1	Observation and control in models of population genetics
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#### 13 Abstract

14 Mathematical systems theory and optimal control have been mostly developed in the context of engineering. In this paper it is shown how these techniques can be applied in population 15 16 genetics. Based on the classical Fisher's selection model, first a very natural monitoring problem 17 is studied: Can the change of the genetic state of a population (described in terms of allele 18 frequencies) be uniquely recovered from the observation of the frequencies of certain phenotypes? We give sufficient conditions for a positive answer to this question in a typical 19 20 case of heterosis (when mixed genotypes are better than the pure ones, implying stable coexistence of all allele types). The second question is: How to effectively estimate the genetic 21 22 composition of the population from phenotypic observation? The answer is observer design, which is carried out for two different dominance structures, determining the manifestation of the 23 24 genetic state. In a model of artificial selection we show how the population can be steered into 25 equilibrium where maximal mean fitness is attained. Finally, the application of the above 26 methodology is also extended to selection-mutation models, where both fitness parameters and 27 mutation rates are controlled.

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31 process, observability, observer design, optimal control; 92D, 93B

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#### 1 1. Introduction

In the applications of mathematical systems theory the reconstruction of the state process from 2 3 available measurements is an important issue for several reasons. E.g. the observation of certain 4 state variables may be difficult, impossible or too expensive. Then, for the monitoring of the state process, we can observe only a transform of it. Observability of a system means that, from 5 this observation, in principle, the original state process can be recovered in a unique way. 6 7 Motivated by requirements of engineering, in terms of a matrix rank, a necessary and sufficient 8 condition for observability of linear systems was obtained in Kalman et al. [1]. The sufficient 9 part of this condition was then generalized to nonlinear systems in Lee and Markus [2]. The 10 latter sufficient condition already could be applied to density-dependent population systems, since the models describing them are typically nonlinear, see e.g. in López et al. [3,4]. 11 12 The observation (or monitoring) of the time-dependent genetic composition of a population is 13 an important issue. Applying tools of mathematical systems theory, our objective is to recover the genetic state from phenotypic observation, in the framework of a dynamic model describing 14 15 the change of the genetic composition of a population. (In static situation, in Garay and Garay [5] biological conditions were given for the allele frequency vector - phenotype frequency 16 17 *vector* correspondence to be one-to-one.) This is motivated by the fact that, usually, it is easier 18 or more economic to observe the phenotypic state of a population than its underlying genetic 19 state. In this sense, in López et al. [6], a similar problem was studied, but considering the so-20 called strategic model, where the state of the population is the allelic frequency vector in the zygote population, the phenotype of a zygote means a behavior strategy uniquely determined by 21 its genotype, and an evolutionary game is played at phenotypic level. The difference between 22 23 this model and Fisher's model we shall consider in this paper, is that the frequencies of the 24 different phenotypes can be calculated from the frequencies of the different genotypes according 25 to the dominance of alleles in the corresponding hereditary system, determining the manifestation of the genetic state. Moreover, in the model of Fisher, a phenotype is not 26 27 necessarily a behavior type, it may also be a physical aspect of individuals.

Observability of Fisher's Model of Natural Selection was considered in Varga [7], giving 1 sufficient condition guaranteeing that, observing phenotypic frequencies in function of time. 2 3 The underlying genetic state in terms of allele frequencies can be recovered. This result was 4 extended to a model with mutation in López [8], López et al. [9]. Later, applying the observer design method of Mathematical Systems Theory, in addition to observability, the genetic 5 process has been effectively calculated from the observation of the mean phenotype. In the 6 7 present paper, in the framework of Fisher's Model of Natural Selection, we illustrate the 8 application of the general observer design methodology to different dominance structures with 9 different phenotypic observations, in order to recover the underlying genetic process.

10 Concerning *controllability*, as a model of artificial selection, in Varga [10], from Fisher's equations, a control system was constructed and, in terms of the model parameters, sufficient 11 conditions were obtained for the system to be controllable to equilibrium, see also López et al. 12 13 [11], where controllability of the population to a state with maximal mean fitness was considered. In Scarelli and Varga [12], controllability of Fisher's model with mutation was 14 15 studied, where time-dependent mutation rates were considered as control functions, while in López et al. [9] the controllability of the same model was investigated with time-dependent 16 17 fitness parameters as control functions. This construction can be considered as a control-18 theoretical model of artificial selection. We also emphasize that a developed methodology is 19 available for induced allele mutations, a quick reference is e.g. McClean [13].

In the present paper, as an illustration of application of this methodology, with a particular choice of the genotype to be controlled, for Fisher's selection model, we not only "theoretically" state local controllability, but also effectively calculate the corresponding equilibrium control, that is a control that steers nearby states to the equilibrium. On the one hand, we will consider the control of fitness parameters, which is a *model of traditional artificial selection*. On the other hand, we also address the control of mutation rates, which can be considered as a *model* for artificial mutation used in *genetic engineering*.

In Section 2, we recall basic results on existence and stability of an equilibrium in Fisher'sselection model. In Section 3, observability of Fisher's model is studied in a particular case of

heterosis (when mixed types are better than the pure ones), implying stable coexistence of all allele types, with maternal inheritance. Section 4 is dedicated to the observer design for the Fisher's model in two different dominance structures. In Section 5, for a given inheritance pattern, we construct a control (selection strategy) that steers the system into equilibrium, where maximal mean fitness is attained. In Sections 6 and 7 we extend the application of the above methodology to selection-mutation processes of population genetics.

7

#### 8 2. Description of model and existence of equilibrium

9 We shall consider a diploid panmictic Mendelian population with alleles  $A_1,...,A_n$ , at an 10 autosomal locus. Assume that the diploid zygote individuals undergo a selection described in 11 terms of a fitness matrix  $W \in \mathbb{R}^{n \times n}$  with non-negative components, where, for each  $i, j \in \overline{1, n}, w_{ij}$ 12 is the Malthusian fitness value of an  $A_iA_j$  zygote (defined as the difference of the birth rate and 13 the death rate of  $A_iA_j$  individuals or the average number of offspring of a zygote of genotype 14  $A_iA_j$ ). Then, according to Fisher's classical model of *natural selection*, for the time-dependent 15 frequency  $x_i$  of allele  $A_i$ , we have

16 
$$\dot{x}_i = x_i \left[ (Wx)_i - \langle x, Wx \rangle \right] \quad (i \in \overline{1, n})$$
 (2.1)

17 where

18 
$$w_i(x) = (Wx)_i = \sum_{j=1}^n w_{ij} x_j$$

19 is the *potential (marginal) fitness* of allele  $A_i$ , and

20 
$$\overline{w}(x) = \langle x, Wx \rangle = \sum_{k,l=1}^{n} w_{kl} x_k x_l$$

is the *mean fitness* of the population in state x. The biological interpretation of Fisher's model is the following: if the potential fitness of  $A_i$  is greater than the average fitness of the whole

- population, then the frequency of  $A_i$  will increase, in the contrary case it will decrease.
- 24 The state vector x of allele frequencies is an element of the standard simplex

1 
$$\Delta_n = \{ x \in \mathbf{R}^n : x_i \ge 0 \ (i \in \overline{1, n}), \sum_{i=1}^n x_i = 1 \}$$

2 It is easy to see that the standard simplex  $\Delta_n \subset \mathbf{R}^n$  and its interior

3 
$$\Delta_n = \{x \in \Delta_n : x_i > 0 \ (i \in \overline{1, n})\}$$

are positively invariant for dynamics (2.1). A state x\* ∈ Δn is called a *polymorphic equilibrium*of the population if in this state all alleles have the same potential fitness, or equivalently,
w<sub>i</sub>(x\*) = w̄(x\*) (i∈1,n).

7 Theorem 2.1. (See e.g. Varga [10]) Assume that the following *regularity condition* holds: W

8 is invertible; with  $\mathbf{1} = (1,...,1)^T \in \mathbb{R}^n$ ,  $\langle W^{-1}\mathbf{1},\mathbf{1} \rangle \neq 0$  holds, and for

9 
$$x^* = \frac{W^{-1}\mathbf{1}}{\left\langle W^{-1}\mathbf{1},\mathbf{1}\right\rangle},$$
 (2.2)

10 we have  $x^* > 0$ . Then  $x^*$  is the unique polymorphic equilibrium. If the matrix

11 
$$P = (p_{ij})_{(n-1)\times(n-1)}, \quad p_{ij} = w_{ij} - w_{in} - w_{nj} + w_{nn}$$

12 is negative definite, then  $x^*$  is globally asymptotically stable for system (2.1) on  $\overset{\circ}{\Delta}_n$ , and  $x^*$  is 13 a global strict maximum point of  $\overline{w} | \overset{\circ}{\Delta}_n$ . If *P* is positive definite, then  $x^*$  is unstable for 14 system (2.1), the state of the population "escapes" from the equilibrium  $x^*$  with minimal mean 15 fitness.

16

# 3. Analysis of observability in a particular case of heterosis in the Fisher's model with maternal inheritance

19 Consider the Mendelian population of Section 2. It is known that, if the hereditary system is 20 maternal, this population can display all possible phenotypic states, i.e. vectors of phenotypic 21 frequencies (Garay and Garay [5]). Suppose that the inheritance is maternal, and consider for 22 simplicity three alleles A<sub>1</sub>, A<sub>2</sub> and A<sub>3</sub>, where the genotypes A<sub>1</sub>A<sub>2</sub> and A<sub>1</sub>A<sub>3</sub> have the same phenotype A
<sub>1</sub> as A<sub>1</sub>A<sub>1</sub>; the genotypes A<sub>2</sub>A<sub>1</sub> and A<sub>2</sub>A<sub>3</sub> have the same phenotype A
<sub>2</sub> as A<sub>2</sub>A<sub>2</sub>;
 and the genotypes A<sub>3</sub>A<sub>1</sub> and A<sub>3</sub>A<sub>2</sub> have the same phenotype A
<sub>3</sub> as A<sub>3</sub>A<sub>3</sub>. Then, by the Hardy Weinberg law, for any allelic frequency vector x ∈ Δ<sub>3</sub> of system (2.1), the corresponding
 phenotypic frequencies are the following:

5  

$$\overline{A}_{1}: \quad x_{1}^{2} + x_{1}x_{2} + x_{1}x_{3},$$

$$\overline{A}_{2}: \quad x_{2}x_{1} + x_{2}^{2} + x_{2}x_{3},$$

$$\overline{A}_{3}: \quad x_{3}x_{1} + x_{3}x_{2} + x_{3}^{2}.$$

#### 6 **3.1.** Existence and stability of a polymorphic equilibrium of the model

7 Let us consider the following, three-allele Fisher model

8 
$$\dot{x}_i = x_i \left[ (Wx)_i - \langle x, Wx \rangle \right] \quad (i \in \overline{1,3}),$$
(3.1)

9 where the fitness matrix is

10 
$$W = \begin{bmatrix} 1 & 1 - \alpha & 1 - \beta \\ 1 - \alpha & 1 & 1 - \alpha \\ 1 - \beta & 1 - \alpha & 1 \end{bmatrix},$$
 (3.2)

11 with parameters 
$$\alpha, \beta \in A = (-1,1) - \{0\}$$

Now we discuss the stability properties of the corresponding Fisher selection equations, for
different parameter values of this fitness matrix. First fix α, β ∈ A, and check the *regularity condition* for the calculation of the polymorphic equilibrium (see e.g. Varga [10]):

,

15 
$$\det W = \beta(4\alpha - 2\alpha^2 - \beta) \neq 0 \text{ if and only if, } 2\alpha(2 - \alpha) \neq \beta$$

16 
$$\langle W^{-1}\mathbf{1},\mathbf{1}\rangle = \frac{\beta - 4\alpha}{\beta(4\alpha - 2\alpha^2 - \beta)} \neq 0$$
 if and only if  $2\alpha(2 - \alpha) \neq \beta$ ,  $\beta \neq 4\alpha$ ,

17 
$$x^* = \frac{W^{-1}\mathbf{1}}{\langle W^{-1}\mathbf{1},\mathbf{1} \rangle} = \left(\frac{-\alpha}{\beta - 4\alpha}, \frac{\beta - 2\alpha}{\beta - 4\alpha}, \frac{-\alpha}{\beta - 4\alpha}\right), \quad (3.3)$$

18 which is positive if and only if,

19 either 
$$\beta - 4\alpha > 0$$
,  $\beta - 2\alpha > 0$ ,  $\alpha < 0$ ; or  $\beta - 4\alpha < 0$ ,  $\beta - 2\alpha < 0$ ,  $\alpha > 0$ .

1 For the analysis of the stability of  $x^*$ , we easily calculate the corresponding auxiliary matrix

2 
$$P = \begin{bmatrix} 2\beta & \beta \\ \beta & 2\alpha \end{bmatrix},$$

3 (see e.g. Varga [10]) whose principal minors are

4 
$$2\beta, \beta(4\alpha - \beta).$$

**5** Case A) Let  $\alpha, \beta \in A$ , and  $4\alpha < \beta < 0$ . Obviously  $\alpha < 0$  and therefore all off-diagonal 6 entries of the fitness matrix are greater than those of the principle diagonal, that is, we are in a 7 case of heterosis, all heterozygotes are fitter than any homozygote. From the principle minors 8 we obtain that in this case matrix P is negative definite, which implies that the polymorphic 9 equilibrium  $x^*$  is (globally) asymptotically stable.

10 Case B) Let α, β∈ A and 4α > β > 0. In this case, all homozygotes are fitter than any
11 heterozygote. Now matrix P is positive definite, which implies that the polymorphic
12 equilibrium x<sup>\*</sup> is unstable.

#### 13 **3.2.** Observability

For the analysis of the observability of the model of the previous subsection, we consider the parameter values where the polymorphic equilibrium  $x^*$  exists and it is asymptotically stable,

16 that is, when  $\alpha, \beta \in A$  and

17 
$$2\alpha(2-\alpha) \neq \beta, \beta \neq 4\alpha, 4\alpha < \beta < 0, \beta - 2\alpha > 0, \alpha < 0,$$

18 or equivalently, when

19 
$$\alpha, \beta \in A \text{ and } 2\alpha < \beta < 0.$$

20

#### 21 *Observation of the first phenotype*

22 If we observe the first phenotype  $\overline{A}_1$ , the observation function is defined by

23 
$$y = h(x) = x_1^2 + x_1 x_2 + x_1 x_3 - ((x_1^*)^2 + x_1^* x_2^* + x_1^* x_3^*).$$
(3.4)

1 (For technical reason the observed quantity is the deviation of the frequency of the first 2 phenotype  $\overline{A}_1$  from its value at equilibrium.)

Now, we provide a sufficient condition for local observability of the system (3.1) with fitness matrix W defined in (3.2). We recall that local observation in this case means that, near the equilibrium, observing only the frequency of the first phenotype, in principle, the whole genetic process (in terms of allele frequencies) can be recovered in a unique way (see Definition A.2 of the Appendix).

8 **Theorem 3.1.** Suppose that

9

$$\alpha, \beta \in A, 2\alpha < \beta < 0, \text{ and } \alpha \neq \beta.$$
(3.5)

10 Then observation system (3.1)-(3.4) is locally observable at  $x^*$  in  $\Delta_3$ .

11 *Proof.* We will apply Theorem A.3 of Appendix with  $H = \Delta_3$ . The tangent space of  $\Delta_3$  at  $x^*$ 12 is

13 
$$T_* = \left\{ z \in \mathbf{R}^3 : \sum_{i=1}^3 z_i = 0 \right\}$$

14 and matrix  $C = h'(x^*)$  is given by

15  $C = \begin{bmatrix} x_1^* + 1 & x_1^* & x_1^* \end{bmatrix}.$ 

16 For a symmetric matrix  $W = (w_{ij})_{3\times 3}$ , matrix  $L = f'(x^*) = (l_{ij})_{3\times 3}$  is determined by

17 
$$l_{ij} = x_i^* (w_{ij} - 2\overline{w}(x^*)).$$
 (3.6)

18 For our case, W is defined in (3.2) and  $x^*$  in (3.3). In order to check condition (A.3) of the 19 Appendix, suppose that  $z \in T_* \cap Ker Q$ . Then, Cz = 0 implies  $z_1 = 0$ . Hence we get 20  $z_2 = -z_3$ . Furthermore, CLz = 0 which gives

21 
$$\frac{\alpha(\beta-\alpha)z_3}{\beta-4\alpha} = 0$$

By condition (3.5),  $\alpha \neq \beta$ ,  $2\alpha < \beta < 0$ , also implying  $\alpha < 0$  and therefore  $\beta - 4\alpha > 0$ . 1 Furthermore, also by the definition of set A we have  $\alpha \neq 0$ . Then all this implies  $z_3 = 0$ , and 2 3 hence z = 0. Applying Theorem A.3 of the Appendix, we obtain local observability of system (3.1)-(3.4) at  $x^*$  in  $\Delta_3$ . 4 **Remark 3.2.** Note that if  $\alpha = \beta$ , we cannot guarantee local observability of system (3.1)-(3.4) 5 with fitness matrix (3.2), at equilibrium  $x^*$  (defined in (3.3)), in  $\Delta_3$ . 6 7 8 Observation of the second phenotype If we observe the second phenotype  $\overline{A}_2$ , the observation function is 9  $y = h(x) = x_2 x_1 + x_2^2 + x_2 x_3 - (x_2^* x_1^* + (x_2^*)^2 + x_2^* x_3^*).$ 10 (3.7)11 Now, we show that the sufficient condition of Theorem A.3 for local observability of system 12 cannot be applied to observation system (3.1)-(3.3), (3.7). Now matrix  $C = h'(x^*)$  is given by 13  $C = \begin{bmatrix} x_2^* & x_2^* + 1 & x_2^* \end{bmatrix},$ 14 and the linearization matrix L is calculated by (3.6), with the corresponding coefficients of 15 16 fitness matrix defined in (3.2). In order to check condition (A.3) suppose that  $z \in T_* \cap Ker Q$ . Then Cz = 0 implies  $z_2 = 0$ . Hence we get  $z_1 = -z_3$ . However, for our particular fitness 17 matrix we have CLz = 0, and  $CL^2z = 0$  for any values of  $\alpha$  and  $\beta$ , since in this model 18  $x_1^* = x_3^*$ . Therefore, any  $z \neq 0$  verifying conditions  $z_2 = 0$  and  $z_1 = -z_3$  belongs to 19 20  $T_* \cap Ker Q$ , therefore conditions of Theorem A.3 are not satisfied. 21 22 Observation of the third phenotype If we observe the third phenotype  $\overline{A}_3$ , the observation function is 23

24 
$$y = h(x) = x_3 x_1 + x_3 x_2 + x_3^2 - (x_3^* x_1^* + x_3^* x_2^* + (x_3^*)^2).$$
 (3.8)

Now matrix  $C = h'(x^*)$  is 1

2

 $C = \begin{bmatrix} x_3^* & x_3^* & x_3^* + 1 \end{bmatrix}.$ 

Next, reasoning in analogous way to the proof of Theorem 3.1, it is easy to obtain the same 3 sufficient condition for local observability of the system (3.1) - (3.3), (3.8) with fitness matrix 4 5 W defined in (3.2):

Theorem 3.3. Suppose that 6

7

$$\alpha, \beta \in A, 2\alpha < \beta < 0$$
, and  $\alpha \neq \beta$ .

8 Then observation system (3.1)-(3.8) with fitness matrix defined in (3.2) is locally observable at

 $x^*$  in  $\Delta_3$ . 9

10 Remark 3.4. In this model when the equilibrium is asymptotically stable and the parameters of model  $\alpha$  and  $\beta$  are different, then observing the first or the third phenotype we can recover 11 12 the allelic state of the population from phenotypic observation.

Remark 3.5. When in this model we are in a case of heterosis where the fitness of all 13 heterozygotes is the same, that is,  $\alpha = \beta$ , we cannot guarantee the local observability of the 14 15 model observing only one phenotype.

16 Remark 3.6. If we observe any two phenotypes in this population (then, of course, all phenotype frequencies are known), and as we are in a case of maternal inheritance, the quadratic 17 18 function that maps allele distributions into phenotypic distributions is invertible (see Garay and 19 Garay [5]). Therefore, it is also possible to recover the allelic state of population, independently 20 from the dynamics.

21

#### 22 4. Design of an observer system from phenotypic observation

23 In this section, for two different situations we shall see how to recover the genetic population 24 from the observation of one phenotype, by the construction of the so-called observer system 25 (see Section A.1 of Appendix).

1 The observer we construct will not only approximate the solution of the original system, but in 2 case of observation of a single phenotype (i.e. in systems-theoretical terms we have a single-3 output system), the solution of the observer is also a substitute of the latter in the sense that the 4 interior of the simplex is long-term invariant for the observer system. In other words, the values 5 z(t) of the solution of the observer system, for t large enough, can be interpreted as frequency 6 vectors.

7 Theorem 4.1. Considering dynamics (2.1) with a scalar-valued the observation function h, 8 suppose that an interior equilibrium  $x^*$  is asymptotically stable for system (2.1), for a matrix

9 
$$K = (k_i)_{n \times 1}$$
 with  $k_i \in \mathbf{R}$ ,  $\sum_{i=1}^n k_i = 0$  holds, and  $L - KC$  is Hurwitz (i.e. its eigenvalues have

10 negative real parts), where  $L = f'(x^*)$  and  $C = h'(x^*)$ . Then

11 
$$\dot{z} = f(z) + K[y - h(z)]$$
 (4.1)

is a local exponential observer for the observation system (see Definition A.4 of the Appendix),
and for any solution of x of system (2.1) initially close enough to x\*, Δ<sub>n</sub> is *locally long-term invariant* for the observer system at equilibrium x\*. (The latter means that for z(0) from an
appropriate neighborhood of x\* in Δ<sub>n</sub>, there exists a t<sub>0</sub> ∈ R<sup>+</sup> such that z(t) ∈ Δ<sub>n</sub> for all
t ∈ (t<sub>0</sub>,∞).

Proof. Under our conditions, from Sundarapandian's theorem (Theorem A.7 of the Appendix),
it follows that (4.1) is an observer system for system (2.1) with observation function h.
Furthermore, by the asymptotic stability of x\*, we can suppose that lim<sub>t→∞</sub> x(t) = x\*. Let us sum the
coordinates of system (4.1):

21 
$$\left(\sum_{i} z_{i}\right) = \sum_{i} f_{i}(z) + \sum_{i} k_{i}(y - h(z)) = \sum_{i} f_{i}(z) + (h(x) - h(z))\sum_{i} k_{i} = 0,$$

1 implying 
$$\sum_{i} z_i(t) = 1$$
, if  $\sum_{i} z_i(0) = 1$ . Moreover, since  $\lim_{t \to \infty} (z(t) - x(t)) = 0$  and

- 2  $\lim_{\infty} x = x^* \in \overset{\circ}{\Delta}_n$ , there exists  $t_0 \in \mathbf{R}^+$  such that  $z(t) \in \overset{\circ}{\Delta}_n$  for all  $t \in (t_0, \infty)$ .
- 3

### 4 *Observation of one phenotype in the case of maternal inheritance*

If we consider a population with n alleles and n phenotypes with a maternal hereditary system
and observe the *l*-th phenotype A<sub>l</sub> of a population, then the observation function is

7 
$$y = h(x) = \sum_{j=1}^{n} x_{l} x_{j} - \sum_{j=1}^{n} x_{l}^{*} x_{j}^{*} = \sum_{j=1}^{n} (x_{l} x_{j} - x_{l}^{*} x_{j}^{*}).$$
(4.2)

Example 4.2. To illustrate the design of an observer we consider the three-allele threephenotype model (3.1) of Section 3.1 with α = -0.5 and β = -0.25. It is easy to check that
x\* = (0.2857, 0.4286, 0.2857) is a positive asymptotically stable equilibrium for this system.
If the first phenotype is observed with observation function (3.4), then as conditions (3.5) are
verified, by Theorem 3.1, we have local observability of system (3.1)-(3.4) at x\* in Δ3.
Now we obtain the following linearization matrices:

14 
$$C = \begin{bmatrix} x_1^* + 1 & x_1^* & x_1^* \end{bmatrix} = \begin{bmatrix} 1.2857 & 0.2857 \end{bmatrix},$$

15 
$$L = \begin{bmatrix} -0.4490 & -0.3061 & -0.3776 \\ -0.4592 & -0.6735 & -0.4592 \\ -0.3776 & -0.3061 & -0.4490 \end{bmatrix}.$$

16 In order to apply Theorem 4.1 we have chosen the following gain matrix satisfying the17 condition of this theorem:

$$K = \begin{bmatrix} 1 \\ 0 \\ -1 \end{bmatrix},$$

19 also obtaining with this choice that matrix L - KC has only eigenvalues with negative real 20 parts. Therefore the observer system for observation system (3.1)-(3.4) is

1 
$$\dot{z}_i = z_i \left[ (Wz)_i - \langle z, Wz \rangle \right] + \left( K(y - h(z)) \right)_i \qquad (i \in \overline{1,3}) .$$
(4.3)

2 At the same time, matrix K satisfies the conditions of Theorem 4.1, therefore  $\Delta_3$  is locally 3 long-term invariant.

In order to show how the observer system approximately provides the solution of the original
system from the phenotypic observation, suppose that the initial condition for the original
system is x(0) = (0.25, 0.35, 0.4) and z(0) = (0.3, 0.4, 0.3) for the observer system (4.3). In
Figure 1, we can see how the solution of the observer system practically ends up in the solution
of the original system.



Fig. 1. Solution of the original system (3.1) and solution of the observer system (4.3) with initial conditions x(0) = (0.25, 0.35, 0.4) and z(0) = (0.3, 0.4, 0.3), respectively

12

9

Example 4.3. We consider a single-locus three-allele, codominant inheritance pattern. Since the most known example is AB0 blood group system, we will us the same notation for the three alleles: A, B and 0. A and B are dominant over 0, A and B are co-dominant. In other words, the genotypes AA, A0 and 0A have the same phenotype  $\overline{A}$ ; BB, B0 and 0B have the same phenotype  $\overline{B}$ , AB and 00 have the respective phenotypes  $\overline{AB}$  and  $\overline{0}$ . According to the Hardy1 Weinberg proportions, for any allele frequency vector  $x \in \Delta_3$ , whose coordinates correspond to

2 frequencies of alleles A, B and 0, respectively, the corresponding phenotype frequencies are:

3  

$$\begin{array}{rcl}
A: & x_1^2 + 2x_1x_3 \\
\overline{B}: & x_2^2 + 2x_2x_3 \\
\overline{AB}: & 2x_1x_2 \\
\overline{0}: & x_3^2 \\
\end{array}$$

We note that at population level these phenotype frequencies, i.e. the phenotypic process, and 4 5 the underlying genetic process may be interesting for healthcare studies. In fact, e.g., it is known that the carriers of blood groups  $\overline{A}, \overline{B}, \overline{AB}$  and  $\overline{0}$  have different susceptibilities to certain 6 diseases such as certain malignant tumors, gastric ulcer or certain infectious diseases (see e.g. 7 8 Vogel and Motulsky [14]). Therefore, the genetic composition (the allele frequencies) of the 9 population, estimated from phenotype frequencies, may have implications for morbidity trends in the population. Assume that the only phenotype we observe is  $\overline{0}$ . Then the observation 10 11 function is

12 
$$y = h(x) = x_3^2 - (x_3^*)^2$$
. (4.4)

13 Just for an illustration we consider the following simple fitness matrix:

14 
$$W = \begin{bmatrix} 1 & 3 & 4 \\ 3 & 1 & 3 \\ 4 & 3 & 1 \end{bmatrix}$$

The corresponding polymorphic equilibrium x\* = (0.4, 0.2, 0.4) is asymptotically stable, and system (3.1)-(4.4) is locally observable in Δ3 (see Varga [7]). Therefore, in this model, although the frequencies of alleles A, B and 0 are not directly observed, they can be reconstructed by observing only the time-dependent frequency of phenotype 0.

19 Next we shall recover (estimate) the genetic process from this phenotypic observation by the 20 construction of the observer system. Moreover, similarly to Example 4.2, the solution of the 21 observer system not only approximates the solution of the original system but also is a kind of 1 substitute of it, since according to Theorem 4.1,  $\Delta_3$  is locally long-term invariant for the 2 observer system at equilibrium  $x^*$ , and therefore the solutions of the observer system can be 3 interpreted as time-dependent allele frequency vectors. The corresponding linearization 4 matrices are

5 
$$C = \begin{bmatrix} 0 & 0 & 2x_3^* \end{bmatrix} = \begin{bmatrix} 0 & 0 & 0.8 \end{bmatrix},$$
$$\begin{bmatrix} -1.68 & -0.88 & -0.48 \end{bmatrix}$$

$$L = \begin{bmatrix} -0.44 & -0.84 & -0.44 \\ -0.48 & -0.88 & -1.68 \end{bmatrix}.$$

7 The choice of gain matrix is

8 
$$K = \begin{bmatrix} 1 \\ -1 \\ 0 \end{bmatrix},$$

9 implying that L - KC is Hurwitz. Applying Theorem 4.1, the observer system is

10 
$$\dot{z}_i = z_i [(Wz)_i - \langle z, Wz \rangle] + (K(x_3^2 - z_3^2))_i \quad (i \in \overline{1,3}).$$
 (4.5)

11 In order to graphically illustrate how the solution of the observer system approximates the 12 solution of the original system, we consider an initial condition for the original system 13 x(0) = (0.35, 0.4, 0.25) and z(0) = (0.45, 0.35, 0.2) for the observer system, see Figure 2.



1

Fig. 2. Solution of the original system (3.1) and solution of the observer system (4.5) with initial
conditions x(0) = (0.35, 0.4, 0.25) and z(0) = (0.45, 0.35, 0.2), respectively

4

#### 5 5. Optimization of mean fitness of the population via artificial selection

6 In mathematical terms, an important implication of the Fisher's Fundamental Theorem is that 7 during the infinite selection process the mean fitness of the population increases. A natural 8 population has the tendency to be in a state of maximum mean fitness. In our model of artificial 9 selection we want to control the population into the state of maximum mean fitness, controlling 10 the population by changing the fitness parameters of certain genotypes, realizing the artificial selection in terms of controlling the number of offspring. Under appropriate conditions, this 11 12 state of maximum mean fitness is reached at an asymptotically stable polymorphic equilibrium  $x^*$ . (If the polymorphic equilibrium is unstable, the state of the population "escapes" from the 13 14 equilibrium with minimal mean fitness.) In case of an asymptotically stable polymorphic 15 equilibrium, the latter is reached in "infinite time". In our model, instead, the genetic state can 16 be controlled to equilibrium (state of maximal mean fitness) in given finite time.

For an illustrative example we consider a population with three alleles  $A_1$ ,  $A_2$  and  $A_3$  at an autosomal locus. It is logical to suppose that we cannot distinguish individuals of the same

1 phenotype. Then for a concrete illustration we consider the same hereditary system used in López et al. [11]: We suppose that homozygotes have different phenotypes, A1 is dominant over 2 3  $A_2$  and  $A_3$ , while  $A_2$  is dominant over  $A_3$ . It is supposed that the fitness of homozygotes  $A_3A_3$  is controlled (that is, a control term  $u \in U_{\varepsilon}[0,T]$  is added to fitness  $w_{33}$ , see Section A.2 of 4 5 Appendix). For a general fitness matrix W, in López et al. [11], in biological terms we obtained 6 a sufficient condition for the existence of an optimal artificial selection strategy: If genotypes 7 A<sub>1</sub>A<sub>3</sub> and A<sub>2</sub>A<sub>3</sub> have different fitness values ( $w_{13} \neq w_{23}$ ), then the system is locally controllable to  $x^*$  within  $\Delta_3$ , guaranteeing maximal mean fitness to the population if the conditions of 8 Theorem 2.1 are satisfied. For  $\varepsilon$  small enough,  $\Delta_n^{\circ}$  is an (n-1)-dimensional regular 9

submanifold positively invariant with respect to controls  $u \in U_{\varepsilon}$ , see (Varga [21]).

In this section, we shall provide an approximate numerical solution of the correspondingoptimal control problem, applying it to a concrete numerical example using a MatLab toolbox.

13 For  $\varepsilon > 0$ , let us consider the corresponding optimal control problem:

14 
$$J(u) = \overline{w}(x(T)) \to \max,$$
 (5.1)

$$u \in U_{\varepsilon}[0,T], \tag{5.2}$$

16 
$$\dot{x}_i = x_i[(W_u x)_i - \langle x, W_u x \rangle] \quad (i \in \overline{1,3}),$$
 (5.3)

17 
$$x(0) = x^0 \in \overset{\circ}{\Delta}_3,$$
 (5.4)

18 where

19 
$$W_{u} = \begin{bmatrix} w_{11} & w_{12} & w_{13} \\ w_{21} & w_{22} & w_{23} \\ w_{31} & w_{32} & u^{*} + u(t) \end{bmatrix}, \text{ with } u^{*} = w_{33}.$$

Now, for a numerical solution of this problem using the MatLab toolbox of Banga *et al.* [15],
see also Hirmajer *et al.* [16], piecewise constant controls will be considered. The application of
these particular step functions is justified by the following theorem guaranteeing an appropriate
suboptimal solution among the piecewise constant controls corresponding to uniform division of

the time interval. Therefore, in the presented numerical example the solution provided by the
toolbox will be considered the *numerical solution* of the optimal control problem (5.1)-(5.4).

Theorem 5.1. Assume that for a parameter choice, in addition to the conditions of Theorem
2.1, inequality w<sub>13</sub> ≠ w<sub>23</sub> also holds. Then, for every initial state x<sup>0</sup> close enough to x\*, the
optimal control problem (5.1)-(5.4) has a solution u<sup>0</sup>. Furthermore, for any δ > 0, this optimal
control problem admits a piecewise constant δ-solution u<sup>δ</sup> in the sense that
J(u<sup>0</sup>) - J(u<sup>δ</sup>) < δ.</li>

Proof. Since under the given conditions, the mean fitness attains a maximum at the equilibrium x\*, and control system (5.3) is locally controllable, there exists a neighborhood G(x\*) such that, with x(0) = x<sup>0</sup> ∈ G(x\*) ∩ Δ3, optimal control problem (5.1)-(5.4) has a solution u<sup>0</sup> ∈ U<sub>ε</sub>[0,T]. From the proof of the sufficient condition for local controllability, Theorem A.12 of the Appendix (see Varga [10]), it can be seen that u<sup>0</sup> can be also chosen from the class C<sup>∞</sup>[0,T].

For fixed positive integer N, let  $t_i = i \cdot (T / N)$  ( $i \in \overline{0, N}$ ) the uniform division of [0, T], and let us define the set of piecewise controls as

16 
$$S_{\varepsilon}[0,T] = \bigcup_{N \in \mathbb{N}} S_{\varepsilon,N}[0,T],$$

#### 17 where

18  $S_{\varepsilon,N}[0,T] = \{ u \in U_{\varepsilon}[0,T] : u \text{ is constant on each interval}(t_{i-1},t_i) \ (i \in \overline{0,N}) \}.$ 

19 It is easy to see that set  $S_{\varepsilon}[0,T]$  is dense in  $U_{\varepsilon}[0,T]$ . Therefore, from the continuous 20 dependence of the solution of system (5.3) on the control (Theorem A.9 of the Appendix), it 21 follows that for every  $\delta > 0$  there exists  $u^{\delta} \in S_{\varepsilon}[0,T]$  with  $J(u^{0}) - J(u^{\delta}) < \delta$ .

22 For the numerical illustration, consider system (5.3) with the fitness matrix of Example 4.2

$$W_{u} = \begin{bmatrix} 1 & 1.5 & 1.25 \\ 1.5 & 1 & 1.5 \\ 1.25 & 1.5 & 1+u(t) \end{bmatrix}.$$

Since  $w_{13} \neq w_{23}$  is verified, we can apply Theorem 5.1, and therefore the considered optimal 2 3 control problem has a numerical solution. 4 We have polymorphic (i.e. positive) asymptotically stable equilibrium а  $x^* = (0.2857, 0.4286, 0.2857)$  for the system without control. 5 Our objective is to determine a control of system (5.3), that steers the system into equilibrium. 6 Fix time duration T = 30, and take initial condition  $x^0 = (0.25, 0.35, 0.4)$  for system (5.3). 7 For the calculation of the corresponding solution, we apply the MatLab toolbox of Banga et al. 8 [15]. Figure 3 shows the corresponding solution x ending up at equilibrium  $x^*$ , and in Figure 4 9 10 we show the obtained optimal control.



11

1



14

15



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2

**Fig. 4.** Optimal control function of system (5.3), plotted for [0, 15]

**Remark 5.2.** If the hereditary system considered in this section were maternal, then in order to intervene in the third phenotype we should control the fitness of all genotypes whose phenotype is  $\overline{A}_3$ , that is, we should add a control to  $w_{31}$ ,  $w_{32}$  and  $w_{33}$ .

6

#### 7 6. Observation in a selection-mutation model

8

9 In this section our systems-theoretical study will be extended to include mutation, as well. In 10 López *et al.* [9] we have only shown that in certain selection-mutation systems, in principle, it 11 may be possible to uniquely recover the underlying population-genetic process from the 12 observation of phenotypes. In this section we present a method that makes it possible to 13 effectively calculate the genetic process from observed phenotype frequencies in selection-14 mutation systems.

Starting from selection model (2.1), we suppose that there may be mutation from allele  $A_j$  to allele  $A_i$  (symbolically  $A_j \rightarrow A_i$ ) with mutation rate  $m_{ij}$ , for each  $i, j \in \overline{1, n}$  with  $i \neq j$ , and in addition we define

$$m_{ii} = -\sum_{j \neq i} m_{ji}$$

Then, with the fitness matrix W of Section 2 and mutation matrix M = [m<sub>ij</sub>]<sub>n×n</sub>, the selectionmutation process, in terms of allele frequencies, can be described by the following system of
differential equations:

$$\dot{x}_i = x_i \left[ (Wx)_i - \langle x, Wx \rangle \right] + (Mx)_i \qquad (i \in \overline{1, n}).$$
(6.1)

5 It is known that system (6.1) leaves invariant both the allele frequency simplex  $\Delta_n$  and its

6 interior  $\Delta_n$ , see e.g. Akin [17].

7 If in addition to the conditions of Theorem 2.1, assumption

8 
$$MW^{-1}l = 0$$
 (6.2)

9 also holds then it is easy to see that x\* defined in (2.2) for the case of pure selection, is also a
10 polymorphic equilibrium of the selection-mutation system (6.1).

11 **Remark 6.1.** It is easy to see that, whenever in the pure selection model (M=0) by linearization 12 asymptotic stability of equilibrium  $x^*$  is obtained, in the case of *weak selection* (i.e. when all 13 entries of M are small enough),  $x^*$  will be asymptotically stable for the selection-mutation 14 system (2.1), too.

15

#### 16 Observability of the selection-mutation model with heterosis

For the analysis of the observability of model (6.1), we start from fitness matrix (3.2) of thepure selection model:

19 
$$W = \begin{bmatrix} 1 & 1 - \alpha & 1 - \beta \\ 1 - \alpha & 1 & 1 - \alpha \\ 1 - \beta & 1 - \alpha & 1 \end{bmatrix},$$

## 20 with parameters $\alpha, \beta \in A = (-1,1) - \{0\}$ such that the polymorphic equilibrium $x^*$ exists and

21 is asymptotically stable, that is, we suppose  $\alpha, \beta \in A$  and

22 
$$2\alpha(2-\alpha) \neq \beta, \beta \neq 4\alpha, 4\alpha < \beta < 0, \beta - 2\alpha > 0, \alpha < 0;$$

23 or equivalently

1

#### $\alpha, \beta \in A$ and $2\alpha < \beta < 0$ .

Now, similarly to the pure selection model, from the observation of a phenotype frequency we can try to reconstruct the underlying allele frequency process, when mutations also "perturb" the selection process. Let us suppose that, considering the dominance relations described at the beginning of Section 3, we observe the first phenotype  $\overline{A}_1$ . Then the observation function is defined by

7

$$y = h(x) := x_1^2 + x_1 x_2 + x_1 x_3 - ((x_1^*)^2 + x_1^* x_2^* + x_1^* x_3^*).$$
(6.3)

8 **Theorem 6.2.** Suppose that for the fitness parameters conditions (3.5) hold, and for the 9 mutation parameters we have

10 either 
$$m_{13} < m_{12}$$
 if  $\alpha < \beta$ , or  $m_{13} > m_{12}$  if  $\alpha > \beta$ . (6.4)

11 Then observation system (6.1)-(6.2) is locally observable at  $x^*$  in  $\Delta_3$ . (We remind that 12 condition (6.2) implies the equilibrium  $x^*$  of the pure selection model is also an equilibrium of 13 the selection-mutation dynamics (6.1).

14 Proof. In analogous way to the proof of Theorem 3.1, we will apply Theorem A.3 of Appendix

15 with  $H = \overset{\circ}{\Delta}_3$ . The tangent space of  $\overset{\circ}{\Delta}_3$  at  $x^*$  is

16 
$$T_* = \left\{ z \in \mathbf{R}^3 : \sum_{i=1}^3 z_i = 0 \right\},$$

17 and matrix  $C = h'(x^*)$  is

18  $C = \begin{bmatrix} x_1^* + 1 & x_1^* & x_1^* \end{bmatrix}.$ 

19 For a symmetric matrix  $W = (w_{ij})_{3\times 3}$ , Jacobian  $L = f'(x^*) = (l_{ij})_{3\times 3}$  is given by

20 
$$l_{ij} = x_i^* (w_{ij} - 2\overline{w}(x^*)) + m_{ij}.$$
 (6.5)

For our W we have equilibrium  $x^*$  in (3.3). In order to check condition (A.3) of the Appendix,

22 suppose that  $z \in T_* \cap \text{Ker } Q$ . Then, Cz = 0 implies  $z_1 = 0$ . Hence we get  $z_2 = -z_3$ .

23 Furthermore, 
$$CLz = 0$$
 which gives

$$\frac{\alpha(\beta-\alpha)z_3}{\beta-4\alpha} + (m_{13}-m_{12})z_3 = 0.$$

By condition (6.4), and applying Theorem A.3 of the Appendix, it is easy to obtain local
observability of system (6.1)-(6.3).

4 We note that the observation of other phenotypes can be also handled with this methodology.

5

#### 6 Observer design for the phenotypic observation in the selection-mutation model

Now we show how our methodology used in Section 4 can be extended to the case when, in
addition to selection, allele mutation is also present. The application of our Theorem 4.1 also
makes it possible to effectively recover the genetic process from phenotypic observation, as it
will be illustrated with the following example:

**Example 6.3.** To illustrate the design of an observer, we consider the three-allele threephenotype model (6.1) with the same selection parameters as in Example 4.2,  $\alpha = -0.5$  and  $\beta = -0.25$ . In that example, for the case of pure selection, we have calculated the asymptotically stable polymorphic equilibrium  $x^* = (0.2857, 0.4286, 0.2857)$ . Now let us consider model (6.1) with mutation matrix

16 
$$M = \begin{bmatrix} -b & b\frac{-\alpha}{\beta - 2\alpha} & 0\\ b - a & -b\frac{-\alpha}{\beta - 2\alpha} & a\\ a & 0 & -a \end{bmatrix}.$$
 (6.6)

\_

17 It is easy to check that, for b > a > 0, we have  $MW^{-1}1 = 0$ , therefore  $x^*$  is also a polymorphic 18 equilibrium for the selection-mutation dynamics (6.1). Furthermore, taking into account Remark 19 6.1, mutation parameters a, b can be chosen small enough to guarantee that  $x^*$  is asymptotically 20 stable for the selection-mutation dynamics, too.

21 If the first phenotype is observed with observation function (6.3), then by conditions (6.4)

Theorem 6.2 implies local observability of system (6.1)-(6.3) at  $x^*$  in  $\Delta_3$ .

1 Now we obtain the following linearization matrices

2 
$$C = \begin{bmatrix} x_1^* + 1 & x_1^* & x_1^* \end{bmatrix} = \begin{bmatrix} 1.2857 & 0.2857 & 0.2857 \end{bmatrix},$$

3 and for a = 0.1; b = 0.2,

4 
$$L = \begin{bmatrix} -0.65 & -0.176667 & -0.38 \\ -0.36 & -0.803333 & -0.36 \\ -0.28 & -0.31 & -0.55 \end{bmatrix}.$$

5 The eigenvalues of the linearization matrix of the pure selection system are -1.26, -0.21, -0.07,

6 and mutation parameters a = 0.1; b = 0.2 turn out to be small enough to guarantee negative

7 eigenvalues (-1.29, -0.44, -0.27) of the above matrix L, too (Cf. Remark 6.1).

8 In order to apply Theorem 4.1, we can choose the following gain matrix satisfying the condition

9 of this theorem:

10 
$$K = \begin{bmatrix} 2\\0\\-2 \end{bmatrix}$$

11 It is easy to check that matrix L - KC has only eigenvalues with negative real parts. Therefore 12 the observer system for (6.1)-(6.3) is

13 
$$\dot{z}_i = z_i [(Wz)_i - \langle z, Wz \rangle] + (Mz)_i + (K(y - h(z)))_i \quad (i \in \overline{1,3}).$$
 (6.7)

14 At the same time, matrix K satisfies the conditions of Theorem 4.1, therefore  $\Delta_3$  is locally 15 long-term invariant for observer system (6.7).

16 In order to show how the observer system approximately provides the solution of the original 17 system from the phenotypic observation, suppose that the initial condition is 18 x(0) = (0.25, 0.35, 0.4) for the original system (6.1), and z(0) = (0.3, 0.4, 0.3) for the 19 observer system (6.7). In Figure 5 we can see how quickly the solution of the observer system 20 approximates the solution of the original system.



1

2

Fig. 5. Solution of the observer system, approximating the allele frequency process

3

#### 4 7. Artificial selection with controlled mutation

In earlier papers Scarelli and Varga [12], and López *et al.* [9] we studied controllability by selection and mutation separately, and in both cases we only proved the existence of appropriate controls (artificial selection) that steer the population into a state of maximum mean fitness. Nevertheless, there was no method given, how to calculate such controls. In this section we fill this gap. Below we will show how the simultaneous artificial selection and induced mutation can be modelled with a joint control system.

11 Let us suppose that, in principle, we can intervene to change the fitness of any genotype 12  $i,j \in \overline{1,n}$ . To describe this, define functions  $R_{ij} : \mathbb{R}^{n \times n} \to \mathbb{R}^{n \times n}$ , with all entries equal to zero, 13 except that with indices i,j, which is 1, if genotype  $A_iA_j$  is artificially selected, and zero 14 otherwise. Now, in terms of matrix-valued function  $\psi(u^W) = \sum_{i,j} u_{ij}^W R_{ij}$ , the modified fitness

- 15 matrix is  $W + \psi(u^W)$ . As for the control of mutation rates, we suppose that, for a given k, we
- 16 can control mutation of allele  $A_k$ . (For artificial mutation technologies we refer to McClean
- 17 [13] and Zhang [18]). Introducing controls  $u^{M,k} = (u_1^M, u_2^M, ..., u_n^M)$ , we define
- 18  $\Phi: \mathbf{R}^{n-1} \to \mathbf{R}^{nxn}$ ,

$$1 \qquad \Phi(u^{M,k}) \coloneqq \begin{bmatrix} -\sum_{j \neq 1} m_{j1} & \dots & m_{1k} + u_1^M & \dots & m_{1n} \\ m_{21} & \dots & m_{2k} + u_2^M & \dots & m_{2n} \\ \vdots & \vdots & \ddots & \vdots & \ddots & \vdots \\ m_{k1} & \dots & -\sum_{j \neq k} m_{jk} - \sum_{j \neq k} u_j^M & \dots & m_{kn} \\ \vdots & \vdots & \ddots & \vdots & \ddots & \vdots \\ m_{n1} & \dots & m_{nk} + u_n^M & \vdots & -\sum_{j \neq n} m_{jn} \end{bmatrix}.$$
(7.1)

2 Therefore, with the joint control  $u = (u^W, u^{M,k})$ , the selection-mutation dynamics is

3 
$$\dot{x}_i = x_i [(Wx)_i - \langle x, Wx \rangle] + x_i [(\psi(u^W)x)_i - \langle x, \psi(u^W)x \rangle] + (\Phi(u^{M,k})x)_i = F_i(x,u). \quad (7.2)$$

4 Now, if to  $u^* = ((u^W)^*, (u^{M,k})^*) = (0,0)$ , there corresponds an equilibrium  $x^*$ , i.e. 5  $F(x^*, u^*) = 0$ , and from our earlier result in Scarelli and Varga [12], we can conclude that 6 control dynamics (7.2) leaves invariant both the allele frequency simplex  $\Delta_n$  and its interior for 7 small controls.

8 For an illustration of the application of control model, we start from the three-allele Fisher9 model with fitness matrix (3.2):

10 
$$W = \begin{bmatrix} 1 & 1 - \alpha & 1 - \beta \\ 1 - \alpha & 1 & 1 - \alpha \\ 1 - \beta & 1 - \alpha & 1 \end{bmatrix},$$

11 with parameters  $\alpha, \beta \in (-1,0)$  satisfying  $2\alpha < \beta$ . (We remind that the latter implies the 12 existence of a polymorphic equilibrium  $x^*$ , where mean fitness attains a strict maximum.). 13 Now on the one hand, as in Section 5, we will carry out an artificial selection intervening on the 14 fitness of homozygote A<sub>3</sub>A<sub>3</sub>. In the present formalism, this means that all matrices  $R_{ij}$  are zero, 15 except

16 
$$R_{33} = \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 1 \end{bmatrix}.$$

On the other hand, unlike Section 5, allele mutation is also controlled. Let the mutation matrixbe the same as in Section 6:

$$M = \begin{bmatrix} -b & b\frac{-\alpha}{\beta - 2\alpha} & 0\\ b - a & -b\frac{-\alpha}{\beta - 2\alpha} & a\\ a & 0 & -a \end{bmatrix},$$

1

with b > a > 0. As we have seen in the previous section, the latter condition implies that x<sup>\*</sup> is a
polymorphic equilibrium for the zero-control selection-mutation dynamics. Let us assume that,
in addition to fitness w<sub>33</sub>, we control the mutations A<sub>1</sub>→A<sub>2</sub> and A<sub>1</sub>→A<sub>3</sub>, i.e. in (7.1) we set k=1.
Now the Jacobian L of the right-hand side of (7.2), with respect to x, is the same we calculated
in (6.5):

7 
$$l_{ij} = x_i^*(w_{ij} - 2\overline{w}(x^*)) + m_{ij}.$$

8 Furthermore, as we easily calculate, the Jacobian of the right-hand side of (7.2) with respect to u9 is

(7.3)

10 
$$B = \begin{bmatrix} -x_1^* (x_3^*)^2 & -x_1^* & -x_1^* \\ -x_2^* (x_3^*)^2 & x_1^* & 0 \\ (x_3^*)^2 (1-x_3^*) & 0 & x_1^* \end{bmatrix}$$

11 In order to apply our Theorem A.12, we have to check if

$$12 \qquad rank[B | LB | L^2B] = 2$$

In fact, it is easy to see that matrix [B | LB | L<sup>2</sup>B] has non-zero 2x2 minors. Furthermore, by a
sufficient condition for local controllability of systems without invariant manifold (see Lee and
Markus [2]),

$$16 \qquad rank[B | LB | L^2B] = 3$$

17 would imply that system (7.2) is locally controllable at  $x^*$  in  $\Delta_n$ , which contradicts to the 18 invariance of  $\dot{\Delta}_n$  for small controls, under dynamics (7.2). Hence, applying Theorem A.12 of 19 the Appendix, we obtain the following controllability result: **1** Theorem 7.1. If  $\alpha, \beta \in (-1,0)$ ,  $2\alpha < \beta$  and b > a > 0, then with controlled fitness of 2 homozygote genotype A<sub>3</sub>A<sub>3</sub> and controlled mutations A<sub>1</sub> $\rightarrow$ A<sub>2</sub> and A<sub>1</sub> $\rightarrow$ A<sub>3</sub>, system (7.2) is

3 locally controllable into  $x^*$  within  $\Delta_n$ .

4 Remark. 7.2. We note that the theoretical background of Section 5 concerning optimization of
5 mean fitness can also be applied to the numerical realization of the control of the general
6 selection-mutation dynamics (7.2).

**Example 7.3.** For a numerical illustration let us consider the selection-mutation model considered in Theorem 7.1, with the same parameters of Examples 4.2 and 6.3:  $\alpha = -0.5$ ,  $\beta = -0.25$ , a = 0.1, b = 0.2. These parameters satisfy the conditions of Theorem 7.1, and the equilibrium corresponding to the zero control  $x^* = (0.2857, 0.4286, 0.2857)$  is an asymptotically stable polymorphic equilibrium for the selection-mutation dynamics (7.2), with  $u^* = ((u^W)^*, (u^{M,1})^*) = (0,0)$ . Now in (7.2) we have

13 
$$W + \psi(u^W) = \begin{bmatrix} 1 & 1.5 & 1.25 \\ 1.5 & 1 & 1.5 \\ 1.25 & 1.5 & 1 + u^W_{33} \end{bmatrix}, \Phi(u^{M,1}) = \begin{bmatrix} -0.2 - u^M_2 - u^M_3 & 0.1333 & 0 \\ 0.1 + u^M_2 & -0.1333 & 0.1 \\ 0.1 + u^M_3 & 0 & -0.1 \end{bmatrix}.$$
 (7.4)

14 Then, from Theorem 7.1, we conclude that the population can be controlled into the equilibrium 15 in given time, at least from nearby states. Now, applying the MatLab toolbox of Banga et al. 16 [15], we will effectively calculate a control which, from a given initial state, steers the population into equilibrium, minimizing the distance of the end point x(T) of the solution from 17 the equilibrium. To this end fix time duration T := 10 and take initial condition 18 x(0) = (0.25, 0.35, 0.4) for system (7.2) detailed in (7.4). Figure 6 shows the solution x 19 20 corresponding to the optimal control, and in Figure 7 the optimal control is plotted. We remind 21 that this control at the same time also maximizes the mean fitness of the population.

22





Fig. 6. Optimal solution of control system (7.2) with initial condition x(0) = (0.25, 0.35, 0.4),

3 plotted for [0,10]





Fig 7. Optimal control function of system (7.2), plotted for [0,10]

- 11
- 12

#### 13 8. Discussion

The tools of mathematical systems theory turn out to be appropriate for monitoring and control of genetic processes. In this context, the object of the study is not a given purely biological situation, but two aspects of systems "Biological object-Man". Concerning monitoring (or observation) problem, there are two basic questions. In our context, the first one is whether a

population genetic process can be uniquely recovered from a corresponding phenotypic 1 observation. If this, in principle, is possible, the second question is how to effectively calculate 2 3 the allelic state process. In static situation, in Garay and Garay [5] biological conditions were 4 given for the allele frequency vector - phenotype frequency vector correspondence to be one-toone. In case of a partial observation of the phenotypic state, however, this invertibility does not 5 hold. In our paper, instead, the *dynamic* situation in many cases, biologically interpretable 6 7 algebraic conditions are given that guarantee the construction of an observer system, the solution of which asymptotically estimates the genetic process from partial phenotypic 8 9 observation.

10 Both observation and control in the considered selection model needed a different theoretical background from the case of density-dependent population models (as studied in earlier papers 11 12 of the authors, and also in some other publications, e.g. Guiro et al. [19] and Sundarapandian [20], for recent reviews see Varga [21], Gámez [22] and Varga et al. [23]). Indeed, 13 mathematically, Fisher's selection model is frequency-dependent, and the interior of the simplex 14 15 allelic frequencies is invariant under Fisher's selection dynamics with small controls (small changes in fitness parameters of certain genotypes), see López [8]. Therefore, instead of the 16 17 classical linearization theorems concerning local controllability and local observability, 18 corresponding theorems for systems with invariant manifold were necessary, which have been 19 proved in Varga [7,10]. For the state estimation of selection processes in noisy environment, the 20 method of Edelmayer et al. [24] might be adapted. Furthermore, for the controllability of 21 discrete-time frequency-dependent models, probably Szigeti and Molnár [25] can be partly 22 extended to the nonlinear case, see also Szigeti et al. [26].

We have shown that the application of the observation and control methodology of selection models can also be extended to selection-mutation models of population genetics. Of course, even simply allele mutation patterns between existing alleles may substantially modify the selection processes. Mutation however may also result in new alleles in the considered locus. Our observation and control models, in the future might also be extended to this case, but then the first arising population genetic issue would be whether the new allele will stably coexist

1 with the resident ones. We emphasize that for the study of the effects of GMO technologies at population genetic level, the introduced observation and control methodology may gain 2 3 importance in the future. For already existing artificial mutation technologies as genetic 4 engineering tools in breeding for resistance to the diseases of plants, see e.g. Zhang et al. [18]. Finally, we also comment on further possible applications of our methodological development 5 published in Varga [7,10], concerning observability and controllability of nonlinear systems 6 7 with invariant manifold. In fact, apart from the above discussed biological context, this technique has already been successfully used for the study of chemical processes in Farkas [27-8 9 28]. Observers for systems without invariant manifold can also be applied in different fields of 10 engineering. For instance, concerning solar heating systems, see Kicsiny and Varga [29-30]. For observer design in a technically different state-space model, we can refer to quite recent issues 11 12 of the present journal: WeiYin Leong et al. [31] and Le Van Hien [32]. As a matter of fact, the state estimation (i.e. observer design) technique, we used in the present paper, is very similar to 13 the so-called full-order state estimation of [32], but the underlying dynamic models are 14 15 different. Unlike our models, [31] and [32] use equations with time delay and probabilistic system parameters. Both aspects would also be important for more realistic modelling of 16 17 biological interactions. In [32] discrete-time model is considered, while our present study is 18 based on a continuous-time dynamics. We note that the issue of discrete-time monitoring (i.e. 19 observation) in ecology has already been addressed in our recently appeared paper Gámez et al. [33]. Since the models of [31] and [32] are linear, for their adaptation to population biology, a 20 substantial development would be necessary. In fact, most dynamic models of population 21 biology (in particular, models of population genetics considered in the present paper) are not 22 23 linear.

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21 Appendix
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- 22
- 23 A.1. Local observability and observer of nonlinear observation systems with invariant manifold

**Definition A.1.** For given  $k \in \{1, 2, ..., n-1\}$ , a set  $H \subset \mathbb{R}^n$  is called a regular k-dimensional

- sub-manifold if there exist an open set  $G \subset \mathbf{R}^n$  and a function  $\phi \in C^1(G, \mathbf{R}^{n-k})$  such that, for
- all  $x \in G$  and for the range of the derivative  $\phi'(x)$ , we have  $R_{\phi'(x)} = \mathbf{R}^{n-k}$  and  $H = \phi^{-1}(0)$ .
- For a continuously differentiable function  $f : \mathbf{R}^n \to \mathbf{R}^n$ , we consider the differential equation

1

$$\dot{x} = f \circ x , \qquad (A.1)$$

2 where  $\circ$  denotes the composition of functions (in traditional form  $\dot{x} = f(x)$ ).

Given a regular k-dimensional sub-manifold M ⊂ R<sup>n</sup>, let x<sup>\*</sup> ∈ M be such that f(x<sup>\*</sup>) = 0
(in other words, an equilibrium of system (A.1)), then there exists a neighborhood of x<sup>\*</sup> and
T ∈ R<sup>+</sup> such that any solution of (A.1) beginning at a point of this neighborhood is defined in
[0, T].

- 7 For this appendix we suppose that M is locally positively invariant for system (A.1) at  $x^*$ , that
- 8 is, any solution of (A.1) beginning at a point of a neighborhood of  $x^* \in M$ , remains in M.
- 9 For a given m∈ N, let h: R<sup>n</sup> → R<sup>m</sup> be a continuously differentiable function with
   10 h(x<sup>\*</sup>) = 0, we define an observation system as

11
$$\begin{cases} \dot{x} = f \circ x \\ y = h \circ x, \end{cases}$$
(A.2)

12 where y is called the *observed function corresponding to the solution* x.

**13** Definition A.2. We shall say that observation system (A.2) is *locally observable (in H) at*  $x^*$ ;

14 if there exists  $\varepsilon \in \mathbf{R}^+$  satisfying the following conditions:

15 Given 
$$z^i \in H$$
, with  $|z^i - x^*| < \varepsilon$   $(i \in \{1,2\})$ , and

16  

$$\dot{x}^{i}(t) = f(x^{i}(t)) \quad (t \in [0,T])$$

$$x^{i}(0) = z^{i} \quad (i \in \{1,2\})$$

$$h(x^{1}(t)) = h(x^{2}(t)) \quad (t \in [0,T]),$$

17 then 
$$z^1 = z^2$$
 (consequently  $x^1(t) = x^2(t)$   $(t \in [0,T])$ ).

18 The local observability in *H* at  $x^*$  means that if, instead of the solution, we can observe a 19 transformation of it then, from this observed function, we can recover the solution in a unique 20 way, provided the solution begins at a point of *H* near the given equilibrium  $x^*$ .

21 To formulate a sufficient condition which guarantees the local observability of system (A.2), we

22 linearize system (A.2) at the equilibrium,

$$L = f'(x^*), \quad C = h'(x^*),$$

2 and define

1

3 
$$Q = \begin{bmatrix} C \\ CL \\ \vdots \\ CL^{n-1} \end{bmatrix}$$

4 Now we recall a basic theorem proved by Varga [10], in which a sufficient condition is given
5 for local observability in "geometric" terms.

6

7 **Theorem A.3.** Suppose that

8

 $T_* \cap KerQ = \{0\},$  (A.3)

9 where  $T_*$  is the tangent space to H at  $x^*$ . Then system (A.2) is locally observable.

10 Next, we recall the construction of an observer system that will be based on Sundarapandian

[34]. We present the standard definition of an observer adapted to the case of an observationsystem (A.2) with invariant manifold.

**13** Definition A.4. Given a continuously differentiable function  $G: \mathbb{R}^n \times \mathbb{R}^m \to \mathbb{R}^n$ , system

14

$$\dot{z} = G(z, y) \tag{A.4}$$

15 is called a *local asymptotic (respectively, exponential) observer for observation system* (A.2) if

16 the composite system (A.2), (A.4) satisfies the following two requirements:

17 i) If  $x(0) \in M$ , and x(0) = z(0), then x(t) = z(t), for all  $t \ge 0$ .

18 ii) There exists a neighbourhood V of the equilibrium  $x^*$  of  $\mathbb{R}^n$  such that for all 19  $x(0), z(0) \in V \cap M$ , the estimation error z(t) - x(t) decays asymptotically (respectively, 20 exponentially) to zero.

**21** Theorem A.5. (Sundarapandian [35]). Suppose that system (A.1) is Lyapounov stable. Then, a

22 necessary and sufficient condition for observation system (A.2) to have a local exponential

- 23 observer is that the system is locally observable at  $x^*$ .
- 24 **Remark A.6.** Below we will use only the "sufficient part" of this theorem.

Theorem A.7. (Sundarapandian [34]). Suppose that the observation system (A.2) is Lyapunov 1 stable at equilibrium, and that there exists a matrix K such that matrix L - KC is Hurwitz (i.e. 2 its eigenvalues have negative real parts), where  $L = f'(x^*)$  and  $C = h'(x^*)$ . Then the 3 dynamic system defined by 4  $\dot{z} = f(z) + K[y - h(z)]$ 5 is a local exponential observer for observation system (A.2). 6 7 A.2. Controllability of nonlinear control systems with invariant manifold 8 Given  $n, r \in \mathbf{N}$ , let  $F: \mathbf{R}^n \times \mathbf{R}^r \to \mathbf{R}^n$  be a continuously differentiable function. For a 9 reference control value  $u^* \in \mathbf{R}^r$ , let  $x^* \in \mathbf{R}^n$  be such that  $F(x^*, u^*) = 0$ . For technical 10 reason we shall need a rather general class of controls. Let us fix a time interval [0,T], and for 11 each  $\varepsilon \in \mathbf{R}^+$  define the class of essentially bounded  $\varepsilon$  -small controls 12  $U_{\varepsilon}[0,T] = \Big\{ u \in L_{\infty}^{r}[0,T] \mid \|u(t)\|_{\infty} \le \varepsilon \text{ for almost every } t \in [0,T] \Big\}.$ 13 14 From Lee and Markus [2] we recall the following two theorems 15 **Theorem A.8.** There exists  $\varepsilon_0 \in \mathbf{R}^+$  such that for all  $u \in U_{\varepsilon_0}[0,T]$  and  $x^0 \in \mathbf{R}^n$  with 16  $\left\|x^{0}-x^{*}\right\|<\varepsilon_{0}$ , the initial value problem 17  $\dot{x}(t) = F(x(t), u^* + u(t))$  (for a.e.  $t \in [0, T]$ ) 18 (A.5)  $x(0) = x^0$ 19 (A.6) has a unique solution. We notice that  $x^*$  is an equilibrium state for the zero-control system. 20 21 **Theorem A.9.** Let  $\Omega \subset \mathbf{R}^r$  be a compact set, and fix a T > 0. For any measurable function 22 (control)  $u:[0,T] \rightarrow \Omega$  consider the system 23  $\dot{x}(t) = F(x(t), u^* + u(t))$  for almost all  $t \in [0, T]$ . 24 (A.7) 37

a) Suppose that for a measurable control  $\overline{u}:[0,T] \to \Omega$ , a solution  $\overline{x}$  of (A.7) is defined on 1 the interval [0,T]. Then there exists an  $\varepsilon_0 > 0$  with the following property: For all  $\varepsilon \in (0, \varepsilon_0)$ 2 and measurable control  $u^{\varepsilon}:[0,T] \to \Omega$  satisfying  $\|u^{\varepsilon}(t) - \overline{u}(t)\| < \varepsilon$  except a set of measure 3  $\varepsilon$ , we have that any solution  $x_{\varepsilon}$  corresponding of system (A.7) with  $||x_{\varepsilon}(0) - \overline{x}(0)|| < \varepsilon$  is 4 defined on [0,T], moreover  $||x_{\varepsilon}(t) - \overline{x}(t)|| < \varepsilon$   $(t \in [0,T])$  holds. 5

b) With the conditions and notation of a), we have that  $x_{\varepsilon} \to \overline{x}$  uniformly on [0,T], when 6 7  $\varepsilon \rightarrow 0$ .

**Definition A.10.** A regular k-dimensional sub-manifold  $H \subset \mathbf{R}^n$  is said to be locally 8 invariant for small controls, with respect to system (A.5)-(A.6) at  $x^*$ , if there exists  $\varepsilon \in [0, \varepsilon_0]$ 9 such that  $x(0) \in H$ ,  $||x^0 - x^*|| < \varepsilon_0$ ,  $u \in U_{\varepsilon}[0,T]$  imply that for solution x of system (A.5)-10 (A.6), we have  $x(t) \in H$   $(t \in [0, T])$ . 11 12 **Definition A.11.** Suppose that H is as required in Definition A.10. System (A.5)-(A.6) is called locally controllable into  $x^*$  within H, if there exists a  $\delta > 0$  and a  $u \in U_{\varepsilon}[0,T]$  such 13 that from any initial state  $x(0) \in H$  with  $||x(0) - x^*|| < \delta$ , for solution x of (A.5)-(A.6) we

15 have 
$$x(T) = x^*$$
.

Let us linearize system (A.5)-(A.6) around  $(x^*, u^*)$ , introducing the corresponding Jacobians 16

17 
$$L = \frac{\partial}{\partial x} F(x^*, u^*), \quad B = \frac{\partial}{\partial u} F(x^*, u^*).$$

18 Then we have the following sufficient condition for local controllability:

20 If

14

21 
$$rank[B|AB|...|A^{n-1}B] = k, \qquad (A.8)$$

then system (A.5)-(A.6) is locally controllable into  $x^*$  within H. 22

23

.