Systems biology

IsoMaTrix: a framework to visualize the isoclines of matrix games and quantify uncertainty in structured populations

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Abstract

Evolutionary game theory describes frequency-dependent selection for fixed, heritable strategies in a population of competing individuals using a payoff matrix. We present a software package to aid in the construction, analysis, and visualization of three-strategy matrix games. The IsoMaTrix package computes the isoclines (lines of zero growth) of matrix games, and facilitates direct comparison of well-mixed dynamics to structured populations on a lattice grid. IsoMaTrix computes fixed points, phase flow, trajectories, (sub)velocities, and uncertainty quantification for stochastic effects in spatial matrix games. We describe a result obtained via IsoMaTrix's spatial games functionality, which shows that the timing of competitive release in a cancer model (under continuous treatment) critically depends on the initial spatial configuration of the tumor.

Availability: The code is available at: https://github.com/mathonco/isomatrix.

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Supplementary information: Supplementary data are available at *Bioinformatics* online.

1 Introduction

Interactions between competing individuals which result in some benefit or cost can broadly be described and analyzed using game theory. Game theory aims to mathematically determine the optimal strategy to employ when in competition with an adversary (Morgenstern and Von Neumann, 1953). The typical ingredients of a game are: 1) the strategies, 2) the players, and 3) the payoffs of each strategy (Hofbauer *et al.*, 1998). This classical definition of game theory can be extended to model evolution by natural selection, known as evolutionary game theory (EGT; (Maynard Smith, 1986)). Most often, EGT is used to describe changes in the prevalence of strategies due to frequency-dependent selection in a population of competing players that adhere to fixed strategies (but see (Kaznatcheev, 2017) for an alternative experiment-focused interpretation of the basic ingredients of EGT). In a typical setting, competition is governed by a "payoff matrix," defining the Darwinian fitness of an individual based upon pairwise interactions with other individuals within the population.

EGT is increasingly used to model cancer as an evolutionary process (Staňková *et al.*, 2019; Archetti and Pienta, 2019), and viewed as one of the central paths forward in the roadmap of mathematical oncology (Rockne *et al.*, 2019). EGT models have shown success in modeling glioma progression (Basanta *et al.*, 2008), growth factor production as a public good (Archetti, 2013), effects of tissue edges on cancer cell motility (Kaznatcheev *et al.*, 2015), vascularization and tumor acidity (Kaznatcheev *et al.*, 2017), metastatic prostate cancer and the bone-remodelling cycle (Warman *et al.*, 2018), competitive release (West *et al.*, 2018), and optimal cancer treatment (Gluzman *et al.*, 2020; West *et al.*, 2020). Recently, the payoff matrices that specify evolutionary games have even been directly measured *in vitro* (Kaznatcheev *et al.*, 2019).

To help mathematical oncologists along the path of EGT modeling, we develop a software package, IsoMaTrix, to systematically analyze three-strategy matrix games. The package places a special focus on boundaries between the positive and negative growth regions of each strategy, known as isoclines. Thus, the name of this package, IsoMaTrix, is a blend of "isocline" and "matrix" games, to describe this key functionality.

Several groups have released similar packages in Mathematica, Dynamo (Sandholm *et al.*, 2012), EvoDyn-3s (Izquierdo *et al.*, 2018),

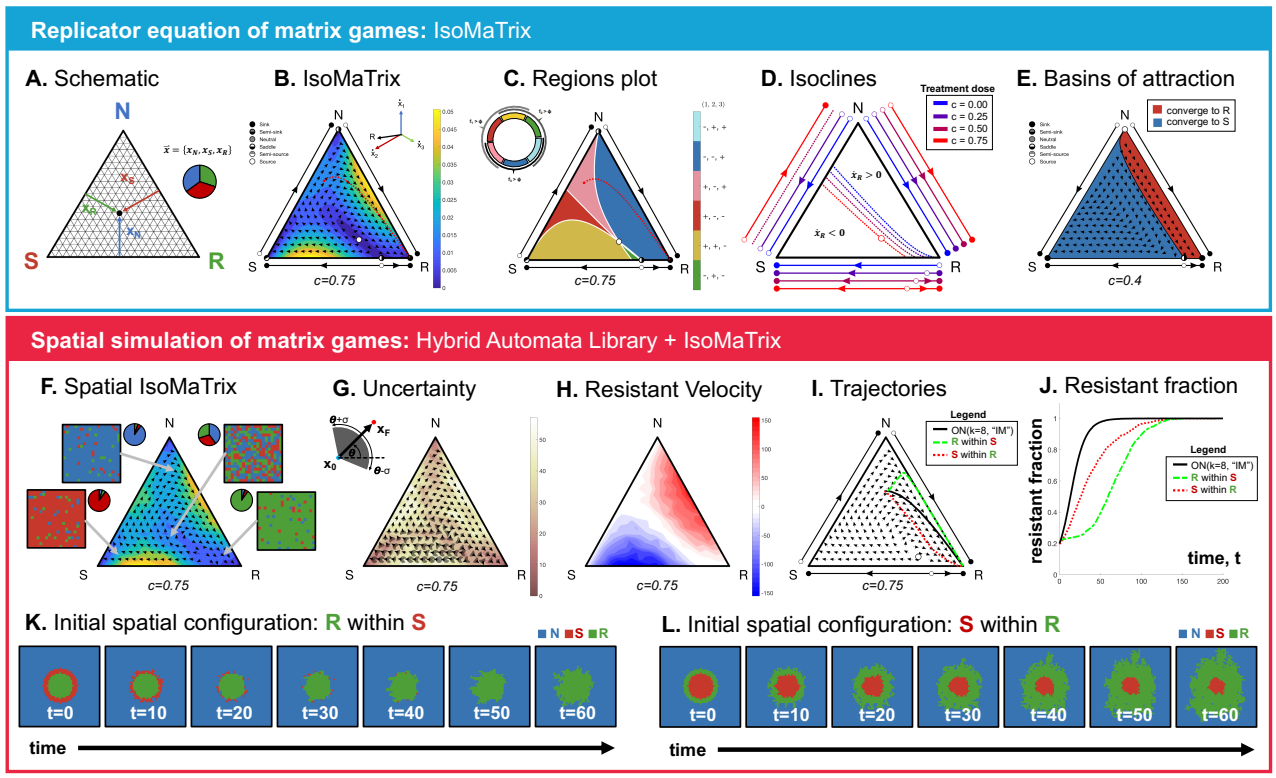

Fig. 1. IsoMaTrix Top section: well-mixed dynamics. (A) Schematic of simplex describing competition between Normal (N), Sensitive (S), and Resistant (R) cells. (B) Example IsoMaTrix diagram describing competitive release. (C) "Region plot" (regions delineated isoclines, $\dot{x}_i = 0$), with example trajectory (red dashed line). (D) Isoclines for resistant strategy ($\dot{x}_3 = 0$) for varied dose, c. (E) Phase flow shown for $c = 0.25$, with simulated spatial structure using the Ohtsuki-Nowak transform ($k = 4$, Death-Birth updating). Color-coded by basins of attraction. (F) Schematic of IsoMaTrix diagrams computation in structured populations. M stochastic realizations are simulated for each initial proportion within a mesh covering the triangle: four examples shown inset. Phase flow is estimated via resultant vector $\vec{x}_F - \vec{x}_0$, after n number of time steps Uncertainty: standard deviation of magnitude (background-color) and direction (gray arc). (H) Resistant subvelocity. The trajectories through space (I) and time (J) for configurations shown in (K,L) compared to well-mixed (black).

DeFinetti (Archetti, 2020), or in Python, EGTplot (Mirzaev *et al.*, 2018), that compute evolutionary game dynamics of three strategy games. The foremost distinguishing feature of the IsoMaTrix package is the extension of explicit spatial structure, including functions to quantify and visualize uncertainty due to stochastic effects, which has not been done in previous packages. This extension allows for easy comparison between non-spatial (replicator dynamics) and spatial (cellular automata; discrete space) model configurations. Other distinguishing features include computation of isoclines, novel region plots, simultaneous visualization of multiple games, and automatic computation of basins of attraction.

2 Methods

Frequency-dependent selection dynamics in IsoMaTrix are governed by the replicator equation:

$$\dot{x}_i = x_i \left(f_i - \phi \right) \tag{1}$$

where x_i is the fraction of each strategy, $f_i = \sum_j a_{ij} x_j$ is the fitness of each strategy, the average fitness is $\phi = \sum_j f_j x_j$ (with $i, j \in [1, 2, 3]$), and a_{ij} are elements of the payoff matrix, A such that $[A]_{ij} = a_{ij}$.

The IsoMaTrix package has functions which display the replicator equation's 1) fixed points, 2) isoclines, 3) phase flow, 4) velocities, 5) trajectories, 6) regions of positive/negative strategy fitness and 7) basins of attraction. See the attached manual for an exhaustive list and tutorial of all IsoMaTrix functionality. Each function is independently called, enabling chaining to facilitate the desired visualization of dynamics. Figure 1 shows a representative example of visualizations possible in IsoMaTrix.

While replicator dynamics has proven quite useful, the dynamics of spatially structured populations can vary dramatically (Gatenbee *et al.*, 2019; Kaznatcheev *et al.*, 2015; You *et al.*, 2017). In some cases, it is possible to spatialize replicator dynamics: i.e., transform the replicator dynamics to account for the specific spatial structures. IsoMaTrix provides an implementation of one such analytic transform to get modelers started with first-order deviations from well-mixed dynamics due to spatial structure (Ohtsuki and Nowak, 2006; Kaznatcheev, 2018).

IsoMaTrix uses the on-lattice cellular automata framework HAL (Bravo *et al.*, 2020) to perform simulation-based analysis of spatial structure. IsoMaTrix uses 'imitation updating' whereby a randomly chosen focal cell updates its strategy to imitate one of its own neighbors in proportion to fitness (Ohtsuki and Nowak, 2006). Either deterministic (maximum fitness neighbor strategy wins) or stochastic (weighted by fitness of all neighbors) updating can be chosen (Nowak, 2006).

3 Example

To illustrate the utility of IsoMaTrix, figure 1 uses a payoff matrix previously used to model competitive release (West *et al.*, 2018) (see supplementary material), which describes competition between Normal (N), Sensitive (S), and Resistant (R) cells within the tumor bed. Competition depends on drug concentration, c. Figure 1 illustrates the dynamics, displayed on a triangular plot (fig. 1A) where each corner

represents a tumor with 100% of the given strategy. Figure 1B shows phase flow under treatment, with fixed points for each two strategy interaction (N-S, S-R, N-R) conveniently offset on each edge. Isomatrix shows the stability of each of the corner, edge, and internal fixed points (solid circles are stable; open are unstable). Any solid circle on the simplex corresponds to an evolutionary stable strategy (ESS; Maynard Smith (1986); Zeeman (1980)). For example in figure 1B, all-R is an ESS and the other fixed points (all-S, all-N, SR-mix, SRN-mix) are not, while in the spatialized figure 1E, all-S and all-R are ESS and the other fixed points (all-N and SR-mix) are not.

The 'regions' plot (fig. 1C) delineates the ternary plot into color-coded regions according to if each strategy ($i \in \{1, 2, 3\}$) is selected for ($f_i > \phi$) or against ($f_i < \phi$). Knowledge of the dose-dependent resistant isocline (fig. 1D) facilitates control of the tumor dynamics by allowing treatment to be discontinued well before resistant regrowth (West *et al.*, 2018, 2016). Importantly, IsoMaTrix allows for multiple games (in this case, multiple values of dose) to be easily displayed on the same ternary diagram.

Figure 1F shows a schematic detailing how IsoMaTrix diagrams are produced for spatially structured populations. M stochastic realizations are simulated for each initial proportion (i.e. $\vec{x}_0 = [x_1, x_2, x_3]$) within the triangle. Phase flow is estimated by calculating the resultant vector between and the initial and final proportion after n time steps. Given the stochastic nature of spatial simulations, uncertainty can be calculated (fig. 1G). IsoMaTrix facilitates comparison of precise spatial configurations. Figures 1I-L compare the well-mixed (black line) dynamics to two spatial configurations: resistant cells trapped inside sensitive cells (K) and vice versa (L). The tumor with resistant cells trapped within the core delays the emergence of resistant cells (fig. 1J) under treatment.

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