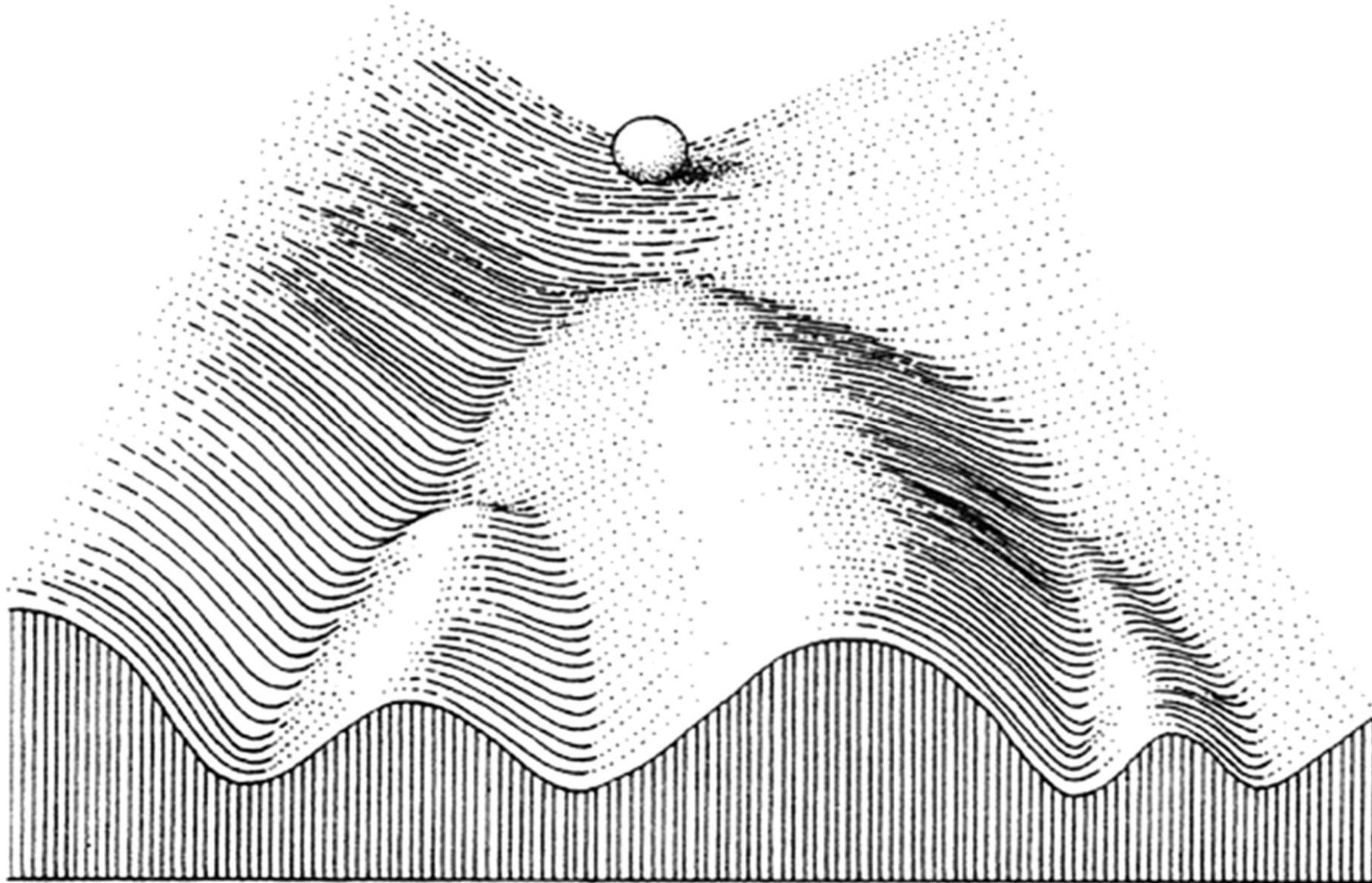


Systems Biology

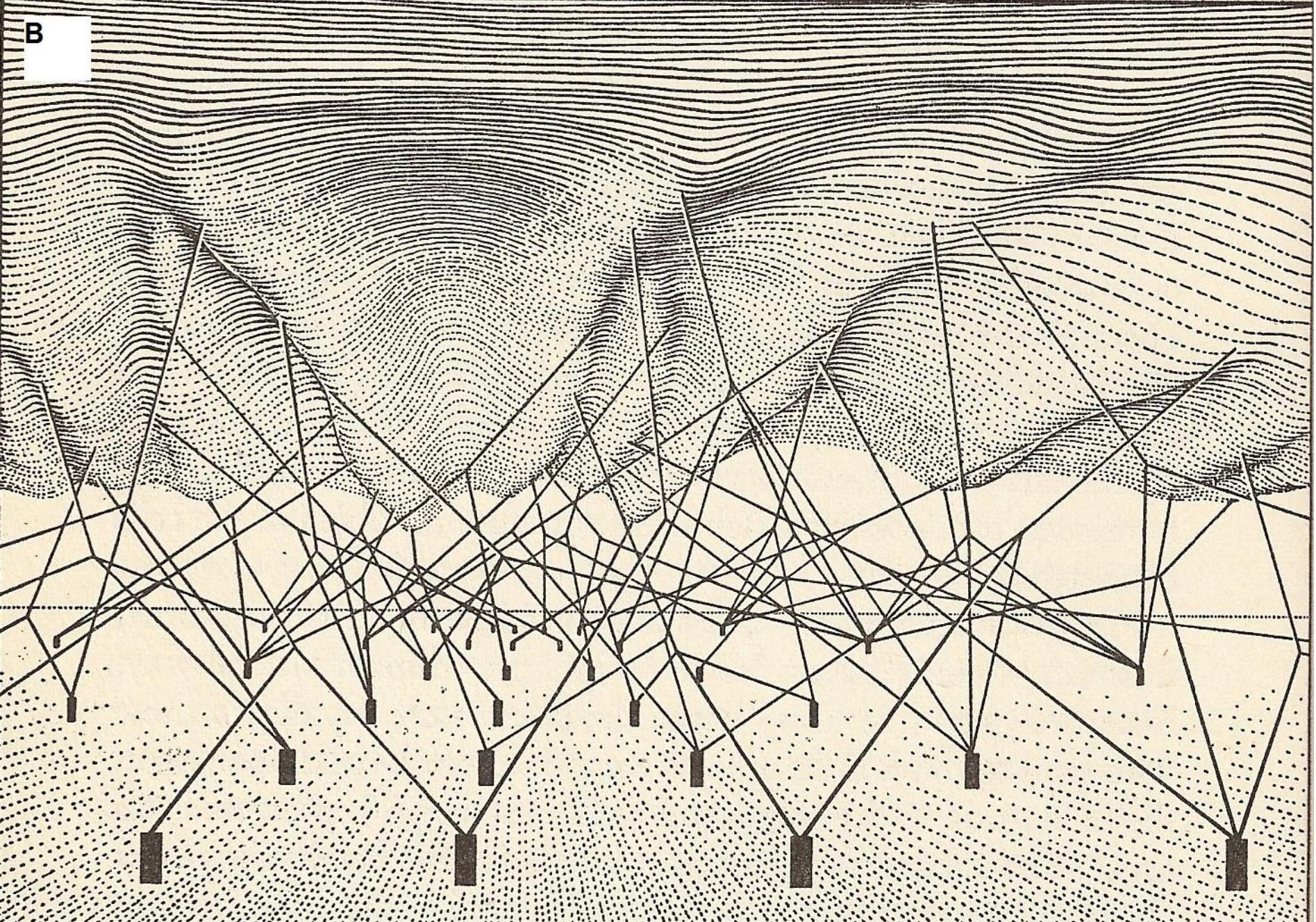
Reinhard Laubenbacher
JAX-GM and UConn Health

Reinhard.Laubenbacher@jax.org
laubenbacher@uchc.edu





C. Waddington, The Strategy of the

B

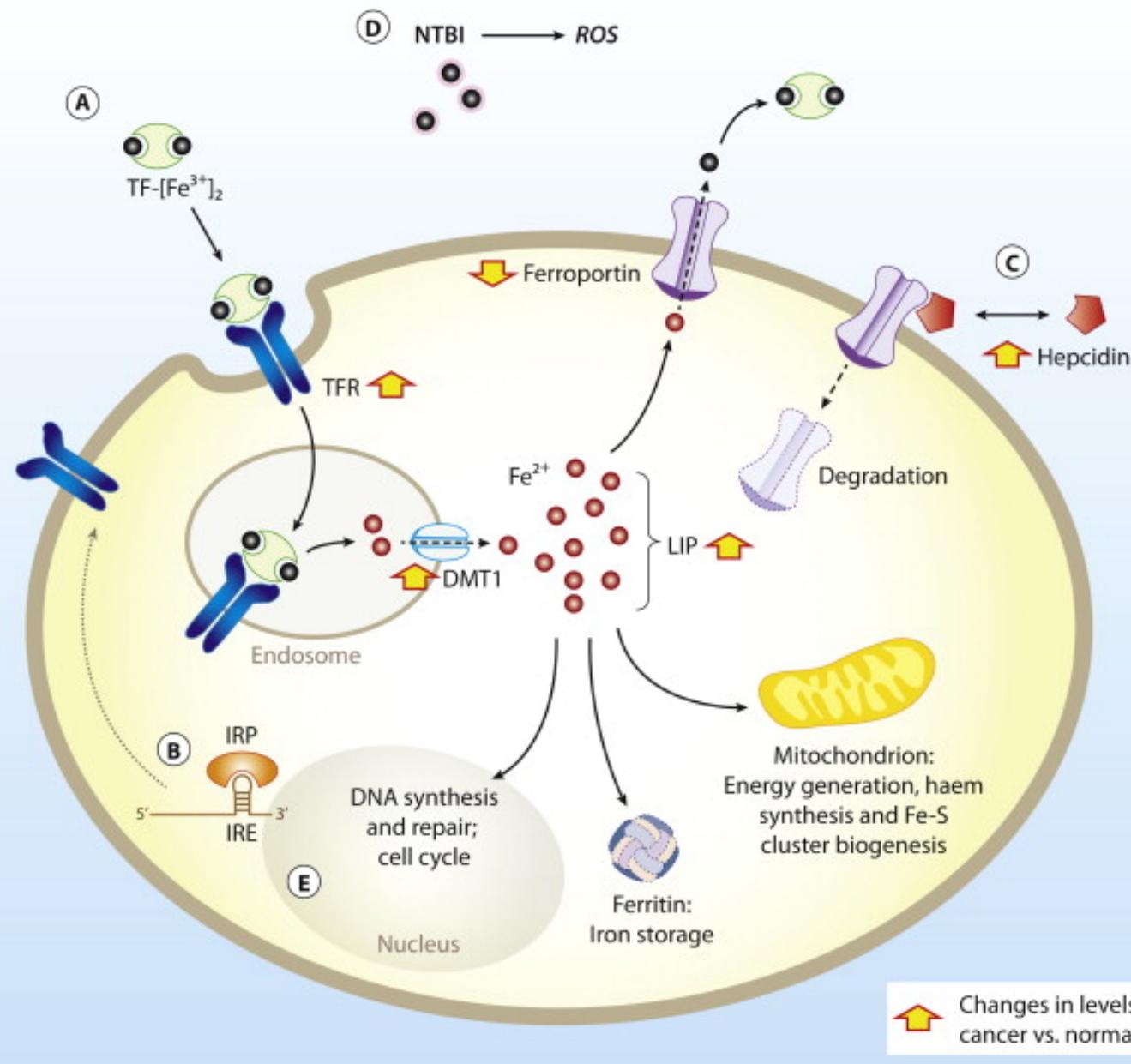
C. Waddington, The Strategy of the

“Like most mathematicians, he takes the hopeful biologist to the edge of a pond, points out that a good swim will help his work, and then pushes him in and leaves him to drown.”

C. Elton,
in a review of work by A. Lotka, 1935

Iron Metabolism and Breast Cancer

- Proteins involved in iron metabolism are expressed differentially in normal and malignant cells.
- Malignant cells contain elevated iron levels.
- Individuals who accumulate excess iron have an increased risk of developing cancer.
- High levels of dietary iron accelerate the growth of breast tumors in animal models.

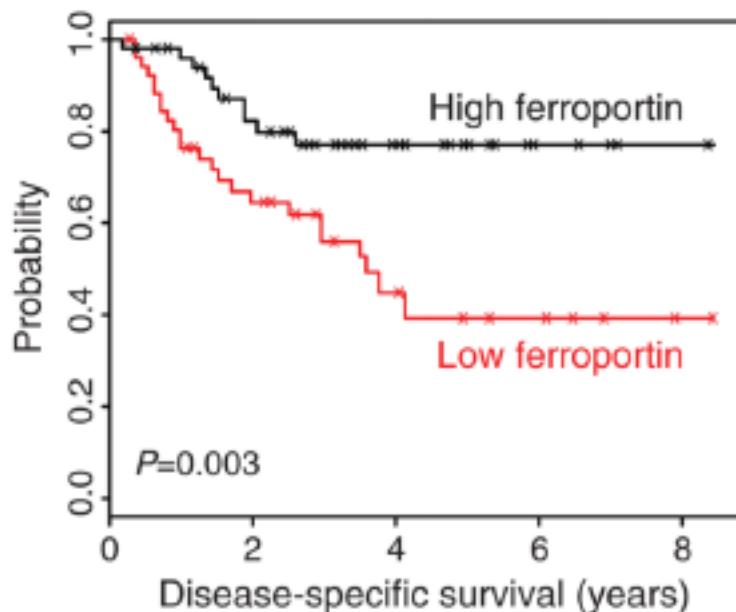


Sci Transl Med. 2010 August 4; 2(43): 43ra56. doi:10.1126/scisignal.3001127.

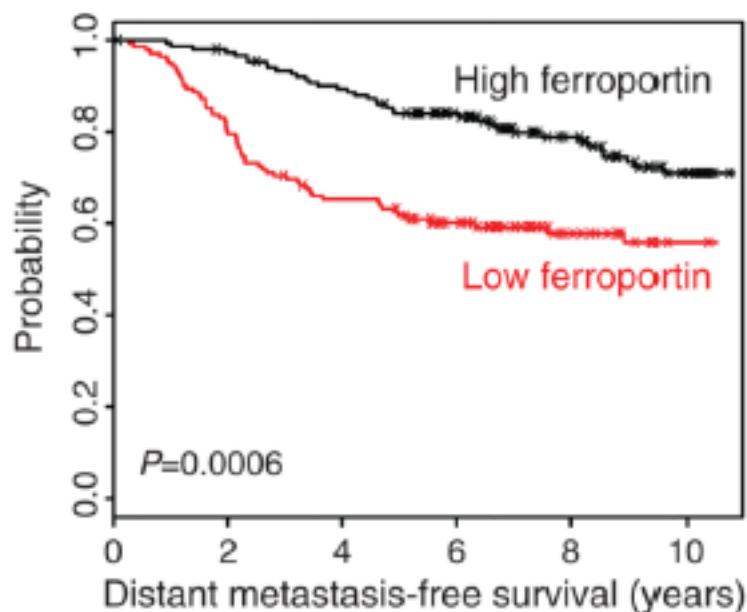
Ferroportin and Iron Regulation in Breast Cancer Progression and Prognosis

Zandra K. Pinnix¹, Lance D. Miller^{2,3}, Wei Wang², Ralph D'Agostino Jr.^{3,4}, Tim Kute⁵, Mark C. Willingham^{3,5}, Heather Hatcher², Lia Tesfay², Guangchao Sui², Xiumin Di², Suzy V. Torti^{1,3}, and Frank M. Torti^{2,3}

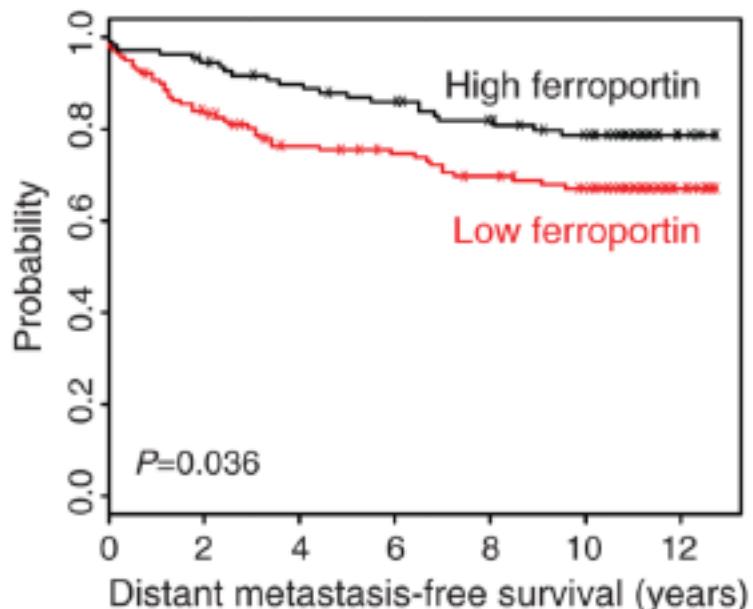
A Norway/Stanford cohort ($n=103$)



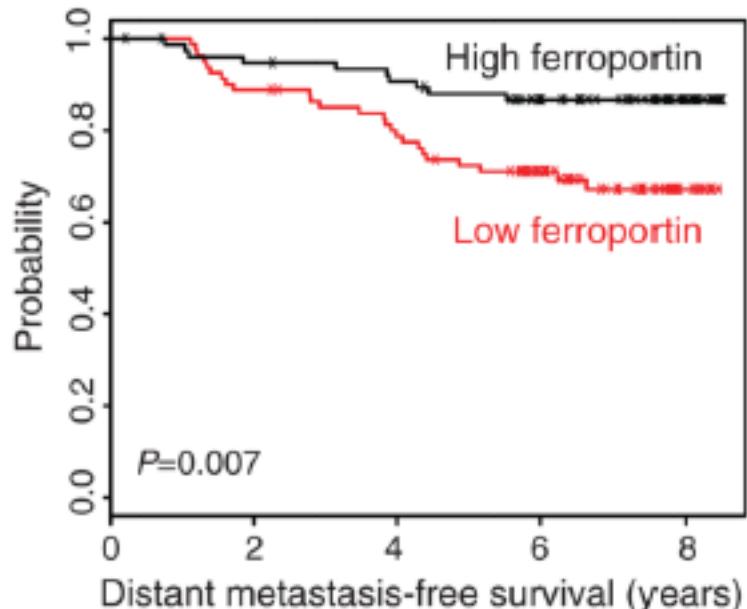
B NKI cohort ($n=295$)



C Uppsala cohort ($n=251$)

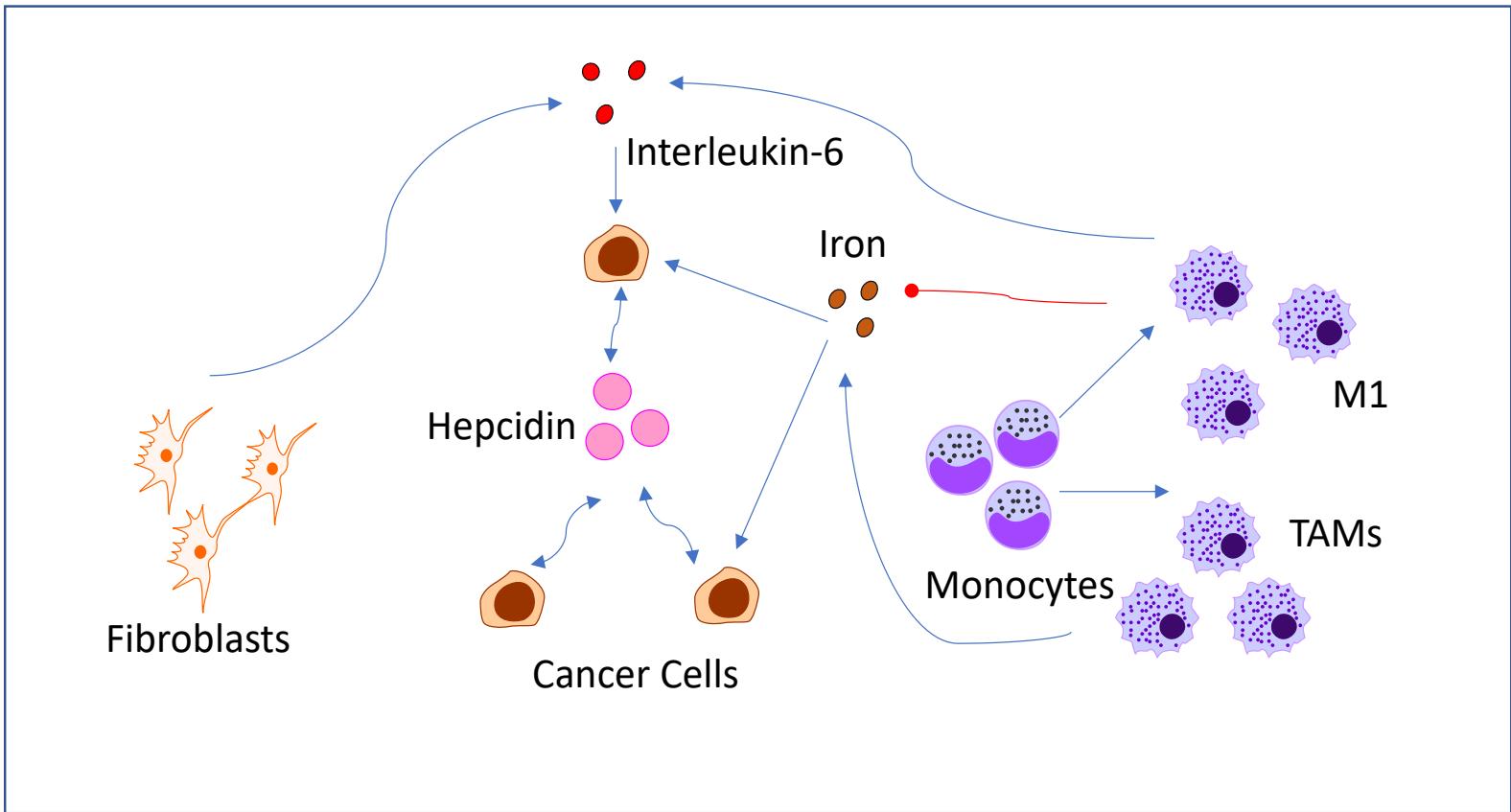


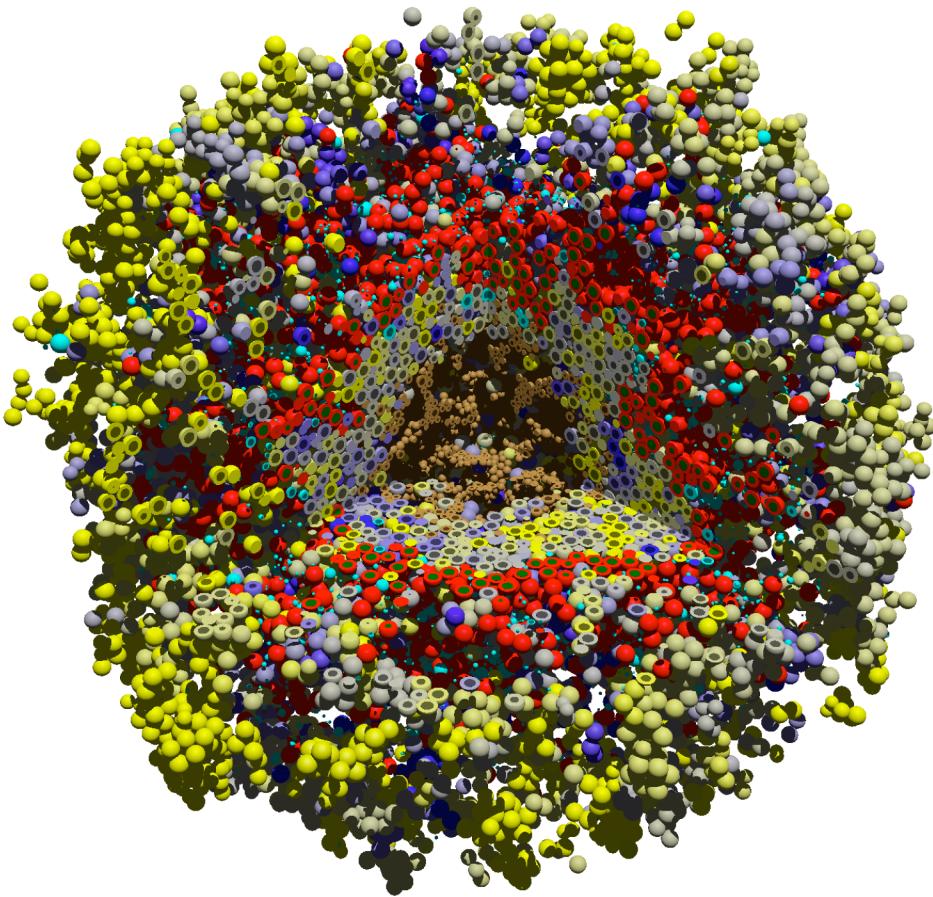
D Stockholm cohort ($n=159$)



Our goal

**Elucidate the mechanisms altering the
iron metabolism network in malignant
breast epithelial cells and the effect on tumor growth.**





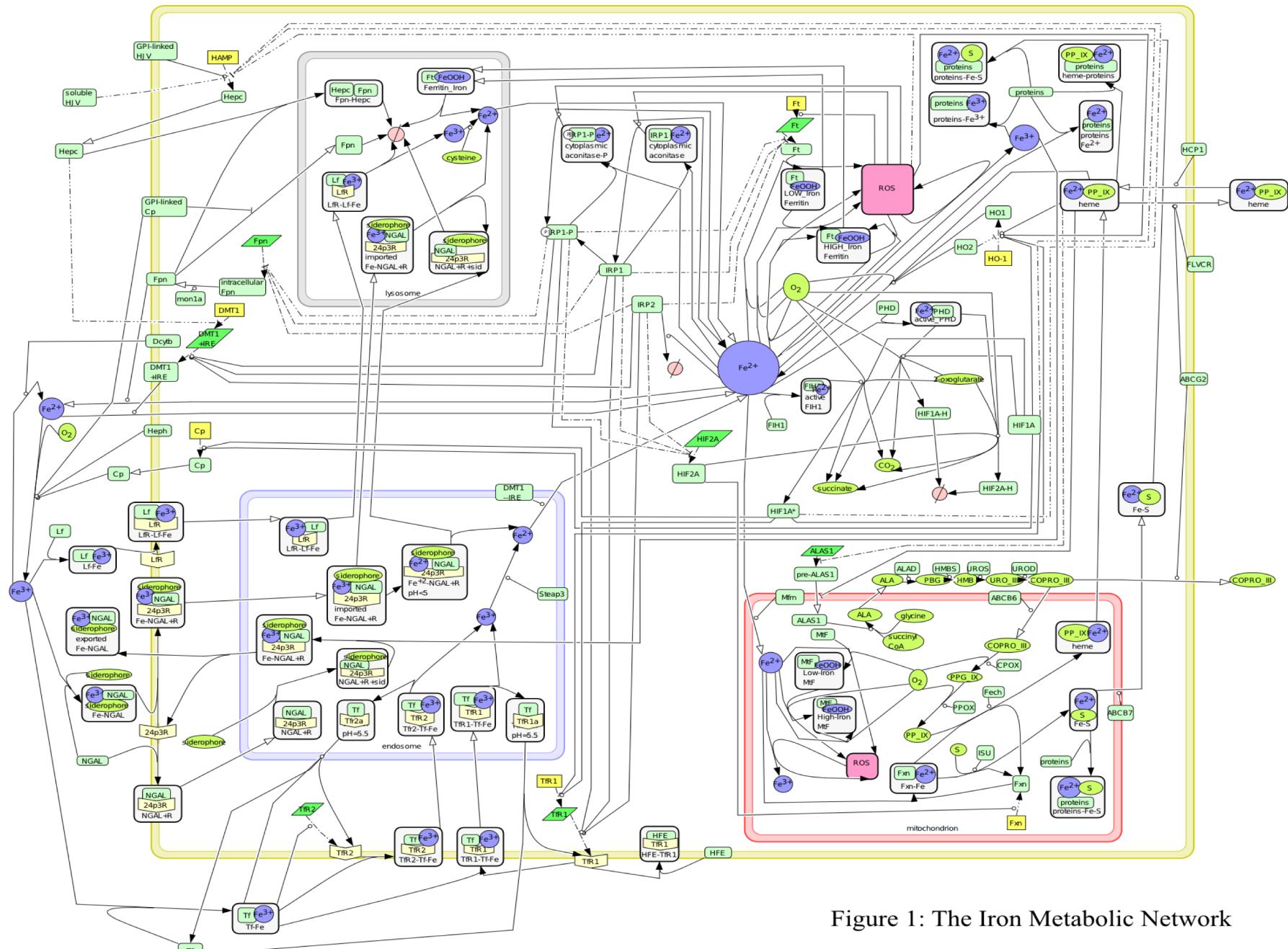


Figure 1: The Iron Metabolic Network

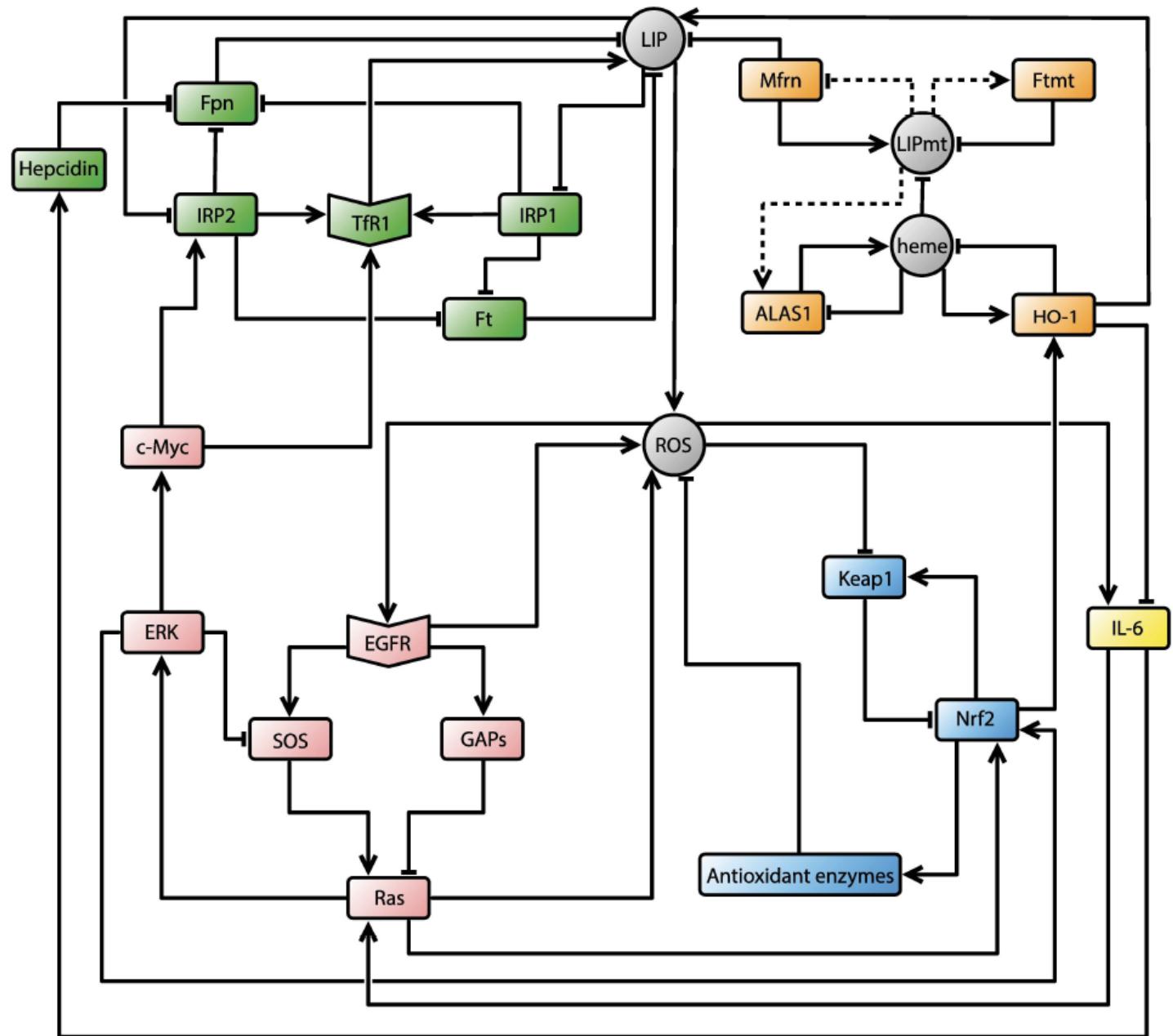
RESEARCH ARTICLE

Activated Oncogenic Pathway Modifies Iron Network in Breast Epithelial Cells: A Dynamic Modeling Perspective

Julia Chifman^{1*}, Seda Arat^{2*}, Zhiyong Deng³, Erica Lemler³, James C. Pino⁴, Leonard A. Harris⁵, Michael A. Kochen⁶, Carlos F. Lopez^{5,6,7}, Steven A. Akman⁸, Frank M. Torti⁹, Suzy V. Torti³, Reinhard Laubenbacher^{10,11*}

Iron Homeostasis Pathway

Iron Utilization Pathway



Oncogenic Pathway

Oxidative Stress Response Pathway

Discrete values for model nodes

0 = low concentration of protein/LIP

1 = moderate ...

2 = high ...

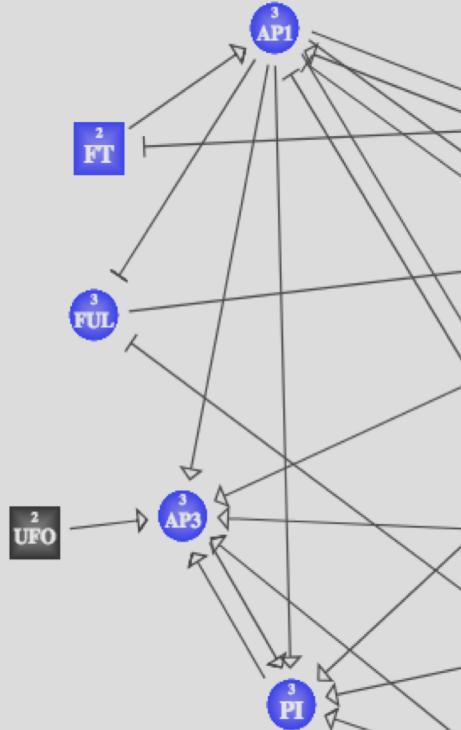
Then a system state is described by:

(LIP, TfR, Fpn, Ft, IRP1, ...) =

(1, 2, 0, 0, 2, ...)

Each network nodes has a logical rule assigned to it:

Classification	Variable	Update Rule
Iron Homeostasis	LIP	$\text{Min}(\text{Max}(\text{TfR1}, \text{HO-1}), \text{Min}(\overline{\text{Fpn}}, \overline{\text{Ft}}, \overline{\text{Mfrn}}))$
	TfR1	$\text{Max}(*\overline{\text{IRP1}}, \text{IRP2}, \text{c-Myc})$
	Fpn	$\text{Min}(*\overline{\text{IRP1}}, \overline{\text{IRP2}}, \text{Hep})$
	Ft	$\text{Min}(*\overline{\text{IRP1}}, \overline{\text{IRP2}})$
	IRP1	LIP
	IRP2	$\text{Max}(\overline{\text{LIP}}, \text{c-Myc})$
	Hep	IL-6



Big State Transition Table

- Use pre-defined updating rules
 Customize updating rules

State Update Speed

Normal

Input(t)					Output(t+Δt)
LFY	TFL1	AG	FT	AP1	AP1
low	low	low	off	low	high ▲
low	low	low	off	med	high ▲
low	low	low	off	high	high ▲
low	low	low	on	low	high ▲
low	low	low	on	med	high ▲
low	low	low	on	high	high ▲
low	low	med	off	low	med ▲
low	low	med	off	med	med ▲
low	low	med	off	med	med ▲
low	low	med	on	low	med ▲
low	low	med	on	med	med ▲
low	low	med	on	high	med ▲
low	low	high	off	low	low ▲

Save

Cancel

Reset Filter

Cancer Phenotype

Use *in vitro* experiments with:

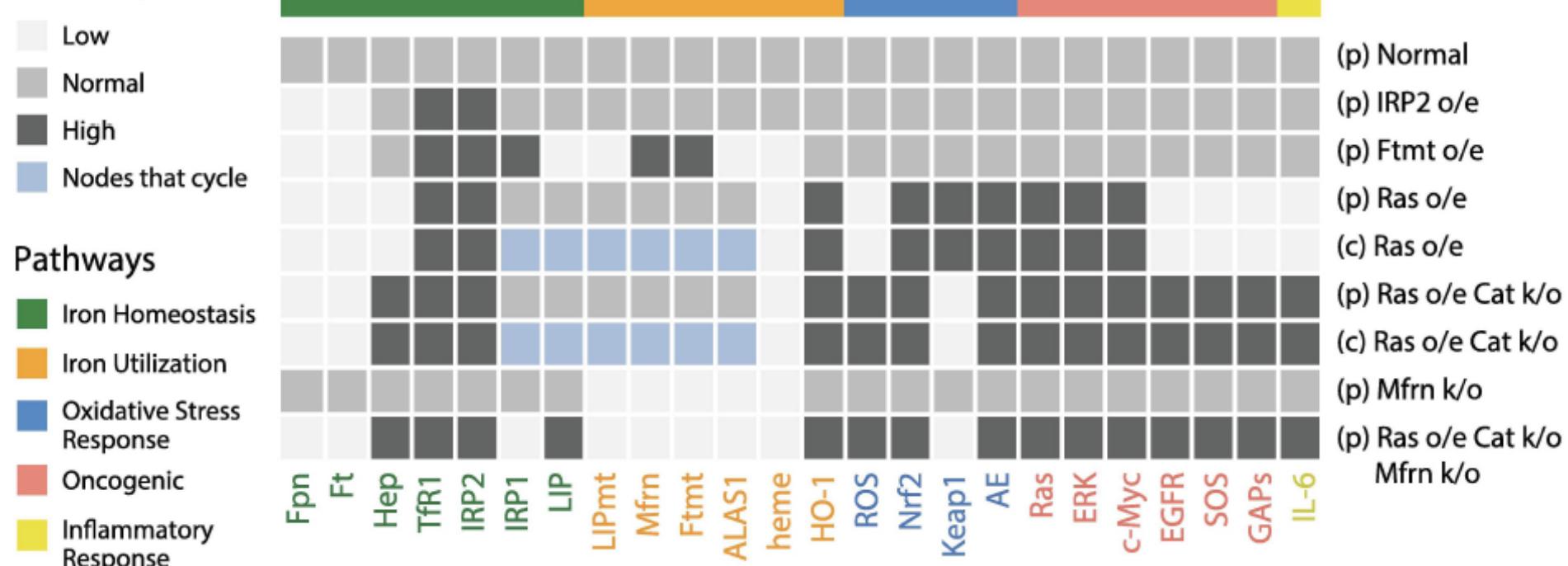
- Wild-type HMEC and transformed version
- MCF7 (ER+ breast cancer cell line)
- MCF10A (non-tumorigenic immortalized)

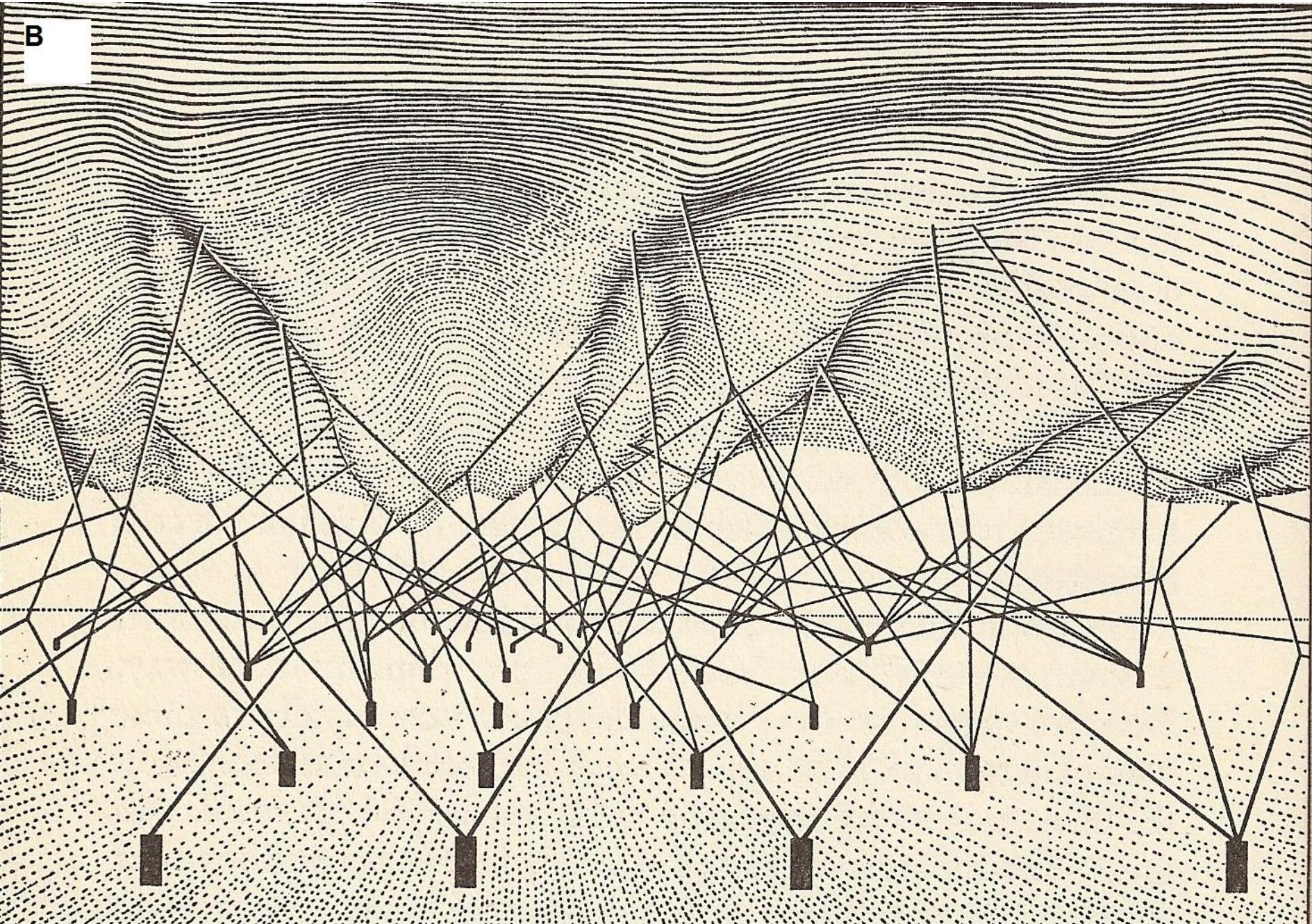
Cancer phenotype for the iron homeostasis pathway:

$$(Fpn, Ft, Hep, TfR1, IRP2, IRP1, LIP) = (0, 0, 2, 2, 2, 2, 2)$$

Point (p) and Cycle (c) attractors

Color Key



B

C. Waddington, The Strategy of the

Mathematical Version of Waddington's Landscape

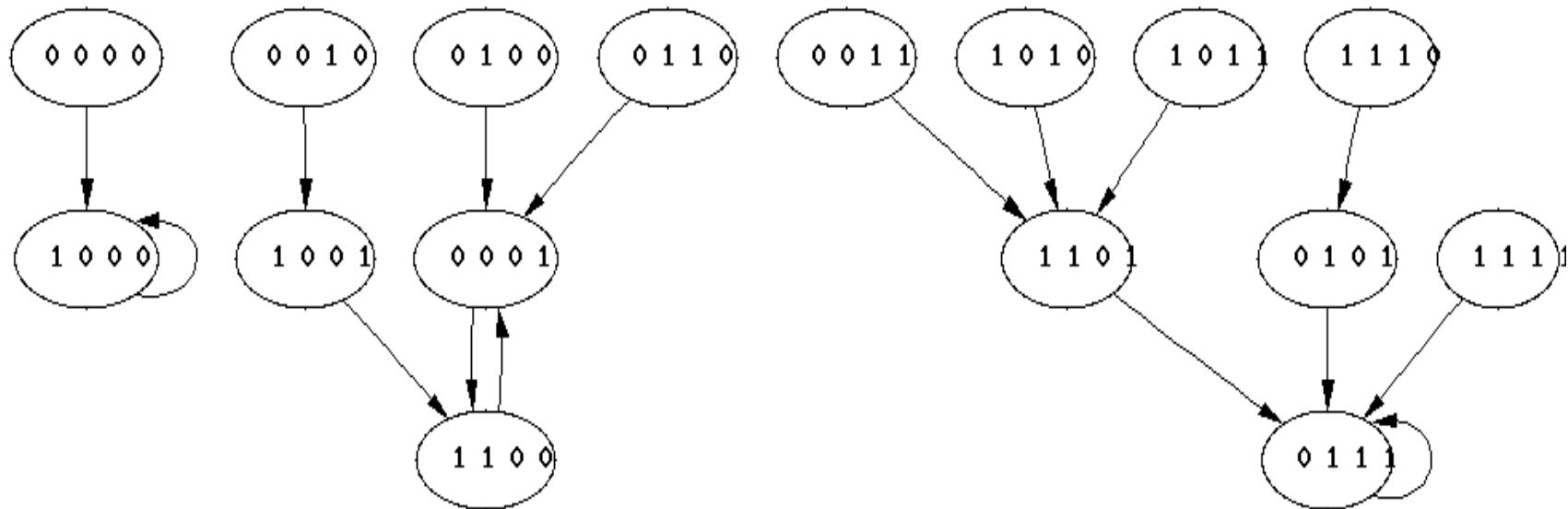
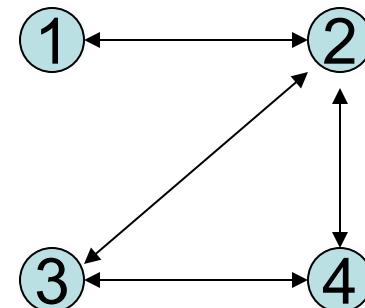
$$f_1 = \text{NOT } x_2$$

$$f_2 = x_4 \text{ OR } (x_1 \text{ AND } x_3)$$

$$f_3 = x_4 \text{ AND } x_2$$

$$f_4 = x_2 \text{ OR } x_3$$

Dependency graph



Software tools for logic models

- GinSim (ginsim.org)
- BoolNet (<https://cran.r-project.org/web/packages/BoolNet/index.html>)
- PlantSimLab
<http://test.plantsimlab.org/index.php#>

Inference of dynamic networks

- Need simultaneous time course data for all genes of interest, including wild type, perturbations, KO, etc.
- Need a selection principle (e.g., Occam's Razor)

Result: one or more phenomenological simulation models

Methods

- Bayesian inference (dynamic BN)
- Parameter estimation in systems of differential equations
- Inferring the logic rules
- Gradient search methods
- Etc.

An Algebra-Based Method for Inferring Gene Regulatory Networks

BMC Systems Biology 2014, **8**:37 doi:10.1186/1752-0509-8-37

Paola Vera-Licona (veralicona@uchc.edu)

Abdul Jarrah (ajarrah@aus.edu)

Luis D. Garcia-Puente (lgarcia@shsu.edu)

John McGee (jjmcgee@radford.edu)

Reinhard Laubenbacher (laubenbacher@uchc.edu)

Systems Biology Pipeline

- Begin with data (e.g. RNA-seq data)
- Extract a list of genes of interest
- Construct a causal network of these genes, through existing information or additional data, or both
- Construct the regulatory rule for each gene in the network
- Use the resulting (validated) model to generate hypotheses and test them in the lab
- Refine the model through an iterative process.