Neuroplex-C Project

Chronic Neural Stressor Agents within Dysautonomic and Arrhythmic Disorders - The Significance of Population Health Equity and Diversity Biometrics for Improved Early Diagnostics

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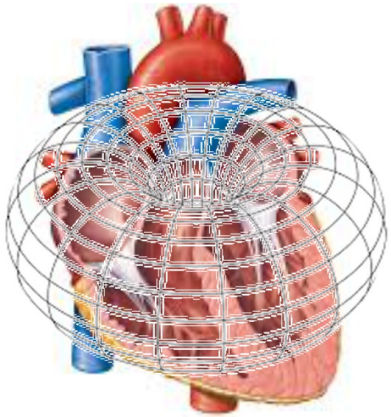
TETRAD Institute of Complex System Dynamics

24.February.2022



About the 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.

About the Speaker:

Martin is principal investigator in the Neuroplex-C Project. 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:

Johns Hopkins
NYU
SUNYAB
NIH
U-Arizona
U-Michigan
U-Alabama
U-Arizona
Dysautonomia Int'l

Göttingen
Karlinska
Trondheim
St. Petersburg
Durham
Brighton
Palma

Seoul
Tianjin
X'ian Jiaotong

Format of the Presentation:

1 - Summary of the main thesis

2 - Historical and scientific background of how this project evolved

3 - Main body – hypotheses, findings, current directions - from theory to praxis

4 - Integral importance of large-acale population-based bioinformatics

5 - Challenges and opportunities in population health equity and diversity

6 - Implications and objectives for future new diagnostics and therapeutics

7 - Conclusions

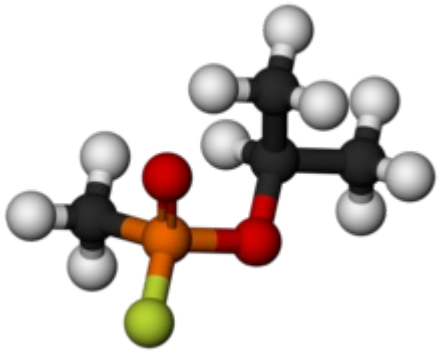
Q/A

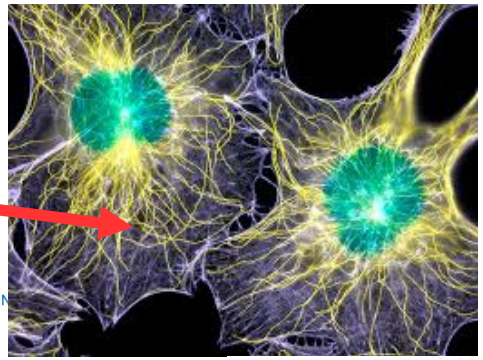
1 - Summary of the Main Thesis:

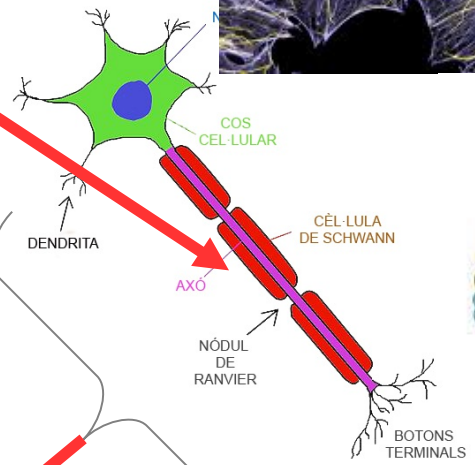
Chronic, sustained stressor agents – molecular-scale but originating from environment by intake and by consequences of psychosocial behavioral processes – contribute to deterioration of intracellular communication pathways including energy transfer within microtubulin and axonal sheaths. Consequences 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 long-term syndromic disease.

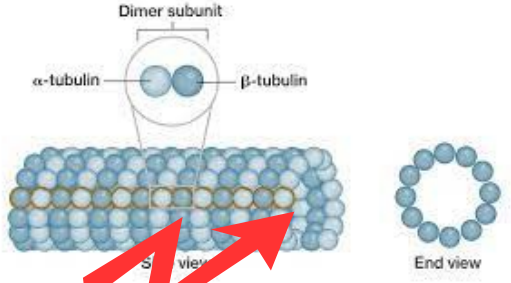
At the fundamental molecular scale this involves cellular structures including microtubulin, actin and other long-filament polymer chains and the disruption of normal, efficient energy transfer. Genetic factors are indicated in several conditions as contributing and exacerbating factors if not fundamental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

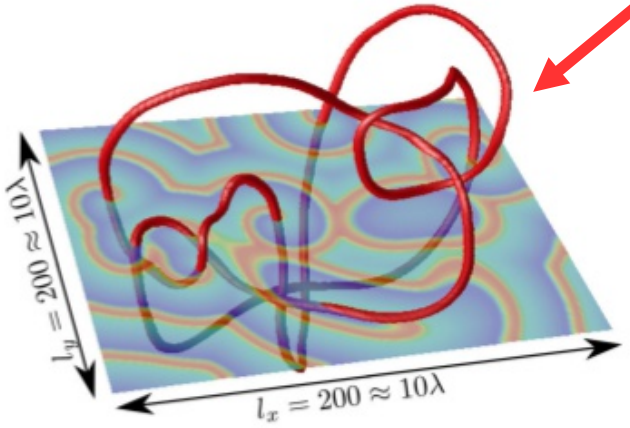
Inflammation effects including from infectious disease (e.g., COVID-19) can progress into and exacerbate pre-existing instabilities, leading to rapid and/or long-term deterioration into several autoimmune and syndromic diseases.











$$\frac{\partial u}{\partial t} = \frac{1}{\varepsilon}\left(u - \frac{1}{3}u^3 - v\right) + \nabla^2 u, \qquad \frac{\partial v}{\partial t} = \varepsilon(u + \beta - \gamma v),$$

Autonomic Neurophysiological Control and Electromolecular Stress

Implications for Multiple Cardiovascular Disorders and Diseases

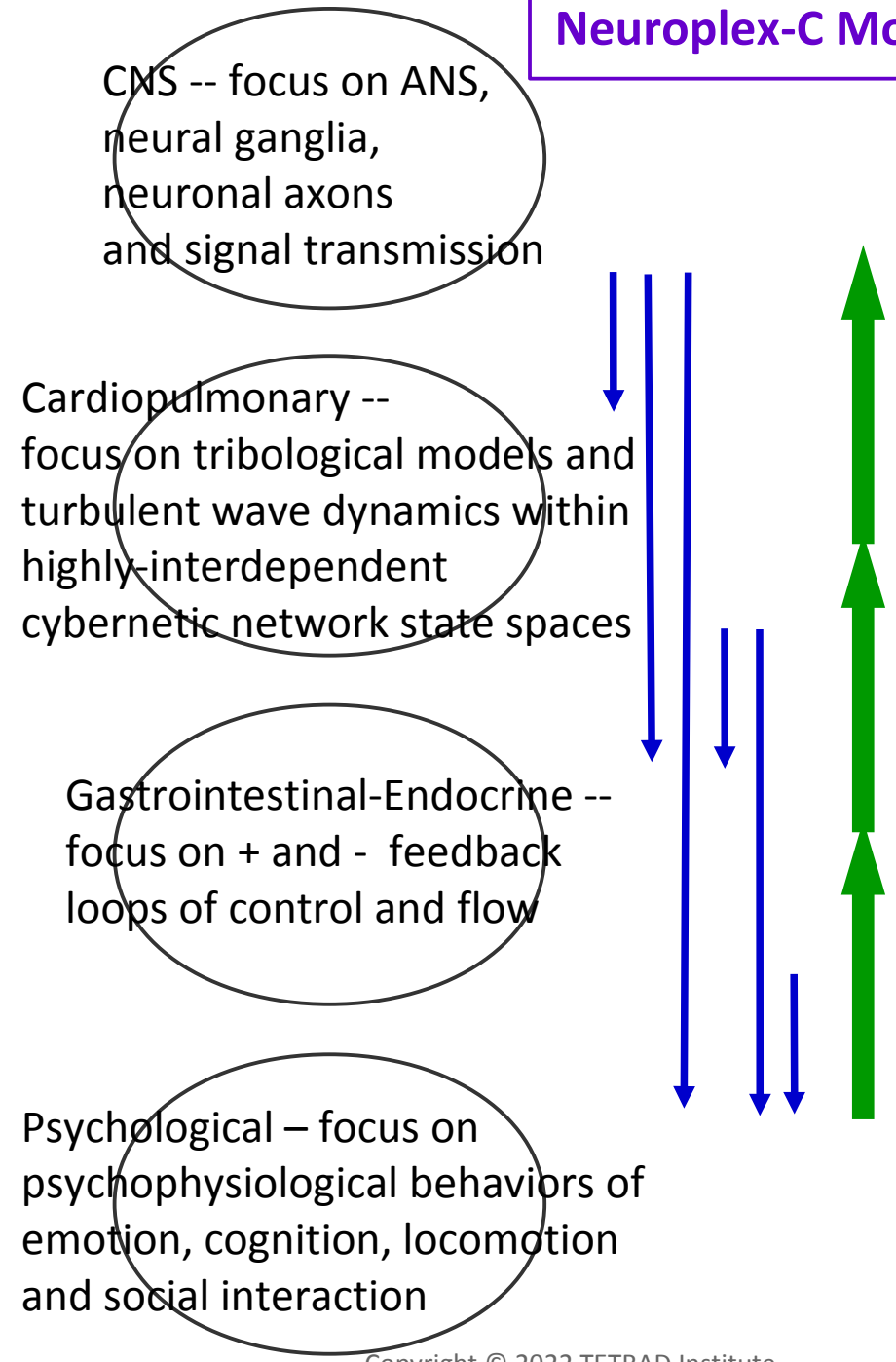
An Exploratory Map of Diverse (known and unknown) Terrain employing both established and novel models of interpreting nonlinear dynamics within biological systems

Goal-Set (comprehensive):

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

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

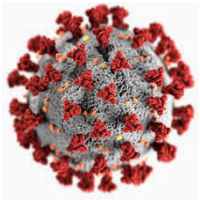
Neuroplex-C Model



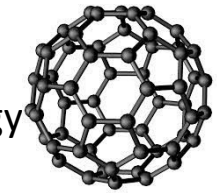
2 - Historical and scientific background of how this project evolved:

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



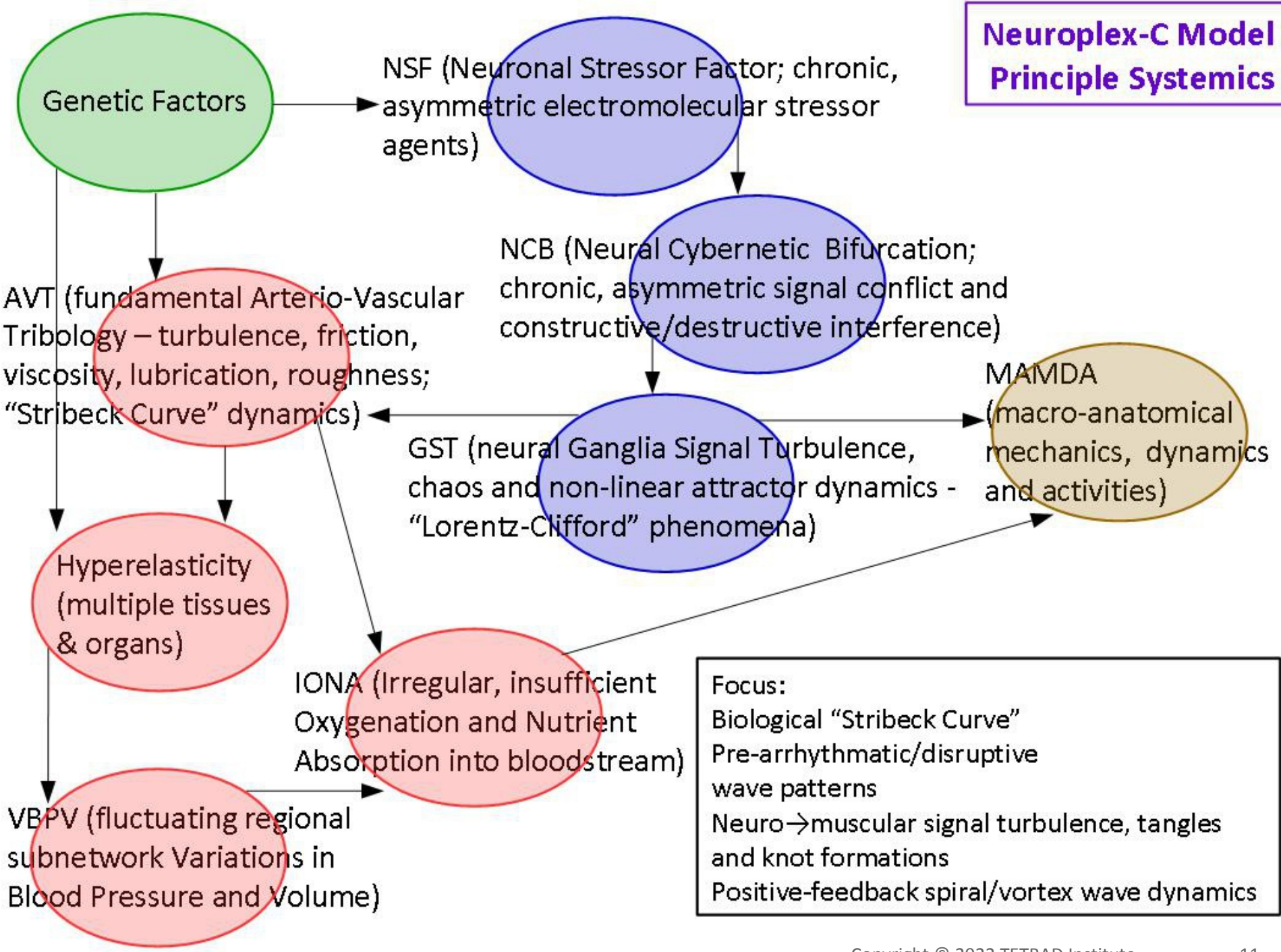
COVID-19 (2020+) + PASC
VESID – Viral Entry Structural Integrity Disruption
Emergent cardiac/neural disruption/arrhythmic pathology
MedAtrium/Eyrie - renewal/revision of earlier H1N1/SARS/Ebola-era public health informatics and diagnostics (PCR, SIMOA)



NpC -- Neuroplex-C -- emerges as a focal project (10/2021+)
Initial: cardiac arrhythmia, POTS, MALS, IBS
Expanding: autoimmune, inflammatory disorders, public/population informatics

3 - Main body – hypotheses, findings, current directions:

Neuroplex-C Model Principle Systemics



Focus:
Biological "Stribeck Curve"
Pre-arrhythmatic/disruptive wave patterns
Neuro→muscular signal turbulence, tangles and knot formations
Positive-feedback spiral/vortex wave dynamics

Neuroplex-C Model Chronic Stressors leading to Inflammatory-and Autoimmune type (IAI) Processes [1]

ANCES - Autonomic Neurophysiological Control and Electrochemical Stress

PC -psycho-catalyst - Psychological origins: neurological processes involving classical emotive and cognitive functions

BMC -behavioral-mechanical-catalyst - biomechanical origins: patterns of chronic movement and/or static postures

CC – chemical-catalyst - External origins: physical substances affecting ANS/CNS through exposure or ingestion, Voluntary or involuntary

AEC -acusto-electronic-catalyst - Acoustic/electromagnetic origins: noise, light, other EMF

Genetic factors linked to either IAI direct-effects, or production of NSF, or reaction to specific CC or AEC stimulant sources

+

NSF (Neuronal Stressor Factor; chronic, asymmetric (equilibrium-disrupting) electromolecular stressors)

=

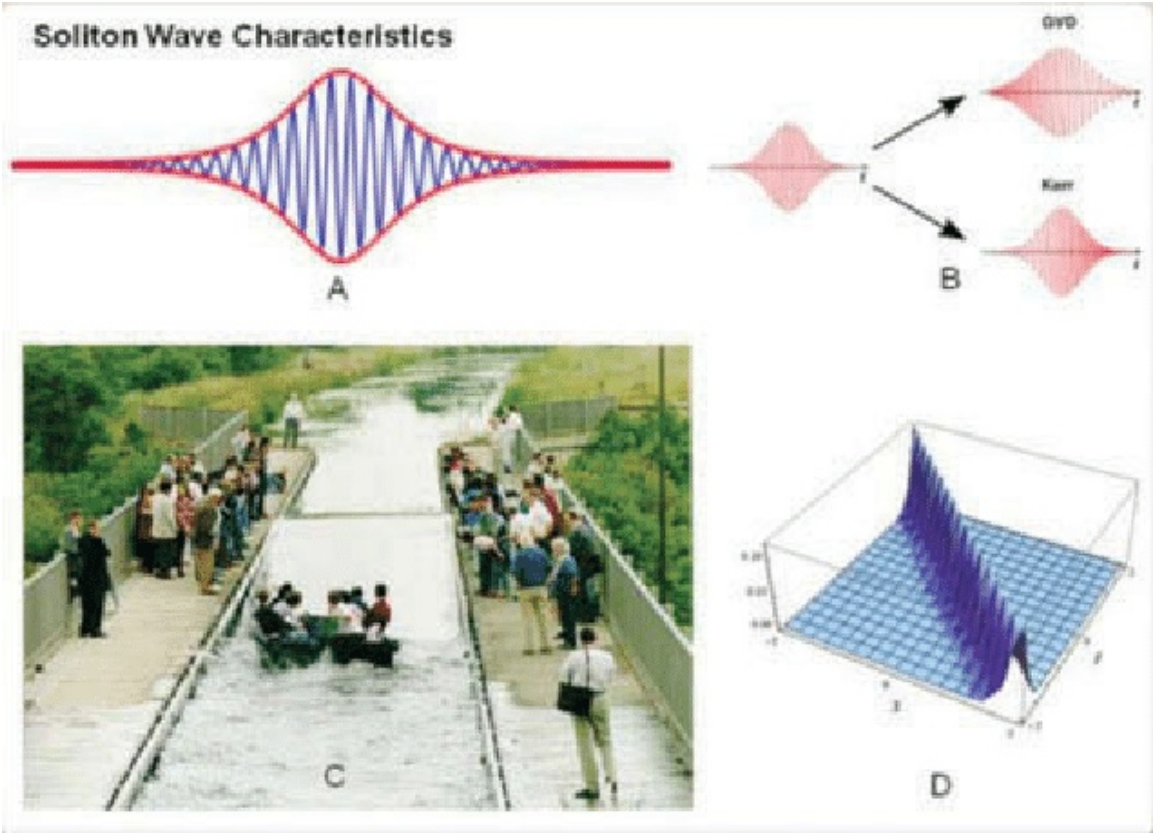
NCB (Neural Cybernetic Bifurcation; chronic, asymmetric signal conflict and constructive/destructive interference)

MAMDA (macro-anatomical mechanics, dynamics and activities)

GST (neural Ganglia Signal Turbulence, chaos and non-linear attractor dynamics; "Lorentz-Clifford" phenomena)

Solitons in water, stars, atoms, internet and molecular biology – they're … everywhere!

Davydov, Frohlich, Ho, Brizhnik (pioneers)



"A brief word from our Sponsor" ---
the mathematics and physics underlying it All

A common equation for describing a soliton wave is given by the Korteveg - de Vries (KdV) partial differential equation:

$$u_t + u_{xxx} + u\,u_x = 0$$

where u=u(x,t) measures amplitude at time t and position x (e.g., height of the water wave above some equilibrium level. The dispersive term is given by u_{xxx} and the nonlinear term by u_x.

The typical soliton shape can be found by direct integration of the KdV equation:

$$u(x,t) = a\,\mathrm{sech}^2[b(x-vt)]$$

into local deformations along the chain through electron transfer. The resulting state involving a bound electron and a lattice deformation behaves according to the classic nonlinear Schrödinger equation

$$i\hbar\frac{\partial\Psi(x,t)}{\partial t}+J\frac{\partial^2\Psi(x,t)}{\partial t^2}+2Jg\left|\Psi(x,t)\right|^2\Psi(x,t)=0,$$

which has a soliton solution presenting the propagation along the polypeptide chain of the deformed lattice:

$$\Psi(x,t)=\Psi_s(x,t)\equiv\frac{1}{2}\sqrt{g}\,Sech\left[g(x-x_0-Vt/a)/2\right]\exp\left(im_eVx/\hbar+i\varphi_s(t)\right),$$

This is represented in Figure 23 as a propagation of a soliton within DNA.

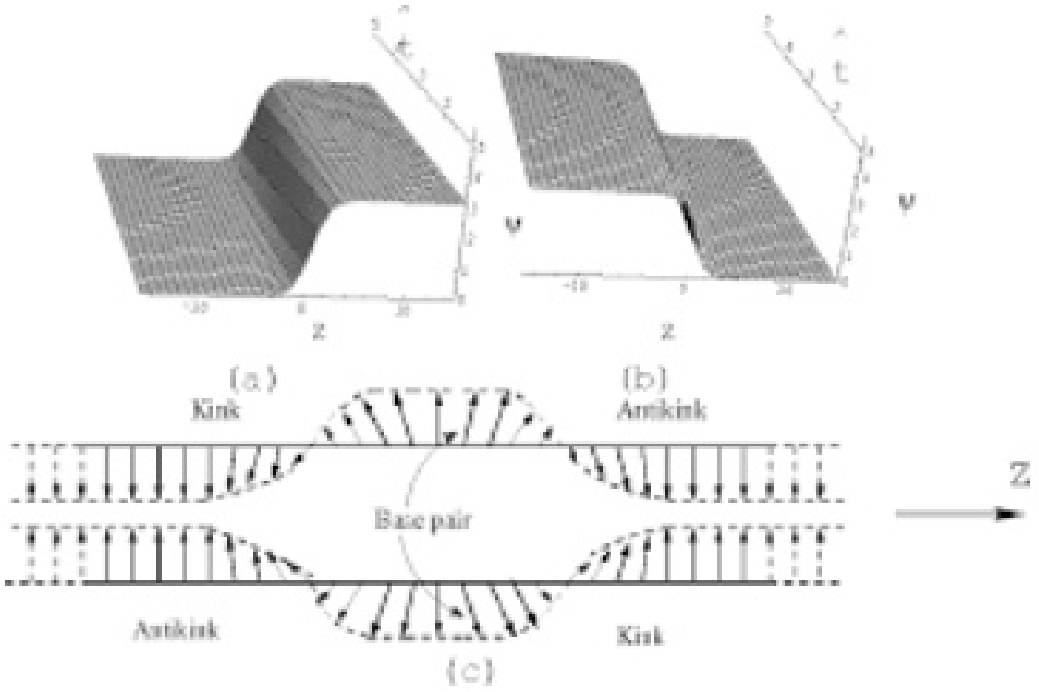
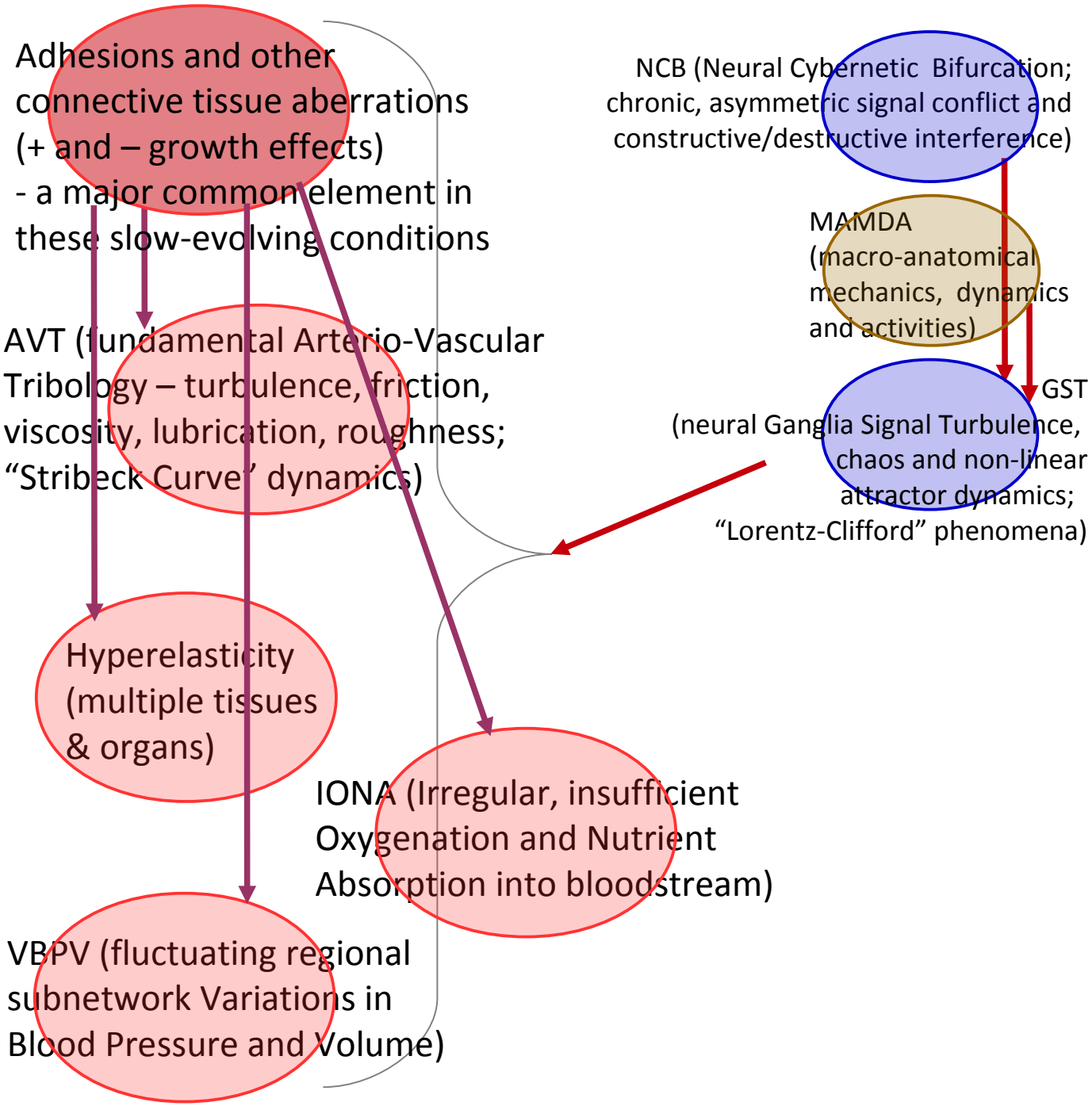


Figure 23 Biosoliton [s]



Neuroplex-C Model Chronic Stressors leading to Inflammatory-and Autoimmune type (IAI) Processes [2]

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ANCES - Autonomic Neurophysiological Control and Electrochemical Stress
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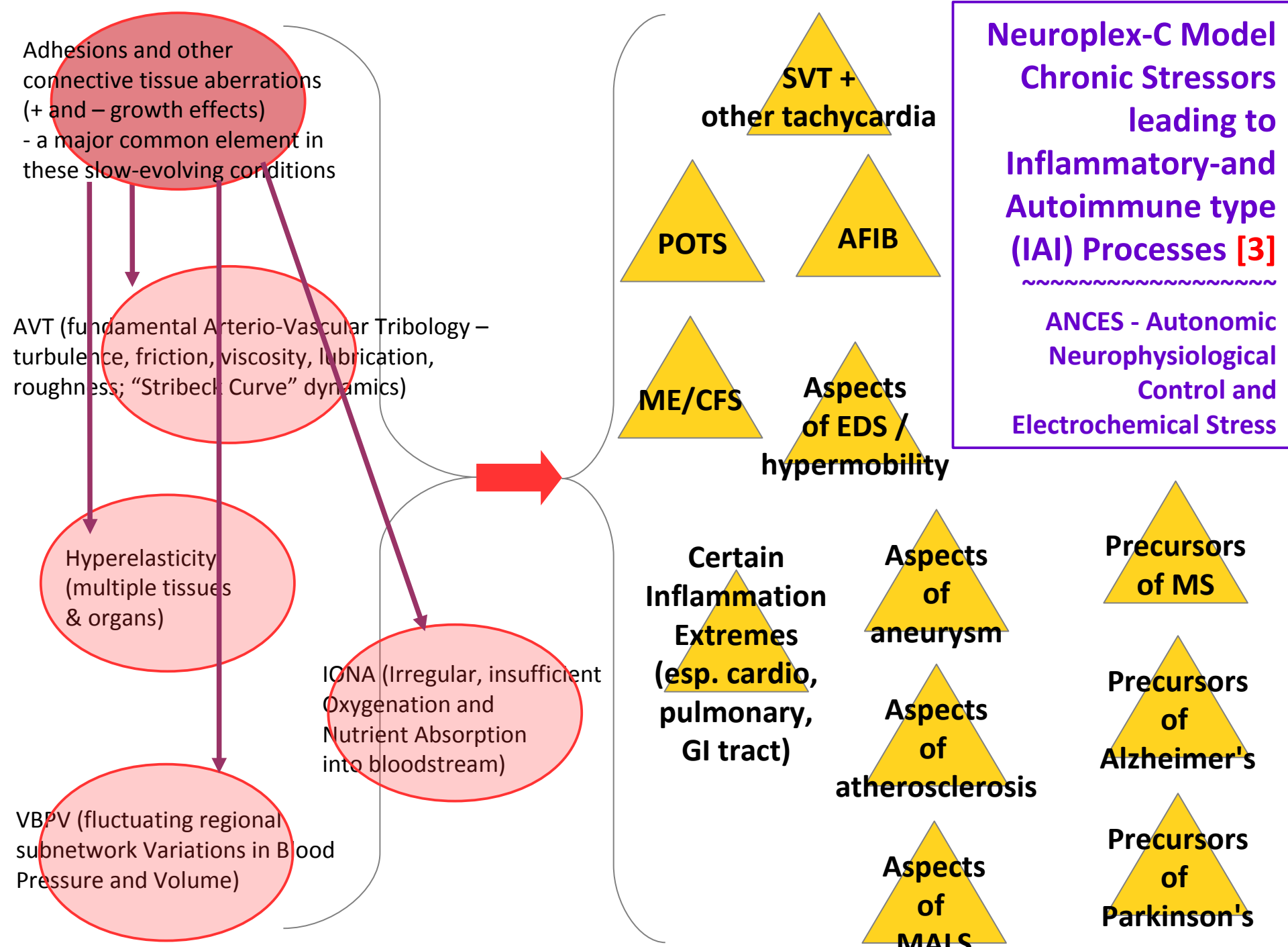
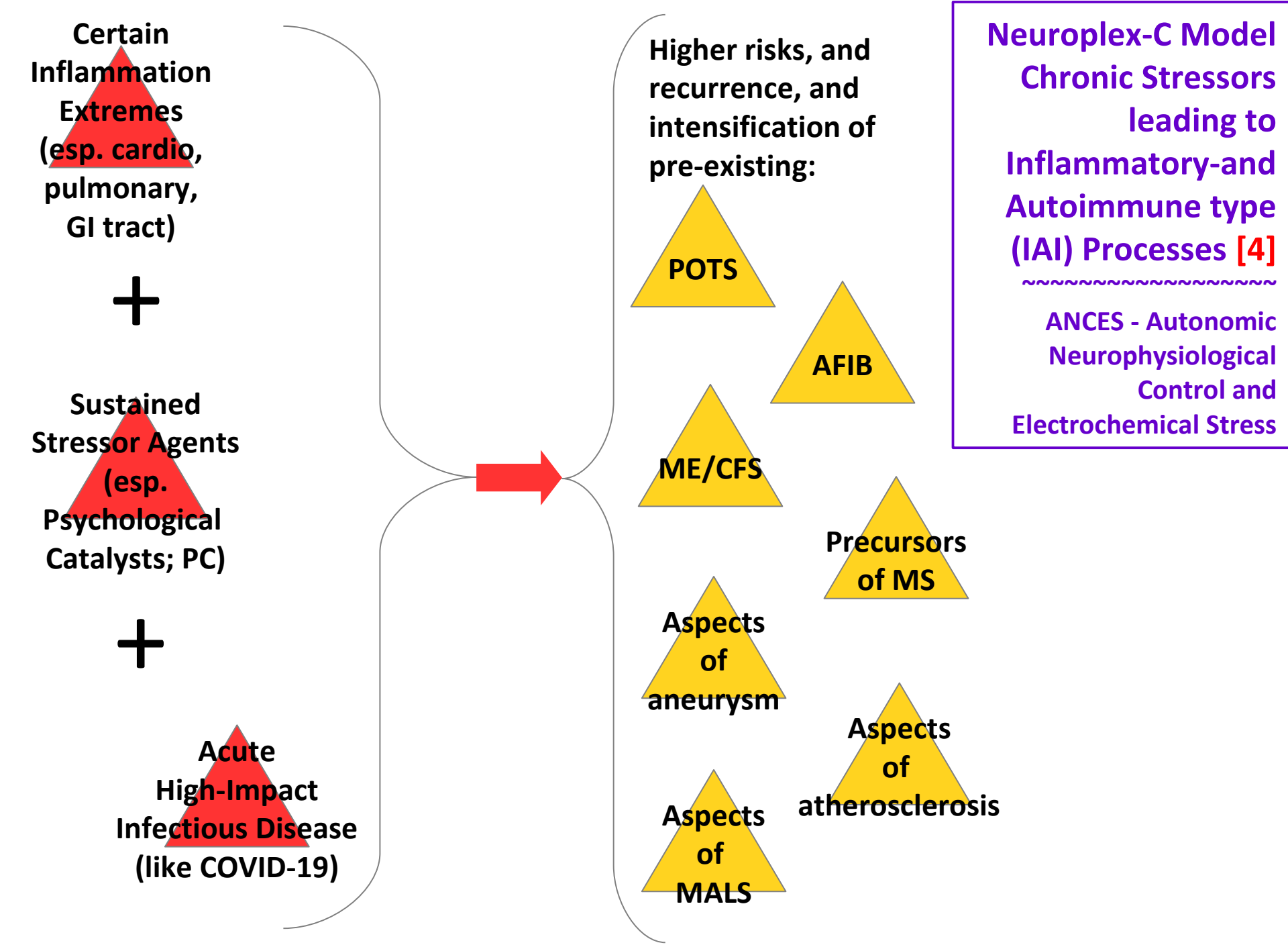
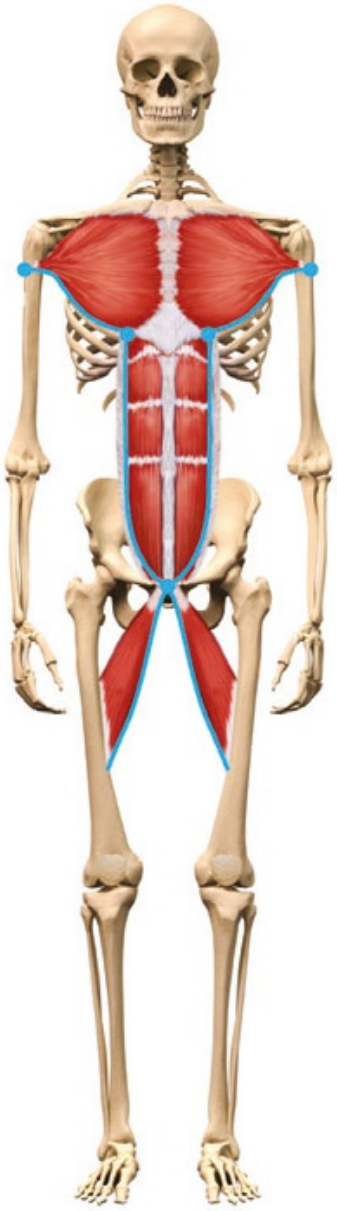
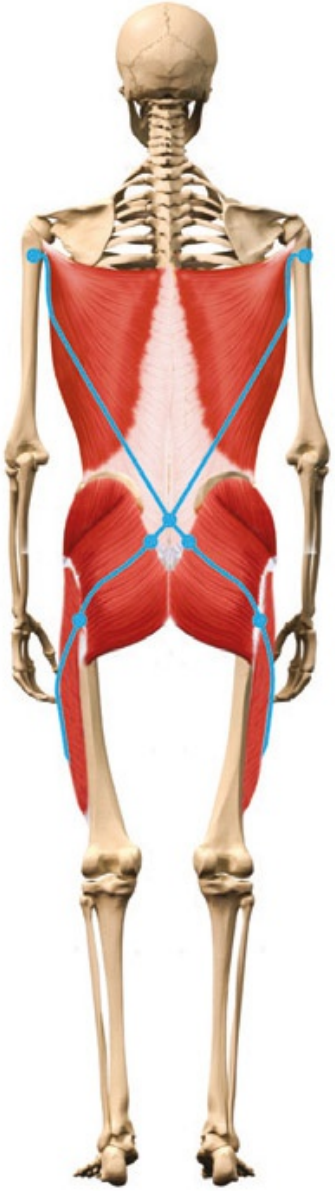




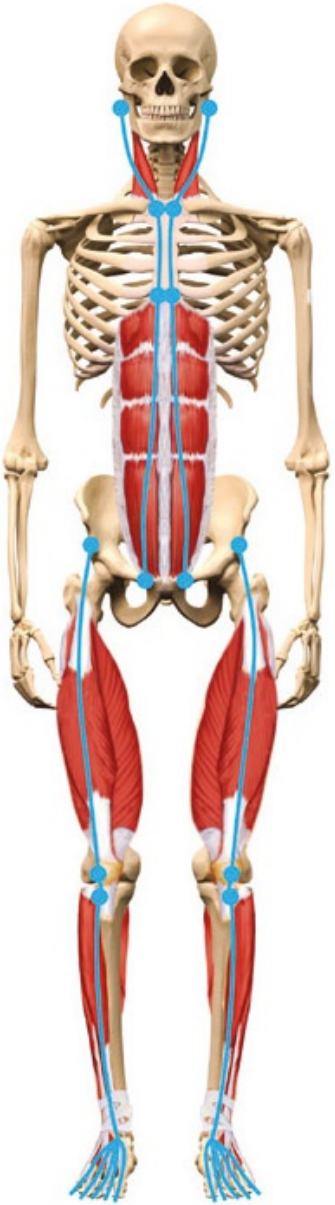


SUPERFICIAL FRONT LINE



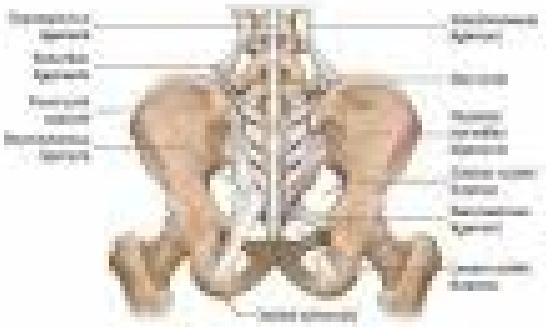
SUPERFICIAL BACK LINE

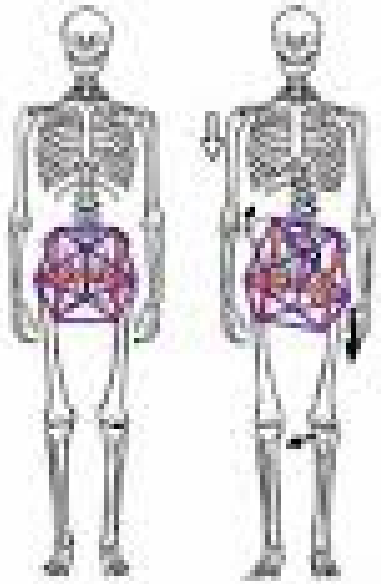
LATERAL LINE

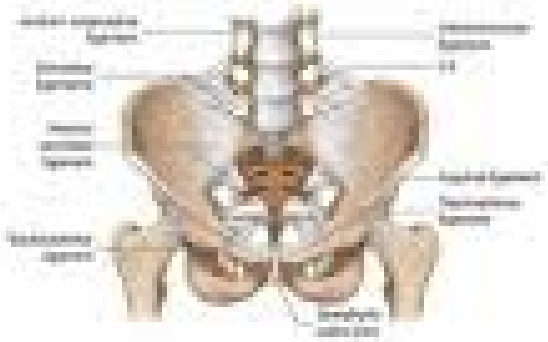


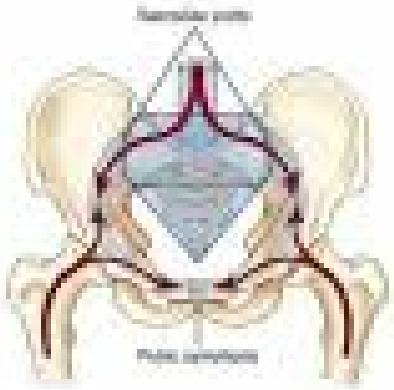
DEEP FRONT LINE

PELVIS TENSEGRITY









POTS, MALS, IBS, Crohn's, and Cardiopulmonary Arrthythmia

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Sustained inbalance in peuromuscular posture, breathing, digestion, under average and high exertion conditions contribute to PNS and ANS dysfunction

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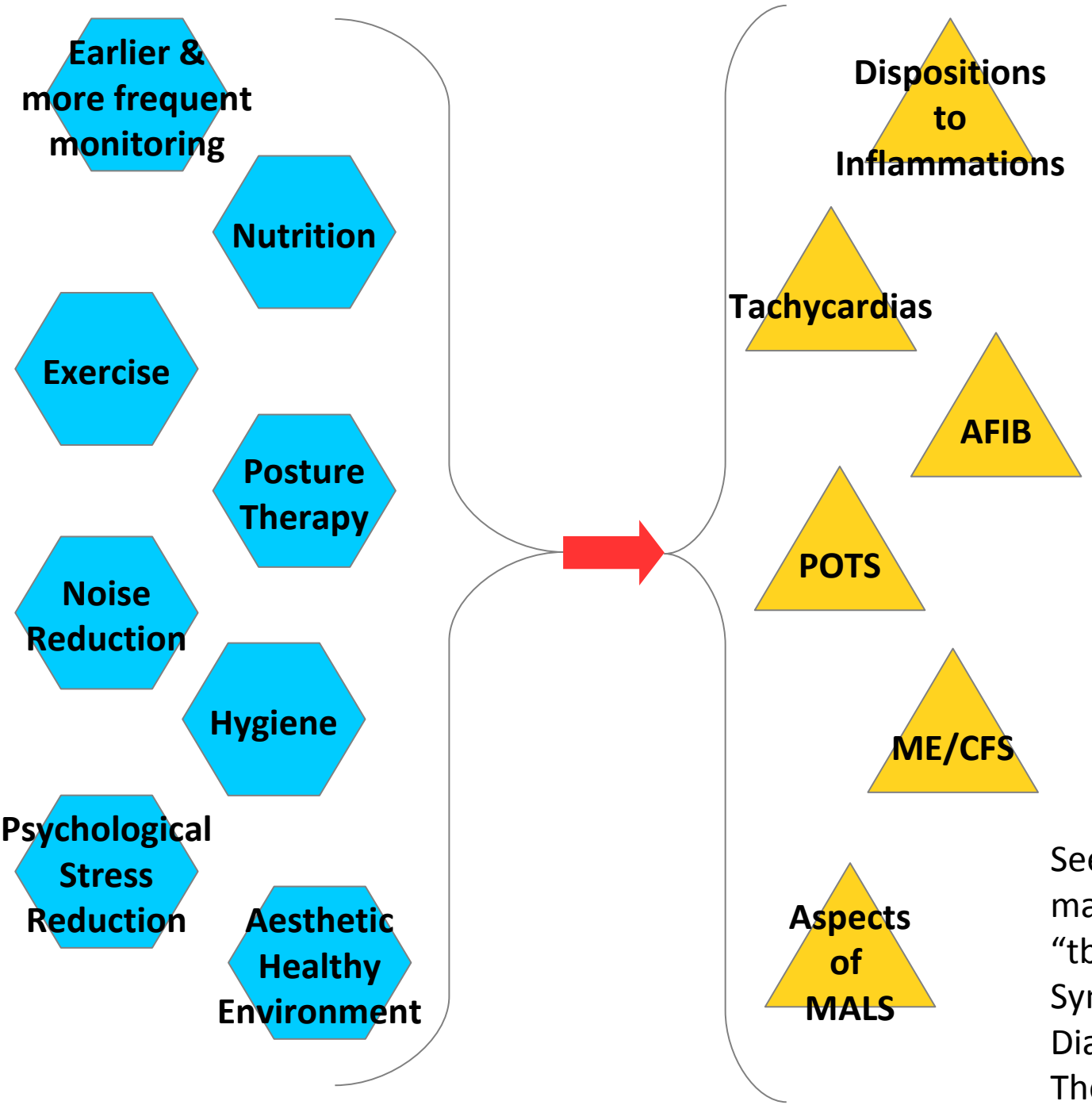
Resetting the inbalances through orthoststic and orthopedic therapies may be an important component of treatment



Diagnostic and Therapeutic Directions

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Reduction of the Stressor Agents (not here addressing pharmaceuticals and surgeries)

See more written in the major "synopsis" document, "tbd-ances-framework-Synopsis...", in sections on Diagnostics and Therapeutics
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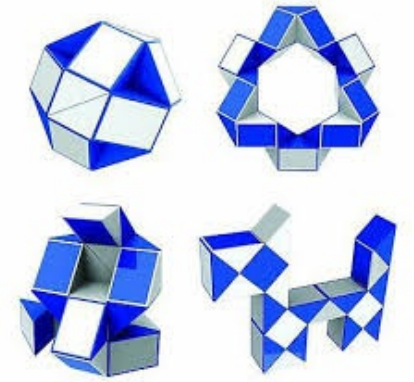
Kinks, twists, knots, tangles – these are in flows of energy transport (biosolitons), in cytoskeletal and cell-to-cell movement and aggregation, in fluidics of blood vessels.

TRIBOLOGY in biology is not only for improved engineering of implants and artificial devices – it matters in the Actual Dynamics of Life – both in progression of dis-ease and dis-order and in restitution of health through combined physical, psychological, environmental therapies – and where required, pharmaceutical and/or surgivcal procedures, including genetic engineering.



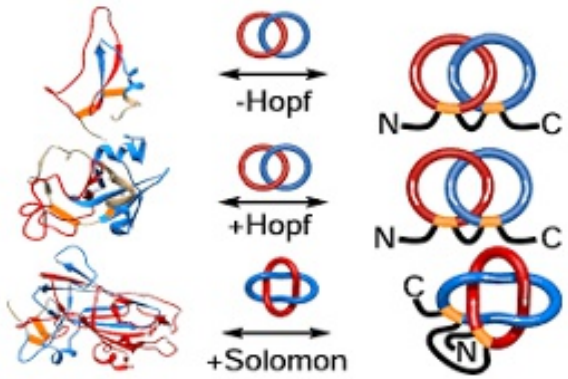


Figure 20c Proteins and knot forms[o]

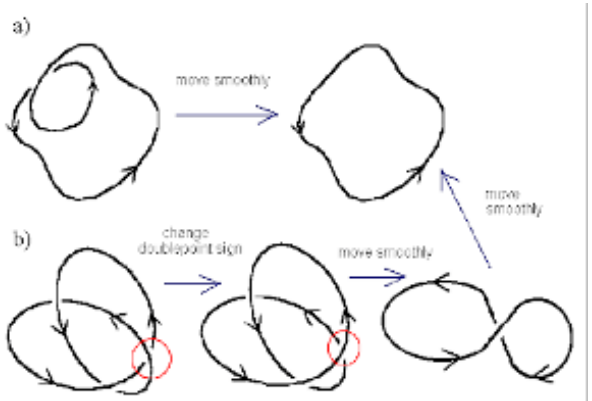
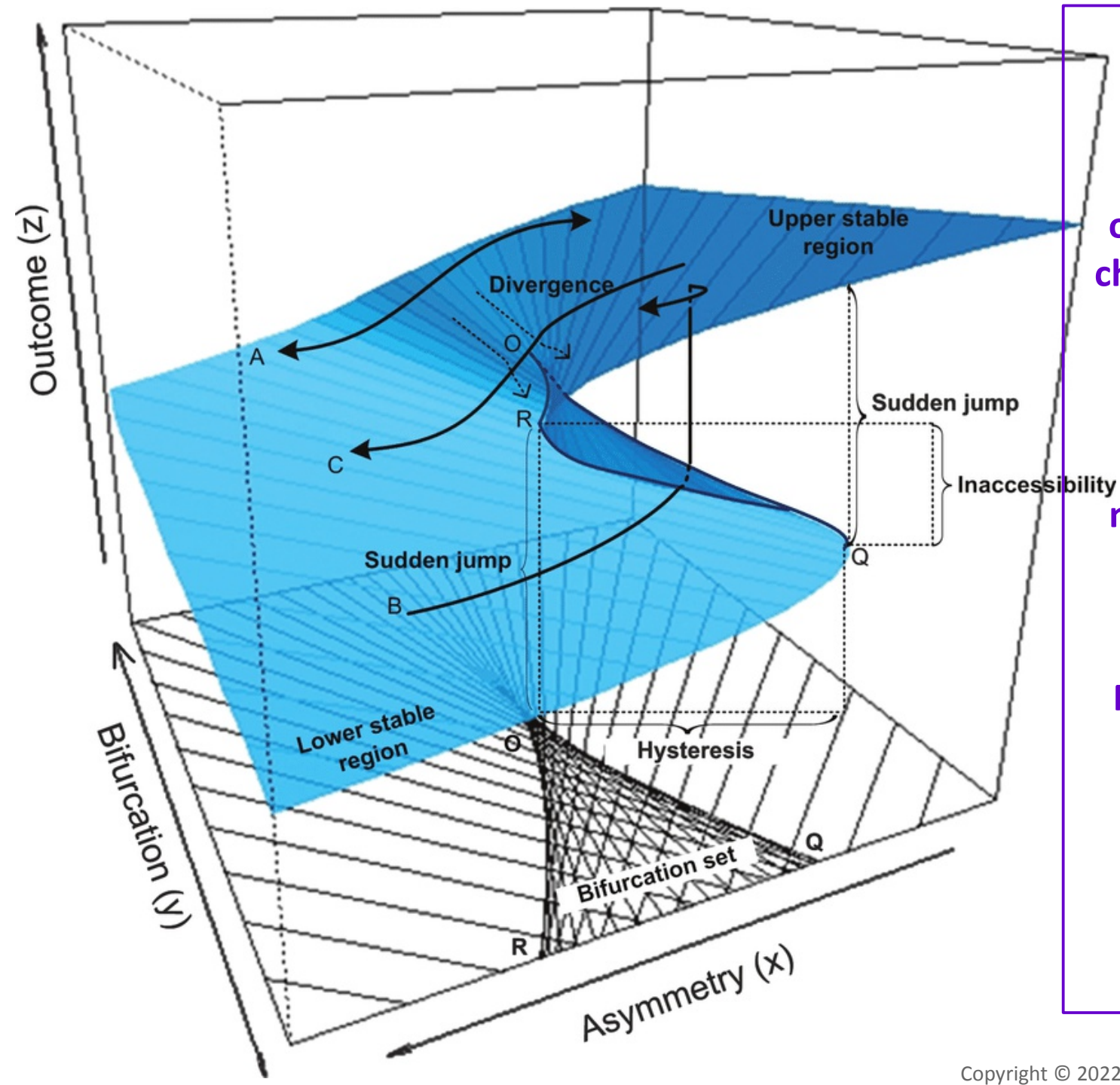


Figure 20b DNA and knot theory [n]



A topological interlude...

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Acute and also onset of prolonged chaotic signal/wave behavior – and inflammation as a Process – can be understood by models such as the catastrophe function

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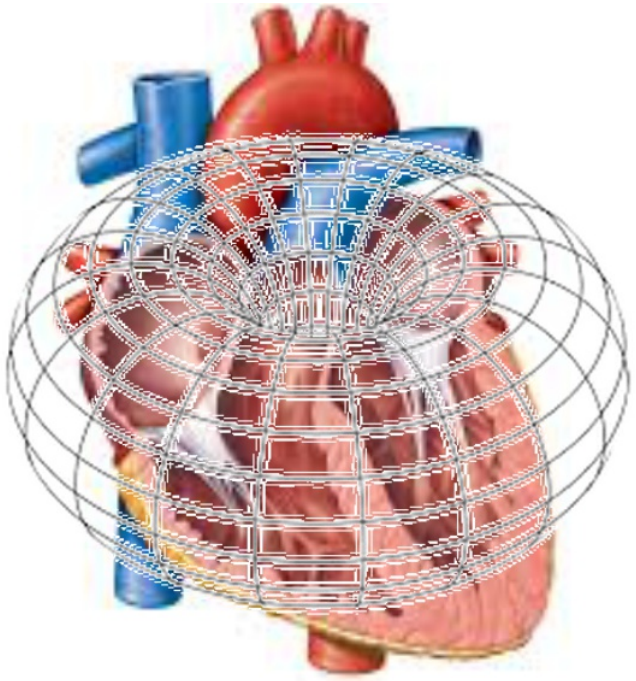
Might the same be said for "bifurcation/ transition" moments in the Therapeutic Process?

Consider the wave dynamics when a system designed to function “forever” as a smooth toroidal process of pumping action is thrown into the spiral wave “tangle” of tachycardia and AFIB in particular:



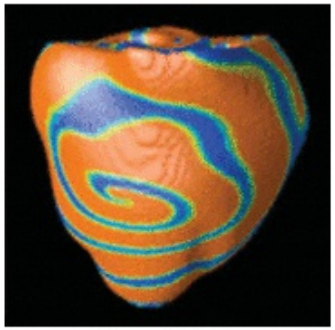


Figure 29 [y]

Now this apparent knot is really, in mathematical terms, an *unknot*. It is clearly a “tangle”, but it can be untangled without cutting and reconnecting. The topology is maintained through the untangling until the apparent knot, the unknot, is untangled into a smooth circle. Figures 30a, 30b and 30c give illustrations of how this proceeds during evolutionary cycles of the basic Fitzhugh-Nagumo equations.

4 - Integral importance of large-scale population-based bioinformatics:

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

Issues:

► Incomplete Data being collected from virtually all patients at risk

► More people than ever at risk due to:

♦ COVID-19 and PASC

♦ Massive Stress, Anciety, 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

More Issues that Demand Population Health Equity and Diversity Satisfaction:

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 Tool for Social Health Change including Policy and Practice (not only "research")**

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

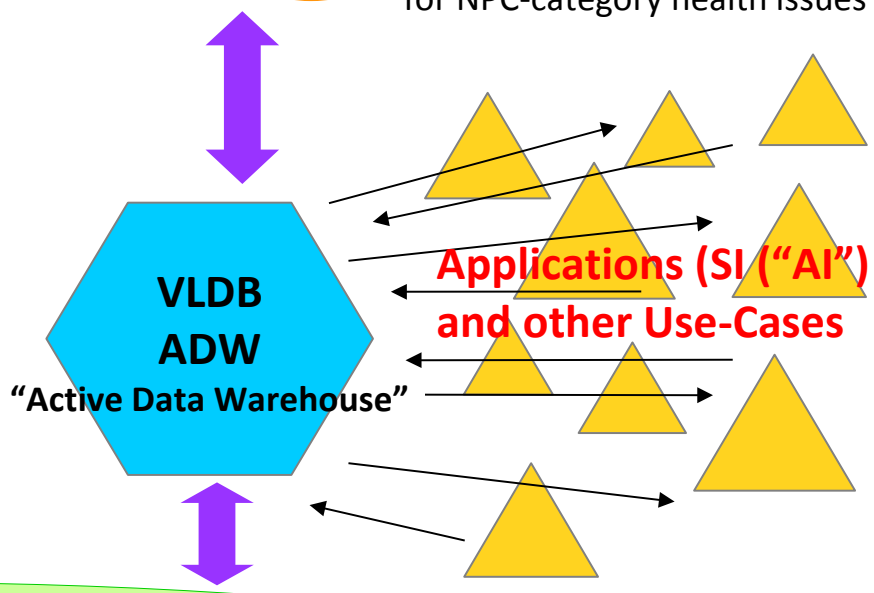
[2] Assist genomics-focused research "across the board"

[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

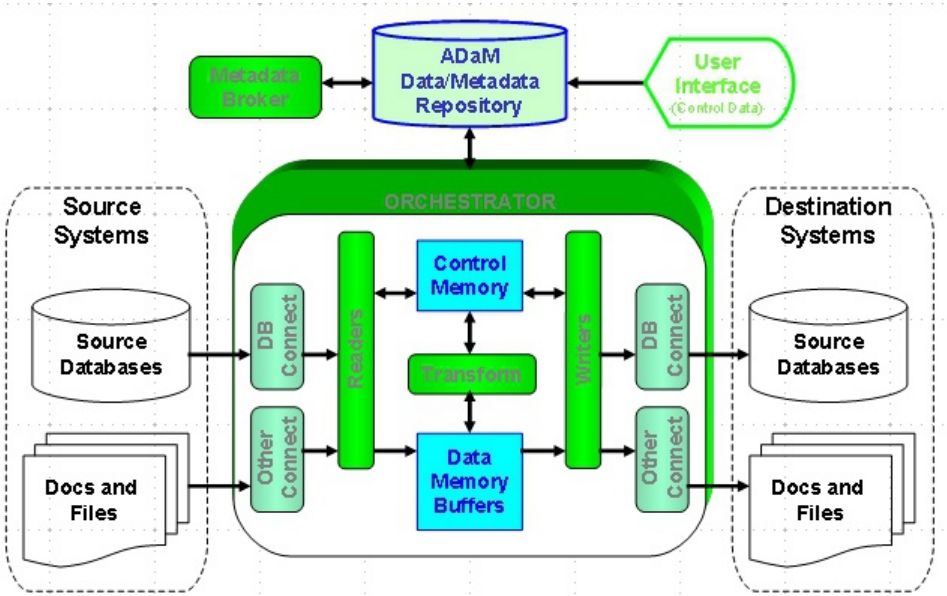
Focus upon Classes of Populations considered to be (known/definite → potential-at-risk) for NPC-category health issues



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? □ □ □

ADAM and EVE



AdaM – Active Data Mover – a VLDB Engine

<u>GOAL with PHEBR</u>:
Adapt EVE logic (Bayesian + NN pattern detection) to task of seeking and identifying patterns within massive data streams of clinical-origin patient medical histories for:

♦ Indicators of risk conditions and causal relations on the basis of acquired data sets in PHEBR

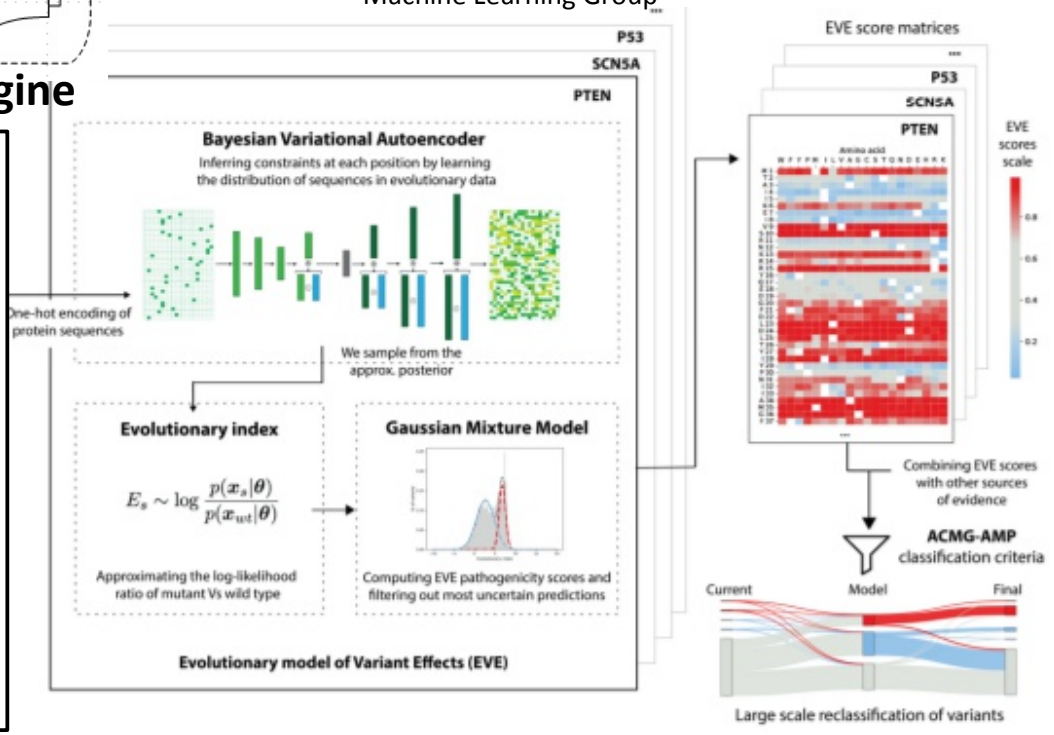
♦ Missing-gaps - types of data to pursue and collect through future clinical measurements (e.g., behavioral, lifestyle)

♦ What-Ifs and Hypotheticals pertinent to NpC for investigation and evaluation and linkage with genetic modeling systems like EVE (HMS/OATML)

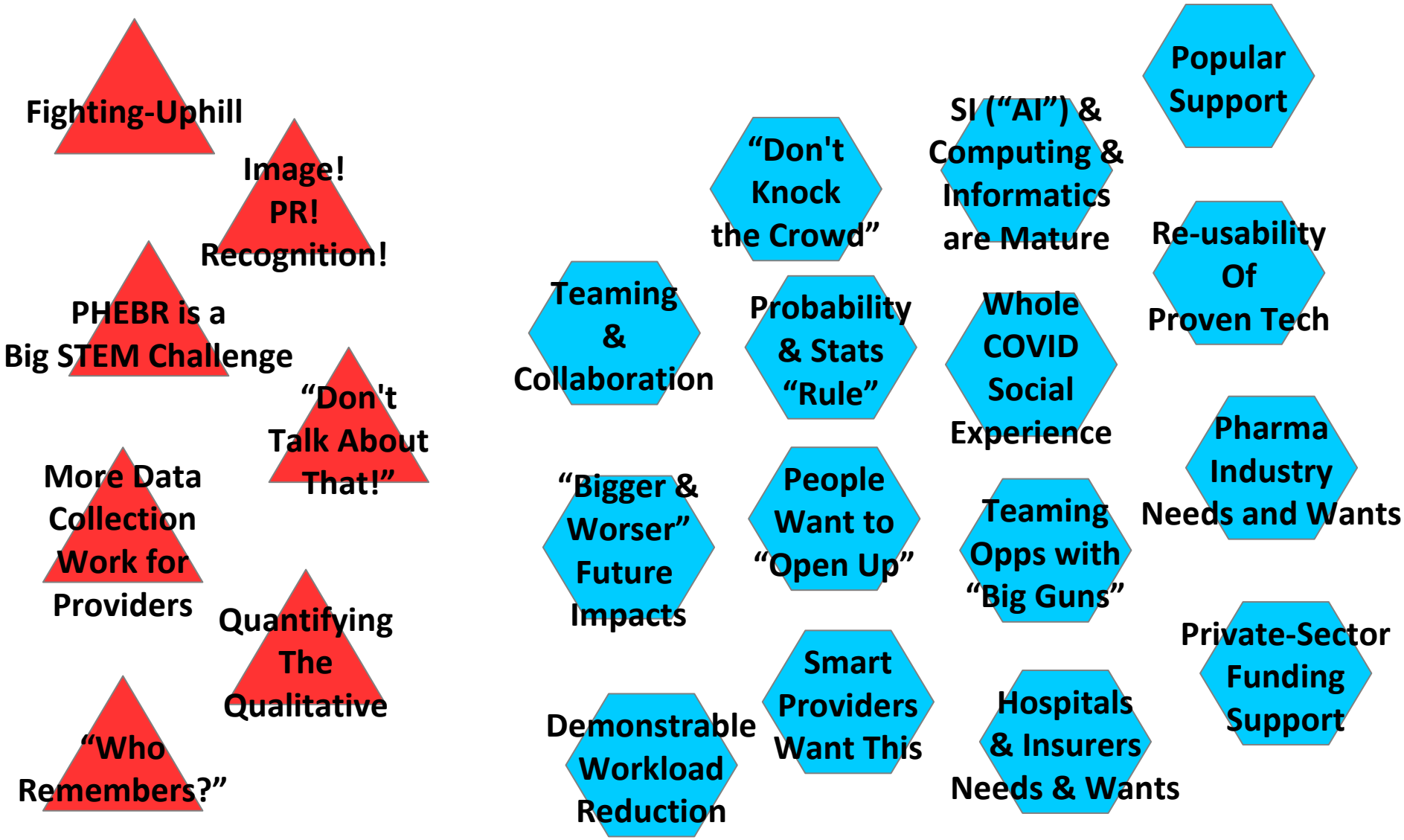
eve

evolutionary model of variant effect

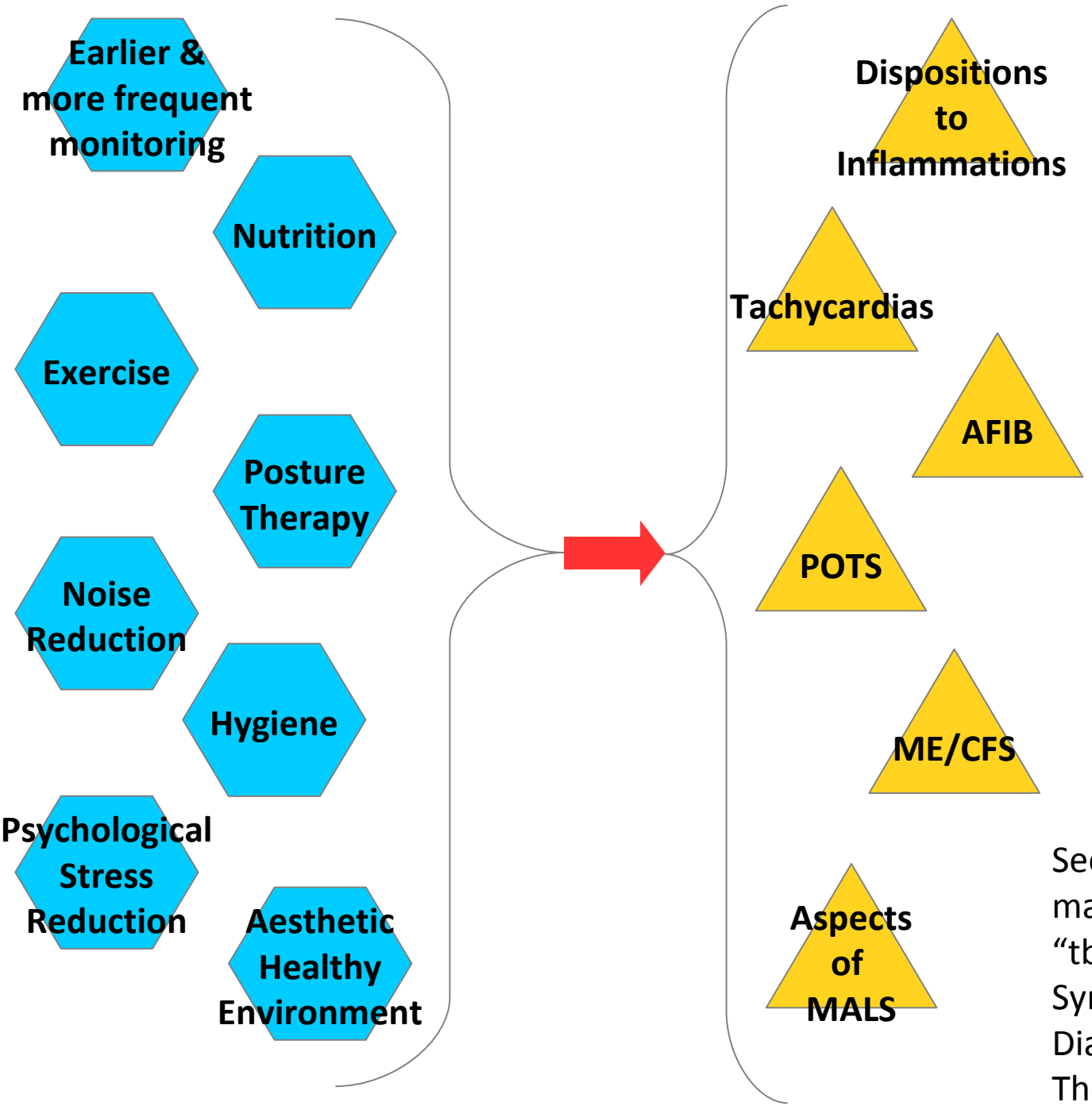
Marks Lab - Harvard Medical School
OATML - Oxford Applied and Theoretical Machine Learning Group



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



6 - Implications and objectives for future new diagnostics and therapeutics:



Diagnostic and Therapeutic Directions

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Reduction of the Stressor Agents (not here addressing pharmaceuticals and surgeries)

See more written in the major "synopsis" document, "tbd-ances-framework-Synopsis...", in sections on Diagnostics and Therapeutics
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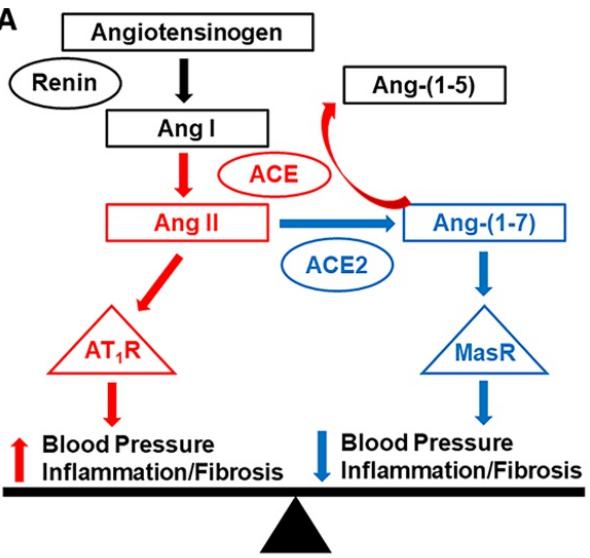
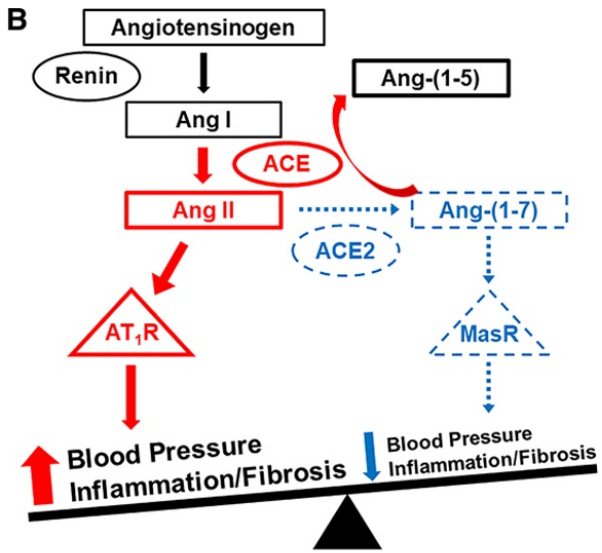
Relevant particularly to COVID and PASC and NpC consequences especially in cardio-pulmonary comorbidities:
Key dynamics of Ang I → Ang II and with ACE2 → Ang-(1-7).

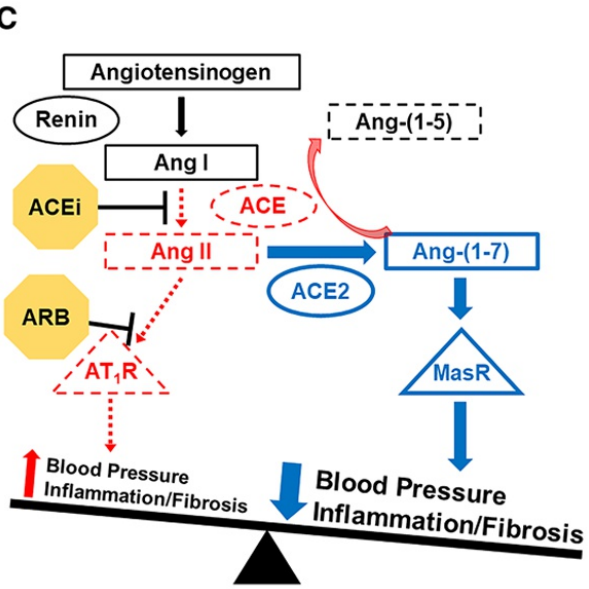


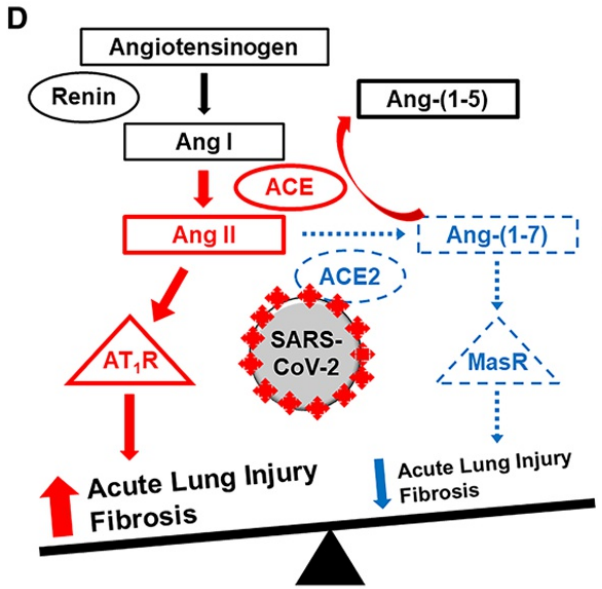


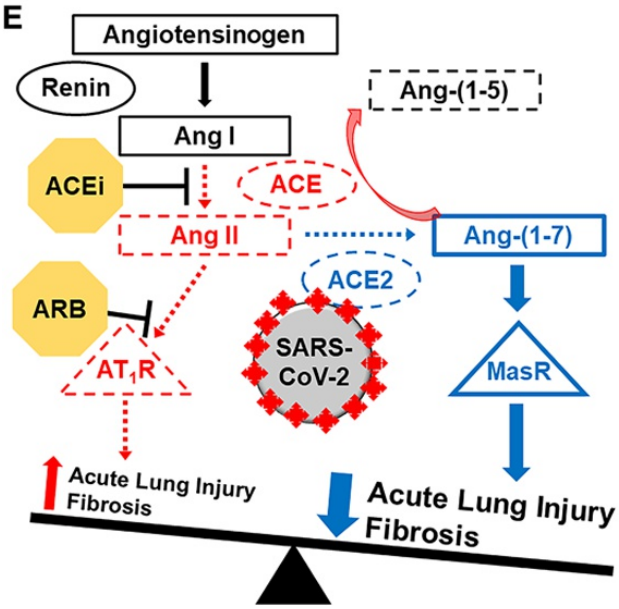
Changes in these pathways due to the SARC-CoV-2 virus itself and also due to medications given to patients –

and also in the case of patients who are regularly taking various blockers as part of, for instance, a cardiovascular regimen -

can be influential in detrimental ways for the outcome of serious comorbidities and life survival after COVID-19.







(from South, Brady, & Flynn [4])

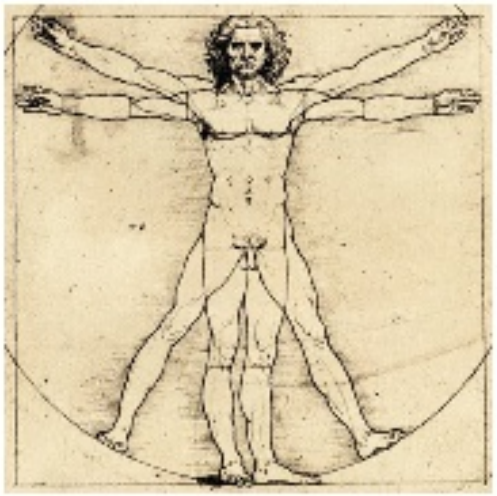


Figure 36 – Two views of wholeness and balance in mind-body [ee]

WHOLE-system dynamics
Can positively change small parts!

We are talking about
Increasing Harmonics and
Reducing Dissonance

Like in an orchestra (for instance!)!

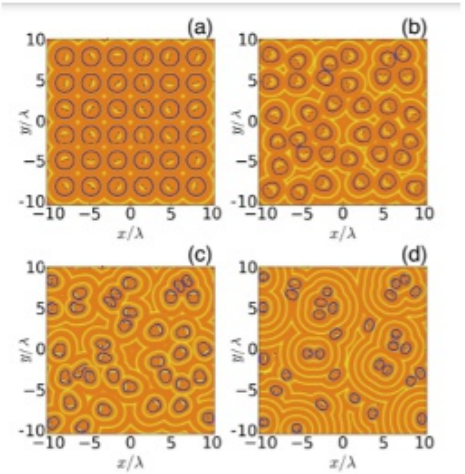
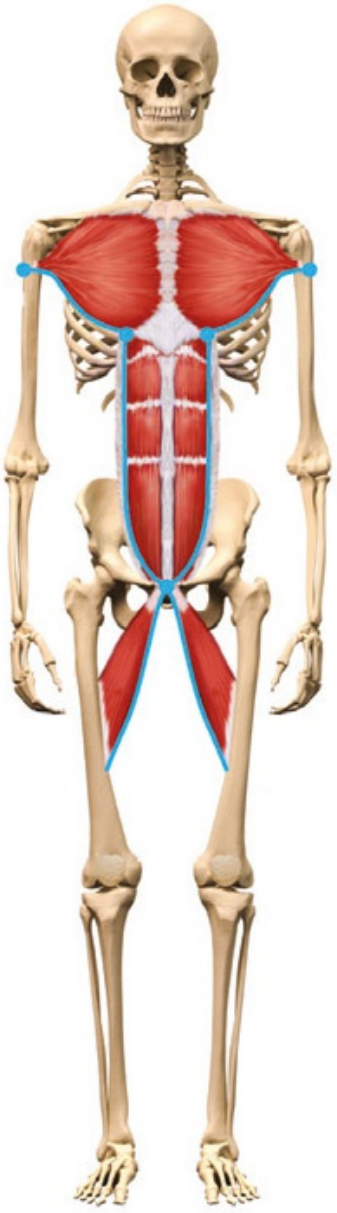
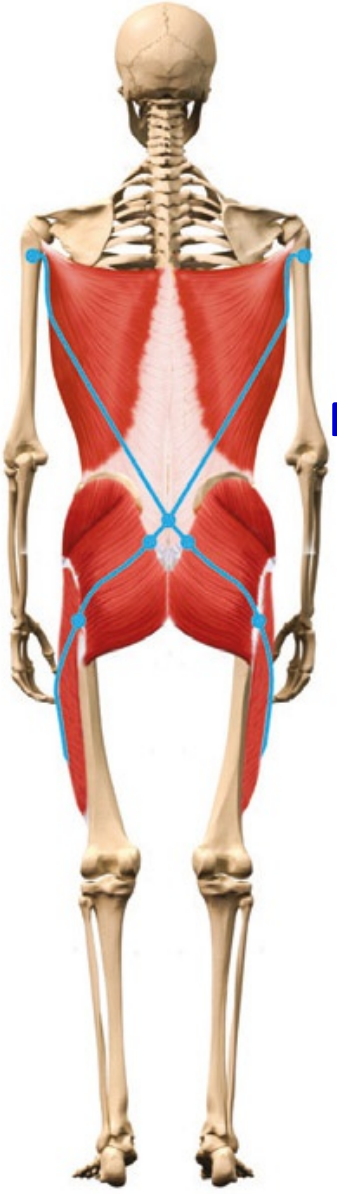


Figure 34 – Evolution of a colony of threaded rings [cc]

Figure 35 – Water Surface with interference patterns [dd]



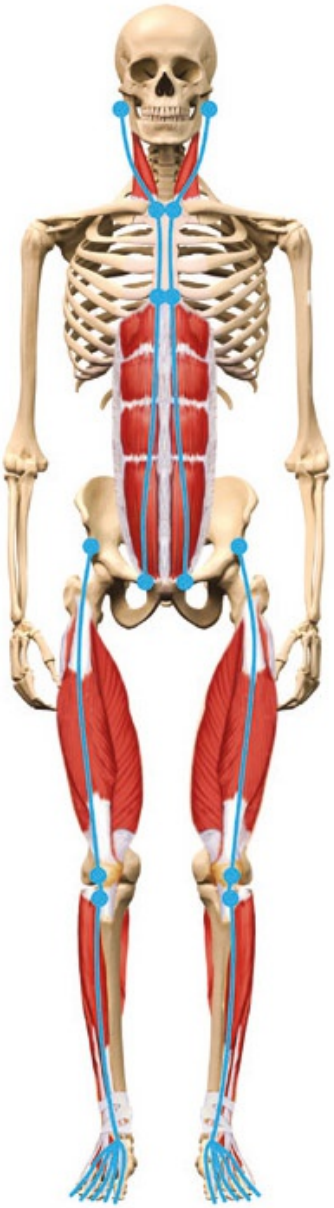
SUPERFICIAL FRONT LINE



SUPERFICIAL BACK LINE

Don't Forget About Me And All our Moving Parts!

LATERAL LINE



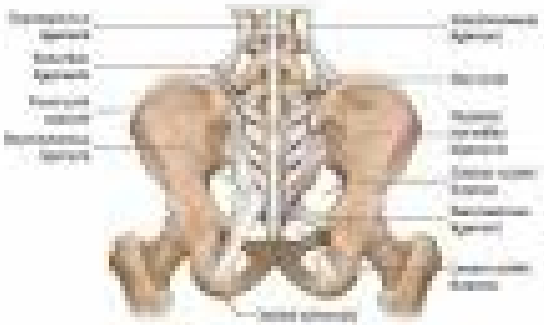
DEEP FRONT LINE

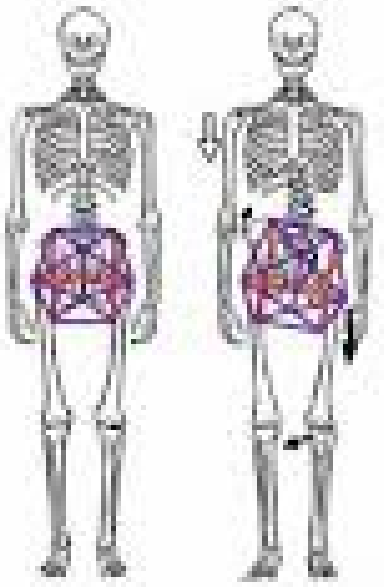
Watch how we all walk, sit, sleep,
How we sit while and after we eat.
Remember that the Body is a Complete Unified System.
All that Connective tissue, and the skin, and the “non-organ stuff” that “holds us together” is *also* fully alive with neurons and is an Intricately-engineered, delicately-balanced

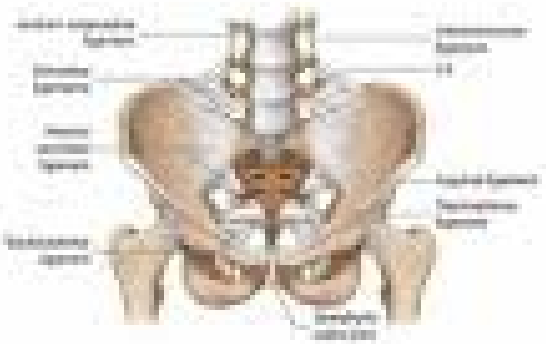
BioMechanical System

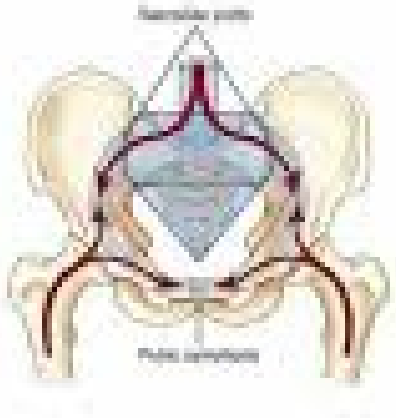
that Obeys Newton's Laws!

Gravity and Mechanics Rule!









7 – Conclusions:

- Things are more connected and interdependent than most of us thought.
- Inflammation has different forms and processes with more complex causal chains.
- Autoimmune reactions start long before immune system gets active and responds.
- Arrhythmia is a concern not only in the heart muscles and not only in the CV system.
- Chronic stressor inputs are real, ubiquitous and many are unavoidable.
- Chronic stressors are tightly coupled with lifestyle and habits.
- Genetics and epigenetics can help us to understand the "Who" and "Why Not" about many aspects of these NpC conditions.
- Understanding NpC type of underlying "inflammatories" can help with other "mainstream" inflammations (e.g.,from infectious diseases).
- COVID-19 has amplified the whole problem of autoimmune and arrhythmia for multiple generations.
- EVE and tools in SI ("AI") and VLDB can help to rapidly build multi-value PHEBR

Next Steps Now

- Establish serious, solid, substantive Collaboration, Teaming, Joining, Committing
- Funding – multiple open doors Now, especially
- Use our combined special strengths and skills, institutional and especially personal
- Get some Visibility as a multiinstitutional, multi-national Team serving People.

Team Members, Collaborators, Advisors, Assistants:

Tae Chung, Taylor Bopp, and the Chang Lab and Clinic at JHU
Svetlana Blishtyin at SUNYAB/Amherst
Daniel Lee and his Lab at NYU
Jessica Eccles and her Lab at Brighton U
David Goldstein at NLHBI @ NIH
Lauren Stiles at Dysautonomia International

-- and --

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Diana Goncharev
Rachael Csensits
Cheryl Sandburg
Patrick Ellis
Ottorino Ori
Jian Ming Tang
Stuart Hameroff

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Thank You!