

A FORMALISM FOR MODELS WITH A METADYNAMICALLY VARYING STRUCTURE

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Abstract

We present hereafter a formalism for system with adaptive structure. The axiomatic structure is fully detailed. We then apply it to a biological problem: the modelling of the problem of coevolution in a bacteria-phage system. The results presenting show how this system organises in a quasi-species like structure under darwinian evolution.

1 Introduction

Recently there has been much interest in the study and formalisation of complex adaptive systems (CAS) ([7], [10], [5], [6] and [14]). Approaches are numerous and at first glance different: artificial chemistries, genetic algorithm like formalism, cellular automata. Actually, most of these systems share one important feature: they are dynamical objects (continuous or discrete) whose structures are sometimes modified by a top level automata-like rule. On the basis of these observations, we have built a two level formalism (section 2) that helped us to design a model of coevolution in bacteria-phages system (section 3). We finish with the presentation of some results (section 3).

2 Formal framework

2.1 Definition of the framework

Before presenting the formalisation of our approach we will have a look at the main ideas behind the formalisation of the concept of dynamical system by Kalman in [9]. The aim of this approach is to demonstrate that some very common mathematical structures plus a few axioms can provide a very general framework where the notion of dynamical systems (of all kinds) is captured.

Time is modelled as an ordered subset of the reals (to cover both the continuous and discrete paradigms). The important objects are the state set (the variables characterising the system) and the transition function. The transition function defines the trajectory in the state set starting from an initial state. Only a

few axioms are required to characterise these objects and allow them to form a “dynamical system”. Among the more important ones, we have: direction of time, consistency, composition property and causality [9].

Now, inspired by Kalman, we propose a formalisation of our MAS:

Definition. A metadynamical system \mathcal{M} is a composite mathematical concept defined by the following axioms:

1. To be coherent with our previous 2-level description, let us start by defining the dynamical level:
 - (a) T_0 , the time set, is modelled as an ordered subset of the reals¹
 - (b) Since our systems may change their state space during their evolution, we must consider not a single state space X but a family of state spaces suitably indexed.
 $\{X_i\}_{i \in I}$ is thus the set of all possible state spaces
The definition of I is not trivial. It has, for example, not to be necessarily countable (see example 2, after the description of the formalism).
 - (c) U is the set of input values
 - (d) Ω the set of acceptable input functions $\Omega = \{\omega : T_0 \rightarrow U\}$
 - (e) $\{\varphi_{i,j}\}_{j \in J}$ are transition functions on state set X_i

$$\varphi_{i,j} : T_0 \times T_0 \times X_i \times \Omega \rightarrow X_i$$

With these definitions we come to: $\forall i, j, \{T_0, X_i, \varphi_{i,j}, U, \Omega\}$ is a dynamical system respecting Kalman axioms [9]

These axioms just say that the basic objects, on which we work are “dynamical systems”.

2. Let us now deal with the metadynamical level.
Let $X = \bigcup_{i \in I} X_i$ be the set of all the possible states of the system
Let $D = \{\varphi_{i,j}\}_{i \in I, j \in J}$ be the set of all possible transition functions

¹Such a general definition could include exotic sets such as fractal cantor sets, for instance, in practice, the sets used are part of \mathbf{R} or \mathbf{N} .

Then we can set a metadynamical rule as a function

$$r : T_1 \times X \times D \rightarrow X \times D$$

(a) With $T_1 \subseteq T_0$ the metadynamical time set

(b) And if $r(t, x_1, \varphi_{i_1, j_1}) \mapsto (x_2, \varphi_{i_2, j_2})$,
 $\forall t \in T_1, x_1 \in X_{i_1} \implies x_2 \in X_{i_2}$

If $t \in T_1$ and $r(t, x, \varphi) = (x, \varphi)$, r is said to be *mute* at (t, x, φ) else (t, x, φ) is a *commutation point*.

Describe the metadynamical rule: it can operate on instants when the system is defined and not necessarily all (a), actually a higher level is usually slower. As the metadynamical rule can change the state and the transition function, we have to pay attention that both match well: the resulting state has to belong to the state set on which the new transition function operates).

3. (Definition and evolution rule)

We describe here how dynamics and the metadynamical rule combine together to make the system change in time. We consider the evolution of the system between two instant t_1 and t_2 from T_0 .

Let $x_t = \varphi(t, t_1, x_1, \omega)$ with ω an input function

(a) (Purely dynamical phase) If r is mute on (t, x_t, φ) ,
 $\forall t \in [t_1, t_2] \cap T_1$

Then \mathcal{M} is defined between t_1 and t_2 and:

- If $t_2 \notin T_1$, then

$$\mathcal{M}(t_2, t_1, x_1, \varphi, \omega) = (x_{t_2}, \varphi)$$

- Else $t_2 \in T_1$ and

$$\mathcal{M}(t_2, t_1, x_1, \varphi, \omega) = r(x_{t_2}, \varphi)$$

(b) (Concatenation rule) If $\exists t_2 \in]t_1, t_3[$ such as \mathcal{M} is defined between t_1 and t_2 and between t_2 and t_3 then \mathcal{M} is defined between t_1 and t_3 and

$$\begin{aligned} & \mathcal{M}(t_3, t_1, x_1, \varphi, \omega) \\ &= \mathcal{M}(t_3, t_2, \mathcal{M}(t_2, t_1, x_1, \varphi, \omega), \omega) \end{aligned}$$

(c) (Stopping rule) \mathcal{M} is defined between t_1 and t_2 if, respecting previous axioms, there is only a finite number of commutation points in $[t_1, t_2]$.

Remarks

- In 3.(a) in the second case, when $t_2 \in T_1$, we consider that $(t_2, r(x_{t_2}, \varphi))$ is mute. We “forget” the case where the metadynamics would “rebound” and have several commutations at the same time. If the system has several commutations, it is always possible to consider this set of commutations as one, with the final state of the last commutation (providing that, we know from 3.(c) that the number of commutations is finite).

- axiom 3.(c) is to avoid Zeno-style system with an infinite number of commutations in a finite amount of time (e.g. with a quantity $x(t) = \sin\left(2\pi\frac{1}{1-t}\right)$ with a commutation each time that $x(t) = 0 \dots$).

Example. On fig.1, we can see a metadynamical system in action. At $t_5 = t_c$, we pass from a 2-dimensional state set to a 3-dimensional one. The dynamics are continuous, so $T_0 = [t_0, t_{end}]$ and the metadynamical time set T_1 is discrete: $T_1 = \{t_1, t_2, t_3 \dots t_8\}$. Since the metadynamics is mute on t_1, t_2, t_3 and t_4 , the evolution from t_0 to t_5 is a purely dynamical phase, ended by a commutation (Axiom 3.(a)). Evolution from t_5 to t_{end} is also purely dynamical (the metadynamics mute on t_6, t_7 and t_8). Junction between the two is made by using the concatenation rule. As we have only one commutation the system is defined.

3 Example: The coevolution of bacteria and phage populations

In this section, we will apply our formalism to a given example: the modelling of the coevolution of bacteria and phages. Coevolution in general and coevolution of bacteria and phage in particular are currently subjects of first importance in evolution biology [lenski], [4]. Phages (short for bacteriophages) are the viruses of bacteria. Bacteria attack by phages is done by the lysis process: a phage hang on the surface of a bacterium cell, injects its DNA in it and then force the bacterium to yield its own replicas inside the cell. When the cell is full, it bursts, releasing a huge quantity of copies of the infecting phage (see diagram 2). The efficiency of the attack, depend of the couple bacterium-phage.

One of the other characteristic of bacterial and phages populations are their high variability: they frequently mutate, creating new populations with new properties.

Such a system has two dynamics to be taken into account: the dynamics of the populations of bacteria and phages (growth of bacteria populations and bacterial-phages interactions), and the “meta”dynamics of evolution geared by mutations and extinction. It is without any doubt a model which is not in the scope of the classical theory of dynamical system, but our formalism applied well to it.

Our variable structure objects are populations of bacteria and phages, with their dynamical interactions as described for instance in ODEs similar to those of population dynamics. The metadynamical rule represents the operations that change the structure of the dynamical equations (mutations and extinctions).

We have first to model the evolution of a set of B/P populations when no special event occur, we choose to use a modified version² of Mosekilde equations [11]. This set of ordinary dif-

²We consider only the interactions with phages originally present in the chemostat and not the population arriving at random by supply, the number of different strains is not necessarily equal in our model ($n_b = n_p$ in Mosekilde

ferential equations describe the interactions of bacterial populations B_i and phage populations P_j in a well-stirred tank reactor (a chemostat) (B_i and P_j are the concentration of that populations and S the nutrient). The process of infection of bacteria by phages j is modelled by three infection stages I_{j_1} , I_{j_2} and I_{j_3} . That means that our transition function φ is given by the integration of the following set of equations:

$$\left\{ \begin{array}{l} \frac{dB_i}{dt} = \underbrace{\frac{\nu SB_i}{\kappa + S}}_{\text{growth}} - \underbrace{B_i \sum_{j=1}^{n_p} \alpha \omega_{ij} P_j}_{\text{infection}} - \underbrace{\rho B_i}_{\text{dilution}} \\ \frac{dI_{j_1}}{dt} = \underbrace{P_j \sum_{i=1}^{n_b} \alpha \omega_{ij} B_i}_{\text{infection}} - \underbrace{3 \frac{I_{j_1}}{\tau_j}}_{\text{incubation}} - \underbrace{\rho I_{j_1}}_{\text{dilution}} \\ \frac{dI_{j_2}}{dt} = \underbrace{\frac{3}{\tau_j} (I_{j_1} - I_{j_2})}_{\text{incubation}} - \underbrace{\rho I_{j_2}}_{\text{dilution}} \\ \frac{dI_{j_3}}{dt} = \underbrace{\frac{3}{\tau_j} (I_{j_2} - I_{j_3})}_{\text{incubation}} - \underbrace{\rho I_{j_3}}_{\text{dilution}} \\ \frac{dP_j}{dt} = \underbrace{3 \frac{\beta_j I_{j_3}}{\tau_j}}_{\text{lyse}} - \underbrace{P_j \left(\sum_{i=1}^{n_b} \alpha B_i + \sum_{j=1}^{n_b} \sum_{k=1}^3 \alpha I_{j_k} \right)}_{\text{hanging}} - \underbrace{\rho P_j}_{\text{dilution}} \\ \frac{dS}{dt} = \rho \left(\underbrace{\sigma}_{\text{supply}} - \underbrace{S}_{\text{dilution}} \right) - \underbrace{\sum_{i=1}^{n_b} \frac{\nu \gamma S B_i}{\kappa + S}}_{\text{consumation}} \end{array} \right. \quad (1)$$

with:

- . ρ , the rate of dilution ($\rho = 0.0045 \text{ min}^{-1}$)
- . κ, ν respectively the saturation term and the growth from the Monod equation ($\kappa = 10 \mu\text{g.l}^{-1}, \nu = 0.024 \text{ min}^{-1}$)
- . α , the theoretical adsorption constant depending on phage and bacteria size ($\alpha = 10^{-9} \text{ ml.min}^{-1}$)
- . τ_j , a time constant ($\tau_j = 30 \text{ min}$)
- . β_j , the number of copies of phage j released during the burst of the infected bacterial cell ($\beta = 100$)
- . σ , the continuous supply of substrate ($\sigma = 10 \mu\text{g.l}^{-1}$)
- . γ , the amount of nutrient consumed in each cellular division ($\gamma = 0.01 n\text{g}$)

In the previous equations, we have still to define ω_{ij} , the probability of infection of B_i by P_j . To do that, we must define a characteristic of bacterial population B_i and a characteristic of

equations), we have more than two values for ω_{ij} and they depend of some characteristic of the populations, and finally it seems righter to make the infected state depend of the phage which infect and not the bacteria infected.

a viral population P_j which together allow us to compute ω_{ij} . To this end, to each bacteria and phage population is attached a symbolic binary string coding its behaviour facing B/P interactions (defense for B, attack for P). ω_{ij} is then depending of the similarity between bit strings s_i^b (attached to bacteria population B_i) and s_j^p (attached to viral population P_j).

$$\omega_{ij} = \left(1 - \frac{d_H(s_i^b, s_j^p)}{n_c} \right)^2 \quad (2)$$

avec $d_H(s_i^b, s_j^p)$ the Hamming distance (the number of differing bits) between s_i^b and s_j^p .

The metadynamical rule is:

- During a simulation step Δt , the probability that a population give birth to k mutant strains is:

$$p(k) = e^{-\lambda} \frac{\lambda^k}{k!} \quad (3)$$

with $\lambda = \frac{B_i}{C_e} p_e$, p_e being the elementary probability that a viable population of concentration C_e arise during time Δt . Then the apparition of all the one-bit-different strains is equiprobable

- All population under a given threshold (different for bacteria and phages) is removed from the system.

4 Results

4.0.1 Presentation of the experiment

We will now discuss in detail a numerical experiment. We took two populations of bacteria and phages, and tuned the mutation rates such as $\mu_B = 0$. That means that bacteria population is stuck in its gene space. At the opposite phages are allowed to mutate. This is to simulate what could happend when $\mu_P \gg \mu_B$, when viruses are much more variable. We can see how the concentrations (dynamical point of view) and the composition in term of genotype (metadynamical point of view) evolve (Fig.3).

It is interesting to see the trajectory of the cloud of phages in gene space (by this, we mean the different populations weighed by their concentrations). For visualising them we chose to plot two values: the trajectory of the centroïdes (the ‘‘gravity centres’’) and their entropies (a measure of their dispersion). The centroïde c of phage population $\{P_j\}$, is the vector $c \in [0, 1]^{n_c}$ (n_c is the size of the binary string coding our genes) given by :

$$c_k = \frac{1}{P} \sum_{j=0}^{n_p} P_j s_j^k$$

where c_k is the k-th component from c and s_j^k the k-th one from s_j the string coding for the behaviour of the population P_j and

$$P = \sum_{j=0}^{n_p} P_j.$$

The entropy is very classically given by

$$eP = - \sum_{j=0}^{n_p} \frac{P_j}{P} \log \frac{P_j}{P}$$

Storing then the trajectory of the centroïdes of phage populations during our simulation, we are able to plot them using a method from statistical analysis called Principal Component Analysis (PCA) [13]. This method allow us to find the best projection from $[0, 1]^n$ to $[0, 1]^2$ (in the sense of maximal conservation of distances inside the set of points). We did it for nine different simulations (same initial conditions but different seed for the random number generator) and we observe that, though the populations “chose” very different paths, eventually they all reach the zone in the gene space corresponding to the best predation (4).

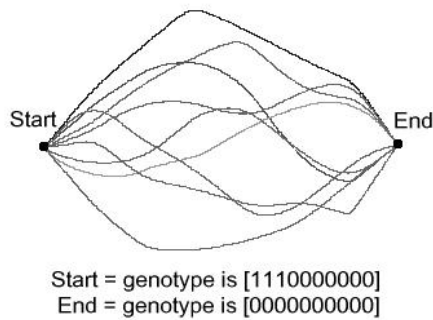


Figure 4: Plot of the centroïdes of phage populations from nine different simulations

A look at the evolution of entropy vs time and the values of the populations at different distances of area of best predation give us an idea of the scenario leading these experiments: after a period of strong expansion with strong increase of entropy, the cloud contract in a favourable area in a state of low entropy (see 5). It reaches an oscillating regime where two kinds of species coexist, the best fitted phages and the ones at a distance of one bit. This organisation in few mutants genotypes closed in a small area of the gene space make us think of a quasi-species-like organisation [12].

5 Conclusions

At the level of modelling adaptive systems, our work provides a formalism able to capture a wide range of examples in a common axiomatic structure. This would provide us with a basis for both the theoretical characterisation of metadynamical objects and for the simulation of these systems. At the biological level, our work shows a scenario of how evolution can lead to a structure of populations with close genomes. It paves also the way toward a simulation of a complete bacterial-phage ecosystem and a study of its properties and their evolution.

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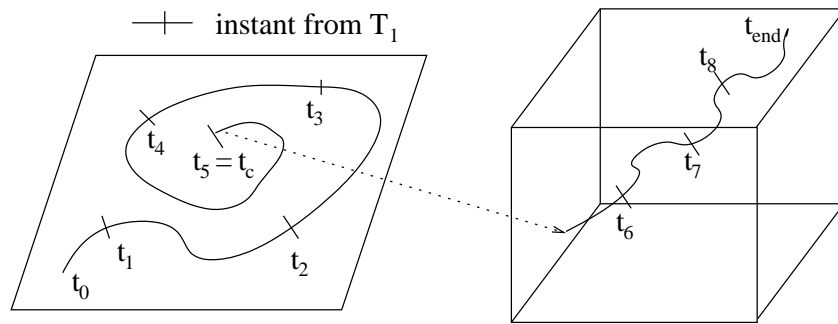


Figure 1: Illustration of some axioms of a metadynamical system

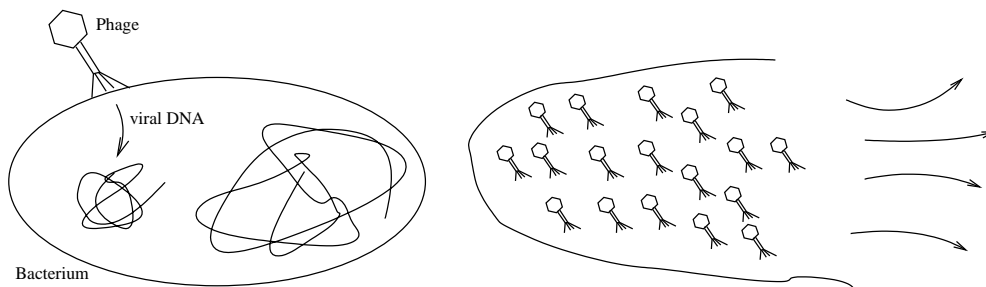


Figure 2: The lysis process

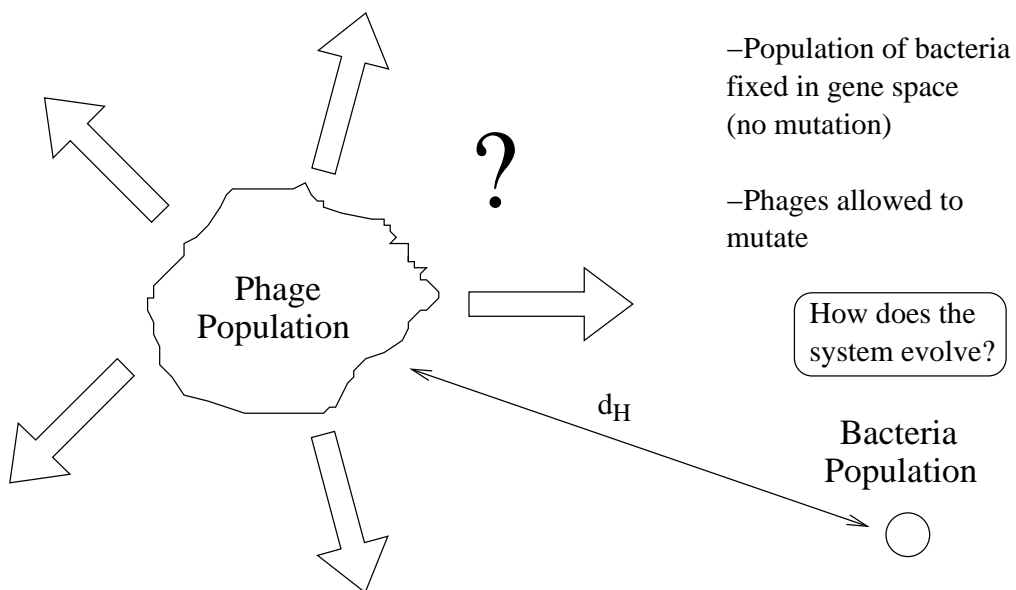


Figure 3: Description of the numerical experiment

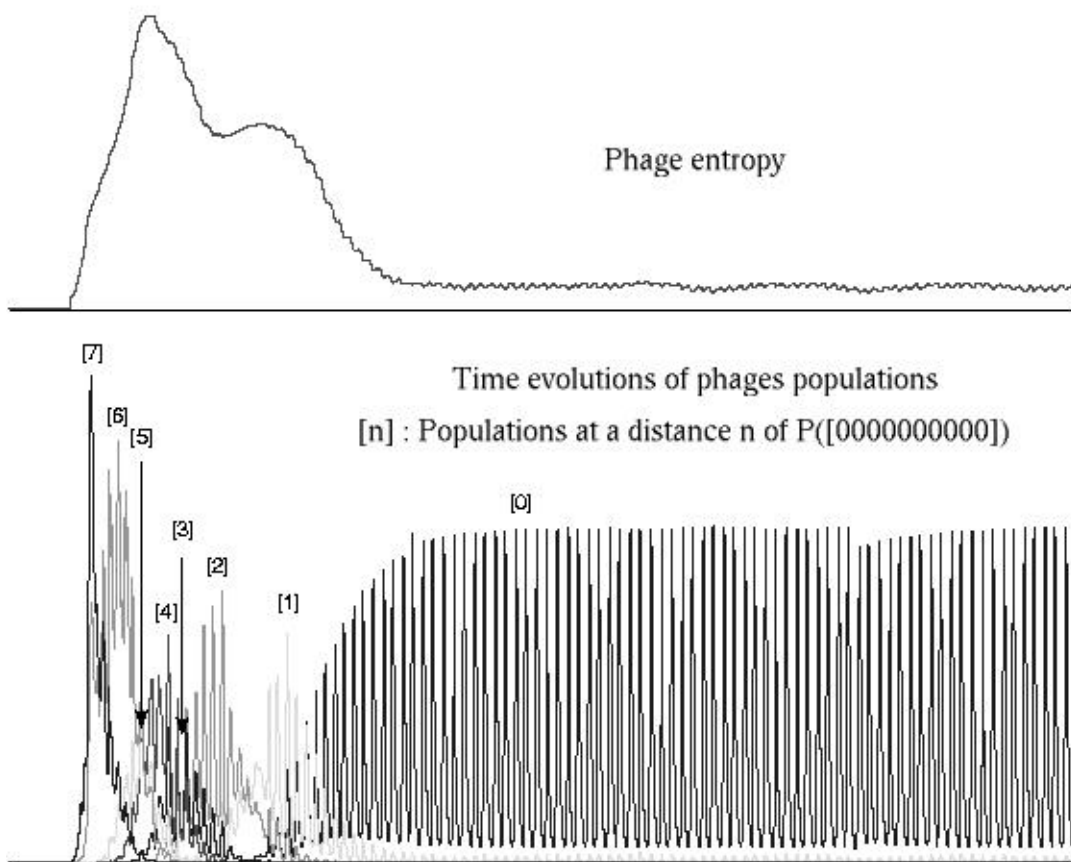


Figure 5: Entropy of the population (above) Dynamics of the different n-bit-distant populations [n] (below)