Branching Random Walks applied to Antibody Affinity Maturation

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Abstract

Antibody Affinity Maturation is a key process in adaptive immunity. During an **Immune Response**, activated B-cells give rise to Germinal Centers in follicles, special micro-environnements where they **proliferate, mutate and differentiate**. Moreover, they are submitted to powerful **selection** mechanisms to produce **high affinity** antibodies against the presented antigen. The purpose of the study is to build and analyse a mathematical model of the mutation-division-selection process of B-cells, aiming to understand how the different **biological parameters** affect the system's **functionality**. We are particularly interested in estimating via probabilistic methods **typical time-scales** to reach a specific configuration (or a set) of the traits of B-cells, as a function of the introduced mutational rule, as well as in **quantifying GCs' efficiency**.

Modeling assumptions and objectives

Hypotheses:

- **Two amino acid classes**: 0 or 1.
- B-cells and antigen's **traits**: N-length **binary strings**. $\mathcal{H}_N := \{0,1\}^N$ is the state-space.
- **Mutation:** define the **transition probability matrix** over $\mathcal{H}_N$.
- **Affinity:** $N-$ **Hamming distance** between B-cell and antigen.

Objectives:

- Evaluating the **typical time-scales of the exploration** of $\mathcal{H}_N$.
- Identify and study the **parameters which mostly influence** the system functionality.

1 Pure mutational models

Simple point mutations: Class switch of a randomly chosen amino acid. The resulting RW is a Simple Random Walk on the N-dimensional hypercube.
We denote by $\boldsymbol{\mathcal{P}}$ the corresponding transition probability matrix.

Multiple point mutations: i independent simple point mutations with probability $1/k$, for all $1 \leq i \leq k$, k being fixed between 1 and N.
We denote by $\mathcal{P}^{(k)}$ the corresponding transition probability matrix: $\boldsymbol{\mathcal{P}^{(k)}} = \frac{1}{k}\sum_{i=1}^{k} \mathcal{P}^i$

1.1 Comparaison of hitting times

Let $\overline{d}$ be **the initial Hamming distance** between B-cell and antigen. We determined **explicit formulas to estimate the hitting time** to cover this distance, as a function of the mutational rule.

Mutational model	Hitting time
Simple point mutations	$H(\overline{d}) = \sum_{d=0}^{\overline{d}-1} \frac{\sum_{j=1}^{N-1-d} C_N^{d+j} + 1}{C_{N-1}^{d}} \sim 2^N$ for N big enough
Multiple point mutations	$\overline{T}_N^{(k)}(\overline{d}) = \sum_{l=2}^{2^N} \mu_l^{(k)} - \frac{1}{2^N C_N^{\overline{d}}} \sum_{l=2}^{2^N} \mu_l^{(k)} R_N(l,\overline{d})$

Table 1: Estimation of hitting times

2 Mutation and division

At $t = 0$ **a randomly chosen node** is labelled as **active**. At each step t, each active node chooses two of its neighbors, independently and with replacement, to become active at time $t+1$. We are not interested here in counting how many times a node is chosen to become active. We obtain a **Branching Random Walk with coalescence** on $\mathcal{H}_N$.

2.1 Portion of $\mathcal{H}_N$ covered in $\mathcal{O}(N)$

Let S_t be the active node set at time t. We estimate the size of S_T, $|S_T|$, for $T = \mathcal{O}(N)$, and depending on the allowed mutational rule.

Model	$\lvert S_T\rvert$ in $\mathbf{T} = \mathcal{O}(\mathbf{N})$
BRW-$\mathcal{P}$	$\lvert S_T\rvert \geq 2^{N-r}$, $r > \frac{N^2e^{-2} + N - 2}{Ne^{-2} + N - 2}$
BRW-$\mathcal{P}^{(k)}$	$\lvert S_T\rvert \geq \delta 2^N$, $\delta \leq 1/2$

Table 2: Portion of $\mathcal{H}_N$ covered in $T = \mathcal{O}(N)$

3 Mutation, division and selection with multiplicity

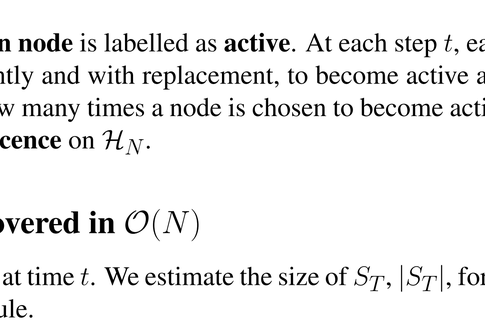

Figure 1: Schematic representation of the process. r_d = death rate; r_{div} = division rate; r_s = selection rate.

3.1 Extinction probability in the GC

We denote by η_{z_0} **the extinction probability** of the GC population, starting from z_0 naive B-cells.

Theorem:

- *if* $r_s \geq 1 - \frac{1}{(1-r_d)(1+r_{div})}$, *then* $\eta_{z_0} = 1$
- *otherwise* $\eta_{z_0} = \eta^{z_0} < 1$ *where* $\eta < 1$ *is the smaller fixed point of* $F(s) := p_0 + p_1 s + p_2 s^2$, *with:*
  - $p_0 := r_d + r_s(1-r_d)(1-r_{div}+r_{div}r_s)$
  - $p_1 := (1-r_d)(1-r_s)(1-r_{div}+2r_{div}r_s)$
  - $p_2 := r_{div}(1-r_d)(1-r_s)^2$

3.2 r_s maximizing the expectation of selected B-cells at time t

Numerical simulations evidence the existence of an optimal r_s which maximizes the expected number of selected B-cells at a given time t.

Theorem:
For any time $t \in \mathbb{N}^*$, *the optimal value of* r_s *wrt the expectation of selected B-cells is:* $r_s(t) = 1/t$.

4 Numerical Simulations

Hitting times to cover a fixed Hamming distance, referring to $\mathcal{P}^{(k)}$ (Section 1)

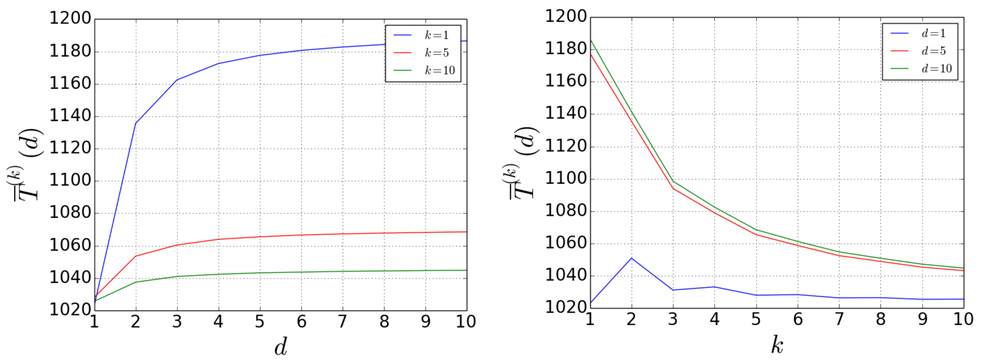

Figure 2: Dependence of $\overline{T}_N^{(k)}(d)$ on d (**left**) and k (**right**).

Evolution of the active set size for the BRW-$\mathcal{P}$ and BRW-$\mathcal{P}^{(k)}$ (Section 2)

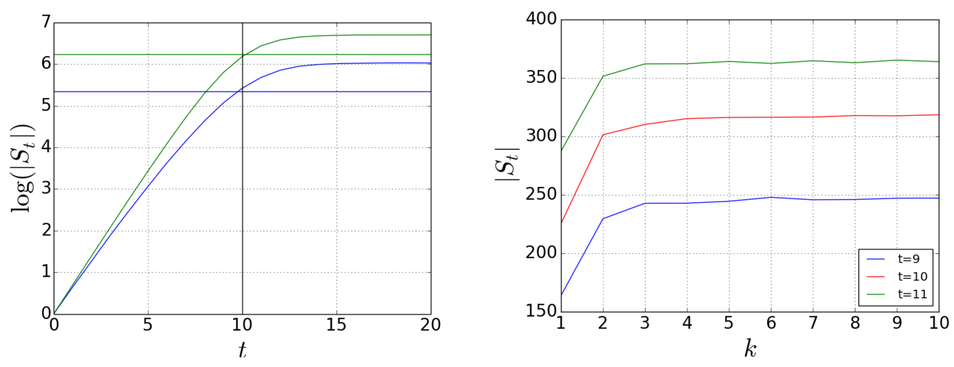

Figure 3: **Left:** Evolution of the active set size comparing the BRW-$\mathcal{P}$ (blue) and the BRW-$\mathcal{P}^{(7)}$ (green) for $N = 10$. **Right:** Average size of $|S_t|$ after $t = N-1, N, N+1$ time steps, comparing the 2-BRW-$\mathcal{P}^{(k)}$ with $k \in \{1, \ldots, N\}$.

Evolution of the selected pool and optimal r_s (Section 3)

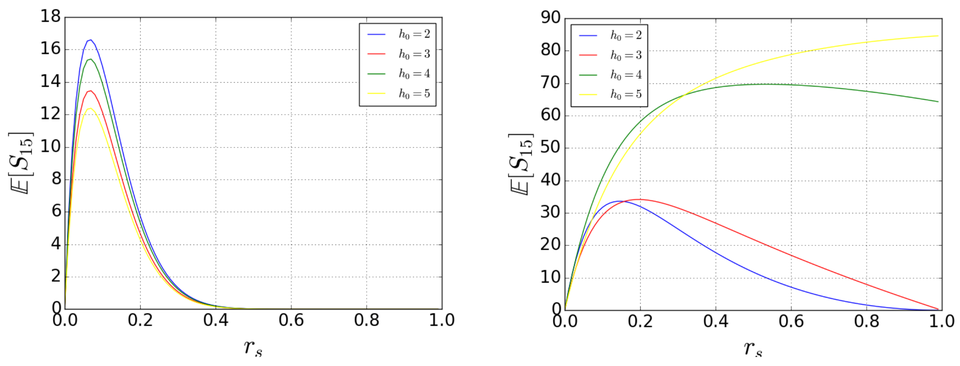

Figure 4: Dependence on r_s of the expected number of selected B-cells after 15 time steps for $N = 10$. **Left:** Model with positive-negative selection. **Right:** Model with only positive selection.

References

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