

Carmen García-Peña
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Aging Research - Methodological Issues

Second Edition

 Springer

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Preface to the Second Edition

This second edition of *Aging Research - Methodological Issues* is presented after 3 years of our first appearance. Drivers of the first edition are the same for this second edition and remain as relevant as in the first one. Aging population process represents the most important demographic issue in the world and particularly in low and middle economies that are currently facing several challenges in the social, economic, welfare, and health services dimensions among others.

The second edition maintains the idea of doing a book with the aim of integrating crucial features in aging research, such as multimorbidity, frailty, function, cognition, healthy aging with the principles of research methodology.

With this in mind, this new edition retains the organization and the general structure of the previous one. The twelve previous chapters were reviewed and updated. The review of the scientific method is presented again as the first chapter, after the introduction, and it includes a new discussion about complex systems applied to human aging. Biomedical research in aging is now written by a team of expert researchers that introduce new lines of investigation and future perspectives. As in the previous edition, classical research designs were included in the first chapters, including descriptive studies, case-control studies, longitudinal studies and clinical trials as well as systematic reviews, with updated information. Qualitative research and mixed methods are now presented by international authors with enormous experience in these topics. Chapter 15 is a discussion about the transference of health research results into aging policy; focusing in the urgent need of evidence in all the health systems to make better decisions in the aging field, taking advantage of what research provides to stakeholders. The discussion about the relationship between technology and aging was also included, with special emphasis on ubiquitous sensing, a continuously growing field both in engineering and aging.

Six new chapters were included: Chapter 4 dedicated to Geroscience which is a modern and emerging discipline based on finding connections between the “hallmarks of aging.” Chapter 12 is focused on health systems research in aging. Health services have been particularly challenged due to an increase of health demands but also of a lack of scientific evidence. We are confident that this chapter will improve the understanding of how societies have to respond to the aging process. Big data

and data mining are discussed in Chap. 14. Both are powerful tools to obtain information that could be used to improve the health status of older people. Ethical considerations in aging research are presented in Chap. 16. This chapter argues that such exceeding medical research should always be accompanied by an ethical stance, specifically focusing on aging population. The ethical stance in research serves to, first and foremost, look to safeguard the dignity of those it researches. Chapter 17 presents a crucial topic, the process involved with searching for aging research funding. Very specific key points are presented in order to write and present a successful grant proposal when focusing on the aging field. Finally, Chap. 18 is focused on discussion of the future of aging research, and how we need to move from disease paradigms to understand the person with a holistic perspective.

We have to say that many aspects of this book have not changed. It was written with several audiences in mind. We hope that under- and post-graduate students who are interested in aging research for the first time find this book challenging and useful. Senior researchers that have not done research in the area also can find a different perspective, and refreshing concepts may be found all over the diverse chapters.

Aging research must be as a top priority of any national research agenda. As in other medical branches, researchers need to be well trained and prepared; enough funds and institutional supports are needed to obtain sounding data that has the potential to impact how older adults are taken care of in all areas of the society.

After all, obtaining results with a standardized methodology will lead in turn to the formulation of new questions that will continue enriching the ever-growing field of aging research. We hope that this book will aid in achieving these goals.

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Chapter 1

The Need for Differentiated Research Methodology in Aging



Mario Ulises Pérez-Zepeda, Carmen García-Peña,
and Luis Miguel Gutiérrez-Robledo

Abstract The global phenomenon of population aging has increased the need of accurate information in the last few years. In order to improve current status of the older adult's care, quality information should be generated by standardized research methodology. Specific issues arise when it comes to aging research, different from those found in younger stages of life. Having this in mind and how could impact the older adult will result in a continuous generation of helpful information for evidence-based decision making in all levels of older adult care.

Keywords Aging · Geriatric research · Evidence-based geriatrics · Older adult care

1.1 Introduction

It is well known that in the years to come the population group with the highest growth will be that of the elderly and that this in turn brings with it a specific demand for health care and in all areas of human activity [1, 2]. Health sciences in particular face a major challenge to maintain the well-being of older adults, since it is at this stage of life where to draw on all disciplines, it is essential to be successful. That is, it is not enough to generate information from a single point of view, it is necessary to integrate the components of a phenomenon into a single vision, for example: diabetes mellitus from the perspective of molecular biology can shed light on the phenomena that occur in this level to give rise to disability in an older adult, but it is also necessary to know what real impact this disease has at the epidemiological level, to know the pharmacology of the different medicines, to know the social influence in the health disease process, to know what elements of technology could

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improve the overall health status of diabetic older adults and once this information is obtained integrate it to establish action plans for diabetic older adults. This is why it is necessary to have solid data that allows to have accurate strategies in the shortest time to achieve this end. The aging process is not synonymous with a decrease in the function of the human body (or any other living organism), however, it does bring with it an increase in the frequency of chronic diseases, mainly diabetes mellitus and systemic hypertension [3]. Today, one of the greatest health challenges of this age group is knowing how to age with a chronic disease, what are the effects of the complications of the diseases themselves, what impact does the long-term use of medications have, it is the role of chronic diseases in the loss of functionality; among many other topics in which there is still not enough information to carry out concrete actions [4]. The most common outcome in recent years has been simply to carry out the same actions that are used in younger adults, a strategy that is not effective and in the worst case has been harmful. There are some examples in elderly Mexicans, where it has been shown that implementing a specific care strategy for older adults can improve their health status [5].

Disability and the so-called geriatric syndromes is another field with a great knowledge gap. As previously mentioned, knowing the different perspectives of these phenomena helps to have global solutions and with less margin of error when taking into account the elderly with their bio-psycho-social environment and with less emphasis on the “organicist” vision that Currently prevails in medicine, in other words, what is good for a kidney is not necessarily good for the heart.

There are two problems of particular attention in the health of older adults: dementia and frailty. Dementia is better known today and many of the resources in research are currently being devoted to its study, however it remains a condition with a high burden for those who have it and particularly for their family and social environment [6]. On the other hand, frailty - understood as the loss of the ability to respond to harmful stimuli - is still an emerging problem and with many questions still to be resolved [7].

The research that nursing has provided for aging has been spearheaded in many ways, just to mention an example, the main interventions in dementia available today are interventions designed, tested and tested within the context of research in care nursing [8]. The research potential in this field is great, however the continuous challenge is to establish links and articulate with other disciplines to perfect the knowledge acquired when the research is done from a unique and isolated perspective.

In addition, it is important to mention that the WHO is trying to shift the paradigm from disability to healthy aging, in order to tackle progression from a starting point, rather than it's too late.

1.2 A Theoretical Frame for Aging Research

Different disciplines are grounded in theories that give the topic a sense and a cohesion that could further be enriched by new knowledge. Aging research has a number of potential theoretical frameworks that could be used for this purpose. However, as it happens in other medical disciplines, there is no agreement on which particular theory is appropriate. Evolution of species is one of the most useful theories to explain aging and has fully translated into aging phenomenon by the disposable soma theory of Kirkwood. Moreover, many of the processes that occur during aging seem to respond to evolution.

1.3 Particular Features of Aging Research

Once the aging of the population and the lack of information on this age group is recognized as a problem, the question arises about what distinguishes scientific research on health in this area from other disciplines [9].

Research into age and aging uses the scientific method to generate knowledge, not unlike other disciplines. However, it incorporates many more elements than those generally used in “traditional” health research. One of the main differences is the focus on the preservation of function of older adults at different levels (with difficulty, independent, dependent, etc.), in contrast to the objective of preserving life, which is more usual in health research in other age groups [9]. On the other hand, the reductionist focus of other medical specialties (internal medicine, surgery, orthopedics, etc.) makes it difficult to study the phenomenon of aging and it is more useful, both conceptually and in practice, to focus on the biology of systems, or a holistic approach [10]. Another type of focus that can be useful is called “subject-centered”, in which the weight of the signs of discomfort by the persons involved acquires more relevancy than the numbers from biochemical measurement [11].

The incorporation of more topics of investigation than is the case at present will be done in the years to come. Among the new items to consider are: services (access, quality, innovation, technology), the incorporation of social determinants of health, deep analysis of these determinants, a multi-disciplinary approach, systematic incorporation of the evidence for creation of public policies, and molecular biology (genomics, proteomics, metabolomics) [9]. As well, in a world of limited resources, research in the economics of health is a fundamental ingredient for the creation of knowledge for improving the clinical care of older adults. Those changes (if any) will have to be adapted to the group of older adults.

Research into age and aging is no different from other research; it simply has emphasized some characteristics that are often harder to investigate in this age group, such as: defining what is normal (normal changes in aging vs. pathological changes), “normalization” of problems/illnesses of age, nihilism (thinking that whether or not something is done, why do research in this age group if they will

soon die or be incapacitated?), non-specific manifestations of problems, coupled with homogenous definitions – bias in classification – (the case of frailty, whose variability shows up in studies of it), the need for adequate sources of information (valid scales, trained interviewers and optimization of obtaining and analyzing data, to name a few) [9, 12].

There are a number of examples on how aging is different from other type of research, in this chapter some of them will be reviewed.

1.3.1 *Heterogeneity in Older Adults*

With the goal of having a framework of heterogeneity in age, what follows is a description of different groups, very differentiated within this population segment. With the advances in knowledge about aging in recent decades, a group that previously appeared to be homogeneous now is known to be made up of distinct sub-groups, whose characteristics must be taken into account in the various domains at the time of doing the research [13]. Even though there is agreement about the age at which a person should start to be called old (older than 60 years), this does not always correlate biologically [14]. There are sub-groups with specific characteristics, whose differences must be taken into account throughout the design and development of any research project into age or aging: sampling (over-sampling of barely representative groups), selection criteria, stratification, allocation of the intervention, statistical adjustments, in a way that real conclusions are arrived at and not derived from population differences established *a priori* (see Table 1.1). Another characteristic that generates different sub-groups, and that it is crucial to take into account, is related to the losses in the trials, since in some cases they are highly characteristic, for example, in subjects with dementia.

Therefore, it is necessary to thoroughly know these different groups within the group of older adults, in order to be able to make the pertinent adjustments in the design of the protocol, or in the last instance, if this is not possible, at least to describe the population group and its distinct characteristics. The following is a detailed description of some of the characteristics that produce the marked differences.

1.3.1.1 Age

The easiest way to look at for this category is chronological: the more years that have passed, the higher the probability of suffering one or more illnesses, and the same with loss of function, frailty and the appearance of geriatric syndromes. Therefore, the division of these groups by age in research has a clinical logic. In addition and depending on the outcome – following the Gompertz curve – it is known that the probability of dying is greater with advancing age, a situation to take into account, for example, when comparing groups of subjects of 60 and 90 years of

Table 1.1 Different groups to take into account in age and aging research

Group	Categories
Age	Young-old 60 to 79
	Old-old 80 to 89
	Extremely old 90 and above
	Nonagenarian 91 to 100
	Super-centenarians older than 101
Function	Effective function without difficulty
	Effective function with difficulty
	Ineffective function without difficulty
	Ineffective function with difficulty
	Loss of function in some activities, with dependence with assistance
	Loss of function in some activities with dependence without assistance
	Loss of function in all activities with dependence with assistance
	Loss of function in all activities with dependency without assistance
Multi-morbidity/ Polypathology	Without non-degenerative chronic illnesses
	With one non-degenerative chronic illness
	With multi-morbidity/polypathology
Life prognosis	Without terminal illness
	With a terminal illness but without probability of dying in the next 6 months
	With terminal illness with probability of dying within the next 6 months; not moribund
	Moribund
Specific pathology	Without a specific pathology
	Dementia
	Cancer
	Frailty
Level of care	Ambulatory
	Acute hospital care
	Chronic hospital care
	Residence
	Hospice
Caregiver	Without a caregiver
	Without caregiver burden
	With caregiver burden

age. If one wants to evaluate the effect of a particular intervention, wants to show the impact on mortality, and is unable to find any, the difference by age – expected and not adjusted – would be the explanation [15]. Finally, the group most advanced in age, the people older than 100 years of age, is much less represented in the studies, being one of the most forgotten groups in all types of research.

Taking into account the foregoing, conventionally the most common way to divide groups of older adults by age is: “old-young” 60 to 79; “old-old” 80 to 90; “ancient old-old” 90 and over; “nonagenarians” 91 to 100; and “super centenarians” greater than 101 years [16]. As can be observed, this is an arbitrary division and within each group there is also a lot of heterogeneity, given that health strategies not only provide for an increase in life expectations, but also an increase in the expectation of a healthy life. Alternatives to the division by age groups could be those given by levels of functioning, the extent of non-transmittable chronic illness, specific pathologies (cancer, dementia, etc.), level of health care required or frailty status.

1.3.1.2 Function

Defined as the capacity to be able to carry out, independently and autonomously, the activities necessary to take care of oneself under optimal conditions and within one’s own surroundings, function is an effective way to classify the elderly. There is a large spectrum between the two extremes (independence and dependence), with a number of activities within which is also a different range of effectiveness in capacity to carry out these functions (independence in function, difficulty in doing this, and total dependence on someone else to be able to do some of the activities). Taking into account the potential effect function can have on a particular intervention improves the possibility of obtaining other appropriate outcomes. Research can also be carried out on specific groups of levels of functional, as is the case in researching the cause of pressure sores in people almost totally dependent; testing an intervention on injuries to cure them. The fact of not taking into account functional could give the false impression of the functional and the effectiveness of the intervention.

1.3.1.3 Multi-Morbidity

Recently there has been emphasis on this concept (suffering from more than one non-transmittable chronic illness for which the person is taking medicine regularly), because it appears that it could involve a problem with characteristics different from the rest of the population and an entity in which there would have to be special care taken in carrying out clinical tests at the time of reporting the interactions. This is the case not only with the medicines but also with the illnesses, and the potential synergies that might exist. The strategy of excluding competing risks is known, that it is not possible to control them and that they could bring about the outcome they intend to change with the intervention. The foregoing is especially true when dealing with cohort studies in which an exposed factor tries to associate with a specific outcome, since with the passage of time there are other exposures that could bring about the same outcome, for example in the case of falls – which can be caused by multiple factors – and not taking into account several causes for the adjustment in one of the moments of the research project [17]. However, several solutions have

been promoted in the area of old people. One of the most common is the use of indices of comorbidity, for example Charlson's, in which the results can be adjusted specifically to this comorbidity burden, and theoretically eliminating this potential source of confusion in the clinical tests. To choose the population *a priori*, in such a way as to exclude some with competing risks would hardly be practical (and hardly realistic) in research in older adults, given the low probability of finding "healthy" old people or people with just one pathology.

1.3.2 Animal Models

Even that it has been said that modeling of aging is somewhat a closed matter, and we do not have the need to discuss it further, there have been some problems with modeling animals due to the complex nature of older adults. The typical example is frailty, a multi-level problem that renders an older adult prone to adverse events in the face of usual stressors, which has been shown to be difficult to model in animals.

1.3.3 The Role of Time

Time is one of the most difficult issues to handle in aging research. One thing is to have age-related problems, which have been defined as those that are only related with time passing by and the other is that of age-dependent problems in which those mechanisms that render an organism old, also have a role in disease.

1.3.4 The Role of Outcomes

Death is more common for the aged ones. In other kind of studies, mortality is the main outcome. However, when it comes to older adults, mortality is not always the best outcome to measure, and other outcomes are more important.

1.3.5 Statistical Approaches

A recent number on the journal of gerontology series B has been devoted exclusively to the description of different solutions to a number of problems faced in aging research. This is particularly true when it comes to analyzing longitudinal studies, in which attrition rates are high. Competitive risks are among other type of

problems faced when analyzing longitudinal studies and related outcomes in population.

1.4 Conclusions

To better understand the problems that could be presented at each stage of the research in areas of age and aging, knowledge is created clearly and with a solid scientific structure that contributes to improvement in the quality of care for older adults and a clearer understanding of the processes that could have impact on their overall health.

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Chapter 2

The Scientific Method as a Point of Departure in Aging Research



Rubén Fossion and Leonardo Zapata-Fonseca

Abstract What makes knowledge scientific is not its content per se but rather the form, in which it is obtained. Following the scientific method is a necessary condition to carry out a sound and methodologically valid research. However, for empirical researchers, it is not common practice to reflect upon the method itself. It has been argued that the scientific method is not so different from the common sense that we use in daily life to reach solutions, but with its successive steps better articulated so that scientific knowledge can approach more robust conclusions over time. Since the last quarter of the previous century, there are indications that reductionist strategy of the scientific method has reached its limits, and that therefore a complementary approach is needed to investigate new complex research problems. Consequently, emergentism and systemic thinking are becoming a new explanatory framework that is currently permeating virtually any field of knowledge and all spatiotemporal scales. In the present chapter, we focus on a very specific system under a rather specific yet common and relevant condition: the aging human being. Particularly, we introduce some notions on how the sciences of complexity can help, not only clinicians but also medical research in general –and in particular aging research– to reach a more complete understanding and assessment of the older adult both at an individual and population levels.

Keywords Philosophy of science · Reductionism · Complexity · Effective theory

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2.1 Introduction: History and Philosophy of Science

Society esteems science for its presumed quality of being based on objective facts, so that scientific research has more weight and authority than a personal opinion [1]. But what makes something scientific? It is not the object or the topic under study but rather the methodology with which a study is carried out and the standards that are used to judge the obtained results [2]. The methodology that is used in science, or the so-called scientific method, is not very different from the way in which we use common sense to interpret events in our daily lives. Common sense analyzes the information we receive through our senses (sight, hearing, touch, smell, taste) as being real and independent from the observer. Without thinking consciously about the steps taken, our common sense is based on a sequence of observation, evidence and verification; scientific thinking follows the same logic, but the scientific train of thought is slowed down for increasing transparency and control during the various steps. Transparency is important because scientific research is a collaborative activity and peers and colleagues must be allowed to repeat experiments, verify results and construct more advanced theories based on previous results [2].

The scientific method developed gradually through several millennia. The Ancient Greeks, such as Socrates (469–399 BC), Plato (427–348 BC), Aristotle (384–322 BC), Ptolemy (90–180 AD) and Galen (130–200 AD), were pioneers in setting up a science independent of religious dogmas; theirs was mostly a contemplative science based on abstract axioms to which they applied deductive logic in order to obtain new statements, at most passive observations of Nature were made and induction was used to obtain new hypotheses. During the dark ages of Europe’s Medieval Period (500–1300 AD), much of the scientific knowledge of the Ancients Greeks was lost. Fortunately, a lot of that knowledge could be recovered thanks to the Arabs (700–1500 AD) who had adopted the science of the Ancient Greeks and who had contributed with active experimentation, which was an important step forward because now theoretical predictions were verified with experiments. The next important period is the scientific revolution (1500–1800 AD), which was caused by various factors. One factor was the foundation of the first universities, which resulted in a gradual “liberalization” of the sciences and leading to a more pluralistic vision not dictated by a few authorities. Another factor was humanism as the new philosophical and ethical current having as one of its purposes to explain all-natural phenomena without any reference to the supernatural. Technological inventions, such as the microscope and the telescope, further accelerated the advance of science. Also, important resulted to be mathematical modeling, which allows researchers to make not only qualitative but also quantitative predictions.

The study of the history of the scientific method and how the scientific method is applied, is a science of science, also called meta-science, and therefore belongs to the field of philosophy of science. Philosophy is a forum to question and clarify concepts that other disciplines believe to be obvious without having investigated these questions explicitly [2]. Philosophy of science analyzes the various steps of a scientific investigation. Consequently, the philosophical approach tends to be

abstract and idealistic, and the goal is to define an absolute and universal scientific method that is valid for all disciplines and for all times.

In the application of the scientific method, the following properties are often taken for granted:

- The data are previous to and independent from theory;
- The data constitute a firm and reliable base for scientific knowledge;
- The experimental data are obtained by impartial observation through the senses.

Philosophers have identified some problems with these assertions, such as theory and subjectivity ladenness [3], confirmation and rejection of the theories [4, 5], and how to evaluate scientific progress [1].

The American physicist and philosopher of science Thomas Kuhn (1922–1996 AD) revolutionized the way in which scientific progress is perceived. Before Kuhn, scientific progress was interpreted as a gradual process; it has been suggested that our textbooks are to blame for reinforcing this view of a continuous accumulation of ideas up to the current state of science, while Kuhn argues that scientific achievements of the past need to be interpreted within the context of sociological factors and scientific perspectives of the time in which they were developed [6]. It appears that within each scientific specialty, prolonged periods of stability and consolidation precede short bursts of major conceptual revision, which Kuhn called paradigm shifts [7]. A paradigm is a coherent set of theories and concepts that guides interpretations, the choice of relevant experiments, and the development of additional theories in a field of study. Examples of contrasting paradigms in physics are: heliocentrism vs. geocentrism, Newtonian gravity as opposed to Einstein's theory of general relativity, and classical physics versus quantum mechanics. In medicine, examples of paradigm shifts are the dissection of human cadavers as introduced by Vesalius, the use of the microscope and the development of synthetic drugs.

Standard science works within the framework of an existing paradigm that guides a field of research. In this case, almost all the research relates to the paradigm: research is carried out according to a fixed scheme, and it is the paradigm that indicates which topics for research are appropriate and worthwhile; theoretical and experimental studies imply the collection of data to verify predictions of the paradigm and consider also efforts to extend the paradigm in order to include apparent problems or ambiguities. Research within an existing paradigm is sometimes described in a pejorative way as “cleaning up”. In a new field, that is, a field in a pre-paradigm state, no fixed scheme exists that indicates how experiments should be done or how data should be interpreted. To draw an analogy: data collection within the framework of an existing paradigm is like a hunter pursuing a prey, while without the guidance of a paradigm it rather resembles going for fishing in a lake to see what comes out [6]. In the absence of a paradigm, lots of data may be available but they are extremely complicated to interpret, and the general pattern and the main principles are vague; several currents of reasoning compete without agreement on which phenomena are worth studying, and no single current of reasoning can offer a more general view of the field.

2.2 A Pragmatic Approach to the Scientific Method

In comparison with philosophers, working scientists are more realistic and conformist, and are satisfied with an approximated scientific method that in the first place must be applicable to their daily research activities. The structure of the scientific method, in its most basic form, can be summarized as successive repetitions of the following sequence, see Fig. 2.1:

Observation→*Taxonomy*→*Working Hypothesis*→*Prediction*→*Empirical Verification*

In the observation phase, relevant data about a natural phenomenon of interest are recognized. The taxonomy stage detects and classifies regular patterns in the data. The inductionⁱ phase enables the researcher to generalize and simplify these patterns in one or more theoretical hypotheses to explain the phenomenon. Abductionⁱⁱ is a type of logical inference that is used to select the most probable hypothesis from a set of possible hypotheses to explain a given phenomenon. Applying deductiveⁱⁱⁱ logic to the working hypothesis allows to derive predictions, which can be verified with the results of carefully controlled experiments. A controlled experiment is one where a certain (independent) variable is manipulated to study the consequent changes in another (dependent) variable. It is preferable that

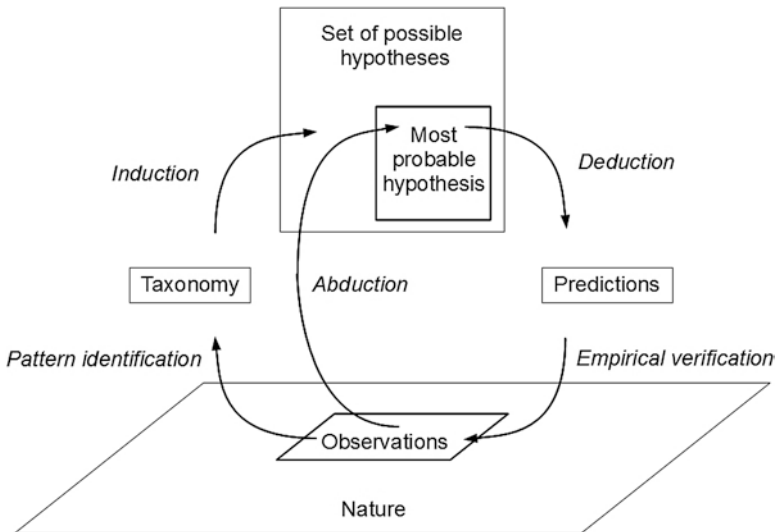


Fig. 2.1 The process of scientific reasoning is iterative and alternates between deduction, induction and abduction. Induction generalizes observed patterns in nature in theoretical models. Abduction selects the most probable working hypothesis from a set of hypotheses to explain an observed phenomenon. Using deduction, predictions are made from the hypothesis to be verified with data from controlled experiments, so that the hypothesis can be checked and corrected if necessary