

# MATHEMATICAL MODELING OF LYNCH SYNDROME CANCER DEVELOPMENT

## SUMMARY

We present mathematical and computational models, as well as statistical and bioinformatics approaches for a better understanding of cancer development on different scales at the example of Lynch syndrome, the most common inherited cancer syndrome.

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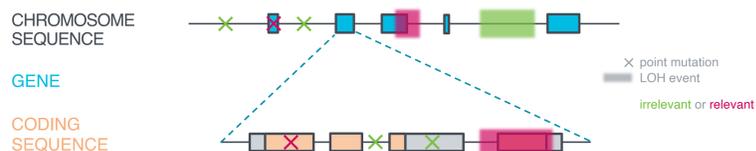


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## GENETICS

### Parametrizing mutation rates in a gene-dependent way [1,2]



Rate of a relevant point mutation per cell division for a specific gene in a cell:

$$\pi_{pt}(\text{gene}) = n_{pt} \frac{n_{hs}(\text{gene})}{n_{bp, \text{genome}}} \cdot \left(1 - \frac{1}{2} n_{mut}(\text{gene})\right)$$

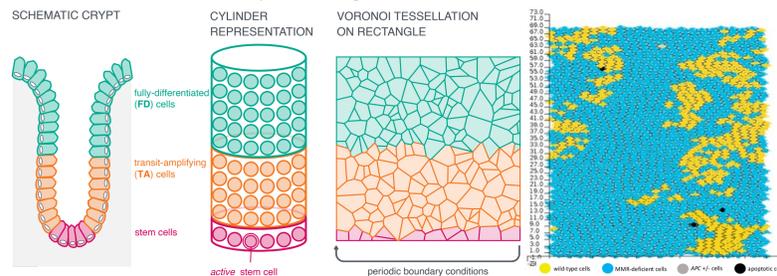
Rate of a relevant loss of heterozygosity (LOH) event per cell division for a specific gene:

$$p_{LOH}(\text{gene}) = \left(1 - \frac{1}{2} n_{mut}(\text{gene})\right) a n_{bp}(\text{gene})$$

## CELL & TISSUE

### Computational cell-based model of intra-crypt dynamics [2]

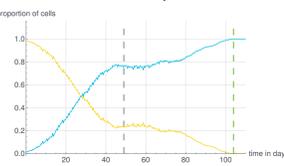
From tissue structure to computational grid Visual evaluation



Cellular rules implemented in the model

	STEM CELLS	TA CELLS	FD CELLS
CELL CYCLE	couple of weeks	one day	quiescent cell
DIVISION	asymmetric or symmetric after cell death	Wnt level determines mode asymmetric or symmetric	no cell division, only upwards migration
MUTATIONS	in APC, CTNNB1 and MMR possibly lethal mutations	in APC, CTNNB1 and MMR possibly lethal mutations due to lethal mutations or mitotic pressure	no additional mutations
DEATH	only due to lethal mutations	due to lethal mutations or mitotic pressure	apoptosis at top of a crypt

Quantitative analysis

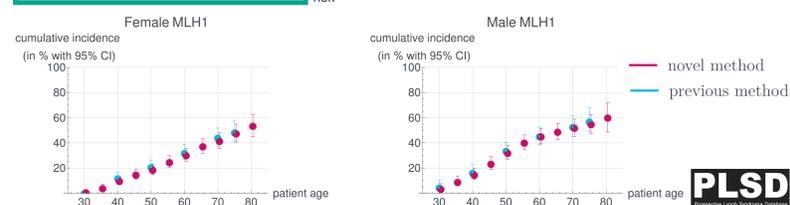


## POPULATION & CLINICS

### Modeling cumulative cancer risk [7]



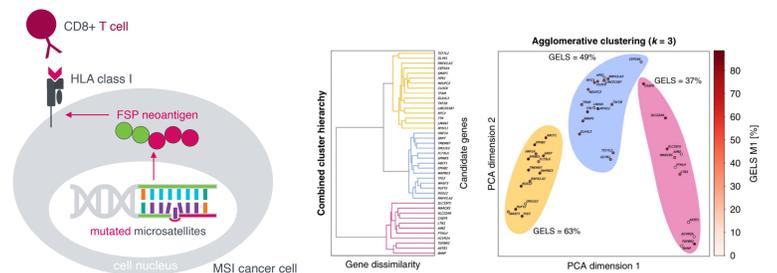
Novel statistical derivation: Nelson-Aalen estimates based on a Poisson distribution with 95% confidence intervals → natural choice for prospective cancer incidence data (previously: normal distribution)



### Quantifying immuno-editing during cancer development [4-6]

Bioinformatics approach

With a novel algorithm, called ReFrame, identify frameshift mutations that are shared by most microsatellite unstable tumors and discover a negative correlation between frameshift mutation frequencies and the predicted immunogenicity of the resulting frameshift peptides



### Mathematically modeling colorectal cancer development [1]

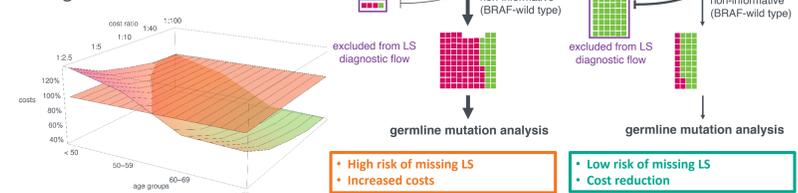
#### MODELING WORKFLOW

- MEDICAL KNOWLEDGE**
  - define pathways of carcinogenesis
  - identify driver genes
  - explore mutational dependencies
- PARAMETER VALUES**
  - define gene-dependent point mutation and LOH event rates
  - determine possible fitness changes and fixation affinities
- GRAPH REPRESENTATION**
  - build gene mutation graphs for each driver gene
  - build graphs for mutational dependencies
- ADJACENCY MATRICES**
  - derive adjacency matrices corresponding to graphs using the Kronecker structure
- LINEAR ODE SOLUTION**
  - set initial condition
  - solve linear ODE explicitly using the matrix exponential
  - extract mutational status of interest from the solution vector

### Cost-benefit analysis of BRAF mutation diagnostic testing [3]

Probabilistic data analysis

Analyze data from previous publications and population-based studies to calculate the risk of erroneously excluding hereditary cases from germline mutation analysis using BRAF mutation testing as a filter



## REFERENCES

[1] Haupt et al., PLOS Computational Biology, 2021



[4] Ballhausen et al., Nature Communications, 2020



[2] Haupt et al., Computational and Systems Oncology, 2021



[3] Bläker et al., International Journal of Cancer, 2020



[5] Ahadova et al., in revision

[6] Witt et al., in revision

[7] Møller et al., Hereditary Cancer in Clinical Practice, accepted