Stochastic Model and Optimization of SELEX

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***Abstract*— Systematic Evolution of Ligands by EXponential enrichment (SELEX) is a process to select the best aptamer sequence in a huge aptamer library that binds a specified target molecule with the highest affinity. There has been a deterministic model of SELEX, and we develop a fully discrete stochastic model to obtain more accurate results when the mass action law does not hold. Specifically, we find that optimal SELEX protocol in the stochastic model differs from that predicted by the deterministic model.**

I. Purpose

A common need across several disciplines of biology is for precise targeting of biological structures and antigens (such as delivering drugs) [1], [2], [3]. A modern molecular targeting method is based on the use of aptamers, namely short DNA or RNA oligonucleotides, usually about 15-60 bases in length [4]. A rapid and cheap method ot obtain such aptamers is the systematic evolution of ligands by exponential enrichment (SELEX) [4], [5].

The goal of a SELEX protocol is to identify and isolate the aptamer sequence that binds a specified target molecule with the highest affinity. The process of SELEX begins with a solution containing target molecules and many different aptamer sequences with different affinities to the target (aptamer library). At equilibrium, unbound aptamers are removed, and the bound aptamers are isolated and amplified through polymerase chain reaction (PCR). After one cycle of target exposure and PCR, those aptamers that best bind the target should have a larger proportion. This SELEX cycle can be repeated several times to further distill the best binders. From cycle to cycle, one can use different numbers of the target and aptamers, but the relative abundances of different aptamer types cannot be tuned. A SELEX protocol or "policy" describes how to assign such molecule numbers in each cycle [6]. Different policies lead to different aptamer abundances.

Some quantitative work models the SELEX protocol with a deterministic dynamics, based on the mass action law [7], [8], [9], [10], [11]. In this deterministic model, the optimal protocol to capture the best binding aptamer sequence with less rounds of SELEX is setting the aptamer number to be large and the target number to be small.

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However, in the early cycles, when there might be a large number of different aptamers in the solution, the number of strongest binders may be small, and the mass action law used in the deterministic model might fail. When the best binder is rare, it might be lost after one cycle of SELEX. Even if the best binder is not lost, stochastic fluctuations in aptamer proportions might affect further cycles of SELEX.

Here, we build a purely stochastic model of SELEX by investigating the stochastic process of aptamer-target binding. We derive an expression for the discrete stationary probability distribution of bound aptamers. Then we determine the upper and lower bounds for the proportion of the best aptamer after one round of SELEX. Most importantly, we study the optimal policy that maximizes the expected proportion of the strongest binding aptamer after multiple rounds of SELEX. The optimal policy in our stochastic model is different from that of the deterministic model.

References

[1] K. Qian, S. L. Morris-Natschke, and K.-H. Lee, "HIV entry inhibitors and their potential in HIV therapy," *Med. Res. Rev.*, vol. 29, pp. 369–393, 2009.

[2] J. P. Moore and R. W. Doms, "The entry of entry inhibitors: A fusion of science and medicine," *P. Natl. Acad. Sci. U.S.A.*, vol. 100, pp. 10 598–10 602, 2003.

[3] S. Qiu, H. Yi, J. Hu, Z. Cao, Y. Wu, and W. Li, "The binding mode of fusion inhibitor T20 onto HIV-1 gp41 and relevant T20-resistant mechanisms explored by computational study," *Curr. HIV Res.*, pp. 182–194, 2012.

[4] S. Meyer, J. P. Maufort, J. Nie, R. Stewart, B. E. McIntosh, L. R. Conti, K. M. Ahmad, H. T. Soh, and J. A. Thomson, "Development of an efficient targeted cell-SELEX procedure for DNA aptamer reagents," *PLoS ONE*, vol. 8, pp. 1–11, 2013.

[5] N. Komarova and A. Kuznetsov, "Inside the black box: what makes selex better?" *Molecules*, vol. 24, no. 19, p. 3598, 2019.

[6] F. Spill, Z. B. Weinstein, A. I. Shemirani, N. Ho, D. Desai, and M. H. Zaman, "Controlling uncertainty in aptamer selection," *Proceedings of the National Academy of Sciences*, vol. 113, no. 43, pp. 12 076–12 081, 2016.

[7] H. A. Levine, Y.-J. Seo, and M. Nilsen-Hamilton, "A discrete dynamical system arising in molecular biology," *Discrete Contin. Dyn. Syst. - B*, vol. 17, pp. 2091–2151, 2012.

[8] J. Wang, J. F. Rudzinski, Q. Gong, H. T. Soh, and P. J. Atzberger, "Influence of target concentration and background binding on in vitro selection of affinity reagents," *PLoS ONE*, vol. 7, pp. 1–8, 2012.

[9] Y.-J. Seo, S. Chen, M. Nilsen-Hamilton, and H. A. Levine, "A mathematical analysis of multiple-target selex," *Bull. Math. Biol.*, vol. 72, no. 7, pp. 1623–1665, 2010.

[10] Y.-J. Seo, M. Nilsen-Hamilton, and H. A. Levine, "A computational study of alternate selex," *Bull. Math. Biol.*, vol. 76, no. 7, pp. 1455–1521, 2014.

[11] T. Aita, K. Nishigaki, and Y. Husimi, "Theoretical consideration of selective enrichment in in vitro selection: Optimal concentration of target molecules," *Math. Biosci.*, vol. 240, no. 2, pp. 201–211, 2012.