

Grand Challenges in Medical Image Processing

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What are the grand mathematical challenges in medical image processing?
Or, what are the grand mathematical challenges in biology and medicine?
Are there any grand mathematical challenges to biology and medicine?
If we had asked the last question for physics the answer would be a resounding YES – physics has flourished under the impact of mathematical thinking. Well, it was not always so. Indeed, there was a time when it was admitted that mechanics was well suited for mathematical analysis, using for example Newton's calculus, while other sub fields, such as magnetism and heat, were considered essentially too complicated for such analysis. And the experimental physicists resisted the theorists which can be seen reading the discussions in the discussions in the Nobel prize committee even as late as in the 1930's.

But we know what happened! A overwhelming triumph for mathematics in understanding physics. Is the same development going to take place in biology/medicine? Perhaps I am preaching to the converted – but I do not think the answer is evident.

Of course mathematics has been applied to biology for many years, but it must be admitted that real, or wet biologists, have often been skeptical, sometimes with good reason. One of the pioneers in mathematical biology, Nicholas Rashevsky, had a grand plan – to create a field of mathematical biophysics – presented in his ambitious work “Mathematical Biophysics”. What a wonderful idea; I was certainly impressed when I read it in the 1950’s.

But professional biologists were less impressed and it seems to have left little impact. What was wrong ? At that time I used to work with medical researchers, physiologists at the University of Stockholm, helping them with the statistical analysis of their

experimental data, analysis of variance and that sort of thing, quite pedestrian, but I was wondering if we could not try some more fundamental applications of mathematics, but with little result. One of them, von Euler, the discoverer of acetylcholine for which he got the Nobel prize, answered, “too early, come back in 50 years!”

Now, much later, it is clear that the early attempt of mathematical formalization contained too little subject matter substance, too little biology, and this was the reason why it was met by some healthy skepticism.

Today, 50 years later, the mental climate is quite different, in some fields of medicine we can see the successful use of mathematical methods, especially among young medical researchers. Here it is natural to mention medical imaging, the subject of this conference.

To formalize the problem say that the organ(s) to be observed is in the plane and forms a region X in the plane or 3-space and is observed by some camera

resulting in an image I^D , perhaps scalar or vector valued. The goal is to use I^D in order to make statements about I .

Here I am only going to describe my own preference for approaching this problem. I think of I^D as the result of a cascade of transformation sof I , for example

- 1) the groups $SO(2)$ or $SO(3)$, registration
- 2) the multiplicative group on R_+ , photometric effect, a correction
- 3) the groups $DIFFEO(2)$ or $DIFFEO(3)$, normal biological variation
- 4) semi-groups CREATION, ANNIHILATION for pathologies
- 5) additive stochastic process, camera noise.

In a Bayesian mode we introduce probability measure on the transformations to represent the various causes of variability.

This can be said to be an anatomical textbook in digital form. A diagnostical aid can then be obtained by inference from the posterior probability measure, at least in principle.

But this can be done in many ways, on many different levels of ambition, let us look at a few. Replacing probabilities with energies, E

$= -\log p$, we have to combine energies from 1) – 5), for example

$$E_3 = \int_X \|\text{grad } \phi\|^2 dx$$

$$E_5 = \int_X [\phi^{-1} \circ I - I^D]^2 dx$$

Then do MAP,
minimize energy

.....

This works fairly well but there is no guarantee that the mapping be bijective. The opposite happens sometimes, the Jacobian takes negative values in part of the image.

To remedy this we can employ flows

$$\frac{\partial \phi[x(t)]}{\partial t} = v[x(t)]$$

With the energies of the form

$$E_3 = \int_X [(Lv)(x)]^2 dx$$

$$E_5 = \int_X [\phi^{-1} \circ I - I^D]^2 dx$$

..... “large deformations”

with L as a linear differential operator of , perhaps of order two. This results in more satisfactory behavior of the mappings induced induced by Bayesian MAP but it is difficult to see any

biological justification for the form of mapping. When we turn to growth the mappings are characterized by discrete events: mitosis, cell death, cell movement and others. To represent this we shall consider

Growth as Random Iterated Diffeomorphisms: GRID

The mapping will be considered as an iteration of elementary cell decisions

$$\phi^{\alpha}(\xi_{seed}^n, t_n) \circ \dots \circ \phi^{\alpha}(\xi_{seed}^2, t_2) \circ \phi^{\alpha}(\xi_{seed}^1, t_1)$$

where each decision is of some type and time stamp (as superscript) and the combinations are function composition. Random decisions...

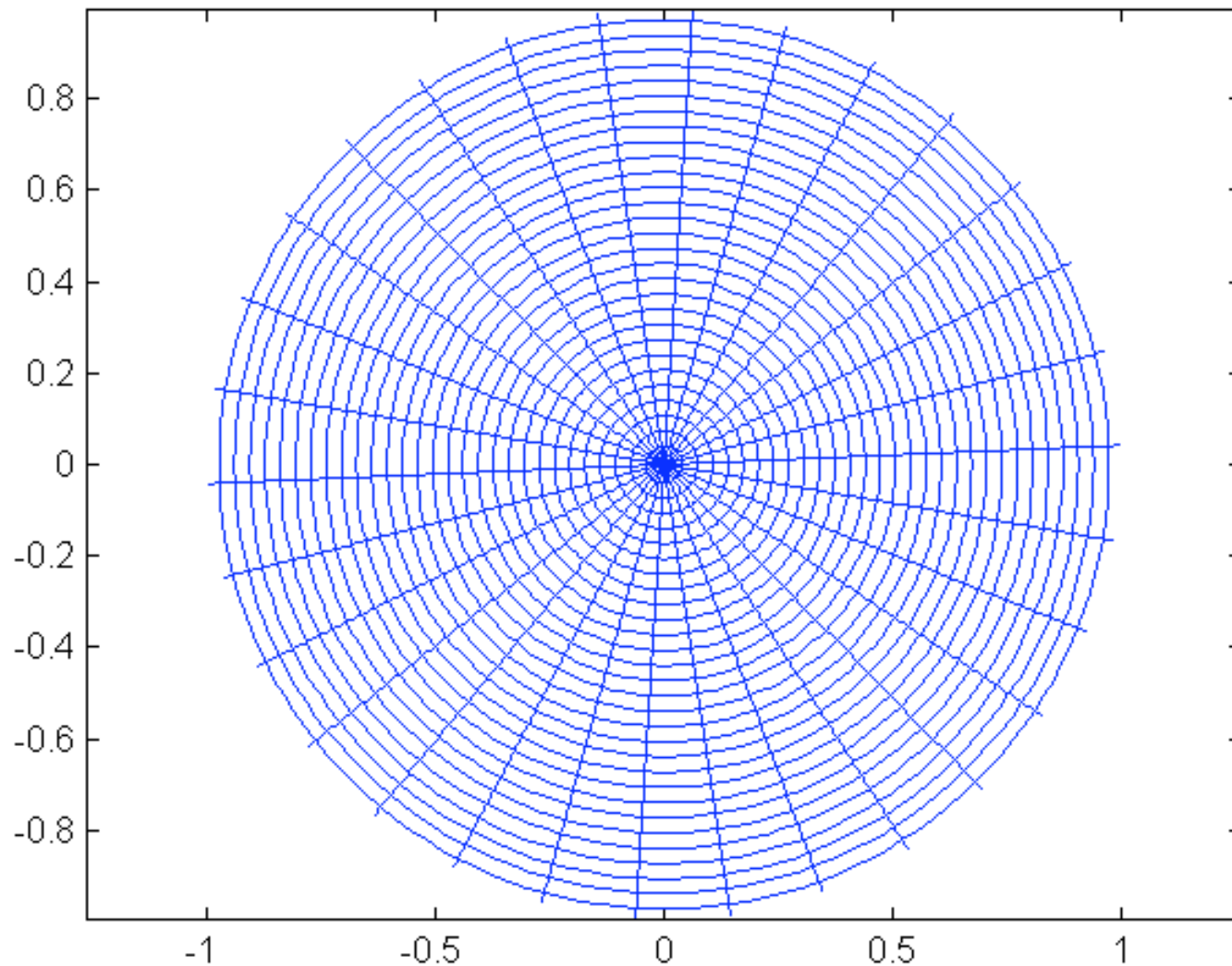
But we shall emphasize that decisions are controlled by biological coordinates

$$\text{darcyan coordinates } \xi = (\xi_1, \xi_2)$$

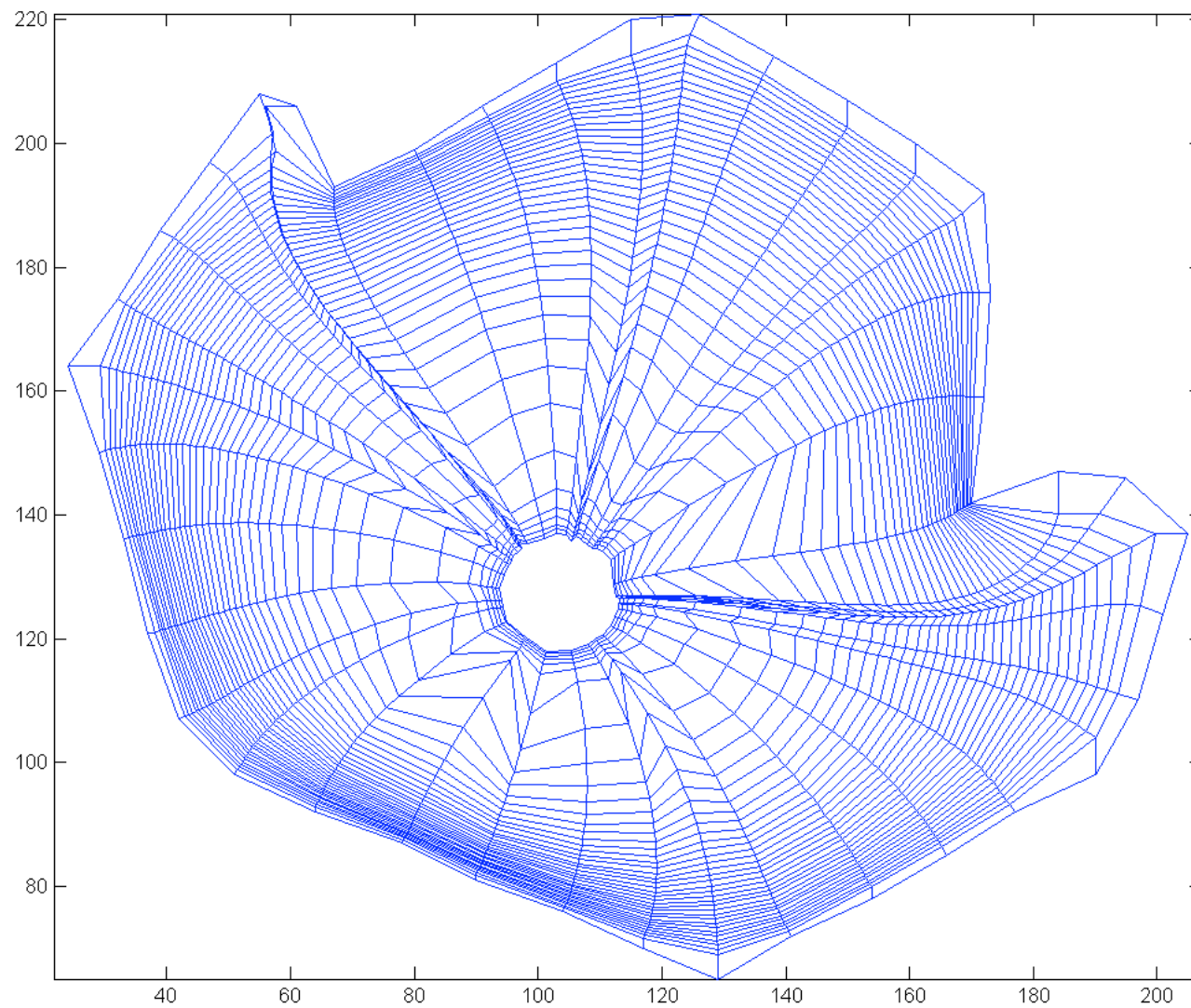
named after d'Arcy Thompson, our great forerunner. The coordinate system should express the topography of the organism and should develop together with it in time. The genetics is therefore given in darcyan coordinates: the organism obeys laws of development given in its own (relative) space, not in absolute space.

This is not the place to describe in detail how we generate darcyan coordinate systems, but let us mention two examples: one of artificial character in polar form and with level functions u satisfying Poisson's equation with a pole

Darcyan coordinates $\underline{r} = (r_1, r_2)$, radial and angular coordinates



And the other for an anatomical slice



. The GRID - Growth as Random Iterated Diffeomorphisms- as a set of mappings on the space of diffeomorphisms $DIFFEO : \Xi \rightarrow X$, The set is generated by the elementary mappings

$$\phi_{radial}(\eta) : x(\xi) \rightarrow x'(\xi); \xi \in \Xi \quad (59)$$

with the property that

$$direction[x'(\xi) - \eta] = direction[x(\xi) - \eta] \quad (60)$$

This means that the displacement vector $x' - \eta$ is parallel to the vector $x - \eta$ itself: the cells grow or decay radially from the seed η . Actually we have used the form

$$x \rightarrow (x - x(\eta))\psi(\|x - x(\eta)\|) \quad (61)$$

where the real valued function of a real argument ψ maps the interval $[0, \infty)$ diffeomorphically onto itself with 0 as a fixed point. This is called the *radial version of GRID*.

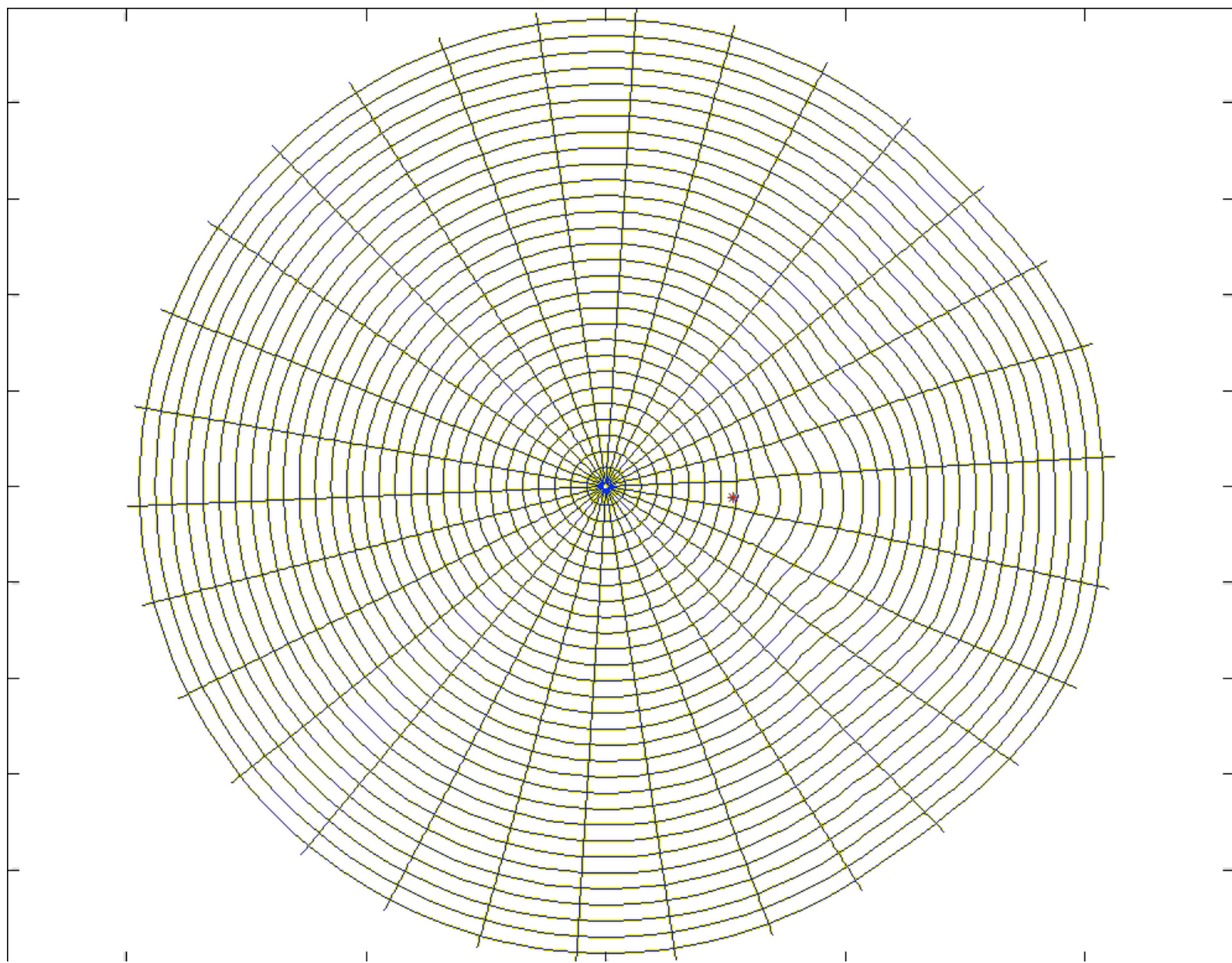
Then form the set

$$radialGRID = \overline{[\phi_{radial}(\eta); \forall \eta \in \Xi]_{\circ}} \quad (62)$$

where $[\cdot]_{\circ}$ means the algebraic closure with respect to function composition and the horizontal bar indicates topological closure with respect to some suitable topology on the set of diffeomorphisms.

The seeds will be distributed according to a Poisson point process with density depending upon $_$ and time as coded genetically; note that the information follows the geometric development as expressed in darcyan coordinates.

This results in growth as the seeds are switched on/off according to the genetic information at the darcyan coordinates, for example the following artificial organ development where red stars indicate the seed currently switched on

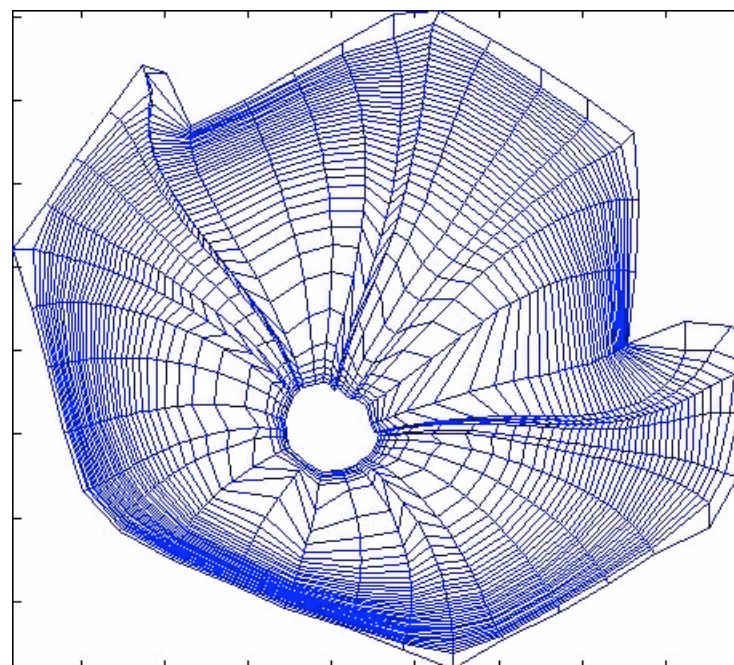


Or, for an anatomical slice where a darcyan system was shown earlier

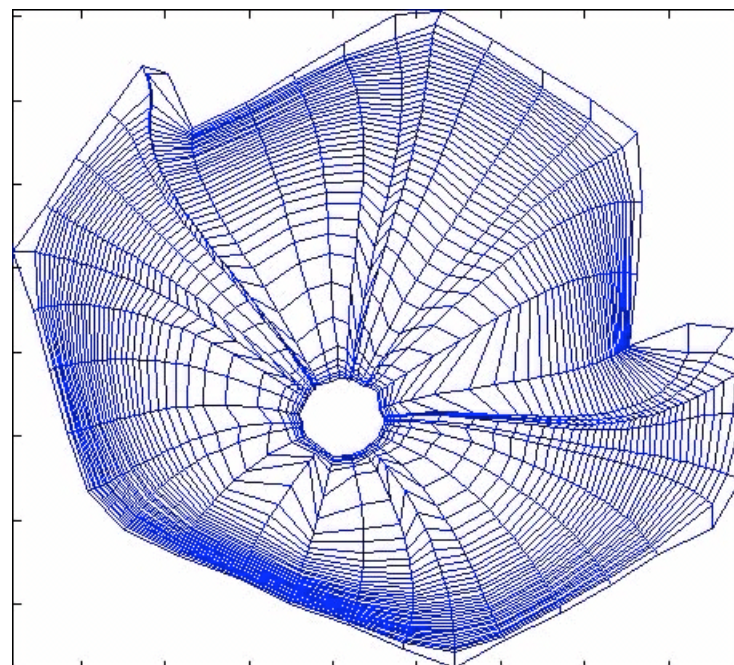
But in a real organism there will be a lot of decisions made at a fast rate, so it is natural to ask if we can apply a LLN paradigm and obtain a limiting behavior This is indeed possible and leads to the differential equation for the “thermodynamic limit”

$$\frac{\partial x(\xi, t)}{\partial t} = \int_{\xi_{seed} \in \Xi} \theta[x(\xi, t) - x(\xi_{seed}, t)] F(d\xi_{seed}); \theta(u) = \psi(u) - u$$

where F is a bounded signed measure, positive variation for growth seeds and negative for decay seeds. The field x takes 2-vectors as values; we assume isotropic growth in this equation.



And a more complicated growth



We believe that anatomical maps of darcyan types should also allow the occurrence of multiple poles to represent the appearance of anatomical sub-structures, for example a slice of the forearm

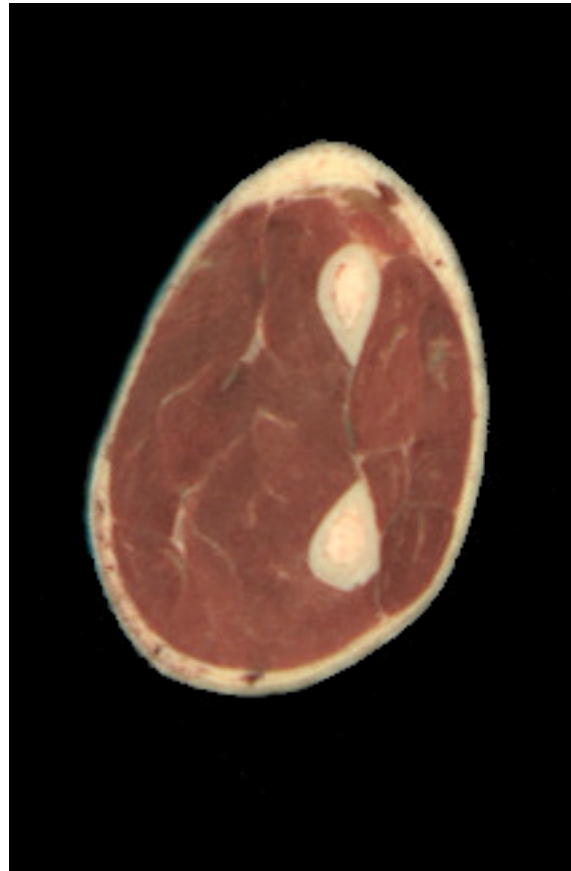
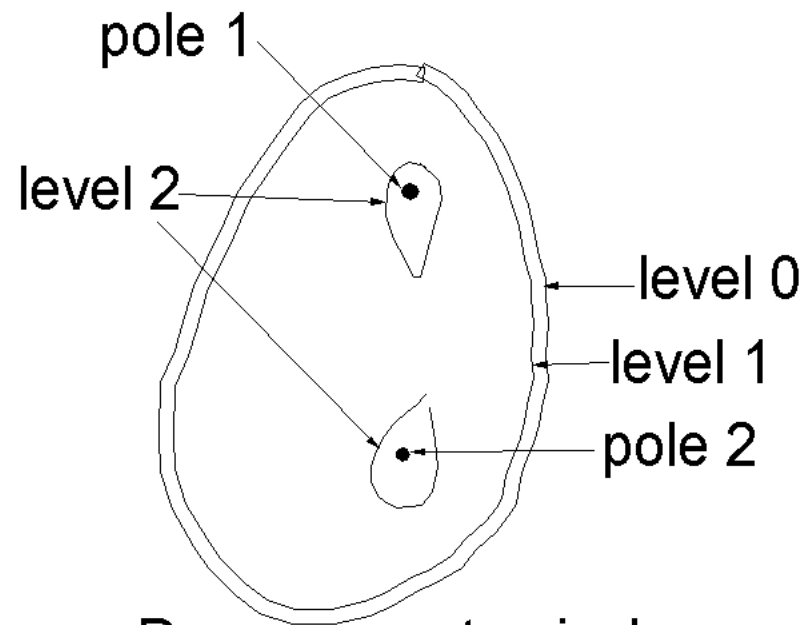


Image courtesy: The Visible Human, NIH



Darcyan anatomical map
of forearm with radius and ulna

Here the level curves are associated with boundary values 0,1,2 the u -field is given as the solution of Laplace's equation in respective regions and by the Poisson equation with a pole for the innermost regions inside level 2.

This is work in progress with ongoing studies of

- 1) Functional analysis of GRID spaces
- 2) Probabilistic limit theorems for GRID
- 3) Inference algorithms, also for pathologies
- 4) Development of code

But most important, a deeper study of the biological basis behind mathematical growth models. This will require close cooperation with developmental biologists, embryologists, radiologists...

Thank you for your attention !