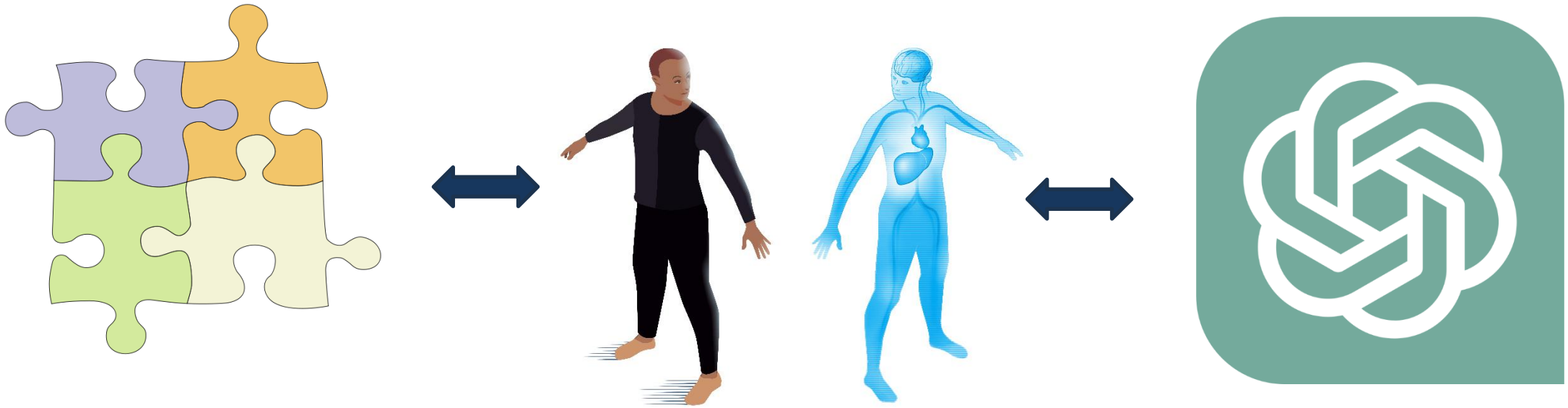
Welcome to TBMT42: Systems Biology, Digital Twins, and AI



Gunnar Cedersund,
Biomedical Engineering (IMT)

Overview of this lecture

Each now block in the lecture is marked with a cloud

- Overview introduction to the three concepts: systems biology, digital twins, and AI (and their interrelations)
- Practical elements and overall structure of the course
- Examinations
- A little bit of inspiration of what this can be used for
- Pedagogical goals and principles

AI is all over the news nowadays

REUTERS®

World Business Markets Sustainability Legal More

svt.se/nyheter/lokalt/vast/ny-chatbot-gor-det-enklare-for-studenter-att-fuska

Technolo

Cha
use

Jonas Ivarsson, professor
boten ChatGPT. Hör mer

Nya chat
enklare fö

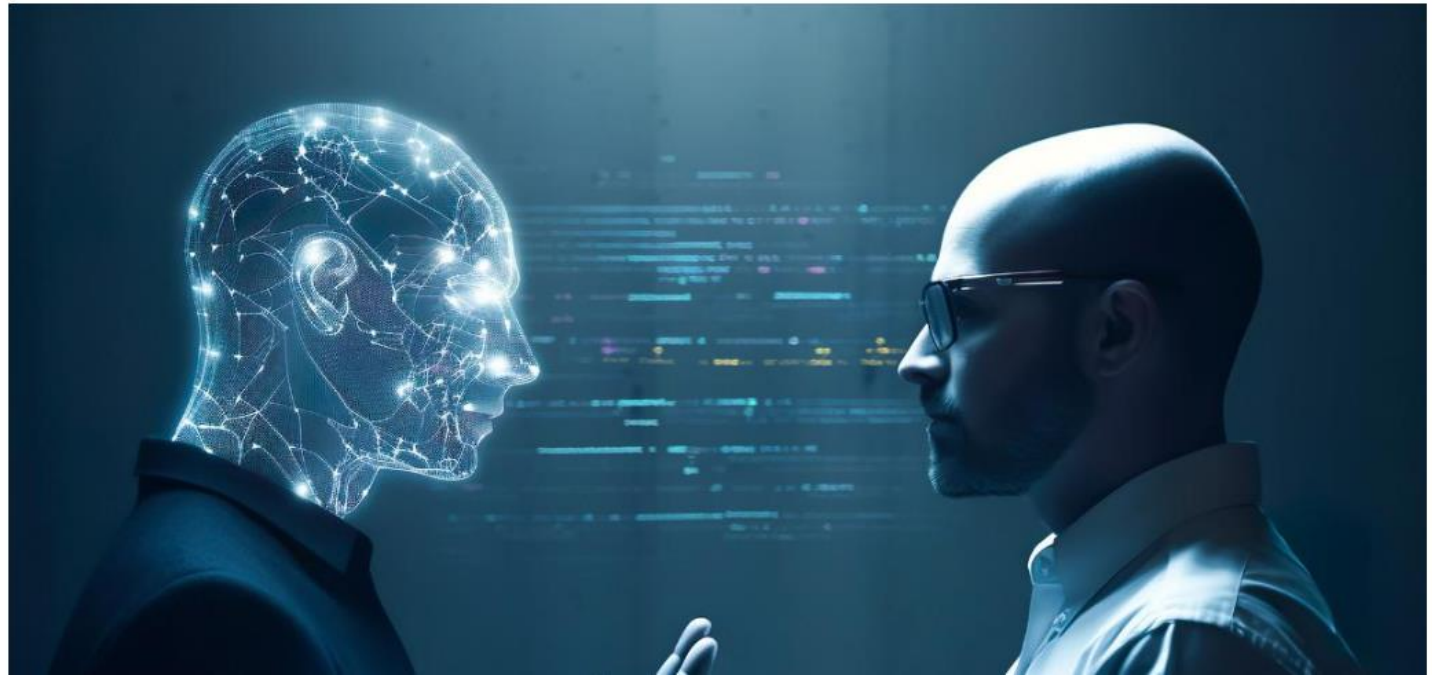
UPPDATERAD 14 MARS 202

Den nya chatboten
för alla, kan svara p
Detta har skapat dis
blir det blir det enkl
– Vill man fuska så
den varit tidigare, s
Göteborgs universit

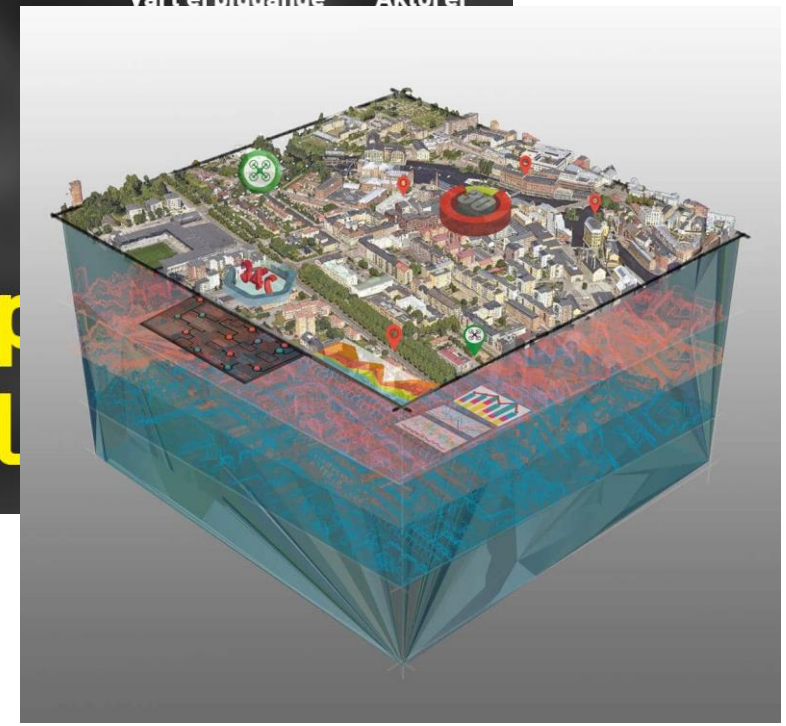
EU AI Act: first regulation on artificial intelligence

Society Updated: 14-06-2023 - 14:06
Created: 08-06-2023 - 11:40

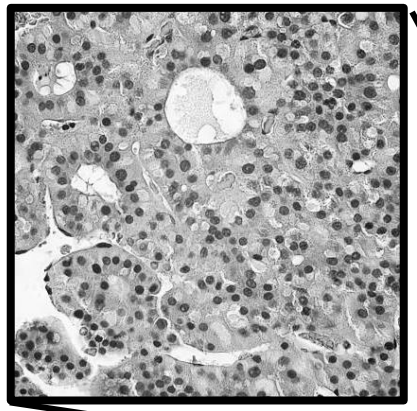
The use of artificial intelligence in the EU will be regulated by the AI Act, the world's first comprehensive AI law. Find out how it will protect you.



Digital twins is used in industry since a long time, and is now returning to biology

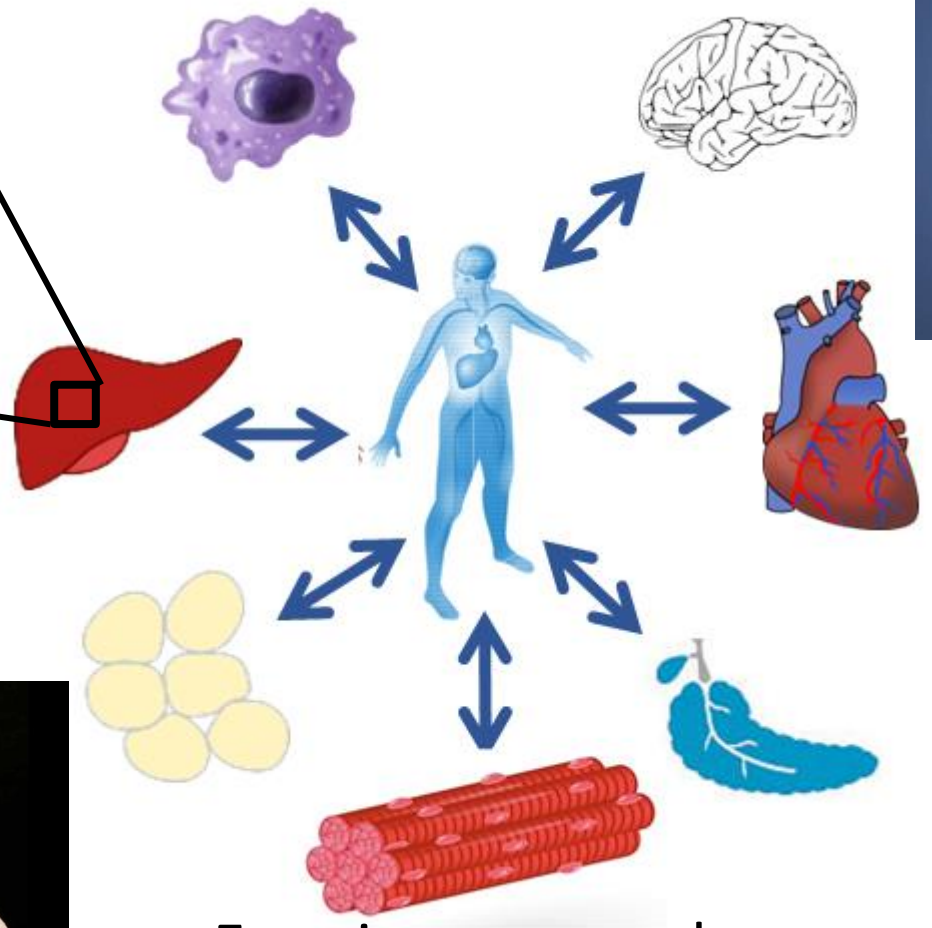


Overview of our digital twins



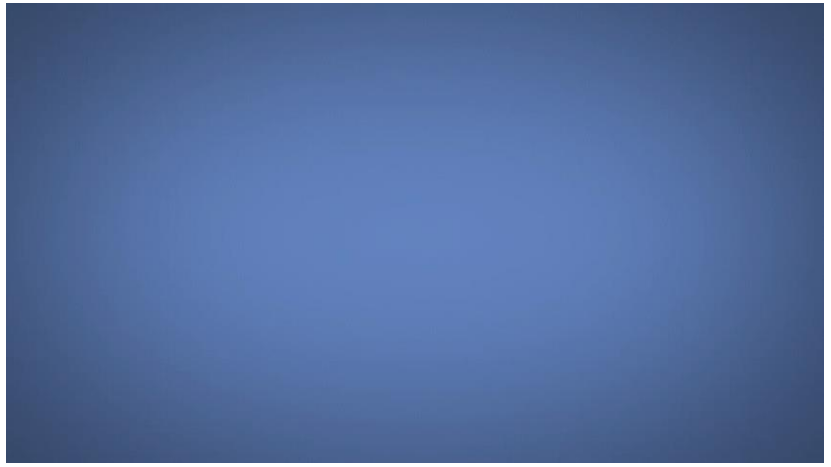
Cellular processes in fat and liver tissue

Immunology and the X-HiDE consortium



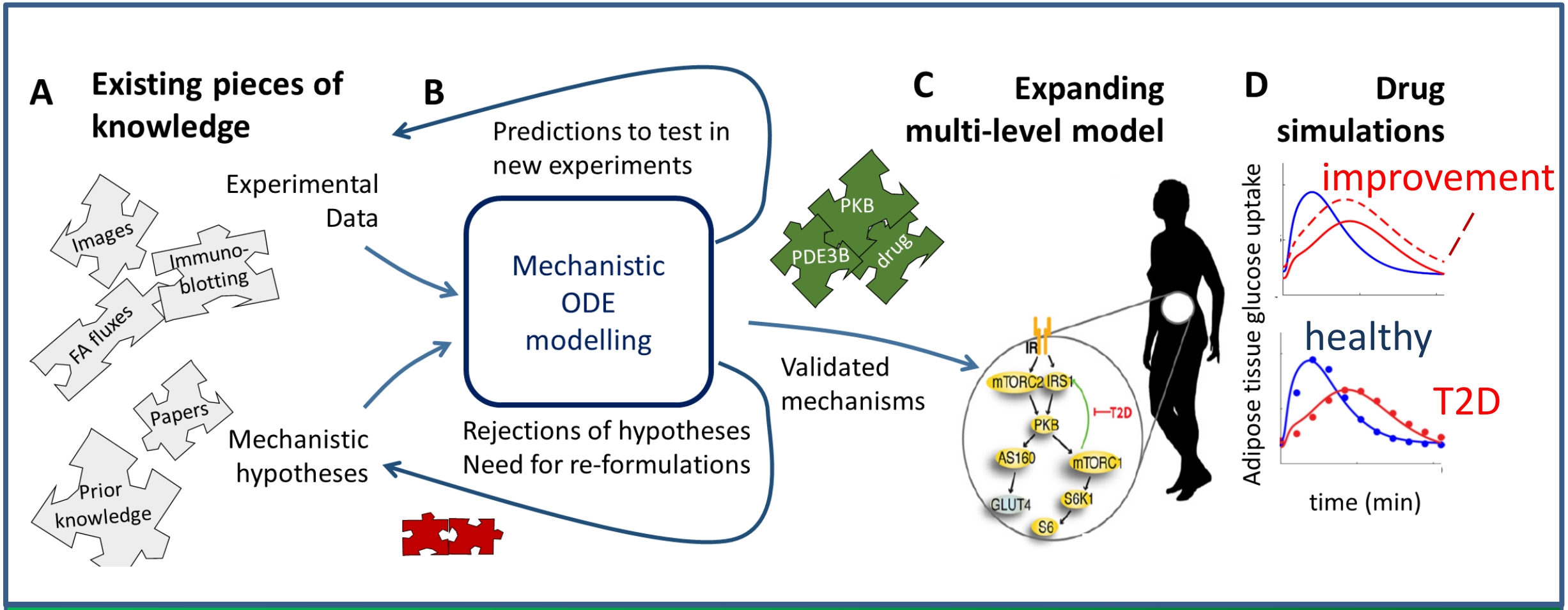
Exercise, yoga and biomechanics

A realistic brain and face – Catalyst project



Blood flow and blood pressure, based on advanced MRI

Systems biology is the art of integrating pieces of knowledge into useful models



Mechanistic insights (systems biology) faster Making a difference (companies, eHealth)

The limitation of only using AI and machine learning: the three generations of eHealth

eHealth 1.0: present data

Clinical data

User data

Show data & communicate with others (no analysis of data)

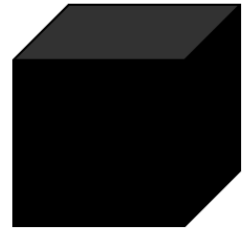
eHealth 2.0: narrow AI & ML

Large clinical studies

Omics

Images

No mechanistic understanding used or gained



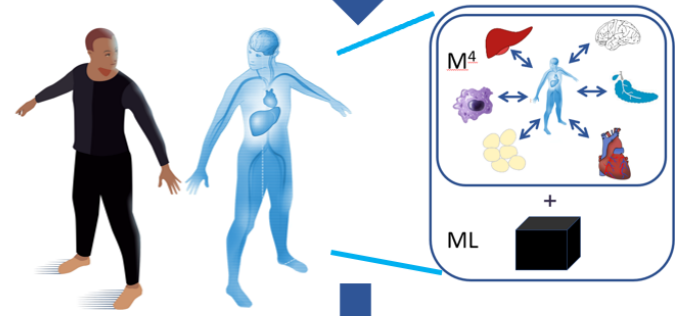
Hard to general underst

Risks, features, & classifications

Generated images

eHealth 3.0: hybrid M^4 & digital twins

All types of data, including new data not originally intended



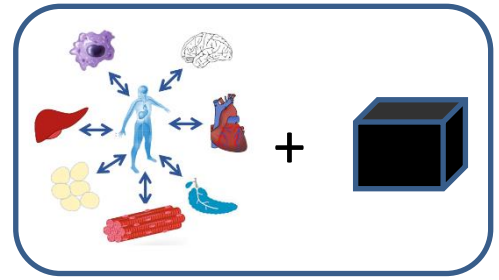
Simulation of user-defined scenarios: mechanistic insights & risks

Systems biology and AI: mechanistic modelling vs bioinformatics and machine learning

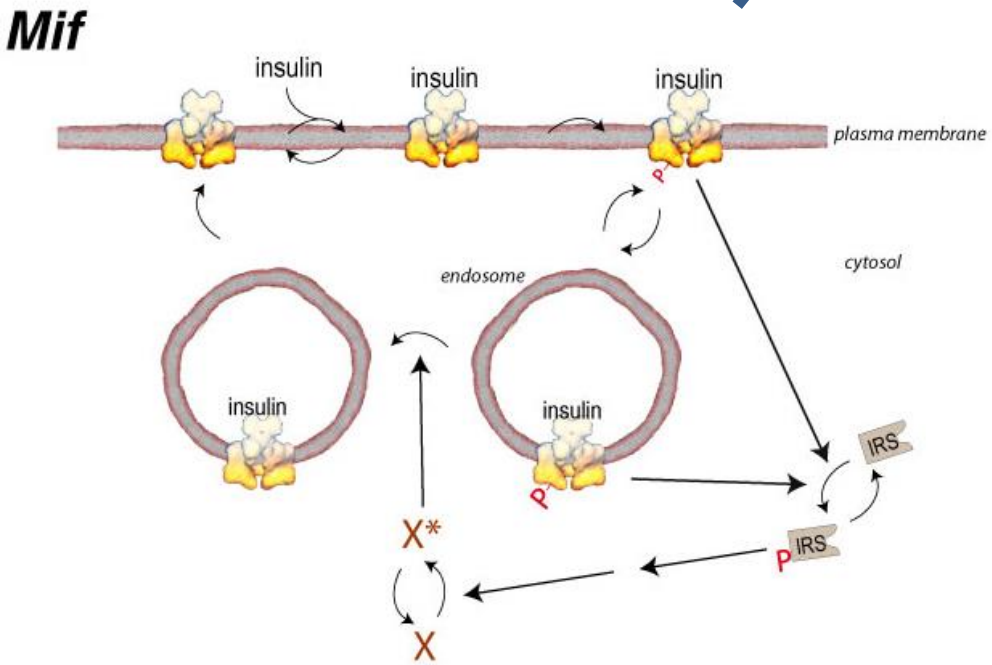
Simulated risk

Simulations & biomarkers

Modules & biomarkers

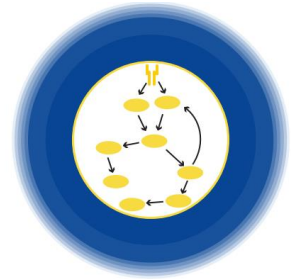


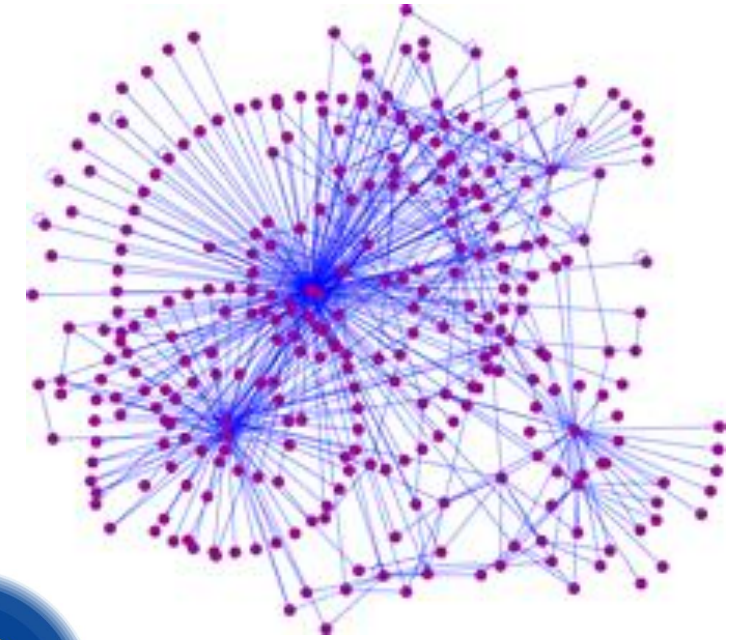
Hybrid digital twins



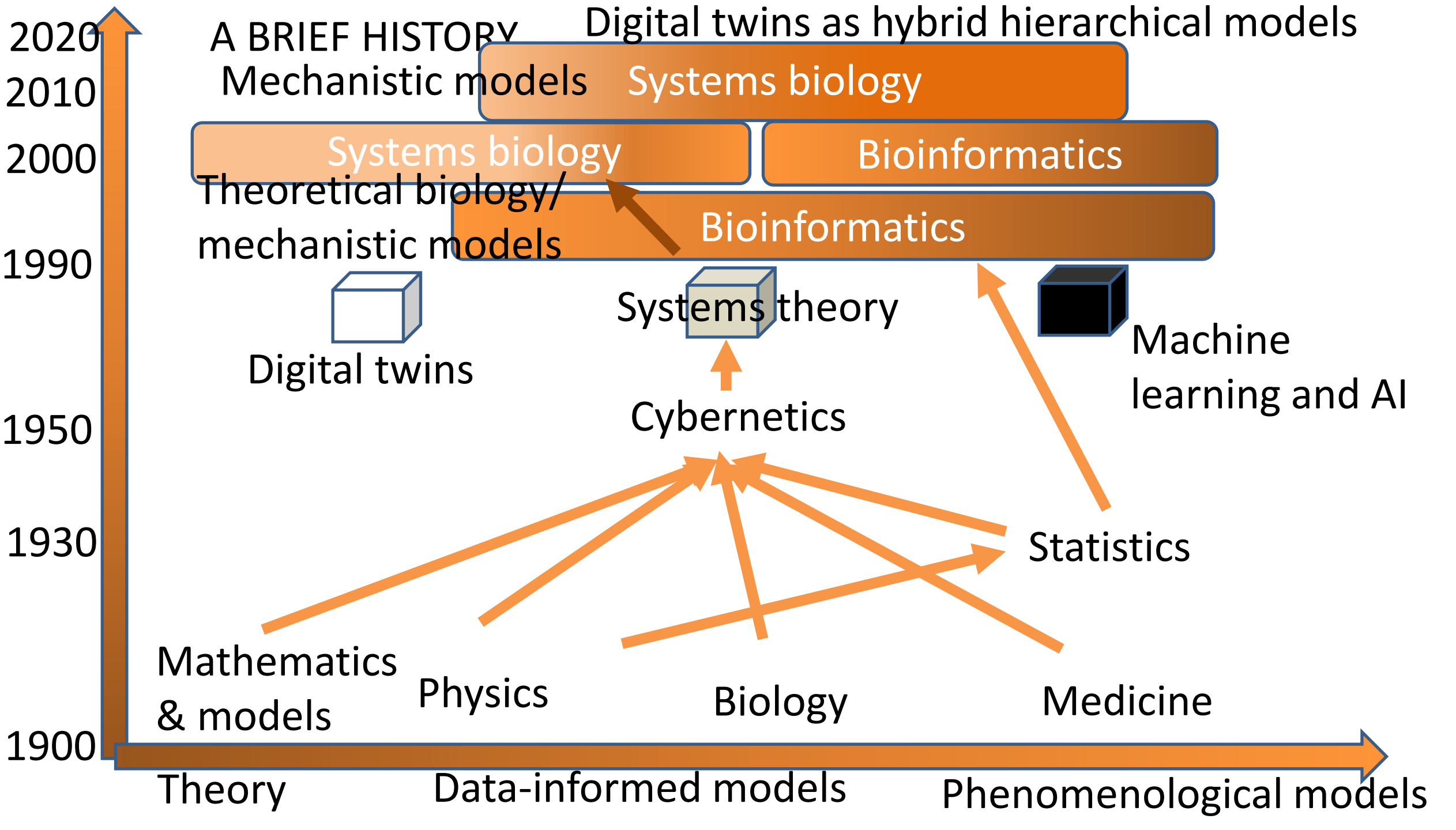
Mechanistic models

Automated modelling to omics-level





Bioinformatics network models


A BRIEF HISTORY
Digital twins as hybrid hierarchical models
2020
2010
2000
1990
1950
1930
1900
Mechanistic models
Systems biology
Systems biology
Bioinformatics
Theoretical biology/
mechanistic models
Bioinformatics
Digital twins
Systems theory
Machine
learning and AI
Cybernetics
Statistics
Mathematics
& models
Physics
Biology
Medicine
Theory
Data-informed models
Phenomenological models

Top-level overview of course

Turning now to the next part: practicalities of the course

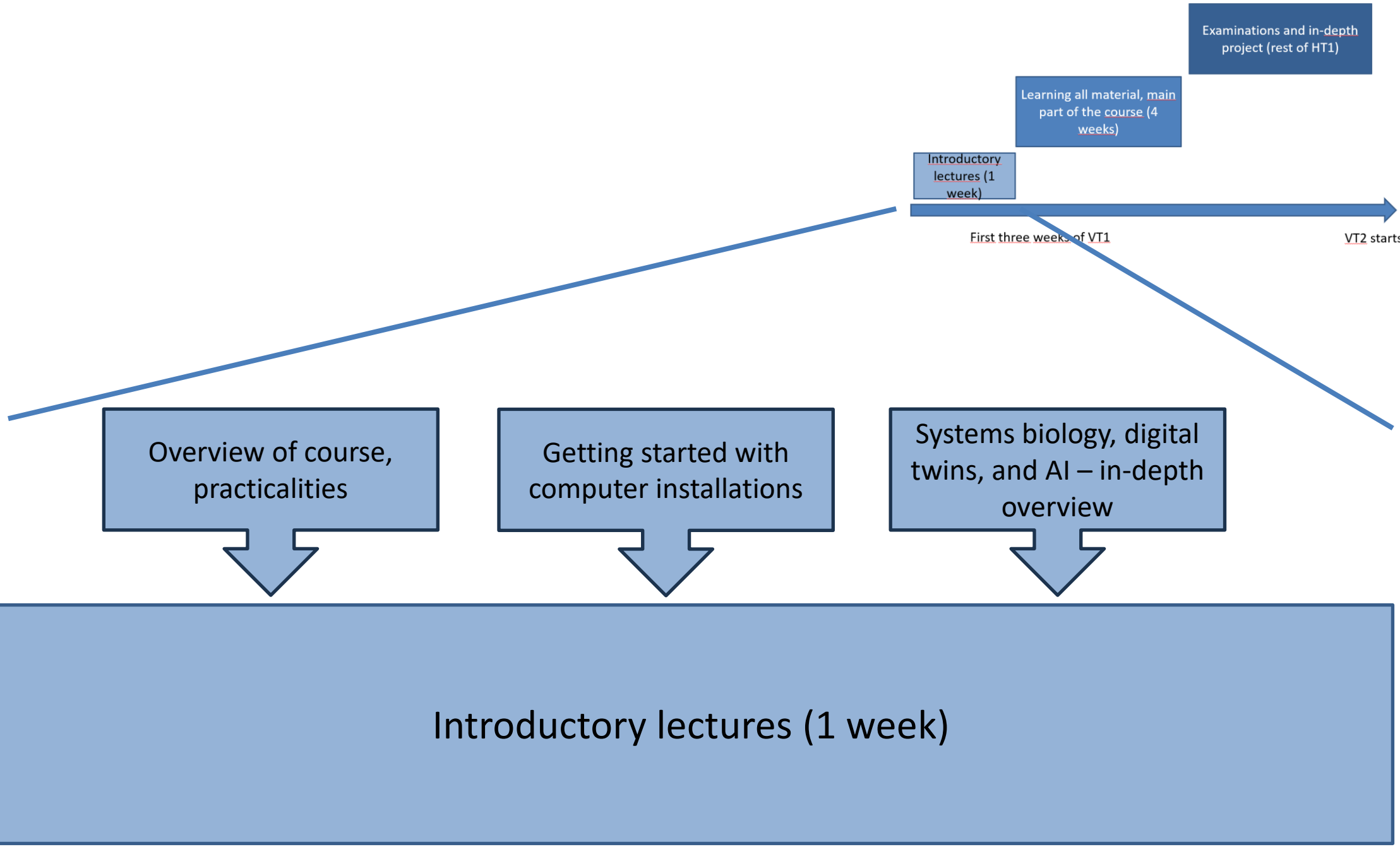
Examinations and in-depth project (rest of HT1)

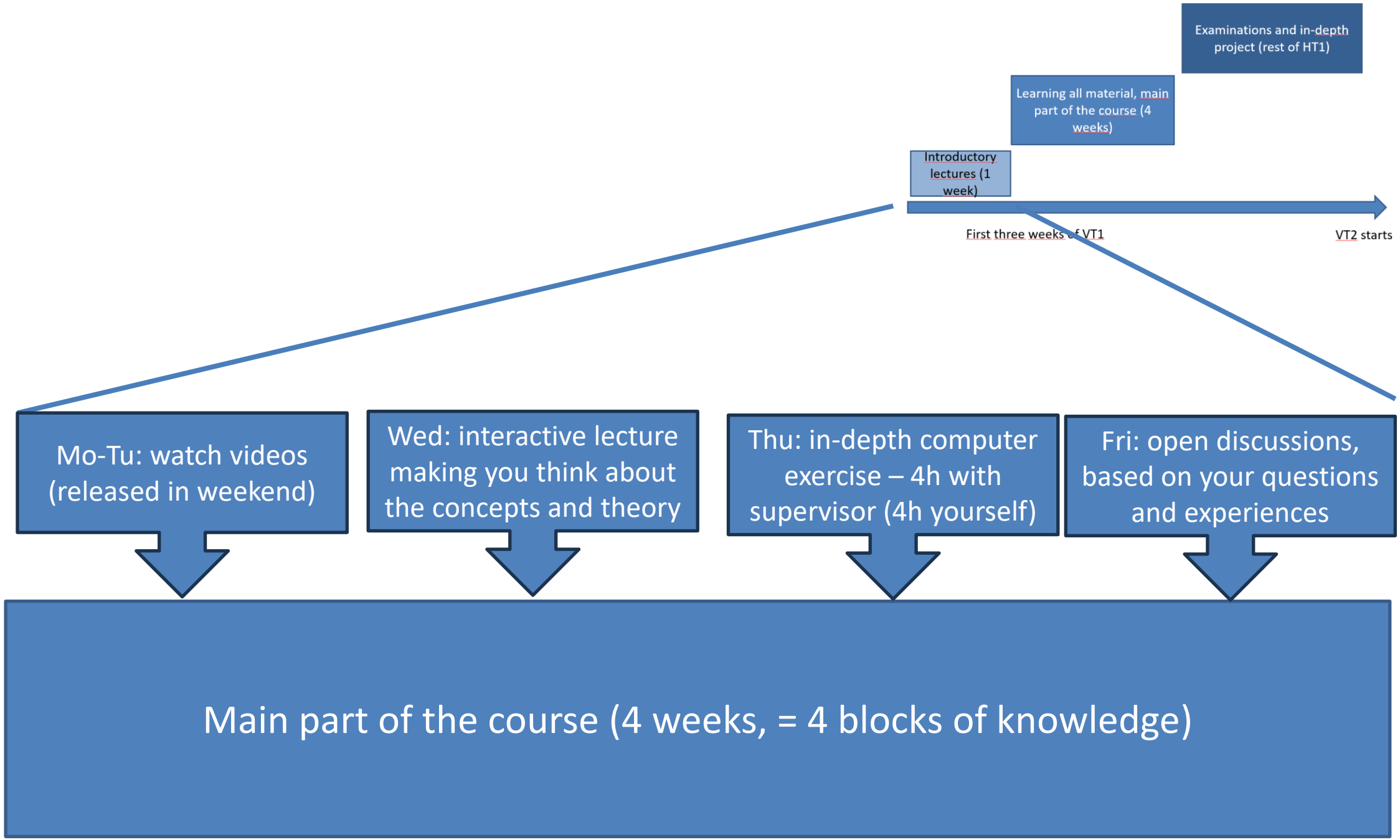
Learning all material, main part of the course (4 weeks)

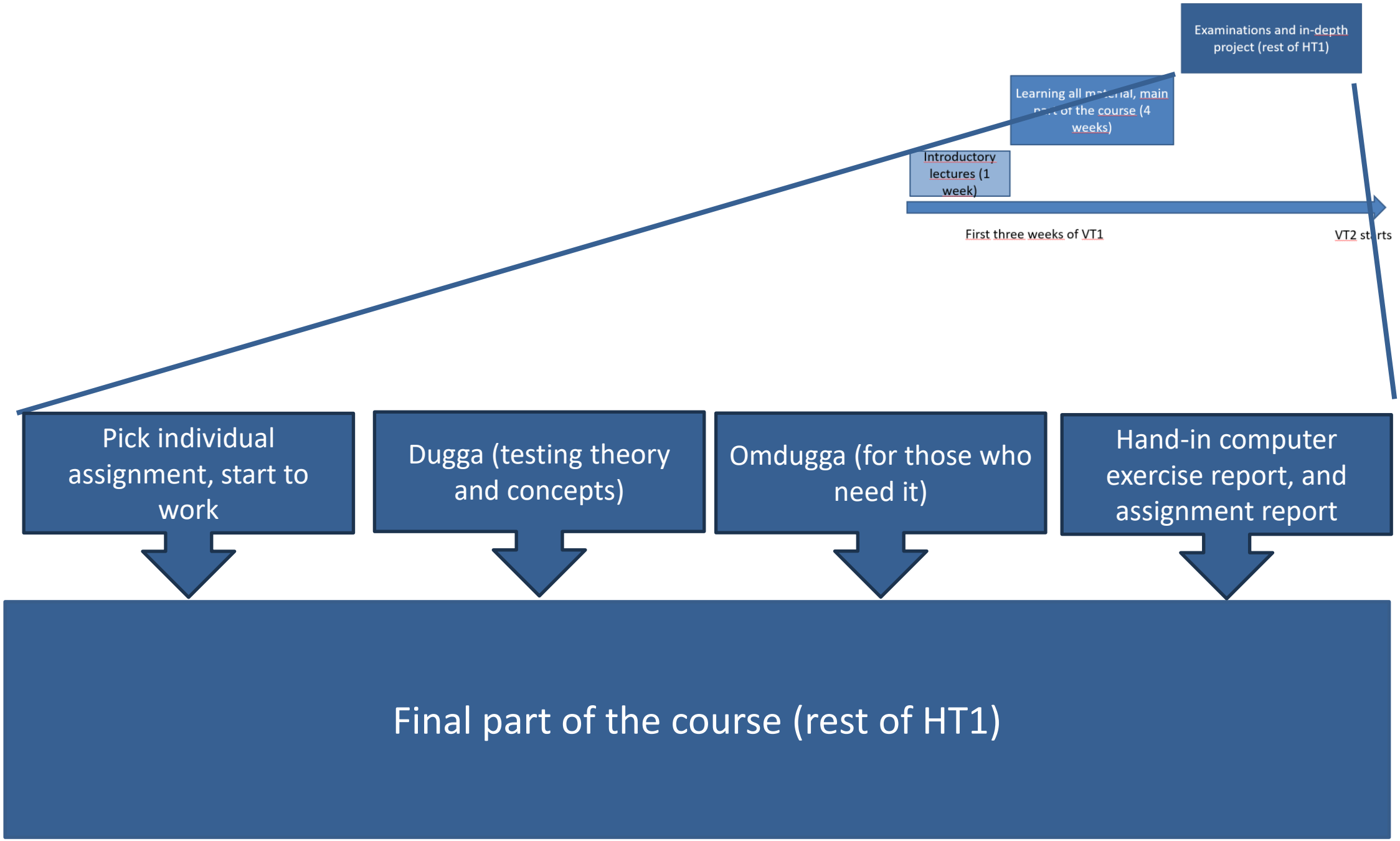
Introductory lectures (1 week)

First three weeks of VT1

VT2 starts


Examinations and in-depth project (rest of HT1)
Learning all material, main part of the course (4 weeks)
Introductory lectures (1 week)
First three weeks of VT1
VT2 starts
Overview of course, practicalities
Getting started with computer installations
Systems biology, digital twins, and AI – in-depth overview
Introductory lectures (1 week)


Examinations and in-depth project (rest of HT1)
Learning all material, main part of the course (4 weeks)
Introductory lectures (1 week)
First three weeks of VT1
VT2 starts
Mo-Tu: watch videos (released in weekend)
Wed: interactive lecture making you think about the concepts and theory
Thu: in-depth computer exercise – 4h with supervisor (4h yourself)
Fri: open discussions, based on your questions and experiences
Main part of the course (4 weeks, = 4 blocks of knowledge)


Examinations and in-depth project (rest of HT1)
Learning all material, main part of the course (4 weeks)
Introductory lectures (1 week)
First three weeks of VT1
VT2 starts
Pick individual assignment, start to work
Dugga (testing theory and concepts)
Omdugga (for those who need it)
Hand-in computer exercise report, and assignment report
Final part of the course (rest of HT1)

The four blocks of material

- Formalisms for model formulation and nonlinear dynamical systems
- Parameter estimation and model uncertainty
- Nonlinear mixed-effects modelling, and applications in drug development and personalized medicine
- Hybrid models, machine learning, and digital twins

Examinations

Turning now to the next part: examinations in the course

1) ***Dugga*** (mini-examination). 6 points per block, i.e 24 points in total. Passed req = 18/24 and at least 2 points in each block.
2) ***Lab report***: one report for all labs. You should answer all questions in the end of the labs
3) ***In-depth project***: oral presentation (ppt or similiar), scripts, and abstract (~250 words)

Overview of systems biology, digital twins, AI and our research group

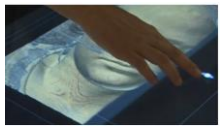
Returning to some inspiration

Sensors, Health Care Records, etc

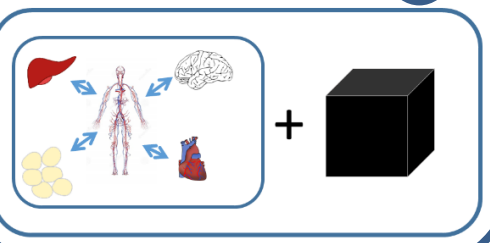
All these are (former) TB*-students!

Blood flow and heart, pressures, vol, heart rate *Casas 2017, 2018*

MeDigiT Interface

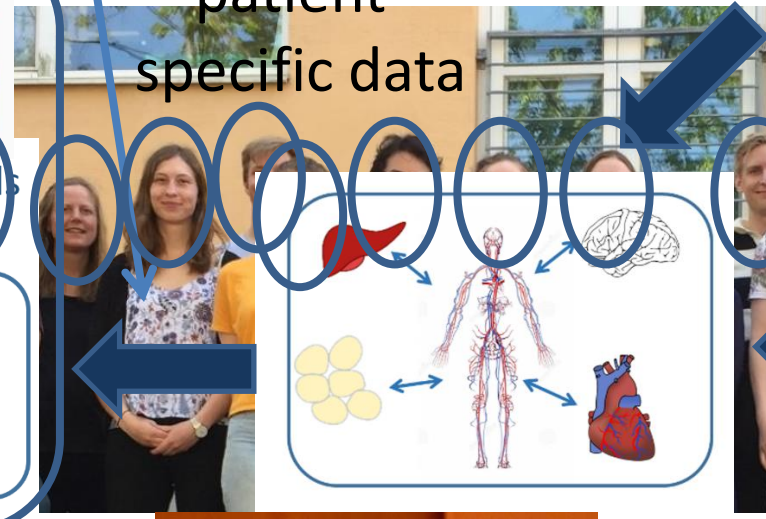


useful personalized models physiological AI



Digital Twin (hybrid model)

patient-specific data



Liver function, uptake, steatosis & NASH *Forsgren 2014, 2017, 2019*

Brain neurovascular coupling *Lundengård 2016, Sten 2017, 2020*

Fat tissue, glucose uptake, insulin resistance *Brännmark 2010, 2013, Nyman 2014, 2016*

Muscle metabolism *Cedersund 2006*

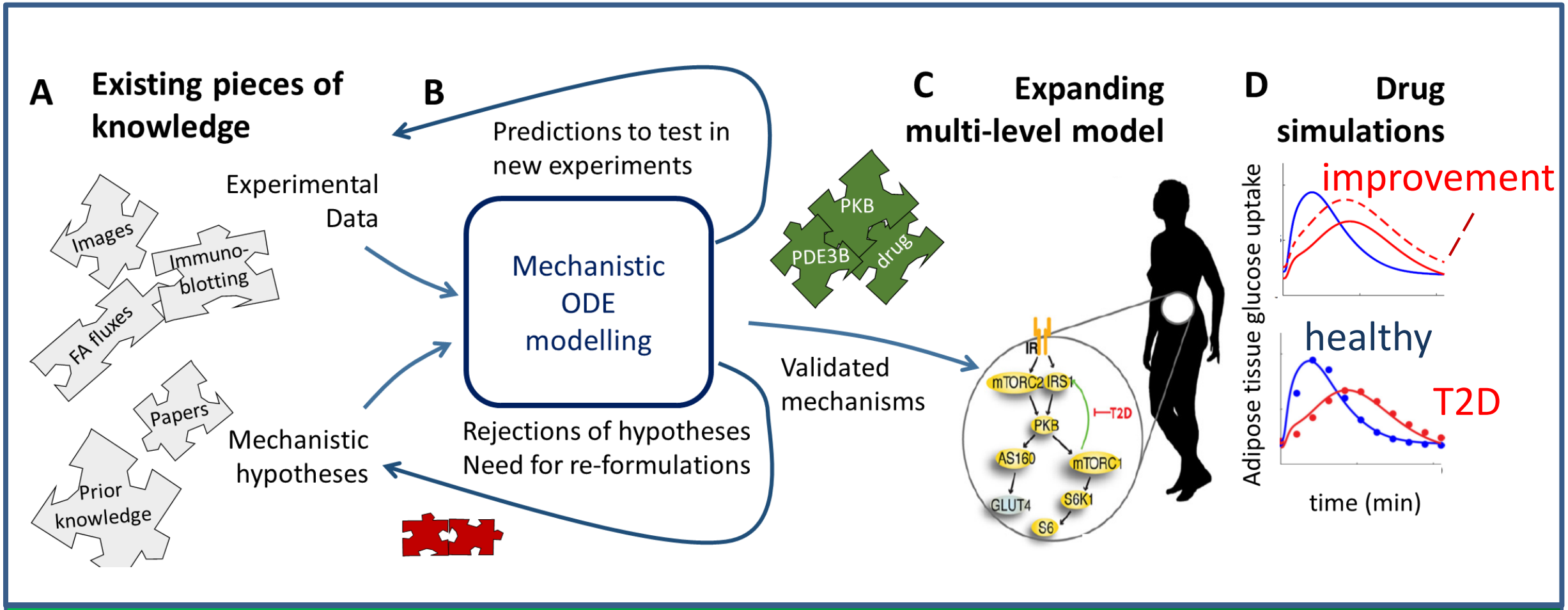
Beta cell, metabolism, oscillation and insulin secretion *Cedersund 2001, Palmér 2014*

Immunology *Magnusson 2017, Nyman 2020*

SUND SOUND MEDICAL DECISIONS

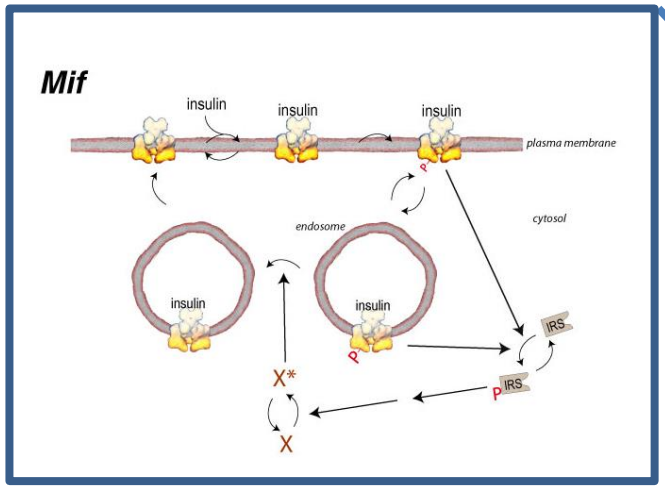
Gunnar Cedersund, LiU

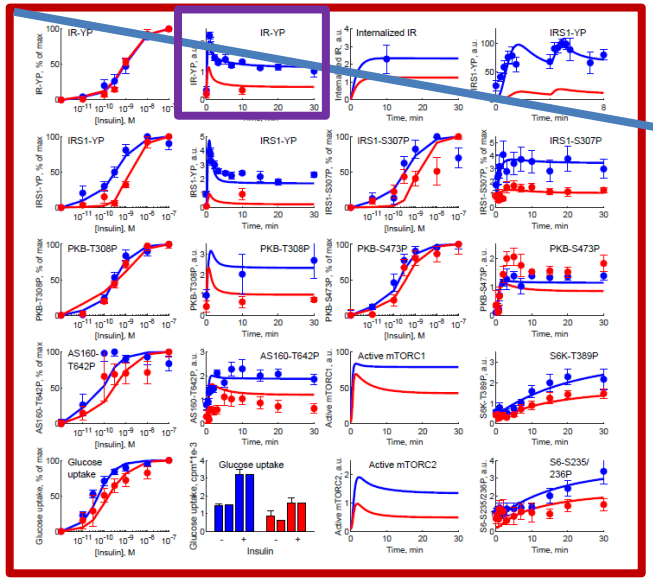
From mechanistic knowledge to end-usage in 3 steps: 1) test sub-system 2) integrate 3) use



Mechanistic insights (systems biology) faster Making a difference (companies, eHealth)

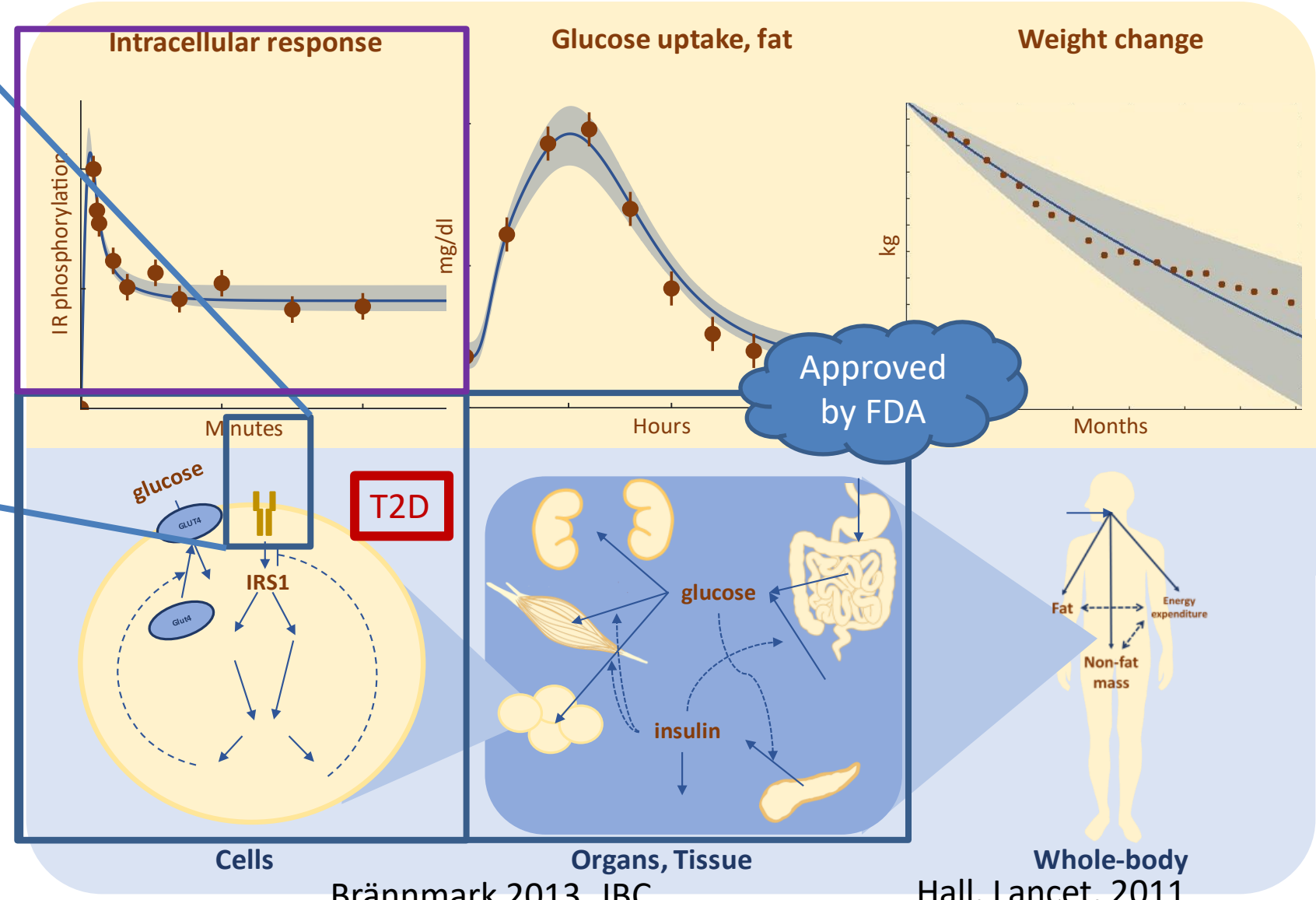
The story of our original multi-level multi-timescale model





Data

Model



Brännmark 2010, JBC

Brännmark 2013, JBC

Nyman 2011, JBC

Hall, Lancet, 2011

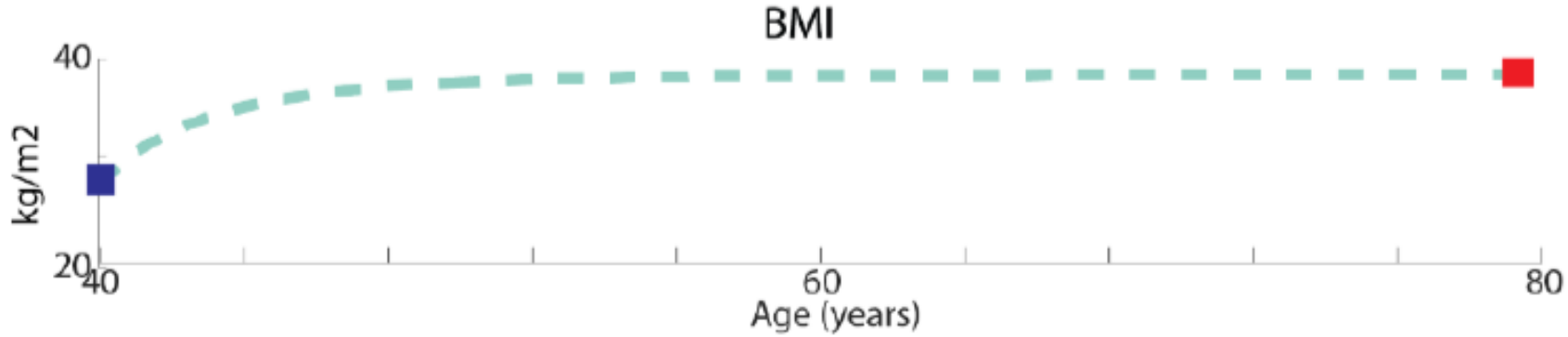
Nyman and Herrgårdh, *in ms*

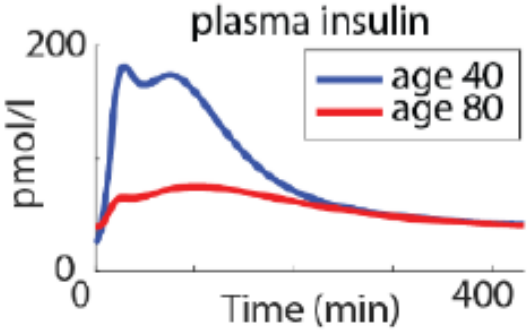
Application 3-4, health conversation and teaching

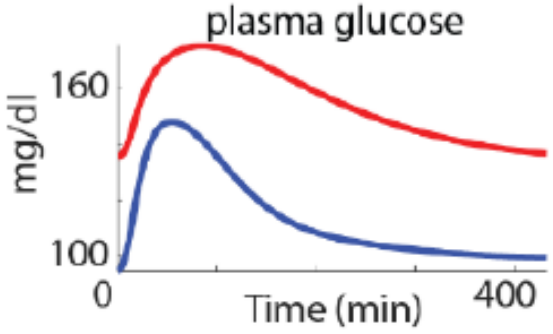
Scenario 1:

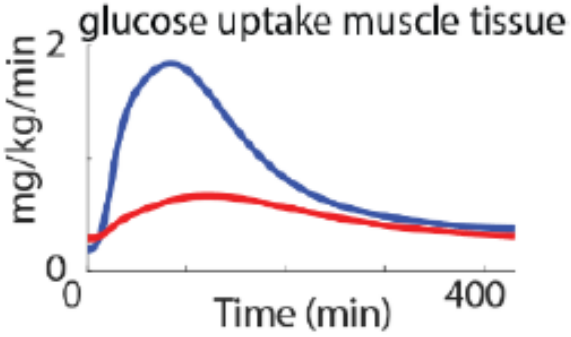
High calorie diet

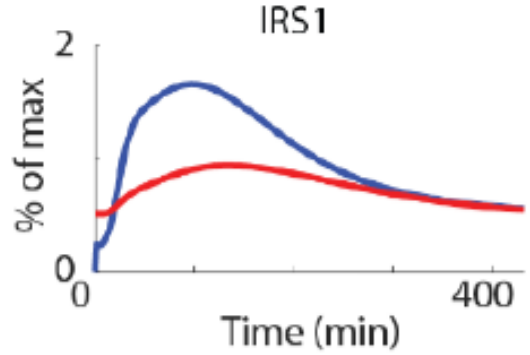
+ 400 kcal/day

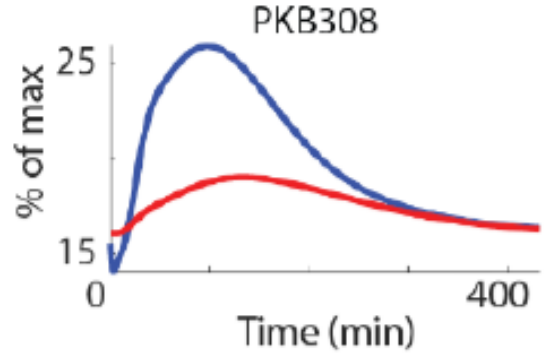


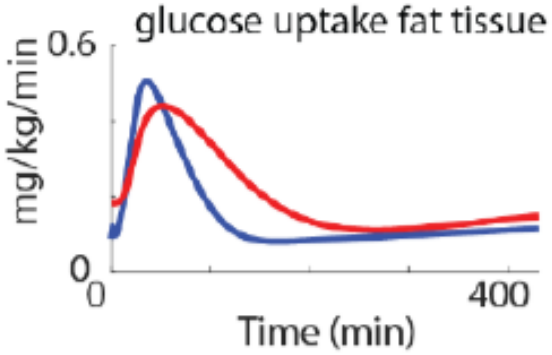










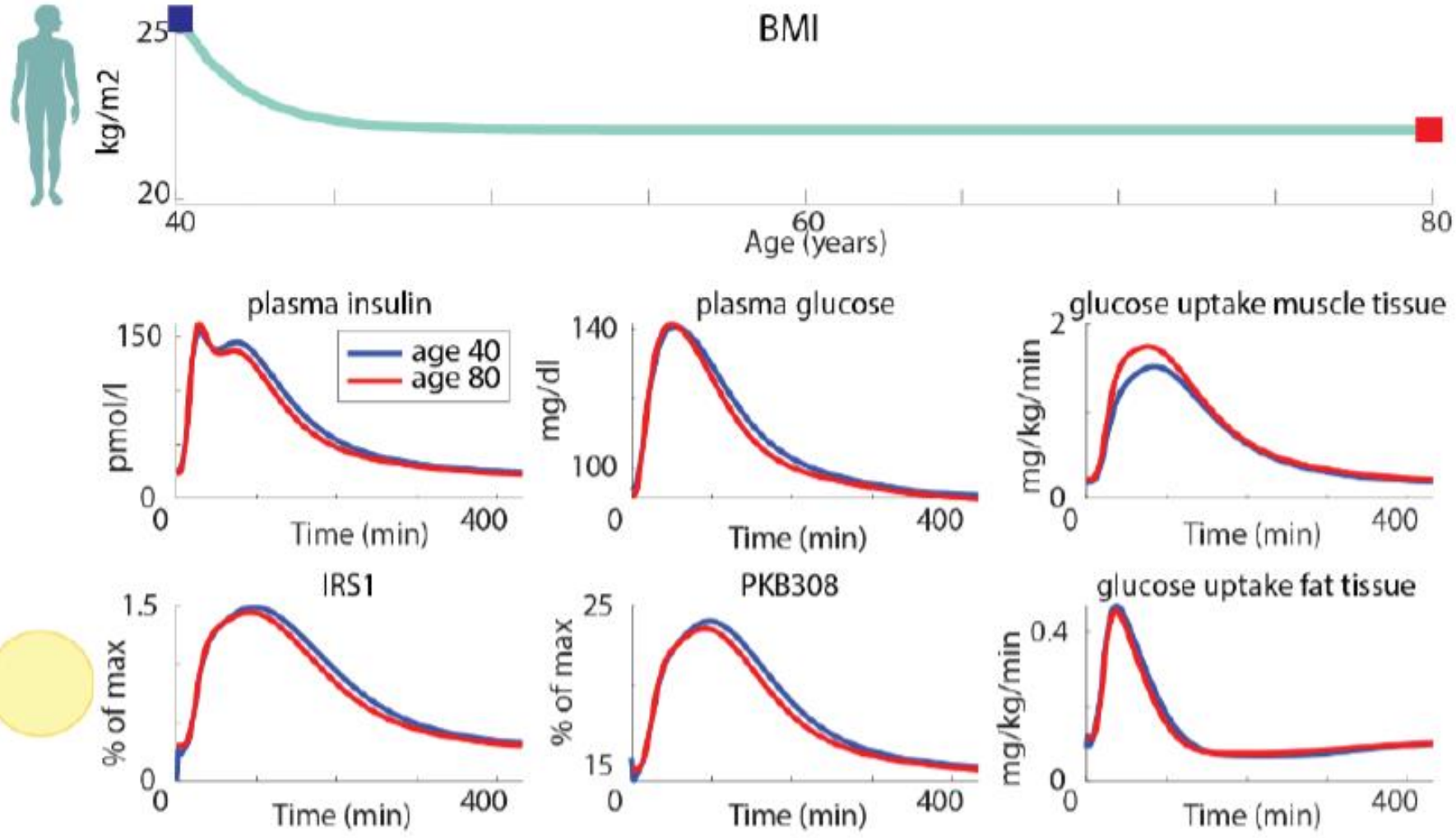


Application 3-4, health conversation and teaching

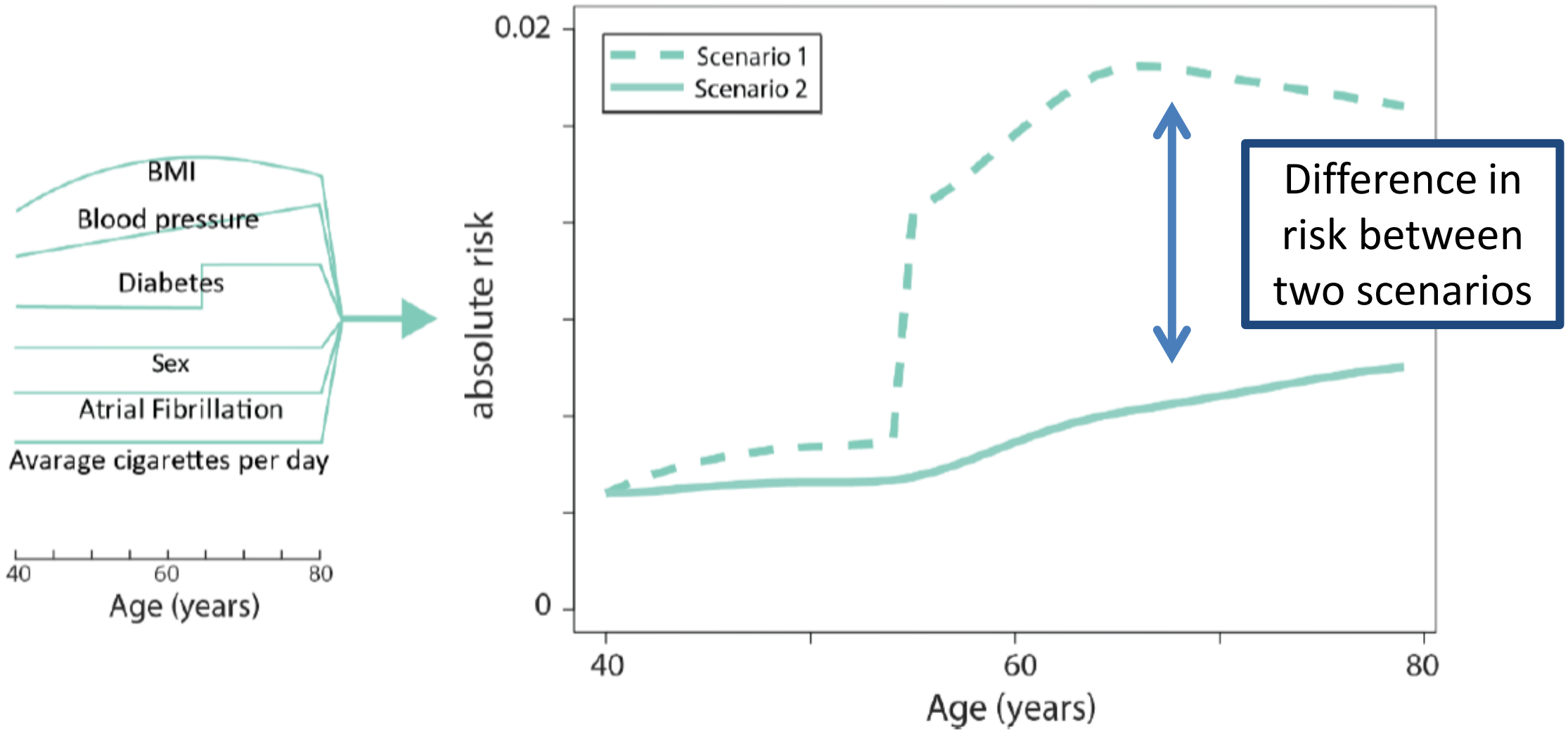
Scenario 2:

Low calorie diet
+ exercise

- 100 kcal/day



Comparison of corresponding risk between the two scenarios



Digital Twin DigitalTwinFrontend

Digital Twin | **Schedule** | **Variables**

Info

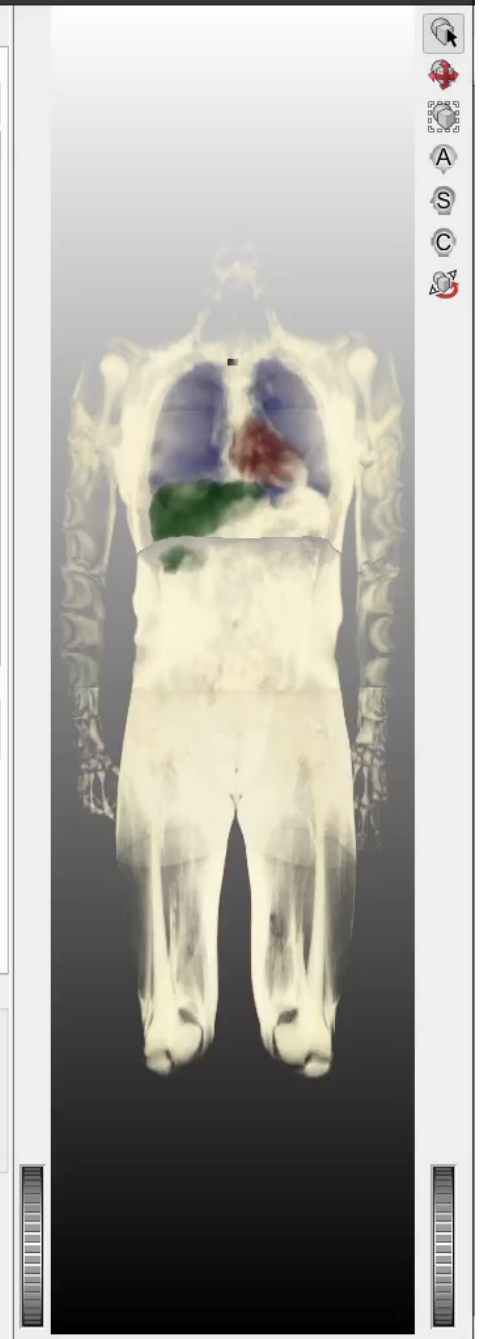
Here you find all info about the digital twin.

Digital twin attributes

Name: Gunnar
Age: 44.0
Height: 183.0
Diabetes: No
Weight: 82.0
Fat percentage (of total weight): 15.0
Sex: Man
Cigarettes per day: 0.0
Atrial fibrillation (before stroke): No
Systolic blood pressure: 145.0
Diastolic blood pressure: 110.0
Time of lowest cortisol levels (in minutes from midnight): 359.0
Time of highest cortisol levels (in minutes from midnight): 1380.0
Fasting glucose (mM): 5.5
Fasting insulin (pM): 150
Cholesterol levels (mg/dl): 178

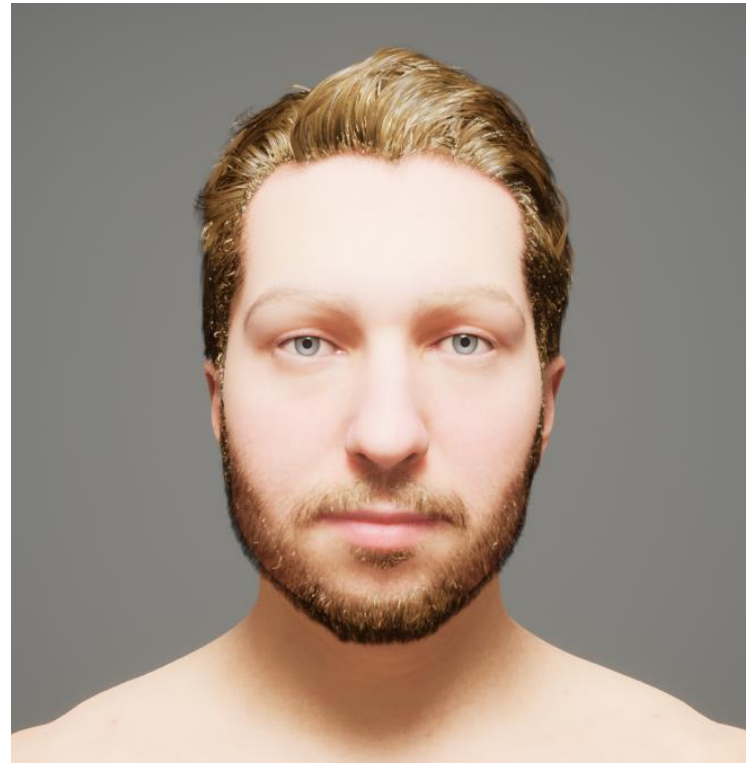
Modify twin | Switch twin

Run simulation | show variable info | Reset simulation



Patient Avatars with Metahuman

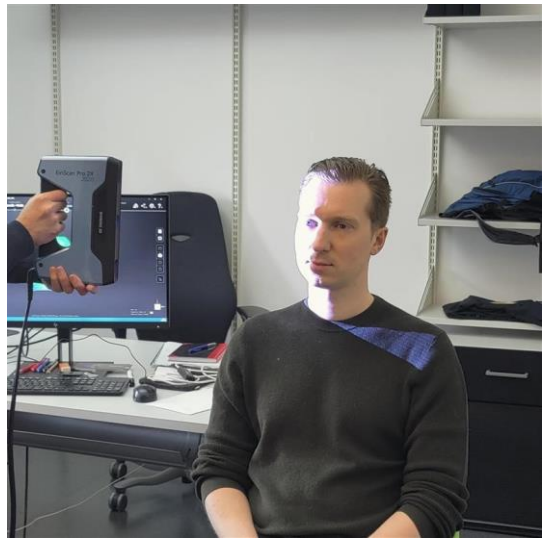
- Free, easy to use tech for creating custom human avatars
- Accessable through browser, no need for powerful computer
- Add into Unreal Engine, comes fully rigged for animation

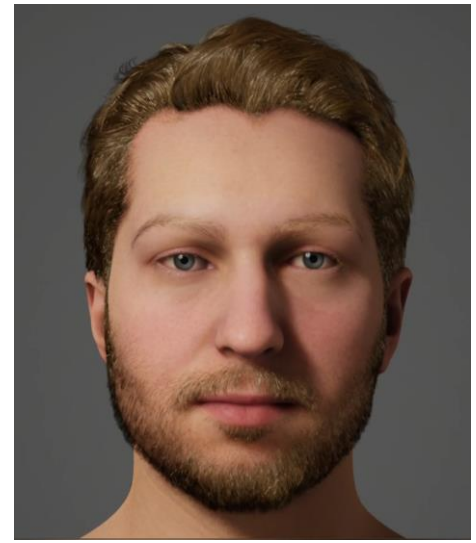


Herrgårdh et al, bioRxiv 2022, *submitted*

Face Scan Mesh to Metahuman

- Face scan -> Geometry -> Conversion -> Body Features

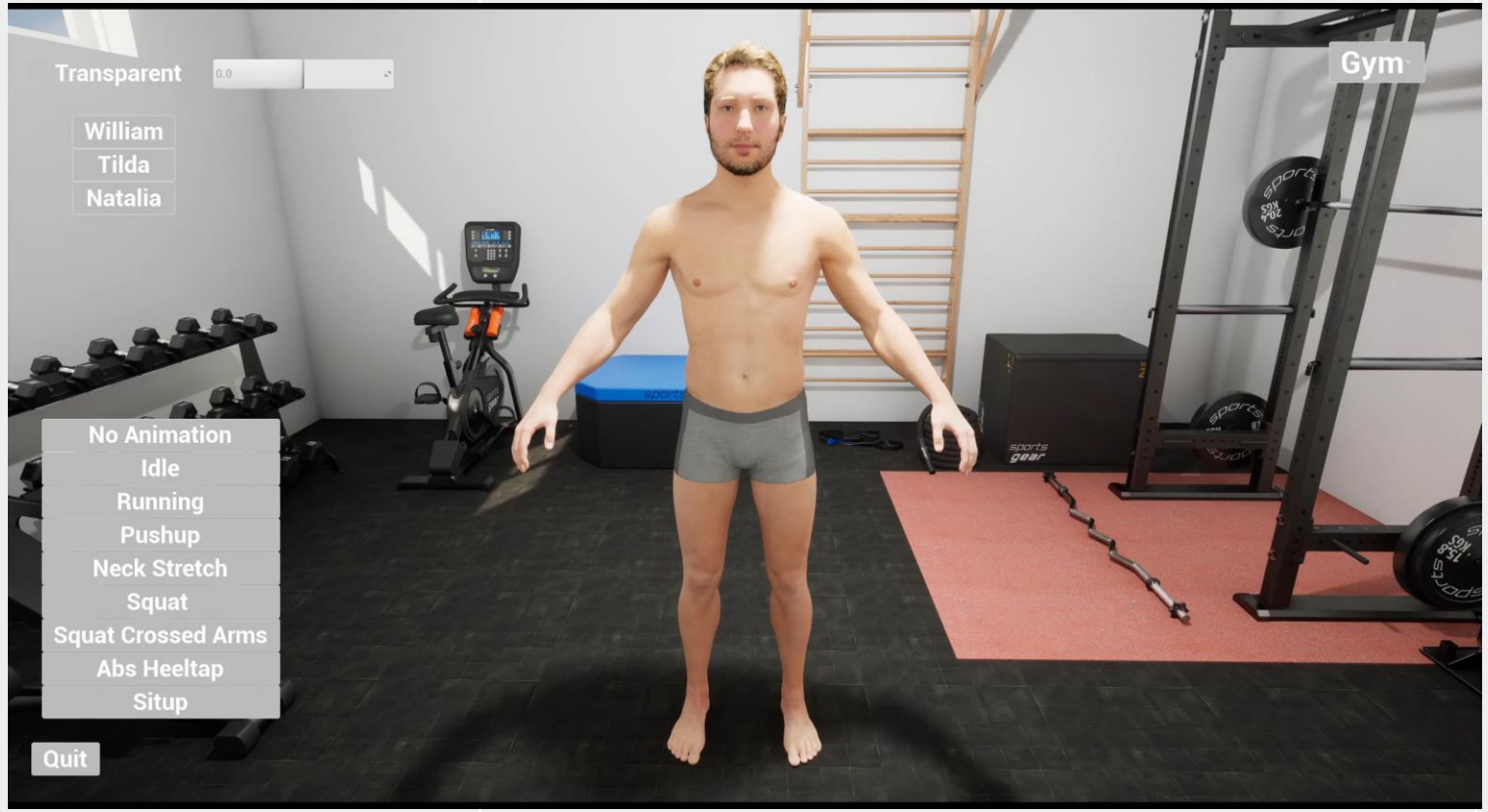




Herrgårdh et al, bioRxiv 2022, *submitted*

Your Metahuman in the app

- The patient customize their Metahumans, based on the face scan, to make it look like themself
- We import it into the to application
- In the final application, patient can only access themself, data is protected

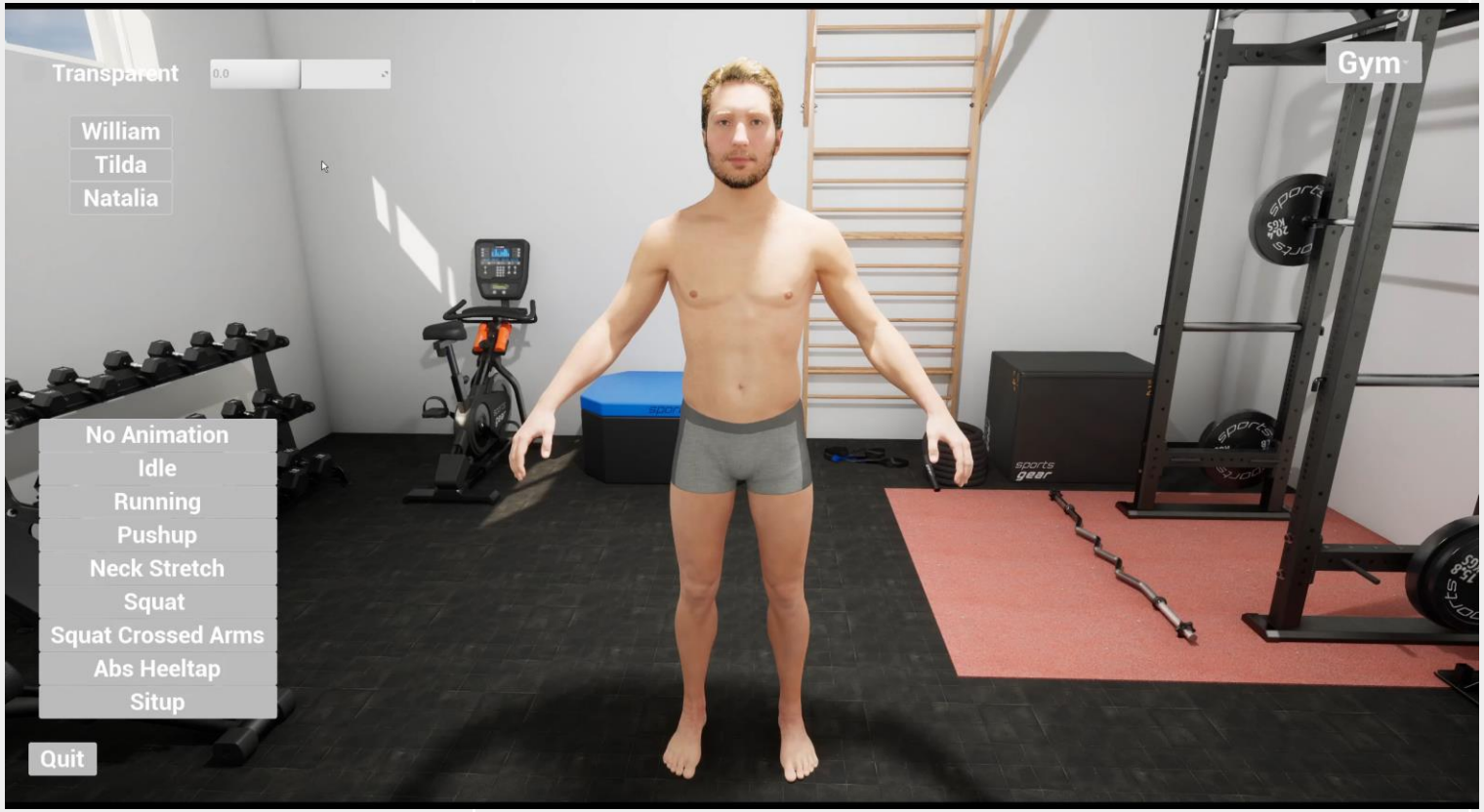


InfraVis

Herrgårdh et al, bioRxiv 2022, *submitted*

Weight Adjustment

- Morph body to different weights
- Connected to simulations
  - Diet
  - Exercise
- Show progress over time on your body

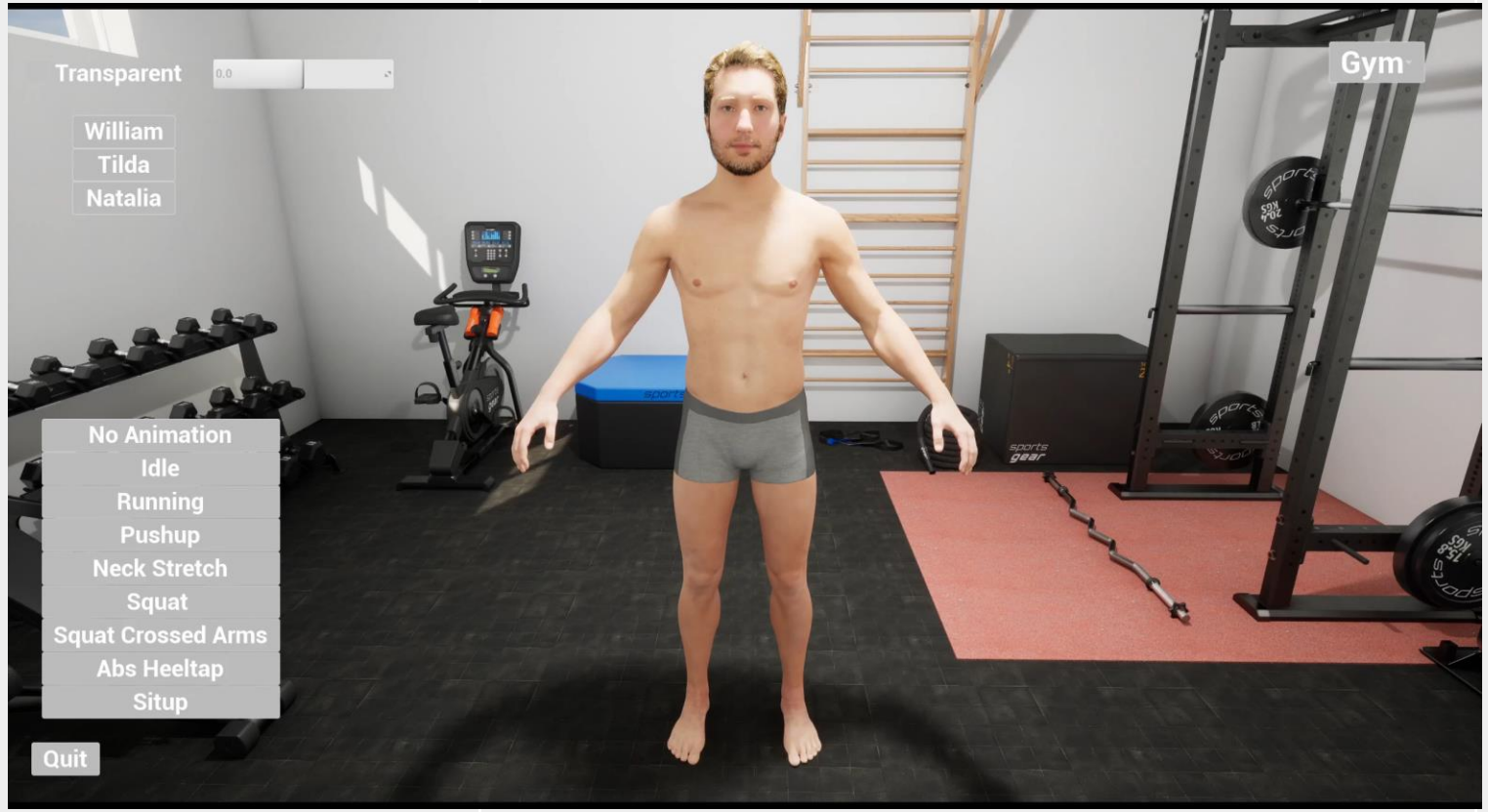


InfraVis

Herrgårdh et al, bioRxiv 2022, *submitted*

Animations

- Play animations on the avatar
- Show yourself performing different motions
  - Work out
  - Rehab
  - Show potential progress if done correctly
- Goal is to record motion capture with medical professionals
  - Stroke rehab exercises



InfraVis

Herrgårdh et al, bioRxiv 2022, *submitted*

Transparent Mode

- Inspection mode, where you can look closer at organs
- Select organs to get information from back end simulations
- Interface to understand what happens in the body
  - Heart during exercise
  - Liver fat based on diet

InfraVis

Herrgårdh et al, bioRxiv 2022, *submitted*

Changing Context

- Allows for different environments
- Contextualize the data that you are looking at
  - Exercise at gym
  - Medical examination at the hospital

InfraVis

Herrgårdh et al, bioRxiv 2022, *submitted*

Pixel Streaming

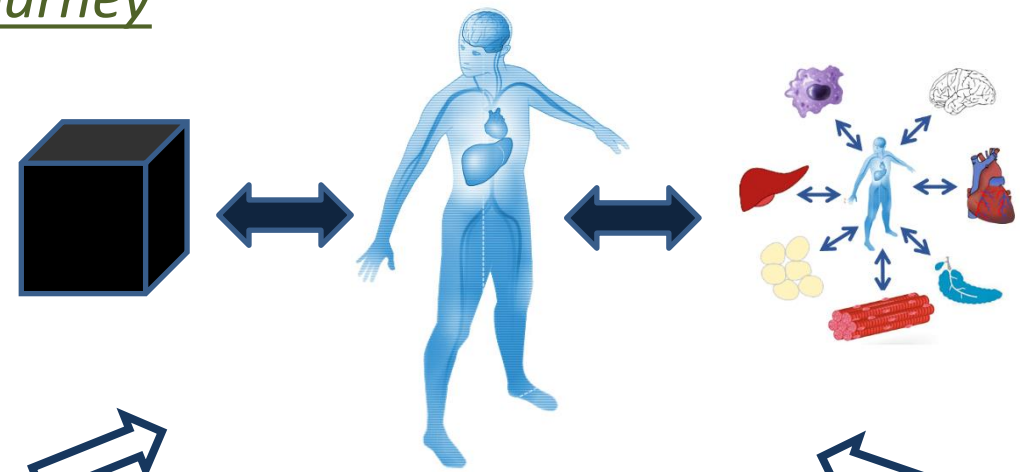
- Pixel Streaming -> WebRTC -> browser or application
- Run avatar program on powerful computer, view and interact in browser or in your phone using a web connection

Herrgårdh et al, bioRxiv 2022, *submitted*

Digital twin benefits – different perspectives

Quick overview of status
Allows for digging deeper
Simulations of scenarios
Tailored treatments
Better communication
Use throughout your entire health journey

Better understanding of own health, and *why* a specific diet is suggested
Integrate all their own data
In charge of their own care
Personalized advice from an eHealth coach that *follows you throughout life*



Big clinical studies:
UKBIOBANK, SCAPIS,
hospital databases, etc

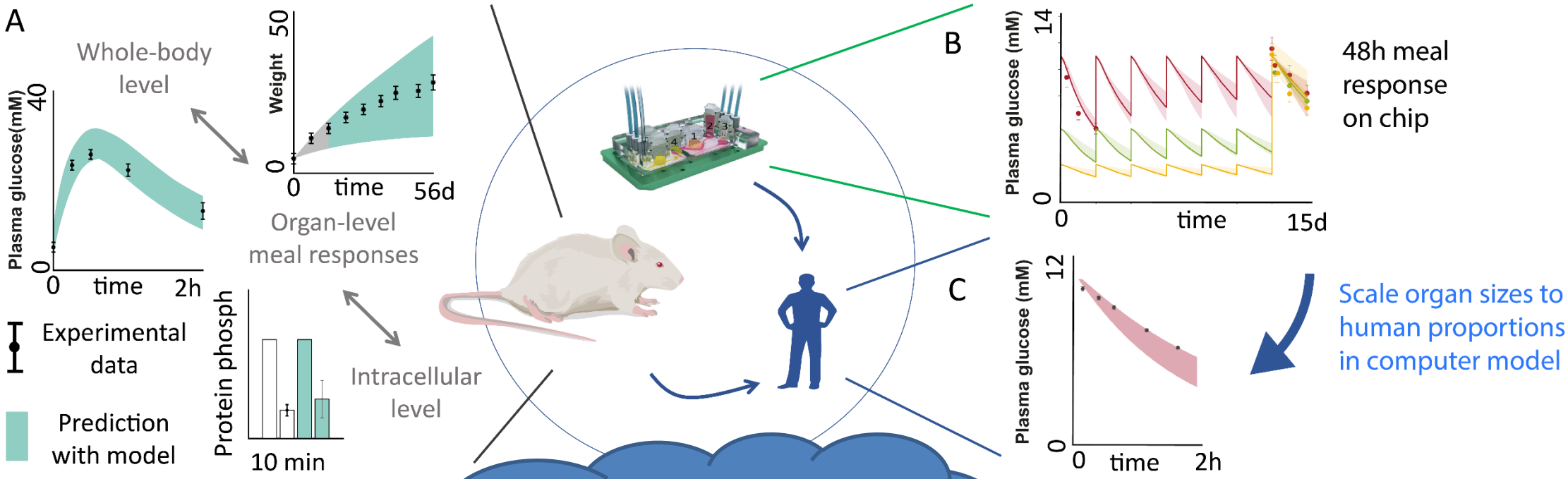
Sociodemographics,
other risk factors

multi-omics, images

Mechanistic knowledge,
”regular papers”

EHR, personal sensor data,
activity clocks, time-series

Translation from organs-on-a-chip and mice to humans using mathematical models



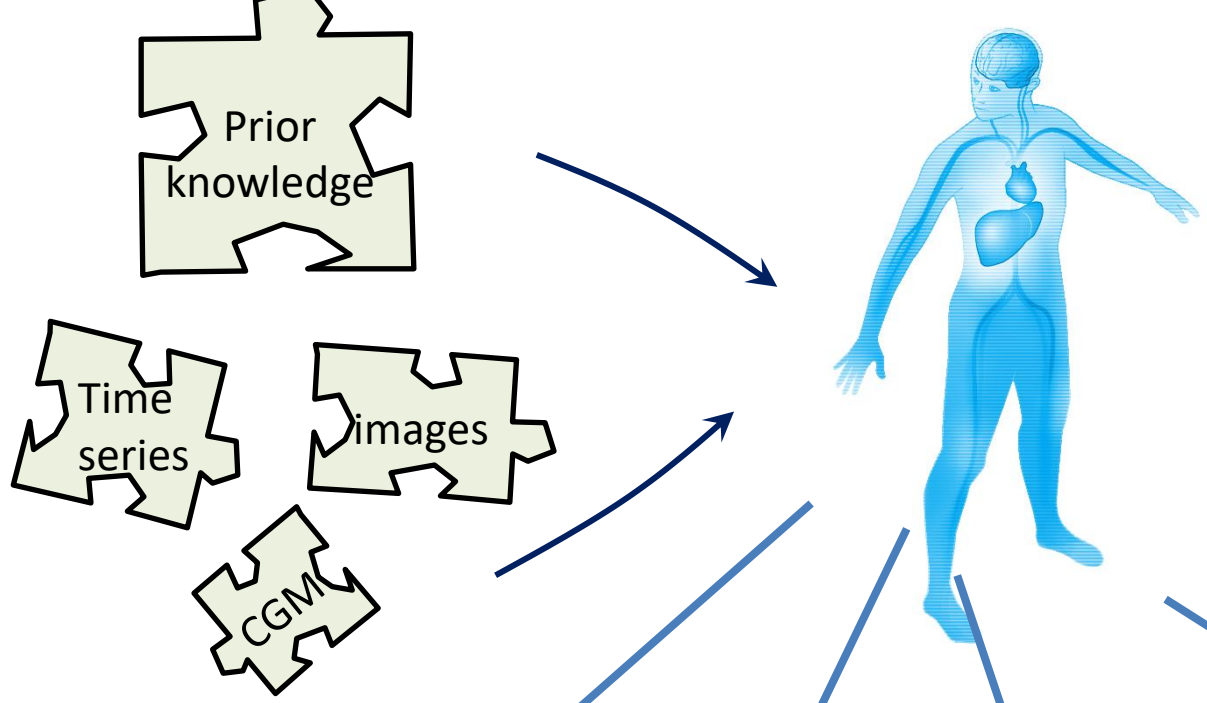
This is a basis for a new type of knowledge-driven drug development, potentially saving years and earning billions of SEK per new drug

Bergqvist et al, JBC, 2017
Simonsson et al, bioRxiv, 2021

Bauer et al, Sci Rep, 2017
Casas et al, bioRxiv, 2021

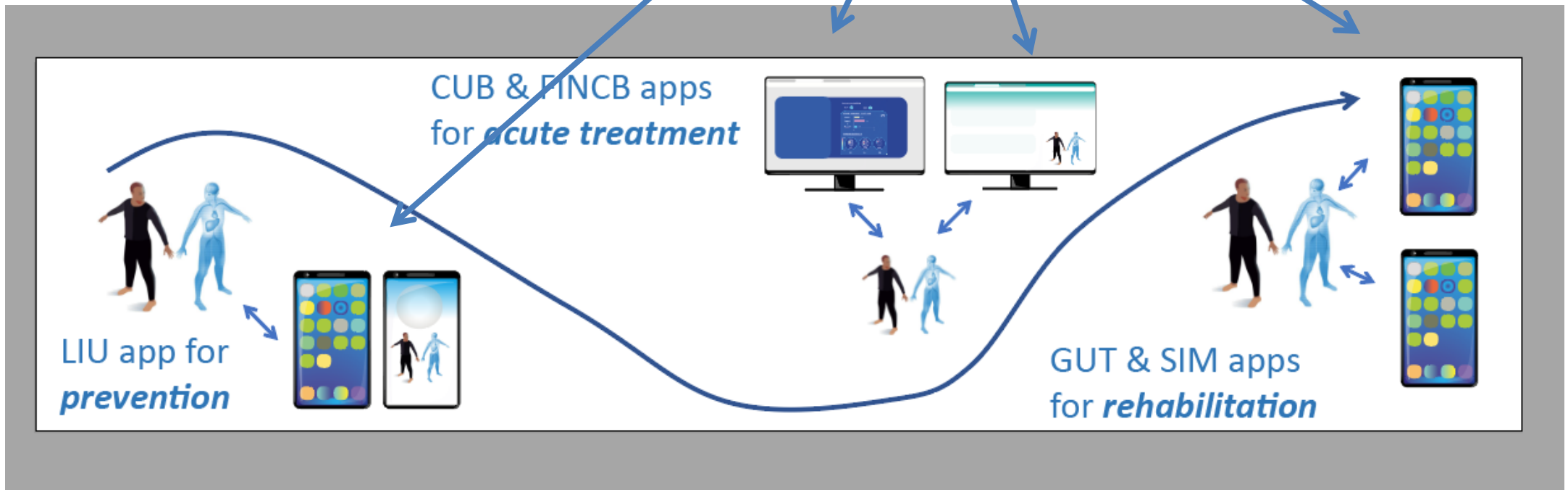
AstraZeneca

Up until now:

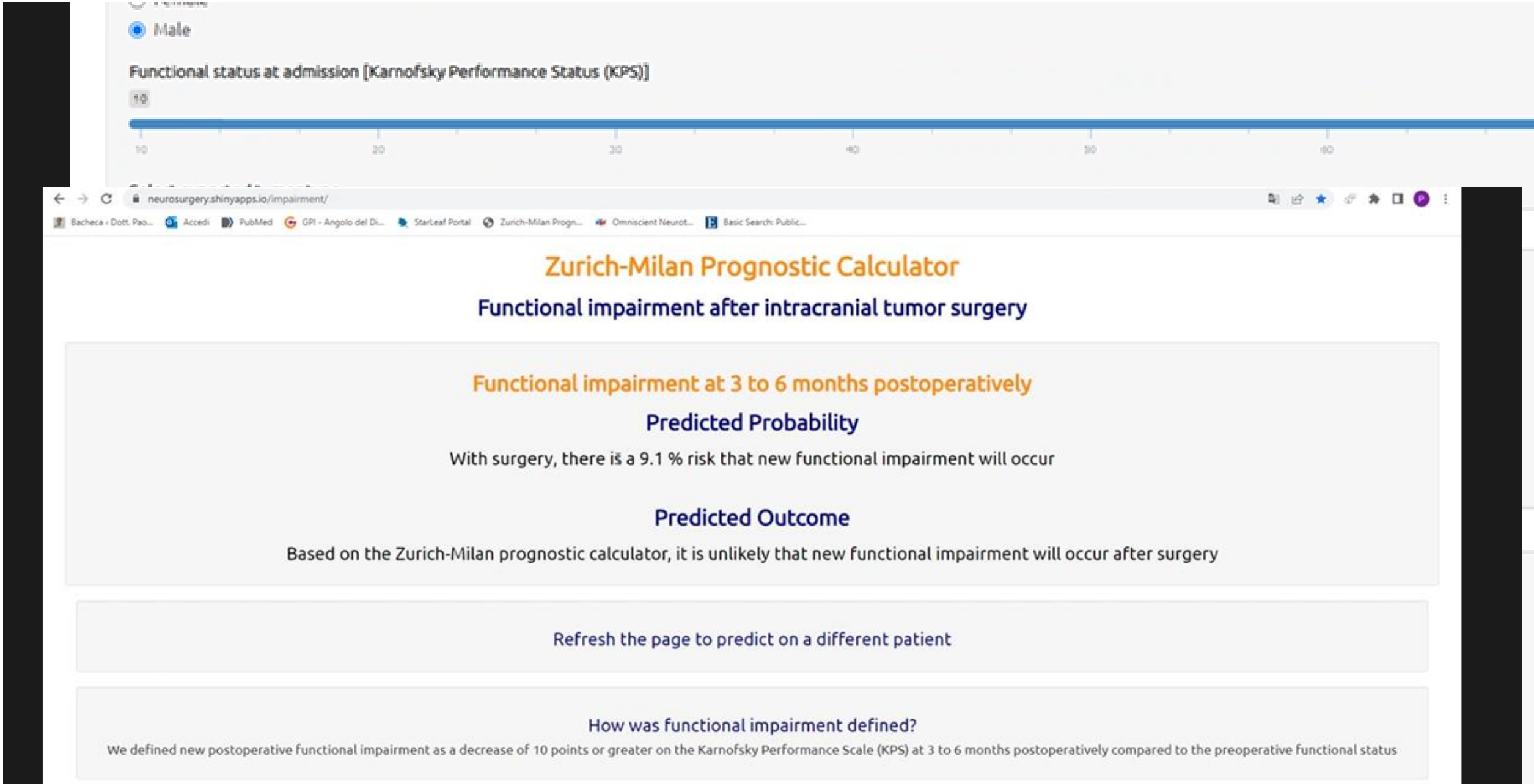


STRATIF-AI – a new 65 MSEK EU project coordinated by us

New vision:

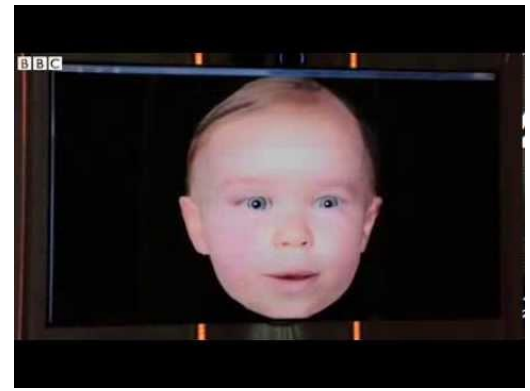


Zurich-Milan Prognostic Calculator for Stroke Surgery, STRATIF-AI project



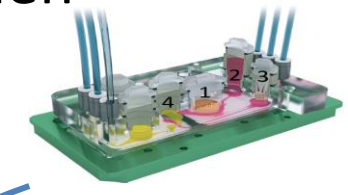
Summary and long-term vision: *a personalized patient-centered interconnected healthcare system*

birth



New cells when needed

First donation of cells



first data

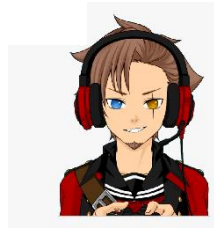
Experiments on your own cells in a little ”mini-you”

Translation of results to your own digital twin

Digital twin

Addition of new data

Usage throughout your Patient Journey



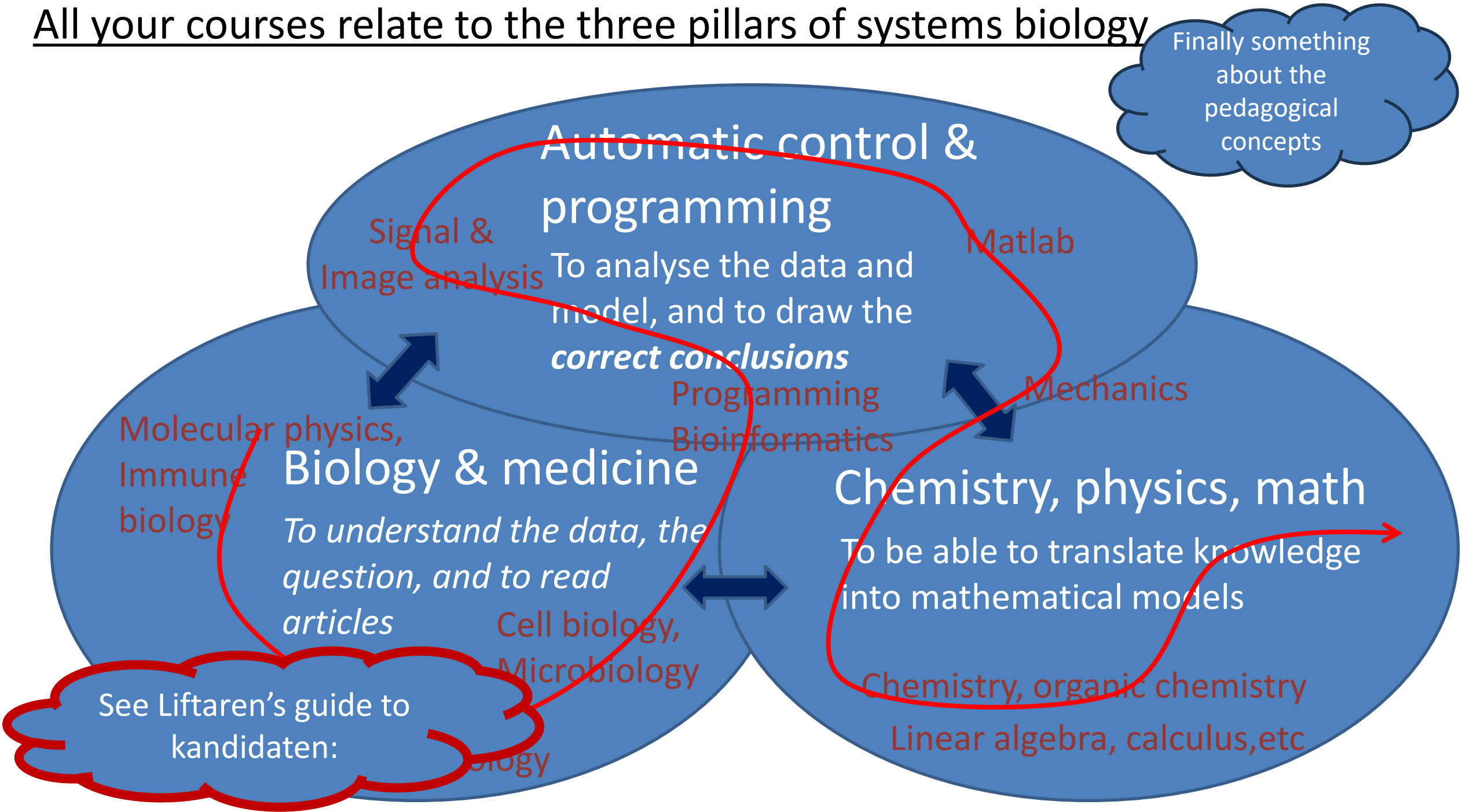
Music, arts, gaming, teaching,etc

Cedersund, *submitted*

AstraZeneca

Performance from VPH
conference, September 2022

All your courses relate to the three pillars of systems biology



”Liftarens guide till kandidaten”

Connected to a growing set of courses in semesters 1-5 (i.e. years 1-3),
we are developing:
- Youtube videos
- exercises

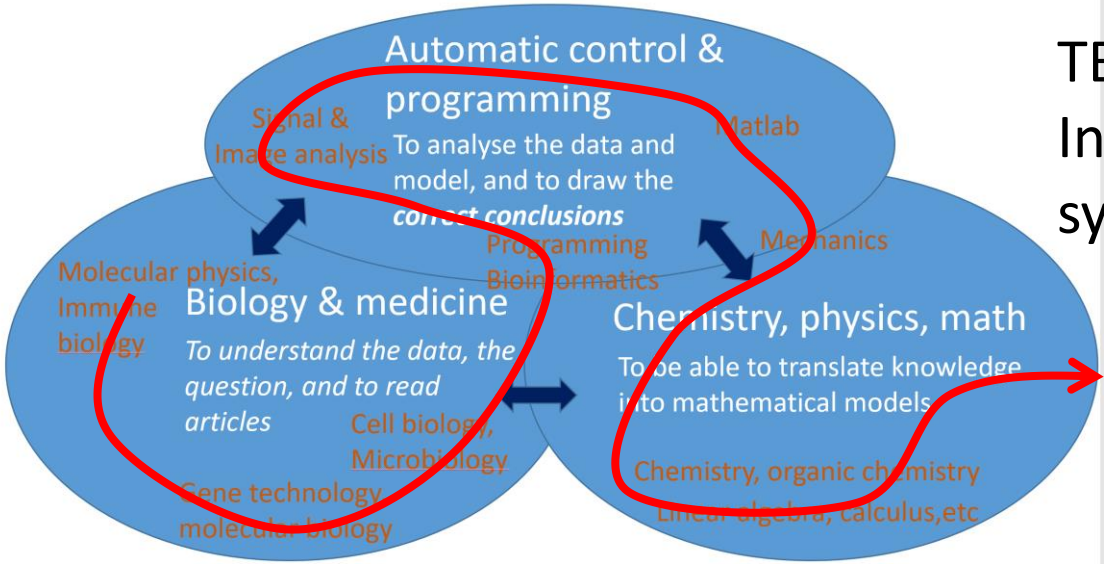
which show the connection between that course and what TB[1]-students at LiU[2] will do in their B.Sc. Project
You should be the first pilot students, if you started in 2020
However, anyone is welcome to use them, and you can contact Elin Nyman, who can give you access: elin.nyman@liu.se
The videos will also be added as a playlist to our youtube-channel

1, TB = Engineering biology students at LiU

2, LiU = Linköping university, Sweden

Zoomed-out view of all 5 years of TB

Building-blocks	First way of integrating skills – first real project	Other ways of integrating skills – more real projects, internships, etc



TBMT19 – Introduction to systems biology

All material available online

Profile 1: Sensor & biomaterials eHealth sub-profile

eHealth ”strimma” TBMT42

TBMT33 – Systems biology B.Sc. project

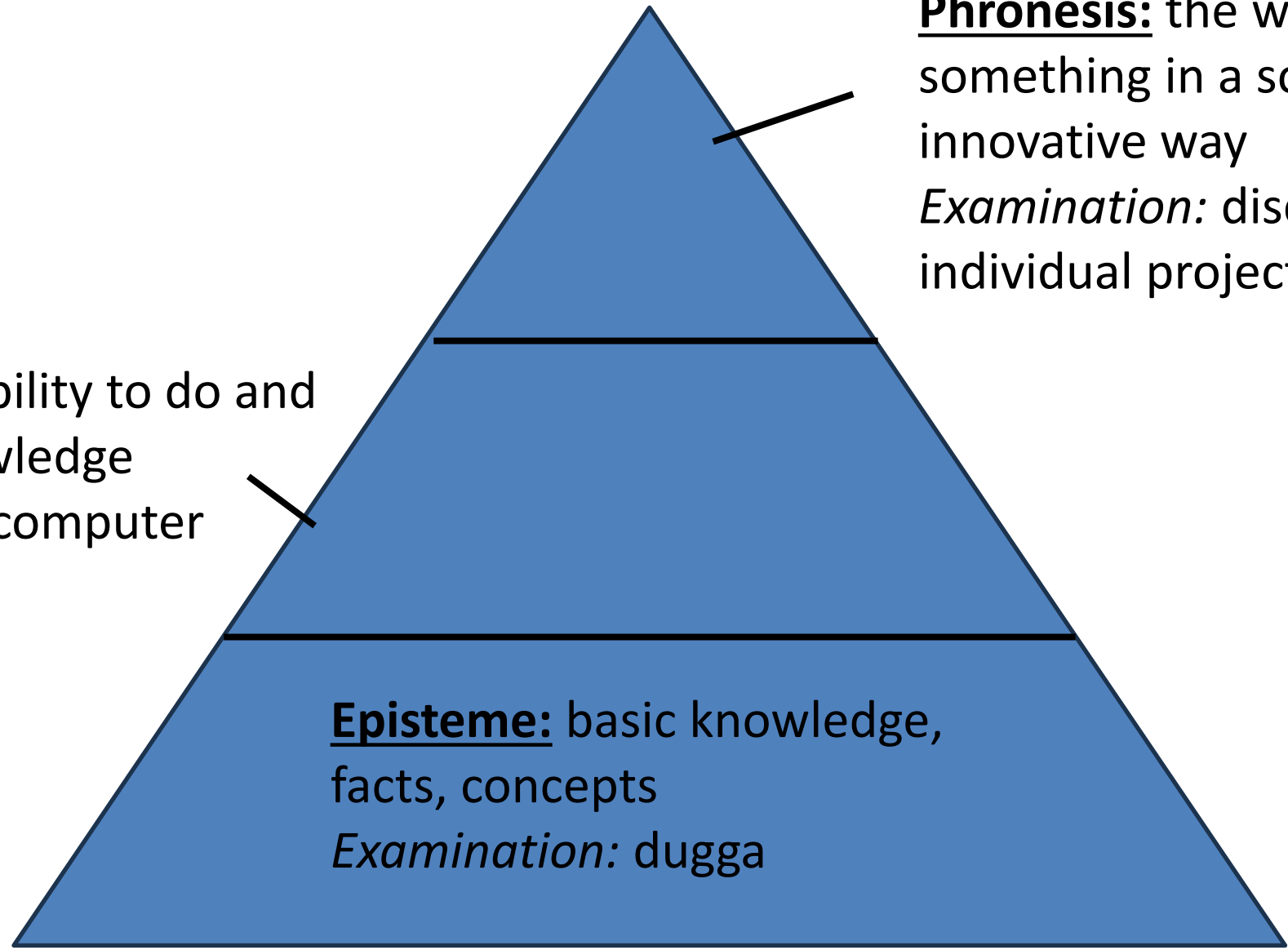
Profile 2: Industrial bio-engineering & production

Year 1 Year 2 Year 3 Year 4-5

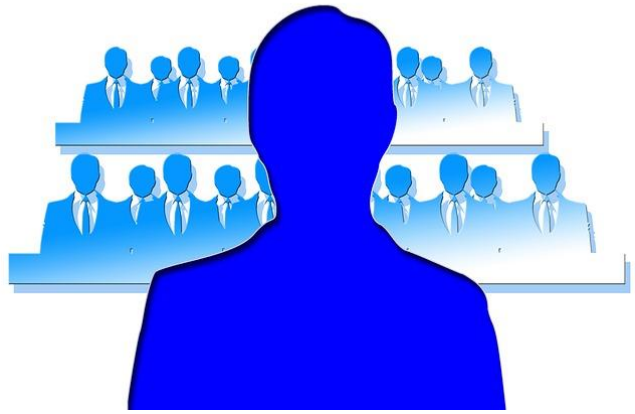
The three layers of knowledge

Phronesis: the wisdom to apply something in a sound and innovative way
Examination: discussion in individual projects

Techne: the ability to do and act upon knowledge
Examination: computer exercises



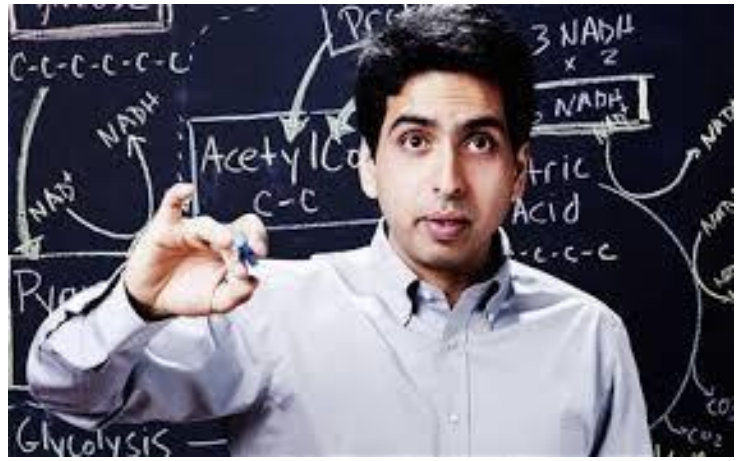
Example of flipped-classrom result



⇒Year 1	Normal teaching	Normal teaching
⇒Year 1	45-55% passed	45-55% passed
Year 2-3	Flipped classroom	Normal teaching
Year 2-3	>90% passed	45-55% passed

Also the good students – who already passed – improved the results

Our goal is to make it possible to study this course in your own pace, way, and from anywhere in the world



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isbgroup.eu/edu for more info and course material on this course