Chemical Game Theory

Jacob Kautzky
Group Meeting
February 26th, 2020
What is game theory?

Game theory is the study of the ways in which interacting choices of rational agents produce outcomes with respect to the utilities of those agents.
Why do we care about game theory?

11 nobel prizes in economics

1994 – “for their pioneering analysis of equilibria in the thoery of non-cooperative games”

John Nash  Reinhard Selten  John Harsanyi

2005 – “for having enhanced our understanding of conflict and cooperation through game-theory”

Robert Aumann  Thomas Schelling
Why do we care about game theory?

2007 – “for having laid the foundations of mechanism design theory”

Leonid Hurwicz  Eric Maskin  Roger Myerson

2012 – “for the theory of stable allocations and the practice of market design”

Alvin Roth  Lloyd Shapley

2014 – “for his analysis of market power and regulation”

Jean Tirole
Why do we care about game theory?

Mathematics
Business
Biology

Engineering
Sociology
Philosophy

Computer Science
Political Science
Chemistry
Why do we care about game theory?

Plato, 5th Century BCE

- Initial insights into game theory can be seen in Plato’s work
- Theories on prisoner desertions

Cortez, 1517

“burn the ships”

Shakespeare’s Henry V, 1599

Henry orders the French prisoners executed in front of the French army

Hobbes’ Leviathan, 1651

First mathematical theory of games was published in 1944 by John von Neumann and Oskar Morgenstern
Chemical Game Theory

Basics of Game Theory

- Prisoners Dilemma
- Battle of the Sexes
- Rock Paper Scissors
- Centipede Game
- Iterated Prisoners Dilemma

Chemical Game Theory

Game Theory in Computer Science

Game Theory in Biology

Game Theory in Chemistry

- Case 1: deciding an optimal dft functional
- Case 2: inverse design
Game theory analyzes the strategic interaction between at least 2 agents in their quest to achieve maximum utility

**game** – a set of circumstances where the outcome is dependent on the actions of two or more decision makers

**utility/payoff** – a quantification of the amount of use a player gets from a particular outcome

**strategy** – a complete plan of action a player will take given the set of circumstances that can arise within the game
Game theory basics

Simultaneous game

- Players take their turns at the same time
- Visualized as a matrix

<table>
<thead>
<tr>
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<tr>
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<td>(20,0)</td>
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Sequential game

- Players take their turns sequentially
- Visualized as a directed graph

Payoffs listed at the base of the tree

Game theory basics

**cooperative vs non-cooperative** – whether players can establish alliances to maximize their winning chances

**symmetric vs asymmetric** – in a symmetric game, all players have the same overall goals, while in an asymmetric game participants have different or conflicting goals

**perfect vs imperfect information** – in perfect information all players can see other players moves, while in imperfect other player’s moves are hidden

**zero-sum vs non-zero sum games** – in zero sum games, if a player gains something another player loses something while in non-zero sum games multiple players can gain at the same time

**perfectly rational vs bounded rational** – perfectly rational assumes all players are rational whereas bounded has individual player’s rationality limited in some form

The scenarios discussed today will be primarily no-cooperative, perfect information, and perfectly rational

The prisoner’s dilemma

“ I’ll give you a lighter sentence if you rat on your co-conspirator”

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“So, ya believe in the Constitution, eh?”

The prisoner’s dilemma

"I'll give you a lighter sentence if you rat on your co-conspirator"

The prisoner’s dilemma

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Not a stable state as B has a reason to snitch to get less jail time

Stable - a state where no player would change their move given the opportunity

The prisoner’s dilemma

"I'll give you a lighter sentence if you rat on your co-conspirator"

Stable - a state where no player would change their move given the opportunity

Equilibrium - a game that has reached a stable state; one where all the casual forces balance each other out

The prisoner’s dilemma

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"So, ya believe in the Constitution, eh?"

Telling is a dominant strategy for player A

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**The prisoner’s dilemma**

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*Telling is a dominant strategy for player A*

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"I'll give you a lighter sentence if you rat on your co-conspirator"

Nash Equilibrium (NE)

- An equilibration of entire sets of strategies
- Every finite game has at least one NE

### Battle of the sexes

A couple trying to decide between multiple options for a date night

<table>
<thead>
<tr>
<th></th>
<th>Partner B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watch Football</td>
<td>(20,10)</td>
</tr>
<tr>
<td>Get a manicure</td>
<td>(0,0)</td>
</tr>
<tr>
<td>Go to a movie</td>
<td>(5,0)</td>
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**Battle of the sexes**

There can be multiple Nash Equilibria

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</tr>
<tr>
<td>Get a manicure</td>
<td>(7,7)</td>
</tr>
<tr>
<td>Go to a movie</td>
<td>(7,5)</td>
</tr>
<tr>
<td>(0,0)</td>
<td>(5,20)</td>
</tr>
<tr>
<td>(5,0)</td>
<td>(5,7)</td>
</tr>
<tr>
<td>(20,20)</td>
<td></td>
</tr>
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</table>

**Battle of the sexes**

There can be multiple Nash Equilibria

**Pareto Optimum** - an outcome where there is no other outcome where every other player is at least as well off

### Rock paper scissors

#### Player 1
- **Rock**
- **Paper**
- **Scissors**

#### Player 2

<table>
<thead>
<tr>
<th></th>
<th>Rock</th>
<th>Paper</th>
<th>Scissors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rock</td>
<td>(0,0)</td>
<td>(-1,1)</td>
<td>(1,-1)</td>
</tr>
<tr>
<td>Paper</td>
<td>(1,-1)</td>
<td>(0,0)</td>
<td>(-1,1)</td>
</tr>
<tr>
<td>Scissors</td>
<td>(-1,1)</td>
<td>(1,-1)</td>
<td>(0,0)</td>
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Rock paper scissors

Player 1

Rock
Paper
Scissors

Player 2

Rock
Paper
Scissors

Pure Strategy - a player chooses one option 100% of the time

Mixed Strategy - a player chooses multiple options with differing probabilities

### Rock paper scissors

![Rock paper scissors hands](image)

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<thead>
<tr>
<th>Player 1</th>
<th>Rock</th>
<th>Paper</th>
<th>Scissors</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>1/3</td>
<td>1/3</td>
<td>1/3</td>
</tr>
<tr>
<td>Rock</td>
<td>(0,0)</td>
<td>(-1,1)</td>
<td>(1,-1)</td>
</tr>
<tr>
<td>Paper</td>
<td>(1,-1)</td>
<td>(0,0)</td>
<td>(-1,1)</td>
</tr>
<tr>
<td>Scissors</td>
<td>(-1,1)</td>
<td>(1, -1)</td>
<td>(0,0)</td>
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Player 1’s Expected Utility: 
\[
\frac{1}{9} \cdot 0 + \frac{1}{9} \cdot -1 + \frac{1}{9} \cdot 1 + \frac{1}{9} \cdot 1 + \frac{1}{9} \cdot 0 + \frac{1}{9} \cdot -1 + \frac{1}{9} \cdot -1 + \frac{1}{9} \cdot 1 + \frac{1}{9} \cdot 0 = 0
\]

The Centipede Game – A game played by two players where starting with $5 each player can either accept the deal and get 4/5 of the pot or pass the deal at which point the money in the pot doubles and the same offer is made to the other player until the pot reaches a grand total of $320 dollars.

Nash equilibria in sequential games

Backward Induction - the process of reasoning backward in time to determine the sequence of optimal events.

(4,1)
(2,8)
(16,4)
(8,32)
(64,16)
(32,128)
(256,64)
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(Nash equilibria in sequential games)

Player 1
- takes deal
  - (4,1) Player 2
    - takes deal
      - (2,8) Player 1
        - takes deal
          - (16,4) Player 2
            - takes deal
              - (8,32) Player 2
            - refuses
              - (64,16)

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Backward Induction - the process of reasoning backward in time to determine the sequence of optimal events.

NE is for player 1 to take the first deal!
What happens when we move away from finite games?
Iterated Prisoners Dilemma

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- Repeat the prisoners dilemma over and over again
- Players can learn about the behavioral tendencies of their opponents

In the early 1980's Robert Axelrod had a tournament where users submitted different algorithms for the iterated prisoners dilemma

**Iterated Prisoners Dilemma**

**Unconditional Cooperator** – always cooperates regardless of what the opponent does

**Unconditional Defector** – always defects regardless of what the opponent does

**Random** – player defects with a given probability p

**GRIM/ TRIGGER** – cooperates until their opponent defects once, at which point it switches to unconditional defection

**Tit for Tat** – cooperates on the first round and imitates their opponents move thereafter

::

and a range of others as well

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**Tit for Tat** – cooperates on the first round and imitates their opponents move thereafter

**Win-stay Lose-shift** – cooperates if it and its opponent moved the same in the previous move and defects otherwise

**Gradual Tit for Tat** – tit for tat, but (1) it gradually increases the number of defections for each additional defection of its opponent and (2) it cooperates the next 2 rounds after it defects

Chemical Game Theory

Basics of Game Theory

Prisoners Dilemma
Battle of the Sexes
Rock Paper Scissors
Centipede Game
Iterated Prisoners Dilemma

Chemical Game Theory

Game Theory in Computer Science

Game Theory in Biology

Game Theory in Chemistry

Case 1: deciding an optimal dft functional

Case 2: inverse design
Chemical Game Theory (CGT)

- Predictive rather than normative
- Takes into account players biases, altruism, deception, imperfect information, and relative pain levels

Considers the player’s strategies as “knowlecules”

CGT is concerned with decision reactions between the players and their choices form decisions

Each player must consider how the other player “reactors” will act and how subsequent reactors will respond

Each reaction has an energy of reaction related to the amount of pain or utility given to that choice

The system then searches for a form of chemical equilibria

Chemical Game Theory (CGT) applied to the prisoners dilemma

Player A

\[ a_1 = \text{quiet} \]
\[ a_2 = \text{tell} \]

<table>
<thead>
<tr>
<th>( b_1 = \text{quiet} )</th>
<th>( b_2 = \text{tell} )</th>
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<tbody>
<tr>
<td>(1,1)</td>
<td>(3,0)</td>
</tr>
<tr>
<td>(0,3)</td>
<td>(2,2)</td>
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Treat each player as a reactor as well as a reactor for the decider

Chemical Game Theory (CGT) applied to the prisoners dilemma

depending on the different parameters selected you get all 4 outcomes as opposed to just the tell–tell for the NE

Chemical Game Theory

Basic of Game Theory
- Prisoners Dilemma
- Battle of the Sexes
- Rock Paper Scissors
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- Iterated Prisoners Dilemma

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Case 1: deciding an optimal dft functional

Case 2: inverse design
General Adversarial Networks (GANs)

- Consists of a generator and discriminator

- The generator is a form of unsupervised learning and it takes numbers random numbers and returns a sample
  - This sample as well as a sample pulled from real data are then put into a discriminator
  - A discriminator is a form of supervised learning that tries to determine if the data is real or fake
  - This data is then returned to the generator and the process is iterated

General Adversarial Networks (GANs)

Viewed as a form of inverse game theory

Inverse game theory aims to design a game based on a player's strategies and aims

Inverse game theory plays an important role in developing AI agent environments

General Adversarial Networks (GANs)

“[GANs] are the most interesting idea in the last 10 years in ML” – Facebook’s AI research director Yann Lecun

faces generated from a GAN

**General Adversarial Networks (GANs)**

“[GANs] are the most interesting idea in the last 10 years in ML” – Facebook’s AI research director Yann Lecun

Trained a GAN by feeding it historical paintings

Christie’s sells its first AI portrait for $432,500, beating estimates of $10,000

*The image was created using a machine learning algorithm that scanned historical artwork*

By James Vincent  |  Oct 25, 2018, 1:03pm EDT
Support Vector Machines (SVM)

- Classifying algorithm
- Supervised learning
- The algorithm searches for a decision boundary or separating hyperplane that leads to the best separation
- Quickly trained, works well for high-dimensional data, relatively good at not overfitting, not very interpretable
- Commonly used method; used by Doyle and Cronin amongst others

Support Vector Machines (SVM)

Determining the hyperplane can be viewed as a two-player game

- one player trying to give the other the most challenging points to classify
- the other player is trying to find the best hyperplane
- the two players will converge to the eventual solution

The method in which the player selects a hyper-plane is traditionally calculated via quadratic programming algorithms, but has also been achieved via iterative game theory and the chip-firing classifier

Chemical Game Theory

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Evolutionary game theory

similar to normal game theory, but the payoff is reproductive success and players don’t need to act rationally

The hawk-dove game

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<th>Hawk</th>
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<tr>
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<td>(\frac{V}{2}, \frac{V}{2})</td>
<td>((0, V))</td>
</tr>
<tr>
<td>Hawk</td>
<td>((V, 0))</td>
<td>(\frac{(V-C)}{2}, \frac{(V-C)}{2})</td>
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\(V\) = Resources \quad C = \text{Cost of Conflict}

4 outcomes

- **Dominance** – one player vanishes
- **Bistability** – either player vanishes depending on the initial mixture
- **Coexistence** – A & B exist in stable proportions
- **Neutrality** – A & B only subject to random drift

**Evolutionary stable** – a strategy that if almost every player of a species follows, no mutant can successfully invade

For a review, see: Nowak, M. A.; Sigmund, K. *Science* **2004**, 303, 793.
Can get into significantly more complicated scenarios

Iterated prisoners dilemma explains altriusm

<table>
<thead>
<tr>
<th>Screams</th>
<th>No scream</th>
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3 species can get into rock-paper-scissors types scenarios

Uta stansburiana Lizard

Newt and gartner snake

Coevolution

- Mutation in virology
- Host–parasite interactions
- Development of language
- Sex-ratio theory
- Resource allocation
- Cancer cell-normal cell interactions
- Mate choice
- Sibling rivalry
- ... and more
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Iterated Prisoners Dilemma

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Case 1: deciding an optimal dft functional

Case 2: inverse design
Selecting a proper DFT functional

There are hundreds if not thousands of functionals with new types being customized for specialized problem types.

Selecting a suitable functional and basis set can be challenging.

Waller and coworkers developed Decider which relies upon game theory techniques to determine an optimal functional.

Selecting a proper DFT functional

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Selecting a suitable functional and basis set can be challenging.

Waller and coworkers developed Decider which relies upon game theory techniques to determine an optimal functional.

3 players

**Accuracy** – the performance of a basis set and functional relative to a reference set (mean absolute percent deviation or MAPD)

**Complexity** – the complexity of the basis set and functional relative to the complexity of the molecule being studied.

**Similarity** – the similarity of the current query relative to a set of benchmark systems; measured as a Tanimoto score.

Decider in action

Created a 3-D matrix and then searched for Nash equilibria

Tested the developed system on Hobza’s S22 benchmarks

<table>
<thead>
<tr>
<th>functional</th>
<th>basis set</th>
<th>score</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLYP-D3</td>
<td>def2-QZVP</td>
<td>1</td>
</tr>
<tr>
<td>SVWN</td>
<td>def2-QZVP</td>
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<tr>
<td>OLYP\textsuperscript{36,35,78}</td>
<td>def2-QZVP</td>
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</table>

The top 5, middle 5, and bottom 5 functionals were then subjected to calculations in Gaussian and Orca

**Challenges of Exploring Novel Chemical Space**

Estimated $10^{60}$ pharmacologically relevant small molecules

Discovering new technologies via conventional methods is time intensive – generally 15 to 20 years

Until 2014, 49% of small molecule cancer drugs were natural products and their derivatives

Can we develop a method to more efficiently explore chemical space and identify potential hits?

*Inverse design starts from desired properties and ends in chemical space*

Direct vs inverse design in exploring chemical space

Direct design - Pick a specific compound and synthesize or simulate it

High Throughput Virtual Screening - Somewhat of a hybrid between inverse and direct design
- Starts with an initial set of molecules built on a researchers intuition
- Molecules are then narrowed down by being sorted through a range of filters

Evolution Strategy - A global optimization strategy that involves structured iterative searches

- parameter vectors (“genotypes”) are perturbed (“mutated”) and their objective functional value (“fitness”) is evaluated

**Generative Models** - Attempts to determine a joint probability distribution $p(x,y)$ - the probability of observing both the molecular representation and the desired property

- differs from a discriminative model which tries to determine a conditional probability $p(x|y)$ – the probability of observing properties $y$ given molecule $x$

Types of generative models

Recurrent Neural Network (RNN)
- common starting point
- create sequences incrementally
- Long short-term memory (LSTM) allows RNN to take into account time-dependent patterns

Variational Autoencoders (VAE)
- An encoder maps the molecule as a vector into a lower dimensional space, known as a latent space.
- A molecule is represented as a probability distribution over latent space.
- The VAE uses probability distributions to estimate the latent space.
- A decoder maps the latent space representation back to a molecule.

Variational Autoencoders (VAE)

- an agent gives an output, which is then evaluated and returned to the agent so it can learn from it

Reinforcement Learning (RL)

- A generator must learn how to add smiles characters to maximize some reward (property)

- As these properties can only be evaluated at the end, a Monte-Carlo tree search is generally used

Types of generative models

Recurrent Neural Network (RNN)

Variational Autoencoders (VAE)

Reinforcement Learning (RL)

Generative Adversarial Networks (GANs)

Applying generative models to pharmacologic systems

ORGANIC (Objective-Reinforced Generative Adversarial Network for Inverse-design Chemistry) and RANC (Reinforced Adversarial Neural Computer) both merge GANs and RL to achieve inverse design.

Fed a subset of 15,000 drug-like compounds into the system.

The system is then run through a number ~100 training epochs.

Applying generative models to pharmacologic systems

Selected compounds generated by ORGANIC and RANC

Applying generative models to pharmacologic systems

Comparing the performance of RANC and ORGANIC against the initial data

<table>
<thead>
<tr>
<th></th>
<th>RANC</th>
<th>ORGANIC</th>
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<tbody>
<tr>
<td><strong>avg. length</strong></td>
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<td>23</td>
</tr>
<tr>
<td><strong>valid %</strong></td>
<td>58</td>
<td>87</td>
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<tr>
<td><strong>unique %</strong></td>
<td>48</td>
<td>18</td>
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https://doi.org/10.26434/chemrxiv.5309668.v3
Inverse design forms a powerful platform

- Pharmacologic properties
- Organic photovoltaics
- OLEDs
- Reaction synthesis planning
- Biological redox potentials
- Flow batteries
Chemical Game Theory

Basics of Game Theory

Prisoners Dilemma

Battle of the Sexes

Rock Paper Scissors

Centipede Game

Iterated Prisoners Dilemma

Chemical Game Theory

Game Theory in Computer Science

Game Theory in Biology

Game Theory in Chemistry

Case 1: deciding an optimal dft functional

Case 2: inverse design
Questions?

**Calvin and Hobbes** by Bill Watterson

**WALLY:** These peer reviews are like the famous "Prisoner's Dilemma."

**IF YOU RAT ON ME BUT**: I say good things about you, you get the biggest raise. But if we praise each other we can both get a small raise.

**WALLY:** If you rat him out, I'll let you look at my "Victoria's Secret" catalog. This is exactly why there are no coed prisons.

**Calvin:** Today at recess, I tried to figure whether to cut or not.

**Hobbes:** And the same brand of misunderstanding produces the same result. No satisfaction ever. Of course, most overcoats aren't made from the same cloth or even the same dye lot.

**Calvin:** I wondered if I could just rationalize my unwillingness to accept the consequences of not starting.

**Hobbes:** People came around success not predecessors.

**Calvin:** You think I could? Nothing. I am not out of line and I was just thinking about a shave.

**Hobbes:** In the real world, rumors can kill as much as success. And I think you've had a rough week. I just a haircut.

**Calvin:** Nothing. I was just trying to figure out what to do with my boss.

**Hobbes:** Now, if only people weren't so quick to judge on an initial reaction.