



11PM

4AM in London (GMT), 1PM in Tokyo (GMT+9)

Multiscale Visualizations

Moderator: *Andreas Bueckle, Indiana University*

Presenters:

- Tobias Isenberg, *National Institute for Research in Digital Science and Technology (Inria)*
- Ludovic Autin, *Scripps Research Institute*
- Griffin Weber, *Harvard Medical School*



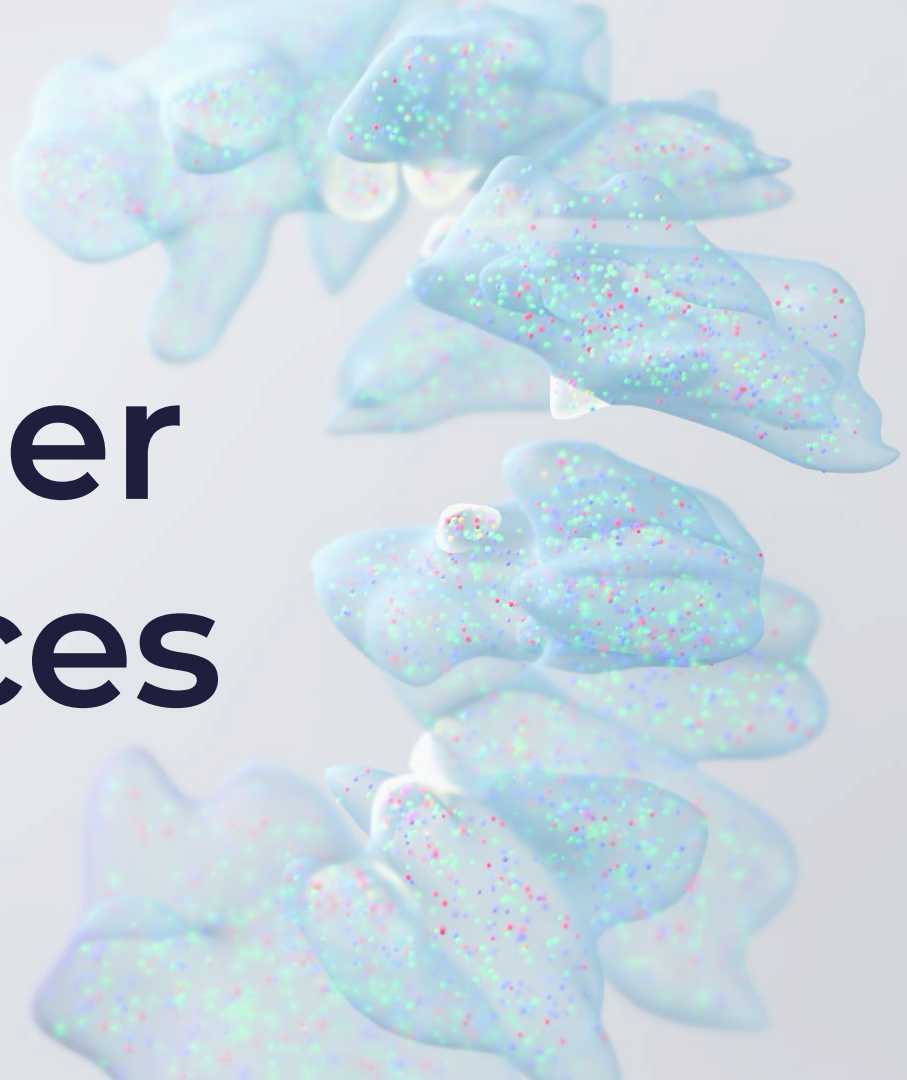
Setting the Stage: Building and Exploring the Human Reference Atlas with Virtual Reality



Andreas "Andi" Bueckle, Ph.D.
Research Lead

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Department of Intelligent Systems Engineering
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Indiana University, Bloomington, IN, USA*

HRA User Interfaces





Registration User Interface (RUI)

HubMAP HRA REGISTRATION

Left Right Anterior Posterior Register 3D Preview

Anatomical Structures

- all anatomical structures
- kidney capsule
- hilum of kidney
- cortex of kidney
- renal column
- outer cortex of kidney
- renal medulla
- renal papilla
- renal pyramid

Landmarks

- all landmarks
- bisection line
- left renal artery
- left renal pelvis
- left renal vein
- left ureter
- major calyces
- minor calyces

Q W E
A S D

X: 95
Y: 59
Z: 41

Registration Metadata

Tissue Block Controls

Tissue Block Dimensions (mm)

Width (X)	Height (Y)	Depth (Z)
10	10	10

Tissue Sections

Thickness	# Sections

Tissue Block Rotation

X	0
Y	0
Z	0

Anatomical Structure Tags

Add Anatomical Structures ...

Assigned Added

Review and Download

<https://apps.humanatlas.io/rui/>



Exploration User Interface (EUI)

HuBMAP HRA EXPLORATION

Sex: **Both** Age: **1-110** BMI: **13-83**

Fallopian Tube, R: 0 Heart: 159 Kidney, L: 66 Kidney, R: 57 Knee, L: 2 Knee, R: 10 Large Intestine: 55 Larynx: 0 Liver: 38 Lungs: 42

body | cell | biomarker

20 Tissue Data Providers
308 Donors
730 Tissue Blocks
939 Tissue Sections
3260 Tissue Datasets

Anatomical Structures (AS) Tissue Blocks: 730

- brain 11
- lymph node 36
- eye 43
- fallopian tube 0

Cell Types (CT) Tissue Blocks: 730

- absorptive 67
- absorptive 61
- adipocyte 225
- adipocyte 16

Biomarkers Tissue Blocks: 730

- BG BL BM BP BF
- a smooth muscle actin 0
- A2M 253
- ABC10-43608400015.1 0
- ABCA1 11
- ABCA13 11
- ABCA3 42
- ABCA4 11
- ABCA8 11
- ABCC9 403
- ABCG2 0

Run Spatial Search

Patient B Cortical biopsy
Entered 4/18/2020, Seth Winfree, KPMP-IU/O...

Patient A Cortical biopsy
Biopsy from Nephrology biobank-salvaged fro...

Cover Nephrectomy
Biopsy from Nephrology biobank-salvaged fro...

Female, Age 38
Entered 7/3/2023, Andrea Radtke, NIH

Male
Entered 5/26/2023, Anna Martinez Casals, ISL...

Male, Age 19, Patient APAP1
Entered 8/24/2023, Jordan Portman, UEdinbu...

Female, Age 48, Patient APAP10
Entered 8/24/2023, Jordan Portman, UEdinbu...

Female, Age 23, Patient APAP2
Entered 8/24/2023, Jordan Portman, UEdinbu...

Male, Age 66, Patient APAP3
Entered 8/24/2023, Jordan Portman, UEdinbu...

Male, Age 38, Patient APAP4
Entered 8/24/2023, Jordan Portman, UEdinbu...

<https://apps.humanatlas.io/eui/>

HRA Organ Gallery in VR

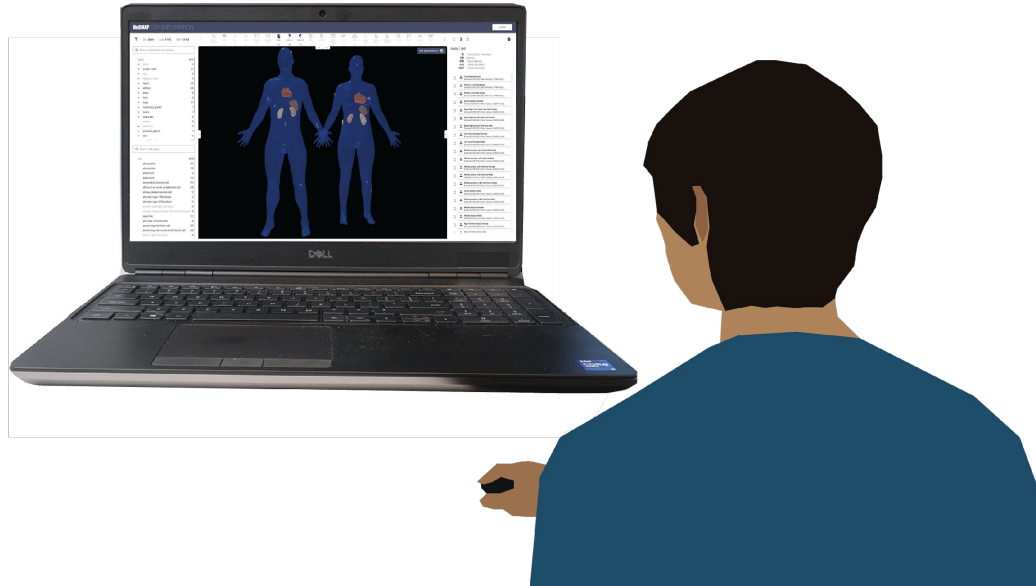


What if...?





What if?



HRA Exploration User Interface: <https://apps.humanatlas.io/eui/>



HRA Organ Gallery in VR



↑
Scan to
download



Identified **3 major use cases**:

- Quality Assurance/Quality Control for registered tissue blocks
- Onboarding to the HRA
- Telling Embodied Data Stories

Paper:

<https://doi.org/10.3389/fbinf.2023.1162723>

HRA Organ Gallery in VR:

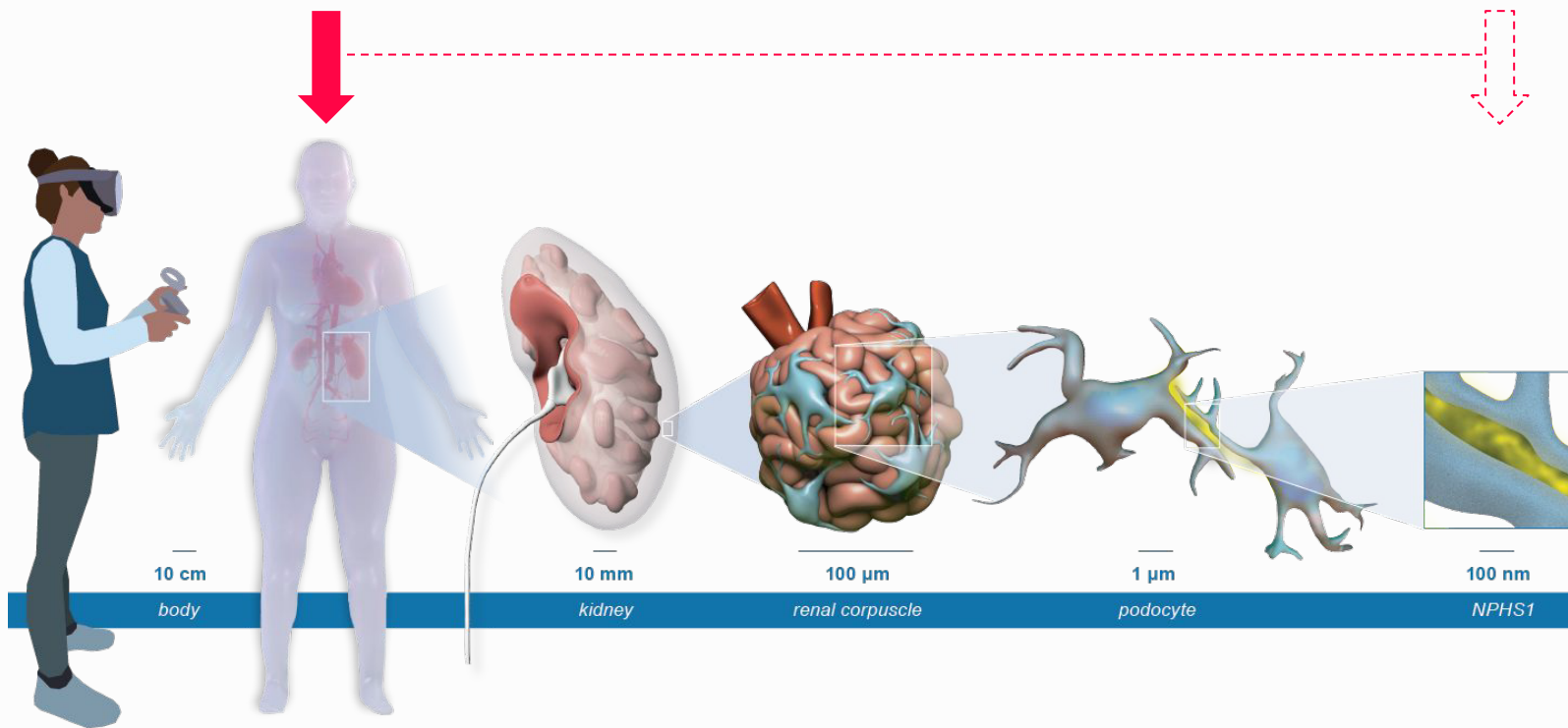
<https://www.meta.com/experiences/5696814507101529>

Exploring Spatial Data in VR



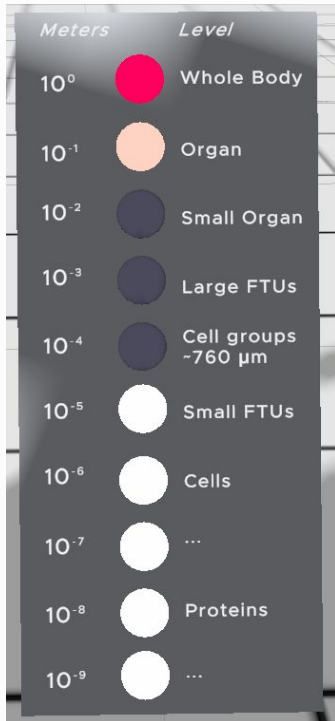


Common Coordinate Framework (CCF)





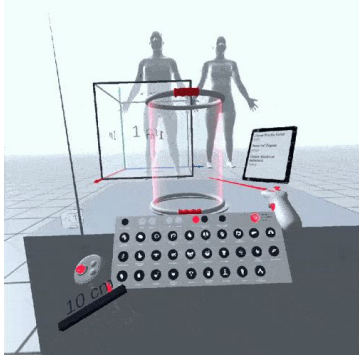
Common Coordinate Framework (CCF)



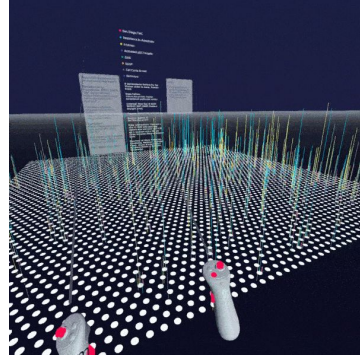
- Start at highest floor
- Take an elevator across levels, from Whole Body to Proteins
- Currently open for business:
 - Whole Body
 - Small Organ
 - Large FTUs
 - Cell Groups (~760 μm)



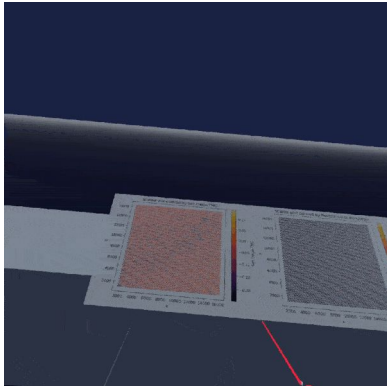
HRA Organ Gallery in VR



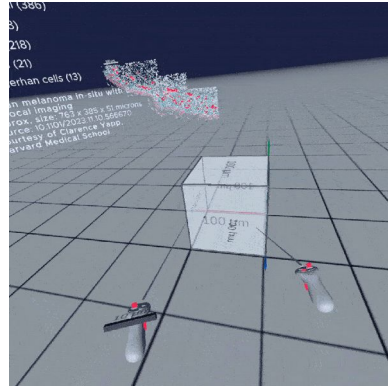
Level 0: Whole Body



Level -3: 3D stepped relief map for senescence hallmarks in Visium slide



Also Level -3: auxiliary 2D scatter graphs



Level -4: Cell groups ~760 microns

Multiscale exploration of the HRA

- **Level 0: Whole Body**
- **Level -2: Small Organ**
- **Level -3: Large FTUs**
- **Level -4: Cell Groups ~760 Microns**

Talk to Andreas “Andi” Bueckle if you would like a demo. Video:

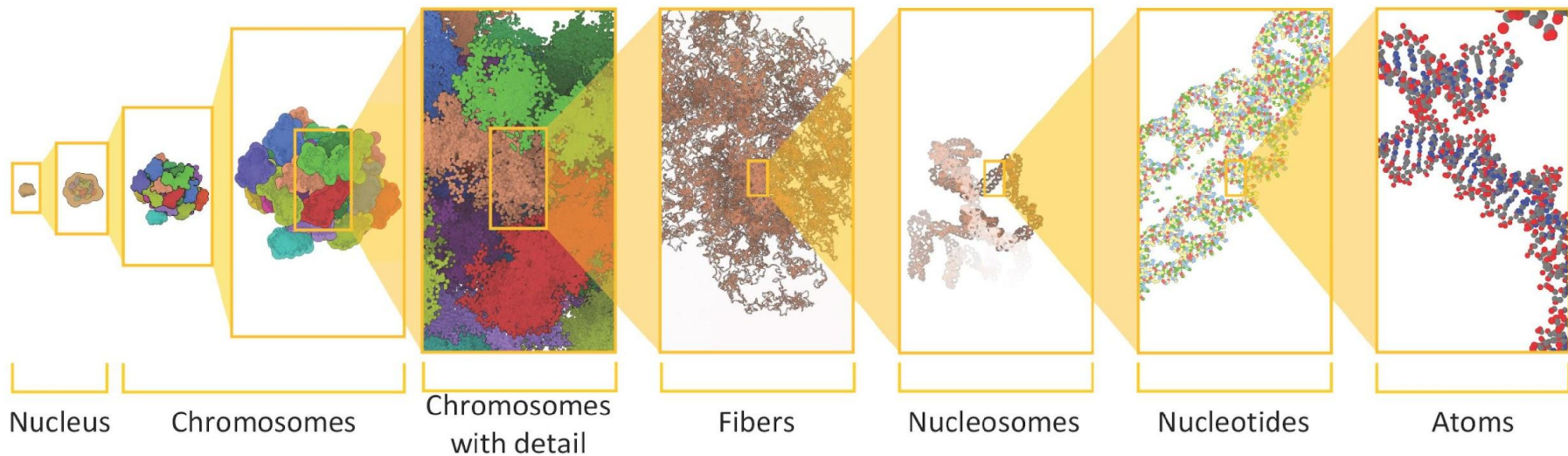
<https://www.youtube.com/watch?v=Wy0BCOFWClk>



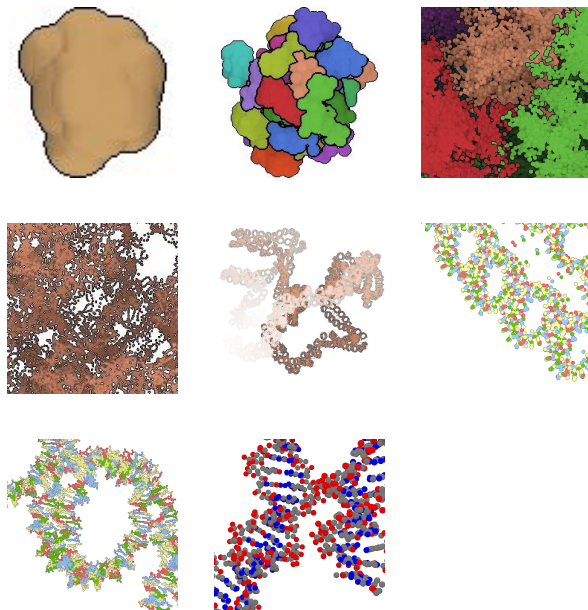
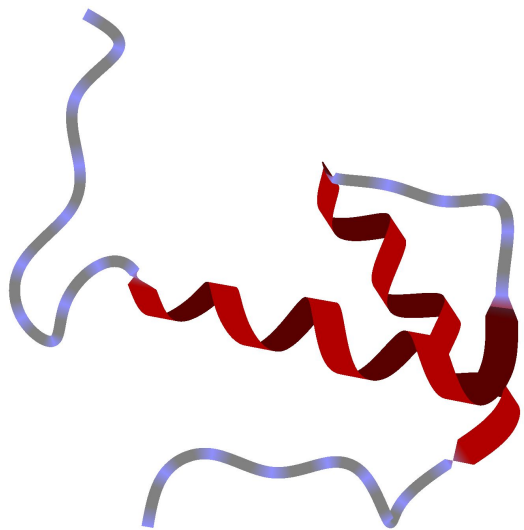
Tobias Isenberg

Inria

ScaleTrotter

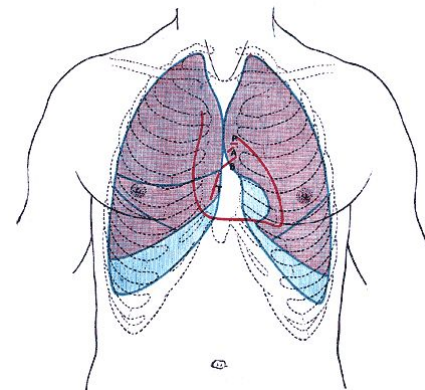
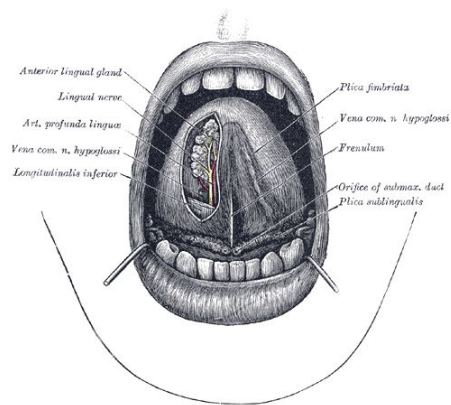
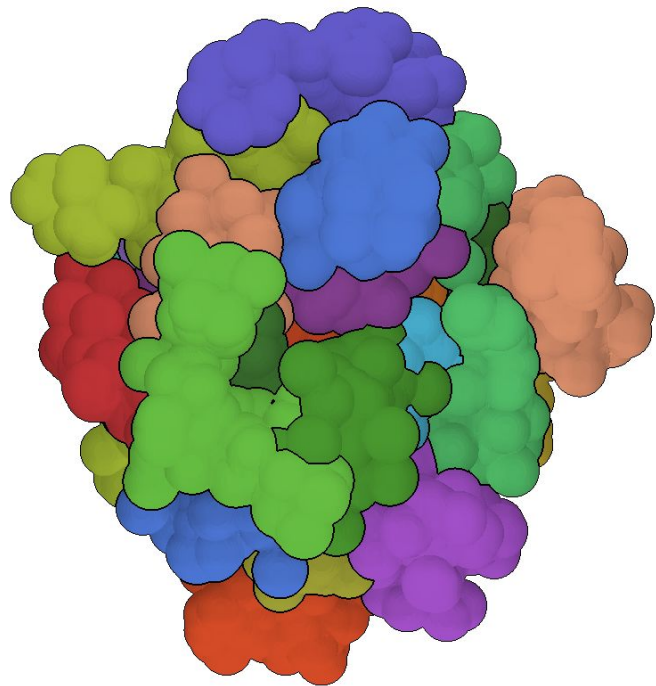


“Simple,” straightforward transitions



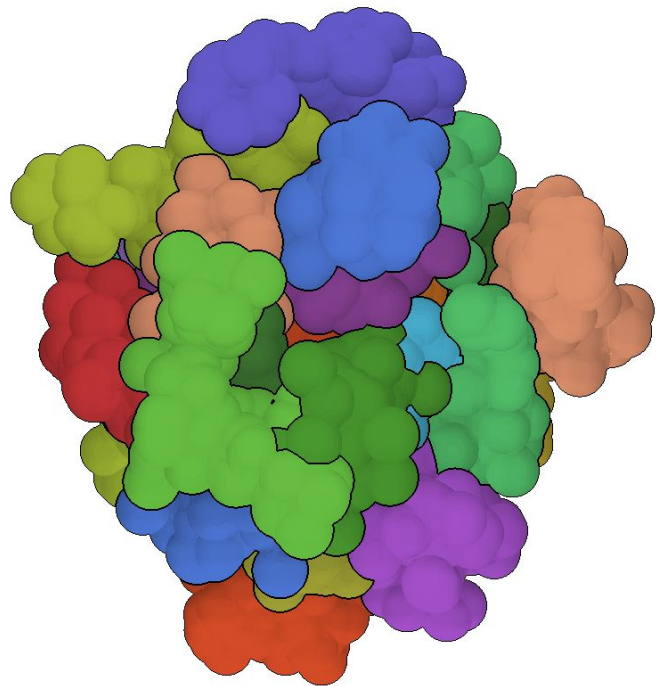
[van der Zwan et al., 2011]

Visual embedding transition



[Gray's Anatomy, 1918]

Visual embedding transition



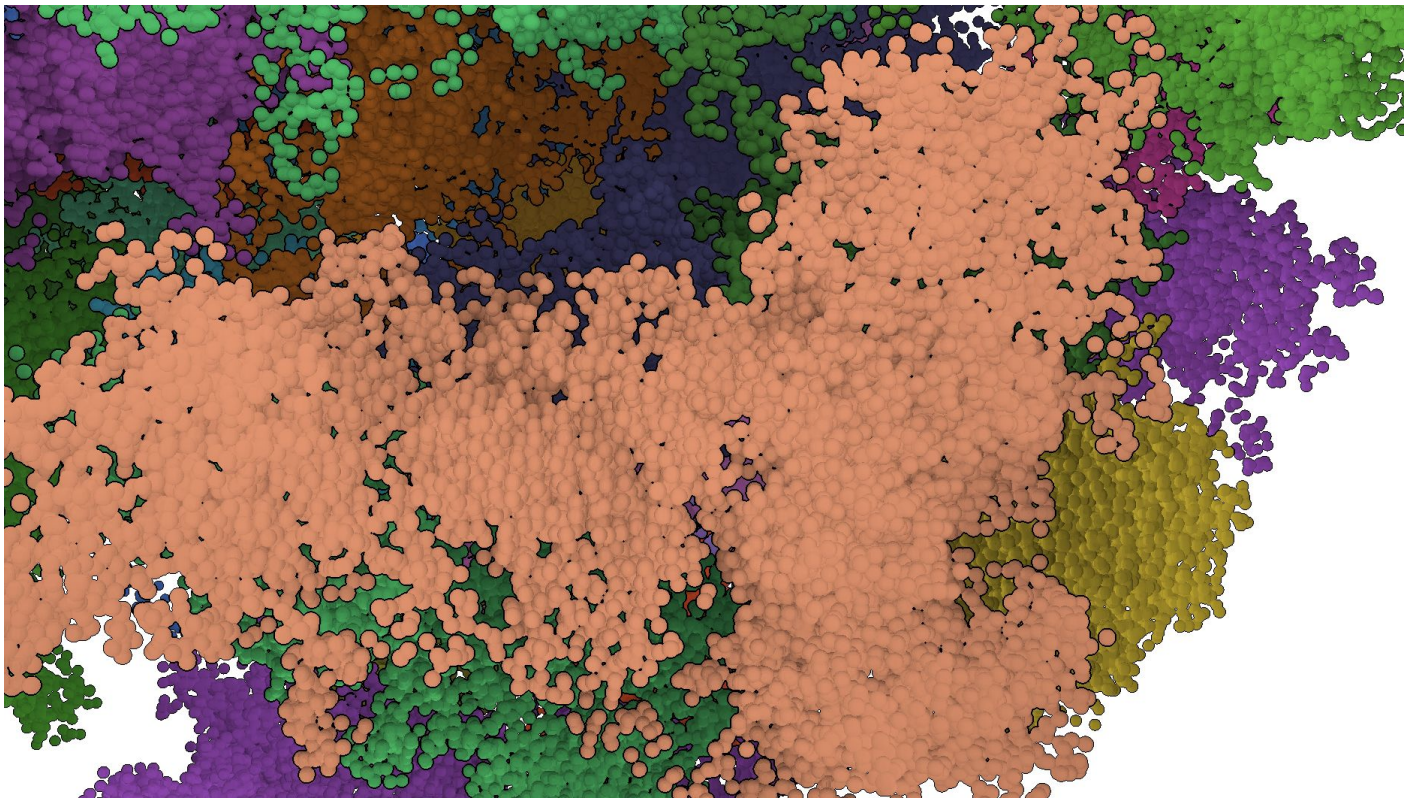
coarse scale in 3D

coarse scale flattened to canvas

detailed scale in 3D on top of canvas

canvas disappears

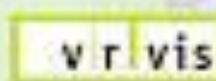
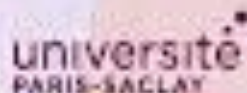
Visual embedding transition



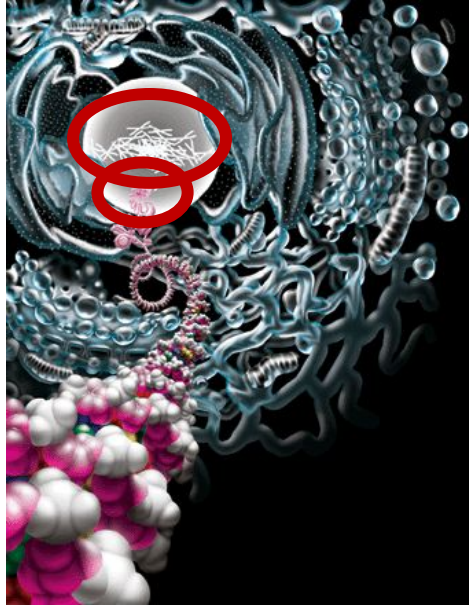
Interactive exploration

ScaleTrotter: Illustrative Visual Travels Across Negative Scales

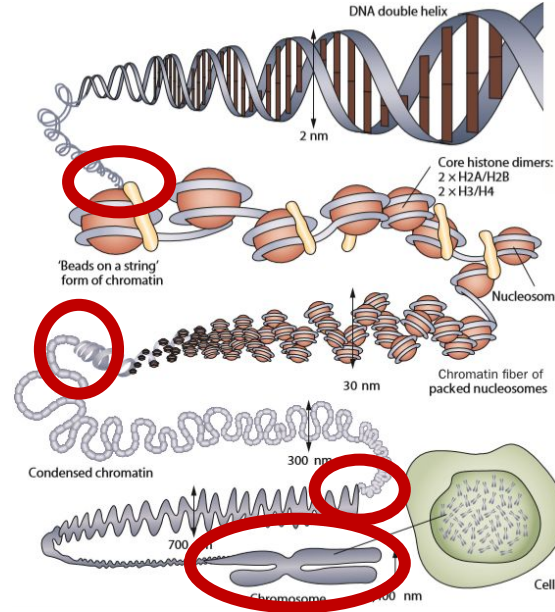
Sarkis Halladjian, Haichao Miao, David Koufil, M. Eduard Gröller, Ivan Viola, Tobias Isenberg



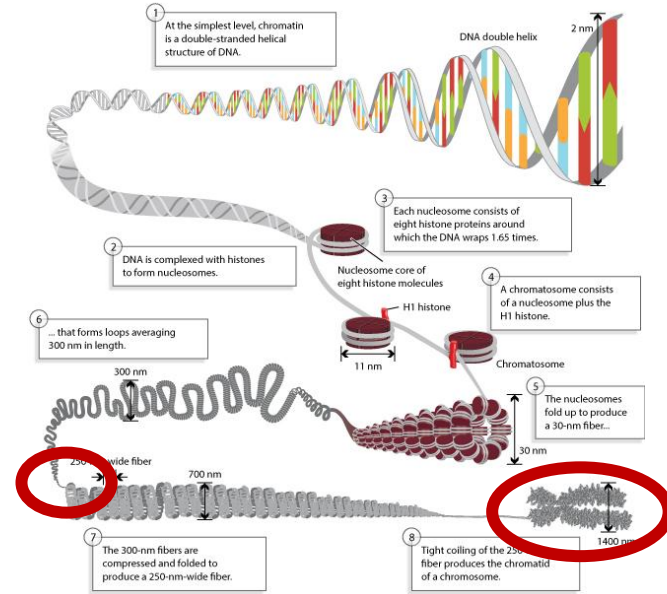
Further Inspiration: Multiscale DNA illustration



[Pennisi, 2001]

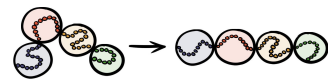


[Tonna et al., 2010]

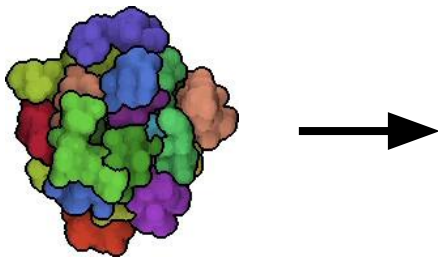


[Nature Education, 2013]

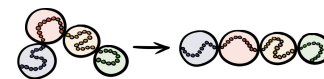
Spatial straightening



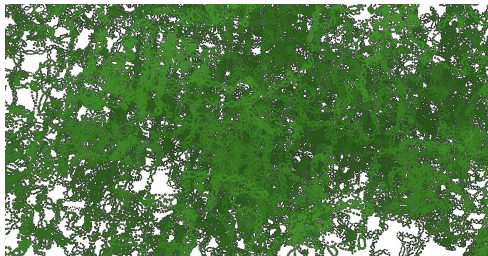
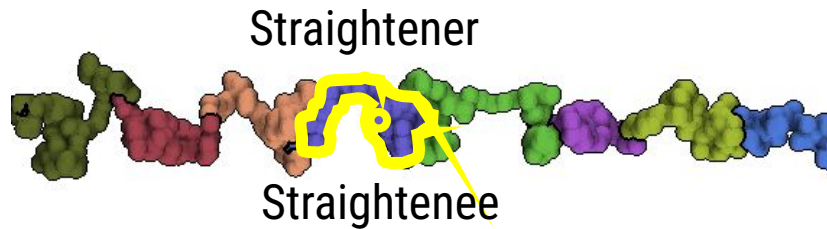
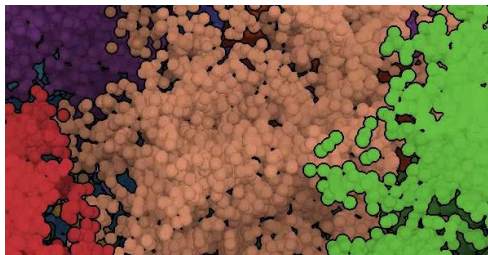
Chromosome scale



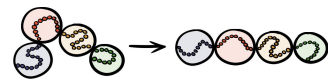
Spatial straightening



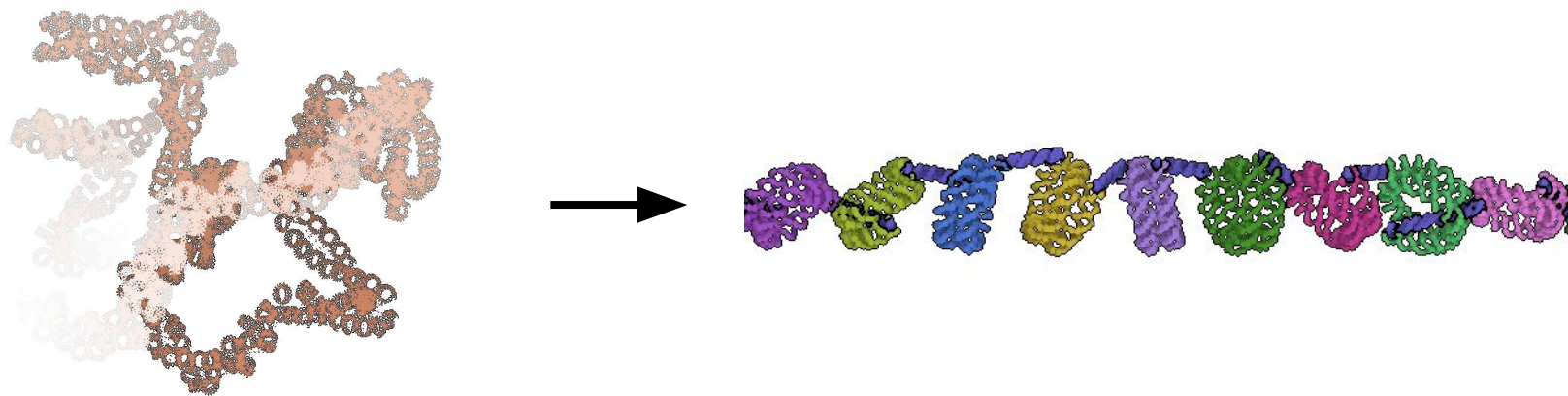
Loci and fiber scales



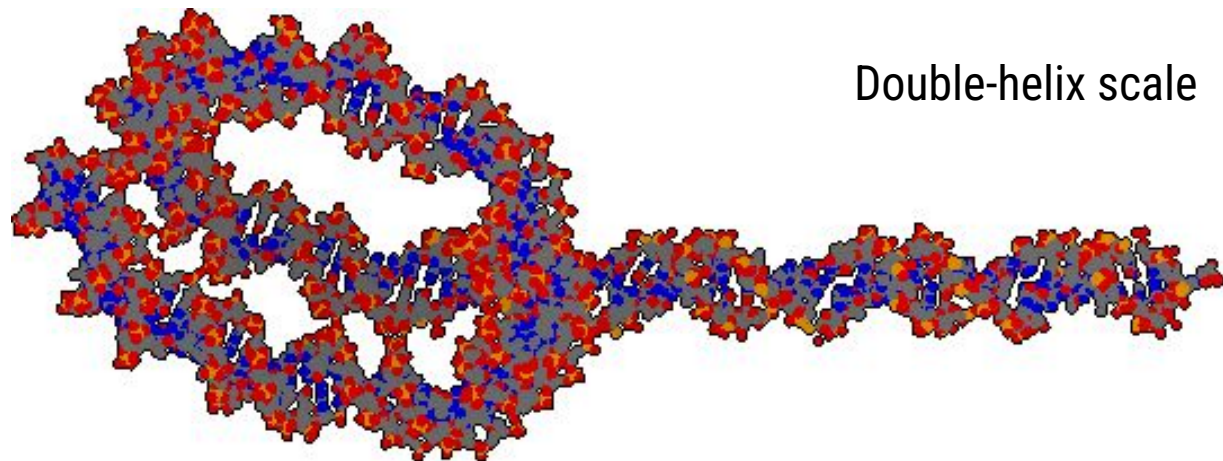
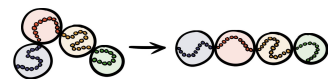
Spatial straightening



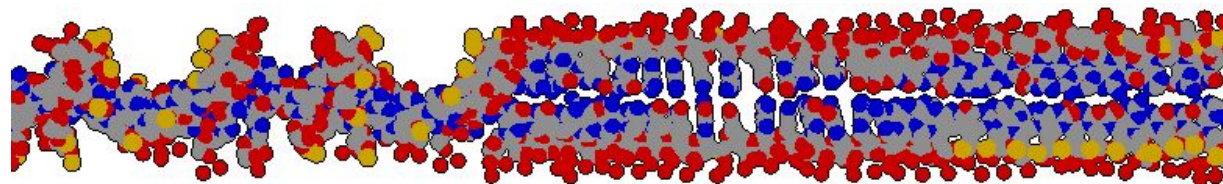
Nucleosome scale



Spatial straightening

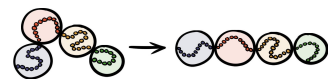


Double-helix scale

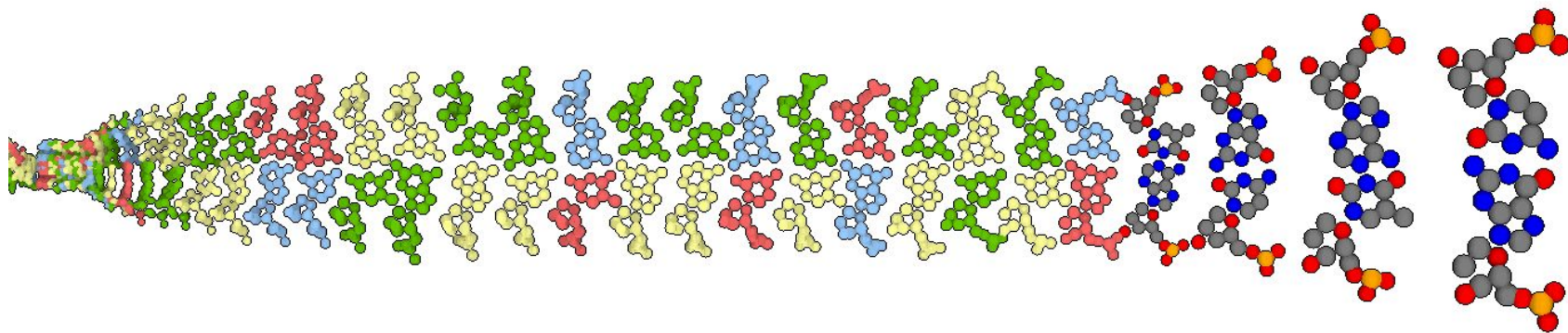


Bases scale

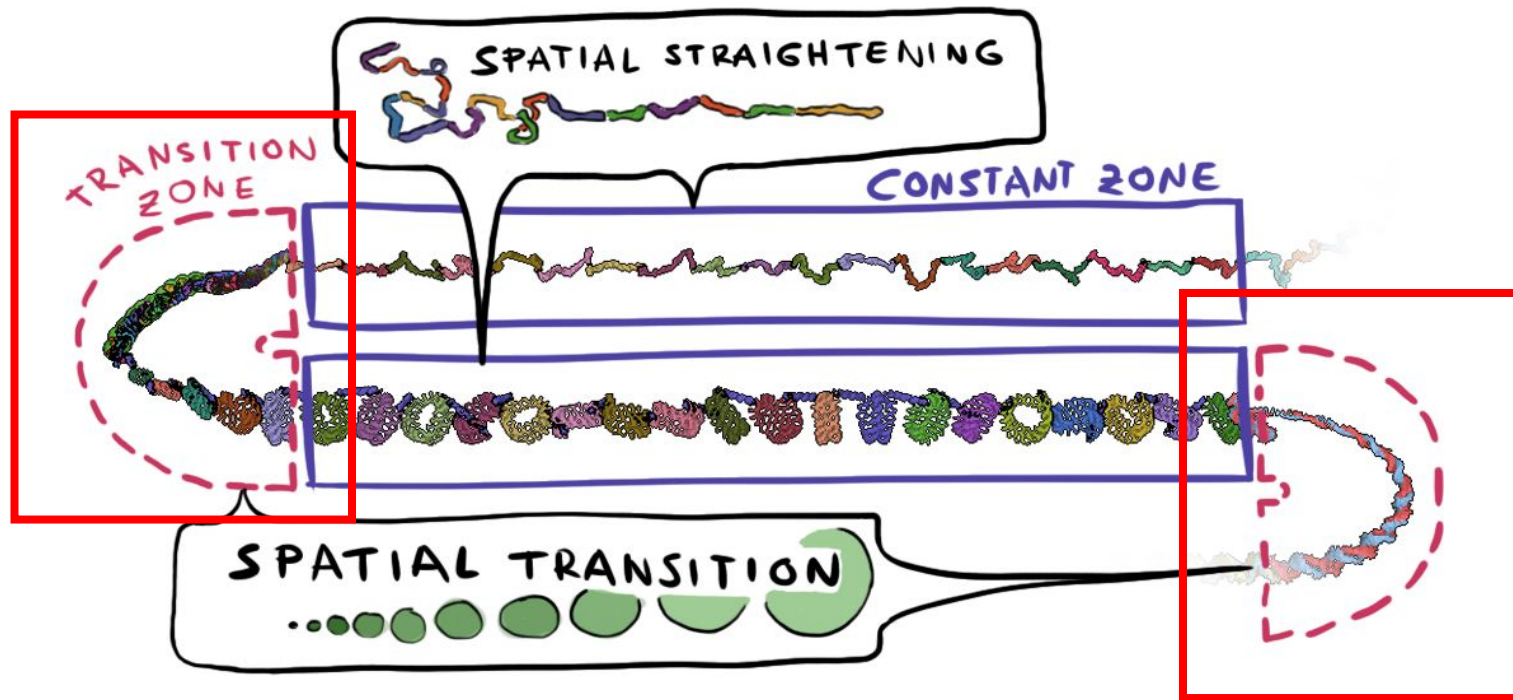
Spatial straightening



Bases scale

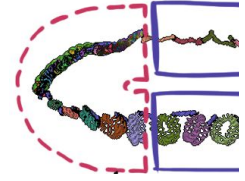
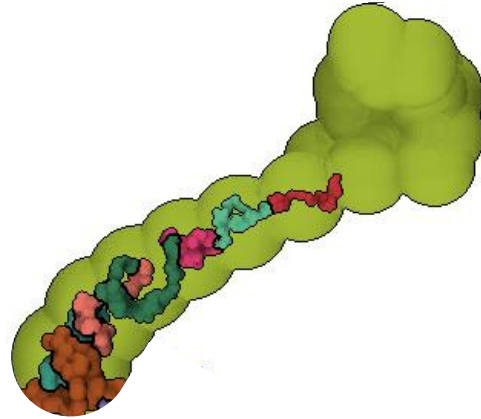
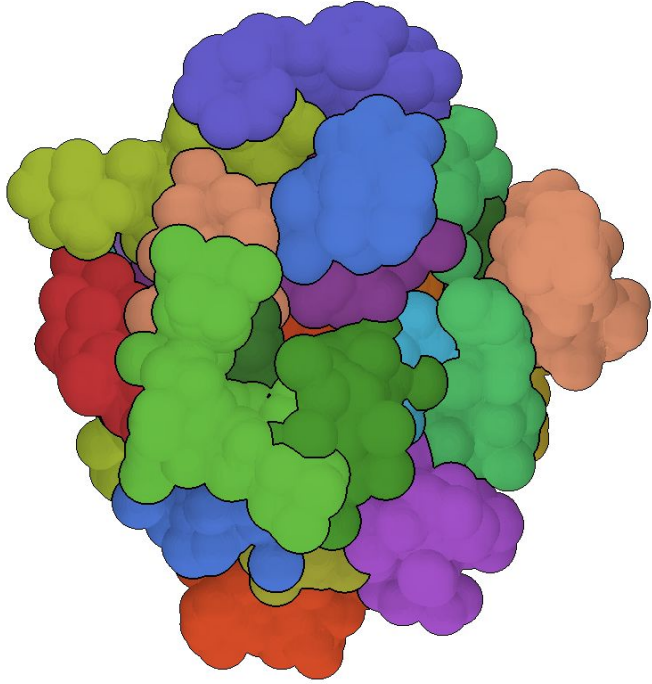


Conceptual arrangement



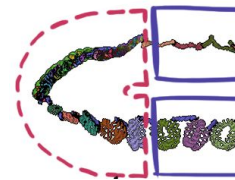
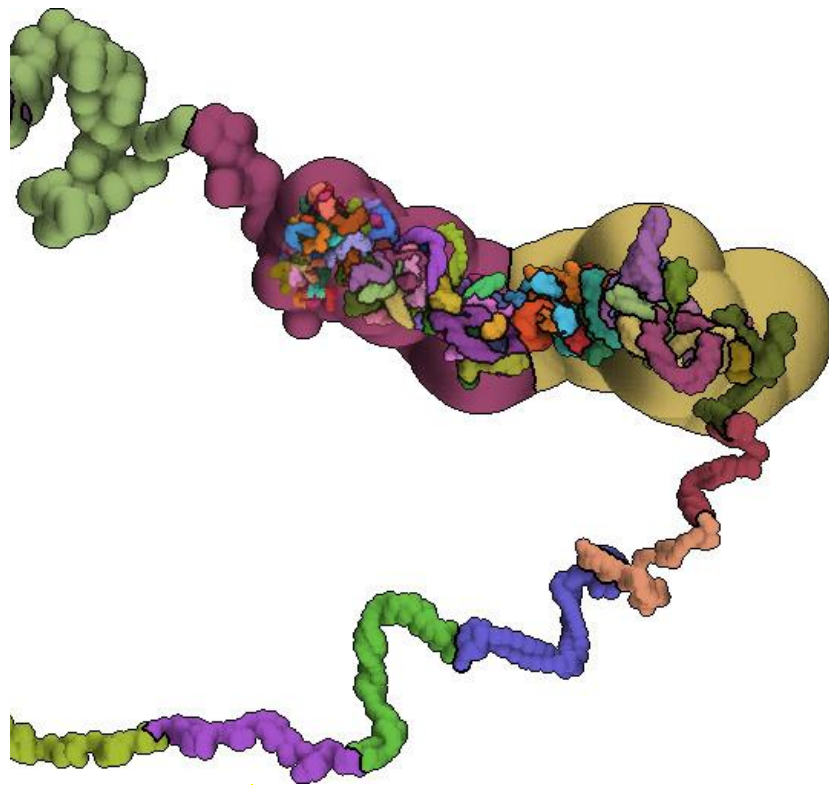
Spatial transitions

Chromosomes-to-loci



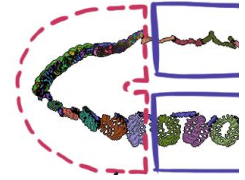
Spatial transitions

Loci-to-fibers



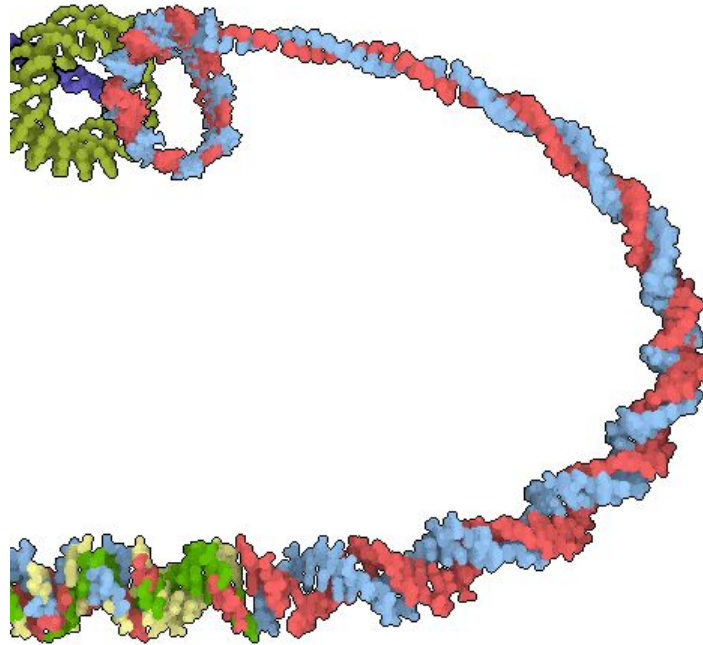
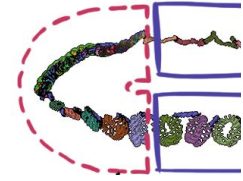
Spatial transitions

Fibers-to-nucleosomes



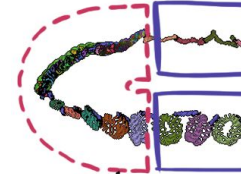
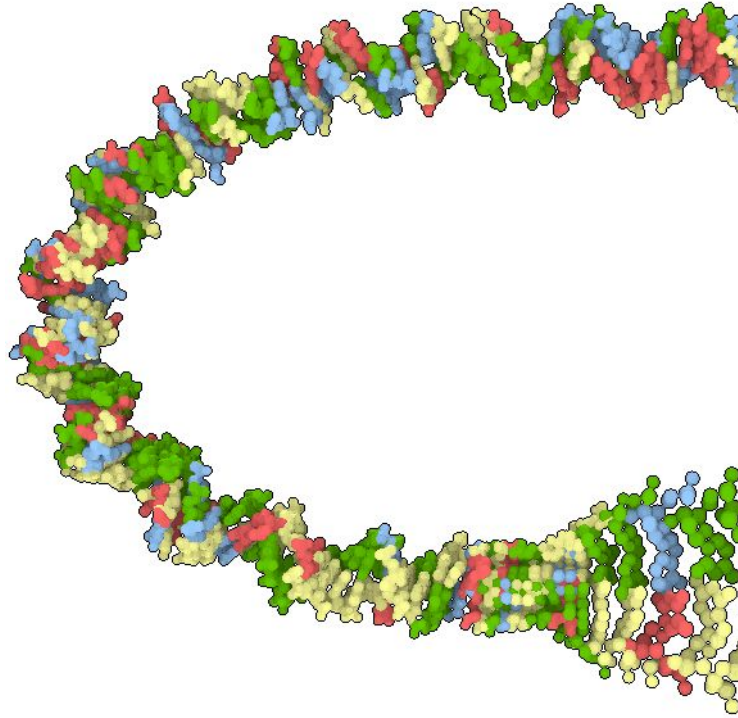
Spatial transitions

Nucleosomes-to-double-helix

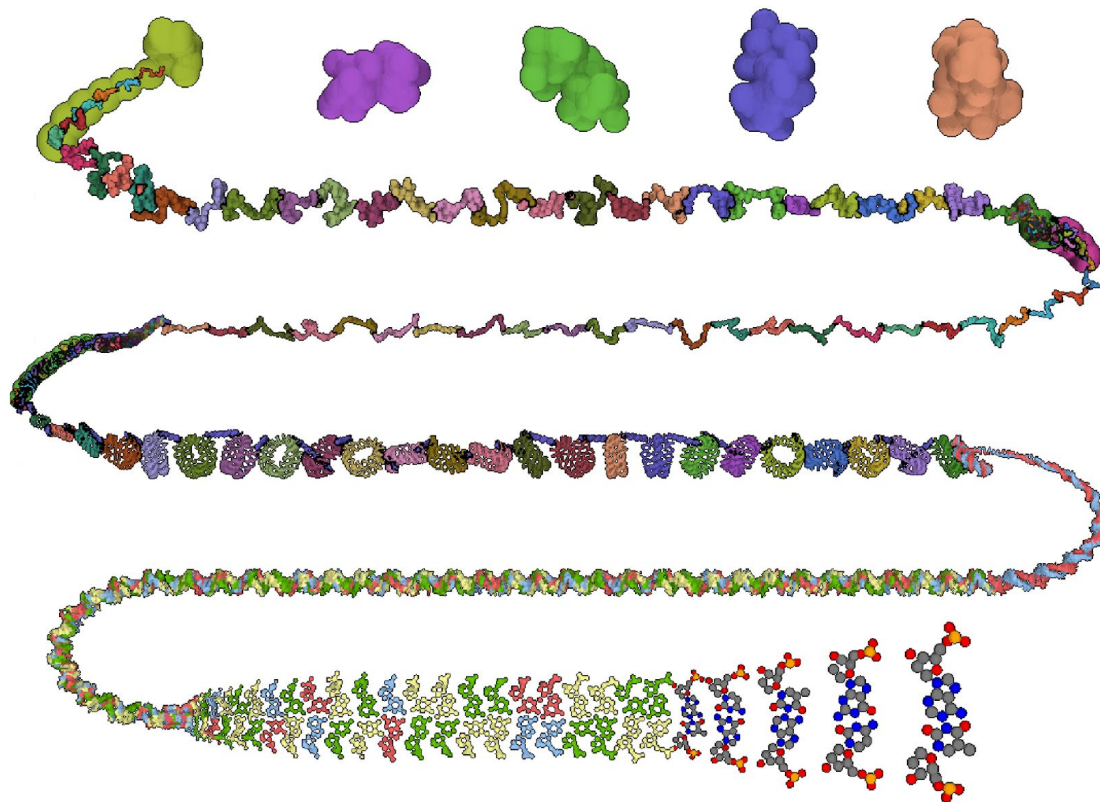


Spatial transitions

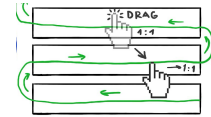
Double-helix-to-bases



Multiscale Unfolding

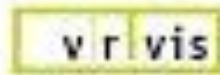
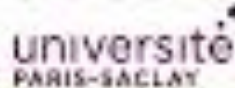


Panning the scales



Multiscale Unfolding: Illustratively Visualizing the Whole Genome at a Glance

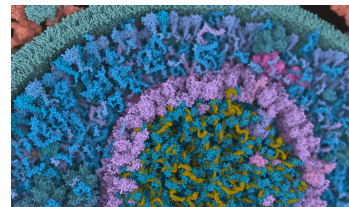
Sarkis Halladjian, David Kouřil, Haichao Miao, M. Eduard Gröller, Ivan Viola, Tobias Isenberg



Collaborators



nanographics



Sarkis
Halladjian



David
Kouřil



Haichao
Miao



Eduard
Gröller



Ivan
Viola

tinyurl.com/scaletrotter

tinyurl.com/multiscale-unfolding

Ludovic Autin

The Mesoscale Challenge

7 octillion
 7×10^{27}

Atoms

Molecules

Cells

Tissues

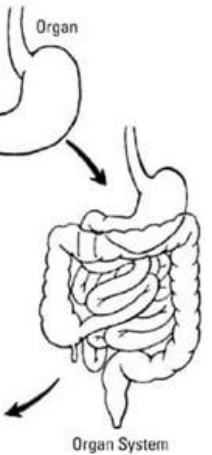
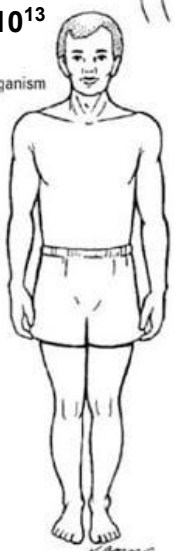
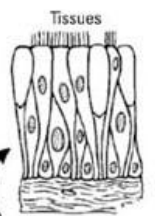
Organ

Organ System

Organism

30 trillion
 3×10^{13}

Organism



METHOD OF STUDY:



RESOLUTION: 10^{-1}

Macro 10^{-2}

Milli 10^{-3}

10^{-4}

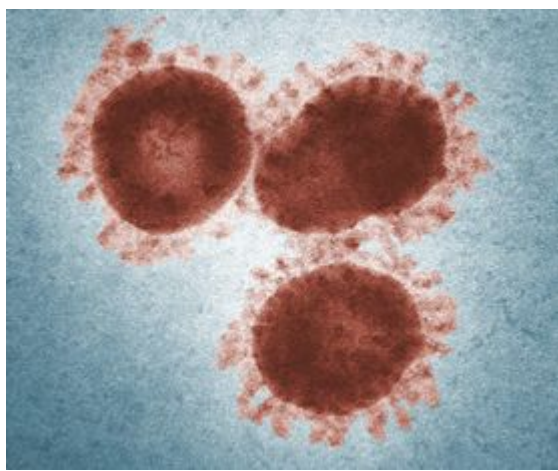
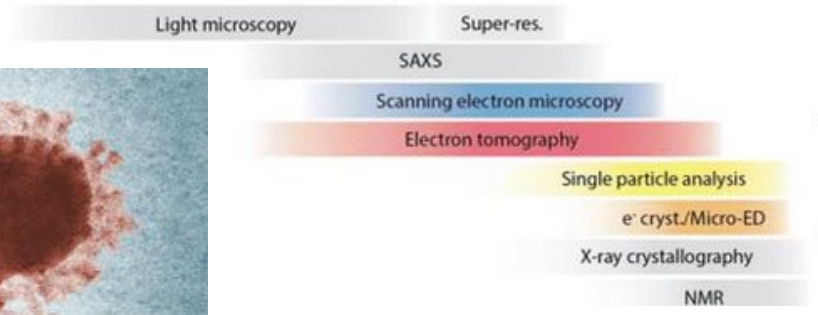
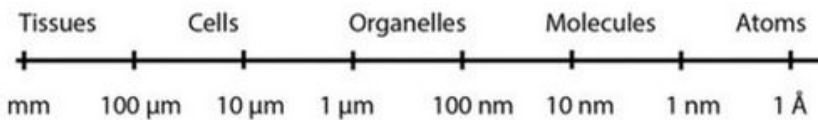
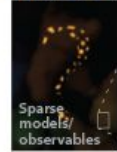
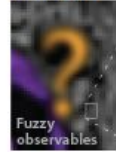
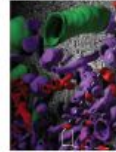
10^{-5}

Micro 10^{-6}

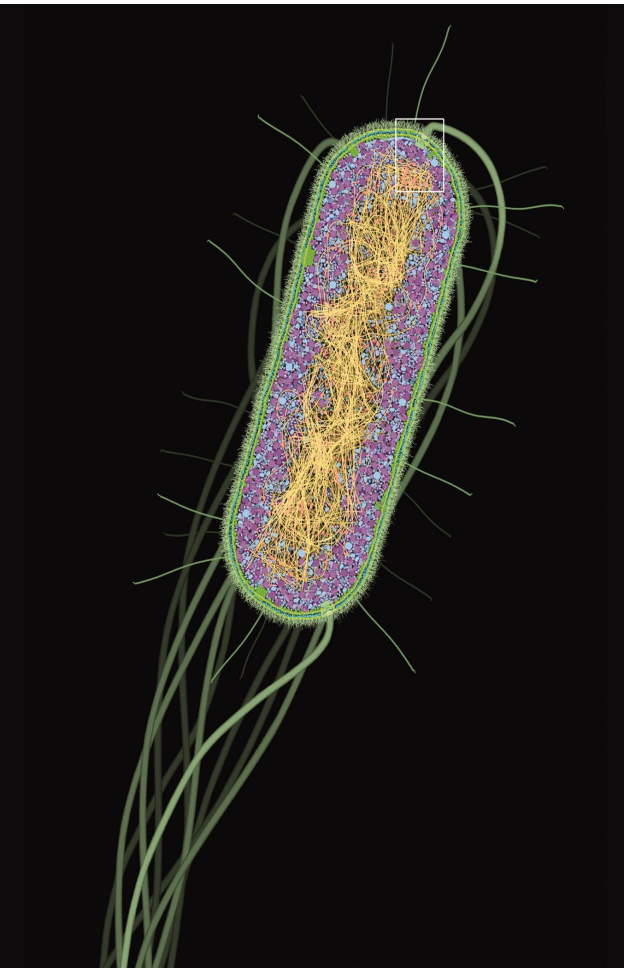
Meso 10^{-7}

Meso 10^{-8}

Nano 10^{-9}

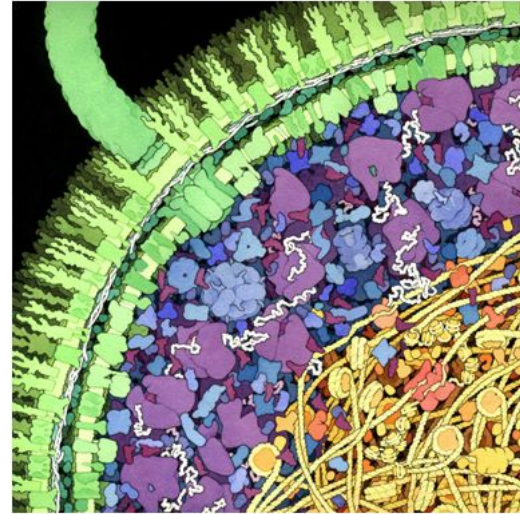
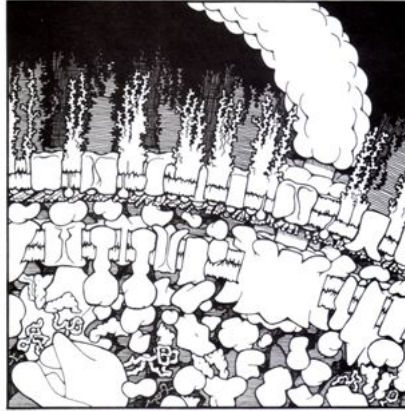


Theodor Escherich 1886
Escherichia coli



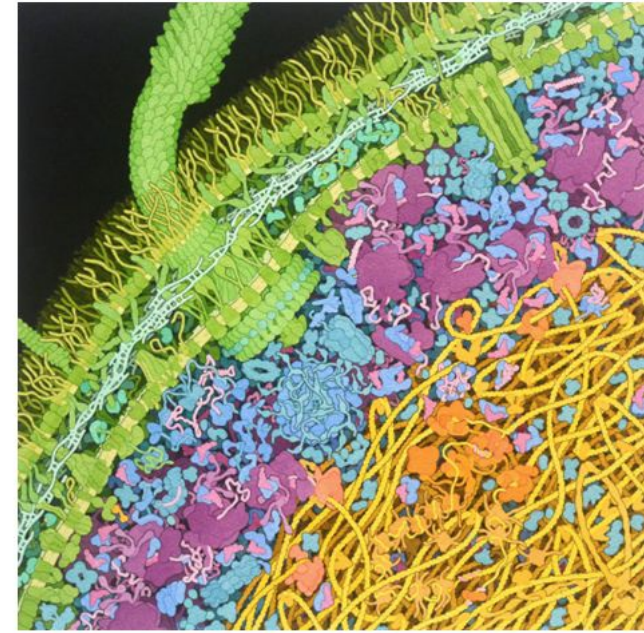
David Goodsell

1991



1999

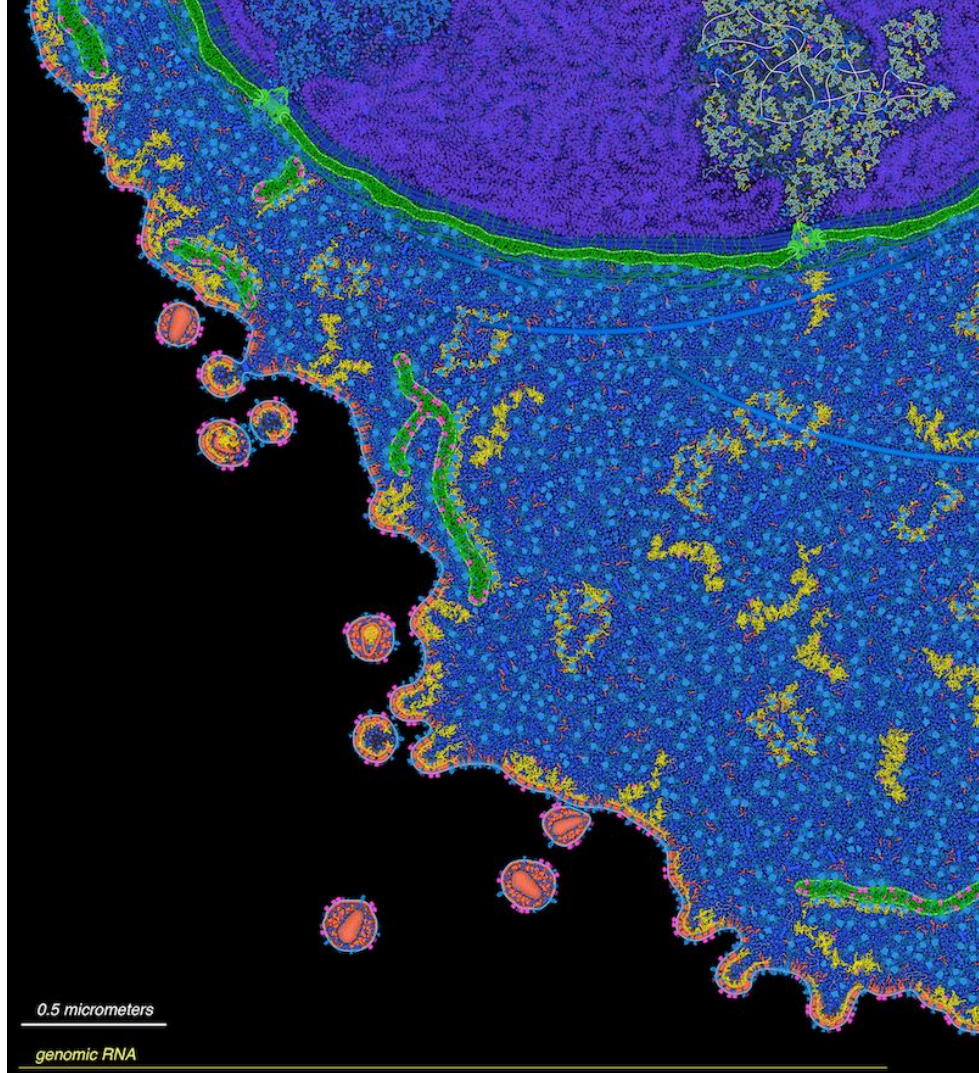
Largely invisible to experiment
Integrates the *current* state of
knowledge



2021



David Goodsell





David Goodsell

Illustrating Cellular Environments



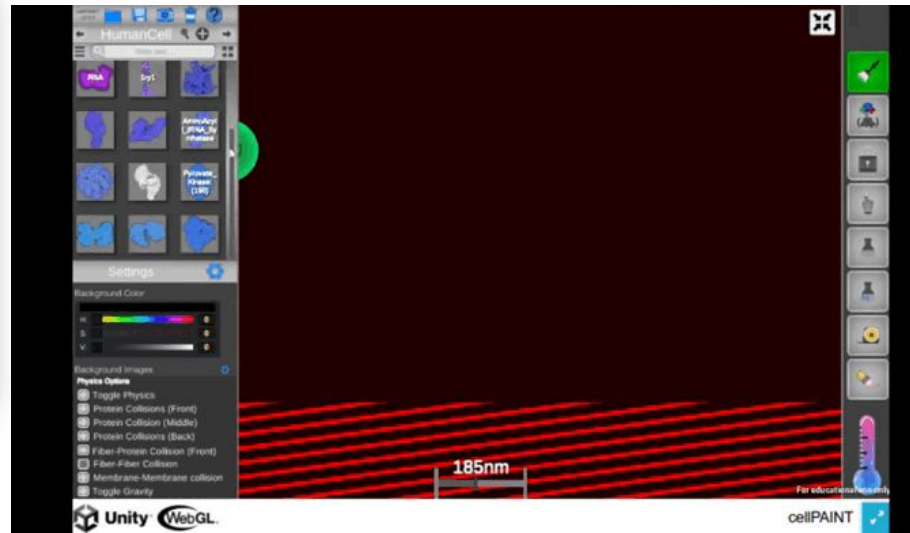
Adam Gardner

User-Friendly Interactive Tools ... CellPAINT Goodsell Watercolor



- Consistent scale
- Simplified iconic shapes
- Cross-sectional view
- Limited depth (3 layers)
- Informative colors

“Goodsell-like” cellPAINT



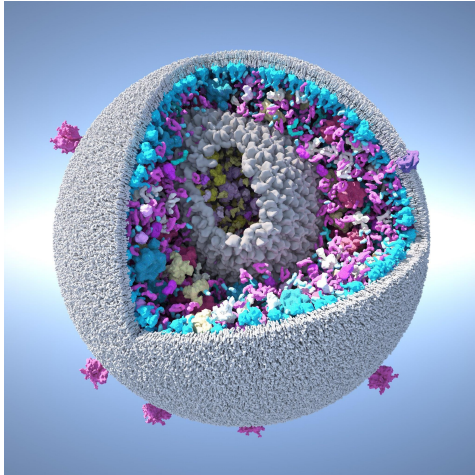
<http://cellpaint.scripps.edu>



Graham Johnson

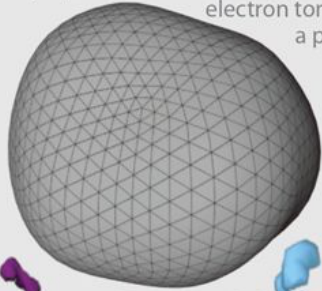
cellPACK: a virtual mesoscope to model and visualize structural systems biology

2014

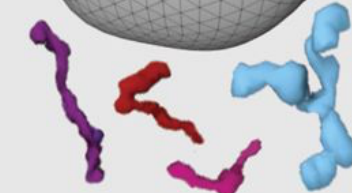


cellPACK models the cellular microscale & the subcellular mesoscale with molecular detail. Here, cellPACK adds a recipe of membrane proteins to a synaptic vesicle.

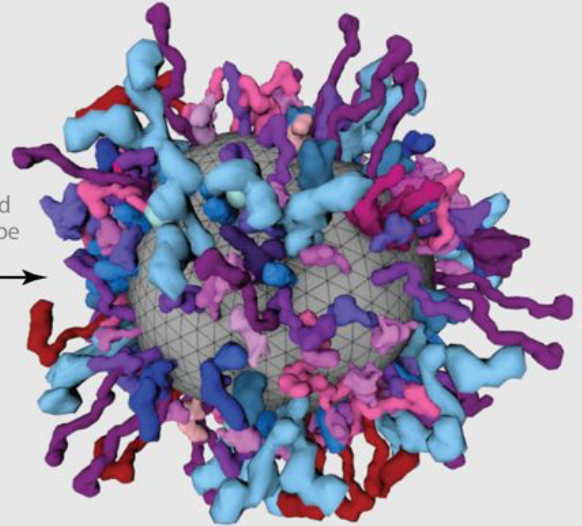
Synaptic vesicle from a segmented & annotated electron tomogram serves as a packing boundary



Packing constrained by ingredient & recipe agent attributes



Transmembrane protein ingredients derived from Takamori et al, *Molecular Anatomy of a Trafficking Organelle*, Cell 2006



Synaptic vesicle coated with recipe of appropriate transmembrane proteins by cellPACK

Instant Construction and Visualization of Crowded Biological Environments - cellpack on the gpu



Mathieu Le Muzic



Tobias Klein



Ivan Viola

2017

2018

Left Panel

Loading

D:\Data\Hivest_simulations\3F(1)\json Load Recipe

Load Positions

Load Series

Reset

Options

- Force align principal axis
- Load fiber as regular ingredient
- Update Visualization real time
- VSize
- Show Bounding Box
- Show Vessels
- Show Vessels Occupied
- Show Procedural Ingredients Mesh
- Show Compartments Mesh
- Populate Exterior Ingredients
- Populate Surface Ingredients
- Populate Lipids Surface
- Populate Interior Ingredients
- Grow Fiber
- Populate Procedural Ingredients
- Grow Fiber real time
- Populate Spawning Ingredients
- Populate Spawning Fiber
- Visual Jitter
- Show all ingredients on a 2D grid

Close Data to Disk

Close Grid Occurrence

Seed and Numbers

Get Random Seed

Reset to zero

Reset to current volume

Load

Protein Number: 13611

Case: 0.55

Ingredients List

Fiber Ingredients List

Overlap Relocation

Workspace

left click camera rotation
wheel or right click zoom
middle/mouse click pan
Shift+Click selection + pan
Ctrl+Click selection + handle

Search for ingredient (select and validate by "enter")

Enter text



Right Panel

Materials

- Enable Move Materials
- Show materials
- Show interfaces

Resolution

Preview

Add new material

Update preview description

Current Outway

OutObject 1

- Enable
- Hide
- Invert
- Hard cut

Add Plane Remove

Reset Outway Objects

Reset Camera

Spot Camera

Track Camera

Tab system

- Load Scene State (camera / outway)
- Save Scene State (camera / outway)

- Enable Light
- Light Follow Camera
- Use HCL coloring
- Enable Fog / Depth Culling
- Hide Lights Ingredients overlap
- Hide Objects

Scale All Particles

Color Filter by: Default

Color Protein by: Default

Show LOD level: LOD axis

Load Colors Palette (json)

Save Colors Palette (json)

Save Lights As

Save Model As

cellPACK legacy

- root
- proteins
- intranveleg_mature
- surface
- interior
- HIV_capsid
- surface

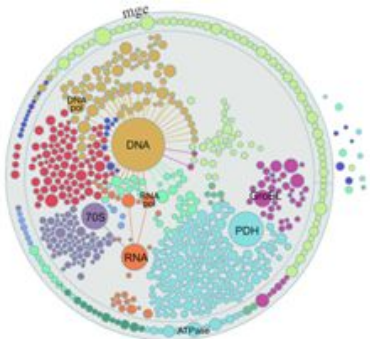
Left Panel

Right Panel

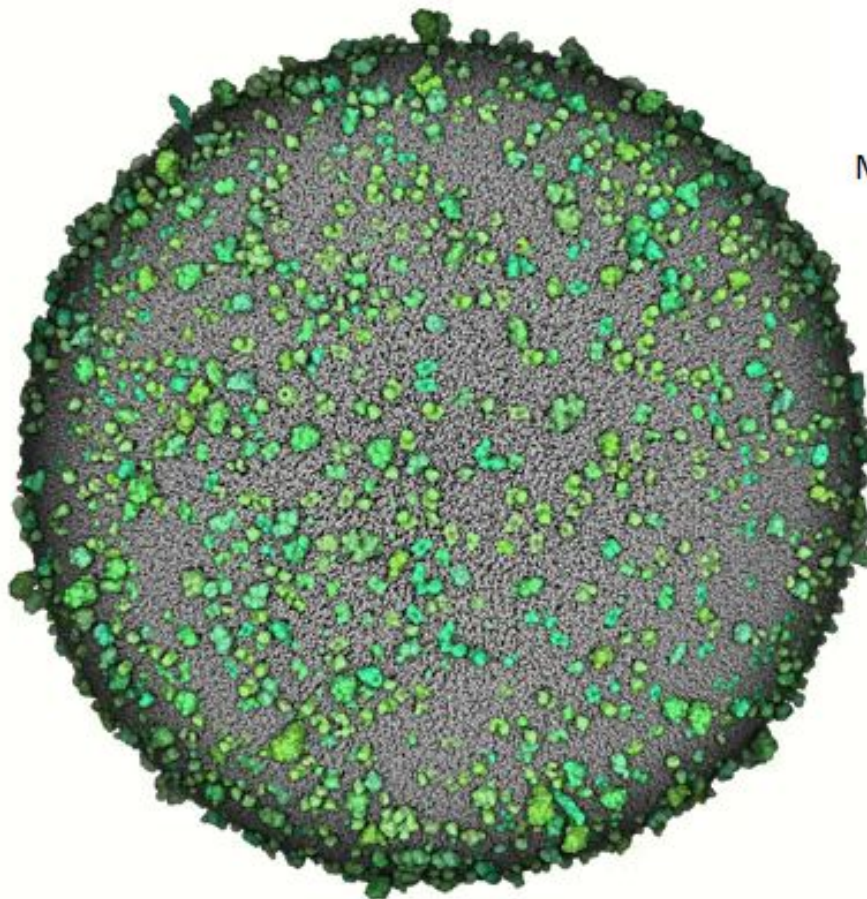
Mycoplasma genitalium, 2022



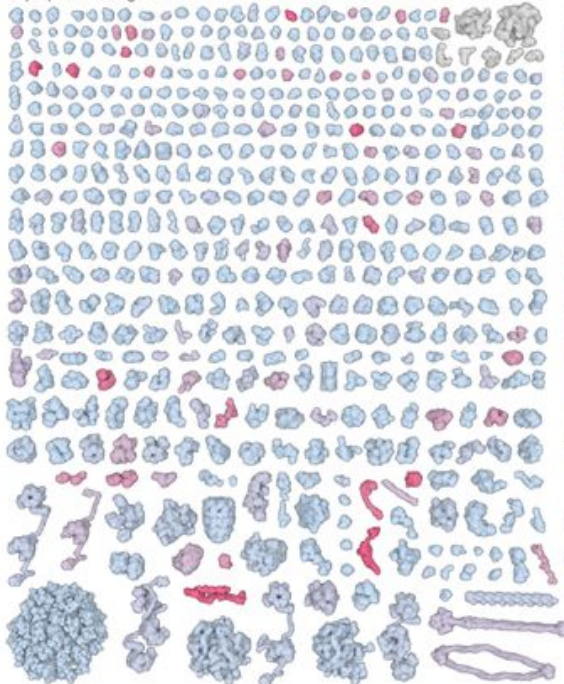
Martina Maritan



- DNA replication / DNA maintenance
- Transcription
- RNA synthesis / RNA maturation
- Translation
- Protein folding / Maturation
- Metabolism
- Protein transport / Signaling
- Host cell interaction
- Cytokinesis / Motility
- Lipoprotein
- MG-specific
- Uncharacterized



Cytoplasmic Ingredients



Membrane Ingredients



Extracellular Ingredients



Low Confidence High



David Sehnal



Alexander Rose



Mesoscale Explorer^{BETA}

<https://molstar.org/me/>

A Mol* app for exploring mesoscale models

The advent of cryo-EM and cryo-ET, coupled with computational modeling, has enabled the creation of integrative 3D models of viruses, bacteria, and cellular organelles. Based on these models, the **Mesoscale Explorer** provides unprecedented access and insight into the molecular fabric of life, enhancing perception, streamlining exploration, and simplifying visualization of diverse data types, showcasing the intricate details with unparalleled clarity.

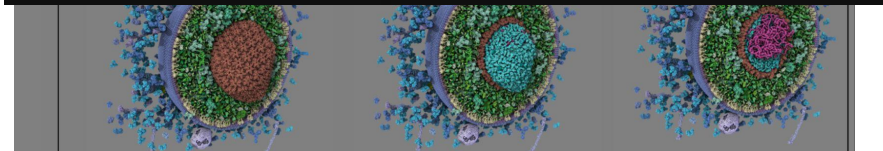
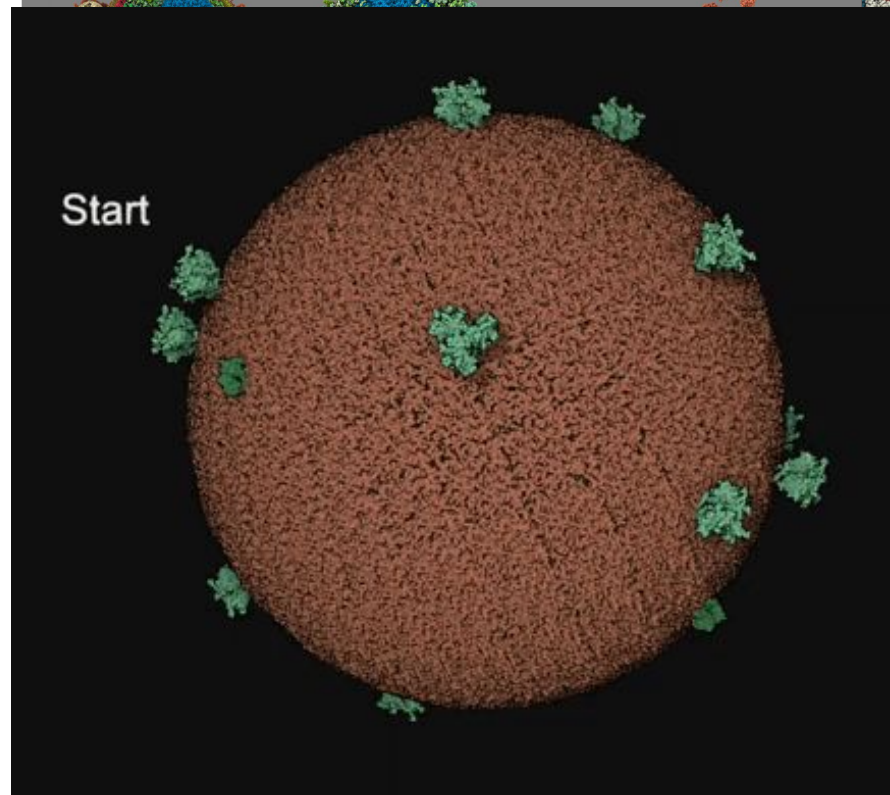
Read about Mesoscale Explorer in Protein Science

When using Mesoscale Explorer, please cite:

Alexander Rose, David Sehnal, David S. Goodsell, Ludovic Autin: [Mesoscale explorer: Visual exploration of large-scale molecular models](#), *Protein Science*, 2024; 10.1002/pro.5177.



Level of Detail



Collaboration is Key

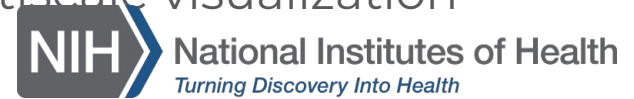
How far are we to visualize a full human cell with molecular details in real-time ?

Data gathering is a bottleneck

Level Of Detail is the common approach for multiscale visualization



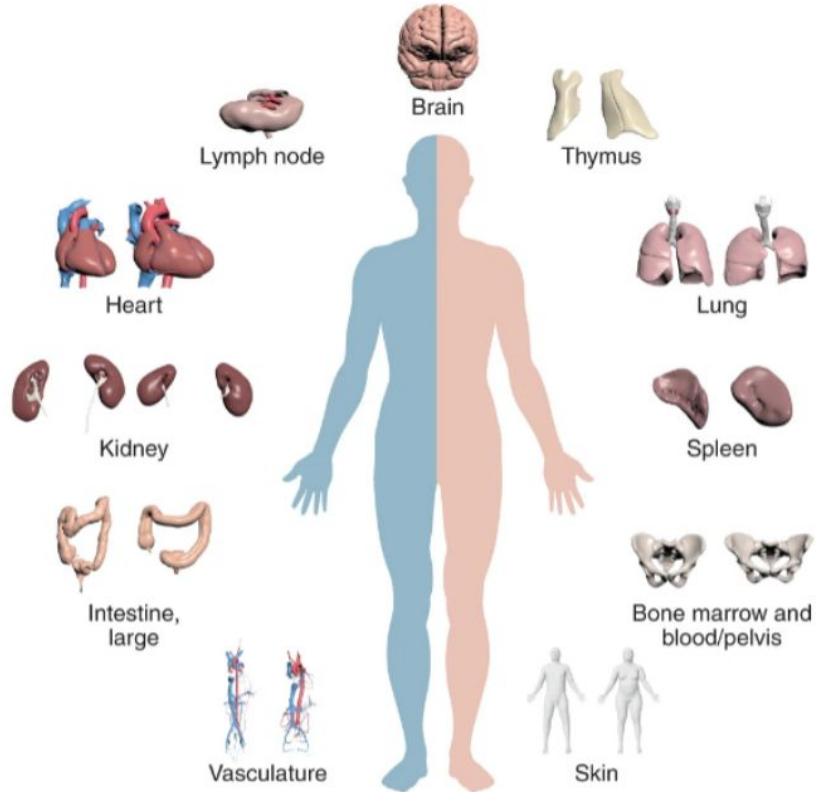
Pr. Arthur Olson



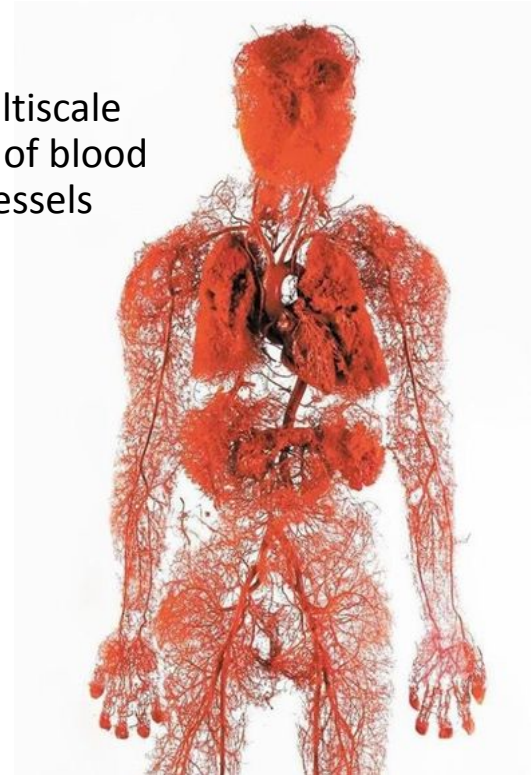
Griffin Weber

Human Reference Atlas (HRA)

<https://humanatlas.io/>



Multiscale
map of blood
vessels



<https://bodyworlds.com/>



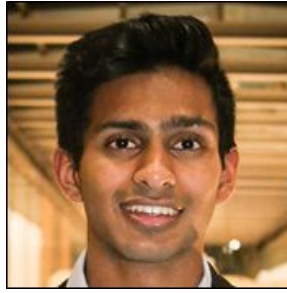
Katherine S Gustilo

Sujin Lee

Rajeev Malhotra

Marc Halushka

Ellen M Quardokus



Avinash Boppana

Bruce W Herr II

Ushma Patel

Zorina Galis

Katy Börner

www.nature.com/scientificdata

scientific data

[Check for updates](#)

OPEN

DATA DESCRIPTOR

Anatomical structures, cell types, and biomarkers of the healthy human blood vasculature

Avinash Boppana¹, Sujin Lee², Rajeev Malhotra³, Marc Halushka⁴, Katherine S Gustilo⁵, Ellen M. Quardokus⁶, Bruce W. Herr II⁷, Katy Börner⁸ & Griffin M. Weber^{9,7}✉

More than 150 scientists from 17 consortia are collaborating on an international project to build a Human Reference Atlas, which maps all 37 trillion cells in the healthy adult human body. The initial release of this atlas provided hierarchical lists of the anatomical structures, cell types, and biomarkers in 11 organs. Here, we describe the methods we used as part of this initiative to build the first open, computer-readable, and comprehensive database of the adult human blood vasculature, called the Human Reference Atlas-Vasculature Common Coordinate Framework (HRA-VCCF). It includes 993 vessels and their branching connections, 10 cell types, and 10 biomarkers. With this paper we are releasing additional details on vessel types and subtypes, branching sequence, anatomoses, portal systems, microvasculature, functional tissue units, mappings to regions vessels supply or drain, geometric properties of vessels, and links to 3D reference objects. Future versions will add variants and connections to the lymph vasculature; and, it will iteratively expand and improve the database as additional experimental data become available through the participating consortia.

Background & Summary
We recently described an ongoing international effort from 17 consortia to construct a Human Reference Atlas (HRA) that maps the entire healthy adult human body down to the single-cell level¹. It is a monumental task, considering the body has an estimated 37 trillion cells². Combined, more than 150 experts worldwide are collaborating on this initiative. At the core of the HRA is a set of ASCT³-B⁴ tables that contain hierarchical lists of Anatomical Structures, the Cell Types they contain, and associated Biomarkers. Many of the anatomical structures are linked to 3D reference objects. There are dozens of ASCT³-B⁴ tables, each representing an organ or organ system. The completed HRA will encode the structure of tissues in the human body and their variability across individuals; it will increase the precision of physiological simulations; and, it will help researchers identify changes that occur during disease. The tables are created by an interdisciplinary team of domain experts who have, to-date, based the tables on existing knowledge, literature review, or experimental datasets. Over time, multimodal imaging and tissue assays applied to specimens being collected by the consortia will generate new knowledge that will be used to expand the ASCT³-B⁴ tables and fill in details⁵.

One of the ASCT³-B⁴ tables represents the blood vasculature. Blood vessels are both the source of life for people, bringing oxygen and nutrients to almost all living cells, as well as pathways that lead to disease, including coagulopathy in COVID-19, vascular abnormalities in metastases, and the spread of metastatic cancers. For 200 years, scientists have been cataloging different parts of the vasculature⁶, but to our knowledge, no one has yet connected the dots to create an open, computer-readable, comprehensive database of all the vessels throughout the healthy adult human body. This paper describes the methods we used to do this. The process involved creating a more extensive vasculature database, called the Human Reference Atlas-Vasculature Common Coordinate Framework (HRA-VCCF)⁷, with additional details beyond what is currently included in the ASCT³-B⁴ tables.

¹Revela, Woburn, Massachusetts, USA. ²Department of Surgery, Massachusetts General Hospital, Boston, Massachusetts, USA. ³Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA. ⁴Department of Pathology, Johns Hopkins Medicine, Baltimore, Maryland, USA. ⁵Department of Intelligent Systems Engineering, Luddy School of Informatics, Computing, and Engineering, Indiana University, Bloomington, Indiana, USA. ⁶Department of Biomedical Informatics, Harvard Medical School, Boston, Massachusetts, USA. ⁷Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA. ✉email: weber@ghm.harvard.edu

SCIENTIFIC DATA | (2023) 10:452 | <https://doi.org/10.1038/s41597-023-02018-0> 3

Boppana A, et al. Anatomical structures, cell types, and biomarkers of the healthy human blood vasculature. *Sci Data*. 2023 Jul 19;10(1):452. doi: 10.1038/s41597-023-02018-0.

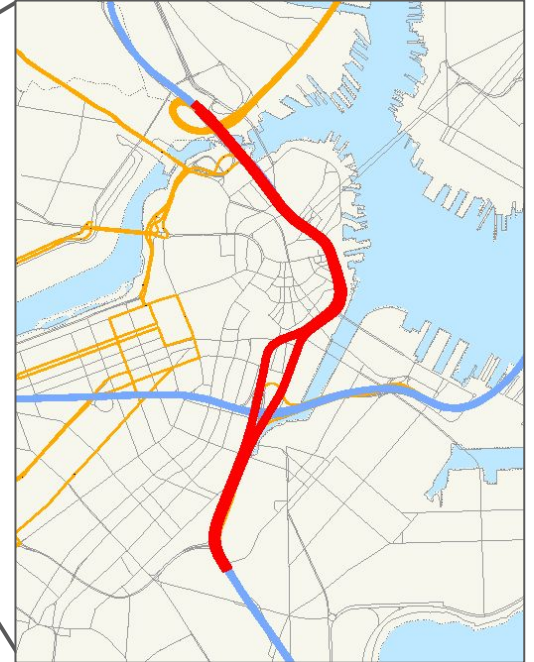
Multiscale Maps of Roads

Daily traffic, U.S. National Highway System



Note: Major flows include domestic and international freight moving by truck on highway segments with more than twenty five FAF trucks per day and between places typically more than fifty miles apart.
Source: U.S. Department of Transportation, Federal Highway Administration, Office of Freight Management and Operations, Freight Analysis Framework, version 4.3, 2017.

Boston "Central Artery"

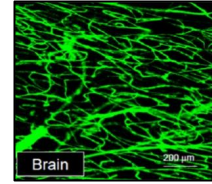


John F. Fitzgerald Expressway, By Sswonk, Public Domain,
<https://commons.wikimedia.org/w/index.php?curid=4538754>

Back Bay

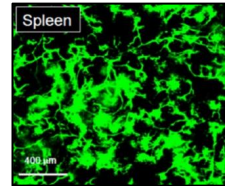


Beacon Hill

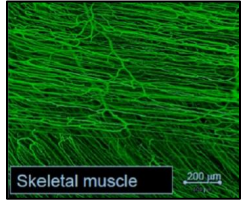


Brain

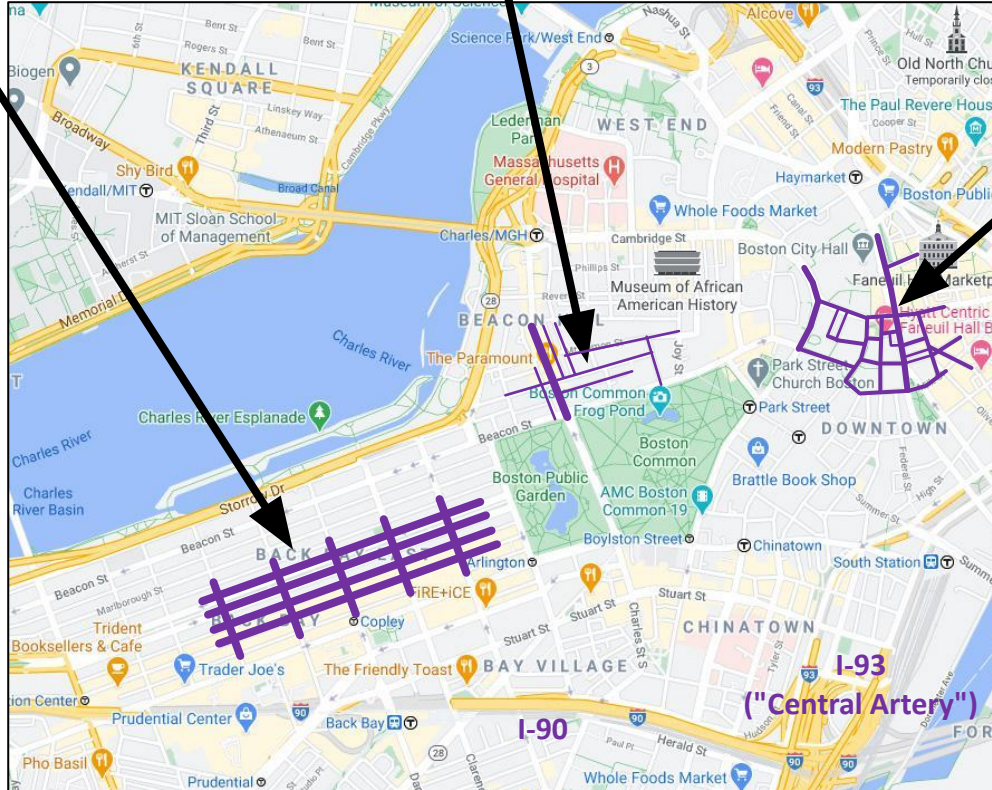
Downtown



Spleen



Skeletal muscle



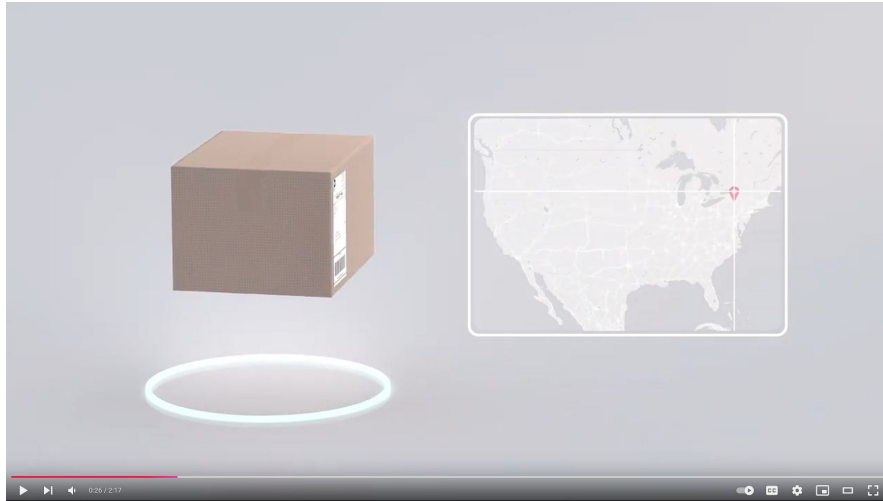
<https://www.zumper.com/blog/best-neighborhoods-in-boston-for-newcomers/>

<https://www.75statestreetgarage.com/nearby-destinations/financial-district/>

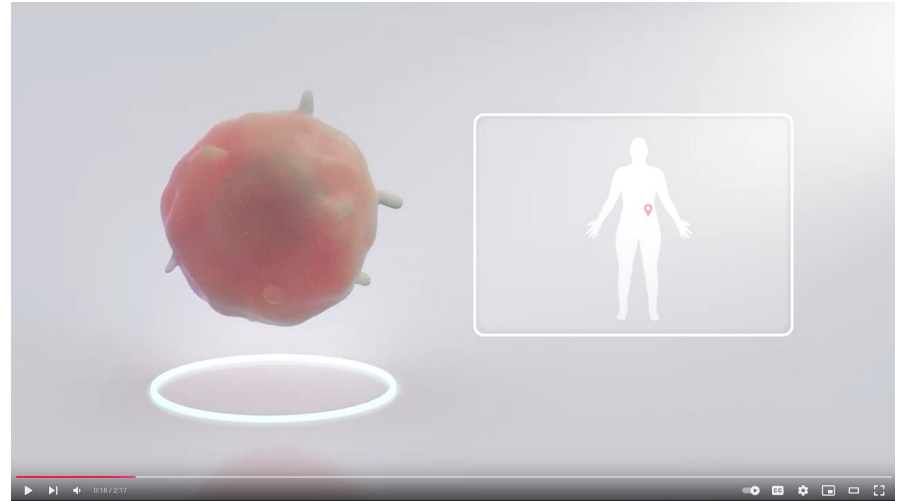
<https://pubmed.ncbi.nlm.nih.gov/27815267/>

Green lines show microvasculature in different tissues

Trucks follow roads to deliver
a package to a house



Blood cells follow vessels to
deliver oxygen to organs

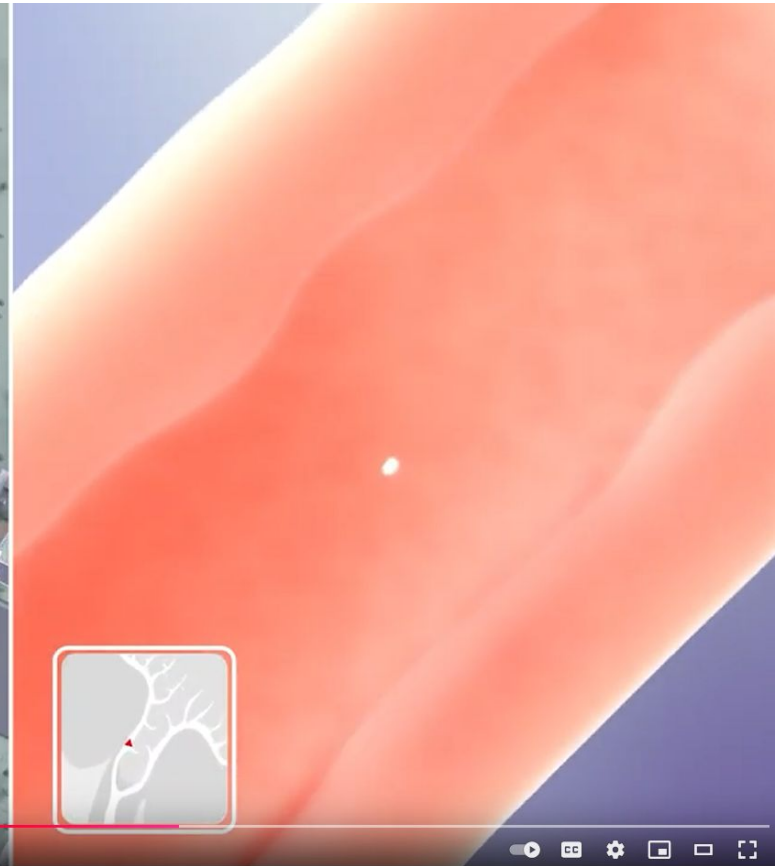


https://www.youtube.com/watch?v=zQeMgxo8n_U

Highway (1000 km)



Artery (1 m)

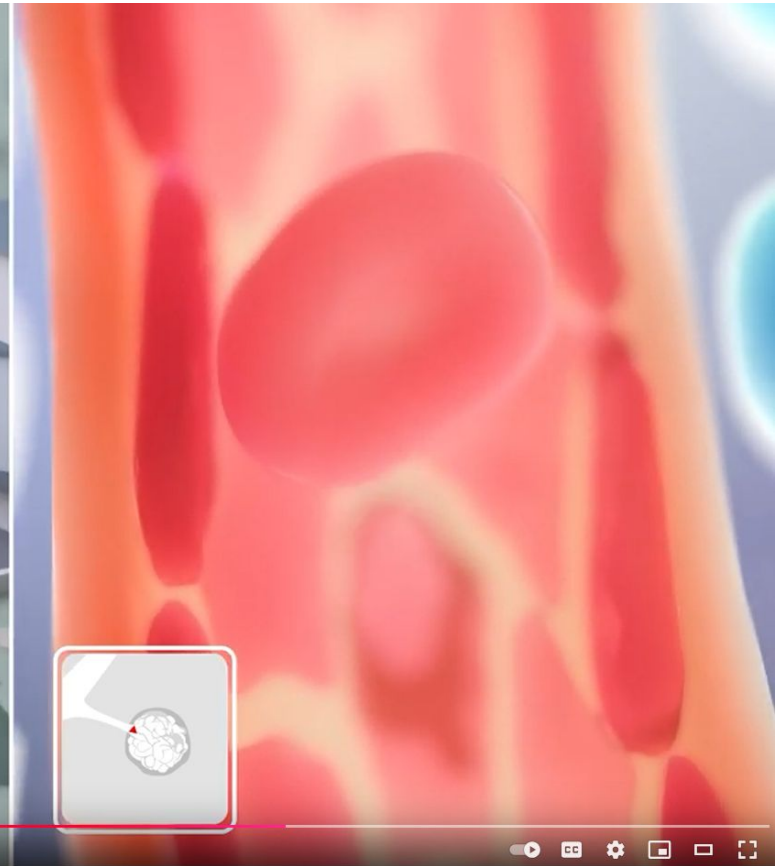


https://www.youtube.com/watch?v=zQeMgxo8n_U

Street (1 km)



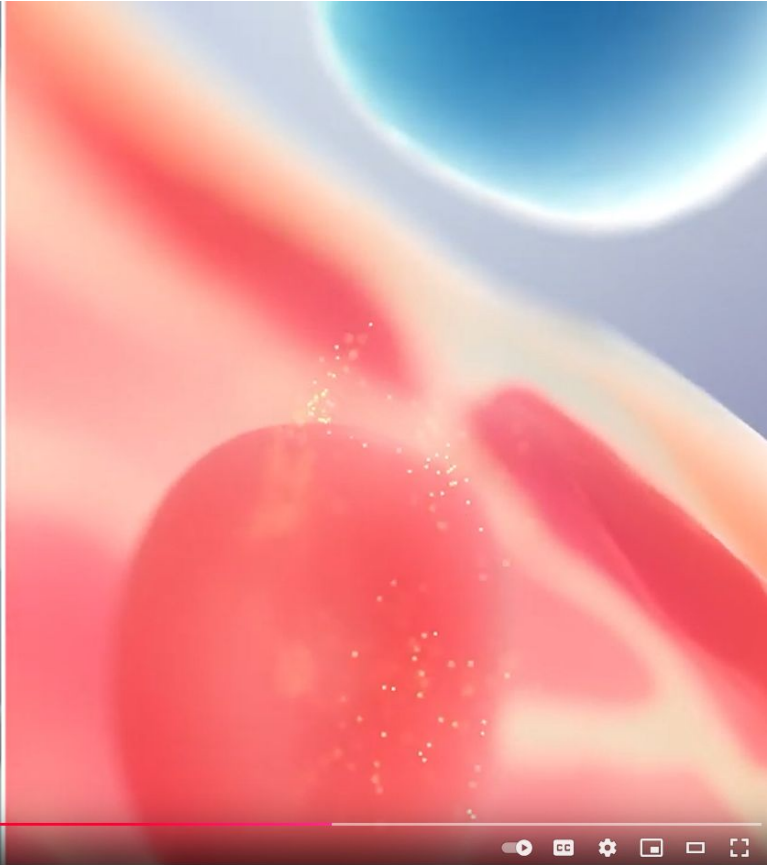
Arteriole (0.5 cm)



https://www.youtube.com/watch?v=zQeMgxo8n_U

Driveway (10 m)

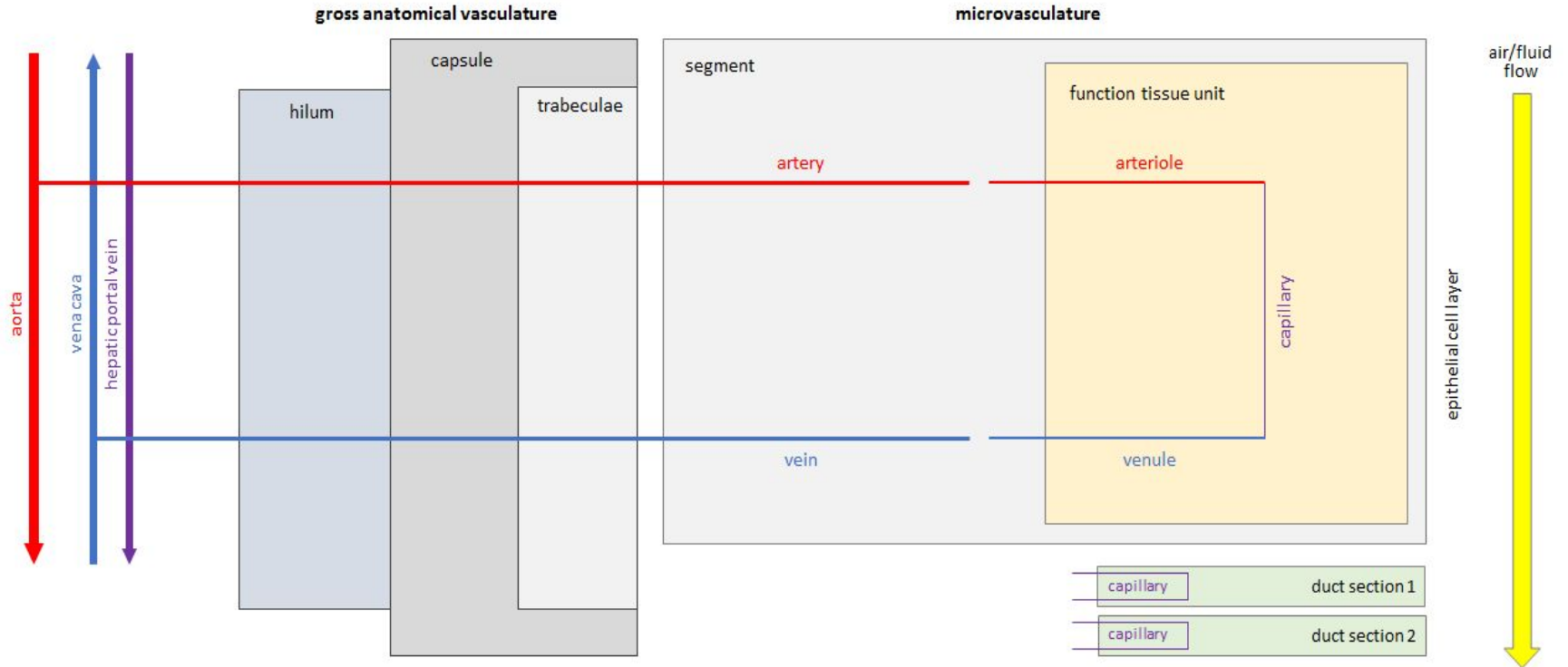
Capillary (0.5 mm x 0.01 mm)



https://www.youtube.com/watch?v=zQeMgxo8n_U

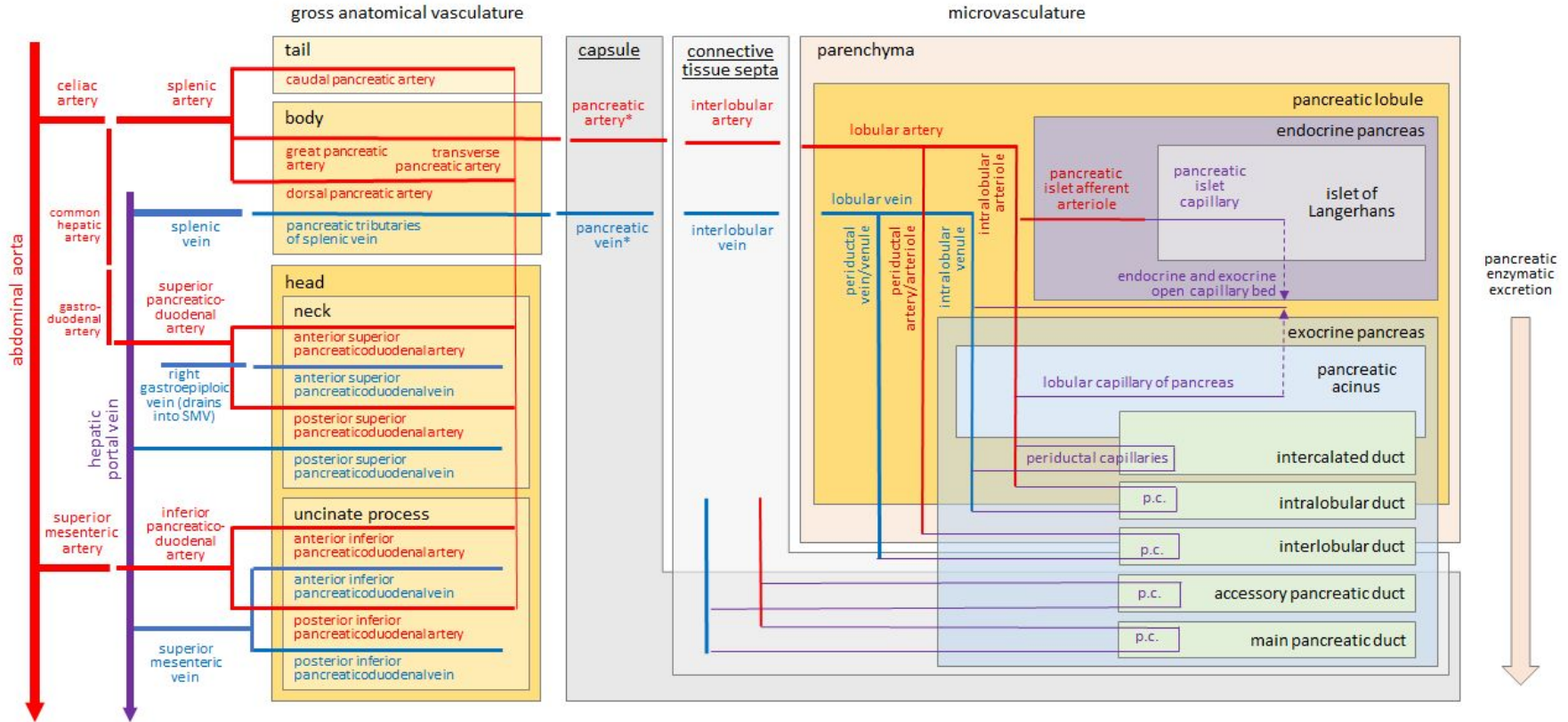
Blood Vasculature to Organ Crosswalk Diagrams

Template



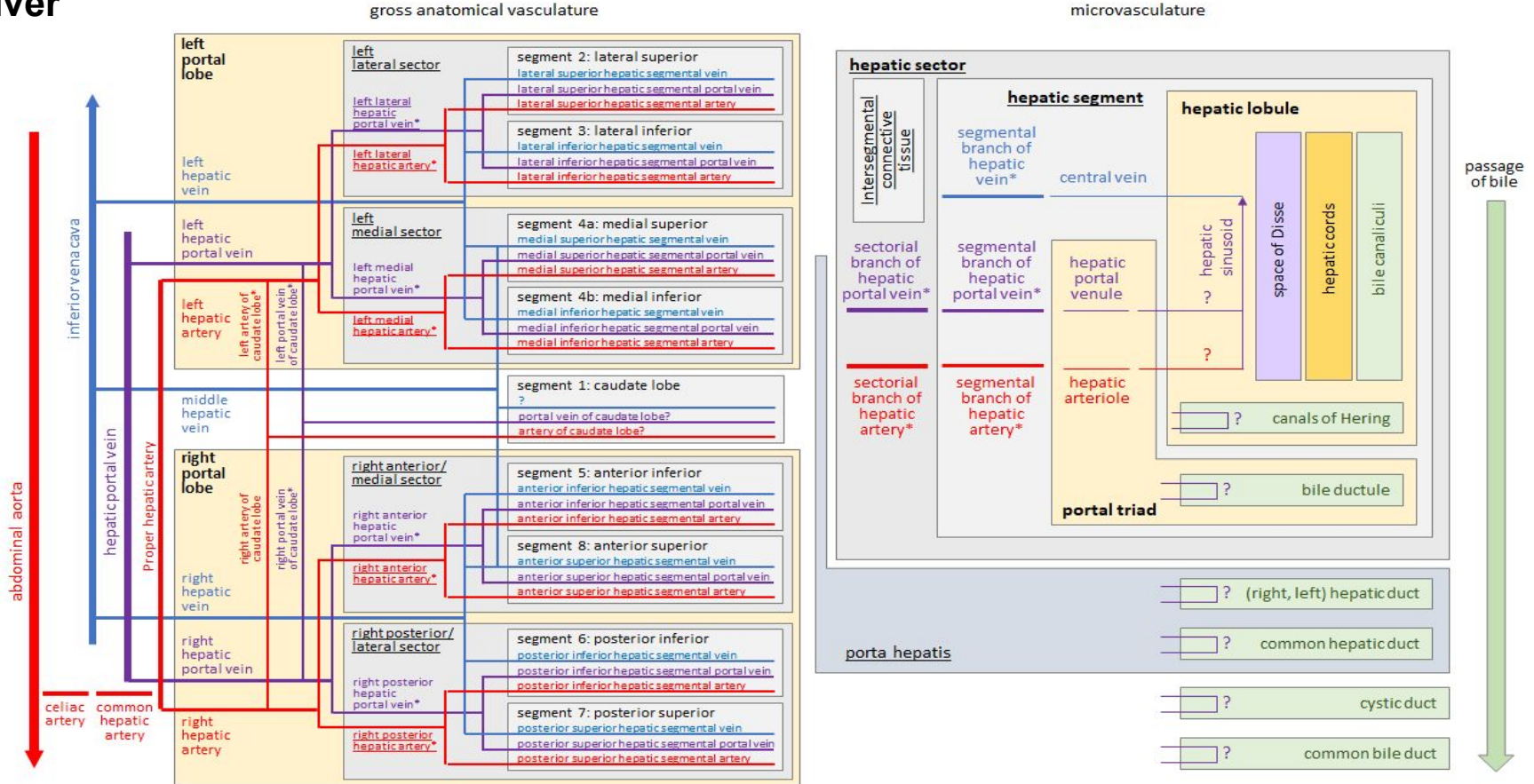
Blood Vasculature to Organ Crosswalk Diagrams

Pancreas



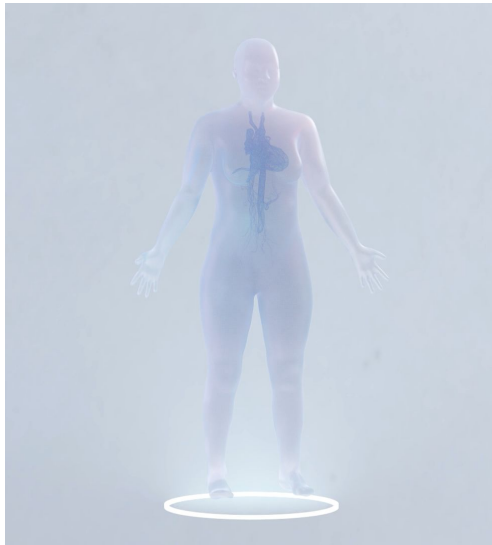
Blood Vasculature to Organ Crosswalk Diagrams

Liver



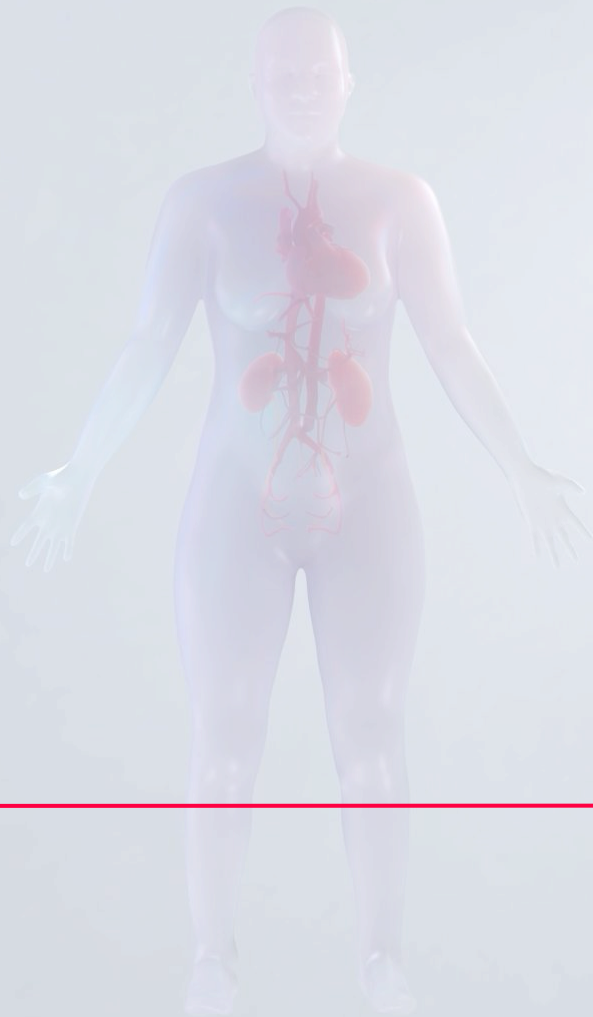


Q&A



- What is the best definition of “multiscale visualizations”?
- What application domains are best and worst served by multiscale visualizations?
- What kinds of conceptual and cognitive challenges exist for constructing and reading multiscale visualizations?
- What kinds of visual encodings make sense only in multiscale visualizations, and which ones do not make much sense?
- What kinds of interactions are needed to make multiscale visualizations usable?
- **What are the opportunities afforded and challenges posed by using extended reality (XR) technologies such as virtual, augmented, and mixed reality (VR, AR, MR) for multiscale visualizations?**
- **What is the relationship between multiscale visualizations and one-scale visualizations, such as bar graphs, scatter graphs, or line graphs? How can one be served by the other?**
- **When are stepless and stepped zooms better, respectively?**

Q&A



<https://humanatlas.io/events/2024-24h>

Thank you
