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Application of Smart Infrastructure Systems approach to precision medicine

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"*... in alkaptonuria and the other conditions… we are dealing with individualities of metabolism and not with the results of morbid processes… and that just as no two individuals of a species are absolutely identical in bodily structure neither are their chemical processes carried out on exactly the same lines.*"—Garrod (1902).

"*It is the uniqueness of the individual – genetics, developmental and experiential – that accounts for human variation, whether in health or disease.*" —Childs et al. (2005).

1. Introduction

Genetic, developmental, demographic and environmental factors influence the distribution of biological diversity among individuals and populations (Lewontin, 1974; Charlesworth and Charlesworth, 2010). As a rule, biological diversity is a conjugated multilevel nested hierarchy of nucleotides within genes, genes within chromosomes, chromosomes and proteins within cells, cells nested among organs within individuals, and individuals within families in populations (Lewontin, 1970; Rand, 2011; Govindaraju, 2014). For instance, in humans, at least 85–95% of genetic diversity is found distributed among individuals, suggesting the corresponding uniqueness of each individual within populations (Lewontin, 1972; Rosenberg et al., 2002). Yet, all components of diversity generally exhibit cooperative or antagonistic relationships at all levels, and operate as "mutualistic networks" among genetic, epigenetic and phenotype space of individuals, facilitating diversity, stability and evolution of populations in ecosystems (Boscompte and Jordano, 2014).

1.1. The centrality of individuality in evolution, disease and medicine

Health and disease states of an individual represent either an integrated or dysregulated phenotypic expression of diverse and linked network of genomic and epigenetic factors embedded in the genotype-epigenetic space in relation to the environment. Accordingly, each individual displays differing degrees of developmental and functional integration, interaction and modifications among its component traits in health and disease throughout life (Charlesworth, 1980; Wagner et al., 2007; Govindaraju, 2015). Hence, the need for recognizing "individuality" in patient care has been emphasized for over a century (chemical individuality; Garrod, 1902). The nature of medical care for any given individual is generally provided by the physician's evaluation of patient specific molecular, physiological, personal, and cultural aspects — "medical individuality" (Childs et al., 2005). Similarly, from an evolutionary perspective, selection may target one or many strata in the imbricate structure of biological organization (molecules, organelles, cells, tissues, organs, individuals, families, populations and metapopulations; Lewontin, 1970; Rand, 2011; Govindaraju, 2014), operating at every age and stage in human life history (generation of gametes, conception, birth, maturation, reproduction, senescence and death; Charlesworth, 1980; Charlesworth and Charlesworth, 2010). Yet, individual is the most fundamental unit of biological organization and also of selection, just as it is a unit of medical intervention imbedded in larger biological, cultural and environmental contexts (Mayr, 1976; Engel, 1977; Childs, 1999; Koster et al., 2015). Such a direct correspondence between biological and medical individuality points toward a need for developing approaches to predict, prevent, cure and care particular patients based on biological principles (Childs et al., 2005; Govindaraju, 2014). The idea of genetic and metabolic individualities traverse inconspicuously across clinical practice and population health (epidemiology), as "… medicine is first of all for individual patients and then for populations" (Childs and Valle, 2000). Thus, in principle, every individual embodies unique ontogenetic, physiological, phenotypic and ecological properties. In practice, however, particulars of individuality are frequently compromised for universals (Childs et al., 2005) conforming to the "one-size-fits-all" paradigm; which is at once odds with both the nature of biological organization and the realities of medical practice. This paradox has profound implications in patient care. For instance, only one individual in 3 to 24 may benefit from the top selling-drugs in the US (Schork, 2015), indicating wastage of finite resources in the face of human suffering.

1.2. Individuals are intrinsic to the Precision Medicine Initiative (PMI)

The Presidential Precision Medicine Initiative (PMI; Collins and Varmus, 2015) is aimed at addressing the above paradox in order to accelerate our understanding of individual variability and its effect on disease onset, progression, prevention and treatment. At least two factors are essential to reach this goal: a) precise identification and isolation of individuals (targets) imbedded in the hierarchical and multi-level organization in human ecosytems, and b) developing appropriate medical interventions to treat those specific targets. Individual patients are the primary and ultimate targets of medical intervention. But, individuals and their component traits as well as individuals within and among populations often show specific latent and emergent properties, hence require efficient clinical designs and computational approaches (Schork, 2015; Collins and Varmus, 2015) in order to identify, predict and isolate properties specific to individuals nested in populations.

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1.3. Examples of classical computational approaches to study hierarchy in biological organization

Many statistical and mathematical approaches, such analysis of variance, principal component analysis, multilevel modeling (Fisher and van Belle, 2004), feature extraction, classification and regression trees, as well as agent based modeling (Railsback and Grimm, 2011), have been employed for quantifying and apportioning variation at various levels of biological organization. Tremendous advances have been made both in biological and medical sciences, using these methods, on relatively small data sets. These approaches, however, may be inadequate for the purpose of isolating specific target (individual for clinical care) embedded in a network of hierarchical and high-dimensional data (big data) emerging from a detailed genome — phenome analysis of individuals and populations (G-P map; Lewontin, 1974) nested in large ethnic groups. These high dimensional data commonly represent complex interconnecting nodal structures, self-organization, emergent behavior and vulnerabilities of individual components to sudden changes (Kuznetsova et al., 2011); hence require novel ways of acquisition, analysis and decision making processes (Stephens et al., 2015; Topol, 2015).

2. Smart infrastructure approach for isolating and understanding the properties of individuals in hierarchical structures

We propose "smart infrastructure system" (SIS) concept to study the properties of individual targets imbedded in families and in populations, and suggest the applicability of this approach in precision medicine programs. Smart grids and smart cities, developed to facilitate integration and transmission of power as well as manage networks of communication systems serve as excellent examples of smart infrastructures (SI). The SI systems have several attractive features. Like biological systems, they are adaptive, predictive, integrated, modular, reactive and optimized. They can also monitor, collect, measure, analyze, communicate, act or return to original states, based on information captured from individual sensors and often take action without human intervention. Of late, several initiatives have emerged in the area of infrastructures, including energy (smart grids, Kuznetsova et al., 2011; Annaswamy, 2013; Nandakumar et al., 2015), transportation (Smart Cities; Sengupta et al., 2015), to name a few, which are all characterized by: (i) complexity, (ii) cooperation (iii) hierarchy, (iv) self-governance, (v) emergent behavior, (vi) real-time decision making, and (vii) redundancy, robustness and resilience (plasticity). The same features are typical for ecological, taxonomic, genealogical, somatic and evolution of self-organized complex and dynamic biological systems (Kauffman, 1993; Bak, 1996; Kuznetsova et al., 2011), operating at every level of biological organization (molecules, organelles, cells, tissues, organs, individuals, families, populations and metapopulations), and at every age and stage in human life history: generation of gametes, conception, birth, maturation, reproduction, senescence and death. The primary objectives of this communication are to: a) provide a brief overview of the concordant aspects of biological complexity and smart infrastructures, b) present some of the salient features of smart infrastructures, and c) emphasize the need for developing trans-disciplinary approaches to realize the broad potential of precision medicine programs spanning individuals, families and populations to global human ecosystems.

2.1. Features of a simple, smart infrastructure system and its analogy with biological systems

Electric power grids constructed to provide efficient flow of electricity from production source, transmission, and distribution to the end-user, via complex connections or "nodes" serve as a useful example for SIS (Fig. 2). These grids represent a systematic topological and hierarchical organization of linked and mutually interacting endogenous hierarchy of agents (individual parts or components), information sources, and communication networks. In turn, networks represent many connections of varying degrees and strength of performance, and are prone to change and even collapse, in relation to the time-dependent or independent intrinsic and extrinsic conditions. For instance, an electric appliance (agent) could serve as a proxy for a "specific individual" in a given household (family). Similarly, a large cluster of households in a neighborhood that show some degree of similarities, could represent a cluster of families or a population. Such similarities between hierarchical organization in biological and in smart infrastructure ecosystems are provided respectively, in Figs. 1 and 2.

Biological organization is typically composed of many interacting individuals from which populations and ecosystems are built and evolve (Mitchell and Newman, 2002). Similarly, complex infrastructures have hierarchical organization of interdependent sub-systems (agents or component traits) many of which are governed by physical laws, and are constrained by safety requirements, as well as show resilience to minor perturbations, so as to meet infrastructure-wise goals (Chappin and Dijkema, 2010). Smart infrastructure systems, by virtue of the added "smarts", are capable of making decisions, learned through algorithms and online observations, display and capture evolutionary features (Gunal, 2012). The resulting SIS dynamically changes or "evolves" over time and without human intervention, due to independent actions and interactions of the component agents. In a strict sense, however, none of the engineering or physical systems could encompass all the features of Darwinian process (Godfrey-Smith, 2009); specifically because they do not obey Mendelian principles. Individual agents in engineering systems are components of the infrastructure; these agents react to exogenous scenarios and on endogenous parts of the systems (analogous to genotype-environment interactions). Since agents are interdependent and exhibit systems properties and behavior, they are emergent (Goldberg and Holland, 1988). Clearly, appropriation of concepts and results from complex systems research may be extended for the purpose of explaining proximate evolutionary processes (which includes human health), *vis-à-vis* evolutionary principles could be employed for modeling energy infrastructures and its components as a system of systems (Goldberg and Holland, 1988; Mitchell and Newman, 2002).

Extensive similarities between evolutionary organization and smart infrastructures may be extended to predict, prevent and manage Mendelian disorders such as sickle cell anemia, cystic fibrosis and Tay–Sachs, as well as common complex diseases like essential hypertension, type-2 diabetes, asthma, to name a few. Typically, all of these diseases differentially affect individuals nested in families, and families within populations, as well as differ among major ethnic populations. For instance, essential hypertension is a complex disorder and is influenced by genetic, environmental and demographic factors. It varies from 7 to 65% among individuals aged 18 to 60 (Hopkins and Hunt, 2003), respectively, affecting cardiovascular, cerebrovascular and renal systems (Kearney et al., 2004). Routine clinical care of the affected individuals is provided on the basis of a panel of genetic, physiological, phenotypic, familial and sociocultural as well as life-style indices. We suggest that SIS approaches could be employed in order to predict, prevent and manage these diseases at all levels of biological hierarchies. For example, essential hypertension is diagnosed on the bases of various markers representing many levels of hierarchies (i.e., from gene to populations). Typical examples include: Angiotensinogen gene (AGT); biochemical markers (Renin) phenotypic markers (high blood pressure) and family history as well as ethnicity. All of these markers, however, vary widely (and often in a non-linear fashion) among individuals, families and populations in relation to environmental and demographic factors (Hopkins and Hunt, 2003). At least a faction of variation in the incidence of hypertension among ethnic groups may be interpreted as evolutionary adaptations to local environmental conditions.

The distribution of essential hypertension in human populations conforms to the requirements of an infrastructure model, in which individuals in a family are part of a population, and biological changes that lead to overt expression of the disease occur at all levels, over time. These changes among specific individuals (agents) in simple hierarchical

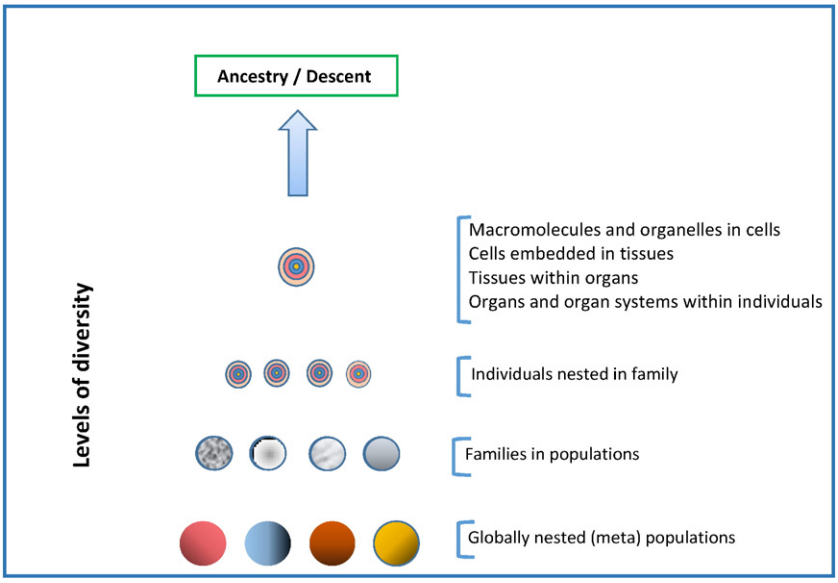
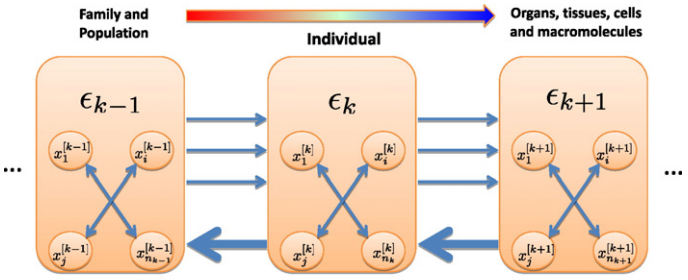


Fig. 1. Hierarchical organization of genetic diversity in humans.

systems is studied using agent based modeling (ABM; Railsback and Grimm, 2011). The component agents in a given ABM system are both autonomous and interacting objects living in an environment. These also incorporate behavioral aspects and learn or adapt themselves to new environments based on their prior experience and respond to the consequences of interventions (Gunal, 2012). Smart infrastructures differ slightly from ABMs, however. They generally operate on a larger scale such as a large region or a society (ecosystems), and respond to a sensor (salt in hypertension) and may revert (resilience) when the sensor is removed. Similarly, the effectiveness of antihypertensive drugs may be studied in clinical trials, on a very large number of individuals from diverse populations. Therefore, SIS models would offer a more realistic approach to study the distribution and management of human disorders.

2.2. A mathematical model of smart infrastructure

In view of the central role of the individual in evolution and medicine, as well as for simplicity, we provide a basic conceptual mathematical model of the complex relationships among three hierarchical levels: prior to the level of individuals (ϵ_{k-1}, i.e., families and populations), the individual level (ϵ_k) and posterior levels (ϵ_{k+1}, i.e., posterior levels or within individuals — organs to macromolecules; see Fig. 1). The prior and posterior designations are for convenience only; hence, interchangeable.



$$\dot{x}_i^{[k]} = f_{1,i}^{[k]}\left(x_i^{[k]}\right) + \sum_{j=1}^{n_k} f_{2,ij}^{[k]}\left(x_j^{[k]}\right) + \sum_{l=1}^{n_{k-1}} f_{3,il}^{[k-1]}\left(x_l^{[k-1]}\right) + f_{4,i}^{[k+1]}\left(x_1^{[k+1]}, \cdots, x_{n_{k+1}}^{[k+1]}\right) + g\left(x^{[k]}\right)u^{[k]}$$

Where: ε_k represents the *relative timescale* that the dynamics in the kth subsystem occurs at;

- $x_i^{[k]}$ represents the ith node/state in the kth subsystem;
- $f_{1,i}^{[k]}$ represents the *intra-dynamics* of the ith node of the kth subsystem;
- $f_{2,ij}^{[k]}$ represents the *inter-dynamics* of how the jth node of the kth subsystem influences the I node/state;
- $f_{3,il}^{[k-1]}$ represents the *disaggregated dynamics* of how the lth node of $(k-1)$th "upstream" subsystem influences the ith node of the kth subsystem;
- $f_{4,i}^{[k+1]}$ represents the *aggregated dynamics* of how the nodes in the $(k+1)$th "downstream" subsystem influence the ith node of the kth subsystem.
- $u^{[k]}$ represents exogenous influences on the entities at the kth subsystem
- $g^{[k]}$ represents the sensitivity of entities at the kth subsystem w.r.t. exogenous influences.

This model indicates slower to faster time scales in the context of the hierarchical nature of biological systems, which ranges from populations, families, individuals, organs, tissues, cells, organelles, and finally to genomic components. Smart infrastructure system design could effectively identify the underlying dynamics at each time-scale $[k]$ and suitably design the disaggregation and aggregation to the adjoining faster and slower time-scales so as to optimize the corresponding performance metrics. For instance, suppose we assume that $x_i^{[k]}$ denotes a particular individual. The component $f_{1,i}^{[k]}$ represents all influences that affects a particular individual, the component $f_{3,il}^{[k-1]}$ represents the influences of the family/population, the component $f_{4,i}^{[k+1]}$ represents the influences from the smaller scales such as organs, tissues and cells; $f_{2,ij}^{[k]}$ represents the influences of other individuals who closely interact (competition and cooperation) with the individual under focus. Although the double-headed arrows link the circles placed diagonally, in each of the three rectangles, horizontal links between any two circles (indicating feedback mechanisms) is assumed. Direction of the arrow represents the potential degree of changes in the respective systems.

3. Discussion and conclusions

As emphasized throughout, individuals are born with distinct genetic, biochemical and morphological "individuality" (Garrod, 1931; Williams, 1956; Engel, 1977), and are the primary units in evolution as well as targets of medical care. All individual phenotypes, healthy or otherwise, are the ultimate products of numerous intersecting networks of embedded genetic and epigenetic pathways (Alon,

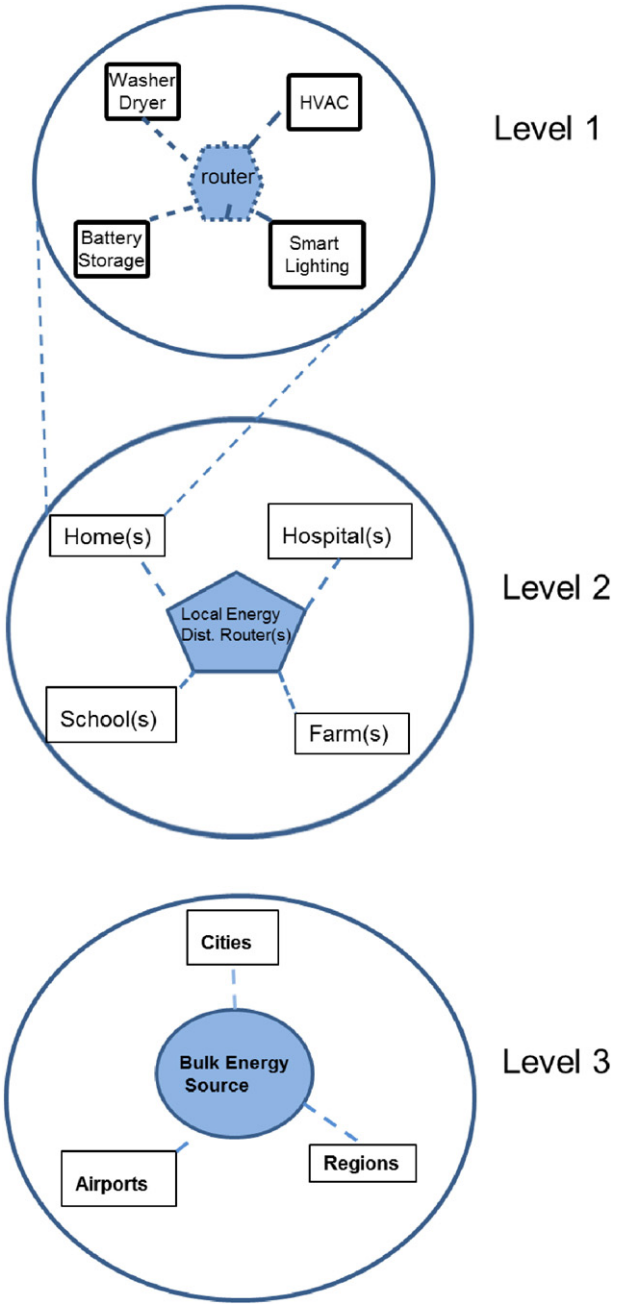


Fig. 2. A schematic representation of energy flow among three levels of networks in smart infrastructure system of an electric grid [appliances within homes and homes nested in cities or urban ecosystems]. Energy flow among various interacting components within and among each of the levels, as well as the influence of exogenous variables on all levels is assumed. Note the topological equivalence between biological and engineering ecosystems shown in Figs. 1 and 2, respectively.

2007); expressed contextually in relation to biological and physical environments (G-E-P space; Lewontin, 1974). These spaces are composed of a hierarchy of additional constituents (genomic components, organelles, cells, tissues, organs and organ systems). The integrated genotype and its phenotype – the individual – is the unit of viability and reproductive (evolutionary) fitness, target of selection as well as clinical care. Individual phenotypes themselves are nested in families, populations and meta-populations or ecosystems. In turn, these individuals are exposed to numerous biological, environmental and social factors, in real or deferred time, which bring about many changes in timing, direction of flow of physiological variables as envisioned by Wright decades ago (Wright, 1934). In fact, with the exception of a few chromosomal and Mendelian disorders, the relative expression of all polygenic disorders may be modulated primarily by developmental and environmental variations. The cascading and cumulative genetic, developmental and environmental changes, ultimately influence health, disease, longevity and senescence of individuals to varying degrees. Additionally, individuals as fundamental biological units, also show direct and indirect feedback interactions as well as flexibility, robustness, self-organizing, latent and emergent properties among intra-individual and inter-individual levels of biological organization. Clearly, it is imperative to understand individuals in the context of complex demographical, biological, environmental and social hierarchical networks in order to develop individualized medical care as long advocated (Garrod, 1902; Mayr, 1976; Engel, 1977; Childs and Valle, 2000; Govindaraju, 2014), as well as to inform "future patients with similar presentation" (Topol, 2015). Despite numerous statistical and mathematical models developed to explore this distinctively critical nexus of individuals both in biology and healthcare, a majority of these approaches hardly reflect or take account of the complexity and adaptive as well as self-organizing properties of biological systems of which the given individual is an integral part of a larger community of interacting individuals.

Multidimensional genomic and phenomic data on thousands of individuals representing different levels of biological hierarchies (big data; Stephens et al., 2015) are becoming a common place both in biology and medicine. The need for using these complex data to predict, prevent and manage human health at the level of the individual is at the heart of the PMI. Therefore, it is imperative to collect data on all phases: the ancestral, familial, environmental and social (Engel, 1977; Childs, 1999) taking the G-E-P mapping approach (Houle et al., 2010), in order to realize most if not all of the goals set by PMI. Smart infrastructure coupled with smart cloud-computing technologies, with seemingly unlimited capacity for data storage, and to incorporate real-time bio-sensor streaming of data (Topol, 2015), would provide powerful approaches to organize, analyze as well as apply the results to improving human health. Most importantly, SIS are analogous to biological systems, and possess many features of evolutionary processes. The latter, in fact involve health, longevity and diseases. Utilization of systems approaches to modeling of human pathological conditions indeed display nearest-neighborhood branching patterns of disease (Loscalzo et al., 2007) — an idea so central to evolutionary biology. Smart infrastructure models have already become indispensable toward monitoring and managing large multi-layered complex systems, consisting of numerous interacting components, often spanning large city and regional landscapes. A combination of high-throughput "omics" technologies, and novel computational methods, has already become an integral aspect of "personalized or individualized" cancer research and treatment. Note that many forms of cancer are primarily treated and managed at four levels of biological hierarchy: tissue, organ, individual and family. Similar approaches coupled with longitudinal data are also showing promising results toward managing late-onset diseases (Chen and Snyder, 2013). Following Domingos (2015), it is reasonable to speculate that "self-learning computers" could self-organize and assemble diverse sources of data (often without human intervention) emerging from living systems imitating evolutionary process. Application of these emerging engineering models to human health would allow us to isolate, observe and monitor individuals and individual components (agents) of health and disease in the hierarchical system of human populations, their interactions with other individuals as well as their latent and emergent behaviors, as required by medical practice. We emphasize the need for further research in this regard. These approaches would complement evolutionary process and perhaps help predict the causes of proximal fluctuations and dysregulation in human health more accurately than ever before. Such concerted and trans-disciplinary efforts would make us realize the full potential of PMI.

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