Drug Discovery for the 2020s and Our New Era

Lead-in "catalysts" for the Discussion Group Quantum, yes § NpC, certainly § M&M, absolutely critical







Martin Dudziak, PhD Director and Senior Research Scientist TETRAD Institute of Complex System Dynamics 06.July.2022 Quantum computing – Turing and "Gödelian" Supercomputers – Turing Network Computers – MIMD PDP BOINC

Emergent Stressor-driven Dysautonomia CNS – Arrhythmia – Autoimmune - Inflammation POTS – CF/ME – MS – AFIB - PASC

M&M – Migration and Mutation

Environment and Climate Nonlinear Changes Habitat Disruption Massive Interface and Exchange Novelty Breeds Contempt and Adaptation

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Virus – bacteria – eukaryotic-organism parasites Flora and fauna Carriers – the vectors

Faster turn-around in natural mutation Disruption of habitat ==> Adaptation, Evolution

Migration in response to climate/environment changes Migration in response to food and water source changes The Human Presence – urbanization, travel, shipment, wastes Mutation in response to species-mixing More change on the Outside ==> More Change on the Inside!

A Brief List

Coronaviruses — COVID-19 was a lightweight compared to SARS-1, MERS Influenzas – H5xx, H7xx, H9xx Hanta Zika Ebola

Yersina pestis – primed for a return in a Big Way

Cholera Measles Monkeypox

Chagas (Trypanosoma cruzi) Tick-borne diseases (multiple)

Meningitis

Yellow fever **ZOONOTIC Diseases**

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ANCES - Autonomic Neurophysiological Control and Electrochemical Stress

NSF (Neuronal Stressor Factor; chronic, asymmetric (equilibriumdisrupting) electromolecular stressors)

> NCB (Neural Cybernetic Bifurcation; chronic, asymmetric signal conflict and constructive/destructive interference)

> > MAMDA (macro-anatomical mechanics, dynamics and activities)

GST (neural Ganglia Signal Turbulence, chaos and non-linear attractor dynamics; "Lorentz-Clifford" phenomena) Copyright © 2022 TETRAD Institute 10 Adhesions and other connective tissue aberrations (+ and – growth effects) - a major common element in these slow-evolving conditions

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Background and Reference Material



PHIBER as a Key Tool to AIM AHEAD

PHIBER – Population Health Informatics Biomedical Equity Resource

Review: Four Goals of AIM-AHEAD

Partnerships, Research, Infrastructure, Data Science Training

Population-tuned, objective, unbiased Intelligence

A resource that can be used to address both explicit and deeply-hidden inequities in healthcare that are unraveling our Society

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NIH's AIM-AHEAD program ->

increase the participation and representation of researchers and communities <u>currently underrepresented</u> in

development of <u>AI/ML models</u>

+

enhancement of <u>AI/ML capabilities</u>, beginning with electronic health record (EHR) data.

Lack of Diversity = and → Incomplete Data and Inbalanced AI Logics Both are killers for any healthcare system that must rely extensively, heavily upon statistical data and AI/ML reasoning

The consequences are NOT ONLY continued health disparities and inequities for underrepresented communities, but <u>serious long-term degradation and degeneration</u> <u>of the Whole Population and its socioeconomic stability</u>.

Underrepresented communities have untapped potential Not only to contribute new expertise, data, recruitment strategies, and cutting-edge science to the AI/ML field, but also to Better Understand the psychophysical and socioeconomic Situations of those underrepresented and poorly understood communities!

To build powerful AI (and more – even true "sients") that will serve humanity best and not in a stilted, biased way, we need to have a "spectrum" of colors of Mind, not only a few "bands"! Copyright © 2022 TETRAD Institute

PHIBER as a Key Tool to AIM AHEAD

PHIBER – Population Health Informatics Biomedical Equity Resource

What it is and how it employs Synthetic Intelligence to Improve Population Health Equity through assessment of Health Risks and identification of Proactive Diagnostics

Our focus began with our long-standing permanent work in Chronic Neural Stressor Agents within Dysautonomic and Arrhythmic Disorders

To properly real-ize the theory and make the models in order to achieve improvements in early diagnostics and non-invasive therapeutics, we Need

Significantly More, Better, and Comprehensive (population-diverse, equitable) health records, assessments, prognostics, both quantitative and qualitative.

Thus a truly accurate (equitable) Population Health Informatics Biomedical Equity Resource (PHIBER)

About the Lead Researcher:

Martin is principal investigator in the PHIBER Project and the primary architect of systems and algoirithms employed in PHIBER. With a PhD in theoretical and computational physics, he has taught in several US and European universities, within physics, biomedical engineering, and computer science, and he has worked in several multinational corporations and non-profit organizations, focused upon both research and applications. His particular interests and accomplishments concern non-linear, chaotic, stochastic and turbulent systems within physical and biological environments, including cybernetic, sensor-fusion and control applications.

About TETRAD Institute:

A private, not-for-profit research organization established by several scientists to address problems in fundamental sciences concerning complexity, self-organization, emergence, and non-linear turbulent systems. Projects have been typically organized by collaborative teams of specialists from international backgrounds. Past and concurrent projects have focused upon fundamental theoretical physics, quantum biology, quantum computing, and synthetic intelligence.

Collaboration and consortium people - interactive research in this Project:





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<u>1 – Introduction</u>:

PHIBER Pilot Project 2022-23

Neuro-Cardio-Autoimmune range of disorders (primarily) [NpC]

Environmental Toxin Exposures (especially chronic, long-undetected, quasi-trace amounts) e.g., Cr, Co, Ni, As, Cd, Hg, Tl, Pb and U

Black, Native/Indigenous, Migrant/Refugee population subgroups

MMC-focus region → (especially) Michigan, Chicago, Ohio, Tennessee, Virginia

- Define the Datasets
- Define the Sources and Build the Infrastructure
 - actual/past-acquired data
 - realistic, near-term acquirable accurate data
 - long-term possible and work-to-goal data
- Define and Build the Intelligence Engine (pattern recognizer/make/predictor)
- Put tools and resources into Hands of People and start using them productively

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PHIBER Pilot Project – Three Specific Aims

[1] Aim #1 An intelligent knowledge base usable by all.

Flexible architecture and implementation that can be employed throughout all public and private healthcare networks for earlier detection of indicators and "look-ahead, heads-up" conditions.

Goal: Works with Epic, Allscripts, Cerner, McKesson and the rest

[2] Aim #2 Machine learning that enables discovery and innovative reasoning.
Bayesian, neural network (VAE, GAN, others) and formal logic systems.
Goal: Inductively provable to be unbiased across population variances

[3] Aim #3 An adaptive, expansive, open-ended architecture for radical public health situations.

Detection of higher-risk and newcomer pathologies earlier, faster, capable of alleviating burdens of the health system due to extraordinary social and healthcare system destabilization such as acute, high-transmission pandemics (e.g., COVID-19), capable of rapid innovation and adaption to dramatic nonlinear conditions. **Goal: Be better than what we had for COVID-19 and up to the present, for general public health and especially public-assistance populations** To understand how people are so easily and subtly affected, so badly in the long run, with such comorbidity-intensive diseases – cancer, cardiovascular arrhythmia and cognitive neuropathy – from environmental toxins that are often treated as sub-trace amounts, or not detected properly or ignored or hidden (the last two are major problems in several modern nations including USA) ----

---- It merits to examine some fundamental etiologies that involve:

- Fundamental biophysics
- Including novel theoretical directions of research in

Coherent quantum entanglement, entrainment and resonance (CQER) Think of it as non-Turing quantum computation at the macromolecular scale involving signal propagation in protein arrays including microtubules and intermediary filaments

This is how a variety of seemingly disparate and multi-scalar STRESSORS act over different scales of time to create Neuromuscular (including cardiovascular) dissonance and dysfunction Herein is where environmental toxins as well as psychological duress and abuse all work to degrade cognitive, muscular and regulatory functions in the organism

Foundations, Priors, and Pertinent Background - Neuroplex-C Project:

An interdisciplinary project investigating common underlying etiologies in multiple disorders and diseases characterized as dysautonomia, arrhythmia, and including several autoimmune classifications.

The initial focus has been on cardiac arrhythmia including SVT, AFIB and syndromes such as POTS. This has expanded with findings emerging from COVID-19 and PASC ("Long COVID").

Variances in pathologies and in population demographics point to the need for integrating more extensive biometrics including genomics and proteomics, in a comprehensive manner across all population groups (racial, ethnic and socioeconomic).

Objectives include modified and expanded diagnostic testing, innovative non-invasive therapeutics, and broader public health education to address contributing factors of stress, nutrition, and lifestyle practices.



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Figure 2

People of Color Fare Worse than their White Counterparts Across Many Measures of Health Status

Number of health status measures for which group fared better, the same, or worse compared to White counterparts:



Note: Measures are for 2018 or the most recent year for which data are available. "Better" or "Worse" indicates a statistically significant difference from Whites at the p<0.05 level. No difference indicates no statistically significant difference. "Data limitation" indicates data are no separate data for a racial/ethnic group, insufficient data for a reliable estimate, or comparisons not possible due to overlapping samples. Persons of Hispanic origin may be of any race but are categorized as Hispanic for this analysis; other groups are non-Hispanic.



Significance of Population Health Equity and Diversity Biometrics for Improved Early Diagnostics and Proactive Treatment and Positive, Sustainable Survival

<u>lssues</u>:

- Incomplete Data being collected from virtually all patients at risk
- More people than ever at risk due to:
- ♦ COVID-19 and PASC
- ◆ Massive Stress, Anxiety, Passive/Active Abuse, Social Deconditioning
- ◆ Variances between Racial and Ethnic Groups Not Understood, Not Examined, Not Considered
- Social / Institutional / Professional Prejudices toward Most-At-Risk Population Sub-Groups for many dysautonomic/autoimmune conditions
- ▶ Need for Massive Biometrics including Behavioral & Genetic Data in order to:
- Ascertain genetic etiology and amplification factors
- Understand the psychosocial, nutrition, lifestyle factors
- Develop personalized plans for individuals at risk and in general

♦ Overcome medical/healthcare prejudices and discrimination which result in misdiagnosis and ignoring problems until Too Late

This is about BOTH

Inequities in diagnostic and therapeutic medicine AND

The GAP in understanding the variances between multiple genotypes and beahavior/lifestyle types which is Required in order to Answer the many questions raised and implied by this Project and many others in related fields

Massive Statistics of a different "order" than what are typically queried or discussed by healthcare providers – particularly in USA

Yes, anonymity and privacy can be preserved and protected – including for critical data pertaining to lifestyle including mobility functions

COVID-19 and PASC must be addressed head-on because This is a Large and Multi-Generational Problem we now face

Psychological Dynamics including parent-child, adult-adult, and societal factors of abuse, bullying(!) and other discrimination – spanning indeed all races and demographics and arguably intensifying in the 2020s – this must be included in the Data Collection and the Biometric Resources to be assembled

This must Not be yet-another-exercise in building a huge database and then it sits there and is used by (maybe) only a handful of researchers

Population Health Equity Biometrics Resource (PHEBR) can and must be a <u>Tool for Social Health Change</u> including Policy and Practice (not only "research") 4 - ADaM and EVE and the Engine:

The main tasks:

VLDB (Very Large DataBase) operations

ETL ("extract-transfer-load")

Communication asynchronous Parallel Processing ("cloud" and "feed" tasks)

Pattern recognition, error-correction and fitting, classification Pattern simulation, mimicking and projecting Probabilistic reasoning, estimation, outcome prediction

VAE (Variational auto-encoder) and GAN (Generative Adversarial Network) methods - well-proven, robust, widely used including in image/text recognition and simulation, and in medical imaging and EHR modeling



Figure 5. Using the VAE/GAN model to reconstruct dataset samples with visual attribute vectors added to their latent representations.

Using the VAE/GAN model to reconstruct dataset samples with visual attribute vectors added to their latent representations.

[14]



Figure 7: Image generation qualitative results, showing five sampled results for two different images. Top: Ours, Middle: SinGan [24], Bottom: ConSinGAN [28].



Figure 8: Additional image applications comparison: harmonization, paint-to-image and editing.

[15]

393 9 7 I 0 2 b) a) . 1 11

Examples of GANs used to Generate New Plausible Examples for Image Datasets. Taken from Generative Adversarial Nets, 2014.

What is and how to build the PHEBR

Prime Objectives:

[1] Resource for Identifying and Reducing Health Inequities
(Inequialities) for Affected, Vulnerable, and Ignored
Minorities and Population Sub-Groups
This, of course, pertains to many (all) aspects of healthcare

[2] Assist genomics-focused research "across the board"

[3] Assist in the challenge of identifying "earlier than later" the at-risk populations for "neuro-cardio-plus" disorders, including other autoimmune types

[4] Other objectives include the benefits to healthcare industry entities: pharmaceutical, medical device, hospital, insurance, others

Clinical medical statistics – massive data sources – properly anonymized (no privacy issues) originating from public/private institutions

Focus upon Classes of Populations considered to be (known/definite → potential-at-risk) for NPC-category health issues

Applications

and other Use-Cases

VLDB ADW "Active Data Warehouse"

Human-Machine Users (Agents) – different use-cases, objectives, applications

- ◆ Genomics, genetic engineering, diagnostics, therapies, pharma, devices
- Public health (equity/inequality problem; pandemic prevention/containment)
- Identifying and refining relations and etiologies of NpC-type disorders and diseases

The PHEBR is a kind of "New Genesis" for studying links between poorly-understood and syndrome-categorized disorders and diseases ----What better way to do this than to "couple" together ADAM and EVE? ③ ④

ADAM and EVE



medical histories for:

- Indicators of risk conditions and causal relations on the basis of acquired data sets in PHEBR
- Missing-gaps types of data to pursue and collect through future clinical measurements (e.g., behavioral, lifestyle)
- What-Ifs and Hypotheticals pertinent to NpC for investigation and evaluation and linkage with genetic modeling systems like EVE (HMS/OATML)

eve

evolutionary model of variant effect

P53

EVE score matrices

Marks Lab - Harvard Medical School OATML - Oxford Applied and Theoretical Machine Learning Group



<u>5 – Implementation ("PHIBER-alpha")</u>:

- acquiring datasets of disparate and varied patient group types
- acquiring real-time per-patient increments
- training the system using VAE, GAN and other algorithms for both data correction and simulated data element creation
- identifying target patient types for follow-up provider-led actions
- recommending follow-up inquiries, observations and diagnostics-totherapeutics action
- providing a logical and systematic basis to proceed into a fuller-scope development of the PHIBER for use on a national+ scale

During this Pilot Project, our focus will be upon the following population and biomedical metrics:

- Environmental toxins originating in mining, smelting, and waste removal and disposal processes connected with principally uranium and other toxic metals
- Health risks primarily linked with cancers and birth defects
- Black, Native and specific disadvantaged other minority populations in preidentified, previously-studied communities within socially and economically disadvantaged regions ("Appalachia-plus") of Tennessee, Kentucky, West Virginia, Virginia, Illinois, Ohio, and Michigan.

5 - Challenges and opportunities in population health equity and diversity:





Team Members, Collaborators, Advisors, Assistants

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-- with collaborative engagement and assistance from --

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Thank You!



Author's Reserved Background and Extra Material -

NOT PART OF PRESENTATION for Delivery or Distribution!

1 - Summary of the Main Thesis:

Chronic, sustained stressor agents – molecular-scale but originating from environment by intake and by consequences of psychosocial behavioral processes – contribute to deterioration of intracellular communication pathways including energy transfer within microtubulin and axonal sheaths. Consequences include signal turbulence and interference within the autonomic nervous system and also involving the peripheral nervous system and muscular-skeletal network. Sustained patterns of dissonance and arrthythmia including spiral, chaotic and knot/vortex wave interference arise within principally cardiovascular, pulmonary, and gastrointestinal neuromuscular action, giving rise to several forms of longterm syndromic disease.

At the fundamental molecular scale this involves cellular structures including microtubulin, actin and other long-filament polymer chains and the disruption of normal, efficient energy transfer. Genetic factors are indicated in several conditions as contributing and exacerbating factors if not fundamental causes.

Inflammation effects including from infectious disease (e.g., COVID-19) can progress into and exacerbate pre-existing instabilities, leading to rapid and/or long-term deterioration into several autoimmune and syndromic diseases.

Autonomic Neurophysiological Control and Electromolecular Stress

Implications for Multiple Cardiovascular Disorders and Diseases

An Exploratory Map of Diverse (known and unknown) Terrain employing both established and novel models of interpreting nonlinear dynamics within biological systems

Goal-Set (comprehensive):

§ Identify discernible early indicators of emergent/potential arrhythmias and neuromuscular control disorders through noninvasive electro-acoustic measurements

§ Identify non-invasive, nonpharmaceutical therapeutic procedures to minimize/restore health-stabilizing function



2 - Historical and scientific background of how this project evolved:

Physics – Quantum Relativity (1990s+) RTD – Reflexive Topological Dynamics → TBD (biomolecular/cellular topological orders; biosolitons, vanderWaals, cytoskeleton) → TND (neuronal organization and topology → quantum biological computing including in virus topologies and methods of host cell endocytosis)

Oasis Clinic for Neurophysiological Wellness (2018-2020)

+ IRI (Elea) Sensor/Monitor Technologies Consultation + Therapeutics Biomagnetics, TMS, PBM, FMRI, SIMOA, Accoustics, Nature, Shaolin Autoimmune (MS), Dysautonomia (POTS), Cardiovascular, Stroke and Motor Disabilities



COVID-19 (2020+) + PASC

VESID – Viral Entry Structural Integrity Disruption Emergent cardiac/neural disruption/arrhythmic pathology MedAtrium/Eyrie - renewal/revision of earlier H1N1/SARS/Ebola-era public health informatics and diagnostics (PCR, SIMOA)

NpC -- Neuroplex-C -- emerges as a focal project (10/2021+)

Initial: cardiac arrhythmia, POTS, MALS, IBS Expanding: autoimmune, inflammatory disorders, public/population informatics



