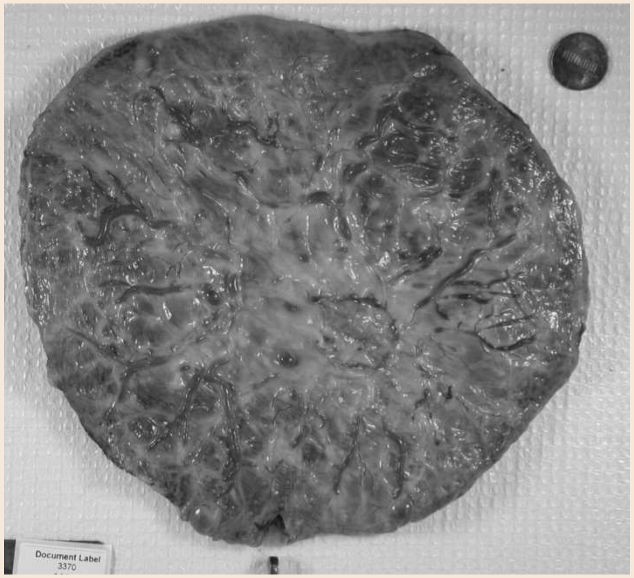
Dynamical modeling of human placental vasculature

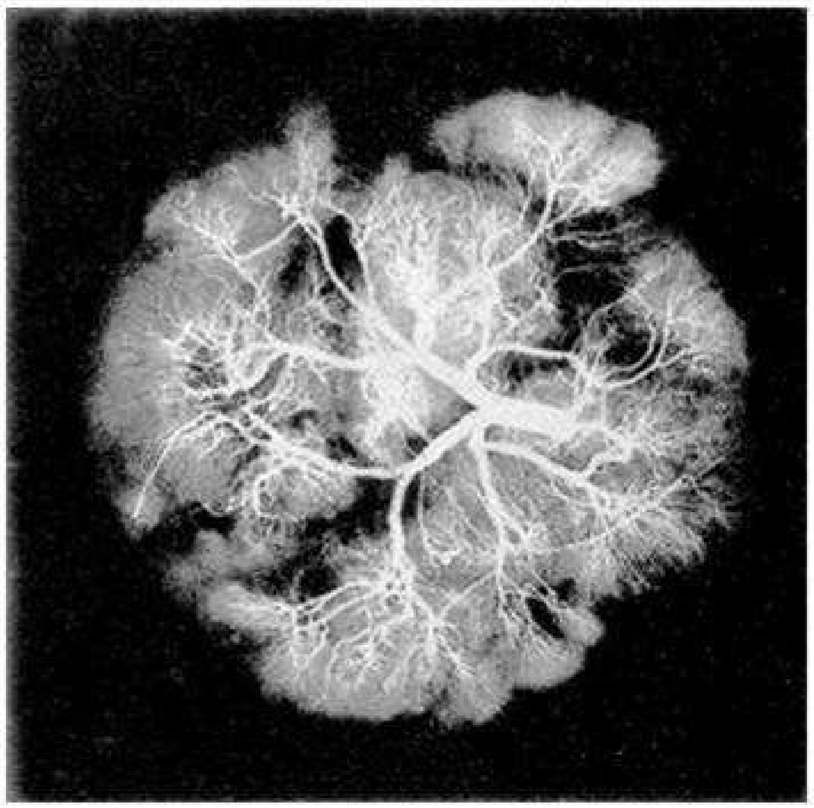
Michael Yampolsky (University of Toronto)

Joint project with Carolyn M. Salafia (*Placental Analytics*, Larchmont, NY)

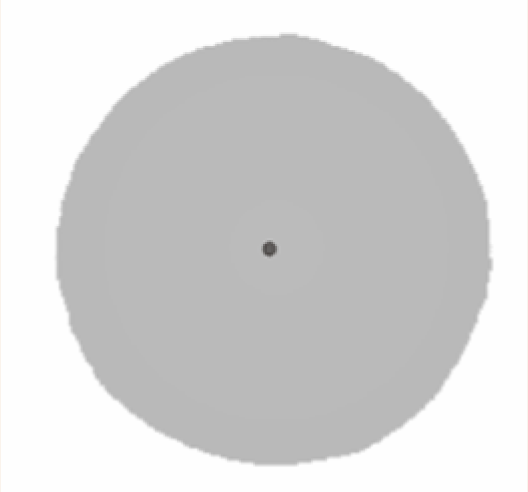
- The placenta is the sole fetal source of oxygen and nutrients. It is a principal regulator of fetal growth and fetal health.
- An important goal: use placenta to predict adult health risks.



- Placenta is little more than a vascular tree, growing from the insertion of the umbilical cord.



- Difficult to analyze the structure
- What about classifying the shape? Normal placentas (75% of all cases) are round, with umbilical cord in the middle…

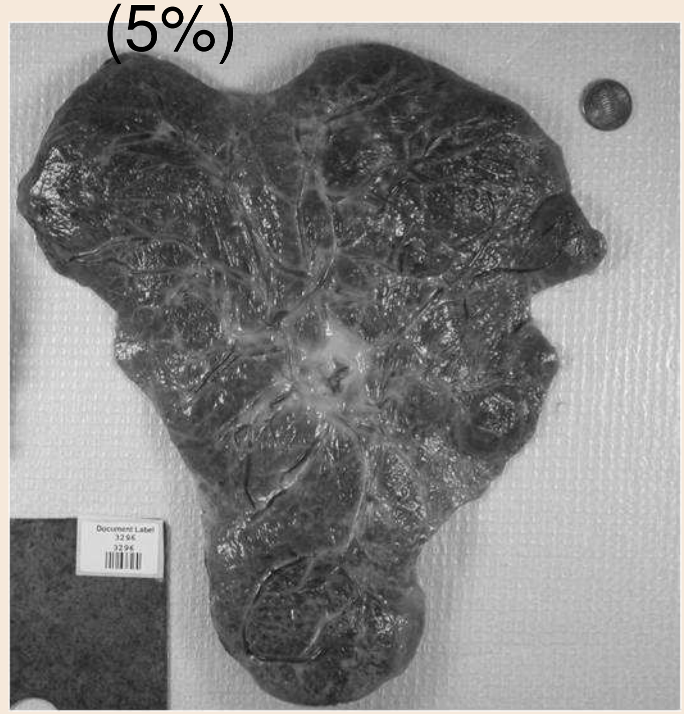


Mean placental shape: disk with radius 9cm [Yampolsky, Shlakhter, Salafia, 2008]

… but irregular ones often have very regular shapes:

star-like (5%)

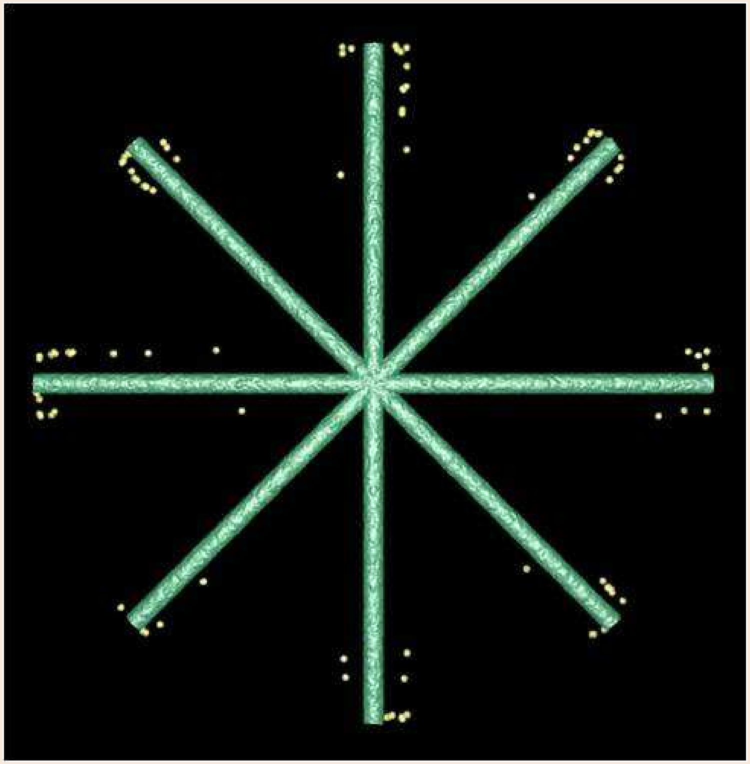
several lobes (5%)



- In the simplest approximation, the vascular tree is a self-similar fractal. This suggests that variation is produced by a change in the branching structure during the growth of the tree.
- Need a dynamical model of growth.

Modeling growth "at the tips" (angiogenesis) using DLA.

- How do we identify the tips of a tree?
- Release a cloud of diffusion particles. The tips are where most of them land.



Diffusion Limited Aggregation (DLA)

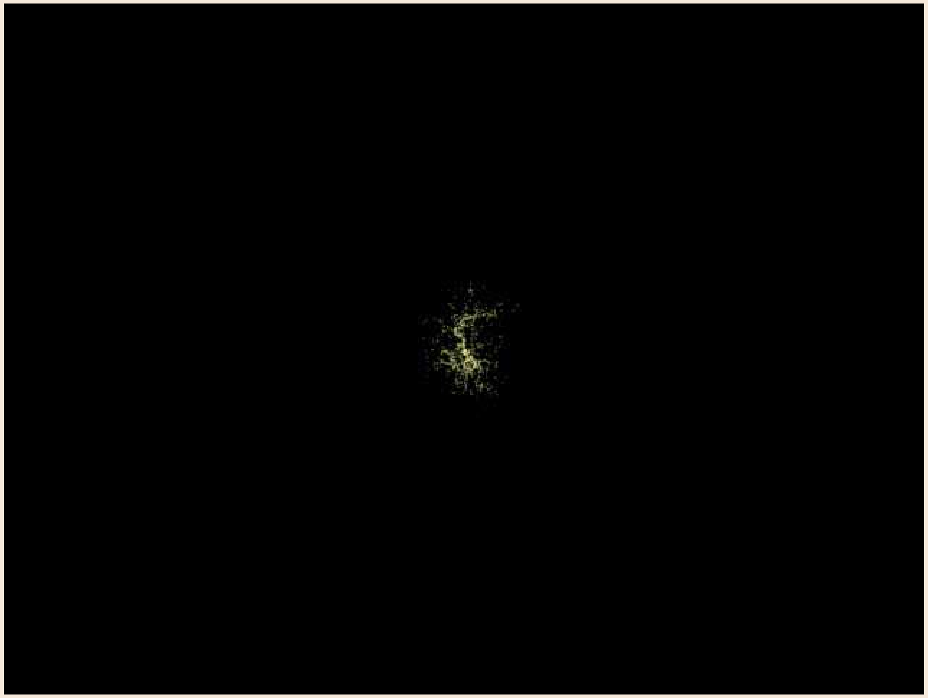
introduced by Witten and Sander (1981)

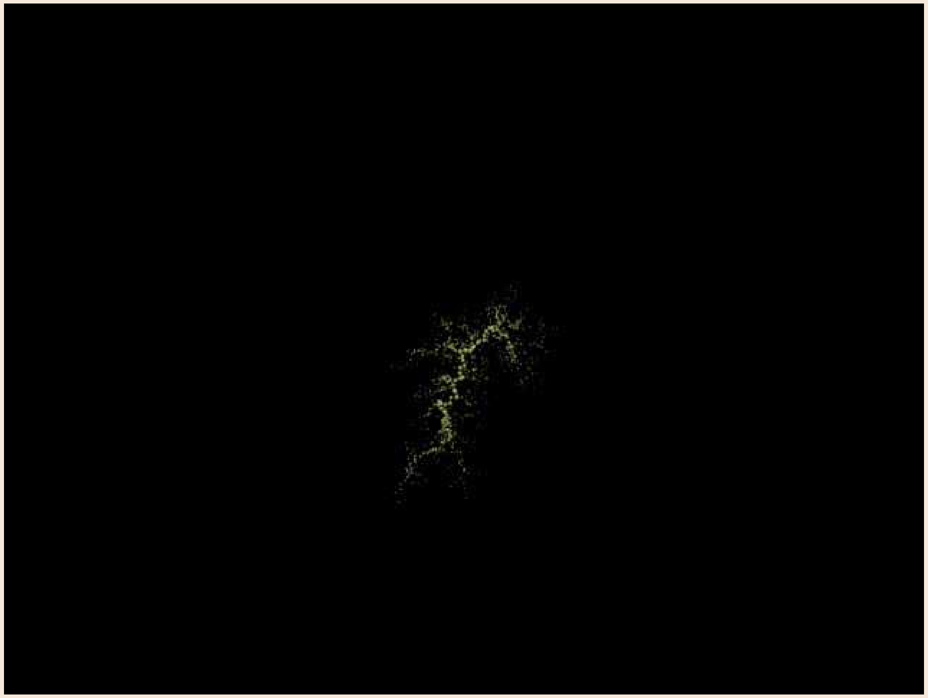
- At a moment of time n have cluster C_n consisting of n units of growth
- Release a random walker far from the cluster, and mark the first place where it makes contact with C_n
- Augment C_n with a unit of growth at the place of contact, producing a new cluster C_{n+1}

Interpretation from Potential Theory

- Assume that C_n is perfectly conducting, and charged with the unit charge. The potential Φ is the Dirichlet solution of the Laplace equation $\Delta\Phi=0$
- The probability of new growth in a boundary patch $P\subset C_n$ is the *harmonic measure* of P, which is the total charge in P.

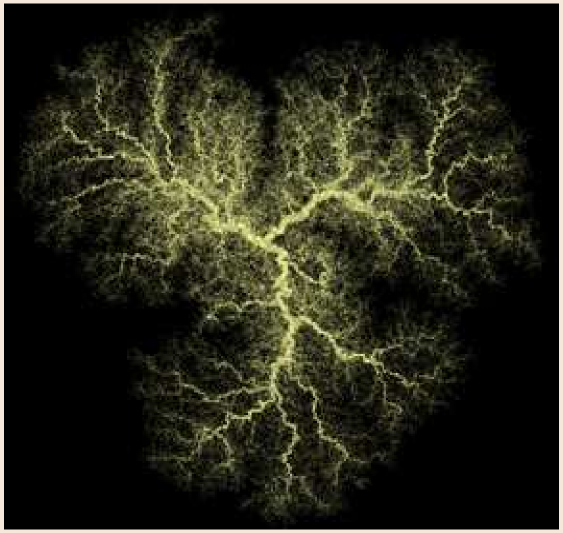
- Dynamical modeling of a 3D vascular tree growth in a hemisphere

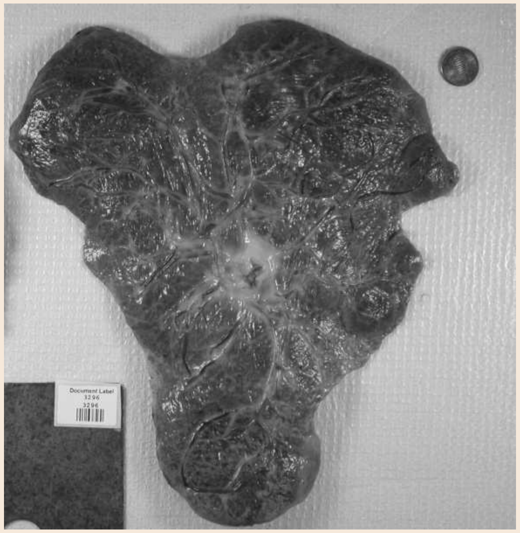




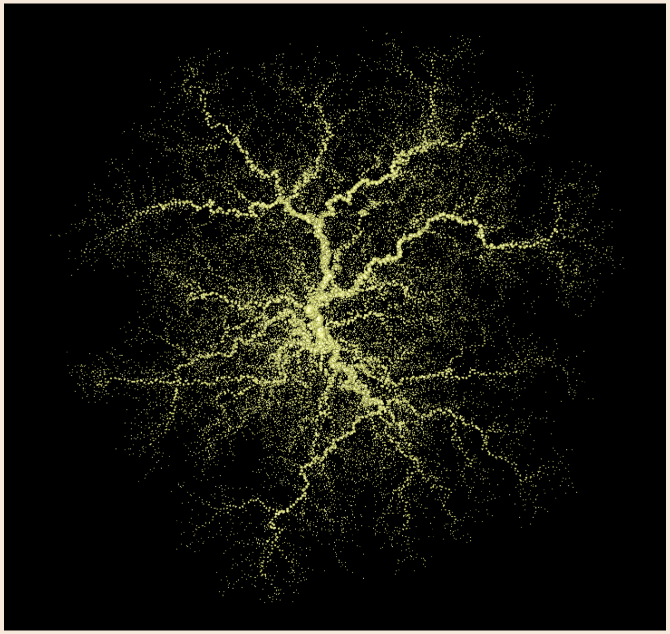
Changing the branching structure

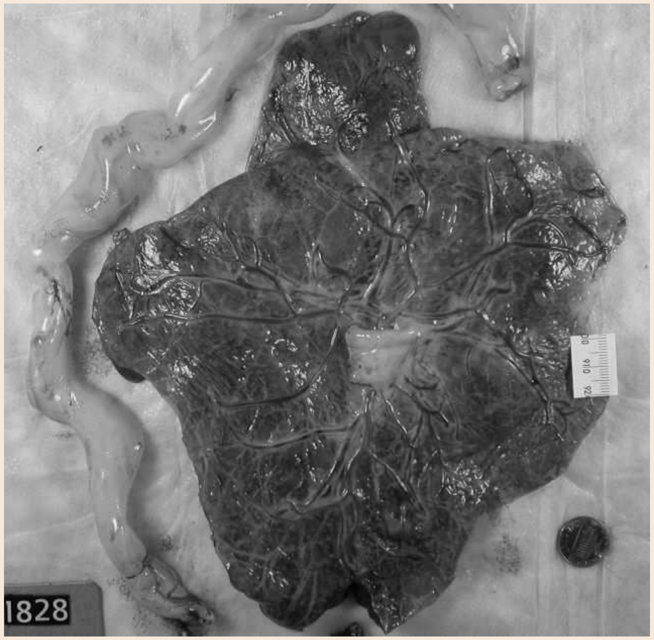
- Change the probability p in $(0,1]$ that a blind fly lands when it hits the tree, or…
- Change the size of the unit of new growth
- If change is made at 5% of overall growth, get several large lobes:





- If change at 50% of overall growth, get a star:





Two placental surfaces on which the larger vessels are traced manually. Note the

relative lack of mid-size branches in the vascular tree of the tri-lobate placenta on the right, as predicted by our model.

How does change in branching affect the effectiveness of a placenta?

- Fetal-placental scaling law [Salafia, Misra, Yampolsky, et al, 2008]

Placental mass = Fetal mass^{5}

- A version of Kleiber's Law:

Metabolic rate ~ Body mass$^{3/4}$

with placental mass used as a proxy for metabolic rate. *Body size and metabolism.* **Kleiber, M.** 1932, Hilgardia, Vol. 6, pp. 315-353.

Kleiber, M. *The Fire of Life. Revised Ed.* 1975.

Controversy

- "Surface theory": metabolic rate is proportional to the surface area.

$$B \sim (diameter)^2, \quad M \sim (diameter)^3$$

Hence,

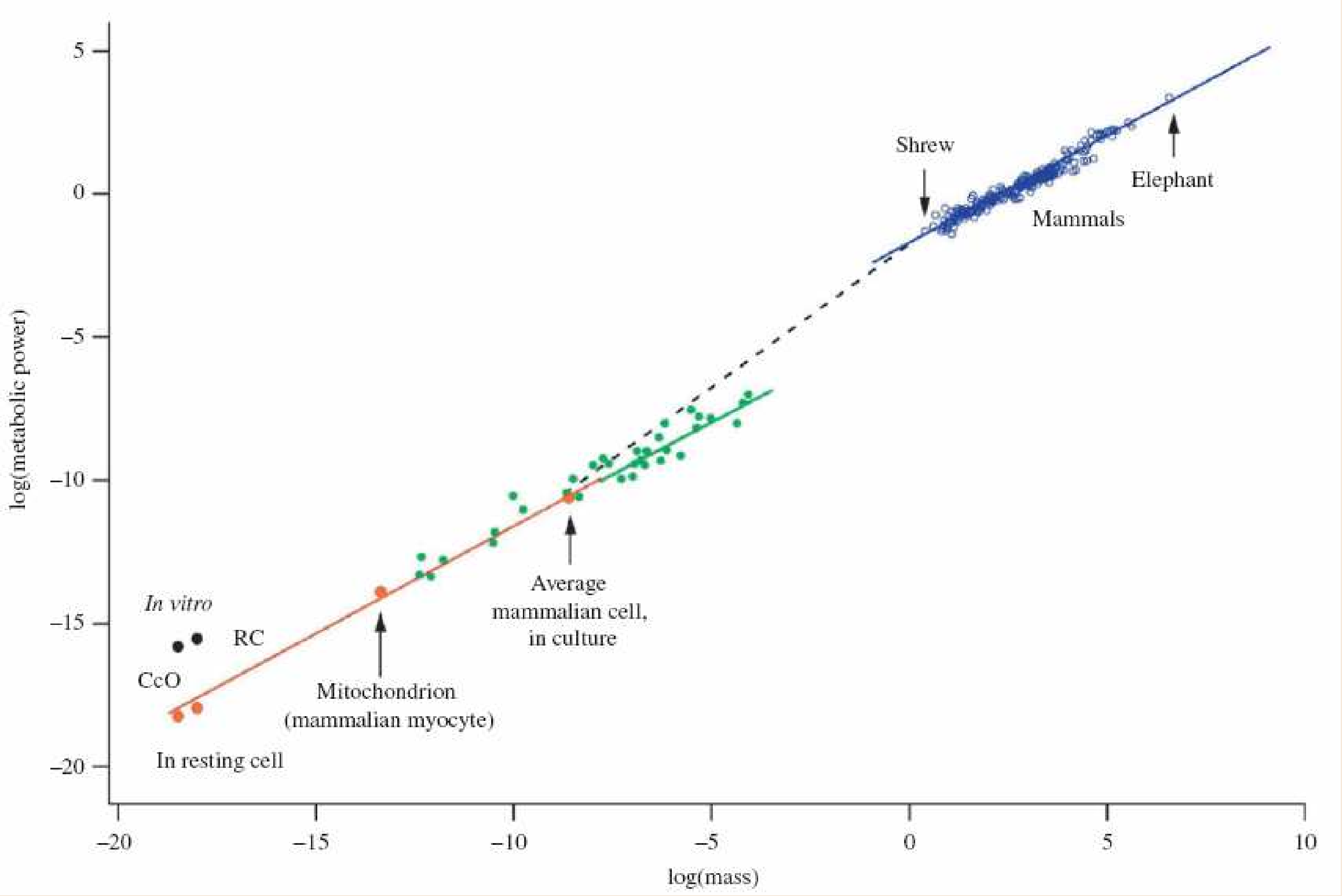
$$B \sim M^{2/3}$$

- Basal metabolic rate is difficult to define and measure

METABOLIC RATE VERSUS BODY WEIGHT

A. Data Used for Calculation of Regression Line

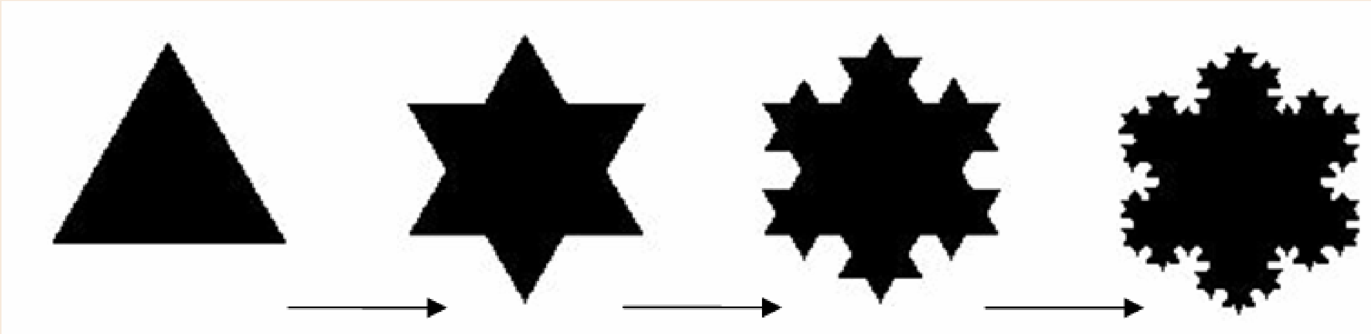
Group	Animal	Author	Body Weight (kg)	Metabolic Rate per Day (kcal)
1	Mouse	Benedict and Lee (1936)	0.021	3.6
2	Rat 230–300 days old	Kleiber, Smith, and Chernikoff (1956)	0.282	28.1
3	Guinea pig	Benedict (1938)	0.410	35.1
4	Rabbit	Tomme and Loria (1936)	2.98	167
5	Rabbit	R. Lee (1939)	1.52	83
6	Rabbit		2.46	119
7	Rabbit		3.57	164
8	Rabbit		4.33	191
9	Rabbit		5.33	233
10	Cat	Benedict (1938)	3.00	152
11	Macaque	Benedict (1938)	4.2	207
12	Dog	Galvao (1942)	6.6	288
13	Dog		14.1	534
14	Dog		24.8	875
15	Dog	de Beer and Hjort (1938)	23.6	872
16	Goat	Benedict (1938)	36.0	800
17	Chimpanzee	Bruhn and Benedict (1936)	38.0	1090
18	Sheep	Lines and Pierce (1931)	46.4	1254
19	Sheep		46.8	1330
20	Women	McKittrick (1936)	57.2	1368
21	Women	Lewis, Iliff, and Duval (1943)	54.8	1224
22	Women	McCrery, Wolf, and Bavousett (1940)	57.9	1320
23	Cow	Benedict and Ritzman (1935)	300	4221
24	Cow	Kleiber, Regan, and Mead (1945)	435	8166
25	Beef heifers	Kleiber, Goss, and Guilbert (1936)	482	7754
26	Cow	Benedict and Ritzman (1935)	600	7877



Extension of Kleiber's 3/4-power law for the metabolic rate of mammals to over 27 orders of magnitude from individuals (blue circles)
to uncoupled mammalian cells, mitochondria and terminal oxidase molecules, CcO of the respiratory complex, RC (red circles). Also shown
are data for unicellular organisms (green circles). Figure taken from West et al. (2002b)

Scaling and the fractal nature of circulatory networks

- Toy model: 2D organism shaped as von Koch Snowflake



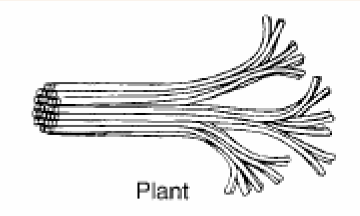
smallest decoration has size l_0

Area ~ (diameter)^2, Perimeter ~ (diameter)$^\gamma$, where γ= log 4/log 3

$$B \sim M^{\beta}, \ \beta = \log 2/\log 3 \approx 0.63 > 0.5$$

- *A general model for the origin of allometric scaling laws in biology.* **West, G.B., Brown, J.H. and Enquist, B. J.** 1997, Science, Vol. 276, pp. 122-126.

Rigid-pipe model (WBE):



self-similar scaling

$$r_{k+1}/r_k = t,\ l_{k+1}/l_k = s,\ N_{k+1}/N_k = n$$

From considerations of blood volume

$$\beta = -\log n / \log (st^2)$$

Total volume supplied by network ~ $(l_k)^3 N_k$. Hence, $s \approx n^{-1/3}$

Total area ~ $(r_k)^2 N_k \approx (r_{k+1})^2 N_{k+1}$. Hence, $t \approx n^{-1/2}$

Fetal-placental scaling law

- PM = placental mass, FM = fetal mass

$$PM \sim FM^{\beta}$$

Suggested by Ahern in 1966 with $\beta = 2/3$

- [Salafia, Misra, Yampolsky, et al, 2008]

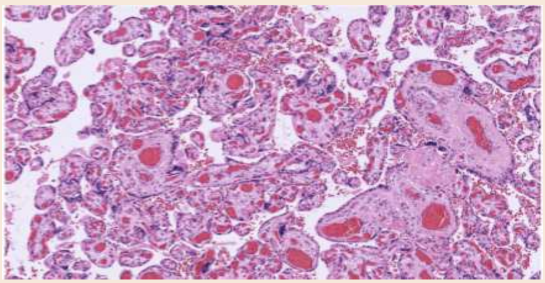
$PM = \alpha \, FM^{\beta}$ with $\beta = 0.78 \pm 0.02$ and $\alpha = 1.03 \pm 0.17$

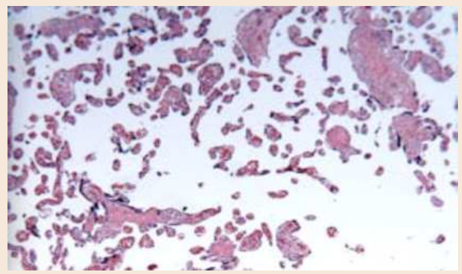
the dataset has 26,000 pairs *(FM, PM)*

- Deviation from ¾ scaling are strongly correlated with variation in shape
- Deformed placentas tend to be less effective

Clinical consequences

- In a dataset of 1,300 placentas computed the correlation of β with three maternal diseases which are known to affect the maternal vasculature either before or early during pregnancy: pre-existing diabetes, hypertension, and preeclampsia.





Histology slides from a normal and preeclamptic placentas

Very significant correlations with the value of β:

with pre-existing diabetes 6%,

with pre-eclampsia 11%,

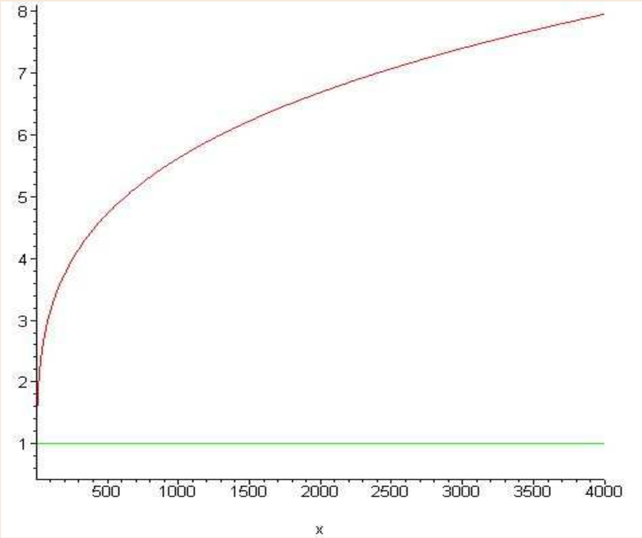
with hypertension 12.5%.

Measuring FPR

- A very common clinical measurement: Feto-Placental Ratio

  $FPR = FM/PM$ measured at birth

- Since $PM \sim FM^{3/4}$, $FPR \sim FM^{0.25}$
- $FPR_{corrected} = FM^{3/4}/PM$



- A sample graph of *FPR* (above) and $FPR_{corrected}$ below for a normally developing fetus.

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Modeling angiogenesis

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