WHITE PAPER

Bioregulatory Systems Medicine Model

Targeting biological networks to enhance autoregulatory capacity

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Bioregulatory Systems Medicine

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Abstract

The purpose of this White Paper is to present a novel model of Bioregulatory Systems Medicine (BrSM), and to convey the value of the bioregulatory approach in addressing many of the most pressing challenges of disease complexity that medicine faces today. We believe that bioregulatory systems medicine enhances the current medical paradigm, potentially bridging the gap to improve patient outcomes. The model described in this document represents a consensus understanding of the core elements fundamental to defining Bioregulatory Systems Medicine and the unique relationships among those elements, as derived from the individual perspectives of medical scientific experts, clinicians, and initiative leaders. A group conceptualization method, concept mapping, was used to systematically aggregate the perspectives of these individuals to produce the resultant model. The implications of the conceptual relationships that emerge within the model and in the broader context of clinical and research settings are discussed. A fundamental outcome of the model development process is the concept that the bioregulatory approach is driven by the goal of stimulating resolution processes through consideration of the communication and information pathways of the human organism. We conclude with a summary of this and other major insights derived from the model and how these findings can contribute to addressing the challenges faced by medicine today.

Contributors

A group of twelve experts from the BrSM Initiative contributed as authors and reviewers to the development of a White Paper in order to consolidate the insights of the initiative on the concept of Bioregulatory Systems Medicine.

The authors believe that the proposed concept of the Bioregulatory Systems Medicine will enhance the current medical paradigm, potentially closing existing gaps to improve patient outcomes.

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The Institute for Integrative Health, Founder & President

Brian Berman is recognized as a pioneer in the field of integrative medicine. In 1991, he founded the Center for Integrative Medicine at the University of Maryland School of Medicine - the first program of its kind at a U.S. academic health center. The recipient of more than $30 million in National Institutes of Health research funding, he has published extensively on acupuncture and mind/body medicine in such prestigious journals as the Annals of Internal Medicine and the New England Journal of Medicine. He served as the first chair of the Consortium of Academic Health Centers for Integrative Medicine, which now includes over 55 member institutions.

Additionally, Dr. Berman co-founded and currently serves as field coordinator for the complementary medicine field within the Cochrane Collaboration, an international organization that evaluates medical practices through systematic reviews of research literature. He is also founder and president of The Institute for Integrative Health, a not-for-profit organization whose purpose is to catalyze new ideas in health care and focus on the promotion of health. He serves on the McCormick Science Institute's Advisory Board, the National Pain Strategy Professional Education and Training Working Group, the American Pain Society Task Force on Complementary and Alternative Medicine, and the NIH/NCAAM Advisory Board. In addition, Dr. Berman is a practicing family physician and pain management specialist.

Dr. Berman was the 2005 recipient of the Bravewell Leadership Award for his achievements in "transforming healthcare in America and ushering in a new practice of medicine."

Yvonne Burmeister, Ph.D.

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Yvonne Burmeister gained her research experience at the Max Planck Institute for Chemical Physics of Solids, the Clinic of Urology of the University Hospital Carl Gustav Carus Dresden and the Robert Koch-Institute in the Department of Immune Defense Mechanisms. While at the Robert Koch-Institute, she studied the role of the inducible co-stimulator molecule for T-cell activation and effector function. Her strong interest in immunological research and its clinical application has developed into a fascination for novel therapy concepts that intend to target and treat complex multifactorial disease patterns.

Dr. Burmeister served as a faculty member of science in the Department of Chemistry at Technische Universität Dresden and earned her Ph.D. in the Department of Biology at Humboldt Universität zu Berlin. In 2010 she joined Biologische Heilmittel Heel GmbH in Baden-Baden, Germany as Preclinical Project Manager to lead various research projects in the specific areas of inflammation, lymphatic biology, gastrointestinal diseases and liver diseases. Since 2016 she took the position of Systems Research Manager.

Konstantin Cesnulevicius, M.D., Ph.D.

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Konstantin Cesnulevicius studied medicine at Lithuanian University of Health Sciences and earned his M.D. in General Practice at Vilnius University in 2003. During undergraduate studies he became especially interested in the molecular biology and genetics of diseases. As a recipient of Georg-Christoph-Lichtenberg Scholarship from the federal

land of Lower Saxony (Germany) joined the Ph.D. Program at the Center for Systems Neuroscience in Hannover in 2004. While working on his Ph.D. he authored and co-authored several publications on stem cell therapy applications in Parkinson's disease and other neurodegenerative diseases. He pursued a postdoctoral appointment at Karolinska University in Sweden where he researched spatiotemporal gene expression patterns during the embryogenesis in the Caenorhabditis elegans model using cutting-edge real-time imaging.

Dr. Cesnulevicius joined Biologische Heilmittel Heel GmbH in Baden-Baden in 2008 to fulfill his interest in bringing scientific innovations closer to medicine, in part through the work of pharmaceutical companies that pursue innovative medical thinking in their mission. Since joining Heel, he has worked in the Department of Medical Affairs & Research in various positions related to scientific communication. Since 2016, he serves as a Senior Medical Advisor Systems Biology/Systems Medicine, Lead Scientific Communication leading projects on scientific dissemination of research at Heel.

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Alyssa Goldman is a Client Services Consultant at Concept Systems, Inc., where she has led a number of client projects in the areas of research, evaluation, strategic planning and needs assessment. She has consulted on the use of group concept mapping in a range of contexts including medical and clinical paradigm development, mental health, chronic disease prevention, health promotion, and criminal justice.

Prior to joining the CSI team, Goldman worked at Cornell University's Johnson Graduate School of Management as a Visiting Scholar in the Management and Organizations Department, where she assisted faculty members with research projects and course development. She holds a Masters degree in Social Sciences from the University of Chicago, and a Bachelors degree in Psychology and Government from Cornell University. She is currently pursuing her doctoral degree at Cornell University in Sociology.

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Martha Herbert is an Assistant Professor of Neurology at Harvard Medical School, a Pediatric Neurologist at the Massachusetts General Hospital in Boston, and an affiliate of the Harvard-MIT-MGH Martinos Center for Biomedical Imaging, where she is director of the TRANSCEND Research Program (Treatment Research and Neuroscience Evaluation of Neurodevelopmental Disorders). She received the first Cure Autism Now Innovator Award, and is Medical Director of the Documenting Hope project, which aims to provide a proof-of-concept laboratory and film documentation of the recovery of children with common serious chronic illness and to lay the foundation for a community-based systems biology of recovery.

Dr. Herbert earned her medical degree at the Columbia University College of Physicians and Surgeons, prior to which she obtained a doctoral degree at the University of California, Santa Cruz, studying evolution and development of learning processes in biology and culture in the History of Consciousness program. She completed postdoctoral work in the philosophy and history of science, and trained in pediatrics at Cornell University Medical Center and in neurology and child neurology at the Massachusetts General Hospital where she continues to work today. Her main research interest lies in using brain imaging to link tissue pathophysiology and electrophysiological signaling, which will help place autism in the context of chronic illness across the lifespan, and show mechanisms by which a whole body-brain systems approach and an appreciation of how environmental vulnerability affects brain and body health may point to avenues for plasticity and recovery. In her recent book, The Autism Revolution: Whole Body Strategies for Making Life All it Can Be, she presents research and case studies that support this paradigm-shift in understanding autism as a collection of problems that can be overcome. She has established the Body-Brain Resilience Center and the Higher Synthesis Science program to implement whole-body based environmentally grounded brain science in a clinical setting.

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David Lescheid is currently a Medical Manager at Heel in Baden-Baden, Germany, where he uses modern scientific literature to support the principles and practice of bioregulatory systems medicine. Prior to this position, he was a Professor of Physiology and Microbiology for five years at the Canadian College of Naturopathic Medicine (CCNM). Additionally, he spent four years practicing full-time in a large multidisciplinary health clinic in Ottawa with specialized interests in the immune system and infectious disease, men's health issues, obesity concerns, and sports medicine. He has been a member of several federal and international committees including the Expert Advisory Committee (EAC) to Health Canada, the Council for Naturopathic Medical Education (CNME), the Canadian Association of Naturopathic Doctors (CAND), and other government and media relations subcommittees.

Dr. Lescheid graduated with honors from the Canadian College of Naturopathic Medicine (CCNM) in 2002. He earned his Ph.D. in Molecular Biology and Protein Chemistry from the University of Victoria, having completed his B.Sc. in Biology. He earned a Diploma in Health and Fitness studies from Simon Fraser University, and has additional training in IV therapies, homotoxicology, homeopathy and different forms of bodywork. He is a frequent guest speaker at various professional seminars, and has published extensively on complementary and alternative medicine.

Timothy A. McCaffrey, Ph.D.

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Timothy A. McCaffrey is the Director of the Division of Genomic Medicine at the George Washington University Medical Center. The Genomic Medicine division is focused on clinical and translational research to facilitate genomically-guided diagnosis and prognosis, with emphasis on creating new diagnostic tests for predicting people who are at risk for developing heart disease. The recipient of multiple research grants, he has published extensively on applications of genomic medicine to the study of cardiovascular disease, and continues to explore related topics on genomics and stem cells in his laboratory. He has taught various courses in the fields of genomics, medical biochemistry and molecular biology, and has also developed courses in personalized genomics for medical and graduate students. He serves as an Executive Editor of Gene, a Senior Investigator for St. Laurent Institute, and as an active Board Member with the Katzen Cancer Center Scientific Board, and The George Washington University Heart & Vascular Institute.

Dr. McCaffrey earned his Bachelor's degree from St. Mary's University, and his Master's and Doctorate degrees from Purdue University. He completed his Post-Doctoral training at Weill Cornell Medical College, where he later became an Associate Professor in the Department of Medicine and founded their Genomics Core Facility.

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Myron Schultz is the Head of Medicine at Biologische Heilmittel Heel GmbH in Germany. Prior to this position, he served as Heel's Head of Global Medical Education and the Head of Global Medical Affairs. Before this he taught pathology at the Durban University of Technology and hosted the pathology practical and ward rounds at the Nelson Mandela School of Medicine and R.K. Khan Hospital respectively, and was in private clinical practice. In addition he also applied his expertise as the Clinical Director of the 5th and 6th year day clinic for the Department of Homeopathy Technikon Natal.

Dr. Schultz assisted Dr. Jan Kersschot in further developing the methodology in Biopuncture and at the University of Johannesburg created and instructed the first undergraduate Biopuncture course. Dr. Schultz completed his Master's Diploma in Technology of Homeopathy at Durban University of Technology in South Africa, and holds advanced training in Biopuncture by Dr. Jan Kersschot in Belgium.

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Bernd Seilheimer has served as the Head of Research at Biologische Heilmittel Heel GmbH in Baden-Baden, Germany since 2009. From 2016 he took the position of the Head of Systems Research & Development. He is recognized for his breakthrough research in the central and peripheral nervous system, completed during both his undergraduate and post graduate work at the University of Heidelberg. While working on his PhD, he published widely on cell adhesion research focusing on Schwann cells. He discovered a functional role of their low-affinity NGF receptors. As a recipient of a Harvard Medical School research fellowship under Professor Huntington Potter, he further expanded his research on the regeneration of the central nervous system, in particular Alzheimer's disease.

As Research Associate at the Harvard Medical School, Dr. Seilheimer was hired as a consultant on NGF by Hoffman La Roche during the acquisition of Genentech. He was later appointed as the Senior CNS and PNS expert in Basel, Switzerland where he initiated innovative, highly prioritized CNS projects. He also headed the CNS Research Department at Schering AG in Berlin, Germany, where he was recognized for his achievements in establishing a global research network of strategic alliances with leading universities and institutions. In this position, he also delivered development candidates in stroke and Alzheimer's disease. He later broadened his expertise across R&D as Head of Global R&D Risk Management.

From 2002 to 2010 Dr. Seilheimer was an active board member of the European Neuroscience Institute (ENI), Göttingen where he has been instrumental in the process of establishing ENI as a leading institute in Neurosciences. He has also served as a member of the Council of Scientific and Business Advisors of the Johnnie B. Byrd Sr. Alzheimer's Center and Research Institute, Florida, USA, for several years.

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Maria A. Shkolnikova is a professor of Medicine and Scientific Supervisor of the Institute (Research and Clinical Institute for Pediatrics at the Pirogov Russian National Research Medical University) and chief of Federal Russian Centre for Children's Arrhythmia. As an experienced cardiologist, she has more than three decades of professional practice in clinical, scientific and administrative work in pediatrics and cardiology. She is an accomplished researcher, authoring and co-authoring over 200 publications in her field in Russian and 85 – in English. Her research interests are related to the analysis of early detection, differential diagnostics, and treatment of life-threatening cardiac arrhythmias, sudden cardiac death, epidemiology of CVD, and issues related to cardiac functioning and its regulation by the autonomic nervous system.

Dr. Shkolnikova collaborates with the Max Planck Institute for Demographic Research in Rostock, Germany in developing a research project that includes 24-hour ECG (Holter) monitoring as a new source of biomarkers in biodemographic surveys. She is also heavily involved in the analysis of other biomarker data and sex differences in health and mortality.

Dr. Shkolnikova received several scientific awards. Among them, the Lenin's Komsomol prize in medicine in 1988, the First Prize for Medical Research in 2002 by the Moscow Government, Honour Reward of Excellence in 2015 by the Ministry of Health and Certificate of Honour in 2015 by the Senate of the Russian Federation, and others. She holds memberships and leadership appointments with multiple prestigious honor societies and associations including the European and Russian Arrhythmia Societies, Russian Pediatric Cardiology Association (President of Association), European Society of Cardiology and European Society for Pediatric Cardiologists, and Society of Cardiologists of the Russian Federation. For many years Maria Shkolnikova was the Chief Pediatric Cardiologist of the Ministry of Health of Russian Federation, and from 2000 till present serves as Moscow's Senior Expert Pediatric Cardiologist.

Dr. Shkolnikova completed her M.D. and Ph.D. in Pediatrics at the Moscow Institute of Pediatrics & Surgery. She has also obtained degrees in Cardiology, Pediatrics, Health Management, and Pharmacology.

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Alta Smit is the Director of Medical Affairs and Research at Biologische Heilmittel Heel GmbH in Baden-Baden, Germany and has held this position since 2009. She has also served as Heel's Head of Medicine and Research since 2005 and as the Director of Medicine and Medical Education since 2007. Additionally, she is the moderator of Heel's Scientific Board and serves on the Scientific Board of the European University Viadrina in Frankfurt an der Oder. She is a founding member of the International Society of Homotoxicology and Homeopathy and is a member of the Institute of Functional Medicine.

Dr. Smit is recognized internationally as an integrative medical doctor and international lecturer, with a focus on bioregulation therapy of modern diseases. She has extensive experience in various areas of medicine including Rheumatology and Clinical Immunology, and has published in numerous medical journals with special interest in acquired mitochondrial myopathies, atopic disease and functional somatic syndromes.

Dr. Smit, in addition to degrees in physiotherapy and medicine, began her training and practice of complementary modalities in 1992, completing several courses in Homotoxicology, Acupuncture and Neural Therapy in Baden-Baden, Germany. In 1997 she completed her fellowship in Homeopathy at the Royal College of Homeopathy in London, England. From 1994-2004 she practiced integrative medicine using the aforementioned modalities as well as orthomolecular manipulation to treat chronic diseases.

(†) Georges St. Laurent III, Ph. D.

Science Director, St. Laurent Institute

Georges St. Laurent III served as the Scientific Director of the St. Laurent Institute (SLI), a non-profit academic research institute dedicated to systems biology and genomics approaches for understanding the molecular mechanisms of chronic disease. While at SLI, he has been instrumental in developing international scientific collaborations. He led an international group of 15 scientists using single molecule sequencing to understand the role of ncRNAs in physiological information processing. Since 2009, he had also championed the use of Helicos technology at SLI to unlock the potential of the human transcriptome for disease diagnostics.

St. Laurent is well recognized in the fields of Molecular Biology and Neuroscience, publishing over 40 peer-reviewed research papers since 2006. Most recently, he had published in BMC Medicine on the role of dark matter RNA in the human genome and disease-associated variants. His publication on non-coding RNA mechanisms in Alzheimer's disease was recognized in Nature Medicine's "Top Ten" list for 2008. Additional research interests include the systems biology of inflammation, the herbal medicine of Amazonia, and the computational mechanisms of non-coding RNA in the mammalian nervous system.

St. Laurent has served as an Adjunct Professor of Biochemistry and Molecular Biology at George Washington University, as a Visiting Professor at S.V. University in Tirupati, India, and at Lanzhou University in Lanzhou, China. He held executive appointments and memberships with various prestigious Scientific Boards and Committees, including the following: the Scientific Advisory Board of Heel GmbH in Baden Baden, Germany, and the FANTOM 5 Genomics Consortium at the RIKEN Genomics Institute in Japan. He served on the Executive Committee of the German Duque Foundation in Colombia, South America, and was the Co-Chair of the Genome Regulation and Structure Conference (BGRS) in Russia in 2008. He earned his B.Sc. in Molecular Biology at Yale University, a Ph.D. from The University of Antioquia in Colombia, and was prepared to defend his second Ph.D. in Molecular and Cellular biology at Brown University when he sadly passed away in September 2015.

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Glossary

Autoregulation: *the property of feedback loops in biological networks to provide stability to a network, thereby limiting the range of network component fluctuations.*

Autoregulatory network: *the biological network of feedback loops that regulates homeostasis and underlies an organism's autoregulatory ability.*

Biological complexity: *a concept referring to the intricate interconnectedness of the multiple units of a human organism based on fairly stable patterns of evolutionary conservation.*

Biological information: *a property of a biological component or components that influences, affects, or directs development and maintenance of the organism. There are two major types of biological information: sequence information encoding molecular machineries, and regulatory network information controlling the behavior of molecular machineries.*

Biological network: *A web-like pattern of connectivity between molecules, cells, tissues, or organs that describes a behavior of a given system (a specific set of molecules characterized by structure or function, a cell, a tissue, a specific set of tissues or organs, or an organism) as a whole. The nodes of such a network represent biological units, and the edges display characteristics (strong or weak, close or distant) of relationships between the biological units.*

Biomarker: *a measurement reflecting the status of a biological system, where the measured response may be functional and physiological, biochemical at the cellular level, or a molecular interaction. Biomarkers provide information that may aid detection, diagnosis and treatment plan decisions.*

Bioregulatory: *having the properties of a therapeutic intervention, pharmacological or non-pharmacological, to induce an active biological process that is able to optimize or restore autoregulation of biological networks.*

Cell turnover: *a process by which older cells are eliminated by apoptosis and replaced by the division of the progenitor cells.*

Disease network (diseasome): *the concept that many diseases are interconnected by shared pathophysiological events, such that correlations between phenotypes can be considered based on shared metabolic networks, gene networks, protein networks or shared networks of clinical data.*

Disease progression: *the worsening of a disease over time as the result of a progressive failure of the autoregulatory process.*

Dynamic reciprocity: *an ongoing, bidirectional interaction amongst cells and their surrounding microenvironment.*

Dynamic equilibrium: *a steady state of a biological network.*

Extracellular matrix (ECM): *a complex network of material such as proteins and polysaccharides that are secreted locally by cells and remain closely associated with them to provide structural, adhesive and biochemical signaling support.*

Functional modules: *a group of directly or indirectly linked molecules (nodes) that work together to achieve an identifiably distinct function.*

Homeostasis: *a fundamental property of biological systems to preserve their stability by maintaining key regulated variables withing an acceptable range.*

Inflammation resolution: *an active biological process that requires activation of endogenous programs that enable the host tissue to maintain homeostasis.*

Information flow: *a concept in bioinformatics referring to the transmission of biological information within or across biological networks.*

Linear: *the idea (or model) suggesting that biological processes occur in a simple, sequential order.*

Low affinity interactions: *interactions between molecules with relatively low intermolecular force.*

Medication with bioregulatory properties: *drugs that execute regulatory activity in perturbed autoregulatory networks.*

Microenvironment: *local surroundings with which cells interact by processing various chemical and physical signals and by contributing their own effects to this*

environment.

Molecular coherence: *the higher order stability in the behavior of molecules in the tissue, in response to the whole network of all other molecules within a cell.*

Network perturbation: *disturbance that causes structural or functional changes to the network that alter stability of a given system (cell, tissue, or organism) induced by internal or external mechanisms.*

Non-linear: *the idea (or model) suggesting that biological processes are determined by complex relational interactions.*

Physiological inflammation: *a stereotyped tightly controlled immune response initiated by the complex integration of tissue turnover and signal recognition by proinflammatory cells, resulting in the maintenance of tissue homeostasis.*

Reductionist: *in biology, a view that biological systems can be explained solely according to the physical and chemical properties of their individual components.*

Robustness: *an ubiquitously observed property of biological systems that maintains functions and performance against internal and external perturbations.*

Stem cells: *pluripotent cells that can divide and differentiate into diverse specialized cell types, or self-renew to produce more stem cells.*

Systems biology: *a study of biology that applies principles of systems theory. The studied systems in biology are comprised of molecules, cells, tissues, organisms and ecosystems.*

Systems theory: *a theory of scientific exploration proposed by L. von Bertanaffly, defining principles for studying complex systems of interrelated elements as a whole.*

Systems medicine: *the implementation of systems biology approaches in medical concepts, research and practice, through iterative and reciprocal feedback between and among data-driven computational and mathematical models, and model driven translation and clinical investigations.*

1. Introduction

Medicine is at a crossroads. According to the World Health Organization, people are healthier, wealthier, and live longer today than 30 years ago (WHO 2015). While knowledge and understanding of health are growing rapidly, the nature of health problems is also changing. There have been significant improvements, especially in the wealthier parts of the world, in prevention and treatment of infectious diseases, though the burden of chronic and non-communicable diseases has increased (WHO 2015). In the United States, by 2023, rates of chronic disease are projected to increase by more than 40%, with medical costs related to these diseases projected to increase by 200% (Bodenheimer et al. 2009). Prevention will remain important, though more research into the development of new medicines and the improvement of existing medicines will be a global public health priority (Kaplan et al. 2013). Recognition that external stressors, including chemical pollutants, diet, and climate change, can have long-lasting effects on human development, metabolism, and health by contributing to the development of disease via underlying epigenetic mechanisms has gained greater acceptance in the scientific community (Feil & Fraga 2012, Weinhold 2012). In addition, iatrogenic complications, with exposure to drugs being the main contributor, have been recognized as a major risk for patients (Lazarou et al. 1998), resulting in annual costs of up to $324 million in the United States alone (Levinson 2010).

The increasing presence of social, psychological, and environmental stressors in today's society also plays a prominent role in the escalating development of pathological states and illnesses. Recently developed comprehensive stress measures indicate that the impacts of chronic stressors on human health are substantial, dramatically affecting both physical and mental wellbeing (Thoits 2010). Research suggests that repeated exposure to acute and chronic stressors may trigger a systemic inflammatory response with potentially maladaptive consequences such as depression or the exacerbation of inflammatory disease (Fleshner 2013).

As more individuals present with more complex symptoms, it has become clear that a new approach is needed that moves beyond the current medical paradigm, which is grounded in classical biomedical science. The scientific understanding of disease is moving, instead, toward a comprehensive view of disease as a complex interplay of genetic factors and changes in DNA, and external factors, including age, diet, gender, stress, and environmental toxins (Schadt 2009). This enhanced understanding requires a broadened approach to medicine that can provide solutions to address both disease complexity and the undesirable, unintended effects of medical treatment, while simultaneously retaining the benefits of recent medical advancements. In the second half of the twentieth century, advances in molecular biology, engineering, and epidemiology catalyzed a wave of progress in medicine that allowed for the eradication of many acute infectious diseases, and fostered the development of exceptional surgical and emergency care techniques. The ability to characterize genetic variations over the entire genome and the achievements in molecular biology have led to an improved understanding of the cell and to the identification of genetic causes for a variety of diseases. Modern advances in molecular high-throughput technologies have generated immense amounts of data correlating genetic predispositions, epigenetic events, and complex molecular regulatory interactions with health-disease status in highly stratified human populations. Importantly, while these represent critical developments in medicine, they also reduce attention to the body as a whole (Schadt 2009).

Whereas the current drug development model, driven by advances in molecular biology, seeks single target synthetic and biological molecules for treatment design, it does not account for the complexity and interconnectedness of molecular events in the biological systems in which disease processes exist. For example, many degenerative diseases that challenge clinicians feature inflammation and immune dysregulation, both of which are complex disease components that may require more comprehensive solutions than those offered today. Patients and the public alike often criticize today's medicine for its focus on symptom alleviation, rather than treatments that target the underlying causes of disease. A more comprehensive and systems-based approach would recognize the underlying causes and complexity of these conditions and strive to address them in the treatment.

A more robust and effective solution for disease complexity includes a therapeutic approach that optimizes the autoregulatory capacity of the patient in order to restore health in the face of perturbation. This approach goes beyond an understanding of disease as a simple linear relationship between a given stressor, its expression, and its elimination by considering the stressor in the context of the patient's genetic and epigenetic predisposition and autoregulatory capacity (Figure1).

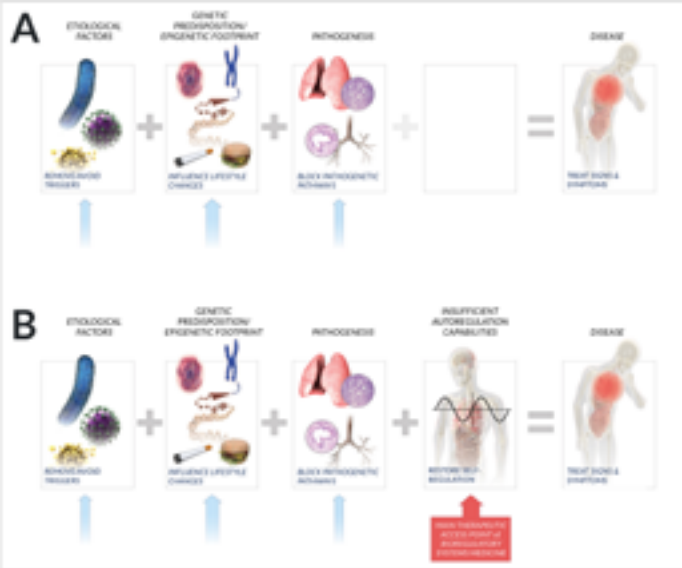

Figure 1. Novel considerations of factors affecting disease. *The current medical paradigm (A) typically consider etiological factors, genetic predisposition and molecular pathways recruited in pathogenesis as key causative agents that lead to disease. Bioregulatory systems medicine (B) also considers the patient's compromised or insufficient autoregulatory capacity to restore homeostasis as a key factor that influences individual disease incidence and manifestation. Restoration of patient autoregulatory capacity is therefore a primary therapeutic objective in bioregulatory systems medicine, in addition to removal of triggers, lifestyle changes, and inhibition of pathogenetic pathways, when appropriate.*

Autoregulation is an inherent feature of regulatory networks, and is a much broader concept than homeostasis. Autoregulation encompasses homeostatic systems from the molecular level (e.g. certain protein homeostasis) to the whole-organism level (e.g. temperature or blood pressure homeostasis). It proposes that these systems are interconnected via webs (or networks) of interactions across all levels, creating the global autoregulation system of the human body. Some authors refer to this system as "the interorgan communication network" (Droujinine & Perrimon 2013, p.1). It was recently suggested that stability is an emergent property of such a network of interconnections at all levels-from genes to organs- and that this stability is the balance of the autonomy and connectedness that sustains health (Buchman 2002). Whereas past approaches to disease have stemmed in large part from simplifications that inevitably result when testing and processing complex theories, next-generation sequencing technologies available today make it possible to adopt a more integrative approach. As a result of these technological advancements, attention can now be given to the body's inherent biological capability to maintain a state of health by regulating information flow across non-linear, multi-scale, and multi-level networks of molecules, cells, tissues, and organs. The autoregulatory network itself, then, offers a novel therapeutic access point beyond eliminating disease causative agents and modifying resulting pathogeneses. This progress in understanding the fundamental interconnectedness of biological systems has revealed the need to re-conceptualize the current healthcare model, moving from a linear, single-target understanding of physiology and pathophysiology to a non-linear, systems-based model (Figure 2).

The field of medical science most aligned with this perspective is broadly referred to as "systems medicine". Systems medicine takes a holistic view of health and disease by aiming to provide holistic multi-modal integrated care based on systems biology approaches (Bousquet et al. 2011). A growing body of evidence in systems biology supports the view that global interconnectedness of multi-tissue biological networks provides the basis for whole-body systems physiology (Bordbar et al. 2011). In this regard, aspects of human physiology cannot be accurately understood or treated in isolation from one another or in isolation from their external environment. This approach is loosely known as bioregulatory systems medicine, but until now, has never been formally organized or defined. It engenders a more individualized approach to health and treatment, allowing clinicians to use more detailed data and systems concepts to better customize treatment based on the particular expression of patient's condition, history and disease progression. The ability to better tailor treatment on an individual basis is expected, in turn, to optimize patient outcomes. For drug development, this implies that a multitarget therapeutic approach, which utilizes the biological complexity of disease processes and the body's own autoregulatory mechanisms to promote healing, may be better suited (Agoston et al. 2005).

The fundamental elements that constitute the scientific and clinical basis for bioregulatory systems medicine have emerged across multiple disciplines. Discoveries from systems biology, genomics, cybernetics, and other fields have generated important and relevant information; however, these elements have not yet been combined in a purposeful and cohesive way that can benefit the clinician and patient alike. A valid model is needed to integrate this knowledge in a way that can address the medical and healthcare needs of today's society, while also establishing a common language between bioregulatory systems medicine and current medicine. This model must be grounded in research, understood, supported and verified by field experts, and integrative of relevant scientific and clinical findings. The development of a BrSM model demands a methodology that can meet each of these requirements, while fully and cohesively capturing the complexity inherent in this new medical paradigm. Further, the model must communicate the relationships among its scientific and clinical components in a standardized way that facilitates the dissemination, translation, and utilization of the bioregulatory systems medicine approach.

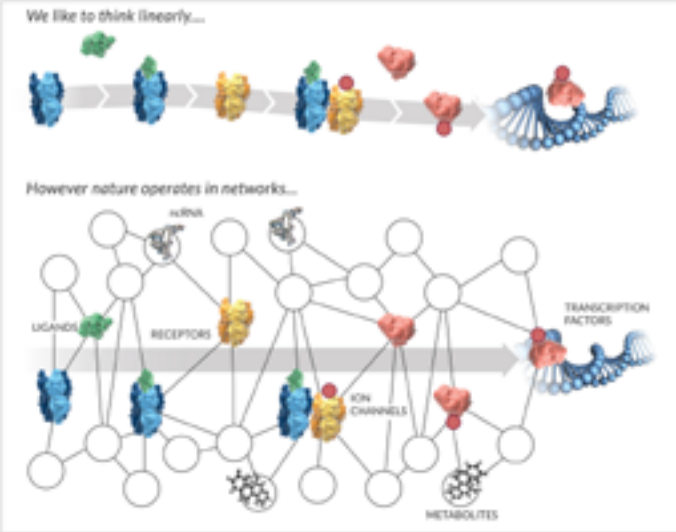

Figure 2. Linear versus non-linear causation model. *The fields of molecular biology and medicine have traditionally considered influence and causality among relevant entities as occurring in a linear manner. This linear framework, often referred to as a reductionist perspective, supports a single-molecule, single-target approach, whereby a particular biological component (e.g. receptor, gene, etc.) is considered individually and in isolation when treating disease. More recently, modern technological advances have allowed for a more comprehensive understanding of the fundamental interconnectedness of biological systems, prompting a reconceptualization toward a non-linear, systems-based model of physiology and pathophysiology. This integrative view acknowledges the spatial and temporal interdependencies among multiple molecular and physiological processes, maintaining that a more effective medical approach utilizes biological networks when treating disease. Bioregulatory systems medicine endorses this network perspective.*

In this white paper, we describe a process used to aggregate diverse expert opinions for the purpose of formalizing a BrSM model, discuss the results of this process, and present the resultant BrSM model. The methodological approach used for this inquiry, group concept mapping, systematically integrates the perspectives of a wide range of experts on both the ideas that should be included in a BrSM model, and the relationships among those ideas. The results include a visual depiction of the expert group's consensus on how BrSM should be conceptualized. We detail the information and implications conveyed by the emergent model, which is grounded in the intersection of resolution processes and biological information as the cardinal axes of the paradigm. A key emphasis of BrSM is the use of a multitarget approach to achieve resolution of distorted information flow throughout the body. The BrSM model anticipates changes and, in turn, requires a dynamic perspective on what is taking place at the micro and macro network levels, and how resolution can be achieved through internal and external means. The document concludes by emphasizing that, collectively, the integrated components of the BrSM model constitute a holistic approach to human health that can potentially close the gap between current medical challenges and ideal patient outcomes. [1]

2. Bioregulatory Systems Medicine Model

2.1 Materials and Methods

The concept of Bioregulatory Systems Medicine was developed by an international team of scientific and clinical experts from various backgrounds. Scientific experts included those in the fields of immunology, neuroscience, genomics, molecular biology, systems biology, and systems medicine. Clinical experts included physicians specialized in various medical areas including family and community medicine, chronic diseases, aging, cardiology, pediatrics and neurology. The BrSM Initiative was launched in 2008 by an input meeting of invited experts in collaboration with experts in bioregulatory medicine from Heel.

The initiative leaders selected group concept mapping as the optimal methodology for the development of a comprehensive, integrated BrSM model. Concept mapping is a mixed-methods approach for model development that integrates qualitative group processes with multivariate statistical analyses to allow a group of individuals to describe its ideas on any topic of interest and represent those ideas through a series of related maps (Kane & Trochim 2007, Baldwin et al. 2004, Kagan et al. 2009). Although the term "concept mapping" is often used to refer to a general method of visualizing how an individual or group thinks about a given topic, the group concept mapping methodology used in the BrSM model development is distinct in four main ways. First, it is a group process, and so it is especially well-suited for allowing a diverse group of clinicians and scientists to develop consensus around a given topic. Second, it uses a highly structured facilitation approach, with a specific sequence of steps to help a group articulate its ideas and understand them more clearly. Third, the core analytic tools of concept mapping consist of several multivariate statistical methods that analyze the input from all individual participants to yield an aggregate group product. Fourth, this concept mapping method employs specialized computer software that is specifically designed to analyze the data from this type of facilitated process and produce the appropriate visual representations (Kane & Trochim 2009).

This method for the development of the BrSM model was selected because of its capacity to acknowledge, capture and assimilate individual conceptualizations, and produce a set of relatively simple visual representations to depict the complex relationships among the scientific and clinical elements that emerge from the sequence of basic participatory steps. The model content was developed through a thorough and rigorous review of existing scientific and clinical research to determine the most relevant elements to defining bioregulatory systems medicine. Of particular importance in the model development process was the emphasis on the elicitation of prior cutting-edge knowledge to form the scientific and clinical substance of the model. In this sense, the model content itself does not constitute an innovative medical paradigm; rather, the relationships that emerge among this existing knowledge as a product of the concept mapping process form a novel, comprehensive, and integrated picture of bioregulatory systems medicine. The flow diagram (Figure 3) describes the development protocol in more detail.

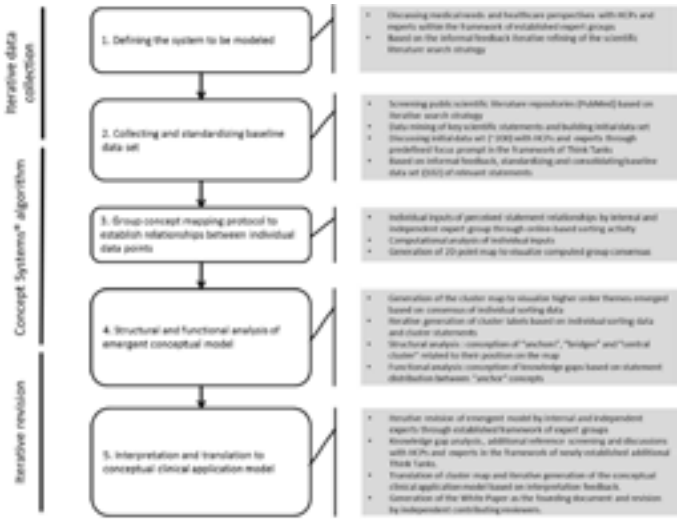

Figure 3. Flow diagram of the model development protocol. *The development protocol consisted of five basic consecutive steps. The key properties of the protocol were iterative processes engaging HCPs and independent scientific experts by establishing the framework of expert group round tables, inquiring for feedback in almost each step, and employing the Concept Systems© algorithm to compute and visualize the emergent consensus of a larger group of participants. The resultant conceptual clinical application model serves as a basis for research program development and further experimental validation.*

The initiative leaders including international scientific experts and clinicians elicited an initial set of approximately 200 statements from current scientific literature[a] and empirical knowledge, vetted through the following focus prompt used to guide content selection: *"A specific idea or element that is fundamental to defining and explaining a model of bioregulatory systems medicine (BrSM) is..."* The initial set of content was subjected to several iterations of review and confirmation. Collectively, this group of individuals possessed considerable breadth and depth of expertise, constituting their role as idea generators in the model development process. The idea generation process was designed to ensure consensus around the clarity, specificity, level of available supporting evidence, relatedness to bioregulatory systems medicine, and transferability of the content across a range of medical and scientific backgrounds. The statement refinement and confirmation process included a discussion with experts and clinicians at two multi-day Think Tank sessions.

Following the Think Tanks, initiative leaders synthesized the meeting results and engaged participants in several iterations of virtual feedback via online discussion boards before confirming a final set of 102 elements to comprise the model content (Appendix A). These statements also provided the input for the next step in the process, which was a structured conceptualization, or sorting, activity. Appendix B includes a more detailed description of the sorting activity and the concept mapping methodology. Sorting participants individually organized the final set of ideas based on their own understanding of the relatedness of the ideas. Participants in this data activity included those involved in the idea generation process and invited experts who did not participate in the Think Tanks. These individuals were invited to participate based on the collective diversity of their specific professional backgrounds and experiences. This intentional inclusion of heterogeneous perspectives helped to ensure that the consensus understanding that emerged from the concept mapping process would resonate with a broad range of health care stakeholders. The aggregation and analysis of these views formed the conceptual foundation of the BrSM model.

[a] *This literature is cited throughout the subsequent sections. Text in* **bold** *refers to statements that are included in the model, and are referenced accordingly.*

2.2 Results

Analysis of the sort data as part of the concept mapping process generated a point map (Figure 4) that displays the 102 points selected through the idea generation process in two-dimensional space. Cluster analysis revealed how these statements, as represented by points, group into ten higher-order themes by which the core elements are considered to be in relation to one another (Figure 5). Next, initiative leaders conducted an extensive review of the statements in each of the clusters to allow for the consideration and subsequent articulation of the ten emergent themes of the model (Figure 6).

Figure 4. Bioregulatory Systems Medicine Emergent Conceptual Model: the Point Map. *In this figure, each point represents one of the 102 statements derived through extensive literature mining and expert consensus, and considered to represent a key component of the bioregulatory systems medicine conceptual model. A number was assigned arbitrarily to each of the 102 statements for reference purposes only. The point map displays each of the 102 statements in two dimensional space based on the aggregation of expert participants' sort data and the subjection of that aggregated sort data to multidimensional scaling. Statements that appear closer to one another on the point map tend to be thought of as more conceptually similar by those who participated; statements that appear farther apart tend to be thought of as more conceptually distinct. We refer readers to Appendix A for a full list of the statements represented by the numbers.*

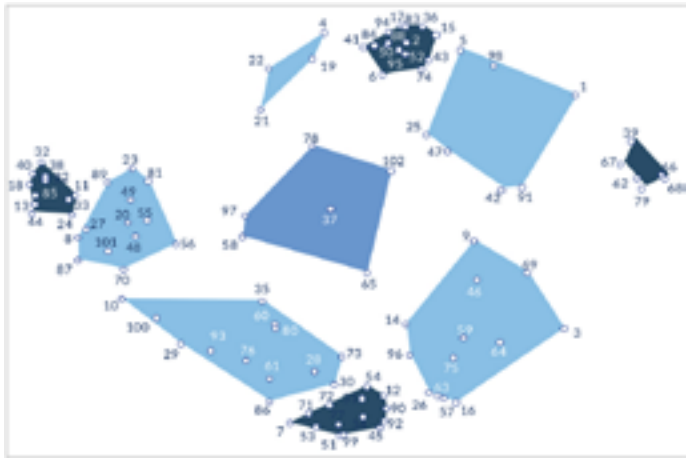

Figure 5. Bioregulatory Systems Medicine Emergent Conceptual Model: the Cluster Map. *The cluster map represents the 102 statements as they are grouped into higher-order themes based on their arrangement in the point map (Figure 4). After reviewing the fit of the map content within multiple cluster arrangements, it was agreed that a ten cluster solution was the most parsimonious representation for meaningfully and heuristically interpreting the relationships among the individual statements within a smaller set of thematic constructs. Each cluster was subsequently labelled (Figure 6).*

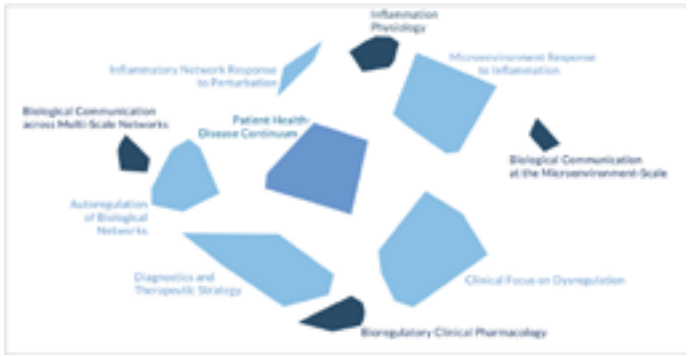

Figure 6. Bioregulatory Systems Medicine Emergent Conceptual Model: The Labeled Cluster Map. *The labels assigned to each cluster reflect the shared higher-order themes that describe the specific statements within each cluster and convey the cluster's meaning in the context of the bioregulatory systems medicine paradigm. Cluster labels were derived and finalized by authors and contributing reviewers that championed the model development initiative. The clusters have been color coded based on the structural analysis: anchor clusters are marked dark blue, intermediate clusters light blue, and central cluster middle blue. Refer to the text for a more detailed explanation of the structural cluster analysis.*

The following sections describe the distinct meaning and scope of each cluster based on the statements it contains, with particular attention to the significance of the individual ideas as they are grouped by cluster in the context of the emergent BrSM model. To begin, of the clusters ***Biological Communication across Multi-Scale Networks, Autoregulation of Biological Networks and Biological Communication at the Microenvironment-Scale***, contain several overarching concepts that emerge throughout the model. A review of the constructs associated with inflammation processes is followed by a description of those clusters that pertain to the clinical context, specifically ***Clinical Focus on Dysregulation, Diagnostics*** and ***Therapeutic Strategy, and Bioregulatory Clinical Pharmacology.*** A discussion of ***Patient Health-Disease Continuum*** as a central concept of the BrSM model and the bioregulatory approach more broadly concludes this section. The explication of the model clusters provides the foundation for the subsequent interpretation of the relationships among clusters, and the meaning of these relationships in conveying the conceptual basis of the bioregulatory systems medicine approach.

2.2.1 Biological Communication Across Multi-Scale Networks

The complexity intrinsic to dynamic biological systems offers critical insight into the behavior and properties of systems/network information regulation that challenges common reductionist thinking. For example, whereas the term homeostasis is used to refer to a steady state or condition of the system, terms such as dynamic equilibrium better illustrate that state-space is limited to a certain range in healthy individuals, but is not static (Knox 2010). Indeed, **biological networks are inherently dynamic; their capability to adapt to constantly changing internal and external inputs is defined as and dictated by their robustness** (Kitano 2004, Kitano et al. 2004, Kitano 2007b, Kitano 2007a). The concept of network robustness encompasses the notion that networks absorb the inputs from their environments, which induce numerous regulatory response actions simultaneously in order to maintain a state of dynamic equilibrium. A robust system can maintain its performance or output characteristics over a relatively wide range of perturbations, inputs, or phase states (Kitano 2004, Kitano et al. 2004, Kitano 2007b, Kitano 2007a).

Bioregulatory systems medicine offers a novel understanding of tissue health-disease status by integrating concepts of biological networks, dynamic equilibrium, and robustness. **Information theory and thermodynamics are fundamental for understanding the principles of a biological system** (e.g. a tissue). Recently, a theory of genomic "dark matter" was proposed suggesting that non-coding, RNA-regulated molecular machineries are at the core of orchestrating dynamic responsiveness of a cell to microenvironmental stimuli (Kapranov & St. Laurent 2012). These machineries establish an "intelligent scaffold" in the nucleus, the high-order molecular structure around DNA, which regulates concentrations of nuclear proteins with immense accuracy (St. Laurent et al. 2009). This "intelligent scaffold" is highly dynamic and capable of directing proteins into specific micro-locations within itself (St. Laurent et al. 2012). Fundamentally, this flow of molecules is not chaotic, but coherent in response to any stimuli that the cell encounters in its immediate microenvironment. Theoretically, this **molecular coherence could be quantified as the ratio between codable systems (information theory) and thermal degrees of freedom (thermodynamics**), providing a measure of cellular, and ultimately, of organismal fitness. Some authors suggest that, using similar principles, it is possible to identify a balance state common to human carcinomas. The dominant deviation from this balance was identified as the cancer-specific disease pattern, a signature comprised of unique mRNAs and miRNAs capable of distinguishing diseased patient samples from normal controls (Zadran et al. 2013).

Important to note are the **two major types of biological information: sequence information encoding molecular machineries and regulatory network information controlling the behavior of molecular machineries.** Sequence information is encoded by 4-digit nucleotide code in DNA and determines the structural and functional specifics of proteins and RNA molecules that constitute molecular machineries. Regulatory network information is revealed in the form of specific interconnected, predictable interactions among different proteins, other molecules, and DNA regulatory elements that describe how molecular machineries behave in a given cellular state. In this sense, regulatory network information connects different levels of biological structure, from molecules to cells, cells to tissues, and tissues to organs and organ systems. Whereas reductionist molecular techniques have successfully decoded sequence information, regulatory information and the role of noncoding RNAs as carriers of this information has only recently been discovered (Wapinski & Chang 2011). Research now suggests that **low affinity interactions (especially RNA-protein interactions) provide a computational matrix to process information and to direct action in molecular networks** (Gutiérrez et al. 2010, St. Laurent et al. 2009). For example, noncoding RNAs have been found to mediate stress response pathways in Alzheimer's disease (St. Laurent et al. 2009), are secreted by immune cells, stem cells, adipocytes, and blood cells (Chen et al. 2012), and can be detected in serum and other body fluids, suggesting their potential use as clinical biomarkers (Etheridge et al. 2011).

In this regard, disease occurs when accumulated stresses overpower autoregulating abilities that support tissue robustness; that is, when they damage biological computation resources of the tissue, causing tissues to dysfunction and, in turn, distorting information flow. Since **tissues and organs are linked together in networks by functional interdependencies**, distortions of information flow propagate

across the network of interconnected tissues from the epicenter of disorder, gradually resulting in disease progression. Tissue health fails as a function of the loss of molecular order, i.e. the loss of quality in its information content (St. Laurent et al. 2009). For example, persistent tissue perturbation that originates in the inflammatory network and causes chronic inflammation may distort DNA repair and tissue regeneration networks causing pathological tissue remodeling (Nathan 2002). As a result, distortion in stem cell regulation networks can occur, ultimately resulting in cellular degeneration or dedifferentiation. This example and others emphasize the need to consider information regulation at the systems and network level in approaching disease comprehensively.

2.2.2 Autoregulation of Biological Networks

Bioregulatory systems medicine embraces a holistic systems biology image of the human body as a multi-scale, multi-level regulatory network of molecules, cells and tissues (Hunter et al. 2002, An 2008, PacificBiosciences 2011). In contrast, the model of homeostatic regulation proposed by Claude Bernard in 1854 (Gross 1998) has been widely adopted by reductionist science to define biological stability. Research to identify mechanisms of restoring and maintaining measurable parameters of homeostatic regulation through linear processes remain a major research focus today.

Systems biology has expanded the homeostatic autoregulation concept into an alternative model termed homeodynamics, in which non-linear processes provide stability to a system. In this context, a system is described as a nested network. Biologically, this corresponds to the associations of cells into tissues, tissues into organs, and organs into the intact organism(Buchman 2002). The nested network uses computational resources provided by coherent interactions of macromolecules in the tissue in order to self-regulate in the face of perturbations introduced to the system. From a clinical perspective, this expanded model of homeodynamics supports the postulation that **blocks to autoregulation are etiological factors that maintain persistent network perturbation and restrict the network from self-regulating toward resolution.** Factors include but are not limited to genetic aberrations, epigenetic changes, chronic infections, nutritional deficiencies, chronic intoxication, persistent psychological stress, epithelial barrier dysfunction, and hormonal dysregulation.

At the biochemical level, at least three types of molecular networks (metabolite, protein, and gene) are interconnected to create a global biochemical network (Brazhnik et al. 2002); the negative feedback loops across these networks provide the basis for autoregulation of the global, organism-wide molecular network (Becskei & Serrano 2000, Kiełbasa & Vingron 2008). This global autoregulatory network can also be viewed as the high-level functional system consisting of numerous function-specific networks. More recently, the existence of interorgan communication network was proposed (Droujinine & Perrimon 2013). It was suggested that the network of brain, gut, muscle, immune, renal, fat, liver and gonad tissues systemically integrate organismal cellular processes and regulate the body's homeostasis and localized stress. These processes may include aging, protein turnover, nutrient uptake, metabolism, cell division, cell movement, detoxification, organelle biogenesis, and secretion of local and systemic signals (Droujinine & Perrimon 2013).

One of the key assertions of bioregulatory systems medicine is that the inflammation network regulates stem cell biology and regeneration on many levels. Evidence indicates that certain inflammatory cytokines direct migration of neural stem cells during brain injury, suggesting that such a strategy for tissue regeneration may be shared by other stem cell systems (Imitola et al. 2004). Moreover, stem cell self-renewal can also be regulated by inflammation networks (Kiger et al. 2001, Singh et al. 2010). Stem cell regulation provides further grounding for the global autoregulatory network, as stem cell function is modulated by circadian rhythms, metabolism, diet, exercise, mating, aging, infection, and disease. It is likely that these physiological changes have systemic effects on stem cells in multiple tissues (Nakada et al. 2011).

Some authors further suggest that cross-tissue interactions via connective tissue establish regulatory networks at the organ level (Langevin 2006). Indeed, the role of fibroblasts and fibroblast-like cells as cellular communicators in such organ circuits as hypothalamus-pituitary-adrenal (HPA) axis (Slominski et al. 2007, Pérez-García et al. 2011), brain-gut axis (Burnstock 2009), or neuro-immune-endocrine network (Galoyan 2012, Julio-Pieper et al. 2011) is well documented. To this end, bioregulatory systems medicine supports the notion that a **multi-scale network of all molecular components and their within- and cross-tissue interactions can serve as a global autoregulation model of the human organism** (Figure 7).

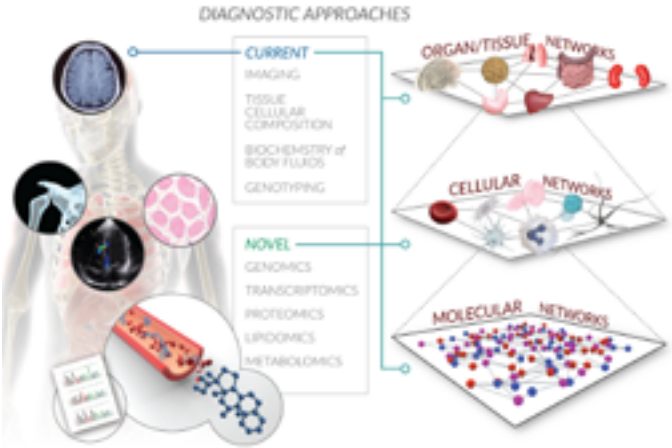

Figure 7. Multi-scale autoregulatory networks. *Bioregulatory systems medicine encompasses a systems biology perspective of interactions within and across multiple levels of biological organization. The complexity of a systems approach challenges common reductionist thinking, and paves the way for medicine that works with rather than against the inherent interconnectivity of biological organization. From the molecular to cellular to organ to whole organism network, the BrSM model acknowledges that human health and disease are driven by the regulatory information flow that propagates throughout this global autoregulatory network. Current diagnostic approaches are limited by capturing only a static snapshot of some of this information. Novel diagnostic approaches will confirm and provide higher resolution of existing snapshots of clinical information, and will expand its scope by adding (surrogate) biomarkers of autoregulatory capacity in one spatiotemporal model specific to the patient.*

As discussed previously, **there is a high level of molecular coherence in healthy tissues and the loss of molecular order corrupts "healthy" information flow in the tissue. Sustained corruption of "healthy" information flow (e.g. blocks to autoregulation) leads to the failure of regulatory networks' ability to restore molecular order.** As disease progresses, **an increase in the thermal degrees of freedom and a decrease in the molecular coherence of the affected tissues** is expected.

Modularity helps networks to contain perturbations and damage locally in order to support autoregulation and minimize the effects of disease on the system (Kitano 2004). Modules are self-organized units of individual components that are grouped according to a certain set of rules (e.g. a common function), and that are relatively independent in self-regulation. Modularity allows networks to optimize their dynamics and adapt to disturbances more effectively. In the event that one module fails, other modules may adapt their functions accordingly so that the whole network can reorganize without loss of overall functionality. Several thousand functional modules in gene and protein regulatory networks have been identified (Suthram et al. 2010, Hwang et al. 2009). These functional modules represent specific physiological processes in the body such as synaptic signal transduction, cell activation, insulin secretion, tissue remodeling, angiogenesis, the development of certain glands, and wound healing. **Signals from the microenvironment may also directly influence many functional modules of molecular networks.**

Another fundamental feature of autoregulatory networks is robustness. **Robustness can be defined as the ability to maintain homeodynamics of living systems in the face of perturbations and uncertainty** (Kitano 2007b). Whereas homeostasis is a property that maintains the state of a system, robustness maintains the functions of a system. More generally, a system is robust as long as it maintains functionality, even if it transitions to a new steady state or if instability helps the system to cope with perturbations (Kitano 2007b). This differentiation further helps to define the concepts of adaptation and compensation that are relevant to the incorporation of autoregulation in clinical practice. Although these concepts are often used interchangeably, we define adaptation as the ability to maintain the functionality of the biological network within the range of physiological parameters (or within homeostatic state), and compensation as the ability to maintain the functionality of the biological network outside the range of physiological parameters.

Metabolic syndrome provides a classic illustration of these two concepts. In the early stages of metabolic syndrome, when poor nutrition and inadequate exercise chronically increase fuel surfeit, a robust regulatory network may engage in certain adaptation mechanisms that will sustain glucose levels within a physiological range. In later stages, the body burden of dysregulation may increase, leading to increased cholesterol levels and possibly increased blood pressure, ultimately resulting in overall decompensation. As Dr. Hiroaki Kitano appropriately summarizes:

"We consider that metabolic syndromes take over inherent dynamics of our body that ensure robustness against unstable food supply and pathogenic infections, and lead to chronic inflammation that ultimately results in cardiovascular disease. This exemplifies how trade-offs between robustness against common perturbations (unstable food and infections) and fragility against unusual perturbations (high–energy content foods and low–energy utilization lifestyle) is exploited to form chronic diseases."(Kitano et al. 2004, p.S6)

A fundamental component of bioregulatory systems medicine is the understanding that robust networks are able to autoregulate (Jangi et al. 2014), **which may explain how functional states are adapted in response to perturbations.** As such, **persistent perturbation of biological networks, including endogenous responses to specific exogenous insults, can manifest as disease** (Schadt 2009, del Sol et al. 2010). In this context, a disease represents the perturbation or breakdown of a specific functional module caused by variation in one or more of the module's components, which, in turn, produces recognizable developmental and/or physiological abnormalities (Loscalzo et al. 2007). More simplistically, the human organism is continuously challenged by genetic, epigenetic, and environmental perturbations that "distort" biological networks and may lead to disease progression. In this context disease progression refers to blocks to autoregulation in relevant biological networks that cause persistent perturbations and may spread widely across the global autoregulatory network. This expansion can result in network "rewiring" and restructuring to new adaptation and compensation states, which gradually progresses throughout various stages of disease. When we consider disease progression and autoregulation in the context of molecular

coherence (discussed in the prior section), we can consider the loss of coherence as the loss of information processing capability of a biological network, which, in turn, leads to the loss of the ability to autoregulate.

Many diseases are interconnected by shared pathophysiological events. Given the hypothesis that human disorders should be viewed as perturbations of highly interlinked cellular networks, researchers predict that "diseases should not be independent from each other, but should instead be themselves highly interconnected"(Vidal et al. 2011, p.993). In light of this hypothesis, researchers constructed the disease network (Goh et al. 2007) based on shared metabolic networks (Lee et al. 2008), gene networks (Goh et al. 2007), protein networks (Suthram et al. 2010), and, importantly, shared networks of clinical data (Christakis et al. 2009). After analyzing shared protein networks in fifty-four diseases, including endometriosis, malaria, depression, Alzheimer's disease and various cancers, Suthram et al. (2010) identified as a set of 59 network modules that were dysregulated in at least half of the diseases and suggested that this network represents a "common disease-state signature".

We can postulate that **this "signature" may represent the common denominator shared by many diseases we see in clinical practice.** For example, it is suggested that a network of neuroimmune interactions controls inflammation in multiple diseases via nervous, endocrine, and immune systems (Otmishi et al. 2008). By treating such a denominator with specific multitarget interventions (e.g. medications with bioregulatory properties), we may alleviate several co-morbidities typically presented in a chronic patient. Additionally, the majority of diseases share a certain number of common functional modules. It is possible that a complete picture of annotated functional modules would allow the clinician to identify and interpret changes in the gene or protein networks obtained from patients' tissue samples (e.g. whole blood) for diagnostic purposes. In this sense, functional modules such as genomic or proteomic panels could serve as biomarkers (Baker 2005) to define a patient's autoregulatory status, though further research is necessary to draw more definitive insight.

The existence of a "common disease-state signature" and common functional modules further encourages the scientific community to design medications that target biological networks instead of single molecules. In this regard, the future of network pharmacology (Erler & Linding 2010, Li et al. 2011) is rooted in the idea that **a network approach can be used to identify common pathological threads between seemingly unrelated diseases, to improve the understanding of the pathogenesis and, therefore, to aide in the discovery of the most influential therapeutic access points.**

2.2.3 Biological Communication at the Microenvironment-Scale

Fundamental to bioregulatory systems medicine is the appreciation of the role of the microenvironment as a critical supporter of healthy cells (Buttle 2007) and as the conduit of biological information in tissues (Xu et al. 2009). A healthy microenvironment consists of the local surrounding with which cells interact by processing various chemical and physical signals and by contributing their own effects to this environment. In addition to tissue-specific cells, immune and nerve cells are also involved in maintaining tissue homeostasis. Cell turnover is a key means of adult tissue homeostasis in many human organs. Defects in cell turnover underlie many adult-onset diseases, such as cancer and degenerative disorders, and may also contribute to aging (Pellettieri & Sánchez Alvarado 2007). Bioregulatory systems medicine considers both the cell and its extracellular matrix (ECM) - not the cell alone - as the collective functional unit in higher organisms.

The ECM is itself an informational entity that is an extension of the intracellular molecular network, and integrates structural and functional signals that allow for differentiation in cell shape and structure. Communication between the ECM and the cell nucleus is dynamic and reciprocal (Bissell et al. 2003), such that dynamic reciprocity explains information flow in the microenvironment. The mature local microenvironment tightly regulates and controls cellular fates to maintain molecular order and healthy cell turnover within the tissue (Huang & Ingber 2006) **via the ECM, intracellular cytoskeleton, and nuclear matrix, which are directly interconnected through a chain of commonly utilized molecules.** The dynamic, bidirectional cross talk between the ECM and the cell membrane influences gene expression by connecting ECM-ECM receptor interactions to the cytoskeleton, nuclear matrix, chromatin, and back again (Nelson & Bissell 2006).

In the context of bioregulatory systems medicine, Biological Communication at the Microenvironment-Scale considers biological networks of the tissue microenvironment as the "terrain of the body"(Genuis 2012), **where signals of various origins (biochemical, physical and neural) are coupled and processed**, and can, in turn, influence network robustness. For example, **excessive breakdown of the ECM components associated with altered levels of reactive oxygen species (ROS) can result in the modification of multiple molecular networks across tissues and subsequent pathology** (Kar et al. 2010, Kashihara et al. 2010, Vacek et al. 2012). **ECM signaling has also been shown to help with immunological synapse formation in the immune system** (Springer & Dustin 2012), control of the inflammatory reflex at the neuro-immune synapse (Dustin 2012), inflammation resolution (Widgerow 2012), and in the maintenance of physiological inflammation (Sansonetti 2011).

In addition to signaling molecules, information flow between

tissues and cells is also regulated by gap junction (GJ) proteins, which are most likely regulated by noncoding RNAs (Rau et al. 2011, Ye et al. 2011). Recent research has revealed the involvement of GJ proteins in the regulation of stem cell niches (Peiris & Oviedo 2013) and in the protection of tissue cells from toxic insults (Klee et al. 2011). This line of research points to gap junctions as an important focal point for further scientific and clinical inquiry, as GJ communication encompasses a physiological phenomenon that modulates cellular behavior at both the local and systemic levels (Peiris & Oviedo 2013).

In the clinical context, the cardinal role of the microenvironment as a cellular information exchange center positions the ECM as a point of intervention. Research supports the existence of pathological links between the microenvironment and diseases such as cancer (Iozzo & Sanderson 2011), poor wound healing (Schultz et al. 2011), airway remodeling disease (Burgess 2009), and hypertensive heart disease (Berk et al. 2007). Moreover, **the ECM is involved in the progression of almost any chronic disease, most notably in fibrotic diseases (e.g. most solid tumors, arthritis, osteoporosis, COPD and emphysema)**, suggesting that molecules associated with ECM metabolism may serve as biomarkers for disease progression (Zannad & Pitt 2009).

Future clinical research may also consider whether bioaccumulation of toxins in tissues can negatively influence cellular health, **as environmental toxins and metabolic waste products can accumulate in the ECM and cause disease.** Recent research in various health disciplines demonstrates that deficiency and toxicity are common etiological determinants of contemporary ill-health (Genuis 2012). Bioaccumulation of pesticides in adipose tissue, for example, increases the total burden of intoxication and may lead to neuro, immune, and endocrine toxicity (Crinnion 2000). Additional research reveals that immune activation occurs not only in response to infection, but also in response to physical, chemical, and genotoxic tissue stress (Papatriantafyllou 2011). This line of research strongly suggests a relationship between bioaccumulation of environmental toxins and perturbations in the immune response/inflammatory network.

In sum, the fundamental role of the ECM in cellular and tissue function supports the microenvironment as a key focal point for therapeutic developments in bioregulatory systems medicine. The involvement of the microenvironment in nearly all pathological conditions, due in large part to its signaling pathways and cross-tissue regulatory molecular networks, positions microenvironment information regulation as a highly influential process at both the local and systemic levels.

2.2.4 Inflammation Physiology

Since Cornelius Celsus defined the four basic signs of inflammation in the first century, the revelation and investigation of its physiological basis has been a major focus of the medical and scientific community. Today, inflammation is commonly associated with many prevalent disorders, and uncontrolled inflammation is seen as one of the key players in many chronic and age-related diseases of Western society (Freund et al. 2010).

Despite this association, not all inflammatory responses are necessarily harmful; rather, inflammation plays an essential physiological role in responding to stress, dysfunctional tissue states and injury (Medzhitov 2008). **Inflammation that is caused by stressed, apoptotic cells, or metabolic changes provides an extension of the autoregulatory capacity of the organism and helps to maintain and/or restore a healthy functional tissue state** (Medzhitov 2010, Serhan & Savill 2005). The scientific community has, in fact, coined the term “sterile inflammation” to refer to inflammation that is induced by endogenous signals released from stressed, malfunctioning, or dead cells and tissues (Chen & Nuñez 2010).

Inflammatory responses also play a critical role in maintaining and/or restoring cell and tissue health. In the case of unfavorable environmental conditions, a specific low level of inflammation called “parainflammation” is induced to restore tissue robustness and deter progression to subsequent damaged states (Medzhitov 2008). Tissue states are also permanently monitored by tissue-resident macrophages that express inflammatory mediators to recruit further inflammatory cells if needed (Medzhitov 2010), as in the event of necrotic or apoptotic tissue removal. In the case of myocardial infarction and stroke, for example, tissue destruction can paradoxically be the result of a restored blood flow in response to the recognition of damage-associated patterns and an inflammatory response to necrotic cells (Eltzschig & Eckle 2011).

The regulation of inflammatory responses is steered by an orchestra of molecules. Pro-inflammatory mechanisms and anti-inflammatory and pro-resolution pathways are activated simultaneously to limit the severity and duration of the inflammatory response, and to **allow for resolution - the ideal outcome of acute inflammation - to occur** (Freund et al. 2010, Nathan & Ding 2010, Serhan et al. 2007, Perretti & Dalli 2009, Serhan et al. 2004, Valledor et al. 2010). Inflammation resolution is an active process triggered at tissue level, in which endogenous anti-inflammatory and pro-resolving mediators actively counter-regulate the onset of inflammation in order to promote resolution (Serhan 2010, Ariel et al. 2006, Perretti & Dalli 2009). Known specialized pro-resolving lipid mediators include resolvins, lipoxins, protectins, and maresins, the expression of which creates defined regulation checkpoints that steer the inflammatory process (Serhan 2010, Serhan et al. 2002, Serhan & Savill 2005, Fredman & Serhan 2011, Recchiuti et al. 2011, Serhan et al. 2009, Serhan et al. 2004).

In this regard, **the inflammatory status of a tissue is determined by its balance of pro- and anti-inflammatory factors, including external signals.** Pathology occurs in the case of inflammatory mediator imbalance, in which the inflammation cannot be resolved. For example, if pro-inflammatory mediators persist without sufficient pro-resolving molecules, inflammation becomes chronic and is maintained by positive feedback loops (Freund et al. 2010, Nathan & Ding 2010, Perretti & Dalli 2009, Serhan et al. 2007). In this way, a local imbalance can lead to systemic inflammation. **It is assumed that local inflammatory pathways in the body are mirrored by systemic inflammation, which is one of the underlying pathological mechanisms of many diseases.**

The cardinal role of inflammation physiology in responding to stressors and restoring autoregulation reveals that the inflammatory process itself is not dangerous; rather, it is an inadequate response to either excessive or insufficient inflammation that leads to pathology (Valledor et al. 2010). Non-resolving, chronic inflammation is the common thread in many chronic diseases such as COPD, obesity, atherosclerosis, cancer, multiple sclerosis, asthma, IBD, rheumatoid arthritis, diabetes, neurological disorders, and others (Raison et al. 2006, Ridker 2009, Nathan & Ding 2010, Serhan 2010, Hellmann et al. 2012). The role of the acute inflammatory response in this context is less clear. Although an acute inflammatory reaction is generally treated as an acute exacerbation that needs to be prevented, some evidence suggests that an acute inflammatory response might be an endogenous feedback loop that primes the immune system for anti-inflammatory action (Wermeling et al. 2013). Moreover, there is evidence that elimination of TNF-α signaling, known to be a key factor in the development of inflammatory bowel disease (IBD), leads to the enhancement of chronic inflammation and increased apoptosis of colonic epithelial cells in the mouse model (Wang et al. 2013). If this is true, **acute inflammation should not be blocked, but rather initiated or supported in order to induce resolution.** This also means that acute inflammation is a homeostatic mechanism that should be allowed to take its natural course toward resolution. In this context, initiation is achieved by improving self-regulatory abilities of the patient that naturally manifests as acute inflammation. Nonetheless, caution should be taken in overgeneralizing this phenomenon, which may not present itself in other tissues or organs, such as the brain, for example. It still remains to be seen whether this approach can be used as a therapeutic tool. Whereas **the pathological consequences of non-resolving inflammation include tissue injury** (Rock & Kono 2008), **fibrosis** (Nathan & Ding 2010), **and scar formation** (Gilroy et al. 2004), **acute inflammation might be necessary to return from a disease state to health** (Serhan & Savill 2005). This distinction is critical for bioregulatory systems medicine, which recognizes that medical challenges associated with inflammation are not tied to the occurrence of inflammation itself, but to the persistence of factors that originally triggered the inflammation, and to the inability of the body to regulate the inflammatory response and, in turn, curtail disease progression.

2.2.5 Inflammatory Network Response to Perturbation

From a molecular network perspective, **the loss of molecular order triggers acute inflammation**. Acute inflammation is subsequently induced by **functionally capable auto-regulating tissue in an effort to maintain or restore the order in the system. As a mechanism switched on by exogenous or endogenous stressors released during tissue injury, malfunction, and stress**, acute inflammation supports the creation of a new homeostasis and functional set-point in cases of severe disturbance (Medzhitov 2008), such as those induced by environmental changes or pathological conditions. Modern advances in molecular biology and genetics shed more light on mechanisms of such inflammatory response, as in the case of mammalian MAPK (mitogen-activated protein kinase) signal transduction pathways. These pathways are activated by environmental stresses and inflammatory mediators including hormones, growth factors, cytokines, pathogen-associated molecular patterns (PAMPS), and danger-associated molecular patterns (DAMPS), and they orchestrate the recruitment of gene transcription factors, cell cycle control, cell death, and differentiation (Kyriakis & Avruch 2012). Nonetheless, some authors propose that the various strategies that an organism uses to deal with specific tissue damage are of general origin and implicate similar genes and transcription factors (Medzhitov et al. 2012).

The human body has the capability to synthesize and control molecules that promote or resolve inflammation. Endogenous inflammatory mediators can have pro- and anti-inflammatory, as well as pro-resolving, effects (Serhan et al. 2008). Acute inflammation can therefore act as a driver of both disease progression and regression (Ariel et al. 2006), depending on the positioning, timing, and population of leukocytes during the course of inflammation (Buckley 2011).

Therapeutic strategies must therefore accurately consider the ways in which nodes of a network should be targeted in the context of the inflammatory response, as well as the risks associated with long-term, partial, or complete interruption of the inflammatory process (Nathan & Ding 2010). Many of the current conventional medical treatments for diseases linked to chronic inflammation are largely focused on achieving relief of prominent symptoms by partly or completely suppressing inflammatory pathways. As such, patients who are given these treatments often experience a recurrence of the symptoms after the cessation of a therapy.

In order to achieve ideal patient outcomes, bioregulatory systems medicine recognizes that medications should not be designed to block or dampen inflammation as a means to relieve symptoms. Medications should instead be designed to mimic and support the body's innate resolution mechanisms based on the specific context of the individual

inflammatory event, thereby increasing the potential to alter disease progression with minimal side effects. The future of therapeutics lies in those treatments that can promote or modulate the resolution process (Perretti & Dalli 2009, Serhan 2011, Rogerio et al. 2012).

2.2.6 Microenvironment Response to Inflammation

Available data point toward promising **treatment options for various human disorders based on the support or modulation of the patient's individual inflammation resolution process** (Tabas 2010, Filep 2009, Li et al. 2009, Merched et al. 2008, Duffield et al. 2006, Martins et al. 2009, Bannenberg 2009, Serhan et al. 2008). Consideration of the environment in which inflammation occurs and its influence on the inflammatory process is of critical importance. **Inflammatory reactions often occur within distinct microenvironments comprised of tissue specific cells (fibroblasts, endothelial cells, and macrophages) and their specialized ECM components** (Serhan et al. 2007, Lax et al. 2007, Buckley 2011). Fibroblasts play an active role in chronic inflammation, as disordered fibroblast behavior can lead to sustained recruitment, inappropriate retention of leukocytes, and enhanced survival of cells (Buckley et al. 2001, Buckley 2011). Thus, it is appropriate to target the tissue microenvironment in addition to the stressor and the infiltrating immune cells in treating chronic inflammation. As mentioned above, chronic inflammation is associated with many age-related diseases including Alzheimer's, atherosclerosis, osteoarthritis and cancer (Caruso et al. 2004). Across the lifespan, individuals regularly encounter internal and external antigenic stress, which activates the immune system and, over time, leads to the accumulation of antigenic burden (Freund et al. 2010). This persistent, low-level immune activation along with the increase of the basal expression of inflammatory factors can initiate and maintain substantial chronic inflammation (Vasto et al. 2007, Caruso et al. 2004, Franceschi et al. 2000). Only when the stressors are addressed can chronic inflammation be resolved. **An active lymphatic system that promotes lymphatic drainage and cell migration is important to help the body to eliminate or minimize those stressors, resolve the inflammation, and to return to a healthy state** (Kataru et al. 2009).

Given that **the communication between a cell and its microenvironment is bidirectional and forms the basis of the homeostatic control of many tissues**, inflammation and changes in the microenvironment can, collectively, have a significant impact on many bodily functions. The promotion of tumorigenesis, as one part of a dual role of the immune system in cancer, is just one example of how changes at the cellular level can drive systemic chronic inflammatory disorders (Grivennikov et al. 2010, Schreiber et al. 2011).

Bioregulatory systems medicine's emphasis on inflammatory processes and the environment in which they occur may be particularly applicable in the context of stem cells niches, due to the ability of niches to alter the long-term regenerative potential of a tissue and the inflammatory system's regulation of stem cells. Stem cells exist in niches, which act as basic physiological units that integrate signals in order to mediate stem cell response to organism needs. Niches essentially regulate the extent to which stem cells are involved in tissue repair, generation, and maintenance. Niche responses are partially mediated by extracellular matrix components, while metabolic products such as calcium also affect stem-cell responses to various tissue states (Scadden 2006). The potential to influence stem-cell niches through medication begs the question of whether using niches as drug targets may be a valuable treatment component. While niche manipulation has been broadly considered in the context of various chronic conditions such as cardiac repair, diabetes, and cancer (National Institutes of Health 2006), these concepts may apply to regulation and mediation of chronic inflammatory conditions. By targeting the inflammatory system in treatment, stem cell niches may be influenced by and, in turn, impact the regeneration of affected tissue.

The ECM is also directly involved in the initiation and resolution of inflammatory responses (Sorokin 2010), as metabolic waste products or exogenous particles that accumulate in the ECM can function as inflammatory inducers. Environmental factors such as diet, exercise, and lifestyle are known to affect metabolic pathways (Turnbaugh et al. 2006) and intestinal mucosal permeability (Conterno et al. 2011, Cani, Neyrinck, et al. 2007, Goebel et al. 2008), potentially inducing mucosal inflammation (Cani, Amar, et al. 2007, de La Serre et al. 2010). Obesity often causes physiological perturbations such as oxidative stress and chronic systemic inflammation (Conterno et al. 2011).

Consideration of the environment or "terrain" in which inflammation takes place offers further insight in targeting the causes of conditions associated with chronic inflammation, beyond targeting symptoms. Due to the biological complexity of chronic inflammation, however, the same intervention could produce different effects in different patients at different times. Future therapeutic systems would benefit from the ability to assess an inflammatory patient's profile, which could then help to identify and locate resolution blockages and underlying pathologies. The ability to measure the history and culmination of an individual's resolution factors over time would allow the clinician better to evaluate and treat the inflammatory status of a patient.

2.2.7 Diagnostics and Therapeutic Strategy

Current therapeutic strategies incorporate the assessment of genetic predisposition (in some cases, even modifying genes by genetic engineering), the elimination of causative agents, and the modification of resulting pathogenesis. However, in order to achieve significant improvements in patient outcomes, the complexity of the human organism and the role of this complexity in health and disease should be considered of critical importance in any therapeutic strategy. Bioregulatory systems medicine therefore employs the following three fundamental principles in guiding its strategic approach:

1. The autoregulatory network is the primary therapeutic target, instead of the trigger or the symptomatic effect of the trigger on the body.

2. The status of the autoregulatory network and the disease progression of the condition determine the intervention.

3. Interventions utilize multicomponent, multitarget medications that act in concordance with the multiple network interactions, feedback loops, and biorhythms inherent in autoregulatory networks.

As discussed in prior sections, bioregulatory systems medicine emphasizes improvement in patient outcomes through the support and modulation of the endogenous autoregulatory network in the context of the disease trigger and individual predisposition (see Introduction). This approach distinguishes bioregulatory systems medicine from the conventional paradigm, which focuses, in many cases, on treating the symptoms that result from the autoregulatory network's response to the stressor. In her Science article Polly Matzinger suggested that immune response can be activated not only by the presense of foreign pathogens, but also by "danger signals" from the microenvironment (Matzinger 2002). This local immunity is primarily determined by the presence of self-reacting tissue-localized immune cells (Matzinger 2002). Local immune responses can induce autoregulatory loops regulating systemic effects, and manifesting as symptoms like fever (Cartmell et al. 2003). It has been demonstrated that suppression of fever is associated with poorer patient outcomes (Sugimura et al. 1994). It was also proposed that blocking fever with antipyretics may interfere with normal immunological development in the brain during pregnancy (Torres 2003). Unsurprisingly, some authors suggest that antipyretic therapy should be used with caution. However, it might be justified if the metabolic costs of fever is exceeded by its physiological benefits, and if the treatment reduces these metabolic costs without adversely affecting the physiological course of the fibrile illness (Greisman & Mackowiak 2002).

Therapeutic decisions in bioregulatory systems medicine are made based on the capacity of the affected autoregulatory network in relation to the causative stressor. Many diseases are not driven by the stressor, which may only be the initiating event, but rather by the organism's failed attempt to regulate in light of the stressor. In an acute infective disease, for example, a patient with a well-functioning autoregulatory network may be able to overcome a stressor such as a bacterial infection, though support from bioregulatory systems medicines may be necessary. Another patient with an impairment of the autoregulatory network, by comparison, may need intervention in the form of an antimicrobial in addition to more comprehensive autoregulatory network support.

Bioregulatory systems medicine views symptoms and signs only as the "footprint" of autoregulatory network activation. Beyond easing patient discomfort, symptoms should not be suppressed, but instead used as a guide to evaluate the status of the autoregulatory network for subsequent clinical decision-making. In accordance with this perspective, diagnostic measurements that concentrate only on causative factors and their effects miss the opportunity to assess the autoregulatory network as an important therapeutic target. **Diagnostic measurements should therefore be expanded beyond current markers to include the assessment of autoregulatory networks and blocks to autoregulation.** Such measurements have yet to be developed, though, as effective methods for assessing patient autoregulatory status, remains an area in need of further research and clinical testing.

A clinical model that guides therapeutic decision-making based on the assessment of tissue molecular networks in the context of the patient's auto-regulatory ability is better suited for accurate prediction of disease outcomes, intervention follow-up, and disease prevention. The autoregulatory state, as determined by homeostatic ability and robustness (see Autoregulation of Bioregulatory Networks), can offer a number of therapeutic targets for diseases with multi-factorial causes or of idiopathic origin. In fibromyalgia, for example, the pathology can be traced to several perturbed networks, such as the pain processing network in the brain and the neuroendocrine network, which encompasses the hypothalamus, pituitary and adrenal glands (Broderick & Craddock 2013, Cifre et al. 2012). However not all of these networks will be equally affected across patients with this condition. The therapeutic decision must therefore be individualized and based on an individual patient's ability to regulate the network perturbation, rather than the blanket, all-inclusive treatment currently favored by the conventional paradigm.

Within this approach, **bioregulatory medical interventions can range from supporting autoregulatory capacity in the relevant networks, to actively provoking a stimulus to restore autoregulatory capabilities and clear the blocks to autoregulation. Medications with bioregulatory properties should not permanently interfere with the body's autoregulatory networks**, but should instead be a temporary intervention with the goal of leaving the system in an optimal

state. The bioregulatory systems medicine approach is also preventative in the sense that the optimization of the relevant autoregulatory networks can (and should) take place even in the absence of disease, or when chronic diseases are in remission. **In diseases with a chronic relapsing course and relatively good health during the remission period, regulation can be regained by eliminating the stressor (spontaneously or via appropriate medical intervention), clearing the blocks to autoregulation, or supporting the autoregulatory network.** Such treatments include medications, manual therapies, and lifestyle changes.

In support of bioregulatory systems medicine's intervention strategy, **the degree of the body's dysregulation can be classified into basic patterns which can then serve therapeutic decision-making.** This classification is currently based on the working hypothesis that the clinical picture of inflammation and its resolution can be used as a surrogate to define the status of the autoregulatory network. It is important to note that this hypothesis recognizes that the inflammatory network is not the only perturbed system of a particular disease, or even the main target of the therapeutic approach; the endocrine, neurological, and other systems are inevitably affected as well. The clinical picture of inflammation, however, may be used as a surrogate marker to classify known diseases in order to predict the status of the autoregulatory network.

In the future, **the integration of all molecular diagnostic techniques will provide a more detailed picture** of the status of the individual's regulation capability and disease progression in the patient. **Novel diagnostic solutions, including measuring heart rate variability, complex molecular biomarker panels, and 'omics' technologies including whole-blood deep sequencing, will allow for the assessment of the global autoregulation/compensation state and the organism's response to the bioregulatory treatment**. This type of assessment will also allow the clinician to make therapeutic decisions and adjust them depending on the outcome of the intervention along the disease-health continuum. Additionally, **the modeling of a disease as a molecular/cellular network will lead to the development of novel diagnostic test systems tailored to multitarget therapies** (Erler & Linding 2010, Kuepfer 2010) that reflect system complexity more accurately than conventional diagnostic techniques.

2.2.8 Clinical Focus on Dysregulation

As a therapeutic strategy, bioregulatory systems medicine holds significant potential in the clinical context, both as a standalone treatment and as an adjuvant treatment. Specifically, there are several benefits to approaching the autoregulatory network as a therapeutic target:

1. By addressing the dysregulated system, the clinician allows for the organism to become resilient against a number of stressors.

An example of this benefit is evident in the treatment of allergies. The allergic patient typically exhibits an immune system that is dysregulated into a Th2 state in the early stages (Robinson 2000). Classical medicine emphasizes the avoidance of and tolerance to the single allergen (stressor). Depending on the main allergen, the patient is often asked to avoid household dust, pollen, nickel, etc., and may also be asked to take small, attenuated doses of the allergen to induce tolerance. This is also the basis for desensitization procedures.

Although this treatment approach may work if the patient is allergic to only one substance, it is often the case that the patient is allergic to numerous substances, or that the specific allergen cannot be determined. The pathophysiology of allergy is complex, however, as immune network perturbation is just one of the factors contributing to the disease. This complexity is clearly illustrated in the case of atopic dermatitis (Eyerich & Novak 2013).

In bioregulatory systems medicine, **the aim is to regulate this state into a balance between Th1 and Th2,** correcting numerous network perturbations and **thereby restoring the normal autoregulation.** This regulation may take months to achieve, or even several seasons in the case of seasonal allergies. In severe cases, bioregulatory systems medicine can provide an adjuvant treatment to conventional treatment in the early stages of treatment. Then, as the autoregulatory network recovers, bioregulatory systems medicine can serve as the standalone treatment.

2. In diseases where the stressor and the dysregulated immune system are engaged in a perpetuating cycle, blocks to recovery can be addressed to allow for regulation to take place.

Patients with chronic eosinophilic (allergic) fungal rhinosinusitis (Van Bruaene et al. 2008), for example, exhibit immune dysregulation into a Th2 state with the resulting predisposition for a fungal infestation (Pakdaman et al. 2011, Pant & Macardle 2014, Wang et al. 2014). The fungal infection perpetuates the eosinophilia via Type I hypersensitivity, while the Th2 state immune dysregulation allows the fungus to flourish, resulting in a vicious cycle. Treatment that targets only the fungus or the eosinophilia-triggered inflammation often does not have the desired result; however, including the immune regulation with bioregulating medicines adds a powerful therapeutic benefit. In this regard, **when treating conditions of severe regulation rigidity without the adequate and timely restoration of regulation, a more comprehensive treatment program is necessary to remove all stressors and blocks to autoregulation/compensation, and to apply the appropriate courses of bioregulating medicines.**

Autoimmune diseases present another case of immune system dysregulation. Extensive research over the past decade on the functions of Treg cells provides evidence that this immune cell population is located in different cellular environments and plays an indispensable role in the maintenance of self-tolerance and immune homeostasis (Sakaguchi et al. 2012). Evidently, many mechanisms in different anatomical locations are contributing, to various extents, to self-tolerance. These mechanisms could be targeted for therapeutic intervention (Sakaguchi et al. 2012). The major challenge bioregulatory systems medicine faces is determining how all critical mechanisms can be influenced in order to achieve the sustainable restoration of physiological regulation.

3. Diseases that share common networks and often manifest together can be treated comprehensively, not only symptomatically.

It has been suggested that **numerous diseases including asthma** (Xiao et al. 2011), **chronic rhinosinusitis** (Tieu et al. 2009), **atopic eczema** (De Benedetto et al. 2011), **chronic fatigue syndrome** (Maes & Leunis 2008), **and fibromyalgia** (Goebel et al. 2008) **are influenced by a breach in the integrity of epithelial membranes.** The so-called functional somatic syndromes, including irritable bowel syndrome, fibromyalgia, and chronic fatigue syndrome, are often considered psychosomatic given the absence of a single biomarker and the inadequacy of current therapeutic solutions. From a system biology perspective, however, the perturbed networks collectively offer a clear picture of dysregulation. By addressing the perturbed networks in the absence of an available biomarker, treatment can both restore regulation and relieve the syndrome.

4. Treatment is possible in the case of asymptomatic disease in order to optimize the autoregulatory network.

Diagnostic methods that assess the status of the autoregulatory network will be of particular use in defining this point of optimization, and in allowing for preventative treatment through medications with bioregulatory properties.

5. **When certain heritable diseases and diseases where organ failure and tissue damage are at the point at which autoregulation is impossible to restore, bioregulatory systems medicine can still be used to treat symptoms and prevent sequelae, rather than as a standalone treatment.** Therefore, bioregulatory systems medicine can serve as an adjuvant **treatment to reduce polypharmacy, provide effective and safe relief of symptoms, and prevent cascade iatrogenesis.**

By approaching the autoregulatory network as the target for clinical focus, bioregulatory systems medicine serves as a powerful adjunct tool for conventional medicine as well as a potential solution to therapeutic gaps that currently exist in the clinical context.

2.2.9 Bioregulatory Clinical Pharmacology

One of the primary distinctions between bioregulatory systems medicine and the conventional paradigm is found in their approaches to intervention. In conventional biomedicine, molecular pharmacology is considered the cornerstone of drug discovery. Paul Ehrlich is often quoted for his postulate of creating "magic bullets" for the use in the fight against human diseases (Gertsch 2011). Bioregulatory practices prefer to focus on using interventions that support the body's own regulation mechanisms.

Given the systemic nature of these regulatory mechanisms, bioregulating interventions must be designed to act on the multiple networks involved in disease processes. In this regard, a fundamental principle of bioregulatory systems medicine is the understanding that **medications with bioregulatory properties can act on multiple organ systems and multiple targets in disease-related molecular networks simultaneously.** The multicomponent medication HE-300, for example, modulates regulatory networks of genes associated with synaptic function and plasticity to treat pathophysiological processes in Alzheimer's disease. The success of this combination lies in its ability to target several functional modules associated with the physiological functions of cognition and learning, synaptic plasticity, vesicle transport, and β-amyloid binding (Schnack et al. 2011). Similarly, Cerebrolysin, a neuropeptide preparation from pig brain tissue lysate (Anderson 2013), mimics the action of endogenous neurotrophic factors on brain protection and repair, and decreases dementia-associated β-amyloid deposition by regulating molecular enzyme machineries, increasing synaptic density and neuronal tissue plasticity, and restoring neuronal cytoarchitecture (Masliah & Díez-Tejedor 2012). Other approaches currently explore the therapeutic potential of multicomponent chemokine-like low-affinity-binding peptide combinations that are designed to modify, but not neutralize, the multiple components of the disease-related networks and display a non-linear dose response (Ezerzer et al. 2009).

When **medications with bioregulatory properties are of natural origin, their functions are determined by natural combination chemistry and synergy,** as their biological activity often results from the additive or synergistic effects of their components. In some cases, the known active ingredients are potentiated by other components, whereas in other cases they may reduce the toxicity of the active ingredient. Some authors argue that "natural" products are particularly effective because their multicomponent nature utilizes complex and diversified strategies to combat disease progression. Indeed, foundational to the BrSM model is the understanding that "about 250,000 living plant species contain a much greater diversity of bioactive compounds than any chemical library made by humans," such that "evolution has been selecting and perfecting diverse bioactive molecules for much longer

than any pharmaceutical company" (Raskin et al. 2002, p.524).

These synergistic strategies can be much more comprehensive and broader in their scope of effects than single-component drugs (Lila 2007), though the underlying concept is not new. Synergy is a ubiquitous phenomenon in nature and is widely used in numerous scientific disciplines, including thermodynamics, biophysics, biochemistry, molecular biology, and neurobiology (Corning 1998). The synergy of biological effects of plants in medicine is well documented, and encompasses synergistic multitarget effects, physicochemical effects based on improved solubility, antagonization of resistance mechanisms, and elimination or neutralization of toxic substances (Wagner 2011). As such, **multi-combination and/or multi-system low dose medications, preferably of natural origin, are well suited for the bioregulatory medical approach and offer the potential for a graded response to treatment.**

In the context of bioregulatory systems medicine, **the efficacy of a complex medication is determined by its ability to influence multiple interactions to reverse the clinical picture of disease.** Combinatorial strategies can be broadly used to design effective formula medications, specifically through the inhibition of pathophysiological pathways implicated in a disease, and the simultaneous modulation of other interconnected pathways that contribute directly or indirectly to the reversal of disease progression. In this regard, **biological information of regulatory networks can be directly and purposefully influenced with multitarget medications** (Figure 8). In addition to new medication design, this strategy can be applied to the vast dataset[b] of existing drugs to create new, unique formulas. This approach is already being used in the development of cancer therapeutics, where eight drugs have currently been launched that inhibit more than one regulatory enzyme. Evidence suggests that "this multiple target activity has proven advantageous in an oncology setting" (Gertsch 2011, p.1087).

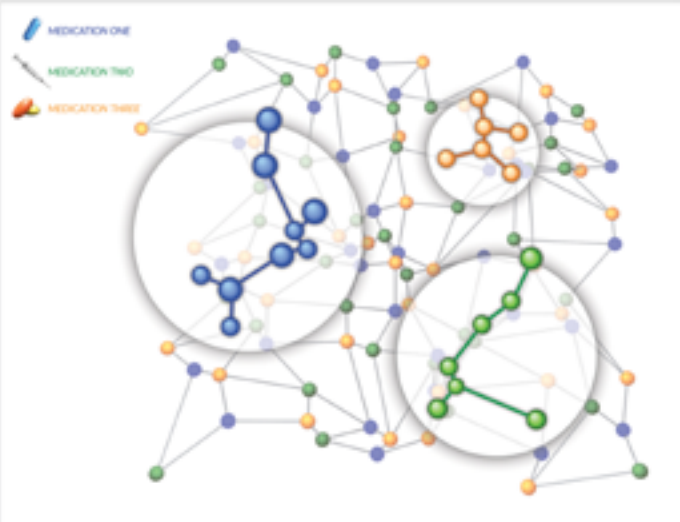

Figure 8. Bioregulatory Clinical Pharmacology. *A fundamental postulation of bioregulatory systems medicine is that medications with bioregulatory properties facilitate autoregulation by acting on multiple targets (nodes) in disease-perturbed networks simultaneously. In this way biological information flow can be directly and purposefully influenced. The efficacy of this multitarget mode of action is determined by the ability to reverse the clinical picture of disease.*

A multitarget medication strategy inevitably raises questions about the number of known molecular targets that can be used for future combination design. Whereas current databases include targets derived from biological information sequencing, there is little evidence on autoregulatory network information. Future database development that considers the complexity of regulatory information will likely expand the drug target landscape to unprecedented levels. Nonetheless, existing knowledge can support the design of multitarget medications that will act on multiple targets across known disease networks. Specifically, three drug design strategies are suggested in the literature:

1. Use multiple individual medications in therapy schemes (Pimenta et al. 2014);

2. Develop multicomponent medications that contain two or more active ingredients (Zimmermann et al. 2007);

3. Develop single-component medications that act on multiple targets simultaneously (Csermely et al. 2005).

Bioregulatory systems medicine embraces all three strategies, to the extent that they support the intent of **neither blocking nor interfering with endogenous resolution pathways that help to reduce therapy side-effects and promote long-term benefits. Inhibitory pharmacological intervention may also be an option of choice when a single disease causative factor is identified and must be eliminated, and there is insufficient time to complete a proper bioregulatory treatment,** as in the case of acute MI or stroke.

Bioregulatory systems medicine also endorses the idea that **when multiple independent targets of the same pathway are inhibited simultaneously, a mild inhibition of each target is sufficient to achieve a much larger therapeutic window and a therapeutically relevant effect** (Yang et al. 2008). Certain natural products in botanical drugs can weakly target different proteins within the same signaling network, thus shutting down the entire signaling process simply through network pharmacology or biochemical synergism (Gertsch 2011). For example, recent evidence shows that a combination of St. John's Wort and passion flower extracts resulted in greater anti-depressant effects at four times lower concentrations than St. John's Wort extract alone (Fiebich et al. 2011). Another study revealed that vasorelaxant properties of Vertigoheel combination are emerging from enhancing cyclic nucleotide (cAMP/cGMP) signaling in the arterial wall by synergistic stimulation of adenylate cyclase and inhibition of phosphodiesterase 5 (Heinle et al. 2010). These examples illustrate the therapeutic potential of synergy through combinations composed from components in relatively low molecular concentrations. Some evidence even indicates

that increasing active ingredient concentration from nano-range dose to micro-range dose may result in the loss of the synergistic action of the whole combination (Crippa et al. 2008).

Generally speaking, medications used in the BrSM model exhibit four fundamental advantages of a multicomponent, combinatorial strategy over a single-component strategy:

1. **Synergistic effects target a wider range of information flow in disease-related biological networks**;

2. Modest modulation allows for more efficient control of biological networks;

3. Low concentrations ensure higher safety of the whole combination;

4. Drug resistance is much less probable (Kong et al. 2009).

Among the advantages of the multicomponent, combinatorial strategy is the potential to target multiple nodes of the autoregulatory networks that are perturbed and involved in disease progression. These networks may be tissue-specific or systemic, encompassing inter-organ interactions. Therapeutics designed to bioregulate these networks may include combinations that target specific tissues and organs, aiming **to restore molecular coherence** and enhance tissue plasticity (e.g. by modulating stem cell regulation). These therapeutics may also influence networks that are present in many tissues (e.g. inflammation molecular network), thereby aiming to achieve resolution of the distorted information flow throughout the whole body. To this end, **bioregulatory systems medicine is a method of choice in treating multi-factorial disease when restoration of autoregulation of perturbed biological networks is still achievable**, although the challenge remains to define the principles by the combination of treatments can be made. Molecular diagnostics and medication "fingerprinting" based on whole-genome analytical platforms (e.g. pharmacogenomics) may provide a solution.

Furthermore, **the concurrent and gentle use of more than one natural substance in alignment with a network medicine approach may offer a safe and effective alternative to the current medical paradigm.** It is still debatable, however, whether all therapeutic interventions inevitably result in changes in biological regulatory networks that influence the body's overall homeodynamics. Some believe that the pharmacological properties of a multicomponent, bioregulating medication should be fully assessed by integrating standard toxicological methods with selected pathway-focused bioassays and unbiased data-acquisition strategies (Gostner et al. 2012). Others emphasize the "rational design" of multitarget medications, stressing the need to validate these combinations and their drug-like properties with experimentally sound data (Gertsch 2011).

It should also be noted that one of the major challenges of the multicomponent approach relates to the unpredictable or arguably atypical pharmacokinetic properties of combinatorial medications, particularly those in concentration ranges lower than those that can be predicted by linear pharmacology models. The dose-response concept of hormesis, for example, is a generalizable model used to characterize the biological pattern of low-dose stimulation and high-dose inhibition (Calabrese 2008, Mattson 2008). This biphasic dose response provides one framework for evaluating low-dose mixtures and their potentially beneficial biological impact and application.

Potential risks of drug-drug interactions are also of concern. In order to address these challenges, some authors suggest utilizing historical experience embedded in conventional medicines to shift drug discovery strategies from finding new-entity drugs to combining existing agents (Kong et al. 2009). As the means for best developing and evaluating the use of multicomponent medications represents an ongoing line of research and inquiry, bioregulatory systems medicine supports the position that a **multicomponent, multitarget medical management model may be a solution to current inadequate treatments for multi-factorial diseases.**

Bioregulatory therapies should also be considered in the context of biological rhythms. It is suggested that modulation of neuroimmune and hormonal regulatory networks by therapeutic interventions should consider biological rhythms in treating diseases such as rheumatoid arthritis (Cutolo & Straub 2008). It is now generally recognized that in addition to the central circadian clock located in hypothalamus (Buijs et al. 2006), peripheral tissues also have their own "local" circadian pacemakers that exhibit oscillatory behavior (Druzd & Scheiermann 2013) and have significant physiological functions that may influence whole-body regulation (Lamia et al. 2008). Moreover, the interconnectedness between molecular regulatory networks (e.g. nuclear receptor signaling pathways) and molecular and central clocks strongly support the idea of the global circadian autoregulatory network coordinating diverse physiological processes among tissues to maintain homeodynamics (Yang 2010). This evidence is clinically relevant, suggesting that therapeutic interventions should not interfere with biological rhythms, as these rhythms may actually determine the proper timing of an intervention. For example, when timing of chemotherapy was investigated with respect to the CRP immune oscillatory cycle, a trend emerged showing an association between the timing of delivery of the drugs and improved outcome. Researches hypothesized that timing drugs at the peaks of the CRP cycle might maximize the immune effector response in patients with cancer (Coventry et al. 2009).

[b] *Comprehensive Medicinal Chemistry database accessible online at: http://accelrys.com/products/collaborative-science/databases/bioactivity-databases/comprehensive-medicinal-chemistry.html*

2.2.10 Patient Health-Disease Continuum

The systemic nature of disease, as understood by bioregulatory systems medicine, provides the basis for recognizing health and pathology as dynamic, integral processes. Bioregulatory systems medicine understands **disease progression as the result of an autoregulatory process that is disturbed or challenged by an overwhelming stressor and cannot function adequately to restore homeodynamics.** In this context the dynamics of patient disease progression contribute to the understanding of a health-disease continuum, along which a patient can be diagnosed, treated at multiple therapeutic access points, and monitored in terms of how networks of pathophysiological processes resolve to a state of health. Mechanisms of disease can be considered in terms of dynamic relationships with clear influences of certain organs and organ systems over other organs or organ systems, **with symptoms being an expression of the body's autoregulation capacities in response to a stressor.** Modern technological methods reveal more and more organ-to-organ relationships that may be otherwise unexpected, such as in the case of the hypothalamus-adipose tissue-liver "axis" (Dobrin et al. 2009).

The progression of a disease is facilitated by disturbed or inadequate autoregulatory abilities of the organism. Genetic variation may contribute to disease largely through misregulation of gene expression. Mutations in the transcription factors that control cell state may impact the autoregulatory loops that are at the core of cellular regulatory circuitry, leading to the loss of a normal healthy cell state. Misregulation of noncoding RNAs can also contribute to disease (Lee & Young 2013). These insights indicate that genetic and epigenetic factors may collectively influence autoregulation at all levels of biological organization. In the case of disease, the effects of these genetic variants can be expressed at the molecular level as persistent perturbations of information flow in biological networks.

Research on such effects at the molecular level allows for a better understanding of the molecular basis of disease progression, and the potential to determine common disease-state signatures that can be useful for drug target identification. In his presentation at the European Molecular Biology Laboratory Conference in 2012, entitled, "Omics and Personalized Health", Leroy Hood demonstrated the identification of four molecular networks perturbed during the progression of a prion disease[c] in mouse models. The global molecular information was monitored at various time points throughout the disease progression: from onset, to the appearance of symptoms, to the final disease stages. Interestingly, the four identified networks of the prion disease are also those perturbed in other neurodegenerative diseases such as Alzheimer's disease, Huntington's disease, Parkinson's disease, and amyotrophic lateral sclerosis. This finding aligns with Hood's proactive P4 medicine paradigm, which uses concepts from systems medicine to develop a model of medicine that is predictive, preventative, personalized, and participatory (Hood & Flores 2012). P4 medicine advocates for the combination of network and systems-level insights, digital technologies, and large sets of individual data to transform medicine into an information science that is better capable of promoting clinical well being.

The ability to identify molecular networks shared by the progression of multiple diseases begs the question as to whether the ability to model an individual's health-disease continuum would also provide clinically relevant information. In a recent study, whole-genome sequencing was applied to a blood sample from a patient with a history of vascular disease and early sudden death as a means of developing a model of the patient's individual disease network. The resultant model displayed an interconnected picture of disease-modifiable factors such as smoking, diet, alcohol, exercise, and medication use, as well as risks for developing coronary artery disease, obesity, osteoarthritis, and Type 2 diabetes. Given the high correlation among these diseases, the authors concluded that information regarding individual patient disease risk and response to drugs can be derived from whole-genome sequence data (Ashley et al. 2010). From a clinical practice perspective, this research suggests that **in any individual patient, disease interconnectedness (by shared molecular events) represents the individual's health-disease continuum, reflected in the patient's medical history.**

Companies in the scientific medical community have already begun developing disease models and validating them in an RCT setting, for example in diabetes (Eddy & Schlessinger 2003). The success of such modeling supports the idea that **simulating the dynamic evolution of health-to-disease processes can be used to predict the response of a whole inflammatory/wound-healing biological network, rather than the response of particular inflammatory mediators.** Given the importance the inflammatory process to the bioregulatory systems medicine approach, the potential to identify and monitor inflammatory network states may provide valuable diagnostic entry points for assessing the functionality of a patient's global autoregulatory network.

Appropriate diagnostic technological platforms are also essential for capturing relevant biological information at the necessary level of detail. In the context of the bioregulatory systems medicine approach, **lipidomics, metabolomics, genomics, and proteomics are technologies that can help to detect and monitor the inflammatory state of a patient in order to diagnose more comprehensively.** Blood may also provide a powerful diagnostic window into health and disease, and certain technologies have the potential to analyze numerous molecular signals from a droplet of blood (Hood et al. 2004). The diagnostic potential of analyzing saliva (Zauber et al. 2012) and urine (Sharma et al. 2011) are also being explored.

In summary, the concept of health-disease continuum incorporates patient's disease progression within the broader

context of individual (multi-)morbidity by integrating patient history, physical examination, routine laboratory tests and cutting-edge molecular diagnostic techniques (e.g. whole-genome profiling) into a disease network. The ability to identify disease stages with resolution at the gene expression level provides the clinician with a more complex, detailed, and accurate picture of multi-factorial, chronic disease than what is typically available through previously developed techniques. Medical practitioners must also be equipped with more complex interventions that are able to influence and modify disease progression. Given the current healthcare and medical challenges, it is evident that the single-molecule, single-target paradigm does not provide the specificity and sophistication that a multitarget, multicomponent model demands. To this end, new medications and treatment protocols are warranted to target and bioregulate perturbed autoregulatory networks toward resolution.

[c] *Prion disease is a neurodegerative disease characterized by toxic accumulation of misfolded prion protein molecules in the brain tissue that leads to the degeneration and death of neurons.*

3. Interpretation of the Bioregulatory Systems Medicine Model

The previous sections described the scope of each cluster of the BrSM model based on the statements each contains and relevant supporting evidence. While these descriptions are structured as ten distinct elements for the purpose of conveying the coherence of each emergent concept, several themes permeate the entire model, revealing a conceptual underpinning that unifies the individual statements and clusters. Autoregulation for example, as a primary objective of bioregulatory systems medicine, is critically important in articulating the relevance of each cluster in achieving improved patient outcomes. Similarly, information flow is incorporated in the explication of each cluster given its cardinal role as something that can be directed or influenced to affect patient health-disease status. Disease progression, biomarkers, and body burden are other examples of elements that are ubiquitous in the model.

The presence of these themes throughout the model suggests interconnectivity among the core elements, and signifies particular relationships that are critical to understanding the principles of bioregulatory systems medicine as a cohesive approach. In recalling the objective of the model to combine existing knowledge in a novel, integrated way, we can now consider the connotations of this integration as it addresses the challenges facing medicine today. Just as the location of each statement in one of the ten clusters is itself a unique and emergent property of the model, so too are the relationships among these clusters and their collective implications for the properties and utility of the BrSM model.

The group concept mapping methodology used to produce the model is a systems methodology driven by participant perceptions that yields simple representations of emergent, complex relationships. The unique scope and contents of each cluster exists as an emergent product of the simple, linear steps in the concept mapping process, and was not predictable beforehand from the 102 statements alone. Therefore, the clusters themselves and their relative location within the framework are dependent upon the collective perceptions of participants and the aggregation (or interaction) of those perceptions by virtue of the analytic process. To this end, we can begin to understand the emergent properties of the BrSM model that lead us to a more in-depth interpretation. This new way of looking at existing information is fundamentally grounded in the connectivity of the parts and their subsequent meaning as a whole.

3.1 Model Dimensions

At the broadest level, we can examine conceptual patterns that reveal how the content is distributed across the two-dimensional model representation (Figure 9). Just as one can reference tendencies across the dimensions of a geographical map (e.g. the weather is colder in the north, warmer in the south), we can reference tendencies across dimensions of the BrSM concept map that integrate the scientific and clinical elements.

For example, the content located closest to the Biological Communication at the Microenvironment-Scale cluster relates most strongly to communication and signaling at the cellular level, particularly as it occurs within and by way of the extracellular matrix. The content located closest to the Biological Communication across Multi-Scale Networks cluster reflects a more systems-level understanding of how information flows between molecular networks/organ systems at the whole organism level. We observe the emergence of a conceptual through-line across the map that contains elements related to the role of **biological information** in the BrSM model. We can label this dimension (or axis) of the map as Biological Information. Whereas we identify a clear delineation between the relatively “micro” and “macro” level focuses of these clusters, we can recognize themes that are common to both of these clusters and the clusters between them. The relevance of autoregulation, for example, is considered at different levels of specificity and in different contexts depending on its location along this dimension.

Next, if we examine the dimension perpendicular to Biological Information, we can recognize a distinction among relatively internal and external resolution mechanisms. The content located closer to the Inflammation Physiology cluster relates strongly to the human organism’s natural ability to reach resolution in the face of perturbation, particularly as it relates to inflammation process mechanisms. The content located closer to the Bioregulatory Clinical Pharmacology cluster pertains to the use and application of therapeutics in the clinical context to reach resolution. We contrast the opposing directions of this dimension to conclude that content located closer to Inflammation Physiology is more relevant to the organism’s internal resolution capability and mechanisms, whereas the content located closer to Bioregulatory Clinical Pharmacology is more relevant to the utilization of external interventions to promote resolution. In this regard, we can label this dimension or axis of the map as **Resolution Processes** (Figure 9).

Figure 9. Bioregulatory Systems Medicine Emergent Conceptual Model: Dimensions and Anchors. *This figure illustrates the conceptual dimensions and anchors of the model that emerged from the group concept mapping process, analysis, and interpretation of the interrelationships among the clusters. The vertical dimension in this figure is labeled "Resolution Processes," as the content along this axis relates to participants' conceptualization of disease resolution occurring through both internal and external mechanisms. This dimension is anchored at one end by the Inflammation Physiology cluster, where the model content relates strongly to the human organism's innate ability to reach disease resolution in the face of perturbation, particularly as it relates to inflammation process mechanisms. The opposite end of this dimension is anchored by the Bioregulatory Clinical Pharmacology cluster, where the content most explicitly relates to the use of medications with bioregulatory properties in order to reach disease resolution. Perpendicular to Resolution Processes is the dimension "Biological Information," along which the content relates to communication within and across micro and macro levels of biological organization. This dimension is anchored at one end by the Biological Communication at the Microenvironment-Scale cluster, where the content describes communication at the cellular level, particularly referring to the extracellular matrix. At the opposite end, this dimension is anchored by the Biological Communication Across Multi-Scale Networks cluster, which describes how biological information flows across molecular (cellular, tissue, organ) networks at the whole organism level.*

All elements (statements and clusters) of the model exist in various places along these dimensions, indicating that, at the theoretical level, the bioregulatory approach is driven by the goal of stimulating resolution processes through consideration of the communication and information pathways of the human organism. In the clinical context, the model conveys the two fundamental concepts for approaching a patient's disease in bioregulatory systems medicine: the development of an integrated picture of biological information, and the utilization of this integrated picture to restore coherence in the event of perturbation. As a guide for clinical decision-making, the Biological Information axis suggests that the clinician consider characteristics of the disease, whereas the Resolution Processes axis considers mechanisms of intervention.

3.2 Anchor Constructs

The meaning of these dimensions in clinical practice can be more specifically distilled by examining the implications of those clusters most centrally aligned on either end of each axis. In essence, the Inflammation Physiology and Bioregulatory Clinical Pharmacology clusters communicate the "how" of physiological coherence and restoration in the overall bioregulatory systems medicine approach. Specifically, these clusters lead the clinician to explore questions about intervention such as: How do the inflammatory processes function to influence autoregulation, and what are the physiological factors involved? How should bioregulating medications be designed and applied to effectively restore homeodynamics?

At opposing ends of the Biological Information dimension, the Biological Communication at the Microenvironment-Scale and Biological Communication across Multi-Scale Networks clusters convey the "what" of the overall bioregulatory systems medicine approach. Along this gradient, the content specifies those elements necessary to understanding the range of biological signaling and communication pathways that underlie autoregulation. Specifically, these clusters lead one to explore questions of: What is taking place at the cellular, or "micro", level of the human organism that influences regulatory capability? What is taking place at the network, or "macro", level to influence regulation across systems? At the "micro" level, emphasis is placed on the role of the extracellular matrix in pathological conditions, particularly with regard to the accumulation of toxins, disease progression, and transcription patterns. At the "macro" level, information and signaling across molecular networks direct regulatory action among organ systems, such that the large-scale complexity of the cellular-level interactions can be understood as an integrated, interconnected picture of human health.

The location of these four clusters (Inflammation Physiology, Bioregulatory Clinical Pharmacology, Biological Communication at the Microenvironment-Scale, Biological Communication across Multi-Scale Networks) at opposing ends of the axes positions these constructs, visually and spatially, as the conceptual anchors of the model. The farther on the concept map an idea is located from Inflammation Physiology , for example, the less it is related to internal resolution processes, and the more it is related to external resolution processes, as articulated by Bioregulatory Clinical Pharmacology, and vice versa. Similarly, the farther an idea is located from Biological Communication at the Microenvironment-Scale, the less it is related to micro level information, and the more it is related to macro level information, as articulated by Biological Communication across Multi-Scale Networks. The content of these four clusters best represents the contrasting ends of their respective dimensions, thereby grounding the gradients of biological information and resolution processes in the context of bioregulatory systems medicine.

The unique, emergent position of these clusters as conceptual anchors is also validated methodologically. Structurally[d], these four clusters are more densely populated with statements than the other clusters of the map, indicating that participants perceived a higher degree of conceptual similarity among the set of items in each of these four clusters, relative to the other clusters. The density of these clusters implies a high degree of consensus among stakeholders, which suggests that participants collectively perceived a greater degree of clarity and distinctiveness in the meaning of these sets of items, relative to the other clusters.

Functionally[e], these clusters demonstrate the highest degree of internal relatedness, indicating that participants understood the statements in each of these four clusters as more strongly related to one another and less related to the statements in the other clusters of the model. (Goldman & Kane 2014). In addition to being the structural anchors of the map, these four clusters are also the functional anchors of the map, in the sense that they function as the cohesive, agreed-upon, foundational classes of information from which the conceptual role of the other six clusters can be considered.

[d] *In group concept mapping, structure refers to points and clusters and their relative location to one another as they appear on the map. Distance between points and clusters can be used as a structural indicator of conceptual similarity; items that appear closer to one another on the map tend to be more conceptually similar than items that appear farther apart.*

[e] *In group concept mapping, functional relatedness refers to the quantifiable degree to which the set of items in a given cluster were perceived as conceptually related to one another (external relatedness) and to themselves (internal relatedness) based the frequency at which participants as a group sorted statements with one another during the structuring activity. More details on the functional analysis can be found in Appendix B.*

3.3 Intermediary and Bridging Constructs

As with the anchors, an in-depth examination of the content that comprises the other six clusters *(Microenvironment Response to Inflammation, Inflammatory Network Response to Perturbation, Autoregulation of Biological Networks, Patient Health-Disease Continuum, Diagnostics and Therapeutic Strategy, Clinical Focus on Dysregulation)* reveals the unique role of these constructs in the architecture of the bioregulatory systems medicine paradigm. The characteristics of these six clusters can be first recognized visually/spatially, and then in terms of their content, which reveals their distinctiveness at a conceptual level. This is further validated methodologically.

Spatially, these six clusters are located between the anchors. as described previously, the information in each of these clusters relates to the anchoring concepts along the relevant conceptual line. Microenvironment Response to Inflammation, for example, brings together the physiology of inflammation with "micro" or local level information regulation in a description of the environment in which inflammation initiation and resolution take place. Inflammatory Network Response to Perturbation articulates the mechanisms of inflammation with a more thorough understanding of the systemic and informational components of this physiological process. In this context, the concepts of molecular order and regulatory molecules introduce the regulation of information associated with inflammation at the network level.

Diagnostics and Therapeutic Strategy conveys the practical use of "macro" or global network level information in the design and application of medication with bioregulatory properties. This cluster emphasizes the use of diagnostics in bioregulatory systems medicine, such that autoregulatory networks can be appropriately assessed and interpreted in a way that will effectively guide treatment. The content in this area also highlights the use of diagnostics for furthering our knowledge of disease progression, thereby enhancing strategic therapeutic decision making. Clinical Focus on Dysregulation identifies specific conditions and pathologies for which bioregulatory systems medicine is well suited, although additional content, particularly regarding toxicity, may be helpful in fully realizing the relationship between the extracellular matrix and the clinical context.

Patient Health-Disease Continuum occupies a unique position in the center of the map, where one can envision the intersection of the Resolution Processes and Biological Information axes. This cluster emerges as the "hub" that personalizes the theoretical foundation of the model, emphasizing the individual, patient-centric basis of bioregulatory systems medicine. As the structural core of the paradigm, the patient considerations articulated in this construct include factors for the clinician to consider in optimizing resolution, as well as conveyors of critical biological information for the clinician to consider in improving patient condition. Symptoms, progression of a disease, autoregulatory abilities, and detection of inflammatory status can all be considered informative expressions of an individual's health status that can be used to personalize treatment.

These six clusters emerge as conceptual bridges whose statements can be used to analyze and articulate the relationships or connections between the anchors and dimensions. Structurally, these clusters occupy a comparatively larger area of the map and are, overall, less densely populated with statements than the anchors. Their relatively expansive area suggests that participants perceived considerable similarity among the set of items in these clusters and the set of items in their respective adjacent anchors. In other words, there was less consensus among participants that these six clusters occupy a conceptual position in the BrSM model that can be utilized independently from the anchors; rather, their value in the approach is optimally derived from their ability to build coherence among the anchor constructs, and logically bridge the core elements in a way that can be practically applied in the clinical context. Thus, we refer to these six clusters as the intermediary clusters.

In physical space, the utility of a bridge that connects two locations can be measured by how easily one can traverse from one end to the other. Similarly, we can consider the strength or utility of each intermediary cluster based on how well their statements logically articulate the relationships between the anchors. A functional interaction analysis of the statements in each intermediary cluster is a means of visualizing how effectively each intermediary cluster bridges the anchors. The degree to which the space between each anchor is relatively evenly populated with statements is suggestive of the extent to which the intermediary cluster(s) functions clearly or completely as a conceptual bridge (Figure 10).

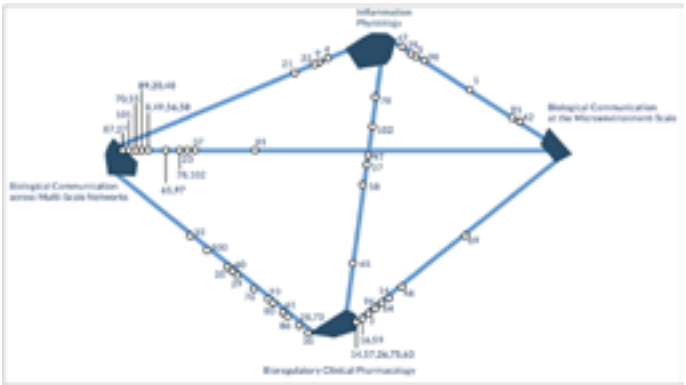

Figure 10. ***Bioregulatory Systems Medicine Emergent Conceptual Model: Intermediary Clusters.*** *The intermediary clusters are spatially located between the anchor clusters, and can be described as conceptual bridges that relate to their respective neighbouring anchors. The figure below illustrates*

the statements of each intermediary cluster as arranged between the cluster's corresponding anchors. A statement's distance from either anchor reflects the relative strength of relatedness that participants collectively perceived among that particular statement and the neighboring anchors. The degree to which the space (blue line) between each anchor is relatively evenly populated with statements may suggest the extent to which the intermediary cluster effectively functions as a conceptual bridge between the anchors.

Those areas that contain more gaps, or where statements are less evenly distributed, between the anchors suggest that the intermediary clusters may function less effectively as a conceptual bridge. Of importance to note is the potential variation in what a gap may signify in the context of the model. In some instances, a gap may indicate that less information was included in the model to fully detail the relationships between anchors. In other instances, it is possible that information is not currently available to more fully bridge the anchors, such that the gap may be suggestive of opportunities for future research concentrations. It is also possible that participants were not able to clearly perceive the conceptual relatedness between some anchors.

While further inquiry is needed to more thoroughly understand the significance of the gaps in each bridge, the development of a formal diagnostic platform for bioregulatory systems medicine is likely to aide in realizing and validating the relationships among its scientific and clinical elements. Diagnostics are also essential in making therapeutic decisions. The ability to evaluate the autoregulatory patterns of a patient is critical in determining the appropriate combination of treatments to achieve homeostasis. Although inflammatory cytokine patterns (Agustí et al. 2012) and allostatic state models (Romero et al. 2009) may provide useful surrogates for measurement in the absence of formal diagnostics, genomic patterns (Mesko et al. 2010) are likely to better delineate the autoregulatory status of a patient. The information elicited from genomic patterns can potentially fill gaps that signify the need increasing understanding of the scientific basis relative to the more conceptually sound anchors of the model.

3.4 Clinical Significance and Overarching Principles

As a whole, the integrated components of the BrSM model constitute a holistic approach to human health that can potentially close the gap between current medical challenges and ideal patient outcomes (Figure 11). The model conveys three overarching principles by which bioregulatory systems medicine addresses the challenges posed by the conventional paradigm.

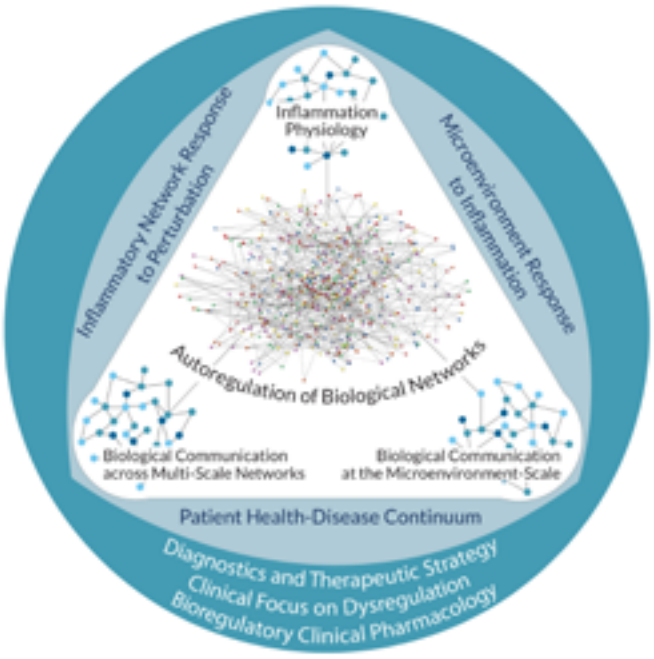

Figure 11. Bioregulatory Systems Medicine Conceptual Clinical Application Model. *The model is depicted as a unified entity of three integrated levels. The fundamental core consists of four autoregulatory clusters (white), enveloped by the layer of dysregulation clusters (light blue), which in turn is enclosed by final layer of therapeutic clusters (dark blue). In this way the model informs the relevant fundamental underpinnings of human biology that result in the clinical picture observed in individual patients. The proper assessment of this clinical picture guides individualized clinical decision making that is based on the underlying cause of disease. For a detailed explanation, refer to Clinical Significance and Overarching Principles.*

First, the existence of dimensions in the model, along which varying degrees of biological information and resolution mechanisms considered, supports the temporal evolution of a patient's condition that is critical to bioregulatory systems medicine. It is proactive in its approach to disease management, with an emphasis on the anticipation and promotion of improvement in a patient's condition, particularly as it relates to addressing the underlying cause of disease,as opposed to focusing exclusively on symptom relief. Whereas many conventional treatments remain static despite changes in patient condition, the BrSM model anticipates changes in patient phenotype, which in turn requires a dynamic perspective on what is taking place at the micro and macro network levels, and how resolution can be achieved through internal and external means.

Secondly, medication with bioregulating properties is purposefully designed to be multitarget, so that it acts therapeutically on multiple biological targets simultaneously. Whereas this design concept is most specifically addressed in the anchor Bioregulatory Clinical Pharmacology the scientific basis that supports a multitarget approach is conveyed by way of the Clinical Focus on Dysregulation and Diagnostics and Therapeutic Strategy clusters that bridge medication design with network physiology at the cellular and system levels. In this regard, the BrSM model portrays strategic alignment between its approach to medication design and its scientific, biological foundation. Local and systemic network regulation provide the physiological basis and rationale for multitarget, multicomponent medication design, thereby reconciling the limitations of single-target, single-molecule pharmacology that does not account for the functional interconnectedness of health and disease processes.

Finally, the central structural and functional position of Patient Health-Disease Continuum in the model denotes emphasis on the individual as an adaptive, robust organism in the context of a continuously changing environment that includes disease. The fact that this cluster is relatively equally functionally related to all other clusters of the model supports the view of a patient's individual health-disease status as being influenced by the multiple pathways (in this case, conceptual clusters) involved in supporting autoregulatory ability. Whereas the conventional paradigm is oriented toward complete and linear inhibition of molecular pathways implicated in disease pathology, bioregulatory systems medicine recognizes disease as a dynamic entity within individual parameters of potential. The BrSM model highlights the interconnectedness and interdependencies among patient health status and all other physiological and therapeutic elements of the bioregulatory approach. Therapeutic treatment of the same condition is readily modified and adjusted according to the dynamic nature of the disease process and the patient's response to treatment.

4. Clinical Application In Practice

The BrSM model and the interrelatedness of the clusters form a comprehensive system for assessing a patient, determining the health-disease continuum, and formulating the necessary and optimal intervention. Furthermore, bioregulatory systems medicine offers the possibility of following the patient's progress during treatment, and therefore equips the physician with the capacity to change the prescription as a patient improves.

The Biological Information axis (Figure 9) can be used to consider the model in two distinct sections. Above this axis, the statements and clusters represent the pathophysiology that will serve as a way to assess the patient. Those statements and clusters below the Biological Information axis can serve as tools for realizing and deriving the bioregulatory intervention. From a more empirical perspective, the ten emergent model clusters can be also considered within three thematic groupings (Figure 11). The autoregulation clusters (Biological Communication across Multi-Scale Networks, Biological Communication at Microenvironment-Scale, Inflammation Physiology and Autoregulation of Biological Networks) describe the physiological autoregulation of biological networks, focusing on the role of inflammation as a "master regulator" of tissue homeostasis. The content of the autoregulation cluster group stresses the importance of biologic communication in human biology both locally, on a microenvironment-scale in tissues, and systemically, across multi-scale networks connecting all tissues and organs in the body. The dysregulation clusters (Inflammatory Network Response to Perturbation, Microenvironment Response to Inflammation and Patient Health-Disease Continuum) describe the human body's response to perturbation. The content of this cluster group emphasizes the role of inflammatory response as possible surrogate marker for the degree of dysregulation in the face of perturbations in biological networks. Non-resolving inflammation is indicative of autoregulation being unable to overcome the perturbation, and, consequently, impairing biological communication on the microenvironment-scale, causing morphologic changes in tissues. As a result of interplay between the inflammatory network response and microenvironment response to inflammation, disease uniquely progresses along the health-disease continuum in every individual patient. The therapeutic clusters (Diagnostics and Therapeutic Strategy, Clinical Focus on Dysregulation and Bioregulatory Clinical Pharmacology) link the patient's autoregulatory status with clinical decision making. While the Diagnostics and Therapeutic Strategy cluster emphasizes an integrative approach in clinical decision making that is dependent upon the assessed autoregulatory capacity of a patient, Clinical Focus on Dysregulation indicates a need to identify the perturbed biological networks as the underlying cause of a disease. The Bioregulatory Clinical Pharmacology cluster describes the properties of medications that are most useful in this context. The model thus serves the clinician as a comprehensive, dynamic approach to the patient.

To illustrate: Figure 12 describes a novel conceptualization of disease progression that integrates information on the autoregulatory status of two hypothetical patients (Patients X and Y). Mapping an individual's autoregulatory status in a temporal fashion produces a visualization of individualized disease progression. This visualization displays areas of robust autoregulation capacity (marked area, Figure 12B) in contrast to other areas where autoregulatory capacity is reduced. The therapeutic strategy proposed by the BrSM model suggests that a therapeutic effort is focused on "moving" a patient's autoregulatory status to a state of more favorable autoregulation capacity, where bioregulatory therapy can be most efficiently applied to strengthen autoregulation (hypothetical Patient X). It is assumed that in more advanced cases, it may not be possible to reach a state of favorable autoregulation capacity (hypothetical Patient Y). Bioregulatory intervention would be based on the patient's position on the map and, depending on the individual case, could serve as primary, secondary, or complementary treatment to suppressive or replacement therapy. In the future, molecular network patterns, yet to be established by means of omics technologies, may serve as more objective diagnostics for this disease state mapping. These patterns would ideally identify which molecular networks should be targeted, and would also guide the selection of appropriate bioregulatory therapeutic intervention.

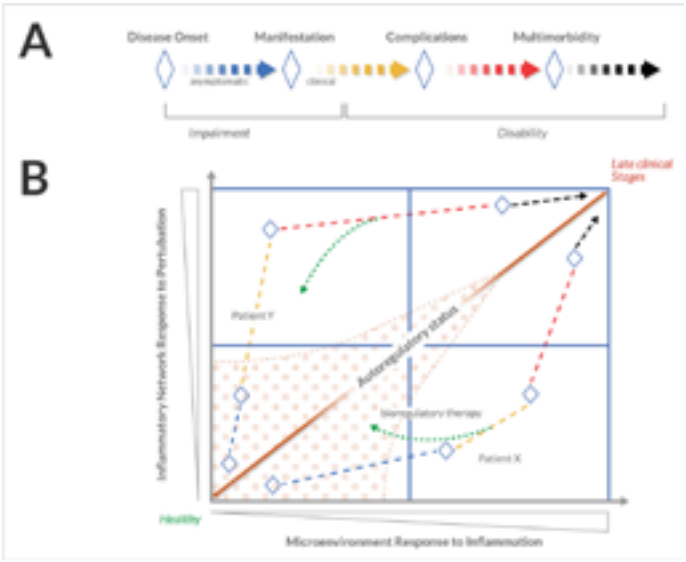

***Figure 12** Novel conceptualization of disease progression introducing patient's autoregulatory status. Disease progression is commonly understood as the worsening of a disease over time. In 1980, the World Health Organization published the International Classification of Impairments, Disabilities and Handicaps (ICIDH) with the objective of providing a widely accepted structure of the consequences of disease and of implications for the lives of patients. Expanding on this model, this figure includes a conceptualization of the*

autoregulatory status of two patients.

A. The concept of disease progression adapted from the 1980 WHO ICIDH model. Blue-to-black colors indicate conceptual disease worsening *stages, and ◊ depicts principal milestones between stages. The dashed line indicates that there is no strict sequential order between stages or milestones, and the linear structure is used for simplicity.*

B. A schematic conceptualization of the disease progression as a four-quadrant map. *In the BrSM model, this is called the Patient's Health-Disease Continuum. The arrowed dashed lines represent the hypothetical disease progression in patients X and Y. In contrast to simplified linear concepts focusing on identifying disease stages in decision-making, the map concept positions these stages in relation to dysregulation parameters represented by horizontal and vertical axes.*

In the BrSM model, systemic dysregulation parameters are conceptualized as Inflammatory Network Response to Perturbation, and local dysregulation parameters are conceptualized as Microenvironment Response to Inflammation. Increased dysregulation is indicated as the lines move toward the top or right. It is suggested that the ratio between these two dysregulation parameters theoretically defines the autoregulatory status of a patient. For a detailed explanation, refer to Clinical Application In Practice.

5. Summary and Outlook

Bioregulatory systems medicine expands the toolbox of medical practitioners, offering solutions to improve and modernize the current paradigm in line with innovative scientific discoveries and thinking. The bioregulatory approach enhances our ability to address the complexity of diseases we face today, benefiting clinicians and patients seeking to resolve acute and chronic conditions while avoiding the harmful side effects of treatments. Looking ahead, ongoing research in systems biology promises to further strengthen the scientific landscape of bioregulatory approaches in medicine. Empirical evidence from clinical experience and the development of patient registries will continue to validate its ability to resolve chronic conditions. Bioregulatory systems medicine does not dismiss the undeniable value of current medicine; rather, it expands the current medical approach and broadens the clinical toolbox. Whereas current medicine is often criticized for focusing too heavily on the alleviation of symptoms, the bioregulatory approach recognizes the value of symptoms as guidance for better understanding patient autoregulatory abilities. Bioregulatory systems medicine supports the autoregulatory network as a means for reaching resolution, rather than compromising or interfering with it in the interest of targeting a specific stressor.

Our purpose in developing this model was to identify and articulate the relationships among the scientific and clinical elements of bioregulatory systems medicine in a way that could trigger and sustain a novel, patient-centric practice transformation and, in turn, lead to improvement in patient outcomes. Whereas the practical and theoretical implications of the model have been discussed, its scientific validity, robustness, and effectiveness in the clinical context still need to be validated. Therefore, the next steps in realizing the potential of BrSM to enhance current medicine are the development of formal diagnostics and ongoing research in the scientific and clinical communities. For example, the ability to measure the multiple networks involved in disease processes will be a critical step in addressing disease at the systems level. Whole genome transcriptome analysis provides an optimal analytic tool for understanding the genomic quantification of disease progression and health-disease status. High resolution transcriptome maps of disease will allow for the identification of therapeutic targets and will further guide diagnosis and medication design, thereby enhancing the practical value of the BrSM model.

Future integration of these diagnostic techniques will provide a more detailed picture of disease progression, allowing for therapeutic decisions to be adjusted depending on the position of the intervention outcome on the disease-health continuum. Modeling disease as a network will lead to novel diagnostic systems tailored to multitarget therapies that may reflect system complexity more accurately than the current paradigm.

While we are still in the early stages of this paradigm shift, emerging conceptual models such as the one presented in this White Paper promise to pave the way for a future of medicine that is cost effective, patient-centered, and better able to achieve ideal medical outcomes.

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7. Appendices

7.1 Appendix A: Statements by Cluster

Cluster 1: Microenvironment Response to Inflammation

1 The extracellular matrix is involved in the initiation and resolution of the inflammatory response.

5 An active lymphatic system that promotes lymphatic drainage and cell migration is essential for the resolution of inflammation.

25 The detection of inflammatory mediator patient profiles could help to identify and locate resolution blockages and underlying pathologies.

42 The communication between the cell and microenvironment is bidirectional, and forms the basis of the homeostatic control of many tissues.

47 The treatment of a wide range of human disorders could be improved by stimulation or optimization of the patient's individual inflammation resolution process.

91 The global autoregulatory network, including input from neural and hormonal pathways, influences the overall form and function of the extracellular matrix.

98 Inflammatory reactions often occur within distinct microenvironments composed of tissue-specific cells, (fibroblasts, endothelial cells, and macrophages) and their highly specialized extracellular matrix (ECM) components.

Cluster 2: Biological Communication at the Micro-environment-Scale

39 The extracellular matrix is the part of the immunological synapse that occurs in the cell microenvironment between antigens and antigen presenting cells.

62 The extracellular matrix, intracellular cytoskeleton and nuclear matrix are directly interconnected through a chain of commonly utilized molecules.

66 The extracellular matrix is involved in the progression of almost any chronic disease, most prominently in any fibrotic disease, most solid tumors, arthritis, osteoporosis, COPD and emphysema.

67 Excessive breakdown of the extracellular matrix components is associated with altered levels of reactive oxygen species (ROS) that can result in modification of multiple molecular networks and subsequent pathology.

68 The extracellular matrix links signals from the microenvironment (e.g. neural, hormonal, biochemical and biophysical) to the cytoplasm and then the nucleus, thereby directly influencing transcription patterns.

79 Environmental toxins and metabolic waste products can potentially accumulate in the extracellular matrix and cause disease.

Cluster 3: Inflammation Physiology

2 Local inflammatory pathways and mechanisms in the body are mirrored by and related to systemic inflammation, which is one of the underlying pathological mechanisms of many diseases.

6 Inflammation where the mechanisms of normal resolution are inadequate or suppressed as well as persistent low grade inflammation resulting from an inability to mount an adequate inflammatory response are the major causes of many diseases.

15 Chronic inflammation often leads to tissue injury, scarring and fibrosis.

17 Inflammation is a part of the immune response, which can be triggered by exogenous and endogenous stimuli in either non-sterile or sterile environments.

36 Acute inflammation supports the removal of damaged tissue.

41 The balance of pro- and anti-inflammatory factors, including external signals, determines the inflammatory status.

43 The purpose of any acute inflammatory response is to eliminate disturbances that are interfering with normal conditions and therefore restore functionality and homeodynamics/homeostasis to the tissue.

50 The physiological mechanisms of inflammation are necessary to maintain health and to return from the disease state to a homeostatic healthy state.

52 Resolution of inflammation is steered by multiple endogenous anti-inflammatory and proresolution molecules and pathways.

74 Inflammation that is suppressed during its normal pathway or is non-resolving causes or contributes to pathological states.

83 Inflammation is regulated by an orchestra of molecules, and persists whenever a component of the complex signaling pathway fails or gets lost.

84 An acute inflammatory response is an adaptive response that should not be blocked and possibly even initiated in order to induce resolution and restore homeodynamics/ homeostasis in a tissue.

88 The ideal outcome of acute inflammation is complete resolution.

94 There are many different potential triggers for inflammation other than damage and infection including dysregulated cell metabolism, hyperpermeable mucosal membrane barriers and alterations of the extracellular matrix.

95 Certain physiological functions (e.g. epithelial cell turnover in the intestinal tract for the maintenance of barrier integrity) rely on a constitutive level of inflammatory signals.

Cluster 4: Inflammatory Network Response to Perturbation

4 Inflammation has various physiological purposes and is induced by exogenous as well as endogenous stressors released during tissue injury, tissue stress and malfunctioning.

19 The loss of molecular order in the cell triggers inflammation.

21 Functionally capable auto-regulating tissue induces acute inflammation response when molecular order is lost in an effort to restore and maintain order in the system.

22 The human body has the capability to synthesize and control regulatory molecules that promote and resolve inflammation.

Cluster 5: Clinical Focus on Dysregulation

3 Atopic diseases, as examples of Th2 regulation rigidity, are well suited for bioregulatory intervention due to the fact that only symptomatic medical solutions are currently available.

9 Bioregulatory systems medicine supports the body's autoregulatory system, thereby triggering endogenous inflammatory mediators and mechanisms that optimize the (time) course of inflammation resolution.

14 Evaluating a disease within disease-health continuum is an important tool for bioregulatory systems medicine in order to design the treatment and follow-up.

16 When certain heritable diseases and diseases where organ failure and tissue damage are at the point at which autoregulation is impossible to restore, bioregulatory systems medicine can be used to treat symptoms and prevent sequelae, rather than as a standalone treatment.

26 The variety of pathways and molecules involved in the complex response to inflammation points to the necessity of multitarget/multicomponent medications.

46 Functional somatic syndromes including rhinitis, fibromyalgia and chronic fatigue syndrome often share similar blocks to autoregulation.

57 Chronic diseases associated with aging can be potentially better managed with a multitarget approach.

59 A patient's individual position along the health-disease continuum in conjunction with the identified stressor(s) will determine the treatment strategy.

63 Bioregulatory systems medicine can serve as an adjuvant treatment to reduce polypharmacy, provide effective and safe relief of symptoms, and prevent cascade iatrogenesis.

64 Functional somatic syndromes are excellent targets for bioregulatory systems medicine due to their multifactorial network pathophysiology and the lack of effective medical solutions currently available.

69 Numerous diseases including asthma, chronic rhinosinusitis, atopic eczema, chronic fatigue syndrome and fibromyalgia syndrome are all influenced by a breach in the integrity of epithelial membranes.

75 When treating conditions of severe regulation rigidity without adequate and timely restoration of regulation, a more comprehensive treatment program is necessary to remove all stressors and blocks to autoregulation/ compensation, and to apply the appropriate courses of bioregulating medicines.

96 Chronic disease management should move towards holistic, multi-modal integrated care, and multi-scale, multi-level system approaches.

Cluster 6: Bioregulatory Clinical Pharmacology

7 Multi-combination and/or multi-system low dose medications, preferably of natural origin, are well suited for the bioregulatory medical approach and offer the potential for a graded response to treatment.

12 Inhibitory pharmacologic intervention is an option of choice when a single disease causative factor is identified and must be eliminated and there is insufficient time to complete a proper bioregulatory treatment (e.g. the treatment of acute MI or stroke).

31 Bioregulatory systems medicine is a method of choice in treating multifactorial disease when restoration of homeodynamics is still achievable.

34 A multicomponent, multitarget medical management model may be a solution to current inadequate treatments for multi-factorial diseases such as dementia, certain cancers, cardiovascular disease and metabolic disorders such as Type II Diabetes and metabolic syndrome.

45 The functions of medications with bioregulatory properties are determined by natural combination chemistry and synergy.

51 The efficacy of a complex medication is determined by its ability to influence multiple interactions to reverse the clinical picture of disease.

53 Multicomponent medications target multiple nodes of a perturbed molecular network simultaneously.

54 Bioregulatory therapies should be considered in the context of biological rhythms.

71 Medications with bioregulatory properties can act on multiple organ systems and multiple targets in disease-related molecular networks simultaneously.

72 Biological information of regulatory networks can be directly and purposefully influenced with multitarget and multicomponent medications.

77 When multiple independent targets of the same pathway are inhibited simultaneously, a mild inhibition of each target is sufficient to achieve a much larger therapeutic window and a therapeutically relevant effect.

90 Medications that neither block nor interfere with endogenous resolution pathways will help to reduce therapy side-effects and promote long-term benefits.

92 Medications with bioregulatory properties influence tissues by helping to restore molecular coherence.

99 The concurrent and gentle use of more than one natural substance in alignment with a network medicine approach may offer a safe and effective alternative to the current medical paradigm.

Cluster 7: Diagnostics and Therapeutic Strategy

10 Fully integrated bioinformatical models will help to mechanistically explain disease states and support the development of targeted therapeutic strategies.

28 Treatment of a symptom alone, without considering the underlying cause, can disturb the autoregulatory process.

29 A more detailed molecular picture of disease evolution will lead to novel treatments, which may involve targeting whole networks.

30 Bioregulatory medical interventions can range from supporting auto-regulatory capacity to actively provoking a stimulus to restore and clear the blocks to autoregulation capabilities.

35 Integration of all molecular diagnostic techniques will provide a more detailed picture of disease evolution.

60 Novel diagnostic solutions, including measuring heart rate variability, complex molecular biomarker panels and omics technologies including whole-blood deep sequencing, will allow for the assessment of the global autoregulation/compensation state and the organism's response to the bioregulatory treatment.

61 Therapeutic decisions in bioregulatory systems medicine are made based on the capacity of the affected autoregulatory network in relation to the causative stressor.

73 In diseases with a chronic relapsing course and relatively good health during the remission period, regulation can be regained by eliminating the stressor (spontaneously or via appropriate medical intervention), clearing the block to autoregulation, or supporting the auto-regulatory network.

76 The modeling of a disease as a molecular/cellular network will lead to the development of novel diagnostic test systems tailored to multitarget therapies.

80 The degree of the body's dysregulation can be classified into basic patterns which then serve to make therapeutic

decisions.

86 Medications with bioregulatory properties should not permanently interfere with the body's autoregulation networks.

93 A clinical model that guides therapeutic decision-making based on assessment of tissue molecular networks in the context of the patient's auto-regulatory ability is better suited for accurate prediction of disease outcomes, intervention follow-up and disease prevention.

100 Diagnostic measurements should be expanded beyond current markers to include the assessment of autoregulatory networks and blocks to autoregulation.

Cluster 8: Patient Health-Disease Continuum

37 Symptoms are an expression of the response of the autoregulatory system to a stressor.

58 The progression of a disease is facilitated by disturbed or inadequate autoregulatory abilities of the organism.

65 In any individual patient, disease interconnectedness (by shared molecular events) represents the individual's disease evolution, reflected in the patient's medical history.

78 Simulating the dynamic evolution of health-to-disease processes can be used to predict the response of a whole inflammatory/wound-healing system, rather than the response of particular inflammatory mediators.

97 Disease progression is the result of an auto-regulatory process that is disturbed or challenged by an overwhelming stressor and cannot function adequately to restore homeodynamics.

102 Lipidomics, metabolomics, genomics and proteomics are technologies which can help to detect and monitor the inflammatory state of a patient in order to diagnose more comprehensively.

Cluster 9: Autoregulation of Biological Networks

8 A multi-scale network of all molecular components and their within- and cross-tissue interactions can serve as a global autoregulation model of the human organism.

20 Blocks to autoregulation are etiological factors that maintain persistent network perturbation and restrict the network from autoregulating towards resolution.

23 There is a high level of molecular coherence in healthy tissues and the loss of molecular order corrupts "healthy" information flow in the tissue.

27 Robust molecular networks are able to autoregulate in order to restore or adapt its functional state in response to external inputs.

48 Disease progression is characterized by an increase in the thermal degrees of freedom and, as a result, a decrease in the molecular coherence of the affected tissues.

49 Sustained corruption of "healthy" information flow leads to the failure of regulatory networks' ability to restore molecular order.

55 Diseases that share molecular/cellular networks show phenotypic similarity and comorbidity (e.g. the link between atherosclerosis and obesity).

56 The majority of diseases share a certain number of common molecular functional modules, each associated with a pathophysiological process.

70 A network approach can be used to identify common pathological threads between seemingly unrelated diseases, to improve the understanding of the pathogenesis and therefore, to aide in the discovery of the most influential therapeutic access points.

81 Signals from the microenvironment directly influence many functional modules of molecular networks representing physiological processes, including angiogenesis, development of certain glands and wound healing.

87 Robustness is the ability to maintain homeodynamics/homeostasis of living systems in the face of perturbations and uncertainty.

89 Persistent perturbation of molecular networks, including endogenous responses to specific exogenous insults, manifests as disease.

101 Many diseases are interconnected by shared molecular events.

Cluster 10: Biological Communication across Multi-Scale Networks

11 The informational nature of a human organism as a biological system allows for the creation of mathematical models of health and disease.

13 A science of systems biology is a holistic approach in biology focused on understanding complex interactions in biological systems.

18 There are two major types of biological information: sequence information encoding molecular machines and regulatory network information controlling the behavior of the molecular machines.

24 Biological networks are inherently unstable and dynamic; their capability to adapt against constantly changing internal and external inputs is dictated by their robustness.

32 Information in the living system can be digital (e.g. 4-digits nucleotide code) or analogous (e.g. 2D-3D spatial structures of molecules).

33 Tissues and organs can be linked together in networks by the functional interdependencies between them.

38 Information theory and thermodynamics are fundamental for understanding the principles of a biological system.

40 Molecular coherence, which can be defined as the behavior of molecules in the tissue in response to the whole network of all other molecules can be quantified as the ratio between codable systems and thermal degrees of freedom.

44 Much of the complexity of living organisms stems from complex regulatory networks, rather than from gene diversity.

82 Low affinity interactions (especially RNA-protein interactions) provide a computational matrix to process information and to direct action in molecular networks.

85 Molecules are informational units that circulate in non-linear, network mode.

7.2 Appendix B: Group Concept Mapping Methodological Details

Forty-three individuals were invited to participate in the web-based sorting activity, including initiative leaders. An international team of scientific and clinical experts from various backgrounds ensured that both the strengths and shortcomings of the current healthcare approach were considered. Scientific experts included those in the fields of immunology, genomics, molecular biology, and systems biology, supporting the scientific basis of the approach that is rooted in emerging work in systems biology. Clinicians specializing in various medical areas participated, from specialties including neuroscience, aging, family medicine, and chronic degenerative diseases. The combination of these perspectives helped to ensure that the resultant model would represent a consensus understanding of bioregulatory systems medicine that would resonate with a broad group of global scientists and clinicians.

Participants were asked to sort the 102 statements into categorical piles of closely related ideas based on their meaning, and assign each pile a name to describe its theme or contents. Four key instructions guided the structuring activity: a) all statements could not be placed into a single pile, b) all statements could not be placed into their own separate piles (although some statements could be grouped by themselves), c) statements could not be placed in two piles simultaneously, and d) there could not be any “miscellaneous” piles (any item thought to be unique was to be placed in its own separate pile). Twenty-nine of the forty-three (67%) invitees completed the structuring activity. The aggregation of individual sort data provided the basis for the concept mapping analysis.

The concept mapping analyses were conducted using the Concept System® software program. The first step in the analysis involved the creation of a similarity matrix to represent each individual’s sort data. In this case, a 102 x 102 binary square similarity matrix (rows and columns represent statements) was created for each participant. Cell values represented whether (1) or not (0) the participant sorted statements into the same pile. All individual sort matrices (29) were summed to create a single similarity matrix representing how the participant group as a whole sorted the statements. The aggregated similarity matrix was analyzed using a multivariate statistical analysis called non-metric multidimensional scaling (MDS) with a two-dimensional solution. This analysis enabled the relative similarity among items to be represented in terms of relative distance between pairs of points.(Kruskal 1964) From these analyses, coordinate estimates and a two-dimensional map of distances between the statements (represented as points) were generated.

The MDS analyses of the similarity matrix converged after 25 iterations, producing a final stress value of 0.25. The stress value is reported as part of the MDS analysis to indicate the goodness of fit of the two-dimensional configuration to the original similarity matrix. A lower stress value indicates a better fit and reflects a stronger relationship between the optimal and actual configurations.(Kruskal 1964) Previous analyses of stress values across multiple concept mapping studies found an average of 0.28 and a range of 0.17 to 0.34.(Rosas & Kane 2012) Thus, the stress value found with the BrSM model was consistent with those found across numerous typical concept mapping projects. The stress value indicates that the point map reflects better-than-average relationships between the respective optimal configurations and how the points actually

appear on the map.

Following the point map generation, hierarchical cluster analysis was conducted using the two-dimensional x-y coordinate data obtained from the MDS analysis. Ward's algorithm was applied as the basis for defining the clusters, (Everitt et al. 2009) and partitioned the MDS configuration into non-overlapping clusters, such that the items placed in the same cluster were in contiguous areas of the map. The output from the cluster analysis was a cluster map, which revealed how the statements, as represented by points, were grouped into a set of ten higher-order constructs ("clusters"). The distances among the points and clusters are fixed in space; however the directionality of the map is subjective, and the map could be rotated in any direction without affecting the distances.

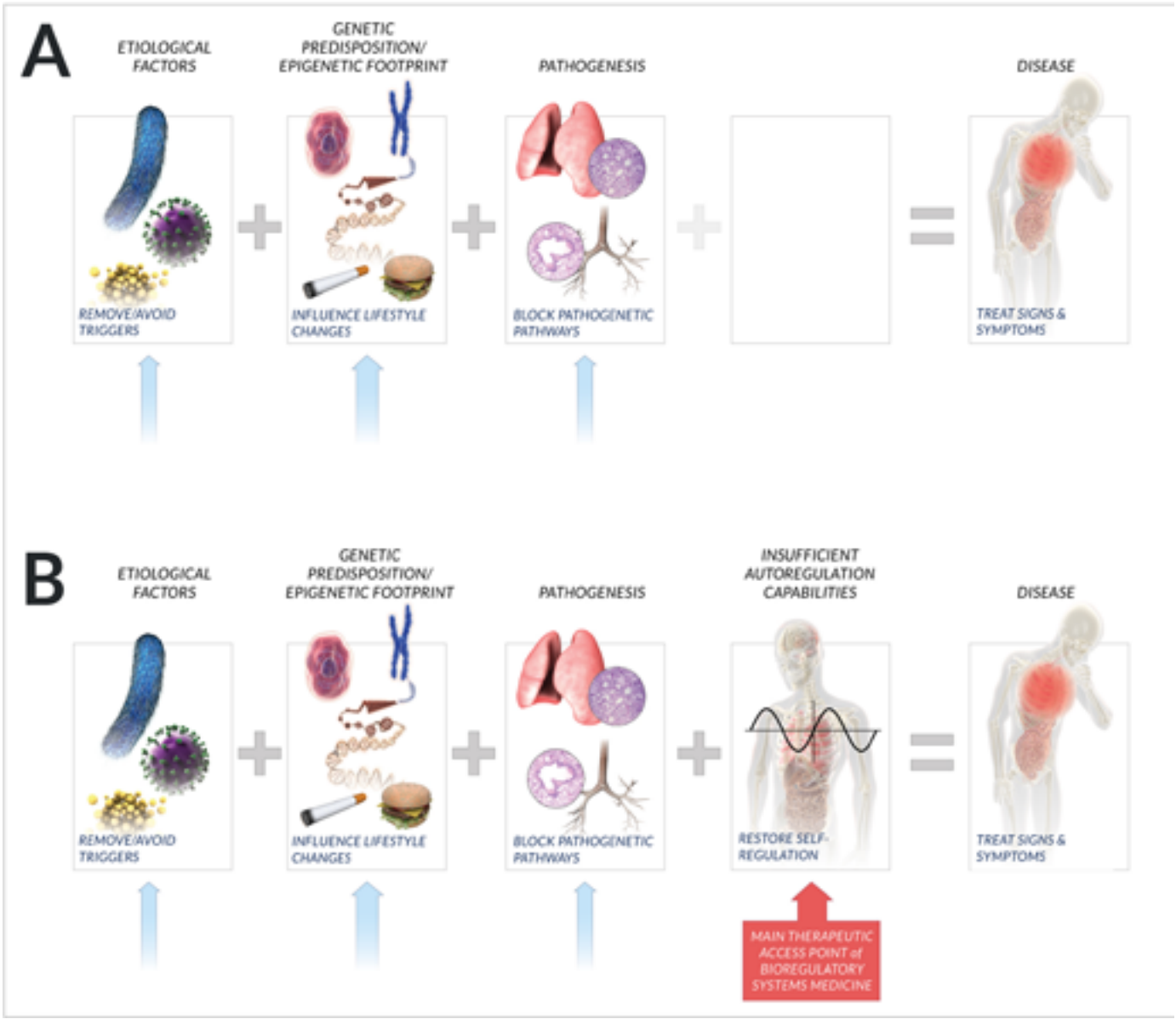
The functional relatedness within and among clusters is calculated as the percentage of participant sorts between statements in a given cluster and statements in all other clusters of the map. Internal relatedness is defined as the frequency at which participants sorted the statements in a given cluster with one another, relative to all other statements on the map. External relatedness is defined as the frequency at which participants sorted the statements in a given cluster with the statements in other clusters of the map. In the table below, the internal relatedness of each cluster is highlighted in yellow.

Cluster	1	2	3	4	5	6	7	8	9	10
1	0.13	0.19	0.15	0.12	0.05	0.03	0.05	0.05	0.05	0.06
2	0.12	0.34	0.02	0.02	0.02	0.01	0.00	0.02	0.04	0.04
3	0.33	0.08	0.53	0.43	0.05	0.02	0.02	0.08	0.04	0.04
4	0.08	0.02	0.12	0.08	0.01	0.01	0.01	0.03	0.03	0.03
5	0.08	0.05	0.04	0.04	0.21	0.21	0.19	0.12	0.09	0.04
6	0.06	0.03	0.02	0.02	0.25	0.41	0.22	0.05	0.06	0.05
7	0.09	0.02	0.02	0.04	0.21	0.21	0.24	0.13	0.13	0.09
8	0.04	0.03	0.03	0.04	0.06	0.02	0.05	0.09	0.08	0.04
9	0.10	0.13	0.04	0.11	0.10	0.05	0.13	0.19	0.26	0.28
10	0.10	0.11	0.03	0.09	0.04	0.04	0.07	0.09	0.23	0.34

Functional relatedness within and among clusters

8. Figures

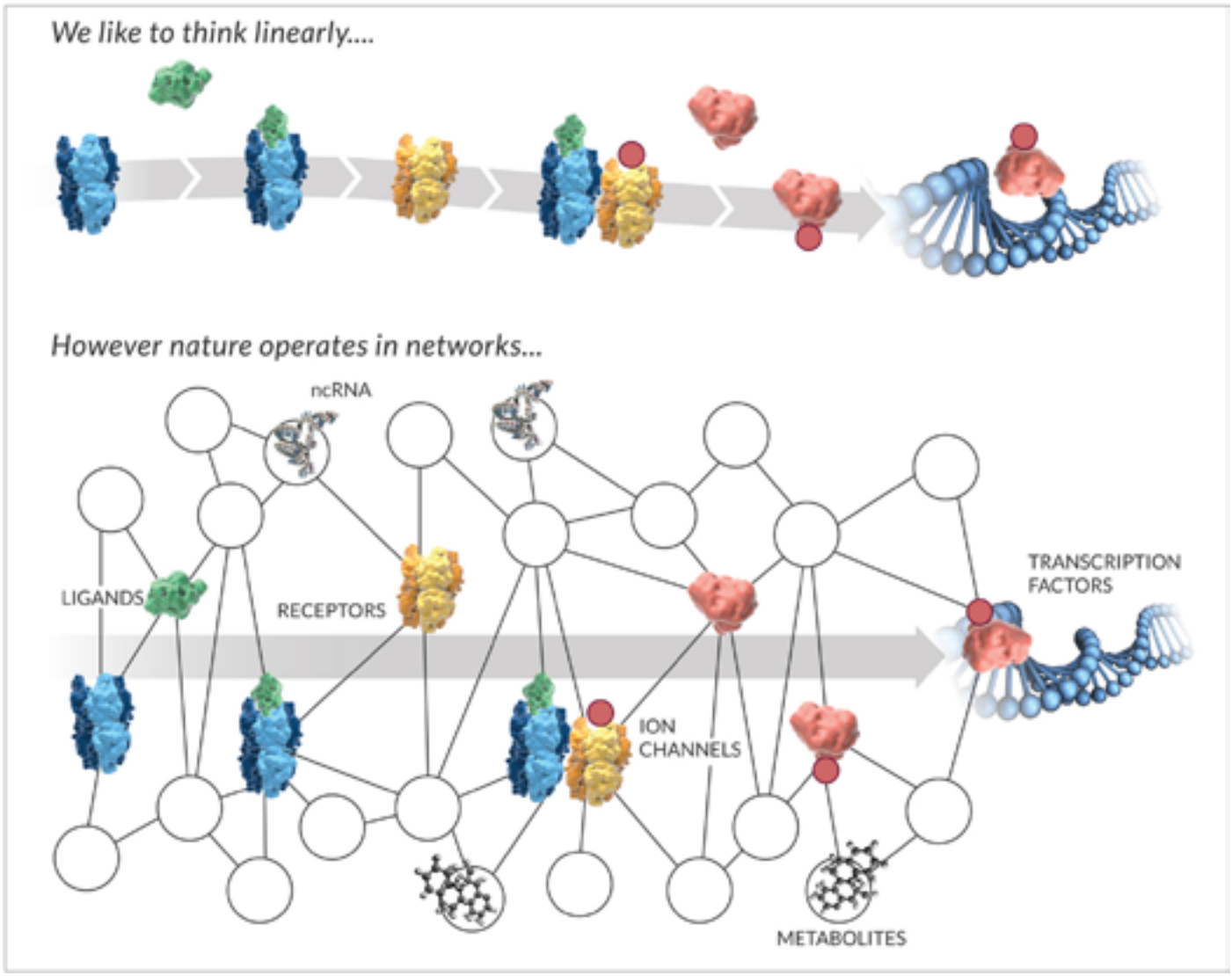
Figure 1. Novel considerations of factors affecting disease.



The current medical paradigm (A) typically consider etiological factors, genetic predisposition and molecular pathways recruited in pathogenesis as key causative agents that lead to disease. Bioregulatory systems medicine (B) also considers the patient's compromised or insufficient autoregulatory capacity to restore homeostasis as a key factor that influences individual disease incidence and manifestation. Restoration of patient autoregulatory capacity is therefore a primary therapeutic objective in bioregulatory systems medicine, in addition to removal of triggers, lifestyle changes, and inhibition of pathogenetic pathways, when appropriate.

(back to text)

Figure 2. Linear versus non-linear causation model.



The fields of molecular biology and medicine have traditionally considered influence and causality among relevant entities as occurring in a linear manner. This linear framework, often referred to as a reductionist perspective, supports a single-molecule, single-target approach, whereby a particular biological component (e.g. receptor, gene, etc.) is considered individually and in isolation when treating disease. More recently, modern technological advances have allowed for a more comprehensive understanding of the fundamental interconnectedness of biological systems, prompting a reconceptualization toward a non-linear, systems-based model of physiology and pathophysiology. This integrative view acknowledges the spatial and temporal interdependencies among multiple molecular and physiological processes, maintaining that a more effective medical approach utilizes biological networks when treating disease. Bioregulatory systems medicine endorses this network perspective.

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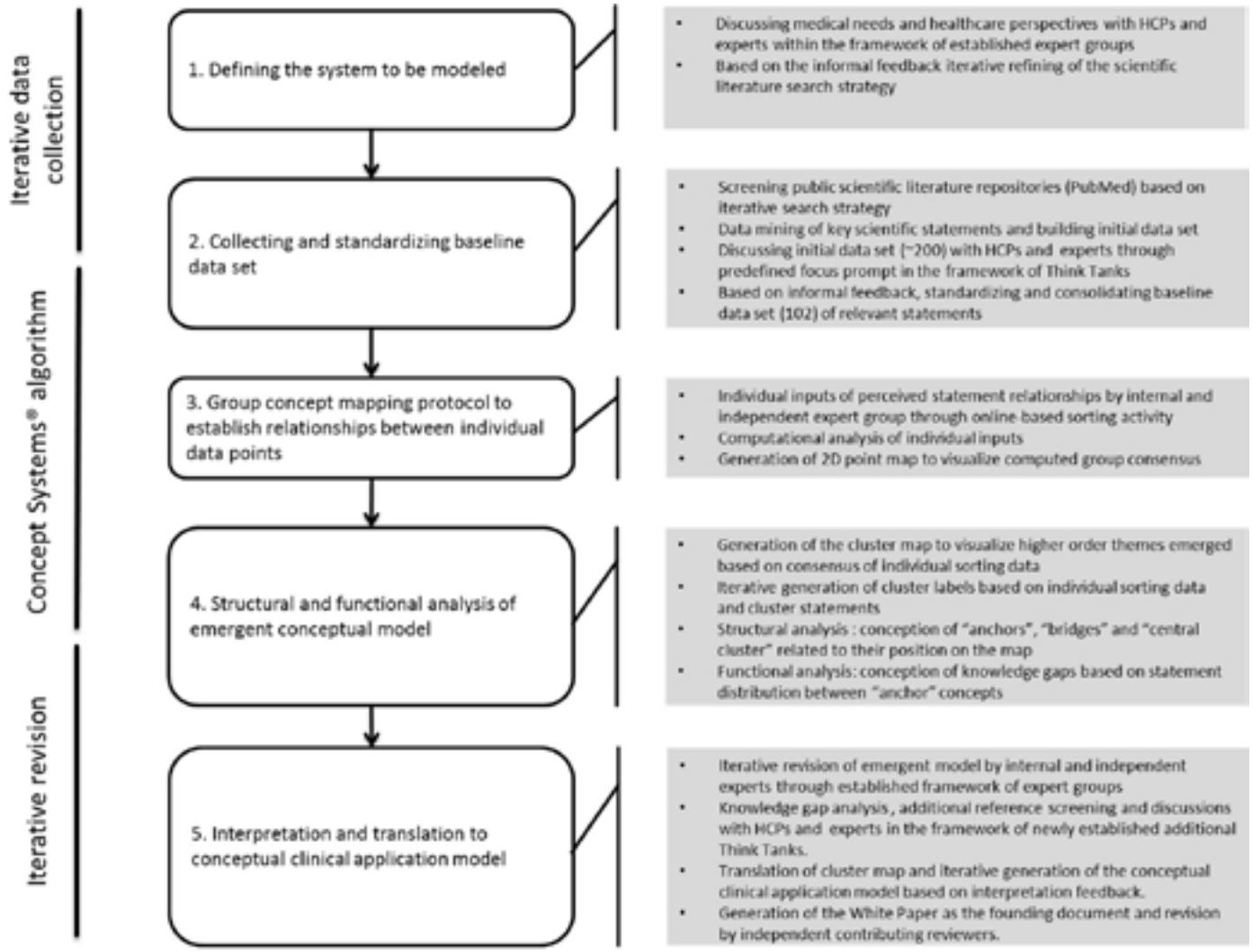
Figure 3. Flow diagram of the model development protocol.



The development protocol consisted of five basic consecutive steps. The key properties of the protocol were iterative processes engaging HCPs and independent scientific experts by establishing the framework of expert group round tables, inquiring for feedback in almost each step, and employing the Concept Systems© algorithm to compute and visualize the emergent consensus of a larger group of participants. The resultant conceptual clinical application model serves as a basis for research program development and further experimental validation.

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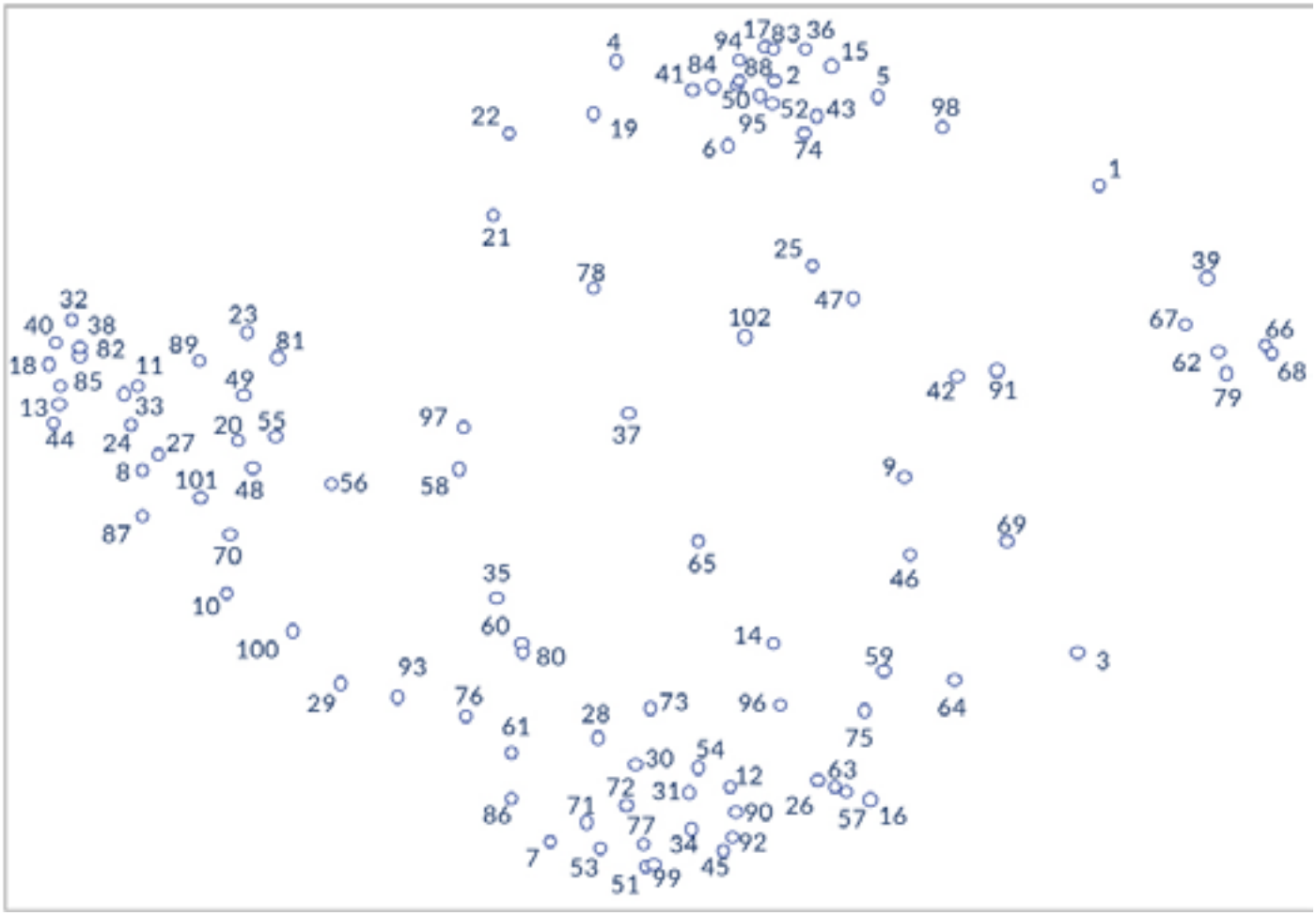
Figure 4. Bioregulatory Systems Medicine Emergent Conceptual Model: the Point Map.



In this figure, each point represents one of the 102 statements derived through extensive literature mining and expert consensus, and considered to represent a key component of the bioregulatory systems medicine conceptual model. A number was assigned arbitrarily to each of the 102 statements for reference purposes only. The point map displays each of the 102 statements in two dimensional space based on the aggregation of expert participants' sort data and the subjection of that aggregated sort data to multidimensional scaling. Statements that appear closer to one another on the point map tend to be thought of as more conceptually similar by those who participated; statements that appear farther apart tend to be thought of as more conceptually distinct. We refer readers to Appendix A for a full list of the statements represented by the numbers.

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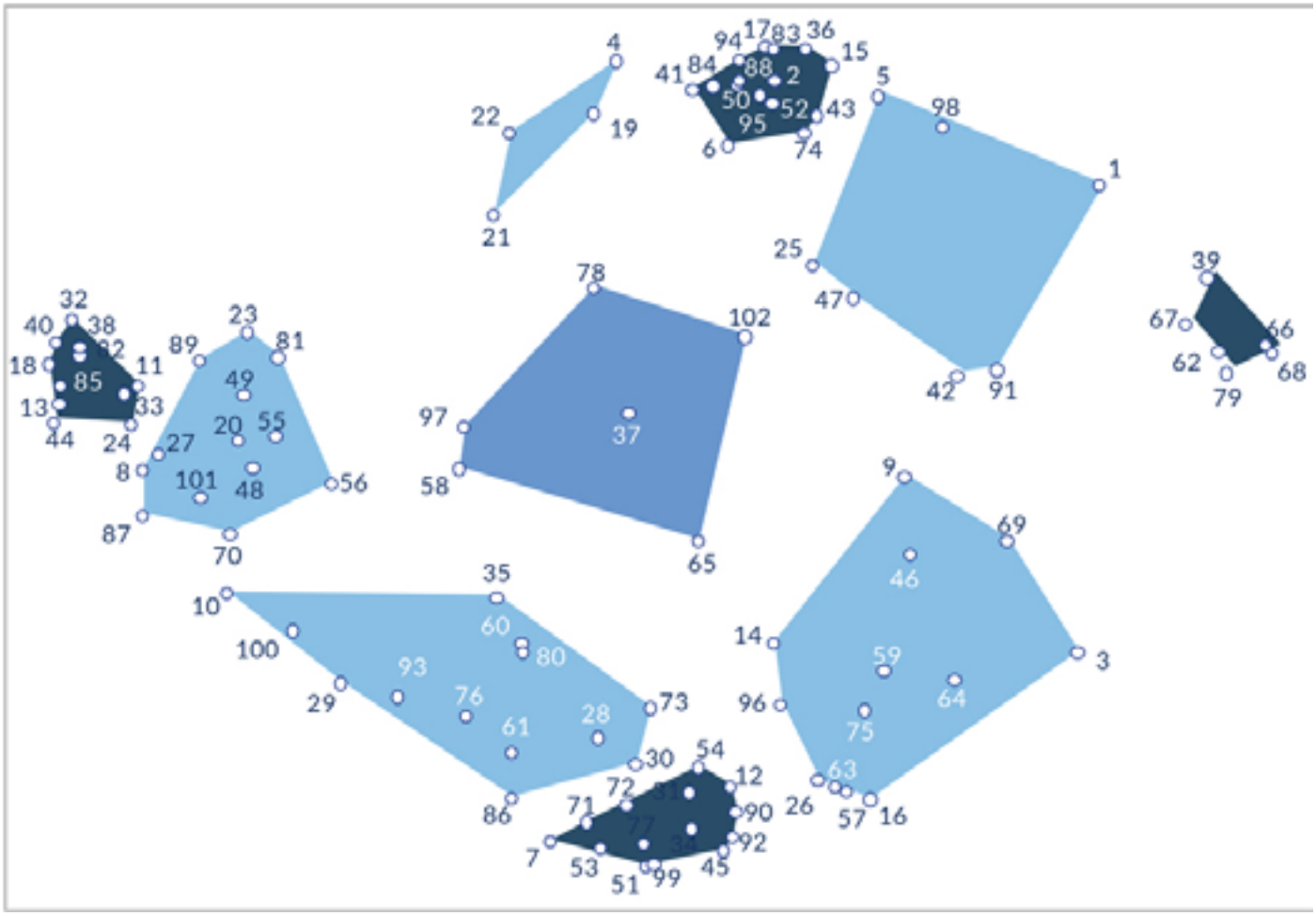
Figure 5. Bioregulatory Systems Medicine Emergent Conceptual Model: the Cluster Map.



The cluster map represents the 102 statements as they are grouped into higher-order themes based on their arrangement in the point map (Figure 4). After reviewing the fit of the map content within multiple cluster arrangements, it was agreed that a ten cluster solution was the most parsimonious representation for meaningfully and heuristically interpreting the relationships among the individual statements within a smaller set of thematic constructs. Each cluster was subsequently labelled (Figure 6).

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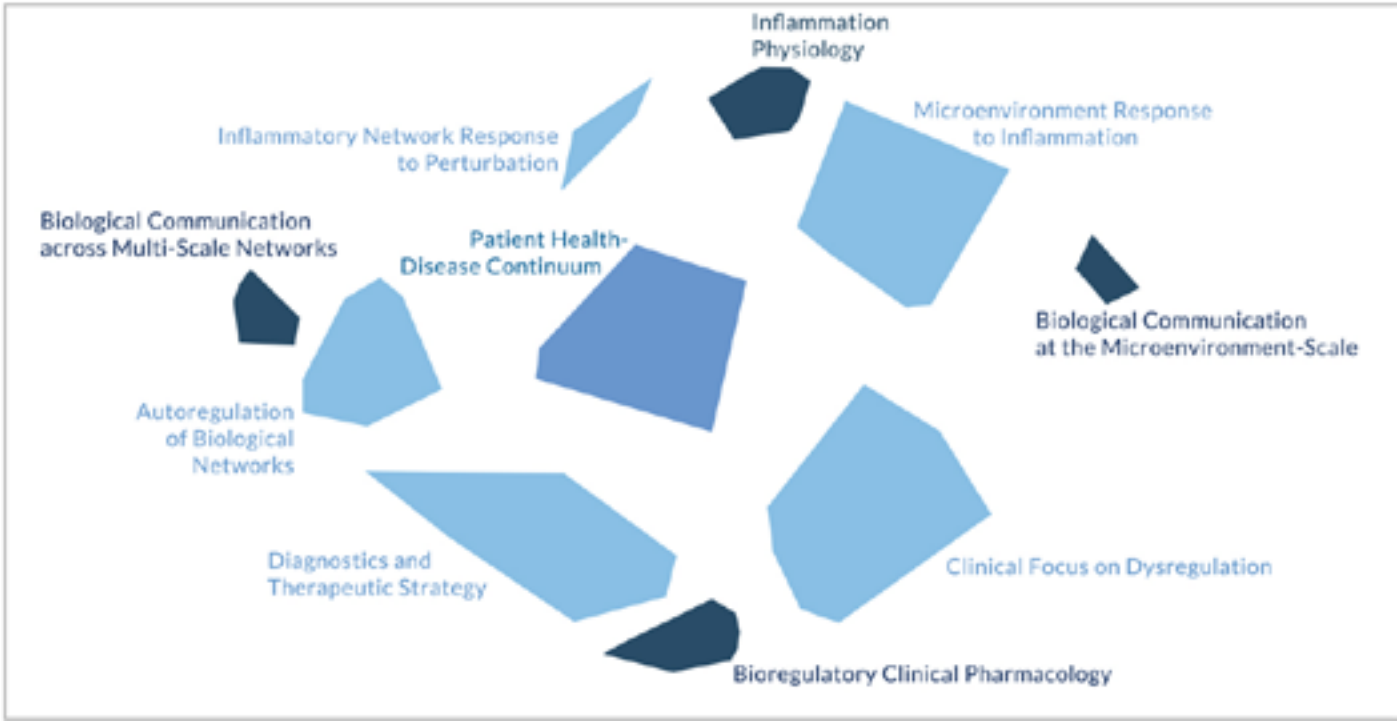
Figure 6. Bioregulatory Systems Medicine Emergent Conceptual Model: The Labeled Cluster Map.



The labels assigned to each cluster reflect the shared higher-order themes that describe the specific statements within each cluster and convey the cluster's meaning in the context of the bioregulatory systems medicine paradigm. Cluster labels were derived and finalized by authors and contributing reviewers that championed the model development initiative. The clusters have been color coded based on the structural analysis: anchor clusters are marked dark blue, intermediate clusters light blue, and central cluster middle blue. Refer to the text for a more detailed explanation of the structural cluster analysis.

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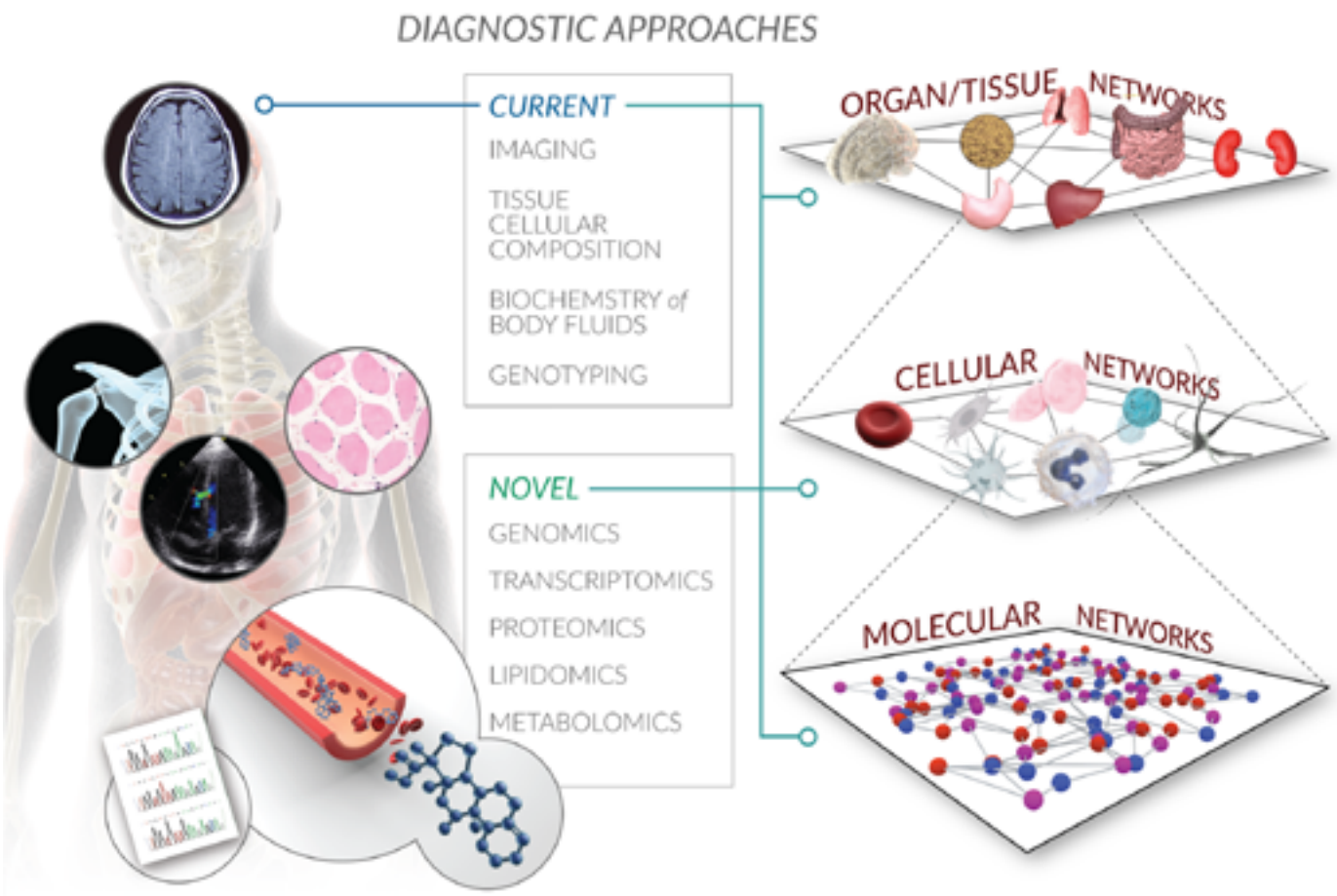
Figure 7. Multi-scale autoregulatory networks.



Bioregulatory systems medicine encompasses a systems biology perspective of interactions within and across multiple levels of biological organization. The complexity of a systems approach challenges common reductionist thinking, and paves the way for medicine that works with rather than against the inherent interconnectivity of biological organization. From the molecular to cellular to organ to whole organism network, the BrSM model acknowledges that human health and disease are driven by the regulatory information flow that propagates throughout this global autoregulatory network. Current diagnostic approaches are limited by capturing only a static snapshot of some of this information. Novel diagnostic approaches will confirm and provide higher resolution of existing snapshots of clinical information, and will expand its scope by adding (surrogate) biomarkers of autoregulatory capacity in one spatiotemporal model specific to the patient.

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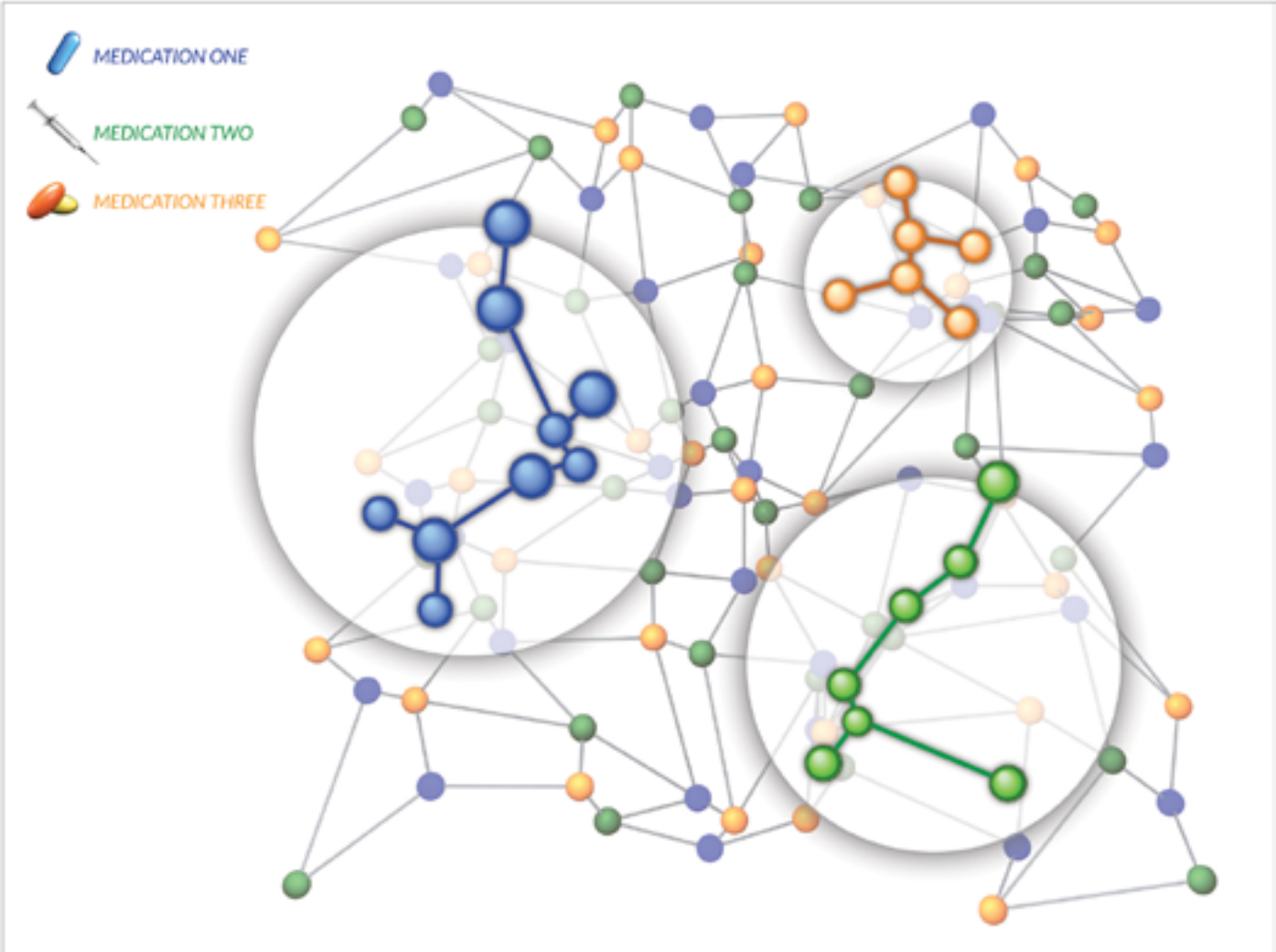
Figure 8. Bioregulatory Clinical Pharmacology.



A fundamental postulation of bioregulatory systems medicine is that medications with bioregulatory properties facilitate autoregulation by acting on multiple targets (nodes) in disease-perturbed networks simultaneously. In this way biological information flow can be directly and purposefully influenced. The efficacy of this multitarget mode of action is determined by the ability to reverse the clinical picture of disease.

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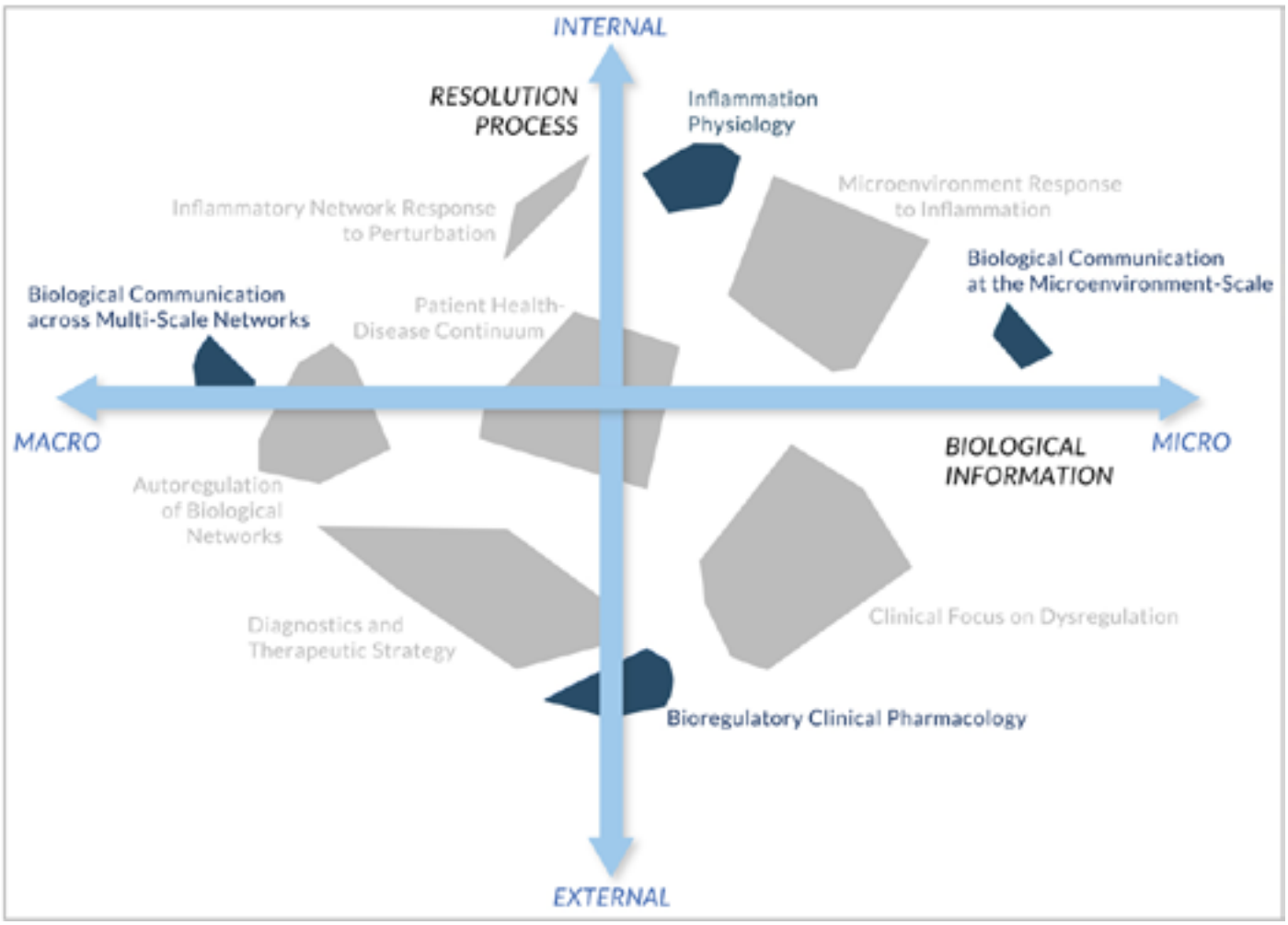
Figure 9. Bioregulatory Systems Medicine Emergent Conceptual Model: Dimensions and Anchors.



This figure illustrates the conceptual dimensions and anchors of the model that emerged from the group concept mapping process, analysis, and interpretation of the interrelationships among the clusters. The vertical dimension in this figure is labeled "Resolution Processes," as the content along this axis relates to participants' conceptualization of disease resolution occurring through both internal and external mechanisms. This dimension is anchored at one end by the Inflammation Physiology cluster, where the model content relates strongly to the human organism's innate ability to reach disease resolution in the face of perturbation, particularly as it relates to inflammation process mechanisms. The opposite end of this dimension is anchored by the Bioregulatory Clinical Pharmacology cluster, where the content most explicitly relates to the use of medications with bioregulatory properties in order to reach disease resolution. Perpendicular to Resolution Processes is the dimension "Biological Information," along which the content relates to communication within and across micro and macro levels of biological organization. This dimension is anchored at one end by the Biological Communication at the Microenvironment-Scale cluster, where the content describes communication at the cellular level, particularly referring to the extracellular matrix. At the opposite end, this dimension is anchored by the Biological Communication Across Multi-Scale Networks cluster, which describes how biological information flows across molecular (cellular, tissue, organ) networks at the whole organism level.

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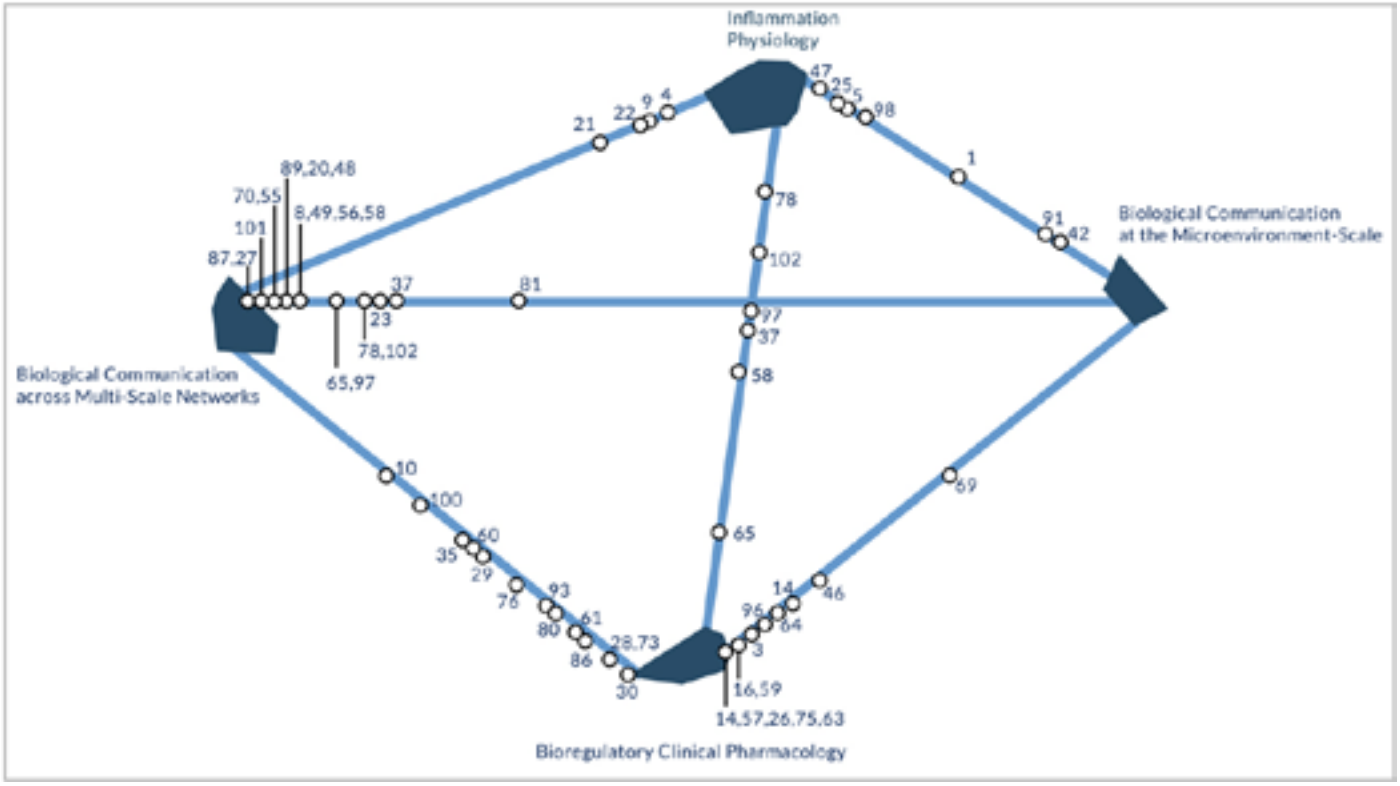
Figure 10. Bioregulatory Systems Medicine Emergent Conceptual Model: Intermediary Clusters.



The intermediary clusters are spatially located between the anchor clusters, and can be described as conceptual bridges that relate to their respective neighbouring anchors. The figure below illustrates the statements of each intermediary cluster as arranged between the cluster's corresponding anchors. A statement's distance from either anchor reflects the relative strength of relatedness that participants collectively perceived among that particular statement and the neighboring anchors. The degree to which the space (blue line) between each anchor is relatively evenly populated with statements may suggest the extent to which the intermediary cluster effectively functions as a conceptual bridge between the anchors.

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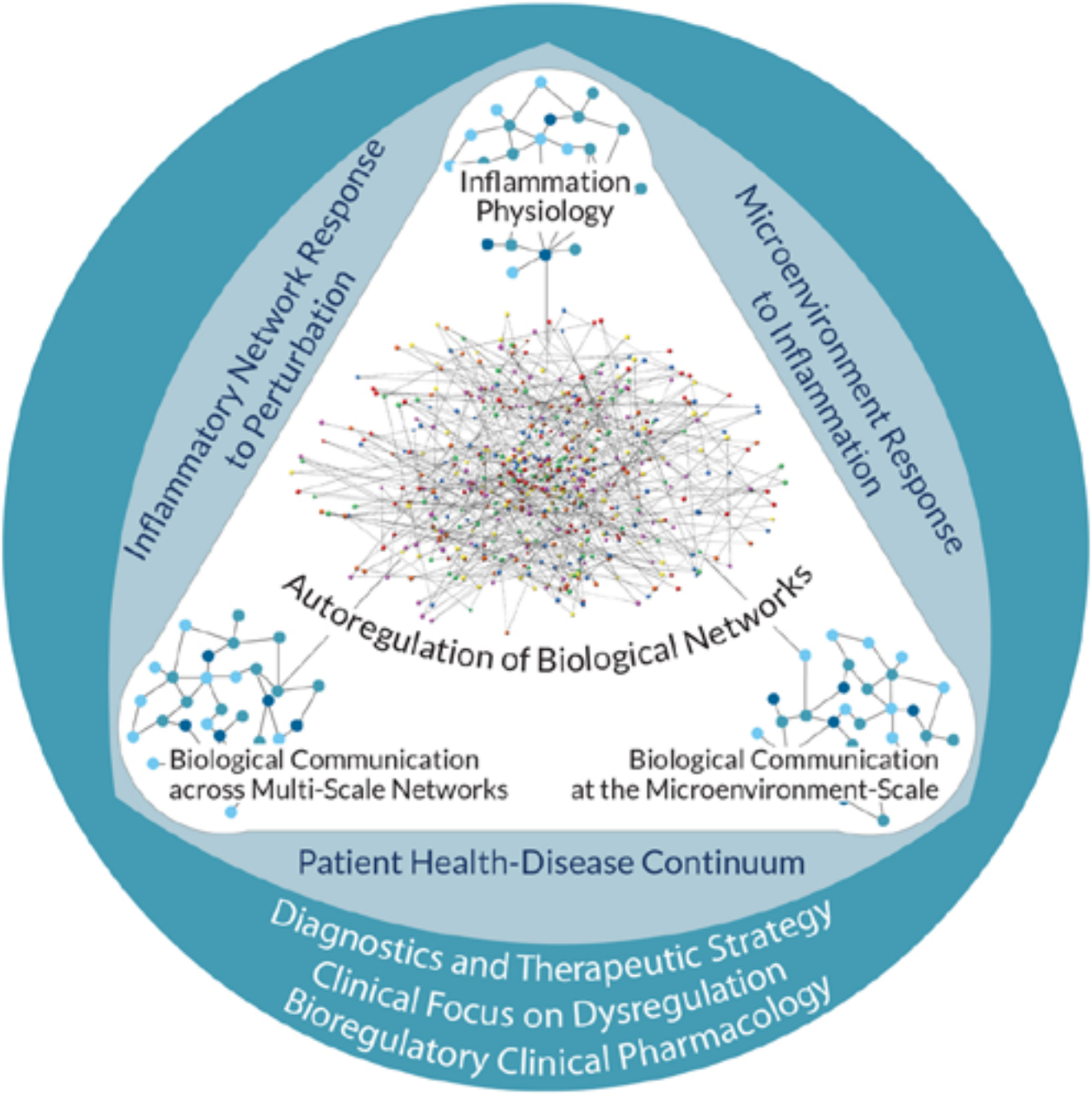
Figure 11. Bioregulatory Systems Medicine Conceptual Clinical Application Model.



The model is depicted as a unified entity of three integrated levels. The fundamental core consists of four autoregulatory clusters (white), enveloped by the layer of dysregulation clusters (light blue), which in turn is enclosed by final layer of therapeutic clusters (dark blue). In this way the model informs the relevant fundamental underpinnings of human biology that result in the clinical picture observed in individual patients. The proper assessment of this clinical picture guides individualized clinical decision making that is based on the underlying cause of disease. For a detailed explanation, refer to Clinical Significance and Overarching Principles.

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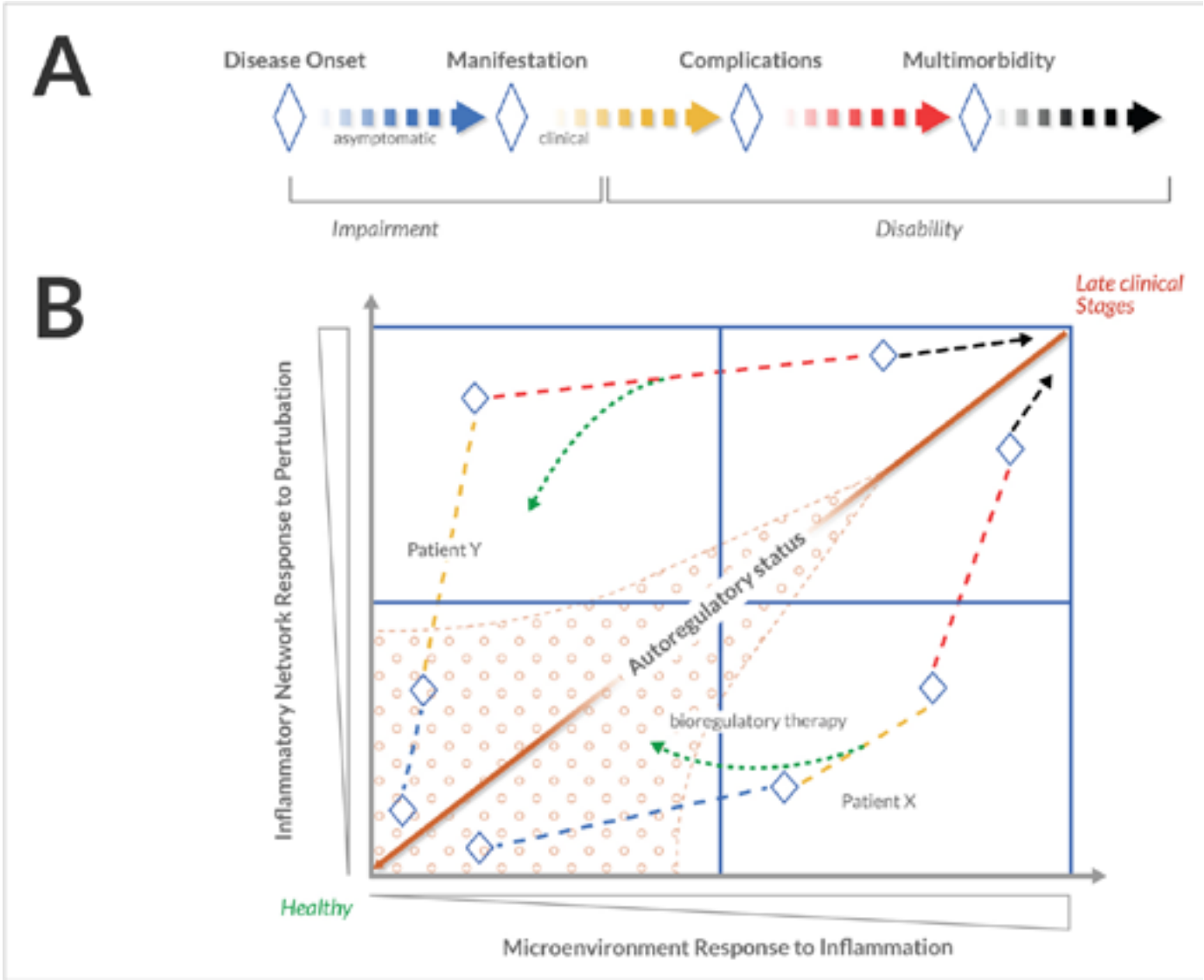
Figure 12. Novel conceptualization of disease progression introducing patient's autoregulatory status.



Disease progression is commonly understood as the worsening of a disease over time. In 1980, the World Health Organization published the International Classification of Impairments, Disabilities and Handicaps (ICIDH) with the objective of providing a widely accepted structure of the consequences of disease and of implications for the lives of patients. Expanding on this model, this figure includes a conceptualization of the autoregulatory status of two patients.

A. The concept of disease progression adapted from the 1980 WHO ICIDH model. Blue-to-black colors indicate conceptual disease worsening stages, and ◊ depicts principal milestones between stages. The dashed line indicates that there is no strict sequential order between stages or milestones, and the linear structure is used for simplicity.

B. A schematic conceptualization of the disease progression as a four-quadrant map. In the BrSM model, this is called the Patient's Health-Disease Continuum. The arrowed dashed lines represent the hypothetical disease progression in patients X and Y. In contrast to simplified linear concepts focusing on identifying disease stages in decision-making, the map concept positions these stages in relation to dysregulation parameters represented by horizontal and vertical axes. In the BrSM model, systemic dysregulation parameters are conceptualized as Inflammatory Network Response to Perturbation, and local dysregulation parameters are conceptualized as Microenvironment Response to Inflammation. Increased dysregulation is indicated as the lines move toward the top or right. It is suggested that the ratio between these two dysregulation parameters theoretically defines the autoregulatory status of a patient. For a detailed explanation, refer to Clinical Application In Practice.

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9. Notes

Bioregulatory
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Medicine