185.A83 Machine Learning for Health Informatics
2016S, VU, 2.0 h, 3.0 ECTS
Week 26 - 29.06.2016 17:00-20:00

Tutorial on
Stochastic Simulation of Tumor Kinetics
From Cell Biology to Computational Modeling

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http://hci-kdd.org/machine-learning-for-health-informatics-course

Red thread through this lecture

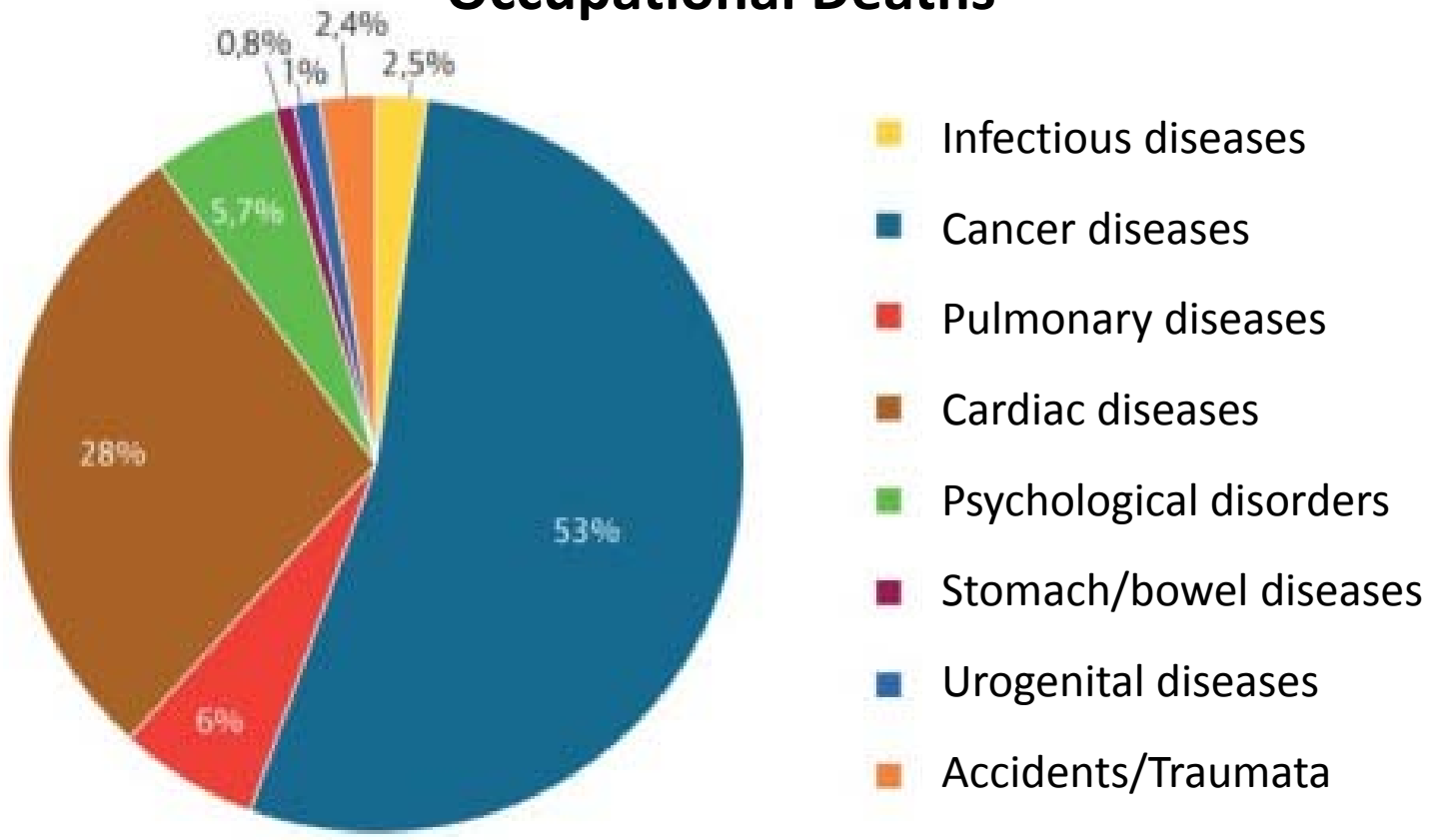
- 1) What is Cancer: A biological introduction
- 2) The multistep process of cancer
- 3) Key Problems for cancer research
- 4) Overview of Machine Learning for cancer
- 4) Tumor Growth Modeling
- 5) Cellular Potts Model > Tumor Growth Simulation
- 6) Implementation of Tumor Growth Visualization
- 7) Summary and Open Problems

Part 1
Cell Biology

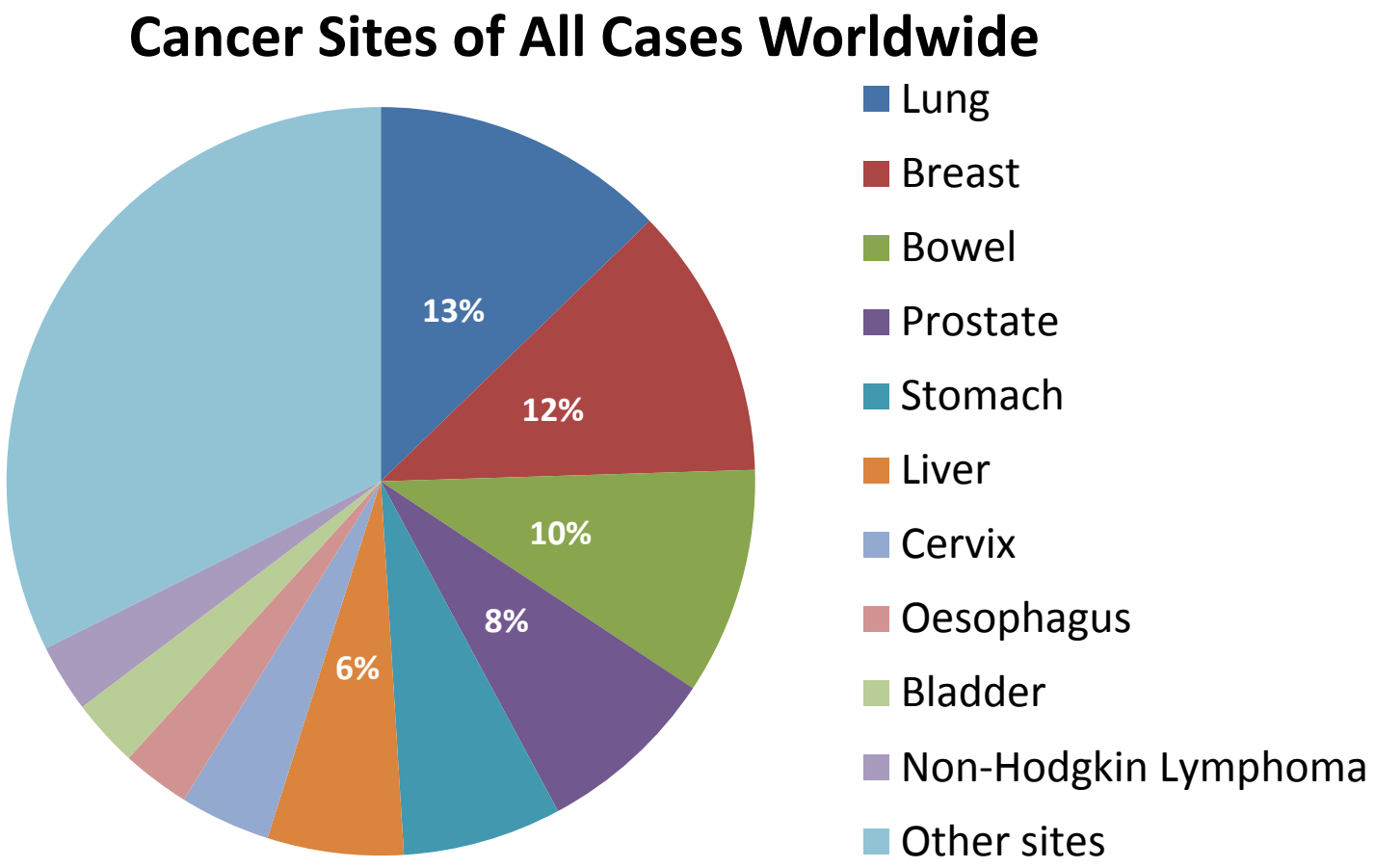
Keywords

- In Silico
- Differentiation
- Benign & Malignant Tumor Cells
- Proliferation
- Migration
- Tissue
- Adhesion
- Tumor Growth Modeling
- Agent Based Modeling
- Cellular Automaton (CA)
- Extra-Cellular Matrix (ECM)
- Cellular Potts Model (CPM)

Occupational Deaths

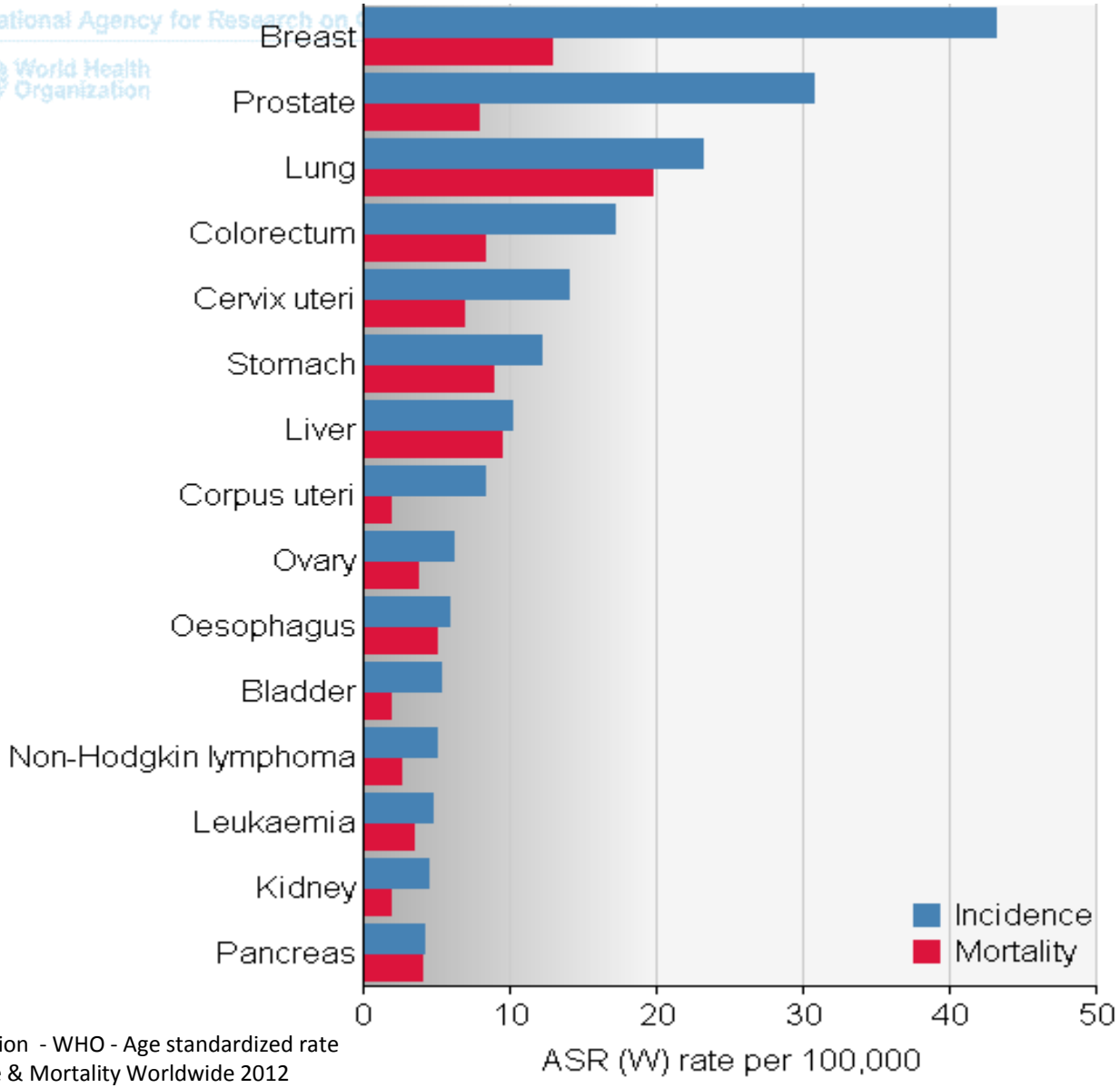


OGB – German Health News, apr 5th 2016 - Annually mortality causes in EU28 and other industrial countries



Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F.GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet].Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 16/01/2014.

Cancer Statistics



World Health Organization - WHO - Age standardized rate of Cancer Site Incidence & Mortality Worldwide 2012

Cancer Definitions

- Tumor / Neoplasm

… Abnormal mass of tissue - cells divide more than they should

- Cancer

… group of diseases in which abnormal cells divide without control, can invade nearby tissues

- Malignant

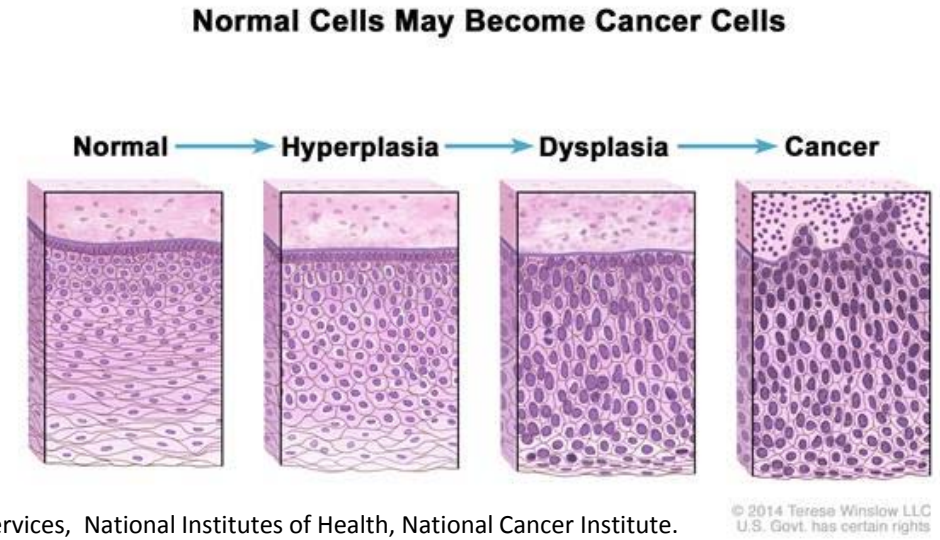
… Cancerous: invasive, destroy nearby tissue, spread to other parts of the body

- Benign / Non-malignant

… normal (not cancerous): grow larger but do not spread

- Hyperplasia / Dysplasia

… increased number / abnormal form



NCI Dictionary of Cancer Terms - US Department of Health & Human Services, National Institutes of Health, National Cancer Institute.

Cancer Classification

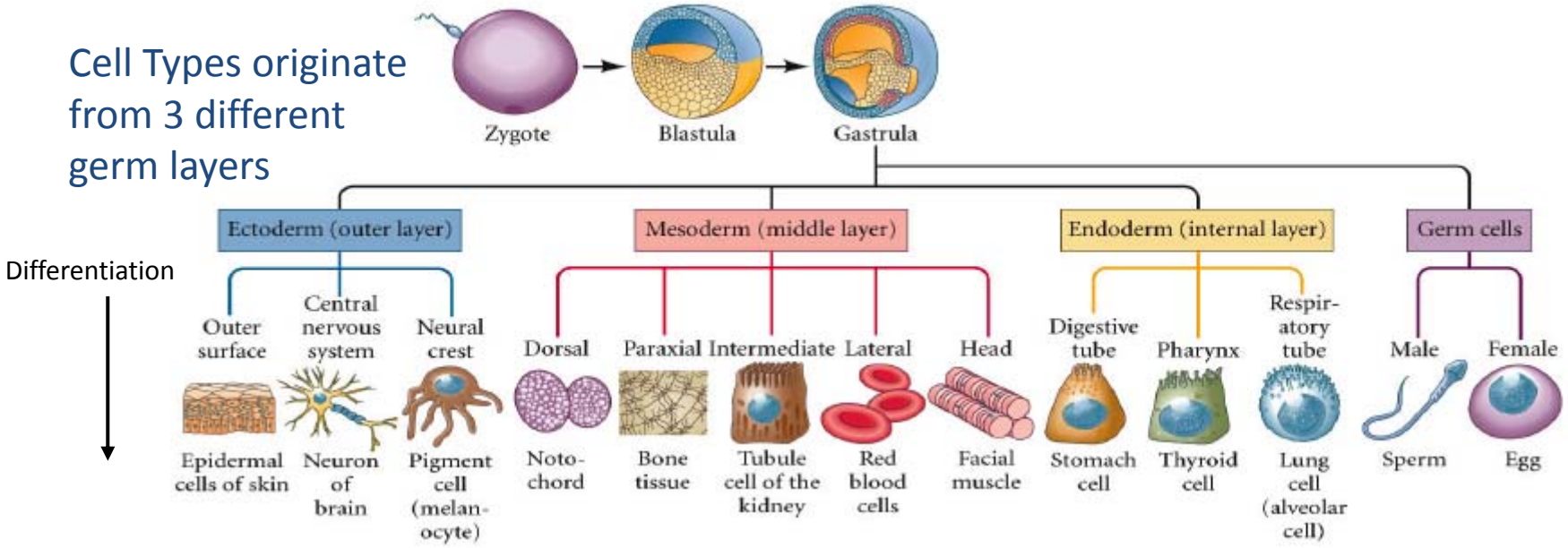
Most common Cancer types, based on their origin (primary manifestation):

- Skin
- Lung
- Breast
- Prostate
- Colon & rectum
- Uterus

ICD-O-3 - The International Standard for the classification and nomenclature of histologies is the International Classification of Diseases for Oncology, 3rd Ed.
NIH SEER Training Modules - US Department of Health & Human Services, National Institutes of Health, National Cancer Institute.

Cell Types

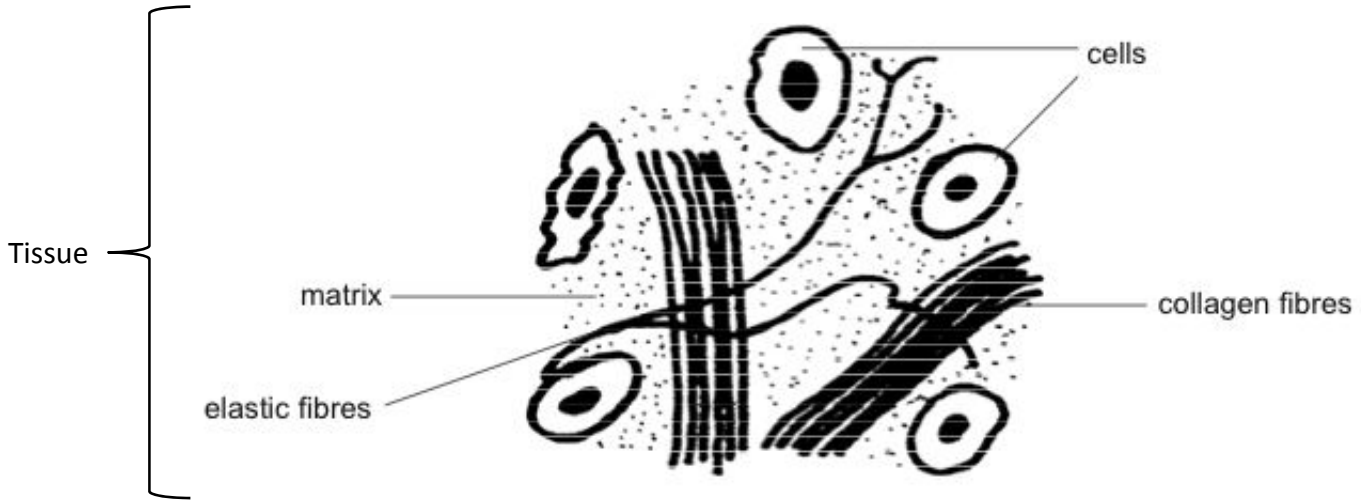
Cell Types originate from 3 different germ layers



- **Endoderm** (inner layer) → digestive tract, liver, lung, pharynx …
- **Ectoderm** (outer layer) → skin, nails, hair, skin glands, salivary glands, nerve tissue …
- **Mesoderm** (middle) → muscles, fibrous tissue, bone, cartilage, adipose tissue, blood cells, blood&lymph vessels

The-three-germ-layers - http://madmnemonics.blogspot.co.at - 06/2015

Cell Types



- Tissue
- Extracellular Matrix (ECM)
- Cell → Organelles
- Microfibril → Fiber → Protein

Loose connective tissue - by Adrignola, Sunshineconelly, Lawson R. 2011

Cancer Classification

Histological Types: Hundreds of different cancers, summed up to 6 major categories:

- **Carcinoma** (epithelial tissue)
- **Sarcoma** (supportive/connective tissue)
- **Myeloma** (plasma/bone marrow cells)
- **Leukemia** (bone marrow → blood production)
- **Lymphoma** (lymphatic system)*
- **Mixed** Types (eg. Carcinosarcoma)

* Hodgkin/Non-Hodgkin lymphoma depending on presence of Reed-Sternberg cells

ICD-O-3 - The International Standard for the classification and nomenclature of histologies is the International Classification of Diseases for Oncology, 3rd Ed.
NIH SEER Training Modules - US Department of Health & Human Services, National Institutes of Health, National Cancer Institute.

Cancer Classification

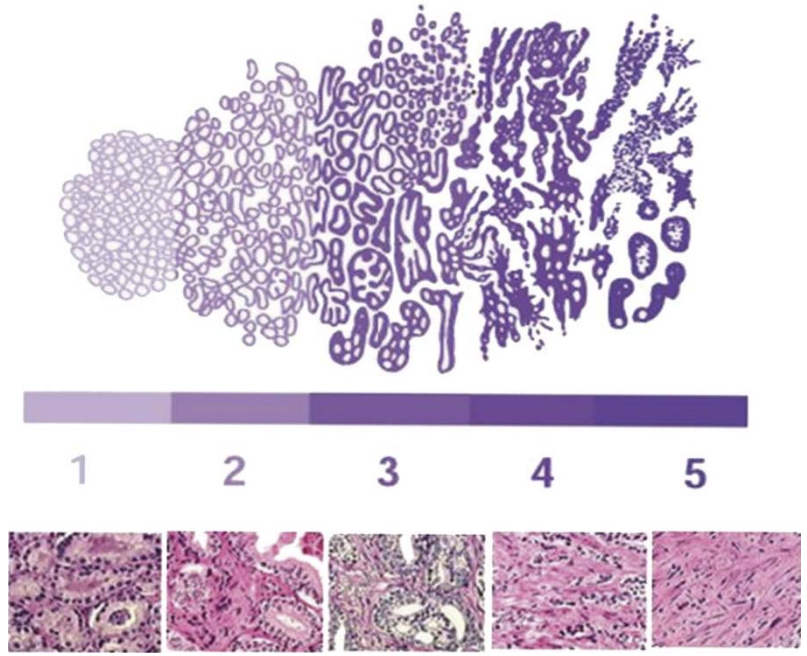
Nomenclature based on tissue type and malignancy/benignancy:

eg. *Adenoma* (benign) & *Adenocarcinoma* (malignant),
Fibroma & *Fibrosarcoma*
Neuroma & *Neuroblastoma*

ICD-O-3 - The International Standard for the classification and nomenclature of histologies is the International Classification of Diseases for Oncology, 3rd Ed.
NIH SEER Training Modules - US Department of Health & Human Services, National Institutes of Health, National Cancer Institute.

Tumor Grading

- **Grades**
  - G1 (undetermined)
  - G2 (well differentiated)
  - G3 (poorly differentiated)
  - G4 (undifferentiated)



- **Cancer type-specific** grading
  - Gleason Scoring - prostate cancer - calculated from pattern 1-5
  - → X, 1-6 (well diff.), 7 (moderately), 8-10 (poorly diff.)
  - Nottingham system - breast cancer
  - (based on tubule formation, nuclear grade, mitotic rate)

NCI – National Cancer Institute, at the National Institutes of Health - About Cancer – Prognosis, May 3rd 2013
American Joint Committee on Cancer. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010
The Gleason grading system - Harnden P. et al. The Lancet Oncology , Volume 8 , Issue 5 , 411 – 419, 2007

Cancer Staging

- Tumor location
- Cell type
- Tumor Size
- Spread to lymph nodes
- Spread to different parts of body
- Tumor grade = cell abnormality
  (proliferation rate, nuclear hyperchromasia, mitoses)

NCI – National Cancer Institute, at the National Institutes of Health - About Cancer – Diagnosis and Staging, March 9th 2015

Cancer Staging

- **TNM** system (extent/number/metastasis)

  X,0,T1-4, N1-3, M1

  eg. T3N0M0 (large tumor, no cancer in nearby lymph nodes/tissue, not spread to distant body parts)

- **Stage**

  0 (carcinoma in situ)

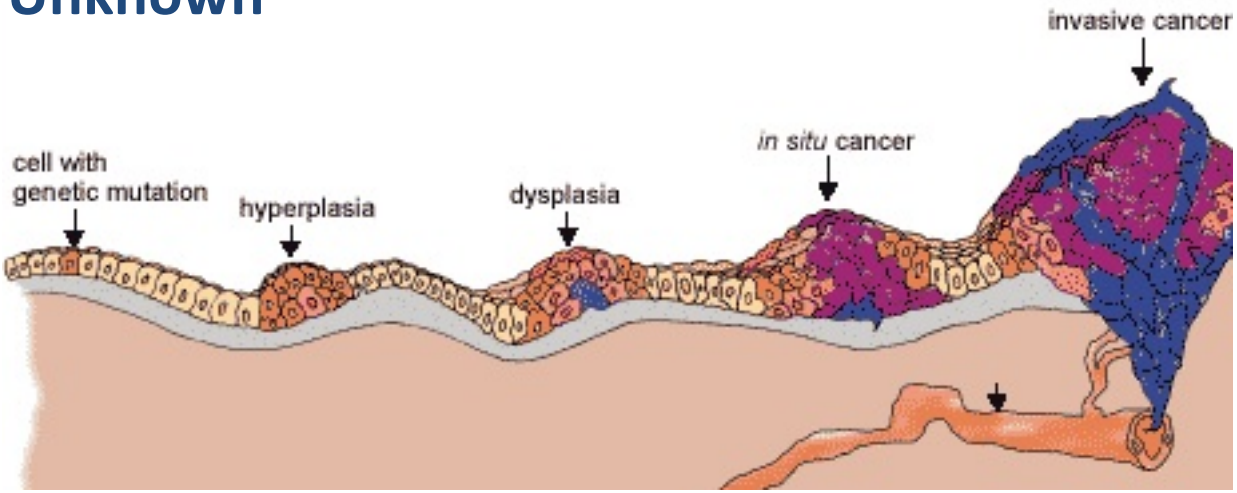
  I-III (size and spread to nearby tissue)

  IV (metastasis to distant parts)

NCI – National Cancer Institute, at the National Institutes of Health - About Cancer – Diagnosis and Staging, March 9th 2015

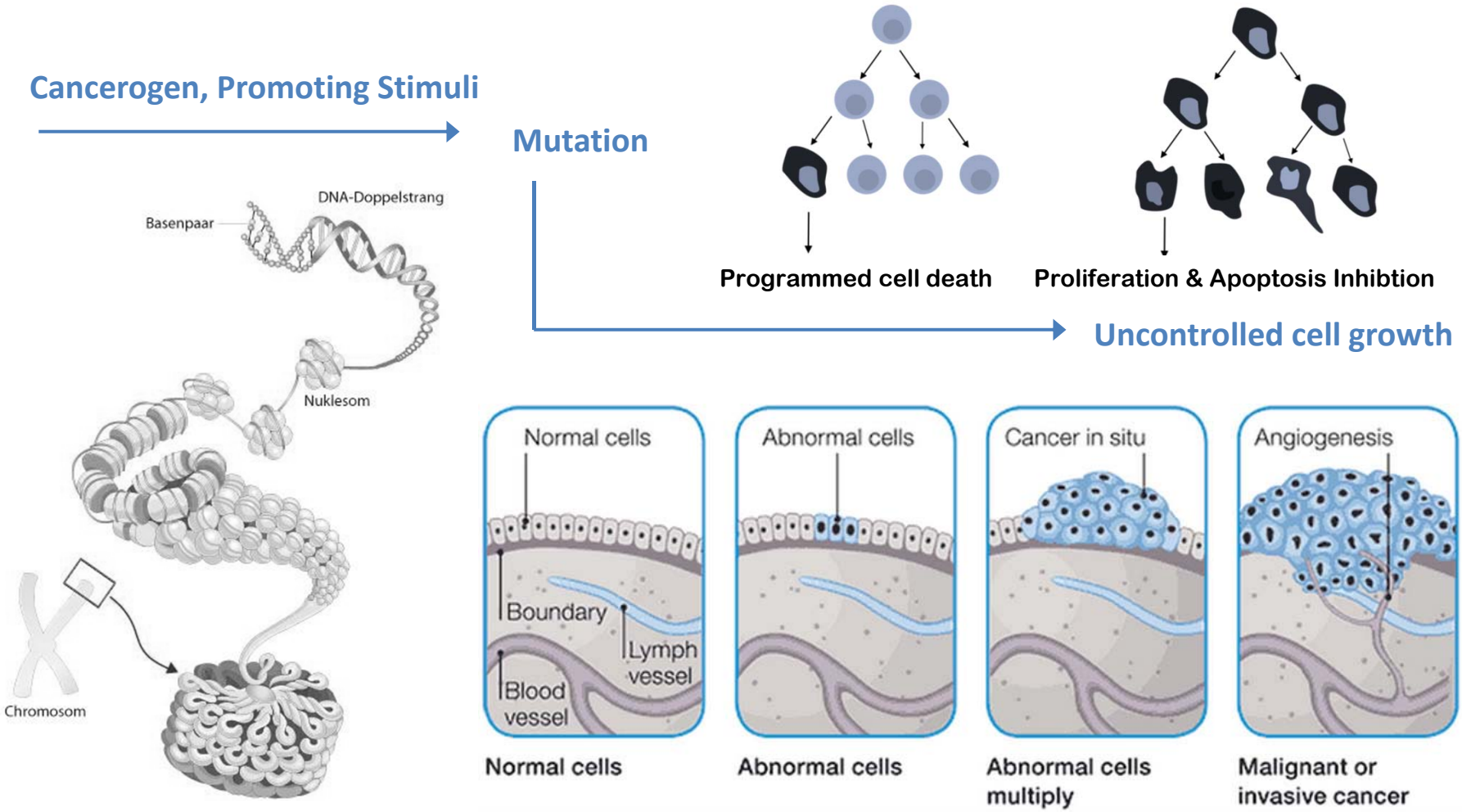
Cancer Staging

- **In situ** - abnormal cells present but not spread to nearby tissue
- **Localized** - cancer limited to origin, not spread
- **Regional** - cancer spread to nearby lymph nodes, tissues, organs
- **Distant** - cancer spread to distant parts of the body
- **Unknown**



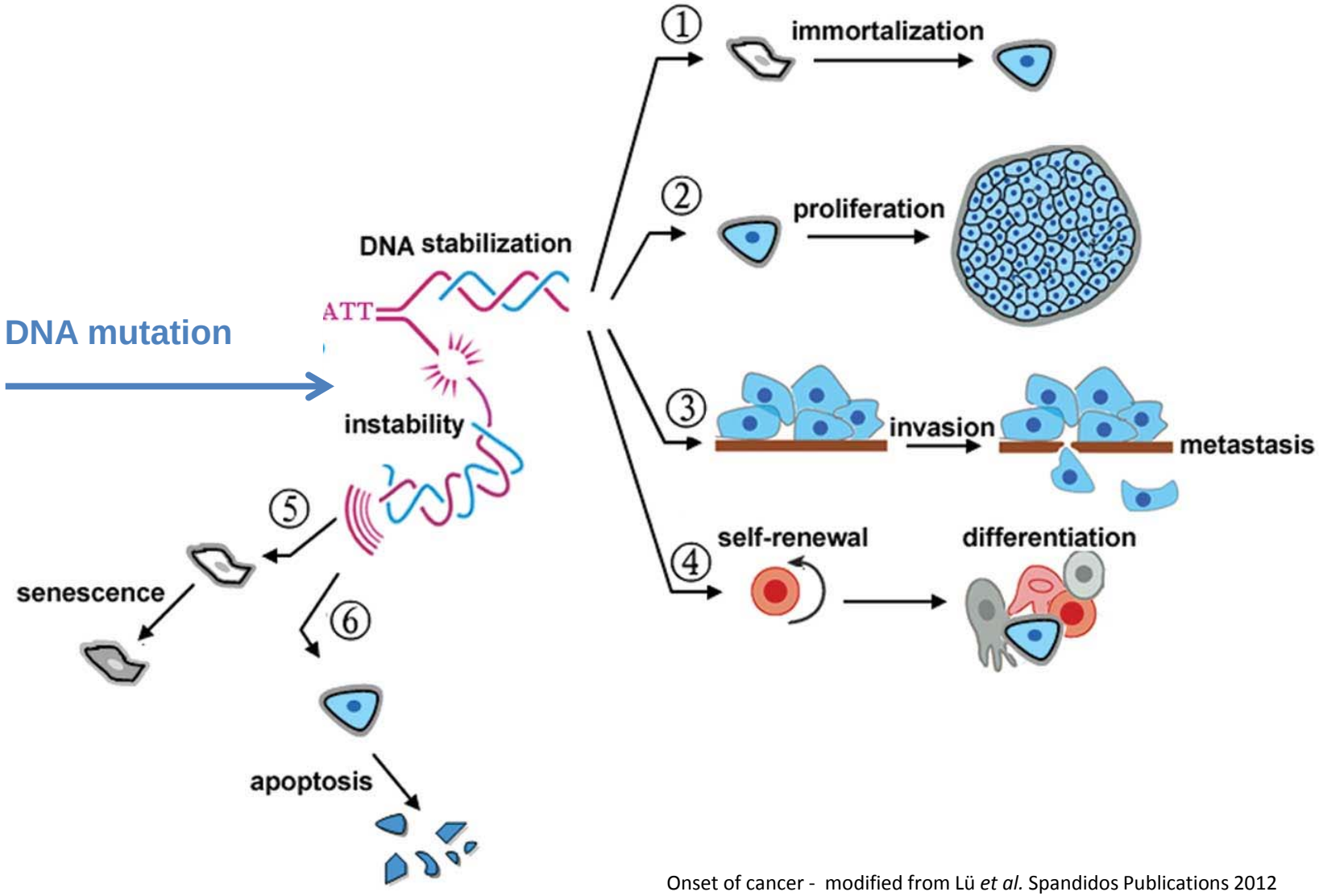
NCI – National Cancer Institute, at the National Institutes of Health - About Cancer - Diagnosis and Staging, March 9th 2015
Cancer progression - http://www.ndhealthfacts.org/wiki/Oncology_%28Cancer%29 - 07/2013

Development of cancer



DNA structure - Krebsinformationsdienst, Deutsches Krebsforschungszentrum Jan 2016.
S.Jorhaa'ir / Garak76, 2010 cell division – normal vs. cancer.
Cancer cycle and cancerous cells - © 2015 OncoSera.

Development of cancer



Onset of cancer - modified from Lü *et al.* Spandidos Publications 2012

What is Cancer: A biological background

- Differentiation

… cell changing to a more specialized cell type

- Proliferation

… growth: increase in cell number via cell division

- Mitosis

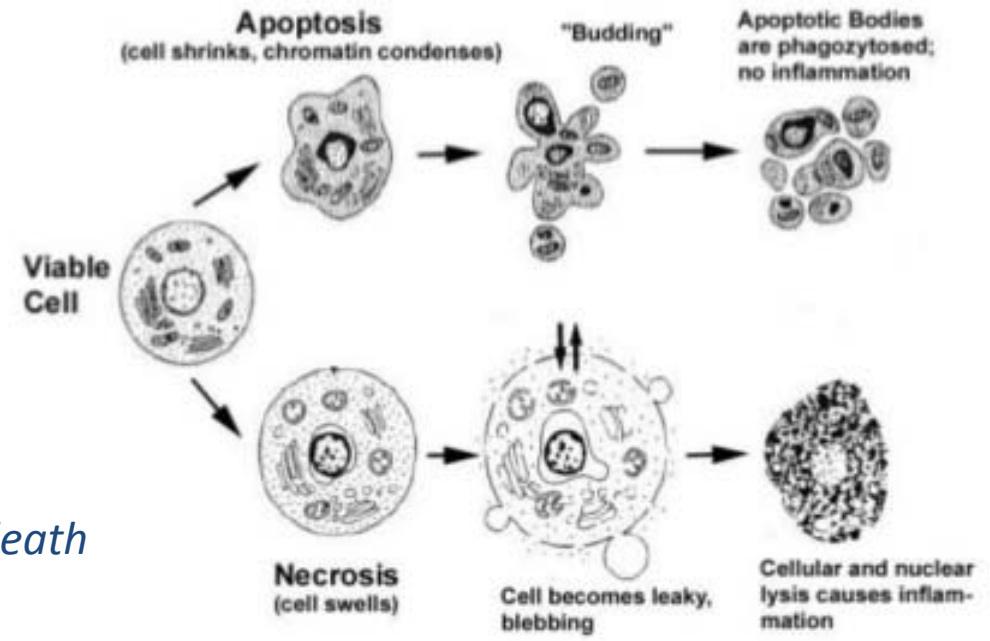
… cell division

- Apoptosis

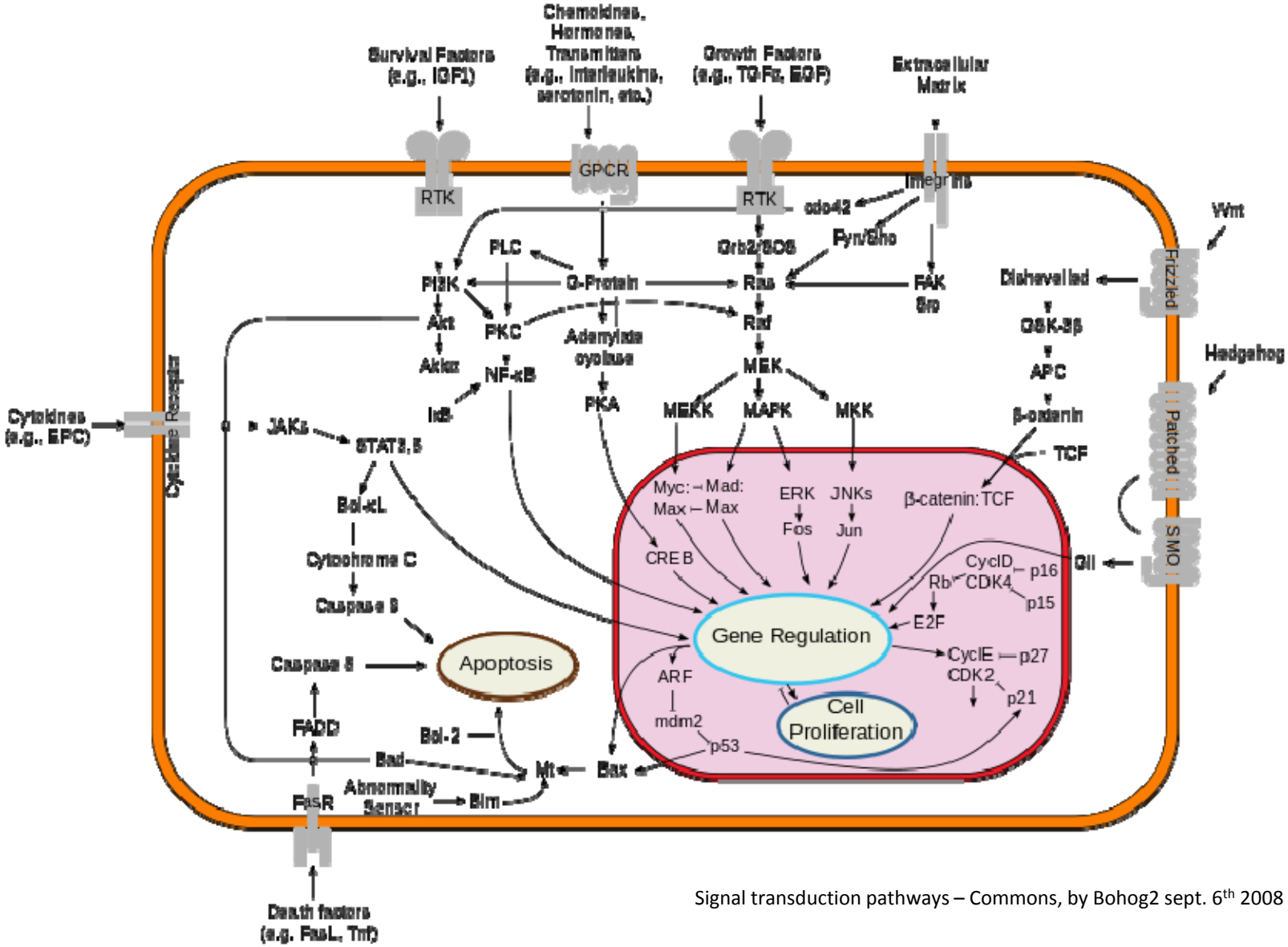
… programmed cell death, blocked in cancer cells

- Necrosis

… unprogrammed / general cell death



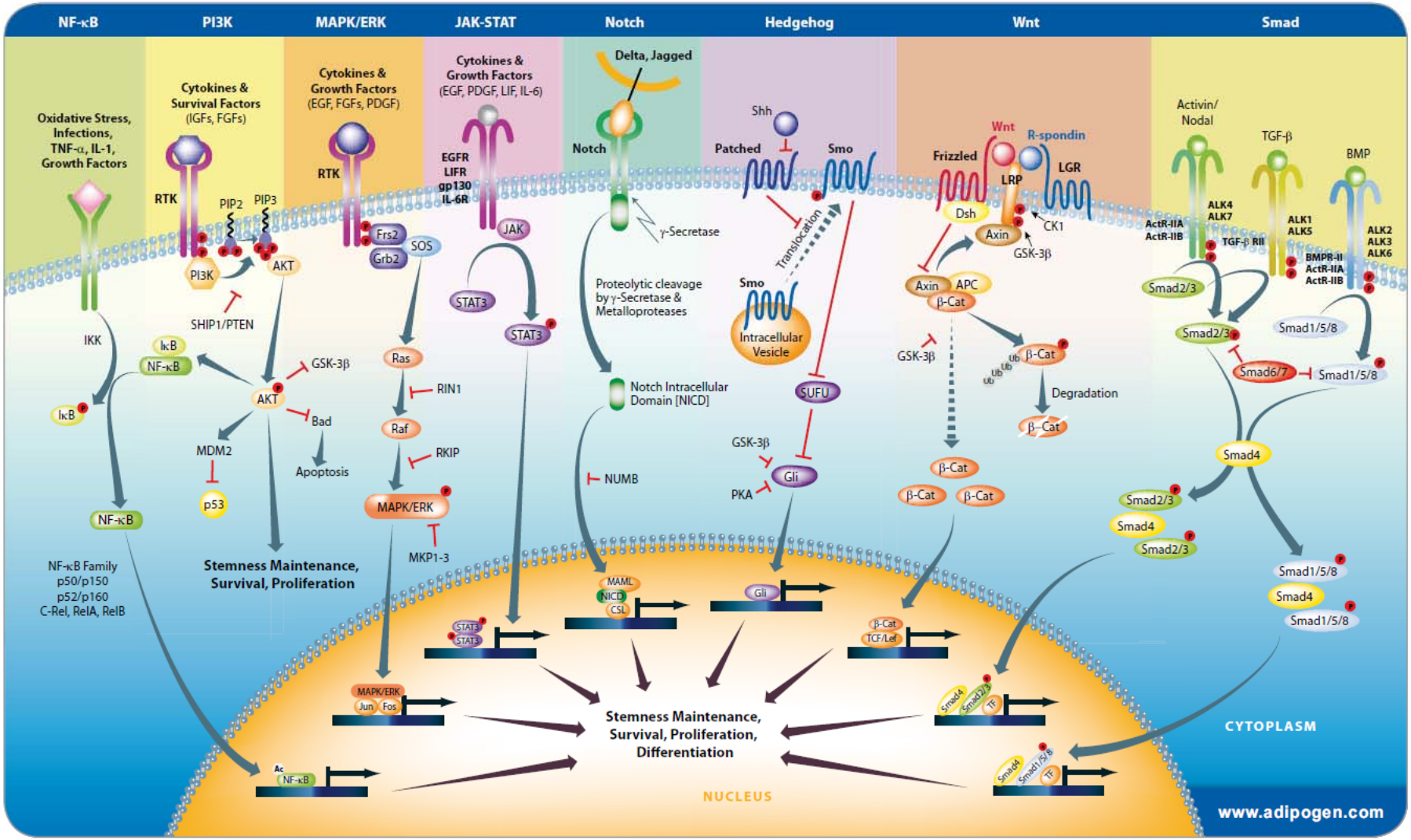
NCI Dictionary of Cancer Terms - US Department of Health & Human Services, National Institutes of Health, National Cancer Institute.
Intro to Apoptosis - Gewies A. Nov. 6th 2014, http://de.slideshare.net/richardhastings589/kumc-measuring-apoptosis-using-flow-cytometry

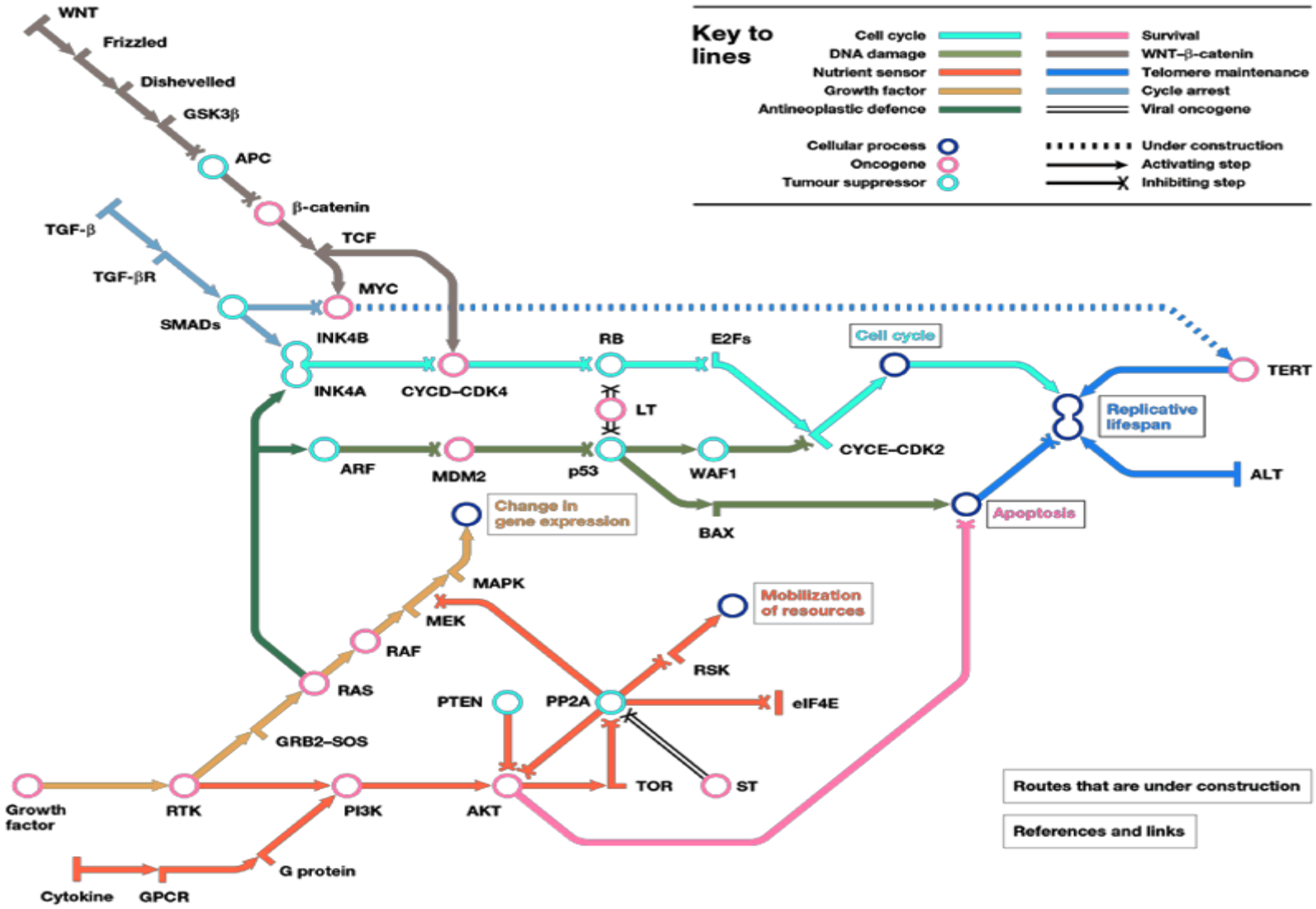


Signal transduction pathways – Commons, by Bohog2 sept. 6th 2008

Pathways on Cancer Signaling

Adipogen International
Schützenstrasse 12 · CH-4410 Liestal · Switzerland
TEL: +41-61-926-60-40 · FAX: +41-61-926-60-49
E-Mail: info@adipogen.com · www.adipogen.com





Subway map of Cancer pathways – Hahn WC, Weinberg RA, designed by Bentley C, edited by Brooksbank C and Clark S, © 2002 Nature Publishing Group.

Carcinogenicity

- Increased frequency in spontaneous formation of tumors
- Reduced latency time
- Tumor occurrence in additional tissues
- Increased number of tumors

- Genotoxicity: direct DNA damage
- Non-genotoxic: indirect damage on external genetic influence factors

GHS08
Health hazard

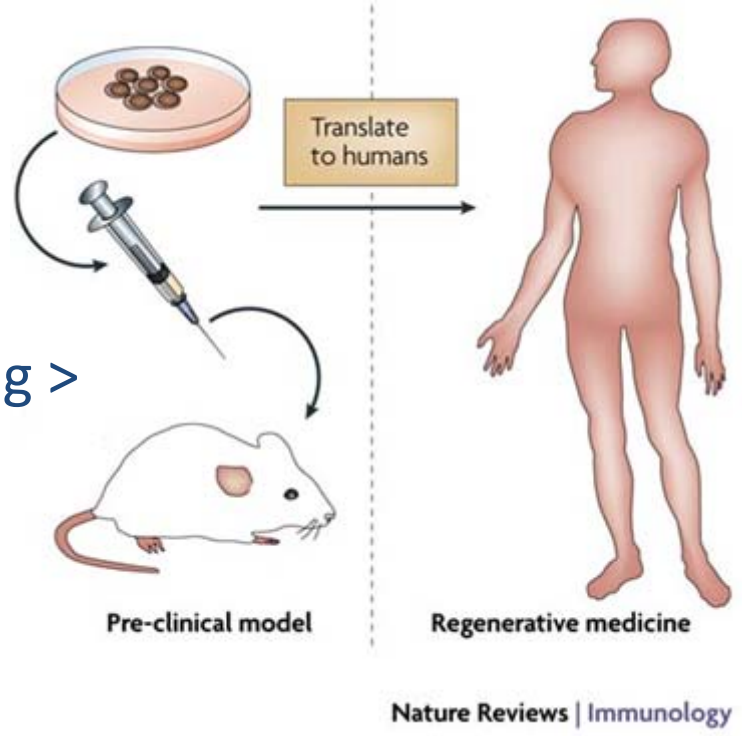
Carcinogenicity (H350, H351), Germ cell mutagenicity (H340, H341), Reproduction toxicity (H360, H361)

categories 1A/B, 2 (probability)

BG BAU – Berufsgenossenschaft der Bauwirtschaft, Berlin 2016, GISBAU – Gefahrstoff-Informationssystem

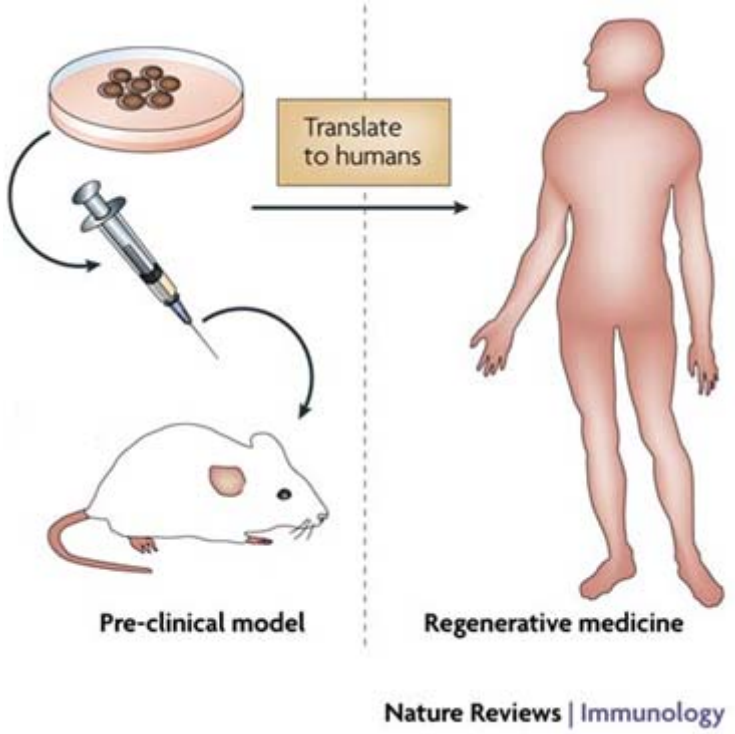
Toxicity / Cancerogenity studies

- Daily administration of test substance to animal (oral, dermal, inhalative) –18-30 months (live-long for rodents)
- Chron. toxicity by repeated dosing > 12 months
- Histopathological changes (hyperplasia, atypia), rates of cell division



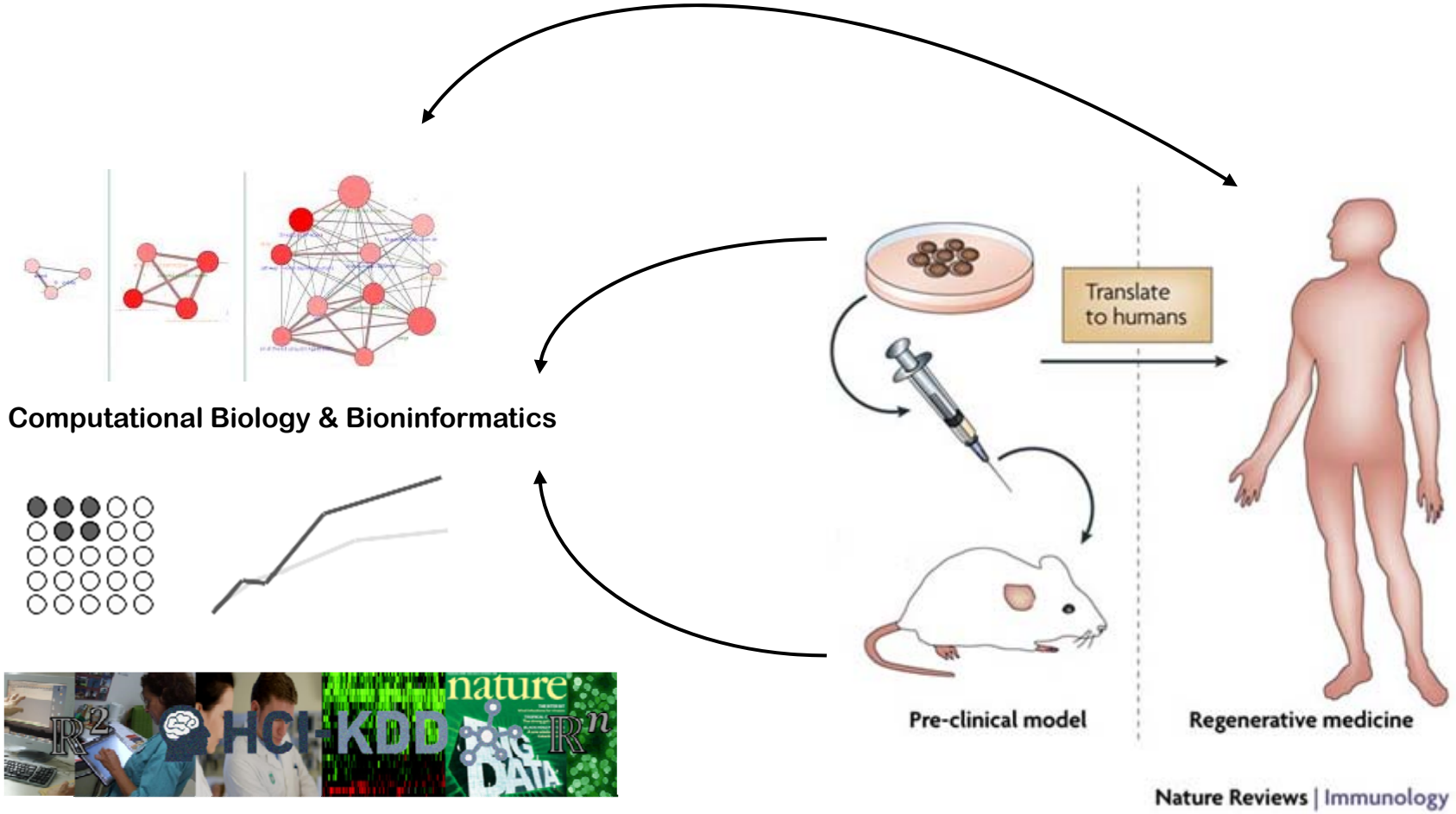
Humanized mice in translational biomedical research, Leonard D. Shultz, Fumihiko Ishikawa and Dale L. Greiner, Nature Reviews Immunology 7, 2007
REACH (EG) Nr. 1907/2006 - registration, evaluation, approval and limitation of chemical substances, updated (EU) 2015/830.
Regulation 440/2008 - agreement on test methods according regulation 1907/2006, last update 07.12.2016 – (EU) 2016/266.

Cancer studies



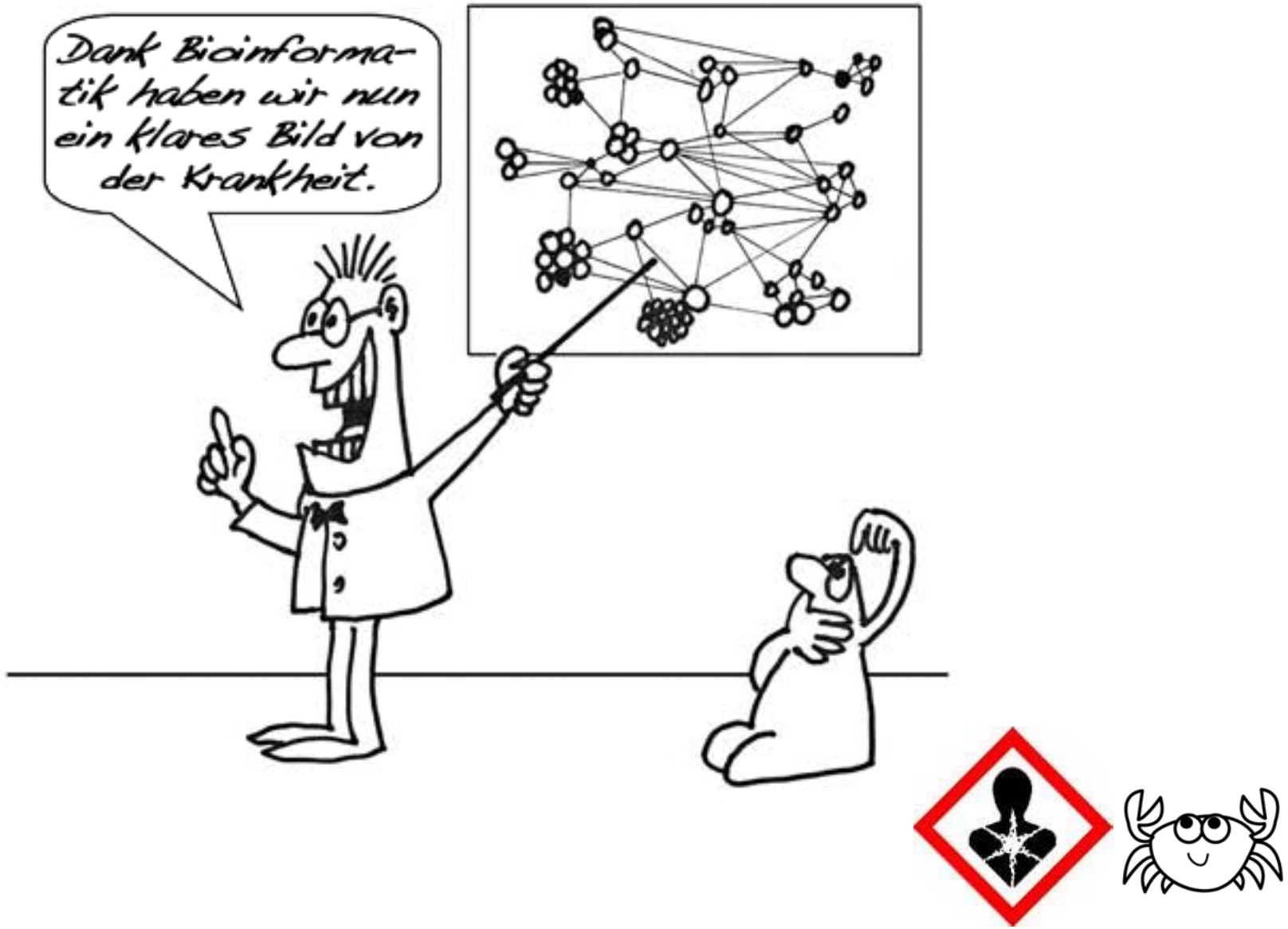
Humanized mice in translational biomedical research, Leonard D. Shultz, Fumihiko Ishikawa and Dale L. Greiner, Nature Reviews Immunology 7, 2007
Mouse xenograft surgery - www.youtube.com/watch?v=R2Wka7YhhAo

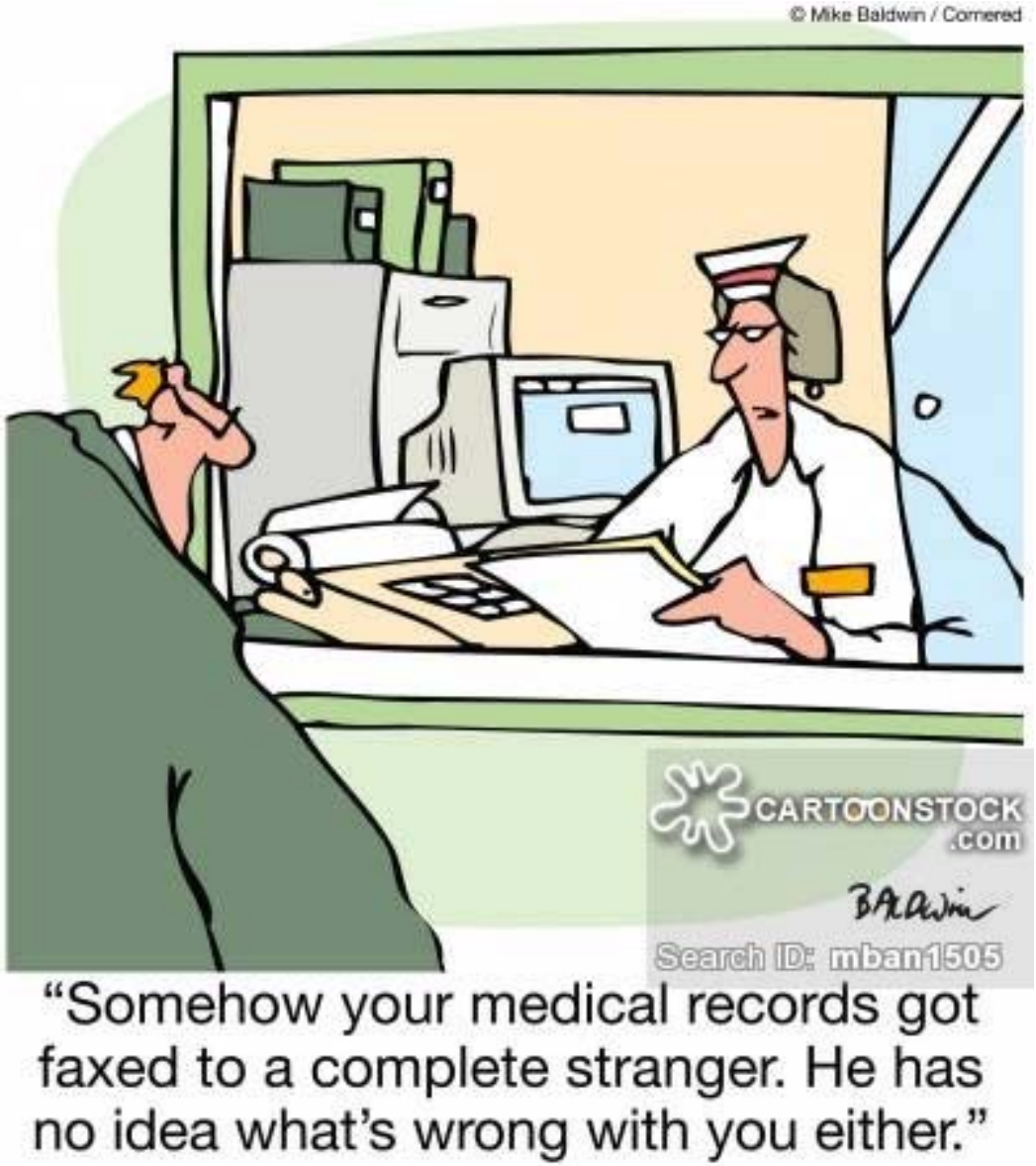
https://www.youtube.com/watch?v=R2Wka7YhhAo



Humanized mice in translational biomedical research, Leonard D. Shultz, Fumihiko Ishikawa and Dale L. Greiner, Nature Reviews Immunology 7, 2007
Jeanquartier et al. 2016

In Silico Biomedicine – Motivation




© Mike Baldwin / Cornered
CARTOONSTOCK .com
Search ID: mban1505
"Somehow your medical records got faxed to a complete stranger. He has no idea what's wrong with you either."

Time for a coffee break !

Part 2
Computational Modelling

In Silico Biomedicine - Motivation

Are Computers better doctors?

Duerr-Specht, M., Goebel, R. & Holzinger, A. 2015. Medicine and Health Care as a Data Problem: Will Computers become better medical doctors? In: Springer Lecture Notes in Computer Science LNCS 8700. pp. 21-40, doi:10.1007/978-3-319-16226-3_2

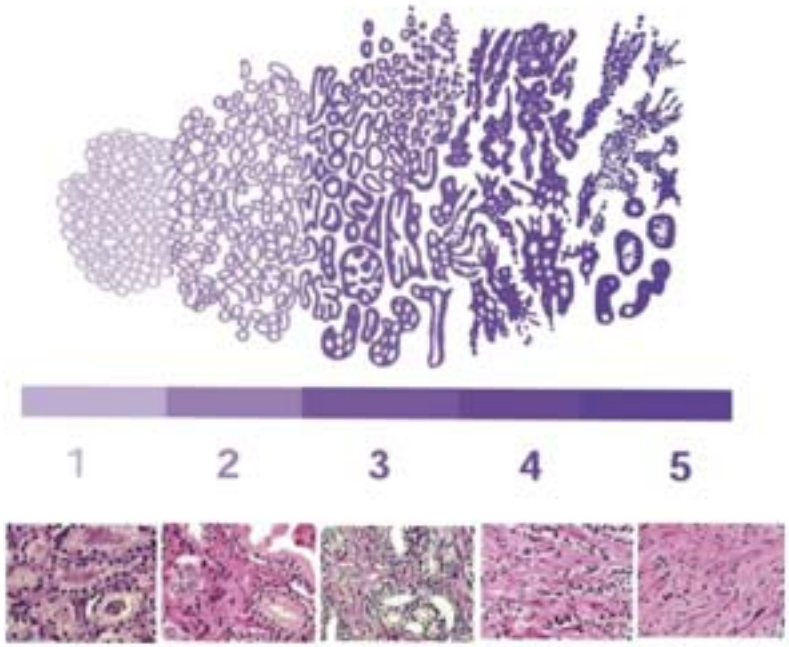
Key Problems

- Inter- and intracellular **dynamics**
- avoiding **hard-to-measure** variables
- **Inflexible** models
- *in silico* **complements** *in vivo*
- *executable (cell) biology*
- **reduce** animal experiments (resources)
- **boost** *in silico* for awareness & breakthrough
- patient-**personalized** prediction

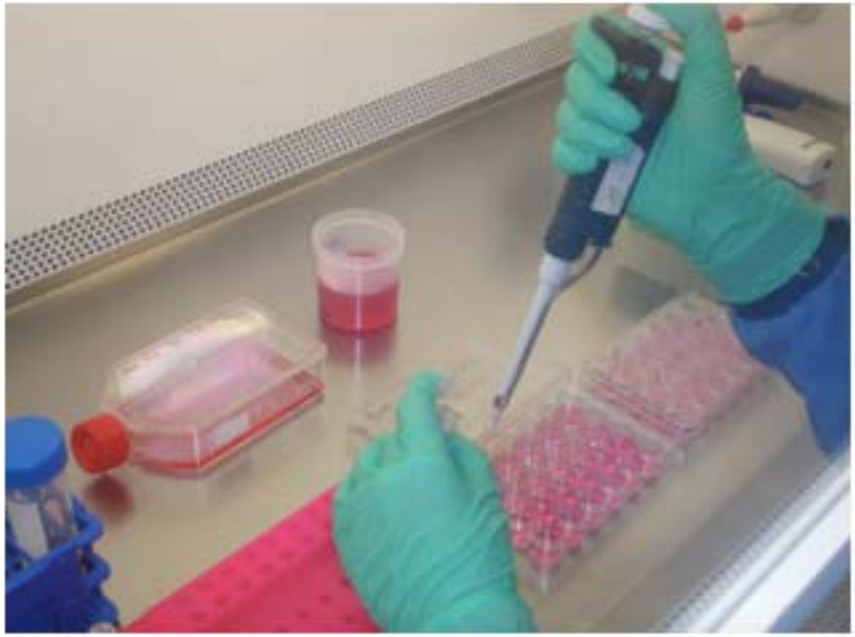
Edelman, L. B., Eddy, J. A. & Price, N. D. 2010. In silico models of cancer. Wiley Interdisciplinary Reviews: Systems Biology and Medicine, 2, (4), 438-459, doi:10.1002/wsbm.75.

Fisher, J. & Henzinger, T. A. 2007. Executable cell biology. Nature biotechnology, 25, (11), 1239-1249, doi:10.1038/nbt1356.

- Images of



tissue



wet research

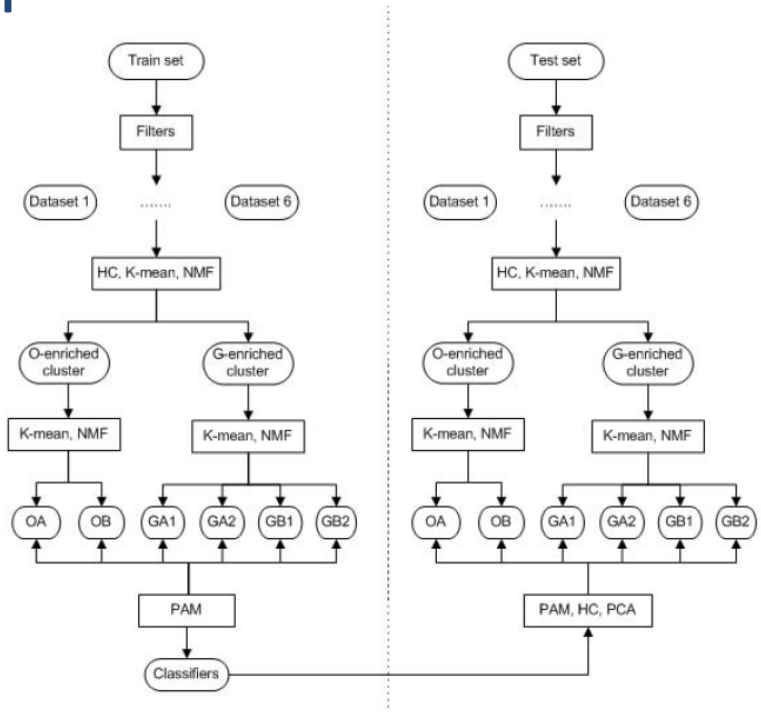
The Gleason grading system - Harnden P. et al. The Lancet Oncology , Volume 8 , Issue 5 , 411 – 419, 2007

Overview of Machine Learning for cancer research

- ML in Genomics
  - such as DNA micro array analysis for cancer classification etc.
  - => for *identification & treatment*
- ML in image analysis
  - such as for classifying and/or differentiating benign from malignant samples etc.
  - => for *diagnosis & prognosis*
- ML in cancer research is growing rapidly
  - combination of molecular patterns and clinical data
  - deep text-mining offers new possibilities
  - etc.

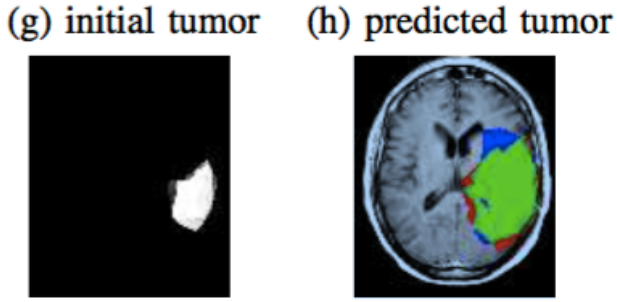
Cruz, J. A., & Wishart, D. S. (2006). Applications of machine learning in cancer prediction and prognosis. Cancer informatics, 2.

- Example: Glioma Classification
  - Using gene expression data
  - Unsupervised ML approach on genome-wide gene expression profiles of 159 gliomas
  - Model predicts
    - two major groups,
    - separated into six subtypes,
    - previously unrecognized prognostic groups within TCGA published data could be found



Aiguo Li, Jennifer Walling, Susie Ahn, Yuri Kotliarov, Qin Su, M. Quezado, J. C. Oberholtzer, J. Park, J. C. Zenklusen, H. A. Fine: Unsupervised Analysis of Transcriptomic Profiles Reveals Six Glioma Subtypes, DOI: 10.1158/0008-5472.CAN-08-2100 Published 1 March 2009

- Example: Modeling glioma tumor growth
  - Using image data (MRI scans)
  - ***Learn*** the parameters of a diffusion model
    - Using patient data
    - Preprocessing images
      - noise reduction, linear register and warp to standard coordinate system, reducing inhomogeneity, Intensity standardization, segmentation between grey and white matter...
    - Feature extraction
  - => **Prediction** through classification & diffusion



Morris, M., Greiner, R., Sander, J., Murtha, A., & Schmidt, M. (2006). Learning a classification-based glioma growth model using MRI data. Journal of Computers, 1(7), 21-31.

- There are **different kinds of models** in biology, such as
  spatial ones, space free ones but also cell descriptive models based on density, or cell-based, or sub-cellular or molecular, (relating to their scale of phenomenon)

Szabó, A., & Merks, R. M. (2013). Cellular potts modeling of tumor growth, tumor invasion, and tumor evolution. Frontiers in oncology, 3

- Visualization Applications At Different Biological Scales

Atoms | DNA/RNA | Proteins | Viruses | Bacteria | Cells | Tissues

nucleic acids and bigger biomolecules…

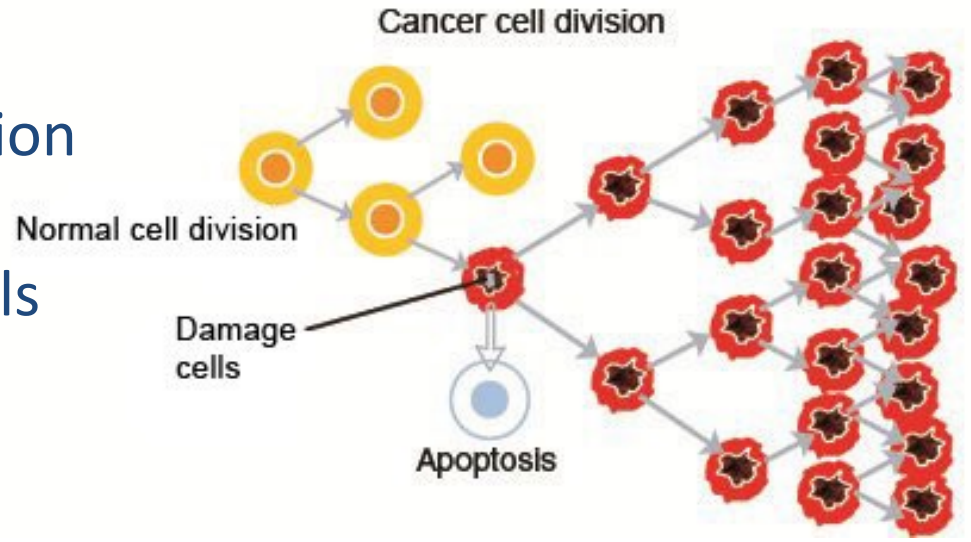
…

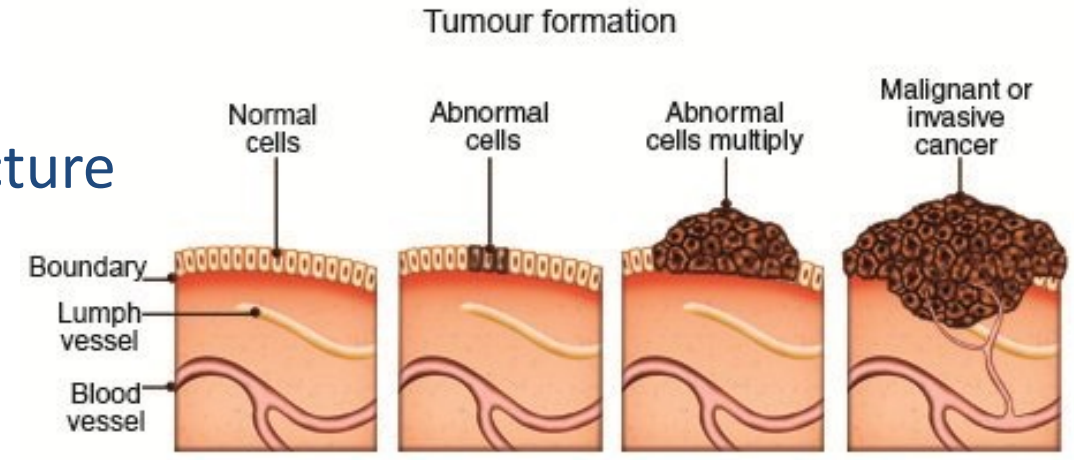
log. scale →

0.1nm | 1nm | 10nm | 100nm | 1micron | 1mm

Nanoscale | *Microscale* | *Mesoscale*

- Tumor growth
- **complex disease**: simplification & approximation
- **differentiation** of normal cells
- excessive **proliferation**
- either **dormant** or **growing**
- **critical** mass
  - growth stops
  - migration (metastasis)
- **underlying** network structure
- environmental heterogeneities





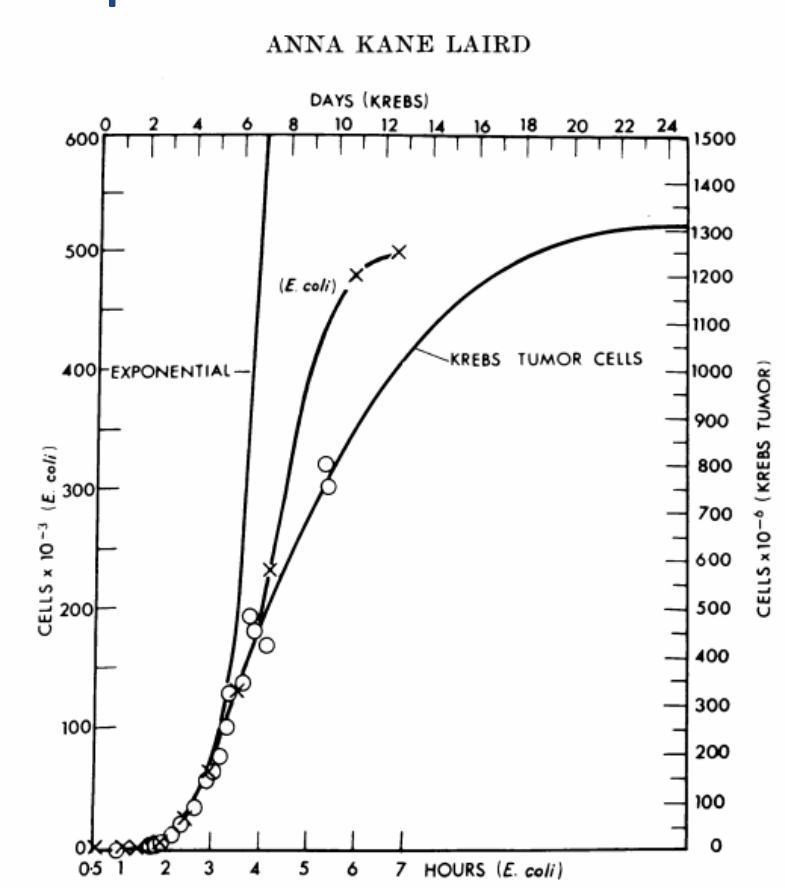
Choe, S. C., Zhao, G., Zhao, Z., et al. (2011). Model for in vivo progression of tumors based on co-evolving cell population and vasculature.
Scientific reports, 1.

- A tumor can be seen as ***spatio-temporal*** pattern formation
- Spatial & temporal data exist an can be used for improving existing simulation & analysis tools
- Several attempts have been made to ***model*** and ***predict*** malignant tumor

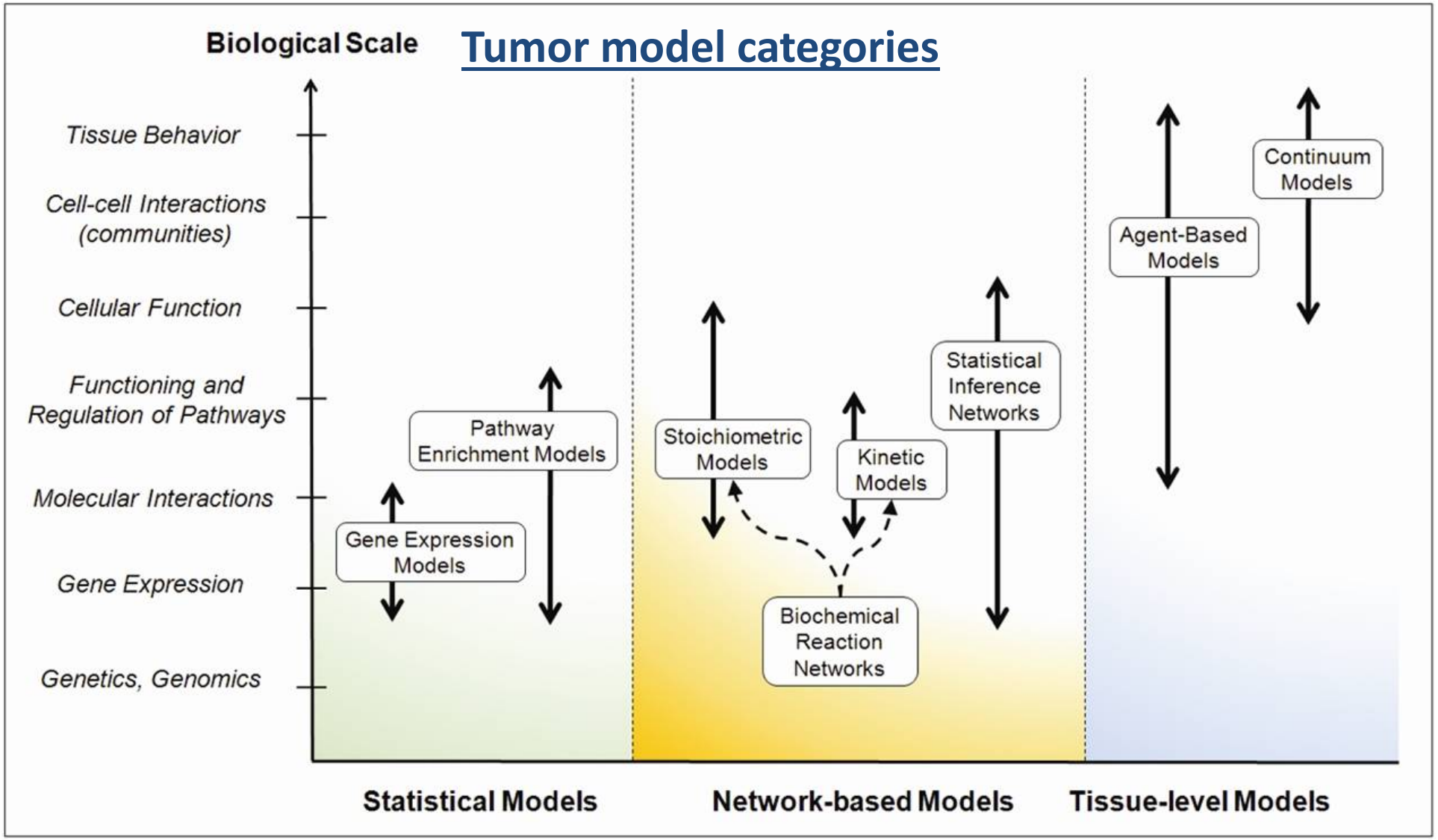
Jeanquartier, F., Jean-Quartier, C., Schreck, T., Cemernek, D. & Holzinger, A. : Integrating Open Data on Cancer in Support to Tumor Growth Analysis.
ITBAM. Springer Lecture Notes in Computer Science. LNCS 9832, 2016.

Moreira, J., & Deutsch, A. (2002). Cellular automaton models of tumor development: a critical review. Advances in Complex Systems, 5, 247-267

- Tumor growth **kinetics follow** simple laws
- Mathematical models **exist**
  f.i. Gompertz or power law
- No **universal** law
- Prediction rate low and/or distinct



Benzekry, S., Lamont, C., Beheshti, et al. (2014). Classical mathematical models for description and prediction of experimental tumor growth.



Edelman, L. B., Eddy, J. A., & Price, N. D. (2010). In silico models of cancer.

- Continuum vs. Discrete/Agent-based Modeling

Continuum	Discrete
continuously distributed variables	discrete entities in discrete time intervals
interactions between factors representing several effects of physiologial/biochemical events	interactions in a single space representation
f.i.: simulating population dynamics, combinatoric effects of several nutrient availability and other parameters etc.	f.i.: simulating agent dynamics, probabilistics of each time step, a small number of individuals

Edelman, L. B., Eddy, J. A., & Price, N. D. (2010). In silico models of cancer.

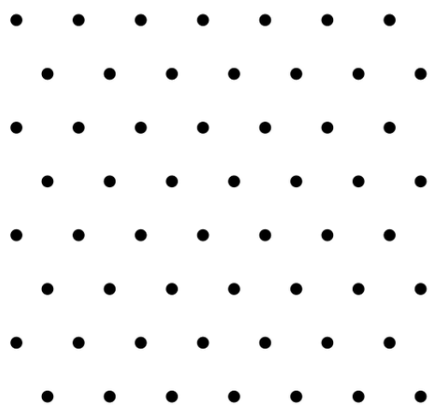
Tumor Growth Modeling

- Cellular Automaton (CA) approach to modeling biological cells
- CAs are:
  - **Discrete**
  - Abstraction of a system
  - **Computational**
  - At each time, each cell instantiates one state of a finite set of states
- CA for tumor growth with rules:
  - Cell division, movement, change or not change state…
- **“On-lattice”** modelling (see next slide)

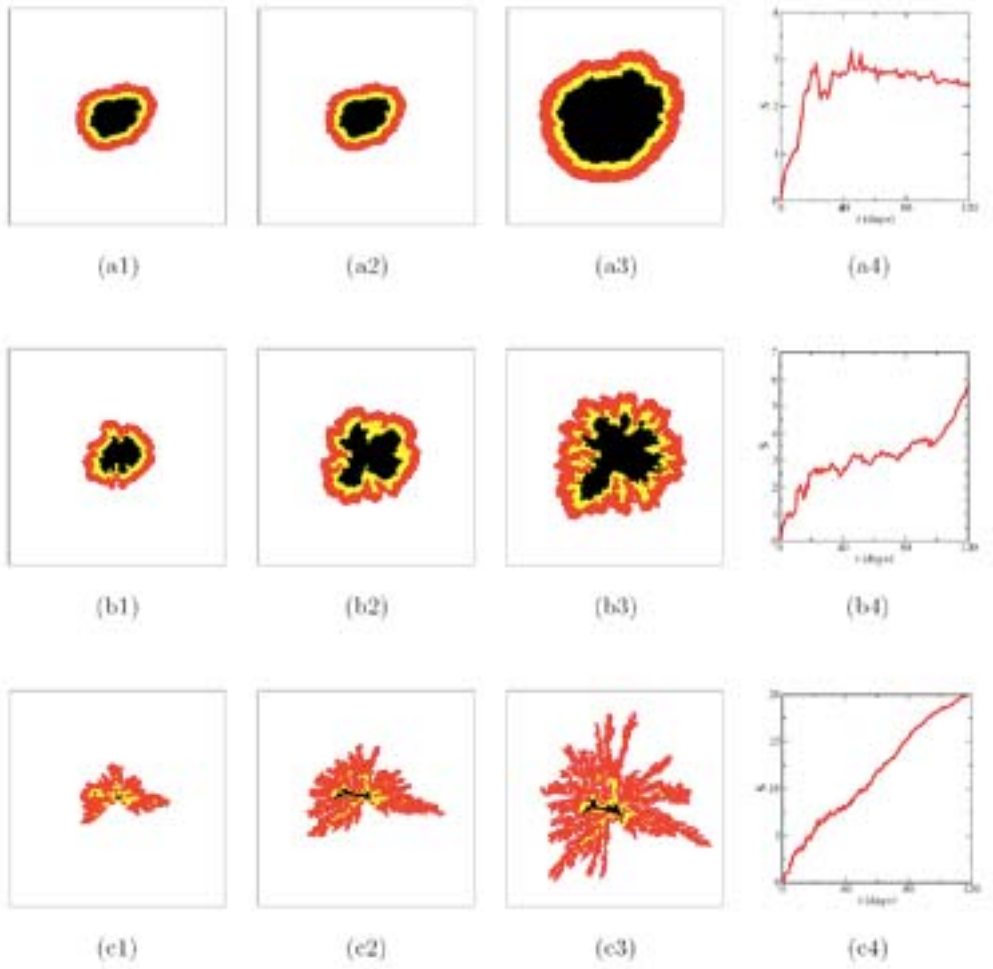
Moreira, J., & Deutsch, A. (2002). Cellular automaton models of tumor development: a critical review. Advances in Complex Systems, 5(02n03), 247-267.

The meaning of “Lattice”

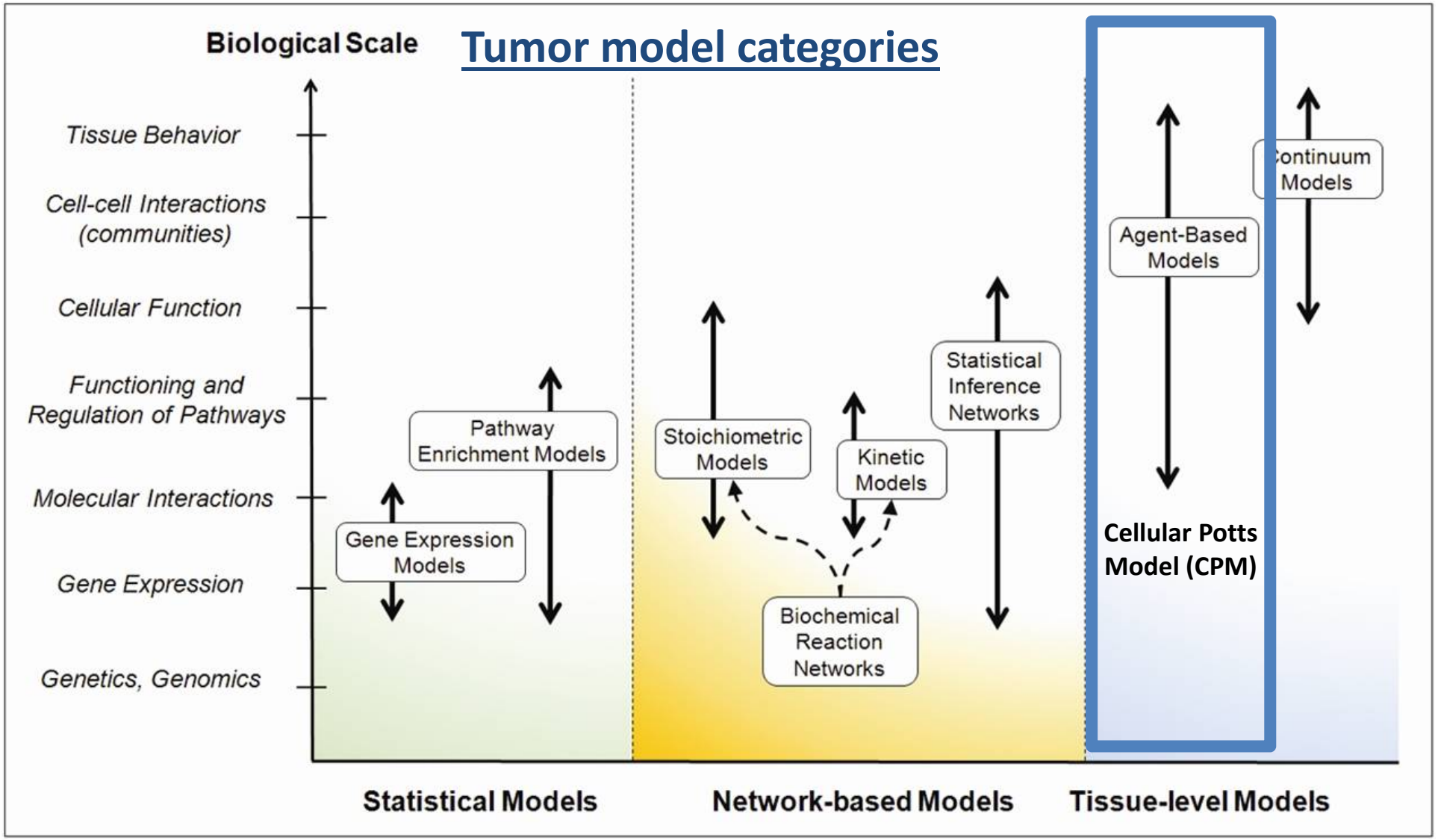
- **In abstract algebra** it is a fundamental algebraic structure, consisting of a partially ordered set in which every two elements have a unique supremum (join) and a unique infimum (meet). An example is given by the natural numbers, partially ordered by divisibility, for which the unique supremum is the least common multiple and the unique infimum is the greatest common divisor.
- **In geometry** a lattice in $\mathbb{R}^n$ is a subgroup of $\mathbb{R}^n$, which is isomorphic to $\mathbb{Z}^n$, and which spans the real vector space $\mathbb{R}^n$, i.e. for any basis of $\mathbb{R}^n$ the subgroup of all linear combinations with integer coefficients of the basis vectors forms a lattice. A lattice may be viewed as a regular tiling of a space by a primitive cell.



- Simulated Growth of Solid Tumors in Confined Heterogeneous Environment



Jiao, Y., & Torquato, S. (2011). Emergent behaviors from a cellular automaton model for invasive tumor growth in heterogeneous microenvironments. PLoS Comput Biol, 7(12)



Edelman, L. B., Eddy, J. A., & Price, N. D. (2010). In silico models of cancer.

CPM

- **Model for cell sorting**
- **Describes** cell-cell interaction, motion, rearrangement, pressure inside tissue
- **Suitable** for pathol. developmental mechanisms in cancer
- **Cell-based** method on the **lattice**
- 2D lattice represents tissue
- Collection of particles to represent the cell
- Each cell is represented as an object with a possible **adhesive** state, spatially extended
- cells are composed of adjacent lattice sites with similar id nr.
- system tends to minimize overall surface energy (energy per unit of area)

Szabó, A., & Merks, R. M. (2013). Cellular potts modeling of tumor growth, tumor invasion, and tumor evolution. Frontiers in oncology, 3

CPM originally developed by Graner & Glazier 1992

$$p(\sigma_{i,j} \rightarrow \sigma_{i',j'}) = \begin{cases} e^{\frac{-\Delta H}{T}} & \text{if } \Delta H > 0; \\ 1 & \text{if } \Delta H \leq 0; \end{cases}$$

Probability of accepting/rejecting a spin copy

Szabó, A., & Merks, R. M. (2013). Cellular potts modeling of tumor growth, tumor invasion, and tumor evolution. Frontiers in oncology, 3

Note that this is an approach with Reals – not discrete – but we are working on discrete multi-agent approaches in the future!

CPM originally developed by Graner & Glazier 1992

$$H = J \sum_{i,j} (1 - \delta_{\sigma_{i,j}\sigma_{i',j'}}) + \lambda \sum_{\sigma} (v(\sigma) - V_t(\sigma))^2$$

Kronecker delta $\delta_{ij} = \begin{cases} 0 & \text{if } i \neq j, \\ 1 & \text{if } i = j. \end{cases}$

σ	spin of a cell
J	surface energies between spins (adhesion)
λ	cellular constraint, function of elasticity
$v(\sigma)$	area/volume of a cell
$V_t(\sigma)$	target area for cells of type

Szabó, A., & Merks, R. M. (2013). Cellular potts modeling of tumor growth, tumor invasion, and tumor evolution. Frontiers in oncology, 3

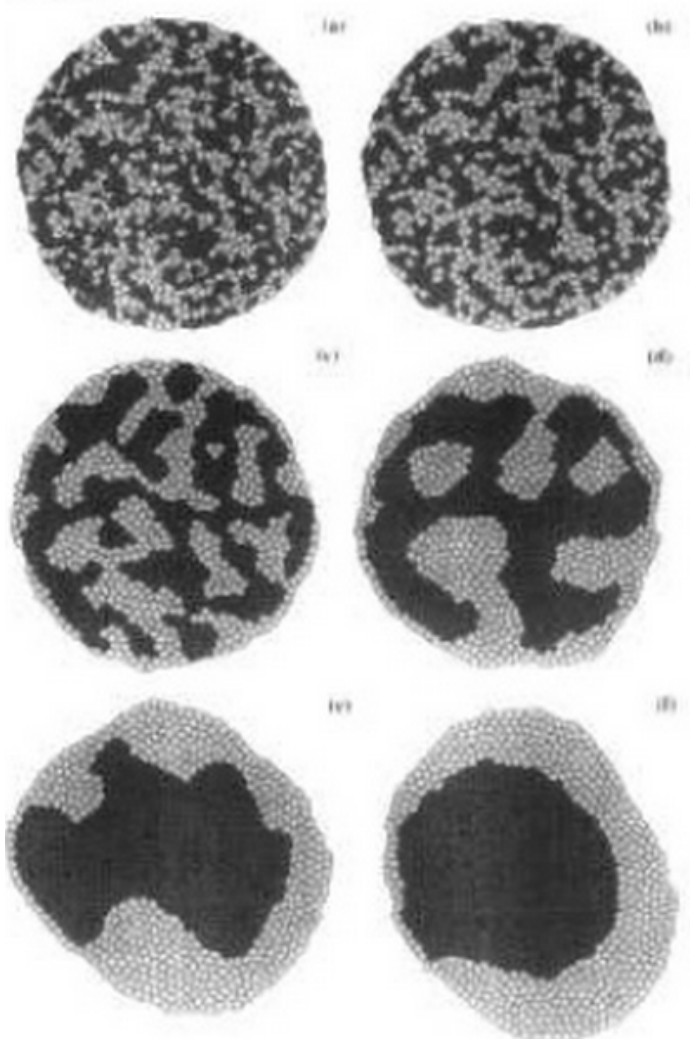


Image of a cell sorting time series

- initial: random assigned cell types
- each step represents a growing number of Monte Carlo Step (MCS)
- figure shows pattern

Graner, F., & Glazier, J. A. (1992). Simulation of biological cell sorting using a two-dimensional extended Potts model. Physical review letters, 69(13), 2013.

Our idea:

- **Reducing** animal experiments
- **Visualizing** tumor dynamics towards better understanding
- **Easy**-to-use
- Easy-to-**extend**
- **Implementation** of Cellular Potts Model
  - visualized with cytoscape.js (web application)
  - other client rendering frameworks
  - … based on network visualization in biology
- **Support** biologists and clinical scientists
  - ultimate goal

Jeanquartier, F., Jean-Quartier, C., Cemernek, D. & Holzinger, A. In Silico Modeling For Tumor Growth Visualization. BMC In revision.
Jeanquartier, F., Jean-Quartier, C., Schreck, T., Cemernek, D. & Holzinger, A. Integrating Open Data on Cancer in Support to Tumor Growth Analysis. Information Technology in Bio- and Medical Informatics, LNCS 9832, 2016.
Jeanquartier, F., Jean-Quartier, C., Cemernek, D. & Holzinger, A. Tumor Growth Simulation Profiling. LNCS 9832, 2016.

Implementation Example: Tumor Growth Visualization

```
for Number of MCS do
  for Appropriate number of samples (substeps) do
    Calculate the Hamiltonian in current state, H0;
    Select a lattice site, i, from the domain at random;
    Select a neighbour, j, of this site at random;
    Change config so that site i refers to same cell as site j
    (if not ecm)
    Calculate the Hamiltonian in new configuration, H1;
    if DeltaH = H1 - H0 <= 0, then
      Accept change;
    else
      Evaluate p = exp((-DeltaH)\(T));
      Sample a number u from U(0, 1);
      if p < u, then
        Accept change;
      end
    end
    If change is rejected, then restore original confirmation.
  end
end
```

J. M. Osborne. (2015). Multiscale Model of Colorectal Cancer Using the Cellular Potts Framework. Cancer Informatics, 14(Suppl. 4), p83-93

Implementation Example: Tumor Growth Visualization

*CPM **implementations** already exist:*

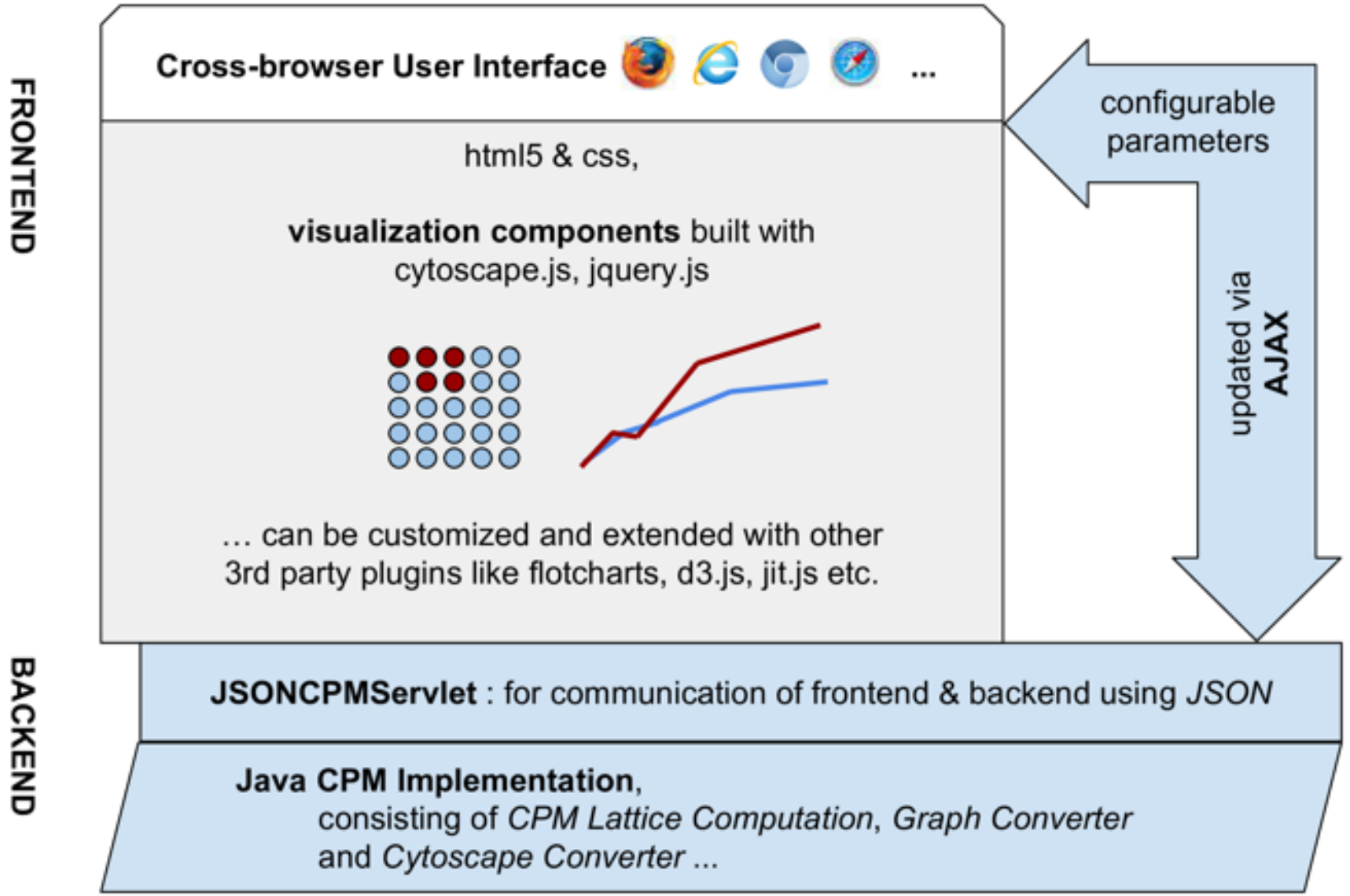
- CompuCell3d
- Tissue Simulation Toolkit

However

- though „community-driven“, not maintained
- context-specific
- static
- lack of re-usability
- hard to be combined with visualization libraries
- no web implementation
- not useful for interactive visualization

Jeanquartier, F., Jean-Quartier, C., Cemernek, D. & Holzinger, A. In Silico Modeling For Tumor Growth Visualization. BMC In revision.
Szabó, A., & Merks, R. M. (2013). Cellular potts modeling of tumor growth, tumor invasion, and tumor evolution. Frontiers in oncology, 3.

Implementation Example: Tumor Growth Visualization

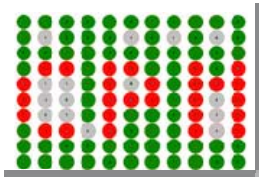


Implementation Example: Tumor Growth Visualization

CPMLattice.java | CPMLatticeCalculationParams.java | JSONCPMServlet.java | GraphToCytoscapeJSONConverter.java | cpm.js

```
energyArea = 0;
newEnergyArea = 0;

//if cell is of type ECM then the Area calculation is suppressed
if (cell > 0) {

    energyArea = params.getLambdaArea() *(Math.pow((area[cell] - getTargetAreaForCell(cell)), 2));
    //logger.debug("energyArea=" + energyArea + "  (0.05 * (" + area[cell] + " - " + getTargetAreaForCell(cell) + ")^2 )");
}

//if cell neighbor is of type ECM then the Area calculation is suppressed
if (cellNeighbour > 0) {

    newEnergyArea = params.getLambdaArea() * (Math.pow((area[cellNeighbour] - getTargetAreaForCell(cellNeighbour)),2));
    //logger.debug("newEnergyArea=" + newEnergyArea + "  (0.05 * (" + area[cellNeighbour] + " - " + getTargetAreaForCell(cellNeighbour) + ")^2 )");

}

/* The overall deltaH = AFTER-BEFORE
deltaH = (newEnergyAdhesion + newEnergyArea) - (energyAdhesion + energyArea);
//logger.debug("deltaH = " + deltaH + "  ((" + newEnergyAdhesion + "+" + newEnergyArea + ") - (" + energyAdhesion + "+" + energyArea + "))");

// spin-copy for a temperature > 0 is accepted
//  with prob = 1.0 if it would decrease the value of globally Hamiltonian
//  or with Boltzmann probability if it would increase the value of Hamiltonian
if (params.getTemperature() > 0) {

    if (deltaH > 0) {

        prob = Math.exp(-deltaH / params.getTemperature()); // Boltzmann
        //logger.debug("prob="+prob);

    } else if (deltaH <= 0) {

        prob = 1.0;

    }

} else if (params.getTemperature() == 0) {

    if (deltaH > 0) {

        prob = 0;
```

CODE PREVIEW



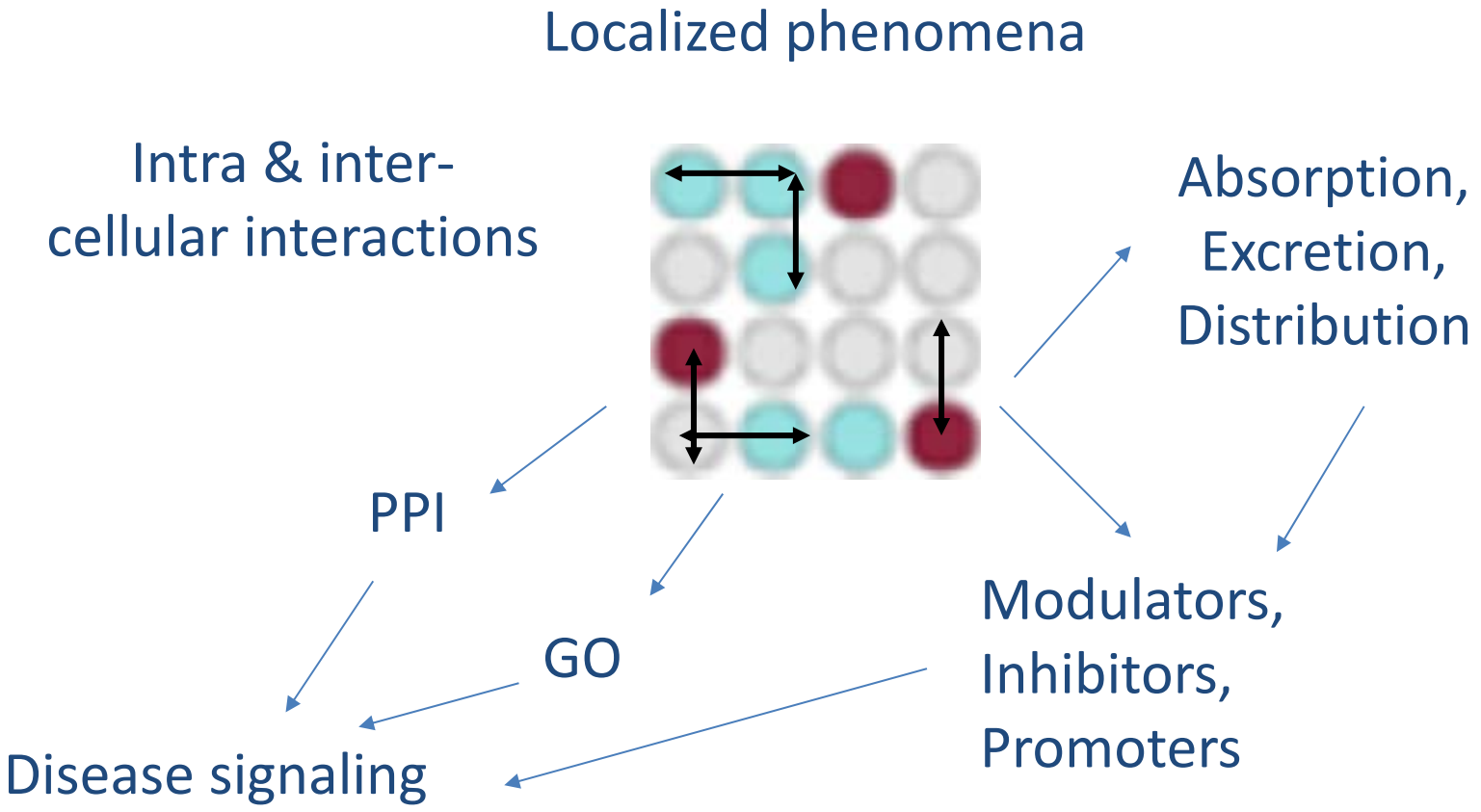
Implementation of Tumor growth visualization

- "**cpm-cytoscape**" already on **GIThub:** **https://github.com/davcem/cpm-cytoscape**
- and available as **online DEMO:** **http://styx.cgv.tugraz.at:8080/cpm-cytoscape/**

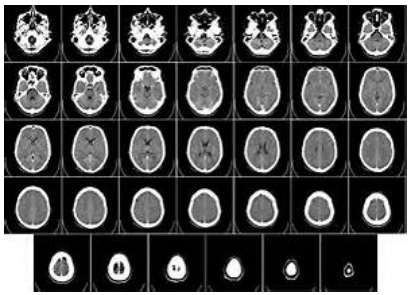
Jeanquartier, F., Jean-Quartier, C., Cemernek, D. & Holzinger, A. In Silico Modeling For Tumor Growth Visualization. BMC, Manuscript in rev

Nodes as *Cellular bricks*

→ Compartmental states:

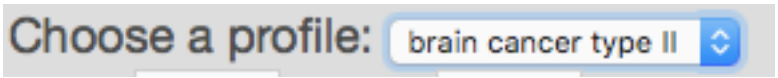


Hot topics:

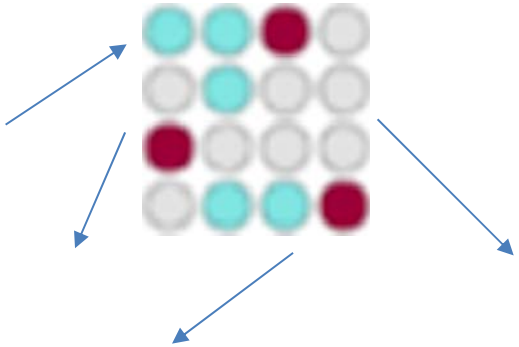


- *Learning from image data for Initialization*
  - *image preprocessing & feature extraction*
  - *comparison, refinement & optimization*

- *ML for tumor growth profiles and model validation*
- *On using open tumor growth data for ML*
  - *Histologic data*
  - *Drug targeting data etc*



- *On multi-scale trends in cancer modelling*
  - *Compare results of different models*
  - *Link between different scales*
  - *Combining microscopic characteristics*
  - *with macroscopic parameters*



- *Sensitivity plots for tumor modelling*
- *Trajectory visualization of tumor dynamics*

Thank you!

Sample Questions (1)

- What is the difference between tumor and cancer?
- What does the term differentiation in biological context stand for? Give an example.
- What means in vivo, in vitro and in silico?
- What types of computational tumor growth models exist?
- What is a cellular automaton?