Assisted reproduction technology: how maths can contribute

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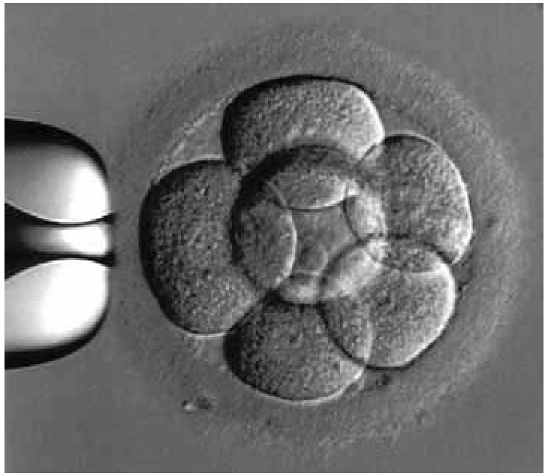
In vitro fertilisation

Egg (oocyte) a few hours after fertilisation.



Day 3, 8 cell stage (6 only visible).

Day 5, blastocyst ready for implantation.

Nick $>$ 9 months later.

Pictures from Advanced Fertility Centre of Chicago www.advancedfertility.com

IVF versus IVM

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Much less successful; more time in the lab.

IVM history

- 1935: G. Pincus & E.V. Enzmann report research on IVM of immature mammalian oocytes.
- 1964, 1969: Further research on IVM of human oocytes by R.G. Edwards et al.
- 1991: First human pregnancy from IVM - 13 yrs after birth of Louise Brown in 1978 (conceived by IVF).
- 1994: First IVM baby using mother's own eggs (in Australia).
- 1999: First IVM baby in Canada.
- 2007: First IVM baby in the UK.

IVF/IVM statistics

IVF 2001–2007 (Reproductive Association of Delaware)

	<35 (%)	35–39 (%)	≥40 (%)
Pregnancy rate per retrieval	52.9	43.2	24.1
Pregnancy rate per transfer	48.8	46.6	24.8
Ongoing pregnancy rate per transfer	48.2	39.4	19.0
Implantation rate	47.0	28.1	11.7

IVM (Durga Rao et al. 2005 *Semin Reprod Med* **23**, 242–7)

	<35 (%)	36–40 (%)
Clinical pregnancy rate per retrieval	38	21
Implantation rate	13	5

Why pursue IVM?

- Lower costs since
  - no expensive gonadotropin stimulation,
  - no extensive monitoring scans.
- Shorter treatment schedule, so less disturbance.
- No 2–3 month wait between treatments as no stimulation involved.
- Remove risk of ovarian hyperstimulation syndrome which can be fatal.
- Remove concerns about development of ovarian cancer from stimulation drugs.
- More acceptable to egg donors.

Culture conditions critical

- Typical oocyte maturation time is 24–48 hrs.
- 2–3 days culture after fertilization, or 5–6 days if taken to blastocyst stage.

“The competence of a fertilized oocyte is profoundly affected by the culture conditions and, therefore, optimal culture conditions are vital for a successful IVM program.”

(G. Durga Rao et al. 2005)

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  - eggs are very small,
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  - in vivo measurements very difficult to obtain.

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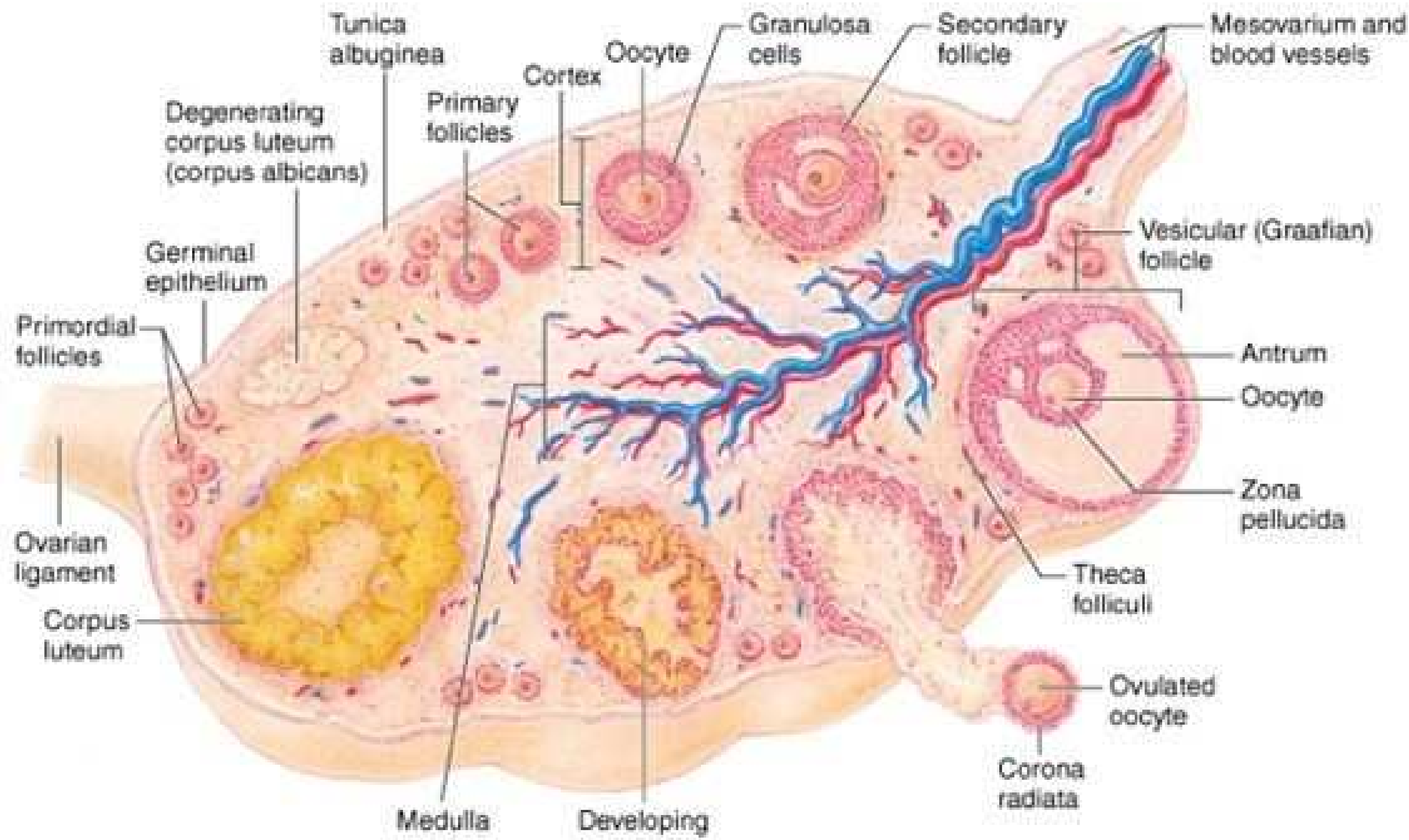
- Much cannot be measured experimentally:
  - eggs are very small,
  - they are enclosed in a shell of cells which controls the environment to some degree,
  - in vivo measurements very difficult to obtain.
- Mathematical modelling of the in-vivo nutrient environment of eggs, in conjunction with experiments is needed.

Ovary, follicle, COC

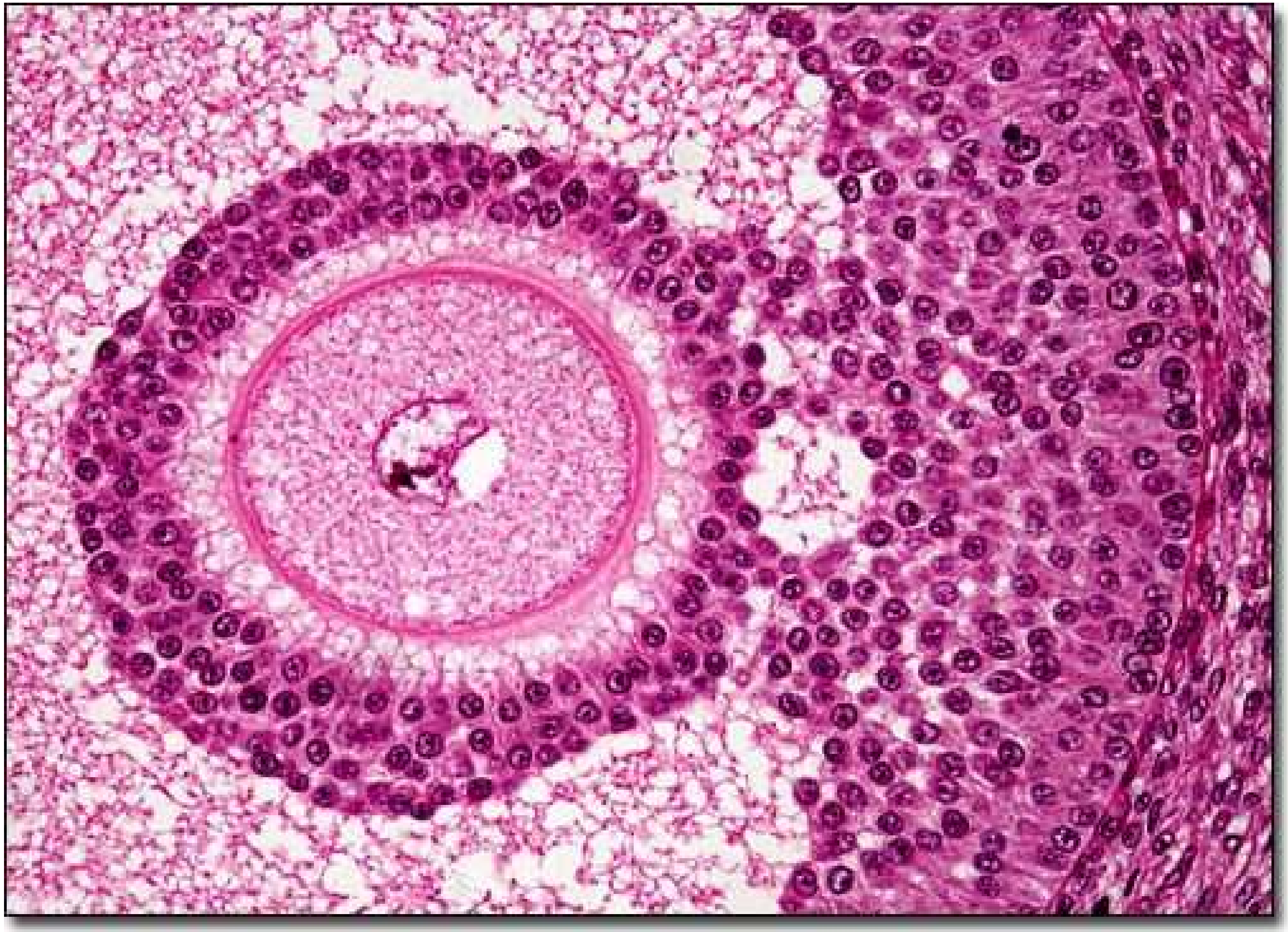


Bovine ovary

Bovine oocyte diameter $\sim 100\,\mu$m, COC diameter $\sim 300\,\mu$m, antral follicle diameter nearing oocyte release $\sim 1 - 2$ cm.

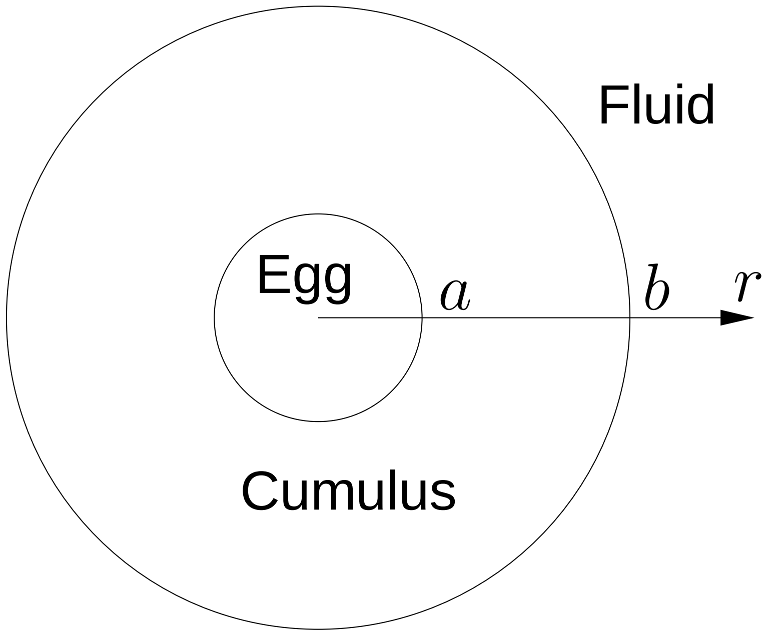
Cumulus oocyte complex

www.microscopy.fsu.edu/primer/anatomy/brightfieldgallery/mammaliangraafianfollicle40xlarge.html



Model assumptions

- Spherical symmetry.
- Known nutrient levels in follicular fluid (F).
- Two regions: Egg and cumulus shell.
- Transport/consumption of one nutrient independent of others.
- Diffusive transport, no flow.
- No time dependence.
- Neglect COC growth.

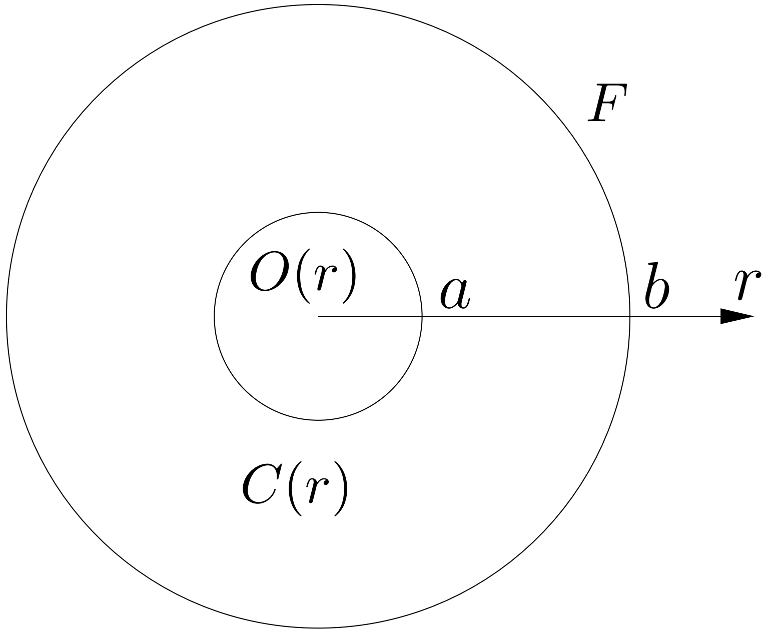


Basic model

Two ODEs

$$\frac{D}{r^2}\frac{d}{dr}\left(r^2\frac{dO}{dr}\right) = Q_{\mathsf{O}},$$

$$\frac{D}{r^2}\frac{d}{dr}\left(r^2\frac{dC}{dr}\right) = Q_{\mathsf{C}},$$



and boundary conditions

$C(b) = F$, $\quad O(0)$ bounded,

$$O(a) = C(a), \quad -D\frac{dO}{dr}(a) = -D\frac{dC}{dr}(a).$$

If we assume Q_O and Q_C are constant we can solve.

Analytic solution

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\Rightarrow\quad & O(r) = \frac{Q_{\mathsf{O}}}{6D}r^2 - \frac{A_1}{r} + A_2, \quad O(0) \text{ bounded} \Rightarrow A_1 = 0
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$$C(r) = \frac{Q_{\mathsf{C}}}{6D}r^2 - \frac{B_1}{r} + B_2$$

Solving for constants

$$\frac{dO}{dr}(a) = \frac{dC}{dr}(a) \Rightarrow \frac{Q_O a}{3D} = \frac{Q_C a}{3D} + \frac{B_1}{a^2} \Rightarrow B_1 = \frac{a^3}{3D}(Q_O - Q_C).$$

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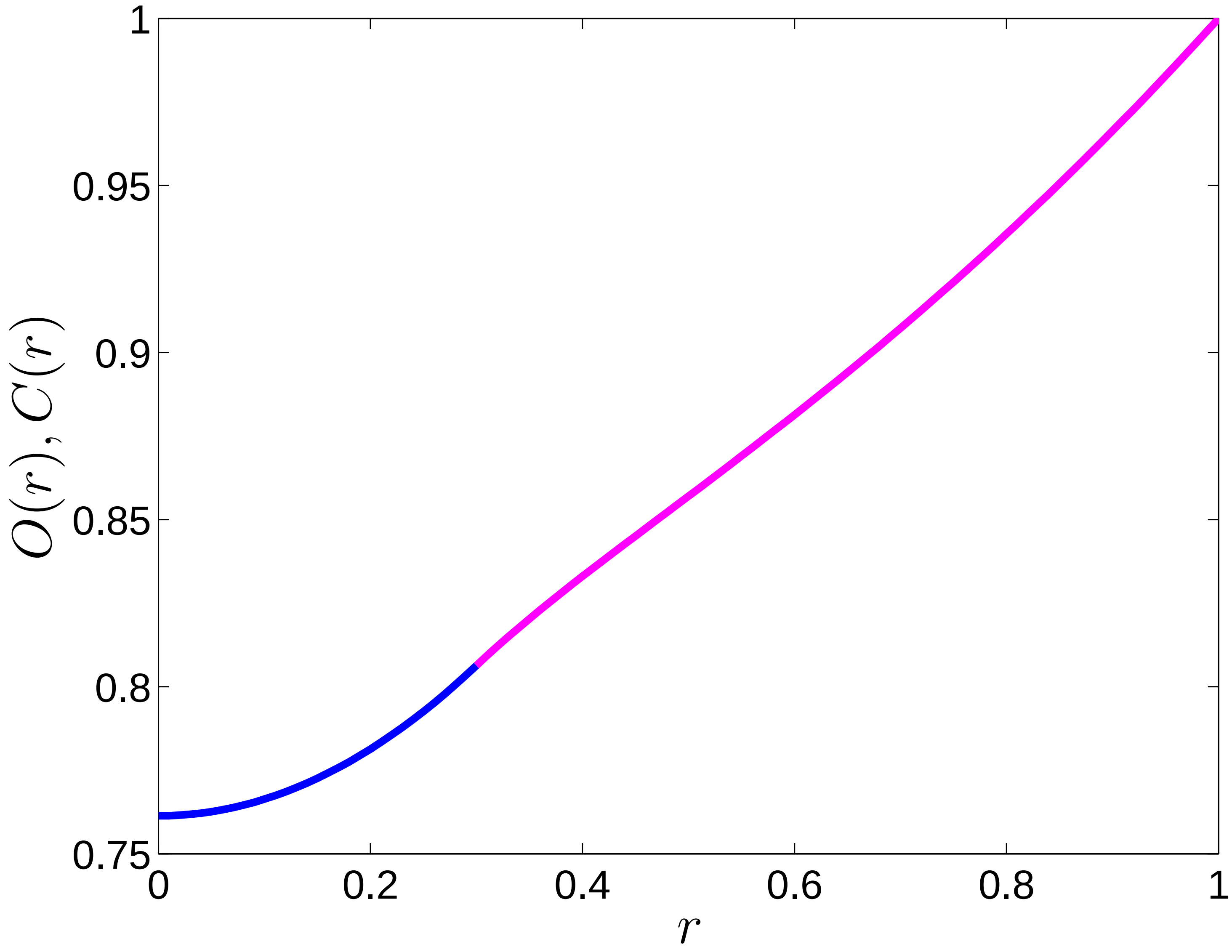
Now we have the solution . . . we can graph it for given parameter values.

Solution

$F = 1,\ Q_O = 3Q_C,\ Q_C = 1,\ D = 1,\ a = 0.3,\ b = 1$:

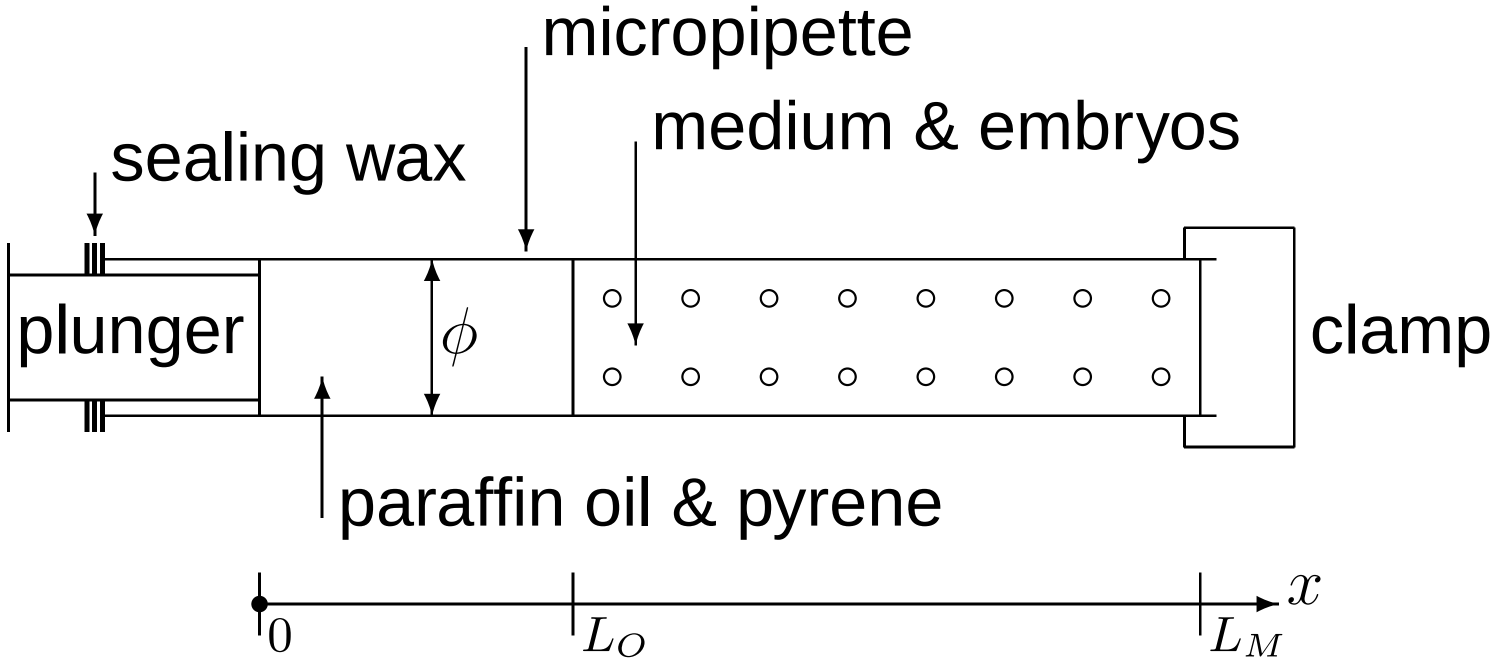


What parameter values?

- This is a very simple model and could be improved, but let's suppose it is sufficiently accurate.
- To use it we still need to determine the true values of the parameters.
- Some can be measured reasonably easily: F, D, a, b.
- Others are hard to measure: Q_O, Q_C. In fact these can't be directly measured and mathematical models are needed again.

Let's look at one example.

An oxygen assay



$\phi = 0.5$ mm, $L_O = 5$ mm, $L_M = 15$ mm.

The oil is the O_2 source (contains $4.5\times$ more O_2 than the medium, at the same partial pressure).

Initial partial pressure in oil and medium is 20% of one atmosphere.

(Houghton et al (1996) Molecular Reprod. & Develop. 44, 476–485)

Experimental data

- Fluorescence of pyrene is quenched in presence of O_2.
- Fluorescence measurements are taken at $x = 0, L_O$ at intervals in time.
- These are converted into O_2 concentrations at $x = 0, L_O$.
- We need a mathematical (diffusion) model to relate concentrations to the O_2 consumption rate of embryos.

Mathematical model

PDEs for O_2 concentrations $C_O(x,t),\ C_M(x,t)$:

$$\frac{\partial C_O}{\partial t} = D_O \frac{\partial^2 C_O}{\partial x^2}, \qquad 0 \le x \le L_O,$$

$$\frac{\partial C_M}{\partial t} = D_M \frac{\partial^2 C_M}{\partial x^2} - k, \qquad L_O \le x \le L_M,$$

Boundary conditions:

$$\frac{\partial C_O}{\partial x}(0,t) = 0, \quad \frac{\partial C_M}{\partial x}(L_M,t) = 0,$$

$$\frac{C_O}{K_O}(L_O,t) = \frac{C_M}{K_M}(L_O,t), \quad -D_O \frac{\partial C_O}{\partial x}(L_O,t) = -D_M \frac{\partial C_M}{\partial x}(L_O,t),$$

Initial conditions: $C_O(x,0) = C_{O0}, \quad C_M(x,0) = C_{M0}$.

Parameters to determine

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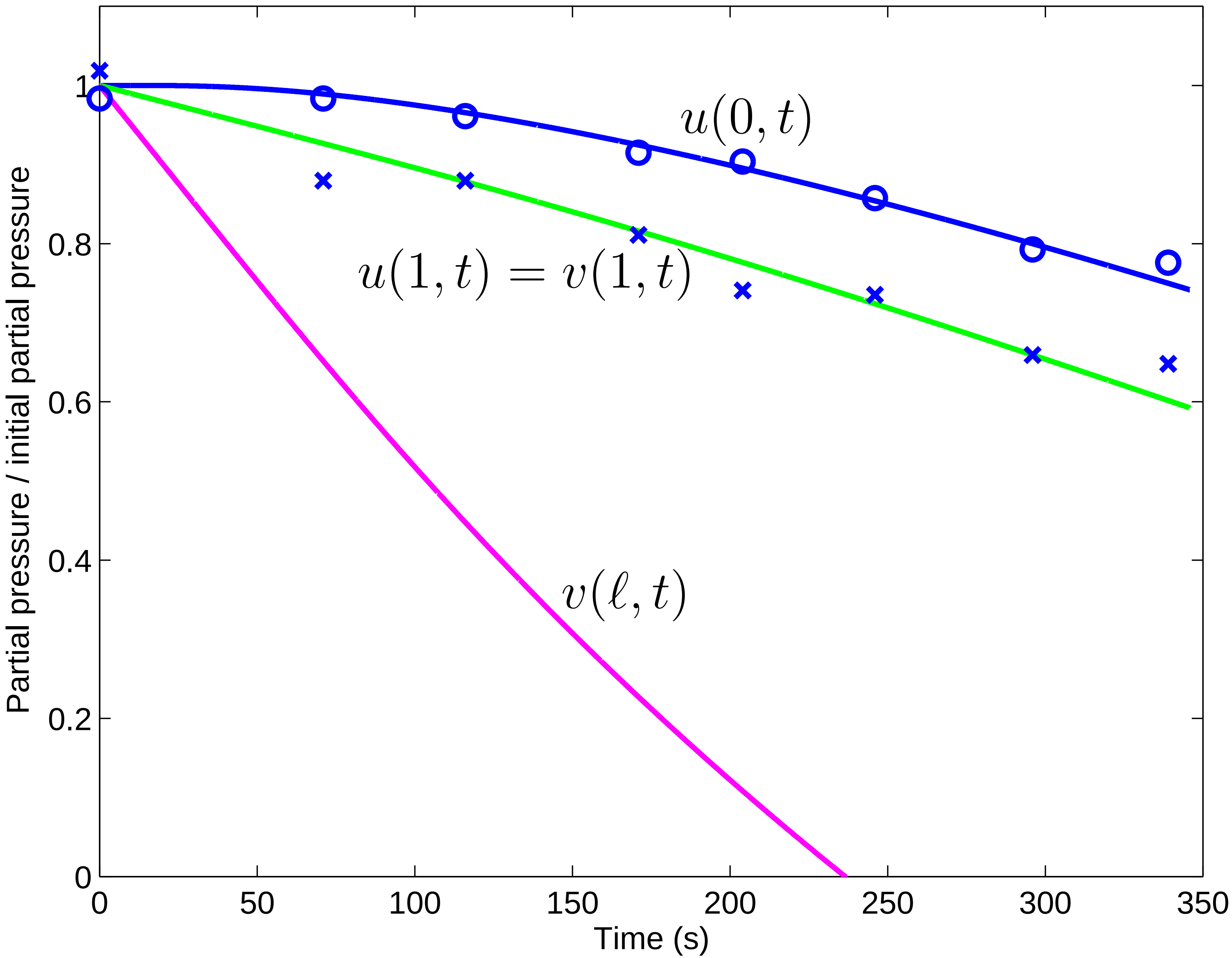
- The time rate of change of concentration is determined by k.

Solution for 18 blastocysts



$u(x,t)=C_O(x,t)/C_{O0},\ v(x,t)=C_M(x,t)/C_{M0}$.

Important findings

- $D_O \approx 1.8 \times 10^{-9}$ m^2/s. This is a new result; previous guess was $D_O \approx 2.5 \times 10^{-7}$ m^2/s.
- For 18 blastocysts,

$$k = 0.0198 \, \text{mol/m}^3\text{/s} \equiv 0.2014 \, \text{nL/embryo/hr}.$$

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This assay and model will also give O_2 consumption rate of COCs.

More modelling is needed to separate this into Q_O and Q_C (consumption rates of egg and cumulus cells).

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THANKYOU . . . ANY QUESTIONS?