BIOCOMPUTATION – AN ALTERNATIVE APPROACH IN COMPUTATION

Calculating using Molecules in Microfluidic Networks

Bio4Comp
Parallel network-based biocomputation:
technological baseline, scale-up and innovation ecosystem

TU Chemnitz, Institut für Physik
Seminar **Theorie, Modellierung, Simulation**

Mittwoch, den 04.11.2020
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BIOCOMPUTATION –
AN ALTERNATIVE APPROACH IN COMPUTATION

Agenda

- *Alternative computing*: approaches in research
  - *DNA-, Quantum-,* ***Biocomputation***
- *Computational complexity:* basics in mathematics & data sciences
  - NP-complete Problems
    - *travelling salesman* (TSP), *subset sum* (SSP), *exact cover* (EXCOV)
- *Biocomputation hardware*: technical foundations
  - Construction, requirements, functional elements (programming)
    - Sub-microchannels, agents and motor proteins, error-free crossings, marking and detection
  - Approaches to fabrication spanning scales (from nano to macro)
    - Electronbeamlithography and systems-integration
- *Biocomputation in action*: solutions and outlook

Alternative Computing

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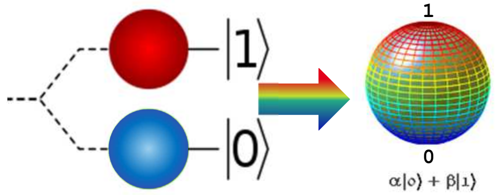
Zentrum für Mikrotechnologien

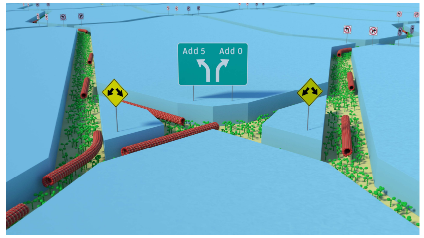
DNA-Computing – calculating with heritage molecules

- Use as
  - Programmable modules to solve mathematical problems
  - Storage (six grams [= 0,006 kg] of DNA do theoretically have a storage capacity of 3072 EiB = 3 ZiB [Zettabyte ~ 3,072 * 10^21 byte])
- Idea:
  - logic gates are made from DNA- and RNA-molecules (bases)
  - massively parallel calculations of about 10^{18} operations/second (commercial computer 10^{16})
    - "DNA-Origami" – self-assembled DNA scaffolds are positioned on surfaces → nanoscaled circuits and devices
- Tractable problems:
  - simple variant of the "travelling salesman"-problem
  - simple mathematical problems (TT-100)

Quantum-Computing – calculating with states



- Use as CPU
- Idea:
  - Superposition principle:
    - Superposition of the states 0 and 1 exist at the same time – no longer classically only 0 and 1
      - N Qubit = 2^N bit (currently about 50 to 70 qubits realised)
    - Massively parallel (quantumgates calculate simultaneously)
- Tractable problems:
  - Prime factorization = cryptography 10^{24} steps KL 10^{10} steps QM
  - Optimization tasks for database searches (economy, logistics)
  - Simulations (finding novel chemical substances, for e.g. biotechnology or medicine; or finding novel materials, e.g. novel accumulators)



BioComputing – molecules under way

- Use as
  - Programmable modules for solving mathematical problems
  - Storage and manipulation of data analogous to processes in the human body
- Idea:
  - Based on biological molecules or bacteria (partly with molecular labels, e.g. DNA, quantum dots)
  - The problem is being coded into the nanoscaled network (semiconductor nanotechnology) as cross-junctions and pass-junctions
  - Physical guiding and biochemical propelling moves agents through network thereby solving problems
- Tractable problems:
  - Satisfiablity problem, SAT
  - Exact-cover problem, EXCOV
  - Subset-sum problem, SSP & travelling salesman problem

Computational complexity

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Abteilung Nano Device Technologies (NDT)

Computational Complexity

EXKURS

Problem, instance, algorithm, runtime

Tractability

NP-complete problems

Tractable by network-based biocomputation

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Complexity in Computer Science

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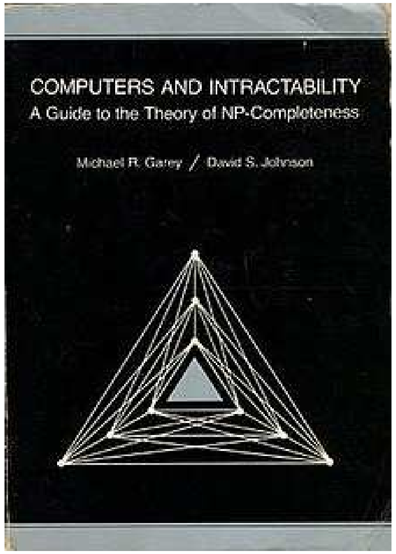
- Complexity:
  - 1. Usage: an *algorithm* for solving instances of a *problem*
    - The complexity of an algorithm is a measure of how many steps the algorithm will require in the worst case for an instance or input of a given size.
  - 2. Usage: the *problem* itself
    - Problems are classified according to their inherent tractability or intractability — that is, whether they are "easy" or "hard" to solve *). This classification scheme includes the well-known classes *P* and *NP*; the terms "*NP*-complete" and "*NP*-hard" are related to the class *NP*.



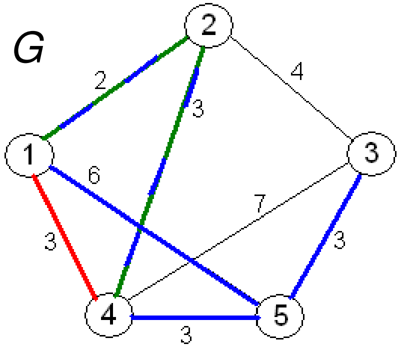
*) Nach Michael R. Garey, David S. Johnson: Computers and Intractability, W. H. Freeman, 1979.
Intractable problems … trudnorešaemye problemy [russisch]

Leslie Hall (Johns Hopkins University): „Computational Complexity", Encyclopedia of Operations Research and Management Science, Springer, 1996.

Complexity in Computer Science

- Problem: function *p* that connects an instance *x* to an answer *p*(*x*)
  - Abstract description coupled with a question requiring an answer
  - Example: Travelling salesman problem, (TSP)
    - „Given Graph *G* with nodes and edges and costs associated with the edges, what is a least-cost closed walk (or tour) containing each of the nodes exactly once?“

- Instance:
  - Exact specification of the problem
  - Example: Travelling salesman problem (TSP)
    - Graph *G* contains the nodes 1, 2, 3, 4 and 5 as well as edges (1,2) with cost 2, the edge (1,5) with cost 6, … etc.
    - Size of an instance: scales with the dimensions of the instance (number of nodes and edges) as well as with the number of bits required to code the numeric information (costs per element of the instance)



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Complexity in Computer Science

- Solution algorithm of a problem: set of instructions, that result in finding the correct solution for all instances of the problem in a finite number of steps
- for a problem (function) *p,* an algorithm is a finite procedure, that computes *p(x)* for any given instance *x* (modeling: Turing machine)
- A step can consist of one of the following operations: addition, subtraction, multiplication, division with finite precision (*floating point*), comparison of two numbers
  - Example: 220 comparisons plus 100 additions = 320 steps for a specific instance of the problem
- Basic question in information theory (-economy): running time
  - *Big-O notation*: given two functions f(t) and g(t) (t … non-negative) then $f(t) = O[g(t)]$, if a constant $c > 0$ exists such that for all sufficiently large t $f(t) \leq c \cdot g(t)$. Thus, the function $c \cdot g(t)$ provides an asymptotic *upper bound of* f.
    Examples: $100(t^2+t) = O(t^2)$; $0{,}0001\, t^3 = O[t^3] > O[t^2]$

Leslie Hall (Johns Hopkins University): „Computational Complexity“, Encyclopedia of Operations Research and Management Science, Springer, 1996.

Complexity in Computer Science

- Complexity ~ running time ~ number of steps in the solution algorithm for a certain size of the instance of the problem (= number of bits required to encode the problem)
  - Example: Travelling salesman problem, TSP
    - Complexity ~ running time ~ number of steps = f(N_N[nodes], N_E[edges], $S_{N, E}$ [coding of the cost per element of the instance])
- An algorithm runs in polynomial time, if the running time f(t) = O[P(t)], where P(t) = f(N_N, N_E, $S_{N, E}$, …) is a polynomial function of the input size.
- Algorithms, that run in polynomial time, are considered **efficient**. Problems, for which efficient algorithms exist, are considered *easy*.
- To establish a formal setting for discussing the *tractability* of problems, it is important to define a class of problems called *decision problems* (*recognition problems*): yes/no answer required.

Leslie Hall (Johns Hopkins University): „Computational Complexity“, Encyclopedia of Operations Research and Management Science, Springer, 1996.

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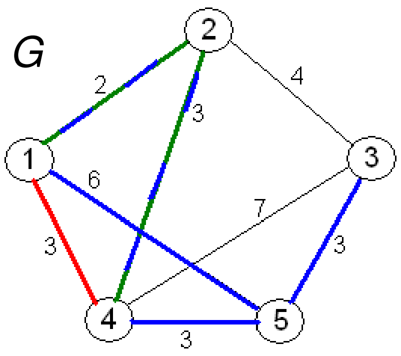
- Optimization problems are not decision problems, but they can have counterparts in the class of decision problems.
  - Example: if for a Graph *G* there exists a TSP-path, then the following applies complexity ~ running time ~ number of steps = f(N_N, N_E, $S_{N, E}$) < *K*
- The *tractability* of an optimization problem is not much larger than the tractability of the associated decision problem. The associated algorithm can be translated into a binary search over the possible objective function values to solve the optimization problem.
- The **class P** („*polynomial time*") is defined as the set of decision problems, for which an efficient (i. e. running in polynomial time) solution algorithm exists.
- The **class NP** („*non-deterministic polynomial time*") contains all decision problems with this property: for a specific instance of the problem („yes", „no") there exists an efficient solution algorithm (i. e. asymmetry between the instances is possible)



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Complexity in Computer Science

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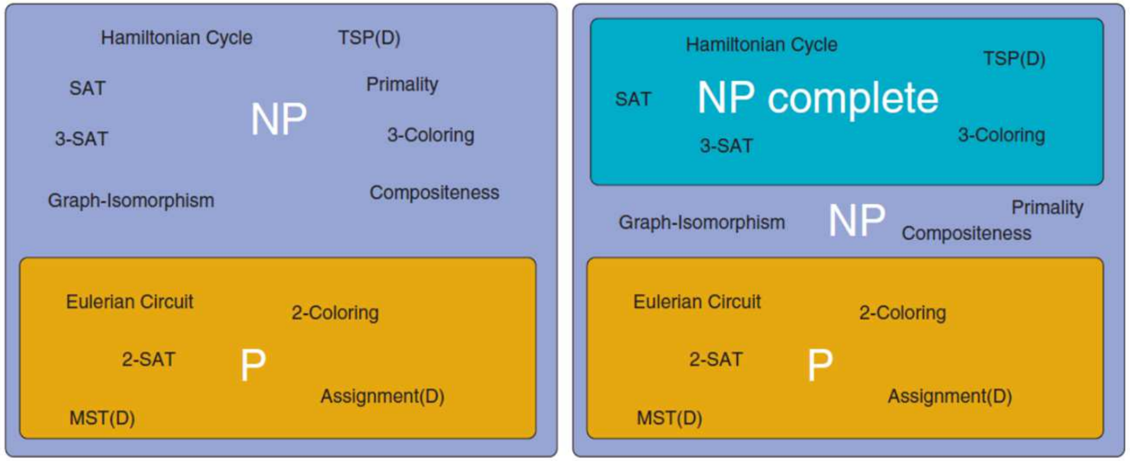
- If an efficient solution algorithm for each single instance of the associated decision problem exists, then there exist efficient solution algorithms for all problems in the class (*NP-complete problems*)
- Further NP-complete problems (besides the travelling salesman problem, *TSP*)
  - Subset-sum problem, SSP
  - Satisfiability problem, SAT
  - Exact-cover problem, EXCOV
- NP-complete problems are the main application area for network-based biocomputation (NBC)



Stephan Mertens, IEEE 2002 (URL https://arxiv.org/abs/cond-mat/0012185).

Leslie Hall (Johns Hopkins University): „Computational Complexity“, Encyclopedia of Operations Research and Management Science, Springer, 1996.

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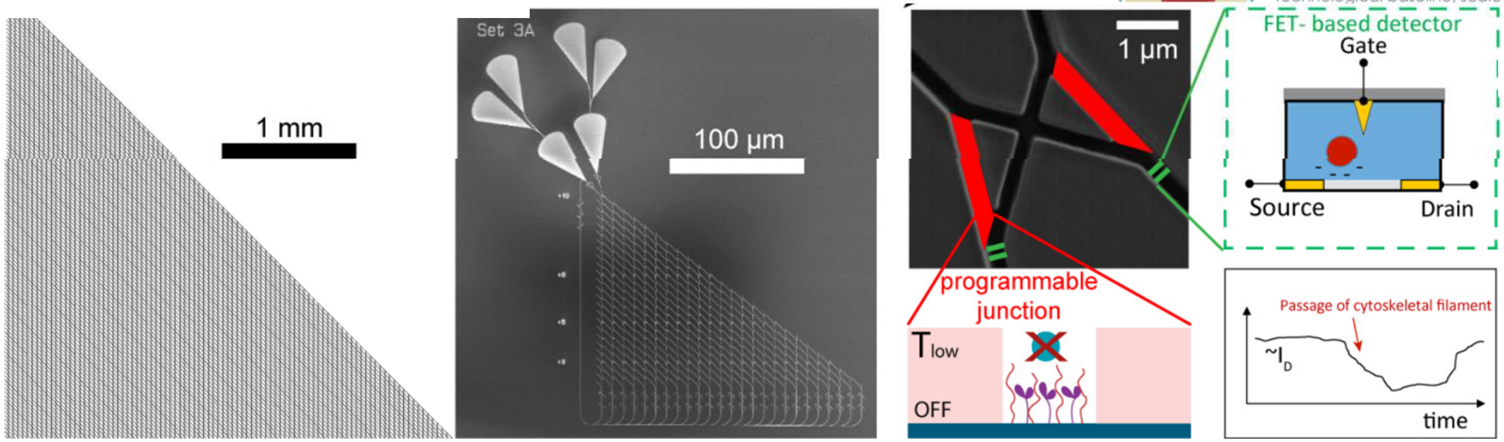

- Challenges for systems integration
  - **Nano-structured fluidic channel-systems** with **biofunctionalisation** (molecular motors) for mobile **agents** and **integration of elements** (e.g error-free and switchable junctions, respectively)
  - **Identification: i**ntegration of physical, chemical and biological methods for marking (*Barcoding, Tagging, Labelling*) of the mobile agents (filaments): fluorescence, DNA, spin (etc.)
  - **Detection:** integration of automatic path-specific read-out of the agents on chip: fluorescence-microscope, alternative detection methods (electrical, biochemical, magnetic)
  - **Scaling**, encapsulation, energy supply, **Data:** readout, storage, transfer

Network-based Molecular Computers

Till Korten

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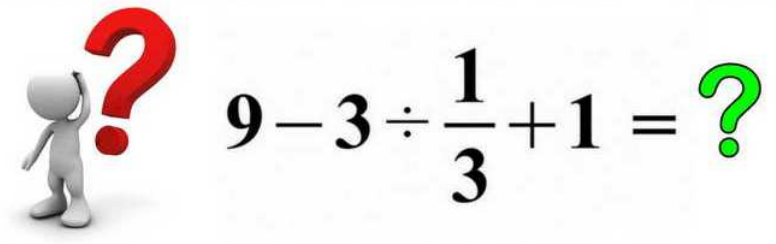
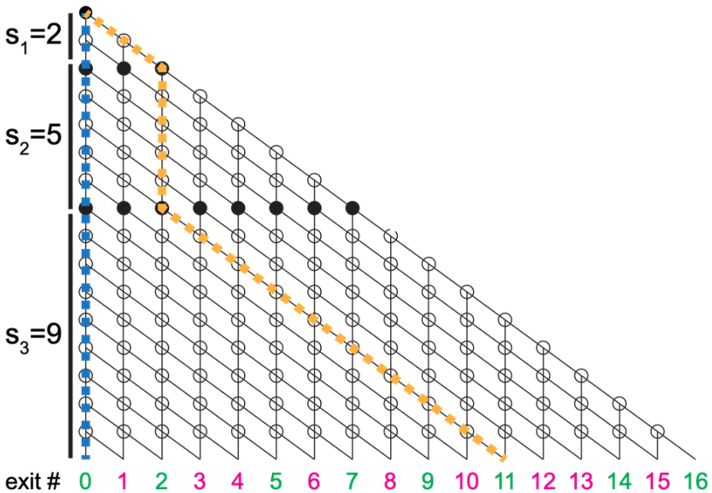
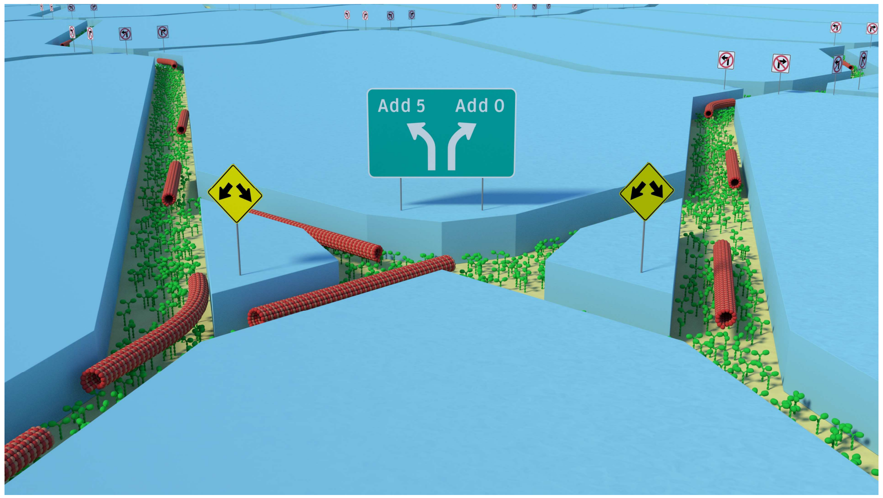
Networkbased molecular computers

- mathematical problems
- networkprogramming
- molecular motors solve the problem







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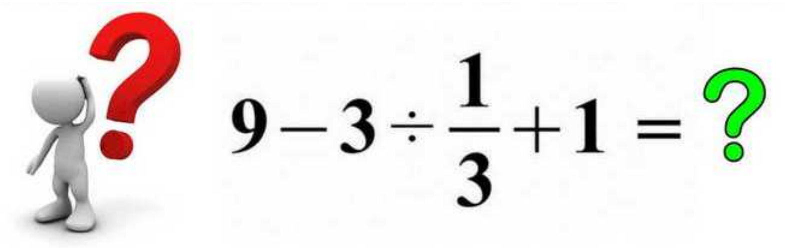
The subset sum problem



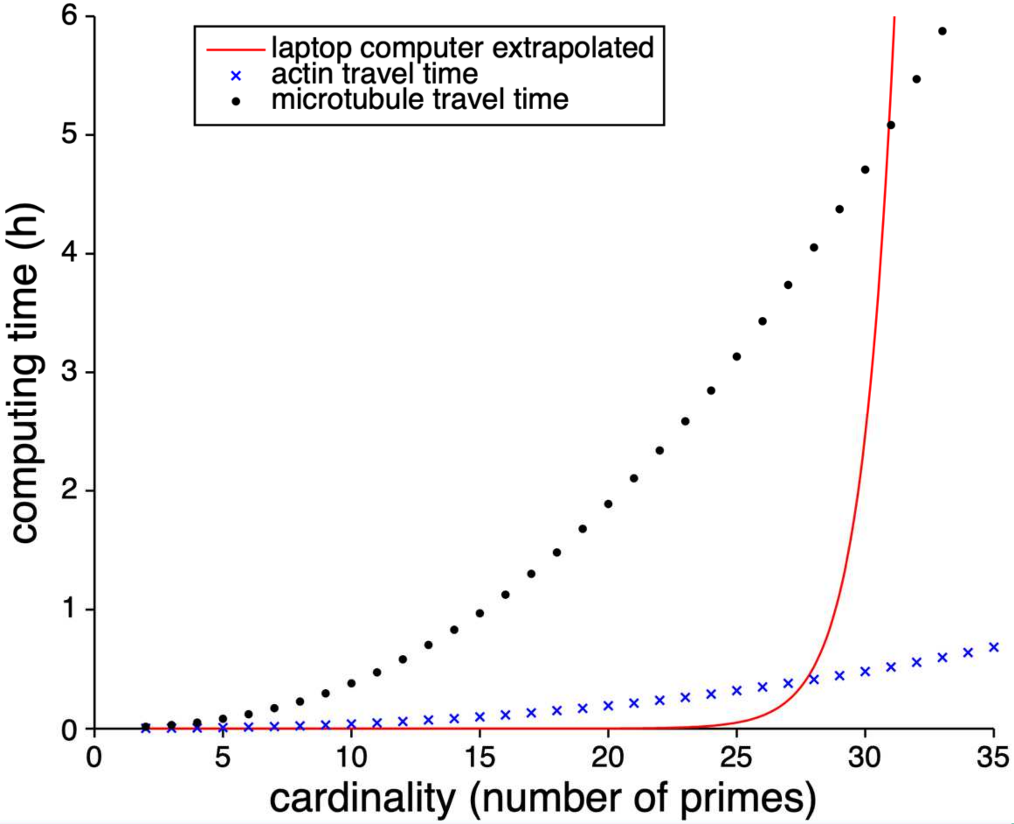
- Set of numbers S = {s_1, s_2, ..., s_N} of N integers
- Question:
  - Can a target sum T be reached by summing up any combination of integers from the number set S?
- Example:
  - S = { 1, 3 }
  - T = 2

  → **There is no possibility, to sum up the numbers 1 and 3 to reach the sum 2!**

Why biocomputation?

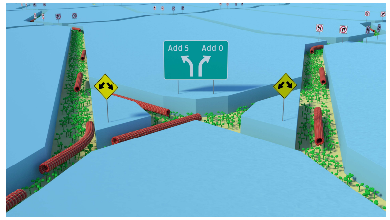
Parallel computing

favourable scalierung conditions



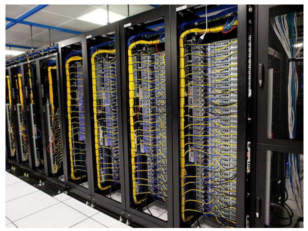
low energy usage

molecular motors



~ 10^{-14} Joule/Operation

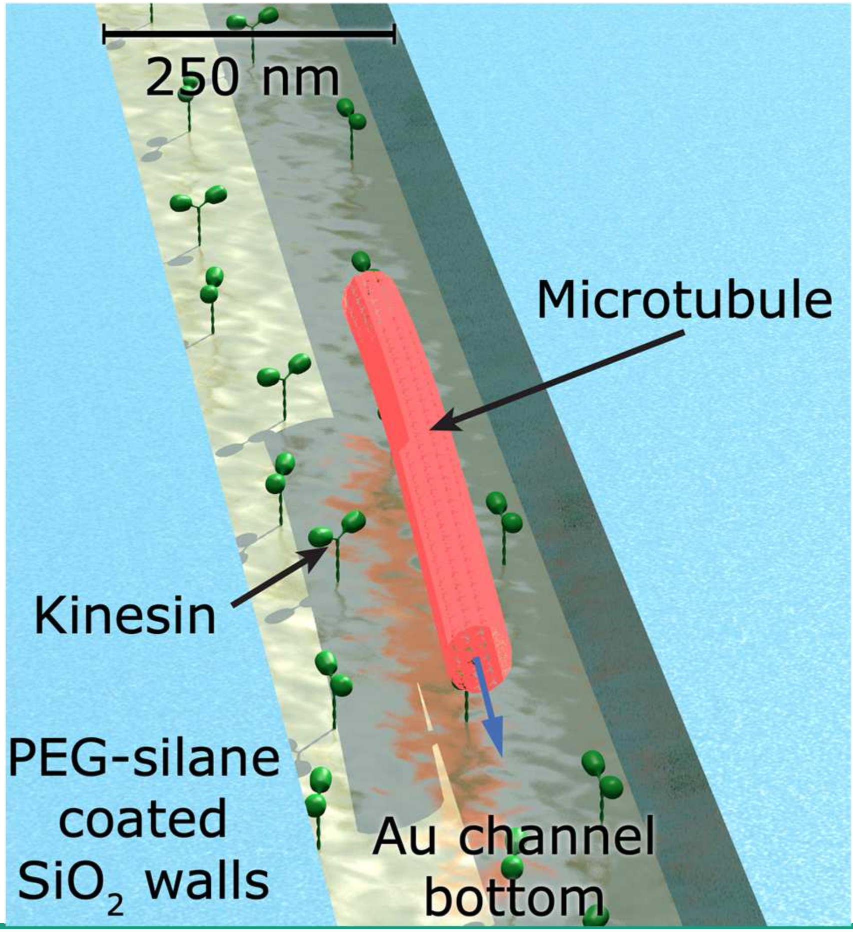
conventional computer

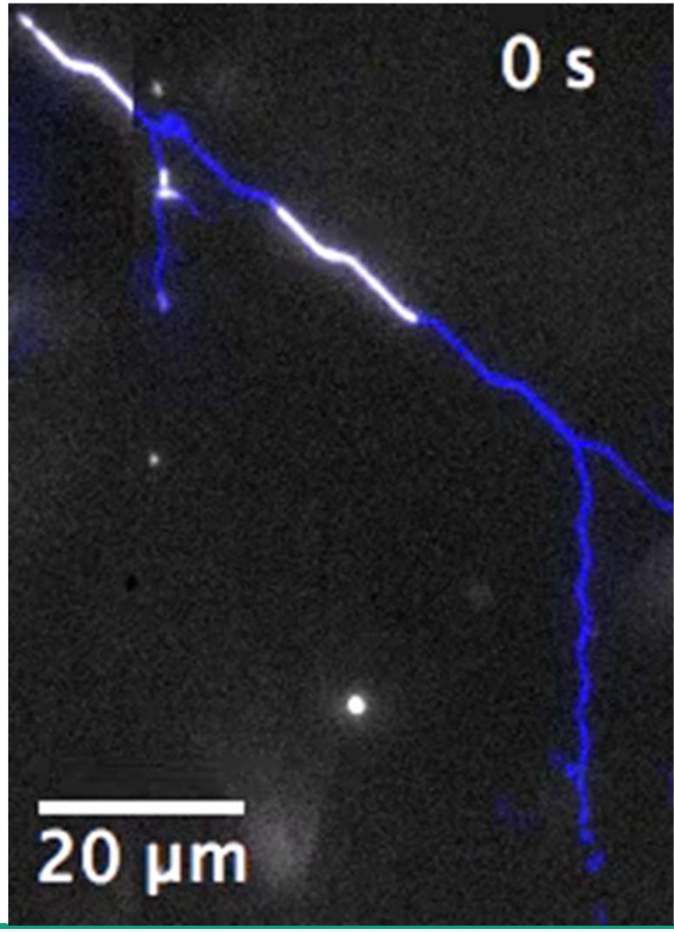


arenatt.com

~ 10^{-10} Joule/Operation

Biomolecular motors transport agents through the network





Elements for an Optimal Performance I

Fluidic channel-systems with optimized junctions

Till Korten
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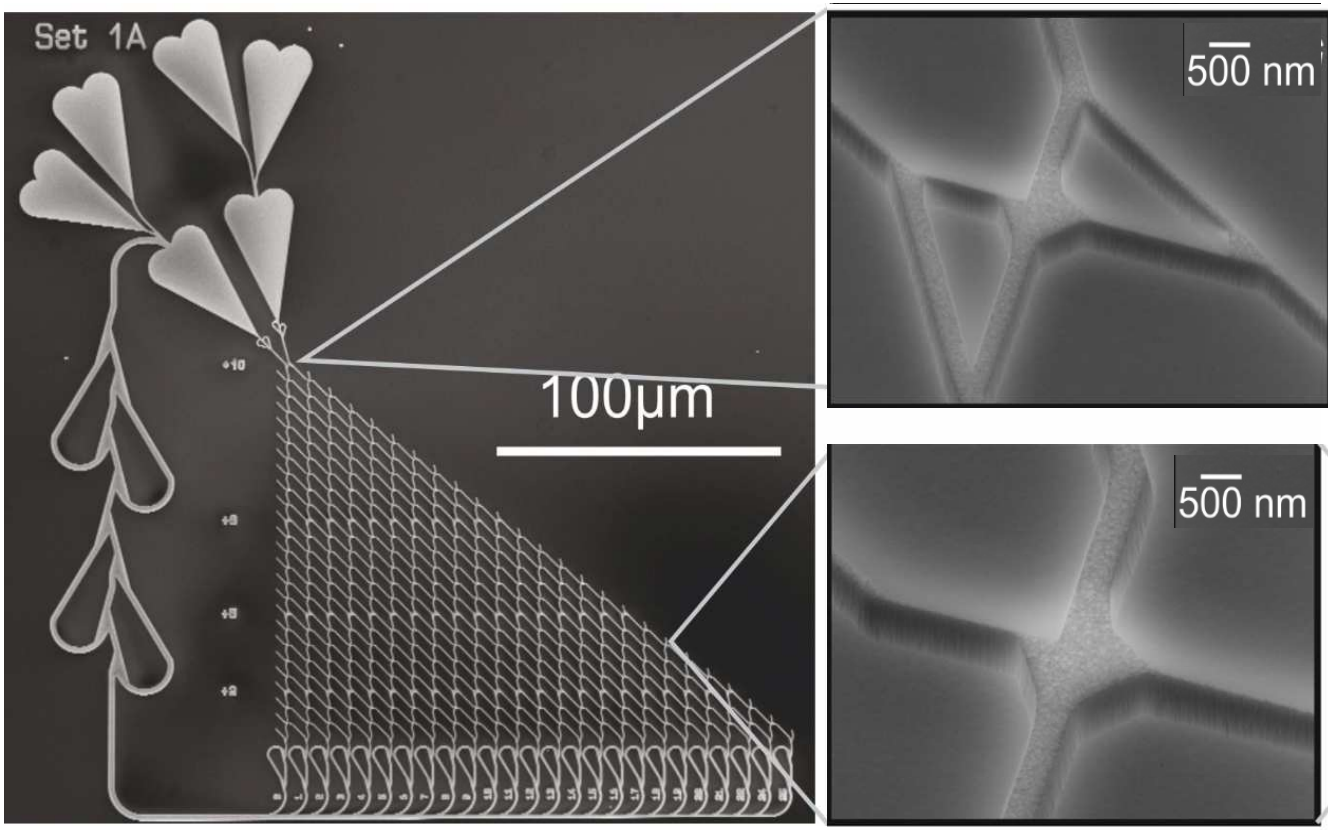
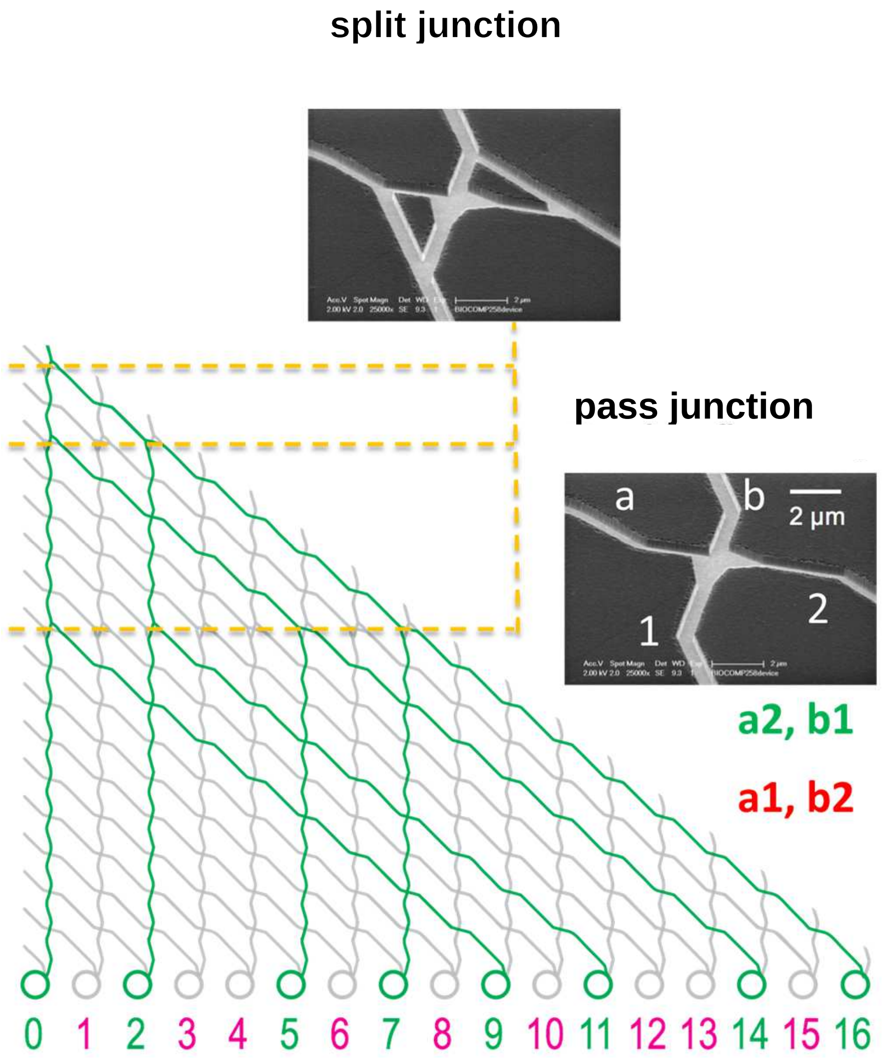
Design of the Junctions



- Split junction:
  - Combination of 2 Y-junctions
  - Designed for 50% probability to turn left or right
- Pass junction:
  - Junctions, where channels meet at a 90˚ angle
  - Funnel-shaped exits
  - Filaments may not turn

Impact of Junction-Errors

- Error rate scales $(1\text{-}E)^P$
  - E: Pass-junction errors
  - P: Number of rows at pass junctions
    ≈ Sum of all numbers of the problem
- 2% Errors → a few dozen lines
- 0,5% Errors → a few hundred lines
- 0,1% Errors → thousands of lines



Elements for an Optimal Performance II

Error-free Junctions

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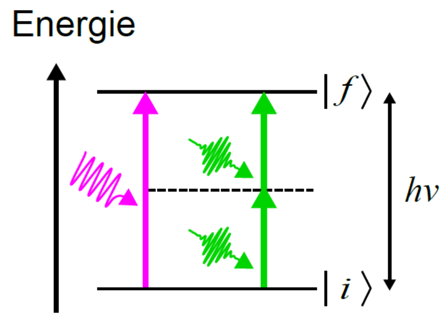
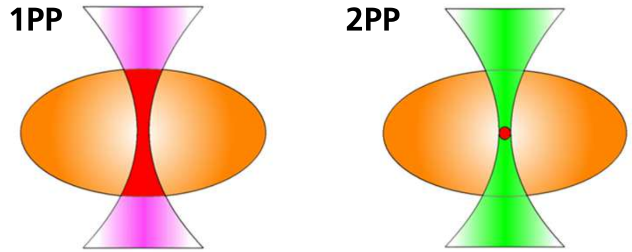
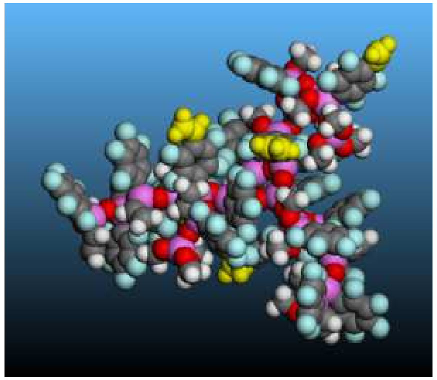
Center for Smart Materials and Adaptive Systems

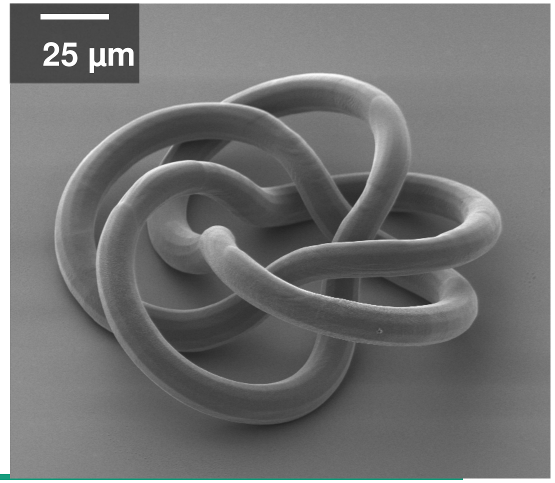
Two-Photon Polymerisation – Principle



- Illumination of (liquid) UV resist (λ) with fs-laser pulses (2λ)
  - ➞ non-linear absorption confined to focal spot
  - ➞ localized polymerization reaction (solidification)
- 3D movement of focal volume + removing liquid resist
  - ➞ true 3D µ-structures
- Ormocer® Hybridpolymer as negative-tone photopolymer







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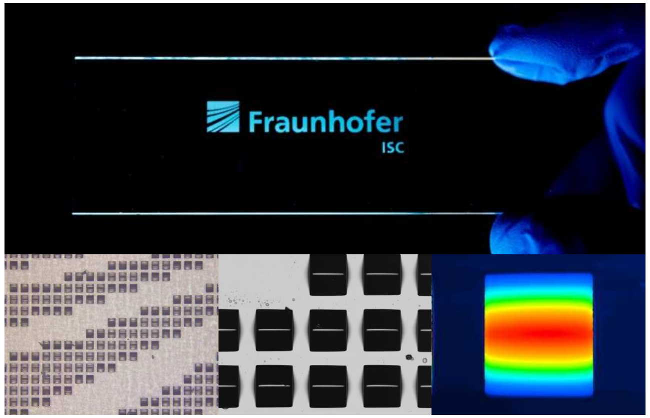
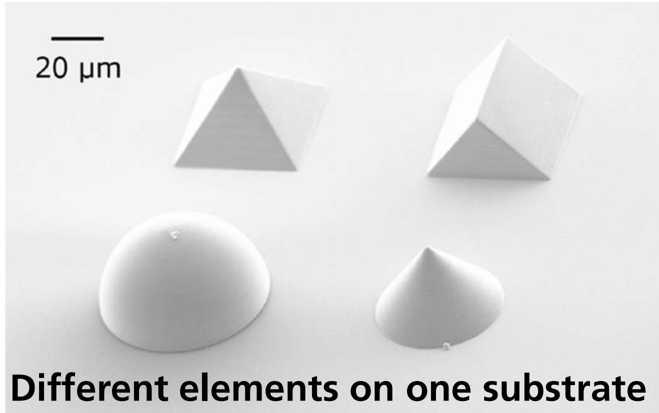
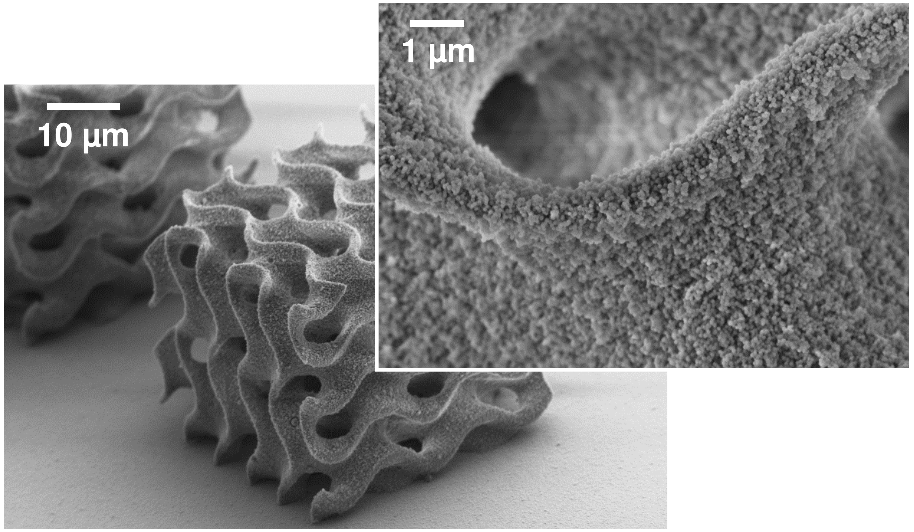
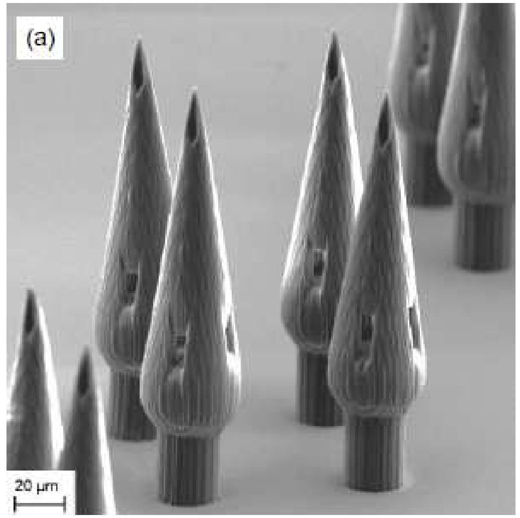
Two-Photon Polymerisation – Applications

- Microoptics
  - Diffractive
  - Refractive
  - Sensors
  - Imaging
  - Illumination
- Life-Science
  - Scaffolds
  - Prostheses
  - Drug Delivery









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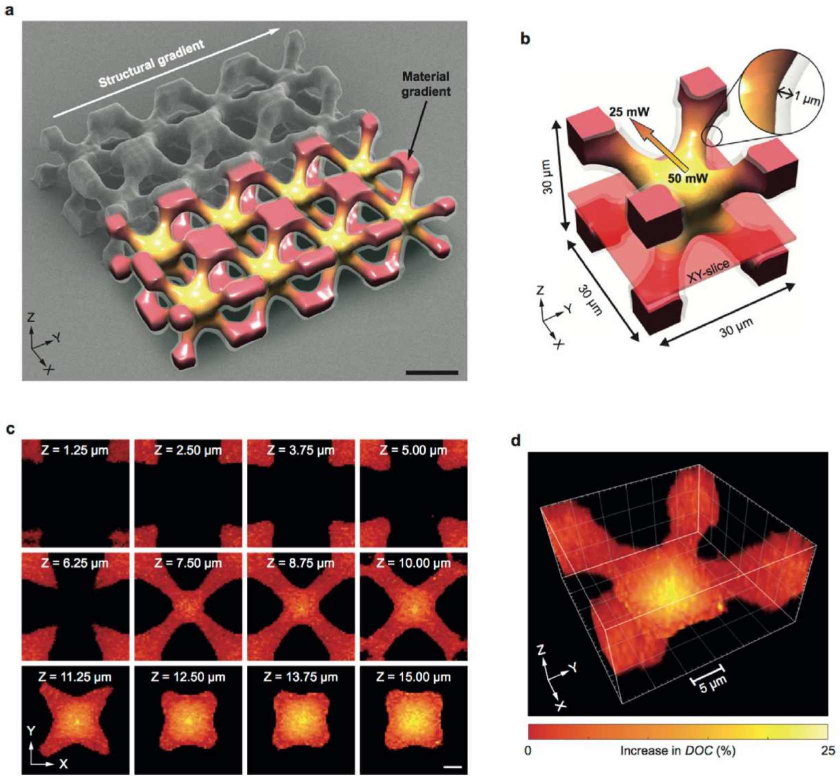
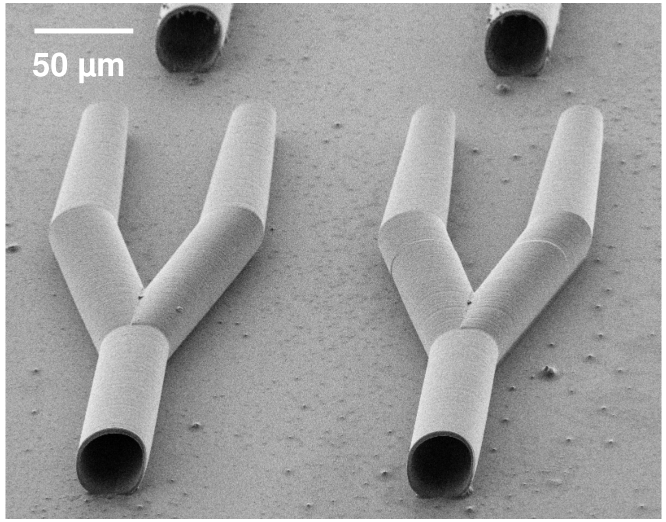
Two-Photon Polymerisation – Applications

- Microoptics
  - Diffractive
  - Refractive
  - Sensors
  - Imaging
  - Illumination
- Life-Science
  - Scaffolds
  - Prostheses
  - Drug Delivery
- Micromechanics
- Microfluidics / Lab-on-Chip





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Two-Photon Polymerisation – Applications to Optimize Performance of Biological Computing

Problem: persistent error-rates in pass junctions impede the upscaling of NBC, thus, the motion of filaments in different channels needs to be separated spatially.

Solution: utilizing two-photon polymerization (2PP) an inherently three-dimensional micropatterning technology.

In 2PP, tightly focused ultrashort laser pulses trigger a confined solidification of photopolymers inside the focal volume. Scanning the focal volume in 3D and performing a subsequent solvent-wash to get rid of the unexposed resin results in the desired 3D structure directly from computer design.

An initial test geometry consisting of an overpass and a tunnel was designed, which separated the allowed paths for filaments between two landing zones entirely. To achieve optimal motility inside that so called “error-free junction” several design parameters (channel width, overpass slop, tunnel height, …) as well as processing conditions (exposure dose, alignment to substrate, …) were optimized. Microscopic characterization using laser scanning microscopy and SEM revealed excellent agreement of the fabricated structure with the design. Finally, several tunneling and overpass events could be observed by fluorescence imaging of filaments.

Elements for an Optimal Performance III

Marking and detecting mobile agents

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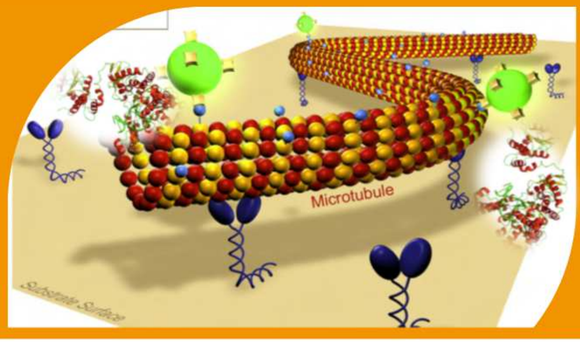
Abteilung Nano Device Technologies (NDT)

Integration of Novel Functional Elements

Time stamp

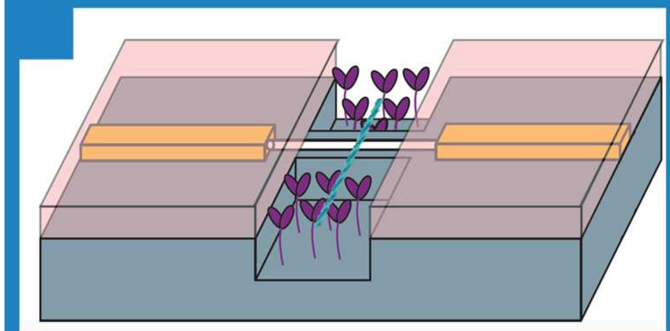
Automatic readout of agents and paths

Identification



Marking the agents (*Tagging, Labelling, Barcoding*) e.g. with fluorophores or biomolecules (challenging with respect to upscaling)

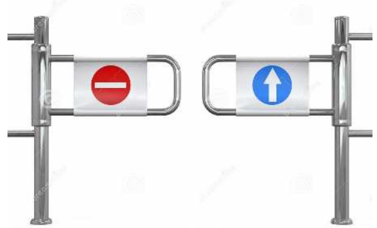
Detection



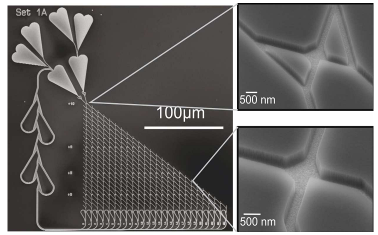
Non-optical (e. g. electronic), error-free, automatic, place- and agent-sepcific recording of passages

Pre-processing of the data *on chip*

Agent #ID



Path #ID



- Goals:
  - Increase of the tractability of NBC-solvable problems
  - Scalable readout (alternatives to fluorescence-microscope for readout)

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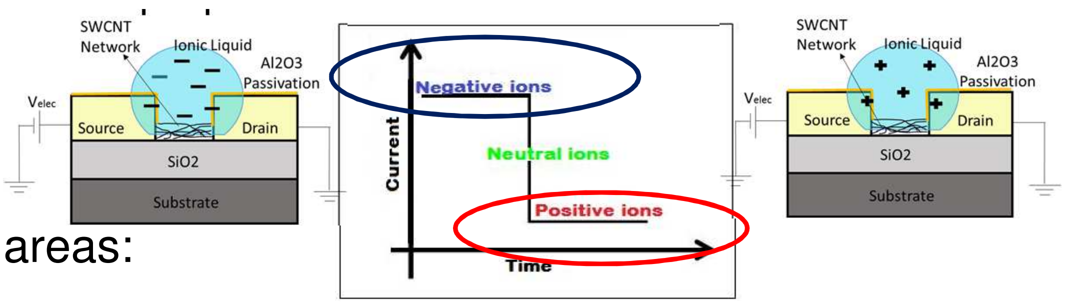
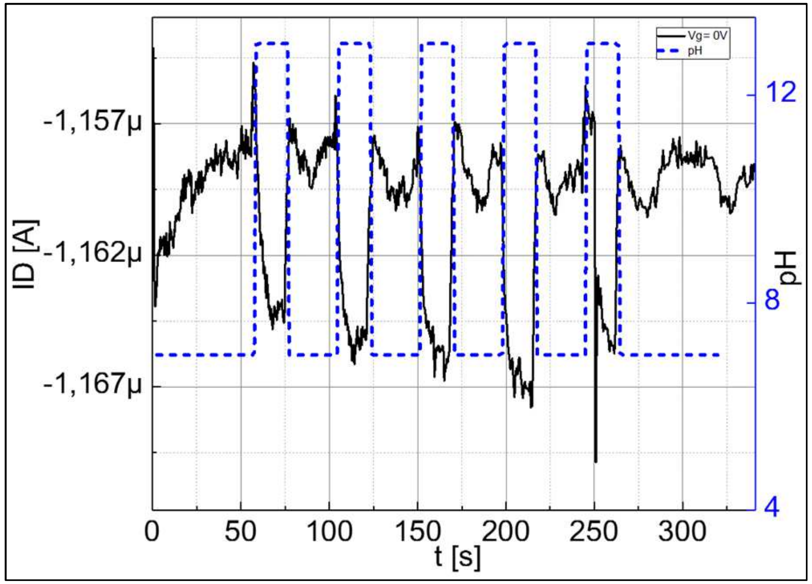
Integration of new Functional Elements

Detection of charge-carriers with carbon-nanowire transistors (CNT-FETs)

- Experimental approaches (separate test-structures, not yet optimized for biocomputation)
  - Actuation of CNT-transistors **in fluidic channelsystem** to measure presence of charge-carriers
  - Amplitude of measured drain-current (DID)
    - ~ 2µA … 2nA per pH in aqueous tensid-solutions
    - ~ 8nA per pH in PBS-standardbuffer



- Work areas:
  - Passivation of the CNT-transistors
  - Sensibility and specificity for agents
  - Effectivity in relevant buffer solutions
  - Skale-up to wafer-level
  - Data readout, -storage



Archa Jain, Thomas Blaudeck, Sascha Hermann, Stefan E. Schulz (TU Chemnitz, ZfM, Master Research Project, 2018)

Scale-spanning Fabrication Approaches (from nano to macro)

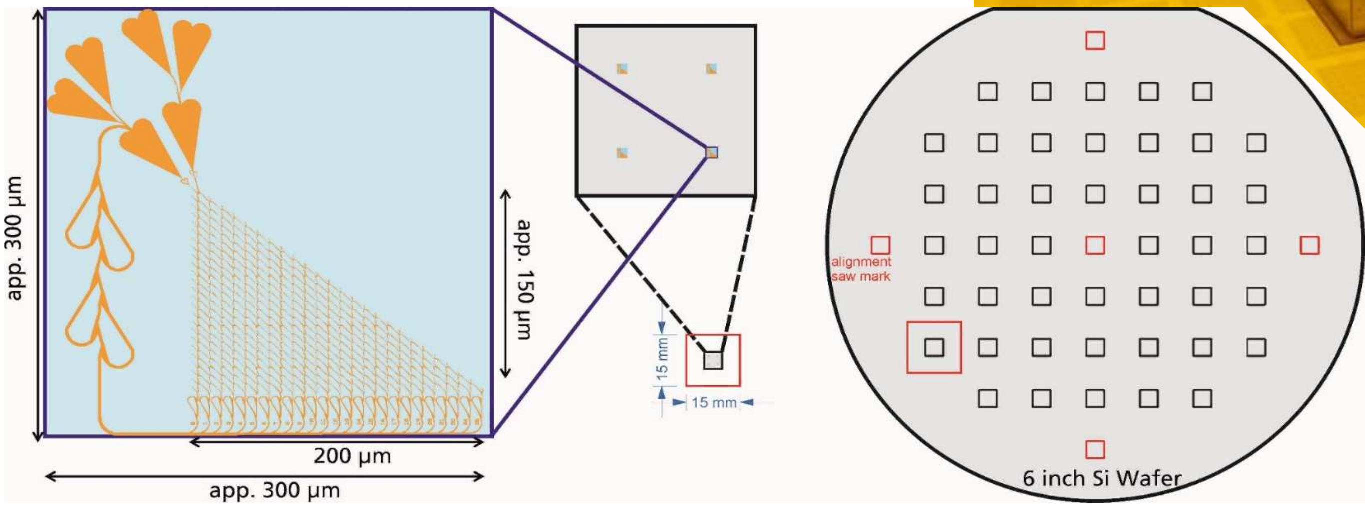
Christoph Meinecke TU

Chemnitz,
Zentrum für Mikrotechnologien

Fabrication of Nanostructured Networks

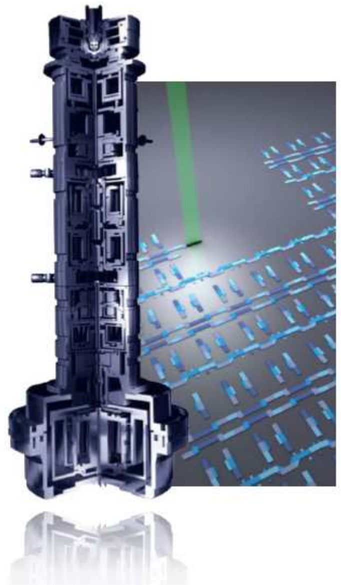
- Numerous networks simultaneously on the same wafer
- Feature-size of 200 nm not possible with optical lithography

  → electonbeam lithography



High Throughput, Accuracy and Resolution patterning below 32 technology node

- 50keV system architecture for high resolution patterning
- Fast patterning by:
  Variable Shaped beam techn
  Write-on-the-fly principle
  Vector scan
- Effective handling of huge data



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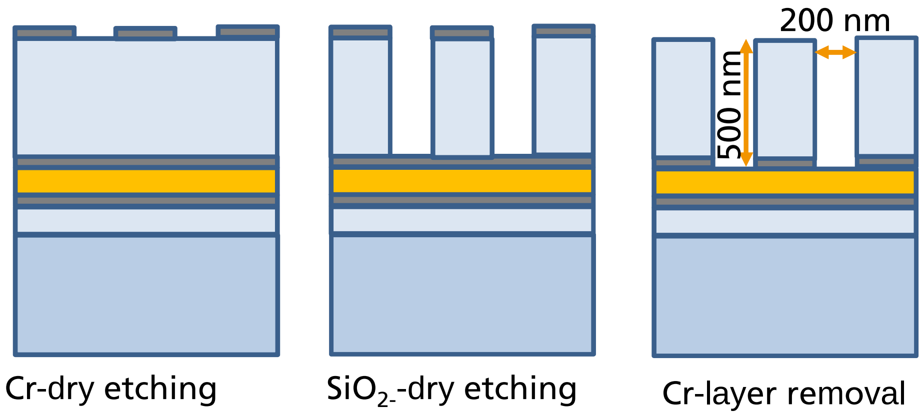
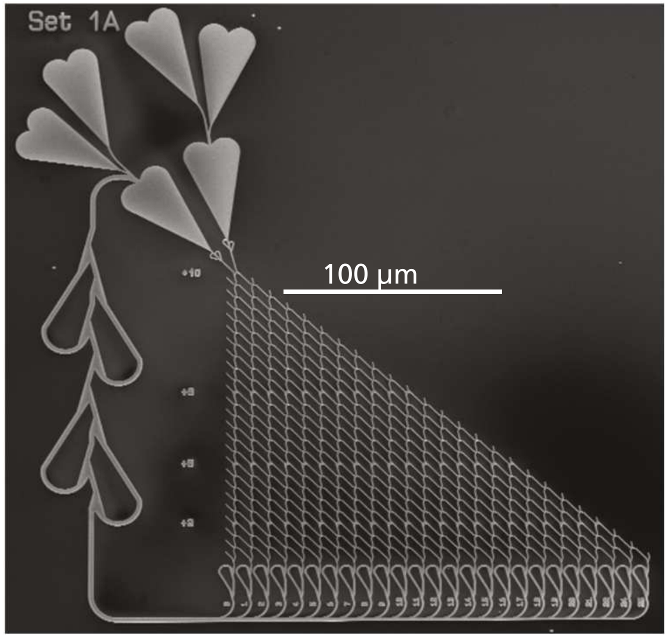
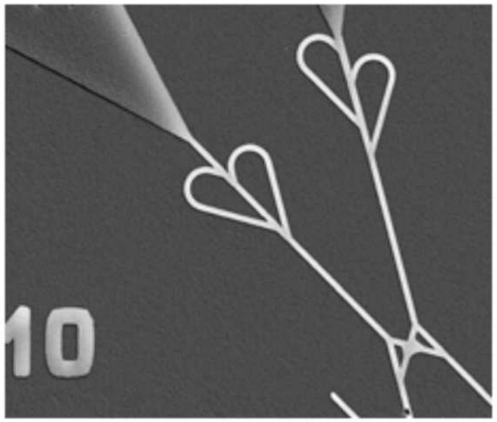
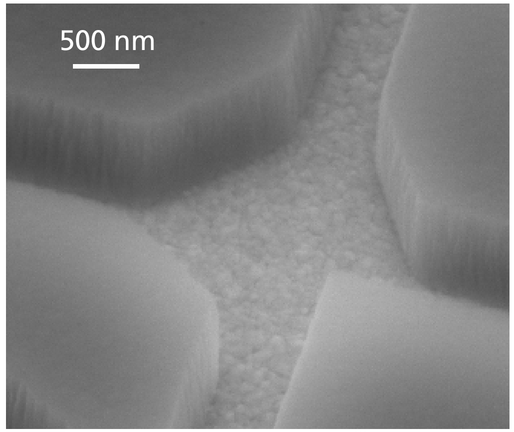
Fabrication of the Networks – Structuring the Nano-Networks

- Plasma etching / high aspect ratios
- smooth surfaces → biofunctionalisation









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Biocomputation in Action

Christoph Meinecke

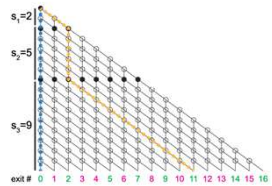
TU Chemnitz,
Zentrum für Mikrotechnologien

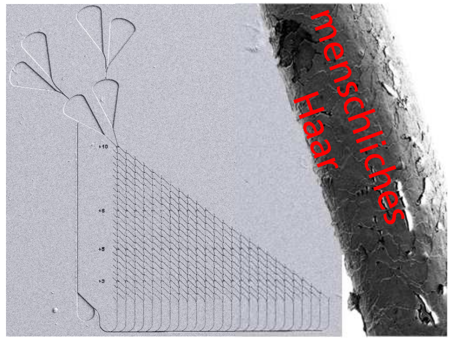
Till Korten

TU Dresden, Center for Molecular Bioengineering (B CUBE)

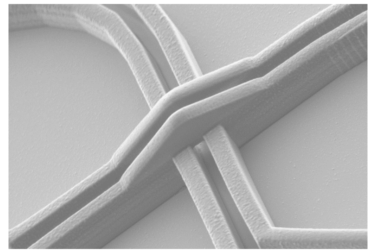
Summary

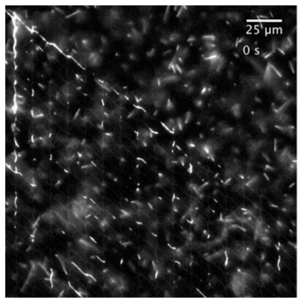
Bio4Comp
Parallel network-based biocomputation: technological baseline, scale-up and innovation ecosystem

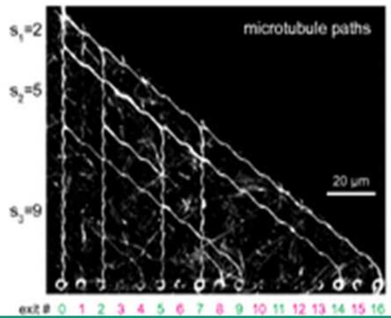


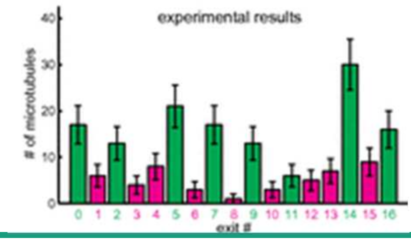


- Biocomputation can be used to solve NP-complete problems
  - Demonstrated for a three-variable-SSP {2, 5, 9}
- Fabrication of nanoscaled networks for physical-biochemical transport of the biological agents is possible
- Scaling (multivariable - problems)
  - *increase the number of junctions and agents*
- Identification and automatic detection









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Acknowledgement

Bio4Comp

Parallel network-based biocomputation: technological baseline, scale-up and innovation ecosystem

- 6 Partners

Lund University NANO LUND A GREAT PLACE TO DO NANOSCIENCE

Technische Universität Dresden

Linnæus University

Fraunhofer

Molecular Sense

אוניברסיטת בר-אילן Bar-Ilan University

Linnæus University (LNU)

Lund University (ULUND)

Molecular Sense Ltd. (MolS)

Fraunhofer ENAS (Fraunhofer)

TU Dresden (TUD)

Fraunhofer ISC (Fraunhofer)

Bar-Ilan University, Israel (BIU)

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www.bio4comp.eu

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