CoMM: Computing for Molecular Medicine

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D CeMSIIS 4PM Data Science 4 Personalized Medicine

Forschungsgruppe Biosimulation und Bioinformatik von Prof. Schreiner

Zentrum für Medizinische Statistik, Informatik und Intelligente Systeme

Wir benutzen Methoden aus Bioinformatik, Mathematik und Informatik zur Aufklärung molekularbiologischer Vorgänge.

Viele Projekte entstehen aus medizinischen Fragestellungen, die von Kooperationspartnern aus Klinik und Laborforschung an uns herangetragen werden. Wir erstellen in diesen Fällen Datenanalysen mit modernsten Methoden, die wir interdisziplinär verfügbar machen. So konnten wir etwa Methoden der Entscheidungstheorie, wie sie in selbstfahrenden Autos angewandt werden, auf die Therapie-Entscheidung bei Brustkrebs übertragen. Mittels cutting-edge mathematischen Compartment-Modellen können wir Transportvorgänge an der Blut-Hirnschranke analysieren, die mit Standardmethoden nicht auswertbar wären.

Aus Kooperationsprojekten resultiert oftmals jedoch der Bedarf, mathematische Methoden zu verbessern oder neu zu entwickeln. Dies ist dann Gegenstand unserer eignen Forschungstätigkeit. Diese ist daher stets besonders anwendungsrelevant.

Insgesamt orientiert sich unser Konzept „CoMM - Compujting for Molecular Medicine“ an jeweils brennenden biomedizinischen Fragestellungen.

Figure 1: Wolfgang Schreiner

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OMICS data *4* Biomarkers (1)

New Math *4* Biomarkers

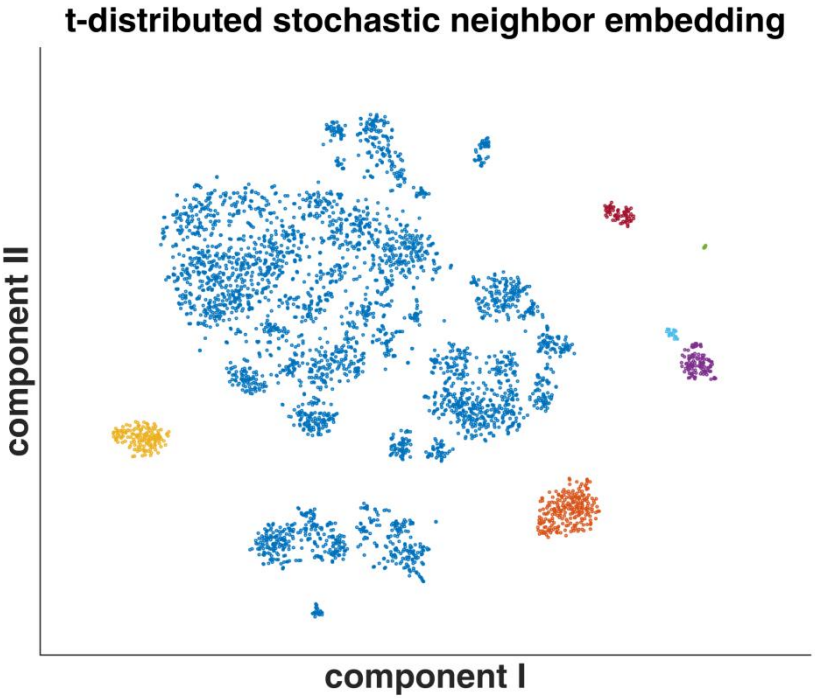

Figure 2: PCA-analysis (e.g. reduction of dimensions based on principal components) of novel Biomarkers.

We look for biomarkers by novel mathematical approaches. These stem from current (non-medical) research fields, e.g. plasma physics, and can be adapted to successfully act on OMICS data. The methods usually draw on 'eigenvectors of operators', other than those known from principal component analysis.

Once dimensions have been reduced, groups of patients (e.g. with different prognoses) are separated on the basis of new topologies, such as isomaps (IM). Based on these new topologies, cluster algorithms are applied, either conventional ones or newly developed ones.

These novel approaches lend themselves to successfully cope with data of low inherent structures, as often faced in OMICS analyses.

Figure 3: Michael Kenn

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OMICS data *4* Biomarkers (2)

OMICS data fusion for Clinical Decision Support

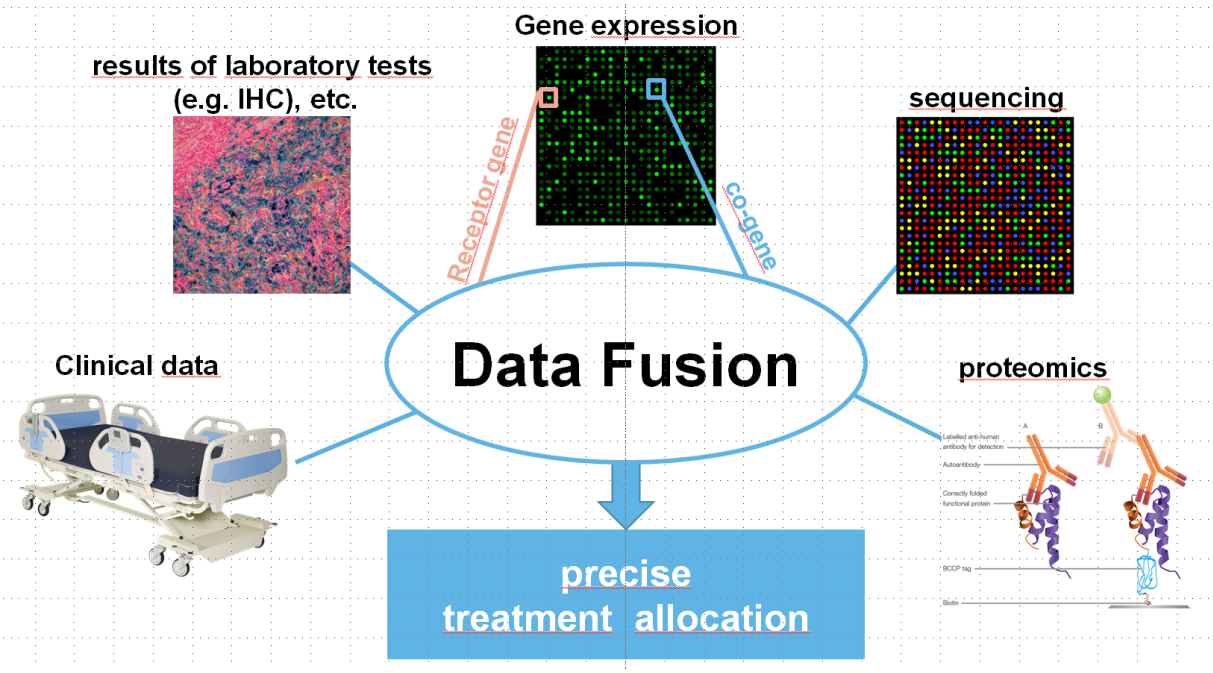

Figure 4: Kenn M, Schlangen K, Cacsire Castillo-Tong D, Singer CF, Cibena M, Koelbl H, Schreiner W (2017). Gene expression information improves reliability of receptor status in breast cancer patients. Oncotarget 8, 77341-77359.

In addition, while conventional decision theory aims at crisp decisions (even if they are uncertain) our proposed approach includes the option to make 'no decision, based on the evidence available'. This in fact raises the call for additional investigations (data acquisition for a patient in question), which might not be undertaken nowadays, relying on conventional decision methods.

We approach the joint evaluation of evidences from different sources (different methods of measurement as well as mixed characteristics of data (continuous / categorial) by cutting edge decision theory (DT). While ordinary DT always is supposed to yield a decision for a distinct endpoint, we also fuse several single endpoints into one 'aggregate'. Several sub-diagnoses may be sub-summed within one larger concept of disease.

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Blood-brain barrier transporters: computer models (1)

Pharmacokinetic Models for PET Imaging Data

The blood-brain barrier (BBB) protects the brain from potentially harmful substances by preventing their access to the central nervous system (CNS). In addition to the tight junctions between the microvascular endothelial cells and the end-feet of astrocytes, efflux transporters play an important role in protecting the brain from xenobiotic substances. In particular, P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), both located at the apical (blood-facing) membranes of the endothelial cells of brain capillaries, are essential for the function of the BBB. On the other hand, P-gp and BCRP can also impede the entry of potential therapeutics to the brain, e.g., anticancer or antiepileptic drugs.

Molecular imaging techniques, such as positron emission tomography (PET) offer the potential for *in vivo* measurement of function and density of efflux transporters in health and disease. However, useful interpretation of raw PET imaging data in terms of functional parameters of efflux transporters requires adequate kinetic modeling. Frequently, nonlinear multi-compartment models are necessary to assess the time-course of radiotracers in the brain. Such nonlinear models may lead to substantial uncertainties in various parameter estimates, calling for sophisticated stochastic or Bayesian methods.

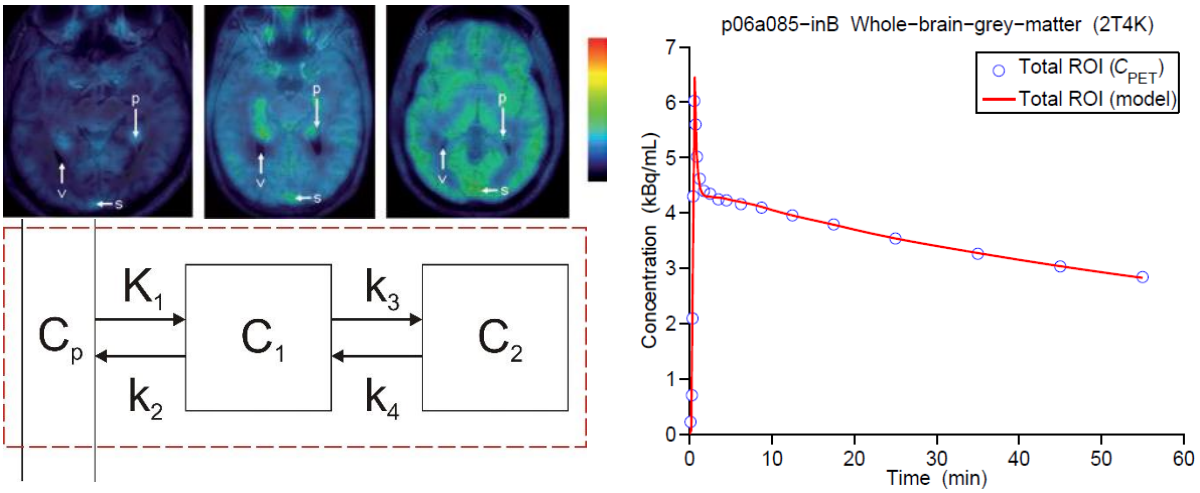

Figure 5: Bauer M, Karch R, Zeitlinger M, Liu J, Koepp MJ, Asselin MC, Sisodiya SM, Hainfellner JA, Wadsak W, Mitterhauser M, Müller M, Pataraia E, Langer O. In vivo P-glycoprotein function before and after epilepsy surgery. Neurology 2014 Oct;83(15):1326-31.

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Blood-brain barrier transporters: computer models (2)

Modelling and Simulation of Biomolecular Transport Phenomena

Biological systems exhibit a degree of complexity that spans many orders of magnitude in space and time. Appropriate modelling and simulation of such systems thus calls for an integration of methods originally developed for specific length- and time-scales. Based on previous experimental and theoretical work, we shall attempt to integrate methods from the molecular to the continuum level to add to the understanding of transport processes of biomolecules in such heterogeneous environments as biological cells and tissues. In particular, we are interested in *passive* diffusion phenomena, which play an important role, e.g., in the distribution of drugs (*pharmacokinetics*), even more so as classical diffusion shows various anomalies that entail profound biological consequences in heterogeneous environments and/or spatially confined geometries (e.g., the interstitial space in tissues, the surface of biological membranes, or the narrow channels in various transport proteins). Moreover, we also plan to model *active* transport phenomena, such as the efflux-transporter *P-glycoprotein* at the human blood-brain barrier and its modulation by various substances. In addition to its role in the resistance to central nervous system drugs (e.g., antiepileptic or anticancer drugs), an improper function of the P-glycoprotein-mediated efflux transport-system is thought to be involved in the pathogenesis of, e.g., Alzheimer's disease and Parkinson's disease.

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Immuno-Simulation meets Oncology (1)

Peptide recognition, MHC – T-Cell – interaction for patient-individual allels

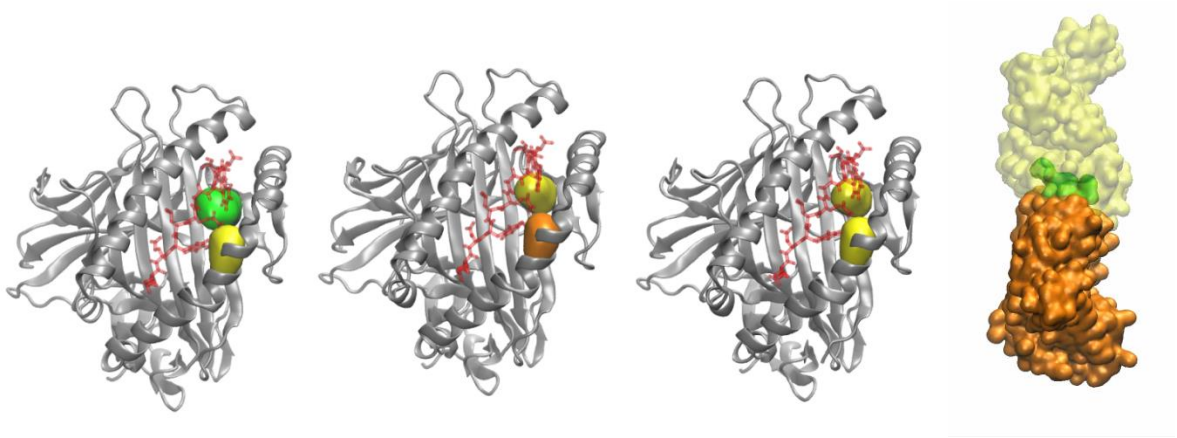

Figure 6: Molecular dynamics of patient-individual alleles reveals mechanisms of binding, recognition and therapeutic access points.

MD delivers protein conformations evolving with time at atomic resolution. To obtain deep insights into the interaction between TCR and pMHC we extracted time evolving pair wise forces acting between all atoms of the complex. We will reconstruct force field footprints from these data and propose that changes in the footprint may identify a complex as agonistic or antagonistic. Peptides may stem from allergens to tumors.
Molecular dynamics and force calculations are performed using the GROMACS molecular dynamics software package.

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Immuno-Simulation meets Oncology (2)

Patient-specific Immune-Checkpoint- inhibition: Computer simulation models

Programmed cell death protein 1 (PD-1) is a cell surface receptor which plays a crucial role as a regulator of immune tolerance and T cell exhaustion. It promotes self-tolerance by inducing apoptosis of antigen-specific T-cells in lymph nodes. Binding of the ligand PD-L1 leads to the recruitment of the tyrosine phosphatases PTPN6 and PTPN11 which in further consequence inhibits the activating T cell receptor (TCR) signal transduction and the expression of proliferation factors. However, this autoimmunity-preventing mechanism is often exploited by cancer cells to evade host immunity. The expression of PD-L1, which is associated with an increased mortality, has been described for a variety of cancer types. Thus, PD-1 has recently emerged as a key target in cancer immunotherapy. Molecular dynamic studies can give insight into the flexibility of residues, conformational movements, interactions and binding energy distributions which may be important for the design of new or the optimisation of already existing PD-1 blocking antibodies.

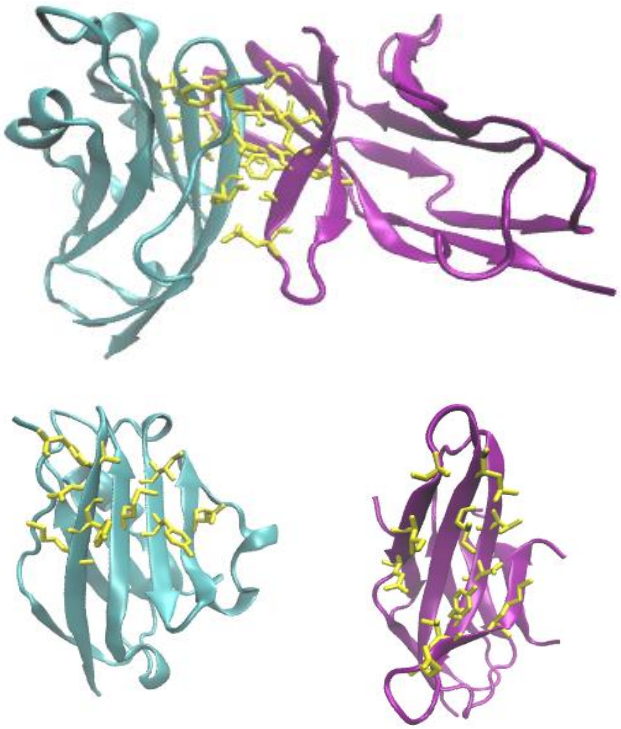

Figure 7: The receptor PD-1 (purple) and its ligand PD-L1 (cyan) in complex (top) and rotated around 90 degrees (bottom) with the binding-associated amino acids highlighted in yellow.

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