Copy number evolution with weighted aberrations in cancer

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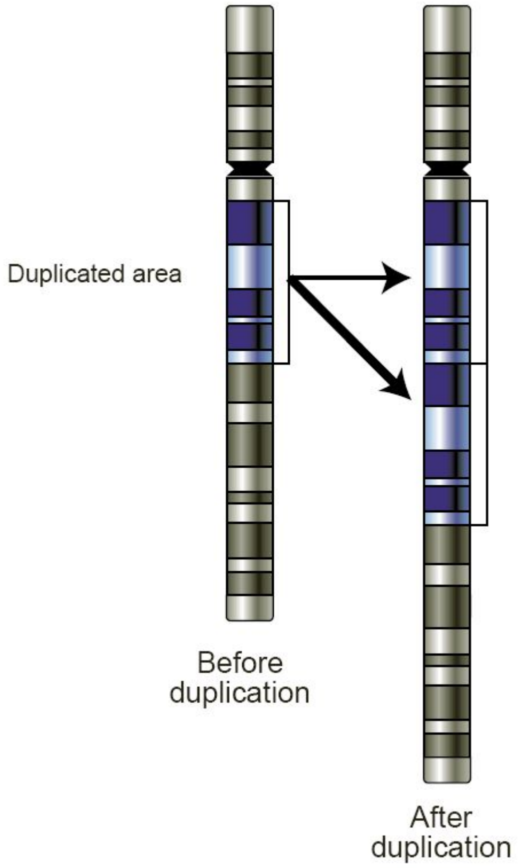
Presented by Mrinmoy

Copy number aberrations (CNAs)

- Deletion or amplification of large genomic regions
- Source of somatic mutation in many cancer type



CNPs and Events

- Copy number profile, $C = (c_1, c_2, .., c_n)$

  Vector of non-negative integers

- Events, $e = (i, j, \tau)$,

  $1 <= i <= j <= n$, $\tau \in \{+1, -1\}$

CNPs and Events

c_0	...	c_{i-1}	c_i	...	c_j	c_{j+1}	...	c_n

(i, j, τ)

c_0	...	c_{i-1}	$\max(C_i+\tau, 0)$	...	$\max(c_j+\tau,0)$	c_{j+1}	...	c_n

CNT & CND

- Copy number transformation from CNP S to CNP T:

  $E = (e_1, e_2, \ldots, e_l)$

  such that - $e_l(...(e_1(S)) = T$

- Copy Number Distance, $d(S,T) = \min_{E:E(S)=T} |E|$
- CNT is not a true distance
- $d(S,T) = \infty$ if $s_i = 0$ for any $1 \le i \le n$

Phase

- $E = (E_1, E_2, ..., E_n)$

  Phase - E_i where (1) E_i is a subsequence of E, (2) all the events in E_i has the same type, and (3) adjacent segments have different types.

- **$op(E_j, i)$** = $\left| \{ (l, r, \tau) \in E_j \mid l \le i \le r \} \right|$

  Change in segment i by events in phase E_j

- CNT E from S to T is **phase-bounded** provided if -

  $op(E_j, i) \le B$ where $B = \max(\max(S), \max(T))$

Ordered CNT

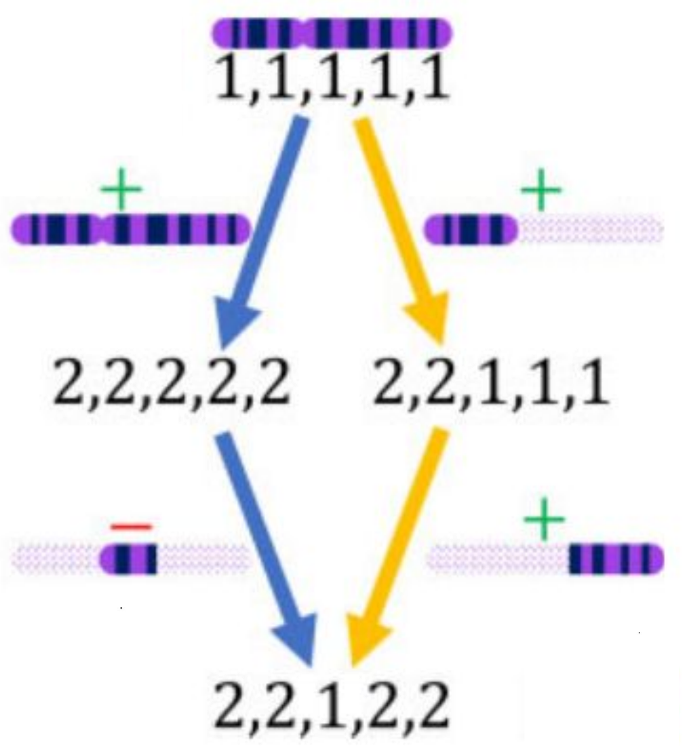
- Ordered CNT, $E = (E_-,E_+)$

  All deletions come before all amplifications

- If $d(S,T) < \infty$, then there exists an ordered phase-bounded CNT E s.t. $E(S)=T$

Semi-ordered CNT

- Which one is more probable?



Semi-ordered CNT

- Semi-ordered CNT:

  $E = (E_1, E_2, E_3)$

  s.t. $\boldsymbol{\tau}(E_1 \cup E_3) = -1$, $\boldsymbol{\tau}(E_2) = +1$

  and $E_1(S_i) = 0$ if $t_i = 0$

- Why?

- Richer space of transformations
- Still tractable

Problems with CND

CND considers all events equally.

Problems -

- CNAs of different length occurs at different rates
- Length dependent uncertainty in real data

Weighted CNT Model

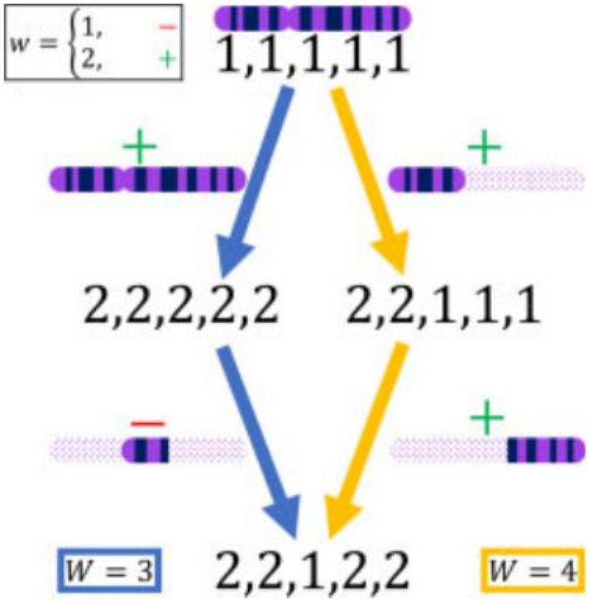
- Event weight function, w: {1..n} x {1...n} x {+,-} -> R

  Takes as input an event e, and outputs its weight

- Weight can change based on position, length and type of CNA
- Weight of CNT E:

  w(E) = \sum_{e \in E} w(e)

Weighted CNT Model



Minimum weight semi-ordered CNT

- **Problem Statement**: Given a source CNP S, a target CNP T and a weight function w, find semi-ordered phase-bounded CNT E having a minimum weight W(E).
- If the weight of an event is the log of the probability of the event, then the problem becomes a Maximum Likelihood problem.

$$E = \min_{E:E(S) = T \mid E \text{ is semi-ordered \& phase bounded}}\left(- \sum_{e \in E} \log p_e \right)$$

Minimum weight semi-ordered CNT Solution

x_{lk}^{j} = Number of events between l and k in phase j

Objective function - $\min \sum_j \sum_{l \le k} w(l,k,j) x_{lk}^{j}$

Constraints -

$$s_i \le \sum_{l \le i \le k} x_{lk}^{1} \quad 1 \le i \le n, \quad \text{if} \quad t_i = 0,$$

$$\sum_{l \le i \le k} x_{lk}^{1} \le s_i - 1 \quad 1 \le i \le n, \quad \text{if} \quad t_i > 0,$$

$$s_i - \sum_{l \le i \le k} x_{lk}^{1} - x_{lk}^{2} + x_{lk}^{3} = t_i \quad 1 \le i \le n, \quad \text{if} \quad t_i > 0$$

Minimum weight semi-ordered CNT Solution

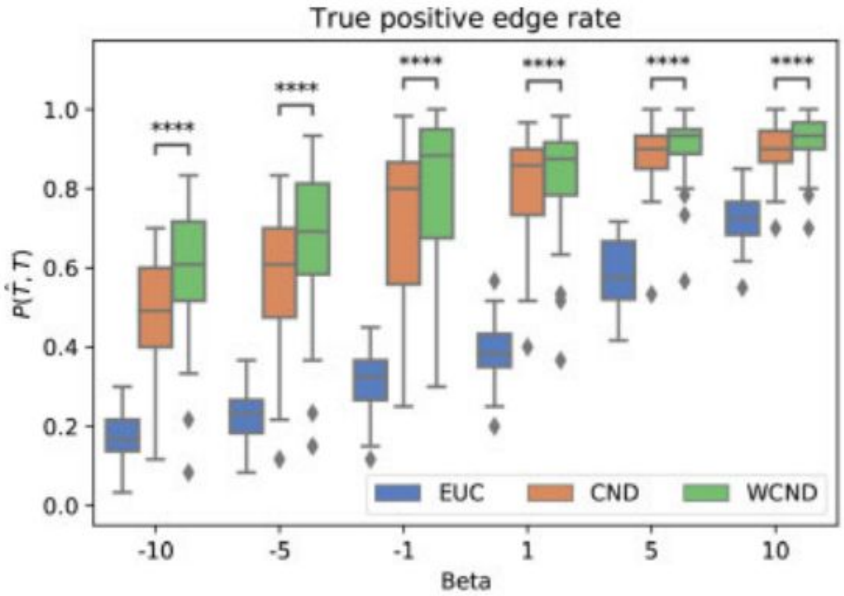
Constraints -

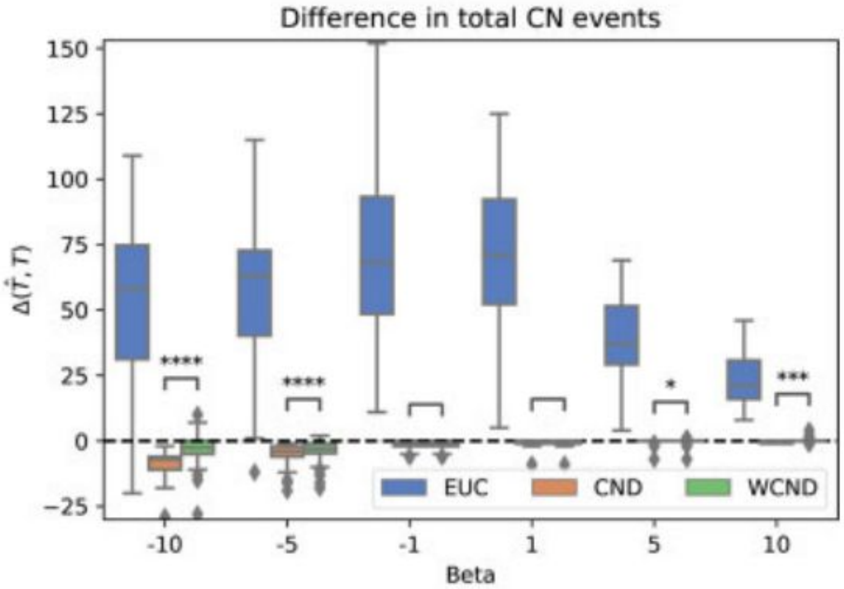
$$s_i - \sum_{l \le i \le k} x_{lk}^1 - x_{lk}^2 + x_{lk}^3 = t_i \quad 1 \le i \le n, \quad \text{if} \quad t_i > 0,$$

$$\sum_{l \le i \le k} x_{lk}^j \le B \qquad 1 \le i \le n, \quad j \in \{1, 2, 3\}$$

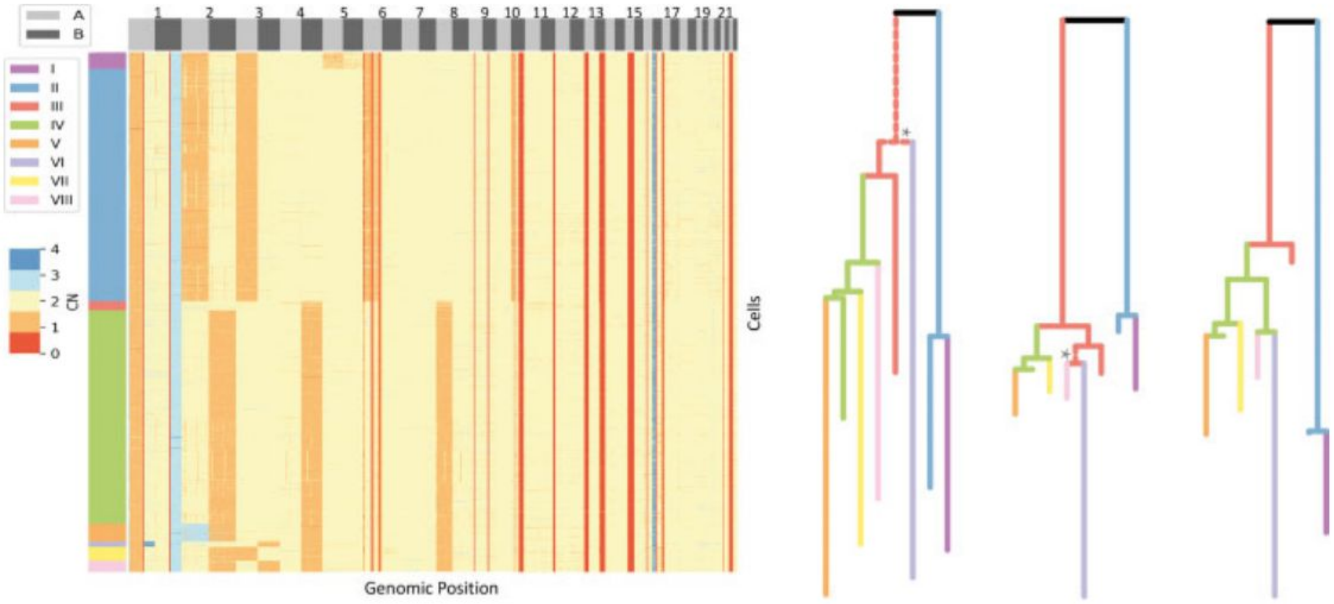
$$0 \le x_{lk}^j \quad 1 \le l \le k \le n, \quad j \in \{1, 2, 3\}.$$

Results on simulated data





Results on real data



Eucledian Unweighted CNT WCNT