Dynamics, Evolution and Information in Nonlinear Dynamical Systems of Replicators

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Along this thesis I have met really amazing people and I have worked in really fascinating places like Venice or Santa Fe in New Mexico. I have also had the fortune to meet, work and collaborate with absolutely brilliant scientists. In the first place, I want to thank all the people involved in the ambitious PACE project, especially Steen Rasmussen and John McCaskill. PACE has definitively caused a breakthrough in the pathway towards the artificial protocell. I also want to thank the hospitality received in the European Center for Living Technology, especially to Irene Poli, Norman Packard and Kristian Lindgren. Especially I would like to thank Santiago F. Elena for his excellent advice and discussions about viruses and the people of his laboratory in València. I also want to thank Ernest Fontich, Juana Díez, Antonio Mas and Miquel Noguera. Thanks for all what I have learnt from you, and for your kindness and interest in my work. I also want to thank Àlex Haro (the story of the trees was really a pity) and Imma Baldomà for listening to me in my first incursions in dynamical systems as well as the rest of people of the UB-UPC Dynamical Systems Group. I am also grateful to the people at The Santa Fe Institute, who warmly welcomed me in the research stay carried out in December 2005. For sure, it was one of the greatest adventures of my life. I also want to thank the computer assistance staff of my department, especially the patience of Alfons, Judit and Miguel. Finally, I would like to thank the administrative staff and the library service of the Universitat Pompeu Fabra

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This thesis has been writen on the booktex template [88] provided for the open source Linux community. The cover shows the HIV virus interacting with the Lorenz attractor.

Abstract

This thesis covers three subjects: The molecular quasispecies (three papers), the hypercycle (four papers) and antagonistic replicator systems (two papers). The main results are briefly summarized and ordered by subject in the following list:

THE MOLECULAR QUASISPECIES

- Although the error catastrophe is typically described in terms of mutation, it can also occur under the presence of critical replication rates. Under the Swetina-Schuster single peak fitness landscape scenario, in agreement with a stochastic bit string model of genome evolution, we qualitatively explain a real data set obtained from a nosocomial HCV outbreak (see [108]).

- We have shown that the survival of the flattest effect is governed by a first-order phase transition with critical scaling down as well as that space involves a lower critical mutation rate, broading the conditions at which the survival of the flattest effect occurs.

- We show that the so-called geometric replication for RNA viruses is more sensitive to the error catastrophe under the Swetina-Schuster single peak fitness landscape, with mild mutations tending to accumulate more in the geometric replication scheme. On the contrary, linear replication has a higher critical mutation rate.

THE HYPERCYCLE

- We analyze symmetric and asymmetric two-member hypercycles. We show, for the first time, the presence of a delaying extinction capacity of hypercycle replicators associated to a ghost arising after a saddle-node bifurcation. We also show that the asymmetry of the hypercycle is of relevant importance for the survival of the entire hypercycle, also finding that diffusion favours the stability of this hypercycle under local spatial correlations.

- We show that the kinetic properties of simple hypercyclic replicators with a weak attached parasite are important in the stability of the hypercycle. In agreement with other works, we show that space broadens the stability scenario for the two-member

hypercycle coexisting with this parasite. Interestingly, we also find that the attachment of a weak parasite in this simple hypercycle triggers the emergence of large-scale spatial patterns (e.g., aggregates confining the hypercycle molecules), as a difference from the same system without the parasite. We find that the consideration of space for the asymmetric hypercycle can generate complex spatio-temporal coexistence dynamics characterized by fractal attractors, suggesting a possible positive effect of the parasite in providing the system with a kind of primitive autocompartmentation.

- We show that the global extinction time, τ, for hypercycles with three and four species differs from the scaling law described for the extinction dynamics of two-member hypercycles, given by $\tau \sim (\varepsilon - \varepsilon_c)^{-1/2}$ (being ε the degradation rate of the polymers and ε_c the bifurcation value, see [145]). Specifically, we show that the effect of increasing the bifurcation parameter above the bifurcation value is not so dramatic as for the two-member hypercycle. The scaling region is found further away from the saddle-node collision, and is shown to be given by $\tau \sim (\varepsilon - \varepsilon_c)^{-1/3}$.

- We numerically describe a mutation-induced delayed transition also governed by a ghost appearing after the saddle-node bifurcation. The saddle remnant involves a kind of concentration memory in phase space which delays the extinction of the functional hypercycle templates once the random replication phase is achieved.

ANTAGONISTIC REPLICATORS

- We provide the bifurcation scenarios and the resulting asymptotic dynamics for a minimal Lotka-Volterra type, predator-prey model describing the coevolution among replicators with a strength of interaction influenced by a pair of haploid diallelic loci, under the so-called matching allele dynamics. We demonstrate the presence of a Hopf bifurcation linked to Red Queen dynamics. We also show, counterintuitively, that the more efficient a predator genotype is, the lower the asymptotic concentration it achieves.

- We investigate stochastic cellular automata models describing the dynamics of host-parasite haploid genomes (with a perfect matching antagonistic dynamics), undergoing replication-mutation-diffusion processes on a two-dimensional lattice. We find that the Red Queen scenario is enlarged as the dimension of the sequence space increases. We characterize the dependence of the phases of survival, extinction and coevolution of host and parasites on mutation and replication rates.

Key words: Antagonistic replicators / Applied mathematics / Biological information / Bifurcations / Bit string models / Catalytic networks / Cellular automata / Complex Systems / Computational biology / Dynamical systems / Error threshold / Hypercycle / *In silico* evolution / Mathematical models / Molecular evolution / Molecular ecology / Mutualism / Nonlinear dynamics / Origin of life / Phase transitions / Population dynamics / Positive feedbacks / Quasispecies / Red Queen dynamics / Replicator systems / RNA viruses / Spatial dynamics / Statistical physics / Systems biology / Stochastic reactions / Theoretical biology / Theoretical ecology

Preface

This thesis has been supervised by Ricard V. Solé and is based on research done during the period 2004-2008 funded by the EU-supported PACE integrated project, EC-FP6-IST-FET-IP-002035 (*Programmable Artificial Cell Evolution*) and by The Santa Fe Institute. During 2008 I was also funded by the Human Frontier Science Program Organization grant RGP12/2008. The works presented here have been physically developed at the Complex Systems Lab which belongs to the Universitat Pompeu Fabra (GRIB) located at the Barcelona Biomedical Research Park (PRBB). Some of the works of this thesis have also been developed at The Santa Fe Institute, at the European Center of Living Technology (ECLT) in Venice as well as at the Instituto de Biología Molecular y Celular de Plantas at CSIC-Universitat Politècnica de València.

The manuscript is divided into two parts. The first part, which consists of 6 chapters, is a brief introduction to the contents of the papers presented in this thesis. Chapter 1 is a general (and not rigurous) introduction about dynamical systems in biology and about the rapidly expanding scientific discipline of complex systems in the framework of systems and synthetic biology. Here I also comment on some personal opinions about the use of theoretical and computational models as a powerful way to study real world processes. Chapter 2 is also a general review about the theory of the molecular quasispecies in relation to the origin of life problem but especially in relation to the study of RNA viruses. Chapter 3 is about the hypercycle theory which is related to the origin of life problem and to the overcoming of the prebiotic information crisis. Chapter 4 deals with antagonistic replicator dynamics, focusing on coevolution and on the *Red Queen* theory of evolution. These four chapters, inspite of dealing with different subjects, should be classified in the general field of replicator nonlinear systems. Actually all these systems are not completely disconnected from each other. This important point is discussed in some of the chapters. Chapter 5 is a more technical section dealing with numerical methods to solve the differential equations. In this chapter the reader can also find explanations about the properties and characteristics of the most typical bifurcations arising in nonlinear dynamical systems used in theoretical biology. Although this part is mainly mathematical, it can be followed by a biologist interested in these topics. The intention of this section is to provide the newcoming reader with a "minimal manual" about the bifurcations described in the papers of this thesis. As the reader will see, the saddle-node bifurcation has the largest weight because it was described for the hypercycle model. For further reading about bifurcations we refer the reader to some excellent books [27, 127, 165]. Finally, in chapter 6, I comment

on the main results of each of the papers presented in the second part of the thesis (chapter 7) in a more expanded way than in the abstract section. In this chapter I also add some comments on some of the results considering the wide view that allows the culmination of the thesis, where the author has a larger knowledge than at the beggining of the thesis, when some of the works were developed.

The second part (chapter 7) consists of 9 selected papers which form the scientific basis of this thesis. These papers, which are listed down here, are ordered by subject: papers 1-3 (Molecular Quasispecies); papers 4-7 (Hypercycles); and papers 8-9 (Antagonistic Replicator Dynamics) (see the following chapters).

List of papers

1. Information catastrophe in RNA viruses through replication thresholds. Solé, R. V. Sardanyés, J., Díez, J. and Mas, A. *Journal of Theoretical Biology* **240**(3), 353-359 (2006).

2. Simple quasispecies models for the survival-of-the-flattest effect: The role of space. Sardanyés, J., Solé, R. V. and Elena, S. F. *Journal of Theoretical Biology* **250**(3), 560-568 (2007).

3. Robustness to Mutations Depends on whether RNA virus Replication Occurs Geometrically or Via a Stamping Machine. Sardanyés, J., Solé, R. V. and Elena, S. F. Submitted to *Journal of Virology* (2009).

4. Bifurcations and phase transitions in spatially-extended two-member hypercycles. Sardanyés, J. and Solé, R. V. *Journal of Theoretical Biology* **243**(4), 468-482 (2006).

5. Spatio-temporal dynamics in simple asymmetric hypercycles under weak parasitic coupling. Sardanyés, J. and Solé, R. V. *Physica D: Nonlinear Phenomena* **231**(2), 116-129 (2007).

6. Delayed transitions in nonlinear replicator networks: About ghosts and hypercycles. Sardanyés, J. and Solé, R. V. *Chaos, Solitons and Fractals* **31**(2), 305-315 (2007).

7. Error threshold ghosts in a simple hypercycle with error prone self-replication. Sardanyés, J. *Chaos, Solitons and Fractals* **35**(2), 313-319 (2008).

8. Matching allele dynamics and coevolution in a minimal predator-prey replicator model. Sardanyés, J. and Solé, R. V. *Physics Letters A* **372**(4), 341-350 (2008).

9. Chaotic Stability in Spatially-Resolved Host-Parasite Replicators: the Red Queen on a Lattice. Sardanyés, J. and Solé, R. V. *International Journal of Bifurcation and Chaos* **17**(2), 589-606 (2007).

I have structured this thesis in chapters and papers sections because I would like this manuscript to become a working tool for present and future researchers. Hence, a more

or less initial detailed description of the subjects related to the papers I present might catalyze the work of people interested on the topics analyzed in this thesis, and might also facilitate the comprehension of my works as well as of other publications in the field of replicator dynamics, which are quite a lot. For a beginner, it is easier if people doing thesis (who in principle have had enough time to digest the concepts, the results and the main ideas in their fields of research) explain their work in a far from technical, didactic way. I have tried to explain more or less what I have learnt during these years, especially directing the text to an audience of biologists interested in theory, and emphasizing in the most important points a biologist should keep in mind when dealing with modelization in general. I hope to have achieved this goal here.

As the reader will see, some of the chapters include new results based on my research, which are used to complete the information of some of the works of the tesis presented in chapter 7, or just to discuss some interesting results of other authors working on the same topics. Moreover, during the development of this thesis we have published more papers and I have participated in two book chapters, which are listed down here. Some of these papers are cited in the references of the chapters or of the articles included in this thesis.

1. Ghosts in the origins of life? Sardanyés, J. and Solé, R. V. *International Journal of Bifurcation and Chaos* **16**(9), 2761-2765 (2006).

2. Red Queen strange attractors in host-parasite replicator gene-for-gene coevolution. Sardanyés, J. and Solé, R. V. *Chaos, Solitons and Fractals* **31**(2), 1666-1678 (2007).

3. The role of cooperation and parasites in nonlinear replicator delayed extinctions. Sardanyés, J. and Solé, R. V. *Chaos, Solitons and Fractals* **31**(5), 1279-1296 (2007).

4. Ghosts in high dimensional non-linear dynamical systems: the example of the Hypercycle. Sardanyés, J. *Chaos, Solitons and Fractals* In press, (2009).

5. General scaling law in the saddle-node bifurcation: a complex phase space study. Fontich, E., Sardanyés, J. *Journal of Physics A: Mathematical and Theoretical* **41**(15102), 1-9 (2008).

6. Dynamical role of the degree of intraspecific cooperation: a simple model for prebiotic replicators and ecosystems. Fontich, E., Sardanyés, J. *Physica A: Statistical Mechanics and its Applications*. In press (2009).

7. On the Metapopulation Dynamics of Autocatalytic Replicators. Sardanyés, J., Fontich, E. Submitted to *International Journal of Bifucartion and Chaos* (2009).

8. Collapse of hypercycle functional templates via nontrivial equilibria collision. Sardanyés, J. Submitted to *Journal of Theoretical Biology* (2009).

9. Models of Protocell Replication. Solé, R. V., Macía, J., Fellermann, H., Munteanu, A., Sardanyés, J., Valverde, S. In *Protocells: Bridging Nonliving and Living Matter* (eds. Steen Rasmussen et al.). MIT Press, 213-231 (2008).

10. The Hypercycle: From Molecular to Ecosystems Dynamics. Sardanyés, J. In *Landscape Ecology Research Trends*, chapter 6 (eds. Arthur Dupont and Hugo Jacobs). Nova Publishers Inc, 1-12 (2009).

Curriculum vitae

Josep Sardanyés was born on August 6, 1976 in Granollers (Vallès Oriental, Barcelona). In 1995 he started with his studies in Biology at the University of Barcelona. He specialised in Theoretical Biology and Complex Systems at the group of Ricard V. Solé at the Universitat Pompeu Fabra. He started a PhD on replicator dynamics in the framework of the European PACE (*Programmable Artificial Cell Evolution*) project. During the development of the PhD, he obtained his Master degree in Biomedicine also at the Universitat Pompeu Fabra. The results of his studies during the period 2004-2008 are described in this thesis.

Chapter 1

Introduction

The whole is more than the sum of its parts

Aristotle, Metaphysica 10f-1045a.

1.1 Dynamical systems in Biology

It can be said that theoretical biology is a fairly young science. Actually, the scientific discipline of replicator dynamics started in the framework of ecology, and was later extended into the context of molecular biology. The first scientific works on replicator dynamics date from many decades ago, for example, the seminal works of Lotka and Volterra [102, 103, 175, 176, 177] or the studies of Nicholson and Bailey [120]. However, a curious and disparate example dates back to the 13th century. Leonardo da Pisa, also known as Fibonacci (derived from filius Bonacci, meaning son of Bonaccio), calculated, by means of a recurrence relation, the success in reproduction of rabbits with a simple model rule, given by

$$a_n = a_{n-1} + a_{n-2}.$$

Actually, this recurrence relation is a minimal system including a memory or historical effect in the future outcome. Fibonacci assumed that a couple of rabbits produces, from its second month onwards, a new couple of rabbits every month. Being a_n the number of couples in the n-th month. Actually, a_n is the sum of a_{n-1} (the number of couples from last month) and a_{n-2} (the number of newborn couples at least two months old). Starting from one pair, $a_0 = a_1 = 1$, one gets a Fibonacci series, which is given by the sequence $1, 1, 2, 3, 5, 8, 13, ...$ This very first example of modelization in biology was of course extremely rather simple, since factors as mortality or fluctuations in the number of offspring were not taken into account. Mathematical models describing biological processes or systems have become more elaborated since then. However, it is yet true saying that a mathematical description of "real life" is up to know extremely difficult to achieve, and even today there is an intense debate on the mapping between theory and reality. A good

question, as stated in [160], would be: *"Can physics be an appropiate framework for the understanding of biological sciences ?"* Most biologists would probably agree that there is little relation between the complexity of natural systems and the simplicity of any example derived from Newtonian physics. Though biologists have long been interested in concepts originally developed by statistichal physics enhanced by dynamical systems theory. These concepts were later applied to explain everything from why stock markets crash to why the blood bessels develop particular branching patterns. The investigation of biological systems through the basis of physics or mathematics might allow a deeper understanding of the fundamental laws or properties associated to several complex systems. The science of complex systems is nowadays growing in a very rapid manner. Fortunately, the entrance of theory in biology dates back from many decades ago, and a lot of work has been done (see for example the excellent review [160]). It seems that the usefulness of theoretical works on biology is widely accepted by the scientific community since there are a lot of people doing research on theoretical biology. There are actually lots of groups working on experiments who are generating lots of interesting data and it would be definitively really interesting to "open" their eyes showing them the potential and the elegance of the world of theory. This will be a great opportunity to deep in the fundamental properties of some biological systems extracting information from theoretical and computational models, one of the interests of the scientific works being developed in the current "Systems biology" age.

A very important subject in complexity theory is the study of deterministic dynamical systems which change in time. The mathematical formulation based on differential equations used to approach to complex systems occupies a wide protagonism in complexity. The idea is what can be said about the behavior of the system at later (or, sometimes, earlier [7]) times on the basis of information about the system at a specific instant (e.g., the present). The origin of dynamical systems theory comes from Newtonian mechanics, which was developed to analyze systems of particles moving under the effect of external forces. Despite the upheavals wrought in physics in the twentieth century due to the discovery of relativity and quantum theory, the ideas of Newtonian dynamics still remain as one of the conceptual cornerstones of physics, and have enriched both physics and mathematics with successive waves of new ideas and concepts which have still not reached their end [138]. The exceptional interest of the approaches based on dynamical systems is the recognition that many other kinds of systems, among them, biological systems, can also be fruitfully described in the same terms as those familiar from Newtonian dynamics. Moreover, the independent descriptions of the systems that have been developed in special areas of biology and engineering improve enormously in generality and power when formulated in dynamical terms [138].

When facing with systems that change in time, for instance physical, chemical or biological systems, one must first decide on the so-called instantaneous description of our system. That is, what information is necessary and sufficient to characterize our system at a particular instant of time. Then, one must express the fashion in which these instantaneous descriptions can change in time, since the behavior of the system in time is the fundamental province of all dynamical theories. The properties of real systems

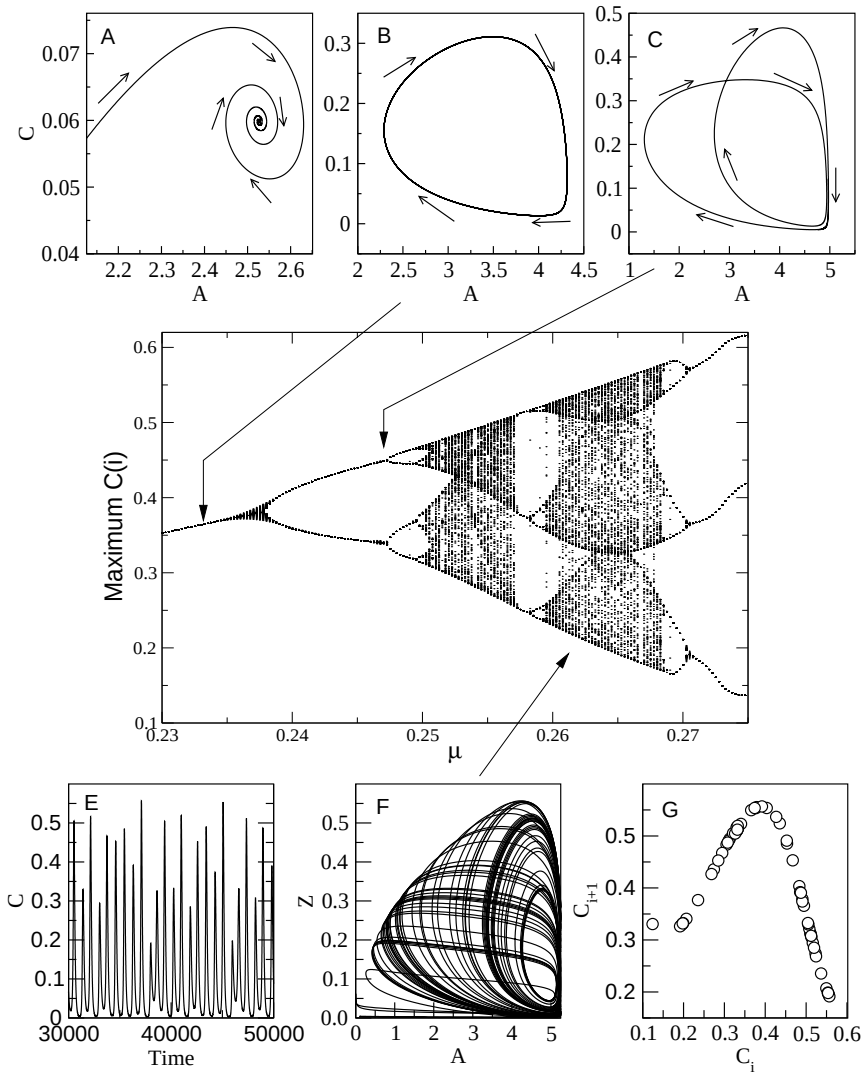

Figure 1.1: Example of nonlinear dynamics in a planktonic ecosystem modeled with ordinary differential equations (see [151]). The central picture shows the bifurcation diagram at increasing the algal growth rate, μ. For each μ, the maxima attained by the population of carnivorous zooplankton (C) are shown. Three examples of different attractors are indicated in (A-C) involving fixed points, periodic orbits, and a period-two orbit. In (E) we show a chaotic trajectory on the attractor for the time evolution of carnivorous zooplankton, C. In (F) we show a projection of the Rössler-like, homoclinic strange attractor in the (A, Z) phase space. When the corresponding set of maxima $\{C_i\}$ for this pattern is plotted in a return map (C_i, C_{i+1}), a nearly one-dimensional shape is recovered (G), consistent with the Feigenbaum scenario displayed by simple discrete models. Variables A, Z and C, represent abundances of algae, and of herbivorous and carnivorous zooplankton, respectively.

have to be ascertained by making specific observations or measurements of such systems. In general, at any instant of time, we will have a measurement that will ideally yield a definite number partially characterizing the system at that instant (difficulties arising from quantum indeterminacy are not relevant to our arguments) [138]. Each of the quantities, named $x_1, x_2, ..., x_n$, and which will be determined by the corresponding measurements on the system, will be called a state variable of the dynamical system. The whole combination of possible numerical values of these state variables constitutes the so-called state or phase space of the system. Such state variables may be regarded as specifying the n axes of a rectangular coordinate system in n-dimensional Euclidean space, and the state space of the system may be regarded as a subset of this space. The first step in the dynamical description of a given system is the specification of the instantaneous states of a system in terms of an appropiate set of state variables. Secondly, we must specify the manner in which our system can change in time. In terms of our representation, the change of a system in time means precisely that its state is temporarily changing; which in turn means that the individual state variables are themselves to be regarded as functions of time [138]. If we know the form of these functions, then the dynamical description of the system is complete.

Let us note that if these functions $x_1(t), x_2(t), ..., x_n(t)$ are known, the dynamical behavior of the system in time takes the form of a curve or a trajectory, in our n-dimensional state space, parametrized by time. In other words, we can follow the dynamical history or evolution of our system by tracing in the appropiate direction along the corresponding system trajectory [138]. Thus our condition on the functions $x_1(t), ..., x_n(t)$ that specify the dynamical behavior of our system is that they satisfy the following set of simultaneous, first-order differential equations:

$$\frac{dx_i}{dt} = f_i(x_i, ..., x_n), \quad i = 1, ..., n \tag{1.1}$$

The fundamental problem of dynamical systems theory is: what can be said about the dynamical properties of the corresponding system from the equations ?

A dynamical system shall consist of the following data:

(a) An open set R in Euclidean n-space E_n (i.e., the state space).
(b) A set of n real-valued functions $\{f_1, ..., f_n\}$ defined on R.
(c) The set of simultaneous first-order equations

$$\frac{dx_1}{dt} = f_1(x_1, ..., x_n)$$

$$...$$

$$\frac{dx_n}{dt} = f_1(x_1, ..., x_n)$$

From the functions describing the dynamical evolution of a given system we can obtain a lot of valuable information. For instance, one can look for the equilibrium or

n = 1	n = 2	n ≥ 3	n ≫ 1	n = ∞
Growth and decay	*Oscillations*	*Chaos*	*Collective phenomena*	*Waves and patterns*
Fixed points	Pendulum	Strange attractors (Lorenz)	Josephson arrays	Solitons
Bifurcations	Anharmonic oscillators	Chemical kinetics	Coupled nonlinear oscillators	Plasmas
Overdamped systems	Limit cycles	3-body problem (Poincaré)	Iterated maps	Quantum field theory
Relaxational dynamics	Heart cells	Fractals (Mandelbrot)	Lasers	Earthquakes
Logistic model (single species)	Neurons	Simple Matching allele dynamics	Immune system	General relativity
Autocatalytic replicator	Nonlinear electronics	Quantum chaos?	"Advanced" hypercycles?	Turbulent fluids
Metapopulations (Levins)	Simple quasispecies (Eigen)	"Large" hypercycles?	Artificial protocell?	Reaction-diffusion
Chemical equilibrium	"Initial" hypercycles?	Trophic food chains	Ecosystems	Epilepsy
Catastrophes	Two-patch metapopulations	Red Queen dynamics	Economics	Protocell replication?
Symmetry breaking	Predator-prey systems		Origin of life?	Ecosystems
				Life

Table 1.1: Classification of several nonlinear systems according to the number of state variables (i.e., dimensions), n, of the ordinary differential equations describing their dynamics. The dynamical behaviors described in italics in the second row correspond to the more complex dynamics found in each dimension. Generically, such behaviors are additive as we move from left to right. That is, for example, the case $n \geq 3$ can also behave like cases $n = 2$ or $n = 1$, but not the other way around (modified from [165]).

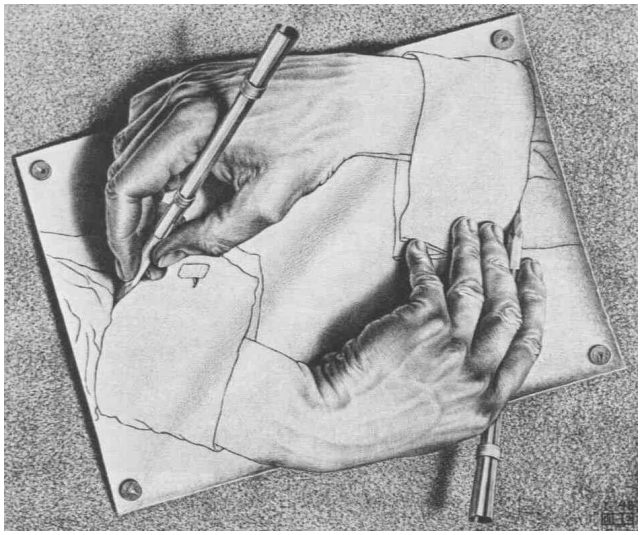

Figure 1.2: Example of nonlinear dynamics, metaphorically represented by Escher's *Drawing hands* (1948), illustrating the principles of self-complementary and heterocatalytic replication. The faster the first hand draws the second one, the faster the first one is drawn. Both hands cooperate with each other, like in the hypercycle (M. C. Escher's "Drawing Hands" (c) 2008 The M.C. Escher Company - the Netherlands. All rights reserved. Used by permission. www.mcescher.com).

fixed points of the system, given by

$$\frac{d\mathbf{x}}{dt} = 0,$$

now expressed in vectorial form. This means that the rate of change in time of the state variables is zero and then the system has achieved equilibrium (i.e., the state variables will not change further in time). Once we have the expression of possible steady states of the system we may calculate their stability. That is, if a small perturbation around these equilibria will vanish (the point is attractor) or will grow (the point is unstable) (see Chapter 2.2). The stability properties of the steady states and its dependence on parameters is crucial in any dynamical study. The classical view of dynamical systems theory is based on differential equations. However, other kinds of dynamical systems exist. Actually, all these theoretical and computational approaches might form the basis and the tools of complex systems theory. Trying to explain all these approaches in detail might be impossible even in a single book, since there are many other classes of dynamical systems. I will just mention some of them also giving some references which might be useful for the reader. Differential equations are used for time continuous systems, and this mean field approach assumes that the interacting entities are perfectly mixed where interactions are equiprobable and local correlations are ignored.

We can include the effect of spatial correlations also in continuous models by means of reaction-diffusion equations, which are built up with partial differential equations (PDEs).

For continuous spatially-extended systems the dimension of the dynamical systems is $n = \infty$. We can also analyze mean field models with discrete time by designing models with difference equations or maps. These models should be used in biological processes in which the populations (i.e., represented with the variables) do not have overlapping of generations, like insects. The dynamics of deterministic discrete- and continuous-time mean field models can hugely vary. For instance, due to the nature of the discreteness of time, the logistic model for the growth of a single species (with a one-dimensional state space) with non-overlapping generations produces chaos for some values of the growth rate (see [109, 12]). Another class of dynamical system, which is a discrete one and also gathers the local spatial correlations is given by so-called cellular automata (CA) models. This kind of approach has been widely used in this thesis. The reader can find detailed information of CA models in [73]. Finally, it is important to say that space is crucial in shaping ecological and evolutionary dynamics. The consideration of space (even in both implicit and explicit ways) in nonlinear dynamical systems can drastically change the results derived from mean field models. For the sake of illustration, just mention that it has been shown that metapopulation systems of single species discrete models can stabilize the survival of the population in the chaotic regime under local and global perturbations [5], as opposed to what might happen in single populations of exponentially growing species which have a higher probability of becoming extinct in the chaotic scenario [12].

Multitude of numerical and experimental results indicate that spatially-extended nonlinear systems involving diffusion, chemotaxis, and/or mechanisms of convection can give raise to complicated time-dependent patterns [86, 58, 117, 90, 126]. Complex spatiotemporal phenomena have been described in several nonlinear systems as in the Belousov-Zhabotinskii reaction [139, 2, 125], the Gray-Scott [58] and the FitzHugh-Nagumo [45, 118] models, the cardiac muscle [182, 130], as well as in molecular biology [14, 13] and ecological dynamics [174, 64, 156, 85, 126, 9]. Although earlier works on theoretical ecology neglected spatial dimensions, it is known that the explicit consideration of space can modify the dynamics of nonlinear interactions [172, 95] also allowing the emergence of macroscopic i.e. large-scale, structures able to introduce new levels of selection and adaptation that go beyond the individual level [14, 15, 161]. The importance of space in the stability of antagonistic (i.e. host-parasite or predator-prey) populations has become a significant subject of debate during the last decades [64, 156, 15, 126, 14, 13]. Moreover, the ubiquity of predator-prey like interactions in natural ecosystems as well as its molecular counterpart in the so-called molecular ecology [106, 107] has bring about the development of several theoretical and empirical studies. It has also been shown that the coupling of periodic oscillators by means of diffusion in locally-correlated systems can unstabilize the populations driving to the emergence of strange attractors (see section 4.3 of chapter 4 and [126]).

The interest of self-organization and spatial pattern formation and its role in the dynamical outcome of nonlinear systems has been claimed by some scientists. As an anecdote I would like to mention that Paulien Hogeweg, who works with spatially-extened complex systems, recently said in a workshop that some years ago she was “shouting in

the desert" [74] when trying to highlight the importance of space in biology. In this sense, it is recommended to use, when meaningful, both mean field and spatially-explicit models for the analysis of ecological or molecular processes. The effect of space, for instance, is of extreme importance for hypercycles, especially when considering the problem of parasites (see Chapter 3). It has been postulated that in spatially-extended systems, where large scale spatial patterns arise, selection is more acting at the community level than at the individual one.

1.2 From simplicity to complexity

This section, entitled like one of the lemmas of The Santa Fe Institute, wants to highlight the paradigm of complexity, that is, that simple dynamics can be analyzed with simple models but so can complex dynamics. For instance, it is known that deterministic chaos can arise from three-variable, continuous time systems (see for example Fig. 1.1 and [101, 140, 96]). In discrete-time systems (modeled with difference equations or maps), chaos can appear from the one dimension [109, 12]. Nonlinear systems of differential equations are typically not integrable and are really hard to solve (when possible) analytically. The main difference between linear and nonlinear systems is that for the linear ones the system can be solved by broken down it into parts, and then finally recombined to obtain the answer. A linear system is exactly equal to the sum of its parts. Linear differential or difference equations can be solved by Fourier transformation and do not lead to chaos. This is not the case for nonlinear systems, in which the superposition principle does not work at all. The reader can catch this idea with the illustrative example stated by Steven H. Strogatz: "*If you listen your two favorite songs at the same time, you won't get the double of pleasure !*".

There is currently no full consensus about a formal definition of complexity. Some definitions can be found in the recently published book *Complexity: 5 questions* [55]. For example, according to some authors, there is a more or less robust consensus in relation to what makes a complex system: some set of elements interacting in such a way that higher-order, system properties emerge. These properties can not be reduced to the properties displayed by individual parts and thus some kind of "irreducible order" is at work [55]. In my opinion the term of complexity allows lots of different possible definitions, but what seems clear is that the term nonlinear should appear in all of them. In Figure 1.3 we show a simple conceptual diagram based on the subject of complexity. Here, complexity is defined as a set of possible dynamical behaviors, as a set of different transitions and critical phenomena, as well as a set of different theoretical and computational tools often used to approach to complex systems. Complementarily, in Table 1.1 several nonlinear systems are classified according to the number of state variables, which can give raise to the potential dynamics of the differential equations. This table is based on the one provided in Strogatz's book. This author made an ambitious classification of several linear and nonlinear systems according to their number of variables and their degree of nonlinearity [165]. This is an excellent classification which provides the reader with a wide vision on

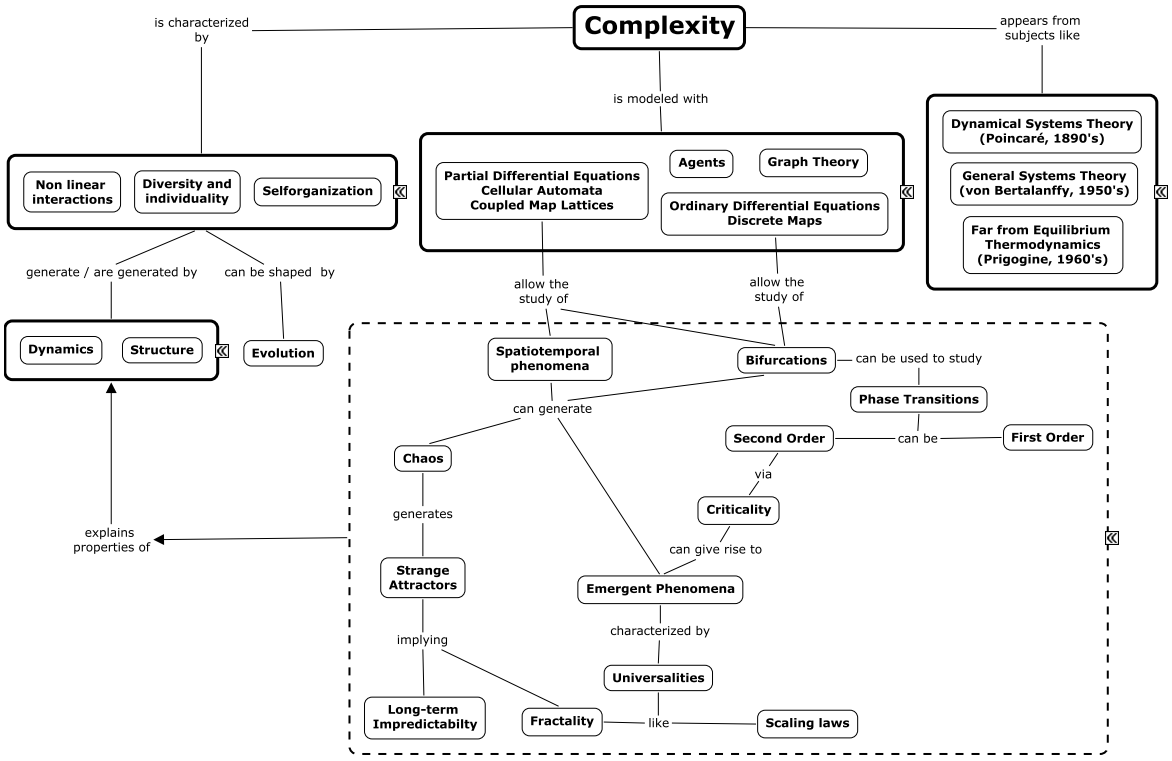

Figure 1.3: Conceptual diagram integrating the main topics and subjects arising in the field of complexity (based on the diagram of Martí Rosas). A definition of complexity should include the term nonlinearity (or feedback), the potential dynamics known from dynamical systems theory and the theoretical and computational tools used for their study. This might provide a unifying framework for the concept of complexity.

the possible dynamics of complex systems. Finally, to end with this more philosophycal part, the notion of nonlinearity or complex system is illustrated with the famous Escher's "Drawing hands" (see Fig. 1.2), trying to represent to effect of mutual cooperation and self-complementarity, which underlies the nonlinear dynamics of hypercycles (see Chapter 3).

Complex systems theory takes advantage of theoretical and computational models to approach to real systems dynamics. Almost all models are based on a set of assumptions and a limited level of description, involving a properly chosen range of details. For the sake of illustration, when studying the dynamics of viruses, one can design simple models gathering the main mechanisms of viral replication in so-called unstructured models, which are studied using low dimensional dynamical systems (see for example Papers 1 and 2 of this thesis or [84, 184]). However, the same type of systems can be analyzed in a more detailed manner by considering several cellular processes or components interacting with the viral populations in so-called structured models, which are instrinsically high-dimensional (see for instance Paper 3 of this thesis and [98]). Which of both methods is

better ? Of course one may think that the more complete a model the better it is. This is not necessarily true, since it may depend on our objectives. If one wants a detailed mathematical analysis of the qualitative scenarios displayed by the system as a function of the parameters, that is, the equilibria and the bifurcations, a low dimensional model will be ideal. For some systems we will also be able to analytically treat the equations being able to rule out periodic orbits, finding Liapunov functions or calculating transient times. On the other hand, for high-dimensional models we will only be able to perform numerical analysis, not being able to provide analytically the fixed points and the critical values of the parameters involved in the bifurcations. Of course a simple model, independently of its dynamics, gives a clearer interpretation of the role of the parameters and their physical or biological meaning. However, if one tries to make a more quantitative approach based on an experiment, the structured models may produce better results. Actually, both approaches do not exclude each other, since often some universal properties (well studied from a mathematical or physical viewpoint) can be found in different models describing the dynamics of the same system. This provides our investigations with consistency, which is very important in science.

1.3 Theory before experiments

This section emphasizes the importance of the theoretical and computational investigations on biological processes (although such an importance could be extended to other scientific disciplines) as a powerful way to understand the underlying dynamics of biological systems and their response to parameter changes. A good example of this fact is the huge effort made in the PACE project in modelization and development of simulation tools to investigate several systems related to the hypothetical artificial protocell (see the *Virtual Lab* webiste: *http://complex.upf.es/∼josep/VirtuaLab.html* and the recently published book of the Massachusetts Institue of Technology (MIT) on protocells developed within PACE [135]). From "simple" models of replication kinetics to detailed systems of protocell models such as the chemoton [134, 53, 54] or the "Los Alamos Bug" [132, 133, 43], the development of theory and of computational tools may be of extreme interest and utility for future experiments on artificial protocells, both at the cellular and at the populational level. In this sense, considerable work has been done, but there are still lots of open questions concerning the artificial protocell and the origin of life problem (see Fig. 3.1). Models based on nonlinear differential equations might be useful to determine the qualitative behaviors of replicator systems but also to make predictions. Even the analysis of extremely simple, abstract models given by low dimensional systems can explain us key features about the dynamics of real systems. It is actually really advisable to burn your neurons building and designing theoretical and computational models as a previous (or why not, parallel) process before starting in the lab. This effort will sure imply the necessity to deep into the details of the interactions and processes occurring in the system under study, and then to have a good comprehension of what is happening. This will also be surely translated into a wide gain of intuition of how things can work at the lab.

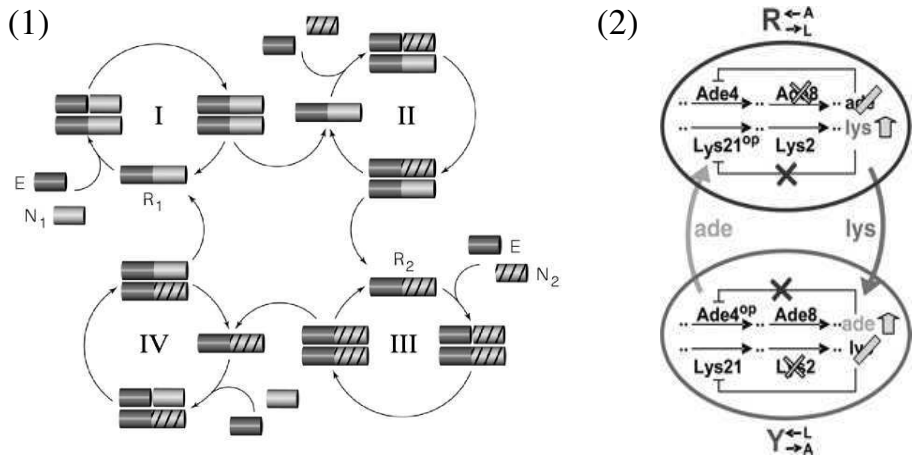

Figure 1.4: Two examples of synthetic hypercycles: (1) artificial coiled coil proteins and (2) engineered yeast (obtained from Nature [92] and PNAS [153] database). The investigation of simple hypercycle models can highlight several interesting and universal properties of catalytic (cooperative) networks. These results can also underly more complex models (sharing the same algebraic skeleton of simple models) describing the cooperative dynamics of real natural or artificial systems.

Regarding replicator dynamics, and as stated by Stadler and Stadler in their excellent review on replicator systems [164], the interest of theoretical models relies more on the logics of the replication mechanism than on the precise molecular mechanisms tied to the replication process. In this sense, in many cases, we can obviate the number or the nature of the macromolecules involved in a process of replication, or which concrete regions of them are involved in the effective interactions (in a biochemical sense). This allows us to build up simple models only based on the reaction kinetics, which can gather universal properties for different replicator systems. It is important to say that replicator dynamics, which is the subject analyzed in this thesis, is of extreme importance in the context of systems and synthetic biology. From molecular replicator systems to complex ecosystems, models (both theoretical and computational) give us valuable information about the dynamical outcome of this type of systems, which sometimes share similar kinetic properties (of course at different scales).

In the context of replicator systems, and in order to highlight the usefulness of theoretical works about replicator models, I would like to emphasize the interest of exploring the kinetics of several engineered, artifical systems with different interactions such as predator-prey [8] or cooperative dynamics [92, 153] (see Fig. 1.4). As a concrete example, the underlying dynamics for the cooperative yeast system explored by Shou and co-workers [153] might correspond to the hyperbolic one, which is described, to some extent of detail, by the hypercycle equations (see Chapter 3). Hence, several results derived

from this thesis could be searched for, tested or contrasted in real systems, which could display the same dynamics shown in the models or, of course, could show important differences which might help us to see the weak points of the theory. This would certainly be a really amazing thing to do. In this context, just mention that the ghost phenomenon associated to the saddle-node bifurcation, which has been explored in some works on the hypercycle developed during the thesis (see papers 4, 6 and 7 of this thesis and [147, 149]), was described in a real physical system given by an electronic circuit modeling Duffing's equations (see [169] for details). Then, this fact opens the possibility of finding the same phenomenon in a real system of replicators. As previously mentioned, synthetic biology is now quite enough advanced to build artificial systems of replicators, in which some results of this thesis could be tested.

As this is an introductory chapter, I would like to finish mentioning some of the books that have been extremely useful for me, especially in the first years of the thesis, and that will sure introduce the reader to the fascinating world of dynamical systems and complexity. These are very didactic and well-explained books, and any biologist interested in theoretical biology and complex systems should have them on the desktop. For instance, those interested in prebiotic evolution and dynamical systems should use the books [87, 110, 78, 69, 141]. Those people more interested in theoretical biology in general and mathematical biology should have the books [117, 39, 138, 136, 34, 158, 160]. A classical book on complex systems is the Nicolis and Prigogine one [119]. If one is more interested in dynamical systems in general, we refer the reader to the most excellent and didactic book on nonlinear dynamics that has fallen into my hands, this is Strogatz's book [165], which has been extremely useful for me and is really advisable for people starting their research in the field of theory. The reader should also know other books on dynamical systems, which have strong mathematics and where the main concepts on topology, bifurcations, attractors, stability, etc..., can be found (see for instance [152, 33, 27, 127]).

Chapter 2

The molecular quasispecies

The work on the error threshold opens a new paradigm for how to fight viruses

Manfred Eigen, 2002

2.1 Quasispecies and the information crisis

The term quasispecies was first coined by Manfred Eigen and Peter Schuster to describe the molecular evolution of primitive sets of replicator molecules. The theory they developed allowed the approach to the problem of the origin of life in terms of selective processes under far-from-equilibrium conditions. If we think about the quasispecies theory in the context of the origins of life, we may first try to imagine a physically-plausible scenario in prebiotic evolution. We will here (and in the next chapter) perhaps jump on some evolutionary steps starting our imaginary travel to past times considering the existence of some simple replicator molecules (which could spontaneoulsy generate by chemical assemblage).

The process of replication in prebiotic molecular systems is thought to be highly error-prone. Actually, in order to have an accurate replication, eukaryotic cells need a huge complex enzymatic machinery to correct mistakes [4]. The error rate for DNA is about $\mu \approx 10^{-9}$. Such enzymes might have not be encoded by earlier replicators. It is known that error-prone replicators (possibly, like the ones in the origin of life) have a sharp limit on the accumulation of information they can encode. This error threshold has been defined as a mutation rate below which populations equilibrate in a traditional mutation-selection balance, and above which the population experiences and error catastrophe, that is, the loss of the favored genotype through deleterious mutations [18]. Actually, beyond the critical mutation rate, the quasispecies enters into a drift phase in sequence space, and the information encoded by the master sequence becomes random. In this sense, the main conclusion of the works developed by Eigen is that the length of a replicating polymer is limited by the replication accuracy per nucleotide, and so primordial replicators would

have to replicate with implausible high accuracy in order to reach the length of today RNA viruses (about $10^3 - 10^4$ nucleotides). This finding, together with the observation that distinct templates cannot coexist in the competition-only scenario [167], come to be known as the information crisis of prebiotic evolution (see the following chapter for the extension of this problem in the framework of the origin of life).

A quasispecies in the context of virus evolution is a dynamic distribution of non-identical but closely related mutant and recombinant viral genomes subjected to a continuous process of genetic variation, competition and selection, and which act as a unit of selection [37]. We can also provide a more informal and perhaps clearer definition of a quasispecies for a newcoming reader. Imagine viral genomes as a collection of manuscripts containing some information which are being diligently copied by monks from generation to generation who, being only humans (and assuming no divine influences), make errors now and then (see Fig. 2.1). As long as the monks make few mistakes, each generation hands down enough error-free copies to transmit the information held in the manuscript intact). However, if the monks make lots of mistakes, at some point the message will become uncomprehensible and the information "encoded" by this manuscript-like genomes will become random, since they will have fallen into error catastrophe. As I will explain in the following sections and in the next chapter, quasispecies theory is crucial to our understanding of the dynamics and evolution of RNA viruses as well as in the origin of life problem.

2.2 RNA virus dynamics

The process of mutation-selection balance is one of the oldest and fundamental pillars of population genetics: natural selection increases the frequency of fit variants while mutations introduce unfit variants, giving raise to an equilibrium distribution balanced between these two effects. The concept of the quasispecies has recently attracted the atention of virologists, because many RNA viruses appear to generate high levels of genetic variation that may favour the evolution of drug resistance and immune escape [18]. For example, a classical observation is the rapid emergence of drug-resistant viruses after therapy by enhancing copying fidelity at the cost of lowering replication down [52, 81, 89, 128].

In order to investigate the so-called error threshold transition we can build a simple quasispecies model by considering a viral genome population divided in so-called master sequence, x_m, and its mutant spectrum, x_M, respectively (the model is the one of Paper 1 of this thesis). Hence, the time evolution of their concentrations can be represented with the following set of nonlinear differential equations:

$$\dot{x}_m = x_m\big(f_m(1-\mu) - \phi(\mathbf{x})\big), \tag{2.1}$$

$$\dot{x}_M = f_m \mu x_m + x_M\big(f_M - \phi(\mathbf{x})\big), \tag{2.2}$$

where f_m and f_M denote the replication rates of master and mutant strands respectively, while μ is mutation rate. The model neglects backward mutations from the pool of mutants

Figure 2.1: Viral genomes can be thought as manuscripts being diligently copied by monks from generation to generation. As long as the monks make few mistakes the message can remain intact along time. Nevertheless, if the monks make lots of mistakes the message will become uncomprehensible in the long term.

to the master sequence. This formulation is equivalent to considering polynucleotides of length $L \to \infty$, whose mutation probability per nucleotide, u, goes to 0 so that the replication accuracy per genome is finite, i.e., $\exp(-Lu) \to (1-\mu)$. We also impose that the sum of the two populations is constant and given by $x_m + x_M = 1$, and thus

$$\frac{d}{dt}(x_m + x_M) = 0.$$

From the previous expression we can find the dilution flux that keeps the total population constant, given by $\phi(\mathbf{x}) = f_m x_m + f_M x_M$. Assuming the constant population condition, we have a linear dependence of x_M on x_m since $x_M = 1 - x_m$, then we can reduce the system Eqs. (2.1)-(2.2), to a one dimensional model now given by

$$\dot{x}_m = f_m x_m [\xi_m - \xi_M x_m], \tag{2.3}$$

where $\xi_m = 1 - \mu - f_M/f_m$ and $\xi_M = 1 - f_M/f_m$. We can actually represent such an equation in a similar way as for the normal form for the transcritical bifurcation (see Chapter 5, Eq. (5.2)) rewriting it as

$$\dot{x}_m = f_m \xi_m x_m - f_m \xi_M x_m^2.$$

This equation can be solved giving a logistic-like solution

$$x_m(t) = \frac{\xi_m}{\xi_M}\left[1 + \left(\frac{\xi_m/\xi_M - x_m(0)}{x_m(0)}\right)\exp(-\xi_m f_m t)\right]^{-1},$$

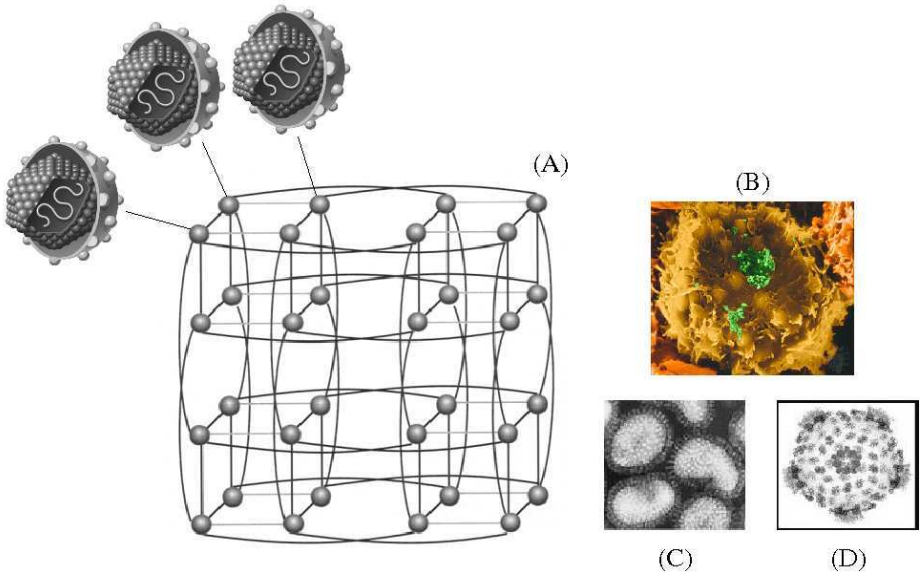

Figure 2.2: (A) Viral genomes live in a sequence space, $\mathcal{H}^{\nu}$ (here represented for sequences of $\nu = 5$ nucleotides length). Each node is a genome sequence (which could correspond to a specific phenotype) surrounded by all possible one-mutation strands. It seems that the error threshold constrains the size of this multidimensional space (limiting the so-called open-ended evolution of RNA viruses), confining the quasispecies to specific regions where the master sequence and its cloud of mutants is maintained along generations. Some examples of RNA viruses: (B) Scanning electron micrograph of HTLV-I virus (green) infecting a human T-lymphocite (yellow), (C) influenza virus, (D) HCV electronic microgaphy.

being $x_m(0)$ the initial condition. This one dimensional dynamical system has two fixed points, given by $x_m^* = 0$ and $x_m^* = \xi_m/\xi_M$. In the following lines we will show that the error catastrophe is achieved via a transcritical bifurcation (see Chapter 5). To show this bifurcation we need to perform linear stability analysis of the equilibrium points, that is, to characterize the local stability of the fixed points. This information is given by the eigenvalue of (2.1), obtained by linearizing the flow for the one-dimensional system $dx_m/dt = \Phi(x_m)$. As the equilibrium point x_m^* is constant, the dynamics of a perturbation is obtained from

$$\frac{dy}{dt} = \Phi(x_m^* + y).$$

Assuming that the perturbation, y, is small, we can perform a Taylor series expansion for the previous function

$$\frac{dy}{dt} = \Phi(x_m^*) + \left[\frac{d\Phi}{dx_m}\right]_{x_m^*} y + \frac{1}{2!}\left[\frac{d^2\Phi}{dx_m^2}\right]_{x_m^*} y^2 + ... + \frac{1}{n!}\left[\frac{d^n\Phi}{dx_m^n}\right]_{x_m^*} y^n + O(y^n)$$

since by defintion $\Phi(x_m^*) = 0$, we can use the first-order term and thus the linear approx-

imation

$$\frac{dy}{dt} = \lambda y + O(y),$$

with

$$\lambda = \left[\frac{d\Phi}{dx_m}\right]_{x_m^*}.$$

This linear system is exactly solvable, with an exponential solution

$$y(t) = y(0)\exp(\lambda t).$$

From the previous expression we can provide a criterion for stability in forward time. If the eigenvalue $\lambda < 0$, then $y(t) \to 0$ as $t \to +\infty$ (i.e., ω-limit), and a small perturbation will asymptotically return to its stable equilibrium. Then, we will say that x_m^* is an attractor, since it will attract close initial conditions. If $\lambda > 0$, a small perturbation will grow and thus the fixed point is unstable. Then, x_m^* will be a repellor. In an intermediate case, $\lambda = 0$, we will have a marginal state, which implies a critical state where the system is not structurally stable (i.e., a small change in the parameters will cause a qualitative change in the dynamics, that is, the system will switch from stable to unstable dynamics or viceversa by means of a bifurcation). For our system, we obtain the first-order Taylor term from

$$\frac{d\dot{x}_m}{dx_m} = f_m(1-\mu-2x_m) - f_M(1-2x_m) = \lambda(x_m).$$

The stability of the trivial fixed point, $x_m^* = 0$, which corresponds to the extinction of the master sequence and to the error catastrophe scenario, is obtained from the eigenvalue

$$\lambda(x_m)_{x_m^*=0} = f_m(1-\mu) - f_M.$$

From the previous expression we can derive the critical mutation rate which is given by

$$\mu_c = 1 - \frac{f_M}{f_m}. \tag{2.4}$$

With $\mu > \mu_c$, this eigenvalue is negative and thus this fixed point is an attractor. On the other hand, with $\mu < \mu_c$, $\lambda(x_m)_{x_m^*=0} > 0$ and thus this equilibrium is unstable. Moreover, it is easy to see the dependence of x_1^* on μ, from

$$x_m^* = 1 - \frac{\mu f_m}{f_m - f_M}.$$

Note that with $\mu < \mu_c$, $x_m^* > 0$. Just at the critical mutation rate, μ_c, both fixed points collide at $x_m^* = 0$. If $\mu > \mu_c$, the nontrivial fixed point becomes negative. As the state variable, $x_m(t)$, corresponds to a concentration of molecules, then in order to be physically meaningful, it is obliged that $x^{m(t)\in\mathbb{R}^+}$, and thus beyond this critical value we shall assume the extinction of the master sequence. This is clearly shown in Fig. 2.3, which displays the bifurcation diagram using mutation rate as control parameter and the equilibrium concentration of the master sequence as order parameter. Note that as the mutation rate

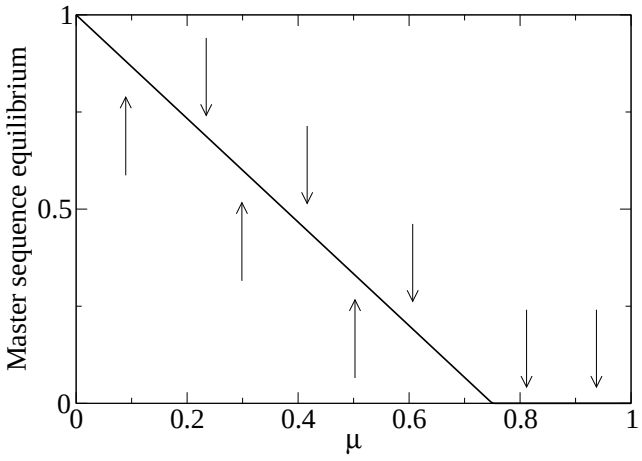

Figure 2.3: Bifurcation diagram obtained from the two dimensional model (2.1)-(2.2), using μ as control parameter, where we compute the effect of mutation in the equilibrium of the population obtained by numerical integration using the standard fourth-order Runge-Kutta method with a constant septsize $\Delta t = 10^{-1}$. Here we assume that mutations are deleterious using $f_m = 1 > f_M = 0.25$. The arrows indicate the stability character of each of the equilibria. Note that the nontrivial equilibrium crosses the origin at $\mu = \mu_c$ (see (2.4)), where the transcritical bifurcation happens.

increases the equilibrium concentration of the master sequence linearly decreases. Once the mutation rate is larger than the critical mutation value given by expression (2.4) (for this example we use $f_m = 1$ and $f_M = 0.25$, being $\mu_c = 0.75$), the equilibrium concentration of the master sequence crosses the coordinate $(\mu_c, 0)$ of the bifurcation diagram, and then the only equilibrium of the system is the extinction value, which becomes stable. The eigenvalue evaluated at the nontrivial fixed point is given by,

$$\lambda(x_m)_{x_m^* \neq 0} = f_m \left(\frac{2\mu f_m}{f_m - f_M} - \mu - 1 \right) + f_M \left(1 - \frac{2\mu f_m}{f_m - f_M} \right).$$

It is easy to show that if we evaluate this eigenvalue at the critical mutation rate we obtain

$$\lambda(x_m)_{x_m^* \neq 0; \mu_c} = 0.$$

Moreover, we can also show the following stability conditions

$$\lambda(x_m)_{x_m^* \neq 0} < 0, \quad \text{with} \quad \mu < \mu_{\rm c},$$

and

$$\lambda(x_m)_{x_m^* \neq 0} > 0, \quad \text{with} \quad \mu > \mu_{\rm c}.$$

From the previous calculations we can conclude that as the mutation rate increases, the nontrivial fixed point, which is stable and has a positive real value, moves to the origin

and collides with the fixed point $x_m^* = 0$ at the critical mutation μ_c. Then there is an exchange of stability, and with $\mu > \mu_c$, the nontrivial equilibrium is unstable and has a negative real value, while the origin becomes an attractor. This is the typical scenario for the transcritical bifurcation.

The error catastrophe has found its greatest appeal in work on RNA viruses (as the HCV, HIV or influenza), whose genomes replicate under large mutation rates, orders of magnitude higher than those in DNA based life-forms. Such an inference can be made from the high levels of viral genetic variation seen within RNA virus samples [18] and among infected hosts [35], in studies on long-term rates of nucleotide substitution [76] and most importantly from direct measurements of error frequency [38]. Due to the lack of proofreading activity of the RNA polymerase, or the reverse transcriptase, the replication mechanism involves high mutation rates. There is now sufficient empirical evidence to suggest that the error threshold is more than just a theoretical result [75]. In this sense, populations of RNA viruses often harbour numerous deffective genomes, which are to be expected if deleterious mutations arise and accumulate at a high frequency (see the example of dengue virus [178]). A more dramatic example comes from experimental studies showing that an increase in the mutation rates beyond the error threshold can result in the extinction of viral populations, which is achieved through "lethal mutagenesis" by means of the application of mutagens [26, 100, 143, 154] (see [60, 75] for a discussion of the role of recombination on the error catastrophe). Lethal mutagenesis consists in eliminating viral populations with an excessive number of deleterious mutations, and as previously mentioned, has been suggested as a candidate therapeutic strategy against RNA viruses (see [6, 17, 36, 57]), although as previously mentioned, several viruses can become robust to artificial mutagenesis enhancing the replicase copying fidelity.

Phylogenetic analysis of 50 RNA viruses showed a negative correlation between rates of nucleotide substitution (a surrogate of mutation rate) and genome size. In other words, the longer the RNA virus genome, the lower its substitution rate [76]. As previously commented, a fundamental importance related to the error threshold as well as to the dynamics of RNA viruses is that there exists an upper limit on genome size. As recognized by Eigen [40], it is not possible to replicate excessively long sequences of RNA because too many deleterious mutations accumulate (this point is put in the context of the origin of life problem in the next chapter). Generically, the larger genomes of RNA viruses are of about ~ 15 Kb, indicating that this is the genome size normally set by the error threshold (coronaviruses are the exception, with ~ 30 Kb) [75]. Due to the limitation of the genome size, RNA viruses are automatically constrained; that is, all viral functions must be encoded within a confined sequence space [75] (see Fig. 2.2). Paradoxically, this counterbalances the enormous potential that allows them to rapidly generate a huge set of potential adaptive phenotypes. This actually means that, due to the restriction in the length of the genome, specific regions of genome sequence will often have multiple and sometimes very diverse functions, and that mutations that adapt a virus to one environment might have a negative effect on another one. Moreover, the lack of largely enough evolutionary room, makes probable that RNA viruses will experience extensive pleiotropy, epistasis and negative fitness trade-offs, which together prevent them from

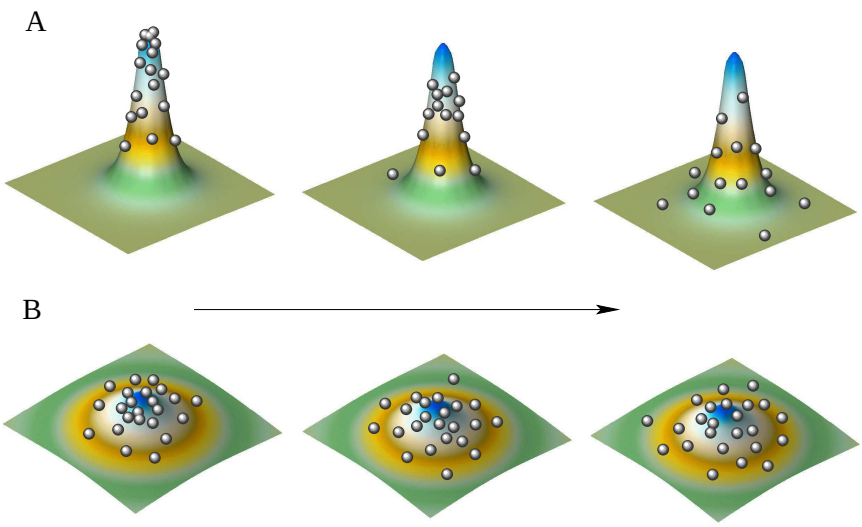

Figure 2.4: Schematic diagram of the effect of increasing the mutation rate (from left to right) in a non-robust (A) and in a robust (B) quasispecies population located in a single-peak fitness landscape. The fitness of the mutants in (A) rapidly decreases as the mutation rate grows. However, the fitness of the mutants in the flat quasispecies (B) slightly decreases at increasing mutation rate.

adapting to all environmental conditions with equal success [75].

The quasispecies models mainly consider deleterious mutations, but we may also consider mutation as an exploratory process for finding new fitness peaks, and, of course, virus dynamics should be understood within the eco-coevolutionary framework of the Red Queen dynamics (see Chapter 4). Logically, the error threshold found in quasispecies systems, as previously mentioned, has been invoked in an important medical application, that is, the extinction of RNA virus populations by lethal mutagenesis, which could be achieved with base analog drugs. The incorporation of base analogs can have two types of effects: (i) chain termination, resulting in immediate death of the progeny strand or (ii) mutation, whereby the base analog is later miscopied when the genome replicates [18]. Case (ii) underlies the antiviral activity of the drug rivabirin for some RNA viruses (see [18]). Several mutagens have been used to artificially increase error rates in RNA viruses such as vesicular stomatitis virus, poliovirus type 1, foot-and-mouth disease virus, lymphocytic choriomeningitis virus, hepatitis C virus, and the human immunodeficiency virus type 1 [6]. One may think that we could force the viral RNA populations to enter error catastrophe by increasing their replication and mutation rate. From an evolutionary point of view, it is not clear, since the generation of a huge spectrum of mutants could provide viral populations with a swarm of potentially useful phenotypes. However, as we show in Paper 1 of this thesis, the possible extinction of viral strands might be achieved by decreasing the replication rate of the fittest genome i.e., master sequence, but also increasing the mutation rate. This would perhaps involve the production of a few mutant

strands which could perhaps easily collapse inside host cells, also having a lower probability to find an adaptive solution to the pressure of the immune systems or to the pharmacs.

2.3 The survival of the flattest effect

In this section we briefly describe the so-called "survival of the flattest" effect, which refers to the ability of inferior phenotypes with large neutral networks to displace superior phenotypes with smaller neutral networks. It is known that many phenotypes have the property to produce, by mutation, multiple related genotypes. The set of genotypes for a particular phenotype is called its neutral network [47]. Mutations within a neutral network preserve the phenotype and thus this genetic redundancy can reduce the phenotypic mutation rate without altering the underlying genetic mutation rate [18]. Hence, slower replicating, robust genomes could become selectively advantaged in comparison with fast replicating, non-robust genomes under high mutation rates. Mutational robustness is defined as the constancy of a phenotype in the face of deleterious mutations [144].

Although whether robustness can be directly favoured by natural selection has remained controversial, several studies have demonstrated this effect on real molecular systems. This phenomenon has been recently demonstrated in digital computer simulations and simulated RNA molecules [180], in viroids [23] and in the rapidly evolving vesicular stomatitis RNA virus [144]. The results of this latter work show that selection can directly favour mutational robustness. As previously mentioned, several theoretical and computational tools have been used to study the dynamical and evolutive consequences of this phenomenon. For instance, computational models of competition between replicating and mutating entities such as computer programs [180] or digital genomes [23] competing under increasing mutation rates. Moreover, some works have investigated the survival of the flattest by means of ordinary differential equations [181]. In this thesis (see paper 2) we have analyzed the effect of space in this system, showing that space broadens the scenario of the survival of the flattest because the critical mutation rate involving the outcompetition of the fit quasispecies by the flat one is lower.

To end this chapter, I would like to stress that the mean field approach is extremely powerful to deep insight the dynamics of quasispecies. However, there are other ways to study the dynamics and evolution of quasispecies in a more realistic way, like the bit string models. By analyzing bit strings as digital genomes one often sees that the predictions of the differential equations are fulfilled, at least while ignoring spatial effects (see Paper 1 and 2 of this thesis). The bit string approach explicitly takes into account the complex population structure of a quasispecies. Although this approach is an oversimplified picture of reality, it retains the key features of the underlying evolutionary dynamics [48, 157]. The idea is that the bits of the sequences simulate purines and pyrimidines, and we can then simplify the four-letter alphabet of RNA macromolecules to an alphabet with two symbols (see [93, 94]). This computational approach is very important for stochastic simulations in which finite population sizes are of importance (as they are in infection processes). We refer the reader to Papers $1-3$ of this thesis as well as to [159, 23].

Chapter 3

Hypercycles

Hypercycles are a principle of natural selforganization

Eigen and Schuster, 1979

3.1 The logics of the origin of life

The origin of life problem is one of the most fascinating fields of research in contemporary science. Beyond the question whether human beings will be able to know what exactly happened more than three thousand million years ago, we might speculate on physically possible or plausible scenarios. Although speculation could be thought as a fantasy, it is possible to make scientific contributions on this subject. The first scientific theory on the origin of life was developed by a russian biochemist and biologist named Aleksandr I. Oparin, who was a member of the Russian Academy of Sciences, and who started the pathway towards the understanding and approach to the origin of life problem with his pamphlet *The Origin of Life* [122, 123]. Actually J. B. S. Haldane proposed, also in the 1920s, a similar theoretical scheme for how life may have originated on Earth [62]. The standard Oparin-Haldane theory claims the formation of organic molecules on the primitive Earth followed by chemical reactions that produced increased organic complexity. This theory is largely precocius, and was developed twenty years before the Watson and Crick discovery of the DNA structure and almost thirty years before the first experiments on prebiotic synthesis.

According to Oparin's theory, the pathway towards life started with a random synthesis of simple organic molecules from atmospheric gases (as later shown by Miller), then from these simple molecules, larger and more complex ones would have been formed. The formation of so-called coacervates-unique droplets would cointain such different organic molecules. These structures would have developed the capacity to take up some types of molecules and discharge other specific molecules, thus maintaining a characteristic chemical pattern or composition. Then so-called "organizers" would have allowed controlled

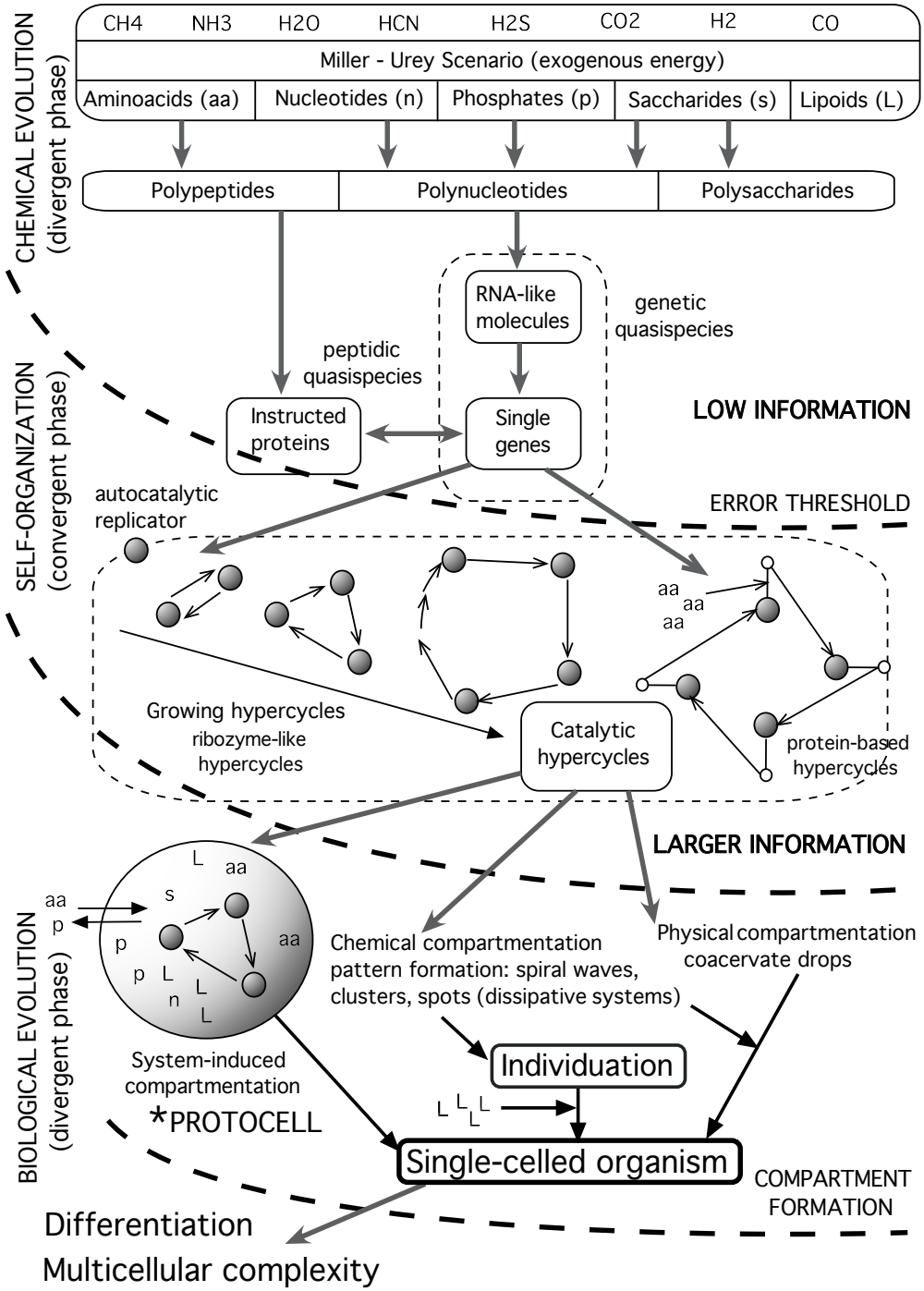

Figure 3.1: The suggested important steps in the transition from the non-living to the living. From Miller's scenario to the necessity of overcoming the information crisis, the protocell has been suggested to arise by the enclosement of catalytic networks. The design and synthesis of the artificial protocell (see the book of the MIT on protocells [135]), which could be a synthetic organism homologous to the hypothetic initial natural protocell (indicated with the asterisk in the diagram), might suppose a giant leap in contemporary science (modified from [87])

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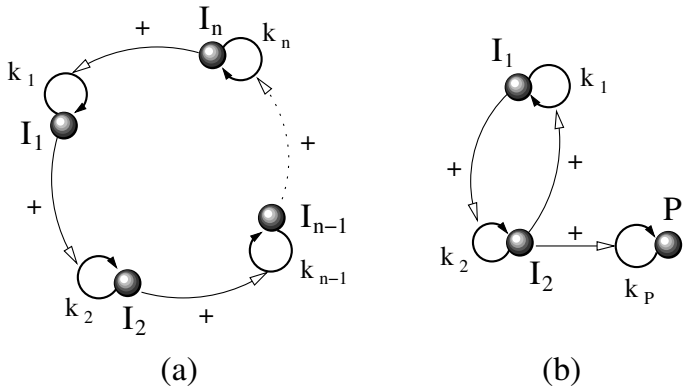

Figure 3.2: Elementary hypercycles: (a) general n member and (b) two-member hypercycle with a parasite, P. Instead of competing, n sequences $I_1, I_2, ..., I_n$, cooperate each other in a closed, cyclic architecture. The catalysis can be directly provided by each of the sequences or each sequence can code for a primitive catalyst, which aids replication of the following sequence.

reproduction ensuring that the produced daughter cells share the same chemical capabilities. This would have given place to evolutionary development so that a group of cells could adapt to changes in the environment over time, being able to undergo so-called open-ended evolution. An extremely important contribution to the understanding of the origins of life was provided three decades after the works of Oparin, and was obtained from the experiments of Miller and Urey [112, 111] as well as Oró [124]. These authors, continuing the works of Oparin, showed that biochemical building blocks such as amino acids or nucleotides can be synthesized under physically and chemically plausible primitive conditions. In the field of the origin of life, theoretical works gain importance since they allow the study of interesting phenomena, under some basic, simplifying assumptions.

In a more general sense, and assuming the origin of life to be a continuous process, three different phases towards life have been suggested: (a) *Chemical evolution*, (b) *Molecular Self-organization* and (c) *Biological evolution* [87] (see Fig. 3.1). The initial phase, (a), would have been characterized by the formation of the chemicals needed for the nucleation of life, among them the two most important types of biological macromolecules, nucleic acids and proteins. During this phase of evolution, the synthesis of biological molecules was non-instructed. The second phase, (b), would have involved the development of a large number of feedback loops between the existing molecules, whose interactions might have driven to the instructed synthesis of biological macromolecules. The products of this second phase must at some point have begun to resemble the complex, organized units we see today in the optimized, self-reproducing cycle of a living cell [135, 162]. Finally, in the third phase, (c), primitive single-celled organisms might have undergone further development driving to their differentiation in highly-developed multicellular beings. At this point of evolution, the great diversity of micro and macroscopic life appeared.

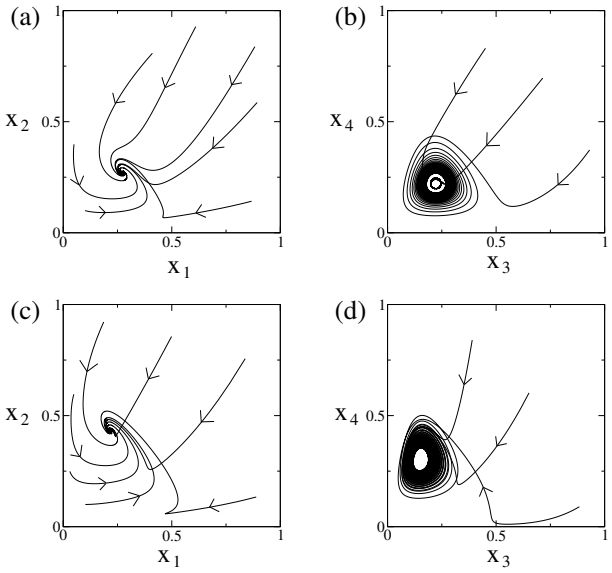

Figure 3.3: Coexistence dynamics of elementary hypercycles. In (a) and (b) we show the attractors for symmetric hypercycles with $n = 3$ and $n = 4$ replicators, respectively. Here we use $k_i = 1$, $\forall i$. In (c) we show the dynamics for asymmetric hypercycles with $n = 3$ and $k_1 = 1.85$, $k_2 = 2$ and $k_3 = 1$. In (d) we use $n = 4$, and $k_1 = k_2 = 1$, $k_3 = 1.85$ and $k_4 = 2$. The arrows indicate the directions of the flows.

The transition from non-living to living matter is clearly attributed to phase (b), when existing biomolecules established several types of interactions, being able to instruct their own synthesis of molecules. Of course, to face the origin of life problem, we need to formulate a meaningful definition of a living being. It is of importance to think whether we are looking for a sharp or a gradual transition from the non-living to the living [87]. In the case of a sharp boundary, we can provide a list of necessary and sufficient conditions, being able to define a living being unambiguously. However, in a gradual transition we can only state necessary conditions for a system to be alive, then there is no general criterion, apart from subjectiveness. Roughly, living organisms follow three properties: a living system has (i) a metabolism, (ii) self-reproduction and (iii) mutability. These criteria were first set up by Aleksander Oparin in order to demarcate living from non-living systems.

A fundamental subject in the origin of life problem is the origin and early evolution of genetic replication. The origin of life can be thought in several ways, being one of them the envisioning of life emerging from nude replicating RNA-like molecules, then considering that template-replicating molecules were the preminent precursors of life (see [79, 80] for a discussion on this subject). One of the best known efforts to understand a possible scenario for the begginings of nude replicating RNA-like sequences relies on the modern theoretical framework on prebiotic evolution, based on the work of Eigen and coworkers [40, 42]. In this section we must provide a deeper attention to the conclusions of these works. Although briefly explained in the previous chapter, we must emphasize the fact that the length of a replicator polymer is limited by the accuracy of replication,

and that earlier replicators would have to replicate with high accuracy to code for large information contents. As mentioned, there exists an error threshold for the accuracy of replication in non-coupled replicators with a quasispecies distribution: for a given total quantity of genetic information there is an upper bound on the error rate of reproduction (see Chapter 3). Roughly, it is predicted that in order to maintain the information, the mutation rate, μ, per nucleotide and replication cycle should be $\mu < \mu_c \approx 1/\nu$, where ν is the length of the sequence. The theory predicts that beyond μ_c genomic information is lost and the population enters into a drift phase. This is known as the information crisis in prebiotic scenario or error catastrophe. The error catastrophe implies that, with a given accuracy of replication per nucleotide and a given fitness superiority of the currently fittest "master sequence" relative to the mutant spectrum around it, there is a maximum sequence length which selection can maintain. This length (in terms of possible prebiotic accuracy) would limit sequences to 50 to 100 nucleotides, far from coding for much of a concerted metabolism [80]. From the previous results arises so-called Eigen's paradox: *how can a replicator code for complex enzymatic machineries to correct the mistakes and increase in length if such a replicator needs such enzymes to increase in length ?* In other words: it is not possible to have either complex genomes without complex enzymatic machineries or complex enzymatic machineries without complex genomes. Then a natural question arises: how could earlier replicators increase the information content under these restrictions ? A possible solution is given by the hypercycle, which is described in the following section.

3.2 The Eigen and Schuster hypothesis: the hypercycle

As briefly mentioned in the previous section, the hypercycle has been suggested as a way to overcome the error threshold. A hypercycle consists of self-replicative units, I_i, with two-fold catalytic functions. The intermediaries I_i are able to instruct their own reproduction and are also able to provide catalytic support for the production of the subsequent intermediate (using some energy-rich building material) [42] (see Fig. 3.2). Their cyclic architecture allows the stable coexistence of several distinct, short templates. The fundamental idea is that the information content can increase beyond the error threshold because, asymptotically, a set of replicating polymers (each of them below the critical length) can coexist. In other words, each of the templates forming the hypercycle is limited by the error threshold, but the hypercycle as a whole is not.

One possible theoretical approach to study elementary hypercycles without considering the mutant spectrum, is by using a mass action kinetics model [1], which can be developed with a mean field model. Mean field models assume perfectly mixed systems, providing a statistical description of an average magnitude (in our case the concentration of each of the replicators), also assuming equiprobability of interactions between the

[1] The *law of mass action* of chemical kinetics states that the rate of an elementary reaction is proportional to the product of the concentrations of the reactants

hypercycle elements. Such a model can be described by

$$\frac{dx_i}{dt} = x_i(A_i + k_i x_{i-1} - \phi),$$

where x_i denotes the relative concentration of the hypercycle template, I_i. Here ϕ is a dilution flow that keeps the total concentration constant (this theoretical approach is known as the constant population approach). The templates are capable of self-replication with productivity values $A_i (i = 1, ..., n)$. The parameters k_i are kinetic constants measuring the strength of the influence that template I_{i-1} has on the reproduction promotion of following template, I_i. This approach considers that $\sum_i x_i = 1$, and thus the dynamics occurs on the so-called simplex

$$\varphi_n = \Big\{(x_1, ..., x_n) \in \mathbb{R}^n : x_i \geq 0; \sum_{i=1}^{n} x_i = 1; \frac{d}{dt}\sum_{i=1}^{n} x_i = 0\Big\}.$$

In general, mathematical models for elementary hypercycles describe the following set of reactions

$$I_i + I_j + s \xrightarrow{k_i} 2I_i + I_j, \tag{3.1}$$

$$I_i \xrightarrow{\varepsilon_i} s, \tag{3.2}$$

where $j = i - 1 + n(\delta_{i1}); i = 1, ..., n$, and s represents some necessary building blocks or resources (which are often ignored as explicit terms). The previous two reactions correspond to the nonlinear reproduction of the templates due to catalysis and the linear degradation of replicator polymers, proportional to ε.

The hypercycle has some interesting properties due to their nonlinear nature (see [42] for further details). Hypercycles allow for coherent growth of all its members, also providing stable and controlled coexistence. The hypercycle competes with any single replicative unit not belonging to the cycle, irrespective of whether that entity is independent, or part of a different hypercycle, or even linked to the particular cycle by parasitic coupling. A hypercycle may reduce or enlarge its size, if this modification offers any selective advantage. Hypercycles do not easily link up in networks of higher order. Two hypercycles of degree p need coupling terms of degree $2p$ in order to stabilize each other. The (deterministic) population dynamics of elementary hypercycles (i.e., hypercycles where species only receive catalysis from the previous one) have been widely investigated with ordinary differential equations.

From these analyses we know that there exists a fixed point inside the state space of the hypercycle involving the coexistence of all the hypercycle species. For instance, for elementary hypercycles with $n = 2$ species, a stable node ensures the asymptotic coexistence of the species. With $n = 3$ and $n = 4$ species, the coexistence equilibrium is a focus, which is achieved with fast- and hardly-damped oscillations, respectively. For hypercycles with $n \geq 5$ coexistence is governed by an attracting periodic orbit [42, 46]. The study of hypercycles with mean field models developed in some of the works of this thesis have elucidated other interesting phenomena. For instance, we have shown that

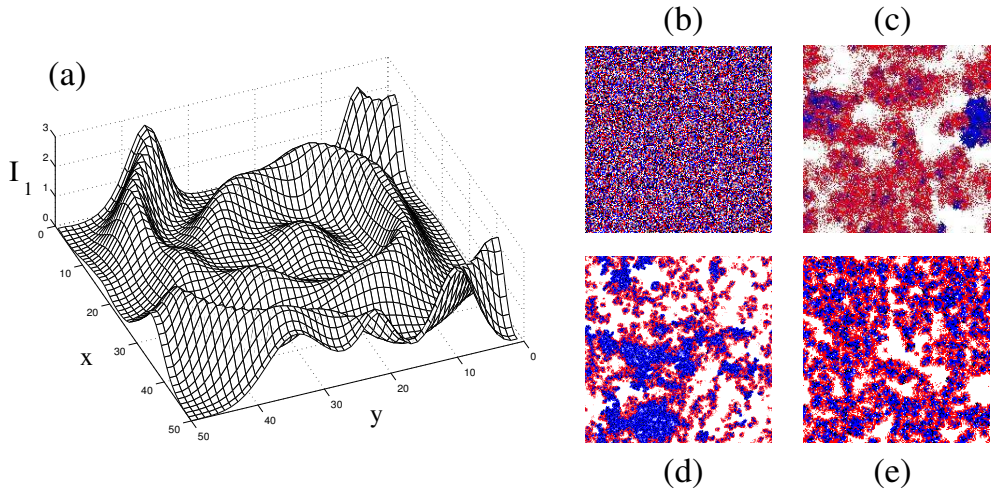

Figure 3.4: Self-structuring and pattern formation for hypercycles extended on surfaces. (a) Spiral waves obtained from a reaction-diffusion model for hypercycles with 5 members (see [24]). In (b) we show the initial conditions given by random distribution of replicators, with two different hypercycle templates (blue and black) and a parasite (red), which are modeled with a stochastic cellular automaton. In (c), (d) and (e) we display the results of some simulations showing spatial pattern formation (see Paper 5 of this thesis).

the extinction scenario for hypercycles reproducing in finite systems (also considering degradation of the species) is governed by a saddle-node bifurcation. From the information we obtain from the differential equations we can increase the previous list of hypercycle properties. For instance, we have conjectured that the delay to extinction found just after the saddle-node collison could have been an important selective property.

The majority of studies on hypercycles have considered symmetric networks, in which all replicators are kinetically indistinguishable. However, a more realistic situation might be given by different replicators encoding different genetic information and thus probably having differential kinetic properties (as commented on and studied in Papers 4 and 5 of this thesis). The asymmetric hypercycles typically share the same type of equilibrium points as the symmetric ones. The difference is the placement of these equilibria in phase space. For example, in figure 3.3 we show the coexistence attractors for hypercycles with $n = 3$ and $n = 4$ members. Here we use the mathematical model which only considers nonlinear reproduction, a logistic restriction in reproduction and density-independent degradation of templates, which is given gy:

$$\dot{x}_i = x_i\Big[k_i x_{i-1}\big(1 - \sum_{j=1}^{n} x_j/c_0\big) - \varepsilon\Big]. \tag{3.3}$$

Here, instead to the constant population constraint, we assume that reproduction is bounded by a logistic-like function, where c_0 is the carrying capacity and ε is the degradation rate of the template polymers. The role of the constant population constraint or

the logistic-like restriction is to provide for boundedness of the solutions, which may be constrained due to ecological factors as resource limitations. By using numerical integrations we show the attractors for symmetric (Fig. 3.3a,b) and asymmetric replicators (Fig. 3.3c,d). This figure shows that the equilibrium points for the asymmetric networks typically move to higher equilibrium concentrations in some of the subspaces of phase space. This phenomenon is discussed in Paper 4.

To finish this part of the chapter I would like to emphasize that the kinetics of quasispecies-like replicators as well as from hypercycles have been deeply investigated independently. However, it might be extremely relevant to investigate the dynamics of competition associated to the appearance of catalytic dynamics (e.g, autocatalysis) in simple populations of replicator polymers with quasispecies-like kinetics (see Fig. 3.1). For instance, the study of the dynamics of a population of replicators growing with Malthusian kinetics competing with another population in which the replicators can grow with distinct kinetics i.e., Malthusian and autocatalytic dynamics (see the approach analysed in [50]). By Malthusian replication we mean a simple replication reaction, where a replicator makes a copy of itsef at a given rate. In the autocatalytic kinetics a given replicator enhances its own replication. The approach in [50] could be thought as equivalent to consider (implicitly) that the second population of replicators has undergone a phenotypic divergence driving to the emergence of the autocatalytic mechanism of replication. A very important and first attempt to the analysis of competition between different types of replicators was developed by Michod [104]. Among other systems, Michod analyzed the competition between a Malthusian replicator and a one-membered (i.e., autocatalytic) hypercycle, as well as the competition between two-membered hypercycles and Malthusian replicators. In this context, the analysis of replicator systems considering, explicitly or implicitly, the transition from quasispecies-like kinetics to catalytic replicator systems has received fewer attention (see for example [104]).

The hypothetical appearance of autocatalytic processes in prebiotic replicators could have been a previous step before the emergence of replicators undergoing more complex biochemical interactions as heterocatalysis, in which a given replicator provides catalytic support to another type of replicator. Such replicators could have been synthesized from simpler, autocatalytic molecules by means of gene duplication and mutation processes. Actually, the autocatalytic replicators could have also been synthesized from simpler self-replicating macromolecules reproducing with Malthusian kinetics. Then, those replicators growing with catalytic feedbacks could have given place to hypercycle networks. As stated by Lee and co-workers [91]: "[...] *Understanding how such self-organized systems may have established themselves in the "beggining", how they might have evolved and grown in complexity, and how they result in the emergent properties that distinguish living systems from inanimate matter, remains a major experimental and theoretical challenge.*"

3.3 Some considerations about hypercycles

The hypercycle theory, despite being more than 30 years old, is a lively field of research within prebiotic evolution and origins of life. The hypercycle opened a new and promising framework for the study of the transition from the non-living to the living. Due to the importance of the architecture and the catalytic interactions among the hypercycle species it is of extreme importance to analyze under which conditions such hypercycles can remain stable and accumulate information as well as study how such stability depends on the details of the couplings between the hypercycle units [80]. We must mention that some weak points have been attributed to this type of organization. For example, the ideal hypercycle implies that all the members of the autocatalytic network have exactly the same connectivity so that they proliferate at the same rate. This does not seem to be close to a possible real scenario.

The hypercycle theory mainly suffers from three concrete problems. Firstly, if a single hypercycle sequence, by mutation, replicates itself well but fails to catalyze the replication of the next hypercycle member, the replicating sequence can outgrow the system capturing all nucleotide resources. These types of replicators are called parasites [42, 110] (see Fig. 3.2), and have been deeply investigated (see for example [24, 25, 14]). The problem of parasites for hypercycles seems to be solved, since spatially-extended hypercycles can become resistant to the action of the parasites (see Fig. 3.4). This was firstly shown by Boerlijst and Hogeweg [14]. These authors showed that a spatially-extended hypercycle can reject the parasites by means of spatial self-organization (see also Paper 5 in this thesis and references therein). Secondly, a catalytic short-circuit can occur between the hypercycle replicators. For this case one sequence catalyzes a more distant sequence around the loop, then the shortened loop grows faster than the overall hypercycle, and as a result the hypercycle will contract to a less complex form. This effect could be more probable in large hypercycles, in which the increase in the information content could be decreased by the appearance of short-circuits. The short-circuit problem has received fewer attention by the scientific community. Thirdly, as the survival of the hypercycle depends on the existence of all the coupled replicators, if the concentration of any of them dropped to zero due to fluctuations, the whole hypercycle would collapse. In spite of these last two latter problems, the original model of Eigen and Schuster only considers positive catalytic couplings. It is possible that there exists an optimal combination of positive and inhibitory couplings driving more homeostatically stable hypercycles less sensitive to short-circuits being also able to offer redundancy with stability so that the concentration of any one sequence could drop to zero and the system would still survive long enough to find another sequence to substitue the extincted one [80].

We may note that a recent paper by Silvestre and Fontanari questions the capacity of storing information in hypercycles [46]. These authors analyzed a n member hypercycle competing with its mutant error tail. The model they use, inspired in the work of Campos et al [20], is given by the following set of nonlinear differential equations:

$$\dot{x}_i = x_i(A_i Q + k_i x_{i-1} Q - \phi), \quad \mathrm{i} = 1, ..., \mathrm{n} \tag{3.4}$$

and

$$\dot{x}_e = x_e(A_e - \phi) + (1 - Q)\sum_{i=1}^{n} x_i(A_i + k_i x_{i-1}), \tag{3.5}$$

where $x_0 \equiv x_n$ are the relative concentrations of each of the functional members of the hypercycle, and x_e is the concentration of the mutant replicators. The dilution flow term which keeps a constant population constraint (i.e., $\sum_{i=1}^{n} x_i + x_e = 1$ and $\sum_{i=1}^{n} \dot{x}_i + \dot{x}_e = 0$) is given by

$$\phi = \sum_{i=1}^{n} x_i(A_i + k_i x_{i-1}) + A_e x_e. \tag{3.6}$$

These authors assumed that functional templates and parasites are selectively neutral and set $A_i = A_e = a$, and $k_i = k = 1$ for $i = 1, ..., n$, then studying so-called symmetric hypercycles, where the functional templates have the same kinetic properties. In their work the authors made several conjectures and comments about their model from their analytical and numerical results. As the authors analyzed the symmetric hypercycle they could automatically obtain the non-trivial fixed point, involving coexistence of functional templates. The condition $\dot{x}_2 = 0$ yields $\phi = Q(a + x_1)$ which, inserted in the equations $\dot{x}_3 = ... = \dot{x}_n = \dot{x}_1 = 0$, yields $x_1 = x_2 = ... = x_n$. Using these results in Eq. (3.6) we find the equilibrium value of x_1 (and extensively of $x_2, ..., x_n$), which can be obtained from the roots of the following quadratic equation [46],

$$n x_1^2 - Q x_1 + a(1 - Q) = 0, \tag{3.7}$$

and are given (now expressed as $x_{\pm}^{*} \equiv x_1$) by:

$$x_{\pm}^{*} = \frac{Q \pm \sqrt{Q^2 - 4na(1 - Q)}}{2n}, \tag{3.8}$$

Note that these equilibrium points have real positive roots provided the condition

$$Q^2 - 4na(1 - Q) \geq 0. \tag{3.9}$$

The authors found that the region of viability in the space (Q, a) (see Fig. 2 in [46]), where the hypercycle has nonzero concentration, either in the static regime or in the periodic orbit condition, is determined by the condition of existence of real fixed points. They actually stated (see Fig. 3.5): "*The periodic solution disappears at* $Q \approx 0.19639$*, the value at which the condition* (3.9) *for the existence of a nontrivial equilibrium is violated. We have no proof for this remarkable coincidence*". As I will show in the following lines, this is not a "remarkable coincidence", since the disappearance of the periodic solutions is associated to the disappearance of the nontrivial equilibrium points from the positive, real number phase space to the complex phase space through the collision of two nontrivial equilibrium points (e.g., via a saddle-node bifurcation) (see chapter 5). This bifurcation

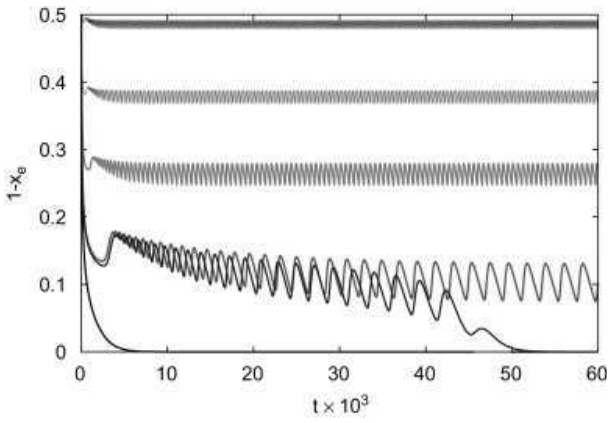

Figure 3.5: (a) Time evolution of the total concentration of functional templates, $1 - x_e$, for hypercycles with $n = 12$ members with $a = 0.001$ and (top to bottom): $Q = 0.5, 0.4, 0.3, 0.2, 0.19639, 0.1$. The periodic solution disappears at $Q \approx 0.19639$, the value at which the condition (3.9) for the existence of a nontrivial equilibrium is violated. Silvestre and Fontanari stated: "*We have no proof for this remarkable coincidence*" (figure obtained from *J. Theor. Biol.* database [46]).

is typical of hypercycles and separates the survival from the extinction phases (see Papers 4, 6 and 7 of this thesis and [145, 147, 149]). Hence, the mathematical explanation of the disappearance of the equilibrium implying coexistence between functional templates can be developed in the context of bifurcation theory. The solutions of the state variables of the dynamical system Eqs. (3.4)-(3.5) are defined in the $(n+1)$-dimensional open space

$$\mathbb{R}^{n+1} := \{x_1, ..., x_n, x_e; -\infty < x_{1...n}, x_e < \infty\},$$

only part of which is physically meaningful i.e.,

$$\mathbb{X}^{n+1} \subset \mathbb{R}^{n+1}; \mathbb{X}^{n+1} := \{x_1, ..., x_n, x_e; x_{i,e} \geqq 0, i = 1, 2, ..., n\},$$

and hence solutions, being chemical concentrations, only exist in the positive real number state space. The expression of the fixed points, $x^*_{\pm}$, involve two different equilibria in $\mathbb{X}^{n+1}$, which must be added to so-called disordered equilibrium, given by $(\mathbf{0}, 1)$, and which involves the extinction of the functional templates and the whole population invaded by the parasites. As analyzed by Silvestre and Fontanari by means of numerical evaluation of the Jacobian eigenvalues, the value of the smaller root i.e., x^*_-, is always unstable, whereas the larger root i.e., x^*_+, is (locally) stable for $n \leq 4$ [46]. In addition, the disordered fixed point $x_i = 0$ and $x_e = 1$ is always stable [20]. This actually means that in the coexistence scenario between functional templates we have: an unstable fixed point (e.g., saddle) given by x^*_-; another fixed point which cam be stable (e.g., a stable node for $n \leq 4$) given by x^*_+; and the origin in the subspaces of the functional templates x_i (note that the topology of

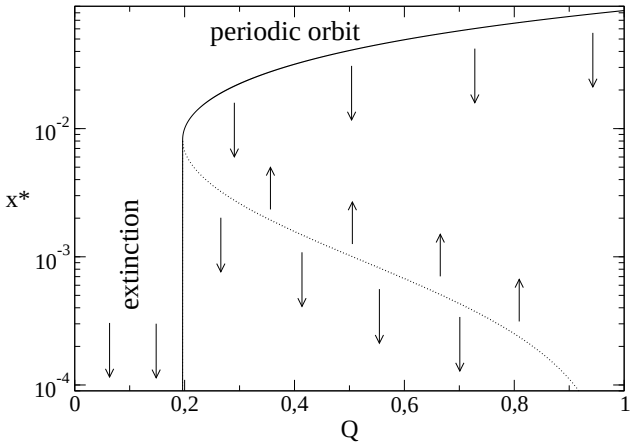

Figure 3.6: Collapse of the functional templates via nontrivial equilibria collision in the model studied by Silvestre and Fontanari [46] (see the previous figure). At decreasing (from right to left) the copying fidelity, Q, both equilibria approach and collide at $Q = Q_c = 0.196399637...$ (see (3.11)), as found numerically in [46]. The solid and dotted branches show the equilibrium points x^*_+ and x^*_-, respectively (in linear-log scale). Here we also use $n = 12$ and $a = 0.001$. The arrows indicate the stability character of each branch. The solid branch, which is also unstable, is surrounded by a periodic orbit.

phase space for this system is equivalent to the one obtained with the works on hypercycles developed in this thesis). From the previous expression (3.9) we can obtain the critical copy fidelity, Q_c, which acts as bifurcation parameter. To obtain the critical value we must solve the quadratic expression (3.9) in terms of Q, which is given by

$$Q_c^{\pm} = 2\big(-na \pm \sqrt{na(1+na)}\big). \tag{3.10}$$

However we must choose as critical value the positive conjugate of Q_c since this parameter is a probability and then $Q \in [0,1]$ (note that $Q_c^- < 0$). This critical value is thus given by,

$$Q_c = 2\big(\sqrt{na(1+na)} - na\big). \tag{3.11}$$

It is not difficult to show that with $Q = Q_c$

$$x^*_- = x^*_+ = \frac{Q}{2n},$$

indicating that both equilibrium points have collided in state space, and that with $Q < Q_c$, such equilibria are complex (i.e., $x^*_\pm \in \mathbb{C} \setminus \mathbb{R}$), and they do not live in $\mathbb{X}^{n+1}$. Actually, the decrease of the copying fidelity in the coexistence scenario between the functional templates involves the approach of x^*_- and x^*_+ in state space and their collision just at Q_c (see Fig. 3.6), independently of the stability of x^*_+, which is determined by the

eigenvalues associated to this fixed point and which can be all negative (when $n \leq 4$). Moreover, as shown numerically, this equilibrium can become unstable (through a Hopf bifurcation) involving the appearance of a periodic orbit (typically with $n \geq 5$). According to the parameter values used in Fig. 3.5 ($n = 12$ and $a = 10^{-3}$) such a critical values is $Q_c = 0.196399637...$, which fits with the numerical results found by Fontanari and Silvestre [46]. After the collision of the two nontrivial equilibria the only equilibrium point in $\mathbb{X}^{n+1}$ is the disordered fixed point $(\mathbf{0}, 1)$, which, being always stable, is now asymptotically globally stable. We note that here we have considered as bifurcation parameter the average copying fidelity, Q, but from expression (3.9) one can see that the number of functional templates, as well as the replication constants of the hypercycle can also be the responsible for the collision of fixed points (e.g., via saddle-node bifurcation). Silvestre and Fontanari [46] identified the viability of the hypercycle depending on the number of functional templates, n_m, with

$$n_m = \frac{Q^2}{4a(1-Q)}. \tag{3.12}$$

We can also calculate the critical replication probability which may also cause the bifurcation, which is given by

$$a_c = \frac{Q^2}{4n(1-Q)}. \tag{3.13}$$

For this case if $a \geq a_c$ the hypercycle will be viable.

I should mention an interesting phenomenon arising in the model analyzed by Silvestre and Fontanari deeply studied during this thesis. The collision of the nontrivial equilibria (e.g., via saddle-node bifurcation) can leave a remnant saddle which is able to continue attracting the flows before allowing them to pass through another fixed point [165]. For the hypercycle system, such an effect involves a delay in the extinction of the hypercycle, which is extremely long just after the bifurcation and follows an inverse square-root power law (see [145, 147, 49, 149, 165] and chapter 5). The ghost can be "seen" in Fig. 3.5 for the trajectory obtained with $Q = 0.19639$. For this value of copying fidelity, which is very near from below to the bifurcation value, the hypercycle asymptotically becomes extinct because the bifurcation due to the collision of both nontrivial equilibria has taken place. Note that before collapsing, this trajectory undergoes the typical plateau due to the action of the ghost, which arises as a result of the collision of the fixed points x^*_- and x^*_+, and delays the extinction (see papers 6 and 7 of this tesis and [145, 147] on the conjecture of the positive selective role of the ghost in the context of prebiotic evolution). Actually, the ghost and its associated inverse square-root scaling law was numerically shown for the same model analyzed by Silvestre and Fontanari for hypercycles with $n = 2$ members (see paper 7 of this thesis and [121]).

To finish, I would like to connect the final part of this chapter with section 1.3., just mentioning that many of the selective advantages of hypercycles have been found and investigated with theoretical and computational analysis. Moreover, some of the conclusions on the positive effects of hypercycles have been conjectured or deduced in a

rationalist way, among them, the solution to the accumulation of information and to the error threshold. Taking advantage of engineered and synthetic biology, many of these conjectures and properties that have been attributed to hypercycles could be investigated in experimental works, which might allow to analyze the dynamical behavior of hypercycles in real systems. For instance, the effect of the parasites and the role of space in spatially extended systems coevolving with parasites could be studied from both molecular or populational level points of view, respectively. The effects of short-circuits and the sensitivity of the catalytically-coupled populations to large fluctuations in concentrations could also be tested in the lab. As mentioned in Chapter 1, some molecular and engineered population systems with hypercycle kinetics can be found in the literature. Finally, just mention that the kinetics associated to hypercycles has been mainly investigated in the framework of prebiotic dynamics. However, we may note that the hypercycle models could also be used to analyze the dynamics of cooperation in ecological systems. For instance, the models only considering nonlinear reproduction might describe species in ecosystems undergoing obligate symbiosis, while models considering both Malthusian and catalytic replication might describe species with facultative symbiosis (see [110, 148].)

Chapter 4

Antagonistic replicator dynamics

Here, you see, it takes all the running you can do, to keep in the same place

Lewis Carroll, 1876

4.1 Antagonistic interactions among replicators

The interactions between species affect the population dynamics of each species. Roughly, there are three main types of interactions [117]: (i) if as a result of the interaction between two species, the growth rate of one population decreases and the other increases the populations are undergoing so-called antagonistic interactions (e.g., predator-prey or host-parasite dynamics); (ii) if the growth rate of each population decreases then it is competition; and (iii) if each population's growth rate is enhanced then it is called mutualism, symbiosis or, in a more general sense, cooperative dynamics (e.g., hypercycles). In this chapter I will focus on (i), although in many of the models we also include competition terms. Of course a model can include some of these interactions or all of them, which might give a more detailed description, for instance, of a network description of an ecosystem [116]. A classical view in theoretical ecology is that species' densities fluctuate in time due to the effect of external perturbations. That is, changes in environmental factors such as in the temperature, seasonality, availability of resources, etc. However, deterministic theory has shown that only the consideration of biotic interactions can involve the appearance of fluctuations in the number of species. The most paradigmatic example of this result is provided by the well-known Lotka-Volterra equations. This model, despite being unrealistic, shows that simple predator-prey interactions can result in oscillatory behavior of the populations governed by a center, in which a continuous family of closed trajectories are found in the phase space of the following two-dimensional model

$$\frac{dN}{dt} = N(a - bP), \tag{4.1}$$

$$\frac{dP}{dt} = P(cN - d), \tag{4.2}$$

where $N(t)$ and $P(t)$ are the population numbers of the preys and predators at time t. Here the assumptions of the model consider that the prey grows, in the absence of any predator, unboundedly in a Malthusian way according to the term aN. The predators reduce the prey's per capita growth rate by a term proportional to the populations of prey and predators, represented with the term $-bNP$. Moreover, the absence of any prey involves an exponential predator's decay, according to the linear term $-dP$. And finally, the contribution of the preys to the predator's growth rate is cNP, which is proportional to the available prey as well as to the size of the population of predators. The analysis of more realistic predator-prey models shows that, depending on the detailed system, such oscillations can grow or decay or can asymptotically reach a stable periodic orbit thus undergoing self-maintained scillations (e.g., a limit cycle for two-dimensional dynamical systems). A limit cycle solution is a closed trajectory in the predator-prey phase space which is not a member of a continuous family of closed trajectories (i.e., it is not a center) (see [117]). The analysis of several models also suggests that ecological systems can be governed by chaotic attractors [150, 109, 65, 5, 66, 105, 44, 51, 131, 29, 30, 31, 32]. However, in this latter case and for time-continuous systems, at least three interacting species are required. It is worth mentioning that some studies on real ecosystems give support to the theoretical finding of chaos in mathematical models [168, 171, 51].

There is a huge literature on predator-prey, host-parasite or host-parasitoid dynamics. Of course, the models developed to analyze this type of interactions can include other relevant features, like some minimal genetic characteristics, and the effect of mutations. This is a key component for the study of coevolution between antagonistic species, which is an extremely important subject related to ecological and molecular dynamics. In the following sections we extend these ideas in the concept of the Red Queen theory, and we comment on a type of antagonistic interaction that has been explored in this thesis, the so-called matching allele dynamics.

4.2 Coevolution: the Red Queen hypothesis

The Red Queen theory of evolution is perhaps one of the most important evolutionary theories postulated after Darwin's theory of natural selection. In 1973, Leigh Van Valen suggested a theoretical explanation for multispecies evolution known as the Red Queen hypothesis [173]. From studies of the fossil record on approximately 50 organic groups (protists, plants and animals), this author found a constant probability of extinction of the constituent taxa, independently of their previous duration, that is, that the probability of extinction of a species is approximately independent of its length of existence. This phenomenon, termed the "Law of Constant Extinction", seems to be in contradiction with the expected long-term effects of natural selection. The idea is that if natural selection involves improvement along evolution through adaptation, shouldn't the older species have a lower probability of extinction in comparison with the newer ones ? In other words,

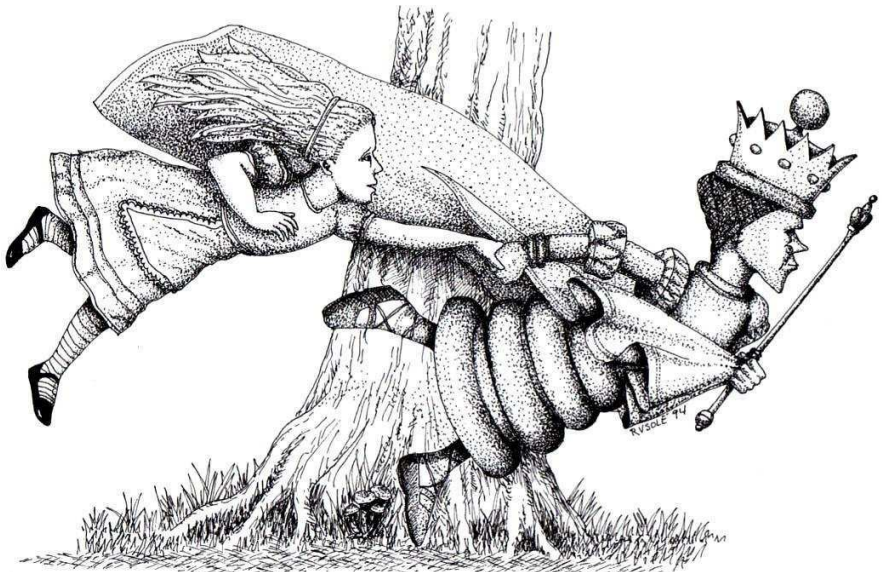

Figure 4.1: The underlying idea of the Red Queen theory is illustrated in the book of Lewis Carroll *Alice in Wonderland* [21], where the Red Queen and Alice must continuously run in order to keep in the same place. Following this idea, species may need to continuously change and adapt to other species changes to maintain themselves in the ecological game (drawing by Ricard Solé).

if adaptation improves species progressively through time, as previously mentioned, we should expect a decreased probability of extinction: old species would last longer. The interpretation of Van Valen's is that species do not evolve to become any better at avoiding extinction. According to this author the constant extinction probability would result from a constantly changing biotic community, in which species continually adapt to each other's changes. The name for this conjecture refers to the Red Queen's remark in Lewis Carroll's *Alice Through the Looking Glass* [21], where the Red Queen says to Alice: "Here, you see, it takes all the running you can do, to keep in the same place" (see Fig. 4.1).

Van Valen's view of evolution is that species change and remain in the evolutionary game, and extinction occurs when no further changes are possible (i.e., if genetic variability is not sufficient). In other words, no previous adaptations assure the safety of a species with respect to future environmental changes and species are forced to evolve (to run) to keep in the same place (survival). The Red Queen hypothesis is indeed profoundly Darwinian, in the sense that it puts emphasis moslty on the biotic interactions between organisms rather than on abiotic factors [70]. In the Red Queen theory: "... the effective environment of any homogeneous group of organisms deteriorates at a stochastically constant rate", where the effective environment here comprises primarily the biota; and consequently, "The Red Queen does not need changes in the physical environment, although she can accomodate them. Biotic interactions provide the basis for a self-driving (at this level) perpetual motion of the effective environment and so of the evolution of species affected

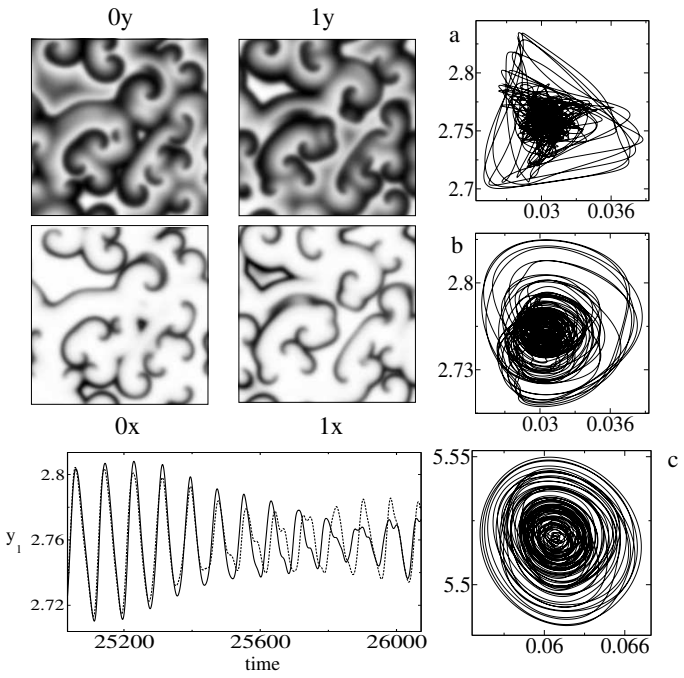

Figure 4.2: Spatiotemporal chaos in the neutral landscape obtained from Eqs. (4.3)-(4.4). The time series display sensitivity to initial conditions, with two trajectories for the genotype $1y$ with slightly different initial conditions. We also show the chaotic spiral self-structuring for all the genotypes and the coevolutionary attractors directly built from the time series, which are projected in (a) $(1x, 0y$, (b) $(0x, 0y)$ phase planes. In (c) we show the global preadator-prey dynamics (x-axis: prey; y-axis: predators) obtained by averaging the densities of both populations over the whole lattice).

by it" [70]. From the perspective of the Red Queen hypothesis, life gains much autonomy from the physical environment since the latter is no longer needed to put evolution into motion [70]. Not surprisingly, the Red Queen hypothesis has attracted the attention of evolutionary biologists. It has been repeatedly dethroned and restored to power [70]. The large biases inherent in the empirical data set on the fossil record used by Van Valen made some biologists doubt whether the survivorship curves were correct. And if the data were suitable, would the Red Queen be the only answer to explain this phenomenon?

4.3 Spatial chaos in matching allele dynamics

Matching-allele models underlie most of the theory constructed to understand the effect of host-parasite coevolution on sex and recombination. In these models, which were inspired by the notion of self-nonself recognition systems that underlie animal immune systems [59], each parasite genotype is better than other parasite genotypes at infecting some subset of host genotypes, but worse at infecting other host genotypes [3]. No single parasite

genotye is better at infecting all host genotypes; no single host genotype is better at resisting all parasite genotypes. Hence, rare genotype advantage and frequency-dependent selection maintains diversity at both hosts and parasite loci. In the following lines I briefly comment on the result of coupling, by means of diffusion, the system analyzed in paper 8 of chapter 7. This model describes the dynamics of a Lotka-Volterra type model coupled with a minimal matching allele model of coevolution. The new model incorporates space and local diffusion of predator-prey genotypes in which the strength of the interaction among both populations is influenced by a pair of haploid diallelic loci in the two species also considering a nonlinear functional response of the predator. I will focus on the neutral fitness landscape for predators, thus considering equal predation rates associated to predators' genotypes. This system cannot exhibit chaos in the absence of spatial diffusion (see paper 8 of this thesis). Thus any chaotic behavior must result from the interaction among non-chaotic local dynamics by means of diffusive spatial coupling. A two dimensional reaction-diffusion model based on partial differential equations is used to simulate the continuous, space-time dynamics of this system, which incorporates a type II functional response and a logistic growth of the prey population:

$$\frac{\partial x_i}{\partial t} = k_i^h x_i \left(1 - \frac{\sum_{j\in\mathcal{H}^\nu} x_j}{\mathcal{K}}\right) - \frac{\mathcal{A}_i k_i^p y_i x_i}{1+x_i} + \frac{\mu_i^h}{\nu}\Big(\sum_{<j>_i} x_j - x_i\Big) - \epsilon_i^h x_i + D_i\nabla^2 x_i, \tag{4.3}$$

$$\frac{\partial y_i}{\partial t} = \frac{k_i^p y_i x_i}{1+x_i} + \frac{\mu_i^p}{\nu}\Big(\sum_{<j>_i} y_j - y_i\Big) - \epsilon_i^p y_i + D_i\nabla^2 y_i, \tag{4.4}$$

with $i = 0, 1$ (i indicating the type of allele). Here the concentration for prey genotypes, x_i, and for predator sequences, y_i, live in the vertexes of two ecologically coupled ν-dimensional boolean sequence space, $\mathcal{H}^\nu$ (with $\nu = 1$, see Fig. 1 of paper 8 of this thesis), and are function of three variables (t, r, s), t being time, r and s being space coordinates. The dynamics is here defined on a two-dimensional $L \times L$ lattice,

$$\Gamma(L) = \{(r, s) \in \mathbb{Z}^{2+} | 1 \leq r, s \leq L\},$$

with periodic boundary conditions. The parameters k_i^h and k_i^p denote self-replication (or intrinsic growth) rates for prey and predator genotypes. Note that k^p parametrizes the Holling "type II" functional response associated to the predator-prey ecology [65, 126]. Here $1/A_i$, is the yield coefficient of prey genotype i to predator genotype i. We consider k^p as self-replication or intrinsic growth rate for predator genotypes because we assume that a higher k^p involves a higher predation rate and thus a prone scenario for predators' reproduction (i.e. predators are well fed and thus can invest in reproduction). Prey genotypes have a logistic-like growth constraint, being

$$\sum_{j\in\mathcal{H}^\nu} x_j,$$

the total prey populations and $\mathcal{K}$ the carrying capacity. The term

$$\sum_{<j>_i} \gamma_j - \gamma_i,$$

with $\gamma = x, y$, denotes mutation among neighboring genotypes, with μ_i^h and μ_i^p as mutation rates for both prey and predator genotypes. The model also includes decay processes (i.e. spontaneous hydrolysis or density-independent death rates), proportional to ϵ_i^h and ϵ_i^p for both prey and predator genotypes. Diffusion is defined to happen among the four nearest neighbours (i.e. von Neumann neighborhood) on the lattice, and is simulated by using the discrete Laplacian operator, according to:

$$d_i \nabla^2 \gamma_i(r,s) \approx \frac{d_i}{(\triangle x)^2}\Big(\sum_{<r,s>} \gamma_k(r',s',t) - q\gamma_k(r,s,t)\Big),$$

with $\gamma = x, y$, and q being the number of nearest neighbours (here $q = 4$), and where $d_i/(\triangle x)^2$ is treated as a constant called $D_i \equiv D$, considering that the four genotypes have the same diffusion rates. In the absence of diffusion, $D = 0$, system (4.3)- (4.4) is an extension of the Rosenzweig-MacArthur model incorporating coevolutionary terms according to a minimal allele-depending interaction. We can analyze the spatio-temporal dynamics of this system solving reaction terms of Eqs. (4.3)- (4.4) numerically by using the standard fourth-order Runge-Kutta method [165] with a constant time stepsize $\delta t = 0.1$. As initial conditions we inoculate the whole lattice with random concentration for all genotypes with values going from 0 to 1. The dynamics of Eqs. (4.3)-(4.4) without diffusion is governed by static, stable equilibria or by an attracting periodic orbit (see paper 8 in chapter 7). However, as we show in Fig. 4.2, the explicit consideration of space and diffusion implies the emergence of spatio-temporal chaos [1]. Under this combination of parameters, the genotypes self-organize into spiral waves, and the resulting time dynamics undergoes sensitivity to slightly initial conditions, a fingerprint of chaotic dynamics. Previous works have shown that diffusion can involve instabilities and the emergence of strange attractors due to the coupling of periodic oscillators [126]. The emergence of chaos in this type of system confirms the suggested results found in paper 9 of this thesis, in which a similar system was analyzed by means of cellular automata models.

Spatiotemporal chaos in species coevolution has been described in some systems [64, 156, 126], and a large amount of discrete and continuous time models indicate that chaotic dynamics might be a likely outcome in biological processes, even without considering space explicitly [150, 109, 82, 65, 72, 158, 131]. In the next section I briefly discuss some issues about the existence of chaos in ecological systems. This subject has become a classical subject of debate among ecologists. Although far away from the scope of this chapter, I would like to mention, for those interested, some nonlinear systems which display deterministic chaos, especially in the context of physical systems. For instance, the forced pendulum [77], fluids near the onset of turbulence [97], lasers [61], nonlinear optical devices [71], Josephson junctions [22], chemical reactions [155], classical many-body problem (e.g., three-body problem) [68], particle accelerators [68], plasmas with interacting nonlinear waves [179] or simulated heart cells [56, 182]. I would also like to mention the finding of deterministic chaos in real systems like the nonlinear electronic oscillator or in disturbed

[1] we use $L = 200$, $\mathcal{K} = 1$, $A_i = 1$, $k_i^h = 1$, $k^p = 0.35$ and $\epsilon_i^h = \epsilon_i^p = 10^{-2}$, $\forall i$, also with the same mutation rates for all predator and prey genotypes i.e. $\mu_i^h \equiv \mu^h$ and $\mu_i^p \equiv \mu^p$. We specifically use $\mu^h = 10^{-5} < \mu^p = 10^{-3}$ and $D = 0.01$

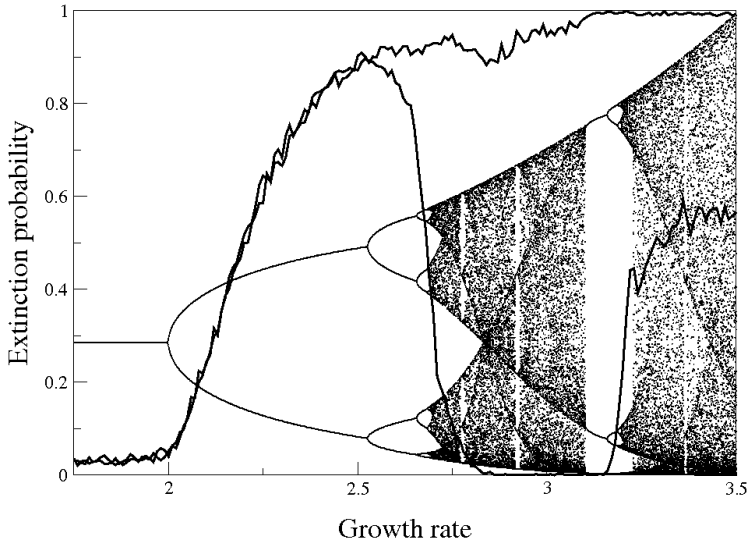

Figure 4.3: Relation between deterministic chaos and the risk of local and global extinction using the Ricker map. The lines represent the probabilities of extinction for the local map with noise (upper line), and for a metapopulation of ten globally coupled Ricker maps with local and global noise (lower line). Note that the risk of global extinction decreases in the chaotic regime. Based on Allen et al., [5] (see also [160]).

heartbeats (see [152] for details). These findings open the possibility of considering the same behavior in several other natural or artificial biological systems.

4.4 Chaos, homeochaos and stability

In this section I will briefly discuss some interesting results on chaos in biology, more specifically in the framework of complex ecosystems. It has been suggested that complex ecosystems might be prone to behave chaotically. In this sense, the presence of multiple state variables inherent to ecological systems, and both nonlinearities in population growth as well as in interspecific interactions might involve the appearance of chaotic dynamics [109, 150, 65, 66, 126, 131]. Although some authors have pointed out the negative effect of chaos in population dynamics [12], some empirical evidences indicate that chaos might arise in ecological systems [168, 171, 51, 10, 11]. Furthermore, some theoretical studies show that chaos in population dynamics might not involve a higher probability of extinction [72, 82, 5]. I want to emphasize this latter point because the initial debate in ecology about chaotic dynamics was related to species survival. If the reader is interestd in this topic, he/she should read carefully the excellent work of Allen and co-workers [5]. These authors showed, by using discrete-time metapopulation (i.e., fragmented populations linked by migration) models, that the survival of the species under external and intrinsic perturbations was increased in the chaotic regime, as opposed to the periodic regime, in which the global

populations were more prone to become extinct (see Fig. 4.3). This is a really important work which shows that chaos does not have a negative role in species survival. Moreover, Ikegami and Kaneko [72, 82], described the so-called homeochaos in multispecies models with antagonistic interactions and evolution. These authors suggested that an evolutionary system with many species can maintain its stability through a weak, high-dimensional chaotic state, rather than in a fixed point or in strong chaos [82]. This dynamic state is labeled *homeochaos*. Homeochaos is characterized by its dynamic stability, which is provided in a complex network whose elements are temporarily updated through their interaction. Homeochaos suppresses strong chaos i.e., the maximal Liapunov exponent is positive, but close to zero. The oscillation amplitude is not so large. And finally, homeochaos is high-dimensional, with many positive Liapunov exponents, although their magnitude is small.

To finish this chapter, and in order to provide the reader with some other interesting general subjects related to chaotic dynamics, we must mention that three main different routes to chaos have been described. These routes account for how the dynamics of a given dynamical system changes as we change some parameter/s until its entrance into the chaotic regime. These routes are: the (i) period-doubling (Feigenbaum scenario); (ii) intermittency (Manneville-Pomeau scenario); and the (iii) quasiperiodic (Ruelle-Takens-Newhouse scenario) routes. The route to chaos (i) is generated via multiple Pitchfork bifurcations; the second one, (ii), is generated via tangent bifurcation; while route (iii) is achieved via multiple Hopf bifurcations. Each of these routes has several associated properties (see [152] for more details). All of these routes have been described experimentally.

Chapter 5

Appendix

5.1 Numerical methods

Nonlinear differential equations can be solved numerically with the aid of a computer. The computer allows us to approximate the solutions of differential equations being of especial interest for the analysis of high dimensional dynamical systems, which are very difficult or almost impossible to solve analytically. There is huge literature and scientific works about numerical integration (see for example [129, 27]). The simplest numerical methods are given by the first- (e.g., *forward Euler* method) or the second- (e.g., *improved Euler* method) order *Runge-Kutta* methods [165]. These methods are very useful to understand the methodology of numerical integration, although they are not very accurate. For instance, the Euler method only estimates the derivative at the left end of the time interval between t_n and t_{n+1}. However, a biologist interested in numerical integrations should start using this method as a way of training. Methods of higher order (suitable for scientific work), which have a lower *truncated error*, require a large number of calculations and the evaluation of functions, and thus they imply a larger computational cost. The fourth-order *Runge-Kutta* method, which I have used in this thesis, provides a good balance [165]. This method involves finding x_{n+1} in terms of x_n, by computing the following numbers

$$k_1 = f(x_n)\Delta t$$

$$k_2 = f\Big(x_n + \frac{1}{2}\ k_1\Big)\Delta t$$

$$k_3 = f\Big(x_n + \frac{1}{2}\ k_2\Big)\Delta t$$

$$k_4 = f(x_n + k_3)\Delta t.$$

Then x_{n+1} is given by

$$x_{n+1} = x_n + \frac{1}{6}\Big(k_1 + 2(k_2 + k_3) + k_4\Big).$$

This method provides quite accurate results without the necessity of using a small stepsize Δt. One may think that the use of a very small stepsize would provide very accurate results. If one uses an extremely small Δt the computer will need to make excessively many computations, and each one carries a penalty in the form of *rounf-off error*. This effect is due to the finite precision of computers. Computers are not infinitely accurate and they do not distinguish between numbers that differ by some amount δ ($\delta \approx 10^{-7}$ and $\delta \approx 10^{-16}$ for single and double precision, respectively). If the Δt is too small, round-off errors ocurring during every calculation will accumulate and the approach to the solutions of the differential equations will not be accurate [165].

5.2 Bifurcations at nonhyperbolic fixed points

Let us consider the following nth-order continuous-time system

$$\dot{x} = f(x, \mu), \tag{5.1}$$

with a parameter $\mu \in \mathbb{R}$. As μ changes, the limit sets (e.g., fixed points) of the system also change. Typically, a small change in μ produces small quantitative changes in a limit set. For instance, perturbing μ could change the position of a limit set slightly, and if the limit set is not an equilibrium point, its shape or size could also change, but the qualititive behavior would be the same. However, there is the possibility that a small change in μ causes a limit set to undergo a qualitative change. This is what is called a bifurcation, and the value of μ at which the bifurcation occurs is called a bifurcation value or a critical bifurcation value, μ_c, for which the $\mathbb{C}^1$-vector field $\mathbf{f}(\mathbf{x}, \mu_c)$ is not structurally stable. We shall assume throughout this section that $\mathbf{f} \in \mathbb{C}^1(E \times J)$, where E is an open set in $\mathbb{R}^n$ and $J \in \mathbb{R}$ is an interval. Bifurcations can involve the disappearance or creation of a limit set and a change in the stability type of a limit set (e.g., stable to non-stable). The definition of bifurcation also includes the case of a non-stable limit set that remains non-stable but undergoes a change in the number of positive Liapunov exponents. In the following subsections we explain the bifurcations identified in the models analyzed in this thesis in a more formal way. Such bifurcations tipically arise in nonlinear models of differential equations for biological systems. These are the transcritical, the saddle-node, the pitchfork and the Hopf bifurcations. These bifurcations can be simultaneously found in some systems. For instance, a transcritical bifurcation can involve the entrance of a fixed point in the positive quadrant, giving place to a non-trivial equilibrium, which can lose its stability if the control parameter continues varying, giving place to a periodic orbit through a supercritical Hopf bifurcation.

5.2.1 Transcritical bifurcation

In some nonlinear systems a given set of fixed points can exist for all possible parameter values and these are never destroyed, as it happens in the transcritical bifurcation. The

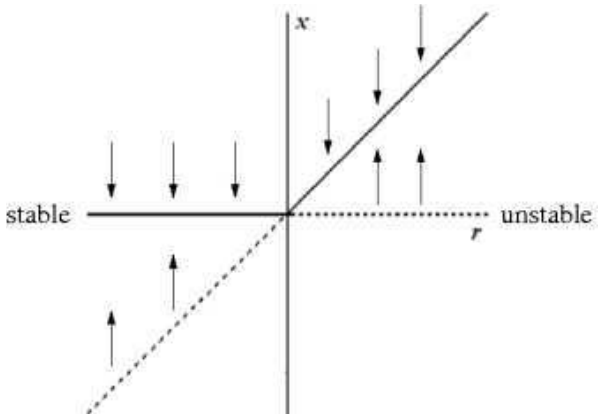

Figure 5.1: Bifurcation diagram for the normal form (5.2). At $r_c = 0$ both equilibria collide and interchange stability. Here the parameter r is regarded as the independent variable, and the fixed points $x^* = 0$ and $x^* = r$ are shown as dependent variables. Stable and unstable equilibria are represented with solid and dashed lines, respectively.

normal form for this type of bifurcation is

$$\dot{x} = f(x, r) = rx - x^2, \tag{5.2}$$

where r is our parameter of control. Figure 5.1 shows the bifurcation diagram associated to the transcritical bifurcation obtained from the normal form at changing r (considering that x and r can be either positive or negative). From the previous equation it is easy to see that there is a fixed point at $x^* = 0$ for *all* values of r. Moreover, there is another fixed point at $x^* = r$. With $r < 0$, the origin is stable and the non-trivial equilibrium unstable. In this scenario, the eigenvalue $\lambda = df/dx$ (obtained from the first-order Taylor expansion term), is $\lambda(0) = r < 0$ and $\lambda(r) = -r > 0$. When increasing r, the unstable fixed point approaches to the origin, and coalesces with it when $r = 0$, that is, when the transcritical bifurcation occurs (in the marginal scenario we have $\lambda(0) = \lambda(r) = 0$). Finally, when $r > 0$ the origin becomes unstable, being $x^* = r$ stable, here with $\lambda(0) > 0$ and $\lambda(r) < 0$.

Let us now show the transcritical bifurcation occurring in the one-dimensional, time continuous logistic model (see also Eq. (2.3)) given by

$$\dot{x} = kx\left(1 - \frac{x}{c_0}\right) - \varepsilon x. \tag{5.3}$$

This equation models the growth of a single species where $x \in \mathbb{R}^+ \cup \{0\}$ denotes the population numbers of an exponentially growing species, whose growth is limited according to the logistic function, $(1 - x/c_0)$, under the assumption of finite resources, where c_0 is the carrying capacity or the maximum population size that the system is able to maintain. The parameters k and ε denote the intrinsic growth and density-independent decay rates,

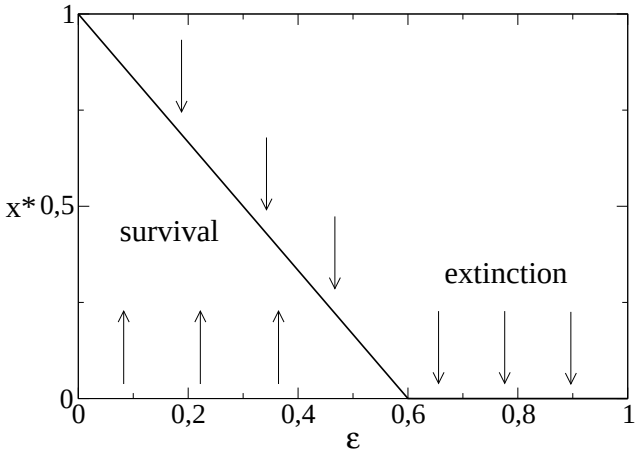

Figure 5.2: The same as in the previous figure for the logistic model Eq. (5.3) with $k = 0.6$ and $c_0 = 1$, using the decay rate, ε, as control parameter. Note that at $k = \varepsilon = 0.6$ the nontrivial equilibrium crosses the origin. In this collision with the fixed point $x_1^* = 0$, both nontrivial and extinction equilibria interchange their stability. The arrows indicate the motion of an arbitrary initial condition starting in the one-dimensional phase space (i.e., vertical axis) for each value of ε.

respectively. This equation has a fixed point at zero population (i.e., extinction) independently of the value of the growth or decay rate. Nevertheless, such a fixed point may change its stability as a parameter is varied. The transcritical bifurcation is the standard mechanism for such changes in stability. In order to analogously investigate this system according to the normal form (5.2), let us rewrite Eq. (5.3) as

$$\dot{x} = (k - \varepsilon)x - \frac{k}{c_0}x^2. \tag{5.4}$$

It is easy to show that this equation has two fixed points given by $x_1^* = 0$ and $x_2^* = c_0(1-\varepsilon/k)$. From linear stability analysis we obtain the following eigenvalues, $\lambda(x_1^*) = k-\varepsilon$ and $\lambda(x_2^*) = \varepsilon - k$. Note that stability does not depend on the carrying capacity, c_0, but the non-trivial equilibrium does. If the reproduction rate, k, is larger than the decay rate, ε, $\lambda(x_1^*) > 0$ and $\lambda(x_2^*) < 0$, and the extinction equilibrium is unstable and then the flows will move towards the survival equilibrium, x_2^*, which is an attractor. Note that at $k = \varepsilon$, $x_1^* = x_2^* = 0$, which means that both fixed points collide, then, with $\varepsilon > k$, the stability is interchanged, and the extinction equilibrium becomes an attractor and the non-trivial fixed point a repellor, respectively. The bifurcation diagram using ε as control parameter with $k = 0.6$ and $c_0 = 1$ is shown in Fig. 5.2.

The transcritical bifurcation is also found in other biological nonlinear systems (see for example [183, 63, 170, 67]). The well-known Levins metapopulation model, which shares the same mathematical core than the logistic equation, also presents a transcritical bifurcation.

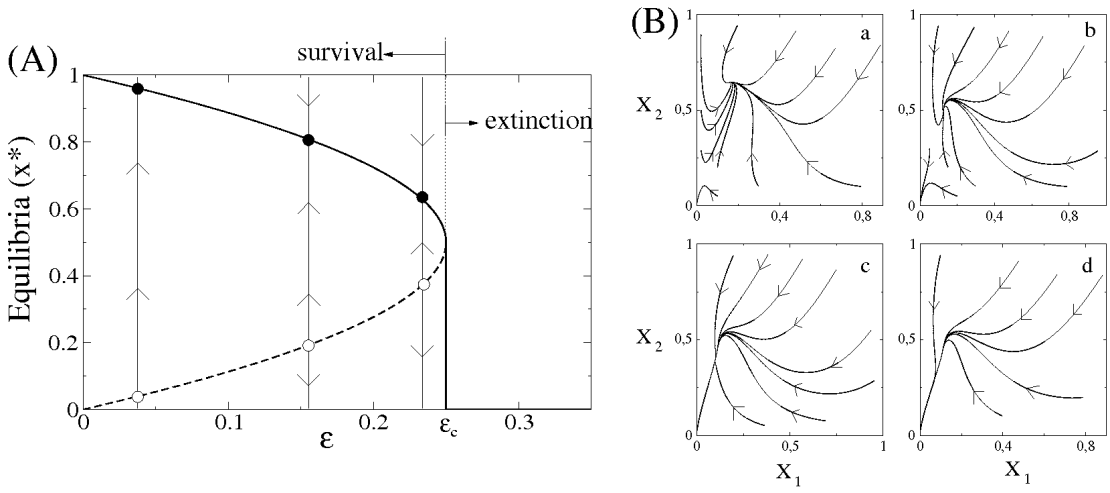

Figure 5.3: (A) Bifurcation diagram for the saddle-node bifurcation of the autocatalytic replicator model (Eq. (5.6)), using ε as control parameter with $k = c_0 = 1$. Solid vertical lines are one-dimensional phase space for different values of ε (See [49]). (B) Two-dimensional saddle-node bifurcation for the asymmetric two-member hypercycle. From (a) to (d) we increase decay rate, and the stable node and the saddle approach. In (c) these fixed points have collided in a saddle-node bifurcation (see Paper 4 of this thesis).

5.2.2 Saddle-node bifurcation

Consider the first-order system

$$\dot{x} = f(x, \mu) = \mu - x^2. \tag{5.5}$$

For $\mu < 0$ Eq. (5.5) has no equilibrium points. At $\mu = 0$, there is a single equilibrium point at the origin and it is a nonhyperbolic fixed point since $Df(0,0) = 0$; the vector field $f(x,0) = -x^2$ is structurally unstable. For $\mu > 0$, there is a stable equilibrium at $\sqrt{\mu}$ with eigenvalue $\lambda_+ = -2\sqrt{\mu}$, and an unstable equilibrium point at $-\sqrt{\mu}$ with eigenvalue $\lambda = 2\sqrt{\mu}$. Since two equilibrium points are created as μ passes through 0, $\mu_c = 0$ is a bifurcation value for this system. For $\mu > 0$ the one-dimensional stable and unstable manifolds of Eq. (5.5) are given by $W^s(\sqrt{\mu}) = (-\sqrt{\mu}, \infty)$ and $W^u(-\sqrt{\mu}) = (-\infty, \sqrt{\mu})$. And for $\mu = 0$ the one-dimensional center manifold is given by $W^c(0) = (-\infty, \infty)$. Note that the difference between the saddle-node and the transcritical bifurcation is that in the saddle-node bifurcation two fixed points are created or destroyed while for the transcritical bifurcation two fixed points do not disappear after the bifurcation, they only switch their stability.

The bifurcation diagram using as example the autocatalytic replicator equation

$$\frac{dx}{dt} = kx^2(1 - x/c_0) - \varepsilon x, \tag{5.6}$$

is shown in Fig. 5.3. Equation (5.6) describes the dynamics of a species, $x \in \mathbb{R}^+ \cup \{0\}$, able to catalyze itself. As for the logistic model, the parameters k and ε denote the intrinsic growth and the density-independent decay rates, respectively. And the term inside the parenthesis corresponds to the logistic restriction in reproduction due to finite resources (c_0 being the carrying capacity). It is easy to show that Eq. (5.6) has three (complex) fixed points: $x^* = 0$ and

$$x^*_{\pm} = \frac{1}{2c_0}\left(1 \pm \sqrt{1 - \frac{4\varepsilon}{k}}\right). \tag{5.7}$$

Here $Df(x, \{k, \varepsilon, c_0\}) = 2kx - (3k/c_0)x^2 - \varepsilon$. For the fixed points (5.7) we can define the bifurcation parameter, $\varepsilon_c = k/4$. If $\varepsilon > \varepsilon_c$ there are no fixed points in the real phase space, since $x^*_{\pm} \in \mathbb{C} \setminus \mathbb{R}$, and the only fixed point in the replicator state space is $x^* = 0$, which corresponds to the extinction point, which is stable since $Df(0, \{k, \varepsilon > \varepsilon_c, c_0\} < 0$. For the survival scenario, $\varepsilon < \varepsilon_c$, $Df(x^*_-, \{k, \varepsilon < \varepsilon_c, c_0\}) > 0$ (i.e., x^*_- is a repellor) and $Df(x^*_+, \{k, \varepsilon < \varepsilon_c, c_0\}) < 0$ (i.e., x^*_+ is an attractor). A detailed analysis on the autocatalytic replicator model can be found in [147, 49]. The saddle-node bifurcation can give place to an interesting phenomenon named "ghost". When a saddle and a node collide in a saddle-node bifurcation, these points are destroyed but a saddle remnant can continue influencing the flow [165]. Such collision leaves a bottleneck region in phase space that sucks trajectories delaying them before the trajectories flow towards another equilibrium point. The time, τ, spent in the bottleneck generically increases as

$$\tau \sim \frac{1}{\sqrt{\varepsilon - \varepsilon_c}}, \tag{5.8}$$

being ε the control parameter and ε_c the bifurcation value. Some applications of this inverse square-root scaling law have been described and discussed in the field of condensed matter physics [166], as well as in some of the works on hypercycles developed during this thesis (see for example Papers 4 and 6 of this thesis). The same phenomenon has been characterized, and even empirically found, in a real electronic circuit modeling Duffing's equation [169]. In Fontich and Sardanyés ([49]) we analyzed the general saddle-node bifurcation which corresponds to the normal form

$$x' = a\varepsilon + bx^{2n}. \tag{5.9}$$

By using complex variable theory, we analytically derived the scaling law for this general one dimensional, analytical, autonomous dynamical system undergoing a not necessarily non-degenerate saddle-node bifurcation. The analytical expression for the time delay derived from (5.9) was shown to be given by

$$\tau_\varepsilon = \int_{x_c+\delta}^{x_c-\delta} \frac{dx}{f(x,\varepsilon)} = \frac{A}{(\varepsilon - \varepsilon_c)^p} + O\left(\frac{1}{(\varepsilon - \varepsilon_c)^{p-1/(2n)}}\right), \tag{5.10}$$

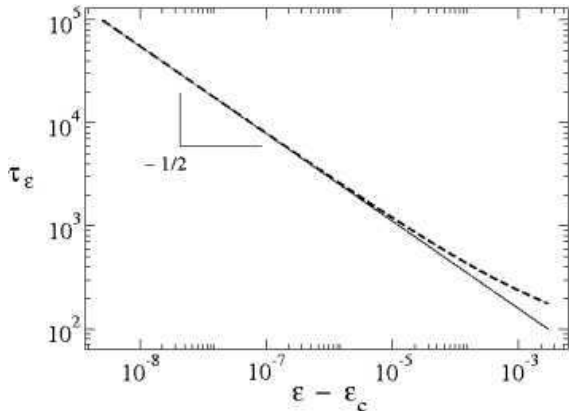

Figure 5.4: Time delay, τ_ε, near (from above i.e., at increasing $\varepsilon \gtrsim \varepsilon_c$) the saddle-node bifurcation (shown in log-log scale). The dashed line corresponds to the delay predicted by Eq. (5.12), and the solid line shows the delay now computed numerically (with the fourth-order *Runge-Kutta* method ($\Delta t = 0.1$)) from Eq. (5.6) using $k = c_0 = 1$ and $x(0) = 0.5$ as initial condition.

for $\varepsilon > \varepsilon_c$. For the particular non-degenerate case, $n = 1$, we have

$$\tau_\varepsilon = \frac{\pi}{\sqrt{ab(\varepsilon - \varepsilon_c)}} + C + O(\sqrt{\varepsilon - \varepsilon_c}), \qquad \varepsilon > \varepsilon_c, \tag{5.11}$$

being C a constant dependent on δ but independent of ε. Expression (5.10), now applied to the non-degenerate case given by the autocatalytic replicator equation (5.6) is given by

$$\tau_\varepsilon = \frac{\pi}{\sqrt{c_0 k(\varepsilon - \varepsilon_c)}} + C + O(\sqrt{\varepsilon - \varepsilon_c}), \qquad \varepsilon > \varepsilon_c, \tag{5.12}$$

where C now depends on δ, k and c_0, but is independent of ε. If we compare the time delay obtained from Eq. (5.12) with the delay numerically computed from Eq. (5.6) we see that our analytical calculation provides a good estimate near bifurcation threshold of such an extinction time, as shown in Fig. 5.4 (see [49] for details).

The saddle-node bifurcation has also been described in other biological systems (see for example [163, 16, 115, 114]).

5.2.3 Pitchfork bifurcations

The pitchfork bifurcation is common in physical systems that have a symmetry. For instance, many problems have a spatial symmetry between left and right, where fixed points tend to appear and disappear in symmetrical pairs [165]. Let us now consider the

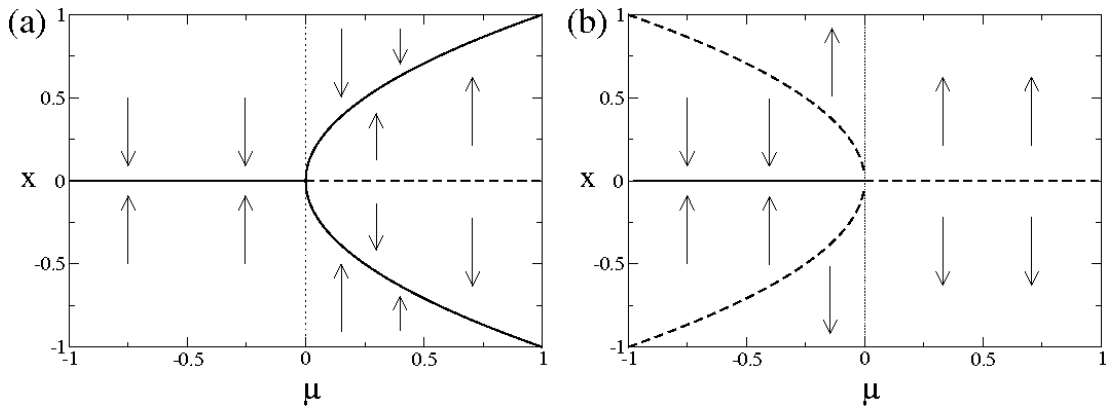

Figure 5.5: *Supercritical* (a) and *subcritical* (b) one-dimensional pitchfork bifurcations undergone for the normal forms (5.13) and (5.14), respectively. Solid and dashed lines indicate, respectively, stable and unstable equilibria. The vertical dotted line indicates the bifurcation value.

one-dimensional system

$$\dot{x} = f(x, \mu) = \mu x - x^3. \tag{5.13}$$

For $\mu > 0$ this normal form has three fixed points, given by: $x^* = 0$ (which exists for any value of μ), and $x^*_\pm = \pm\sqrt{\mu}$. For $\mu > 0$ both these equilibrium points, $x^*_\pm$, are stable because they share the same eigenvalue $\lambda(x^*_\pm) = -2\mu$. For $\mu \leq 0$, $x^* = 0$ is the only fixed point. For $\mu = 0$, $x^* = 0$, is nonhyperbolic since $Df(0,0) = 0$; the vector field $f(x) = -x^3$ is structurally unstable, being $\mu_c = 0$ a bifurcation value. Finally, for $\mu < 0$, we only have the fixed point $x^* = 0$, which is stable since $Df(0, \mu < 0) = \mu$. This type of bifurcation is the simplest and is called *supercritical pitchfork* bifurcation, and is shown in Fig. 5.5a. Note that while $\mu < 0$ only the (real) fixed point $x^* = 0$ exists (and is stable), and when $\mu \gtrsim \mu_c = 0$ two more (real) fixed points appear, $x^*_\pm$ (which are stable), becoming $x^* = 0$ unstable. The so-called *subcritical pitchfork* bifurcation occurs in the one-dimensional normal form

$$\dot{x} = \mu x + x^3. \tag{5.14}$$

Compared to the previous expression (5.13), the pitchfork is inverted (see Fig. 5.5b). The nontrivial equilibrium points, $x^* = \pm\sqrt{-\mu}$, are now unstable, existing only below the bifurcation (with $\mu < 0$), which motivates the name subcritical. Under this scenario (i.e, $\mu < 0$), the origin is stable, while with $\mu > 0$ is unstable, as happened for the supercritical case. The instability for $\mu > 0$ is not opposed by the cubic term. Actually, the cubic term involves the escape of trajectories out to infinity, since as the origin is unstable and there are no more attracting points the trajectories are not confined to some bounded domain.

Finally, just mention that the supercritical pitchfork bifurcation is often called a forward bifurcation, which is closely related to a continuous or second-order phase transition

in statistical mechanics. On the other hand, the subcritical pitchfork bifurcation is often called an inverted or backward bifurcation, and is related to discontinuous or first-order phase transitions [165]. The pitchfork bifurcation has been described in some nonlinear models of biological systems [83, 113, 1].

5.2.4 Hopf bifurcations

The previous bifurcations have been described mainly for one-dimensional systems. If we analyze higher dimensional systems, new bifurcations can occur which can not happen in one-dimensional differential equations. For example, the so-called Hopf bifurcation, which in two-dimensional systems gives place to limit cycles, but can also occur in any dimension $n \geq 2$ (mathematicians often use the term periodic orbits instead of limit cycles for $n > 2$). Imagine a two-dimensional system, given by

$$\Phi_{\mu}^{(1)}(\vec{x}) = \frac{dx_1}{dt} = f_1(x_1, x_2), \tag{5.15}$$

$$\Phi_{\mu}^{(2)}(\vec{x}) = \frac{dx_2}{dt} = f_2(x_1, x_2), \tag{5.16}$$

that has a stable fixed point, x^*. What are all the possible stability characteristics of such a fixed point ? The answer is found in the eigenvalues, named λ_1 and λ_2, obtained from the diagonalization of the the Jacobian matrix, J, given by

$$J = \begin{pmatrix} \frac{\partial \Phi_{\mu}^{(1)}(\vec{x})}{\partial x_1} & \frac{\partial \Phi_{\mu}^{(1)}(\vec{x})}{\partial x_2} \\ \\ \frac{\partial \Phi_{\mu}^{(2)}(\vec{x})}{\partial x_1} & \frac{\partial \Phi_{\mu}^{(2)}(\vec{x})}{\partial x_2} \end{pmatrix}. \tag{5.17}$$

Hence, the eigenvalues are obtained from $\det |J(x^*) - \lambda I| = 0$ (where I is the identity matrix). If $\mathrm{Re}\ \lambda_{1,2} < 0$ the fixed point is stable. Since the eigenvalues satisfy a quadratic equation with real coefficients, we have two possibilities: both eigenvalues are real and negative or they are complex conjugate. To destabilize the fixed point, the real part of one or both eigenvalues must become positive. Like in the pitchfork bifurcation, Hopf bifurcations can be supercritical or subcritical. Here I will only comment on the supercritical one (see [165] for further information). Imagine a two-dimensional system that achieves its equilibrium via exponentially damped oscillations, and that small disturbances decay after oscillating for a while. Moreover, suppose that the decay rate of such oscillations depends on a control parameter, named μ. If, when changing the parameter μ, the decay becomes slower and slower and finally changes to growth at μ_c (i.e., the bifurcation value), the equilibrium state loses its stability. In many cases, the result is the appearance of small-amplitude, limit cycle oscillation about the former steady state [165]. To illustrate the Hopf bifurcation, let us consider the second-order system

$$\dot{x} = y - x(x^2 + y^2 - \mu), \tag{5.18}$$

$$\dot{y} = -x - y(x^2 + y^2 - \mu). \tag{5.19}$$

This system only has a single fixed point, placed in the coordinate $x^* = (0, 0)$. The Jacobi matrix for Eqs. (5.18)-(5.19) is

$$J = \begin{pmatrix} -3x^2 - y^2 + \mu & 1 - 2xy \\ -1 - 2xy & -x^2 - 3y^2 + \mu \end{pmatrix}. \tag{5.20}$$

From $\det|J(0,0) - \lambda I| = 0$, we obtain the characterstic polynomial $\lambda^2 - 2\mu\lambda + \mu^2 + 1 = 0$, which gives us the eigenvalues of x^*, $\lambda = \mu \pm i$ where $i = \sqrt{-1}$. Then, for $\mu < 0$ the equilibrium is stable. When μ reaches $\mu_c = 0$, the equilibrium point becomes nonhyperbolic (it has pure imaginary eigenvalues), and for $\mu > 0$, the equilibrium point becomes unstable since the real part of the eigenvalues is positive. Furthermore, a stable limit cycle, given by the solution set $x^2 + y^2 = \mu$, exists for $\mu > 0$. Hence, a pair of complex conjugate eigenvalues passes through the imaginary axis as $\mu > \mu_c$, and gives place to the Hopf bifurcation.

In this thesis we have characterized (analytically or numerically) several Hopf bifurcations (see Paper 8 of this thesis and [149]). We have especifically shown the appearance of periodic orbits in the four-dimensional matching allele dynamics model and in hypercycles with $n \geq 5$, in agreement with previous works [42, 46]. The reader can find multitude of models for biological systems undergoing Hopf bifurcations (see for example [19, 137, 99, 28, 1]).

Chapter 6

Comments on the papers

Paper 1. Information catastrophe in RNA viruses through replication thresholds

In this paper we have analyzed a simple, two-dimensional system of nonlinear differential equations describing the dynamics of a quasispecies under the assumption of the Swetina-Schuster single peak fitness landscape. The main goal was to qualitatively explain a real data set obtained from a nosocomial outbreak of hepatitis C [108]. We study the mean field model providing the critical replication rate of the master strands replicating close to the error threshold, showing that the decrease of this replication rate can make the quasispecies enter error catastrophe. We also analyze the same phenomenon using a bit string description of the quasispecies, implicitly considering the complex population structure of a quasispecies. This computational model, which considers stochastic events of replication and mutation, also shows the entry into error catastrophe due to the decrease of the replication probability of the master sequence. Consistently with the real data set, we find an inverse correlation between viral load and quasispecies complexity.

Paper 2. Simple quasispecies models for the survival-of-the-flattest effect: The role of space

We investigate the dynamics of two competing quasispecies with three different models: (i) a mean field model, (ii) a stochastic *in silico* bit string model of genome evolution, (iii) and a spatial bit string model modelled with a two-dimensional stochastic cellular automata model. We show, in agreement with previous studies, that the increase of the mutation rate drives to the survival of the flat quasispecies. The transition from the survival of the fittest to the survival of the flattest scenarios is shown to be governed by a first-order phase transition with critical slowing down. The results obtained with the non-spatial stochastic bit string model are in agreement with the mean field approach. We also show that space enlarges the scenario of the survival of the flattest, where the

critical mutation rate separating the transition from survival of the fittest to survival of the flattest is shown to be lower.

Erratum: Fig. 3(A) and 3(B): x_0 should be x_1 and viceversa.

Paper 3. Robustness to Mutations Depends on whether RNA virus Replication Occurs Geometrically or Via a Stamping Machine

In this work we analyze the effect of the replication mode (i.e., linear or geometric) of a quasispecies on the accumulation of deleterious mutations and on the entrance into error catastrophe by means of both structured and unstructured models of viral replication for RNA viruses that make no subgenomic RNAs. For both models we analyze the Swetina-Schuster single peak fitness landscape. The structured model is based on nonlinear differential equations and describes the intracellular amplification cycle of the virus considering as state variables the positive- and negative-sense master and mutant strands, the viral polyprotein precursors, the translational complexes and the mature virions. The unstructured model is a stochastic bit string model simulating the processes of replication and mutation. These two models, which incorporate the dual polarity of the RNA virus strands explicitly, consistently show that the quasispecies is more sensitive to the accumulation of mutations and to the error catastrophe when replicating geometrically. However, if the quasispecies replicates linearly, the strands do not collapse so quickly. We also find that, under large mutation rates, the optimum in the production of virions is found for close-to-linear replication and high synthesis of replicase.

Paper 4. Bifurcations and phase transitions in spatially-extended two-member hypercycles

In this work we provide a detailed characterization of the dynamics and bifurcation scenarios for a two-member hypercycle. We study the symmetric and the asymmetric two-member hypercycles with a two-dimensional mean field model, a one-dimensional, spatially-implicit mean field model, both one- and two-dimensional (CA) models and a metapopulation-like approach. In the asymmetric hypercycle, both replicators have differential kinetic properties, which may be attributed to different encoded information contents. All the models show two different asymtpotic dynamics: (i) extinction and (ii) survival of the entire hypercycle. We show that the transition between scenarios (i) and (ii) is governed by a saddle-node bifurcation, and we provide the critical decay rate acting as a bifurcation parameter. We also show that the bifurcation leaves a ghost in phase space able to delay the flows before extinction. In the spatial models we show the presence of an absorbing first-order phase transition homologous to the saddle-node bifurcation described with the mean field models. We find no spatial self-structuring, and the spatio-temporal dynamics is characterized by a full and empty phase, associated to survival and extinction of the hypercycle, respectively. We show that diffusion provides the hypercycle with stability. Moreover, we also show that the differential kinetics within

the hypercyclic coupling can increase the parameter space at which the hypercycle survives.

Paper 5. Spatio-temporal dynamics in simple asymmetric hypercycles under weak parasitic coupling

In this work we analyze the symmetric and asymmetric two-member hypercycle with an attached weak parasite by means of a mean field model and a two-dimensional cellular automaton. The mean field model showed three different asymptotic behaviors: (i) extinction of the entire system, (ii) extinction of the parasite and survival of the hypercycle and (iii) coexistence between the hypercycle and the parasite. Scenario (iii) is shown to be structurally unstable without considering spatial correlations, and coexistence is only possible when the parasite replicates at the same rates as the hypercycle. The consideration of space, consistently with previous works, is shown to enlarge the coexistence scenario where the hypercycle survives within the presence of the parasite. We also characterize the conditions for the appearance of large scale spatial patterns, which are given by clusters and mixed patterns of replicators. The asymmetries in the hypercycle members are shown to be important in the spatio-temporal dynamics of the entire system. When the parasite is attached to the fittest hypercycle replicator, the dynamics is shown to be governed by coexistence attractors with fractal dimension, suggesting the presence of low-dimensional chaos. Finally, we show the negative role of diffusion in the survival and stability of this system.

Paper 6. Delayed transitions in nonlinear replicator networks: About ghosts and hypercycles

We analyze the dynamics of hypercycles with $n = 3$ and $n = 4$ members with nonlinear ordinary differential equations. We provide a description of the equilibrium points and their stability. In agreement with previous works (see [42]), we show that the dynamics of three member hypercycles is governed by a stable node which is achieved by means of fastly damped spiral waves. The four-member hypercycle survival is also given by a stable node, which is achieved by means of hardly damped oscillations. We also provide the critical degradation rates involving the extinction of both hypercycle networks. Our main goal of this work is to analyze the properties of the ghost appearing in phase space once the critical decay rate is overcome, and the system enters the asymptotic extinction phase. As a difference of the two-member hypercycle, we show that the power law of the time extinction curve as a function of the bifurcation parameter is displaced at higher values of $\phi = (\varepsilon - \varepsilon_c)$, which is now given by $\tau \sim \phi^{-1/3}$. This phenomenon is attributed to the increase in the complexity of the transients due to the higher state space dimensions, which allow the appearance of transiently oscillating dynamics.

Erratum: The term Φ_i between Eqs. 4 and 5 in page 3 should be Ψ_i.

Paper 7. Error threshold ghosts in a simple hypercycle with error prone

self-replication

In this paper and by means of a three-dimensional dynamical system, we characterize a saddle-node bifurcation involving the entrance of a simple hypercycle with error prone replication into the random replication state when considering the mutant error tail. We numerically study the bifurcations of the model showing the appearance of a ghost due to the increase of mutation rate. We here also characterize the inverse square-root scaling law in the extinction delay in the vicinity of the saddle-node bifurcation. This result is discussed for systems or error prone replicators with hypercycle coupling, as shown for the phage QB. We conjecture that for viral strains taking advantage of hypercyclic growth, this might suppose an advantage due to the possibility of delaying the extinction at increasing mutation rates near the bifurcation value.

Paper 8. Matching allele dynamics and coevolution in a minimal predator-prey replicator model

In this work we analyze a minimal Lotka-Volterra replicator model describing predator-prey dynamics with matching allele dynamics and mutation processes. We show two possible asymptotic coevolutionary dynamics, static equilibrium of genotypes or a Red Queen, continuous, periodic cycling of genotype's densities achieved via Hopf bifurcation. The investigation of a rugged fitness landscape shows that the fittest predator genotype achieves lower equilibrium concentrations, as opposed to the least fit one, which asymptotically has a higher concentration value.

Paper 9. Chaotic Stability in Spatially-Resolved Host-Parasite Replicators: the Red Queen on a Lattice

By means of stochastic CA models we explore a host-parasite system considering small haploid genomes undergoing replication-mutation-diffusion processes on a two-dimensional, toroidal lattice, under a perfect matching antagonistic dynamics. We explore one-, two-, and three-dimensional sequence space with neutral kinetic properties among genotypes. We find that the Red Queen dynamics scenario, involving a continuously coevolutionary race, is enlarged as the dimension of the sequence space increases. The simulations also show that hosts are able to escape from parasites if they combine high mutation rates with very low replication rates, implying the extinction of parasites. However, the whole host-parasite system becomes exctinct when parasites have higher replication and mutation rates than hosts. We also analyze the population dynamics of both populations in the indefinite coevolutionary regime. We show the presence of sustained cyclic and irregular fluctuations in populations numbers. The power spectrum analysis of the filtered time series, which have a broad band, suggest the presence of chaotic attractors in the Red Queen scenario.

Note: The possibility of a chaotic coevolutionary scenario in this type of system is confirmed by using the model of Paper 9 ("Matching allele dynamics and coevolution in a minimal predator-prey replicator model") now studied with a reaction-diffusion model on a two-dimensional lattice (see section 4.3 in Chapter 4). Moreover, a mean field model for the three-dimensional sequence space with similar interactions to those in Paper 9 is shown to have chaotic coevolutionary attractors (see [146]).

Erratum: The Hamming distance provided in Eq. 14 should be the one of Eq. 15.

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Chapter 7

PAPERS

Molecular Quasispecies

Paper 1

Information catastrophe in RNA viruses through replication thresholds

Ricard V. Solé, Josep Sardanyés, Juana Díez and Antonio Mas

Article published in *Journal of Theoretical Biology* **240(3)**, 353-359 (2006)

Solé RV, Sardanyés J, Díez J, Mas A.
Information catastrophe in RNA viruses through replication thresholds.
J Theor Biol. 2006 Jun 7;240(3):353-9. Epub 2005 Nov 8.

Molecular Quasispecies

Paper 2

Simple quasispecies models for the Survival-of-the-flattest effect: The role of space

Josep Sardanyés, Ricard V. Solé and Santiago F. Elena

Article published in *Journal of Theoretical Biology* **250(3)**, 560-568 (2008)

Sardanyés J, Elena SF, Solé RV.
Simple quasispecies models for the survival-of-the-flattest effect: The role of space.
J Theor Biol. 2008 Feb 7;250(3):560-8. Epub 2007 Oct 30.

Molecular Quasispecies

Paper 3

Robustness to Mutations Depends on whether RNA virus Replication Occurs Geometrically or Via a Stamping Machine

Josep Sardanyés, Ricard V. Solé and Santiago F. Elena

Article submitted to *Journal of Virology* (2009)

Sardanyés J, Solé RV, Elena SF.
Replication Mode and Landscape Topology Affect Differentially RNA Virus Mutational Load and Robustness.
J Virol. 2009 Sep 23. [Epub ahead of print]

Hypercycles

Paper 4

Bifurcations and phase transitions in spatially-extended two-member hypercycles

Josep Sardanyés and Ricard V. Solé

Article published in *Journal of Theoretical Biology* **243(4)**, 468-482 (2006)

Sardanyés J, Solé RV.
Bifurcations and phase transitions in spatially extended two-member hypercycles.
J Theor Biol. 2006 Dec 21;243(4):468-82. Epub 2006 Jul 21.

Hypercycles

Paper 5

Spatio-temporal dynamics in simple asymmetric hypercycles under weak parasitic coupling

Josep Sardanyés and Ricard V. Solé

Article published in *Physica D* **231(2)**, 116-129 (2007)

Sardanyés J, Solé RV.
Spatio-temporal dynamics in simple asymmetric hypercycles under weak parasitic coupling.
Physica D. 2007 Jul 15;231(2):116–29

Hypercycles

Paper 6

Delayed transitions in nonlinear replicator networks: About ghosts and hypercycles

Josep Sardanyés and Ricard V. Solé

Article published in *Chaos, Solitons and Fractals* **31(2)**, 305-315 (2007)

Sardanyés J, Solé RV.
Delayed transitions in non-linear replicator networks: About ghosts and hypercycles
Chaos Soliton Fract. 2007 Jan;31(2):305-15

Hypercycles

Paper 7

Error threshold ghosts in a simple hypercycle with error prone self-replication

Josep Sardanyés

Article published in *Chaos, Solitons and Fractals* **35(2)**, 313-319 (2008)

Sardanyés J.
Error threshold ghosts in a simple hypercycle with error prone self-replication.
Chaos Soliton Fract. 2008 Jan;35(2):313-9

Antagonistic Replicator Dynamics

Paper 8

Matching allele dynamics and coevolution in a minimal predator-prey replicator model

Josep Sardanyés and Ricard V. Solé

Article published in *Physics Letters A***372(4)**, 341-350 (2008)

Sardanyés J, Solé RV.
Matching allele dynamics and coevolution in a minimal predator–prey replicator model.
Phys Lett A. 2008 Jan 21;372(4):341-50

Antagonistic Replicator Dynamics

Paper 9

Chaotic Stability in Spatially-Resolved Host-Parasite Replicators: the Red Queen on a Lattice

Josep Sardanyés and Ricard V. Solé

Article published in *International Journal of Bifurcation and Chaos***17(2)**, 589-606 (2007)

Sardanyés J, Solé RV.
Chaotic stability in spatially-resolved host-parasite replicators: the red queen on a lattice
Int J Bifurcat Chaos. 2007 Feb; 17(2):589-606.