CO-EVOLUTION OF VIRUSES AND GAMES

Mayte Pérez-Llanos,
U. Sevilla

IN COLLABORATION WITH

Natalia Kontorovsky and Juan Pablo Pinasco
U. Buenos Aires

Román D. González-Mora, Pablo Aguilera and María Inés Gismondi
Instituto de Agrobiotecnología y Biología Molecular (CONICET-INTA).

Classical Game Theory

- The classical Game Theory (CGT), conceived by John von Neumann, focus on one **rational player**, who interacts with other players as part of a game.
- They have to decide among different options or strategies, with the aim of maximizing a reward, known as pay-off (non-cooperative games), which depends on the other players strategies.
- This does not enter in conflict with taking an strategy that benefits all of the players: **Nash Equilibria**.
- It is only the best result for each of the individual players, given the rest of the strategies played by the others. This way any player has any incentive on modifying its strategy.
- A Nash Equilibria does not mean the best result for the global population.

Evolutionary Game Theory

- **The Evolutionary Game Theory** (EGT) was born to explain the ritualized animal behaviour in a conflict situation: Why animals behave *chivalrously* in some competitions for resources?
- Some ethologists argued that this fact was due as benefit for the species and tried to explain it within the classical theory of cooperative games, without success.
- John Maynard Smith asserted that this approach is incompatible with the Darwinist thought: selection occurs at individual level.
- This way, the own interest is rewarded while the common benefit does not.
- Maynard made use of CGT, realizing that **the players do not need to behave rationally**.
- It is only assumed that each of the players has an strategy.

Evolutionary Game Theory

- In Biology the strategies are inherited traits. Players are born with them and they cannot change them.
- The success of a strategy or trait is determined by how good results it in presence of competitive strategies, included itself, and the frequencies of use of such strategies.
- High paid strategies will extend among the population, through learning, imitation, inheritance or even infection.
- The **reward, fitness** or **pay-off** depends on coplayers strategies and their frequencies, which at the same time, depend on the results of previous games.
- It results into a feedback cycle known as **Replicator Dynamics**.

Maynard Smith, J., *Evolution and The Theory of Games*, Cambridge University Press, Cambridge, MA, 1982.

Description of the finite replicator dynamics

- Consider a population of N agents, who play with a finite set of pure strategies or traits $\mathcal{S}_M = \{S_1, \cdots, S_M\}$.
- The state of the population at time t is described by the vector $(q_1(t), \cdots, q_M(t))^T$, where $q_i(t)$ accounts for the proportion of players playing strategy S_i at time t.
- Each strategy $S_i \in \mathcal{S}_M$ has assigned a linear continuous function $f_i(q) = f_i(q_1, \cdots, q_M) : \mathbb{R}^M \to \mathbb{R}$, representing its fitness or pay-off.
- The fitness or pay-off matrix $J \in \mathcal{M}_{M\times M}$ collects the fitness of each strategy by rows.
- The replicator dynamics takes the form

$$\frac{d}{dt}\Big[\ln(q_i(t))\Big] = E[q_i(t), q(t)] - E[q(t), q](t)$$

$$\frac{q_i'(t)}{q_i(t)} = \sum_{j=1}^{M} J_{ij} q_j(t) - \sum_{k=1}^{M}\sum_{j=1}^{M} J_{kj} q_k(t) q_j(t).$$

Necessity of continuous replicator dynamics

A wide range of biological process, as well as, economical o social, are modeled considering a **continuum set of strategies**:

- war of attrition
- timing
- duopolies and oligopolies
- auctions modeling
- price wars among different brands, etc

A continuum of strategies approach in the (finite) replicator, implies to generate an ODE for each of the strategies, which now is a continuous set. This generates problems related to measure theory.

J. Oechssler & F. Riedel, Journal of Economic Theory, 2001, 2002.

. I. Kavallaris, J. Lankeit, & M. Winkler *On a degenerate nonlocal parabolic problem describing infinite dimensional replicator dynamics.*, SIAM Journal on Mathematical Analysis, 2017.

Necessity of continuous replicator dynamics

In particular, in virology strategies correspond to viral variants or genotypes.

While real viral populations consist of a finite number of variants, the combinatorial diversity of possible mutations arising from high mutation rates and large population sizes makes the genotype space efectively continuous.

A **quasispecies** is a set of viral variants that are genetically very similar, arising because the virus makes frequent errors during replication.

It is not only the *fittest* variant that evolves, but the entire ensemble, which forms a kind of mutational cloud around a *master* genome. However, it is essential to model gradual evolutionary changes in response to selection pressures

Description of a discrete dynamics model.

- Consider a population of N agents or players.
- At time $t = 0$ each agent A_i is assigned with an initial pure strategy, identified with a real number $\sigma_i(0) \in \Omega = [-L, L]$, $i \in \{1, \cdots, N\}$.
- Agent's strategies are allowed to change in time due to pairwise interactions between agents engaged in the game. Consider the function $\sigma : \{1, 2, \ldots, N\} \times [0, \infty) \to \mathbb{R}$, where $\sigma(i, t)$ accounts for the strategy of the $i-$th player at time $t \geqslant 0$.
- Subdivide Ω in a family of $M \in \mathbb{N}$ intervals $\{I_j\}_{j=1}^{M}$ of same length. Denote the proportion of agents with strategy in the interval I_j as

$$s(j, t) = \frac{\#\{i : \sigma(i, t) \in I_j\}}{N}, \quad j \in \{1, \ldots M\}.$$

- The continuous pay-off function $J : \Omega \times \Omega \to \mathbb{R}$ is adapted as follows: he restriction $J_{|I_k \times I_j} \equiv J(y_k, y_j) = J_{kj}$ is piecewise constant, such that where $y_k \in I_k$ is for example the midpoint of the interval.

Derivation of master equations for the discrete densities

For each $j = 1, \cdots, M$, we would like to precise the expected change

$$s(j, t + \Delta t) - s(j, t) \text{ in a small time interval } [t, t + \Delta t].$$

Assume that the probability that one interaction arises is determined by a Poisson process of parameter $\lambda = 1$. Consequently, for Δt small

- The probability for an interaction to occur in the interval $[t, t + \Delta t]$ is approximately equal to Δt.
- Two or more interactions take place with a neglectful probability $o(\Delta t)$.
- Accordingly, with probability $1 - \Delta t$ none interaction come to pass.

The master equation for $s(j, t + \Delta t)$:

$$s(j, t + \Delta t) = (1 - \Delta t) s(j, t) + \Delta t s^*(j, t),$$

where $s^*(j, t)$ is the expected value of the proportion of agents with strategies at the interval I_j when an interaction occurs.

Description of a pairwise interaction

Two agents A and B are randomly chosen among the N agents.

Agent A adopts the strategy of agent B, with a probability related to the expected payoff of agent B strategy.

Precisely, the expected pay-off corresponding to a strategy belonging to interval I_j can be expressed by

$$P(j,t) = \sum_{k=1}^{M} J(j,k)s(k,t),$$

where $J(j,k) = J_{jk}$ stands for the (single) pay-off for an agent with a strategy from interval I_j, when she plays against an agent whose strategy corresponds to I_k.

Description of a pairwise interaction

The value $s^*(j,t)$ is determined according to the following three possibilities:

1. $s^*(j,t) = s(j,t) + \frac{1}{N}$:
   Agent A adopts the strategy of agent B, with $\sigma(A,t) \in [-L,L] \setminus I_j$ and $\sigma(B,t) \in I_j$.
   This occurs with probability
   $$\sum_{i \neq j} s(i,t)s(j,t)P(j,t).$$
2. $s^*(j,t) = s(j,t) - \frac{1}{N}$:,
   Agent A adopts the strategy of agent B, with $\sigma(A,t) \in I_j$ and $\sigma(B,t) \in [-L,L] \setminus I_j$. This happens with probability
   $$s(j,t)\sum_{i \neq j} s(i,t)P(i,t).$$
3. $s^*(j,t) = s(j,t)$: The proportion I_j does not experience any changes.

Description of a pairwise interaction

The value $s^*(j,t) = s(j,t)$ occurs when:

1. We choose two agents with strategies in intervals other than I_j with probability
$$(1 - s(j,t))^2.$$
2. Both players have strategies belonging to I_j. This takes place with probability
$$s(j,t)^2.$$
3. $\sigma(A,t) \in I_j$ and $\sigma(B,t) \in [-L,L] \setminus I_j$ but A does not copy B. This occurs with probability
$$s(j,t) \sum_{i \neq j} s(i,t)(1 - P(i,t)).$$

Master equation for the discrete dynamics

Therefore,

$$s(j,t+\Delta t)-s(j,t)=\Delta t\frac{1}{N}s(j,t)\left[P(j,t)\sum_{i\neq j}s(i,t)-\sum_{i\neq j}s(i,t)P(i,t)\right].$$

After time rescaling, since $\sum_{i=1}^{M}s(i,t)=1$ and

$$P(j,t)=\sum_{k=1}^{M}J(j,k)s(k,t),$$

we obtain the following approximation of the equations describing the classic discrete replicator dynamics for $j=1,\cdots,M$.

$$\frac{s_j(t+\Delta t)-s_j(t)}{\Delta t}=s_j(t)\left[\sum_{k=1}^{M}J_{j,k}s_k(t)-\sum_{i=1}^{M}\sum_{k=1}^{M}J_{i,k}s_i(t)s_k(t)\right].$$

Heuristic deduction of the continuous dynamics

Our aim is to pass to the limit as the finite set of M pure strategies tends to cover the whole $[-L, L]$. Hence, the length of the intervals $h = 2L/M$, $h \to 0$ as $M \to +\infty$.

We need to pass from discrete and finite proportions of players $s(j, t)$, to infinite number of players described by a global density

$$u : [-L, L] \times [0, T) \to \mathbb{R}_0^+,$$

such that for every $t \in [0, T)$ it holds

$$\int_{-L}^{L} u(x, t)dx = 1 \text{ and } s(j, t) = \int_{I_j} u(x, t)dx \sim hu(y_j, t), \quad j = 1, \cdots M.$$

Then,

$$\frac{s_j(t + \Delta t) - s_j(t)}{h\Delta t} = \frac{s_j(t)}{h} \left[\sum_{k=1}^{M} hJ_{j,k} \frac{s_k(t)}{h} - \sum_{i=1}^{M} \sum_{k=1}^{M} h^2 J_{i,k} \frac{s_i(t)}{h} \frac{s_k(t)}{h} \right].$$

Heuristic deduction of the continuous dynamics

Our aim is to pass to the limit as the finite set of M pure strategies tends to cover the whole $[-L, L]$. Hence, the length of the intervals $h = 2L/M$, $h \to 0$ as $M \to +\infty$.

We need to pass from discrete and finite proportions of players $s(j, t)$, to infinite number of players described by a global density

$$u : [-L, L] \times [0, T) \to \mathbb{R}_0^+,$$

such that for every $t \in [0, T)$ it holds

$$\int_{-L}^{L} u(x,t)dx = 1 \text{ and } s(j,t) = \int_{I_j} u(x,t)dx \sim hu(y_j, t), \quad j = 1, \cdots M.$$

Then,

$$u_t(x,t) = u(x,t) \left[\int_\Omega J(x,y)u(y,t)dy - \int_\Omega \int_\Omega J(y,z)u(z,t)dz\, u(y,t)dy \right].$$

Existence and uniqueness result

Let $\Omega \in \mathbb{R}^N$ be a bounded and regular domain. Assume that $u_0 \in C(\overline{\Omega})$ and the kernel $J : \Omega \times \Omega \to \mathbb{R}$, satisfying $J \in C(\overline{\Omega} \times \overline{\Omega})$. We define the space $X_{t_0} = C([0, t_0]; C(\overline{\Omega}))$ endowed with the norm

$$\|u\|_{X_{t_0}} = \max_{t \in [0,t_0]} \|u(\cdot, t)\|_{L^\infty(\overline{\Omega})},$$

which makes X_{t_0} a Banach Space.

Let $T > 0$ and $t_0 \in [0, T)$. A function $u \in X_{t_0}$ is a solution to the continuous dynamics, if it satisfies for all $x \in \Omega$ and $t \in [0, t_0]$ that

$$\begin{aligned} u(x,t) = u_0(x) &+ \int_0^t u(x,s) \int_\Omega J(x,y) u(y,s) dyds \\ &- \int_0^t u(x,s) \int_\Omega \int_\Omega J(y,z) u(z,s) dz \; u(y,s) dyds =: \mathcal{F}_{u_0} u(x,t). \end{aligned}$$

Given some $R > 0$, there exists t_0 small enough such that $\mathcal{F}_{u_0}$ is a strict contraction in the ball $B(u_0, R) \subset X_{t_0}$

Existence and uniqueness result

Let $u_0 \in C(\overline{\Omega})$ and $J \in C(\overline{\Omega} \times \overline{\Omega})$. There exists a unique solution $u \in C^1([0, T); C(\overline{\Omega}))$ to the continuous dynamics.
Define the following operators

$$A(x,t) = \int_\Omega J(x,y)u(y,t)dy, \quad a(t) = \int_\Omega \int_\Omega J(y,z)u(y,t)u(z,t)dy\,dz,$$

and then

$$u_t(x,t) = u(x,t)\Big(A(x,t) - a(t)\Big).$$

Conservation of mass if $\|u_0\|_{L^1(\Omega)} = 1$, is well observed

$$\frac{d}{dt}\int_\Omega u(x,t)dx = \int_\Omega u(x,t)[A(x,t) - a(t)]\,dx = a(t)\left[1 - \int_\Omega u(x,t)dx\right].$$

Moreover, $\|A(\cdot,t)\|_{L^\infty(\overline{\Omega})} \leqslant \|J\|_{L^\infty(\overline{\Omega}\times\overline{\Omega})}$ and $a(t) \leqslant \|J\|_{L^\infty(\overline{\Omega}\times\overline{\Omega})}$, hence Gronwall's Lemma gives

$$\|u(\cdot,t)\|_{L^\infty(\overline{\Omega})} \leqslant \|u_0\|_{L^\infty(\overline{\Omega})} e^{2t\|J\|_{L^\infty(\overline{\Omega}\times\overline{\Omega})}} \quad \text{for any } t > 0.$$

Numerical discretization of the continuous equation

Bridging Maynard's replicator dynamics and integro-differential equations via numerical analysis:

Consider $u_0 \in C^2(\overline{\Omega})$, $\|u_0\|_{L^1(\Omega)} = 1$, $J \in C^2(\overline{\Omega} \times \overline{\Omega})$ *and let* $u \in C^3([0,\infty); C^2(\overline{\Omega}))$ *be the solution to the continuous dynamics corresponding to the initial datum* u_0.

Let q_h *the piecewise-constant function satisfying Maynard system of ODEs, with* $M = 1/(2h)$ *strategies and* $q_h(x,0) = I_h(u_0)$ *a piecewise-constant approxiamtion of* q_h.

Then, for any $\tau > 0$,

$$\max_{t\in[0,\tau]} \left\| \frac{q_h(t)}{h} - u(t) \right\|_{L^2(\Omega)} \leqslant \exp(C\tau) O(h^2).$$

N. Kontorovsky, MPL, J. P. Pinasco Replicator dynamics for continuous strategies: bridging agent-based models and integro-differential equations via numerical analysis, Preprint

Two players symmetric games

Consider a *symmetric game* (players are not distinguished) with two players: *Player I* and *Player II*, with the same finite discrete sets of *pure strategies*, S.

Let $J \in \mathcal{M}_{M\times M}$ be the payoff matrix for *Player I* (J^T for *Player I*) being M the cardinality of S.

A *mixed strategy* is defined as

$$\sum_{j=1}^{M} p_j \sigma_j, \text{ where } \sigma_1, \cdots \sigma_M \in S \text{ and } \sum_{j=1}^{M} p_j = 1.$$

The respective simplex of mixed strategies is defined as:

$$\mathbb{S}_M = \{p \in \mathbb{R}^M : \sum_{i=1}^{M} p_i = 1\}$$

The state $p \in \mathbb{S}_M$ is a Nash equilibria iff $p^T Jp \geqslant q^T Jp, \quad \text{for all } q \in \mathbb{S}_M.$

. J. Hopfbauer, & K. Sigmund *Evolutionary game dynamics.*, Bulletin of the AMS, 2003.

Folk's Theorem and Nash Equilibria

Evolutionary Equilibria include and generalize Nash Equilibria:

- Every symmetric Nash equilibrium is also an equilibrium of the replicator dynamics.
- But not conversely: the replicator dynamics also identify unstable equilibria or another states not identified by Nash equilibria.

The Replicator Dynamics Select "Stable" Equilibria
Classical game theory only states: "if everyone plays this profile, no one wants to deviate." But

- how does the system reach such a profile?
- Is it robust to small perturbations?
- could another population invade it?

Replicator dynamics answer these questions:A stable equilibrium of the replicator dynamics corresponds to an evolutionarily stable Nash equilibrium (ESS).

Co-existence of cooperators and defectors viruses

Certain virus variants evolve to exploit co-infecting viruses' gene products.

Experimentally, they determined a payoff matrix that aligns with the Prisoner's Dilemma, where defection yields higher individual payoffs at low defector frequency, but decreases overall fitness as defection becomes prevalent.

Biologically, a predominance of defectors risks population extinction, suggesting that other evolutionary mechanisms should be operating to support the persistence of cooperators.

P. E. Turner and L. Chao, *Sex and the evolution of intrahost competition in RNA virus* Φ6, Genetics, 1998.

P. E. Turner and L. Chao, *Prisoner's dilemma in an RNA virus, Nature, 1999*

Prisioner's Dilemma

It is a classic game scenario showing why two rational individuals may fail to cooperate even when cooperation is mutually beneficial.

Two prisoners each choose to either

- **Q (cooperate):** remain silent
- **D (defect):** betray the other.

The payoffs satisfy: $T > R > P > S$, where T is the temptation payoff, R the reward for mutual cooperation, P the punishment for mutual defection, and S the sucker's payoff.

The general symbolic matrix is:

	Cooperate (Q)	Defect (D)
Cooperate (Q)	$(R,\ R)$	$(S,\ T)$
Defect (D)	$(T,\ S)$	$(P,\ P)$

The unique Nash equilibrium is mutual defection (D, D).

Rational self-interest leads both to defect, producing a worse collective outcome.

Co-existence of cooperators and defectors viruses

Further research showed that viruses acting as cooperators, can escape the Prisioners dilemma through clonal selection at low multiplicity of infection, resulting in a stable mixed polymorphism where cooperators and defectors coexist.

Consequently, the payoff matrix shifts to favor evolved cooperators over cheaters, preventing cheater viruses from dominating the population.

When they measured the fitness of the evolved cooperators they obtained a different matrix with the structure of Snowdrift (SD) game and it has a mixed Nash equilibrium.

.L. Chao and S. F. Elena, *Nonlinear trade-offs allow the cooperation game to evolve from Prisoner's Dilemma to Snowdrift*, Proceedings of the Royal Society B: Biological Sciences, 2017.

P. E. Turner and L. Chao, *Escape from prisoner's dilemma in RNA phage* $\Phi 6$, The American Naturalist, 2003.

Snowdrift Game

Imagine you and another person are driving and encounter a snowdrift blocking the road. You can:

- **Q (cooperate):** get out and clear the snow.
- **D (defect):** stay in the car without helping.

The joint benefit is that if at least one clears the snow, both can pass, but clearing it has a cost. Assume that $(B > C > 0)$

$B =$ benefit of having the road cleared, $C =$ cost of clearing the snow,

A typical Snowdrift payoff matrix is:

	Cooperate (Q)	Defect (D)
Cooperate (Q)	$(B - C/2,\ B - C/2)$	$(B - C,\ B)$
Defect (D)	$(B,\ B - C)$	$(0,\ 0)$

Evolutionary payoffs

We consider the homotopy $\mathcal{J}(x,y,t) = Q(t)\mathcal{J}_1(x,y) + (1–Q(t))\mathcal{J}_2(x,y)$:

$$\mathcal{J}_1(x,y) = 2x - 2y + 2 - xy;$$

$$\mathcal{J}_2(x,y) = x - y + 3 - 3xy.$$

Observe that

- $\mathcal{J}_1$ generalizes the structure of a PD, in the sense that being a defector at $x = 1$ is the only Nash equilibrium, despite the fact that $x = 0$ offers a better payoff,
- while $\mathcal{J}_2$ generalizes the SD game, and admits a mixed Nash equilibrium.

The function $Q(u,t)$ accounts for the public goods contributed by a viral population,

$$Q(u,t) = \int_0^1 q(x)u(x,t)dx = \int_0^1 (1-x)u(x,t)dx$$

Here, $q(x)$ represents the contribution by each genotype x, and refers to molecular products shared during replication that benefit other genotypes.

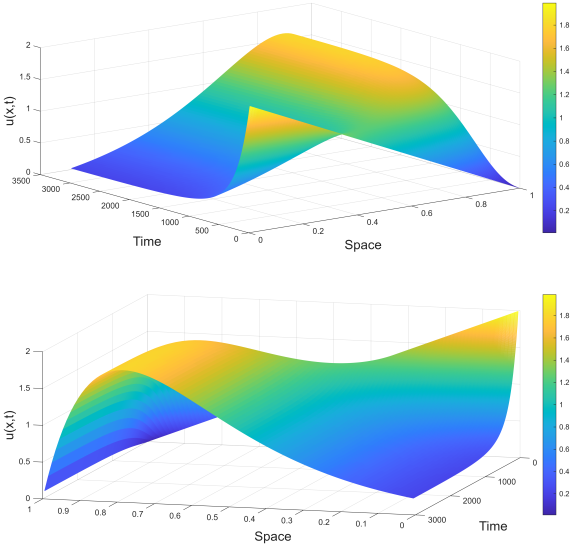

Figure: Time evolution of the initial condition $u_0(x) = 2(1-x)$ according the previous payoff being $\mathcal{J}_i$, $i = 1, 2$ and $q(x) = 1 - x$.

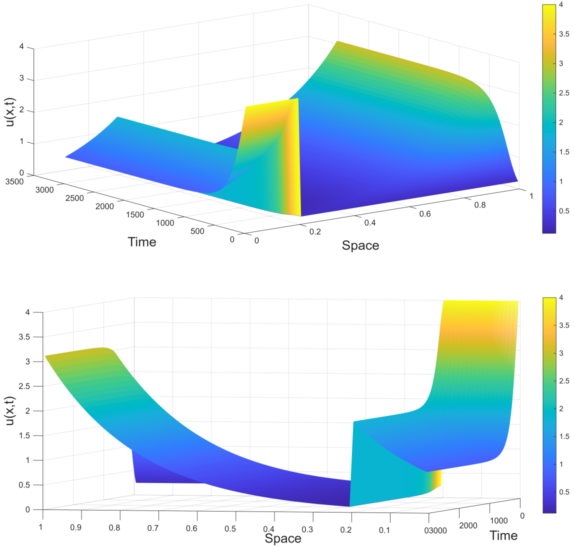

Figure: Time evolution of the initial condition $u_0(x) = 4$ on $[0, 0.2]$ and $u_0(x) = 0.25$ on $(0.2, 1]$ according the previous payoff

Long term behaviour

From a strictly mathematical point of view, the long-term behavior of solutions presents many interesting problems:

- Since the space of strategies is compact an convex, we can expect the existence of at least one Nash equilibria, via Brauer fix point Theorem.
- For finite replicator dynamics the number of Nash equilibria could increase with the dimension of the ODE system. We could explore the number of Nash equilibria for finite systems with evolving payoff matrices.
- We can expect some Folk Theorem, where Nash equilibria are stationary points of the dynamics, and asymptotically stable equilibria of the dynamics are Nash equilibria when the initial data are strictly positive.

Mutations to new viral genotypes

A key limitation of our model is that it does not explicitly model the generation of new viral genotypes through mutation.

However, the continuous strategy space accounts for the vast diversity of viral variants. Future extensions could incorporate mutation explicitly by adding a Laplacian operator to the model, enabling the exploration of new strategies.

The singular term u in front of the evolution operator prevents the growth of strategies that are not present in the initial datum, so we can reach steady states that are not Nash equilibria, as in the finite-dimensional case.

The inclusion of stochastic effects, such as random mutations, can alter the dynamics, potentially leading to more complex evolutionary outcomes.

Control problems

Control theory arises naturally in these types of problems.

In fact, it is precisely what virologists aim to achieve. One would want to regulate the payoffs.

For example, if the focal trait is virulence, rather than defectors and cooperators, we would seek to reduce the payoff only for the more virulent types, while leaving the non-virulent types unaffected.

This selective pressure would naturally allow the less virulent population to dominate the more virulent one.