A Petri-Net-Based Approach for Enhancing Clinical Reasoning in Medical Education

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***Abstract*—Medical students are called to acquire competence to manage disease in its dynamic evolution over time, learning to analyze how clinical conditions evolve in a patient's history and how each condition interferes with the evolution of the other coexisting conditions. In this article, the health issue network (HIN) approach is introduced as a formal language based on Petri nets (PNs) to model properties that are particularly apposite for the graphical representation of HIN evolutionary paths. Moreover, the PNs' underlying mathematical model allows users to draw coherent and well-formed graphs representing rather complex clinical cases. Finally, HIN can be easily integrated into a simulation environment to support case-based learning activities and assessment. The examples of the exercises provided in this article show, on the one hand, the ways the introduced methodology is figured out and implemented; on the other hand, they outline the variety of learning questions that users may deal with when deploying the HIN approach.**

***Index Terms*—Health issue network (HIN), modeling, Petri nets (PNs), teaching/learning strategies.**

I. INTRODUCTION

THERE is an overall consensus that education and professional development must be addressed to the ability to practice with competence within healthcare systems in constant evolution: New knowledge and skills are therefore needed to develop effective approaches in facing medical problems [22].

As western societies, in particular, are increasingly dealing with the so-called "epidemiological transition" [31], which means the rising incidence of chronic diseases and disabilities due to the increase in life expectancy, physicians must nowadays provide healthcare to patients with multiple chronic diseases and, eventually, with an acute concomitant condition. This means that medical students are called to acquire additional competence to manage the disease in its dynamic evolution over time and identify and anticipate possible conditions that may reciprocally influence a patient's health state in the complexity of concurrent as well as past physiopathological processes [26].

Unfortunately, the concept of time is neither clearly present in current models of clinical reasoning nor in the related teaching/learning methods [16], [19], [42]. These models and methods focus on the cognitive process of making a diagnosis and do not address the problem of how clinical conditions evolve over time in a patient's history and/or how each condition interferes with the evolution of the other coexisting conditions. Although the clinical question "What the diagnosis in this patient is?" remains pivotal, medical educators should also consider the ability to answer the following three other important questions, starting from the available information on a patient in their present state.

1) How can their conditions evolve in the future from the present patient's health state?
2) Which past health conditions have possibly evolved into the present health state?
3) Which health conditions have influenced the evolution of other health issues?

Among the most effective methods for teaching/learning clinical reasoning, case-based learning (CBL) aims at preparing students for clinical practice, by making use of real or realistic clinical cases. It connects theory to practice through the application of knowledge to the cases and fosters the use of inquiry-based learning methods. CBL can help students develop critical thinking skills in evaluating the information provided and in identifying logical defects or false hypotheses [39]. However, in current literature, CBL applications are mainly aimed at acute, hospital-based cases or to situate a procedure or a guideline [5], [12], [14], [24]. This use of CBL does not reflect the case mix of the epidemiological transition: multiple associated chronic conditions, with many possible long-term evolutions, that most likely demand for tailor-made care paths. Moreover, CBL is usually narrative based, either with written text or with simulated patients. Both methods make it very difficult for the students to perceive the course of time. Hence, medical trainers need an enhancement of the usual CBL methods, allowing them to represent the evolution of the patterns of disease over time and the mutual interactions among the diseases at their different stages [46].

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In this perspective, this article introduces the health issue network (HIN) model as a suitable approach to support the development of the ability of clinical reasoning over time in multimorbidity patients. HIN graphically represents the network among a set of health issues (HIs) that affect an individual throughout his/her life span and describes how HIs evolve over time. HIN allows us to explore some of the implicit knowledge that lies behind and shapes the physician's way of thinking, turning it into explicit knowledge and represent the evolutions of the individual's HIs through the Petri nets (PNs) formalism (e.g., [35]), which is capable of translating HIN's key concepts into a sound formal language.

This article aims at describing the main features of the HIN model to formally represent the evolution of a patient's health state over time, so as to provide an innovative simulation environment for medical education, which fits CBL characteristics and potentialities [40]. After a preliminary validation conducted in both pregraduate and postgraduate learning contexts [31], the model is currently in use at the Faculty of Medicine and Dentistry of the Sapienza University of Rome. Medical students do not use the HIN model in its formal format (i.e., as a PN). Based on the model, a software application (fHIN-scene) has been developed to provide a user-friendly environment for the students to study graphically represented clinical cases and to perform exercises [33], [43].

The rest of this article is organized as follows. Section II outlines the issues and objectives of this study. Section III provides a brief description of PNs' characteristics linked with the representation of health evolution. The description of the HIN model, together with a discussion as to the reasons why PNs were used to support it, is reported in Section IV. In Section V, some examples of exercises are provided, and the added value of the HIN model to support the education of clinical reasoning in chronic multimorbidity patients is highlighted. Some conclusions and future prospects are shown in Section VI.

II. CLINICAL REASONING: ISSUES AND OBJECTIVES

The ability of clinical reasoning over time in complex, multimorbidity cases is a fundamental competence in the medical sciences for physicians and medical students. Diagnostic clinical reasoning has been more often framed within the paradigm of cognitivism [50], in which learning is a matter of manipulation of logical symbolic objects, like the frame or the illness scripts [44]. On the contrary, clinical reasoning over time can be framed within the theory of situated cognitivism [7]. This theory reacted to the rigid dualism of pure cognitivism (the mind versus the object to be known), to move toward a representation of learning as a transaction among the languages of representation, the mind, the body, and the social context.

In our view, the clinical reasoning over time has to develop the ability to [15], [36]:

1) manage the disease as a dynamic phenomenon, in its temporal evolution (from what it originates, which phases it has gone through, and what its future evolutions may be);
2) anticipate the reciprocal influences between multiple diseases and concurrent conditions. Influences are primarily intended as variations in the probability of evolution of each disease/condition. Furthermore, they are caused by the pathophysiological processes that produce the diseases (e.g., a proinflammatory condition increases the probability of oncogenesis) and/or by the therapies practiced (an anticoagulant therapy increases the probability of bleeding);
3) hypothesize which condition/s not yet known is/are likely to be associated with the known disease or disability.

Carrying out these tasks in a timely manner has become even more critical nowadays as, besides the already mentioned increasing prevalence of chronic and multimorbidity conditions registered in most western countries [33], new challenges are about to show up because of the current pandemic scenario [18], [54]. In any case, a clear and wide knowledge of the patient's clinical history is needed. To that end, the deployment of an educational environment is requested, which grants:

1) a combination of formal logics with a simpler language;
2) an effective representation of the complexity of real clinical situations embedded in its related flow of time;
3) the implementation of CBL activities and assessment.

In particular, the learner could carry out exercises on situations extracted from the electronic health record (EHR) of a real patient, with actual problems already faced by actual doctors. Modeling the evolution of a patient's health state starting from the information contained in a real medical record is important because the learner is challenged by all the positive and negative aspects of daily work, such as redundancies, errors, and uncertainty. In other words, the need arises to address the instances of topics such as science education, language learning, and conceptual mapping, with the objective of achieving positive effects on learning performances, as well as on students' and teachers' attitudes [1], [11].

III. PNS IN HEALTH STATE EVOLUTION

The guiding idea of HIN is the network of clinical problems as a basis for modeling a person's clinical history, seen as a set of episodes of care. Each episode starts with a clinical problem and is described by its evolution. The healthcare activities performed to cope with the problem (test ordering, drug prescription, reports of exams, surgery, etc.) are to be considered as part of it. The care episode is then characterized by the following two key concepts underlying the evolution of a health state:

1) HI, which means any problem related to a patient's health state. According to the ContSys standard [13], an HI describes a diagnosis, diagnostic hypothesis, symptom, sign, evidence, condition or risk factor, iatrogenic problem, general class of problems, pathophysiological event, or social issues. International HI classifications, like the International Classification of Diseases (e.g., [53]), the International Classification of Primary Care [52], or the Systematized Nomenclature of Human and Veterinary Medicine [14], are used to assign a code to an HI in a record and make its meaning nonambiguous;
2) evolution, which is any change in an HI through which the patient moves from one health state to another.

Based on the above-mentioned two concepts, HIN models a medical history using the formalism of directed graphs represented by the PNs. The formal semantics, the intuitive graphical/visual representation, and the underlying mathematical model make PNs suitable for a wide range of applications. PNs and subsequent extensions are an abstract formal model used in different domains [28], [47] to analyze and design information processing systems characterized as being concurrent, asynchronous, distributed, parallel, nondeterministic, and/or stochastic [20], [29]. With reference to the broad medical domain, the applications of PNs relate, e.g., to the representation of clinical guidelines and workflows [4], [6], [51] as well as to the analysis and simulation of physiobiological processes [3], [26], [37], up to health care systems (see, e.g., [2]). Other applications that, even if indirectly, share some similarities with the educational purpose of HIN are those connected with knowledge representation and reasoning [23], [25], [45]. A PN consists of the following [29], [34], [35], [38]:

1) place nodes;
2) transition nodes;
3) directed edges, which connect a place to a transition and vice versa.

PNs are bipartite graphs, so two nodes of the same type (place or transition) cannot be directly connected by an edge. Nodes (places and transition) are labeled (Labeled PNs). Places can contain a number of tokens that are used to simulate the dynamic and concurrent activities within the system. A distribution of tokens on the set of places in the network is called marking. The marking in a PN changes according to the firing rules. A transition is enabled if it can be fired, i.e., if there is at least the number required by the edge weight at each input place. The fire of a transition withdraws as many tokens from all input places of the transition as the weight of each input edge and adds as many tokens to all output places of the same transition according to the weight of each output edge. The firing of a transition is instantaneous (indivisible) and nondeterministic. This means that:

1) if more transitions are enabled at the same time, only one, any of them, can be fired;
2) there is no guarantee that an enabled transition will be fired. An enabled transition can be fired immediately, after any waiting time (as long as it remains enabled), or it is not fired at all (i.e., it remains a possibility).

An exhaustive method to analyze the dynamics of a PN is based on the reachability graph; it allows analysis of all the reachable markings, with enabled firing sequences, from a given initial marking. This graph is composed of nodes, each of which represents a specific marking, and the directed edge between two markings describes the transition from the input marking to the output marking.

The properties of the PN formalism match well with the characteristics of an HIN evolutionary path, as PNs' underlying mathematical model provides a sound representation of rather complex clinical cases as well as of patients with multimorbidity. Moreover, PNs allow us to model the complex concepts of evolution of HIs and the relations between them in a simple way. PNs properties are suitable in an HIN-based simulation environment to represent clinically meaningful situations, as a PN has the following characteristics [41].

1) It is a linear system, composed of a series of clinical states, through which the evolution of the patient's health state over time is modeled. We have the fact that a) at any given time, the set of active HIs models the patient's health state; and b) the "sum" of the evolutions of each HI models the patient's clinical history. Thanks to the possibility of PNs to break down a linear problem, by summing the effects generated by each single perturbation, we have the effect of a "sum" of input perturbations. Therefore, PNs model the transitions of an HI in a deterministic way when they refer to clinical cases related to a real patient.
2) It is a discrete distributed system. The patient's clinical history is composed of subnets of independent clinical HI evolutions as not all HIs are connected to each other.
3) It is an asynchronous system. HI evolutions are fired one at a time. This implies that each single firing of an evolution concerns only a part of a patient's clinical history because the history is made up of subnets of HI evolution independent from each other. In this way, we have the locality of evolution of the HIN graph.
4) It is a system without memory. When an evolution of an HI is fired, the new health state must be evaluated to identify potential evolutions of HIs: a) Some previous evolutions may be disabled; b) some previous evolutions may continue to be enabled; and c) new possible evolutions may be enabled. The identification of potential evolutions does not depend on how the new health state has been reached.

The main correspondences between the concepts of the evolution for a PN system and those for a patient's health state are shown in Table I.

TABLE I
MAIN CORRESPONDENCES BETWEEN EVOLUTION FOR PNS AND FOR A PATIENT'S HEALTH STATE

PETRI NETS	EVOLUTION OF A PATIENT'S HEALTH STATE
Place	Health Issue
Transition	Evolution
Firing sequence	Evolution path of a Health Issue
Marking	Health State
Path of the reachability graph	Clinical history

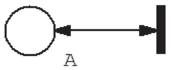
IV. HIN MODEL

The HIN model is based on the predicate/transition PN formalism, which extends the place/transition notation to

TABLE II
List of the Main Evolutions of the HIN Model, With the Related PN-Based Representation and Clinical Examples

Type of Evolution	Definition (a)	Example
Recurrence	A HI occurs and recovers repeatedly over time (the number of repetitions may be known or not). The token in this case goes in and out from the same place.	Recurrent episodes of headache (A)

HIN Representation

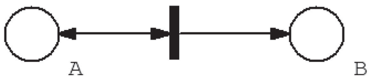


Type of Evolution	Definition (b)	Example
Worsening	The HI changes into a different and more severe one that belongs to the same class of HIs. The token moves from the originating HI to the worsened one.	An acute bronchitis (A) worsens into a pneumonia (A1)
Improvement	It is the reciprocal of worsening.	A general condition of allergy-related events improves. Asthma (A) evolves in rynithis (A1)
Examining in–depth	The originating HI is a symptom, a sign or another kind of information, that is interpreted and evolves usually into a diagnosis. The token moves from the originating HI to the new one.	A hyperglicemia (A) is diagnosed as a type 2 diabetes mellitus (A1)

HIN Representation

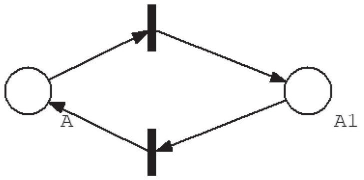
Type of Evolution	Definition (c)	Example
Complication	The HI complicates and generates a new issue that belongs to a different class of HIs. The token doubles, so it remains in the originating HI, while a new one is put into the complicating HI.	Type 2 Diabetes Mellitus (A) is complicated by a nephropathy (B)
Cause	A HI that represents a pathophysiological process (like inflammation) generates through a causal link a symptom/sign, a diagnostic hypothesis or a diagnosis. The difference between complication and cause is that the former only refers to clinical HIs, while the latter is used to manage pathophysiological correlations between biomolecular mechanisms and symptoms or diseases.	An alteration of fat metabolism (A) causes overweight (B)

HIN Representation



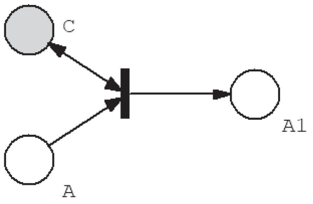
Type of Evolution	Definition (d)	Example
Cycle "recurrence–like"	Two HIs evolve into each other repeatedly. Their nature does not change with the evolution and the token moves from the one to the other.	A multiple sclerosis alternates aggravations (A → A1) and improvements (A1 → A)

HIN Representation



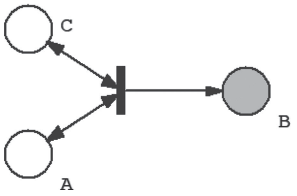
Type of Evolution	Definition (e)	Example
Worsening with Comorbidity (or Risk Factor)	The HI changes into a different and more severe one that belongs to the same class of HIs. This evolution is facilitated by a concurrent HI, such as another disease, a risk factor, an iatrogenic issue.	A patient with a mild cognitive impairment (A) suffers from a pneumonia (C), which facilitates the worsening towards dementia (A1)
Improvement by co-presence	The health state gets better thanks to an external factor that "protects" the HI from being affected by other disease/s	A patient sees a general improvement of T2DM (A → A1) after being operated from diverticular disease (C)
Examining in–depth with Comorbidity (or Risk Factor)	A disease co-exists with another HI (e.g. a diagnosis, a sign or symptom, the result of a test, a risk factor). This coexistence facilitates the evolution leading to the interpretation of the overall patient's state as a new diagnosis.	In a patient with biliary tract stones (C), an increase of serum lipases (A) is interpreted as a biliary acute pancreatitis (A1)

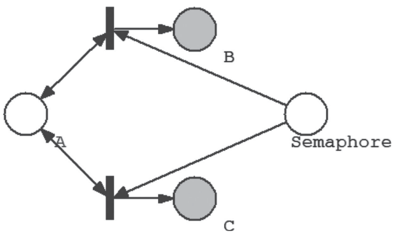
HIN Representation



Type of Evolution	Definition (f)	Example
Complication with Comorbidity (or Risk Factor)	Like in worsening, the co-existence of two or more HIs facilitates the onset of a complication as an evolution of the overall patient's state.	A heart failure (A) associated with a renal failure (C) cause a condition of anasarca (B)

HIN Representation



TYPE OF EVOLUTION	DEFINITION (g)	EXAMPLE
Complication in presence of mutual exclusion between two transitions	The evolutions may be mutually exclusive: only one of the HIs can occur. In HIN the evolutions must be linked with the exclusive OR (XOR) logic operator by means of the semaphore node.	Obesity (A) can complicate with low back pain with radiation to the leg (B) or without radiation (C)
HIN REPRESENTATION		
		

simplify the graphical representation customized by a set of specific constraints specifically related to the clinical problem evolution. The HIN model is composed of the following two node types:

1) place, adopted to represent the following two primitives:
   a) HI, drawn as a circle and coded according to the definition of the ISO 13940:2015 standard [13];
   b) semaphore, depicted as an HI with the specific label "semaphore." In particular, this PN primitive is adopted to control the firing sequence and ensure the mutual exclusion between a set of possible concurrent HIs that can evolve from a given patient's health state.
2) transition, drawn as a bar and describes the evolutions between places.

Places and transitions are connected through directed edges that specify the path of the patient's health state. Detailed information related to both places and transitions is reported in data sheets that specify some features of the network, e.g.,: 1) define the main data that should be captured by a physician; 2) define the values that are able to identify an HI evolution. The HIN model also inherits from PNs the distribution of tokens over the places and their migration across HIs. Each place may contain a token that identifies whether the patient is affected by a certain HI in a precise period of time. In particular, each place can only contain one token at a time (one-bounded PN, or safe net). An HIN transition is enabled, if it can be fired, i.e., if there is one token at each input place and there is no token at each output.

The marking of the HIN at a precise moment of time, therefore, describes the patient's overall health state (active HIs) at that moment. Accordingly, the change in the health state caused by HIs' evolutions over time corresponds to the migration of the token/s across places through transitions. Each transition, which therefore points out a specific HI evolution, may only occur once. For this reason, the health state changes as each transition fires, so transitions are assigned in turn with a state that can only assume 0 and 1 values: Firing the transition causes the transition state to change from 1 to 0. See the Appendix for a mathematical formalization of the HIN model. The main set of evolutions in the HIN model is reported in Table II, which are depicted adopting the Snoopy software application [21]. These represent the building blocks of the HIN model, which can be combined to describe the evolution of the patient's health state over time.

The resulting graph can be analyzed by also considering the reachability graph in order to accomplish the following properties.

1) Reachability: the set of HIs that can be reached from a specific patient's health state.
2) Coverage: whether or not a specific HI is reachable from another specific HI.
3) Liveness: whether a given evolution of a health state can be enabled and by which health state or, as the opposite, for which health state/s it can never be reached.

Moreover, HIN also features the following main characteristics based on the PN formal model.

1) HIN is minimum: The graph is composed of only one place that represents an HI.
2) HIN can be composed of isolated places that depict clinical problems that are neither the evolution of nor evolve into another HI.
3) An HIN source place (i.e., no input edges) can be either an HI or a semaphore, whereas a sink place (i.e., no output edges) can only be an HI.
4) Between the two sets of place nodes (i.e., HIs) only one transition node (i.e., evolution) is possible. In other words, two HIs/sets of HIs cannot be connected through two different evolutions.
5) The initial and the final nodes of a path of an HIN graph are HIs. These nodes represent the evolutionary path that starts with the initial HI/s and ends with the final one/s.

Once the HIN model is defined and the initial marking (i.e., patient's health state at a given time) is set, the reachability graph can be determined. It captures all the possible occurrence sequences of the HIN graph, highlighting both the initial and the final HIs, as well as the intermediate set of HIs that may affect the patient, thus reconstructing how each health problem evolved over time. An example of an HIN graph, along with the reachability graph, is reported in Fig. 1 for a patient with an original stenosis of the sigma and a chronic renal failure that undergoes several complications.

Besides the forward navigation of the HIN graph, the concept of the inverse HIN model can also be introduced as a tool to represent, starting from a specific patient's health state, the original and the intermediate HIs through which to achieve such state, so as to work out the evolution of each HI and its relevant causes. In order to achieve this goal, the following steps have to be performed:

1) remove the recurrences [see case (a) in Table II];
2) remove the returning edges between a transition/evolution and a place/HI related to a complication or a comorbidity [see cases (c)/(e)/(f) in Table II];
3) remove the semaphores;

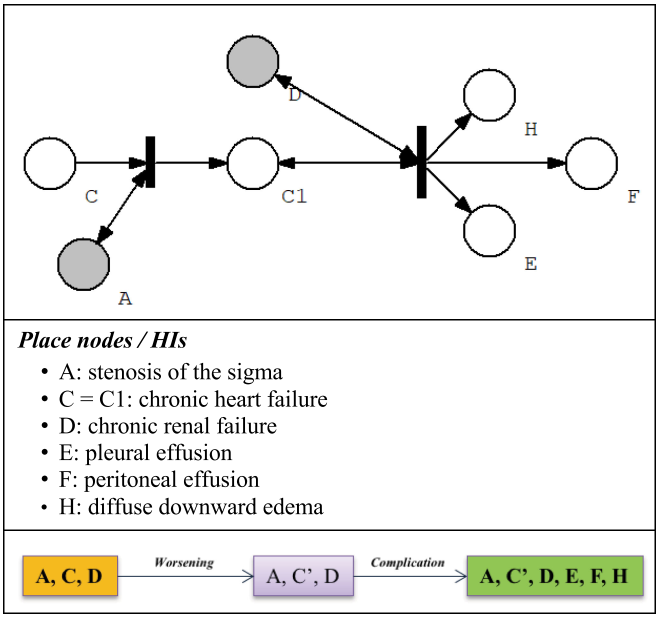


Fig. 1. HIN graph for a generic patient with colon- and renal-related issues (up); reachability graph (down).

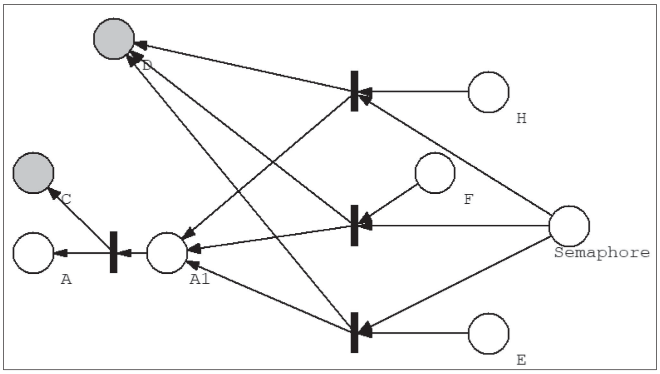
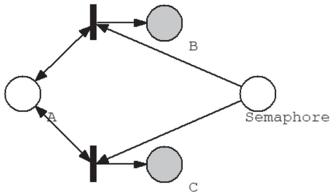
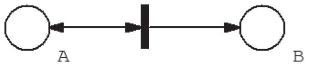


Fig. 2. Inverse graph of the HIN model reported in Fig. 1 (see also Fig. 1 for legend).

TABLE III
Comparison Between Evolutions for a Generic and a Specific Real Patient

Type of Evolution	Description
	HIN of a theoretical evolution for a generic patient. Obesity (A) can complicate by either a not radiated (B) or radiated (C) low back pain
	HINe for Patient 1: Obesity (A) is complicated by a not radiated low back pain (B)
	HINe for Patient 2: Obesity (A) is complicated by a radiated low back pain (C)

4) split the transitions with multiple outputs, featuring as many transitions as output nodes. Each new inverse transition only features one HI in input and as many outputs as the number of original inputs. A semaphore node is also linked to all new transitions;
5) reversing the direction of the remaining edges. Once the inverse HIN is defined, the reachability graph can be determined.

Starting from the original HIN described in Fig. 1, the inverse network is reported in Fig. 2. Note that due to the limited number of problems that can occur in a patient's life and considering that the HIN graph is safe (i.e., each place contains no more than 1 token), the reachability graphs of both direct and inverse HINs are finite.

The robustness and the expressive power of the HIN allow us to model not only the evolution of a generic patient's health state in a theoretical high-level situation on the basis of the physician's experience, but also to represent the clinical history of a specific real patient, for instance, extracting data directly from a problem-oriented electronic medical record system (POMR, see e.g., [9], [10], and [30]).

The models adopted to represent these two situations are designed to share the same primitives; however, in order to simplify this distinction, we denote the HIN of a real patient as HINe (where the "e" stands for exemplar). A clear difference between a network referred to as a real patient and a theoretical patient is the possibility, for the latter case, to represent alternative paths through the adoption of a semaphore. A real case describes instead an already occurred sequence of HIs and evolutions (i.e., transitions have already been fired).

In Table III, an example is described via the comparison of three different situations. In the first row, for a generic patient, a semaphore is deployed to capture two alternative evolutions that can occur starting from the same initial HI [the case (g) in Table II]. In the other rows, the two possible (and mutually exclusive) paths are reported by depicting two specific networks for two distinct actual patients, as obesity cannot be complicated by both radiated and not radiated low back pain at the same time: On the one side, Patient 1 only reports a transition from obesity (A) to a not radiated low back pain (B); on the other side, for Patient 2, obesity (A) is complicated by a radiated low back pain (C).

V. PNs at Use: An Example of a Clinical Exercise

Different learning objectives may be achieved using the HIN model to support students' clinical reasoning focused on the dynamic of HI evolution in the framework of a multimorbidity chronic patient. The following is not an exhaustive list of objectives.

1) To identify the relevant HI to evaluate possible evolutions in the health state of a patient with chronic conditions.
2) To develop hypotheses of possible evolutions of the health state, given a patient's condition.

TABLE IV
SELECTED CASE

The patient M. R. suffers also from hip arthrosis, arterial hypertension, and benign prostatic hyperplasia (BPH). He experienced several recurrent episodes of acute diverticulitis and, in the same period, he was operated for the BPH, that improved. On the contrary, in the same period the hip arthrosis worsened, and he was finally operated for a prosthetic implant. After this second operation, the patient developed a complication of the diverticular disease (a paracolic abscess), diabetes worsened, and the hip prosthetic implant got infected. Both paracolic abscess and the prosthetic infection were treated, and diabetes control improved. No evolution occurred instead for the co-present arterial hypertension.

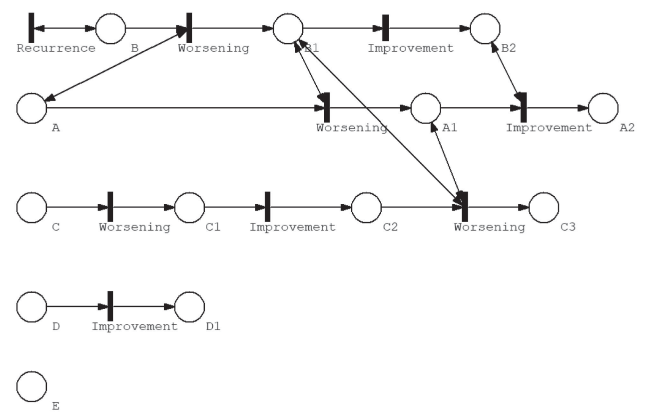
3) To identify the evolutions over time of an HI along with their correlations in a patient with a chronic multimorbidity health state.
4) To identify the possible concurrent causal factors of the worsening of an HI in a patient with a chronic multimorbidity health state.
5) To check the evolution of a specific HI in a patient with a functional deficit and/or disabilities.

On the basis of a patient's clinical history, these kinds of objectives can be translated into learning questions and related exercises, such as the following.

1) What is the role of this specific HI in the overall evolution of this clinical case?
2) What are the direct evolutions of this specific HI?
3) Where did this specific HI originate from?
4) What caused this specific HI to worsen?
5) Starting from this specific HI: Where did it originate from? Which are the possible health state evolutions in the future? Which HIs could possibly influence the health state evolution in the future?

To design and produce a clinical exercise, the first step is to extract a set of real clinical cases from a database of POMRs, with the method based on HIN and reported in [39]. This method allows us to describe with an HIN the features of the cases (for example, patients with diabetes that evolved into one from a set of possible complications), according to the established learning objectives, and then perform a semiautomated search in the database. The second step is to select a case (anonymized) from those retrieved from a POMR and describe it as an HINe (together with the data sheets). This HINe will include the same HIs and evolutions of the HIN used to search the database, but it will be richer in details because it models a real case, possibly with more HIs than those originally considered. This formal description is the basis of a dynamic display of the clinical case in a simulation environment and of the computer-assisted assessment of the performance of the learner.

The following example, represented in Table IV by means of a clinical vignette [8], shows the process and some possible exercises supported by the HINe model. In this example, the teacher stated the learning objective as "to predict, identify and manage the evolution of colonic diverticular disease in a patient with type 2 diabetes." An HINe is designed, which represents the HI "diverticular disease" that, via an evolution "complication," turns into "complicated diverticula disease." An HI "type 2 diabetes mellitus" is copresent. The teacher chooses a case among the retrieved and represents it with an HINe (together with the data sheets). In the selected case, the patient not only has the requested HIs, but he also suffers from hip arthrosis, arterial hypertension, and benign prostatic hyperplasia (BPH; see Table IV).



Place nodes / HIs

- A / A1 / A2: T2DM
- B / B1 / B2: non-complicated/complicated/ operated diverticular disease
- C / C1: left hip arthrosis
- C2: operated left hip arthrosis
- C3: infection of hip prosthesis
- D / D1: symptomatic / operated benign prostatic hyperplasia
- E: arterial hypertension

Fig. 3. Case of the evolution of colonic diverticular disease in a patient with type 2 diabetes.

The HINe model of the case selected is shown in Fig. 3. Any clinical exercise starts with the availability of a summary of clinical information about the patient. The detailed information is linked to each HI and evolution. The students act in a simulation environment in which they can observe the HIN according to different time scales, access the detailed clinical information, draw an HIN, and do the exercises.

Different kinds of clinical exercises can be designed for the case presented in Fig. 3, such as the following.

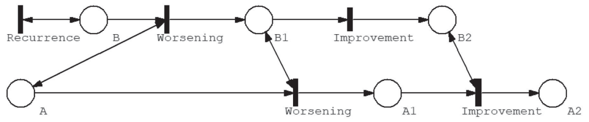
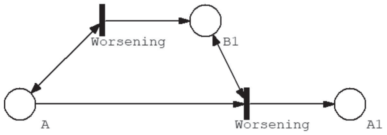
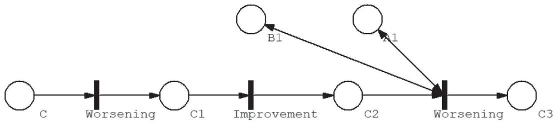
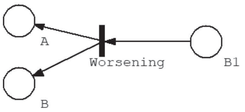
1) The learner analyzes the complete HINe or a subset of it.
2) The HIN with missing HIs and/or evolutions is shown, and the learner is called to answer questions.
3) The learner must draw part of the HINe—or even the whole HINe—starting from the provided clinical information or the full medical record.

The expected value of the model is to enhance clinical reasoning by providing an overall view over the time of a patient's history, with a visual display of the evolutions and the correlations among the HIs. Table V lists some possible questions to be answered by the students, to whom the full or partial HINe is shown. The second column of the table shows how the properties of PN are used to assist the teacher in the generation of questions as well as in the assessment of the learner's performance.

TABLE V
EXAMPLES OF POSSIBLE QUESTIONS BASED ON A CASE STUDY IN HINE

QUESTION	METHOD OF ANALYSIS	ANSWER
To identify the relationship between diverticular disease and diabetes	Analysis of the path of the reachability graph with the initial health state as initial marking: forward research of the evolutions linked to diverticular disease and diabetes	The diverticular disease is co-morbidity for diabetes: first time → worsening; second time → improvement The diabetes is co-morbidity for diverticular disease: worsening
To identify the co-morbidities that caused the diabetes to worsen	Analysis of the path of the reachability graph with the initial health state as initial marking: forward searching of the worsening evolutions with diabetes as input	Worsened into type 2 diabetes, complicated by a diverticular disease
To identify the co-morbidities that produced an improvement of the operated benign prostatic hyperplasia	Analysis of the path of the reachability graph with complete initial marking: forward searching of the improvement evolutions with diverticular disease and diabetes as input	No health issue as co-morbidity
To identify the path that led to the infection of the hip prosthesis	Analysis of the path of the reachability graph of inverse graph with the initial marking only comprising the infection of the hip prosthesis. Path starting from the infection of the hip prosthesis	Complication from operated left hip arthrosis with co-morbidities type 2 diabetes and complicated diverticular disease
To identify the forward and backward paths of complicate diverticular disease	Forward path: analysis of the path of the reachability graph with the initial health state as initial marking	Forward path: operated diverticular disease
	Backward path: analysis of the path of the reachability graph of the inverse graph with the initial marking only comprising the complicate diverticular disease	Backward path: uncomplicated diverticular disease and diabetes as morbidity

TABLE VI
ANSWERS IN THE FORM OF AN HINE GRAPH TO THE QUESTIONS PRESENTED IN TABLE V (SEE FIG. 3 FOR LEGEND)

1		
2		
3		
4		
5	Forward Path 	Backward Path 

If the questions allow multiple choice, the analysis of the HINe allows the computer-assisted generation of the right and wrong answers; if the task is the completion of the HINe or the drawing of a subnet of the HINe, the assessment of the distance between the original HINe designed by the teacher and the learner's response is possible. Table VI shows the answers to the questions listed in Table V, which are displayed in the HINe graphical format.

VI. CONCLUSION AND FUTURE PROSPECTS

In this article, the HIN approach was introduced as a suitable way to support the formal representation of a patient's clinical history. This approach helped students improve their competence in clinical reasoning in terms of health state evolution over time and complexity of HI interactions (e.g., comorbidities), which sometimes remain as hidden knowledge in the textbooks.

More specifically, it supported them in learning how to manage disease in its dynamics through the identification of the types of relationships between health state conditions. In this way, students were supported in reasoning about the interactions between HIs in the presence of diverse concurrent physiopathology processes, thus learning to deal with the complexity of a patient's clinical path [48].

At present, the model and its implementation still have some limitations. First, if the clinical case is very complex (i.e., many HIs, many evolutions, many interactions, a long time span), even if from the conceptual point of view there is no limit to the size of the net, a student could hardly grasp the sense of the whole clinical history dispersed through too many details. Nevertheless, it is the teacher's choice—as the author of a specific HIN—to make overt the implicit knowledge hidden in the pathophysiology of a complex clinical situation, with the level of granularity the teacher considers as an optimum, from the educational point of view. We are developing a set of indicators and methods to compute the complexity of an HIN, in order to provide the teacher with a metric.

A second limitation is that psychological and socioeconomic issues can hardly be represented. We are working with a team of clinical psychologists and social workers to find the best way to include this dimension in the model.

Based on these premises, HIN models the patient's clinical history using the formalism of directed graphs represented by the PNs, whose properties are particularly apposite for the graphical representation of HIN evolutionary paths. Moreover, the PNs' underlying mathematical model HIN allows users to draw coherent and well-formed graphs representing rather complex clinical cases. Finally, HIN can be easily integrated into a simulation environment to support CBL activities and assessment. The examples of the exercises provided in this article show, on the one hand, the application of this robust methodology; on the other hand, they outline the variety of learning questions that may be dealt with when using the proposed approach.

As mentioned before, the development of the HIN model is embedded in a larger set of research and testing activities. A laboratory was organized in the first place within the National Congress of the Italian Society for Medical Education, held in Naples in October 2019, to showcase and validate the basic principles of HIN with physicians and healthcare professionals. Currently, HIN has been adopted in classes within the Medicine Department of the Sapienza University of Rome [29]. It has also been introduced as an innovative didactic method in the Department of Public Health as well as in the Department of Veterinary Medicine and Animal Productions of the "Federico II" University of Naples [43].

Feedback deriving from these didactic practices allowed us to continuously finetune our approach, leading us to develop and deploy the first version of fHINscene, a software learning environment with an end-user interface that makes use of a diagrammatic representation of the patient's clinical history (f-HIN model). The main functionalities of fHINscene are the following:

1) draw a clinical history;
2) verify that the HIN graph respects all the characteristics of a clinical history;
3) compare two HIN graphs representing the same clinical history.

The f-HIN model is based on the same mathematical properties as the HIN model, and therefore the f-HIN diagram and the HIN graph are "equivalent," as they are based on a few simple rewriting rules. The characteristics and main functionalities of fHINscene have been introduced and extensively described in [33].

In parallel, HIN was already tested [40] as a tool to query problem-oriented EHRs (POMRs) so as to support tutors/teachers in the detection of real cases following the CBL approach. Additional research activities are being planned to complete the development of the educational platform to support the retrieval of clinical cases from EHRs, as well as the development of exercises that may use a verbatim description and/or a graphical one. We also intend to develop a simulation environment for students, where they can manage their portfolios of cases autonomously, so as to check their acquired skills, also through self-evaluation activities, according to the principles of the deliberate practice model [49].

The next steps of our research on the more formal topics will therefore focus on the following:

1) the definition of a thorough algebra for the management of HIN models;
2) the definition of an algorithm for extracting clinical history views for multimorbidity patients;
3) design of a computer–aided design environment to assist the extraction and modeling of data from general practitioners EHRs not compliant with the POMR features.

APPENDIX
FORMALIZATION OF THE HIN MODEL

The HIN model is based on the formalism of PNs, in particular predicate/transition (P/T) networks, which extend the place/transition notation [29], [35], [38], augmented by some constraints related to the clinical problem evolution. A straightforward presentation is shown here.

Definition 1: The PN related to HIN (called *HN net*) is a four-tuple: $\mathrm{HN} = < \mathrm{P, T, In, Out} >$
where

1) P is a finite set of place nodes;
2) T is a finite set of transitions nodes, with $\mathrm{T} \sqsubseteq \mathrm{P} \times \mathrm{P}$;
3) In: $\mathrm{T} \rightarrow 2\mathrm{P}$, the places as input of a transition;
4) Out: $\mathrm{T} \rightarrow 2\mathrm{P}$, the places as output of a transition.

Definition 2: Let $\mathrm{HN} = < \mathrm{P, T, In, Out} >$ be an HN net. The *transition state* (st) is described as follows:

$$\mathrm{st} : \mathrm{T} \rightarrow \{0,1\} \subset \mathbb{N}.$$

The HN net is based on the following axioms:

1) P and T are two disjoint sets: The HN net is a bipartite graph.
2) The places set is composed of a partition of HIs and semaphores: $\mathrm{P} = < \mathrm{H} \cup \mathrm{S} >$.
3) The semaphore nodes are the only source nodes, and each semaphore is connected to at least two different transitions.
4) Each transition features at least one HI place node in input and one HI place node in output; there is also the possibility that the input and the output place nodes are the same (recurrence).
5) There is one and only one path that connects a couple of place nodes.
6) The initial value of the transition state is always 1. When the transition is fired, the value of the transition state turns to 0.

Corollary 1: Only HI place nodes can be isolated nodes.

Definition 3: Let $\mathrm{HN} = < \mathrm{P, T, In, Out} >$ be an HN net. The *marking* is described as follows:

$$\mathrm{M} : \mathrm{P} \rightarrow \{0,1\} \subset \mathbb{N}.$$

Corollary 2: The HN net is a one-bounded (safe) PN.

Definition 4: The *marked* HN is a five-tuple

$$\mathrm{HNM} = \langle \mathrm{HN}, \mathrm{M} \rangle = \langle \mathrm{P}, \mathrm{T}, \mathrm{In}, \mathrm{Out}, \mathrm{M} \rangle$$

where HN is the HN net and M is the marking.

The transition from one marking to another in an HN net occurs by firing a well-defined transition; as any PN, the execution of PNs is nondeterministic: When multiple transitions are enabled at the same time, they may fire in any order; however, a transition can fire one per time. A firing can occur at any time and is considered to be instantaneous. The new marking is provided as follows.

Definition 5: Let HNM $= <$ HN, M $>$ be a marked HN. The *next marking function* (dm), which takes into account the marking Mk and the firing of t_j, is

$$\mathrm{dm}: \mathbb{N}^{|P|} \times T \rightarrow \mathbb{N}^{|P|}$$

or

$$\mathrm{dm}\left(M^k, t_j\right) = M^{k+1}.$$

where

1) M^k is the marking before the firing;
2) M^{k+1} is the marking after the firing;
3) $t_j \in T$ is the transition fired.

Starting from the M^k marking, the M^{k+1} marking after t_j is fired, thanks to the next marking function, is

$M^{k+1}(p_r) = \mathrm{dm}(M^k, t_j) = M^k(p_r)$:
if $(p_r \notin \mathrm{In}(t_j) \wedge p_r \notin \mathrm{Out}(t_j)) \vee (p_r \in \mathrm{In}(t_j) \wedge p_r \in \mathrm{Out}(t_j))$,
$M^{k+1}(p_r) = \mathrm{dm}(M^k, t_j) = 0$:
if $p_r \in \mathrm{In}(t_j) \wedge p_r \notin \mathrm{Out}(t_j)$,
$M^{k+1}(p_r) = \mathrm{dm}(M^k, t_j) = 1$:
if $p_r \notin \mathrm{In}(t_j) \wedge p_r \in \mathrm{Out}(t_j)$.

where $p_r \in P$ is the generic place node of the net.

Definition 6: Let HNM $= <$ HN, M $>$ be a marked HN. The *next state function* (ds), after the firing of t_j, is:

$$\mathrm{ds}: \mathbb{N}^{|T|} \times T \rightarrow \mathbb{N}^{|T|}$$

or

$$\mathrm{ds}\left(\mathrm{st}^k, t_j\right) = \mathrm{st}^k + 1$$

where:

1) st^k is the state before the transition;
2) st^{k+1} is the state after the transition;
3) t_j is the transition fired.

The st^{k+1} transition state after $t_j \in T$ fire, thanks to the next state function (starting from the st^k), is

$$\mathrm{st}^{k+1}(t_r) = \mathrm{ds}\left(\mathrm{st}^k, t_j\right) = 0$$

$$\mathrm{if}\left(t_r = t_j\right) \wedge \left(\mathrm{Out}\left(t_j\right) \neq \mathrm{In}\left(t_j\right)\right).$$

$$\mathrm{st}^{k+1}(t_r) = \mathrm{ds}\left(\mathrm{st}^k, t_j\right) = \mathrm{st}^k(t_r)$$

$$\mathrm{if}(t_r \neq t_j) \vee \left(\mathrm{Out}\left(t_j\right) = \mathrm{In}\left(t_j\right)\right).$$

Firing rules: Let HNM $= <$ HN, M $>$ be a marked HN. A transition t_j is enabled, if the following conditions are satisfied:

1) $\mathrm{st}(t_j) = 1$;
2) $\forall p_k \in \mathrm{In}(t_j)$: $M(p_k) = 1$;
3) $(\exists p_k \in \mathrm{Out}(t_j) – \mathrm{In}(t_j)$: $M(p_k) = 0) \vee (\mathrm{Out}(t_j) = \mathrm{In}(t_j))$.

This means that a transition is enabled if

1) the transition has not been fired and, consequently, its state is 1.
2) each input place of the transition contains one token, and at least one output place does not contain tokens, or all input places are all output places (i.e., recurrence).

Definition 7: Let HNM $= <$ HN, $M^0 >$ be a marked HN, the *set of reachable markings* from the M0 marking is

$$\mathrm{RG} = \left\langle T, \mathbb{N}^{|P|}, M^0 \right\rangle$$

where

1) T is the edge set, composed of the HN transitions so that the direct edge allows the shift from the marking M^i to the marking M^j, thanks to the transition t_k: $M^j = \mathrm{dm}(M^i, t_k)$;
2) $\mathbb{N}^{|P|}$ is the places set, which is composed of the marking of the HNM. M^0 is the initial marking.

Corollary 3: Let HNM be a marked HN, the set of reachable markings is a finite graph.

Reachability (given an HN, if it is possible to obtain a well-defined marking) is a hard but decidable problem [17], and therefore, it is possible to find the necessary conditions to reach a state, or to demonstrate that these conditions cannot be met. When the reachability graph is finite and the dimensions of an HIN graph are not very large, the problem is simple to solve.

Definition 8: Let HN $= <$ H $\cup$ S, T, In, Out $>$ be an HN net, where the following specific nodes are defined.

1) $T_a = \{ t_h \in T \mid \mathrm{In}(t_h) = \mathrm{Out}(t_h) \}$ indicates transitions that describe recurrence evolutions.
2) $H_{ci} = \{p_k \in H \mid \forall t_h \in T – T_a, p_k \in \mathrm{In}(t_h) \wedge p_k \in \mathrm{Out}(t_h) \}$ indicates places that are inputs of a complication evolution.
3) $T_m = \{ t_k \in T \mid |\mathrm{Out}(t_h)| = k > 1\}$ indicates HN transitions with multiple (*k*) output node places.

Definition 9: Let HN $= <$ H $\cup$ S, T, In, Out $>$ be an HN net as defined in Definition 8, and the *inverse HNI net* is the 4-ple

$$\mathrm{HNI} = \langle H \cup S_i, (T \cup T_n) - T_m - T_a, \mathrm{In}_i, \mathrm{Out}_i \rangle$$

where:

1) $T_a = \{t_h \in T \mid \mathrm{In}(t_h) = \mathrm{Out}(t_h)\}$ indicates HN transitions that describe recurrence evolutions;
2) $T_n = \{t_k \in T_u \mid \forall\, t_h \in T_m\ \forall\, h_j \in \mathrm{Out}(t_h)$: $\exists! t_k \notin T\}$ indicates the set of k transitions ($T^1{}_n \ldots T^k{}_n$) derived from the split of T_m, where $T_n \cap T = \emptyset$ and T_u is the transitions universe. Each T_n transition features: a) one specific output place node of T_m, as input node; b) all input place node(s) of T_m, as output node(s);
3) S_i indicates the new semaphore nodes as inputs to the new T_n transitions that have split the T_m transitions; one semaphore S_i is defined for each deleted transition T_m, i.e., $S_i = \{s_k \in S_u \mid \forall\, t_h \in T_m : \exists! s_k \notin S\}$, where $S_i \cap S = \emptyset$ and S_u is the semaphore universe;
4) gt is a function that associates each deleted transition T_m with the corresponding set of new transitions T_n, i.e., gt: $T_m \rightarrow 2^{Tn}$, where: $\mathrm{gt}(t_k) = \{t_h \in T_n \mid \mathrm{In}(t_h) = \mathrm{Out}(t_k)\}$;

5) gs is a function that associates each deleted transition T_m with the corresponding new semaphore, i.e., gs: $T_m \rightarrow S_i$, where the constraint is: $|S_i| = |T_m|$;
6) $In_i =$
   - ○ $In_i |_T = Out$
   - ○ $In_i |_{Tm} : T_m \rightarrow 2^{H \cup Si}$

with $In_i\ (t_k) = \{\ h_j \in H|\ \forall\ t_h \in T_m,\ t_k \in gt(t_h)\text{: } \exists!\ h_j \in Out(t_h)\}$ $\cup \{s_j \in S_i\ |\ \forall\ t_h \in T_m,\ s_i = gs(t_h)\}$;

7) $Out_i =$
   - ○ $Out_i |_T = In$
   - ○ $Out_i |_{Tm} : T_m \rightarrow 2^H$

with $Out_i\ (t_k) = In(t_h)$,
where $t_h \in gt(t_k)$.

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