**Cancer Dynamics**

**q-bio Summer School**

**Colorado State University, Fort Collins, CO**

**July 10-22, 2016**

**David Axelrod’s Schedule**

**Didactic Lectures & Research Seminars & Panel Discussion**

**Tuesday, July 12, 2016**

8:30-9:30 AM (75 min) Research Seminar, Scott Rm 229

“Breast Cancer – Deterministic Modeling of Tumor Progression Based Upon Clinical Histopathology Data”

**Tuesday, July 12, 2016**

9:30-10:45 AM (60 min) Panel Discussion, Scott 229

“Choosing the Right Research Project”

**Wednesday, July 13, 2016**

8:30-9:30 AM (60 min) Research Seminar, Scott Rm 229

“Colon Cancer – Stochastic Modeling of Stem Cell Dynamics to Improve Treatment and Prevention”

**Wednesday, July 13, 2016**

3:15-5:30 PM (75 min) Didactic lecture, Scott 209

“Cancer Biomedical Background I”

**Thursday, July 14, 2016**

3:15-5:30 PM (75 min) Didactic lecture, Scott 209

“Cancer Biomedical Background II”

**Topics and References**

**Wednesday, July 13, 2016**

3:15-5:30 PM (75 min) Didactic lecture, Scott 209

“Cancer Biomedical Background I”, David Axelrod

*Topics:*

Introduction to cancer, Benign and malignant neoplasms, Clonal origin of cancer. Tumor progression, Invasion and metastasis

**Thursday, July 14, 2016**

3:15-5:30 PM (75 min) Didactic lecture, Scott 209

“Cancer Biomedical Background II”, David Axelrod

*Topics:*

Tumor microenvironment, Cancer stem cells, Cancer therapy, Cancer Prevention

*References*:

Weinberg, R.A. 2014. The Biology of Cancer. Garland Science. NY.Ch. 2. The Nature of Cancer, pp. 31-50. <http://www.garlandscience.com/res/pdf/tboc2_ch2_draft.pdf>

*Additional references:*

Byrne, H.M. 2010. Dissecting cancer through mathematics: from the cell to the animal model. Nature Rev. Cancer 10:221-230.

Hanin, L. 2011. Why victory in the war on cancer remains elusive: Biomedical hypotheses and mathematical models. Cancers 3:340-367.

Merlo, L.M.F., J.W.Pepper, B.J. Reid, and C.C. Maley. 2006. Cancer as an evolutionary and ecological process. Nature Rev. Cancer 6:924-935.

Michor, F., Y. Iwasa, and M.A. Nowak. 2004. Dynamics of cancer progression. Nature Rev. Cancer 4:197-205.

*Online resources:*

Medline database of biomedical literature (Follow links: Advanced, Field (Title/Abstract), search terms, subject heading “models, theoretical”, or search key word “mathematical model”

http://www.ncbi.nlm.nih.gov/pubmed

National Cancer Institute: Cancer types, Grants & Training, Research areas (biology, causes, genomics, diagnosis, prevention, treatment, screening, clinical trails).

http://www.cancer.gov/cancertopics

Statistical tools and population data for researchers

<http://www.cancer.gov/research/resources/statistical-tools>

PubMed, publically accessible interface for Medline database of biomedical literature

<http://www.ncbi.nlm.nih.gov/pubmed/>

Kufe, D.W., R.E. Pollock, R.R. Weichselbaum, R.C. Bast Jr., T.S. Gansler, J.F. Holland, E. Emil (eds.). 2003. Cancer Medicine, 6th ed. Decker, Inc. NY. Table of contents available online. Contents searchable online at <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Books&itool=toolbar>)

*Reference books***:**

Kimmel, M. and D.E. Axelrod. 2015. Branching Processes in Biology. Springer, NY (Includes several topics related to cancer dynamics: cancer chemotherapy, cell cycle, population models, gene amplification, drug resistance, mutations, stathmokinesis, cancer progression and metastasis, etc.)

DeVita, V.T., T.S. Lawrence, S.A. Rosenber (eds.) 2011. Cancer : principles & practice of oncology. 9th edition.Wolters Kluwer/Lippincott Williams & Wilkins Health, Philadelphia. (Medical School level textbook)

Pecorino, L. 2012. Molecular Biology of Cancer: Mechanisms, Targets, and Therapeutics, 3rd edition. Oxford University Press, NY. (Undergraduate level textbook)

Weinberg, R.A. 2014. The Biology of Cancer, 2nd edition. Garland Science. NY. Includes CD. (Graduate level textbook)

Wodarz, D. and N.L. Komarova. 2005. Computational Biology of Cancer: Lecture Notes and Mathematical Modeling. World Sci. Publ., Singapore

Wodarz, D. and N.L. Komarova. 2014. Dynamics of Cancer: Mathematical Foundations of Oncology. World Sci. Publ., Singapore

*Reviews series:*

Advances in Cancer Research

Cancer and Metastasis Reviews

Cancer Reviews Online (only online, [www.cancerreviews.org](http://www.cancerreviews.org))

Cancer and Metastasis Reviews

Nature Reviews Cancer

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**Tuesday, July 12, 2016**

8:30-9:30 AM (75 min) Research Seminar, Scott Rm 229

“Breast Cancer – Deterministic Modeling of Tumor Progression Based Upon Clinical Histopathology Data” , David Axelrod

*Outline*:

Breast cancer, ductal carcinoma in situ (DCIS), invasive ductal carcinoma, prognosis by pathologist’s nuclear grade is insufficient, conventional linear model of tumor progression, clinical data, differential equations of candidate progression models, only parallel progression model is consistent with clinical data, prognostic predictions, image analysis quantitative nuclear grade, successful prognosis of survival

*References*:

Subramanian, B. and D.E. Axelrod. 2001. Progression of heterogeneous breast tumors. J. Theoret. Biol. 210: 107-119.

Sontag, L. and D.E. Axelrod. 2005. Evaluation of pathways for progression of heterogeneous breast tumors. J. Theoret. Biol. 232: 179-189.

Chapman, J.-A.W., N.A. Miller, H.L.A. Lickley, J. Qian, W.A. Christens-Barry, Y. Fu, Y. Yuan, and D.E. Axelrod. 2007. Ductal carcinoma in situ of the breast (DCIS) with heterogeneity of nuclear grade: Prognostic effects of quantitative nuclear assessment. BMC Cancer 2007, 7:174

doi: 10.1186/1471-2407-7-174, URL <http://www.biomedcentral.com/1471-2407/7/174>

Axelrod, D.E., N.A. Miller, H.L. Lickely J.Qian, W.A. Christens-Barry, Y. Yuan, Y. Fu,. J.-A.W. Chapman. 2008. Effect of quantitative nuclear image features on recurrence of ductal carcinoma in situ (DCIS) of the breast. Cancer Informatics 4:99-109.

URL http://la-press.com/article.php?article\_id=583. PubMed Central ID 2531292.

Axelrod, D.E., N. Miller, and J.-A. Chapman. 2009. Avoiding pitfalls in the statistical analysis of heterogeneous tumors. Biomedical Informatics Insights 2:11-18.

http://la-press.com/article.php?article\_id=1374

Miller, N.A., J.-A. Chapman, J. Qian, W.A. Christens-Barry, Y. Fu, Y. Yuan, H.L.A. Lickley, D.E. Axelrod. 2010. Heterogeneity Between Ducts of the Same Nuclear Grade Involved by *In Situ* Duct Carcinoma (DCIS) of the Breast**.** Cancer Informatics 9:201-216.

<http://www.la-press.com/heterogeneity-between-ducts-of-the-same-nuclear-grade-involved-by-article-a2250>

Axelrod, D.E., Shah, K, Yang, Q., Haffty, B.G. 2012. Prognosis for Survival of Young Women with Breast Cancer by Quantitative p53 Immunohistochemistry. Cancer and Clinical Oncology 1:52-64.

<http://dx.doi.org/10.5539/cco.v1n1p52>

*Additional references:*

Lin, S. 2007. Mixture modeling of progression pathways of heterogeneous breast tumors. Journal of Theoretical Biology 249:254-261.

Norton, K.-A., M. Wininger, G. Bhanot, S. Ganesan, N. Barnard, and T. Shinbrot. 2010. A 2D mechanistic model of breast ductal carcinoma in situ (DCIS) morphology and progression. J. Theoret. Biol. 263:393-406.

Macklin, P., M.E. Edgerton, A.M. Thompson, and V. Cristini. 2012. Patient-calibrated agent-based modeling of ductal carcinoma in situ (DCIS) from microscopic measurements to macroscopic predictions of clinical progression. J. Theoret. Biol. 301:122-140.

Franks, S.J., H.M. Byrne, J.C.E. Underwood, and C.E. Lewis. 2005. Biological inferences from a mathematical model of comedo ductal carcinoma in situ of the breast. J. Theoret. Biol. 232:523-543.

Franks, S.J., H.M. Byrne, J.R. King, J.C.E. Underwood, and C.E. Lewis. 2003. Modeling the early growth of ductal carcinoma in situ of the breast. J. Math. Biol. 47:424-452.

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**Wednesday, July 13, 2016**

8:30-9:30 AM (60 min) Research Seminar, Scott Rm 229

“Colon Cancer – Stochastic Modeling of Stem Cell Dynamics to Improve Treatment and Prevention” , David Axelrod

*Outline:*

Colon cancer, clinical motivation, modeling challenge, agent-based computer model, assumptions, implementation, calibration with measurements of human biopsy specimens, verification, simulations that suggest treatment schedule dynamics for improved therapy and prevention.

*References:*

Bravo, R and D.E. Axelrod. 2013. A calibrated agent-based computer model of stochastic cell dynamics in normal human colon crypts useful for in silico experiments. Theoretical Biology and Medical Modeling 10:66-90 (2013) <http://www.tbiomed.com/content/10/1/66> (Includes links to additional files with computer program of the virtual crypt, videos, and links to open source application.)

Axelrod, D.E. and R. Bravo (submitted). The advantage of intermittent pulse treatment schedules for the chemoprevention of colon cancer quantified by computer simulation of human colon crypts.

*Additional references:*

Boman BM, Fields JZ, Bonham-Carter O, Runquist OA: Computer modeling implicates stem cell overproduction in colon cancer initiation. *Cancer Res* 2001, 61:8408-8411.

Boman BM, Fields JZ, Cavanaugh KL, Guetter A, Runquist OA: How dysregulated colonic crypt dynamics cause stem cell overpopulation and initiate colon cancer. *Cancer Res* 2008, 68:3304-3313.

Britton NF, Wright NA, Murray JD: A mathematical model for cell population kinetics in the intestine. *J Theor Biol* 1982, 98:532-541.

Buske, P, Galle, J, Barker N, Aust G, Clevers H, Loeffler, M: A comprehensive model of the spatio-termporal stem cell and tissue organization in the intestinal crypt. *PLoS Comp Biol* 2011, 7:31001045.

Dunn S-J, Appleton PL, Nelson SA, Näthke IS, Gavaghan DJ, Osborne JM:. A Two-dimensional model of the colonic crypt accounting for the role of the basement membrane and pericryptal fibroblast sheath. PLoS Comp Biol 2012, 8:e1002515.

Fletcher AG, Breward CJW, Chapman SJ: Mathematical modeling of monoclonal conversion in the colonic crypt. *Theoret Biol* 2012, 300:118-133.

Johnston, MD, Edwards CM, Bodmer WF, Maini PK, Chapman SJ: Mathematical modeling of cell population dynamics in the colonic crypt and in colorectal cancer. *Proc Natl Acad Sci USA* 2007, 104:4008-4013.

Komarova NL, Cheng P: Epithelial tissue architecture protects against cancer. *Math Biosci*, 2006, 200:90-117.

Komarova, NL: Principles of regulation of self-renewal cell lineages. PLoS One 2013, 8:e72847.

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Leder K, Pitter K, LaPlant Q, Hambardzumyan D, Ross BD, Chan TA, Holland EC, Michor F: Mathematical modeling of PDGF-driven glioblastoma reveals optimized radiation dosing schedules. *Cell* 2014, 156:603-616.

Loeffler M, Birke A, Winton D, Potten C: Somatic mutation, monoclonality and stochastic models of stem cell organization in the intestinal crypt. *J Theoret Biol* 1993, 160:471-491.

Loeffler M, Potten CS, Paulus U, Glatzer J, Chwalinski S: Intestinal crypt proliferation. II. Computer modeling of mitotic index data provides further evidence for lateral and vertical cell migration in the absence of mitotic activity.

Loeffler, M, Bratke T, Paulus U, Li YQ, Potten CS: Clonality and life cycles of intestinal crypts explained by a state dependent stochastic model of epithelial stem cell organization. *J Thoret Biol* 1997, 186:41-54.

Lopez-Garcia C, Klein AM, Simons BD, Winton DJ: Intestinal stem cell replacement follows a pattern of neutral drift. *Science* 2010, 330:822-825.

Paulus U, Potten CS, Loeffler M: A model of the control of cellular regeneration in the intestinal crypt after perturbation based solely on local stem cell regulation. *Cell Prolif* 1992, 25:559-578.

Snippert HJ, van der Flier LG, Sato T, van Es JH, van den Born M, Kroon-Veenboer C, Barker N, Klein AM, van Rheenen J, Simons BD, Clevers H: Intestinal crypt homeostasis results from neutral competition between symmetrically dividing Lgr5 stem cells. 2010, *Cell* 143:134-144.

van Leeuwen IMM, Byrne HM, Jensen OE, King JR: Crypt dynamics and colorectal cancer: advances in mathematical modeling. *Cell Prolif* 2006, 39:157:181.

van Leeuwen IMM, Mirams GR, Walter A, Fletcher A, Murray P, Osborne J, Varma S, Young SJ, Cooper J, Doyle B, Pitt-Francis J, Momtahan L, Pathmanathan P, Whiteley JP, Chapman SJ, Gavaghan DJ, Jensen OE, King JR, Maini PK, Waters SL, Byrne HM: An integrative computational model for intestinal tissue renewal. *Cell Prolif* 2009, 42:617-636.

Wong SY, Chiam K-H, Lim ST, Matsudaira P: Computational model of cell positioning: directed and collective migration in the intestinal crypt epithelium. *J Royal Society Interface* 2010, 7 Suppl 3:S351-S363.

Youssefpour H, Li X ,Lander AD, Lowengrub JS: Multispecies model of cell lineages and feedback control in solid tumors. *J Theoret Biol* 2012, 304:39-59.

*July 6, 2016*