

Reverse engineering the embryo: a graduate course in developmental biology for engineering students at the University of Manitoba, Canada

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ABSTRACT Our desire to educate engineers to be able to understand the component processes of embryogenesis, is driven by the notion that only when principles borrowed from mathematics, fluid mechanics, materials science, etc. are applied to classical problems in developmental biology, will sufficient comprehension be achieved to permit successful understanding and therapeutic manipulation of embryos. As it now stands, biologists seldom possess either skills or interest in those areas of endeavor. Thus, we have determined that it is easier to educate engineers in the principles of developmental biology than to help biologists deal with the complexities of engineering. We describe a graduate course that has been taken, between 1999 and 2002, by 17 engineering students. Our goal is to prepare them to reverse engineer the embryo, i.e., to look at it as an object or process whose construction, albeit self-construction, might be explicable in terms of engineering principles applied at molecular, cellular and whole embryo levels.

KEY WORDS: *reverse engineering, embryo, developmental biology, education, biomedical engineering*

Background Information

Scholarly Interests of the Authors

R.G. wrote his first paper (Gordon, 1966) on a simple model for development of an organism, and has been fascinated by development ever since. While he has a second career in medical imaging, especially for the detection of early breast cancer (Gordon and Sivaramakrishna, 1999), even his hobby of research on single-celled diatoms (Gordon and Drum, 1970) has been half on their morphogenesis (Gordon and Drum, 1994). This has taken a surprising turn into "growing" nanotechnology (Parkinson and Gordon, 1999). After delving into "computational embryology" (Gordon, 1983) and neural tube defects (Gordon, 1985), he predicted the existence of differentiation waves in urodele embryos (Gordon and Brodland, 1987), which were subsequently discovered by Natalie K. Björklund (Brodland *et al.*, 1994). These led to a fruitful collaboration with Pieter D. Nieuwkoop (Gordon *et al.*, 1994; Nieuwkoop *et al.*, 1996, 1999) and to a new theory of the relationship between evolution and development (Gordon, 1999). He is now working on the mechanics of the genome during differentiation in embryos (Gordon and Maniotis, <http://www.umanitoba.ca/faculties/medicine/radiology/stafflist/rfgordon.html>).

C.A.M. started his newborn career in biomedical engineering in the area of diagnostic imaging (Melvin *et al.*, 2002). His interests

have expanded to embryonic development and tissue engineering. In addition, he has developed a keen interest in engineering applications within biology and medicine, particularly in educating and encouraging engineering students to tackle the challenges of problems in biology and medicine. For example, he is the founding chair of the University of Manitoba student chapter of EMBS/IEEE (Engineering in Medicine & Biology Society/Institute of Electrical and Electronics Engineers: <http://ewh.ieee.org/sb/manitoba/embs/>).

Contrasts between Classical Engineering and Traditional Biology Educational Paradigms

Engineering education - compared to biology education - is unique in its method and in its product. Engineers have a heavy math and physics background. Generally, engineers avoid abstract math, but when they do encounter it, it doesn't intimidate them as it does students in many other fields (Figs. 1, 2). Different disciplines of engineering lead to focuses in different areas; for instance, electrical and computer engineers focus more on math and relativistic mechanics, while mechanical, civil, and biosystems engineers study more chemistry and Newtonian mechanics.

As engineering students progress through their education, they learn the "Engineering Approach." Regardless of their discipline or

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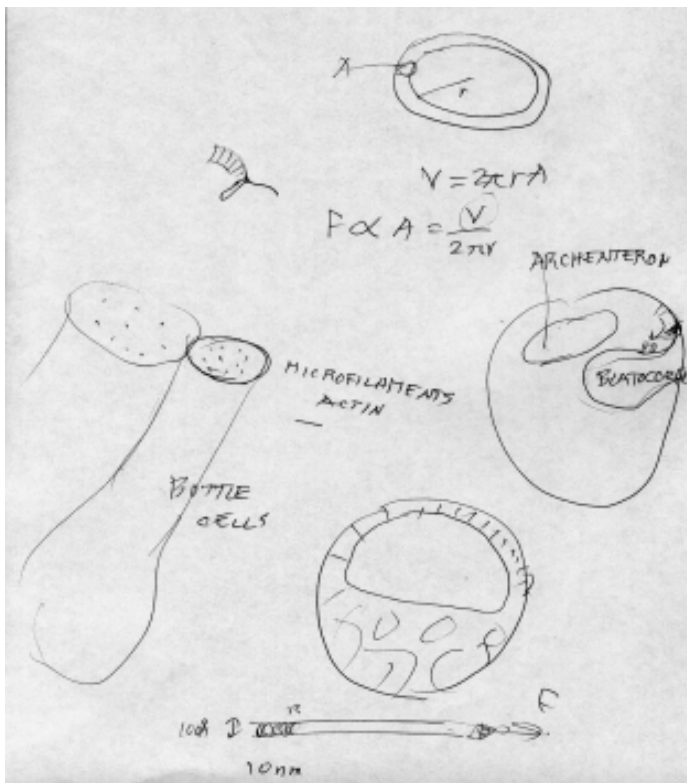


Fig. 1. Unaltered classroom sketch made during a discussion, showing the relationship of volume (V) and force (F) to the cross sectional area (A) of a microfilament ring of radius (r) at the apical end of a bottle cell. At the bottom, force generation by microtubule polymerization is illustrated.

specialty, engineers approach a problem in the following (general) stepwise fashion:

1. They first look for an obvious, apparent answer.
2. They then try to find an analogue in their own domain of understanding.
3. They then attempt to develop a new mathematical model to suit the circumstances.

Engineering students who do not follow this path in some form or another usually encounter academic problems. Occasionally, of course, an exceptional student emerges who manages to follow a novel path, but in most cases the above scenario is the rule. It's a fluid process, and the steps often blend together - each student customizes it to take advantage of her or his own skills and aptitudes.

Biologists usually subscribe to the notion that that they deal with the most complex structures in the universe. Thus, it is ironic how little math, chemistry and physics supports their education. Introductory textbooks eschew math: we challenge the reader to find a single equation in any of the popular introductory biology textbooks. Even the level of math taught in high school is avoided. It is not as if math isn't well represented in biology by the fields of biophysics, mathematical biology, and theoretical biology (Gordon, 1993), but that these fields are not introduced to the general biology student. A minor exception is statistics, which are widely used in ecology.

Traditionally, biology students have learned only the rudiments of chemistry and physics, and thus are unaware of the vast variety of phenomena to which organisms are exposed, or the intricacies of the processes that can occur within them. Thus, most biology students are unfortunately innumerate (Paulos, 1990), and have little understanding of post-Newtonian physics or modern chemistry, except for symbol manipulation in biochemistry and molecular genetics.

This lack of background in math, chemistry, and physics of biologists has impacted on us. Our graduate course, initially called Cell and Embryo Engineering, has been given five times at the graduate level, with two to four students in attendance each time. None of them has been in a biology discipline. Biology students have occasionally shown up for the first session, but disappeared, despite reassurances that no math would be required of them. Our experience has been that it is much easier to teach biology to engineering students than to teach engineering to biology students. (The same goes for physics: See Gordon, 1992, reprinted in Gordon, 1999.) As a consequence, much of the course is spent introducing basic concepts in biology, as they come up in our discussions.

Reverse Engineering as a Conceptual Approach

Reverse engineering represents the process of analyzing a subject system with two goals in mind:

- (1) to identify the system's components and their interrelationships; and,
- (2) to create representations of the system in another form or at a higher level of abstraction (IEEE Technical Council on Software Engineering, 2002, quoted at <http://tcse.org/revengr/taxonomy.html>; cf. Chikofsky and Cross, 1990).

It is a strategy that is commonly used by engineers to gain insights into the workings of a reaction, machine, or process. Indeed, often it amounts to an approach which is akin to "intellectual theft" (Samuelson, 1990). For example, a device produced by a commercial competitor might be x-rayed, taken apart, and tested until a reasonable model of its functioning can be made. It is then ready for copying, perhaps with minor modifications to get around its patent. The field has recently grown (van den Brand *et al.*, 1997) into one of which might be termed "legal industrial espionage."

Adapting the Principles of Reverse Engineering to Understanding Embryogenesis

Science is often taught as the enterprise of uncovering "mother nature's secrets." Embryology is the attempt to understand the "miracle of birth." Embryology is thus at the core of the science and religion debate on design (Gordon, 2000), with the creationist side now using the phrase "intelligent design" (Gingerich, 1994; Dembski, 1999; Fitelson *et al.*, 1999; Sober, 2003). Whether we wish to answer the question "How did God do that?" or "How does a living organism do that?" we are faced with a reverse engineering problem. Of course, we must assume that the question has an answer within the current paradigms of physics and chemistry in order to proceed. To believe otherwise has been labeled vitalist. Now engineers, like scientists, come in a spectrum of beliefs about such matters, but with an open mind, and a realization on the part of all that we haven't yet reached answers to the ultimate

questions of existence, we plod on in this course to see how much can be explained within current paradigms and what tools we might bring to bear. Given that many eggs develop on their own, requiring only a sufficiently humid environment of the right temperature, the engineering question we ask is “How does the embryo build itself?”

Although it has been well over a century since Wilhelm His (1888) declared “To think that heredity will build organic beings without mechanical means is a piece of unscientific mysticism,” no systematic effort has yet started to bring the implied research program to fruition. This is why it is so important to bring embryology to engineers, for here are people mastering the skills that may be needed:

1. Mechanics, mechanical engineering, civil engineering, finite elements, to begin to understand the relationships between locally generated and applied forces and morphogenesis;
2. Statistical mechanics, materials science, chaos theory and stochastic processes, to appreciate the relationships between the wild activity at the molecular level and macroscopic properties;
3. Electromagnetism, electrochemistry, the flow of ions in solution and perhaps even plasmas, to unravel the role of electrical phenomena in development;
4. Mathematics, mathematical physics, applied mathematics, and computer simulation, for clarity of thought, formulation of problems, and solving of problems, without the handicap of mathematical illiteracy (Paulos, 1990);
5. Instrumentation, medical imaging, optronics, optics, microscopy, to know and experience what is feasible with our present technology, and to push it further;
6. History and philosophy of science, to actually build on the work of our predecessors, and to keep perspective and some humility (Gordon, 1999).

Our Goal: Raise Questions for which Answers are Not Yet Available

What we try to do in this course, then, is take the engineering student through the stages of early development, raising questions whose answers are unknown at each step. Why is cleavage uneven in early amphibian embryos (See Dictus *et al.*, 1984)? How are Hans Driesch’s questions about getting the right cells in the right place at the right time to be answered (§1.02 in Gordon, 1999)? Why are left and right different (§8.02 in Gordon, 1999)? What is the role of ionic currents in development (§9.27 in Gordon, 1999)? Will we succeed in creating artificial life analogous to multicellular organisms without the construction process itself imitating embryological development (Prop. 16 in Gordon, 1999)? What is the role of evolution in development, or development in evolution? What is the relationship between the physical organization of the genome and its role in embryology and evolution (§10.13 in Gordon, 1999)? What tools can we bring to bear on these questions (§1.13 in Gordon, 1999)?

We tried to expand the course to tissue engineering, with readings from Lanza *et al.* (2000), but it became obvious that most of the engineers who have entered that field are in chemical engineering, which is not represented in our university.

The discussions are sometimes intense, and it is refreshing to see the excitement raised in young engineering minds by basic biological questions. Tangents upon tangents occur, as we follow the interests of the students. The instructor (R.G.) learns as much

as the students because their essays review applicable technology or even invent new technology (Chrusch *et al.*, 2002). At only three credit hours, the course can at best whet appetites, but it is a start. It is not a substitute for a proper embryology course, with labs, but, unlike such a course, it takes the engineering and reverse engineering perspective, and so introduces the thinking of an engineer to the problem. Given the predictions that biology cannot advance much further without engineering, and that engineering over the next century will be dominated by biology (Jayas, 2002), reverse engineering of the embryo may be the place to start.

Course Format and Topical Outline

The course roughly follows the 10 chapters in *The Hierarchical Genome: Novel Unification of Development, Genetics and Evolution* (Gordon, 1999), with sample sections available online at <http://www.wspc.com.sg/books/lifesci/2755.html>):

- Introduction
- Neural Induction and the Organizer

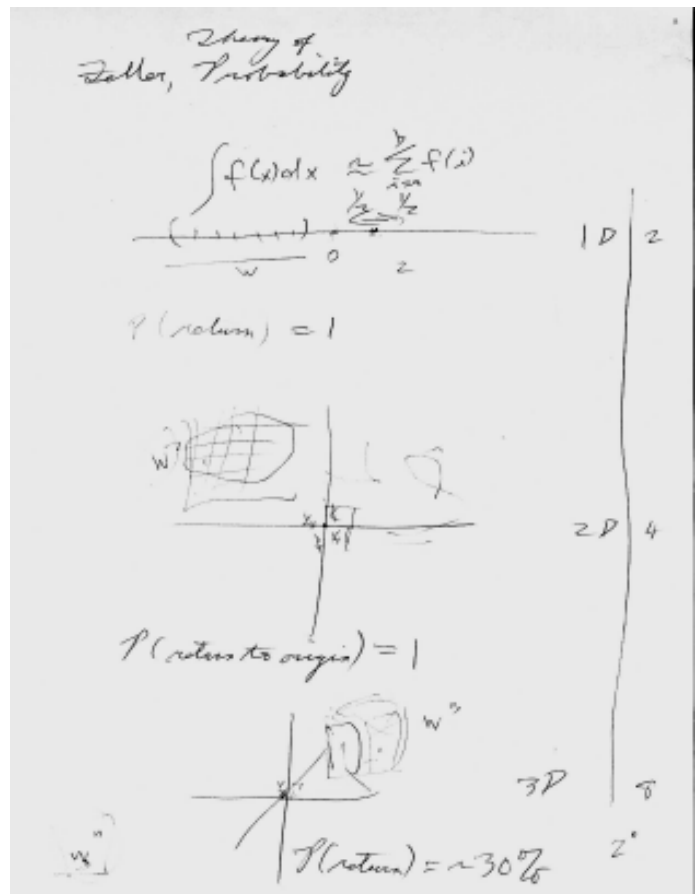
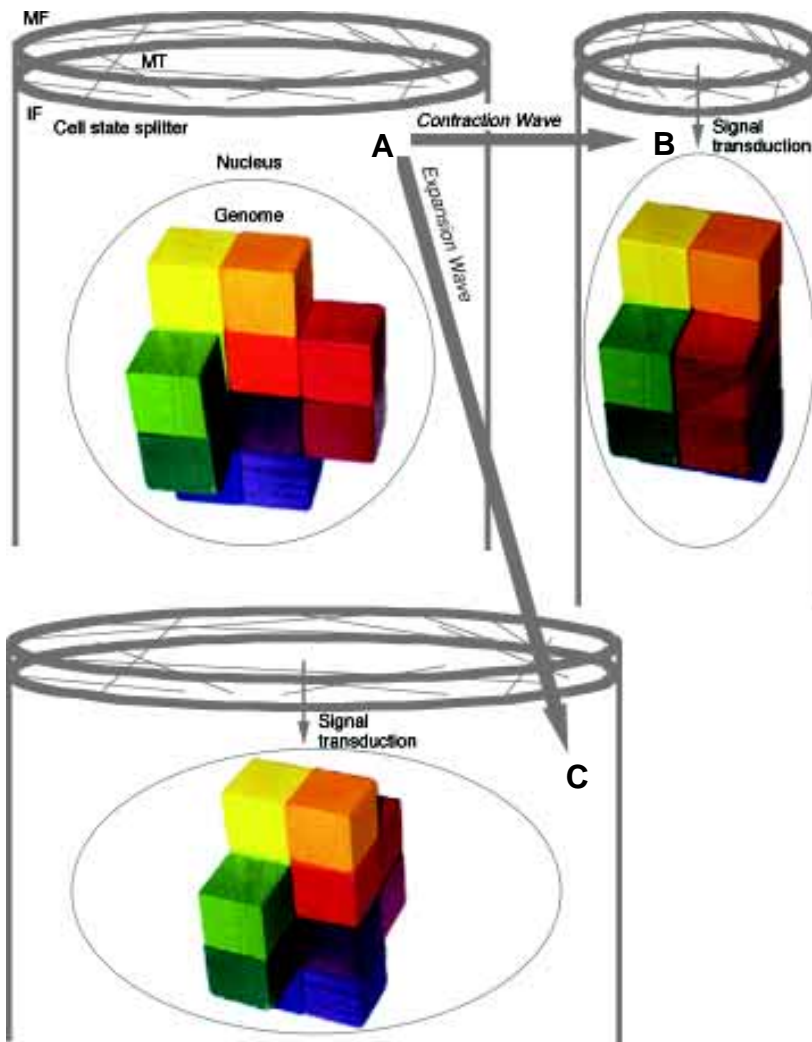


Fig. 2. Sketch made during discussion of diffusion in one, two and three dimensions, showing that the probability of return of a random walk to the origin, is 1 for 1-D and 2-D, but only about 35% for 3-D (Feller, 1968). This was used to illustrate both dimension reduction when a molecule adsorbs to a linear or planar structure from 3-D (Adam and Delbrück, 1968; §10.08 “The Blessings of Ever Increasing Dimensionality” in Gordon 1999) and the folly of the argument of a “wall of simplicity” in evolution (Gould, 1996; §10.03 in Gordon, 1999).



- Theory of the Cell State Splitter
- Development and Genetics
- Development and Evolution
- Macroevolution
- The Biogenetic Law
- The Homeobox
- A Cornucopia of Differentiation Waves
- Conclusion

But we meander at every session because of nearly continuous discussion, asides, in-class web searches, tangents and frequent impromptu tutorials on aspects or techniques of biology. Resources such as PubMed, web pages devoted to model animals, etc., are brought in. The fundamental questions of developmental biology and evolution, sometimes of life itself, our lack of answers, and tools for seeking answers, make up a typical 3-h session, which occurs once a week for a full semester (16 weeks). Thus, some philosophy of biology is interjected. Each student picks or suggests two topics to review. These are presented in class with the same lively give and take. Each student writes a 10- to 20-page review on each chosen topic, modifying it in the light of verbal and written comments before turning in a final version. Grades are based on these two reports and on participation. Here are some examples of topics students have chosen:

- Acoustic Microscopy: Application in Biological and Material Research
- An Associative Memory and Natural Computing in Ciliates based on Molecular Computing Techniques
- An Introduction to the World of Micromanipulation
- An Introduction to the World of Microtools
- Bioinformatics: What? Why? How? Where?
- Confocal Microscopy and Deconvolution
- Cytobots: Intracellular Robotic Micromanipulators
- Digital Biota
- General Description of Evolution Simulation
- Laser Tweezers
- Microfabricated Biological Devices
- The Kinesin Motor Molecule

The emphasis on building tools is evident. The course has not yet created a working bioengineer embryologist. But given that most of the students have had no more formal biology classes than those they took in high school, if that, it's too soon to pass judgment. Some students take it upon themselves to recruit others for the next time the course is given. In the past year, a student chapter (<http://ewh.ieee.org/sb/manitoba/embs/>) of IEEE/EMBS (Institute of Electrical and Electronics Engineers/Engineering in Medicine & Biology Society; <http://www.eng.unsw.edu.au/embs/index.html>) has formed, which publicizes this course to more students.

Fig. 3. Models are frequently brought into the classroom to illustrate biological phenomena. A tensegrity structure consists of stiff elements (such as microtubules supported by intermediate filaments: Brodland and Gordon, 1990) held together by elastic elements, such as actin microfilaments (Ingber et al., 1994). Most tensegrity cell modeling is of structures that have essentially only one mechanically stable configuration when there is no change in chemistry (Ingber, 1997). The cell state splitter has two stable configurations accessible from its initial, metastable structure. The cell state splitter is a nonlinear tensegrity apparatus (presumed capable of snapping between configurations) at the apical end of an ectoderm cell. It consists of a contractile microfilament ring (MF) in radial tension with a subtending annular mat of apical microtubules (MT). An intermediate filament ring (IF) prevents immediate contraction or expansion of the cell state splitter by keeping it in a mechanically metastable state (Gordon and Brodland, 1987; Martin and Gordon, 1997). Cell (A) participates in either a contraction wave (MF-based), which turns it into a cell of type (B), or an expansion wave (MT-based), which turns it into a cell of type (C). The thick arrows represent one branch of the organism's differentiation tree. The wave is transmitted to the next cell(s) in the epithelium. Signal transduction sends a single bit of information from the cell state splitter to the nucleus, which indicates whether the cell just participated in a contraction wave or an expansion wave. A Wurfel is a tensegrity toy consisting of 12 blocks connected by a loop of elastic that enters and exits each block with a 90° turn (Gordon 1999). The Wurfel-like structure of the genome changes to one of two new configurations. This results in a change in gene expression, represented by the newly exposed and sequestered surfaces of the Wurfel. The change in genome structure may be reflected by a change in shape of the nucleus. (From Gordon, R. and Maniotis, A.J., Differentiation waves versus gradients of positional information: cause and effect in embryogenesis; preprint available at <http://www.umanitoba.ca/faculties/medicine/radiology/stafflist/rgordon.html>, with permission.)

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