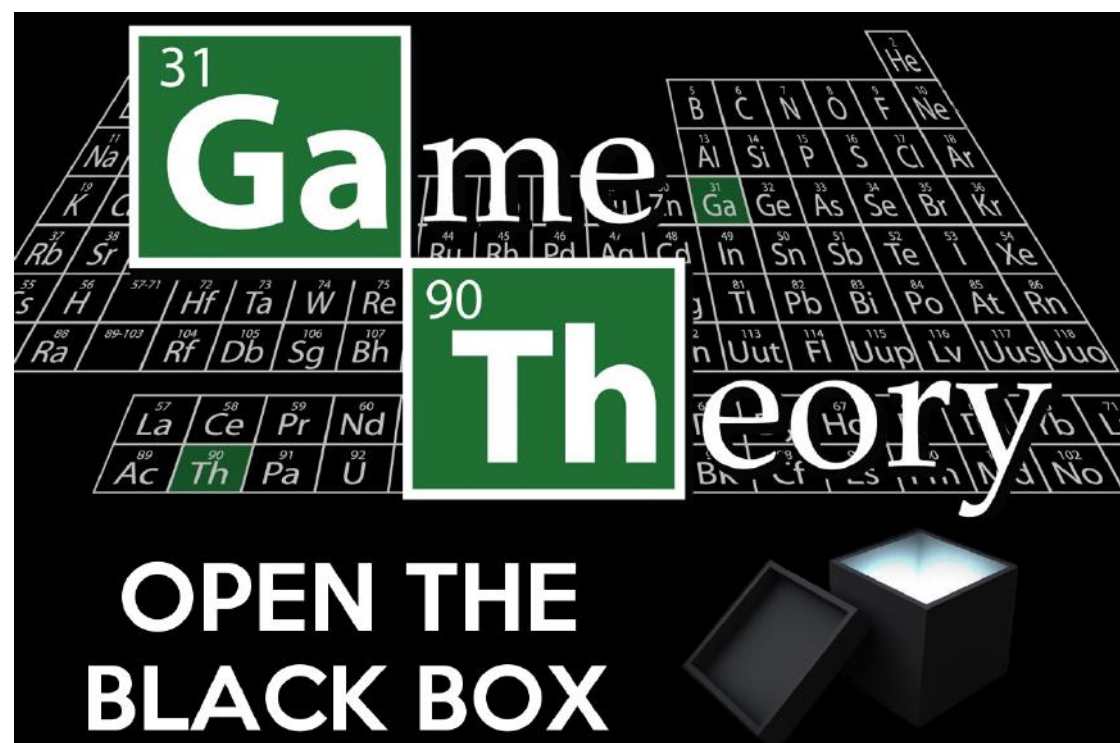


# *Chemical Game Theory*



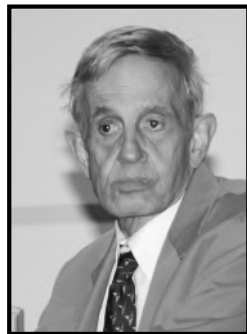
*Jacob Kautzky  
Group Meeting  
February 26<sup>th</sup>, 2020*

## *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?*

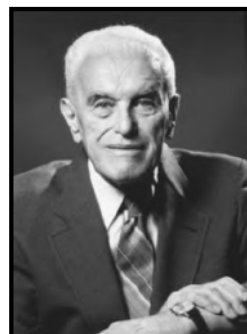
**11 nobel prizes in economics**



John Nash



Reinhard Selten



John Harsanyi

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

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

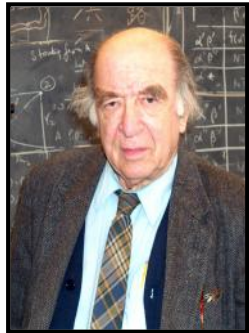


Robert Aumann



Thomas Schelling

# *Why do we care about game theory?*



Leonid Hurwicz



Eric Maskin



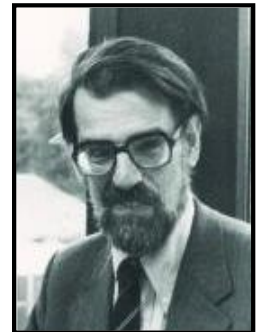
Roger Myerson

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

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



Alvin Roth



Lloyd Shapley

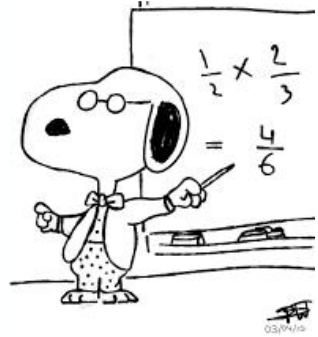


Jean Tirole

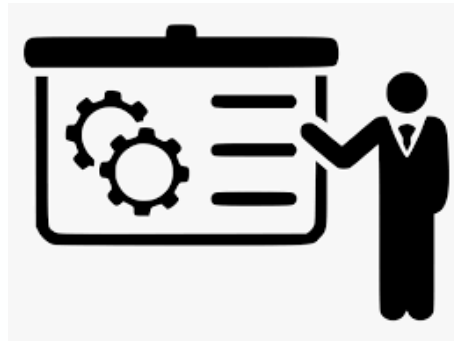
*2014 – “for his analysis of market power and regulation”*

# *Why do we care about game theory?*

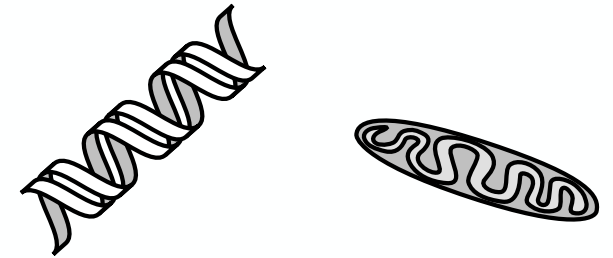
## Mathematics



## Business



## Biology



## Engineering



## Sociology



## Philosophy



## Computer Science



## Political Science



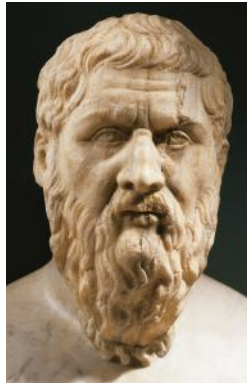
## Chemistry





# Why do we care about game theory?

## Plato, 5th Century BCE



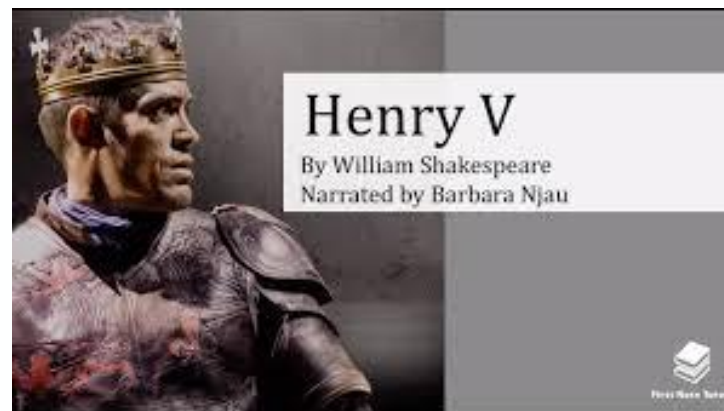
- Initial insights into game theory can be seen in Plato's work
- Theories on prisoner desertions

## 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**

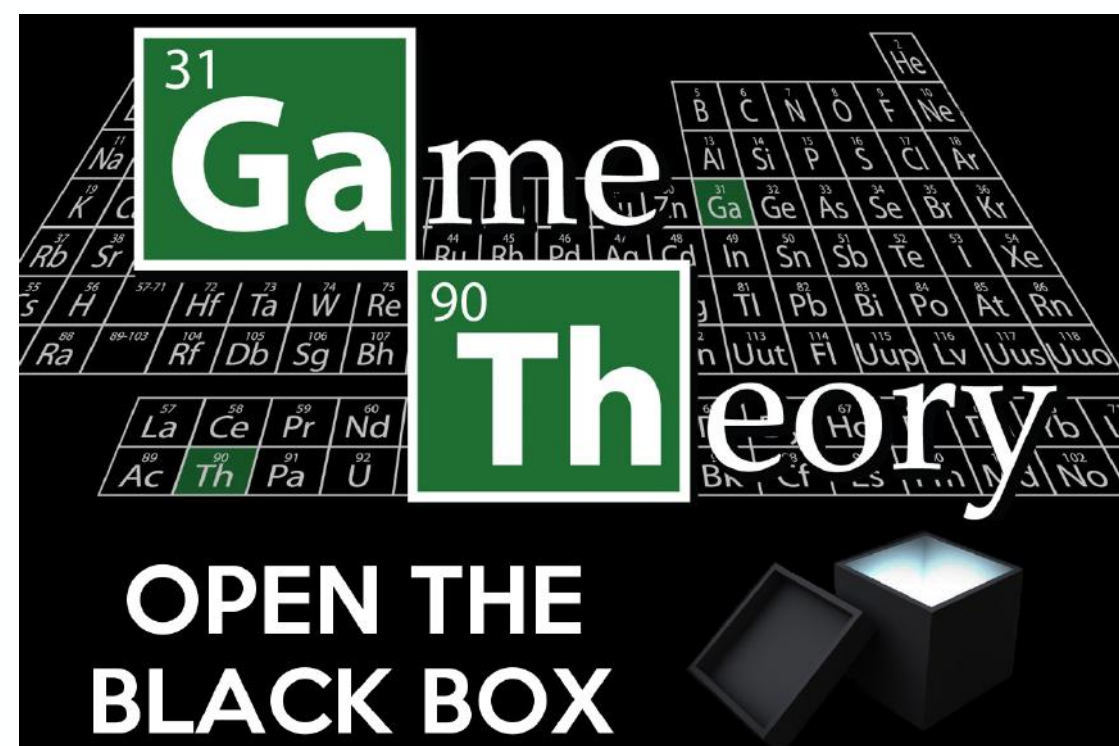
**Game Theory in Computer Science**

**Game Theory in Biology**

**Game Theory in Chemistry**

Case 1: deciding an optimal dft functional

Case 2: inverse design



## *Game theory basics*

**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

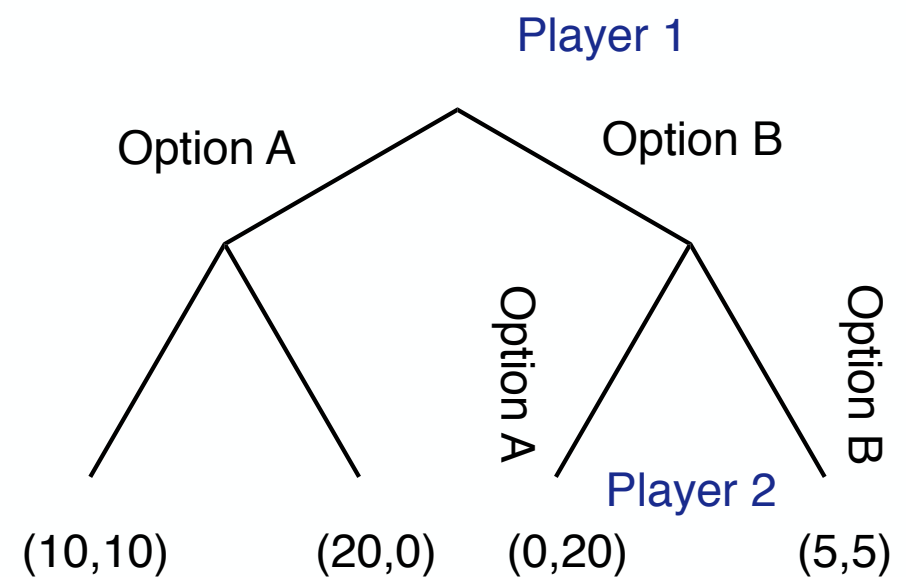
- players take their turns at the same time
- visualized as a matrix

	Option A	Option B
Option A	(10,10)	(0,20)
Option B	(20,0)	(5,5)

payoffs for both players listed in each box

## 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 noncooperative, perfect information, and perfectly rational*

## The prisoner's dilemma



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

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

	Prisoner B tells	Prisoner B stays silent
Prisoner A tells	(10,10)	(0,20)
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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



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



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Prisoner A tells

Prisoner A stays silent

Prisoner B tells

Prisoner B stays silent

Prisoner B tells	Prisoner B stays silent
(10,10)	(0,20)
(20,0)	(5,5)

***Telling is a dominant strategy for player A***

**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

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### 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



Partner A

Watch Football

Get a  
manicure

Go to a movie

Partner B

Watch Football

Get a  
manicure

Go to a movie

	Watch Football	Get a manicure	Go to a movie
Watch Football	(20,10)	(7,7)	(7,5)
Get a manicure	(0,0)	(5,20)	(0,5)
Go to a movie	(5,0)	(5, 7)	(20,20)

# Battle of the sexes

*There can be multiple Nash Equilibria*



**Partner A**

Watch Football

Get a  
manicure

Go to a movie

**Partner B**

Watch Football

Get a  
manicure

Go to a movie

	Watch Football	Get a manicure	Go to a movie
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Go to a movie	(5,0)	(5, 7)	(20,20)

# Battle of the sexes

*There can be multiple Nash Equilibria*



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Get a manicure	(0,0)	(5,20)	(0,5)
Go to a movie	(5,0)	(5, 7)	(20,20)

**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

Player 2

Rock  
  
Paper  
  
Scissors

	Rock	Paper	Scissors
Rock	(0,0)	(-1,1)	(1,-1)
Paper	(1,-1)	(0,0)	(-1,1)
Scissors	(-1,1)	(1, -1)	(0,0)

# Rock paper scissors



Player 1

Player 2

	Rock	Paper	Scissors
Rock	(0,0)	(-1,1)	(1,-1)
Paper	(1,-1)	(0,0)	(-1,1)
Scissors	(-1,1)	(1,-1)	(0,0)

The table includes curved arrows indicating the cyclical nature of the game: Rock beats Scissors, Scissors beats Paper, and Paper beats Rock. The cells (1,-1) for (Paper, Rock) and (Rock, Paper) are highlighted with a light purple circle. The cell (-1,1) for (Paper, Scissors) is highlighted with a light red circle. The entire Scissors row is highlighted with a light blue background.

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

**Mixed Strategy** - a player chooses multiple options with differing probabilities



# Rock paper scissors



Player 1

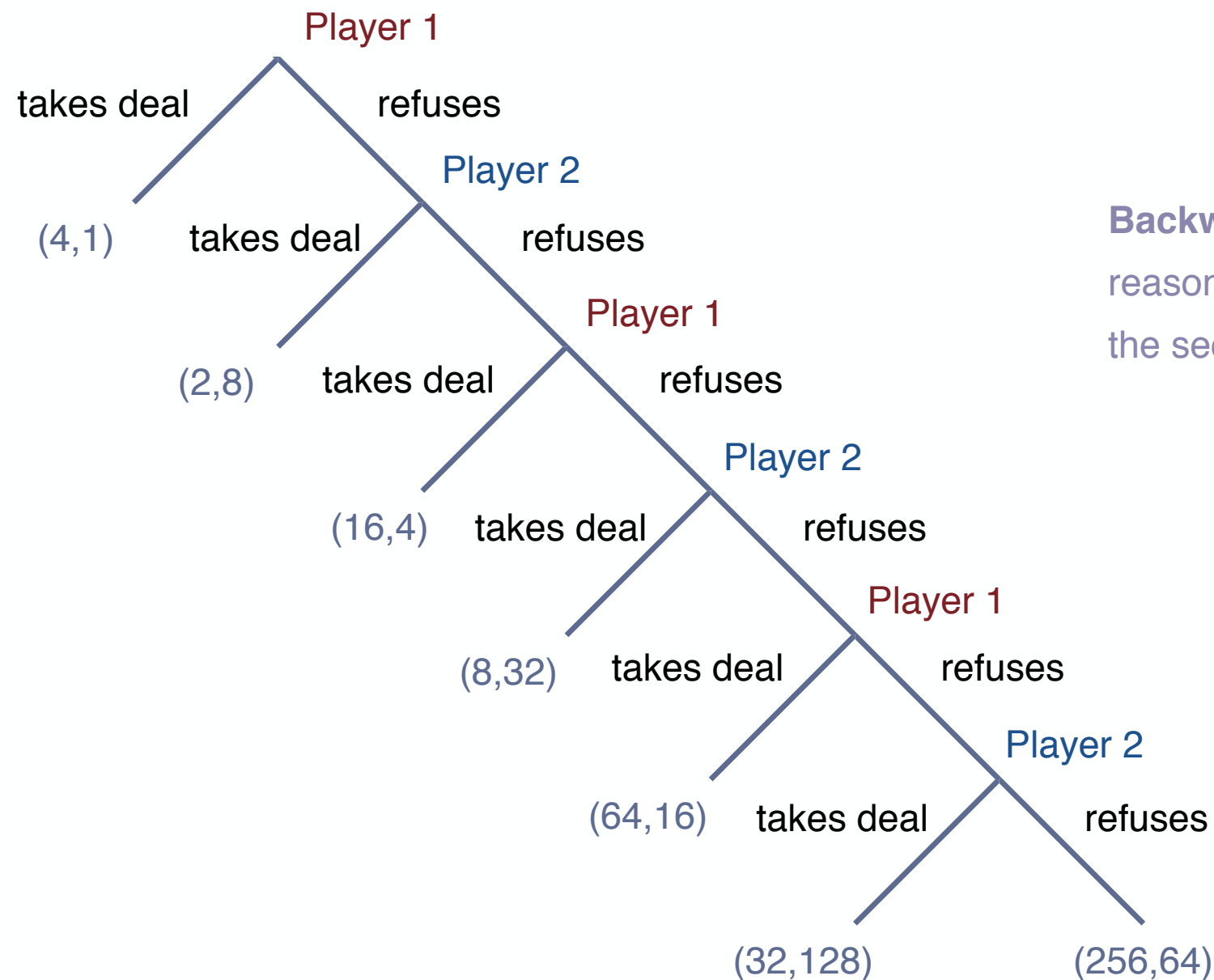
Player 2

		Rock	Paper	Scissors
		1/3	1/3	1/3
Player 1	Rock	(0,0)	(-1,1)	(1,-1)
	Paper	(1,-1)	(0,0)	(-1,1)
	Scissors	(-1,1)	(1, -1)	(0,0)

Player 1's Expected Utility :  $\frac{1}{9} * 0 + \frac{1}{9} * -1 + \frac{1}{9} * 1 + \frac{1}{9} * 1 + \frac{1}{9} * 0 + \frac{1}{9} * -1 + \frac{1}{9} * -1 + \frac{1}{9} * 1 + \frac{1}{9} * 0 = 0$

## *Nash equilibria in sequential games*

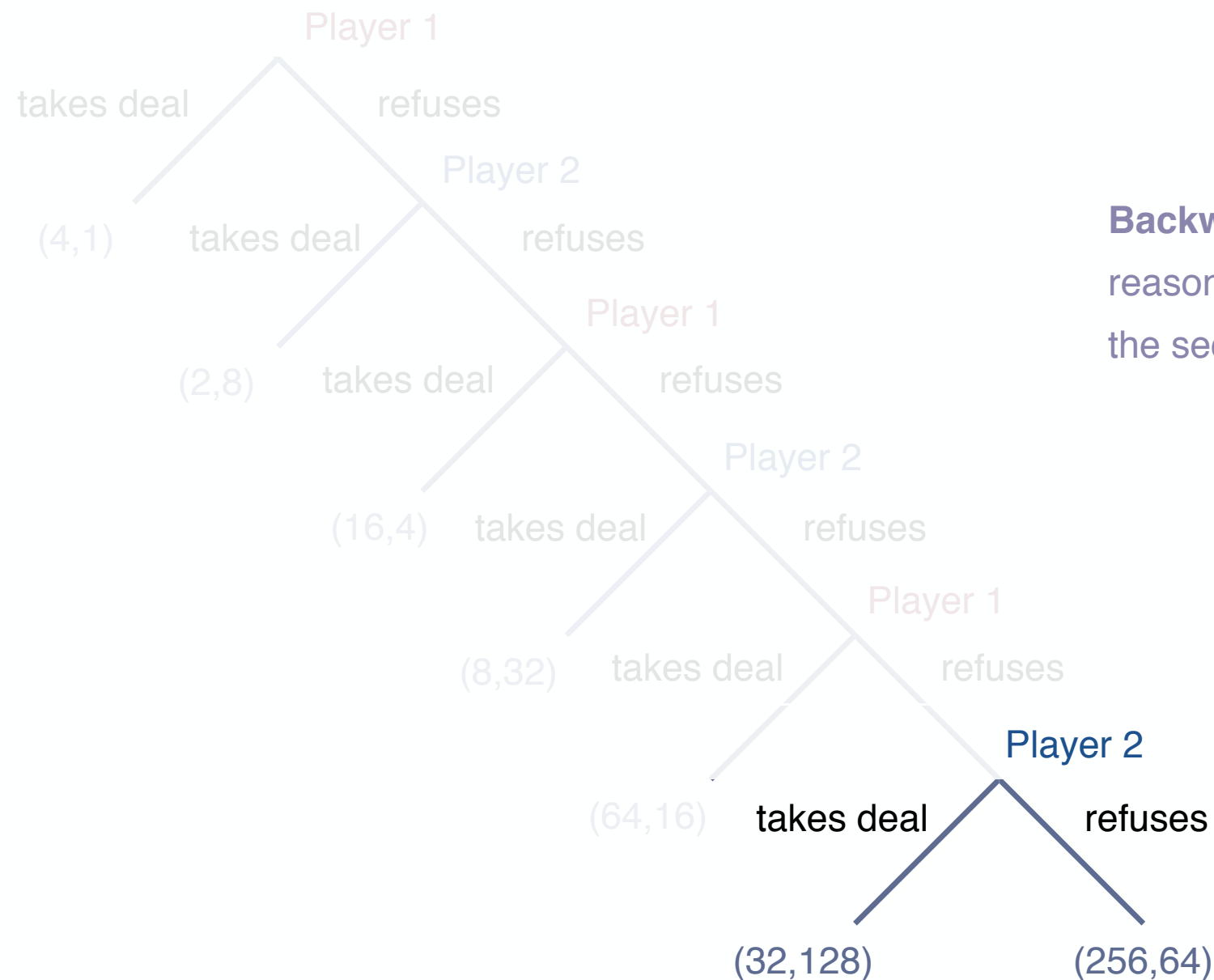
The Centipede Game – A game played by two players where starting with \$5 each player can either accept the deal and get 4/5 of the pot or pass the deal at which point the money in the pot doubles and the same offer is made to the other player until the pot reaches a grand total of \$320 dollars



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

## *Nash equilibria in sequential games*

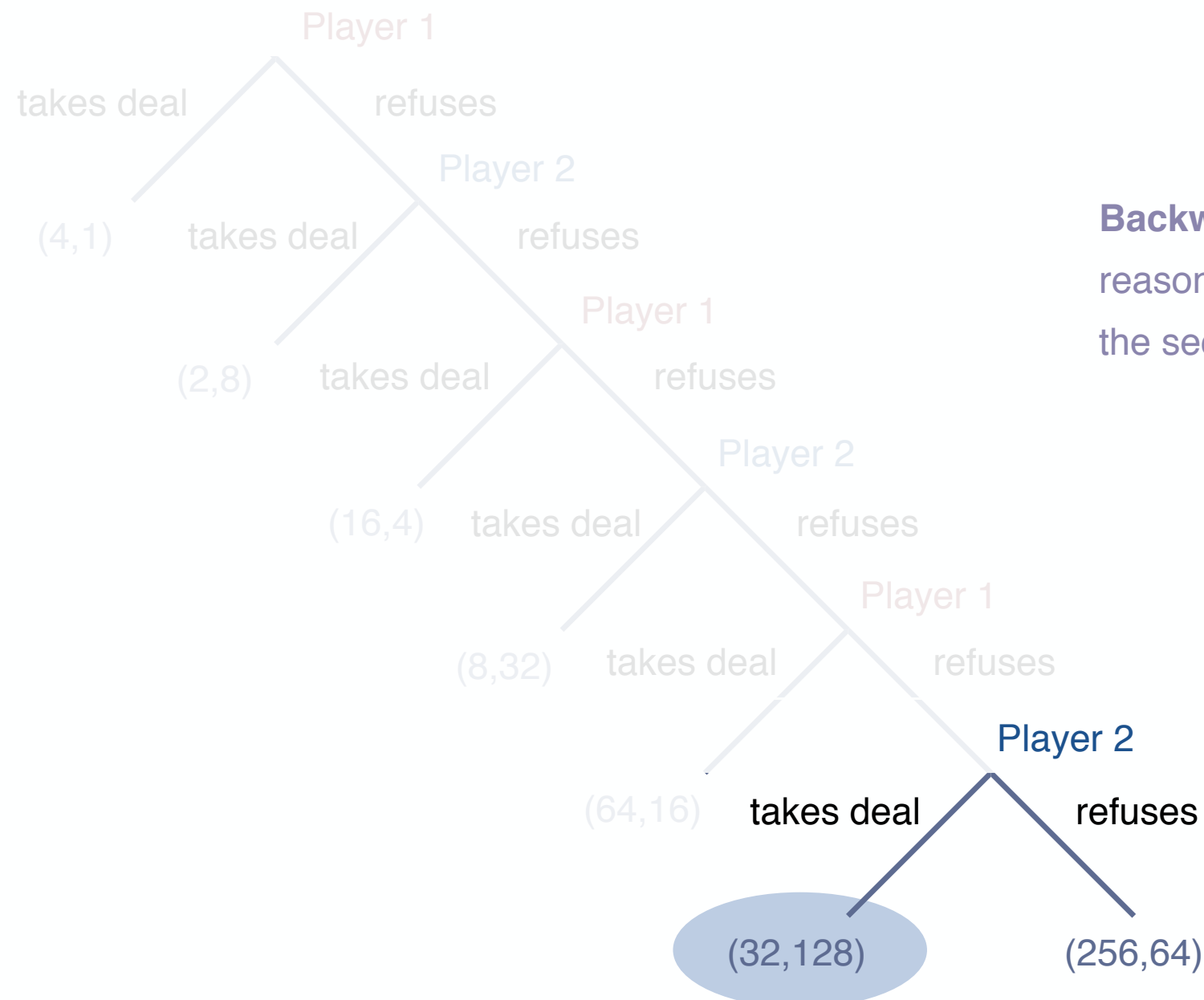
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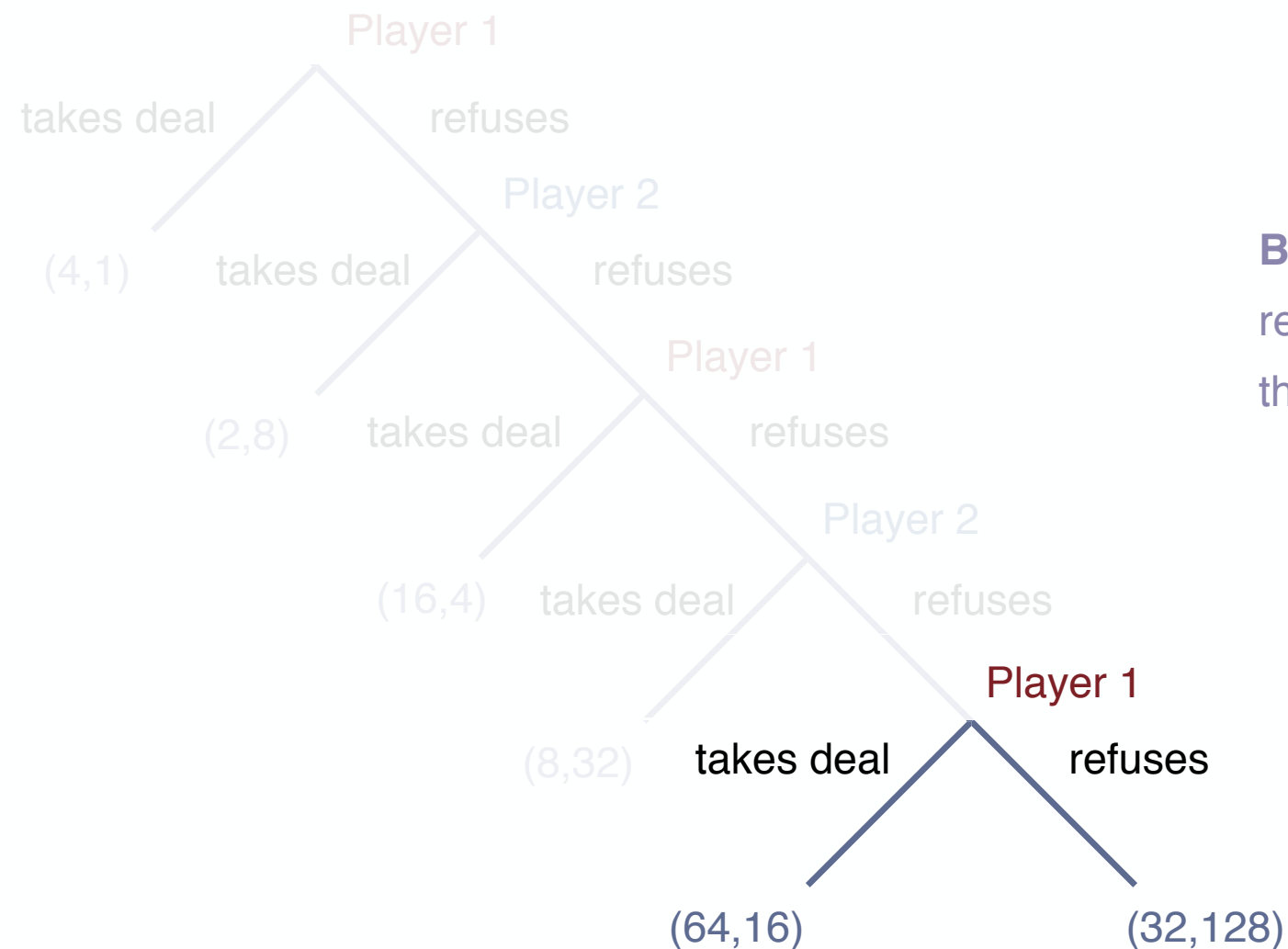
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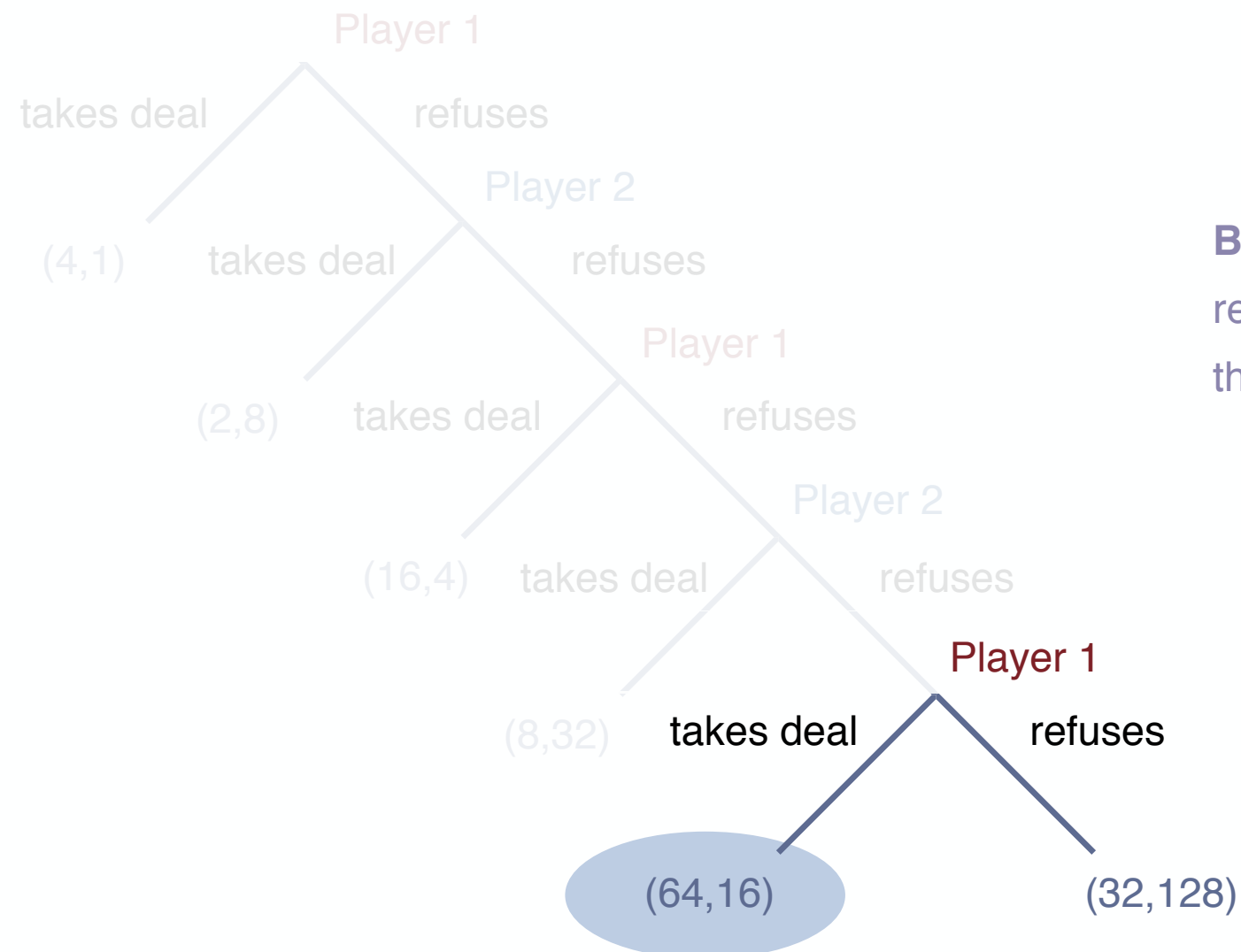
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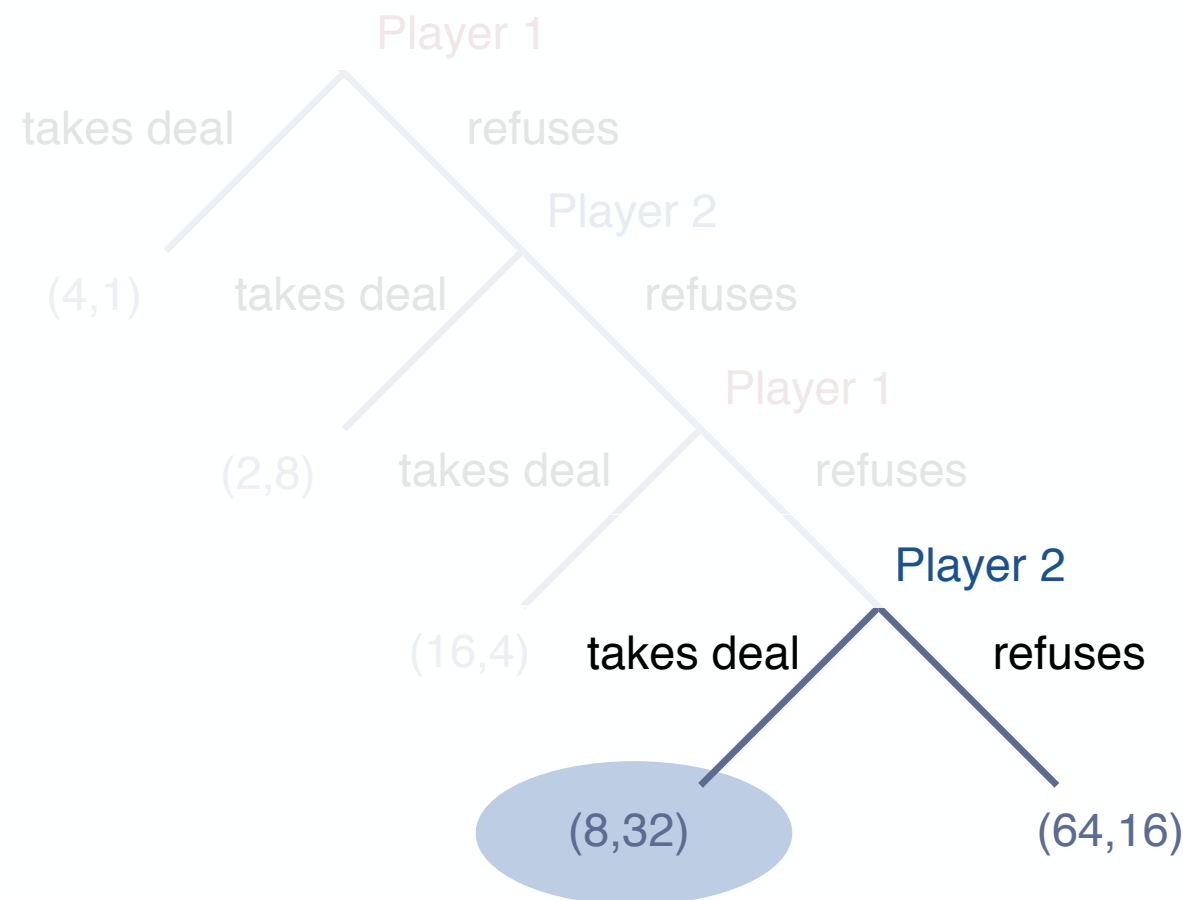


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## *Nash equilibria in sequential games*

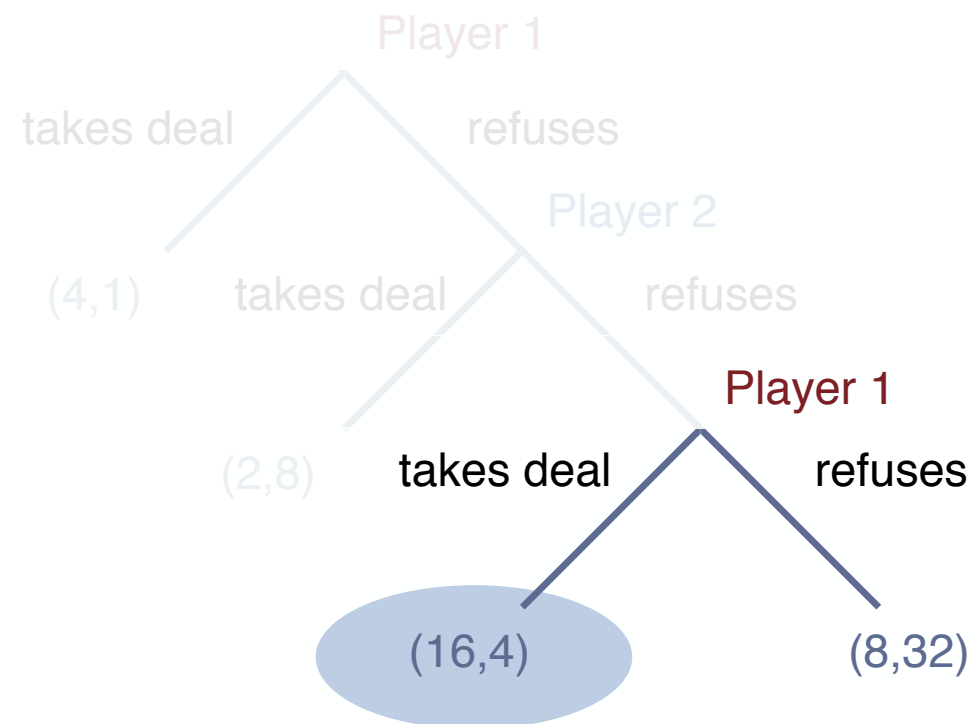
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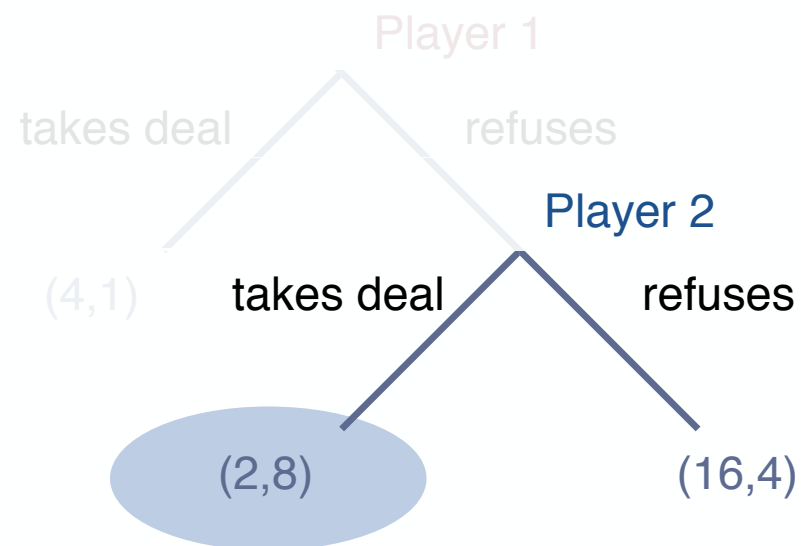
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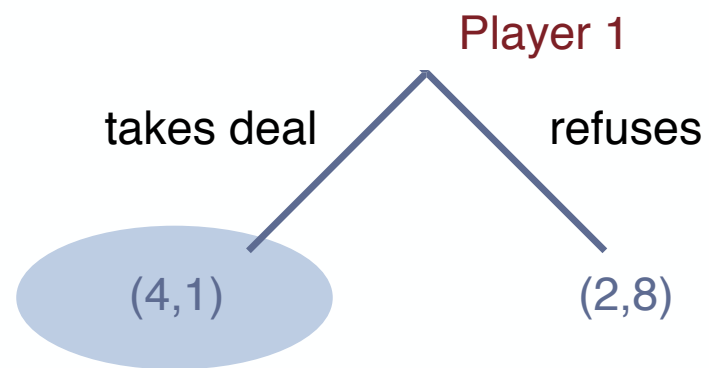
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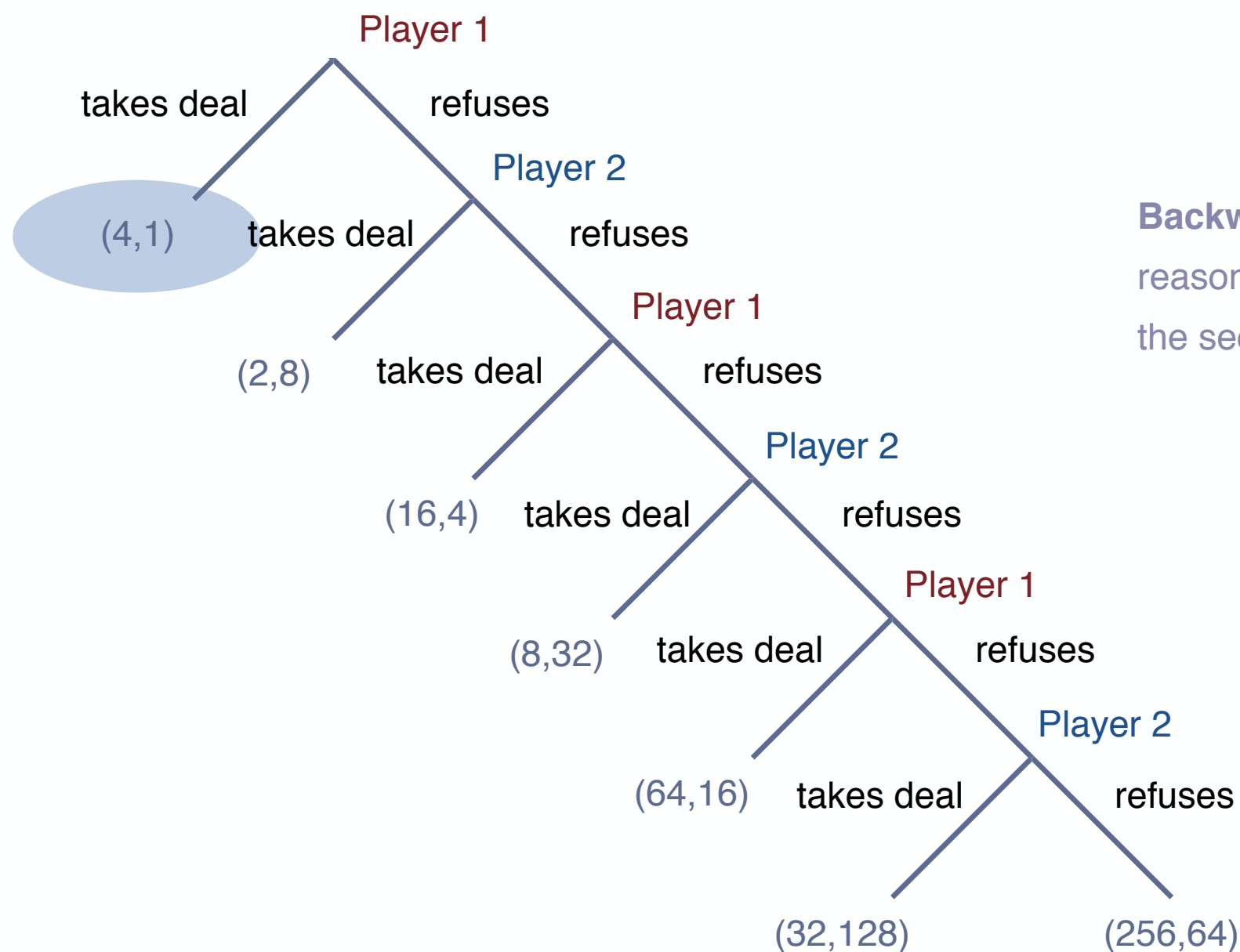
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## Nash equilibria in sequential games

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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*

	Prisoner B tells	Prisoner B stays silent
Prisoner A tells	(10,10)	(0,20)
Prisoner A stays silent	(20,0)	(5,5)

- 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 immitates their opponents move thereafter

⋮

and a range of others as well

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**Tit for Tat** – cooperates on the first round and immitates 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

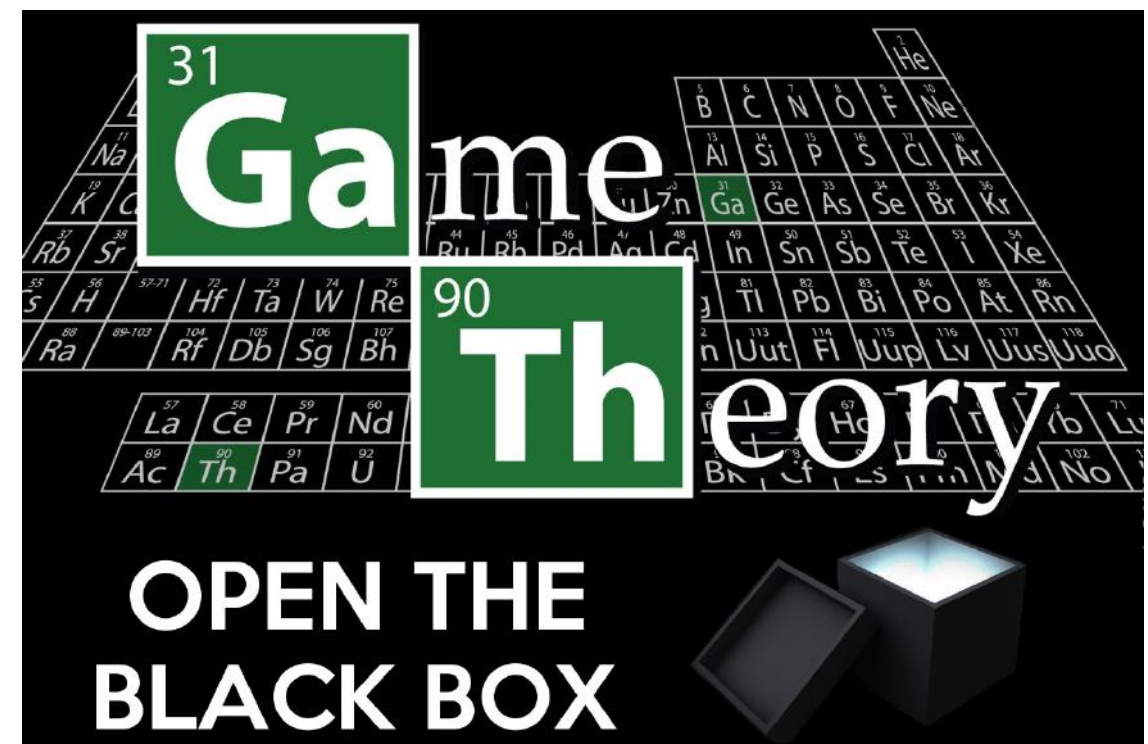
## Game Theory in Computer Science

## Game Theory in Biology

## Game Theory in Chemistry

Case 1: deciding an optimal dft functional

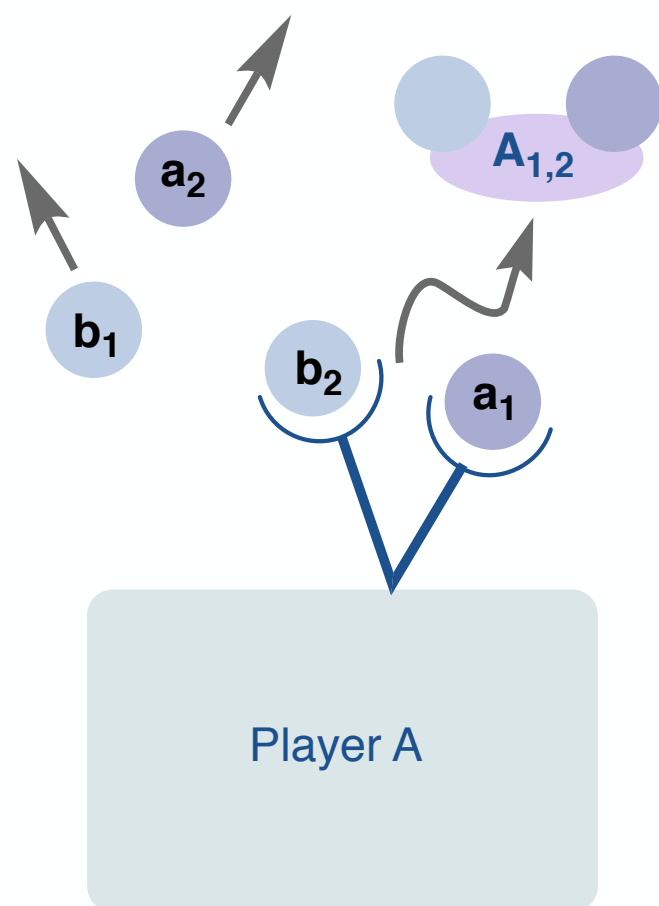
Case 2: inverse design





# 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**”*

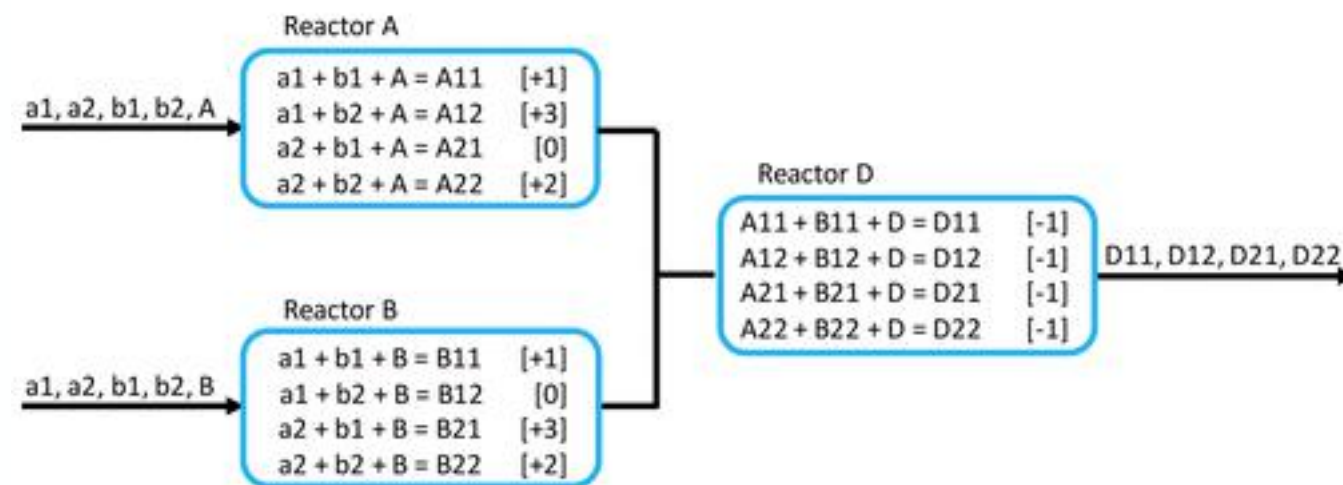
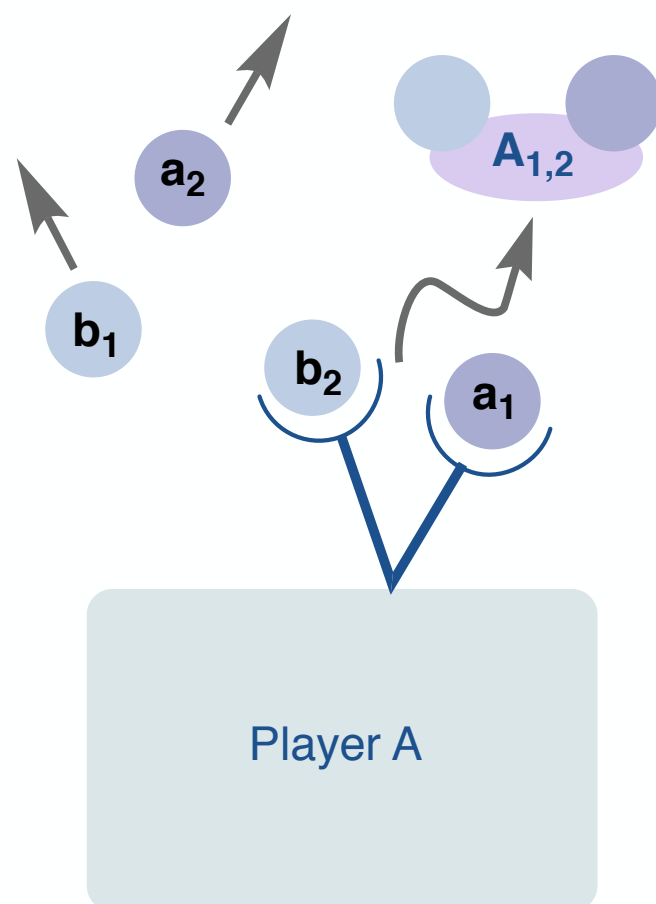
*CGT is concerned with **decision reactions** between the players and their choices form decisions*

*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*

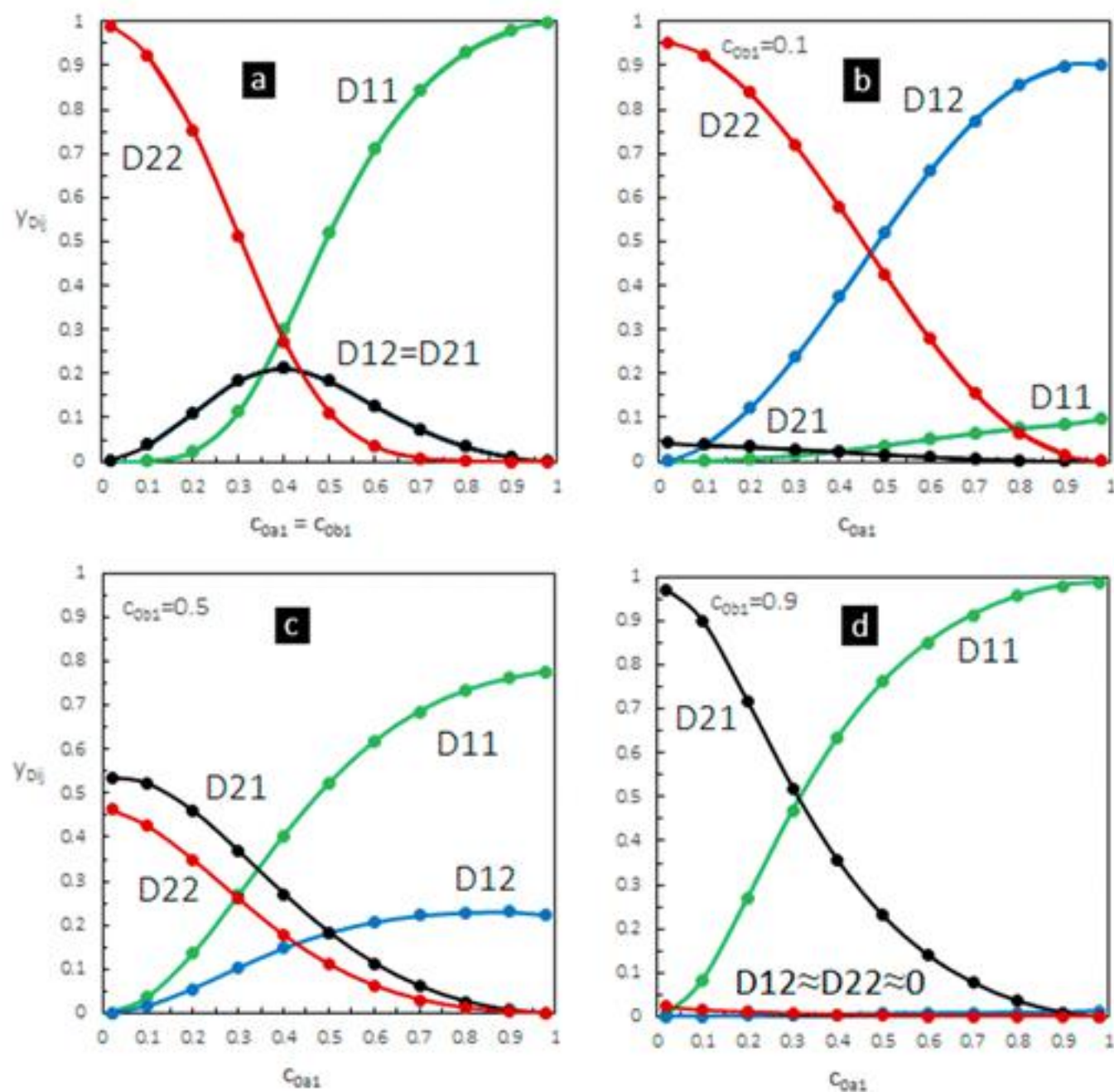
# Chemical Game Theory (CGT) applied to the prisoners dilemma



*Treat each player as a reactor as well as a reactor for the decider*

	$b_1 = \text{quiet} \quad b_2 = \text{tell}$	
$a_1 = \text{quiet}$	(1,1)	(3,0)
$a_2 = \text{tell}$	(0,3)	(2,2)

## 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*

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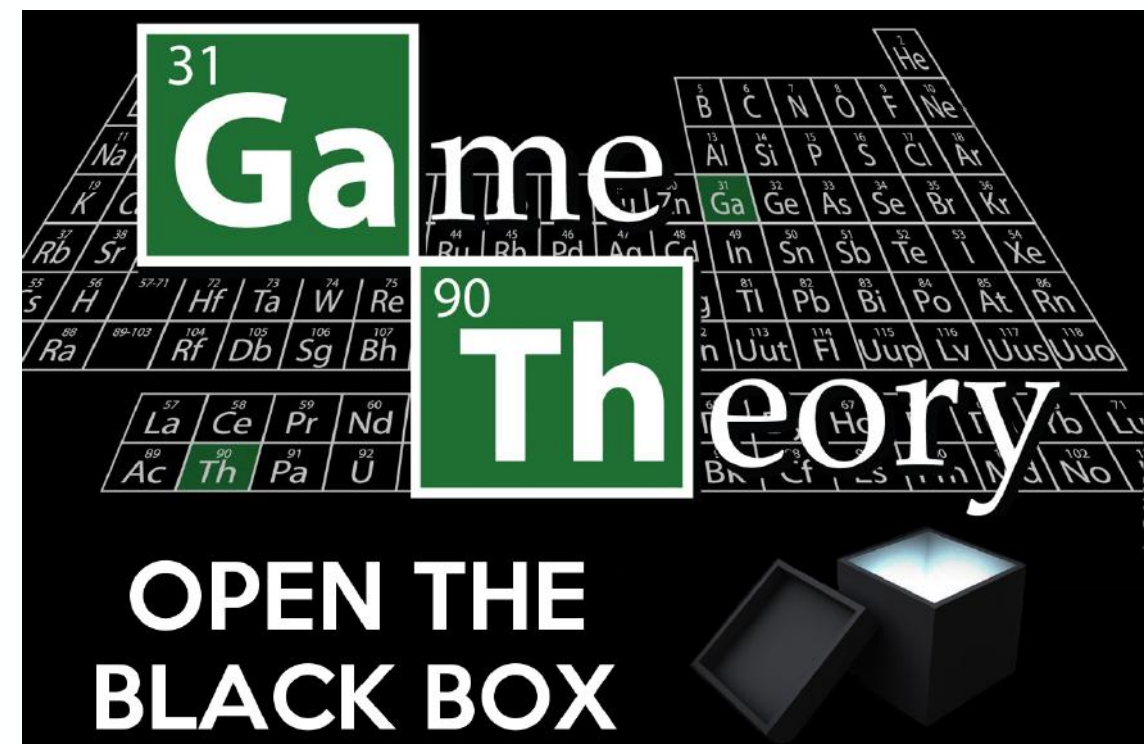
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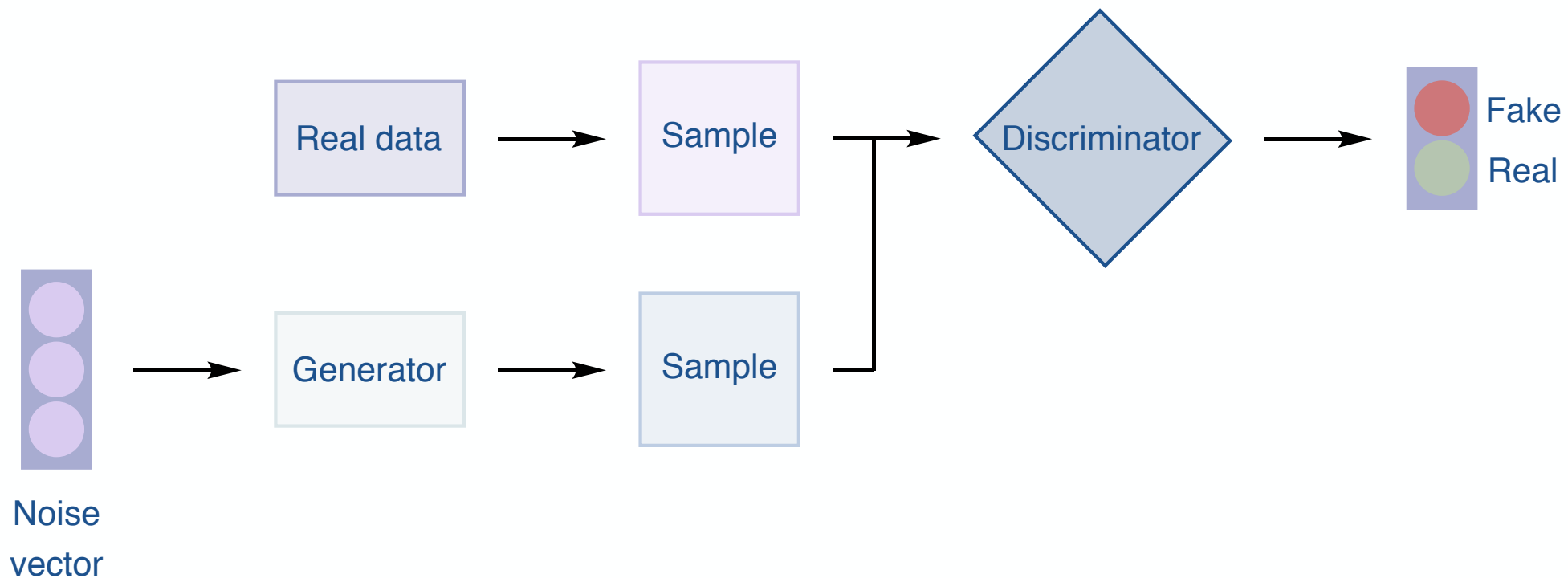
Case 1: deciding an optimal dft functional

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



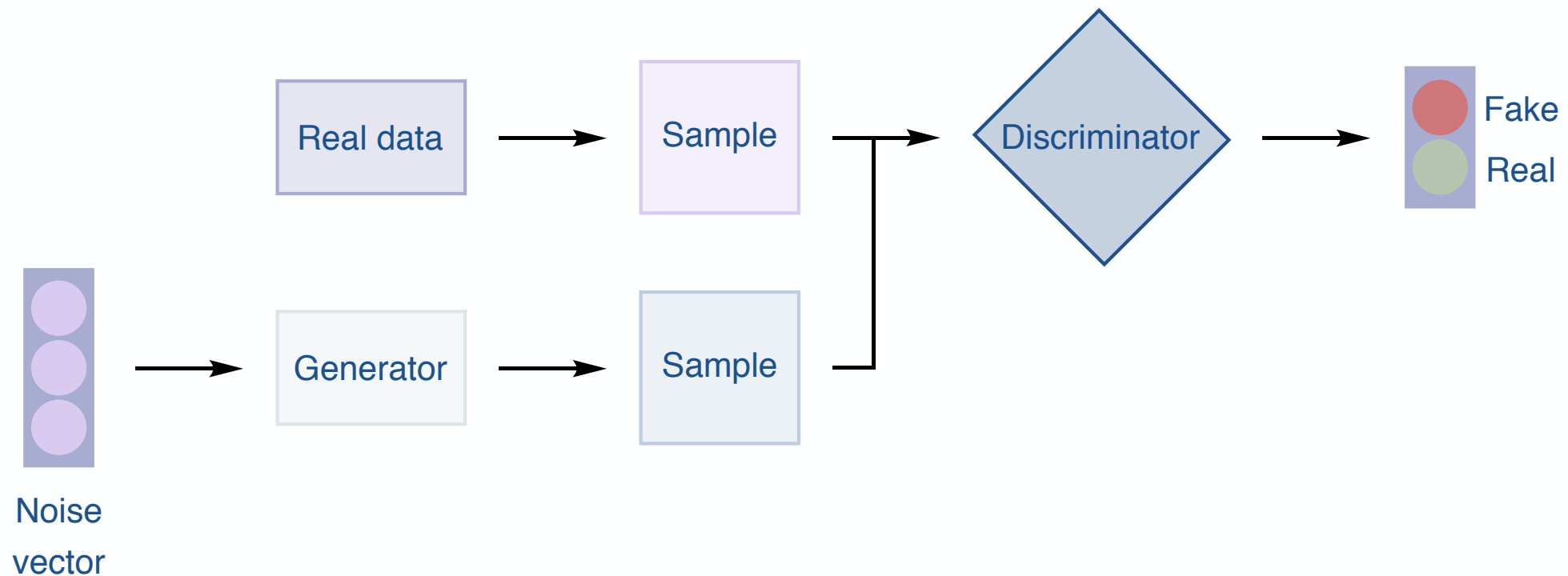


# General Adversarial Networks (GANs)

Viewed as a form of inverse game theory

Inverse game theory aims to design a game based on a players 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

TECH / ARTIFICIAL INTELLIGENCE / CULTURE

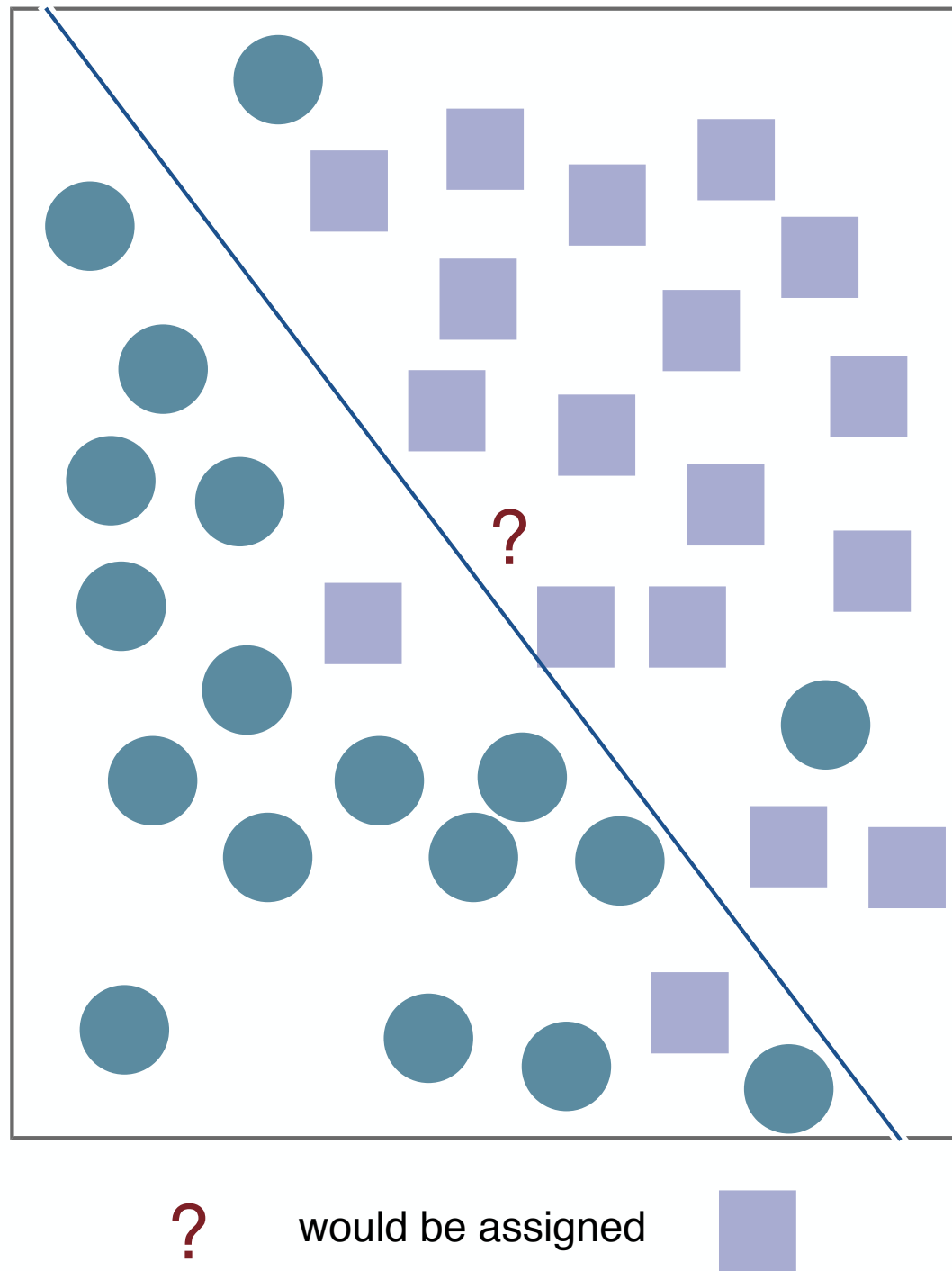
## Christie's sells its first AI portrait for \$432,500, beating estimates of \$10,000

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

By James Vincent | Oct 25, 2018, 1:03pm EDT

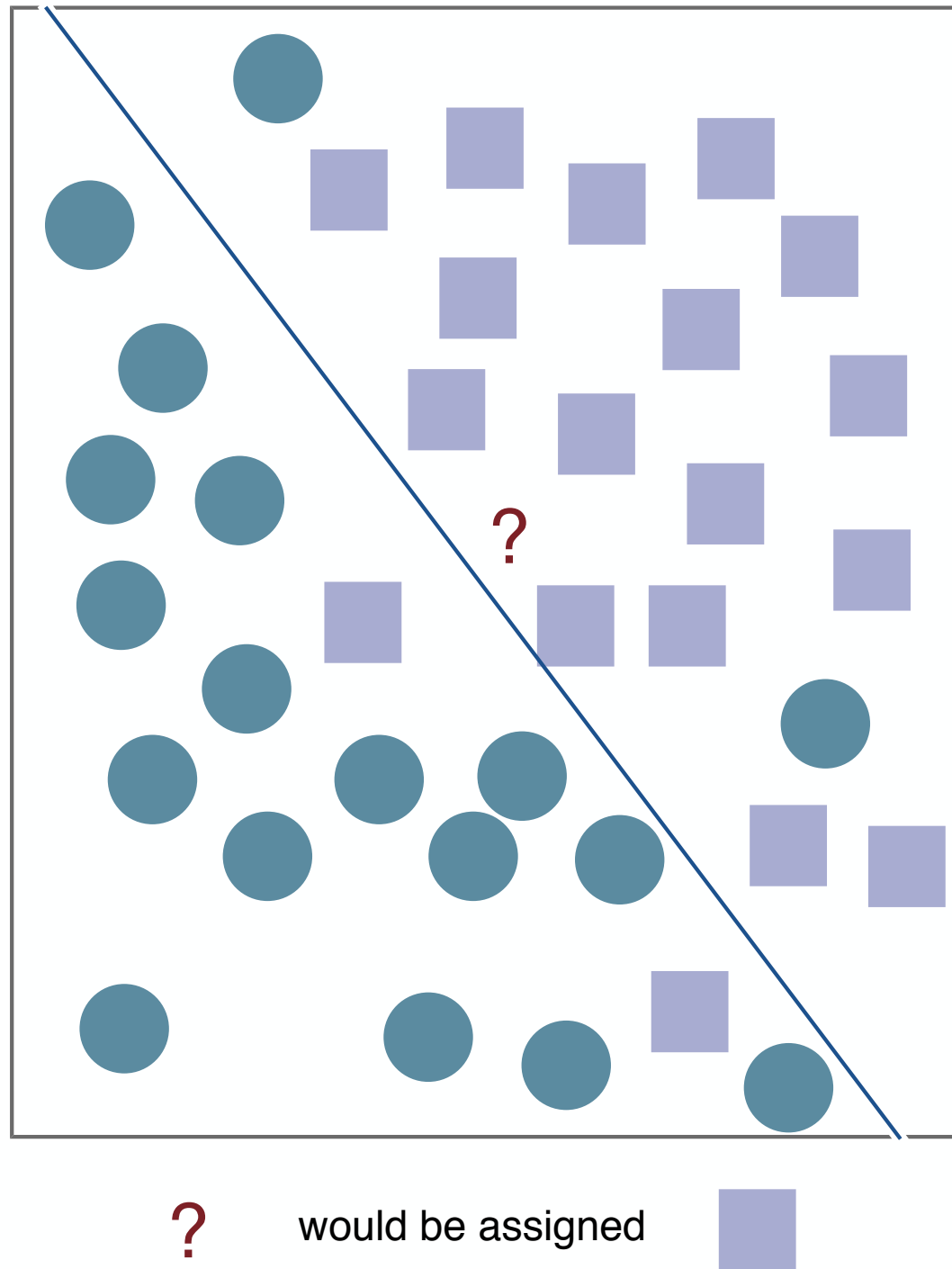


# Support Vector Machines (SVM)



- 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*

## Basics of Game Theory

Prisoners Dilemma

Battle of the Sexes

Rock Paper Scissors

Centipede Game

Iterated Prisoners Dilemma

## Chemical Game Theory

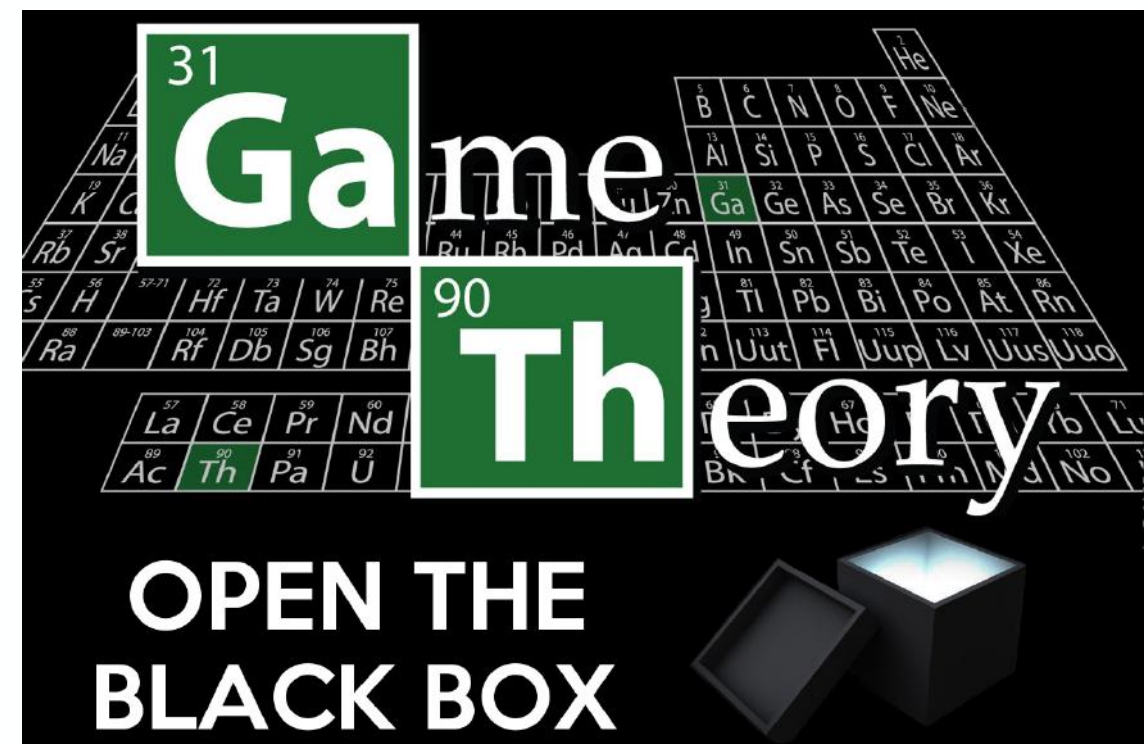
## Game Theory in Computer Science

## Game Theory in Biology

## Game Theory in Chemistry

Case 1: deciding an optimal dft functional

Case 2: inverse design



## 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**

	Dove	Hawk
Dove	$(V/2, V/2)$	$(0, V)$
Hawk	$(V, 0)$	$((V-C)/2, (V-C)/2)$

$V$  = Resources       $C$  = 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

## Can get into significantly more complicated scenarios

*iterated prisoners dilemma explains altrism*



	Screams	No scream
Screams	$(-1, -1)$	$(-1, 0)$
No scream	$(0, -1)$	$(-10, -10)$

**3 species can get into rock-paper-scissors types scenarios**



*Uta stansburiana* Lizard

**Coevolution**



newt and garter snake

- 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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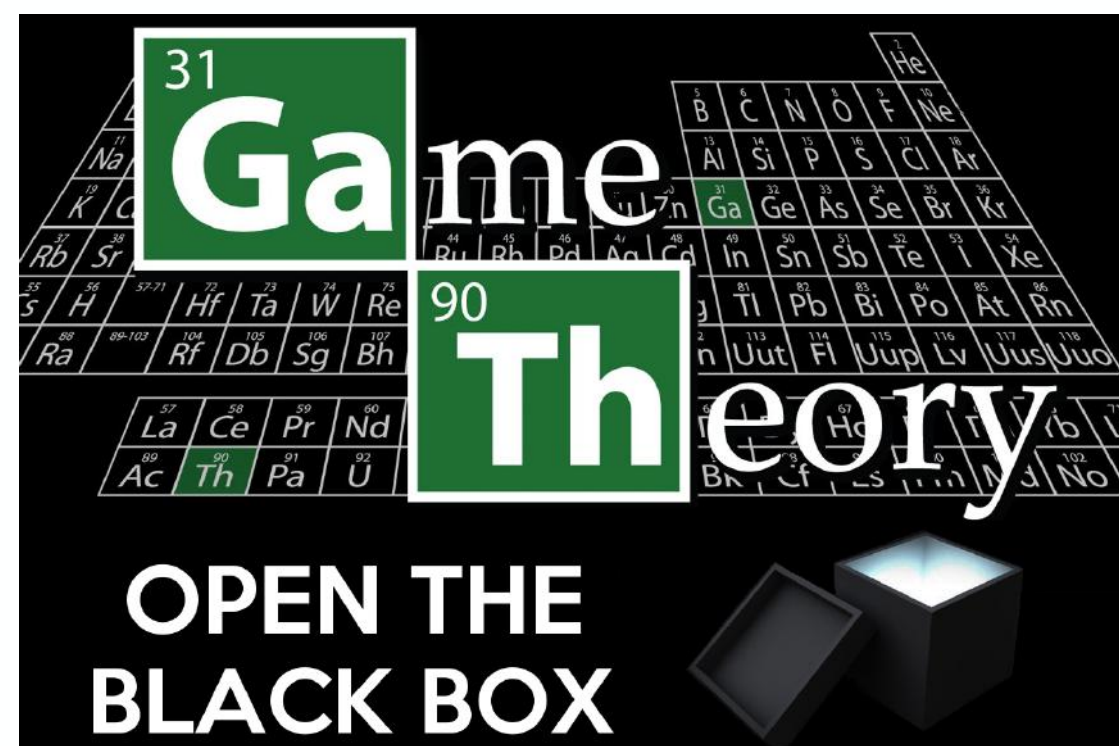
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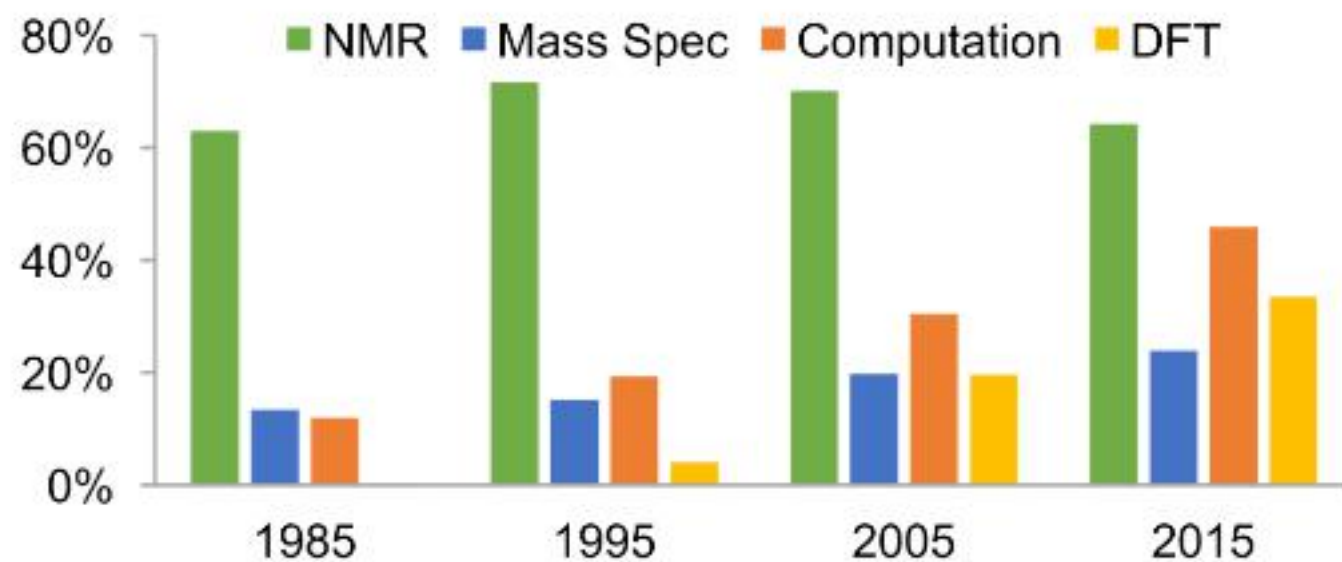


## Selecting a proper dft functional

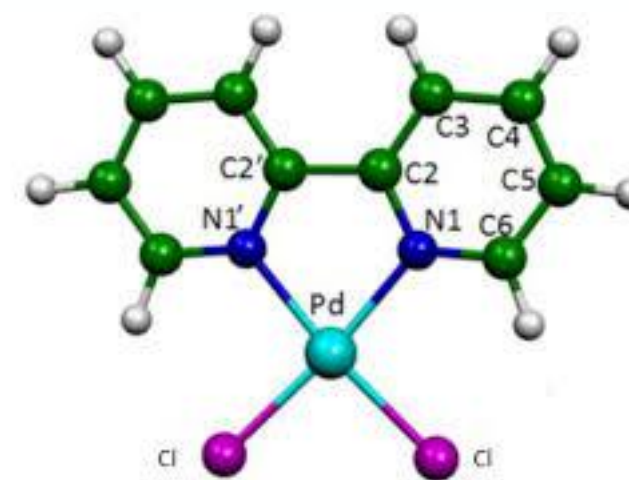
*There are hundreds if not thousands of functionals with new types being customized for specialized problem types*

*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*



percentage of ACS publications using the given tool



## *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*

3 players

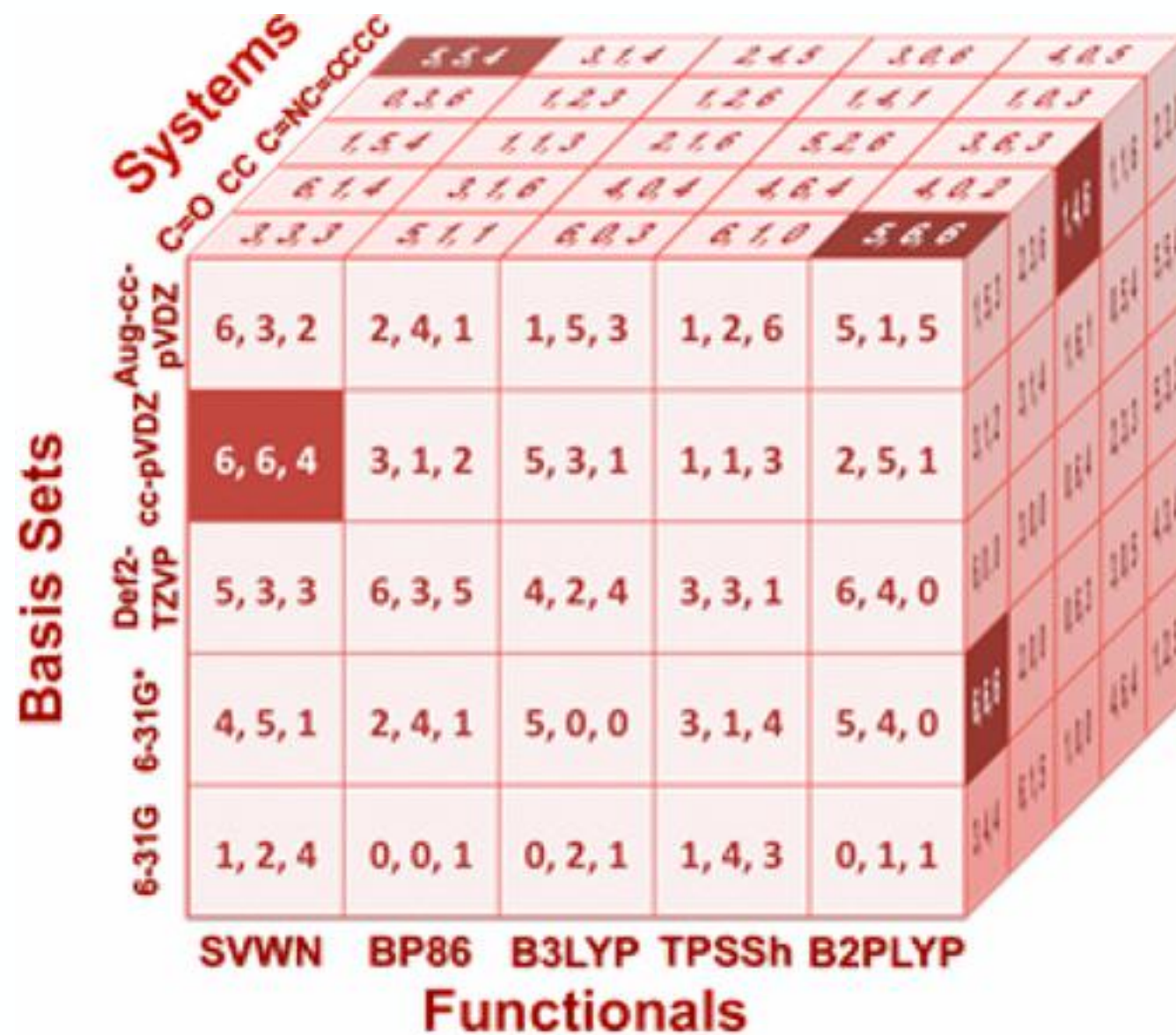
**Accuracy** – the performance of a basis set and functional relative to a reference set (mean absolute percent deviation or MAPD)

**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



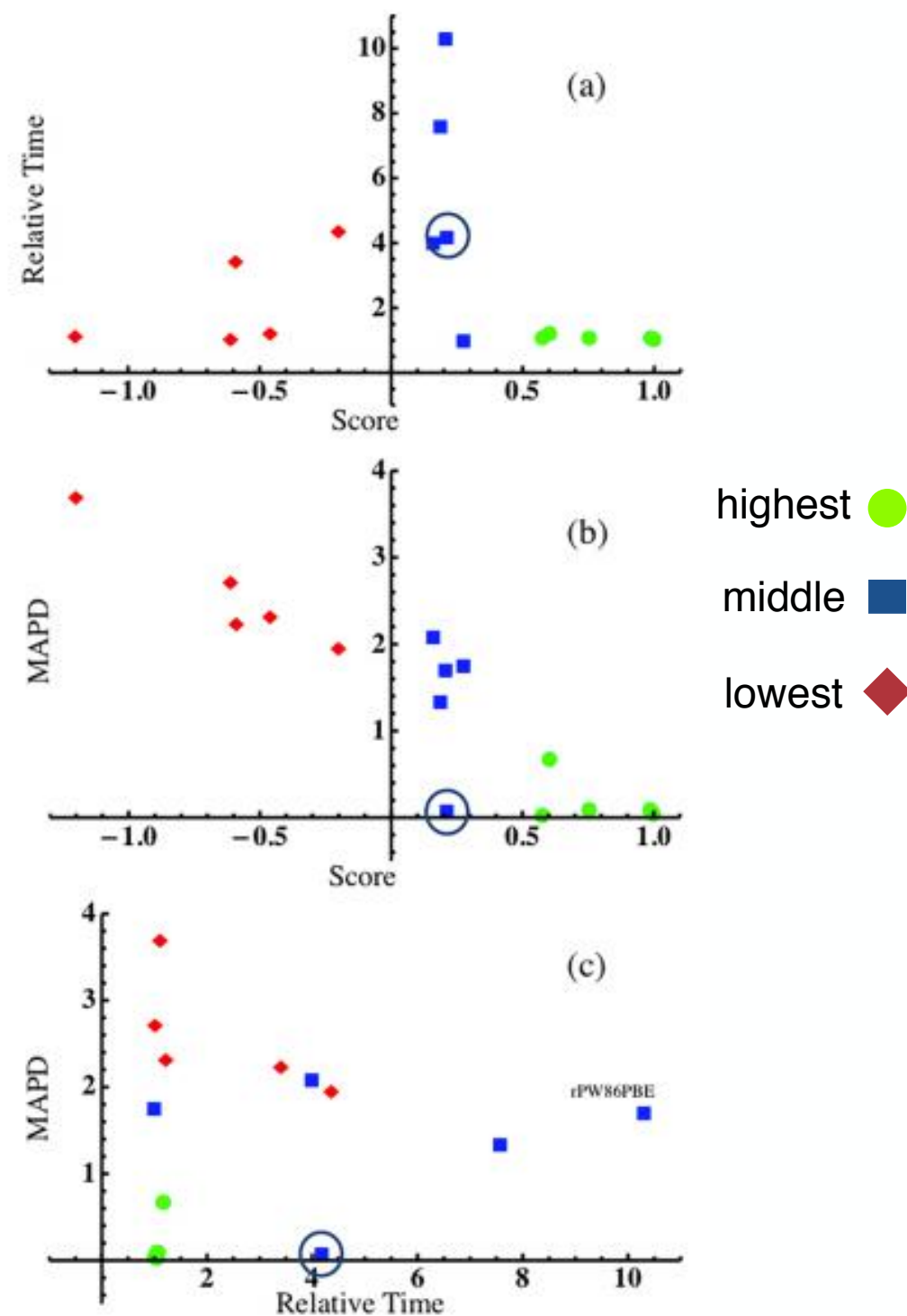
Created a 3-D matrix and then searched for Nash equilibria

## Decider in action

Tested the developed system on  
Hobza's S22 benchmarks

functional	basis set	score <sup>a</sup>
BLYP-D3	def2-QZVP	1
SVWN	def2-QZVP	0.988
PBE-D3	def2-QZVP	0.755
OPBE-D3	def2-QZVP	0.604
TPSS-D3	def2-QZVP	0.577
●		
●		
●		
mPWLYP <sup>34,35,75</sup>	def2-QZVP	-0.2
BP86	def2-QZVP	-0.46
B97 <sup>76,77</sup>	def2-QZVP	-0.59
BLYP	def2-QZVP	-0.61
OLYP <sup>34,35,78</sup>	def2-QZVP	-1.2

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**

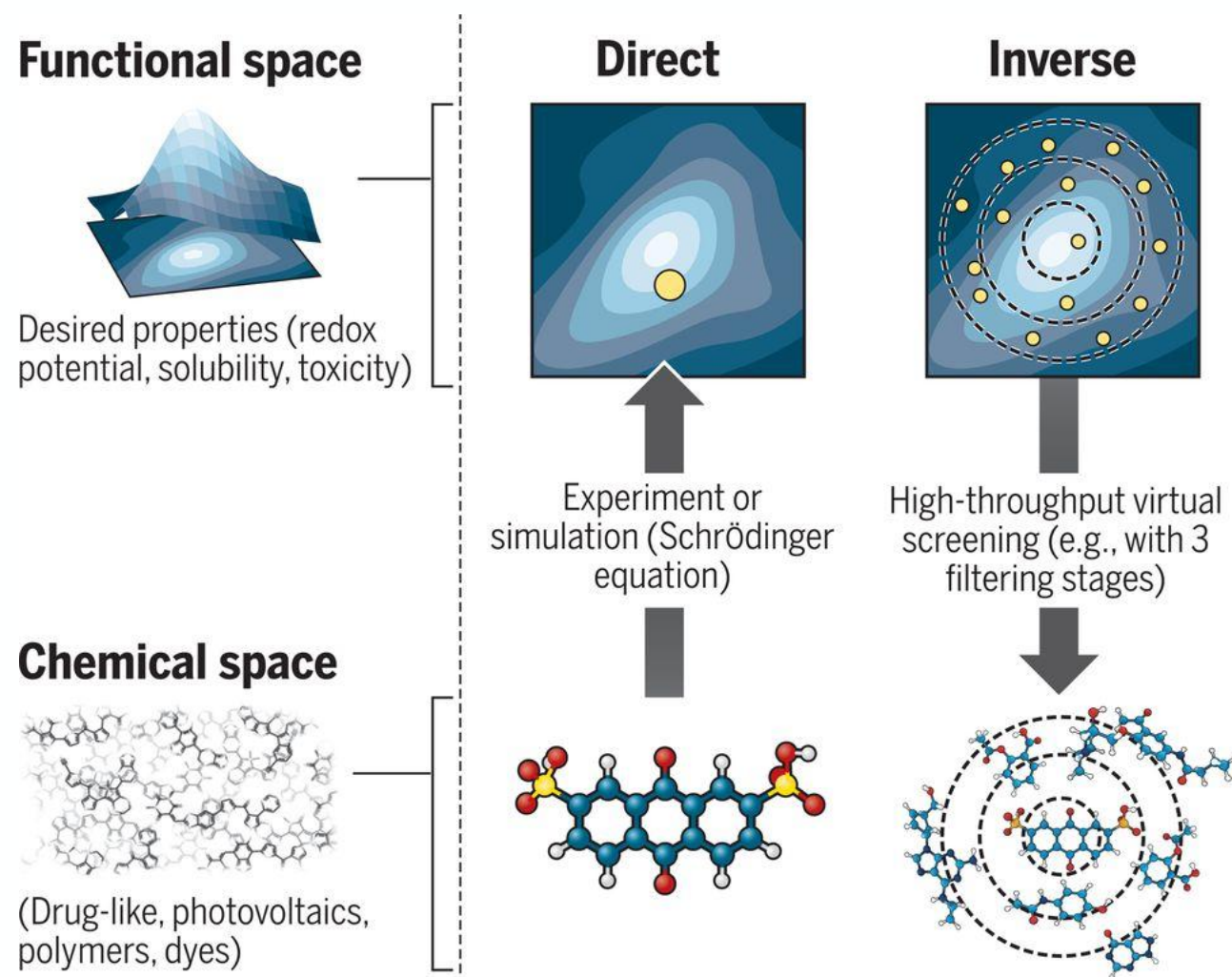
**Discovering new technologies via conventional methods is time intensive – generally 15 to 20 years**

**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



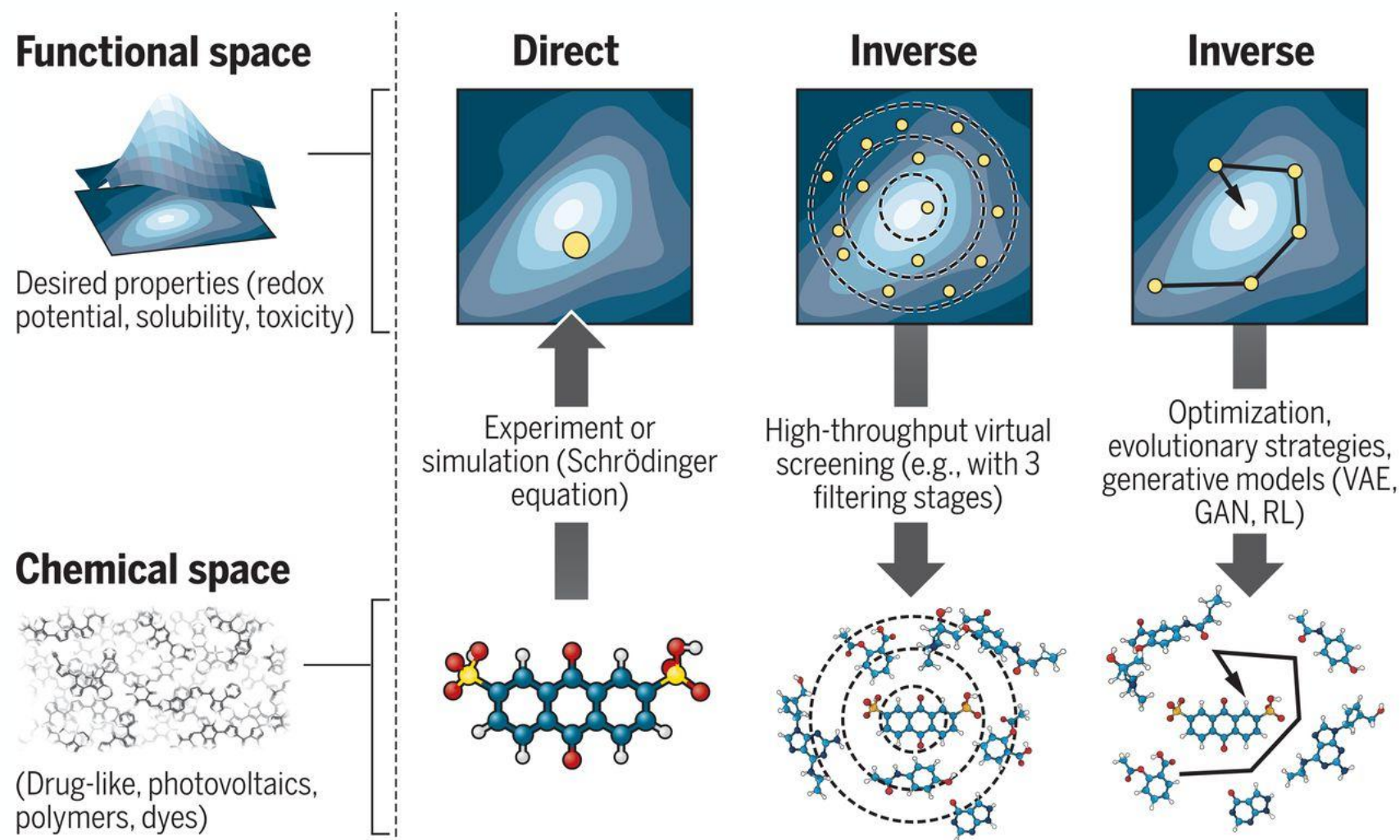
**Direct design** - Pick a specific compound and synthesize or simulate it

**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



## Direct vs inverse design in exploring chemical space

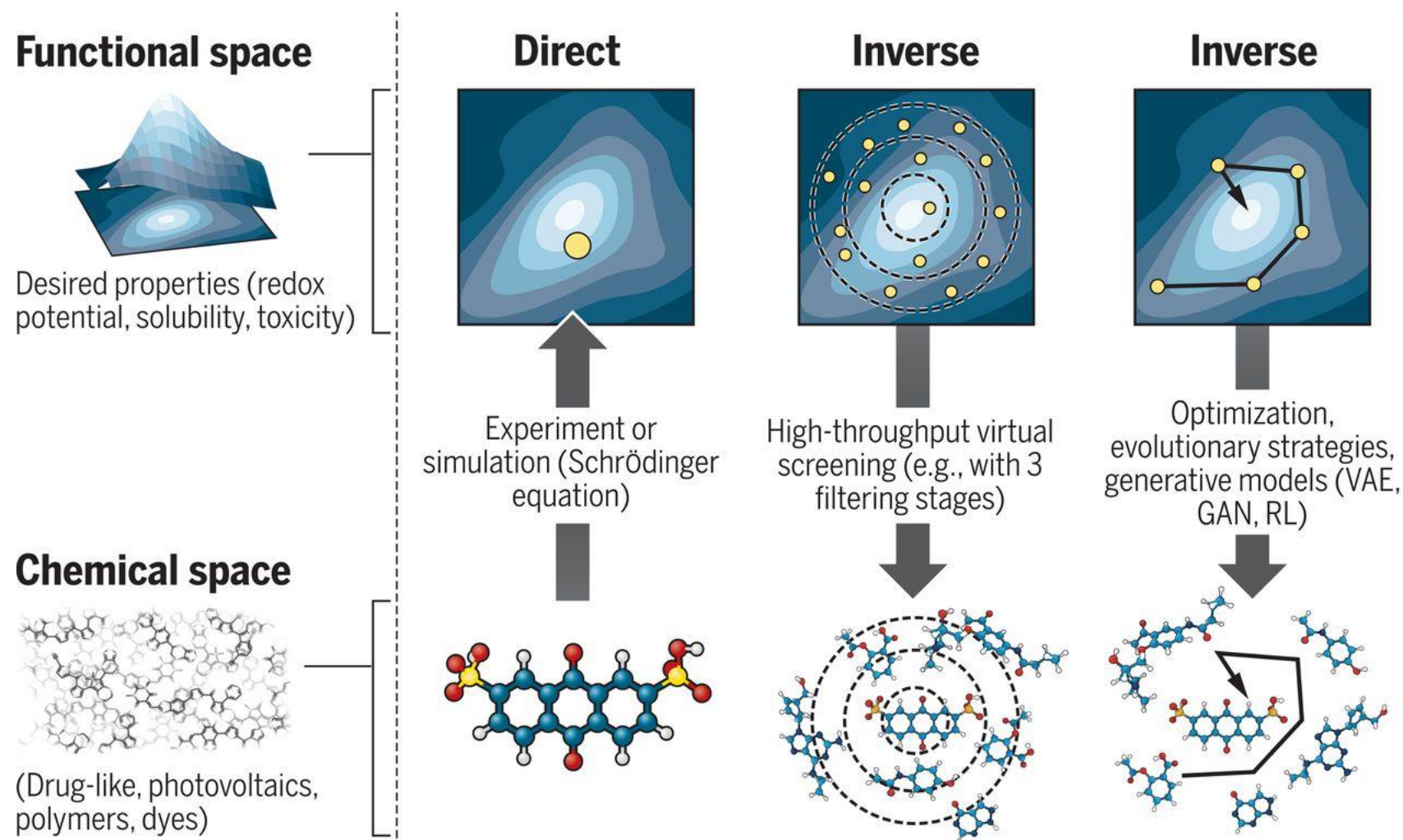


### Pure Inverse Design

**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

## Direct vs inverse design in exploring chemical space



### Pure Inverse Design

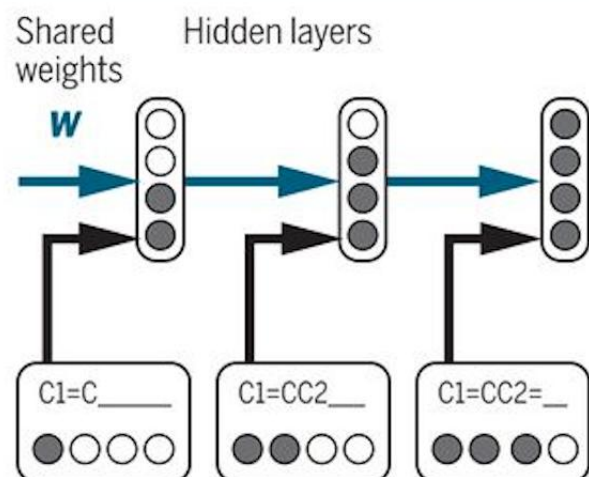
**Generative Models** - Attempts to determine a joint probability distribution  $p(x,y)$ - the probability of observing both the molecular representation and the desired property

- 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)

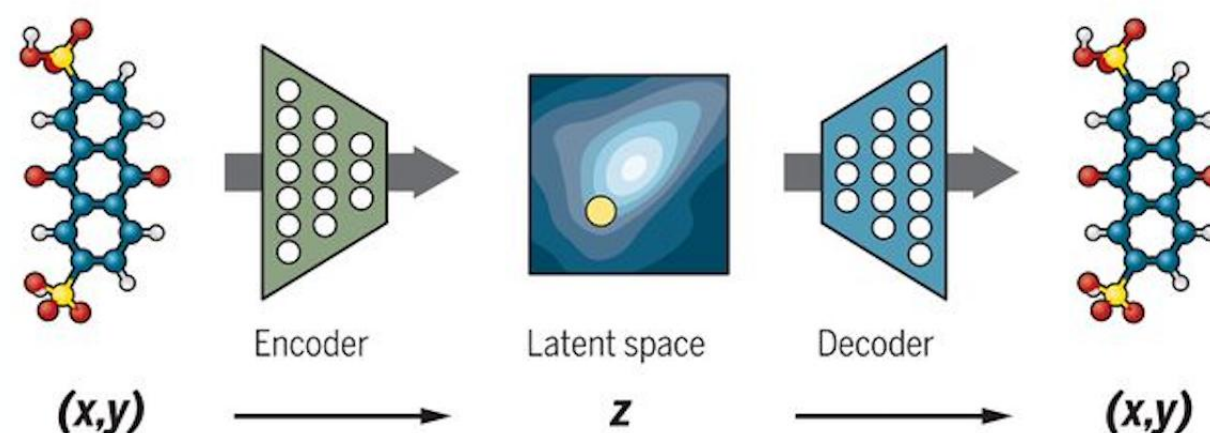


- common starting point

- 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

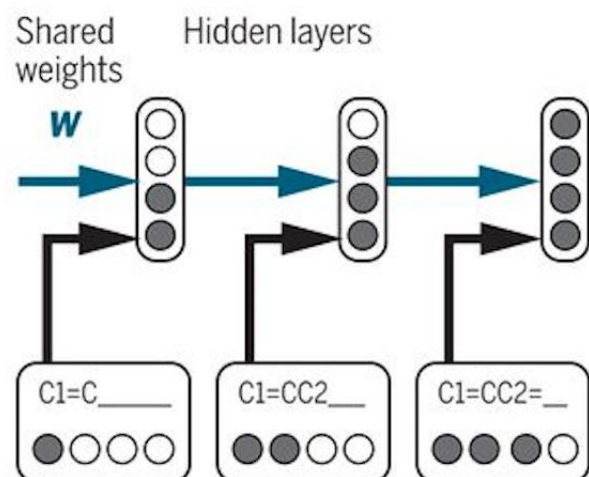
A molecule is represented as a probability distribution over latent space

The VAE uses probability distributions to estimate the latent space

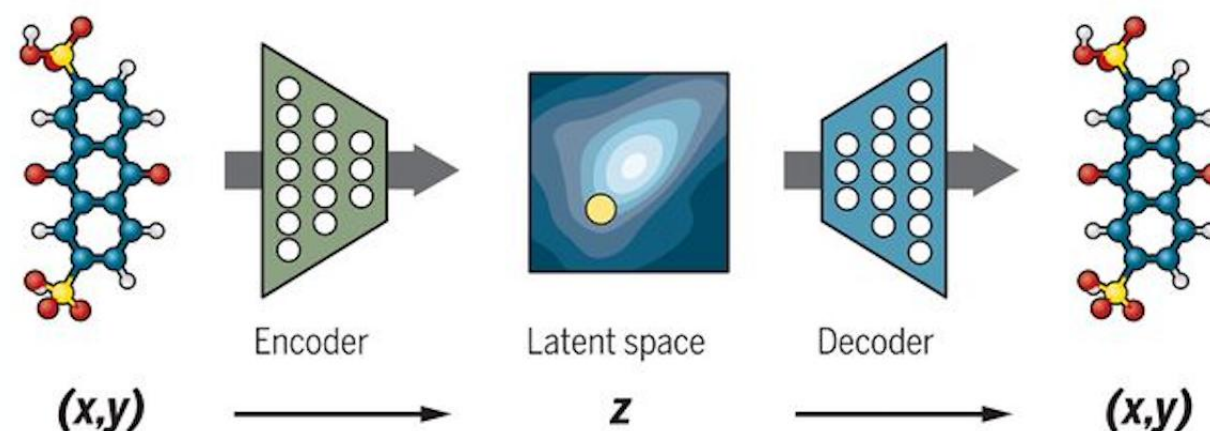
A decoder maps the latent space representation back to a molecule

# Types of generative models

## Recurrent Neural Network (RNN)

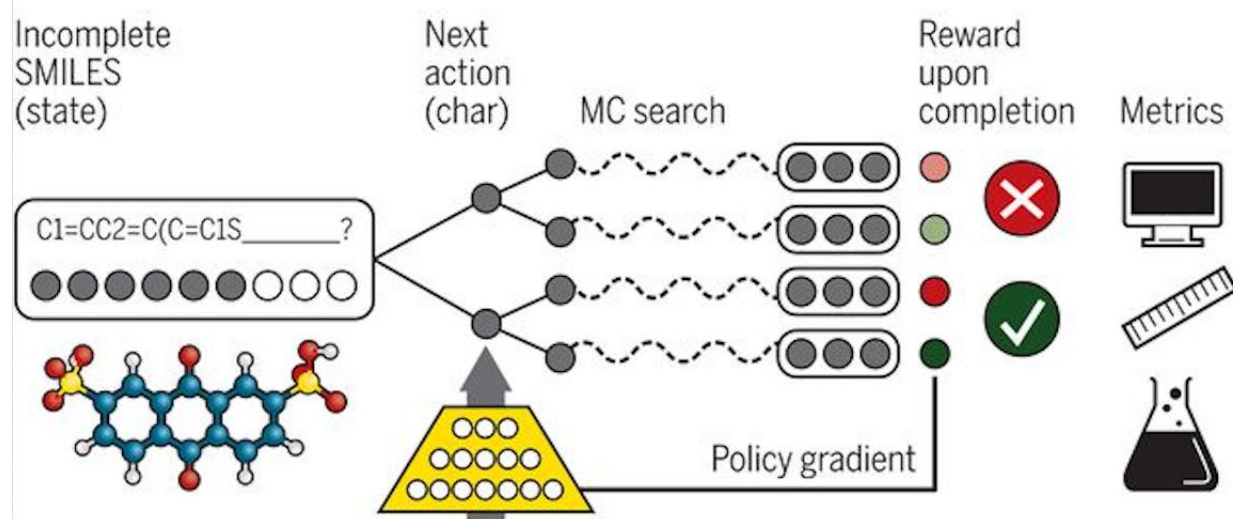


## Variational Autoencoders (VAE)



## Reinforcement Learning (RL)

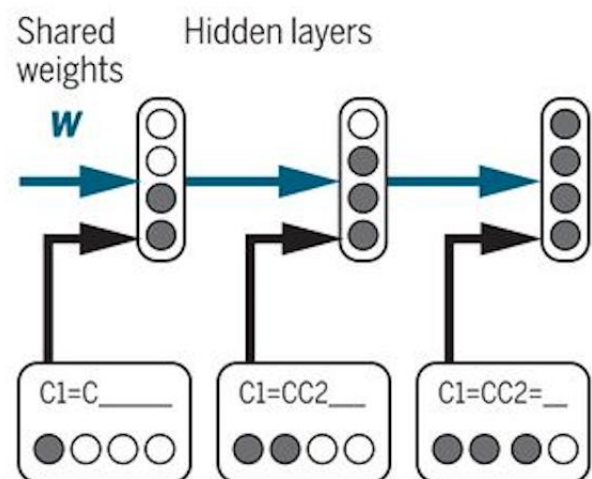
### Policy gradient with Monte Carlo tree search (MCTS)



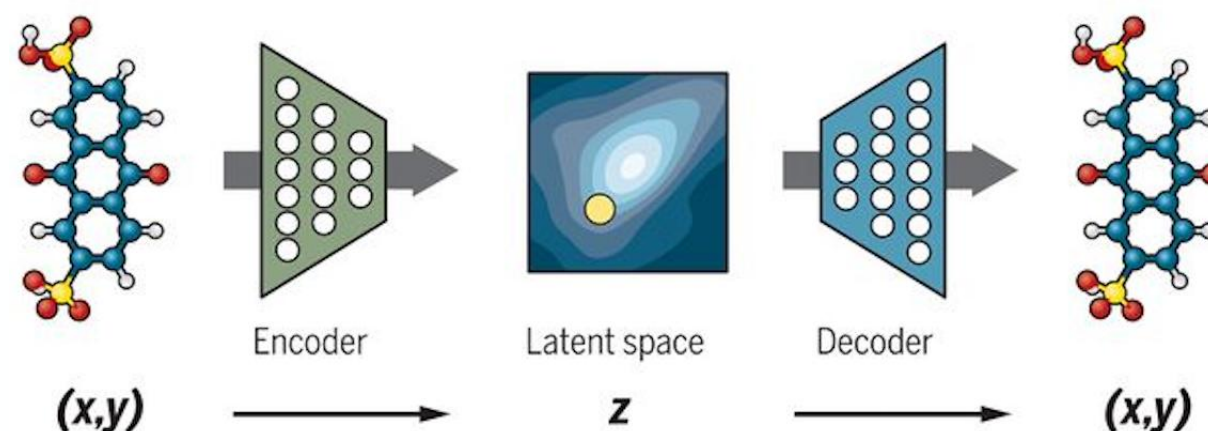
- an agent gives an output, which is then evaluated and returned to the agent so it can learn from it
- A generator must learn how to add smiles characters to maximize some reward (property)
- As these properties can only be evaluated at the end, a Monte-Carlo tree search is generally used

# Types of generative models

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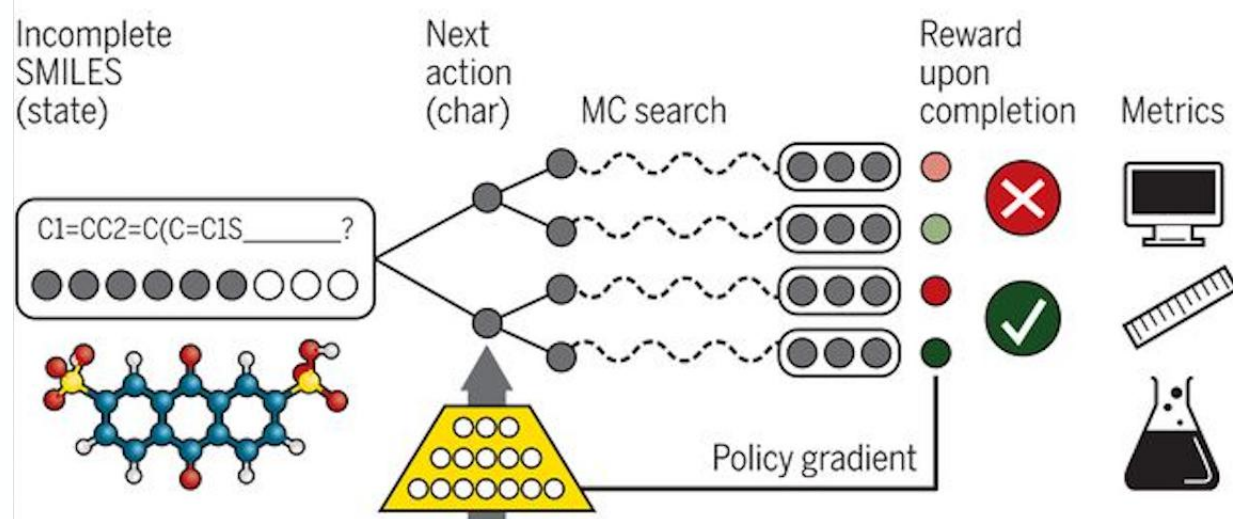


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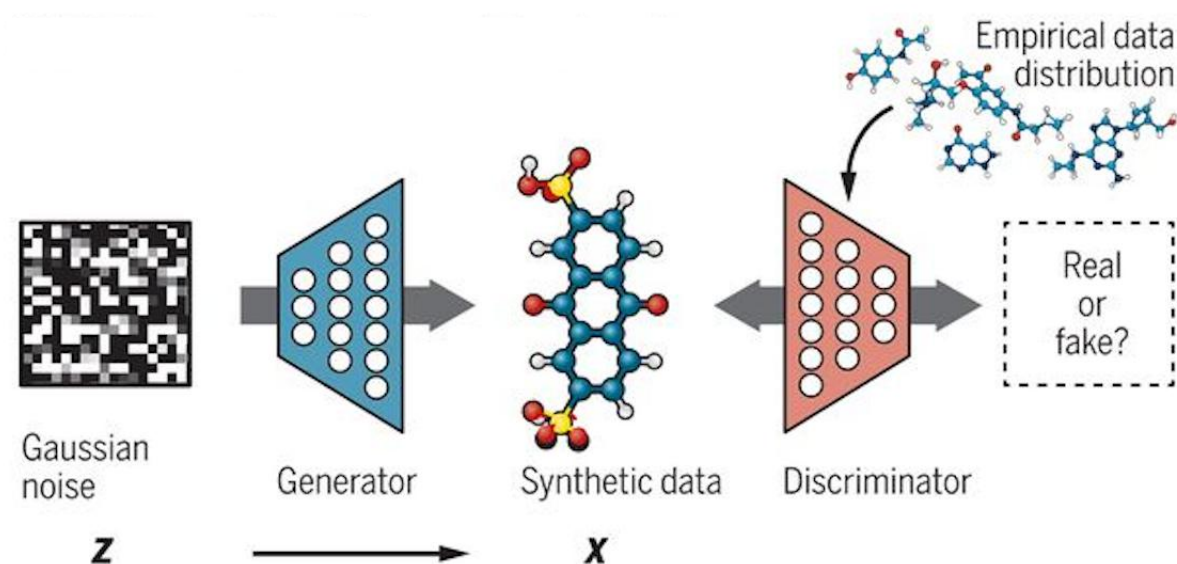


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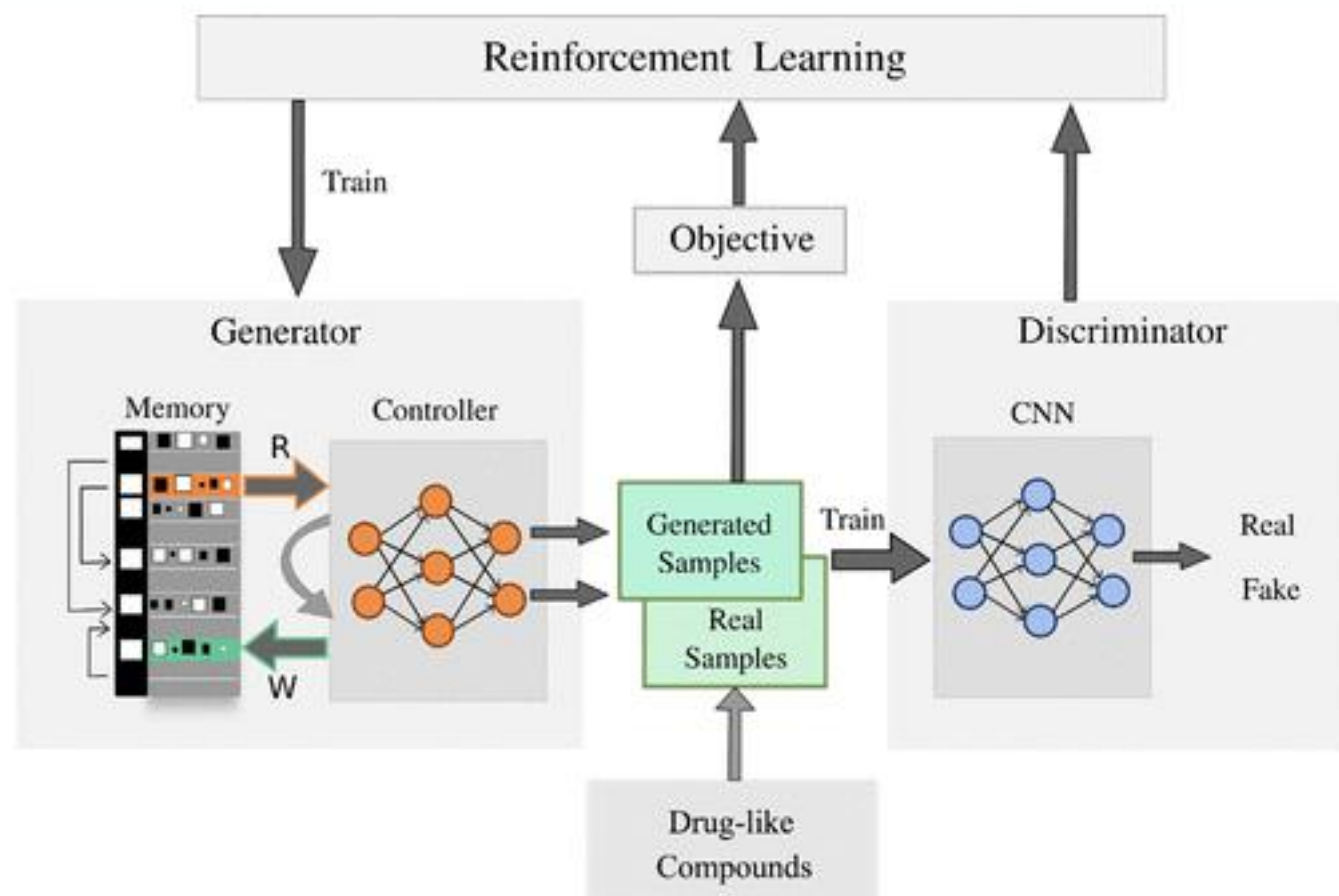
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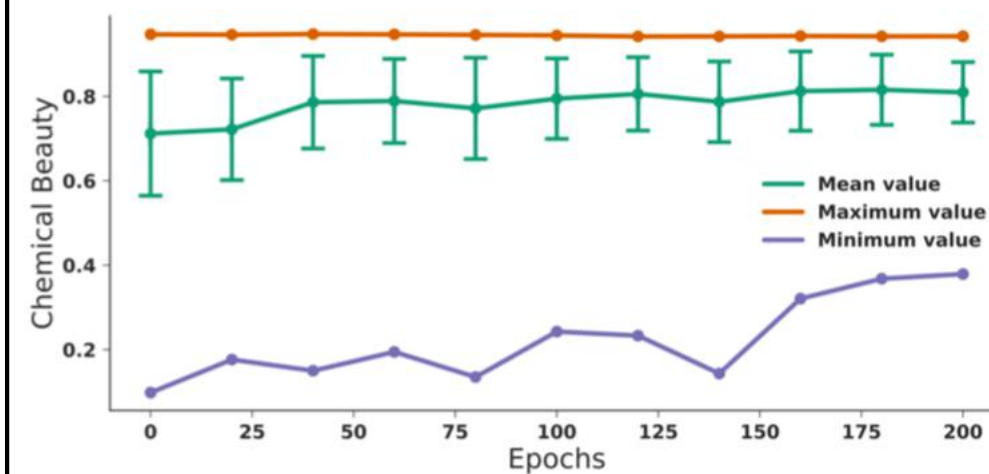


## Applying generative models to pharmacologic systems

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



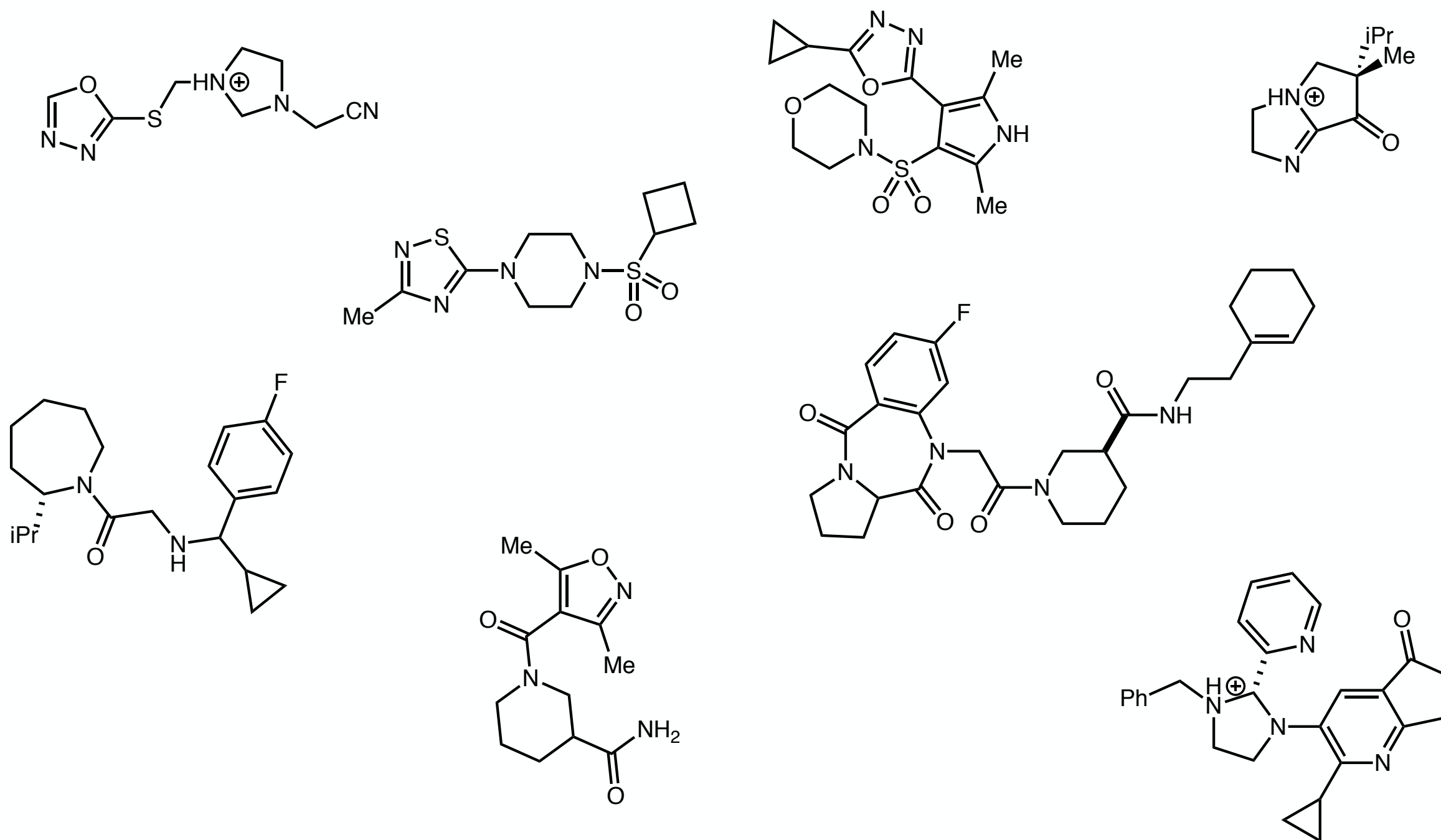
The system is then run through a number ~100 training epochs



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

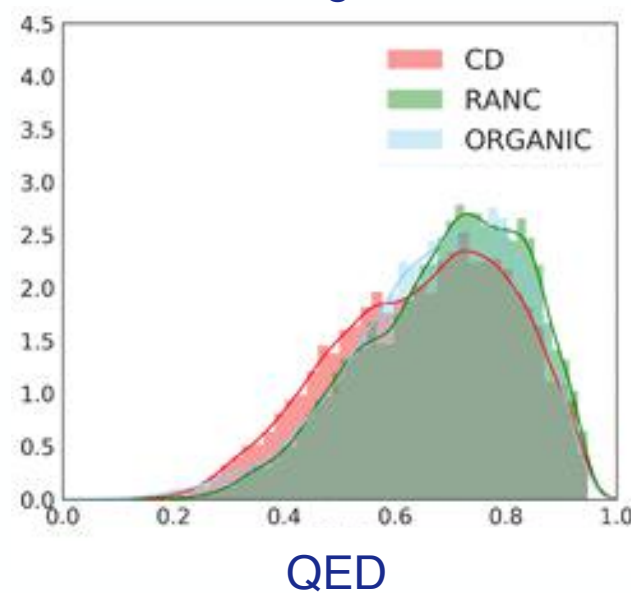
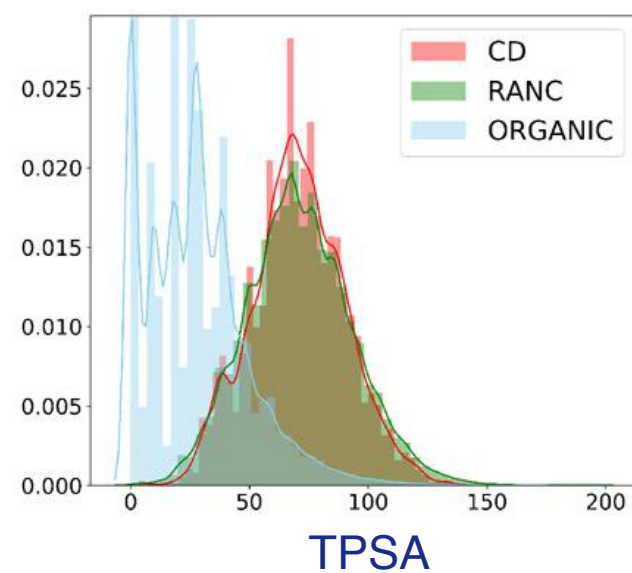
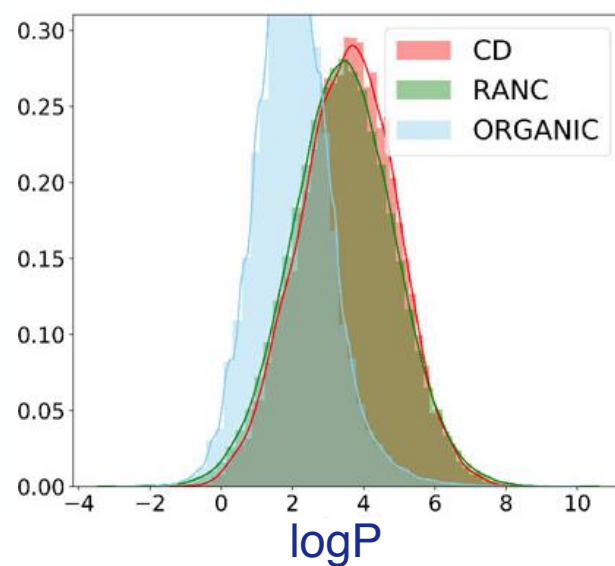
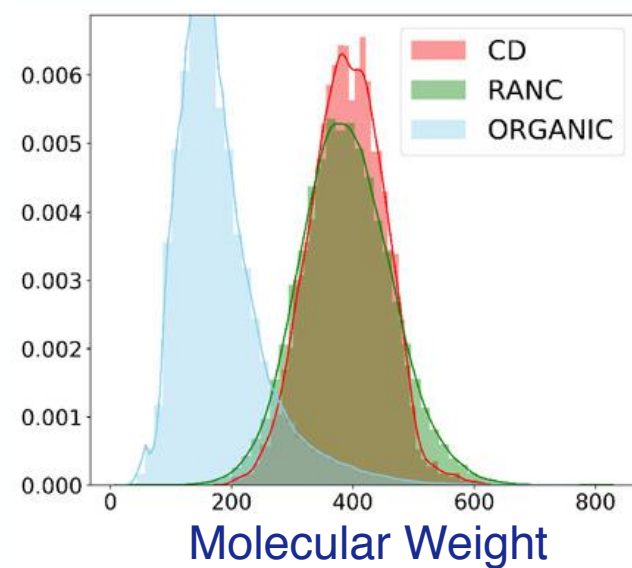
# Applying generative models to pharmacologic systems

Selected compounds generated by ORGANIC and RANC



# Applying generative models to pharmacologic systems

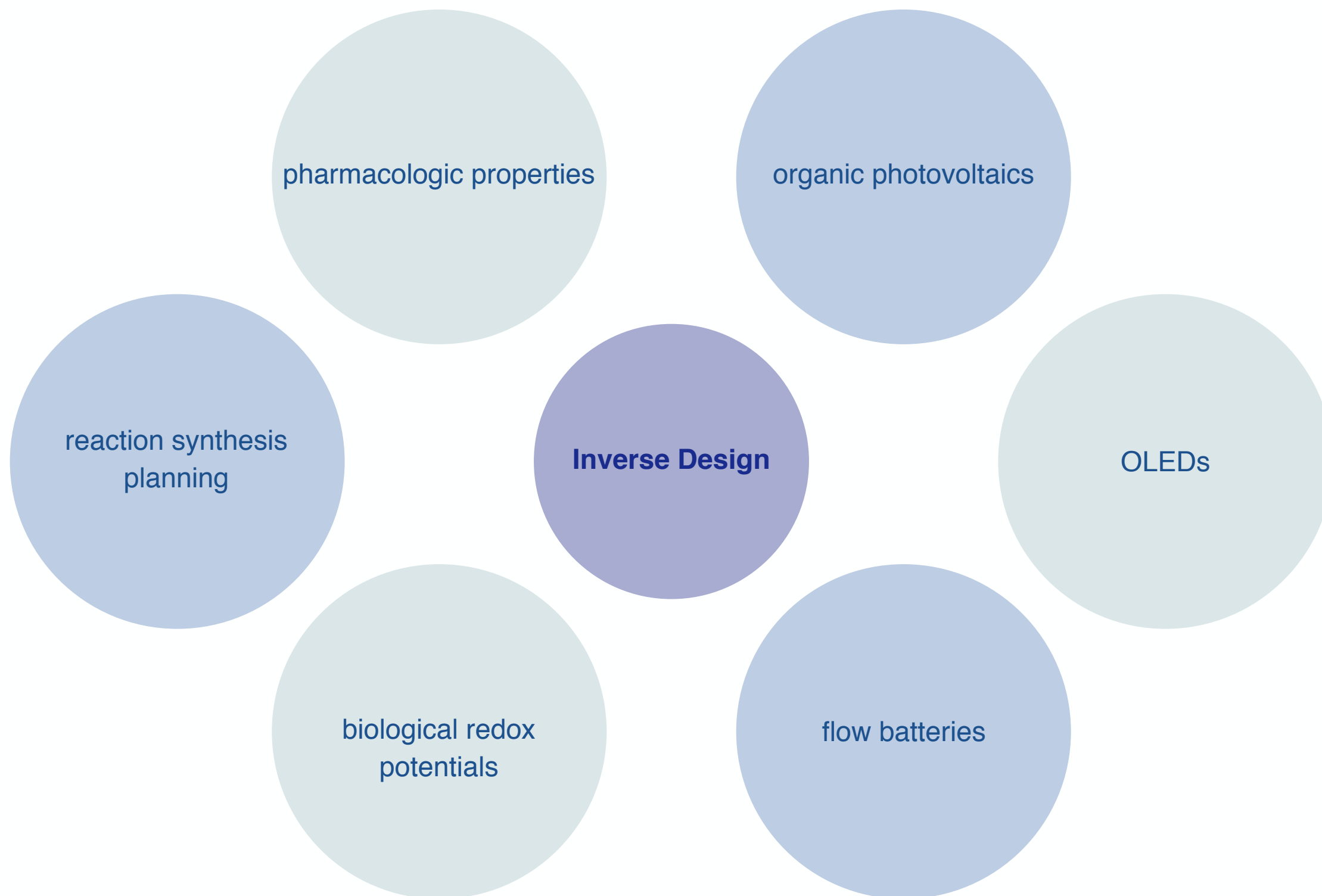
Comparing the performance of RANC and ORGANIC against the initial data



	<i>RANC</i>	<i>ORGANIC</i>
avg. length	46	23
valid %	58	87
unique %	48	18



*Inverse design forms a powerful platform*



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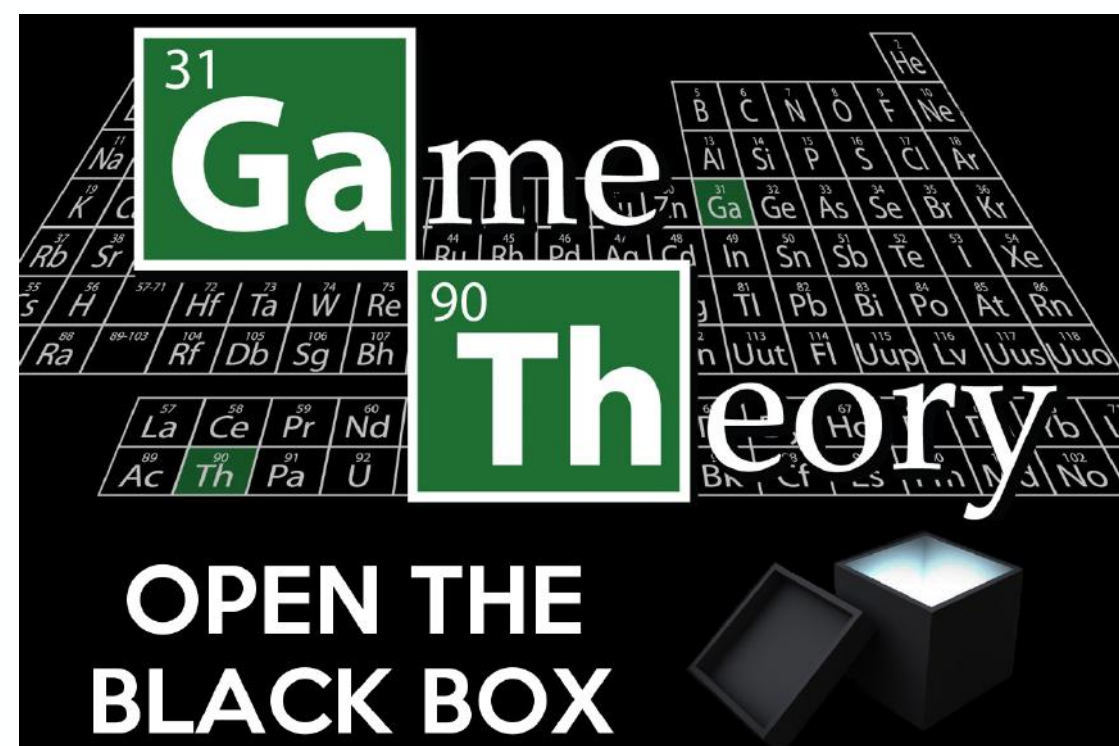
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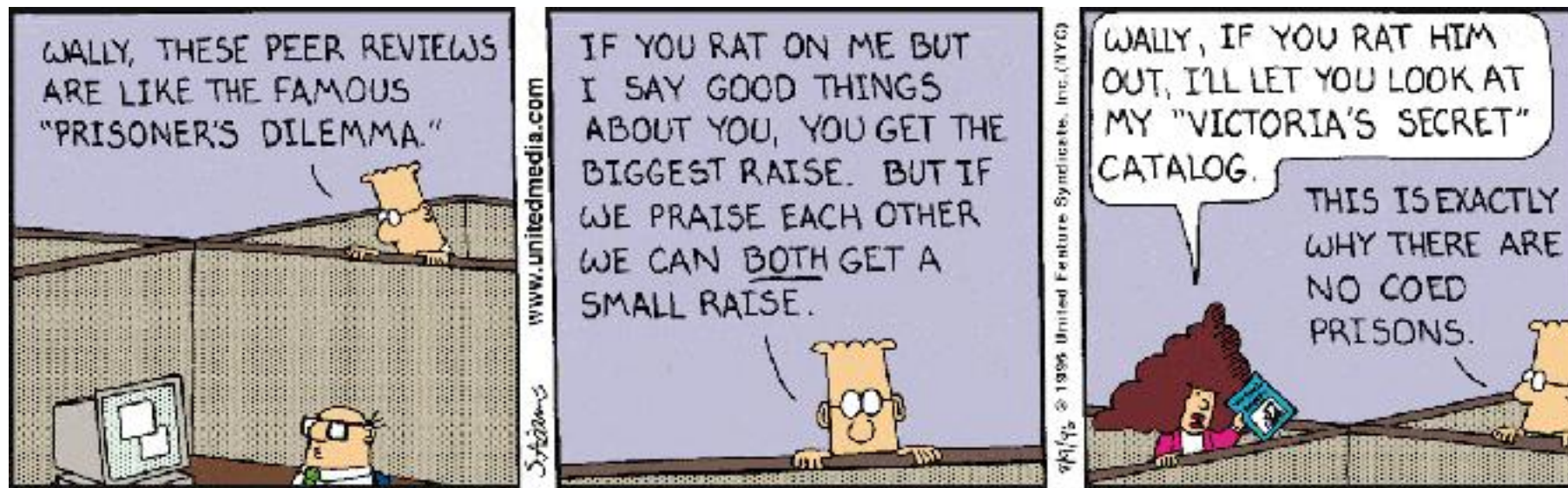
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## Questions?



Calvin and Hobbes by Bill Watterson

