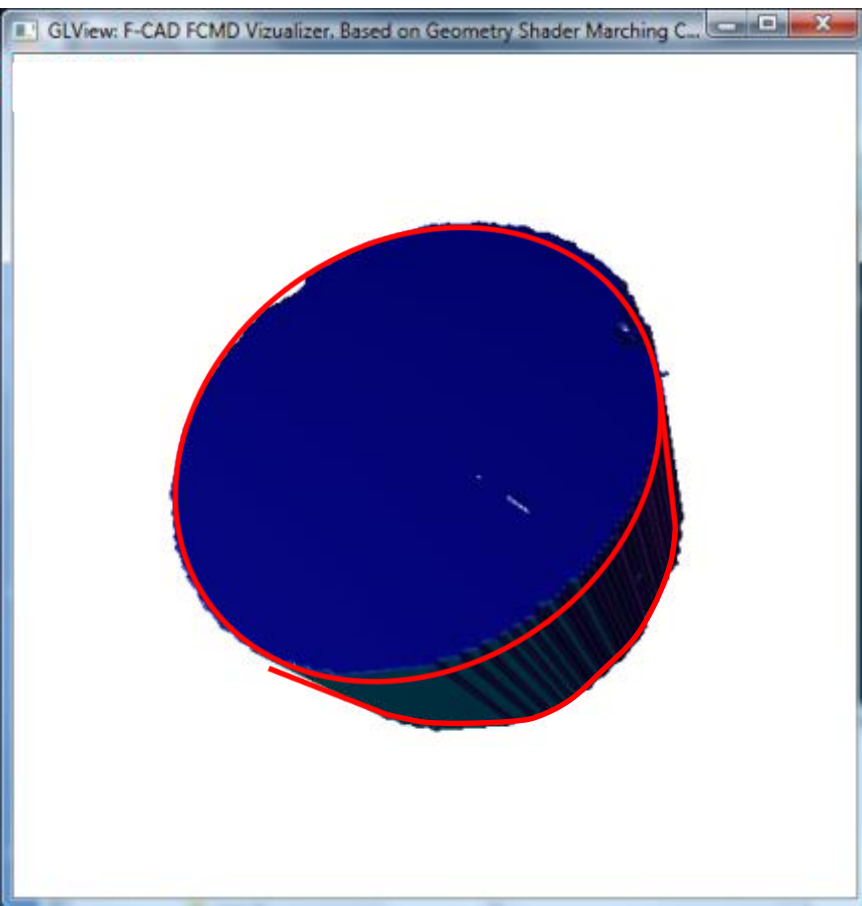# Artificial Intelligence, Digital Revolution in Formulation Science & New Avenues in Drug Discovery

Hans Leuenberger, PhD,

Prof emeritus Pharmaceutical Technology University of Basel;

Adjunct Professor,

University of Florida, College of Pharmacy, Lake Nona Campus, Orlando FL.
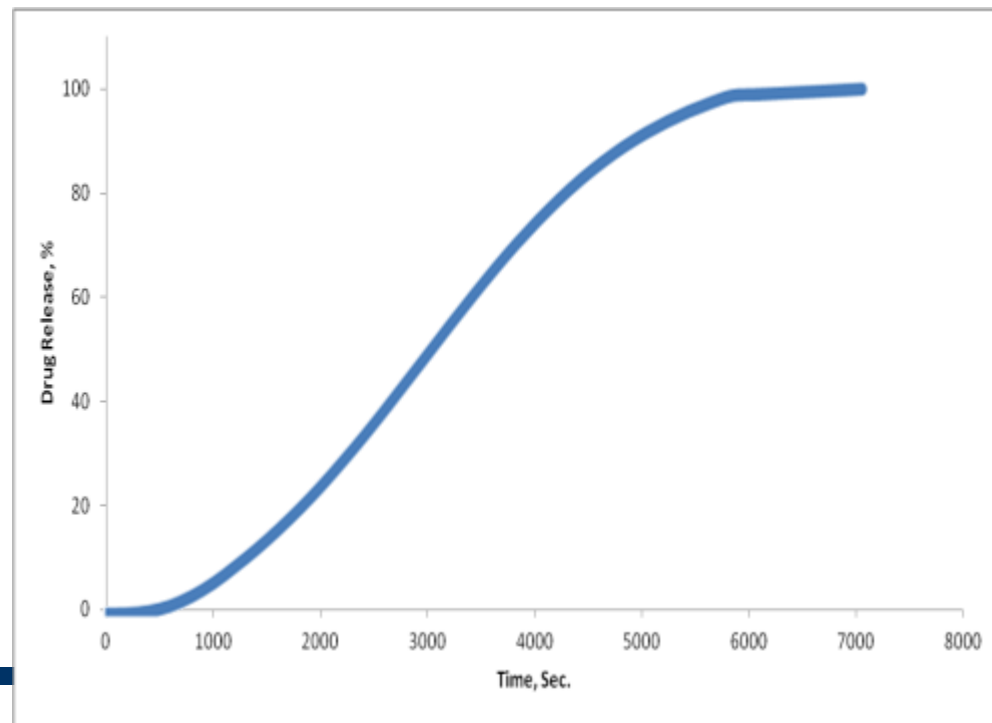
hans.leuenberger@ufl.edu;

# AI & Digital Revolution:

- *Affect the Future of Formulation Science\*.*
- *The software platform F-CAD (Formulation- Computer Aided Design) by CINCAP allows the pharmaceutical industry to adopt the workflow of the automotive and aircraft industry.*
- *Dr. Go Kimura, my former PhD student, introduced successfully F-CAD by CINCAP at the company Shionogi in Japan for optimizing drug delivery vehicles.*
- *PhD thesis at http://edoc.unibas.ch/diss/DissB_9886.*
- *The first prototype of the drug delivery vehicle is prepared virtually by mimicking the composition and the tableting process.*
- *The software is based on a cellular automaton (CA) approach mimicking the dissolution profile of the formulation.*

*In-silico design of n formulations: design space exploration according to ICH Q 8 (R2)*
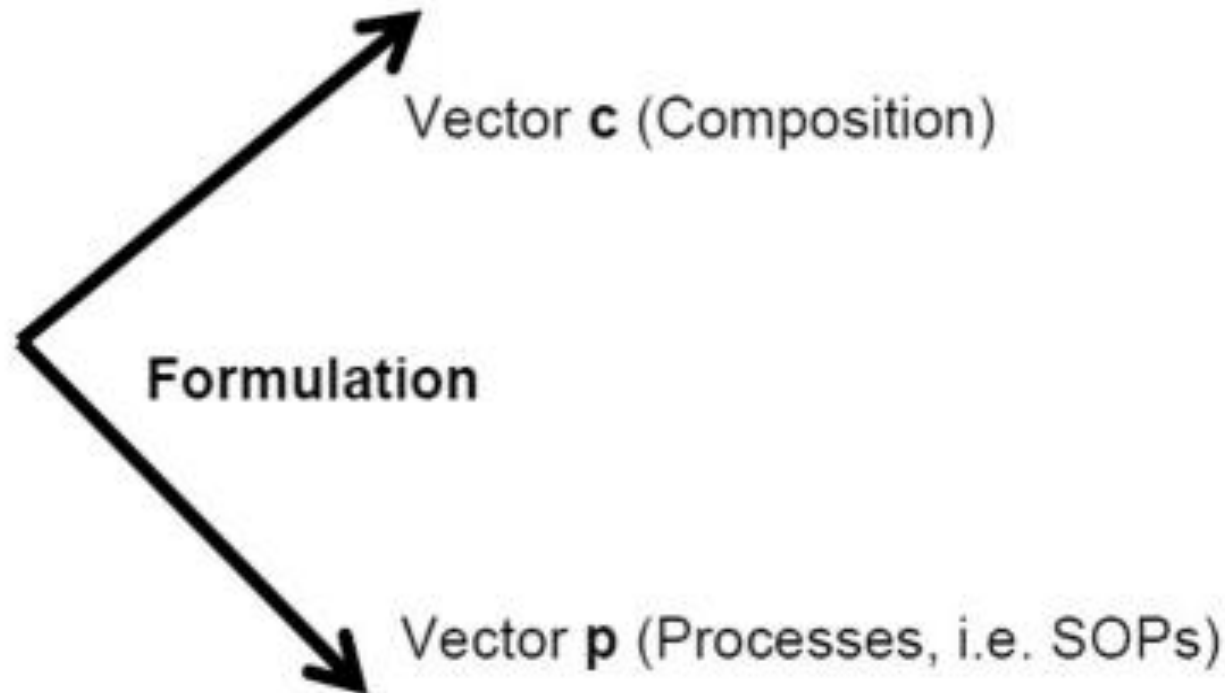


● Calculation of dissolution

# AI & Digital Revolution:

- *To take account of the type of dissolution equipment and all **SOPs** (Standard Operation Procedures) such as a single punch press to manufacture the tablet, a calibration of the F-CAD dissolution profile of the virtual tablet is needed.*
- *Thus, the **virtual tablet** becomes a **copy of the real tablet.***
- *This statement is valid for all tablets manufactured within the same formulation design space.*
- *For this reason, it is important to **define** already for **Clinical Phase I the final dosage form** such as a capsule or tablet  formulation (composition &  and the process). Thus,*
- *not to use a simple capsule formulation for Clinical Phase I & II and to switch in Phase III to a tablet formulation, which  needs a bioequivalence test. In other words,*
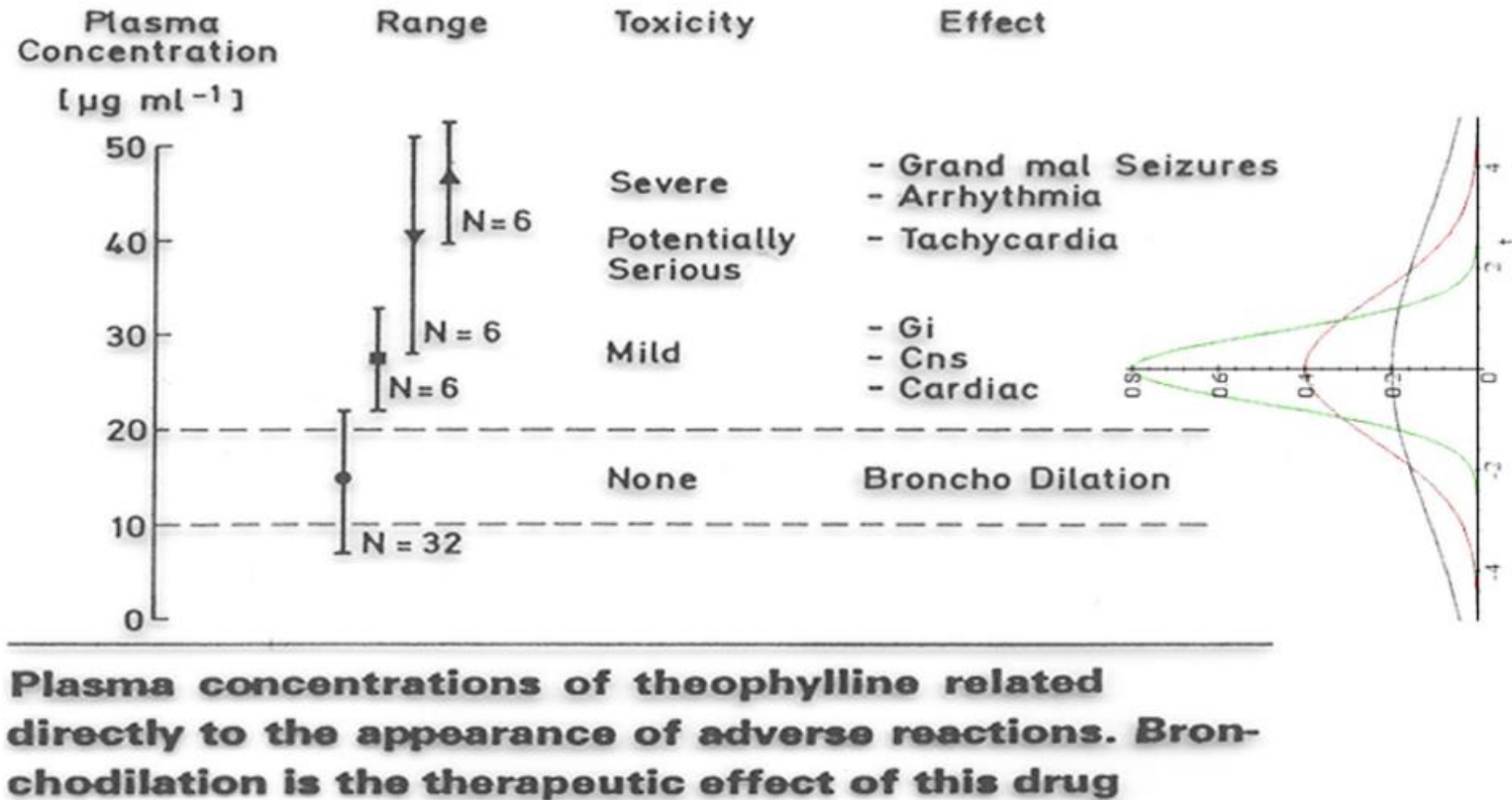- *The formulation design space needs to be constant\* !!!*

# AI & Digital (Twin) Revolution:

- **H. & M. Leuenberger, *Impact of the Digital Revolution on the Future of Formulation Science\*:***



Vector **c** (Composition)

Formulation

Vector **p** (Processes, i.e. SOPs)

- ***Fig. 2: 2D projection of the Formulation Design Space.***

# AI & Digital (Twin) Revolution:



Plasma concentrations of theophylline related directly to the appearance of adverse reactions. Bronchodilation is the therapeutic effect of this drug

*Fig\*. 3: A six-sigma quality formulation is needed already for Clinical Phase I & II, especially in case of a Narrow Therapeutic Window of the API . This goal can be achieved thanks to the DIGITAL TWIN.*

# AI & Digital (Twin) Revolution:

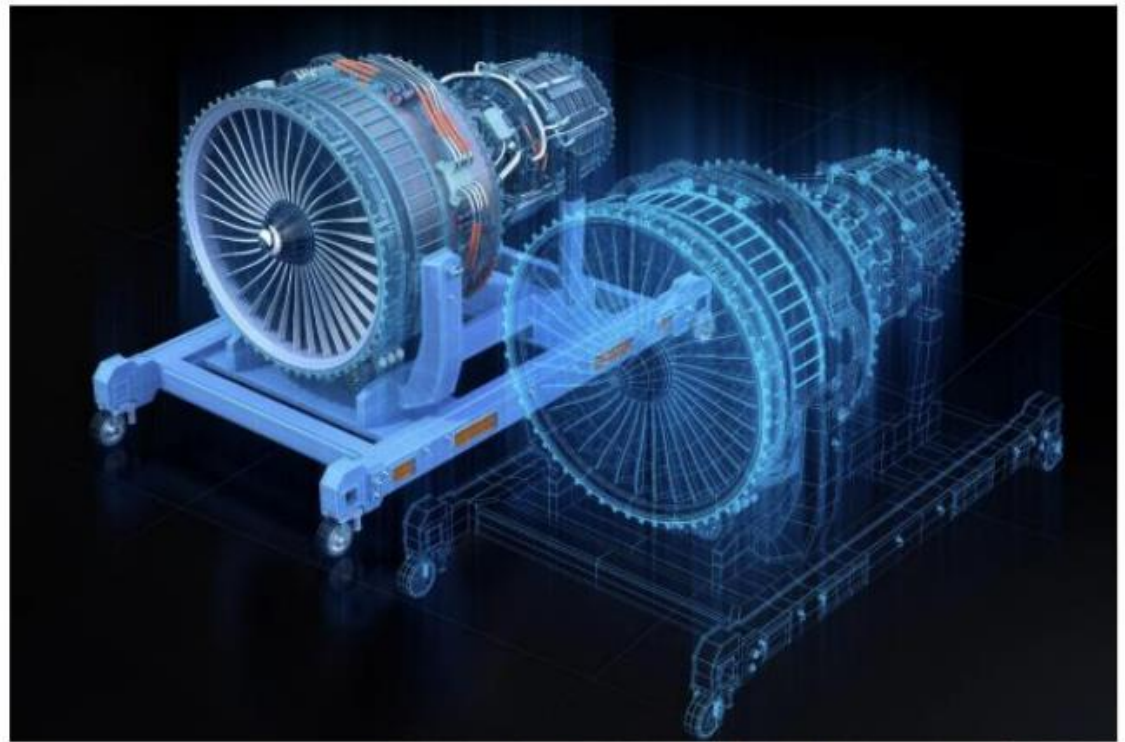*F-CAD by CINCAP at SHIONOGI is the first DIGITAL TWIN\* of the SOP "Tablet Design, Dev., Manufacture & Testing\*".*
*The DIGITAL TWIN Industry has a bright future: $183B Annual revenue by 2031*
*(Reference: www.gartner.com/eng/documents/4011590).*
*Fig. 4: Digital Twin of a Turbine* ➡️

"GE: No unscheduled downtime"



https://www.ingenjor40.se/module/cyber-physical-systems-and-digital-twins/

* D. Maneerojpakdee et al. An attempt to adopt the workflow of the automotive and aircraft industry for the design of drug delivery vehicles , Pharm. Tech. Japan, 33,11 (2017) 145-156.

# AI & Digital (Twin) Revolution:

Let us discuss the creation of a digital twin of a turbine. Thus, we need to consider the following situations.

1.  The *turbine is not running* leading to a *deterioration* as in case of an *automobile not used*. Thus, there is no influx of Energy representing a **closed conservative system**. Such a system is prone to *deterioration, to aging according to the* **Second Law of Thermodynamics**.


2. This law defines the *time arrow of our aging process* that the *entropy is continuously increasing*.  Also, in the case of an *open system with influx of energy*, this *time arrow in general cannot  be reversed*.

3. However, there exist *some exceptions leading to a "local" decrease in entropy* to an *"Order out of Chaos*"!!!*

*The efficiency $E_C$ of the idealized Carnot engine $E_C = 1 - (T_L/T_H)$ with $T_H$ = temp (hot source) & $T_L$ = ambient temp.

# Conclusion: Digital (Twin)Revolution:

1. In general the **DIGITAL TWIN of a pharmaceutical SOP corresponding to work** done needs to use an *open system with influx of energy*.

2. A typical example is the continuous wet agglomeration process*: *Regarding Quality by Design (QbD),* it is important, that the result of the SOP leads to *a TWIN & in reality* to a *thermodynamic equilibrium*. For this reason, I prefer the *concept* of a *quasi-continuous* process based on the definition of *a large batch size* $N = n$ *a* with $n = 1$-$100$ and *a = small QbD validated batch* size *in a thermodynamic equilibrium, instead of a real continuous process* with no evident definition of the batch size.

3. A special case is the *TWIN of a living biological system = VIRTUAL PATIENT.* According to Nicolis & Prigogine in Exploring Complexity (ISBN 0-7167-1859-6) *the current science is in an state of transition.*
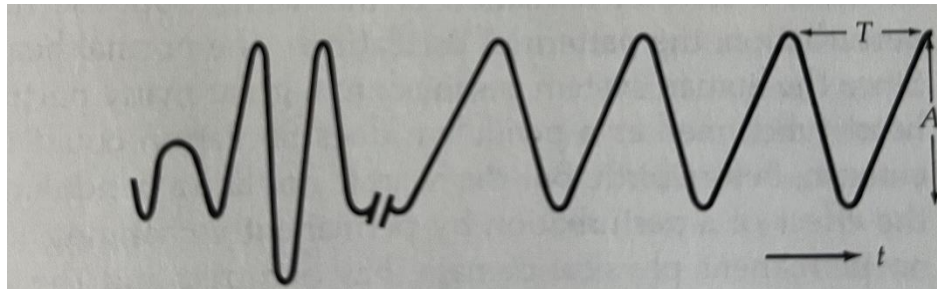
# Our Science in a State of Transition

1.   Our  cScience is based on **Quantum Mechanics** (QM) & **Einstein's Relativity Concept**, but does not explain the dark matter of the standard cosmological model (see* http://www.kaltura.com/tiny/v5fzs).
QM explains the strange behavior of matter **close to  zero °K  Temperature** such as Superfluid Helium and "Superconductivity".

2. However, NL Mueller & Bednorz showed that **superconductive** ceramic **material** exists **at higher temperatures**. Mueller admitted at the University of Basel that they searched *by trial & error* for an optimal ceramic composition like industrial pharmacists *optimizing a tablet formulation*.

3. Emerging tools of AI  are (1) Reactive **Machine Learning**  (ML); (2) ML with memory (**Deep Learning**); (3) **Theory of Mind**; (4) **Self Awareness** (Consciousness). AI tools prompt the questions, whether AI **(Deep Learning**) will help us to design & manufacture a quantum computer at room temperature, to help us to develop DIGITAL TWIN  = VIRTUAL PATIENT  & *new therapies for promoting health & peace in the world*.

*H. Leuenberger, invited lecture, Virtual Patient & in-silico Design of Solid Dosage Forms (12th PBP World Meeting 2021).

**Human Being = A Supercomputer:**
**Study based on the work of Nobel Laurate I. Prigogine**

**In case of a system far from Equilibrium Conditions:**
*1.(Prigogine): Transformations exist from disorder into order, leading to the creation of life: Chaos ➡ Order, and to new laws in nature linked to Chaos Theory. Thus, the heart rate can be disturbed, but remains asymptotically stable\*:*

➡



*This is an important result regarding existing mechanistic PK and PD models!*

**\* G. Nicolis & I. Prigogine, Exploring Complexity, ISBN 0-7167-1859-6, P.19.**

**Human Being =  A Supercomputer:**
**Study based on the work of I. Prigogine &  I. Stengers**

**"Order out of Chaos, Man's New Dialogue with Nature"(U of M, Bantam Books,1984) and on my work in SWISS PHARMA 41 (2019) Nr. 1, 20–36, In case of a system** far from Equilibrium Conditions**:**

**1.*(Prigogine): Transformations exist *from disorder into order, *leading to the *creation of life:*
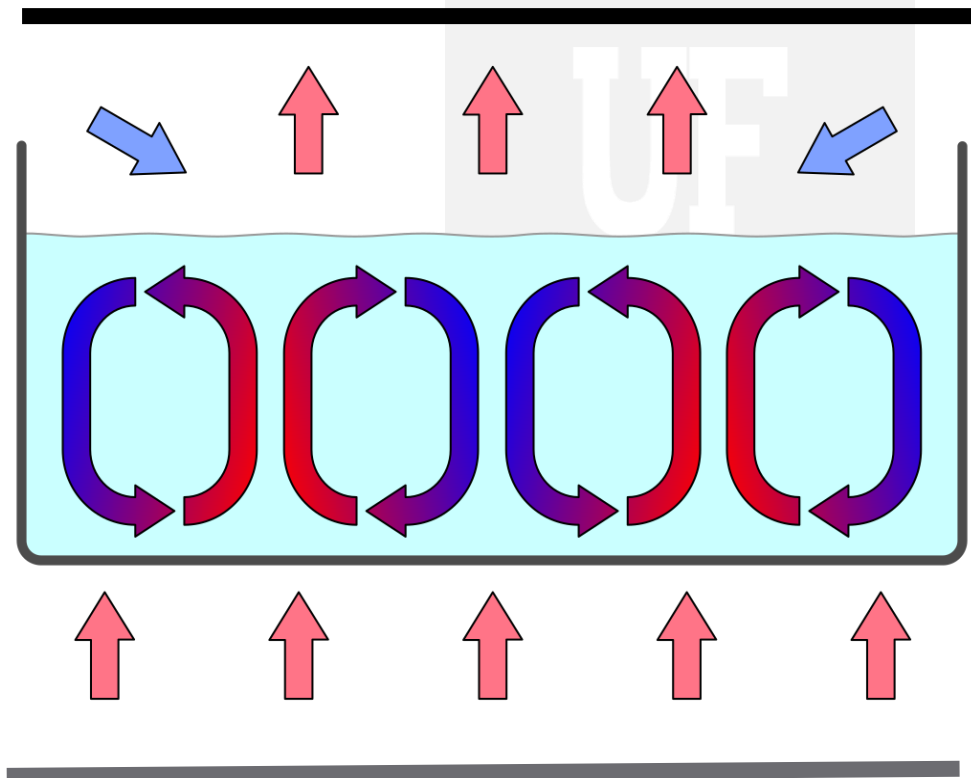*Chaos ⇒ Order.*
**2. (Leuenberger): The same process is responsible for "inorganic life" such as for the formation of Bénard cells or highly ordered (e.g. Pyrite) crystals in nature: Chaos ⇒  Order.**

# Bénard cells* & thermal convection as "Inorganic Life"?

**Plate at the temperature $T_1$** ➡

**A simple & exciting experiment:**
**Notice Fig.5** ➡ **The direction of rotation of the adjacent Bénard cells, representing *complexity* & *long range order* (*Out of Chaos*) in a system *under non equilibrium conditions*, i.e. start of *thermal convection* between the heated lower plate at the temperature $T_2$** ➡

**& the upper plate at $T_1$ with $T_2 > T_1$ for $(T_2 - T_1) > \Delta T_{critical}$ .**
**Below $\Delta T_{critical}$ there are no cells formed an there is a simple *thermal conduction* for small $\Delta T$ values.**
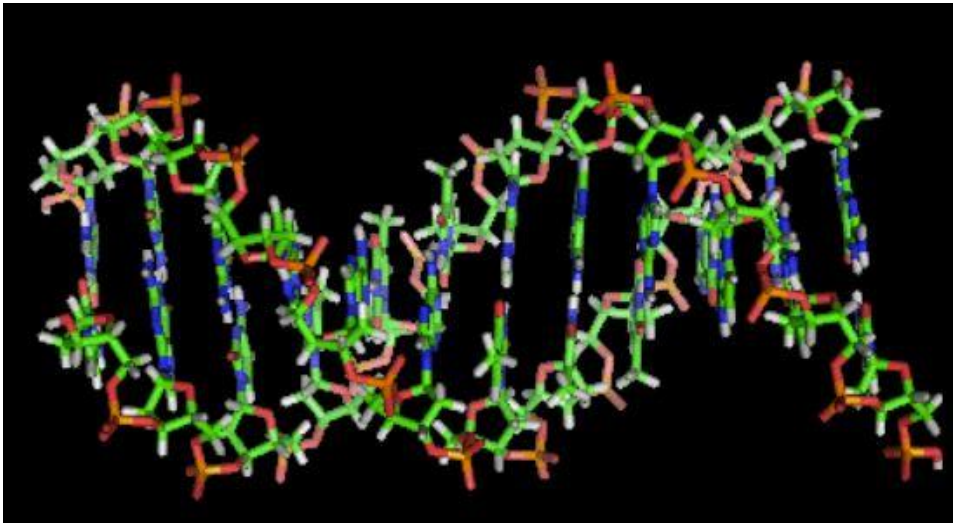
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* **Bénard cells, Nicolis, Prigogine in Exploring Complexity, p.8-15.**

# Pyrite Crystals as "Inorganic Life"?

**The main difference is that inorganic chemistry has not the capability of storing so much information as DNAs!**

# 3. (Schrödinger): Life = Information = Software = Genetic Code



This is the concept of a *Virtual Patient* based on the idea that each human cell is a microprocessor: **Number** of cells in the human body $\approx$**37.2 x $10^{12}$** without Microbiom!

4. (Schrödinger / Prigogine): **The human being is a living (super) computer!** The latest NVIDIA GPU technology of the Ampere A100 GPU has arrived at UF (NVIDIA SuperPod). UF is the first university in the world to get to work with this technology.
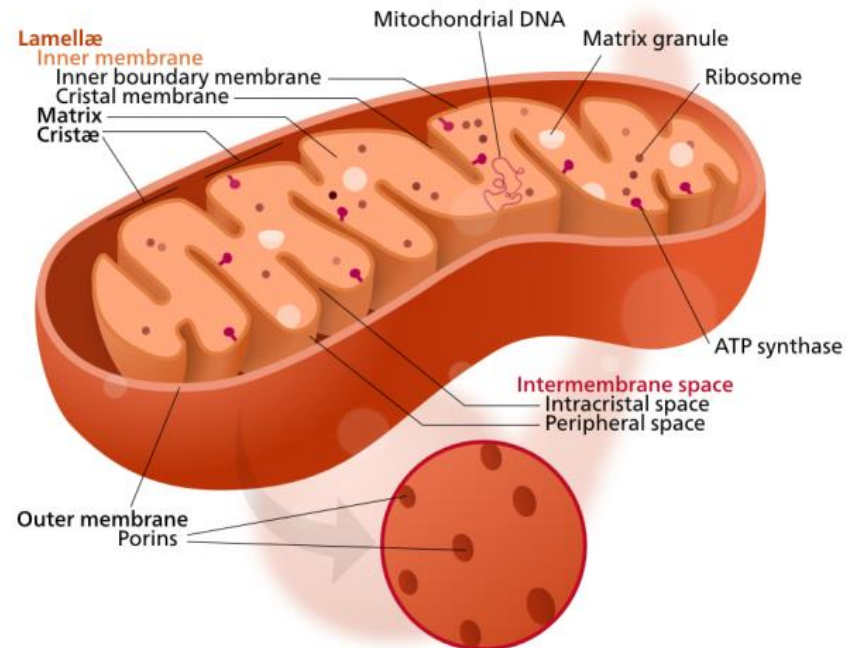
# VIRTUAL PATIENT

**4. (Schrödinger/ Prigogine):**
**= Super Computer?**

**This is the concept of a *Virtual Patient* based on the idea that each human cell is a microprocessor.**

**Mitochondrium = power supply of the cell = Microprocessor of the Human Super Computer Number of cells in the human body $\approx$ 37.2 x $10^{12}$ without Microbiom!**
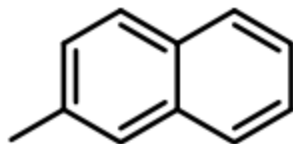
**Human Being = a Multi-processor = Super Computer!**



Lamellæ
Inner membrane
Inner boundary membrane
Cristal membrane
Matrix
Cristæ
Mitochondrial DNA
Matrix granule
Ribosome
ATP synthase
Intermembrane space
Intracristal space
Peripheral space
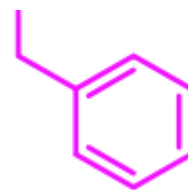Outer membrane
Porins

**VIRTUAL PATIENT = SUPERCOMPUTER:**

- Thus, the *Computer Operating System* of the VIRTUAL PATIENT is sensitive to *single drugs* (APIs), to *toxins,* to complex toxins such as trajans inducing multiple organ failures, to *food* (such as Grapefruit), to *parasites* such as *worms*, *to the combination of drugs*, to *bugs* and to *viruses*.

- If the hardware of VIRTUAL PATIENT (Supercomputer) is damaged failing to work, it is questionable, whether the system can be rebooted or reanimated in an emergency room.

- What are our conclusions: ➡ Should we continue our normal expensive search for new single APIs or look for new research avenue

# AI (**Deep Learning**) & Drug Design

**Today, the design of a new better drug (API) uses among other AI (Deep Learning) tools and includes an incredible effort such as preclinical animal studies regarding efficacy, safety etc. This example describes the Search for a Dihydropyridine analog of Nifedipine as an anticancer agent:**
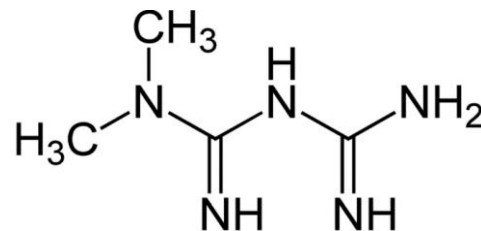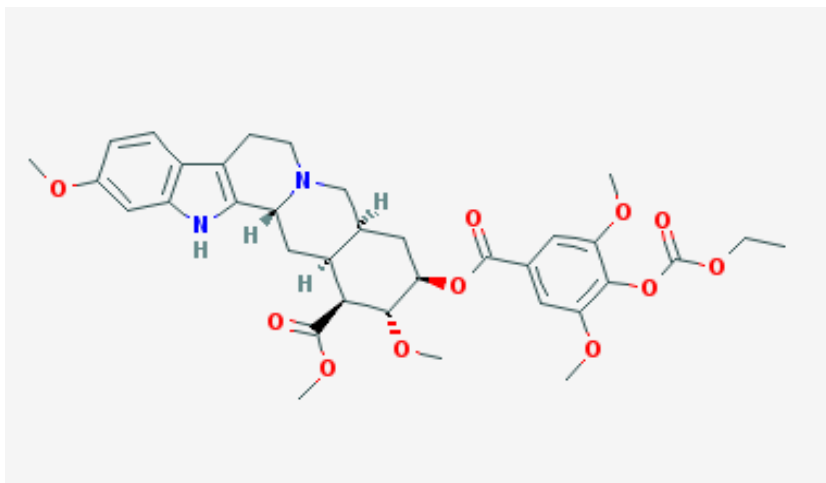
**With $R^1$ =** and **$R^2$ =**



**Thus, Nifedipine as a Dihydropyridine Analog also may induce Apoptosis in the presence of Metformin***

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*Benjamin et al, Syrosingopine sensitizes cancer cells to killing by metformin. Sci. Adv. 2, e1601756 (2016).

# VIRTUAL PATIENT

**Our human computer operating system is e. g. sensitive to Syrosingopine, a Reserpine deriv. to treat hypertension. Reserpine is an interesting single API scaffold for fine-tuning our computer operating system! Metformin is used to treat Diabetic type 2 patient as a Single API! The Combination is an effective Anticancer Agent!\***



**Metformin has attracted interest as potential anticancer agent & as mild ETC (Electron Transport Chain), i. e. mitochondrial inhibitor\*.**
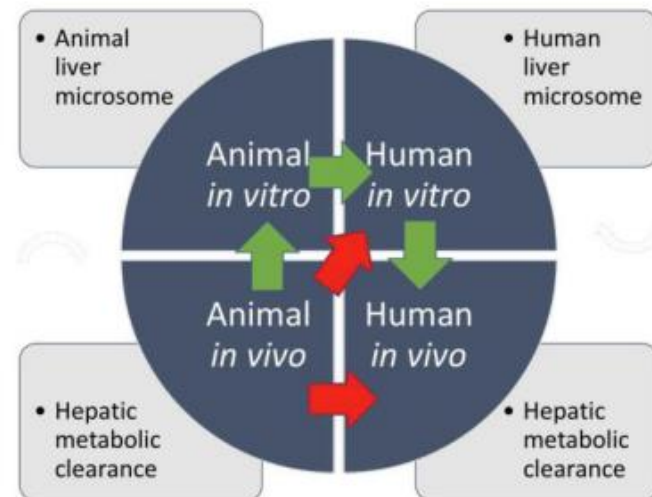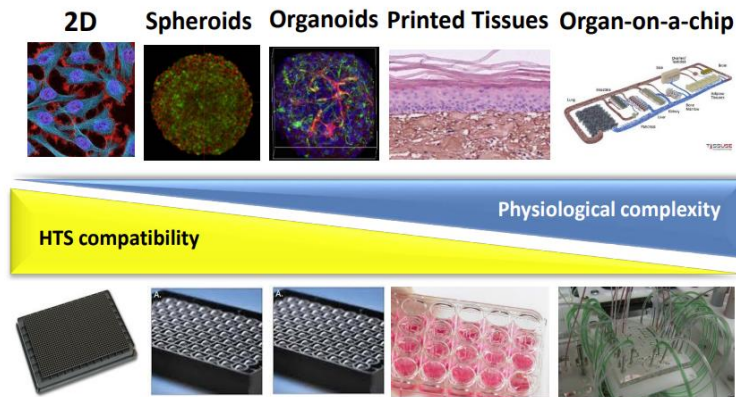
**\***Benjamin et al, Syrosingopine sensitizes cancer cells to killing by metformin. Sci. Adv. 2, e1601756 (2016).

# New Avenues in Drug Discovery

- Thus, the *combination registered generic drugs* * leads to a new Research Avenue *replacing the expensive efforts of finding a new single API.*
- Thus, instead of designing & developing an expensive single API let us test low dose *Generic Combinations*!
- It is expected that the AI (Deep Learning) tool leads to a better knowledge *of our Computer Operating System* to the combination of n APIs.
- *Curiosity is the driving force of science:*
- Can we achieve with a combination of n generic drugs *new safe therapies with less side effects*?
- By adopting this idea, is it possible *to reduce costs* of developing new therapies and *to reduce the number* of preclinical & *animal studies* (see next slide)

*Benjamin et al, Syrosingopine sensitizes cancer cells to killing by metformin. Sci. Adv. 2, e1601756 (2016).

# Research Topic: Improved translational/animal replacement models

**Improved (more predictive?) translational models/assays**



**FDA Modernization Act 2.0** **act authorizes the use of certain alternatives to animal testing, including cell-based assays and computer models, to obtain an exemption from the**

**Food and Drug Administration to investigate the safety and effectiveness of a drug.**

**EMA - Regulatory acceptance of 3R (replacement, reduction, refinement) testing approaches.**

CPSP UF CENTER FOR PHARMACOMETRICS & SYSTEMS PHARMACOLOGY

# VIRTUAL PATIENT

**The Project and Concept:**

**The concept of the "Virtual Patient" is described in the publication "What is Life?" in SWISS PHARMA 41 (2019) Nr. 1, 20 – 36 and was first presented on November 27, 2018 at the UF College of Pharmacy in Gainesville FL; see Videopoint of the Galenus Privatstiftung (http://www.galenusprivatstiftung.at/60.0.html).**

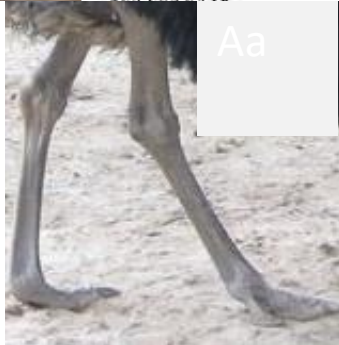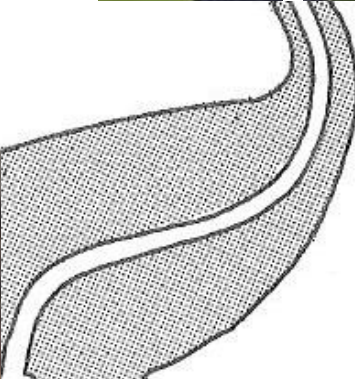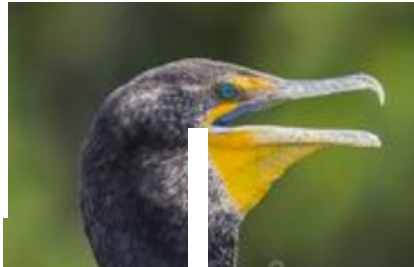**The SWISS PHARMA article "What is Life?" can be downloaded at www.ifiip.ch/downloads**

*What is Life?  The initial axioms*

*define "Life of a Virtual Patient" = Supercomputer, who can suffer from Viral Infections.*

- *Second Law of Thermodynamics: Aging Process!*
   *Degradation of a Tablet; Expiry date also of humans!*
- *Percolation Law & Threshold    Anti-Aging Effect!*
   *Creation of a Tablet:  $X = S (p-p_c)^q$ ➡    (Axiom 2)*
- *Society: Solutions depend on framework conditions!*
- *Change of the conditions leads to solution!*

- *Natural peaceful evolutionary process with no collateral damage in a healthy person ➡ and in a healthy society!*
- *3D Percolation Threshold: Switch function of Computer Operating System!*

**Life needs food to digest!**

➡️



**Percolation theory shows quantitatively that life can only exist in ≥ 3D due to the 3D percolation threshold = bio switch function. Thus, the influx of an ingredient in a 3D compartment such as Ca-ions changes its functionality.**

**Bird is cut into 2 pieces in a 2D drawing!**

**Percolation thresholds also exists for dimensions >3D: After our death do we live In another dimension?**

**VIRTUAL PATIENT:  Final Conclusion**

- *We need to be humble, since we do not know enough!*
- *We know, how to go to the Moon and soon to Mars, but we cannot predict the next financial crisis nor the next viral pandemic!*
- *We  have no idea of the origin of the placebo effect! The placebo effect of non–steroidal pain killers is about 70%. The patient may also suffer from side-effects noted in the leaflet!*
- *The concept of the VIRTUAL PATIENT is an exciting project leading us to new research avenues!*

- *Please contact me\*, your investment in the VIRTUAL PATIENT project will be rewarded!*

**\*** hans.Leuenberger@ifiip.ch