Towards the Virtual Ovary

Concepts & Challenges

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Overview

- Background & motivation
- Aims
- The Problem
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  - Ovarian physiology 101
- Tasks & approaches
  - Follicular population dynamics
  - Follicular distributions
  - Follicular spatio-temporal dynamics
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- Summary

Background & Motivation

- Work with Hamish Wallace and others to quantify sequelae of treatment on the fertility of survivors of childhood cancer
    - Radiosensitivity of the human oocyte [1]
    - Effective sterilising dose for humans [2]
- Insufficient results for girls having **zero** dose
- Re-position research towards the healthy population
    - Ovarian volume as a surrogate for ovarian reserve [3;4]
    - Wallace-Kelsey model of ovarian reserve [5]
    - First model of AMH for the healthy population [6]
- Many of the experiments we'd like data from are impossible to perform
- Others are expensive, use animal models, or have ethical concerns

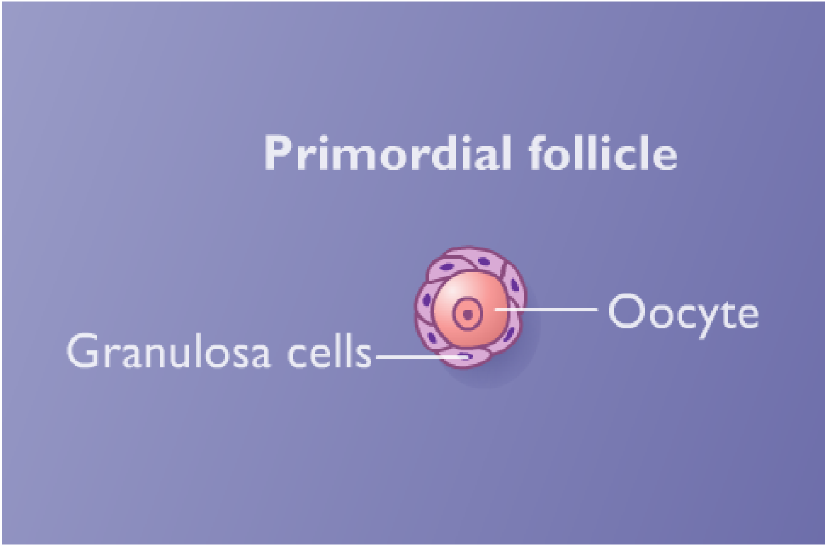
Aims (taken from http://www.virtual-liver.de/)

- A dynamic model that represents, rather than fully replicates, human ovarian physiology morphology and function, integrating quantitive data from all levels of organisation
  - **not** a comprehensive model that replicates the ovary and all its component parts in silico
- A "tool box" of approaches to support:
  1. Understanding of dynamics of ovarian function in normal and diseased states
  2. Generation of experimentally testable hypotheses
  3. Generation of simulations
  4. Informed decision making based on network interactions rather than reductionist data
- A platform that can be modified, supplemented and improved over time

Review of Existing Approaches

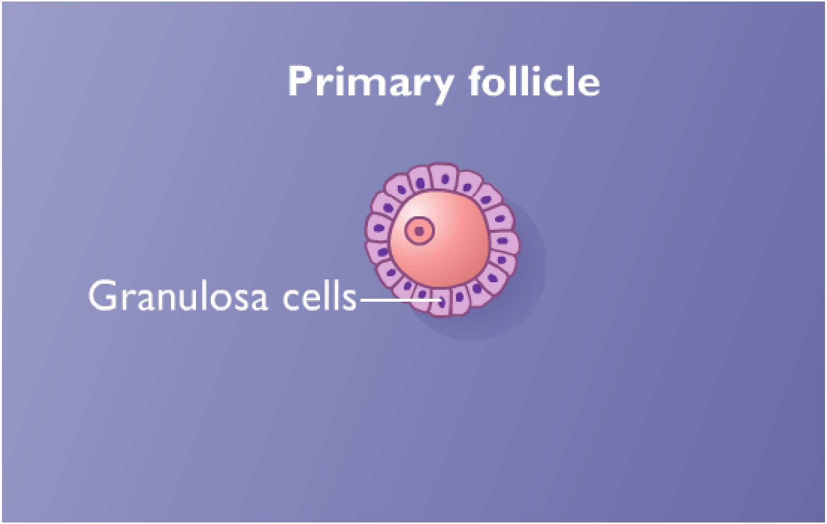
- Tissue reconstruction from confocal laser scans, MRI, histology, etc.
  - marching cubes
- Wavelet, Fourier and other derived data from ECGs
  - systems of PDEs based on beats and pulses
- Spatial models of cell-cell or cell-matrix interactions
  - lattice-free models
- Cell transistion, proliferation, atresia, apoptosis, etc.
  - compartmental models [7;8]
- Knowledge discovery from mined data
  - ARIMA, GLR, regression trees, neural networks, etc.
- 4-D visualisation of spatio-temporal models
  - http://www.humanbody3d.com/organs.html

Ovarian Physiology



http://highered.mcgraw-hill.com/sites/dl/free/0072495855/291136/FolliclOocyteMature.swf

Ovarian Physiology



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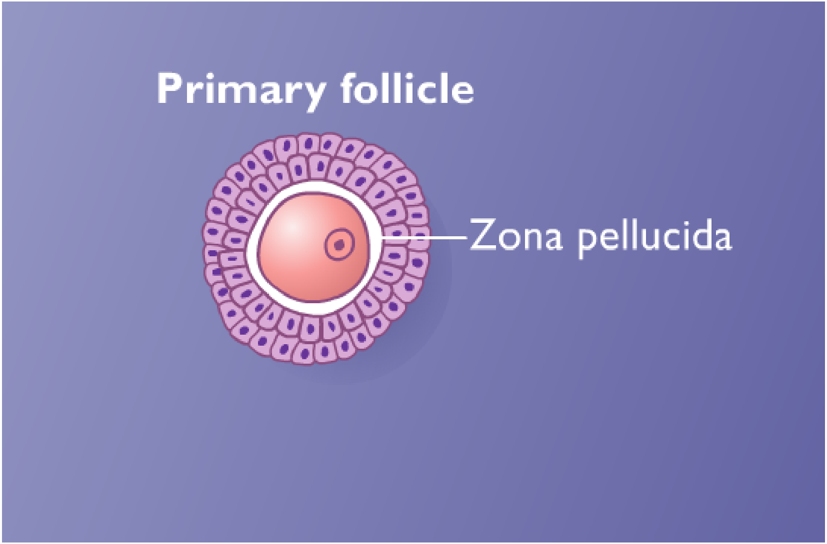

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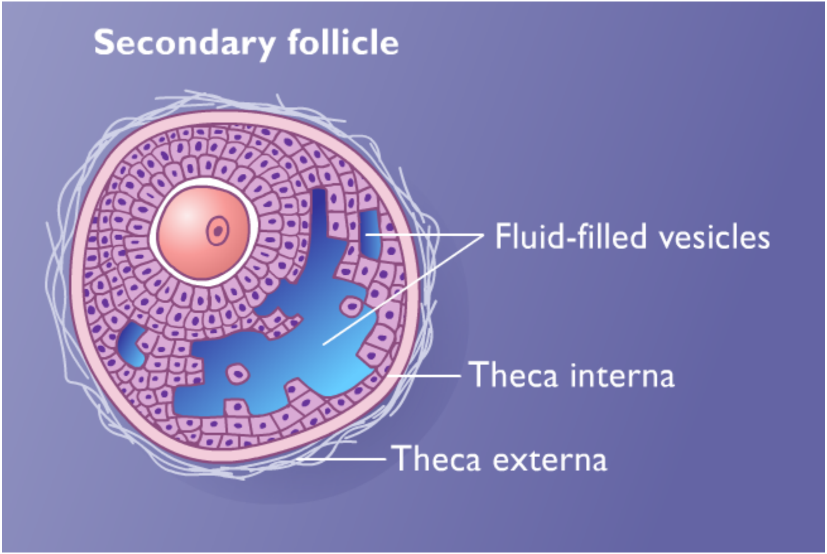

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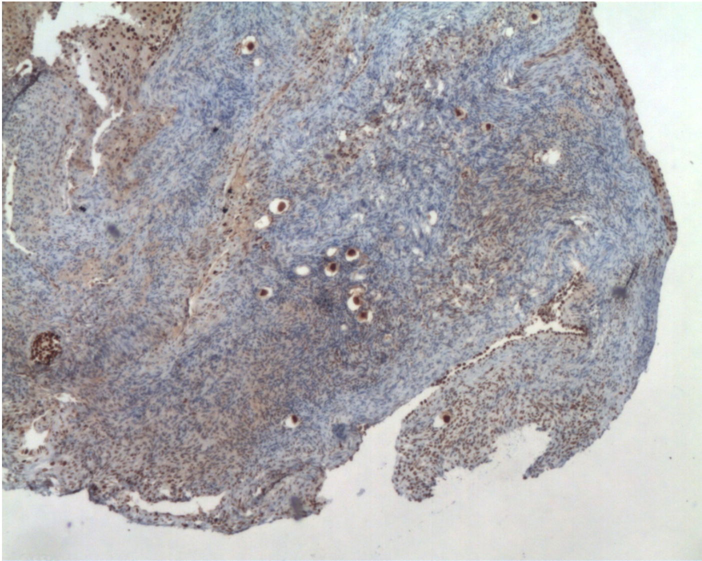
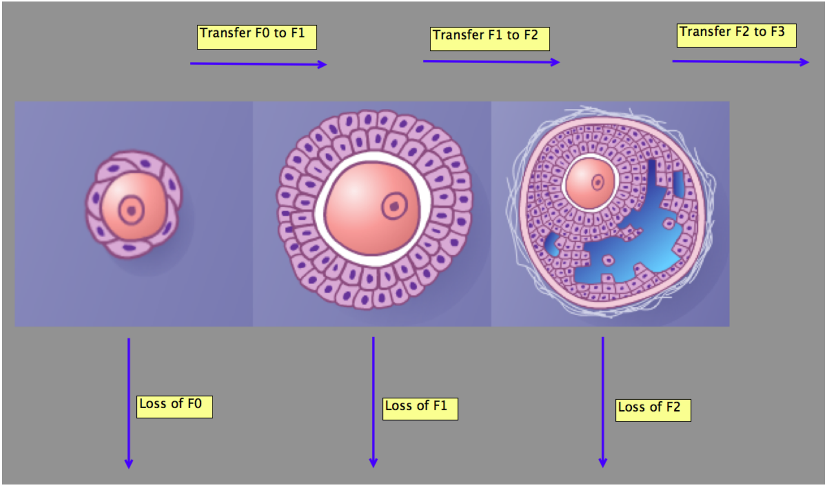


Kelsey, T. et al., 2010. PCNA allows the automatic identification of follicles in microscopic images of human ovarian tissue. PLMI, 2010(2), pp.99-105.

Follicular Population Dynamics



Follicular Population Dynamics

3-Compartment model:

$$\frac{dF_0}{dt} = -k_{T_0}F_0 - k_{L_0}F_0$$

$$\frac{dF_1}{dt} = k_{T_0}F_0 - k_{T_1}F_1 - k_{L_1}F_1$$

$$\frac{dF_2}{dt} = k_{T_1}F_1 - k_{T_1}F_2 - k_{L_2}F_2$$

Kinetic parameters found by estimating populations at known ages, then fitting ODE solutions that minimise residual errors

Issues

- Data not from the same ovaries
- Human data in short supply
- No gold standard for classification
- No gold standard for losses:
  - no losses for F_1, losses for F_2, losses for F_0 after age 38[7]
  - no losses after F_0 for mouse model[8]

- All data is estimated from 1–2% of the tissue for that ovary
- Quality of fit due to good model selection or luck?
- Validation
- No problems with solution
- Standard, well-understood approach from the PK community
- Better data → better model
- More data → options for validation

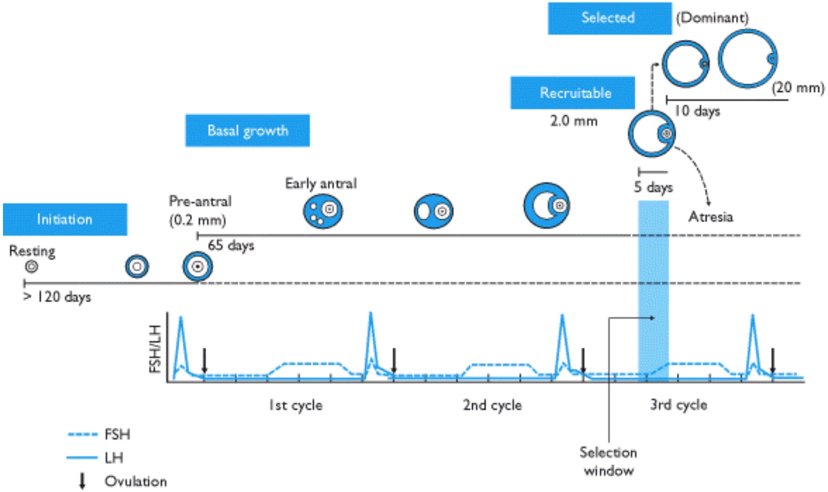
Follicular Distributions

- Assume a regulary sliced ovary
- Impose a distribution of follicles for each slice
- Distribution of the follicles over slices at instant t is given by

$$F(t) = \sum_S F_{s_i} \delta_{s_i}$$

- Many follicles found near edges
- Recent evidence for NGFs in the stem
- Data has huge gaps
- Danger of a "virtual" virtual ovary

Spatio-temporal Dynamics



http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=endocrin.box.1226

Spatio-temporal Dynamics

- Textbooks refer to 80 day, 90 day and 120 day cycles for recruitment towards maturation to release of egg
- **No** *in vivo* evidence for these numbers – plausible folklore
- Data is becoming available from *in vitro* studies of maturation
  - Develop eggs from frozen tissue to avoid re-implantaion of cancerous tissue
  - Evelyn Telfer, Edinburgh
- Endocrine milieu has changed
- Effects of freezing and thawing are poorly understood

Other Ovarian Tissue

- Follicles have no blood supply
- Granulosa cells release hormones such as AMH and estradiol
- FSH is governed by the pituitary
- So there is an Endocrine/Paracrine milieu
- Position, number and shape of granulosa cells change through maturation
- ECM is known to effect morphology, aggregation & communication, survival and proliferation [9]
- The mechanisms are still poorly understood

Visualisation

http://www.humanbody3d.com/

"...we use scanned (CT) data whenever possible. We compare detailed data from scans to representative anatomy sources from our extensive library and discuss them with anatomists from local institutions (universities, hospitals). We make our own digital scans and photographs in hospitals of the vicinity when necessary, the medical team creates a working plan and finally veteran modelers put it all together in 3d..."

- This approach is problematic for ovarian tissue
- Computer-game technology seems attractive, however
- Describe morphologies, dynamics & distributions
- Generate CGI from these

Summary

Virtual ovaries are **easy**:

- Anything that fits in with current perceptions will be deemed a success

Virtual ovaries are **difficult**:

- No longitudinal human data at high resolutions
- Few physiological reference points for construction & validation
- We need a virtual ovary to investigate, say, ECM effects
- We need a detailed understanding of, say, ECM effects to derive a high-quality virtual ovary

References I

[1] Wallace WHB, Thomson AB, Kelsey TW (2003) The radiosensitivity of the human oocyte. Human reproduction (Oxford, England) 18: 117–21.

[2] Wallace WHB, Thomson AB, Saran F, Kelsey TW (2005) Predicting age of ovarian failure after radiation to a field that includes the ovaries. International journal of radiation oncology, biology, physics 62: 738–44.

[3] Wallace WH, Kelsey TW (2004) Ovarian reserve and reproductive age may be determined from measurement of ovarian volume by transvaginal sonography. Human reproduction (Oxford, England) 19: 1612–7.

[4] Brett S, Bee N, Wallace WHB, Rajkhowa M, Kelsey TW (2009) Individual ovarian volumes obtained from 2-dimensional and 3-dimensional ultrasound lack precision. Reproductive biomedicine online 18: 348–51.

[5] Wallace WHB, Kelsey TW (2010) Human ovarian reserve from conception to the menopause. PloS one 5: e8772.

[6] Kelsey TW, Wright P, Nelson SN, Anderson RA, Wallace WHB (2011) A validated model of serum anti-Müllerian hormone from conception to menopause. PloS one 6.

References II

[7] Faddy MJ, Gosden RG (1995) A mathematical model of follicle dynamics in the human ovary. Human reproduction (Oxford, England) 10: 770–5.

[8] Bristol-Gould SK, Kreeger PK, Selkirk CG, Kilen SM, Mayo KE, et al. (2006) Fate of the initial follicle pool: empirical and mathematical evidence supporting its sufficiency for adult fertility. Developmental biology 298: 149–54.

[9] Berkholtz CB, Shea LD, Woodruff TK (2006) Extracellular matrix functions in follicle maturation. Seminars in reproductive medicine 24: 262–9.