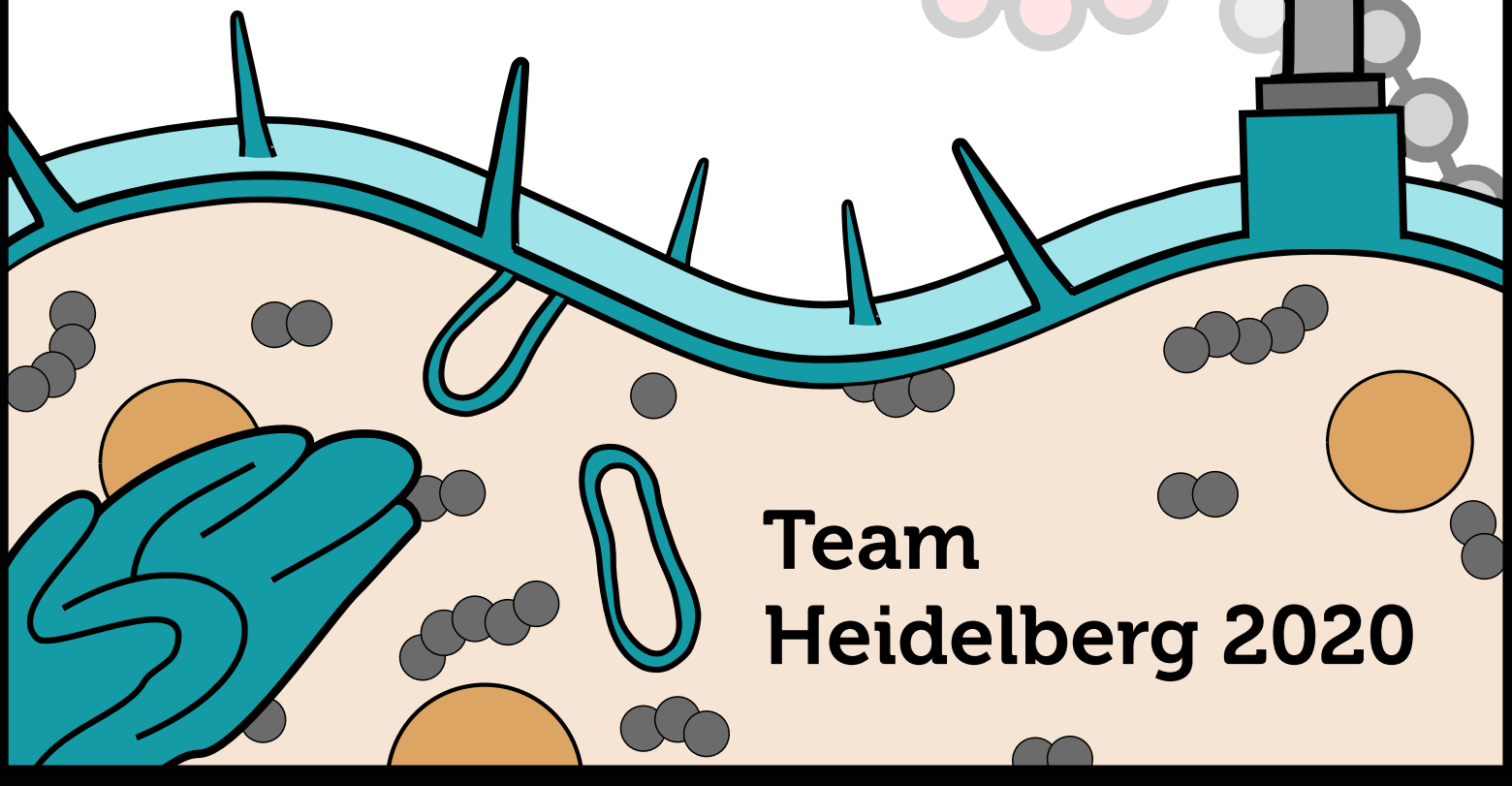
Creating Novel Mechanisms of Cell Regulation



Team Heidelberg 2020

International Genetically Engineered Machine Competition

The international Genetically Engineered Machine competition (iGEM) is the world's biggest competition in synthetic biology. Here, students from all over the world can engage in research trying to solve real and pressing problems of society at large and push the boundaries of our understanding of synthetic biology, with diverse projects ranging from fields like environment protection to disease therapeutics.

Every year, numerous teams gather at the Hynes Veterans Memorial Convention Center in Boston to present their work to some of the greatest living minds in the life sciences and mingle with other biotechnology enthusiasts and compete for the Grand Prize of iGEM – the BioBrick trophy.

Thus, iGEM provides a platform enabling young scientists to learn crucial aspects of research early on in their careers and helps to promote the beneficial use of synthetic biology in society.

You can find in this Proposal a detailed description about us, our project, our further engagement and our contact details.

At a glance

This year, we aim to extend the capabilities of synthetic biology by creating a modular **RNA-based toolbox** for runtime bioengineering inside living cells. We harness the broad variety of specific RNA-protein interactions found in nature and combine it with cutting-edge machine learning towards the completion of our goal.

Timelime:

March 1st - May 1 st:

- Online Corona School: We help High-School Students graduating this year through Online Courses
- Drylab Introduction: We start designing ribozymes, protein-in-RNA binding pairs and model regulatory networks

April 30th: Registration

May 1st: Labwork Begins

Labwork & Outreach

- We plan to devel a toolbox for the scientific community- and applications, like CAS-less gene editing
- Outreach: We are planning to host a Science Slam and several events with experts

October 28th:
Finishing Results,
Collection

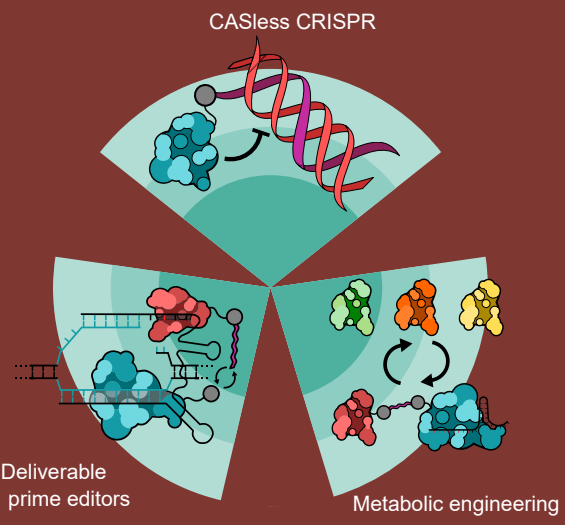
October 29th:
Result Presentation
in Boston

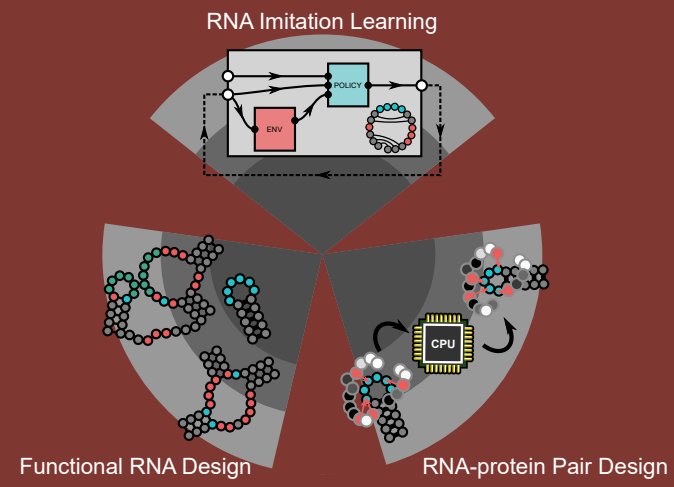
Wetlab

Our goal is to create a dynamic toolbox providing the tools for RNA and protein mediated cell regulation. Thereby we want to tackle the following modular interactions:

1. RNA-guided RNA modification
2. RNA-RNA interaction
3. RNA-protein interaction
4. Protein-protein interaction

These modules can be used to implement Cas-less gene editing and various tools for industrial and therapeutic applications.





Drylab

Designing functional nucleic acids is far from trivial. To reach our goals, we aim to use powerful machine-learning techniques towards rational design of functional RNAs:

1. Designing RNA secondary structure
2. Imitation learning for design
3. Designing trans-splicing ribozymes
4. Generating protein-RNA binding pairs
5. Modelling dynamic regulatory networks

Team Heidelberg 2017 iGEM 2020 Team Heidelberg 2020

About Us: Now and in the Past

Heidelberg has a long tradition in iGEM. Since 2008, Heidelberg's iGEM teams have contributed many successful projects to the competition and, among numerous side prizes, won the Grand Prize in 2013 & 2014 and reached the 3rd place in 2015 & 2017. With diverse projects like "Ring of Fire", a project about circularized proteins, or "The Phage and the Furious", a project around phage assisted evolution, Heidelberg has earned a reputation for innovative projects especially in the foundational advance sector.

A successful past, that we strive to continue once more this year.

We are iGEM Heidelberg, 17 young students from Heidelberg University with a shared passion for synthetic biology and a common ambition to participate in the iGEM 2020 competition. Consisting of members with diverse academic backgrounds like physics, chemistry, biology and biotechnology, we cover a broad spectrum of theoretical knowledge and practical know-how.

Our team is well equipped to navigate the highly interdisciplinary landscape of modern biology. In the drylab, we have team members with years of expertise in practical computer science and experience with machine learning, enabling us to develop reliable modelling software for our project.

Our research group is completed by two veterans of synthetic biology: our advisors Prof. Dr. Wölfl and Prof. Dr. Wade, two reliable partners that can help us to find new paths if we get stuck in dead ends. Together we make up a strong team that is well prepared for the fierce challenges of iGEM.

The Phage and the Furious

- iGEM Heidelberg 2017

Second Runner Up

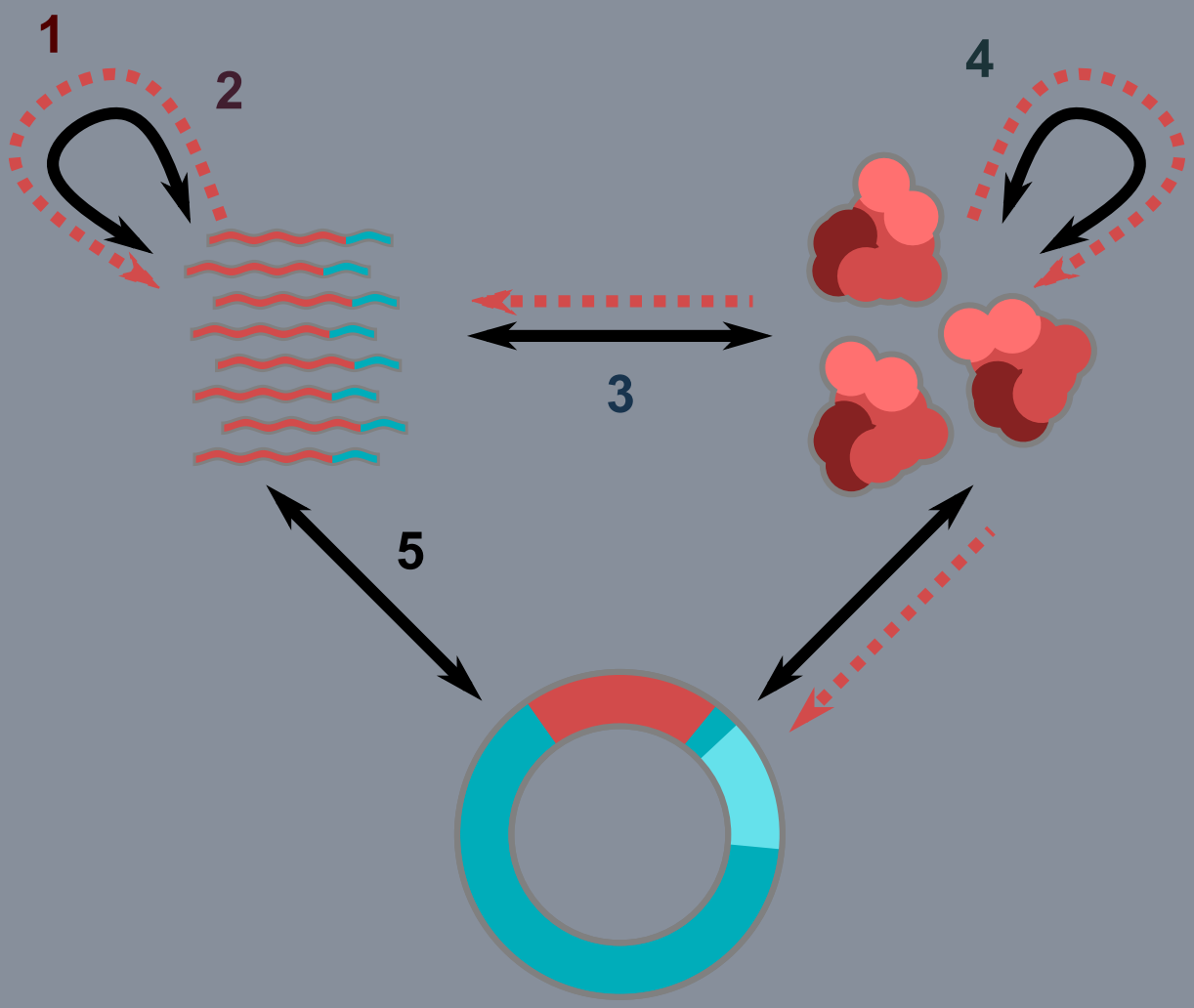
The Ring of Fire

- iGEM Heidelberg 2014

Grand Prize Winner

Fantastic Yeasts and How to Evolve Them

- iGEM Heidelberg 2019



1. MODULAR RNA-GUIDED RNA MODIFICATION
2. MODULAR RNA-RNA INTERACTION
3. MODULAR RNA-PROTEIN INTERACTION
4. MODULAR PROTEIN-PROTEIN INTERACTION
5. MODULAR RNA-PROTEIN INTERACTION

Our work in the Wetlab

An introduction

Cells are wonderfully complicated systems that are the fabric which makes up all living creatures. Several decades of studies have been spent on determining the key levels of regulation that govern processes that make cells grow, reproduce and interact with the environment.

As cell biology has come of age, every 10th grader knows full well that all the information about a cell's building blocks is stored in its genome – a blueprint, written in the form of DNA. For creating any given protein, the cell first needs to copy the information from the gene to an RNA and then use the RNA and the ribosomes – cellular protein factories made up of both protein and RNA – to create the desired protein. The cell controls the processes at all levels and can intervene using **RNA, proteins or complexes of both**.

From the very beginning of cell biology as a science, researchers tried not only to understand what happens in the cell and what rules it is governed by, but also to harness its power to control the processes themselves and redirect them to do their bidding. In the spirit of Feynman's 'What I cannot create, I do not understand', researchers modified existing genes, created new ones and played around with controlling their activation and repression. Engineering gene regulatory pathways allowed for creation of organisms extremely tolerant to harsh environments, or cells producing anything from ethanol to biofuel. All of them are actively used in industry to feed and sustain our vastly growing population and economy. This desire, to **rationally design** new biological systems to stand against today's problems, serves the needs of humankind, and deepening our understanding

through this creative process is what has been the driving force of synthetic biology to date.

The top labs, which conduct cutting edge research, are constantly coming up with new ideas of what other organisms or regulatory networks to use to achieve the common goal. A recent development, that is just emerging in the field, is the regulation of organisms not only through various modifications at the DNA level, but at the RNA and protein level. As it stands, this aspect of gene regulatory networks has been left almost criminally underused, and just by a quick glance, one can see all the raw potential and unused possibilities to be found lying there, ready to be picked up by a curious mind.

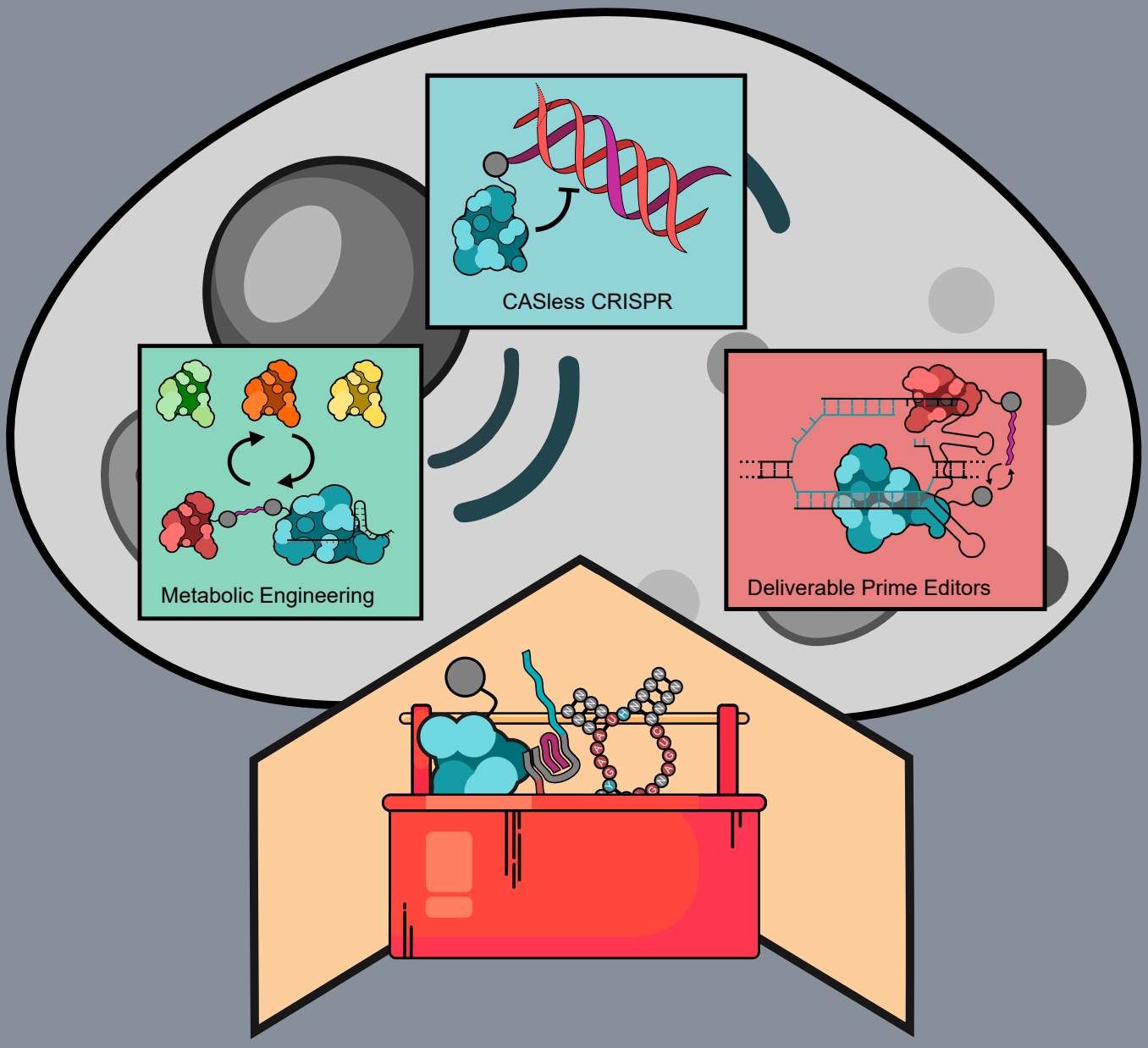
This is something we, as a young and motivated iGEM team, want to dedicate our work to during this summer term. Our goal is to create a dynamic toolbox providing the tools for RNA and protein mediated cell regulation. Thereby, we want to tackle the following interactions:

1. Modular RNA-guided RNA modification
2. Modular RNA-RNA interaction
3. Modular RNA-protein interaction
4. Modular protein-protein interaction
5. Modular RNA-protein interaction

Here a few nice applications for such systems:

Delivery of complex regulatory proteins into cells.

A way to **deliver large proteins** in the form of their subunits with a later assembly into a functional protein is a crucial obstacle in bringing such systems as Prime editors to the medical and biotech market. These proteins are used for controllable and accurate editing of DNA in the cells. Thus, they present a possibility for healing some of the known genetic disorders (Anzalone et al. 2019). Sadly, the proteins themselves are so large, that a delivery of the entire complex into the cell is nearly impossible (Domenger and Grimm 2019). Division of the proteins



TOOLBOX FOR RNA AND PROTEIN BASED GENE REGULATION

into **subunits** and coupling them with **RNA linkers**, which will navigate the correct assembly (Truong et al. 2015) after the successful delivery of the parts into the cell, might solve this issue.

CRISPR without a Cas

CRISPR Cas9 systems are valued for their specificity and efficiency in genome editing. Furthermore, the Cas part of the system is also actively used for various biological assays which require delivery of regulatory elements to a specific point in the genome. Nevertheless, Cas9 has a serious disadvantage - its size. Consisting out of 1053 AA and with a weight around 123 kDa (Hsu et al. 2014), this protein cannot access some heterochromatic areas, especially when it is linked to another transcriptional factor (Qi et al. 2013). Using RNA, only the guide RNA with an RNA stabilizing construct instead of the large Cas-protein would solve the problem providing a similar accuracy of the system. Whereas this may sound promising in theory, in practice, designing such a complex functional RNA would constitute a daunting task. Fortunately, nature provides a similar functionality via **RNA·DNA–DNA triplex** formation – a process, by which single-stranded RNA (ssRNA) forms high-affinity (Kd < 200 nM) sequence-specific binding interactions with double stranded DNA (dsDNA), effectively performing the function of a DNA-binding protein (Kunkler et al. 2019). The engineering potential of RNA·DNA–DNA triple helices to date is vastly underexplored in synthetic biology, partly due to the fact that the energetics of triplex formation were only fully elucidated in late 2019 (Kunkler et al. 2019). We plan to harness this underused tool to provide all the benefits of CRISPR-based transcriptional regulation – compact, simple and without the need for Cas.

Combinatorial metabolic engineering

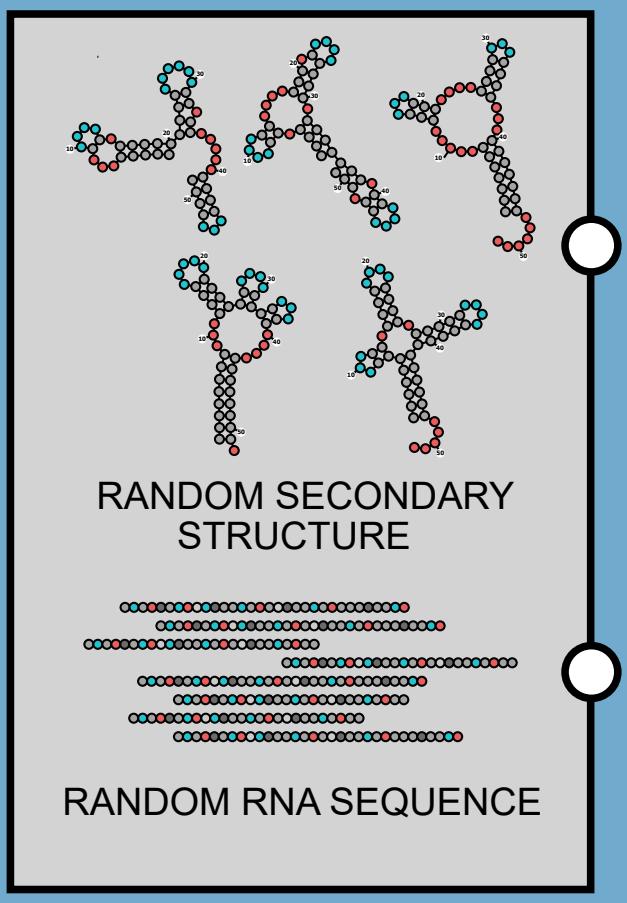
In the last few years, a few combinatorial systems for metabolic engineering have been presented in the synbio community. A prominent example is the orthogonal trifunctional **CRISPR protein system**. This system provides separate activational,

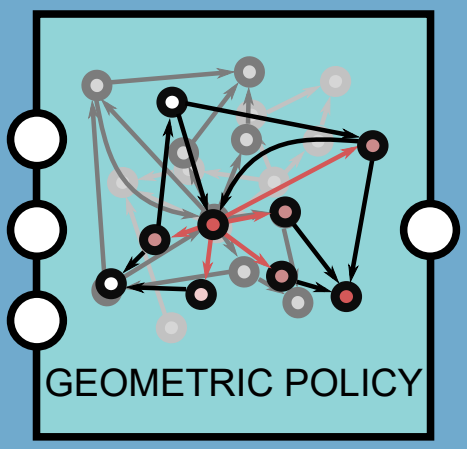
interfering and gene-deleting complexes based on Cases (Lian et al. 2017). This is a novel system that has already proven to be a valuable tool for basic research. Nevertheless, it has one major disadvantage: the Cases, which are comparatively large (see above). Also, the fact that each tool requires an own specific Cas severely limits the experiment one can perform with this type of system. Substituting the Cas with a **ribozyme** might solve the problem by making them smaller without losing the specificity. Making them **modular**, such that the same RNA protein complex could switch functions through ligand binding and the addition and following binding of the corresponding functional domain, might be the solution.

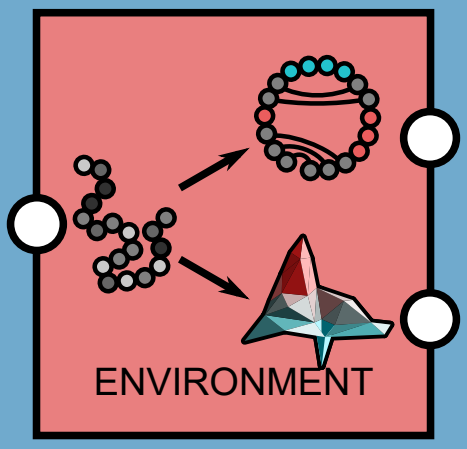
For our project, our goal is to produce a tunable toolbox for the key-interactions in the presented scenarios with the corresponding wetlab protocols, necessary assays and proof of concept experiments.

We are planning to start with the characterization of different available RNA-based linkers and probing simple specific RNA-protein complex engineering. When solving these tasks (as well as making the corresponding DNA sequences biobrick compatible, we will go for tethering experiments with functional proteins (transcriptional activators, repressors to DNA or fluorescent proteins to each other - FRET and quenching). Similar experiments will also be performed using the engineered triple-helix.

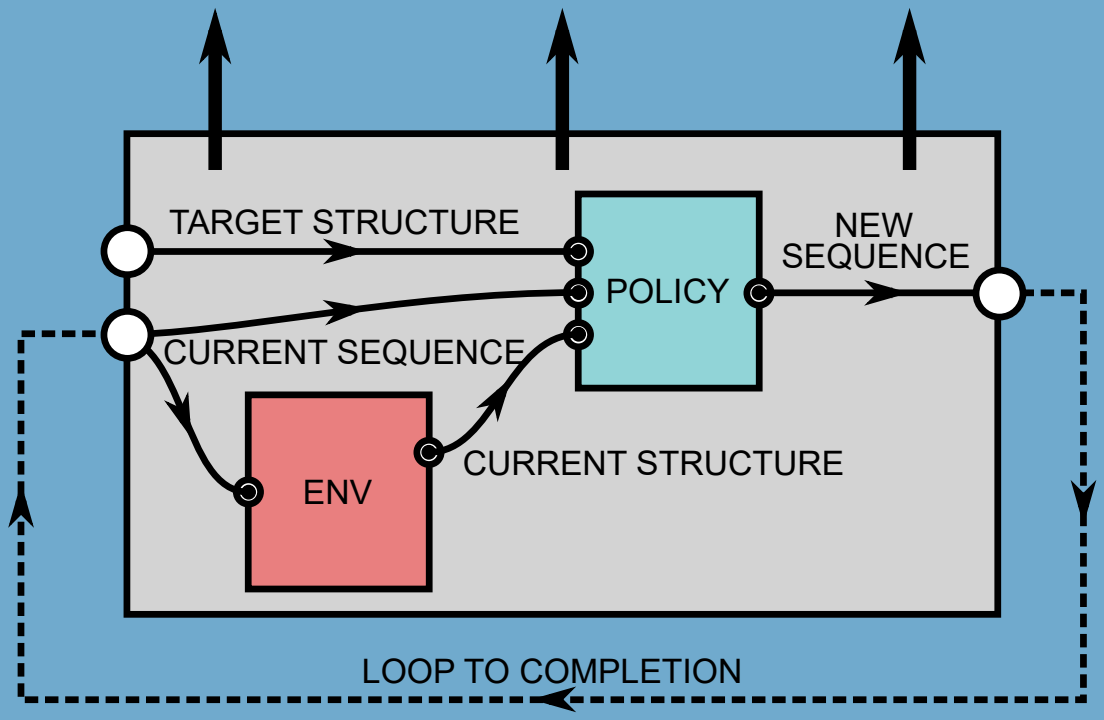
All the steps will be performed in constant communication with the drylab, improving the computational models based on our experimental results and applying the outcoming changes to the wetlab planning.







EXTRACT TRIALS FOR TRAINING



GENERATIVE LOOP

Our work in the Drylab

Designing RNA secondary structure and function

As with proteins, RNA structure is intimately related to its function – specifically, binding or catalytic bases need to be aligned properly for a given RNA to realize its function (Lorenz et al. 2011). Therefore, the ability to design RNA sequences folding into a specified structure is a necessary prerequisite towards designing functional, catalytic RNAs for a given purpose. While RNA structure prediction is much less computationally expensive and hard to get right, than its protein counterpart, its inverse problem of RNA design is as daunting as fixed-backbone protein design (Runte et al. 2019). While **RNA design** given a fixed secondary structure is feasible using a number of simulated annealing or genetic algorithm-based approaches, these approaches rely on efficient samplers of viable RNA sequences as well as multiple evaluations of the forward problem. This makes them computationally inefficient and does not guarantee to return reasonable results in finite time (Lorenz et al. 2011).

We plan to apply **machine learning** to implement efficient samplers for RNA sequence conditioned on secondary structure. This is a highly non-trivial machine learning problem, as the conditional distribution of sequences is highly multimodal since multiple RNA sequences may fold to the same secondary structure. Furthermore, a good model should capture this multimodality and return diverse sequences for any target secondary structure (Runge et al. 2019). Additionally, RNA sequences show many of the same properties that make training powerful language models a highly non-trivial problem. Thus, they require

similar algorithmic and architectural considerations for machine learning to be successful (Shi et al. 2019, Runge et al. 2019, Ingraham et al. 2019). Both supervised learning (Shi et al. 2018) and reinforcement learning (Eastman et al. 2018, Runge et al. 2019) of policies for structure-conditional RNA design have previously been explored and shown to outperform classical approaches to the design problem. Despite being successful, both methods fall short of a complete solution for RNA inverse folding. While reinforcement learning learns the design rules of RNA without human interaction, training is unstable and data intensive. Supervised learning, on the other hand, needs a large corpus of human-generated and labelled data to be successful while allowing for stable and data-efficient training. Furthermore, both approaches are currently limited to single-state RNA design.

To address these limitations, imitation learning provides a principled framework for RNA design learning in a data-efficient manner, without the need for human intervention (Ghosh et al. 2019, Singh et al. 2020). We plan to train self-imitating policies towards realising efficient human-level, multi-state RNA design. This allows us to design and test our RNA-based constructs at unprecedented throughput.

Differentiable Programming

In recent years, supervised learning of (possibly deep) neural networks has brought forth many astonishing advances in computational approaches to various scientific fields. Most recently, neural network models providing good solutions to both the protein folding (Senior et al. 2020) and design problems (Ingraham et al. 2019) have advanced structural studies of proteins by leaps and bounds. In this context, **neural network** are nothing but a special case of the more general computational paradigm of differentiable programming (Huot et al. 2020, Elliot 2018), allowing programs to be trained for example via gradient descent (Kingma and Ba 2014). Differentiable programming treats programs as compositions of parameterised differentiable functions. These functions have a set of modifi-

able parameters bundled with the information of how to compute their derivative for gradient-based optimization. The class of programs representable by differentiable functions is much larger than the matrix products and convolutions making up the usual neural network and thus allows for training programs with complex logic. This is important when processing **non-standard types of data** and learning parametric subroutines of larger programs as commonly needed in the context of protein and RNA bioinformatics (Lorenz et al. 2011). We aim to use differentiable programming to learn powerful samplers for RNA-design procedures, working as part of classical search routines.

Imitation Learning

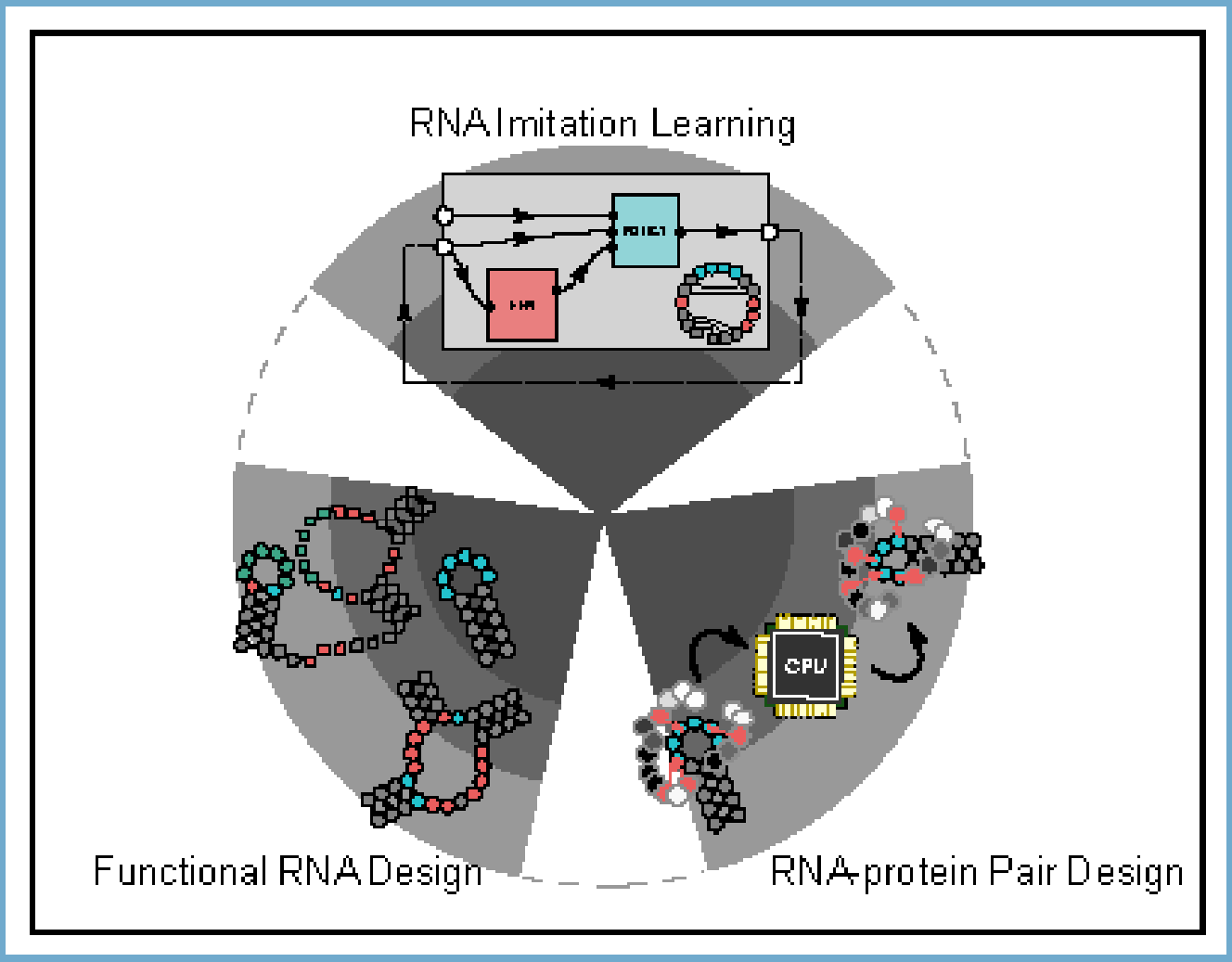
As human beings, we tend to learn many skills by demonstration. A parent or a teacher shows us how to complete a task by performing it in front of our eyes and we learn by imitating their movements. A similar line of thinking when applied to training machines is known as imitation learning. A model is trained from a set of **expert demonstrations** of a task by standard supervised learning (Ghosh et al. 2019, Kumar et al. 2019, Singh et al. 2020). To date, imitation learning has successfully been applied to a variety of robotics tasks (Singh et al. 2020) as well as to jump-start learning in challenging environments, where an agent would struggle to learn without first experiencing expert demonstrations (Silver et al. 2017, Vinyals et al. 2019). Notable examples of the latter include AlphaGo (Silver et al. 2017) – learning to play the game of Go with superhuman prowess – as well as AlphaStar (Vinyals et al. 2019) – learning to beat professional players in StarCraft II, one of the most popular, competitive and hardest-to-master real-time strategy games. By itself, imitation learning suffers from a number of fatal flaws. Firstly, for complex problems, it requires a large amount of expert demonstrations; Secondly, those demonstrations need to be close to flawless for the algorithm to be able to learn an optimal policy (Ghosh et al. 2019, Kumar et al. 2019). Fortunately, we can reformulate imitation learning such

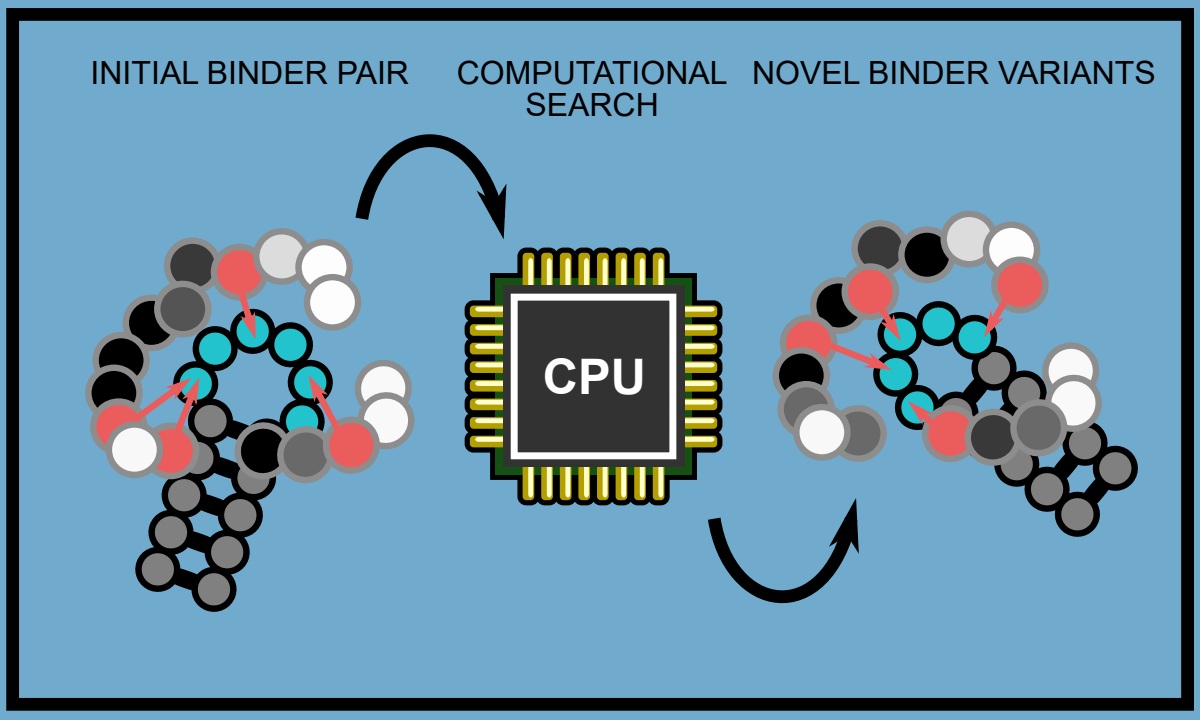
that we can easily sample new perfect demonstrations of a given task. The key observation is the following: A bad demonstration for one task might be a perfect demonstration of another. In our case, an RNA sequence misfolding badly with respect to some target structure provides a perfect demonstration for the goal being its own optimal secondary structure. This approach of self-supervised imitation learning has very recently attracted interest as a more stable and data-efficient alternative to standard reinforcement learning (Ghosh et al. 2019, Kumar et al. 2019, Srivastava et al. 2019, Singh et al. 2020). We aim to use self-supervised imitation learning to learn strong policies for the constrained RNA design problem, as a means towards more powerful and efficient design of functional nucleic acids.

Designing trans-splicing ribozymes

As mentioned above, one of the major problems of Cas9 is that it is far too large to be delivered into human cells directly. One solution is viral delivery part by part, which increases the specificity but drastically lowers the effectiveness. A different approach would be to avoid Cas9 and use a more compact alternative instead – in our case, f**unctional RNA**. As shown in multiple publications (Ikawa and Matsumura 2018), RNA is capable of manipulating other RNA and DNA in living cells. There are several advantages of RNA based manipulations over Cas9. First, it is more amenable to computational design due to its simpler structure. Second,RNA-based manipulations show their effects on phenotype faster as they bypass transcription and in some cases translation. Third, the applied changes are mostly on the level of RNA and only on DNA if explicitly required . This eliminates the possibility of introducing persistent errors via off-target editing and further endows editing with a speed boost since there is no need for transcription.

Our claim in this aspect is to develop a state-of-the-art system for designing specific trans-splicing ribozymes. We are confident this is feasible since it was already done successfully with





COMPUTATIONAL BINDER REDESIGN

classical methods and similar methods have been successfully implemented for protein design (Ingraham et al. 2019). Classical approaches are extremely slow, and to date there has been no approach to speed them up using machine learning. Bringing together the established knowledge gathered in the land of proteins, to the new born realm of RNA and machine learning will yield tasteful low hanging fruit of progress and improvement.

Designing protein-RNA binding pairs

Our very project depends on our ability to create specific, high-affinity interactions between chosen proteins and RNAs. Without good protein-RNA binding pairs, all could be lost. But we need not fear for our endeavour, for as is the case with many things, nature provides. In their bid to correctly pack their components and genetic information, many viruses have evolved specific protein-RNA interactions, tethering RNAs of interest to viral coat proteins. Many of them have unique and orthogonal RNA sequences and structure specificities (Katz et al. 2019, Adamala et al. 2016). While nature's array of binding RNAs and their protein partners is certainly impressive, as synthetic biologists, we want to go beyond its confines. More precisely, we wish to apply differentiable programming in order to discover novel, **orthogonal protein-RNA binding pairs**. To this end, we make use of **geometric deep learning** – a framework for machine learning on spatially structured data – (Wu et al. 2019) to learn representations of protein-RNA interfaces. The goal is a virtual screening of various RNA stem-loops against a common protein structure. If time permits, a supplementary high-throughput screening of a library of random RNAs against mutated proteins will be implemented to provide additional data on functional RNA-protein interfaces (Katz et al. 2019).

Modelling dynamic gene regulatory networks

Gene-regulatory networks involving RNA-based regulation are complex and diverse in behaviour. Their RNA-logic components may stochastically fold

into different secondary structures, endowing them with different functions. Successfully designing and deploying such networks is feasible, but usually requires a number of design-clone-test cycles until the regulatory circuits perform their desired function within reasonable parameters. As with simpler regulatory networks, modelling them helps to keep the number of design cycles minimal. A number of non-obvious, bad designs may be discarded by preliminary model checking. As our project is very time-sensitive, within the rigid time frame of the iGEM competition, we absolutely require good modelling to keep the number of design cycles minimal. Therefore, we plan to model gene regulatory networks and RNA secondary structure in the ensemble formulation, to construct **probabilistic models** of gene regulation under multi-state RNA control. These models help us to design and model-check such networks and subsequently accelerating progress in our project.

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Reaching the people - Human Practices

Apart from our laboratory work, we want to create a dialogue with people yet to be interested in the marvelous realms of life sciences, make research accessible and help to spread excitement for synthetic biology around the world. In this spirit, we are planning several projects to reach numerous groups among society. To quicken the interest of children, we will give **lessons** in fundamental molecular and synthetic biology at local schools.

Furthermore, we are organising a **Science-Slam** in Heidelberg, where we will invite other iGEM-Teams to excite people from Heidelberg with their ideas. We also plan to invite a speaker to Heidelberg University to catch the attention of biology greenhorns. Through the support of „Wissenschaft im Dialog gGmbH“, we are able to promote our project publicly through their social media channels and an interview on their platform „wissenschaftskommunikation.de“.

Finally, to address the current and controversial political aspects of synthetic biology and to find out more about the research other groups are undertaking, we are reaching out to the minister for science in Baden-Württemberg, Theresia Bauer, and further researchers for **interviews** and exchanging ideas.

Science Slam

5th of June, Marstallhof 3, 69117 Heidelberg (Marstall Cafe) - Reminder for myself: Invite all friends and sponsors!

Contact us.


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Please do not hesitate to contact us directly via telephone or via digital services for questions or discussing possibilities.