Chulián, Salvador; **Martínez-Rubio, Álvaro**; **Marciniak-Czochra, Anna**; **Stiehl, Thomas**; **Goñi, Cristina Blázquez**; **Rodríguez Gutiérrez, Juan Francisco**; **Ramírez Orellana, Manuel**; **Castillo Robleda, Ana**; **Pérez-García, Víctor M.**; **Rosa, María**

Dynamical properties of feedback signalling in B lymphopoiesis: a mathematical modelling approach. (English) Zbl 1465.92009

J. Theor. Biol. 522, Article ID 110685, 16 p. (2021).

Summary: Haematopoiesis is the process of generation of blood cells. Lymphopoiesis generates lymphocytes, the cells in charge of the adaptive immune response. Disruptions of this process are associated with diseases like leukaemia, which is especially incident in children. The characteristics of self-regulation of this process make them suitable for a mathematical study.

In this paper we develop mathematical models of lymphopoiesis using currently available data. We do this by drawing inspiration from existing structured models of cell lineage development and integrating them with paediatric bone marrow data, with special focus on regulatory mechanisms. A formal analysis of the models is carried out, giving steady states and their stability conditions. We use this analysis to obtain biologically relevant regions of the parameter space and to understand the dynamical behaviour of B-cell renovation. Finally, we use numerical simulations to obtain further insight into the influence of proliferation and maturation rates on the reconstitution of the cells in the B line. We conclude that a model including feedback regulation of cell proliferation represents a biologically plausible depiction for B-cell reconstitution in bone marrow. Research into haematological disorders could benefit from a precise dynamical description of B lymphopoiesis.

MSC:

92C15 Developmental biology, pattern formation
34C11 Growth and boundedness of solutions to ordinary differential equations
34D20 Stability of solutions to ordinary differential equations

Keywords:

mathematical medicine; haematopoiesis; mathematical modelling; lymphopoiesis

Software:

flowPeaks; Bioconductor; flowCore

Full Text: DOI

References:

[1] Abbas, A. K.; Lichtman, A. H.; Pillai, S., Cellular and molecular immunology, Elsevier Health Sciences (1994)

[2] Abbas, A.; Lichtman, A.; Pober, J., Cellular and Molecular Immunology (2015), Elsevier

[3] Ahmad, Z.; Durrani, N.; Hazir, T., Bone marrow examination in itp in children: is it mandatory?. Journal of the College of Physicians and Surgeons-Pakistan, JCPSP, 17, 6, 347-349 (2007), https://doi.org/06.2007/jcpsp.347349

[4] Alberts, B.; Bray, D.; Lewis, J.; Raff, M.; Roberts, K.; Watson, J., Molecular Biology of the Cell, Garland (2002)

[5] Andreoni, C.; Rigal, D.; Bonnard, M.; Bernaud, J., Phenotypic analysis of a large number of normal human bone marrow sample by flow cytometry, Blut, 61, 5, 271-277 (1990)

[6] Bendall, S. C.; Davis, K. L.; Amir, E.-A. D.; Tadmor, M. D.; Simonds, E. F.; Chen, T. J.; Shenfeld, D. K.; Nolan, G. P.; Pe'er, D., Single-cell trajectory detection uncovers progression and regulatory coordination in human b cell development, Cell, 157, 3, 714-725 (2014)

[7] Biasco, L.; Pellin, D.; Scala, S.; Dionisio, F.; Basso-Ricci, L.; Leonardelli, L.; Scaramuzza, S.; Baricordi, C.; Ferrua, F.; Cicalese, M. P., In vivo tracking of human hematopoiesis reveals patterns of clonal dynamics during early and steady-state reconstitution phases, Cell Stem Cell, 19, 1, 107-119 (2016)

[8] Busch, K.; Klapproth, K.; Barile, M.; Flossdorf, M.; Holland-Letz, T.; Schlenner, S. M.; Reth, M.; Höfer, T.; Rodewald, H.-R., Fundamental properties of unperturbed haematopoiesis from stem cells in vivo, Nature, 518, 7540, 542-546 (2015)

[9] Caldwell, C. W.; Poje, E.; Helikson, M. A., B-cell precursors in normal pediatric bone marrow, American Journal of Clinical Pathology, 95, 6, 816-823 (1991)

[10] Caocci, G.; Greco, M.; La Nasa, G., Bone marrow homing and engraftment defects of human hematopoietic stem and progenitor

cells, Mediterranean Journal of Hematology and Infectious Diseases, 9, 1 (2017)

[11] Clapp, G.; Levy, D., A review of mathematical models for leukemia and lymphoma, Drug Discovery Today: Disease Models, 16, 1-6 (2015)

[12] Clark, P.; Normansell, D.; Innes, D.; Hess, C., Lymphocyte subsets in normal bone marrow, Blood, 67, 6, 1600-1606 (1986)

[13] Deenen, G. J.; Van Balen, I.; Opstelten, D., In rat b lymphocyte genesis sixty percent is lost from the bone marrow at the transition of nondividing pre-b cell to sigm+ b lymphocyte, the stage of ig light chain gene expression, European Journal of Immunology, 20, 3, 557-564 (1990)

[14] Dingli, D.; Pacheco, J. M., Modeling the architecture and dynamics of hematopoiesis, Wiley Interdisciplinary Reviews: Systems Biology and Medicine, 2, 2, 235-244 (2009)

[15] Doulatov, S.; Notta, F.; Laurenti, E.; Dick, J. E., Hematopoiesis: a human perspective, Cell Stem Cell, 10, 2, 120-136 (2012)

[16] Finak, G.; Langweiler, M.; Jaimes, M.; Malek, M.; Taghiyar, J.; Korin, Y.; Raddassi, K.; Devine, L.; Obermoser, G.; Pekalski, M. L., Standardizing flow cytometry immunophenotyping analysis from the human immunophenotyping consortium, Scientific Reports, 6, 1, 1-11 (2016)

[17] Fuertinger, D. H.; Kappel, F.; Thijssen, S.; Levin, N. W.; Kotanko, P., A model of erythropoiesis in adults with sufficient iron availability, Journal of Mathematical Biology, 66, 6, 1209-1240 (2013) · Zbl 1303.92023

[18] Ganusov, V. V.; Auerbach, J., Mathematical modeling reveals kinetics of lymphocyte recirculation in the whole organism, PLoS Computational Biology, 10, 5, Article e1003586 pp. (2014)

[19] Ge, Y.; Sealfon, S. C., flowpeaks: a fast unsupervised clustering for flow cytometry data via k-means and density peak finding, Bioinformatics, 28, 15, 2052-2058 (2012)

[20] Guillaume, T.; Rubinstein, D. B.; Symann, M., Immune reconstitution and immunotherapy after autologous hematopoietic stem cell transplantation, Blood, The Journal of the American Society of Hematology, 92, 5, 1471-1490 (1998)

[21] Hahne, F.; LeMeur, N.; Brinkman, R. R.; Ellis, B.; Haaland, P.; Sarkar, D.; Spidlen, J.; Strain, E.; Gentleman, R., flowcore: a bioconductor package for high throughput flow cytometry, BMC Bioinformatics, 10, 1, 106 (2009)

[22] Hardy, R. R.; Kincade, P. W.; Dorshkind, K., The protean nature of cells in the b lymphocyte lineage, Immunity, 26, 6, 703-714 (2007)

[23] Hu, S.; Smirnova, O. A.; Cucinotta, F. A., A biomathematical model of lymphopoiesis following severe radiation accidents-potential use for dose assessment, Health physics, 102, 4, 425-436 (2012)

[24] Jones, D. S.; Plank, M.; Sleeman, B. D., Differential Equations and Mathematical Biology (2009), Chapman and Hall/CRC · Zbl 1298.92003

[25] Jumaa, H.; Hendriks, R. W.; Reth, M., B cell signaling and tumorigenesis, Annual Review of Immunology, 23, 415-445 (2005)

[26] Kawamoto, H.; Wada, H.; Katsura, Y., A revised scheme for developmental pathways of hematopoietic cells: the myeloid-based model, International Immunology, 22, 2, 65-70 (2010)

[27] Kleiveland; Charlotte, R., Peripheral Blood Mononuclear Cells, 161-167 (2015), Springer International Publishing: Springer International Publishing Cham

[28] Knauer, F.; Stiehl, T.; Marciniak-Czochra, A., Oscillations in a white blood cell production model with multiple differentiation stages, Journal of Mathematical Biology, 80, 3, 575-600 (2020) · Zbl 1440.34047

[29] Koch, U.; Radtke, F., Mechanisms of t cell development and transformation, Annual Review of Cell and Developmental Biology, 27, 539-562 (2011)

[30] Komarova, N. L., Principles of regulation of self-renewing cell lineages, PloS One, 8, 9 (2013)

[31] Kraus, H.; Kaiser, S.; Aumann, K.; Bönelt, P.; Salzer, U.; Vestweber, D.; Erlacher, M.; Kunze, M.; Burger, M.; Pieper, K.; Sic, H.; Rolink, A.; Eibel, H.; Rizzi, M., A feeder-free differentiation system identifies autonomously proliferating b cell precursors in human bone marrow, The Journal of Immunology, 192, 3, 1044-1054 (2014)

[32] Laurenti, E.; Göttgens, B., From haematopoietic stem cells to complex differentiation landscapes, Nature, 553, 7689, 418-426 (2018)

[33] LeBien, T. W., Fates of human b-cell precursors, Blood, The Journal of the American Society of Hematology, 96, 1, 9-23 (2000)

[34] LeBien, T. W.; Tedder, T. F., B lymphocytes: how they develop and function, Blood, 112, 5, 1570-1580 (2008)

[35] Leitenberg, D.; Rappeport, J. M.; Smith, B. R., B-cell precursor bone marrow reconstitution after bone marrow transplantation, American Journal of Clinical Pathology, 102, 2, 231-236 (1994)

[36] León-Triana, O.; Sabir, S.; Calvo, G. F.; Belmonte-Beitia, J.; Chulián, S.; Martínez-Rubio, Á.; Rosa, M.; Pérez-Martínez, A.; Orellana, M. R.; Pérez-García, V. M., CAR T cell therapy in B-cell acute lymphoblastic leukaemia: Insights from mathematical models, Communications in Nonlinear Science and Numerical Simulation, 94, 105570 (2021) · Zbl 1461.92043

[37] Lorenzi, T.; Marciniak-Czochra, A.; Stiehl, T., A structured population model of clonal selection in acute leukemias with multiple maturation stages, Journal of Mathematical Biology, 79, 5, 1587-1621 (2019) · Zbl 1423.35383

[38] Lúcio, P.; Parreira, A.; van den Beemd, M.; van Lochem, E.; van Wering, E.; Baars, E.; Porwit-MacDonald, A.; Bjorklund, E.; Gaipa, G.; Biondi, A.; Orfao, A.; Janossy, G.; van Dongen, J.; Miguel, J. S., Flow cytometric analysis of normal b cell differentiation: a frame of reference for the detection of minimal residual disease in precursor-b-all, Leukemia, 13, 3, 419-427 (1999)

[39] Mackey, M. C.; Rudnicki, R., Global stability in a delayed partial differential equation describing cellular replication, Journal of Mathematical Biology, 33, 1, 89-109 (1994) · Zbl 0833.92014

[40] Maddaly, R.; Pai, G.; Balaji, S.; Sivaramakrishnan, P.; Srinivasan, L.; Sunder, S. S.; Paul, S. F., Receptors and signaling mechanisms for b-lymphocyte activation, proliferation and differentiation-insights from both in vivo and in vitro approaches, FEBS Letters, 584, 24, 4883-4894 (2010)

[41] Manesso, E.; Teles, J.; Bryder, D.; Peterson, C., Dynamical modelling of haematopoiesis: an integrated view over the system in homeostasis and under perturbation, Journal of the Royal Society Interface, 10, 80, 20120817 (2013)

[42] Marciniak-Czochra, A.; Stiehl, T.; Wagner, W., Modeling of replicative senescence in hematopoietic development, Aging, 1, 8, 723-732 (2009)

[43] Marciniak-Czochra, A.; Stiehl, T.; Ho, A. D.; Jäger, W.; Wagner, W., Modeling of asymmetric cell division in hematopoietic stem cells—regulation of self-renewal is essential for efficient repopulation, Stem Cells and Development, 18, 3, 377-386 (2009)

[44] Marciniak-Czochra, A.; Mikelić, A.; Stiehl, T., Renormalization group second-order approximation for singularly perturbed nonlinear ordinary differential equations, Mathematical Methods in the Applied Sciences, 41, 14, 5691-5710 (2018) · Zbl 1404.34071

[45] Mehr, R.; Shahaf, G.; Sah, A.; Cancro, M., Asynchronous differentiation models explain bone marrow labeling kinetics and predict reflux between the pre-and immature b cell pools, International Immunology, 15, 3, 301-312 (2003)

[46] Monroe, J. G.; Bannish, G.; Fuentes-Panana, E. M.; King, L. B.; Sandel, P. C.; Chung, J.; Sater, R., Positive and negative selection during b lymphocyte development, Immunologic Research, 27, 2-3, 427-442 (2003)

[47] Mostolizadeh, R.; Afsharnezhad, Z.; Marciniak-Czochra, A., Mathematical model of chimeric anti-gene receptor (car) t cell therapy with presence of cytokine, Numerical Algebra, Control \& Optimization, 8, 1, 63 (2018) · Zbl 1406.92318

[48] Murphy, K.; Weaver, C., Janeway's immunobiology, Garland Science (2016)

[49] Nakata, Y.; Getto, P.; Marciniak-Czochra, A.; Alarcón, T., Stability analysis of multi-compartment models for cell production systems, Journal of Biological Dynamics, 6, sup1, 2-18 (2012) · Zbl 1447.92126

[50] Nombela-Arrieta, C.; Manz, M. G., Quantification and three-dimensional microanatomical organization of the bone marrow, Blood Advances, 1, 6, 407-416 (2017)

[51] O'Shea, J. J.; Gadina, M.; Siegel, R. M., Cytokines and cytokine receptors, (Clinical Immunology (2019), Elsevier), 127-155

[52] Osmond, D. G., Population dynamics of bone marrow b lymphocytes, Immunological Reviews, 93, 1, 103-124 (1986)

[53] Park, Y.-H.; Osmond, D. G., Dynamics of early b lymphocyte precursor cells in mouse bone marrow: proliferation of cells containing terminal deoxynucleotidyl transferase, European Journal of Immunology, 19, 11, 2139-2144 (1989)

[54] Parrado, A.; Casares, S.; Prieto, J.; Carmona, M.; Vaquero, A.; Rodriguez-Fernandez, J., Repopulation of circulating t, b and nk lymphocytes following bone marrow and blood stem cell transplantation, Hematology and Cell Therapy, 39, 6, 301-306 (1997)

[55] Petkau, G.; Turner, M., Signalling circuits that direct early b-cell development, Biochemical Journal, 476, 5, 769-778 (2019)

[56] Pujo-Menjouet, L., Blood cell dynamics: Half of a century of modelling, Mathematical Modelling of Natural Phenomena, 11, 1, 92-115 (2016) · Zbl 1384.92027

[57] Rego, E. M.; Garcia, A. B.; Viana, S. R.; Falcão, R. P., Age-related changes of lymphocyte subsets in normal bone marrow biopsies, Cytometry: The Journal of the International Society for Analytical Cytology, 34, 1, 22-29 (1998)

[58] Reya, T.; Morrison, S. J.; Clarke, M. F.; Weissman, I. L., Stem cells, cancer, and cancer stem cells, Nature, 414, 6859, 105-111 (2001)

[59] Roeder, I., Quantitative stem cell biology: computational studies in the hematopoietic system, Current Opinion in Hematology, 13, 4, 222-228 (2006)

[60] Saeys, Y.; Van Gassen, S.; Lambrecht, B. N., Computational flow cytometry: helping to make sense of high-dimensional immunology data, Nature Reviews Immunology, 16, 7, 449 (2016)

[61] Setty, M.; Tadmor, M. D.; Reich-Zeliger, S.; Angel, O.; Salame, T. M.; Kathail, P.; Choi, K.; Bendall, S.; Friedman, N.; Pe'er, D., Wishbone identifies bifurcating developmental trajectories from single-cell data, Nature Biotechnology, 34, 6, 637-645 (2016)

[62] Shahaf, G.; Zisman-Rozen, S.; Benhamou, D.; Melamed, D.; Mehr, R., B cell development in the bone marrow is regulated by homeostatic feedback exerted by mature b cells, Frontiers in Immunology, 7, 77 (2016)

[63] Skipper, H. E.; Perry, S., Kinetics of normal and leukemic leukocyte populations and relevance to chemotherapy, Cancer Research, 30, 6, 1883-1897 (1970)

[64] Smirnova, O. A.; Hu, S.; Cucinotta, F. A., Analysis of the lymphocytopoiesis dynamics in nonirradiated and irradiated humans: a modeling approach, Radiation Research, 181, 3, 240-250 (2014)

[65] Steliarova-Foucher, E.; Colombet, M.; Ries, L. A.; Moreno, F.; Dolya, A.; Bray, F.; Hesseling, P.; Shin, H. Y.; Stiller, C. A.; Bouzbid, S., International incidence of childhood cancer, 2001-10: a population-based registry study, The Lancet Oncology, 18, 6, 719-731 (2017)

[66] Stiehl, T.; Marciniak-Czochra, A., Characterization of stem cells using mathematical models of multistage cell lineages, Mathematical and Computer Modelling, 53, 7-8, 1505-1517 (2011) · Zbl 1219.34068

[67] Stiehl, T.; Marciniak-Czochra, A., Stem cell self-renewal in regeneration and cancer: insights from mathematical modeling, Current Opinion in Systems Biology, 5, 112-120 (2017)

[68] Stiehl, T.; Baran, N.; Ho, A. D.; Marciniak-Czochra, A., Clonal selection and therapy resistance in acute leukaemias: mathematical modelling explains different proliferation patterns at diagnosis and relapse, Journal of The Royal Society Interface, 11, 94 (2014), 20140079

[69] Talmadge, J. E.; Reed, E.; Ino, K.; Kessinger, A.; Kuszynski, C.; Heimann, D.; Varney, M.; Jackson, J.; Vose, J. M.; Bierman, P. J., Rapid immunologic reconstitution following transplantation with mobilized peripheral blood stem cells as compared to bone marrow, Bone Marrow Transplantation, 19, 2, 161-172 (1997)

[70] Van Dongen, J.; Lhermitte, L.; Böttcher, S.; Almeida, J.; Van der Velden, V.; Flores-Montero, J.; Rawstron, A.; Asnafi, V.; Lecrevisse, Q.; Lucio, P., Euroflow antibody panels for standardized n-dimensional flow cytometric immunophenotyping of normal, reactive and malignant leukocytes, Leukemia, 26, 9, 1908-1975 (2012)

[71] van Lochem, E.; van der Velden, V.; Wind, H.; te Marvelde, J.; Westerdaal, N.; van Dongen, J., Immunophenotypic differentiation patterns of normal hematopoiesis in human bone marrow: Reference patterns for age-related changes and disease-induced shifts, Cytometry, 60B, 1, 1-13 (2004)

[72] Viswanathan, S.; Zandstra, P. W., Towards predictive models of stem cell fate, Cytotechnology, 41, 2/3, 75-92 (2003)

[73] Walenda, T.; Stiehl, T.; Braun, H.; Fröbel, J.; Ho, A. D.; Schroeder, T.; Goecke, T. W.; Rath, B.; Germing, U.; Marciniak-Czochra, A., Feedback signals in myelodysplastic syndromes: increased self-renewal of the malignant clone suppresses normal hematopoiesis, PLoS Computational Biology, 10, 4 (2014)

[74] Wang, W.; Stiehl, T.; Raffel, S.; Hoang, V. T.; Hoffmann, I.; Poisa-Beiro, L.; Saeed, B. R.; Blume, R.; Manta, L.; Eckstein, V., Reduced hematopoietic stem cell frequency predicts outcome in acute myeloid leukemia, Haematologica, 102, 9, 1567-1577 (2017)

[75] Wilson, A.; Laurenti, E.; Oser, G.; van der Wath, R. C.; Blanco-Bose, W.; Jaworski, M.; Offner, S.; Dunant, C. F.; Eshkind, L.; Bockamp, E., Hematopoietic stem cells reversibly switch from dormancy to self-renewal during homeostasis and repair, Cell, 135, 6, 1118-1129 (2008)

[76] Zafar, H.; Anwar, S.; Faizan, M.; Riaz, S., Clinical features and outcome in paediatric newly diagnosed immune thrombocytopenic purpura in a tertiary care centre, Pakistan Journal of Medical Sciences, 34, 5, 1195 (2018)