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EDITED AND REVIEWED BY
Jean-Marc Cavaillon,
Institut Pasteur, France

*CORRESPONDENCE
Pietro Ghezzi
pietro.ghezzi@gmail.com

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Societal factors in network medicine and causation

Pietro Ghezzi[1,2]*

[1]Department of Biomolecular Sciences, University of Urbino Carlo Bo, Urbino, Italy, [2]Emeritus, Brighton and Sussex Medical School, Brighton, United Kingdom

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A Viewpoint on the Frontiers in Science Lead Article

A multiscale inflammatory map: linking individual stress to societal dysfunction

Key points

- The concept of network medicine must extend to cover social determinants of health and disease that contribute to the exposome as well as biological factors such as the genome, proteome, interactome, and metabolome.
- Vodovotz et al. propose a mathematical model attempting to integrate the various determinants of stress and their relation to inflammation; its future developments should also address causality.
- It will be interesting to use existing datasets to test how this model could help identify mechanisms of disease endotypes and to explore whether inflammation contributes to the link between socioeconomic status and health.

The *Frontiers in Science* Lead Article by Vodovotz et al. proposes a mathematical model that describes the links between inflammation and stress (1). All theoretical models need to be validated in a relevant population, but the authors address the need to integrate the various causal components of disease to derive new definitions of diseases that go beyond the old, organ-centered classifications (neurological, musculoskeletal, cardiovascular, etc.) and towards mechanism-centered ones. To this end, three key concepts have been developed.

The first concept is that of multicausal diseases and the "sufficient/component causes" model defined by Rothman in 1976, wherein different component causes can add up to different sufficient causes (2). This model is normally visualized through so-called Rothman pies.

The second concept is that of network medicine originally developed by Barabási and colleagues (3). In the first study on the diseasome, a network of all human diseases was made based on the known disease-gene associations reported in genome-wide association studies. However, the genome is only one of the layers of our personal "omes". The other layers are represented by the expression of proteins (proteome), the protein–protein interaction (interactome), and the levels of metabolites (metabolome) among others. Partial extensions

of the diseasome to the interactome and to non-coding RNA have been published (4, 5). However, the network medicine concept will need to be extended to the least individual layer—the exposome—that describes all environmental influences (including infections and exposures to environmental chemicals as well as our behaviors) that affect our body, including the social factors discussed by Vodovotz et al.

This brings us to the third concept, particularly relevant to the study by Vodovotz et al., which is that the exposome also includes the following: "partnership/social contacts, stress, education, financial security, water quality and green living environment" (6). This concept relates to the "social determinants of health" (7), describing how socioeconomic status is a key determinant of the risk of disease and thus highlights the importance of addressing social inequalities. A 2020 update on the pioneering study by Sir Michael Marmot stated that "the situation has become worse" (8), i.e., inequalities in health associated with social/socioeconomic determinants are growing. Notably, though the Marmot review was originally focused on England, the social determinants concept is becoming increasingly relevant globally (7). Moreover, the importance of social determinants of health, including structural inequality and intersectionality, was highlighted during the COVID-19 pandemic (9–12), linking the biological aspects of the disease to social and political ones (13). Consequently, the development of mathematical models taking stress into account will need to be more granular when considering the various components that can result in what we generically define as stress. For example, sociomarkers, such as income and education, that can be used in the study of the causal pathway of disease will need to be identified and included in any analysis (14).

A key question is how the development of mathematical models will help to improve health going forward, both on a global scale and an individual one. To answer this, one should explore how mathematical models fit into visions of what the "medicine of the future" will look like. Big data is already redefining disease; as mentioned above, this is apparent with the development of the concept of the diseasome and what is now called system medicine or network medicine. Big data will increasingly need to expand to a larger set of information, beyond the genetic risk factors and the various -omics described above, to the exposome and sociomarkers. This is where the Internet of Things, or more specifically the Internet of Medical Things, will help to collect individual data using technology such as smartphones and smartwatches. Artificial intelligence (AI) will be needed to interpret big data, but its accuracy (both in diagnosing disease and in providing personalized indications with regard to their prevention and therapy) will depend on the size of the training set and the growth in the number of individuals providing their medical data to public databases. The likely future growth in individuals sharing their personal data will make issues of data regulation even more important. Some of these issues are already being addressed; for instance, the European Commission has launched the Alliance for Internet of Things Innovation (15).

The article by Vodovotz et al. attempts to develop a model to integrate the various determinants of stress and their relation to inflammation as a possible mediator of their effect. This may be helpful in extending the mathematical models and directed acyclic graphs commonly used to study causation in medicine to ensure these take into account all the external factors, including societal ones, that can act as modifiers of the biological causal mechanisms.

Although the article does not discuss causality, this will be an important aspect to incorporate in the model. For instance, inflammation can be a non-sufficient causal component, or risk factor, for disease but can also be a consequence of disease, as it is a response/reaction to injury. Likewise, "social unrest" can be seen as a response/reaction to social inequalities and, in some cases, might contribute to the resolution of the problem. Future developments of this model will have to distinguish between socioeconomic inequalities and social unrest. Most models of causation in medicine take into account the problem of confounding or "the third variable": if socioeconomic inequality caused both inflammation and social unrest, then the causal link between social unrest and inflammation will disappear.

It will be interesting to test the model of Vodovotz et al. in one of the many existing datasets to evaluate how it can help in the identification of the mechanisms of endotypes of disease. Furthermore, it will be interesting to see how the model could be used to investigate the possibility that inflammation may represent a link between socioeconomic status and its importance as a determinant of health.

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