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Applying game theory in cell biology

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„Der Mensch spielt nur, wo er in voller Bedeutung des Wortes Mensch ist, und er ist nur da ganz Mensch, wo er spielt.“

Friedrich Schiller (1795)

„Man only plays when he is in the fullest sense of the word a human being, and he is only human when he plays.”

Introduction

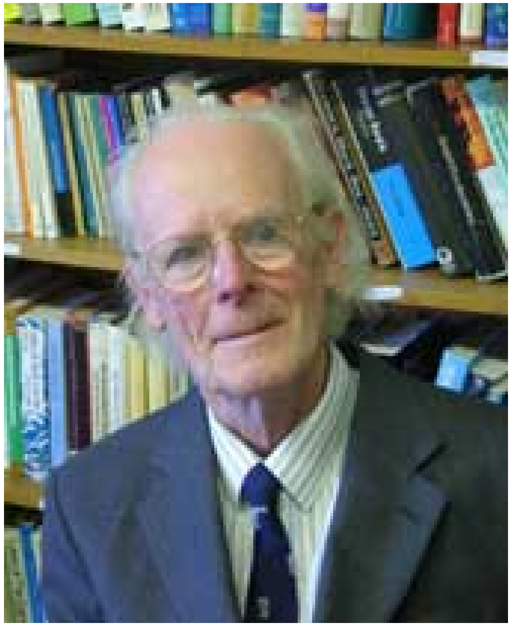
- **Charles Darwin**: Survival of the fittest = optimization (theory in Germany disseminated by Ernst Haeckel, Jena)
- Better and better adaptation to environment
- 
- However: When environment is shaped by other evolving organisms, evolution is actually co-evolution
- Therefore, theory of optimization needs to be extended, e.g. to game theory

John von Neumann (1903 -1957)

Established Game Theory in the 1940's in Princeton (together with others)

He also introduced cellular automata.

John Maynard Smith (1920-2004)



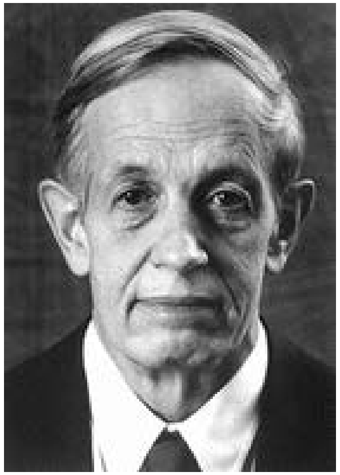
Founder of concept of „evolutionarily stable strategy“ and one of the first who applied game theory in biology

Game Theory

- **Players** can adopt **strategies**
- **Payoff** depends on own strategy and that of other players
- Equlibrium situations can be determined – **Nash equilibria**

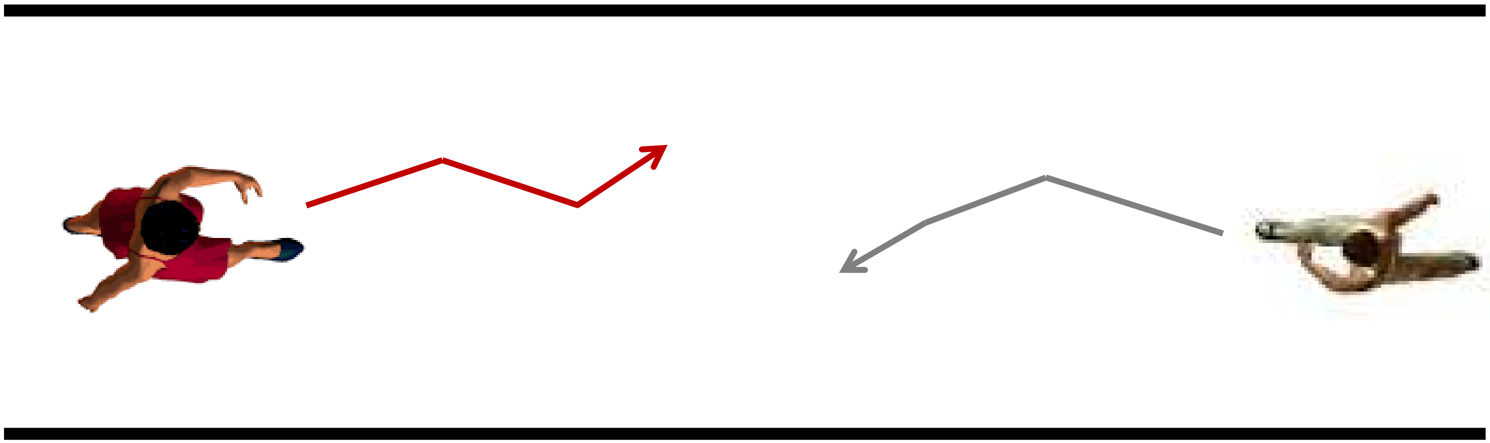
Nash equilibrium

- A situation in which neither player can increase payoff by changing strategy unilaterally



John F. Nash
(1928-2015)

Iterations in agreeing about the Nash equlibrium

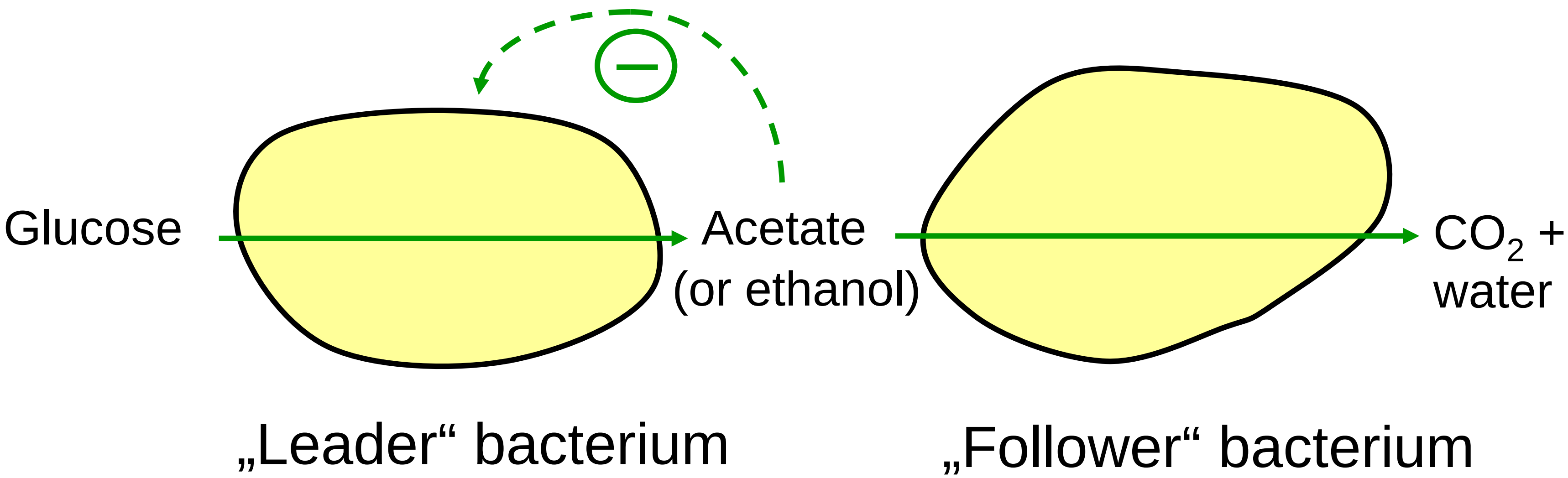


„After you, please…“

Criticism of Nash equilibrium

- Ignores psychological and moral factors (e.g. trust)
- Concept of Nash equilibrium in cell biology and microbiology perhaps better suited than in organismic biology or sociology
- In some games (e.g. Ultimatum game) too many Nash equilibria
- Alternative solution concepts:
  - Correlated equilibrium (Aumann, 1974)
  - Kantian equilibrium (Roemer, 2010)
  - Co-action equilibrium (Sasidevan and Sinha [Chennai], 2015)
  - For Ultimatum game: Golden ratio (Suleiman, 2014; Schuster, 2017)

Example:
Sequential Cross-feeding



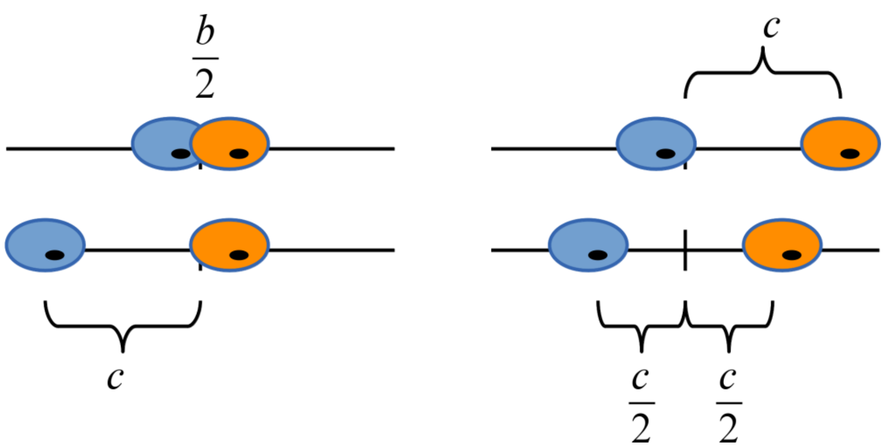
Payoff matrix for cross-feeding

B / A	**Glucose** (preferred)	**Acetate**
Glucose (preferred)	1/1	3/2 **Nash equilibrium**
Acetate	2/3 **Nash equilibrium**	0/0

Battle of the sexes (Leader III)

Game-theoretical description of competition between cancer cells

- 2 tumour cells
- Can switch between 2 different types: proliferative and motile
- *b*, availability of nutrients; *c*, costs for motility
- Payoff matrix:



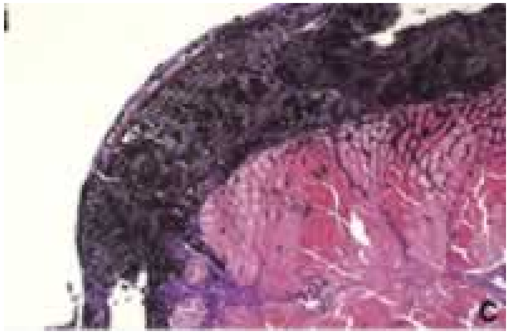
	proliferative	motile
proliferative	$\frac{b}{2}, \frac{b}{2}$	*b*, *b-c*
motile	*b-c*, *b*	$b - \frac{c}{2}, b - \frac{c}{2}$

D. Basanta, H. Hatzikirou, A. Deutsch, *Eur. Phys. J.* **63**, 393–397 (2008)

Game-theoretical description of competition between cancer cells

- 2 tumour cells
- Can switch between 2 different types: proliferative and motile (metastasis)
- Benefit *b* and costs *c*
- Payoff matrix:

	proliferative	**motile**
proliferative	$b/2$	b
motile	$b-c$	$b-c/2$



D. Basanta, H. Hatzikirou, A. Deutsch, *Eur. Phys. J.* **63**, 393–397 (2008)

Hawk-Dove-Game

Alternative names: Snowdrift game, Game of Chicken
In simplest form, 2 strategies: „Hawk“ (aggressive) and „Dove“ (peaceful)

Game-theoretical description of metastasis

If *c* < *b*/2 (high benefit): Hawk-dove game.
Then „go or grow“ phenomenon. Metastases.

	proliferative	**motile**
proliferative	b/2	b
motile	b-c	b-c/2

Nash

In a population, this leads to coexistence of strategies.

Game-theoretical description of metastasis

If $c < b/2$: Hawk-dove game.
Then „go or grow“ dichotomy. Metastases.

	proliferative	motile
proliferative	b/2	b
motile	b-c	b-c/2

Nash

In a population, this leads to coexistence of strategies.

Game-theoretical description of metastasis

If *c* > *b*: Deadlock 1 game.

Nash

	proliferative	**motile**
proliferative	b/2	b
motile	b-c	b-c/2

Deadlock 1 game

Related to Route choice (a.k.a. Deadlock 2 game): 2 car drivers can each choose among a highway and a narrow road.

Best case: driving on highway alone. Sharing the highway is better than narrow road alone.

Similarly, a motile tumour cell provides high advantage to other cell, which can stay and then has the highest payoff.

In Route choice: narrow road alone is better than sharing it.

In Deadlock game: Sharing it is better, perhaps helping each other.

Game-theoretical description of metastasis

If $2c > b > c$: Prisoner‘s Dilemma.
Both cells stay although it would be better for both of them to go. Temptation to stay if the other goes.

Nash

	proliferative	motile
proliferative	b/2	b
motile	b-c	b-c/2

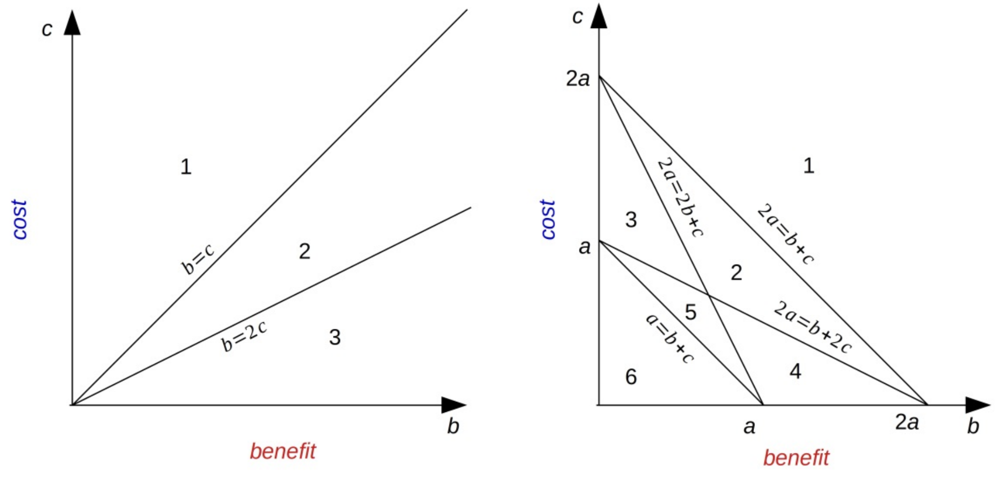
Modifications of the metastasis game

- Benefit b at primary site, benefit a at secondary site, costs c
- Payoff matrix:

	proliferative	**motile**
proliferative	$b/2$	b
motile	$a–c$	$a–c/2$

S. Dwivedi, …, H. Stark, S. Schuster: Game-theoretical description of the go-or-grow dichotomy in tumor development for various settings and parameter constellations. *Sci. Rep.* 13 (2023) 16758

Benefit-cost plane



(A) (B)

BHD model
1, deadlock game
2, Prisoner‘s dilemma
3, hawk-dove game

Modification 1,
different benefit
at secondary site
1, deadlock game
2, Prisoner‘s dilemma
3, stag-hunt game
4, hawk-dove game
5, harmony I
6, harmony II

Harmony game

- Only one Nash equilibrium, in which both players adopt the cooperative strategy.
- Examples: animals forming groups to protect against the cold

General Scheme

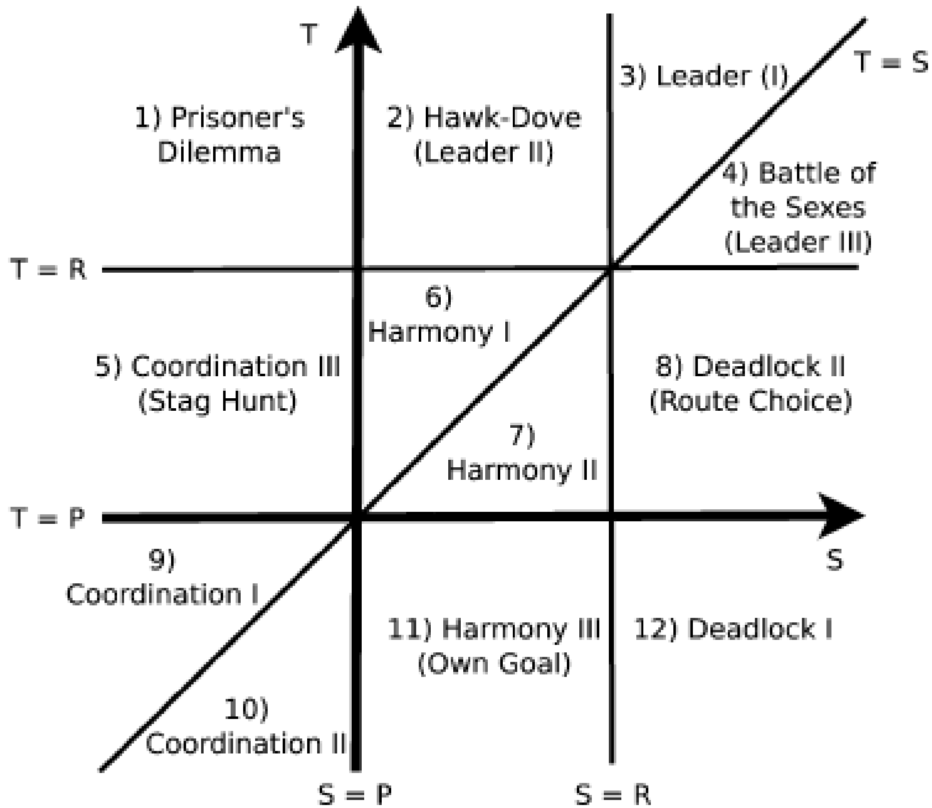
Symmetric games: All players have the same basic properties, the same set of choices, and the same set of payoffs.

B	1	2
A		
1	*R*	*S*
2	*T*	*P*

In the Prisoner‘s Dilemma: $S < P < R < T$

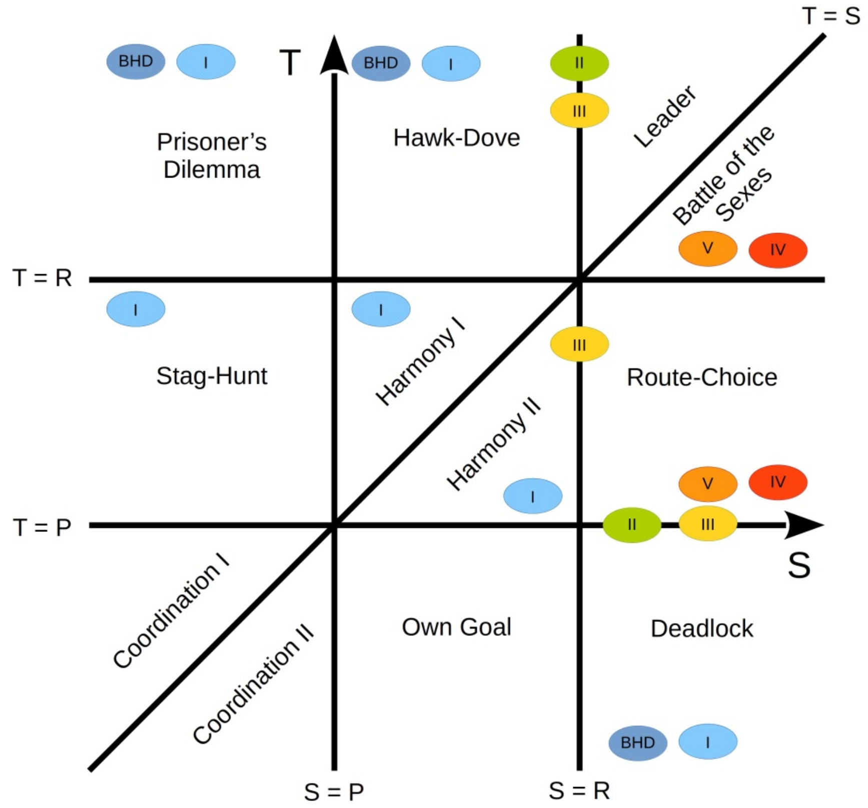
Classification of symmetric two-player two-strategy games

B	1	2
A		
1	*R*	*S*
2	*T*	*P*



After H.U. Stark, Evolution, 64 (2010) 2458-2465

All types in metastasis game in the S, T plane



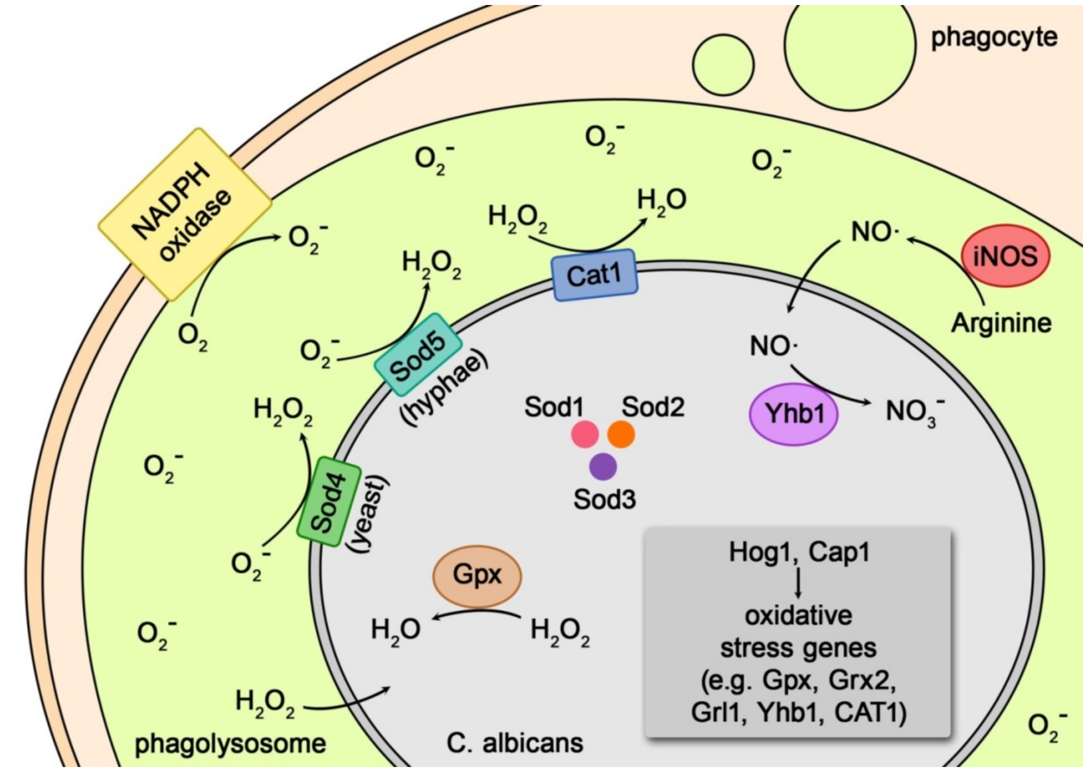
S. Dwivedi, …, H. Stark, S. Schuster: *Sci. Rep.* 13 (2023) 16758

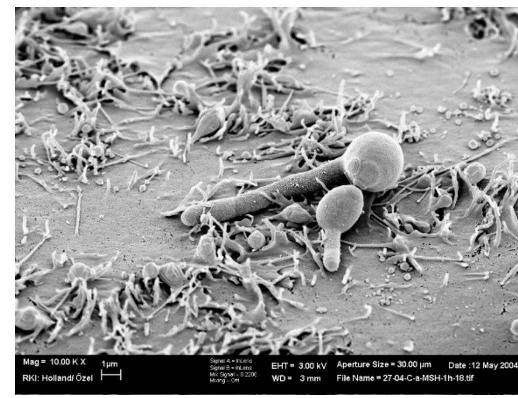
Symmetric vs. asymmetric games

- In symmetric games, all players have the same possibilities for choosing strategies and getting payoffs
- Symmetric 2-player-, 2-strategy games always have at least one pure Nash equilibrium
- Symmetric 2-player-, 3-strategy games do not always have a pure Nash equilibrium and have a mixed NE instead. Famous example: Rock-scissors-paper game

- The same with asymmetric 2-player-, 2-strategy games. Example: Matching pennies game (e.g. penalty shooting in soccer).

Molecular host-pathogen interactions



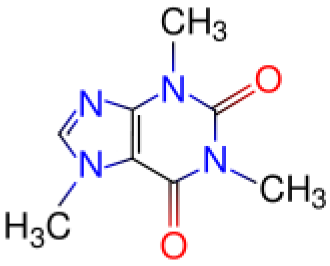


Pathogenic fungus
Candida albicans

S. Dühring, …, T. Dandekar, S. Schuster:
Host-pathogen interactions between the human innate immune system and *Candida albicans* - Understanding and modeling defense and evasion strategies
Front. Microbiol. 6 (2015) 625

Defense chemicals

- Glucosinolates in plants
- Various other substances in plants: caffeine, nicotine, aspirine, cocaine etc.
- Antibiotics in fungi
- Antheminthics in fungi
- Bacteriocins in bacteria
- …



Caffeine

Counter-defense mechanisms

- Some insects produce enzymes degrading toxin precursors, others produce inhibitors of plant enzymes that activate precursors, a third group inactivates the final toxins

- Some bacteria produce beta-lactamases to inactivate penicillin

The endless cycle of defense and counter-defense

- If the attacking organism produces an efficient enzyme degrading the toxin, the latter becomes useless
- Then the enzyme becomes useless
- Now, the toxin becomes useful again
- Etc. etc.

S. Dwivedi, R. Garde, S. Schuster: How hosts and pathogens choose the strengths of defense and counter-defense. A game-theoretical view *Front. Ecol. Evol.* (2024) in press

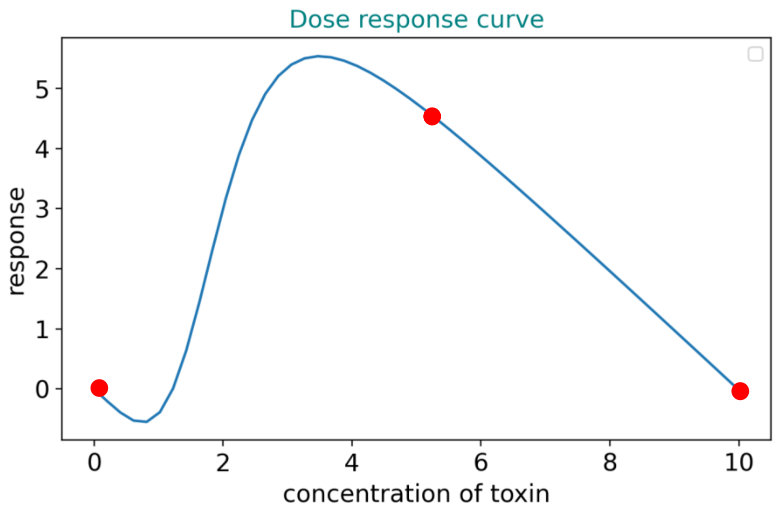
Mixed Nash equilibrium

Host	Pathogen	
	No counter-defense (NCD)	Counter-defense (CD)
No defense (ND)	$(h, p) \downarrow$	$\leftarrow (h, p - c)$
Defense (D)	$(h + b - c, p - b) \rightarrow$	$\uparrow (h - c, p - c)$

In the high-benefit case (*b* > *c*), no pure Nash equilibrium occurs. A path following incentives of the two players leads to a cycle (arrows).
Is generalized Matching pennies game.
In the low-benefit case (*b* < *c*), the equilibrium is ‘ND/NCD’.

The endless cycle resolved

- Hill kinetics for response and linear costs
- Similar to Simms-Rauscher model, which uses Michaelis-Menten kinetics



- Intermediary toxin concentration is best
- Stationary compromise

Three-strategy game

Host	Pathogen		
	No counter-defense	Partial counter-defense	Counter-defense
No defense	3, 2	3, 1	3, 0
Partial defense	11.7, -7.7	3.6, -0.62	2.8, -0.8
Defense	10.9, -7.9	2.6, -0.66	1.9, -0.9

Pure Nash equilibrium:
Partial defense / Partial counter-defense

S. Dwivedi, R. Garde, S. Schuster: How hosts and pathogens choose the strengths of defense and counter-defense. A game-theoretical view *Front. Ecol. Evol.* (2024) in press

Conclusions (1)

- Concept of optimality very helpful in biology, for example, for understanding biochemical pathways
- Some paradoxical or apparently meaningless phenomena can be understood by Evol. Game Theory but not by optimization theory
- Concept of Nash equilibrium in cell biology and microbiology perhaps better suited than in organismic biology or sociology because no psychological and moral factors

Conclusions (2)

- Usually, study of asymptotic behaviour by Game Theory requires less kinetic parameters than simulation of time course by differential equations
- Game-theoretical approaches take into account systemic properties, Systems Biology
- Biotechnological and medical relevance

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