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Branching random walks applied to modeling of germinal center reaction

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Abstract

We consider a mathematical model of the functioning of a germinal center of the lymphatic system. This model is constructed in terms of branching random walks with particles of several types on a discrete lattice. The types of particles correspond to the types of B-lymphocytes: centroblasts, centrocytes, plasma cells and memory cells. Lattice coordinates correspond to nucleotide representations of B-cell receptors. Equations of mathematical expectations of local numbers of particles are given and their solutions are obtained.
Keywords: multitype branching process; random walk; adaptive immune system; germinal center reaction.

1. Introduction

We consider a mathematical model of the functioning of a germinal center of the lymphatic system. Germinal centers (GCs) are transiently formed structures within B cell zone (follicles) in secondary lymphoid organs, where mature B cells proliferate, differentiate, and mutate their antibody genes (through somatic hypermutation aimed at achieving higher affinity) during a normal immune response. These develop dynamically after the activation of follicular B cells by T-dependent antigen.

Many publications are devoted to the problem of modeling germinal center reaction. In [3] authors construct a mathematical model of the maturation of the affinity of B-cell antibodies in germinal centers during the immune response, thereby investigating the interaction between division, mutation and selection in a simplified evolutionary model. The model is built on a branching discrete process (generations of descendants) with a finite number of particle types that characterize different classes of antibody affinity. In [4] authors presented a model built on a branching random walk (the state graph is a vector of finite length from 0 and 1) with discrete time (generations of descendants). In [2] authors present a model of B-cell mutation-selection-proliferation in the germinal center, which is based on a nonlinear inhomogeneous second-order partial differential equation, and an analysis is given in the case of piecewise constant coefficients in various asymptotic regimes. In [5] a mathematical model of the dynamics of the germinal center is developed. The authors provide a numerical study of populations that consist of B-cells that originate from one strain-specific clone, one broadly reactive clone, or both. In [6] authors propose a model (a branching process with several types of particles, a numerical solution of a system of differential equations), which simulates the process of maturation of the affinity of antibodies in the germinal center with tracking of individual subclones. The model reflects the general dynamics of the germinal center, the degree of increase in the number of subclones is qualitatively comparable with the data of B cells isolated from human lymph nodes.

2. Methodology

We consider the population dynamics of B-lymphocytes, which proliferate, differentiate and undergo somatic hypermutagenesis processes in the germinal center. We describe the configuration (BCR) of a lymphocyte using a nucleotide (A, C, G, T) sequence of length L. The space of possible states is denoted by Ω ($|\Omega| = 4^L$). In [1] it was shown that during the transition of the cell type from centrocyte to centroblast, the subsequent intensity of centroblast proliferation depends on the strength of the signal received from the T-cell, which depends on the BCR configuration. We model this by dividing the centroblasts into 2 subgroups: $R = \{r_1, r_2\}$. We assume a finite number of K cell generations: in the k-th generation, transitions are possible within the k generation or to the next generation $k + 1$:

1. centroblast (generation k) $\to$ 2 centroblasts (generation k) with intensity $\beta_{2cb_r}^{(k)} := \beta_{2cb_r}$, $r \in R$, $k = 1, \ldots, K$;

2. centroblast $(k) \to$ centrocyte (k) with intensity $\beta_{cc_r}^{(k)}$, $r \in R$;
3. centrocyte (k, from x) $\to$ plasma cell (k) with intensity $\beta_{pc}^{(k)}(x)$;
4. centrocyte (k, from x) $\to$ memory cell (k) with intensity $\beta_{mc}^{(k)}(x)$;
5. centrocyte (k, from x) $\to$ centroblasts $(k+1)$ with intensity $\beta_{cb_r}^{(k)}(x)$, $r \in R$;
6. centroblast (k) dies with intensity $\mu_{cb_r}^{(k)}$, $r \in R$;
7. centrocyte (k, from x) dies with intensity $\mu_{cc}^{(k)}(x)$;
8. plasma cell (k) dies with intensity $\mu_{pc}^{(k)}$;
9. memory cell (k) dies with intensity $\mu_{mc}^{(k)}$.

We denote $S := \{cb_{r_1}, cb_{r_2}, cc, pc, mc\}$ and the corresponding set of pairs $S_k := \{(cb_{r_1}, k), (cb_{r_2}, k), (cc, k), (pc, k), (mc, k)\}$, $k = 1, \dots, K$. We denote the number of descendants of the j-th type of generation k_j at y at the moment of time t, originating from one particle of the i-th type of generation k_i, located at the point x at the initial moment of time, through $n_{i \to j}(t, x, y)$, where $i, j \in \cup_{k=1}^{K} S_k$. We denote $z := (z_{cb_1}, z_{cb_2}, z_{cb_3}, z_{cc}, z_{pc}, z_{mc})$ and introduce generating functions: for $k = 1, \dots, K$

$$F_s^{(k)}(t, x, y, z) = \mathsf{E} \prod_{s' \in S} z_{s'}^{n_{(s,k) \to (s',k')}(t,x,y)}, \ s \in S, \ k \in K, \ k' = k, k+1.$$

We introduce a system of differential equations characterizing the population dynamics of the process

$$\begin{aligned}
\frac{\partial F_{cb_r}^{(k)}(t,x,y,z)}{\partial t} &= \mu_{cb_r}^{(k)} - (\mu_{cb_r}^{(k)} + \beta_{2cb_r} + \beta_{cc_r}^{(k)}) F_{cb_r}^{(k)}(t,x,y,z) \\
&\quad + \beta_{2cb_r} \Big(\sum_{x' \in \Omega} a(x,x') F_{cb_r}^{(k)}(t,x',y,z) \Big)^2 + \beta_{cc_r}^{(k)} F_{cc}^{(k)}(t,x,y,z), \ r \in R; \\
\frac{\partial F_{cc}^{(k)}(t,x,y,z)}{\partial t} &= \mu_{cc}^{(k)}(x) - \Big(\mu_{cc}^{(k)}(x) + \sum_{r \in R} \beta_{cb_r}^{(k)}(x) + \beta_{pc}^{(k)}(x) + \beta_{mc}^{(k)}(x) \Big) F_{cc}^{(k)}(t,x,y) \\
&\quad + \sum_{r \in R} \beta_{cb_r}^{(k)}(x) F_{cb_r}^{(k+1)}(t,x,y) + \beta_{pc}^{(k)}(x) F_{pc}^{(k)}(t,x,y) \\
&\quad + \beta_{mc}^{(k)}(x) F_{mc}^{(k)}(t,x,y) \text{ for } k < K; \\
\frac{\partial F_{cc}^{(K)}(t,x,y,z)}{\partial t} &= \mu_{cc}^{(K)}(x) - \Big(\mu_{cc}^{(K)}(x) + \beta_{pc}^{(K)}(x) + \beta_{mc}^{(K)}(x) \Big) F_{cc}^{(K)}(t,x,y,z) \\
&\quad + \beta_{pc}^{(K)}(x) F_{pc}^{(K)}(t,x,y,z) + \beta_{mc}^{(K)}(x) F_{mc}^{(K)}(t,x,y,z) \text{ for } k = K; \\
\frac{\partial F_{pc}^{(k)}(t,x,y,z)}{\partial t} &= \mu_{pc}^{(k)} - \mu_{pc}^{(k)} F_{pc}^{(k)}(t,x,y,z); \\
\frac{\partial F_{mc}^{(k)}(t,x,y,z)}{\partial t} &= \mu_{mc}^{(k)} - \mu_{mc}^{(k)} F_{mc}^{(k)}(t,x,y,z).
\end{aligned}$$

Boundary conditions for $k = 1, \dots, K$:

$$F_s^{(k)}(0,x,y,z) = z_s^{\delta(x,y)}.$$

3. Result

We denote

$$\begin{aligned}
m_{(s,k) \to (s',k)}(t,x,y) &= \mathsf{E} n_{(s,k) \to (s',k)}(t,x,y), \ s \in S, \ s' \in S, \ k = 1, \dots, K; \\
m_{(cc,k) \to (cb_r,k+1)}(t,x,y) &= \mathsf{E} n_{(cc,k) \to (cb_r,k+1)}(t,x,y), \ r \in R, \ k = 1, \dots, K-1.
\end{aligned}$$

Note that

$$m_{(s,k)\to(s',k)}(t,x,y) = \left.\frac{\partial F_s^{(k)}(t,x,y,z)}{\partial z_{s'}}\right|_{z=(1,\dots,1)},\ s\in S,\ s'\in S;$$

$$m_{(cc,k)\to(cb_r,k+1)}(t,x,y) = \left.\frac{\partial F_{cc}^{(k)}(t,x,y,z)}{\partial z_{cb_r}}\right|_{z=(1,\dots,1)},\ r\in R.$$

Here we obtain following representations:

$$m_{(pc,k)\to(pc,k)}(t,x,y) = e^{-\mu_{pc}^{(k)}t}\delta(x,y); \tag{1}$$

$$m_{(mc,k)\to(mc,k)}(t,x,y) = e^{-\mu_{mc}^{(k)}t}\delta(x,y); \tag{2}$$

$$m_{(cc,k)\to(cc,k)}(t,x,y) = e^{-\left(\mu_{cc}^{(k)}(x)+\sum\limits_{r\in R}\beta_{cb_r}^{(k)}(x)+\beta_{pc}^{(k)}(x)+\beta_{mc}^{(k)}(x)\right)t}\delta(x,y); \tag{3}$$

$$\begin{aligned} m_{(cc,k)\to(pc,k)}(t,x,y) &= \frac{\beta_{pc}^{(k)}(x)e^{-\mu_{pc}^{(k)}t}\delta(x,y)}{\mu_{cc}^{(k)}(x)+\sum\limits_{r\in R}\beta_{cb_r}^{(k)}(x)+\beta_{pc}^{(k)}(x)+\beta_{mc}^{(k)}(x)-\mu_{pc}^{(k)}} \\ &+ e^{-(\mu_{cc}^{(k)}(x)+\sum\limits_{r\in R}\beta_{cb_r}^{(k)}(x)+\beta_{pc}^{(k)}(x)+\beta_{mc}^{(k)}(x))t}\delta(x,y); \end{aligned} \tag{4}$$

$$\begin{aligned} m_{(cc,k)\to(mc,k)}(t,x,y) &= \frac{\beta_{mc}^{(k)}(x)e^{-\mu_{mc}^{(k)}t}\delta(x,y)}{\mu_{cc}^{(k)}(x)+\sum\limits_{r\in R}\beta_{cb_r}^{(k)}(x)+\beta_{pc}^{(k)}(x)+\beta_{mc}^{(k)}(x)-\mu_{mc}^{(k)}} \\ &+ e^{-(\mu_{cc}^{(k)}(x)+\sum\limits_{r\in R}\beta_{cb_r}^{(k)}(x)+\beta_{pc}^{(k)}(x)+\beta_{mc}^{(k)}(x))t}\delta(x,y). \end{aligned} \tag{5}$$

Consider the following problem: let in a short time one centroblast of type $r\in R$ in generation k mutates from state x into state y with intensity $2\beta_{2cb_r}$. We get the Cauchy problem

$$\begin{aligned} \frac{\partial m_{(cb_r,k)\to(cb_r,k)}(t,x,y)}{\partial t} &= -2\beta_{2cb_r}m_{(cb_r,k)\to(cb_r,k)}(t,x,y) \\ &+ 2\beta_{2cb_r}\sum_{x'\in\Omega}a(x,x')m_{(cb_r,k)\to(cb_r,k)}(t,x',y); \\ m_{(cb_r,k)\to(cb_r,k)}(0,x,y) &= \delta(x,y). \end{aligned}$$

Denoting $A_{x,y} := a(x,y)$, we get its solution in the form

$$p_r^{(k)}(t,x,y) = e^{2\beta_{2cb_r}(A-I)t}.$$

Let the intensity of substitution of one nucleotide to another be $1/s$. Then for $L=1$

$$A = \begin{pmatrix} -3/s & 1/s & 1/s & 1/s \\ 1/s & -3/s & 1/s & 1/s \\ 1/s & 1/s & -3/s & 1/s \\ 1/s & 1/s & 1/s & -3/s \end{pmatrix}$$

Then denoting

$$\begin{aligned} a_0(s,\beta_{2cb_r},t) &:= \frac{1}{4}(e^{-2\beta_{2cb_r}t}+3e^{\frac{-2\beta_{2cb_r}t(s+4)}{s}}); \\ a_1(s,\beta_{2cb_r},t) &:= -\frac{1}{4}(e^{\frac{-2\beta_{2cb_r}t(s+4)}{s}}-e^{-2\beta_{2cb_r}t}). \end{aligned}$$

we obtain

$$(e^{2\beta_{2cb_r}(A-I)t})_{x,y} = a_0(s,\beta_{2cb_r},t)^{\delta(x,y)}a_1(s,\beta_{2cb_r},t)^{1-\delta(x,y)}$$

and for $L > 1$ due to the independence of mutations

$$(e^{2\beta_{2cb_r}At})_{x,y} = a_0(s, \beta_{2cb_r}, t)^{L-dist(x,y)} a_1(s, \beta_{2cb_r}, t)^{dist(x,y)} e^{2\beta_{2cb_r}t}.$$

Thus, representations (3), (1), (2), (4) and (5) include possible transitions of particles in the considered system.

4. Discussion and Conclusion

We have proposed an approach for modeling the reactions in germinal centers using branching random walks with particles of several types on a discrete lattice. We have presented the equations of local moments of particles and their solutions. Further steps in this area involve building a computer simulation of the process.

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