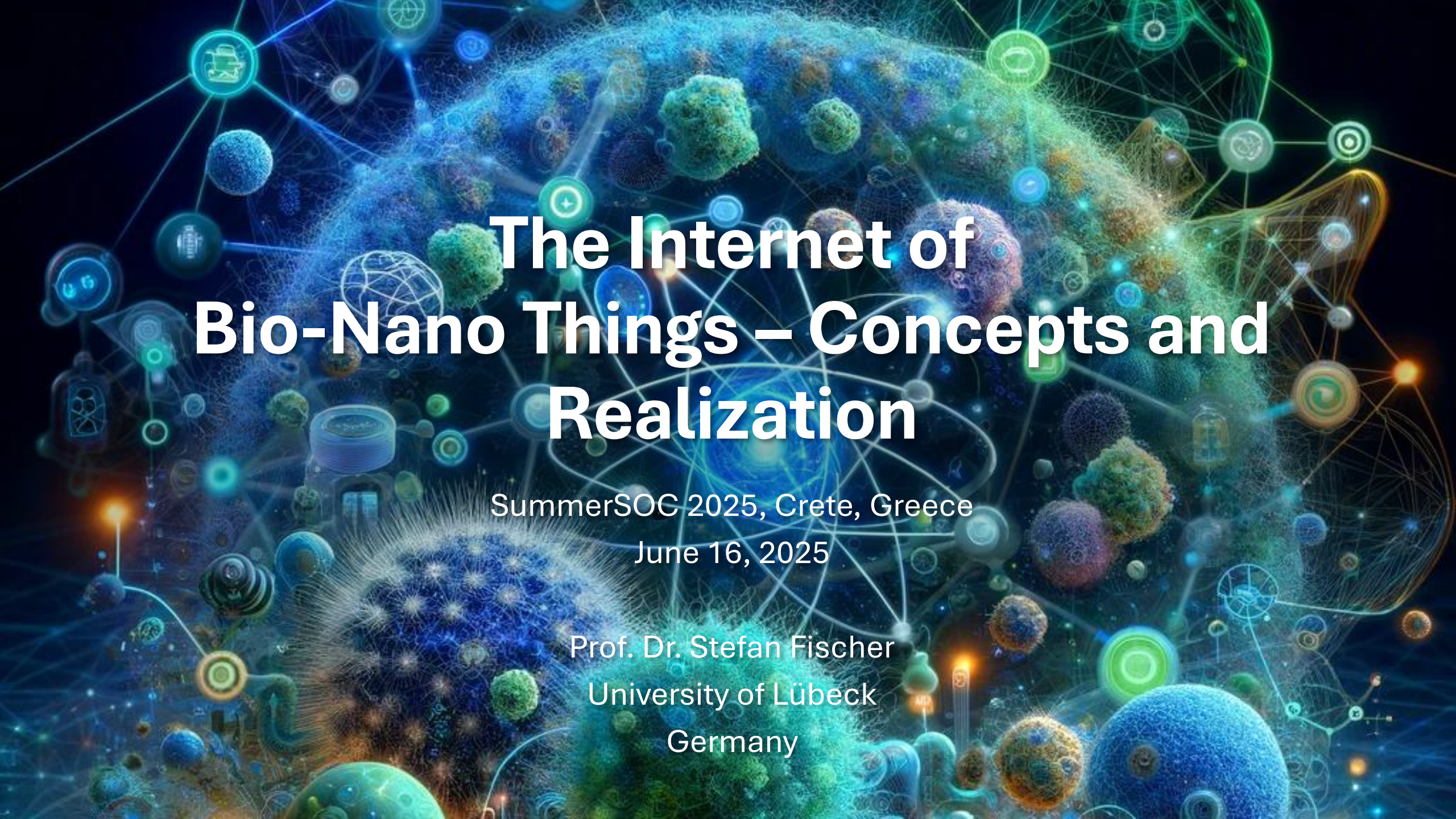


The Internet of Bio-Nano Things – Concepts and Realization

SummerSOC 2025, Crete, Greece

June 16, 2025

Prof. Dr. Stefan Fischer

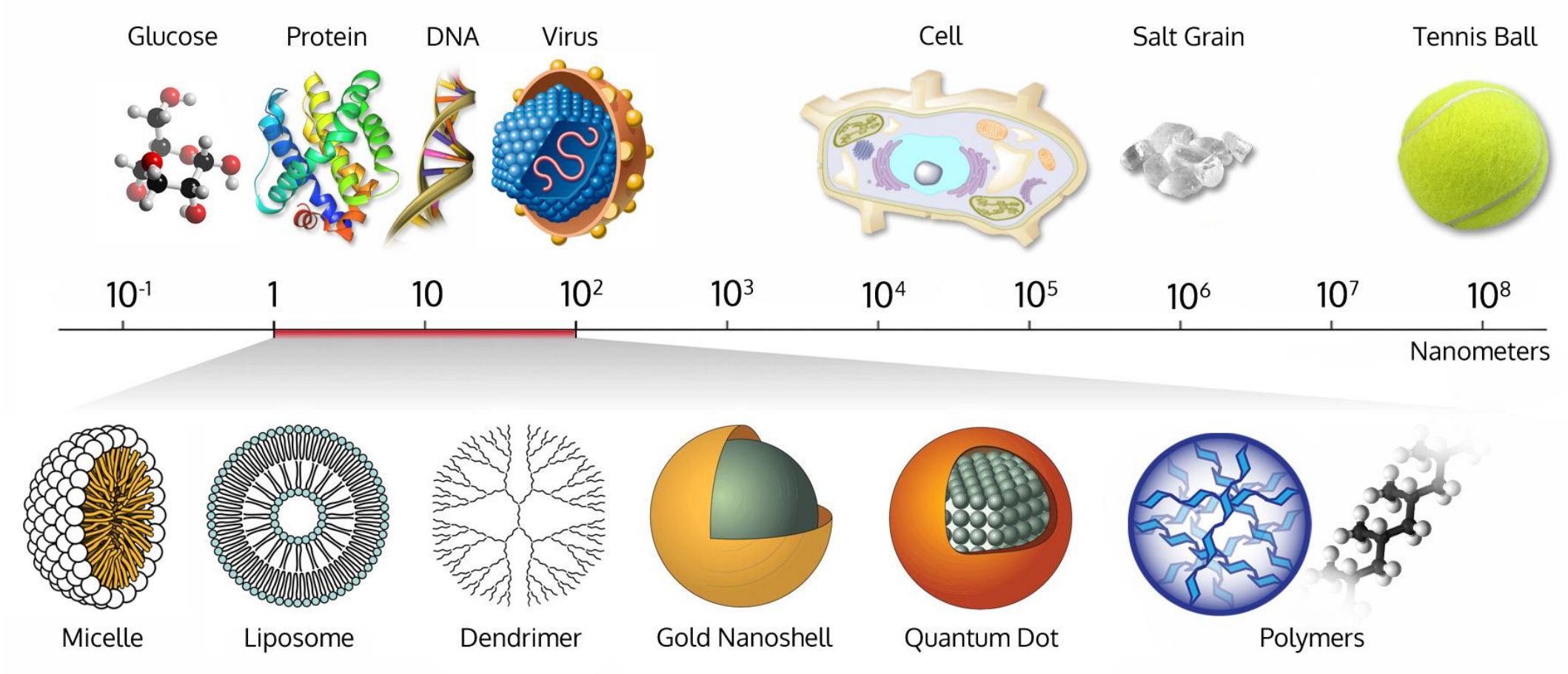
University of Lübeck

Germany

Overview

- Nano Robotics/Communication & the IoBNT
- The IoBNT in precision medicine
- DNA-based nanonetworks
  - Idea and concept
  - In-message computation
- Gateway Technologies
- Towards realization: wet lab and in-vivo experiments
- Medical application examples
- How far are we?

What is „nano“?



Nanobots

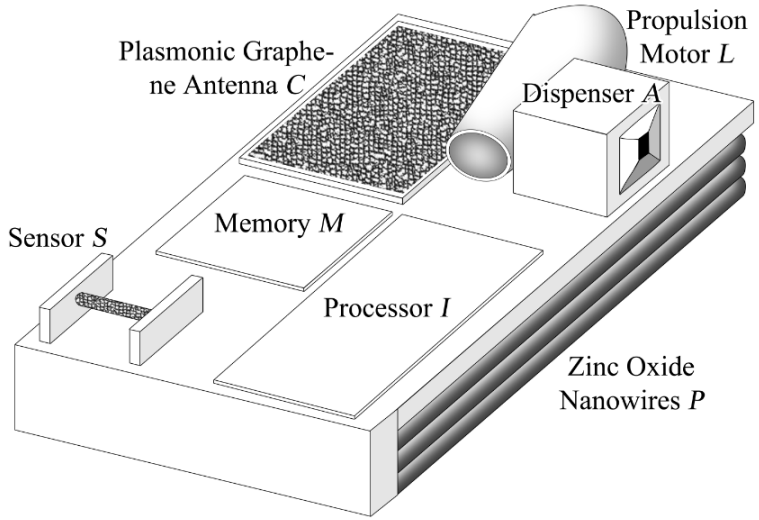
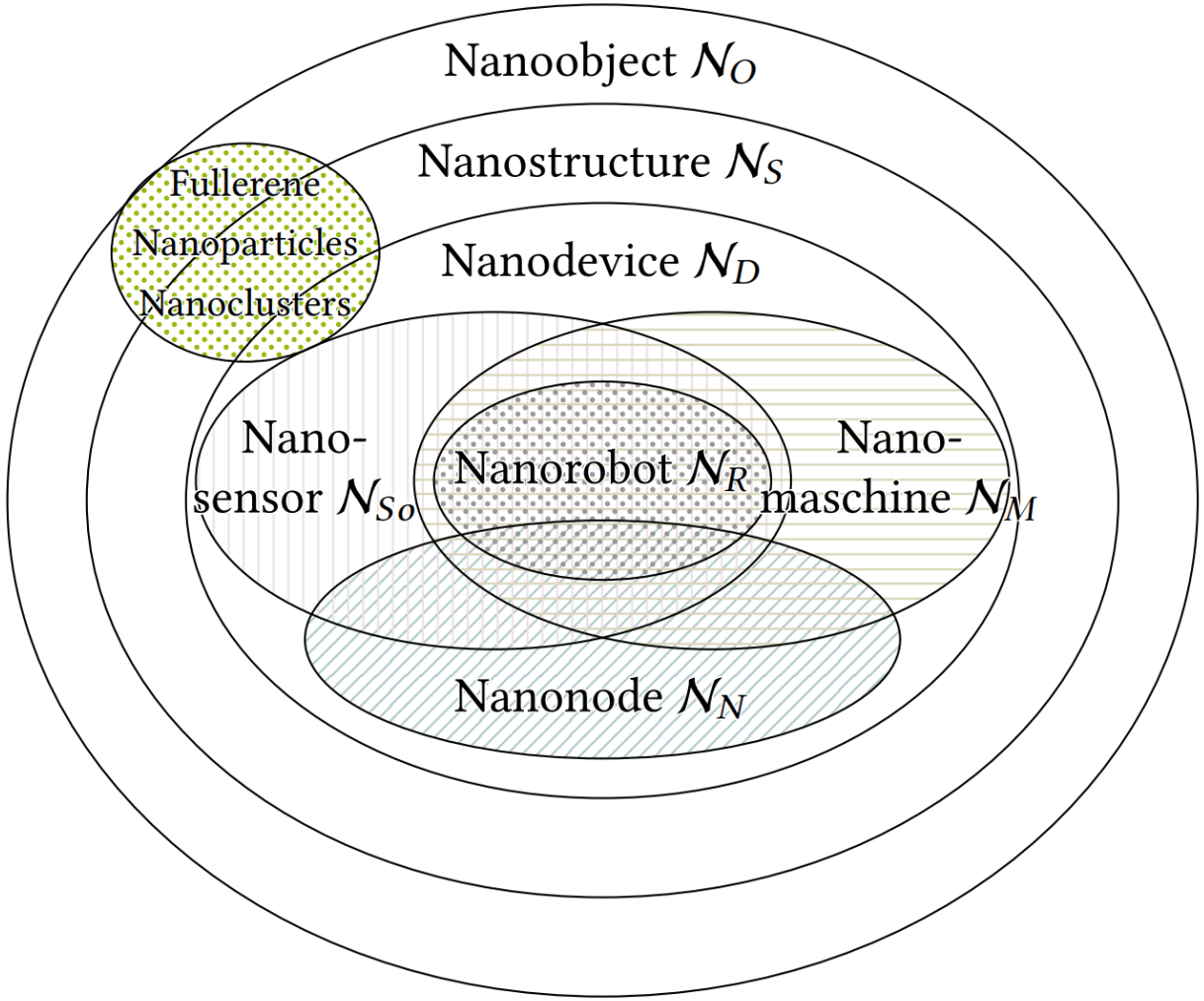


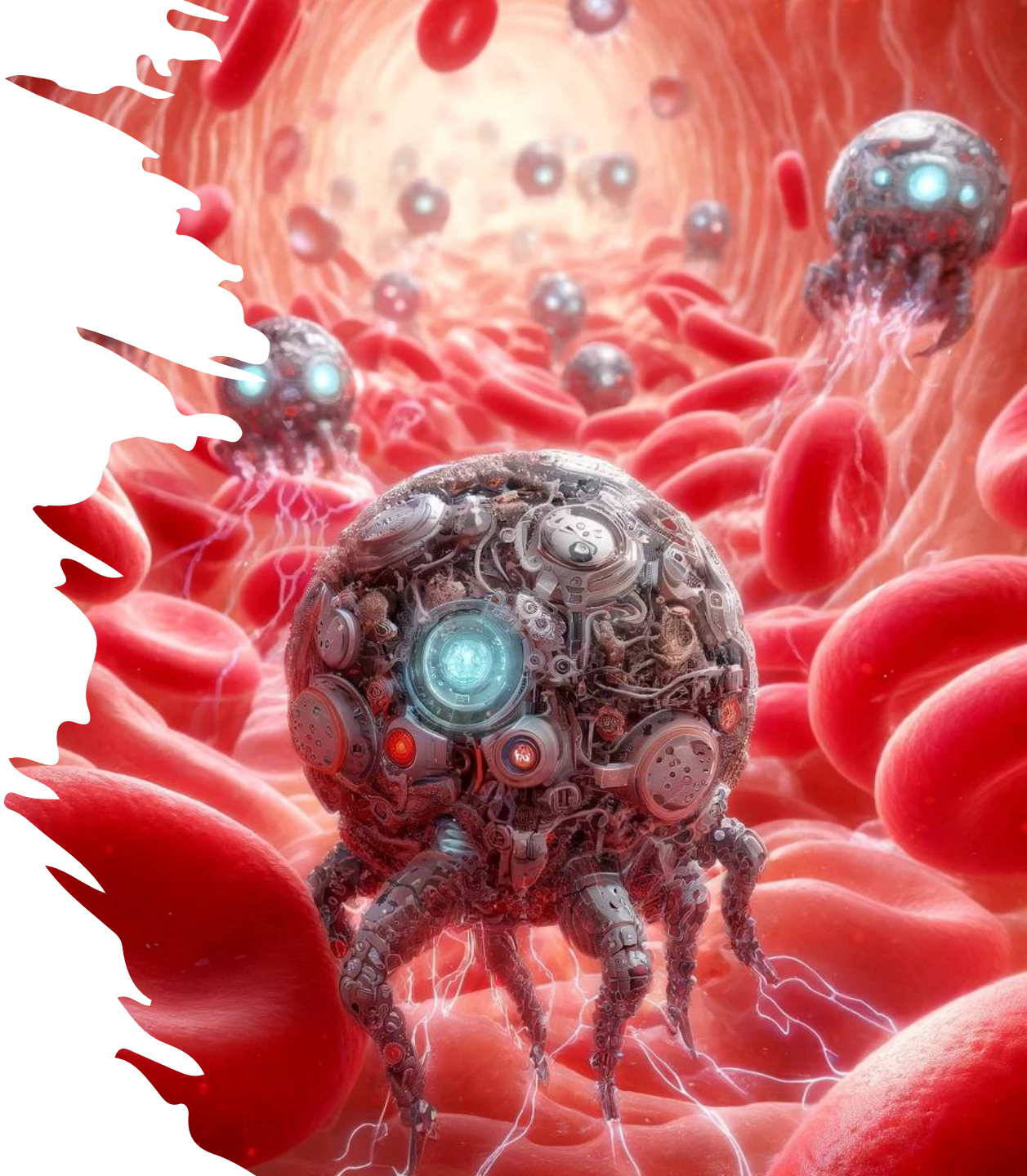
Fig. 2. An example of an electronic Nanodevice with the components $\{A, C, I, L, M, P, S\}$.



Definition 3 *A* Nanodevice $\mathcal{N}_D = (K_{mand}, K_{opt})$ *is an artificial construct with an overall nanoscale size, designed to perform a predefined function in an environment* Γ*. It consists of mandatory components* $K_{mand} = \{P\}$ *and a set of zero or more optional components* $K_{opt} \subseteq \{A, C, I, L, M, S, T\}$.

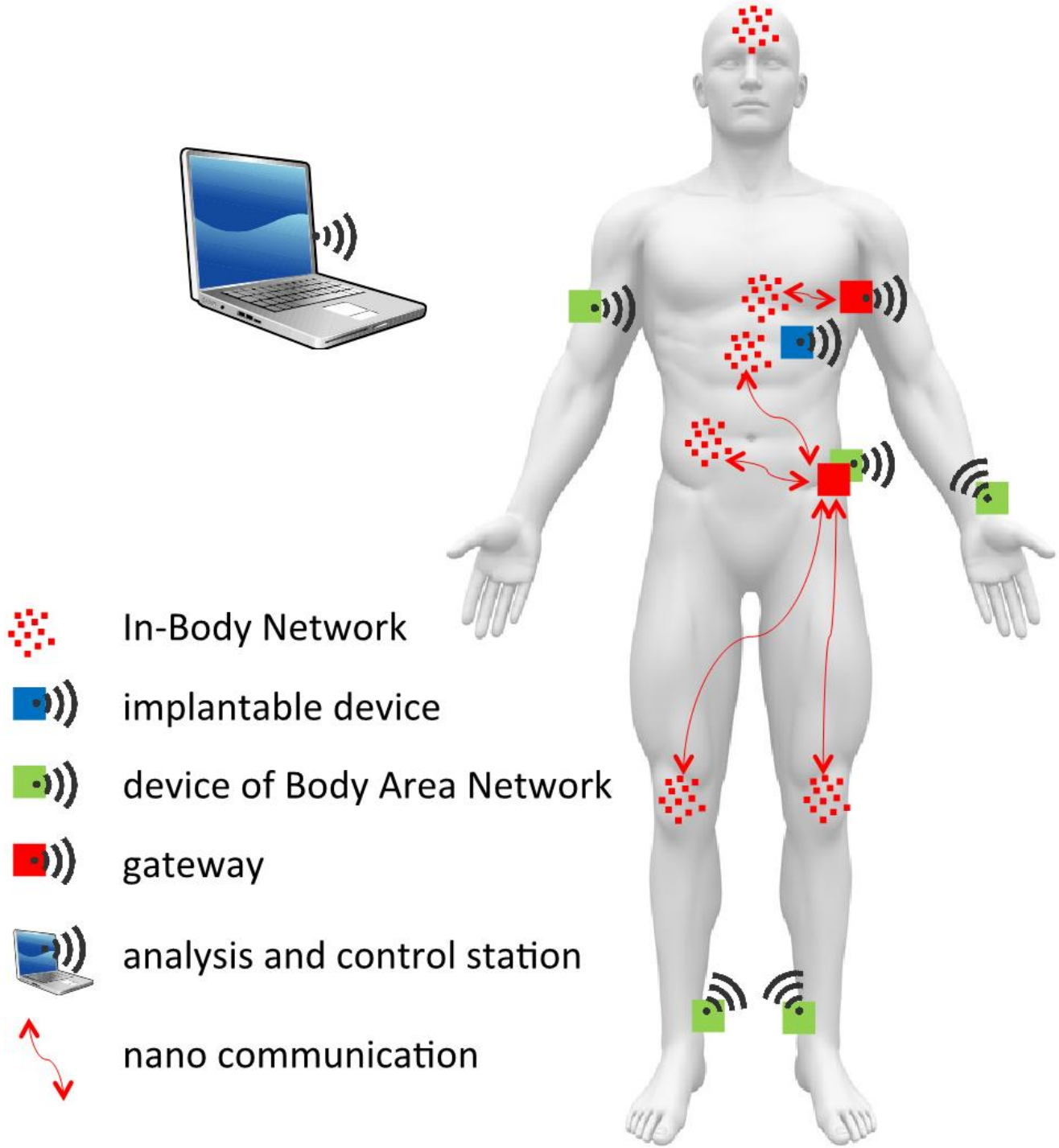
Nanonetworks

- A (huge) number of nanodevices/nanomachines /nanobots
- Operating in the human body
- Communicating with each other
- Fulfilling certain jobs



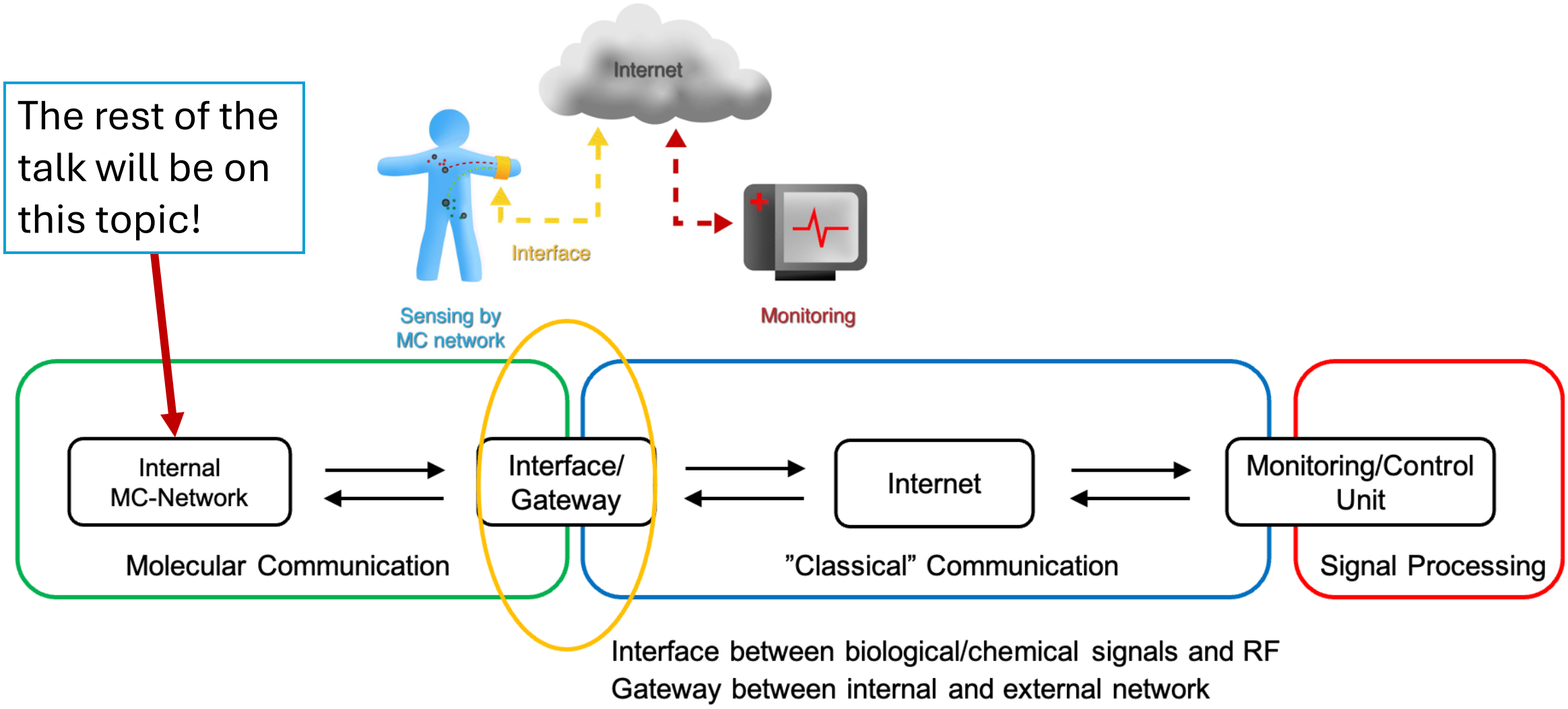
Integrating Nanonetworks:

The Internet of Bio-Nano Things



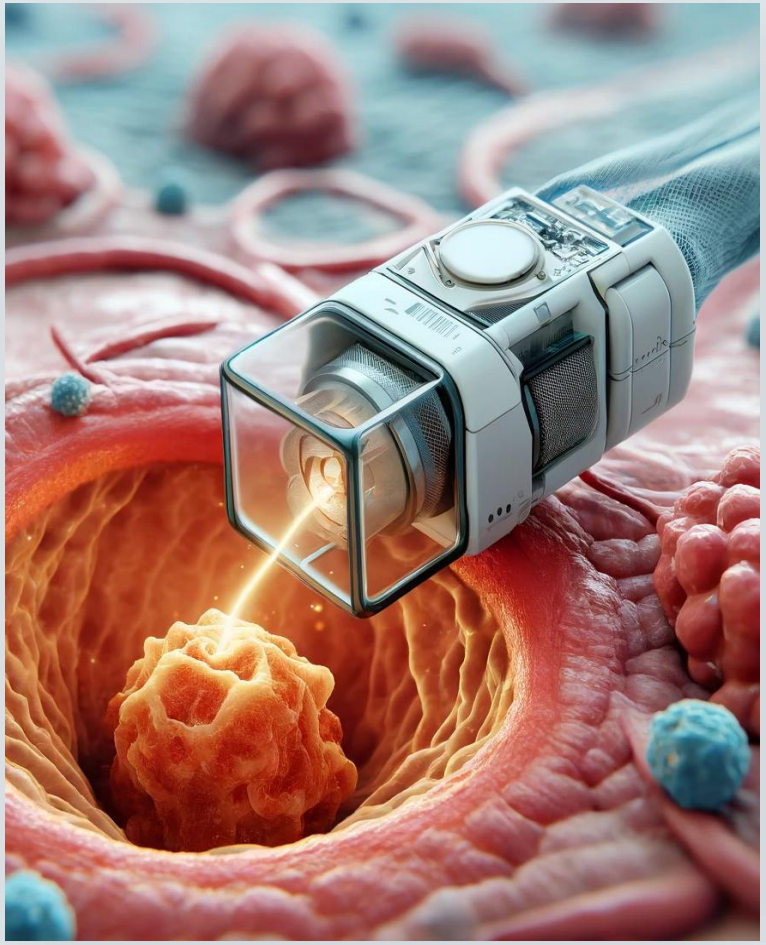
The Internet of Bio-Nano Things – technically

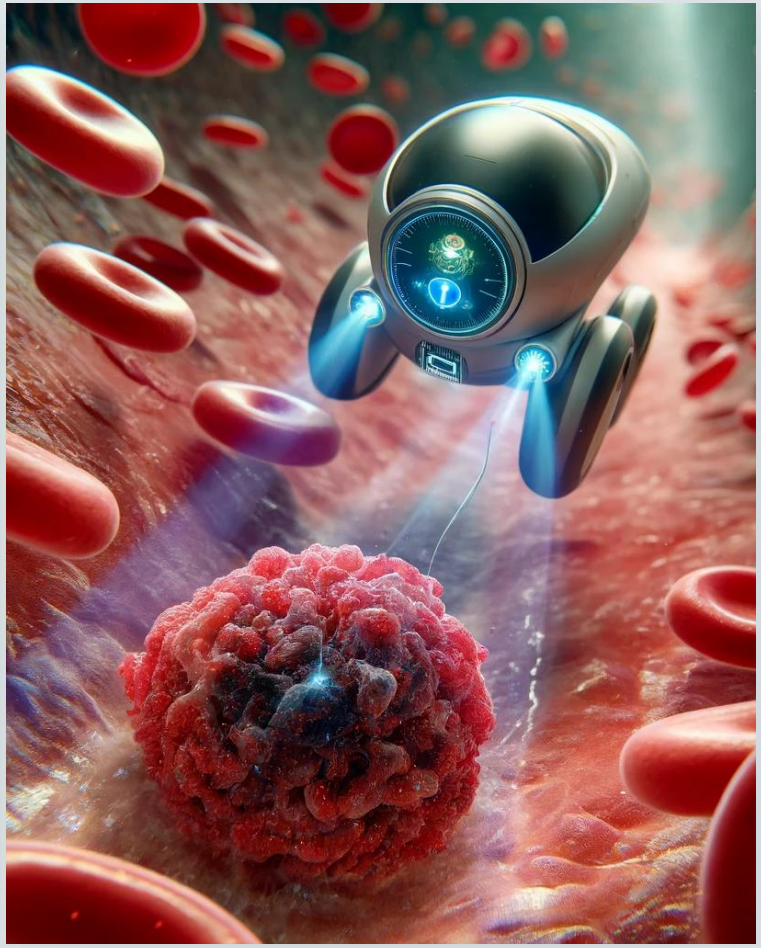
The rest of the talk will be on this topic!

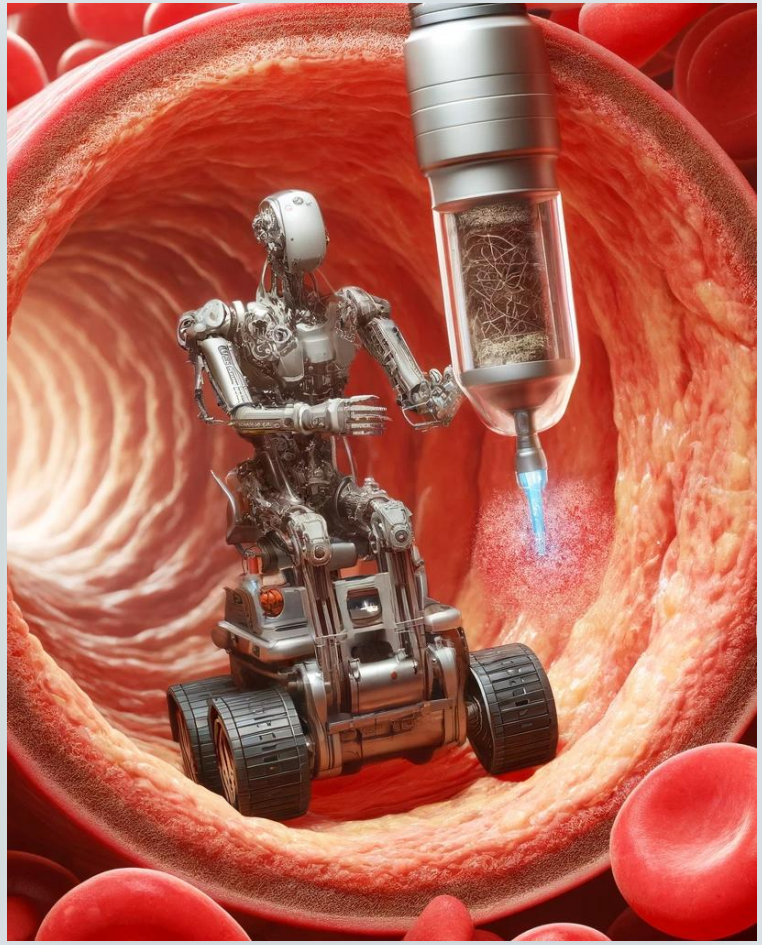


Interface between biological/chemical signals and RF
Gateway between internal and external network

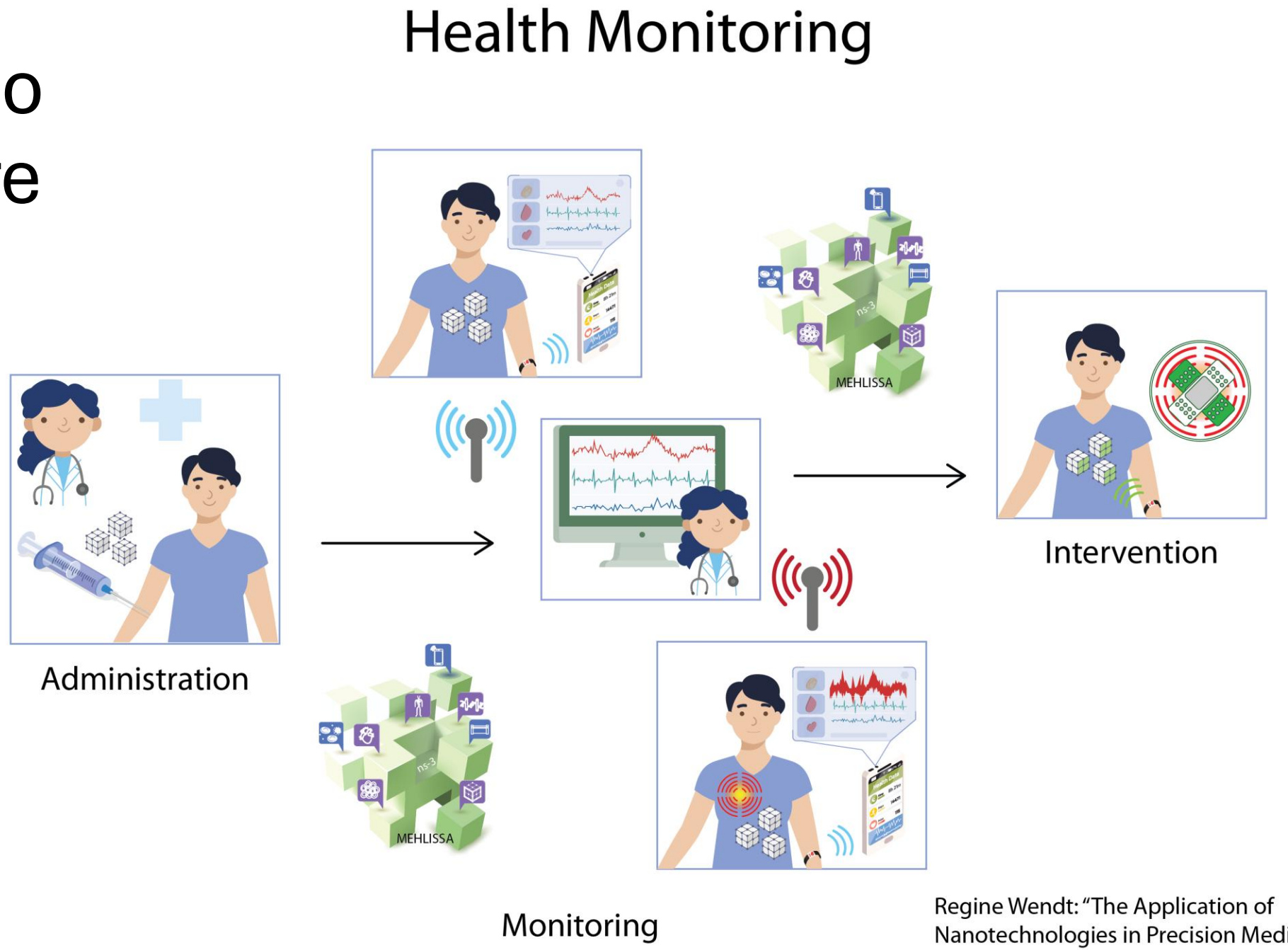
Use in Medicine:
Prevention, Diagnosis, Therapy







A Scenario (a bit more realistic)

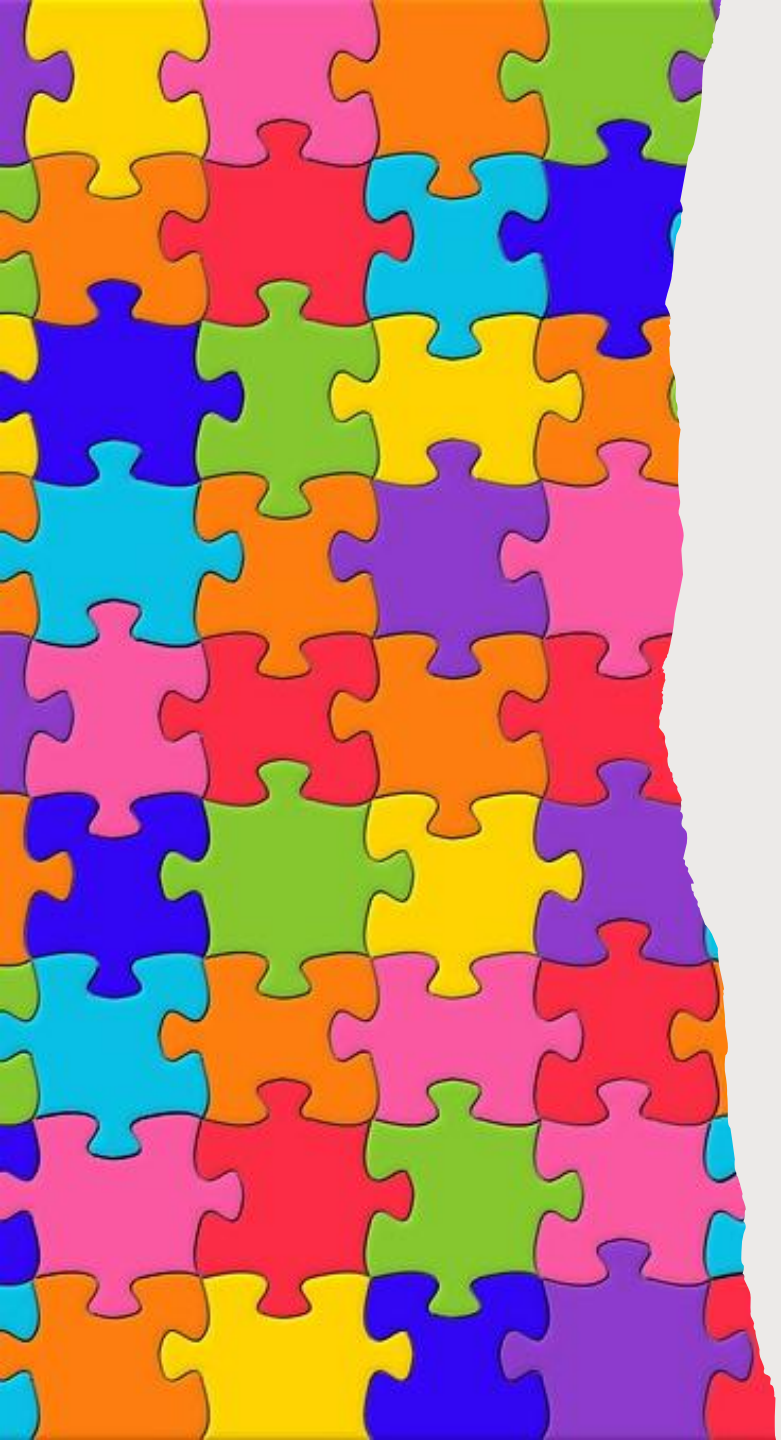


Regine Wendt: "The Application of Nanotechnologies in Precision Medicine" Diss. 2024

Requirements of a Solution

- Bio-compatible
- Very small size → very little functionality → distributed system solution necessary
- Solution for construction of devices on the nano level

DNA-based Nano Networks



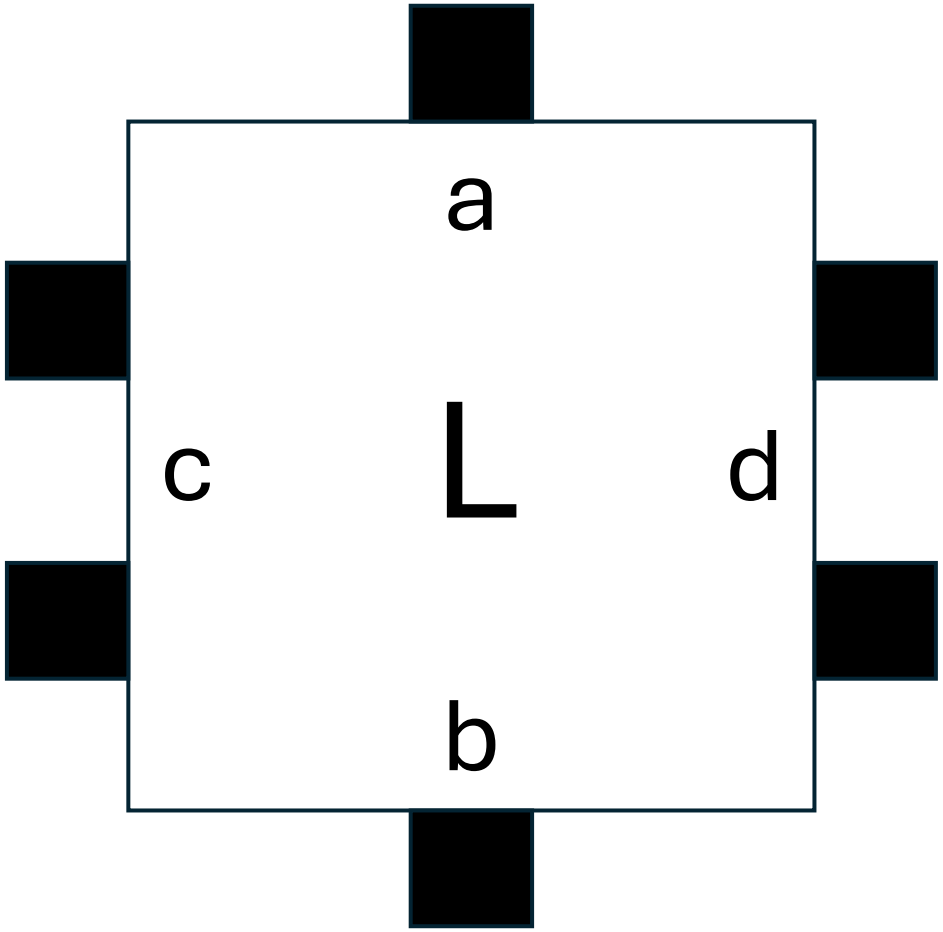
The Basics: DNA Tiles

- Concept: tile-based self-assembly systems invented by Eric Winfree
- DNA tiles as basic building blocks of all structures presented here
- Similar to Lego bricks
- Important difference: can be designed to only stick to very specific other tiles
- And, more importantly: they master self-assembly

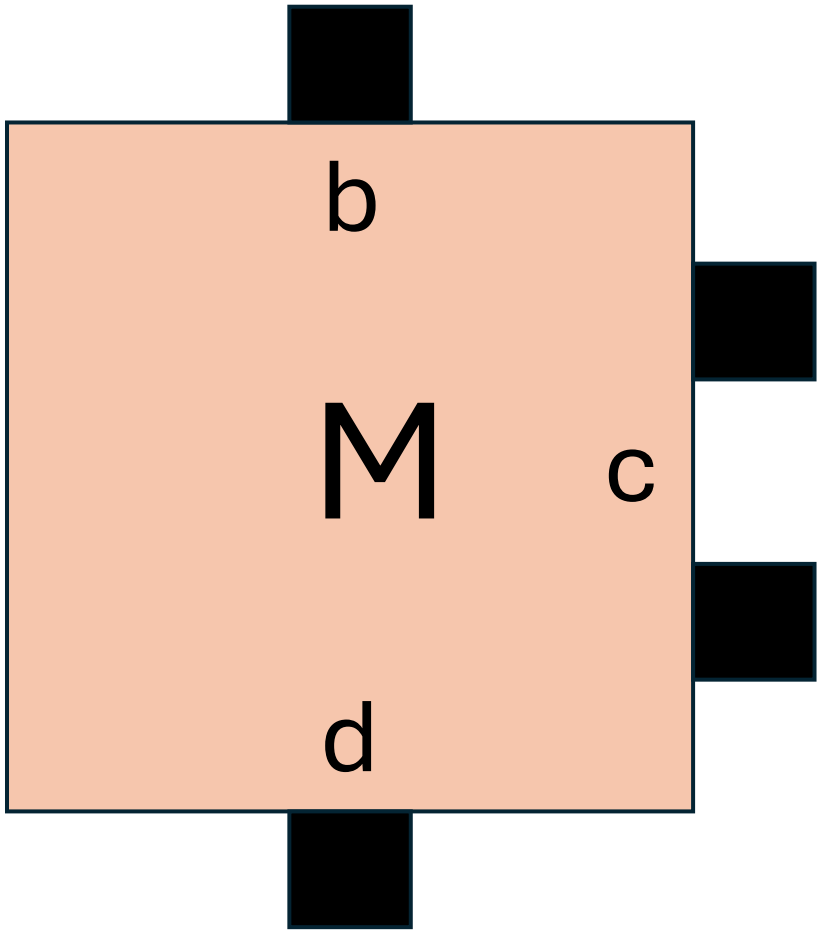
→ no need for complex engineering on the nano level!

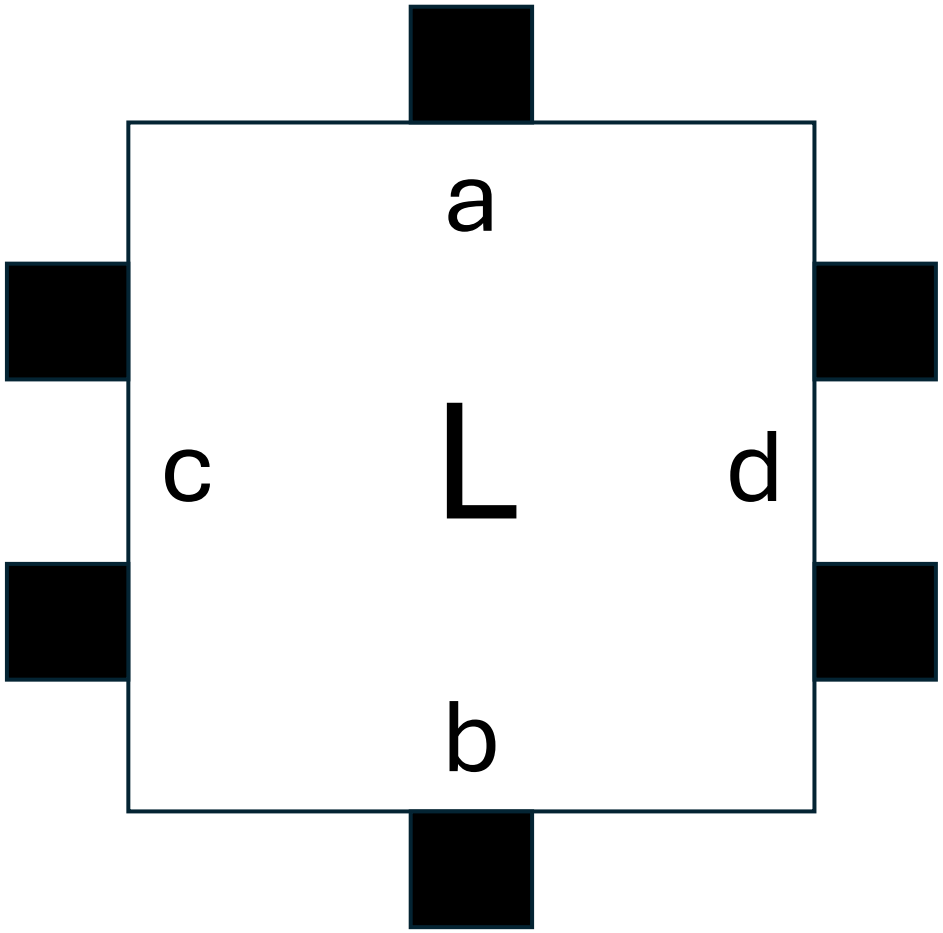
The Mathematical Model of a DNA Tile

- Non-rotatable blocks
- Glues on each side of different strength (here: top, down: 1, left, right: 2)
- Glues have labels
- Marker in the middle
- Simply speaking, tiles connect to other tiles when they have the same glues on neighboring sites



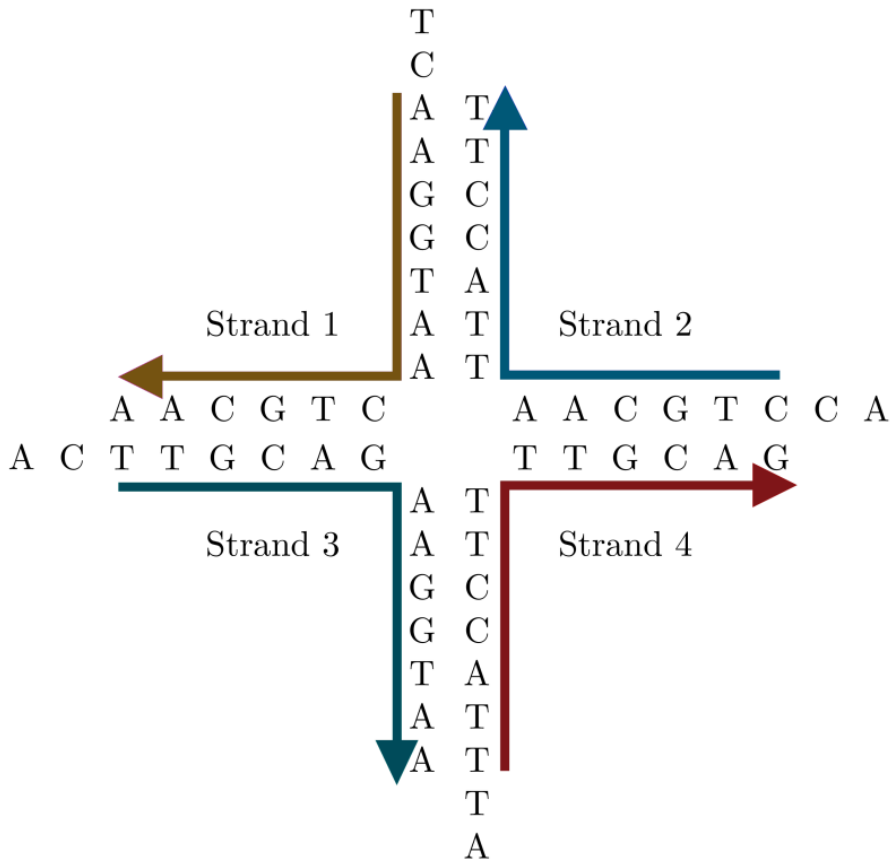
The Mathematical Model of a DNA Tile





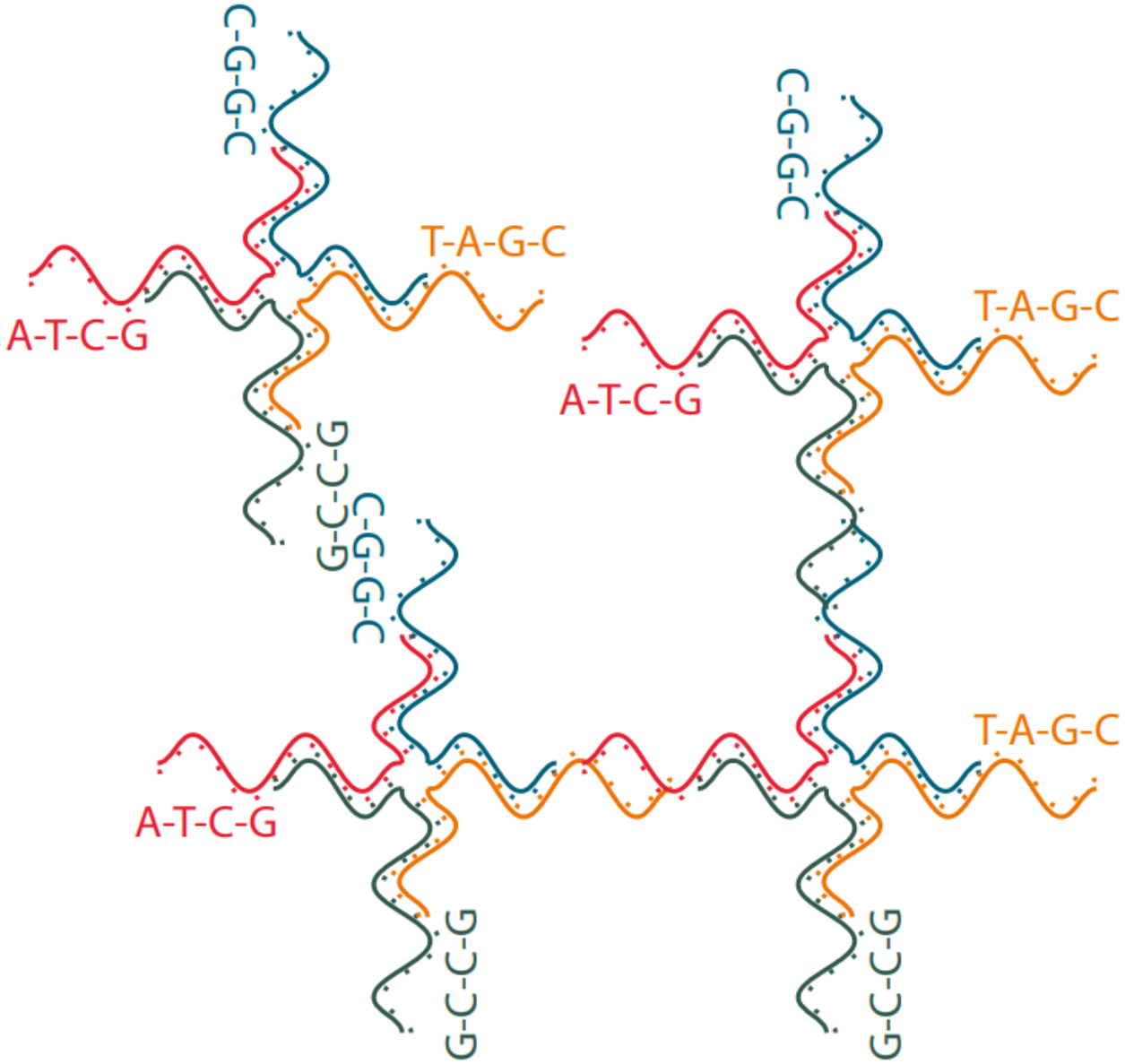
… and the Biological Equivalent

- The tiles consist of four intertwined DNA strands with open ends in all cardinal directions.
- Typical size: 20 x 20 x 2 nm^3
- The length of the open ends can be chosen at will and depends on the intended use case.
- Longer open ends result in stronger bindings, while shorter ends lead to smaller tiles with weaker binding strength.
- Further, the bases Cytosin and Guanin bind roughly twice as strongly as Adenine and Thymine.



DNA-tile with glues in all directions.

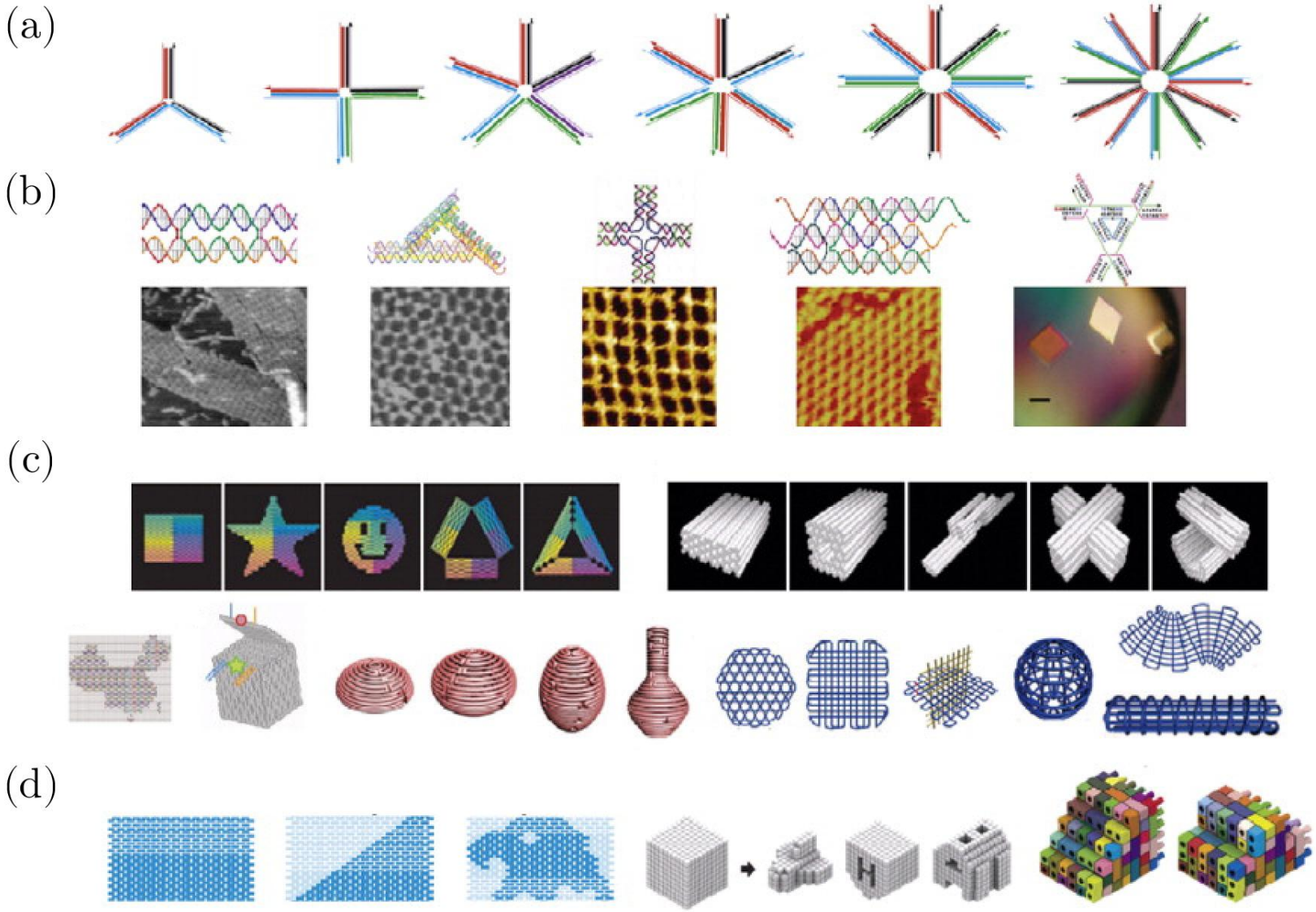
A more Biological Visualization



Now, what can you do with tiles?

- Biology does its job by „glueing“ matching tiles together
- With the right tiles, you can do:
  - Build nanodevices (bots)
  - Compute
  - Communicate
- Let‘s see how this works!

Nanodevices (Structures)

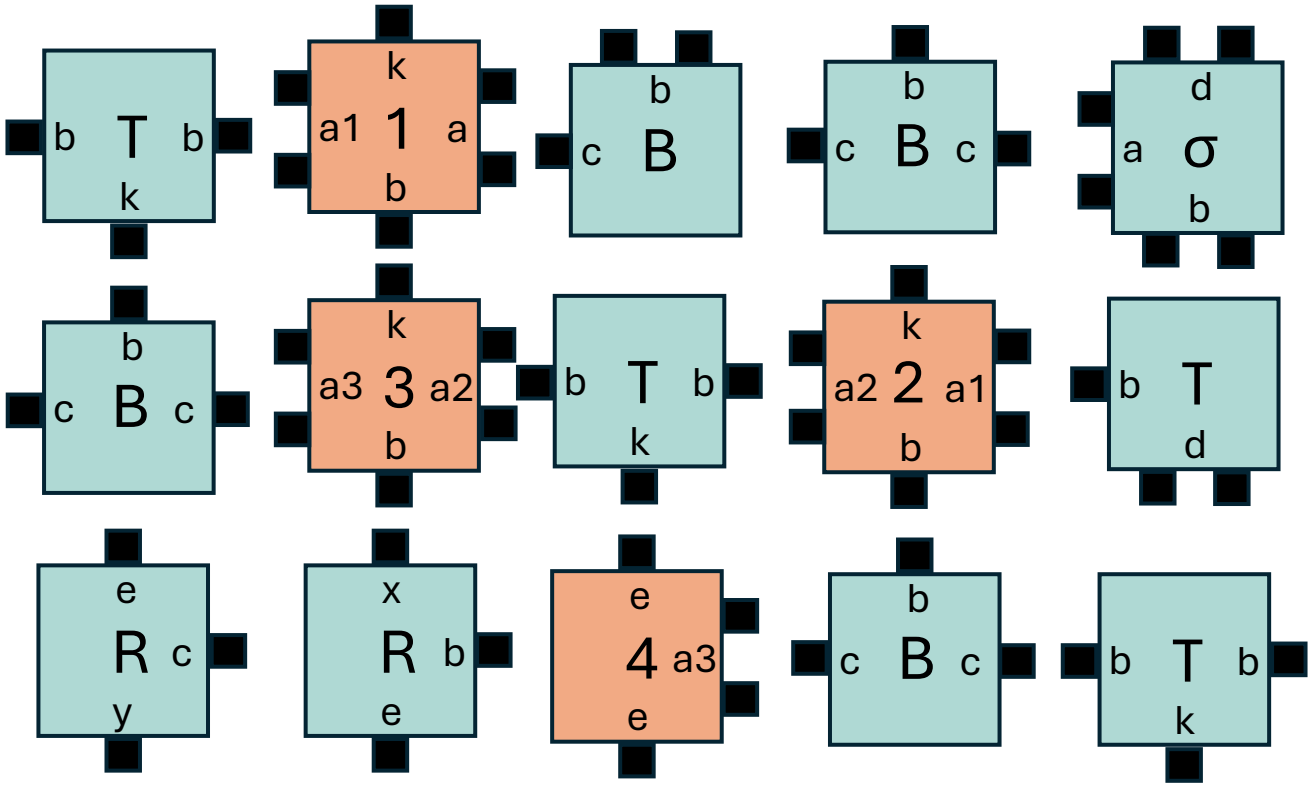


Jie Chao, Yunfeng Lin, Huajie Liu, Lianhui Wang und Chunhai Fan: „DNA-based plasmonic nanostructures“ · Materials Today Bd. 18, Nr. 6 (2015), S. 326–335

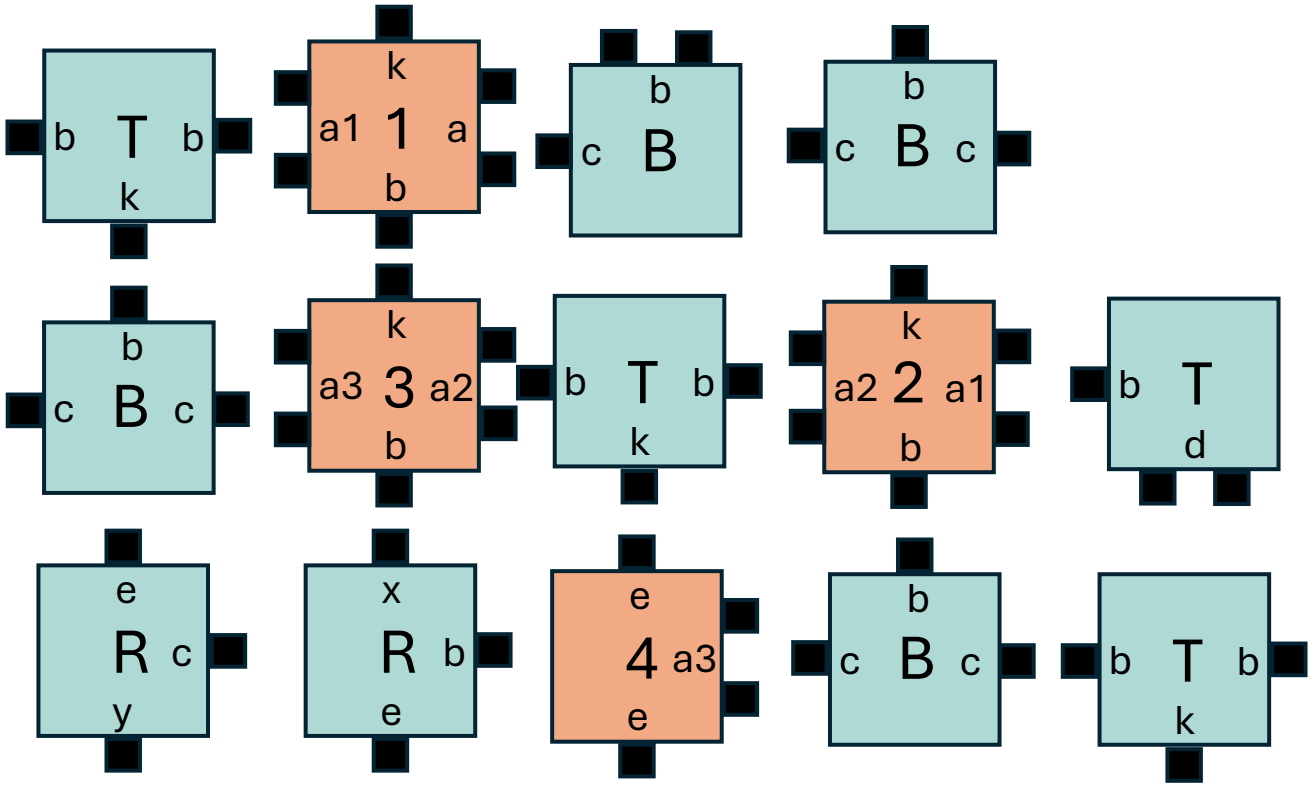
Computation

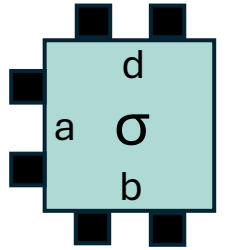
Logical Formulas: 4-way AND

Self-Assembly: 4-way AND

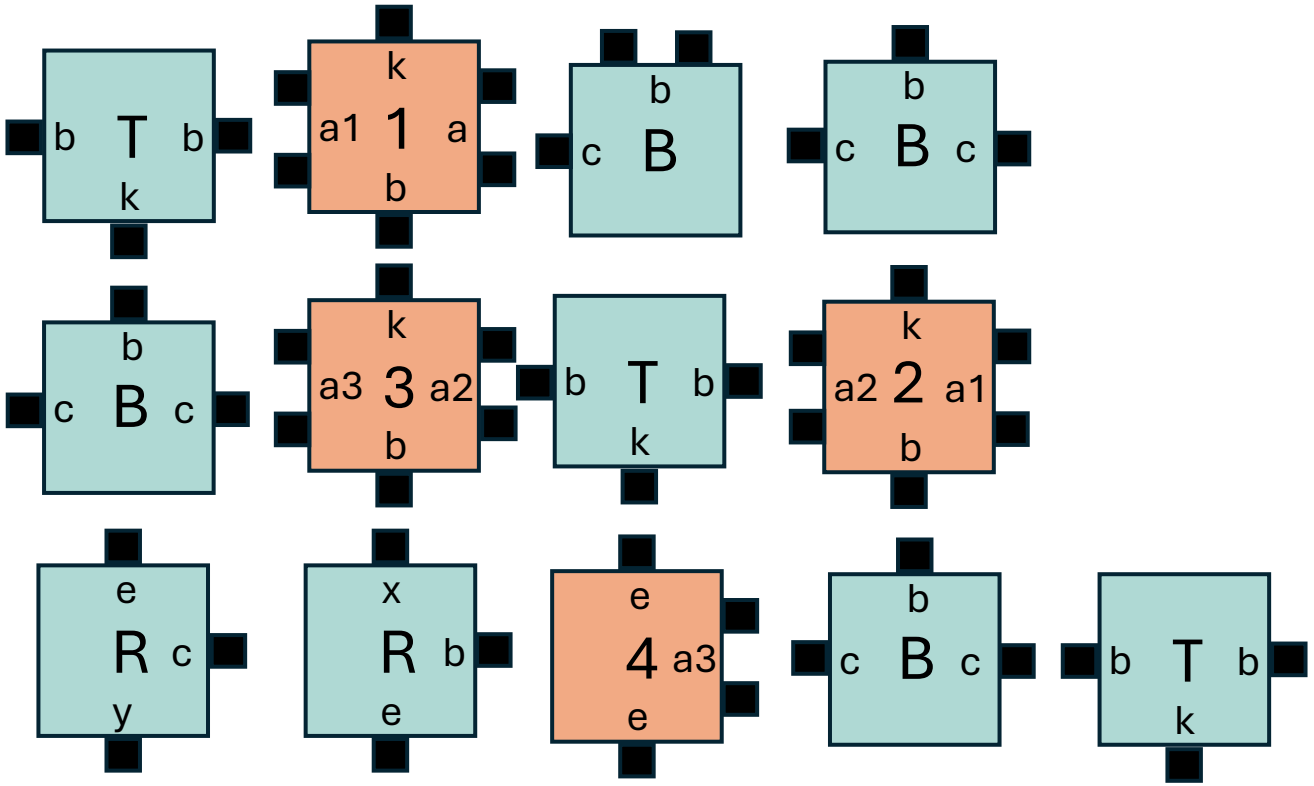


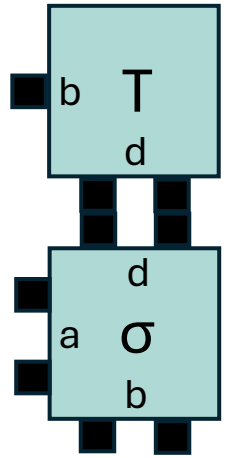
Self-Assembly: 4-way AND





Self-Assembly: 4-way AND





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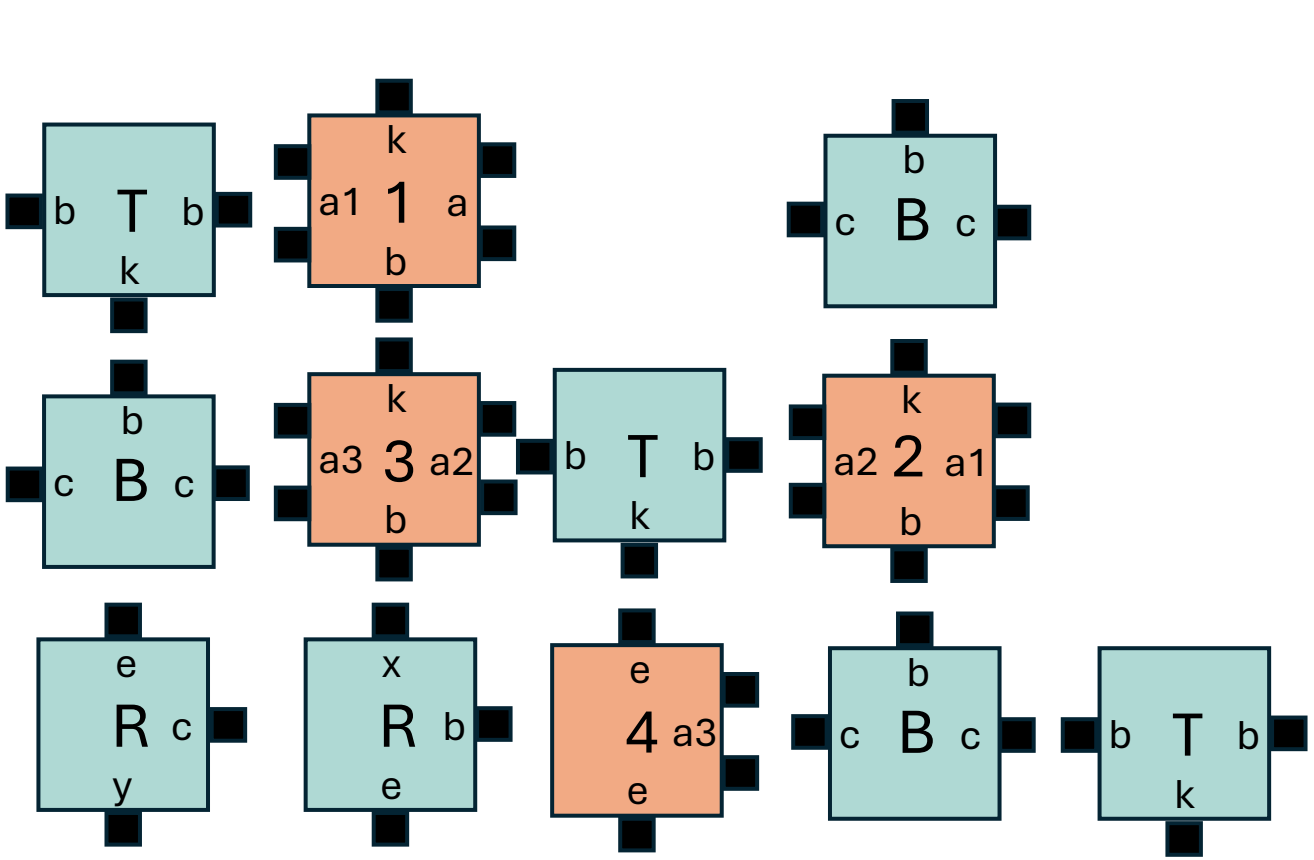
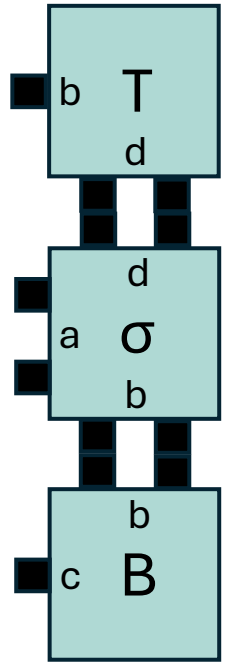
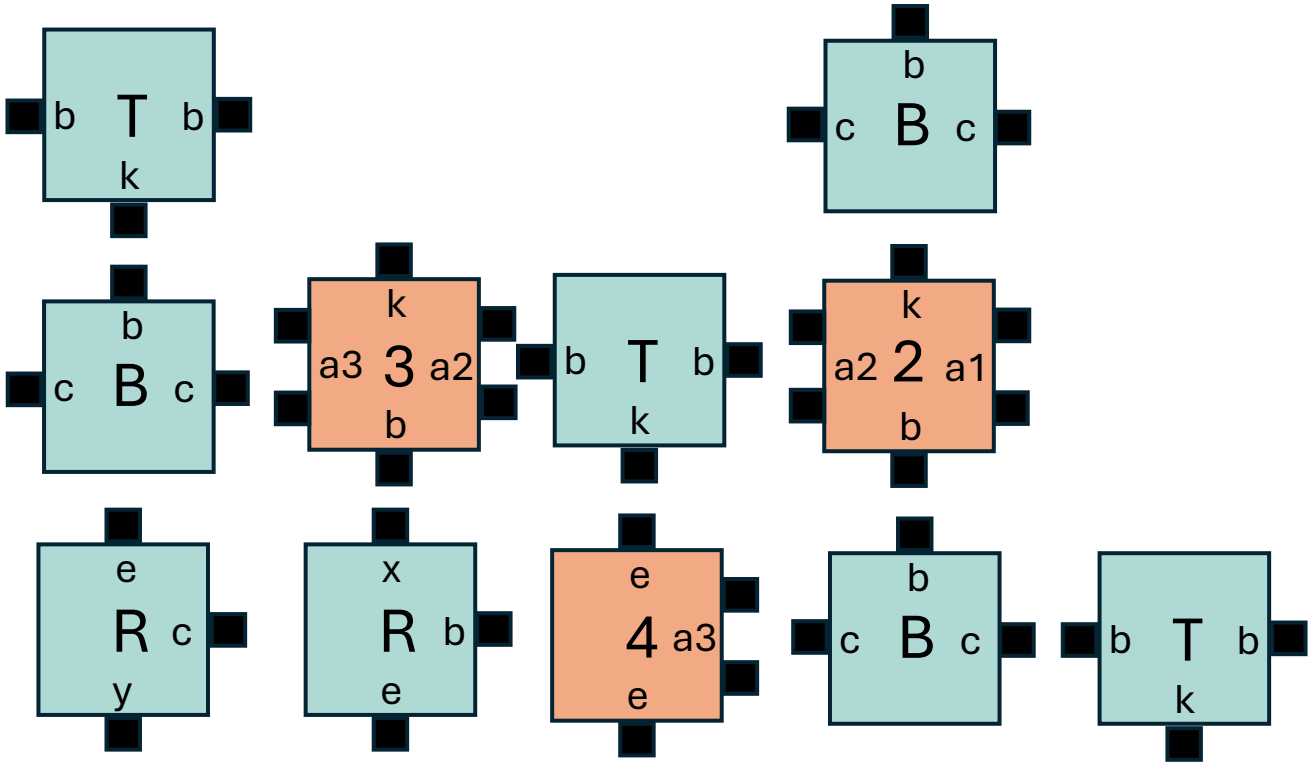
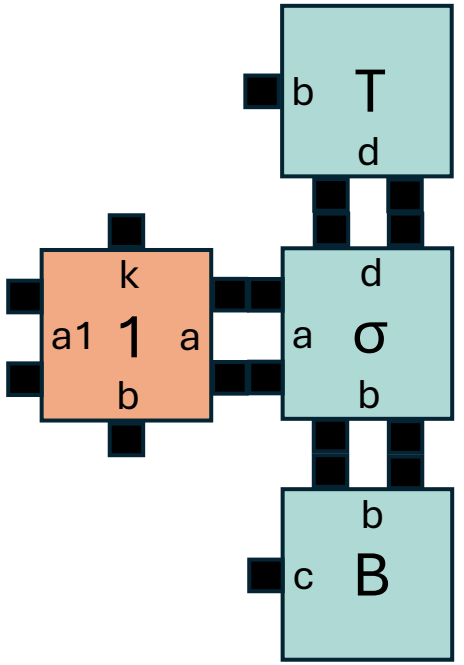


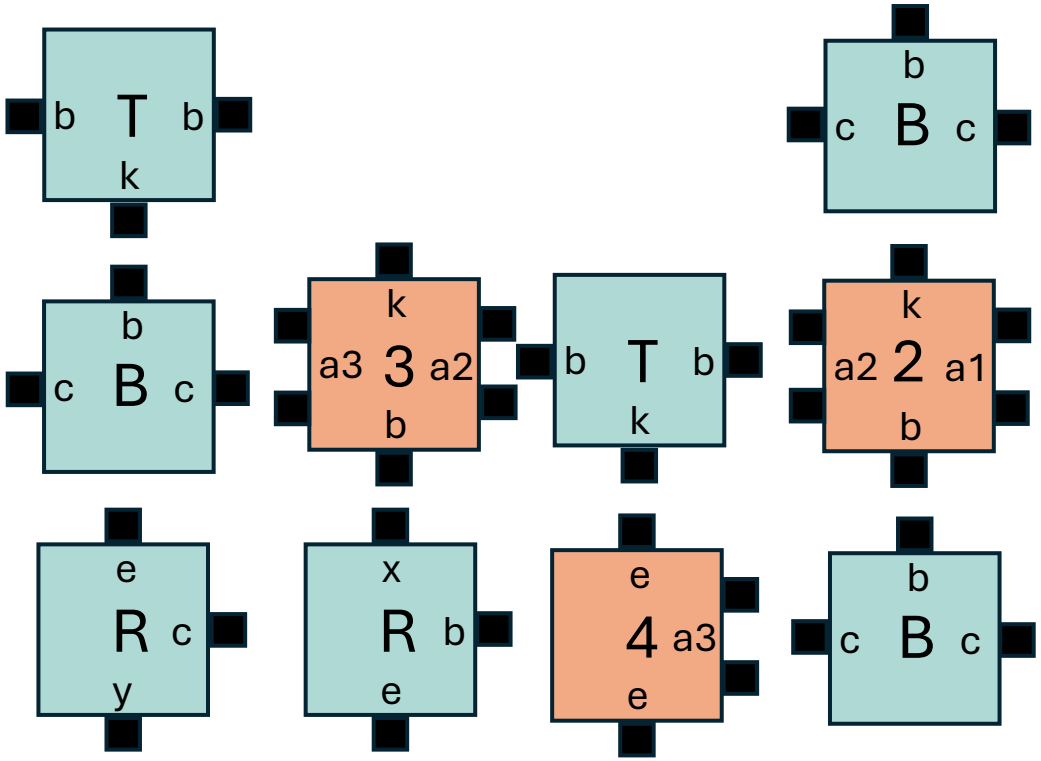


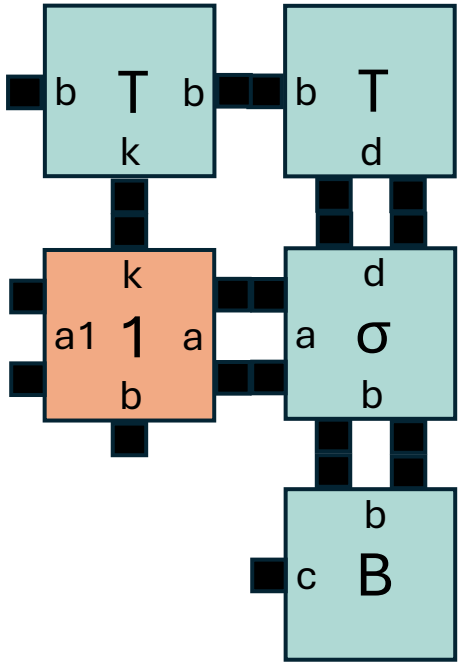
Self-Assembly: an Example





Self-Assembly: 4-way AND





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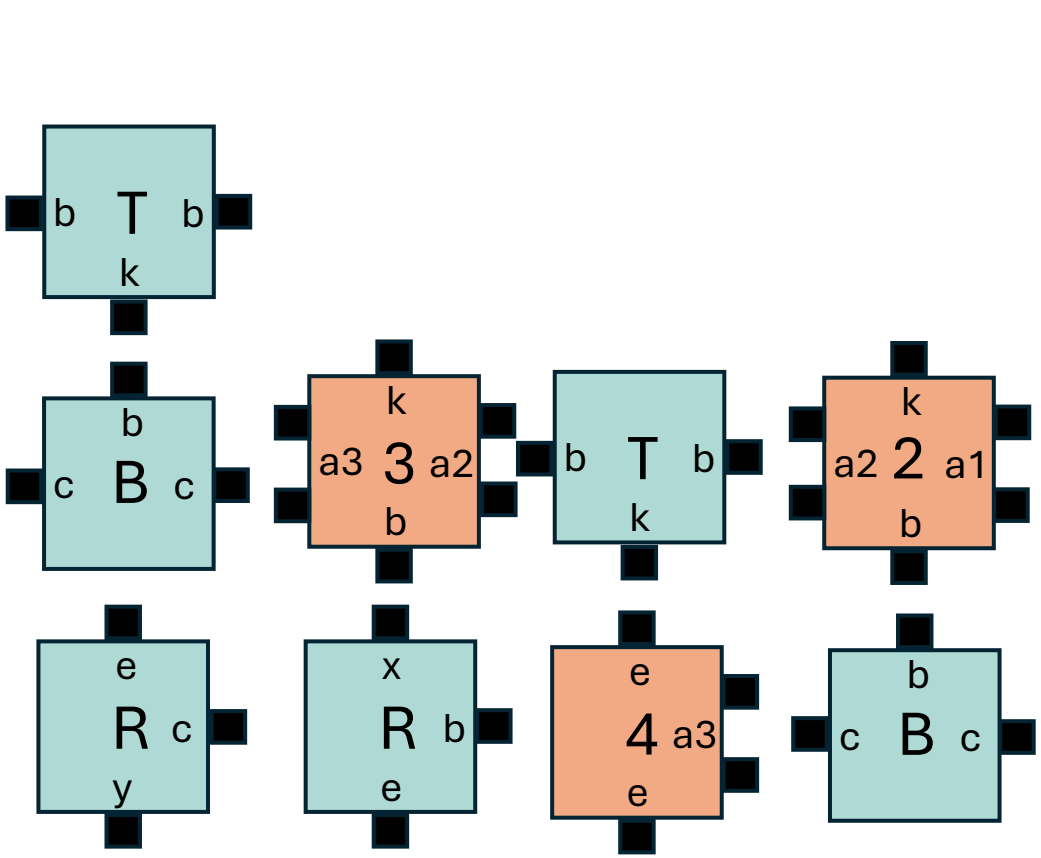

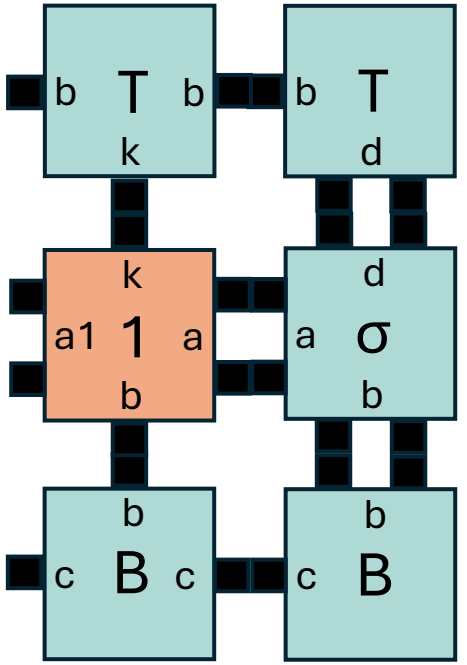

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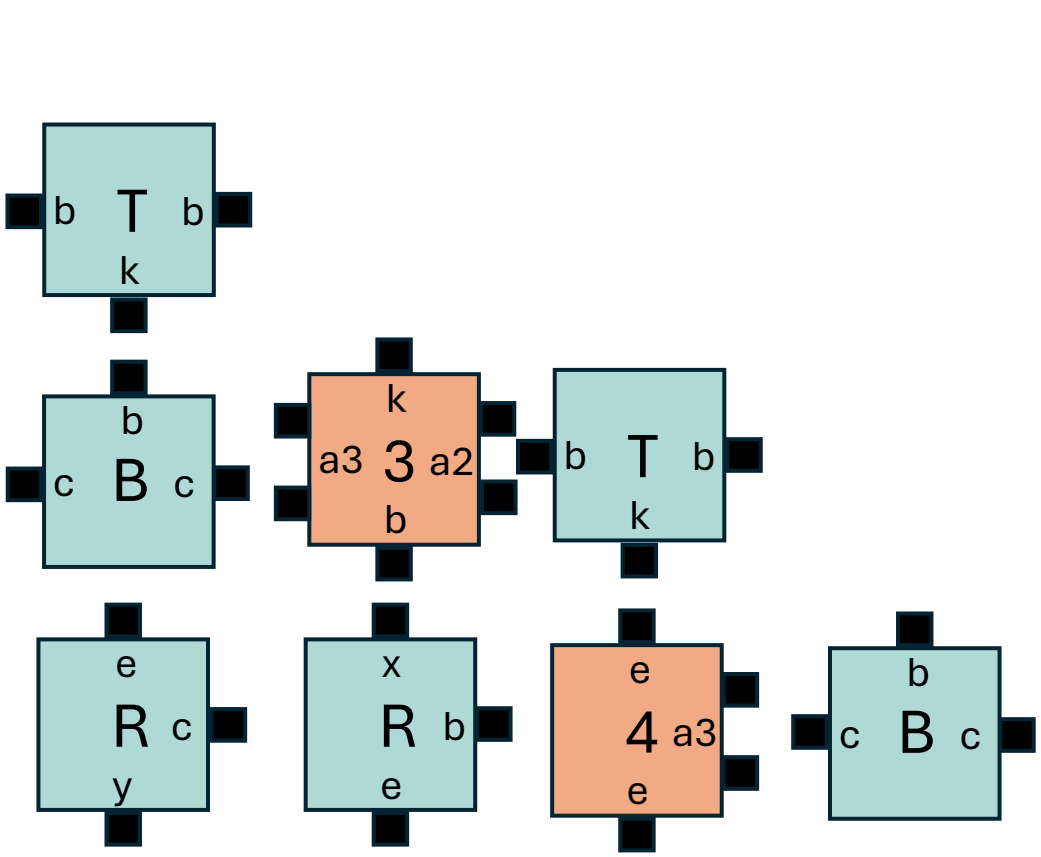

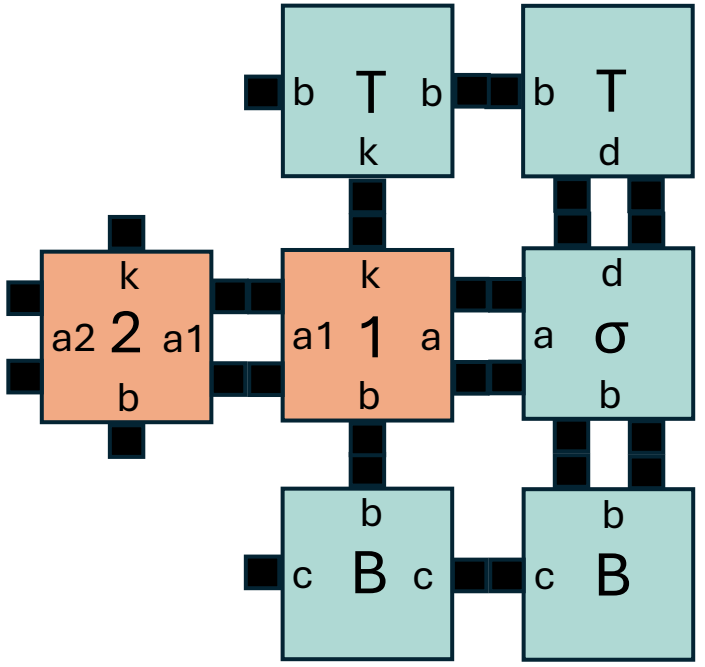

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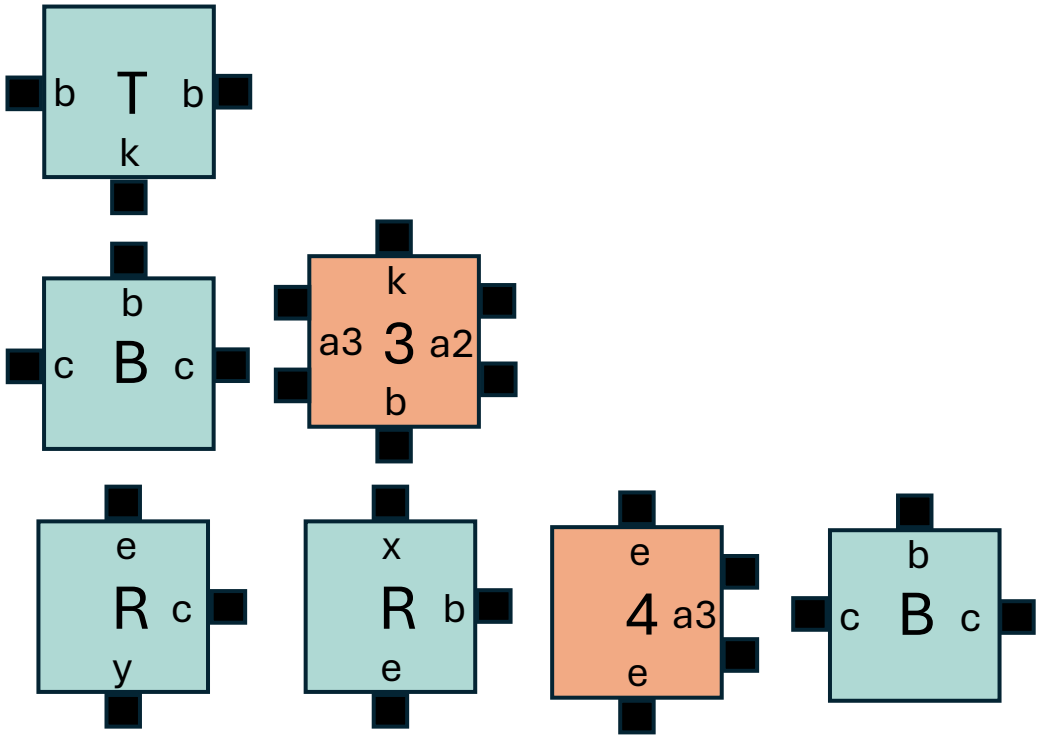

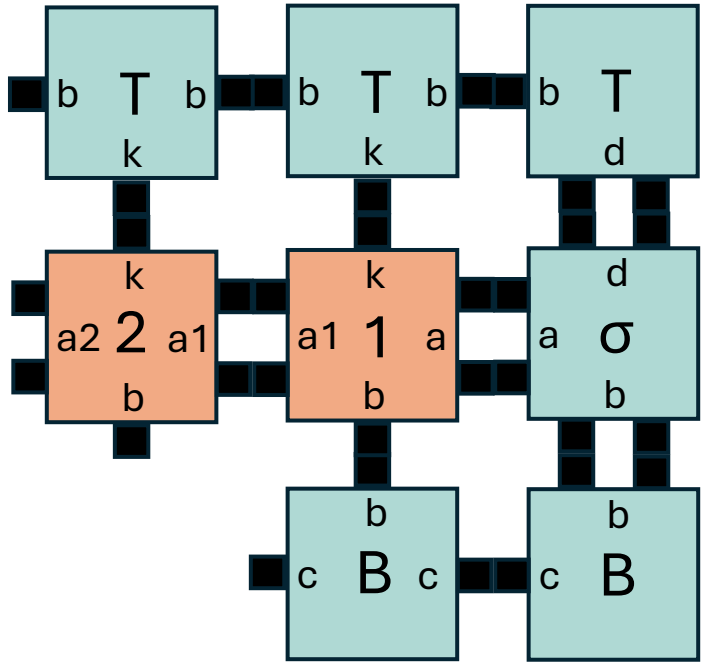

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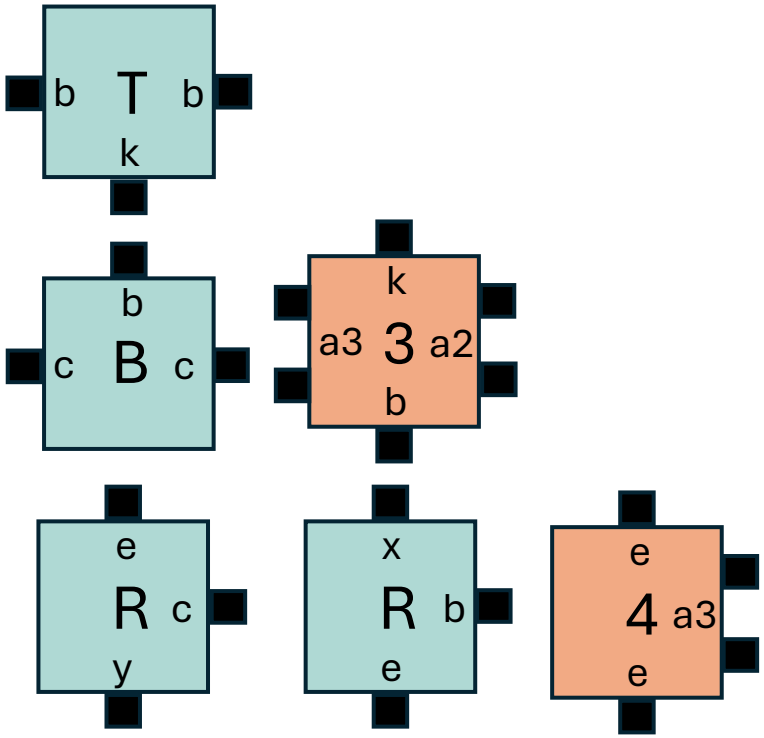

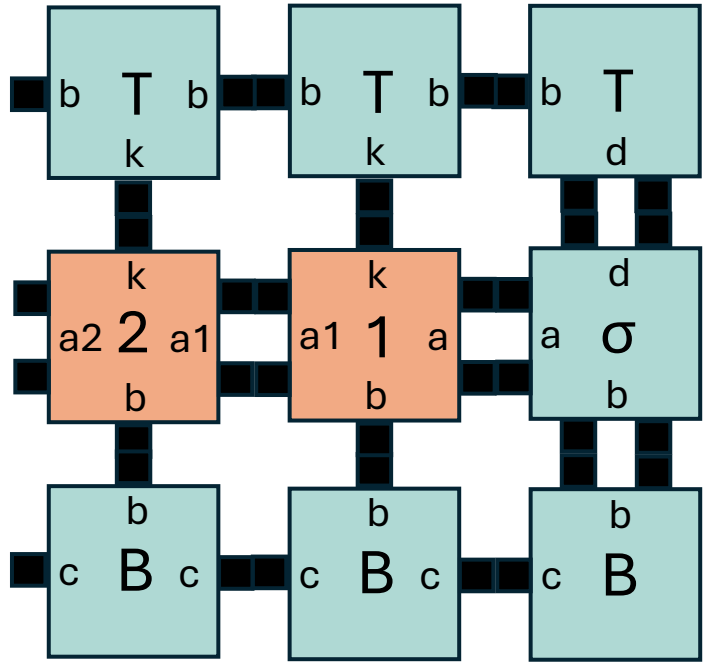

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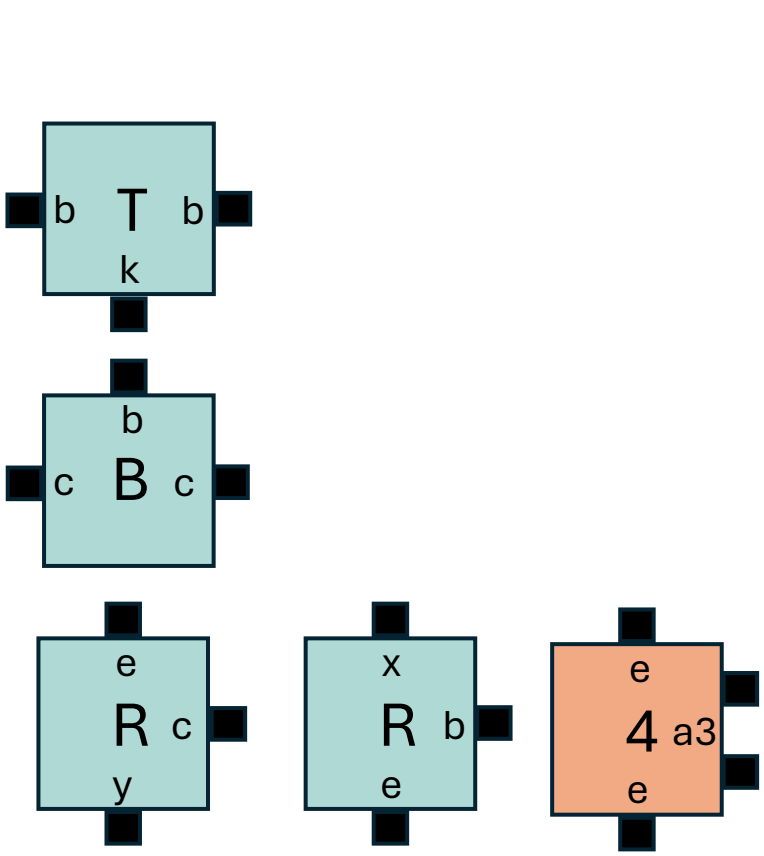

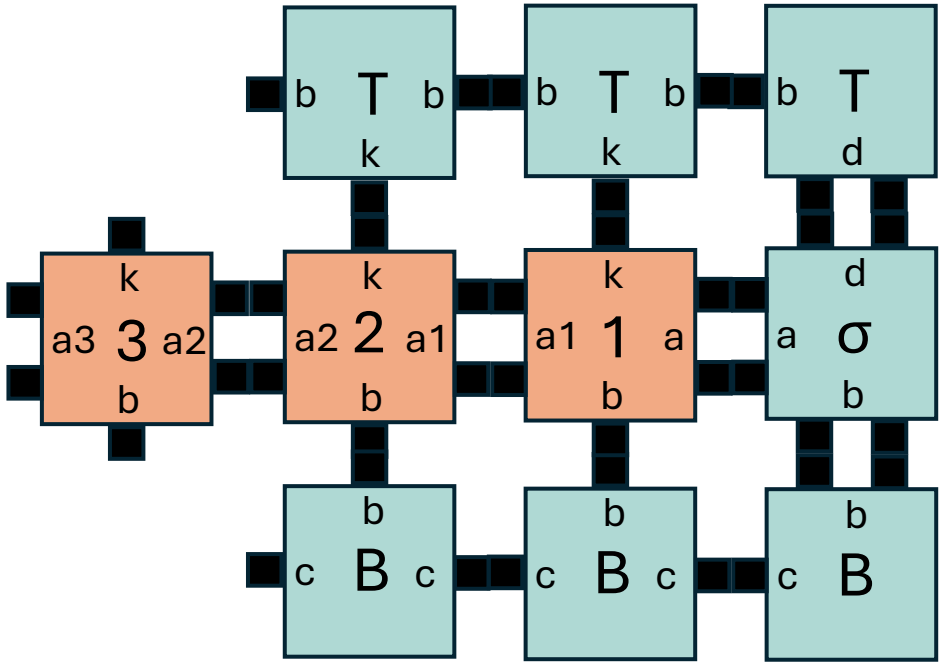

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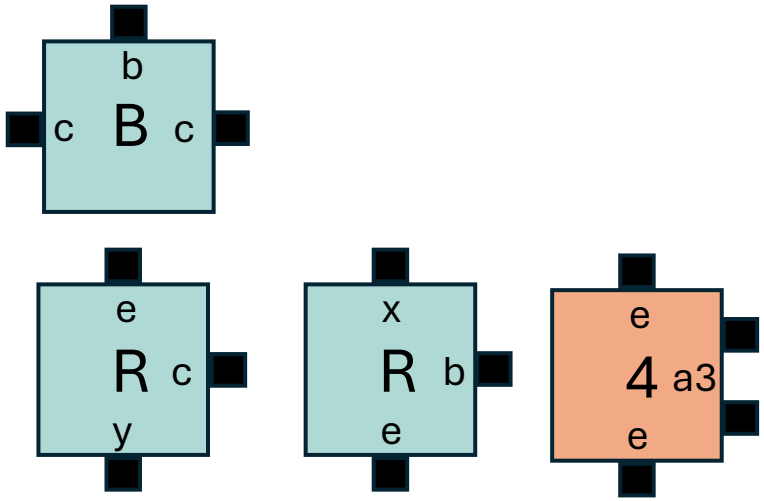

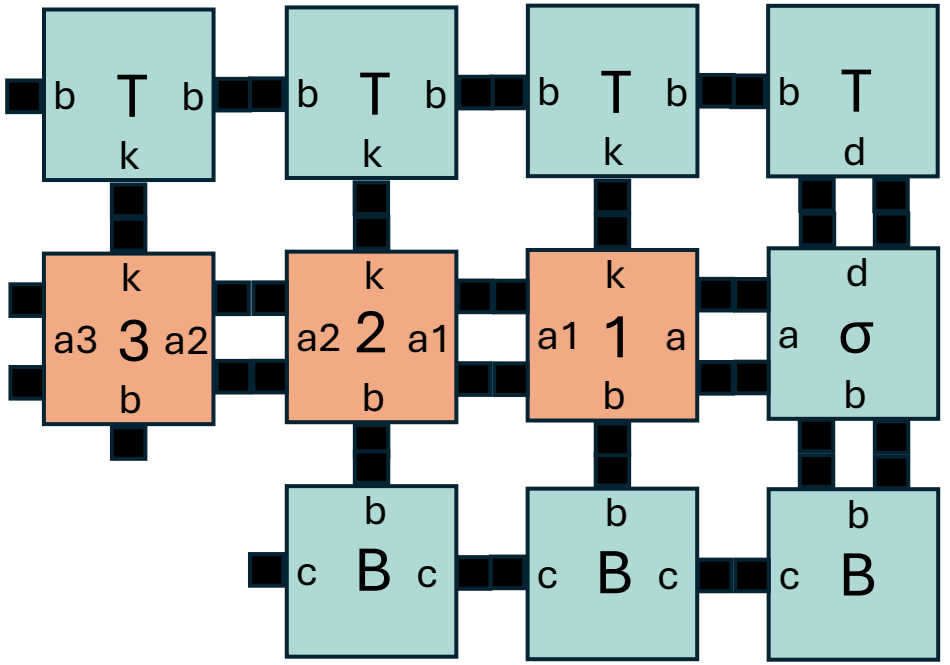

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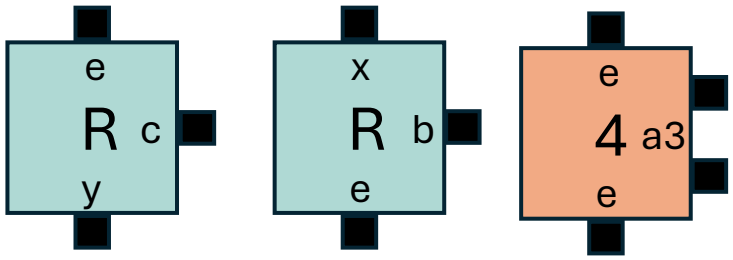

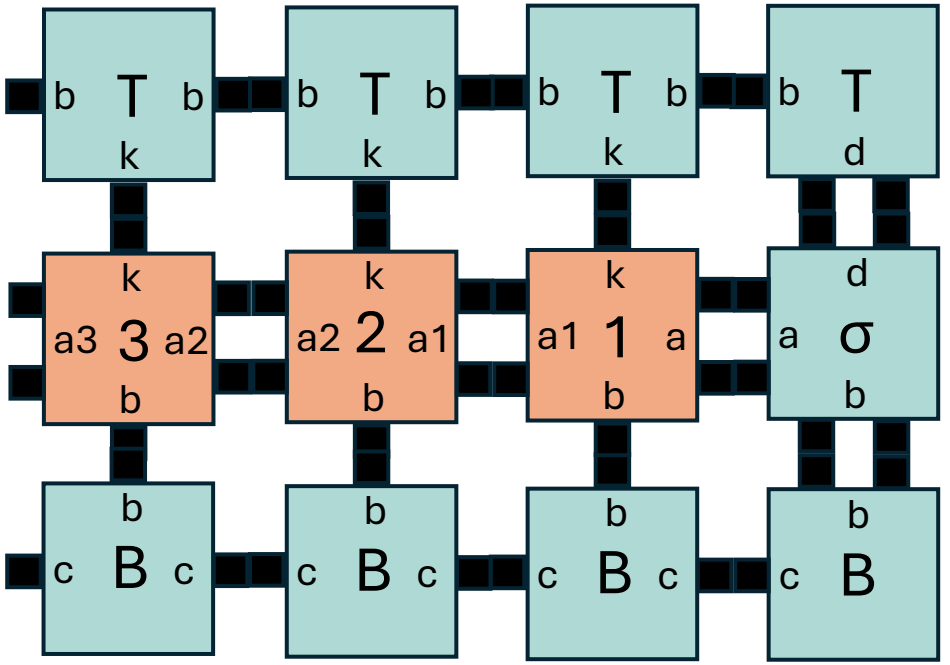

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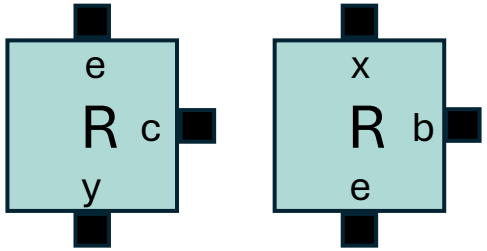

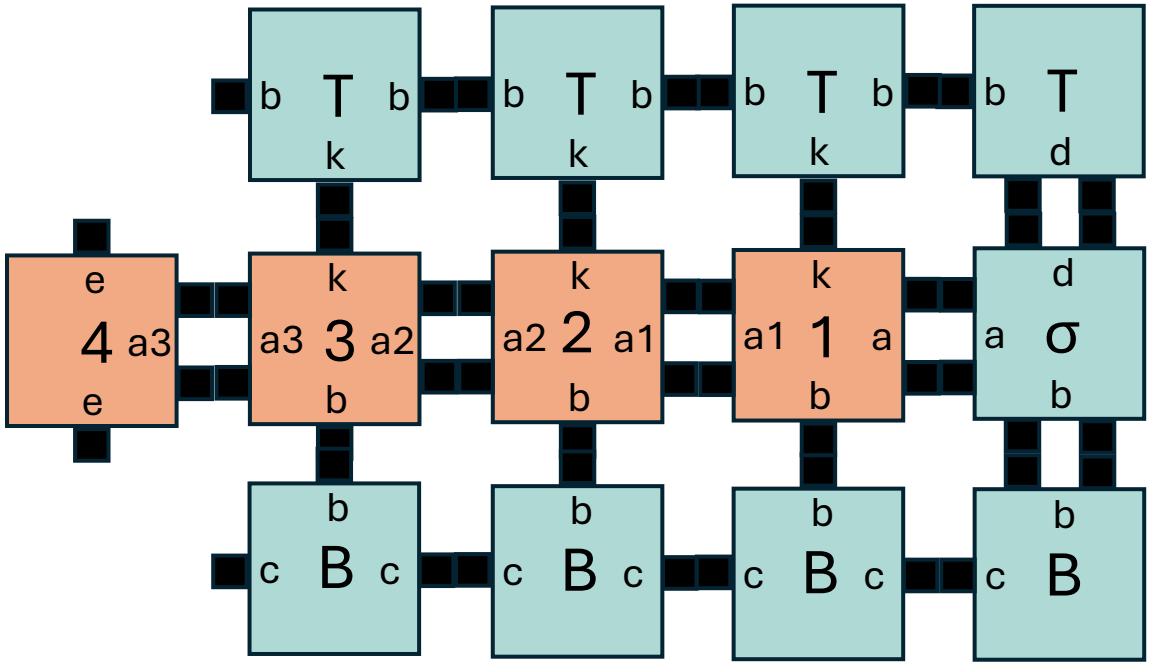

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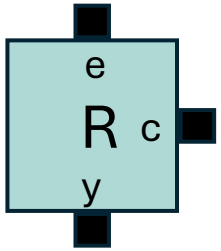

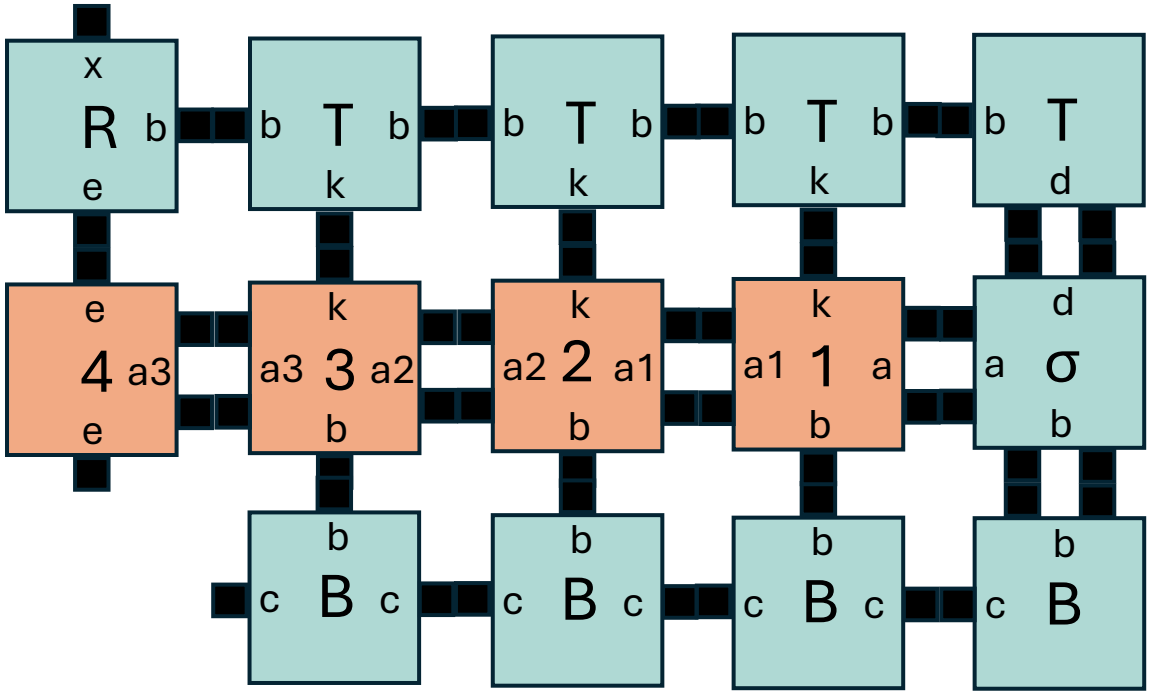

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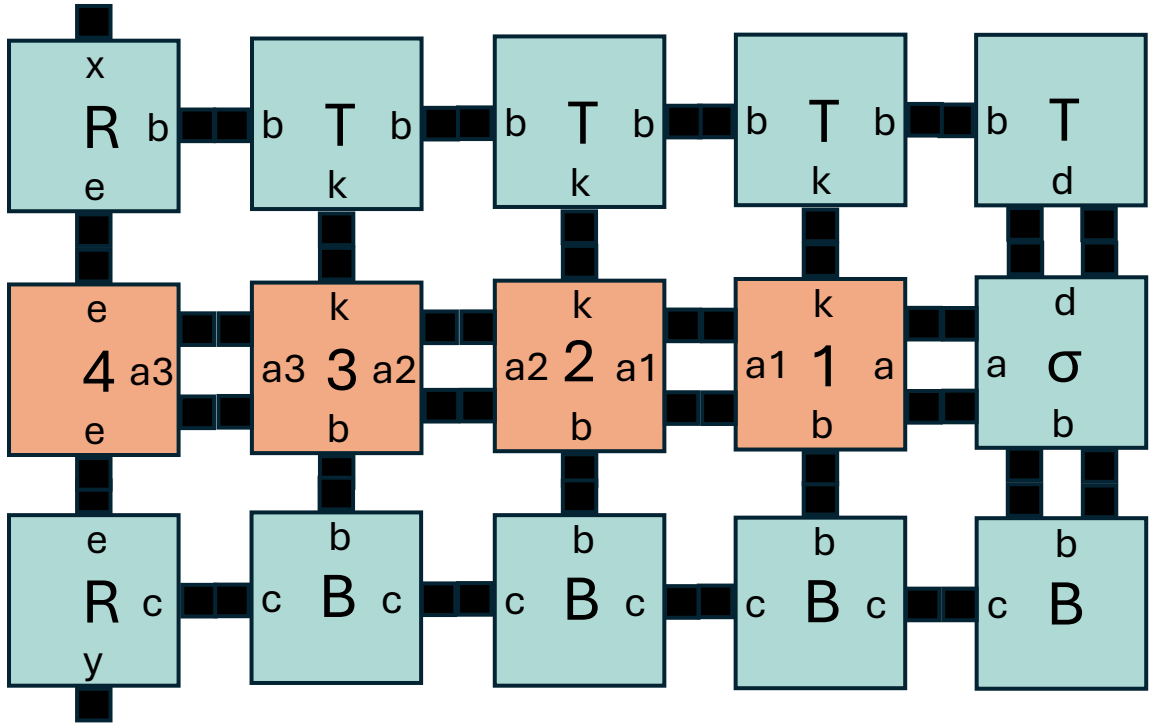
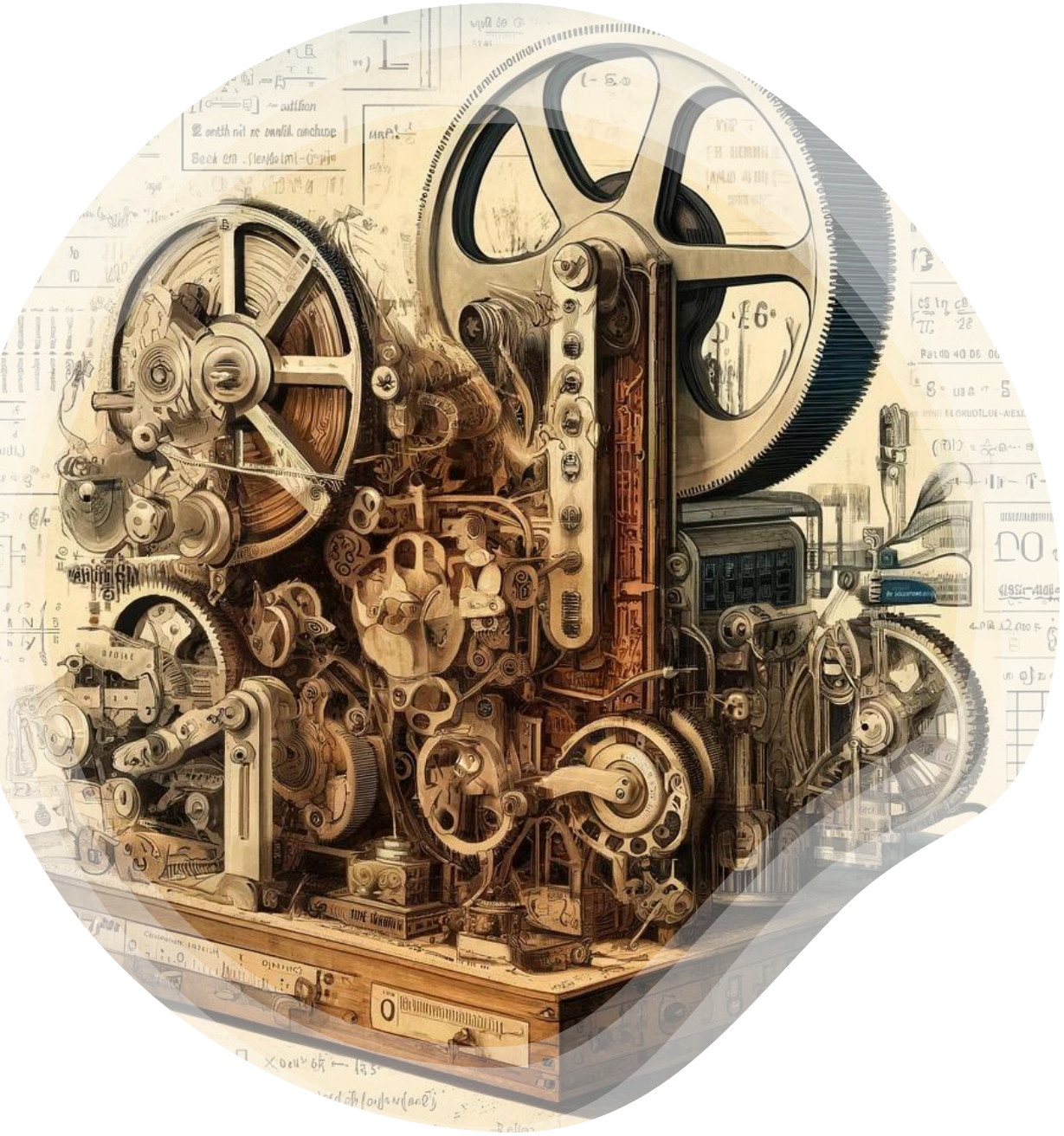


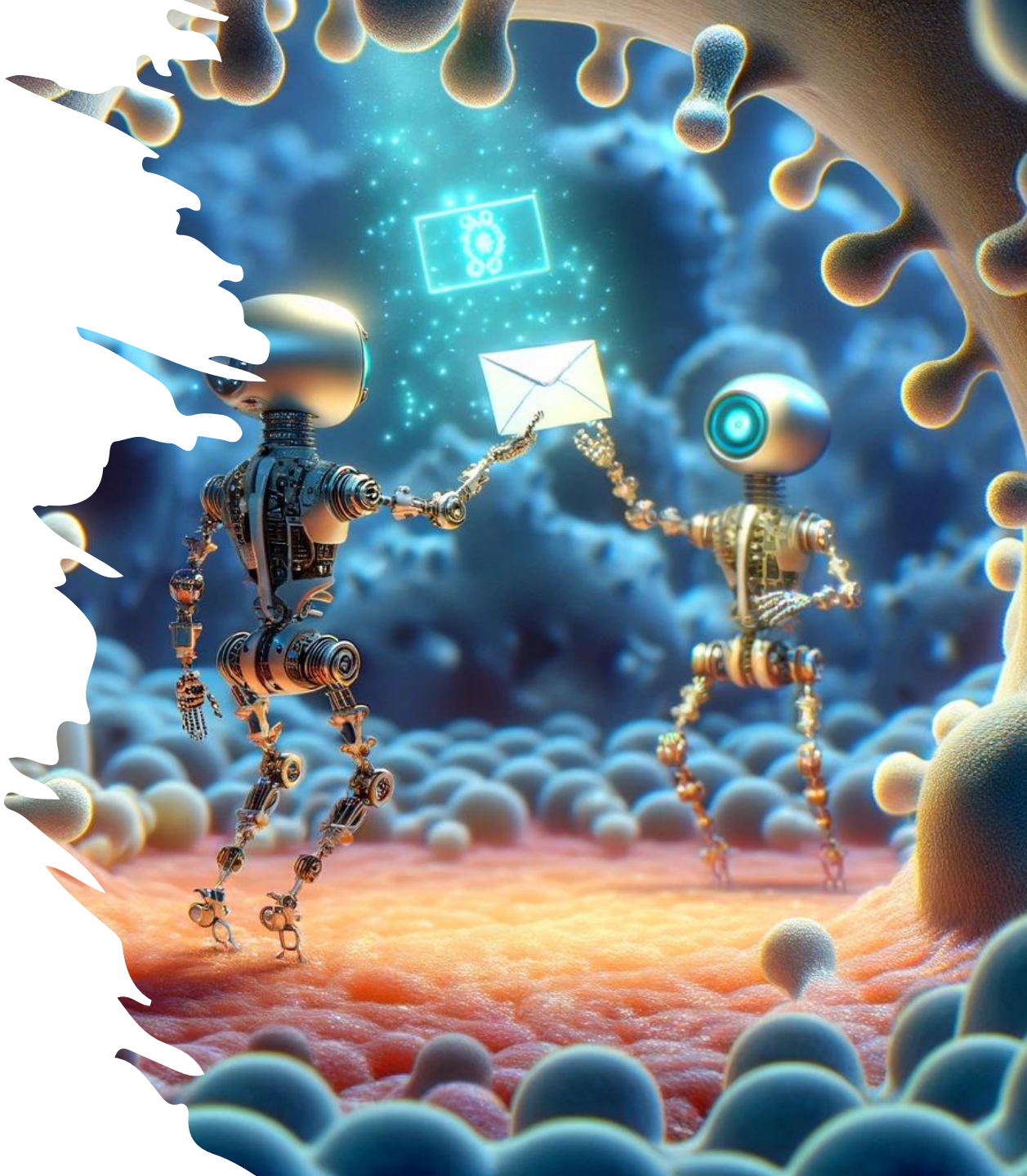


Turing-completeness!

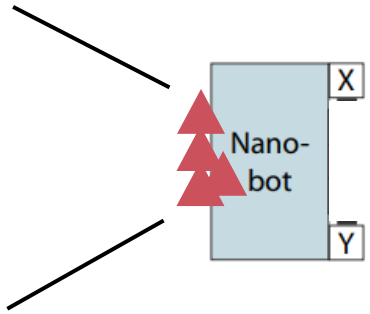
- We have shown that this approach is Turing-complete – every computable function can be modelled by this technique (though there might be size restrictions).
- (Simple) Examples:
  - AND, OR
  - ADD, SUB, MULT, DIV
  - THRESHOLD (at least x)
  - AVG
  - ….
- The example above was a 4-way-AND (the red tiles)
- Obviously, one needs specific tile sets for specific functions – how can we obtain them?
- Later!

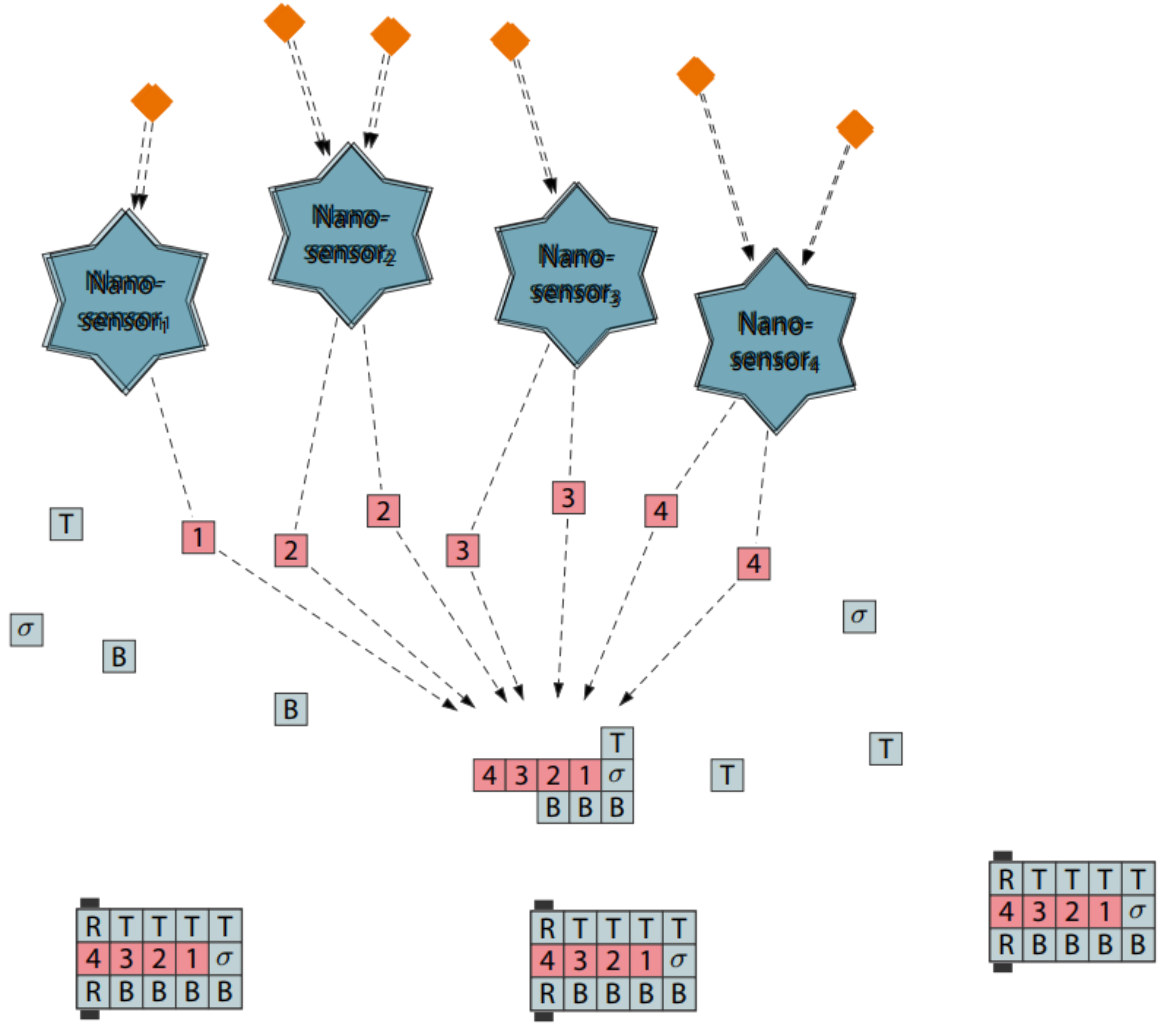
In-Message Computing

- Now, such structures can also be messages, especially when transported in a liquid medium.
- Actually, computing and communication can be combined into one process which we call in-message computation.
- Let‘s see how this can be used to let nanobots of different types exchange information,
  - thereby fulfilling a complex job even though they are rather primitive



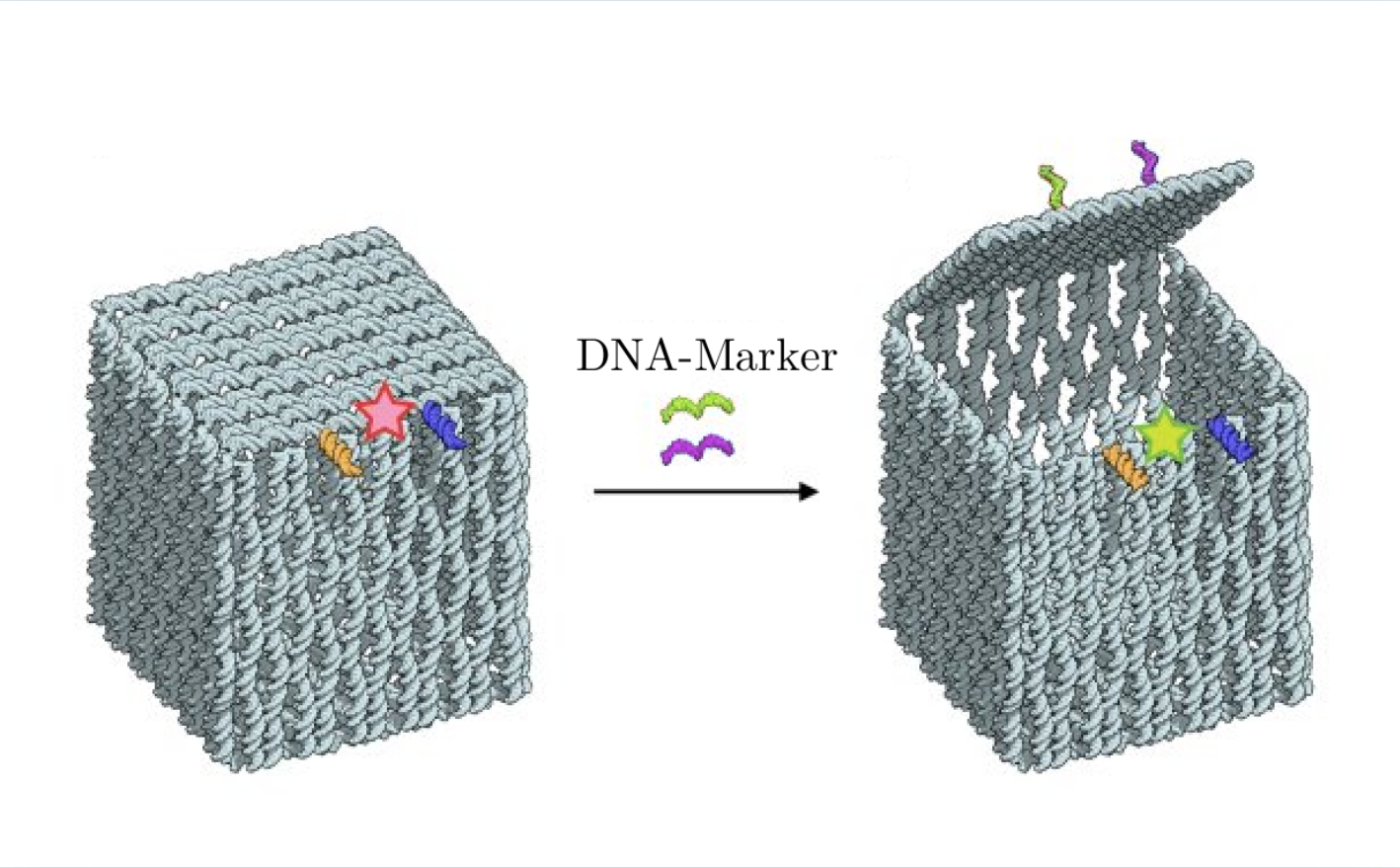
In-message Computation

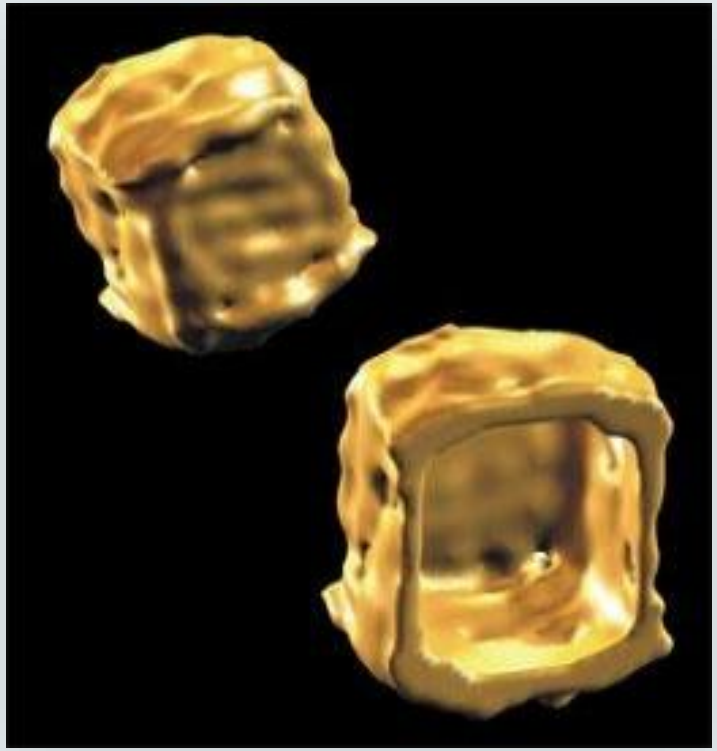




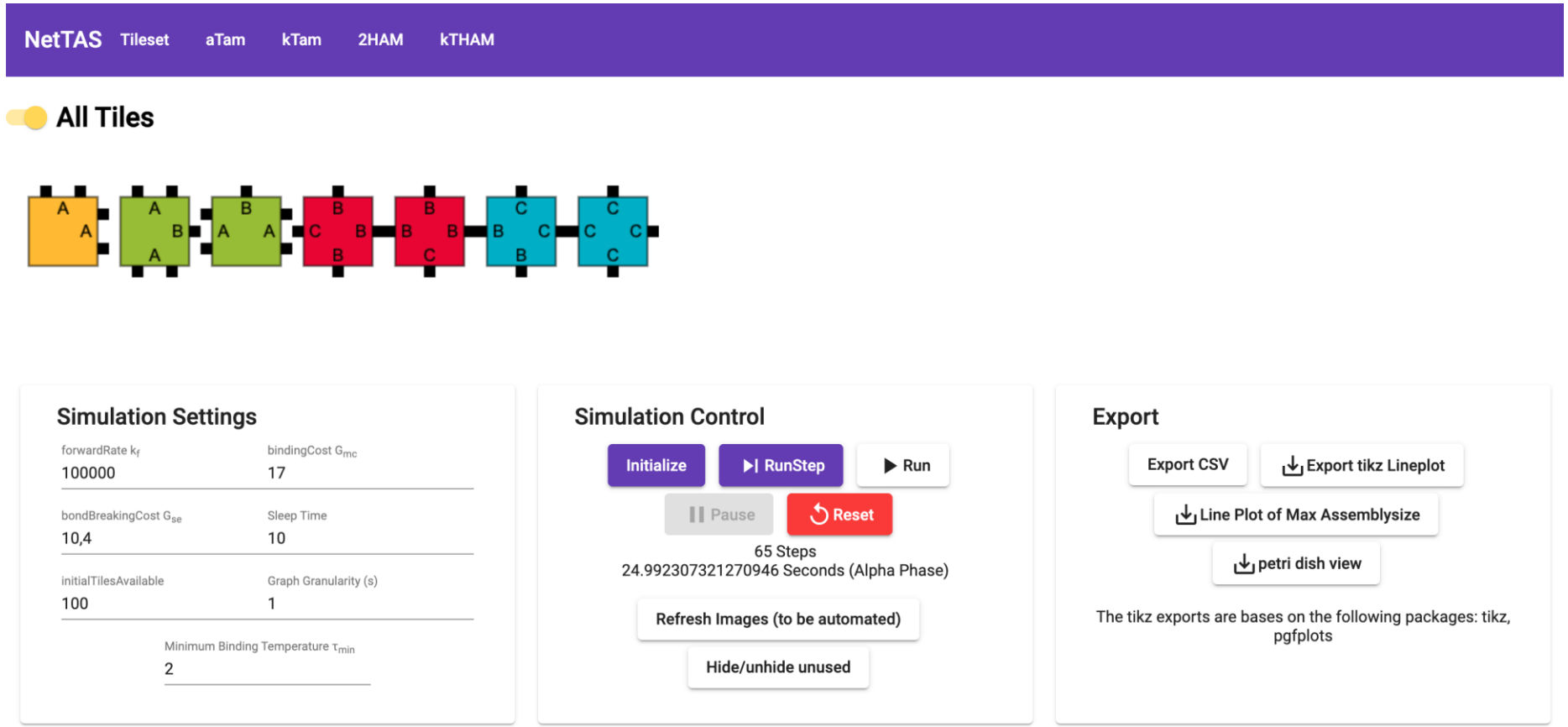
Nanoboxes

Nanoboxes, as used here in nanosensors have already been shown to work!



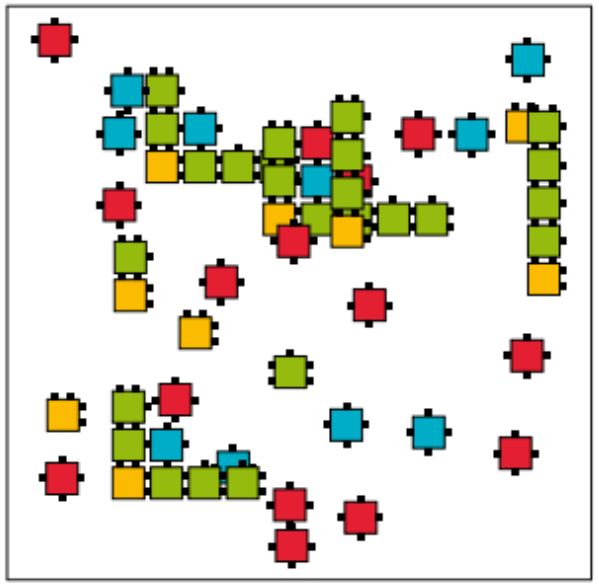


netTAS: a Simulator for Tile-based Self-assembly Systems

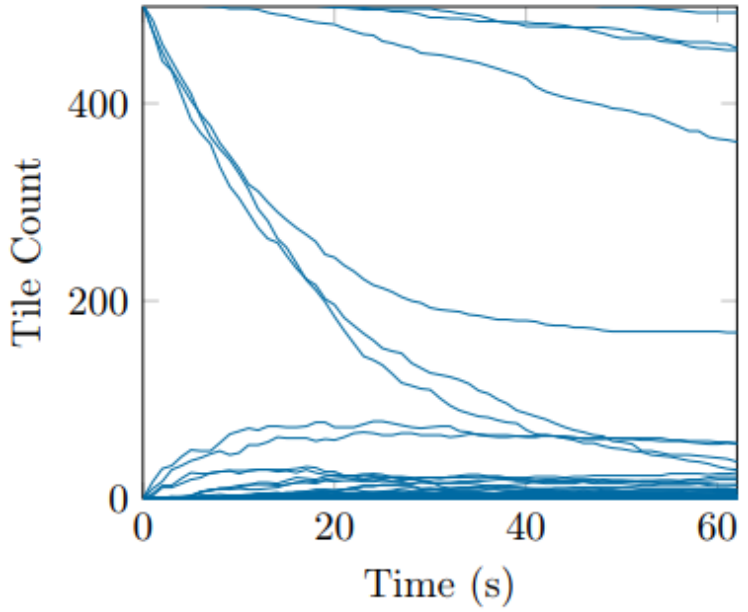


https://nettas.itm.uni-luebeck.de/

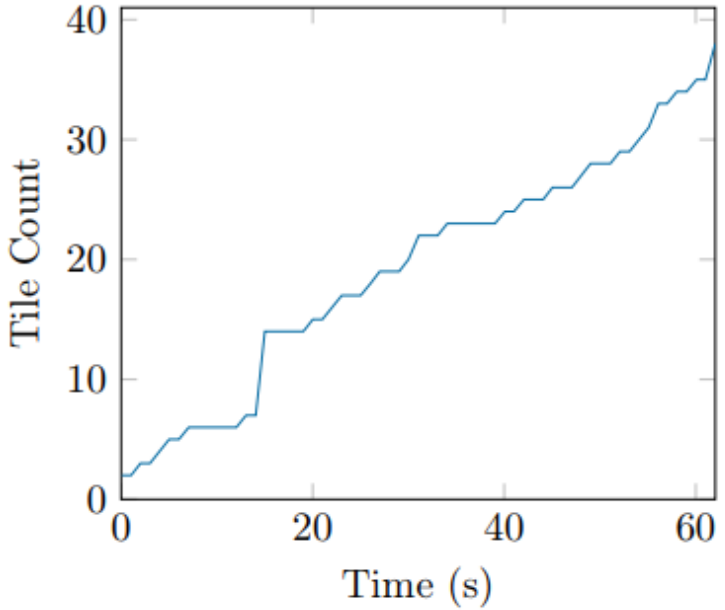
netTAS: Typical Output Sample

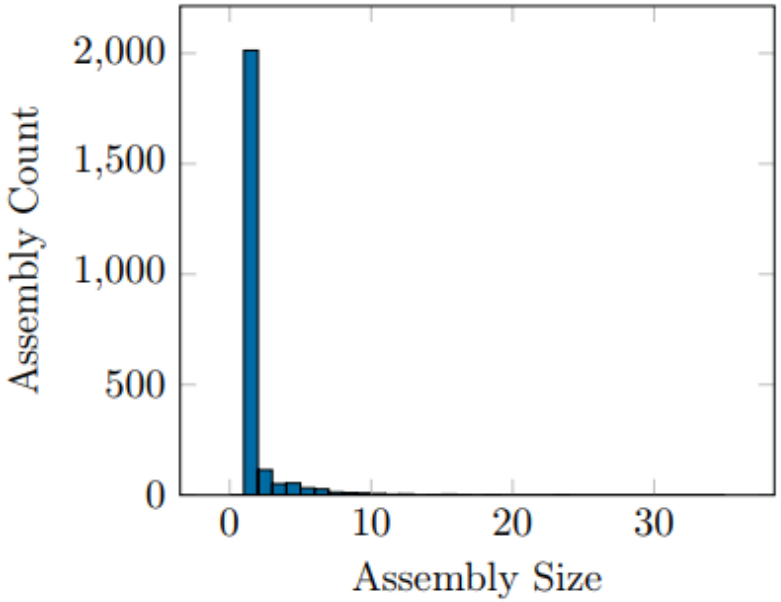


(a) Petri dish view of a sample of 30 Assemblies



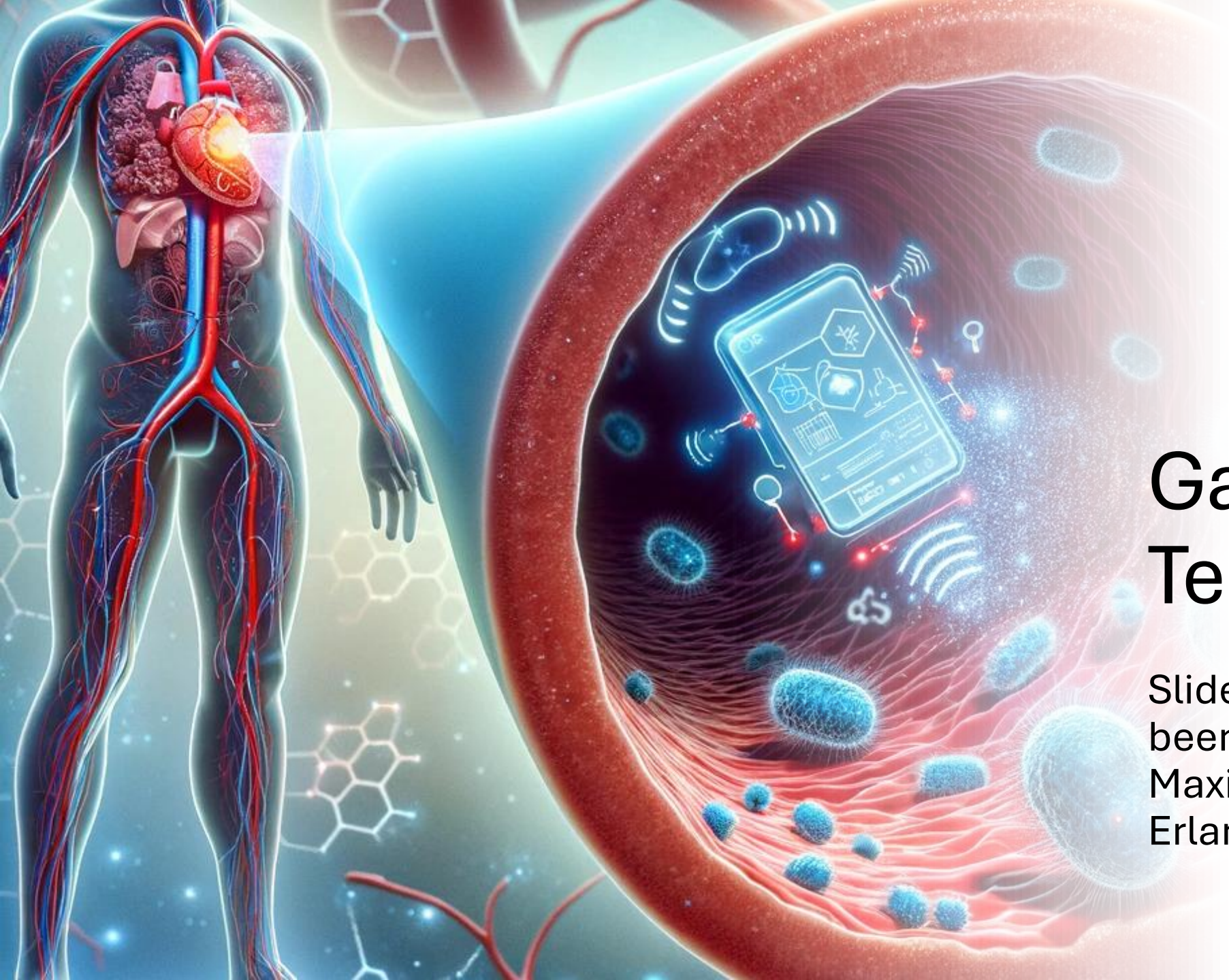
(b) Lineplot of the number of Assemblies over time





Tileset Generator: Construction of the Nanonetwork

- Tiles are constructed BEFORE deployment.
- We need an algorithm that designs tiles in a way that
  - they connect with those other tiles we want them to connect
  - and only those
  - and in a stable way.
- Ultimate goal:
  - A tool which takes as input the results of the simulation,
  - designs the tile types we need for the job (prevention, diagnosis, therapy),
  - creates a production plan for the necessary number of tiles to be deployed



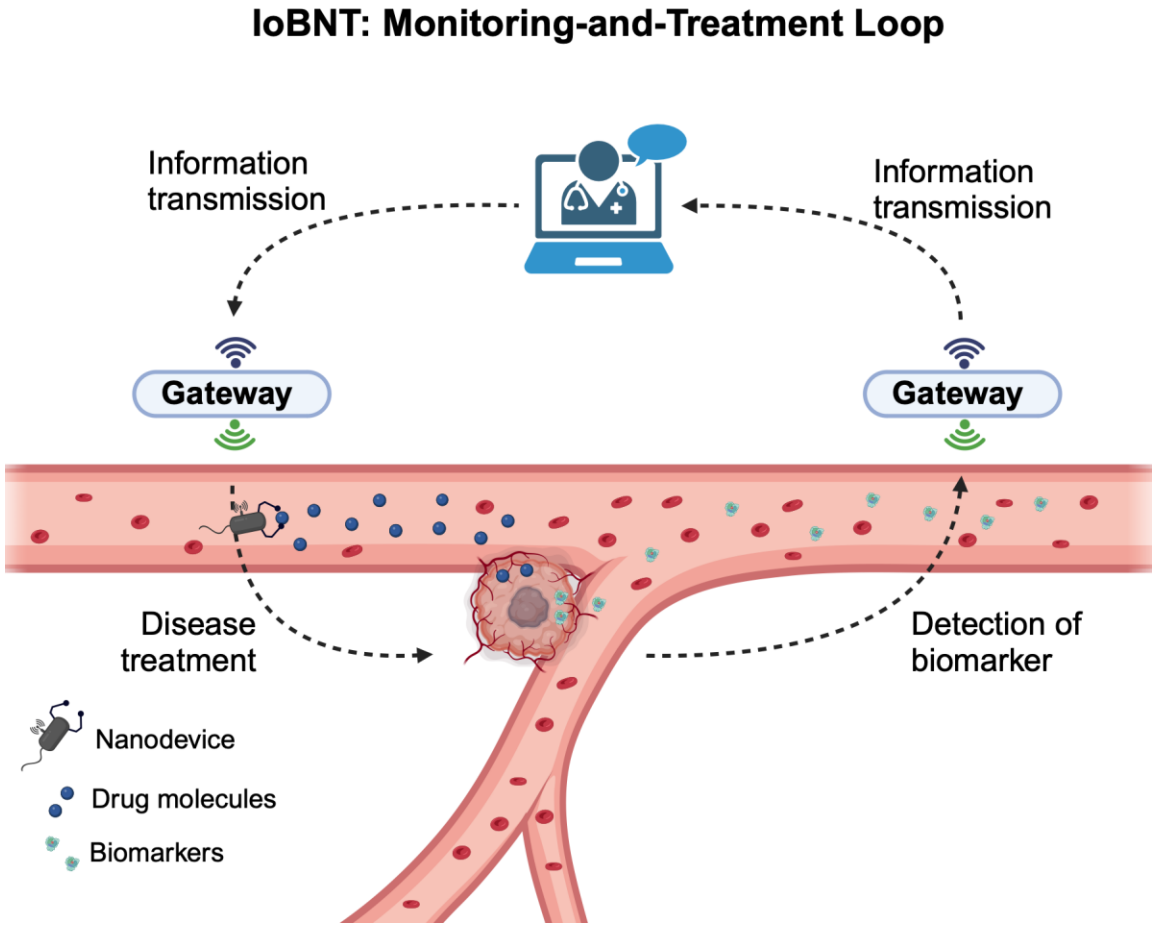
Gateway Technologies

Slide contents have been provided by Maximilian Schäfer, FAU Erlangen-Nürnberg. Thx!

Why do we need gateways?

Automatic Detection and Treatment:

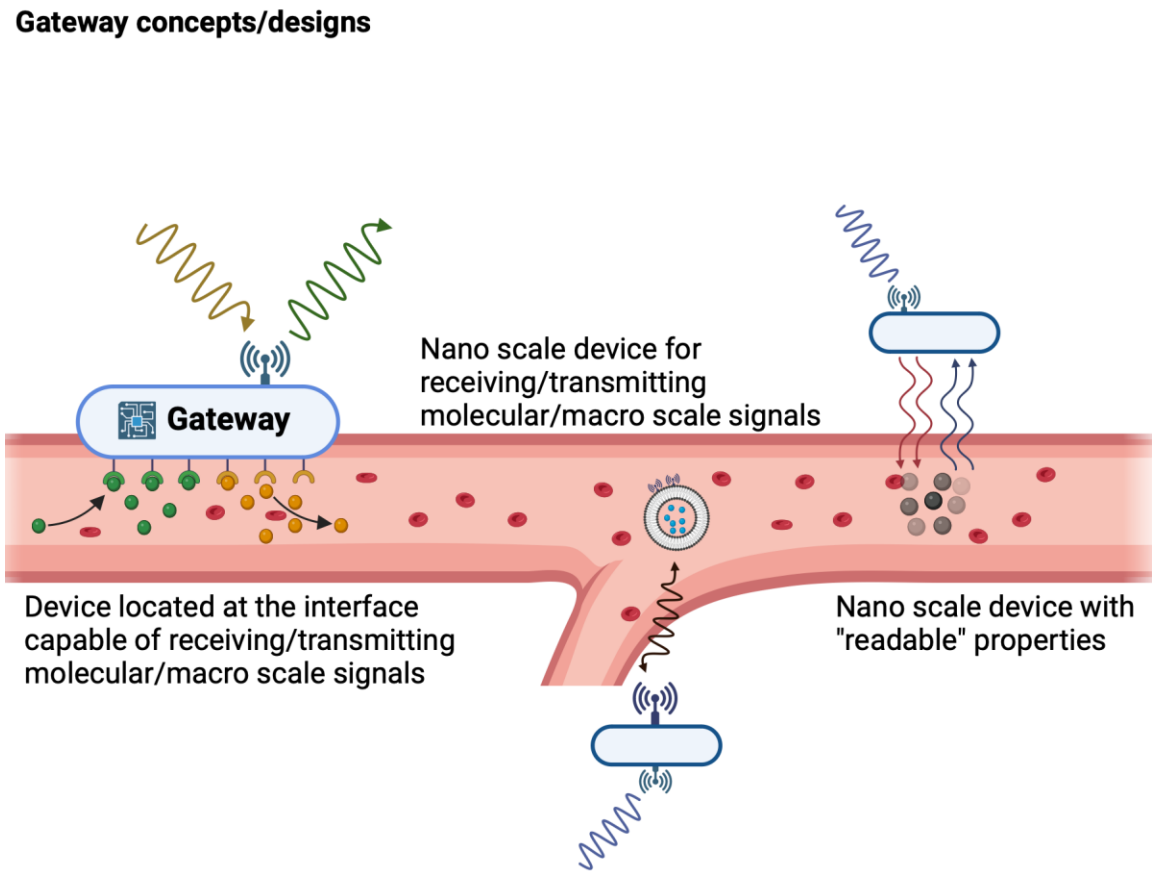
- **Tumor releases biomarkers** which propagate by diffusion and flow
- **A gateway translates** the biological signal into a macro scale signal
- **Outside the body conventional communication** and signal processing approaches can be applied
- **“Operator” decides** to treat the tumor and transmits a signal towards a nanodevice
- **A gateway translates** the macro scale signal into a signal that can be received by the nanodevice
- **The nanodevice starts treatment**, e.g., by releasing drug molecules



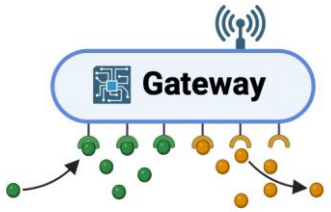
Interfacing and Gateway Concepts

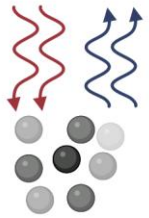
Three exemplary concepts:

- **Engineered device** with RF and molecular interface located at the transition (can be also an implanted device!)
- **Nanoscale "device"** capable of receiving or transmitting RF signals
- **Nanoscale "device"** (e.g., nanoparticles or molecules) with readable properties



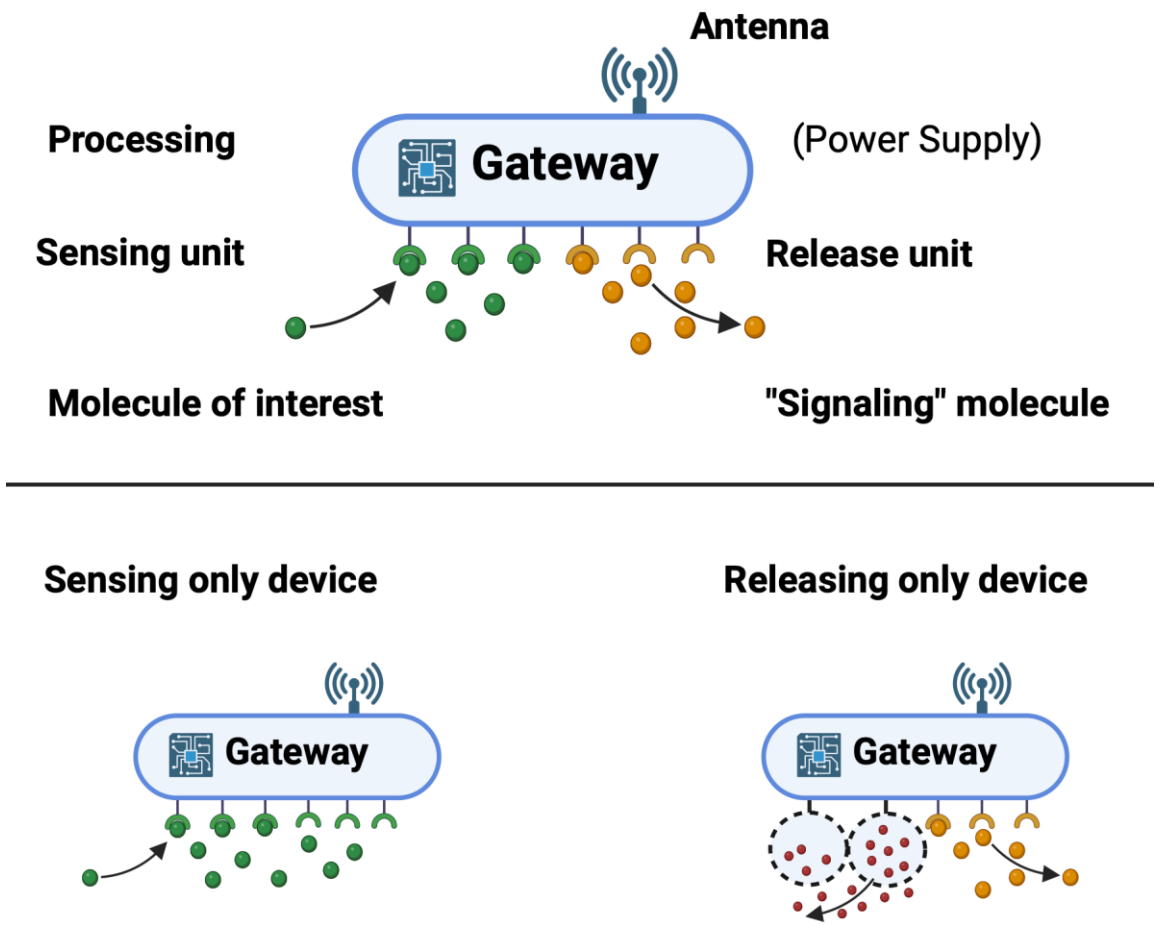
Design Considerations





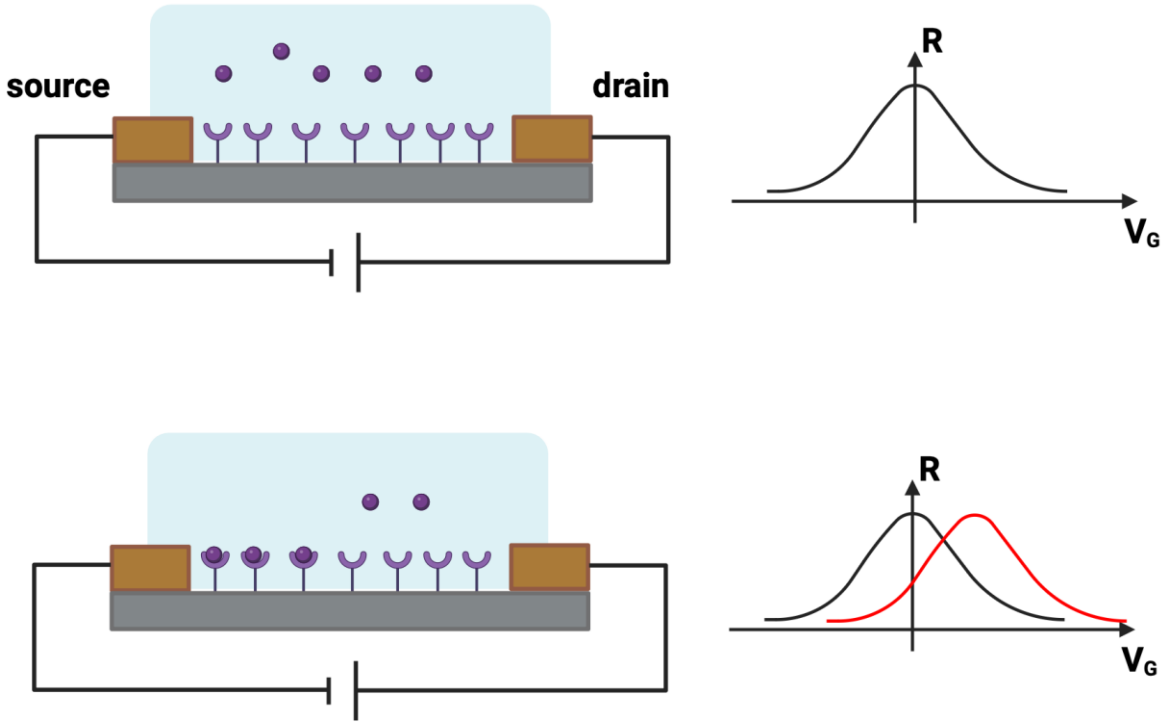
- **The task:**
  - Which type of molecule do I want to sense/release?
  - What is my actual goal (e.g., information transmission, monitoring, treatment) and the resulting required sensitivity?
- **The environment:**
  - Fixed position vs. mobile in the blood stream?
  - Integrated in “larger” device?
- **The components** (based on the other considerations)**:**
  - Which practical components meet the previous requirements (e.g., synthetic, natural)?
  - Which components are available and **feasible**?
  - What is a compatible macro scale signal?

Engineered device - Transition/Implanted



- Requires the bio-functionalization of the sensing/release unit
- **Sensing unit:**
  - Capable of receiving the "molecule of interest" (e.g., a biomarker or signaling molecules released by a TX)
  - Signal conversion of the received molecular signal into a macro scale signal (= producing a macro scale response)
- **Release unit:**
  - Capable of receiving a macro scale signal
  - Signal conversion of the received macro signal into a molecular signal (= producing a nano/micro scale response)

Example from practice: Bio-FET



- **Field effect transistor-based biosensors** are well investigated and applied for different biological sensing applications
- Capable of detecting the presence of a molecule of interest
- Signal conversion into a signal detectable on the macro scale (e.g., change in resistance)
- **In a nutshell:**
- Conventional FET: Charge placed on the gate using an electrode changes conductivity of gate material
- BioFET: Binding molecule dopes the graphene causing a change in measured resistance

Wet Lab and In-vivo Experiments

Wet Lab

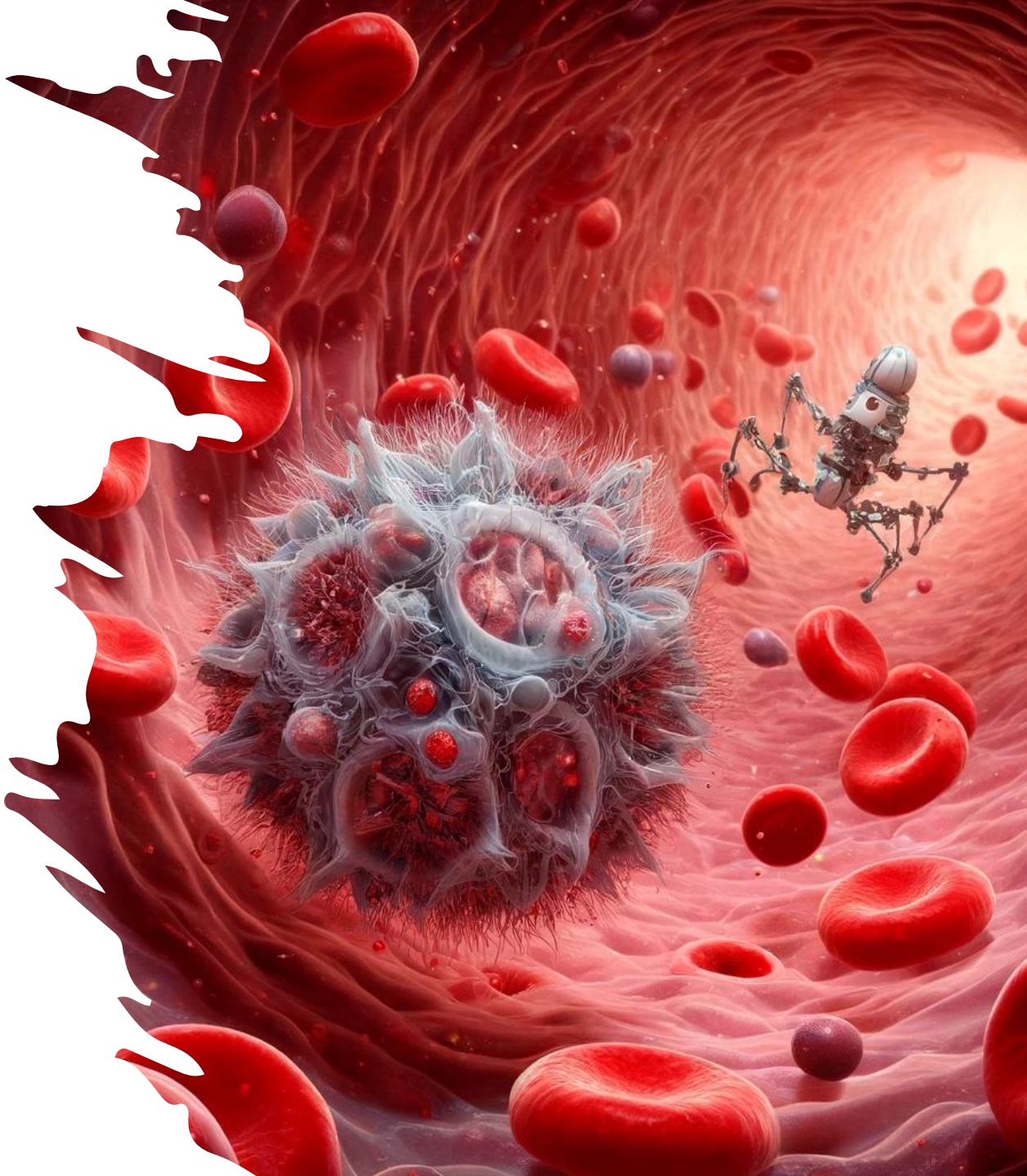
- Goal: proof of concept
- Process:
  - Design experiment
  - Design tileset
  - Let the tiles be built by some company
  - Pour sufficiently many tiles into a Petri dish
  - Wait … until the desired outcome occurs
- Simple example: fluorescence when certain biomarkers are present

In-vivo Experimentation

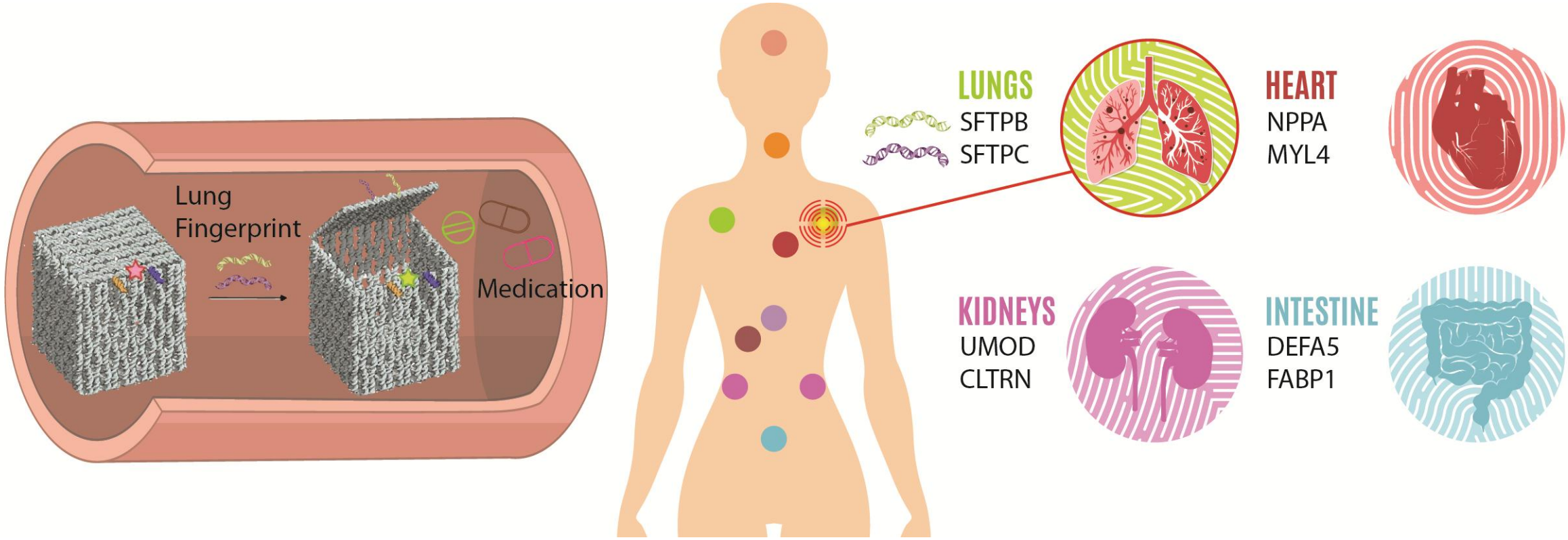
- Let‘s assume the technology works → the computer scientist and engineer in me is happy ☺
- But: will this also work in a living body? In other words: how about the real medical application?
- At some point, this will require in-vivo experiments with, e.g., a mouse model

Things that might not work

- DNA might be destroyed by the immune system.
- The immune system may even go berserk.
- Glueing of tiles might work much worse in reality than in simulations or Petri dish experiments.

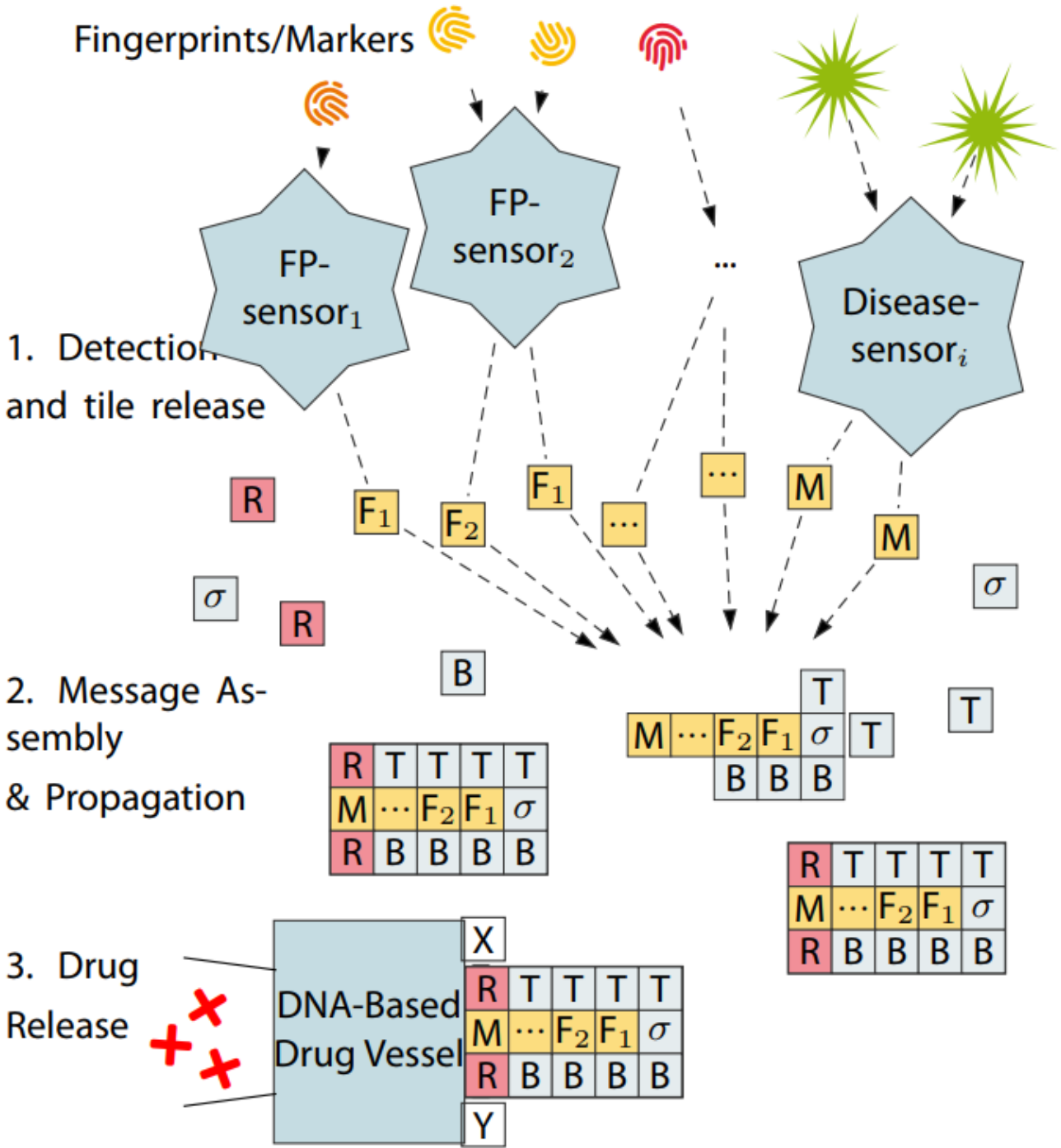


Medical Applications



Targeted Drug Delivery based on Localization

Targeted Drug Delivery based on Localization



Detection of very small Quantities

- With blood tests, certain threshold of substances necessary to detect an infection
- DNA networks could theoretically provide evidence if only a handful of pathogens are present:
  - even with only one single message molecule assembled
  - we can be absolutely sure that something has been detected.

→ Disease detection really really early, long before any symptoms

- Especially suitable for oncology

Detection of complex diseases

- There are diseases that "disguise" themselves as another disease where many factors have to be taken into account for a diagnosis.
- DNA networks can also do this:
  - You can query any number of parameters/values in a logical formula.
  - You can even create “smart medication” which contains drugs against all candidate diseases, and only those drugs will be released that work
- far superior to conventional laboratory tests

PCR Alternative

Covid 19 Test with PCR ...

1. Take a sample
2. prepare in such a way that potentially present virus RNA is extracted
3. Translate into DNA
4. PCR now "recognizes" specific sections of DNA (using DNA primers) and amplifies them (takes time)
5. Detection is then carried out by fluorescence labeling of the DNA that is now sufficiently present in the disease (5).

... and with DNA nano networks

- you could get around almost all of this with the DNA boxes.
- They "simply" open when the virus RNA has been extracted (step 2).
- The successfully formed message can then also be made to bind to fluorescence markers
- Basically, we need the boxes and steps 2 and 5

Summary and Outlook

- Nanonetworks and precision medicine are potentially excellent partners
- We are on a good way to create the necessary technologies.
- Apart from technology, other challenges remain:
  - Ethical issues
  - Regulatory affairs

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