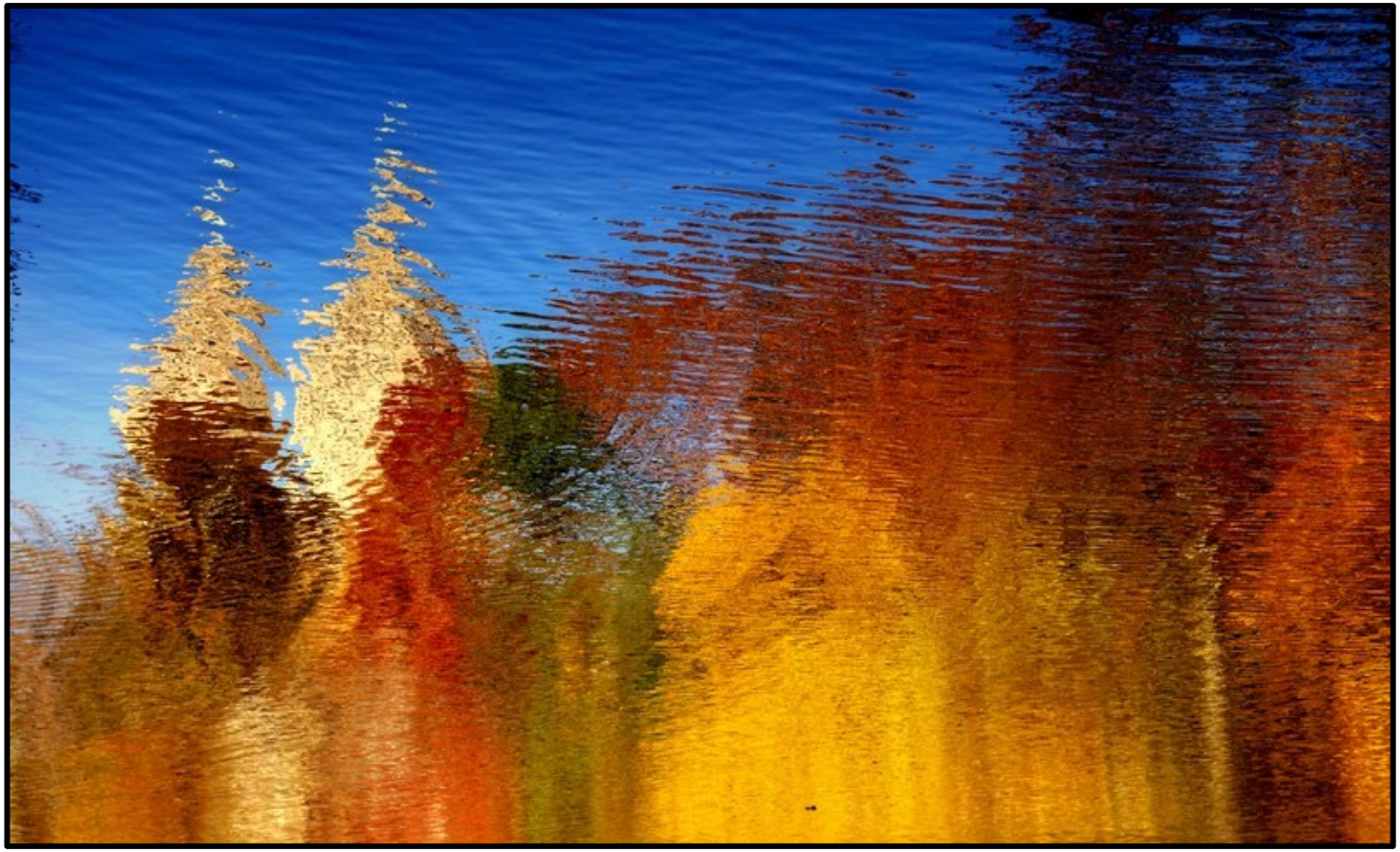
LARVA: An integrative framework for Large-scale Analysis of Recurrent Variants in noncoding Annotations



M Gerstein, Yale

Slides freely downloadable from **Lectures.GersteinLab.org**
& “tweetable” (via @markgerstein). See last slide for references & more info.

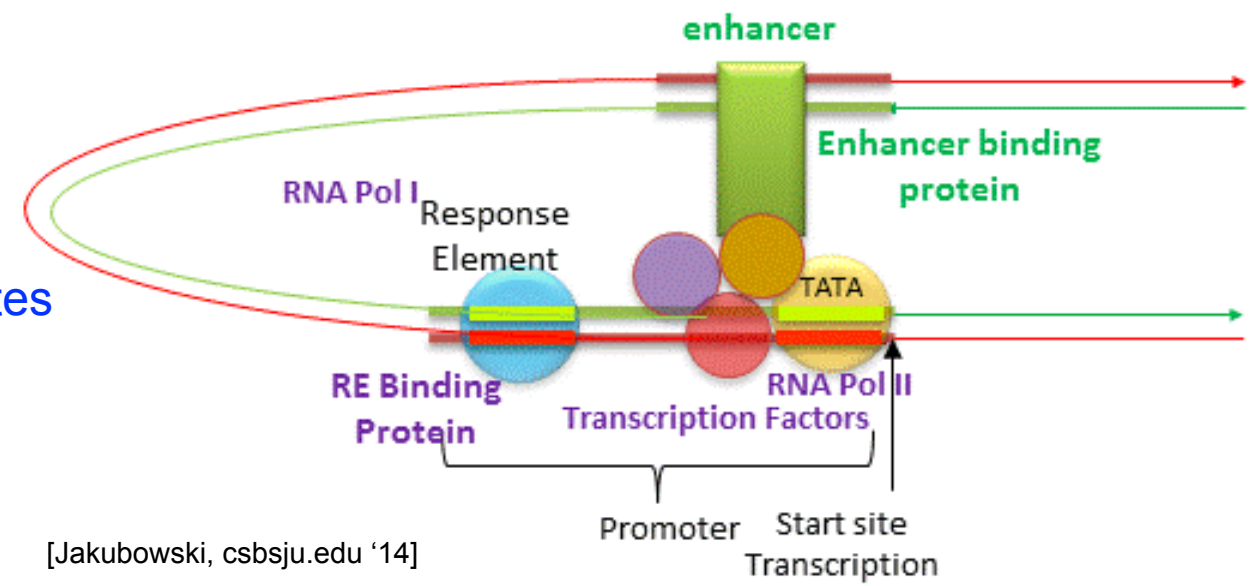
Finding Key Variants in Cancer Genomes: the Needle in the Haystack

[Image credit: www.yourgrantauthority.com '15]

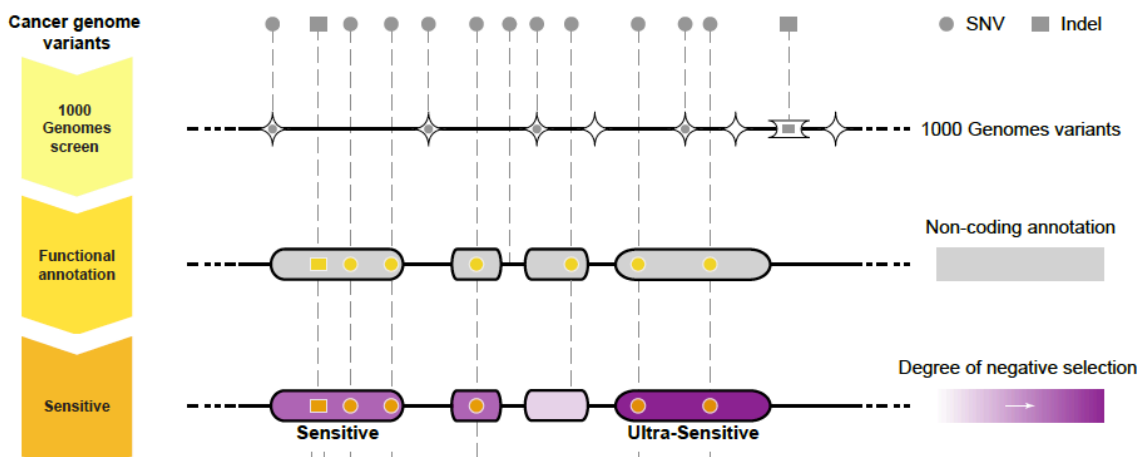
- Increasing number of whole genome sequenced for tumor/normal pairs
  - Eg >2500 for PCAWG
- Lots of somatic mutations in an average tumor (~5K/sample), particularly in non-coding regions
- A focus is distinguishing drivers & passengers
  - Canonical **Drivers** are mutations driving cancer progression
    - Thought to be under positive selection
    - Recur in the same position, gene or functional element across tumors in different individuals
  - **Passengers** are thought not be significant to driving cancer progression
    - Collateral damage
    - Could result from impaired DNA repair processes
- Most driver work has focused on genes
  - eg Youn & Simon ('11). *Bioinformatics*; Lawrence et al. ('13). *Nature*

Noncoding Annotations

- Promoters
- TF binding sites
- Transcription start sites
- DHS sites
- Enhancers

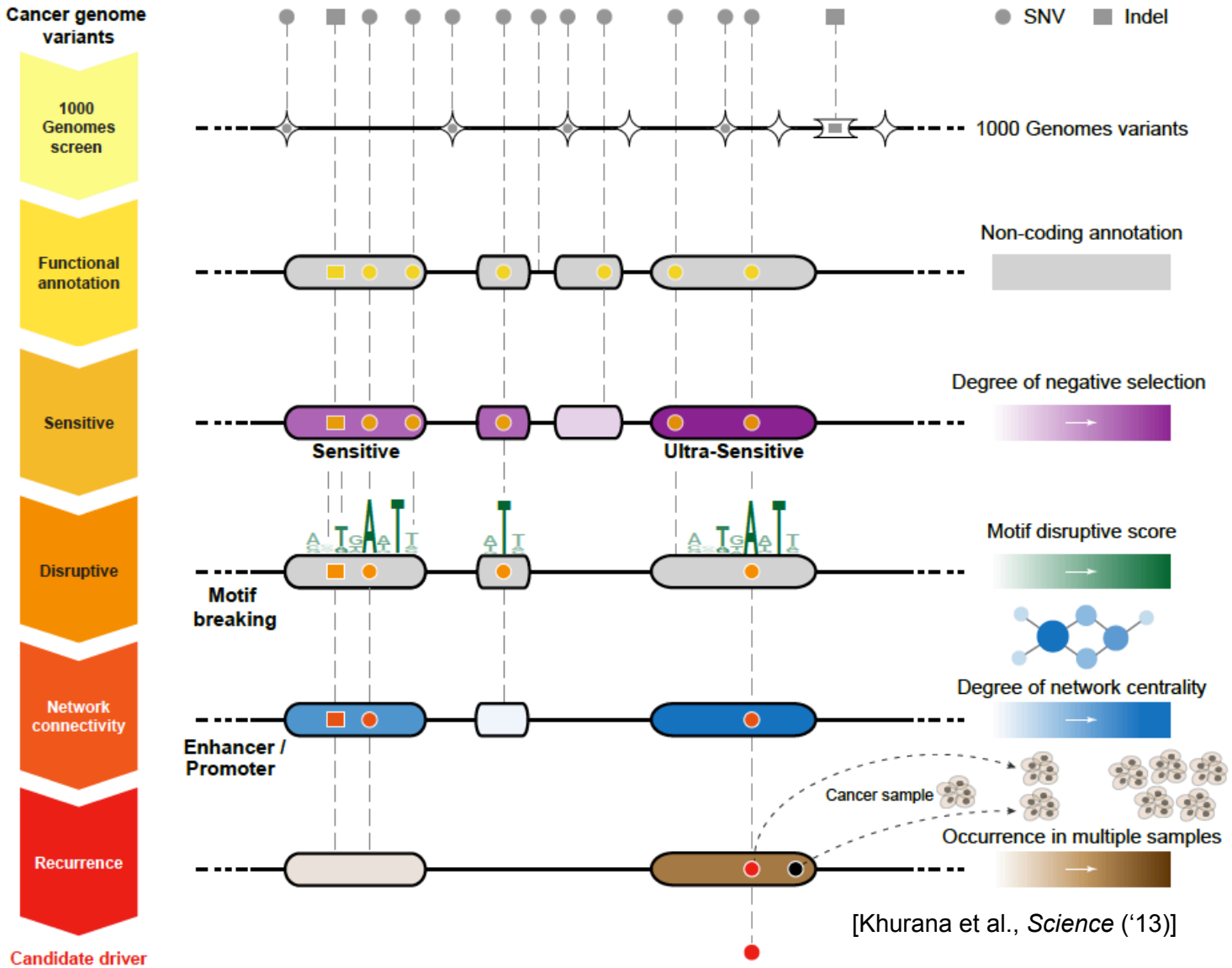


[Jakubowski, csbsju.edu '14]



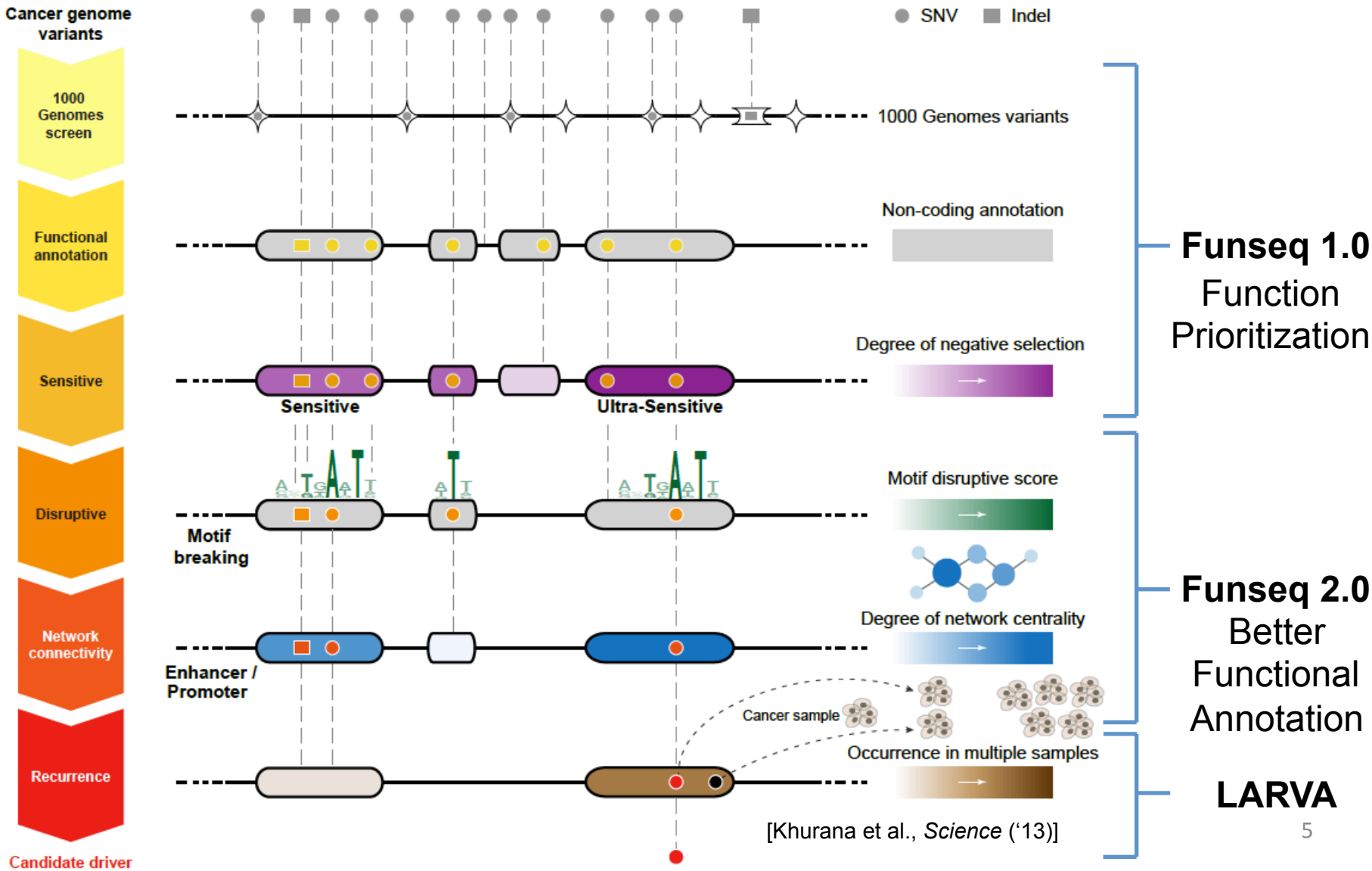
Ultra-sensitive & Ultra-conserved elements Non-coding regions more conserved than expectation across the human population & between species [Bejerano et al. ('04). Science; Khurana et al., Science ('13)]

Identification of non-coding candidate drivers amongst somatic variants: FunSeq



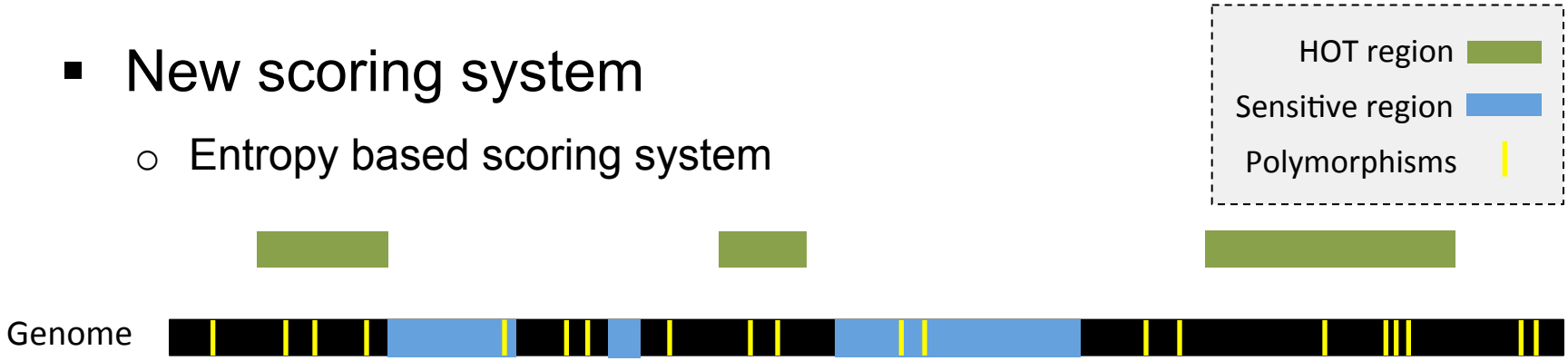
[Khurana et al., *Science* ('13)]

Identification of non-coding candidate drivers amongst somatic variants: FunSeq



From Funseq 1.0 to Funseq 2.0

- Elaborated features
  - Motif disruption score: changes in PWMs
  - Network centrality analysis: PPI, regulatory, and phosphorylation networks
- New scoring system
  - Entropy based scoring system



$$p = \frac{3}{20}$$

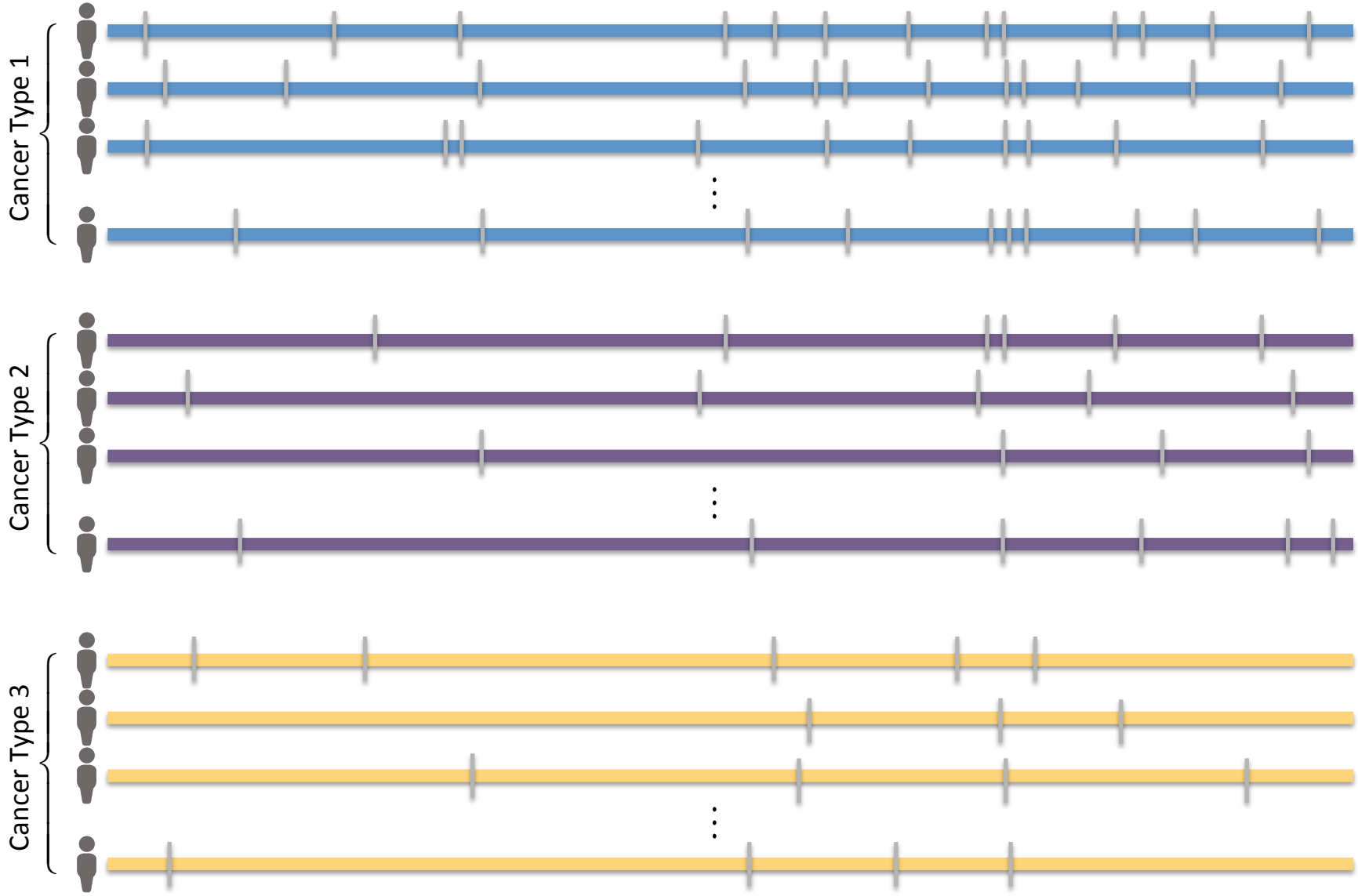
Feature weight: $w_d = 1 + p_d log_2 p_d + (1 - p_d) log_2 (1 - p_d)$

$p \uparrow \quad w_d \downarrow$ *p = probability of the feature overlapping natural polymorphisms*

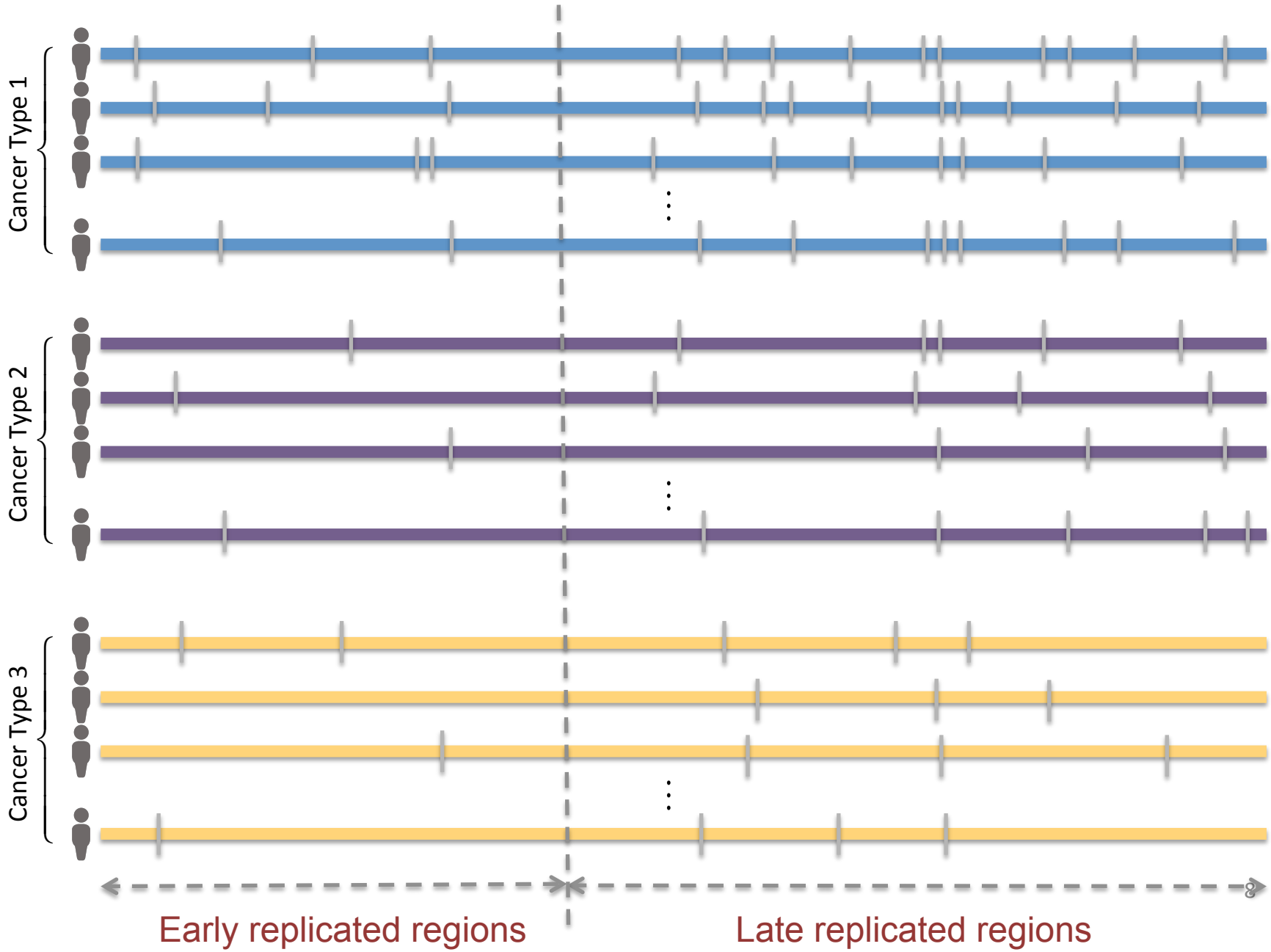
For a variant: $Score = \sum w_d \quad of\ observed\ features$

[Fu et al., GenomeBiology ('14)]

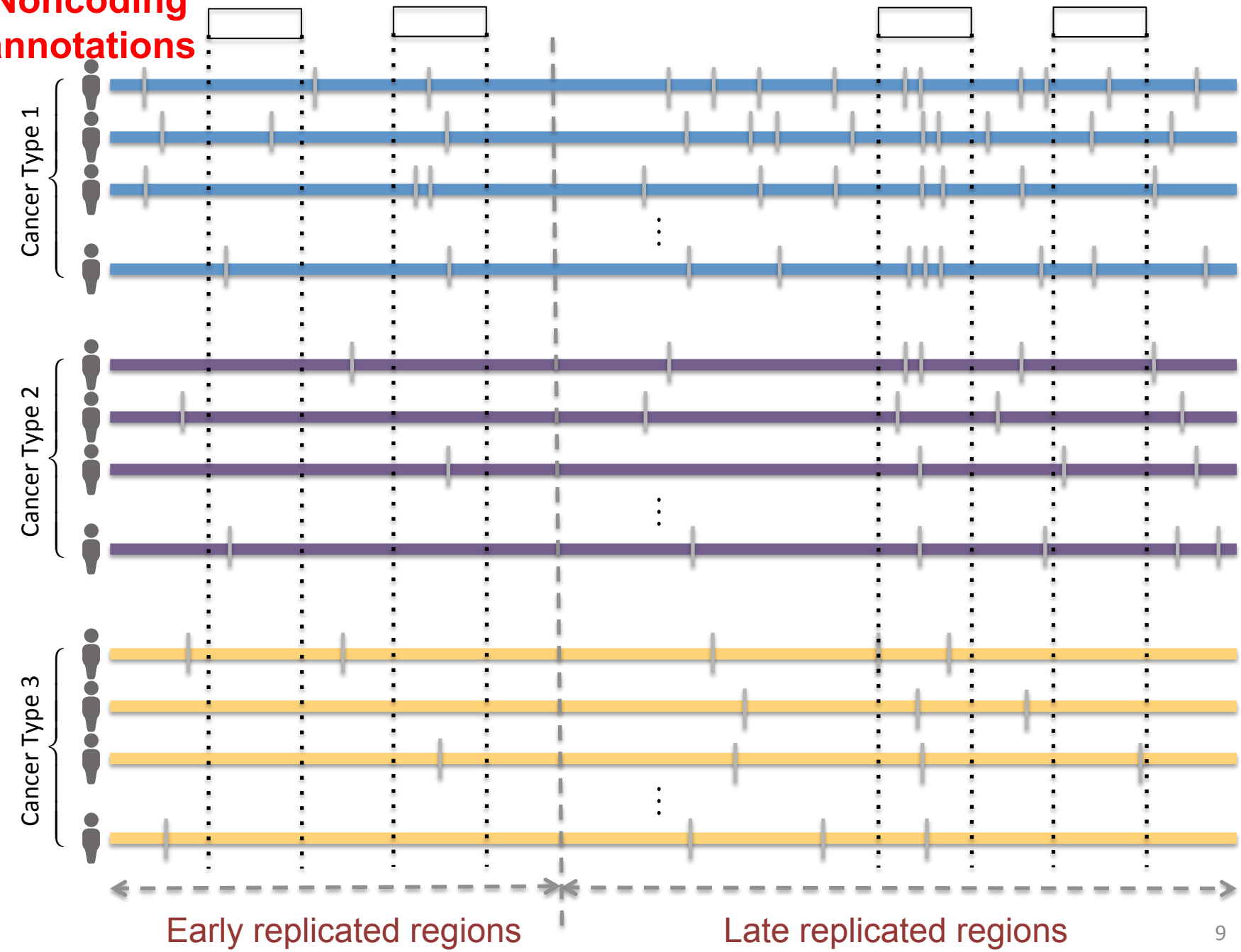
Mutation recurrence

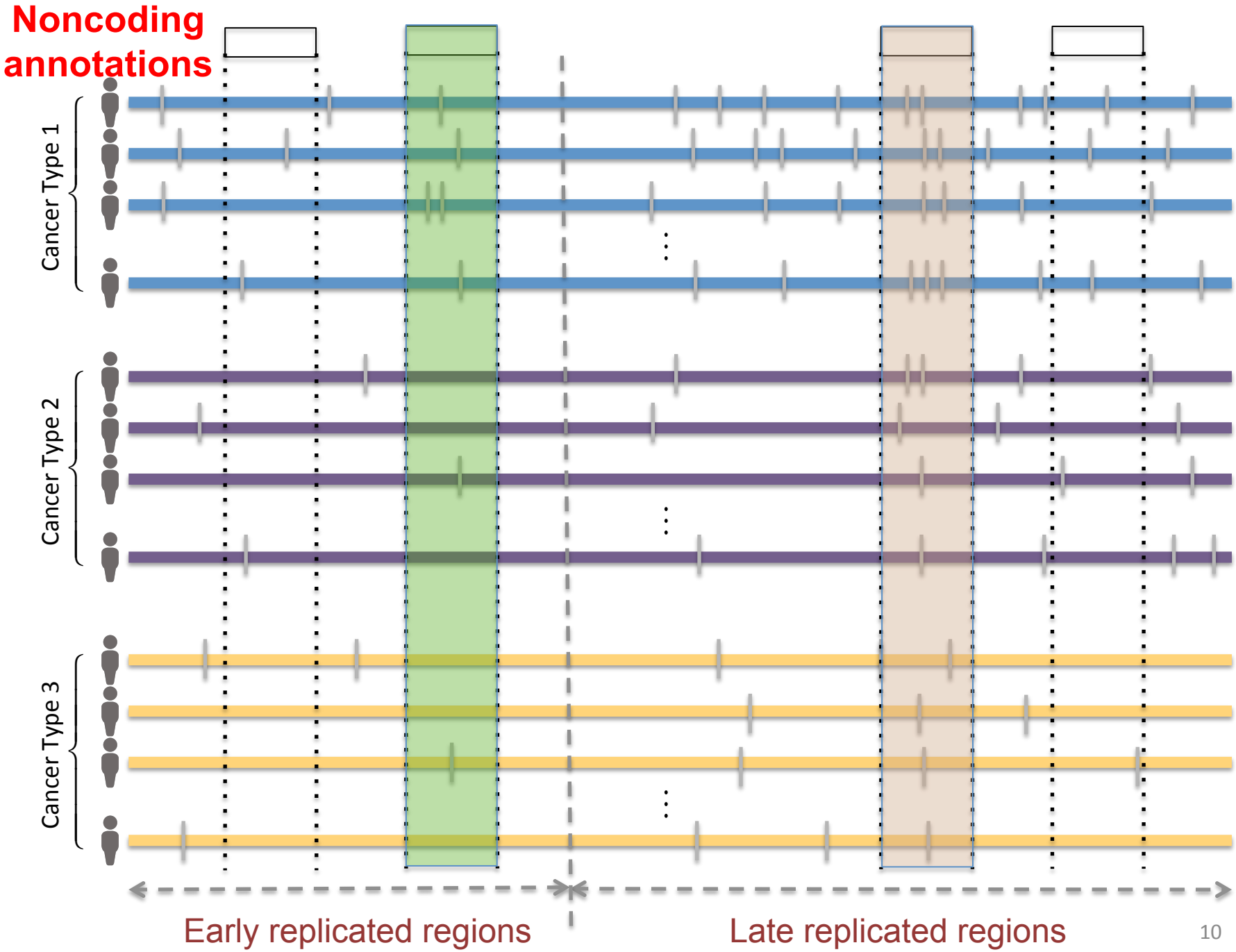


Mutation recurrence

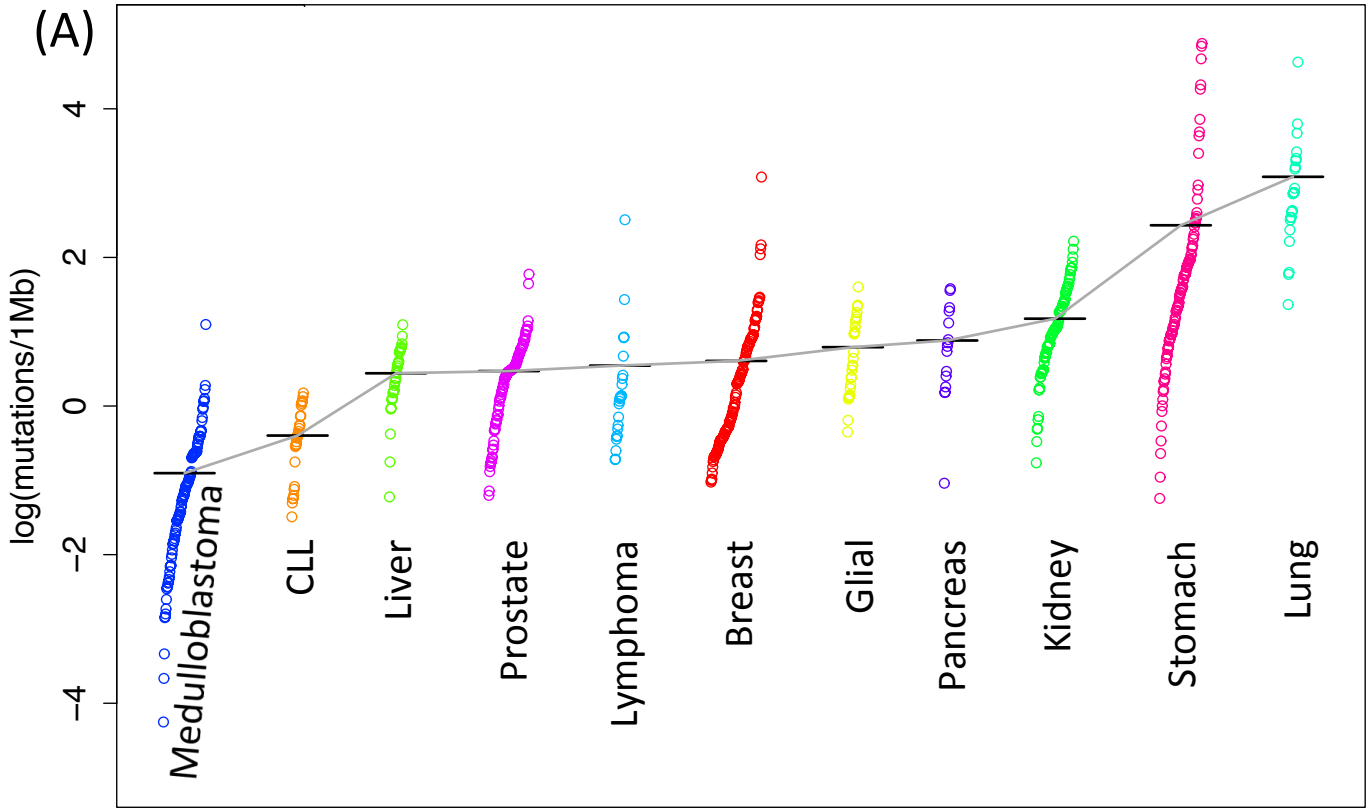


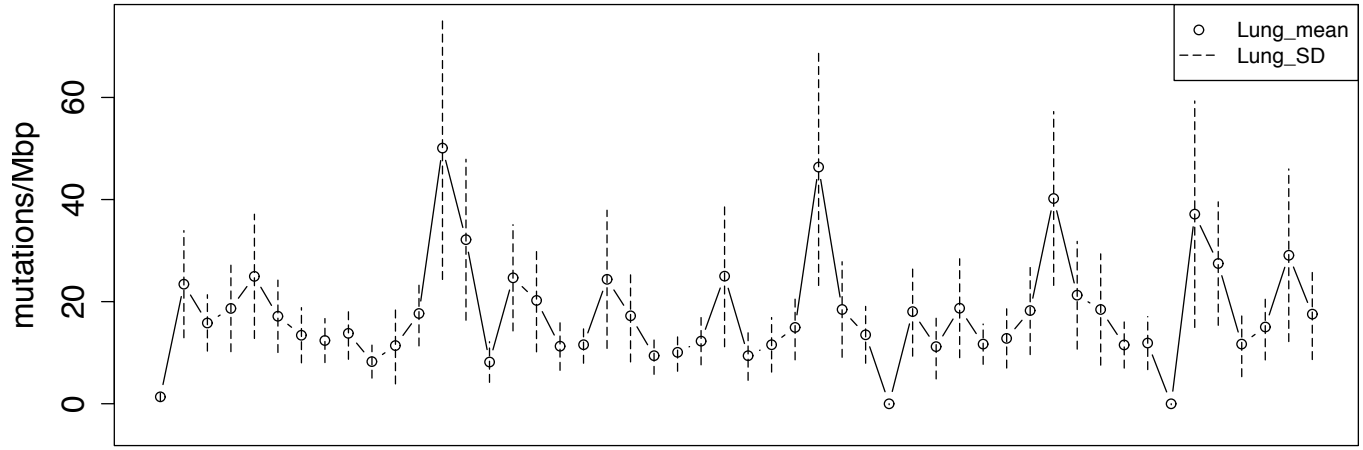
Noncoding annotations





Cancer Somatic Mutational Heterogeneity, across cancer types, samples & regions





1 Mbp genome regions (locations chosen at random)

[Lochovsky et al. *NAR* ('15)]

Cancer Somatic Mutation Modeling

- 3 models to evaluate the significance of mutation burden
- Suppose there are *k* genome elements. For element *i*, define:
  - n_i: total number of nucleotides
  - x_i: the number of mutations within the element
  - p: the mutation rate
  - R: the replication timing bin of the element

Model 1: Constant Background Mutation Rate (Model from Previous Work)

$$\mathbf{x_i} : Binomial(\mathbf{n_i}, \mathbf{p})$$

Model 2: Varying Mutation Rate

$$\mathbf{x_i}|\mathbf{p_i} : Binomial(\mathbf{n_i}, \mathbf{p_i})$$

$$\mathbf{p_i} : Beta(\mu, \sigma)$$

Model 3: Varying Mutation Rate with Replication Timing Correction

$$\mathbf{x_i}|\mathbf{p_i} : Binomial(\mathbf{n_i}, \mathbf{p_i})$$

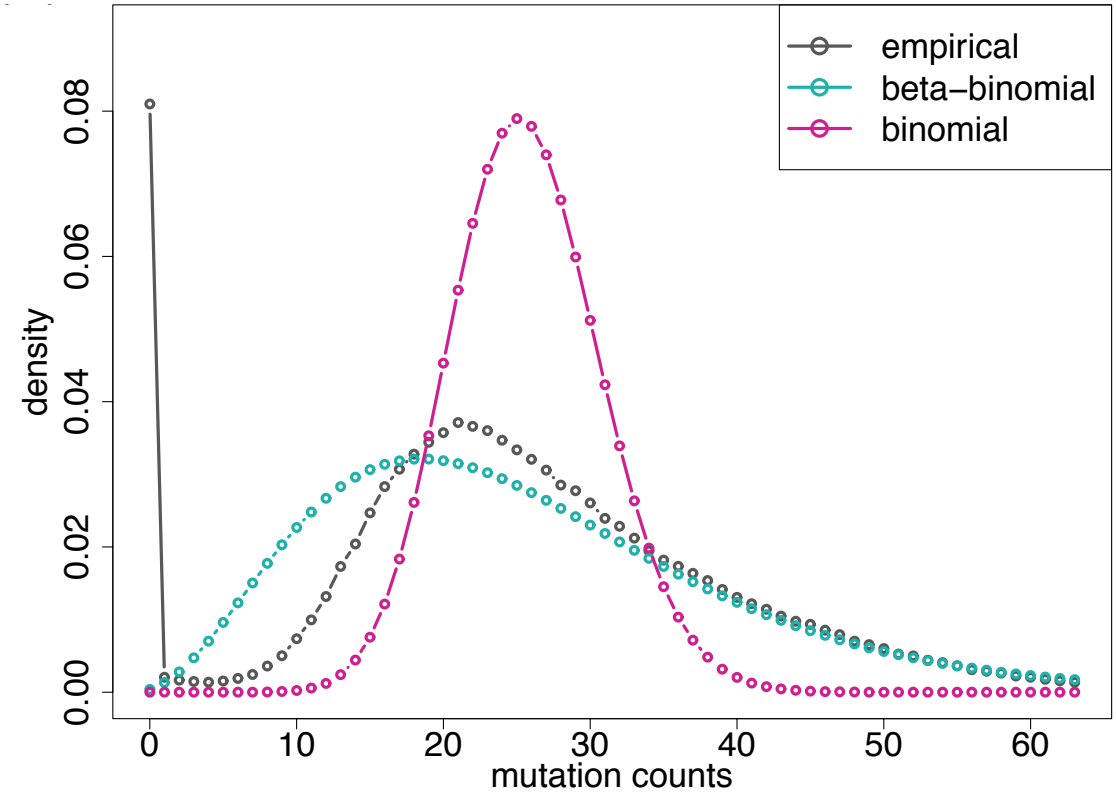
$$\mathbf{p_i} : Beta(\mu|\mathbf{R}, \sigma|\mathbf{R})$$

$$\mu|\mathbf{R}, \sigma|\mathbf{R} : \text{constant within the same } \mathbf{R} \text{ bin}$$

[Lochovsky et al. *NAR* ('15)]

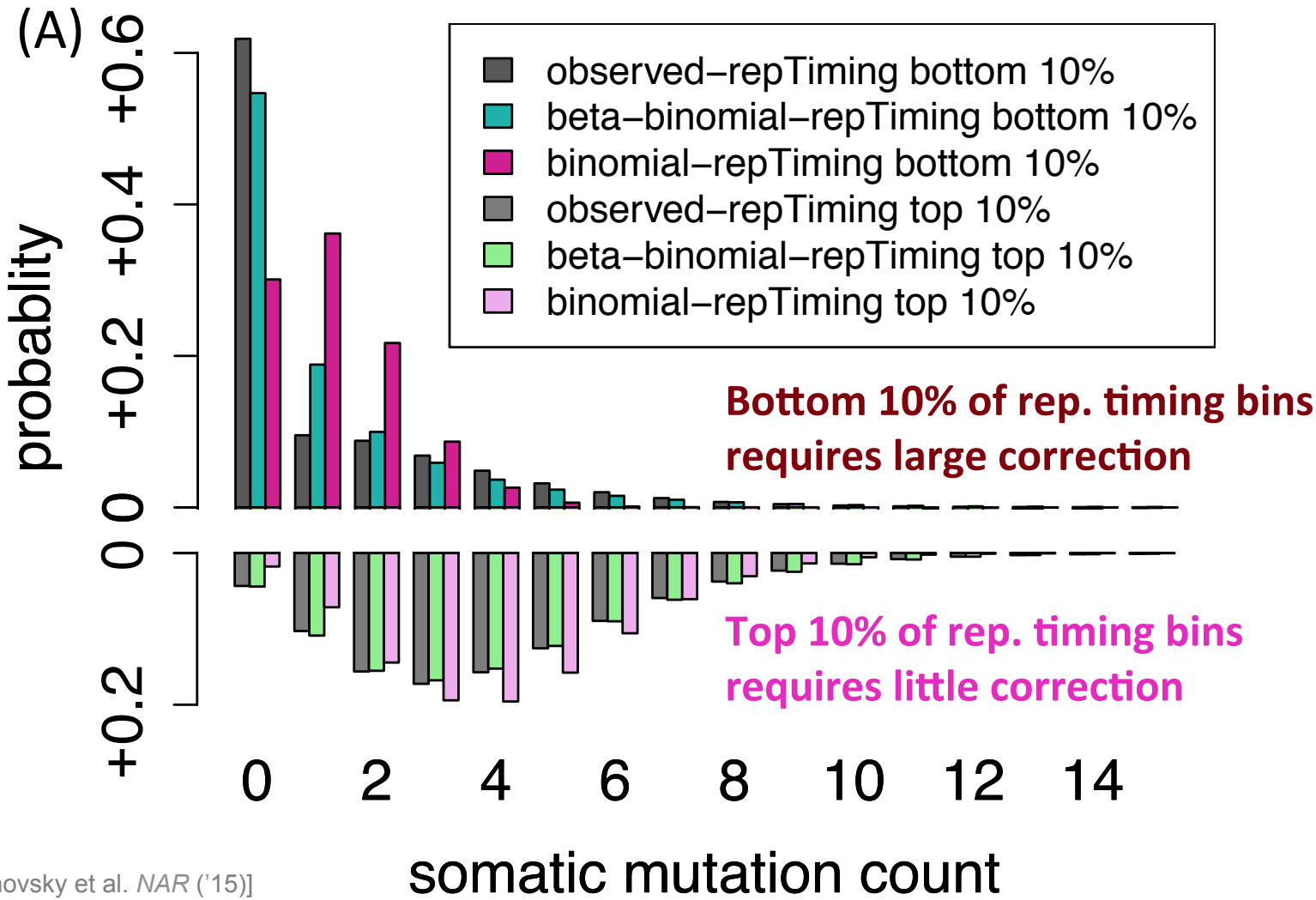
LARVA Model Comparison

- Comparison of mutation count frequency implied by the binomial model (model 1) and the beta-binomial model (model 2) relative to the empirical distribution
- The beta-binomial distribution is significantly better, especially for accurately modeling the over-dispersion of the empirical distribution



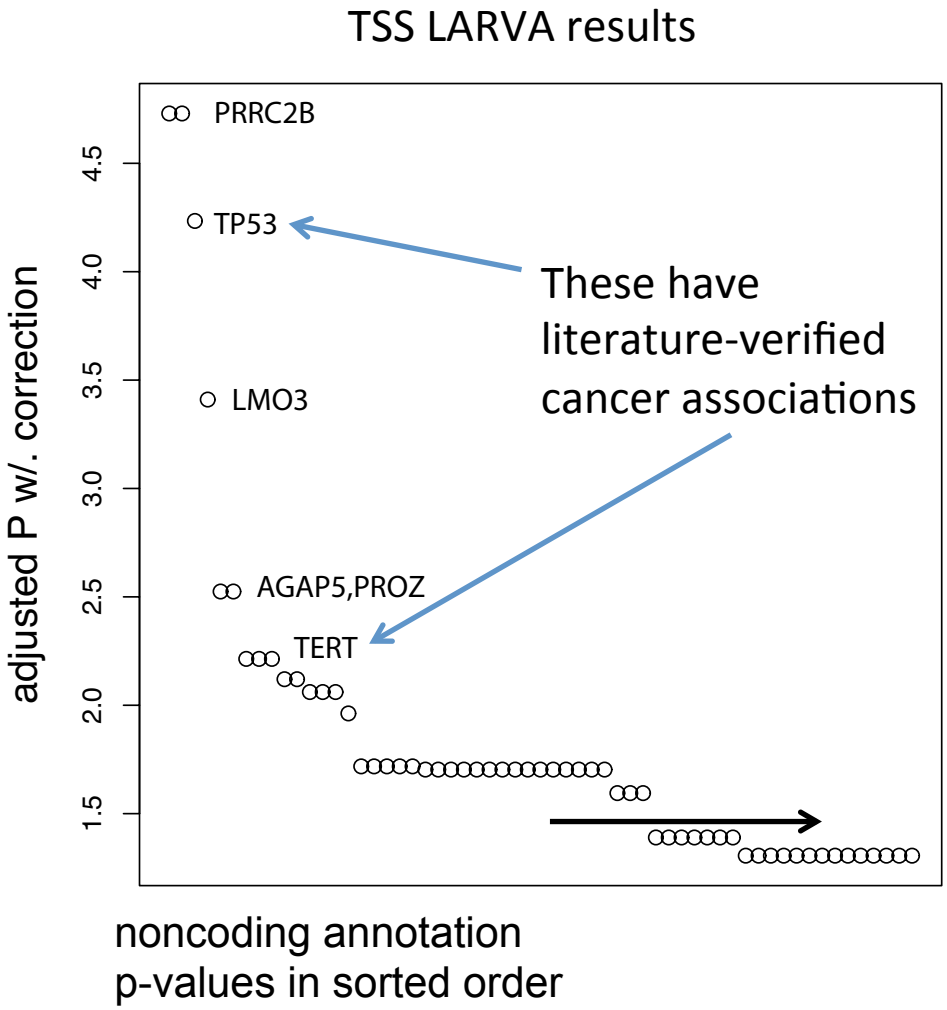
[Lochovsky et al. *NAR* ('15)]

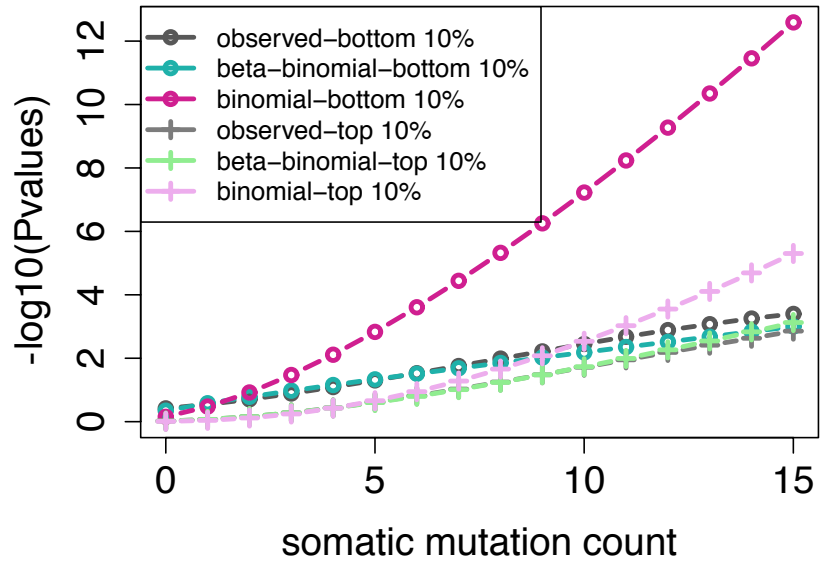
Adding DNA replication timing correction further improves the beta-binomial model

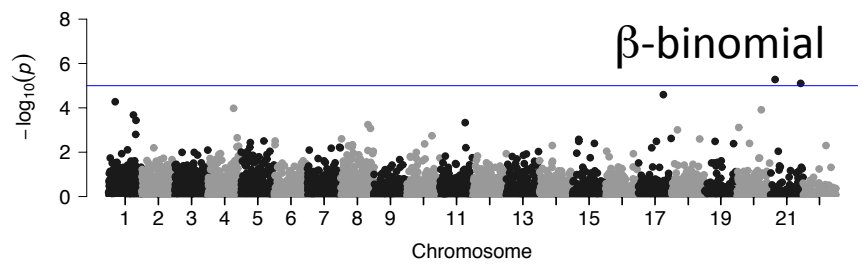


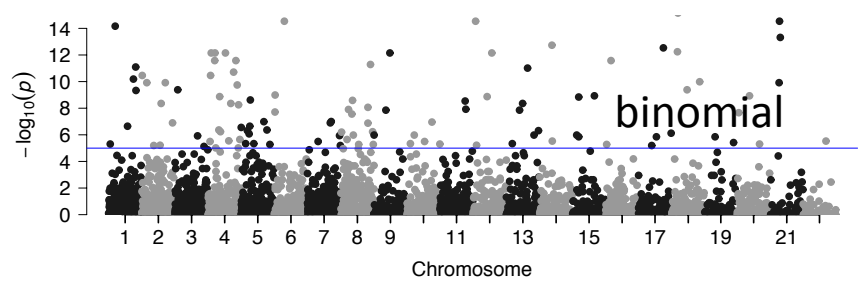
[Lochovsky et al. *NAR* ('15)]

LARVA Results





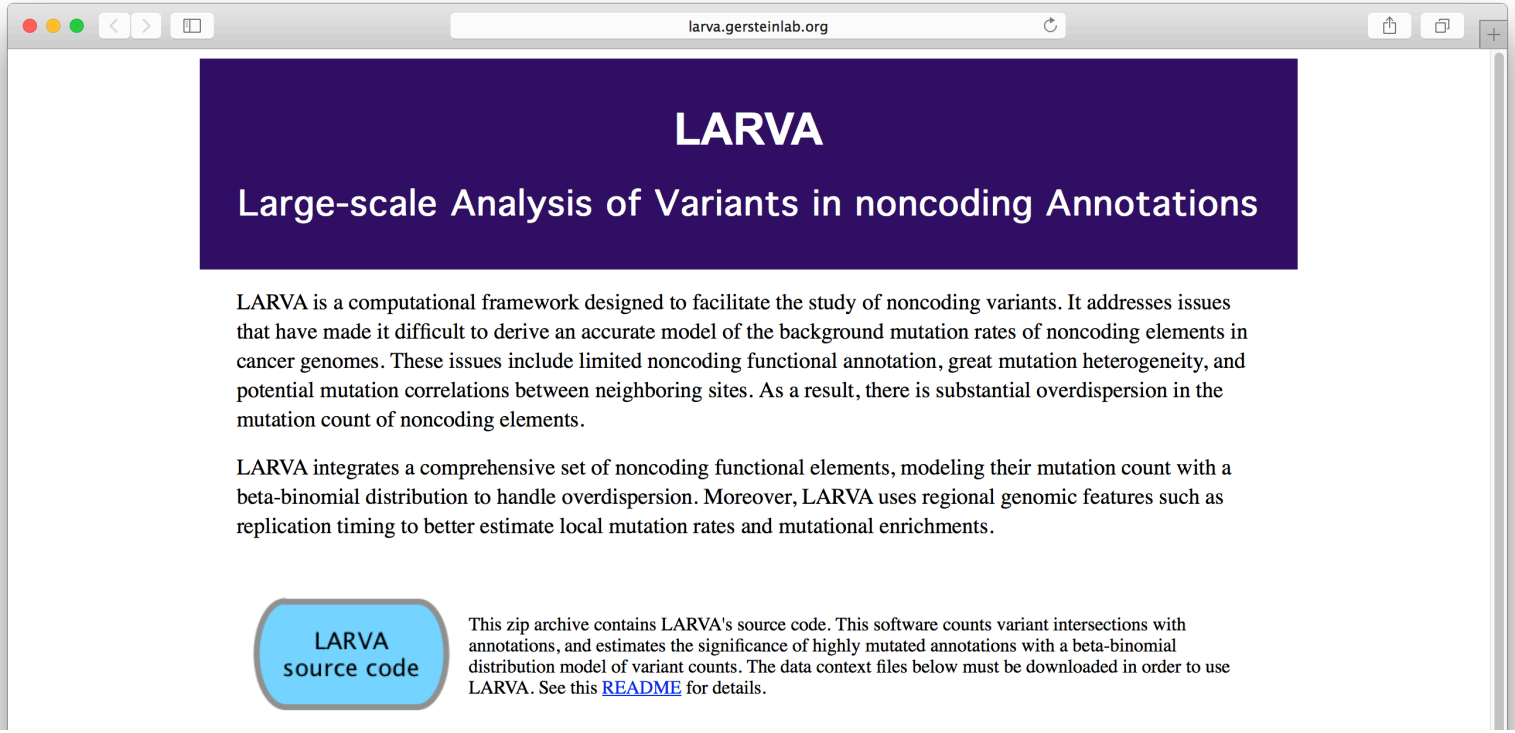




[Lochovsky et al. *NAR* ('15)]

LARVA Implementation

- http://larva.gersteinlab.org/
- Freely downloadable C++ program
  - Verified compilation and correct execution on Linux
- A Docker image is also available to download
  - Runs on any operating system supported by Docker
- Running time on transcription factor binding sites (a worst case input size) is ~80 min
  - Running time scales linearly with the number of annotations in the input



Acknowledgements

- **LARVA**.gersteinlab.org
  - L **Lochovsky***, J **Zhang***, Y Fu, E Khurana
- **FunSeq2**.gersteinlab.org
  - Y **Fu**, Z Liu, S Lou, J Bedford, X Mu, K Yip, E Khurana

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