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.

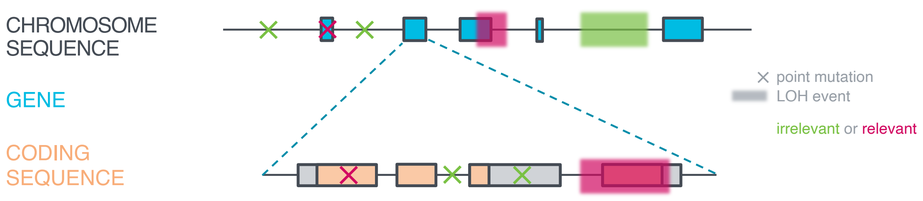
Saskia Haupt[1,3]
Aysel Ahadova[2], Nils Gleim[1],
Alexander Zeilmann[1,3], Valentin Schmid[1,3],
Magnus von Knebel Doeberitz[2],
Matthias Kloor[2], Vincent Heuveline[1,3]

[1] EMCL, Heidelberg University, [2] ATB, Heidelberg University Hospital,
[3] Heidelberg Institute for Theoretical Studies (HITS)

SaskiaHaupt.de

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:

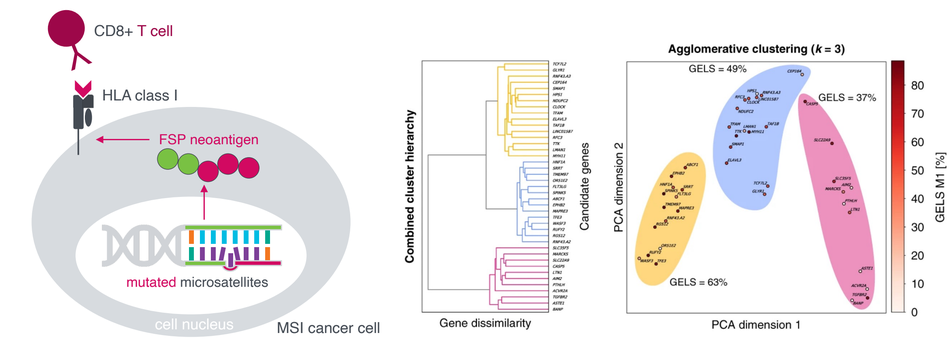
$$\pi_{\mathrm{pt}}(\mathrm{gene}) = n_{\mathrm{pt}} \frac{n_{\mathrm{hs}}(\mathrm{gene})}{n_{\mathrm{bp,genome}}} \cdot \left(1 - \frac{1}{2} n_{\mathrm{mut}}(gene)\right)$$

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

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

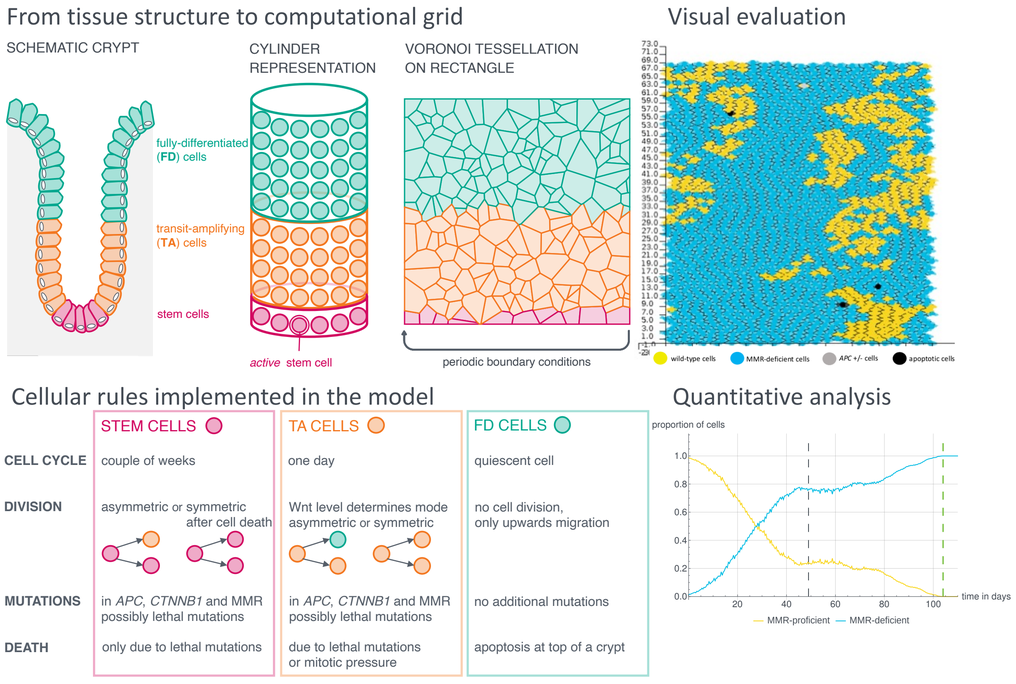
Quantifying immuno-editing during cancer development [4-6]

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

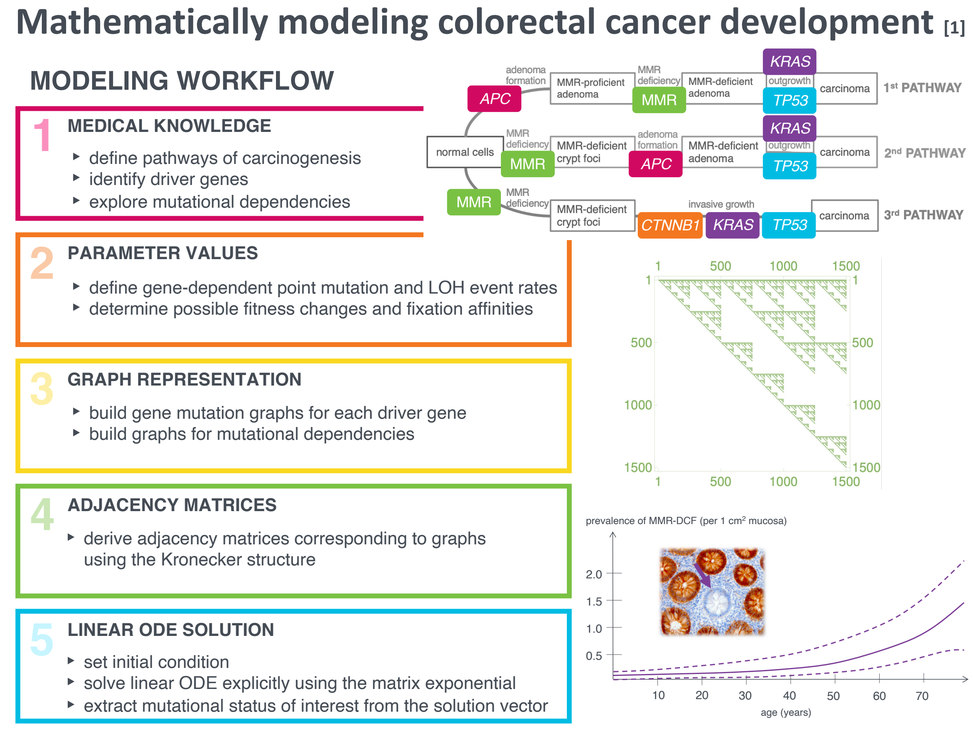


CELL & TISSUE

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

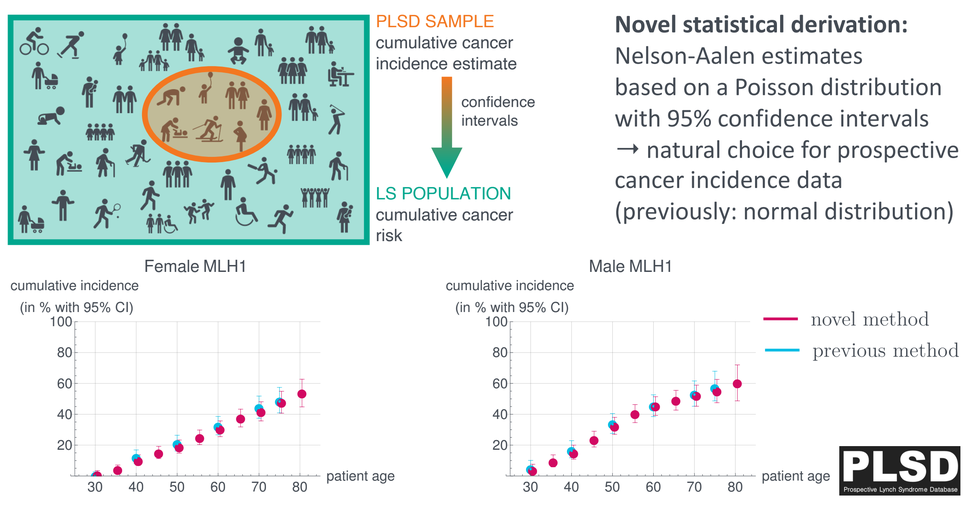


Mathematically modeling colorectal cancer development [1]



POPULATION & CLINICS

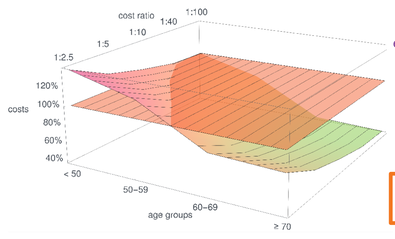
Modeling cumulative cancer risk [7]

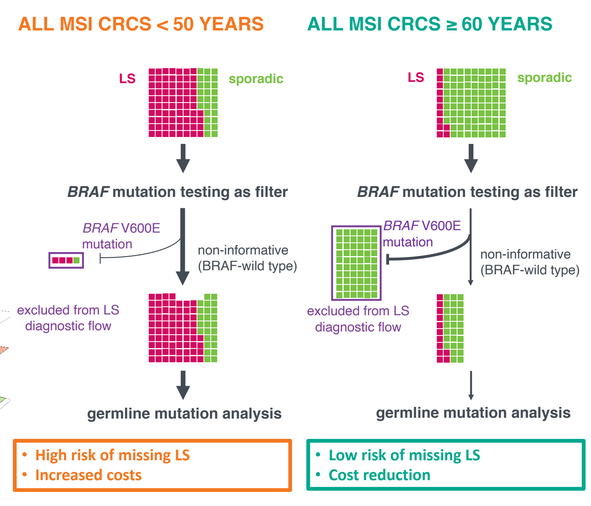


Novel statistical derivation:
Nelson-Aalen estimates
based on a Poisson distribution
with 95% confidence intervals
→ natural choice for prospective
cancer incidence data
(previously: normal distribution)

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

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

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

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

[5] Ahadova et al., *in revision*

[6] Witt et al., *in revision*

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

Universität Heidelberg Zukunft. Seit 1386. IWR Interdisciplinary Center for Scientific Computing
EMCL
Heidelberg University Hospital
atb applied tumor biology
HITS
Klaus Tschira Stiftung gemeinnützige GmbH
KTS
MATHEMATICS IN ONCOLOGY