Identifying Hard-to-Define Problems in Regenerative Biology





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Levin Lab at Tufts:





PI: Dr. Michael Levin

* area of study: regenerative medicine in metazoa.

* model organisms: flatworm (Planaria), tadpole.

Recent Publication: Lobo, D., Beane, W.S., and Levin, M. Modeling Planarian Regeneration: A Primer for Reverse-Engineering the Worm. PLoS Computational Biology, 8(4), e1002481 (2012).

Spontaneous Remission in Cancer

So-called "irreversible" syndrome heals or goes away (becomes reversible).



Irreversible State Change in a Physical System COURTESY: <u>Wikipedia</u> * typically found in a small subset of the general population. Thus, medical observations are a rare event

MORE INFORMATION: Heim, E. and Kobele, C. Spontaneous Remission in Cancer. Onkologie, 18(5), 388-392 (1995).



Spontaneous Remission of ITP (low platelet count) in a Human Population. COURTESY: <u>NPLate Website</u>

Inexplicable lack of repeatability/variation

* In a population of clonal flatworms, treated with the same procedure, 60% exhibit one response, 40% exhibit another.



* after amputation of the tail, tadpoles will exhibit a refractory period (during which there is no regeneration). Sometimes, this refractory period is spontaneously overcome.







Sodium Spurs a Tadpole to Regenerate Its Tail. COURTESY: Discover magazine

Variability in Pharmacological Effects

Treatment of a group of animals with a certain drug (with certain, known effects):

* work very well in some animals, but not at all in others (not due to genotype or phenotypic mutant status).



* effect may also be variable over time (for one treatment.

EXAMPLE: 80% of animals are affected, for another treatment, 20% of animals are affected.



Essential Genes: Not Predictive of Errors

Genes **required** for normal developmental phenotypes and function are **bad markers** for errors in development.



Figures 1 and 2. TGF-beta Ligands in Left-Right Development. R&D Systems Catalogue (2003). **Example (Nodal):** around 20% of embryos with abnormal expression of Nodal have normal-looking phenotypes.



Rare Phenotypes

Many possible perturbations to test, but what is the right combination?

* probably not the same combination every time (no exact solution).

* chaos hypothesis: small changes amplified produce changes in state.

Small-scale Perturbation (environment + physiological)	+	Feedback/Nonlinear Dynamics	=	Large-scale Differences
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Current paradigm: less variation means "better" (e.g. more acceptable) result.

•is this a "natural" outcome, useless "noise", or useful "noise"?

* Are there algorithmic solutions to this problem? Can we design useful evolutionary and/or adaptive computational representations for modeling this problem?