Swiss Federal Institute of Technology Zürich

Semester Project

Biocompatible and conductive fiber for implant applications

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Abstract

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Contents

1 Introduction

Biomedical Engineering has experienced a surge in interest during the last few years and transforms the whole healthcare sector. [14] Recently established technologies like optogenetics [3], where protein transcription is modified upon photonic stimulation, or exciting technologies like Medical AI [2] hold the potential to truly disrupt the industry. The market

In recent years, stretchable electronics have gained a tremendous amount of attention. [1, 10] A lot of reasearch has been done on how to design stretchable electronics devices, adressing different needs, ranging from wearable to implantable bioelectronic devices. Studies that parse the possible future applications of stretchable conductive bioelectronic devices describe possible applications. Mapping lesions of cardiac tissue in real-time, development of a human-machine-interface or skin-based status monitors are just some to name a few. [7, 8] Current methods however, fail to satisfy high conductivity, mechanical stability and biocompatibility at the same time. Lee et al. [10] showed a facile and cost-effective approach to production of highly sensitive fibers. Yet, the long-term biocompatibility remains to be determined. For successful realisation of said concepts, we need a highly stretchable, biocompatible, conductive fiber that reflect the nonplanar curvilinear surface of the site of application.

In this work, making use of electroless coating of a non-conductive material, which is widely used in biomedical applications [16], we succeeded in designing an simple protocol to fabricate highly sensitive fiber with good strain sensing capabilities in ambient conditions. Advances in Biomedical Applications have great value... Innovate medicine and allow better therapy, faster diagnostic and more authentic implants. Biosensors have reached to measure biological and chemical sensors. Mechanical modalities underepresented. With mechanobiology we have field, where influence is shown. Stem Cells, Cancerous Cells, Tissue adapt and form according to mechanical influence. High-energy tissue (tendon/ligaments) largely black box, many things still open. We need strain sensing. Current methods have drawbacks. Our stuff, best stuff.

There's a need for yadayada.

In this work...

2 Theory

2.1 Strain Sensing

Resistance R of a conducting material is governed by the equation (1), where l is the length, A the area of the crossection and ρ the electric resistivity, which inherently depends on the conducting material.

$$R = \frac{l}{A} * \rho \tag{1}$$

When applying transaxial strain, in most cases, a compression in transversal direction can be observed. The ration between those two forces is described by the material dependent Poisson's ratio, which in most cases ranges between 0 and 1. [5] In terms of conductivity-mediated strain sensing, this means, that the resulting decrease in $A = (A' - \Delta A)$ and the increase in length $l = (l' + \Delta l)$ leads to a measurable increase in resistance R upon strain. In resistance-mediated strain sensing we make use of this exact dynamic.

Add Schematic of Strain Sensing

2.2 Polyurethane

Polyurethanes (PUR) are biocompatible and biostable polymers, with urethane as the characteristic group. Due to most PUR being classically synthesised using polycondensation of diisocyanates with alcohols and amines, two side groups per monomer are introduced. This leaves the option for functionalization, depending on the requirement of the application.

On one hand, they're moldable and have favourable tensile and fatigue properties, all of which makes them a suitable choice of material for the development of most complex biomedical devices. [16] Until now, PUR has been extensively studied in the context of small vascular shunts and cardiac assist devices, where the thromboresistant property of the PUR fit formidable. Under most physiologic conditions, PUR are degradation resistant and can handle stresses very well [18].

However, PUR, is not electrically conductive. This makes it impossible to introduce electrical functionalities without further processing of PUR, like coating or introducing charged side-groups. Find Reference of Paper where charges have been introduced.

2.3 Gold Salt

Mention that gold NP's change color depending on size. Due to plasmonics interactions in matter. When evaluating, which conductive material to use, noble metals seem to host quite some promising candidates. The two main properties we wanted to base our decision on were specific conductivity and biocompatibility.

IDEA Focus on the specific conductivity chart suggests, that we should find

/IDEA

As a consequence we decided on using gold, as it strikes the balance between conductivity and biocompatibility. What's with other noble metals. Also there is robust evidence, that gold stays biocompatible, even as gold nanoparticles (AuNP). Why shouldn't it stay biocompatible as nanoparticles This is especially important, when considering that this is the relevant size range for this work. [12, 17]

Due to practical reasons, we had an interest in increasing the efficiency. Rephrase/Elaborate This is typically done by minimizing the amount of substance that is wasted in non-targeted interactions. Gold in bulk is highly inert and therefore difficult to incorporate in a directed chemical approach, whereas the ionic form is a well studied agent in Redox-reactions (i.e.the method that was chosen in this work). The increase in efficiency can be achieved using a spatially selective approach, where gold salt located only in and on the fiber is reduced to become solid gold.

Gold(III) chloride trihydrate was therefore the oxidation agent of choice. Check out other gold salts. Maybe this salt has highest potential, therefore easier to be reduced.

2.4 Reduction agent

Redox-reactions are electrochemical reactions where electrons are exchanged between the participating agents. Typically the reaction is described by using two so-called half-reactions.The reduction half-reaction describes the process of loosing, whereas the oxidation counterpart describes gaining electrons, respectively. As one might expect, the presence of a specific half reaction to happen and the direction in which it happens (Oxidation or Reduction), depends on its inherent likelihood of happening and its relation to the likelihood of the present alternatives of half-reactions. Rephrase. In the Redox-regime,

the likelihood is coupled to a so-called standard-reduction potential or SRP. Volt is the unit of the SRP and the SRP of a specific half reaction is denoted by E^0. The more negative the SRP of a half-reaction, the more likely the reaction to happen. Every half reaction is reversible and will be reversed when a half reaction with a lower E^0 is encountered.

$$[AuCl_4]^- + 3e^- \longrightarrow Au(s) + 4Cl^-,\ E^0{}_{Gold} = +0.93\ V$$

Maybe tweak with centerline

$$3Red \longrightarrow 3Red^+ + 3e^-,\ E^0{}_{Red} < +0.93\ V$$

The desired reaction to happen, is the reduction of the gold-chloride to get gold in its solid form (denoted by Au(s)). Gold in bulk is electrically conductive and highly bioinert. Consider Wojnicki When choosing potential candidates, we defined several qualities, which the desired reduction agent should have.

First, it should reduce gold efficiently and exclusively. On one hand, this confines the list of potentially chosen agents to those who comply with $E^0{}_{Red} < +0.93$ V, according to Redox-Theory. On the other hand we want to minimise interactions between the reduction agent and PUR, due to possibly modified mechanical, chemical or biocompatible properties. This happens more often with very aggressive reduction agents, which have been shown to introduce radicals and modification of the surface properties. Ref Hence, we want to avoid very strong reaction agents.

Second, we want it to be biocompatible. Since the goal of this work lies in applying knowledge in biomedical applications, the importance of biocompatibilty is given. If the reduction agents itself fulfils this requirement, then there is no need for introducing another washing-step, which could possibly introduce additional insecurities with its degree of freedom with multiple failure modes. Ref

Third, the reduction agent should be easily accessible and not too expensive, to facilitate access to technology and faster iterations when developing applications.

2.5 Nucleation and Percolation

When non-polar singular atoms of metallic species are produced in polar liquid, they want to continually aggregate to atoms of the same species,

since it's energetically favourable when compared to their existence in the singular atomic state. This leads to the formation of so called embryos. [6] But embryos still mark a non-solid-state phase, since they are subject to a continuous dissociation-aggregation process. If the system allows for an advancement through enough available free energy, eventually the embryos will grow to become nuclei. Nuclei are physically stable and don't dissociate spontaneously anymore. As the name suggest, they act as an atomic 'seed' where newly produced atoms can adhere to instead of trying to become embryos themselves. In terms of redox-reaction, this means that weaker reduction agents should lead to less but bigger nanoparticles. For stronger ones, the opposite case applies. [15]

To elucidate how this process is important to us, I have to introduce percolation. Percolation whose behaviour is governed by laws of Percolation Theory, describes the successful transmission of current through a random path, where each edge (air, PUR) between two nodes (gold nanoparticles) carries a probability of conducting the current. We say that something percolates if the transmission is successful from one end to the other of our sample space. The very important point here is that the exact way through which the current is conducted is not known, we only the know the probabilities. Intuitively, it becomes clear, that bigger nanoparticles have fewer but bigger overlap with other nanoparticles. This might lead to smaller resistance. However, as soon as we apply strain, those bigger nanoparticles become an uncertainty since the overall percolation depends much more on individual conduction events, leading to a broader probability-distribution, whereas in the small-but-a-lot-case the percolation distribuition is much narrower. Reference taken from Wikipedia, Percolation Theory.

Taken those insights from nucleation and percolation together, should lead to one main insight: Namely, that stronger reduction agents, according to theoretical induction, should lead to better conductivity, when compared to weak reduction agents.

3 Methods

3.1 Manufacturing

3.1.1 Preparation of reagent

All reagents were of analytic grade and were used as received from the suppliers without further purification. Every chemical was bought from Sigma Aldrich, unless stated otherwise. Next for facilitation we introduced the formula making use of stoichiometry:

$$\frac{m' \cdot v \cdot M}{1000} = m(m', v, M) \tag{2}$$

where m' denotes the molecular weight of the reagent, v the desired end-volume of the solution, M the molar concentration and m the needed amount of the substance with unit 'grams', assuming the chemical to be pure. (Example: We want to make 4ml ($= v$) of solution with NaOAc ($m'_{\mathrm{NaOAc}} = 82.03\frac{g}{mol}$) at a concentration of 0.25 M ($= M$). We now know, that we need to dilute $m \approx 82mg$ NaOAc in 4ml of solvent!)

Gold solution We used Gold(III) chloride trihydrate, dissolved in 100 % ethanol (EtOH). The concentration, unless stated otherwise, was 0.25M and was prepared using the formula (2).

Reduction agent solution From the identified reduction agents, the reagent was produced by taking the calculated amount and diluting it in Milli-Q H_2O until the concentration given was reached. Were the reduction agent was light-sensitive, we put aluminium-foil around the containing reservoir to decrease exposure.

3.1.2 Sample Fabrication

Define Experiment. We identified 5 independent variables that can be changed.

- Gold concentration (c_{gold})
- Gold immersion time (t_{gold})
- Choice of reduction agent
- Reduction agent concentration (c_{Red})
- Reduction agent immersion time (t_{Red})

Initial Protocol

1. Define which parameters are fixed and which are experimental parameters. Define range you want to investigate.

2. Define concise naming concept, which allows every sample to be uniquely identified.

3. Per sample reserve two petri dishes (PD) and label them in accordance with above mentioned concept. You might add the tag "Pre" and "Post" to existing description. (*PDPre/PDPost*).

4. Put 0.75ml of Gold Solution with c_{gold} in small, optimally non-translucent viol to account for the light-sensitivity of the gold salt (*Viol*). One viol per sample you wish to investigate. Further decrease of translucency can be achieved by putting aluminium around viol.

5. Put fiber in corresponding *viol* and let immerse according to your defined t_{gold}.

6. Take fiber out *viol* and put in *PDPre* to let dry. Note change in colour and/or structure. Experience shows that 30 minutes is sufficient.

7. Gently pour 1ml of reduction agent solution with c_{Red} over fiber, while making sure the whole fiber is immersed. Note colour gradient in fiber and temporal resolution. Let immerse according to defined t_{Red}.

8. After passing of time, transfer the fiber gently to *PDPost*, where it will dry.

This marks the end of the fiber fabrication.

Optimized Protocol

1. / 2. are identical to initial protocol.

3. Per sample reserve one petri dish (PD) and one glass slide (GS). Label them in accordance with above mentioned concept, whereas you might add the tag "Pre" to the PD and "Post" to GS description. (*PDPre/GSPost*).

4. Put 0.75ml of Gold Solution with c_{gold} in small, optimally non-translucent viol to account for the light-sensitivity of the gold salt (*Viol*). One viol per sample you wish to investigate. Further decrease of translucency can be achieved by putting aluminum around viol.

5. Put fiber in corresponding *viol* and let immerse according to your defined t_{gold}.

6. Take fiber out viol and put in *PDPre* to let dry. Note change in color and/or structure. Experience shows that 30 minutes is sufficient.

7. Gently pour 1ml of reduction agent solution over fiber, while making sure the whole fiber is immersed. Note color gradient in fiber and temporal resolution. Let immerse according to defined t_{Red}.

8. After passing of time, transfer the fiber gently to *GSPost*, where it will dry.

This marks the end of the fiber fabrication.

3.2 Measurement

3.2.1 Preparation

Prerequisites:

- Sample with size l
- Silver Epoxy
- A small piece of paper
- 8 Pieces of Tape
- Derubberized Cable

Protocol:

1. On piece of paper, put 1 piece of tape (Tape 1) on each side with distance $d < l$ from each other

2. Now fix both ends of the sample gently without stretching (!) on Tape 1 with another piece of tape (Tape 2).

3. Then, put free end of cable on end of sample, which is free and over Tape 1. Establish contact and fix cable with Tape 3.

4. Put Silver Epoxy on sample-cable-interface to facilitate sample-cable-transmission. Bake at 80°C for 2h. After taking out the oven, put tape 4 perfectly aligned with the medial edge of Tape 1.

TODO Refer to actual figure (Add label, fix picture organisation.) TODO
See figure number 4 in Appendix for visual description of resistance measurement preparation.

3.2.2 Resistance Measurements

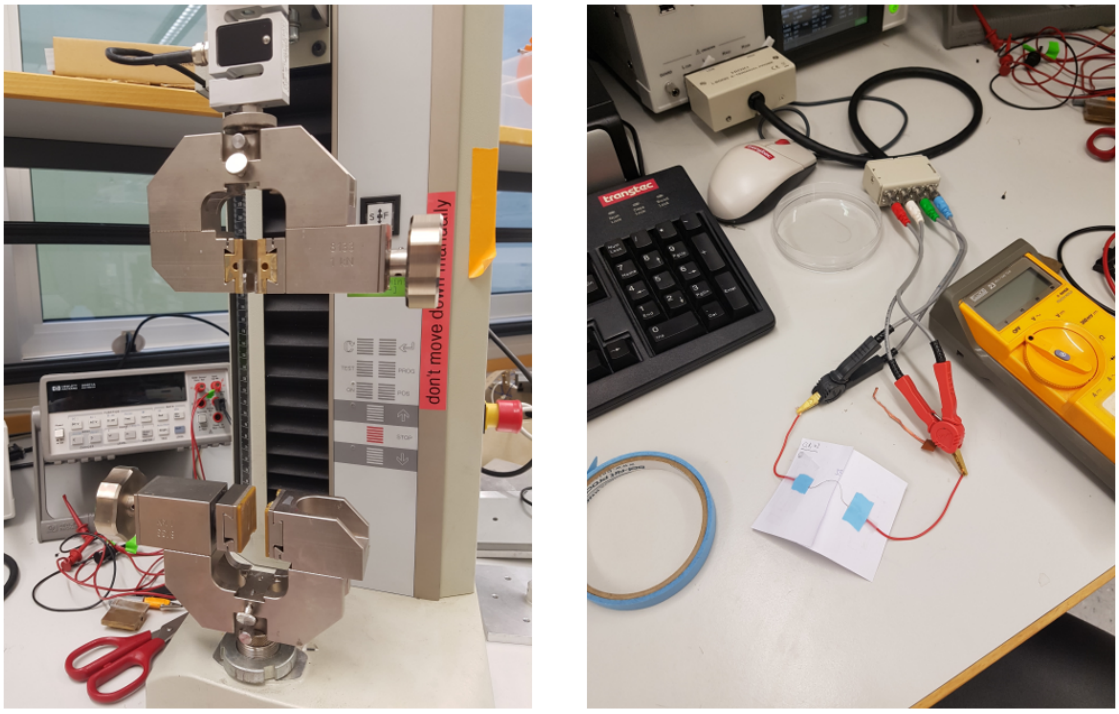

Figure 1: Setup of Continuous Resistance Measurement

4 Results & Discussion

4.1 Identification of reduction agent

Put up list of reduction agents tried Add label!!

NaBH4 has been described in the literature to produce gold nanoparticles in tunable sizes, depending on the ratio between NaBH4- and gold concentration [13]. To account for the already acidic environment coming from the gold salt itself, we introduced another group, that consisted of a combination of $NaBH_4$ and NaOH by 1:1 ratio, where NaOH as a sodium base, should moderate the reduction to happen in a less acidic environment. Hydroxylamine as reducing agent is widely known and has already been described in the context of production of silver colloids [11]. As proposed by work done by Goia, Kimming and Turkevich, we added Ascorbic Acid (AscAc), Citric Acid (CitrAc) and a reducing sugar (here: Glucose) to the tested reduction agents. [6, 9, 4]

There were 3 samples per reduction agent. Following the heuristic approach, where we optimised the knowledge gain per sample-ratio, we subdivided each group by three different reduction agent immersion times, which were 20 minutes, 40 minutes and 2 hours, respectively. This means that every permutation-group [Reduction Agent/Reduction agent Immersion Time] had one sample.

AddGraph of t_{Red} v R_0
Add Label too

NaBH4 During Production we followed the standard procedure with the concentration stated. $NaBH_4$ is known to hydrolyse in solute and therefore, the intended reactivity is reduced. To decrease premature hydrolation, the $NaBH_4$-solution was prepared just before usage and put on ice between production and use. Upon immersion of fiber in $NaBH_4$, the production of bubbles could be observed as can be seen in figure **??** Add Label for Bubbly picture in Appendix..

The following equation describes the oxidation-half reaction in this sample:

$$[BH_4]^- + H^+ + 3H_2O \longrightarrow H_3BO_3 + 4H_2(g),$$

With the stated concentration in table **??**, we were able to measure conductivity in all three samples as can be seen in figure **??**. We acknowledge the fact that one sample is not sufficient for any significant statement. Nevertheless, we see a tendency of a decreasing resistance when increasing the immersion time, exhibiting a time-dependency in this relation. As a general rule, chemical reactions are known to target a certain ratio between reactant

and product add reference. This principle could explain the time-dependency. The produced hydrogen gas evades the liquid reaction solution continuously as seen in picture addRef for bubbly Picture. This imbalance between reactant and product is counter-steered by a shift towards the product side present in the solution, which over time would lead to a steady-state, where the increased concentration of H_3BO_3 compensates for the lack of H_2(g). However, as long the reaction did not reach the steady state, gold atoms will be produced and nuclei will grow. Implicitly this includes the decrease in resistance whose end is marked by a critical point that is governed by reaching the ratio described above or the nanoparticle size.

Scanning Electron Microscopy (SEM) pictures showed a largely heterogeneous distribution of nanoparticles. However, EDS analysis of the cross-section of the fiber reveals gold coating. Add Ref

$NaBH_4$/NaOH Check if there are lab-pictures. Refer to them. We did not take SEM/EDS pictures.

Hydroxylamine Production was done according to protocol and with the concentration stated. No conductivity was measured. Nevertheless, SEM pictures revealed successful reduction of gold into round nanoparticles that at some location formed large colloids. Add Ref for HyA Picture Following the principle of Occam's razor, we hypothesise that in the process of the reaction, eventually, the nanoparticles grew to big and subsequently "fell off" the fiber. This explains the phenomenon of no conductivity without any particles.

Ascorbic Acid Production was done according to protocol and with the concentration stated. The conductivity measured was 25-43 Ω and outperforms the next best reduction agent by almost 4 orders of magnitude in the described setup.

Citric Acid The citric acid protocol was slightly changed, upon suggestion by work done by Kimling [9] to include an initiating element to facilitate the formation of nuclei, which then - according to explanation found in chapter 2.5 - should suffice for produced gold atoms to associate to the nucleus and finally nanoparticles to grow. The identified initiators where heat-exposition

and UV-irradiation. For each of those two subgroups, only one sample was prepared.

We prepared the heat exposition group following standard procedure up until the immersion of the fiber in the reduction agent (i.e. citric acid in this case). Using the hot plate, we prepared the citric acid solution to be between 100-120 °C, before the fiber was immersed. Over the course of 35 minutes the solution changed from faintly blue and turbid to a clear solution with red particles floating in the solution. A picture of the solution after letting it cool down is shown on page **??** Add Citric Acid Picture. The described behaviour replicates the description by Frens[4]. Yet, we were not able to measure current.

Using a Demetron Optilux 500, we irradiated one sample after immersion citric acid solution. The picture on page **??** Add Picture of Bubbly and reference it shows the emergence of bubbles at the fiber-solution-interface during irradiation. Comparison with a control citric acid group, where bubble formation was absent, leads to conclusion the phenomenon is caused by the irradiation. However, the integrity of the fiber was impaired. Attempts to take it out the petri dish, showed that the polyurethan fiber was thinned out substantially and sticked on the petri dish. Obviously, there was an influence of the UV-light on the fiber. Further experiments with variable irradiation times and/or intensities, could lead to a more thorough explanation. No conductivity measurement was done in this group.

Add UV-Fiber Picture

Glucose Upon suggestion by Kimling [9], we kept the reduction agent solution at around 30 °C during the whole immersion time, using the hot plate. After 15 minutes, some of the solution clearly visible condensed on the closing lid of the petri dish Add Picture of PetriDish. We were not able to measure any conductivity in this sample. However, SEM pictures revealed the formation of gold nanoparticles. Upon further magnification, the peculiar structure of those nanoparticles became visible. The nanoparticles had cracks, which in bigger ones would reveal the pitch black cavities. Due to technical difficulties, the SEM in this setup is not able to image those, but it looks like the nanoparticles are hollow, with the apparent nanoparticles being merely a nanoparticle-shell. The cracks can also be seen on the surface of the fiber. Further experiments with variable temperature and heating times maybe can provide more information on the origin of this behaviour.

All reduction agents tested effectuated a change in fiber colour when following the described protocol. As indicated in chapter 2.3, this shows that in the experimental setup the reduction of gold was successful. If not stated otherwise the sample did not lead to any behaviour that was worth noting, neither when analysing the reduction agent solution after sample immersion or the fiber by eye.

However, due to the fact no reduction agent but $NaBH_4$ and AscAc did lead to conduction in our fibers, we also conclude that the sheer reduction of gold is not enough to functionalise our fiber with conductivity. In order to explain the relation ship between the reduction agents and the conductivity of the fiber, we have to introduce another metric, which we propose to be the quality of the gold nanoparticles.

Here SEM/EDS Pictures Pictures

As can be seen in the SEM pictures ref The SEM pictures we can partially explain the conductivity by uniformity in spatial distribution and size of the nanoparticles. Further experiments could elucidate which of these factors weigh how much into the equation that explains conductivity in our fibers.

4.2 Optimisation

Encouraged by the good results we decided to optimise for AscAc before making baseline resistance tests for new reduction agents. Additionally, we now took not only the baseline resistance into account but also its behaviour when put under strain stress. This measurement reflects now more the true use case and should reduce misdirected optimisation. The five independent variables defined in chapter 3.1.2 are now reduced to four. If not different stated, following applies:

$$c_{AscAc} = 0.19M,\ t_{AscAc} = 20min,\ c_{Gold} = 0.25M \text{ and } t_{Gold} = 1h$$

Next we assigned each of those independent variables an anticipated effect size. By intuition we assigned them in the following order, where $>$ marks "has the bigger anticipated effect size than":

$$c_{AscAc} > c_{Gold} > t_{AscAc} > t_{Gold} \tag{3}$$

4.2.1 Variation of Gold Concentration

Gold concentration was varied to be $0.025M, 0.25M$ and $0.6M$, respectively.

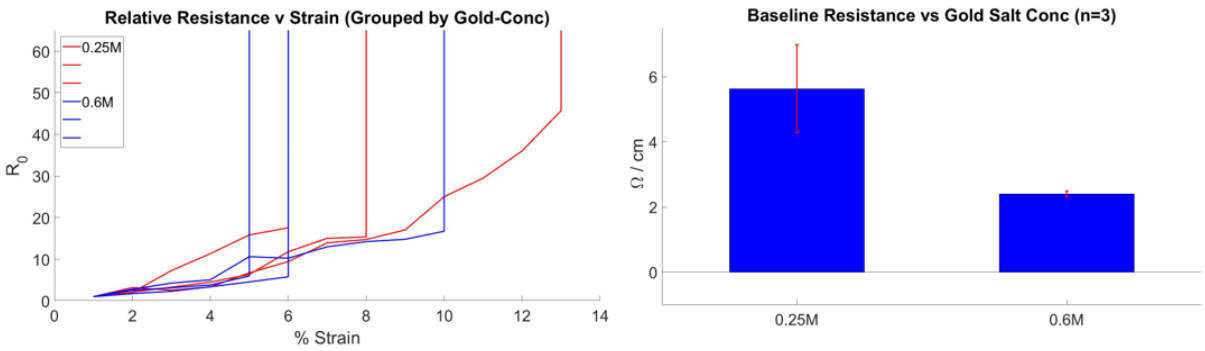

Figure 2: Variation of Gold Concentration

The $0.025M$-samples did not lead to measurable conduction. The result of the baseline resistance seemingly favours a higher gold concentration. However, the data of strain resistance does not allow for a similarly clear statement, neither when plotting the absolute resistance nor when plotting the normalised one, as we see in figure 2, left. The sudden peak out of the plotted range mark the critical point, where conductivity in the fiber was lost and no current was measured. Relaxation of strain also led to regain of measurable conductivity similar to a priori values (not shown). Intuitive reasoning where a higher gold concentration leads to lower baseline resistance but faster loss of conductivity due to more rigid behaviour, doesn't seem to manifest in the acquired data.

4.2.2 Variation of Reduction Agent

Why no P{0%/1}?? Redo graph!!, Also change positions of two graphs

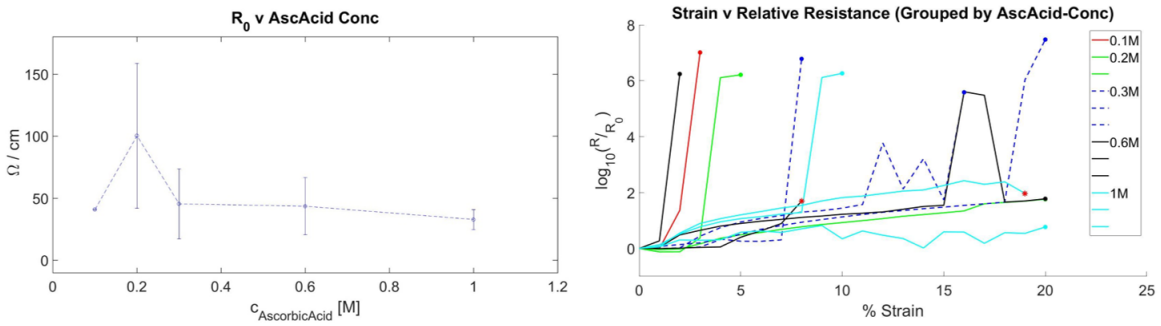

Figure 3: Variation of Gold Concentration

In the next experiment we varied the AscAc-concentration to be either $0.1M, 0.2M, 0.3M, 0.6M$ or $1M$, respectively. Sadly, this this lead to only inconclusive data. Similar to the plot 2, the sudden surge in resistance marks the critical point where conductivity was lost. Aditionally, at the red crosses, we had to manually stop the measurement due to the resistance measured jumping between multiple orders of magnitude, which wasn't representative.

5 Outlook

Appendices

Add Pictures of SEM-HyA

$HyA1_2 and HyA1_3$

A Figures

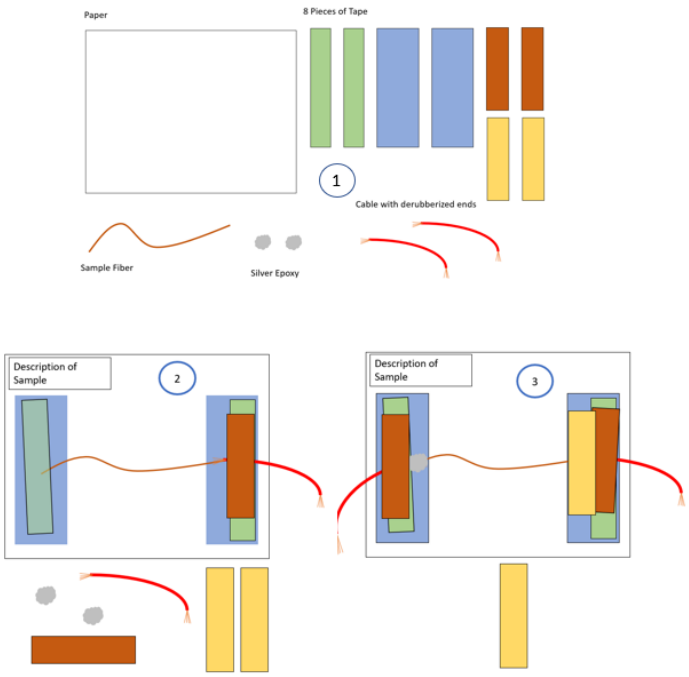

Figure 4: Preparation for Strain-Resistance-Measurement

B Pictures

Add Picture of bubbly sample

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