The Generalised Isolation-With-Migration Model: a Maximum-Likelihood Implementation for Multilocus Data Sets

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Abstract

Statistical inference about the speciation process has often been based on the isolation-with-migration (IM) model, especially when the research aim is to learn about the presence or absence of gene flow during divergence. The generalised IM model introduced in this paper extends both the standard two-population IM model and the isolation-with-initial-migration (IIM) model, and encompasses both these models as special cases. It can be described as a two-population IM model in which migration rates and population sizes are allowed to change at some point in the past. By developing a maximum-likelihood implementation of this GIM model, we enable inference on both historical and contemporary rates of gene flow between two closely related species. Our method relies on the spectral decomposition of the coalescent generator matrix and is applicable to data sets consisting of the numbers of nucleotide differences between one pair of DNA sequences at each of a large number of independent loci.

Keywords: speciation, coalescent, maximum-likelihood, gene flow, isolation

1 Introduction

Coalescent-type stochastic models can be used as a statistical inference tool to extract information from a sample of genomic sequences. When the aim is to learn about the role of gene flow during speciation, most inferential methods are based on the isolation-with-migration (IM) model (see, e.g., Nielsen and Wakeley 2001, Hey and Nielsen 2004).
Hey, 2005; Hey and Nielsen, 2007; Hey, 2010). A survey of research that has used the
IM model in the context of speciation can be found in Pinho and Hey (2010). In recent
years, as more extensions of the IM model became available, some authors have taken
on the task of finding the evolutionary scenario, represented by some version of the IM
model, that best explains a given polymorphism data (see, e.g., Wang and Hey, 2010
Lohse et al., 2011; Lohse and Frantz, 2014).

A recent addition to the list of implementable IM models is the so-called isolation-
with-initial-migration (IIM) model (Wilkinson-Herbots, 2012; Wilkinson-Herbots, 2015;
Costa and Wilkinson-Herbots, 2016). This is a 2-population IM model in which gene flow
may stop at some point in the past (see Figure 1). As a result of this development, it is
now possible to assess which of three divergence scenarios is most supported by a given
data set: divergence without gene flow, divergence with constant gene flow until the
present, or divergence with initial gene flow and subsequent isolation. In fact, one way
to perform this comparison is to fit the three models depicted in Figure 2: a complete
isolation model, a standard IM model, and a version of the IIM model in which the sizes
of the diverging populations are kept constant. The aim of this latter restriction is to
separate, as much as possible, the effect of allowing for different gene flow scenarios from
the effect of allowing for population size changes.

Figure 1: The isolation-with-initial-migration (IIM) model (Wilkinson-Herbots, 2012; Costa
and Wilkinson-Herbots, 2016). Population size parameters $a$, $b$, $c_1$, and $c_2$ are in units of $2N$
sequences, where $N$ is the effective population size of the species on the left of the diagram,
during the migration stage. From a forward-in-time perspective, $\tau_0$ denotes the splitting time
of the ancestral population and the beginning of the gene flow stage; after $\tau_1$, gene flow ceases.
The rates of gene flow are represented by $m_1$ and $m_2$.

In practice, however, one is often ignorant of whether the sizes of the populations
during divergence have changed significantly or not, and allowing for population size
changes may improve the fit of the models substantially. Therefore, we would like to be

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able to compare the three gene flow scenarios in a framework which incorporates the full IIM model shown in Figure 1. The aim of this paper is to build such a framework, by developing a maximum-likelihood implementation of a model which we call the generalised isolation-with-migration (GIM) model. This will enable us to compare the three models shown in Figure 3, which include the full GIM model (central diagram) and two models nested in it. More specifically, our goal is to enable these models to be fitted to data sets consisting of observations on the number of segregating sites between pairs of DNA sequences from a large number of independent, non-recombining loci.

This paper follows a series of papers on estimation methods which are based on explicit likelihood expressions and are suited for multilocus data sets. The likelihood of the number of pairwise differences under the IM model was derived in Wilkinson-Herbots (2008) and later extended to the isolation-with-initial-migration (IIM) model in Wilkinson-Herbots (2012) and Costa and Wilkinson-Herbots (2016). The results of Lohse et al. (2011) for the IM model included the likelihood of data on triplets and are based on the solution of systems of generating functions. Making use of spectral decomposition and lumpability of continuous-time Markov chains, Andersen et al. (2014) obtained explicit results for an IM model with an arbitrary number of lineages in an arbitrary number of populations. Lohse and Frantz (2014) derived the likelihood of full mutational configurations of sequences under both admixture and ancestral structure scenarios.

2 Theory and methods

From a backward-in-time perspective, the fullest GIM model we consider consists of two successive 2-island models and one ancestral Wright-Fisher population, as illustrated in the central diagram of Figure 3. The population on the left of the diagram will be
referred to as ‘population 1’ and the population on the right as ‘population 2’. The
time parameters $\tau_1 > 0$ and $\tau_0 > \tau_1$ are in units of $2N$ generations, where $2N$ is
the number of haploid genomes in population 1 during the second stage of migration.
The relative sizes of the remaining populations with respect to the size of population
1 between $\tau_1$ and $\tau_0$ are given by the parameters $a$, $b$, $c_1$ and $c_2$. The parameters $m_i$ and $m'_i$, with $i \in \{1, 2\}$, represent the backward migration rates from population $i$ to $j$
($i \neq j$) per generation, i.e. the fraction of population $i$ which migrates to population $j$
in each generation. The reproduction in each population follows the neutral Wright-Fisher
model. It is assumed that, in each generation, the process of reproduction restores
the population to its original size, in case the number of immigrants is different from
the number of emigrants. All parameters of the GIM model are strictly positive, except for
the migration rates, which are non-negative.

We are interested in the genealogical process of a random sample of two DNA se-
quences at the same locus, taken from either of the present populations (or one from
each population), under the GIM model. This process is a succession of discrete-time
Markov chains tracing the lineages ancestral to the sample back in time. It is absorbed
whenever the two lineages coalesce at their most recent common ancestor. The process
can start in one of three states: if both sequences are sampled from population 1, the
initial state is ‘1’; if both come from population 2, or there is one from each population,
the initial states are denoted ‘2’ and ‘3’ respectively. Until time $\tau_0$ into the past, the
process is either in one of these three states or coalescence has occurred (state ‘4’). Af-
ter $\tau_0$, only two situations are possible: either there are two distinct ancestral lineages
(states ‘1’, ‘2’ and ‘3’), or coalescence has occurred (state ‘4’).

The genealogy of the sample under the GIM model is a stochastic process that runs
in discrete time. But if time is measured in units of $2N$ generations and $N$ is large, it is
well approximated by the coalescent under the GIM model, which is composed of three
consecutive continuous-time Markov chains (Kingman, 1982; Notohara, 1990).

2.1 The coalescent under the GIM model

The coalescent under the GIM model is defined by the following generator matrices. For $0 \leq t \leq \tau_1$,

$$Q_1 = \begin{bmatrix}
(1) & (3) & (2) & (4) \\
(1) & -\left(\frac{1}{c_i} + M_i\right) & M_i' & 0 & \frac{1}{c_i} \\
(3) & \frac{M_i'}{2} & -\left(\frac{M_i'M_i'}{2}\right) & \frac{M_i'}{2} & 0 \\
(2) & 0 & M_2' & -\left(\frac{1}{c_2} + M_2'\right) & \frac{1}{c_2} \\
(4) & 0 & 0 & 0 & 0
\end{bmatrix}$$

(Notohara, 1990), where $M_i'/2 = 2Nm_i'$ is the rate of migration of a single lineage when in population $i$ ($i \in \{1, 2\}$). The rate $\frac{1}{c_i}$ is the rate of coalescence of two lineages if both are in population $i$. Note that, for mathematical convenience, state 2 corresponds to row and column three, whereas state 3 corresponds to row and column 2: this makes $Q_1$ as symmetric as possible, while reserving states 1 and 2 for the states in which two lineages are present in population 1 and population 2 respectively. If $\tau_1 < t \leq \tau_0$,

$$Q_2 = \begin{bmatrix}
(1) & (3) & (2) & (4) \\
(1) & -(1 + M_1) & M_1 & 0 & 1 \\
(3) & \frac{M_2}{2} & -\left(\frac{M_1'M_1}{2}\right) & \frac{M_1}{2} & 0 \\
(2) & 0 & M_2 & -\left(\frac{1}{c_2} + M_2\right) & \frac{1}{c_2} \\
(4) & 0 & 0 & 0 & 0
\end{bmatrix}$$

where $1$ and $\frac{1}{c}$ are the coalescence rates of two lineages in population 1 and population 2 respectively, and $M_i'/2 = 2Nm_i$. Finally, for $t > \tau_0$,

$$Q_3 = \begin{bmatrix}
(1) & (3) & (2) & (4) \\
(1) & -\frac{1}{a} & 0 & 0 & \frac{1}{a} \\
(3) & 0 & -\frac{1}{a} & 0 & \frac{1}{a} \\
(2) & 0 & 0 & -\frac{1}{a} & 1 \\
(4) & 0 & 0 & 0 & 0
\end{bmatrix}$$
(Kingman 1982), where $\frac{1}{a}$ is the rate of coalescence of two lineages in the ancestral population.

The matrix of transition probabilities $P(t)$ of the coalescent under the GIM model has the following form:

$$P(t) = \begin{cases} 
    e^{Q_1 t} & \text{for } 0 \leq t \leq \tau_1, \\
    e^{Q_1 \tau_1} e^{Q_2 (t-\tau_1)} & \text{for } \tau_1 < t \leq \tau_0, \\
    e^{Q_1 \tau_1} e^{Q_2 (\tau_0-\tau_1)} e^{Q_3 (t-\tau_0)} & \text{for } \tau_0 < t < \infty, \\
    0 & \text{otherwise.} 
\end{cases} \quad (4)$$

Recall that all time and population size parameters are assumed strictly positive. In Section 2.1 of Costa and Wilkinson-Herbots (2016), we prove that, if both migration rates are also strictly positive, the matrices $Q_1$ and $Q_2$ are diagonalisable and have non-positive real eigenvalues. Moreover, the matrix

$$\begin{bmatrix}
    1 & 0 & 1 & 0 \\
    1 & 1 & 0 & 0 \\
    1 & 0 & 0 & 1 \\
    1 & 0 & 0 & 0 
\end{bmatrix} \quad (5)$$

contains a set of four independent right eigenvectors of $Q_3$, and the corresponding vector of eigenvalues is $(0, -1/a, -1/a, -1/a)$. Hence, for $M_1, M_2, M'_1, M'_2 > 0$, $P(t)$ can be written as:

$$P(t) = \begin{cases} 
    G e^{-A t} G & \text{for } 0 \leq t \leq \tau_1, \\
    e^{Q_1 \tau_1} e^{Q_2 (\tau_0-\tau_1)} e^{Q_3 (t-\tau_0)} & \text{for } \tau_1 < t \leq \tau_0, \\
    e^{Q_1 \tau_1} e^{Q_2 (\tau_0-\tau_1)} e^{Q_3 (t-\tau_0)} e^{Q_4 (t-\tau_0)} & \text{for } \tau_0 < t < \infty, \\
    0 & \text{otherwise.} 
\end{cases} \quad (6)$$

where $G$, $C$, and $D$ are the matrices of right eigenvectors of $Q_1$, $Q_2$, and $Q_3$ respectively, and $-A$, $-B$ and $-\Gamma$ are the corresponding diagonal matrices of (non-positive, real) eigenvalues. The entries in the main diagonals of $A$, $B$ and $\Gamma$ contain the absolute values of the eigenvalues, and are represented by the letters $\alpha_i = (A)_{ii}$, $\beta_i = (B)_{ii}$ and $\gamma_i = (\Gamma)_{ii}$.

If a matrix $Q$ is a generator matrix of a migration stage in the GIM model, with migration parameters $M_i = M_j = 0$ ($i, j \in \{1, 2\}$ and $i \neq j$) and relative population size parameters $c_i$ and $c_j$, then its right eigenvectors are those shown in matrix (5) and its vector of eigenvalues is $(0, 0, -1/c_1, -1/c_2)$. So when there is no gene flow between $\tau_0$ and $\tau_1$, or no gene flow between $\tau_1$ and the present, $P(t)$ can still be decomposed as in equation (6).

For all values of $M_1$ and $M_2$, the characteristic polynomial of $Q$, denoted $P_Q(\beta)$, is
of the form $\beta \times \mathcal{P}_{Q_1}(\beta)$, where $Q^{(r)}$ is the three by three upper-left submatrix of $Q$. So $Q$ has a zero eigenvalue and its remaining eigenvalues are the eigenvalues of $Q^{(r)}$. If $Q$ has migration parameters $M_i = 0$ and $M_j > 0$, $Q^{(r)}$ becomes triangular. The eigenvalues of $Q^{(r)}$ will be the entries in its main diagonal. Hence the vector of eigenvalues of $Q$ will be $\lambda = [-1/c_i, -M_j/2, -(M_j + 1/c_j), 0]$. If there are no repeated eigenvalues in $\lambda$, we can be sure that $Q$ is diagonalisable (and its eigenvalues are non-positive and real).

In other words, even if there is unidirectional migration between $\tau_1$ and the present, or between $\tau_0$ and $\tau_1$, the probability transition matrix $P(t)$ can still be decomposed as in $0$, as long as there are no repeated entries in $\lambda$. Two comments are in order here: first, repeated eigenvalues will occur if and only if $1/c_i = M_j/2$ or $1/c_i = M_j + 1/c_j$; second, the set of parameter values that make these equalities true is negligible when compared to the whole parameter space, so it is very unlikely that the likelihood maximisation procedure chooses values from this set (although one should be careful to avoid using them as initial values).

The probability that, starting in state $i$ ($i \in \{1, 2, 3\}$), the process has reached state 4 by time $t$ is given by the entry corresponding to the $i$th row and 4th column of $P(t)$. This is also the cumulative distribution function (cdf) of $T_i$, the time until coalescence, which we denote $F_{T_i}(t)$. If the initial state is $i$, and $p_{ij}^{(1)}(t)$, $p_{ij}^{(2)}(t)$ and $p_{i4}^{(3)}(t)$ denote transition probability functions of the Markov chains with generator matrices $Q_1$, $Q_2$ and $Q_3$ respectively, then:

$$F_{T_i}(t) = \begin{cases} p_{i4}^{(1)}(t) & \text{for } 0 \leq t \leq \tau_1, \\ \sum_{j=1}^{4} p_{ij}^{(1)}(\tau_1) p_{j4}^{(2)}(t - \tau_1) & \text{for } \tau_1 < t \leq \tau_0, \\ \sum_{j=1}^{4} p_{ij}^{(1)}(\tau_1) \sum_{l=1}^{4} p_{jl}^{(2)}(\tau_0 - \tau_1) p_{l4}^{(3)}(t - \tau_0) & \text{for } \tau_0 < t < \infty, \\ 0 & \text{otherwise.} \end{cases}$$

(7)

Representing by $A_{mn}$ the $(m, n)$ entry of a matrix $A$, and by $A^{-1}_{mn}$ the same entry of the matrix $A^{-1}$, we have that $p_{ij}^{(1)}(t) = \sum_{k=1}^{4} G_{ik}^{-1} G_{kj} e^{-\alpha_k t}$, $p_{ij}^{(2)}(t) = \sum_{k=1}^{4} C_{ik}^{-1} C_{kj} e^{-\beta_k t}$ and $p_{i4}^{(3)}(t) = \sum_{k=1}^{4} D_{ik}^{-1} D_{k4} e^{-\gamma_k t}$.
Differentiating the expression above gives the following density for $T_i$:

$$f_{T_i}(t) = \begin{cases} 
    f^{(1)}_i(t) & \text{for } 0 \leq t \leq \tau_1, \\
    \sum_{j=1}^{4} p^{(1)}_{ij}(\tau_1) f^{(2)}_j(t - \tau_1) & \text{for } \tau_1 < t \leq \tau_0, \\
    \sum_{j=1}^{4} p^{(1)}_{ij}(\tau_1) \sum_{l=1}^{4} p^{(2)}_{jl}(\tau_0 - \tau_1) f^{(3)}_l(t - \tau_0) & \text{for } \tau_0 < t < \infty, \\
    0 & \text{otherwise,} 
\end{cases} \quad (8)$$

where $f^{(1)}_i(t) = \sum_{k=1}^{4} -\alpha_k C_{ik}^{-1} G_{k4} e^{-\alpha_k t}$, $f^{(2)}_j(t) = \sum_{k=1}^{4} -\beta_k C_{ik}^{-1} C_{k4} e^{-\beta_k t}$ and $f^{(3)}_l(t) = \sum_{k=1}^{4} -\gamma_k D_{ik}^{-1} D_{k4} e^{-\gamma_k t}$.

### 2.2 The distribution of the number of pairwise nucleotide differences

We assume the infinite sites model of Watterson [1975], according to which: a) in each generation, the number of mutations occurring in a sequence at a particular locus follows a Poisson distribution with mean $\mu$; and b) no two mutations ever occur at the same nucleotide site. In the coalescent approximation (measuring time in units of $2N$ generations), mutations accumulate on a pair of lineages according to a Poisson process of rate $\theta = 4N\mu$ ($\theta$ is the scaled mutation rate at the locus considered). Given the coalescence time $T_i$ of two DNA sequences at this locus, their number of segregating sites $S_i$ is Poisson distributed with mean $\theta T_i$. Denoting $g_s(t) := \frac{(\theta t)^s}{s!} e^{-\theta t}$, we have, for $s \in \{0, 1, 2, \ldots\}$,

$$P(S_i = s) = E[g_s(T_i)]$$

$$= \int_0^{\tau_1} g_s(t) f^{(1)}_i(t) dt + \sum_{j=1}^{4} p^{(1)}_{ij}(\tau_1) \int_{\tau_1}^{\tau_0} g_s(t) f^{(2)}_j(t - \tau_1) dt$$

$$+ \sum_{j=1}^{4} p^{(1)}_{ij}(\tau_1) \sum_{l=1}^{4} p^{(2)}_{jl}(\tau_0 - \tau_1) \int_{\tau_0}^{\infty} g_s(t) f^{(3)}_l(t - \tau_0) dt \quad , \quad (9)$$
where \( i \) is again the initial state of the coalescent, corresponding to the sampling locations of the two sequences. Changing the limits of integration, equation (9) becomes:

\[
P(S_i = s) = \int_0^{\tau_1} g_s(t) f_i^{(1)}(t) dt + \sum_{j=1}^{4} p^{(1)}_{ij}(\tau_1) \int_0^{\tau_0 - \tau_1} g_s(\tau_1 + t) f_j^{(2)}(t) dt \\
+ \sum_{j=1}^{4} p^{(1)}_{ij}(\tau_1) \sum_{l=1}^{4} p^{(2)}_{jl}(\tau_0 - \tau_1) \int_0^{\tau_0} g_s(\tau_0 + t) f_l^{(3)}(t) dt.
\]

Denoting by \( W_i, Y_j \) and \( Z_l \) the random variables with pdf’s \( f_i^{(1)}, f_j^{(2)} \) and \( f_l^{(3)} \) respectively, the above equation can be written as:

\[
P(S_i = s) = E[g_s(W_i) W_i \leq \tau_1] P[W_i \leq \tau_1]
+ \sum_{j=1}^{4} p^{(1)}_{ij}(\tau_1) E[g_s(\tau_1 + Y_j) | Y_j \leq \tau_0] P[\tau_1 + Y_j \leq \tau_0]
+ \sum_{j=1}^{4} p^{(1)}_{ij}(\tau_1) \sum_{l=1}^{4} p^{(2)}_{jl}(\tau_0 - \tau_1) E[g_s(\tau_0 + Z_l)] .
\]

Recall that \( f_i^{(1)}(t) = \sum_{k=1}^{4} -\alpha_k G_{ik}^{-1} G_{k4} e^{-\alpha_k t} \), \( f_i^{(2)}(t) = \sum_{k=1}^{4} -\beta_k C_{ik}^{-1} C_{k4} e^{-\beta_k t} \) and \( f_i^{(3)}(t) = \sum_{k=1}^{4} -\gamma_k D_{ik}^{-1} D_{k4} e^{-\gamma_k t} \), and that some eigenvalues of \( Q_1, Q_2 \) and \( Q_3 \) are equal to zero, i.e. some of the \( -\alpha_k, -\beta_k \) and \( -\gamma_k \) are zero. For those \( \alpha_k, \beta_k \) and \( \gamma_k \) that are strictly positive, we let \( W_k^*, Y_k^* \) and \( Z_k^* \) denote exponentially distributed random variables with rates \( \alpha_k, \beta_k \) and \( \gamma_k \) respectively. The equation above can then be written
as:

$$P(S_i = s) = \sum_{k: \alpha_k > 0} G_{ik}^{-1} G_{k4} \{ E[g_s(W^*_k)] - E[g_s(W^*_k)|W^*_k > \tau_1] P[W^*_k > \tau_1] \}$$

$$- \sum_{j=1}^{4} p_{ij}^{(1)}(\tau_1) \sum_{k: \beta_k > 0} C_{jk}^{-1} C_{k4} \{ E[g_s(\tau_1 + Y^*_k)] \}

- E[g_s(\tau_1 + Y^*_k)|\tau_1 + Y^*_k > \tau_0] P[\tau_1 + Y^*_k > \tau_0]$$

$$- \sum_{j=1}^{4} p_{ij}^{(1)}(\tau_1) \sum_{l=1}^{4} p_{jl}^{(2)}(\tau_0 - \tau_1) \sum_{k: \gamma_k > 0} D_{ik}^{-1} D_{k4} E[g_s(\tau_0 + Z^*_k)] .$$

Finally, making use of the lack of memory property of the exponential distribution gives:

$$P(S_i = s) = \sum_{k: \alpha_k > 0} G_{ik}^{-1} G_{k4} \{ E[g_s(W^*_k)] - E[g_s(\tau_1 + W^*_k)] e^{-\alpha_k \tau_1} \}$$

$$- \sum_{j=1}^{4} p_{ij}^{(1)}(\tau_1) \sum_{k: \beta_k > 0} C_{jk}^{-1} C_{k4} \{ E[g_s(\tau_1 + Y^*_k)] \}

- E[g_s(\tau_0 + Y^*_k)|\tau_0 - \tau_1] e^{-\beta_k (\tau_0 - \tau_1)} \}

$$- \sum_{j=1}^{4} p_{ij}^{(1)}(\tau_1) \sum_{l=1}^{4} p_{jl}^{(2)}(\tau_0 - \tau_1) \sum_{k: \gamma_k > 0} D_{ik}^{-1} D_{k4} E[g_s(\tau_0 + Z^*_k)] .$$

To give an explicit statement of the expectations in this probability mass function, we use the results of equations (16) and (17) in Wilkinson-Herbots (2012): for a random variable $U$ following an exponential distribution with rate $\lambda$,

$$E[g_s(U)] = \left( \theta \lambda / \lambda + \theta \right)^{\tau} \left( \lambda \lambda / \lambda + \theta \right)$$

and

$$E[g_s(\tau + U)] = \left( \theta \lambda / \lambda + \theta \right)^{\tau} \left( \lambda \lambda / \lambda + \theta \right) e^{-\theta \tau} \sum_{l=0}^{\infty} \frac{(\lambda + \theta)^{l+1}}{l!} \sum_{j=0}^{\tau^l} \frac{\lambda^j}{j!} .$$

2.3 The likelihood of a multilocus data set

Recall that, for the purposes of this paper, an observation consists of the number of nucleotide differences between two DNA sequences at a given locus. To fit the GIM model, we need a large set of observations from each of the three possible initial states:
both sequences sampled from species 1 (state 1); both sequences sampled from species 2 (state 2); and one sequence from each species (state 3). To compute the likelihood of such a set, we make use of the assumption of free recombination between loci.

Let $\mathbf{\rho}$ be the vector of parameters of the coalescent under the GIM model, i.e.

$$\mathbf{\rho} = \begin{bmatrix} a & b & c_1 & c_2 & \tau_1 & \tau_0 & M_1 & M_2 & M_1' & M_2' \end{bmatrix}. $$

Furthermore, let $\theta$ now denote the average mutation rate over all loci in the data set, and let the mutation rate at a given locus $l$ be represented by $\theta_l$. The parameter $\theta_l$ can be written as $\theta_l = r_l \theta$, where $r_l = \frac{\theta_l}{\theta}$ is the relative mutation rate of locus $l$. If the $r_l$ are known, the likelihood of a set of observations from independent loci can be written as

$$L(\mathbf{\rho}, \theta; x, \mathbf{r}) = \prod_l L(\mathbf{\rho}, \theta; x_l, r_l),$$

where $L(\mathbf{\rho}, \theta; x_l, r_l)$, the likelihood of the observation from locus $l$, has the same form as equation (10), but with $\theta$ replaced by $r_l \theta$ in equations (11) and (12).

For real data sets, the relative mutation rates must be estimated and substituted into the likelihood before any inference can be carried out. Estimates of $r_l$ can be computed by means of the following estimator suggested by Yang (2002), in which $L$ is the total number of loci, and $\bar{d}_l$ is the average, at locus $l$, of the ingroup-outgroup pairwise distance estimates (i.e. the average is over all the distance estimates that can be computed at locus $l$ using pairs of sequences that are composed of one ingroup sequence and one outgroup sequence):

$$\hat{r}_l = \frac{L \bar{d}_l}{\sum_{m=1}^L \bar{d}_m}. $$

### 3 Discussion

The main aim of this paper is to enable the comparison of three different scenarios for the divergence of closely related pairs of species (divergence without gene flow, with ancestral gene flow followed by isolation, and with continuous gene flow until the present), in a setting that allows for population sizes and migration rates to change during the divergence process. We achieve this aim by developing a maximum-likelihood method to fit the models illustrated in Figure 3 to DNA sequence data sets. A formal comparison of the different versions of the GIM model, by means of likelihood ratio tests or AIC scores, can easily be carried out. In Wilkinson-Herbots (2015) and Costa and Wilkinson-Herbots (2016), we show how to implement this sort of model selection procedure for the isolation-with-initial-migration model.

The likelihood given in equation (10) allows the estimation of the GIM model (see
Figure 3 and any model nested in it, including models with a single divergence stage, such as the complete isolation and the IM models represented in Figure 2. A special case of the GIM model which may be of particular interest represents a scenario of introgression as illustrated in Figure 4, where gene flow occurs between two diverging species after a period of isolation. Such a scenario may have been caused, for example, by climatic changes leading to habitat fragmentation and subsequent reconnection of populations.

![Figure 4](image)

**Figure 4:** A model of divergence in which current gene flow is preceded by a period of isolation (a GIM model with $m_1 = m_2 = 0$).

The extension of the present method to the Jukes-Cantor model of mutation should be relatively straightforward. Under this model of mutation, the probability mass function of the number of pairwise differences given $T$, the coalescence time, can be written as the sum of moment generating functions of pairwise coalescence times (see [Lohse et al., 2011](#) equation (3)). Hence integrating out $T$ analytically is still possible. This is left for future work.

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