MORPHOLOGICAL CONTROL AS GUIDING PRINCIPLE IN PHYSIOLOGY AND MEDICAL APPLICATIONS

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Content

- Inflatable actuated support systems for patients with movement impairments
- Spatially organized reaction environments for the synthesis of branched oligomors
- Cells as dynamical systems: optimizing therapies by modeling
- Morphological danger signals
We can't rejuvenate your body.
But maybe, we can rejuvenate your attractor landscape!
Gait Patterns
Gait Patterns

- **Brain** chooses red or green basin of attraction.
- **Body-dynamics** drives system into attractor (and keeps it there).
• Transient time should be short.
• Fluctuations: Strong damping
• Attractor landscape can be changed.
Morphological Control: Adapting Attractors

Training → Brains learns posture such that specific movements are optimally supported by morphology.

Experienced skiers: Posture is essential for precise reactions on unexpected bumps.

Brain & Body: A Recent Result from Robotics

- **Feed-forward neural networks:** Some but not universal computational power.
- **Mechanical mass-spring systems:** Can generate time-dependent signals.

**Recent result (H. Hauser et al.):** A properly interfaced hybrid system (mass-spring + feed forward neural network) can emulate/compute large classes of filters (functions onto functions).

Aging: Loss of Control over Movements

Elderly patients sometimes suffer from a decrease of control over movement patterns, especially walking.

Conventional explanation:

Aging ➔ decrease of neural performance ➔ loss of control
Aging changes mechanical properties of the body

⇒ Attractor landscape less suited for support of movement patterns (less efficient damping, longer transients, etc.)
Aging: Loss of Morphological Control

**Vision:** External mechanical means “reshape” the parameterized attractor landscape

- No local repair of sinews, ligaments
- Goal: Re-establish morpho-computation power of the body.
- Attractor landscapes and parameterization are made more functional.
Support Systems: Exoskeleton

Bleex

Hulc™

eLEGS

50 best inventions 2010
Time magazine
Tensairity®

Synergetic combination of an airbeam with conventional cables and struts.

Tension (cable)
Compression (strut)
Stabilization (air)

Tensairity® = Tension + Air + Integrity

Rolf Luchsinger, EMPA Dübendorf
Tensairity

- 8m span, 2 tons max. load
- Fits in the trunk of a car
- Set up time < 30 min (two persons)
- Weight 70 kg (one girder)
Tensairity actuator
First Steps Towards Support System

Test system for supporting and stabilizing knee dynamics: **Not a servo!**

A.Dzyakanchuk, Kenneth Hunt, R. Füchslin, R. Luchsinger, M. Muster
Advantages of actuated inflatable elements:

1. **Low weight.**

2. Inflatable structures may exert significant total forces but can’t apply strong local forces → **Generic safety.**

3. Tensairity structures as well as the signals administered by them can easily be **personalized.**

4. **Actuated tensairity opens novel therapeutic strategies and higher levels of personalization.**

5. Vibratory signals need **not to be generated at its point of their administration.**

6. Forces/Signals are applied over broad areas → **Reduction of local stress.**
Why Tensairity?

Soft robots are safe(r) robots!
Spatial structuring is programmable and can increase yield rates in the synthesis of branched polymers.
Programmable Chemical Microfabs

Conditions have to be suitable for all reactions.
Each branch of the reaction can take place in an optimal environment.
Optimization by Compartmentalization

- **Pro:** Compartmentalization $\rightarrow$ optimization by branch-specific choice of chemical conditions.
- **Con:** Matter and information has to be transported between the compartments.
Programming by Arranging

- Matter and signal transport takes place between adjacent containers.
- The arrangement influences the overall reaction.

Optimization by compartmentalization
Control by influencing matter transport
Artificial Branched Molecules

Monomer: Up to 3 linkers

Same linkers allow wrong assembly

Multiple use of monomers

Monomer: Up to 3 linkers
Synthetizing Branched Molecules *in silico*

• Each type of container performs a specific synthesis step.
• Containers arranged by stochastic self-assembly.

Benedikt Reller, R. Füchslin (MATCHIT)
Scalability

- How scales the relative yield with size of molecule to be synthetized?
MATCHIT Automaton

- FP 7 Project MAtrix for CHe mical IT

- 1 dim channel
- So called chemtainers (e.g. vesicles) interact with channel and each other.
- Control by DNA – computing
- Mathias Weyland and Harold Fellermann developed compiler for synthesis of branched polymers.
Evolution vs. Compilation

1. a) b) 

2. a) b) 

Evolved

Compiled
Morphology may amplify specific reaction pathways.

⇒ Increase of yield.
Modifying total probabilities for reaction pathways (especially in non-equilibrium systems) is beyond the attractor perspective.
Golgi Apparatus

Production of oligosaccharides (among other things)

Pictures from http://jennarever.weebly.com/index.html
Cells as dynamical systems -
Consequences to therapy optimization
Multi-Scale Processes: Endocytosis

Receptor-mediated endocytosis:
- Chemical reactions
- Supramolecular self-assembly
- Membrane physics

Endocytosis is an attractor of a non-equilibrium system.
Lesson learnt: Molecular pathways have to be complemented by multi-scale dynamics.


Visualization: N. Mennes and T. Maeke
The Network Picture

Cell as a dynamical network of physico-chemical interaction
Two Types of Diseases

One or several nodes are dysfunctional $\Rightarrow$ network functionality may be affected.

All system components are functional, but system is in wrong basin of attraction.
Evolutionary Medicine

Darwinian medicine: a case for cancer

Mel Greaves

Abstract | Epidemiological, genetic and molecular biological studies have collectively provided us with a rich source of data that underpins our current understanding of the aetiology and molecular pathogenesis of cancer. But this perspective focuses on proximate mechanisms, and does not provide an adequate explanation for the prevalence of tumours and cancer in animal species or what seems to be the striking vulnerability of Homo sapiens. The central precept of Darwinian medicine is that vulnerability to cancer, and other major diseases, arises at least in part as a consequence of the ‘design’ limitations, compromises and trade-offs that characterize evolutionary processes.

A Dynamical Model of Genetic Networks for Cell Differentiation

Marco Villani¹,², Alessia Barbieri¹, Roberto Serra¹,²*

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A Puzzle in Radiotherapy

Conundrum: Reaction of cells to irradiation highly non-linear. "The more intensity, the more (long-term) damage" does not hold (Fig. by S. Scheidegger).
Combination Therapy

- Apply multiple stresses to cells:
  - hyperthermia (43°C)
  - radiation
- Taken alone, stresses are not lethal
- Their combination is chosen such that healthy cells are not affected too strongly
Dose Equivalent Models (HT – RT)

\[
dN_i \over dt = f(N_i, N_k, ..., \Gamma, \Lambda) \ ; \ \ \ \ dN_k \over dt = g(N_i, N_k, ..., \Gamma, \Lambda)
\]

\[
d\Gamma \over dt = R - h(\Gamma) \ ; \ \ \ \ d\Lambda \over dt = u(\Lambda) - w(\Lambda)
\]

\[
dN_i \over dt = f(N_i, N_k, ..., \Gamma) \ ; \ \ \ \ dN_k \over dt = g(N_i, N_k, ..., \Gamma)
\]

\[
d\Gamma \over dt = R - h(\Gamma, \Lambda) \ ; \ \ \ \ d\Lambda \over dt = u(\Lambda) - w(\Lambda)
\]

\[N_i\] : Tumor cells not damaged by heat or radiation

\[N_k\] : Tumor cells lethally damaged by heat or radiation

\[\Gamma\] : Radiation - related dose equivalent

\[\Lambda\] : Heat related dose equivalent

\[R\] : Dose rate

\[f,g,h\] : Functions describing induced death/repair/survival

Phenomenological top - down model of synergistic effect of hyperthermia and radiotherapy.

Four - parameter model
Are Four Parameters Really Enough?

E. Wanker et al. Human protein network

Four - parameter model
Detecting danger by morphology

Question (Roland Scholz, ETHZ): Is there a non–enumerative way to detect non-default states in the states of tissues?
Danger Signals

- Matzinger developed an alternative view: The immune system is activated by general signs of danger, not (only) by foreignness.
- Among other things, the model explains
  - Why the immune system can respond to tumors
  - Why one needs adjuvants to make vaccines effective.

Detecting Danger by Morphology

- Fact: Chain molecules may fold up and get a non-trivial morphology.
- Fact: This fold is determined by
  - the molecules sequence (proteins: amino acids)
  - the conditions under which the fold takes place.
Assume a molecule M with a fold that is evolved to be highly susceptible to chemical conditions.

Default fold

“Something is wrong” fold
Epitope D activates IS
Detecting Danger by Morphology

- **Cell ok, Environment ok** ➔ **Default fold**
  - Immune system remains passive

- **Cell not ok, Environment ok** ➔ **Danger fold**
  - Immune system activated

- **Cell ok, Environment not ok** ➔ **Danger fold**
  - Immune system activated
Detecting Danger by Morphology

- Morphology of the molecule is sort of a "checksum".
- We don't claim that the mechanism is present in biological systems, but it may be implemented in artificial evolvable replication systems.

The chemical immune systems know that and what is going wrong.

- The nervous system knows where it is going wrong.
Hypothesis

- Nervous and immune system are coupled.
- Rolf Pfeifer: Find the optimal balance between nervous system and morphological control
Summary

- Morpho - computational power of body may be restored by mechanical means.
- Spatial organization enables programmable control of chemical reactions by enhancing the probability of specific reaction pathways.
- The dynamic systems perspective opens a new look on cell dynamics.
- Morphological control offers a non – enumerative mechanism for protecting replication systems.
- From an engineering perspective, a coupling between nervous and immune system is plausible.
Acknowledgements

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• ECLT, Venice
• ZHAW, School of Engineering
Counterargument: Depression

• There is only limited evidence for an influence of the psyche on the immune system.
• BUT: Mental processes have, if at all, only indirect influence on chemical processing.

Free interpretation of a concept developed by Roland Scholz