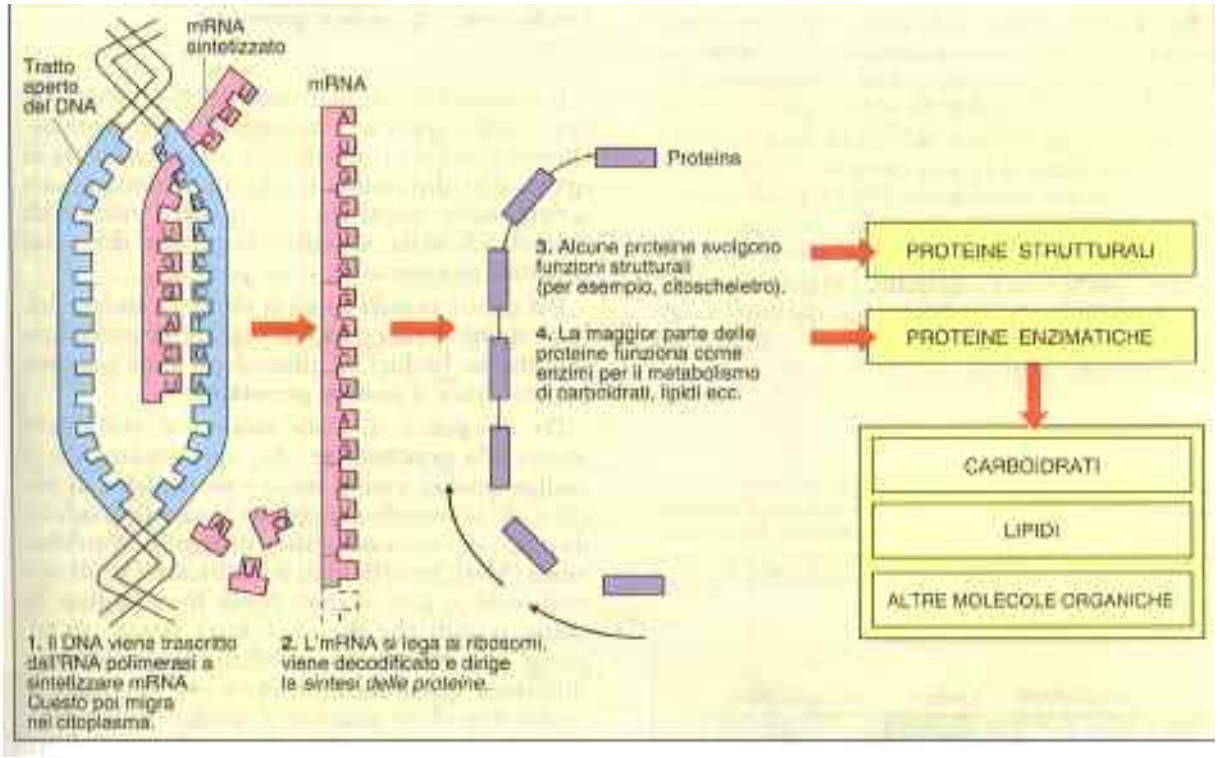
La vista sistemica

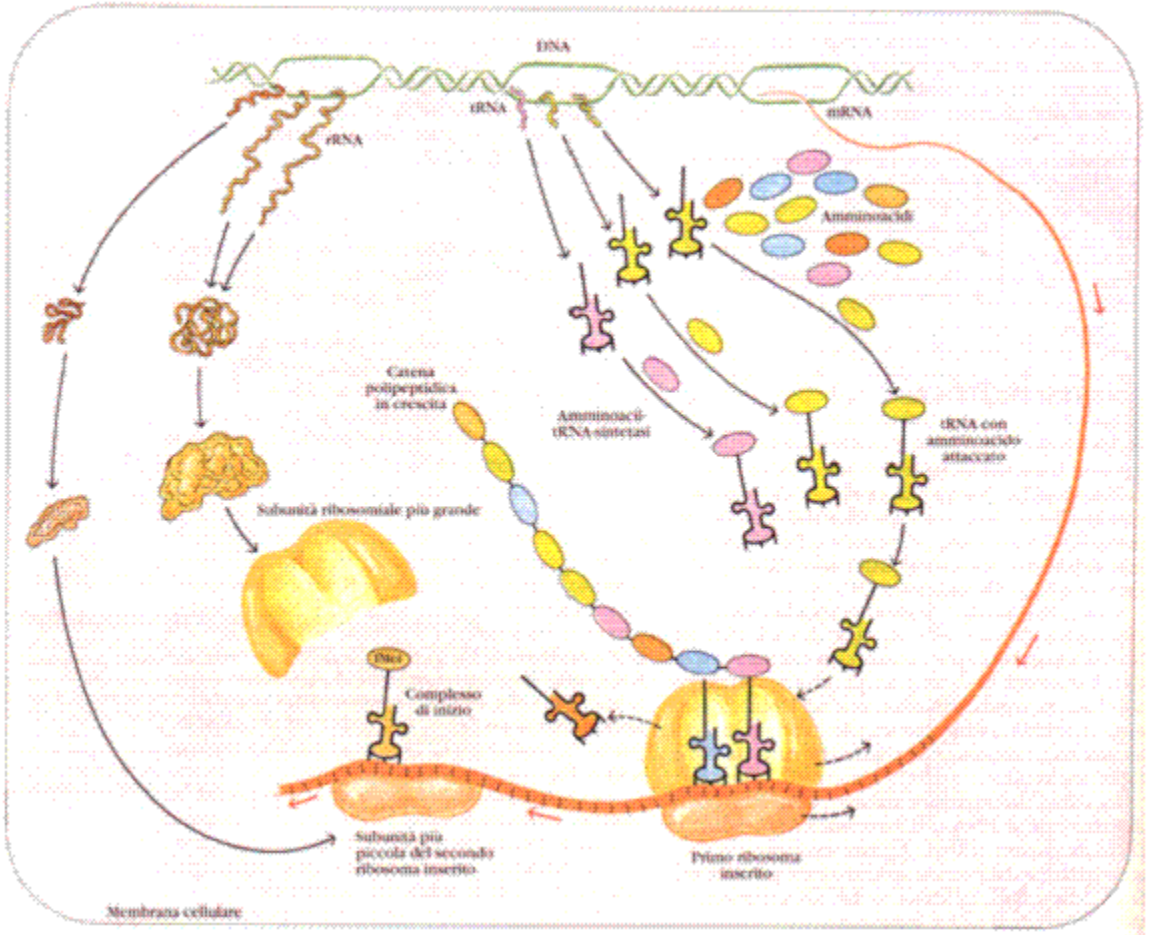
Alessandro Giuliani
Istituto Superiore di Sanità, Roma

Il nucleo (riduzionista) della regolazione biologica è un paradigma logico-informatico

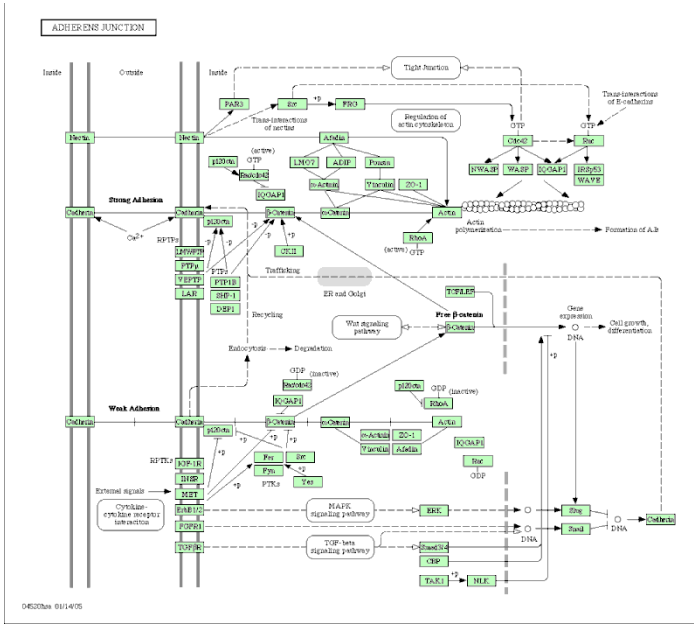


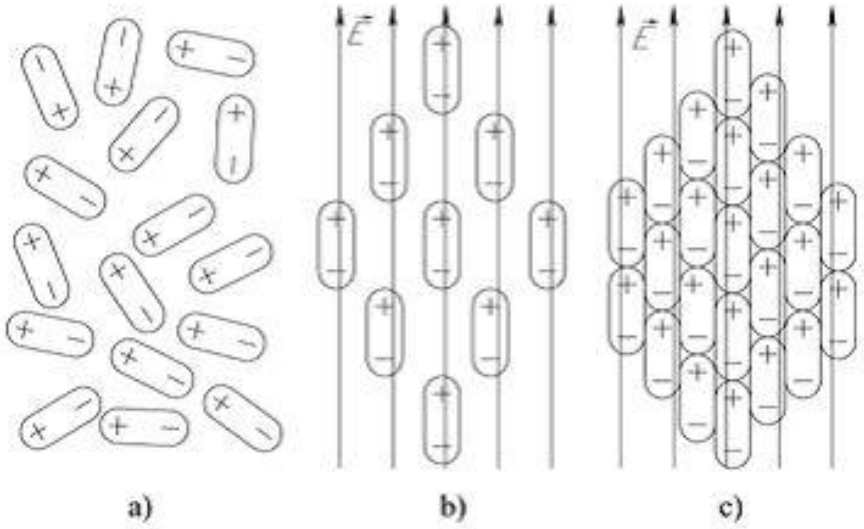
..con un circolo (vizioso ?)…

La fedeltà del sistema di codifica è affidata alla periferia, al legame cioè tra t-RNA e aminoacido corrispondente..



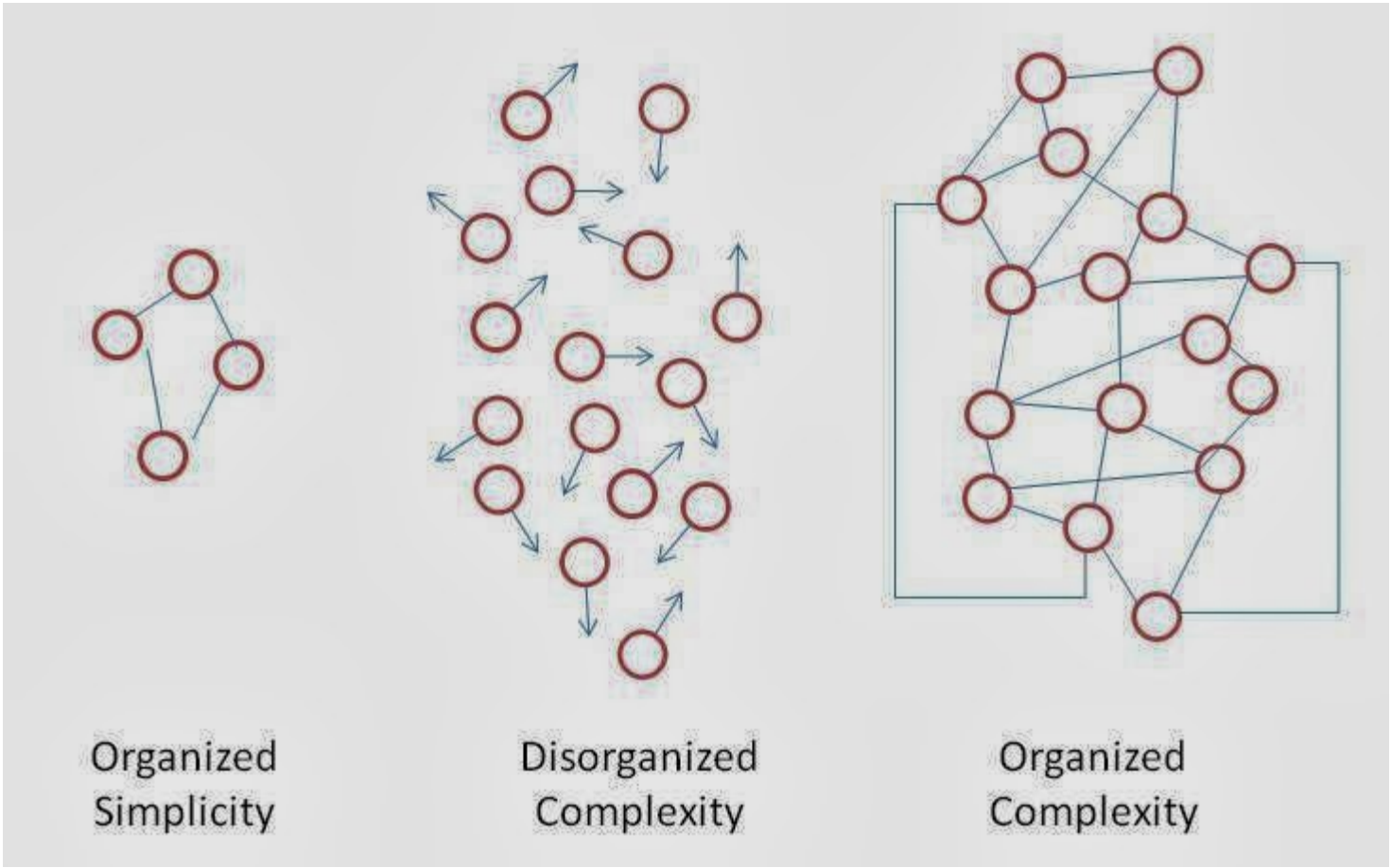
Due idee alternative sull'origine della regolarità:





'A la Newton'

'A la Boltzmann'


Organized
Simplicity
Disorganized
Complexity
Organized
Complexity

Il solo livello ‘causalmente rilevante’ nel paradigma logico-informatico è quello del programma, i ‘passaggi di scala’ dall’interno della singola cellula al sistema globale sono solo ‘epifenomeni’ (la parola ‘epigenetica’ è una spia di questo atteggiamento)… indipendentemente dalla loro evidenza fenomenologica (e.g. sviluppo embrionale, onde di sincronizzazione del tessuto cardiaco.

L’idea è che, anche se ancora non ci siamo arrivati, al livello inferiore risieda la ‘spiegazione’ che rende inutili i livelli superiori.

Da ciò una letteratura sterminata (spesso inconcludente) sui ‘geni per.. ogni cosa’.

Open access, freely available online

Essay

Why Most Published Research Findings Are False

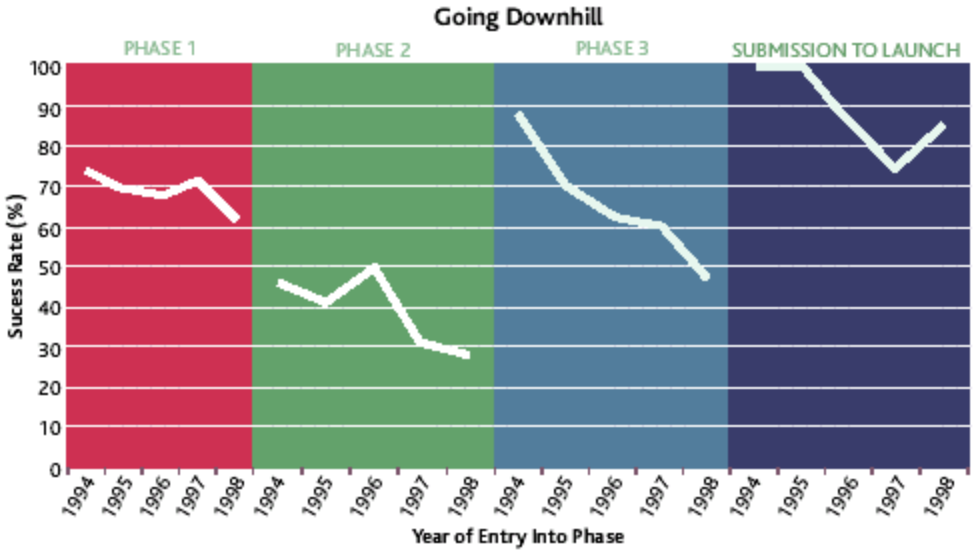
John P. A. Ioannidis

August 2005 | Volume 2 | Issue 8 | e124

Table 4. PPV of Research Findings for Various Combinations of Power (1 − β), Ratio of True to Not-True Relationships *(R)*, and Bias *(u)*

1 − β	*R*	*u*	Practical Example	PPV
0.80	1:1	0.10	Adequately powered RCT with little bias and 1:1 pre-study odds	0.85
0.95	2:1	0.30	Confirmatory meta-analysis of good-quality RCTs	0.85
0.80	1:3	0.40	Meta-analysis of small inconclusive studies	0.41
0.20	1:5	0.20	Underpowered, but well-performed phase I/II RCT	0.23
0.20	1:5	0.80	Underpowered, poorly performed phase I/II RCT	0.17
0.80	1:10	0.30	Adequately powered exploratory epidemiological study	0.20
0.20	1:10	0.30	Underpowered exploratory epidemiological study	0.12
0.20	1:1,000	0.80	Discovery-oriented exploratory research with massive testing	0.0010
0.20	1:1,000	0.20	As in previous example, but with more limited bias (more standardized)	0.0015

La crisi del modello riduzionistico in tutti i campi del sapere (particolarmente drammatica nella ricerca biomedica) ci costringe a tornare ad un altro tipo di approccio geometrico e sapienziale in cui il concetto di forma (e quello, strettamente collegato di bellezza e appropriatezza delle forme) torna ad avere un ruolo centrale.



SULLE FUNZIONI BILINEARI

DI

E. BELTRAMI

LIII. *On Lines and Planes of Closest Fit to Systems of Points in Space.* *By* KARL PEARSON, *F.R.S., University College, London* *.

(1) IN many physical, statistical, and biological investigations it is desirable to represent a system of points in plane, three, or higher dimensioned space by the "best-fitting" straight line or plane. Analytically this consists in taking

$$y = a_0 + a_1 x, \quad \text{or} \quad z = a_0 + a_1 x + b_1 y,$$

$$\text{or} \quad z = a_0 + a_1 x_1 + a_2 x_2 + a_3 x_3 + \ldots + a_n x_n,$$

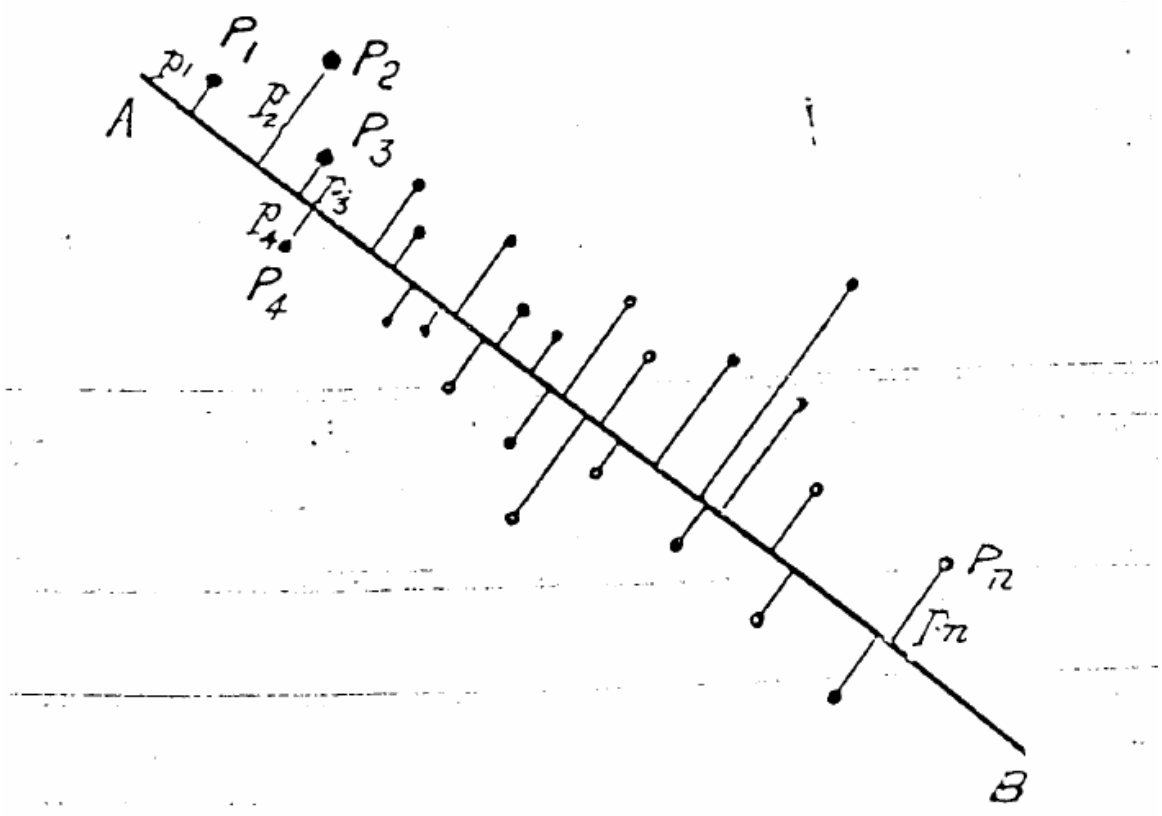
where y, x, z, x_1, x_2, $\ldots x_n$ are variables, and determining the "best" values for the constants a_0, a_1, b_1, a_0, a_1, a_2, a_3, $\ldots a_n$

For example:—Let $P_1, P_2, \ldots P_n$ be the system of points with coordinates $x_1, y_1; x_2, y_2; \ldots x_n y_n$, and perpendicular distances $p_1, p_2, \ldots p_n$ from a line A B. Then we shall make

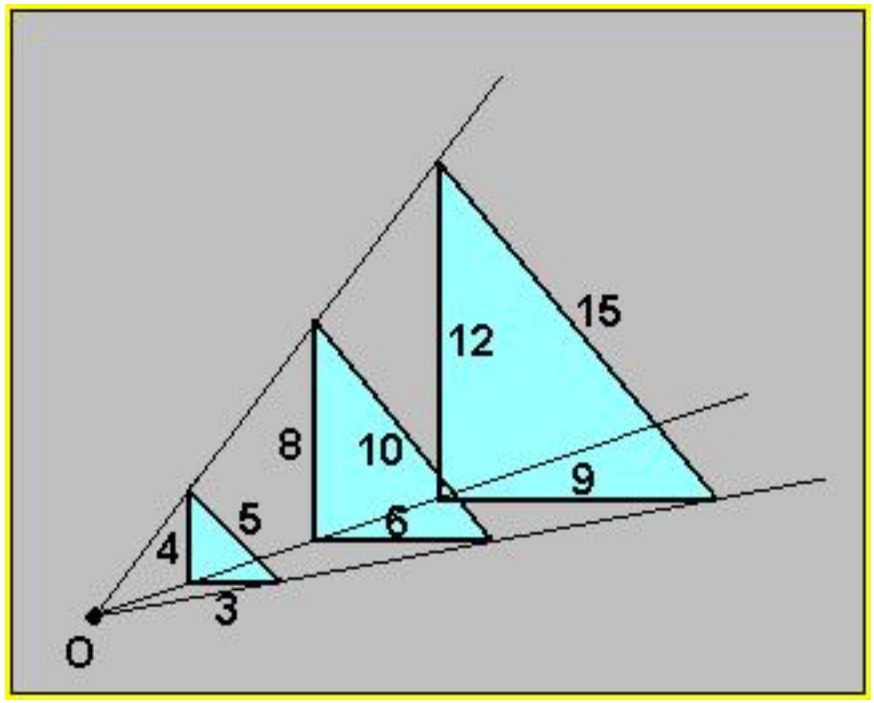
$$U = S(p^2) = \text{a minimum.}$$

If y were the dependent variable, we should have made

$$S(y' - y)^2 = \text{a minimum}$$



Una forma è un insieme costante di relazioni



Growth, 1960, **24**, 339-354.

SIZE AND SHAPE VARIATION IN THE PAINTED TURTLE.[1] A PRINCIPAL COMPONENT ANALYSIS

PIERRE JOLICOEUR AND JAMES E. MOSIMANN[2]

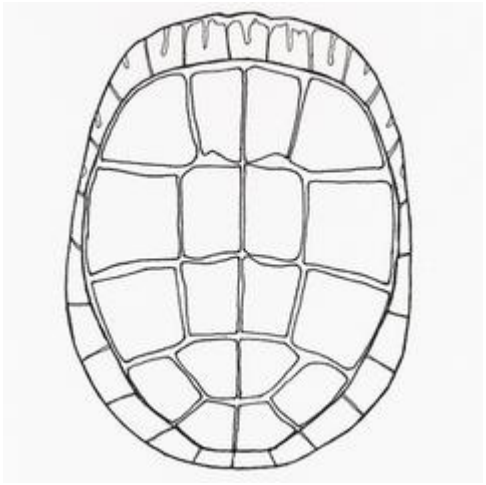
Walker Museum, University of Chicago
and
Institut de Biologie, Université de Montréal

(Received for publication July 11, 1960)

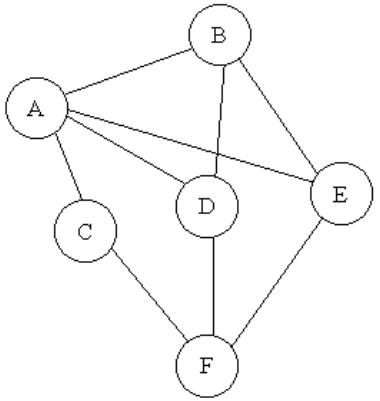
TABLE 1

CARAPACE DIMENSIONS OF PAINTED TURTLES (*Chrysemys picta marginata*) IN MM.

24 Males			24 Females		
length	width	height	length	width	height
93	74	37	98	81	38
94	78	35	103	84	38
96	80	35	103	86	42
101	84	39	105	86	40
102	85	38	109	88	44
103	81	37	123	92	50
104	83	39	123	95	46
106	83	39	133	99	51
107	82	38	133	102	51
112	89	40	133	102	51
113	88	40	134	100	48
114	86	40	136	102	49
116	90	43	137	98	51
117	90	41	138	99	51
117	91	41	141	105	53
119	93	41	147	108	57
120	89	40	149	107	55
120	93	44	153	107	56
121	95	42	155	115	63
125	93	45	155	117	60
127	96	45	158	115	62
128	95	45	159	118	63
131	95	46	162	124	61
135	106	47	177	132	67

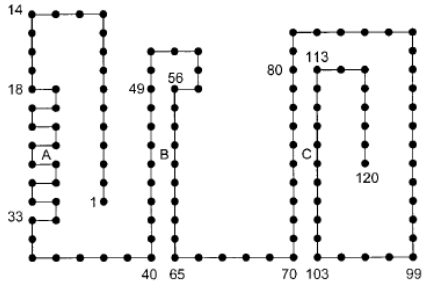


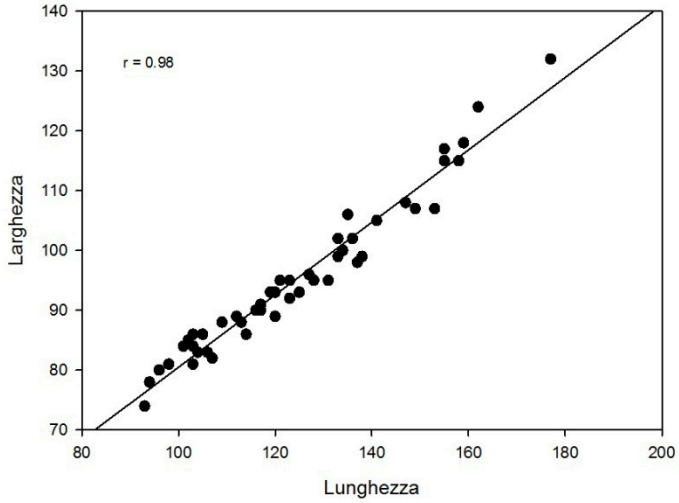
	A	B	C	D	E	F
A	-	1	1	1	1	
B	1	-		1	1	
C	1		-			1
D	1	1		-		1
E	1	1			-	1
F			1	1	1	-

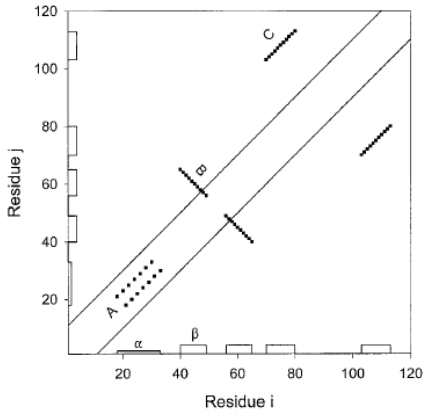


Pearson Correlation Coefficients,

	lunghezza	larghezza	spessore
lunghezza	1.00000	0.97831	0.96469
larghezza	0.97831	1.00000	0.96057
spessore	0.96469	0.96057	1.00000







Width = 19,94 + 0,605*Length

	PC1 (98%)	PC2 (1.4%)
Length	0,992	-0,067
Width	0,990	-0,100
Height	0,986	0,168

PC1= 33.78*Length +33.73*Width + 33.57*Height

PC2 = -1,57*Length – 2,33*Width + 3,93*Height

The presence of an overwhelming size component explaining system variance comes from the presence of a ‘typical’ common shape. The displacement along pc1 corresponds to purely size variation (all positive terms), the displacement along pc2 to shape deformation (both positive and negative terms).

Physica A 388 (2009) 1738–1746

Contents lists available at ScienceDirect

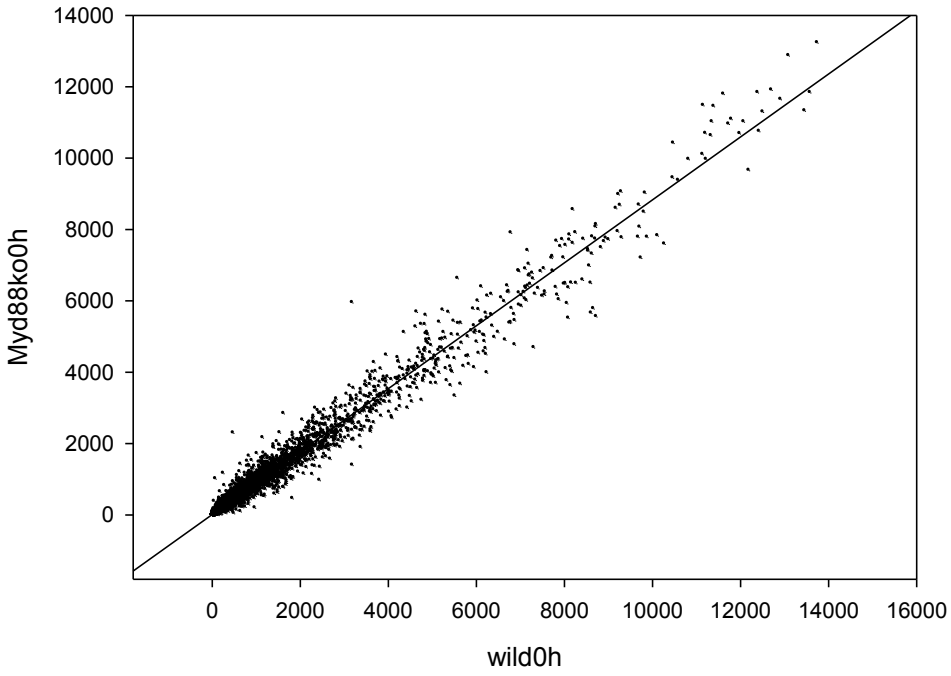
Physica A

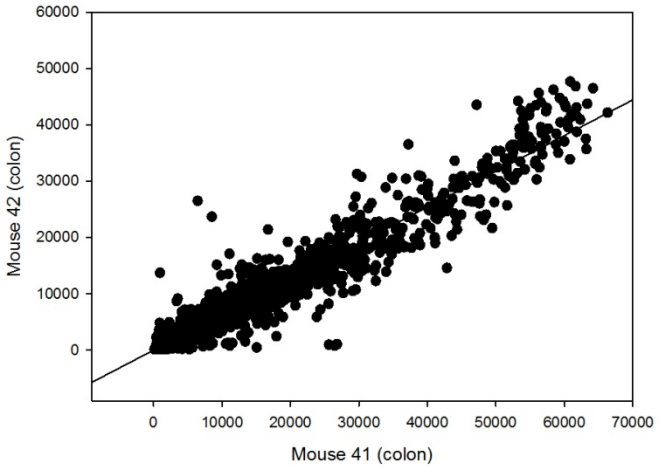
journal homepage: www.elsevier.com/locate/physa

Local and global responses in complex gene regulation networks

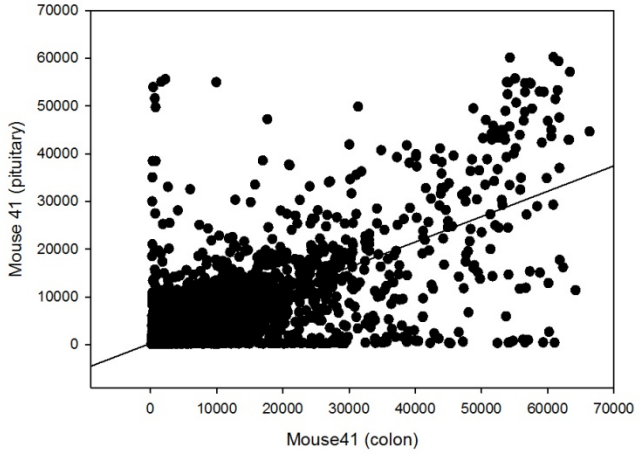
Masa Tsuchiya [a,1], Kumar Selvarajoo [a,1], Vincent Piras [a], Masaru Tomita [a], Alessandro Giuliani [b,*]

[a] Institute for Advanced Biosciences, Keio University, 14-1 Baba-cho, Tsuruoka, Yamagata 997-0035, Japan
[b] Istituto Superiore di Sanita', Environment and Health Department, Viale Regina Elena 299, 00161, Rome, Italy





The ‘tissue attractor’ is much stronger than the organism individuality

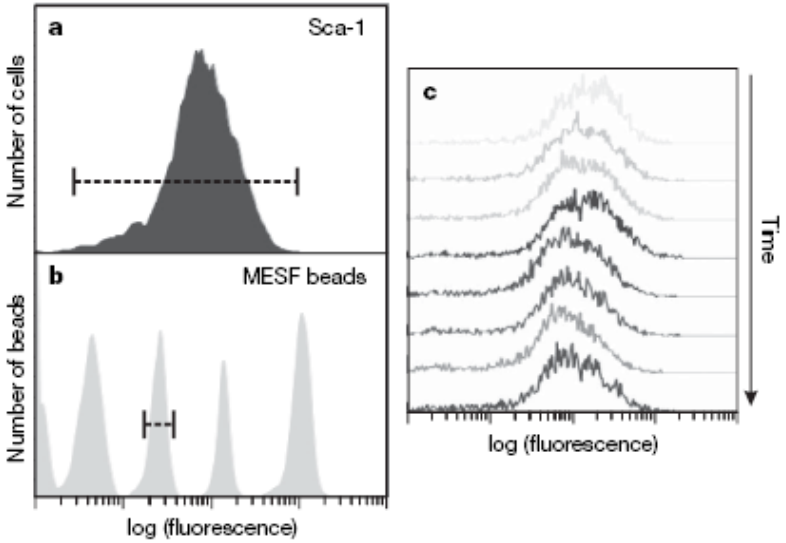


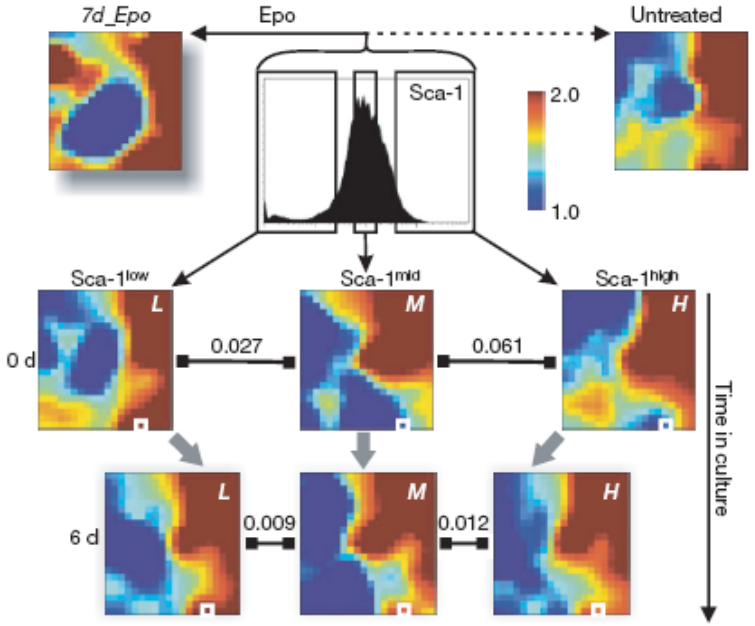
nature Vol 453|22 May 2008|doi:10.1038/nature06965

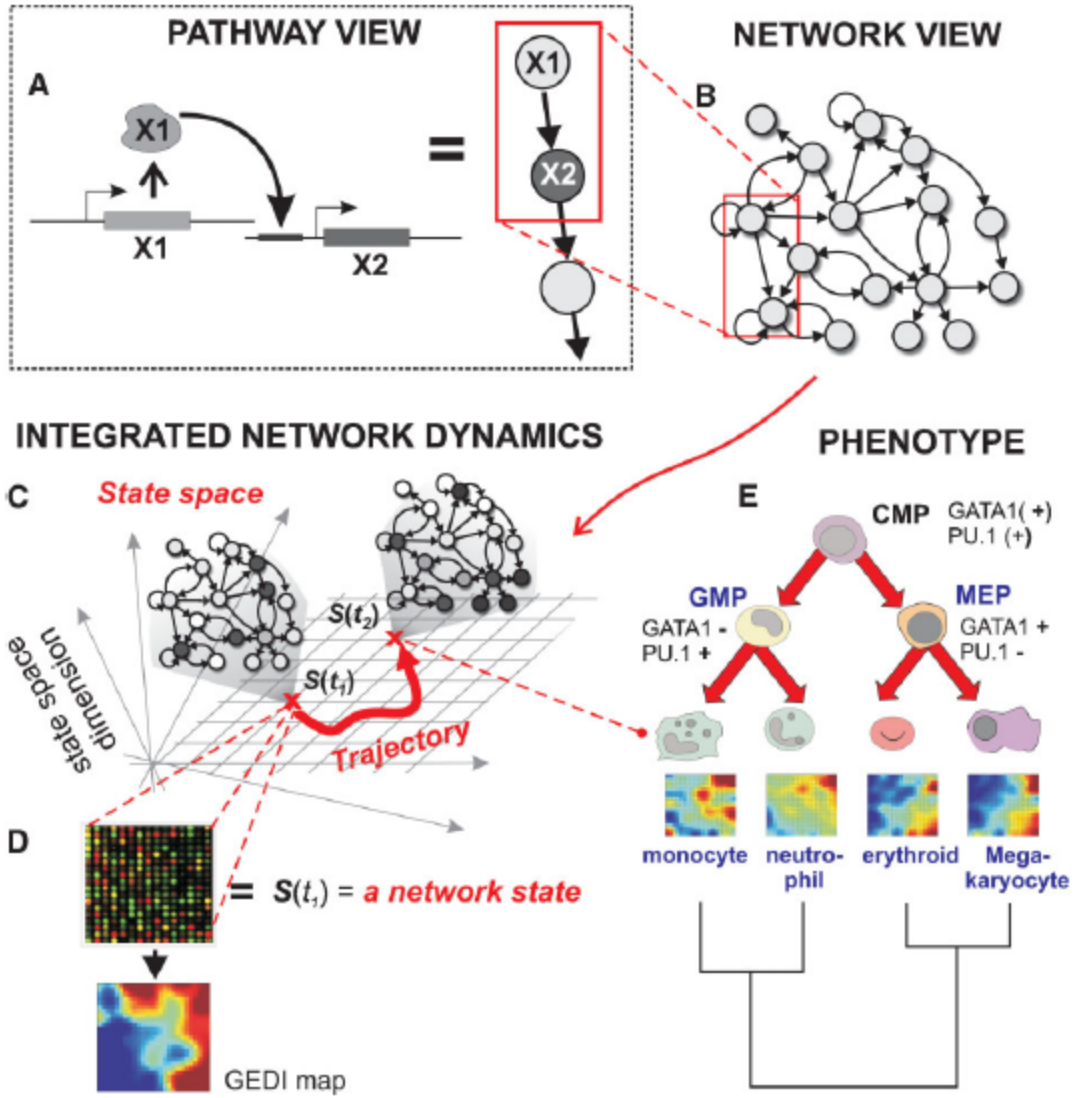
LETTERS

Transcriptome-wide noise controls lineage choice in mammalian progenitor cells

Hannah H. Chang[1,2,3], Martin Hemberg[4]†, Mauricio Barahona[4], Donald E. Ingber[1,5] & Sui Huang[1]†






PATHWAY VIEW
NETWORK VIEW
A
B
X1
X2
X1
X2
INTEGRATED NETWORK DYNAMICS
PHENOTYPE
C
State space
S(t2)
S(t1)
Trajectory
State dimension
D
= S(t1) = a network state
GEDI map
E
CMP
GATA1(+)
PU.1 (+)
GMP
GATA1 -
PU.1 +
MEP
GATA1 +
PU.1 -
monocyte
neutro-
phil
erythroid
Mega-
karyocyte

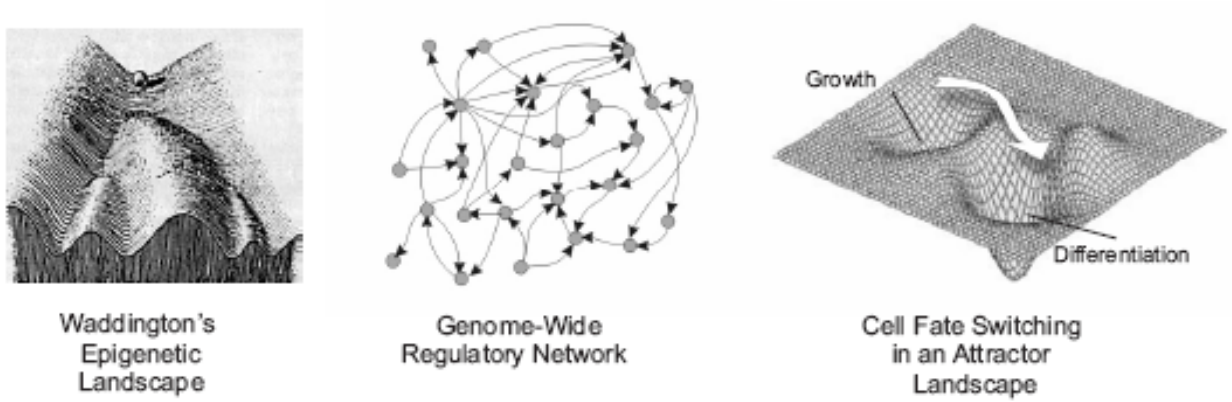


Fig. 8. The epigenetic landscape: from metaphor to mechanism. (Left) *The model Waddington first proposed as a metaphor in 1940 to explain how a cell decides between «discrete» fates during development. Recent work suggests that this concept may be regarded as a manifestation of dynamic constraints of the underlying genome-wide regulatory network* **(center)** *which creates a gene state space with the character of an "attractor landscape"* **(right)**. *In this landscape, distinct cell fates, such as growth, differentiation, apoptosis and different stem cell lineages represent distinct valleys (attractors) in the common landscape. Cells may take multiple paths to cross over a hill, however, they will roll until they come to a stop at a common end point at the bottom of the next valley; these low points or attractors are the limited number of default states that a cell can exhibit. (Image at left reprinted from Waddington, 1956; for more details, see Huang and Ingber, 2000, Ingber, 2003b, Huang* et al., *2005).*

Cell

Leading Edge
Essay

Statistical Mechanics of Pluripotency

Ben D. MacArthur[1,*] and Ihor R. Lemischka[2]
[1]Centre for Human Development, Stem Cells and Regeneration, Institute of Developmental Sciences, School of Mathematics, and Institute for Life Sciences, University of Southampton, SO17 1BJ, UK
[2]Department of Developmental and Regenerative Biology, Department of Pharmacology and Systems Therapeutics, Black Family Stem Cell Institute, Mount Sinai School of Medicine, New York, NY 10029, USA
*Correspondence: b.d.macarthur@soton.ac.uk
http://dx.doi.org/10.1016/j.cell.2013.07.024

Recent reports using single-cell profiling have indicated a remarkably dynamic view of pluripotent stem cell identity. Here, we argue that the pluripotent state is not well defined at the single-cell level but rather is a statistical property of stem cell populations, amenable to analysis using the tools of statistical mechanics and information theory.

In general, regulatory interactions between genes and proteins introduce correlations in expressions that reduce uncertainty in expression patterns and therefore reduce the entropy of the population at equilibrium. **Informally, the equilibrium distribution maximizes entropy subject to satisfying any imposed regulatory constraints**. **This connection suggests a broad principle: at equilibrium cell populations that are subject to strict regulatory constraints should exhibit well-defined and low entropy expression patterns, whereas those that are subject to weaker regulatory constraints should exhibit more diverse, higher entropy expression patterns.** Viewing variability in this light indicates that PSC **populations** may be more diverse than differentiated populations because they are subject to weaker regulatory constraints.

The middle way

R. B. Laughlin*, David Pines†‡§, Joerg Schmalian¶, Branko P. Stojković‖**, and Peter Wolynes††

32–37 | PNAS | January 4, 2000 | vol. 97 | no. 1

Mesoscopic organization in soft, hard, and biological matter is examined in the context of our present understanding of the principles responsible for emergent organized behavior (crystallinity, ferromagnetism, superconductivity, etc.) at long wavelengths in very large aggregations of particles. Particular attention is paid to the possibility that as-yet-undiscovered organizing principles might be at work at the mesoscopic scale, intermediate between atomic and macroscopic dimensions, and the implications of their discovery for biology and the physical sciences. The search for the existence and universality of such rules, the proof or disproof of organizing principles appropriate to the mesoscopic domain, is called the middle way.

Felli *et al. BMC Systems Biology* 2010, **4**:85
http://www.biomedcentral.com/1752-0509/4/85

BMC
Systems Biology

RESEARCH ARTICLE Open Access

Hematopoietic differentiation: a coordinated dynamical process towards attractor stable states

Nadia Felli[†1], Luciano Cianetti[†1], Elvira Pelosi[1], Alessandra Carè[1], Chang Gong Liu[3], George A Calin[3], Simona Rossi[3], Cesare Peschle[4], Giovanna Marziali[*1] and Alessandro Giuliani[*2]

A

SEQUENCES SIGNAL	SEQUENCES SIGNAL	SEQUENCES SIGNAL	SEQUENCES RATIO	SEQUENCES RATIO
54630 0-71337 All	17655 >500 Expressed	3019 >5000 High Expression	7642 >3x Changed	3561 >6x High Change
		14636 500-5000 Medium Expression		4081 3-6x Medium Change
	36975 <500 No/Low Expression			

B

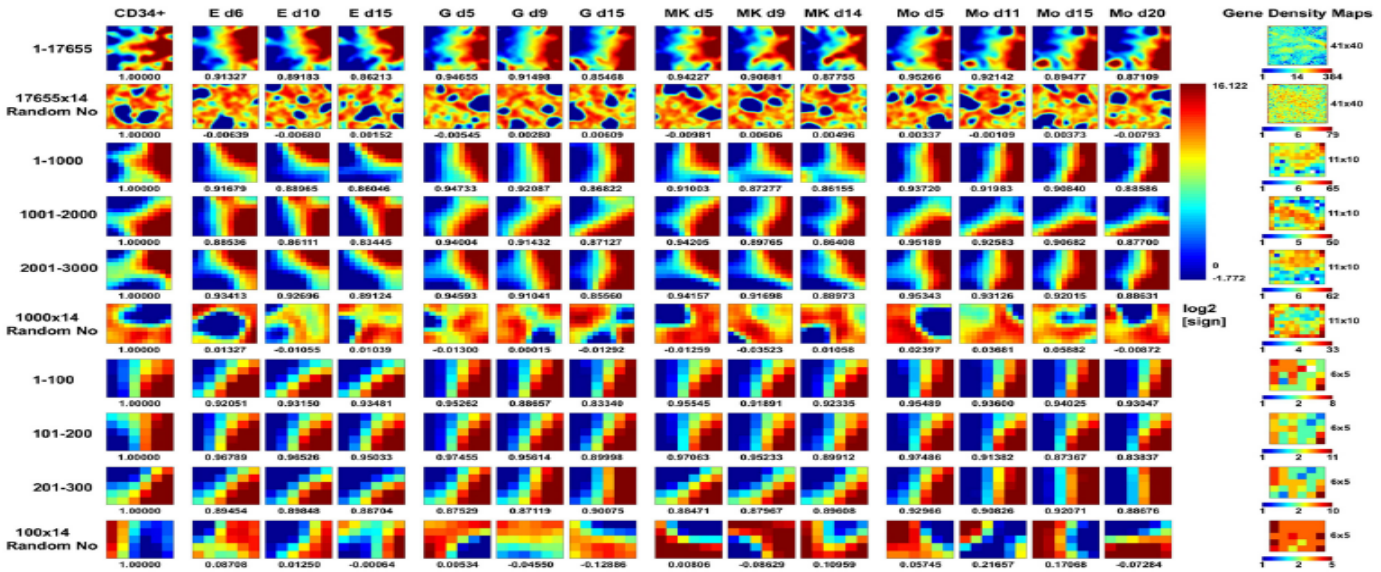
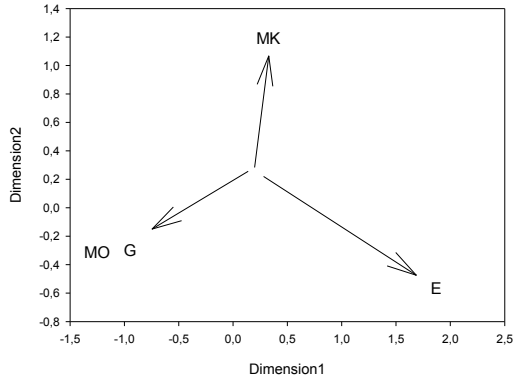


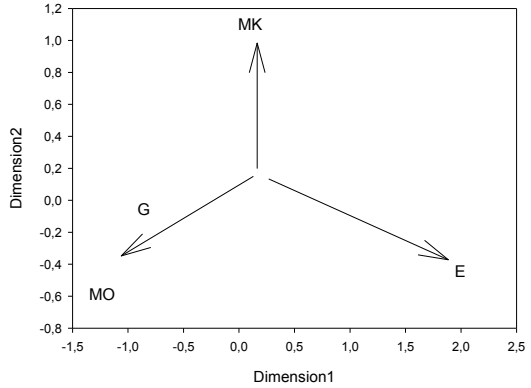
Figure 3 Expression profile of protein coding genes (PCGs) in unilineage culture of cord blood HPCs. **(A)** Gene microarrays were representative of a 54630 redundant set of sequences having linear normalized signal values ranging from 0 to 71337. Only sequences having at least one value >500 (an under-expression arbitrary threshold roughly corresponding to 1% of maximum value) were considered significantly expressed (Expressed Sequences) and sub-grouped according to two different criteria: i) expression level, by using a second arbitrary threshold (5000) in signal values that results in Medium Expressed (maximum value in the range 500-5000) and High Expressed (at least one value >5000) genes; ii) fold increase/decrease calculated as the ratio of differentiated cells (t_{max}) to CD34+HPCs (t_0) signal, obtaining Changed, Medium Changed and High Changed subsets of sequences showing in at least a lineage a signal fold change >3×, 3-6× or >6× respectively. **(B)** Self-organizing maps of global gene expression for the E, G, MK and Mo differentiation pathways. The array data set of N = 17655 Expressed Sequences, multiple randomly sampled 1000 or 100 sequence subsets and same-sized Random Numbers sets were clustered using the GEDI software into nearly-squared grids composed by miniclusters. On the left data or number set analysed (progressive number) for each line is defined, on the top of each column lineage and culture time are indicated. Below each grid the Pearson correlation with CD34+ (or with the first sample for Random Numbers) is reported. In the grids each pixel corresponds to a minicluster that is located at the same position in all the grids of the same line and is composed by a variable small group of sequences sharing a similar expression pattern, whose number is indicated by the Gene Density Map. On the right grid size (pixel number) is indicated. Colour of each minicluster indicates the mean of log_2-transformed expression value of corresponding sequences or Random Numbers, as indicated on the column bar on the right.

step1	step2	step3	
0,0552	0,0928	0,1619	e-mk
0,0678	0,1145	0,1537	e-g
0,0747	0,1269	0,1750	e-mo
0,0260	0,0653	0,1192	g-mk
0,0159	0,0496	0,0546	g-mo
0,0289	0,0808	0,1413	mo-mk



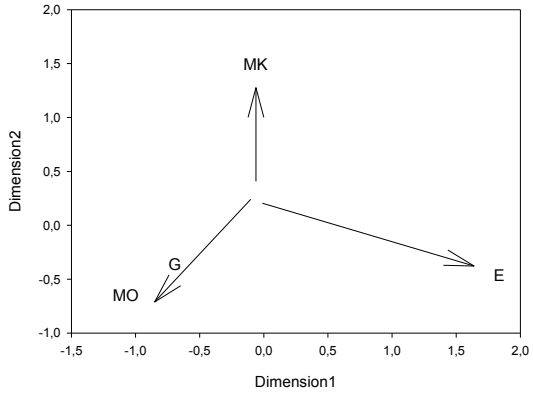
Step 1 configuration

average radius = 0.045



Step 2 configuration

average radius = 0.088



Step 3 configuration

average radius = 0.131

Conclusioni:

1.I sistemi biologici mostrano, a tutte le scale di osservazione, un continuo di comportamenti che va dalla specificità (locale) alla scalabilità (generale).

2.Il paradigma della rete consente di rendere ragione di questo spettro di comportamenti in termini di zone relativamente ‘isolabili’ della rete, rispetto a comportamenti collettivi dell’intero sistema reticolare.

3. La singola cellula non è necessariamente il luogo delle ‘spiegazioni definitive’ in biologia, comportamenti macroscopici deterministici a livello dell’intera cultura emergono grazie all’interazione dei componenti.

4. Se i singoli ‘destini’ della cellula sono attrattori del comportamento di una popolazione eterogenea di cellule, allora le nostre possibilità di intervento non possono immaginare una singola cellula tipo ma una popolazione a cui modificare globalmente lo spettro di probabilità dei diversi attrattori…..

Che cosa ho fatto per tutta la vita? Ho contemplato il mondo come un insieme , come un quadro e una realtà compatta, ma ad ogni tappa della mia vita da un determinato punto di vista […]. Le sue angolature mutano, l'una arricchendo l'altra; è qui la ragione della continua dialettica del pensiero assieme al costante orientamento di guardare il mondo come un unico insieme (Pavel Florenskij *"Non dimenticatemi"*, p. 385)