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Systems Thinking: a Bridge between Chinese and Western Perspectives in Biomedical Field

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Quasi tutto quello che osserviamo è un sistema complesso, compresi noi stessi.

- Giorgio Parisi -

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Preface

Systems Thinking (ST) may be defined as a conceptual and analytical framework meant to describing the behaviour of systems consisting of complex interconnections, allowing to move from a traditional liner cause-effect way of thinking to a mutual causation description of the system. ST allows to understand how and why things happen and not only what and when. The systemic approach may be applied in a variety of sectors, and it is useful in different medical fields, finding application in the description of health care systems and in the description of epidemics. For instance, ST was particularly efficient in dealing with the COVID-19 pandemic in South Korea, where the application of a mitigation strategy was effective in avoiding major social actions, as true lockdowns, while keeping the daily new infections between 50 and 100 cases.[1]

In recent times, also the biomedical field started to open its doors to ST in the analysis of complex diseases. ST approach may lead to a new way of conceiving complex diseases, such as systemic cancers, allowing dynamic descriptions and leading to the representation of different evolution scenarios, taking into consideration different patterns of interaction between the involved agents and different periods of time.

The present works aims at showing the role of ST as a bridge between Western and Chinese Traditional approach in the biomedical field, referring to a concrete and "complex" disease as Multiple Myeloma (MM). Indeed, ST could potentially fill the gap existing between Traditional Chinese Medicine (TCM), which is characterized by an holistic (though not analytical) perspective that takes into consideration all the different elements that enter into play when a disease arises, and Western medicine which can find its roots in a linear cause-effect way of thinking, in which every symptom is treated individually and in which the main goal is to find the "magic bullet" that can solve each respective physical problem in the shortest possible time.

In showing the role of ST as a bridge between two different medical approaches, great attention will be devoted to the technical language; indeed, the present works identifies an English – Chinese terminographic repertoire that can be employed in the description of ST, MM and TCM. The terminographic repertoire aims at providing to English or Chinese speakers the key terms to understand an article dealing with ST, MM or TCM and to be able to express an opinion on that. The choice to opt for an English – Chinese correspondence is mainly determined by the country of origin of the above-mentioned disciplines and by the current location of the

[1] Imad HASSAN, et al., "A Systems Thinking approach for responding to the COVID-19 pandemic", *East Mediterranean Health Journal*,26, 8, 2020, 872–876, (last access June 2, 2023).

greatest research hubs. Indeed, nowadays, China and US represent the avant-garde in the development of the Systems Thinking and Multiple Myeloma disciplines.

The present work will develop its discourse trough three main sections, each of which will provide the reader with the necessary knowledge to understand how ST can efficiently fulfil the role of connecting element between two worlds that, at a first glance, seem to be completely incompatible: in section 1, a general overview over ST, MM and TCM is provided; section 2 includes English – Chinese terminographic repertoire; section 3 is dedicated to the English – Chinese and Chinese – English glossary, whose main scope it to sum up the information provided by the terminographic cards in section 2.

Chapter 1 deals with the basics of ST, also referred to other different approaches as Network Medicine, Systems Biology, Systems Pharmacology and P4 medicine, which also originated from Systems Theory, but developed on a parallel path. As we mentioned in the first paragraph, ST is an approach which tries to overcome the limits given by linear thought, by analysing how different elements interact with each other, giving birth to the system complexity. The main characteristic of ST is that it has a different starting point with respect to linear thinking; in ST every problem is analysed within the definition of a complex system made of stocks, flows and processes. Once a system diagram has been set up and the main flows and feedback loops have been defined, it is possible to create a computational simulator to study the systems upon external drivers' changes.[2] The system, resulting from the interaction of different stocks with different processes, is "complex" because the involved agents endlessly change the patters of interaction made by the network of feedbacks existing among them, and are themselves subjected to changes in their proper nature. We should note that everything can be rethought in a systemic way, shifting from simple "linear chains of causation"[3] providing static "photographs" of systems to "mutual causation structures"[4] able to describe the very dynamics of the system, used not to "give a picture" of the reality but to show "how reality works".

Chapter 2 deals with pathogenesis, risk factors and staging of MM. In this chapter, great attention is devoted to the staging system of MM which plays a crucial role not only in determining life expectancies and in symptoms classification, but also in deciding which is the most appropriate treatment option. Three stages are identified in the disease progress, respectively Monoclonal Gammopathy of Undetermined Significance (MGUS), in which the disease is totally silent, Smouldering Multiple Myeloma (SMM), characterized by an increase

[2] Francesco GONELLA, "A gentle introduction to Systems Thinking and its application in the context of regenerative city patterns", in A. Reith and J. Braikovic (eds.), *Scale Jumping - Regenerative Systems Thinking within the Built Environment*, 2021, COST Action CA16114 RESTORE: REthinking Sustainability TOwards a Regenerative Economy.
[3] *Ibidem*
[4] *Ibidem*

in the malignant cells and symptomatic Multiple Myeloma, which is the last stage of the illness and the most complex to deal with.

Chapter 3 explores the basics of Traditional Chinese Medicine (TCM), clarifying the main concepts of Yin-Yang and Qi. In this chapter particular focus will be casted on TCM diagnostic tools as pulse analysis and tongue inspection which represent the most objective criteria in TCM. Furthermore, the role of blood and fluids will be explained, mainly in relation to the complex network of meridians which radiate throughout the whole body. Finally, consideration over TCM relationship with western medicine will be made; in particular, great attention will be casted on the role of ST is playing the role of a bridge between TCM and western medicine.

The second section of the present dissertation is dedicated to the terminographic repertoire which consists of terminographic and bibliographic cards whose main objective is to provide readers with a complete comprehension of the most relevant terms used in this discourse. The present terminographic repertoire has been conceived to be included into databases as MultiTerm, employed within Computer Assisted Translation (CAT) software, as Trados® (developed by SDL MultiTerm). The terminographic cards have been written with the word processor Microsoft Word, respecting the Standard Generalized Markup Language (SGML), a metalanguage defined as standard ISO (ISO 8879:1986 SGML), which defines the code used to draft texts mean to be transmitted and stored with computer tools.[5] Bibliographic cards include the systematic collection of sources used in the drafting of terminology card, used to fill in the <source> field.

The terminographic compilation includes 89 cards, which constitute a starting point in the terminographic description of ST and MM and it is open to further additions and expansions as the research in this fields progresses, and new words are developed and systematized.

The last section of the present work is reserved to the English – Chinese and Chinese – English glossary, which summarizes the information of section 2 by simply providing the correspondence between the English, Chinese and pinyin version of each term. This section is meant to work as a quick reference for those who already read the terminographic cards.

All things considered, even if this dissertation represents only the preliminary stage of the research on the technical language used in ST, it should be noted that in understanding the role of ST as a "bridge" between two different medical approaches, the language itself constitute

[5] International Standard Organization. ISO, ISO 8879:1986. Information processing — Text and office systems — Standard Generalized Markup Language (SGML), in "ISO official website", 2020, https://www.iso.org/standard/16387.html, (last access May 22, 2023).

a powerful element which may the determine the degree of efficiency in communicating contents through diagrams.

SECTION I

CHAPTER 1

Systems Thinking: an overview

In this chapter the basics of Systems Thinking (ST) will be provided, taking into consideration its history, its core principles, and its composing elements; in particular, a light will be casted on the approaches that have been developing parallelly to ST and that originated from the same original theory, as Network Analysis, Systems Pharmacology, Systems Biology and P4 medicine. Part of this chapter will also be devoted to the description of the application of ST in the health field, focusing on two main examples: the COVID-19 pandemic and the management of an hospital ward.

1.1 Systems Thinking: introduction

Systems Thinking (ST) may be defined as a conceptual framework that is meant to overcome the linear approach in describing the behaviour of systems consisting of complex interconnections; in this sense ST allows the individual to move from a traditional cause-effect way of thinking to a mutual causation structure. ST allows individuals to understand how and why things happen and not only what and when they happen as in the linear view.

ST can also be thought of as a language, as it involves some specific vocabulary to describe the reality. ST focus on the macrolevel, trying to determine the "global" behaviour of the system and providing information about the dynamics that regulate the system. When analysing the system, it is necessary to move from "detailed complexity", which is caused by totality of the element in the system, to "dynamic complexity" in which generalization is necessary to understand the dynamics of the system, since the more variables the system tries to consider, the weaker it is the ability to understand the whole.

Strictly related to ST is the concept of mental modelling which refers to "explicitly map the understanding of the problem and making it transparent and visible for others trough Causal Loop Diagrams (CLD)".[6] CLD "provide a framework for seeing interrelationships rather than things, for seeing patters of change rather than static snapshots".[7] A good CLD should be self-explanatory which means that it shouldn't need additional explanation to be intelligible to the reader.

ST comprehends two other concepts: System Analysis (SA) and System Dynamics (SD). The former refers to the process of discovering the structures that are present in the system and

[6] Hördur V. HARALDSSON, *Introduction to System Thinking and Casual Loop Diagrams*, Lund, KFS AB, 2004.
[7] Peter SENGE, The Fifth Discipline. The Art and Practice of the Learning Organizations, New York, Doubleday Currency, 1990.

involves the creation of mental structures using CLD. The latter, instead, refers to the mathematical representation of the system once a mental map has been created.

1.1.1 The system

A system is "a network of multiple variables that are connected to each other through causal relationship and expresses some sort of behaviour, which can only be characterized through observation as a whole".[8]

A system is characterized by four main traits:[9]

1. Systems have a purpose: the purpose act as the pivotal organizing force in the system and provide the system with the integrity that holds all the elements together. The understanding of the purpose is necessary to take appropriate actions and to fully understand their impact on the system.
2. Every element of the system is necessary to carry out the system's purpose: if the individual takes one piece out of the system, it won't be able to work in properly anymore to reach the final purpose.
3. The order in which the elements are organized affects the system's performance: the arrangement of the elements in the system plays a great role in determining the functioning of the system and different ways of locating the elements may determine the non-functioning of the system.
4. The stability of the system is achieved through feedback: feedbacks provide information to the system and allow the system to organize itself to fulfil a specific purpose.

1.1.2 Evolution of System theories

The first framework that referred to the idea of "system" was elaborated by Alexander Bogdanov, a Russian researcher, who defined three characteristics of the complex systems:[10]

1. Organized complexities: the whole is bigger than the sum of the single parts.
2. Disorganized complexities: the whole is smaller than the sum of the single parts.
3. Neutral complexities: organizing and disorganizing activities offset each other.

In the 1920s also Paul Weiss proposed a system view after conducing some experiments in the Viennese Prater Vivarium.

Ludwig von Bertalanffy expanded the work of Bogdanov and opened the way to the system theories in the 1940s. Bertalanffy firstly proposed its theory in 1937 at the University of

[8] Dietrich DÖRNER, *The Logic of failure. Recognizing and Avoiding Error in Complex Situations*, Reading, Perseus Books, 1996.
[9] Daniel H. KIM, *Introduction to Systems Thinking,* Arcadia, Pegasus Communication, 1999.
[10] Fritjof CAPRA, *The web of life. A new synthesis of mind and matter*, New York, Flamingo Publisher, 1997.

Chicago and as Bogdanov did, he pointed out that system theory is focusing of the whole and not on the single parts; indeed only by considering the system as a whole it is possible to fully understand the different relationships and reaction that are taking place.

In the 1920s another prominent researcher appeared on the ST panorama: Paul Weiss was a biology professor who proposed the concept of "system reaction" according to which when one element of the system is altered, the other elements in the system are consequently altered by the system itself to maintain a situation of equilibrium.

The system theory was further developed by the Cybernetic movement led by Norbert Wiener and John von Neumann: they developed the concept of feedback and self-regulation, spotting new light of the system theory. Indeed, the greatest achievement of the group refers to the discovery of a specific feature of ST: they clarified that in ST it is possible to move freely through the different levels of the system and to observe how different laws act on the different levels of the system.

The Nobel Laureate Ilya Prigonine highlighted that all sciences are non-linear and only non-linear equations are able to fully describe systems that are not in perfect equilibrium.
In the 1960s and 1970s, it became clear that system theory was applicable to a variety of sectors and field of study, and it acquired a trans-disciplinary nature; "sustainable development" is the best example of the interdisciplinary nature of system theory. The adoption of the system theory in a variety of disciplines is positive but at the same time it leads to contradictory positions that are weakening the prime intention of the ST theory. Since the death of Bertalanffy in 1972, the development of system theory has not been systematically described and this partially confirmed that the interdisciplinary research across different fields is still very limited.

Rupert Riedl, in 2000, tried to establish a bridge between different scientific fields and he stated three aspect that need to be considered concerning the research on system theory. Firstly, it is so be accepted that since ST is used differently in different fields, expansion and incompleteness will arise; secondly, the ontological reductionism needs to be corrected and lastly it is needed to show how the system theory can contribute to evolutionary epistemology and theory of evolution.

In the present time, the main issue related to system theory is that the interdisciplinary approach that constituted a novelty at the time of Bertalanffy, seems to be overcome by an overspecialization in each field of study, which made it clear which are the borders of each discipline and as, Mtjaz Mulej pointed out, this renders harder to deal with problems on a global scale.

1.1.3 “The Iceberg” model

To fully understand how a system fits into reality, it is necessary to consider reality from multiple perspectives and “The iceberg” model provide us with three main levels: events, patterns, and system structures.

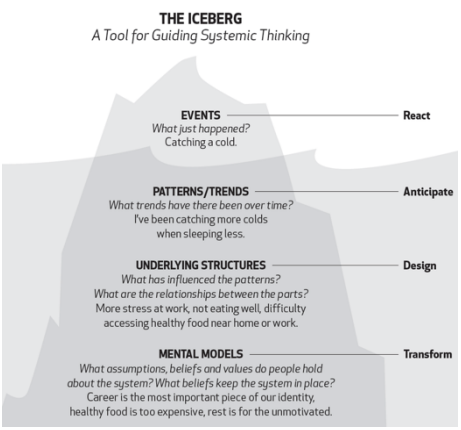

Figure 1: The Iceberg Model

Systemic structures constitute the basics of the iceberg and refer to “the way in which the system is organized”.[11] System structures can be physical, such as the way in which a ward is organized, or intangible, such as the way in which the shifts in the hospital are scheduled. Patterns are the memories and the information that individuals accumulate in time regarding a specific event, for example it can be considered a pattern that during Friday and Saturday evenings the incidence of patients in the ER is higher than in other day of the week. Events are the phenomenon that individuals face daily.

Since our world is event-oriented it is much easier for individuals to identify events rather than patters or systemic structures and this leads to the fact that individuals try to solve and to answer to events without understanding the causes and the patterns that exist behind them. To “The Iceberg” structure it is possible to add two more levels that are the mental models and vision.

Mental models refer to the ideas and beliefs that individuals have about the reality around them. Mental models would be located at the basis of the pyramid, below the system structures as the way in which individuals organize the systems, strongly depends on their perception of reality.

Vision refers to the idea that individuals have about the future and about what they want from the future, and it would be located below the mental models as the way in which we perceive the reality is determined by what we want from the future. Vision acts a force that drives our actions to achieve a specific goal.

The “Levels of Perspective”[12] framework is developed upon the different levels of “The Iceberg” model and provides individuals with a configuration useful to identify leverage points, actions patters and systemic structures. According to this framework, the individual first reaction is *reactive,* and it is located at the level of the events; this type of action is usually immediate, meant to solve the problem in first phase but not useful to understand the dynamics of the

[11] Daniel H. KIM, *Introduction to Systems Thinking,* Arcadia, Pegasus Communication, 1999.
[12] *Ibidem*

problem. At the level of the pattern, the reaction is *adaptive*; in this case the individual, by looking at the problem for a consistent period, is able to adapt to the situation to find the best solution for the current system. Adaptation can be intentional, if it is the result of a process, but can also be unconscious. Coming to the systemic structure, the individual action is *creative*, because by changing the systemic structures the individual changes the activities that characterize its daily life, creating new routines and habits. A *reflective* reaction takes place at the level of the mental models, indeed, by changing the systemic structures the individual must also change the basic assumptions and beliefs on which his life is built upon, and this may require a great effort. Since the change of the mental models is complex and puts the individual in a discomfort situation, the individual enters it only if he has a specific vision of something he wants to create; therefore, the type of action that takes place at the level of the vision is *generative* as it creates something new that did not exist before.

All things considered, "The Iceberg" model and the "Level of perspective" framework are useful to the individual to have a full comprehension of the reality and to really put into action a circular view, overcoming the linear one.

1.1.4 Mental modelling

Human beings use mental models in daily life to organize the world that surrounds them, and decisions depends on the routines and mental models that characterize the mind of people. Routines are positive because they allow human beings to live in harmony and to act within a comfort zone but at the same time, they have side effects in the sense in which they are so rooted in the life and behaviour of human beings that they are not able to detour from them to learn new things.

The presence of this mental models leads to the fact that individuals understand reality when it is linear and static and when time is not an independent variable; however, it is to be considered that the majority of problems constituting reality are dynamic which means that they are influenced by the time lag. Generally, human mind performs poorly when it comes to complex problems, and this is mainly determined by the fact that traditional education teaches that reality is made of linear relationship and not of circular events.

1.1.5 Systems Thinking Diagrams

In ST a relevant role is played by the creation of diagrams that are meant to graphically shows how the system is working and to simplify the understanding of the dynamics of the complex whole, by showing the system's main actors, patterns, processes, and concepts.

The stock-flow representation has an intrinsic abstract nature, and it is not a "photograph" of the whole of stocks that constitutes the system, but it is rather a symbolic representation meant to show a precise dynamic or a set of dynamics on which the researcher is interested into. The identification of these dynamics helps in understanding how the system is working and to identify leverage points on which to intervene; the leverage point can be defined as "an area where small changes can yield large improvements in a system"[13] and they constitute the "point of power"[14] of the system. Empirical data shows that focusing on isolated problems leads to the solving of the symptoms of the problem but does not discover and verify the underlying causes.

The goal of ST is to unravel the leverage points so that to be able to act on a larger scale and to have an impact on the whole system, rather than on single symptoms. However, "the areas of highest leverage are often the least obvious"[15] and therefore it is difficult to understand which is the right point on which to act. Furthermore, the higher is the leverage point, the more the system will resist the change because the consequences on the whole would be dramatic. Donatella Meadows suggests that in order to understand which are the most powerful leverage points it is necessary first of all to fully understand the goals of the system and then to clarify which is the paradigm underlying the system goals,[16] this way it will be possible to have a picture of which are the points into the system in which it is possible to act. The greatest impediment in the identification of leverage points is the obsession with short-term results and quick and easy solutions to problems. In the book "*Thinking in Systems: A primer",* Meadows identifies some elements in the system that works as leverage points such as system goals, which if changed can have a great impact on the system; but also, stocks can work as leverage points. Indeed, the bigger is the stock the stable is the system and therefore to stabilize a system it is possible to act on the size of the stock, always keeping in mind that if a stock is too big this will impact the ability of the system to be responsive to external changes.

The fundamental elements on which the graphic representation of the system is based are:

- Stock
- Boundary
- Flow
- Process

[13] Daniel H. KIM, *Introduction to Systems Thinking,* Arcadia, Pegasus Communication, 1999.
[14] Donella H. MEADOWS, *Thinking in Systems: A primer*, London, Earthscan, 2009.
[15] Peter SENGE, The Fifth Discipline. The Art and Practice of the Learning Organizations, New York, Doubleday Currency, 1990.
[16] Donella H. MEADOWS, Leverage Points: Places to Intervene in a Systems, Stellenbosch, The Sustainability Institute, 1999.

Stock

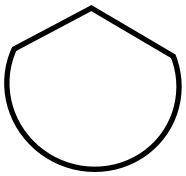

Figure 2: stock symbol

"A stock is the foundation of any system. Stocks are the elements of the system that you can see, feel, country, or measure at any given time".[17] A stock can also be defined as an accumulator which is "anything that builds up or dwindles".[18] A stock may be consisting of a variable number of concrete objects which occupies a specific space (quantitative) but may also be a variable number of abstract elements that plays a role in the system (qualitative). Stocks act in the system as delays or buffers or shock absorbers.[19] It is the system itself that determines the best choice of the stocks: when describing a system, not all the elements that constitute the system are represented by a stock, indeed, the stocks are the elements of the system that are functional to the representation of a specific dynamic; therefore the system description may include stocks that are not considered pertinent in the traditional description of the phenomenon but that are necessary to the systemic description. It is necessary to choose stocks that are specific, unambiguous and price so that they convey a clear picture of the system.

Boundary

Figure 3: boundary symbol

The boundary is an abstract element that has the role of isolating the elements that are necessary to provide the description of the interested dynamics.[20] A system usually contains sub-systems and is generally part of a larger system, so when analysing a system is very important to clearly understand which is the boundary of the system that the researcher is interested into. By outlining the boundaries, it is possible to analyse the behaviour of the system, its stocks, the inflows and outflows. Important it is to distinguish those components that are enclosed by the system boundaries and those that are outside the system but still influence the system;[21] this distinction is mainly useful for stocks, which may be internal to the system but may also be external. In this case it is necessary to consider these stocks when they influence the dynamics of the system even if they are not part of it. A key role in defining system boundaries is played by the supersignals. Supersignals are "the variables that create the patters or the feedbacks we observe from the interaction of the variables within the system".[22]

[17] Donella H. MEADOWS, *Thinking in Systems: A primer*, London, Earthscan, 2009.
[18] Daniel H. KIM, *Introduction to Systems Thinking,* Arcadia, Pegasus Communication, 1999.
[19] Donella H. MEADOWS, *Thinking in Systems: A primer*, London, Earthscan, 2009.
[20] Francesco GONELLA, *Basics of Systems Thinking*, Venice, Ca' Foscari University of Venice.
[21] John D. STERMAN, Business Dynamics. System Thinking and Modeling for a Complex World, New York, Irwin McGraw-Hill, 2000.
[22] Dietrich DÖRNER, *The Logic of failure. Recognizing and Avoiding Error in Complex Situations*, Reading, Perseus Books, 1996.

Supersignals provide the researcher with the necessary key variables to move from different levels in the system, in terms both of time and space.

Flow

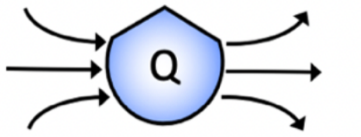

Figure 4: Symbolic representation of inflows and outflows on a stock

The flow represents "the amount of change something undergoes during a particular length of time".[23] Flows mainly play two roles: they can constitute a physical connection between different stocks, or they can constitute the controllers or the activators of the processes. Since they play the role of activators, flows can be considered also as flows of information that allow the happening of the process. Control flows are extremely relevant in systemic diagramming since they play a pivotal role in defining the feedback formation at different levels. The arrow, symbol of the flow, is usually accompanied by a "+" or a "–" sign, which shows the relationship between the two stocks that the flow is connecting and determines the polarity between the two stocks. If the arrow is accompanied by a "+", this means that the influence is "positive" and determines an increase, while if the arrow is accompanied by a "–", the influence will be "negative", and this will determine a decrease. The "+" entails that the two stocks are moving in the same directions, therefore they are all increasing or decreasing, while "–" entails that the two stocks are moving in opposites directions.

Process

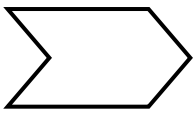

Figure 5: Process symbol

"Processes are any occurrence capable to alter a flow, triggered by the action of one or more further elements within or outside the system".[24]

To take place, processes need to be activated by an external element that is usually a flow and that is usually called "driver".

1.1.6 Feedback networks

In the creation of a stock-flow representation a three-step procedure should be followed, this way it will be possible to identify the feedbacks that are working within the system. The first step consists in the identification of the stocks and in the definition of a proper boundary, the second step consists in the identification of the flows and the last step is the identification of the processes that are affecting the flows.

[23] Daniel H. KIM, *Introduction to Systems Thinking,* Arcadia, Pegasus Communication, 1999.
[24] Francesco GONELLA, *Basics of Systems Thinking*, Venice, Ca' Foscari University of Venice.

Thanks to these three steps, it will be possible to clearly identify the presence of feedback which represents the "transmission and the return of information".[25] Thanks to the feedback loop perspective it is possible to see the world as a set of circular relationships, where elements are influencing one to another, instead of a linear view where events are flowing one after another.

Feedbacks may be divided into two categories: reinforcing (positive) and balancing (negative) feedback and "whether the feedback is considered positive or negative depends on what is does to changes in the system".[26]

In the first case, the inflow will be boosted by the feedback flow, and this will lead the stock and the flow itself to increase. Reinforcing feedbacks constitute the basis of the evolutionary mechanisms, since, thanks to the reinforcing dynamic, the system is able to maximize the profitability, to optimize the exploitation of the resources and this leads to the capability to adapt to the environmental pressures. In general reinforcing feedbacks lead to a situation that is far away from the equilibrium which can be a systematic growth, or a decline. If the reinforcing feedback leads to a decline, this is often call "vicious cycle"; in this case, the system registers the activation of a negative situation which is reinforced by the repetition of the action itself. Drug addiction is an example of "vicious cycle" in which the more the individual consumes the drug, the more he will be craving for it since it developed an addition.

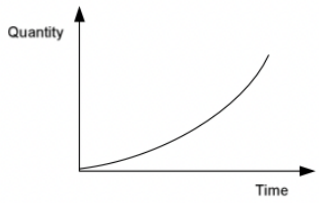

Figure 6: Reinforcing feedback trend

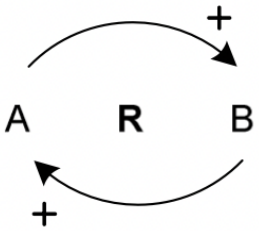

Figure 7: Reinforcing feedback

In balancing feedback, the increase in the value of the stock will determine the decrease of the inflow, this will lead to a decrease in the stock itself and a following increase in the inflow. In the case in which the action is located on the outflow, the increase in the outflow will determine a decrease in the value of the stock and this will lead to a decrease in the outflow to allow the system to survive.

The balancing feedback is always characterized by a goal, which can be identified by the condition of equilibrium; what makes the feedback working is the gap between the "real" condition and the "desired" condition, as the system will take action to adjust the situation until the gap decreases and the equilibrium is re-established. Therefore, the balancing feedback leads

[25] Daniel H. KIM, *Introduction to Systems Thinking,* Arcadia, Pegasus Communication, 1999.
[26] Draper L. Jr. KAUFFMAN, *Systems 1: An Introduction to Systems Thinking*, Minnesota, Future Systems, 1980.

to a situation of equilibrium or of proximate equilibrium since the changes in one direction are offset by the changes in the opposite direction. Properly because of this characteristic, the balancing feedback can be defined as a self-regulating mechanism. A complex system usually has many balancing feedback that are working in the inside so that it can self-correct under diverse situations; balancing feedback are also often working as "emergency" mechanism that ensure the existence of the system. These mechanisms are not frequently in action and therefore, they are often eliminated to save resources, but this could be a big mistake because in the long term this could affect the ability of the system to survive in adverse conditions.

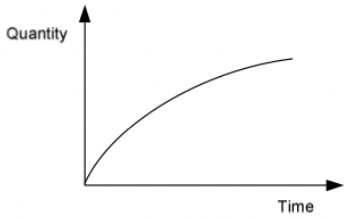

Figure 8: Balancing feedback trend

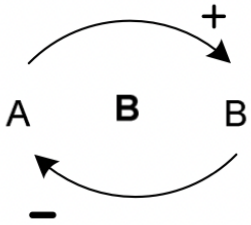

Figure 9: Balancing feedback

Both the reinforcing and the balancing feedbacks provide the system with the elasticity that is necessary to the system to reorganize itself and to survive during time. It is necessary to consider that reinforcing loops constitute a temporary state of the system and what is relevant is to understand how this temporary state will perdure.

When considering ST and feedbacks loops the notion of "limit to growth" should be taken into consideration; it refers to "the result of the interaction between a reinforcing loop and one or more balancing loops".[27] In this case the turning points happens when the balancing loop starts to overtake the reinforcing loop.

Considering feedbacks, both balancing and reinforcing, also the notion of delay comes to be very relevant as it can influence the ability to recognize feedbacks inside the system. Delays are usually indicated with parallel bars symbol "||" on the arrow (flow). The delay refers to the fact that the action that constitutes the feedback takes place a slower rate compared to the rest of system. Delay can be divided into four categories:[28]

1. Physical delay: it refers to the physical time that is necessary to move an element from one location to another or to pass from a state to another.
2. Transactional delay: it refers to the time that is necessary to complete a transaction.
3. Informational delay: it refers to the time that is necessary to communicate an information about a change or a decision.

[27] Kambiz MAANI, *Multi-stakeholder Decision Making For Complex Problems: A Systems Thinking Approach with Cases*, Singapore, World Scientific Publishing, 2017.
[28] Daniel H. KIM, *Introduction to Systems Thinking,* Arcadia, Pegasus Communication, 1999.

4. Perceptional delay: it refers to the time that is necessary for a decision to be accepted and to become part of the daily life of individuals.

The presence of a delay is unpredictable and in general the longer is the delay, the greater is the effect on the system since it is more difficult to identify the patter on a global level. Indeed, delays mask the cause-effect relationships between different elements as it is difficult for the individual to connect a short-term action with a long-term consequence; this leads to poor organizational decisions and counterproductive interventions. Delays are also common causes of oscillations in stock values, because if the individual is trying to act on the system to reach the condition of equilibrium but the information reaches him with delay, this will affect his real ability to reach the equilibrium and instead it will cause the overshooting or undershooting of the goal.

1.2 Systems Thinking in medicine

As stated in the above paragraph, ST is meant to provide individuals with a new way to interpret reality considering how the different elements of a system are connected one to another. The tools provided by the ST theory are useful in a variety of fields and this brought together scientists coming from many different disciplines, allowing the transfer of knowledge and the development of inter-disciplinary contents.

Generally speaking, it is possible to say that theories and methods in ST are addressed to complex problems which are defined "complex" because they involve various interactive agents, because the environment in which they act constantly changes or because the considered problem has the ability to adapt to the external context by constantly absorbing new information. The health field makes a consistent use of ST tools and methods since it usually deals with complex problems which may need an analysis that considers different factors, forces, and drivers at the same time, providing an overall picture of the problem. For instance, in 2008, Leischow et al. showed how collaboration from different disciplines and fields is necessary for preventing and containing "pandemic influenza", as single activities itself are not sufficient to beat the pandemic.[29] ST also allows players in the health system to design some scenario planning, which can be used to forecast the future and to solve one of the main problems that affect health researchers and planners: in a large number of instances, the main constrain researchers and planners face is the inability to apply the same solution to small-scale and large-scale problems. Indeed, what may be effective in a small-scale problem often turns out not to be applicable in the large scale. This problem can partially be solved thanks to ST because it

[29] Scott J. LEISCHOW, et al., "Systems thinking to improve the public's health", *American Journal of Preventive Medicine*, 35, 2 2008.

provides a larger vision of the problem, overlooking the details and focusing on the main dynamics present both in small and large scale. In the case described in paragraph 1.2.2 which deals with the recourse to ST to solve the mask suppliance crisis in Korea, it is shown how ST was efficient to solve a large-scale complex problem in a short time, by overlooking those factors that were not considered relevant as the ultimate date of use for mask, and focusing on the main dynamics which could guarantee the perdurance of the system and the avoidance of the system collapse.

When considering the system methodologies, a distinction should be made between "hard" and "soft" methodologies to identify leverage points: the former refers to quantitative dynamic model building, the latter refers to qualitative methodologies.

According to Carey et al. modelling and simulations can play a crucial role in improving decision-making in health policy, as they can help to highlight the possible consequences of actions and their side effects.[30] However, at the same time, research shows that the implementation of systemic interventions based on a ST analysis, carried out without proper training and guidelines, resulted in reductionist and inappropriate actions which were not consistent with the complex system.

Therefore, even if systems modelling is considered to be the most promising area of action for solving public health problems, public health is still far from taking full advantages of it and this is mainly determined by the lack of accountability of the models realized. Indeed, actual validation is still rare to achieve since models are not explained and developed in sufficient details to determine whether they are actually reliable or not. Some major critiques that have been directed to the application of ST in the health system are mainly related to the use of systems concept in the evaluation practice; indeed, they tend to be focused more on how and when the systems concepts are used rather than on how these concepts are improving the system itself.[31] Overall, system-based approaches should not be considered as a substitute way to analyse the public health system, its problems and difficulties, because as researchers showed, it could result in a reductionist and limited perspective; but, instead, it should be considered as a complementary tool which should work alongside with traditional approaches, bringing a brand new contribution to the public health administration but also to the field of the research.

[30] Gemma CAREY, et al., "Systems science and systems thinking for public health: a systematic review of the field", *BMJ open*, 5, 12, 2015.
[31] Adam TAGHREED, Don DE SAVIGNY, "Systems thinking for strengthening health systems in LMICs: need for a paradigm shift", *Health policy and planning*, 27, 4, 2012.

1.2.1 Systems thinking in the analysis of COVID-19

Considering COVID-19 pandemic, ST tools allow the analysis of the pandemic as a complex system which is made of many different elements, such as the epidemiological one, the economic one, the social one etc.; in this sense, ST allows a complete knowledge of the pandemic, not only as a health issue but a multifaceted phenomenon. Trying to solve COVID-19 related problems with a linear approach, referring to them as single problems instead of multiple factors contributing to same problem, would lead to excessive anti-COVID-19 measures with a non-effective use of resources.[32]

SARS-COV-2 appeared in Wuhan, China, in December 2019; it started as an epidemic of a respiratory syndrome and then it became a global pandemic after expanding into 114 countries all over the world.

After the outcome of the COVID-19 pandemic, The World Trade Organization (WTO) itself, advocated the use of the Systems Thinking approach, to analyse the pandemic situation and to formulate comprehensive responsive actions and solutions.

When analysing COVID-19 as a complex system, it is possible to observe that a great variety of elements contribute to the perdurance of the pandemic, not only elements strictly related to the virus itself, but also social elements related to the communication and to the flow of information. Indeed, information influences people's perception of risk and therefore their capability to perform protective behaviours, which may affect the number of new infections. Delays in the information flows reduce the capability to control the dynamics of the system and therefore reduce the effectiveness of the control measures applied to reduce the rate of infection. Another relevant dynamic is the balancing loop that determines the increase and the decrease of the infections based on the risk perception of people: when the rate of infection decreases, people's perception of risk decreases and therefore also the protection measure will be relaxed, however this will cause a new increase in the rate of infection.

Considering COVID-19 pandemic as a complex system and not as a cause-effect process, can help governments to clearly understand that countermeasures should not be totally dependent upon the rate of infection. Indeed, by considering them as independent variables, they could be used as a precautionary measure that are applied for a defined period of time regardless of the changes in the rate of infection. This kind of policy has been adopted by the Korean government as further explained in the following paragraph. This policy, made of promotion of work from home, flexible working hours, reduction of environmental contamination and

[32] Rainer J. KLEMENT, "The SARS-CoV-2 crisis: A crisis of reductionism?", *Public Health*, 185, 2020.

improvement of ventilation systems, can also be useful in reducing the rate of infection in seasonal influenza.[33]

All things considered, the outbreak of COVID-19 has shown how risk reduction should be based on global changes in the system and not on a direct response to the single treat; policies should be developed to build a "protective structural system"[34] that is always ready to face the risk of new infections and that is able to take precautionary actions that are independent of the number of cases.

1.2.2 Korea Mask production: A case study

In this section we will analyse how ST was useful to respond the lack of masks supply after the outbreak of COVID-19 in Korea. The first case of COVID-19 in Korea was registered on January 20th, 2020. After only 2 days (January 22nd, 2020), the government of Korea called an emergency committee to discuss an immediate response to the illness outbreak. Instead of adopting a strong policy made of lockdowns and the shout down of all the production activities, Korea decided to adopt a "Dynamic response system"[35] which is based on the building up of sensing and response capabilities to fight the pandemic. The government tried to encourage Korean citizens to frequently wash their hands, to wear marks and to maintain social distancing, to be able to keep the society "alive" and to maintain the everyday normality.

However, the policy adopted by the Korean government has led to an enormous increase in the demand for healthcare, respiratory and medical masks. To face this difficult situation, the Task Force of Mask Supply Stabilization Measures was established in February 2020. The goal of the task force was to guarantee a fair distribution of masks and to develop measures to increase the production and to keep it sustainable; in other words, to create a "resilience strategy". Since, the persistence and the development of the pandemic were unknown in 2020, this "resilience strategy" had to behave like a learning being, able to modify itself according to the specific changes in the external environment.

As we mentioned in the introduction to ST, a system is a "adaptive being" and therefore the strategy adopted by the Korean government can be interpreted and worked on as a complex system made of stock, processes, and flows.

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[33] Declan T. BRADLEY, MANSOURI, Mariam A., KEE, Frank, GARCIA, Leandro M. T., "A systems approach to preventing and responding to COVID-19", *EClinicalMedicine,* 21, 2020.
[34] *Ibidem*
[35] Eun Su LEE, et al., "Dynamic Response Systems of Healthcare Mask Production to COVID-19: A Case Study of Korea", *Systems*, 8, 18, 2020.

Each system is also made of inputs and outputs and the performance of the system can be defined according to the outputs that the system is able to produce. The performance of the system is also determined by the ability of the system itself to select and regulate the inputs.

As in the picture below,[36] the system of medical mask production is made of inputs such as raw materials, facilities, equipment, and staff, while the outputs can be measured by the number of masks, the unit costs, the profit, and the dimension of the inventory.

In order to produce the outputs, it is necessary that the inputs undergo specify processes which are determined by drivers such as R&D, regulation, market condition, quality standards and automation.

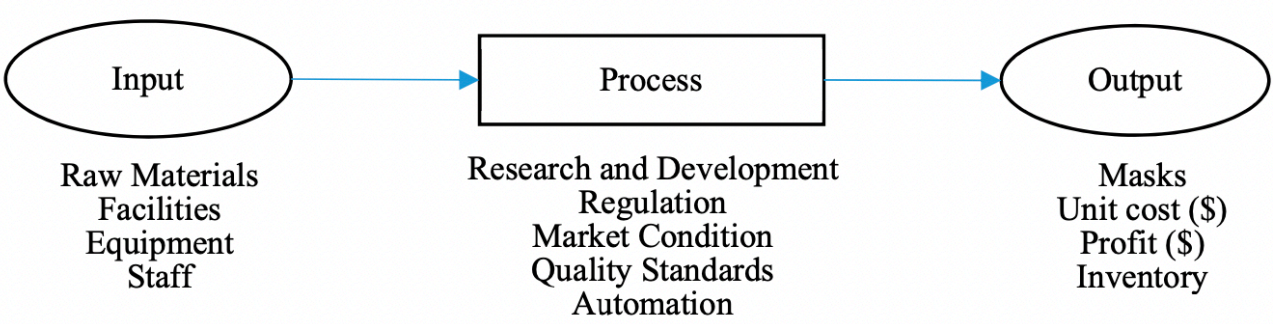

Figure 10: Generalized process diagram of medical mask production.

Considering the above-mentioned inputs, the Korean government adopted many policies to guarantee that all of them were available to face the situation determined by the outbreak of the pandemic. The government provided financial supports and incentives to corporations to increase the production capacity by upgrading the existing facilities and purchasing new one. Furthermore, the government also established favourable policies for all those companies that were able to switch their production into the one of masks; this happened mainly in those companies that were producing similar products as clothing and household goods. The government also adopted some specific and temporary rules that allowed companies to organize longer working shifts to keep the production always on and to maximize the results. Companies succeeded in establishing longer shifts, thanks to the strong increase in salaries which was supported by government financial support.

Actions were taken also on the drivers that allowed the process of transformation of the inputs into outputs; indeed, some regulations concerning the packaging and the date of expiring of the mask were loosened up, to fasten the production processes and meet the great needs of products.

[36] Eun Su LEE, et al., "Dynamic Response Systems of Healthcare Mask Production to COVID-19: A Case Study of Korea", *Systems*, 8, 18, 2020.

Ultimately, the Korean government adopted a ST approach as instead of looking and trying to act on single elements, it looked at the whole picture first and then acted on those drivers that could produce some positive changes meant to reach the final goal. This way the Korean government was able to greatly increase the mask production without producing any imbalance into the society.

Another consideration that should be done is that the mask production can be identified as a sub-system into the bigger system of the "Dynamic response system", indeed, the outputs produced by this sub-system are elements that contribute to the endurance of the main policy established by the Korean government which allows the society to behave "normally" avoiding extreme measures but still guarantying protection from the virus.

1.2.3 The Neurosurgical Hospital Treatment system: A case study

The previous paragraphs showed how ST can be useful in analysing a complex phenomenon as the COVID-19 pandemic; in this paragraph it will be showed how ST can be deployed in the organization of a neurosurgical ward, considering diagrams and feedback mechanisms. Indeed, differently from the previous analysis, in this second one a greater focus will be casted on the drawing of the diagram and in the analysis on the feedback mechanisms that are present.

The neurosurgical ward is a complex system, made of stocks, flows and processes, which is itself part of greater complex system as the hospital. In this second analysis, the scope of the research is much more limited than the one referred to the analysis on the COVID-19 pandemic, but it can be useful to understand how it is possible to transform a real situation in a diagram and to identify the feedback mechanisms.

The system will be called "Neurosurgical hospital treatment" and it is meant to describe the dynamics that characterize the Neurosurgical ward, the Surgical Ward, the Intensive care ward, and the processes that interest patients in critical conditions that need to undergo any type of neurosurgical treatment.

The main input of this system are patients with neurological issues that need to undertake a surgical treatment; the main output are patients who undertook the surgical treatment and, in the best option, recovered. However, it is necessary to consider that not all the patients exit the system as "Recovered patient" but some of them, for different reasons, exit the system as "Dead patient".

The main system under consideration is the "Neurosurgical hospital treatment", and the main boundary is given by the Neurosurgical ward. However, inside the main system we can identify two other systems that represent the "Surgical ward" and the "Intensive care ward". Even though in the actual organization of the hospital the surgical ward and the intensive care

ward are not localized within the Neurosurgical Ward, to provide a clear explanation of the different dynamics that characterize the neurosurgical treatment and not just the neurosurgical ward, it is functional to describe them as part of the main system.

The system comprehends two main processes: surgery and intensive care hospitalization. The two main processes will be analysed in two single diagrams that concentrate on the Surgical Ward and on the Intensive Care Ward.

The system is to be considered within a period of one year, as to take into consideration the different variables that may influence the flow of patients, resources, doctors, and others stock.

1.2.3.1 Feedback mechanisms

It is possible to identify two main feedback mechanisms in the three systems under consideration (the main one and the two sub-systems).

In the main system the "medicine feedback" (pointed at with a red arrow and a red square in figure 11) can be identified; this balancing feedback shows the feedback that regulates the supply of medicines within the system. Outside the system is located an unlimited stock of medicine which is the main source of the stock of medicine that is located in the system; the decision to buy more medicine depends upon the administration and this decision is determined by the information that are coming from the stock of medicine itself. Indeed, when the stock of medicine sends the information that new medicines are needed, the administration will transmit the information and new medicine will be purchased; once the new medicine replenishes the stock, the stock of medicine will send to the administration the information that there is no need to buy new one. Therefore, the exchange of information between the stock of medicine and administration and the consequent action of administration creates balancing feedback that allows the system not to run out of medicine neither to have a surplus of them.

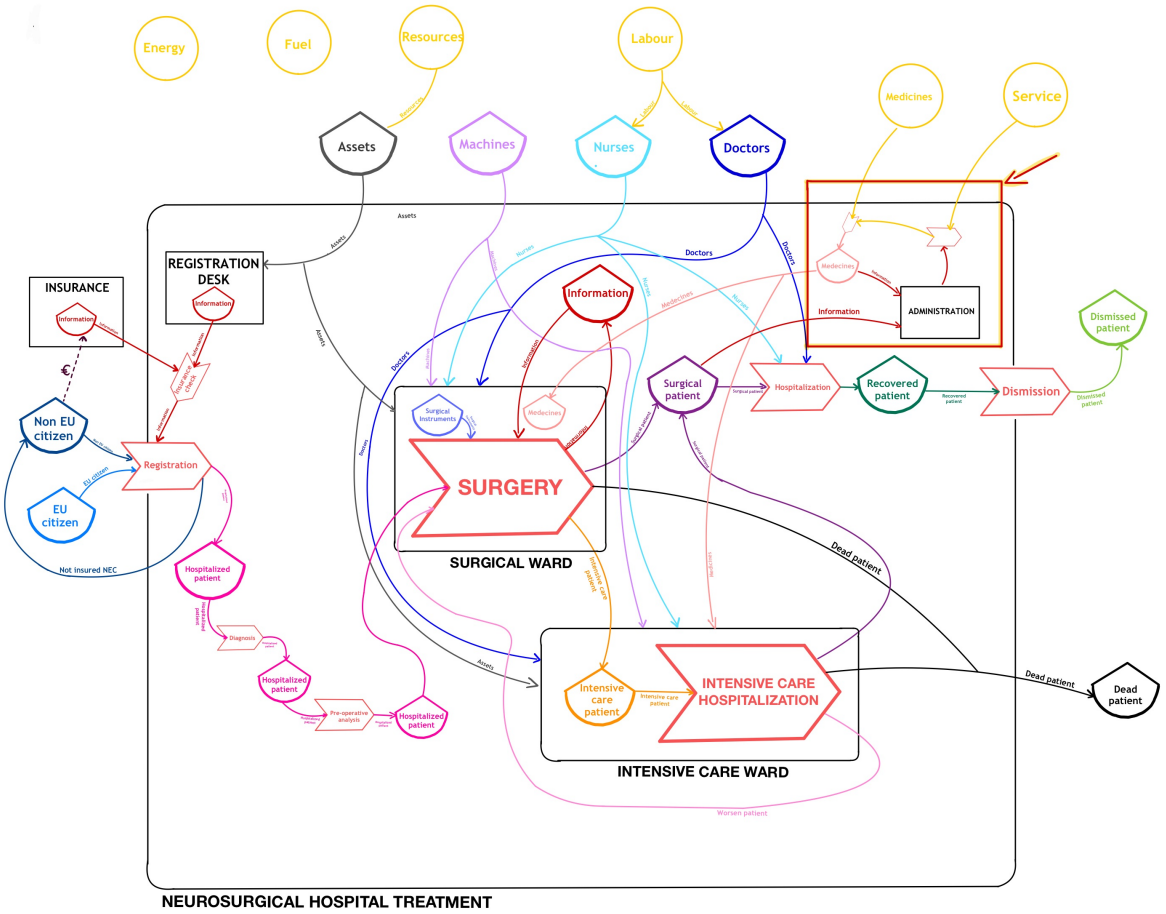

Figure 11: Neurosurgical hospital treatment diagram and reinforcing feedback

Stocks, flows, processes list: Neurosurgical hospital treatment

Stocks	***In-flows***	***Out-flows***	***Processes***
Energy	Non-EU citizens	Not insured non-EU citizens	Registration
Fuel	EU citizens	Hospitalized patients	Diagnosis
Resources	Information	Non suitable to surgery patients	Pre-operative analysis
Labour	Hospitalized patients	Intensive care patients	Surgery
Assets	Worsen patients	Surgical patients	Hospitalization
Machines	Intensive care patients	Dead patients	Intensive care hospitalization
Medicines	Surgical patients	Worsen patients	Dismission
Surgical instruments	Recovered patients	Recovered patients	
Nurses	Surgical instruments	Dismissed patients	
Doctors	Doctors		
Information	Nurses		
Non-EU citizens	Assets		
EU citizens	Medicines		
Hospitalized patients	Machines		
Intensive care patients	Labour		
Surgical patients	Resources		
Recovered patients			
Dismissed patients			

Dead patients			

In the two sub-systems, information feedback can be identified (pointed at with a red arrow and a red square in figure 3 and figure 4) and in both cases they work as reinforcing feedbacks. In the "operating room" system, the information exits the main surgery process and then enters the stock of information that is going to act as a driver for future surgeries. In the "Intensive care department" system, the information exits diagnosis and new diagnosis processes, then enters the stock of internal information that is going to act as a driver for future diagnosis to determine how the process of disconnecting from life-saving machines should take place. In both cases, doctors will rely on all the information exiting the processes to identify which is the best surgical option or the best treatment for the patient. These types of information are significant to reduce the flow of dead patients.

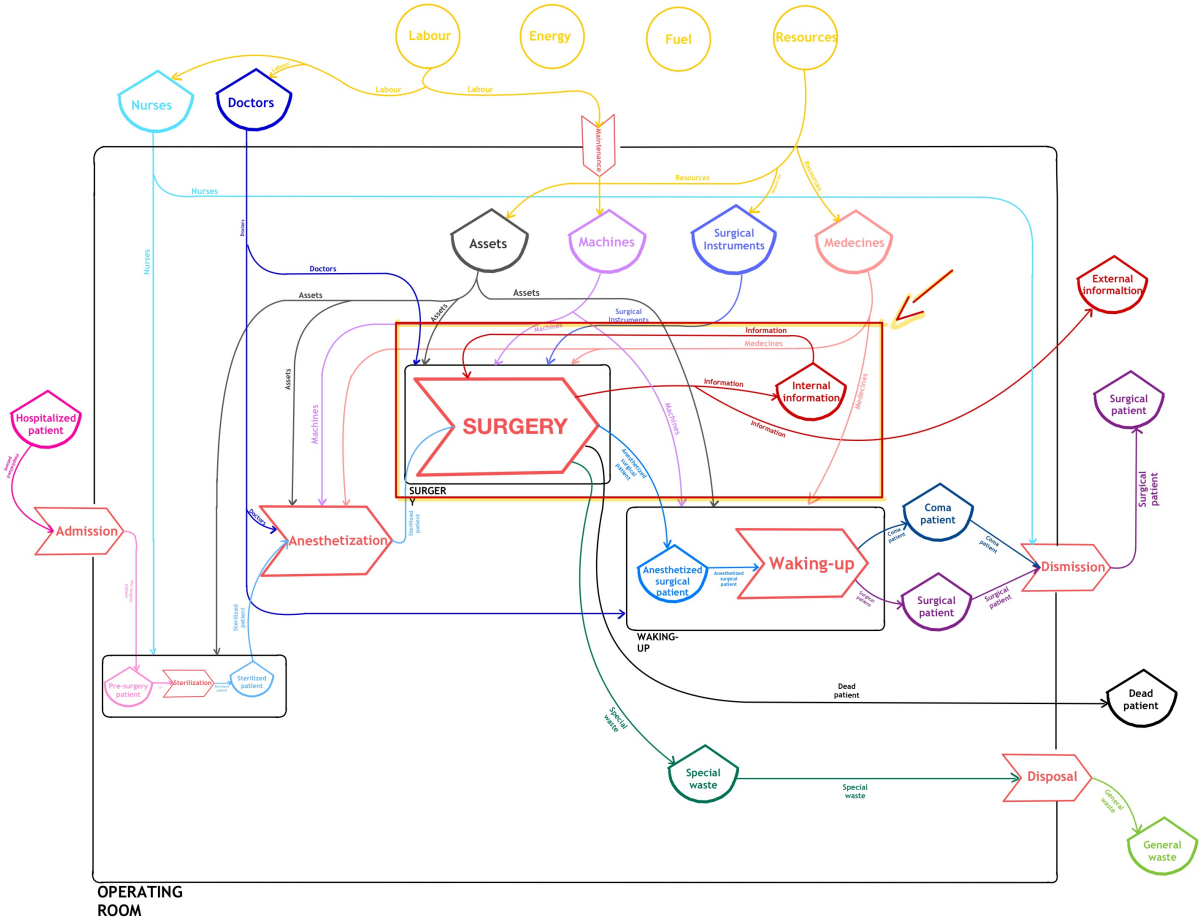

Figure 12: Operating room diagram and reinforcing feedback

Stocks, flows, processes list: Operating Room

Stocks	***In-flows***	***Out-flows***	***Processes***
Energy	Hospitalized patients	Pre-surgery patients	Maintenance
Fuel	Pre-surgery patients	Sterilized patients	Admission
Resources	Sterilized patients	Information	Sterilization

Labour	Anesthetized surgical patients	Anesthetized surgical patients	Anesthetization
Assets	Surgical patients	Dead patients	Surgery
Machines	Coma patients	Special waste	Waking-up
Medicines	Special waste	General waste	Dismission
Surgical instruments	Nurses	Surgical patients	Disposal
Nurses	Doctors	Coma patients	
Doctors	Assets	Labour	
Internal information	Surgical instruments		
External information	Medicines		
Hospitalized patients	Machines		
Pre-surgery patients	Information		
Sterilized patients	Labour		
Anesthetized surgical patients	Resources		
Surgical patients			
Coma patients			
Dead patients			
Special waste			
General waste			

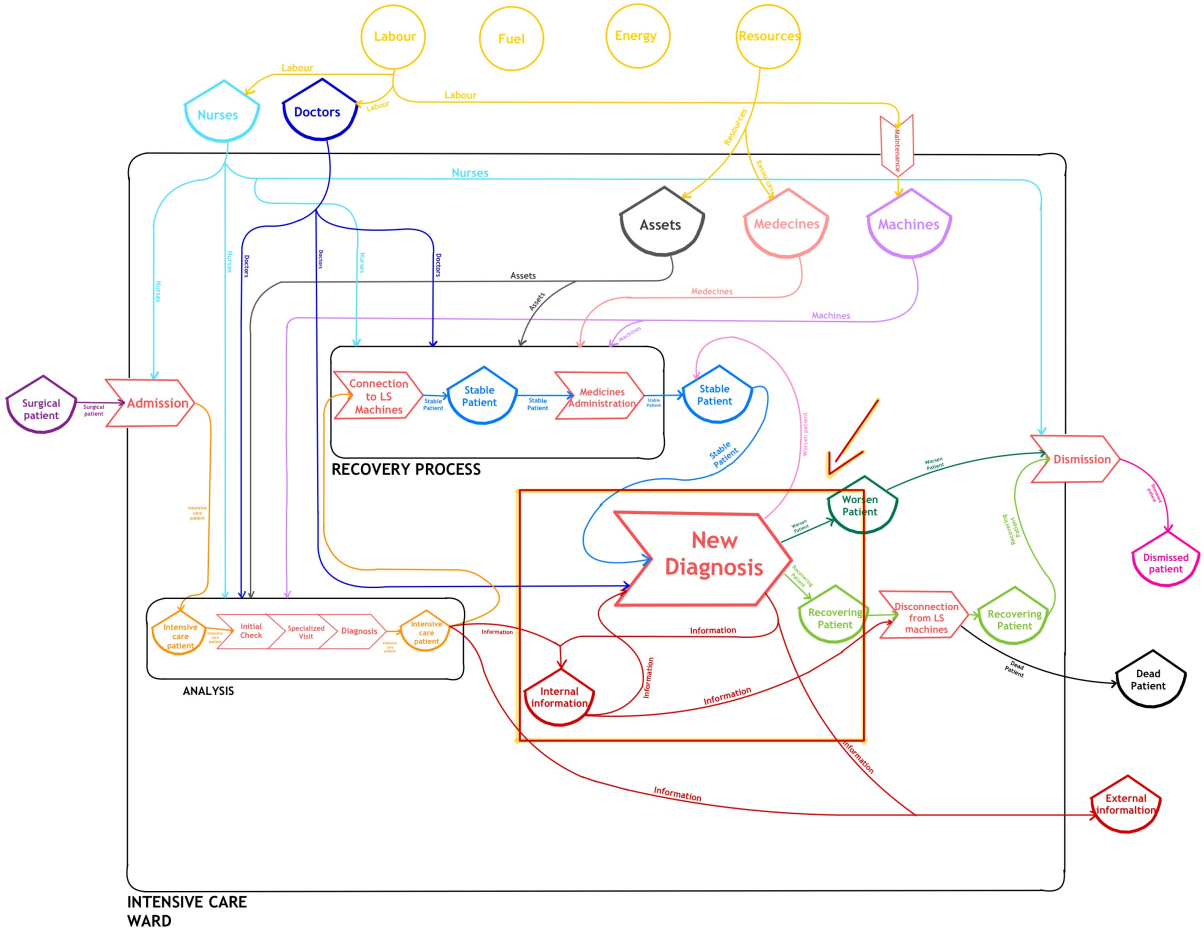

Figure 13: intensive care ward diagram and reinforcing feedback

Stocks, flows, processes list: Intensive care ward

Stocks	***In-flows***	***Out-flows***	***Processes***
Energy	Surgical patients	Intensive care patients	Maintenance
Fuel	Intensive care patients	Sterilized patients	Admission
Resources	Stable patients	Stable patients	Initial check
Labour	Worsen patients	Worsen patients	Specialized visit
Assets	Recovering patients	Recovering patients	Diagnosis
Machines	Labour	Dead patients	Connection to life-saving machines
Medicines	Resources	Dismissed patients	Medicines administration
Doctors	Nurses	Labour	New diagnosis
Nurses	Doctors	Information	Disconnection from life-saving machines
Surgical patients	Assets		Dismission
Intensive care patients	Medicines		
Stable patients	Machines		
Worsen patients	Information		
Recovering patients			
Dismissed patients			
Dead patients			
Internal information			
External information			

1.2.3.2 Stock and Flows

Looking at the three diagrams some considerations should be made on some relevant flows and stocks. Concerning the flows, it is remarkable that in none of the diagrams is present the flow of money. Indeed, as the system under consideration is part of the public health care system, the flow of money is potentially limitless and above all it is not linked to any other flow that characterizes the general functioning of the Neurosurgical Hospital Treatment. Different would be the situation if the system under consideration was the Neurosurgical Hospital Treatment of a private hospital or of a country that does not provide the citizens with public health care. In this latter case, the flows of assets, machines, medicines, surgical instruments, doctors, and nurses would be highly dependent upon the flow of money, but also the admission of patients or the decision to undertake surgeries would be determined by the abundance or by the lack of financial resources.

Concerning the stocks, it is remarkable to clarify the reason behind the distinction between the stock of doctors and the stock of nurses. The two stocks could have been expressed with one general stock of labour but to guarantee the functioning of the whole system is not

sufficient to have labour but is necessary to have specialized labour. If the labour stock consisted in a great number of nurses but very few doctors this could have a great impact, determining the inefficiency of the whole system. Therefore, to determine the actual efficiency of the system, it is necessary to consider two different stocks, each of which linked to a specific value.

Differently from the first one, which was meant to show why it is important to use the principles of ST in the analysis of a complex phenomenon as COVID-19 pandemic, this second analysis was meant to show in a more concrete way how it is possible to transform a complex system in a diagram, physically showing the relationships existing between the different stocks that constitute the system.

1.3 Systems Thinking: parallels paths

The thirds section of this chapter will deal with a review of the most famous systemic approach that have been developed parallelly to ST and that comprehends Network Medicine, Systems Pharmacology, Systems Biology (SB) and P4 medicine. It is important to clarify that in our ST conceptual framework the words "system" and "systemic" have not the same meaning they assume in some SB contexts, and in general within the related computational approaches. While both SB and ST aim at describing a system as a whole, the former still retains the scale of the microlevel, in as much it considers a system as a collection of a large number of local elements, whose dynamics is investigated thanks to the availability of big data and sophisticated mathematical and statistical tools. On the contrary, ST approach starts from the identification of a limited number of state variables, those necessary to model the resource flows and the feedback networks that describe the configuration patterns of the system dynamics. Network analysis (NA), agent-based modelling, causal loop diagrams, while effectively describing the (often static) complexity of a system, may not capture the complexity of its dynamics. Nevertheless, the complementarity between ST and NA can present itself an enormous potential, as "The integration of systems thinking with dynamic computational modelling can lead to the development of a 'virtual sandbox' in which researchers can utilize their creativity and intuition to try out and explore multiple different hypotheses and lines of investigation".[37]

1.3.1 Network medicine

The expression "Network medicine" refers to a particular analytic approach towards medicine: network medicine uses network's dynamics and network's topology to understand the behaviour

[37] Bibiana BIELEKOVA, et al., "How implementation of systems biology into clinical trials accelerates understanding of diseases", *Frontiers in neurology*, 5, 102, 2014.

of molecular interconnections and cellular interactions, which constitute the basis of diseases, pathologies, and basic functioning of the human organism. Network medicine provide scientists and doctors with the possibility to comprehend the complexity of diseases and at the same time to create models which, through computational methods, provide information about the relationship existing between this complexity and manifestations, comorbidities, and therapies of a peculiar disease.[38]

Network medicine assumes that networks that characterize biological, technological, or social systems in general are not casual, but they are based on a series of organizing principles and core composing elements. Crucial elements to the description of a biological network are nodes which refer to the elements that constitute the network, such as biological factors; modules which refer to a cluster of nodes connected one to another by links; hubs which refer to nodes of particular relevance for the number of links that are inserted on them. Hubs are not only characterized by a significant number of links, but they are also encoded by essential genes,[39] which distinguish themselves from normal genes since they are older, and they evolve slower.[40]

As we mentioned before, human beings as well as diseases are characterized by a countless number of connections between the elements they are made of; this network of connections implies that the impact of a change in the activity of a cell or of a gene abnormality is not restricted to that specific cell or gene, but it is spread around in the whole system. This way of interpreting diseases opens the way to the assumption that the "disease phenotype is rarely a consequence of an abnormality in a single effector gene product but reflects various pathobiological processes that interact in a complex network".[41] Therefore, according to this assumption, doctors and physicians should not research the origin of a disease in single elements but they should understand which are the mechanisms that are not working in the whole system. In trying to understand complex systems, clustering process may be helpful; indeed, when disease components are identified it is probable to find disease-related components in the same cluster. Three types of clusters, also called modules, can be identified, and it should be noted that even though these three types of clusters are different in their substance, they are intrinsically connected one to another and sometimes they are even overlapping.[42]

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[38] Stephen CHAN, Joseph LOSCALZO, "The emerging paradigm of network medicine in the study of human disease", *Circulation Research*, 111, 3, 2012, 359-374.
[39] Hawoong JEONG, et al., "Lethality and centrality in protein networks", *Nature*, 411, 6833, 2001, 41-42.
[40] Hunter B. FRASER, et al., "Evolutionary rate in the protein interaction network", *Science* 296, 5568, 2002, 750-752.
[41] Albert-László BARABASI, et al., "Network medicine: a network-based approach to human disease", *Nature reviews. Genetics*, 12, 1, 2011, 56-68.
[42] Leland H. HARTWELL, et al., "From molecular to modular cell biology", *Nature*, 402, 6761, 1999, C47-52.

1. Topological modules: they consist in networks' zones which are particularly dense in nodes.
2. Functional modules: they consist of nodes that are characterized by same or similar function.
3. Disease modules: they consist of nodes which actions contribute to the development of a peculiar disease phenotype. Disease modules in many cases are partially overlapping with one topological or functional modules.[43]

Considering this clustering activity, we may affirm that the emergence of a disease is always a combination of several defects and perturbations that may interest one module or even more modules that interact one another. Therefore, when looking for disease genes, it is primarily necessary to identify disease modules and then analysing the components to look for mutation or alterations in their normal activity.

Network medicine also casts a doubt on the idea according to which different diseases present in the same human being act independently one to another; if anything, network medicine proposes the notion of "diseasome" which represents a map in which diseases are identified as nodes and they are linked one to another according the peculiar molecular relationships existing between them.[44] The idea of the "diseasome" may help physicians in the treatment of diseases comorbidities, as well as, in the identification of new approaches for disease prevention and treatment, since it reveals the relationships existing between different pathologies and also the potential comorbidities that may arise when presenting a particular disease.

All things considered, network medicine provides new tools in the analysis and in the understanding of the connections between the components of a disease as well as in the reveal of the relationships existing between different disease with common elements. The systematic adoption of network medicine is still limited due to the lack of data but also due to the lack of analytic tolls which would allow a comprehensive and massive realization of "diseasomes". However, even though the practical application of network medicine may still be limited, the idea behind this approach, that is thinking globally, is spreading in the medical environment.

1.3.2 Network medicine in drug development

In the previous paragraph we extensively described how network medicine can be useful in the identification of a disease, however, it should be noted that the deployment of network medicine

[43] Erzsebet RAWASZ, et al., "Hierarchical organization of modularity in metabolic networks", *Science,* 297, 5586, 2002, 1551-1555.
[44] Kwang-Il GOH, et al., "The human disease network", *Proceedings of the National Academy of Sciences of the United States of America*, 104, 21, 2007, 8685-9860.

is also potentially crucial in the process of drug development since it can speed up the process while allowing a more targeted action, thus reducing the number of unwanted and dangerous side effects.

The potentially beneficial role of network medicine in drug development finds its basis in the clustering activity; indeed, the first step in drug design consists in identifying the disfunction behind the disease and since we know that this dysfunction is necessarily located within the disease module, the search for therapeutic agents can be reduced to those that may act on that module.[45] Furthermore, the network analysis may help researchers to forecast side effects, by considering all the potential partners to that drug within the module and inhibiting those that could lead to unwanted negative outcomes.[46]

Network medicine is playing a great role in changing the paradigm of the "magic bullet", according to which researchers and pharmaceutical companies were looking for chemical combinations which were able to act on the single node considered responsible for the insurgence of the disease.[47] Nowadays, partially thanks to the principles of network medicine, the concept of "system pharmacology"[48] is applied and more attention is given to therapies which act on multiple nodes, hoping for a stronger and combined action which is able to reverse the disease phenotype.[49]

System pharmacology has been successfully used to create a quantitative framework able to compare different diseases based on the analysis of the mRNA expression.[50] The creation of these frameworks is particularly useful in the perspective of developing personalized therapies, since they constitute a solid basis on which physicians can work on to define the best treatment for a peculiar patient considering the variation in his gene expression.

Furthermore, other studies related to system pharmacology are focusing on the process of "rewiring" molecular networks so that cells which were previously resistant to a particular drug could become responsive once again. This project has been mainly carried out by Lee et al.; the working group was adopting a system approach to prove how it was possible to make

[45] Albert-László BARABASI, et al., "Network medicine: a network-based approach to human disease", *Nature reviews. Genetics*, 12, 1, 2011, 56-68.
[46] Leland H. HARTWELL, Michael B. KASTAN, "Cell cycle control and cancer", *Science,* 266, 5192, 1994, 1821-1828.
[47] Garry P. NOLAN, "What's wrong with drug screening today", *Nature chemical biology*, 3, 4, 2007, 187-191.
[48] Peter K. SORGER, et al., "Quantitative and systems pharmacology in the post-genomic era: new approaches to discovering drugs and understanding therapeutic mechanisms", NIH White Paper by the QSP Workshop Group, 2011, 1–47.
[49]Péter CSERMELY, et al., "The efficiency of multi-target drugs: the network approach might help drug design", *Trends in pharmacological sciences*, 26, 4, 2005, 178-82.
[50] Stephen CHAN, Joseph LOSCALZO, "The emerging paradigm of network medicine in the study of human disease", *Circulation Research*, 111, 3, 2012, 359-374.

breast cancer cells responsive to genotoxic drugs to which they were previously refractive, by manipulating large-scale dynamics to obtain a specific phenotype.[51]

All things considered, system pharmacology is a promising area in drug discovery because not only it could help to reduce side effects and developing time, but it could also minimize drug-drug interaction while maximizing the outcome for patients, leading to higher rates of success both for patients and pharmaceutical companies. Furthermore, system pharmacology opens the way to a completely new way on interpreting and conceiving drug discovery and drug development, which could then be expanded to other small molecules libraries, related to other chemical sectors.

1.3.3. Systems biology

"Systems biology" represents the merger of Systems Thinking and traditional biology; its goal is to understand how interactions between different elements form functional networks and how their dysfunctions lead to the development of a particular disease.[52]

The appeal to System Biology (SB) is proven to be particularly useful in polygenic diseases; indeed, since they are characterized by genetic heterogeneity, complex environmental influences and multifaced pathophysiology, they are difficult to analyse in traditional terms and to reproduce for experimental testing. In this situation, the recourse to SB can help to reduce the complexity in reaching the comprehension of the disease's mechanisms.[53] Indeed, considering the basics of ST, since the interactions existing between the elements which compose a system or a subsystem are much more relevant than the elements themselves, it is not anymore necessary to carefully understand all the different components of an organism or a disease in order to define how it is working but it is sufficient to define those variables that are involved in relevant interactions. The outlining of the dynamics is proven to produce greater understanding compared to the simple listing all the components and this is determined by the possibility to define the operational protocols which are re-used in different networks, providing this way predictive understanding of several system's dynamics.[54]

Considering the practical application of SB for understanding complex biological issues, three steps are of considerable relevance: firstly, the identification of system's components; secondly, the deployment of system's perturbation and the observation of the subsequent

[51] Michael J. LEE, et al., "Sequential application of anticancer drugs enhances cell death by rewiring apoptotic signaling networks", *Cell*, 149, 4, 2012, 780-94.
[52] Bibiana BIELEKOVA, et al., "How implementation of systems biology into clinical trials accelerates understanding of diseases", *Frontiers in neurology*, 5, 102, 2014.
[53] Sergio E. BARANZINI, "Systems-based medicine approaches to understand and treat complex diseases. The example of multiple sclerosis", *Autoimmunity*, 39, 8, 2006, 651-662.
[54] Mihajlo D. MESAROVIC, et al., "Search for organising principles: understanding in systems biology", *Systems biology*, 1, 1, 2004, 19-27.

changes; lastly, the comparison of the results obtained by the in vivo experiment with the prediction of the computational models.

Concerning the first step, as we said before it is not necessary to identify all the elements that compose the system but only those that are necessary to the description of the interested dynamic; however, it should be noted, that even the identification of these elements could be hampered by the lack of the data or by the unreliability of the existent data. In this case, it is necessary to define a temporary hierarchical structure which tries to define the relevant dynamics based on the elements available that will then be modified as soon as new information are disclosed. Therefore, it should be recognized that developing a complete model is a multistep process in which several adjustments are needed before reaching a final result.[55]

With regards to the deployment of exogenous perturbations, this action mode represents an opportunity to collect several data related to the same human being in different times and under the administration of different stimulus. The action mechanism of an exogenous perturbation consists in submitting an organism to an external stimulus, and then observe which are the changes that this stimulus creates in the system. This mechanism allows the identification of the key elements which are the ones that react to the stimulus and produce reactions inside the system, allowing researchers to have clearer and clearer pictures of the system's organization. Exogenous perturbations play a significant role in clinical trials where they constitute the key element to understand if a candidate drug has the expected effects when administered to people and not only on the *in vitro* experimentation.[56]

The last step is the comparison between the experiment's results and the ones predicted by the computational models. A crucial concept in this last step is that the more complex is the system the more complex is to realize computational models which actually reflect reality and therefore provide similar results to *in vivo* experiments.[57] However, it is noteworthy, that failures in obtaining similar results usually carry out more information than positive results, as they may determine a shift in the way of thinking and considering the system as well as a more in-depth research on the issue.[58]

These three steps show how the application of SB, which is based on the analysis of the relationship existing between the different relevant elements of a system, can improve the interpretation of laboratory results, producing information that goes beyond the traditional

[55] Yoram VODOVOTZ, Gary AN, "Systems biology and inflammation", *Methods in molecular biology,* 662, 2010, 181-201.
[56] Bibiana BIELEKOVA, et al., "Regulatory CD56(bright) natural killer cells mediate immunomodulatory effects of IL-2Ralpha-targeted therapy (daclizumab) in multiple sclerosis", *Proceedings of the National Academy of Sciences of the United States of America*, 103, 15, 2006, 5941-5946.
[57] Donella H. MEADOWS, *Thinking in Systems: A primer*, London, Earthscan, 2009.
[58] Peter KOHL, et al., "Systems biology: an approach", *Clinical pharmacology and therapeutics*, 88, 1, 2010, 25-33.

classification of "normal" and "abnormal", as it is able to pinpoint the homeostatic failure which is producing particular reactions or the laboratory mistake which did not allow the reaching of the desired outcome.

All things considered, the combination between ST and biology can lead to the creation of a "virtual sandbox" in which laboratory tests and intuitive actions can be performed together to explore new multiple paths and line of investigations.[59]

1.3.4 P4 medicine

P4 medicine represents a new approach towards medicine which constitute a complete revolution. P4 medicine, also defined as "personalized medicine", considers the patients as the center of the healthcare system and it is characterized by four main principles: predictivity, prevention, personalization, and participation. P4 medicine, as network medicine, system pharmacology and system biology, arises from the combination of Systems Thinking principles, digitalization of medicine and medical knowledge and it could be a potent weapon to reduce the costs in healthcare while improving people wellness and quality of life.[60]

P4 medicine combines the tools and the strategies provided by the systems medicine to understand which is the best treatment solution for patients, ensuring high quality of life and general wellness.[61] P4 medicine is based on four main pillars:

1. Predictivity: P4 medicine assumes that in 10 years the analysis of the genome will be part of the medical routine, allowing physicians to provide patients with crucial information on how to prevent the emergence of specific diseases but also on how to conduct a healthier lifestyle.
2. Preventive: P4 medicine is based on the idea that the study of disease perturbation networks will provide great insights for drug development, allowing drugs to have a more targeted action as well as to reduce their refractivity rate. Furthermore, the systems approach may allow pharmaceutical companies and researchers to understand how to effectively induce cellular immunity and produce vaccines for diseases that are now incurable or even unmanageable.[62]
3. Personalized: The core of P4 medicine relies in this third pillar which is aims at the creation of personalized treatments for patients based on the gene expression. The

[59] Bibiana BIELEKOVA, et al., "How implementation of systems biology into clinical trials accelerates understanding of diseases", *Frontiers in neurology*, 5, 102, 2014.
[60] Leroy HOOD, et al., "Revolutionizing medicine in the 21st century through systems approaches", *Biotechnology journal*, 7, 8, 2012, 992-1001.
[61] Leroy HOOD, Stephen H. FRIEND, "Predictive, personalized, preventive, participatory (P4) cancer medicine", *Nature reviews. Clinical oncology*, 8, 3, 2011, 184-187.
[62] Larry SMARR, "Quantifying your body: a how-to guide from a systems biology perspective", *Biotechnology journal*, 7, 8, 2012, 980-991.

possibility to realize this aim relies on the presence of a massive database which contains complete genomes, molecular, medical, and cellular data. However, the availability of these data is not only subjected to the reduction of complete gene-sequencing costs, but it is mostly hampered by people's right to privacy. Therefore, in order to be able to have all of these data available, it will be necessary to develop technological tools which ensure people with proper legal insurance against the inappropriate use of these data.

4. Participation: the last pillar is participation, and it implies that patients will be involved in several dimensions of P4 medicine. First, patients will need to be informed about the use of their personal data and about the benefits of the creation of a comprehensive database; to do so, constant communication between promoters of P4 medicine and patients will be required, so that patients will be willing to provide their data. Secondly, patients will be involved in patients-driven social networks to promote the acceptance of P4 medicine. Lastly, patients and physicians will be involved in the creation of a "gold standard" for medical information, so that patients are able to find information that are well crafted and reliable.[63]

Considering these four principles as the foundations of P4 medicine and keeping in mind that the individual represents the center of this new approach, it is possible to comprehend why the main goal of P4 medicine is to understand the "network of network" of each patient. The expression "network of network" refers to the "hierarchy of networks operating across multiple, complex dynamics, and intertwined levels of biological organization encompassing both the individual and his or her environment".[64] Since P4 medicine interprets the individual as the combination of different networks which are constantly exchanging stimulus and information, it is obvious that a disease will interest several networks at the same time; therefore, in order to provide efficient treatments and therapies, the identification of this complex system is necessary to understand which drugs may be more effective.

P4 medicine is thus in direct contrast with the traditional medical perspective; indeed, while P4 medicine is proactive and preventive, traditional medicine is reactive and evidenced-based. However, the strength of this traditional system may lead to delay in the discovery of the disease as well as to the administration of ineffective treatments.

All things considered, P4 medicine represents a great opportunity for modern medical and health systems, since it could lead to more effective and less expensive treatments, but it is

[63] Stephen CHAN, Joseph LOSCALZO, "The emerging paradigm of network medicine in the study of human disease", *Circulation Research*, 111, 3, 2012, 359-374.
[64] *Ibidem*

also a great challenge since it requires new technology, significant legislative effort, and great communication between all the involved parts.

CHAPTER 2

Multiple Myeloma: an overview

2.1 Multiple Myeloma

Multiple Myeloma (MM) is a hematologic malignancy characterized by the proliferation and the accumulation of plasma cells in the bone marrow, which synthetizes monoclonal immunoglobulin (Ig) protein (also called M-protein), leading to end-organ damage. In this section an overview over the disease will be provided. Particular attention will be devoted to the biological characteristics of the disease and to its staging which will be deeply analysed, while epidemiology and risk factors will be briefly presented.

2.1.1 Biological characteristics

As above mentioned, multiple myeloma (MM) is a hematologic malignancy characterized by the proliferation and the accumulation of plasma cells in the bone marrow.

The progress of MM can be divided into three phases: the first one called Monoclonal Gammopathy of Undermined Significance (MGUS); the second one called Smouldering Multiple Myeloma (SMM) and the third one, which is the final stage of the disease, which is intra or extra-medullary, symptomatic Multiple Myeloma.

The first stage of the disease is characterized by the asymptomatic presence of the malignancy and by a M-protein below 1.5 g/dl.[65] The rate of progression from MGUS to MM is roughly 1% every year and it has been keeping constant since the early 2000.

The second stage of the disease is characterized by an increase of neoplastic plasma cells and of M-protein (superior to 3 g/dl), but by the absence of organ damage and CRAB symptoms.[66] In SMM, the risk of progression to MM is higher than in MGUS with a rate of 10% every year, within 5 years from the diagnosis.[67]

The final stage of the disease is characterized by a high level of M-protein, hypercalcemia, osteolytic lesions, kidney damage, immunodeficiency, and renal function impairment.[68]

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[65] Neha KORDE, et al., "Monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM): novel biological insights and development of early treatment strategies", *Blood*, 117, 21, 2011, 5573-5581.

[66] Vincent RAJKUMAR, et al., "Smoldering Multiple Myeloma", *Blood*, 125, 20, 2015, 3069-3075.

[67] Robert A. KYLE, et al., "Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma", *The New England journal of medicine*, 356, 25, 2007, 2582-2590.

[68] Anuj MAHINDRA, et al., "Multiple myeloma: biology of the disease", *Blood reviews*, 24, 1, 2010, 5-11.

Different studies show that MM is an heterogenous disease;[69] indeed, once the neoplastic clone has been created, the tumour cells can differentiate themselves due to stochastic, external events which are independent one to another. One of the causes that may lead to these modifications is the competition between tumour cells to get nutrients and other vital resources. These stochastic modifications play a great role in determining the characteristics of the disease itself, as different patients may have different traits but also the therapy itself may alter the development of the disease.[70]

2.1.1.1. Genesis of Multiple Myeloma

To have a complete picture of MM it is primarily necessary to understand how this disease originates. MM can develop through different stages: an inactive stage in which tumour cells are non-proliferating mature plasma cells; an active stage with a limited percentage (<1%) of proliferating plasma blasts and a fulminant stage characterized by an increase in the plasma blasts and a diffusion of the disease out of the bone marrow.

Normally, cells deputed to carry out B lymphocytopoiesis, undergo a rearrangement of V (variable region), D (diversity region) and J (joining region) sequences of the genes coding heavy chains (IgH) and of the V and J sequences of the genes coding for the light chains (IgL) of the immunoglobulins. The outcome of this process is the creation of *naïve* B-cells, which will move from the bone marrow to lymphoid organs where will find the antigen.

B-cells may, at this point, face two different situations: in the first situation, they will become short-lived plasma cells which will stay in secondary lymphoid tissue; in the second case, the encounter of B-cells with protein-based antigens will determine the germinal centre reaction and the production of Memory B-Cells (MBC) and plasma blasts. Plasma blasts and MBC will then migrate back to the bone marrow (homing process) and will differentiate into long-lived plasma cells thanks to the interactions with the medullary microenvironment.[71][72]

This process of transformation is not determined by a single event, but it is the results of multiple stochastic genomic alterations undergone by the tumour cells.[73] The changes that happens on a cellular level correspond to the changes in the different stages of the disease, from

[69] Niccolò BOLLI, et al., "Heterogeneity of genomic evolution and mutational profiles in multiple myeloma", *Nature communications*, 5, 2014, 2997.
[70] Jonathan J. KEATS, et al., "Clonal competition with alternating dominance in multiple myeloma", *Blood*, 120, 5, 2012, 1067-1076.
[71] Abul ABBAS, et al., *Cellular and Molecular Immunology,* Amsterdam, Elsevier, 2021.
[72] Niccolò BOLLI, Francesco DI RAIMONDO, "Mieloma Multiplo: biologia, criteri diagnostici e prognostici", *Seminari di ematologia clinica,* 2016, 5-18.
[73] Jens G LOHR, et al., "Widespread genetic heterogeneity in multiple myeloma: implications for targeted therapy", *Cancer cell*, 25, 1, 2014, 91-101.

those that have a limited impact on the individual, to those that are more aggressive and imply stronger clinical manifestations.

The rearrangement of the cells of B lymphocytopoiesis is thought to be promoted by the break of the DNA double-strand, caused by the activation-induced cytidine deaminase (AID enzyme).[74] Considering this, the risk of developing any sort of plasma cell cancer is connected to the physiological mechanisms of production of antibody response.

Myeloma cells (observable in Figure 1) can be identified as tumoral cells originated from the maturation process that takes place into the secondary lymphoid organs. They are characterized by a strong dependence from BM and represent the "malignant counterparts of post-Germinal Center (GC) long-lived PCs".[75] MM cells, once reached the bone marrow, will interact with the microenvironment, and will stimulate the production of neoplastic clones.

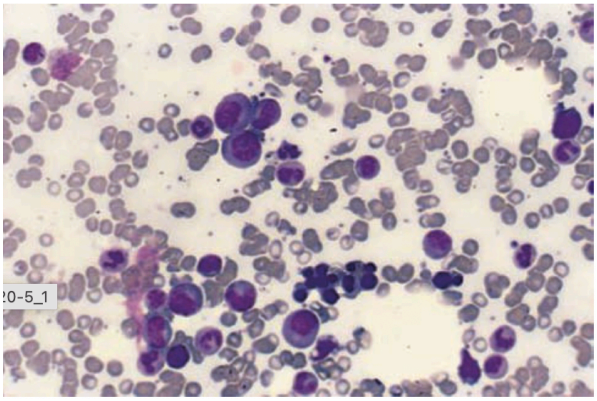

Figure 14: Myeloma Cells. The larger cells with concentric nuclei are the myeloma cells

2.1.1.2 Medullary microenvironment

The medullary microenvironment consists of two different sections: the cellular compartment and the non-cellular compartment. The former consists of hematopoietic elements as stem cells, lipocytes and platelets, and non-hematopoietic elements as grow factors and cytokines. The latter consists of Extracellular Matrix Protein (ECM).

MM is characterized by a modification of the regulation process carried out by the cell-signalling molecules. The effects of such modification can be observed in the survival and proliferation of the malignant clone B-cell, but also in the appearance of osteolytic lesions and in the resistance to diverse treatments. Osteolytic lesions and drug resistance are mainly determined by mechanisms of cells adhesions in which the main contribution is provided by

[74] David GONZÁLEZ, et al., "Immunoglobulin gene rearrangements and the pathogenesis of multiple myeloma", *Blood*, 110, 9, 2007, 3112-3121.
[75] Marta CHESI, P. Leif BERSAGEL, "Molecular pathogenesis of multiple myeloma: basic and clinical updates", *International journal of hematology*, 97, 3, 2013, 313-323.

Bone Marrow Stromal Cells (BMSC).[76] The process of cells adhesion starts when circulating tumoral cells adhere to the tissue of bone marrow thanks to their adhesion molecules; this will lead to the activation of paths of intracellular signal transduction. The activation of these pathways will determine inhibition of apoptosis, bone damage and drug resistance.

Medullary microenvironment will also play a great role in the development of relapsed MM; indeed, research shows that tumoral B-cells are able to modify themselves according to the external environment and therefore are able to perpetuate the disease autonomously.[77]

2.1.1.3 Angiogenesis

The angiogenesis plays a crucial role in the development of MM. Tumour angiogenesis is a multistep process which originates from the increase in the need of oxygen and nutrients in tissues, and it is characterized by the appearance of vascular structures made of disorganized and premature blood vessels. This process is mainly determined by the imbalance between anti-angiogenic and pro-angiogenic factors, in favour of the last ones, during the progression of the malignancy, which leads to the proliferation of new blood vessels.[78] One of the main factors which stimulates the angiogenesis is the growth of the tumour mass.

It has been showed that, in patients with MM, the medullary microenvironment is characterized by a high density of blood vessels, compared to healthy patients. In MM, the angiogenic process is strongly connected to the degree of diffusion of tumour cells into the bone marrow and to the stage of the disease; indeed, in MGUS and SMM, the angiogenic process has not started yet. The "angiogenic switch" takes place when the tumour mass is of considerable size, and it is started by the secretion of the Vascular Endothelial Grow Factor (VEGF) which stimulates the proliferation of blood vessels.

Overall, angiogenesis contributes to the nourishment, growth and spread of tumour cells and to the development of osteolytic lesions; these two main contributions of angiogenesis make it clear that it is a trait proper of the disease in its active stage.[79]

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[76] Constantine S. MITSIADES, et al., "The role of the bone microenvironment in the pathophysiology and therapeutic management of multiple myeloma: interplay of growth factors, their receptors and stromal interactions", *European journal of cancer,* 42, 11, 2006, 1564-1573.

[77] Bruno PAIVA, et al., "Differentiation stage of myeloma plasma cells: biological and clinical significance", *Leukemia*, 31, 2, 2017, 382-392.

[78] Nektaria MAKRILIA, et al., "The role of angiogenesis in solid tumors: an overview", *European journal of internal medicine*, 20, 7, 2009, 663-671.

[79] Nikhil MUNSHI, "Increased bone marrow microvessel density in newly diagnosed multiple myeloma carries a poor prognosis", *Seminars in oncology,* 28, 6, 2001, 565-569.

2.1.1.4 Osteolytic lesions

Osteolytic lesions are one of the main traits of MM and predispose to calcinosis, hypercalcemia, mobility issues, fracture, and strong pain. Osteolytic lesions may be caused by a modification of the bone remodelling process (process in which the mature bone tissue is removed from the skeleton and replaced with new one). This modification may be produced by two different situations: the first one refers to the stimulation of the process of osteoclast genesis, which causes the osteoclast hyper-activation.[80] The expression "osteoclast hyper-activation" refers to an increase in the activity of the osteoclasts which are responsible for the disintegration of the bone matrix.

The second situation refers to the reduction of the osteoblastic activity, which consists in a reduction the activity of bone matrix creation.[81]

2.1.2 Epidemiology

Multiple Myeloma is a moderately common disease associated with older age and mainly diffused in developed countries.

According to the Global Cancer Observatory (GLOBOCAL), in 2018, MM accounted for 0,9% of all the cancer diagnoses, with approximately 160,000 cases globally,[82] representing the second most common hematologic malignancy after lymphoma.

Since 1990, the global incidence of MM registered an increase of 126%,[83] and the disease is more common in developed countries; Australia, New Zealand, the USA, and Europe, are the countries with the highest incidence.

The ethnic analysis carried out within the population of the USA, has showed that MM is more common in black people rather than in white ones; the incidence of MM in black people is almost two times the incidence of MM in white people, and furthermore, the age of development of the disease tends to be lower, with a greater number of patients diagnosed before the age of 60. On the other hand, Asian people, especially Chinese and Japanese, tends to be less exposed to the development of the disease.

Epidemiological studies showed that MM is more diffused in men rather than in women, with a ratio of 1,5;[84] of the total 160,000 cases in 2018, 90,000 cases were male, while 70,000

[80] G. David ROODMAN, "Pathogenesis of myeloma bone disease", *Leukemia*, 23, 3, 2009, 435-441.
[81] *Ibidem*
[82] Global Cancer Observatory: Cancer Today, International Agency for Research on Cancer, Lyon, France. Available online: https://gco.iarc.fr/today/home (accessed on 2 March 2023).
[83] Andrew J. COWAN, et al., "Global Burden of Multiple Myeloma: A Systematic Analysis for the Global Burden of Disease Study 2016", *JAMA oncology*, 4, 9, 2018, 1221-1227.
[84] The ratio was calculated dividing the incidence of the disease in man (2.1/100,000) by the incidence of the disease in women (1.4/100,000).

were female.[85] The disease is also more diffused in older people rather than in younger one; the median age for the diagnosis is 66 to 70 years; only 10% of the patients were diagnosed before they turned 50, and the percentage decrease to 2% for the patients that were diagnosed before they turned 40.[86]

With regards to the mortality rate, in 2018, MM mortality rate accounted for 1,1% of all the cancer deaths, with 106,000 registered deaths. The risk of death from MM is slightly higher in men rather than in women, respectively 0,15% and 0,10%.[87] In the last decades, the rate of survival has increased significantly due to the development of effective therapy and improvement of the general living conditions. This improvement is shown by the extended survival of patients with relapsed MM, indeed, before 2000 the survival expectancy was less than 12 moths, while after 2000 it reached 24 months.[88]

The risk of death and the rate of survival are also strongly related to the stage at which the disease is diagnosed; indeed, if the disease is diagnosed when it is still localized (only 5% of all the diagnosed cases), the survival rate over 5 years is 74,8%, while if it diagnosed when it is already systemic (95% of all the diagnosed cases) the rate of survival over 5 years decreases to 52,9%.[89] In Figure 3, it is possible to see the incidence and mortality rate; the diagram makes it clear that the disease is more diffused in developed countries rather than in developing or underdeveloped ones.

[85] Freddy BRAY, et al., "Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries", *CA: a cancer journal for clinicians,* 68, 6, 2018, 394-424.
[86] Anuj MAHINDRA, et al., "Multiple myeloma: biology of the disease", *Blood reviews*, 24, 1, 2010, 5-11.
[87] Global Cancer Observatory: Cancer Today, International Agency for Research on Cancer, Lyon, France. Available online: https://gco.iarc.fr/today/home (accessed on 2 March 2023)
[88] Shaji K. KUMAR, et al., "Improved survival in multiple myeloma and the impact of novel therapies", *Blood*, 111, 5, 2008, 2516-2520.
[89] Nadia HOWLANDER, et al., *SEER Cancer Statistics Review 1975-2016*, National Cancer Institute: Bethesda, 2019.

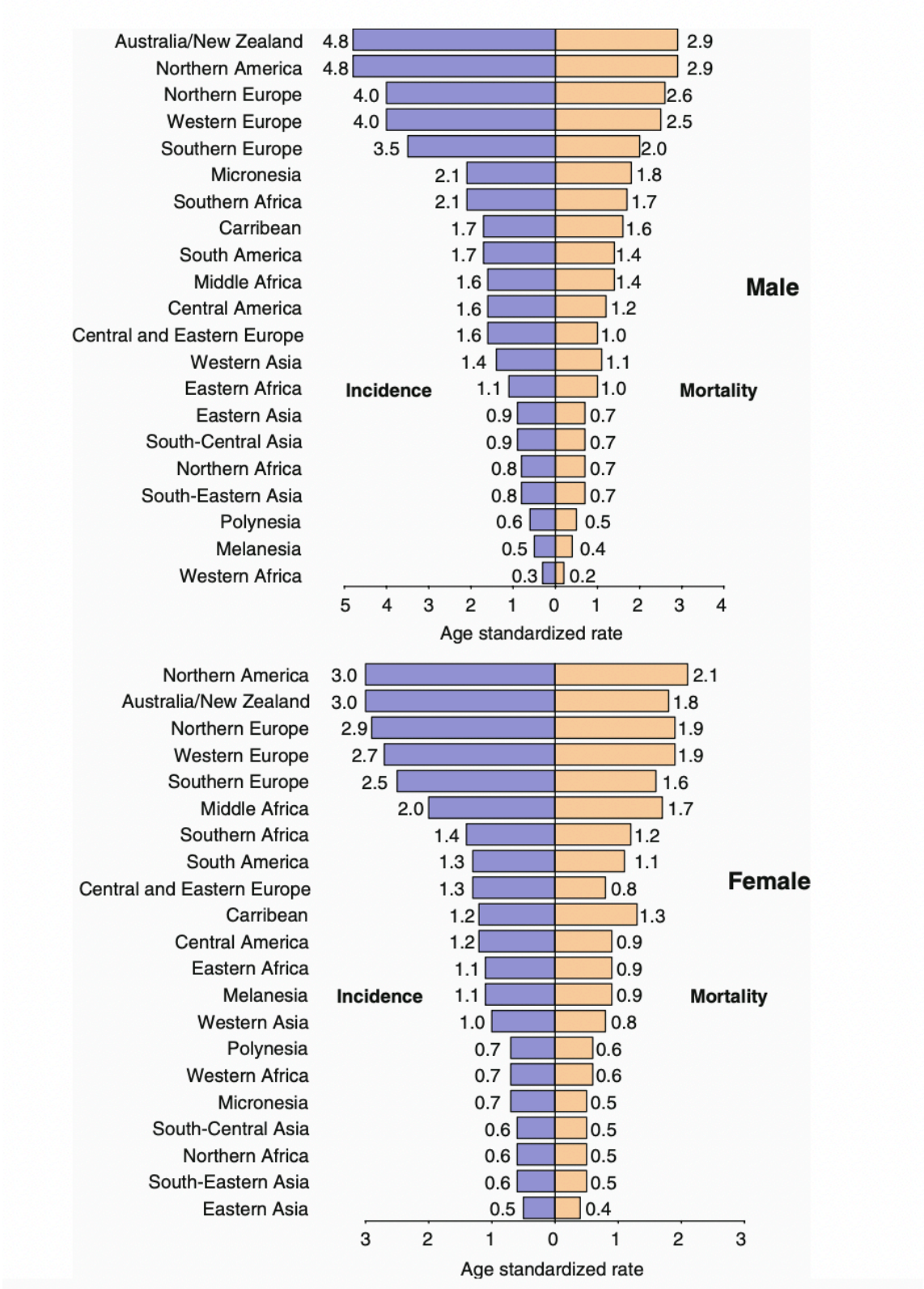

Figure 15: Incidence and mortality rates for MM

2.1.3 Multiple Myeloma risk factors

As we explained in the above paragraphs, Multiple Myeloma (MM) is a multifaced disease with many factors incurring in its development and in its peculiar traits. MM is also characterized by a variety of risk factors, both biological, as genetic peculiarities, age, race, and precursor diseases but also environmental, usually related to occupation and exposition to chemicals. In the last years, there has been a growing effort in the identification of risk factors, which may lead to new prevention measures as well as to a reduction of mortality rate.

2.1.3.1 Biological risk factors

Biological risk factors include age, race and social status and family history.

Generally, the incidence of haematological malignancies increases with age, and MM does not represent an exception to this paradigm. The median age for the diagnosis of MM is 70 years, and limited is the number of patients that are diagnosed before the age of 65.[90] The rate of survival and the efficiency of treatments decreases with age and this is mainly determined by a lower tolerance of the treatment, a higher discontinuity rate in the drug assumption, and by a limited physical response to the treatment due to the malfunction of the organism itself.

Concerning the influence of race in the development of MM, different studies provided controversial results; some of them proved that race is a discriminating factor, showing that black people were more subjected to MM insurgence,[91] while others showed that the discrepancy in the incidence in black and white people was not consistent.[92] Considering the results of the different studies concerning the role of race in the development of the illness, the most probable conclusion is that there is no substantial genetic and biological variation in the response to the disease, but the differences emerging in the rate of survival and in the drug effectiveness may be determined by the socio-economical context, which strongly influences the efficiency of the health system.[93]

The last biological risk factor is medical family history; individuals whose relatives have been affected by breast, prostate, or colorectal cancer, show a risk of developing the disease that is 2 times higher than other individuals. This evidence suggests that MM shares genetic

[90] Rafael RÍOS-TAMAYO, et al., "Trends in survival of multiple myeloma: a thirty-year population-based study in a single institution", *Cancer epidemiology*, 39, 5, 2015, 693-699.
[91] Angela BAKER, et al., "Uncovering the biology of multiple myeloma among African Americans: a comprehensive genomics approach", *Blood*, 121, 16, 2013, 3147-3152.
[92] Hakan KAYA, et al., "Impact of age, race and decade of treatment on overall survival in a critical population analysis of 40,000 multiple myeloma patients", *International journal of hematology*, 95, 1, 2012, 64-70.
[93] David SAVAGE, et al., "Race, poverty, and survival in multiple myeloma", *Cancer*, 54, 12, 1984, 3085-3094.

susceptibility as many other cancers.[94] However, even though family clusters have been described, there is no real evidence of the hereditary trait of MM.

2.1.3.2 Environmental risk factors

The most relevant environmental risk factors are obesity, occupation and exposure to chemicals and ionizing radiation.

Obesity is one of the biggest problems in health and it constitutes both a risk factor and a comorbidity in MM; overweight (BMI 25.0-29.9) and obesity (BMI ≥30) are thought to determine, respectively, a 12% and 27% risk in developing MM. 32% of all the Newly-Diagnosed Multiple Myeloma patients (NDMM) are obese, and this usually determines a higher drug-resistance due to a higher Body-Mass Index (BMI), but also to a lower OS since the organism itself is already compromised and therefore shows a lower resistance to the disease.

Concerning occupational risk factors, several occupations have been associated to a higher risk of developing MM, such as farmers, firefighters, and hairdressers. All of these occupations are characterized by a high and extended exposure to chemicals and metals, so it is possible to affirm that all of the occupations where the individual is exposed to higher levels of chemical agents and metal dust present a higher possibility to develop the active form of MM.

Research related to the effect of ionizing radiation as a risk factor for MM are controversial; indeed, studies based on the data of atomic-bomb survivors, associated the exposure to ionizing radiation to a higher risk of developing MM.[95] However, later evaluations of the same data found some discrepancies in the first analysis and did not confirm the connection between the exposure to ionizing ration and MM. Considering the general limited exposure of patients to radiations, nowadays there are no sufficient data to prove whether ionizing radiations are a concrete risk factor in the development of MM.

2.1.4 The Staging of the disease

The great heterogeneity of MM clinical manifestations and progress conveys the need to identify precise parameters to distinguish high-risk and aggressive disease from the low-risk one.

Three staging systems are to be considered with regards to MM: Durie-Salmon System, International Staging System (ISS) and Revised International Staging System (R-ISS). The Durie-Salmon System represents the first attempt to provide a reference system for the progress of MM, but it is no longer in use, since its criteria are currently obsolete. On the other hand, the

[94] Christopher FRANK, et al., "Search for familial clustering of multiple myeloma with any cancer", *Leukemia*, 30, 3, 2016, 627-632.
[95] Dominik ALEXANDER, et al., "Multiple Myeloma: a review of the epidemiologic literature", *International Journal of Cancer,* 120, 12, 2007, 40-61.

R-ISS constitutes the most updated system, and it is therefore the one that is mostly used, even if it still presents some criticalities. The process of defining a complete staging system for MM is an ongoing and complex process which requires constant improvement and modifications based on the advent of new therapies and on the increase of the OS.

2.1.4.1 Durie–Salmon System

The Durie-Salmon (DS) System was introduced in 1975 by Brian Durie and Sydney Salmon and constitutes the first classification system for MM. Durie and Salmon study was meant to show how myeloma mass was related to clinical manifestations, response to treatment and patients' survival rate.

According to their study, the most significant clinical manifestations associated with the mass of the tumour are osteolytic lesions, level of M-component, level of haemoglobin and level of calcium.

This system identifies three clinical stages (I, II, III), each of which distinguish a precise tumour size, which becomes progressively bigger moving from stage I to stage III. Each stage is also differentiated in two varieties (A and B) which provide information about the renal functioning based on the presence of serum creatinine; indeed, creatinine is a major indicator of response to treatments and higher rate of survival. "A" refers to a normal renal functioning while "B" corresponds to an abnormal renal functioning (A – Creatine < 2mg/dL; B – Creatine ≥ 2mg/dL).[96]

Stage I of DS shows a low myeloma cell mass and a good response to treatment; stage II has an intermediate tumour mass and neither good or poor response to treatment; stage III is characterized by a high cell mass, poor response to treatment and low survival perspectives (Table 1).

Stage I	All the following: Hb > 10g/dL Normal calcium No or Single bone lesion Low M-component production	Low tumor mass <$0.5x10^{12}/m^2$
Stage II	Between stage I and stage III	Intermediate tumor mass $0.5\text{-}1.2x10^{12}/m^2$

[96] Brian G. DURIE, Sydney E. SALMON, "A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival", *Cancer*, 36, 3, 1975, 842-854.

Stage III	Any of the following: Hb < 8.5g/dL Calcium <12 mg/dL Multiple Osteolytic lesions and fractures High M-component production	High tumor mass $>1.2x10^{12}/m^2$

Table 1:Durie-Salmon Staging System

2.1.4.2 International Staging System (ISS)

The International Staging System (ISS) was introduced in 2005, and it distinguishes 3 stages of MM, based on two main parameters: the level of serum *β_2-microglobulin* and the level of serum albumin (Table 2).

Stage I	Serum *β_2-microglobulin < 3.5 mg/L* *Serum albumin ≥ 3.5 g/dl*
Stage II	Not stage I or III[97]
Stage III	Serum *β_2-microglobulin > 5.5 mg/L*

Table 2: ISS Staging System

The three stages of ISS are strongly related to the prognosis of MM: stage I implies an OS of 62 months, stage II implies an OS of 44 months and stage II implies an OS of 29 months.[98]

The capability to estimate the median survival of the patient, depends upon the two main variables that are used to assess the stage: the level of serum *β_2-microglobulin* is strongly related to the size of the neoplasm and to the degree of renal impairment, while the low level of serum albumin reflects the high level of IL-6.[99]

The replacement of the DS system with the ISS is mainly determined by the greater prognostic accuracy of the ISS and also because the tests conducted to assess the *level of serum* β_2-microglobulin and serum albumin are inexpensive and therefore widely available.

2.1.4.3 Revised International Staging System (R-ISS)

In 2015, the International Myeloma Working Group (IMWG), revised the ISS, providing an improved system named Revised ISS (R-ISS). The R-ISS adds to the traditional ISS two new

[97] Stage II identifies two possible situations: *serum* β_2-microglobulin < 3.5 mg/L but serum albumin < 3.5 g/dL; or *serum* β_2-microglobulin between 3.5 and 5.5 mg/L, regardless of the serum albumin level.

[98] Antonio PALUMBO, et al., "Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group", *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*, 33, 26, 2015, 2863-2869.

[99] Joth L. JACOBSON, et al., "A new staging system for multiple myeloma patients based on the Southwest Oncology Group (SWOG) experience", *British journal of haematology*, 122, 3, 2003, 441-450.

variables: the level of serum Lactate DeHydrogenase (LDH) and the presence of Chromosomal Abnormalities (CA) (Table 3).

Stage I	Serum *β_2-microglobulin < 3.5 mg/L* *Serum albumin ≥ 3.5 g/dl* No high-risk chromosomal abnormalities (presence of standard-risk chromosomal abnormalities) Normal LDH
Stage II	Not R-ISS stage I or III
Stage III	Serum *β_2-microglobulin > 5.5 mg/L* High-risk chromosomal abnormalities High LDH

Table 3: R-ISS staging system

CA tracked thanks to interphase Fluorescent in Situ Hybridization (iFISH) constitute a crucial element in defining the biological features of MM; indeed, the presence of standard-risk CA corresponds to an OS of 50.5 months, while the presence of high-risk CA halves the OS to 24.5 months. The enormous gap in the OS existing between the two conditions shows the high relevance of this data in defining the prognosis.

LDH is another significant element as it is an indicator of the aggressiveness of the disease; indeed, high levels of LDH denote high proliferation of the tumour mass, and the presence of extraosseous or extramedullary disease, which sensibly shorten the OS.[100]

The R-ISS represents the most complete staging system available now and it plays a crucial role in outlining the prognosis of MM, as it allows to define both Progression-Free Survival (PFS) and OS. According to R-ISS, 5 years PFS, is 55% in R-ISS stage I, 36% in R-ISS stage II and 24% in R-ISS stage III; while 5 years OS, is 82% in R-ISS stage I, 62% in R-ISS stage II and 40% in R-ISS stage III.

However, even if R-ISS is now the most accurate and the most complete staging system available, there are still some criticalities and limits to its efficiency; indeed, since MM is an heterogenous disease, which may appear in different forms, especially in R-ISS II patients, in some cases it is necessary to provide some more detailed subclassifications.[101] Furthermore, it

[100] Bart BARLOGIE, et al., "High serum levels of lactic dehydrogenase identify a high-grade lymphoma-like myeloma", *Annals of internal medicine*, 110, 7, 1989, 521-525.

[101] Since it is not the aim of this thesis to provide detailed information about the staging system of MM, for further clarification about the subclassification of MM, see: Sung-Hoon JUNG, et al., "A prognostic scoring system for patients with multiple myeloma classified as stage II with the Revised International Staging System", *British journal of haematology* vol. 181,5 (2018): 707-710.

should also be taken into account that R-ISS does not consider the presence of circulating neoplastic plasma cells and the presence of extra-medullary disease, which have been proven, in the last years, to be extremely relevant in the prognosis of MM.

2.2 Multiple Myeloma in China

Concerning the presence of Multiple Myeloma in China, as mentioned in the above section, the rate of MM patients in China is lower than the one in US or Europe and Chinese people also tend to have better outcomes. However, if Asian people, particularly Chinese ones, seem to be advantaged from a genetic point of view, poorer outcomes can be seen in diagnosis, treatment, and quality of life of Asian patients compared to western ones. In the following paragraphs general situation, epidemiology, risk factors and treatment options for Chinese MM patients will be investigated, highlighting the inefficiency of the Chinese health system and the limitation of available therapies.

2.2.1 General situation

Multiple Myeloma is a relatively rare haematological malignancy which affects a limited portion of the Chinese population. However, even if statistics show a lower incidence of MM in Chinese patients, some studies suppose that the incidence of MM in China is underestimated due to high miss diagnosis rate.[102] Delay in diagnosis and miss diagnosis constitute a great issue in MM landscape; indeed, great part of MM patients are never diagnosed with MM, discovering the illness only if autopsy is carried out after death, while many others are diagnosed only when severe complication arises, reducing their OS and producing inferior outcomes compared to patients in western countries. This situation leads to a paradox in the study of the disease: Asian people, due to their genetic inheritance, could have the best outcomes, but due to the inefficiency of the health system, they show the lowest OS and OR.[103]

Concerning delay in diagnosis, it is mainly determined by three main factors: 1. Chinese patients do not frequently take routine body examination and they tend to ignore symptoms once they appear; 2. Chinese patients, if acknowledge the presence of symptoms, seek relief in Traditional Chinese Medicine, which may lack a complete picture of the disease; 3. Physicians do not recognize MM and ascribe the symptoms to other pathologies, prescribing inefficient therapies. Therefore, because of all of these factors, Chinese patients are diagnosed only when

[102] Jing LI, et al., "The impact on early diagnosis and survival outcome of M-protein screening-driven diagnostic approach to multiple myeloma in China: a cohort study", *Journal of Cancer*, 10, 20, 2019, 4807-4813.
[103] Jun LU, et al., "Clinical features and treatment outcome in newly diagnosed Chinese patients with multiple myeloma: results of a multicenter analysis", *Blood Cancer Journal*, 4, 8, 2014, e239.

CRAB symptoms are already present and the possibilities to effectively act on the disease are limited.

Delay in diagnosis and inefficiency of the health system lead to poor quality of life for Chinese patients, who not only have to face difficulties in the management of the disease and in treatment's side effects, but they also have to overcome the burden of expensive therapies and inadequate medical infrastructures.

The Guandong Natural Science Foundation carried out research meant to assess the health-related quality of life (HRQOL) of Chinese patients with MM.[104] Patients were provided with a questionnaire crafted according to the guidelines established by the European Organization for Research and Treatment of Cancer (EORTC). This study outlined that, even though several improvements have been made in the treatment of MM, the chronic nature of the disease strongly reduce patients' quality of life. Indeed, MM status as a chronic disease requires continuous treatment which reduces patients' capability to take care of themselves, requiring the presence of a caregiver, and leading to enormous expenses.[105] Nowadays, many Chinese patients lack the support or a caregiver or decide to refuse the treatment because they cannot bear the economic expenses; in particular, those families whose income is <30.000 RMB (4000 euros approximately) decide to refuse any kind of treatment or support as this could be fatal to the economy of the family.[106]

It should be noted that these difficulties appear to be even more burdensome for patients living in the countryside; indeed, rural infrastructures are in the majority of cases inadequate, and people do not have the economic possibilities to reach urban infrastructures. The situation in the countryside is worsened also by the low level of education which does not allow people to be aware of their clinical situation.

All things considered, the general assessment of MM situation in China is characterized by several negative points, from the lack of awareness to the lack of appropriate infrastructures and economic support from the government. Many are the areas of improvement which could enhance people quality of life and general OS and OR, but this would require a substantial joint action between State, insurance companies, health system and physicians' network.

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[104] Xiaozhe LI, et al., "Health-related quality of life of patients with multiple myeloma: A real-world study in China", *Cancer Medicine*, 9, 21, 2020, 7896-7913.

[105] Alex MOLASSIOTIS, et al., "Living with multiple myeloma: experiences of patients and their informal caregivers", *Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer*, 19, 1, 2011, 101-111.

[106] Shankar PRINJA, et al., "Cost-Effectiveness of Autologous Stem Cell Treatment as Compared to Conventional Chemotherapy for Treatment of Multiple Myeloma in India", I*ndian journal of hematology & blood transfusion: an official journal of Indian Society of Hematology and Blood Transfusion*, 33, 1, 2017, 31-40.

2.2.2 Epidemiology

The incidence of MM in the Asian population is relatively low compared to the one in Caucasians or in the black population.

According to data provided by the National Medical Insurance Database, gathered from January 1, 2012, to December 31, 2016, in China, MM incidence is 1.15/100,000, which is significantly lower compared to USA or Europe. However, it is noteworthy than in China, the incidence of MM is strongly dependent upon the geographical area; indeed, northern, and eastern China show high rates of MM compared to the rest of China. This difference may be determined by differences in climate, lifestyle patterns but also in genetic background (taller individual are proved to be more exposed to the development of the disease).[107]

Differently from USA and Europe, in China, the mean age of MM patients is 58 years old, roughly 10 years younger than Caucasians. The reason behind this gap could be found in ethnic disparity, considering the great differences existing between the bone geometry, strength and quality of Asians and Caucasians.[108]

Another difference in the Chinese epidemiology refers to the diffusion of the disease in man and women; while in USA and Europe, men tend to be more exposed to MM, in China, not only women are more prone to develop the disease but also the age at which it is diagnosed is lower in women rather than in men. Indeed, as in figure 2,[109] while the peak for women is registered between 55 and 59 years old, the peak for men is registered between 64 and 74 years old.[110]

It should be considered that the diffusion of MM has registered an intense increase in the last 3 years, which casts the light on the necessity to establish an effective disease prevention and to purse the path of the research to develop new treatments and therapies.

2.2.3 Risk factors

In describing MM in China, great relevance should be reserved to risk factors as there are several peculiarities that make the Chinese situation an interesting area of research.

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[107] Lauren TERAS, et al., "Body size and multiple myeloma mortality: a pooled analysis of 20 prospective studies", *British journal of haematology*, 166, 5, 2014, 667-676.
[108] Anna L. KEPLEY, et al., "Differences in bone quality and strength between Asian and Caucasian young men", *Osteoporosis international: a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA,* 28, 2, 2017, 549-558.
[109] Shengfeng WANG, et al., "Prevalence and Incidence of Multiple Myeloma in Urban Area in China: A National Population-Based Analysis", *Frontiers in Oncology,* 9, 1513, 2020.
[110] *Ibidem*

It should be noted that the general positive outcome that characterize Asian patients tends to be higher in Asian living in Asia, rather than in Asia living in US or Europe.[111] This is not determined by differences in medical infrastructures or treatment options because, as we saw in the previous paragraphs, these two elements need to be furtherly improved in Asia and especially in China, but the greater outcomes of Chinese patients are to be sought in their lifestyles and in their nutrition habits.

Some evidence supports the idea of a beneficial action of garlic and shallot in prevention of both haematological and solid cancers; furthermore, a multicentre hospital-based case-control study of multiple myeloma carried out in 5 hospitals in Xi'an showed how these bulbs can play a significant role in reducing the risk of MM.[112] Soybean is another vegetable which is under research to determine whether it has beneficial action to prevent MM but the outcomes are still controversial, as some research proved its effectiveness [113] but others considered it not sufficiently significant.[114]

Concerning tea intake, the Xi'an case-control study showed that high consumption of green tea can significantly reduce MM risk; the reason of this beneficial action can be found in the high number of polyphenols and catechins present in tea leaves. These two substances are antioxidants which are known to play a significant role in cancer prevention.[115]

On the other hand, the high consumption of brined and picked vegetables, typical of northern China, is associated with an increase in the risk of MM.[116] This depends upon the fact that the high consumption of salt may induce DNA synthesis and cell proliferation, contributing to carcinogenesis.[117]

Overall, the dietary habits of the Chinese population play a great role in increasing or reducing the risk to develop MM and this should be taken into consideration when designing preventive strategies to reduce the risk of MM.

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[111] Jacqua FERLAY, et al., "Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008", *International journal of cancer*, 127, 12, 2010, 2893-2917.
[112] Qixia WANG, et al., "Risk factors for multiple myeloma: a hospital-based case-control study in Northwest China", *Cancer epidemiology*, 36, 5, 2012, 439-444.
[113] Dai CHIHARA, et al., "Inverse association between soy intake and non-Hodgkin lymphoma risk among women: a case-control study in Japan", *Annals of oncology: official journal of the European Society for Medical Oncology*, 23, 4, 2012, 1061-1066.
[114] Vicky CHAN, et al., "Lower incidence of plasma cell neoplasm is maintained in migrant Chinese to British Columbia: findings from a 30-year survey", *Leukemia & lymphoma*, 52, 12, 2011, 2316-2320.
[115] Carmen CABRERA, et al., "Beneficial effects of green tea--a review", *Journal of the American College of Nutrition*, 25, 2, 2006, 79-99.
[116] Le JIAN, et al., "Do preserved foods increase prostate cancer risk?", *British journal of cancer*, 90, 9, 2004, 1792-1795.
[117] Chow H. LEE, et al., "Control of hepatocyte DNA synthesis by intracellular pH and its role in the action of tumor promoters", *Journal of cellular physiology*, 195, 1, 2003, 61-69.

2.2.4 Treatment options

Many treatment options in China are still limited by their price which makes them unavailable for great part of the population. In this section two main treatments will be taken into consideration: bortezomib-based treatments and autologous stem cell transplantation (ASCT).

Bortezomib is the first-generation proteasome inhibitor, and it was firstly approved in 2006 in China for the treatment of MM. In first place, bortezomib was administered intravenously but different studies showed that subcutaneous administration could reduce its toxicity, and now this second procedure represents the standard for administration.[118] The main action mechanism of bortezomib depends upon its capability to reversibly binds itself to and inhibit the proteasome 20S proteolytic site, leading to protein accumulation and activation of apoptotic mechanisms.[119] Other secondary mechanisms of bortezomib include apoptosis stimulation, drug-resistance inhibition and reduction of pro-inflammatory cytokines who play a great role in leading to cast nephropathy.[120]

Bortezomib main side effects are Peripheral Neuropathy (PN) (present in 40% of the patients), thrombocytopenia (present in 30% of the patients) and myelotoxicity.[121]

Until 2013, bortezomib was not covered by the National Health Insurance and the cost of one cycle treatment was more than 50.000 RMN, therefore it was not frequently used by physicians, and when prescribed were patients to interrupt the treatment because they could not cover the expenses. In 2013, the Chinese Cancer Foundation, together with the Xi'an-Janssen Pharmaceutical Co. Ltd., launched the VELCADE Patient Assistance Program whose main goal was to increase the use of bortezomib by rendering it available to greater portion of the population.[122] This program increased the use of bortezomib as a first-line therapy for MM, but the real switch occurred in 2017, when the National Health Insurance started to cover the expenses of bortezomib administration. Nowadays, bortezomib-based treatments constitute the "gold standard" in the treatment of MM also in China, both for Newly Diagnosed Multiple Myeloma (NDMM) patients and Relapsed Refractory Multiple Myeloma (RRMM) patients.[123]

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[118] Philippe MOREAU, et al., "Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study", *The Lancet. Oncology*, 12, 5, 2011, 431-440.
[119] Kristin BREITSCHOPF, et al., "Ubiquitin-mediated degradation of the proapoptotic active form of bid. A functional consequence on apoptosis induction", *The Journal of biological chemistry*, 275, 28, 2000, 21648-21652.
[120] Wanqiu ZHU, Wenming CHEN, "Bortezomib-based treatment for multiple myeloma patients with renal impairment: A systematic review and meta-analysis of observational studies", *Medicine*, 95, 46, 2016.
[121] Antonia FIELD-SMITH, et al., "Bortezomib (Velcadetrade mark) in the Treatment of Multiple Myeloma", *Therapeutics and clinical risk management*, 2, 3, 2006, 271-279.
[122] Jingsong HE, et al., "Bortezomib-Based Regimens for Newly Diagnosed Multiple Myeloma in China: A Report of 12-Year Real-World Data", *Frontiers in pharmacology*, 11, 2020.
[123] *Ibidem*

Concerning ASCT, it represents the main non-drug treatment for MM. Different factors as comorbidities, age and performance status influence the feasibility of the procedure and even if ASCT is the treatment that provides the most benefits to patients, and Treatment-Related Mortality (TRM) is only 1-2%,[124] it may not represent the best choice in all situations.

ASCT can be distinguished in early ASCT (carried out immediately after the induction therapy) or delayed ASCT (resorted as a salvage therapy at the moment of first relapse). Considering the impact on quality of life determined by high-dose chemotherapy and its economic burden, if there is no specific preference on the side of the patient, early ASCT is recommended. It may be preferrable to opt for delayed ASCT only if the patient is well tolerating and responding to the initial therapy and the risk of progression is low.

ASCT can be performed once or twice (tandem ASCT) according to the specific condition of the patient. In tandem ASCT, the patient will receive a second transplant once he recovered from the first one.[125] Different studies[126][127] showed an improvement in PFS when ASCT is performed twice, but they all failed to show any improvement in OS, mainly because of the significant toxicity of the treatment, which in the long run affects the possibility to increase the survival rate. Since no significant benefits can be obtained from tandem ASCT, patients are considered for this procedure only when they show a high-risk disease with no complete response after the first transplant.

ASCT is widely performed in China and the transplantations number has increased greatly from 2006 to 2015, mainly because of the greater number of transplantation centers that have been built on the Chinese territory.[128] However, it should be noted that the majority of these centers are located in developed cities such as Beijing, Tianjin and Shanghai, which showed the highest rate of transplantation utilization, respectively 60.9%, 44.0% and 23.8%, while the lowest rates are registered in southern regions as Hainan (1.2%), Jiangsu (1.1%) and Guizhou (0.9%).[129]

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[124] Morie A. GERTZ, et al. "Autologous stem cell transplant in 716 patients with multiple myeloma: low treatment-related mortality, feasibility of outpatient transplant, and effect of a multidisciplinary quality initiative", *Mayo Clinic proceedings*, 83, 10, 2008, 1131-1138.

[125] Bart BARLOGIE, et al., "Superiority of tandem autologous transplantation over standard therapy for previously untreated multiple myeloma", *Blood*, 89, 3, 1997, 789-793.

[126] Umit Yavuz MALKAN, et al., "Comparison of single and double autologous stem cell transplantation in multiple myeloma patients", *Open medicine,* 16, 1, 2021, 192-197.

[127] Michele CAVO, et al., "Double Autologous Stem Cell Transplantation Significaly Prolongs Progression-Free Survival and Overall Survival in Comparison with Single Autotransplantation in Newly Diagnosed Multiple Myeloma: An Analysis of Phase 3 EMN02/HO95 Study", *Blood*, 130, 401, 2017.

[128] Minako IIDA, et al., "Advances in hematopoietic stem cell transplantation in the Asia-Pacific region: the second report from APBMT 2005-2015", *Bone marrow transplantation*, 54, 12, 2019, 1973-1986.

[129] Weiping LIU, et al., "Autologous hematopoietic stem cell transplantation activity for lymphoma and multiple myeloma in China", *Bone marrow transplantation*, 58, 3, 2023, 349-352.

These differences show how the access to healthcare and special treatments in China is still strongly influenced by the geographical location and how this does not allow the Chinese population to have full access to medical practices and to adequate treatments.

Overall, even though the Chinese pharmaceutical industry is strongly developed and, in many cases, it represents the vanguard in several sectors, the access of the Chinese population to the medical progress is limited by the inefficiency of the healthcare system and by the high cost of treatments and therapies.

CHAPTER 3

Traditional Chinese Medicine: the holistic principle

In this chapter the basics of Traditional Chinese Medicine (TCM) will be explored and consideration over its relationship with western medicine will be made; in particular, great attention will be casted on the role of Systems Thinking as a possible bridge between TCM and western medicine.

3.1 Chinese medicine: an overview

Traditional Chinese Medicine is often defined as the "healing art"[130], a broad range of practices which originated more than 3000 years ago in ancient China, and which are still widely practiced in modern China. In recent years, TCM have diffused also in western countries as part of the Complementary and Alternative Medicine (CAM), which is meant to work parallelly with western medicine to provide support and palliative cares to patients, or even to substitute it in the case of western Medicine ineffectiveness.

In this section, an overview of the TCM will be provided starting with its history and core text and moving to its philosophical roots and basic organizing principles.

3.1.1 History of Traditional Chinese Medicine

As mentioned in the introduction, Traditional Chinese Medicine (TCM) originated probably 3000 years ago during Yin and Shang Dynasties[131]; however, there is some evidence which proves that acupuncture was already practiced in the Neolithic age (8000-5000 B.C.). In the Neolithic age, acupuncture spots were probably stimulated with sharpened stones or other easily reachable materials, while in the XVI-XI century B.C. acupuncture was already performed with real needles made of bronze, copper, tin, gold, or silver.

In the Spring and Autumn Period (771-476 B.C.), the "Yellow Emperor's Canon of Medicine" (黃帝內經 Huang Di Nei Jing) was published; it represents the main comprehensive text of TCM and it still works as a guide for the understanding its basic principles.[132]

It was during the Warring States period (475-221 B.C.) that TCM took proper form thanks to the development of the different philosophical schools, as Daoism and Confucianism; indeed, TCM owes to Daoism the notion of Dao (道), the law at the basis of all the natural

[130] Gary NESTLER, "Traditional Chinese medicine", *The Medical clinics of North America*, 86, 1, 2002, 63-73.
[131] J.W. LI, Z. G. LIN, "A General History of Chinese Medicine", Beijing, People's Medical Publishing House, 2010
[132] *Ibidem*

phenomena, and the notion of Qi (氣), the energy that determines the existence of human beings. In the same period, the Yin-Yang school developed the Yin-Yang theory which offers individuals with a way to interpret reality. The Warring States period was also particularly productive from the literature point of view, in fact, three main volumes were written in the period: the "Shennong Emperor Classic of Materia Medica" (神農本草經 Shennong Bencao Jing), which is a comprehensive corpus of applied pharmacology; the "Treatise on Cold Diseases and Miscellaneous Diseases" (傷寒雜病論 Shanghan za bung lun), which for the first time highlights the relationship between acupuncture and pharmacotherapy; the "Systematic Classic of Acupuncture and Moxibustion" (針灸甲乙經 *Zhenjiu jiayi jing*), which provides the location of all the 649 acupoints and extensively describes the acupuncture and moxibustion practice.

During Jin and North and South Dynasties (265-618 B.C.), TCM and especially acupuncture gained a great diffusion in different social classes; in Tang Dynasty, TCM was so relevant that it was inserted to the knowledge required to successfully pass the imperial examination. During Western Jin Dynasty, the "Pulse Classis" (脈經 Mai Jing) was published, building a milestone in the practice of pulse's studies.[133]

During Song and Tang Dynasties, the government ordered the recompilation of the first medical text published during the Spring and Autumn Period; the result was the publication of the "Newly Revised Materia Medica" (新秀本草 Xin Xiu Ben Cao) which constitutes the basic volume for pharmacology, opening the way to many other revisions of the original Huang Di text.[134]

Ming Dynasty represents the period of maximum development of TCM; in this period, several studies and research were carried out to deepen knowledge and improve medical practices, especially regarding acupuncture and moxibustion. In this period, the Imperial Medical Academy and the Medicine Bureau were established; they were responsible for the dissemination of TCM knowledge and for its medical administration. During Ming Dynasty, exchanges with Asia, Europe and Africa started to become more common, leading to the export of Chinese culture and medical principles as well as the import of much western knowledge. This intense cultural exchange benefitted China under different aspects: it strengthened China relationship with other reigns; it brought a strong development from scientific and translation studies point of view; it introduced knowledge about vaccines and anatomy; it stimulated the creation of new terms, leading to the first sign of language renovation.

[133] Danning MA, et al., "The development of traditional Chinese medicine", Journal of Traditional Chinese Medical Sciences, 8, 1, 2021, S1-S9.
[134] Shi Xiu LI, "Compendium of Materia Medica", Beijing, Foreign language press, 2004.

After the Opium Wars (1839-1842), TCM started to decline due to the presence of western medicine, which in many cases proved to be more effective especially for acute diseases. This gradual fall was then followed by a severe repression which detained TCM to a superstitious practice only surviving in the countryside.

The establishment of the Popular Republic of China (PRC) determined a switch in the attitude to the TCM; indeed, if at the beginning of the new historical period some discriminations were still present, in 1954 the Ministry of Health established the principle of integration between the western medicine and the TCM and founded a TCM research institute as well as many TCM university courses.

However, even if the inclusion and the recourse to TCM had been established by the law, there was still great mistrust, and this became clear during the Great Revolution, in which people were divided in those that considered TCM as a part of the Chinese culture which needed to be transmitted to the new generations and those that considered TCM as heritage of the feudalism. Nowadays, TCM is widely recognized in China as a mean of prevention and health maintenance, and several schools are present worldwide. TCM is also the object of many studies which try to integrate it with the western Medicine.[135] The spread of TCM in more than 180 countries led to the necessity to establish some rules and international cooperation agreements, which were signed in more than 70 countries.[136]

3.1.2 Yin & Yang

Yin-Yang theory appeared for the first time in the "Classic of Changes" (易經 Yi Jing) and its roots can be found in Confucianism, Buddhism and Taoism.[137] Yin-Yang Theory is one of the core theories of TCM, being the backbone of diagnostic, physiology, and pathology. The School of Yin-Yang, active during the IV-III century B.C., is the first school that tried to provide a systematization to the theory of Yin-Yang, determining a significant shift in the interpretation of the universe. Indeed, Yin-Yang theory brought to light a new idea of universe, no longer seen as magic or mythological, but it was rather speculative and naturalistic. Thanks to this change of perception, medical practice detached from the figure of Fangshi (方士), members of the high Chinese society who were devoted to divination, astrology and medicine, and became an independent practice relaying on more logical principles.

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[135] Rosario PUGLIARELLO, "Medicina Tradizionale Cinese", in P. Bellavite, A. Conforti, A. Lechi, F. Menestrina (a cura di), *Le medicine complementari*, Milano, Utet Periodici, 2000.
[136] J.P. ZHU, Centennial History of Traditional Chinese Medicine, Shanghai, Shanghai Science and Technology Press, 2016
[137] Wang WEI, "Genomics and Traditional Chinese Medicine", in Genomics and Society, Dhavendra Kumar, Ruth Chadwick (eds), Cambridge, Academic Press, 2016, 293-308.

Yin (陰) and Yang (陽) can be defined as "virtues", concrete elements of time and space which are opposite each other . Yang represents "sun on the horizon" and is associated to the idea of movement and activity; Yin represents "clouds over the mountain", associated to the idea of inactivity and rest. As mentioned before, Yin and Yang are opposites but at the same time they complementary, as they cannot exist on their own. The relationship between Yin and Yang is regulated by five main principles: 1. Each phenomenon on Earth consists of both Yin and Yang; 2. Each Yin or Yang phenomenon can be further divided into Yin and Yang; 3. Yin and Yang mutually define each other; 4. Yin and Yang control each other; 5. Yin and Yang will ultimately transform one into another.[138]

Yin-Yang theory is thus based on a strong duality in which none of the two antipodes can prevail on the other and the application of Yin-Yang theory in TCM led to the assumption that human beings are made of both external and concrete elements as body (Yin) and internal functions as spirit (Yang).[139] Yin and Yang are also used to describe two patterns on change in the human body: Yin is cooling while Yang is warming; therefore, chill is present when there is an excess in Yin, while fever appears when there is an excess in Yang.[140] The ultimate goal of a TCM physician is to maintain the balance between Yin and Yang, since, health into the human being can only be achieved if Yin and Yang are perfectly balanced. If this balance could be eventually achieved in the past, in the present is more and more difficult due to the existence of a society made of extremes.[141]

3.1.3 Qi

Classical Chinese literature defines Qi (氣) as "the basic element of human vital energy";[142] however, a unique definition of Qi does not exist, because each school of thought as well as each historical period provided a different definition.

Qi can be classified into four basic types: 1. Primordial Qi or Congenital Qi (元氣 Yuan Qi) which is the one inherited by parents; 2. Pectoral Qi (宗氣 Zong Qi) which is located in the chest and is responsible for the correct functioning of heart and lungs; 3. Nutritive Qi (營氣 Ying Qi) which circulates in body vessels to spread nutrients to the organs; 4. Defensive Qi (衛

[138] Anita Chen MARSHALL, "Traditional Chinese Medicine and Clinical Pharmacology", *Drug Discovery and Evaluation: Methods in Clinical Pharmacology*, Franz J. Hock, Michael R. Gralinski (eds), 2020, 455-482.
[139] Jin Ling TANG, et al., "Traditional Chinese medicine", *Lancet,* 372, 9654, 2008, 1938-1940.
[140] Gary NESTLER, "Traditional Chinese medicine", *The Medical clinics of North America*, 86, 1, 2002, 63-73.
[141] Rosario PUGLIARELLO, "Medicina Tradizionale Cinese", in P. Bellavite, A. Conforti, A. Lechi, F. Menestrina (a cura di), *Le medicine complementari*, Milano, Utet Periodici, 2000.
[142] Ju LING, "Qi, Blood, Essence and Body Fluid", Xutian Stevenson, Shusheng Tai, Chun-su Yuan (eds), Handbook of Traditional Chinese Medicine, 2014, 73-86.

氣 Wei Qi) which is responsible for the protection against pathogens and circulates outside body vessels.

Qi is considered the "motor of all activities".[143] After birth, Qi starts moving through organs and meridians and once it stops the human being dies. Four peculiar Qi movements can be identified: ascending, descending, exiting, and entering. These four movements can transform one into another and by their constant mixing, impacting, and colliding they boost the physiology of the human being.[144] When the Qi movement is not perfectly balanced, deficiency into the human body is produced and it manifests as an illness. Qi movement imbalance can appear into different forms: "Stagnation of Qi" which is the obstruction of the Qi flow, "Exhaustion of Qi" when an excessive amount of Qi leaves the body and "Depression of Qi" when Qi is not able to exit the body. Deficiency can manifest itself through fatigue, drowsiness, and asthenia and the treatment for this condition is known as "tonification" or "supplementation".[145] On the other hand, Qi excess may manifest as swelling and strong pain, in this case the treatment is meant to dissolve the main blockage.

Qi has five main physiological functions each of which is necessary for the preservation of the human body; indeed, if one of these functions does not work perfectly, this will determine the arising of a deficiency and a consequent illness. Physiological functions include: 1. Propelling function in which Qi is in charge of guaranteeing growth and development of the organism; 2. Warming function as Qi is the source of human heat; 3. Defending function in which Qi is responsible for fighting infections and repel pathogens; 4. Fixating and controlling in which Qi controls fluids and liquids to avoid excessive accumulation or excessive dispersion; 5. Transformation of Qi, also referred to as Qihua (氣話) which is the energy source of daily activities and physiological process.[146]

It should be noted that, even though the main goal of the human being is to maintain balance in the organization of Qi, it is possible for Qi to rebel suddenly and autonomously, in this case. nausea or asthma can manifest, and sedation treatment is required. The causes of Qi rebellion are not still clear, but some texts report that it may be the human manifestation of the disruption of the comprehensive equilibrium between the individual and the universe.

[143] Gary NESTLER, "Traditional Chinese medicine", *The Medical clinics of North America*, 86, 1, 2002, 63-73.
[144] Ju LING, "Qi, Blood, Essence and Body Fluid", Xutian Stevenson, Shusheng Tai, Chun-su Yuan (eds), Handbook of Traditional Chinese Medicine, 2014, 73-86.
[145] Xutian, STEVENSON et al., "New exploration and understanding of traditional Chinese medicine", *The American journal of Chinese medicine*, 37, 3, 2009, 411-426.
[146] Zuyin LU, Scientific Qigong Exploration: The Wonders and Mysteries of Qi, Malvern, Amber Leaf Press, 1997.

3.1.4 Blood & Fluids

Many texts define the human being as "blood and Qi being".[147] For TCM, blood has a strong energetic power which, together with Qi, allows the organism to survive. Furthermore, TCM considers that "Qi is the commander of Blood and Blood is the mother of Qi";[148] in this sense blood and Qi are inseparable because Qi is what infuses life into blood which in turn infuses life into the organism.

The main goal of blood is to moisten and nourish the body while providing material for the mind; blood can transport the nutrients all around the body thanks to the meridians, which constitute a complex network of vessels that allow the circulation of blood and Qi. The meridians' network explains why the imbalance of a single organ can determine the insurgence of an illness in the whole body; indeed, since all the organs are connected through 12 main meridians and many other secondary ones, the deficiency registered in one location is then spread all around the body causing a comprehensive deficit.

Another relevant function of blood is to ensure that all the different organs have the correct amount of oxygen they need to work properly;[149] in particular, according to the idea introduced by Qian Xue Sen, the chemical reaction taking place in blood between oxygen and hydrogen is the main driving force behind the ability of the brain to process information. This chemical reaction is enhanced by the heart which provides blood and oxygen with the information-specific hydrogen necessary to carry out this chemical reaction.[150] Therefore, if blood transports an adequate amount of oxygen, the Mind (brain) will have sufficient energy to work properly, while if blood is deficient of oxygen, abnormalities in the mind, as anxiety, stress and panic will arise.

Concerning blood disorders, three main situations should be analysed: blood stagnation, blood heat and blood deficiency.[151] Blood stagnation implies the creation of blood clots in coronary arteries and in menstrual flow, as well as the creation of hematomas; to cure blood stagnation, it is necessary to fluidify blood, activate blood circulation and clear the stagnation. Blood heat represents the more severe clusters of blood-related diseases; it manifests as scarlet fever, leukaemia, aplastic anaemia, and severe bleeding. To cure blood heat is necessary to cool down the blood and counteract the negative energies that are affecting the blood. The last

[147] Claude LARRE, Fabrizia BERERA, Filosofia della Medicina Tradizionale Cinese, Milano, Jaca Book, 1997.
[148] Ju LING, "Qi, Blood, Essence and Body Fluid", Xutian Stevenson, Shusheng Tai, Chun-su Yuan (eds), Handbook of Traditional Chinese Medicine, 2014, 73-86.
[149] Annotation and Correction of the Inner Canon of the Yellow Emperor — the Basic Questions, Beijing, People's Health Publishing House, 1991.
[150] Xin YAN, et al., "External Qi of Yan Xin Qigong differentially regulates the Akt and extracellular signal-regulated kinase pathways and is cytotoxic to cancer cells but not to normal cells", *The international journal of biochemistry & cell biology*, 38, 12, 2006, 2102-2113.
[151] Gary NESTLER, "Traditional Chinese medicine", *The Medical clinics of North America*, 86, 1, 2002, 63-73.

category of blood illnesses is blood deficiency which consists in a shortage of blood due to unexpected loss of blood or haematological diseases which limit blood production; it can manifest though anaemia, neurosis, and chronic fatigue. Blood deficiency should be cured with blood tonification and energy strengthening.

Concerning body fluids, the term "fluid" indicates all the normal body liquids as water, urine, and nutrients. Body fluids can be distinguished in two types: "lucid" (津 Jin) and "thick" (液 Ye). The former belongs to Yang and flows quicky though blood vessels, muscles, and membranes, nourishing the skin; the latter belongs to Yin, and it is located into cavities, lubricating the viscera and nourishing brain and bones. Water is the main fluid that can be found in the human body, and it is a fundamental element to distinguish living and non-living things; furthermore, water is also essential in the movement of blood and Qi through the meridians as it acts as carrier of Qi and it fluidifies blood to allow a better circulation.

Of great relevance in body fluids is the role of kidneys, since they play a key role in production and in metabolism of fluids, and all the organs involved in the fluids' circulation are dependent upon the warming power of kidneys. Kidneys are defined as "water organs"[152] because they take care of water circulating into the body and they ensure water transformation into specific body fluids.

All things considered, Qi, blood and fluids are all basic components of the body, which are independent but interactive as the life of each of them is linked to the life and functioning of the others.

3.1.5 Diagnosis in Traditional Chinese Medicine

As we saw in the first paragraph, TCM was fully institutionalized during the Song Dynasty (960-1279 A.D.), and it was in this period that comprehensive diagnostic tools, disease symptoms profile and treatment protocols were officially put into TCM.[153]

To formulate a correct diagnosis, it is necessary to collect patient's clinical data and to interpret them according to several rules, which allow the identification of the failing mechanism that is determining the illness. The key in TCM diagnosis is the ability to detect internal imbalances by observing and investigating external manifestations.

In TCM, data collection is based on four main pillars: observation, listening, questioning, and touching.

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[152] Gary NESTLER, "Traditional Chinese medicine", *The Medical clinics of North America*, 86, 1, 2002, 63-73.
[153] Anita Chen MARSHALL, "Traditional Chinese Medicine and Clinical Pharmacology", in Franz J. Hock and Michael R. Gralinski (eds), *Drug Discovery and Evaluation: Methods in Clinical Pharmacology*, Springer, Berlin, 2020, 455-482.

Observation implies a careful analysis of the appearance of different body parts, in particular great relevance is given to the analysis of the tongue. The analysis of the tongue plays a key role in the formulation of the diagnosis as certain area of the tongue can provide information about the condition of related internal organs. In the tongue analysis, it is necessary to observe: 1. the colour of the tongue, 2. the shape of the tongue, the patina, and the humidification degree of the tongue.

The second step of data collection is the listening: this step includes analysing the voice of the patients and its strength, the noisiness of the breath and the presence of peculiar, alarming sounds. This step also includes the analysis of the smells coming from the patient's body.

Listening is followed by questioning; this step is similar to the anamnesis practice carried out in Western medicine as it focuses on all the information that can be provided by the patient and that the patient himself considers as relevant.

The last step is touching, based on seeking pain in specific spots located on the 12 main meridians. The main practice carried out in this last step is the analysis of the pulse, which together with the analysis of the tongue constitutes the more objective diagnostic toll in TCM. Chinese pulse analysis is an effective tool to understand the condition of internal organs, by analysing the strength and the speed of blood and fluids flow in the meridians. In pulse analysis, the physician will use three fingers to delicately press on the wrist to catch the Pulse Wave Velocity (PWV). This analysis allows the identification of 28 different pulse that can be distinguished according to depth, frequency, rhythm, strength, extent, length, and shape and should be useful in understanding the nature of the disease.[154]

Once the diagnosis has been completed, disease can be classified according to the eight-syndrome classification which includes: 1. Yang syndrome, which may appear as fever and constipation, and implies a rapid and excessive pulse; 2. Yin syndrome, which causes fatigue and weak breathing and in which the pulse is weak, deep and slow; 3. Superficial syndrome, which usually manifests as conditions in hair and skin; 4. Deep syndrome, which interests the internal organs; 5. Cold syndrome, which manifests through cold, fatigue, foetal position sleeping and craving for hot drinks; 6. Hot syndrome, which manifests itself in red skin, high fever and craving for cold drinks; 7. Deficiency syndrome, which is caused by a decrease in vital energy and shows symptoms as fatigue and shortness of breath; 8. Excess syndrome, which is caused by an excess of energy and manifests itself through delirium, fever and abdominal pain.

[154] Rosario PUGLIARELLO, "Medicina Tradizionale Cinese", in P. Bellavite, A. Conforti, A. Lechi, F. Menestrina (a cura di), *Le medicine complementari*, Milano, Utet Periodici, 2000.

Each of these eight syndromes requires specific treatment plans which have been institutionalized and constitute now the basics in the treatment of each illness in TCM. These eight treatment plans will not be discussed in this thesis but for further information see Wu et al., 2021.[155]

3.2 Systems thinking: the western holistic view

3.2.1 Traditional Chinese Medicine Philosophy

Traditional Chinese Medicine (TCM) is defined as an "holistic medicine" as it considers health reality as whole.[156] In TCM, all the vital phenomena are related one another as they depend upon one single energy "Qi" (氣), which constantly changes and moves. Man can be thus defined as an open system related with the external environment, with which it constantly exchanges energy; because of this idea of the human being, TCM can be defined as "phenomenology of the human being" and it is an example of the practical application of the Chinese traditional philosophy.[157]

In fact, TCM finds its root in Chinese Ancient Philosophy, especially in Taoism which gave shape to the whole ancient Chinese scientific thought. Taoism revitalized different aspects of the Chinese culture, as the idea of an omnipotent and natural universe, by providing them with solid bases and systematization. This gave birth to a way of thinking that spread all over Asia and contributed to the maintenance and transmission of TCM beyond borders and through the centuries.

Noteworthy is the Taoist idea of human being; indeed, as mentioned before, Taoism considers human beings as part of the nature with which they have a "relationship of mutual inclusion, connection and coordination".[158] In this perspective, the only way through which human beings can stay healthy is adapting to the changes in nature and constantly interact with them. Therefore, to understand the individual is necessary to understand the whole environment of which the human being is part of. This peculiar view of the human being emphasizes the relationship existing between the human and the universe and considers the human body itself as a universe which it is to be understood in its complexity.[159]

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[155] Gaosong WU, et al., "Exploring biological basis of Syndrome differentiation in coronary heart disease patients with two distinct Syndromes by integrated multi-omics and network pharmacology strategy", *Chinese Medicine,* 16, 109, 2021.

[156] Rosario PUGLIARELLO, "Medicina Tradizionale Cinese", in P. Bellavite, A. Conforti, A. Lechi, F. Menestrina (a cura di), *Le medicine complementari*, Milano, Utet Periodici, 2000.

[157] Claude LARRE, Fabrizia BERERA, Filosofia della Medicina Tradizionale Cinese, Milano, Jaca Book, 1997.

[158] Danning MA, et al., "The development of traditional Chinese medicine", Journal of Traditional Chinese Medical Sciences, 8, 1, 2021, S1-S9.

[159] I.L. MA, Approaching Traditional Chinese Medicine-Eight Compulsory Courses for Modern People to Know about Traditional Chinese Medicine. Beijing, China Press of Traditional Chinese Medicine, 2013.

The philosophical background of TCM can be found also in the main texts that constitute the medical tradition. As many other philosophical texts written by literates, scholars and philosophers belonging to the highest level of the society and characterized by a strong class-conscious way of thinking, many TCM classical texts were written with a complex and hermetic language, meant to preserve the content of the texts, and avoiding its diffusion in the lowest levels of the society. However, this stratagem, whose main goal was to maintain the principle of traditional medicine in the highest levels of the society, led to difficulties of comprehension of these ancient Chinese texts, not only in the past but also in the current time. The main obstacle that readers need to overcome is the plurality of sense, which is itself emphasized by the monosyllabic and ideogrammatic nature of the Chinese language.

3.2.2 Systems Thinking and its role as a bridge within Chinese medicine and Western medicine

As mentioned in the above paragraph Traditional Chinese Medicine (TCM) is an "holistic medicine" in which the human body is considered as a whole, complex system in which all the composing elements are intertwined one to another and which cannot be understood in its singularity, but that should be considered in light of its relationship with the universe. This peculiar vision of TCM can be related to the main underlying assumption of Systems Thinking (ST) according to which the world should be analysed as a complex system made of interconnections which constantly influence one another. The similarity between the basic assumptions of these two massive frameworks of thought casts two questions: can Systems Thinking play a role in promoting the cooperation between TCM and western medicine? And if so, how can it do that?

To understand why the answer to these questions is so relevant and of common interest, it should be clarified that, even if western medicine is often reliable and effective in the cure of different diseases, it is not always successful in guaranteeing high quality of life and effective pain management. Thus, a combination of Chinese and western medical practices could provide patients with effective treatments and at the same time higher quality of life. This approach works well with patients with cancers, for which western medicine is aimed at reducing tumours, while TCM seeks to reduce patients' pain and impact of adverse events.[160]

In understanding why ST can promote the cooperation between TCM, and western medicine is first of all necessary to carry out, a terminological reflection on the terms "holism" and "systemic". The Oxford Dictionary of English[161] provides the following definition of the term

[160] Danning MA, et al., "The development of traditional Chinese medicine", Journal of Traditional Chinese Medical Sciences, 8, 1, 2021, S1-S9.

[161] Lesley BROWN, et al., *Oxford Dictionary of English,* Oxford, Oxford University Press, 2013.

holism: "The idea that the whole of something must be considered in order to understand its different parts", while the term systemic is defined as followed "Affecting or connected with the whole of something, especially the human body or a society". In both cases, the reference point is the whole and the need to consider all its composing elements to gain a full understanding; therefore, it could be stated that in both TCM and ST the human body is considered as a complex system, made of closely related sub-systems and interconnections that form a network.[162]

Acknowledged the similarity existing between TCM and ST, it necessary now to understand how ST can play a role in improving the cooperation between Chinese and Western medicine. Western medicine has its roots in the idea that each disease has a clear cause, which can be identified in a single external pathogen or in malfunctioning and once this single element is eliminated, fixed, or cured the whole body will restart its normal activity. This view is also reflected in the drug-development process, in which drugs are created for targeting a specific and single agent.

However, this way of thinking misses a point in acknowledging that a disease is not only made of a "specificity" identified in pathological changes, but it is also made of a "non-specificity" which takes into consideration the reactions occurring when the disease enters into contact with the environment.[163] This missing point seems not to be relevant when clear cause and pathology of a disease can be easily identified, but when these two cannot be identified because of the peculiarities of the disease, the ability to act on the "non-specificity" becomes crucial to provide an efficient treatment. It is in this situation that ST get involved; indeed, if many physicians are still reluctant to recognize the value and the effectiveness of TCM practices, they are more prone to consider ST as a valuable approach to solve a complex situation in which the traditional cause-effect framework is not working.

The greater consideration of physicians towards ST can be found in the computational side of ST; indeed, it should be considered that ST, differently from TCM, is equipped with an analytic and quantitative approach. While in TCM, the analysis of the whole is mainly based on natural, spiritual and philosophical principles, which lack of a substantive and concrete base, in ST, the analysis of the complex system is based on feedback networks which not only define the relationship existing between elements composing the system, but also can be transformed in a system of equations able to mathematically describe the dynamics of the system, thus providing a tangible framework of analysis.

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[162] Ai Ping LU, et al., "Theory of traditional Chinese medicine and therapeutic method of diseases", *World Journal of Gastroenteroly*, 10, 13, 2004, 1854-1856.
[163] George TSOKOS, Gerald NEPOM, "Gene therapy in the treatment of autoimmune diseases", *The Journal of clinical investigation*, 106, 2, 2000, 181-183.

All things considered, ST not only aims at creating a comprehensive system of thought which, in this case, encompasses Chinese and Western medicine taking the holistic view from TCM and the chemical and technological advancement from Western medicine, but it also provides quantitative and concrete foundations to an otherwise only abstract approach.

SECTION II

TERMINOGRAPHIC CARDS

REPERTOIRE I – Systems Thinking and related disciplines

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<Source>^Haraldsson 2004^:4
<Definition>Systems Thinking is a science that deals with the organization of logic and integration of disciplines for understanding patterns and relations of complex problems.
<Source>^Haraldsson 2004^:4
<Context>Systems Thinking is also known as principles of organization or theory of self-organization and the way of using it involves “systemic” or “holistic thinking”. It is a science based on understanding connections and relations between seemingly isolated things. All models, in the form of written text, conceptual or mathematical, have an inherent “Systems Thinking” structure built in them, since they are built according to certain thinking and logic. A model is successful when the thinking behind it is successfully transferred from the model builder to the observer. A model that lacks explanation of its principles is essentially useless.
<Source>^Haraldsson 2004^:4-5
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<Related words>^systems dynamics^
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<Related words>^system^
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<Source>^Haraldsson 2004^:4
<Variant of>systems thinking

<zh>系统思维
<Morphosyntax>noun group
<Source>^钟韵，彭华 2001^
<Definition>系统思维就是把认识对象作为系统，从系统和要素、要素和要素、系统和环境的相互联系、相互作用中综合地考察认识对象的一种思维方法。

<Source>^钟韵，彭华 2001^
<Context>系统思维以系统论为思维基本模式的思维形态，它不同于创造思维或形象思维等本能思维形态。系统思维能极大地简化人们对事物的认知，给我们带来整体观。
<Source>^钟韵，彭华 2001^
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<Definition>Mental modelling means to explicitly map the understanding of the problem and making it transparent and visible for others through Causal Loop Diagrams.
<Source>^Haraldsson 2004^:4
<Context>Finding simplicity in complexity is the driving force behind any scientific modelling process. Simplification is a process that is initiated by the desire to capture the essence of a complex problem. In modelling, it is important to distinguish between “good model” and “bad models”, and “good performance” and “bad performance. The definition of a “good model” is when everything inside it is visible, inspectable and testable. It can be communicated effortlessly to others. A “bad model” is a model that does not meet to these standards, where parts are hidden, undefined or concealed and cannot be inspected or tested.
<Source>^Haraldsson/Sverdrup 2004^:211-213
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<en>modelling
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<Source>^Haraldsson/Sverdrup 2004^:211

<zh>心智模式
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<Source>^孙天鹏，等 2020^:1794
<Definition>心智模式是一个系统的内部表征，或者说是一种映射，一种特殊的对外界事物的反应，人们通过它来认识世界，对事物进行预测，对事件进行归因以及做出解释。
<Source>^孙天鹏，等 2020^:1794
<Context>根据心智模式作用的个体数量可分为个体心智模式以及团体心智模式。每个人的心智模式都各不相同，在个体发展初期个体还无法认识到这个问题。随着个体发展，个体逐渐认识到个体之间知识结构与意志的差异。拥有不同心智模式的个体组成了团体，因此不同团体之间的心智模式也各不相同，团体共享的心智模式会影响团体认识、解释、处理与他人或其他团体的关系从而更加深远地影响其学习生活和发展。心智模式主要有描述、解释和预测三种功能。心智模式允许个体预见未来的事件，解释事件和现象的原因，并选择合适行动的过程。
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<Definition>Causal Loop diagrams (CLDs) are a relatively disciplined way of looking at a system, which places the existence and effects of feedbacks at its core.
<Source>^Barbrook-Johnson/Penn 2022^:48
<Context>CLDs represent a system in three basic elements: boxes, connections, and feedback loops. The boxes, or nodes, represent variables in the system; these can be anything as long it makes sense to think of them going up or down over some scale. The maps always show and focus on feedback loops, both in the construction of the map and in its visualisation. It is common to see both simple (per- haps five or ten nodes) and more complex CLDs.
<Source>^Barbrook-Johnson/Penn 2022^:47-48
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<Synonyms>The term “causal loop diagram” is often substituted by its initials “CLD”.

<en>CLD
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<Variant of>causal loop diagram

<zh>因果回路图
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<Source>^穆夕 2018^，https://www.jianshu.com/p/e01b2584d9a6
<Definition>因果回路图是以因果关系链路的形式来描述影响系统行为的结构，它是系统思考的基本工具。
<Source>^穆夕 2018^，https://www.jianshu.com/p/e01b2584d9a6
<Context>因果回路图由变量和连接两类要素组成，它们构成一系列闭合的回路，反映了影响系统行为的各种关键因素（变量）及其之间的相互关系。
<Source>^穆夕 2018^，https://www.jianshu.com/p/e01b2584d9a6
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<Related words>^系统动力学^
<Type of relation>super.
<Related words>^系统^
<Type of relation>super.
<Synonyms>“系统循环图”和“因果回路图”是近义词。

<zh>系统循环图
<Morphosyntax>noun group
<Usage label>common
<Source>^穆夕 2018^，https://www.jianshu.com/p/e01b2584d9a6
**
<Subject>计算机科学、信息和普通工程 /Computer science, information & general works (000)
<Subfield>系统 / Systems (003)
<en>systems analysis
<Morphosyntax>noun group
<Usage label>main term
<Source>^Barrier 2003^:345

<Definition>Systems analysis, more correctly referred to as information systems analysis, is the process by which an individual(s) studies a system such that an information system can be analysed, modelled, and a logical alternative (independent of technology) can be chosen.
<Source>^Barrier 2003^:345
<Context>The basic systems analysis project consists of two basic steps: (1) analysis (study of the system) and (2) modelling the system and choosing the logical alternative. Systems analysis describes a specific set of steps (methodology) for analysing, modelling, and choosing a logical alternative for an information system, which ultimately identifies the logical (human) requirements of an information system (software specifications, people's duties, logical procedures, data required, and information produced).
<Source>^Barrier 2003^:345
<Concept field>systems thinking
<Related words>^systems thinking^
<Type of relation>super.
<Related words>^mental modelling^
<Type of relation>coord.
<Related words>^causal loop diagram^
<Type of relation>sub.
<Related words>^systems dynamics^
<Type of relation>coord.
<Related words>^system^
<Type of relation>sub.
<Synonyms>The term "information systems analysis" is synonym to "systems analysis" and it is commonly used.

<en>information systems analysis
<Morphosyntax>noun group
<Usage label>common
<Source>^Barrier 2003^:345

<zh>系统分析
<Morphosyntax>noun group
<Source> 資 訊 管 理 與 決 策 科 學 院 ，
https://sfsu.chu.edu.tw/var/file/83/1083/img/698/482891144.pdf
<Definition>系统分析的目的是为了了解现有系统是如何进行，并可依照开发方法循序且逻辑化的建立，能够纪录系统的行成，开发过程若有错误或遗失，则可马上进行修改，以确保系统品质，并且制定解决方法。
<Source> 資 訊 管 理 與 決 策 科 學 院 ，
https://sfsu.chu.edu.tw/var/file/83/1083/img/698/482891144.pdf
<Context>开发系统的方法有很多种，有广受采用的传统结构化分析，一步步经过确认再执行的瀑布模式，不在乎是否有完整 规划的雏型模式，将处理工作和资料分开的物件导向分析，和以小组完成的联合应用系统开发及快速应用系统开发，依照产品的不同，将选用不同的模式。系统开发方法有下列几种.
<Source> 資 訊 管 理 與 決 策 科 學 院 ，
https://sfsu.chu.edu.tw/var/file/83/1083/img/698/482891144.pdf
<Concept field>系统思维
<Related words>^系统思维^
<Type of relation>super.
<Related words>^心智模式^
<Type of relation>coord.

<Related words>^因果回路图^
<Type of relation>sub.
<Related words>^系统动力学^
<Type of relation>coord.
<Related words>^系统^
<Type of relation>sub.
**
<Subject>计算机科学、信息和普通工程 /Computer science, information & general works (000)
<Subfield>系统 / Systems (003)
<en>systems dynamics
<Morphosyntax>noun group
<Usage label>main term
<Source>^University of Bergen 2023^, https://www.uib.no/en/rg/dynamics/39282/what-system-dynamics
<Definition>Systems Dynamics is a computer-based mathematical modelling approach for strategy development and better decision making in complex systems.
<Source>^University of Bergen 2023^, https://www.uib.no/en/rg/dynamics/39282/what-system-dynamics
<Context>The purpose of Systems Dynamics is to help people understand complex and dynamic systems and help them make better decisions. The field provides a philosophy and tools to model and analyse dynamic systems. Equally important, the field provides techniques and tools to investigate current decision making and to help decision makers learn. Like Systems Thinking, Systems Dynamics has also a holistic and causality driven approach to describe and understand the relations between components or variables within a system which influences it internally or externally. But unlike the Systems Thinking, Systems Dynamics quantifies relations between variables to develop a view of behaviour of the system over time through computer simulations.
<Source>^University of Bergen 2023^, https://www.uib.no/en/rg/dynamics/39282/what-system-dynamics
<Concept field>systems thinking
<Related words>^systems thinking^
<Type of relation>super.
<Related words>^mental modelling^
<Type of relation>coord.
<Related words>^causal loop diagram^
<Type of relation>sub.
<Related words>^systems analysis^
<Type of relation>coord.
<Related words>^system^
<Type of relation>sub.

<zh>系统动力学
<Morphosyntax>noun group
<Usage label>main term
<Source>^上海卡见信息技术有限公司 2008^，https://www.cabit.com.cn/help/read.asp?id=32
<Definition>系统动力学是研究分析有关复杂信息反馈系统动态趋势的学科，英文缩写SD。
<Source>^上海卡见信息技术有限公司 2008^，https://www.cabit.com.cn/help/read.asp?id=32

<Context>系统动力学以控制论、控制工程、系统工程、信息处理和计算机仿真技术为基础研究复杂系统随时间推移而产生的行为模式。系统动力学把系统的行为模式看成是由系统内部的信息反馈机制决定的。通过建立系统动力学模型，利用 DYNAMO 仿真语言在计算机上实现对真实系统的仿真，可以研究系统的结构、功能和行为之间的动态关系，以便寻求较优的系统结构和功能。
<Source>^ 上 海 卡 见 信 息 技 术 有 限 公 司 2008^ ，https://www.cabit.com.cn/help/read.asp?id=32
<Concept field>系统思维
<Related words>^系统思维^
<Type of relation>super.
<Related words>^心智模式^
<Type of relation>coord.
<Related words>^因果回路图^
<Type of relation>sub.
<Related words>^系统分析^
<Type of relation>coord.
<Related words>^系统^
<Type of relation>sub.
<Synonyms>“SD”和“系统动力学”是近义词。

<zh>SD
<Morphosyntax>noun
<Category>initials
<Usage label>common
<Source>^ 上 海 卡 见 信 息 技 术 有 限 公 司 2008^ ，https://www.cabit.com.cn/help/read.asp?id=32
<Variant of>系统动力学
**
<Subject>计算机科学、信息和普通工程 /Computer science, information & general works (000)
<Subfield>系统 / Systems (003)
<en>system
<Morphosyntax>noun
<Source>^Haraldsson 2004^:11
<Lexica>Found in ^Oxford Dictionary of English 2013^
<Definition>A system is a network of multiple variables that are connected to each other through causal relationship and expresses some sort of behaviour, which can only be characterized through observation as a whole.
<Source>^Haraldsson 2004^:11
<Context>The principal attribute of a system is that we can only understand its dynamic behaviour and interaction by viewing it as a whole.
<Source>^Haraldsson 2004^:11
<Concept field>systems thinking
<Related words>^systems thinking^
<Type of relation>super.
<Related words>^mental modelling^
<Type of relation>super.
<Related words>^causal loop diagram^
<Type of relation>super.
<Related words>^systems analysis^

<Type of relation>super.
<Related words>^systems dynamics^
<Type of relation>super.

<zh>系统
<Morphosyntax>noun
<Source>^漢典^，https://www.zdic.net/hans/%E7%B3%BB%E7%BB%9F
<Lexica>Found in ^现代汉语词典 2013^
<Definition>系统是运动着的若干部分，在相互联系、相互作用之中形成的具有某种确定功能的整体。
<Source>^漢典^，https://www.zdic.net/hans/%E7%B3%BB%E7%BB%9F
<Context>系统一词创成于英文 system 的音译，并对应其外文内涵加以丰富。系统是指将零散的东西进行有序的整理、编排形成的具有整体性的整体。
<Source>^漢典^，https://www.zdic.net/hans/%E7%B3%BB%E7%BB%9F
<Concept field>系统思维
<Related words>^系统思维^
<Type of relation>super.
<Related words>^心智模式^
<Type of relation>super.
<Related words>^因果回路图^
<Type of relation>super.
<Related words>^系统分析^
<Type of relation>super.
<Related words>^系统动力学^
<Type of relation>super.
**
<Subject>计算机科学、信息和普通工程 /Computer science, information & general works (000)
<Subfield>系统 / Systems (003)
<en>systemic structure
<Morphosyntax>noun group
<Source>^Monat/Gannon 2023^:2
<Definition>Systemic structures are the ways in which the parts of a system are organized. These structures actually generate the patterns and events we observe. Structures can be physical (such as the way a workspace is organized, or the way a machine is built) as well as intangible.
<Source>^Monat/Gannon 2023^:2
<Context>In Systems Thinking, the Iceberg Model posits that the systemic structure lies between underlying forces mental models) and patterns. The model argues that in huma-designed systems, structures form as a result of mental models and that patterns, in turn, form as a result of structures.
<Source>^Monat/Gannon 2023^:1-2
<Concept field>iceberg model
<Related words>^pattern^
<Type of relation>coord.
<Related words>^event^
<Type of relation>coord.

<zh>系统结构
<Morphosyntax>noun group

<Source>^ 百 科 知 識 ^, https://www.easyatm.com.tw/wiki/%E7%B3%BB%E7%B5%B1%E7%B5%90%E6%A7%8B
<Definition>系统结构是从系统目的出发按照一定规律组织起来的、相互关联的系统元素的集合。
<Source>^ 百 科 知 識 ^, https://www.easyatm.com.tw/wiki/%E7%B3%BB%E7%B5%B1%E7%B5%90%E6%A7%8B
<Context>系统结构也用来表述对计算机系统中各级机器间界面的划分和定义，以及对各级界面上、下的功能进行分配。各级都有自己的系统结构。系统结构可以用系统构造示意图表示。
<Source>^ 百 科 知 識 ^, https://www.easyatm.com.tw/wiki/%E7%B3%BB%E7%B5%B1%E7%B5%90%E6%A7%8B
<Concept field>冰山模型
<Related words>^规律^
<Type of relation>coord.
<Related words>^事件^
<Type of relation>coord.
**
<Subject>计算机科学、信息和普通工程 /Computer science, information & general works (000)
<Subfield>系统 / Systems (003)
<en>pattern
<Morphosyntax>noun
<Source>^Monat 2018^:2
<Lexica>Found in ^Oxford Dictionary of English 2013^
<Definition>A pattern is a consistent and recurring characteristic or trait that helps in the identification of a phenomenon or problem and serves as an indicator or model for predicting its future behaviour.
<Source>^Monat 2018^:2
<Context>Patterns may be physical, temporal, behavioural, psychological, or some combination. In systems, the presence of a pattern indicates that there are several factors acting in feedback loops. The patterns are often emergent, meaning that they cannot be predicted from knowledge of the system components; only when those components interact do the patterns emerge.
<Source>^Monat 2018^:1-2
<Concept field>iceberg model
<Related words>^systemic structure^
<Type of relation>coord.
<Related words>^event^
<Type of relation>coord.

<zh>规律
<Morphosyntax>noun
<Source>^漢典^， https://www.zdic.net/hans/%E8%A7%84%E5%BE%8B
<Lexica>Found in ^现代汉语词典 2013^
<Definition>规律是事物之间的内在的必然联系，决定着事物发展的必然趋向。 规律是客观的，不以人的意志为转移。
<Source>^漢典^， https://www.zdic.net/hans/%E8%A7%84%E5%BE%8B
<Context>规律决定自然界和社会诸现象之间必然、本质、稳定和反复出现的关系。
<Source>^漢典^， https://www.zdic.net/hans/%E8%A7%84%E5%BE%8B
<Concept field>冰山模型

<Related words>^系统结构^
<Type of relation>coord.
<Related words>^事件^
<Type of relation>coord.
**
<Subject>计算机科学、信息和普通工程 /Computer science, information & general works (000)
<Subfield>系统 / Systems (003)
<en>event
<Morphosyntax>noun
<Source>^Kim 1999^:4
<Lexica>Found in ^Oxford Dictionary of English 2013^
<Definition>Events are the occurrences we encounter on a day-to-day basis.
<Source>^Kim 1999^:4
<Context>The events are the results of deeper patterns and systemic structures.
<Source>^Kim 1999^:4
<Concept field>iceberg model
<Related words>^systemic structure^
<Type of relation>coord.
<Related words>^pattern^
<Type of relation>coord.

<zh>事件
<Morphosyntax>noun
<Source>^ 翁 炫 2019^ ，https://www.toutiao.com/article/6731695919596585486/?wid=1684509369279
<Lexica>Found in ^现代汉语词典 2013^
<Definition>事件是我们身边的各种事情，比如公司中某某离职了、某某公司上市了、某某球队获胜了。
<Source>^ 翁 炫 2019^ ，https://www.toutiao.com/article/6731695919596585486/?wid=1684509369279
<Context>事件源源不断地吸引着我们的注意力，有的事让我们惊喜、有的事件让我们意外。善于思考的人会收集不同时期的事件，分析这些事件的趋势，根据趋势来预测系统会行为。这就进入了系统行为层次的分析。该层次分析只能看到系统变化的趋势，还是弄不清系统变化的原因。
<Source>^ 翁 炫 2019^ ，https://www.toutiao.com/article/6731695919596585486/?wid=1684509369279
<Concept field>冰山模型
<Related words>^系统结构^
<Type of relation>coord.
<Related words>^规律^
<Type of relation>coord.
**
<Subject>计算机科学、信息和普通工程 /Computer science, information & general works (000)
<Subfield>系统 / Systems (003)
<en>system diagram
<Morphosyntax>noun group
<Usage label>main term
<Source>^Meadows 2009^:19

<Definition>System diagrams are simplified versions of the real world.
<Source>^Meadows 2009^:19
<Context>Each diagram distinguishes the stock, the flow that changes the stock, and the information link (shown as a thin, curved arrow) that directs the action. It emphasizes that action or change always proceeds through adjusting flows.
<Source>^Meadows 2009^:26
<Concept field>systems thinking diagram
<Related words>^stock-flow diagram^
<Type of relation>coord.
<Synonyms>The term “diagram” is synonym to “system diagram” and it is commonly used.

<en>diagram
<Morphosyntax>noun
<Usage label>common
<Source>^Meadows 2009^:26

<zh>系统图
<Morphosyntax>noun group
<Usage label>main term
<Source>^Edraw 亿图^，https://www.edrawsoft.cn/electrical/xitongtuzmha/
<Definition>系统图，又称树图，是将事物或现象分解成树枝状的一种图表，由方框和带箭头的线条组成。
<Source>^Edraw 亿图^，https://www.edrawsoft.cn/electrical/xitongtuzmha/
<Context>利用系统图可以问题问题的原因并且找到解决问题的办法，系统图被广泛的运用于质量管理当中，比如质量管理因果图、质量管理措施等。
<Source>^Edraw 亿图^，https://www.edrawsoft.cn/electrical/xitongtuzmha/
<Concept field>系统思维图
<Related words>^系统动力流图^
<Type of relation>coord.
<Synonyms>“树图”和“系统图”是近义词。

<zh>树图
<Morphosyntax>noun group
<Usage label>common
<Source>^Edraw 亿图^，https://www.edrawsoft.cn/electrical/xitongtuzmha/
**
<Subject>计算机科学、信息和普通工程 /Computer science, information & general works (000)
<Subfield>系统 / Systems (003)
<en>stock-flow diagram
<Morphosyntax>noun group
<Usage label>main term
<Source>^Transentis consulting^, https://www.transentis.com/page/stock-and-flow-diagrams
<Definition>Stock-flow diagram is a diagram that enables to create a business prototype of the system that will allow to explore its behaviour and to test the effect of changes to the system’s structure and the policies governing its behaviour.
<Source>^Transentis consulting^, https://www.transentis.com/page/stock-and-flow-diagrams
<Context>Stock-flow diagrams provide a richer visual language than causal loop diagrams, and they distinguish six main kinds of elements: stocks, flows, converters, connectors, sources and sinks.

<Source>^Transentis consulting^, https://www.transentis.com/page/stock-and-flow-diagrams
<Concept field>systems thinking diagram
<Related words>^system diagram^
<Type of relation>coord.

<zh>系统动力流图
<Morphosyntax>noun group
<Source>^蘇昀柏 2007^:1
<Definition>系统动力流图是一种系统图虽将变数间的传递关系表现出来，但未明显地将变 数间的逻辑关系与因果关系表示出来。
<Source>^蘇昀柏 2007^:1
<Context>故将系统动力流图中的存量与流量两种物件隐藏，并在变数与变数之间的连接线加上正向与负向的关系，产生因果回馈图，借以从复杂的动 态结构中整理出因果回馈网路及其对应之内生与外生变数。
<Source>^蘇昀柏 2007^:1
<Concept field>系统思维图
<Related words>^系统图^
<Type of relation>coord.
**
<Subject>计算机科学、信息和普通工程 /Computer science, information & general works (000)
<Subfield>系统 / Systems (003)
<en>leverage point
<Morphosyntax>noun group
<Source>^Abson, et al. 2017^:30
<Definition>A leverage point is a place in complex systems where a small shift may lead to fundamental changes in the system as a whole.
<Source>^Abson, et al. 2017^:30
<Context>Leverage points ranging from ‘shallow’—places where interventions are relatively easy to implement yet bring about little change to the overall functioning of the system—to ‘deep’ leverage points that might be more difficult to alter but potentially result in transformational change. In the context of studying deep leverage points (i.e. ‘where’ to intervene), it is necessary to consider the effectiveness of particular ‘levers’, that is, specific measures by which influence can be applied to a given leverage point. Different leverage points are not independent, and changes resulting from the application of a given lever may be complex and unexpected.
<Source>^Abson, et al. 2017^:31-36
<Concept field>systems thinking diagram
<Related words>^stock^
<Type of relation>coord.
<Related words>^flow^
<Type of relation>coord.
<Related words>^feedback loop^
<Type of relation>super.
<Related words>^reinforcing feedback^
<Type of relation>super.
<Related words>^balancing feedback^
<Type of relation>super.

<zh>杠杆点
<Morphosyntax>noun group

<Source>^搜狐 2019^， https://www.sohu.com/a/314295582_120070819
<Definition>杠杆点是在系统中某处施加一个很小的变化，就能导致系统行为发生显著的转变。
<Source>^搜狐 2019^， https://www.sohu.com/a/314295582_120070819
<Context>虽然身处系统之中的人们通常会凭直觉去判断到哪里寻找杠杆点，但多半是往错误的方向推动系统的变化，这是因为，复杂系统的特征之一就是“反直觉”，也就是，经常选错方向，而把事情变得更糟。任何一个动态变化的系统，其复杂程度都远超想象，通过观察和研究，系统论专家总结出了系统的 12 大杠杆点。
<Source>^搜狐 2019^， https://www.sohu.com/a/314295582_120070819
<Concept field>系统思维图
<Related words>^存量^
<Type of relation>coord.
<Related words>^流量^
<Type of relation>coord.
<Related words>^回馈循环^
<Type of relation>super.
<Related words>^正回馈^
<Type of relation>super.
<Related words>^负反馈循环^
<Type of relation>super.
**
<Subject>计算机科学、信息和普通工程 /Computer science, information & general works (000)
<Subfield>系统 / Systems (003)
<en>stock
<Morphosyntax>noun
<Source>^Meadows 2009^:17
<Lexica>Found in ^Oxford Dictionary of English 2013^
<Definition 1>Stocks are the elements of the system that you can see, feel, count, or measure at any given time.
<Definition 2>A stock is the memory of the history of changing flows within the system.
<Source>^Meadows 2009^:17
<Context>A system stock is just what it sounds like: a store, a quantity, an accumulation of material or information that has built up over time. A stock does not have to be physical. Stocks change over time through the actions of a flow. A stock, then, is the present memory of the history of changing flows within the system.
<Source>^Meadows 2009^:17-18
<Concept field>systems thinking diagram
<Related words>^leverage point^
<Type of relation>coord.
<Related words>^flow^
<Type of relation>coord.
<Related words>^feedback loop^
<Type of relation>super.
<Related words>^reinforcing feedback^
<Type of relation>super.
<Related words>^balancing feedback^
<Type of relation>super.

<zh>存量

<Morphosyntax>noun
<Source>^Sherwood 2014^:278
<Lexica>Found in ^现代汉语词典 2013^
<Definition>指在任何时刻都能观察、感知、计数和测量的系统要素。
<Source>^Sherwood 2014^:278
<Context>储蓄、图书馆的书、石油存储量、个人信用等都是存量。经济上，存量是某一时点结存的量，体现了某一时点上持有的经济价值或物量。
<Source>^Sherwood 2014^:278
<Concept field>系统思维图
<Related words>^杠杆点^
<Type of relation>coord.
<Related words>^流量^
<Type of relation>coord.
<Related words>^回馈循环^
<Type of relation>super.
<Related words>^正回馈^
<Type of relation>super.
<Related words>^负反馈循环^
<Type of relation>super.
**
<Subject>计算机科学、信息和普通工程 /Computer science, information & general works (000)
<Subfield>系统 / Systems (003)
<en>flow
<Morphosyntax>noun
<Usage label>main term
<Source>^Kim 1999^:19
<Lexica>Found in ^Oxford Dictionary of English 2013^
<Definition>The amount of change something undergoes during a particular length of time.
<Source>^Kim 1999^:19
<Context>Flows go up and down, on and off, in all sorts of combi- nations, in response to stocks, not to other flows.
<Source>^Meadows 2009^:90
<Concept field>systems thinking diagram
<Related words>^leverage point^
<Type of relation>coord.
<Related words>^stock^
<Type of relation>coord.
<Related words>^feedback loop^
<Type of relation>super.
<Related words>^reinforcing feedback^
<Type of relation>super.
<Related words>^balancing feedback^
<Type of relation>super.
<Synonyms>The term “rate” is synonym to “stock” and it is commonly used.

<en>rate
<Morphosyntax>noun
<Usage label>commom
<Source>^Kim 1999^:19

<zh>流量
<Morphosyntax>noun
<Source>^Sherwood 2014^:278
<Lexica>Found in ^现代汉语词典 2013^
<Definition>流量指出任何增加或减少股票的变量。
<Source>^Sherwood 2014^:278
<Context>流量会使存量随着时间的变化而不断改变。经济上，流量是一段时期内累计发生的量，反映了一段时期内经济价值或物量的产生、转换、交换、转移和消失，体现一个时期内经济价值或物量的变化
<Source>^Sherwood 2014^:278
<Concept field>系统思维图
<Related words>^杠杆点^
<Type of relation>coord.
<Related words>^存量^
<Type of relation>coord.
<Related words>^回馈循环^
<Type of relation>super.
<Related words>^正回馈^
<Type of relation>super.
<Related words>^负反馈循环^
<Type of relation>super.
**
<Subject>计算机科学、信息和普通工程 /Computer science, information & general works (000)
<Subfield>系统 / Systems (003)
<en>feedback loop
<Morphosyntax>noun group
<Usage label>main term
<Source>^Meadows 2009^:27
<Definition>A feedback loop is a closed chain of causal connections from a stock, through a set of decisions or rules or physical laws or actions that are dependent on the level of the stock, and back again through a flow to change the stock.
<Source>^Meadows 2009^:27
<Context>A feedback loop is the consistent behaviour pattern over a long period of time that is the first hint of the existence of a feedback loop. A feedback loop is formed when changes in a stock affect the flows into or out of that same stock. A feedback loop can be quite simple and direct. Feedback loops can cause stocks to maintain their level within a range or grow or decline. Not all systems have feedback loops. Some systems are relatively simple open-ended chains of stocks and flows.
<Source>^Meadows 2009^:25-26-27
<Concept field>systems thinking diagram
<Related words>^leverage point^
<Type of relation>sub.
<Related words>^stock^
<Type of relation>sub.
<Related words>^flow^
<Type of relation>sub.
<Related words>^reinforcing feedback^
<Type of relation>coord.
<Related words>^balancing feedback^
<Type of relation>coord.

<zh>回馈循环
<Morphosyntax>noun group
<Source>^ 農 業 科 技 決 策 資 訊 平 台 2023^ ， https://agritech-foresight.atri.org.tw/article/contents/4197
<Definition>回馈循环系指一个系统中变数的变化与其他变数的相互作用结果会造成初始状态的增强(正回馈)或抑制(负回馈)，即使最初的变化相当微小，透过回馈循环的作用，也可能对整个系统产生巨大的影响。
<Source>^ 農 業 科 技 決 策 資 訊 平 台 2023^ ， https://agritech-foresight.atri.org.tw/article/contents/4197
<Concept field>系统思维图
<Related words>^杠杆点^
<Type of relation>sub.
<Related words>^存量^
<Type of relation>sub.
<Related words>^流量^
<Type of relation>sub.
<Related words>^正回馈^
<Type of relation>coord.
<Related words>^负反馈循环^
<Type of relation>coord.
**
<Subject>计算机科学、信息和普通工程 /Computer science, information & general works (000)
<Subfield>系统 / Systems (003)
<en>reinforcing feedback
<Morphosyntax>noun group
<Usage label>main term
<Source>^Anderson/Jonhson 1997^:129
<Definition>A reinforcing loop in a causal loop diagram depicts a reinforcing process.
<Source>^Anderson/Jonhson 1997^:129
<Context>Along with balancing loops, reinforcing loops form the building blocks of dynamic systems. Reinforcing processes compound change in one direction with even more change in that same direction. As such, they generate both growth and collapse. Also known as vicious cycles or virtuous cycles.
<Source>^Anderson/Jonhson 1997^:129
<Concept field>systems thinking diagram
<Related words>^leverage point^
<Type of relation>sub.
<Related words>^stock^
<Type of relation>sub.
<Related words>^flow^
<Type of relation>sub.
<Related words>^feedback loop^
<Type of relation>coord.
<Related words>^balancing feedback^
<Type of relation>coord.
<Synonyms>The term “positive feedback” is synonym to “reinforcing feedback” and it is commonly used.

<en>positive feedback

<Morphosyntax>noun group
<Usage label>common
<Source>^Anderson/Jonhson 1997^:129

<zh>正回馈
<Morphosyntax>noun group
<Source>^Wordwow^, http://zh.wordow.com/english/dictionary/positive%20feedback
<Definition>正回馈是反馈的一种，是指一系统的输出影响到输入，使得输出变动后会影响到输入，造成输出变动持续加大的情形；同理，如果输出变动持续减少，就称为负回馈。
<Source>^Wordwow^, http://zh.wordow.com/english/dictionary/positive%20feedback
<Context>当 A 产生了更多的 B，B 会回过来产生更多的 A，这个过程就称为正回馈。在机械、电机、电子、化学、经济或是其他系统都会有类似的情形。
<Source>^Wordwow^, http://zh.wordow.com/english/dictionary/positive%20feedback
<Concept field>系统思维图
<Related words>^杠杆点^
<Type of relation>sub.
<Related words>^存量^
<Type of relation>sub.
<Related words>^流量^
<Type of relation>sub.
<Related words>^回馈循环^
<Type of relation>coord.
<Related words>^负反馈循环^
<Type of relation>coord.
**
<Subject>计算机科学、信息和普通工程 /Computer science, information & general works (000)
<Subfield>系统 / Systems (003)
<en>balancing feedback
<Morphosyntax>noun group
<Usage label>main term
<Source>^Anderson/Jonhson 1997^:127
<Definition>A balancing loop in a causal loop diagram depicts a balancing process.
<Source>^Anderson/Jonhson 1997^:127
<Context>Combined with reinforcing loops, balancing processes form the building blocks of dynamic systems. Balancing processes seek equilibrium: They try to bring things to a desired state and keep them there. They also limit and constrain change generated by reinforcing processes.
<Source>^Anderson/Jonhson 1997^:127
<Concept field>systems thinking diagram
<Related words>^leverage point^
<Type of relation>sub.
<Related words>^stock^
<Type of relation>sub.
<Related words>^flow^
<Type of relation>sub.
<Related words>^feedback loop^
<Type of relation>coord.
<Related words>^reinforcing feedback^
<Type of relation>coord.

<Synonyms>The term “negative feedback” is synonym to “balancing feedback” and it is commonly used.

<en>balancing feedback
<Morphosyntax>noun group
<Usage label>common
<Source>^Anderson/Jonhson 1997^:127

<zh>负反馈循环
<Morphosyntax>noun group
<Usage label>main term
<Source>^ 香 港 經 濟 日 報 HKET 2018^ ，https://service.hket.com/knowledge/2179932/%E4%BD%95%E8%AC%82%E8%B2%A0%E5%8F%8D%E9%A5%8B%E5%BE%AA%E7%92%B0%EF%BC%9F
<Definition>负反馈循环（Negative Feedback Loop）是指一个机制的平衡值被外来的变动影响时，机制会释放某些制衡力量，令本来受影响的地方受到抵制，造成跟原来变动的趋势呈相反的变化，回到原来的平衡值，抵销所造成的影响。
<Source>^ 香 港 經 濟 日 報 HKET 2018^ ，https://service.hket.com/knowledge/2179932/%E4%BD%95%E8%AC%82%E8%B2%A0%E5%8F%8D%E9%A5%8B%E5%BE%AA%E7%92%B0%EF%BC%9F
<Context>负反馈循环能有效地抵抗该变化的行为，用以纠正偏离目标值的差异，控制系统保持稳定的状态。
<Source>^ 香 港 經 濟 日 報 HKET 2018^ ，https://service.hket.com/knowledge/2179932/%E4%BD%95%E8%AC%82%E8%B2%A0%E5%8F%8D%E9%A5%8B%E5%BE%AA%E7%92%B0%EF%BC%9F
<Concept field>系统思维图
<Related words>^杠杆点^
<Type of relation>sub.
<Related words>^存量^
<Type of relation>sub.
<Related words>^流量^
<Type of relation>sub.
<Related words>^回馈循环^
<Type of relation>coord.
<Related words>^正回馈^
<Type of relation>coord.
<Synonyms>“negative feedback loop”和“负反馈循环”是近义词。

<zh>negative feedback loop
<Morphosyntax>noun group
<Category>translation
<Usage label>common
<Source>^ 香 港 經 濟 日 報 HKET 2018^ ，https://service.hket.com/knowledge/2179932/%E4%BD%95%E8%AC%82%E8%B2%A0%E5%8F%8D%E9%A5%8B%E5%BE%AA%E7%92%B0%EF%BC%9F
<Variant of>负反馈循环
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>人身健康及安全 / Personal health & safety (613)
<en>biological network

<Morphosyntax>noun group
<Source>^Lee/Loscalzo 2019^:1311
<Definition>A biological network consists of multiple nodes that represent distinct individual biological entities, such as genes, proteins, or metabolites.
<Source>^Lee/Loscalzo 2019^:1311
<Context>Relationships among nodes are depicted by connecting lines and denoted edges, which may represent a wide variety of molecular interactions, such as gene regulation, physical protein-protein interaction, or substrate metabolism. Most established networks represent static relationships among biological entities (eg, topological relationships). There is, however, increasing interest in creating dynamic biological network models that capture nonstatic network properties, such as flux analyses. Biological systems are best understood as a collection of multiple dynamic and static networks whose interactions determine the outcomes of biological (and pathobiological) processes.
<Source>^Lee/Loscalzo 2019^:1311-1312
<Concept field>network medicine
<Related words>^network medicine^
<Type of relation>general
<Related words>^node^
<Type of relation>sub.
<Related words>^module^
<Type of relation>sub.
<Related words>^hub^
<Type of relation>sub.

<zh>生物网络
<Morphosyntax>noun group
<Source>^李梢，等 2019^:856
<Definition>生物网络是构成复杂生物系统的基础，反映人体内部基因和基因产物等各种生物分子的相互关系、生物分子与疾病和药物等不同层次的关系，生物网络已被广泛用于生物医学大数据的分析。
<Source>^李梢，等 2019^:856
<Context>生物网络是利用信息科学理解人体复杂系统运行规律，实现中西医药与信息科学交叉创新的一个重要突破点。而复杂生物网络研究的一个根本问题便是对于生物要素之间各种复杂“关系”的理解，包括“关系”的实体化、数学化。
<Source>^李梢，等 2019^:857
<Concept field>网络医学
<Related words>^网络医学^
<Type of relation>general
<Related words>^节点^
<Type of relation>sub.
<Related words>^模块^
<Type of relation>sub.
<Related words>^枢纽^
<Type of relation>sub.
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>人身健康及安全 / Personal health & safety (613)
<en>network medicine
<Morphosyntax>noun group
<Usage label>main term

<Source>^Farina^, https://web.uniroma1.it/stitch/node/5613
<Definition>Network medicine is the study of cellular, disease, and social networks which aims to quantify the complex interlinked factors contributing to individual diseases.
<Source>^Farina^, https://web.uniroma1.it/stitch/node/5613
<Context>Network medicine is new field which combine principles and approaches from systems biology and network science in trying to understand the causes of human diseases and find and develop new treatments. It represents the marriage of network science and systems biology applied to human biology and human disease. It reflects the fact that human phenotypes and patho-phenotypes are driven by complex interactions among a variety of molecular mediators. The basic hypothesis of network medicine is: Diseases arise as a consequence of one or more biological networks in the relevant organ (or organs) that have become disease-perturbed through genetic and/or environmental changes.
<Source>^Farina^, https://web.uniroma1.it/stitch/node/5613
<Concept field>network medicine
<Related words>^biological network^
<Type of relation>general
<Related words>^node^
<Type of relation>sub.
<Related words>^module^
<Type of relation>sub.
<Related words>^hub^
<Type of relation>sub.

<zh>网络医学
<Morphosyntax>noun group
<Usage label>main term
<Source>^Silverman, et al. 2020^:1
<Definition>网络医学是应用网络科学方法来研究疾病的发病机理。
<Source>^Silverman, et al. 2020^:1
<Context>Network Medicine 使用计算生物学工具将这些集成方法应用于 Omics 大数据（包括遗传学，表观遗传学，转录组学，代谢组学和蛋白质组学），因此具有改善复杂疾病的诊断，预后和治疗的潜力。已经报道了分子网络分析在肺动脉高压，冠心病，糖尿病，慢性肺病和药物开发中的成功应用。网络医学中的重要知识缺口包括分子相互作用组的不完整，在遗传关联区域内鉴定关键基因的挑战以及对人类疾病的有限应用。
<Source>^Silverman, et al. 2020^:1
<Concept field>网络医学
<Related words>^生物网络^
<Type of relation>general
<Related words>^节点^
<Type of relation>sub.
<Related words>^模块^
<Type of relation>sub.
<Related words>^枢纽^
<Type of relation>sub.
<Synonyms>“network medicine”和“网络医学”是近义词。

<zh>network medicine
<Morphosyntax>noun group
<Category>translation
<Usage label>common
<Source>^Silverman, et al. 2020^:1

<Variant of>网络医学
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>人身健康及安全 / Personal health & safety (613)
<en>node
<Morphosyntax>noun
<Usage label>main term
<Source>^Barabasi, et al. 2011^:57
<Lexica>Found in ^Oxford Dictionary of English 2013^
<Definition>A node is a system component that, by interacting with other components, forms a network. In biological networks, nodes can denote proteins, genes, metabolites, RNA molecules or even diseases and phenotypes.
<Source>^Barabasi, et al. 2011^:57
<Context>In a random network, most nodes have approximately the same number of links, and highly connected nodes (hubs) are rare. Nodes with a high betweenness centrality (a measure of the number of shortest paths that go through each node) are often called bottlenecks. In networks with directed edges, such as regulatory networks, bottlenecks tend to correlate with essentiality. Perturbing the state of a given node can affect the activity of most nodes in their vicinity as well as of the behaviour of the network itself.
<Source>^Barabasi, et al. 2011^:58
<Concept field>network medicine
<Related words>^biological network^
<Type of relation>super
<Related words>^network medicine^
<Type of relation>super.
<Related words>^module^
<Type of relation>coord.
<Related words>^hub^
<Type of relation>coord.
<Synonyms>The term “vertex” is synonym to “node” but it is not commonly used.

<en>vertex
<Morphosyntax>noun
<Usage label>uncommon
<Source>^Barabasi, et al. 2011^:57

<zh>节点
<Morphosyntax>noun
<Source>^黄柯鑫 2022^, https://zhuanlan.zhihu.com/p/542313632
<Definition>节点表示网络拓扑中，线相交或分支的点。
<Source>^黄柯鑫 2022^, https://zhuanlan.zhihu.com/p/542313632
<Context>节点分为物理的节点，即真实的、或者逻辑的，即虚拟的两种。网络拓扑，指构成网络的节点间特定的排列方式。
<Source>^黄柯鑫 2022^, https://zhuanlan.zhihu.com/p/542313632
<Concept field>网络医学
<Related words>^生物网络^
<Type of relation>super.
<Related words>^网络医学^
<Type of relation>super.
<Related words>^模块^
<Type of relation>coord.

<Related words>^枢纽^
<Type of relation>coord.
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>人身健康及安全 / Personal health & safety (613)
<en>module
<Morphosyntax>noun
<Usage label>main term
<Source>^Barabasi, et al. 2011^:59
<Lexica>Found in ^Oxford Dictionary of English 2013^
<Definition>A module is a dense subgraph on the network that often represents a set of nodes that have a joint role. In biology, a module could correspond to a group of molecules that interact with each other to achieve some common function.
<Source>^Barabasi, et al. 2011^:59
<Context>Most networks show a high degree of clustering, implying the existence of topological modules that represent highly interlinked local regions in the network. Although the identification of such modules can be computationally challenging, a wide array of network-clustering tools have emerged over the past few years.
<Source>^Barabasi, et al. 2011^:58
<Concept field>network medicine
<Related words>^biological network^
<Type of relation>super
<Related words>^network medicine^
<Type of relation>super.
<Related words>^node^
<Type of relation>coord.
<Related words>^hub^
<Type of relation>coord.
<Synonyms>The term “community” is synonym to “module”, but it is not commonly used.

<en>community
<Morphosyntax>noun
<Usage label>uncommon
<Source>^Barabasi, et al. 2011^:59

<zh>模块
<Morphosyntax>noun
<Usage label>proposal
<Source>^Burgio 2023^
<Lexica>Found in ^现代汉语词典 2013^
<Definition>模块是网络上的一个密集子图，通常代表一组具有联合作用的节点。
<Source>^Burgio 2023^
<Context>在生物学中，一个模块可以对应于一组分子，它们相互作用以实现一些共同的功能。
<Source>^Burgio 2023^
<Concept field>网络医学
<Related words>^生物网络^
<Type of relation>super.
<Related words>^网络医学^
<Type of relation>super.
<Related words>^节点^

<Type of relation>coord.
<Related words>^枢纽^
<Type of relation>coord.
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>人身健康及安全 / Personal health & safety (613)
<en>hub
<Morphosyntax>noun
<Source>^Barabasi, et al. 2011^:57
<Lexica>Found in ^Oxford Dictionary of English 2013^
<Definition>A hub is a highly connected node.
<Source>^Barabasi, et al. 2011^:57
<Context>Evidence from model organisms indicates that hub proteins tend to be encoded by essential genes, and that genes encoding hubs are older and evolve more slowly than genes encoding non-hub proteins. The deletion of genes encoding hubs also leads to a larger number of phenotypic outcomes than for other genes. This assumption has led to the hypothesis that, in humans, hubs should typically be associated with disease genes.
<Source>^Barabasi, et al. 2011^:57-58
<Related words>^biological network^
<Type of relation>super
<Related words>^network medicine^
<Type of relation>super.
<Related words>^node^
<Type of relation>coord.
<Related words>^module^
<Type of relation>coord.

<zh>枢纽
<Morphosyntax>noun
<Usage label>main term
<Source>^黄柯鑫 2022^, https://zhuanlan.zhihu.com/p/542313632
<Lexica>Found in ^现代汉语词典 2013^
<Definition>枢纽是有大量链接的节点。
<Source>^黄柯鑫 2022^, https://zhuanlan.zhihu.com/p/542313632
<Context>非必需疾病基因倾向于避开 hub 并集中在网络的外围。必需的基因往往与 hub 相关联。Goh et al. 研究表明与疾病无关的必需基因表现出与 hub 相关联的强烈趋势，并在多个组织中表达——也就是说，它们往往位于相互作用组的功能中心。然而，非必需疾病基因通常没有大量节点，它们往往是组织特异性的，并且位于相互作用组的功能外围。这个定律给研究网络医学的研究者一个更好的概念关于疾病是如何在网络中分布的，也解释了为什么目前疾病靶标通常不会导致大规模的副作用，因为它们坐落于网络的周边而且不会有很多链接节点。
<Source>^黄柯鑫 2022^, https://zhuanlan.zhihu.com/p/542313632
<Concept field>网络医学
<Related words>^生物网络^
<Type of relation>super.
<Related words>^网络医学^
<Type of relation>super.
<Related words>^节点^
<Type of relation>coord.
<Related words>^模块^

<Type of relation>coord.
<Synonyms>“Hub”和“枢纽”是近义词。

<zh>hub
<Morphosyntax>noun
<Category>translation
<Usage label>common
<Source>^黄柯鑫 2022^, https://zhuanlan.zhihu.com/p/542313632
<Variant of>枢纽
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>人身健康及安全 / Personal health & safety (613)
<en>topological module
<Morphosyntax>noun group
<Source>^Barabasi, et al. 2011^:58
<Definition>A ‘topological module’ represents a locally dense neighbourhood in a network, such that nodes have a higher tendency to link to nodes within the same local neighbourhood than to nodes outside it.
<Source>^Barabasi, et al. 2011^:58
<Context>Topological modules represent a pure network property, and a set of methods assumes that all cellular components that belong to the same topological module have a high likelihood of being involved in the same disease.
<Source>^Barabasi, et al. 2011^:59
<Concept field>network medicine
<Related words>^functional module^
<Type of relation>coord.
<Related words>^disease module^
<Type of relation>coord.
<Related words>^diseasome^
<Type of relation>general

<zh>拓扑模块
<Morphosyntax>noun group
<Usage label>proposal
<Source>^Burgio 2023^
<Definition>拓扑模块是网络中的一个局部密集邻域，即节点与同一局部邻域内的节点的链接趋势高于与该邻域外的节点的链接。
<Source>^Burgio 2023^
<Concept field>网络医学
<Related words>^功能模块^
<Type of relation>coord.
<Related words>^疾病模块^
<Type of relation>coord.
<Related words>^病情组^
<Type of relation>general
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>人身健康及安全 / Personal health & safety (613)
<en>functional module
<Morphosyntax>noun group
<Source>^Barabasi, et al. 2011^:58

<Definition>A ‘functional module’ represents the aggregation of nodes of similar or related function in the same network neighbourhood, where function captures the role of a gene in defining detectable phenotypes.
<Source>^Barabasi, et al. 2011^:58
<Context>A functional module requires to define some nodal characteristics and relies on the hypothesis that nodes that are involved in closely related cellular functions tend to interact with each other and are therefore located in the same network neighbourhood. Disease pairs that are associated with mutations that affect the same functional domain of a protein show higher comorbidity than do disease pairs with mutations that occur in different functional domains.
<Source>^Barabasi, et al. 2011^:61
<Concept field>network medicine
<Related words>^topological module^
<Type of relation>coord.
<Related words>^disease module^
<Type of relation>coord.
<Related words>^diseasome^
<Type of relation>general

<zh>功能模块
<Morphosyntax>noun group
<Usage label>proposal
<Source>^Burgio 2023^
<Definition>功能模块是指在同一网络邻域中具有类似或相关功能的节点的集合，其中功能捕捉到基因在定义可检测表型方面的作用。
<Source>^Burgio 2023^
<Concept field>网络医学
<Related words>^拓扑模块^
<Type of relation>coord.
<Related words>^疾病模块^
<Type of relation>coord.
<Related words>^病情组^
<Type of relation>general
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>人身健康及安全 / Personal health & safety (613)
<en>disease module
<Morphosyntax>noun group
<Source>^Lee/Loscalzo 2019^:1313
<Definition>A disease network module is defined as a subgroup of interactive nodes whose altered states (eg, gene deletions, mutations, copy number variations, or differential expressions) are associated with specific disease phenotypes.
<Source>^Lee/Loscalzo 2019^:1313
<Context>Disease modules can be constructed by mapping a set of genes or gene products (proteins) that are altered (mutated) or differentially expressed in individuals with specific disease phenotypes into an established human interactome. The disease module hypothesis posits that genes and gene products associated with a given disease are more likely to interact and segregate with one another in a local subnetwork than be distributed randomly throughout the human interactome.
<Source>^Lee/Loscalzo 2019^:1313
<Concept field>network medicine
<Related words>^topological module^

<Type of relation>coord.
<Related words>^functional module^
<Type of relation>coord.
<Related words>^diseasome^
<Type of relation>general

<zh>疾病模块
<Morphosyntax>noun group
<Usage label>proposal
<Source>^Burgio 2023^
<Definition>疾病模块是一个交互式节点的子组，其改变的状态（如基因缺失、突变、拷贝数变异或差异表达）与特定的疾病表型相关。
<Source>^Burgio 2023^
<Concept field>网络医学
<Related words>^拓扑模块^
<Type of relation>coord.
<Related words>^功能模块^
<Type of relation>coord.
<Related words>^病情组^
<Type of relation>general
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>人身健康及安全 / Personal health & safety (613)
<en>diseasome
<Morphosyntax>noun
<Source>^Barabasi, et al. 2011^:60
<Definition>A diseasome represents disease maps whose nodes are diseases and whose links represent various molecular relationships between the disease-associated cellular components.
<Source>^Barabasi, et al. 2011^:60
<Context>The comorbidity of conditions that are culled from the diseasome offers insights that may yield new approaches to disease prevention, diagnosis and treatment. Diseasome-based approaches could also aid drug discovery, in particular when it comes to the use of approved drugs to treat molecularly linked diseases.
<Source>^Barabasi, et al. 2011^:60
<Concept field>network medicine
<Related words>^topological module^
<Type of relation>general
<Related words>^functional module^
<Type of relation>general
<Related words>^disease module^
<Type of relation>general

<zh>病情组
<Morphosyntax>noun group
<Usage label>proposal
<Source>^Burgio 2023^
<Definition>病情组是一个疾病地图，其节点是疾病，其链接代表疾病相关的细胞成分之间的各种分子关系。
<Source>^Burgio 2023^
<Concept field>网络医学
<Related words>^拓扑模块^

<Type of relation>general
<Related words>^功能模块^
<Type of relation>general
<Related words>^疾病模块^
<Type of relation>general
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>药理学和治疗学 / Pharmacology & therapeutics (615)
<en>systems pharmacology
<Morphosyntax>noun group
<Usage label>main term
<Source>^van der Graaf^, https://www.universiteitleiden.nl/en/science/drug-research/systems-pharmacology/systems-pharmacology
<Definition>Systems Pharmacology is the quantitative analysis of the dynamic interactions between drugs and a biological system to understand the behaviour of the system as a whole, as opposed to the behaviour of its individual constituents; thus, it has become the interface between pharmacometrics and systems biology.
<Source>^van der Graaf^, https://www.universiteitleiden.nl/en/science/drug-research/systems-pharmacology/systems-pharmacology
<Context>Systems Pharmacology applies the concepts of Systems Engineering, Systems Biology, and pharmacokinetics-pharmacodynamics (PKPD) to the study of complex biological systems through iteration between computational and mathematical modelling and experimentation.
<Source>^van der Graaf^, https://www.universiteitleiden.nl/en/science/drug-research/systems-pharmacology/systems-pharmacology
<Concept field>pharmacology
<Related words>^network medicine^
<Type of relation>coord.
<Related words>^systems biology^
<Type of relation>coord.
<Related words>^P4 medicine^
<Type of relation>coord.

<zh>系统药理学
<Morphosyntax>noun group
<Source>^张文娟，王永华 2015^:280
<Definition>系统药理学是从系统水平研究药物与机体相互作用及其规律和作用机制的一门新兴学科。
<Source>^张文娟，王永华 2015^:280
<Context>即从分子、网络、细胞，到组织、器官等不同水平上研究药物治疗疾病时引起机体功能变化机制，建立药物对于机体的作用从微观(分子、生化网络水平)到宏观（组织、器官、整体水平）的各个水平间相互关联的学问。系统药理学应用理论计算结合实验的方法和技术发现药物小分子，确认新的药物靶标、预测药物不良反应、研究疾病发病和治疗机制，从而为精确调控细胞内复杂网络，改变疾病病理生理学，提高药物疗效和降低不良反应提供新的策略和工具。
<Source>^张文娟，王永华 2015^:280
<Concept field>药理学
<Related words>^网络医学^
<Type of relation>coord.
<Related words>^系统生物学^

<Type of relation>coord.
<Related words>^P4 医学^
<Type of relation>coord.
**
<Subject>生命科学;生物学 / Life sciences; biology (570)
<Subfield>生理学和相关学科 / Physiology and related subjects (571)
<en>systems biology
<Morphosyntax>noun group
<Usage label>main term
<Source>^Bielekova, et al. 2014^:1
<Definition>Systems biology is a compendium of scientific methods complementary to the use of pre-clinical experimental models, since pre-clinical models invariably represent simplified versions of the actual disease process.
<Source>^Bielekova, et al. 2014^:1
<Context>The goal of systems biology is to re-integrate putatively critical elements extracted from multi-modality datasets in order to understand how interactions among multiple components form functional networks at the organism/patient-level, and how dysfunction of these networks underlies a particular disease. Implementation of systems biology principles to interventional clinical trials represents a unique opportunity to gain predictive understanding of complex diseases in comparatively small cohorts of patients.
<Source>^Bielekova, et al. 2014^:1
<Concept field>biology
<Related words>^polygenic disease^
<Type of relation>general
<Related words>^network medicine^
<Type of relation>coord.
<Related words>^systems pharmacology^
<Type of relation>coord.
<Related words>^P4 medicine^
<Type of relation>coord.

<zh>系统生物学
<Morphosyntax>noun group
<Source>^孙之荣，吴雪兵 2006^:56
<Definition>系统生物学指在基因组、转录组、蛋白质组和代谢组等复杂性的全局分析的基础上，建立生物系统的模型，从中归纳假设，并利用这些假设对生物系统进行反复的、整合性的干扰响应研究。
<Source>^孙之荣，吴雪兵 2006^:56
<Context>作为生物学的一个新领域，系统生物学的兴起及发展为研究生命活动提供了一个全新的思路和方法,它将各种组学的方法综合起来，通过高通量的实验手段，从转录组、蛋白质组、代谢组等方面多层次、全方位地对生物体内的生命活动进行检测，同时利用生物信息学的方法和手段对相关的数据进行分析及整合，并在此基础上，对相关的生命活动进行模拟，以期系统地研究和阐明生命活动的规律。
<Source>^石铁流，李亦学 2005^:282
<Concept field>生物学
<Related words>^多基因疾病^
<Type of relation>general
<Related words>^网络医学^
<Type of relation>coord.
<Related words>^系统药理学^

<Type of relation>coord.
<Related words>^P4 医学^
<Type of relation>coord.
**
<Subject>生命科学;生物学 / Life sciences; biology (570)
<Subfield>生理学和相关学科 / Physiology and related subjects (571)
<en>polygenic disease
<Morphosyntax>noun group
<Source>^Lvovs, et al. 2012^:59
<Definition>Polygenic diseases are diseases are caused by the joint contribution of a number of independently acting or interacting polymorphic genes; the individual contribution of each gene may be small or even unnoticeable.
<Source>^Lvovs, et al. 2012^:59
<Context>The individual contribution of each gene to the development of a polygenic disease can be small or modest. the carriage of certain allelic combinations of genes can also determine the emergence of clinically heterogeneous forms of diseases and the therapeutic efficacy of certain pharmaceutical agents. In humans, polygenic disorders occur much more frequently than monogenic ones; they have a great social and economic impact.
<Source>^Lvovs, et al. 2012^:59
<Concept field>disease
<Related words>^systems biology^
<Type of relation>general

<zh>多基因疾病
<Morphosyntax>noun group
<Source>^ 中共中国科学院泸区委员会 2008^, http://www.shb.cas.cn/kjjz2016/200812/t20081203_1784735.html
<Definition>多基因遗传病是遗传信息通过两对以上致病基因的累积效应所致的遗传病，其遗传效应受环境因素的影响。
<Source>^ 中共中国科学院泸区委员会 2008^, http://www.shb.cas.cn/kjjz2016/200812/t20081203_1784735.html
<Context>与单基因遗传病相比，多基因遗传病不是只由遗传因素决定，而是遗传因素与环境因素共同起作用。在多基因遗传病中，遗传因素所起的作用大小叫遗传度，用百分数表示。如精神分裂症是多基因遗传病，其遗传度为 80%，也就是说精神分裂症发病因素中，遗传起了很大作用，而环境所起的作用则相对较小。
<Source>^ 中共中国科学院泸区委员会 2008^, http://www.shb.cas.cn/kjjz2016/200812/t20081203_1784735.html
<Concept field>疾病
<Related words>^系统生物学^
<Type of relation>general
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>疾病的发病率和预防/ Incidence and prevention of disease (614)
<en>P4 medicine
<Morphosyntax>noun group
<Usage label>main term
<Source>^Fiala, et al. 2019^:109
<Definition>P4 medicine is the clinical manifestation of systems biology and stands for predictive, preventative, personalized, and participatory medicine.
<Source>^Fiala, et al. 2019^:109

<Context>P4 medicine arises from the confluence of a systems approach to medicine and from the digitalization of medicine that creates the large data sets necessary to deal with the complexities of disease. We predict that systems approaches will empower the transition from conventional reactive medical practice to a more proactive P4 medicine focused on wellness, and will reverse the escalating costs of drug development and will have enormous social and economic benefits.
<Source>^Hood, et al. 2012^:992
<Concept field>disease prevention
<Related words>^network medicine^
<Type of relation>coord.
<Related words>^system pharmacology^
<Type of relation>coord.
<Related words>^system biology^
<Type of relation>coord.
<Related words>^genome^
<Type of relation>sub.
<Synonyms>The term “personalized medicine” is synonym to “P4 medicine” and it is commonly used.

<en>personalized medicine
<Morphosyntax>noun group
<Usage label>common
<Source>^Hood, et al. 2012^:992

<zh>P4 医学
<Morphosyntax>noun group
<Source>^乳癌防治基金會2014^, https://www.breastcf.org.tw/contents/news_ct?c=4&id=34&page=14
<Definition>P4 医学就是 Preventive（预防）、Predictive（预测）、Personalized（个人化）与 Participatory（参与）等四大要素。将是消费者驱动的前瞻式健康管理，有别于过去是由提供者驱动的回应式之医疗行为。
<Source>^乳癌防治基金會2014^, https://www.breastcf.org.tw/contents/news_ct?c=4&id=34&page=14
<Context>P4 医学强调由消费者(全民)自己当家做主，一切措施与处置都是因应个人做出量身订制之健康照护，从预防医学做起，仅是在未发病时避免发生，即所谓初段预防；即使发病也要早期诊断及早期治疗，即所谓次段预防；尽量避免到疾病末期要耗费昂贵之医药成本及漫长之身心复健，即所谓末段预防。
<Source>^乳癌防治基金會2014^, https://www.breastcf.org.tw/contents/news_ct?c=4&id=34&page=14
<Concept field>疾病预防
<Related words>^网络医学^
<Type of relation>coord.
<Related words>^系统药理学^
<Type of relation>coord.
<Related words>^系统生物学^
<Type of relation>coord.
<Related words>^基因组^
<Type of relation>sub.
**
<Subject>医学与卫生 / Medicine & health (610)

<Subfield>解剖学、细胞学和组织学 / Human anatomy, cytology & histology (611)
<en>genome
<Morphosyntax>noun
<Usage label>main term
<Source>^National Human Genome Research Institute 2023^, https://www.genome.gov/genetics-glossary/Genome
<Lexica>Found in ^Oxford Dictionary of English 2013^
<Definition>The genome is the entire set of DNA instructions found in a cell.
<Source>^National Human Genome Research Institute 2023^, https://www.genome.gov/genetics-glossary/Genome
<Context>In humans, the genome consists of 23 pairs of chromosomes located in the cell's nucleus, as well as a small chromosome in the cell's mitochondria. A genome contains all the information needed for an individual to develop and function.
<Source>^National Human Genome Research Institute 2023^, https://www.genome.gov/genetics-glossary/Genome
<Concept field>cytology
<Related words>^P4 medicine^
<Type of relation>super.

<zh>基因组
<Morphosyntax>noun
<Source>^香港基因組中心^，https://hkgp.org/tc/discover-genomics/genomics/?tab=2
<Lexica>Found in ^现代汉语词典 2013^
<Definition>基因组是指生物体内的所有遗传物质，而人类的基因组内有超过两万个基因。
<Source>^香港基因組中心^，https://hkgp.org/tc/discover-genomics/genomics/?tab=2
<Context>每人的基因组都是独一无二的，犹如身体的说明书，决定了每人拥有的不同特征，例如肤色、高度及患上不同疾病的潜在风险等等。若比较两位没有血缘关系的人，两者的基因组有 99.9%相同，不同之处只占 0.1%；然而，这看似微细的 0.1%，却已包含数以百万计基因排序上的不同，足以为每人造就不同的身体特征及功能结构。
<Source>^香港基因組中心^，https://hkgp.org/tc/discover-genomics/genomics/?tab=2
<Concept field>细胞学
<Related words>^P4 医学^
<Type of relation>super.

REPERTOIRE II – Multiple Myeloma

<Subject>医学与卫生 / Medicine & health (610)
<Subfield>疾病 / Diseases (616)
<en>multiple myeloma
<Morphosyntax>noun group
<Usage label>main term
<Source>^Mahindra, et al. 2010^:1
<Lexica>Found in ^Merriam/Webster 2016^
<Definition>Multiple Myeloma (MM) is a clonal B-cell malignancy characterized by the aberrant expansion of plasma cells within the bone marrow, as well as at extramedullary sites.
<Source>^Mahindra, et al. 2010^:1
<Context>Multiple Myeloma arises in most cases from monoclonal gammopathy of undetermined significance or smouldering MM, which are characterized by the presence of M-protein, bone marrow plasmacytosis, and renal impairment attributable to the plasma cell proliferation disorder. The risk of progression to MM is substantially different between MGUS and SMM, about 1% per year versus 10–20% per year, respectively.
<Source>^Mahindra, et al. 2010^:1
<Concept field>haematology
<Related words>^neoplasm^
<Type of relation>super.
<Related words>^plasma cells^
<Type of relation>general
<Related words>^monoclonal gammopathy of undermined significance^
<Type of relation>sub.
<Related words>^smouldering Multiple Myeloma^
<Type of relation>sub.
<Synonyms>The terms “plasma cell myeloma”, “myelomatosis” and “kahler disease” are synonyms to “multiple myeloma” but they are hardly used to identify the disease.

<en>plasma cell myeloma
<Morphosyntax>noun group
<Usage label>uncommon
<Source>^National Cancer institute dictionary 2022^, https://www.cancer.gov/publications/dictionaries/cancer-terms/def/plasma-cell-myeloma

<en>myelomatosis
<Morphosyntax>noun
<Usage label>uncommon
<Source>^Bommer, et al. 2018^

<en>kahler disease
<Morphosyntax>noun group
<Usage label>uncommon
<Source>^National Cancer institute dictionary 2022^, https://www.cancer.gov/publications/dictionaries/cancer-terms/def/plasma-cell-myeloma

<en>MM
<Morphosyntax>noun
<Category>initials
<Usage label>common
<Source>^Mahindra, et al. 2010^:1

<Variant of>Multiple Myeloma

<zh>多发性骨髓瘤
<Morphosyntax>noun group
<Source>^路瑾，等2020^:2
<Definition>多发性骨髓瘤是一种浆细胞恶性增殖性疾病，其特征为异常浆细胞没润骨路和/或软组织，并产生大量单克隆免疫球蛋白或轻链。
<Source>^路瑾，等2020^:2
<Context>由于浆细胞属于分化成熟的细胞，所以大多数多发性骨髓瘤是一种疾病进展相对缓慢、恶性程度相对较低的恶性肿瘤。但也有少数病情进展快,恶性程度较高。最常见的临床表现为骨质破坏、肾功能不全、贫血、高钙血症、反复感染以及高黏滞血症等。
<Source>^路瑾，等2020^:2-3
<Concept field>血液学
<Related words>^恶性肿瘤^
<Type of relation>super.
<Related words>^浆细胞^
<Type of relation>general
<Related words>^意义不明的单克隆丙种球蛋白^
<Type of relation>sub.
<Related words>^冒烟性多发性骨髓瘤^
<Type of relation>sub.
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>解剖学、细胞学和组织学 / Human anatomy, cytology & histology (611)
<en>plasma cell
<Morphosyntax>noun group
<Usage label>main term
<Source>^Allen/Sharma 2022^
<Lexica>Found in ^Merriam/Webster 2016; Oxford Concise Medical Dictionary 2020^
<Definition>Plasma cells are differentiated B-lymphocyte white blood cells capable of secreting immunoglobulin or antibody.
<Source>^Allen/Sharma 2022^
<Context>Plasma cells play a significant role in the adaptive immune response, namely, being the main cells responsible for human immunity.
<Source>^Allen/Sharma 2022^
<Concept field>histology
<Related words>^multiple myeloma^
<Type of relation>general
<Related words>B cell
<Type of relation>sub.
<Related words>lymphocyte
<Type of relation>coord.
<Synonyms>The term “plasmacyte” is synonym to “plasma cell” and it is commonly used to identify the lymphocyte secreting immunoglobulins.

<en>plasmacyte
<Morphosyntax>noun
<Usage label>common
<Source>^Merriam/Webster 2016^

<en>PL
<Morphosyntax>noun
<Category>initials
<Source>^Allen/Sharma 2022^
<Variant of>plasma cell

<zh>浆细胞
<Morphosyntax>noun group
<Source>^路瑾，等2020^:2
<Definition>浆细胞是B淋巴细胞在抗原刺激下分化增殖的一种终末细胞，可合成和分泌免疫球蛋白。
<Source>^路瑾，等2020^:2
<Context>正常人体内有许多不同的浆细胞克隆，而浆细胞疾病则是由单克隆浆细胞异常增殖浸润及分泌M蛋白，同时正常浆细胞功能受到抑制导致的一组疾病，包括意义未明单克隆免疫球蛋白血症、多发性骨髓瘤、系统性轻链型淀粉样变性、髓外浆细胞瘤和孤立性骨髓瘤、POEMS综合征、浆细胞白血病、有肾脏损害意义的单克隆免疫球蛋白病等。
<Source>^路瑾，等2020^:2
<Concept field>组织学
<Related words>^多发性骨髓瘤^
<Type of relation>general
<Related words>淋巴细胞
<Type of relation>coord.
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>解剖学、细胞学和组织学 / Human anatomy, cytology & histology (611)
<en>M Protein
<Morphosyntax>noun group
<Usage label>main term
<Source>^Batuman 2020^:54
<Lexica>Found in ^Merriam/Webster 2016^
<Definition>M proteins are monoclonal immune globulin fragments or intact immune globulins produced by usually a malignant cone of plasma cells or B cells.
<Source>^Batuman 2020^:54
<Context>Since M proteins are produced by plasma cells or B cells, and their presence in blood or urine indicates clonal proliferation of either of these cell lines, that is, multiple myeloma (plasma cells), or lymphomas (B cells). M proteins fragments have relatively unrestricted access to kidneys and kidney tubules, causing an expanding spectrum of kidney disorders caused by deposition of intact immune globulins or their fragments in the glomeruli or along the kidney tubules.
<Source>^Batuman 2020^:54
<Concept field>histology
<Related words>^plasma cell^
<Type of relation>super.
<Related words>antibody
<Type of relation>super.
<Synonyms>The terms “monoclonal immunoglobulin” and “paraprotein” are synonym to “M-protein” and they are commonly used.

<en>monoclonal immunoglobulin
<Morphosyntax>noun group
<Usage label>common
<Source>^Batuman 2020^:55

<en>paraprotein
<Morphosyntax>noun group
<Usage label>common
<Source>^Batuman 2020^:54

<zh>单克隆免疫球蛋白
<Morphosyntax>noun group
<Usage label>main term
<Source>^Kumar 2022^, https://bestpractice.bmj.com/topics/zh-cn/891
<Definition>单克隆蛋白是单个浆细胞克隆产生的异常免疫同质性免疫球蛋白或其片段。
<Source>^Kumar 2022^, https://bestpractice.bmj.com/topics/zh-cn/891
<Context>单克隆蛋白可能是基础淋巴组织恶性肿瘤的结果，可能是无症状性浆细胞克隆扩增的一部分，并且可以是单克隆丙种球蛋白病的潜在异常表现。这些浆细胞可见于骨髓、外周循环或软组织内。它们通常可在骨髓检查中发现，其中克隆性浆细胞的存在可能伴随或不伴随浆细胞比例的绝对增加。
<Source>^Kumar 2022^, https://bestpractice.bmj.com/topics/zh-cn/891
<Concept field>组织学
<Related words>^浆细胞^
<Type of relation>super.
<Related words>抗体
<Type of relation>super.
<Synonym>“M 蛋白”和“单克隆免疫球蛋白”是近义词。

<zh>M 蛋白
<Morphosyntax>noun group
<Usage label>common
<Source>^路瑾，等 2020^:2
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>疾病 / Diseases (616)
<en>monoclonal gammopathy of undermined significance
<Morphosyntax>noun group
<Usage label>main term
<Source>^Korde, et al 2011^:5573
<Lexica>Found in ^Merriam/Webster 2016^
<Definition>Monoclonal gammopathy of undermined significance (MGUS) is an asymptomatic plasma cell dyscrasia that is present in more than 3% of the general white population older than age 50 and has an average multiple myeloma progression risk of 1% per year.
<Source>^Korde, et al 2011^:5573
<Context>Monoclonal gammopathy of unknown significance (MGUS) is present in more than 3% of the general white population older than age 50 and has an average multiple myeloma progression risk of 1% per year. The aetiology of MGUS remains unclear and it is a current topic of investigation, but different studies have demonstrated that most cases of multiple myeloma are preceded by MGUS.
<Source>^Korde, et al 2011^:5573
<Concept field>haematology

<Related words>^multiple myeloma^
<Type of relation>super.
<Related words>^smouldering multiple myeloma^
<Type of relation>coord.
<Synonyms>The term “monoclonal gammopathy of undermined significance” is often substituted by its initials “MGUS”.

<en>MGUS
<Morphosyntax>noun
<Category>initials
<Usage label>common
<Source>^Korde, et al 2011^:5573
<Variant of>monoclonal gammopathy of undermined significance

<zh>意义未明的单克隆免疫球蛋白病
<Morphosyntax>noun group
<Source>^Berenson 2021^, https://www.msdmanuals.cn/home/blood-disorders/plasma-cell-disorders/multiple-myeloma
<Definition>意义未明的单克隆丙种球蛋白病是指异常但非恶性浆细胞生成的单克隆抗体积聚。
<Source>^Berenson 2021^, https://www.msdmanuals.cn/home/blood-disorders/plasma-cell-disorders/multiple-myeloma
<Context>意义未明的单克隆免疫球蛋白病在老年男性中最为常见；通常不会引起任何问题。但这种疾病有时会发展成更严重的疾病。如果您的血液中含有大量的这种蛋白，务必定期接受检查，这样一旦病情有所恶化，您便能尽早接受治疗。如果病情未恶化，则无需对意义未明的单克隆丙种球蛋白病进行治疗。
<Source>^Mayo Clinic 2021^
<Concept field>血液学
<Related words>^多发性骨髓瘤^
<Type of relation>super.
<Related words>^冒烟性多发性骨髓瘤^
<Type of relation>coord.
<Synonym>“MGUS”和“意义未明的单克隆免疫球蛋白病”是近义词。

<zh>MGUS
<Morphosyntax>noun
<Category>initials
<Usage label>common
<Source>^Berenson 2021^
<Variant of>意义未明的单克隆免疫球蛋白病
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>疾病 / Diseases (616)
<en>smouldering multiple myeloma
<Morphosyntax>noun group
<Usage label>main term
<Source>^Korde 2011^:5573
<Definition>Smouldering multiple myeloma (SMM) is asymptomatic plasma cell disorder which carries a high risk of progression to active multiple myeloma (10% per year the first 5 years).
<Source>^Korde 2011^:5573

<Context>SMM is characterized by serum M-protein level >3 g/dL and/or clonal plasma cell population in bone marrow <10%, while maintaining lack of end-organ damage. Risk of progression from SMM to multiple myeloma is 10% per year for the first 5 years, 3% per year for the next 5 years, and 1% for the subsequent 10 years.
<Source>^Korde 2011^:5574
<Concept field>haematology
<Related words>^multiple myeloma^
<Type of relation>super.
<Related words>^monoclonal gammopathy of undermined significance ^
<Type of relation>coord.
<Synonyms>The expression “Smouldering Multiple Myeloma” is often substituted by its initials “SMM”.

<en>SMM
<Morphosyntax>noun
<Category>initials
<Usage label>common
<Source>^Korde 2011^:5573
<Variant of>smouldering multiple myeloma

<zh>冒烟性多发性骨髓瘤
<Morphosyntax>noun group
<Source>^Mayo Clinic 2021^, https://www.mayoclinic.org/zh-hans/diseases-conditions/mgus/symptoms-causes/syc-20352362
<Definition>冒烟性多发性骨髓瘤（SMM）是一种异质性极高的无症状浆细胞病，病程介于意义未明的单克隆丙种球蛋白血症（MGUS）与多发性骨髓瘤（MM）之间。
<Source>^Mayo Clinic 2021^, https://www.mayoclinic.org/zh-hans/diseases-conditions/mgus/symptoms-causes/syc-20352362
<Context>冒烟性多发性骨髓瘤表示：血清 M 蛋白≥3 g / dL 或 24 h 尿单克隆蛋白≥0.5 g，和（或）骨髓单克隆浆细胞的比例介于 10%～60%，无骨髓瘤相关事件。SMM 在诊断后 5 年内进展为 MM 的风险约为每年 10%，6～10 年内则为每年 3%，而后降为每年 1%。
<Source>^Mayo Clinic 2021^, https://www.mayoclinic.org/zh-hans/diseases-conditions/mgus/symptoms-causes/syc-20352362
<Concept field>血液学
<Related words>^多发性骨髓瘤^
<Type of relation>super.
<Related words>^意义未明的单克隆免疫球蛋白病^
<Type of relation>coord.
<Synonym>“SMM”和“冒烟性多发性骨髓瘤”是近义词。

<zh>SMM
<Morphosyntax>noun
<Category>initials
<Usage label>common
<Source>^Korde 2011^:5573
<Variant of>冒烟性多发性骨髓瘤
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>疾病 / Diseases (616)
<en>hypercalcemia
<Morphosyntax>noun

<Source>^Turner 2017^:270
<Lexica>Found in ^Merriam/Webster 2016^
<Definition>Hypercalcemia is a common disorder normally caused by primary hyperparathyroidism (PHPT) or malignancy. It is characterized by high serum calcium concentration in the biochemical screen.
<Source>^Turner 2017^:270
<Context>Hypercalcemia accounts for approximately 0.6% of all acute medical admissions. Its prevalence in the general population is up to 1/1,000. The classical symptomatic presentation of hypercalcemia is seen relatively rarely in the developed world, it is more common the asymptomatic presentation of the disease. Severe hypercalcemia (>3.5 mmol/L) requires emergency management, based on intravenous rehydration with normal saline, while asymptomatic mild hypercalcemia is amenable to conservative management.
<Source>^Turner 2017^:270
<Concept field>symptoms
<Related words>CRAB symptoms
<Type of relation>super.
<Related words>^osteolytic lesion^
<Type of relation>coord.
<Related words>^immunodeficiency^
<Type of relation>coord.
<Related words>^anemia^
<Type of relation>coord.
<Related words>renal impairment
<Type of relation>coord.

<zh>高钙血症
<Morphosyntax>noun group
<Source>^Mayo Clinic 2021^, https://www.mayoclinic.org/zh-hans/diseases-conditions/hypercalcemia/symptoms-causes/syc-20355523
<Definition>高钙血症是血液中钙水平高于正常值的疾病。血液中钙含量过高会削弱骨骼，产生肾结石，并干扰心脏和大脑的运作。
<Source>^Mayo Clinic 2021^, https://www.mayoclinic.org/zh-hans/diseases-conditions/hypercalcemia/symptoms-causes/syc-20355523
<Context>高钙血症通常由甲状旁腺功能亢进所致。高钙血症的其他病因包括癌症、某些其他疾病、某些药物，以及服用过多钙和维生素D补充剂。高钙血症体征和症状的程度从无症状到重度不等。如果您的高钙血症较轻微，您可能不会出现任何体征或症状。更严重病例产生的体征和症状与血液中的高钙含量所影响的身体部位相关。
<Source>^Mayo Clinic 2021^, https://www.mayoclinic.org/zh-hans/diseases-conditions/hypercalcemia/symptoms-causes/syc-20355523
<Concept field>症状
<Related words>CRAB症状
<Type of relation>super.
<Related words>^溶骨性病变^
<Type of relation>coord.
<Related words>^免疫缺陷^
<Type of relation>coord.
<Related words>^贫血^
<Type of relation>coord.
<Related words>肾功能损伤
<Type of relation>coord.
**

<Subject>医学与卫生 / Medicine & health (610)
<Subfield>疾病 / Diseases (616)
<en>osteolytic lesions
<Morphosyntax>noun group
<Usage label>main term
<Source>^Merz, et al. 2022^:2
<Definition>Osteolytic lesions (OL) are areas of circumscribed bone loss caused by malignant PC infiltration.
<Source>^Merz, et al. 2022^:2
<Context>Osteolytic lesions (OL) characterize symptomatic multiple myeloma. OL can be visualized by positron emission computed tomography (PET/CT) in up to 80% of patients, but their underlying biology remains to be clarified. Some patients show subtotal plasma cells infiltration of the bone marrow in the iliac crest without signs of bone destruction while in the same patients, plasma cells cause bone disease in distant locations such as the vertebral bodies. Therefore, OL might represent regions of increased infiltration as well as areas containing biologically different PC.
<Source>^Merz, et al. 2022^:2
<Concept field>symptoms
<Related words>CRAB symptoms
<Type of relation>super.
<Related words>^hypercalcemia^
<Type of relation>coord.
<Related words>^immunodeficiency^
<Type of relation>coord.
<Related words>^anaemia^
<Type of relation>coord.
<Related words>renal impairment
<Type of relation>coord.
<Synonyms>The term “osteolytic lesion” is often substituted by its initials “OL”.

<en>OL
<Morphosyntax>noun
<Category>initials
<Usage label>common
<Source>^Merz, et al. 2022^:2
<Variant of>osteolytic lesion

<zh>溶骨性病变
<Morphosyntax>noun group
<Source>^路瑾，等2020^:176
<Definition>溶骨性病变是多发性骨髓瘤的基本病变之一。溶骨性病变是是骨质流失区，所以出现此病变，病人易发生骨折.
<Source>^路瑾，等2020^:176
<Concept field>症状
<Related words>CRAB症状
<Type of relation>super.
<Related words>^高钙血症^
<Type of relation>coord.
<Related words>^免疫缺陷^
<Type of relation>coord.
<Related words>^贫血^

<Type of relation>coord.
<Related words>肾功能损伤
<Type of relation>coord.
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>疾病 / Diseases (616)
<en>immunodeficiency
<Morphosyntax>noun
<Source>^Raje/Dinakar 2015^:599
<Lexica>Found in ^Merriam/Webster 2016^
<Definition>Immunodeficiency is a group of heterogeneous disorders with immune system abnormalities that lead to an abnormal production of antibodies. It is characterized by recurrent infections, autoimmunity, lymphoproliferation and malignancy.
Source>^Raje/Dinakar 2015^:599
<Context>The overall clinical picture is dictated by the specific type of underlying immune defect. Based on the type of immunodeficiency disorders, the types of infections can vary. Some immunodeficiency disorders are characterized by cutaneous, respiratory, or gastrointestinal tract granulomas caused by immune dysregulation. Atopic features such as asthma, atopic dermatitis, and food allergies can be observed in some patients.
Source>^Raje/Dinakar 2015^:599-600
<Concept field>symptoms
<Related words>^hypercalcemia ^
<Type of relation>coord.
<Related words>^osteolytic lesion^
<Type of relation>coord.
<Related words>renal impairment
<Type of relation>coord.

<zh>免疫缺陷
<Morphosyntax>noun group
<Source>^张文静，等 2021^:796
<Definition>免疫缺陷是一类由免疫细胞和（或）分子缺陷所致的异质性疾病。
<Source>^张文静，等 2021^:796
<Context>免疫缺陷通常以反复和（或）严重感染、自身免疫、自身炎症、肿瘤和过敏性疾病的风险增加为特征。前几者已见于较多的报道,而过敏相对少,尤其是过敏中的食物过敏在国内文献中提及甚少。截止 2019 年国际免疫学联合会（IUIS）统计,免疫缺陷病已达 430 种。
<Source>^张文静，等 2021^:796
<Concept field>症状
<Related words>^高钙血症^
<Type of relation>coord.
<Related words>^溶骨性病变^
<Type of relation>coord.
<Related words>肾功能损伤
<Type of relation>coord.
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>解剖学、细胞学和组织学 / Human anatomy, cytology & histology (611)
<en>plasmablast
<Morphosyntax>noun group

<Source>^Nutt, et al. 2015^:160
<Lexica>Found in ^Merriam/Webster 2016^
<Definition>Plasmablasts are the rapidly produced and short-lived effector cells of the early antibody response.
<Source>^Nutt, et al. 2015^:160
<Context>Plasmablast are dividing cells which have migratory potential and can further mature into plasma cells, which do not divide. Plasmablasts also develop B cells which are characterized by their capacity to secrete large amounts of antibodies.
<Source>^Nutt, et al. 2015^:160
<Concept field>histology
<Related words>^plasma cell^
<Type of relation>super.
<Related words>neoplastic clone
<Type of relation>general

<zh>浆母细胞
<Morphosyntax> noun group
<Usage label>main term
<Source>^生物通 2023^，https://www.ebiotrade.com/newsf/2022-9/202297153051262.htm
<Definition>浆母细胞是短寿命的活化B细胞，可在分裂时分泌抗体。
<Source>^生物通 2023^，https://www.ebiotrade.com/newsf/2022-9/202297153051262.htm
<Context>为了有效地产生抗体，B细胞最终从初始状态分化为分泌抗体的浆母细胞和浆细胞。浆母细胞的早期抗体应答可能来自T细胞依赖性和非依赖性活化。浆母细胞群可以来自B1细胞、MZB细胞、FOB细胞和记忆B细胞，并有可能进一步成熟为浆细胞。
<Source>^生物通 2023^，https://www.ebiotrade.com/newsf/2022-9/202297153051262.htm
<Concept field>组织学
<Related words>^浆细胞^
<Type of relation>super.
<Related words>肿瘤性克隆
<Type of relation>general.
<Synonym>“原浆细胞”和“浆母细胞”是近义词；但是“浆母细胞”是不常使用的。

<zh>原浆细胞
<Morphosyntax>noun group
<Usage label>uncommon
<Source>^A+ 医 学 百 科 2001^ ， http://www.a-hospital.com/w/%E6%B5%86%E6%AF%8D%E7%BB%86%E8%83%9E
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>解剖学、细胞学和组织学 / Human anatomy, cytology & histology (611)
<en>lymphopoiesis
<Morphosyntax>noun
<Source>^Sue, et al. 2018^:89
<Lexica>Found in ^Merriam/Webster 2016^
<Definition>Lymphopoiesis is a tightly regulated sequence of events that leads to the expression of a functional antigen receptor on the surface of the lymphocyte.
<Source>^Sue, et al. 2018^:89
<Context>In lymphopoiesis, for B lymphocytes, it is the B-cell receptor (BCR) that represents surface immunoglobulin molecule, and for T lymphocytes, it is the T-cell receptor (TCR) complex. Cellular micro-environment, transcription factors, and posttranscriptional regulators

such as microRNAs, cytokines, and chemokines, along with silencing or activation of certain genes at different stages of lineage commitment, are some of the multiple factors contributing to a successful and mature lymphocyte.
<Source>^Sue, et al. 2018^:89
<Concept field>histology
<Related words>lymphocytes
<Type of relation>sub.

<zh>淋巴细胞增殖
<Morphosyntax>noun group
<Source>^邵安良，等 2019^:1355
<Definition>淋巴细胞增殖是机体免疫应答过程的一个重要阶段，抗原刺激淋巴细胞产生各种细胞因子或白介素，这些细胞因子或白介素将激活并刺激淋巴细胞分化，从而使增殖反应放大。
<Source>^邵安良，等 2019^:1355
<Context>T细胞或B细胞受特异性抗原或非特异性有丝分裂原刺激后，细胞代谢和形态发生变化，主要发生一系列增殖反应，进而影响机体内的免疫应答（包括刺激效应与抑制效应）。检测淋巴细胞增殖水平是细胞免疫研究和临床免疫功能检测的一种常用方法。
<Source>^邵安良，等 2019^:1355
<Concept field>组织学
<Related words>淋巴细胞
<Type of relation>sub.
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>解剖学、细胞学和组织学 / Human anatomy, cytology & histology (611)
<en>immunoglobulin light chains
<Morphosyntax>noun group
<Usage label>main term
<Source>^Nakano, et al. 2011^:843
<Lexica>Found in ^Merriam/Webster 2016^
<Definition>Immunoglobulin light chain (IgLC) is a component of antibodies, while its free form is observed in the circulation, which originates from 10 to 40% excess synthesis over heavy chain, in B cells.
<Source>^Nakano, et al. 2011^:843
<Context>Light chains are asynchronously synthesized on the different ribosomes; because of the excess production of light chains over heavy chains and their secretion competency, excess light chain is secreted as a free form. The excess production of light chain over heavy chain maintains a constant intracellular pool of light chains. This pool of light chains mediates the release of the relatively insoluble heavy chains from their ribosomes and hampers the formation of toxic heavy chain aggregates.
<Source>^Nakano, et al. 2011^:843
<Concept field>histology
<Related words>^heavy chains ^
<Type of relation>coord
<Related words>antibody
<Type of relation>sub
<Related words>B cell
<Type of relation>super
<Synonyms>The term “immunoglobulin light chain” is often substituted by its initials “IgLC”.

<en>IgLC
<Morphosyntax>noun
<Category>initials
<Usage label>common
<Source>^Nakano, et al. 2011^:843
<Variant of>immunoglobulin light chains

<zh>免疫球蛋白轻链
<Morphosyntax>noun group
<Usage label>main term
<Source>^安必奇生物^，https://www.abace-biology.com/tech-antibody-structure.htm
<Definition>免疫球蛋白轻链是免疫球蛋白的多肽链。轻链含有一系列重复的、同源性的单元，每一单元大约有 110 个氨基酸残基，它们独立折叠成球状，称为球蛋白功能区（domain）。
<Source>^安必奇生物^，https://www.abace-biology.com/tech-antibody-structure.htm
<Context> 轻链大大约由 214 个氨基酸残基组成，通常不含碳水化合物。每条轻链含有两个由链内二硫键所组成的环肽。轻链共有两型：kappa(κ)与 lambda(λ)。
<Source>cf.^安必奇生物^，https://www.abace-biology.com/tech-antibody-structure.htm
<Concept field>组织学
<Related words>^重链^
<Type of relation>coord.
<Related words>抗体
<Type of relation>sub.
<Related words>B 细胞
<Type of relation>super.
<Synonyms>“免疫球蛋白轻链”、“L 链”、“轻链” 是近义词。“轻链”是最常用的词。

<zh>L 链
<Morphosyntax>noun
<Category>initials
<Usage label>uncommon
<Source>^安必奇生物^，https://www.abace-biology.com/tech-antibody-structure.htm

<zh>轻链
<Morphosyntax>noun
<Usage label>common
<Source>^安必奇生物^，https://www.abace-biology.com/tech-antibody-structure.htm
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>解剖学、细胞学和组织学 / Human anatomy, cytology & histology (611)
<en>immunoglobulin heavy chains
<Morphosyntax>noun group
<Source>^Janeway, et al. 2005^
<Lexica>Found in ^Merriam/Webster 2016^
<Definition>Immunoglobulin heavy chains are a component of immunoglobulin. An Ig molecule is made up of 2 identical heavy chains and disulphide bonds link the heavy chain to a light chain and link the two heavy chains together.
<Source>cf.^Janeway, et al. 2005^
<Context>Each Ig heavy chain has a variable (V) region containing the antigen-binding site and a constant (C) region that determines the isotype of the antibody and provides signalling

functions. The heavy chain V region is encoded by 1 each of 3 types of genes: Variable genes, joining genes and diversity genes.
<Source>cf.^Janeway, et al. 2005^
<Concept field>histology
<Related words>^light chains^
<Type of relation>coord.
<Related words>antibody
<Type of relation>sub.
<Related words>B cell
<Type of relation>super.

<zh>免疫球蛋白重链
<Morphosyntax>noun group
<Usage label>main term
<Source>^安必奇生物^, https://www.abace-biology.com/tech-antibody-structure.htm
<Definition>免疫球蛋白重链是分子质量较大的肽链。重链都含有一系列重复的、同源性的单元，每一单元大约有 110 个氨基酸残基，它们独立折叠成球状，称为球蛋白功能区。
<Source>cf.^安必奇生物^, https://www.abace-biology.com/tech-antibody-structure.htm
<Context>重链大约含 450~550 个氨基酸残基。每条重链含有 4~5 个链内二硫键所组成的肽环。由于氨基酸组成的排列顺序以及二硫键的位置、数目等的不同，因此不同重链的抗原性也不同，根据重链抗原性的不同可将其分为五类，分别以希腊字母 γ、α、μ、δ、和 ε 表示，并以此将免疫球蛋白相应地分为 IgG、 IgA、 IgM、IgD 和 IgE。
<Source>^安必奇生物^, https://www.abace-biology.com/tech-antibody-structure.htm
<Concept field>组织学
<Related words>^轻链^
<Type of relation>coord.
<Related words>抗体
<Type of relation>sub.
<Related words>B 细胞
<Type of relation>super.
<Synonyms>“免疫球蛋白重链”、“H 链”、“重链” 是近义词。“重链”是最常用的词。

<zh>H 链
<Morphosyntax>noun
<Category>initials
<Usage label>uncommon
<Source>^安必奇生物^, https://www.abace-biology.com/tech-antibody-structure.htm

<zh>重链
<Morphosyntax>noun
<Usage label>common
<Source>^安必奇生物^, https://www.abace-biology.com/tech-antibody-structure.htm
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>解剖学、细胞学和组织学 / Human anatomy, cytology & histology (611)
<en>memory B-cells
<Morphosyntax>noun group
<Source>^Palm/Henry 2019^

<Lexica>Found in ^Merriam/Webster 2016; Oxford Concise Medical Dictionary 2020^
<Definition>Memory B-cells are defined as long-lived and quiescent cells that are poised to quickly respond to antigen upon recall.
<Source>^Palm/Henry 2019^
<Context>Memory B cells and antibody-secreting cells (ASCs) are the product of antigen activation and, most often, interaction with cognate T helper cells. Although generation of memory B cells does require ligation of CD40 (protein required for the activation of antigen), an early burst of both memory B cells and ASCs can form independently of Germinal Centers, as well as in T-cell independent responses. In contrast, activation and differentiation of B cells within Germinal Centers allow the generation of plasma cells of high affinity that will then migrate to the bone marrow, where they can survive for decades and provide long-term humoral protection. They persist in the absence of antigen for decades after the original exposure. Although they exist in multiple lymphoid organs, the bone marrow is the home of the majority of plasma cells.
<Source>^Palm/Henry 2019^
<Concept field>histology
<Related words>antigen
<Type of relation>general
<Related words>B-cell
<Type of relation>super.
<Related words>germinal center
<Type of relation>general.

<zh>记忆B细胞
<Morphosyntax>noun group
<Source>^贾卫红，等 2009^:362
<Definition>记忆性B细胞（BM）是初次免疫应答后克隆消除保留下来的高亲和力细胞，它们有其独特的表型以及特殊的生物活性，如同Bm相似的异质性及其活化特点。
<Source>^贾卫红，等 2009^:362
<Context>记忆性B细胞对浆细胞的产生、抗体的生成以及持久的免疫保护起关键的作用。对其记忆机制还不完全明了，但最近有报道指出，Bm的长期免疫记忆机制在免疫应答及免疫保护方面起着重要的作用，在临床治疗及疫苗研制方面也起着一定的指导作用。
<Source>^贾卫红，等 2009^:362
<Concept field>组织学
<Related words>抗原
<Type of relation>general
<Related words>B 细胞
<Type of relation>super.
<Related words>生发中心
<Type of relation>general.
<Synonym>“BM”和“记忆B细胞”是近义词。

<zh>BM
<Morphosyntax>noun
<Category>initials
<Usage label>common
<Source>^贾卫红，等 2009^
<Variant of>记忆 B 细胞
**
<Subject>医学与卫生 / Medicine & health (610)

<Subfield>解剖学、细胞学和组织学 / Human anatomy, cytology & histology (611)
<en>activation-induced cytidine deaminase
<Morphosyntax>noun group
<Source>^Gómez-González/Aguilera 2007^:8408
<Definition>Activation-induced cytidine deaminase (AID) is a specific B cell enzyme believed to be responsible for the initiation of somatic hypermutation (SHM) and class switch recombination (CSR) during B cell differentiation.
<Source>^Gómez-González/Aguilera 2007^:8408
<Context>Activation-induced cytidine deaminase acts directly on DNA, the natural target for AID action in the variable and switch (S) regions for SHM and CSR, respectively. The specific mechanisms of AID function are still unclear, but evidence suggests that the preferential target of AID may be ssDNA (single strand DNA). Transient formation of ssDNA during transcription facilitates AID action.
<Source>^Gómez-González/Aguilera 2007^:8408
<Concept field>histology
<Related words>^lymphopoiesis^
<Type of relation>super.
<Related words>B-cell
<Type of relation>general
<Related words>DNA
<Type of relation>general
<Synonyms>The term “activation-induced cytidine deaminase” is often substituted by its initials “AID”.

<en>AID
<Morphosyntax>noun
<Category>initials
<Usage label>common
<Source>^Gómez-González/Aguilera 2007^:8408
<Variant of>activation-induced cytidine deaminase

<zh>活化诱导性胞苷脱氨酶
<Morphosyntax>noun group
<Source>^周光全/顾伟英 2016^:350
<Definition>活化诱导胞嘧啶核苷脱氨酶是一种酵素作为基因的诱导突变体，将胞嘧啶脱氧核糖核苷酸脱氢转变为尿嘧啶脱氧核糖核苷酸，从而引起基因突变山。
<Source>^周光全/顾伟英 2016^:350
<Context>激活诱导的胞苷脱氨酶(AID)对于通过同种型类别转换和体细胞突变产生 Ig 多样性至关重要，然后直接影响克隆选择。活化的 B 细胞在稳定状态下形成生发中心并促进 B 细胞库的持续多样化。
<Source>^Bao, et al. 2022^:2632
<Concept field>组织学
<Related words>^淋巴细胞增殖^
<Type of relation>super.
<Related words>B细胞
<Type of relation>general
<Related words>DNA
<Type of relation>general
<Synonym>“活化诱导性胞苷脱氨酶”和“AID”是近义词。

<zh>AID

<Morphosyntax>noun
<Category>initials
<Usage label>common
<Source>^Bao, et al. 2022^:2632
<Variant of>活化诱导性胞苷脱氨酶
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>解剖学、细胞学和组织学 / Human anatomy, cytology & histology (611)
<en>hemopoietic microenvironment
<Morphosyntax>noun group
<Source>^Mayani, et al. 1992^:225
<Definition>Hemopoietic microenvironment is a highly organized structure that regulates the location and physiology of Hemopoietic/progenitor cell (HPC).
<Source>^Mayani, et al. 1992^:225
<Context>The hemopoietic microenvironment is composed of stromal cells (fibroblasts, macrophages, endothelial cells, adipocytes), accessory cells (T lymphocytes, monocytes), and their products (extracellular matrix and cytokines). Microenvironmental cells can regulate hemopoiesis by interacting directly (cell-to-cell contact) with HPC and/or by secreting regulatory molecules that influence, in a positive or negative manner, HPC growth. Functional abnormalities of the hemopoietic microenvironment may be implicated in the manifestation of certain haematological disorders.
<Source>^Mayani, et al. 1992^:225
<Concept field>histology
<Related words>hemopoietic stem cell
<Type of relation>sub.
<Related words>^extracellular matrix^
<Type of relation>sub.
<Related words>^bone marrow stromal cell^
<Type of relation>sub.
<Related words>hemopoiesis
<Type of relation>general
<Synonym>The terms “hemopoietic microenvironment”, “hematopoietic microenvironment” and “medullary microenvironment” are synonyms and are all equally used.

<en>hematopoietic microenvironment
<Morphosyntax>noun
<Usage>common
<Source>^Greenberger 1991^:65

<en>medullary microenvironment
<Morphosyntax>noun
<Usage>common
<Source>^Mancuso 2021^:9

<zh>造血微环境
<Morphosyntax>noun group
<Source>^宫跃敏/程涛 2015^:74
<Definition>造血微环境是由一群组织细胞和细胞外基质构成的，通过细胞间接触和信号分子的作用维持和调控造血干细胞（HSC）的局部组织微环境。
<Source>^宫跃敏/程涛 2015^:74

<Context>造血微环境功能单元称为 niche。按解剖位置，骨髓造血微环境可分为骨内膜微环境和血管微环境，前者主要由成骨细胞、破骨细胞等组成，后者主要由血管内皮细胞。其他 niche 细胞包括 Nestin+间充质干细胞（MSC）、巨噬细胞、无髓鞘 Schwann 细胞等。
<Source>^宫跃敏/程涛 2015^:74
<Concept field>组织学
<Related words>造血干细胞
<Type of relation>sub.
<Related words>^细胞外基质^
<Type of relation>sub.
<Related words>^骨髓基质细胞^
<Type of relation>sub.
<Related words>造血作用
<Type of relation>general
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>解剖学、细胞学和组织学 / Human anatomy, cytology & histology (611)
<en>extracellular matrix
<Morphosyntax>noun group
<Usage label>main term
<Source>^Frantz, et al. 2010^:4195
<Definition>The extracellular matrix (ECM) is the noncellular component present within all tissues and organs and provides not only essential physical scaffolding for the cellular constituents but also initiates crucial biochemical and biomechanical cues that are required for tissue morphogenesis, differentiation and homeostasis.
<Source>^Frantz, et al. 2010^:4195
<Context>Although, the ECM is composed of water, proteins and polysaccharides, each tissue has an ECM with a unique composition and topology that is generated during tissue development through a dynamic and reciprocal, biochemical and biophysical dialogue between the various cellular components (e.g. epithelial, fibroblast, adipocyte, endothelial elements) and the evolving cellular and protein microenvironment. The ECM is a highly dynamic structure that is constantly being remodelled, either enzymatically or non-enzymatically, and its molecular components are subjected to a myriad of post-translational modifications. Through these physical and biochemical characteristics, the ECM generates the biochemical and mechanical properties of each organ, such as its tensile and compressive strength and elasticity, and also mediates protection by a buffering action that maintains extracellular homeostasis and water retention.
<Source>^Frantz, et al. 2010^:4195
<Concept field>histology
<Related words>^hemopoietic microenvironment^
<Type of relation>super.
<Related words>extracellular matrix protein
<Type of relation>sub.
<Synonyms>The term “extracellular matrix” is often substituted by its initials “ECM”.

<en>ECM
<Morphosyntax>noun
<Category>initials
<Usage label>common
<Source>^Frantz, et al. 2010^:4195
<Variant of>extracellular matrix

<zh>细胞外基质
<Morphosyntax>noun group
<Usage label>main term
<Source>^CORNING Biocoat™^, https://www.unimed.com.tw/upload/200522_053950.pdf
<Definition>细胞外基质是由动物细胞合成并分泌至胞外的大分子糖蛋白，和其所组成的复杂网状结构；细胞外基质的成份决定结缔组织的特性，常见的成份有collagen、fibronectin、及laminin等等。
<Source>^CORNING Biocoat™^, https://www.unimed.com.tw/upload/200522_053950.pdf
<Context>细胞与局部ECM之间的相互作用显示出细胞内的影响。这可能促进细胞迁移、分裂和其它细胞反应。其中一些反应包括基因表达和细胞信号级联的改变。此外，已知ECM与信号分子结合，信号分子在ECM降解时释放。由于动物细胞需要有降解和重塑细胞外基质的能力，因此，细胞通常具有分解细胞外基质所必需的酶。ECM的降解和重塑对包括血管分支在内的健康组织生长具有重要意义。另一方面，当癌细胞在体内扩散时，细胞外基质重塑也有助于癌细胞的转移。
<Source>^MyJove Corporation^, https://www.jove.com/science-education/10695/the-extracellular-matrix?language=Chinese
<Concept field>组织学
<Related words>^造血微环境^
<Type of relation>super.
<Related words>细胞外基质蛋白
<Type of relation>sub.
<Synonym>“ECM”和“细胞外基质”是近义词。

<zh>ECM
<Morphosyntax>noun
<Category>initials
<Usage label>common
<Source>^MyJove Corporation^, https://www.jove.com/science-education/10695/the-extracellular-matrix?language=Chinese
<Variant of>细胞外基质
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>解剖学、细胞学和组织学 / Human anatomy, cytology & histology (611)
<en>bone marrow stromal cell
<Morphosyntax>noun group
<Usage label>main term
<Source>^Bianco, et al. 2001^:180
<Definition>Bone marrow stromal cells are progenitors of skeletal tissue components such as bone, cartilage, the haematopoiesis-supporting stroma, and adipocytes.
<Source>^Bianco, et al. 2001^:180
<Context>Marrow stromal cells showed an unexpected differentiation potential into neural tissue or muscle grant them membership in the diverse family of putative somatic stem cells. These cells exist in a number of post-natal tissues that display transgermal plasticity; that is, the ability to differentiate into cell types phenotypically unrelated to the cells in their tissue of origin. BMST have a variety of property with enormous potential therapeutic application.
<Source>cf.^Bianco, et al. 2001^:180-181
<Concept field>histology
<Related words>^osteolytic lesion^
<Type of relation>general

<Synonyms>The term “bone marrow stromal cell” is often substituted by its initials “BMSC”.

<en>BMSC
<Morphosyntax>noun
<Category>initials
<Usage label>common
<Source>^Bianco, et al. 2001^:180
<Variant of>bone marrow stromal cell

<zh>骨髓基质细胞
<Morphosyntax>noun group
<Usage label>main term
<Source>^姚红英/李小兵 2005^:123
<Definition>骨髓基质细胞是指从骨髓中分离出来后，在体外长期的细胞培养中能够附着生长的、非造血系统源的细胞。
<Source>^姚红英/李小兵 2005^:123
<Context>BMSC 在骨髓腔内相互连接成连续网状结构，通过散布于造血细胞中的基质扩展，使骨与骨髓在物理和生理上成为功能统一的结构。非造血系统中早期的 BMST 外表与前成骨细胞相似且分裂活跃，但在造血功能活跃的骨髓中，其有丝分裂为静止状态。骨髓基质形成动脉外膜并顺其延至窦腔。
<Source>^姚红英/李小兵 2005^:123
<Concept field>组织学
<Related words>^溶骨性病变^
<Type of relation>general
<Synonym>“BMSC”和“骨髓基质细胞”是近义词。

<zh>BMSC
<Morphosyntax>noun
<Category>initials
<Usage label>common
<Source>^姚红英/李小兵 2005^:123
<Variant of>骨髓基质细胞
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>解剖学、细胞学和组织学 / Human anatomy, cytology & histology (611)
<en>apoptosis
<Morphosyntax>noun group
<Usage label>main term
<Lexica>Found in ^Merriam/Webster 2016^
<Source>^Elmore 2007^:495
<Definition>Apoptosis is a distinctive and important mode of “programmed” cell death, which involves the genetically determined elimination of cells.
<Source>^Elmore 2007^:495
<Context>The process of programmed cell death, or apoptosis, is generally characterized by distinct morphological characteristics and energy-dependent biochemical mechanisms. Apoptosis is considered a vital component of various processes including normal cell turnover, proper development and functioning of the immune system, hormone-dependent atrophy, embryonic development and chemical-induced cell death. Inappropriate apoptosis (either too little or too much) is a factor in many human conditions including neurodegenerative diseases,

ischemic damage, autoimmune disorders and many types of cancer. The ability to modulate the life or death of a cell is recognized for its immense therapeutic potential.
<Source>^Elmore 2007^:495
<Concept field>histology
<Related words>osteoporosis
<Type of relation>general
<Related words>drug resistance
<Type of relation>general
<Synonyms>The terms “cell suicide” and “programmed cell death” are synonyms to “apoptosis”; while the use of the expression “cells suicide” is not very common, the expression “programmed cell death” is frequently used to substitute the term “apoptosis” or in combination with it.

<en>cell suicide
<Morphosyntax>noun group
<Usage label>uncommon
<Source>^Merriam/Webster 2016^

<en>programmed cell death
<Morphosyntax>noun group
<Usage label>common
<Source>^Merriam/Webster 2016^

<zh>细胞凋亡
<Morphosyntax>noun group
<Usage label>main term
<Source>^楊繼江 2005^:9
<Definition>细胞凋亡是在生物进化中保存下来的一种导致细胞程序性死亡的基本调节机制。
<Source>^楊繼江 2005^:9
<Context>根据细胞的种类不同可产生各种不同的细胞凋亡传导途径。细胞凋亡与自身免疫性疾病、病毒感染性疾病、神经变异性疾病等多种疾病的发生、发展相关。
<Source>^楊繼江 2005^:9
<Concept field>组织学
<Related words>骨质疏松症
<Type of relation>general
<Related words>耐药性
<Type of relation>general
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>疾病 / Diseases (616)
<en>relapsed refractory multiple myeloma
<Morphosyntax>noun group
<Usage label>main term
<Source>^Sonneveld/Broijl 2016^:396
<Definition>Relapsed/refractory MM (RRMM) is defined as a disease which becomes non-responsive or progressive on therapy or within 60 days of the last treatment in patients who had achieved a minimal response (MR) or better on prior therapy.
<Source>^Sonneveld/Broijl 2016^:396
<Context>RRMM is still inevitable in the majority of patients, including those who achieved deep remissions becoming progressively shorter. Criteria for RRMM include the IMWG criteria

for progressive disease (PD), progressive disease on treatment or after at least minimal response (MR), or progressive disease ≤60 days following the most recent treatment, the absence of at least minimal response on a given therapy (primary refractory disease), the presence of PD criteria in the absence of features for RRMM, or primary refractory MM. Treatment goals vary among patients with RRMM and should consider disease control, extension of survival, and maintenance of quality of life (QoL). Specifically, in frail MM patients, treatment should focus on symptom relief rather than on attaining a deep and durable response. In contrast, in patients with aggressive disease, treatment should be initiated immediately.
<Source>^Podar/Leleu 2021^
<Concept field>haematology
<Related words>^multiple myeloma^
<Type of relation>super.
<Related words>drug resistance
<Type of relation>general
<Synonyms>The term “relapsed refractory multiple myeloma” is often substituted by its initials “RRMM”.

<en>RRMM
<Morphosyntax>noun
<Category>initials
<Usage label>common
<Source>^Podar/Leleu 2021^
<Variant of>relapsed refractory multiple myeloma

<zh>复发难治性多发性骨髓瘤
<Morphosyntax>noun group
<Usage label>main term
<Source>^施菊妹 2014^，https://www.haodf.com/neirong/wenzhang/1367968924.html
<Definition>复发且难治性 MM 是指对挽救性治疗无反应，或在接受末次治疗达微小缓解(MR)后，60 天内出现疾病进展的患者。
<Source>^施菊妹 2014^，https://www.haodf.com/neirong/wenzhang/1367968924.html
<Context>残留的骨髓瘤干细胞是 MM 复发的根源，而其生物学改变以及耐药克隆的增加是MM耐药的主要原因。同时药物转运障碍、骨髓微环境和克隆性浆细胞相互作用、细胞黏附等因素也在 MM 耐药中发挥重要作用。因此，复发、难治 MM 的治疗 关键在于尽可能清除骨髓瘤王细胞，干扰骨髓瘤细胞和骨髓微环不境之间的相互作用，从而延缓疾病复发，克服 MM 的耐药性。
<Source>^施菊妹 2014^，https://www.haodf.com/neirong/wenzhang/1367968924.html
<Concept field>血液学
<Related words>^多发性骨髓瘤^
<Type of relation>super.
<Related words>耐药性
<Type of relation>general
<Synonym>“复发难治性MM”和“复发难治性多发性骨髓瘤”是近义词。

<zh>复发难治性 MM
<Morphosyntax>noun
<Category>abbreviation
<Usage label>common
<Source>^施菊妹 2014^，https://www.haodf.com/neirong/wenzhang/1367968924.html
<Variant of>复发难治性多发性骨髓瘤

**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>疾病 / Diseases (616)
<en>angiogenesis
<Morphosyntax>noun
<Usage label>main term
<Source>^Makrilia, et al. 2009^:663
<Lexica>Found in ^Merriam/Webster 2016; Oxford Concise Medical Dictionary 2020^
<Definition>Angiogenesis is the physiological process of the formation of new blood vessels from pre-existing ones.
<Source>^Makrilia, et al. 2009^:663
<Context>Multiple molecules regulate angiogenesis, such as the vascular endothelial growth factor, angiopoietins, the fibroblast growth factor, the platelet-derived growth factor and the transforming growth factor-β. Angiogenesis plays an important role in the growth, progression and metastasis of a tumour. Inhibiting the angiogenic process or targeting existing tumour vessels can be used for treatment of tumours as an alternative or in parallel with conventional chemotherapy.
<Source>^Makrilia, et al. 2009^:663
<Concept field>hematology
<Related words>^multiple myeloma^
<Type of relation>super.
<Related words>blood vessel
<Type of relation>sub.
<Related words>^vascular endothelial growth factor^
<Type of relation>sub.

<zh>血管新生
<Morphosyntax> noun group
<Source>^陳俊宏 2014^, https://highscope.ch.ntu.edu.tw/wordpress/?p=26705
<Definition>血管新生是人体一种正常的生理现象。当组织中需要血管时，有一些促使因子的分泌量会增加，以造就新血管的生长机会。
<Source>^陳俊宏 2014^, https://highscope.ch.ntu.edu.tw/wordpress/?p=26705
<Context>血管新生和癌细胞的生长亦有重大关系。癌细胞本身或周围的结缔组织，会分泌许多促使血管新生的物质，例如血管内皮细胞生长因子（VEGF），这些物质会活化血管内皮细胞，形成新的微血管。肿瘤内新生的血管系统和正常组织大不相同，这些血管弯弯曲曲异常混乱，没有任何规则可循。血管内的血液流速也很怪异，有些流动快速，有些则血流迟滞。这些种种异常的情形，造成肿瘤内微环境状况特殊，同时也使得肿瘤的治疗窒碍难行。由于血管新生是肿瘤生长坐大的必经过程，理论上若能适时抑制血管新生，应能抑制肿瘤的生长。根据这项理论，目前医学上发展出一种抗癌的新策略，称为“抗血管新生疗法”。
<Source>^陳俊宏 2014^, https://highscope.ch.ntu.edu.tw/wordpress/?p=26705
<Concept field>血液学
<Related words>^多发性骨髓瘤^
<Type of relation>super.
<Related words>血管
<Type of relation>sub.
<Related words>^血管内皮生长因子^
<Type of relation>sub.
**
<Subject>医学与卫生 / Medicine & health (610)

<Subfield>解剖学、细胞学和组织学 / Human anatomy, cytology & histology (611)
<en>angiogenic switch
<Morphosyntax>noun group
<Source>^Baeriswyl/Christofori 2009^:329
<Definition>Angiogenic switch refers to a time-restricted event during tumour progression where the balance between pro- and anti-angiogenic factors tilts towards a pro-angiogenic outcome, resulting in the transition from dormant avascularised hyperplasia to outgrowing vascularized tumour and eventually to malignant tumour progression.
<Source>^Baeriswyl/Christofori 2009^:329
<Context>As the angiogenic switch is controlled by changes in the fine-tuned balance between pro- and anti-angiogenic factors secreted either by tumour cells or by cells of the tumour microenvironment, various angiogenic factors and different cells of the tumour microenvironment contribute to the occurrence of the angiogenic switch. To inhibit the angiogenic switch various pro- and anti-angiogenic therapies that are currently tested in clinical trials or are already in clinical use.
<Source>^Baeriswyl/Christofori 2009^:329
<Concept field>cytology
<Related words>^angiogenesis^
<Type of relation>super.
<Related words>blood vessel
<Type of relation>sub.
<Related words>^vascular endothelial growth factor^
<Type of relation>sub.
<Related words>tumour mass
<Type of relation>sub.

<zh>血管新生开关
<Morphosyntax>noun group
<Source>^吴銘斌，等 2004^:125
<Definition>这种血管新生开关是基于平衡假说，由血管新生促进因子与抑制因子两者互相撷抗所控制。在不同种类肿瘤，血管新生开关启动的时间点，可发生在转变为恶性肿瘤之前、转变为恶性肿瘤的同时、或转变为恶性肿瘤之后发生。
<Source>^吴銘斌，等 2004^:125
<Context>肿瘤的生长与血管新生是密不可分的，当肿瘤长到 1-2 mm 大小以上时，即必须有血管新生开关启动的现象才能维持肿瘤继续生长。抗血管新生疗法是一种新型对抗癌症的策略。借着降低血管新生促进因子或增加血管新生抑制因子等方法，特异性地抑制肿瘤血管的内皮细胞，而造成肿瘤的萎缩，称之为蛰伏疗法。使用抗血管新生疗法于治疗肿瘤，是以肿瘤血管的内皮细胞为攻击标的，而非肿瘤细胞本身为攻击标的，所以抗血管新生疗法比起传统化学疗法是更具疗效的潜力。
<Source>^吴銘斌，等 2004^:125
<Concept field>细胞学
<Related words>^血管新生^
<Type of relation>super.
<Related words>血管
<Type of relation>sub.
<Related words>^血管内皮生长因子^
<Type of relation>sub.
<Related words>肿瘤肿块
<Type of relation>sub.
**

<Subject>医学与卫生 / Medicine & health (610)
<Subfield>解剖学、细胞学和组织学 / Human anatomy, cytology & histology (611)
<en>vascular endothelial growth factor
<Morphosyntax>noun group
<Usage label>main term
<Lexica>Found in ^Merriam/Webster 2016^
<Source>^Melincovici, et al. 2018^:455
<Definition>Vascular endothelial growth factor (VEGF) represents a growth factor with important pro-angiogenic activity, having a mitogenic and an anti-apoptotic effect on endothelial cells, increasing the vascular permeability, promoting cell migration, etc. Due to these effects, it actively contributes in regulating the normal and pathological angiogenic processes.
<Source>^Melincovici, et al. 2018^:455
<Context>VEGF plays an important role in pathological angiogenesis, inducing the development and progression of certain pathological conditions in the postnatal period, such as: tumor growth and metastasis, macular degeneration, diabetic retinopathy, inflammatory processes (e.g., rheumatoid arthritis), ischemic processes (myocardial ischemia), preeclampsia, etc. In humans, the VEGF family includes several members that perform various functions.
<Source>^Melincovici, et al. 2018^:455
<Concept field>histology
<Related words>^angiogenesis^
<Type of relation>super.
<Related words>^angiogenic switch^
<Type of relation>general
<Related words>blood vessel
<Type of relation>general
<Related words>tumour mass
<Type of relation>general
<Synonyms>The term “vascular endothelial growth factor” is often substituted by its initials “VEGF”.

<en>VEGF
<Morphosyntax>noun
<Category>initials
<Source>^Melincovici, et al. 2018^:455
<Variant of>vascular endothelial growth factor

<zh>血管内皮生长因子
<Morphosyntax>noun group
<Usage label>main term
<Source>^Abcam plc^, https://www.abcam.cn/cancer/the-role-of-vegf-in-angiogenesis-3
<Definition>血管内皮生长因子（VEGF）是新血管形成的关键因素。VEGF 能诱导已有血管的再生（血管再生）或新血管的生长（血管发生），因此是胚胎发育、血管修复的关键。VEGF 还能被实体瘤所用，促进实体瘤的生长。
<Source>^Abcam plc^, https://www.abcam.cn/cancer/the-role-of-vegf-in-angiogenesis-3
<Context>VEGF 在不同类型的细胞（比如肌肉细胞、神经元细胞）中均有活性，但是它主要作用于内皮细胞。胚胎发育过程中，可观察到 VEGF 高表达；在此过程中，VEGF 与多种胚胎发育因子协同控制新血管的形成。出生后，VEGF 的表达显著减少。但是，在进行伤口愈合或骨折修复的组织中，VEGF 的局部表达水平会上调。VEGF 及其家族成员的免疫组化分析与多种癌症的预后相关。
<Source>^Abcam plc^, https://www.abcam.cn/cancer/the-role-of-vegf-in-angiogenesis-3

<Concept field>组织学
<Related words>^血管新生^
<Type of relation>super.
<Related words>^血管新生开关^
<Type of relation>general
<Related words>血管
<Type of relation>general
<Related words>肿瘤肿块
<Type of relation>general
<Synonym>“VEFG”和“血管内皮生长因子”是近义词。

<zh>VEGF
<Morphosyntax>noun
<Category>initials
<Usage label>common
<Source>^Abcam plc^, https://www.abcam.cn/cancer/the-role-of-vegf-in-angiogenesis-3
<Variant of>血管内皮生长因子
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>疾病 / Diseases (616)
<en>calcinosis
<Morphosyntax>noun
<Usage label>main term
<Source>^Elahmar, et al. 2022^:980
<Lexica>Found in ^Merriam/Webster 2016; Oxford Concise Medical Dictionary 2020^
<Definition>Calcinosis refers to deposition of calcium salts (hydroxyapatite and calcium phosphate crystal) in the skin.
<Source>cf.^Elahmar, et al. 2022^:980
<Context>Calcinosis within the extracellular matrix of the dermis and subcutaneous tissue is a frequent manifestation of adult and paediatric systemic autoimmune rheumatic diseases, specifically systemic sclerosis, dermatomyositis, mixed connective tissue disease, and systemic lupus erythematosus. Calcinosis can be classified into 5 subtypes: dystrophic, metastatic, idiopathic, tumoral, and calciphylaxis. Dystrophic presents as nodules, plaques, extensive small dermal, or large subcutaneous deposits; metastatic is seen occasionally in the skin subcutaneous tissue as hard nodules located mainly in the vicinity of large joints; idiopathic is characterized by multiple, asymptomatic nodules, which begin to appear in childhood or in early adult life; tumoral presents as large subcutaneous calcium deposits near joints and pressure areas; calciphylaxis shows subcutaneous nodules of infarction vessel and necrotizing skin ulcers.
<Source>cf.^Elahmar, et al. 2022^:980-981
<Concept field>symptoms
<Related words>^hypercalcemia^
<Type of relation>coord.
<Related words>^osteolytic lesion^
<Type of relation>super.
<Synonyms>The term “calcinosis cutis” is a synonym to “calcinosis” but it is hardly used.

<en>calcinosis cutis
<Morphosyntax>noun
<Usage label>uncommon
<Source>^Elahmar, et al. 2022^:980.

<zh>皮肤钙化
<Morphosyntax>noun group
<Source>^Fernandez/Ward 2021^, https://www.uptodate.com/contents/zh-Hans/calcinosis-cutis-etiology-and-patient-evaluation
<Definition>皮肤钙化是指不可溶的钙盐在皮肤和皮下组织中沉积。
<Source>^Fernandez/Ward 2021^, https://www.uptodate.com/contents/zh-Hans/calcinosis-cutis-etiology-and-patient-evaluation
<Context>根据钙沉积的病因，皮肤钙化有 5 种类型：营养不良性、转移性、特发性、医源性和钙化防御。1.营养不良性皮肤钙化–由局部组织损伤导致，全身钙代谢正常。2.转移性皮肤钙化–病因是钙或磷代谢异常，导致钙沉积在皮肤和皮下组织中。3.特发性皮肤钙化–没有任何基础组织损伤和代谢障碍时发生的皮肤钙化。4.医源性皮肤钙化–钙盐沉积于皮肤是对其他疾病进行医疗干预的副作用。5.钙化-钙化表现为中小血管的钙化，特别是真皮或皮下组织的钙化。这被认为是由于钙和磷酸盐的代谢紊乱而发生的；常常存在甲状旁腺功能亢进。
<Source>^Fernandez/Ward 2021^, https://www.uptodate.com/contents/zh-Hans/calcinosis-cutis-etiology-and-patient-evaluation
<Concept field>症状
<Related words>^高钙血症^
<Type of relation>coord.
<Related words>^溶骨性病变^
<Type of relation>super.
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>解剖学、细胞学和组织学 / Human anatomy, cytology & histology (611)
<en>bone remodelling
<Morphosyntax>noun group
<Source>^Hadjidakis/Androulakis 2006^:385
<Definition>Bone remodelling is a process which involves the removal of mineralized bone by osteoclasts followed by the formation of bone matrix through the osteoblasts that subsequently be-come mineralized.
<Source>^Hadjidakis/Androulakis 2006^:385
<Context>The remodelling cycle consists of three consecutive phases: resorption, during which osteoclasts digest old bone; reversal, when mononuclear cells appear on the bone surface; and formation, when osteoblasts lay down new bone until the resorbed bone is completely replaced. Bone remodelling serves to adjust bone architecture to meet changing mechanical needs and it helps to repair microdamage in bone matrix preventing the accumulation of old bone.
<Source>^Hadjidakis/Androulakis 2006^:385
<Concept field>histology
<Related words>^osteolytic lesion^
<Type of relation>general
<Related words>^osteoclast^
<Type of relation>general
<Related words>^osteoblast^
<Type of relation>general

<zh>骨重塑
<Morphosyntax>noun group
<Source>^王雪娥/陳明宏 2004^:68
<Definition>骨重塑是指老旧的骨组织由饮骨细胞吸收后，再由成骨细胞形成新骨，这是—个反覆循环的反应。

<Source>^王雪娥/陳明宏 2004^:68
<Context>骨重塑生化标记随着每天的日韵律、每月的月经周期、每年的季节变化，及饮食、运动和任何改变骨重塑的因素等，呈波动性变化。生体骨重塑的活性与本衡，可以藉由测量血液或尿液中的生化标记，包括触骨标记如胶原蛋白片断、造骨标记如碱性磷酸酶，来作为判断依据。骨质流失是因旧骨的吸收速率大于新骨的形成速率，开始于中年以后或更早，许多疾病或是生理状态上雌激素的缺乏会加重此种不衡。
<Source>^王雪娥/陳明宏 2004^:68
<Concept field>组织学
<Related words>^溶骨性病变^
<Type of relation>general
<Related words>^破骨细胞^
<Type of relation>general
<Related words>^成骨细胞^
<Type of relation>general

**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>解剖学、细胞学和组织学 / Human anatomy, cytology & histology (611)
<en>osteoclast
<Morphosyntax>noun
<Source>^Boyce, et al. 2009^:171
<Lexica>Found in ^Merriam-Webster 2016; Oxford Concise Medical Dictionary 2020^
<Definition>Osteoclasts are the cells that degrade bone to initiate normal bone remodelling and mediate bone loss in pathologic conditions by increasing their resorptive activity.
<Source>^Boyce, et al. 2009^:171
<Context>Osteoclasts are derived from precursors in the monocyte lineage that circulate in the blood after their formation in the bone marrow. These osteoclast precursors (OCPs) are attracted to sites on bone surfaces destined for resorption and fuse with one another to form the multinucleated cells that resorb calcified matrixes under the influence of osteoblastic cells in bone marrow. OCPs and osteoclasts regulate the differentiation of osteoblast precursors and the movement of hematopoietic stem cells from the bone marrow to the bloodstream; they participate in immune responses, and secrete cytokines that can affect their own functions and those of other cells in inflammatory and neoplastic processes affecting bone.
<Source>^Boyce, et al. 2009^:171
<Concept field>histology
<Related words>^osteoblast^
<Type of relation>coord.
<Related words>^bone remodelling^
<Type of relation>super.
<Related words>^osteolytic lesion^
<Type of relation>general

<zh>破骨细胞
<Morphosyntax>noun group
<Source>^石玉 2021^:504
<Definition>破骨细胞是一种个体大、多细胞核、在体内负责吸收骨基质的细胞，同时也是维持骨稳态的主要细胞种类。
<Source>^石玉 2021^:504
<Context>破骨细胞是骨骼系统中重要的细胞类型，直接参与并影响成 年个体的骨骼重建。由破骨细胞介导的骨吸收共同调控着骨稳态;如果骨形成与骨吸收的平衡被打破，

极易造成骨量丢失，进而导致骨质疏松的发生。因此，研究对破骨细胞的分化、活性和功能的调控机制对于更好地了解骨质疏松的发病原理以及 发现新的治疗方案至关重要。
<Source>cf.^石玉 2021^:502
<Concept field>组织学
<Related words>^成骨细胞^
<Type of relation>coord.
<Related words>^骨重塑^
<Type of relation>super.
<Related words>^溶骨性病变^
<Type of relation>general
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>解剖学、细胞学和组织学 / Human anatomy, cytology & histology (611)
<en>osteoblast
<Morphosyntax>noun
<Source>^Bassi, et al. 2011^:95
<Lexica>Found in ^Merriam/Webster 2016; Oxford Concise Medical Dictionary 2020^
<Definition>Osteoblasts are mononucleate cuboid cells that are responsible for bone formation.
<Source>^Bassi, et al. 2011^:95
<Context>Osteoblasts originate from immature mesenchymal stem cells, which can also differentiate and give rise to chondrocytes, muscle, fat, ligament, and tendon cells. Mesenchymal stem cells undergo several transcription steps to form mature osteoblast cells. Osteoblasts produce alkaline phosphatase, an enzyme that is involved in the mineralization of bone. Alkaline phosphatase is an early marker of osteoblast differentiation, and its increased expression is associated with the progressive differentiation of osteoblasts.
<Source>cf.^Bassi, et al. 2011^:95-96
<Concept field>histology
<Related words>^osteoclast^
<Type of relation>coord.
<Related words>^bone remodelling^
<Type of relation>super.
<Related words>^osteolytic lesion^
<Type of relation>general

<zh>成骨细胞
<Morphosyntax>noun group
<Usage label>main term
<Source>^陈珺，等 2017^:1491
<Definition>成骨细胞是维持骨代谢平衡的主要功能细胞，负责骨基质的合成、分泌和矿化。
<Source>^陈珺，等 2017^:1491
<Context>成骨细胞数量和功能情况直接影响着代谢性骨病的发生发展，因此，研究不同因素对成骨细胞的调节作用，也是目前代谢性骨病药物研发的主要内容。
<Source>^陈珺，等 2017^:1491
<Concept field>组织学
<Related words>^破骨细胞^
<Type of relation>coord.
<Related words>^骨重塑^
<Type of relation>super.
<Related words>^溶骨性病变^

<Type of relation>general
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>疾病的发病率和预防/ Incidence and prevention of disease (614)
<en>fluorescent in situ hybridization
<Morphosyntax>noun group
<Usage label>main term
<Source>^Cui, et al. 2016^:1
<Lexica>Found in ^Oxford Concise Medical Dictionary 2020^
<Definition>Fluorescence in situ hybridization (FISH) is a hybridization-based macromolecule recognition tool which uses DNA fragments incorporated with fluorophore-coupled nucleotides as probes to examine the presence or absence of complementary sequences in fixed cells or tissues under a fluorescent microscope.
<Source>^Cui, et al. 2016^:1
<Context>Fluorescence in situ hybridization was initially developed as a physical mapping tool to delineate genes within chromosomes. Its high analytical resolution to a single gene level and high sensitivity and specificity enabled an immediate application for genetic diagnosis of constitutional common aneuploidies, microdeletion/microduplication syndromes, and subtelomeric rearrangements. FISH has also been used to detect infectious microbias and parasites like malaria in human blood cells. Clinical application of FISH technology had upgraded classical cytogenetics to molecular cytogenetics.
<Source>^Cui, et al. 2016^:1-2
<Concept field>laboratory test
<Related words>bone marrow
<Type of relation>general
<Related words>chromosomal set
<Type of relation>general
<Related words>^plasma cell^
<Type of relation>general
<Synonyms>The term “fluorescent in situ hybridization” is often substituted by its initials “FISH”.

<en>FISH
<Morphosyntax>noun
<Category>acronym
<Usage label>
<Source>^Cui, et al. 2016^:1
<Variant of>fluorescent in situ hybridization

<zh>萤光原位杂交
<Morphosyntax>noun group
<Usage label>main term
<Source>^義大醫療財團法人。醫學檢驗部 2023^，https://exdep.edah.org.tw/cp/index.php/2017-06-26-08-19-55/2017-06-28-09-06-14/539-fish-analysis
<Definition>萤光原位杂交（FISH）是一种细胞遗传学技术，可以用来对核酸进行检测和定位。萤光标记的核酸探针只和具有高度相似性的核酸杂交，可用于染色体上基因的定位。
<Source>^義大醫療財團法人。醫學檢驗部 2023^，https://exdep.edah.org.tw/cp/index.php/2017-06-26-08-19-55/2017-06-28-09-06-14/539-fish-analysis

<Context>萤光原位杂交(FISH)，检测染色体某区域是否有缺失。须注意：FISH 无法侦测某些致病遗传缺失，如染色体缺失不在侦测区域内、点突变或臂内倒位，遗传诊断需配合细胞遗传学分析结果与临床资讯。
<Source>^ 義 大 醫 療 財 團 法 人 。 醫 學 檢 驗 部 2023^ ，https://exdep.edah.org.tw/cp/index.php/2017-06-26-08-19-55/2017-06-28-09-06-14/539-fish-analysis
<Concept field>实验室检查
<Related words>骨髓
<Type of relation>general
<Related words>染色体组
<Type of relation>general
<Related words>^浆细胞^
<Type of relation>general
<Synonym>“FISH”和“萤光原位杂交”是近义词。

<zh>FISH
<Morphosyntax>noun
<Category>acronym
<Usage label>common
<Source>^ 義 大 醫 療 財 團 法 人 。 醫 學 檢 驗 部 2023^ ，https://exdep.edah.org.tw/cp/index.php/2017-06-26-08-19-55/2017-06-28-09-06-14/539-fish-analysis
<Variant of>萤光原位杂交
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>疾病的发病率和预防 / Incidence & prevention of disease (614)
<en>international staging system
<Morphosyntax>noun group
<Usage label>main term
<Source>^Greipp, et al 2005^:1
<Definition>The International Staging System (ISS) is a simple, reliable staging system for multiple myeloma that can be applied internationally for patient classification and stratification. ISS is based on two variables, Serum β_2-microglobulin and serum albumin.
<Source>cf.^Greipp, et al 2005^:1
<Context>Serum β_2-microglobulin and serum albumin were selected from the various potential prognostic factors both because of the statistical power in various models as well as the known wide availability of these two simple inexpensive laboratory tests. Serum β_2-microglobulin is widely recognized as the single most important variable predicting survival as it reflects not only tumour mass and renal function but also other parameters, including immune function, while a low albumin may reflect effects on the liver by interleukin-6 produced by the microenvironment of myeloma cells.
<Source>cf.^Greipp, et al 2005^:5-6-7
<Concept field>staging system
<Related words>durie-salmon staging system
<Type of relation>general
<Related words>^revised international staging system^
<Type of relation>general
<Synonyms>The term “International Staging System” is often substituted by its initials “ISS”.

<en>ISS
<Morphosyntax>noun

<Category>acronym
<Source>^Greipp, et al 2005^:1
<Variant of>international staging system

<zh>国际分期系统
<Morphosyntax>noun
<Usage label>main term
<Source>cf.^杜辰星，等 2017^:113
<Definition>国际分期系统（ISS）是一个简单有效的 MM 预后分期系统。国际分期系统主要虑 β2-MG 及血清白蛋白水平。
<Source>cf.^杜辰星，等 2017^:113
<Context> 国际骨髓瘤基金会于 2005 年建立了国际分期系统。国际分期系统(ISS)包括三期：I期为 β2-MG 水平<3.5 mg/L，白蛋白水平≥3.5 g/dL；II期为不符合I期与III期者；III期为 β2-MG 水平≥5.5 mg/L，ISS I、II、III期 MM 患者的中位 OS 期分别为 62、44、29 个月。
<Source>cf.^杜辰星，等 2017^:113
<Concept field>分期系统
<Related words>durie-salmon 分期系统
<Type of relation>general
<Related words>^修订的国际分期系统^
<Type of relation>general
<Synonyms>“ISS”和“国际分期系统”是近义词。

<zh>ISS
<Morphosyntax>noun
<Category>initials
<Source>cf.^杜辰星，等 2017^:113
<Variant of>国际分期系统
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>疾病的发病率和预防 / Incidence & prevention of disease (614)
<en>revised international staging system
<Morphosyntax>noun group
<Usage label>main term
<Source>^Palumbo et al. 2015^:2863
<Definition>The R-ISS staging system is a new risk stratification algorithm with an improved prognostic power which includes CA and LDH parameters.
<Source>cf.^Palumbo, et al. 2015^:2863
<Context>The International Staging System (ISS) is a simple risk stratification algorithm based on two parameters: serum β_2-microglobulin and serum albumin. The R-ISS introduce chromosomal abnormalities (CA) and serum lactate dehydrogenase (LDH). CA detected by interphase fluorescent in situ hybridization (iFISH), are a key element to define the biologic features of MM, while LDH is a relevant bio-marker in MM. LDH level above the upper limit of normal denotes an increased disease aggressiveness and suggests high proliferation rate and/or the presence of tumour mass, in particular extramedullary and extraosseous disease.
<Source>cf.^Palumbo, et al. 2015^:2863-2864
<Concept field>staging system
<Related words>durie-salmon staging system
<Type of relation>general
<Related words>^international staging system^

<Type of relation>general
<Synonyms>The term “revised international staging system” is often substituted by its initials “R-ISS”.

<en>R-ISS
<Morphosyntax> noun
<Category>initials
<Source>^Palumbo, et al. 2015^:2863
<Variant of>revised international staging system

<zh>修订的国际分期系统
<Morphosyntax>noun
<Usage label>main term
<Source>^卢静，等 2017^:476
<Definition>修订的国际分期系统（R-ISS）是最新的 MM 分期系统，R-ISS 纳入了细胞遗传学因素和血清 LDH 作为判断预后的指标。
<Source>cf.^卢静，等 2017^:476
<Context>由于国际分期系统（ISS）在新药时期已不能完全满足目前临床需求，因此在 2015 年，国际骨髓瘤工作组依据 11 个临床试验中心的数据，总结了 4445 例新诊断的 MM 患者的临床资料，更新修订的国际分期系统。R-ISS 能更好地区分初诊 MM 患者的 OS 时间，尤其对年轻、未行移植患者的预后评估价值较为突出。
<Source>cf.^卢静，等 2017^:475-476
<Concept field>分期系统
<Related words>durie-salmon 分期系统
<Type of relation>general
<Related words>^国际分期系统^
<Type of relation>general
<Synonyms>“R-ISS”和“修订的国际分期系统”是近义词

<zh>R-ISS
<Morphosyntax>noun
<Category>initials
<Source>^卢静，等 2017^:475
<Variant of>修订的国际分期系统
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>解剖学、细胞学和组织学 / Human anatomy, cytology & histology (611)
<en>creatinine
<Morphosyntax>noun group
<Usage label>main term
<Source>^Mayer/Donnelly 2013^:615
<Lexica>Found in ^Merriam/Webster 2016^
<Definition>Creatinine is a nitrogenous waste product produced by the breakdown of creatine, which is an important part of muscle.
<Source>^Mayer/Donnelly 2013^:615
<Context>Creatinine is filtered mainly by the kidney. Any changes in levels of creatinine in the blood are related to excretion and therefore reflect kidney function. Higher creatinine level can be indicative of dehydration. A serum creatinine test measures the amount of creatinine in the blood; it is an indirect indicator of renal glomerular filtration rate.
<Source>^Mayer/Donnelly 2013^:615

<Concept field>histology
<Related words>durie-salmon staging system
<Type of relation>general
<Related words>renal impairment
<Type of relation>general
<Synonyms>The term “creat” is a synonym to “creatinine” but it is not frequently used.

<en>creat
<Morphosyntax>noun
<Usage label>uncommon
<Source>^Mayer/Donnelly 2013^:615

<zh>肌酸酐
<Morphosyntax>noun
<Usage label>main term
<Source>^新隆醫事檢驗所^，https://www.sl-lab.com.tw/creatinine/
<Definition>肌酐酸是人体肌肉中肌酸的分解产物，属于代谢废物的一种，由肾脏将其排出至尿中。
<Source>^新隆醫事檢驗所^，https://www.sl-lab.com.tw/creatinine/
<Context>肌酐酸是非常稳定的肾功能指标，常用于评估肾功能障碍的严重程度及肾脏病的病情监控。当肾功能出现障碍时，代谢功能降低，肌酐酸会累积在血中而无法排出体外，导致血中浓度上升，因此可借血液肌酐酸浓度来判定肾功能的好坏。一般血液肌酐酸经多次测定均在 2.0mg/dl 以上时，为广义的肾功能衰竭。
<Source>^新隆醫事檢驗所^，https://www.sl-lab.com.tw/creatinine/
<Concept field>组织学
<Related words>durie-salmon分期系统
<Type of relation>general
<Related words>肾功能损伤
<Type of relation>general
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>解剖学、细胞学和组织学 / Human anatomy, cytology & histology (611)
<en>albumin
<Morphosyntax>noun
<Source>^Moman 2022^, https://www.ncbi.nlm.nih.gov/books/NBK459198/
<Lexica>Found in ^Merriam/Webster 2016; Oxford Concise Medical Dictionary 2020^
<Definition>Albumin is a small globular protein with a molecular weight of 66.5 kilodaltons (kDa). It consists of 585 amino acids which are organized into three repeated homologous domains and are made up of two separate sub-domains, A and B.
<Source>^Moman 2022^, https://www.ncbi.nlm.nih.gov/books/NBK459198/
<Context>Albumin represents half of the total protein content of plasma in healthy human patients. Albumin is synthesized by liver hepatocytes and rapidly excreted into the bloodstream. Serum albumin functions as a significant modulator of plasma oncotic pressure and transporter of endogenous and exogenous ligands. In clinical medicine, serum albumin can be measured via standard serum laboratory testing, and this measure has been advocated as a marker for an individual patient's nutritional status. As a laboratory value, serum albumin can also aid clinicians regarding insight into patients' liver function or the ability to biosynthesize proteins and factors vital to total body homeostasis.
<Source>^Moman 2022^, https://www.ncbi.nlm.nih.gov/books/NBK459198/
<Concept field>histology

<Related words>^international staging system^
<Type of relation>general
<Related words>^*β₂-microglobulin*^
<Type of relation>coord.

<zh>白蛋白
<Morphosyntax>noun
<Usage label>main term
<Source>^ 南 京 建 成 生 物 工 程 研 究 所 2014^ ，
http://www.njjcbio.com/contents.asp?cid=5&wid=2&id=827
<Definition>白蛋白是属于球蛋白的一种蛋白质；白蛋白是由肝实质细胞合成.
<Source>^ 南 京 建 成 生 物 工 程 研 究 所 2014^ ，
http://www.njjcbio.com/contents.asp?cid=5&wid=2&id=827
<Context>白蛋白是血浆中含量最多的蛋白质，占血浆总蛋白的 40%-60%。白蛋白广泛分布在各种动植物中，在人体血液，组织液中含有白蛋白，它最重要的作用是维持胶体渗透压。在肝功能检查中，检查白蛋白的作用是根据白蛋白的检查结果来判断某些疾病。一般情况下，白蛋白增高主要见于血液浓缩而致相对性增高，如严重脱水和休克、严重烧伤、急性出血、慢性肾上腺皮质功能减低症。白蛋白降低常见于肝硬化合并腹水及其他肝功能严重损害(如急性肝坏死、中毒性肝炎等)营养不良、慢性消耗性疾病、糖尿病、严重出血肾病综合征等。
<Source>^ 南 京 建 成 生 物 工 程 研 究 所 2014^ ，
http://www.njjcbio.com/contents.asp?cid=5&wid=2&id=827
<Concept field>组织学
<Related words>^国际分期系统^
<Type of relation>general
<Related words>^β_2微球蛋白^
<Type of relation>coord.
<Synonyms>“白蛋白”和“清蛋白”是近义词。

<zh>清蛋白
<Morphosyntax>noun
<Usage label>uncommon
<Source>^ 南 京 建 成 生 物 工 程 研 究 所 2014^ ，
http://www.njjcbio.com/contents.asp?cid=5&wid=2&id=827
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>解剖学、细胞学和组织学 / Human anatomy, cytology & histology (611)
<en>β_2-microglobulin
<Morphosyntax>noun group
<Usage label>main term
<Source>^Bernier 1980^:323
<Lexica>Found in ^Merriam/Webster 2016^
<Definition>β_2-microglobulin is a low molecular weight protein with sequence homology to immunoglobulins.
<Source>^Bernier 1980^:323
<Context>Under normal conditions *β_2-microglobulin* is synthesized and shed by many cells, particularly lymphocytes, and is detectable in the circulation of normal individuals. Because of its small size it is normally filtered readily at the glomerulus and is catabolized by proximal tubular cells of the kidney. Impaired renal function and hyperproduction of *β_2-microglobulin* are both associated with increased serum levels.

<Source>^Bernier 1980^:323
<Concept field>histology
<Related words>^international staging system^
<Type of relation>general
<Related words>^albumin^
<Type of relation>coord.

<zh>β_2微球蛋白
<Morphosyntax>noun
<Usage label>main term
<Source>^天津市肿瘤医院（天津医科大学肿瘤医院）2021^，http://www.tjmuch.com/system/2021/05/11/030005810.shtml
<Definition>β_2微球蛋白（β_2-MG）是一种内源性低分子量血清蛋白质，由淋巴细胞和其他大多数的有核细胞分泌，在免疫应答中起重要作用。
<Source>^天津市肿瘤医院（天津医科大学肿瘤医院）2021^，http://www.tjmuch.com/system/2021/05/11/030005810.shtml
<Context>血清 β2-MG 极易通过肾小球滤过膜，滤过的 β2-MG 99.9%被近曲小管细胞重吸收和降解。临床上检测血或尿中的 β2-MG 浓度为临床肾功能测定、肾移植成活、糖尿病肾病、重金属镉、汞中毒以及某些恶性肿瘤的临床诊断提供较早、可靠和灵敏的指标。血 β2-MG 是以淋巴细胞增殖性疾病的主要标志物，如多发性骨髓瘤，血 β2-MG 浓度明显增加。
<Source>^天津市肿瘤医院（天津医科大学肿瘤医院）2021^，http://www.tjmuch.com/system/2021/05/11/030005810.shtml
<Concept field>组织学
<Related words>^国际分期系统^
<Type of relation>general
<Related words>^白蛋白^
<Type of relation>coord.
<Synonyms>“β_2-MG”和“β_2微球蛋白”是近义词。

<zh>β_2-MG
<Morphosyntax>noun
<Category>initials
<Source>^天津市肿瘤医院（天津医科大学肿瘤医院）2021^，http://www.tjmuch.com/system/2021/05/11/030005810.shtml
<Variant of>β_2微球蛋白
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>解剖学、细胞学和组织学 / Human anatomy, cytology & histology (611)
<en>lactate dehydrogenase
<Morphosyntax>noun group
<Usage label>main term
<Source>^Farhana/Lappin 2022^, https://www.ncbi.nlm.nih.gov/books/NBK557536/
<Lexica>Found in ^Merriam/Webster 2016^
<Definition>Lactate dehydrogenase (LDH) is an important enzyme of the anaerobic metabolic pathway. It belongs to the class of oxidoreductases and its function is to catalyse the reversible conversion of lactate to pyruvate.
<Source>^Farhana/Lappin 2022^, https://www.ncbi.nlm.nih.gov/books/NBK557536/
<Context>Lactate dehydrogenase is ubiquitously present in all tissues and serves as an important checkpoint of gluconeogenesis and DNA metabolism. Conditions that can cause

increased LDH in the blood may include liver disease, anaemia, heart attack, bone fractures, muscle trauma, cancers, and infections such as encephalitis, meningitis, encephalitis, and HIV. Many cancers cause a general increase in LDH levels, thus it can be a non-specific tumour marker.
<Source>^Farhana/Lappin 2022^, https://www.ncbi.nlm.nih.gov/books/NBK557536/
<Concept field>histology
<Related words>^revised international staging system^
<Type of relation>general
<Related words>chromosomal abnormalities
<Type of relation>coord.
<Synonyms>“Lactic dehydrogenase” and “LDH” are synonyms to “Lactate Dehydrogenase”. The first term is not frequently used while the initials are frequently used in substitution to the full term.

<en>lactic dehydrogenase
<Morphosyntax>noun group
<Usage label>uncommon
<Source>^Merriam/Webster 2016^

<en>LDH
<Morphosyntax>noun
<Usage label>common
<Category>initials
<Source>^Farhana/Lappin 2022^, https://www.ncbi.nlm.nih.gov/books/NBK557536/
<Variant of>lactate dehydrogenase

<zh>乳酸脱氢酶
<Morphosyntax>noun
<Usage label>main term
<Source>^郑雪香，等 2020^
<Definition>乳酸脱氢酶（LDH）是糖酵解途径中一种重要的酶，广泛存在于组织细胞中，其中以肝脏中活性最高，其次为心脏、骨骼肌、肾脏。
<Source>^郑雪香，等 2020^
<Context>乳酸脱氢酶用于体外定量测定血清或血浆中的乳酸脱氢酶。在临床医学上乳酸脱氢酶用于心肌梗塞，肝硬化，肾病以及流行性肝炎疾病的体外辅助诊断。
<Source>^富士胶片和光纯药株式会社^，https://diagnostic-wako.fujifilm.com/cn/products/clinical-diagnostics-reagents/ldh.html
<Concept field>组织学
<Related words>^修订的国际分期系统^
<Type of relation>general
<Related words>^染色体异常^
<Type of relation>coord.
<Synonyms>“LDH”和“乳酸脱氢酶”是近义词。

<zh>LDH
<Morphosyntax>noun
<Category>initials
<Source>^郑雪香，等 2020^
<Variant of>乳酸脱氢酶

REPERTOIRE III – Traditional Chinese Medicine

**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>人身健康及安全 / Personal health & safety (613)
<en>traditional chinese medicine
<Morphosyntax>noun group
<Usage label>main term
<Source>^NIH^, https://www.cancer.gov/publications/dictionaries/cancer-terms/def/traditional-chinese-medicine
<Definition>Traditional Chinese Medicine is a medical system that has been used for thousands of years to prevent, diagnose, and treat disease. Also called Oriental medicine and TCM.
<Source>^NIH^, https://www.cancer.gov/publications/dictionaries/cancer-terms/def/traditional-chinese-medicine
<Context>It is based on the belief that qi (the body's vital energy) flows along meridians (channels) in the body and keeps a person's spiritual, emotional, mental, and physical health in balance. Traditional Chinese medicine aims to restore the body's balance and harmony between the natural opposing forces of yin and yang, which can block qi and cause disease. Traditional Chinese medicine includes acupuncture, diet, herbal therapy, meditation, physical exercise, and massage. Also called Oriental medicine and TCM.
<Source>^NIH^, https://www.cancer.gov/publications/dictionaries/cancer-terms/def/traditional-chinese-medicine
<Concept field>traditional chinese medicine
<Related words>^acupuncture^
<Type of relation>sub.
<Related words>^moxibustion^
<Type of relation>sub.
<Synonyms>The term "traditional chinese medicine" is often substituted by its initials "TCM"; the term "oriental medicine" is a synonym to "traditional chinese medicine" but it is not frequently used.

<en>oriental medicine
<Morphosyntax>noun group
<Usage label>uncommon
<Source>^NIH^, https://www.cancer.gov/publications/dictionaries/cancer-terms/def/traditional-chinese-medicine

<en>TCM
<Morphosyntax>noun
<Category>initials
<Usage label>common
<Source>^NIH^, https://www.cancer.gov/publications/dictionaries/cancer-terms/def/traditional-chinese-medicine
<Variant of>traditional chinese medicine

<zh>中医
<Morphosyntax>noun
<Source>^桂林市喜爱中文培训学校 2022^, https://studycli.org/zh-CN/chinese-culture/traditional-chinese-medicine/
<Lexica>Found in ^现代汉语词典 2013^
<Definition>中医药是在中国发展了数百年甚至数千年的各种医学治疗和实践的统称。

<Source>^桂林市喜爱中文培训学校 2022^, https://studycli.org/zh-CN/chinese-culture/traditional-chinese-medicine/
<Context>中医从业者对健康采取整体方法。他们不是孤立地治疗疾病的特定症状，而是将身体视为一个整体并努力确定疾病的根本原因。
<Source>^桂林市喜爱中文培训学校 2022^, https://studycli.org/zh-CN/chinese-culture/traditional-chinese-medicine/
<Concept field>中医
<Related words>^针灸^
<Type of relation>sub.
<Related words>^艾灸^
<Type of relation>sub.
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>人身健康及安全 / Personal health & safety (613)
<en>acupuncture
<Morphosyntax>noun
<Source>^NCCIH 2022^, https://www.nccih.nih.gov/health/acupuncture-what-you-need-to-know
<Lexica>Found in ^Oxford Dictionary of English 2013^
<Definition>Acupuncture is a technique in which practitioners insert fine needles into the skin to treat health problems.
<Source>^NCCIH 2022^, https://www.nccih.nih.gov/health/acupuncture-what-you-need-to-know
<Context>In acupuncture, needles may be manipulated manually or stimulated with small electrical currents (electroacupuncture). Acupuncture has been in use in some form for at least 2,500 years. It originated from traditional chinese medicine but has gained popularity worldwide since the 1970s. According to the World Health Organization, acupuncture is used in 103 of 129 countries that reported data.
<Source>^NCCIH 2022^, https://www.nccih.nih.gov/health/acupuncture-what-you-need-to-know
<Concept field>traditional chinese medicine
<Related words>^traditional chinese medicine^
<Type of relation>super.
<Related words>^moxibustion^
<Type of relation>coord.

<zh>针灸
<Morphosyntax>noun
<Source>^中医管理委员会注册管 2007^:2
<Lexica>Found in ^新编汉语中医药分类词典 2022^
<Definition>针灸是指通过刺激在人体表面或接近人体表面上的某个或某些刺激点的技能（不论是否有进针），来调整人体的生理功能或治疗人体的病痛。
<Source>^中医管理委员会注册管 2007^:2
<Context>刺激技能包括应用电流、磁场、光能、声能、拔罐、灸等手法。针灸是中国以外较受欢迎的中医疗法之一，用于治疗从慢性疼痛到不孕不育的各种疾病。与其他传统中医实践一样，关于针灸的有效性。
<Source>^桂林市喜爱中文培训学校 2022^, https://studycli.org/zh-CN/chinese-culture/traditional-chinese-medicine/
<Concept field>中医
<Related words>^中医^

<Type of relation>super.
<Related words>^艾灸^
<Type of relation>coord.
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>人身健康及安全 / Personal health & safety (613)
<en>moxibustion
<Morphosyntax>noun
<Source>^Schlaeger, et al. 2018^:309
<Definition>Moxibustion, a form of traditional Chinese medicine (TCM), is the burning of the herb moxa (*Folium Artemisiae argyi* or mugwort) over acupuncture points.
<Source>^Schlaeger, et al. 2018^:309
<Context>For moxibustion, moxa can be rolled into stick form, placed directly on the skin, or placed on an acupuncture needle and ignited to warm acupuncture points. There are several types of moxibustion: direct moxibustion, indirect moxibustion, and the warm needle technique. The application of moxibustion is not limited to only acupuncture points, but it is usually administered at acupuncture points as opposed to nonacupuncture points.
<Source>^Schlaeger, et al. 2018^:309-310
<Concept field>traditional chinese medicine
<Related words>^traditional chinese medicine^
<Type of relation>super.
<Related words>^acupuncture^
<Type of relation>coord.

<zh>艾灸
<Morphosyntax>noun
<Source>^CCTV.com 央 视 网 2018^, http://jiankang.cctv.com/2018/08/21/ARTIzFl7bZwo8uIypSmxNh29180821.shtml
<Lexica>Found in ^新编汉语中医药分类词典 2022^
<Definition>艾灸是中国传统灸疗法的一种，利用点燃的艾条、艾柱产生的艾热刺激体表穴位，通过激发经气的活动来调整人体紊乱的生理功能，并广泛应用于内科、外科、妇科、五官科等疾病。
<Source>^CCTV.com 央 视 网 2018^, http://jiankang.cctv.com/2018/08/21/ARTIzFl7bZwo8uIypSmxNh29180821.shtml
<Context>艾灸还能达到强身健体治未病的效果，是养生保健的主要方法。艾灸的作用可主要概括为以下几点：预防保健，可以改善慢性疲劳综合征，温经散寒，扶阳固脱，化瘀散结，引热外行。
<Source>^CCTV.com 央 视 网 2018^, http://jiankang.cctv.com/2018/08/21/ARTIzFl7bZwo8uIypSmxNh29180821.shtml
<Concept field>中医
<Related words>^中医^
<Type of relation>super.
<Related words>^针灸^
<Type of relation>coord.
**
<Subject>哲学和心理学 / Philosophy & psychology (100)
<Subfield>杂项 / Miscellany (102)
<en>yin-yang
<Morphosyntax>noun group
<Usage label>main term

<Source>^Yolles, et al., 2008^:856
<Definition>Yin-yang is a Chinese metaphysical concept developed in the Han dynasty.
<Source>^Yolles, et al., 2008^:856
<Context>Yin-yang comes from the perception that the universe is run by a single principle, the Tao, in which two opposite principles exist that oppose one another in their actions: yin and yang.
<Source>^Yolles, et al., 2008^:856
<Concept field>yin-yang theory
<Related words>^yin^
<Type of relation>sub.
<Related words>^yang^
<Type of relation>sub.

<zh>阴阳
<Morphosyntax>noun group
<Source>^中华人民共和国驻委内瑞拉玻利瓦尔共和国大使馆 2005^，http://ve.china-embassy.gov.cn/zwgx/whjl/qian564/200510/t20051031_4787105.htm
<Lexica>Found in ^新编汉语中医药分类词典 2022^
<Definition>阴阳是古人对宇宙万物两种相反相成的性质的一种抽象，也是宇宙对立统一及思维法则的哲学范畴。
<Source>^中华人民共和国驻委内瑞拉玻利瓦尔共和国大使馆 2005^，http://ve.china-embassy.gov.cn/zwgx/whjl/qian564/200510/t20051031_4787105.htm
<Context>其基本思路：阴阳交感而生宇宙万物，宇宙万物是阴阳的对立统一。阴阳学说是在气说的基础上建立起来的。阴阳学说的基本内容可用"对立，互根，消长，转化"八字括之。
<Source>^中华人民共和国驻委内瑞拉玻利瓦尔共和国大使馆 2005^，http://ve.china-embassy.gov.cn/zwgx/whjl/qian564/200510/t20051031_4787105.htm
<Concept field>阴阳学说
<Related words>^阴^
<Type of relation>sub.
<Related words>^阳^
<Type of relation>sub.
**
<Subject>哲学和心理学 / Philosophy & psychology (100)
<Subfield>杂项 / Miscellany (102)
<en>yin
<Morphosyntax>noun
<Source>^Augustyn 2023^, https://www.britannica.com/topic/yinyang
<Lexica>Found in ^Oxford Dictionary of English 2013^
<Definition>Yin is a symbol of earth, femaleness, darkness, passivity, and absorption.
<Source>^Augustyn 2023^, https://www.britannica.com/topic/yinyang
<Context>It is present in even numbers, in valleys and streams, and is represented by the tiger, the colour orange, and a broken line.
<Source>^Augustyn 2023^, https://www.britannica.com/topic/yinyang
<Concept field>yin-yang theory
<Related words>^yin-yang^
<Type of relation>super.
<Related words>^yang^
<Type of relation>coord.

<zh>阴
<Morphosyntax>noun
<Source>^中华人民共和国驻委内瑞拉玻利瓦尔共和国大使馆 2005^，http://ve.china-embassy.gov.cn/zwgx/whjl/qian564/200510/t20051031_4787105.htm
<Lexica>Found in ^新编汉语中医药分类词典 2022^
<Definition>阴代表消极、退守、柔弱的特性和具有这些特性的事物和现象。
<Source>^中华人民共和国驻委内瑞拉玻利瓦尔共和国大使馆 2005^，http://ve.china-embassy.gov.cn/zwgx/whjl/qian564/200510/t20051031_4787105.htm
<Concept field>阴阳学说
<Related words>^阴阳^
<Type of relation>super.
<Related words>^阳^
<Type of relation>coord.
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<Subject>哲学和心理学 / Philosophy & psychology (100)
<Subfield>杂项 / Miscellany (102)
<en>yang
<Morphosyntax>noun
<Source>^Augustyn 2023^, https://www.britannica.com/topic/yinyang
<Lexica>Found in ^Oxford Dictionary of English 2013^
<Definition>Yang is conceived of as heaven, maleness, light, activity, and penetration.
<Source>^Augustyn 2023^, https://www.britannica.com/topic/yinyang
<Context>It is present in odd numbers, in mountains, and is represented by the dragon, the colour azure, and an unbroken line.
<Source>^Augustyn 2023^, https://www.britannica.com/topic/yinyang
<Concept field>yin-yang theory
<Related words>^yin-yang^
<Type of relation>super.
<Related words>^yin^
<Type of relation>coord.

<zh>阳
<Morphosyntax>noun
<Source>^中华人民共和国驻委内瑞拉玻利瓦尔共和国大使馆 2005^，http://ve.china-embassy.gov.cn/zwgx/whjl/qian564/200510/t20051031_4787105.htm
<Lexica>Found in ^新编汉语中医药分类词典 2022^
<Definition>阳代表积极、进取、刚强的特性和具有这些特性的的事物和现象。
<Source>^中华人民共和国驻委内瑞拉玻利瓦尔共和国大使馆 2005^，http://ve.china-embassy.gov.cn/zwgx/whjl/qian564/200510/t20051031_4787105.htm
<Concept field>阴阳学说
<Related words>^阴阳^
<Type of relation>super.
<Related words>^阴^
<Type of relation>coord.
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>人身健康及安全 / Personal health & safety (613)
<en>qi
<Morphosyntax>noun
<Source>^Cheng 2010^:84

<Definition>Qi is the most basic substance of the human body, as well as the fundamental substance in maintaining the vital activities of the human body.
<Source>^Cheng 2010^:84
<Context>The Qi of the human body is derived from the congenital Essence of the parents, the nutrients of food (the Essence of food and water), and the clear Qi from the natural air. Qi is sufficient only when the physiological functions of the Kidneys, Spleen, Stomach and Lungs are in balance; if the physiological functions of the Stomach and Lungs and other organs lose this balance, the formation of Qi will be affected.
<Source>^Cheng 2010^:84-85
<Concept field>traditional chinese medicine
<Related words>^meridian^
<Type of relation>general

<zh>气
<Morphosyntax>noun
<Source>^神農氏(資訊站)^, http://www.shen-nong.com/chi/principles/qi.html
<Lexica>Found in ^新编汉语中医药分类词典 2022^
<Definition>气是构成人体及生命活动的最基本及最重要的物质，并构成人体脏腑及经络生理功能。
<Source>^神農氏(資訊站)^, http://www.shen-nong.com/chi/principles/qi.html
<Context>气有着像气体一般的流动特性，并可以理解为体内构成生命的能量或动力，这能量会流遍全身，以维持人体的生命活动。人体的气主要有两个来源，一是自父母传下来的气，称为先天之精气；二是来自自然界的物质，包括空气、食物及水。
<Source>^神農氏(資訊站)^, http://www.shen-nong.com/chi/principles/qi.html
<Concept field>中医
<Related words>^经络^
<Type of relation>general
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<Subject>医学与卫生 / Medicine & health (610)
<Subfield>人身健康及安全 / Personal health & safety (613)
<en>meridian
<Morphosyntax>noun
<Source>^Acupuncture & Massage college 2017^, https://www.amcollege.edu/blog/what-are-meridians-in-traditional-chinese-medicine-tcm
<Lexica>Found in ^Oxford Dictionary of English 2013^
<Definition>A meridian is a channel through which *qi* and the other fundamental substances flow.
<Source>^Acupuncture & Massage college 2017^, https://www.amcollege.edu/blog/what-are-meridians-in-traditional-chinese-medicine-tcm
<Context> The meridians function as a network that can be mapped out throughout the entire body. They are similar to the circulatory system in western medicine, but it needs to be emphasized that meridians are non-physical. Meridians are divided divide into two major categories: the main meridian channels and the collateral vessels.
<Source>^Acupuncture & Massage college 2017^, https://www.amcollege.edu/blog/what-are-meridians-in-traditional-chinese-medicine-tcm
<Concept field>traditional chinese medicine
<Related words>^qi^
<Type of relation>general

<zh>经络
<Morphosyntax>noun

<Source>^ 福 建 省 人 民 医 院 2019^, https://www.srmyy.com/index.php?m=medicine&a=show&id=4800
<Lexica>Found in ^新编汉语中医药分类词典 2022^
<Definition>经络是气血运行的通道，是脏腑与体表及全身各部的联系通路。
<Source>^ 福 建 省 人 民 医 院 2019^, https://www.srmyy.com/index.php?m=medicine&a=show&id=4800
<Context>经络学阐述人体经络的循行分布、生理功能、病理变化及其与脏腑的相互关系，是针灸学的基础，也是中医基础理论的重要组成部分。经络理论贯穿于中医的生理、病理、诊断和治疗等各个方面。经络系统，包括十二经脉、奇经八脉、十二经别、十五络脉、十二经筋和十二皮部。
<Source>^ 福 建 省 人 民 医 院 2019^, https://www.srmyy.com/index.php?m=medicine&a=show&id=4800
<Concept field>中医
<Related words>^气^
<Type of relation>general
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<Subject>医学与卫生 / Medicine & health (610)
<Subfield>疾病 / Diseases (616)
<en>leukaemia
<Morphosyntax>noun
<Source>^Chennamadhavuni, et al. 2023^, https://www.ncbi.nlm.nih.gov/books/NBK560490/
<Lexica>Found in ^Merriam/Webster 2016; Oxford Concise Medical Dictionary 2020^
<Definition>Leukaemia is a heterogeneous group of hematologic malignancies that arise from the dysfunctional proliferation of developing leukocytes.
<Source>^Chennamadhavuni, et al. 2023^, https://www.ncbi.nlm.nih.gov/books/NBK560490/
<Context>Leukaemia is classified as either acute or chronic based on the rapidity of proliferation and as myelocytic or lymphocytic based on the cell of origin. Treatment depends on the type of leukaemia but generally involves chemotherapy. Multiple genetic and environmental risk factors are identified in the development of leukaemia. According to the Surveillance, Epidemiology, and End Results (SEER) database, there are 61,090 estimated new cases of leukaemia in 2021, accounting for 3.2% of all new cancer cases, making leukaemia the 10th most common cancer in the United States.
<Source>^Chennamadhavuni, et al. 2023^, https://www.ncbi.nlm.nih.gov/books/NBK560490/
<Concept field>blood disease
<Related words>^aplastic anaemia^
<Type of relation>coord.
<Related words>^necrosis^
<Type of relation>coord.

<zh>白血病
<Morphosyntax>noun group
<Source>^Mayo Clinic 2021^, https://www.mayoclinic.org/zh-hans/diseases-conditions/leukemia/symptoms-causes/syc-20374373
<Lexica>Found in ^现代汉语词典 2013^
<Definition>白血病是身体造血组织（包括骨髓和淋巴系统）的癌症。
<Source>^Mayo Clinic 2021^, https://www.mayoclinic.org/zh-hans/diseases-conditions/leukemia/symptoms-causes/syc-20374373
<Context>白血病有多种类型。有些类型的白血病在儿童中更常见。其他类型的白血病则更常见于成人。白血病通常牵涉到白细胞。白细胞是强大的感染抵抗者，它们通常根

据身体需求有序生长和分化。但白血病患者的骨髓则会产生过量的异常白细胞，这些白细胞无法正常工作。根据白血病的类型和其他因素，白血病的治疗方式可能很复杂。
<Source>^Mayo Clinic 2021^, https://www.mayoclinic.org/zh-hans/diseases-conditions/leukemia/symptoms-causes/syc-20374373
<Concept field>血液病
<Related words>^再生障碍性贫血^
<Type of relation>coord.
<Related words>^坏死^
<Type of relation>coord.
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<Subject>医学与卫生 / Medicine & health (610)
<Subfield>疾病 / Diseases (616)
<en>aplastic anaemia
<Morphosyntax>noun group
<Source>^Moore/Koyamangalath 2022^, https://www.ncbi.nlm.nih.gov/books/NBK534212/
<Lexica>Found in ^Merriam/Webster 2016; Oxford Concise Medical Dictionary 2020^
<Definition 1>Aplastic anaemia refers to the syndrome of chronic primary hematopoietic failure from injury leading to diminished or absent hematopoietic precursors in the bone marrow and attendant pancytopenia.
<Definition 2>Aplastic anaemia is a condition in which the body is unable to make blood cells that perform vital functions including infection control, oxygen transport, and tissue repair following injury.
<Source>^Moore/Koyamangalath 2022^, https://www.ncbi.nlm.nih.gov/books/NBK534212/
<Context>Two interrelated explanations exist for aplastic anaemia: extrinsic immune-mediated suppression of hematopoietic stem cells and intrinsic abnormality of marrow progenitors. Aplastic anemia presents at any age with equal distribution among gender and race. While there are many causes for this disease, many patients never find the underlying issue. Recovery is excellent for patients with identifiable causes or disease that resolves spontaneously. Patients can opt for bone marrow transplant and additional medications to provide blood products to the body. Monitor for disease complications such as bleeding, cancers or infections, and notify physicians of any changes.
<Source>^Moore/Koyamangalath 2022^, https://www.ncbi.nlm.nih.gov/books/NBK534212/
<Concept field>blood disease
<Related words>^leukaemia^
<Type of relation>coord.
<Related words>^necrosis^
<Type of relation>coord.

<zh>再生障碍性贫血
<Morphosyntax>noun group
<Source>^Mayo Clinic 2021^, https://www.mayoclinic.org/zh-hans/diseases-conditions/aplastic-anemia/symptoms-causes/syc-20355015
<Definition>再生障碍性贫血是一种身体新生成的血细胞不足时出现的病症。
<Source>^Mayo Clinic 2021^, https://www.mayoclinic.org/zh-hans/diseases-conditions/aplastic-anemia/symptoms-causes/syc-20355015
<Context>再生障碍性贫血是一种罕见且严重的疾病，可以在任何年龄段发病。它可能突然发生，也可能缓慢发展、逐渐恶化。病情可能轻微，也可能很严重。患者会感到疲劳，更容易感染和出血失控。再生障碍性贫血的治疗可能包括药物、输血，也可能需要干细胞移植，即骨髓移植。
<Source>^Mayo Clinic 2021^, https://www.mayoclinic.org/zh-hans/diseases-conditions/aplastic-anemia/symptoms-causes/syc-20355015

<Concept field>血液病
<Related words>^白血病^
<Type of relation>coord.
<Related words>^坏死^
<Type of relation>coord.
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<Subject>医学与卫生 / Medicine & health (610)
<Subfield>疾病 / Diseases (616)
<en>necrosis
<Morphosyntax>noun
<Source>^Khalid/Azimpouran 2023^, https://www.ncbi.nlm.nih.gov/books/NBK557627/
<Lexica>Found in ^Merriam/Webster 2016; Oxford Concise Medical Dictionary 2020^
<Definition 1>Necrosis is irreversible cell injury and eventual cell death due to pathological processes.
<Definition 2>Necrosis is an uncontrolled cell death that results in swelling of the cell organelles, plasma membrane rupture and eventual lysis of the cell, and spillage of intracellular contents into the surrounding tissue leading to tissue damage.
<Source>^Khalid/Azimpouran 2023^, https://www.ncbi.nlm.nih.gov/books/NBK557627/
<Context>Unlike programmed cell death known as apoptosis which generates from intrinsic signals, necrosis occurs due to overwhelming noxious stimulus from outside the cell and is almost always associated with inflammatory responses due to the release of heat shock proteins, uric acid, ATP, DNA, and nuclear proteins, which cause inflammasome activation and secretion of proinflammatory cytokine interleukin-1 beta (IL1). Typically, necrosis is not associated with caspase activation or normal development, but different types of regulated necrosis have been described, such as necroptosis, pyroptosis, and ferroptosis.
<Source>^Khalid/Azimpouran 2023^, https://www.ncbi.nlm.nih.gov/books/NBK557627/
<Concept field>blood disease
<Related words>^leukaemia^
<Type of relation>coord.
<Related words>^aplastic anaemia^
<Type of relation>coord.

<zh>坏死
<Morphosyntax>noun
<Source>^Wasserman 2022^, https://www.mypathologyreport.ca/zh-CN/pathology-dictionary/definition-necrosis/
<Lexica>Found in ^现代汉语词典 2013^
<Definition>坏死是一种不受控制的细胞死亡类型，发生在细胞自然寿命结束之前。
<Source>^Wasserman 2022^, https://www.mypathologyreport.ca/zh-CN/pathology-dictionary/definition-necrosis/
<Context>病理学家使用坏死这个词来描述因坏死而死亡的大面积组织。最常见的原因是接触毒素、感染、血流减少和外伤。 快速分裂的癌细胞也可能死于坏死。常见的坏死类型包括肿瘤坏死，缺血性坏死、粉刺坏死、坏疽性坏死、纤维素样坏死和脂肪坏死。一种称为坏死性肉芽肿性炎症的坏死模式也可见于 肉芽肿.
<Source>^Wasserman 2022^, https://www.mypathologyreport.ca/zh-CN/pathology-dictionary/definition-necrosis/
<Concept field>血液病
<Related words>^白血病^
<Type of relation>coord.
<Related words>^再生障碍性贫血^

<Type of relation>coord.
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>疾病的发病率和预防/ Incidence and prevention of disease (614)
<en>tongue inspection
<Morphosyntax>noun group
<Usage label>main term
<Source>^Kim, et al. 2008^:527
<Definition>Tongue inspection is an important method that involves examination of the tongue body, coat, and crack conditions.
<Source>^Kim, et al. 2008^:527
<Context>Changes in tongue features, such as changes in tongue body color or presence of crack, provide significant information for TCM differential diagnosis in clinical practice. Tongue inspection represents a commonly used and important source of the information required for a TCM diagnosis.
<Source>^Kim, et al. 2008^:527
<Concept field>diagnosis
<Related words>^pulse analysis^
<Type of relation>coord.

<zh>舌诊
<Morphosyntax>noun
<Source>^衛生福利部中醫藥司 2017^，https://dep.mohw.gov.tw/DOCMAP/cp-772-5723-108.html
<Lexica>Found in ^新编汉语中医药分类词典 2022^
<Definition>舌诊就是透过观察病人舌质、舌苔的变化以诊察疾病。
<Source>^衛生福利部中醫藥司 2017^，https://dep.mohw.gov.tw/DOCMAP/cp-772-5723-108.html
<Context>在诊断中，我们常藉由舌诊来判定正气的盛衰、辨别病位的深浅、区别病邪之性质及推断病状之进退，在临床中具有相当重要的诊断价值。舌诊将着重介绍舌色及苔质这两方面，所要介绍的将有：正常苔、薄苔、厚苔、腻苔、腐苔，以及淡红舌、红舌、红绛舌、淡白舌、青紫舌。
<Source>^衛生福利部中醫藥司 2017^，https://dep.mohw.gov.tw/DOCMAP/cp-772-5723-108.html
<Concept field>诊断
<Related words>^脉诊^
<Type of relation>coord.
**
<Subject>医学与卫生 / Medicine & health (610)
<Subfield>疾病的发病率和预防/ Incidence and prevention of disease (614)
<en>pulse analysis
<Morphosyntax>noun group
<Source>^Lan, et al. 2020^:1
<Definition>Pulse diagnosis is one of the most important methods for diagnosis. A pulse can be felt by applying firm fingertip pressure to the skin where the arteries travel.
<Source>^Lan, et al. 2020^:1
<Context>In the past, Chinese medicine practitioners relied on their accumulated experience and intuition, where the sensitivity of different physicians varied. Currently, through a combination of medical expertise and digital signal processing technologies, TCM pulse-measuring instruments not only greatly improve reproducibility, but also instantly visualize and

analyse the measured pulse profile. There are about 29 pulse types in a TCM pulse diagnosis. The key point of pulse-measuring instruments is to obtain important information from the pulse in order to distinguish between different pulse types. A comprehensive analysis of the pulse types can lead to an understanding of a disease and provide a basis for the dispensing of prescriptions.
<Source>^Lan, et al. 2020^:1-2
<Concept field>diagnosis
<Related words>^tongue inspection^
<Type of relation>coord.

<zh>脉诊
<Morphosyntax>noun
<Source>^王燕 2005^:118
<Lexica>Found in ^新编汉语中医药分类词典 2022^
<Definition>脉诊作为无创检测的手段和方法，中医通过施以特殊压力的切脉，可以了解人体健康的大部分信息。
<Source>^王燕 2005^:118
<Context>脉诊对深人发掘中医理论、提高中医临床诊疗水平，发展现代医学都有重要意义。观察脉图的形态不仅能了解机体循环系统功能活动的情况，并可通过脉图参数的分析，辨别中医脉象的位、数、形、势特征，为中医辨症提供客观指标。
<Source>^王燕 2005^:118
<Concept field>诊断
<Related words>^舌诊^
<Type of relation>coord.

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SECTION III

English – Chinese glossary
英/汉词典

<en> 英语	<zh> 中文	Pinyin 拼音
Activation-induced cytidine deaminase	活化诱导性甘肝脱氨酶	Huóhuà yòudǎo xìng gān gān tuō ān méi
Acupuncture	针灸	Zhēnjiǔ
Albumin	白蛋白	Bái dànbái
Angiogenesis	血管新生	Xuèguǎn xīnshēng
Angiogenic switch	血管新生开关	Xuèguǎn xīnshēng kāiguān
Aplastic anaemia	再生障碍性贫血	Zàishēng zhàng'ài xìng pínxiě
Apoptosis	细胞凋亡	Xìbāo diāo wáng
B lymphocytopoiesis	淋巴细胞增殖	Línbā xì xìbāo zēng jī
Balancing feedback	负反馈循环	Fù fǎnkuì xúnhuán
Biological network	生物网络	Shēngwù wǎngluò
Bone marrow stromal cell	骨髓基质细胞	Gǔsuǐ jīzhì xìbāo
Bone remodelling	骨重塑	Gǔ chóng sù
Calcinosis	皮肤钙化	Pífū gàihuà
Causal loop diagram	因果回路图	Yīnguǒ huílù tú
Creatinine	肌酸酐	Jī suāngān
Disease module	疾病模块	Jíbìng mókuài
Diseasome	病情组	Bìngqíng zǔ
Event	事件	Shìjiàn
Extracellular matrix	细胞外基质	Xìbāo wài jīzhì
Feedback loop	回馈循环	Huíkuì xúnhuán
Flow	流量	Liúliàng
Fluorescent in situ hybridization	荧光原位杂交	Yíngguāng yuán wèi zájiāo
Functional module	功能模块	Gōngnéng mókuài
Genome	基因组	Jīyīnzǔ
Heavy chain	免疫球蛋白重链	Miǎnyì qiú dànbái zhòng liàn
Hematopoietic microenvironment	造血微环境	Zàoxiě wēi huánjìng
Hub	枢纽	Shūniǔ
Hypercalcemia	高钙血症	Gāo gài xiě zhèng
Immunodeficiency	免疫缺陷	Miǎnyì quēxiàn
International Staging System	国际分期系统	Guójì fēnqí xìtǒng
Lactate dehydrogenase	乳酸脱氢酶	Rǔsuān tuō qīng méi
Leukaemia	白血病	Báixiěbìng
Leverage point	杠杆点	Gànggǎn diǎn
Light chain	免疫球蛋白轻链	Miǎnyì qiú dànbái qīng liàn
Memory B-cell	记忆 B 细胞	Jìyì B xìbāo
Mental modelling	心智模式	Xìtǒng sīwéi

Meridian	经络	Jīngluò
Module	模块	Mókuài
Monoclonal gammopathy of undermined significance	意义未明的单克隆免疫球蛋白	Yìyì wèimíng de dān kèlóng miǎnyì qiú dànbái
Monoclonal immunoglobulin	单克隆免疫球蛋白	Dān kèlóng miǎnyì qiú dànbái
Moxibustion	艾灸	Ài jiǔ
Multiple Myeloma	多发性骨髓瘤	Duōfā xìng gǔsuǐ liú
Necrosis	坏死	Huàisǐ
Network medicine	网络医学	Wǎngluò yīxué
Node	节点	Jiédiǎn
Osteoblast	成骨细胞	Chéng gǔ xìbāo
Osteoclast	破骨细胞	Pò gǔ xìbāo
Osteolytic lesion	溶骨性病变	Róng gǔ xìng bìngbiàn
P4 medicine	P4 医学	P4 yīxué
Pattern	规律	Guīlǜ
Plasma blast	原浆细胞	Yuán jiāng xìbāo
Plasma cell	浆细胞	Jiāng xìbāo
Polygenic disease	多基因疾病	Duō jīyīn jíbìng
Pulse analysis	脉诊	Mài zhěn
Qi	气	Qì
Reinforcing feedback	正回馈	Zhèng huíkuì
Relapsed Refractory Multiple Myeloma	复发难治性多发性骨髓瘤	Fù fà nánzhì xìng duōfā xìng gǔsuǐ liú
Revised International Staging System	修订的国际分期系统	Xiūdìng de guójì fēnqí xìtǒng
Smouldering multiple myeloma	冒烟性多发性骨髓瘤	Mào yān xìng duōfā xìng gǔsuǐ liú
Stock	存量	Cúnliàng
Stock – flow diagram	系统动力流图	Xìtǒng dònglì liú tú
System	系统	Xìtǒng
System diagram	系统图	Xìtǒng tú
Systemic structure	系统结构	Xìtǒng jiégòu
Systems analysis	系统分析	Xìtǒng fēnxī
Systems biology	系统生物学	Xìtǒng shēngwù xué
Systems dynamic	系统动力学	Xìtǒng dònglì xué
Systems pharmacology	系统药理学	Xìtǒng yàolǐ xué
Systems Thinking	系统思维	Xìtǒng sīwéi
Tongue inspection	舌诊	Shé zhěn
Topological module	拓扑模块	Tàpū mókuài
Traditional Chinese Medicine	中医	Zhōngyī
Vascular endothelial grow factor	血管内皮生长因子	Xiěguǎn nèipí shēngzhǎng yīnzǐ
Yang	阳	Yáng
Yin	阴	Yīn

Yin-Yang	阴阳	Yīnyáng
β_2-microglobulin	β_2 微球蛋白	β_2 wēi qiú dànbái

Chinese – English glossary
汉/英词典

Pinyin 拼音	<zh> 中文	<en> 英语
Ài jiǔ	艾灸	Moxibustion
Bái dànbái	白蛋白	Albumin
Báixiěbìng	白血病	Leukaemia
Bìngqíng zǔ	病情组	Diseasome
Chéng gǔ xìbāo	成骨细胞	Osteoblast
Cúnliàng	存量	Stock
Dān kèlóng miǎnyì qiú dànbái	单克隆免疫球蛋白	Monoclonal immunoglobulin
Duō jīyīn jíbìng	多基因疾病	Polygenic disease
Duōfā xìng gǔsuǐ liú	多发性骨髓瘤	Multiple Myeloma
Fù fà nánzhì xìng duōfā xìng gǔsuǐ liú	复发难治性多发性骨髓瘤	Relapsed Refractory Multiple Myeloma
Fù fǎnkuì xúnhuán	负反馈循环	Balancing feedback
Gànggǎn diǎn	杠杆点	Leverage point
Gāo gài xiě zhèng	高钙血症	Hypercalcemia
Gōngnéng mókuài	功能模块	Functional module
Gǔ chóng sù	骨重塑	Bone remodelling
Guīlǜ	规律	Pattern
Guójì fēnqí xìtǒng	国际分期系统	International Staging System
Gǔsuǐ jīzhì xìbāo	骨髓基质细胞	Bone marrow stromal cell
Huàisǐ	坏死	Necrosis
Huíkuì xúnhuán	回馈循环	Feedback loop
Huóhuà yòudǎo xìng gān gān tuō ān méi	活化诱导性甘肝脱氨酶	Activation-induced cytidine deaminase
Jī suāngān	肌酸酐	Creatinine
Jiāng xìbāo	浆细胞	Plasma cell
Jíbìng mókuài	疾病模块	Disease module
Jiédiǎn	节点	Node
Jīngluò	经络	Meridian
Jìyì B xìbāo	记忆 B 细胞	Memory B-cell
Jīyīnzǔ	基因组	Genome
Línbā xì xìbāo zēng jī	淋巴细胞增殖	B lymphocytopoiesis
Liúliàng	流量	Flow
Mài zhěn	脉诊	Pulse analysis
Mào yān xìng duōfā xìng gǔsuǐ liú	冒烟性多发性骨髓瘤	Smouldering multiple myeloma
Miǎnyì qiú dànbái qīng liàn	免疫球蛋白轻链	Light chain
Miǎnyì qiú dànbái zhòng liàn	免疫球蛋白重链	Heavy chain
Miǎnyì quēxiàn	免疫缺陷	Immunodeficiency
Mókuài	模块	Module

P4 yīxué	P4 医学	P4 medicine
Pífū gàihuà	皮肤钙化	Calcinosis
Pò gǔ xìbāo	破骨细胞	Osteoclast
Qì	气	Qi
Róng gǔ xìng bìngbiàn	溶骨性病变	Osteolytic lesion
Rǔsuān tuō qīng méi	乳酸脱氢酶	Lactate dehydrogenase
Shé zhěn	舌诊	Tongue inspection
Shēngwù wǎngluò	生物网络	Biological network
Shìjiàn	事件	Event
Shūniǔ	枢纽	Hub
Tàpū mókuài	拓扑模块	Topological module
Wǎngluò yīxué	网络医学	Network medicine
Xìbāo diāo wáng	细胞凋亡	Apoptosis
Xìbāo wài jīzhì	细胞外基质	Extracellular matrix
Xiěguǎn nèipí shēngzhǎng yīnzǐ	血管内皮生长因子	Vascular endothelial grow factor
Xìtǒng	系统	System
Xìtǒng dònglì liú tú	系统动力流图	Stock – flow diagram
Xìtǒng dònglì xué	系统动力学	Systems dynamic
Xìtǒng fēnxī	系统分析	Systems analysis
Xìtǒng jiégòu	系统结构	Systemic structure
Xìtǒng shēngwù xué	系统生物学	Systems biology
Xìtǒng sīwéi	心智模式	Mental modelling
Xìtǒng sīwéi	系统思维	Systems Thinking
Xìtǒng tú	系统图	System diagram
Xìtǒng yàolǐ xué	系统药理学	Systems pharmacology
Xiūdìng de guójì fēnqí xìtǒng	修订的国际分期系统	Revised International Staging System
Xuèguǎn xīnshēng	血管新生	Angiogenesis
Xuèguǎn xīnshēng kāiguān	血管新生开关	Angiogenic switch
Yáng	阳	Yang
Yīn	阴	Yin
Yíngguāng yuán wèi zájiāo	荧光原位杂交	Fluorescent in situ hybridization
Yīnguǒ huílù tú	因果回路图	Causal loop diagram
Yīnyáng	阴阳	Yin-Yang
Yìyì wèimíng de dān kèlóng miǎnyì qiú dànbái	意义未明的单克隆免疫球蛋白	Monoclonal gammopathy of undermined significance
Yuán jiāng xìbāo	原浆细胞	Plasma blast
Zàishēng zhàng'ài xìng pínxiě	再生障碍性贫血	Aplastic anaemia
Zàoxiě wēi huánjìng	造血微环境	Hematopoietic microenvironment
Zhèng huíkuì	正回馈	Reinforcing feedback
Zhēnjiǔ	针灸	Acupuncture

Zhōngyī	中医	Traditional Chinese Medicine
β_2 wēi qiú dànbái	β_2 微球蛋白	β_2-microglobulin

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Images and tables

Figure 1
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Figure 2-3-4-5
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Figure 10
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Figure 14
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Figure 15
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Table 1-2-3
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