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From pig ears to smart technology:

A physiological approach for the development of microneedle-based wearables.

Prof. Dr. Lukas Scheef

From bench to bedside: a stony and risky path

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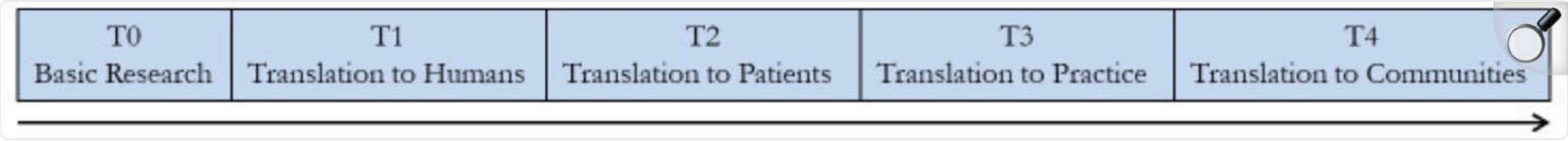

bench ⟷ bedside

- Failure rate about 90 – 95 % for therapeutics [1]
- Failure rate about 75% for medical devices [2]
- FUS Foundation 2024 and industry reports:

  "75 % of US-based medical device start-ups fail, and 98 % of digital health startups fail"

[1] Lalu MM, et al. Identifying and understanding factors that affect the translation of therapies from the laboratory to patients: a study protocol, 2020.; PMID: 33123348
[2] Sha NP, Navigating challenges in new product development,2024, : https://doi.org/10.30574/wjarr.2024.22.3.1740

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Major reasons for failure

1. **Lack of market and user orientation**
   Many innovations do not address a real need ("no market need"), or the clinical problem is already satisfactorily solved with existing means.

2. **Regulatory and compliance hurdles**
   MDR in the EU or FDA in the US) are complex, time-consuming, and costly, and often overwhelm smaller companies and startups.

3. **Technical defects and development problems**
   - Design errors, poor material selection, manufacturing problems, or incompatibilities lead to functional failures or problems in clinical use.
   - Low transferability of preclinical data to humans.

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Major reasons for failure

4. Weak study design and inadequate clinical validation

Too small or unsuitable sample sizes, poor selection of comparison groups, inadequate study protocols, or a lack of human factors testing mean that the clinical added value cannot be demonstrated or proven.

5. Financial and resource problems

- Medical device development is capital-intensive; companies often fail due to a lack of follow-up financing during long, regulatory-driven development phases.
- Unexpected cost increases (i.e. changed requirements, additional tests, or unexpected technical setbacks …)

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Our goal: Development of a microneedle-based multi-modal health patch

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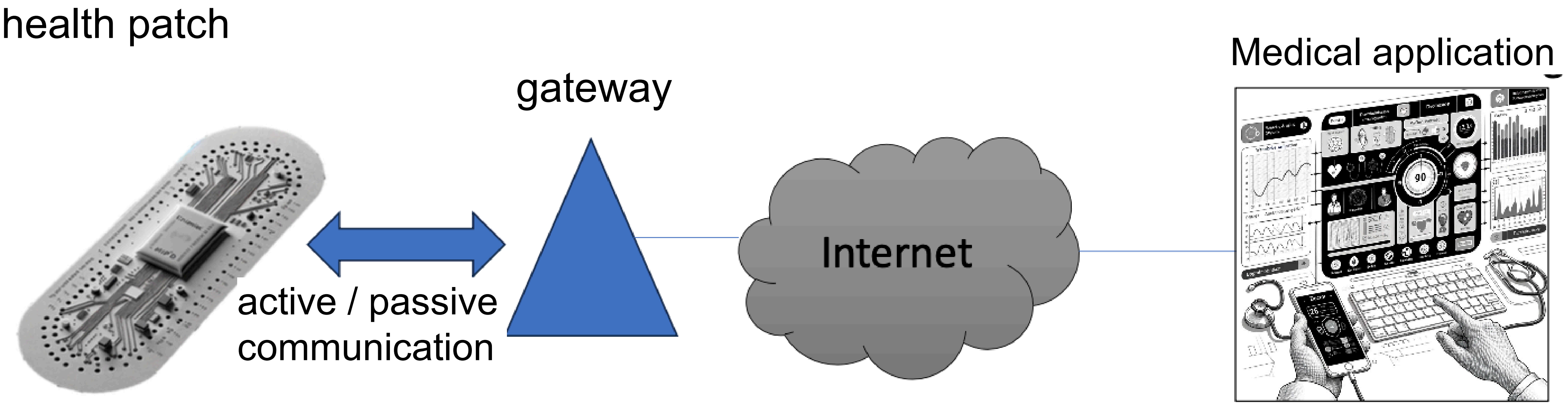


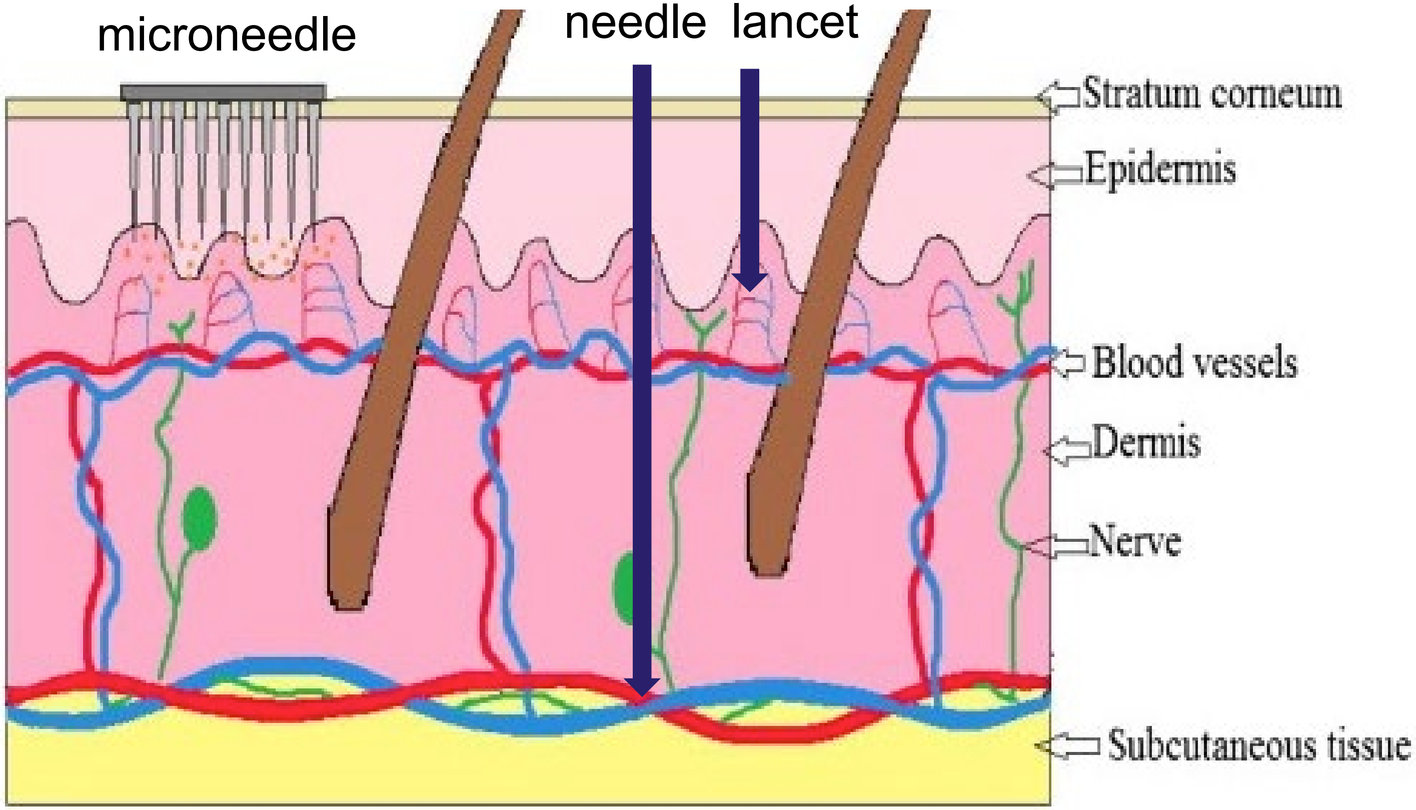
Target substances: lactate, glucose, electrolytes, cortisol …

Additional quantities: heart frequency, hydration status, pO_2

Why microneedle-based?

one (major) reason: compliance …

Microneedle: Overview



Epidermis: 0,3 – 4 mm

~ 0,1 mm (100 µm)

Stratum corneum:

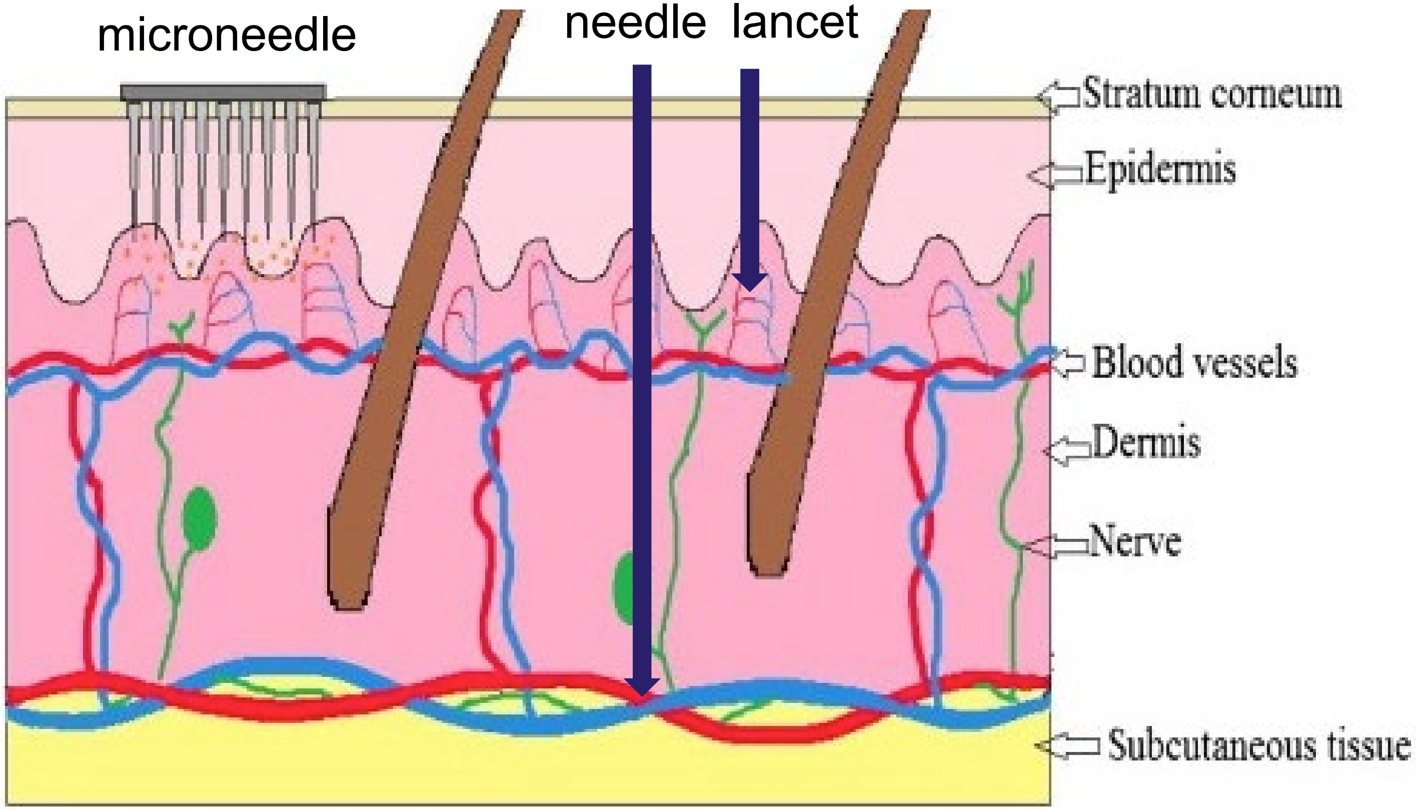
10 bis 40µm
10 µm (cheek)
173 µm (palm/sole of the foot)

Length:

- needle: 10 – 40 mm
- lancet: 0,9–2,0 mm
- microneedle: 0,2–1,5 mm

(1) https://img.chemie.de/Portal/News/160875_B75Y9-JrS.png?tr=n-xzoom, (2) Martanto et al. Side-Opening Hollow Microneedles for Transdermal Drug Delivery, 2005, (3) Waghule et al., Microneedles: A smart approach and increasing potential for transdermal T drug delivery system, Biomedicine & Pharmacotherapy 109, (2019) 1249–1258

Microneedle: Problems



Analysis of the interstitial fluid rather than the blood composition

→ indirect measure

→ dynamic depends on physiological parameters:

- blood pressure
- perfusion
- hydration

(+ static aspects like diffusion distance)

KEY-Idea to (hopefully) reduce the failure risk

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3. Technical defects and development problems

- Design errors, poor material selection, manufacturing problems, or incompatibilities lead to functional failures or problems in clinical use.
- Low transferability of preclinical data to humans.

Design a model or test bench that:

- allows for testing the properties of the device at a very early development stage
- get as close as possible to the physiology of the human body
- reduce the regulatory burden to a minimum

The „Pig Ear Model“

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Pigs have become firmly established as the main research models in some areas of biomedical and pharmacological research.

1. anatomical similarities to humans:

- body size,
- skin,
- cardiovascular system
- urinary system,

2. functional similarities:

- gastrointestinal system
- immune system

3. availability of disease models

- arteriosclerosis, metabolic syndrome, gastric ulcer and wound healing

The „Pig-(Ear)-Model“

Feature	Domestic Pig (Sus scrofa domesticus)	Human
Skin layers	epidermis, dermis, subcutis	epidermis, dermis, subcutis
Layer structure / histology	Very similar to human skin	—
Stratum corneum (SC)-thickness	approx. 11 ± 2 µm	10 – 20 µm upper arm & sternal region
Epidermis-thickness (basale–granulosum)	approx. 72 µm	sternal region 70-90 µm
Rete peg depth (interlocking)	Ø 102,3 ± 4,4 µm	Ø 100 µm
Dermis-structure	Papillary and reticular areas, capillary networks, parallel collagen fibres	Papillary and reticular areas, capillary networks, parallel collagen fibres
Dermis-thickness	Ear skin: approx. 1.86 mm	1.5 mm – 2.00 mm upper arm & sternal region
Immunohistochemical markers	Similar keratin and biomarker expression	Similar keratin and biomarker expression

Animal Experiments?

Problems:

- Ethically questionable
- The regulation burden is extremely high
- An implementation in a technical research environment is not possible

Solution:

- restriction to perfused pig-ear model

→

Pig-Ear Model: Procedures

- Sampling immediately after slaughter, transport on ice and processing of skin samples within 1–6 hours
- Start thrombolysis and anticoagulation as soon as possible (if possible , immediately, directly after slaughter)
- Controlled perfusion of the pig ear (including sufficient oxygenation, nutrition and dialysis)
- Monitoring and control of blood pressure, flow, temperature, pH, pO_2, pCO_2 …
- Variation of the target substances

Experimental Set Up:

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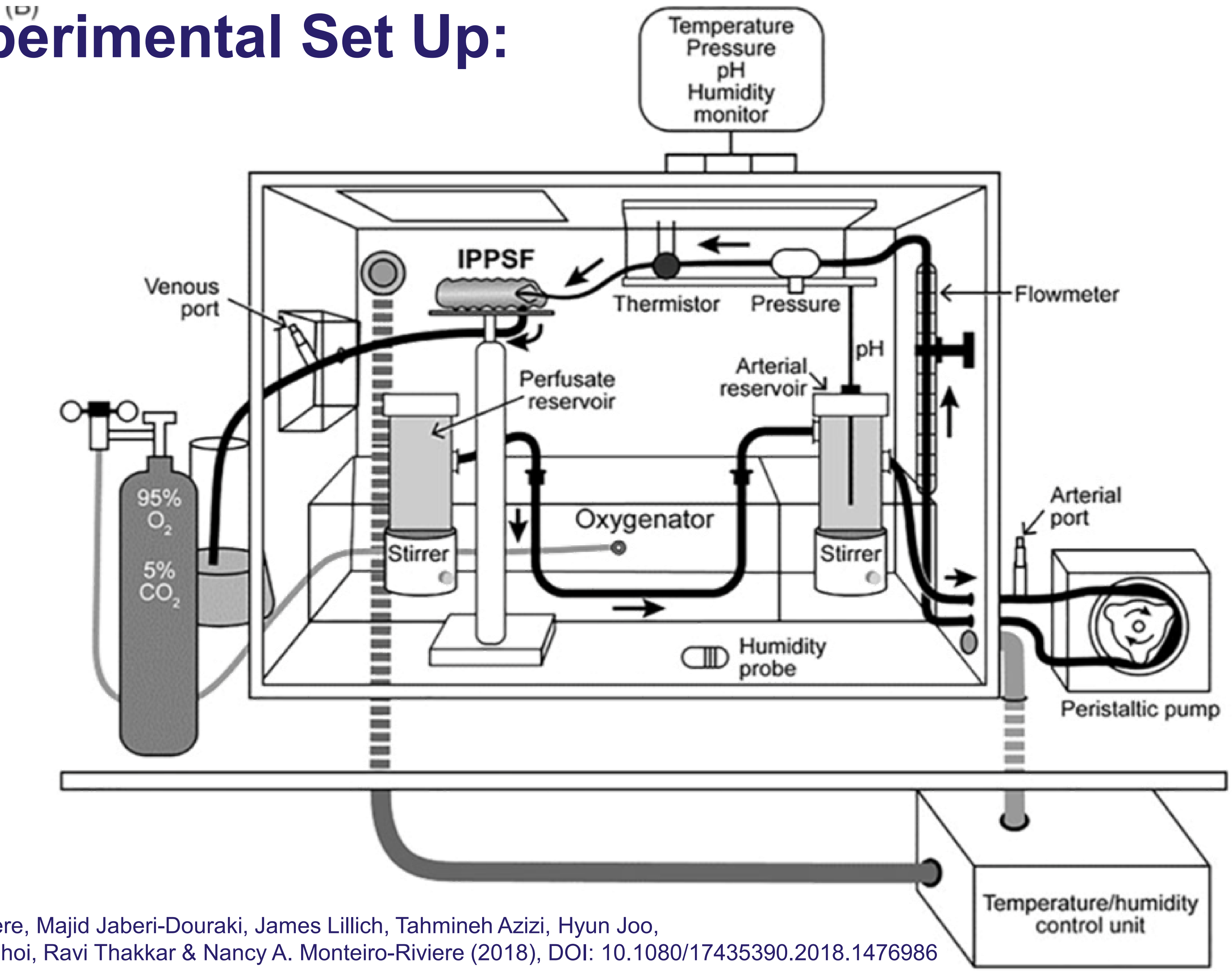

Jim E. Riviere, Majid Jaberi-Douraki, James Lillich, Tahmineh Azizi, Hyun Joo, Kyoungju Choi, Ravi Thakkar & Nancy A. Monteiro-Riviere (2018), DOI: 10.1080/17435390.2018.1476986

Experimental Set Up:

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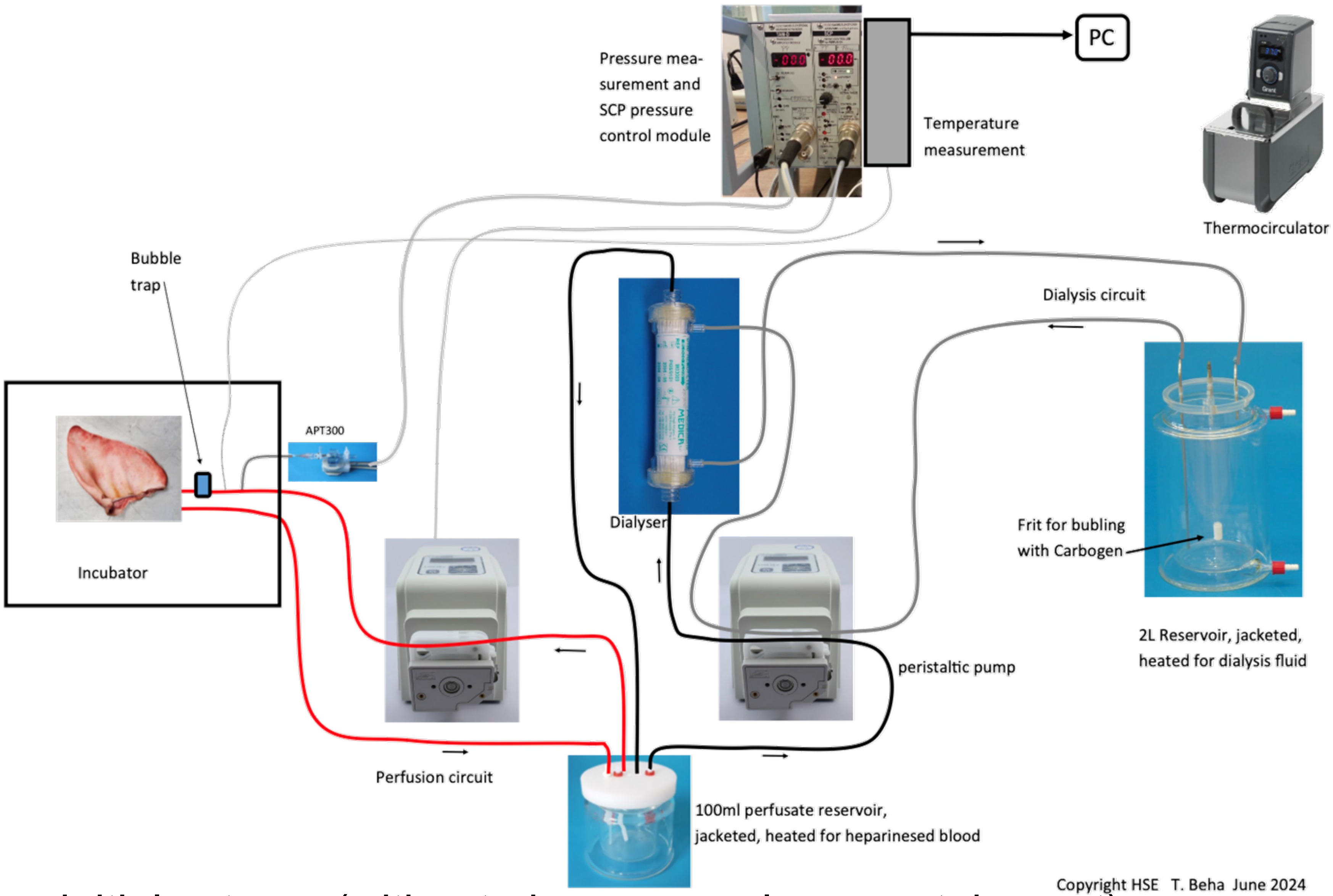

initial setup – (without pig ear sample or containment)

Pig-ear model: adjusting screws / open questions

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Adjusting screws:

Solution used for perfusion:

Krebs-Henseleit-Solution vs. pig blood

Flow profile:

Constant flow vs. pulsatile flow profile

Open question:

How long can we keep the pig ear alive – without relevant tissue degeneration?

Thank you very much for your attention!

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