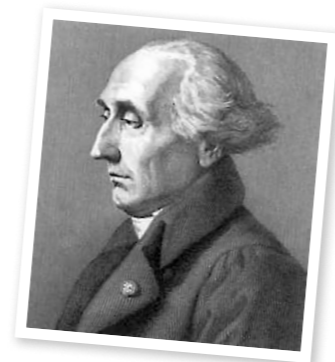


Stress, our hated guard

Or how theoretical physics could explain the phenomenon of life



Giuseppe Luigi Lagrangia

In his new book – *Generalized Lagrangian Approach and Behavior of Living Systems* – Professor Uziel Sandler, from the Lev Academic Centre (JCT), explains how a specific generalisation of a Lagrangian function can help theoretical physics to describe the phenomenon of life. He demonstrates how the generalised Lagrangians allow Lagrangian dynamics to be used to describe the behaviour of living objects. Notably, he points out that the terms which make up the Lagrangians all have clear biological meanings and the proceeding results have a biological interpretation.

In his new book – *Generalized Lagrangian Approach and Behavior of Living Systems* – Professor Uziel Sandler, Bioinformatics Department Chair at Lev Academic Centre (JCT), explores how a generalised Lagrangian approach can be used to help physics describe living systems and social behaviour. Professor Sandler remarks that this is not a book about the mathematical modelling of living systems; nor does it explain how the physical phenomenon exposed in non-living systems can be applied to living objects. Instead, this book explains how theoretical physics can describe the phenomenon of life. Although it is intended for students and researchers of physics and mathematics, readers solely interested in the theory's biological applications can omit the mathematical foundations and concentrate on the methodology and examples. This book is the result of

research carried out over a quarter of a century. It is based on the author's series of papers, published between 1994 and 2019, with the addition of previously unpublished results.

THE LAGRANGIAN

In 1788 Giuseppe Ludovico De la Grange Tournier first published his discovery of the specific function, the Lagrangian, together with the general equations of motion for physical systems, known as Lagrangian equations. The Lagrangian approach offers a systematic and sophisticated means of deriving the trajectory of a system of particles. The mathematical function, known as the Lagrangian, is made up of information pertaining to the dynamics of the system in terms of the generalised coordinates and their time derivatives ("velocities"). Unlike Newtonian mechanics, where we are required to deduce the analytical forms of all forces that influence the system, the fundamental attribute of the Lagrangian approach is that the Lagrangian function encapsulates the dynamics of the entire system of interest.

LAGRANGIAN/HAMILTONIAN APPROACHES

Approximately half a century later, Sir William Hamilton demonstrated that a system's trajectory that satisfies the Lagrangian equation also minimises a particular quantity that he referred to as an action. These Lagrangian/Hamiltonian approaches have generated significant success in theoretical physics, both in the description and understanding of the behaviour of non-living physical systems. Hamilton's principle, also known

as the principle of least action, can be employed to derive the Lagrange equation. This has been applied to many areas of fundamental theoretical physics including quantum mechanics and the theory of relativity.

LAGRANGIAN LIMITATIONS

Unfortunately, while Lagrangian equations were successfully applied to non-living physical systems, the Lagrangian, in its original form, is limited in that

it cannot be applied to living systems. The common Lagrangian/Hamiltonian dynamics and the principle of least action with time-independent Lagrangians lead to time-reversible equations of motion and to energy conservation, which cannot be true for living objects.

AN UNEXPECTED GENERALISATION

In his book, Professor Sandler explains how revisiting a lost opportunity that was not considered in the development of contemporary physics leads to a natural, but somewhat unexpected, generalisation of the Lagrangian function (referred to as S-Lagrangian), so Lagrangian equations lose their time-reversibility and conservation of energy. Since in the inference presented in the book, the Lagrangian equation and the generalised Lagrangian are not associated with specific properties of any particular system, these equations should be able to describe the behaviour of living beings as well. The author goes on to demonstrate how S-Lagrangian dynamics allow us to describe a wide spectrum of the behaviour of living systems.

THE MAJOR PARADOX

While the primary distinction between living and non-living things is commonly regarded to be the ability to produce offspring, when considering individual life and not the population, the fundamental difference is that living creatures actively counteract their degradation within a continuously changing environment. A rudimentary attribute of living organisms is their endeavour to minimise the likelihood of death, a trait that even exists in an individual cell.

AN INDICATOR OF THE LIKELIHOOD OF DEATH

Environmental conditions are unpredictable, and this makes it impossible to produce a suite of programmable responses for all possible situations. It seems that living systems possess a generic indicator of the likelihood of death, and they try to

A rudimentary attribute of living organisms is their endeavour to minimise the likelihood of death.

minimise its value. Professor Sandler found stress, defined by its discoverer Hans Selye as "the non-specific response of the body to any demand placed upon it", to be the most appropriate indicator due to its association with an organism's undesirable states. Just as the common physical Lagrangians depend on the generalised position coordinates and their velocities, the S-Lagrangian depends on the stress, its conjugated variable, which relates to quantum mechanics rather than to classical physics, and relevant parameters of a living system and their time-derivatives (which play the roles of the system's "coordinates" and "velocities"). This forms the biological basis for Professor Sandler's physics of life.

In this book, Professor Sandler demonstrates how assigning stress as the indicator of interest facilitates the design of the S-Lagrangians for a diverse range of living systems. In living systems, stress is an analogy of the Hamiltonian Action that should be minimised. Further exploration revealed that even the lowest approximation of these S-Lagrangians enables a satisfactory description of a broad class of behaviours of living organisms. Example applications presented in the text range from simple chemotaxis to the relationship between homeostasis and drug addiction, and to the behaviour of human populations in an environment.

FUZZY LOGIC

The classical Two-Valued-Logic, where every proposition is either true or false, is not satisfactory to provide a means of modelling vagueness and lack of certainty (which is a common feature in the

description of living systems). Therefore, it should be replaced by continuous Fuzzy Logic, which is similar to our innate logic. In Fuzzy Logic, the truth variable can take on any real number value between zero as false and one as true. Amazingly, such a replacement allows Professor Sandler to find direct relation between the causality principle and the principle of least action

together with generalisation of the Lagrangian function. This has enabled him to deploy the powerful mathematical

apparatus of theoretical physics to describe living objects.

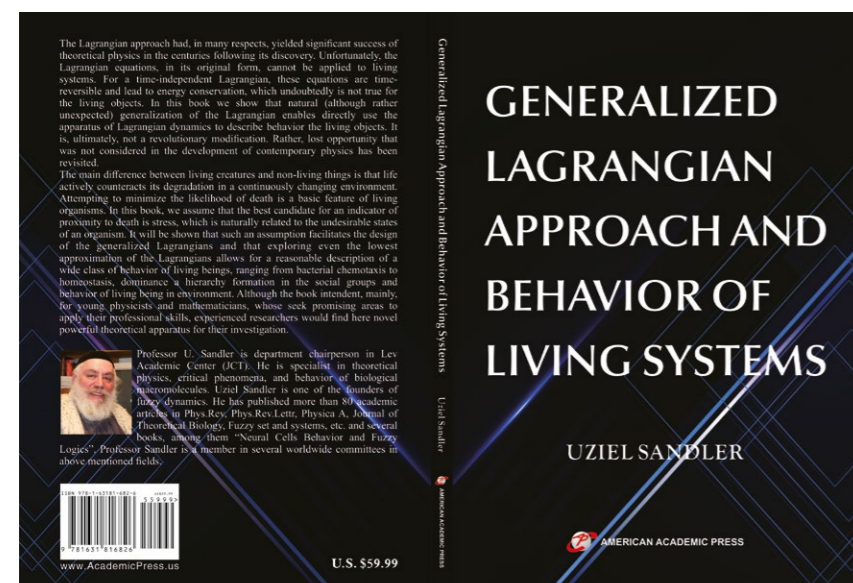
In creating this work, Professor Sandler finds himself in a similar situation to that of approximately three centuries ago, when the discovery of the Lagrangian approach enabled the resolution of problems that seemed extremely complex when viewed from the standpoint of Newtonian mechanics.

Having dealt with the underpinning mathematical concepts in the early chapters, the author presents a variety of examples of the considered approach illustrating the biological application of this methodology.

STRUGGLE FOR LIFE – HOMEOSTASIS

The S-Lagrangian underpins Sandler's dynamic theory of homeostasis. Homeostasis refers to the self-regulating processes deployed by biological systems to sustain their viability and stability while they adjust to a continuously changing external environment. If homeostasis is successful, a system's life continues; if it is unsuccessful, the system faces disaster and death. A paradox of living organisms is their ability to use homeostatic protection to offset degradation or injury in a changing environment.

Although homeostasis involves numerous different biochemical and physiological processes, it embraces surprisingly analogous features and behaviours in all living systems. Such universal behaviour is not unique in nature and has been observed, for example, in critical behaviour of



Professor Uziel Sandler's recently published book.

numerous non-living systems ranging from crystals to large biomolecules, irrespective of the significant disparities in their structures and intermolecular interactions. It happens because the system's critical behaviour is determined by the analytical features of free energy near its critical points, while the individualities of the system's structure and its intermolecular interactions are concealed within the phenomenological parameters of the free energy.

Correspondently, Professor Sandler has assumed that universality of the homeostatic dynamics is achieved via the analytical properties of the S-Lagrangian, while the phenomenological parameters of the S-Lagrangian are determined by the idiosyncrasies of the biochemical and physiological mechanisms of homeostasis. He chronicles computer simulations using the S-Lagrangian that establish the agreement between his theoretical descriptions and the observed biological properties of homeostasis.

FROM PROTECTOR TO ASSASSIN

Homeostasis protection involves the rapid reduction of stress followed by a more gradual repairing process. In humans, the swift decrease in stress results from the release of chemicals like endorphins, known as endogenous opioids, which are hastily produced in a natural response to severe injury and pain. However, inappropriate artificial replication of this emergency mechanism can have the opposite effect, inhibiting natural homeostasis with detrimental results.

In the late 1890s, the company now known as Bayer-Pharmaceutical synthesised an artificial opiate, diamorphine, which was aggressively marketed. This new drug became known as heroin (derived from 'heroic') because it was initially used to treat injured soldiers before it became one of the most powerful narcotic drugs.

Recently, the economic cost of the opioid crisis was estimated to be more than 2.5 trillion US dollars for the four-year period from 2015 to 2018. Over 33,000 Americans died of a drug overdose in 2015, rising to more than

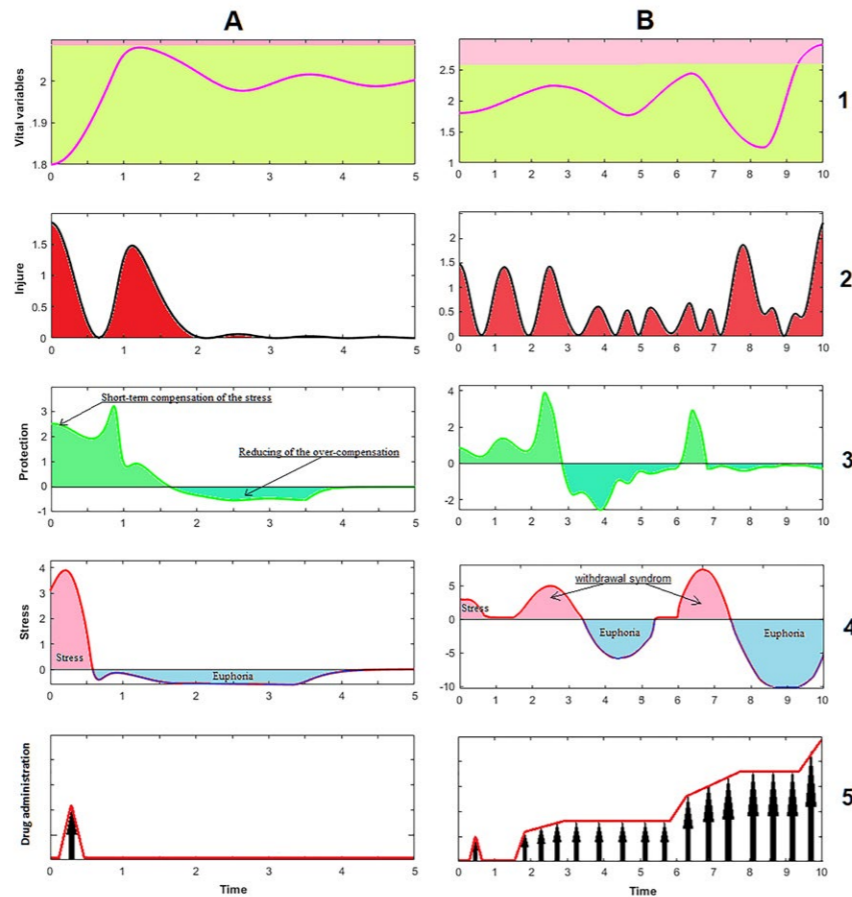


Figure 1 Development of drug abuse. A - acute administration. B - chronic administration with dose-escalation. The green area in the first row designates the life-compatible zone, while the pink area designates the life-incompatible zone. Row 5 shows drug administration. The black arrows represent drug application and the Red curves represent the Damage factor.

47,000 deaths in 2017, with many more suffering from the drugs' side effects.

Heroin and other opioids affect the same areas of the brain as naturally produced endorphins and result in the same physiological effects, such as reducing stress and relieving pain, imitating the natural action of homeostasis. There is a critical issue, however, with artificially administered drugs. Homeostasis precisely regulates the amount of endogenous morphine it produces whereas any amount of heroin opioid can be administered voluntarily in order to achieve a feeling of euphoria. Moreover, a large amount of heroin will over-compensate for stress. Since homeostasis works in both directions, it attempts to correct this over-compensation. So every time heroin is administered, the endogenous morphine receptors become desensitised: an equal dose of heroin will no longer compensate for stress or induce euphoria and higher doses are required each time. This results in chronic, dose-escalating drug abuse,

with the result that the endogenous morphine cannot compensate for stress, leading to withdrawal symptoms.

The author has extended the theory of homeostasis to demonstrate the dynamics of drug abuse. He adds the artificially administered drugs to the S-Lagrangian, which results in a decrease of stress. He also takes into account how the intrusion of this external stress reducer inhibits the natural homeostasis-protection mechanisms. His simulations include modelling the dynamics of a single administration of the drug to an injured organism where homeostasis repairs and stabilises the organism. Contrastingly, modelling the development of dose-escalating drug abuse demonstrates that drug abuse impairs homeostasis. Repeated administration of the drug results in an organism becoming vulnerable to injury and disease, leading to premature disability and death. This demonstrates that overdosing is not the sole cause of death due to drug addiction. So, the actual number of Americans who have

died as a result of drug abuse must be much higher than was mentioned above. [Figure 1]

The modelling of homeostasis revealed that if an organism is likely to die under high stress, it will consolidate all available resources in order to neutralise this outcome. Surprisingly, simulations of voluntary, repeated suppression of stress by a non-specific external stress-reducer confirmed that this leads to the development of addiction, because in a state of euphoria an organism subconsciously perceives that it is doing well since it has reduced the inner indicator of proximity to death (the stress). As a result, weak intellectual objections are disregarded in lieu of powerful emotional feelings. Addiction kills us by a "sweet" death. So, voluntary, repeated suppression of stress by an external stress reducer regardless of the primary source of the stress, could be more harmful than the stress itself.

STRUGGLE FOR DOMINANCE IN SOCIAL GROUPS

Hierarchical structures and dominance exist in most social groups of living things ranging from groups of cancer cells or neurons in the brain to human societies. Commonly these hierarchies are attributed to competition for better resources and breeding, leading to antagonistic interactions between members of the group. Those that win most of the contests move higher within the group, while those that lose are dropped to the lower ranks.

However, the same dominance hierarchies still exist in friendly environments with abundant resources even though aggressive interactions are not present. Regardless of the disparities between species and their behaviours, dominance hierarchies are comparable among most social groups. This suggests that dominance hierarchies are the product of some common characteristics of the behaviour of living things.

The author demonstrates that the incentive for living beings to form hierarchical structures may result from their attempts to cope with stress, which results from disparity between the "real world" (actual states of the

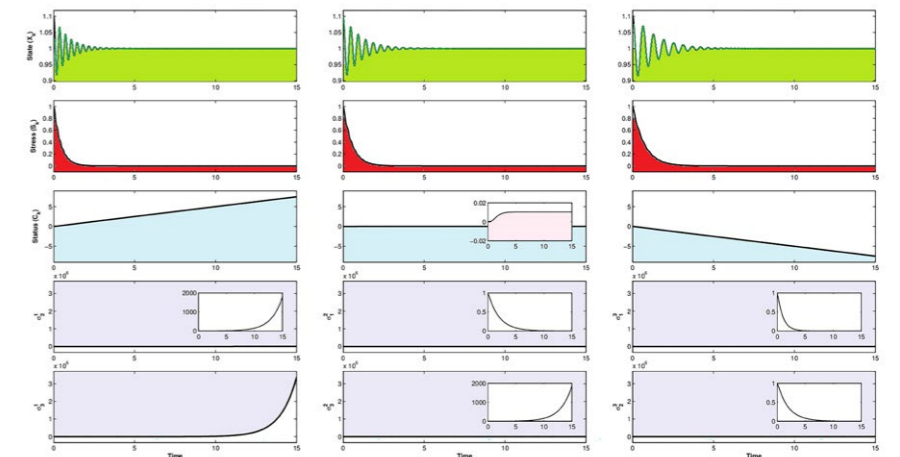


Figure 2.1 A group with imitative behavior under low stress $S_k(0) \gg S_0$. Each column corresponds to one individual. The parameters are $\gamma_1 = 5.0$, $\gamma_2 = 4.0$, $\gamma_3 = 3.0$, $\omega_2 1 = 300$, $\omega_2 2 = 180$, $\omega_2 3 = 90$.

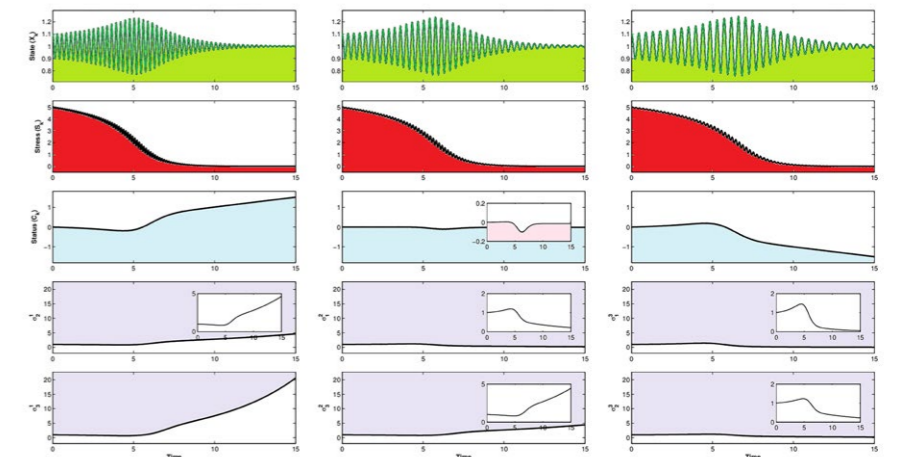


Figure 2.2 A group with imitative behavior under high stress $S_k(0) > S_0$.

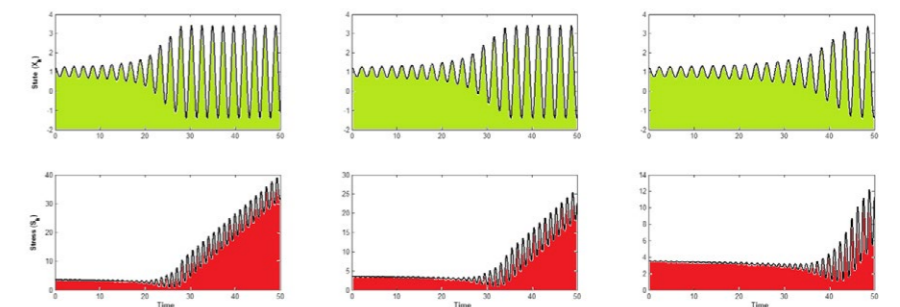


Figure 2.3 Separate individuals under high stress $S_k(0) > S_0$.

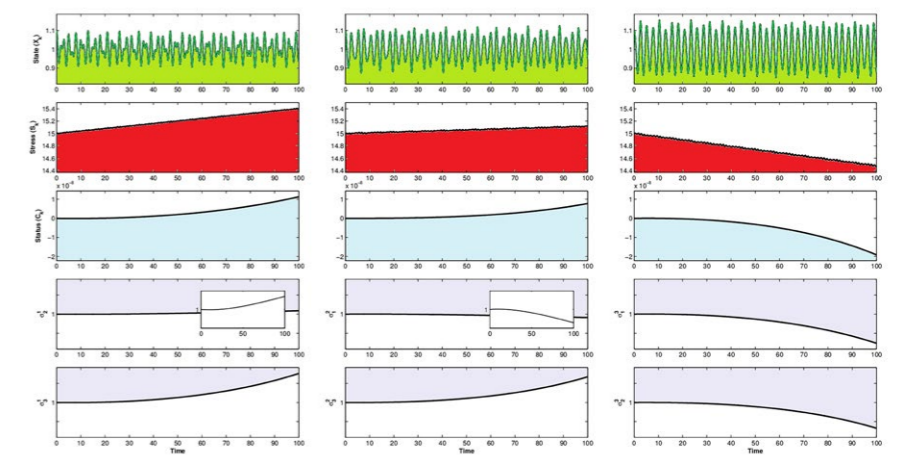


Figure 2.4 A group under fatal stress $S_k(0) \gg S_0$.

group's members) and the "ideal world" (stereotypes of desirable behaviour of the group's members). This forms the biological foundation for his theory of hierarchical structures and dominance in social groups.

Applying S-Lagrangian dynamics enables the main features of hierarchy formation and dominance to be described. After performing a number of simulations, the theory predicts three levels of dominance and hierarchy formation. The first level occurs if a group is made up of individuals who take noticeably different lengths of time to cope with stress: the individual with the fastest coping time becomes dominant and assumes leadership of the group. The second level occurs when the group members take similar lengths of time to cope with stress, then the member with the largest stress-threshold assumes leadership of the group. The third level occurs if the individuals within the group take similar times to cope with stress and have similar stress-thresholds. In this case, the individual with the highest tolerance to the difference between the group members' actual states and their desirable behaviour stereotypes becomes dominant. [Figures 2.1–2.4, previous page]

While the first and second levels have a physiological nature, the third level depends on the emotional spirit and training of group members. The first level creates a despotic hierarchy, where an individual member is the dominant leader of the group and all the other members are submissive servants. The other levels are more likely to create linear hierarchies with each individual member dominating those individuals of a lower ranking. It should be emphasised that this hierarchy formation is pure "dynamical effect", because it appears as a consequence of the equations of evolution, while initially all a group's members were assumed to have an equal status.

The study detailed in this book connects the commonly suggested mechanisms of dominance formation to the inner physiological features of living species and correlates with the frequently used winner-loser hypothesis of dominance behaviour.

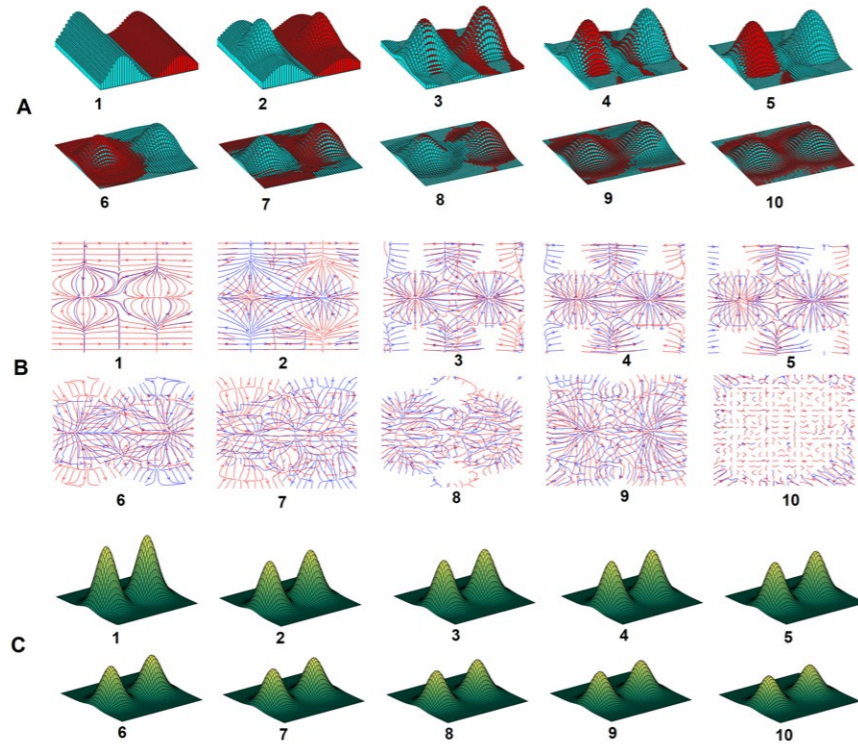


Figure 3.1 Co-evolution of coexisting species. A: evolution of population densities (XY-plane: inhabited area, Z-axis: population densities); blue - species 1 and red - species 2. B: migration flows. C - food supply. Bold numbers designate the time points.

Assigning stress as the indicator of interest facilitates the design of the S-Lagrangians for a diverse range of living systems.

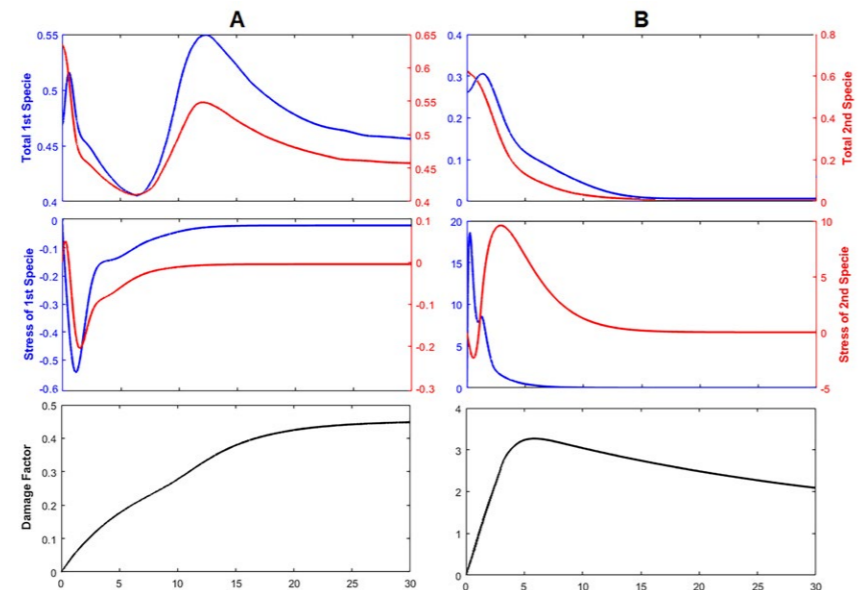


Figure 3.2 A: Total number of coexisting species, their Stress-indexes and damage factor. B: Ecological catastrophe (species 1 highly produces the damage factor).

STRUGGLE FOR EXISTENCE – POPULATION DYNAMICS

Theoretically, the equations derived in the study of social groups are valid for

any size of system. Practically, however, describing the behaviour of a very large group, or the interactions between large groups and their environments,

requires the further development of field mechanics for systems with S-dependent Lagrangians and Hamiltonians.

In order to apply S-Lagrangian dynamics to the description of the behaviour of living species in the environment, the author assumes that the primary motivation of the activity of living species is to avoid death by coping with a general indicator of proximity to death – stress. This forms the biological foundation for the author's theory of the behaviour of living species in the environment. In this case, stress is the result of both the pressure from other neighbourhood species, including competition for food and aggression, and unfavourable environmental pressure, such as food deficit, i.e. the intensity of food deprivation. Conversely, as with homeostasis, stress is decreased by inner stress protection and by regulating population densities and generating migration flow.

Computer simulations were performed using MATLAB. The results presented in the text are derived from modelling two populations of moderately dense species within a habitat. It is also assumed that during its life, one species can generate harmful factors which damage the environment and that all species have similar adaptability, corresponding to static dominance.

PEACE

Consider two coexisting species where there is no particular dominance of one species over another and individual members of the population have only a moderate intolerance of their neighbours. Initially, mainly due to population pressure, the densities of both species decrease and the communities soon achieve stable coexistence. Once the population pressure is adjusted, both species can occupy the entire habitat area. [Figures 3.1 & 3.2]

WAR

In this situation, one species dominates the other and the species are strongly intolerant of one another. There are two scenarios to consider. When the dominant species, which is producing a damage factor, invades an area of high food supply, originally occupied by the weaker species, the weaker species

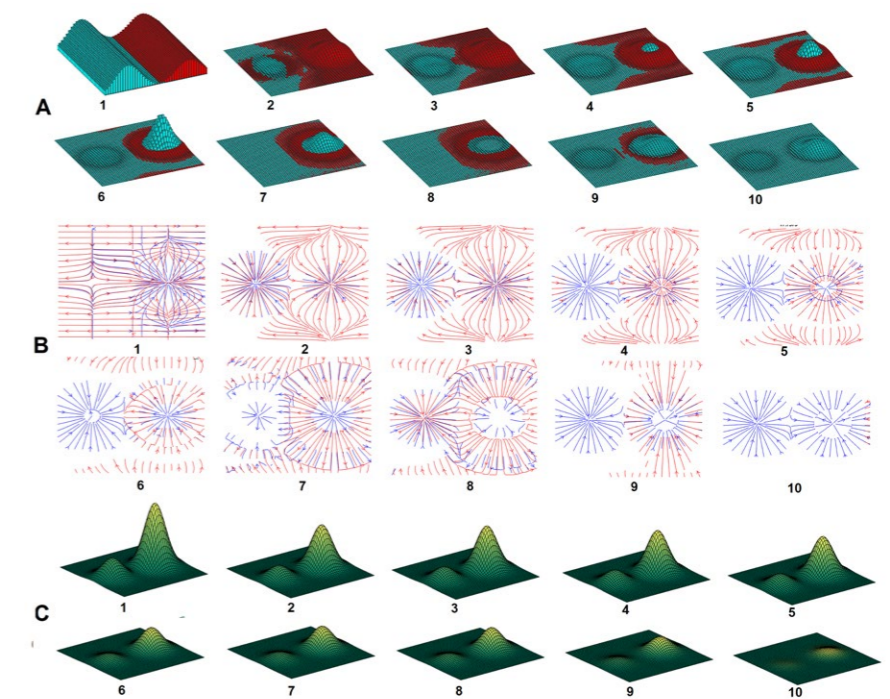


Figure 3.3 Co-evolution of species with high competition for food supply. A: Population densities; species 1 (blue) dominates species 2 (red). B: migration flows. C: food supply.

is suppressed and abolished from the habitat. However, this is a pyrrhic victory as the dominant species destroys the habitat and their density declines considerably. [Figure 3.3]

Alternatively, if a weaker species can produce a damage factor, when the

area of high food supply is invaded by the dominant species, the weaker species employs 'knock in stomach' tactics and destroys the habitat in order to defend itself and eliminate the intruding species. Initially, this tactic was successful, but the upshot is this species suffered from starvation and

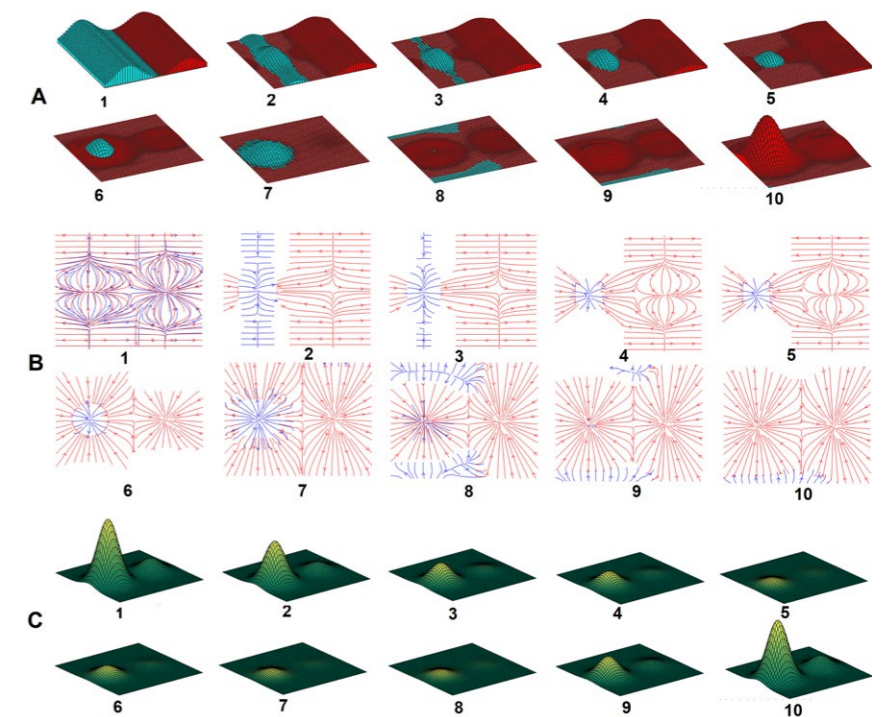


Figure 3.4 Co-evolution of species with high competition for food supply. A: Population densities; species 2 (red) dominates species 1 (blue). B: migration flows. C: food supply.



Behind the Research

Professor Uziel Sandler

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W: <https://www.researchgate.net/publication/343696463>
 W: <https://www.researchgate.net/publication/341358463>

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Bio

Professor Uziel Sandler is department chairperson in Lev Academic Centre (JCT). He is a specialist in theoretical physics, critical phenomena and the behaviour of biological systems. Uziel Sandler is one of the founders of fuzzy dynamics. He has published more than 80 academic articles in *Physical Review*, *Journal of Theoretical Biology*, *Fuzzy Set and Systems*, etc. and several books, among them *Neural Cell Behavior and Fuzzy Logics*. Professor Sandler is a member of several worldwide committees in the abovementioned fields.

Collaborators

Professor Sandler thanks the blessed memory of Prof. L. Zadeh (founder of the Fuzzy Logic) and Profs. L. Tsitolovsky and Y. Friedman for wonderful collaboration.

Personal Response

What initially sparked your interest in physics?

The blessed memory of my mother, the brilliant scientist, who inculcated in me a proclivity for science and, in particular, for physics.

Why do you think that the 'lost opportunity' was not considered until your discovery of the generalised Lagrangian?

Initially, physicists were describing the mechanical systems, where time-reversibility and energy conservation were experimentally well established. So, any form of the Lagrangians that could break these features was automatically rejected. On the other hand, direct relations between the principle of least action and "First Principles", like causality principle and topology of a system's state space, were not recognised, because Fuzzy Logic and fuzzy set theory were unknown at that time.

What inspired you to find that the causality principle would underpin S-Lagrangian dynamics?

Initially (a long time ago in 1994–1998), I developed Fuzzy Dynamics in another form (so called "triple-product" dynamics equations). In this form, Fuzzy Dynamics was successfully applied to many problems, in particular to descriptions of the behaviour of neuron cells. It was necessary, however, that fuzzy dynamics equations could transform to common dynamical equations in limited cases. Unfortunately, only after a dozen years did I recognise that this could be done by using the fuzzy form of the causality principle

together with common assumptions about local topology of a system's state space.

What was your motivation in applying the S-Lagrangian to living things?

The S-Lagrangian dynamic equations are not associated with specific properties of any particular system, and the causality principle applies equally to both physical and living systems, so these equations can be used to describe the behaviour of living beings.

What prompted you to extend the theory of homeostasis to modelling the dynamics of drug abuse?

Both homeostasis activity and the administration of opiates have one goal: reducing stress levels. Therefore, it was understood that these actions should be inter-related. Since homeostasis should be active over a long time, I recognised that prolonged drug administration would lead to drug abuse.

How did your development of field mechanics for systems with S-dependent Lagrangians come about?

More than a century ago, the ordinary Lagrangian approach was extended to field dynamics, so I have only repeated this extension.

What are the main barriers to applying S-Lagrangian dynamics to global warming?

Because in the Lagrangian approach one function (the Lagrangian) should describe the dynamics of the whole system (Earth together

Research Objectives

Professor Sandler explores how a Lagrangian approach can be used to help physics describe living systems.

References

Sandler, U. (2020). *Generalized Lagrangian Approach and Behavior of Living Systems*. American Academic Press. (Salt Lake City, USA), pp.1-187.

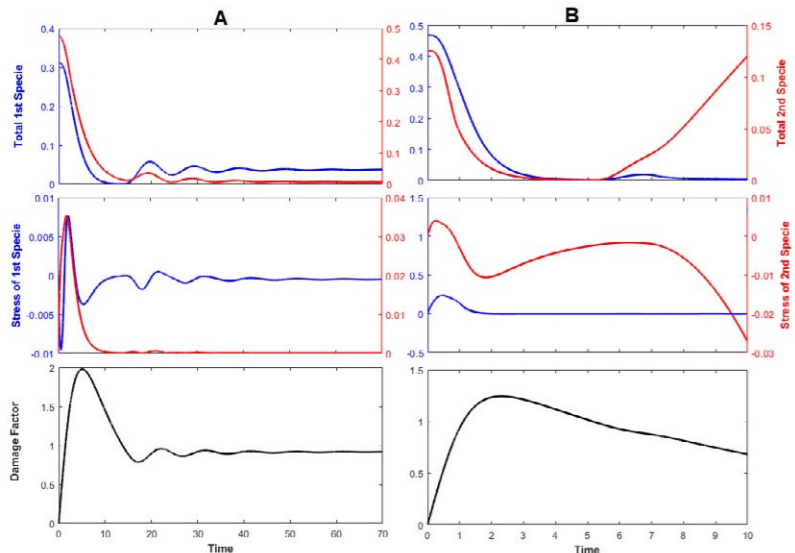


Figure 3.5 Species fighting for food supply. A: species 1 (blue) is dominant. B: species 2 (red) is dominant.

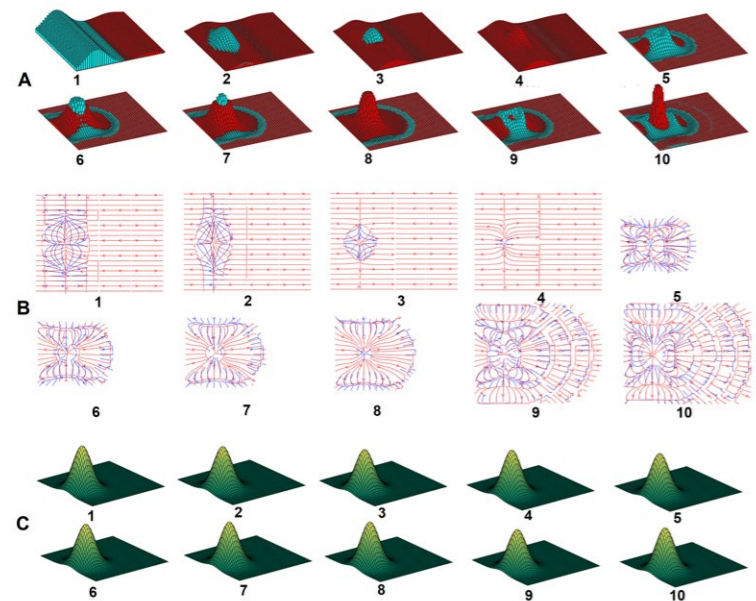


Figure 3.6 Prey-predator co-evolution. Prey - blue, predator - red. Competitive behavior. It should be noted that to improve the "visuality" of the results, we have shown populations of the prey and predator in different scales, while the density of the predator is actually much smaller than that of the prey.

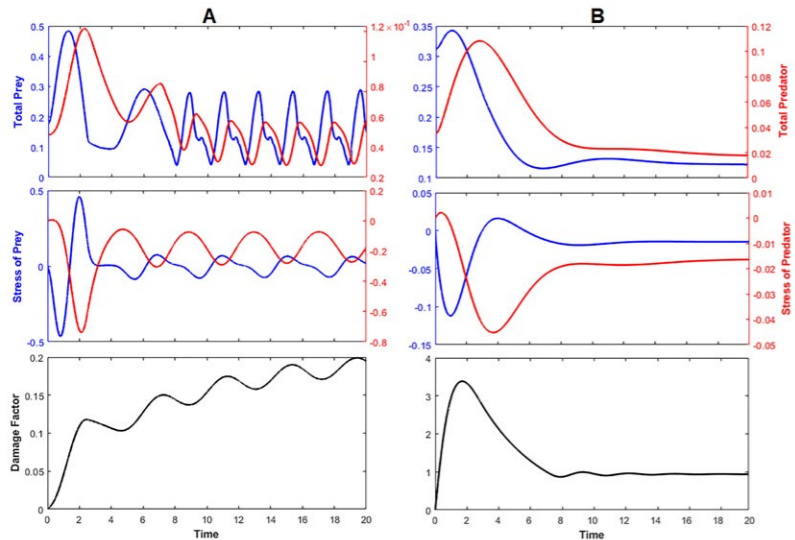


Figure 3.7 Total number of species, Stress-index and damage factor under prey-predator coevolution. A: competition, B: coexistence. (Left and right parts of the Y-axis have different scales).

was defeated, leading to the eventual improvement of the habitat. [Figures 3.4 & 3.5]

ECOLOGICAL CATASTROPHE

Ecological catastrophe simulations result in both species competing for the food supply but the damage to their environment means that both species are eliminated from the habitat. Since production of the damage factor was interrupted, the habitat recovers over time. It should be emphasised, however, that unlike the war scenarios, extinction of the population transpires with low levels of stress.

PREY AND PREDATOR

The co-evolution of a prey-predator ecosystem is explored via competition and coexistence. In these scenarios the author has assumed that the population density of the prey is much higher than the predator's initial population density and that the prey is capable of damaging the environment. Where competition exists, both population densities are shown to oscillate. Both prey and predator exhibit low, slightly oscillating levels of stress showing that they actually co-evolve peacefully. In the coexistence situation, both prey and predator co-evolve with low levels of stress. The habitat is improved by the predator suppressing the harmful prey. [Figures 3.6 & 3.7]

BROADER IMPACT

In common with any Lagrangian (or Hamiltonian) dynamics, there is only one S-Lagrangian for an entire system, so the behaviour of the system's parts cannot be analysed independently. This means that a planet made up of various habitats of living beings will appear to display the behaviour of a living creature, particularly the attributes of homeostasis and the planet's tendency to maintain stable states and integrity. Professor Sandler remarks that "in this sense, our Earth is a living planet". Examples of this behaviour are recorded in relation to the aforementioned struggle for existence. The account of what happens when sub-systems try to operate strongly independently is, however, a widespread phenomenon. Prof Sandler explains: "A world, where we live, is the result of the mutual co-evolution of both living beings and the environment."