

IDENTIFICATION OF REPLICATOR-MUTATOR MODELS

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Abstract: The complexity of biology literally calls for quantitative tools in order to support and validate biologists intuition and traditional qualitative descriptions. In this paper, the Replicator-Mutator models for Evolutionary Dynamics are validated/invalidated in a worst-case deterministic setting. These models analyze the DNA and RNA evolution or describe the population dynamics of viruses and bacteria. We identify the Fitness and the Replication Probability parameters of a genetic sequences, subject to a set of stringent constraints to have physical meaning and to guarantee positiveness. The conditional central estimate is determined in order to validate/invalidate the model. The effectiveness of the proposed procedure has been illustrated by means of simulation experiments while tests on real data are under concern.

Keywords: Biomedical Systems, Evolutionary Dynamics, Nonlinear systems, Positive systems, Uncertain Dynamical Systems

Introduction

In this paper we consider the problem of identifying the model of evolutionary dynamics. Darwinian evolution is based on three fundamental principles, reproduction, mutation and selection, which describe how populations change over time and how new forms evolve out of old ones.

The aim is validate/invalidate in a worst-case deterministic setting the Replicator-Mutator models. The model is well-known in its structure and is in general positive and nonlinear.

Replicator-Mutator and Quasispecies Models

There are numerous mathematical descriptions of the resulting evolutionary dynamics. In (Page

and Nowak, 2002) apparently very different formulations that have been studied in literature are presented as part of a single unified framework. In particular the two most common models are the **Quasispecies Equation** (see (Eigen *et al.*, 1989)) of molecular evolution and the **Replicator-Mutator Equation** (see (Hadeler, 1981), (Eigen and Schuster, 1979)). Eigens quasispecies model was developed as a framework for studying the dynamics of replicating DNA and RNA macromolecules. Later it has been used to describe the population dynamics of more advanced biological systems such as viruses and bacteria. It considers an individual as a finite sequence of elementary building blocks or bases. The quasispecies model has proved to be very fruitful as a reasonably general model of Darwinian evolution that incorporates selection mutation and a genome length larger than one. It has been an excellent theoretical framework to ap-

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proach RNA virus dynamics. Theoretical as well as empirical research has been used for medical or pharmaceutical strategies to face viruses.

As well described in (Komanova, 2004), the *Replicator-Mutator equation* appears in three different contexts in biology:

Population genetics:

see (Hadeler, 1981), (Hofbauer and Sigmund, 1998). Here x_i denotes the relative frequencies of alleles at the time of mating.

Autocatalytic reaction networks:

see (Stadler and Schuster, 1992), (Schuster and Stadler, 2003). Here x_i are the concentrations of molecules, RNA or DNA, which are capable of self-replications.

Population language learning:

see (Nowak *et al.*, 2001), (Komanova, 2004). Here x_i are the relative abundance of individuals which use a specific grammar.

Let us focus on a specific context and x_i denotes the relative abundance of a genetic sequence i in a population. The fitness, f_i of this sequence is determined by its replication rate. The average fitness of the population is given by $\bar{f} = \sum_i f_i x_i$. We consider n genetic sequences. According to (Nilsson, 2000), the matrix Q has been introduced to describe how mutations affect a population. In particular q_{ij} is defined as the the probability that replication of genome j gives genome i as offspring. For perfect copying accuracy Q equals the identity matrix. Mutations give rise to the off-diagonal elements in q_{ij} . Below, we report an explicit expression for Q in terms of the copying fidelity as given by (Nilsson, 2000),

$$q_{ij} = q^\nu \left(\frac{1-q}{q} \right)^{h_{ij}} \quad (1)$$

where h_{ij} is the Hamming distance between genomes j and i , and ν is the genome length and q is the copying accuracy. The Hamming distance h_{ij} is defined as the number of positions where genomes j and i differ.

The **Quasispecies Equation** describes the dynamics of the genomes x_i :

$$\dot{x}_i = \sum_{j=1}^n x_j f_j q_{ij} - \bar{f} x_i \quad (2)$$

This is a nonlinear quadratic model exhibiting bilinear dependence in the parameters. It can be equivalently recast in a more concise form as follows:

$$\dot{x} = (Q \text{diag}(f) - (f^T x) I) x \quad (3)$$

where the state variable is $x = [x_1 \dots x_n]^T$ and $f = [f_1 f_2 \dots f_n]^T$. Putting together the quasi-

species equation with the Lotka-Volterra equation, that takes into account the fact that the reproductive fitness f_i is function of the abundance of other species and is $f_i(x)$, in (Nowak *et al.*, 2001) or (Wilke *et al.*, 2001) it has been derived the **Replicator-Mutator equation**:

$$\dot{x}_i = \sum_{j=1}^n x_j f_j(x) q_{ji} - \bar{f} x_i \quad (4)$$

Clearly, depending on how the fitness is related to x_i , various model have been developed in literature. In particular, according to (Komanova, 2004), we consider a polynomial expansion:

$$f_j = w_j + \sum_{k=1}^n \gamma_{jk} x_k + \dots \quad 1 \leq j \leq n \quad (5)$$

If we keep only the linear terms, then

$$f = w + \Gamma x \quad (6)$$

where $\Gamma = [\gamma_{ij}]$ and $w = [w_1 \dots w_n]^T$.

Then, the *replicator-mutator* equation can be recasted as

$$\begin{aligned} \dot{x} &= (Q(\text{diag}(w) + \text{diag}(\Gamma x)) - (w^T x + x^T \Gamma^T x) I) x \\ &= (Q(\text{diag}(w) + \text{diag}(x) \Gamma) - (w^T x) I - x^T \Gamma^T x I) x \end{aligned} \quad (7)$$

Clearly, if $\gamma_{ij} = 0$ we obtain the quasispecies models given in (3), and if $q_{ij} = 1$ for $i = j$ and $q_{ij} = 0$ for $j \neq i$ we obtain the replicator model (see (Hofbauer and Sigmund, 1998)).

Model Parametrization

Quasispecies Models in (3) enjoys the following properties:

- P.1** Starting with $\sum_i x_i(0) = 1$ then $\sum_i x_i(t) = 1, \forall t > 0$. This can be expressed as: $\mathbf{1}^T x = 1$ where $\mathbf{1}^T$ denotes a row-vector of ones. This means that the state variables take value in the unitary simplex Σ .
- P.2** The system is positive: starting from any initial condition $x(0) > 0, x(t) > 0 \forall t > 0$.
- P.3** $q_{ij} \in [0, 1]$
- P.4** $f_i \geq 0$

From the above assumptions, we can derive some constraints on the parameters q_{ij} and f_i .

Lemma 1

For the unitary simplex Σ to be positively invariant conditions **P.3**, **P.4** and

$$\mathbf{1}^T Q = \mathbf{1}^T \quad (8)$$

need to be satisfied. \square

The models (3) and (7) are overparameterized. In the next Lemma, it is shown that f is defined up to simultaneous translation of its entries.

Lemma 2

Let \tilde{Q} and \tilde{f} satisfy

$$\tilde{f} = f + \lambda \mathbf{1} \quad (9)$$

$$\tilde{f}_i > 0 \quad \forall i \quad (10)$$

$$\tilde{Q} = [Q \text{diag}(f) + \lambda I][\text{diag}(f) + \lambda I]^{-1} \quad (11)$$

for a real number λ , and $\tilde{x}(t)$ denotes the solution of equation (3) where f and Q are replaced by \tilde{f} and \tilde{Q} . Then, starting from the same initial conditions,

$$\tilde{x}(0) = x(0) \quad (12)$$

the systems has the same dynamics:

$$\tilde{x}(t) = x(t) \quad \forall t \geq 0 \quad (13)$$

□

Identification

Despite the identification methodologies are well established in many application fields, their use in the parameters estimation of the evolutionary systems is quite rare. Most of the literature in this area deals with the modeling of the systems, without a rigorous validation and/or data-based parameter estimation. In some applications, the solution is based on statistical approaches like the Maximum Likelihood Principle (see (Bielawski and Z., 2003) for a recent survey, or the parameter estimation based on time-series (i.e. (Bonhoeffer *et al.*, 2002)).

On the other hand, if we consider literature on identification of positive systems there are some results for linear systems. In this case the positive systems are compartmental. Some results are based on statistical approaches (Benvenuti *et al.*, 2002)) with solution based on the Maximum Likelihood Principle, other results are based on the interval literature, (Kieffer and Walter, 2004). For nonlinear positive systems (that are not compartmental), not much can be found in the identification literature.

Almost all these contributions assume a statistical description of the noise and are mainly devoted to point estimation while little attention is devoted to the computation of confidence regions for the parameter estimates although they are important for the assessment of the model quality. Conversely, the assumption of Unknown But Bounded (U.B.B.) noise (see (Milanese and Vicino, 1991) for an extensive survey) naturally rises the issue of computing the Feasible Parameter Set (FPS).

Regressor Form

In order to identify the parameters q_{ij} and f_i , first we must recast the model in a regressor form. The model in (3) and (7) is formed by $n = 2^\nu$ continuous-time differential equations. Assume that we discretize it with a standard first-order Euler approximation with sampling time T . Then the discrete-time system becomes

$$\begin{aligned} x_i(t+1) &= \sum_{\substack{j=1 \\ j \neq i}}^n \alpha_j^i x_j(t) + \sum_{k=1}^n \bar{\beta}_k^i x_k(t) x_i(t) + \\ &+ \sum_{\substack{j=1 \\ j \neq i}}^n \sum_{\substack{k=1, k \neq j \\ k \neq i}}^n \delta_{j,k}^i x_k(t) x_j(t) + \\ &+ x_i(t) \sum_{j=1}^n \sum_{\substack{k=1 \\ k \neq j}}^n \mu_{j,k}^i x_j(t) x_k(t) \\ &+ e_i(t) \\ &= g(x(t)) + e_i(t) \\ &\text{for } i = 1, \dots, n \end{aligned} \quad (14)$$

where

$$\begin{aligned} \alpha_i^i &= 1 + T q_{ii} (w_i + \gamma_{ii}) \\ \alpha_j^i &= T q_{ij} (w_j + \gamma_{jj}) \\ \bar{\beta}_i^i &= \alpha_i^i - T (w_i + \gamma_{ii}) \\ \bar{\beta}_k^i &= 1 + T (q_{ki} w_i - w_k - \gamma_{kk}) + \\ &\quad + T (\gamma_{ki} q_{ik} + \gamma_{ik} q_{ii} - q_{ik} \gamma_{kk}) \\ \delta_{j,k}^i &= T (\gamma_{jk} q_{ij} + \gamma_{kj} q_{ik} - \gamma_{kk} q_{ik} - \gamma_{jj} q_{ij}) \\ \mu_{j,k}^i &= T (\gamma_{jj} - \gamma_{jk} + \gamma_{kk} - \gamma_{kj}) \end{aligned} \quad (15)$$

We note that in equation (14) we have already exploited the condition **P.1**. In fact if **P.1**. is satisfied ($\sum_j x_j = 1$), we have that:

$$x_j(t) = x_j(t) \sum_{k=1}^n x_k(t)$$

and

$$x_i(t) x_j(t) = x_i(t) x_j(t) \sum_{k=1}^n x_k(t)$$

giving raise to the elimination of the following $2n$ terms: x_i, x_j^2 , for $j \neq i$ and $x_i x_j^2$.

Notice also that in equation (14) we have considered a process error e_i on which we make the following assumption:

E.1 The error term is U.B.B. :

$$|e|_\infty \leq \epsilon. \quad (16)$$

Moreover, in order to guarantee the invariance of the simplex Σ , the error term is such that:

E.2
$$\sum e_i = 0. \quad (17)$$

E.3
$$0 \leq g(x(t)) + e_i(t) \leq 1. \quad (18)$$

Moreover we assume that the state variables are measurable without any further noise error; we have output variables:

$$y_i = x_i \quad (19)$$

The system can be recast in a *regressor-like form* as follows. Let us consider a single measurement.

$$Y(t+1) = \Phi(t)\Theta + E(t) \quad (20)$$

where $Y(t) = [y_1(t) \ y_2(t) \ \dots \ y_n(t)]^T$, $e(t) = [e_1(t) \ e_2(t) \ \dots \ e_n(t)]^T$,

$$\text{for } i = 1, \dots, n \quad (21)$$

$$y_i(t+1) = \phi_i(t)\theta^i + e_i(t)$$

$$\Phi(t) = \begin{bmatrix} \phi_1(t) & 0 & 0 & \dots & 0 \\ 0 & \phi_2(t) & 0 & \dots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \dots & \phi_n(t) \end{bmatrix}, \quad (22)$$

$$\Theta = [\theta^1 \ \theta^2 \ \dots \ \theta^n]^T \quad (23)$$

Each θ^i is composed by the n^2 parameters defined in (15) that have to be determined:

$$\theta^i = [\alpha_1^i \ \dots \ \alpha_{i-1}^i \ \alpha_{i+1}^i \ \dots \ \alpha_n^i \ \dots \ \bar{\beta}_1^i \ \dots \ \bar{\beta}_n^i \ \delta_{1,2}^i \ \dots \ \delta_{n,(n-1)}^i \ \mu_{1,2}^i \ \dots \ \mu_{n,(n-1)}^i]^T \quad (24)$$

and each row component $\phi_i(t)$ of the regressor is a vector defined at time t as

$$\phi_i^T = \begin{bmatrix} y^{(i)} \\ y_i Y \\ z^{(i)} \\ y_i h \end{bmatrix} \quad (25)$$

where

$$y^{(i)} = [y_1 \ \dots \ y_{i-1} \ y_{i+1} \ \dots \ y_n]^T,$$

$$y_i Y = [y_1 y_i \ \dots \ y_{i-1} y_i \ y_i^2 \ y_{i+1} y_i \ \dots \ y_n y_i]^T,$$

$$z^{(i)} = [z_1^{(i)} \ \dots \ z_{\frac{(n-2)(n-1)}{2}}^{(i)}]^T$$

and

$$h = [h_1 \ \dots \ h_{\frac{(n)(n-1)}{2}}]^T$$

being $z_j^{(i)} = y_k^{(i)} y_l^{(i)}$ for $k = 1, \dots, n-2; l = k+1, \dots, n-1$, and $h_j = y_k y_l$ for $k = 1, \dots, n-1, l = k+1, \dots, n$. Note that each i -regressor ϕ_i is formed by n^2 terms $(n + (n-1) + \frac{(n-2)(n-1)}{2} + \frac{n(n-1)}{2} = n^2)$.

Experiment setup and constraints

For the sake of simplicity, let us consider now the quasispecies models, when $\gamma_{ij} = 0$.

In order to guarantee *experimental identifiability*, the system is initialized from m different (randomly generated) *initial conditions*. For each initial condition, the identification experiment is

composed by $N * n$ measurements, and the overall data is a vector of $n * N * m$ elements:

$$\mathcal{Y} = \begin{bmatrix} Y(t+1) \\ Y(t+2) \\ \vdots \\ Y(t+N * m) \end{bmatrix} \quad (26)$$

$$\Psi = \begin{bmatrix} \Phi(t) \\ \Phi(t+1) \\ \vdots \\ \Phi(t+N * m - 1) \end{bmatrix} \quad (27)$$

$$\mathcal{E} = \begin{bmatrix} E(t) \\ E(t+1) \\ \vdots \\ E(t+N * m - 1) \end{bmatrix} \quad (28)$$

so that:

$$\mathcal{Y} = \Psi\Theta + \mathcal{E} \quad (29)$$

In order to guarantee the *structural identifiability* we notice that at each time t the original parameters to be identified (q_{ij} and f_i) are $n^2 + n$. Recalling that the f_i parameters are subject to the constraint (9) and that the q_{ij} parameters are subject to n constraints corresponding to eq. (8). The effective number of *free* parameters to be determined is $n^2 + n - 1 - n = n^2 - 1$. In the Θ -space, we need to estimate $n(2n-1)$ parameters subject to n constraints obtained from the relation (8) and $(n-1)(n-1)$ constraints obtained transforming relation (9) into the new space. Then, the *free* parameters to be estimated are $2n^2 - n + n + (n-1)(n-1) = n^2 - 1$. The problem is well posed. The new-constraints in the Θ -space have been simply determined, and their expression is reported hereafter in terms of its components. The n constraints (8) are equivalent to the n equality constraints

$$\text{for } j = 1, \dots, n$$

$$\sum_{\substack{k=1 \\ j \neq k}}^n \alpha_j^k + \bar{\beta}_j^j = 1 \quad (30)$$

The constraint (9) is equivalent to the $(n-1)(n-1)$ equality constraints:

$$\text{for } j = 2, \dots, n$$

$$\text{for } k = 2, \dots, n$$

$$\bar{\beta}_j^1 - \bar{\beta}_1^1 - \bar{\beta}_j^k + \bar{\beta}_1^k = 0 \quad (31)$$

Moreover, we recall that the model must satisfy further disequality constraints given in **P.3** and **P.4**. In the Θ -parameter space, correspondingly, we can impose that:

$$\text{for } j = 1, \dots, n$$

$$\text{for } i = 1, \dots, n$$

$$\alpha_j^i \geq 0 \quad i \neq j \quad (32)$$

Under the assumption of bounded error given in **E.1** it is possible to define an extended Feasible Parameter Set (FPS) as:

$$\Omega = \{\Theta : |\mathcal{Y} - \Psi\Theta| \leq \epsilon\} \quad (33)$$

Let us define \mathcal{M} the set of all the feasible parameters subject to the constraints (30), (31) and (32):

$$\mathcal{M} = \{\Theta : (31), (30) \text{ and } (32) \text{ are satisfied}\} \quad (34)$$

The following identification problem have been considered and solved.

Problem : Least Squares Conditional Central Estimate

$$\Theta^* = \operatorname{argmin}_{\Theta \in \mathcal{M}} \|\mathcal{Y} - \Psi\Theta\|_2 \quad (35)$$

The computational burdens of this problem amounts to solving one constrained Quadratic Programming (QP) Problem.

Numerical Example

The effectiveness of the proposed Procedure obtained by solving **Problem 1** and **Problem 2** is now illustrated on some numerical examples. For sake of clarity we report hereafter only the results corresponding to the simple case of a genetic sequence obtained considering $\nu = 2$ in equation (1) that gives raise to $n = 4$ state variables. More complex genetic sequences have been tested. The system is sampled with $T = 0.01s$. In the identification experiment, carried out with $N = 151$ measurements using ℓ_∞ noise bounds with $\epsilon = 0.015$, the system is initialized with $m = 60$ different randomly generated initial conditions $x(0)$. The overall data are $Nmn = 36240$.

The real parameters are:

$$Q = \begin{bmatrix} 0.1600 & 0.2400 & 0.2400 & 0.3600 \\ 0.2400 & 0.1600 & 0.3600 & 0.2400 \\ 0.2400 & 0.3600 & 0.1600 & 0.2400 \\ 0.3600 & 0.2400 & 0.2400 & 0.1600 \end{bmatrix} \quad (36)$$

$$F = \begin{bmatrix} 9.5013 \\ 2.3114 \\ 6.0684 \\ 4.8598 \end{bmatrix} \quad (37)$$

Solving **Problem** we obtain the $(2n - 1)n = 28$ θ_i components of Θ .

We carry out the inversion procedure and we find that $h = 2$. We set $\tilde{f}_2 = 1.6384$. The obtained Conditional Central Estimate are :

$$Q^* = \begin{bmatrix} 0.1620 & 0.2825 & 0.1921 & 0.4120 \\ 0.2387 & 0.1221 & 0.3535 & 0.2186 \\ 0.2393 & 0.3925 & 0.1961 & 0.2196 \\ 0.3600 & 0.2029 & 0.2583 & 0.1498 \end{bmatrix} \quad (38)$$

$$F^* = \begin{bmatrix} 9.4354 \\ 1.6384 \\ 7.7782 \\ 4.7299 \end{bmatrix} \quad (39)$$

Validating the model on a different set-up (different initial condition and noise) the resulting dynamics evolution is reported in Fig. 1. In Fig. 2 the difference of true and estimated evolution is reported.

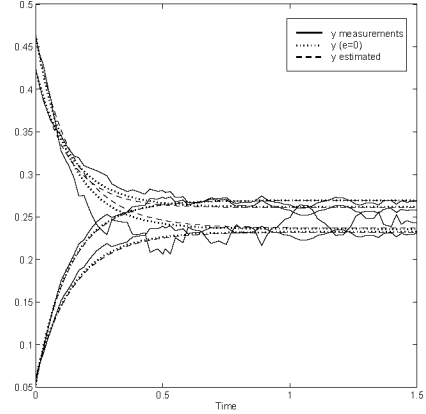


Fig. 1. Validation: evolution comparison.

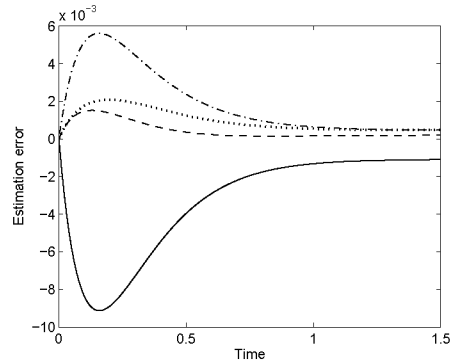


Fig. 2. Validation: error evolution.

Given the estimated $\Theta^* \in \mathcal{M}$, we should invert relations (15) in order to find a solution in the original space of parameters. Proposition in (Falugi and Giarré, 2006) gives solution and conditions to the determination of the unique inversion.

We note that the determination of the central estimate is very good. This is true also for simulation examples with greater n .

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Table 1. True and identified θ_i

| | true θ | identified θ |
|---------------|---------------|---------------------|
| θ_1 | 0.0055 | 0.0064 |
| θ_2 | 0.0146 | 0.0120 |
| θ_3 | 0.0175 | 0.0151 |
| θ_4 | 0.9202 | 0.9210 |
| θ_5 | 0.9921 | 0.9969 |
| θ_6 | 0.9545 | 0.9614 |
| θ_7 | 0.9666 | 0.9724 |
| θ_8 | 0.0228 | 0.0225 |
| θ_9 | 0.0218 | 0.0221 |
| θ_{10} | 0.0117 | 0.0121 |
| θ_{11} | 0.9087 | 0.9044 |
| θ_{12} | 0.9806 | 0.9803 |
| θ_{13} | 0.9430 | 0.9448 |
| θ_{14} | 0.9551 | 0.9558 |
| θ_{15} | 0.0228 | 0.0225 |
| θ_{16} | 0.0083 | 0.0081 |
| θ_{17} | 0.0117 | 0.0123 |
| θ_{18} | 0.9147 | 0.9106 |
| θ_{19} | 0.9866 | 0.9865 |
| θ_{20} | 0.9490 | 0.9510 |
| θ_{21} | 0.9611 | 0.9620 |
| θ_{22} | 0.0342 | 0.0340 |
| θ_{23} | 0.0055 | 0.0052 |
| θ_{24} | 0.0146 | 0.0149 |
| θ_{25} | 0.9128 | 0.9091 |
| θ_{26} | 0.9847 | 0.9850 |
| θ_{27} | 0.9471 | 0.9495 |
| θ_{28} | 0.9592 | 0.9605 |

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