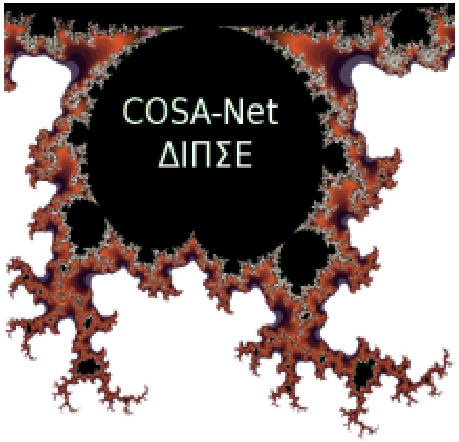
25 Θερινό Σχολείο-Συνέδριο

"Δυναμικά Συστήματα και Πολυπλοκότητα"

ΕΚΕΦΕ "Δημόκριτος" Αθήνα, 9-17 Ιουλίου 2018



Complexity in Medical Informatics

Καθηγητής Παναγιώτης Βλάμος,
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Εργαστήριο Βιοπληροφορικής & Ανθρώπινης Ηλεκτροφυσιολογίας

Current & Potential Needs

- Need to provide efficient, individualized and affordable medical care.
- Accordingly, if we are to keep up with medical progress and promote technological and organizational innovation, modern information technologies are urgently needed.
- The interface between medicine, information science and society involves any number of varied, fascinating and responsible assignments and, at the same time, calls for a large number of well-trained and qualified experts.

What is Medical Informatics?

- encompasses both methodological developments and software engineering for diagnosis and treatment.
- promotes simulation and modelling for increasingly individualized medical care and the development of new procedures in the areas of e-health and telemedicine.

What is Medical Informatics?

- Medical informatics is found at the intersection of healthcare and technology. It is where skills in both medical and computer sciences come together in an effort to improve healthcare and patient outcomes. Professionals in this hybrid field draw on expertise from both disciplines to put technology to its best use in patient care, clinical and research settings.

The 4 Core Research Areas of Medical Informatics

- Natural Language Processing
- Precision Medicine
- Wearable technologies
- Virtual & Augmented Reality

Natural Language Processing

- is designed to derive meaningful and actionable data from freely written text.

- continues to be refined and provides countless benefits.

- Through effective NLP, health care professionals are doing more than saving time. They are communicating more effectively, identifying crucial data, and pushing the boundaries of health care forward.

Precision Medicine

- The healthcare IT field, and world in general, is full of hot trends and buzzwords. One important and popular trend that is continuously gaining more traction is the practice of “precision medicine.” Advances in health care research and the industry as a whole have led to more providers and hospitals utilizing precision medicine treatments.

Wearable technologies

- In 2016, we were no longer limited to a few options in terms of smart watches. Most first generation designs have since been replaced by second and third generation versions with many improvements. As the market for wearable devices grows, we will more than likely find more wearable smart devices clinging to our bodies.

Augmented Reality

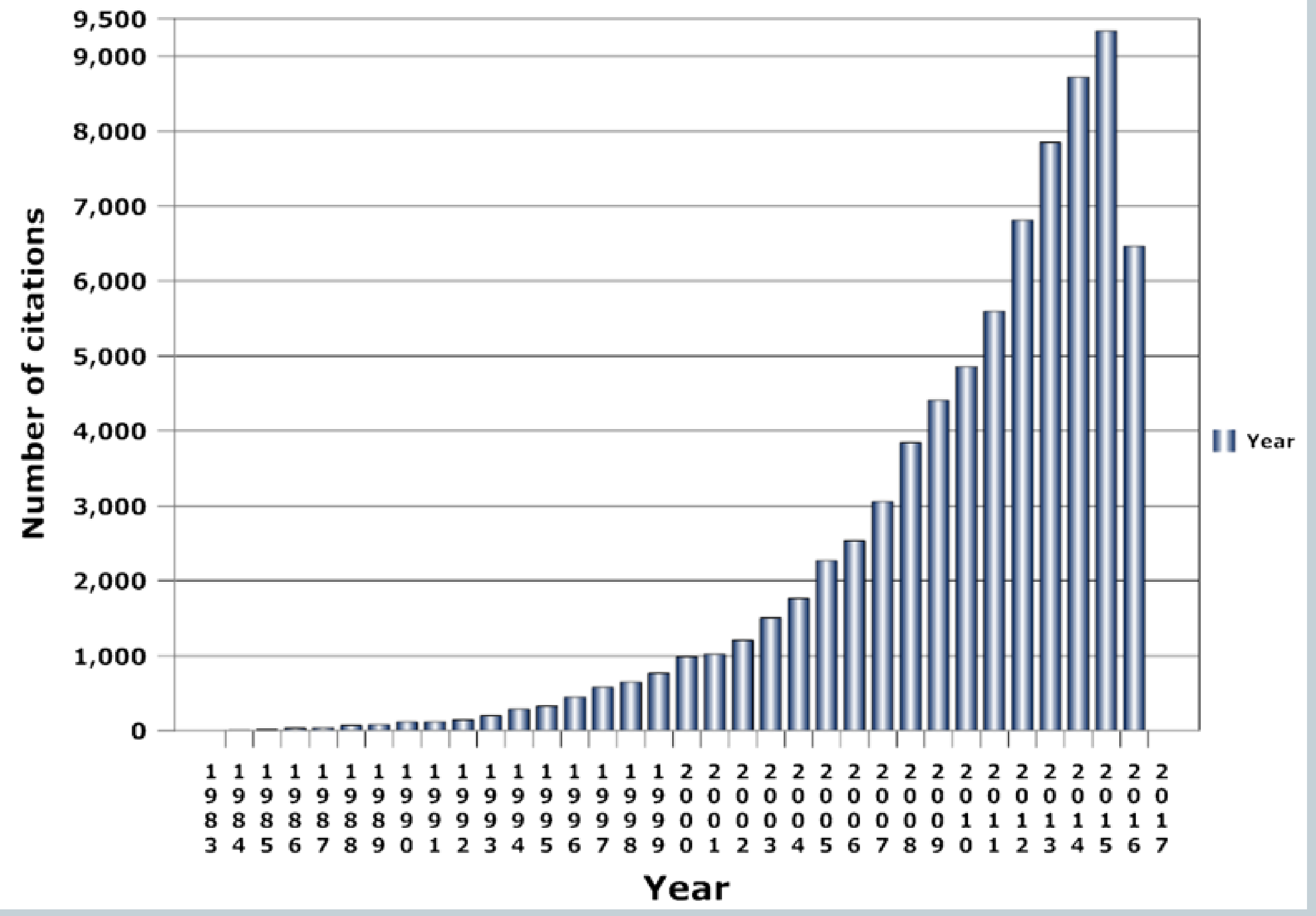
- Virtual and augmented reality (VR and AR, respectively) has been an area of intrigue for some time now. Initially it was little more than a novelty but, the technology is improving by leaps and bounds. Naturally, its practical applications have also including everything from improved physician training, to pain management.

Virtual reality

- As this technology is further refined and more widely adopted, there is massive potential for truly revolutionized care.

- Apart from these areas, research work is being carried out in health mobile applications, artificial intelligence, health care big data analytics and large EHR technologies.

The distribution of the 100 top cited articles on Medical Informatics by Citations per year, Web of Knowledge



Nadri, H., Rahimi, B., Timpka, T. et al. J Med Syst (2017) 41: 15

Types of Work in Medical Informatics

- Creating, maintaining or facilitating new ways for medical facilities and practices to keep electronic health records (EHR),
- Improving communication between healthcare providers and facilities to ensure the best patient outcomes,
- Storing, managing and analyzing data for research,
- Assisting with complex, technology-dependent research, such as that involved in human genome sequencing.

Complexity

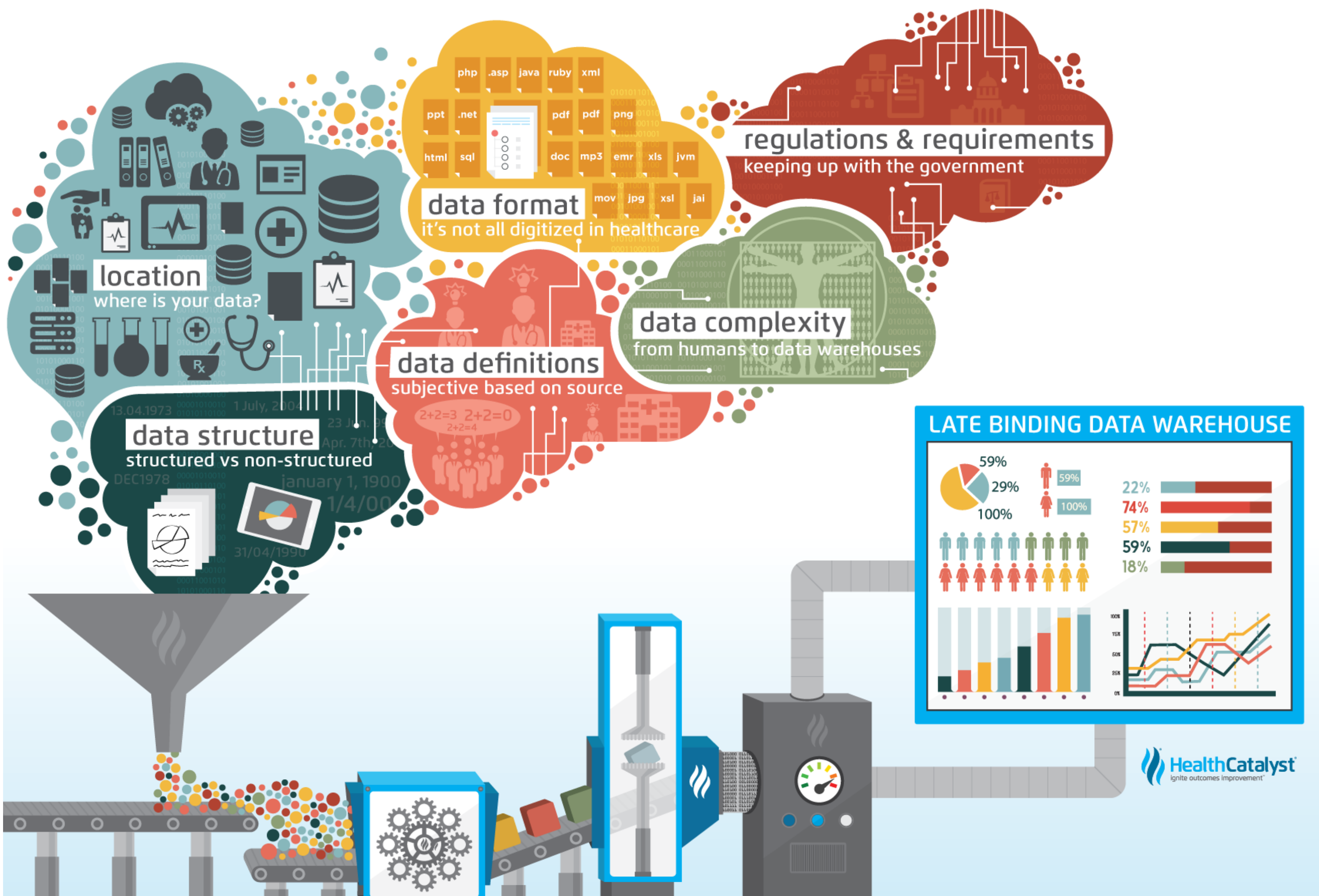
"Complexity is that property of a model which makes it difficult to formulate its overall behavior in a given language, even when there is reasonably complete information about its atomic components and their inter-relations".

Bruce Edmonds, Univ. of Manchester , 1999

Complexity

- These factors are having another very important effect, consisting of a very sharp increase of complexity:
  - available knowledge about diseases, diagnostic and therapeutic procedures,
  - the environment in which we work (health care levels, jurisdictions, management models),
  - multiple stressing forces (aging population, increasing number of chronic patients, sustainability of the system, legal regulation).
- All these elements are also reflected in the complexity of the information space in which we have to carry out our work as well as in the systems that we have to design and develop.

WHY HEALTHCARE DATA IS DIFFICULT



Time*	Stakeholders	Technical Focus	Objectives	Disciplinary Drivers	Breadth and Complexity
	Health system managers IT experts Health care organizations	Infrastructures Hardware Operating systems Databases	Managing clinical and organizational information (eg, billing, purchasing)	**Specialist** (eg, computer science, management)	
	Medical researchers Health professionals Support staff	Clinical administration systems Clinical decision support systems Medical imaging	Auditing practice Implementing procedures Supporting evidence-based practice	Clinical needs Policy needs Research drivers (eg, artificial intelligence, decision science, epidemiology, evaluation science)	
	Policy makers System vendors Patients General public Mass media	Electronic libraries E-prescribing, booking, etc Clinical email Internet-based health information/support Electronic consulting Mobile disease monitoring Health grids	Changing professional behavior Engaging clinicians Engaging patients and the public Supporting health self-management Protecting patient confidentiality and safety	Medicine, ethics, law, economics, business, sociology, social anthropology, psychology, information science, education science, policy studies, bioinformatics, e-science **Interdisciplinary**	

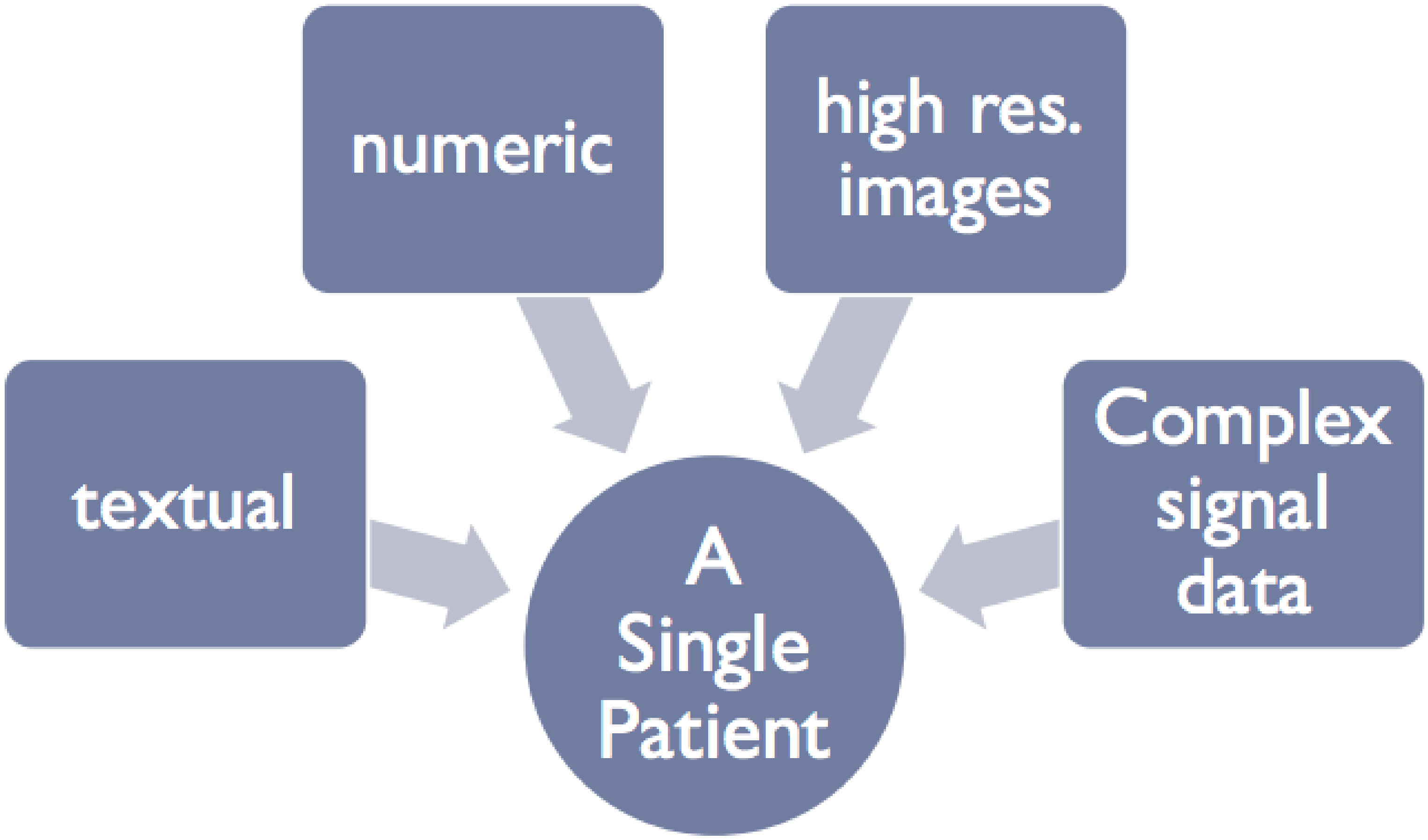
*Cumulative and not strictly chronological

Data Complexity

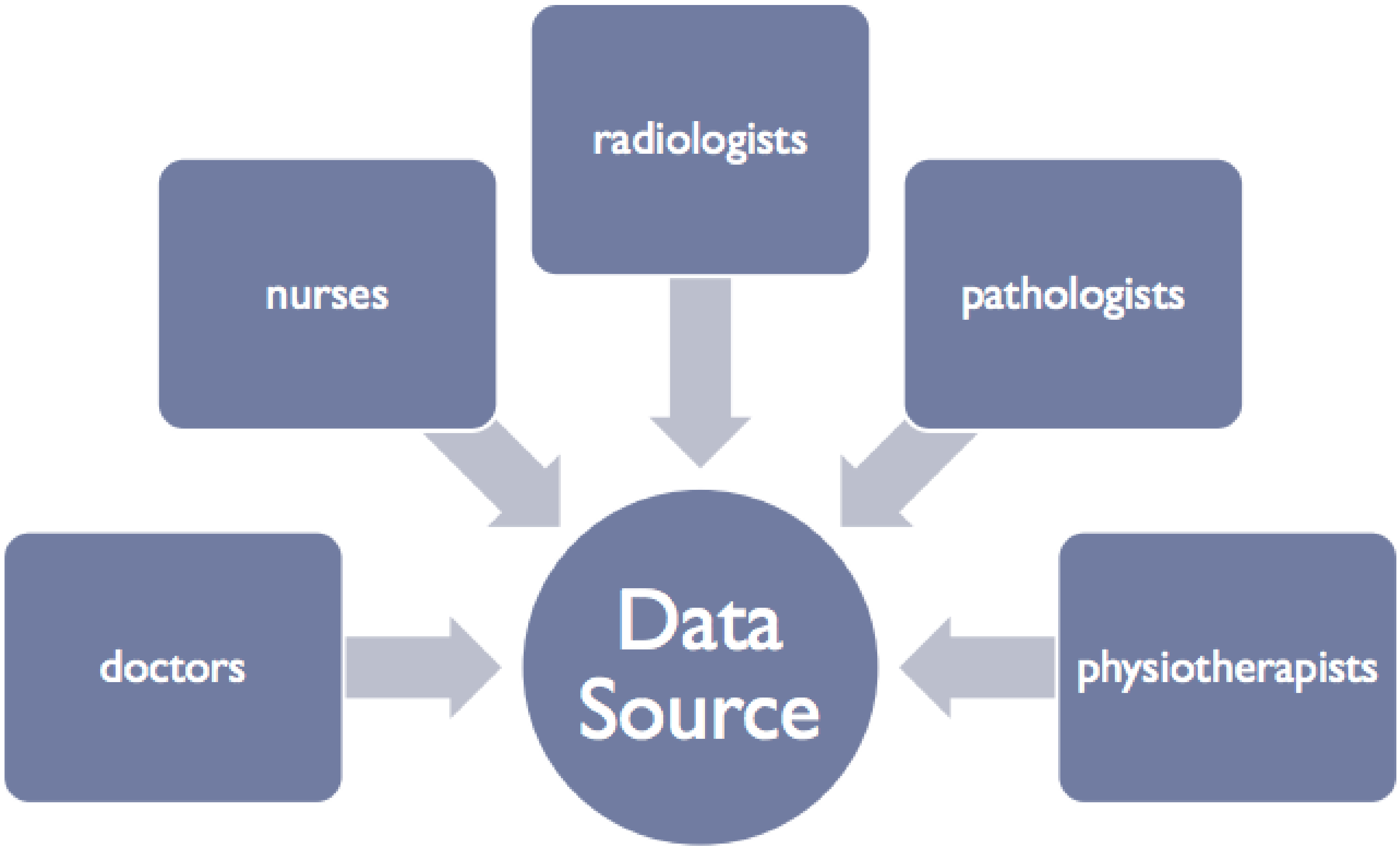
What to consider when electronic medical records are to be developed?

Data complexity!

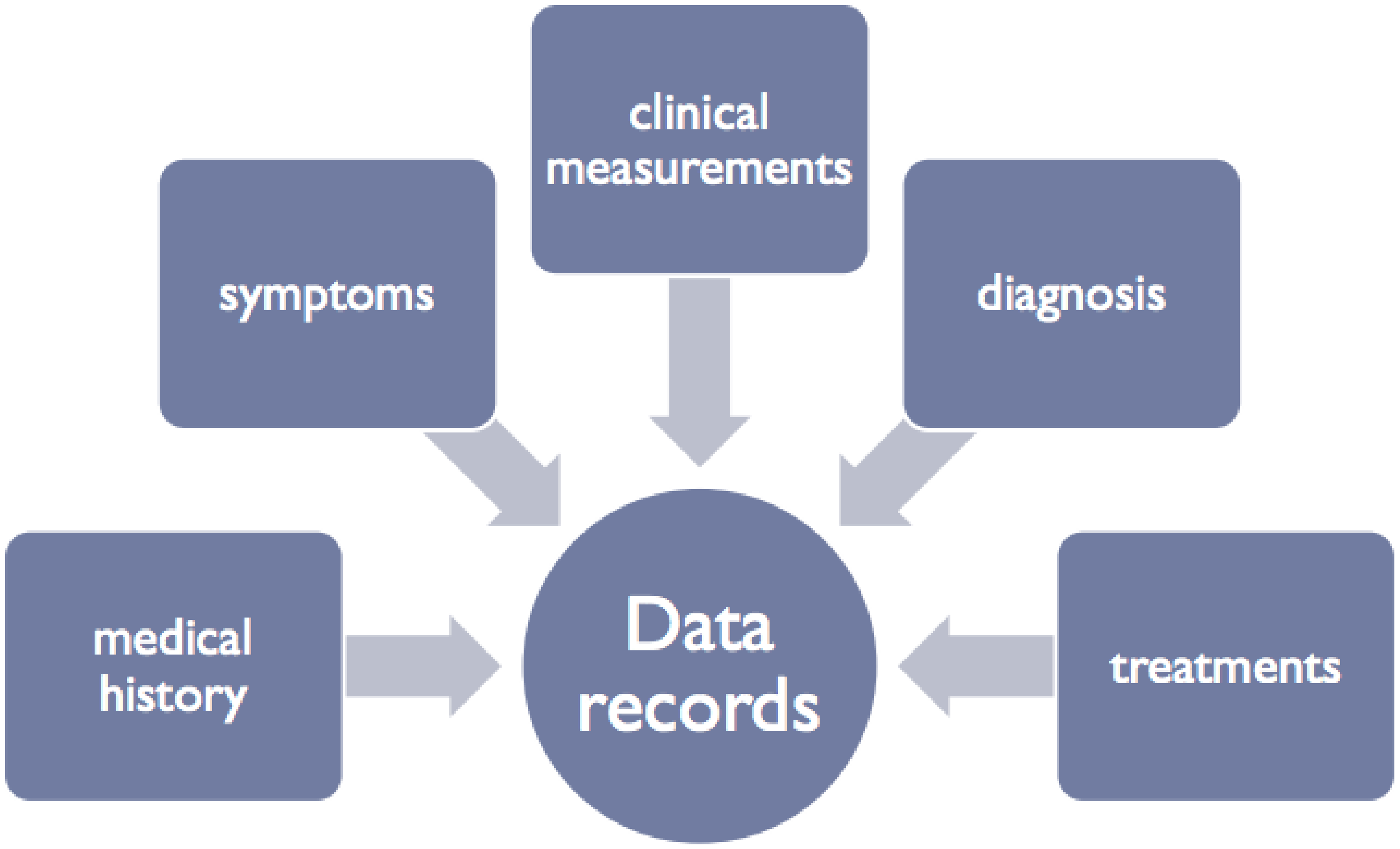
Complexity of health information: data types.



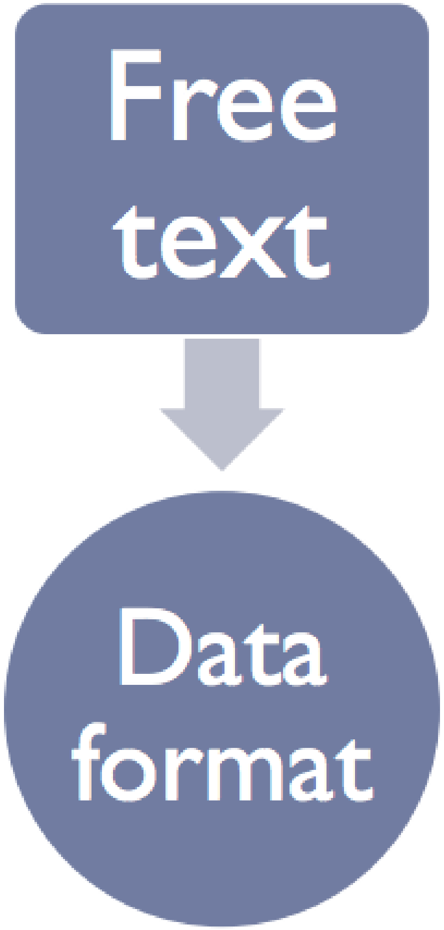
Complexity of health information: data sources



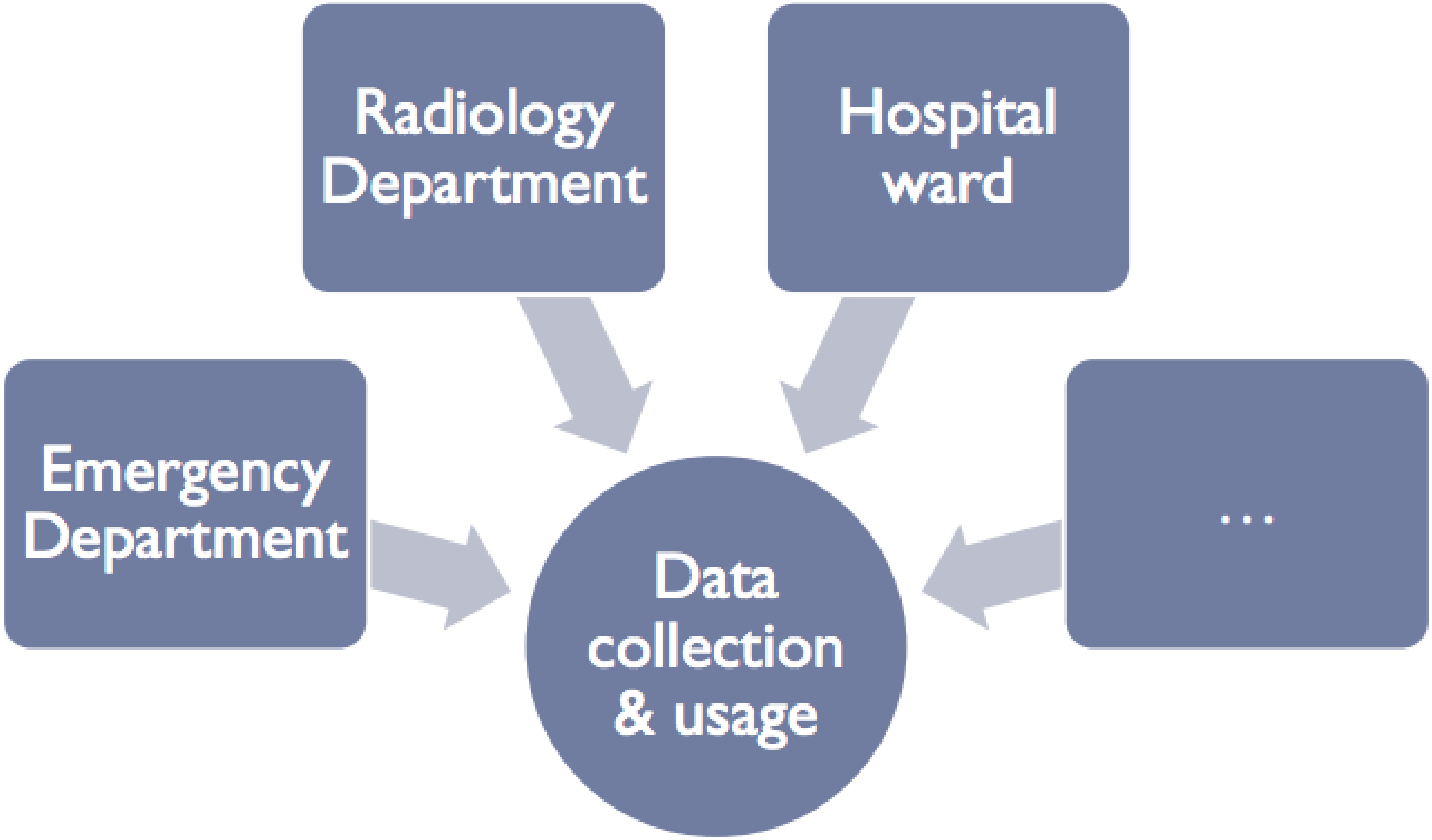
Complexity of health information: data records



Complexity of health information: data format



Complexity of health information: data collection and usage



Data Mining

- What is data mining?

  - Knowledge discovery in database (KDD)
  - Analyze large amount of data & identify hidden patterns and relationship among variables.

- What do we want to pay attention when applying data mining to medical informatics?

  - Applying data mining on stock market vs health informatics?
  - Safety issue & statistical relationship SHOULD NOT overrule clinical importance AND domain experts.
  - Other issue & data set size, missing data, etc.

Ethical Issue

- General Issues:

Patients records stored, transferred, and access from one location to another.

- Online Security
- Online Privacy & Confidentiality
- Human rights …

open questions:

- Data access control. (Can your parents access your record? Brother? Spouse?)
- Can a patient with mental problem access his own record?
- Should health professional obtain certification regarding ethical use of patients info.?
- How about information professionals? (U.S. currently only require to sign a Health Insurance Portability and Accountability Act (HIPAA) Agreement.

Medical informatics job growth

- Medical informatics job growth is predicted at about 21% through 2020, (U.S. Bureau of Labor Statistics)
- mid-range salaries for health informatics consultants in the upper $80,000s. Those in management circles can see salaries climb as high as $200,000 (American Health Information Management Association (AHIMA)

Challenges in Medical Informatics

Initial Cost

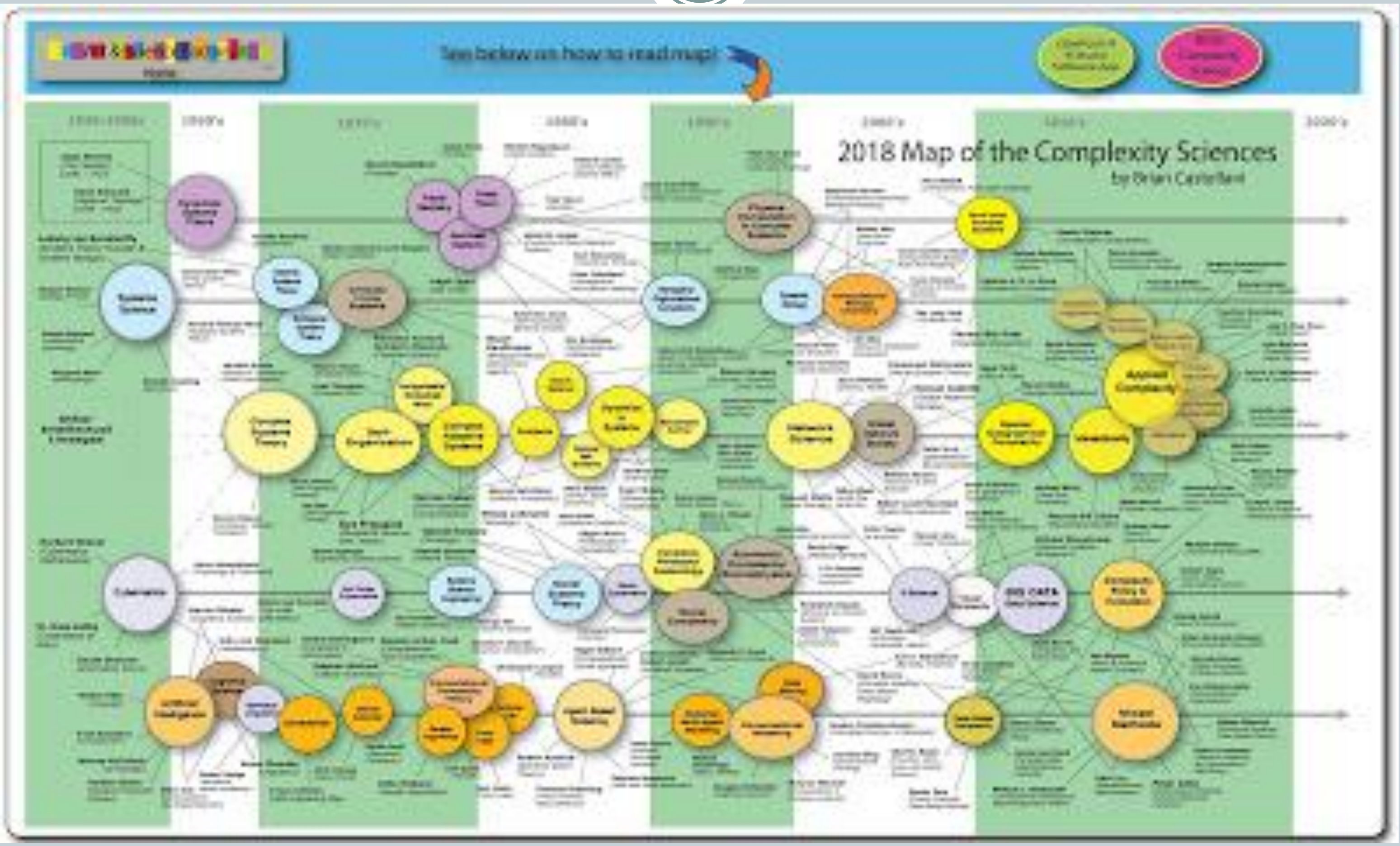
Health Professionals and Managers:
comfortable with current methods.

ICTs systems in place:
(further problems)

Incorrect data entry → training

Not trusting the system → have health
professionals involve designing the system.

2018 version of the map of the complexity sciences

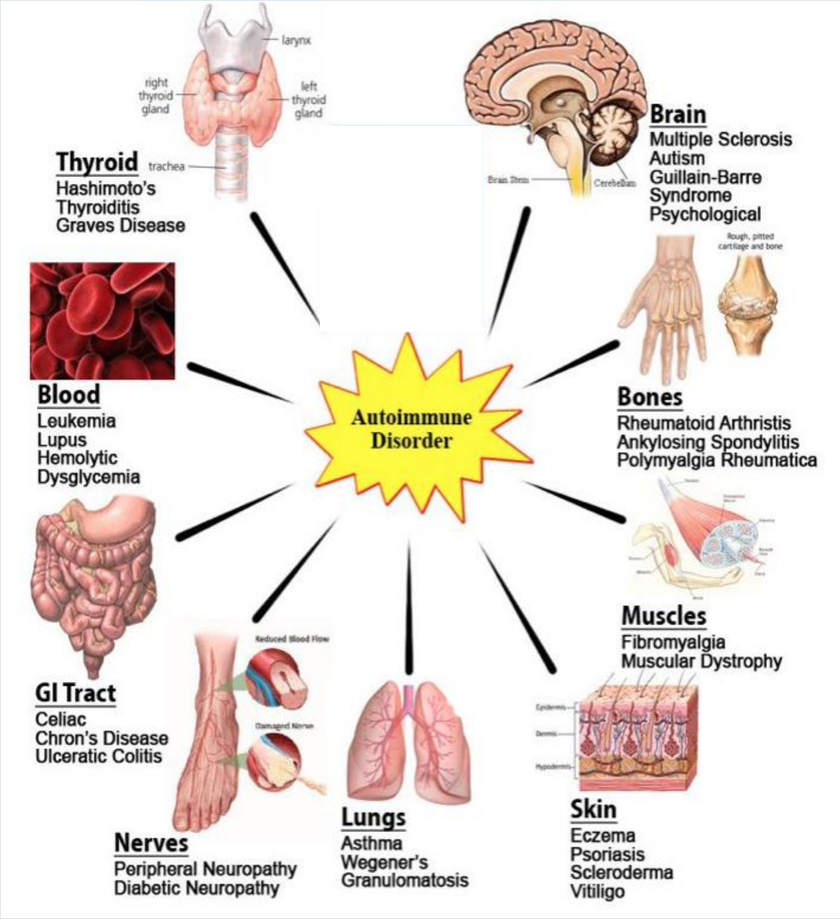


http://www.art-sciencefactory.com/complexity-map_feb09.html

Autoimmune diseases : an unexpectable threat

- Human autoimmune diseases (AD) occur frequently (affecting in aggregate more than 5% of the population worldwide), and impose a significant burden of morbidity and mortality on the human population.

- Autoimmune diseases refer to problems with the body's natural defense system, which usually fights off viruses, bacteria and infection. The problem causes your immune cells to attack your body by mistake. These cells can't recognise the difference between your own cells and foreign cells, causing the body to mistakenly attack normal cells.



Most known Autoimmune diseases

1. **Rheumatoid arthritis**, a form of arthritis that attacks the joints

2. **Type 1 diabetes.** The pancreas produces the hormone insulin, which helps regulate blood sugar levels. In type 1 diabetes, the immune system attacks and destroys insulin-producing cells in the pancreas.

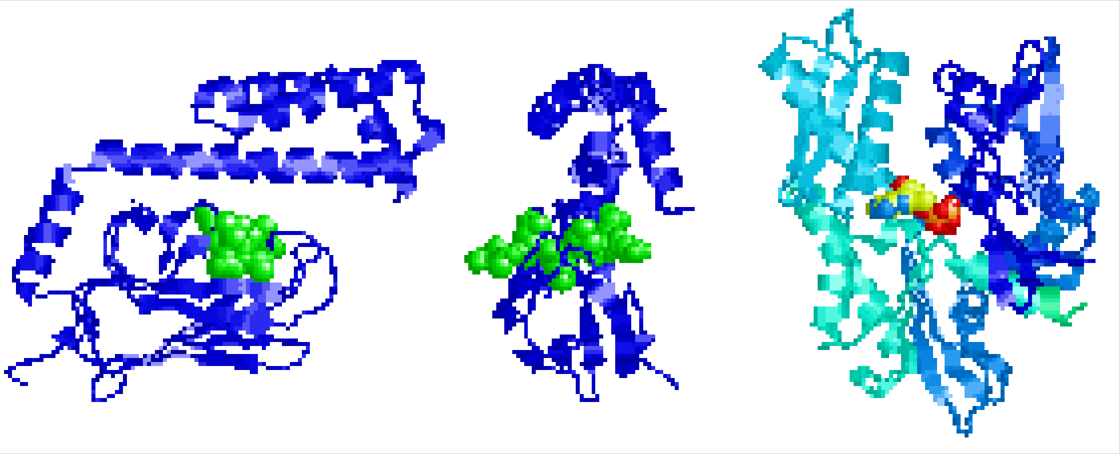
3. **Psoriasis,** a condition marked by thick, scaly patches of skin

4. **Lupus,** a disease that damages areas of the body that include joints, skin and organ

5. **Thyroid diseases**, including Graves' disease, where the body makes too much thyroid hormone (hyperthyroidism), and Hashimoto's thyroiditis, where it doesn't make enough (hypothyroidism) of the hormone

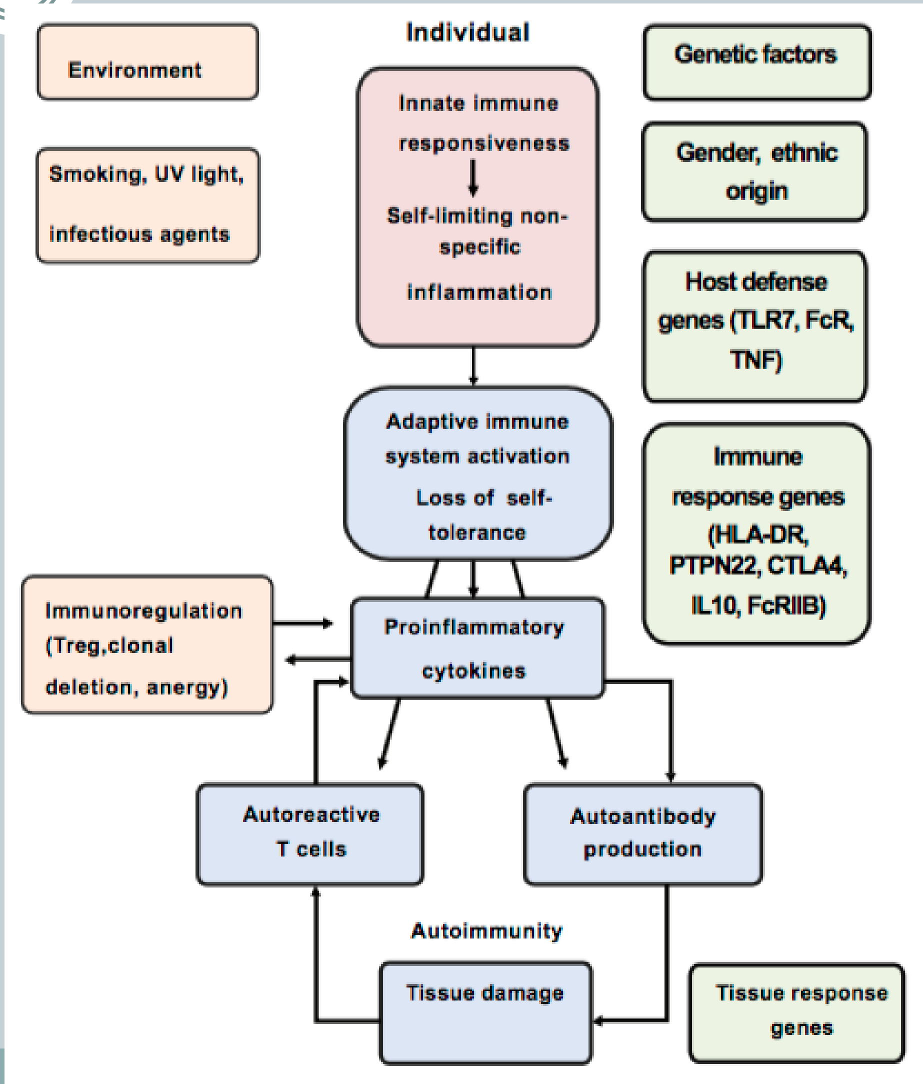
Less known Autoimmune diseases

1. **Sickle Cell Anemia Carrell and Lomas**
2. **Creutzfeldt-Jacob Syndrom**
3. **Cystic fibrosis**



Pathways influencing the development and perpetuation of autoimmune diseases

- **Build the network of interactions**
- **Generate data**
- **Determine the differences that exist between the normal (healthy) and disease networks**
- **Test these hypotheses.**
- **Update the network structure and restart the loop.**

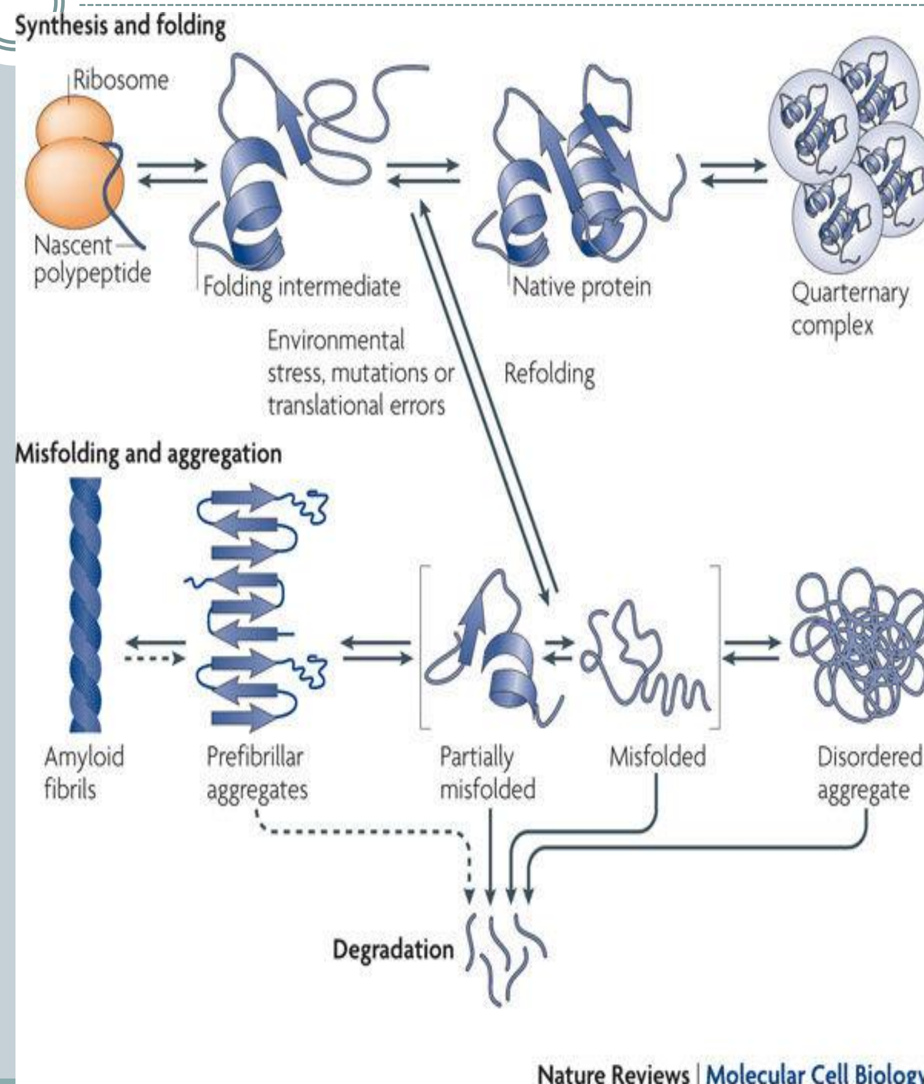


Pathways influencing the development and perpetuation of autoimmune diseases

- **Disordered proteins:** Denatured proteins, natively disordered or misfolded proteins can trigger immune responses against self-proteins.

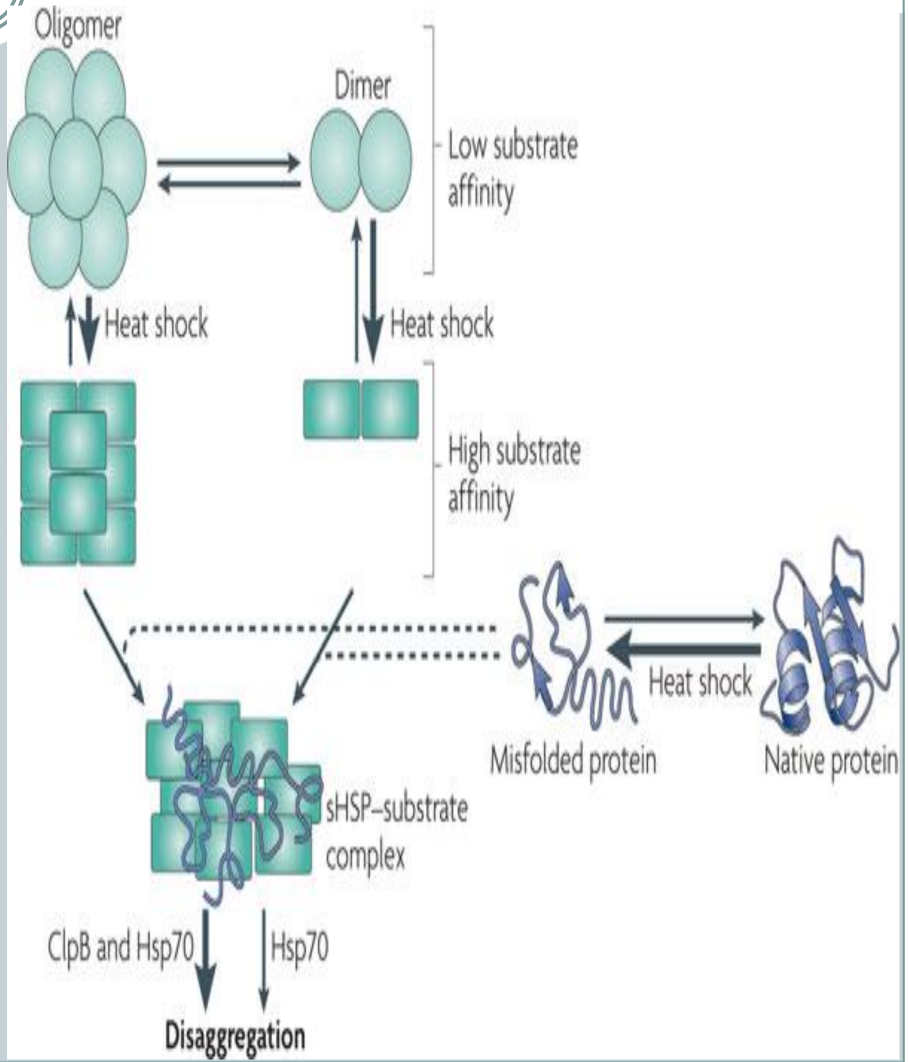
- Misfolding produces molecular species that have incorrectly- formed three-dimensional structures.

Nature Reviews Molecular Cell Biology **11**, 777–788 (2010)



A Heat-Diffusion process

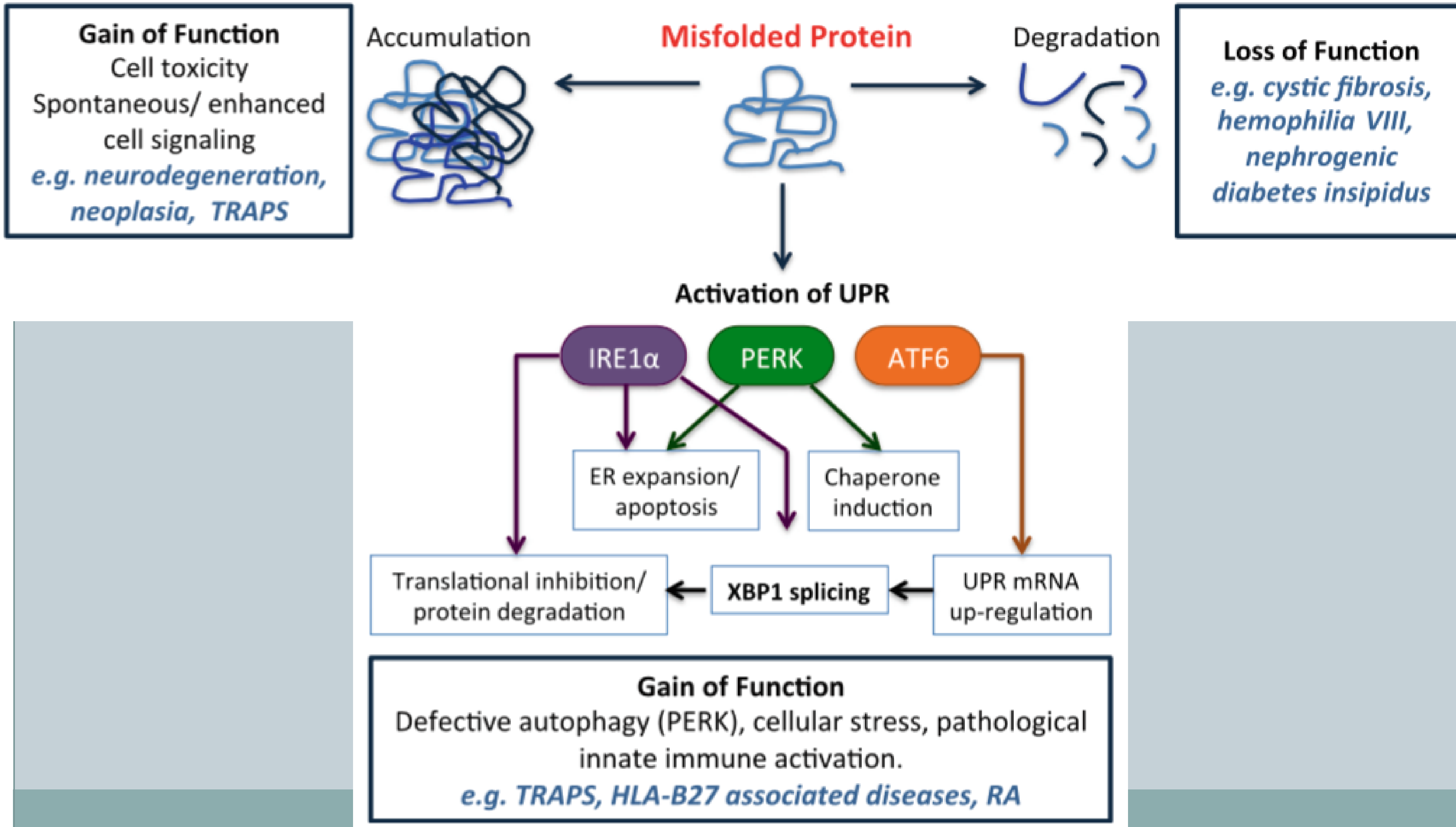
- Heat-shock proteins and other molecular chaperones assist the correct folding, stabilization, and translocation of proteins.
- Defects in the function or expression of heat- shock proteins and other molecular chaperones might play a causative role in the stimulation of autoimmunity.
- Antibodies against heat-shock proteins have been found to recur in ADs. Such autoantibodies can interfere with the ability of heat-shock proteins to effect their function in protein refolding.



Effects of protein misfoldings

- Effects of protein misfolding that can lead to disease.
- Misfolded proteins are potentially highly dangerous and may accumulate leading to cell toxicity or inappropriate/excessive cell signaling.
- Cells therefore attempt to restore protein homeostasis by activating one or more of three major branches of the UPR; IRE1a, PERK, and/ or ATF6; which regulate genes involved in protein production, degradation, and/or refolding. Failure of these mechanisms often results in cell apoptosis; however, chronic UPR activation may promote pathological innate immune activation and defective autophagy.
- Key: TRAPS tumor necrosis factor receptor-associated periodic syndrome, IRE1α inositol- requiring enzyme 1-alpha, UPR unfolded protein response, PERK protein kinase-like endoplasmic reticulum kinase, ATF6 activating transcription factor 6, XBP1 X-box binding protein 1, HLA-B27 human leukocyte antigen B27, RA rheumatoid arthritis

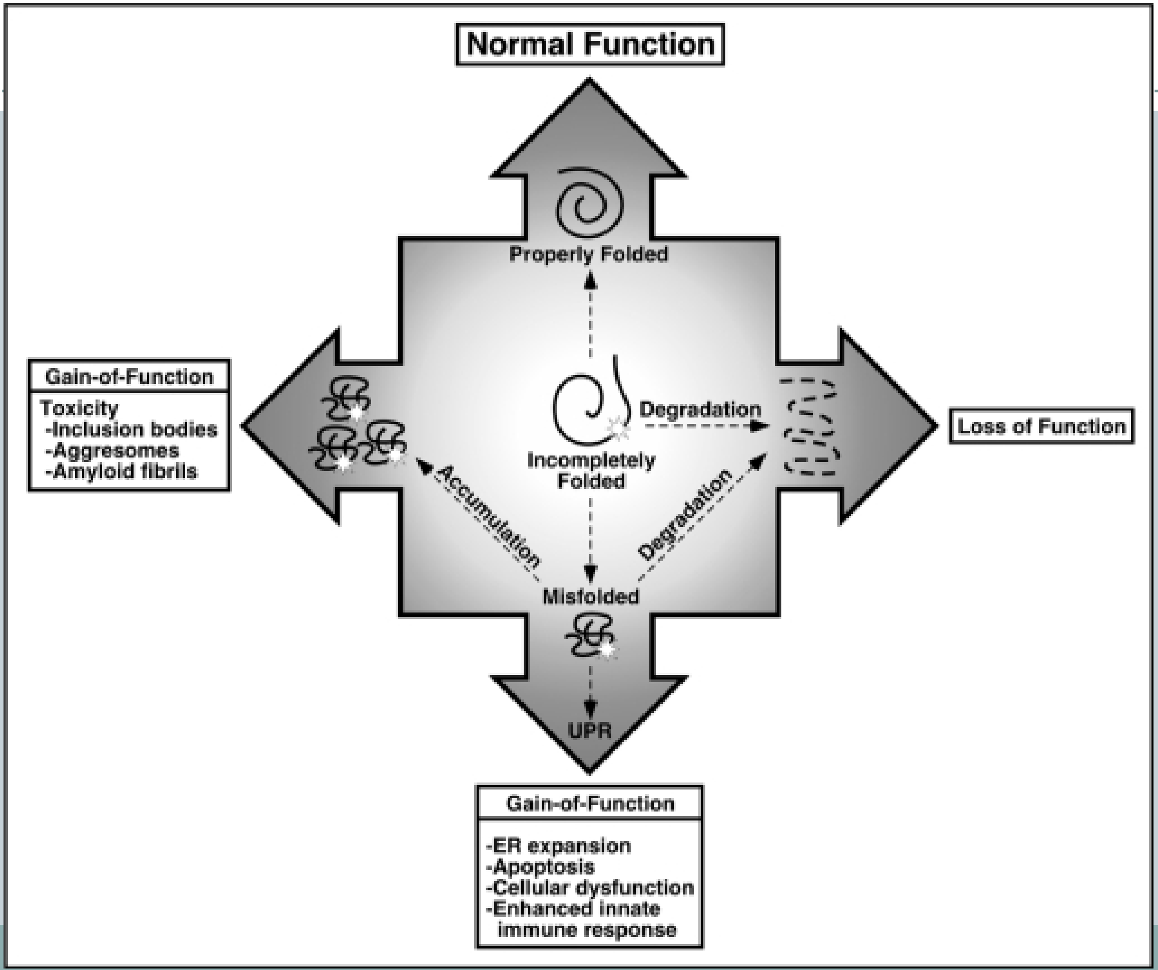
Effects of protein misfoldings



Consequences of protein misfoldings

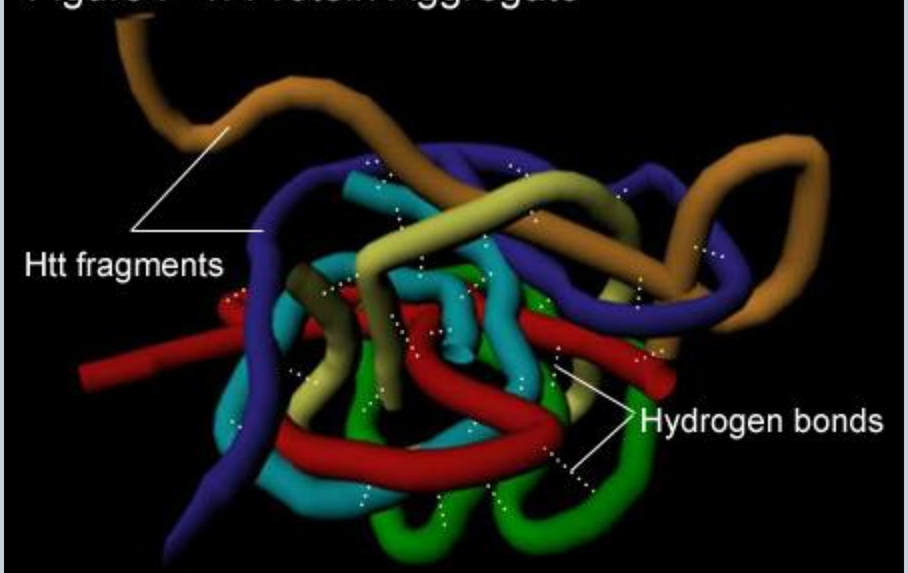
- Proper folding of newly synthesized proteins is critical for normal function.
- Protein misfolding has been linked to a number of diseases that can be broadly categorized as loss-of-function or gain-of-function.
- Loss-of-function phenotypes result from destruction of partially folded or misfolded proteins by elaborate quality control processes.
- Gain-of-function phenotypes can result from toxicity if the gene product accumulates and/or activation of cellular stress response pathways such as the UPR. HLA-B27 misfolding is hypothesized to result in gain-of-function abnormalities through sensitization of immune response cells such as macrophages to other exogenous stimul

Consequences of protein misfoldings



Unexpected results : TranslaTUM - DFKZ

EXISTING TYPES OF CANCER ARE CAUSED BY PROTEIN MISFOLDING!!!



A protein aggregate is a tangled, rigid grouping of altered huntingtin protein fragments (Htt's). Amino acids are represented as tubes. The hydrogen bonds between Htt fragments link them together.

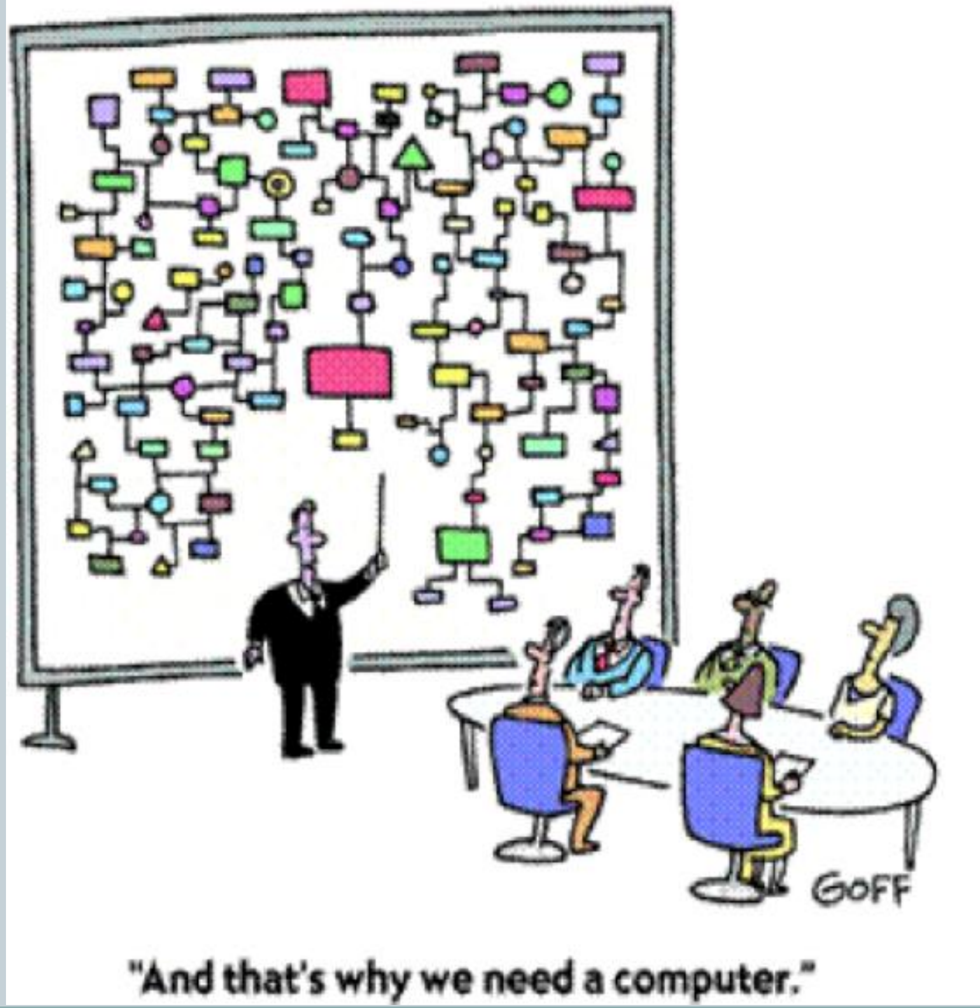
Up to now sophisticated attempts

- **Ssgs Algorithm : puzzle of proteinic structures**
- **Building blocks of proteins**
- **Cutting proteins**

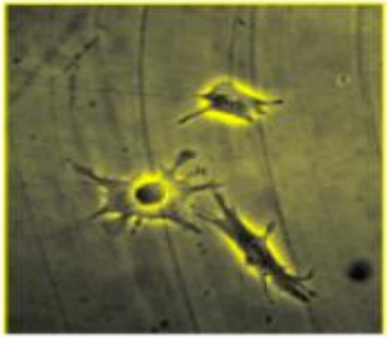
- **Biotechnology approach**
- **Biological Mechanism completed in 5-10 msec**

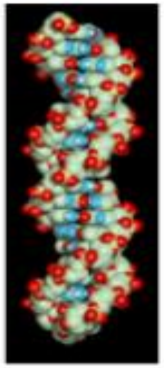
- **Bioinformatics approach : protein structure prediction**

- **Technological approach : JPK Force Robot**



Integration vs Reductionism





The driving force in 20th century biology has been reductionism:

From the population to the individual
From the individual to the cell
From the cell to the biomolecule
From the biomolecule to the genome
From the genome to the genome sequence
With the publication of genome sequences, reductionist biology has reached its endpoint

The driving force for 21st century biology will be integration:

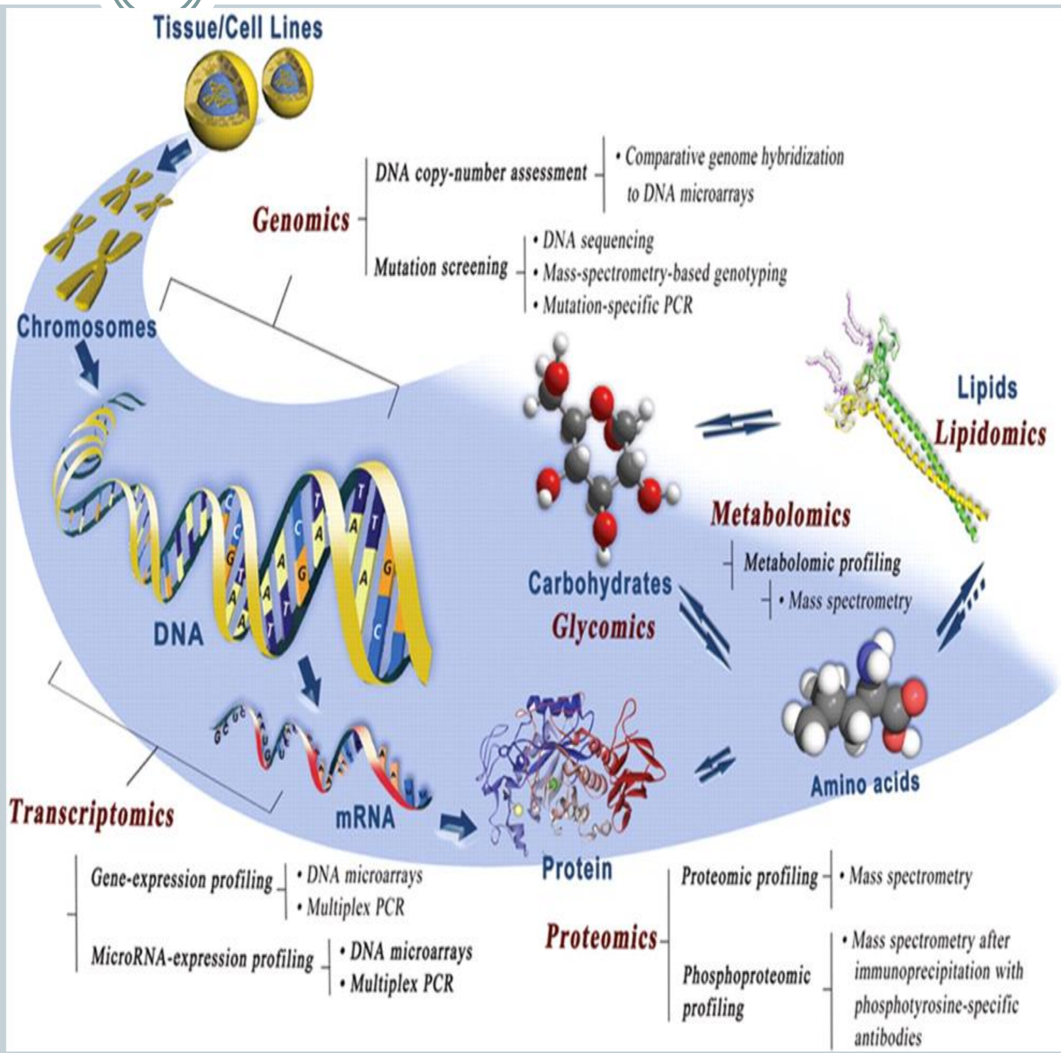
Integrating the activity of genes and regulators into regulatory networks
Integrating the interactions of amino acids into protein folding predictions
Integrating the interactions of metabolites into metabolic networks
Integrating the interactions of cells into organisms
Integrating the interactions of individuals into ecosystems

Initializing the motivation of research

- The proper investigation of the complexity of the disease requires new integrative Systems Biology approaches, at both the experimental and computational level.

The practical goals of such investigation include

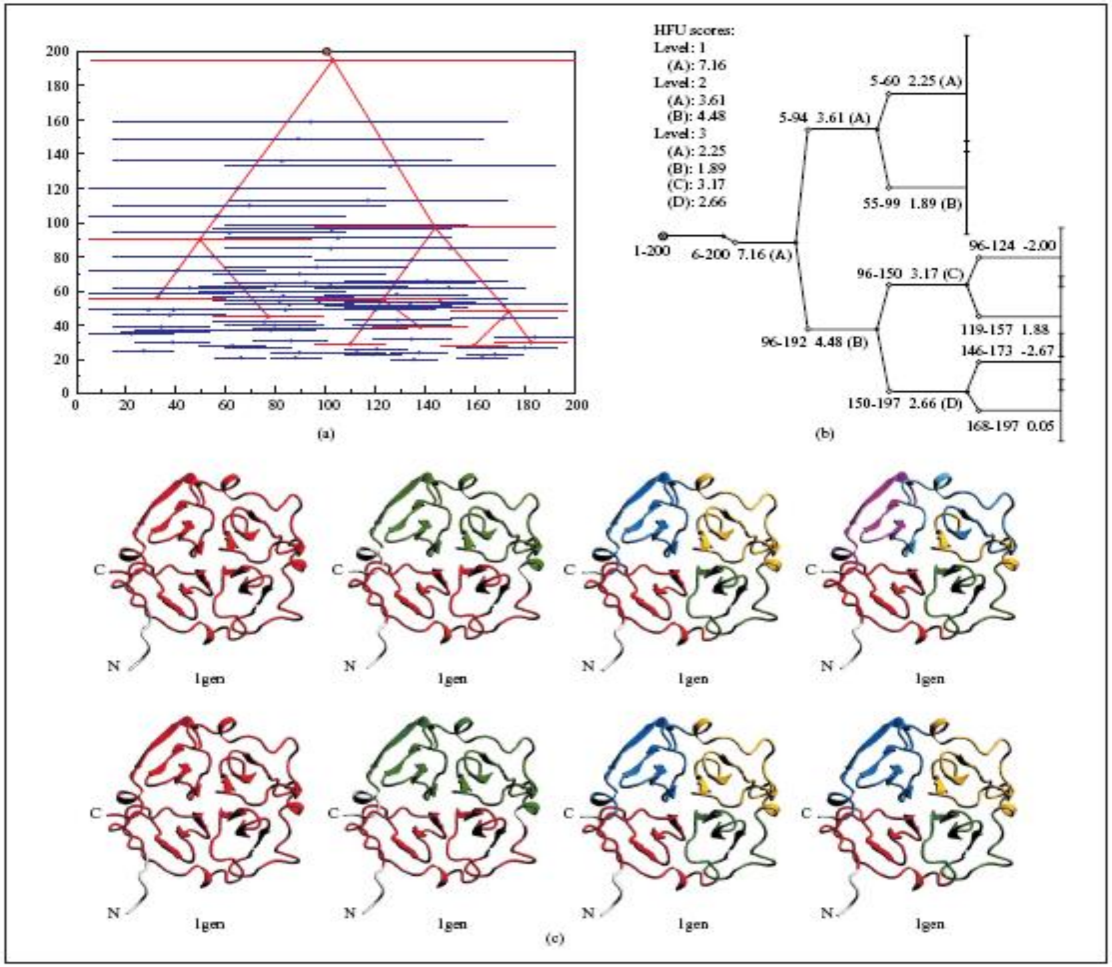
- improved classification of risks
- the characterization and detection of the first imbalances that underlie the onset of the disease



Features of a new methodology : Representation

Building blocks representations:

- **As statistical maps**
- **As trees**
- **As information interactions**

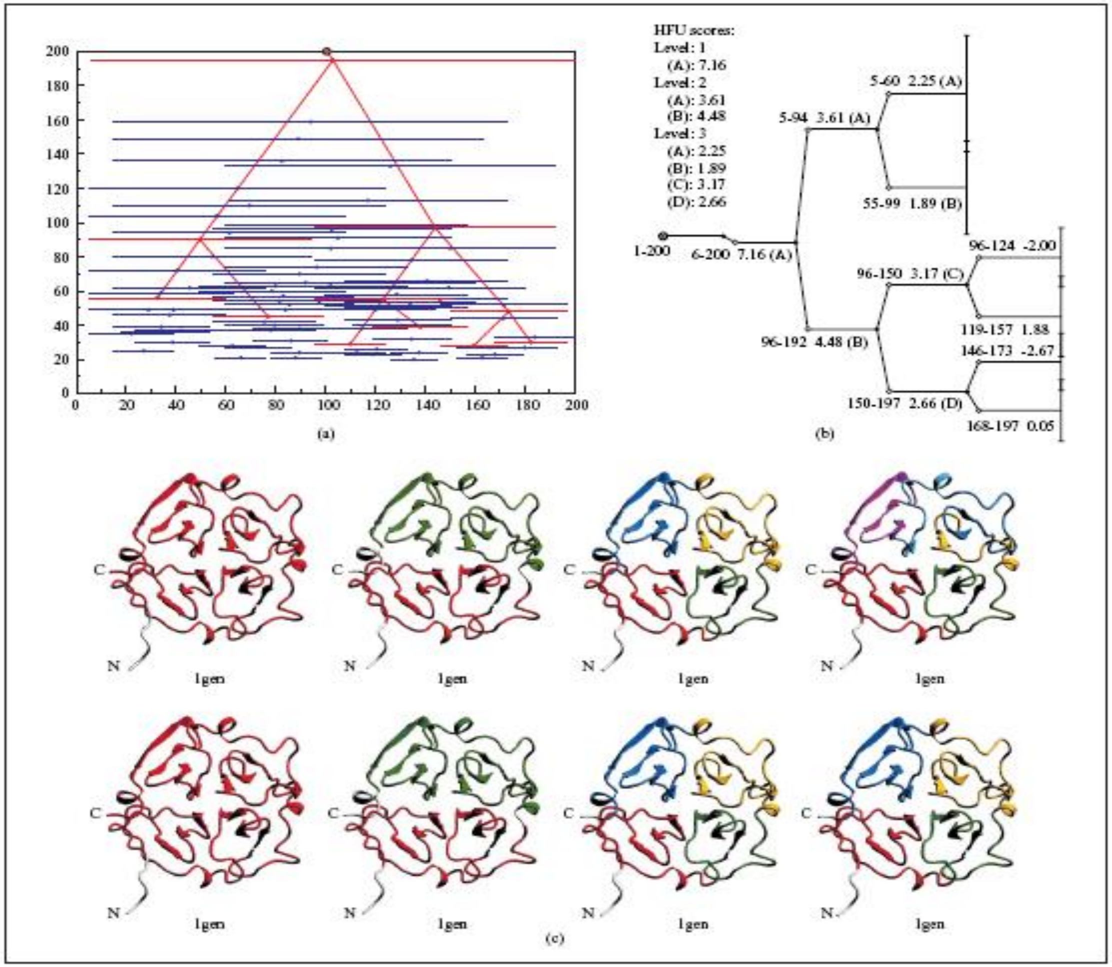


A new representation

Bioinformatics & Human Electrophysiology Lab
Department of Informatics, Ionian University

Building blocks representations:

- **As statistical maps**
- **As trees**
- **As information interactions**



Missing infos : Energy vs Topology

Systems of nonlinear PDEs can define the energy set of a protein.

$$\left.\begin{aligned}\frac{dC}{dt} &= D\Delta C - \varepsilon\eta f\left(T,C\right)\\ \frac{dT}{dt} &= k\Delta T + \eta f\left(T,C\right)\end{aligned}\right\}\frac{dT}{dt} = k\Delta T + \eta f\left(T,C_0\right)$$

Source term carries out the parameters of the biological mechanism

Source term as a deterministic function

- $Lu = u_t - \nabla(k(u)\nabla u)$
- k(u): Diffusion term from one part
- $\lambda_{ID} * \frac{f(u)}{\left(\int_v f(u)dx\right)^p}$: from the other part
- Equilibrium provides the existence potential and stability of solutions for the frailty function

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Simulation of energy functions

Simulation platform made from the scratch using BioAmbients Calculus, for the simulation of the evolution of the mechanism

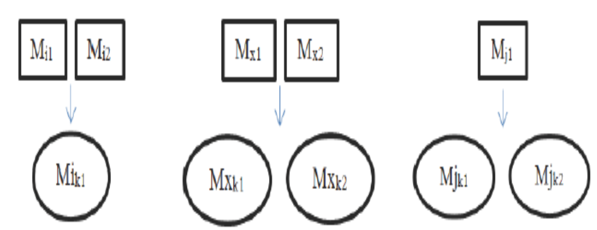


Figure 3: Complete fusion, transient fusion and fission.

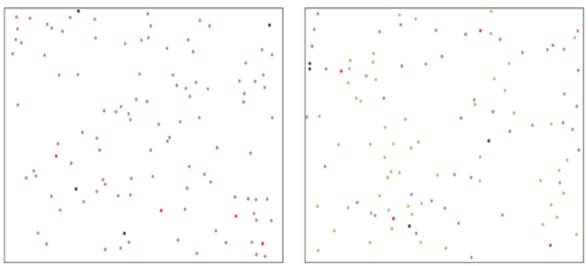
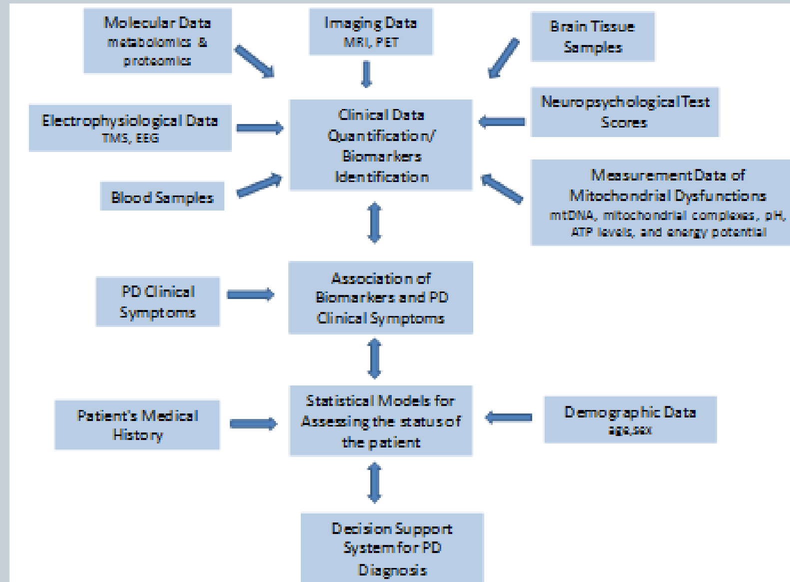


Figure 2A: Initialization of population

Figure 2B: Simulation results after N Steps

Hybrid DSS ontology-based system



Can we derive the topology from the energy functions?

Bioinformatics & Human Electrophysiology Lab
Department of Informatics, Ionian University

- Finsler Geometry provides us this opportunity.
- Representations of the RNA SS of the proteins can be handled by algorithms
- Non-crossing planar permutations can have an isomorphic representation with RNA SS
- The isomorphic representation is exactly stated with 2-colours elevated Motzkin paths
- The matching criteria in isomorphic non-crossing planar permutations is equivalent with areas of protein misfoldings
- We can trace those areas in words of 10^21 length in real time.

Can we cut proteins ?

April 17, 2007

Researchers 'hammer' proteins

A team of chemists, led by an ASU professor, has come up with an elegant method for cutting proteins into more manageable pieces for analysis. The method, which uses industrial fillers commonly found in paint and light, could significantly aid the development of bioanalysis tools that identify human remains – and might aid ushering in the age of personalized medicine.

A prototype sample preparation method uses ultraviolet light and titanium dioxide to cut proteins. It could be ideal for field devices and new microfluidic lab-on-chip devices designed to rapidly analyze minute amounts of biological samples. The method was detailed in the article “Cleavage of Peptides and Proteins Using Light Generated Radicals from Titanium Dioxide,” in a recent issue of Analytical Chemistry.

Proteins are relatively large and complex molecules made up of hundreds of thousands of amino acids. Cutting them into smaller sections allows researchers to work with more manageable pieces for analysis.

Currently, cutting proteins is achieved by using special enzymes called proteases that sever the chains of proteins at well-known locations. The protease trypsin, for example, cuts proteins at the locations of the amino acids lysine and arginine. Analyzing the residual fragments can identify the original protein.

The new work was led by Mark Hayes, an ASU associate professor of chemistry and biochemistry. Researchers working with Hayes include his former student, Barbara Jones, and Matthew Vergne, David Bunk and Laurie Locascio, all of the National Institutes of Standards and Technology.

Titanium dioxide is commonly used in paint as a white pigment, but it also is a photocatalyst, so when it is exposed to ultraviolet light its surface becomes highly oxidizing, converting nearby water molecules into hydroxyl radicals – a short-lived, highly reactive chemical species.

Yes, we can now cut proteins

- "We are basically taking semiconductor phenomena and semiconductor materials and getting elegant specificity in biochemical applications," Hayes says. "It shouldn't happen, but it did."
- In the experiments, titanium dioxide coatings were applied to a variety of typical microanalysis devices, including microfluidic channels and silica beads in a microflow reactor. By shining strong UV light on the area, the presence of a protein solution creates a small cleavage zone of hydroxyl radicals that cut nearby proteins at the locations of the amino acid proline.
- The result surprised the team.
- "The hydroxyl free radical is one of the most reactive species known," Hayes says. "It wanders around desperately trying to steal electrons from anything. To find specificity and having things break at this proline residue was just a stunning result.
- "From a chemist's or biochemist's point of view, we never would have predicted it. People who are trying to break up peptides and proteins work very hard at getting specificity, and that is why the enzymes they use are so valuable – because they provide an exact cleavage location. We are basically hitting these poor things with a hammer."
- The titanium oxide technique offers several advantages over enzyme cleavage of proteins. It's not too sensitive to temperature or acidity, like enzymes are, and it needs no additional reagents other than dissolved oxygen in the solution. It is a simple arrangement, Hayes adds, easy to incorporate into a wide range of instruments and devices, and titanium dioxide will last virtually forever in a wide range of conditions.

A new technological diagnostic verification!!

- JPK Force Robot is unfolding a protein into 80.000 different energy steady states
- Cut the protein at the area that the mathematical model is providing us and unfold it
- Compare the energy status with the ones of a well folded
- Make the existing medical correlation with the autoimmune disease
- A new diagnostic method with low cost and high accuracy is in progress!

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Thank you!

Computer Science is no more about computers as astronomy is about telescopes.

There should be no such thing as boring Mathematics!

Edsger Dijkstra