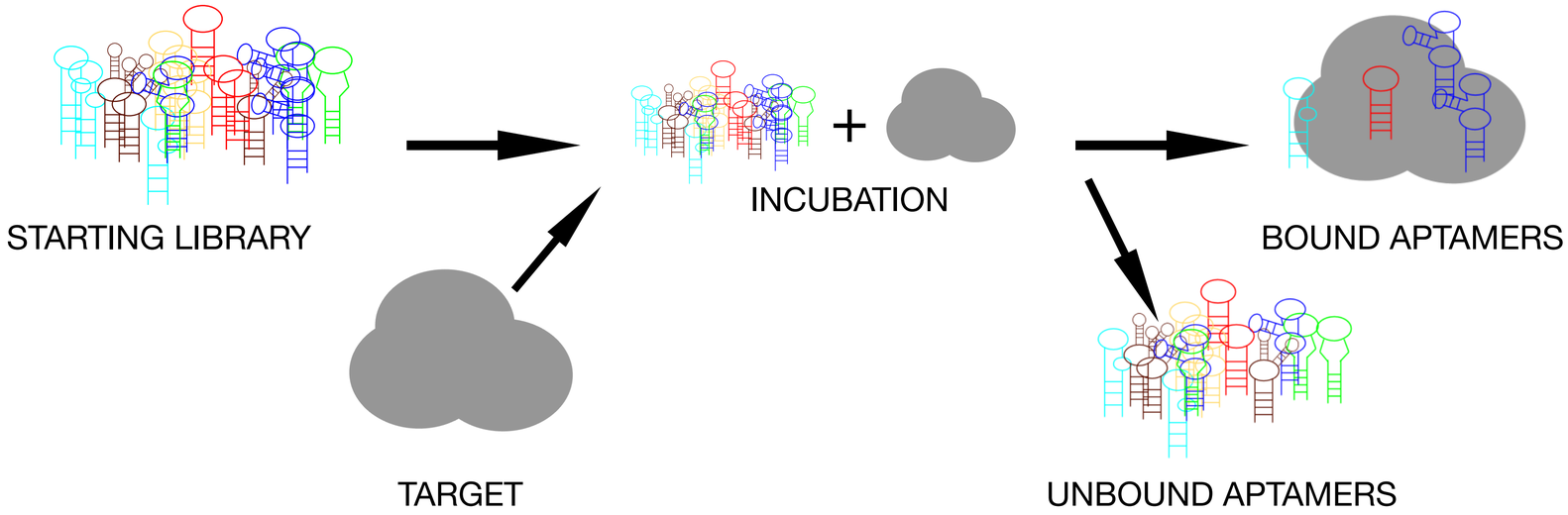

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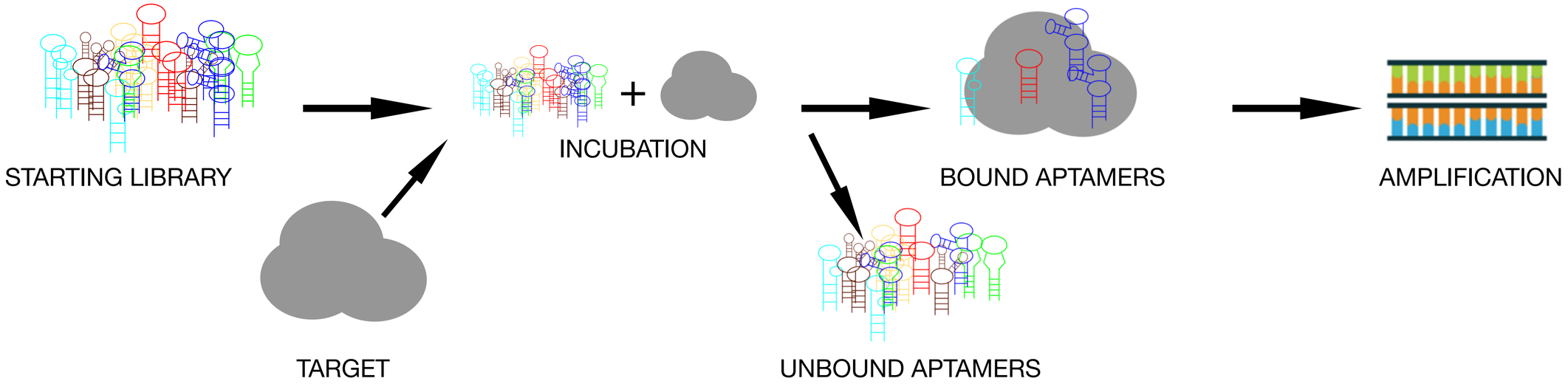

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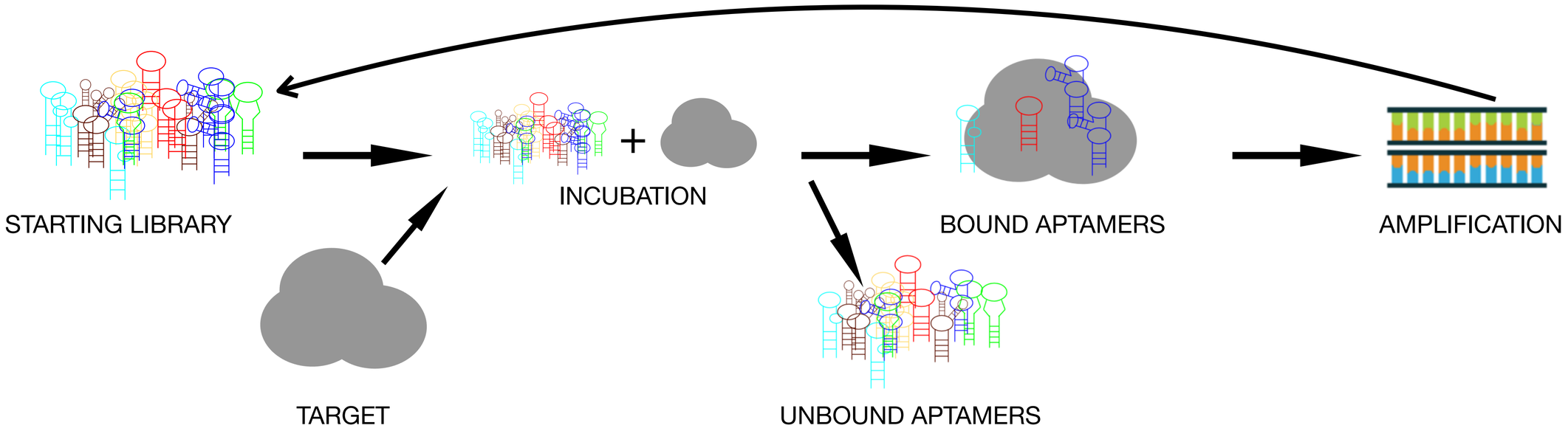

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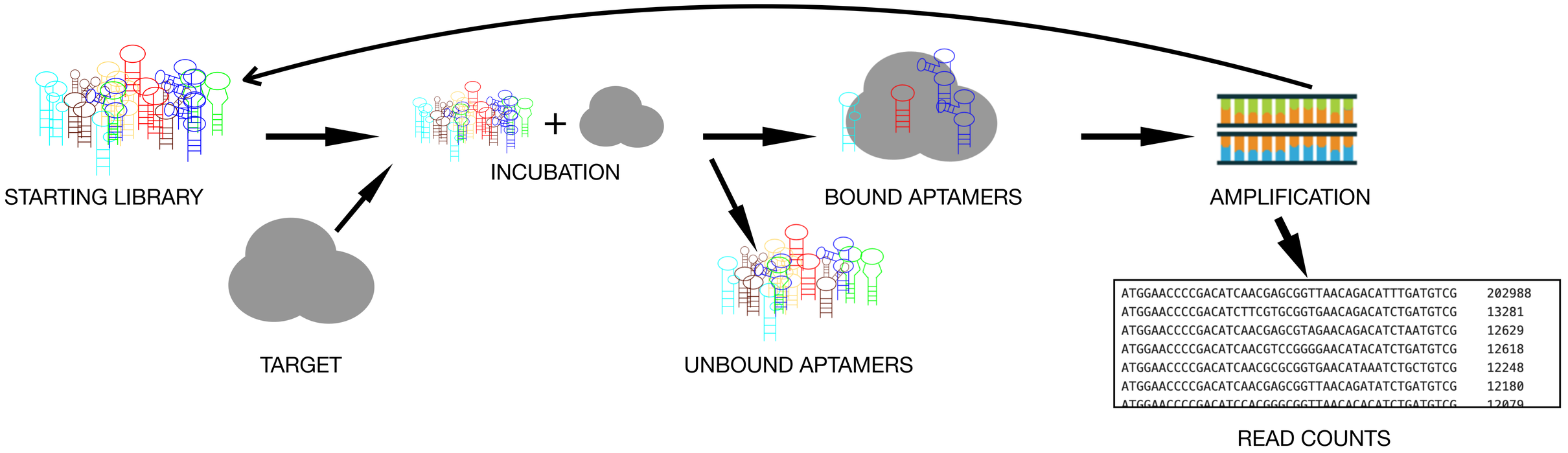

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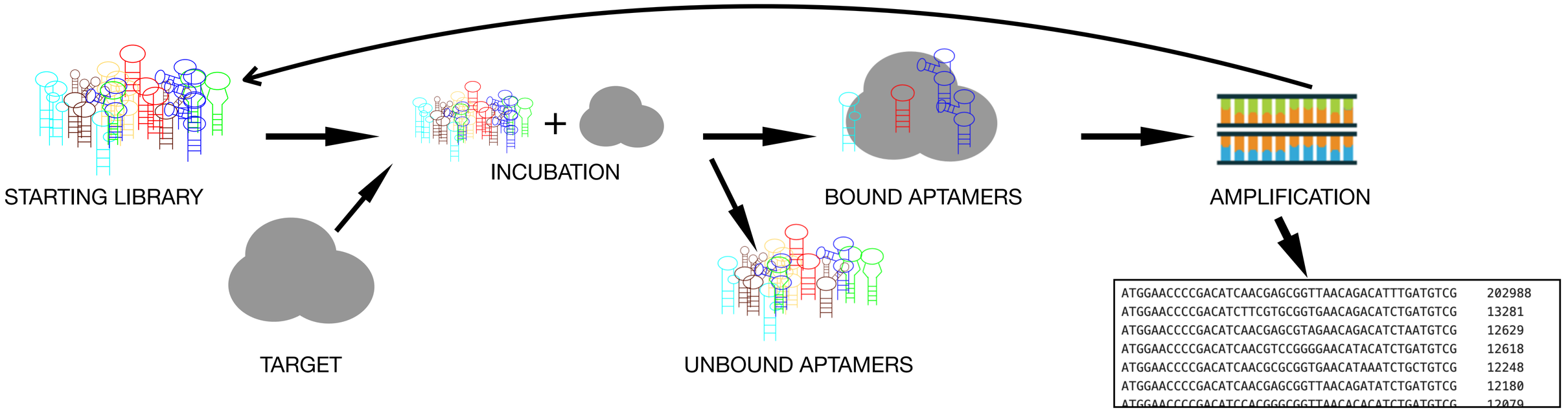
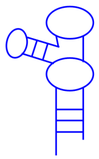


Limitations:

- Only explores a **subset** of the **combinatorially large** sequence **space**
- **No insight** about binding mechanism
- Hard for **multiple targets**

Mathematical model

Mathematical modeling

Work at the level of **sequences**:  $\leftrightarrow s \in \{A, C, G, U\}^L$

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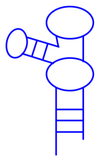
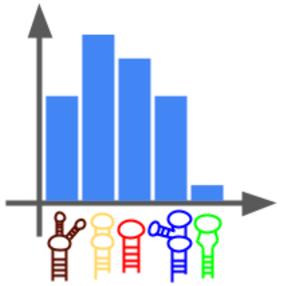
Work at the level of **sequences**:  $\leftrightarrow s \in \{A, C, G, U\}^L$

$N^{round\ t-1}$



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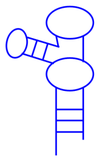
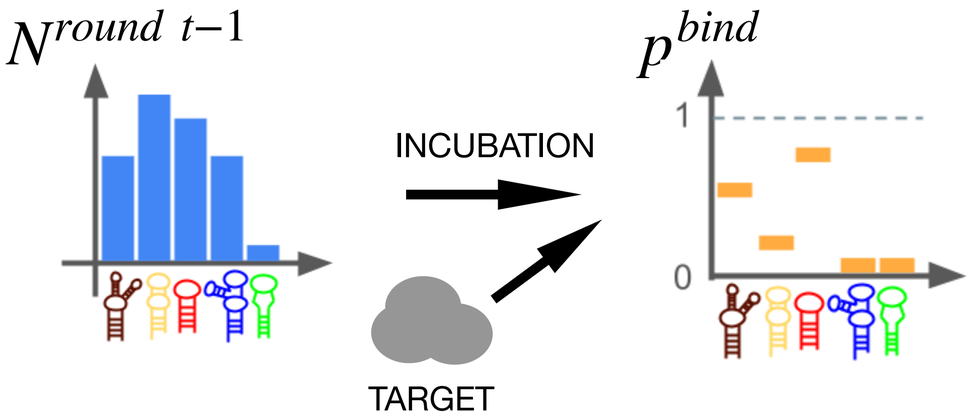
Work at the level of **sequences**:  $\leftrightarrow s \in \{A, C, G, U\}^L$



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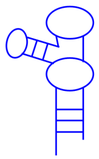
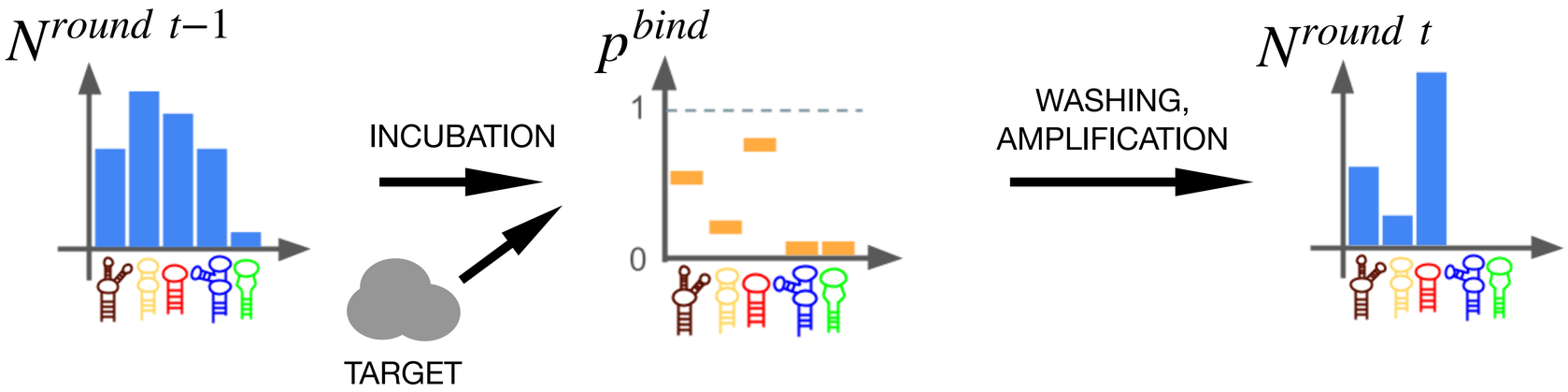
Work at the level of **sequences**:  $\leftrightarrow s \in \{A, C, G, U\}^L$



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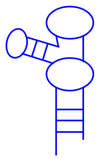
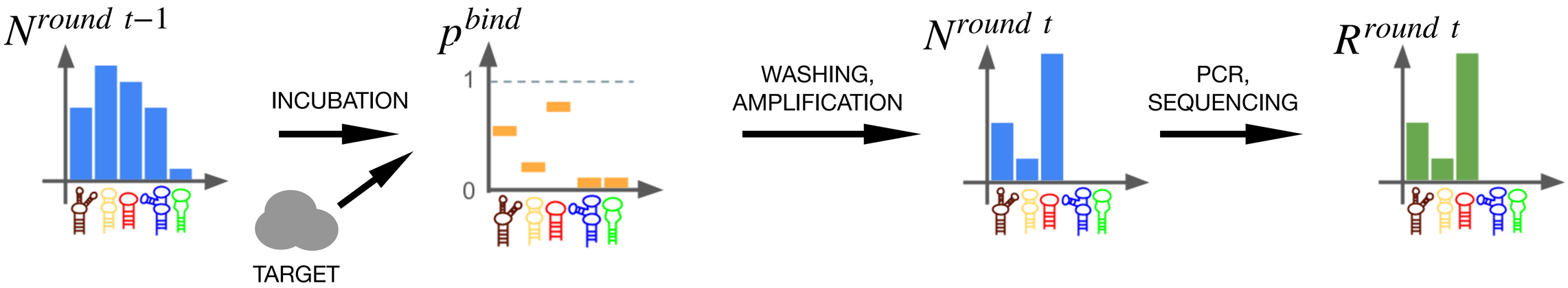
Work at the level of **sequences**:  $\leftrightarrow s \in \{A, C, G, U\}^L$



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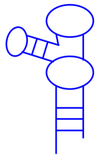
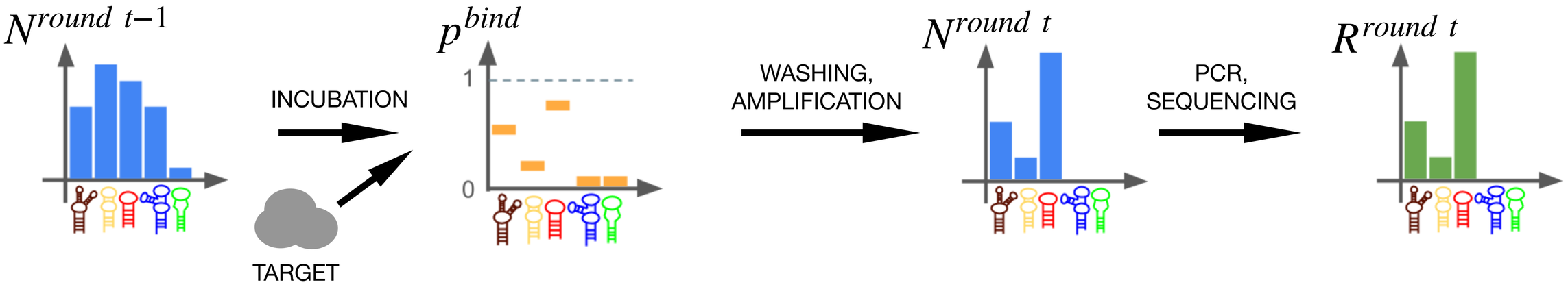
Work at the level of **sequences**:  $\leftrightarrow s \in \{A, C, G, U\}^L$



$$\mathbb{P}\left(N^{round\ t} \mid N^{round\ t-1}, p^{bind}\right) \qquad \mathbb{P}\left(R^{round\ t} \mid N^{round\ t}\right)$$

$$N^{round\ 0}(s) \qquad p^{bind}(s)$$

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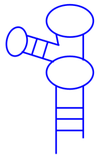
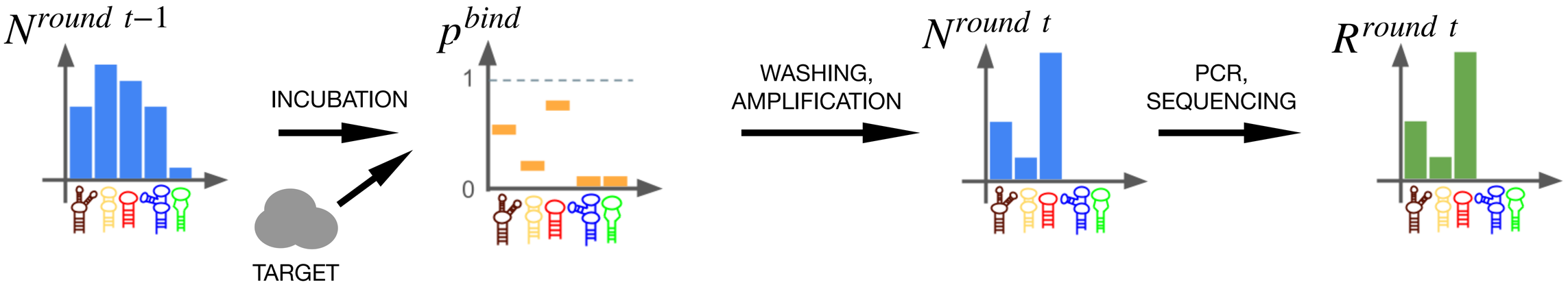
Work at the level of **sequences**:  $\leftrightarrow s \in \{A, C, G, U\}^L$



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Biology-informed

E.g. Poisson, Negative Binomial

$$N^{round\ 0}(s) \qquad p^{bind}(s)$$

Learned from data

E.g. Independent-sites, Pairwise interactions, Neural Network

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Generation of novel sequences

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Challenges

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Modeling choices

Parametrization of initial library and selection: accuracy vs robustness.

- **Selection** mechanism $\mathbb{P}\left(N^{round\ t} \mid N^{round\ t-1}, p^{bind}\right)$: concentration around mean?
- **Noise** on **read counts** $\mathbb{P}\left(R^{round\ t} \mid N^{round\ t}\right)$: PCR amplification, nucleotide -> amino-acid translation. Poisson vs Negative Binomial.
- **Noise** from various **sub-sampling** stages: between preparation and initial library, before sequencing.

Computation

- Unsupervised learning of an **energy-based model**: needs MCMC for intractable partition functions.

Misc

- Hard to evaluate model goodness, Multiple targets, localized datasets, spurious selection for plastic support

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Initial library

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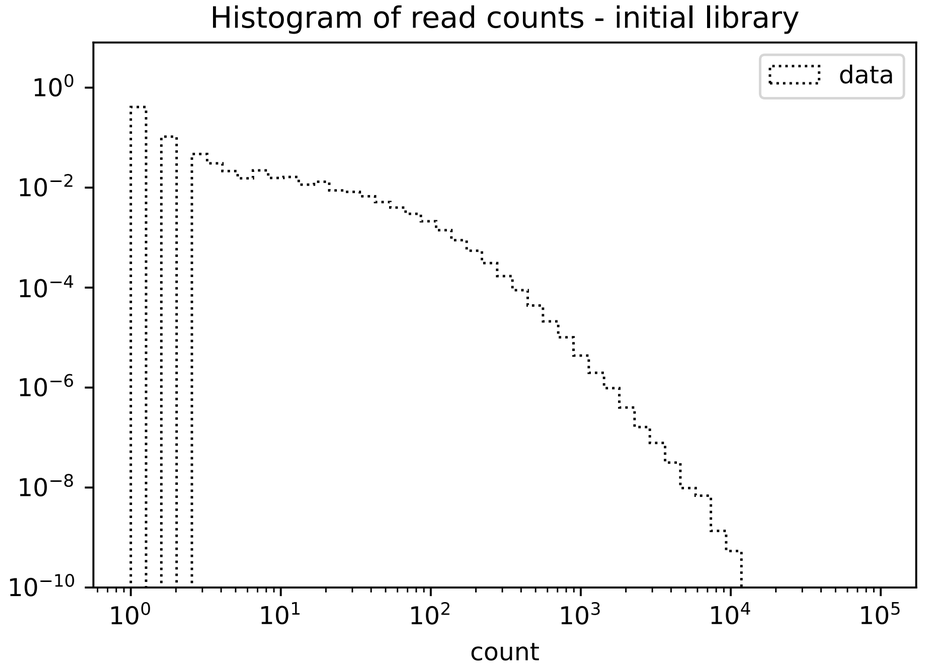
Parametrized

$$N_{indep}^{round\ 0}(s) = \prod_{i=1}^{L} f_i(s_i)$$

- Strong assumption
- 4L parameters
- If correct, more robust to noise

Initial library distribution

Checking model assumptions: fit and re-sample



Data from from phage display experiments, Fernandez-de-Cossio-Diaz et al. *PLoS Computational Biology* 20.10 (2024)

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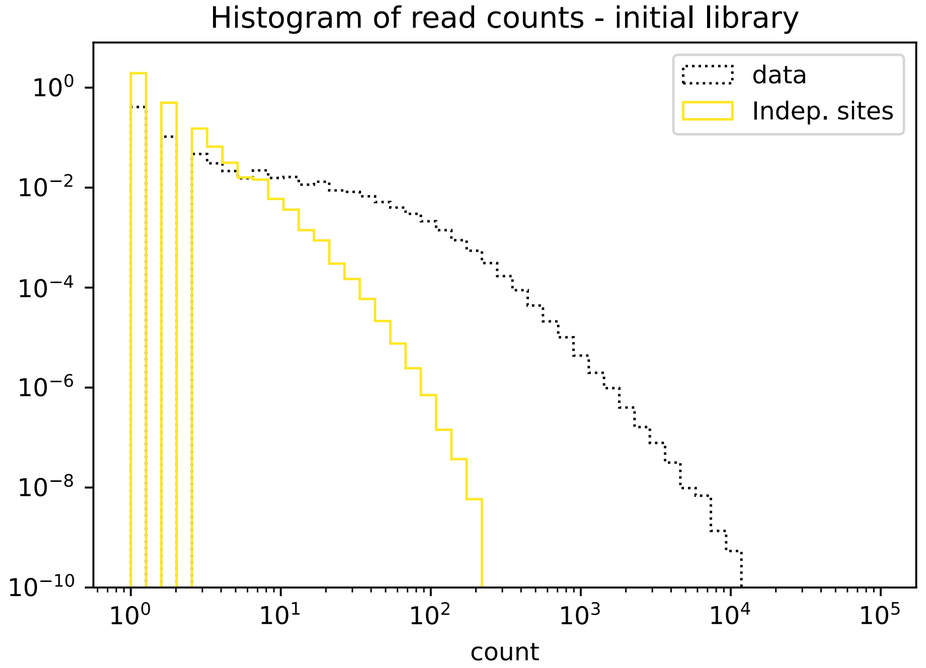

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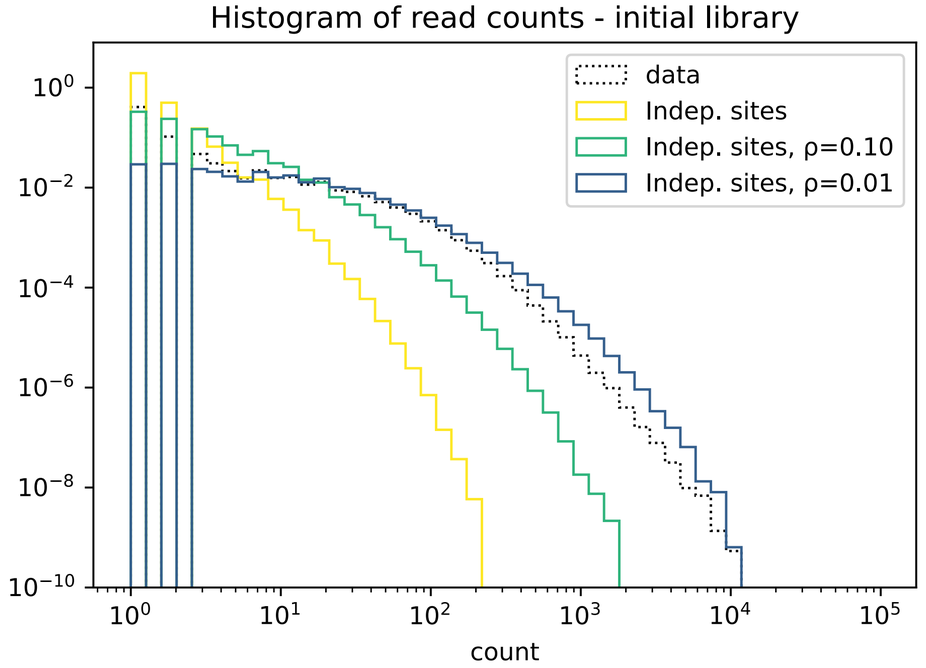
Truncated Independent-sites

$$N^{round\ 0}(s) \propto \begin{cases} N_{indep}^{round\ 0}(s) & \text{with prob } \rho \\ 0 & \text{with prob } 1-\rho \end{cases}$$



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- Mathematical model to **generate novel** ligands
- Good model needs **good assumptions**
- **Parametric** vs non-parametric, **initial library** distribution

Thank you!

stefano.crotti@ipht.fr

Collaborators

Jorge Fernandez-de-Cossio-Diaz

RNA aptamers for virus purification

Fréderic Ducongé

Lisa Le Dortz

Nicolas Destombes

Phage display for antibody design

Clément Nizak

Matilde Pattanaro

Olivier Rivoire

Guido Uguzzoni