Can one use the notion of a ground state in description of a living cell?

Vasily Ogryzko
Institut Gustave Roussy
France
vogryzko@gmail.com
33-(0)1 42 11 65 25
http://sites.google.com/site/vasilyogryzko

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NUS National University of Singapore

What this talk is not about?

- *Not about development*
- *Not about differentiation*
- *Not about growth/cell division*
- *Not about evolution or adaptation*
- *Not about any irreversible process associated with Life*

It is about finding a problem that is easiest for a physicist, but still interesting for a biologist

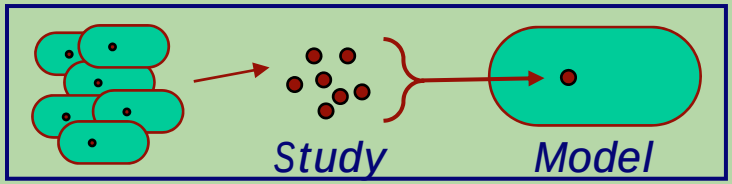
Why do we need quantum theory for this?

Because for the last several decades molecular biology was not studying the object that it purported to study –

An individual cell with all its relevant properties

Challenge of 'omics'x'nanobiology' to stability of biological order

Studying one property
using many copies of an object

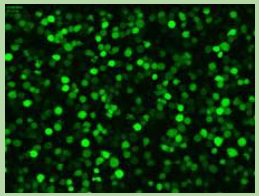


No challenge yet…

'Classical' molecular biology

Study one property
focusing on a single object

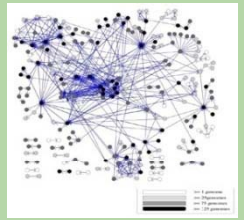
Nanobiology



Fluctuations

Study all properties
on many copies of an object

Systems biology



Networks

Systems nanobiology?

Study of all properties
of a single object

Fluctuations in context of high dimensionality of intracellular dynamics

Expect a challenge!

Problem:

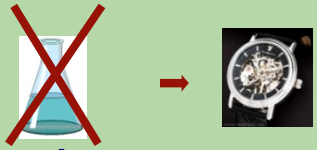
Cannot uncritically use coarse graining anymore

Coarse graining – average out irrelevant degrees of freedom to make the relevant degrees of freedom smooth and well behaved

NanoBiology

No large numbers to average over

The notion of concentration is under question



Each element might play a unique role 'in context' of larger structure

Increase in dimensionality of the mathematical model.

Omics

When taking to a logical extreme, all degrees of freedom have to be considered as a priory relevant

Cannot take a complementary part of the system (environment) and simply average over it

In any case, leaves much less room for maneuvre with the coarse graining.

Combination of nano- and –omics approaches severely limits the applicability of the coarse graining procedure.

Tradeoff between dimensionality and stability

The more of relevant degrees of freedom we expect cell to have, the more difficult it becomes to account for its stability

Property of high-dimensional spaces:
Almost all volume of a high-dimensional sphere is concentrated near its surface

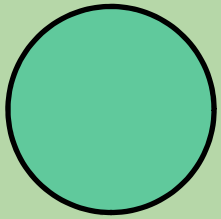
Carving a multidimensional pumpkin:

Boundary/Total volume

1D

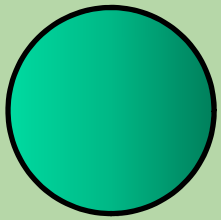
10%

2D



19%

3D



27%

ND ($N \to \infty$)

100%

The fraction of the volume occupied by a concentric ball of diameter 0.9d will be $(0.9)^N$, and it will tend to 0 as d increases

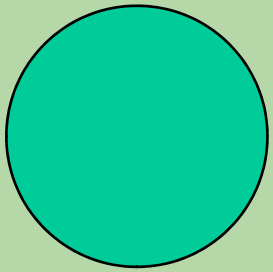
Tradeoff between dimensionality and stability

Difficulty with separation between macro- and micro-scales

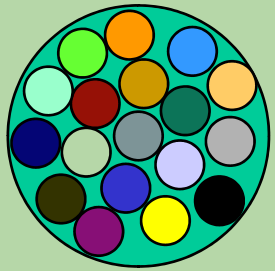
A typical number of elements 10^{11} in a bacterial cell (Could be 10^{9})

Assume that the acceptable variation of an essential Degree Of Freedom (DOF) is 10%

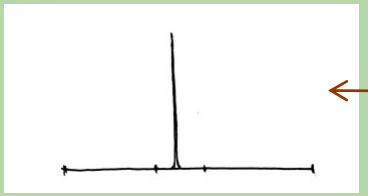
How many relevant degrees of freedom we need?

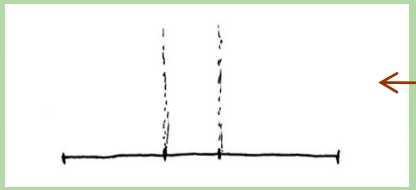


Homogenous blob (one relevant DOF only)



Highly differentiated (each element represents a separate relevant DOF)





Most of the states are: *Concentrated in the middle* *Concentrated at the border*

The higher number of relevant degrees of freedom we expect our system to have, the more chance that it is in a state close to the boundary of acceptability

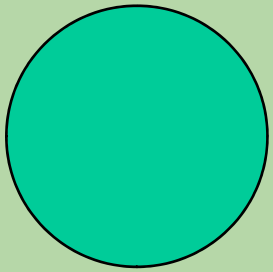
Can it be addressed experimmentally (microcalorimetry)?

Landauer limit – kTln2 for error correction

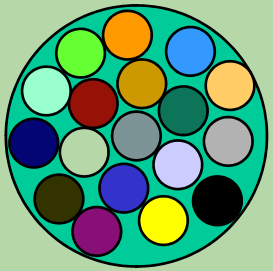
A typical number of elements 10^{11} in a bacterial cell (Could be 10^{9})

Assume that the acceptable variation of an essential Degree Of Freedom (DOF) is 10%

What is fluctuating? Two limiting cases:



Homogenous blob (one relevant DOF only)



Highly differentiated (each element represents a separate relevant DOF)

If the variation is higher than threshold 10% - error correction.

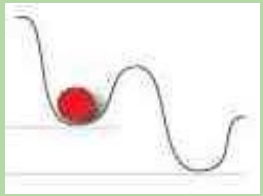
Need to dissipate at least kTln2 energy per error (Landauer's limit)

The higher number of relevant degrees of freedom we expect our system to have, the more energy it needs to dissipate to support its stability

Ground state mechanism as passive error correction

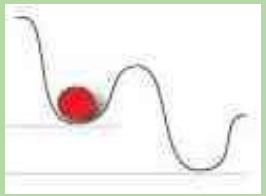
Active

Norm



Error

Correction



Norm

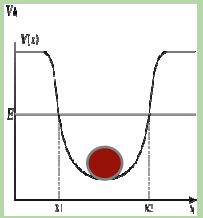
kTln2

R. Landauer

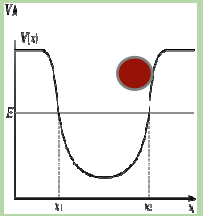
Not economical

Passive

Norm

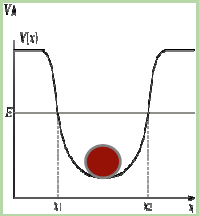


Error



Correction

Norm



Economical

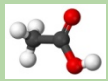
Schroedinger ('What is life?')

How to deal with the small numbers problem?

In manifest contrast with thermodynamic systems, 'incredibly small groups of atoms, much too small to display exact statistical laws, do play a dominating role in the very orderly and lawful events within a living organism'

'...New physics should be involved...'

'...It is nothing else than the principle of quantum theory...'

(Molecular structure) 

Became a part of a standard historical narrative:

"The book promoted the idea of molecular code-script as the basis for genetic inheritance and inspired Watson and Crick to work on DNA..."

Erwin Schroedinger, Francis Crick and epigenetic stability

Ogryzko VV. Biol Direct. 2008 Apr 17;3:15.

- *Problem of stability in biology cannot be reduced to the structure of DNA alone.*

(epigenetic information)

- *Role of quantum entanglement in stabilizing the dynamic state of the cell:*

Acknowledgement of entanglement can help the problem of stability by reducing the dimensionality
(via non-classical correlations between fluctuations)

In hindsight, the notion of quantum discord could be better?

In this talk:

An alternative avenue of how quantum theory could be involved

Main question: Stability of a complex macroscopic object

A: In the spirit of condensed matter physics:

« Notion of ground state and new physical field (effective field)

due to the coordinated enzymatic catalysis. »

Importantly: 1. The proposed field is not a fundamental field, but an approximation to EM.

2. We ask about stability of biological order only,

but as an independent bonus get some insight into its origin as well

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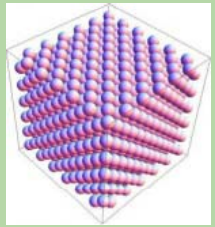
Plan:

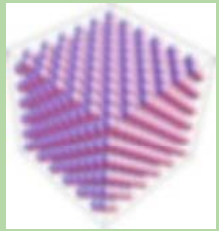
- *Why do we need a notion of a ground state?*
- *What are the forces responsible for its stability?*
- *Implications for biology*

Ground state



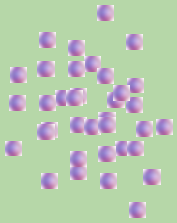
Ideal 'perfect' ordered state

Thermal environment



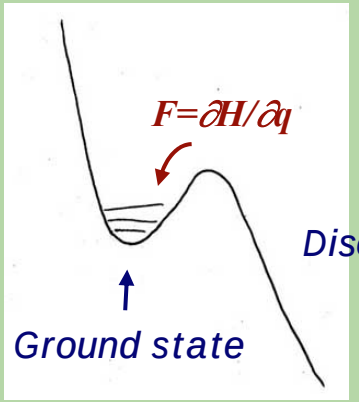
Real ordered state
(perturbed)

More heat



Disordered state
(Forces of order overcome by the forces of disorder)

Harmonic 'reaction' forces



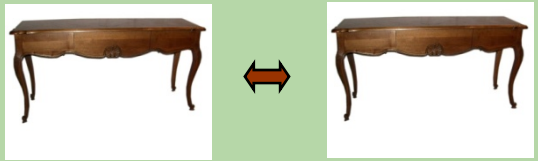
What do we need from this notion?

1. 'Ideal' ordered state that does not really exist

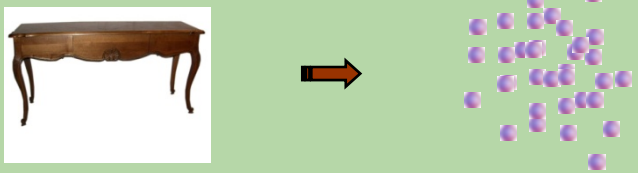
But it is relevant, because

2. The 'real' state is in a sufficiently close neighborhood to this state, maintained by the reaction forces

3. Applicability of the 'ground state' notion is time scale-dependent:



1 day

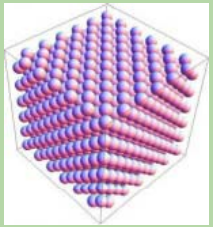


1 mln years

<u>Conversely</u>:
Systems that are percieved as non-equilibrium, could be treated as in equilibrium at a sufficiently short time scale

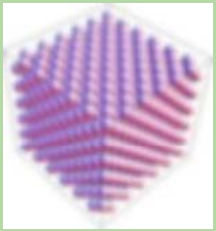
i.e. the notion of ground state applies to metastable cases (e.g., biological systems) as well.

Ground state for Philosophers



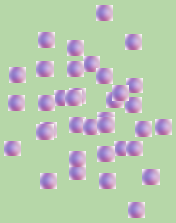
Ideal 'perfect' ordered state

Thermal environment



Real ordered state
(perturbed)

More heat



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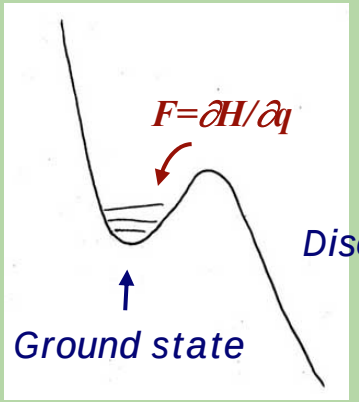
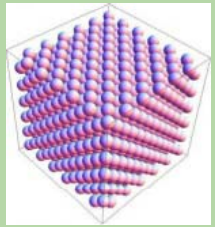


Ground state for Philosophers

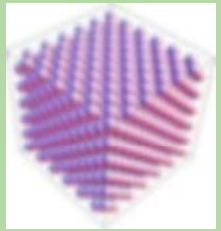
Platonic form
(exists in the 'ideal world' of mathematical ideas)



Ideal 'perfect' ordered state

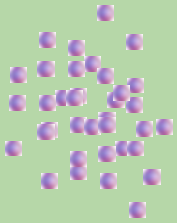
Thermal environment

Its imperfect realization
(observed in the real world)



Real ordered state
(perturbed)

More heat



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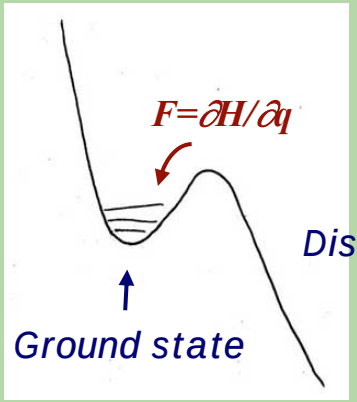
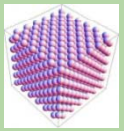
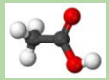


Technical advantages of starting with the notion of ground state:

- *reversibility,*
- *equilibrium,*
- *many constraints (e.g., equipartition of energy)*
  - therefore, easier to describe and understand

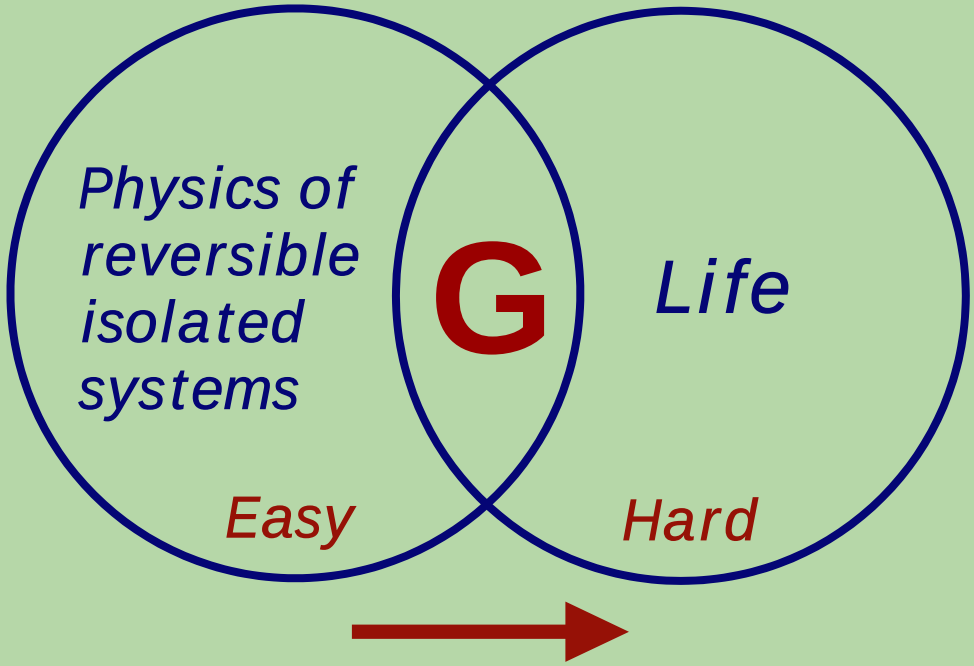
A very common first step to approach many physical problems:

Ordered states in condensed matter theory 

Molecular structure 

But Life is also kind of condensed matter!

Potential strategy to understand biological order



Multitude of phenomena in need of explanation:

- *Growth,*
- *Reproduction,*
- *Evolution,*
- *Development*
- *Morphogenesis*
- *Adaptation,*
- *Responsiveness,*

Dissipative,
Irreversible dynamics,
Open systems

After understanding the ground state G,
expand the solution to other biological phenomena,
associated with irreversibility, open character etc…

Unlike in condensed matter physics

Where ground states are more or less unique (modulo a symmetry transformation)

In biology:

One should expect astronomical variety of different ground states, corresponding to different 'life forms'

Life on Earth corresponds to only a minute sampling of this variety of potential forms

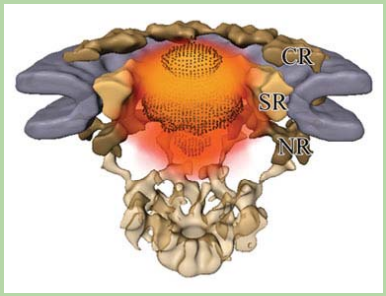
Understanding Life involves a healthy dose of historical reasoning (evolutionary thinking)

OK

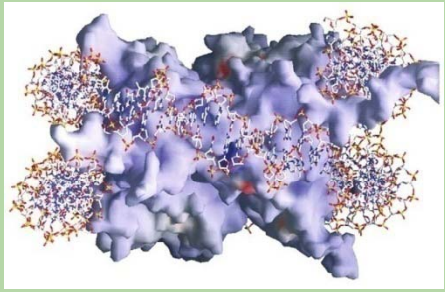
If it is so convenient,

Why the notion of ground state is not used in biology?

Clarification



Nuclear pore



Nucleosome

Ribosome

In fact, it is widely used in structural biology

But, 1) to understand what the structure is for:
(question of 'design' or 'meaning'- specific for biology)

To answer this question - need to involve much larger evolutionary scales:

- *Put the molecular structure in the context of the organism*
- *Consider populations of organisms*
- *Consider many generations*

At this scale:

- *Have to give up reversible equilibrium physics*
- *The notion of ground state becomes useless*

Ground state in biology

But, 2)

Common wisdom:

Maybe OK for description of structure of macromolecules or macromolecular complexes (ribosomes, nucleosomes etc)

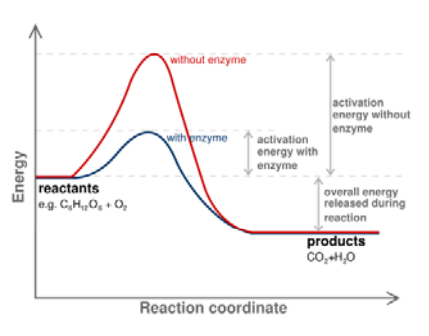
but

Certainly not OK to describe organization of a living cell, which is a dynamic system far from equilibrium

whereas equilibrium is equated with death

Why a cell is a dynamic system far from equilibrium?

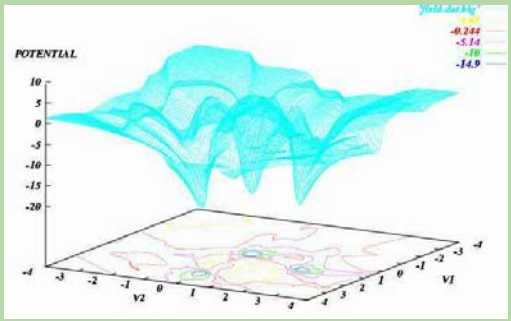
Because of the enzymatic activity, which transforms one configurational state of cell to another one



Which is associated with physical irreversibility

Even if we can take a sufficiently short time scale, where the configuration states of the whole cell are stable and thus the ground state can be used, the description of enzymatic transitions will require longer time scales, and the notion of ground state is useless

Energy

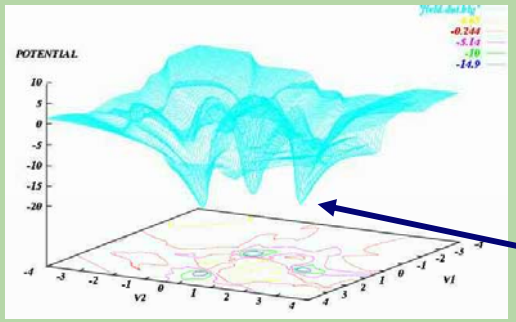


Configurational states of cell

What we propose?

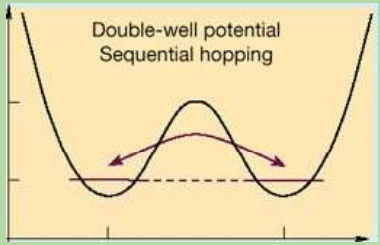
Keep the picture of intracellular dynamics as hopping between metastable states

Classical view



Metastable states correspond to configuration states of cell

Transitions correspond to enzymatic catalysis, diffusion etc thermally activated

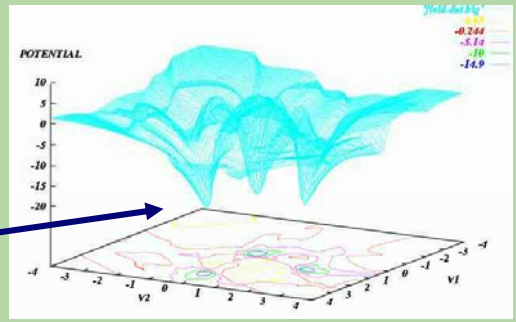


State 1 ↔ State 2

Enzyme
Diffusion

What is metastable state?

Proposed view

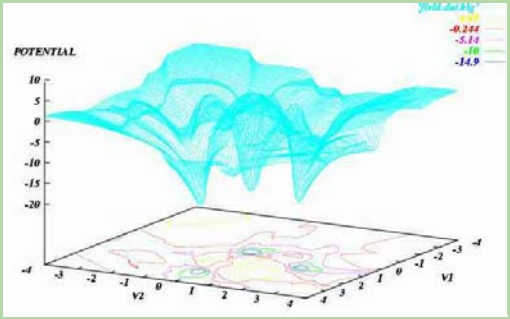


Metastable states are combinations of configuration states

The description of a metastable state includes transitions via enzymatic catalysis, diffusion etc

But reconsider what corresponds to a metastable state!

What is necessary for the new view?



Metastable states are combinations of configuration states

The description of a metastable state includes transitions via enzymatic catalysis, diffusion etc

---

Reconsider physics of catalysis in vivo

The time-scale separation:

$$\tau_c << \tau_e$$

τ_c – *characteristic time of catalysis*

τ_c – *characteristic time of exchange with outside environment*

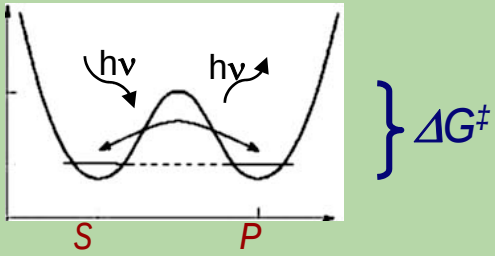
It is all about time scales and their interplay

⬇

Implications for the forces holding the order together

Need to reconsider physics of enzymatic catalysis

In vitro: activation energy = thermal energy



$$k = \frac{k_{\mathrm{B}}T}{h}\mathrm{e}^{-\frac{\Delta G^{\ddagger}}{RT}}$$

Thermal energy (Eyring-Polanyi)

In vivo: activation energy ≠ thermal energy?

Clarification:

Need to reconsider physics of catalysis:

Do not need to change fundamental physics

(it is always Electromagnetism + QM)

But choose more appropriate approximation to the 'from the first principles description', more applicable for the in vivo situation:

The time-scale separation:

$$\tau_c << \tau_e$$

τ_c – *characteristic time of catalysis*

τ_c – *characteristic time of exchange with environment*

The familiar intra- and inter- molecular forces that operate in the cell, are also approximations to the 'from the first principles' (Electromagnetism + QM) description

They are convenient 'rules of thumb' that work well in particular situations (e.g., in vitro)

We need different 'rules of thumb' for in vivo

'Chess rules' versus 'chess strategy and tactics'

Initial setup	**Values of figures and positions**
Basic moves	**Fork, pin, sacrifices…**
Etc…	**Opening, middlegame, endgame…**

Unlike the fundamental rules, the 'rules of thumb' are not absolute and could be in some curcumstances counterproductive

Bishop sacrifice by moving the white bishop on f5 to g6 with check. The only way for black to get out of check is to take the checking bishop with black's pawn on h7.

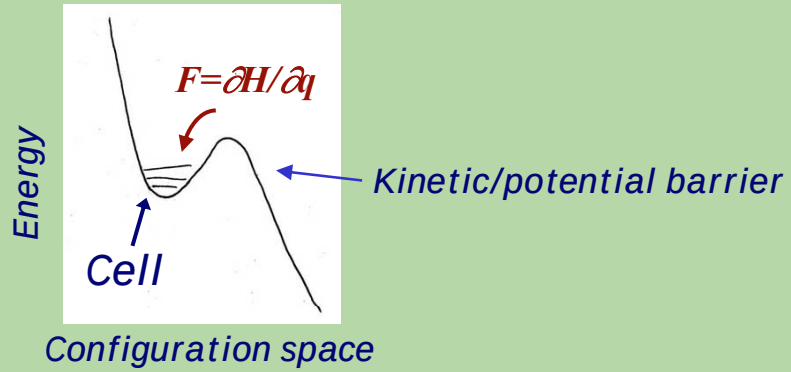
White's queen retakes the pawn now on g6 producing checkmate.

1. Bg6+ h7xg6
2. Qxg6 #

As a rule of thumb, a bishop should not be exchanged for a pawn, but there are circumstantial exceptions

Summary so far:

Cell in a ground state, or sufficiently close to it

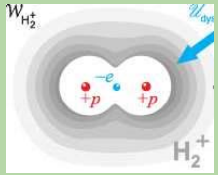


The main question is the nature of the forces that hold the cell close enough to a ground state. Is enzymatic catalysis involved?

↕

Interplay between different time scales. Catalytic force

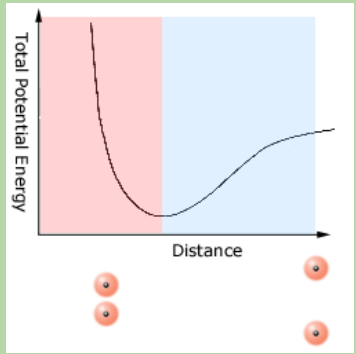
Example of interplay between two time scales: Molecular Hydrogen Ion H_2^+



$$|\quad\rangle = (|\quad\rangle + |\quad\rangle)/\sqrt{2}$$

Born-Oppenheimer approximation

$\Psi_{total} = (\psi_{electronic})X(\psi_{nuclear})$



The 'attraction' part of the potential surface

Two degrees of freedom: fast 'e' - position of e (near p1 or p2), and slow 'p' - distance between p1 and p2.

Efficient exchange of e is facilitated by a particular value of p and at the same time leads to lowering of energy

Quite general interaction mechanism: electrostatic, hydrogene bond etc.

In Biology

There is an unprecedented range of different time scales

Could we use the same logics of the time scale interplay one level higher, e.g., to description of catalysis in vivo?

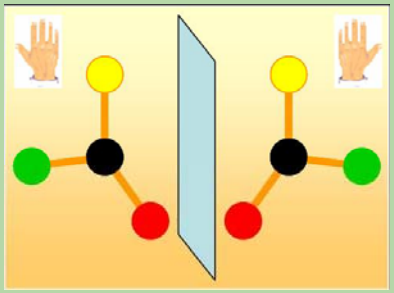
- *What does it mean?*
- *Why could it be interesting for biologists?*

Modest proposal

‘Catalytic Force’

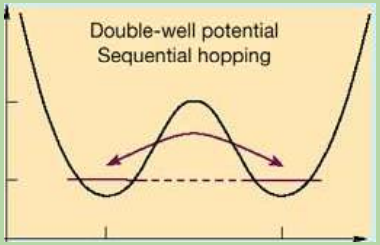
New ‘physical force’
in vivo

Molecular chirality as a toy model of a catalytic transition



$|L\rangle$ $|R\rangle$

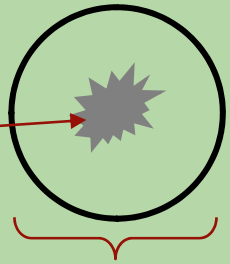
Racemization



$\Delta G^{\ddagger}$

Substrate *Product*

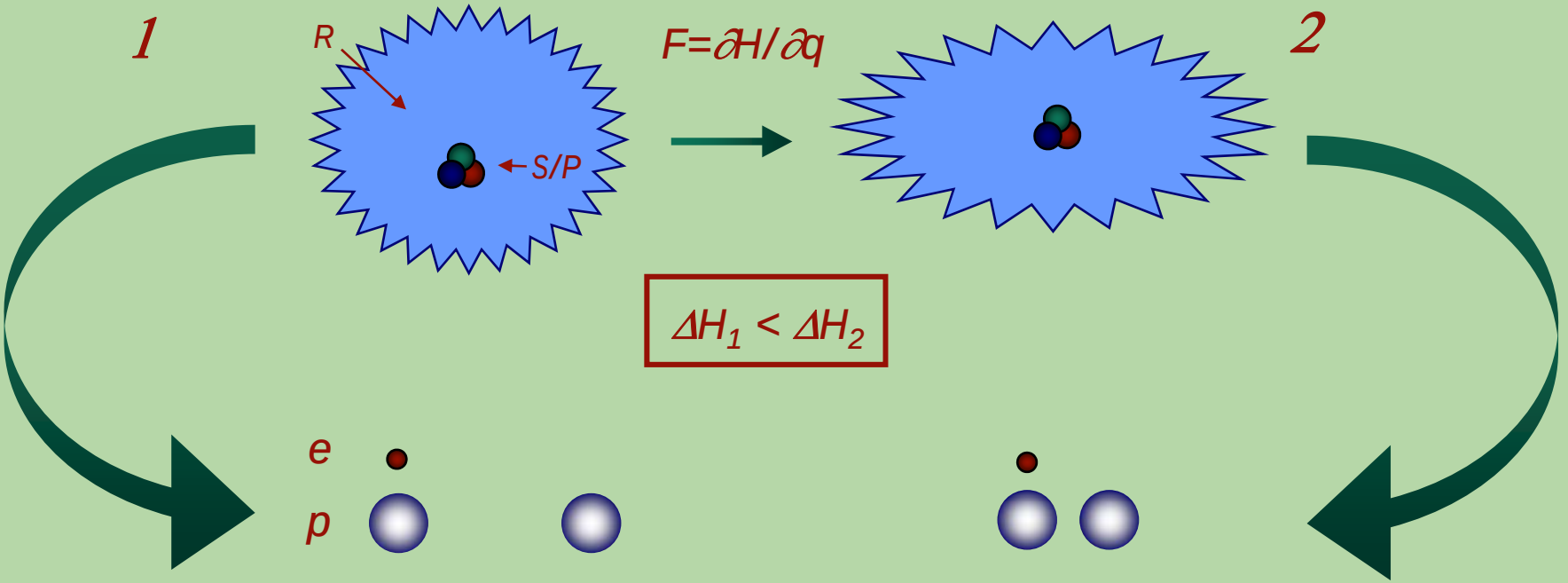
Substrate



In vivo

Whole cell as catalytic microenvironment

Catalytic act in vivo as an 'exchange force'



'e' - Substrate or Product (S/P); 'p' - configuration of the rest of the cell (R)

$|+\rangle = (|Cell_S\rangle + |Cell_P\rangle)/\sqrt{2}$

$|-\rangle = (|Cell_S\rangle - |Cell_P\rangle)/\sqrt{2}$

Assume that the value of coherence gap depends on the state of R

Conclusion: a backaction (recoil) force that acts on the rest of the cell.

There should be a physical force F=∂H/∂q that adjusts the rest of the cell towards a configuration that facilitates the enzymatic act!

In Biology

There is an unprecedented range of different time scales

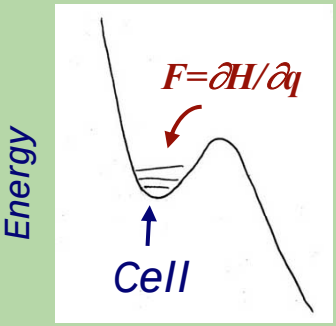
Could we use the same logics of the time scale interplay one level higher, e.g., to description of catalysis in vivo?

- *What does it mean?*

- *Why could it be interesting for biologists?*

Physical implications

- *Additional physical force, contributing into stability of an ordered state of the cell in vivo*
- *Not a fundamental force, but a derivative of electromagnetism and quantum principles – in the spirit of effective field theory (a la hydrogen bond, covalent bond, etc)*

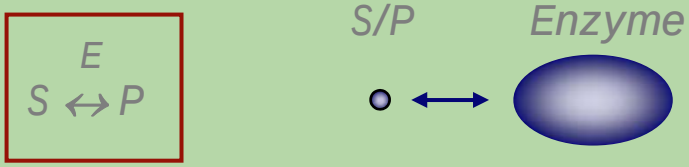


Biological implications

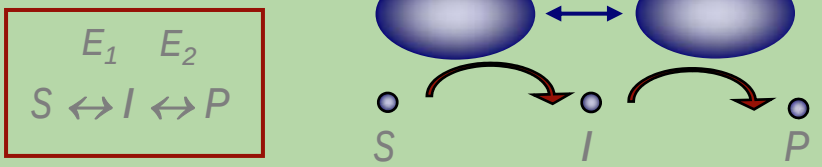
(optimization without natural selection)

Although not a binary interaction

Manifestations in 3D space:



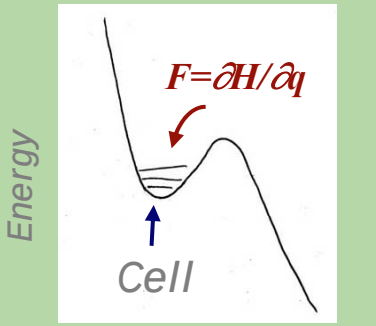
Attraction between enzyme and its substrate/product



Attraction between enzymes via intermediate

Physical implications

- *Additional physical force, contributing into stability of an ordered state of the cell in vivo*
- *Not a fundamental force, but a derivative of electromagnetism and quantum principles – in the spirit of effective field theory (a la hydrogen bond, covalent bond, etc)*

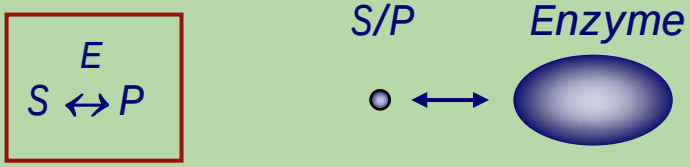


Biological implications

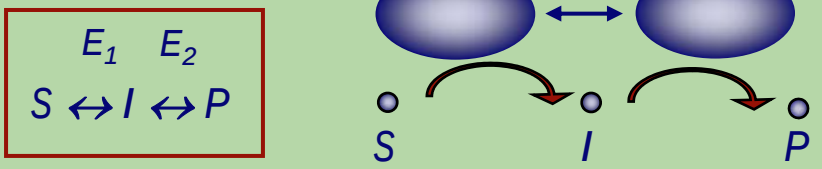
(optimization without natural selection)

Although not a binary interaction

Manifestations in 3D space:



Attraction between enzyme and its substrate/product



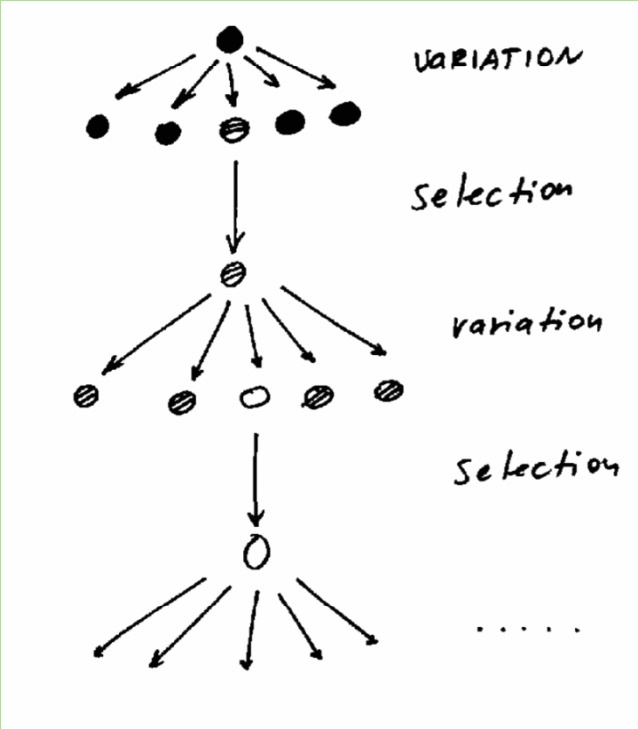
Attraction between enzymes via intermediate

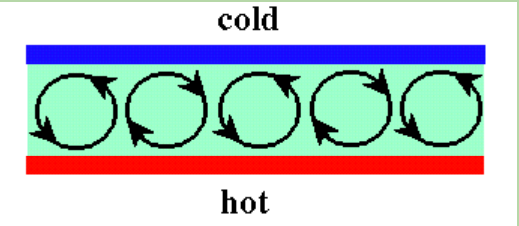
Physical justification of self-organization principle

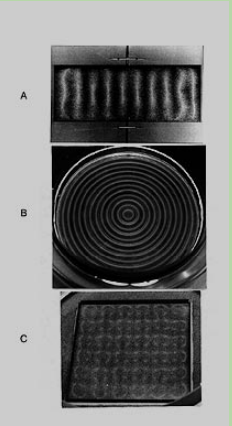
Molecular Biology and NeoDarwinism:
Optimization via natural selection of replicators

Vs

Self-organization:
Optimization without natural selection of replicators







Bénard convection cells

Dynamic flow organizes system to ensure 'optimal performance'

Function is a consequence of structure

Can help to deal with the challenge of 'irreducible complexity'

But!

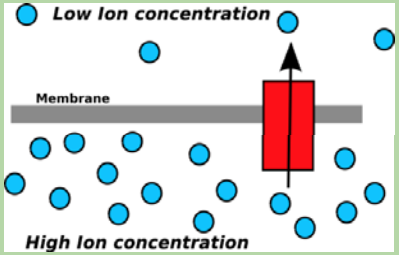
Is life a dissipative structure?

I. Prigogine: Mathematical theory of dissipative structures requires large numbers (to satisfy the criterium of local equilibrium)

But physics of Life is Nanophysics:

Number of free protons in E.coli - 5 per cell:
Volume of one cell 0.88um3
At pH 7, [H+] = 10(-7)M, or 6X10(-16)/L, or 5 per cell

Nanocells of Micoplasma Acholeplasma laidlawii, (0.2microm)
Have volume 0.008 um3, therefore have 0.05 free proton per cell



How the chemiosomotic hypothesis of Mitchell is possible?
Can proton gradient serve as a source of thermodynamic force?

Problem:

1. The notion of self-organization is attractive,

but

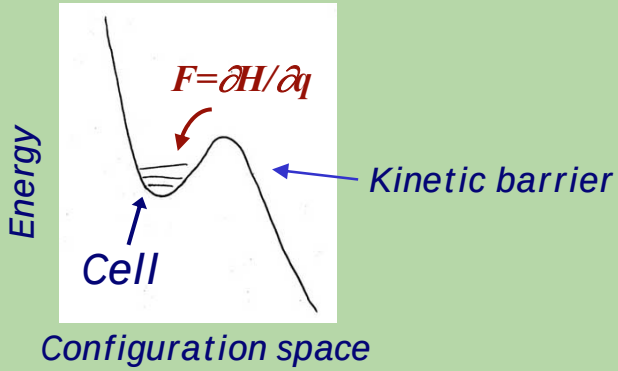
2. Its current theoretical justification
- statistical mechanics –
does not apply to the single cell level

Solution?

Justification of self-organization on new
– quantum theoretical - principles

Summary so far:

Cell in a ground state, or sufficiently close to it



The main question is the nature of the forces that hold the cell close enough to a ground state.

↕

Interplay between different time scales.

Catalytic force:

- *Additional physical force, contributing into stability of an ordered state of the cell in vivo*
- *Has intriguing 'self-organizing' property.*

(optimization without natural selection of replicators)

Open questions:

- *How Quantum Theory could remain relevant at the larger that atomic time scales?*

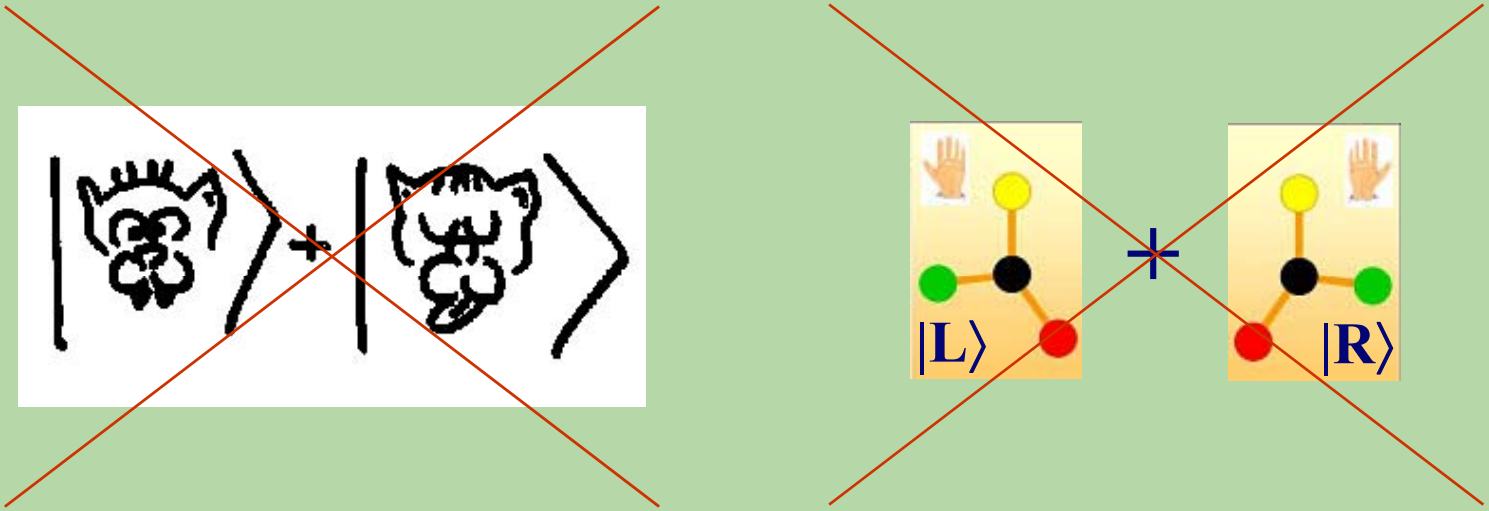
- *How enzymatic activities can be compatible with the stability of the ground state?*

- *Would the idea of 'catalytic force' work for other than a toy model of 'reversible enzymatic act'?*

- *How strong the catalytic force could be?*

1. How Quantum Theory could remain relevant at the larger that atomic time scales?

What about decoherence, responsible for the 'quantum to classical transition?'



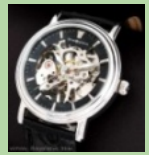
Environment acts as an observer that distinguishes between dead and alive cat, effectively destroying macroscopic superposition

Main argument:

- *Decoherence mechanism works well for 'generic environment'*
  i.e., apply to molecular structure in vitro

But

<u>In vivo</u> is not a generic environment,
a priori all bets are off



In vitro vs in vivo:

- *Small numbers of many components*
- *Highly structured*
- *Molecular crowding*

Most important:

Presence of catalytic activity

What are the preferred states of cell?

$$\rho^{c}(t_0) = Tr_e |\Psi_{EC}\rangle\langle\Psi_{EC}| = \Sigma\alpha_i\alpha^*_j\langle e_i|e_j\rangle |c_i\rangle\langle c_j|$$

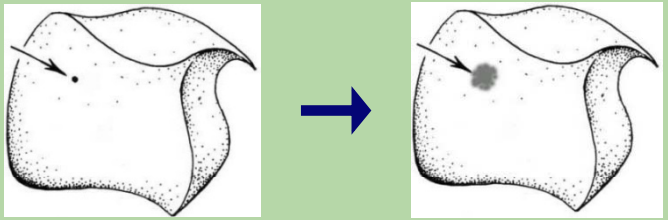
decoherence ↓

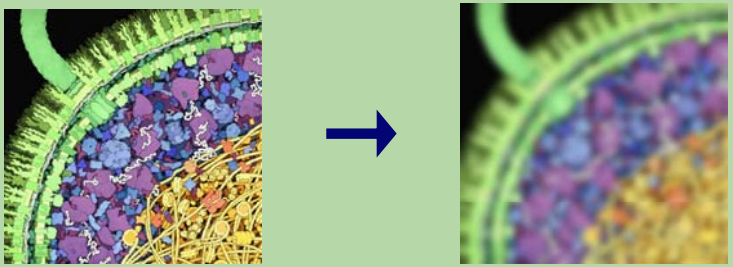
$$\rho^{c}(t) = \Sigma\alpha^2_i |c_i\rangle\langle c_i| \quad -$$

localization in configuration space?
(With all atomic positions specified)

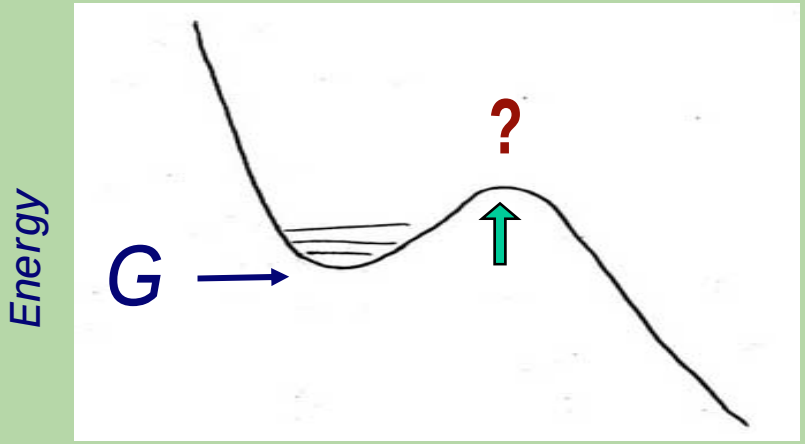
Idea

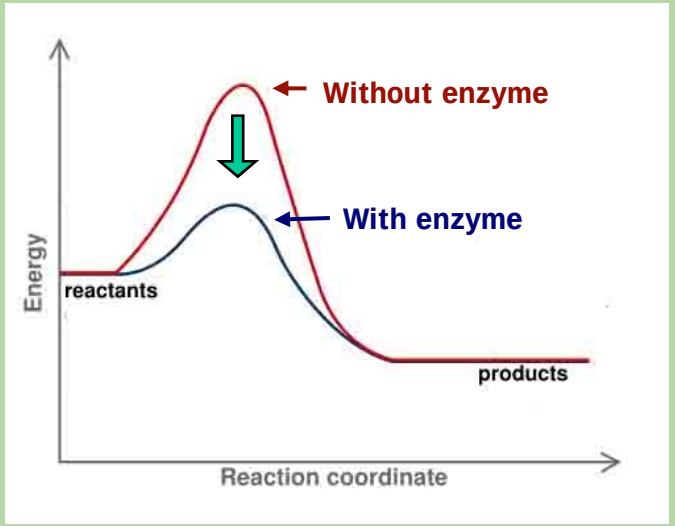
Because of the catalytic activity, preferred states $|c_i\rangle\langle c_i|$ *of the cell are not 'points in configuration space'*





2. How enzymatic activities can be compatible with the stability of the ground state?





?

The job of enzymes is to lower kinetic barriers, not to erect them!

"What is the mechanism of negative catalysis?..." L. Brillouin 'Life, Thermodynamics, and Cybernetics'. 1949

What kinetic barriers are from the 'first principles' point of view?

Kinetic barriers reflect small off-diagonal terms in reduced density matrix ρ

Values of off-diagonals depend on the choice of basis for ρ

$$a \quad b \quad \rho = \begin{array}{c} \begin{matrix} a & b & c & d \end{matrix} \\ \begin{pmatrix} aa^* & ab^* & ac^* & ad^* \\ ba^* & bb^* & bc^* & bd^* \\ ca^* & cb^* & cc^* & cd^* \\ da^* & db^* & dc^* & dd^* \end{pmatrix} \end{array} \longrightarrow \begin{array}{c} \begin{matrix} x & y & z & w \end{matrix} \\ \begin{pmatrix} \lambda_1 & 0 & 0 & 0 \\ 0 & \lambda_2 & 0 & 0 \\ 0 & 0 & \lambda_3 & 0 \\ 0 & 0 & 0 & \lambda_4 \end{pmatrix} \end{array}$$

$x \quad y$

Molecular configuration basis
aa, bb* - configurations*
ab, cd* - transitions*

Preferred states basis
λ_i - preferred states

Tentative answer

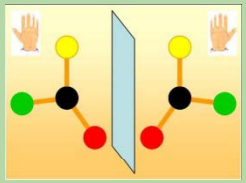
Preferred states are separated by kinetic barriers, and enzymes contribute into the stability of preferred states

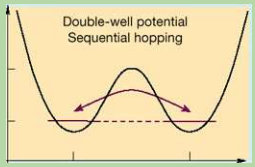
Can the idea of catalytic force be taken seriously?

- *How Quantum Theory could remain relevant at the larger that atomic time scales?*

What about decoherence, responsible for the 'quantum to classical transition'?

- *We used the toy model of 'reversible enzymatic act', which is not trivial for other than chiral molecules*





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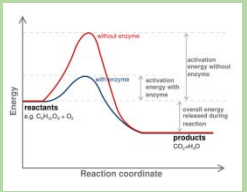

Can, generally, an enzymatic act be described in this way, - instead of the more traditional 'thermally activated barrier crossing'?

- *How strong the catalytic force could be?*

Can it be comparable with the thermal energy?

Can the idea of catalytic force be taken seriously?

- *How Quantum Theory could remain relevant at the larger that atomic time scales?*

What about decoherence, responsible for the 'quantum to classical transition'?

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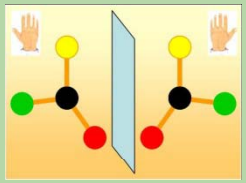

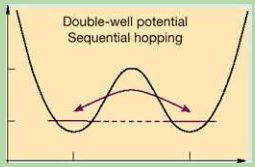

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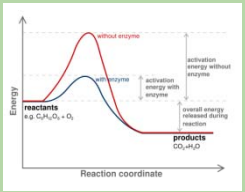


Can, generally, an enzymatic act be described in this way, - instead of the more traditional 'thermally activated barrier crossing'?

- *How strong the catalytic force could be?*

Can it be comparable with the thermal energy?

Justification of '$\tau_c << \tau_e$' and its consequences

•Order in condensed matter is stable because the interactions inside the system are stronger than interactions between the system and its environment

↓

•Reformulate in terms of time scales:
The time scale of processes inside the system τ_c is much faster than the time scale of exchange with environment τ_e

↓

•Consider enzymatic catalysis as part of the internal processes

↓

•Activation energy is confined to cell (because $\tau_c << \tau_e$, and energy is conserved on τ_c)

↓

•Apply the principle of energy minimum – on the larger time scale τ_e
the cell will tend toward the state where activation energy is minimized (assuming everything else being equal)

↓

•A new 'force', which together with other forces will contribute to the stability of biological order

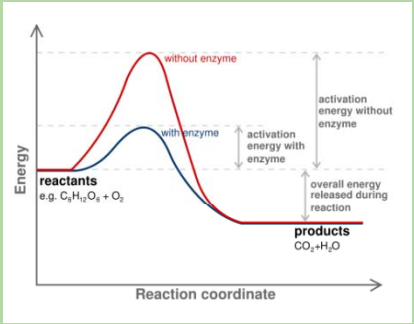
↓

•Reinterpretation – lower activation energy implies more efficient catalytic processes – an optimization without natural selection.
Meaningful order for free!

Conditions for the time-scale separation:

Catalysis $\tau_c << \tau_e$ Exchange with environment

More general than chiral states



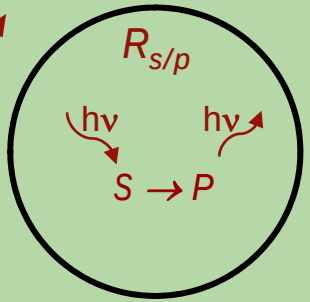
Describe catalytic events as changes in the state of the whole cell

1. $E_{CS} = E_{CP}$ *Energy compensation at the level of whole cell*

The energy difference between substrate and product is taken care of by extending description to the whole cell.

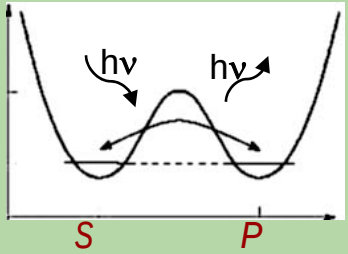
2. *Activation energy confined to cell*

External environment



hν hν

EnzS → EnzP



$\Delta G^{\ddagger}$

$$k = \frac{k_B T}{h} e^{-\frac{\Delta G^{\ddagger}}{RT}}$$

Thermal energy (Eyring-Polanyi)

Activation energy ≠ thermal energy

Requirements for energy conservation on scale τ_c seem to be very stringent

Conditions for $\tau_c << \tau_e$ seem to be very stringent

Optimistic perspective:

On other hand, they can serve as the new strong constraints for systems biology!

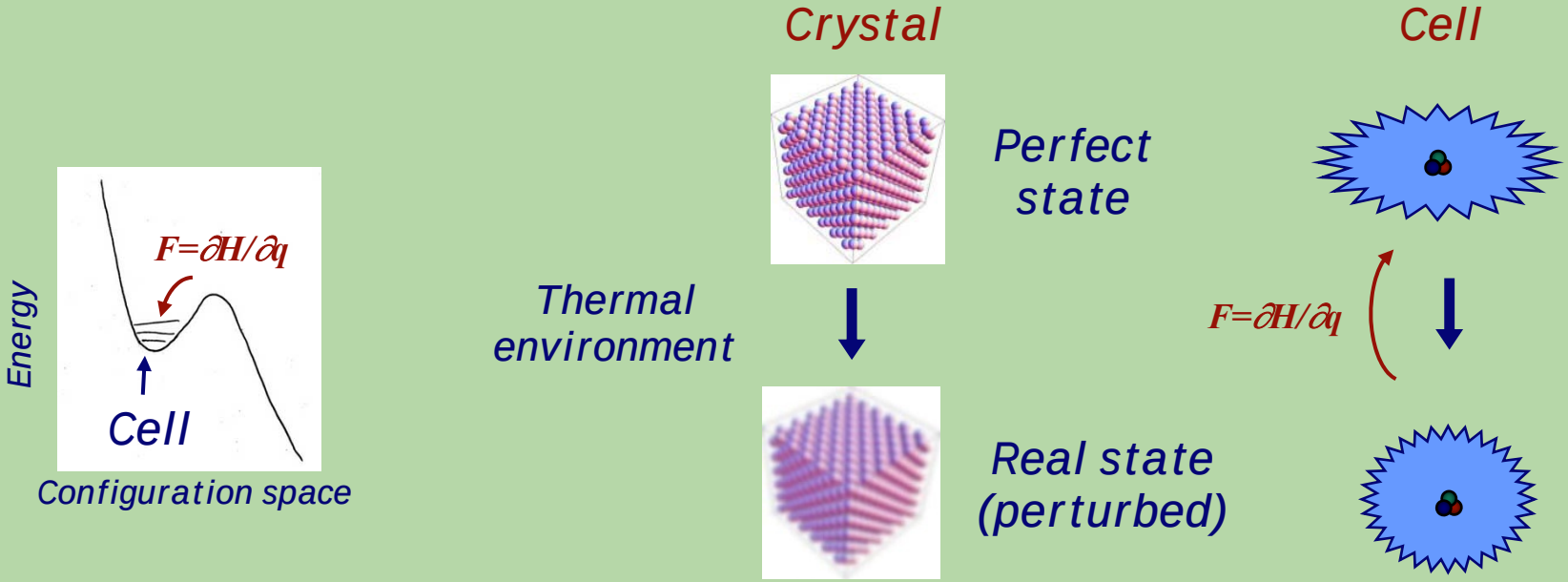
For every enzymatic act (every bi-partition of the cell to a target molecule and microenvironment environment) – we have such a requirement. 10^{11} new constraints!

But how physically plausible such a state can be?

Back to the notion of ground state:

Q: How such 'fine-tuning' of the microenvironment is physically possible if a cell is a 'wet and warm' system?

A: Real cell does not need to be in such a fine-tuned state
Because the condition $\tau_c << \tau_e$ describes a <u>ground state!</u>



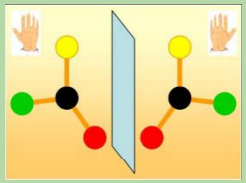
Catalytic forces as a reaction forces responsible for the stability of the ground state, where all works 'perfectly well'

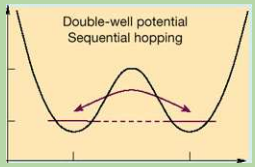
Can the idea of catalytic force be taken seriously?

- *How Quantum Theory could remain relevant at the larger that atomic time scales?*

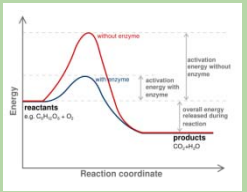
What about decoherence, responsible for the 'quantum to classical transition?'

- *We used the toy model of 'reversible enzymatic act', which is not trivial for other than chiral molecules*





?

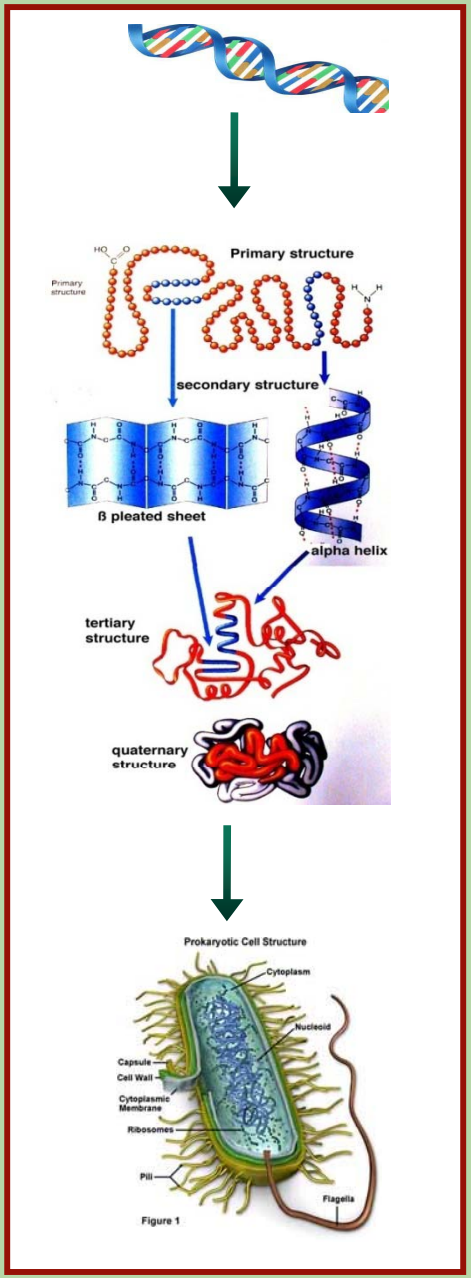


Can, generally, an enzymatic act be described in this way, - instead of the more traditional 'thermally activated barrier crossing'?

- *How strong the catalytic force could be?*

Can it be comparable with the thermal energy?

Force to recon with



Some common binary interactions in cell:

Dipole-dipole ~ 4kT

Hydrogen bonds ~ 5-19kT

Covalent bonds ~ 100 -150kT

New force

Estimate:

Typical enzymatic rate enhancement is 10^{10} - 10^{15}, which corresponds to 23kT - 34.5kT lowering of energy of TS

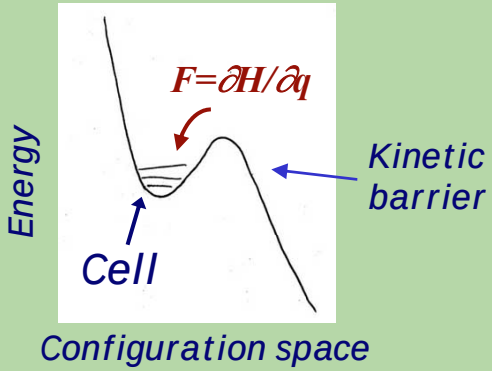
Decceleration of transition rate 100 times corresponds to increasing of energy of perturbed state 4.6kT

Could be comparable in strength to weak interactions

Did not take into account that one perturbation can affect many transitions

Summary so far:

Cell in a ground state, or sufficiently close to it



The main question is the nature of the forces that hold the cell close enough to a ground state.

↕

Interplay between different time scales.

Catalytic force:

- *Additional physical force, contributing into stability of an ordered state of the cell in vivo*
- *Has intriguing 'self-organizing' property. (optimization without natural selection of replicators)*
- *Catalysis could act against decoherence*
- *The energy could be comparable to thermal energy*

More questions:

1. *Condition* $\tau_c << \tau_e$*:*

But the enzymatic rates (and thus time scales) vary widely

No answer at the moment

---

2. So far, we were describing a ground state of cell or a state close to it.

How to move on to description of irreversible processes, such as growth and reproduction?

More questions:

1. *Condition $\tau_c << \tau_e$:*

But the enzymatic rates (and thus time scales) vary widely

No answer at the moment

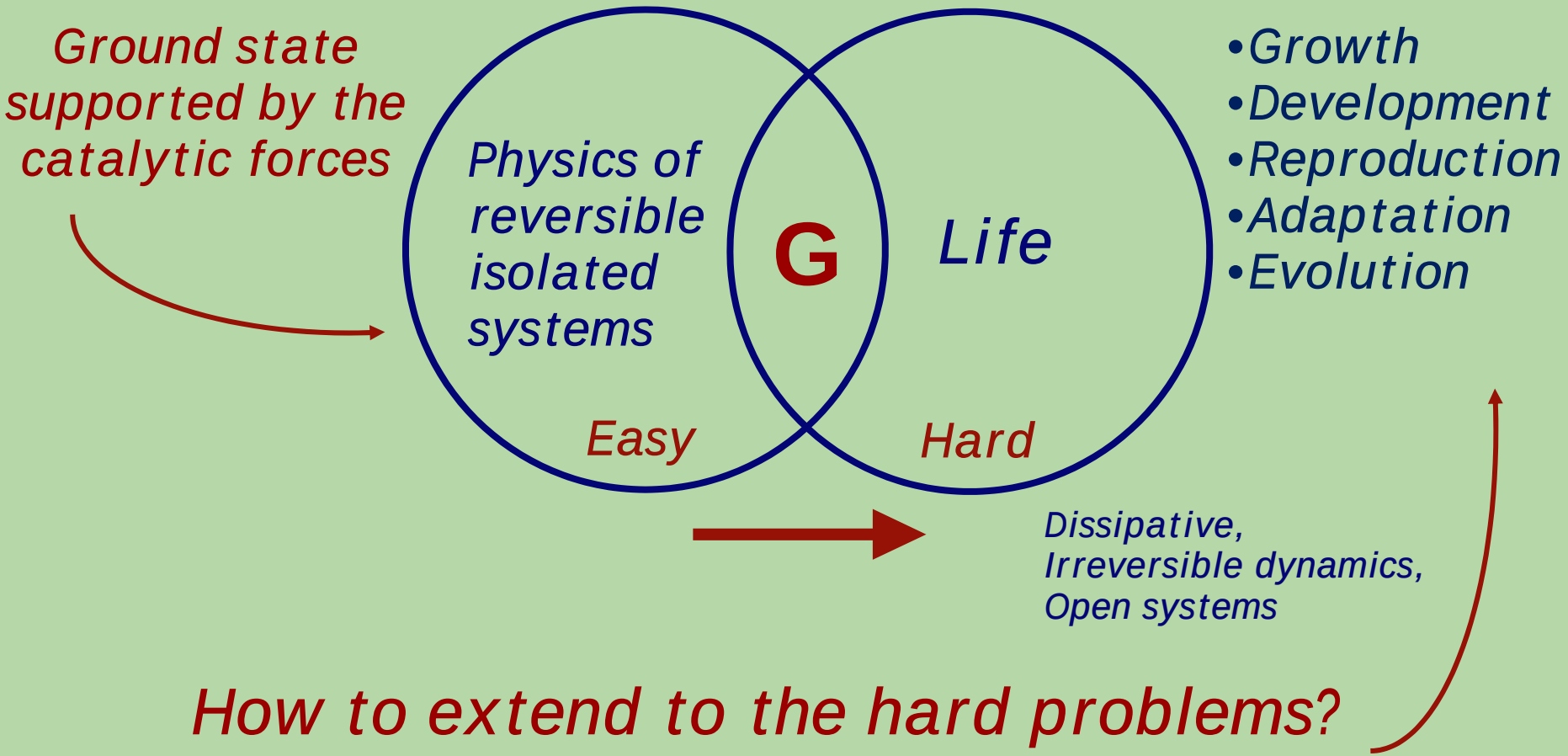
---

2. So far, we were describing a ground state of cell or a state close to it.

How to move on to description of irreversible processes, such as growth and reproduction?

How they do it in physics

Ground state description: Next step.



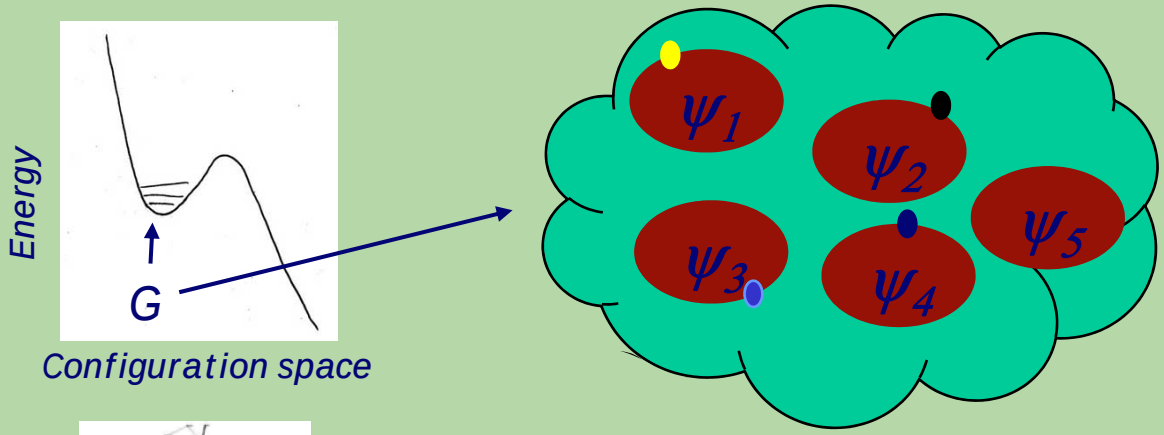
How to extend to the hard problems?

Fluctuation-dissipation theorem

Ground state as a fluctuating state

Every consumable substrate can be reversibly generated in it with a finite amplitude

$$|G\rangle = \alpha_1|\psi_1\rangle + \alpha_2|\psi_2\rangle + \alpha_3|\psi_3\rangle + \alpha_4|\psi_4\rangle \ldots$$



Plausibility:

Nano-system, reversibility, Fluctuation Theorem

$$\frac{\Pr(\overline{\Sigma}_t = A)}{\Pr(\overline{\Sigma}_t = -A)} = e^{At}.$$

Can help to describe real growth

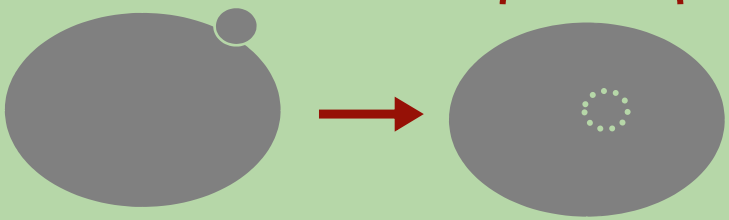
Arguments from the fluctuation-dissipation theorem

Conversion of a substrate to 'stuff of cell'

Relaxation of fluctuation in starving state

Molecule of substrate as a result of reversible fluctuation

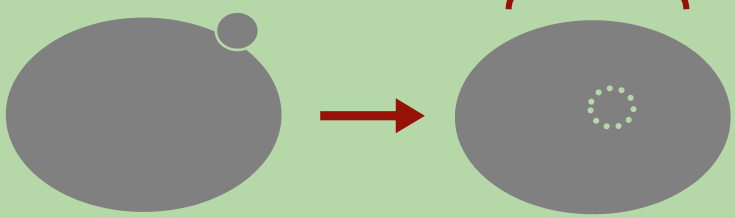
'Relaxed' state

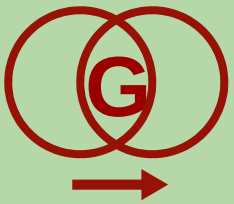


Assimilation of substrate by growing state

Molecule of substrate added externally

'Grown' state

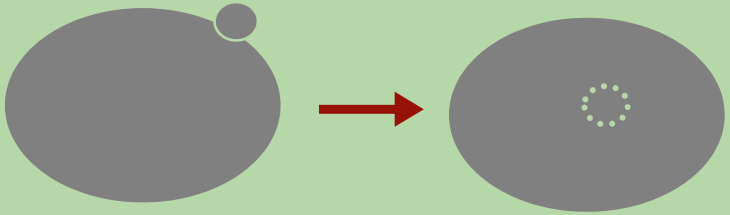




Looks the same

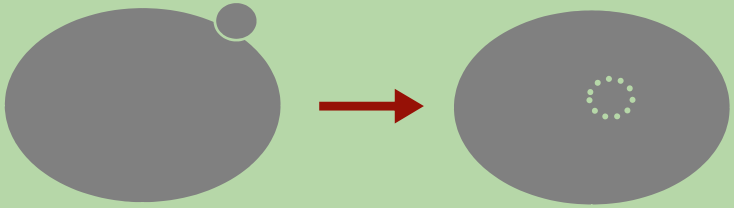
Reproduction in imaginary time?

No external substrate
(Cannot control)



Growth in imaginary time

External substrate added
(Under control, can be represented as a product state)

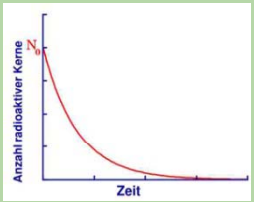


Real growth

Wick rotation?

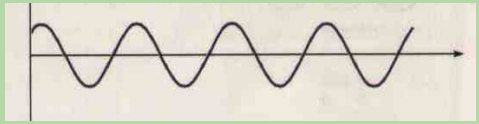
Schroedinger equation

$$\frac{\partial u}{\partial t} = k\nabla^2 u$$



Diffusion

$$i\hbar\frac{\partial}{\partial t}\Psi = -\frac{\hbar^2}{2m}\nabla^2\Psi$$



Unitary evolution as analytic continuation of…

$$\frac{\partial u}{\partial t} = k\nabla^2 u$$

Growth

Plan:

- *Why we need a notion of a ground state?*
- *What are the forces responsible for its stability?*
- *Implications for biology*

A new perspective on natural selection

Darwin:

The spectrum of variations does not depend on the selection conditions

Quantum:

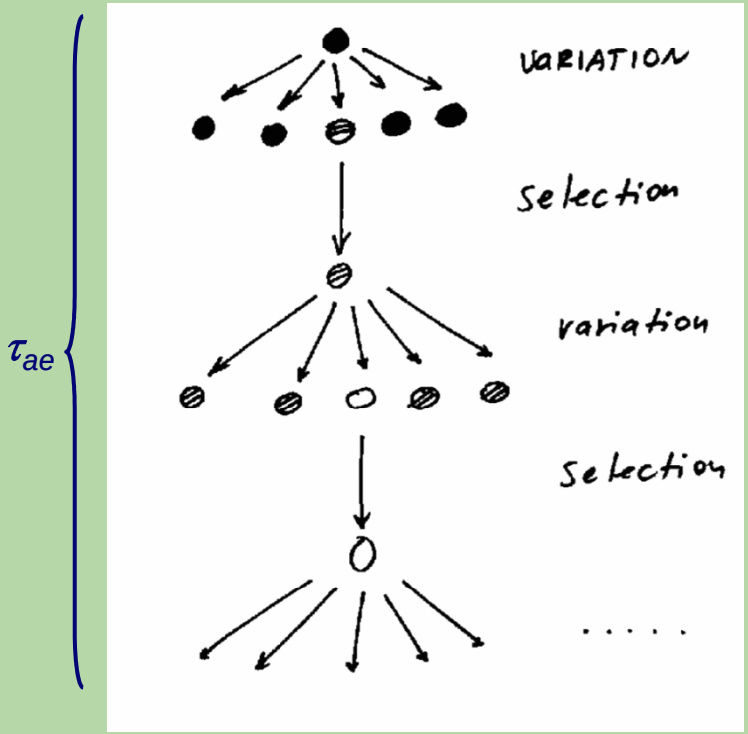
The spectrum of variations (the sample space) depends on the selection conditions

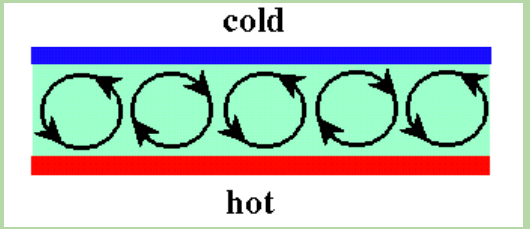
Ogryzko V (1997) BioSystems, 43:83-95, 'A Quantum-theoretical approach to the phenomenon of directed mutations in bacteria'

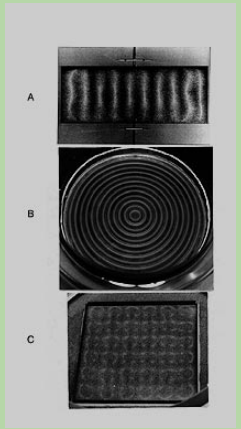
Ogryzko (2008) NeuroQuantology 'On two quantum approaches to adaptive mutations in bacteria'

Self-organization

NeoDarwinism: *Vs* *Self-organization:*







Scale separation:

Changes on the short generation-to generation time scale τ_g happen without any consideration for their utility. Adaptive evolution typically occurs at a many-generation time scale τ_{ae}

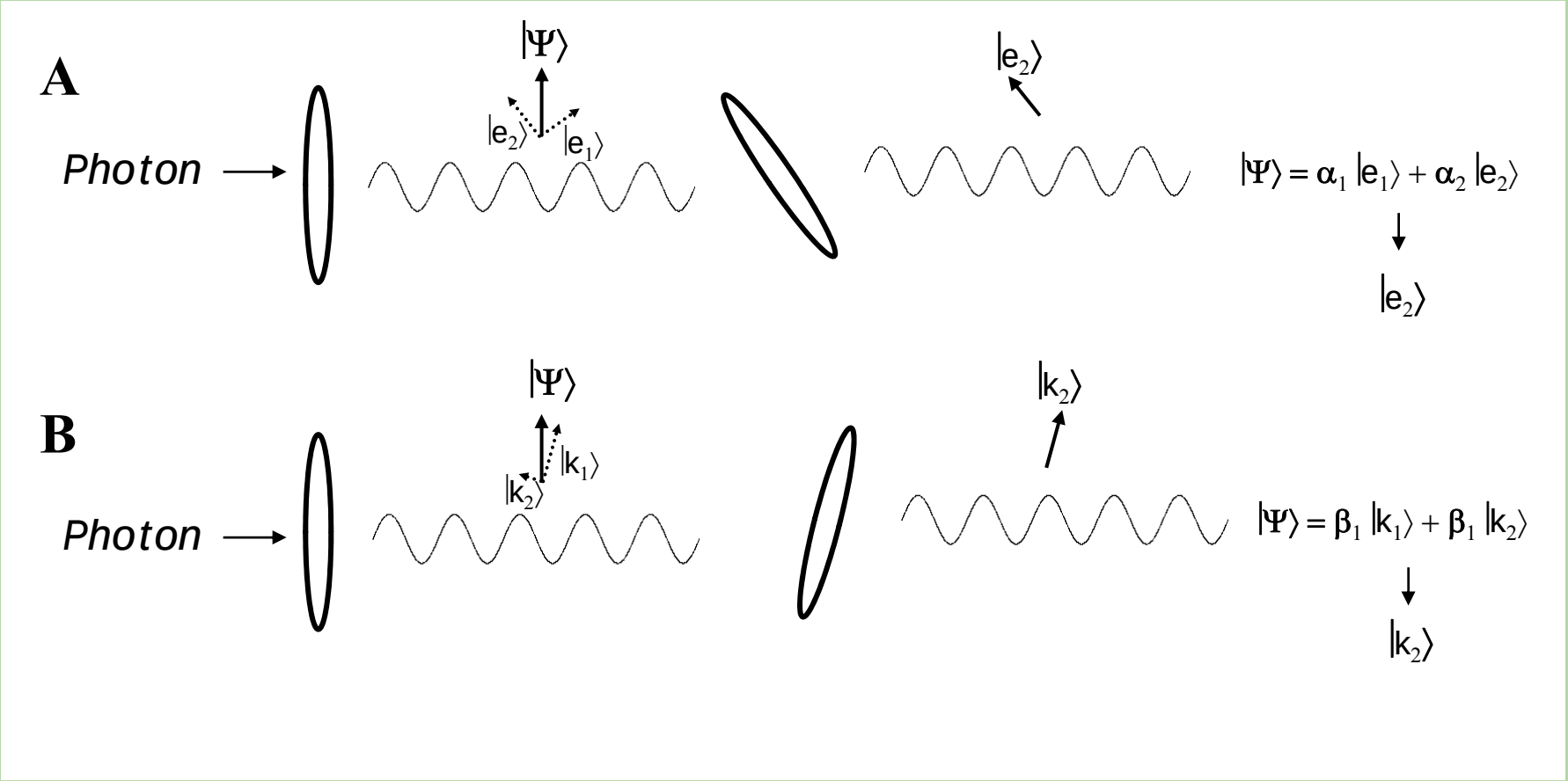
No scale separation

"Adaptive changes" happen at the level of individual object

i.e.,

An individual object directly contributes to (evolutionary?) adaptation

Adaptation via state vector reduction



Adaptation that happens via selection of a 'fit' variant

But the spectrum of variants to choose from depends on selection setup!

Related to Projection Postulate in Quantum Mechanics

Thank you for your attention!

For more details, read:

Erwin Schroedinger, Francis Crick and epigenetic stability
http://www.biology-direct.com/content/3/1/15

Quantum information processing at the cellular level. Euclidean approach
(arXiv:0906.4279)

A quantum-theoretical approach to the phenomenon of directed mutations in bacteria
(arXiv:q-bio/0701050)

Origin of adaptive mutants: a quantum measurement? (arXiv:0704.0034)

Quantum approach to adaptive mutations. Didactic introduction
(arXiv:0802.2271)

On two quantum approaches to adaptive mutations in bacteria
(NeuroQuantology, Vol 7, No 4.)

Use of high throughput sequencing to observe genome dynamics at a single cell level (Proc Natl Acad Sci U S A. 2009;106(49):20830-5)