

Wright, Thomas; Stark, Ian

Modelling patterns of gene regulation in the bond-calculus. (English) [Zbl 1458.92039](#)

Gupta, Ankit (ed.) et al., Proceedings of SASB 2018, the 9th international workshop on static analysis and systems biology, Freiburg, Germany, August 28, 2018. Amsterdam: Elsevier. Electron. Notes Theor. Comput. Sci. 350, 117-138 (2020).

Summary: The bond-calculus is a language for modelling interactions between continuous populations of biomolecular agents. The calculus combines process-algebra descriptions of individual agent behaviour with affinity patterns, which can specify a wide variety of patterns of interactions between the sites of different agents. These affinity patterns extend binary molecular affinities to multiway reactions, general kinetic laws, and cooperative interactions. In this paper we explore bond-calculus modelling of gene regulation at both the molecular and network levels. At the molecular level, we show how affinity patterns can succinctly describe the λ -switch, a prototypical example of cooperative regulation. Moving to the network level, we develop a general model of gene regulatory networks using affinity patterns and an expanded Hill kinetic law. We illustrate the approach with a specific example: the complex plant circadian clock. We analyse these models via the bond-calculus's differential equation and stochastic semantics, and validate our results against existing models from the literature.

For the entire collection see [\[Zbl 1448.92002\]](#).

MSC:

[92C42](#) Systems biology, networks
[92D10](#) Genetics and epigenetics

Keywords:

[process algebra](#); [gene regulation](#); [biochemical networks](#); [multiway](#)

Software:

[BIOCHAM](#); [BioNetGen](#); [Bio-PEPA](#); [BlenX](#); [PEPA](#); [SpiCO](#); [StochPy](#)

Full Text: [DOI](#)

References:

- [1] Ackers, G. K.; Johnson, A. D.; Shea, M. A., Quantitative model for gene regulation by lambda phage repressor, Proceedings of the National Academy of Sciences, 79, 1129-1133 (1982)
- [2] Akman, O.; Ciocchetta, F.; Degasperi, A.; Guerriero, M., Modelling biological clocks with Bio-PEPA: stochasticity and robustness for the neurospora crassa circadian network, (Computational Methods in Systems Biology (2009), Springer), 52-67
- [3] Akman, O. E.; Guerriero, M. L.; Loewe, L.; Troein, C., Complementary approaches to understanding the plant circadian clock, (Merelli, E.; Quaglia, P., Proceedings Third Workshop From Biology To Concurrency and back. Proceedings Third Workshop From Biology To Concurrency and back, Paphos, Cyprus, 27th, March 2010. Proceedings Third Workshop From Biology To Concurrency and back. Proceedings Third Workshop From Biology To Concurrency and back, Paphos, Cyprus, 27th, March 2010, Electronic Proceedings in Theoretical Computer Science, vol. 19 (2010)), 1-19
- [4] Arkin, A.; Ross, J.; McAdams, H. H., Stochastic kinetic analysis of developmental pathway bifurcation in phage λ -infected escherichia coli cells, Genetics, 149, 1633-1648 (1998)
- [5] Banks, C.; Clark, A.; Georgoulas, A.; Gilmore, S.; Hillston, J.; Milios, D.; Stark, I., Stochastic modelling of the Kai-based circadian clock, Electronic Notes in Theoretical Computer Science, 296, 43-60 (2013)
- [6] Banks, C.; Stark, I., A Logic of Behaviour in Context, Inf. Comput., 236, 3-18 (2014) · [Zbl 1311.68083](#)
- [7] Beica, A.; Guet, C. C.; Petrov, T., Efficient reduction of kappa models by static inspection of the rule-set, (International Workshop on Hybrid Systems Biology (2015), Springer), 173-191 · [Zbl 1412.92075](#)
- [8] Bintu, L.; Buchler, N. E.; Garcia, H. G.; Gerland, U.; Hwa, T.; Kondev, J.; Kuhlman, T.; Phillips, R., Transcriptional regulation by the numbers: applications, Current Opinion in Genetics & Development, 15, 125-135 (2005), chromosomes and expression mechanisms
- [9] Bintu, L.; Buchler, N. E.; Garcia, H. G.; Gerland, U.; Hwa, T.; Kondev, J.; Phillips, R., Transcriptional regulation by the

- numbers: models, *Current Opinion in Genetics & Development*, 15, 116-124 (2005), chromosomes and expression mechanisms
- [10] Blinov, M. L.; Faeder, J. R.; Goldstein, B.; Hlavacek, W. S., *BioNetGen: software for rule-based modeling of signal transduction based on the interactions of molecular domains*, *Bioinformatics*, 20, 3289-3291 (2004)
 - [11] Blossey, R.; Cardelli, L.; Phillips, A., A compositional approach to the stochastic dynamics of gene networks, (Priami, C.; Cardelli, L.; Emmott, S., *Transactions on Computational Systems Biology IV* (2006)), 99-122 · [Zbl 1179.92021](#)
 - [12] Blossey, R.; Cardelli, L.; Phillips, A., Compositionality, stochasticity, and cooperativity in dynamic models of gene regulation, *HFSP journal*, 2, 17-28 (2008)
 - [13] Bodei, C.; Brodo, L.; Bruni, R., Open multiparty interaction, (Martí-Oliet, N.; Palomino, M., *Recent Trends in Algebraic Development Techniques. Recent Trends in Algebraic Development Techniques, 21st International Workshop, WADT 2012, Salamanca, Spain, June 7-10, 2012* (2013)), 1-23, *Revised Selected Papers* · [Zbl 1394.68244](#)
 - [14] Bodei, C.; Brodo, L.; Bruni, R.; Chiarugi, D., A flat process calculus for nested membrane interactions, *Scientific Annals of Computer Science*, 24, 91 (2014) · [Zbl 1424.68101](#)
 - [15] Bortolussi, L.; Policriti, A., Stochastic concurrent constraint programming and differential equations, *Proceedings of the Fifth Workshop on Quantitative Aspects of Programming Languages (QAPL 2007)*. *Proceedings of the Fifth Workshop on Quantitative Aspects of Programming Languages (QAPL 2007)*, *Electronic Notes in Theoretical Computer Science*, 190, 27-42 (2007) · [Zbl 1279.92031](#)
 - [16] Bortolussi, L.; Policriti, A., Hybrid dynamics of stochastic programs, *Hybrid Automata and Oscillatory Behaviour in Biological Systems. Hybrid Automata and Oscillatory Behaviour in Biological Systems*, *Theoretical Computer Science*, 411, 2052-2077 (2010) · [Zbl 1198.68175](#)
 - [17] Bundschuh, R.; Hayot, F.; Jayaprakash, C., Fluctuations and slow variables in genetic networks, *Biophysical journal*, 84, 1606-1615 (2003)
 - [18] Bundschuh, R.; Hayot, F.; Jayaprakash, C., The role of dimerization in noise reduction of simple genetic networks, *Journal of Theoretical Biology*, 220, 261-269 (2003) · [Zbl 07196935](#)
 - [19] Calder, M.; Gilmore, S.; Hillston, J., Modelling the influence of RKIP on the ERK signalling pathway using the stochastic process algebra PEPA, (Priami, C.; Ingólfssdóttir, A.; Mishra, B.; Riis Nielson, H., *Transactions on Computational Systems Biology VII* (2006)), 1-23
 - [20] Calder, M.; Hillston, J., Process algebra modelling styles for biomolecular processes, (*Transactions on computational systems biology XI* (2009), Springer), 1-25 · [Zbl 1260.92030](#)
 - [21] Camporesi, F.; Feret, J.; Lý, K. Q., A tool to compile Kappa rules into (reduced) ODE models, (Feret, J.; Koepl, H., *Computational Methods in Systems Biology. Computational Methods in Systems Biology, KaDE* (2017)), 291-299
 - [22] Cardelli, L., On process rate semantics, *Converging Sciences: Informatics and Biology. Converging Sciences: Informatics and Biology*, *Theoretical Computer Science*, 391, 190-215 (2008) · [Zbl 1133.68054](#)
 - [23] Cardelli, L.; Caron, E.; Gardner, P.; Kahramanoğlu, O.; Phillips, A., A process model of actin polymerisation, *Proceedings of the Second Workshop From Biology to Concurrency and Back (FBTC 2008)*. *Proceedings of the Second Workshop From Biology to Concurrency and Back (FBTC 2008)*, *Electronic Notes in Theoretical Computer Science*, 229, 127-144 (2009) · [Zbl 1283.92047](#)
 - [24] Ciobanu, G., From gene regulation to stochastic fusion, (*International Conference on Unconventional Computation* (2008), Springer), 51-63 · [Zbl 1166.68319](#)
 - [25] Ciobanu, G., General patterns of interaction in stochastic fusion, *Natural Computing*, 12, 429-439 (2013) · [Zbl 1334.68147](#)
 - [26] Ciocchetta, F., The BlenX language with biological transactions, (Priami, C., *Transactions on Computational Systems Biology IX* (2008)), 114-152 · [Zbl 1241.92026](#)
 - [27] Ciocchetta, F., Bio-PEPA with events, (Priami, C.; Back, R.-J.; Petre, I., *Transactions on Computational Systems Biology XI* (2009)), 45-68 · [Zbl 1260.92021](#)
 - [28] Ciocchetta, F.; Hillston, J., Bio-PEPA: A framework for the modelling and analysis of biological systems, *Theoretical Computer Science*, 410, 3065-3084 (2009) · [Zbl 1173.68041](#)
 - [29] Ciocchetta, F.; Priami, C., Biological transactions for quantitative models, *Proceedings of the First Workshop on Membrane Computing and Biologically Inspired Process Calculi (MeCBIC 2006)*. *Proceedings of the First Workshop on Membrane Computing and Biologically Inspired Process Calculi (MeCBIC 2006)*, *Electronic Notes in Theoretical Computer Science*, 171, 55-67 (2007) · [Zbl 1277.68173](#)
 - [30] Danos, V.; Laneve, C., Formal molecular biology, *Theoretical Computer Science*, 325, 69-110 (2004) · [Zbl 1071.68041](#)
 - [31] De Caluwé, J.; de Melo, J. R.F.; Tosenberger, A.; Hermans, C.; Verbruggen, N.; Leloup, J.-C.; Gonze, D., Modeling the photoperiodic entrainment of the plant circadian clock, *Journal of theoretical biology*, 420, 220-231 (2017)
 - [32] De Caluwé, J.; Xiao, Q.; Hermans, C.; Verbruggen, N.; Leloup, J.-C.; Gonze, D., A compact model for the complex plant circadian clock, *Frontiers in plant science*, 7 (2016)
 - [33] Degano, P.; Prandi, D.; Priami, C.; Quaglia, P., Beta-binders for biological quantitative experiments, *Proceedings of the 4th International Workshop on Quantitative Aspects of Programming Languages (QAPL 2006)*. *Proceedings of the 4th International Workshop on Quantitative Aspects of Programming Languages (QAPL 2006)*, *Electronic Notes in Theoretical Computer Science*, 164, 101-117 (2006)
 - [34] Dematté, L.; Priami, C.; Romanel, A., The BlenX language: A tutorial, (*Proceedings of the Formal Methods for the Design of Computer, Communication, and Software Systems 8th International Conference on Formal Methods for Computational Systems Biology, SFM'08* (2008)), 313-365 · [Zbl 1160.68678](#)
 - [35] Fages, F., Modelling and querying interaction networks in the biochemical abstract machine BIOCHAM, *Journal of Biological*

Physics and Chemistry, 4, 64-73 (2002)

- [36] Fogelmark, K.; Troein, C., Rethinking transcriptional activation in the arabidopsis circadian clock, *PLOS Computational Biology*, 10, 1-12 (2014)
- [37] Galpin, V., Modelling a circadian clock with HYPE, (Proceedings of the 9th workshop on process algebra and stochastically timed activities (PASTA) (2010)), 92-98
- [38] Geisweiller, N.; Hillston, J.; Stenico, M., Relating continuous and discrete PEPA models of signalling pathways, *Membrane Computing and Biologically Inspired Process Calculi. Membrane Computing and Biologically Inspired Process Calculi, Theoretical Computer Science*, 404, 97-111 (2008) · [Zbl 1151.68038](#)
- [39] Guerriero, M. L.; Pokhilko, A.; Fernández, A. P.; Halliday, K. J.; Millar, A. J.; Hillston, J., Stochastic properties of the plant circadian clock, *Journal of The Royal Society Interface* (2011)
- [40] Hasty, J.; Isaacs, F.; Dolnik, M.; McMillen, D.; Collins, J. J., Designer gene networks: Towards fundamental cellular control, *Chaos: An Interdisciplinary Journal of Nonlinear Science*, 11, 207-220 (2001) · [Zbl 1029.92011](#)
- [41] Hasty, J.; Pradines, J.; Dolnik, M.; Collins, J. J., Noise-based switches and amplifiers for gene expression, *Proceedings of the National Academy of Sciences*, 97, 2075-2080 (2000)
- [42] Hayden, R. A.; Bradley, J. T., A fluid analysis framework for a markovian process algebra, *Theoretical Computer Science*, 411, 2260-2297 (2010) · [Zbl 1334.68151](#)
- [43] Hill, A., The possible effects of the aggregation of the molecules of haemoglobin on its dissociation curves, *J Physiol (Lond)*, 40, 4-7 (1910)
- [44] Hillston, J., *Compositional Markovian modelling using a process algebra, (Computations with Markov chains (1995), Springer)*, 177-196 · [Zbl 0861.90121](#)
- [45] Hillston, J., Fluid flow approximation of PEPA models, (Proceedings of the Second International Conference on the Quantitative Evaluation of Systems, QEST '05 (2005)), 33
- [46] Hofmeyr, J.-H. S.; Cornish-Bowden, H., The reversible Hill equation: how to incorporate cooperative enzymes into metabolic models, *Bioinformatics*, 13, 377-385 (1997)
- [47] Imada, J.; Ross, B. J., Evolutionary synthesis of stochastic gene network models using feature-based search spaces, *New Generation Computing*, 29, 365-390 (2011)
- [48] John, M.; Lhoussaine, C.; Niehren, J., Dynamic Compartments in the Imperative Pi Calculus, 5688, 235-250 (2009)
- [49] John, M.; Lhoussaine, C.; Niehren, J.; Uhrmacher, A. M., The attributed pi calculus, (Heiner, M.; Uhrmacher, A. M., *Computational Methods in Systems Biology, Proceedings. Computational Methods in Systems Biology, Proceedings, 6th International Conference CMSB 2008, Rostock, Germany, October 12-15, 2008* (2008)), 83-102
- [50] John, M.; Lhoussaine, C.; Niehren, J.; Versari, C., Biochemical reaction rules with constraints, (European symposium on programming (2011), Springer), 338-357 · [Zbl 1326.68050](#)
- [51] John, M.; Schulz, H.-J.; Schumann, H.; Uhrmacher, A. M.; Unger, A., Constructing and visualizing chemical reaction networks from pi-calculus models, *Formal Aspects of Computing*, 25, 723-742 (2013) · [Zbl 1298.92128](#)
- [52] Kuttler, C., Simulating bacterial transcription and translation in a stochastic π calculus, (Priami, C.; Plotkin, G., *Transactions on Computational Systems Biology VI* (2006)), 113-149
- [53] Kuttler, C.; Lhoussaine, C.; Nebut, M., Rule-Based Modeling of Transcriptional Attenuation at the Tryptophan Operon, 199-228 (2010), Springer Berlin Heidelberg: Springer Berlin Heidelberg Berlin, Heidelberg · [Zbl 1275.92024](#)
- [54] Kuttler, C.; Lhoussaine, C.; Niehren, J., A stochastic pi calculus for concurrent objects, *Ab*, 4545, 232-246 (2007) · [Zbl 1126.92003](#)
- [55] Kuttler, C.; Niehren, J., Gene regulation in the pi calculus: Simulating cooperativity at the lambda switch, (Priami, C.; Ingólfssdóttir, A.; Mishra, B.; Riis Nielson, H., *Transactions on Computational Systems Biology VII* (2006)), 24-55
- [56] Kwiatkowski, M., A formal computational framework for the study of molecular evolution (2010), Edinburgh, supervised by Ian Stark
- [57] Kwiatkowski, M.; Stark, I., The continuous π -calculus: A process algebra for biochemical modelling, (Computational Methods in Systems Biology: Process of the Sixth International Conference CMSB 2008. *Computational Methods in Systems Biology: Process of the Sixth International Conference CMSB 2008, Lecture Notes in Computer Science*, vol. number 5307 (2008)), 103-122
- [58] Kwiatkowski, M.; Stark, I., On executable models of molecular evolution, (Proceedings of the 8th International Workshop on Computational Systems Biology WCSB 2011. *Proceedings of the 8th International Workshop on Computational Systems Biology WCSB 2011, TICSP Report*, vol. number 57 (2011)), 105-108
- [59] Larcher, R.; Priami, C., From BlenX to chemical reactions via SBML (2008), University of Trento, Technical report
- [60] Lecca, P.; Priami, C.; Laudanna, C.; Constantin, G., A biospi model of lymphocyte-endothelial interactions in inflamed brain venules, (Biocomputing 2004 (2003), World Scientific), 521-532
- [61] Locke, J.; Millar, A.; Turner, M., Modelling genetic networks with noisy and varied experimental data: the circadian clock in *Arabidopsis thaliana*, *Journal of Theoretical Biology*, 234, 383-393 (2005) · [Zbl 1445.92014](#)
- [62] Maarleveld, T. R.; Olivier, B. G.; Bruggeman, F. J., StochPy: A comprehensive, user-friendly tool for simulating stochastic biological processes, *PLOS ONE*, 8, 1-10 (2013)
- [63] McAdams, H. H.; Arkin, A., Stochastic mechanisms in gene expression, *Proceedings of the National Academy of Sciences*, 94, 814-819 (1997)

- [64] Nagasaki, M.; Onami, S.; Miyano, S.; Kitano, H., Bio-calculus: Its concept and molecular interaction, *Genome Informatics*, 10, 133-143 (1999)
- [65] Nagel, D. H.; Kay, S. A., Complexity in the wiring and regulation of plant circadian networks, *Current Biology*, 22, R648 (2012), R657
- [66] Paulevé, L.; Magnin, M.; Roux, O., Refining dynamics of gene regulatory networks in a stochastic π -calculus framework, (*Transactions on computational systems biology xiii* (2011), Springer), 171-191 · [Zbl 1326.92027](#)
- [67] Phillips, A.; Cardelli, L., A correct abstract machine for the stochastic pi-calculus, *Bioconcur'04. Bioconcur'04, ENTCS* (2004)
- [68] Pokhilko, A.; Hodge, S. K.; Stratford, K.; Knox, K.; Edwards, K. D.; Thomson, A. W.; Mizuno, T.; Millar, A. J., Data assimilation constrains new connections and components in a complex, eukaryotic circadian clock model, *Molecular Systems Biology*, 6 (2010)
- [69] Pokhilko, A.; Mas, P.; Millar, A. J., Modelling the widespread effects of TOC1 signalling on the plant circadian clock and its outputs, *BMC Systems Biology*, 7, 23 (2013)
- [70] Priami, C., Stochastic π -calculus, *The Computer Journal*, 38, 578-589 (1995)
- [71] Priami, C.; Quaglia, P., Beta binders for biological interactions, (Danos, V.; Schachter, V., *Computational Methods in Systems Biology, Revised Selected Papers. Computational Methods in Systems Biology, Revised Selected Papers, International Conference CMSB 2004, Paris, France, May 26-28, 2004* (2005)), 20-33 · [Zbl 1088.68646](#)
- [72] Priami, C.; Regev, A.; Shapiro, E.; Silverman, W., Application of a stochastic name-passing calculus to representation and simulation of molecular processes, *Information Processing Letters*, 80, 25-31 (2001) · [Zbl 0997.92018](#)
- [73] Regev, A.; Silverman, W.; Shapiro, E., Representation and simulation of biochemical processes using the π -calculus process algebra, 6, 459-470 (2001)
- [74] Ross, B. J., Using multi-objective genetic programming to evolve stochastic logic gate circuits, (2015 *IEEE Conference on Computational Intelligence in Bioinformatics and Computational Biology (CIBCB)* (2015)), 1-8
- [75] Salazar, J. D.; Saithong, T.; Brown, P. E.; Foreman, J.; Locke, J. C.; Halliday, K. J.; Carré, I. A.; Rand, D. A.; Millar, A. J., Prediction of photoperiodic regulators from quantitative gene circuit models, *Cell*, 139, 1170-1179 (2009)
- [76] Sangiorgi, D., π -calculus, internal mobility, and agent-passing calculi, *Theoretical Computer Science*, 167, 235-274 (1996) · [Zbl 0874.68103](#)
- [77] Santillán, M.; Mackey, M. C., Why the lysogenic state of phage λ is so stable: a mathematical modeling approach, *Biophysical journal*, 86, 75-84 (2004)
- [78] Schmal, C.; Leloup, J.-C.; Gonze, D., Modeling and simulating the *Arabidopsis thaliana* circadian clock using XPP-AUTO, (Staiger, D., *Plant Circadian Networks: Methods and Protocols* (2014), Springer New York: Springer New York New York, NY), 337-358
- [79] Shea, M. A.; Ackers, G. K., The OR control system of bacteriophage lambda: A physical-chemical model for gene regulation, *Journal of molecular biology*, 181, 211-230 (1985)
- [80] Stefanek, A.; Vigliotti, M.; Bradley, J. T., Spatial extension of stochastic pi calculus, (8th *Workshop on Process Algebra and Stochastically Timed Activities* (2009)), 109-117
- [81] Tian, T.; Burrage, K., Bistability and switching in the lysis/lysogeny genetic regulatory network of bacteriophage lambda, *Journal of Theoretical Biology*, 227, 229-237 (2004) · [Zbl 1439.92096](#)
- [82] Ting-Chao, C.; TaLaLay, P., Generalized equations for the analysis of inhibitions of Michaelis-Menten and higher-order kinetic systems with two or more mutually exclusive and nonexclusive inhibitors, *European journal of biochemistry*, 115, 207-216 (1981)
- [83] Tribastone, M.; Gilmore, S.; Hillston, J., Scalable differential analysis of process algebra models, *IEEE Transactions on Software Engineering*, 38, 205-219 (2012)
- [84] Versari, C.; Gorrieri, R., $\pi@$: A π -based process calculus for the implementation of compartmentalised bio-inspired calculi, (Bernardo, M.; Degano, P.; Zavattaro, G., *Formal Methods for Computational Systems Biology: 8th International School on Formal Methods for the Design of Computer, Communication, and Software Systems, SFM 2008 Bertinoro, Italy, June 2-7, 2008 Advanced Lectures* (2008)), 449-506
- [85] Weiss, J. N., The Hill equation revisited: uses and misuses, *The FASEB Journal*, 11, 835-841 (1997)
- [86] Wright, T., Bond calculus workbench repository
- [87] Wright, T.; Stark, I., The Bond-Calculus: A process algebra for complex biological interaction dynamics (2018), arXiv preprint
- [88] Zeilinger, M. N.; Farré, E. M.; Taylor, S. R.; Kay, S. A.; Doyle, F. J., A novel computational model of the circadian clock in *Arabidopsis* that incorporates PRR7 and PRR9, *Molecular Systems Biology*, 2 (2006)

This reference list is based on information provided by the publisher or from digital mathematics libraries. Its items are heuristically matched to zbMATH identifiers and may contain data conversion errors. It attempts to reflect the references listed in the original paper as accurately as possible without claiming the completeness or perfect precision of the matching.