Stochastic Model and Optimization of SELEX

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Outline

- Introduce SELEX: a process to select aptamers.
- Review the traditional deterministic model of SELEX.
- Build a stochastic model for SELEX.
- Search for the optimal protocol of SELEX.

Introduction

- Aptamers are short, single-stranded DNA or RNA molecules that bind to a specific target.
- Targets can be various molecules or even whole cells.
- Certain aptamers (linked with fluorescent tracers) can bind selectively to biomarkers on cancer cells, but not to healthy cells. This test can identify cancer cells in a tissue sample.

Introduction

- Given a target, we want to obtain the best aptamer with the highest affinity (binding ability) to this target.
- It is difficult to design and synthesize the best aptamer directly.
- Systematic Evolution of Ligands by EXponential enrichment (SELEX): a convenient method to select the best aptamers from a huge aptamer library.
- The idea is to use targets to select out the best aptamers.
- For simplicity, consider two types of aptamers: type 1 (strong), type 2 (weak).

Aptamers and targets can bind and unbind reversibly.

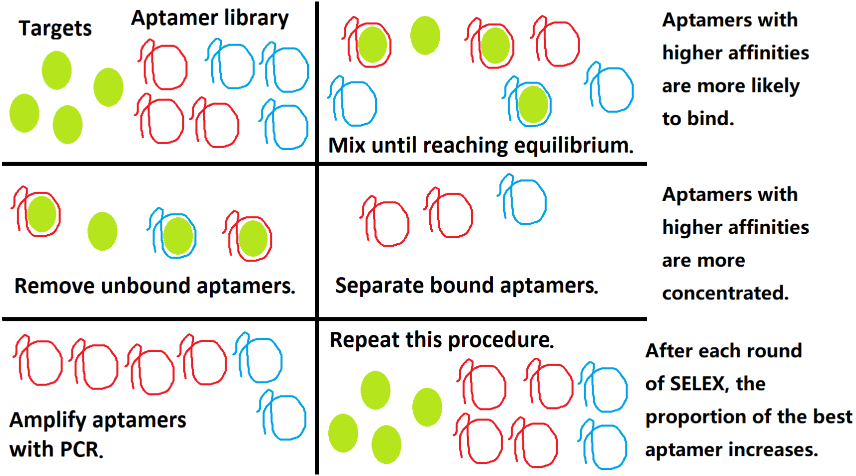
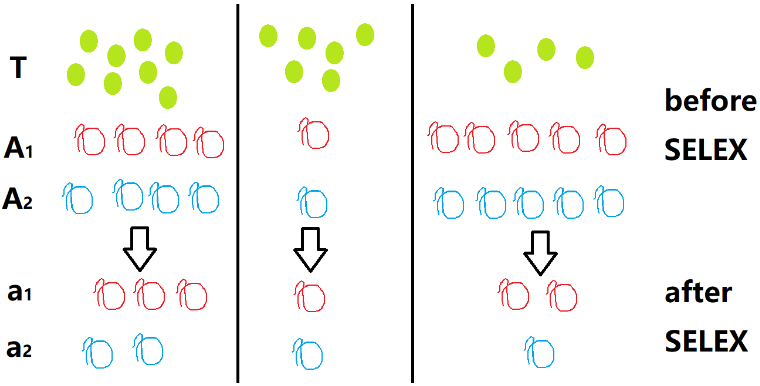


Figure: Protocol of SELEX



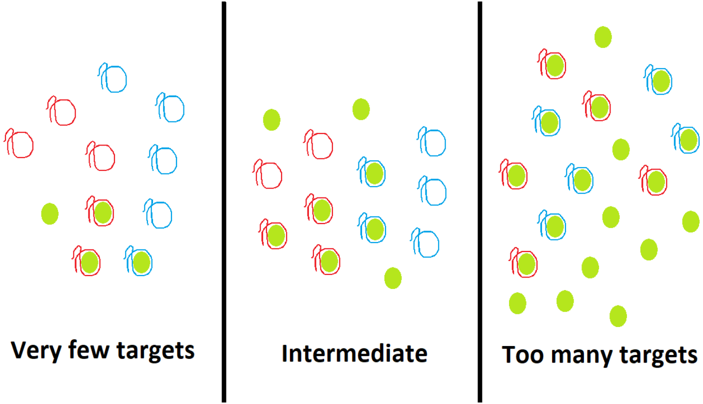
Before SELEX, we can control the target number T and the aptamer number $A_1 + A_2$, but not the ratio A_1/A_2. We obtain an optimization problem: maximize the best aptamer proportion $a_1/(a_1 + a_2)$ after SELEX.

Deterministic model

- A traditional deterministic approach (ODE model) uses the law of mass action, which is valid when the number of molecules is sufficiently large.
- In this deterministic model, $a_1/(a_1 + a_2)$ increases with $A_1 + A_2$, and decreases with T.
- The optimal policy in the deterministic model for any rounds of SELEX: add as many aptamers as possible, and as few targets as possible.

Deterministic model

Optimal policy: $A_1 + A_2 \gg T$.



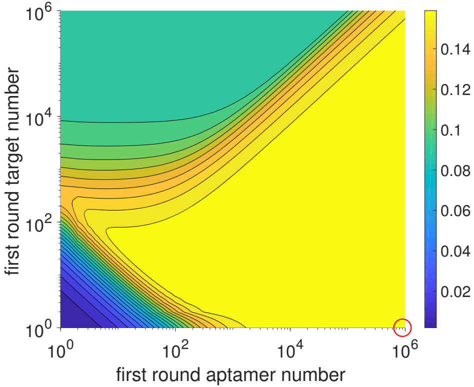
Deterministic model

- When T is too small, randomness is inevitable, and the law of mass action does not hold. Thus the deterministic model is invalid.
- We build a stochastic (Markov chain) model.
- The stationary probability distribution satisfies

$$\begin{aligned}\mathbb{P}(a_1, a_2) =&\mathbb{P}(0,0) \times \binom{T}{T - a_1 - a_2, a_1, a_2} \\ &\times \left[\binom{A_1}{a_1}\binom{A_2}{a_2}\right] \times [a_1!a_2!\,] \times \left[\bar{K}_1^{a_1}\bar{K}_2^{a_2}\right]\end{aligned}$$

  Here $\bar{K}_1, \bar{K}_2$ are the affinities.
- We want to optimize the expected type 1 aptamer proportion, $\mathbb{E}[a_1/(a_1 + a_2)]$.

Stochastic model

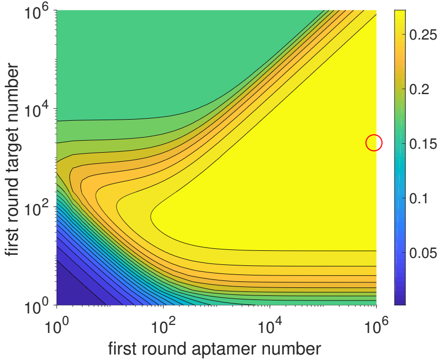


Contour plot of $\mathbb{E}[a_1/(a_1 + a_2)]$ for one round of SELEX. Unlike the deterministic model, in the stochastic model, $\mathbb{E}[a_1/(a_1 + a_2)]$ does not always increase with $A_1 + A_2$ ($A_1/A_2 = \text{const.}$), and does not always decrease with T. The circle is the optimal policy.

Stochastic model

- Optimal policy for one round of SELEX in the stochastic model: $T = 1$ and very large A_1, A_2.
- However, since there is only one target, after one round of SELEX, only one aptamer type is left (more likely type 1, less likely type 2).
- After further rounds of SELEX, the expected type 1 aptamer proportion does not increase.

- Contour plot of the type 1 aptamer proportion $\mathbb{E}[a_1/(a_1 + a_2)]$ after two rounds of SELEX:



- For the first round, a policy with large A_1 and very small T does not perform well. The circle is the optimal policy.

Stochastic model

Theorem

The optimal policy for multiple rounds of SELEX in the stochastic model is $A_1, A_2 \gg T$ and $T \gg 1$.

- In comparison, in the deterministic model, the optimal policy for any rounds of SELEX is $A_1, A_2 \gg T$, and T should be very small.
- Mathematics underpinning: When $A_1, A_2 \gg T$, if T is too small, $\mathbb{E}[a_1/(a_1 + a_2)]$ for the current round is not affected, but the variance of $a_1/(a_1 + a_2)$ is large. Due to Jensen's inequality, this large variance can lower $\mathbb{E}[a_1/(a_1 + a_2)]$ for later rounds.

Summary

- We introduce SELEX, a process to select the best aptamer for binding a target.
- For multiple rounds of SELEX, the optimal policies in the deterministic model and the stochastic model are different.
- Yue Wang, Bhaven A. Mistry, and Tom Chou. (2022). “Discrete stochastic models of SELEX: aptamer capture probabilities and protocol optimization.” Journal of Chemical Physics, 156(24), 244103.