CANCER GENOMICS
Lecture 3: Probabilistic Methods for Profiling Copy Number Alterations

GENOME 541
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CURES START HERE®

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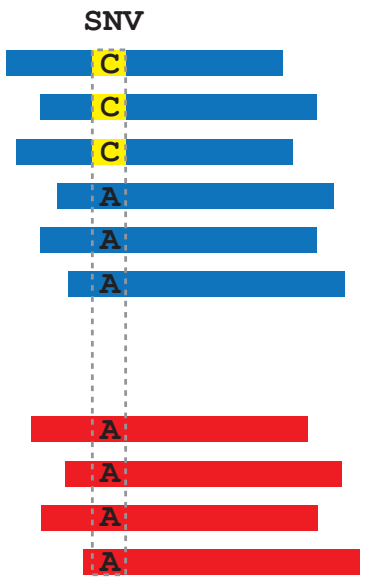
Outline

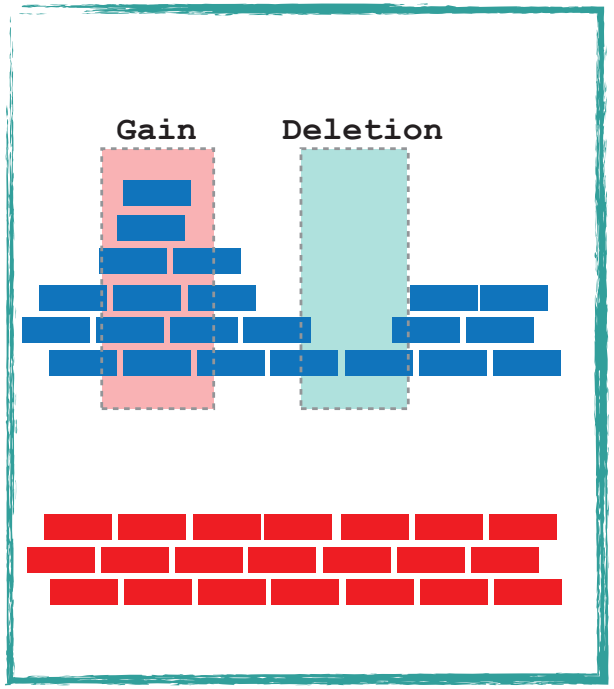
1. Detecting Copy Number Alterations in Cancer Genomes
    - Predicting copy number features from sequence data
    - Copy number analysis workflow
    - Data normalization
2. Continuous Hidden Markov Model (HMM)
    - Graphical model representation
    - Components of a continuous HMM
    - Inference & parameter estimation using expectation-maximization (EM)
3. Copy Number Profiling using a Hidden Markov Model
    - Probabilistic model for copy number analysis
    - Predicting copy number segments using the Viterbi algorithm

1. Detecting Copy Number Alterations in Cancer Genomes

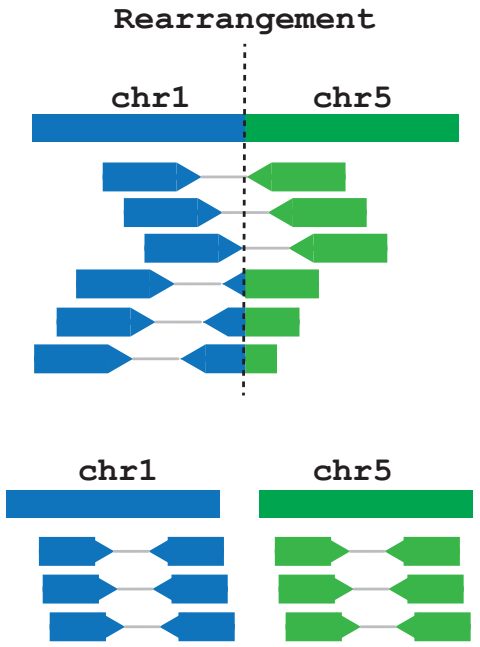
Mutations (SNV, INDEL)



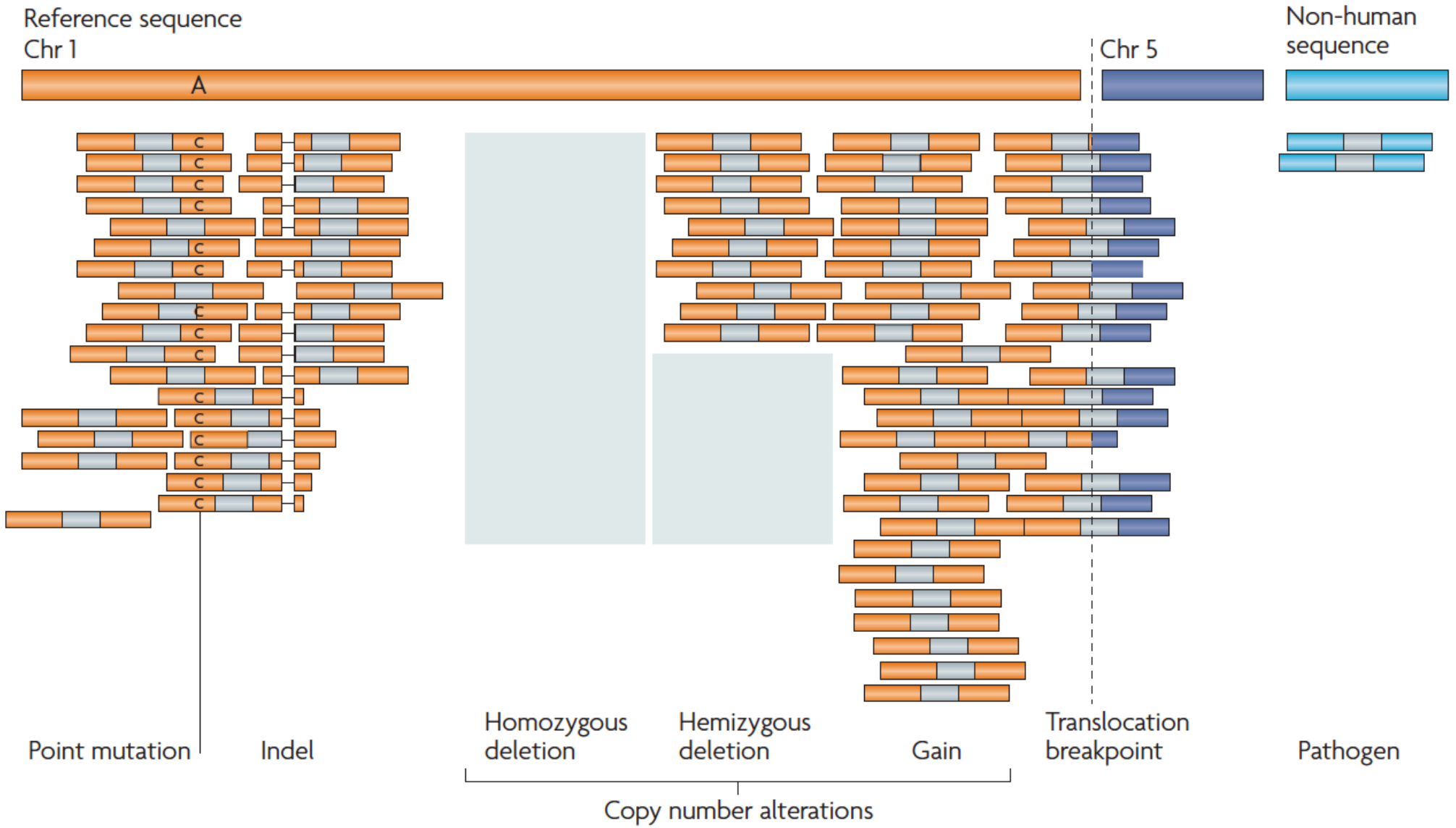
Copy Number Alterations



Structural Variants



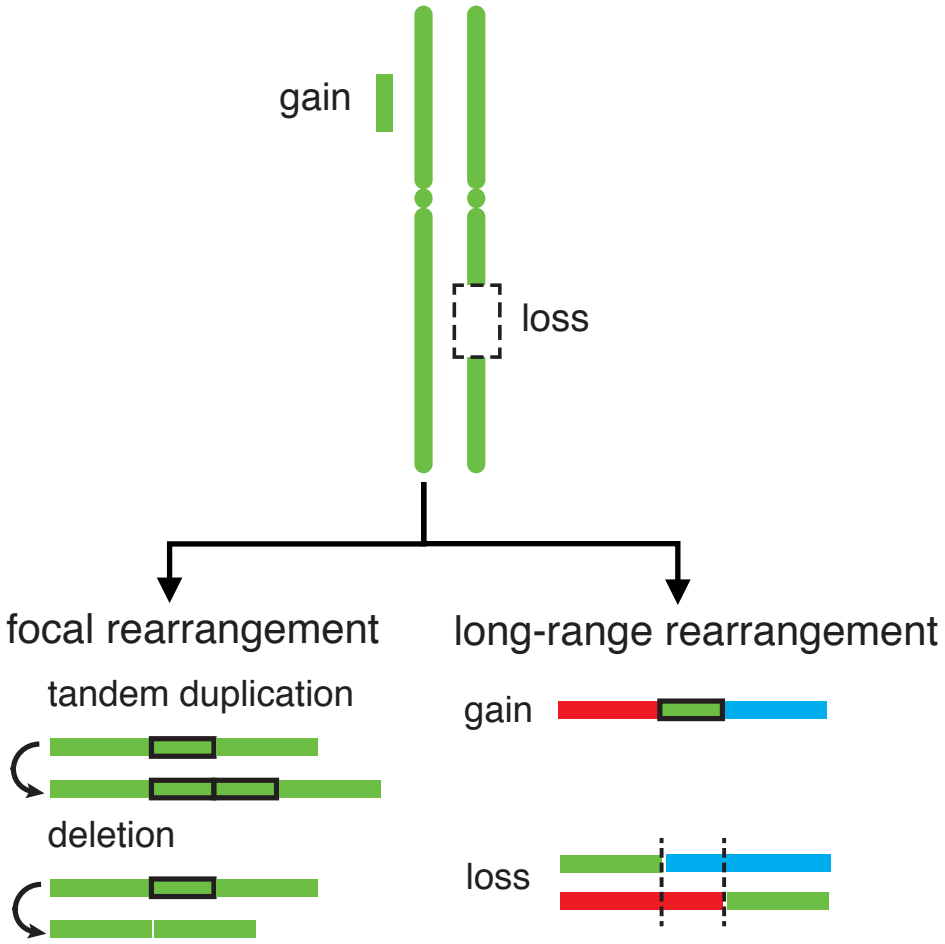
Predicting genomic alterations from sequence data



Meyerson, Gabriel & Getz. *Nature Review Genetics* **11**:685-96 (2010)

Predicting genomic alterations from sequence data

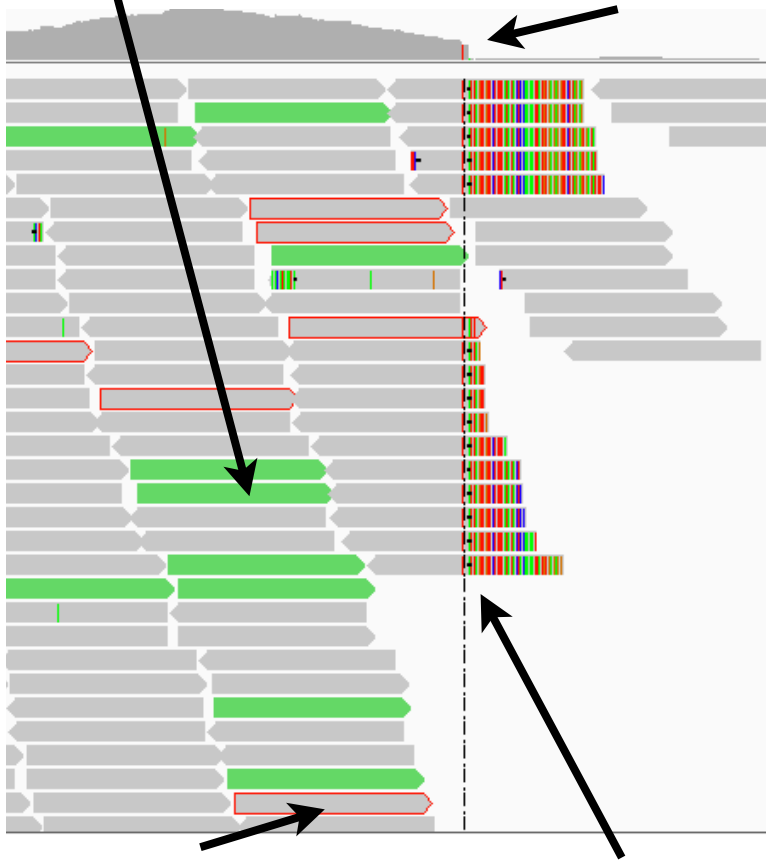
Copy number alterations
(amplitude/dosage)



Structural rearrangements
(location/configuration)

"discordant read pair"
read pairs with aberrant inferred fragment length

"copy number change"
abrupt change in read coverage



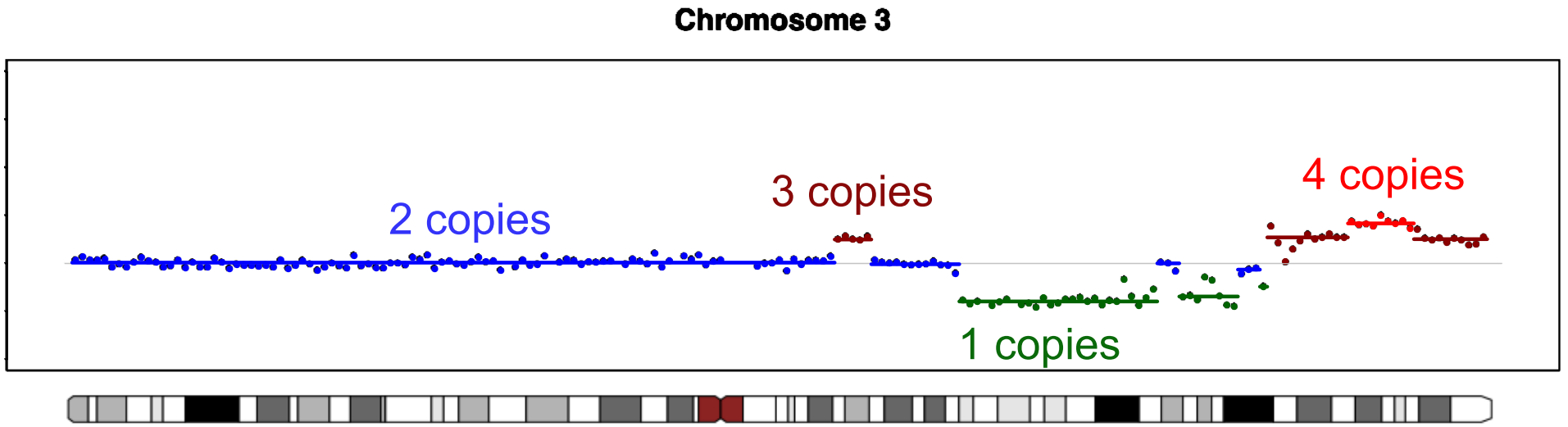
pair-mates unmapped

"split read"
split alignments

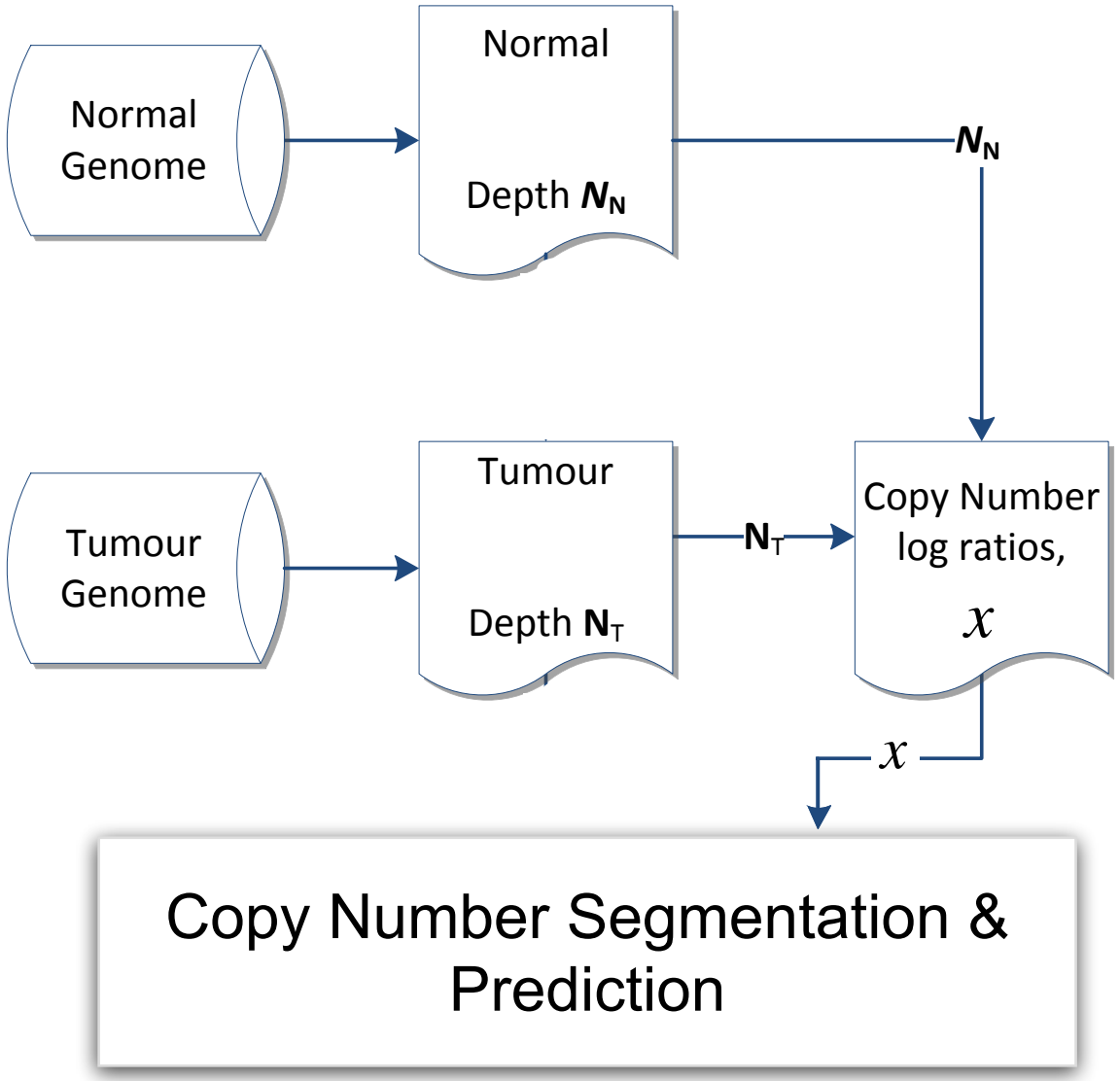
Zhang and Pellman. *CSH Symp Quant Biol.* **80**:117-37 (2016)

Tumor DNA Copy Number Analysis Strategy

1. Using sequencing read coverage as a measure for DNA copy number
2. Identifying segments of coverage changes
3. Predicting the number of copies for each segment

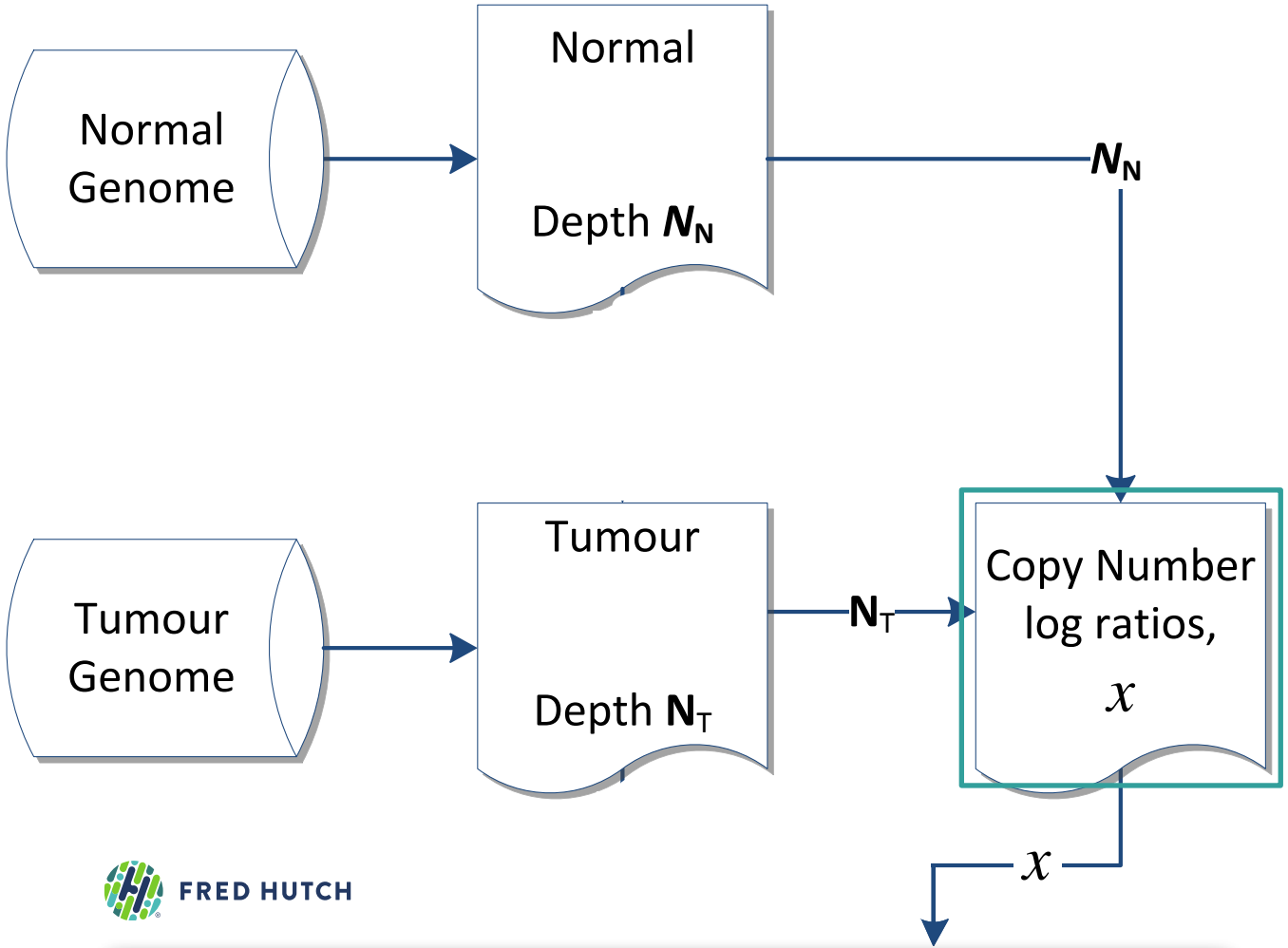


Cancer Genome Copy Number Analysis Workflow



Copy Number Analysis Workflow: Normalization

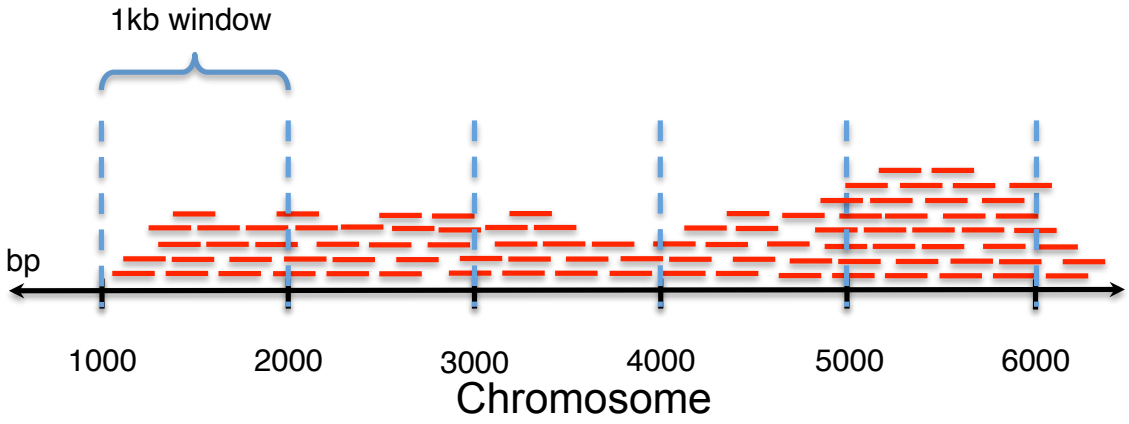
1. Correct GC/mappability biases for tumor read depth



$$N^{normal} = normal\ read\ depth$$

$$N^{tumor} = tumor\ read\ depth$$

$$\frac{N^{tumor}}{N^{normal}} = copyratio$$



Copy Number Analysis Workflow: GC content bias

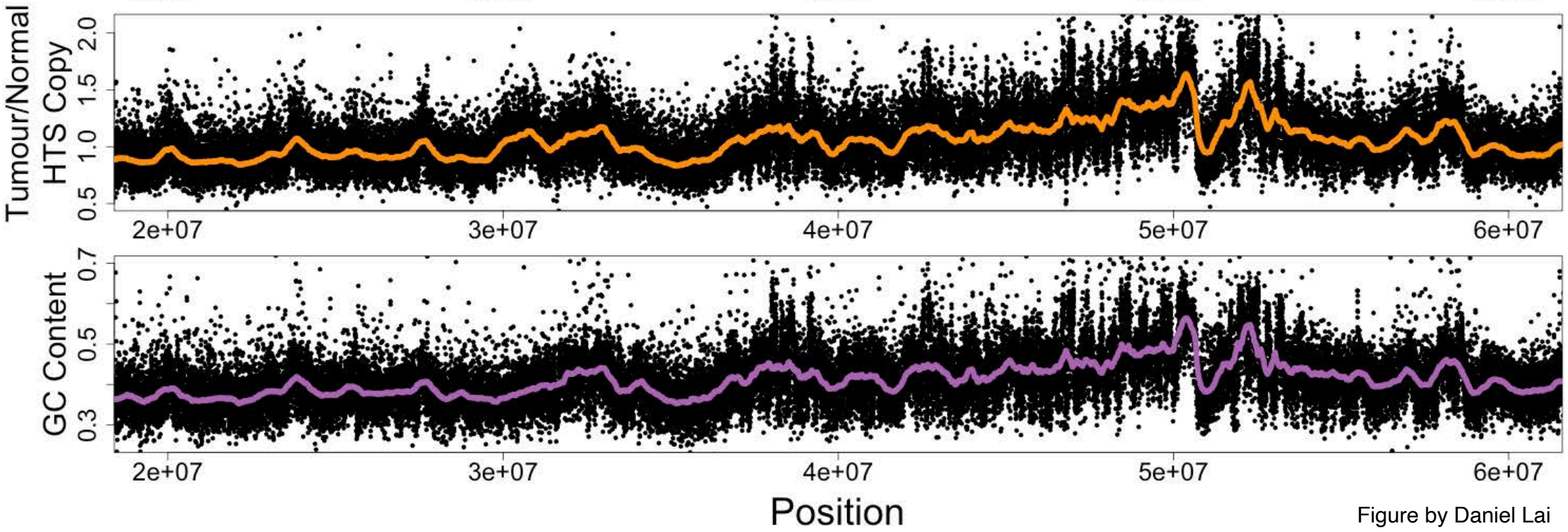
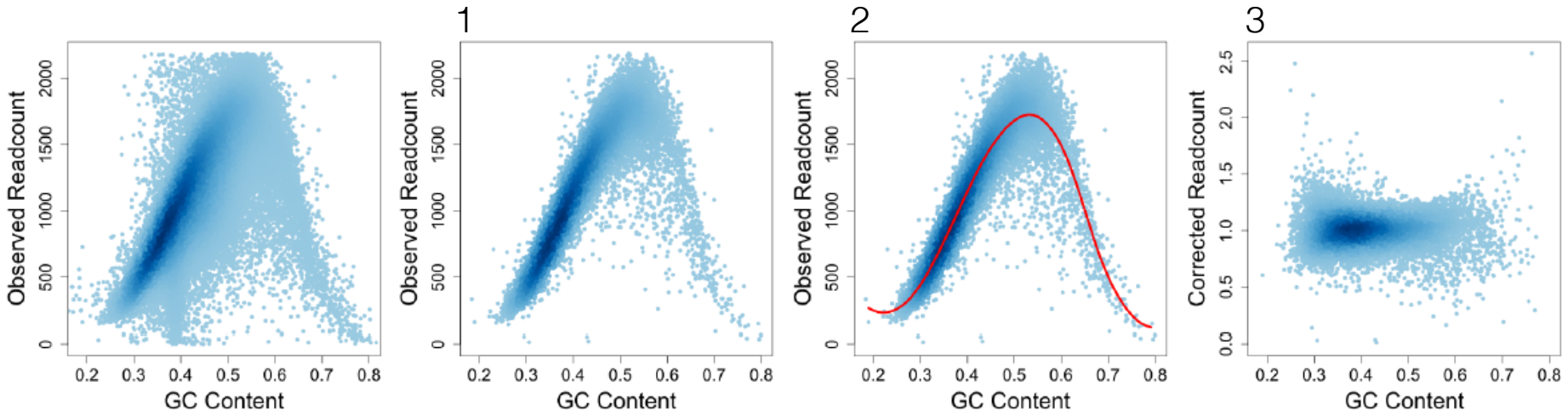


Figure by Daniel Lai

Benjamini and Speed. *Nucleic Acids Research* **40**:e72-86 (2012)
Boeva et al. *Bioinformatics* **29**(3):423-5 (2012)
Ha et al. *Genome Research* **22**:1995-2007 (2012).
Adalsteinsson*, Ha* Freeman* et al. *Nature Communications* **8**:1324 (2017)

Copy Number Analysis Workflow: GC correction (1)

1. Randomly select 50k bins and filter outliers (bottom & top 1%)
2. Fit `loess()` curve
   - local nonlinear regression
   - smoothing parameter (bandwidth): amount of local data to fit
3. $$corrected\ read\ count = \frac{observed\ read\ count\ (blue\ dot)}{expected\ read\ count\ (red\ line)}$$
   - relative differences between observed and predicted read counts



https://github.com/shahcompbio/hmmcopy_utils
https://github.com/GavinHaLab/ichorCNA

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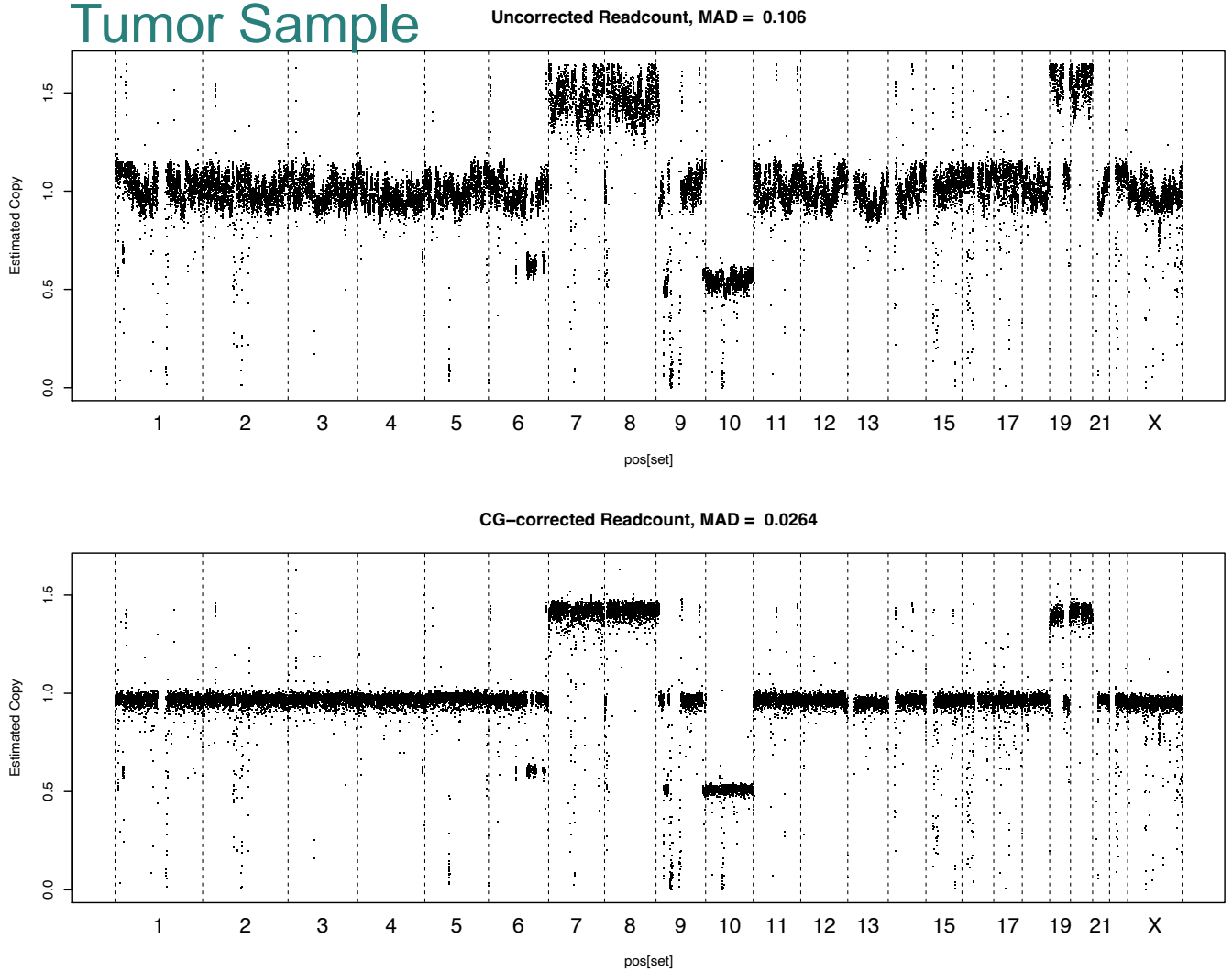
Boeva et al. *Bioinformatics* **29**(3):423-5 (2012)
Ha et al. *Genome Research* **22**:1995-2007 (2012).
Adalsteinsson*, Ha* Freeman* et al. *Nature Communications* **8**:1324 (2017)

Copy Number Analysis Workflow: GC correction (2)

Tumor Sample



Un-corrected read counts

GC-corrected read counts

https://github.com/shahcompbio/hmmcopy_utils
https://github.com/GavinHaLab/ichorCNA

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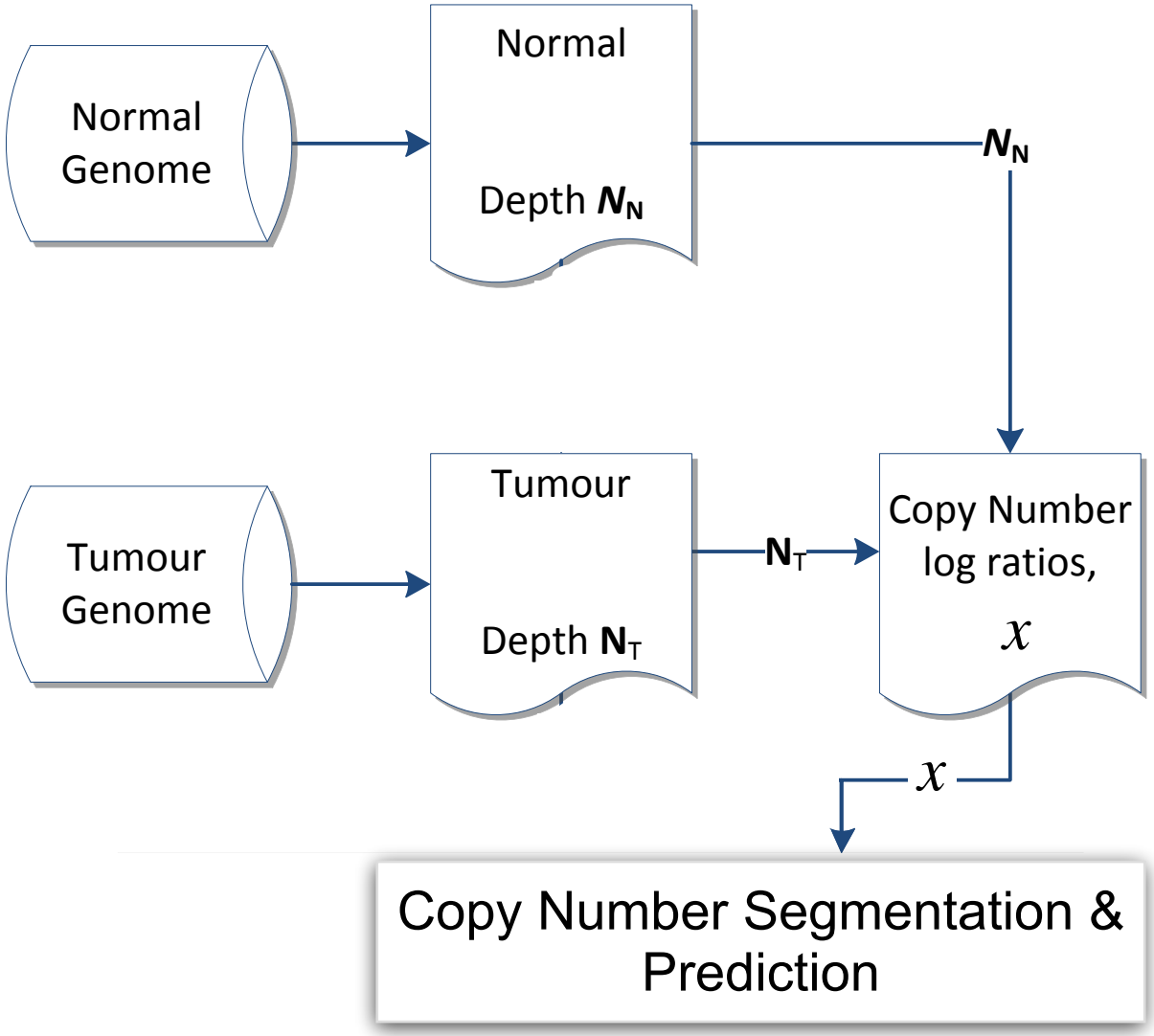
Ha et al. *Genome Research* **22**:1995-2007 (2012).
Adalsteinsson*, Ha* Freeman* et al. *Nature Communications* **8**:1324 (2017)

Copy Number Analysis Workflow: Normalization



1. **Correct GC/mappability biases for tumor read depth**

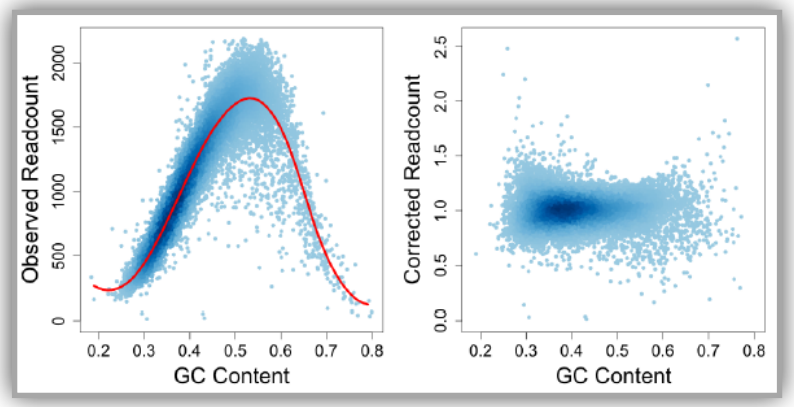
$$N^{normal} = normal\ read\ depth$$
$$N^{tumor} = tumor\ read\ depth$$
$$\hat{N}^{normal} = corrected\ normal\ read\ depth$$
$$\hat{N}^{tumor} = corrected\ tumor\ read\ depth$$
$$\log_2\left(\frac{\hat{N}^{tumor}}{\hat{N}^{normal}}\right) = corrected\ log\ ratio$$

2. **Perform segmentation and copy number prediction**

Input Sequencing Data for Copy Number Analysis

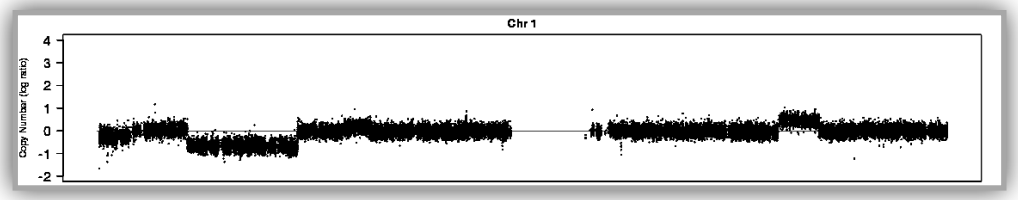
Input Data After Normalization

- GC-content bias correction applied to separately for
  - tumor sample reads $N_{1:T}^{Tumor}$
  - normal sample reads $N_{1:T}^{Normal}$



- Normalize tumor corrected read counts $\hat{N}_i^{Tumor}$ with normal corrected read counts $\hat{N}_i^{Normal}$ to obtain the log ratio for bin $t \in \{1,\ldots,T\}$

$$x_t = \log_2\left(\frac{\hat{N}_t^{Tumor}}{\hat{N}_t^{Normal}}\right)$$



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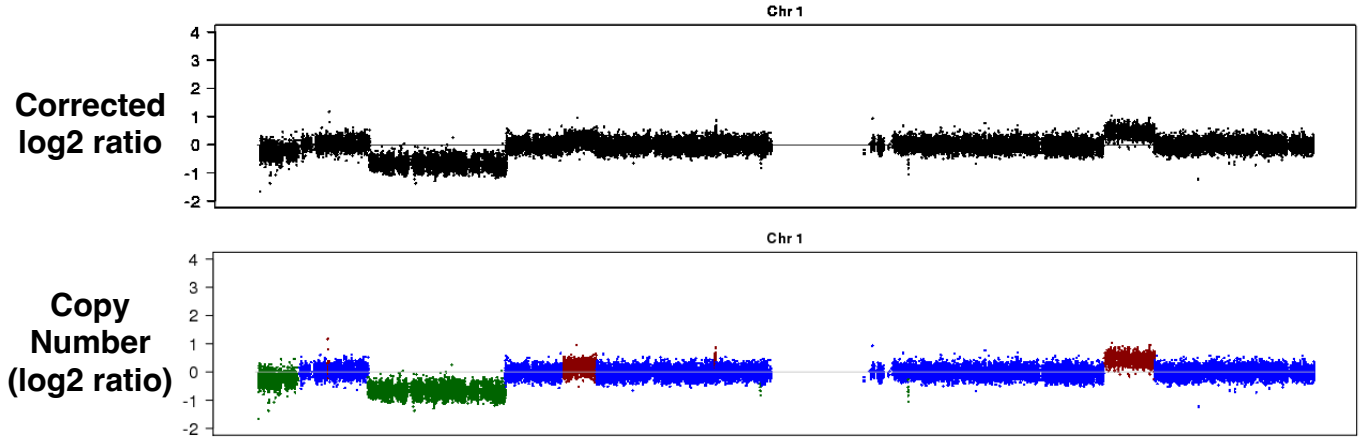
Boeva et al. *Bioinformatics* **29**(3):423-5 (2012)
Ha et al. *Genome Research* **22**:1995-2007 (2012).
Adalsteinsson*, Ha* Freeman* et al. *Nature Communications* **8**:1324 (2017)

Copy Number Segmentation and Prediction



Data normalization

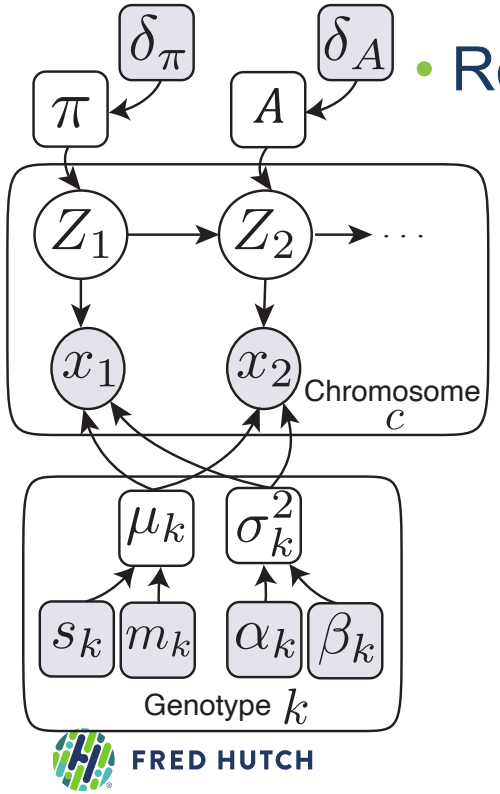
Copy Number Segmentation

- What are the genomic segments of copy number alterations?
- What is the copy number value for each segment?
- How do we account for variability/noise in the data?

Continuous hidden Markov model (HMM)

2. Continuous hidden Markov model

- Hidden Markov Models vs Mixture Models
- Components of a Continuous HMM
- Inference and Parameter Learning using EM
- References:



- **HMMcopy** - Ha et al. *Genome Research* **22**:1995-2007 (2012).
- **ichorCNA** - Adalsteinsson*, Ha* Freeman* et al. *Nature Communications* **8**:1324 (2017).
- **TitanCNA** - Ha et al. TITAN: inference of copy number architectures in clonal cell populations from tumor whole-genome sequencing data. *Genome Research* **24**:1881-1893 (2014).
- Murphy, K. (2012). Machine Learning: A Probabilistic Perspective. MIT Press. ISBN: 9780262018029
- Bishop, C. M. (2006). Pattern Recognition and Machine Learning (Information Science and Statistics). Springer. ISBN: 0387310738

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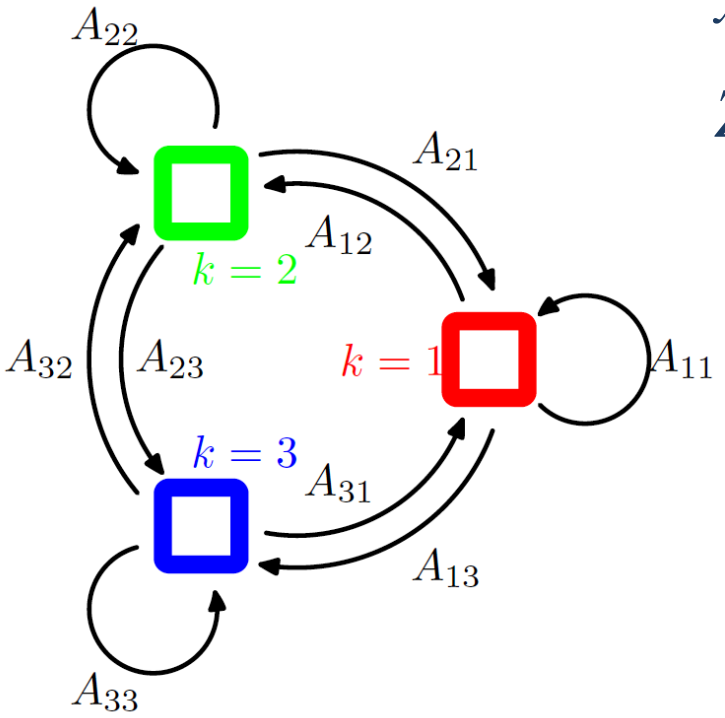
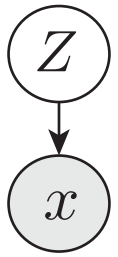
Probabilistic Graphical Model for HMMs



Transition Diagram

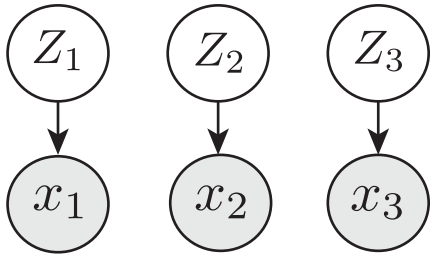
$x_{1:T}$ observed data

$Z_{1:T}$ latent variables



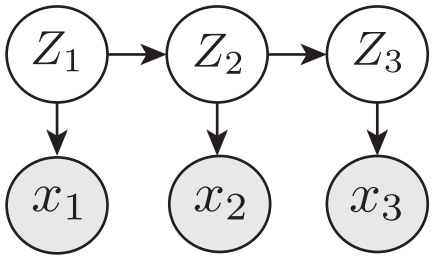
$$p(x, Z) = p(Z)p(x \mid Z)$$

Mixture Model



$$p(x_{1:3}, Z_{1:3}) = p(Z_{1:3})p(x_{1:3} \mid Z_{1:3}) = \left[\prod_{t=1}^{3} p(Z_t)\right]\left[\prod_{t=1}^{3} p(x_t \mid Z_t)\right]$$

Hidden Markov Model



1. Markov Property $Z_3 \perp\!\!\!\perp Z_1 \mid Z_2$
2. Conditional independence of observations $x_3 \perp\!\!\!\perp x_{1:2} \mid Z_3$

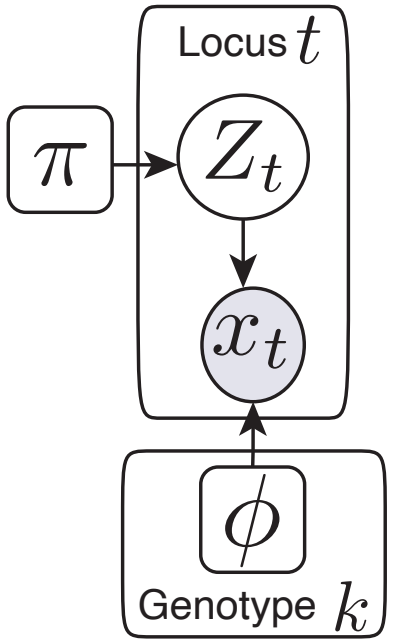
$$p(Z_1)\left[p(Z_2 \mid Z_1)p(Z_3 \mid Z_2)\right]\left[p(x_1 \mid Z_1)p(x_2 \mid Z_2)p(x_3 \mid Z_3)\right] = p(Z_1)\left[\prod_{t=2}^{3} p(Z_t \mid Z_{t-1})\right]\left[\prod_{t=1}^{3} p(x_t \mid Z_t)\right]$$

Chapter 17 in Murphy (2012). Machine Learning: A Probabilistic Perspective. MIT Press
Chapter 13 in Bishop (2006). Pattern Recognition and Machine Learning. Springer

From Mixture Models to Hidden Markov Models

- Mixture model for iid data is a special case of the HMM

Mixture Model



$$p(x_{1:T}, Z_{1:T}) = p(Z_{1:T})p(x_{1:T}|Z_{1:T})$$

Joint Probability Distribution (Complete data likelihood)

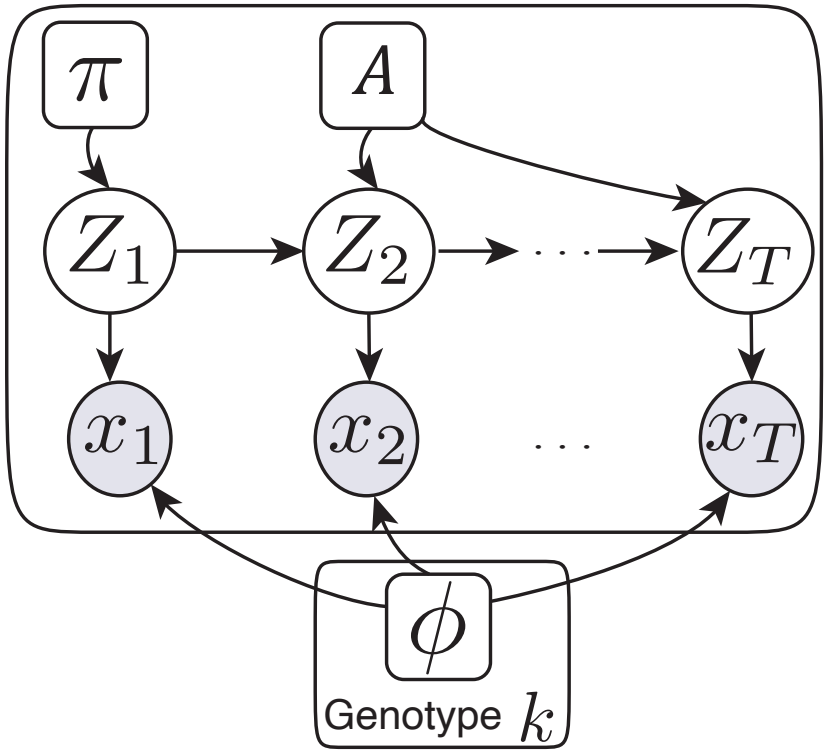
$x_{1:T}$ observed data

$Z_{1:T}$ latent variables

$\boldsymbol{\pi}$ mixture weights

$\boldsymbol{\phi}$ observation parameters

Hidden Markov Model



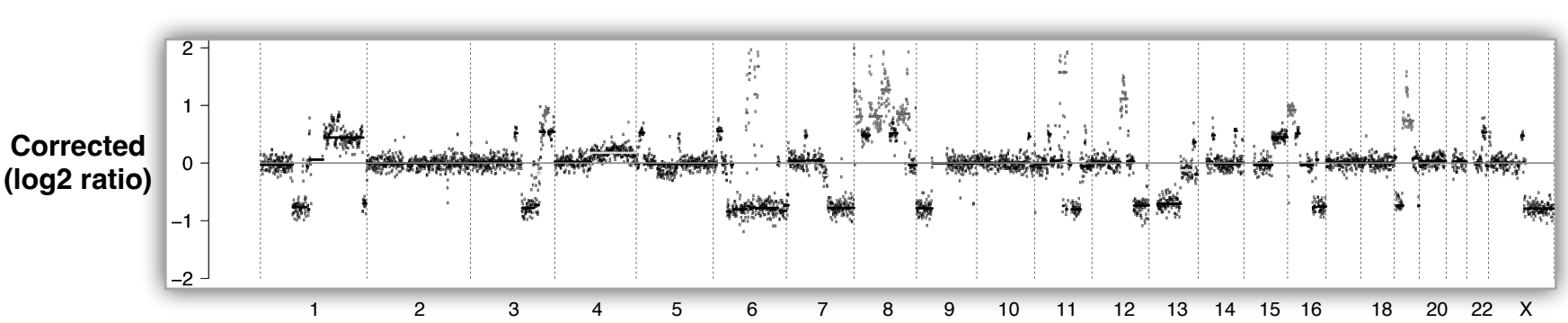
$$p(x_{1:T}, Z_{1:T}|\boldsymbol{\theta}) = \left[\prod_{t=1}^{T} p(Z_t|\boldsymbol{\pi})\right] \prod_{t=1}^{T} p(x_t|Z_t, \boldsymbol{\phi})$$

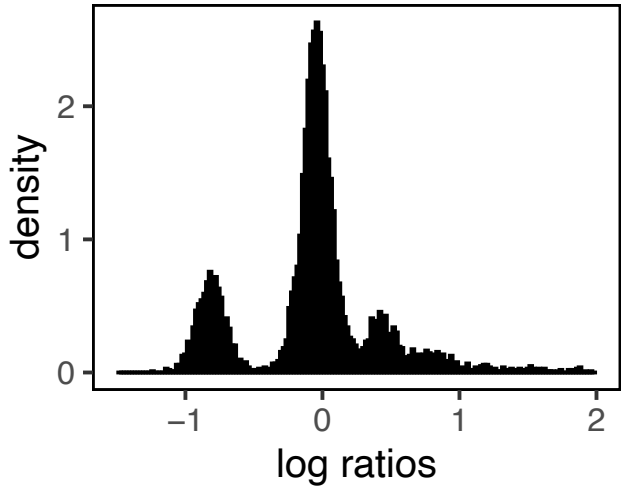
$$\boldsymbol{\theta} = \{\boldsymbol{\pi}, \boldsymbol{\phi}\}$$

$$p(x_{1:T}, Z_{1:T}|\boldsymbol{\theta}) = \left[p(Z_1|\boldsymbol{\pi}) \prod_{t=2}^{T} p(Z_t|Z_{t-1}, \boldsymbol{A})\right] \prod_{t=1}^{T} p(x_t|Z_t, \boldsymbol{\phi})$$

$$\boldsymbol{\theta} = \{\boldsymbol{\pi}, \boldsymbol{\phi}, \boldsymbol{A}\}$$

Gaussian Mixture Model for Log Ratio Data





The ratios $\frac{\hat{r}_t^{Tumor}}{\hat{r}_t^{Normal}}$, for all t loci are log-normal distributed, so the log ratios $x_{1:T}$ follow a normal distribution.

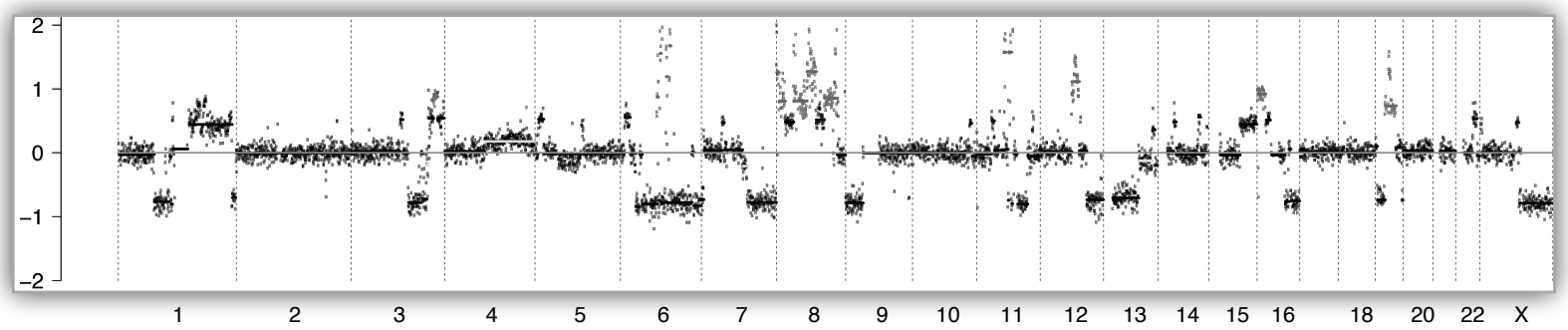
The Gaussian Distribution

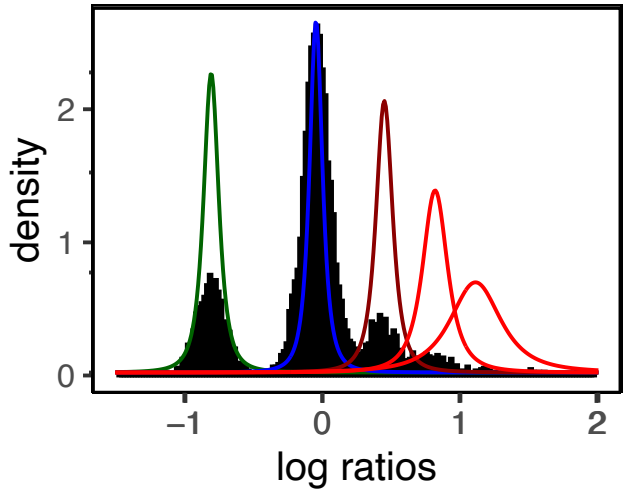
Let X be a continuous measurement with mean μ and variance σ^2, then X has a Gaussian distribution,

$X \sim \mathcal{N}(\mu, \sigma^2)$ or $p(X = x) = \mathcal{N}(x \mid \mu, \sigma^2)$ where

$$\mathcal{N}(x \mid \mu, \sigma^2) = \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{1}{2\sigma^2}(x-\mu)^2}$$

Gaussian Mixture Model for Log Ratio Data





The ratios $\frac{\hat{r}_t^{Tumor}}{\hat{r}_t^{Normal}}$, for all t loci are log-normal distributed, so the log ratios $x_{1:T}$ follow a normal distribution.

The Gaussian Mixture Model

Define a likelihood for a ***K-component mixture of Gaussians*** with means $\boldsymbol{\mu} = \{\mu_1, \ldots, \mu_K\}$ and variance $\boldsymbol{\sigma^2} = \{\sigma_1^2, \ldots, \sigma_K^2\}$, where the observation model is a conditional Gaussian

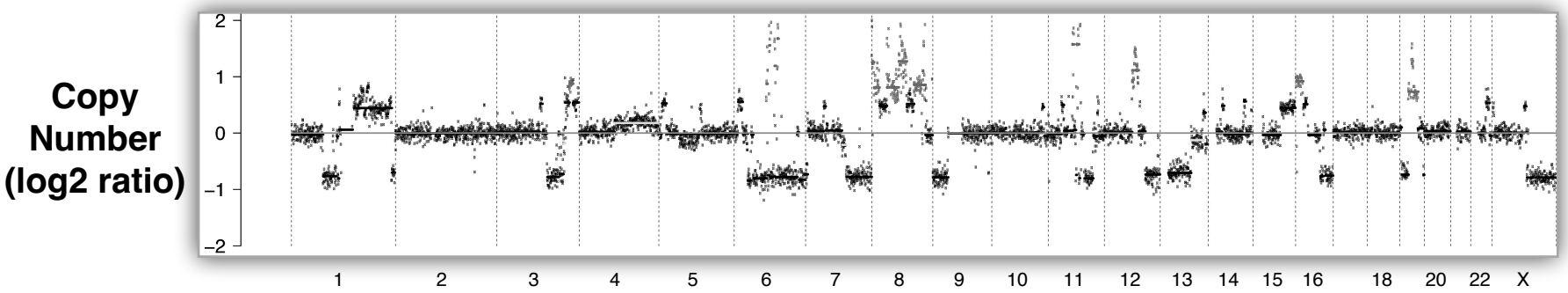
$$p(x_t \mid Z_t = k, \boldsymbol{\mu}, \boldsymbol{\sigma^2}) = \mathcal{N}(x_t \mid \mu_k, \sigma_k^2)$$

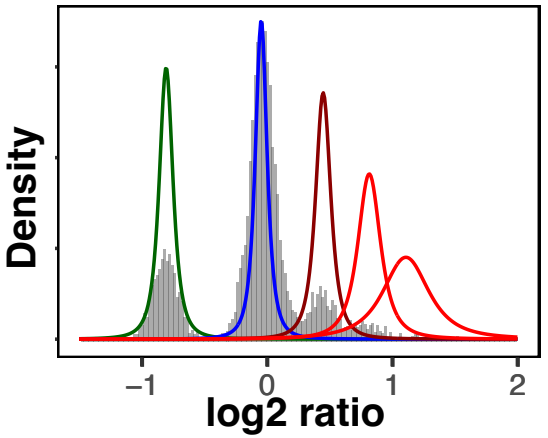
Rationale for Estimating Likelihood Parameters

Why are the data multi-modal?

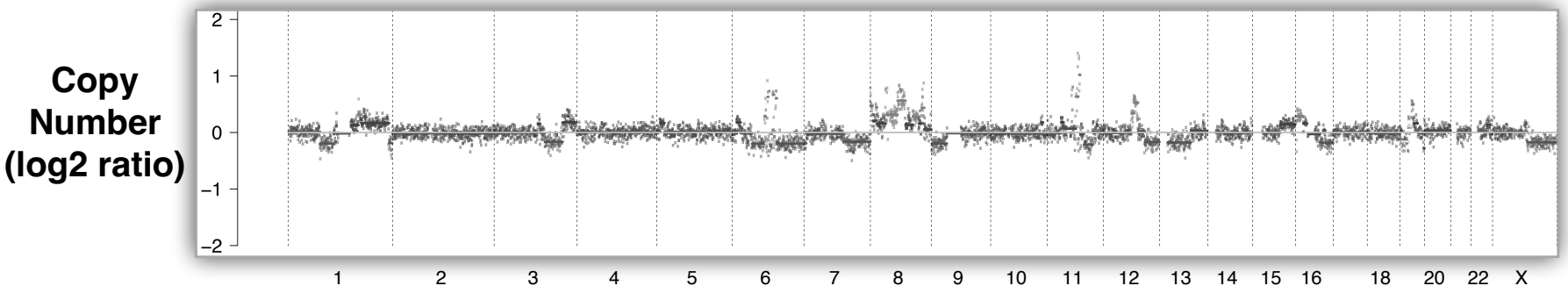
Why should we estimate the mixture distribution parameters?

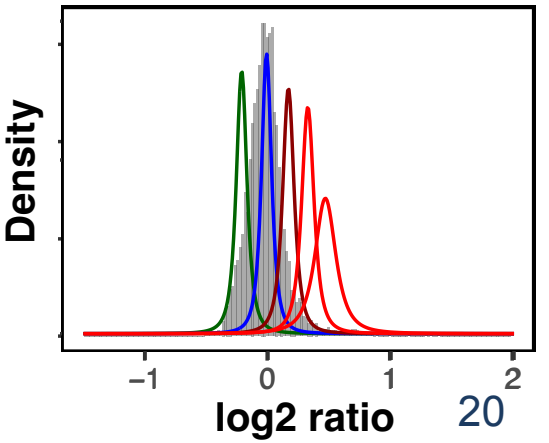
Patient 288 - Time 1





Patient 288 - Time 2





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Components of a continuous HMM

Input Data: log ratios

There are T different data points with continuous values $\boldsymbol{x} = \{x_1, \ldots, x_T\}$.

Latent State Model

- The latent variables $\boldsymbol{Z} = \{Z_1, \ldots, Z_T\}$ can be assigned values from a set of K discrete states with probability

Initial state distribution

- The probabilities of the states for the first latent variable Z_1 is the parameter $\boldsymbol{\pi} = \{\pi_1, \ldots, \pi_K\}$
- $\boldsymbol{\pi}$ follows a prior distribution $p(\pi_k \,|\, \delta_k) = Dir(\pi_k \,|\, \delta_k)$

Transition Model (homogenous HMM)

- The conditional distribution between adjacent data i and j corresponds to a table $\boldsymbol{A}$ of transition probabilities

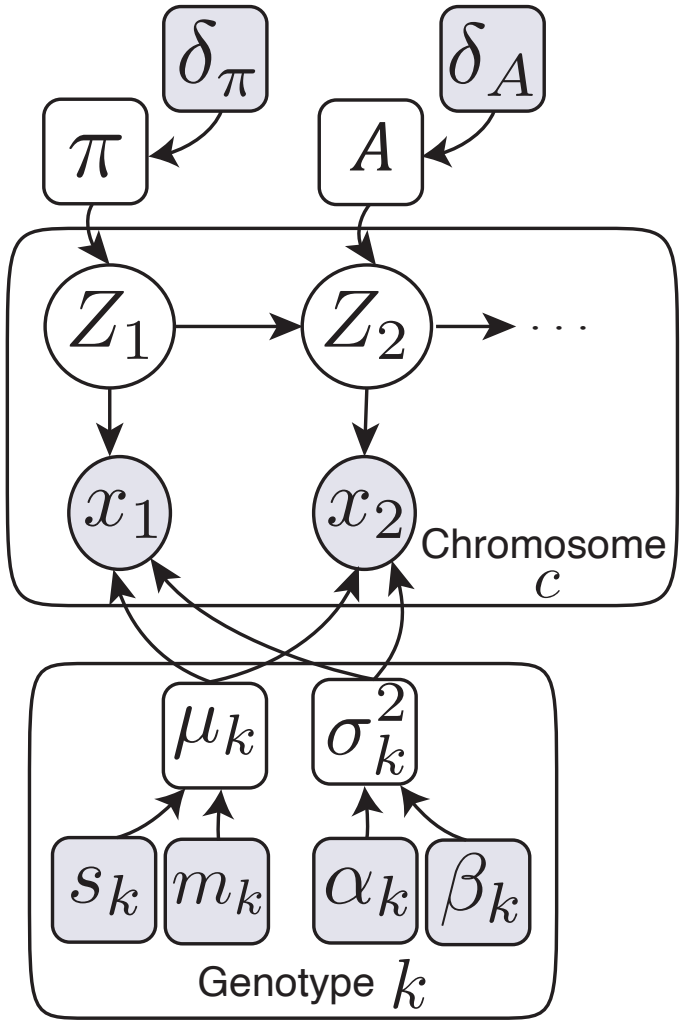
$$p(Z_t = j \,|\, Z_{t-1} = i) = A_{ij}$$

Emission Model (Continuous HMM)

- The emission is modeled using a mixture of Gaussians with the likelihood model

$$p(x_t \,|\, Z_t = k, \boldsymbol{\mu}, \boldsymbol{\sigma^2}) = \mathcal{N}(x_t \,|\, \mu_k, \sigma_k^2)$$

- $\boldsymbol{\mu}$ is modeled with a prior $p(\mu_k \,|\, m_k, s_k) = \mathcal{N}(\mu_k \,|\, m_k, s_k)$
- $\boldsymbol{\sigma^2}$ is modeled with prior $p(\sigma_k^2 \,|\, \alpha_k, \beta_k) = InvGamma(\sigma_k^2 \,|\, \alpha_k, \beta_k)$



Probabilistic Graphical Model

Chapter 17 in Murphy (2012). Machine Learning: A Probabilistic Perspective. MIT Press
Chapter 13 in Bishop (2006). Pattern Recognition and Machine Learning. Springer

Inference & parameter estimation using EM

Expectation-Maximization: Inference and parameter training

Initialize parameters: $\boldsymbol{\pi}, \boldsymbol{A}, \boldsymbol{\mu}$

E-Step: Inference using Forwards-Backwards Algorithm (Baum-Welch)

1. Compute "responsibilities" (Posterior of the latent states $\gamma(Z_{1:T})$)
   - State $Z_t = k$ is "responsible for generating observation x_t"
2. Compute "2-slice marginals" (Posterior of state transitions $\xi(Z_{t-1}, Z_t)$)
   - Expected number of transitions from state k to j

M-Step: Update parameters (learning)

1. Initial state distribution, $\boldsymbol{\pi}$
2. Transition probabilities, $\boldsymbol{A}$
3. Emission likelihood parameters, $\boldsymbol{\mu}$

Iterate between E-Step and M-Step, check when log posterior likelihood, $\log \mathbb{P}$, stops increasing.

Inference & parameter estimation using EM (E-Step)

E-Step: Forwards-backwards Algorithm (Baum-Welch; Sum-Product)

- Forward, $\alpha(\mathbf{Z}_t)$: joint prob. of observing all *past* data up to time t when given Z_t
- Backward, $\beta(\mathbf{Z}_t)$: conditional prob. of all *future* data from time $t+1$ to T when given Z_t

Forward Probabilities ($T \times K$) - Past

$$\alpha(Z_t = k) = \mathcal{N}(x_t \,|\, \mu_k, \sigma_k^2) \sum_{j=1}^{K} \left\{ A_{jk} \alpha(Z_{t-1} = j) \right\}$$

Backward Probabilities ($T \times K$) - Future

$$\beta(Z_t = k) = \sum_{j=1}^{K} \left\{ \mathcal{N}(x_{t+1} \,|\, \mu_j, \sigma_j^2) A_{kj} \beta(Z_{t+1} = j) \right\}$$

See extra slides for more details

Chapter 13 in Bishop (2006). Pattern Recognition and Machine Learning. Springer

Chapter 17 in Murphy (2012). Machine Learning: A Probabilistic Perspective. MIT Press

Inference & parameter estimation using EM (E-Step)

E-Step: Compute Responsibilities & 2-Slice Marginals

- Responsibilities, $\gamma(Z_t = k)$: is the posterior on the latent states

$$\gamma(Z_t = k) = \frac{\alpha(Z_t = k)\beta(Z_t = k)}{p(\boldsymbol{x})}$$

Responsibilities
Matrix $K \times T$

- 2-Slice Marginals, $\xi(Z_{t-1} = k, Z_t = j)$: is the expected number of transitions between k to j

$$\xi(Z_{t-1} = k, Z_t = j) = \frac{\alpha(Z_{t-1} = k)A_{kj}\mathcal{N}(x_t \,|\, \mu_j, \sigma_j^2)\beta(Z_t = j)}{p(\boldsymbol{x})}$$

2 Slice Marginals
Matrix $K \times K \times (T-1)$

- The likelihood $p(\boldsymbol{x}) = p(\boldsymbol{x} \,|\, \boldsymbol{\mu}, \boldsymbol{\sigma^2}, \boldsymbol{\pi})$ is computed in the forwards recursion

$$\ell = \log p(\boldsymbol{x}) = \sum_{t=1}^{T} \log \left(\sum_{k=1}^{K} \alpha(Z_t = k) \right)$$

Log likelihood

See extra slides for more details

Chapter 13 in Bishop (2006). Pattern Recognition and Machine Learning. Springer

Chapter 17 in Murphy (2012). Machine Learning: A Probabilistic Perspective. MIT Press

Inference & parameter estimation using EM (M-Step)

Expected complete data log likelihood

Initial State Dist | Transition | Emission | Priors

$$Q = \sum_{k=1}^{K} \gamma(Z_1 = k) \log \pi_k + \sum_{t=2}^{T} \sum_{j=1}^{K} \sum_{k=1}^{K} \xi(Z_{t-1} = k, Z_t = j) \log A_{kj} + \sum_{t=1}^{T} \sum_{k=1}^{K} \gamma(Z_t = k) \log \mathcal{N}(x_t \mid \mu_k, \sigma_k^2) + priors$$

M-Step: update parameters, π, μ, σ^2

$$\hat{\pi}_k = \frac{\gamma(Z_1 = k) + \delta^{\pi}(k) - 1}{\sum_{j=1}^{K} \left\{ \gamma(Z_1 = j) + \delta^{\pi}(j) - 1 \right\}}$$

MAP for initial state distribution

$$\hat{\mu}_k = \frac{s_k \sum_{t=1}^{T} \gamma(Z_t = k) x_t + m\sigma_k^2}{s_k \sum_{t=1}^{T} \gamma(Z_t = k) + \sigma_k^2}$$

MAP for for Gaussian means

$$\hat{\sigma}_k^2 = \frac{\sum_{t=1}^{T} \gamma(Z_t = k) \left(x_t - \bar{x}_k \right)^2 + 2\beta_k}{\sum_{t=1}^{T} \gamma(Z_t = k) + 2(\alpha_k + 1)}$$

MAP for for Gaussian variance

Where $\bar{x} = \frac{\sum_{t=1}^{T} \gamma(Z_t = k) x_t}{\sum_{t=1}^{T} \gamma(Z_t = k)}$

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See extra slides for more details

https://www.cs.ubc.ca/~murphyk/Papers/bayesGauss.pdf

Inference & parameter estimation using EM (M-Step)

M-Step: Update transition matrix, A

Expected number of transitions from k to j

Prior counts

$$\hat{A}_{kj} = \frac{\sum_{t=2}^{T} \xi(Z_{t-1} = k, Z_t = j) + \delta_j^A(k)}{\sum_{l=1}^{K} \left\{ \sum_{t=2}^{T} \xi(Z_{t-1} = k, Z_t = l) + \delta_j^A(l) \right\}}$$

"Pseudo-counts"

Expected number of transitions from k to any other state

Evaluate the log posterior

$$\log \mathbb{P} = \ell + \log Dir(\hat{\boldsymbol{\pi}} \mid \boldsymbol{\delta}) + \sum_{k=1}^{K} \left\{ \log \mathcal{N}(\hat{\mu}_k \mid m_k, s_k) + \log InvGamma(\hat{\sigma}_k^2 \mid \alpha_k, \beta_k) + \log Dir(A_{k,1:K}^{(0)} \mid \hat{A}_{k,1:K}) \right\}$$

Log likelihood

Log priors

Iterate between E-Step and M-Step: stop when $\log \mathbb{P}$ changes less than ϵ compared to previous EM iteration.

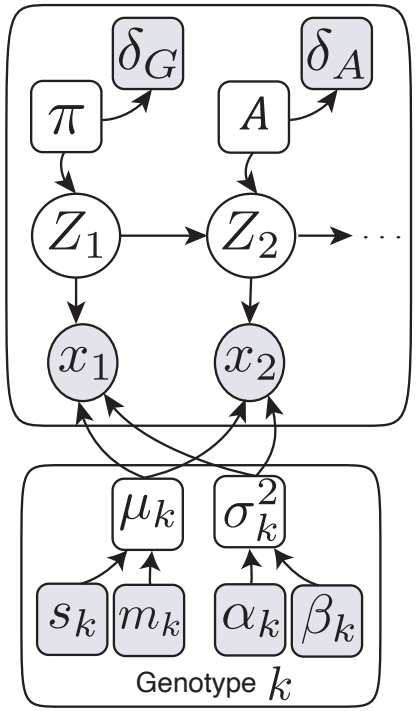
See extra slides for more details

Algorithm 1 HMM Parameter Learning using EM

Inputs:
Data: $x_{1:T}$
Initial parameters: $\pi^{(0)}$, $\mu_{1:K}^{(0)}$, $\left(\sigma_{1:K}^2\right)^{(0)}$, $A^{(0)}$
Hyperparameters: δ^{π}, $m_{1:K}$, $s_{1:K}$, $\alpha_{1:K}$, $\beta_{1:K}$, δ^{A}
Initialize:
$\pi \leftarrow \pi^{(0)}$, $\mu_{1:K} \leftarrow \mu_{1:K}^{(0)}$, $\sigma_{1:K}^2 \leftarrow \left(\sigma_{1:K}^2\right)^{(0)}$, $A \leftarrow A^{(0)}$
Compute observed likelihood using initial parameters:
    `obs.lik` $\leftarrow$ `compute.gauss.lik()`
while `converged = false` **do**
    E-Step: Compute responsibilities using current parameters:
        $(\gamma(Z_{1:T})$, `loglik`$)$ $\leftarrow$ `.Call("forward_backward")`
    M-Step: Update parameters:
        $\hat{\pi} \leftarrow$ `update.pi()`
        $\hat{\mu}_{1:K} \leftarrow$ `update.mu()`
        $\hat{\sigma}_{1:K}^2 \leftarrow$ `update.var()`
        $\hat{A} \leftarrow$ `update.A()`
    Assign updated parameters:
        $\pi \leftarrow \hat{\pi}$, $\mu_{1:K} \leftarrow \hat{\mu}_{1:K}$, $\sigma_{1:K}^2 \leftarrow \hat{\sigma}_{1:K}^2$, $A \leftarrow \hat{A}$
    Re-compute observed likelihood using updated parameters:
        `obs.lik` $\leftarrow$ `compute.gauss.lik()`
    Compute log Posterior:
        `logP[curr.iter]` $\leftarrow$ `compute.log.posterior(loglik,...)`
    if (`logP[curr.iter] - logP[prev.iter] <` ϵ) **then**
        `converged = true`
    end if
    `logP[prev.iter]` $\leftarrow$ `logP[curr.iter]`
end while
return Converged parameters $\hat{\pi}$, $\hat{\mu}_{1:K}$, $\hat{\sigma}_{1:K}^2$, $\hat{A}$

3. Copy Number Profiling using a HMM

- Defining the HMM for copy number analysis
- Copy number segmentation using Viterbi
- References:



- **HMMcopy** - Ha et al. *Genome Research* **22**:1995-2007 (2012).
- **ichorCNA** - Adalsteinsson*, Ha* Freeman* et al. *Nature Communications* **8**:1324 (2017).
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- Murphy, K. (2012). Machine Learning: A Probabilistic Perspective. MIT Press. ISBN: 9780262018029
- Bishop, C. M. (2006). Pattern Recognition and Machine Learning (Information Science and Statistics). Springer. ISBN: 0387310738

Probabilistic Model for Copy Number Analysis

Input Data: log ratios

There are T different genomic bins with log ratio data $\boldsymbol{x} = \{x_1, \ldots, x_T\}$.

Latent State Model: copy number states

There are 5 different possible copy number states (genotypes), $K = \{1, 2, 3, 4, 5\}$

1. A specific genotype $k \in K$ can be assigned to the each of the **latent states** $\boldsymbol{Z} = \{Z_1, \ldots, Z_T\}$
2. The **initial state distribution** $\boldsymbol{\pi} = \{\pi_1, \ldots, \pi_5\}$ is used for the first latent state Z_1

Transition Model

3. The probabilities for transitioning to copy number state j in bin t from state i in bin $t-1$ are contained in matrix $\boldsymbol{A} \in \mathbb{R}^{K \times K}$

$$p(Z_t = j \,|\, Z_{t-1} = i) = A_{ij}$$

Emission Model: likelihood for log ratio data

For each copy number state, the log ratio means are $\boldsymbol{\mu} = \{\mu_1, \ldots, \mu_5\}$ and variance $\boldsymbol{\sigma^2} = \{\sigma_1^2, \ldots, \sigma_5^2\}$

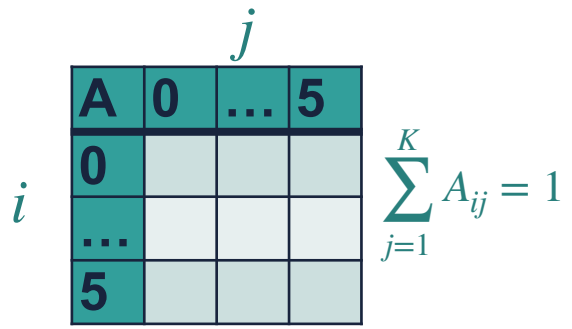
4. The **emission model** is a mixture of Gaussians with *unknown* parameters, $\boldsymbol{\mu}$ and $\boldsymbol{\sigma^2}$,

$$p(x_t \,|\, Z_t = k, \boldsymbol{\mu}, \boldsymbol{\sigma^2}) = \mathcal{N}(x_t \,|\, \mu_k, \sigma_k^2)$$

Prior Model

5. The **priors** in the model have hyper-parameters $\boldsymbol{\delta^{\pi}}$, $m_{1:K}$, $s_{1:K}$, $\alpha_{1:K}$, $\beta_{1:K}$, $\boldsymbol{\delta^A_{1:K}}$

$$p(\boldsymbol{\pi} \,|\, \boldsymbol{\delta^{\pi}}) = Dirichlet(\boldsymbol{\pi} \,|\, \boldsymbol{\delta^{\pi}})$$
$$p(\mu_k \,|\, m_k, s_k) = \mathcal{N}(\mu_k \,|\, m_k, s_k)$$
$$p(\sigma_k^2 \,|\, \alpha_k, \beta_k) = InvGamma(\sigma_k^2 \,|\, \alpha_k, \beta_k)$$
$$p(\boldsymbol{A_{k,1:K}} \,|\, \boldsymbol{\delta^A}) = Dirichlet(\boldsymbol{A_{k,1:K}} \,|\, \boldsymbol{\delta^A_k})$$



Ha et al. *Genome Research* **22**:1995-2007 (2012).
Adalsteinsson*, Ha* Freeman* et al. *Nat Commun* **8**:1324 (2017)

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E-Step: Compute Responsibilities

M-Step: Update parameters

Transition Model

3. The probabilities for transitioning to copy number state j in bin t from state i in bin $t-1$ are contained in matrix $\boldsymbol{A} \in \mathbb{R}^{K \times K}$

$$p(Z_t = j \,|\, Z_{t-1} = i) = A_{ij}$$

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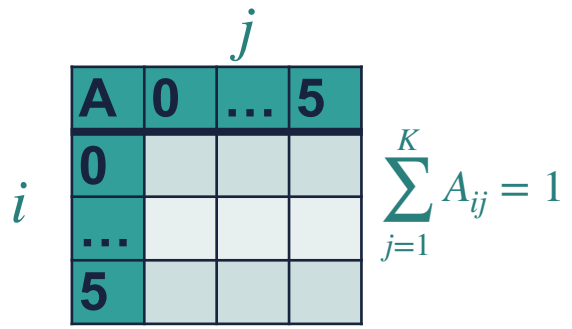
$$p(x_i \,|\, Z_i = k, \boldsymbol{\mu}, \boldsymbol{\sigma^2}) = \mathcal{N}(x_i \,|\, \mu_k, \sigma_k^2)$$

Prior Model

5. The **priors** in the model have hyper-parameters $\boldsymbol{\delta^{\pi}}$, $m_{1:K}$, $s_{1:K}$, $\alpha_{1:K}$, $\beta_{1:K}$, $\boldsymbol{\delta^{A}_{1:K}}$

$$p(\boldsymbol{\pi} \,|\, \boldsymbol{\delta^{\pi}}) = Dirichlet(\boldsymbol{\pi} \,|\, \boldsymbol{\delta^{\pi}})$$
$$p(\mu_k \,|\, m_k, s_k) = \mathcal{N}(\mu_k \,|\, m_k, s_k)$$
$$p(\sigma_k^2 \,|\, \alpha_k, \beta_k) = InvGamma(\sigma_k^2 \,|\, \alpha_k, \beta_k)$$
$$p(\boldsymbol{A_{k,1:K}} \,|\, \boldsymbol{\delta^{A}}) = Dirichlet(\boldsymbol{A_{k,1:K}} \,|\, \boldsymbol{\delta^{A}_{k}})$$



Ha et al. *Genome Research* **22**:1995-2007 (2012).
Adalsteinsson*, Ha* Freeman* et al. *Nat Commun* **8**:1324 (2017)

Copy number segmentation using Viterbi

Viterbi algorithm (Max-Sum)

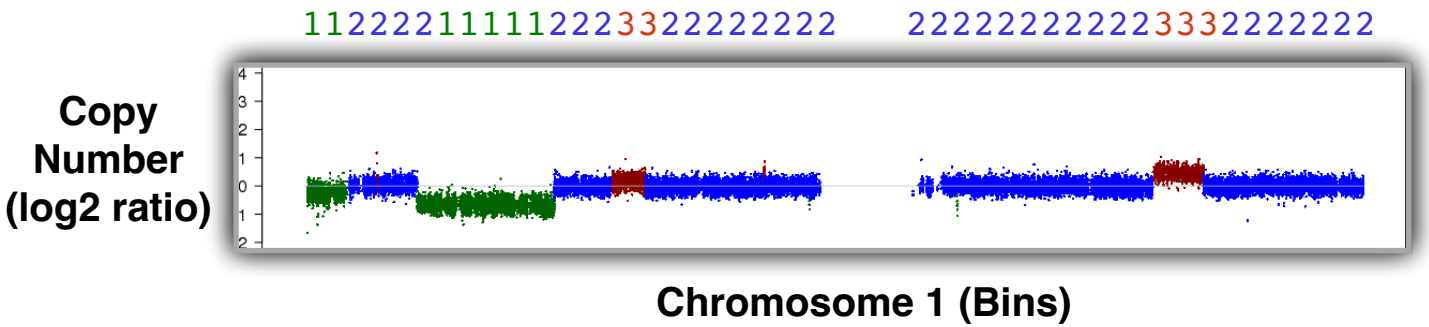
- Find the most probable sequence of copy number states

$$\hat{Z}_{1:T} = \max_{Z_{1:T}} \log p(Z_{1:T} | x_{1:T})$$

- Perform max-sum of probabilities in trellis

$$\omega(Z_{t+1} = k) = \log \mathcal{N}(x_{t+1} | \mu_k, \sigma_k^2) + \max_{Z_t} \left\{ \log A_{Z_t,k} + \log \omega(Z_t) \right\}$$

- Back trace from $\omega(Z_T)$ to find overall most probable path

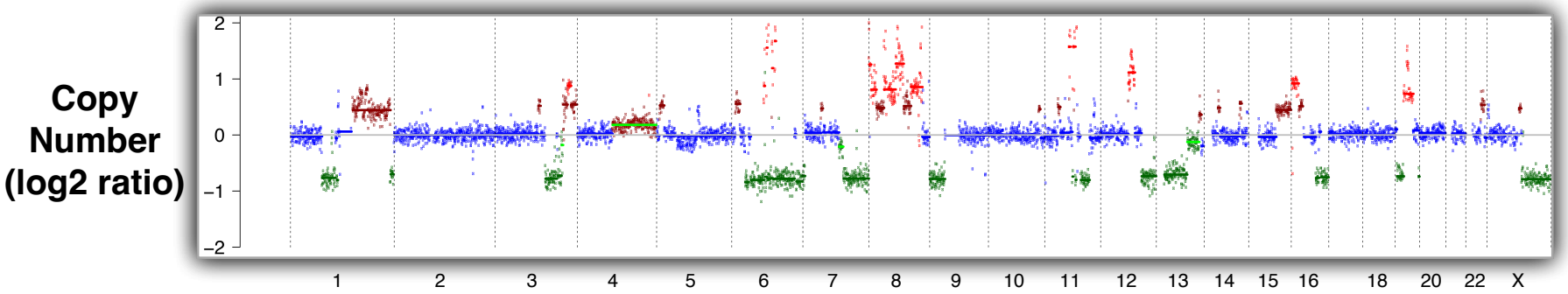


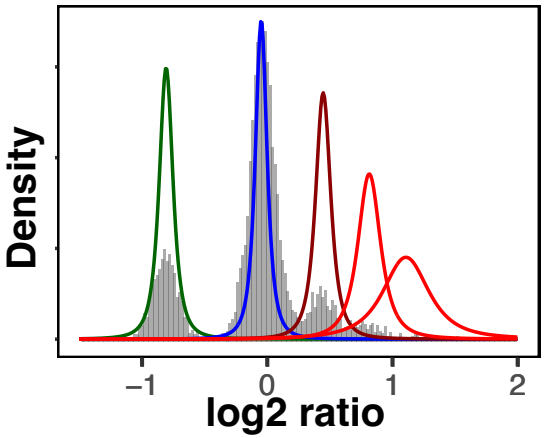
Rationale for Estimating Likelihood Parameters

Why should we estimate the mixture distribution parameters?

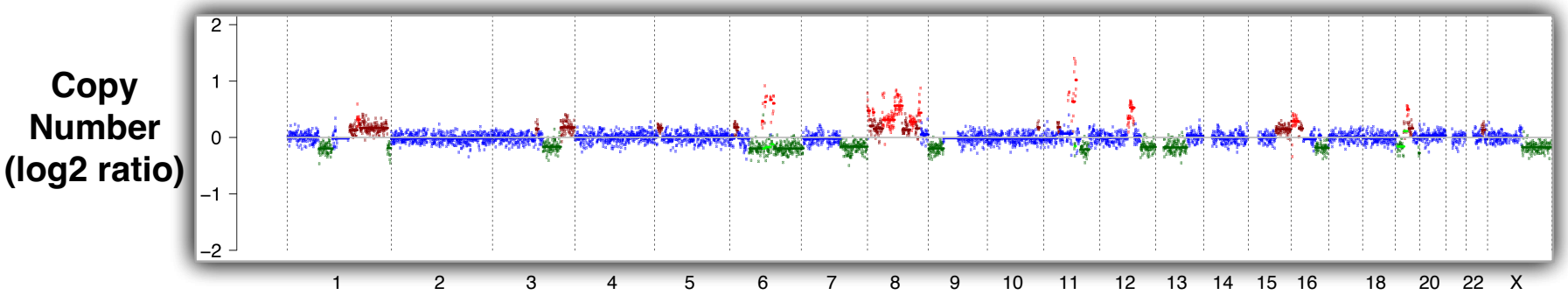
- Can account for technical and biological "noise" by estimating model parameters $\boldsymbol{\mu} = \{\mu_0, \ldots, \mu_5\}$ and $\boldsymbol{\sigma^2} = \{\sigma_0^2, \ldots, \sigma_5^2\}$?

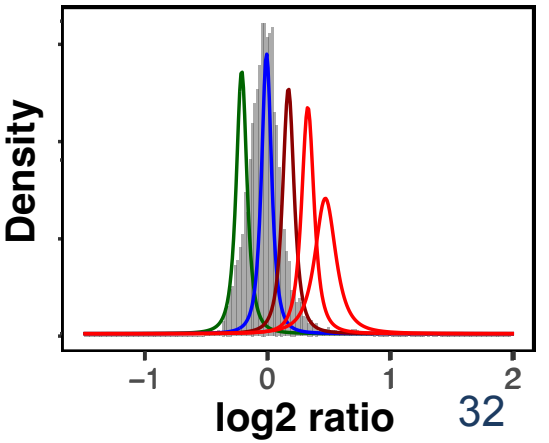
Patient 288 - Time 1





Patient 288 - Time 2





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Copy Neutral Deletion Gain Amplification

Homework #6: Profiling copy number alterations

A. Implement a copy number alteration (CNA) caller described in Lecture 3
   - Implement components of a continuous HMM in a Bayesian framework
   - Learn the parameters and infer the genotypes using EM
   - Predict the copy number alteration segments for a chromosome.
   - Expected outputs for each question will be provided so that you can check your code.

B. Power calculations for mutation detection described in Lecture 4

Due: May 15th

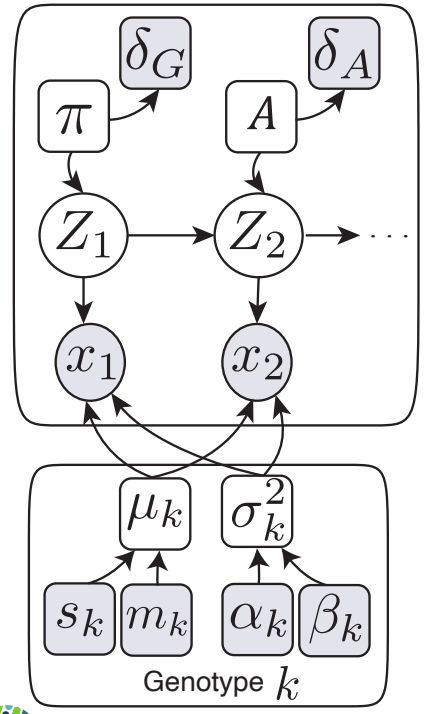
Office Hours with Anna-Lisa Doebley (adoebley@uw.edu)

Zoom Meeting ID: 446 356 7725 Password: GS541

- Wednesday, May 7, 2-3pm (Homework 5 questions)
- Monday, May 11, 2-3pm
- Wednesday, May 13, 2-3pm

Extra Slides

- Continuous hidden Markov models (HMMs)
- Parameter inference using EM and copy number segmentation
- References:



- **ichorCNA** - Adalsteinsson*, Ha* Freeman* et al. *Nature Communications* **8**:1324 (2017).
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- Murphy, K. (2012). Machine Learning: A Probabilistic Perspective. MIT Press. ISBN: 9780262018029
- Bishop, C. M. (2006). Pattern Recognition and Machine Learning (Information Science and Statistics). Springer. ISBN: 0387310738

ichorCNA: Model inference using EM (extra slide 1)

Complete data likelihood: joint distribution of latent and observed variables

$$p(x_{1:T}, Z_{1:T}|\boldsymbol{\theta}) = p(Z_1|\pi_{1:K})\left[\prod_{t=2}^{T} p(Z_t|Z_{t-1}, \boldsymbol{A})\right]\prod_{t=1}^{T} p(x_t|Z_t, \mu, \sigma^2)$$

$$= \prod_{k=1}^{K} \pi_k^{\mathbb{I}(Z_i=k)}\left[\prod_{t=2}^{T}\prod_{k=1}^{K}\prod_{j=1}^{K} A_{jk}^{\mathbb{I}(Z_{t-1}=j)\mathbb{I}(Z_t=k)}\right]\prod_{t=1}^{T}\prod_{k=1}^{K}\mathcal{N}(x_t|\mu_k, \sigma_k^2)^{\mathbb{I}(Z_t=k)}$$

where $\boldsymbol{\theta} = \{\pi_{1:K}, \mu_{1:K}, \sigma^2_{1:K}, \boldsymbol{A}\}$

Complete data log likelihood

$$\log p(x_{1:T}, Z_{1:T}|\boldsymbol{\theta}) = \sum_{k=1}^{K}\mathbb{I}(Z_i = k)\log\pi_k + \sum_{t=2}^{T}\sum_{j=1}^{K}\sum_{k=1}^{K}\mathbb{I}(Z_{t-1} = j, Z_t = k)\log A_{jk} + \sum_{t=1}^{T}\sum_{k=1}^{K}\mathbb{I}(Z_i = k)\log\mathcal{N}(x_t|\mu_k, \sigma_k^2)$$

Expected complete data log likelihood

$$Q = \sum_{k=1}^{K}\gamma(Z_1 = k)\log\pi_k + \sum_{t=2}^{T}\sum_{j=1}^{K}\sum_{k=1}^{K}\xi(Z_{t-1} = j, Z_t = k)\log A_{jk} + \sum_{t=1}^{T}\sum_{k=1}^{K}\gamma(Z_t = k)\log\mathcal{N}(x_t|\mu_k, \sigma_k^2)$$

Chapter 13 in Bishop (2006). Pattern Recognition and Machine Learning. Springer

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Additional definitions for your reference

ichorCNA: Model inference using EM (extra slide 2)

E-Step: compute responsibilities using the forwards-backwards algorithm (Baum-Welch)

$$\gamma(\mathbf{Z}_t) = p(\mathbf{Z}_t \mid \boldsymbol{x}, \theta^{old}) = \frac{p(\boldsymbol{x} \mid \mathbf{Z}_t \mid \boldsymbol{\theta^{old}}) p(\mathbf{Z}_t \mid \theta^{old})}{p(\boldsymbol{x} \mid \theta^{old})}$$

$$\gamma(\mathbf{Z}_t) = \frac{p(x_1, \ldots, x_t, \mathbf{Z}_t) p(x_{t+1}, \ldots, x_T \mid \mathbf{Z}_t)}{p(\boldsymbol{x})}$$

$$\gamma(\mathbf{Z}_t) = \frac{\alpha(\mathbf{Z}_t)\beta(\mathbf{Z}_t)}{p(\boldsymbol{x})}$$

Responsibilities
Matrix $K \times T$

Where $\alpha(Z_t = k) = \mathcal{N}(x_t \mid Z_t = k) \sum_{j=1}^{K} \left\{ A_{jk} \alpha(Z_t = j) \right\}$ is the forward recursion probability

Forward Probabilities
Matrix $K \times T$

Where $\beta(Z_t = k) = \sum_{j=1}^{K} \left\{ \mathcal{N}(x_{t+1} \mid Z_{t+1} = j) A_{kj} \alpha(Z_{t+1} = j) \right\}$ is the backward recursion probability

Backward Probabilities
Matrix $K \times T$

$$\xi(\mathbf{Z}_{t-1}, \mathbf{Z}_t) = p(\boldsymbol{x} \mid \mathbf{Z}_{t-1}, \mathbf{Z}_t) P(\mathbf{Z}_{t-1}, \mathbf{Z}_t)$$

$$\xi(\mathbf{Z}_{t-1}, \mathbf{Z}_t) = \frac{\alpha(\mathbf{Z}_{t-1}) p(x_t \mid \mathbf{Z}_t) p(\mathbf{Z}_t \mid \mathbf{Z}_{t-1}) \beta(\mathbf{Z}_t)}{p(\boldsymbol{x})}$$

2 Slice Marginals
Matrix $K \times K \times (T-1)$

Likelihood function

$$\ell = \log p(\boldsymbol{x}) = \sum_{t=1}^{T} \log \left(\sum_{k=1}^{K} \alpha(Z_t = k) \right)$$

Chapter 13 in Bishop (2006). Pattern Recognition and Machine Learning. Springer

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Additional definitions for your reference

ichorCNA: Model inference using EM (extra slide 3)

M-Step: Update the parameters given the responsibilities

$$\mathbb{P}rior(\pi_{1:K}, \mu_{1:K}, \sigma^2_{1:K}, A) = \prod_{k=1}^{K} Dir(\pi_k \mid \delta_k) Dir(A_k \mid \delta_A) \mathcal{N}(\mu_k \mid \alpha, \beta) InvGamma(\sigma^2_k \mid \alpha_k, \beta_k)$$

Priors

$$\mathcal{O} = Q + \log \mathbb{P}(\pi_{1:K}, \mu_{1:K}, \sigma^2_{1:K}, A)$$

Complete data log likelihood + log priors

- The object function $\mathcal{O}$ is used to obtain the update equations for $\pi_{1:K}$ and $\mu_{1:K}$

$$\frac{\partial \mathcal{O}}{\partial \pi_k} = 0, \text{ find } \hat{\pi}_k$$

MAP for initial state distribution

$$\frac{\partial \mathcal{O}}{\partial \mu_k} = 0, \text{ find } \hat{\mu}_k$$

MAP for for Gaussian means

$$\frac{\partial \mathcal{O}}{\partial \sigma^2_k} = 0, \text{ find } \hat{\sigma}^2_k$$

MAP for for Gaussian variance

$$\frac{\partial \mathcal{O}}{\partial A_{jk}} = 0, \text{ find } \hat{A}_{jk}$$

MAP for transition probabilities

EM Convergence: after each iteration, monitor the log posterior

$$\ell = \log p(\boldsymbol{x}) = \sum_{t=1}^{T} \log \left(\sum_{k=1}^{K} \alpha(Z_t = k) \right)$$

Incomplete Data Log likelihood

$$\log \mathbb{P} = \ell + \log \mathbb{P}rior(\pi_{1:K}, \mu_{1:K}, \sigma^2_{1:K}, A)$$

Log posterior

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Additional definitions for your reference

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