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Article

Physiological Expression Mapping in Cardiometabolic Disease: A State-Space Framework with Clinical and Hemodynamic Evidence

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Abstract

Contemporary clinical medicine relies on a risk-factor paradigm in which individual diseases are managed using population-derived thresholds. This reductionist approach is increasingly limited in cardiometabolic multimorbidity, where abnormalities arise from interacting dysregulations across cardiovascular, metabolic, renal, and endocrine systems, and interpretation of patient condition often requires an organism-level representation of physiological state. We introduce the digiphysiomic framework, which proposes a transition from isolated risk-factor management to a multidimensional state-space representation centered on physiological expression mapping. In this framework, patient condition is represented as a point in a coordinate system defined by measurable and therapeutically relevant physiological processes. Clinical measurements are transformed into a normalized phenotype vector relative to reference models derived from population and clinical datasets. A knowledge-informed weighting structure—refinable using observational data, randomized trials, and guideline-based evidence—defines the geometry of the space and enables construction of the physiological expression map, a structured visualization of regulatory imbalance designed to support mechanism-oriented clinical decision making. Cardiometabolic disease provides a representative application because it inherently involves multiple interacting regulatory systems. The digiphysiomic space can be constructed using routinely collected clinical variables together with measurements previously used in physiological and hemodynamic phenotyping studies, while maintaining a stable coordinate structure that allows heterogeneous datasets to be integrated without redefining physiological dimensions. Within this space, longitudinal change and therapeutic effects can be represented as transitions, enabling alternative treatment strategies to be compared within a unified physiological framework. By establishing an explicit physiological coordinate system centered on the physiological expression map, the digiphysiomic framework may provide an intermediate layer between raw clinical data and predictive algorithms. Prior work on multidimensional physiological phenotyping and mechanism-guided therapy supports the feasibility of this representation, and with further validation, this approach may support future AI-assisted decision-support systems for individualized management of cardiometabolic multimorbidity while remaining consistent with clinical reasoning and guideline-based care.

Keywords: digiphysiomic framework; physiological expression map; state-space medicine; cardiometabolic disease; multimorbidity; clinical decision support; systems physiology; precision medicine

1. Introduction

Cardiometabolic disease, including hypertension, diabetes, dyslipidemia, and obesity, remains the leading cause of morbidity and mortality worldwide and is increasingly characterized by

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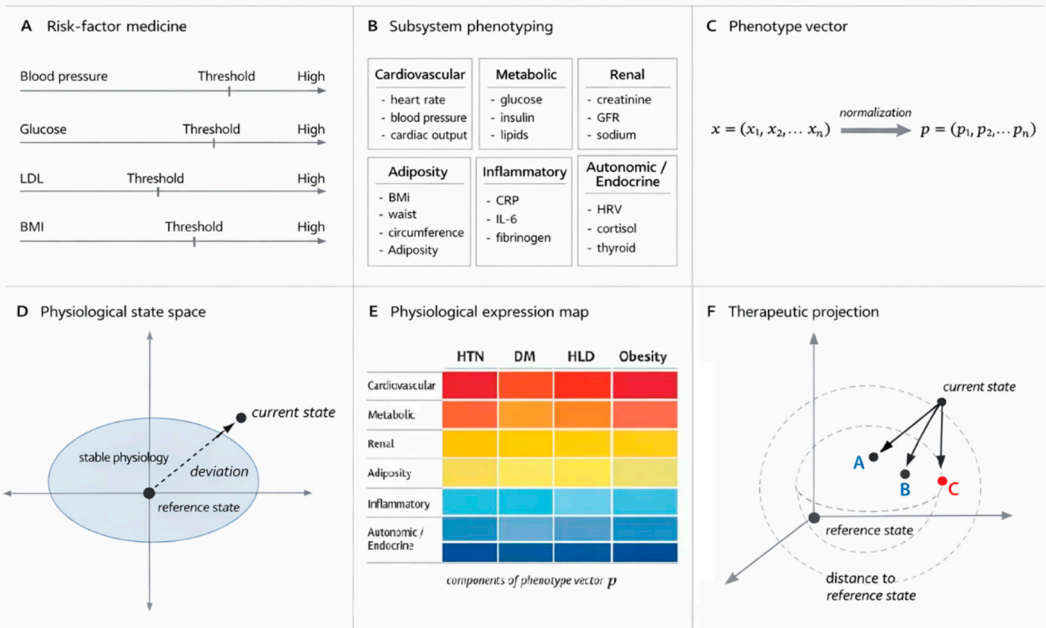
multimorbidity involving multiple interacting physiological systems [1,2]. Despite major advances in pharmacotherapy and clinical guidelines, management of these conditions continues to rely largely on the control of individual risk factors, with treatment decisions guided by population-based thresholds for blood pressure, glucose, lipid levels, and body mass index. Although this risk-factor–based paradigm has improved outcomes at the population level, it often fails to account for the substantial heterogeneity in disease mechanisms and treatment response observed among individual patients [3–6]. These limitations highlight the need for frameworks that represent patient condition at the organism level rather than as isolated risk factors.

Recent work on clinical artificial intelligence and digital-twin–based modeling has further highlighted the difficulty of translating complex data-driven models into routine clinical use. High predictive performance alone does not ensure safe or reliable decision support, as models must remain robust across populations, interpretable at the level of individual patients, and compatible with real-world clinical workflows. However, some current machine-learning and digital-twin approaches depend on assumptions that limit generalizability, making their application in routine clinical decision making challenging [7–12].

In this study, we propose a multidimensional physiological state-space modeling framework, termed the digiphysiomic framework, for representing organism-level condition using integrated clinical and physiological measurements. In this framework, the patient is represented as a point in a coordinate system defined by physiologically meaningful regulatory domains across interacting organ systems. The coordinate structure is defined independently from the weighting rules used for interpretation, allowing heterogeneous clinical variables to be integrated while preserving physiological meaning. Deviations across domains can be summarized as a physiological expression map, providing a structured description of regulatory imbalance that may assist clinical decision support without replacing clinical judgment.

As an initial application, we focus on cardiometabolic disease, in which abnormalities arise from interactions among cardiovascular, metabolic, renal, endocrine, and autonomic systems. These conditions often involve multimorbidity and require simultaneous evaluation of multiple mechanisms. They therefore provide a suitable setting for constructing the digiphysiomic space and demonstrating physiological expression mapping using routinely available clinical measurements (Figure 1).

Figure 1. The digiphysiomic framework for physiological expression mapping



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2. The Digiphysiomic Framework for Physiological Expression Mapping

This section describes the construction of the digiphysiomic state space and the representation of patient condition within it. We define the physiological domains that form the coordinate system, the phenotype vector used to represent individual state, and the weighting structure that determines how domain-level deviations are interpreted. The section also introduces physiological expression maps as a clinically interpretable representation of organism-level regulation and outlines approaches for handling incomplete observations in real-world clinical data.

2.1. Construction of Normalized Phenotype Vectors for an Individual

Let the clinical and physiological measurements obtained from an individual be represented as a vector

$$\boldsymbol{x} = (x_1, x_2, \ldots, x_n),$$

where each component x_i corresponds to a measurable variable. Because clinical data are heterogeneous and differ in scale, variability, and modality, normalization is required before these variables can be integrated into a common coordinate system.

In the digiphysiomic framework, the dimensions of the state space are defined by variables that represent physiological processes potentially modifiable by therapeutic intervention. These variables (continuous or ordinal) are used to construct the phenotype vector and define the axes of the digiphysiomic space because they describe the current physiological condition that may be the target of clinical decision making.

Other clinical variables may be highly relevant to interpretation but do not themselves represent the current physiological state and are not directly modifiable by therapy. These include demographic attributes (such as age, sex, or genetic background), contextual factors (such as region of residence or hospital site), historical information (such as medical history or previous treatments), and nominal categories (such as blood type or diagnostic labels). Such variables are not used as primary coordinates of the space. Instead, they may incorporated in the normalization procedure or in the estimation of reference parameters so that expected values can be adjusted for individual characteristics. In practice, statistical or machine-learning models may be used to estimate the expected value of each physiological variable conditional on these additional factors.

For each variable i that defines a dimension of the space, an expected value μ_i and dispersion parameter σ_i are estimated from an appropriate reference population, potentially conditioned on demographic, clinical, or contextual variables. A normalized coordinate is then defined as

$$p_i = \frac{x_i - \mu_i(z)}{\sigma_i(z)}.$$

where $\boldsymbol{z}$ denotes the set of demographic, contextual, and historical variables, that are not directly modifiable by therapies and are not dimensions of digiphysiomic space. The normalized phenotype vector

$$\boldsymbol{p} = (p_1, p_2, \ldots, p_n)$$

defines the position of the individual in the digiphysiomic space. In this formulation, heterogeneous physiological measurements are expressed on a common scale.

Importantly, only the phenotype vector $\boldsymbol{p}$ represents the current physiological state used for subsequent analysis within the digiphysiomic framework. All calculations of distance, similarity, visualization, weighting, and clinical decision support are performed in the space defined by $\boldsymbol{p}$. This reflects the intended role of the digiphysiomic space in clinical decision support. Therapeutic decisions aim to modify physiological processes rather than demographic or contextual attributes. By separating variables that define the physiological state from those that only affect normalization, the framework provides a stable and interpretable representation of organism-level condition.

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2.2. Distance, Weighting, and Geometry in Digiphysiomic Space

Similarity between physiological states can be defined using a weighted metric in the digiphysiomic space. Because the coordinates represent heterogeneous physiological variables that may differ in clinical importance, distances are computed using a weighting structure rather than a simple Euclidean norm.

Let $\boldsymbol{W}$ denote a symmetric positive matrix that defines the geometry of the space. The squared distance of a phenotype vector from the reference state is written as

$$\boldsymbol{d_W^2(p) = p^T W p},$$

and the distance between two individuals with phenotype vectors $\boldsymbol{p_a}$ and $\boldsymbol{p_b}$ is

$$\boldsymbol{d_W^2(p_a, p_b) = (p_a - p_b)^T W (p_a - p_b)}.$$

In the simplest formulation, the matrix (W) is diagonal,

$$\boldsymbol{W} = \mathrm{diag}(w_1, w_2, \ldots, w_n),$$

so that the contribution of each physiological dimension to the overall deviation is determined by a scalar weight w_i. In this case, the squared distance can be written as the sum of dimension-specific contributions,

$$d_W^2(p) = \sum_i w_i p_i^2,$$

and the quantity

$$c_i = w_i p_i^2$$

represents the contribution of the i-th physiological domain to the overall deviation from the reference state.

More generally, off-diagonal elements of $\boldsymbol{W}$ allow correlations between physiological domains to be incorporated, so that deviations in one system may influence the contribution of another. This makes it possible to represent known interactions among cardiovascular, renal, metabolic, endocrine, inflammatory, and autonomic regulation within a single metric structure.

In the digiphysiomic framework, the weighting matrix is not determined solely by statistical properties of a dataset. Instead, the initial geometry of the space is specified using prior physiological knowledge, clinical evidence, and guideline-based understanding of the relative importance of different regulatory domains. Variables known to have stronger influence on organism-level stability, clinical risk, or treatment response may receive larger weights, whereas variables with weaker or indirect effects contribute less to the overall deviation.

Because the phenotype vector has been normalized, the weighting matrix does not represent differences in measurement scale but defines how deviations should be interpreted. To ensure that distances are well defined, $\boldsymbol{W}$ is required to be symmetric and positive definite. In addition, the overall scale of the matrix is not identifiable, and therefore a normalization constraint may be imposed so that the geometry of the space remains stable. In practice, the weighting structure is parameterized so that these constraints are preserved when the matrix is refined using empirical data.

The geometry of the digiphysiomic space may depend on clinical context variables used in normalization, such as demographic characteristics, comorbidities, or prior therapy. The weighting matrix used for interpretation may then be written as

$$\boldsymbol{W} = \boldsymbol{W(z)},$$

indicating that the relative importance of physiological dimensions may vary across clinical situations while the coordinate system itself remains fixed. This allows guideline-based or subgroup-specific knowledge to influence interpretation of the state without redefining the underlying physiological variables.

In cardiometabolic disease, for example, patients with similar blood pressure values may occupy different regions of the digiphysiomic space if the underlying contributions of vascular resistance, cardiac output, metabolic status, or renal function differ. Conversely, patients located near each other in the space may share similar physiological mechanisms despite differences in individual

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measurements. This continuous, knowledge-informed geometry provides a basis for comparing individuals, identifying dominant contributors to physiological imbalance, and supporting structured interpretation of organism-level state.

2.3. Clinical Decision Support Using Physiological Expression Maps

The digiphysiomic framework is intended to provide a representation of organism-level physiological state that can support clinical decision making. Once the phenotype vector $\boldsymbol{p}$ and the weighting matrix $\boldsymbol{W}$ have been defined, the current condition of an individual can be interpreted through the geometry of the digiphysiomic space. Although the scalar distance from the reference state

$$d_W^2(p) = \sum_i W_{ii} p_i^2,$$

provides a measure of overall deviation, clinical decision support is based on the decomposition of this deviation into contributions from individual physiological domains

$$c_i = W_{ii} p_i^2.$$

Because each coordinate corresponds to a physiologically interpretable variable, the domain-specific contributions provide a representation of organism-level state that can be visualized as a multidimensional physiological expression map, analogous to expression profiles used in genomics. In this representation, the condition of the organism is described by a pattern of deviations across regulatory systems rather than by a single measurement.

The weighting matrix determines the relative influence of each physiological domain, while the expression map identifies which domains account for the current deviation. Domains with large contributions indicate regulatory processes that may play a dominant role in the current condition and may therefore represent potential targets for therapeutic intervention.

Clinical decision support therefore operates on the phenotype vector and the corresponding physiological expression map, which organize heterogeneous clinical measurements into a structured representation of therapeutically relevant physiological processes.

2.4. Refinement of the Weighting Structure Using Clinical Evidence

The weighting matrix **W**, which defines the geometry of the digiphysiomic space, represents current knowledge about the relative importance and relationships of physiological domains. Because medical knowledge evolves, the weighting structure is not assumed to be fixed and may be refined using new clinical evidence while preserving the definition of the physiological coordinates. Refinement modifies the weighting structure but does not change the underlying dimensions, ensuring that the meaning of each axis remains stable across studies and over time.

The initial specification of **W** reflects prior knowledge derived from physiology, clinical experience, and guideline-based understanding of regulatory mechanisms. Empirical data may then be used to refine the weighting structure so that distances in the digiphysiomic space better correspond to clinically meaningful differences in patient condition or treatment response.

One way to formalize this refinement is in Bayesian terms,

$$P(\boldsymbol{W} \mid D) \propto P(D \mid \boldsymbol{W}), P(\boldsymbol{W}),$$

where $P(\boldsymbol{W})$ represents prior knowledge about the weighting structure and $P(\boldsymbol{D} \mid \boldsymbol{W})$ represents the likelihood of the observed data given a particular geometry of the digiphysiomic space. Weighting structures that produce deviations more strongly associated with clinical outcomes or treatment response receive higher posterior probability, allowing the geometry of the space to be updated without redefining its axes.

Contextual factors may also influence interpretation through a context-dependent weighting matrix $\boldsymbol{W}(\boldsymbol{z})$, where $\boldsymbol{z}$ represents demographic or clinical variables used in normalization. In this formulation, physiological variables define the coordinates of the space, while clinical knowledge

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and data refine the weighting structure, allowing the framework to incorporate new evidence while maintaining a stable representation for clinical decision support.

2.5. Handling Incomplete Observations in Digiphysiomic Space

In real-world clinical data, not all physiological variables are available for every individual, and different datasets may contain different subsets of dimensions. Because the digiphysiomic framework defines organism-level state within a fixed physiological coordinate system, incomplete observations are handled without redefining the axes of the space.

When only a subset of variables is observed, distances and domain-specific contributions are computed in the corresponding subspace.

Let $\boldsymbol{S}$ denote the set of observed dimensions. The squared distance is computed as

$$d_W^2(\boldsymbol{p}) = \sum_{i \in S} W_{ii} p_i^2.$$

To maintain comparability across individuals with different numbers of observed variables, the weights are renormalized within the observed subspace,

$$W'_{ii} = \frac{W_{ii}}{\sum_{j \in S} W_{jj}}, i \in \boldsymbol{S}.$$

This preserves the relative importance of observed domains while preventing the overall deviation from being artificially reduced when fewer variables are available.

Physiological expression maps are constructed using the same principle. When some domains are not measured, the map is computed in the observed subspace with renormalized weights, so that the result represents a partially observed state within the same coordinate system rather than a different space. Missing domains may increase uncertainty in interpretation but do not change the definition of the physiological axes.

Incomplete observations must also be considered when refining the weighting structure. Different studies may include different subsets of variables, and the likelihood used to update $\boldsymbol{W}$ is evaluated in the corresponding subspace. Unobserved dimensions may be treated as latent components that are implicitly marginalized, allowing evidence from heterogeneous datasets to be combined without redefining the space.

By separating the definition of physiological dimensions from the availability of measurements, the digiphysiomic framework can operate with incomplete real-world data while maintaining a stable and interpretable representation of organism-level state for clinical decision support.

2.6. Projecting Treatment Effects for Personalized Therapy Selection in Digiphysiomic Space

Because the digiphysiomic space represents organism-level physiological state within a consistent coordinate system, the expected effect of therapy can be interpreted as a projected change within the same space. Rather than evaluating individual measurements independently, therapeutic interventions may be assessed according to their predicted influence on the overall physiological state represented by the phenotype vector.

Let $\mathbf{p}$ denote the phenotype vector and $\boldsymbol{W}(\boldsymbol{z})$ the weighting matrix that defines the geometry of the digiphysiomic space under clinical context $\boldsymbol{z}$, where $\boldsymbol{z}$ may include demographic characteristics, comorbidities, prior therapies, or other factors used in normalization and interpretation. The current deviation from the reference state is given by

$$d^2 = \mathbf{p}^T \boldsymbol{W}(\boldsymbol{z}) \mathbf{p}.$$

For a given therapeutic strategy, the expected physiological effect may be represented by a transition matrix $\boldsymbol{W}_T(\boldsymbol{z})$, which modifies the weighting structure according to the known or estimated influence of that therapy on specific physiological variables under the same clinical context. The projected weighting after therapy can be written as

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$$\boldsymbol{W'(z) = W_T(z)\, W(z).}$$

The projected deviation after therapy is then

$$d_T^2 = \mathbf{p}^T \boldsymbol{W'(z)}\mathbf{p} = \mathbf{p}^T \boldsymbol{W_T(z) W(z)}\mathbf{p}.$$

Because the weighting structure determines the relative contribution of individual variables, the transition matrix changes the pattern of contributions across physiological measurements and therefore modifies the resulting physiological expression map. Different therapeutic strategies may produce different projected maps, reflecting their expected influence on cardiovascular, metabolic, renal, adiposity, or inflammatory regulation.

This formulation allows alternative therapies to be compared within the same physiological space. A treatment may be considered favorable if the projected state moves closer to the reference condition or reduces the contribution of variables associated with unstable regulation. In practice, candidate therapies may be evaluated either by examining the projected physiological expression maps or by comparing projected distances from the reference state under different transition matrices.

The weighting matrix $\boldsymbol{W(z)}$ and the transition matrix $\boldsymbol{W}_T\boldsymbol{(z)}$ are not assumed to be fixed. Both may depend on clinical context and may be refined using observational data, randomized trials, or guideline-informed physiological knowledge. Because the coordinate system defined by physiological variables remains unchanged, heterogeneous datasets can be incorporated to improve estimation of these matrices without redefining the digiphysiomic space.

In this formulation, the digiphysiomic space may be viewed as a latent physiological state space in which both current condition and expected response to therapy are represented within a unified framework. Although the present work focuses on representation rather than prediction, this approach provides a conceptual basis for future decision-support systems capable of guiding individualized therapy by comparing the projected physiological effects of different treatment strategies.

3. Application of Digiphysiomic Space for Cardiometabolic Clinical Decision Support

Cardiometabolic disease comprises a group of interrelated conditions in which abnormalities in cardiovascular, metabolic, renal, endocrine, and inflammatory regulation arise through shared and interacting physiological mechanisms. Contemporary clinical guidelines from major cardiovascular, diabetes, lipid, and kidney societies increasingly emphasize that hypertension, diabetes, dyslipidemia, obesity, and chronic kidney disease should not be managed as isolated disorders, but as components of an integrated cardiometabolic continuum requiring coordinated evaluation across multiple organ systems rather than risk-factor–specific treatment alone [13–17].

The digiphysiomic framework generalizes this concept from a single regulatory domain to a multi-system representation of organism-level physiology. In this approach, variables from multiple regulatory domains are integrated into a unified phenotype vector, normalized relative to reference models, and represented within a physiological state space in which deviation patterns across systems can be visualized, compared, and used to guide therapy selection.

In this section, we describe the construction of a digiphysiomic space for cardiometabolic disease as a clinically practical implementation of the framework. We first define regulatory domains and representative physiological variables across major cardiometabolic systems, then construct a normalized phenotype vector, and finally represent the resulting state as a physiological expression map that can be used for mechanism-guided clinical decision support.

3.1. Construction of the Digiphysiomic Space for Cardiometabolic Disease

Regulatory domains, representative physiological variables, and corresponding therapeutic classes relevant to cardiometabolic disease are summarized in Table 1, organized as a two-dimensional domain-by-indicator structure that defines the coordinate framework of the

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digiphysiomic space. Regulatory domains provide a higher-level structure that groups correlated measurements reflecting the same underlying mechanism.

Table 1. Selected regulatory domains, representative measurements, and corresponding therapeutic classes in cardiometabolic disease used to construct physiological expression maps in the digiphysiomic framework

Regulatory domain	Hypertension	Hyperglycemia / diabetes	Dyslipidemia	Obesity	Phenotype vector p	Corresponding therapeutic classes
Cardiac / hemodynamic	CI HR	CI BNP	--	CI HR	CI HR BNP	β-blockers ivabradine inotropes
Vascular / arterial	SBP DBP SVR PWV	PWV BP	LDL non-HDL PWV	BP PWV	SBP DBP SVR PWV LDL non-HDL	ACEi ARB CCB vasodilators
Renal / volume	creatinine eGFR sodium	eGFR albuminuria	--	sodium eGFR	creatinine eGFR sodium albuminuria	diuretics SGLT2 inhibitors MRA
Metabolic / endocrine	--	glucose HbA1c HOMA-IR	LDL-C HDL-C TG ApoB	glucose insulin TG	glucose HbA1c insulin HOMA-IR TG ApoB	metformin GLP-1RA insulin statins
Neurohormonal / autonomic	HR HRV renin aldosterone	HRV autonomic test	renin	HR HRV	HR HRV renin aldosterone CRP	β-blockers RAAS inhibitors central agents

Large cohort and biobank datasets provide the empirical basis for constructing such multidimensional representations. Studies such as the UK Biobank, the Framingham Heart Study, and the ARIC and MESA cohorts include measurements across multiple cardiometabolic domains together with longitudinal follow-up and clinical outcomes, covering cardiovascular, metabolic, renal, inflammatory, vascular, and imaging variables [22–24]. These datasets illustrate that clinically relevant physiological states are inherently multidimensional and support the feasibility of defining a state space that spans multiple regulatory systems.

Because physiological measurements vary with demographic characteristics, body size, and clinical context, phenotype vectors are constructed using normalized coordinates rather than raw values. For example, cardiac index and systemic vascular resistance index vary with age, sex, and body size even in the absence of disease, and identical measurements may represent different physiological states in different individuals. In the digiphysiomic framework, expected values are estimated from appropriate reference populations, and coordinates are expressed as deviations from these expectations so that the phenotype vector reflects the current regulatory state rather than baseline characteristics.

The weighting structure that defines the geometry of the digiphysiomic space is initially guided by the relative importance of regulatory domains in contemporary cardiometabolic guidelines. Empirical data, including longitudinal observations and randomized trials, may subsequently be used to refine this structure so that distances in the space correspond to clinically meaningful differences in physiological state.

3.2. Physiological Expression Map and Clinical Decision Support

The digiphysiomic space represents organism-level physiological state using the phenotype vector defined in Section 2.1, in which each component corresponds to a normalized physiological measurement. The overall deviation from a reference physiological state is quantified by the weighted quadratic form

$$d^2 = \mathbf{p}^T W \mathbf{p},$$

where $\boldsymbol{W}$ is the weighting matrix encoding the relative importance of different physiological variables.

The contribution of each measurement to the overall deviation is defined as

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$$c_i = W_{ii} p_i^2,$$

so that the current physiological state can be described by the pattern of weighted deviations across individual variables rather than by a single summary value. The set of contributions c_i forms the physiological expression map, which provides a structured representation of organism-level regulation across multiple cardiometabolic measurements.

The organization of variables into mechanism domains, as summarized in Table 1, provides a framework for clinical interpretation of the physiological expression map. Because variables belonging to the same domain reflect related regulatory processes, patterns of deviation across measurements can be evaluated in relation to cardiovascular, metabolic, renal, adiposity, and inflammatory mechanisms without redefining the underlying coordinate system. This two-dimensional structure allows heterogeneous clinical data to be interpreted within a unified representation while preserving the connection between measurements and their physiological meaning.

Clinical decision support is based on interpretation of the physiological expression map. Measurements with large contributions indicate physiological processes that may play an important role in the individual's condition, whereas measurements with smaller contributions are less likely to influence immediate treatment decisions. Because each measurement corresponds to a specific physiological variable, the map can be directly related to potential therapeutic targets without requiring additional transformation of the state representation.

3.3. Clinical Variations of Physiological Expression Map

The physiological expression map may be interpreted using different reference states depending on the clinical context. In many applications, the reference corresponds to normalized physiological values derived from population data. However, in some clinical situations the most informative reference is not normal health but a stable disease-specific condition. Patients with chronic heart failure, chronic kidney disease, or resistant hypertension may have persistent deviations from normal physiological ranges even when clinically compensated. In such cases, expression mapping relative to a disease-specific reference population may improve sensitivity for detecting clinically meaningful change, because deterioration is defined relative to expected stability rather than to healthy values.

In longitudinal care, comparison with the patient's own prior state may provide the most relevant reference. Repeated measurements allow construction of individualized baselines, and deviation from this baseline may indicate treatment response, emerging instability, or disease progression even when absolute values remain within the range typical of the broader population. This individualized interpretation is particularly useful in chronic cardiometabolic disease, where clinical decisions often depend on trends over time rather than on single measurements.

These variations do not change the physiological variables used to define the digiphysiomic space, which remain based on the same set of measurable regulatory processes. Instead, they modify the reference state used for interpretation and may also influence the weighting structure when new clinical data or context-specific information indicate different relative importance of individual variables. As a result, physiological expression maps can be constructed using population-level, disease-specific, or patient-specific references while preserving a consistent coordinate system. This flexibility allows the framework to incorporate new evidence and clinical context without redefining the underlying physiological dimensions.

3.4. Clinical Evidence

Previous studies have demonstrated that mechanism-based phenotyping can be achieved within individual physiological regulatory domains. In hypertension, hemodynamic investigations using impedance cardiography have shown that patient condition can be characterized using variables such as cardiac output, stroke volume, and systemic vascular resistance, allowing classification of physiologic phenotypes not captured by blood pressure alone. These studies also showed that meaningful comparison across individuals requires normalization relative to reference populations,

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because raw physiological measurements vary systematically with age, sex, and body size [18–20]. The Hemodynaomics Map represents a domain-level implementation of physiological state mapping within the cardiovascular subsystem, illustrating how multidimensional measurements can be organized into a structured coordinate representation suitable for mechanism-guided therapy [21].

Mechanism-guided treatment based on physiological measurements has been evaluated in hypertension using hemodynamic profiling, in which therapy selection is guided by variables such as cardiac output and systemic vascular resistance. Randomized and pragmatic clinical studies have shown that hemodynamic-guided treatment strategies improve blood-pressure control compared with conventional care, supporting the clinical relevance of physiologically defined phenotypes within a single regulatory domain [25–30].

Large population-based cohorts further indicate that cardiometabolic disease is intrinsically multidimensional. Studies such as the Framingham Heart Study, ARIC, MESA, and the UK Biobank demonstrate that cardiovascular, metabolic, renal, inflammatory, and vascular variables interact to determine clinical outcomes, and that risk cannot be fully explained by isolated factors alone. These observations support the feasibility of representing patient condition within a multidimensional physiological space spanning multiple regulatory systems.

4. Discussion

Modern medicine achieved a high degree of standardization by decomposing the human body into individual variables and organ systems, allowing clinical decisions to be guided by measurable parameters and population-based thresholds. This reductionist framework has enabled major advances in diagnosis and therapy, but its limitations become increasingly apparent as multimorbidity becomes the dominant clinical reality. When cardiovascular, metabolic, renal, endocrine, and autonomic systems are simultaneously dysregulated, the clinical meaning of any single measurement depends on the state of multiple interacting processes, and treatment decisions based solely on isolated variables may become less reliable.

Several existing approaches attempt to move beyond risk-factor–based reasoning, but they differ in how patient state is represented. Data-driven methods such as clustering or latent-variable models identify patterns within a given dataset but do not necessarily define a stable coordinate system that can be preserved across populations or over time. Mechanistic and digital-twin models aim to simulate individual physiology in detail, but their goal is to reproduce system behavior rather than to provide a shared representation suitable for routine clinical interpretation.

In contrast, the digiphysiomic framework defines patient condition within a physiologically interpretable state space whose axes correspond to regulatory domains constrained by measurable variables and established knowledge of biological regulation. In this formulation, the coordinate system is specified by physiology rather than learned from data, and the dimensions of the space correspond to processes that are observable in practice and potentially modifiable by therapy. Observational studies, randomized trials, and guideline-based knowledge are used to refine the weighting structure and treatment-related transitions, while the coordinate system itself remains stable. This separation allows patient states, datasets, and therapeutic effects to be compared within a common representation, enabling clinical reasoning to operate on organism-level state rather than on isolated variables or dataset-specific groupings.

The digiphysiomic framework is intended to support clinical decision making by providing a structured representation of organism-level physiological state rather than replacing physician judgment or guideline-based practice. In cardiometabolic medicine, treatment decisions are influenced by multiple factors, including disease-specific recommendations, comorbidities, prior therapies, adverse effects, contraindications, and patient preferences, many of which cannot be fully represented within a mathematical model. The physiological expression map therefore serves as an interpretive tool that helps organize complex physiological information by highlighting the measurements that contribute most strongly to the current state. This may be particularly useful in patients with multimorbidity, in whom abnormalities often involve several interacting regulatory

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systems and evaluation based on isolated variables or disease-specific thresholds may not clearly indicate which mechanism should be addressed first. Clinical guidelines define appropriate treatment options for individual conditions, but frequently allow multiple acceptable choices. In such situations, physiological mapping may assist prioritization by indicating which regulatory processes appear most abnormal, while final decisions remain the responsibility of the clinician. By representing different diseases within a single physiological space, the framework allows interacting abnormalities to be interpreted together rather than as separate problems, supporting individualized therapy selection while remaining consistent with guideline-based care and clinical judgment.

5. Limitations

Several limitations should be considered. First, the digiphysiomic space is proposed as a representation-level framework rather than a fully validated clinical decision system. Although the coordinate structure is informed by physiological knowledge, clinical guidelines, and existing datasets, the optimal definition of domains, normalization procedures, and weighting parameters has not yet been established and will require evaluation in prospective clinical studies. In particular, different choices of normalization models, weighting schemes, and transition matrices may lead to different interpretations of physiological state, and their impact on clinical decision support and patient outcomes remains to be determined.

Second, the current formulation assumes that the physiological variables used to define the coordinate system correspond to regulatory processes that can be measured in routine clinical practice. This assumption allows the framework to be applied using available clinical data but also limits the representation to observable variables. Important aspects of organism-level regulation may not be captured when measurements are unavailable or imprecise. As new biomarkers, imaging modalities, and continuous monitoring technologies become available, the phenotype vector and domain structure may need to be extended while maintaining compatibility with the existing coordinate system.

Third, estimation of the weighting structure and treatment-related transitions requires large longitudinal datasets and, ideally, randomized trial data. In the present work, these components are described conceptually rather than derived from a single dataset, because the goal is to define a stable representation within which heterogeneous sources of evidence can be integrated. Practical implementation of the framework will therefore depend on the availability of high-quality data to refine both the weighting matrix and the transition models under different clinical contexts.

Fourth, the digiphysiomic representation does not capture all factors that influence clinical decision making. In complex cardiometabolic disease, treatment choices depend not only on physiological state but also on comorbidities, contraindications, prior therapy, medication tolerance, patient preferences, and clinical judgment. The physiological expression map is intended to assist interpretation of organism-level regulation, but it cannot by itself determine the optimal treatment strategy.

Finally, the present work focuses on cardiometabolic disease as an initial application because these conditions involve multiple interacting regulatory systems and are supported by extensive clinical data. Whether a physiologically defined state-space representation provides similar advantages in other areas of medicine, such as critical care, inflammatory disease, or oncology, will require further investigation.

6. Conclusions

The digiphysiomic framework defines a physiological state space in which patient condition is represented using measurable regulatory processes as coordinate axes. By combining physiologically interpretable dimensions with a knowledge-informed weighting structure that can be refined using clinical evidence, the framework provides a stable representation for integrating heterogeneous data, guideline knowledge, and treatment effects. Physiological expression maps derived from this space

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offer a structured description of organism-level state that may assist clinical reasoning when multiple interacting mechanisms must be considered simultaneously.

This framework is intended to complement, not replace, clinical judgment by providing a common coordinate structure in which physiological information and therapeutic strategies can be interpreted together. With further validation, such a representation may support future decision-support systems for individualized management of complex multisystem disease.

Figure Legends:

Figure 1. The digiphysiomic framework for physiological expression mapping

A, Risk-factor medicine.

Independent variables—blood pressure, glucose, lipids, and body mass index—are managed separately using population-based thresholds.

B, Subsystem phenotyping.

Multidimensional assessment within individual physiological subsystems reveals heterogeneity not captured by single risk factors but remains confined to organ-level measurements.

C, Phenotype vector.

Heterogeneous clinical measurements are integrated into a normalized phenotype vector

$p = (p1, p2, \ldots, pn)$,

where each component represents a normalized physiological variable.

D, State space.

The phenotype vector defines the individual as a point in a physiological state space $S \subset R^n$.

The shaded region represents states compatible with stable physiological regulation.

E, Physiological expression mapping.

Weighted deviations across variables define a physiological expression map that visualizes the pattern of regulatory imbalance across measurable processes, providing an interpretable representation of organism-level state.

F, Therapeutic projection.

Different therapies define transition operators that project the current state to predicted post-treatment states within the same physiological space.

Projected states (A, B, C) lie closer to the reference state than the current state, allowing alternative treatment strategies to be compared according to their predicted distance from the reference condition.

Data availability: This study presents a methodological framework and does not report new empirical data. The framework is designed to be implementable using existing multidimensional clinical datasets. All referenced studies and datasets are cited in the manuscript.

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