Stochastic Model and Optimization of SELEX

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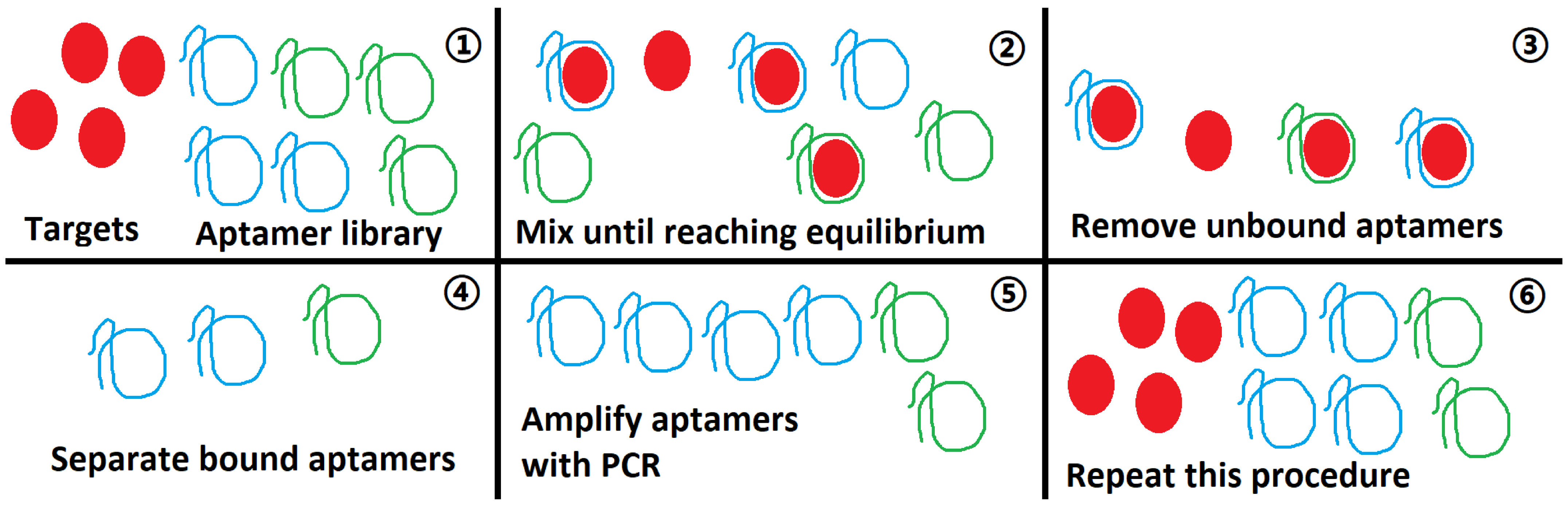
Introduction

- Aptamers are oligonucleotide or peptide molecules that bind to a specific target molecule.
- Some aptamers have high affinity to a pathogen. If there is an easy method to find such aptamers, they can be used as a cheap alternative of antibodies.
- In general, we start with a large library of randomly generated aptamers, and they have different affinities to the target.
- Systematic Evolution of Ligands by EXponential enrichment (SELEX): a convenient method to select the best aptamers with the highest affinities to the targets.
- Aptamers with higher affinities to the targets are more likely to bind to the targets. We can use the targets to pick out such aptamers.

Protocol of SELEX

- The detailed procedure of SELEX:



- We start with some target molecules and different types of aptamer molecules.
- Mix targets and aptamers until they reach equilibrium. Aptamers with higher affinities are more likely to bind to targets.
- Unbound aptamers are removed. Then we separate bound aptamers.
- Separated aptamers are amplified with PCR.
- One round of SELEX finishes. Aptamers with higher affinities are more concentrated.
- Start more rounds of SELEX to further concentrate aptamers with higher affinities.

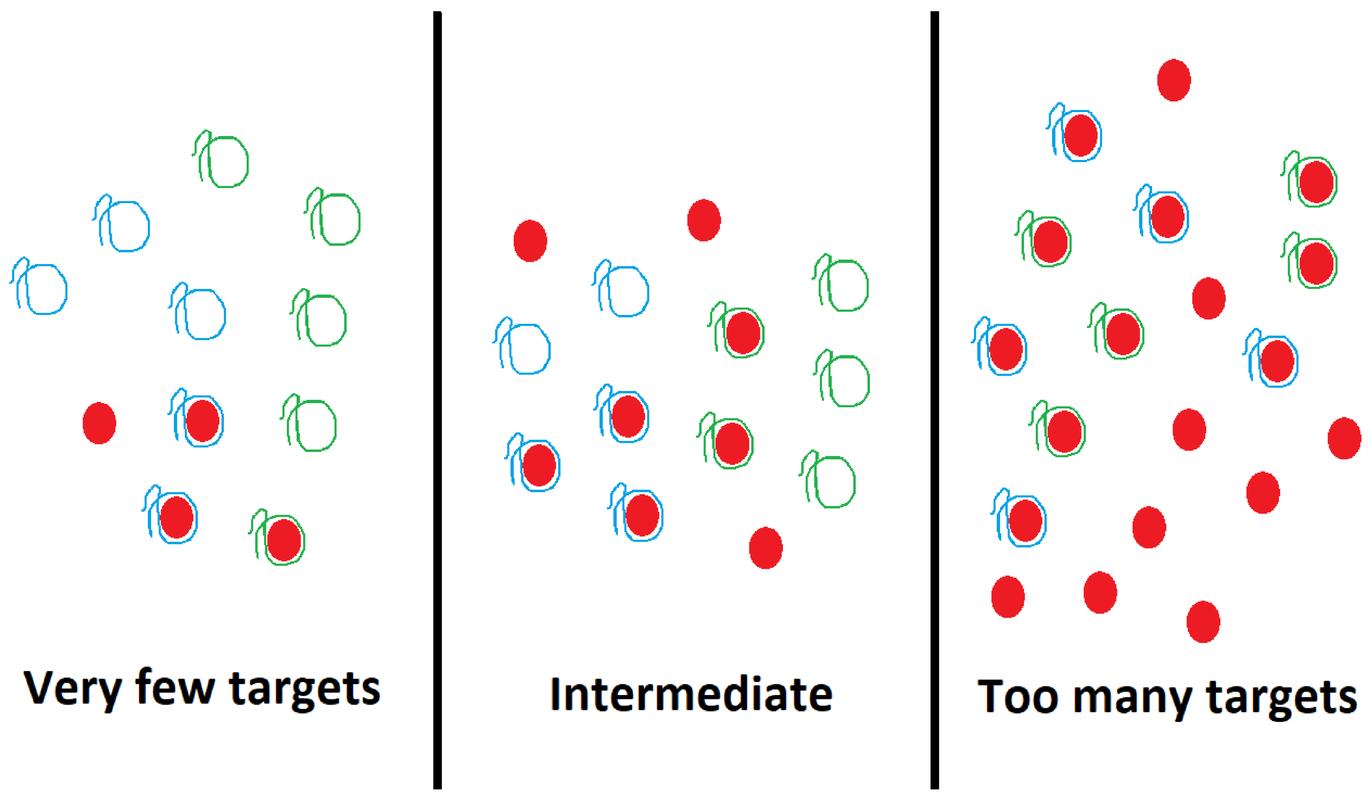
- When starting one round of SELEX, we can choose the quantity of targets and the quantity of aptamers, but the proportions of different aptamer types cannot be controlled.
- The goal is to maximize the proportion of the best aptamer (with the highest affinity) after this round of SELEX.

Deterministic model

- The traditional deterministic model of SELEX uses the law of mass action.
- At stationary, for each reaction $\mathrm{S} + \mathrm{A}_i \rightleftharpoons \mathrm{SA}_i$, we have:

$$[\bar{s}][\bar{a}_i]K_i^+ = [a_i]K_i^- .$$

- Notations: $[\bar{s}]$: concentration of unbound targets; $[\bar{a}_i]$: concentration of unbound type i aptamers; $[a_i]$: concentration of type i aptamers that are bound to targets. K_i^+, K_i^-: reaction constants.
- Define $K_i = K_i^+/K_i^-$, and assume $K_1 \geq K_2 \geq \cdots \geq K_N$, so that A_1 is the best aptamer with the highest affinity.
- In the deterministic model, the proportion of A_1, $[a_1]/\sum_{i=1}^{M}[a_i]$, increases with the initial aptamer concentration $[A_1]$ (while $[A_i]/[A_1] \equiv$ const), and decreases with the initial target concentration $[S]$.
- The optimal policy for any rounds of SELEX in the deterministic model: add as many aptamers as possible, and as few targets as possible.



- When the number of targets is too small, randomness cannot be ignored, and the law of mass action does not hold. We need a novel stochastic model.

Stochastic model

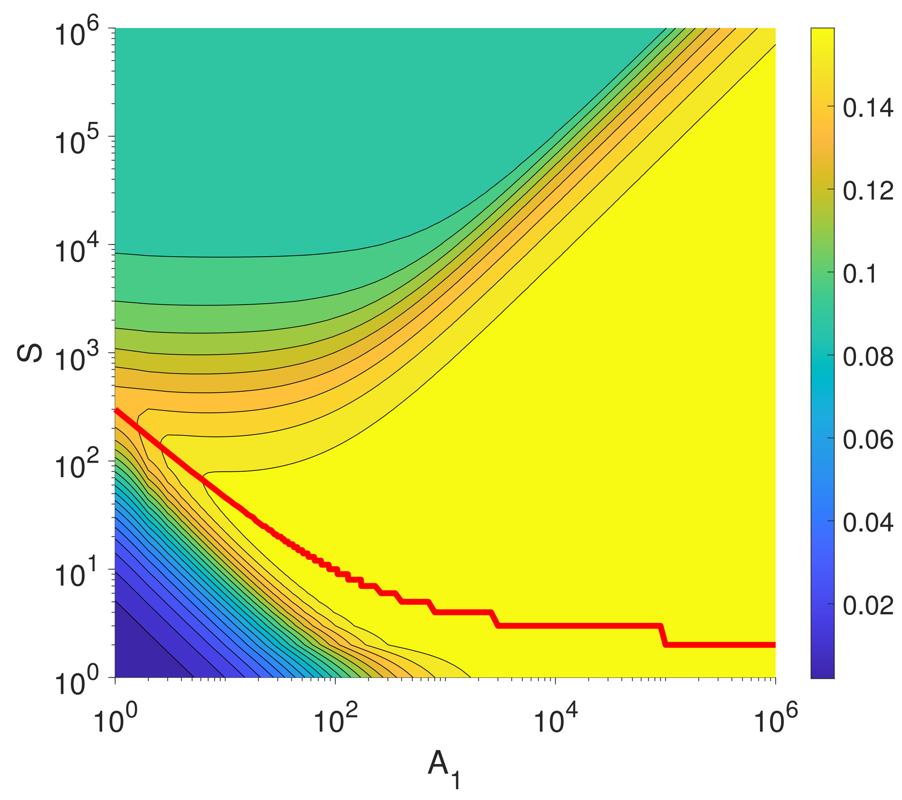
- We consider a continuous-time Markov process on M-dimensional lattice $\mathbb{Z}^M$, where the states are the bound aptamer counts $(a_1, \dots, a_i, \dots, a_M)$.
- The stationary probability distribution satisfies

$$\frac{\mathbb{P}(a_1, \dots, a_M)}{\mathbb{P}(0, \dots, 0)} = \binom{S}{S - \sum_{j=1}^{M} a_j, a_1, \dots, a_M} \times \left[\prod_{i=1}^{M} \binom{A_i}{a_i}\right] \times \left[\prod_{i=1}^{M} a_i!\right] \times \left[\prod_{i=1}^{M} \bar{K}_i^{a_i}\right]$$

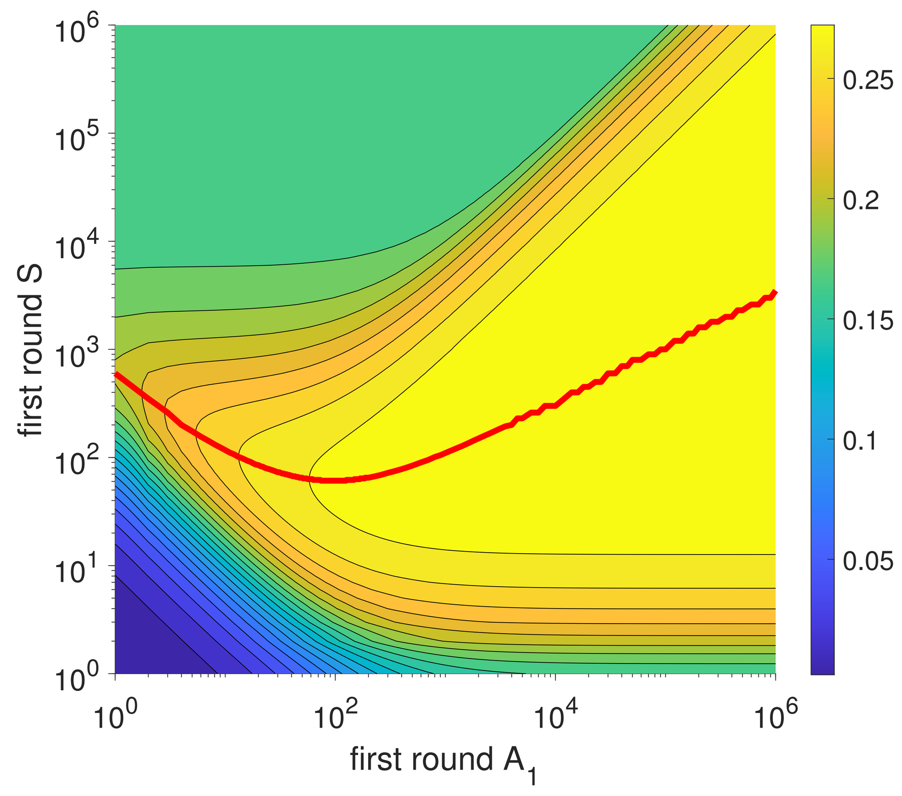
- We consider the expected proportion of A_1: $\mathbb{E}[a_1/(\sum_i a_i)]$. When $\sum_i a_i = 0$, we stipulate that $a_1/(\sum_i a_i) = 0$.

Optimal policy

- Contour plot of the A_1 proportion $\mathbb{E}[a_1/(\sum_i a_i)]$ after one round of SELEX. The red curve shows the optimal S for each A_1:



- For one round of SELEX, the optimal policy in the stochastic model is also setting very large A_1 (and A_i) and very small S.
- However, if we set $S = 1$, then after one round of SELEX, only one type of aptamer is left, and further rounds of SELEX cannot purify any more.
- Contour plot of the A_1 proportion $\mathbb{E}[a_1/(\sum_i a_i)]$ after two rounds of SELEX:



- For multiple rounds of SELEX, the optimal policy in the stochastic model is $A_i \gg S$ and $S \gg 1$.

Summary

Our stochastic model is more accurate, and the optimal policy for multiple rounds of SELEX is different from that of the deterministic model.