Adaptation free energy: The third generation of models of physiological adaptation

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Plan

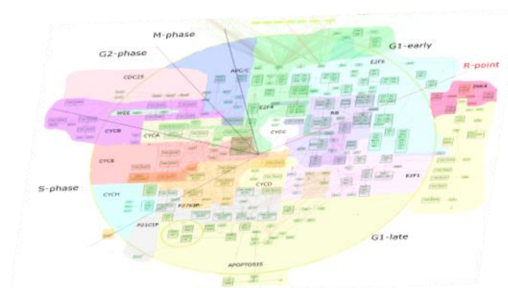
- Top-down modelling in the bottom-up era;
- Homeostasis and stabilisation;
- Selye's "Adaptation energy" – the universal currency for adaptation;
- Goldstone's critics and development of Selye's concept;
- Factor-resource models: resource, reserve and oscillating death;
- Two adaptation in Selye's experiments: Adaptation ***in*** a fitness landscape and adaptation ***of*** the fitness landscape;
- Adaptation entropy and free energy;
- Adaptation to load of many factors;
- Questions.

Between bottom-up and top-down

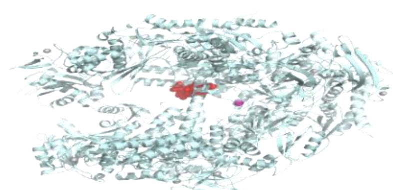
The ‘top-down’ modelling:

- **Describes the world in terms of dynamics, interaction and control of macroscopic processes.**
- **Starts from the most general phenomena and aggregated variables.**

http://learnandreturn.com/



https://navicell.curie.fr/navicell/

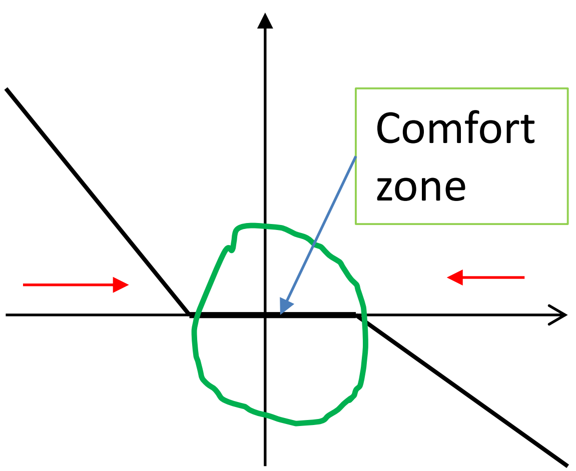


The ‘bottom-up’ modelling:

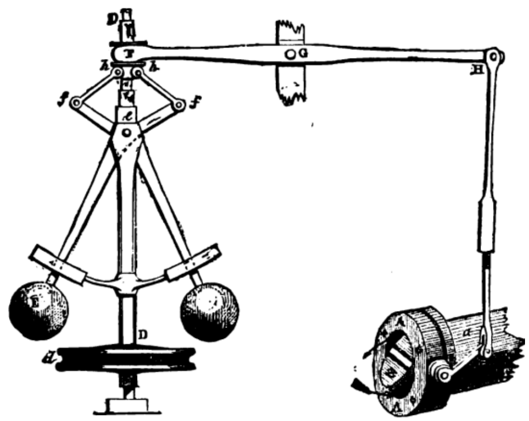
- **Describes the world in terms of elementary processes.**
- **Starts from the level of functioning and interaction of individual entities.**

Homeostasis is, in its essence, automatic stabilisation of the body:

- “Whenever conditions are such as to affect the organism harmfully, factors appear within the organism itself that protect or restore its disturbed balance” (Cannon W.B. The wisdom of the body. 1932)



A formal scheme

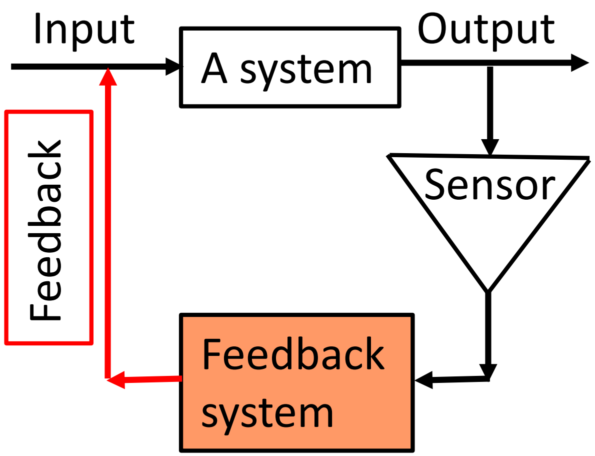


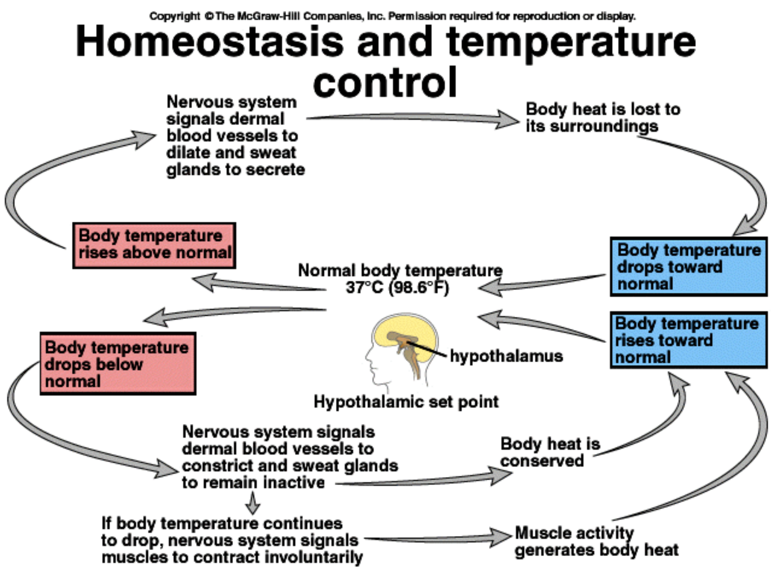
This idea in *engineering*, centrifugal governor, 1788

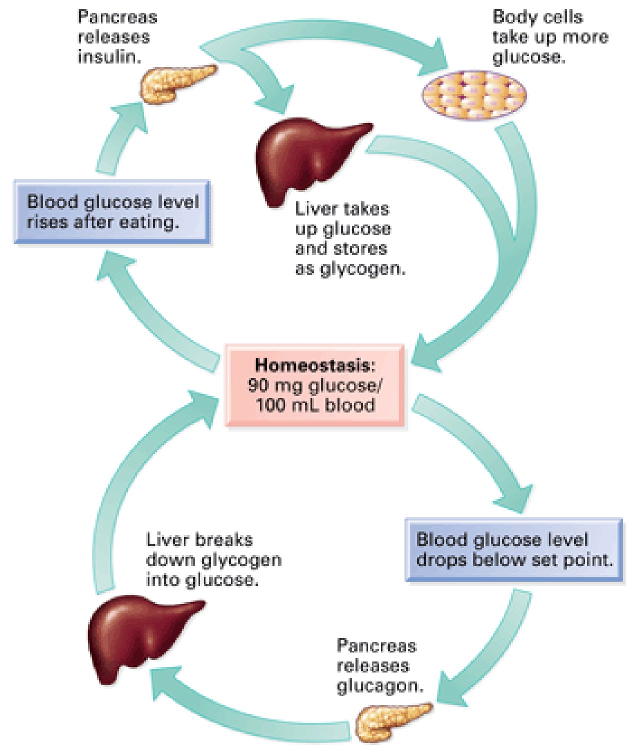
*Any change in **equilibrium** prompts an opposing reaction in the responding system*

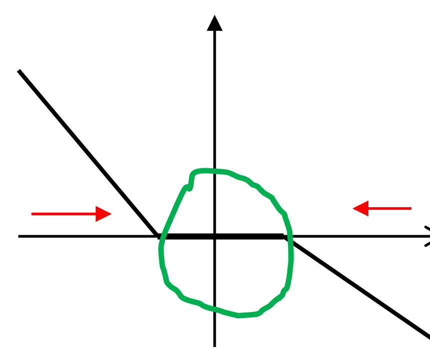
Le Chatelier's principle (1898) in *chemistry* (and beyond)

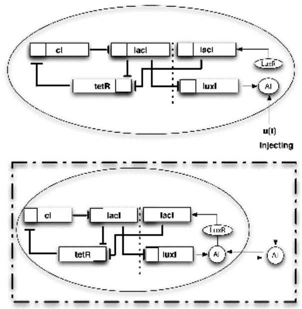
“Textbook” material: feedback loops



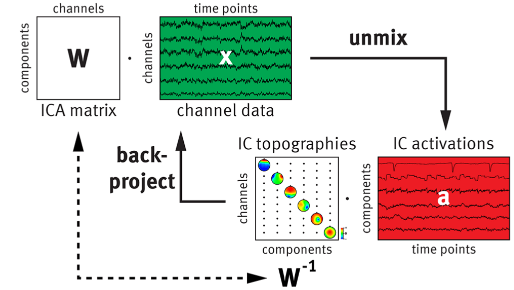








Beyond elementary one-parametric loops



- Decomposition into relatively independent subsystems (functional systems, PCA, ICA, lumping, …);
- Restructuring of the systems under stress;
- Dynamics of complex systems;
- Robustness and canalization;
- ………………..
- Small Models–Qualitative Insights and Large Models–Quantitative Insights (mechanisms driven versus data driven models).
- Tools: Combination of system analysis, dynamics, control theory, and modern data mining.

Cannon’s world – the first generation of adaptation models is developed far enough

1. Organism is represented as ***a structure of relatively independent systems*** (groups of parameters);
2. ***This decomposition is dynamical*** and may change under the load of harmful factors;
3. Homeostasis is provided by **a rich *structure of feedback loops***;

More and more detailed mechanisms of regulation are revealed and supported by the data-driven approach.

The second generation: Selye’s world

Universal dynamic properties and phases of adaptation

General Adaptation Syndrome (H. Selye, 1926)

"Experiments on rats show that if the organism is severely damaged by acute nonspecific nocuous agents such as *exposure to cold, surgical injury, production of spinal shock,…, excessive muscular exercise, or intoxications with sublethal doses of diverse drugs…,* a typical syndrome appears, the symptoms of which are independent of the nature of the damaging agent or the pharmacological type of the drug employed, and represent rather **a response to damage as such**."

…during adaptation to a certain stimulus the resistance to other stimuli decreases.

EXPERIMENTAL EVIDENCE SUPPORTING THE CONCEPTION OF "ADAPTATION ENERGY"

HANS SELYE

From the Department of Anatomy, Histology and Embryology, McGill University, Montreal, Canada

Received for publication May 23, 1938

Am. J. Physiol. 123 (1938), 758-765.

This conception receives further support by experiments showing that rats pretreated with a certain agent will resist such doses of this agent which would be fatal for not pretreated controls. At the same time, their resistance to toxic doses of agents other than the one to which they have been adapted decreases below the initial value.

Selye’s “Adaptation energy” – the universal currency for adaptation

(and the term was a political mistake of Selye because everybody asked him to demonstrate the physical nature of this “energy”; an abstract “adaptation resource” may be better)

Selye's conclusion

- These findings are tentatively interpreted by the assumption that the ***resistance*** of the organism to various damaging stimuli **is dependent on its adaptability**.
- This ***adaptability*** is conceived to depend upon ***adaptation energy*** of which the organism possesses only a limited amount, so that if it is used for adaptation to a certain stimuli will necessarily decrease.
- We conclude that adaptation to any stimulus, is always acquired at a ***cost***, namely, at the cost of adaptation energy.

Goldstone’s critics and development of Selye’s concept

An attempt has been made to decide how one stimulus will affect an individual's power to respond to a different stimulus.

THE GENERAL PRACTITIONER AND THE GENERAL ADAPTATION SYNDROME

BERNARD GOLDSTONE, B.Sc., M.B., B.S. (LOND.), F.R.C.S. (EDIN.)
East London

S. Afr. Med. J. 26 (1952), 88-92, 106-109.

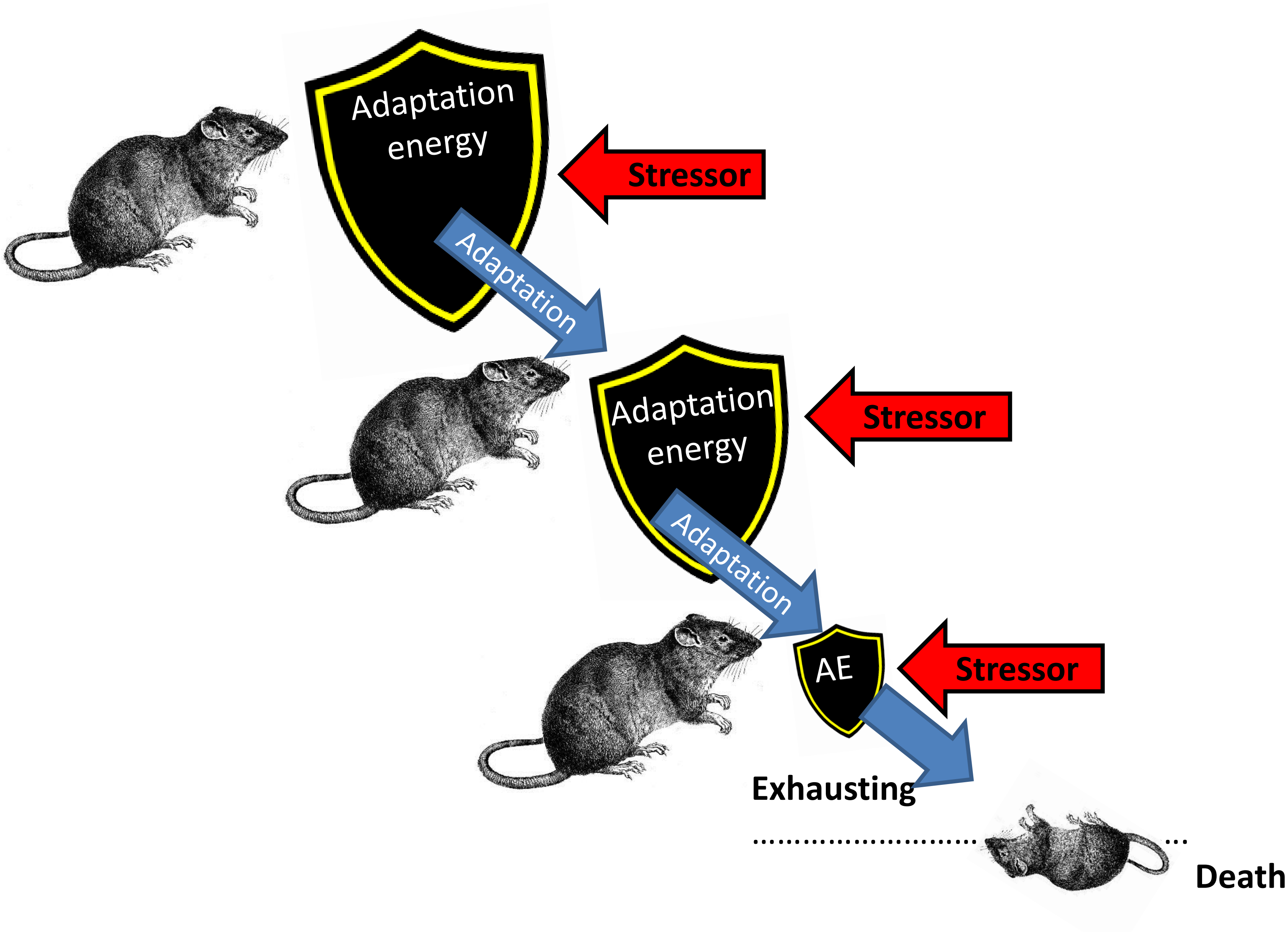
There are several different and apparently contradictory answers; *yet, in different circumstances each of these answers is probably true*:

1. If an individual is failing to adapt to a disease he may succeed in so doing, if he is exposed to a totally different mild stimulus (such as slight fall of oxygen tension).
2. In the process of adapting to this new stimulus he may acquire the power of reacting more intensely to all stimuli.
3. As a result of a severe stimulus an individual may not be able to adapt successfully to a second severe stimulus (such as a disease).
4. If he is already adapting successfully to a disease this adaptation may fail when he is exposed to a second severe stimulus.
5. In some diseases (those of Adaptation) exposure to a fresh severe stimulus may cure the disease. Here, too, exposure to an additional stressor will bring him nearer to death but the risk may be justifiable if it is likely to re-mould the adaptive mechanism to a normal form.

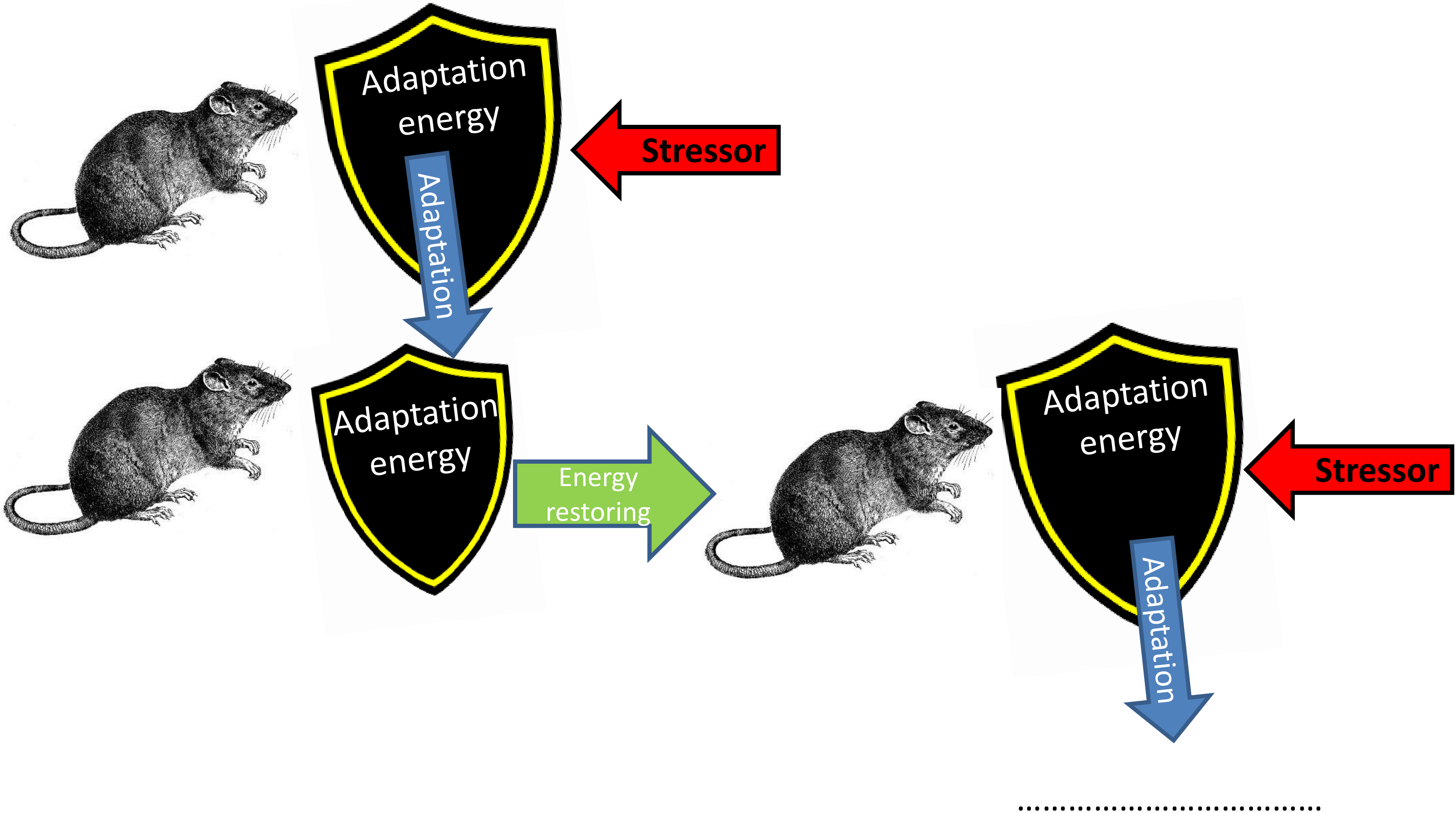
Goldstone found evidences suggesting that previous adaptation strengthens the individual to resist future stressors

- Goldstone proposed the conception of a constant *production* or income of Adaptation Energy which may be stored (up to a limit), as a capital reserve of adaptation.
- He showed that this conception best explains the clinical and Selye's own laboratory findings.
- It is possible that, had Selye's experimental animals been asked to spend adaptation at a lesser rate (below their energy income), they might have coped successfully with their stressor indefinitely.

Selye’s picture of adaptation



Goldstone's picture of adaptation



Selye's axioms of Adaptation Energy (AE)

1. AE is a finite supply, presented at birth.
2. As a protective mechanism, there is some upper limit to the amount of AE that an individual can use at any discrete moment in time. It can be focused on one activity, or divided among other activities designed to respond to multiply occupational challenges.
3. There is a threshold of AE activation that must be present to potentiate an occupational response.
4. AE is active at two levels of awareness: a primary level at which creating the response occurs at a high awareness level, with high usage of finite supply of adaptation energy; and a secondary level at which the response creation is being processing at a sub-awareness level, with a lower energy expenditure.

(Following Schkade & Schultz, 2003)

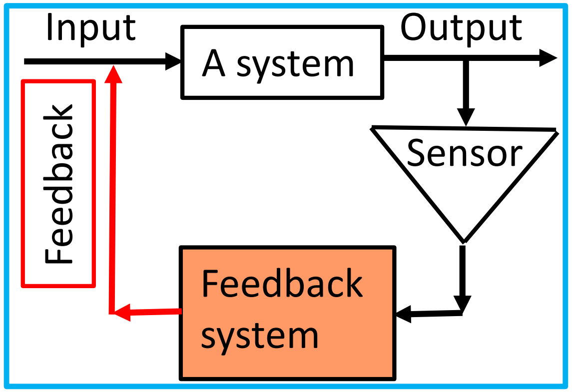
Goldstone's axiom 1'

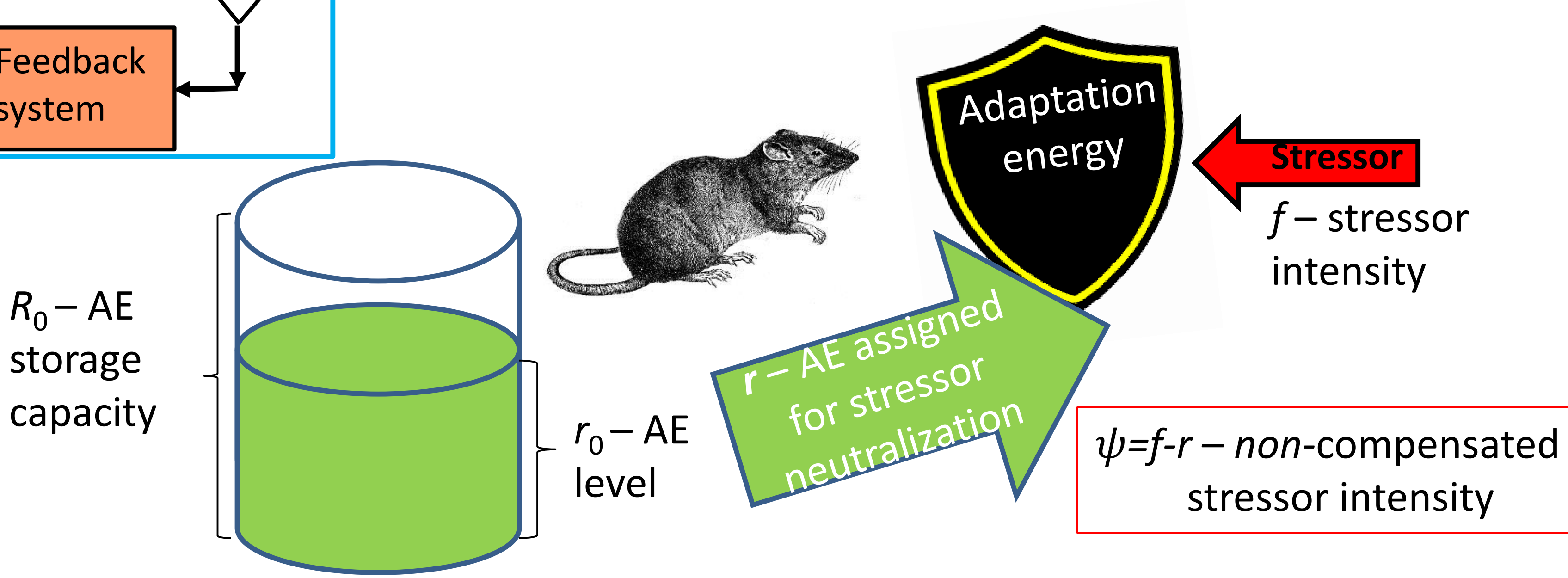
- Adaptation Energy can be created, though the income of this energy is slower in old age;
- It can also be stored as Adaptation Capital, though the storage capacity has a fixed limit.
- If an individual spends his Adaptation Energy faster than he creates it, he will have to draw on his capital reserve;
- When this is exhausted he dies.

Factor-resource models

We try to formalize the findings of physiologists in *simple* dynamic models

Simplest resource dynamics ("superficial AE")





Degradation

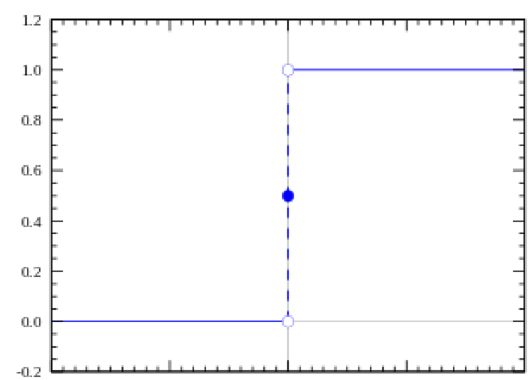
Supply for stressor neutralization

Production

$$\frac{dr}{dt} = -k_d r + k r_0 \psi h(\psi);$$

$$\frac{dr_0}{dt} = -k_d r_0 - k r_0 \psi h(\psi) + k_{pr}(R_0 - r_0).$$

$h(\psi)$ - the Heaviside step function



Correction is necessary

Degradation

Supply for stressor neutralization

Production

$$\frac{dr}{dt} = -k_d r + k r_0 \psi h(\psi);$$

$$\frac{dr_0}{dt} = -k_d r_0 - k r_0 \psi h(\psi) + k_{pr}(R_0 - r_0).$$

For large f

$$r_0 \approx \frac{k_{pr} R_0}{kf}; \quad r \approx \frac{k r_0 f}{k_d} \approx \frac{k_{pr} R_0}{k_d}$$

When f→∞ no crises appear. Immortality is possible.
Something is wrong…

Correction is necessary: threshold of death

Non-compensated stressors ψ=*f*-*r*

Degradation

Supply for stressor neutralization

Production

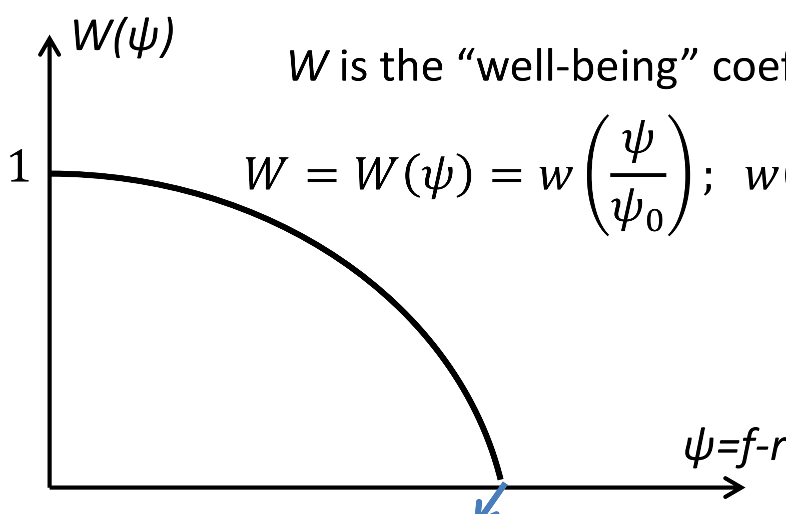
$$\frac{dr}{dt} = -k_d r + k r_0 \psi h(\psi);$$

$$\frac{dr_0}{dt} = -k_d r_0 - k r_0 \psi h(\psi) + k_{pr}(R_0 - r_0) \times W.$$

AE production should decrease for large non-compensated stressors ψ=*f*-*r*

W is the “well-being” coefficient (fitness)

$$W = W(\psi) = w\left(\frac{\psi}{\psi_0}\right); \;\; w(x) = 0 \; if \; x > 1$$



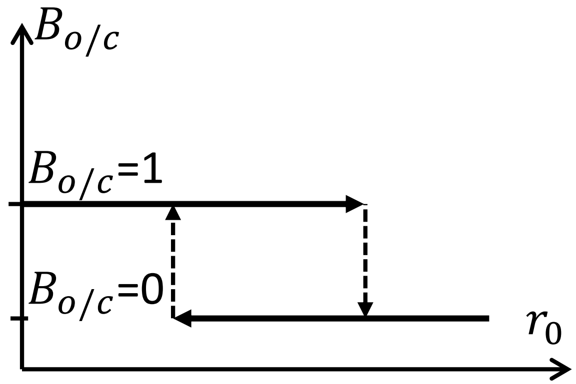
Threshold appears: If $f > \psi_0$ then a threshold $\theta > 0$ exists: if $r(0) + r_0(0) < \theta$ then $r(t) + r_0(t) \to 0$ as $t \to \infty$

$\psi = \psi_0$ – the critical value of the non-compensated stressor intensity

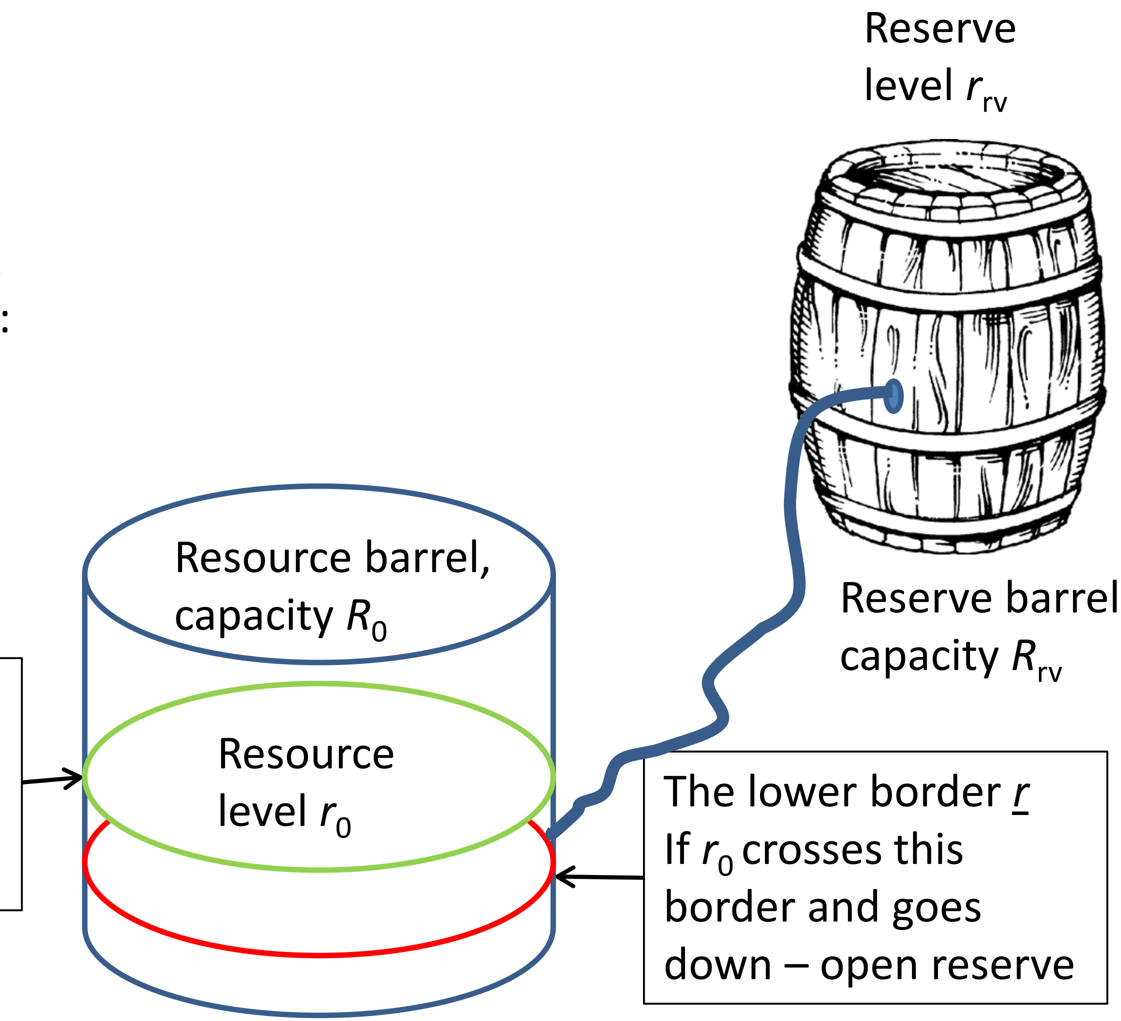
If $f < \psi_0$ then life is possible (*W*>0) without adaptation (with *r*=0)

Resource (superficial AE) & reserve (deep AE)

Reserve



Hysteresis of reserve supply:
$B_{o/c}$=0 – reserve is closed
$B_{o/c}$=1 – reserve is open



Resource & reserve model

The simplest dynamical model has three real variables and one Boolean

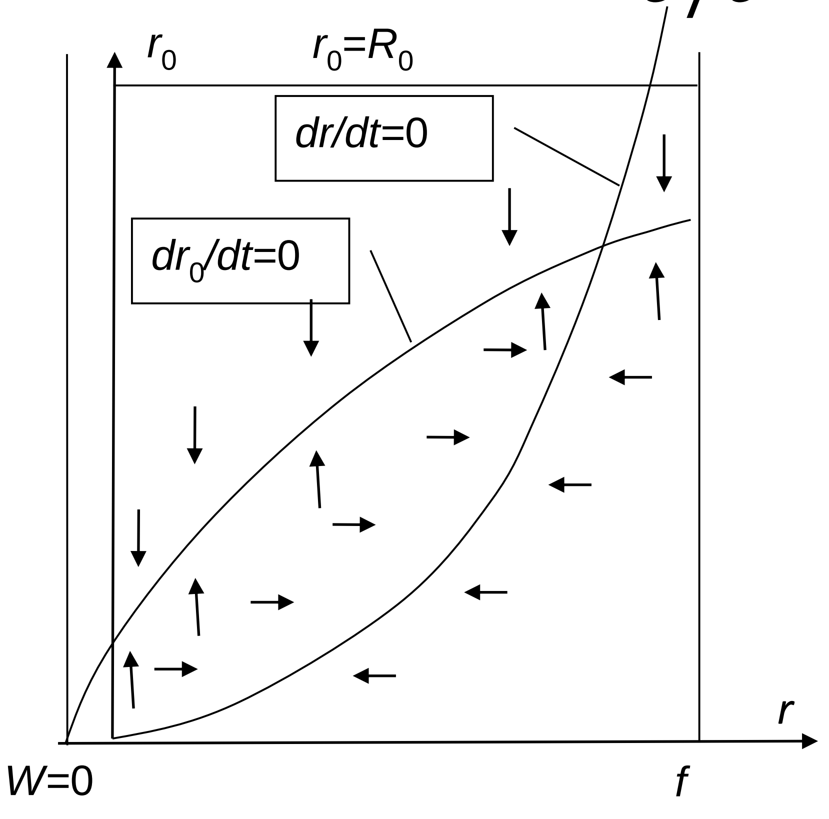
$$\frac{dr}{dt} = -k_d r + k r_0 \psi h(\psi);$$

$$\frac{dr_0}{dt} = -k_d r_0 - k r_0 \psi h(\psi) + k_{pr} r_{\mathrm{rv}} B_{o/c}(R_0 - r_0) + k_{pr}(R_0 - r_0)W;$$

$$\frac{dr_{\mathrm{rv}}}{dt} = -k_d r_{\mathrm{rv}} - k_{pr} r_{\mathrm{rv}} B_{o/c}(R_0 - r_0) + k_{pr1}(R_{\mathrm{rv}} - r_{\mathrm{rv}})W$$

If reserve is open then $r_0 < \bar{r}$. It closes when $r_0 = \bar{r}$. If reserve is closed then $r_0 > \underline{r}$. It opens when $r_0 = \underline{r}$.

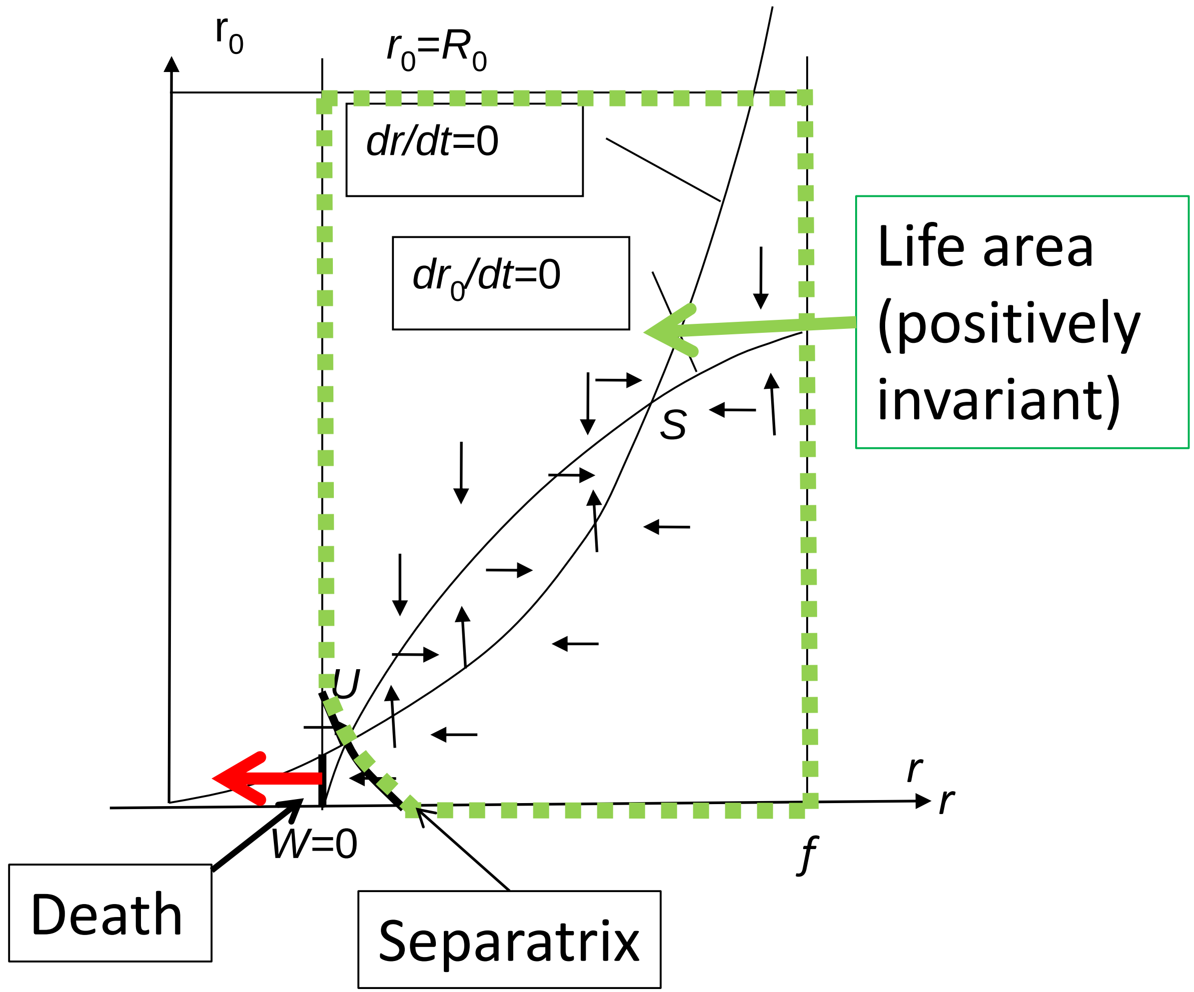
Null-isoclines on (r, r_0) plane for $B_{o/c}$=0 and $f < \psi_0$



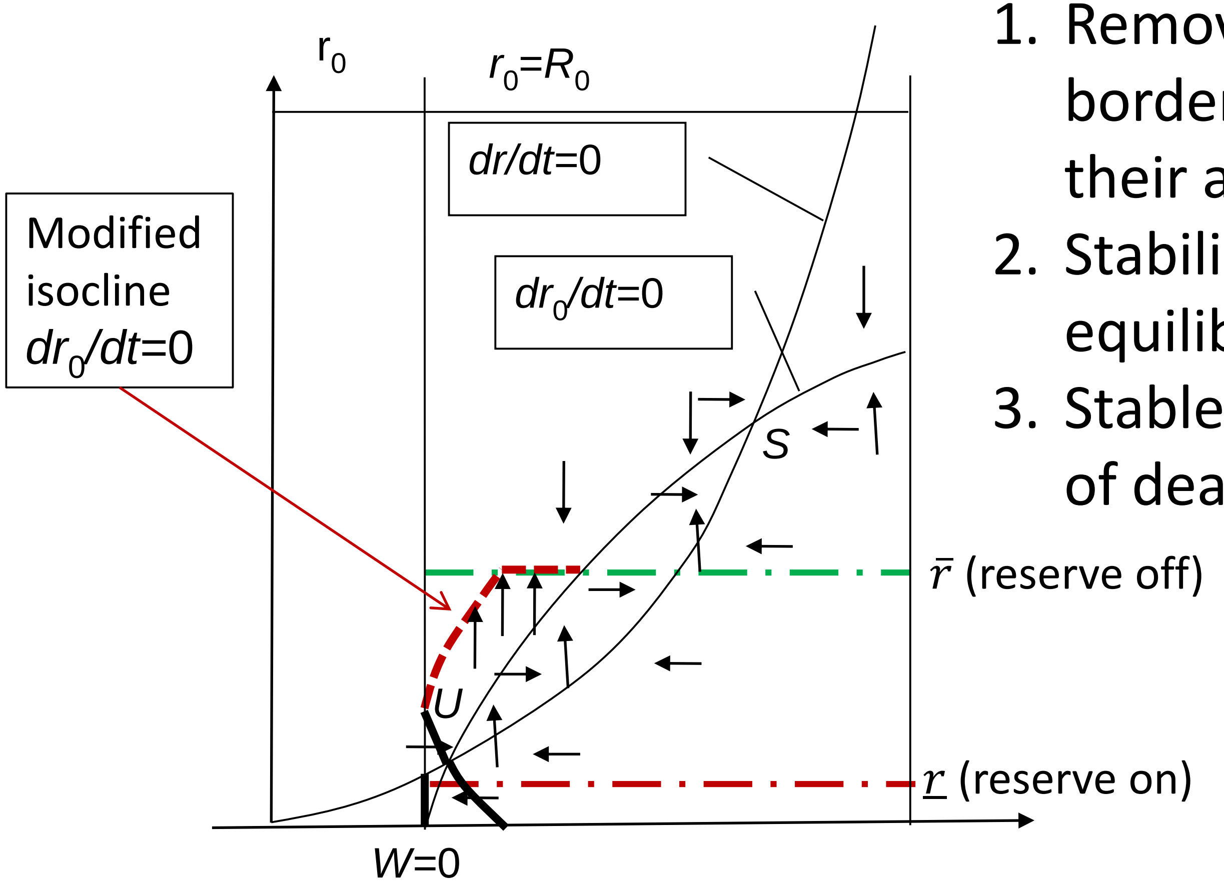
The safe situation.

- Equilibrium is unique and stable.
- The "death border" *W*=0 is in the negative area.
- It is unattainable from the positively invariant rectangular $0 \le r \le f, 0 \le r_0 \le R_0$

Null-isoclines on (r, r_0) plane for $B_{o/c}$=0 and $f > \psi_0$



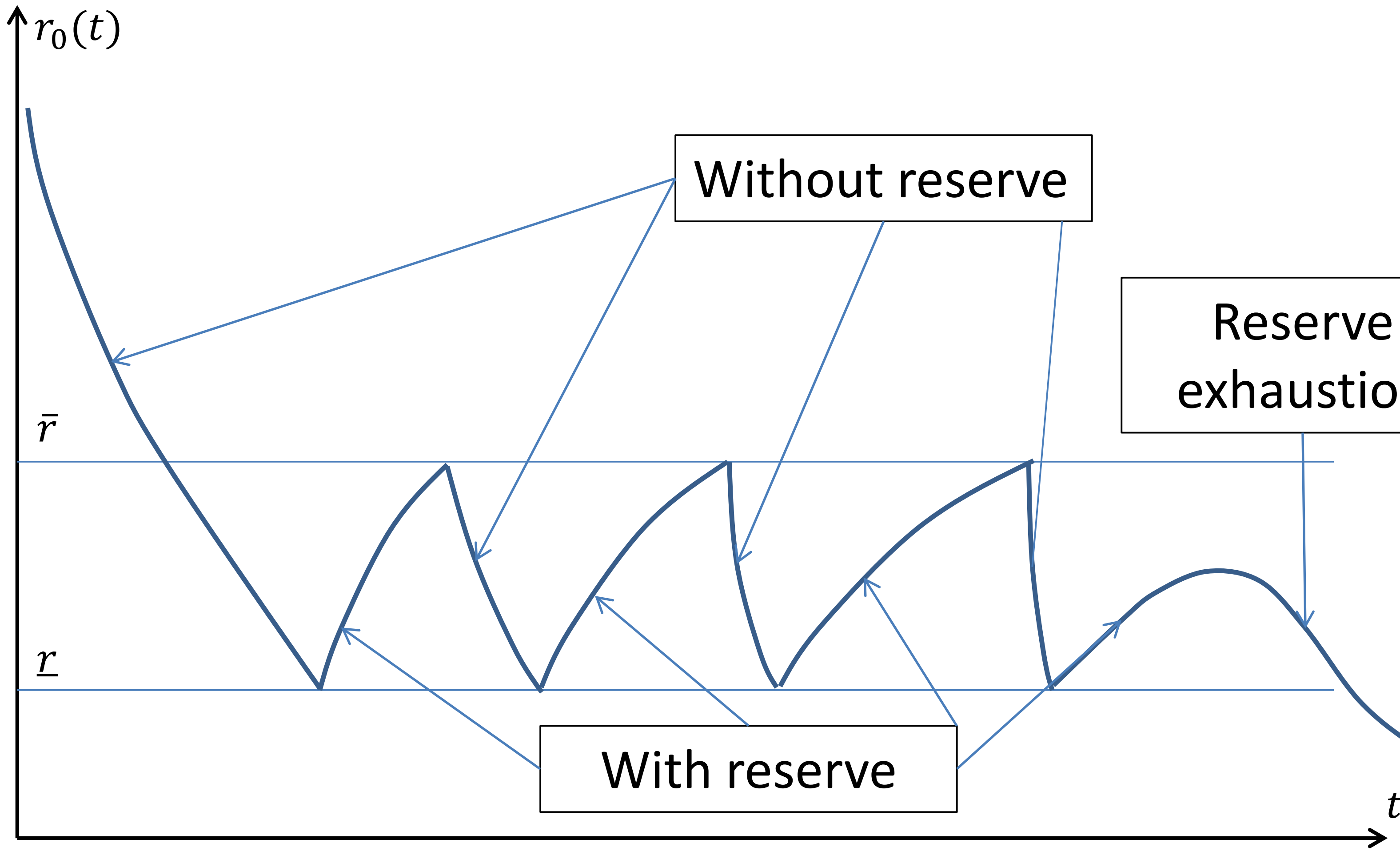
Stabilisation by reserve



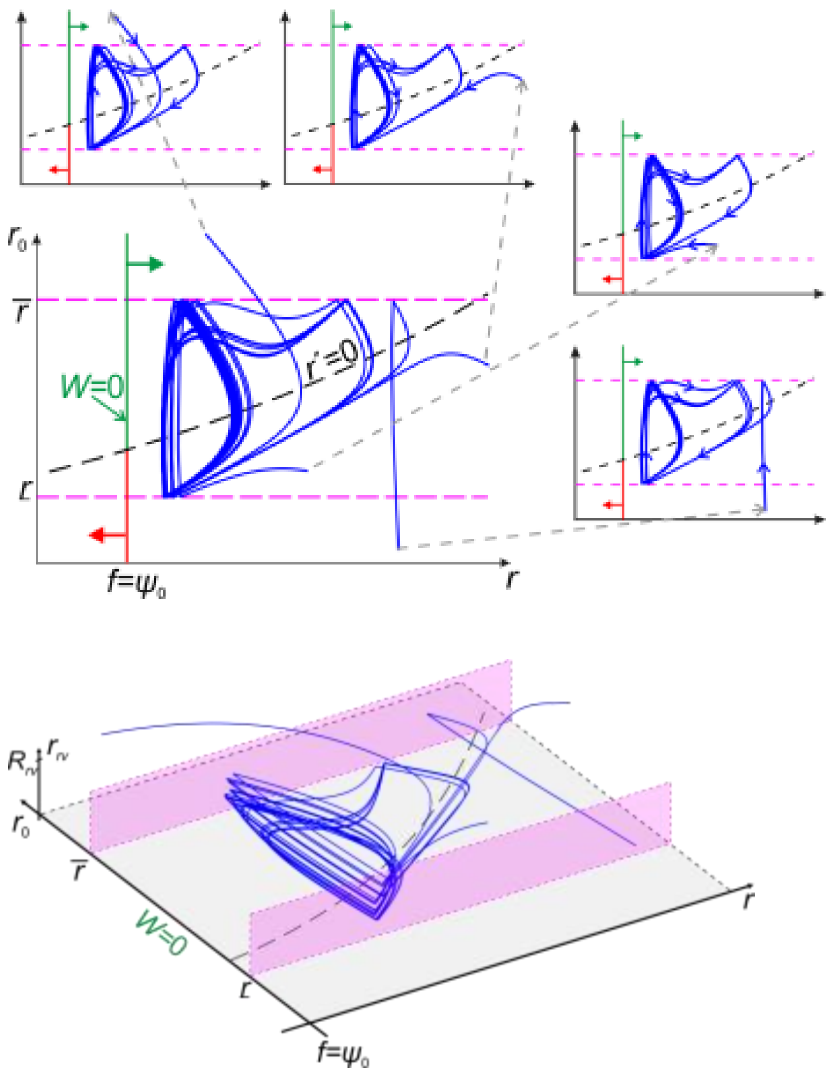
Three types of stabilisation:

1. Removing dangerous borders or reduction of their attainability regions;
2. Stabilisation of unstable equilibria;
3. Stable oscillations instead of deaths.

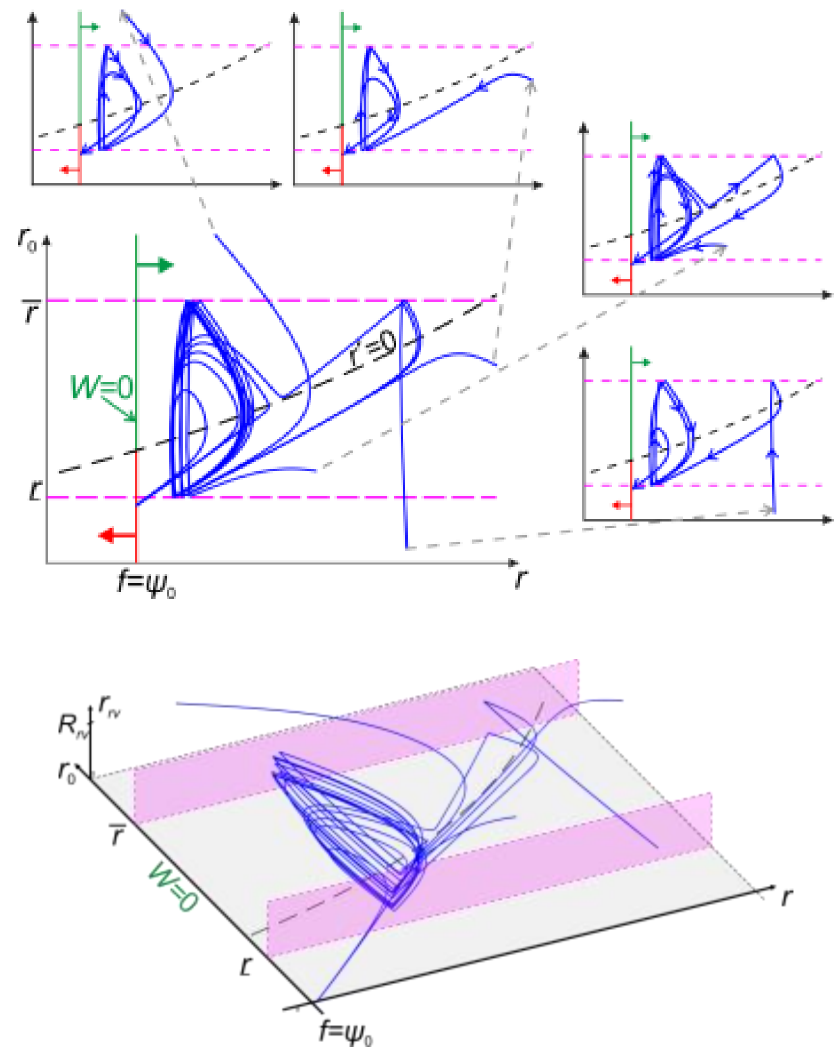
Phenomenon of oscillating death



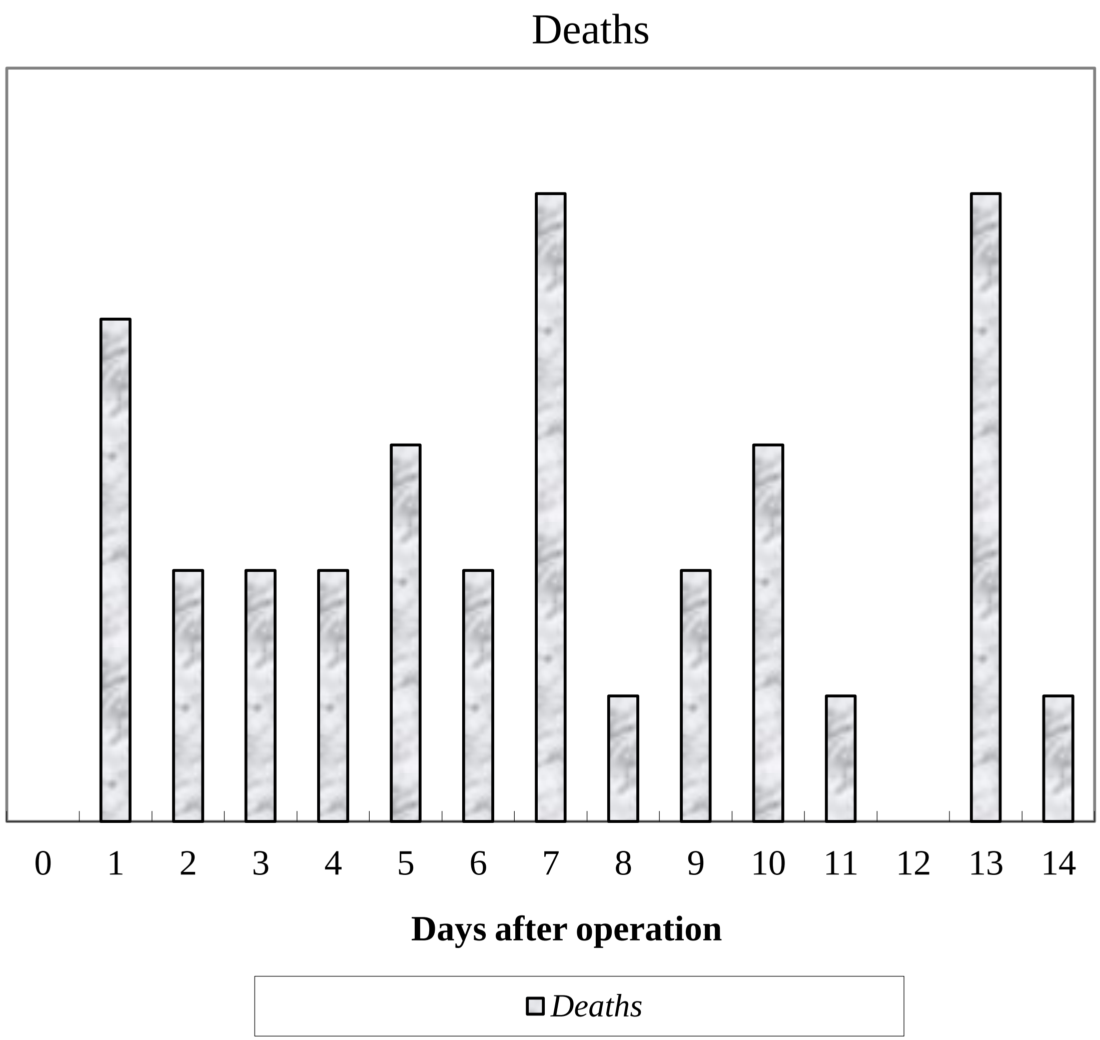
Stable oscillations for various initial conditions



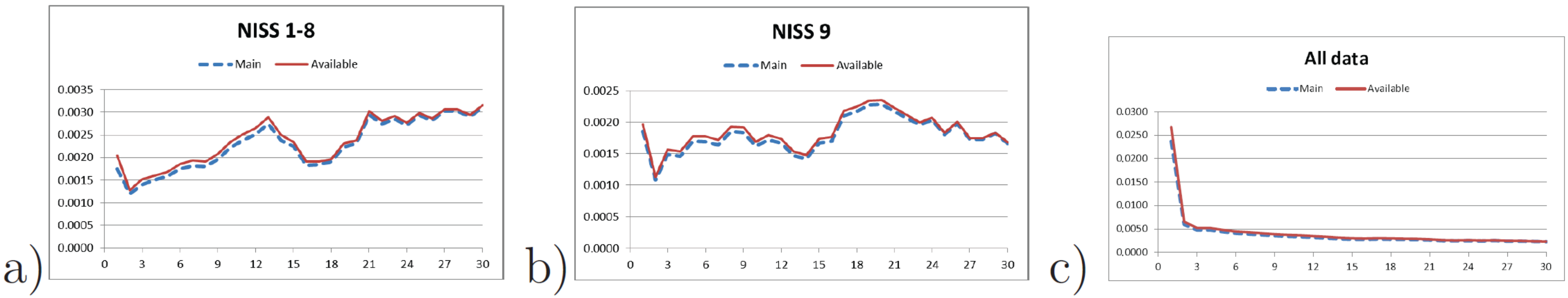
Metastable oscillations for various initial conditions (oscillating death)



Oscillating mortality after cancer surgery operation (high severity cohort)



Oscillating mortality for trauma (low severity cohort)



Daily coefficient of mortality -- evaluated probability of a patient to die on day *t* under condition that he survived during days [1,*t*-1]:

a) for NISS severities 1-8,

b) for NISS severity 9,

c) for the whole dataset (monotonically decreases).

NISS= New Injury Severity Score

E.M. Mirkes, T.J. Coats, J. Levesley, A.N. Gorban, **Handling missing data in large healthcare dataset: a case study of unknown trauma outcomes,** *Computers in Biology and Medicine* 75 (2016), 203-216.

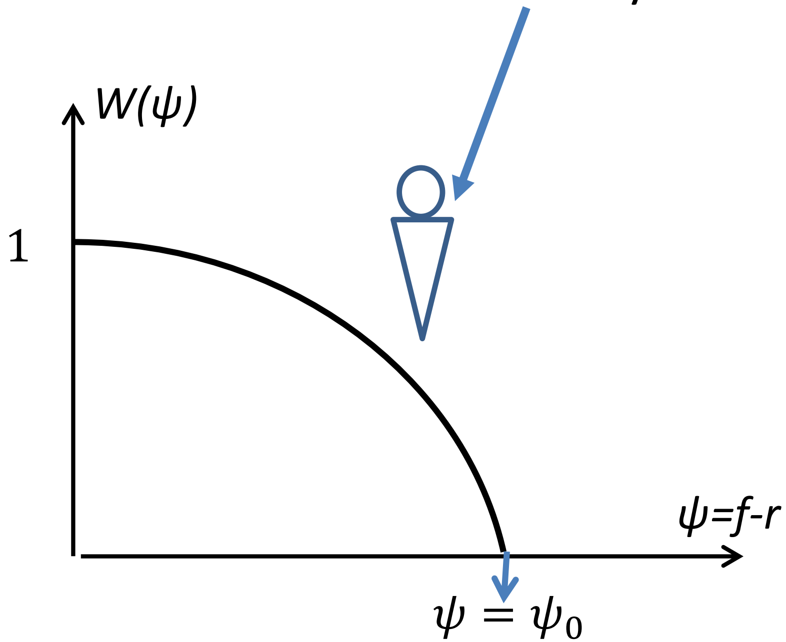
Training problem, adaptation entropy and the third generation of adaptation models

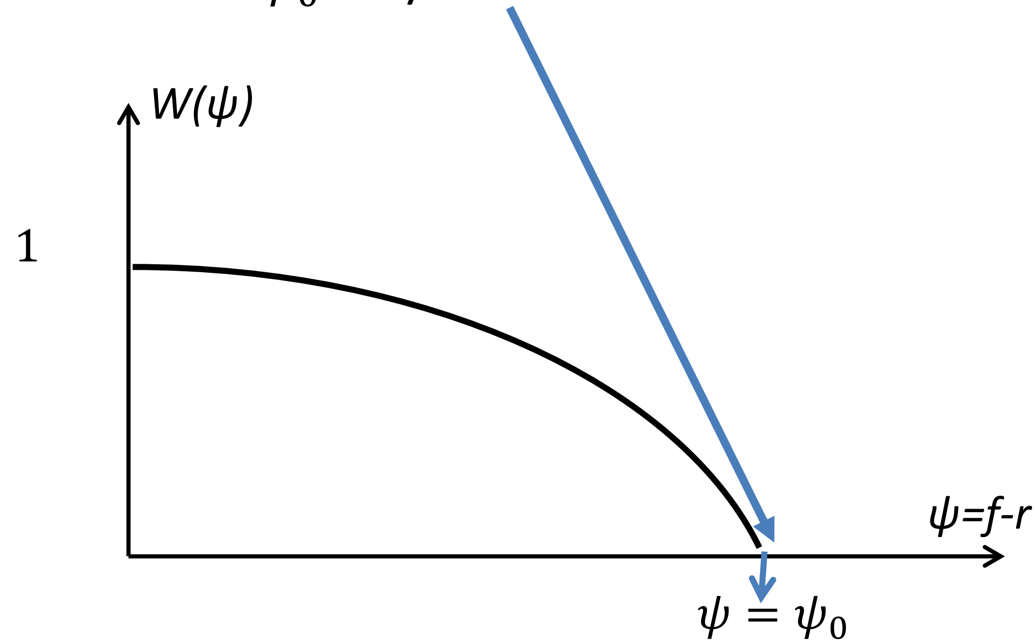
We have lost the training effects.
Where?

I do not understand: is training possible? Something seems to be wrong!

ψ_0 may be ***non-constant.***

If I stay here for time *T* then ψ_0 may increase

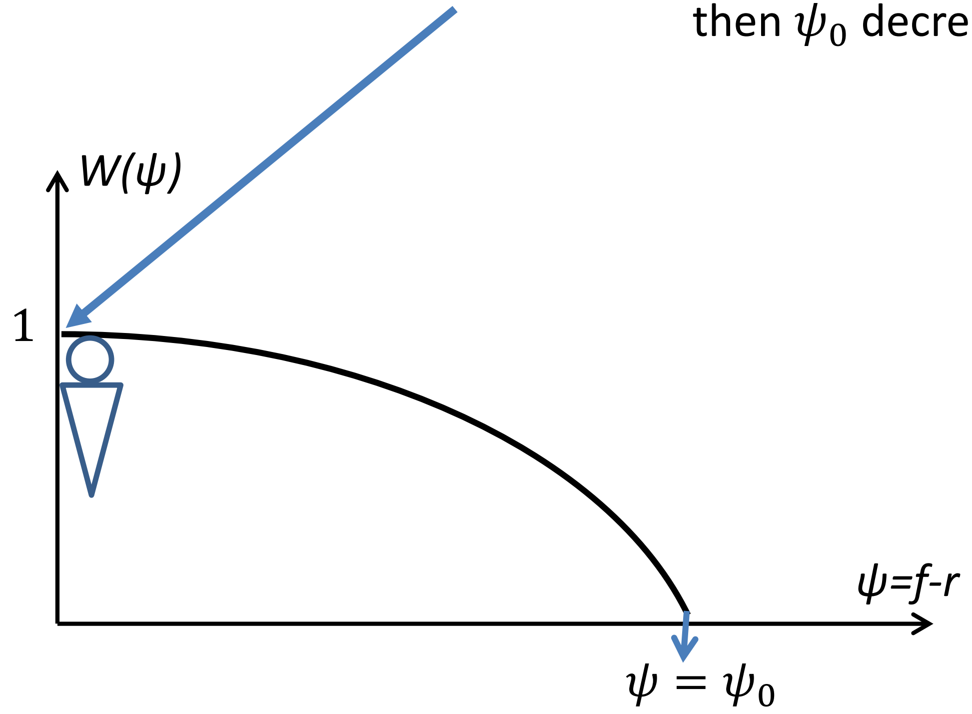


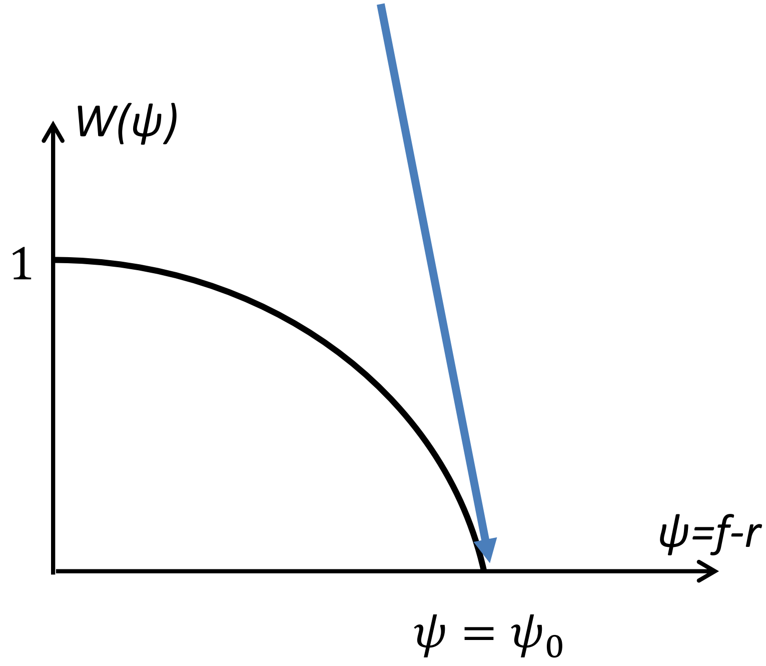


Training is increasing of ψ_0. This process consumes AE. The rate of this process depends on available AE and on the well-being *W*. One more simple ODE for dynamics of ψ_0 should be added.

Detraining

If I stay in the area with small ψ for sufficiently long time then ψ_0 decreases





Dynamics of adaptation with training effects

Rescaling of AE demand and supply

$$\frac{dr}{dt} = -k_d r + k r_0 \frac{\psi}{\psi_0} h(\psi) - k_{\text{training}} \frac{\psi}{\psi_0} w\left(\frac{\psi}{\psi_0}\right) r;$$

$$\frac{dr_0}{dt} = -k_d r_0 - k r_0 \frac{\psi}{\psi_0} h(\psi) + k_{pr} r_{\text{rv}} B_{o/c}(R_0 - r_0) + k_{pr}(R_0 - r_0) w\left(\frac{\psi}{\psi_0}\right);$$

$$\frac{dr_{\text{rv}}}{dt} = -k_d r_{\text{rv}} - k_{pr} r_{\text{rv}} B_{o/c}(R_0 - r_0) + k_{pr1}(R_{\text{rv}} - r_{\text{rv}}) w\left(\frac{\psi}{\psi_0}\right);$$

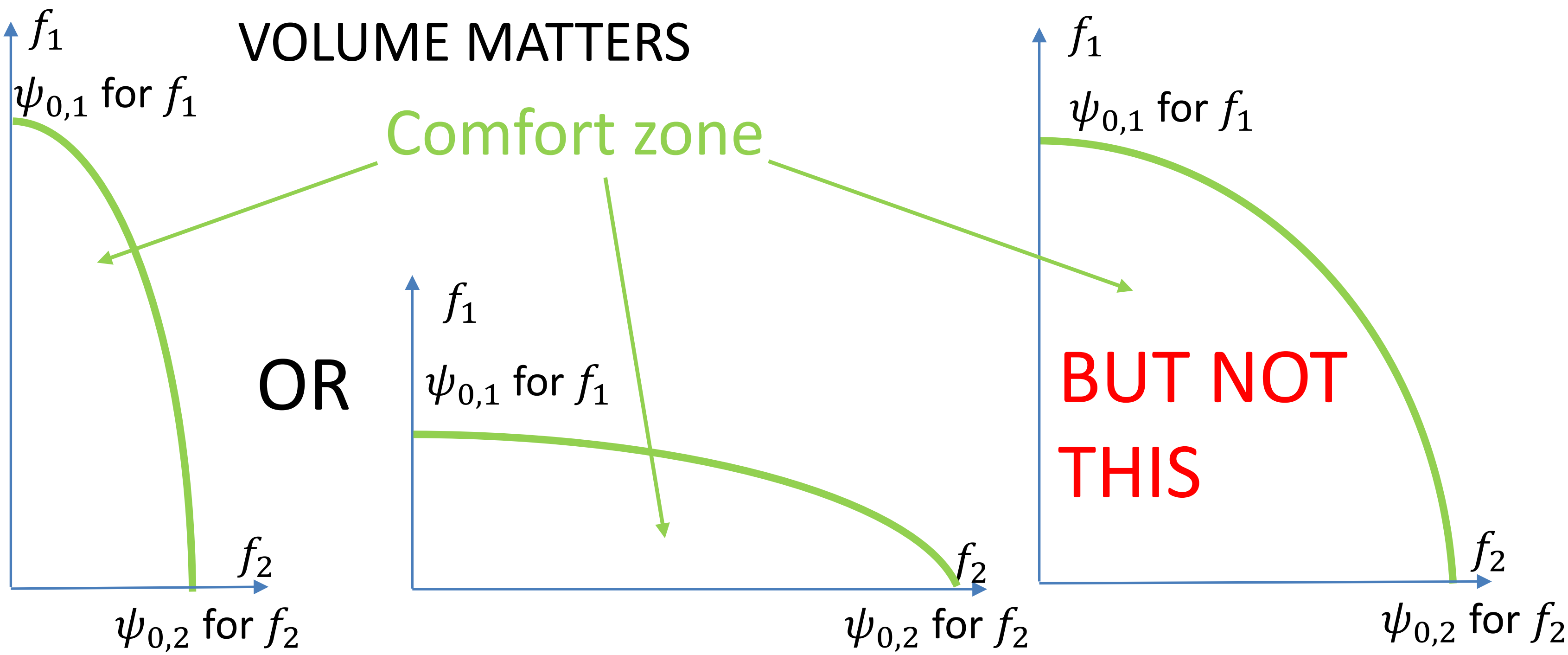
$$\frac{1}{\psi_0}\frac{d\psi_0}{dt} = -k_{\text{detraining}} + \alpha k_{\text{training}} \frac{\psi}{\psi_0} w\left(\frac{\psi}{\psi_0}\right) r.$$

α>0 – *efficiency of AE supply for training*

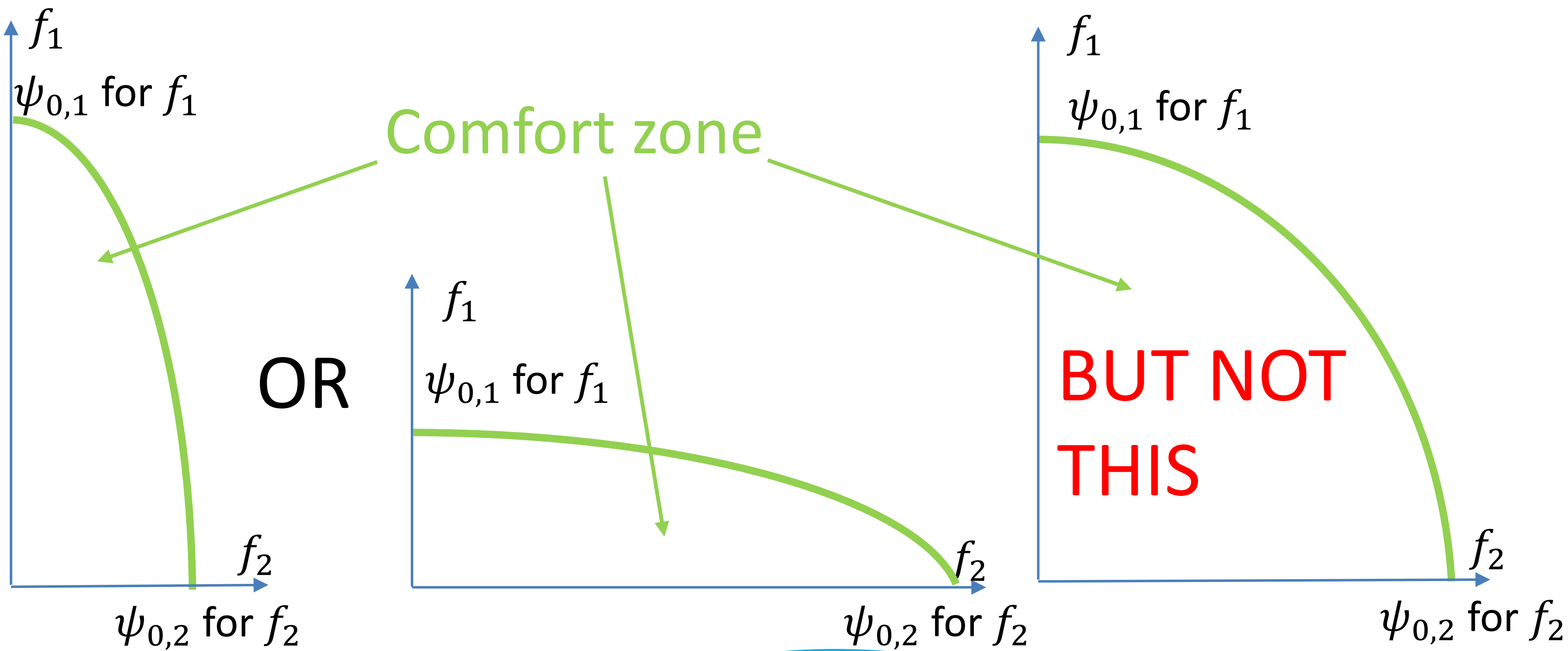
The last equation generalises the popular models of athletic training and performance, see, for example, a review in
Clarke DC, Skiba PF. Rationale and resources for teaching the mathematical modeling of athletic training and performance. *Advances in physiology education*. 2013 Jun 1;37(2):134-52.

Adaptation to several factors (Selye's experiments, 1938)

This conception receives further support by experiments showing that rats pretreated with a certain agent will resist such doses of this agent which would be fatal for not pretreated controls. At the same time, their resistance to toxic doses of agents other than the one to which they have been adapted decreases below the initial value. *Am. J. Physiol. 123 (1938), 758-765*.



Volume matters



$$Vol \propto \prod_i \psi_{0,i}\,;\ \ln(Vol) = \sum_i \ln \psi_{0,i} + \cdots$$

$\ln(Vol)$ is entropy, the main term is additive in the logarithms of the comfort zone widths $\ln \psi_{0,i}$ for various stressors

Pumping of adaptation energy into an entropic reservoir

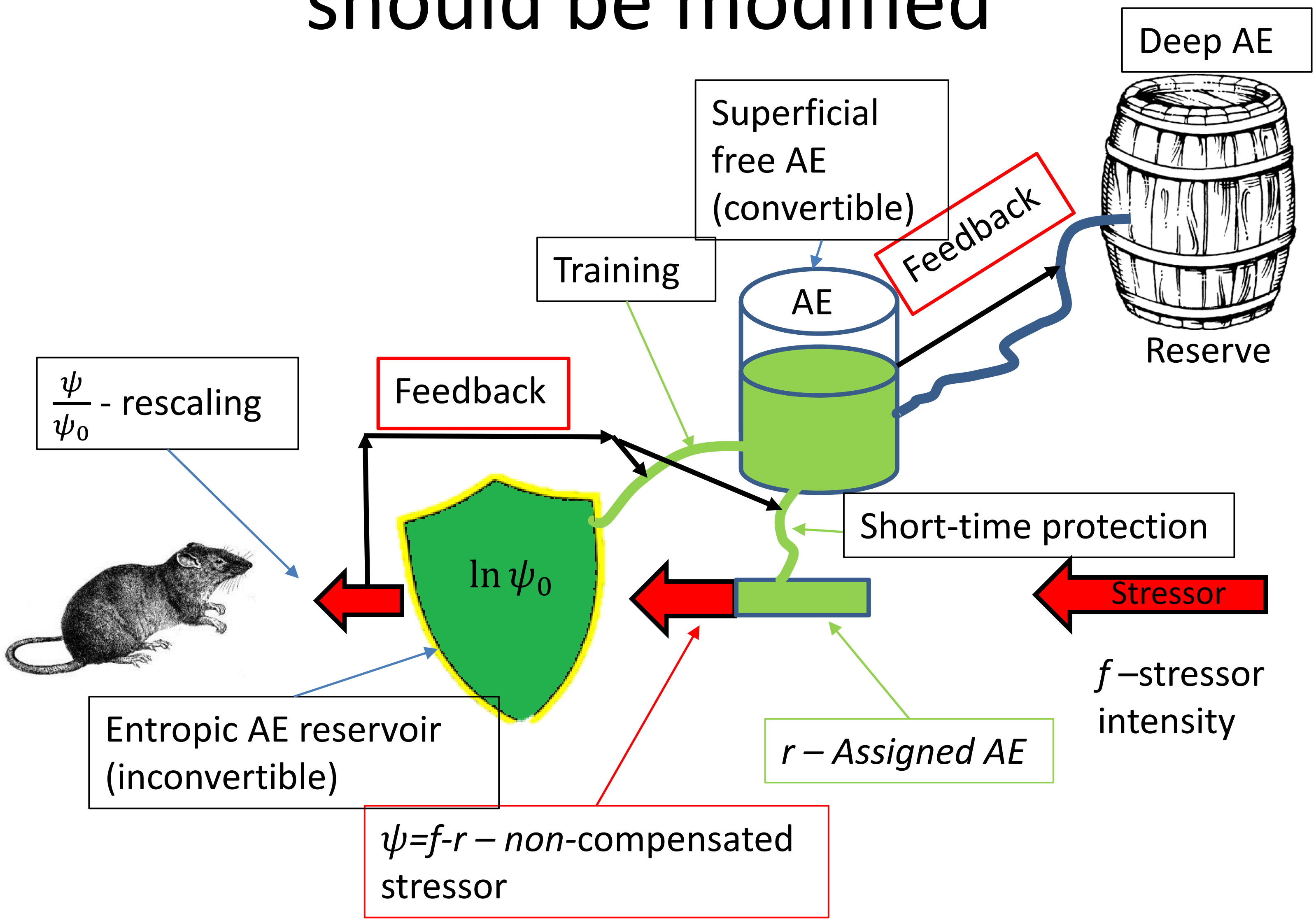
$$\frac{dr}{dt} = \cdots - k_{\text{training}} \frac{\psi}{\psi_0} w\left(\frac{\psi}{\psi_0}\right) r;$$

……………………………………………………………………..

$$\frac{1}{\psi_0}\frac{d\psi_0}{dt} = -k_{\text{detraining}} + \alpha k_{\text{training}} \frac{\psi}{\psi_0} w\left(\frac{\psi}{\psi_0}\right) r.$$

- Training is a medium-term adaptation process with transformation of the adaptation energy into entropic form, $\ln \psi_0$.
- Following Selye, this transformation is irreversible and the transformed energy cannot be spent to other purposes.
- Life lengths of this entropic form is determined by the detraining constant $k_{\text{detraining}}$.
- According to sport medicine models, $k_{\text{detraining}}$ may be rather small and $1/k_{\text{detraining}} \sim 10$ weeks in some cases.

The "adaptation shield" metaphor should be modified



Distribution of adaptation resource for neutralization of several factors

(Adaptation of adaptation to many stressors)

Definition of deep questions:

A question is deep if it allows at least two answers which are true but contradict each other.

(Scientific folklore)

Adaptive systems under load of many factors: do they become ***more*** or ***less*** similar under stress?

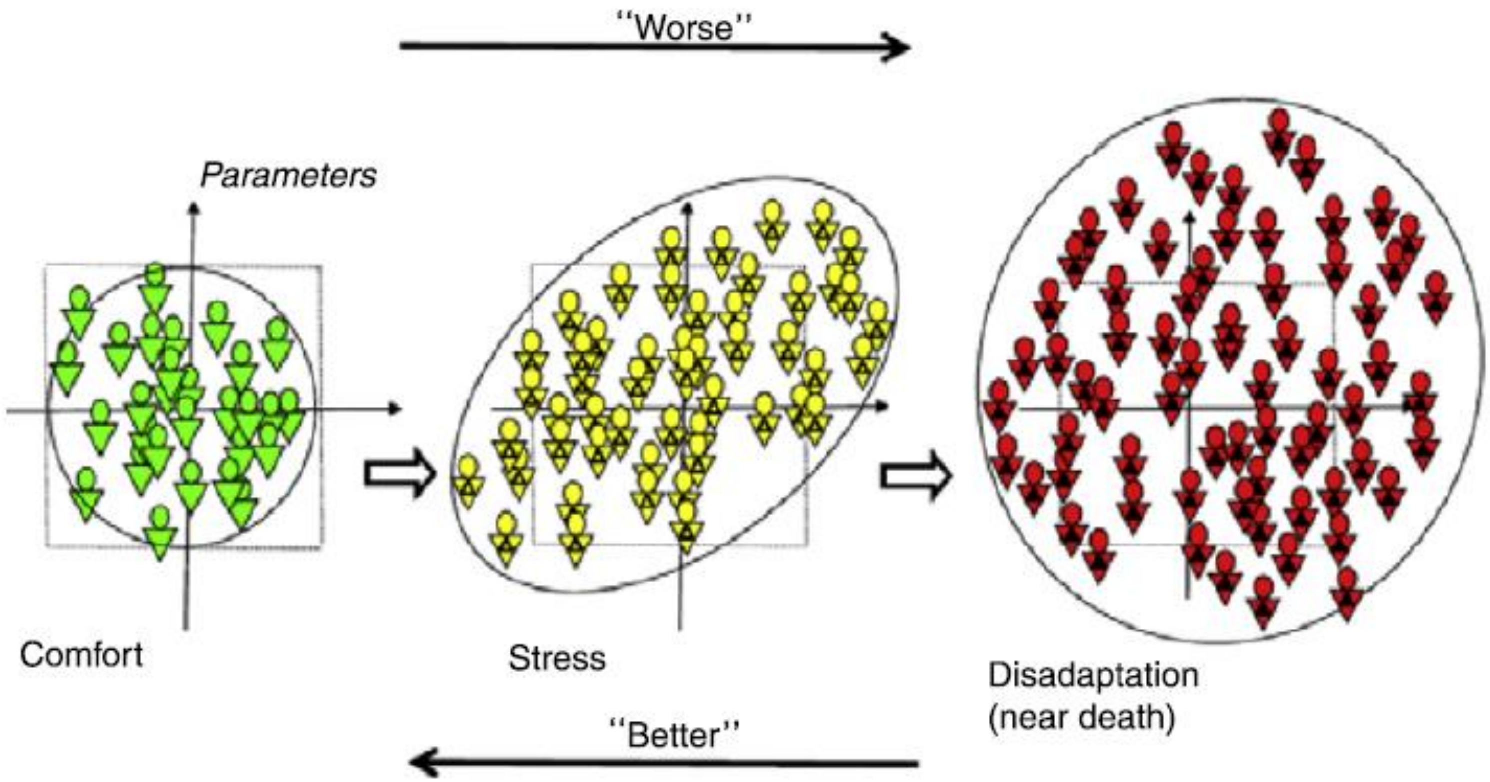
Both answers are correct simultaneously:

1. They become more similar because stress!
2. They become less similar because stress!

This is a deep question.

How it may occur? See the next slide

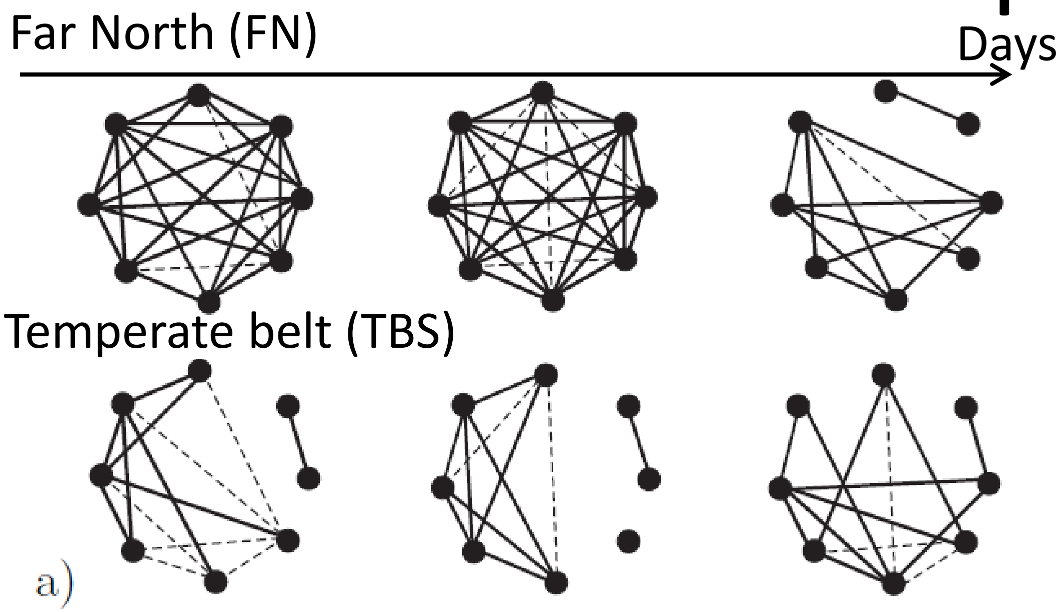
Correlations and variance in crisis

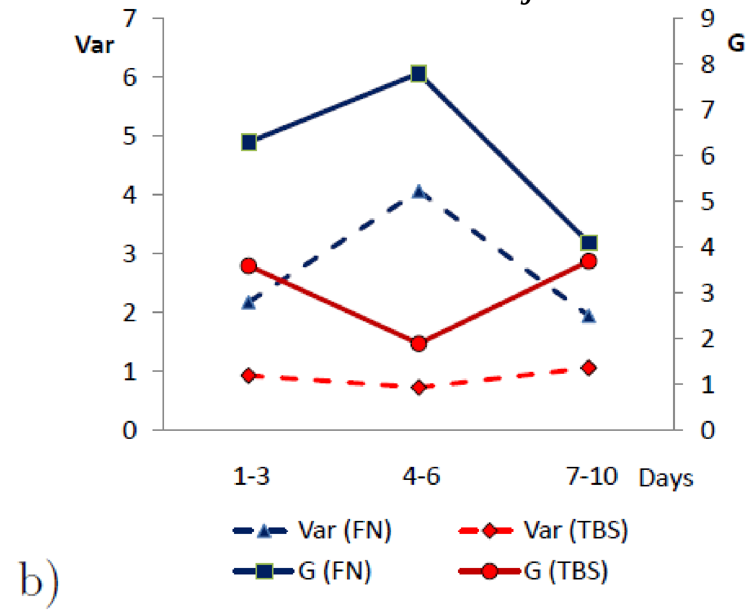


The typical picture:
Cor↑ Var ↑ stress; (correlations increase – more similarity;
variance increases – more differences)
Cor ↓ Var ↓ recovering;
Cor ↓ Var ↑ approaching the disadaptation catastrophe.
Axes correspond to attributes, normalized to the unite variance in the comfort state.

Example

$$G = \sum_{i \neq j} |r_{ij}|$$





a) Correlation graphs of lipid metabolism for newborn babies.

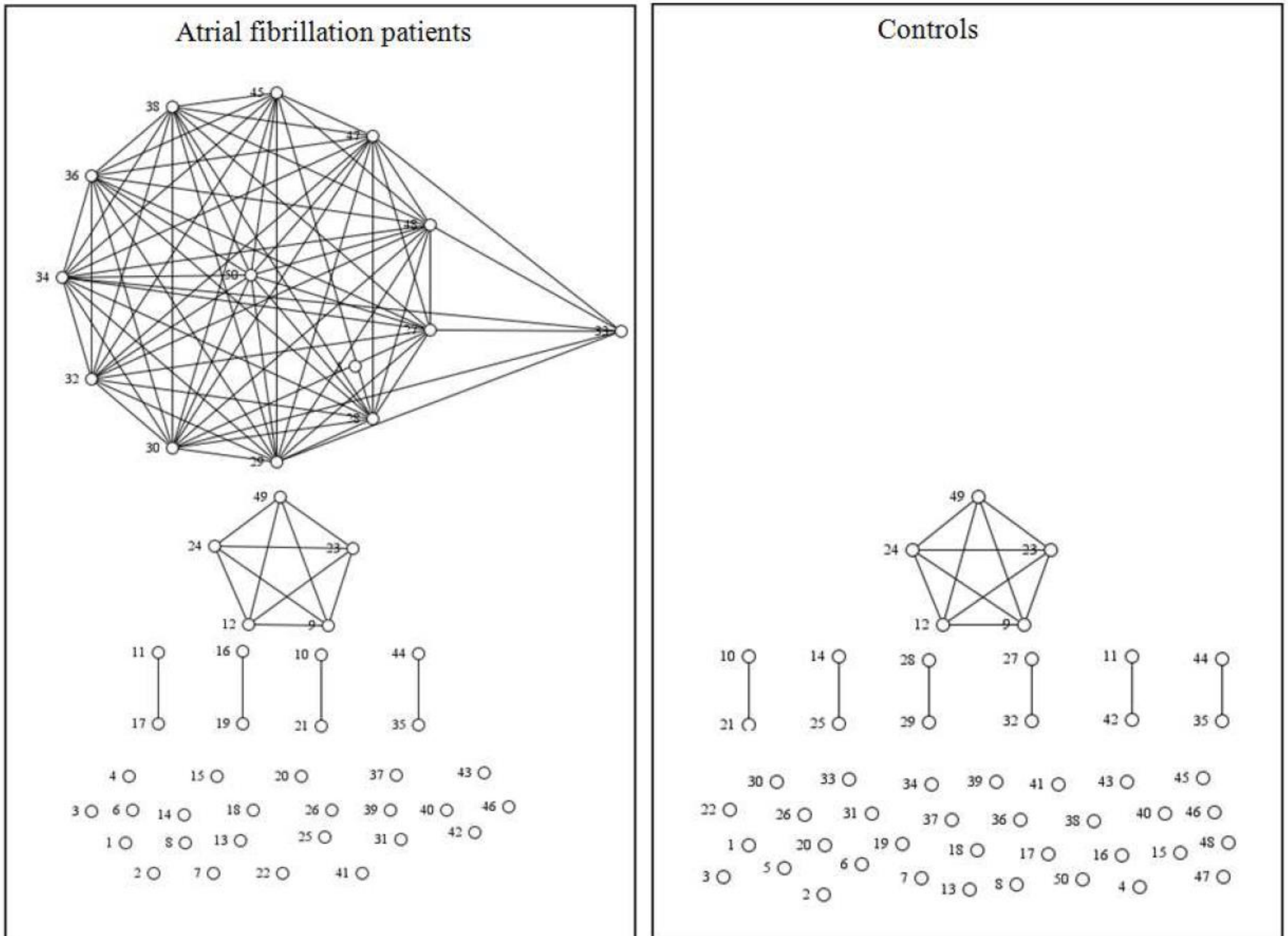
- Vertices – fractions of lipids, solid lines – correlation coefficient between fractions $|r_{ij}| \geq 0.5$, dashed lines $0.5 > |r_{ij}| \geq 0.25$.
- Upper row – Far North (FN), lower row – the temperate belt of Siberia (TBS).
- From the left to the right: 1st-3rd days, 4th-6th days, 7th-10th days.

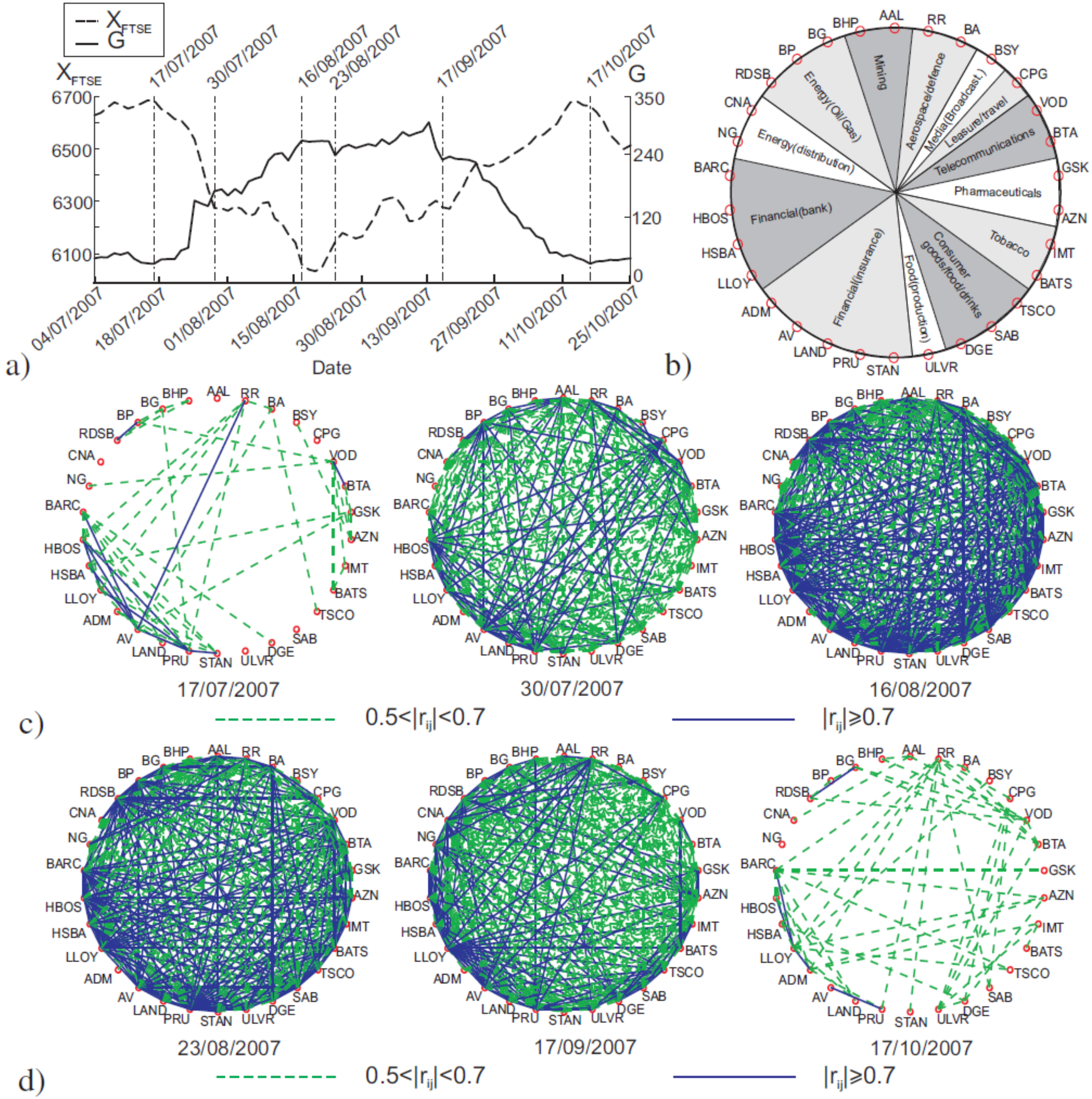
b) The weight of the correlation graphs (solid lines) and the variance (dashed lines)

Gorban, Smirnova, 1987

The gene regulatory networks formed by the 50 genes best discriminating Atrial fibrillation patients from control

(microarray data, *Censi, Giuliani, Bartolini, Calcagnini*, 2011)





Financial crisis 2007: 30 larges companies from FTSE, correlations between daily closing price log-returns in sliding windows

Gorban, Smirnova, Tykina, 2010

Distribution of resources for neutralisation of several factors

Assume that adaptation should maximize a fitness function *W* which depends on the compensated values of factors,

$$\psi_i = f_i - a_i r_i$$

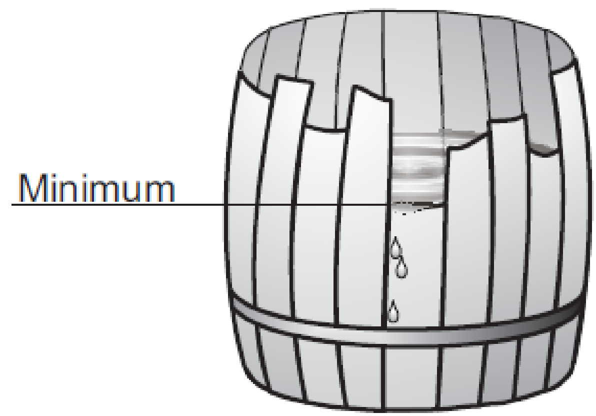
for the given amount of available resource:

$$\begin{cases} W(f_1 - a_1 r_1, f_2 - a_2 r_2, \dots f_q - a_q r_q) \;\to\; \max \; ; \\ r_i \geq 0,\; f_i - a_i r_i \geq 0,\; \sum_{i=1}^{q} r_i \leq R \; . \end{cases}$$

The structure of solution depends on the properties of function *W.*

Law of the Minimum

Liebig's law



Liebig's barrel: the capacity of the barrel is limited by the shortest stave.

$$W = W\left(\max_{1\leq i\leq q}\{f_i - a_i r_i\}\right) \;;\; \frac{\partial W(x)}{\partial x} \leq 0 \qquad (20)$$

under conditions $r_i \geq 0$, $f_i - a_i r_i \geq 0$, $\sum_{i=1}^{q} r_i \leq R$, $f_i \geq 0$ for all i.

Adaptation acts as a cooper that repairs Liebig's barrel

- If the system satisfies the Law of the Minimum, then the adaptation process makes the tension produced by different factors more uniform.
- Adaptation decreases the effect from the limiting factor and hides manifestations of the Law of the Minimum.
- The cooper starts to repair Liebig's barrel from the shortest stave and after reparation the staves are more uniform than they were before.
- After adaptation, the factors become equally important and the dimension of the "data cloud" increases but its variance decreases.

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ELSEVIER

Evolution of adaptation mechanisms: Adaptation energy, stress and oscillating death

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H I G H L I G H T S

- We formalize Selye's ideas about adaptation energy and dynamics of adaptation.
- A hierarchy of dynamic models of adaptation is developed.
- Adaptation energy is considered as an internal coordinate on the 'dominant path' in the model of adaptation.
- The optimal distribution of resources for neutralization of harmful factors is stu
- The phenomena of 'oscillating death' and 'oscillating remission' are predicted.

Math. Model. Nat. Phenom.
Vol. 4, No. 6, 2009, pp. 1-53

DOI: 10.1051/mmnp/20094601

General Laws of Adaptation to I
from Ecological Stress to

A.N. Gorban[1] *, E.V. Smirnova[2

Bull Math Biol
DOI 10.1007/s11538-010-9597-1

ORIGINAL ARTICLE

Law of the Minimum Paradoxes

Alexander N. Gorban · Lyudmila I. Pokidysheva
Elena V. Smirnova · Tatiana A. Tyukina

Physica A 389 (2010) 3193–3217

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Physica A

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ELSEVIER

Correlations, risk and crisis: From physiology to financ

Alexander N. Gorban [a,*], Elena V. Smirnova [b], Tatiana A. Tyukina [a]

Take-home messages
1. Adaptation Energy, resource and reserve

- Selye's "Adaptation energy" is an abstract adaptation resource, the universal currency for adaptation.
- It can be defined through its place in the mathematical "factor-resources" models.
- We should introduce two types (at least) of the adaptation resource supply: from "checking account" of the ***superficial resource*** and from "saving account" of the ***reserve***.
- Existence of these two types determines rich family of dynamical regimes including limiting cycles and oscillating death.

Take-home messages
2. Adaptation entropy

- Analysis of training models leads to introduction of ENTROPIC form of adaptation energy.
- This energy, is irreversibly pumped into the entropic reservoir, extends the volume of comfort zone and cannot be reassigned.
- Models with adaptation energy and adaptation entropy capture main phenomenological effects and can be used in the top-down modelling of physiological adaptation.

Take-home messages
3. Interaction on various stressors

- In ensembles of multifactor multidimensional systems under stress, ***both correlations and variance increase***.
- This behaviour is supported by many observations in ecological physiology, medicine, economics and finance and may serve for ***early diagnosis of crises.***
- It is determined by the (generalised) Liebig's organization of the system of stressors (harmful factors): Fitness is a ***quasiconcave*** function of factors' pressure.
- The opposite organization with quasiconvex fitness (***synergy of stressors***) leads to opposite behaviour: under stress, correlations may be destroyed but variance increases.

Take-home messages
4. **It is a great pleasure to read the classical papers**

Our goal was:

- to understand the classical experiments
- and to build the basic top-down models of physiological adaptation

TO DO: dynamical models with many stressors: there exist too many possibilities. Discrimination is needed.