

# Evolution of adaptation mechanisms: adaptation “energy”, stress, and oscillating death

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# Plan

- 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;
- Adaptation of adaptation to many stressors:
  - under stress, both correlations and variance increase,
  - Liebig's and anti-Liebig's systems of factors,
  - Anticipating critical transition.

# 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)

# **...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 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.

# The General Adaptation Syndrome (G.A.S.)

- Selye's work is concerned with *adaptation to gross stimuli*. He calls such stimuli stressors.
- The great merit of his work is that he showed that there is *the same reaction* to every sort of unfamiliar stressor.
- This is *non-specific adaptation*:
- An *unknown factor* causes the first stage of the G.A.S.
- There are three stages in the G.A.S.:
  - (a) *The Stage of Onset, Shock or 'Alarm Reaction'*.
  - (b) The next stage is that of *Resistance*.
  - (c) With continuous application of the stressor, the last stage eventually appears. This is the stage of *Exhaustion*.
- When there is a continuous large-scale demand for adaptation, the power to adapt is eventually exhausted and the patient *dies*.

# 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.

## How one stimulus will affect an individual's power to respond to a different stimulus?

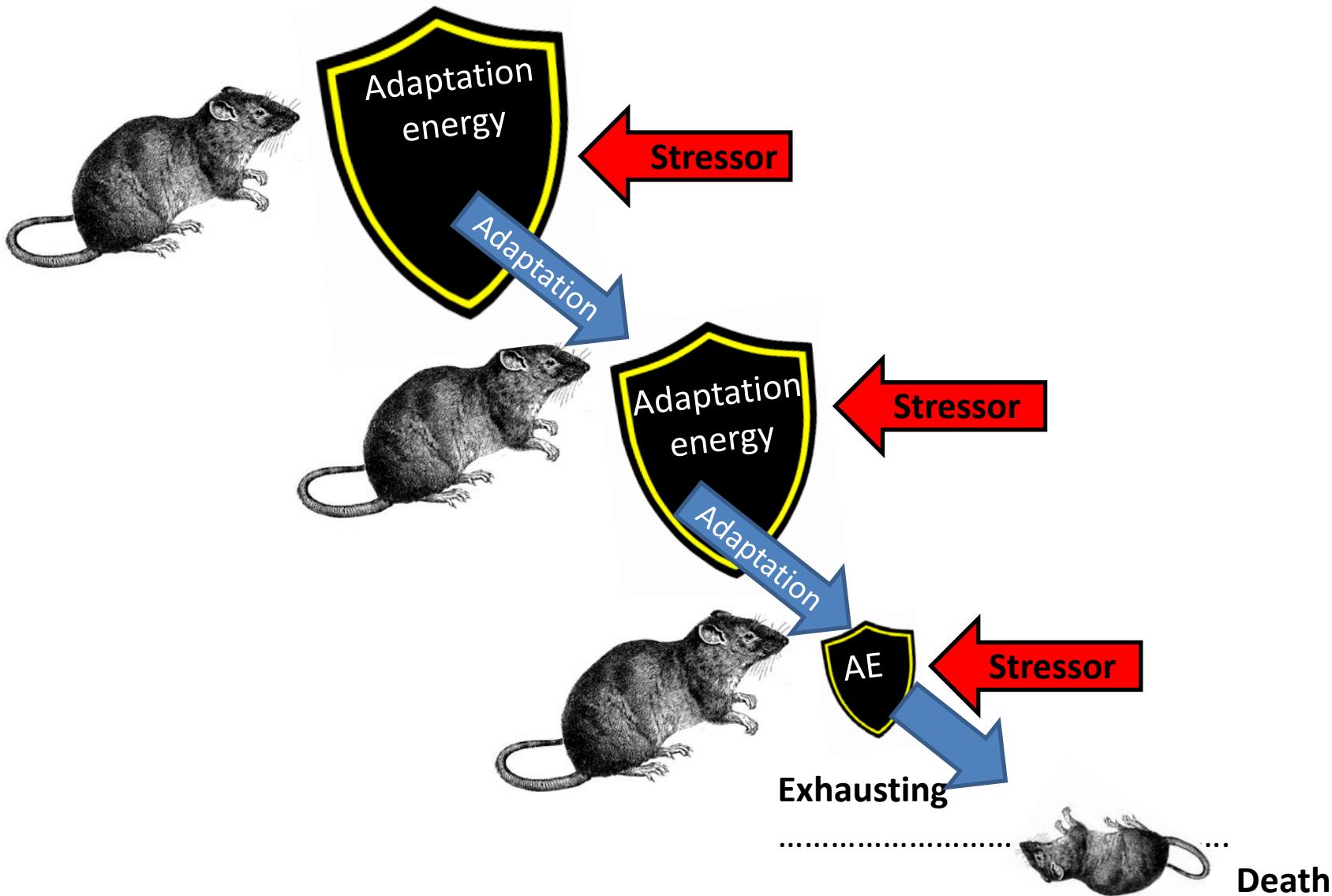
***There are several different and apparently contradictory answers; yet, in different circumstances each of these answers is probably true:***

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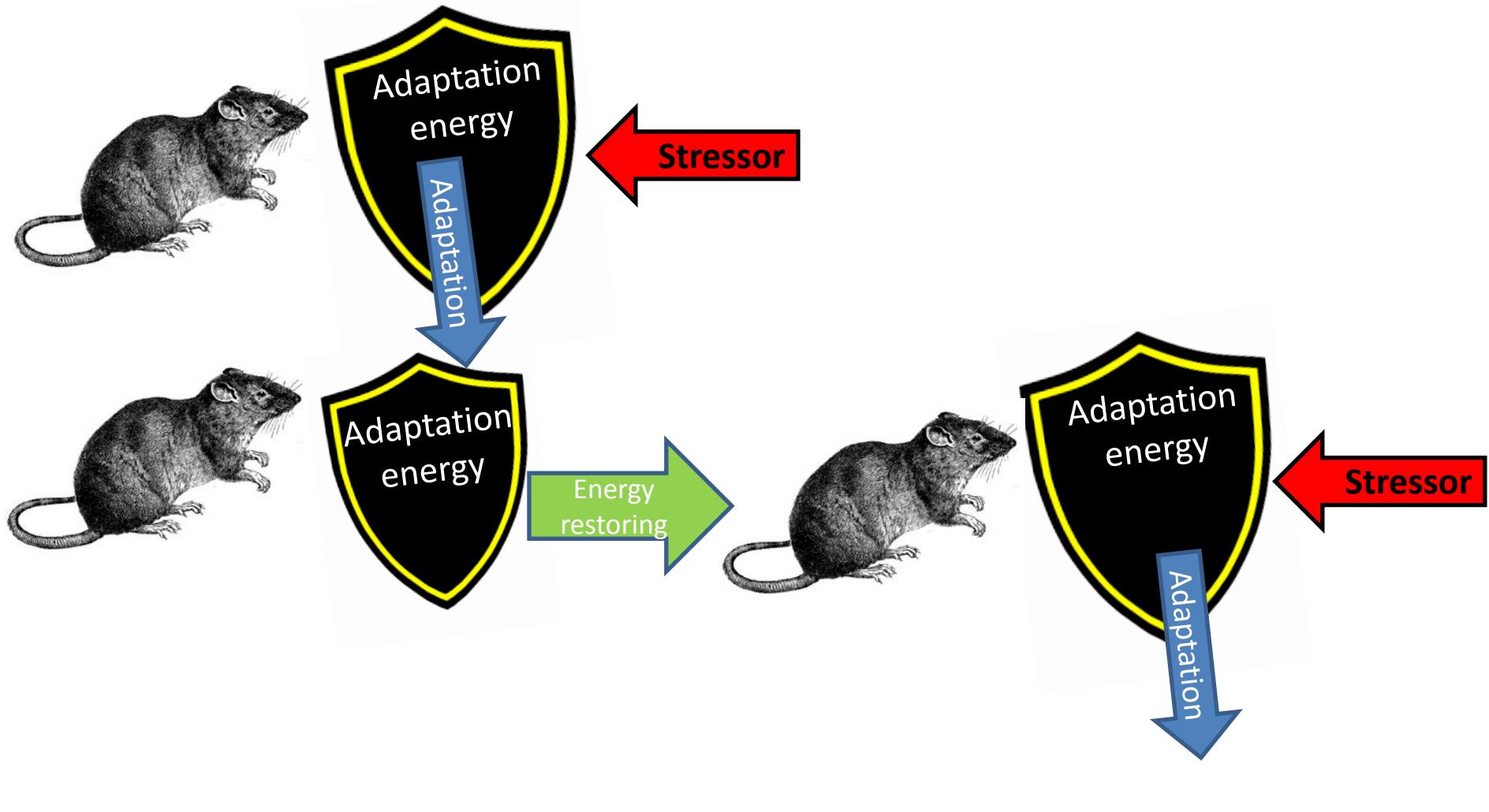
Goldstone found evidences suggesting that previous adaptation strengthens the individual to resist future stressors

- 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)

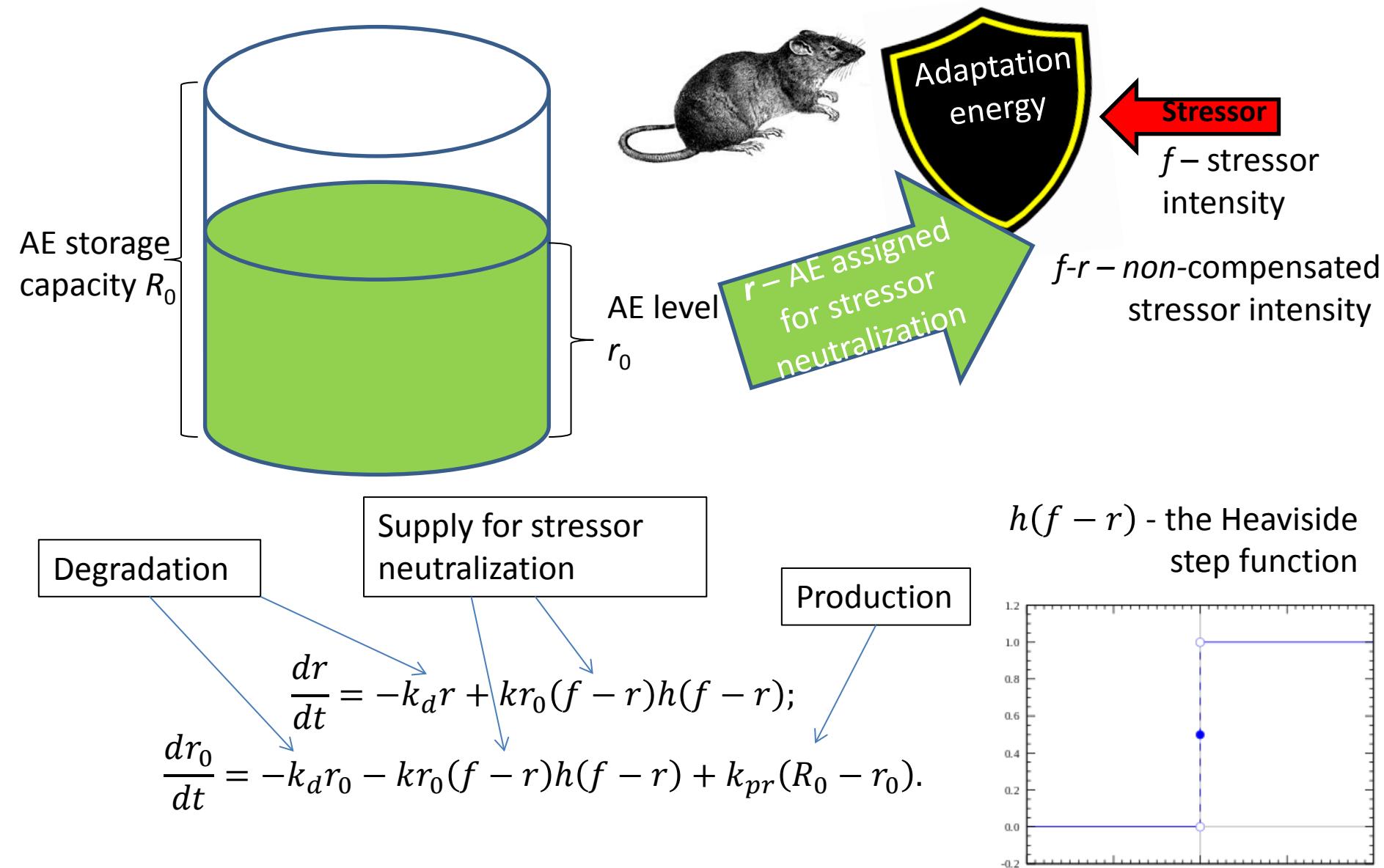
# Goldstone's axiom 1'

- 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.

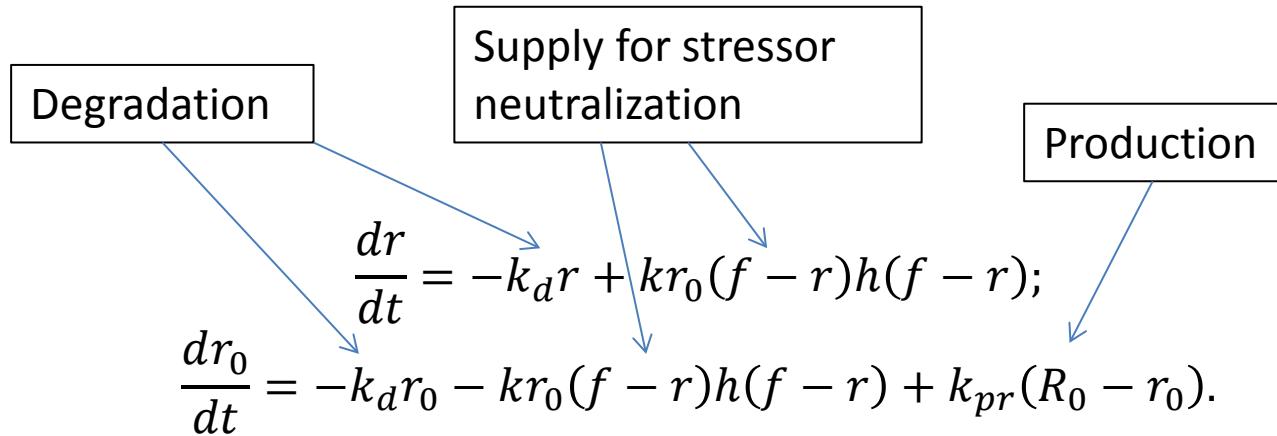
# Factor-resource models

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

# Simplest resource dynamics



# Correction is necessary

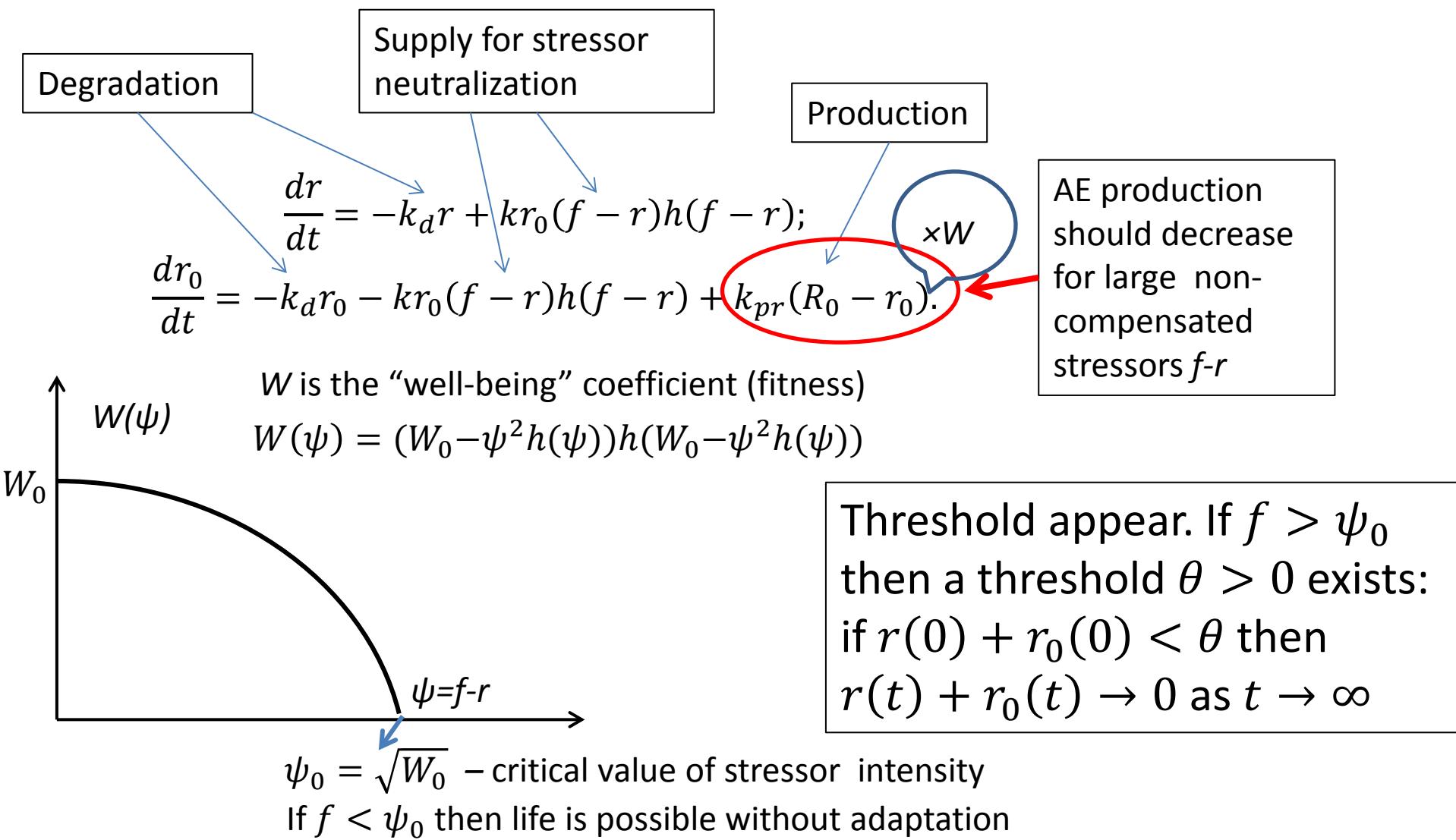


For large  $f$

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

When  $f \rightarrow \infty$  no crises appear. Immortality is possible.  
Something is wrong...

# Correction is necessary: threshold of death

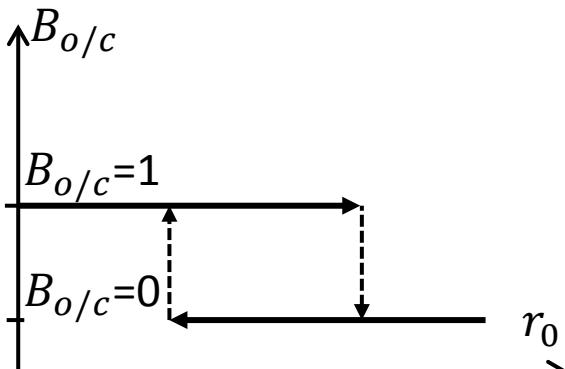


# Some generalizations are published in

- A.N. Gorban, E.V. Smirnova, T.A. Tyukina, *General Laws of Adaptation to Environmental Factors: from Ecological Stress to Financial Crisis.* Math. Model. Nat. Phenom. Vol. 4, No. 6, 2009, pp. 1-53.
- A.N. Gorban, E.V. Smirnova, T.A. Tyukina, *Correlations, risk and crisis: From physiology to finance,* Physica A, Vol. 389, Issue 16, 2010, 3193-3217.
- A.N. Gorban, L.I. Pokidysheva, E.V. Smirnova, T.A. Tyukina. *Law of the Minimum Paradoxes,* Bull Math Biol 73(9) (2011), 2013-2044.

# Resource & reserve

# Reserve



Hysteresis of reserve supply:

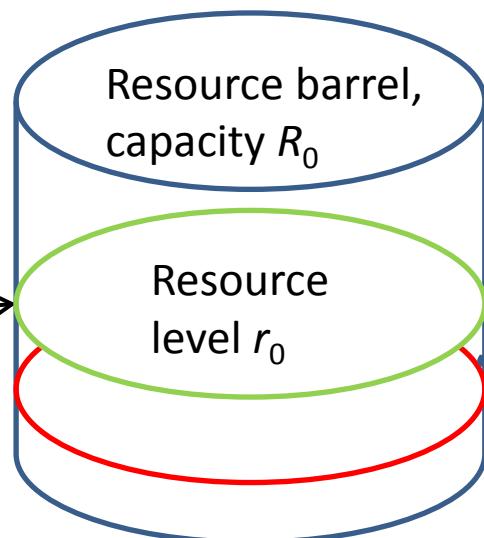
$B_{o/c}=0$  – reserve is closed

$B_{o/c}=1$  – reserve is open



Reserve level  $r_{rv}$

The upper border  $\bar{r}$ .  
If  $r_0$  crosses this border and goes up – close reserve



The lower border  $r$ .  
If  $r_0$  crosses this border and goes down – open reserve

# Resource & reserve model

The simplest dynamical model has three real variables and one Boolean

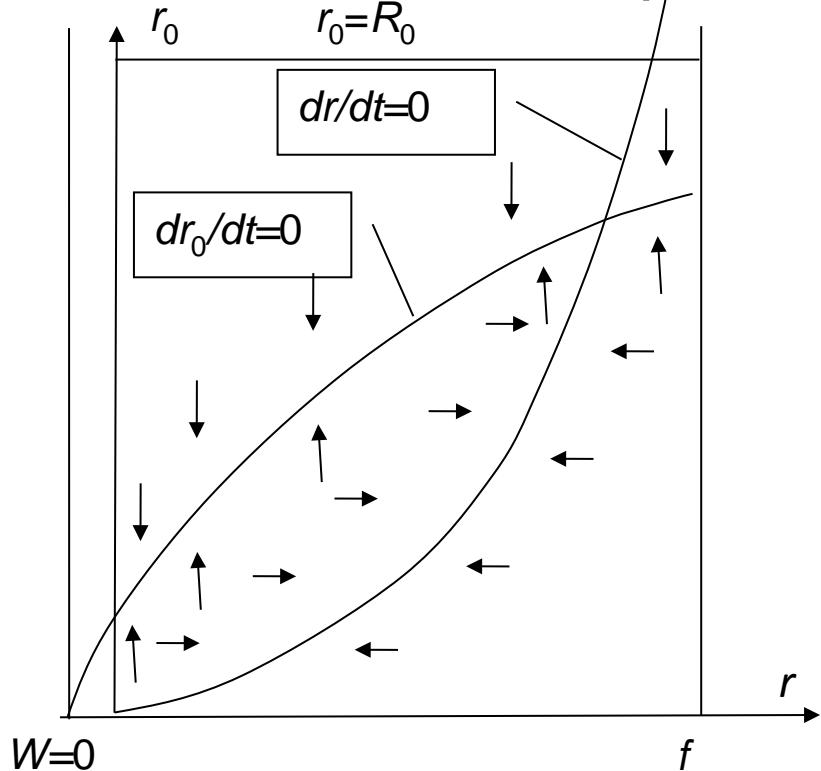
$$\frac{dr}{dt} = - k_d r + kr_0(f - r)h(f - r) ;$$

$$\begin{aligned} \frac{dr_0}{dt} = & - k_d r_0 - kr_0(f - r)h(f - r) + k_{rv}B_{o/c}r_{rv}(R_0 - r_0) \\ & + k_{pr}(R_0 - r_0)W ; \end{aligned}$$

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

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  $r_0 = \underline{r}$ .

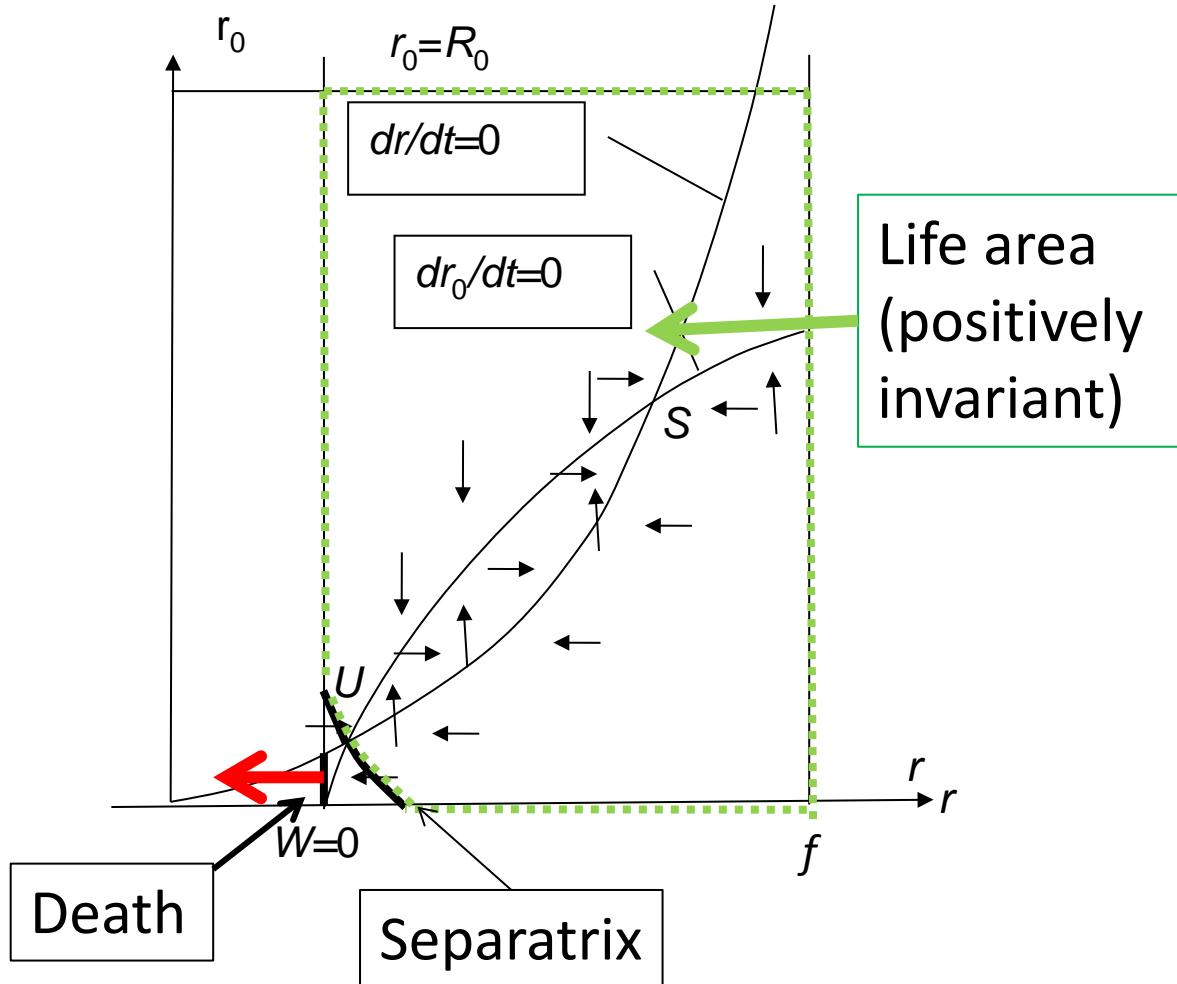
# Null-isoclines on $(r, r_0)$ plane for $B_{o/c}=0$ and $f < \sqrt{W_0}$



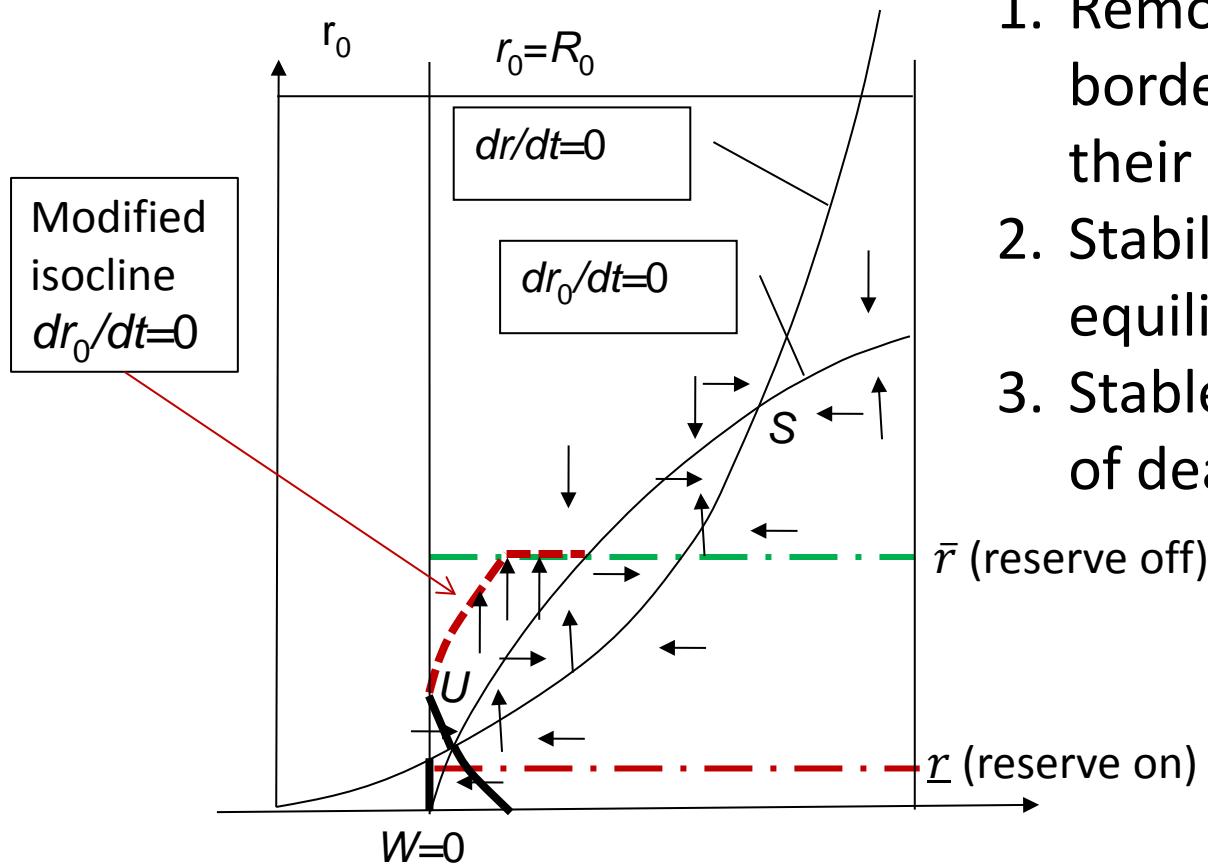
The safe situation.

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

# Null-isoclines on $(r, r_0)$ plane for $B_{o/c}=0$ and $f > \sqrt{W_0}$



# Stabilisation by reserve

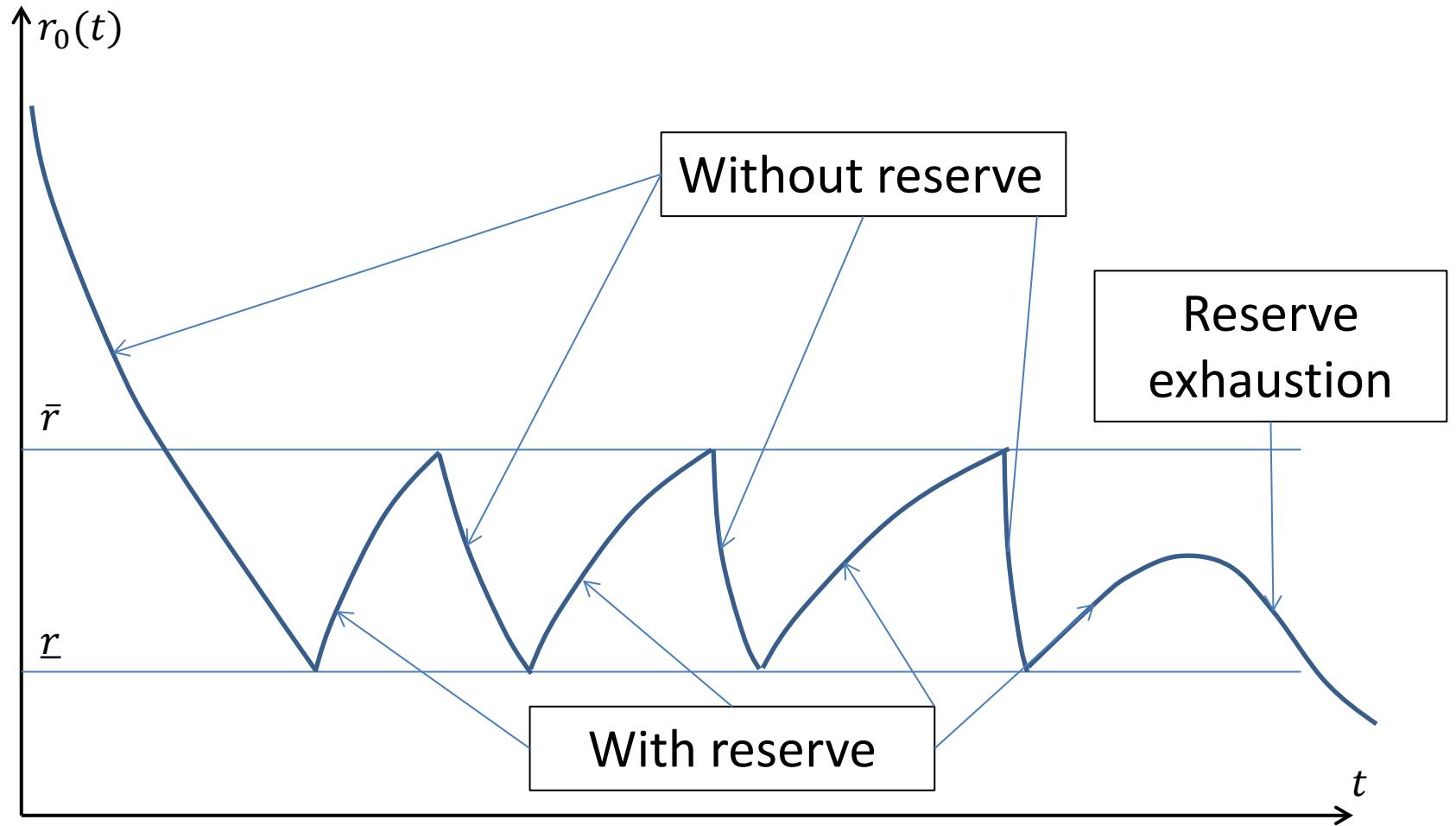


Three types of stabilisation:

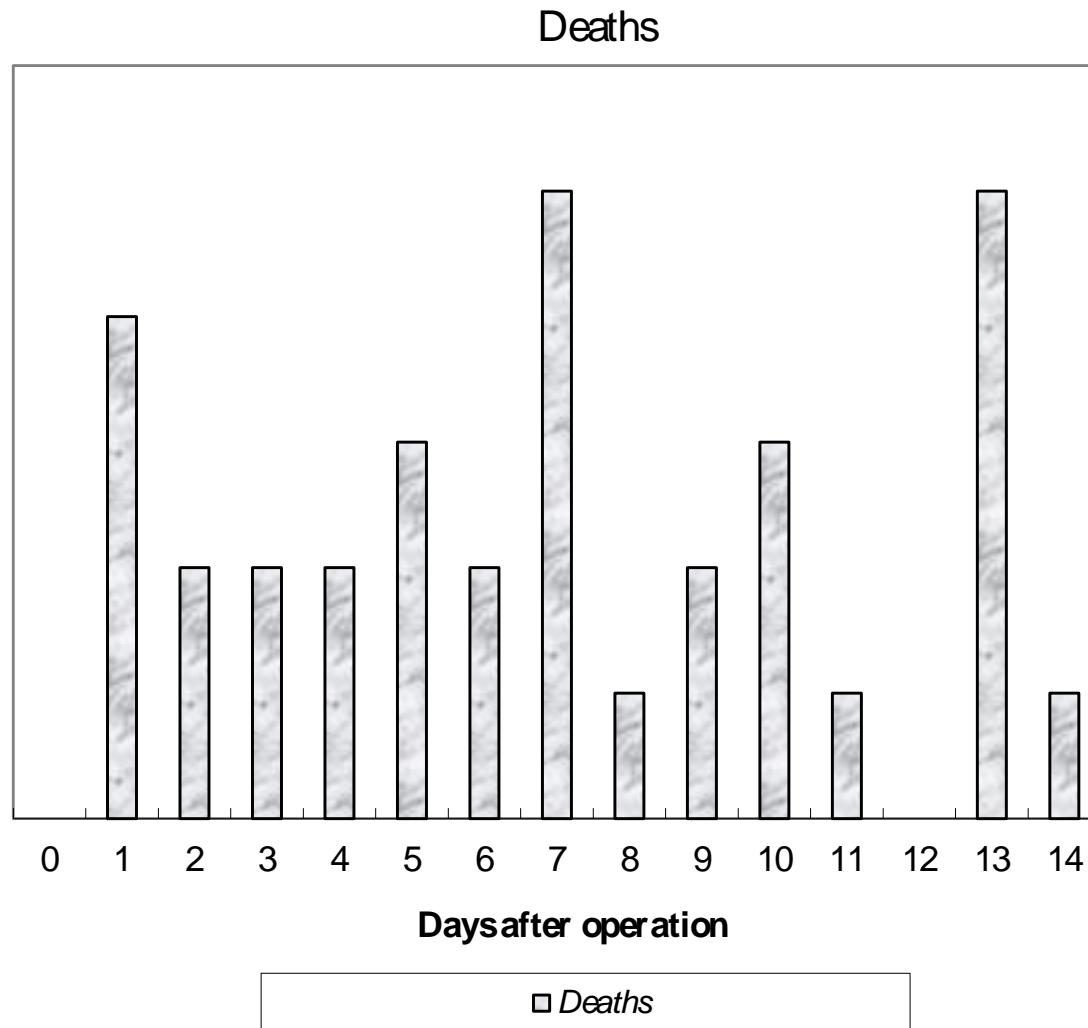
1. Removing dangerous borders or reduction of their attainability regions;
2. Stabilisation of unstable equilibria;
3. Stable oscillations instead of deaths.

# Oscillating death

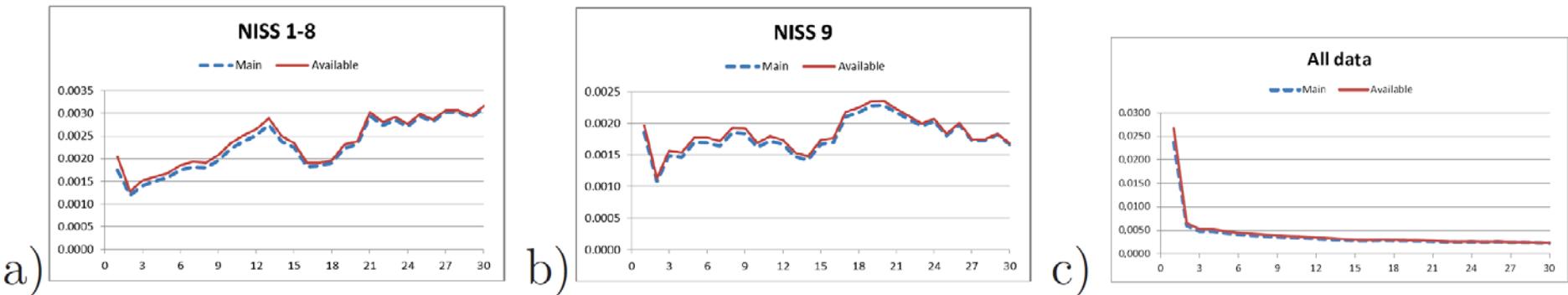
# Phenomenon of oscillating death



# 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

# General Laws of Adaptation to Environmental Factors: from Ecological Stress to Financial Crisis

A.N. Gorban<sup>1</sup> \*, E.V. Smirnova<sup>2</sup> and T.A. Tyukina<sup>1</sup>

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ORIGINAL ARTICLE

Correlations, risk and crisis: From physiology to finance  
Alexander N. Gorban<sup>a,\*</sup>, Elena V. Smirnova<sup>b</sup>, Tatiana A. Tyukina<sup>a</sup>

## Law of the Minimum Paradoxes

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

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)

# Multidimensional adaptive systems under load of many factors: do they become more or less similar under stress?

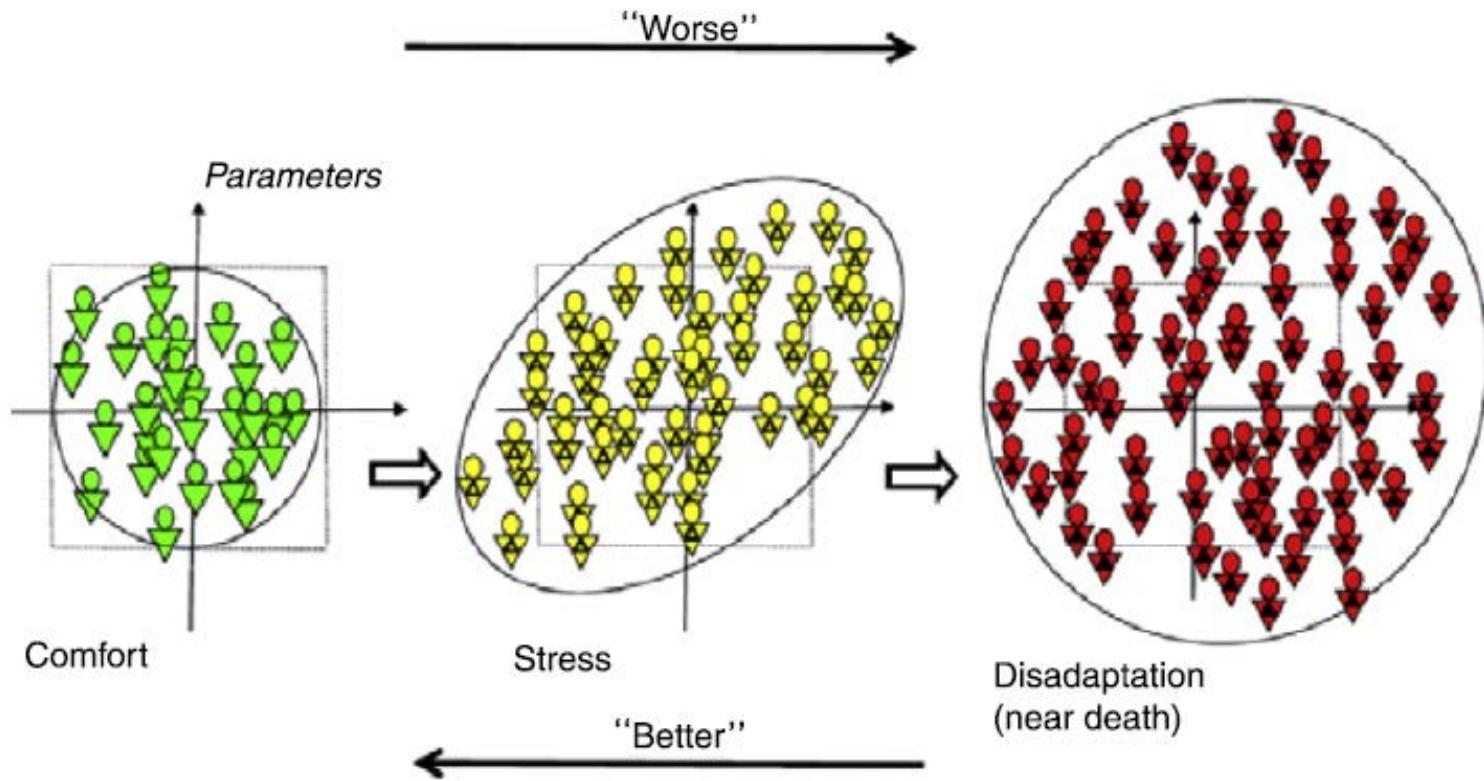
Both answers are correct simultaneously:

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;

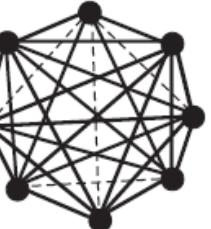
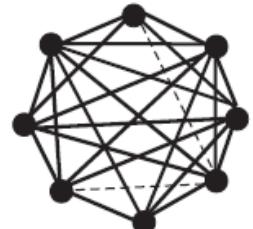
Cor↓ Var↑ approaching the disadaptation catastrophe.

Axes correspond to attributes, normalized to the unite variance in the comfort state.

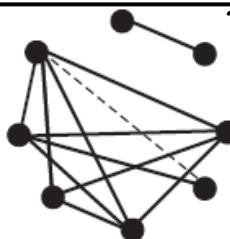
# Example

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

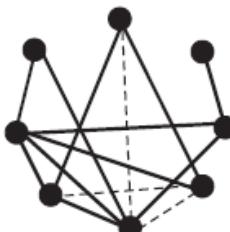
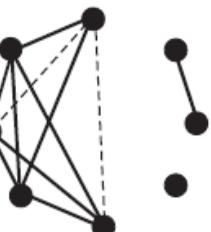
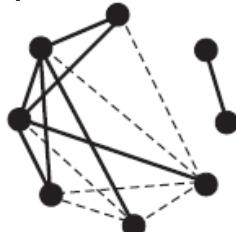
Far North (FN)



Days

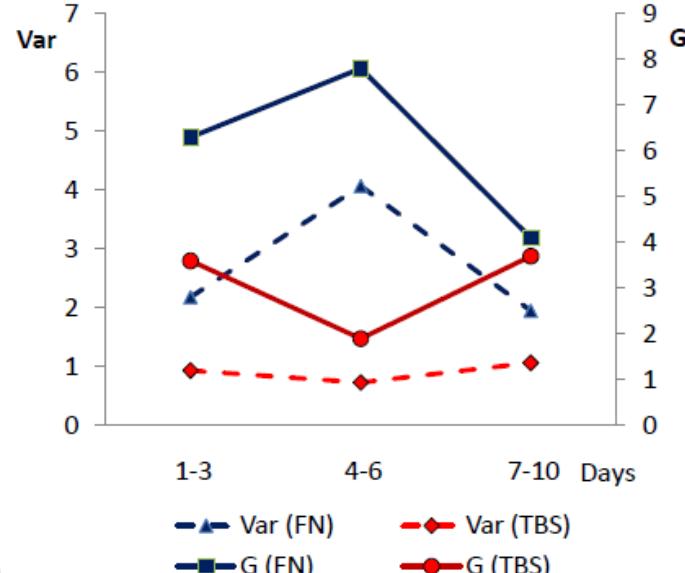


Temperate belt (TBS)



a)

b)



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)

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

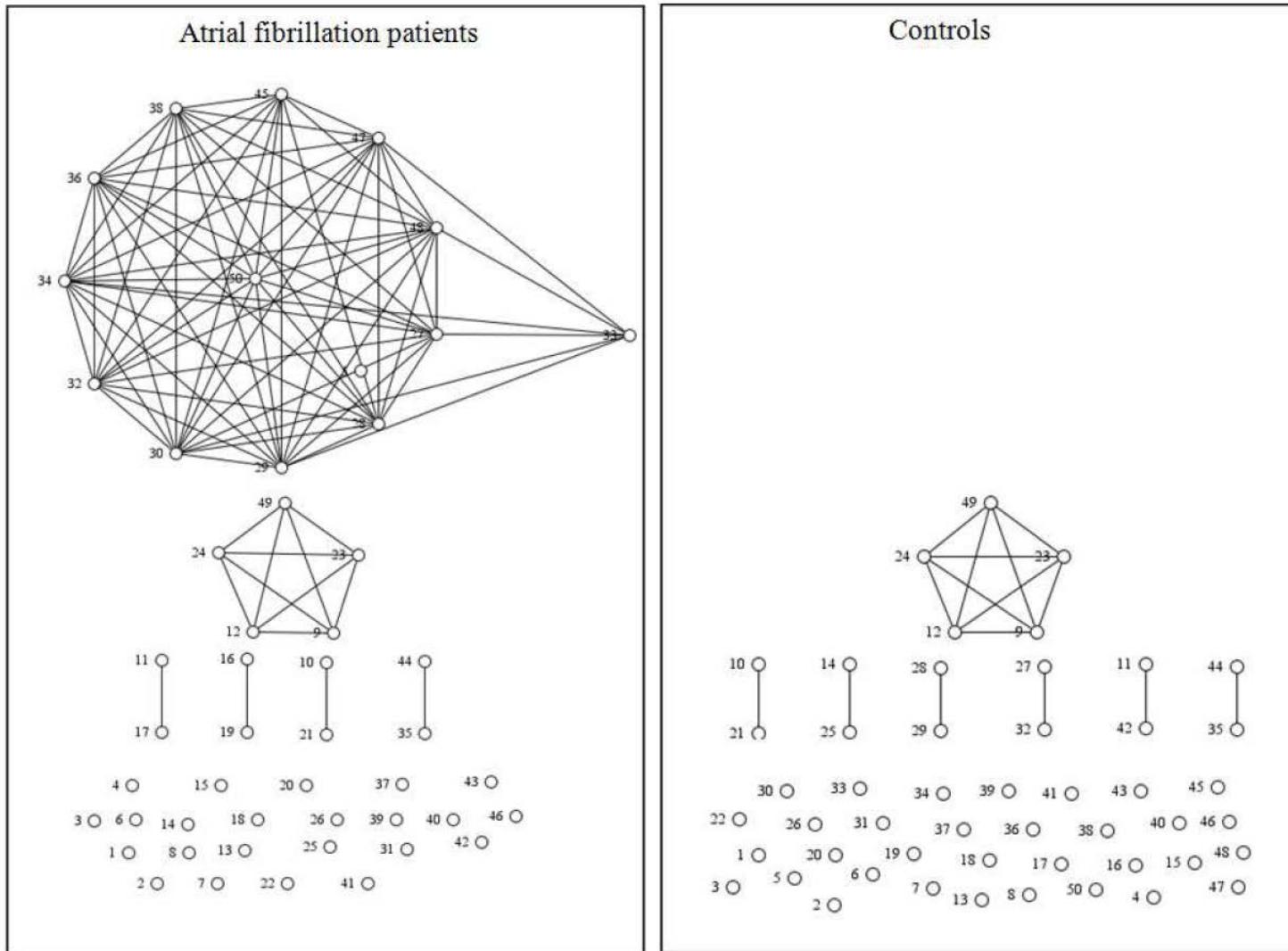
# Example

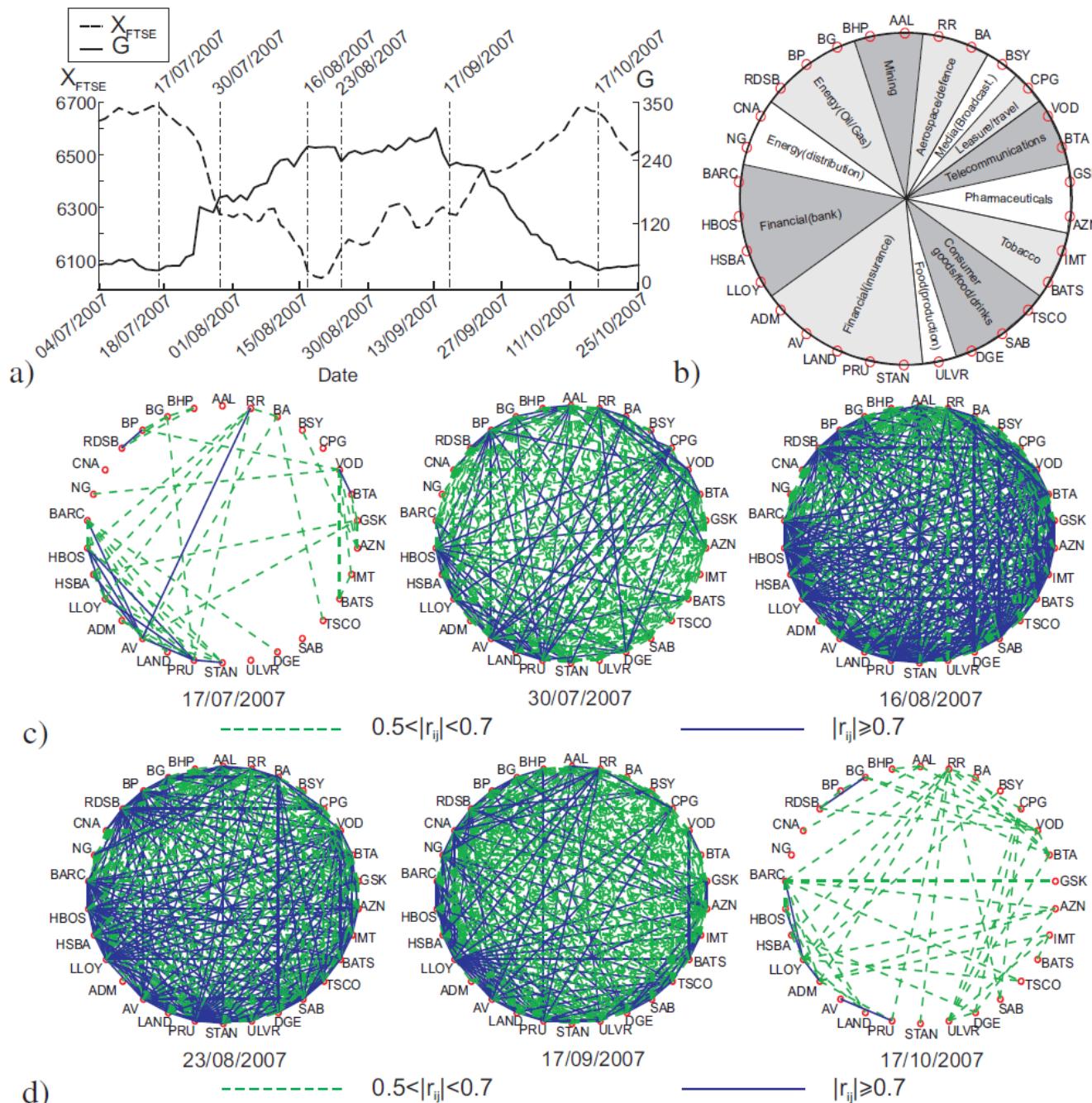
## Obesity and Treatment

Weight  $G$  of the correlation graph for different groups of obese patients before and after 30 day complex treatment

Group #	$G$ before treatment	$G$ after treatment
1	7.29	6.63
2	9.93	7.49
3	12.99	10.03

# 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

# 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,

$$\psi_i = f_i - a_i r_i$$

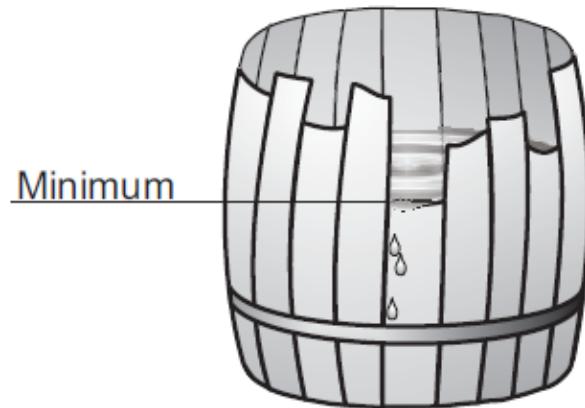
for the given amount of available resource:

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

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

# Law of the Minimum

## Liebig's law



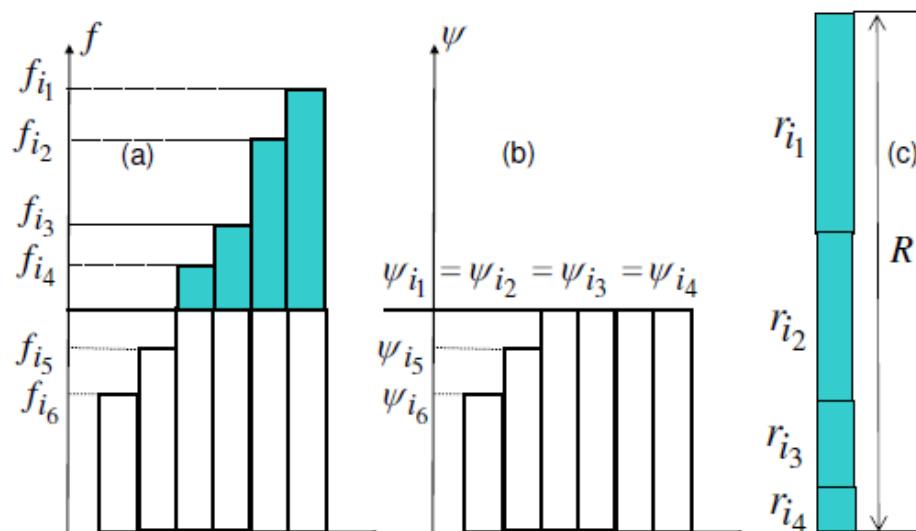
Liebig's barrel: the capacity of the barrel is limited by the shortest stave.

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

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  $i$ .

# Optimal distribution under Liebig's law equalizes factors

## Illustration of Optimization



Optimal distribution of resource for neutralization of factors under Liebig's Law. (a) histogram of factors intensity , (b) distribution of tensions  $\psi_i$  after adaptation becomes more uniform, (c) the sum of distributed resources. All  $a_i = 1$ .

# Thus,

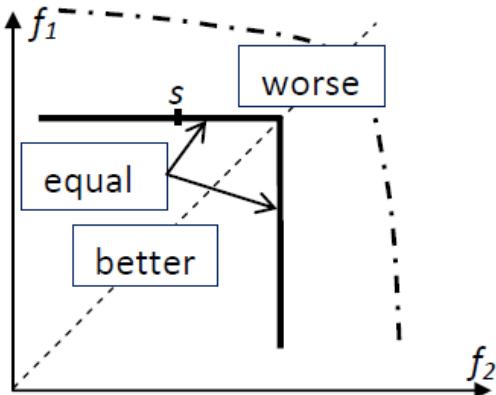
- If the system satisfies the Law of the Minimum, then the adaptation process makes the tension produced by different factors more uniform.
- Adaptation decreases the effect from the limiting factor and hides manifestations of the Law of the Minimum.
- The Law of the Minimum paradox is a theorem: if the Law of the Minimum is true then microevolution, ecological succession, phenotype modifications, and adaptation decrease the role of the limiting factors and bring the tension produced by different factors together.
- 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.

# Supported by thousands of observations

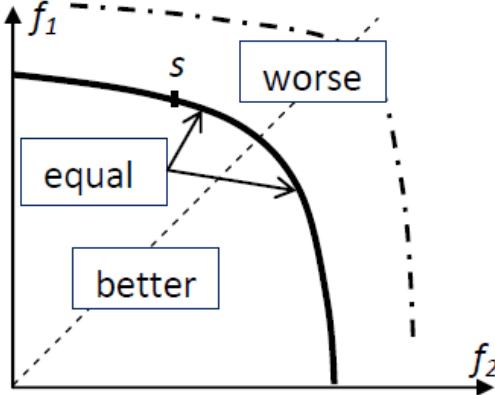
- In crisis, typically, even before obvious symptoms of crisis appear, the correlations increase, and, at the same time, variance (volatility) increases too.
- After the crisis achieves its bottom, it can develop into two directions: recovering (both correlations and variance decrease) or fatal catastrophe (correlations decrease, but variance continue to increase).

*We should guess that the real organisation of the systems of factors is not very far from Liebig's law.  
But other types of functions are also possible – next slide.*

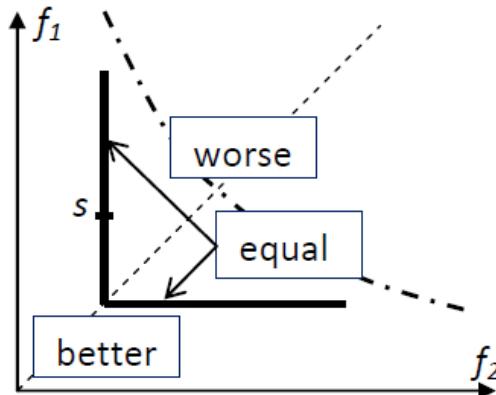
# Various types of $W$



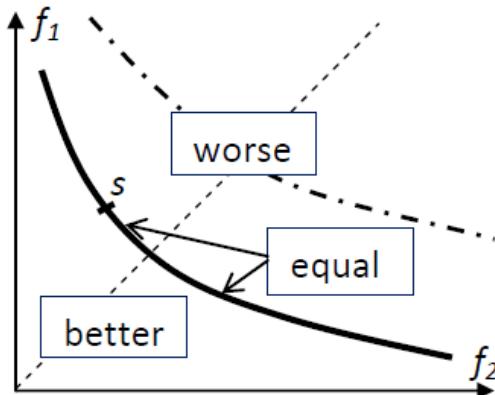
(a) Liebig's system



(b) Generalized Liebig's system



(c) Anti-Liebig's system



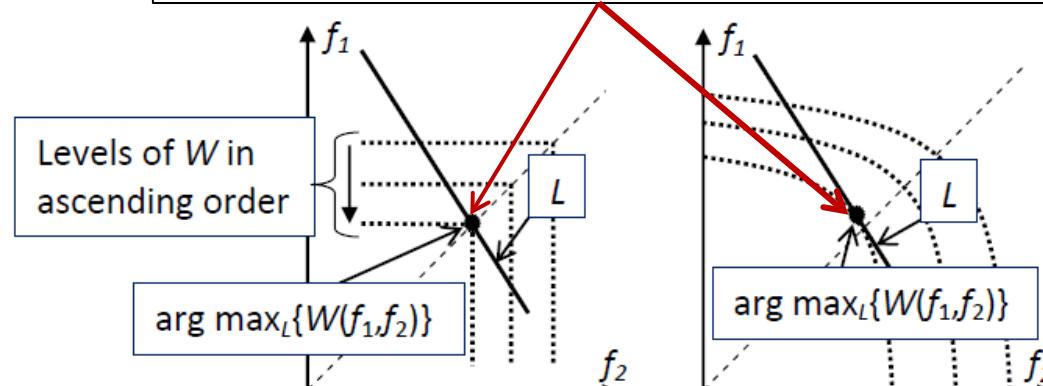
(d) Synergistic system

1. A system of factors is the *generalized Liebig system* if the fitness  $W$  is a **quasiconcave** function of factors' pressure: for any level  $w_0$  the **superlevel** set  $\{f \in U \mid W(f) \geq w_0\}$  is **convex** (Fig. b).

2. A system of factors is the *synergistic* (generalized anti-Liebig) system, if the fitness  $W$  is a **quasiconvex** function of factors' pressure: for any level  $w_0$  the **sublevel** set  $\{f \in U \mid W(f) \leq w_0\}$  is **convex** (Fig. d).

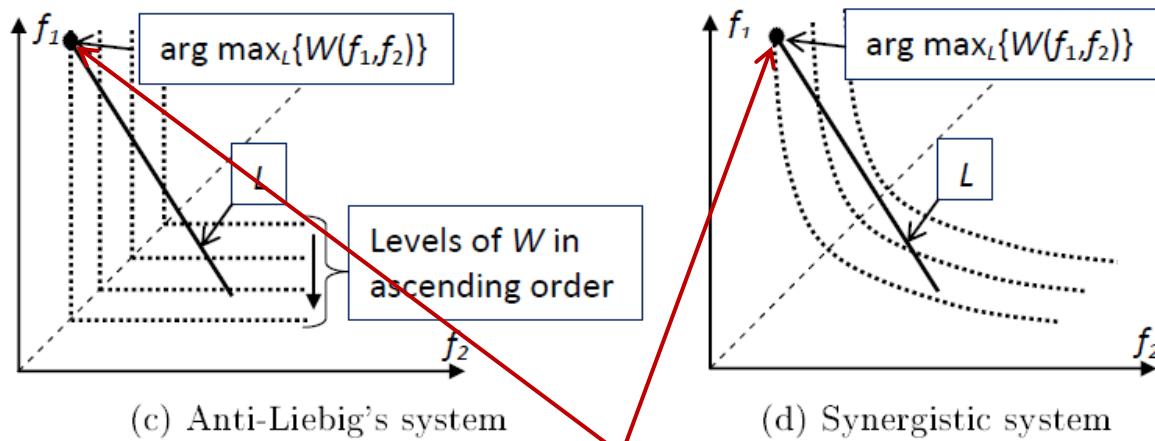
# Optimization for various types of $W$

## Equalizing of factors in optimum



(a) Liebig's system

(b) Generalized Liebig's system

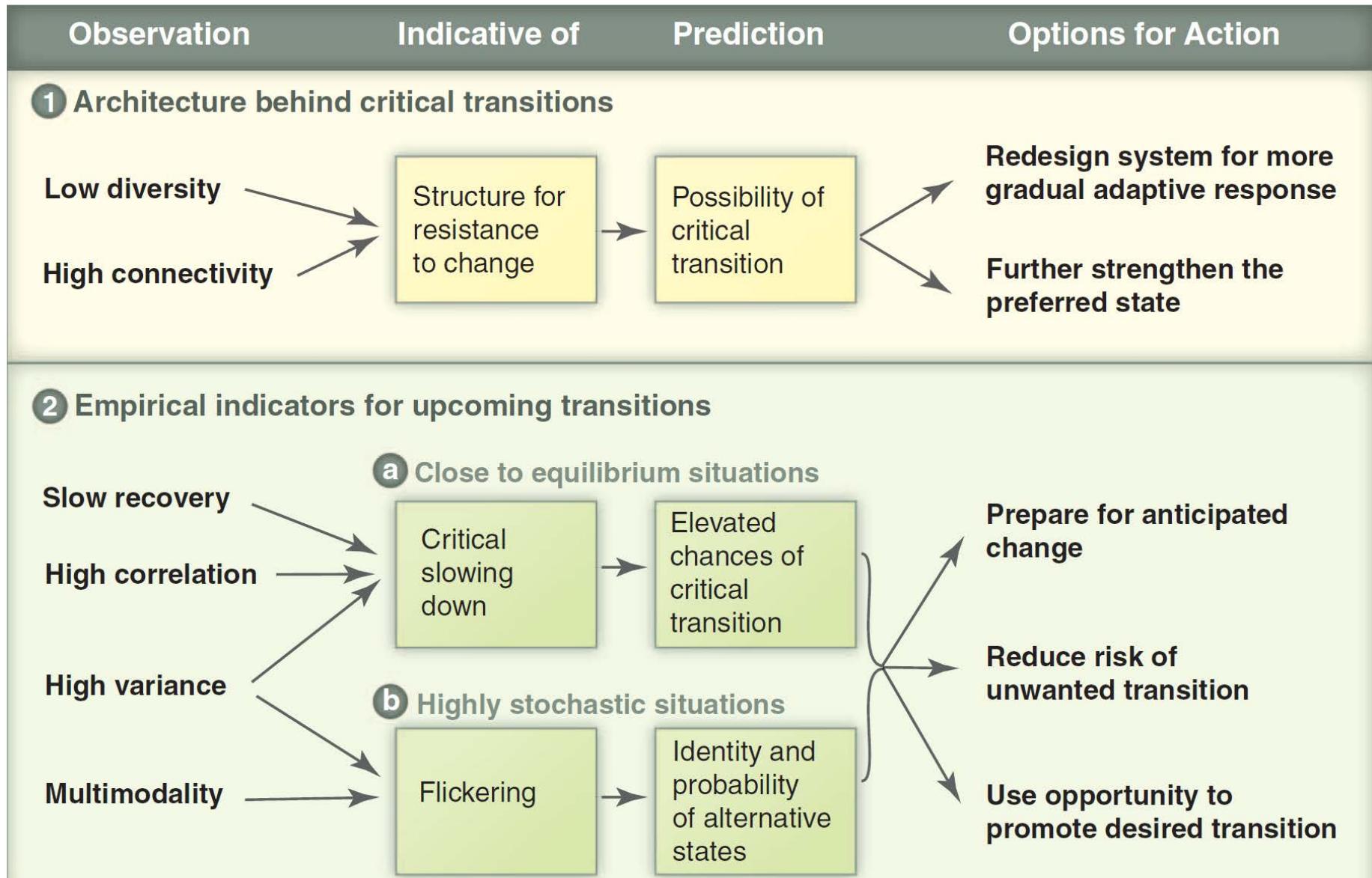


(c) Anti-Liebig's system

(d) Synergistic system

## Imbalance of factors in optimum

# More general context



# Several references

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## Law of the Minimum Paradoxes

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Elena V. Smirnova · Tatiana A. Tyukina

# Take-home messages

## 1. Adaptation Energy

- 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.
- Production of adaptation energy is an important process and it should be included into the adaptation models (Goldstoun's "axiom").

# Take-home messages

## 2. Resources and reserves

- In the factor-resource models of adaptation should exist two types (at least) of the adaptation resource supply: from “checking account” of the ***available resource*** and from “saving account” of the ***reserve***.
- Existence of these two types determine rich family of dynamical regimes including limiting cycles and oscillating death.

# 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  
classical papers**