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

In-vitro fertilisation (IVF):
- drugs used to stimulate maturation of eggs in the ovary;
- surgical removal of mature eggs;
- laboratory fertilisation, implantation in the uterus.
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**In-vitro maturation (IVM):**
- surgical removal of immature eggs from the ovary;
- maturation in the laboratory;
- laboratory fertilisation, implantation in the uterus.

Much less successful; more time in the lab.
IVM history

- 1935: G. Pincus & E.V. Enzmann report research on IVM of immature mammalian oocytes.
- 1999: First IVM baby in Canada.
- 2007: First IVM baby in the UK.
# IVF/IVM statistics

## IVF 2001–2007 (Reproductive Association of Delaware)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Pregnancy rate per retrieval (%)</th>
<th>Pregnancy rate per transfer (%)</th>
<th>Ongoing pregnancy rate per transfer (%)</th>
<th>Implantation rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35</td>
<td>52.9</td>
<td>48.8</td>
<td>48.2</td>
<td>47.0</td>
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<tr>
<td>35–39</td>
<td>43.2</td>
<td>46.6</td>
<td>39.4</td>
<td>28.1</td>
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<tr>
<td>≥40</td>
<td>24.1</td>
<td>24.8</td>
<td>19.0</td>
<td>11.7</td>
</tr>
</tbody>
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<tr>
<td>&lt;35</td>
<td>38</td>
<td>13</td>
</tr>
<tr>
<td>36–40</td>
<td>21</td>
<td>5</td>
</tr>
</tbody>
</table>
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)
Maths can help!

We need to better understand the natural environment in which eggs develop in order to create better lab environments.
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Much cannot be measured experimentally:
- eggs are very small,
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- in vivo measurements very difficult to obtain.
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  - they are enclosed in a shell of cells which controls the environment to some degree,
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- 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

©1998-2006 Michael W. Davidson, Mortimer Abramowitz, Olympus America Inc., and The Florida State University.
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

\[
\frac{D}{r^2} \frac{d}{dr} \left( r^2 \frac{dO}{dr} \right) = Q_O,
\]

\[
\frac{D}{r^2} \frac{d}{dr} \left( r^2 \frac{dC}{dr} \right) = Q_C,
\]

and boundary conditions

\[ C(b) = F, \quad O(0) \text{ bounded}, \]

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

If we assume \(Q_O\) and \(Q_C\) are constant we can solve.
Analytic solution

\[ \frac{D}{r^2} \frac{d}{dr} \left( r^2 \frac{dO}{dr} \right) = Q_0, \]
Analytic solution

\[ D \frac{d}{r^2 dr} \left( r^2 \frac{dO}{dr} \right) = Q_O, \]

\[ \Rightarrow \quad \frac{d}{dr} \left( r^2 \frac{dO}{dr} \right) = \frac{Q_O}{D} r^2, \]
Analytic solution

\[
\frac{D}{r^2} \frac{d}{dr} \left( r^2 \frac{dO}{dr} \right) = Q_0, \\
\Rightarrow \quad \frac{d}{dr} \left( r^2 \frac{dO}{dr} \right) = \frac{Q_0}{D} r^2, \\
\Rightarrow \quad r^2 \frac{dO}{dr} = \frac{Q_0}{3D} r^3 + A_1,
\]
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\frac{dO}{dr} = \frac{Q_0}{3D} r + \frac{A_1}{r^2} ,
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O(r) = \frac{Q_O}{6D} r^2 - \frac{A_1}{r} + A_2, \quad O(0) \text{ bounded } \Rightarrow A_1 = 0
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\[
\frac{D}{r^2} \frac{d}{dr} \left( r^2 \frac{dO}{dr} \right) = Q_\circ,
\]

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\]

\[\Rightarrow \quad r^2 \frac{dO}{dr} = \frac{Q_\circ}{3D} r^3 + A_1,
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\[
C(r) = \frac{Q_c}{6D} r^2 - \frac{B_1}{r} + B_2
\]
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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\[
C(b) = \frac{Q_C b^2}{6D} - \frac{a^3}{3bD} (Q_O - Q_C) + B_2 = F
\Rightarrow B_2 = F - \frac{Q_C b^2}{6D} + \frac{a^3}{3bD} (Q_O - Q_C)
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\[ \Rightarrow A_2 = F - \frac{Q_C b^2}{6D} - \frac{a^2}{3D} (Q_O - Q_C) \left( \frac{3}{2} - \frac{a}{b} \right) \]
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\]

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

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

\[ O(r), C(r) \]
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

\( \phi = 0.5 \text{ mm}, \ L_O = 5 \text{ mm}, \ L_M = 15 \text{ mm}. \)

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.

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 $C_O(x, t)$, $C_M(x, t)$:

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

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

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: $C_O(x, 0) = C_{O0}$, $C_M(x, 0) = C_{M0}$. 
Parameters to determine

Both $D_O$ (the diffusivity of $O_2$ in paraffin oil) and $k$ ($O_2$ consumption rate) are unknown. Other parameters are known.
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The time rate of change of concentration is determined by $k$. 
Solution for 18 blastocysts

\[ u(0, t) \]

\[ u(1, t) = v(1, t) \]

\[ v(\ell, t) \]

\[ u(x, t) = \frac{C_O(x, t)}{C_{O0}}, \quad v(x, t) = \frac{C_M(x, t)}{C_{M0}}. \]
Important findings

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

- 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?