Genome Chaos

Creating New System Information to Drive Macroevolution

Henry H. Heng

Wayne State University, Detroit

14 Oct 2020

Current framework

Somatic Mutation Theory

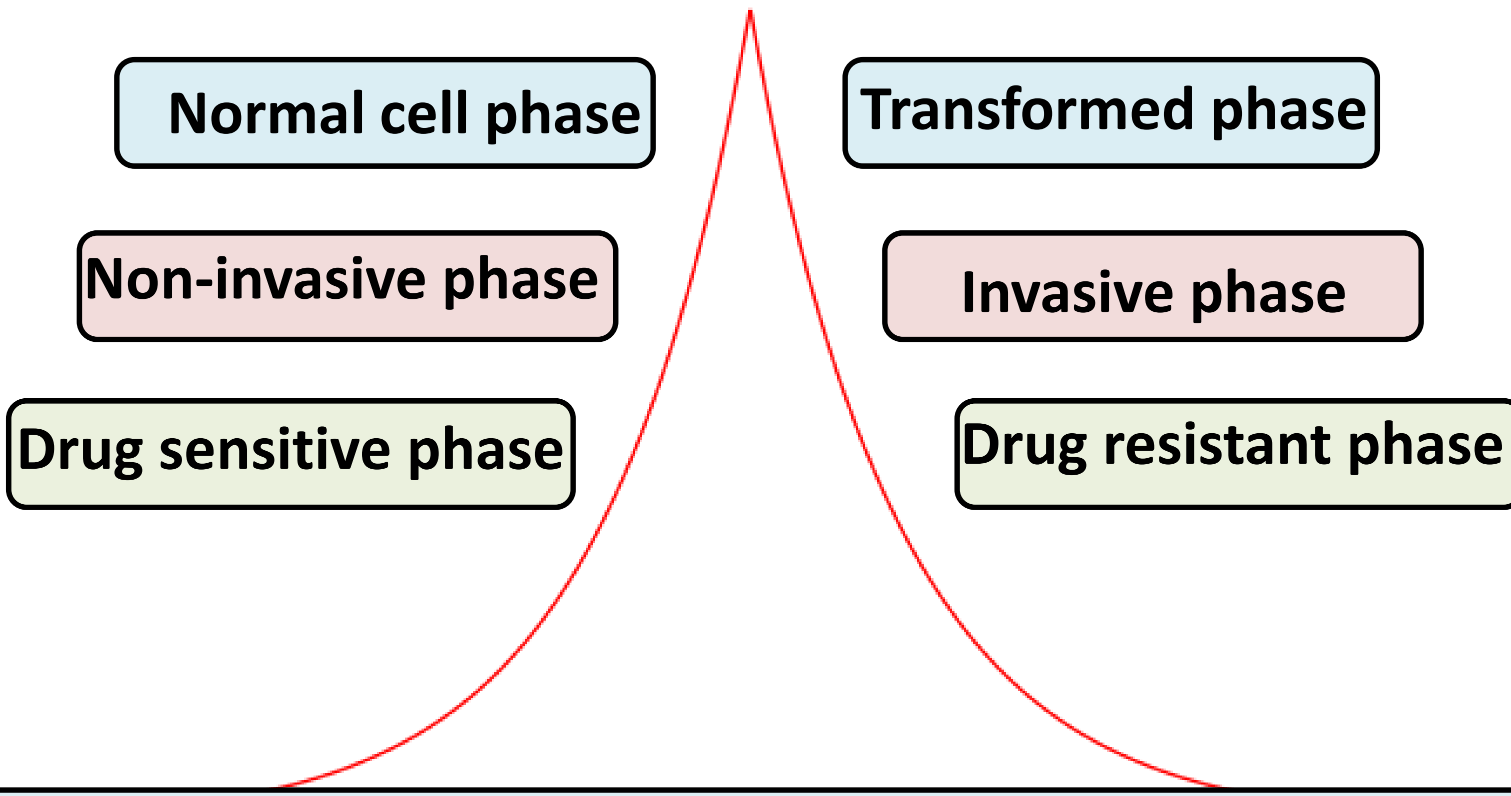
Out of control growth → Phenotype

Key gene mutations → Genotype

Stepwise evolution → Process

Accumulated cancer gene mutations are key drivers

Cancer: new systems emergent from various constraints via evolution



Key shared phenotype: Phase Transition

Genome theory of Cancer Evolution

Systems replacement via macroevolution

Phase transition ← Phenotype

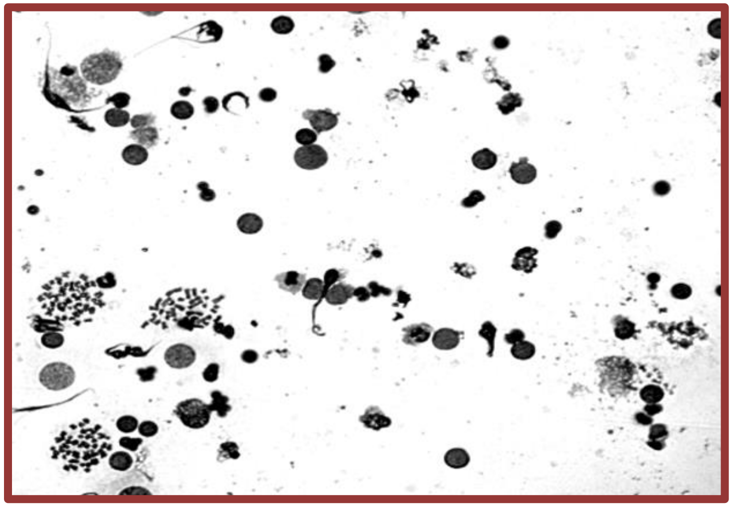
Karyotype heterogeneity ← Genotype

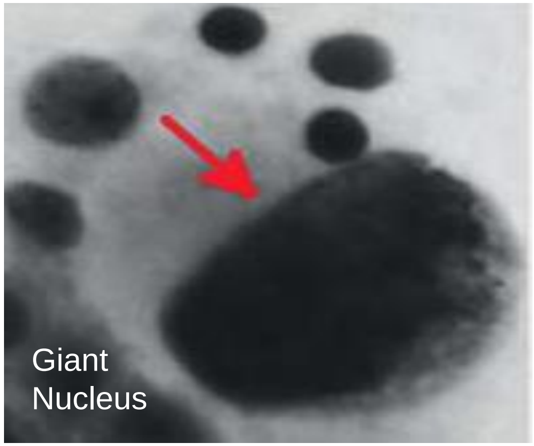
Genome chaos - Selecting ← Mechanism

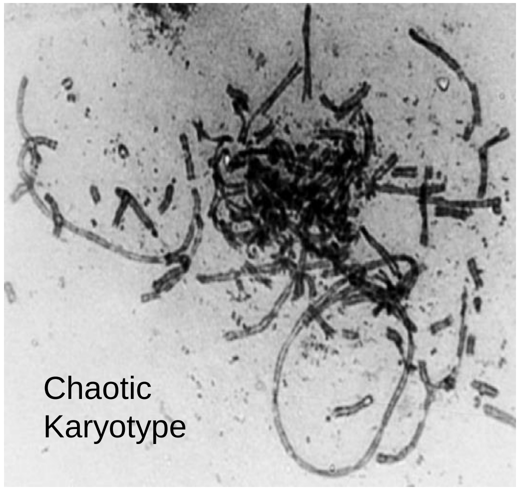
Two phased evolution ← Process

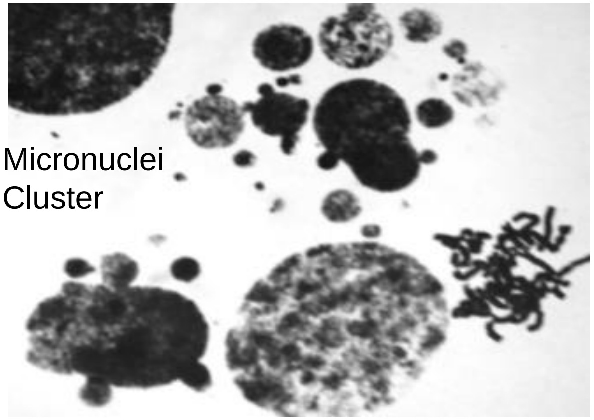
Karyotype heterogeneity & non clonal chromosome aberrations (NCCAs)

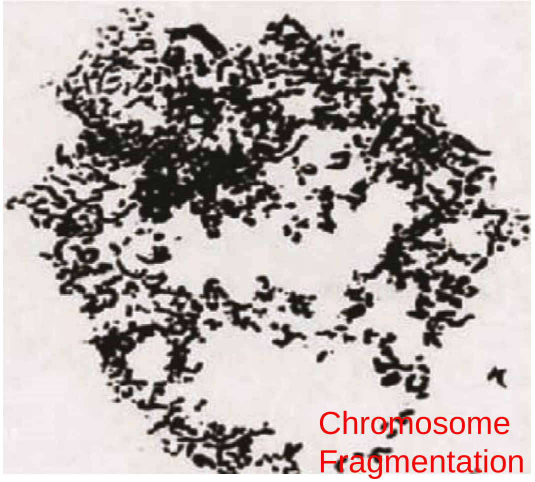
They are not "noise" but transitional structures for creating new genomes for information surival











Watch evolution in action experiments

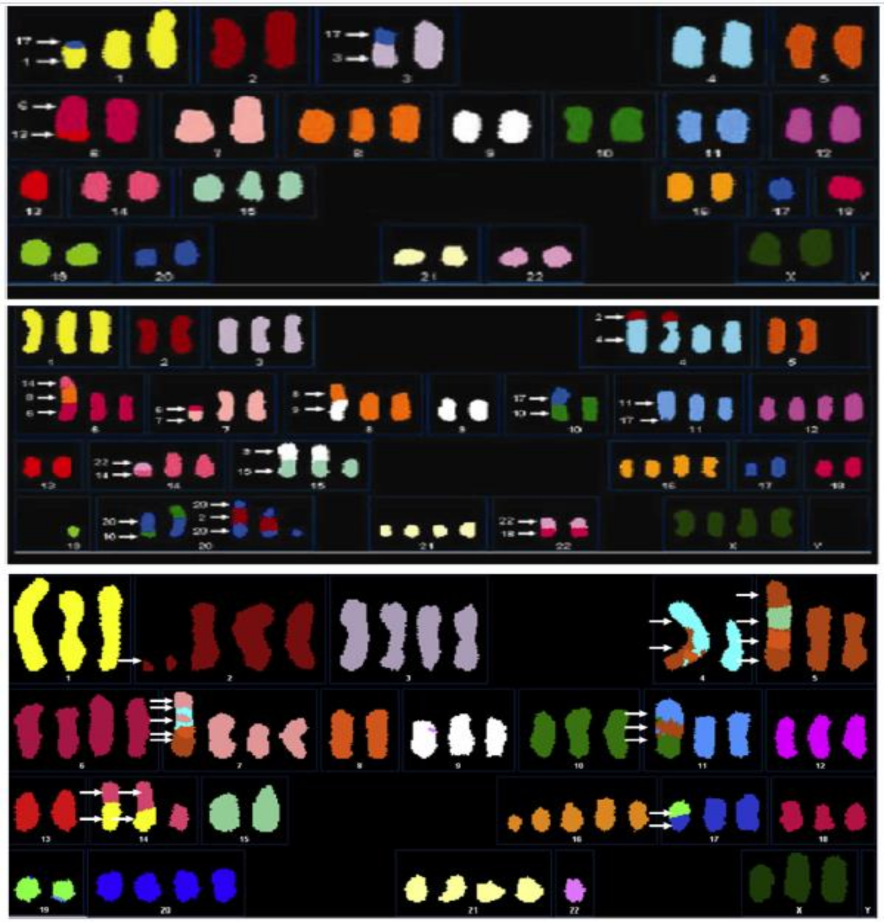
DNA clones differ from karyotype clones

Normal cells

Pre-immortal cells

Phase transition

Post-immortal cells



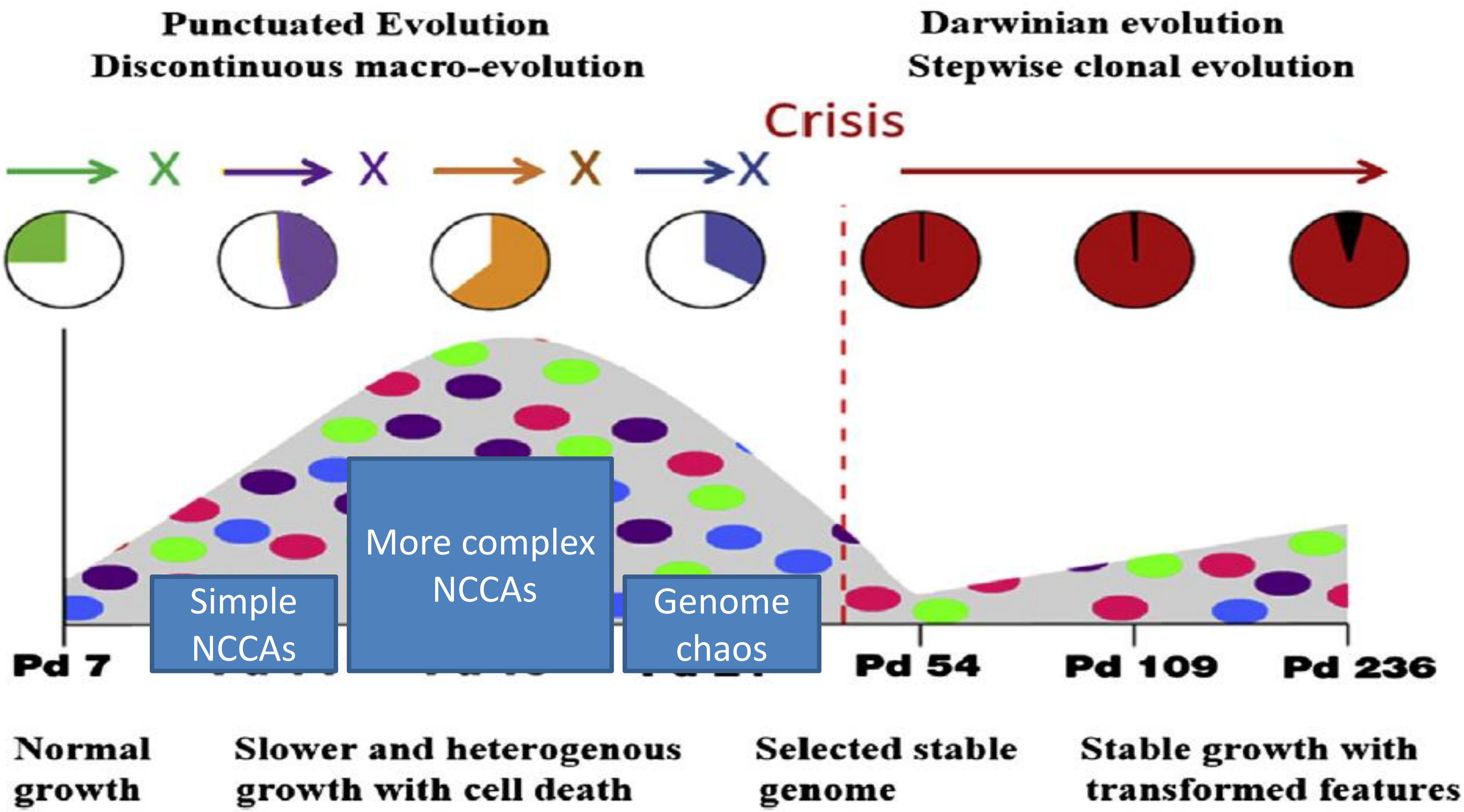
Non clonal

Clonal

(in vitro immortalization model: Li-Fraumeni fibroblast)

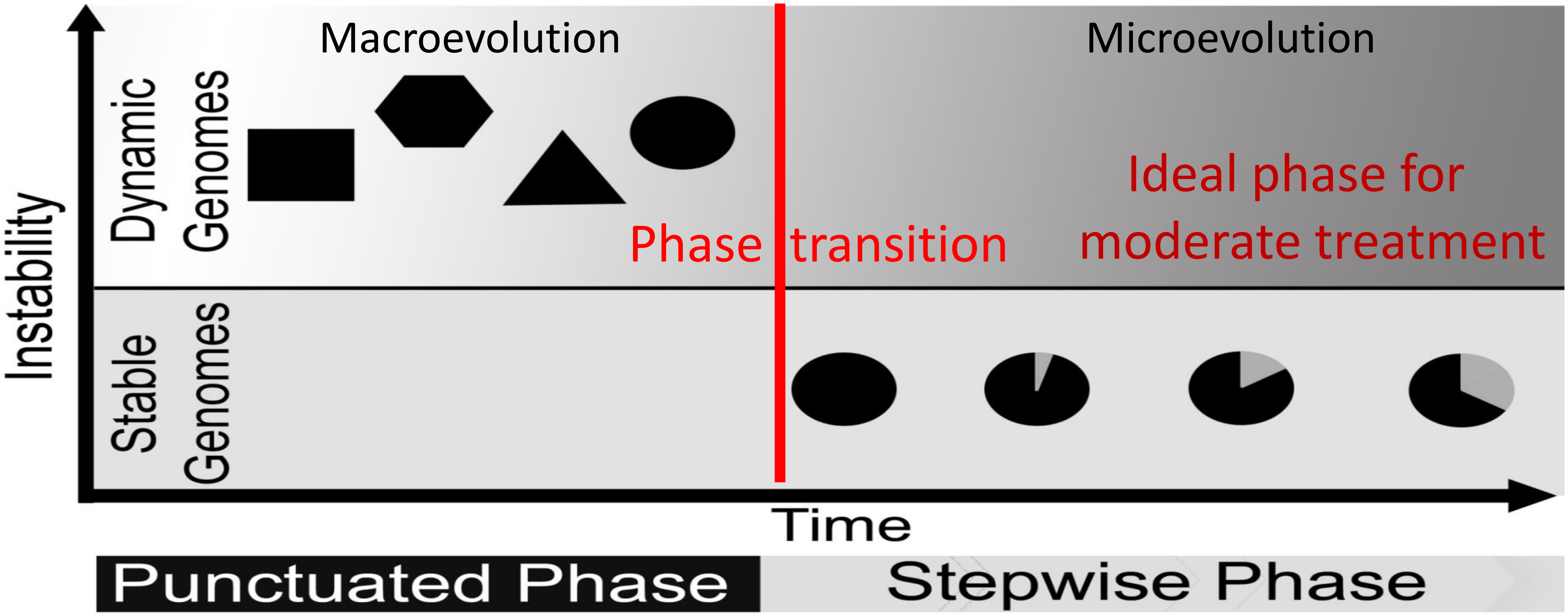
Two phased evolution

Macroevolution differs Microevolution + Time



Heng et al., JCP 2006

Phase transition is common for cancer

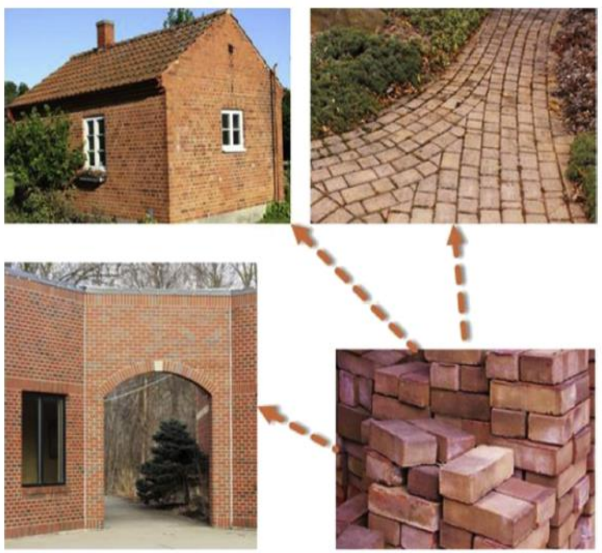


- **Each run of evolution is achieved by different molecular pathways**
- **The evolutionary pattern unifies diverse molecular mechanisms of cancer**

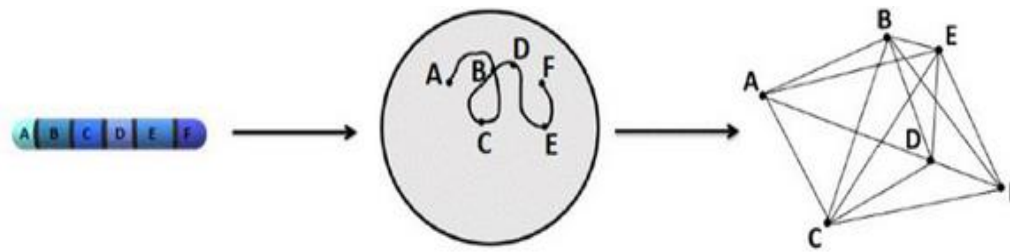
Karyotype heterogeneity is the common driver, but why ?

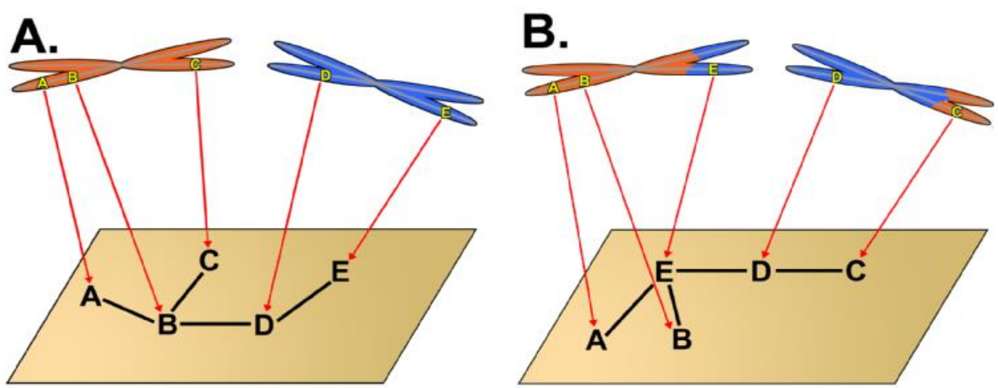
Karyotype Coding

Karyotype organizes gene interactive network
Order of genes along chromosome is a new coding



Architecture is a key information



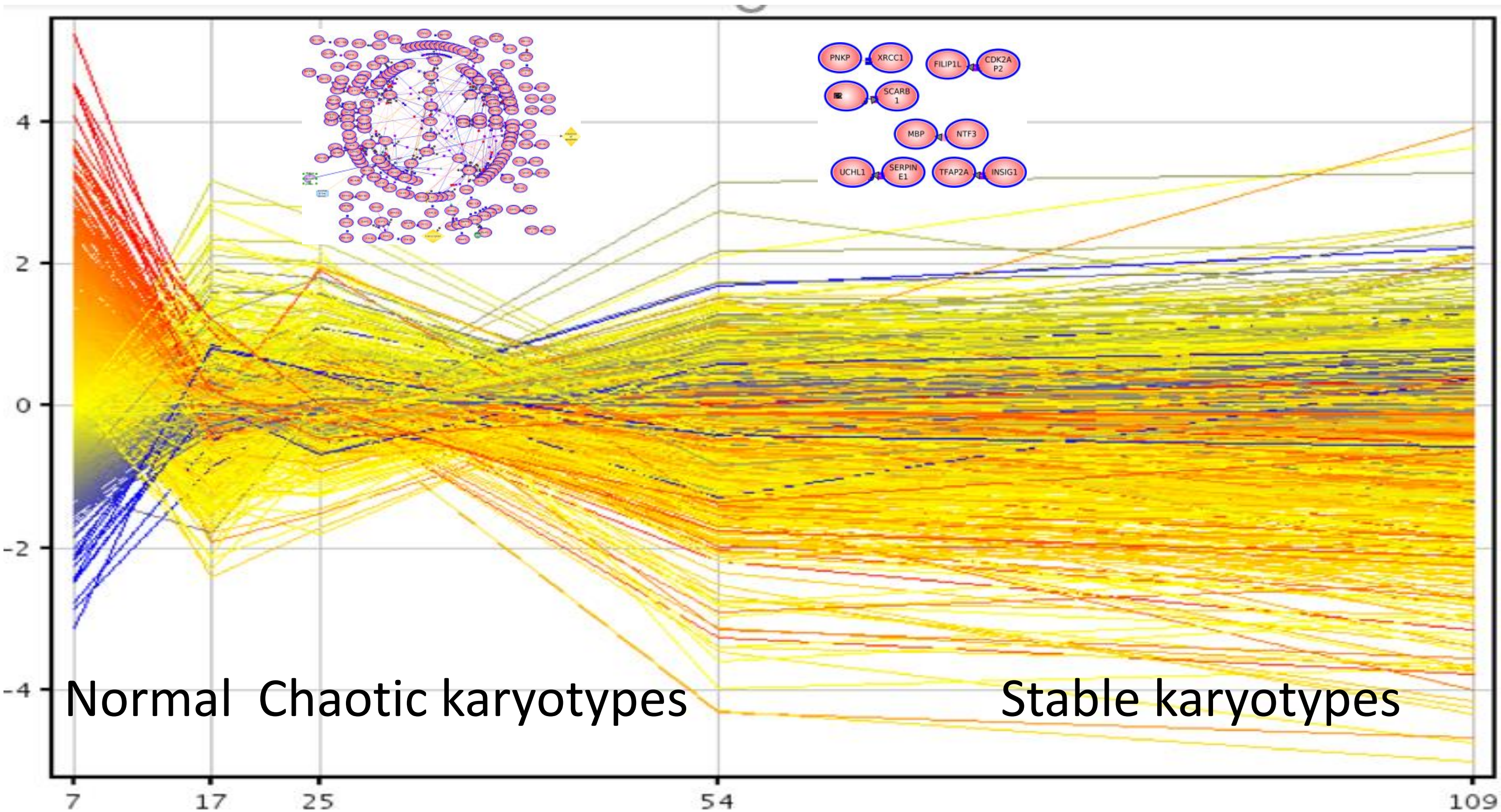


Gene codes “parts inheritance”
Karyotype codes “System inheritance”
Blueprint

Heng 2009, BioEssays
Heng et al, 2011, Genomics
Heng et al, 2013, Can Metastasis Rev

Karyotype defines transcriptome

Different successful karyotypes display different transcriptomes



Stevens et al, 2014 IJC

Most animals and plants display unique karyotypesi

How genes are arranged within the genome matters

Genes + topo = function
Species specific

Sponges have 18,000 genes (immune- and neuro-), but no “designed” functions

Spatial is key information

Chromosome has 3D address; It impacts genes’ function; position effect

Gene’s order matters

Hox gene cluster; Histone gene cluster;
Synteny: conserved blocks of gene order

Karyotype rules gene

Aneuploidy restores gene-/- phenotype;
Translocation brings gene’s new function

Karyotype and disease

Chromosome changes are overwhelming
Better clinical prediction power

Mechanism of preserving karyotype coding

The main function of sexual reproduction is to maintain the karyotype for species identity

Maintaining gene coding

Replication by A-T and G-C pairing → clone

Fact: Asexual organisms and cell populations are not clonal!

Maintaining karyotype coding for sexual organisms

Meiotic pairing to check gene order

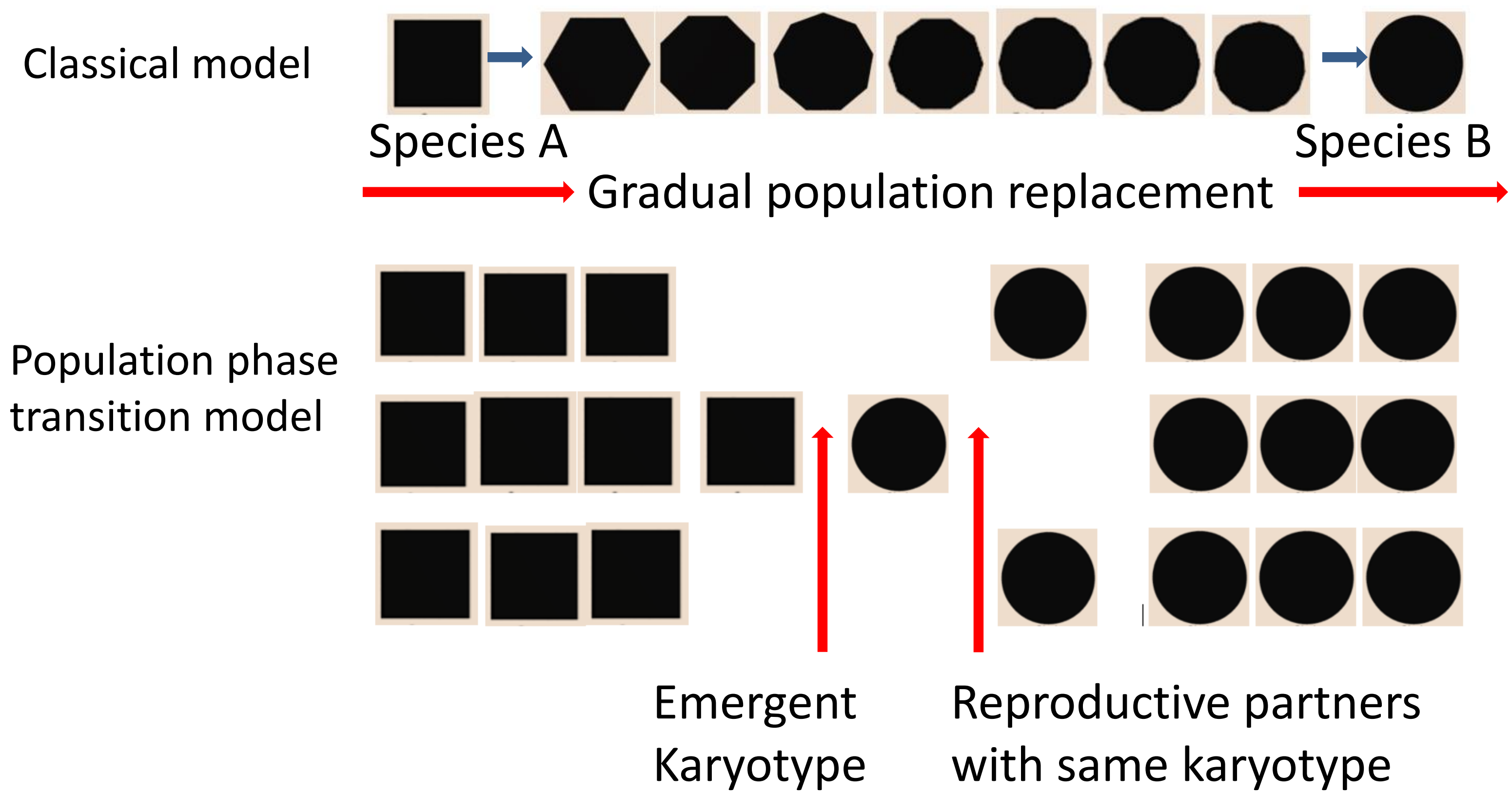
Fertilization and development eliminate altered karyotypes

Sexual reproduction = "Filter" to maintain "core" genome
The genome defines species, the genes modify some features

"The conclusion is surprising: <u>the initial function of chromosome pairing was to *limit*, not enhance, recombination"</u>. *Wilkins AS, Holliday R. Genetics. 2009*

Cancer evolution: no constraint of sexual reproduction

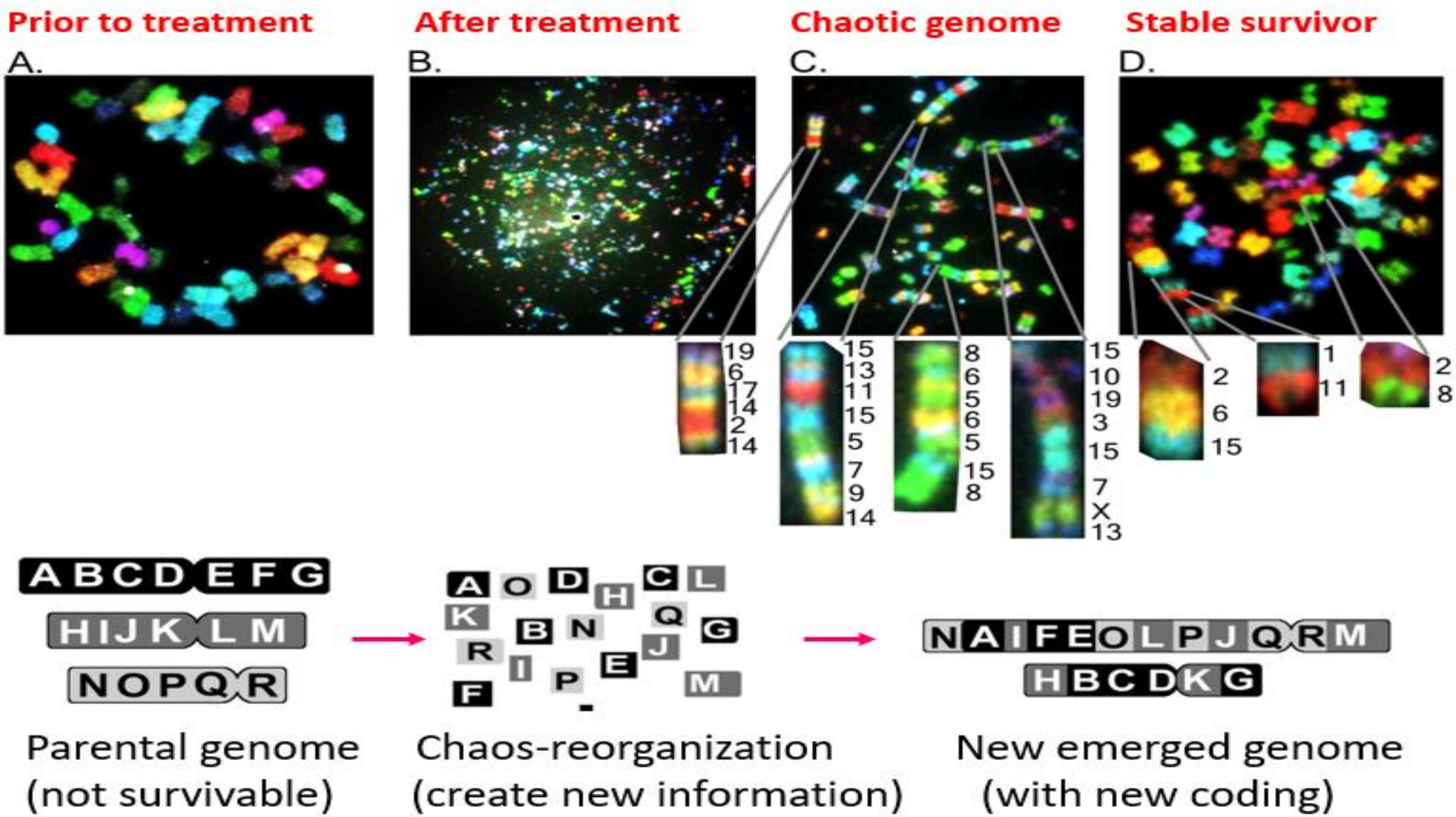
The main function of sexual reproduction is to maintain the karyotype for species identity



Mechanism of cancer: rapid and massive speciation by reorganizing genomes without constraint of sex

Genome chaos: rapid massive macroevolution

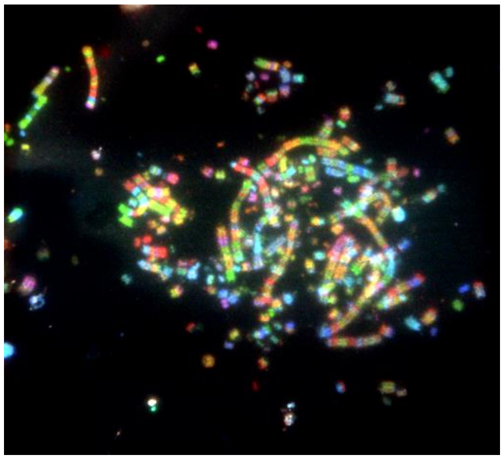
Re-organizing karyotypes to create new information



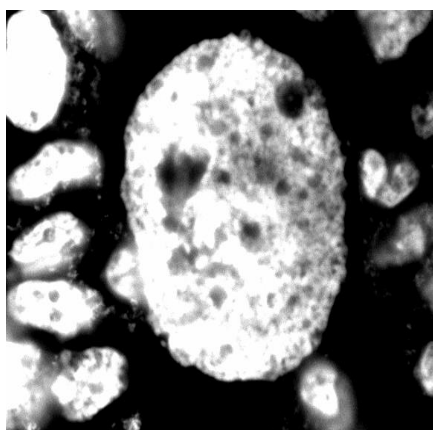
Each runs of genome chaos leads to new karyotype

Chaotic genomes are responsible for phase transition
Drug induces chaotic genomes (structural/numerical)

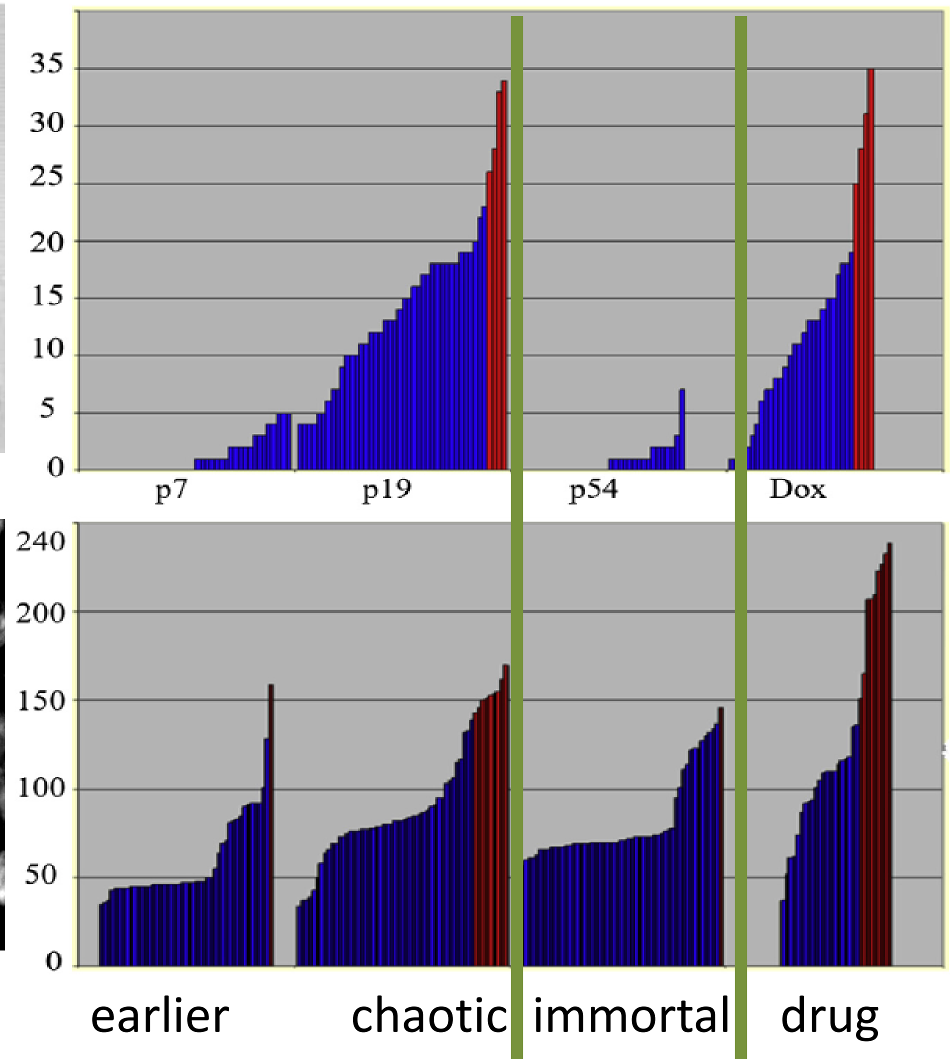
Pattern of chaotic genomes in phase transition: populational view



Structural chaotic



Numerical chaotic

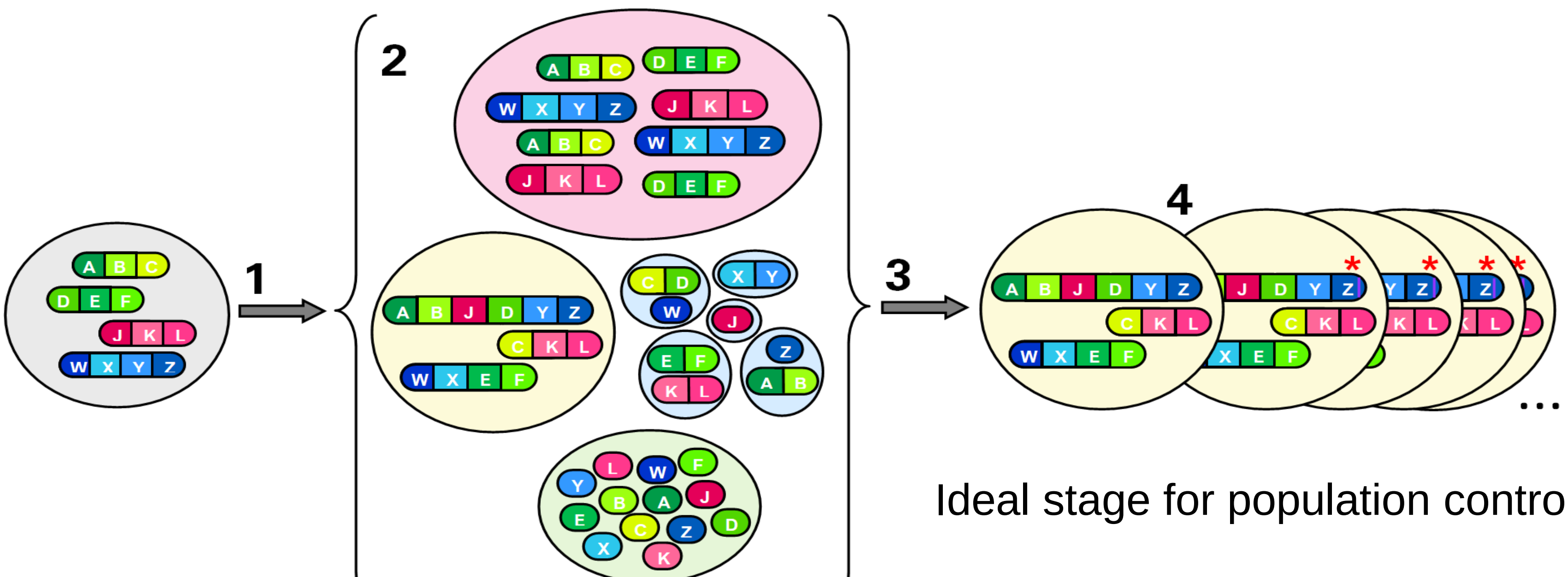


Causes: surival strategy under crisis via passing life-info
Consequences: creating new species with new genomes
The pattern of genome chaos is often predictable

Diverse stresses: Massive death chaos is active

Diverse forms of chaotic karyotypes: micronuclei, translocations, giant cells, chromosome fragmentation

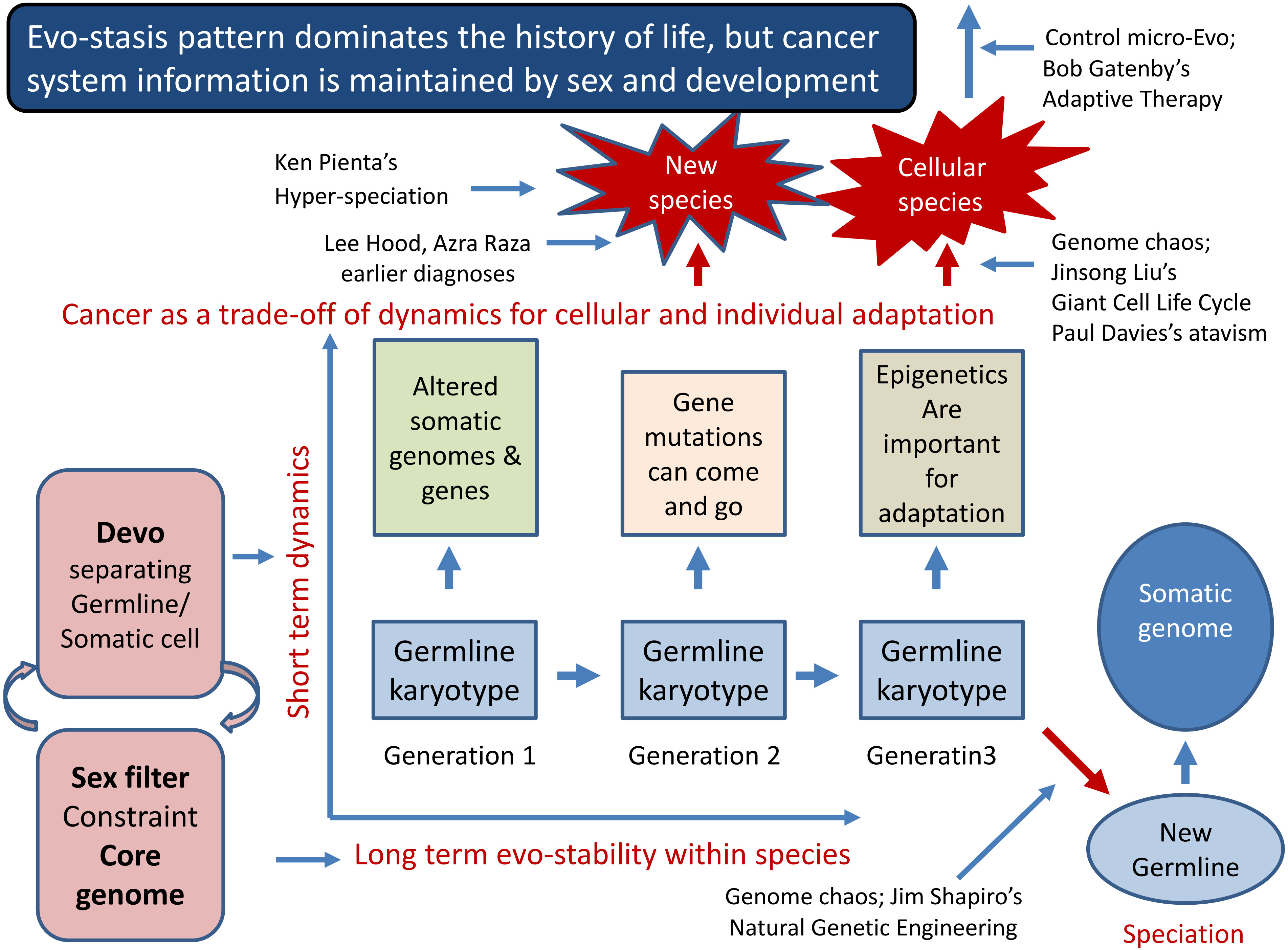
Population growth for Survived cells (new karyotypes). A key mechanism for generating cellular mass of cancer



Parental genome prior to phase transition

Chaotic genomes under macroevolution

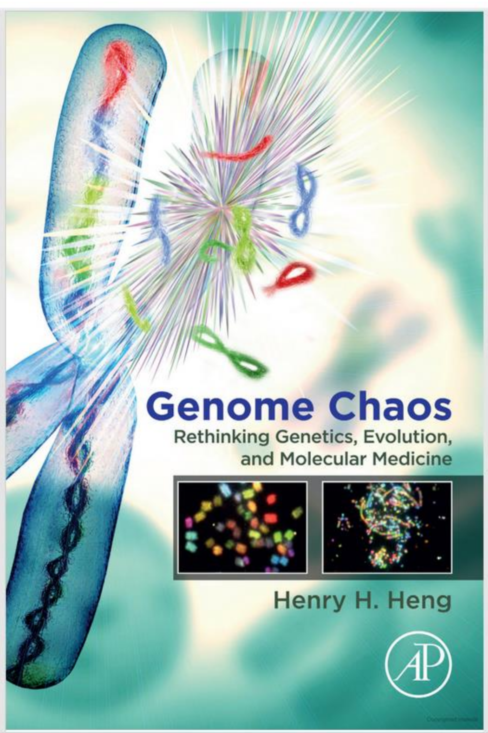
Microevolution with cancer genes and epigenetics



Evo-stasis pattern dominates the history of life, but cancer system information is maintained by sex and development
Control micro-Evo; Bob Gatenby's Adaptive Therapy
Ken Pienta's Hyper-speciation
New species
Cellular species
Lee Hood, Azra Raza earlier diagnoses
Genome chaos; Jinsong Liu's Giant Cell Life Cycle Paul Davies's atavism
Cancer as a trade-off of dynamics for cellular and individual adaptation
Altered somatic genomes & genes
Gene mutations can come and go
Epigenetics Are important for adaptation
Devo separating Germline/ Somatic cell
Short term dynamics
Germline karyotype
Germline karyotype
Germline karyotype
Somatic genome
Generation 1
Generation 2
Generatin3
Sex filter Constraint Core genome
Long term evo-stability within species
New Germline
Genome chaos; Jim Shapiro's Natural Genetic Engineering
Speciation

Implications in cancer research/treatment

1. Two-phased evolution is the key for research/diagnosis/treatment
2. Avoiding induced genome chaos should reduce drug resistance
3. Maximal killing initially reduces cancer cells, but could harm patients by induced genome chaos. Cancer is a game of outliers



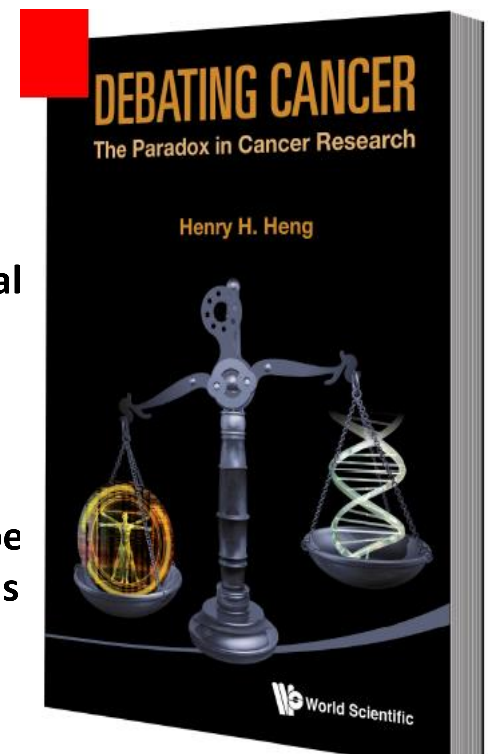
ACKNOWLEDGMENTS

Anna Barke
Donald Coffey
Jim Crow
Peter Duesberg
YB Fu
Rafe Furst
Bob Gatenby
Wayt Gibbs
Root Gorelick
Gloria Heppner
Steve Krawetz

Jinsong Liu
Carlo Maley
O.J. Miller
Peter Moens
Ken Pienta
Harry Rubin
James Shapiro
Gary Stein
Lap-Chee Tsui
Douglas Wallace
Adam Wilkins
Christine Ye

<u>Heng's group</u>

Batoul Abdallal
Steve Bremer
Steven Horne
Guo Liu
Sarah Regan
Zachary Sharpe
Joshua Stevens
Karan Ye



A new genomic coding system?

What defines a systems ?

How does karyotype, impact system inheritance?

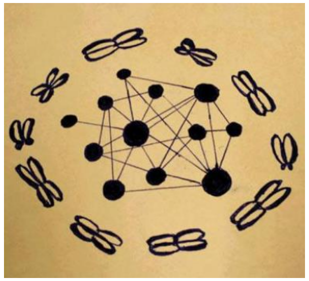
Gene centric inheritance: "Gene-protein-Phenotype"

chromosomes are carrier of gene

1. Gene defined inheritance is limited ("Missing heritability")

2. Gene codes: Parts inheritance; how to make parts (protein)

   New codes: System inheritance; how to organize genes' interaction, the blueprint



New genomic coding: organize gene interactive network

Chromosome set is the highest genomic information