Scales of carcinogenesis: cells, crypts and cancer

Georg Luebeck (PI) – Carlo Maley (Co-PI)

FRED HUTCHINSON CANCER RESEARCH CENTER

A LIFE OF SCIENCE

Reid Lab (Barrett's Esophagus)

Dennis Chao*
Tom Paulson
Brian Reid

Biomathematics/Biostatistics

Bill Hazelton
Jihyoun Jeon*
Suresh Moolgavkar

THE WISTAR INSTITUTE

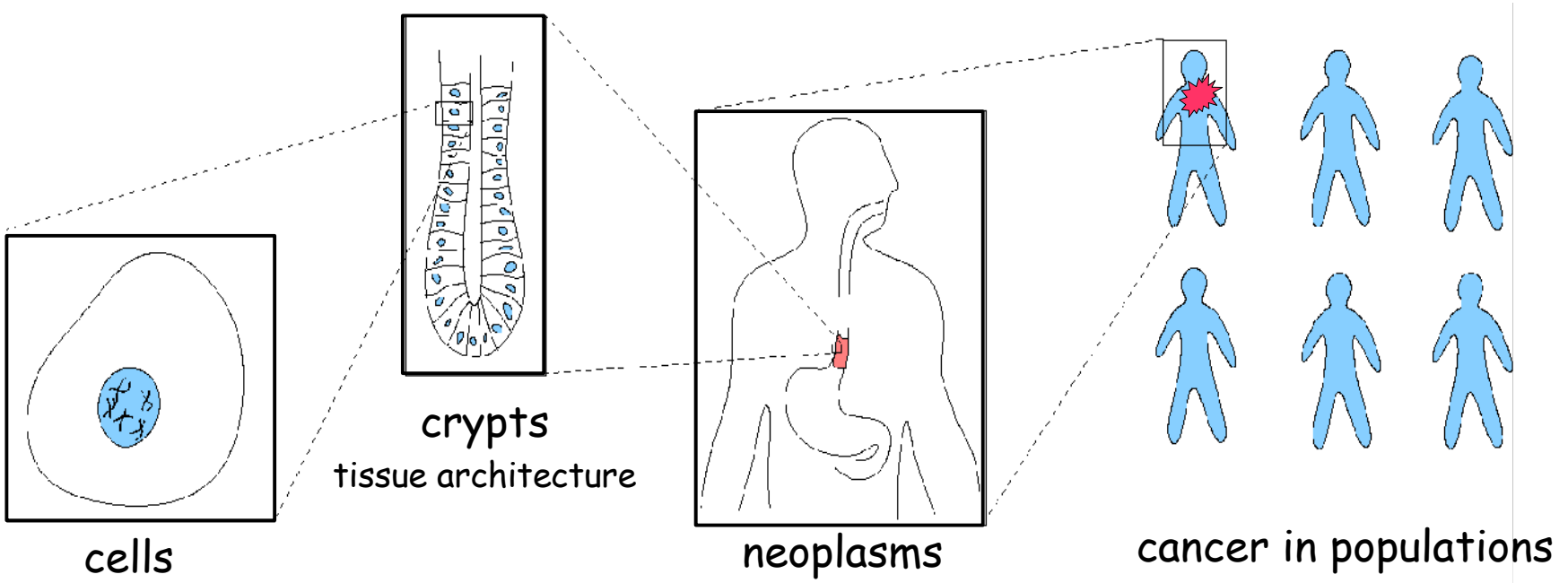
TODAY'S DISCOVERIES – TOMORROW'S CURES

Maley Lab (Computational Biology)

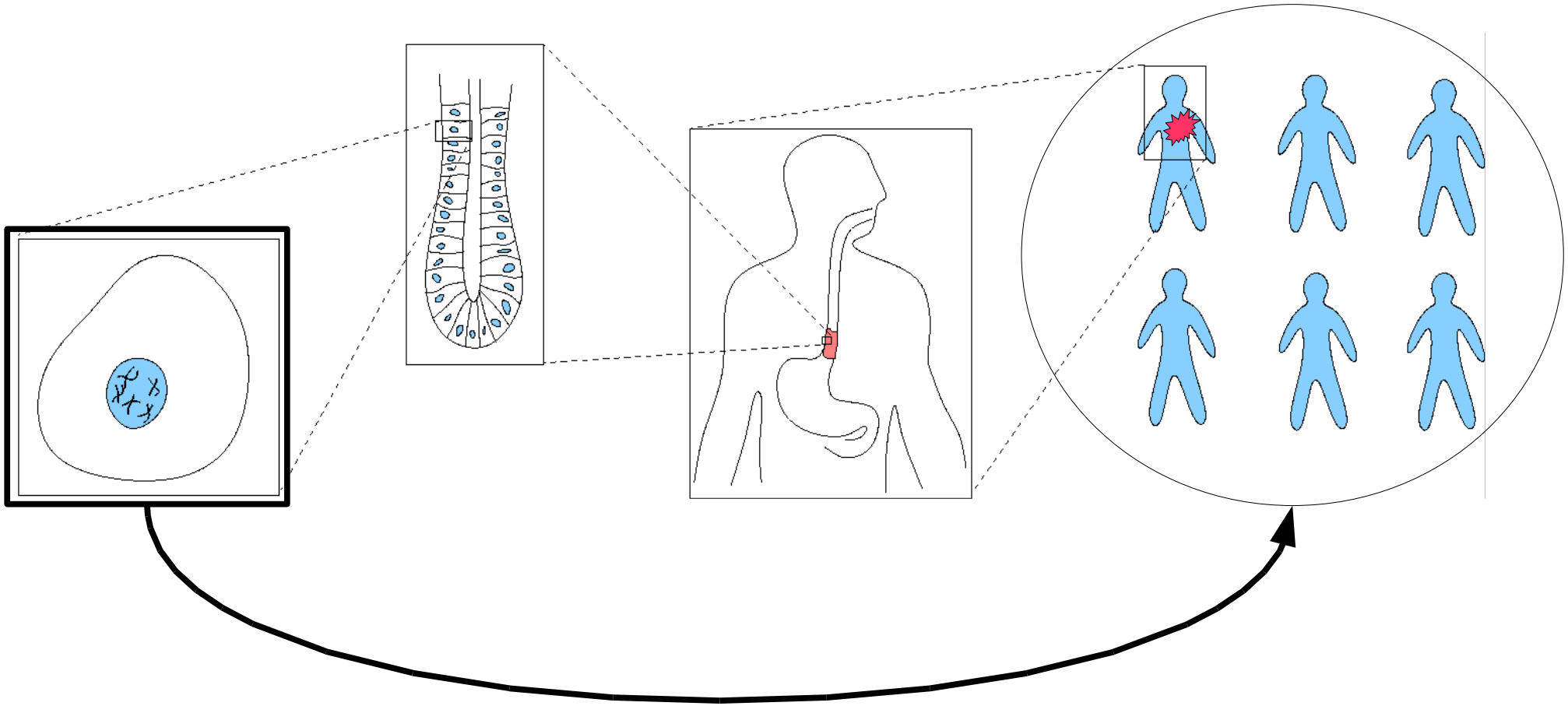
David Birtwell*
Tom Eck*
Doug West*

Scales of neoplastic progression:

example: Barrett's esophagus



first attempts (1950's)

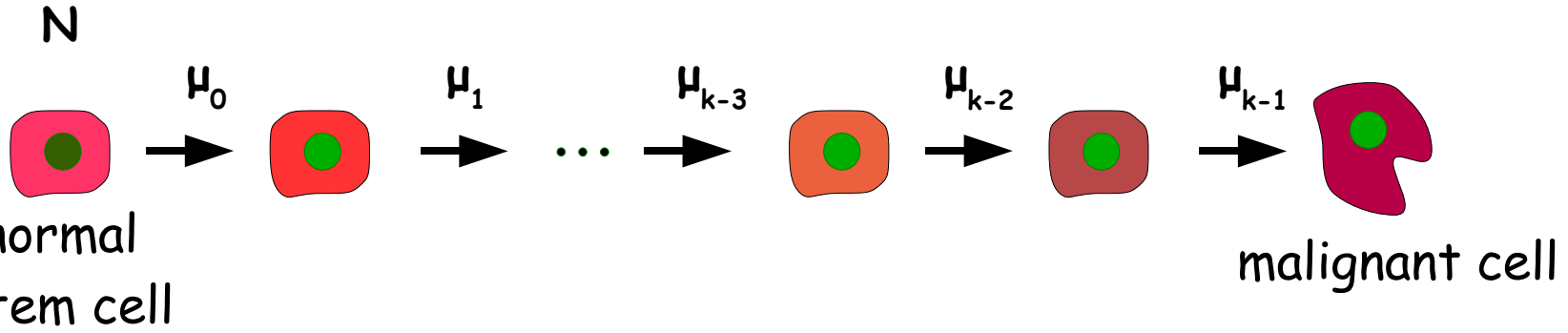


acquisition of requisite mutations,

(LOH, translocations, amplifications, DNA (hyper)methylation,...)

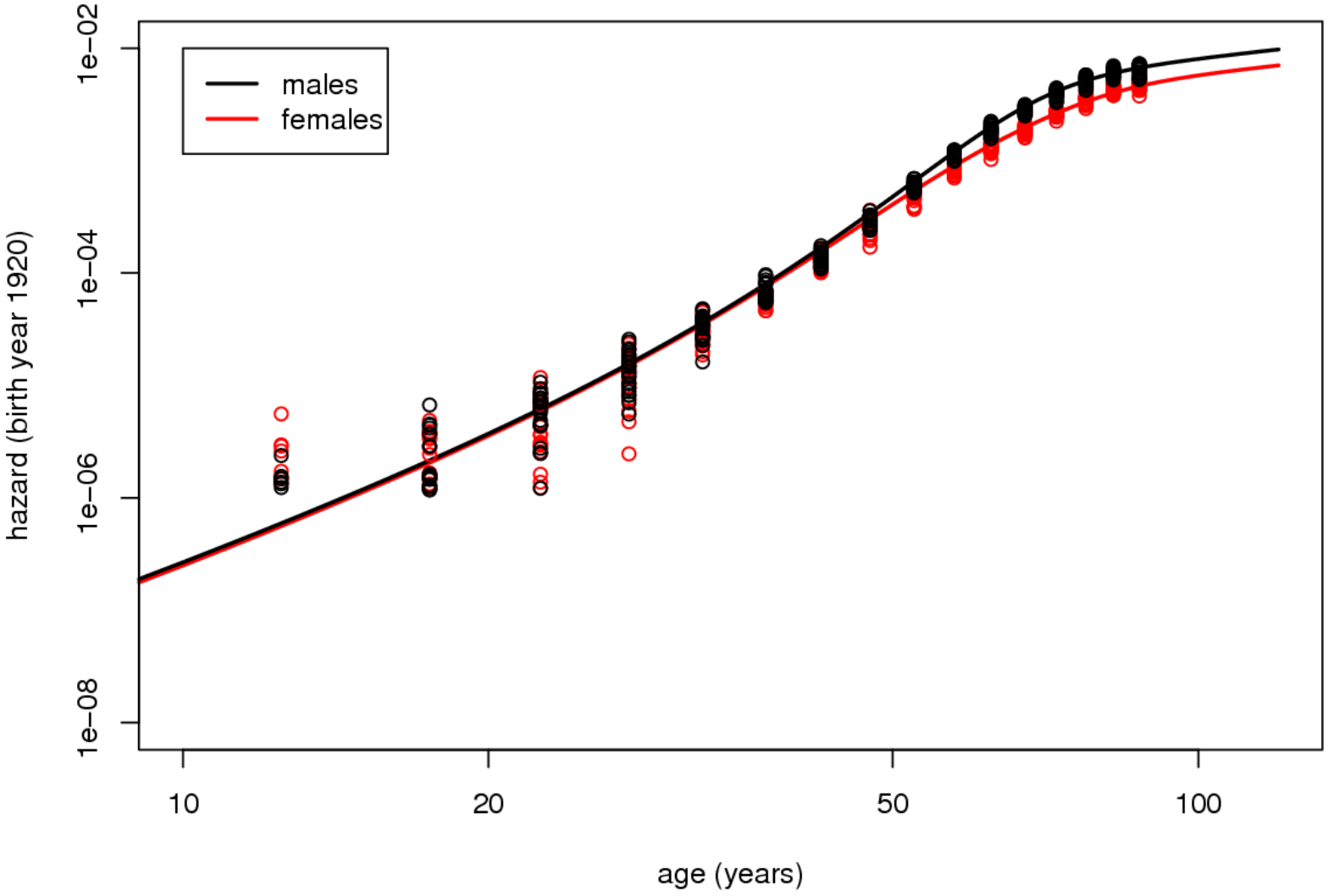
multistage carcinogenesis

(Armitage & Doll, Nordling – 1950's)

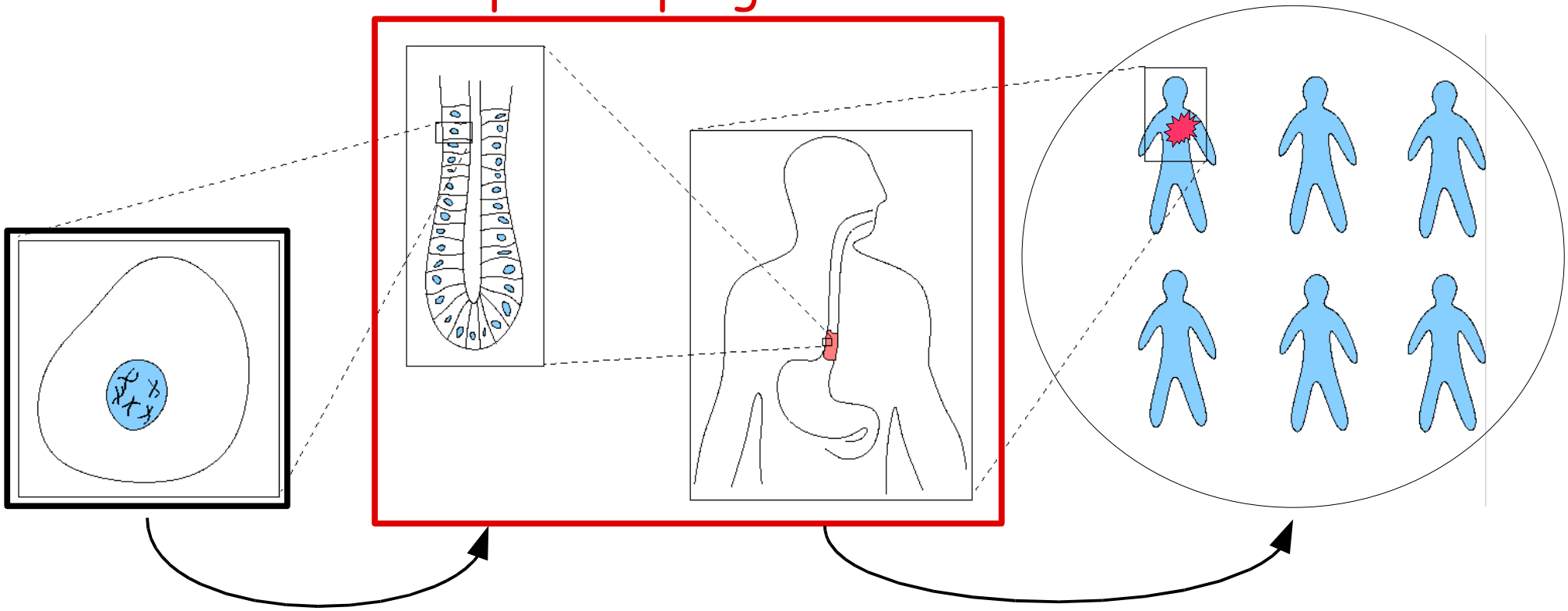


age-specific incidence $I(a) \approx a^{k-1}$

SEER (1973-2000) **colorectal cancer**



neoplastic progression



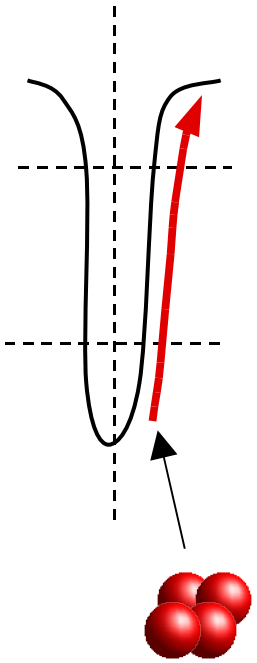
acquisition of (epi)genetic events leading to neoplastic alterations in cellular organization

tumor progression & clinical detection

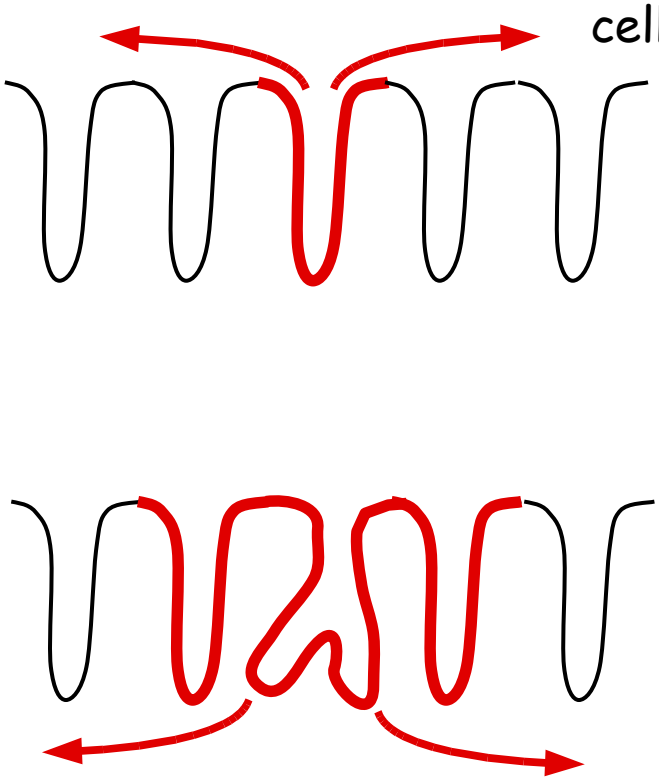
spatial & temporal scales:

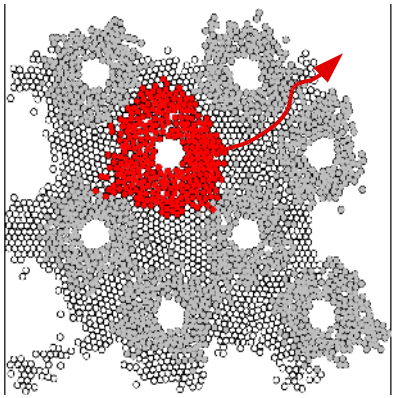
compartments	parameters
stem cells	mutation rates
stem cell niche	time to fixation or extinction
tissue level	cell kinetic parameters (birth and death rates)
population level	incidence rates (hazard fct)

we don't know how clones expand across crypt structured tissue



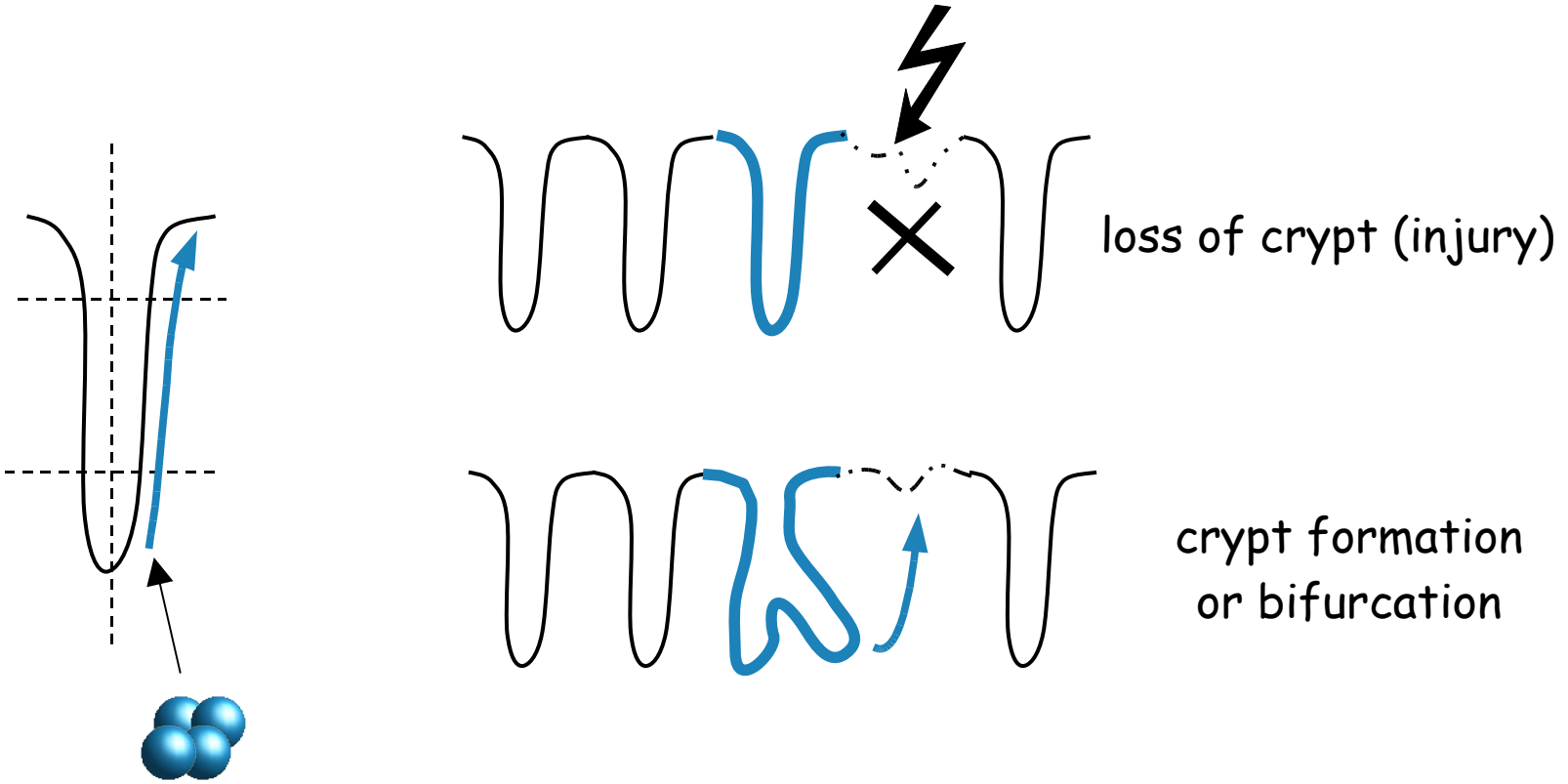
altered crypt with reproductive or survival advantage



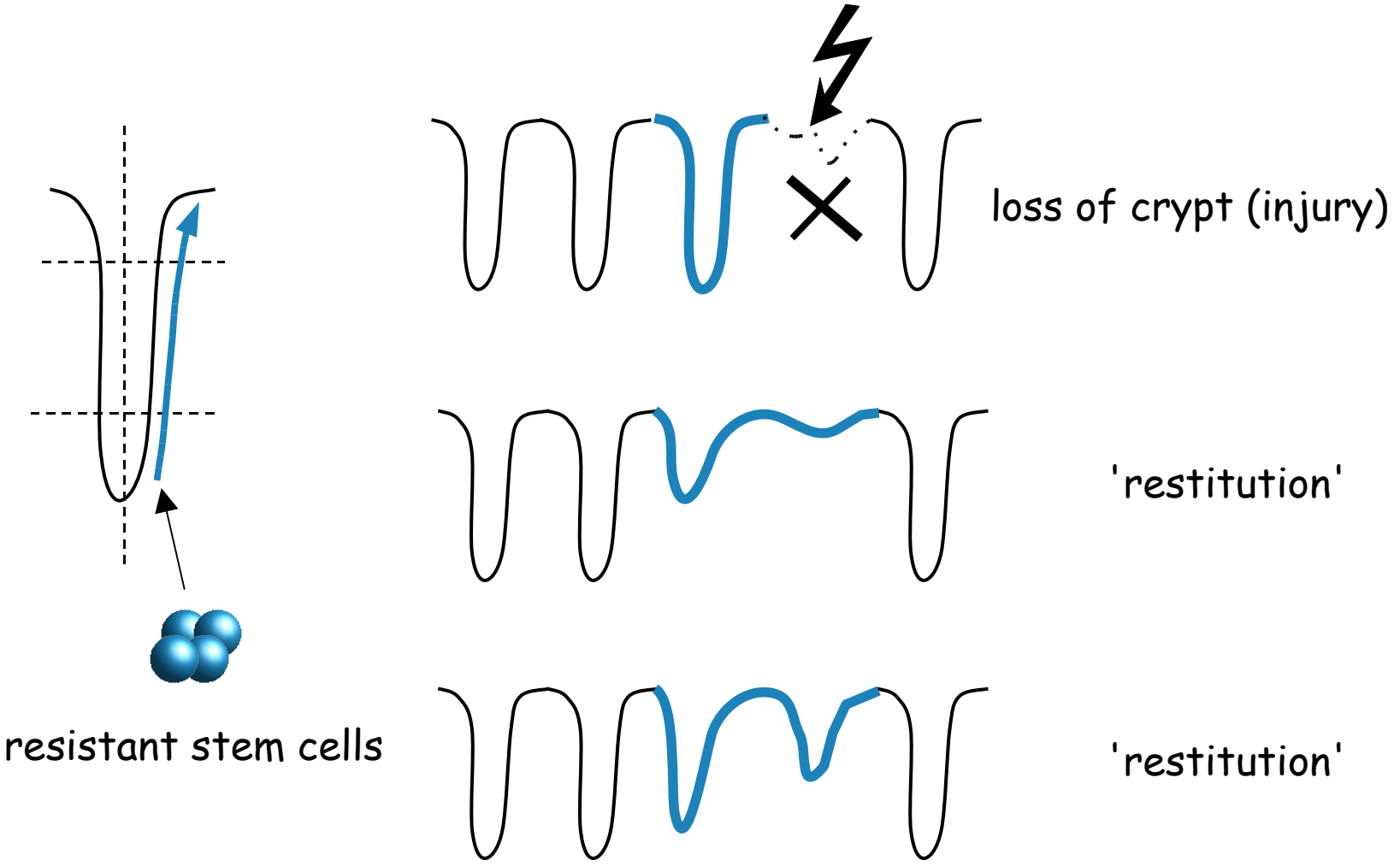


carcinogenesis is virtually impossible without clonal expansion

clonal expansion of (injury)resistant population

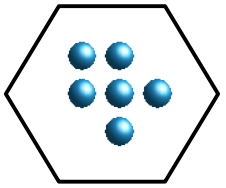


clonal expansion of (injury)resistant population



connecting the scales

module 1: from a cell to a proliferative unit (Potten, Loeffler,...)

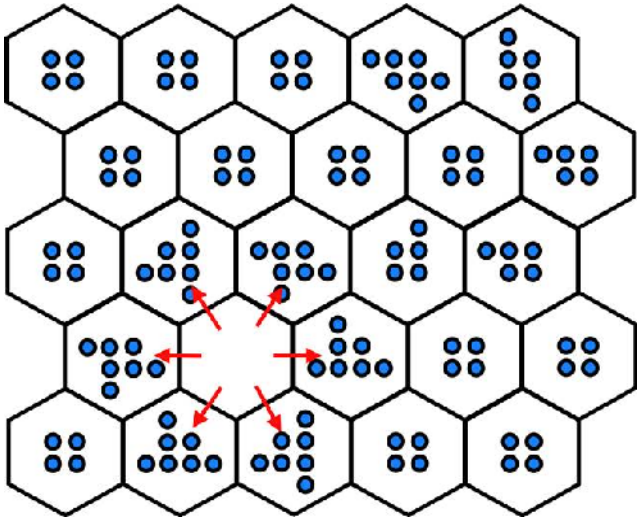


questions:

1. how are crypts organized?
   - Number(distribution) of stem cells
   - Stem cell kinetics
   - Homeostatic regulation/differentiation (David Birtwell)
2. how do mutant cells fare in a crypt that undergoes cell turnover (extinction/fixation)?
3. number of rate-limiting events to 'initiation'? (Jihyoun Jeon)

connecting the scales

module 2: from a proliferative unit to a tissue unit (organ)



David Birtwell
Dennis Chao
Tom Eck

questions:

1. how do the number of stem cells per crypt affect carcinogenesis?
2. how does the proportion of deleterious to advantageous mutations affect carcinogenesis?

(see David Birtwell's poster)

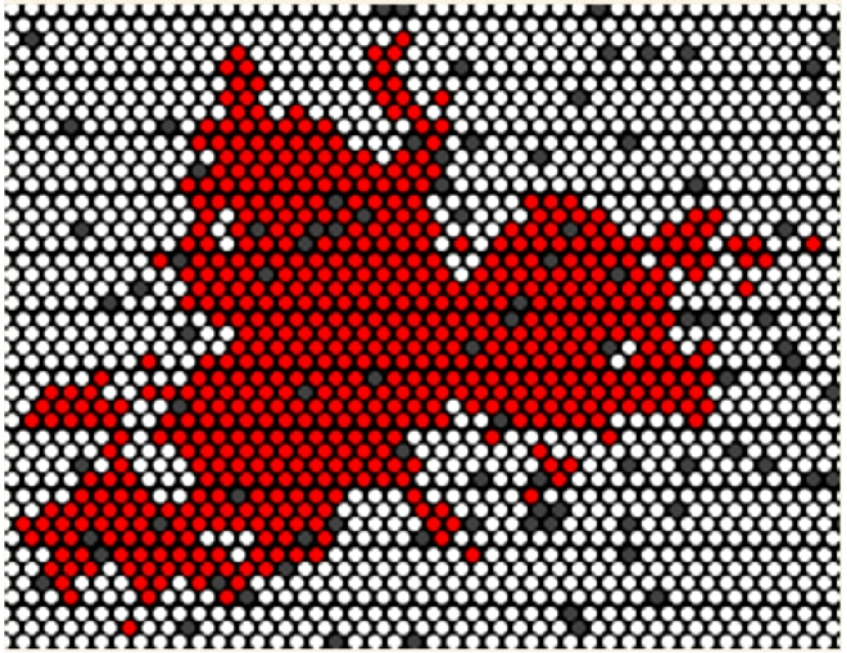
connecting the scales

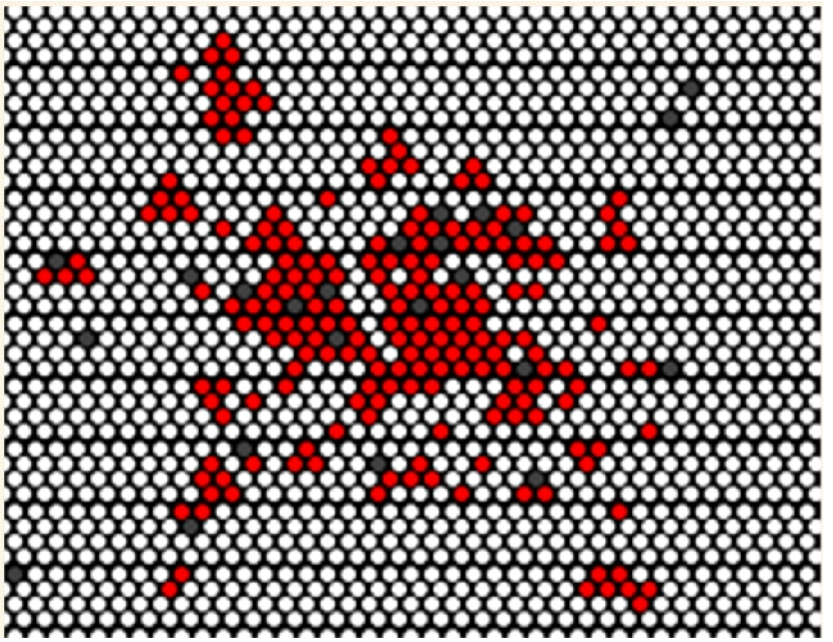
module 2: from a proliferative unit to a tissue unit (organ)

questions:

1. what can the shape of clones tell us?

(see Tom Eck's poster)





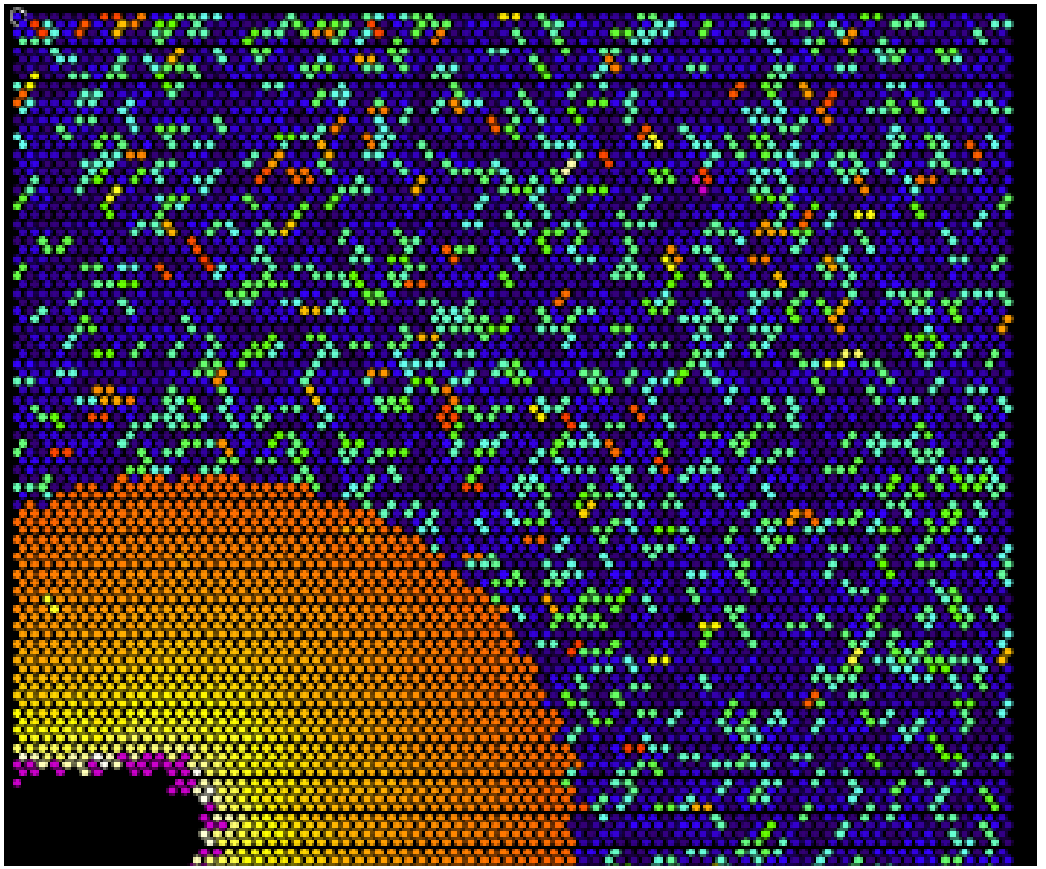
connecting the scales

module 2: from a proliferative unit to a tissue unit (organ)

questions:

1. can the genetic distance between proliferative units reveal the history and mechanism of wounding?

(see Doug West's poster)



connecting the scales

module 3: from a tissue unit to cancer in populations
(tumor progression, invasion, detection, screening)

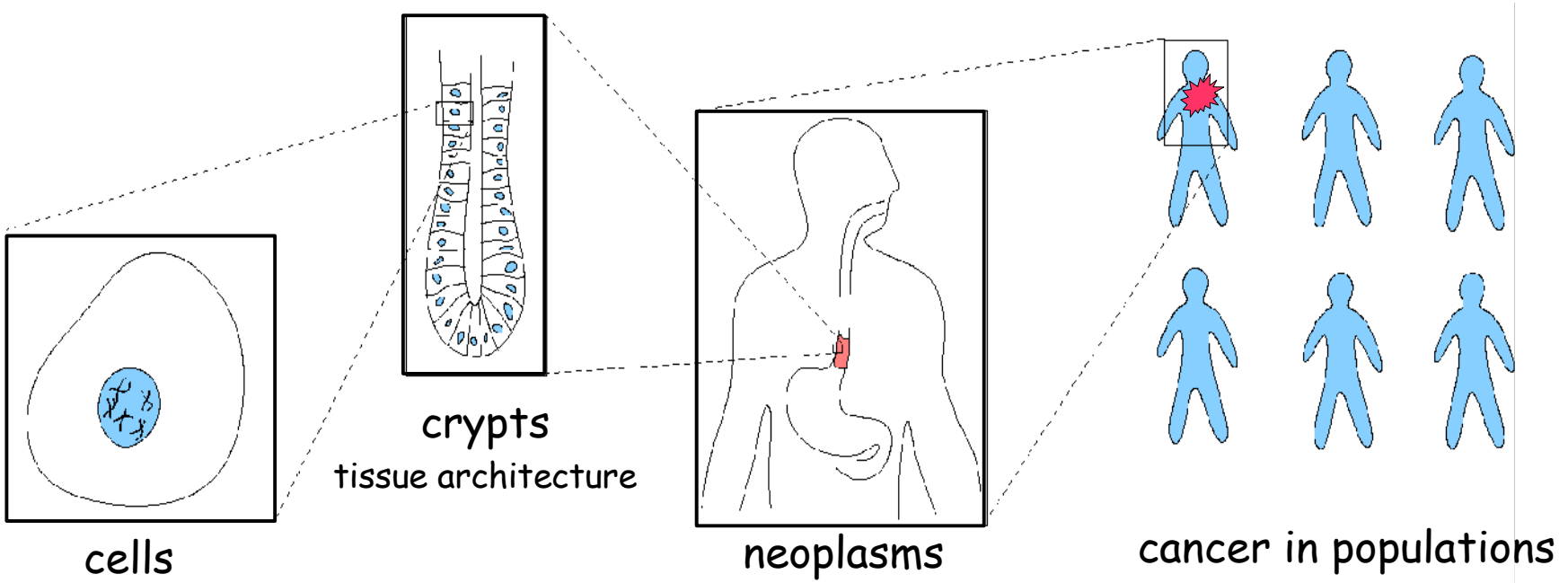
questions:

1. what modifies cancer incidence rates (effect modifiers, trends)?
2. what is the prevalence of individuals at specific stages in carcinogenesis?

Use model to improve cancer screening/surveillance.

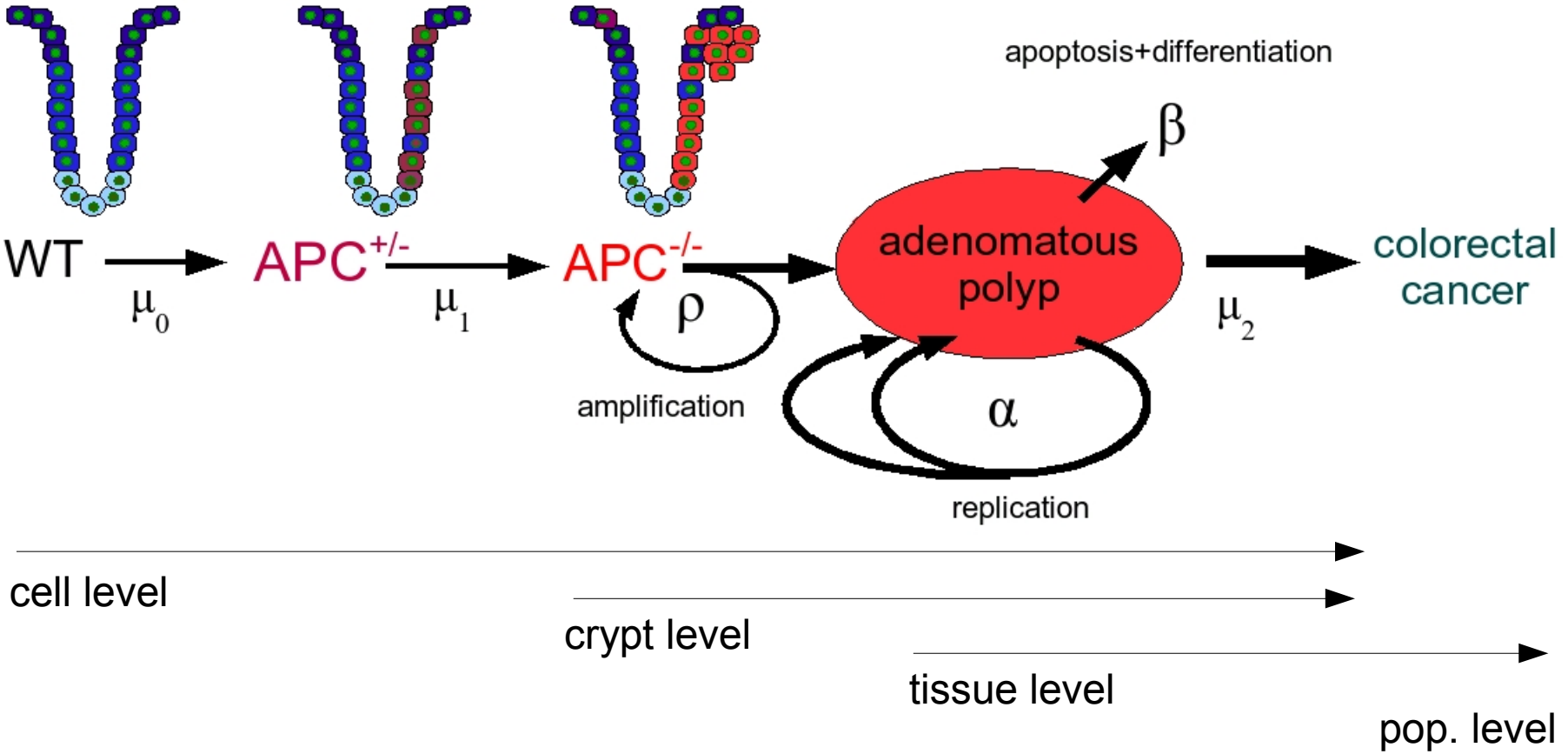
(see Jihyoun Jeon's poster)

Significance of modeling neoplastic progression



- generating hypotheses for phenomena in carcinogenesis
- guiding experiments
- focusing interventions on parameters that have the greatest effect on carcinogenesis

example: colon cancer



Luebeck and Moolgavkar Proc Natl Acad Sci U S A. 2002 Nov 12;99(23)