Cellular Darwinism: regulatory networks, stochasticity, and selection in cancer development

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Stage 1 of the argument

Cellular stochasticity
exists and is very extensive even in cloned tissues

Selection at cellular level
Early and recent ideas

1896. August Weismann, 1896: proposed selection of cells in the germ line.
1983. 2020. Jean-Jacques Kupiec: Stochasticity and selection underlie cell differentiation.
2008. Huang et al: large variation in expression levels in mammalian progenitor cells confirms stochasticity, and that the pattern is a tissue-level attractor.

Weismann, A. (1896) *On germinal selection as a source of definite variation*. Chicago: Open Court.
Kupiec, J-J (2020), A probabilistic theory for cell differentiation, embryonic mortality and DNA c-value paradox, *Organisms. Journal of Biological Sciences*, vol. 4, no. 1 (2020), pp. 8-10.
Transcriptome-wide noise controls lineage choice in mammalian progenitor cells
Chang, Hemberg, Barahona, Ingber, & Huang (2008), *Nature*, **453**, 544-548

Clonal heterogeneity is large & robust

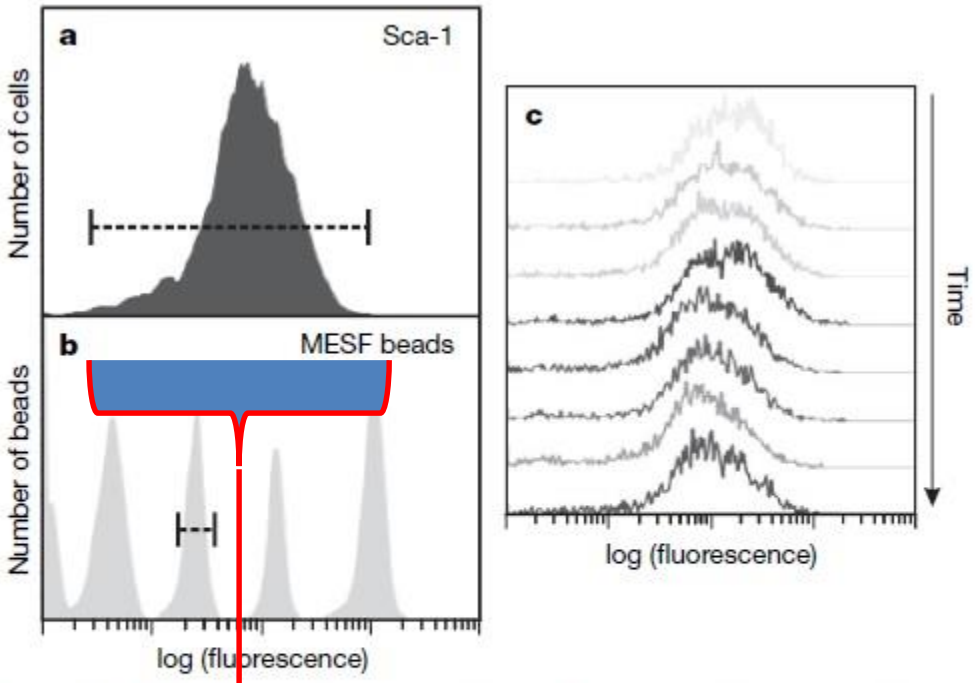
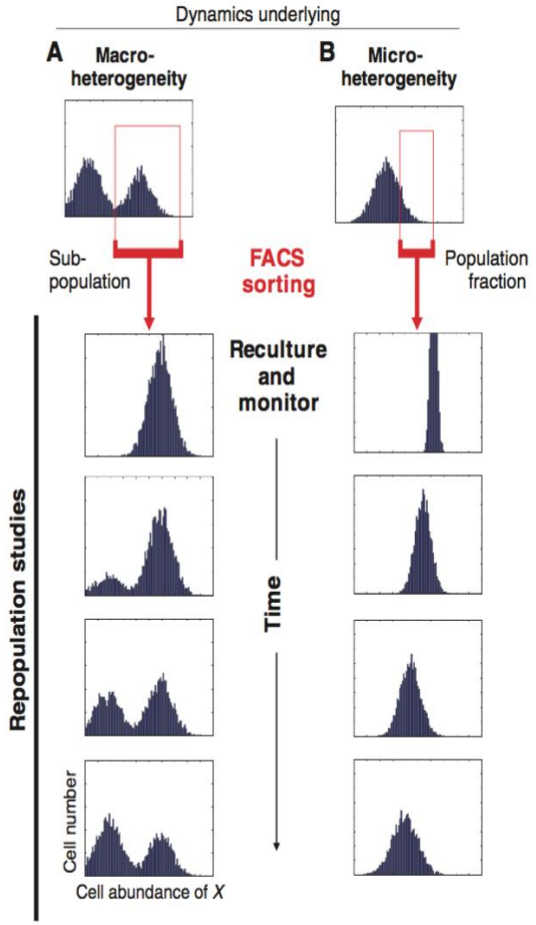


Figure 1 | Robust clonal heterogeneity. **a**, **b**, Heterogeneity among clonal cells in Sca-1 protein expression, detected by immunofluorescence flow cytometry (**a**), was significantly larger than the resolution limit of flow cytometry approximated by measurement of reference fluorescent MESF[24] beads (**b**). The dashed lines show the difference in spread of the distributions as explained in the text. **c**, Stability of clonal heterogeneity in Sca-1 over three weeks.

Note that the range is 1000 fold

Distribution of expression is a Tissue-level attractor

Left: cloning from high expression peak initially follows high peak. Later the bimodel distribution re-establishes itself.



Right: cloning from high expressors in a mono-model distribution initially follows high expression. Later the original distribution re-establishes itself.

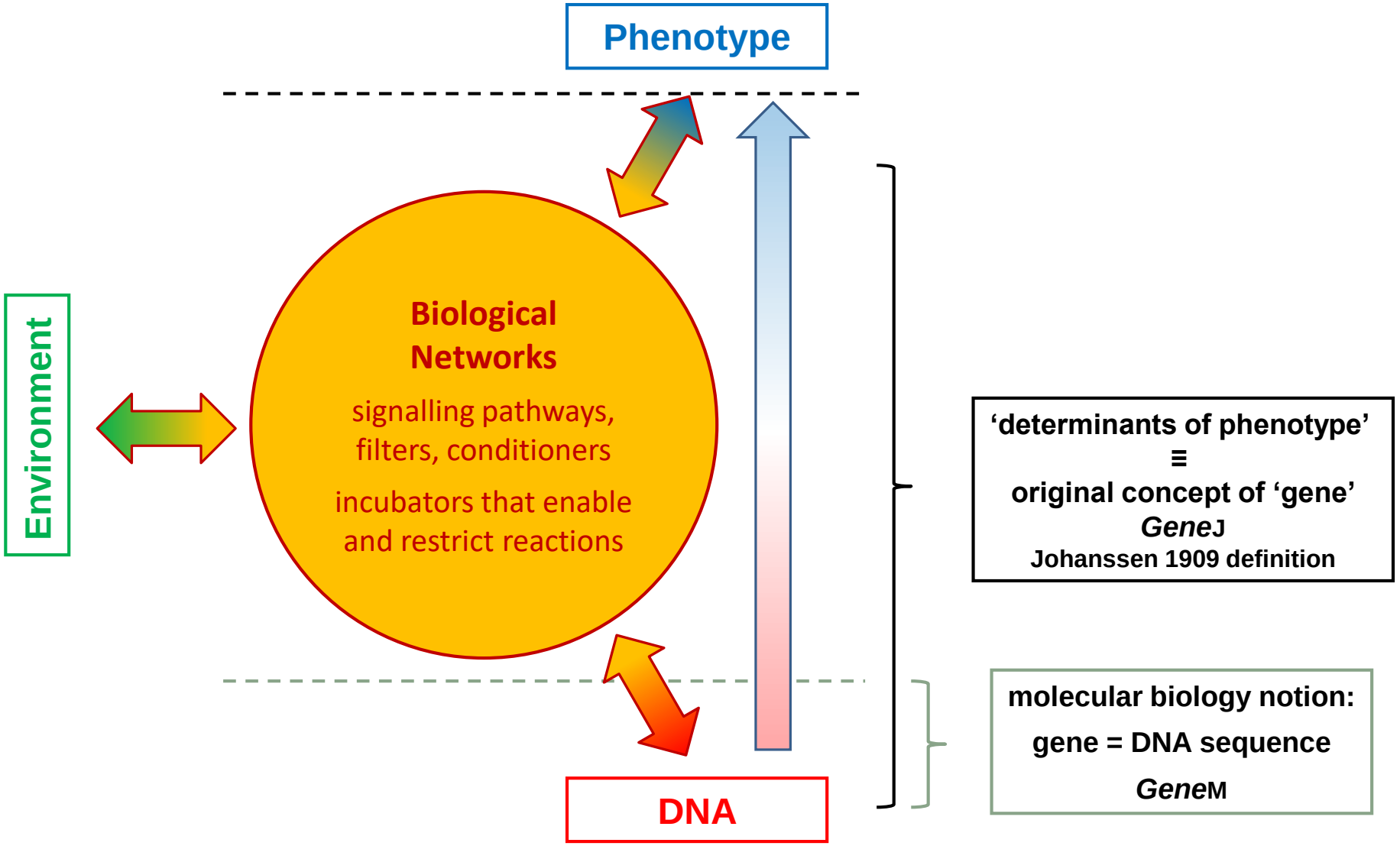
Huang, S. 2009. Non-genetic heterogeneity of cells in development: more than just noise. *Development*, **136**, 3853-3862

Why cell networks determine expression levels and phenotype

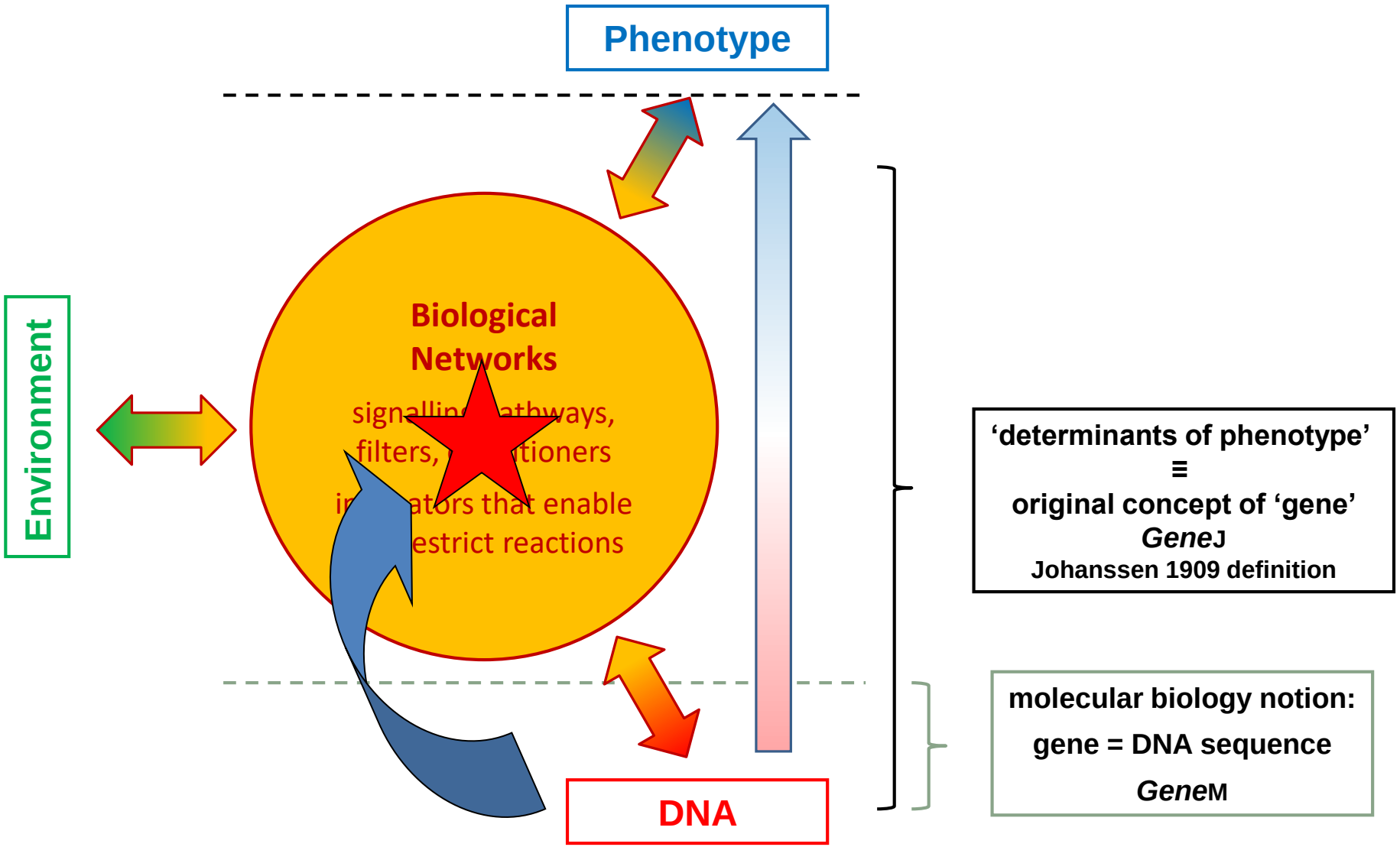
Cell networks dominate in determining phenotype

EVIDENCE:

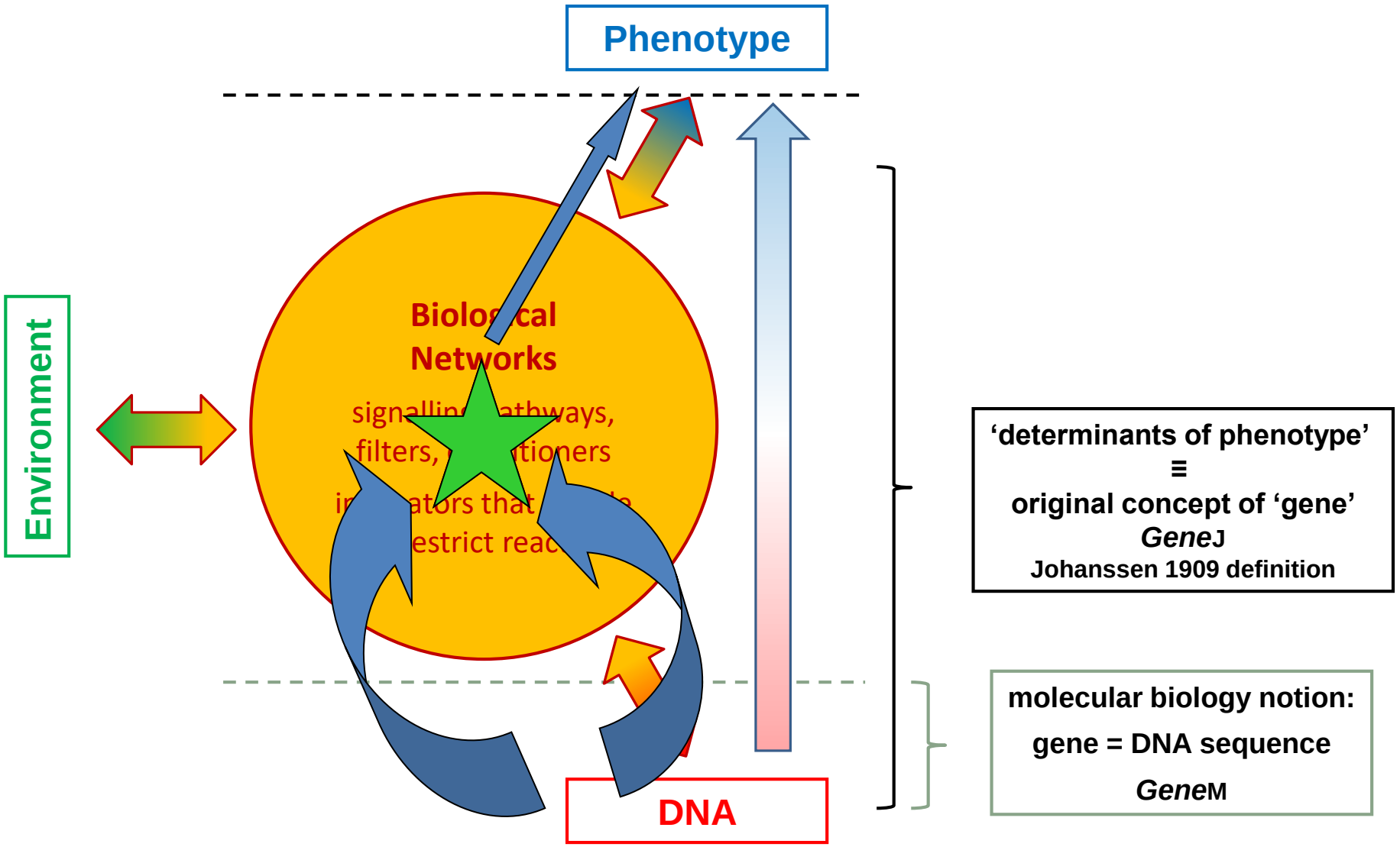
- Knockouts and protein blockers often silent: Examples: cardiac and circadian rhythms
- Very low Genome Wide Association scores: Omnigenic hypothesis



Kohl P, Crampin E, Quinn TA & Noble D. (2010). Systems Biology: an approach. *Clinical Pharmacology and Therapeutics* **88,** 25-33.



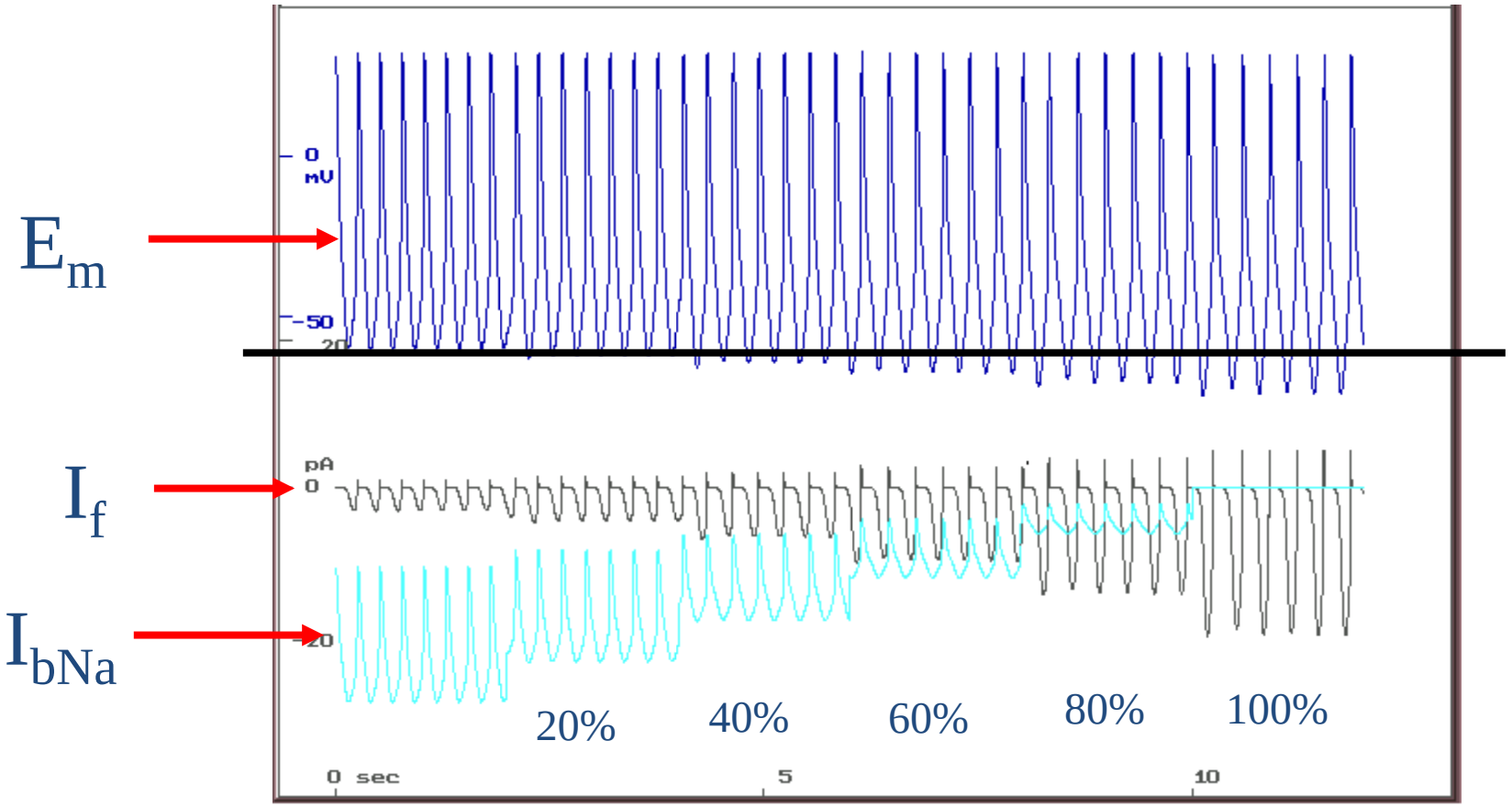
Most knock-outs and mutations are buffered by the networks



Most knock-outs and mutations are buffered by the networks

Model of cardiac rhythm

Example of gene knock-out or channel block



Noble, D., J. C. Denyer, H.F. Brown. & D DiFrancesco (1992). Proc Royal Society **B 250**: 199-207.

GWAS: Omnigenic theory

Cell. 2017 Jun 15; 169(7): 1177–1186.
doi: 10.1016/j.cell.2017.05.038
PMID: 28622505

An expanded view of complex traits: from polygenic to omnigenic

Evan A. Boyle,[1,†] Yang I. Li,[1,†] and Jonathan K. Pritchard[1,2,3,†]

- All genes contribute to many or even all functions
- Many genes show very low association data
- Linear addition of such data invalid
- Gene-centric views of development & evolution need revising

"We propose that gene regulatory networks are sufficiently interconnected that all genes expressed in disease- relevant cells are liable to affect the functions of core disease-related genes and that most heritability can be explained by effects on genes outside core pathways."

Stage 2 of the argument

Cellular stochasticity
is harnessed and is functional

Theory formulated at Royal Society 2016 meeting: *New Trends in Evolutionary Biology*

Stochasticity is harnessed by organisms to generate functionality. Randomness does not, therefore, necessarily imply lack of function or 'blind chance' at higher levels. In this respect, biology must resemble physics in generating order from disorder. This fact is contrary to Schrödinger's idea

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Stochasticity is harnessed by organisms to generate functionality. Randomness does not, therefore, necessarily imply lack of function or 'blind chance' at higher levels. In this respect, biology must resemble physics in generating order from disorder. This fact is contrary to Schrödinger's idea of biology generating phenotypic order from *molecular*-level order, which inspired the central dogma of molecular biology. The order originates at higher levels, which constrain the components at lower levels. We now know that this includes the genome, which is controlled by patterns of transcription factors and various epigenetic and reorganization mechanisms.

Consequences for Evolutionary Biology profound. Evolution does have a direction

biology

MDPI

Review

Was the Watchmaker Blind? Or Was She One-Eyed?

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Abstract: The question whether evolution is blind is usually presented as a choice between no goals at all ('the blind watchmaker') and long-term goals which would be external to the organism, for example in the form of special creation or intelligent design. The arguments either way do not address the question whether there are short-term goals within rather than external to organisms.

Question
Is development of a cancer directed?

Early stage: cancerous cells under stress

- The population under stress shuffles genomes
- Result could be very rapid radiation of cell forms

3rd Stage of the argument

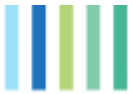
Tumours develop by harnessing stochasticity

Hypothesis

- Cells under stress hypermutate, and shuffle DNA
- Speed of change can be up to 10^6 times normal (cf immune system hypermutation)
- Drug development cannot keep up with that
- Anti-cancer therapy stimulates EV formation
- EVs can promote metastasis (presentation by Scott Bonner in this session)

Speculation

- Could EVs communicate the interactions proposed by the Tissue Organisation Field Theory (TOFT) of cancer?
- Soto & Sonnenschein, 2011, *Bioessays* **33**, 332-340



Insights & Perspectives

Special feature: **point** ↔ counterpoint

The tissue organization field theory of cancer: A testable replacement for the somatic mutation theory

*Ana M. Soto and Carlos Sonnenschein**

Concluding summary

- Tissue stochasticity exists and is extensive
- Stochasticity is harnessed and is directional
- Cells under stress will hypermutate
- Hypermutation could be very rapid
- This would explain ineffectiveness of treatment of late stage cancers