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Calculating hazard rates of introgression with branching processes

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CHAPTER 5: QUANTIFYING STOCHASTIC INTROGRESSION PROCESSES IN RANDOM ENVIRONMENTS WITH HAZARD RATES

To be submitted

ABSTRACT

Introgression is the permanent incorporation of genes from the genome of one population into another. Fears that genetically modified genes might introgress from crop populations into their wild relatives has prompted many theoretical attempts to quantify the risk of introgression. Previous studies have found that stochasticity in number of offspring, hybridization, and environment are important aspects of introgression risk, but so far studies have considered these factors separately, and they have not yet been combined into one framework. In this paper we develop such a framework. In previous papers we introduced a measure of risk known as the hazard rate of introgression, that accurately takes demographic stochasticity into account. Here, we extend the methodology to incorporate random temporal environmental variation. We find that introgression risk varies much in time, and in some periods it can be much enhanced in such environments. Furthermore, effects of plant life history parameters, such as flowering and survival probabilities, depend on environmental variation.

1. INTRODUCTION

The permanent incorporation of genes from the genome of one population into another, a process known as introgression, is a topical area of research which has garnered much attention due to fears that transgenes might enter wild populations from crop populations, e.g. Kwit et al. (2011), Ellstrand et al. (1999) and Hails and Morley (2005). Potential consequences of introgression are, for example, the displacement of local species (as described in Huxel (1999)) or the creation of so-called super weeds via the transfer of herbicide resistance to wild individuals (e.g. Reichmann et al. (2006)).

A key factor in modeling introgression risks is the randomness of the environment. Davis et al. (1999) and Thompson et al. (2003) included environmental stochasticity in their models, but they did not consider demographic stochasticity. Ghosh and Haccou (2010) showed that demographic stochasticity is an important factor that should not be disregarded, especially with repeated outcrossing. The combined effects of environmental and demographic stochasticity have, until now, hardly been examined at all. In a previous paper (Ghosh et al. in press) we initiated such a study, by looking at stochastic changes in outcrossing rates. This can be caused, e.g., by variation in weather conditions. In the present paper we further generalize the methods to include randomness in other environmental conditions, which may affect the survival and reproduction of hybrids and further backcrosses. This type of environmental randomness is technically more difficult

to include, since every environmental change influences the complete future of an introgression process.

Ghosh and Haccou (2010), were the first to propose the hazard rate as a measure of introgression risk when there are repeated invasions. This measure is defined as the probability per time unit that the first introgressed lineage is initiated. Hazard rates are commonplace in medical statistics and behavior analysis (e.g. Kalbfleisch and Prentice (2002) and Haccou and Meelis (1994)), but they provide an intuitive measure to quantifying invasion risks too. Ghosh and Haccou (2010) calculated hazard rates of introgression by considering the repeated invasion of a gene conferring some fitness advantage into a large wild population in a temporally homogeneous environment. We showed that such environments lead to a monotonically increasing hazard rate that converges to some asymptote. Ghosh et al. (In press) demonstrated that deterministic temporal inhomogeneities can lead to a non-monotonic hazard rate, and thus that introgression risks can be higher at some times than at others. Generalizing the approaches first presented in Ghosh and Haccou (2010) to random environments involves incorporating theory on branching processes in random environments. Specifically, we will make use of the numerical methods for determining extinction probabilities in random environments, which were developed by Haccou and Iwasa (1996) and Haccou and Vatutin (2003). The methods presented in this paper may also be applied in contexts other than plant gene introgression that concern invasion with repeated immigration, for example in the study of invasive species, or epidemiological problems.

2. THE MODEL

We consider the model used in Ghosh et al. (In press) as an example. The methodology can straightforwardly be generalized to more complex ecological and life history settings. The model is in discrete time, with one time unit corresponding to one year. Plants are assumed to be monocarpic (i.e. they flower once then die), and there is no age-dependence in the life-history parameters. We assume that the recipient wild population is large and stable. A random number of hybrid seeds is produced each year, due to pollen flow from a neighboring crop. Seeds might germinate with some probability at the beginning of a year, and can flower in the same year. Whereas, previously, these germination and flowering probabilities were assumed to be fixed, in the present paper they may vary randomly in time.

As before, we will incorporate hybridization into the model by means of an artificial type, called type-0. There is always one single type-0 individual that produces a stochastic number of hybrid seeds each year. We will refer to hybrids as type-1 individuals.

The hybrids can backcross with the wild population, and subsequent backcrosses can backcross again with wild plants. All backcrosses are assumed to be equivalent, i.e. we assume that there are no fitness effects of further backcrossing after BC1. Also, we assume that there are no relevant genetical differences between hybrid or backcrossed individuals of the same generation. In Ghosh et al. (Submitted) we present methods for incorporating more realistic genetical mechanisms and fitness effects. Backcrossed individuals are called type- E (as in escape type) individuals.

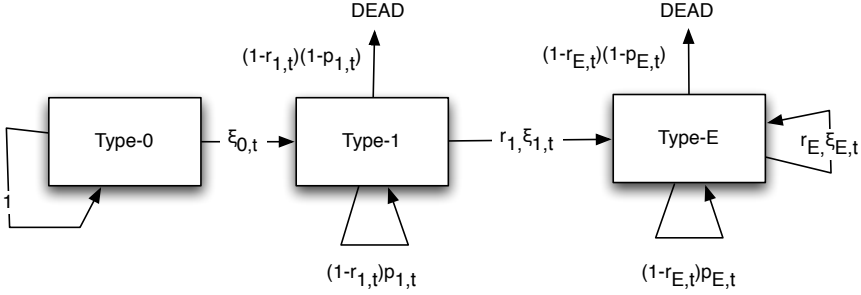


FIGURE 1. A schematic representation of the plant types used in the model.

We assume that the wild population is large relative to the initial numbers of hybrids and backcrossed individuals, so that the probability of interaction between individuals carrying crop genes is negligibly small. Consequently, individuals carrying crop genes interact solely with wild type individuals. This implies that a branching process model can be used to study the invasion dynamics.

In year t , a type-0 individual produces one individual of type-0 and a random number, $\xi_{0,t}$, of F1 hybrid seeds, each of which germinates with a probability of $p_{0,t}$ to become a type-1 plant of the next generation. Type-1 individuals at a time- t flower with probability $r_{1,t}$ to produce a random number of backcrossed seeds, through both male and female functions. Each of these seeds germinates with probability $p_{0,t}$ as before, to make type- E individuals belonging to the next generation. In the case that a type-1 individual does not flower, it may survive with a probability $p_{1,t}$. Similar dynamics hold for type- E individuals (see Fig. 1). The flowering and survival probabilities, as well as the distributions of the offspring numbers, may depend on the environmental state.

3. DERIVATION OF THE HAZARD RATE

To calculate the hazard rate, we first determine the sequence of extinction probabilities of a process initiated by a single individual at time t , by means of the methods that were developed by Haccou and Iwasa (1996) and Haccou and Vatutin (2003). Define $Q_{t,n}$ to be the probability that the lineage initiated by a single type- E individual at a time t becomes extinct at or before time n , conditioned on all environment states. This leads to the following expression for $t < n$:

$$Q_{t,n} = (1-r_{E,t})(1-p_{E,t}) + (1-r_{E,t})p_{E,t}Q_{t+1,n} + r_{E,t}G_E(t; p_{0,t}Q_{t+1,n} + 1 - p_{0,t}), \tag{1}$$

with $Q_{n,n} = 0$. Note that $G_i(t; s)$ ($i \in \{0, 1, E\}$) represents the probability generating function (p.g.f.) of $\xi_{i,t}$. $Q_{t,n}$ is calculated for all t and n for the simulated sequence of environmental states. For large n this gives the asymptotic extinction probability of the lineage initiated by a single type- E individual belonging to generation t , which we will write as Q_t .

Now define $I_i(k, n)$ ($i \in \{0, 1\}$) to be a random vector of length $n - k$, where the j th ($j \in \{1, 2, \dots, n - k\}$) element represents the total number of type- E individuals

belonging to generation $k + j$ produced in the lineage initiated by a single type- i individual belonging to generation- k .

We now introduce the joint p.g.f. of $I_i(k, n)$, which is called $F_{I_i(k,n)}(s_{k+1}, s_{k+2}, s_{k+3}, \dots, s_n)$ and is defined as:

$$F_{I_i(k,n)}(s_{k+1}, s_{k+2}, \dots, s_n) = E \left[s_{k+1}^{Z_{k,k+1}^{(i)}} s_{k+2}^{Z_{k,k+2}^{(i)}} s_{k+3}^{Z_{k,k+3}^{(i)}} \dots s_n^{Z_{k,n}^{(i)}} \mid \text{environmental sequence} \right], \quad (2)$$

where $Z_{k,j}^{(i)}$ represents the j th element of the vector $I_i(k, n)$.

We define the time of an introgression event, T , as the time where the first type- E individual appears, whose lineage escapes extinction. Using the value of Q_t already calculated, along with the definition in (2), we find:

$$P(T > n \mid \text{environmental sequence}) = F_{I_0(0,n)}(Q_1, Q_2, \dots, Q_n), \quad (3)$$

since introgression occurs after n if and only if all lineages initiated by type- E individuals up to that time go extinct.

Using $i = 1$ in (2) with the definitions of the life-history parameters in section 2, we arrive at the following expression:

$$F_{I_1(k,n)}(s_{k+1}, s_{k+2}, \dots, s_n) = (1 - r_{1,k})(1 - p_{1,k}) + (1 - r_{1,k})p_{1,t}F_{I_1(k+1,n)}(s_{k+2}, \dots, s_n) + r_{1,t}G_1(k; p_{0,t}s_{k+1} + 1 - p_{0,t}). \quad (4)$$

This can be computed for all $k < n$ using $F_{I_1(n,n)} = 1$ for any given sequence of environmental states.

It can be shown (see A.1) that the following holds.

$$F_{I_0(0,n)}(s_1, s_2, \dots, s_n) = \prod_{l=0}^{n-1} G_0(l; p_{0,l}F_{I_1(l,n)}(s_{l+1}, s_{l+2}, \dots, s_n) + 1 - p_{0,l}) \quad (5)$$

which can be computed using (4) and a sequence of environmental states.

The hazard rate conditioned on the environment, \tilde{H}_n (with $n \in \mathbb{N}_0$), is the probability that introgression occurs at a time n , given that it has not occurred before, and given the environmental sequence. Using this definition with (3) and (5), the following expression is reached:

$$\tilde{H}_n = 1 - \frac{\prod_{l=0}^{n-1} G_0(l; p_{0,l}F_{I_1(l,n)}(s_{l+1}, s_{l+2}, \dots, s_n) + 1 - p_{0,l})}{\prod_{l=0}^{n-2} G_0(l; p_{0,l}F_{I_1(l,n-1)}(s_{l+1}, s_{l+2}, \dots, s_n) + 1 - p_{0,l})} \quad (6)$$

Note that \tilde{H}_n is a random variable. The hazard rate can be simulated to study its distribution, by using the procedure outlined above, which we summarize here:

- (1) Simulate an environmental sequence.
- (2) Use this environmental sequence to calculate (1) backwards in time. It is important to choose a suitably large value of time from which to start so that (1) sufficiently converges to the asymptotic extinction probability.
- (3) Use the values of (1) to calculate (4) for all values k and n .
- (4) Use the results from calculating of (4) to calculate the hazard rate in (6)

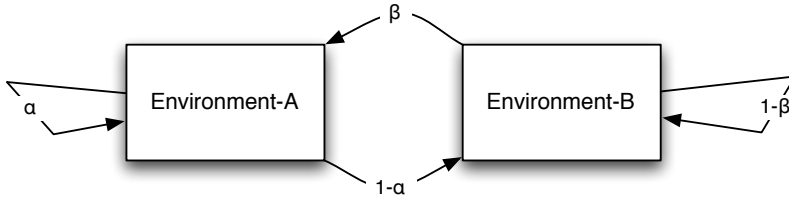


FIGURE 2. A schematic representation of the environment states and their transition probabilities.

- (5) Store this value of the hazard rate and loop from step 1 again to arrive and multiple realizations of (6) from which expectations may be taken.

4. RESULTS

To illustrate the methodology, we will consider a situation where the environment changes according to a two-state Markov chain, with states *A* and *B*. The transition probability from state-*A* to itself is written as α , and the transition probability from state-*B* to state-*A* as β . The scheme is summarized in Fig. 2. The initial environment at time zero is chosen from the stationary distribution of environmental states:

$$\pi_A = \frac{\beta}{1 - \alpha + \beta}, \quad \pi_B = \frac{1 - \alpha}{1 - \alpha + \beta}, \tag{7}$$

and then evolves according to the defined transition probabilities. We now investigate how environmental randomness and plant life-histories together affect introgression risks. We assume that environment-*A* is a favorable environment and environment-*B* an unfavorable environment, so germination rates, hybridization rates, survival probabilities, and number of seeds produced by different plants are larger when the environmental state is *A*.

For convenience, all offspring distributions in the model are taken to be Poisson. The p.g.f. of a Poisson-distributed random variable is given by:

$$G(s) = e^{-m(1-s)}, \tag{8}$$

where m denotes the expectation. The means of $\xi_{i,j}$ ($i \in \{0, 1, E\}$, $j \in \{A, B\}$) are denoted by $m_{i,j}$.

Figure 3(a) shows how the hazard rate changes with time. The hazard rate averaged over all environments is zero for the first year, because it is impossible to create a type-*E* individual after just one year (as shown in Fig. 1), but then quickly approaches an asymptote. However, the dynamics for a specific environmental sequence can be much more capricious, and this leads to a large variance as is also shown in Fig. 3(a).

4.1. Hazard rates in random and deterministically varying environments.

For comparison, Fig.3(b) shows the hazard rates in deterministically alternating environments when the starting condition is state *A* (blue) or *B* (red). As can be seen, the average level is nearly the same, but the deviations from the mean

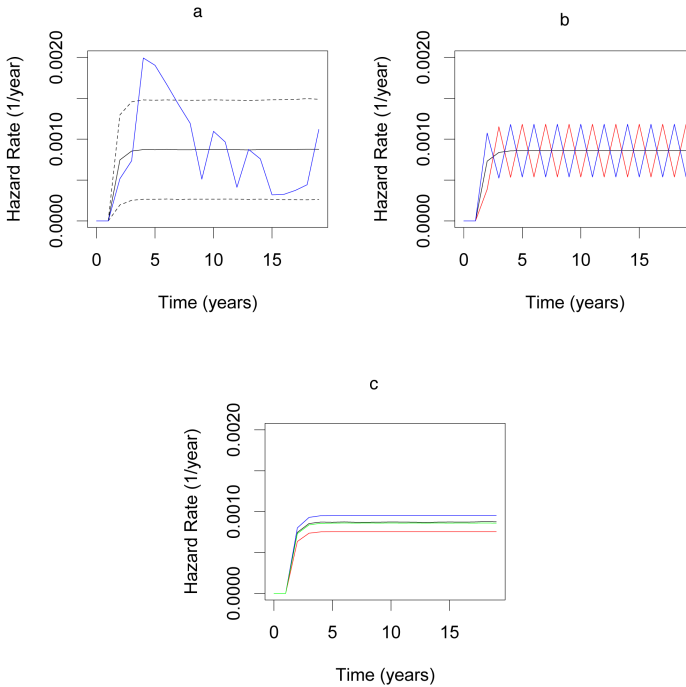


FIGURE 3. The hazard rate for different environmental processes. (a) Random environments, with a realization (blue), the mean (black) and standard deviations above and below the mean (dotted). (b) Deterministically alternating environments, starting with environmental state A (blue) or B (red), and the time-average (black). (c) Mean hazard rate in the case of random environments (black), deterministically alternating environments (green), and time-homogeneous environments with life-history parameters equal to the arithmetic mean (blue) and the geometric mean (red). Parameter values: $\alpha = \beta = 0.5$, $m_{0,A} = 10$, $m_{0,B} = 5$, $m_{1,A} = 1100$, $m_{1,B} = 800$, $m_{E,A} = 1400$, $m_{E,B} = 1000$, $p_{1,A} = p_{1,B} = p_{E,B} = 0.8$, $p_{E,A} = 0.9$, $r_{1,A} = r_{1,B} = r_{E,A} = r_{E,B} = 0.8$

in the random environment situation are much higher than those in the alternating environment case. Thus, random environments can induce periods of much higher risk. In Fig.3(c) we show the average hazard rates for respectively random environments, alternating environments, and constant environments with life history parameters equal to the geometric time-average, and to the arithmetic time-average. The average hazard rates are similar for random and alternating environments. Arithmetic time-averaged environments give a higher-than-average hazard rate, and geometric time-averaged environments a smaller one.

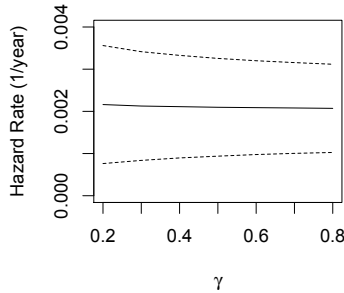


FIGURE 4. Effect of environmental autocorrelation on the hazard rate. Parameter values: $m_{0,A} = 10$, $m_{0,B} = 5$, $m_{1,A} = 1200$, $m_{1,B} = 800$, $m_{E,A} = 1400$, $m_{E,B} = 1200$, $p_{0,A} = 0.001$, $p_{0,B} = 0.0009$, $p_{1,A} = 0.9$, $p_{1,B} = 0.8$, $r_{1,A} = r_{e,A} = r_{e,B} = 0.8$, $r_{1,B} = 0.7$. The solid black line represents the mean hazard rate. The dotted lines represent one standard deviation over and under the average hazard rate.

4.2. Environmental autocorrelation. To examine the effects of environmental autocorrelation on the hazard rate, we take $1 - \alpha = \beta = \gamma$, with $\gamma \in (0, 1)$. Under this scheme, the expected amount of time in each environment state is the same. If $\gamma = 0.5$, the environment states are independent. They are negatively autocorrelated if $\gamma > 0.5$, and positively autocorrelated if $\gamma < 0.5$. Fig. 4 shows the effects of γ on the hazard rate. As illustrated, the autocorrelation does not affect the mean hazard rate very much, whereas increasing γ causes a small decrease in its standard deviation. This implies that for the parameter combinations that we investigated overall introgression risk is reduced in autocorrelated environments.

4.3. Life history parameters. The effect of life-history parameters depends on the environmental process. To illustrate this, we consider the effect of flowering probability $r_{1,B}$ and survival probability $p_{1,B}$ on the hazard rate. Varying other flowering and survival probabilities leads to similar effects.

Figure 5 shows the hazard rate as a function of the flowering probability $r_{1,B}$ for different environmental scenarios and different values of $p_{1,B}$. As seen in the figure, the effect of flowering probability on the hazard rate depends on the combination of β and $p_{1,B}$. When the survival probability in bad environments is low ($p_{1,B} = 0.1$, Figs.5 (a) and (c)) the hazard rate increases with increasing flowering probability, regardless of the value of β .

Figure 5 (b), on the other hand, shows an scenario where, given that one is in an unfavorable environment, one is likely to stay in that environment ($\beta = 0.1$), and also the survival probability of a non-flowering plant is high (0.9). In this scenario, the hazard rate is more or less independent of $r_{1,B}$.

As shown in Fig. 5 (d), the asymptotic level of the mean hazard rate can also decrease with $r_{1,B}$. This happens when the probability that an environment

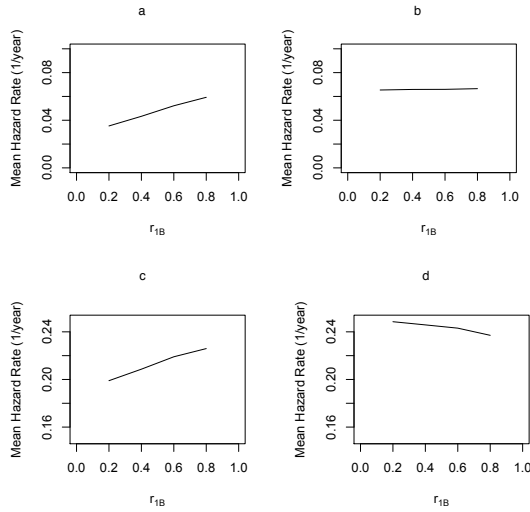


FIGURE 5. Effects of flowering probabilities $r_{1,B}$ on the mean hazard rate. Parameter values: $\alpha = 0.5$, $m_{0,A} = 1400$, $m_{0,B} = 1000$, $m_{1,A} = 1200$, $m_{1,B} = 550$, $m_{E,A} = 1300$, $m_{E,B} = 1200$, $p_{0,A} = 0.001$, $p_{0,B} = 0.0009$, $p_{1,A} = 0.9$, $p_{E,A} = 0.9$, $p_{E,B} = 0.8$, $r_{1,A} = 0.8$, $r_{E,A} = r_{E,B} = 0.8$, with subplot (a) showing $\beta = 0.1$, $p_{1,B} = 0.1$, subplot (b) showing $\beta = 0.1$, $p_{1,B} = 0.9$, subplot (c) showing $\beta = 0.9$, $p_{1,B} = 0.1$ and subplot (d) showing $\beta = 0.9$, $p_{1,B} = 0.9$

changes from unfavorable to favorable is high, and the probability of surviving is also high.

5. DISCUSSION

In this paper we extended the methodology first presented in Ghosh and Haccou (2010) to deal with repeated invasions to situations with environmental stochasticity. This has led to many new, and sometimes surprising, results concerning introgression risk. As shown in subsection 4.1, introgression risks in random environments can be very different from those in deterministically varying environments, or in constant deterministic environments with the same time-averaged values of the life history parameters (see Fig. 3). As can be expected, the average hazard rate is higher in constant environments with the arithmetic mean life history parameters, since extinction probabilities of invasions are lower in such environments (see e.g. Haccou and Iwasa (1996)). Average hazard rates are lower in environments with geometric time-averaged parameters than in the random environment. Thus, using the arithmetic mean hazard rate overestimates the mean risk, whereas the geometric mean hazard rate underestimates it. As shown in Fig. 3(a), however, the hazard rate in random environments varies much in time, and there can be times at which it is much higher than its mean. Therefore, average

hazard rates are generally not a good measure of risk in random environments. We recommend that at least the variance of the hazard rate distribution is also taken into account. A closer examination of the distribution of the asymptotic hazard rate is also possible with the methods that we presented in this paper. In this way for instance a 95 percent upper bound can be established for the value of the hazard rate, which would provide a conservative estimate of the risk.

The value of the hazard rate is slightly affected by environmental autocorrelation (Fig. 4). We found that risks are reduced in strongly autocorrelated environments. This agrees with the results of Haccou and Vatutin (2003), who showed that success of sequential invasions is lower in environments with stronger positive autocorrelation, due to the increased length of 'runs of bad luck' in such environments. The effect that we found is, however, quite small.

Besides affecting the magnitude of introgression risks, random environments also change the effects that life history parameters have on introgression risks, as shown in subsection 4.3. If a plant in a poor environment can expect to be in a better environment where it would have a higher fecundity the next year, then it is better not to delay flowering. In this case, introgression risks decreases with flowering probability, as shown in Fig. 5 (d). However in delaying flowering, the plant also exposes itself to the risk of not surviving to the next flowering season. Thus, if survival probability is low, it is better to flower quickly. In this case introgression risk will increase with flowering probability (see Figs. 5 (a,c)). When the probability that a bad environment improves is low, and the survival probability of a non-flowering plant in a bad environment is high, it makes little difference if a hybrid flowers or not, and the hazard rate is more or less independent of $r_{1,B}$ (Fig. 5 (b)). Consequently, there is an interactive effect of environmental stochasticity, flowering probabilities, survival probabilities and plant fecundities. As a result, the consequences of life history parameters for introgression risks are much more difficult to predict in random environments. This is a subject of further study.

While some aspects of environmental stochasticity were considered in introgression studies before by, for example, Davis et al. (1999) and Thompson et al. (2003), the combined effect of environmental and demographic stochasticity has not been examined before. In this paper we combine the two sources of stochasticity. Davis et al. (1999) found that environmental stochasticity increases the introgression rate. Our results suggest that this is not the whole story—while there might be periods where environmental stochasticity increases hazard rates, there can also be prolonged times of low introgression risk. Note, however, that the approach we present is very different to theirs. They consider the time for the wild-population to contain 90 percent of the transgene as a measure of introgression rate, whereas we consider the hazard rate of a permanent lineage being formed. In our view, the hazard rate is a less arbitrary measure, since it does not involve choosing a threshold frequency in the way that Davis et al. (1999) does. Even though Davis et al. (1999) and Thompson et al. (2003) fail to incorporate demographic stochasticity, they do include more specific information about the number of individuals carrying a transgene in a wild-population, whereas our approach concentrates on the risk of a transgene escaping in the first place. The growth of the transgene

frequency in the population given a successful invasion is another matter, that remains to be examined.

Even though this paper has outlined how to handle several types of stochasticity in introgression models, further research is needed to have a complete understanding of the mechanisms involved in introgression. For instance, potential invading genes will be linked to other genes, which can affect introgression risks. We are currently working on extending the methodology to incorporate such genetics, and to include effects of drift in small wild populations.

Another important generalization would be to incorporate multiple wild populations and to investigate how a metapopulation structure affects the spread of invading genes, which would involve elaborating on work by Hanski et al. (1999).

We would like to conclude by remarking that much must still be done to develop full models of introgression, but effects of demographic and environmental stochasticity are important aspects to include in introgression studies.

6. ACKNOWLEDGMENTS

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APPENDIX A. APPENDIX

A.1. Derivation of (5). Putting $i = 0$ and $k = 0$ in (2) with the definitions from section 2, we find the following:

$$\begin{aligned}
 F_{I_0(0,n)}(s_1, s_2, \dots, s_n) &= F_{I_0(1,n)}(s_2, s_3, \dots, s_n)G_0(0; p_{0,0}F_{I_1(1,n)}(s_2, s_3, \dots, s_n) + 1 - p_{0,0}) \\
 &= F_{I_0(2,n)}(s_3, s_4, \dots, s_n)G_0(0; p_{0,0}F_{I_1(1,n)}(s_2, s_3, \dots, s_n) + 1 - p_{0,0}) \\
 &\quad \times G_0(1; p_{0,1}F_{I_1(1,n)}(s_2, s_3, \dots, s_n) + 1 - p_{0,1}) \\
 &= \prod_{l=0}^{n-1} G_0(l; p_{0,l}F_{I_1(l,n)}(s_{l+1}, s_{l+2}, \dots, s_n) + 1 - p_{0,l}) \tag{9}
 \end{aligned}$$

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