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# Comorbidity: a multidimensional approach

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**Comorbidity represents an extremely complex domain of research. An individual entity, the patient, is the center of gravity of a system characterized by multiple, complex, and interrelated conditions, disorders, or diseases. Such complexity is influenced by uncertainty that is difficult to decipher and is proportional to the number of associated morbidities. Computational scientists usually provide meta-analysis studies aimed at integrating various types of evidence, but in our opinion they may help reformulate comorbidity by emphasizing, in particular, two aspects: (i) a systems approach, which allows for an ensemble view of comorbidity, and offers a model representation generalizable to multimorbidity; and (ii) a dynamic network inference approach, which is indicated for the analysis of links among morbidities and evaluation of risk. Notably, the main question remains whether such instruments suggest a shift of paradigm providing prospective impact on medical practice. We have identified in the simultaneous consideration of multiple dimensions linked to comorbidity complexity the rationale for such translation.**

## Comorbidity: what definition?

Comorbidity addresses the concomitant occurrence of different medical conditions or diseases, usually complex and often chronic, in the same patient. Defining comorbidity is not immediate. A definition available from the US National Library of Medicine (http://www.nlm.nih.gov/mesh/MBrowser.html) refers to 'the presence of co-existing or additional diseases with reference to an initial diagnosis or with reference to the index condition that is the subject of study…'.

Although aging is naturally inherent to comorbidity, whose role is central within a specific disease context [1], other factors too can offer a wide spectrum of possible characterizations. Examples of comorbidity studies are many, often referring to chronic obstructive pulmonary disease (COPD) [2–5], obesity [6], mental disorders [7], immune-related diseases [8], cancer [9], just to mention a few. Reviewing such studies is not the goal of this work, despite their stimulating interest; rather, such studies also emphasize weaknesses, and these are of greater interest here. For example, the use of selected cohorts with specific sample sizes is a matter of concern, which explains why biases are thus generated. Apart from such limitations, all conditions such as frailty, immunological changes, inflammation, and infections represent a huge concern for both patients and doctors, and for healthcare in general. This introductory illustration offers sufficient rationale for our analysis.

## Representation

A coarse mapping of comorbidity is shown in Figure 1. The top panel (reproduced from [10]) casts comorbidity in a disease space (left plot), from which to infer disease relationships. A coordinate system with clinical and molecular data leads to a patient disease network (right plot) in which to assess the associations (links) between the diseases (nodes). The bottom panel lists some of the bottlenecks affecting the complexity of the systems. Consequently, the possibility of discriminating between causality and correlation remains highly uncertain and thus difficult to quantify.

Figure 2 proposes a view centered on the concept of time. Seen sequentially, and in relation with the occurrence of events, time allows for a remodulation of the comorbidity map based on the changes of conditions induced by the events. Apart from aging, also environmental factors, stress, infections, therapeutic interventions, unexpected side effects, or adverse interactions between drugs and

### Glossary

**Perturbation phase**: characterized by the occurrence of events that cause deviation from stationarity of the system and require interventions.
**Return to stationarity phase**: characterized by restoration of stationarity, when the impact of changes are assessed.
**Risk-driven inference**: refers to the predictive approach, based on risk factor evaluation and predictive modeling. How can the risk be accounted to determine the prediction of trajectories in comorbidity maps, and with what confidence networks help estimating them?
**Time space-driven inference**: refers to the intervention approach, based on state space model representation. Does differential network analysis suggest testable hypotheses for optimal intervention strategies?
**Topology-driven inference**: refers to the diagnostic approach, based on topology properties and modularity of the map. Do network configurations support diagnostics? How?
**Transition phase**: characterized by uncertainty during which stabilization of conditions is pursued through therapies. The comorbidity map may significantly change in relation to newly established functional interdependencies between conditions.

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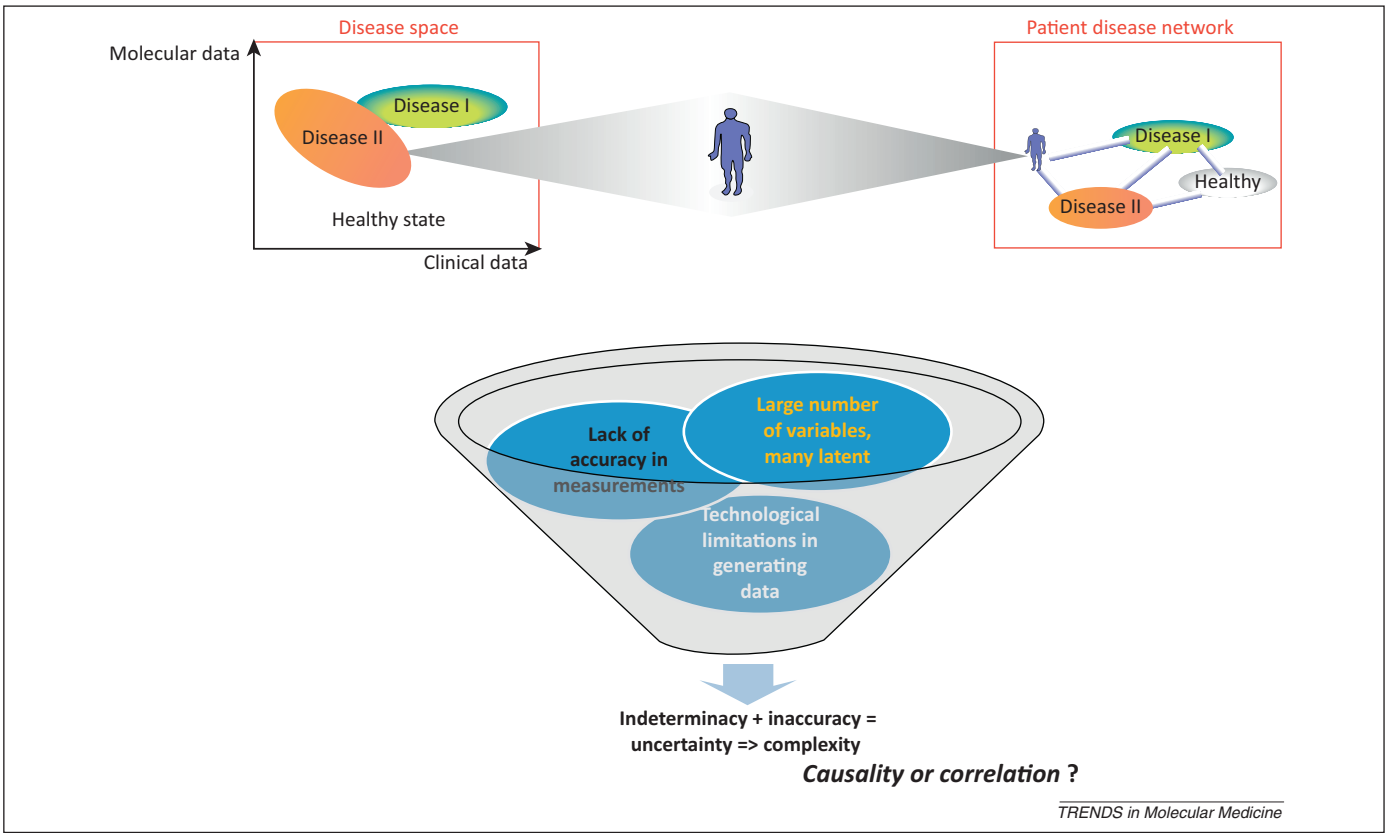


**Figure 1**. (Top) The 'patient disease network' generates a space of multiple interactions depending on the relationships in the disease space. (Bottom) 'Exogenous factors' exist as sources of uncertainty and complexity.

diseases are crucial events. With frailty, for example, data correlating and integrating different contexts, from personal to environmental and social, are fundamental to model the complex nature of a pathological episode, and the consequences directly on such condition and its related comorbidities. Correspondingly, the impact of clinical frailty, an age-related vulnerability state created by loss of physiological reserve, remains difficult to assess. Once a time horizon has been established, transient or persistent contributions to the comorbidity map by each condition can be determined based on the changes observed in their relationships (usually measured by weights assigned to the connectivity links).

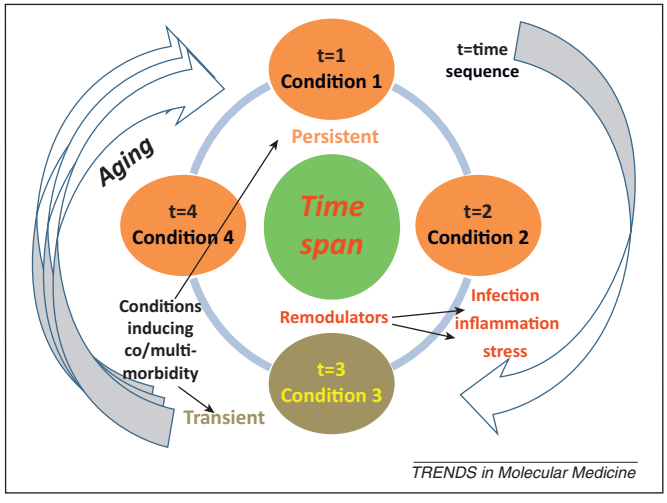


**Figure 2**. The 'time sequence' (outer circle) indicates the evolution of the comorbidity map through the concatenation of events. The 'time span' indicates the horizon, differentiated between transient or persistent contributions to comorbidity, coming from each disease, and associated with the global map remodulators (such as, acute events).

## Insight from a multidimensional approach

Two dimensions clearly appear insufficient to explain the entire disease space relationships (e.g., the space complexity). In patient disease networks, the role played by time is crucial as both the diseases and their 'connectivity strengths' can change. A systemic 'endogenous' uncertainty exists in relation to time, then amplified by exogenous factors augmenting such uncertainty, and offering a representation of the overall space complexity. Owing to heterogeneous measurements and interdependence among variables, perturbations of systems (see Glossary) can trigger a wide range of dynamics at both local and global scales. Locally, the effects would be referring to just a limited number of components of the comorbidity map; globally, the effects would be determining a diffuse impact.

Notably, a certain degree of remodulation observed in response to factors perturbing the comorbidity conditions would then be measurable in terms of risk referred to identified factors, severity with regard to acute versus non-acute states, responsiveness in relation to treatment, pathway activation versus inhibition, and possibly other variables (see, for example, [11] for the analysis of patient management-related aspects, and also related work on predictive, preventive, personalized, and participatory, P4, medicine in [12] and [13]). In principle, complex biological systems operate in time space, but how they work is often poorly understood. A multidimensional approach to

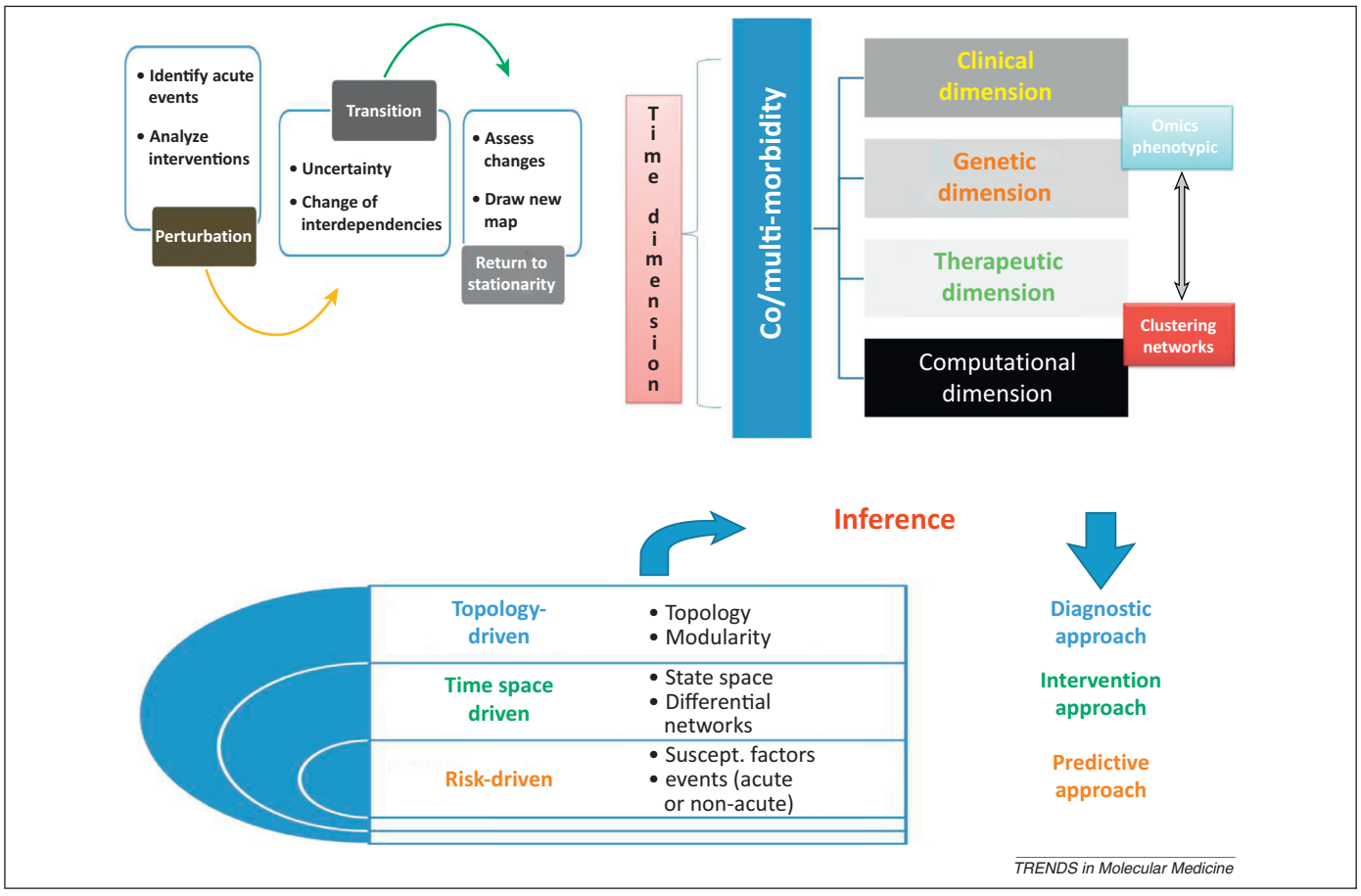


**Figure 3.** (Top-left plot) 'Perturbation, Transition and Return to Stationarity phases'. (Top-right plot) 'Dimensions' contributing to shape comorbidity or multimorbidity maps. (Bottom plot) Characterization of inference according to a variety of approaches based on topology, time space, and risk-driven factors.

comorbidity maps thus seems a natural framework for inference approaches aimed to decipher part of the complexities [14].

The 'clinical dimension' is the paradigm of such complexities, involving diagnostics as well as intervention strategies (treatments) in response to changing conditions and cascade effects of the system. Apart from prevention management in non-acute states, the acute cases present the challenging condition of a system observed in transition between stationary, non-stationary, and possibly newly stationary states (Figure 3, top-left plot).

Stationarity reflects the equilibrium of the system (patient homeostasis). Each disease refers to the clinical dimension, also depending on its contribution to comorbidity. For example, loss of functions might be induced, and related treatments undertaken, but other dimensions must be integrated (Figure 2, top-right plot). The 'therapeutic dimension' aims at restoring stationarity. However, it may also add further complexity depending on the positive/negative effects of interventions (especially with regard to pharmacological interactions in terms of unexpected side effects of different degrees, and adverse interactions between drugs and diseases).

In general, the 'genetic dimension' also affects stationarity, and in a dynamic way. Expression levels, pathway activation/inhibition, and epigenetic influences are often altered by disease mechanisms, susceptibility, and risk factors (e.g., diabetes is a risk factor for death and a comorbidity enhancer through augmented cardiovascular risks; chronic inflammation is involved with major health conditions, from heart diseases to COPD and Alzheimer's disease; aging is a major risk factor for all chronic diseases).

In particular, regulation by common pathways at the genetic scale may suggest diagnostic tests and therapeutic strategies for targeting the molecular causes of several associated diseases. The 'omics dimension' extends the genetic one by integrating evidence elucidating multiple common causes behind comorbidity, and by functionally characterizing it. Functional analysis based on gene sets can explain the crossover influences between different conditions. The question to address is thus what degree of functional overlap can be observed. The molecular relationships between diseases involve genome, epigenome, proteome, interactome, metabolome and other omics layers [15,16].

Although, in principle, causal influences should be separated from simply correlative ones based on propagation or cascade effects, in practice causality is very difficult to detect, and requires ad hoc inference to test the underlying hypotheses. The 'computational dimension' thus aims to embrace all the complexities related to the other dimensions by a variety of inference approaches (Figure 3, bottom). We reserve the last part of our study to the analysis of this topic.

## Complexity of the clinical dimension

### COPD

Commonly associated with comorbidities such as hypertension, diabetes, heart failure, ischemic heart disease, cancer, osteoporosis, depression, and anemia, one main difficulty with COPD is defining causality relatively to the coexisting conditions (see, for example, [3,2,17]). Comorbidity was identified as an independent predictor of mortality in several studies, and among them: an evaluation [18] of the USA National Hospital Discharge Survey with an analysis of 47 million hospital discharges for COPD from 1979 to 2001 in adults >25 years of age; a study of 135 patients hospitalized with acute exacerbation of COPD [19]; the use of administrative databases involving 71 130 patients [20]; earlier work [21] showing the prognostic role of comorbidities in COPD from a cohort of 270 patients.

COPD is an independent risk factor for cardiovascular disease, as suggested by epidemiological evidence and by a longitudinal population-based study [22] showing association between poor lung function and increased risk of cardiovascular mortality. COPD is also a risk factor for lung cancer [23]; further support to such association comes from the Copenhagen City Heart Study [24]. In some comorbidity associations, for example, with atherosclerosis, ischemic heart disease, and stroke, the underlying mechanisms linking COPD are uncertain. However, a role may be played by persistent systemic low-grade inflammation measured by increased circulating cytokines, chemokines, and acute phase proteins (i.e., C-reactive protein), or by abnormal circulating cells (see [4]), a key factor leading to plaque formation [25]. In addition, anemia has been shown to be an independent risk factor for increased mortality in COPD patients [26].

A key factor is drug interactions, particularly in elderly patients with COPD receiving an increasing number of drugs, often in doses that cannot be reduced. Reference, for example, goes to the interaction between selective β-blockers and β2-agonists, whose effects are central to several clinical studies [27–31]. Two important developments involve effective anti-inflammatory treatments aimed at both COPD and systemic inflammation, thus treating the patient at the whole comorbidity scale (e.g., by elucidating corticosteroid resistance molecular mechanisms), and dealing with accelerated aging (through knowledge of the molecular pathways), thus leading to new therapeutic targets, that is, sirtuin 1 and peroxisome proliferator-activated-γ co-activator 1α [32].

The COPD landscape is particularly complex, with some of the conditions that are persistent and other ones only transient, for example, in the presence of systemic inflammation. Therefore, the temporal dimension is crucial for assessing the COPD evolution, in association with the therapeutic dimension.

### Cancer

Comorbidity and cancer form a high-impact domain. Despite that concurrent and etiologically independent chronic health conditions can appear unrelated to cancer, a certain influence is expected to be exerted on treatment strategies and survival rates. In general, when specific cancer therapeutic options cannot be undertaken due to associated comorbidity conditions, the effect is an increased risk of dying of cancer. Vice versa, the risk of dying from comorbidity conditions can increase for patients subject to cancer treatment. In particular, recent studies [8,33,34] showed associations between specific comorbid conditions and breast cancer (BC), considering, for example, hypertension, cardiovascular disease, diabetes mellitus, COPD, and also previous cancer. A review of 18 studies covering the past 10 years allowed to verify that: (i) comorbidity at early BC diagnosis is an important prognostic factor regardless of stage and age; (ii) social and ethnic inequalities are factors relevant to survival; and (iii) effects of BC treatment need to include the severity of the conditions.

The role of comorbidity in such studies was assessed based on the effect of adjuvant treatment and age in early BC patients (cohort of 62 591 women diagnosed within 1990–2008, and with treatment information for 39 943, with 7–40% of comorbidity incidence depending on age) [33,34]. Comorbidity represented an adverse prognostic factor for BC-related death, varying by age at diagnosis and by treatment. Limitations were also pointed out, concerning selection bias (no treatment information for 36% of the cohort), severity of conditions (same weight adopted in the comorbidity index), absence of confounders (associated with weight, alcohol, etc.) related to life style, such as environmental aspects, psychological profile, disease/treatment coping (stress management), family/social support.

In particular, in cancer–comorbidity combined studies, establishing comorbidity levels, or states, can thus be very relevant. Such stratified construction requires consideration of a series of factors, such as: (i) the impact of the severity of conditions, due, for example, to the occurrence of acute events, that is, infections; (ii) the effects of treatments (toxicity from individual drugs or their interaction, exacerbation of some conditions versus improvement of others, temporary versus persistent therapies); (iii) the role of confounders related to life style, such as environmental aspects; and (iv) the prediction power embedded in the comorbidity state, in relation to mortality, for example, but also to both functional decline and quality of life.

All such factors are particularly important for risk assessment purposes, as they allow to determine a range of prognostic paths associated with comorbidity states. Maps of risk associated with comorbidity and cancer could thus be drawn and characterized according to cancer type.

### Immunology

The complexities of the innate and adaptive immune response generate a large number of connections with all the organs at the signaling pathway, cell and tissue scales, and complicate the diagnosis of many autoimmune diseases, including those still to be diagnosed as impaired immunity conditions and comorbidities. These pathological states are often characterized by immune tissues populated with differently or less functional immune cells, known to produce qualitatively and quantitatively abnormal populations of cytokines.

Immunology refers to two distinct inflammatory components with a role in various comorbidities. The first component is the metabolic-related inflammation, which

appears in metabolic diseases, such as obesity and type 2 diabetes, and has inhibitory effects on insulin action through inflammatory kinases in metabolic tissues (e.g., adipocytes) [35,36]. Evidence was found [37] that Toll-like response, which is part of the innate immunity, is also involved. A second component is a chronic low-grade inflammation which accompanies aging, and is also characterized by the remarkable weakening of the immune response in the elderly (immune senescence). Therapies may trigger exaggerated pathogen-specific immune responses that threaten a patient's life (an example is given by the immune reconstitution inflammatory syndrome – IRIS [38]).

Overall, inflammation is likely to be an underlying yet pervasive condition in many comorbidity maps, varying with time, assuming different states, and driving comorbidity dynamics. This applies to atherosclerosis and associated cardiovascular diseases, for which inflammatory biomarkers are investigated [39], and also to cancer microenvironment, representing a paradigm of such associations.

## Computational framework

The standard analysis involves some indices as a first step. Correlation and risk measures have been widely used in comorbidity studies, and it is always the type and frequency of disease that determine the outcomes. Additionally, biases arising when measuring the interdependence between diseases and their corresponding variability should be considered and estimated. In [40], comparative evaluation of comorbidity indices was combined with an assessment of cancer site-specific condition weights. Indicators for cancer site (lung, prostate, colorectal), gender, and stage were used as explanatory variables, and allowed to interact when modeled. Criticism involved multicollinearity among comorbid conditions, which can generate instability of the individual condition weights (variability by cancer site). As a result, maintaining the attention focused on the magnitude and predictive value of the global comorbidity index was the final suggestion. Previously, an early review in [41] defines and describes in detail the most popular indices, stimulating the following critical questions.

- Does comorbidity represent a global burden, or is it required that just some of its components are considered to establish an impact?
- How the cumulative effects of comorbidities on patients should be quantified: do they combine together just additively (linearity is implied), or also multiplicatively (more convoluted dynamics would be involved)?
- How disease prediction power can be measured: in terms of mortality, functional decline, loss of quality of life, toxicity from treatment?
- Can classification of comorbidity (based on qualitative and quantitative information) bridge between clinical trials and hospital care/practice?
- What strategies can be considered optimal (differential) therapeutic ones for comorbidity?

Classes of comorbidity can lead to the specification of weighted comorbidity indices, which might only apparently improve the accuracy due to an associated increase of the risk of multicollinearity between comorbid conditions. However, the problem is somehow ill-posed. The underlying state of conditions is usually presenting a concatenated sequence of events for which both correlative and/or causative effects could be valid hypotheses. A multidimensional problem needs to be considered in order to infer the degree of multicollinearity possibly present between conditions; in turn, this suggests that comorbidity can be an informative entity measured by possible indices, unless the interdependence can be demonstrated to require a modular or clustered configuration based on statistical or network inference methods. Comorbidity modules or clusters could represent intermediate aggregate entities addressing more specifically the role of comorbidity, in terms of cumulative effects (in space and time), stratification across states, and increased power of tuning therapeutic strategies. Recent studies [42] have emphasized the strength of comorbidity relationships and their quantitative assessment based on certain 'distances' between diseases. But given the available contextual descriptions, empirical measurements, and model frameworks, what distances are appropriate, and how to measure them?

Central to clustering applications is similarity search, which basically performs nearest neighbors in Euclidean space [43]. The problem with multiple dimensions, variables, and factors is how the corresponding measures scale with dimensionality, suggesting the need of statistical models to control such complexities. Disease data have also further structural features that with comorbidities can be close due to the interdependencies, reducing the possibility of exploiting variation when computing distance measures. 'Disease clusters' remain central to comorbidity research. Clinical aspects have been considered in relation to clusters, and listed, in [44], as follows: (i) 'causal' – as for the presence of common pathophysiological characteristics; (ii) 'complicating' – due to disease-specific effects; (iii) 'concurrent' – when coexisting without causal relation to the index disease; and (iv) 'intercurrent' – due to interacting acute and transient conditions.

Diseases somehow cluster naturally if they have common patterns of influence over the vulnerability of a patient. Also, etiological associations between conditions have been classified, in [45], according to 'direct causation', 'associated risk factors', 'heterogeneity', and 'independence'. Unlike the first two classes, the other classes show lack of correlation and require further investigation of possible causative aspects (other risk factors and diseases, respectively). Phenotypic disease networks have been proposed [46] to assess disease progression and association strengths across the 'phenotypic dimension', and with emphasis on variation induced by gender, ethnicity, and other variables. After inferring comorbidities from a human disease network, the compatibility of databases and datasets in light of various specificities was questioned (see, e.g., [47] with discussion on the limitations from noisy mapping, i.e., lack of correspondence between OMIM (Online Mendelian Inheritance in Man) [48] diseases and database entries stored in the US Medicare database [49] about the elderly American population).

At this point of our analysis, we cannot yet provide an answer to the basic question: do interconnected diseases imply that comorbidity conditions exist?

Combined dimensions might suggest different computational strategies. Therefore: how to determine what space time constraints are needed for the multidimensional factors to build maximally informative clusters?

In particular, most clustered diseases show metabolic links, whereas subcellular localization was shown to be valuable for enriching clusters of phenotypically similar diseases [50]. Despite the impact that these results can have for patient stratification and targeted treatments, it is currently lacking a rigorous assessment of the significance of comorbidity relationships at the various possible dimensions and across independently validated datasets. Significance and validation call for statistical inference approaches designed to: (i) achieve novel stratification approaches of patients based on complex risk profiles; (ii) identify composite biomarkers for disease progression and response to therapy; and (iii) address new therapeutic strategies for combinatorial targets.

## A dynamic dimension is worth general attention

Modules or clusters in comorbidity maps are entities not to be interpreted statically as currently done, or even statistically, due to the current data paucity and fragmentation. The common patterns of influences shared by diseases that are grouped together could be disrupted by events inducing the generation of new modules. Regarding statistical aspects, data consistency and validation that would be needed require additional efforts (collection, standardization, processing, analysis, and inference models).

The centrality of including a 'dynamic dimension' in the analysis is thus considered crucial, as it still represents an unmet need for at least three reasons deserving future investigation:

(i) *Comorbidity usually relies on an index condition, which is in general the subject of the study becoming a sort of 'attractor state' or dominant disease driving other associated diseases*. Attractors are stable points to which the system would return after small shocks (see [51] for omics application). However, what condition should be indexed, or how the index can change with time, are both open questions.

(ii) *Multimorbidity addresses disease co-occurrence in a person without reference to any index, which solves part of the relativity in (i)*. Assuming that diseases assemble or cluster together, dynamically assessed maps would be very informative in such an unconstrained system, and unsupervised learning would remove some of the uncertainty related to causality, probably delivering modular configurations.

(iii) *Networks, however, should be tuned to sense 'early warning signals'* [52], particularly the ones predicting the occurrence of perturbations that potentially induce critical transition phases, for example, disease progression, switching disease regimes, and any other condition that would cause remodulation.

Advances towards designing indices beyond just static constructs, generating multimorbidity maps, and making predictive use of networks are likely to be possible achievements in the near future, in particular ensuring an evolution of the comorbidity field. It also appears, from our opinion, the necessity of a multidisciplinary integrative approach involving a mix of expertise along the described dimensions, and targeted to a global assessment of the patient. Building network-based predictive models could be a valid support to clinicians, for example, suggesting the definition of protocols aimed at personalization of the therapy during and after hospitalization. The context of comorbidity exemplifies such need; whereas sorting the morbidities and trying to prioritize (also through indexing) them, further therapy calibration may be supported by predictive evidence obtained by the network centric and dynamic analysis of the stationarity (homeostasis) patterns of the system (patient).

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