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1 **Multi-type Galton-Watson processes with**
2 **affinity-dependent selection applied to antibody**
3 **affinity maturation**

4 Irene Balelli · Vuk Milišić · Gilles Wainrib

5
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7 **Abstract** We analyze the interactions between division, mutation and selec-
8 tion in a simplified evolutionary model, assuming that the population observed
9 can be classified into fitness levels. The construction of our mathematical
10 framework is motivated by the modeling of antibody affinity maturation of
11 B-cells in Germinal Centers during an immune response. This is a key pro-
12 cess in adaptive immunity leading to the production of high affinity antibodies
13 against a presented antigen. Our aim is to understand how the different biolog-
14 ical parameters affect the system’s functionality. We identify the existence of
15 an optimal value of the selection rate, able to maximize the number of selected
16 B-cells for a given generation.

17 **Keywords** Multi-type Galton-Watson process · Germinal center reaction ·
18 Affinity-dependent selection · Evolutionary landscapes

19 **Mathematics Subject Classification (2010)** 60J80 · 60J85 · 60J85

20 **Contents**

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34 1 Introduction

35 Antibody Affinity Maturation (AAM) takes place in Germinal Centers (GCs),
 36 specialized micro-environments which form in the peripheral lymphoid or-
 37 gans upon infection or immunization [37, 10]. GCs are seeded by ten to hun-
 38 dreds distinct B-cells [34], activated after the encounter with an antigen, which
 39 initially undergo a phase of intense proliferation [10]. Then, AAM is achieved
 40 thanks to multiple rounds of division, Somatic Hypermutation (SHM) of the B-
 41 cell receptor proteins, and subsequent selection of B-cells with improved ability
 42 of antigen-binding [20]. B-cells which successfully complete the GC reaction
 43 output as memory B-cells or plasma cells [38, 10]. Indirect evidence suggests
 44 that only B-cells exceeding a certain threshold of antigen-affinity differentiate
 45 into plasma cells [30]. The efficiency of GCs is assured by the contribution of
 46 other immune molecules, for instance Follicular Dendritic Cells (FDCs) and
 47 follicular helper T-cells (Tfh). Nowadays the key dynamics of GCs are well
 48 characterized [20, 10, 13, 34]. Despite this there are still mechanisms which re-
 49 main unclear, such as the dynamics of clonal competition of B-cells, hence
 50 how the selection acts. In recent years a number of mathematical models of
 51 the GC reaction has appeared to investigate these questions, such as [22, 40],
 52 where agent-based models are developed and analyzed through extensive nu-
 53 merical simulations, or [45] where the authors establish a coarse-grained model,
 54 looking for optimal values of *e.g.* the selection strength and the initial B-cell
 55 fitness maximizing the affinity improvement.

56
 57 Our aim in this paper is to contribute to the mathematical foundations
 58 of adaptive immunity by introducing and studying a simplified evolutionary
 59 model inspired by AAM, including division, mutation, affinity-dependent selec-
 60 tion and death. We focus on interactions between these mechanisms, identify
 61 and analyze the parameters which mostly influence the system functionality,
 62 through a rigorous mathematical analysis. This research is motivated by im-
 63 portant biotechnological applications. Indeed, the fundamental understanding
 64 of the evolutionary mechanisms involved in AAM have been inspiring many
 65 methods for the synthetic production of specific antibodies for drugs, vac-
 66 cines or cancer immunotherapy [2, 19, 32]. This production process involves

67 the selection of high affinity peptides and requires smart methods to gener-
68 ate an appropriate diversity [9]. Beyond biomedical motivations, the study
69 of this learning process has also given rise in recent years to a new class of
70 bio-inspired algorithms [7, 27, 35], mainly addressed to solve optimization and
71 learning problems.

72
73 We consider a model in which B-cells are classified into $N + 1$ affinity
74 classes with respect to a presented antigen, N being an integer big enough to
75 opportunely describe the possible fitness levels of a B-cell with respect to a
76 specific antigen [41, 43]. A B-cell is able to increase its fitness thanks to SHMs
77 of its receptors: only about 20% of all mutations are estimated to be affinity-
78 affecting mutations [31, 33]. By conveniently defining a transition probability
79 matrix, we can characterize the probability that a B-cell belonging to a given
80 affinity class passes to another one by mutating its receptors thanks to SHMs.
81 Therefore we define a selection mechanism which acts on B-cells differently de-
82 pending on their fitness. We mainly focus on a model of *positive and negative*
83 *selection* in which B-cells submitted to selection either die or exit the GC as
84 output cells, according to the strength of their affinity with the antigen. Hence,
85 in this case, no recycling mechanism is taken into account. Nevertheless the
86 framework we set is very easy to manipulate: we can define and study other
87 kinds of affinity-dependent selection mechanisms, and eventually include recy-
88 cling mechanisms, which have been demonstrated to play an important role in
89 AAM [39]. We demonstrate that independently from the transition probability
90 matrix defining the mutational mechanism and the affinity threshold chosen
91 for positive selection, the optimal selection rate maximizing the number of
92 output cells for the t^{th} generation is $1/t$, $t \in \mathbb{N}$ (Proposition 6).

93
94 From a mathematical point of view, we study a class of multi-types Galton-
95 Watson (GW) processes (*e.g.* [14, 3]) in which, by considering dead and sel-
96 lected B-cells as two distinct types, we are able to formalize the evolution of
97 a population submitted to an affinity-dependent selection mechanism. To our
98 knowledge, the problem of affinity-dependent selection in GW processes has
99 not been deeply investigated so far.

100
101 In Section 2 we define the main model analyzed in this paper. We give
102 as well some definitions that we will use in next sections. Section 3 contains
103 the main mathematical results. A convenient use of a multi-type GW process
104 allows to study the evolution of both GC and output cells over time. We de-
105 termine the optimal value of the selection rate which maximizes the expected
106 number of selected B-cells at any given maturation cycle in Section 3.3. We
107 conclude Section 3 with some numerical simulations. In Section 4 we define two
108 possible variants of the model described in previous sections, and provide some
109 mathematical results and numerical simulations as well. This evidences how
110 the mathematical tools used in Section 3 easily apply to define other affinity-
111 dependent selection models. Finally, in Section 5 we discuss our modeling
112 assumptions and give possible extensions and limitations of our mathematical

113 model. In order to facilitate the reading of the paper, some technical mathe-
 114 matical demonstrations, as well as some classical results about Galton-Watson
 115 theory are reported in the Appendix for interested readers.

116

117 2 Main definitions and modeling assumptions

118 This section provides the mathematical framework of this article. Let us sup-
 119 pose that given an antigen target cell $\bar{\mathbf{x}}$, all B-cell traits can be divided in
 120 exactly $N + 1$ distinct affinity classes, named 0 to N .

121 **Definition 1** Let $\bar{\mathbf{x}}$ be the antigen target trait. Given a B-cell trait \mathbf{x} , we
 122 denote by $a_{\bar{\mathbf{x}}}(\mathbf{x})$ the affinity class it belongs to with respect to $\bar{\mathbf{x}}$, $a_{\bar{\mathbf{x}}}(\mathbf{x}) \in$
 123 $\{0, \dots, N\}$. The maximal affinity corresponds to the first class, 0, and the
 124 minimal one to N .

Definition 2 Let \mathbf{x} be a B-cell trait belonging to the affinity class $a_{\bar{\mathbf{x}}}(\mathbf{x})$ with
 respect to $\bar{\mathbf{x}}$. We say that its affinity with $\bar{\mathbf{x}}$ is given by:

$$\text{aff}(\mathbf{x}, \bar{\mathbf{x}}) = N - a_{\bar{\mathbf{x}}}(\mathbf{x})$$

125 Of course, this is not the only possible choice of affinity. Typically affinity
 126 is represented as a Gaussian function [40, 22], having as argument the distance
 127 between the B-cell trait and the antigen in the shape space of possible traits.
 128 In our model this distance corresponds to the index of the affinity class the
 129 B-cell belongs to (0 being the minimal distance, N the maximal one). Never-
 130 theless the choice of the affinity function does not affect our model.

131

132 During the GC reaction B-cells are submitted to random mutations. This
 133 implies switches from one affinity class to another with a given probability.
 134 Setting these probability means defining a mutational rule on the state space
 135 $\{0, \dots, N\}$ of affinity classes indices (the formal mathematical definition will
 136 be given in Section 3.2).

137

138 The main model we study in this paper is represented schematically in
 139 Figure 1. It is defined as follows:

Definition 3 The process starts with $z_0 \geq 1$ B-cells entering the GC, belong-
 ing to some affinity classes in $\{0, \dots, N\}$. In case they are all identical, we
 denote by a_0 the affinity class they belong to, with respect to the antigen tar-
 get cell $\bar{\mathbf{x}}$. At each time step, each GC B-cell can eventually undertake three
 distinct processes: division, mutation and selection. First of all, each GC B-
 cell can die with a given rate $r_d \in [0, 1]$. If not, each B-cell can divide with
 rate $r_{div} \in [0, 1]$: each daughter cell may have a mutated trait, according to
 the mutational rule allowed. Hence it eventually belongs to a different affinity
 class than its mother cell. Clearly, it also happens that a B-cell stays in the
 GC without dying nor dividing. Finally, with rate $r_s \in [0, 1]$ each B-cell can

be submitted to selection, which is made according to its affinity with $\bar{\mathbf{x}}$. A threshold \bar{a}_s is fixed: if the B-cell belongs to an affinity class with index greater than \bar{a}_s , the B-cell dies. Otherwise, the B-cell exits the GC pool and reaches the selected pool. Therefore, for any GC B-cell and at any generation, we have:

$$\begin{cases} \text{Probability of cellular apoptosis: } \mathbb{P}(\text{death}) &= r_d \\ \text{Probability of cellular division: } \mathbb{P}(\text{division}) &= r_{div} \\ \text{Probability of selection challenge: } \mathbb{P}(\text{selection}) &= r_s \end{cases}$$

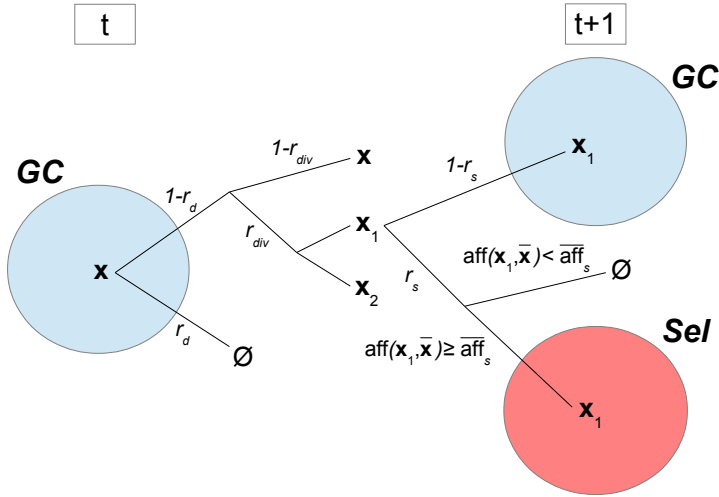


Figure 1: Schematic representation of model described by Definition 3. Here we denote by $\bar{\text{aff}}_s := N - \bar{a}_s$, the fitness of each B-cell in the affinity class whose index is \bar{a}_s (see Definitions 1 and 2).

140 Once the GC reaction is fully established (\sim day 7 after immunization), it
 141 is polarized into two compartments, named Dark Zone (DZ) and Light Zone
 142 (LZ) respectively. The DZ is characterized by densely packed dividing B-cells,
 143 while the LZ is less densely populated and contains FDCs and Tfh cells. The
 144 LZ is the preferential zone for selection [10]. The transition of B-cells from the
 145 DZ to the LZ seems to be determined by a timed cellular program: over a 6
 146 hours period about 50% of DZ B-cells transit to the LZ, where they compete
 147 for positive selection signaling [6, 36].

148
 149 Through the entire paper one should keep in mind the following main
 150 modeling assumptions:

151 *Modeling assumption 1* In our simplified mathematical model we do not take
 152 into account any spatial factor and in a single time step a GC B-cell can
 153 eventually undergo both division (with mutation) and selection. Hence the
 154 time unit has to be chosen big enough to take into account both mechanisms.

155 *Modeling assumption 2* In this paper we are considering discrete-time models.
 156 The symbol t always denote a discrete time step, hence it is an integral value.
 157 We will refer to t as time, generation, or even maturation cycle to further
 158 stress the fact that in a single time interval $[t, t + 1]$ each B-cell within the GC
 159 population is allowed to perform a complete cycle of division, mutation and
 160 selection.

161 *Modeling assumption 3* Throughout the entire paper, when we talk about
 162 death rate (respectively division rate or selection rate) we are referring to
 163 the probability that each cell has of dying (respectively dividing or being sub-
 164 mitted to selection) in a single time step.

165

166 3 Results

167 In this Section we formalize mathematically the model introduced above. This
 168 enables the estimation of various qualitative and quantitative measures of the
 169 GC evolution and of the selected pool as well. In Section 3.1 we show that a
 170 simple GW process describes the evolution of the size of the GC and determine
 171 a condition for its extinction. In order to do this we do not need to know the
 172 mutational model. Nevertheless, if we want to understand deeply the whole
 173 reaction we need to consider a $(N + 3)$ -type GW process, which we introduce
 174 in Section 3.2. Therefore we determine explicitly other quantities, such as the
 175 average affinity in the GC and the selected pool, or the evolution of the size
 176 of the latter. We conclude this section by numerical simulations (Section 3.4).

177 3.1 Evolution of the GC size

178 The aim of this section is to estimate the evolution of the GC size and its
 179 extinction probability. In order to do so we define a simple GW process, with
 180 respect to parameters r_d, r_{div} and r_s . Indeed, each B-cell submitted to selection
 181 exits the GC pool, independently from its affinity with \bar{x} . Hence we apply some
 182 classical results about generating functions and GW processes ([14], Chapter
 183 I), which we recall in Appendix A. Proposition 1 gives explicitly the expected
 184 size of the GC at time t and conditions for the extinction of the GC.

185 **Definition 4** Let $Z_t^{(z_0)}, t \geq 0$ be the random variable (rv) describing the GC-
 186 population size at time t , starting from $z_0 \geq 1$ initial B-cells. $(Z_t^{(z_0)})_{t \in \mathbb{N}}$ is a
 187 Markov Chain (MC) - since each cell behaves independently from the others
 188 and from previous generations - on $\{0, 1, 2, \dots\}$.

189 If $z_0 = 1$ and there is no confusion, we denote $Z_t := Z_t^{(1)}$. By Definition
 190 4, Z_1 corresponds to the number of cells in the GC at the first generation,
 191 starting from a single seed cell. Thanks to Definition 3 one can claim that
 192 $Z_1 \in \{0, 1, 2\}$, with the following probabilities:

$$\begin{cases} p_0 := \mathbb{P}(Z_1 = 0) = r_d + (1 - r_d)r_s(1 - r_{div} + r_{div}r_s) \\ p_1 := \mathbb{P}(Z_1 = 1) = (1 - r_d)(1 - r_s)(1 - r_{div} + 2r_{div}r_s) \\ p_2 := \mathbb{P}(Z_1 = 2) = r_{div}(1 - r_d)(1 - r_s)^2 \end{cases} \quad (1)$$

193 As far as next generations are concerned, conditioning to $Z_t = k$, *i.e.* at
 194 generation t there are k B-cells in the GC, Z_{t+1} is distributed as the sum of
 195 k independent copies of Z_1 : $\mathbb{P}(Z_{t+1} = k' | Z_t = k) = \mathbb{P}\left(\sum_{i=1}^k Z_1 = k'\right)$.

196
 197 Equalities in (1) are derived by identifying the events leading to 0, 1 or
 198 2 offspring in the GC coming from a single clone. Since these events are in-
 199 dependent and disjoint, the result follows. For instance there will be 0 new
 200 individuals in the GC if either the mother cell dies, or it does not die, does
 201 not divide and is submitted to selection, or it does not die, it does divide and
 202 both daughter cells are submitted to selection :

$$\begin{aligned} \mathbb{P}(Z_1 = 0) &= \mathbb{P}\left(\text{death} \cup (\text{death}^C \cap \text{division}^C \cap \text{selection}) \cup (\text{death}^C \cap \text{division} \cap \text{selection} \cap \text{selection})\right) \\ &= \mathbb{P}(\text{death}) + \mathbb{P}(\text{death}^C)\mathbb{P}(\text{division}^C)\mathbb{P}(\text{selection}) + \mathbb{P}(\text{death}^C)\mathbb{P}(\text{division})\mathbb{P}(\text{selection})^2 \\ &= r_d + (1 - r_d)(1 - r_{div})r_s + (1 - r_d)r_{div}r_s^2 \end{aligned}$$

203 We have denoted by A^C the complement of A . Expressions for p_1 and p_2 are
 204 obtained proceeding as before.

Definition 5 Let X be an integer valued rv, $p_k := \mathbb{P}(X = k)$ for all $k \geq 0$. Its probability generating function (pgf) is given by:

$$F_X(s) = \sum_{k=0}^{+\infty} p_k s^k$$

205 The pgf for Z_1 :

$$\begin{aligned} F(s) &= p_0 + p_1 s + p_2 s^2 \\ &= r_d + (1 - r_d)r_s(1 - r_{div} + r_{div}r_s) \\ &\quad + (1 - r_d)(1 - r_s)(1 - r_{div} + 2r_{div}r_s)s + r_{div}(1 - r_d)(1 - r_s)^2 s^2 \end{aligned} \quad (2)$$

206 By using classical results on Galton-Watson processes (see Appendix A),
 207 one can prove:

208 **Proposition 1**

209 (i) *The expected size of the GC at time t and starting from z_0 initial B-cells*
 210 *is given by:*

$$\mathbb{E}(Z_t^{(z_0)}) = z_0 ((1 - r_d)(1 + r_{div})(1 - r_s))^t \quad (3)$$

211 (ii) Denoted by η_{z_0} the extinction probability of the GC population starting
 212 from z_0 initial B-cells, one has:

213 – if $\mathbb{E}(Z_1^{(1)}) \leq 1 \Leftrightarrow r_s \geq 1 - \frac{1}{(1-r_d)(1+r_{div})}$, then $\eta_{z_0} = 1$: the process is
 214 subcritical

215 – otherwise $\eta_{z_0} = \eta^{z_0} < 1$, η being the smallest fixed point of (2): the
 216 process is supercritical

217 In particular, the initial number of seed cells z_0 does not affect the crit-
 218 icality of the process. Nevertheless, in the supercritical case, increasing the
 219 number of seed B-cells at the beginning of the process makes the probabili-
 220 ty of extinction decrease. More precisely, in the case $\eta < 1$, then $\eta_{z_0} \rightarrow 0$ if
 221 $z_0 \rightarrow \infty$, but we recall that GCs seem to be typically seeded by few B-cells,
 222 varying from ten to hundreds [34].

223

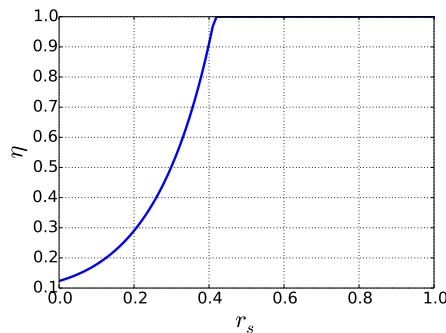


Figure 2: Numerical estimation of the extinction probability η of the GC with respect to r_s for $r_d = 0.1$ and $r_{div} = 0.9$.

224 This section shows that a classical use of a simple GW process enables
 225 to understand quantitatively the GC growth. Moreover, Proposition 1 (ii)
 226 gives a condition on the main parameters for the extinction of the GC: if
 227 the selection pressure is too high, with probability 1 the GC size goes to 0,
 228 independently from the initial number of seed cells. Intuitively, a too high
 229 selection pressure prevents those B-cells with bad affinity to improve their
 230 fitness undergoing further rounds of mutation and division. Most B-cells will
 231 be rapidly submitted to selection, hence either exit the GC as output cells or
 232 die by apoptosis if they fail to receive positive selection signals [20]. In Figure
 233 2 we plot the extinction probability of a GC initiated from a single seed cell
 234 as a function of r_s (r_d and r_{div} are fixed), in order to stress the presence of
 235 a threshold effect of the selection probability over the extinction probability.
 236 The extinction probability of the GC process can give us some further insights
 237 on factors which are potentially involved in determining the success or failure
 238 of a GC reaction. This simplified mathematical model suggests that if the

239 selection pressure is too high compared to the division rate (*c.f.* due to Tfh
 240 signals in the LZ), the GC will collapse with probability 1, preventing the
 241 generation of high affinity antibodies against the presented antigen, hence an
 242 efficient immune response.

243 3.2 Evolution of the size and fitness of GC and selected pools

244 The GW process defined in the previous Section only describes the size of
 245 the GC. Indeed, we are not able to say anything about the average fitness of
 246 GC clones, or the expected number of selected B-cells, or their average affini-
 247 ty. Hence, we need to consider a more complex model and take into account
 248 the threshold for positive selection \bar{a}_s , and the transition probability matrix
 249 characterizing the mutational rule. Indeed, the mutational process is described
 250 as a Random Walk (RW) on the state space $\{0, \dots, N\}$ of affinity classes in-
 251 dices. The mutational rule reflects the edge set associated to the state-space
 252 $\{0, \dots, N\}$: this is given by a transition probability matrix.

Definition 6 Let $(\mathbf{X}_t)_{t \geq 0}$ be a RW on the state-space of B-cell traits descri-
 bing a pure mutational process of a B-cell during the GC reaction. We denote
 by $\mathcal{Q}_N = (q_{ij})_{0 \leq i, j \leq N}$ the transition probability matrix over $\{0, \dots, N\}$ which
 gives the probability of passing from an affinity class to another during the
 given mutational model. For all $0 \leq i, j \leq N$:

$$q_{ij} = \mathbb{P}(a_{\bar{x}}(\mathbf{X}_{t+1}) = j \mid a_{\bar{x}}(\mathbf{X}_t) = i)$$

253 From a biological point of view, these probabilities could be obtained *e.g.* by
 254 identifying which key mutations are the most relevant in determining changes
 255 in the fitness of a clone to a specific antigen and at which frequency they are
 256 produced.

257 We introduce a multi-type GW Process (see for instance [3], chapter V).

259 **Definition 7** Let $\mathbf{Z}_t^{(i)} = (Z_{t,0}^{(i)}, \dots, Z_{t,N+2}^{(i)})$, $t \geq 0$ be a MC where for all $0 \leq$
 260 $j \leq N$, $Z_{t,j}^{(i)}$ describes the number of GC B-cells belonging to the j^{th} -affinity
 261 class with respect to \bar{x} , $Z_{t,N+1}^{(i)}$ the number of selected B-cells and $Z_{t,N+2}^{(i)}$ the
 262 number of dead B-cells at generation t , when the process is initiated in state
 263 $\mathbf{i} = (i_0, \dots, i_N, 0, 0)$.

264 Let $m_{ij} := \mathbb{E}[Z_{1,j}^{(i)}]$ the expected number of offspring of type j of a cell of
 265 type i in one generation. We collect all m_{ij} in a matrix, $\mathcal{M} = (m_{ij})_{0 \leq i, j \leq N+2}$.
 266 We have:

$$\mathbb{E}[\mathbf{Z}_t^{(i)}] = \mathbf{i} \mathcal{M}^t \quad (4)$$

267 Supposing matrix \mathcal{Q}_N given (Definition 6), describing the probability to
 268 switch from one affinity class to another thanks to a single mutation event,
 269 one can explicitly derive the elements of \mathcal{M} .

Proposition 2 \mathcal{M} is a $(N+3) \times (N+3)$ matrix defined as a block matrix:

$$\mathcal{M} = \begin{pmatrix} \mathcal{M}_1 & \mathcal{M}_2 \\ \mathbf{0}_{2 \times (N+1)} & \mathcal{I}_2 \end{pmatrix}$$

270 Where:

- 271 – $\mathbf{0}_{2 \times (N+1)}$ is a $2 \times (N+1)$ matrix with all entries 0;
 272 – \mathcal{I}_n is the identity matrix of size n ;
 273 – $\mathcal{M}_1 = 2(1-r_d)r_{div}(1-r_s)\mathcal{Q}_N + (1-r_d)(1-r_{div})(1-r_s)\mathcal{I}_{N+1}$
 274 – $\mathcal{M}_2 = (m_{2,ij})$ is a $(N+1) \times 2$ matrix where for all $i \in \{0, \dots, N\}$:
 275 – if $i \leq \bar{a}_s$:

276
$$m_{2,i1} = (1-r_d)(1-r_{div})r_s + 2(1-r_d)r_{div}r_s \sum_{j=0}^{\bar{a}_s} q_{ij},$$

277
$$m_{2,i2} = r_d + 2(1-r_d)r_{div}r_s \sum_{j=\bar{a}_s+1}^N q_{ij}$$

- 278 – if $i > \bar{a}_s$:

279
$$m_{2,i1} = 2(1-r_d)r_{div}r_s \sum_{j=0}^{\bar{a}_s} q_{ij},$$

280
$$m_{2,i2} = r_d + (1-r_d)(1-r_{div})r_s + 2(1-r_d)r_{div}r_s \sum_{j=\bar{a}_s+1}^N q_{ij}$$

281 The proof of Proposition 2 is available in Appendix B. It is based on the
 282 computation of the probability generating function of \mathbf{Z}_1 .

283 *Remark 1* Independently from the given mutational model, the expected number
 284 of selected or dead B-cells that each GC B-cell can produce in a single time
 285 step is given by $\alpha := r_d + (1-r_d)(1+r_{div})r_s$. All rows of \mathcal{M}_2 sum to α in-
 286 dependently from the probability that each clone submitted to selection has
 287 of being positive selected, which we recall is 1 if it belongs to the i^{th} affinity
 288 class, $i \leq \bar{a}_s$, zero otherwise.

289 Of course in the multi-type context we recover again results from Section
 290 3.1, such as the extinction probability of the GC (detailed in Appendix C).

291

292 In order to determine the expected number of selected cells at a given time
 293 t , we need to introduce another multi-type GW process.

294 **Definition 8** Let $\tilde{\mathbf{z}}_t^{(i)} = (\tilde{z}_{t,0}^{(i)}, \dots, \tilde{z}_{t,N+2}^{(i)})$, $t \geq 0$ be a MC where for all $0 \leq$
 295 $j \leq N$, $\tilde{z}_{t,j}^{(i)}$ describes the number of GC B-cells belonging to the j^{th} -affinity
 296 class with respect to $\bar{\mathbf{x}}$, $\tilde{z}_{t,N+1}^{(i)}$ the number of selected B-cells and $\tilde{z}_{t,N+2}^{(i)}$ the
 297 number of dead B-cells at generation t , when the process is initiated in state
 298 $\mathbf{i} = (i_0, \dots, i_N, 0, 0)$ and before the selection mechanism is performed for the
 299 t^{th} -generation.

300 Proceeding as we did for $\mathbf{Z}_t^{(i)}$, we can determine a matrix $\widetilde{\mathcal{M}}$ whose elements
 301 are $\widetilde{m}_{ij} := \mathbb{E}[\widetilde{Z}_{1,j}^{(i)}]$ for all $i, j \in \{0, \dots, N+2\}$.

Proposition 3 $\widetilde{\mathcal{M}}$ is a $(N+3) \times (N+3)$ matrix, which only depends on matrix \mathcal{Q}_N , r_d and r_{div} and can be defined as a block matrix as follows:

$$\widetilde{\mathcal{M}} = \begin{pmatrix} \widetilde{\mathcal{M}}_1 & \widetilde{\mathcal{M}}_2 \\ \mathbf{0}_{2 \times (N+1)} & \mathcal{I}_2 \end{pmatrix}$$

302 Where:

- 303 – $\widetilde{\mathcal{M}}_1 = 2(1-r_d)r_{div}\mathcal{Q}_N + (1-r_d)(1-r_{div})\mathcal{I}_{N+1}$
- 304 – $\widetilde{\mathcal{M}}_2 = (\mathbf{0}_{N+1}, r_d \cdot \mathbf{1}_{N+1})$, where $\mathbf{0}_{N+1}$ (resp. $\mathbf{1}_{N+1}$) is a $(N+1)$ -column
 305 vector whose elements are all 0 (resp. 1).

306 One could prove that:

$$\mathbb{E}[\widetilde{\mathbf{Z}}_t^{(i)}] = \mathbf{i}\mathcal{M}^{t-1}\widetilde{\mathcal{M}} \quad (5)$$

307 **Proposition 4** Let \mathbf{i} be the initial state, $|\mathbf{i}|$ its 1-norm ($|\mathbf{i}| := \sum_{j=0}^{N+2} \mathbf{i}_j$).

- 308 – The expected size of the GC at time t :

$$\sum_{k=0}^N (\mathbf{i}\mathcal{M}^t)_k \left(= |\mathbf{i}| ((1-r_d)(1+r_{div})(1-r_s))^t \right) \quad (6)$$

- 309 – The average affinity in the GC at time t :

$$\frac{\sum_{k=0}^N (N-k)(\mathbf{i}\mathcal{M}^t)_k}{\sum_{k=0}^N (\mathbf{i}\mathcal{M}^t)_k} \quad (7)$$

- 310 – Let S_t , $t \geq 1$ denotes the random variable describing the number of selected
 311 B-cells at time t . By hypothesis $S_0 = 0$. $(S_t)_{t \in \mathbb{N}}$ is a MC on $\{0, 1, 2, \dots\}$.
 312 The expected number of selected B-cells at time t , $t \geq 1$:

$$\mathbb{E}(S_t) = r_s \sum_{k=0}^{\bar{a}_s} (\mathbf{i}\mathcal{M}^{t-1}\widetilde{\mathcal{M}})_k \quad (8)$$

- 313 – The expected number of selected B-cells produced until time t :

$$\mathbb{E} \left[\sum_{n=0}^t S_n \right] = \mathbb{E} \left[\left(\mathbf{Z}_t^{(i)} \right)_{N+1} \right] = (\mathbf{i}\mathcal{M}^t)_{N+1} \quad (9)$$

314 – The average affinity of selected B-cells at time t , $t \geq 1$:

$$\frac{\sum_{k=0}^{\bar{a}_s} (N-k) \left(\mathbf{iM}^{t-1} \widetilde{\mathcal{M}} \right)_k}{\sum_{k=0}^{\bar{a}_s} \left(\mathbf{iM}^{t-1} \widetilde{\mathcal{M}} \right)_k} \quad (10)$$

315 – The average affinity of selected B-cells until time t :

$$\frac{r_s \sum_{n=1}^t \sum_{k=0}^{\bar{a}_s} (N-k) \left(\mathbf{iM}^{n-1} \widetilde{\mathcal{M}} \right)_k}{\left(\mathbf{iM}^t \right)_{N+1}} \quad (11)$$

316 *Proof* Equations (6) and (9) are a direct application of what stated in Equation
 317 (17). Indeed, Equation (17) states that \mathbf{iM}^t contains the expectation of
 318 the number of all types cells at generation t when the process is started in
 319 \mathbf{i} . Hence the expectation of the size of the GC at the t^{th} generation is given
 320 by $\sum_{k=0}^N (\mathbf{iM}^t)_k$, since the GC at generation t contains all alive non-selected
 321 B-cells, irrespectively from their affinity. Similarly, the expected number of selected
 322 B-cells until time t (9) corresponds to the expectation of the $(N+1)^{\text{th}}$ -
 323 type cell, $(\mathbf{iM}^t)_{N+1}$.

324

The proof of Equation (8) is based on Equation (5), which allows to estimate the number of GC B-cells at generation t which are susceptible of being challenged by selection. One can remark that the expected number of selected B-cells at time t is obtained from the expected number of B-cells in GC at time t (before the selection mechanism is performed) having fitness good enough to be positive selected. This is given by $\sum_{k=0}^{\bar{a}_s} \left(\mathbf{iM}^{t-1} \widetilde{\mathcal{M}} \right)_k$, thanks to (5). The result follows by multiplying this expectation by the probability that each of these B-cells is submitted to mutation, *i.e.* r_s . Finally, results about the average affinity in both the GC and the selected pool (Equations (7), (10) and (11)) are obtained from the previous ones (*c.f.* (6), (8) and (9)) by multiplying the number of individuals belonging to the same class by their fitness (Definition 2), and dividing by the total number of individuals in the considered pool. The definition of affinity as a function of the affinity classes, determines Equations (7), (10) and (11). Indeed, the affinity of the k^{th} -affinity class is given by $N - k$. \square

325 *Remark 2* The expected size of the GC at time t can be obtained applying a
 326 simple GW process (Section 3.1) and is given by (3). It is possible to prove
 327 the equality in brackets in Equation (6) starting from the $(N+3)$ -type GW
 328 process. The interested reader can address to Appendix D for the detailed
 329 proof.

330 3.3 Optimal value of r_s maximizing the expected number of selected B-cells
331 at time t

332 What is the behavior of the expected number of selected B-cells as a function
333 of the model parameters? In particular, is there an optimal value of the selec-
334 tion rate which maximizes this number? In this section we show that, indeed,
335 the answer is positive.

336
337 To do so we detail hereafter the computation of $\mathbb{E}(S_t)$ (Equation (8)), given
338 by Proposition 4.

339
340 Let us suppose, for the sake of simplicity, that \mathcal{Q}_N is diagonalizable:

$$\mathcal{Q}_N = R\Lambda_N L, \quad (12)$$

341 where $\Lambda_N = \text{diag}(\lambda_0, \dots, \lambda_N)$, and $R = (r_{ij})$ (resp. $L = (l_{ij})$) is the transition
342 matrix whose rows (resp. lines) contain the right (resp. left) eigenvectors of
343 \mathcal{Q}_N , corresponding to $\lambda_0, \dots, \lambda_N$.

344

Proposition 5 *Let us suppose that at $t=0$ there is a single B-cell entering the GC belonging to the i^{th} -affinity class with respect to the target cell. Moreover, let us suppose that $\mathcal{Q}_N = R\Lambda_N L$. For all $t \in \mathbb{N}$, the expected number of selected B-cells at time t , is:*

$$\mathbb{E}(S_t) = r_s(1-r_s)^{t-1}(1-r_d)^t \sum_{\ell=0}^N (2\lambda_\ell r_{div} + 1 - r_{div})^t \sum_{k=0}^{\bar{a}_s} r_{i\ell} l_{\ell k},$$

345 The proof of Proposition 5 is detailed in Appendix E.

346

347 As an immediate consequence of Proposition 5, we can claim:

Proposition 6 *For all $t^* \in \mathbb{N}$ fixed, the value $r_s^* := r_s(t^*)$ which maximizes the expected number of selected B-cells at the $t^{*\text{th}}$ maturation cycle is:*

$$r_s^* = \frac{1}{t^*}$$

Proof Since $(1-r_d)^t \sum_{\ell=0}^N (2\lambda_\ell r_{div} + 1 - r_{div})^t \sum_{k=0}^{\bar{a}_s} r_{i\ell} l_{\ell k}$ is a non negative quantity independent from r_s , the value of r_s which maximizes $\mathbb{E}(S_{t^*})$ is the one that maximizes $r_s(1-r_s)^{t^*-1}$. The result trivially follows. \square

348 This result suggests that the selection rate in GCs is tightly related to
349 the timing of the peak of a GC response, *i.e.* the timing corresponding to the
350 maximal production of output cells (this timing can be determined *e.g.* by ob-
351 serving the concentration in blood of produced specific B-cells after infection
352 or vaccination). In particular, following this model, GCs which peak early (*e.g.*
353 for whom the maximal output cell production is reached in a few days) are

possibly characterized by a higher selection pressure than GCs peaking later. The peak of a typical GC reaction, measured as the average GC volume, has been estimated to be close to day 12 post immunization or a few days before [42], which is consistent with the observation of plasma cell response peak after immunization, *e.g.* [24]. Moreover, an high selection rate could also prevent a correct and efficient establishment of an immune response (*c.f.* results about extinction probability - Proposition 1). In addition, from a biological viewpoint, a too demanding selection pressure could avoid the generation of advantageous mutations, hence their fixation.

Remark 3 Under certain hypotheses about the mutational model and the GC evolution, one could justify the claim of Proposition 6 by heuristic arguments, without considering the $(N+3)$ -type GW process. This leads to approximately estimate the expected number of selected B-cells at time t (Appendix F). Figure 4 (a) shows the peak of positive selected B-cells at generation t for a certain set of parameters.

3.4 Numerical simulations

We evaluate numerically results of Proposition 4. The $(N+3)$ -type GW process allows a deeper understanding of the dynamics of both populations: inside the GC and in the selected pool. Through numerical simulations we emphasize the dependence of the quantities defined in Proposition 4 on parameters involved in the model.

In previous works [5, 4] we have modeled B-cells and antigens as N -length binary strings, hence their traits correspond to elements of $\{0, 1\}^N$. In this context we have characterized affinity using the Hamming distance between B-cell and antigen representing strings. The idea of using a N -dimensional shape space to represent antibodies traits and their affinity with respect to a specific antigen has already been employed (*e.g.* [28, 22, 17]), and N typically varies from 2 to 4. In the interests of simplification, we chose to set $N = 2$. Moreover, from a biological viewpoint, this choice means that we classify the amino-acids composing B-cell receptors strings into 2 classes, which could represent amino-acids negatively and positively charged respectively. Charged and polar amino-acids are the most responsible in creating bonds which determine the antigen-antibody interaction [26].

While performing numerical simulations (Sections 3.4 and 4.2) we refer to the following transition probability matrix on $\{0, \dots, N\}$:

Definition 9 For all $i, j \in \{0, \dots, N\}$:

$$q_{ij} = \mathbb{P}(a_{\bar{\mathbf{x}}}(\mathbf{X}_{t+1}) = j \mid a_{\bar{\mathbf{x}}}(\mathbf{X}_t) = i) = \begin{cases} i/N & \text{if } j = i - 1 \\ (N - i)/N & \text{if } j = i + 1 \\ 0 & \text{if } |j - i| \neq 1 \end{cases}$$

392 $\mathcal{Q}_N := (q_{ij})_{0 \leq i, j \leq N}$ is a tridiagonal matrix where the main diagonal consists
393 of zeros.

394 If we model B-cell traits as vertices of the state-space $\{0, 1\}^N$, this cor-
395 responds to a model of simple point mutations (see [5] for more details and
396 variants of this basic mutational model on binary strings).

397 *Example 1* One can give explicitly the form of matrix \mathcal{M}_2 (Proposition 2)
398 corresponding to the mutational model defined in Definition 9:

$$\mathcal{M}_2 = \begin{matrix} & & 0 \\ & & \vdots \\ & \bar{a}_s - 1 & \\ & \bar{a}_s & \\ & \bar{a}_s + 1 & \\ & \bar{a}_s + 2 & \\ & \vdots & \\ N & & \end{matrix} \begin{pmatrix} \alpha & & r_d & & \\ \vdots & & \vdots & & \\ \alpha - \beta + \beta \frac{\bar{a}_s}{N} & & r_d & & \\ \beta \frac{\bar{a}_s + 1}{N} & & r_d + \beta \frac{N - \bar{a}_s}{N} & & \\ 0 & & r_d + \alpha - \beta + \beta \frac{N - (\bar{a}_s + 1)}{N} & & \\ \vdots & & \vdots & & \\ 0 & & r_d + \alpha & & \end{pmatrix},$$

399 where:

400 - $\alpha := (1 - r_d)(1 + r_{div})r_s$
401 - $\beta := 2(1 - r_d)r_{div}r_s$
402

403 Indeed, due to the particular form of matrix \mathcal{Q}_N one has straightforward:

$$404 - \sum_{j=0}^{\bar{a}_s} q_{ij} = \begin{cases} 1 & \text{if } i < \bar{a}_s \\ \bar{a}_s/N & \text{if } i = \bar{a}_s \\ (\bar{a}_s + 1)/N & \text{if } i = \bar{a}_s + 1 \\ 0 & \text{if } i > \bar{a}_s + 1 \end{cases}$$

$$405 - \sum_{j=\bar{a}_s+1}^N q_{ij} = \begin{cases} 0 & \text{if } i < \bar{a}_s \\ (N - \bar{a}_s)/N & \text{if } i = \bar{a}_s \\ (N - (\bar{a}_s + 1))/N & \text{if } i = \bar{a}_s + 1 \\ 1 & \text{if } i > \bar{a}_s + 1 \end{cases}$$

406 *Remark 4* Note that all mathematical results obtained in previous sections are
407 independent from the mutation model defined in Definition 9.

408 We suppose that at the beginning of the process there is a single B-cell
409 entering the GC belonging to the affinity class a_0 . Of course, the model we set
410 allows to simulate any possible initial condition. Indeed, by fixing the initial
411 vector \mathbf{i} , we can decide to start the reaction with more B-cells, in different
412 affinity classes. When it is not stated otherwise, the employed parameter set
413 for simulations is given in Table 1.
414

Table 1: Parameter choice for simulations in Sections 3.4 (unless stated otherwise).

N	r_s	r_d	r_{div}	a_0	\bar{a}_s
10	0.1	0.1	0.9	3	3

415 We perform numerical simulations to better appreciate how the dynam-
 416 ics of the GC and positive selected clones populations are related and evolve
 417 depending on model parameters. In the case of a subcritical GC, by model
 418 definition selected clones stabilize at a given level once the GC becomes ex-
 419 tinct. Hence we conveniently chose a parameter set (Table 1) which implies
 420 a supercritical GC (Proposition 1): with great probability the simulated GC
 421 goes through explosion, and so the selected population does.

422 3.4.1 Evolution of the GC population

423 The evolution of the size of the GC can be studied by using the simple GW
 424 process defined in Section 3.1. Equation (3), in the case of a single initial B-cell,
 425 evidences that the expected number of B-cells within the GC for this model
 426 only depends on r_d , r_{div} and r_s and it is not driven by the initial affinity, nor
 427 by the threshold chosen for positive selection \bar{a}_s , nor by the mutational rule.

428 Equation (3) evidences that, independently from the transition probabili-
 429 ty matrix defining the mutational mechanism, the GC size at time t increases
 430 with r_{div} and decreases for increasing r_s and r_d . Moreover, the impact of these
 431 last two parameters is the same for the growth of the GC. One could expect
 432 this behavior since the effect of both the death and the selection on a B-cell
 433 is the exit from the GC.

434 In order to study the evolution of the average affinity within the GC, we
 435 need to refer to the $(N + 3)$ -type GW process defined in Section 3.2.

Proposition 7 *Let us suppose that $\mathcal{Q}_N = R\Lambda_N L$. The average affinity within the GC at time t , starting from a single B-cell belonging to the i^{th} -affinity class with respect to $\bar{\mathbf{x}}$ is given by:*

$$N - \frac{\sum_{\ell=0}^N (2\lambda_{\ell} r_{div} + 1 - r_{div})^t \sum_{k=0}^N k \cdot r_{i\ell} l_{\ell k}}{(1 + r_{div})^t},$$

Proof It follows directly from Equations (7) and by considering the eigende-
 composition of matrix \mathcal{Q} . One has to consider the expression of the t^{th} power
 of matrix \mathcal{M} (which can be obtained recursively, see Appendix E): one can

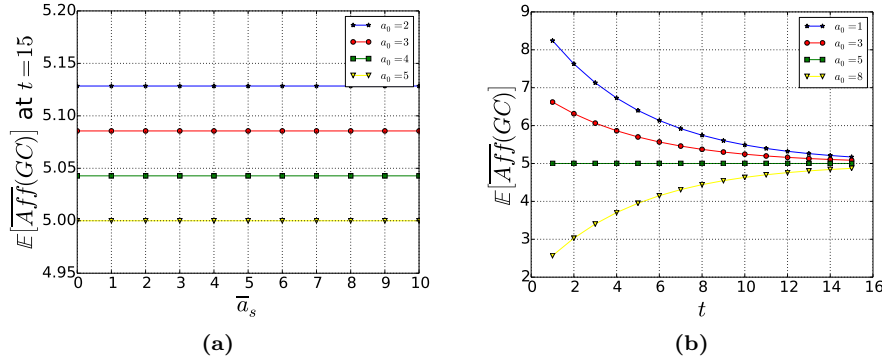


Figure 3: (a) Dependence of the expected average affinity in the GC on \bar{a}_s at time $t = 15$, for different values of a_0 . The average affinity in the GC is constant with respect to \bar{a}_s . (b) The evolution during time of the expected average affinity in the GC for different values of a_0 . The average affinity converges through $N/2$, due to the stationary distribution of Q_N , the binomial probability distribution.

prove that the first $N + 1$ components of the i^{th} -row of matrix \mathcal{M}^t are the elements of the i^{th} -row of matrix RD^tL , where $D = 2(1 - r_d)r_{div}(1 - r_s)A_N + (1 - r_d)(1 - r_{div})(1 - r_s)\mathcal{I}_{N+1}$ is a diagonal matrix. \square

438 It is obvious from Proposition 7 that this quantity only depends on the
 439 initial affinity with the target trait, the transition probability matrix Q_N and
 440 the division rate r_{div} . The average affinity within the GC does not depend on
 441 \bar{a}_s (as one can clearly see in Figure 3 (a)), nor by r_s or r_d . One can intuitively
 442 understand this behavior: independently from their fitness, all B-cells submitted
 443 to mutation exit the GC. Moreover, r_s and r_d impact the GC size, but
 444 not its average affinity, as selection and death affect all individuals of the GC
 445 independently from their fitness.

446
 447 It can be interesting to observe the evolution of the expected average affini-
 448 ty within the GC during time. Numerical simulations of our model show that
 449 the expected average affinity in the GC converges through $N/2$, independently
 450 from the affinity of the first naive B-cell (Figure 3 (b)). This depends on the
 451 mutational model we choose for these simulations. Indeed, providing that the
 452 GC is in a situation of explosion, for t big enough the distribution of GC clones
 453 within the affinity classes is governed by the stationary distribution of matrix
 454 Q_N . Since for Q_N given by Definition 9 one can prove that the stationary
 455 distribution over $\{0, \dots, N\}$ is the binomial probability distribution [5], the
 456 average affinity within the GC will quickly stabilizes at a value of $N/2$. Note
 457 that for these simulations we chose $N = 10$, hence affinities are in the range
 458 $[0, 10]$.

3.4.2 Evolution of the selected pool

The evolution of the number of selected B-cells during time necessarily depends on the evolution of the GC. In particular, let us suppose we are in the supercritical case, *i.e.* the extinction probability of the GC is strictly smaller than 1. Then, with positive probability, the GC explodes and so does the selected pool. On the other hand, if the GC extinguishes, the number of selected B-cells will stabilize at a constant value, as once a B-cell is selected it can only stay unchanged in the selected pool.

As demonstrated in Section 3.3, there exists an optimal value of the parameter r_s which maximizes the expected number of selected B-cells at time t . Figure 4 (a) evidences this fact. Moreover, as expected, simulations show that the expected size of selected B-cells at a given time t increases with the threshold \bar{a}_s chosen for positive selection (Figure 4 (b)). This is a consequence of Proposition 5: \bar{a}_s determines the number of elements of the sum $\sum_{k=0}^{\bar{a}_s} r_{i\ell} l_{\ell k}$.

Figure 4 (c) underlines the correspondence between theoretical results given by Proposition 4 and numerical values obtained by simulating the evolutionary process described by Definition 3. In particular Figure 4 (c) shows the expected (resp. average) number of selected B-cells produced until time $t = 15$ depending on the threshold chosen for positive selection, \bar{a}_s .

Remark 5 We recall that values expressed on y-axes of all graphs in Figure 4 (and later in Figures 8 to 10) describe the expected number of some groups of B-cells (*e.g.* GC B-cells, output B-cells) generated at a given time step or after a given number of maturation cycles. Henceforth this is an adimensional number. It is of course envisageable to translate these values into concentrations of some specific B-cell phenotypes into *e.g.* blood or tissue samples in order to interpret theoretical results and compare them to biological data.

4 Extensions of the model

Proceeding as in Section 3.2, we can define and study many different models of affinity-dependent selection. Here we propose a model in which we perform only positive selection and a model reflecting a Darwinian evolutionary system, in which the selection is only negative. For the latter, we will take into account only $N + 2$ types instead of $N + 3$: we do not have to consider a selected pool. Indeed the selected population remains in the GC. Here below we give the definitions of both models. In Section 4.1 we formalize these problems mathematically, then in Section 4.2 we show some numerical results.

496 4.1 Definitions and results

497 Let us consider the process described in Definition 3. We change only the
 498 selection mechanism.

499 **Definition 10 (Positive selection)** If a B-cell submitted to selection be-
 500 belongs to an affinity class with index greater than \bar{a}_s , nothing happens. Other-
 501 wise, the B-cell exits the GC pool and reaches the selected pool.

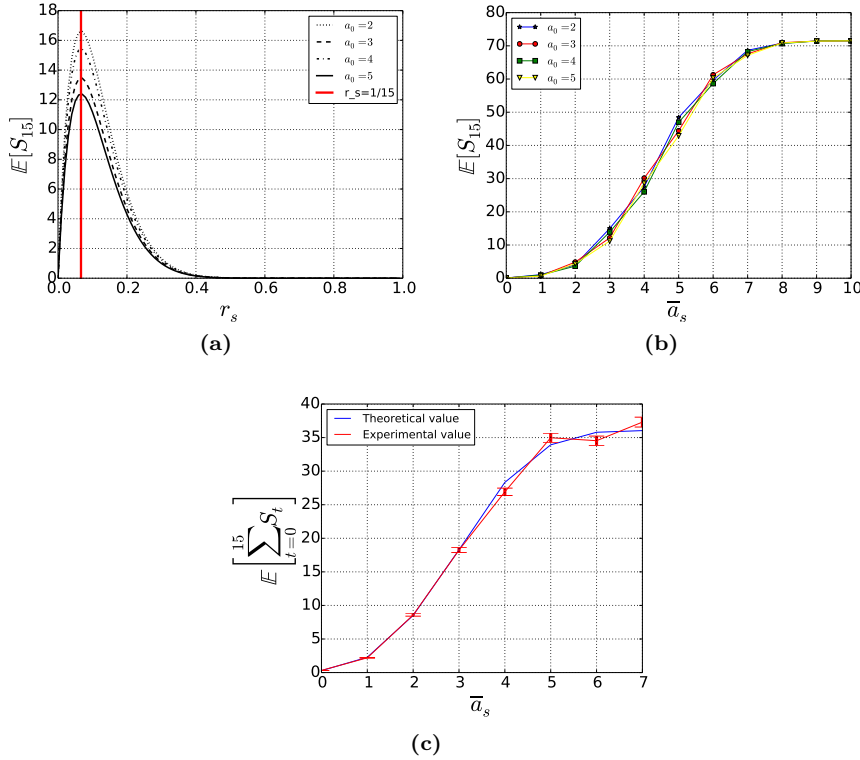
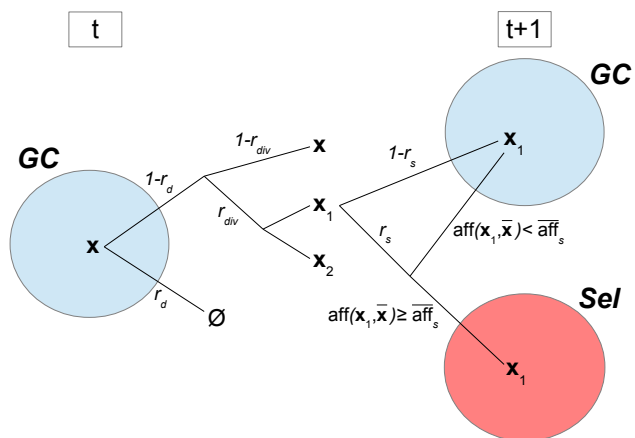
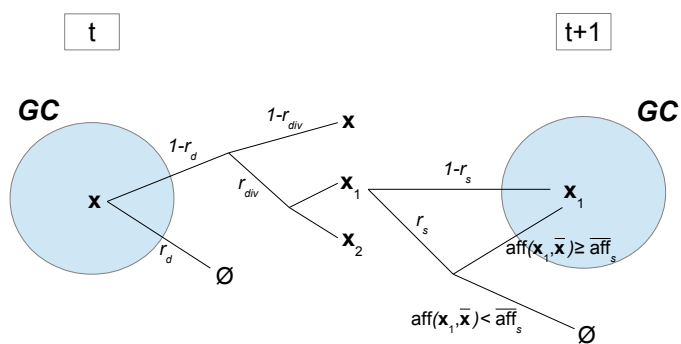


Figure 4: (a-b) Expected number of selected B-cells for the time step $t = 15$ for different values of a_0 , depending on r_s and \bar{a}_s respectively. There exists an optimal value of r_s maximizing the expected number of selected B-cells for a given generation. This value is independent from a_0 and is equal to $1/t$ as demonstrated in Proposition 6: the red vertical line in (a) corresponds to this value. (c) Comparison between the expected number of selected B-cells until time t given by evaluation of the theoretical formula (Equation (9)), and the empirical value obtained as the mean over 4000 simulations. Vertical bars denotes the corresponding estimated standard deviations. Here $N = 7$ and $r_s = 0.3$.



(a) Positive selection



(b) Negative selection

Figure 5: Schematic representations of models described (a) by Definitions 10 and (b) by Definitions 11 of exclusively positive (resp. exclusively negative) selection.

502 **Definition 11 (Negative selection)** If a B-cell submitted to selection be-
 503 longs to an affinity class with index greater than \bar{a}_s , it dies. Otherwise, nothing
 504 happens.

505 In Figure 5 we represent schematically both processes of positive selection
 506 and of negative selection. It is clear from Figure 5 (b) that in the case of
 507 Definition 11 we do not need to consider the selected pool anymore.

508 *Positive selection*

509 **Definition 12** Let $\mathbf{Z}_t^{+(\mathbf{i})} = (Z_{t,0}^{+(\mathbf{i})}, \dots, Z_{t,N+2}^{+(\mathbf{i})})$, $t \geq 0$ be a MC where for
 510 all $0 \leq j \leq N$, $Z_{t,j}^{+(\mathbf{i})}$ describes the number of GC B-cells belonging to the
 511 j^{th} -affinity class with respect to $\bar{\mathbf{x}}$, $Z_{t,N+1}^{+(\mathbf{i})}$ the number of selected B-cells
 512 and $Z_{t,N+2}^{+(\mathbf{i})}$ the number of dead B-cells at generation t , when the process
 513 is initiated in state $\mathbf{i} = (i_0, \dots, i_N, 0, 0)$, and following the evolutionary model
 514 described by Definition 10.

515 Let us denote by $\mathcal{M}^+ = (m_{ij}^+)_{0 \leq i, j \leq N+2}$ the matrix containing the expected
 516 number of type- j offspring of a type- i cell corresponding to the model
 517 defined by Definition 10. We can explicitly write the value of all m_{ij}^+ depending
 518 on r_d , r_{div} , r_s , and the elements of matrix \mathcal{Q}_N .

Proposition 8 \mathcal{M}^+ is a $(N+3)^2$ matrix, which we can define as a block matrix in the following way:

$$\mathcal{M}^+ = \begin{pmatrix} \mathcal{M}_1^+ & \mathcal{M}_2^+ \\ \mathbf{0}_{2 \times (N+1)} & \mathcal{I}_2 \end{pmatrix}$$

519 *Where:*

- 520 – $\mathcal{M}_1^+ = (m_{1,ij}^+)$ is a $(N+1)^2$ matrix. For all $i \in \{0, \dots, N\}$:
 521 – $\forall j \leq \bar{a}_s$: $m_{1,ij}^+ = 2(1-r_d)r_{div}(1-r_s)q_{ij} + (1-r_d)(1-r_{div})(1-r_s)\delta_{ij}$
 522 – $\forall j > \bar{a}_s$: $m_{1,ij}^+ = 2(1-r_d)r_{div}q_{ij} + (1-r_d)(1-r_{div})\delta_{ij}$
 523 where δ_{ij} is the Kronecker delta.
- 524 – $\mathcal{M}_2^+ = (m_{2,ij}^+)$ is a $(N+1) \times 2$ matrix where for all $i \in \{0, \dots, N\}$, $m_{2,i1}^+ =$
 525 $m_{2,i1}$, and $m_{2,i2}^+ = r_d$. We recall that $m_{2,i1}$ is the i^{th} -component of the first
 526 column of matrix \mathcal{M}_2 , given in Proposition 2.

527 *Negative selection*

528 **Definition 13** Let $\mathbf{Z}_t^{-(\mathbf{i})} = (Z_{t,0}^{-(\mathbf{i})}, \dots, Z_{t,N+1}^{-(\mathbf{i})})$, $t \geq 0$ be a MC where for
 529 all $0 \leq j \leq N$, $Z_{t,j}^{-(\mathbf{i})}$ describes the number of GC B-cells belonging to the
 530 j^{th} -affinity class with respect to $\bar{\mathbf{x}}$ and $Z_{t,N+1}^{-(\mathbf{i})}$ the number of dead B-cells
 531 at generation t , when the process is initiated in state $\mathbf{i} = (i_0, \dots, i_N, 0)$, and
 532 following the evolutionary model described by Definition 11.

533 Let us denote by $\mathcal{M}^- = (m_{ij}^-)_{0 \leq i, j \leq N+1}$ the matrix containing the expected
 534 number of type- j offspring of a type- i cell corresponding to the model
 535 defined by Definition 13.

Proposition 9 \mathcal{M}^- is a $(N+2)^2$ matrix, which we can define as a block matrix in the following way:

$$\mathcal{M}^- = \begin{pmatrix} \mathcal{M}_1^- & \mathbf{m}_2^- \\ \mathbf{0}'_{N+1} & 1 \end{pmatrix}$$

536 Where:

- 537 – $\mathcal{M}_1^- = (m_{1,ij}^-)$ is a $(N+1)^2$ matrix. For all $i \in \{0, \dots, N\}$:
- 538 – $\forall j \leq \bar{a}_s$: $m_{1,ij}^- = 2(1-r_d)r_{div}q_{ij} + (1-r_d)(1-r_{div})\delta_{ij}$
- 539 – $\forall j > \bar{a}_s$: $m_{1,ij}^- = 2(1-r_d)r_{div}(1-r_s)q_{ij} + (1-r_d)(1-r_{div})(1-r_s)\delta_{ij}$
- 540 – \mathbf{m}_2^- is a $(N+1)$ column vector s.t. for all $i \in \{0, \dots, N\}$ $m_i^+ = m_{2,i2}$,
- 541 $m_{2,i2}$ being the i^{th} -component of the second column of matrix \mathcal{M}_2 , given
- 542 in Proposition 2.
- 543 – $\mathbf{0}'_{N+1}$ is a $(N+1)$ row vector composing of zeros.

544 We do not prove Propositions 8 and 9, since the proofs are the same as for

545 Proposition 2 (Appendix B).

546 Results stated in Proposition 4 hold true for these new models, by simply

547 replacing matrix \mathcal{M} with \mathcal{M}^+ (resp. \mathcal{M}^-). Of course, in the case of negative

548 selection, as we do not consider the selected pool, we only refer to (6) and (7)

549 quantifying the growth and average affinity of the GC. Matrix $\widetilde{\mathcal{M}}$ is the same

550 for both models as only selection principles change.

551

552 Because of peculiar structures of matrices \mathcal{M}^+ and \mathcal{M}^- , we are not able

553 to compute explicitly their spectra. Henceforth we can not give an explicit

554 formula for the extinction probability or evaluate the optimal values of the

555 selection rate r_s as we did in Sections 3.2 and 3.3.

556

557 Nevertheless, by using standard arguments for positive matrices, the great-

558 est eigenvalue of both matrices \mathcal{M}_1^+ and \mathcal{M}_1^- can be bounded, and hence

559 give sufficient conditions for extinction. Indeed, from classical results about

560 multi-type GW processes, the value of the greatest eigenvalue allows to dis-

561 criminate between subcritical case (*i.e.* extinction probability equal to 1) and

562 supercritical case (*i.e.* extinction probability strictly smaller than 1) [3].

563

564 **Proposition 10** Let \mathbf{q}^+ (resp. \mathbf{q}^-) be the extinction probability of the GC

565 for the model corresponding to matrix \mathcal{M}_1^+ (resp. \mathcal{M}_1^-).

- 566 – If $r_{div} \leq \frac{r_d}{1-r_d}$, then $\mathbf{q}^+ = \mathbf{q}^- = \mathbf{1}$.
- 567
- 568 – If $r_s < 1 - \frac{1}{(1-r_d)(1+r_{div})}$, then $\mathbf{q}^+ < \mathbf{1}$ and $\mathbf{q}^- < \mathbf{1}$.

569 *Proof* Since both matrices \mathcal{M}_1^+ and \mathcal{M}_1^- are strictly positive matrices, the

570 Perron Frobenius Theorem insures that the spectral radius is also the greatest

571 eigenvalue. Then the following classical result holds [23]:

Theorem 1 Let $A = (a_{ij})$ be a square nonnegative matrix with spectral radius $\rho(A)$ and let $r_i(A)$ denote the sum of the elements along the i^{th} -row of A . Then:

$$\min_i r_i(A) \leq \rho(A) \leq \max_i r_i(A)$$

Simple calculations provide:

$$\begin{aligned} \min_i r_i(\mathcal{M}_1^+) &= (1-r_d)(1+r_{div}) - r_s(1-r_d) \left(2r_{div} \min_i \sum_{j=0}^{\bar{a}_s} q_{ij} + 1 - r_{div} \right) \\ \max_i r_i(\mathcal{M}_1^+) &= (1-r_d)(1+r_{div}) - 2r_s r_{div} (1-r_d) \max_i \sum_{j=0}^{\bar{a}_s} q_{ij} \\ \min_i r_i(\mathcal{M}_1^-) &= (1-r_d)(1+r_{div}) - r_s(1-r_d) \left(2r_{div} \min_i \sum_{j=\bar{a}_s+1}^N q_{ij} + 1 - r_{div} \right) \\ \max_i r_i(\mathcal{M}_1^-) &= (1-r_d)(1+r_{div}) - 2r_s r_{div} (1-r_d) \max_i \sum_{j=\bar{a}_s+1}^N q_{ij} \end{aligned}$$

The result follows by observing that for all $i \in \{0, \dots, N\}$, $0 \leq \sum_{j=0}^{\bar{a}_s} q_{ij}$, $\sum_{j=\bar{a}_s+1}^N q_{ij} \leq 1$, and applying Theorem 3. \square

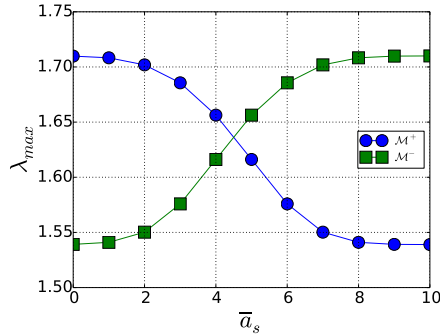


Figure 6: Dependence of greatest eigenvalues of matrices \mathcal{M}^+ (blue circles) and \mathcal{M}^- (green squares) respectively on \bar{a}_s for $N = 10$, $r_{div} = 0.9$, $r_d = r_s = 0.1$. Hence $(1-r_d)(1+r_{div})(1-r_s) = 1.539$ and $(1-r_d)(1+r_{div}) = 1.71$.

572 *Remark 6* One can intuitively obtain the second claim of Proposition 10, as
 573 this condition over the parameters implies that the probability of extinction
 574 of the GC for the model underlined by matrix \mathcal{M}_1 of positive and negative
 575 selection is strictly smaller than 1 (Proposition 1). Indeed keeping the same

576 parameters for all models, the size of the GC for the model of positive and ne-
 577 gative selection is smaller than the size of GCs corresponding to both models
 578 of only positive and only negative selection. Consequently if the GC corre-
 579 sponding to \mathcal{M} has a positive probability of explosion, it will be necessarily
 580 the same for \mathcal{M}^+ and \mathcal{M}^- .

581 *Remark 7* The values of both $\rho(\mathcal{M}_1^+)$ and $\rho(\mathcal{M}_1^-)$ depend on \bar{a}_s , varying from
 582 a minimum of $(1-r_d)(1+r_{div})(1-r_s)$ and a maximum of $(1-r_d)(1+r_{div})$.
 583 Figure 6 evidences the dependence on \bar{a}_s of the spectral radius of \mathcal{M}_1^+ and
 584 \mathcal{M}_1^- , using matrix \mathcal{Q}_N given by Definition 9 as transition probability matrix.

585 Remark 7 and Figure 6 evidences that, conversely to the previous case
 586 of positive and negative selection, in both cases of exclusively positive (resp.
 587 exclusively negative) selection the parameter \bar{a}_s plays an important role in
 588 the GC dynamics, affecting its extinction probability. In particular, keeping
 589 unchanged all other parameters, if $\bar{a}_s \rightarrow N$ (resp. $\bar{a}_s \rightarrow 0$), then $\rho(\mathcal{M}_1^+)$ (resp.
 590 $\rho(\mathcal{M}_1^-)$) $\rightarrow (1-r_d)(1+r_{div})(1-r_s)$, which implies $\mathbf{q}^+ \rightarrow \mathbf{1}$ (resp. $\mathbf{q}^- \rightarrow \mathbf{1}$). From
 591 a biological viewpoint we expect that the GC dynamics should be influenced
 592 by the threshold required for selection. B-cell affinity determines the ability
 593 of a B-cell to internalize antigen, and present it to Tfh cells to receive appropri-
 594 ate rescue signals. Experimental evidence indicates that B-cell affinity is
 595 extremely important to determine differential decision in GCs, *i.e.* if a B-cell
 596 submitted to selection is committed to become either a plasma cell or a mem-
 597 ory B-cell, recycle back to the dark zone to perform further rounds of somatic
 598 hypermutations, or die [16].

599

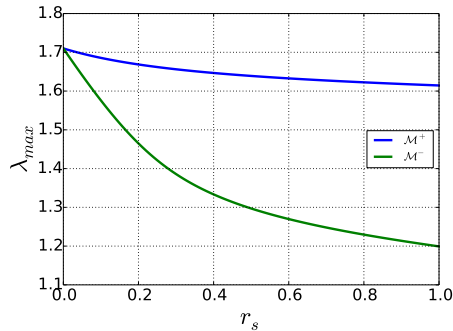


Figure 7: Dependence of greatest eigenvalues of matrices \mathcal{M}^+ (blue) and \mathcal{M}^- (green) respectively on r_s for $N = 10$, $r_{div} = 0.9$, $r_d = 0.1$, $\bar{a}_s = 3$.

600 In Figure 7 we plot the dependence of greatest eigenvalues of both matrices
 601 \mathcal{M}^+ and \mathcal{M}^- with respect to r_s . We fix $r_d = 0.1$ and $r_{div} = 0.9$ as for Figure
 602 2. One can note that with this parameter set and if the threshold for positive
 603 selection \bar{a}_s is chosen not “too small” nor “too large” with respect to N , then

the greatest eigenvalue for both matrices is always greater than 1 independently from r_s , *i.e.* the extinction probability is always strictly smaller than 1. From a biological viewpoint we expect that a physiological threshold for positive selection should not be too strict nor too weak. Indeed, a too demanding threshold for positive selection is not optimal since B-cells should have gained an extremely high affinity in order to be positive selected, which would at least require too much time, avoiding a prompt immune response against the invading pathogen. On the other hand, a too weak threshold results in an unchallenging affinity maturation process: almost any B-cell would be positive selected, irrespective from its affinity level with respect to the presented antigen. This could also entail the generation of auto-reactive clones.

4.2 Numerical simulations

The evolution of GCs corresponding to matrices \mathcal{M}^+ and \mathcal{M}^- respectively are complementary. Moreover, in both cases, keeping all parameters fixed one expects a faster expansion if compared to the model of positive and negative selection, since the selection acts only positively (resp. negatively) on good (resp. bad) clones. In particular, the model of negative selection corresponds to the case of 100% of recycling, meaning that all positively selected B-cells stay in the GC for further rounds of mutation, division and selection.

Figure 8 shows the dependence on \bar{a}_s of the GC size and fitness, comparing \mathcal{M}^+ (left column) and \mathcal{M}^- (right column). Indeed, for these models the GC dynamics depends on the selection threshold, conversely to the previous case of positive and negative selection, and not only on the selection rate. The effects of \bar{a}_s on the GC are perfectly symmetric: it is interesting to observe that when both selection mechanisms are coupled, then \bar{a}_s does not affect the GC dynamics anymore, as shown for instance in Figure 3 (a). Moreover, Figures 8 (c,d) evidence the existence of a value of \bar{a}_s that minimizes (resp. maximizes) the expected average affinity in the GC for \mathcal{M}^+ (resp. \mathcal{M}^-). In both cases this value is approximately $N/2$. This certainly depends on the transition probability matrix chosen for the mutational model, which converges to a binomial probability distribution over $\{0, \dots, N\}$.

The evolution of the selected pool for the model of positive selection have some important differences if compared to the model described in Section 3. For instance, it is not easy to identify an optimal value of r_s which maximizes the expected number of selected B-cells at time t . Indeed it depends both on a_0 and \bar{a}_s : if $a_0 \leq \bar{a}_s$ we find curves similar to those plotted in Figure 4 (a), otherwise Figure 9 (a) shows a substantial different behavior. Indeed, if $a_0 > \bar{a}_s$, choosing a big value for r_s does not negatively affect the number of selected B-cells at time t . In this case, for the first time steps no (or a very few) B-cells will be positively selected, since they still need to improve their affinity to the

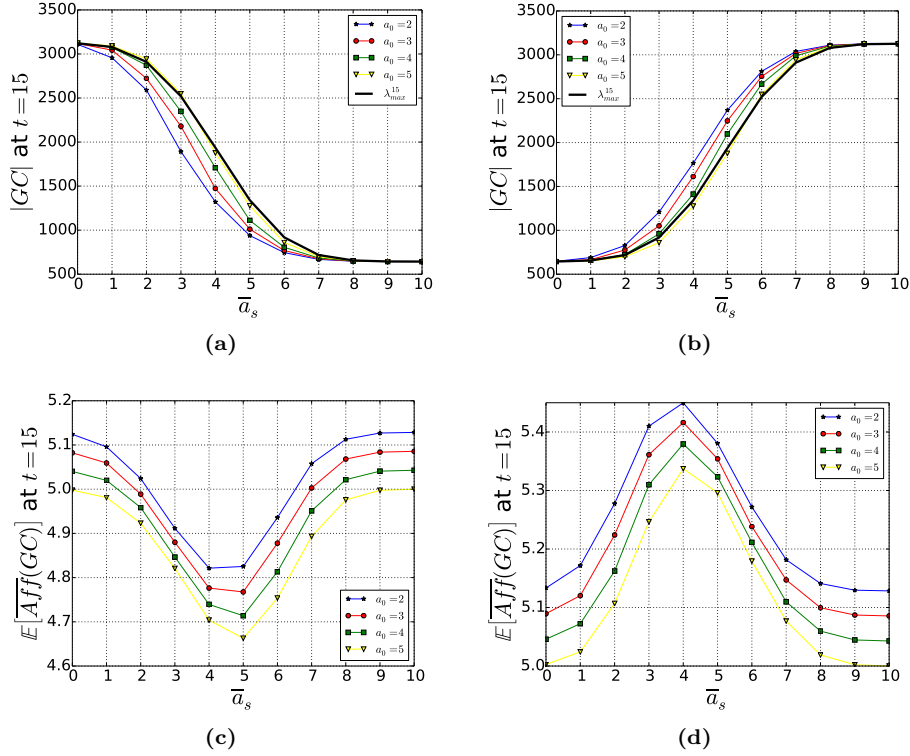


Figure 8: (a,b) Dependence of the expected size of the GC after 15 time steps on \bar{a}_s for different values of a_0 . The thick black line corresponds in both figures to the value of the greatest eigenvalue of matrices \mathcal{M}_1^+ and \mathcal{M}_1^- respectively, raised to the power of $t = 15$ (see Figure 6). Note that thanks to Proposition 1 we know that for this parameter choice the expected size of the GC for the model of positive and negative selection corresponds to $((1 - r_d)(1 + r_{div})(1 - r_s))^{15}$, which is equivalently λ_{max}^{15} for $\bar{a}_s = 10$ in Figure 8 (a) or λ_{max}^{15} for $\bar{a}_s = 0$ in Figure 8 (b). (c,d) Dependence of the expected average affinity in the GC after $t = 15$ time steps on \bar{a}_s for different values of a_0 . The left column of Figure 8 refers to the model of positive selection, while the right column to the model of negative selection.

647 target. Therefore, they stay in the GC and continue to proliferate for next
648 generations. This fact is further underlined in Figure 9 (b), where we estimate
649 numerically the optimal r_s^* which maximizes the expected number of selected
650 B-cells at time t . Simulations show that for $a_0 \leq \bar{a}_s$ the value of r_s^* for the
651 model of positive selection is really close to the one obtained by Proposition
652 6. On the other hand if we start from an initial affinity class $a_0 > \bar{a}_s$ the result
653 we obtain is substantially different from the previous one, especially for small

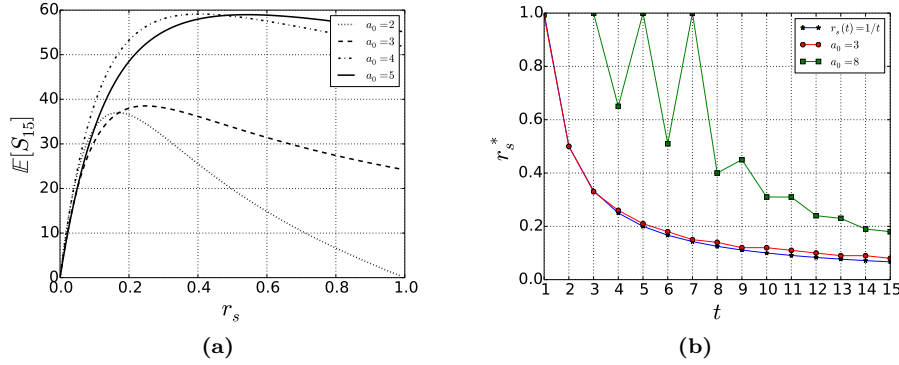


Figure 9: Model of positive selection. (a) Expected number of selected B-cells for the time step $t = 15$ for different values of a_0 , depending on r_s . (b) Estimation of the optimal r_s^* maximizing the expected number of selected B-cells for a given generation, comparing the model of positive selection for different values of a_0 and the model described in Section 3 (we plot the exact value, $r_s(t) = 1/t$, as obtained by Proposition 6). In (b), for simulations corresponding to the model of positive selection we set $\bar{a}_s = 5$.

654 t . Moreover we observe important oscillations, which are probably due to the
 655 mutational model, and to the fact that the total GC size is still small for small
 656 t , since the process starts from a single B-cell. Nevertheless, it seems that for
 657 t big enough also in this case the value of r_s^* tends to approach $1/t$.

658

659 Since in the case of negative selection there is no selected pool, one can
 660 suppose that at a given time t the process stops and all clones in the GC pool
 661 exit the GC as selected clones. Hence it can be interesting to compare the selected
 662 pool of the model of positive selection and the GC pool of the model of
 663 negative selection at time t . Clearly to make these two compartments comparable, the
 664 main parameters of both systems have to be opportunely chosen. In
 665 Figure 10 we compare the size and average fitness of the selected pool for \mathcal{M}^+
 666 and the GC for \mathcal{M}^- at time $t = 30$. We test different values of the parameter
 667 r_s . In particular, we observe that increasing r_s the GC size for the model of
 668 negative selection decreases and its average fitness increases. For the parameter
 669 choices we made for these simulations, Figure 10 (a) shows that the size of the
 670 GC for \mathcal{M}^- is comparable to the size of the selected pool for \mathcal{M}^+ at time
 671 $t = 30$ if, keeping all other parameters fixed, $r_s = 0.15$ for \mathcal{M}^- . Nevertheless,
 672 this does not implies a comparable value for the average affinity: the clones
 673 of the selected pool for \mathcal{M}^+ have a significantly greater average affinity than
 674 those of the GC for \mathcal{M}^- . In order to increase the average fitness in the GC
 675 for the model of negative selection one has to consider greater values for the
 676 parameter r_s , but this affects the probability of extinction of the process.

677

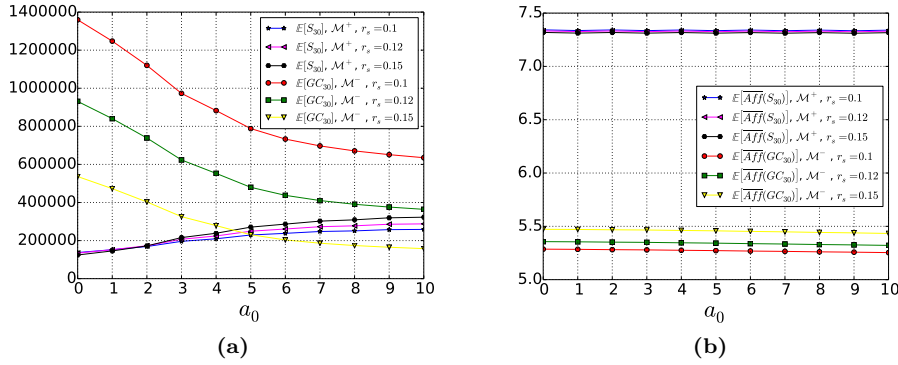


Figure 10: (a) Expected number of B-cells which have been selected until time $t = 30$ for \mathcal{M}^+ compared to the expected size of the GC for \mathcal{M}^- for different values of r_s . (b) Expected corresponding average affinity for the selected pool (case of positive selection) and the GC (case of negative selection). For some choice of the parameter r_s , the size of the selected pool for \mathcal{M}^+ , and the GC for \mathcal{M}^- , are comparable. Nevertheless, the corresponding average affinities are significantly different.

678 We can expect this discrepancy between the average affinity for the selected
679 pool for \mathcal{M}^+ and the one of the GC for \mathcal{M}^- . Indeed, in the first case we are
680 looking to all those B-cells which have been positive selected, hence belong at
681 most to the \bar{a}_s^{th} -affinity class. On the contrary in the case of \mathcal{M}^- , we consider
682 the average affinity of all B-cells which are still alive in the GC at a given time
683 step. Among these clones, if $r_s < 1$, with positive probability there are also
684 individuals with affinity smaller than the one required for escaping negative
685 selection. They remain in the GC because they have not been submitted to
686 selection. These B-cells make the average affinity decrease. Of course r_s is not
687 the only parameter affecting the quantities plotted in Figure 10. In particular,
688 one can observe that choosing a greater value for \bar{a}_s also have a significant
689 effect over the growth of both pools, as discussed in Remark 7.

690 5 Conclusions and perspectives

691 In this paper we formalize and analyze a mathematical model describing an
692 evolutionary process with affinity-dependent selection. We use a multi-type
693 GW process, obtaining a discrete-time probabilistic model, which includes
694 division, mutation, death and selection. This is employed in the context of an-
695 tibody affinity maturation in GCs. We believe that a probabilistic approach is
696 well suited to the study of Darwinian-like processes such as the one taking place
697 in GCs during an immune response. Indeed, this kind of approaches allows to
698 better take into account local inhomogeneities related to the discrete nature

699 of cells and stochastic fluctuations intrinsic to these processes, conversely to
700 more popular deterministic continuum approaches. There, cell concentrations
701 are described by a set of coupled ODEs changing deterministically and contin-
702 uously during time, which has many computational advantages and has often
703 been employed to model biological systems (*e.g.* [21, 15, 25] for applications to
704 the GC reaction). In the main model developed here, we choose a selection
705 mechanism which acts both positively and negatively on individuals submit-
706 ted to selection. This choice is motivated by the fact that there are biological
707 evidence supporting both kind of selection mechanisms: positive affinity-based
708 selection by antigen binding as well as selection-dependent apoptosis [38, 16].
709 The simplified mathematical framework proposed here allow to investigate how
710 different kind of B-cell population evolves during the immune response both
711 in the initial explosion phase and in the later relaxation phase of typical GCs.
712 Indeed, mathematical analysis of the model leads to build matrix \mathcal{M} , which
713 contains the expectations of each type (Proposition 2) and enables to describe
714 the average behavior of all components of the process. Moreover, thanks to the
715 spectral decomposition of \mathcal{M} we were able to obtain explicitly some formulas
716 giving the expected dynamics of all types. In addition, we exhibited an optimal
717 value of the selection rate maximizing the expected number of selected clones
718 for the t^{th} -generation (Proposition 6).

719
720 This is one possible choice of the selection mechanism. From a mathema-
721 tical point of view, matrix \mathcal{M} is particularly easy to manipulate, as we can
722 obtain explicitly its spectrum. On the other hand, the positive and negative
723 selection model leads, for example, to a selection threshold that does not have
724 any impact on the evolution of the GC size. From a biological point of view
725 this seems counterintuitive, since we could expect that the GC dynamics is
726 sensible to the minimal fitness required for positive selection. Moreover, this
727 process does not take into account any recycling mechanism, which has been
728 confirmed by experiments [39] and which improves GCs' efficiency. In addition,
729 we considered that only the selection mechanism is affinity dependent, while
730 in the GC reaction other mechanisms, such as the death and proliferation rate,
731 may depend on fitness [13, 1]. Of course it is possible to define models with
732 affinity-dependent division and death mechanisms with our formalism. This
733 would clearly lead to a more complicated model, which can be at least studied
734 numerically.

735
736 Mathematical tools used in Section 3 can be applied to define and study
737 other selection mechanisms. For instance in Section 4 we propose two variants
738 of the model analyzed in Section 3, in which selection acts only positively, resp.
739 only negatively. This Section shows how our mathematical environment can
740 be modified to describe different selection mechanisms, which can be studied
741 at least numerically. Moreover, it gives a deeper insight of the previous model
742 of positive and negative selection, by highlighting the effects of each selection
743 mechanism individually, when they are not coupled.

From a biological viewpoint there exist many possibilities to improve the models proposed in this paper. First of all it is extremely important to fix the system parameters, which have to be consistent with the real biological process. The choice of N defines the number of affinity level with respect to a given antigen. This value can be interpreted in different ways. On the one hand it can correspond to the number of key mutations observed during the process of Antigen Affinity Maturation, hence be even smaller than 10. On the other hand, each mutational event implies a change in the B-cell affinity, slight or not if it is a key mutation. In this case the affinity can be modeled as a continuous function, hence N corresponds to a possible discretization [41, 43]. To this choice corresponds an appropriate choice of the transition probability matrix defining the mutational model over the affinity classes, \mathcal{Q}_N . In most numerical simulations we set $N = 10$, which is a sensible value since experimentalists observe that high-affinity B-cells differ in their BCR coding gene by about 9 mutations from germline genes [15, 45]. Nevertheless all mathematical results are independent from this choice and hold true for all $N \geq 1$. The selection, division and death rates have also an important impact in the GC and selected pool dynamics: in the simulations we set them in order to be in a case of explosion of the GC hence appreciate the effects of all parameters over the main quantities, but they are not biologically justified. For instance, the typical proliferation rate of a B-cell has been estimated between 2 and 4 per day and in the literature we found B-cell death rates of the order of 0.5-0.8 per day [22, 45, 18]. Hence, if we suppose that a single time step corresponds *e.g.* to 6 hours, a consistent proliferation rate would be $r_{div} \simeq 0.75$, while the death rate r_d should be around 0.175. Since over a 6 hours period about 50% of B-cells transit from the DZ to the LZ, where they compete for positive selection signaling [6, 36], we should choose $r_s \leq 0.5$. It could be further characterized taking into account its tightly relation with the time of GC peak, as highlighted in Section 3.3.

In Section 3.3 we have explicitly determined the optimal value of the selection rate maximizing the production of output cells at time t for the main model of positive and negative selection. It is equal to $1/t$ independently from all other parameters. Moreover, numerical estimations for the model of positive selection (Section 4.2) suggest that also in this case there exists an optimal value of $r_s(t)$, which tends to $1/t$ at least for t big enough. One has to interpret this result as the ideal optimal strength of the selection pressure to obtain a peak of the GC production of output cells at a given time step. For example, let us suppose again that a time step corresponds to 6 hours. The peak of the GC reaction has been measured to be close to day 12 [42], *i.e.* after ~ 48 maturation cycles in our model: for the kind of models we built and analyzed in this paper, a constant selection pressure r_s of $1/48 \simeq 0.02$ assures that the production of plasma and memory B-cells at the GC peak is maximized. Note that with the parameter choice $r_d = 0.175$, $r_{div} = 0.75$ and $r_s = 0.02$, the extinction probability of the GC is $\simeq 0.3^{z_0}$, z_0 being the number of initial seed cells. Since the extinction probability is strictly smaller than 1, such a GC

will explode with high probability and will be able to assure an intense and efficient immune response.

The particular form $1/t$ of the optimal selection rate for the t^{th} generation obtained in Section 3.3 certainly derives from the simplified structure of the model of positive and negative selection, even if this trend is further confirmed in the model of exclusively positive selection. Nevertheless it should be interesting to test the existence of an inverse relation between the selection rate and the timing of GC peak. Selection pressure can be quantified *e.g.* through comparative analysis between groups of sequences derived from different germline V(D)J segments, as proposed by the statistical framework for Bayesian estimation of Antigen-driven SElectIoN (BASELINE) [44]. BASELINE takes into account both mutation targeting bias and substitution bias and identifies point mutations grouped by location. Moreover it addresses the question of positive versus negative selection: positive selection is identified by an increased frequency of replacements, while a decreased frequency indicates negative selection. According to [44], the selection strength seems to vary and also switch from positive to negative in a different way depending on the location, *i.e.* if we are looking to complementary determining regions (CDRs), which are more significant for functional selection, or to framework regions. This gives stronger motivation to analyse both kind of selection mechanisms, acting both separately and simultaneously, and observe their effects over affinity maturation, as we have done in this paper using our simplified mathematical framework.

In our models the selection pressure is constant. Since the optimal selection rate above depends on time, this suggests to go further in this direction. Moreover, a time-dependent selection pressure would allow to take into account, for instance, the early GC phase in which simple clonal expansion of B-cells with no selection occurs [10]. The hypothesis of a selection pressure changing over time can be easily integrated in our model. Indeed let us suppose that a selection rate $r_{s,1}$ until time t_1 and $r_{s,2}$ for all $t > t_1$ are fixed. Starting from the initial condition \mathbf{i} the expectations of each type at time t are given by $(\mathbf{i}\mathcal{M}_{r_{s,1}}^t)$ if $t \leq t_1$ and $(\mathbf{i}\mathcal{M}_{r_{s,1}}^{t_1}\mathcal{M}_{r_{s,2}}^{t-t_1})$ if $t > t_1$, where $\mathcal{M}_{r_{s,i}}$ is the matrix containing the expectations of each type for an evolutionary process with constant selection rate $r_{s,i}$, $i = 1, 2$. In Figure 11 we plot the expected evolution during time of all types considering an increasing selection rate. We evaluate the expectations of all types following a process with positive and negative selection. We set $r_s = 0$ until $t = 5$, $r_s = 0.1$ from $t = 6$ to $t = 15$ and $r_s = 0.3$ for $t > 15$. Numerical simulations show that a time dependent selection rate allows initial explosion of the GC, and then progressive extinction, while when parameters are fixed, a GW process gives only rise either to explosion or to extinction, as shown above. The regulation and termination of the GC reaction has not yet been fully understood. In the literature, an increasing differentiation rate of GC B-cells is thought to be a good explanation [25], here we show that other

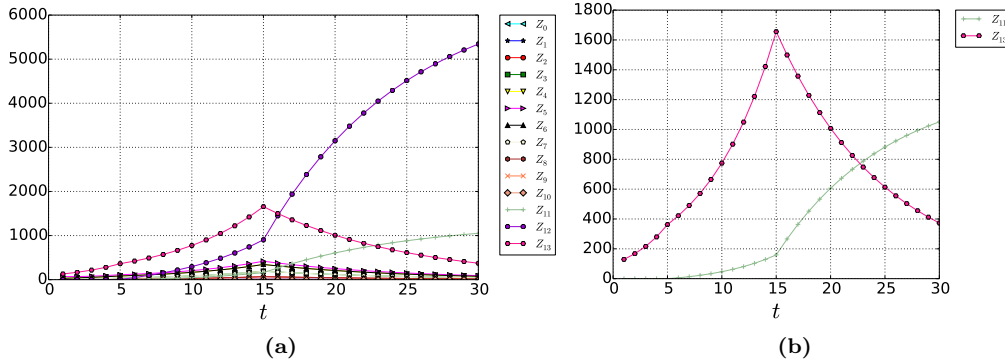


Figure 11: (a) Evolution during time of the expected value of all types for the model of positive and negative selection, with r_s varying during time and $N = 10$. In particular we set $r_s = 0$ until $t = 5$, $r_s = 0.1$ from $t = 6$ to $t = 15$ and $r_s = 0.3$ from $t = 16$ to $t = 30$. Z_{13} denotes the total size of the GC (*i.e.* $\sum_{k=0}^N Z_k$), and we recall that Z_{11} corresponds to selected B-cells and Z_{12} to dead B-cells. We set $r_{div} = 0.3$, $r_d = 0.005$ and $z_0 = 100$ initial naive B-cells. All initial B-cells belong to $a_0 = 5$, and the selection threshold is $\bar{a}_s = 3$. (b) Evolution during time of the expected total size of the GC and the selected pool respectively, for the same set of parameters as in Figure 11 (a).

836 reasons could be of importance as well. Similarly, we can let other parameters
 837 vary for fixed time intervals, as well as decide to alternatively switch on and off
 838 the mutational mechanism, as already proposed in [29]. This can be obtained
 839 by alternatively use the identity matrix in place of Q_N .

840

841 Applications of the models presented here to real biological problems and
 842 data should be further investigated. We propose here some contexts for which
 843 we believe that our kind of modeling approach could be employed to address
 844 biologically relevant questions.

845 Even if it is still extremely hard to have precise experimental information
 846 about the evolution of Antibody Affinity Maturation inside GCs, new refined
 847 techniques start to be available to measure clonal diversity in GCs. As an ex-
 848 ample, in [34] the authors combine multiphoton microscopy and sequencing
 849 to understand how different clonal diversification patterns can lead to efficient
 850 affinity maturation. The models we propose could be used to infer which are
 851 reasonable mutational transitional probability matrices and selection mecha-
 852 nisms/pressure to obtain such different scenario and infer if the tendency of
 853 GC to go or not through homogenizing selection is solely due to the hazard
 854 or if this is dependent on the kind of antigenic challenge and/or some specific
 855 characteristics of the host. If this is the case, these results could be particularly
 856 relevant *e.g.* in the context of vaccination design, where we are interested in
 857 find new way to improve the quality of the immune response after vaccination

challenge.

Another potential interesting application field is the study of some diseases entailing a dysfunction of the immune system, such as in particular Chronic Lymphocytic Leukemia (CLL), derived from antigen-experienced B-cells that differ in the level of mutations in their receptors [8]. This is the commonest form of leukemia in the Western world [12]. In CLL, leukemia B-cells can mature partially but not completely, are unable to opportunely undergo mutations in GCs, and survive longer than normal cells, crowding out healthy B-cells. Prognosis varies depending on the ability of host B-cells to mutate their antibody gene variable region. Even if major progresses have been made in the identification of molecular and cellular markers predicting the expansion of this disease in patients, the pathology remains incurable [11,12]. Our modeling approach could be employed to understand how an “healthy” mutational matrix is modified in patients affected by CLL, and if other mechanisms could contribute to get the prognosis worse. This could eventually provide suggestions about the causes that lead to CLL, and motivation for further research on possible treatments.

6 Acknowledgements

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989 Appendix

990 A Few reminders of classical results on GW processes

991 We recall here some classical results about GW processes we employed to derive Proposition
992 1 (Section 3.1). For further details the reader can refer to [14].

Definition 14 Let X be an integer valued rv, $p_k := \mathbb{P}(X = k)$ for all $k \geq 0$. Its probability generating function (pgf) is given by:

$$F_X(s) = \sum_{k=0}^{+\infty} p_k s^k$$

993 F_X is a convex monotonically increasing function over $[0, 1]$, and $F_X(1) = 1$. If $p_0 \neq 0$
994 and $p_0 + p_1 < 1$ then F is a strictly increasing function.

Definition 15 Given F , the pgf of a rv X , the iterates of F are given by:

$$\begin{aligned} F_0(s) &= s \\ F_1(s) &= F(s) \\ F_t(s) &= F(F_{t-1}(s)) \text{ for } t \geq 2 \end{aligned}$$

995 Proposition 11

- 996 (i) If $\mathbb{E}(X)$ exists (respectively $\mathbb{V}(X)$), then $\mathbb{E}(X) = F'_X(1)$ (respectively $\mathbb{V}(X) = F''_X(1) -$
997 $(\mathbb{E}(X))^2 + \mathbb{E}(X)$).
- 998 (ii) If X and Y are two integer valued independent rvs, then $X + Y$ is still an integer valued
999 rv and its pgf is given by $F_{X+Y} = F_X F_Y$.

Definition 16 We denote by η the extinction probability of the process $(Z_t)_{t \in \mathbb{N}}$:

$$\eta := \lim_{t \rightarrow \infty} F_t(0)$$

Theorem 2

- 1000 (i) The pgf of $Z_t^{(z_0)}$, $t \in \mathbb{N}$, which represents the population size of the t^{th} -generation
 1001 starting from $z_0 \geq 1$ seed cells, is $F_t^{(z_0)} = (F_t)^{z_0}$, F_t being the t^{th} -iterate of F (Equation
 1002 (2)).
 1003
 1004 (ii) The expected size of the GC at time t and starting from z_0 B-cells is given by:

$$\mathbb{E}(Z_t^{(z_0)}) = z_0 (\mathbb{E}(Z_t)) = z_0 (\mathbb{E}(Z_1))^t, \quad (13)$$

- 1005 (iii) η is the smallest fixed point of the generating function F , i.e. η is the smallest s s.t.
 1006 $F(s) = s$.
 1007 (iv) If $\mathbb{E}(Z_1) =: m$ is finite, then:
 1008 – if $m \leq 1$ then F has only 1 as fixed point and consequently $\eta = 1$;
 1009 – if $m > 1$ then F has exactly a fixed point on $[0, 1[$ and then $\eta < 1$.
 (v) Denoted by η_{z_0} the probability of extinction of $(Z_t^{(z_0)})$, one has:

$$\eta_{z_0} = \eta^{z_0}$$

1010 where η is given by (iii).

1011 Proposition 1 of Section 3.1 follows by applying Theorem 2 and Equation (1).

1012 B Proof of Proposition 2

1013 For all $j \in \{0, \dots, N+2\}$ the generating function of Z_j gives the number of offspring of each
 1014 type that a type j particle can produce. It is defined as follows:

$$f^{(j)}(s_0, \dots, s_{N+2}) = \sum_{k_0, \dots, k_{N+2} \geq 0} p^{(j)}(k_0, \dots, k_{N+2}) s_0^{k_0} \cdots s_{N+2}^{k_{N+2}}, \quad (14)$$

$$0 \leq s_\alpha \leq 1 \text{ for all } \alpha \in \{0, \dots, N+2\}$$

1015 where $p^{(j)}(k_0, \dots, k_{N+2})$ is the probability that a type j cell produces k_0 cells of type 0, k_1
 1016 of type 1, ..., k_{N+2} of type $N+2$ for the next generation.

1017 We denote:

- 1018 – $\mathbf{p}(\mathbf{k}) = (p^{(0)}(\mathbf{k}), \dots, p^{(N+2)}(\mathbf{k}))$, for $\mathbf{k} = (k_0, \dots, k_{N+2}) \in \mathbb{Z}_+^{N+3}$
 1019 – $\mathbf{f}(\mathbf{s}) = (f^{(1)}(\mathbf{s}), \dots, f^{(N+1)}(\mathbf{s}))$, for $\mathbf{s} = (s_0, \dots, s_{N+2}) \in \mathcal{C}^{N+3} := [0, 1]^{N+3}$

1020 Then the probability generating function of \mathbf{Z}_1 is given by:

$$\mathbf{f}(\mathbf{s}) = \sum_{\mathbf{k} \in \mathbb{Z}_+^{N+3}} \mathbf{p}(\mathbf{k}) \mathbf{s}^{\mathbf{k}}, \quad \mathbf{s} \in \mathcal{C}^{N+3} \quad (15)$$

Again, the generating function of \mathbf{Z}_t , $\mathbf{f}_t(\mathbf{s})$, is obtained as the t^{th} -iterate of \mathbf{f} , and it holds true that:

$$\mathbf{f}_{t+r}(\mathbf{s}) = \mathbf{f}_t[\mathbf{f}_r(\mathbf{s})], \quad \mathbf{s} \in \mathcal{C}^{N+3}.$$

Let $m_{ij} := \mathbb{E}[Z_{1,j}^{(i)}]$ the expected number of offspring of type j of a cell of type i in one generation. We collect all m_{ij} in a matrix, $\mathcal{M} = (m_{ij})_{0 \leq i, j \leq N+2}$. We have [3]:

$$m_{ij} = \frac{\partial f^{(i)}}{\partial s_j}(\mathbf{1})$$

1021 and:

$$\mathbb{E}[Z_{t,j}^{(i)}] = \frac{\partial f_t^{(i)}}{\partial s_j}(\mathbf{1}) \quad (16)$$

1022 Finally:

$$\mathbb{E}[\mathbf{Z}_t^{(1)}] = \mathbf{i}\mathcal{M}^t \quad (17)$$

1023 One can explicitly derive the elements of matrix \mathcal{M} for the process described in Defini-
1024 tion 13.

Proposition \mathcal{M} is a $(N+3) \times (N+3)$ matrix defined as a block matrix:

$$\mathcal{M} = \begin{pmatrix} \mathcal{M}_1 & \mathcal{M}_2 \\ \mathbf{0}_{2 \times (N+1)} & \mathcal{I}_2 \end{pmatrix}$$

1025 Where:

- 1026 – $\mathbf{0}_{2 \times (N+1)}$ is a $2 \times (N+1)$ matrix with all entries 0;
- 1027 – \mathcal{I}_n is the identity matrix of size n ;
- 1028 – $\mathcal{M}_1 = 2(1-r_d)r_{div}(1-r_s)\mathcal{Q}_N + (1-r_d)(1-r_{div})(1-r_s)\mathcal{I}_{N+1}$
- 1029 – $\mathcal{M}_2 = (m_{2,ij})$ is a $(N+1) \times 2$ matrix where for all $i \in \{0, \dots, N\}$:
- 1030 – if $i \leq \bar{a}_s$:

$$1031 \quad m_{2,i1} = (1-r_d)(1-r_{div})r_s + 2(1-r_d)r_{div}r_s \sum_{j=0}^{\bar{a}_s} q_{ij},$$

$$1032 \quad m_{2,i2} = r_d + 2(1-r_d)r_{div}r_s \sum_{j=\bar{a}_s+1}^N q_{ij}$$

- 1033 – if $i > \bar{a}_s$:

$$1034 \quad m_{2,i1} = 2(1-r_d)r_{div}r_s \sum_{j=0}^{\bar{a}_s} q_{ij},$$

$$1035 \quad m_{2,i2} = r_d + (1-r_d)(1-r_{div})r_s + 2(1-r_d)r_{div}r_s \sum_{j=\bar{a}_s+1}^N q_{ij}$$

1036 *Proof* One has to compute all $f^{(i)}(\mathbf{s})$ for $i = 0, \dots, N+2$, which depend on $r_d, r_{div}, r_s,$
1037 \bar{a}_s and the elements of \mathcal{Q}_N . First, the elements of the $(N+2)^{\text{th}}$ and $(N+3)^{\text{th}}$ -lines are
1038 obviously determined: all selected (resp. dead) cells remain selected (resp. dead) for next
1039 generations, as they can not give rise to any other cell type offspring (we do not take into
1040 account here any type of recycling mechanism). Let $i \in \{0, \dots, N\}$ be a fixed index: we
1041 evaluate m_{ij} for all $j \in \{0, \dots, N+2\}$. The first step is to determine the value of $p^{(i)}(\mathbf{k})$ for
1042 $\mathbf{k} = (k_0, \dots, k_{N+2}) \in \mathbb{Z}_+^{N+3}$. There exists only a few cases in which $p^{(i)}(\mathbf{k}) \neq 0$, which can
1043 be explicitly evaluated:

$$1044 \quad - p^{(i)}(0, \dots, 0, 1) = \begin{cases} r_d & \text{if } i \leq \bar{a}_s \\ r_d + (1-r_d)(1-r_{div})r_s & \text{otherwise} \end{cases}$$

$$1045 \quad - p^{(i)}(0, \dots, 0, 1, 0) = \begin{cases} (1-r_d)(1-r_{div})r_s & \text{if } i \leq \bar{a}_s \\ 0 & \text{otherwise} \end{cases}$$

$$1046 \quad - p^{(i)}(0, \dots, 0, \underset{i}{1}, 0, \dots, 0, 0) = (1-r_d)(1-r_{div})(1-r_s)$$

$$1047 \quad - p^{(i)}(0, \dots, 0, 2) = (1-r_d)r_{div}r_s^2 \sum_{j_1=\bar{a}_s+1}^N q_{ij_1} \sum_{j_2=\bar{a}_s+1}^N q_{ij_2}$$

$$1048 \quad - p^{(i)}(0, \dots, 0, 2, 0) = (1-r_d)r_{div}r_s^2 \sum_{j_1=0}^{\bar{a}_s} q_{ij_1} \sum_{j_2=0}^{\bar{a}_s} q_{ij_2}$$

$$\begin{aligned}
1049 \quad & - p^{(i)}(0, \dots, 0, 1, 1) = 2(1-r_d)r_{div}r_s^2 \sum_{j_1=0}^{\bar{a}_s} q_{ij_1} \sum_{j_2=\bar{a}_s+1}^N q_{ij_2} \\
1050 \quad & - \text{For all } j_1 < j_2 \in \{0, \dots, N\}: \\
1051 \quad & - p^{(i)}(0, \dots, 0, 2, 0, \dots, 0, 0) = (1-r_d)r_{div}(1-r_s)^2 q_{ij_1}^2 \\
1052 \quad & - p^{(i)}(0, \dots, 0, 1, 0, \dots, 0, 1, 0, \dots, 0, 0) = 2(1-r_d)r_{div}(1-r_s)^2 q_{ij_1} q_{ij_2} \\
1053 \quad & - p^{(i)}(0, \dots, 0, 1, 0, \dots, 0, 1) = 2(1-r_d)r_{div}r_s(1-r_s)q_{ij_1} \sum_{j_2=\bar{a}_s+1}^N q_{ij_2} \\
1054 \quad & - p^{(i)}(0, \dots, 0, 1, 0, \dots, 0, 1, 0) = 2(1-r_d)r_{div}r_s(1-r_s)q_{ij_1} \sum_{j_2=0}^{\bar{a}_s} q_{ij_2} \\
1055 \quad & - p^{(i)}(\mathbf{k}) = 0 \text{ otherwise}
\end{aligned}$$

1056 We can therefore evaluate $f^{(i)}(\mathbf{s})$, with $\mathbf{s} = (s_0, \dots, s_{N+2}) \in \mathcal{C}^{N+3}$.

1057

1058

For all $i \leq \bar{a}_s$:

$$\begin{aligned}
f^{(i)}(\mathbf{s}) &= r_d s_{N+2} + (1-r_d)(1-r_{div})r_s s_{N+1} + (1-r_d)(1-r_{div})(1-r_s)s_i \\
&+ (1-r_d)r_{div}r_s^2 \left(\sum_{j_1=\bar{a}_s+1}^N q_{ij_1} \sum_{j_2=\bar{a}_s+1}^N q_{ij_2} s_{N+2}^2 \right. \\
&\left. + \sum_{j_1=0}^{\bar{a}_s} q_{ij_1} \sum_{j_2=0}^{\bar{a}_s} q_{ij_2} s_{N+1}^2 + 2 \sum_{j_1=0}^{\bar{a}_s} q_{ij_1} \sum_{j_2=\bar{a}_s+1}^N q_{ij_2} s_{N+1} s_{N+2} \right) \\
&+ (1-r_d)r_{div}(1-r_s)^2 \left(\sum_{j_1=0}^N q_{ij_1}^2 s_{j_1}^2 + 2 \sum_{j_1=0}^N q_{ij_1} \sum_{j_2 < j_1=0}^N q_{ij_2} s_{j_1} s_{j_2} \right) \\
&+ 2(1-r_d)r_{div}r_s(1-r_s) \sum_{j_1=0}^N q_{ij_1} \left(\sum_{j_2=\bar{a}_s+1}^N q_{ij_2} s_{N+2} + \sum_{j_2=0}^{\bar{a}_s} q_{ij_2} s_{N+1} \right) s_{j_1}
\end{aligned} \tag{18}$$

If $i > \bar{a}_s$ then $f^{(i)}(\mathbf{s})$ is the same except for the first line, which becomes:

$$(r_d + (1-r_d)(1-r_{div})r_s) s_{N+2} + (1-r_d)(1-r_{div})(1-r_s)s_i$$

The values of each m_{ij} are now obtained by evaluating all partial derivatives of $f^{(i)}(\mathbf{s})$ in $\mathbf{1}$, keeping in mind that for all $i \in \{0, \dots, N\}$, $\sum_{j=0}^N q_{ij} = 1$. \square

1059

1060

C Deriving the extinction probability of the GC from the multi-type GW process (Section 3.2)

1061

Let us recall some results about the extinction probability for multi-type GW processes [3].

1062

1063

1064

Definition 17 Let $q^{(i)}$ be the probability of eventual extinction of the process, when it starts from a single type i cell. As above bold symbols denote vectors *i.e.* $\mathbf{q} := (q^{(0)}, \dots, q^{(N+2)}) \geq 0$.

1065 **Definition 18** We say that (\mathbf{Z}_t) is singular if each particle has exactly one offspring, which
 1066 implies that the branching process becomes a simple MC.

1067 **Definition 19** Matrix \mathcal{M} is said to be strictly positive if it has non-negative entries and
 1068 there exists a t s.t. $(\mathcal{M}^t)_{ij} > 0$ for all i, j . (\mathbf{Z}_t) is called positive regular iff \mathcal{M} is strictly
 1069 positive.

1070 *Notation 1* Let $\mathbf{u}, \mathbf{v} \in \mathbb{R}^n$. We say that $\mathbf{u} \leq \mathbf{v}$ if $u_i \leq v_i$ for all $i \in \{1, \dots, n\}$. Moreover, we
 1071 say that $\mathbf{u} < \mathbf{v}$ if $\mathbf{u} \leq \mathbf{v}$ and $\mathbf{u} \neq \mathbf{v}$.

1072 **Theorem 3** Let (\mathbf{Z}_t) be non singular and strictly positive. Let ρ be the maximal eigenvalue
 1073 of \mathcal{M} . The following three results hold:

- 1074 1. If $\rho < 1$ (subcritical case) or $\rho = 1$ (critical case) then $\mathbf{q} = \mathbf{1}$. Otherwise, if $\rho > 1$ (su-
 1075 percritical case), then $\mathbf{q} < \mathbf{1}$.
- 1076 2. $\lim_{t \rightarrow \infty} \mathbf{f}_t(\mathbf{s}) = \mathbf{q}$, for all $\mathbf{s} \in \mathcal{C}^{N+3}$.
- 1077 3. \mathbf{q} is the only solution of $\mathbf{f}(\mathbf{s}) = \mathbf{s}$ in \mathcal{C}^{N+3} .

1078 The spectrum of matrix \mathcal{M} defined in Definition 2 (and recalled in Appendix B) is
 1079 obtained as follows:

1080 **Proposition 12** Let \mathcal{M} be defined as a block matrix as in Proposition 2. Let $\lambda_{\mathcal{M},i}$ be its
 1081 i^{th} -eigenvalue. The spectrum of \mathcal{M} is given by:

- 1082 – For all $i \in \{0, \dots, N\}$, $\lambda_{\mathcal{M},i} = (1 - r_d)(1 - r_s)(1 + r_{div}(2\lambda_i - 1))$, where λ_i is the i^{th} -
 1083 eigenvalue of matrix \mathcal{Q}_N .
- 1084 – whereas $\lambda_{\mathcal{M},N+1} = 1$ with multiplicity 2.

Proof As \mathcal{M} is a block matrix with the lower left block composed of zeros, then $\text{Spec}(\mathcal{M}) =$
 $\text{Spec}(\mathcal{M}_1) \cup \text{Spec}(\mathcal{I}_2)$. The result follows. \square

1085 Therefore we obtain the same condition as in Proposition 1 for the extinction probability
 1086 in the GC:

1087 **Proposition 13** Let \mathbf{q} be the extinction probability for the process (\mathbf{Z}_t) defined in Defini-
 1088 tion 13 and restricted to the first $N + 1$ components (i.e. we refer only to matrix \mathcal{M}_1 , which
 1089 defines the expectations of GC B-cells). Therefore:

- 1090 – if $r_s \geq 1 - \frac{1}{(1 - r_d)(1 + r_{div})}$, then $\mathbf{q} = \mathbf{1}$
- 1091 – otherwise $\mathbf{q} < \mathbf{1}$ is the smallest fixed point of $\mathbf{f}(\mathbf{s})$ in \mathcal{C}^{N+3} .

Proof \mathcal{Q}_N is a stochastic matrix, therefore its largest eigenvalue is 1. The corresponding
 eigenvalue of matrix \mathcal{M}_1 is: $\lambda_{\mathcal{M}_1,1} = (1 - r_d)(1 - r_s)(1 + r_{div})$. The proposition is proved by
 observing that $\lambda_{\mathcal{M}_1,1} \leq 1 \Leftrightarrow r_s \geq 1 - \frac{1}{(1 - r_d)(1 + r_{div})}$ and applying Theorem 3 (note that
 \mathcal{M}_1 is positive regular: this is not the case for matrix \mathcal{M}). \square

1092 D Expected size of the GC derived from the multi-type GW 1093 process (Section 3.2)

Proposition Let \mathbf{i} be the initial state, $z_0 := |\mathbf{i}|$ its 1-norm ($|\mathbf{i}| := \sum_{j=0}^{N+2} \mathbf{i}_j$). The expected
 size of the GC at time t :

$$\sum_{k=0}^N (\mathbf{i}\mathcal{M}^t)_k = |\mathbf{i}| ((1 - r_d)(1 + r_{div})(1 - r_s))^t$$

1094 *Proof* For the sake of simplicity, let us suppose that the process starts from a single B-cell
 1095 belonging to the affinity class $a_0 = i$ with respect to the target trait. We do not need to
 1096 specify the transition probability matrix used to define the mutational model allowed.

1097

We recall the expression of \mathcal{M}^t obtained by iteration:

$$\mathcal{M}^t = \begin{pmatrix} \mathcal{M}_1^t & \sum_{k=0}^{t-1} \mathcal{M}_1^k \mathcal{M}_2 \\ \mathbf{0}_{2 \times (N+1)} & \mathcal{I}_2 \end{pmatrix}$$

1098 Therefore we can claim that $(\mathbf{i}\mathcal{M}^t)_k$ corresponds to the k^{th} -component of the i^{th} -row
 1099 of matrix $\mathcal{M}_1^t = (2(1-r_d)r_{div}(1-r_s)\mathcal{Q}_N + (1-r_d)(1-r_{div})(1-r_s)\mathcal{I}_{N+1})^t$, where \mathcal{Q}_N is
 1100 a stochastic matrix. Matrices $\mathcal{A} := 2(1-r_d)r_{div}(1-r_s)\mathcal{Q}_N$ and $\mathcal{B} := (1-r_d)(1-r_{div})(1-r_s)\mathcal{I}_{N+1}$
 1101 clearly commute, therefore:

$$(\mathcal{A} + \mathcal{B})^t = \sum_{j=0}^t C_t^j \mathcal{A}^{t-j} \mathcal{B}^j \quad (19)$$

1102 For all j , $0 \leq j \leq t$:

$$\begin{aligned} \mathcal{A}^{t-j} \mathcal{B}^j &= 2^{t-j} (1-r_d)^{t-j} r_{div}^{t-j} (1-r_s)^{t-j} (1-r_d)^j (1-r_{div})^j (1-r_s)^j \mathcal{Q}_N^{t-j} \\ &= (1-r_d)^t (1-r_s)^t (2r_{div})^{t-j} (1-r_{div})^j \mathcal{Q}_N^{t-j} \end{aligned}$$

Hence:

$$(\mathcal{A} + \mathcal{B})^t = (1-r_d)^t (1-r_s)^t \sum_{j=0}^t C_t^j (2r_{div})^{t-j} (1-r_{div})^j \mathcal{Q}_N^{t-j}$$

1103 And consequently:

$$\begin{aligned} \sum_{k=0}^N (\mathbf{i}\mathcal{M}^t)_k &= \sum_{k=0}^N (\mathbf{i}(\mathcal{A} + \mathcal{B})^t)_k \\ &= (1-r_d)^t (1-r_s)^t \sum_{j=0}^t C_t^j (2r_{div})^{t-j} (1-r_{div})^j \sum_{k=0}^N (\mathbf{i}\mathcal{Q}_N^{t-j})_k \end{aligned}$$

1104 Since \mathcal{Q}_N is a stochastic matrix, for all n , \mathcal{Q}_N^n is still a stochastic matrix, *i.e.* the entries of
 1105 each row of \mathcal{Q}_N^n sum to 1. Therefore:

$$\begin{aligned} \sum_{k=0}^N (\mathbf{i}\mathcal{M}^t)_k &= (1-r_d)^t (1-r_s)^t \sum_{j=0}^t C_t^j (2r_{div})^{t-j} (1-r_{div})^j \\ &= (1-r_d)^t (1-r_s)^t (2r_{div} + 1 - r_{div})^t = (1-r_d)^t (1-r_s)^t (1+r_{div})^t, \end{aligned}$$

1106 as stated by Equation (3) for $z_0 = 1$. This result can be easily generalized to the case of
 1107 $z_0 \geq 1$ initial B-cells.

1108 E Proof of Proposition 5

Proposition *Let us suppose that at time $t = 0$ there is a single B-cell entering the GC belonging to the i^{th} -affinity class with respect to the target cell. Moreover, let us suppose that $\mathcal{Q}_N = R\Lambda_N L$. For all $t \geq 1$, the expected number of selected B-cells at time t , is:*

$$\mathbb{E}(S_t) = r_s (1-r_s)^{t-1} (1-r_d)^t \sum_{\ell=0}^N (2\lambda_\ell r_{div} + 1 - r_{div})^t \sum_{k=0}^{\bar{a}_s} r_{i\ell} l_{\ell k},$$

1109 *Proof* Let us suppose, for the sake of simplicity, that \mathcal{Q}_N is diagonalizable:

$$\mathcal{Q}_N = R\Lambda_N L, \quad (20)$$

1110 We can prove by iteration that:

$$\mathcal{M}^t = \begin{pmatrix} \mathcal{M}_1^t & \sum_{k=0}^{t-1} \mathcal{M}_1^k \mathcal{M}_2 \\ \mathbf{0}_{2 \times (N+1)} & \mathcal{I}_2 \end{pmatrix} \quad (21)$$

1111 It follows from (20) and (21) that for all $t \geq 1$, \mathcal{M}^t can be written as:

$$\mathcal{M}^t = \begin{pmatrix} RD^t L & \left(R \sum_{k=0}^{t-1} D^k L \right) \mathcal{M}_2 \\ \mathbf{0}_{2 \times (N+1)} & \mathcal{I}_2 \end{pmatrix}, \quad (22)$$

1112 where $D = 2(1-r_d)r_{div}(1-r_s)\Lambda_N + (1-r_d)(1-r_{div})(1-r_s)\mathcal{I}_{N+1}$ is a diagonal matrix. We
1113 obtain its expression thanks to Proposition 2.

1114

1115 Moreover, by Proposition 3 and Equation (20) we have:

$$\widetilde{\mathcal{M}} = \begin{pmatrix} R\widetilde{D}L & \widetilde{\mathcal{M}}_2 \\ \mathbf{0}_{2 \times (N+1)} & \mathcal{I}_2 \end{pmatrix}, \quad (23)$$

1116 where $\widetilde{D} = 2(1-r_d)r_{div}\Lambda_N + (1-r_d)(1-r_{div})\mathcal{I}_{N+1}$ is a diagonal matrix.

1117

Proposition 4 claims:

$$\mathbb{E}(S_t) = r_s \sum_{k=0}^{\bar{a}_s} \left(\mathbf{i} \mathcal{M}^{t-1} \widetilde{\mathcal{M}} \right)_k$$

From Equations (22) and (23):

$$\mathcal{M}^{t-1} \widetilde{\mathcal{M}} = \begin{pmatrix} RD^{t-1} \widetilde{D}L & RD^{t-1} L \widetilde{\mathcal{M}}_2 + \left(R \sum_{k=0}^{t-2} D^k L \right) \mathcal{M}_2 \\ \mathbf{0}_{2 \times (N+1)} & \mathcal{I}_2 \end{pmatrix}$$

1118 Since, by hypothesis, $\mathbf{i} = (0, \dots, 0, 1, 0, \dots, 0, 0)$, with the only 1 being at position i , $0 \leq i \leq N$,

1119 then $\left(\mathbf{i} \mathcal{M}^{t-1} \widetilde{\mathcal{M}} \right)$ denotes the i^{th} -row of matrix $\mathcal{M}^{t-1} \widetilde{\mathcal{M}}$. Therefore, we are interested in the

1120 sum between 0 and \bar{a}_s of the elements of the i^{th} -row of matrix $\mathcal{M}^{t-1} \widetilde{\mathcal{M}}$, *i.e.* of the i^{th} -row
1121 of matrix $RD^{t-1} \widetilde{D}L$, since clearly $\bar{a}_s \leq N$. $D^{t-1} \widetilde{D}$ is a diagonal matrix whose ℓ^{th} -diagonal
1122 element is given by:

$$\begin{aligned} \left(D^{t-1} \widetilde{D} \right)_\ell &= (2(1-r_d)r_{div}(1-r_s)\lambda_\ell + (1-r_d)(1-r_{div})(1-r_s))^{t-1} \\ &\quad \cdot (2(1-r_d)r_{div}\lambda_\ell + (1-r_d)(1-r_{div})) \\ &= (1-r_s)^{t-1} (1-r_d)^t (2\lambda_\ell r_{div} + 1 - r_{div})^t \end{aligned}$$

The result follows observing that: $\left(RD^{t-1} \widetilde{D}L \right)_{ik} = \sum_{\ell=0}^N \left(D^{t-1} \widetilde{D} \right)_\ell r_{i\ell} \ell_{\ell k}$. \square

1123 F Heuristic proof of Proposition 6

Proposition For all $t \in \mathbb{N}$ the value $r_s(t)$ which maximizes the expected number of selected B-cells at the t^{th} maturation cycle is:

$$r_s(t) = \frac{1}{t}$$

1124 *Hypothesis 1* \mathcal{Q}_N converges through its stationary distribution, denoted by $\mathbf{m} = (m_i)$, $i \in$
1125 $\{0, \dots, N\}$.

1126 *Hypothesis 2* Z_t explodes, where $(Z_t)_{t \in \mathbb{N}}$ is given by Definition 4.

1127 Let \tilde{Z}_t , $t \geq 0$ be the random variable describing the GC-population size at time t before
1128 the selection mechanism is performed for this generation. For the sake of simplicity, let us
1129 suppose $\tilde{Z}_0 = 1$. $(\tilde{Z}_t)_{t \in \mathbb{N}}$ is a MC on $\{0, 1, 2, \dots\}$. Denoted by $\tilde{p}_k := \mathbb{P}(\tilde{Z}_1 = k)$, $k \in \{0, 1, 2\}$:

$$\begin{cases} \tilde{p}_0 = r_d \\ \tilde{p}_1 = (1 - r_d)(1 - r_{div}) \\ \tilde{p}_2 = (1 - r_d)r_{div} \end{cases} \quad (24)$$

1130 It follows: $\tilde{m} := \mathbb{E}(\tilde{Z}_1) = (1 - r_d)(1 - r_{div}) + 2(1 - r_d)r_{div} = (1 - r_d)(1 + r_{div})$.

1131

1132 Conditioning to $Z_t = k$, \tilde{Z}_{t+1} is distributed as the sum of k independent copies of \tilde{Z}_1 ,
1133 which gives:

$$\mathbb{E}(\tilde{Z}_t) = \mathbb{E}(Z_{t-1})\mathbb{E}(\tilde{Z}_1) = \mathbb{E}(Z_1)^{t-1}\mathbb{E}(\tilde{Z}_1) = (1 - r_d)^t(1 + r_{div})^t(1 - r_s)^{t-1} \quad (25)$$

1134 Thanks to Hypotheses 1 and 2, if t is big enough, there is approximately a proportion
1135 of m_i elements in the i^{th} -affinity class with respect to $\bar{\mathbf{x}}$. Therefore, on average at time t
1136 there are approximately $\sum_{i=0}^{\bar{a}_s} m_i \mathbb{E}(\tilde{Z}_t)$ B-cells in the GC belonging to an affinity class with
1137 index at most equal to \bar{a}_s with respect to $\bar{\mathbf{x}}$, before the selection mechanism is performed
1138 for this generation. Each one of these cells can be submitted to selection with probability
1139 r_s , and in this case it will be positively selected. Hence:

$$\mathbb{E}(S_t) \simeq r_s \sum_{i=0}^{\bar{a}_s} m_i \mathbb{E}(\tilde{Z}_t) = (1 - r_d)^t(1 + r_{div})^t(1 - r_s)^{t-1} r_s \sum_{i=0}^{\bar{a}_s} m_i, \quad (26)$$

1140 which is maximized at time $t \geq 1$ for $r_s(t) = 1/t$.

1141 *Remark 8* One observes that the approximation in (26) gives the same value for the optimal
1142 $r_s(t)$ as in Proposition 6. Nevertheless, it does not allow to describe exactly the behavior of
1143 $\mathbb{E}(S_t)$, since it is obtained by approximating the distribution of B-cells in the GC with their
1144 stationary distribution.